Supporting Information

Suzuki-Miyaura Reaction in the Presence of *N*-Acetylcysteamine Thioesters Enables Rapid Synthesis of Biomimetic Polyketide Thioester Surrogates for Biosynthetic Studies

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Table of Content

General Methods

Chemistry methods and materials

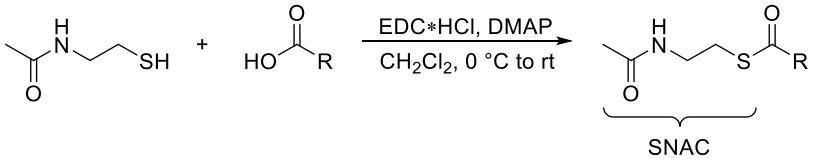
All chemicals and solvents were obtained from ABCR, ACROS ORGANICS, BLD PHARM, CARBOLUTION, CHEMIPUR, EURISOTOP, FISHER CHEMICAL, FLUOROCHEM, GRÜSSING, ROTH, SIGMA-ALDRICH, TCI and VWR and were, unless otherwise stated, used without further purification. Dry solvents were obtained from ACROS ORGANICS. All reactions were performed under argon gas with dry solvents and reagents. Light-sensitive substances were handled in brown glass- or aluminium foil wrapped flasks. The reactions were monitored *via* TLC with Alugram SilG/UV254 TLC-foils from MACHEREY-NAGEL. The substances were detected with UV-light and a $KMnO_4$-stain (1.50 g $KMnO_4$, 10.0 g K_2CO_3, 2.50 mL 5%-NaOH, 200 mL H_2O). Products were purified by flash chromatography on SiO_2 (Macherey-Nagel MN Kieselgel 60, 40-63 μm).[1] Semi-preparative HPLC was performed with a WATERS HPLC (600 controller, 2487 Dual wavelength absorbance detector) using a C18-SP stationary phase (H_2O:MeCN = 95:5 {5 min}, Gradient H_2O:MeCN 95:5 → 5:95 {20 min}, H_2O:MeCN = 5:95 {5 min}, 20 mL/min).

All NMR spectra were recorded with BRUKER AVANCE III HD 500 with the residual solvent signal as internal standard: $CDCl_3$ 7.26 ppm for ^1H, 77.16 ppm for ^{13}C.[2] Signal multiplicities are stated, using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. For ^{13}C-NMR, the following abbreviations were used: q = quarternary, t = tertiary, s = secondary, p = primary. The chemical shifts are reported as values of the δ-scale in [ppm] and the coupling constants *J* in [Hz]. Signal assignments were made with 2D-NMR spectra (COSY, HSQC, HMBC, NOESY). High resolution mass spectra (HRMS) were obtained with a THERMO FISHER SCIENTIFIC Q EXACTIVE (Orbitrap) mass spectrometer. Optical rotation was recorded on a JASCO P-1020 polarimeter (10 cm cell) using the sodium D line (589 nm). The given value of $[\alpha]^D$ represents the average of 50 individual measurements and is stated as $deg \cdot mL \cdot g^{-1} \cdot dm^{-1}$. Elemental analyses were carried out with a *2400 CHN elemental analyzer* from PERKIN-ELMER.

Substrate syntheses

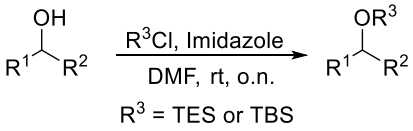
General procedures

General Procedure 1: STEGLICH esterification for SNAC thioester formation



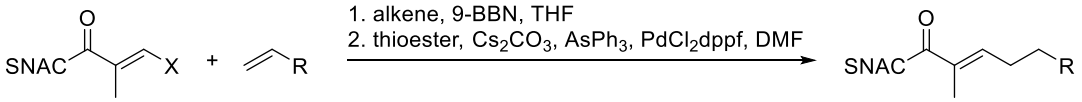
A solution of carboxylic acid (1.0 eq.) and *N*-acetylcysteamine (1.5 eq.) in CH_2Cl_2 (0.2 M) was cooled to 0 °C. Subsequently, DMAP (0.1 eq.) and EDC*HCl (1.5 eq.) were added. After warming to room temperature, the solution was stirred for 2 h, before diluting with saturated aqueous NH_4Cl solution. The resulting phases were separated and the aqueous one was extracted three times with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$ and filtrated. The solvent was removed *in vacuo* and the crude thioester purified *via* flash chromatography.

General Procedure 2: Protection of hydroxyls as silylethers



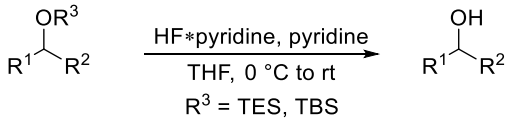
To a stirred solution of secondary alcohol (1.0 eq.) in DMF (1 M) were added silylchloride (1.5 eq.) and imidazole (2.5 eq.). After stirring the mixture at room temperature overnight, pentane and water were added. The resulting phases were separated and the aqueous one was extracted three times with pentane. Subsequently, the combined organic phases were washed with brine, dried over $MgSO_4$ and filtrated. The solvent was removed *in vacuo* and the crude silylether was purified *via* filtration over a short plug of silica (pentane).

General Procedure 3: Hydroboration-SUZUKI-MIYAURI reaction



A solution of terminal alkene (1.5 eq.) in freshly degassed THF (1 M) was cooled to 0 °C and 9-BBN (1.5 eq., 0.5 M in THF) was added dropwise. The mixture was stirred overnight while being allowed to slowly warm to room temperature. Subsequently, freshly degassed DMF (total 0.2 M), thioester vinylhalogenide (1.0 eq.), $PdCl_2$(dppf) (5 mol%), $AsPh_3$ (5 mol%) and Cs_2CO_3 (2.0 eq.) were added and the suspension was heated to 50 °C. After complete consumption of starting material (TLC), EtOAc was added, and the mixture was transferred to a separating funnel containing aqueous LiCl solution (10% wt). After separation and extraction of the aqueous phase with EtOAc (3x), the combined organics were washed with brine and dried over $MgSO_4$. After concentration *in vacuo* the crude product was purified *via* flash chromatography.

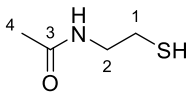
General Procedure 4: Deprotection



The silylether (1.0 eq.) was dissolved in HF-containing stock-solution (70% HF*pyridine/pyridine/THF (1:2:8)) at 0 °C. After warming to room temperature and complete consumption of starting material according to TLC, saturated aqueous $NaHCO_3$ solution was added dropwise until no more formation of CO_2 was observed. Subsequently, phases were separated and the aqueous one was extracted three times with EtOAc. The combined organics were washed with brine and dried over $MgSO_4$. After concentration *in vacuo*, the crude product was purified *via* semi-preparative HPLC.

Synthetic reactions

N-acetylcysteamine (15)



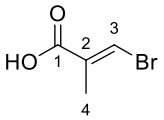
15

A solution of Cysteamine hydrochloride (30.0 g, 264 mmol, 1.0 eq) in H_2O (300 mL, 0.88 M) was cooled to 0 °C. NaOH (84.5 g, 2.11 mol, 8.0 eq) was added in small portions. After dropwise addition of acetic anhydride (68.0 mL, 719 mmol, 2.7 eq) the mixture was stirred for 1 h at room temperature. A pH of 7 was adjusted by adding concentrated HCl solution. The resulting phases were separated and the aqueous one was extracted three times with CH_2Cl_2. Subsequently, the combined organic phases were washed with brine, dried over $MgSO_4$ and filtrated. Removal of the solvent *in vacuo* yielded *N*-Acetylcysteamine (**15**, 26.3 g, 221 mmol, 84%) as colourless oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.92 (br, 1H, NH), 3.45-3.41 (m, 2H, 2-H), 2.67 (dt, J = 8.4, 6.4 Hz, 2H, 1-H), 2.01 (s, 3H, 4-H), 1.35 (t, J = 8.4 Hz, 1H, SH) ppm.

Analytical data are in accordance with those reported in the literature.[1]

(*E*)-3-bromo-2-methylacrylic acid (16)



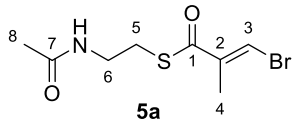
16

A solution of methacrylic acid (1.69 mL, 20.0 mmol, 1.00 eq.) in $CHCl_3$ (25.0 mL, 0.8 M) was heated to 45 °C. Bromine (1.04 mL, 20.4 mmol, 1.02 eq.) was added and the mixture was stirred for 1.5 h. After cooling down to room temperature, saturated aqueous $NaHCO_3$ solution was added and the resulting phases were separated. The organic phase was extracted three times with saturated aqueous $NaHCO_3$ solution and the combined aqueous phases were added to an aqueous KOH solution (25%, 150 mL). After stirring for three hours at room temperature, a pH < 3 was adjusted with concentrated HCl. Subsequently, the aqueous solution was extracted three times with Et_2O and the combined organics were dried over $MgSO_4$ and filtered. Removal of the solvent *in vacuo* yielded crude **16** which was used directly in the next step without further purification. Only a small amount was recrystallised from hexane for analytical purposes and obtained from this as white, needle-shaped crystals.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.71 (s, 1H, 3-H), 2.01 (s, 3H, 4-H) ppm.

Analytical data are in accordance with those reported in the literature.[2]

***S*-(2-acetamidoethyl) (*E*)-3-bromo-2-methylprop-2-enethioate (5a)**

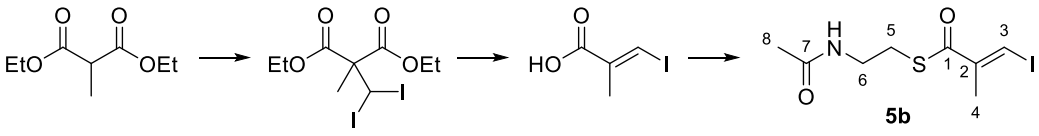


5a

The reaction was carried out as described in general procedure 1. A solution of brominated methacrylic acid **16** (3.30 g, 20.0 mmol, 1.0 eq.) and HSNAC **15** (3.57 g, 30.0 mmol, 1.5 eq.) in CH_2Cl_2 (100 mL, 0.2 M), DMAP (244 mg, 2.00 mmol, 0.1 eq.) and EDC*HCl (5.75 g, 30.0 mmol, 1.5 eq.) were used. Purification by flash chromatography (SiO_2, cyclohexane:EtOAc / 1:1 → EtOAc) yielded product **5a** (4.52 g, 17.0 mmol, 85% over two steps) as a white solid.

R_f: (cyclohexane:EtOAc / 1:1) = 0.24; (EtOAc) = 0.35. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 7.56 (q, J = 1.3 Hz, 1H, 3-H), 5.82 (br, 1H, NH), 3.48-3.44 (m, 2H, 6-H), 3.11 (t, J = 6.4 Hz, 2H, 5-H), 2.05 (d, J = 1.3 Hz, 3H, 4-H), 1.97 (s, 3H, 8-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 190.8 (q, C-1), 170.4 (q, C-7), 141.6 (q, C-2), 122.0 (t, C-3), 39.6 (s, C-6), 29.0 (s, C-5), 23.4 (p, C-8), 16.0 (p, C-4) ppm. **HRMS** [ESI$^+$]: *m/z* for $C_8H_{13}O_2N^{79}BrS$ $[M+H]^+$: calculated = 265.9844, found = 265.9838; *m/z* for $C_8H_{13}O_2N^{81}BrS$ $[M+H]^+$: calculated = 267.9824, found = 267.9814.

***S*-(2-acetamidoethyl) (*E*)-3-iodo-2-methylprop-2-enethioate (5b)**



5b

A suspension of NaH (1.44 g, 36 mmol, 1.2 eq.) in Et_2O (10 mL) was cooled to 0 °C. Subsequently, a solution of diethyl methylmalonate (5.11 mL, 30.0 mmol, 1.0 eq.) in Et_2O (50.0 mL, 0.6 M) was added dropwise. After heating on reflux for 1.5 h, iodoform (11.8 g, 30.0 mmol, 1.0 eq.) was added in one portion and heating was continued for 18 h. The reaction was quenched by addition of HCl (1 M) and H_2O. The resulting phases were separated and the aqueous one was extracted three times with Et_2O. Subsequently, the combined organic phases

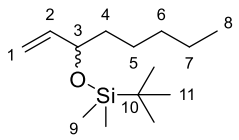
were washed with brine, dried over $MgSO_4$ and filtrated. The crude product was directly used in the next step without further purification.

Crude alkylation product was dissolved in EtOH (90 mL), before H_2O (32 mL) and KOH (8.40 g, 150 mmol, 5.0 eq.) were added. After heating on reflux for 4 h, the solvent was removed *in vacuo* and the residue was dissolved in aqueous K_2CO_3-solution (10%). A pH < 3 was adjusted with concentrated HCl, the aqueous solution was extracted three times with Et_2O and the combined organics were dried over $MgSO_4$ and filtered. Removal of the solvent *in vacuo* yielded crude carboxylic acid which was used in the next step without further purification.

The esterification was carried out as described in general procedure 1. A solution of crude iodinated methacrylic acid and HSNAC **15** (5.36 g, 45.0 mmol, 1.5 eq.) in CH_2Cl_2 (150 mL, 0.2 M), DMAP (364 mg, 3.00 mmol, 0.1 eq.) and EDC*HCl (8.54 g, 45.0 mmol, 1.5 eq.) were used. Purification by flash chromatography (SiO_2, cyclohexane:EtOAc / 1:1) yielded product **5b** (6.67 g, 21.3 mmol, 71% over three steps) as a yellowish solid.

R_f: (EtOAc) = 0.45. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 7.86 (q, *J* = 1.1 Hz, 1H, 3-H), 5.83 (br, 1H, NH), 3.48-3.44 (m, 2H, 6-H), 3.09 (t, *J* = 6.4 Hz, 2H, 5-H), 2.09 (d, *J* = 1.1 Hz, 3H, 4-H), 1.97 (s, 3H, 8-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 189.8 (q, C-1), 170.4 (q, C-7), 147.2 (q, C-2), 97.7 (t, C-3), 39.5 (s, C-6), 29.2 (s, C-5), 23.4 (p, C-8), 20.6 (p, C-4) ppm. **HRMS** [ESI$^+$]: *m/z* for $C_8H_{13}O_2NIS$ $[M+H]^+$: calculated = 313.9706, found = 313.9702.

***tert*-butyldimethyl(oct-1-en-3-yloxy)silane (6)**



6

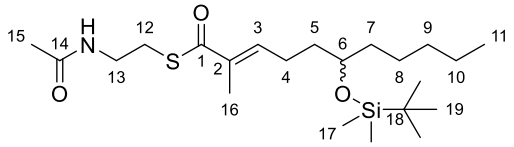
The reaction was carried out as described in general procedure 2. A solution of 1-octen-3-ol (200 mg, 1.56 mmol, 1.0 eq.) in DMF (1.56 mL, 1 M), TBSCl (351 mg, 2.34 mmol, 1.5 eq.) and Imidazole (265 mg, 3.90 mmol, 2.5 eq.) were used. Purification by filtration over a short plug of silica (SiO_2, pentane) yielded product **6** (378 mg, 1.56 mmol, quant.) as a colourless liquid.

R_f: (pentane) = 0.56. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 5.79 (ddd, *J* = 17.0, 10.3, 6.0 Hz, 1H, 2-H), 5.13 (ddd, *J* = 17.0, 1.9, 1.3 Hz, 1H, 1 × 1-H), 5.01 (ddd, *J* = 10.3, 1.9, 1.3 Hz, 1H,

1 × 1-H), 4.09-4.05 (m, 1H, 3-H), 1.51-1.40 (m, 2H, 4-H), 1.35-1.24 (m, 6H, 5-H, 6-H, 7-H), 0.89-0.86 (m, 12H, 11-H, 8-H), 0.05 (s, 3H, 9-H), 0.03 (s, 3H, 9-H) ppm.

Analytical data are in accordance with those reported in the literature.[3]

_S_-(2-acetamidoethyl) (_E_)-6-((_tert_-butyldimethylsilyl)oxy)-2-methylundec-2-enethioate (7)

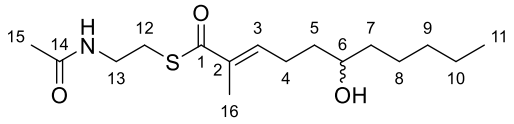


7

The reaction was carried out as described in general procedure 3. A solution of alkene **6** (50.0 mg, 206 µmol, 1.5 eq.) in THF (137 µL, 1 M), 9-BBN (412 µL, 206 µmol, 1.5 eq., 0.5 M in THF), DMF (685 µL, total 0.2 M), vinyl iodide **5b** (43.0 mg, 137 µmol, 1.0 eq.), $PdCl_2$(dppf) (5.0 mg, 7.00 µmol, 5 mol%), $AsPh_3$ (2.1 mg, 7.00 µmol, 5 mol%) and Cs_2CO_3 (89.0 mg, 275 µmol, 2.0 eq.) were used. Purification by flash chromatography (SiO_2, cyclohexane:EtOAc / 1:1) yielded product **7** (45.2 mg, 107 µmol, 78%) as a brown oil.

R_f : (cyclohexane:EtOAc / 1:1) = 0.45; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 6.78 (tq, J = 7.3, 1.3 Hz, 1H, 3-H), 5.85 (br, 1H, NH), 3.71-3.66 (m, 1H, 6-H), 3.47-3.43 (m, 2H, 13-H), 3.07 (t, J = 6.3 Hz, 2H, 12-H), 2.34-2.17 (m, 2H, 4-H), 1.96 (s, 3H, 15-H), 1.88 (s, 3H, 16-H), 1.60-1.53 (m, 2H, 5-H), 1.47-1.41 (m, 2H, 7-H), 1.32-1.26 (m, 6H, 8-H, 9-H, 10-H), 0.90-0.87 (m, 12H, 19-H, 11-H), 0.06 (s, 3H, 17-H), 0.05 (s, 3H, 17-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 194.2 (q, C-1), 170.4 (q, C-14), 142.5 (t, C-3), 135.9 (q, C-2), 71.8 (t, C-6), 40.0 (s, C-13), 37.1 (s, C-7), 35.6 (s, C-5), 32.2 (s, C-9), 28.5 (s, C-12), 26.0 (p, C-19), 25.1 (s, C-8), 24.8 (s, C-4), 23.4 (p, C-15), 22.8 (s, C-10), 18.3 (q, C-18), 14.2 (p, C-11), 12.6 (p, C-16), -4.2 (p, C-17), -4.3 (p, C-17) ppm. **HRMS** [ESI$^+$]: *m/z* for $C_{22}H_{44}NO_3SSi$ $[M+H]^+$: calculated = 430.2805, found = 430.2796.

_S_-(2-acetamidoethyl) (_E_)-6-hydroxy-2-methylundec-2-enethioate (17)

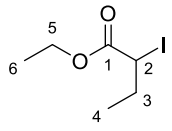


17

A solution of silylether **7** (20.0 mg, 46.5 µmol, 1.0 eq.) in MeOH (465 µL, 0.1 M) was treated with PPTS (70.0 mg, 279 µmol, 6.0 eq.). After stirred heating to 50 °C overnight, the reaction was quenched by the addition of water and Et_2O. The resulting phases were separated and the aqueous one was extracted three times with Et_2O. Subsequently, the combined organic phases were washed with brine, dried over $MgSO_4$ and filtrated. Removal of the solvent in vacuo and purifying *via* flash chromatography (SiO_2, EtOAc) yielded secondary alcohol **17** (7.3 mg, 24.2 µmol, 52%) as a colourless oil.

R_f : (EtOAc) = 0.29. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 6.78 (tq, *J* = 7.3, 1.2 Hz, 1H, 3-H), 5.92 (br, 1H, NH), 3.63-3.59 (m, 1H, 6-H), 3.46-3.42 (m, 2H, 13-H), 3.06 (t, *J* = 6.3 Hz, 2H, 12-H), 2.41-2.27 (m, 2H, 4-H), 1.96 (s, 3H, 15-H), 1.89 (s, 3H, 16-H), 1.70 (br, 1H, OH), 1.66-1.54 (m, 2H, 5-H), 1.46-1.41 (m, 3H, 7-H, 1 × 8-H), 1.33-1.24 (m, 5H, 1 × 8-H, 9-H, 10-H), 0.89 (t, *J* = 6.9 Hz, 3H, 11-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 194.2 (q, C-1), 170.4 (q, C-14), 141.8 (t, C-3), 136.2 (q, C-2), 71.5 (t, C-6), 40.0 (s, C-13), 37.8 (s, C-7), 36.0 (s, C-5), 32.0 (s, C-9), 28.5 (s, C-12), 25.4 (s, C-8), 25.3 (s, C-4), 23.4 (p, C-15), 22.8 (s, C-10), 14.2 (p, C-11), 12.6 (p, C-16) ppm. **HRMS** [ESI$^+$]: *m/z* for $C_{16}H_{30}NO_3S$ $[M+H]^+$: calculated = 316.1940, found = 316.1934.

ethyl 2-iodobutanoate (**18**)

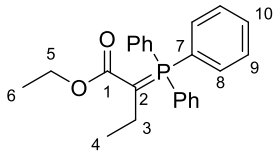


18

To a light protected, stirred suspension of sodium iodide (28.4 g, 190 mmol, 2.0 eq.) in acetone (63.2 mL, 1.5 M) was added ethyl 2-bromobutanoate (14.0 mL, 94.8 mmol, 1.0 eq.). After 30 minutes, excess Et_2O (200 mL) was added and the suspension was filtered. Washing the organic solution with saturated aqueous $Na_2S_2O_3$ solution and brine and removing the solvent *in vacuo* yielded **18** (21.2 g, 87.7 mmol, 93%) as a light sensitive, colourless liquid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.26-4.17 (m, 3H, 5-H, 2-H), 2.04-1.95 (m, 2H, 3-H), 1.28 (t, *J* = 7.1 Hz, 3H, 6-H), 0.97 (t, *J* = 7.3 Hz, 3H, 4-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 171.5 (q, C-1), 61.9 (s, C-5), 29.7 (s, C-3), 23.5 (t, C-2), 14.2 (p, C-4), 13.9 (p, C6) ppm. **EA**: calculated for $C_6H_{11}IO_2$: C = 29.77, H = 4.58; found: C = 30.01, H = 4.56.

ethyl 2-(triphenyl-λ^5-phosphaneylidene)butanoate (**19**)



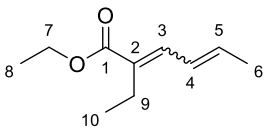
19

To a light protected, stirred solution of Iodide **18** (21.2 g, 87.7 mmol, 1.0 eq.) in toluene (58.0 mL, 1.5 M) was added PPh_3 (45.9 g, 175 mmol, 2.0 eq.). After heating to 65 °C overnight, the supernant was carefully removed and the residue was washed with toluene. Subsequently, CH_2Cl_2 and an aqueous K_2CO_3 solution (10%) were added and the emulsion was stirred for 40 minutes at room temperature. The resulting phases were separated and the aqueous one was extracted three times with CH_2Cl_2. Subsequently, the combined organic phases were washed with brine, dried over $MgSO_4$ and filtrated. Removal of the solvent *in vacuo* yielded crude **19** (31.2 g, 82.8 mmol, 95%) as viscous, yellow oil which was used directly in the next step without further purification.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.64-7.60 (m, 6H, 9-H), 7.55-7.52 (m, 3H, 10-H), 7.46-7.44 (m, 6H, 8-H), 4.05 (br, 0.5H, 5-H), 3.69 (br, 1.5H, 5-H), 1.96 (br, 2H, 3-H), 1.24 (br, 1H, 1 × 6-H), 0.86 (t, *J* = 7.1 Hz, 3H, 4-H), 0.42 (br, 2H, 2 × 6-H) ppm.

Analytical data are in accordance with those reported in the literature.[4]

ethyl (2*E*,4*E*)-2-ethylhexa-2,4-dienoate (**20**)

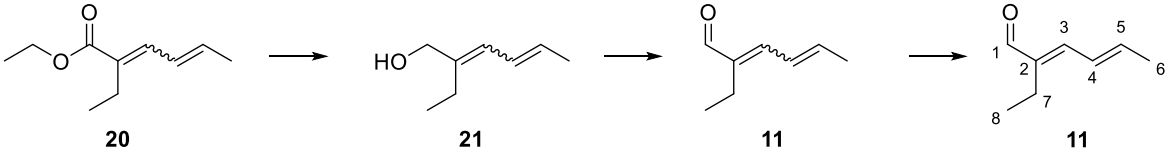


20

A stirred solution of phosphorous ylide **19** (30.6 g, 81.3 mmol, 1.5 eq.) and crotonaldehyde (4.47 mL, 54.2 mmol, 1.0 eq.) in toluene (162 mL, 0.5 M) was heated to 70 °C for 5 h. Afterwards it was allowed to cool to room temperature and stirred overnight. Removal of the solvent *in vacuo* and purification *via* flash chromatography (SiO_2, cyclohexane → cyclohexane:EtOAc / 39:1) yielded ethyl ester **20** (8.94 g, 53.1 mmol, 98%, *E*:*Z* = 10:1) as colourless liquid.

Major (*E*)-isomer: $\mathbf{R_f}$: (cyclohexane:EtOAc / 39:1) = 0.27. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 11.4 Hz, 1H, 3-H), 6.37 (ddq, *J* = 14.9, 11.4, 1.4 Hz, 1H, 4-H), 6.10 (dq, *J* = 14.9, 6.8 Hz, 1H, 5-H), 4.21 (q, *J* = 7.1 Hz, 2H, 7-H), 2.40 (q, *J* = 7.5 Hz, 2H, 9-H), 1.88 (dd, *J* = 6.8, 1.4 Hz, 3H, 6-H), 1.30 (t, *J* = 7.1 Hz, 3H, 10-H), 1.03 (t, *J* = 7.5 Hz, 3H, 8-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 168.5 (q, C-1), 138.2 (t, C-3), 138.0 (t, C-5), 131.5 (q, C-2), 127.2 (t, C-4), 60.5 (s, C-7), 20.4 (s, C-9), 19.1 (p, C-6), 14.5 (p, C-10), 14.4 (p, C-8) ppm. **HRMS** [ESI$^+$]: *m/z* for $C_{10}H_{17}O_2$ $[M+H]^+$: calculated = 169.1223, found = 169.1219.

(2*E*,4*E*)-2-ethylhexa-2,4-dienal (11)



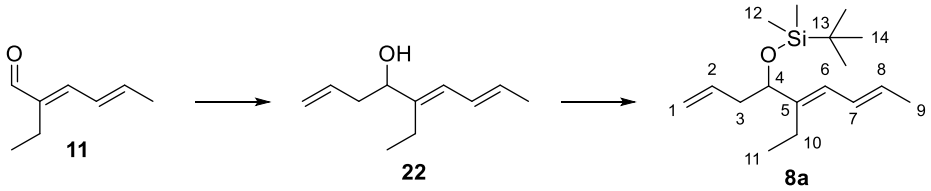
20 **21** **11** **11**

A stirred solution of ethyl ester **20** (1.00 g, 5.94 mmol, 1.0 eq.) in CH_2Cl_2 (30.0 mL, 0.2 M) was cooled to -78 °C. After dropwise addition of DIBAL-H (17.8 mL, 17.8 mmol, 3.0 eq., 1 M in hexane), the mixture was stirred for 30 minutes at -78 °C. Quenching with saturated aqueous NaK-tartrate solution was followed by stirring at room temperature for 2 h. The resulting phases were separated and the aqueous one was extracted three times with CH_2Cl_2. Subsequently, the combined organic phases were washed with brine, dried over $MgSO_4$ and filtrated. Removal of the solvent *in vacuo* yielded crude allylic alcohol **21** which was used directly in the next step without further purification.

The crude product was dissolved in CH_2Cl_2 (40.0 mL, 0.15 M) and DMP (2.77 g, 6.54 mmol, 1.1 eq.) was added at room temperature. After stirring for 40 minutes, saturated aqueous $NaHCO_3$ solution and Et_2O were added and stirring was continued for another 40 minutes. The resulting phases were separated and the aqueous one was extracted three times with Et_2O. Combined organic phases were washed four times with saturated aqueous $Na_2S_2O_3$ solution, once with brine, dried over $MgSO_4$ and filtrated. The solvent mixture was removed *in vacuo* and the crude aldehyde **11** was taken up again in Et_2O (40.0 mL, 0.15 M). After adding I_2 (4.52 g, 17.8 mmol, 3.0 eq.), the solution was heated to reflux overnight. Washing with saturated aqueous $Na_2S_2O_3$ solution and brine was followed by removing the solvent *in vacuo*. Purification *via* flash chromatography (SiO_2, pentane:Et_2O / 49:1) yielded *all-trans*-aldehyde **11** (575 mg, 4.63 mmol, 78% over three steps) as a colourless, slightly volatile liquid.

R_f : (pentane:Et_2O / 49:1) = 0.28. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 9.38 (s, 1H, 1-H), 6.75 (d, *J* = 11.2 Hz, 1H, 3-H), 6.55 (ddq, *J* = 14.9, 11.2, 1.6 Hz, 1H, 4-H), 6.26 (dq, *J* = 14.9, 6.8 Hz, 1H, 5-H), 2.35 (q, *J* = 7.5 Hz, 2H, 7-H), 1.94 (dd, *J* = 6.8, 1.6 Hz, 3H, 6-H), 1.00 (t, *J* = 7.5 Hz, 3H, 8-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 195.0 (t, C-1), 149.1 (t, C-3), 142.1 (q, C-2), 140.8 (t, C-5), 127.2 (t, C-4), 19.3 (p, C-6), 17.6 (s, C-7), 13.8 (p, C-8) ppm. **HRMS** [ESI^+]: *m/z* for $C_8H_{13}O$ $[M+H]^+$: calculated = 125.0960, found = 125.0957.

***tert*-butyl(((5*E*,7*E*)-5-ethylnona-1,5,7-trien-4-yl)oxy)dimethylsilane** (**8a**)



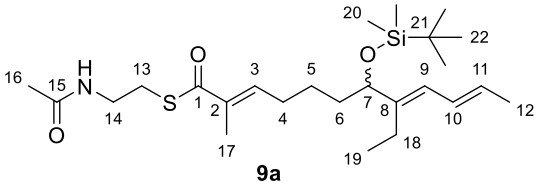
To a stirred suspension of magnesium chips (264 mg, 10.9 mmol, 3.0 eq.) in THF (15.0 mL) at 0 °C was added allyl bromide (625 µL, 7.24 mmol, 2.0 eq.). Once the addition was complete, the cooling bath was removed and the mixture was heated to reflux for 1 h. After cooling to room temperature, the supernant was dripped to a ice-cooled solution of aldehyde **11** (450 mg, 3.62 mmol, 1.0 eq.) in THF (20.0 mL, 0.1 M) and stirred at 0 °C for 3 h. Quenching with saturated aqueous NH_4Cl solution was followed by warming up to room temperature. The resulting phases were separated and the aqueous one was extracted three times with Et_2O. Subsequently, the combined organic phases were washed with brine, dried over $MgSO_4$ and filtrated. Removal of the solvent *in vacuo* yielded crude allylic alcohol **22** which was used directly in the next step without further purification.

The TBS-protection was carried out as described in general procedure 2. A solution of crude secondary alcohol **22** in DMF (3.60 mL, 1 M), TBSCl (818 mg, 5.43 mmol, 1.5 eq.) and Imidazole (616 mg, 9.05 mmol, 2.5 eq.) were used. Purification by filtration over a short plug of silica (SiO_2, pentane) yielded product **8a** (551 mg, 1.96 mmol, 54% over two steps) as a colourless liquid.

R_f : (pentane) = 0.49. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 6.25 (ddq, *J* = 15.0, 11.1, 1.5 Hz, 1H, 7-H), 5.92 (d, *J* = 11.1 Hz, 1H, 6-H), 5.77 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H, 2-H), 5.66 (dq, *J* = 15.0, 6.7 Hz, 1H, 8-H), 5.04-4.98 (m, 2H, 1-H), 4.04 (t, *J* = 6.3 Hz, 1H, 4-H), 2.27-2.22 (m, 2H, 3-H), 2.20 (dq, *J* = 14.0, 7.6 Hz, 1H, 1 × 10-H), 2.08 (dq, *J* = 14.0, 7.6 Hz, 1H, 1 × 10-H), 1.79 (dd, *J* = 6.7, 1.5 Hz, 3H, 9-H), 1.05 (t, *J* = 7.6 Hz, 3H, 11-H), 0.88 (s, 9H, 14-H), 0.02 (s,

3H, 12-H), -0.02 (3H, 12-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 143.2 (q, C-5), 136.0 (t, C-2), 128.9 (t, C-8), 127.5 (t, C-7), 124.9 (t, C-6), 116.4 (s, C-1), 77.0 (t, C-4), 42.1 (s, C-3), 26.0 (p, 3 × C-14), 20.6 (s, C-10), 18.6 (p, C-9), 18.4 (q, C-13), 14.9 (p, C-11), -4.4 (p, 1 × C-12), -4.8 (p, 1 × C-12) ppm. **EA**: calculated for $C_{17}H_{32}OSi$: C = 72.79, H = 11.50; found: C = 73.12, H = 11.09.

_S_-(2-acetamidoethyl) (2_E_,8_E_,10_E_)-7-((_tert_-butyldimethylsilyl)oxy)-8-ethyl-2-methyldodeca-2,8,10-trienethioate (9a)

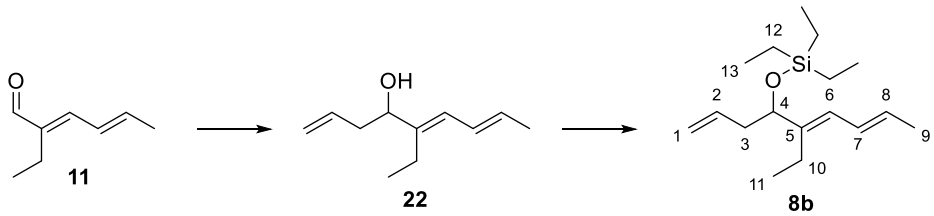


9a

The reaction was carried out as described in general procedure 3, except small changes in the used ratios. A solution of alkene **8a** (60.6 mg, 210 µmol, 1.5 eq.) in THF (210 µL, 1 M), 9-BBN (420 µL, 210 µmol, 1.5 eq., 0.5 M in THF), DMF (840 µL, total 0.2 M), vinyl bromide **5a** (38.3 mg, 140 µmol, 1.0 eq.), $PdCl_2$(dppf) (5.1 mg, 7.00 µmol, 5 mol%) and K_2CO_3 (38.7 mg, 280 µmol, 2.0 eq.) were used. Purification by flash chromatography (SiO_2, cyclohexane:EtOAc / 1:1) yielded product **9a** (17.7 mg, 37.8 µmol, 27%) as a brown oil.

R_f : (cyclohexane:EtOAc / 1:1) = 0.41; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 6.75 (tq, J = 7.3, 1.3 Hz, 1H, 3-H), 6.28-6.22 (m, 1H, 10-H), 5.92-5.82 (m, 2H, 9-H, NH), 5.66 (dq, J = 14.7, 6.9 Hz, 1H, 11-H), 4.02 (t, J = 5.6 Hz, 1H, 7-H), 3.47-3.43 (m, 2H, 14-H), 3.07 (t, J = 6.3 Hz, 2H, 13-H), 2.22-2.16 (m, 3H, 4-H, 1 × 18-H), 2.07-2.03 (m, 1H, 1 × 18-H), 1.97 (s, 3H, 16-H), 1.86 (d, J = 1.3 Hz, 3H, 17-H), 1.79 (dd, J = 6.9, 1.4 Hz, 3H, 12-H), 1.52-1.48 (m, 3H, 6-H, 1 × 5-H), 1.40-1.37 (m, 1H, 1 × 5-H), 1.04 (t, J = 7.6 Hz, 3H, 19-H), 0.89 (s, 9H, 22-H), 0.03 (s, 3H, 20-H), -0.02 (s, 3H, 20-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 194.2 (q, C-1), 170.4 (q, C-15), 143.2 (q, C-8), 142.3 (t, C-3), 136.0 (q, C-2), 129.0 (t, C-11), 127.5 (t, C-10), 125.0 (t, C-9), 76.8 (t, C-7), 40.0 (s, C-14), 36.8 (s, C-6), 29.0 (s, C-4), 28.6 (s, C-13), 26.0 (p, 3 × C-22), 24.7 (s, C-5), 23.4 (p, C-16), 20.6 (s, C-18), 18.6 (p, C-12), 18.4 (q, C-21), 15.0 (p, C-19), 12.6 (p, C-17), -4.4 (p, C-20), -4.9 (p, C-20) ppm. **HRMS** [ESI$^+$]: *m/z* for $C_{25}H_{45}NNaO_3SSi$ $[M+Na]^+$: calculated = 490.2781, found = 490.2775.

triethyl(((5*E*,7*E*)-5-ethylnona-1,5,7-trien-4-yl)oxy)silane (8b)

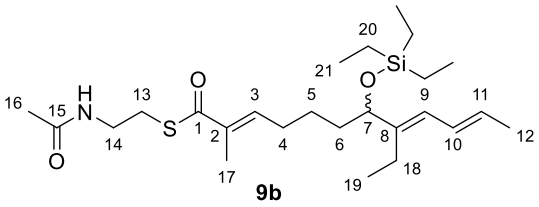


To a stirred suspension of magnesium chips (117 mg, 4.83 mmol, 3.0 eq.) in THF (6.50 mL) at 0 °C was added allyl bromide (278 µL, 3.22 mmol, 2.0 eq.). Once the addition was complete, the cooling bath was removed and the mixture was heated to reflux for 1 h. After cooling to room temperature, the supernant was dripped to a ice-cooled solution of aldehyde **11** (200 mg, 1.61 mmol, 1.0 eq.) in THF (10.0 mL, 0.1 M) and stirred at 0 °C for 3 h. Quenching with saturated aqueous NH_4Cl solution was followed by warming up to room temperature. The resulting phases were separated and the aqueous one was extracted three times with Et_2O. Subsequently, the combined organic phases were washed with brine, dried over $MgSO_4$ and filtrated. Removal of the solvent *in vacuo* yielded crude allylic alcohol **22** which was used directly in the next step without further purification.

The TES-protection was carried out as described in general procedure 2. A solution of crude secondary alcohol **22** in DMF (1.60 mL, 1 M), TESCl (406 µL, 2.42 mmol, 1.5 eq.) and Imidazole (274 mg, 4.02 mmol, 2.5 eq.) were used. Purification by filtration over a short plug of silica (SiO_2, pentane) yielded product **8b** (260 mg, 927 µmol, 58% over two steps) as a colourless liquid.

R_f : (pentane) = 0.33. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 6.28-6.22 (m, 1H, 7-H), 5.92 (d, J = 11.0 Hz, 1H, 6-H), 5.76 (ddt, J = 17.2, 10.1, 7.1 Hz, 1H, 2-H), 5.66 (dq, J = 13.5, 6.7 Hz, 1H, 8-H), 5.04-4.98 (m, 2H, 1-H), 4.05 (t, J = 6.3 Hz, 1H, 4-H), 2.29-2.25 (m, 2H, 3-H), 2.20 (dq, J = 14.6, 7.6 Hz, 1H, 1 × 10-H), 2.10 (dq, J = 14.6, 7.6 Hz, 1H, 1 × 10-H), 1.78 (dd, J = 6.7, 1.5 Hz, 3H, 9-H), 1.05 (t, J = 7.6 Hz, 3H, 11-H), 0.93 (t, J = 7.9 Hz, 9H, 13-H), 0.57 (q, J = 7.9 Hz, 6H, 12-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 143.2 (q, C-5), 135.9 (t, C-2), 128.9 (t, C-8), 127.5 (t, C-7), 124.9 (t, C-6), 116.4 (s, C-1), 76.9 (t, C-4), 42.1 (s, C-3), 20.6 (s, C-10), 18.6 (p, C-9), 14.9 (p, C-11), 7.1 (p, 3 × C-13), 5.0 (s, 3 × C-12) ppm. **EA**: calculated for $C_{17}H_{32}OSi$: C = 72.79, H = 11.50; found: C = 72.52, H = 11.63.

***S*-(2-acetamidoethyl) (2*E*,8*E*,10*E*)-8-ethyl-2-methyl-7-((triethylsilyl)oxy)dodeca-2,8,10-trienethioate (9b)**

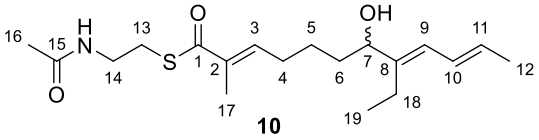


9b

The reaction was carried out as described in general procedure 3. A solution of alkene **8b** (40.0 mg, 143 µmol, 1.5 eq.) in THF (95.0 µL, 1 M), 9-BBN (286 µL, 143 µmol, 1.5 eq., 0.5 M in THF), DMF (500 µL, total 0.2 M), vinyl iodide **5b** (29.8 mg, 95.0 µmol, 1.0 eq.), $PdCl_2$(dppf) (3.5 mg, 4.75 µmol, 5 mol%), $AsPh_3$ (1.5 mg, 4.75 µmol, 5 mol%) and Cs_2CO_3 (61.9 mg, 190 µmol, 2.0 eq.) were used. Purification by flash chromatography (SiO_2, cyclohexane:EtOAc / 1:1) yielded product **9b** (38.6 mg, 82.7 µmol, 87%) as a yellowish oil.

R_f : (cyclohexane:EtOAc / 1:1) = 0.29; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 6.75 (tq, *J* = 7.2, 1.3 Hz, 1H, 3-H), 6.28-6.22 (m, 1H, 10-H), 5.91 (d, *J* = 11.1 Hz, 1H, 9-H), 5.87 (br, 1 H, NH), 5.66 (dq, *J* = 13.5, 6.6 Hz, 1H, 11-H), 4.03 (t, *J* = 5.8 Hz, 1H, 7-H), 3.47-3.43 (m, 2H, 14-H), 3.06 (t, *J* = 6.3 Hz, 2H, 13-H), 2.22-2.16 (m, 3H, 4-H, 1 × 18-H), 2.11-2.04 (m, 1H, 1 × 18-H), 1.96 (s, 3H, 16-H), 1.86 (d, *J* = 1.3 Hz, 3H, 17-H), 1.79 (dd, *J* = 6.6, 1.4 Hz, 3H, 12-H), 1.55-1.49 (m, 3H, 6-H, 1 × 5-H), 1.45-1.37 (m, 1H, 1 × 5-H), 1.04 (t, *J* = 7.6 Hz, 3H, 19-H), 0.93 (t, *J* = 7.9 Hz, 9H, 21-H), 0.57 (q, 6H, 20-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 194.2 (q, C-1), 170.4 (q, C-15), 143.2 (q, C-8), 142.2 (t, C-3), 136.0 (q, C-2), 129.0 (t, C-11), 127.5 (t, C-10), 125.0 (t, C-9), 76.8 (t, C-7), 40.0 (s, C-14), 36.8 (s, C-6), 29.0 (s, C-4), 28.5 (s, C-13), 24.7 (s, C-5), 23.4 (p, C-16), 20.5 (s, C-18), 18.6 (p, C-12), 15.0 (p, C-19), 12.6 (p, C-17), 7.1 (p, C-21), 5.0 (s, C-20) ppm. **HRMS** [ESI$^+$]: *m/z* for $C_{25}H_{45}NNaO_3SSi$ $[M+Na]^+$: calculated = 490.2781, found = 490.2774.

***S*-(2-acetamidoethyl) (2*E*,8*E*,10*E*)-8-ethyl-7-hydroxy-2-methyldodeca-2,8,10-trienethioate (10)**

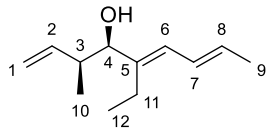


10

The reaction was carried out as described in general procedure 4. A solution of silylether **9b** (15.0 mg, 32.1 µmol, 1.0 eq.) in THF (80 µL), HF*pyridine (10 µL, ~70% HF) and pyridine (20 µL) were used and the reaction ran overnight. Purification by semi-preparative HPLC yielded product **10** (9.1 mg, 26.0 µmol, 81%) as a colourless oil.

R_f : (cyclohexane:EtOAc / 1:1) = 0.27; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 6.75 (tq, *J* = 7.3, 1.3 Hz, 1H, 3-H), 6.29-6.24 (m, 1H, 10-H), 5.97 (d, *J* = 11.0 Hz, 1H, 9-H), 5.87 (br, 1 H, NH), 5.72 (dq, *J* = 13.7, 6.8 Hz, 1H, 11-H), 4.08 (t, *J* = 5.8 Hz, 1H, 7-H), 3.47-3.43 (m, 2H, 14-H), 3.06 (t, *J* = 6.3 Hz, 2H, 13-H), 2.26-2.19 (m, 3H, 4-H, 1 × 18-H), 2.16-2.09 (m, 1H, 1 × 18-H), 1.96 (s, 3H, 16-H), 1.87 (d, *J* = 1.3 Hz, 3H, 17-H), 1.80 (dd, *J* = 6.8, 1.5 Hz, 3H, 12-H), 1.60-1.55 (m, 3H, 6-H, 1 × 5-H), 1.47-1.45 (m, 1H, 1 × 5-H), 1.06 (t, *J* = 7.6 Hz, 3H, 19-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 194.2 (q, C-1), 170.4 (q, C-15), 143.3 (q, C-8), 141.9 (t, C-3), 136.1 (q, C-2), 130.2 (t, C-11), 127.1 (t, C-10), 125.4 (t, C-9), 76.5 (t, C-7), 40.0 (s, C-14), 35.3 (s, C-6), 28.8 (s, C-4), 28.6 (s, C-13), 25.0 (s, C-5), 23.4 (p, C-16), 20.8 (s, C-18), 18.6 (p, C-12), 15.1 (p, C-19), 12.6 (p, C-17) ppm. **HRMS** [ESI$^+$]: *m/z* for $C_{19}H_{31}NNaO_3S$ $[M+Na]^+$: calculated = 376.1916, found = 376.1912.

(3*S*,4*R*,5*E*,7*E*)-5-ethyl-3-methylnona-1,5,7-trien-4-ol (**12**)



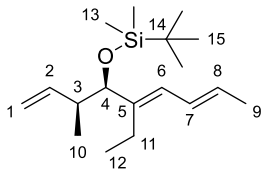
12

A stirred solution of KO*t*Bu (651 mg, 5.80 mmol, 1.8 eq.) in THF (5.80 mL, 1 M) was cooled to -78 °C and precooled *cis*-butene (1.20 mL, 12.9 mmol, 4.0 eq.) was added. Subsequently, *n*-BuLi (2.32 mL, 5.80 mmol, 1.8 eq., 2.5 M in hexane) was added dropwise. The resulting yellow solution was warmed to -50 °C and stirred for 30 minutes. After re-cooling to -78 °C, a solution of (+)-Ipc_2BOMe (2.14 g, 6.76 mmol, 2.1 eq.) in Et_2O (6.80 mL, 1 M) was added slowly, which resulted in loss of yellow colour. Stirring for 30 minutes was followed by addition of BF_3×Et_2O (1.02 mL, 8.05 mmol, 2.5 eq.), ten minutes of stirring and addition of a solution of aldehyde **11** (400 mg, 3.22 mmol, 1.0 eq.) in Et_2O (4.60 mL, 0.7 M). After stirring for 6 h at -78 °C, a premixed solution of NaOH (10.0 mL, 3 M) and H_2O_2 (10.0 mL, 30%) was added and the solution was stirred overnight at room temperature. The resulting phases were separated and the aqueous one was extracted three times with Et_2O. Combined organic phases were washed with brine, dried over $MgSO_4$ and filtrated. Removal of the solvent *in vacuo* and

purification *via* flash chromatography (SiO_2, pentane:Et_2O / 29:1) yielded secondary alcohol **12** (418 mg, 2.31 mmol, 71%, 86% *e.e.*) as yellowish oil.

$\mathbf{R_f}$: (*n*-Pentan:Et_2O / 29:1) = 0.32. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 6.31-6.25 (m, 1H, 7-H), 6.00 (d, *J* = 11.0 Hz, 1H, 6-H), 5.82 (ddd, *J* = 17.3, 10.5, 6.8 Hz, 1H, 2-H), 5.70 (dq, *J* = 14.9, 6.7 Hz, 1H, 8-H), 5.09-5.04 (m, 2H, 1-H), 3.99 (d, *J* = 5.5 Hz, 1H, 4-H), 2.47-2.41 (m, 1H, 3-H), 2.23 (dq, *J* = 15.0, 7.6 Hz, 1H, 1 × 11-H), 2.06 (dq, *J* = 15.0, 7.6 Hz, 1H, 1 × 11-H), 1.79 (dd, *J* = 6.7, 1.4 Hz, 3H, 9-H), 1.07 (t, *J* = 7.6 Hz, 3H, 12-H_3), 1.00 (d, *J* = 6.8 Hz, 3H, 10-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 141.8 (q, C-5), 141.6 (t, C-2), 129.7 (t, C-8), 127.2 (t, C-7), 125.5 (t, C-6), 114.8 (s, C-1), 78.7 (t, C-4), 41.4 (t, C-3), 21.7 (s, C-11), 18.6 (p, C-9), 14.7 (p, C-12), 13.7 (p, C-10) ppm. **EA**: calculated for $C_{12}H_{20}O$: C = 79.94, H = 11.18; found: C = 79.38, H = 11.32. $[\boldsymbol{\alpha}]_{\mathbf{22}}^{\mathbf{D}}$: + 4.8 ° (c = 1.0 in CH_2Cl_2).

***tert*-butyl(((3*S*,4*R*,5*E*,7*E*)-5-ethyl-3-methylnona-1,5,7-trien-4-yl)oxy)dimethylsilane** (**13a**)

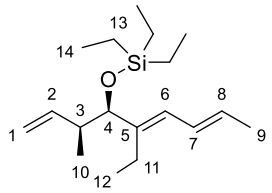


13a

The TBS-protection was carried out as described in general procedure 2. A solution of secondary alcohol **12** (150 mg, 832 µmol, 1.0 eq.) in DMF (830 µL, 1 M), TBSCl (187 mg, 1.24 mmol, 1.5 eq.) and Imidazole (142 mg, 2.08 mmol, 2.5 eq.) were used. Purification by filtration over a short plug of silica (SiO_2, pentane) yielded product **13a** (222 mg, 754 µmol, 91%) as a colourless liquid.

$\mathbf{R_f}$: (pentane) = 0.79. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 6.28-6.23 (m, 1H, 7-H), 5.90 (d, *J* = 11.1 Hz, 1H, 6-H), 5.77 (ddd, *J* = 17.4, 10.3, 7.3 Hz, 1H, 2-H), 5.64 (dq, *J* = 13.6, 6.7 Hz, 1H, 8-H), 4.99-4.92 (m, 2H, 1-H), 3.85 (d, *J* = 5.5 Hz, 1H, 4-H), 2.32-2.28 (m, 1H, 3-H), 2.20 (dq, *J* = 15.2, 7.6 Hz, 1H, 1 × 11-H), 2.01 (dq, *J* = 15.1, 7.6 Hz, 1H, 1 × 11-H), 1.78 (dd, *J* = 6.7, 1.4 Hz, 3H, 9-H), 1.04 (t, *J* = 7.6 Hz, 3H, 12-H), 0.94 (d, *J* = 6.7 Hz, 3H, 10-H), 0.90 (s, 9H, 15-H), 0.01 (s, 3H, 13-H), -0.05 (s, 3H, 13-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 142.7 (t, C-2), 141.9 (q, C-5), 128.6 (t, C-8), 127.5 (t, C-7), 126.0 (t, C-6), 113.6 (s, C-1), 80.3 (t, C-4), 42.4 (t, C-3), 26.1 (p, C-15), 21.3 (s, C-11), 18.6 (p, C-9), 18.4 (q, C-14), 14.6 (p, C-12), 14.4 (p, C-10), -4.2 (p, C-13), -4.9 (p, C-13) ppm. **EA**: calculated for $C_{18}H_{34}OSi$: C = 73.40, H = 11.64; found.: C = 73.51, H = 11.70. $[\boldsymbol{\alpha}]_{\mathbf{22}}^{\mathbf{D}}$: + 12.4 ° (c = 1.0 in CH_2Cl_2).

triethyl(((3*S*,4*R*,5*E*,7*E*)-5-ethyl-3-methylnona-1,5,7-trien-4-yl)oxy)silane (**13b**)

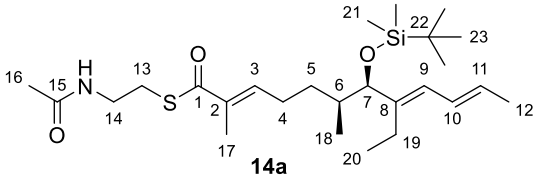


13b

The TES-protection was carried out as described in general procedure 2. A solution of secondary alcohol **12** (80.0 mg, 443 µmol, 1.0 eq.) in DMF (440 µL, 1 M), TESCl (112 µL, 666 µmol, 1.5 eq.) and Imidazole (75.5 mg, 1.11 mmol, 2.5 eq.) were used. Purification by filtration over a short plug of silica (SiO_2, pentane) yielded product **13b** (110 mg, 373 µmol, 84%) as a colourless liquid.

$\mathbf{R_f}$: (pentane) = 0.53. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 6.28-6.23 (m, 1H, 7-H), 5.90 (d, *J* = 11.1 Hz, 1H, 6-H), 5.77 (ddd, *J* = 17.5, 10.4, 7.3 Hz, 1H, 2-H), 5.65 (dq, *J* = 13.7, 6.8 Hz, 1H, 8-H), 4.99-4.93 (m, 2H, 1-H), 3.88 (d, *J* = 5.5 Hz, 1H, 4-H), 2.32-2.28 (m, 1H, 3-H), 2.19 (dq, *J* = 15.0, 7.6 Hz, 1H, 1 × 11-H), 2.04 (dq, *J* = 15.0, 7.6 Hz, 1H, 1 × 11-H), 1.79 (dd, *J* = 6.8, 1.5 Hz, 3H, 9-H), 1.04 (t, *J* = 7.6 Hz, 3H, 12-H), 0.95-0.92 (m, 12H, 10-H, 14-H), 0.56 (q, *J* = 7.9 Hz, 6H, 13-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 142.6 (t, C-2), 142.1 (q, C-5), 128.7 (t, C-8), 127.6 (t, C-7), 125.9 (t, C-6), 113.6 (s, C-1), 80.6 (t, C-4), 42.4 (t, C-3), 21.2 (s, C-11), 18.6 (p, C-9), 14.62 (p, C-12), 14.57 (p, C-10), 7.1 (p, C-14), 5.0 (p, C-13) ppm. **EA**: calculated for $C_{18}H_{34}OSi$: C = 73.40, H = 11.64; found: C = 73.56, H = 11.55. $[\boldsymbol{\alpha}]_{\mathbf{22}}^{\mathbf{D}}$: + 12.5 ° (c = 1.0 in CH_2Cl_2).

***S*-(2-acetamidoethyl) (2*E*,6*S*,7*R*,8*E*,10*E*)-7-((*tert*-butyldimethylsilyl)oxy)-8-ethyl-2,6-dimethyldodeca-2,8,10-trienethioate** (**14a**)



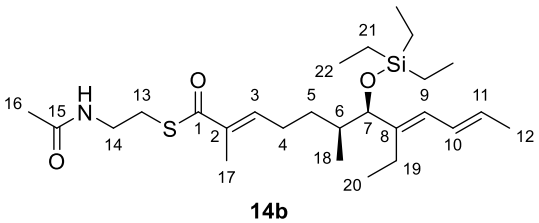
14a

The reaction was carried out as described in general procedure 3 with changes to the equivalents used. A solution of alkene **13a** (42.5 mg, 144 µmol, 1.0 eq.) in THF (145 µL, 1 M), 9-BBN

(288 µL, 144 µmol, 1.0 eq., 0.5 M in THF), DMF (720 µL, total 0.2 M), vinyl bromide **5a** (57.5 mg, 216 µmol, 1.5 eq.), $PdCl_2$(dppf) (5.3 mg, 7.20 µmol, 5 mol%) and K_2CO_3 (39.8 mg, 288 µmol, 2.0 eq.) were used. Purification by flash chromatography (SiO_2, cyclohexane:EtOAc / 1:1) yielded product **14a** (20.8 mg, 43.2 µmol, 30%) as a yellowish oil.

$\mathbf{R_f}$: (cyclohexane:EtOAc / 1:1) = 0.31; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 6.73 (t, *J* = 7.3 Hz, 1H, 3-H), 6.28-6.22 (m, 1H, 10-H), 5.91 (br, 1H, NH), 5.88 (d, *J* = 11.1 Hz, 1H, 9-H), 5.64 (dq, *J* = 13.6, 6.7 Hz, 1H, 11-H), 3.78 (d, *J* = 5.4 Hz, 1H, 7-H), 3.46-3.42 (m, 2H, 14-H), 3.06 (t, *J* = 6.4 Hz, 2H, 13-H), 2.29-2.23 (m, 1H, 1 × 4-H), 2.20-2.14 (m, 2H, 1 × 4-H, 1 × 19-H), 2.00-1.96 (m, 4H, 16-H, 1 × 19-H), 1.86 (s, 3H, 17-H), 1.79 (dd, *J* = 6.7, 1.2 Hz, 3H, 12-H), 1.57-1.55 (m, 1H, 6-H), 1.51-1.48 (m, 1H, 1 × 5-H), 1.23 -1.20 (m, 1H, 1 × 5-H), 1.03 (t, *J* = 7.6 Hz, 3H, 20-H), 0.90 (s, 9H, 23-H), 0.85 (d, *J* = 6.6 Hz, 3H, 18-H), 0.02 (s, 3H, 21-H), -0.06 (s, 3H, 21-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 194.2 (q, C-1), 170.4 (q, C-15), 142.4 (t, C-3), 141.8 (q, C-8), 135.8 (q, C-2), 128.8 (t, C-11), 127.4 (t, C-10), 126.3 (t, C-9), 80.3 (t, C-7), 40.0 (s, C-14), 37.1 (t, C-6), 32.7 (s, C-5), 28.5 (s, C-13), 26.9 (s, C-4), 26.1 (p, 3 × C-23), 23.4 (p, C-16), 21.1 (s, C-19), 18.6 (p, C-12), 18.4 (q, C-22), 14.8 (p, C-20), 14.3 (p, C-18), 12.6 (p, C-17), -4.2 (p, C-21), -4.9 (p, C-21) ppm. **HRMS** [ESI$^+$]: *m/z* for $C_{26}H_{47}NNaO_3SSi$ $[M+Na]^+$: calculated = 504.2938, found = 504.2928. $[\boldsymbol{\alpha}]_{\mathbf{22}}^{\mathbf{D}}$: + 3.5 ° (c = 1.0 in CH_2Cl_2).

_S_-(2-acetamidoethyl) (2_E_,6_S_,7_R_,8_E_,10_E_)-8-ethyl-2,6-dimethyl-7-((triethylsilyl)oxy)dodeca-2,8,10-trienethioate (14b)



14b

a.)

The reaction was carried out as described in general procedure 3 with changes to the equivalents used. A solution of alkene **13b** (40.0 mg, 136 µmol, 1.0 eq.) in THF (135 µL, 1 M), 9-BBN (272 µL, 136 µmol, 1.0 eq., 0.5 M in THF), DMF (680 µL, total 0.2 M), vinyl bromide **5a** (54.2 mg, 204 µmol, 1.5 eq.), $PdCl_2$(dppf) (5.0 mg, 6.28 µmol, 5 mol%) and K_2CO_3 (37.5 mg,

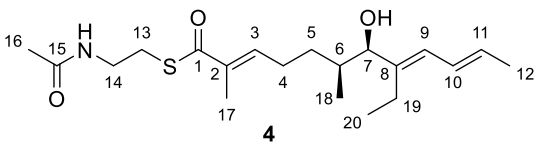
272 µmol, 2.0 eq.) were used. Purification by flash chromatography (SiO_2, cyclohexane:EtOAc / 1:1) yielded product **14b** (33.4 mg, 69.4 µmol, 51%) as a yellowish oil.

b.)

The reaction was carried out as described in general procedure 3. A solution of alkene **13b** (40.0 mg, 136 µmol, 1.5 eq.) in THF (140 µL, 1 M), 9-BBN (272 µL, 136 µmol, 1.5 eq., 0.5 M in THF), DMF (450 µL, total 0.2 M), vinyl iodide **5b** (28.3 mg, 90.5 µmol, 1.0 eq.), $PdCl_2$(dppf) (3.3 mg, 4.50 µmol, 5 mol%), $AsPh_3$ (1.4 mg, 4.50 µmol, 5 mol%) and Cs_2CO_3 (58.9 mg, 181 µmol, 2.0 eq.) were used. Purification by flash chromatography (SiO_2, cyclohexane:EtOAc / 1:1) yielded product **14b** (32.4 mg, 67.2 µmol, 74%) as a yellowish oil.

$\mathbf{R_f}$: (cyclohexane:EtOAc / 1:1) = 0.31. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 6.75 (t, J = 7.3, 1.3 Hz, 1H, 3-H), 6.29-6.23 (m, 1H, 10-H), 5.88 (d, J = 11.1 Hz, 1H, 9-H), 5.86 (br, 1 H, NH), 5.65 (dq, J = 13.5, 6.6 Hz, 1H, 11-H), 3.80 (d, J = 5.7 Hz, 1H, 7-H), 3.47-3.43 (m, 2H, 14-H), 3.06 (t, J = 6.3 Hz, 2H, 13-H), 2.29-2.23 (m, 1H, 1 × 4-H), 2.19-2.13 (m, 2H, 1 × 4-H, 1 × 19-H), 2.08-2.03 (m, 1H, 1 × 19-H), 1.96 (s, 3H, 16-H), 1.87 (s, 3H, 17-H), 1.79 (dd, J = 6.6, 1.4 Hz, 3H, 12-H), 1.54-1.46 (m, 2H, 6-H, 1 × 5-H), 1.24-1.17 (m, 1H, 1 × 5-H), 1.03 (t, J = 7.6 Hz, 3H, 20-H), 0.93 (t, J = 7.9 Hz, 9H, 22-H), 0.87 (d, J = 6.6 Hz, 3H, 18-H), 0.57 (q, J = 7.9 Hz, 6H, 21-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 194.2 (q, C-1), 170.4 (q, C-15), 142.4 (t, C-3), 142.0 (q, C-8), 135.8 (q, C-2), 128.9 (t, C-11), 127.4 (t, C-10), 126.2 (t, C-9), 80.7 (t, C-7), 40.0 (s, C-14), 37.2 (t, C-6), 32.6 (s, C-5), 28.5 (s, C-13), 26.9 (s, C-4), 23.4 (p, C-16), 20.9 (s, C-19), 18.6 (p, C-12), 14.8 (p, C-20), 14.5 (p, C-18), 12.6 (p, C-17), 7.1 (p, 3 × C-22), 5.1 (s, 3 × C-21) ppm. **HRMS** [ESI$^+$]: *m/z* for $C_{26}H_{47}NNaO_3SSi$ $[M+Na]^+$: calculated = 504.2938, found = 504.2929. $[\boldsymbol{\alpha}]_{\mathbf{22}}^{\mathbf{D}}$: + 5.4 ° (c = 1.0 in CH_2Cl_2).

***S*-(2-acetamidoethyl) (2*E*,6*S*,7*R*,8*E*,10*E*)-8-ethyl-7-hydroxy-2,6-dimethyldodeca-2,8,10-trienethioate** (**4**)



4

The reaction was carried out as described in general procedure 4. A solution of silylether **14b** (10.0 mg, 20.8 µmol, 1.0 eq.) in THF (80 µL), HF*pyridine (10 µL, ~70% HF) and pyridine (20 µL) were used and the reaction ran overnight. Purification by semi-preparative HPLC yielded product **4** (6.2 mg, 16.8 µmol, 81%) as a colourless oil.

$\mathbf{R_f}$: (cyclohexane:EtOAc / 1:1) = 0.19. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 6.75 (tq, J = 7.3, 1.3 Hz, 1H, 3-H), 6.31-6.26 (m, 1H, 10-H), 5.97 (d, J = 11.0 Hz, 1H, 9-H), 5.87 (br, 1 H, NH), 5.71 (dq, J = 13.6, 6.7 Hz, 1H, 11-H), 3.90 (d, J = 5.8 Hz, 1H, 7-H), 3.46-3.43 (m, 2H, 14-H), 3.06 (t, J = 6.4 Hz, 2H, 13-H), 2.31-2.25 (m, 1H, 1 × 4-H), 2.22-2.15 (m, 2H, 1 × 4-H, 1 × 19-H), 2.09-2.04 (m, 1H, 1 × 19-H), 1.96 (s, 3H, 16-H), 1.87 (s, 3H, 17-H), 1.80 (dd, J = 6.7, 1.3 Hz, 3H, 12-H), 1.70-1.66 (m, 1H, 6-H), 1.58-1.51 (m, 1H, 1 × 5-H), 1.34-1.27 (m, 1H, 1 × 5-H), 1.06 (t, J = 7.6 Hz, 3H, 20-H), 0.93 (d, J = 6.7 Hz, 3H, 18-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 194.1 (q, C-1), 170.4 (q, C-15), 142.4 (q, C-8), 142.2 (t, C-3), 135.9 (q, C-2), 129.9 (t, C-11), 127.1 (t, C-10), 125.7 (t, C-9), 79.6 (t, C-7), 40.0 (s, C-14), 36.2 (t, C-6), 32.6 (s, C-5), 28.5 (s, C-13), 26.7 (s, C-4), 23.4 (p, C-16), 21.4 (s, C-19), 18.6 (p, C-12), 14.9 (p, C-20), 14.2 (p, C-18), 12.6 (p, C-17) ppm. **HRMS** [ESI$^+$]: *m/z* for $C_{20}H_{33}NNaO_3S$ $[M+Na]^+$: calculated = 390.2073, found = 390.2064. $[\boldsymbol{\alpha}]_{\mathbf{22}}^{\mathbf{D}}$: − 11.4 ° (c = 0.7 in CH_2Cl_2).

References Supporting Information

[1] Li Y.; Zhang W.; Zhang H.; Tian W.; Wu L.; Wang S.; Zheng M.; Zhang J.; Sun Ch.; Deng Z.; Sun Y.; Qu X.; Zhou J., *Angew. Chem. Int.Ed.* **2018**, *57*, 5823–5827; *Angew. Chem.* **2018**, *130*, 5925–5929. https://doi.org/10.1002/ange.201802805.

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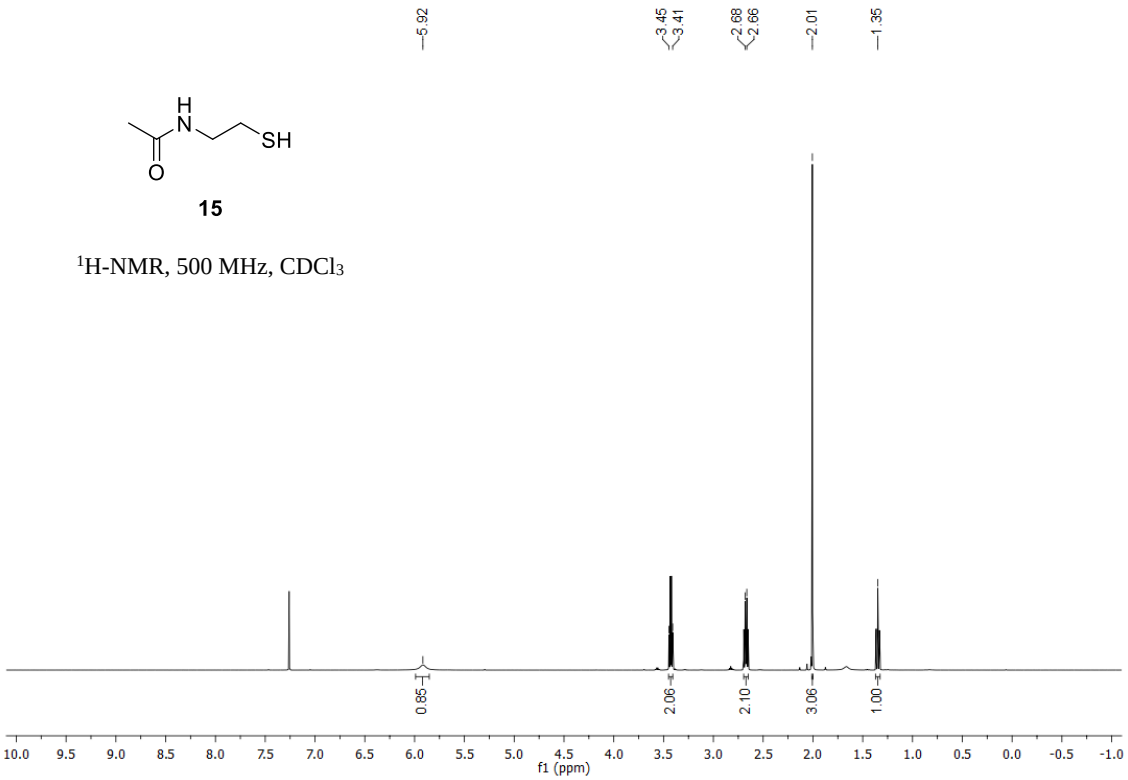
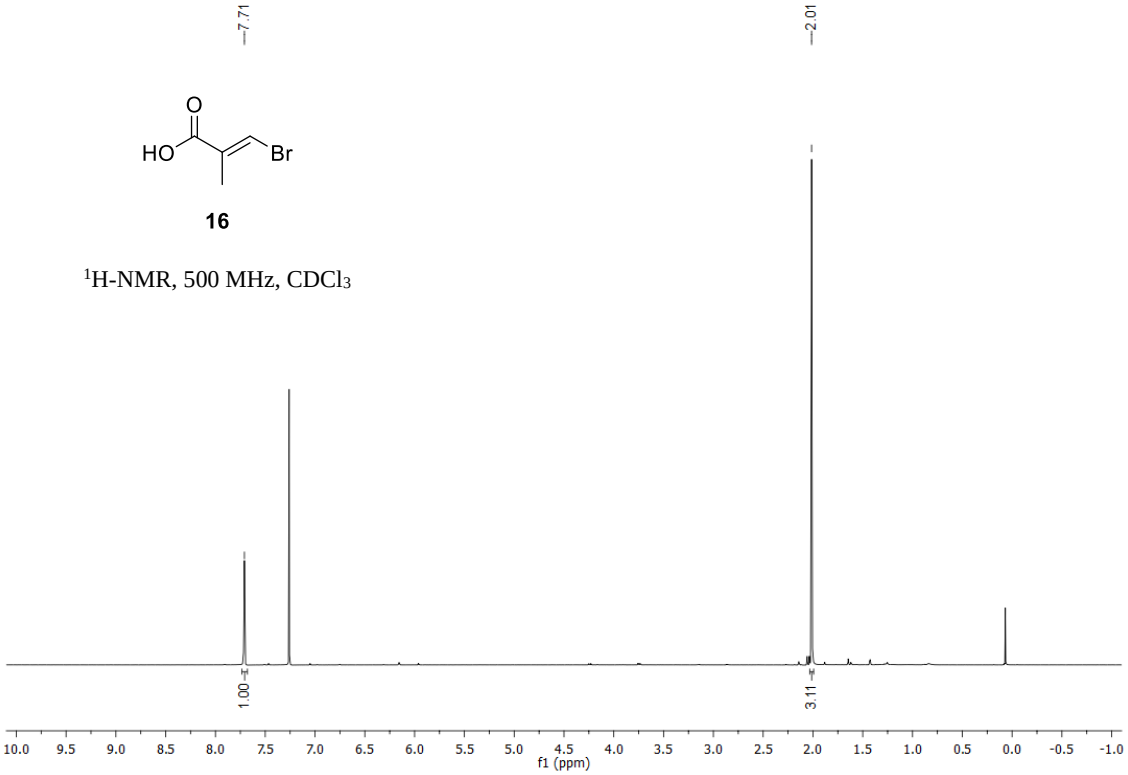
NMR-Spectra



15

^{1}H-NMR, 500 MHz, $CDCl_3$

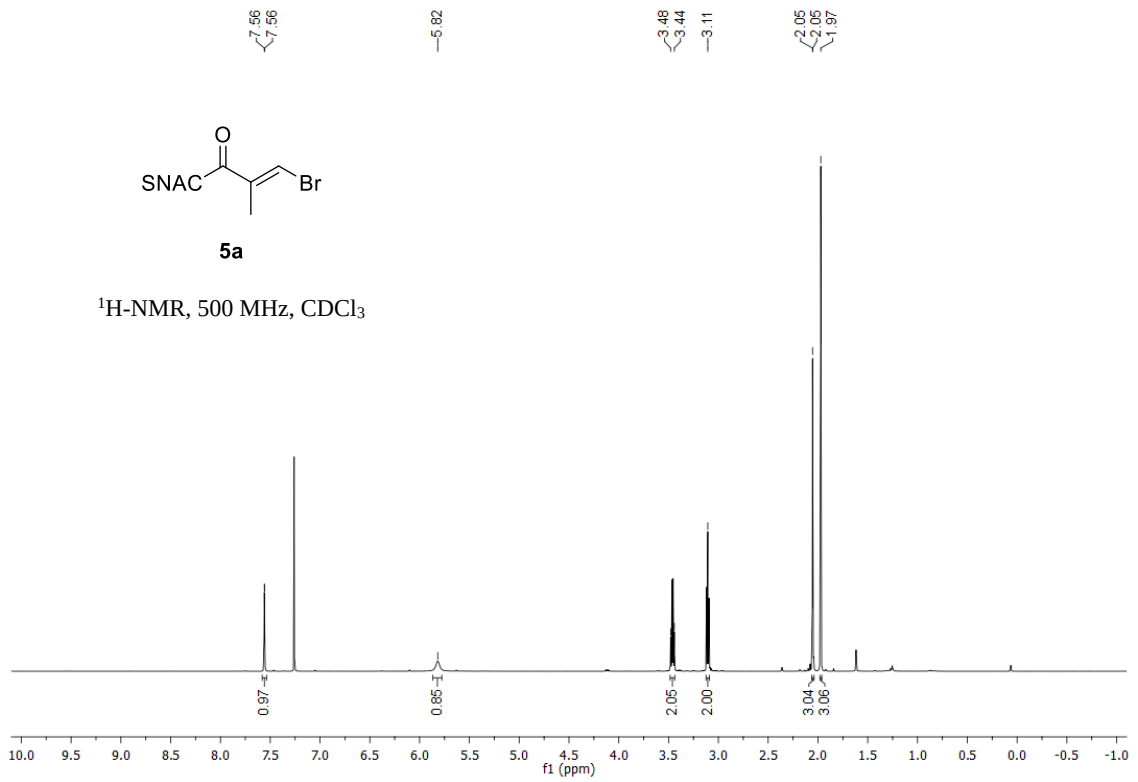
Figure **S1**: ^{1}H-NMR-spectrum of *N*-acetylcysteamine (**15**) in $CDCl_3$.



16

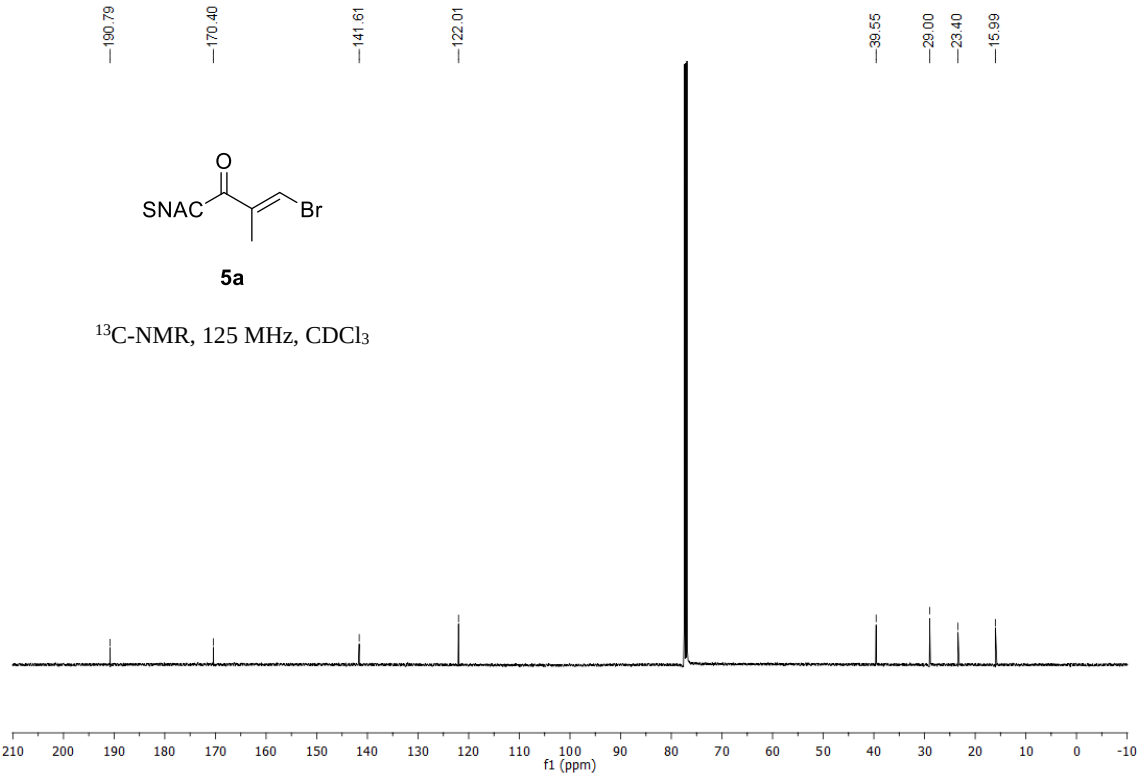
^{1}H-NMR, 500 MHz, $CDCl_3$

Figure **S2**: ^{1}H-NMR-spectrum of carboxylic acid **16** in $CDCl_3$.



^{1}H-NMR, 500 MHz, $CDCl_3$

Figure **S3**: ^{1}H-NMR-spectrum of thioester **5a** in $CDCl_3$.



^{13}C-NMR, 125 MHz, $CDCl_3$

Figure **S4**: ^{13}C-NMR-spectrum of thioester **5a** in $CDCl_3$.

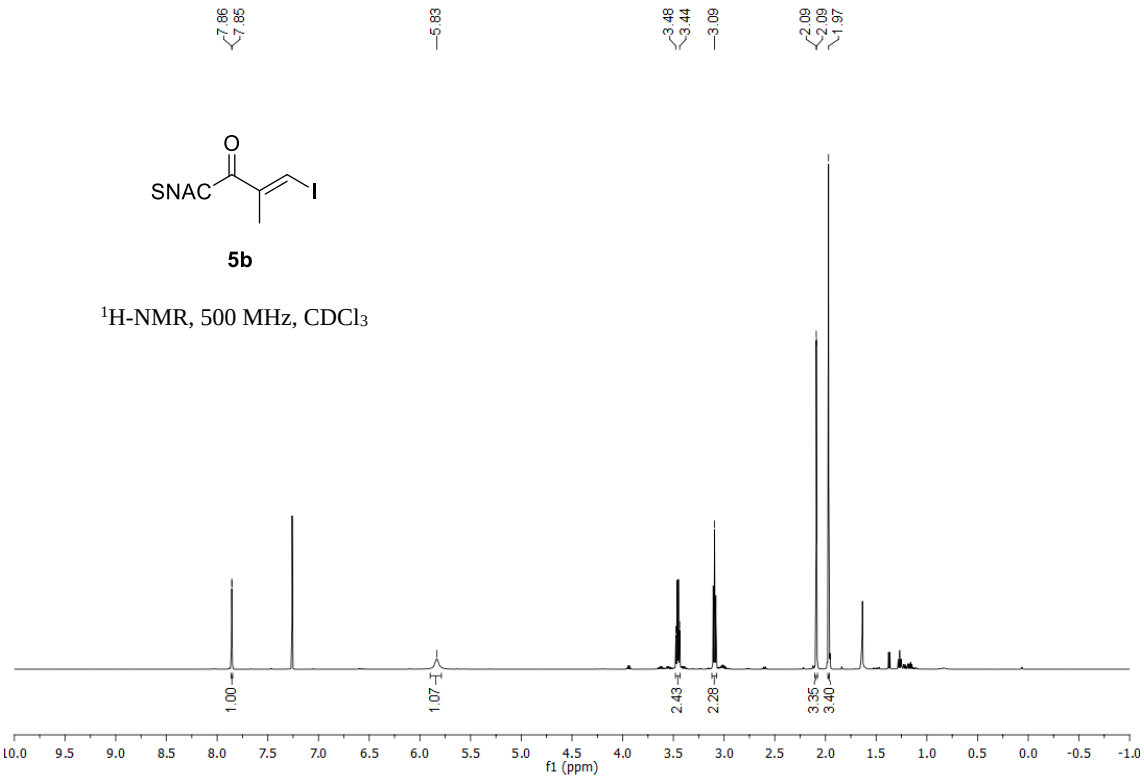


Figure **S5**: ^{1}H-NMR-spectrum of thioester **5b** in $CDCl_3$.

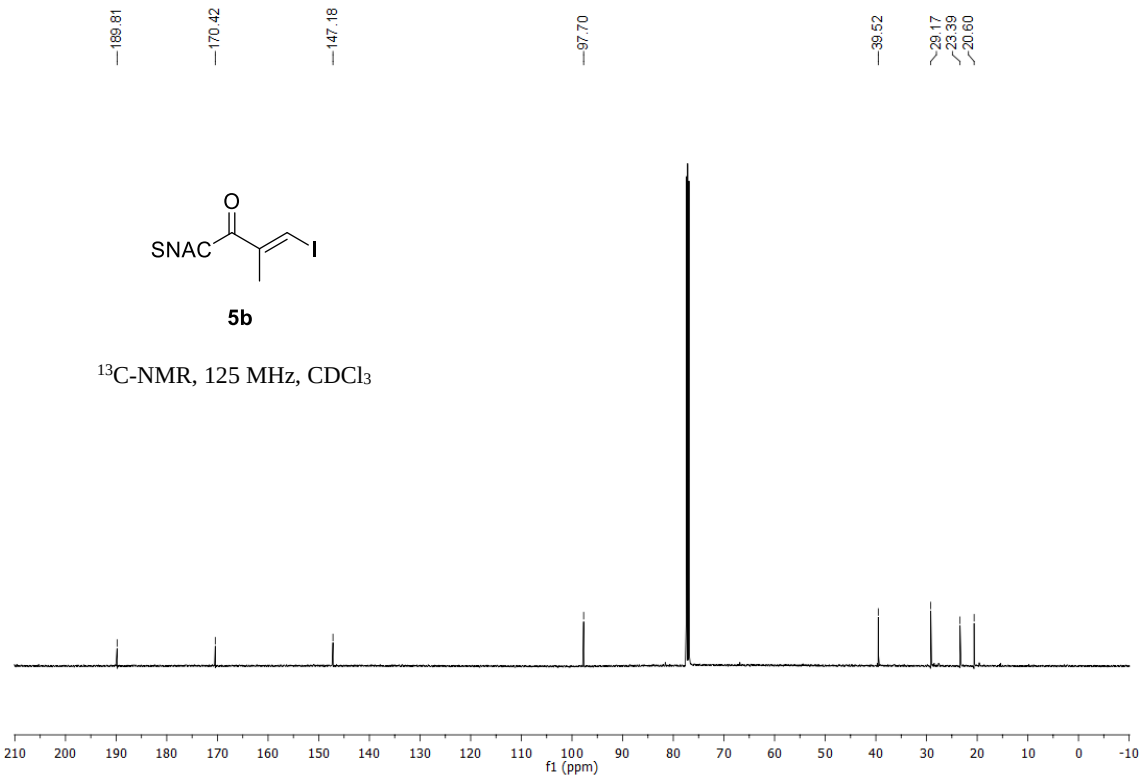


Figure **S6**: ^{13}C-NMR-spectrum of thioester **5b** in $CDCl_3$.

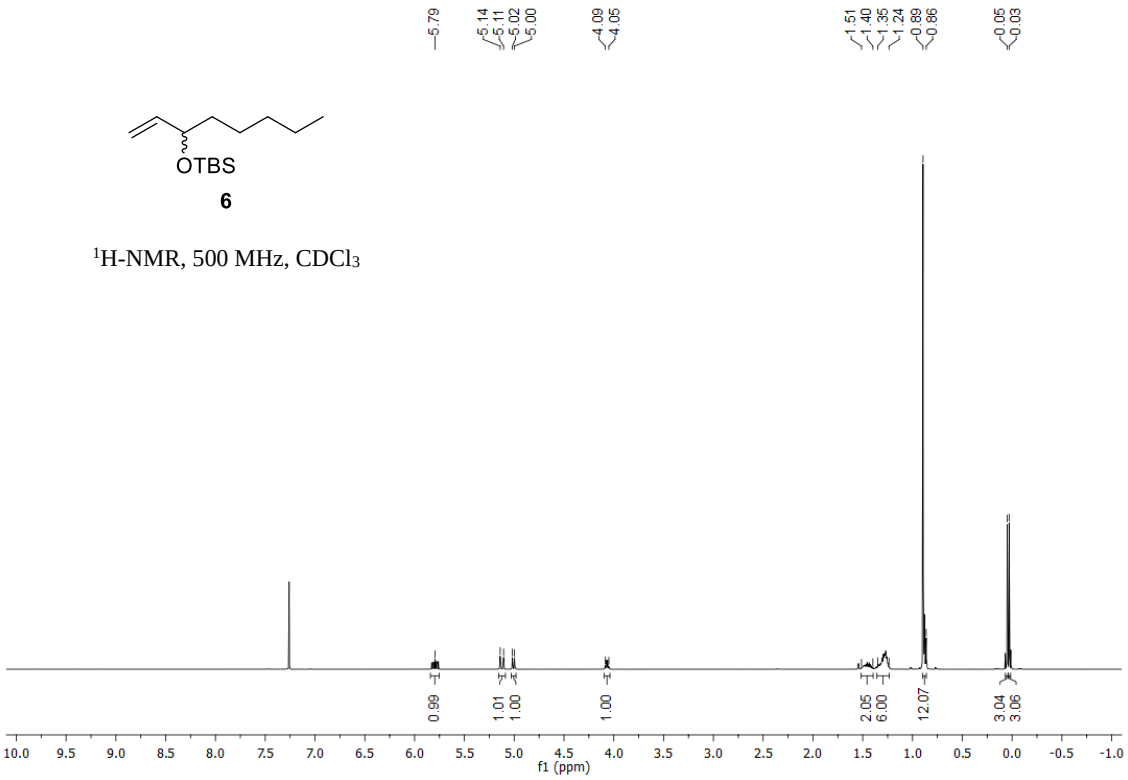


Figure **S7**: ^{1}H-NMR-spectrum of silyl ether **6** in $CDCl_3$.

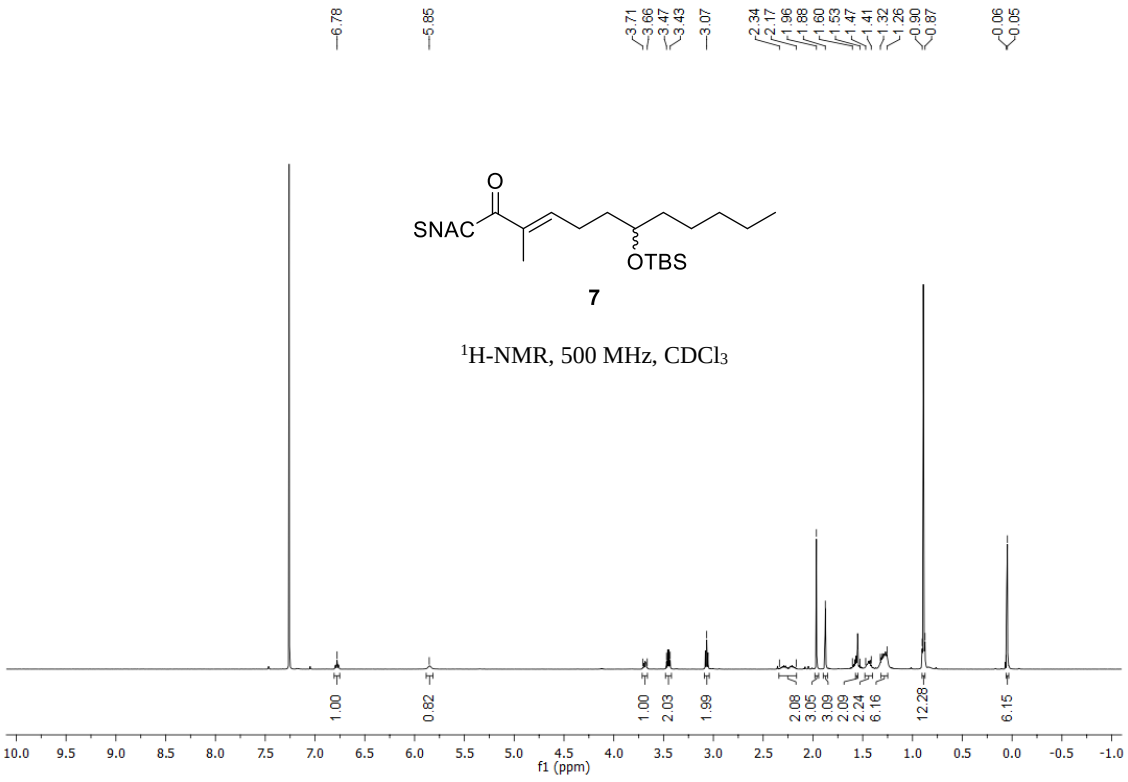


Figure **S8**: ^{1}H-NMR-spectrum of α,β-unsaturated thioester **7** in $CDCl_3$.

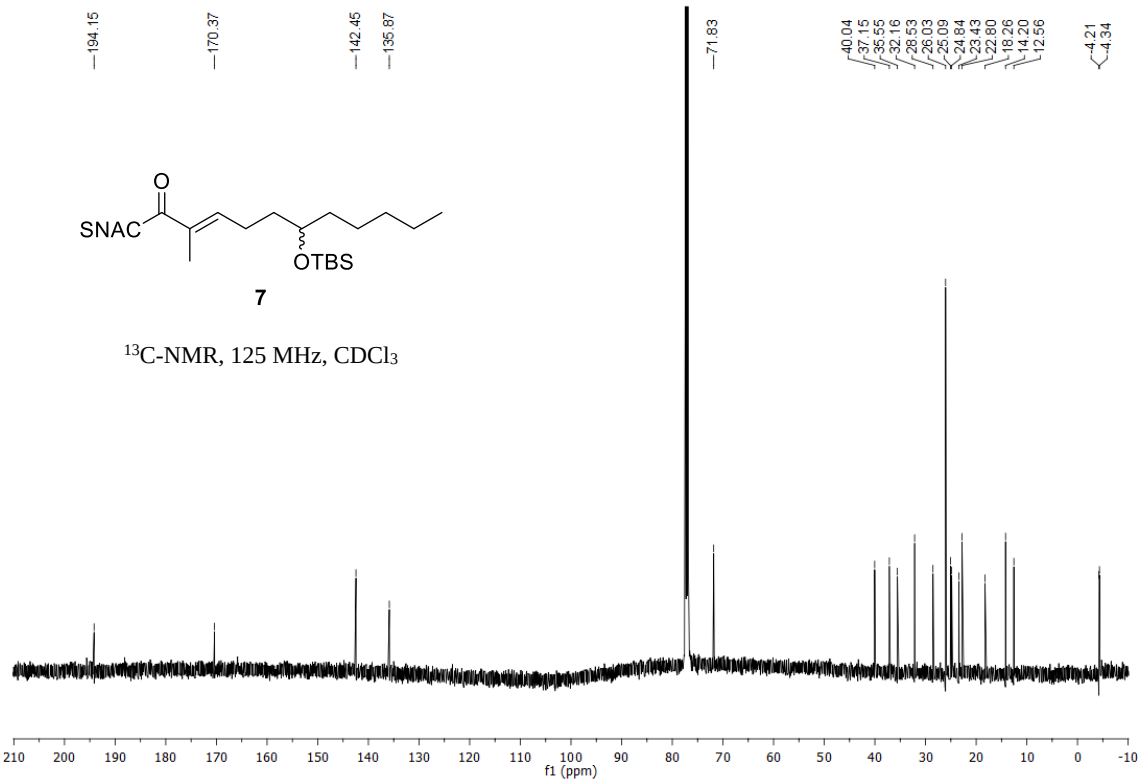


Figure **S9**: ^{13}C-NMR-spectrum of α,β-unsaturated thioester **7** in $CDCl_3$.

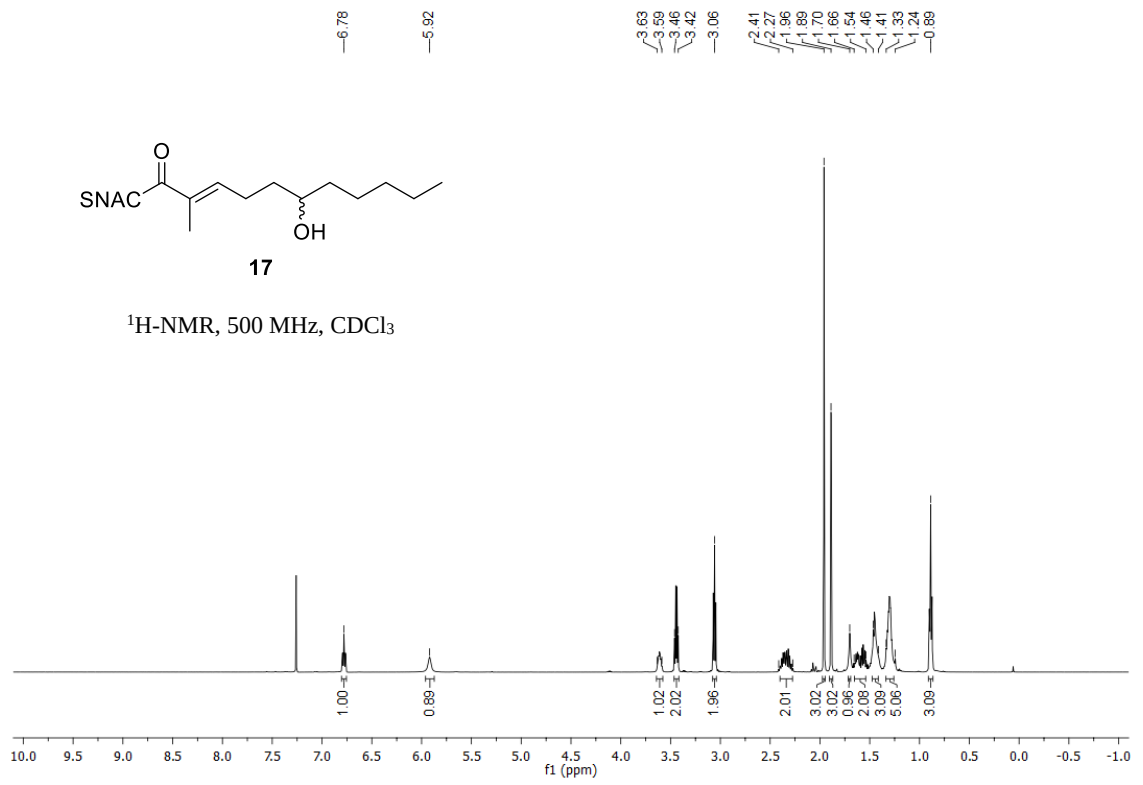


Figure **S10**: ^{1}H-NMR-spectrum of α,β-unsaturated thioester **17** in $CDCl_3$.

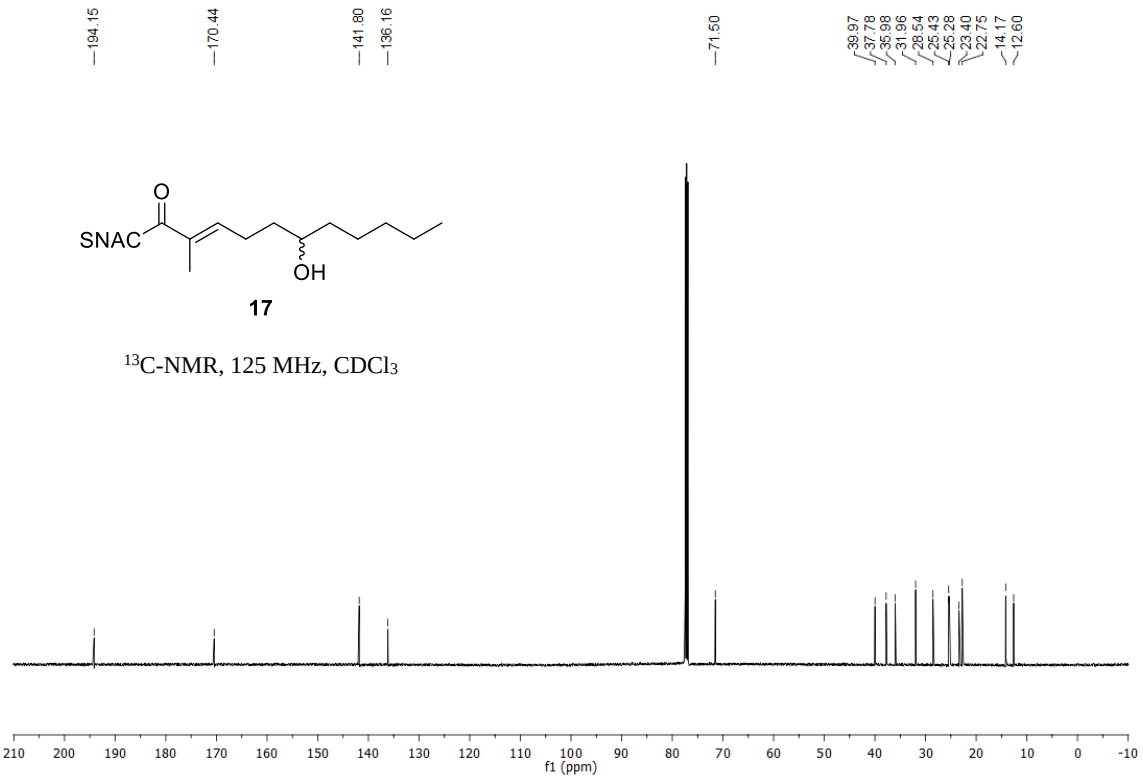


Figure **S11**: ^{13}C-NMR-spectrum of α,β-unsaturated thioester **17** in $CDCl_3$.

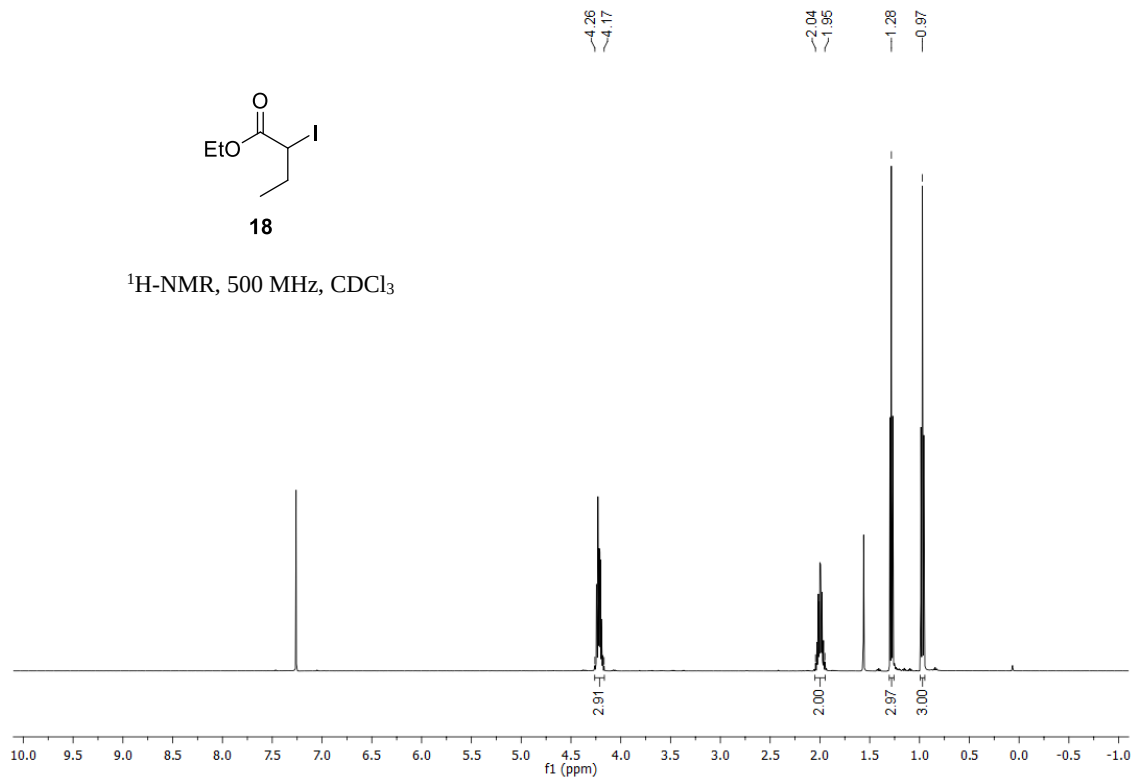


Figure **S12**: ^{1}H-NMR-spectrum of alkyl iodide **18** in $CDCl_3$.

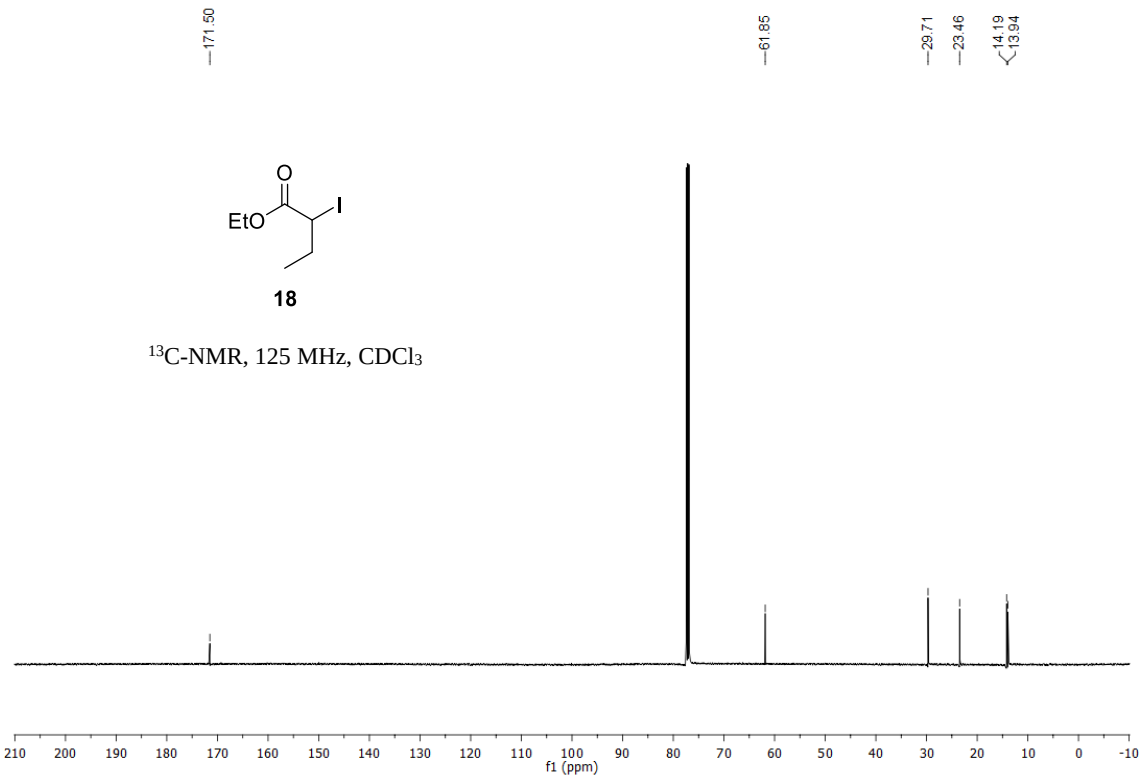


Figure **S13**: ^{13}C-NMR-spectrum of alkyl iodide **18** in $CDCl_3$.

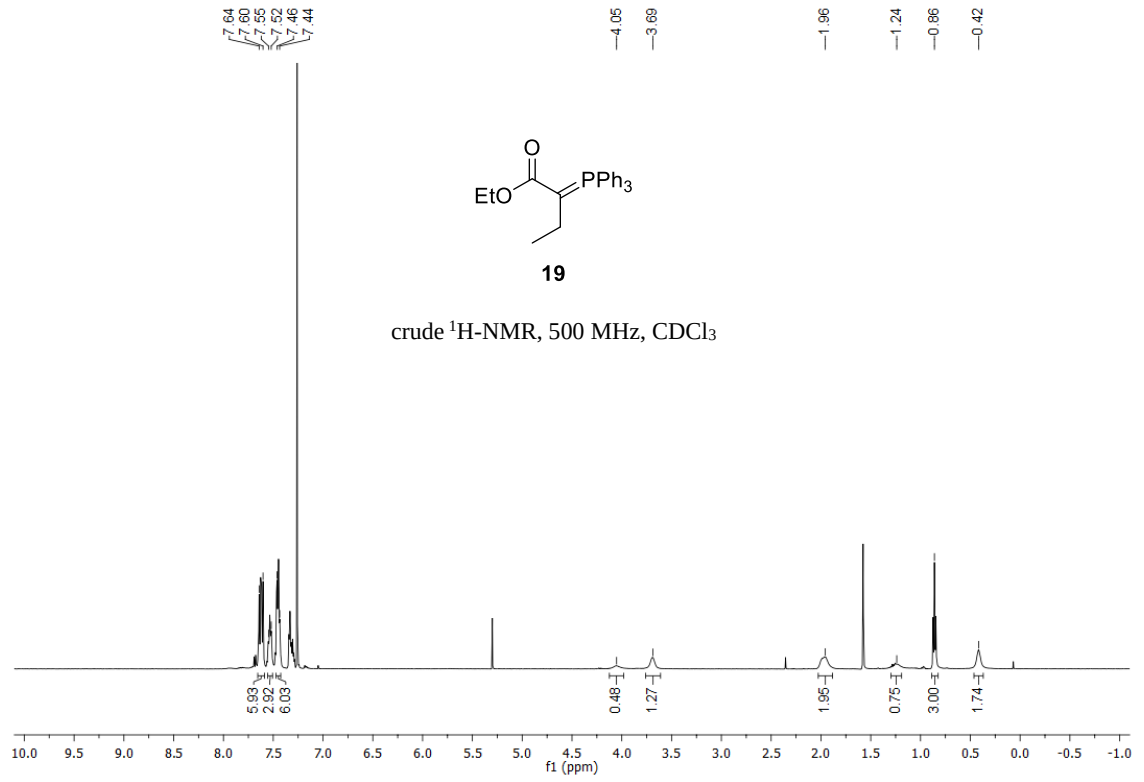


Figure **S14**: ^{1}H-NMR-spectrum of crude ylide **19** in $CDCl_3$, containing residual signals of CH_2Cl_2 and toluene.

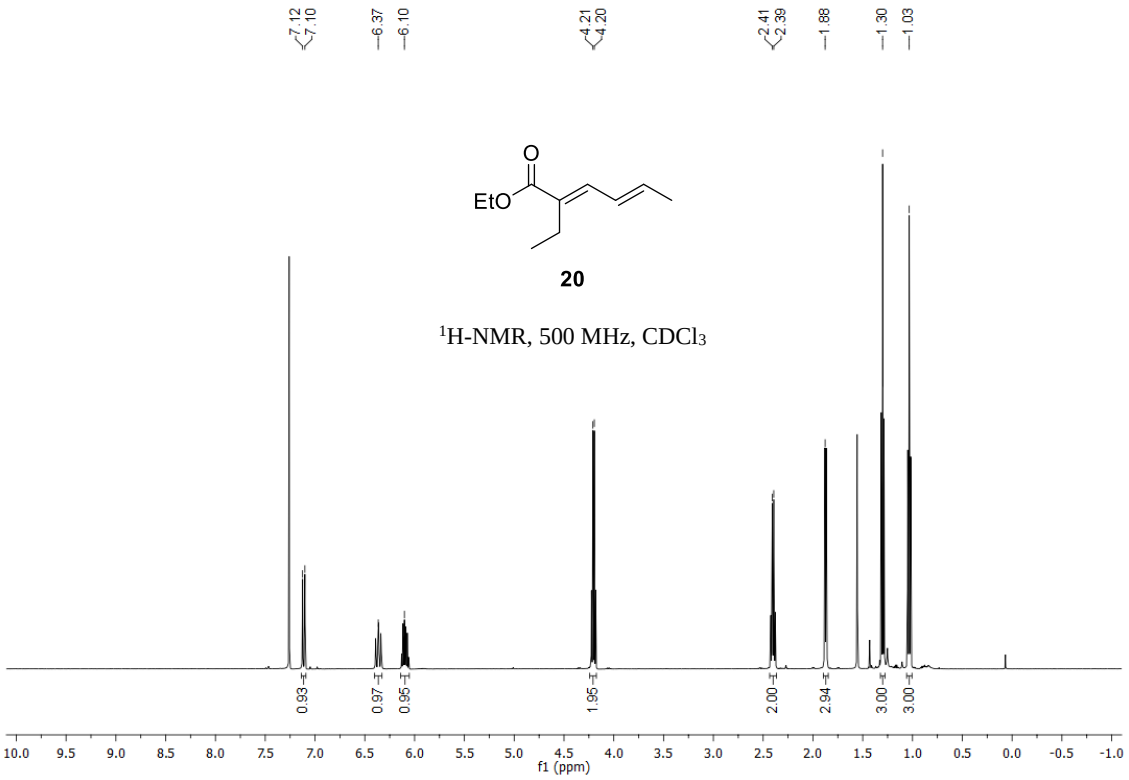


Figure **S15**: ^{1}H-NMR-spectrum of ethyl ester **20** in $CDCl_3$.

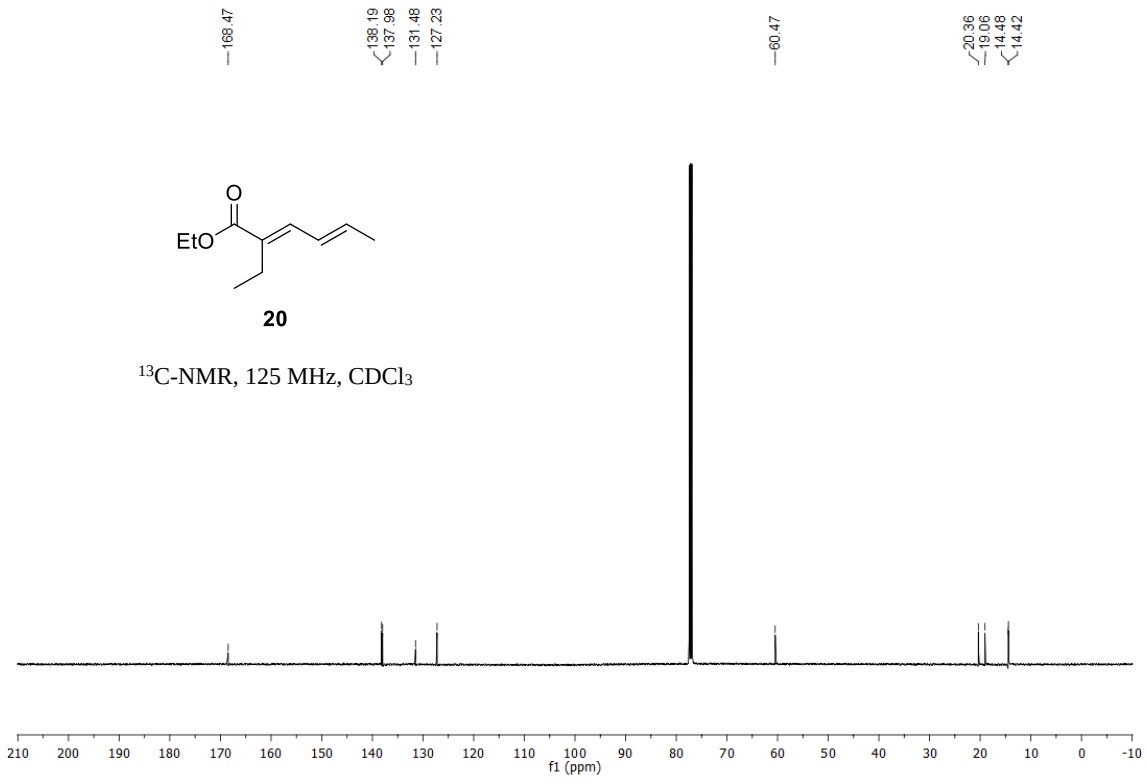


Figure **S16**: ^{13}C-NMR-spectrum of ethyl ester **20** in $CDCl_3$.

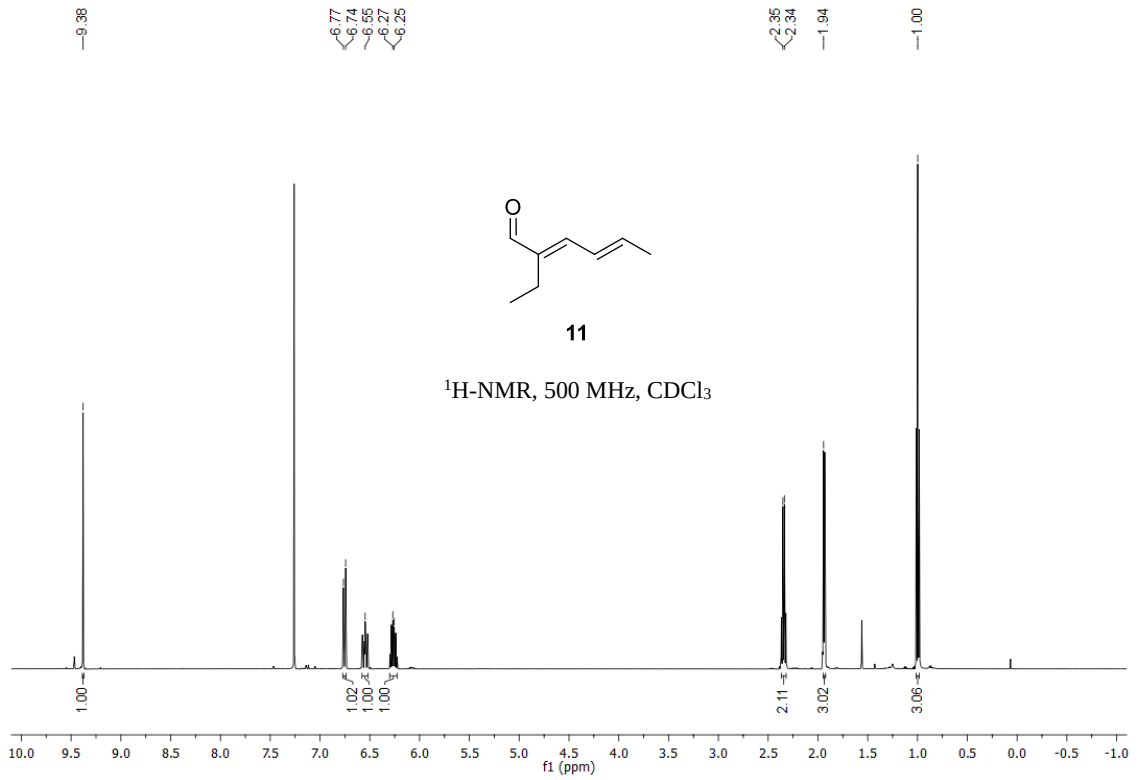


Figure **S17**: ^{1}H-NMR-spectrum of aldehyde **11** in $CDCl_3$.

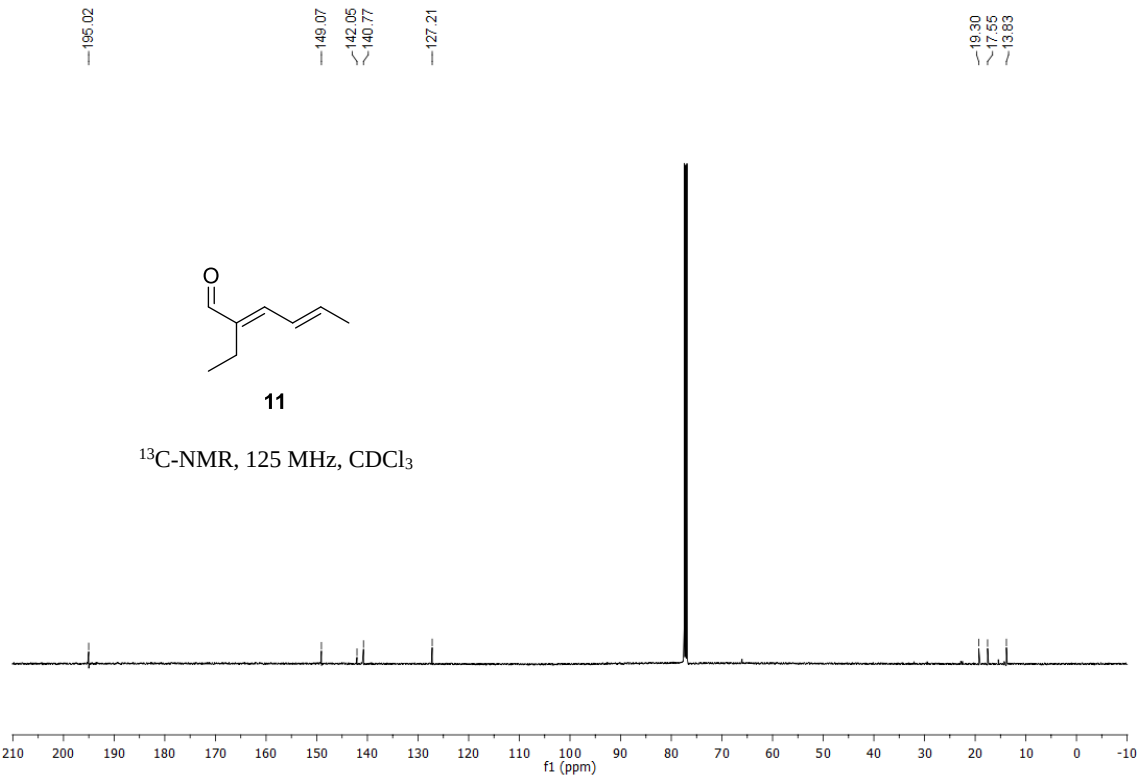
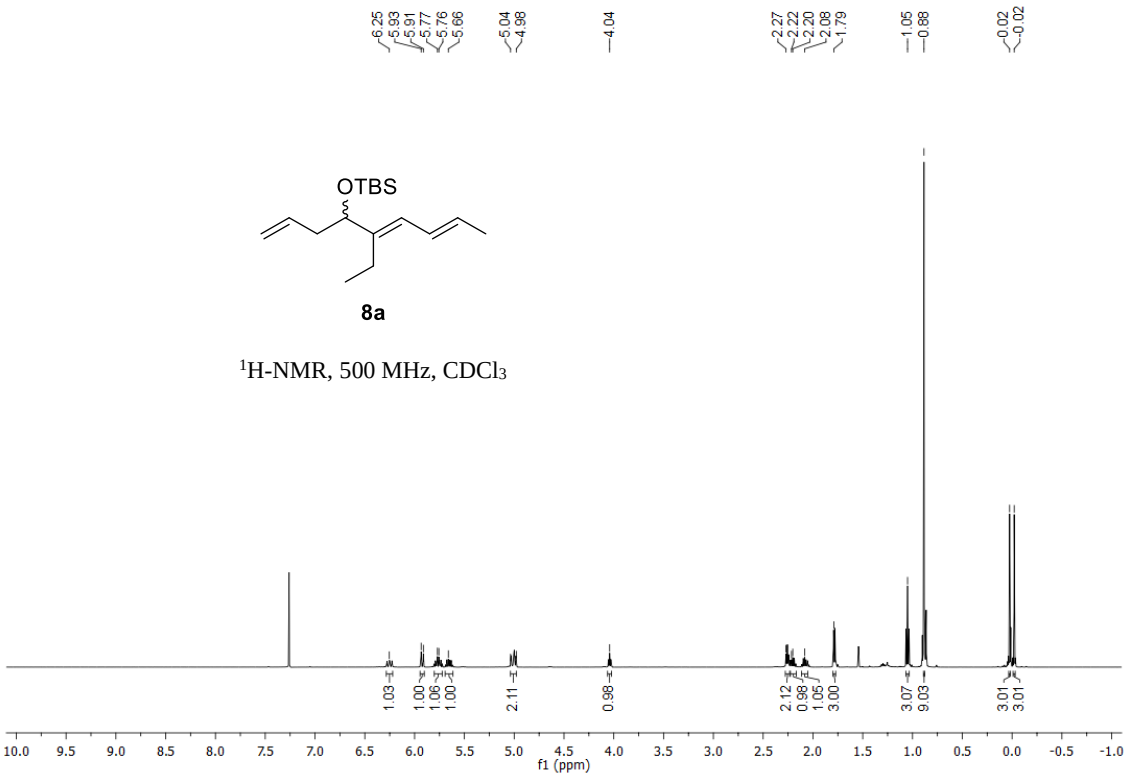
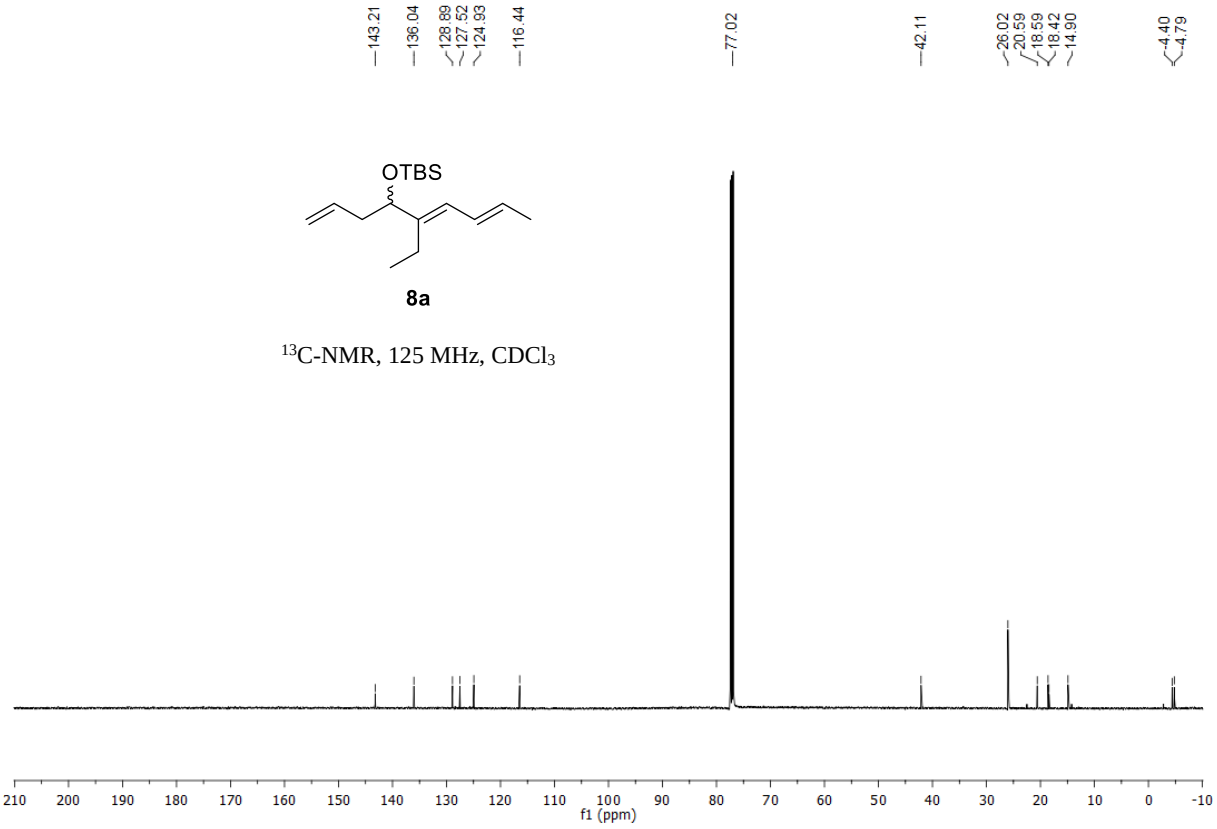


Figure **S18**: ^{13}C-NMR-spectrum of aldehyde **11** in $CDCl_3$.



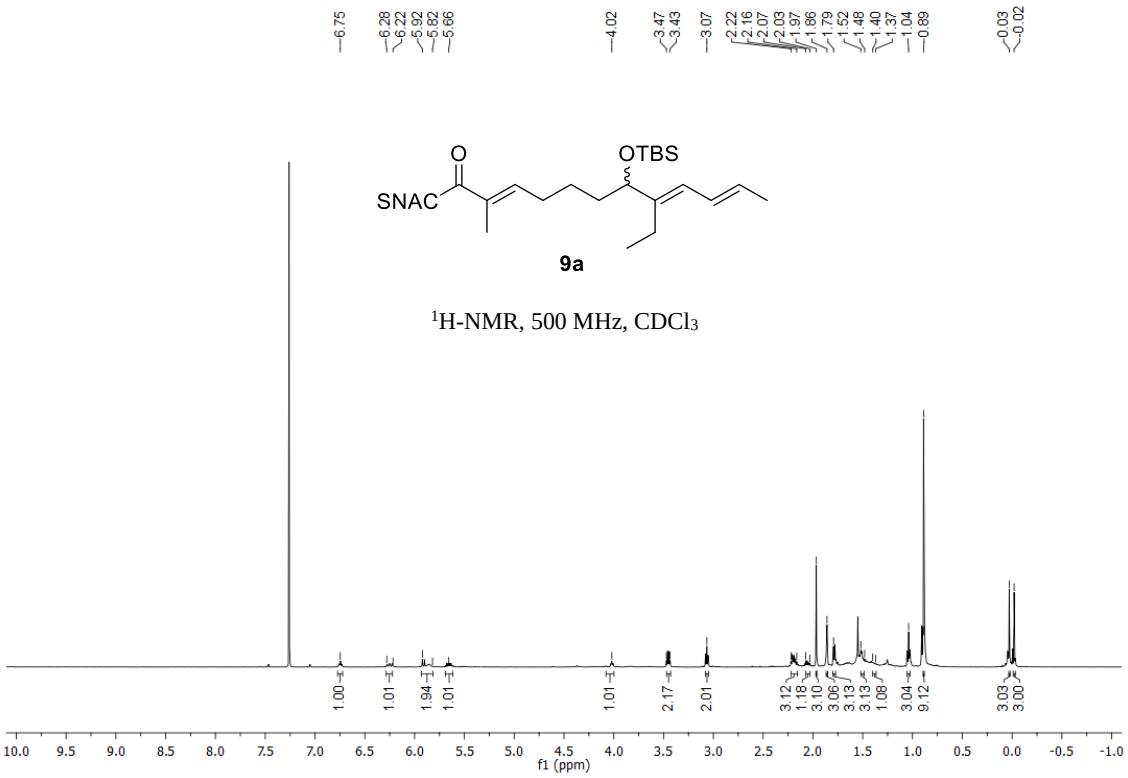
^{1}H-NMR, 500 MHz, $CDCl_3$

Figure **S19**: ^{1}H-NMR-spectrum of silyl ether **8a** in $CDCl_3$.



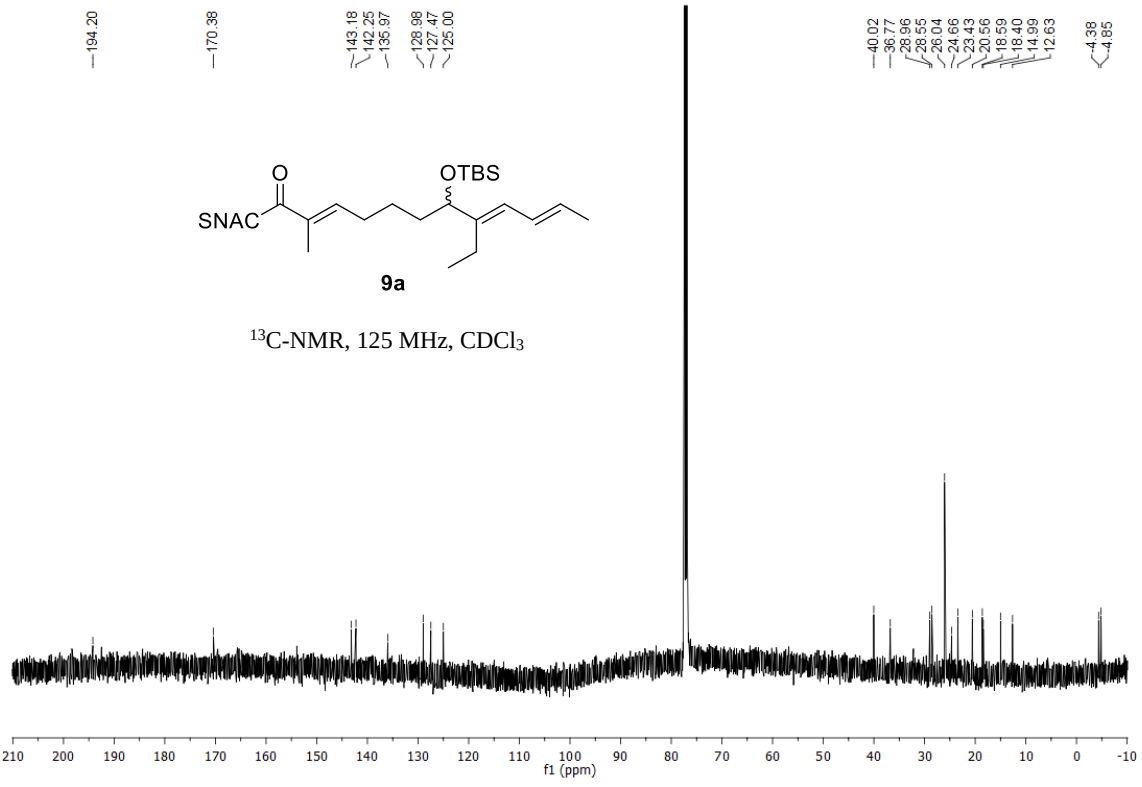
^{13}C-NMR, 125 MHz, $CDCl_3$

Figure **S20**: ^{13}C-NMR-spectrum of silyl ether **8a** in $CDCl_3$.



^{1}H-NMR, 500 MHz, $CDCl_3$

Figure **S21**: ^{1}H-NMR-spectrum of α,β-unsaturated thioester **9a** in $CDCl_3$.



^{13}C-NMR, 125 MHz, $CDCl_3$

Figure **S22**: ^{13}C-NMR-spectrum of α,β-unsaturated thioester **9a** in $CDCl_3$.

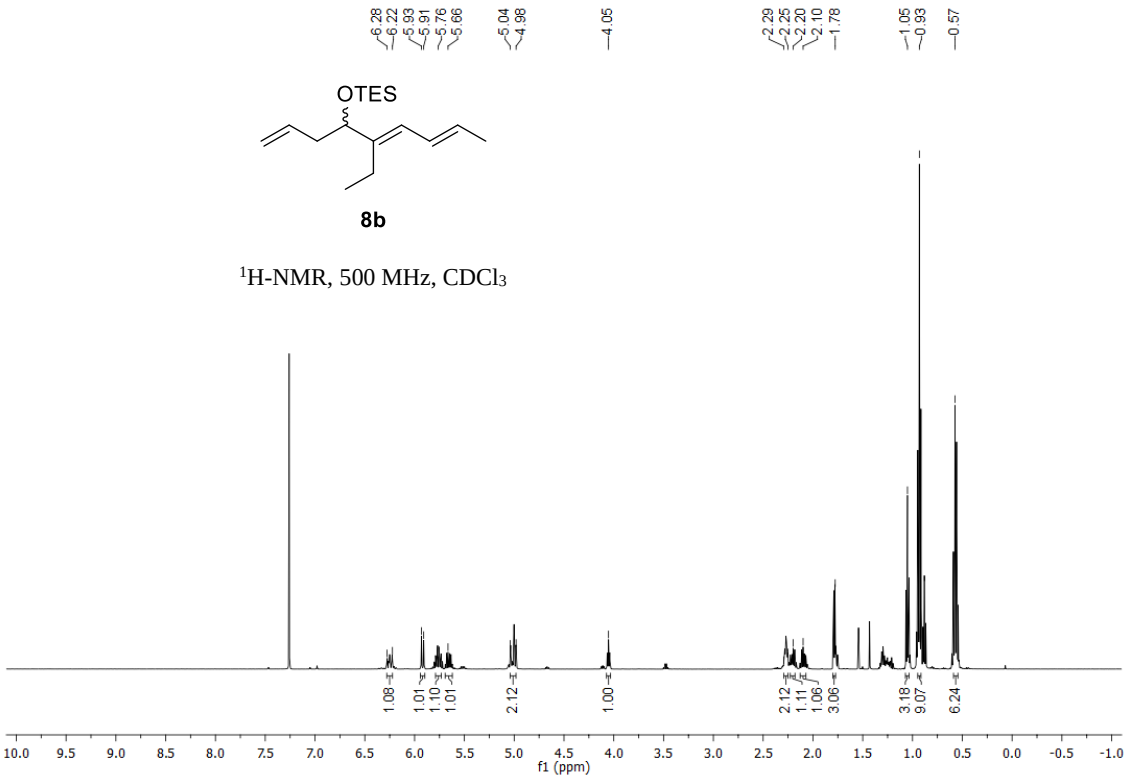


Figure **S23**: ^{1}H-NMR-spectrum of silyl ether **8b** in $CDCl_3$.

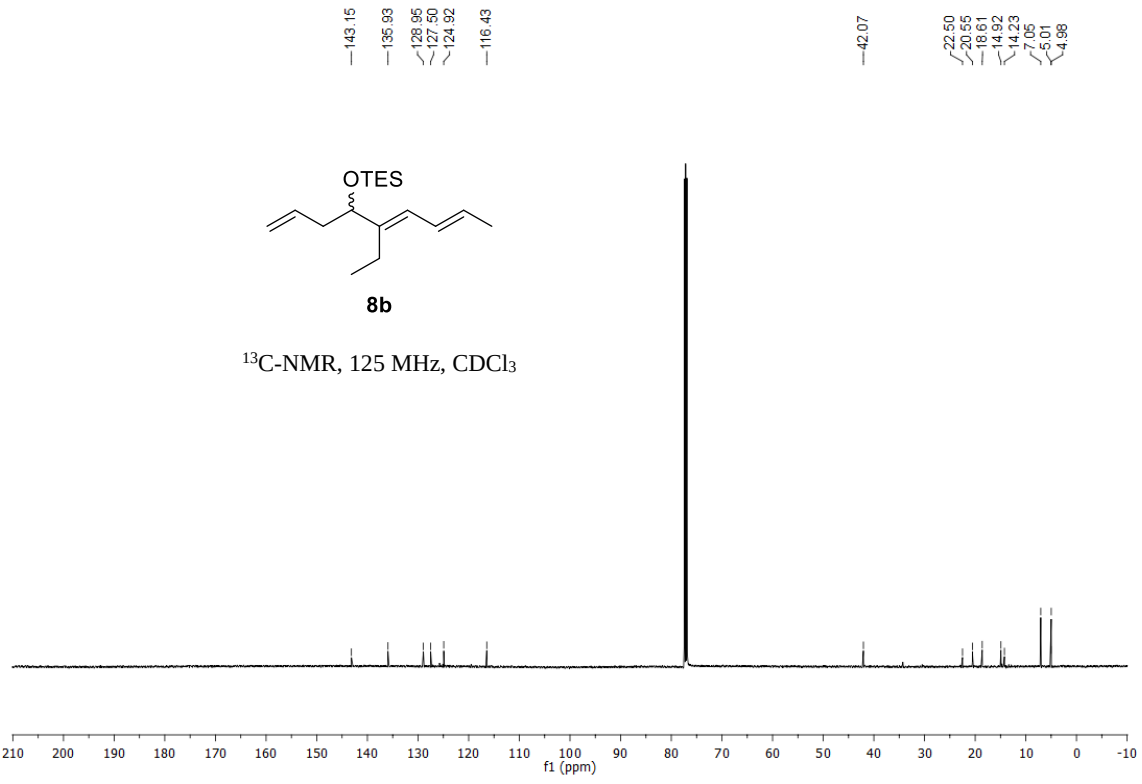


Figure **S24**: ^{13}C-NMR-spectrum of silyl ether **8b** in $CDCl_3$.

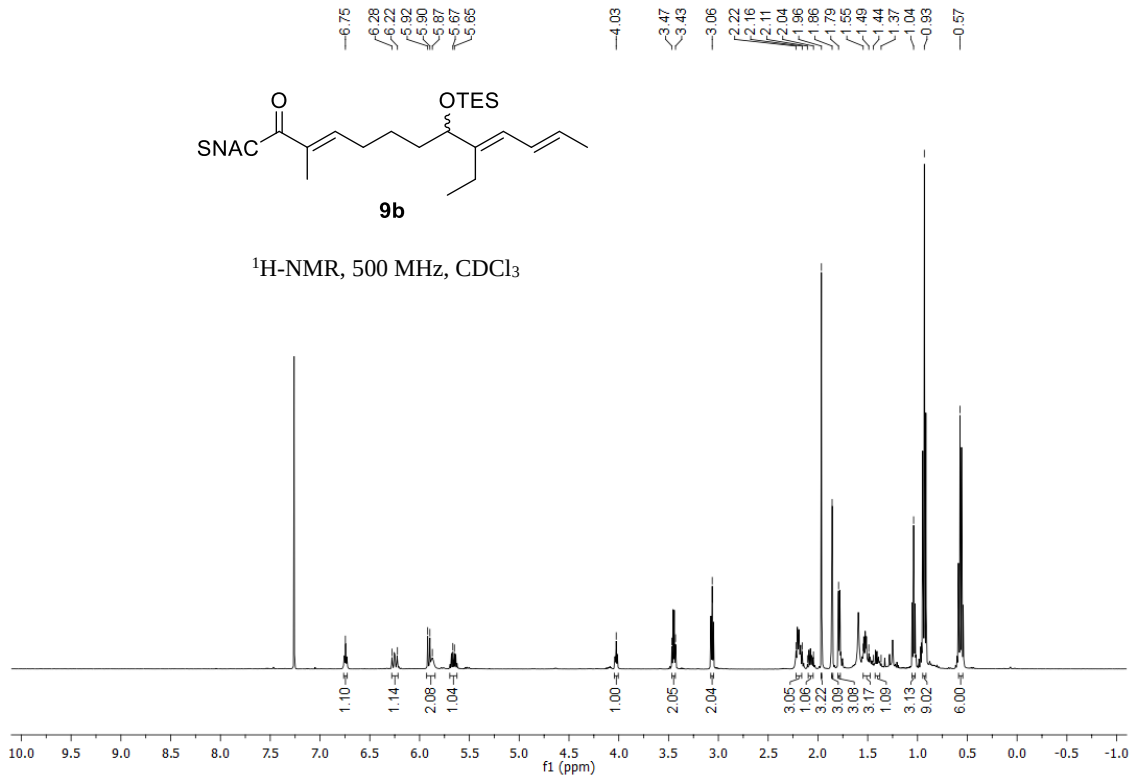


Figure **S25**: ^{1}H-NMR-spectrum of α,β-unsaturated thioester **9b** in $CDCl_3$.

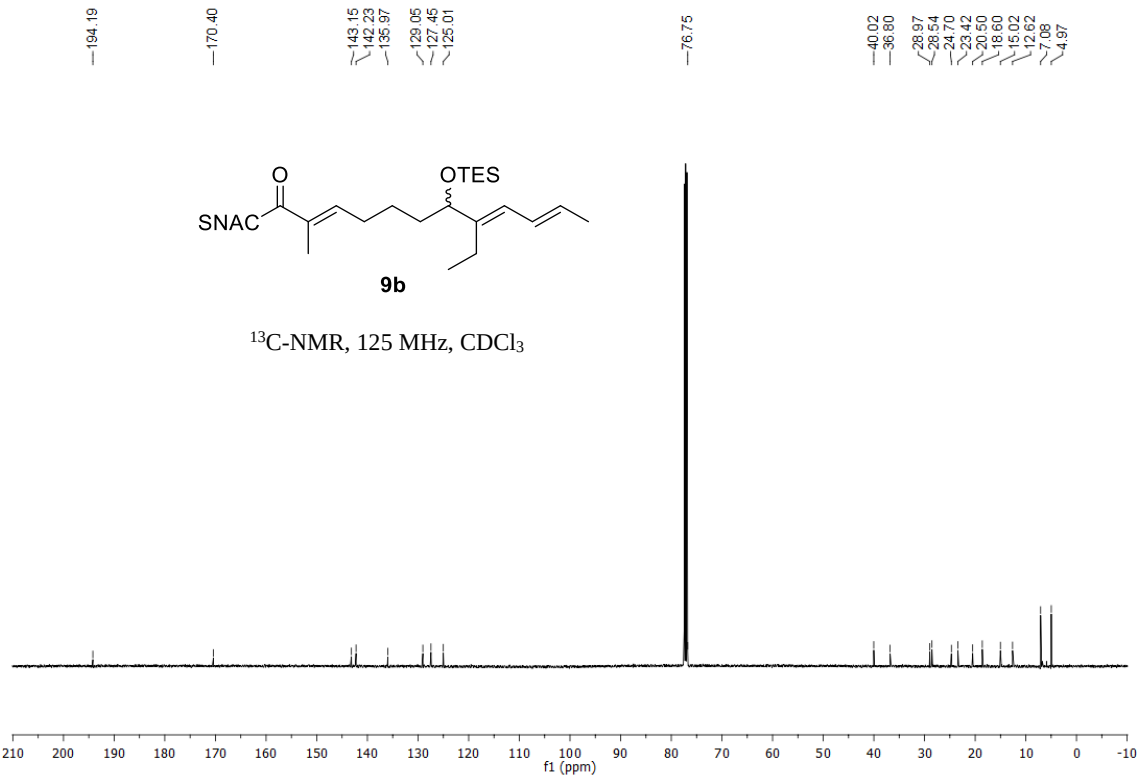
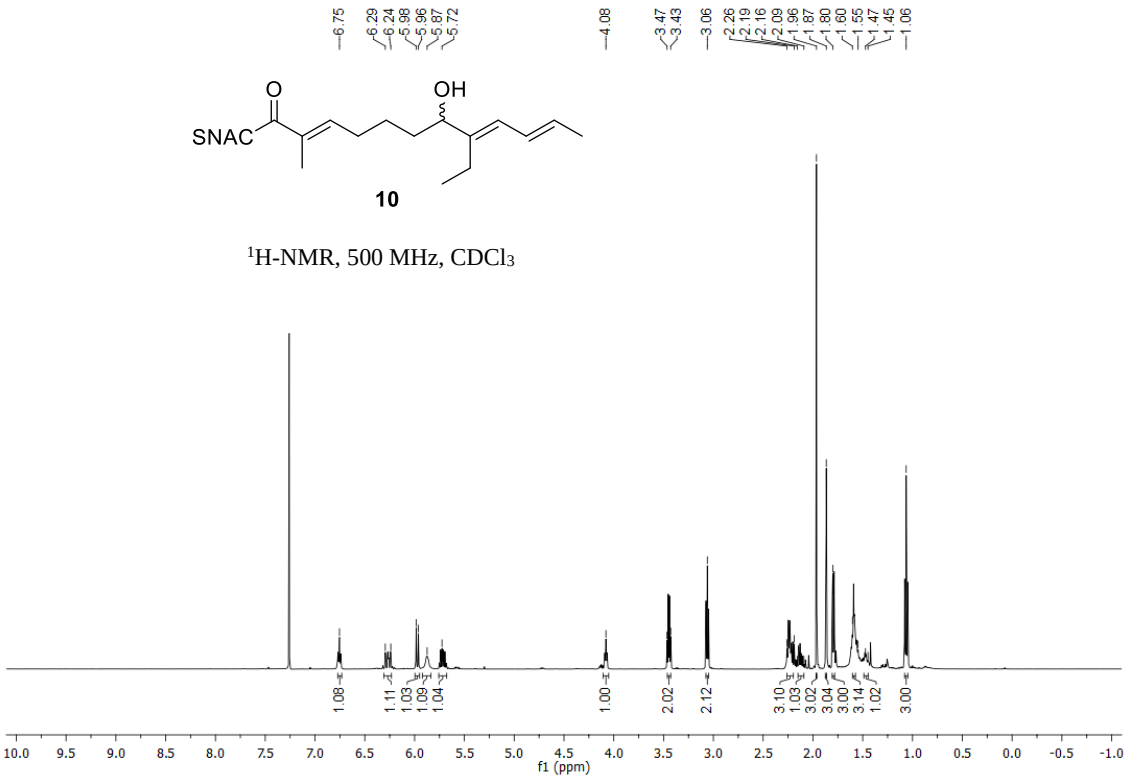
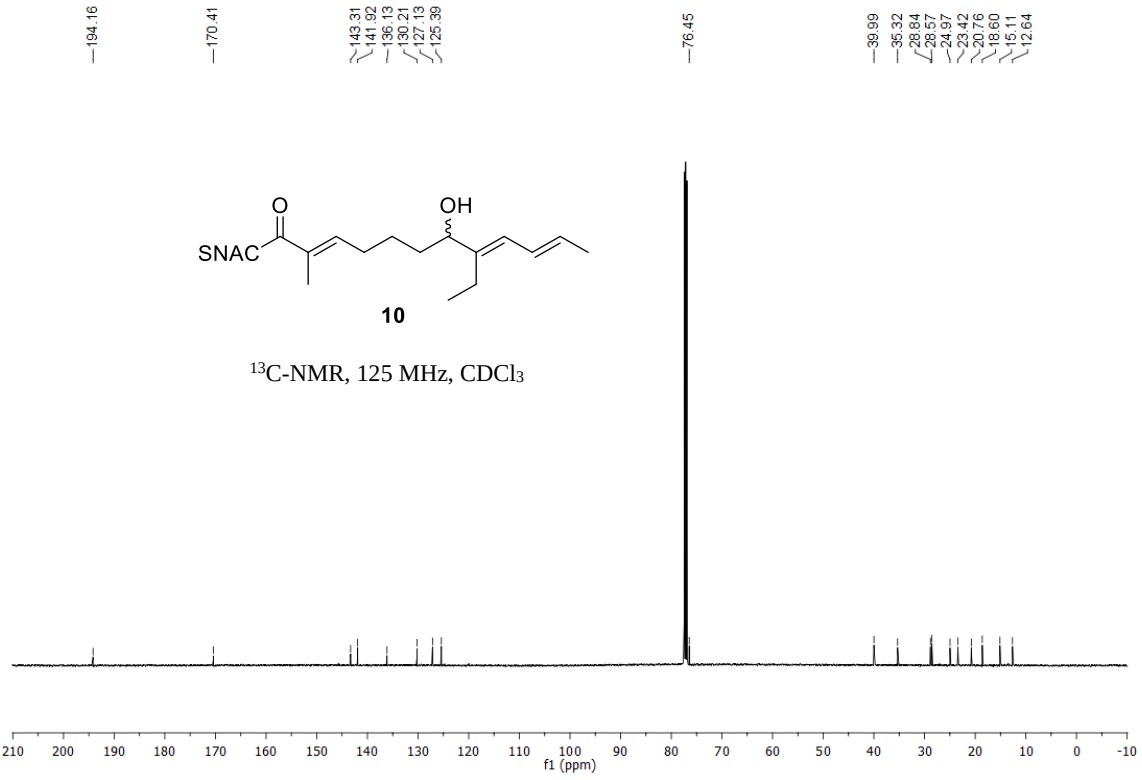


Figure **S26**: ^{13}C-NMR-spectrum of α,β-unsaturated thioester **9b** in $CDCl_3$.



^{1}H-NMR, 500 MHz, $CDCl_3$

Figure **S27**: ^{1}H-NMR-spectrum of α,β-unsaturated thioester **10** in $CDCl_3$.



^{13}C-NMR, 125 MHz, $CDCl_3$

Figure **S28**: ^{13}C-NMR-spectrum of α,β-unsaturated thioester **10** in $CDCl_3$.

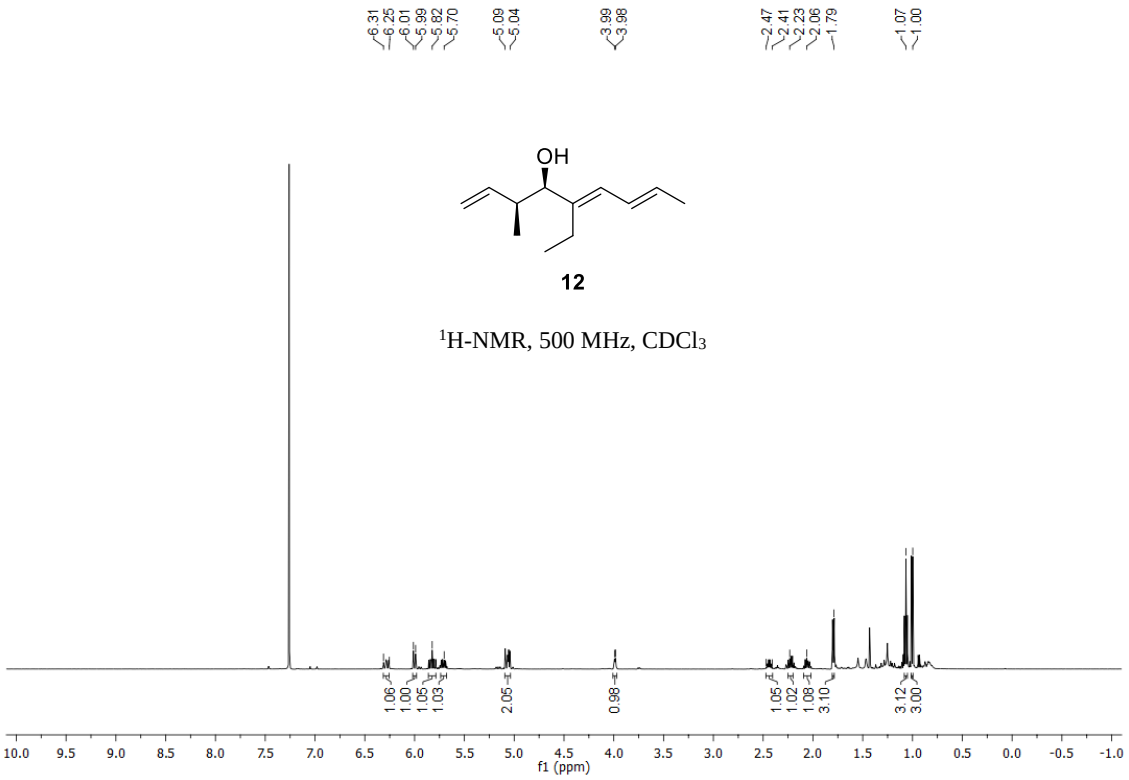


Figure **S29**: ^{1}H-NMR-spectrum of secondary alcohol **12** in $CDCl_3$.

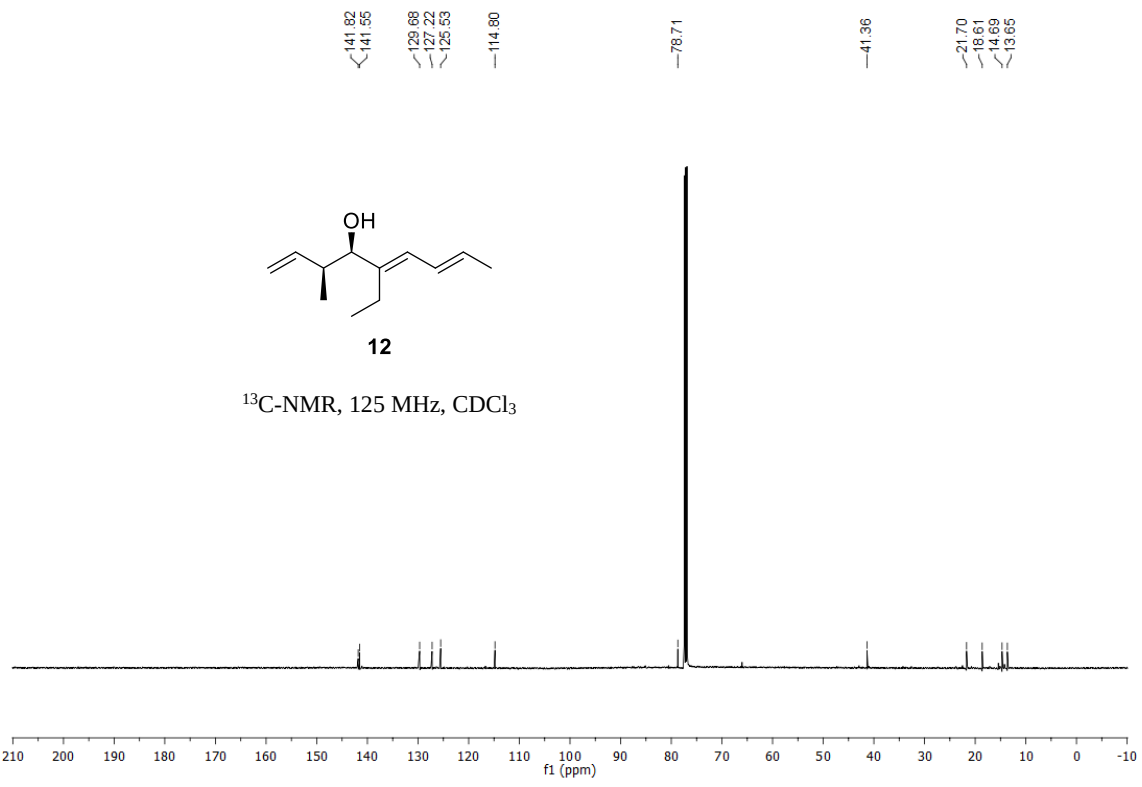
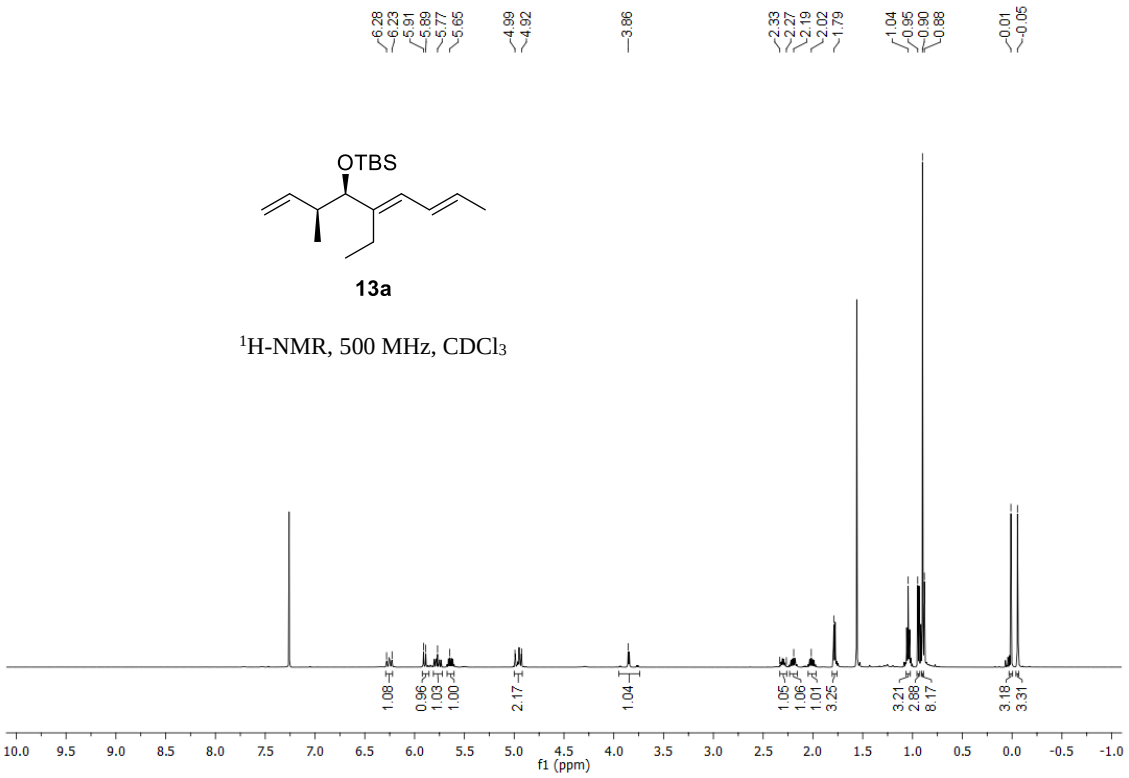
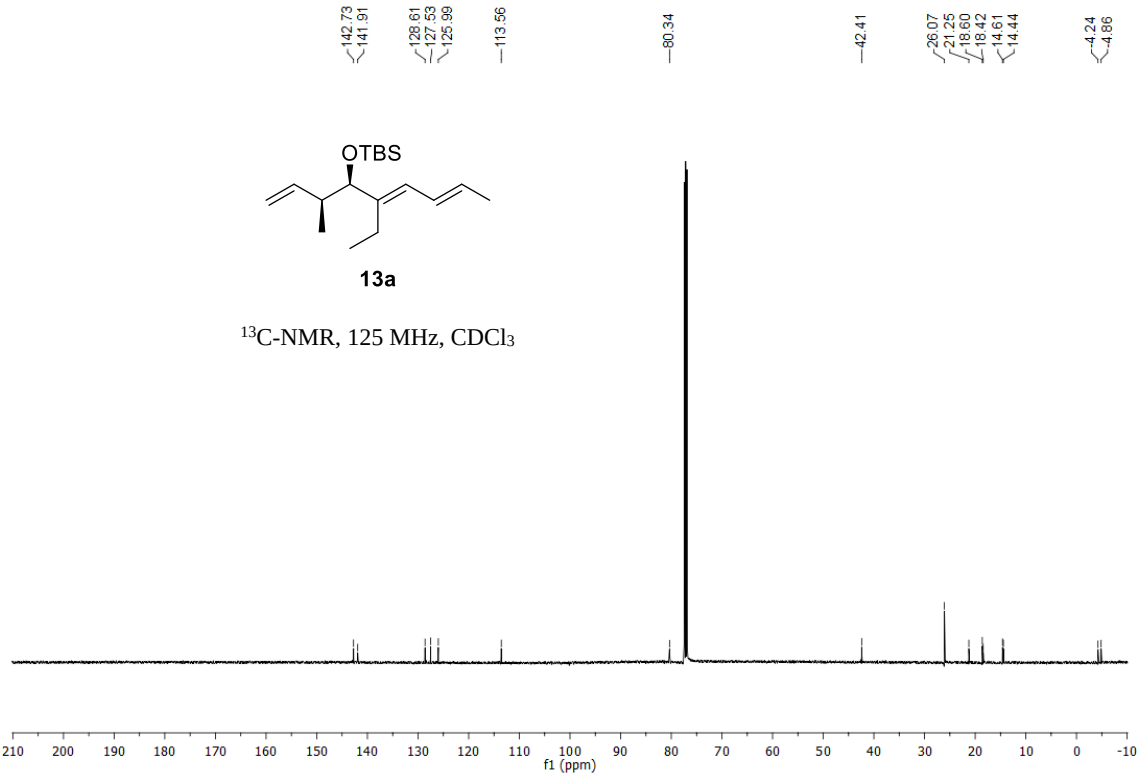


Figure **S30**: ^{13}C-NMR-spectrum of secondary alcohol **12** in $CDCl_3$.



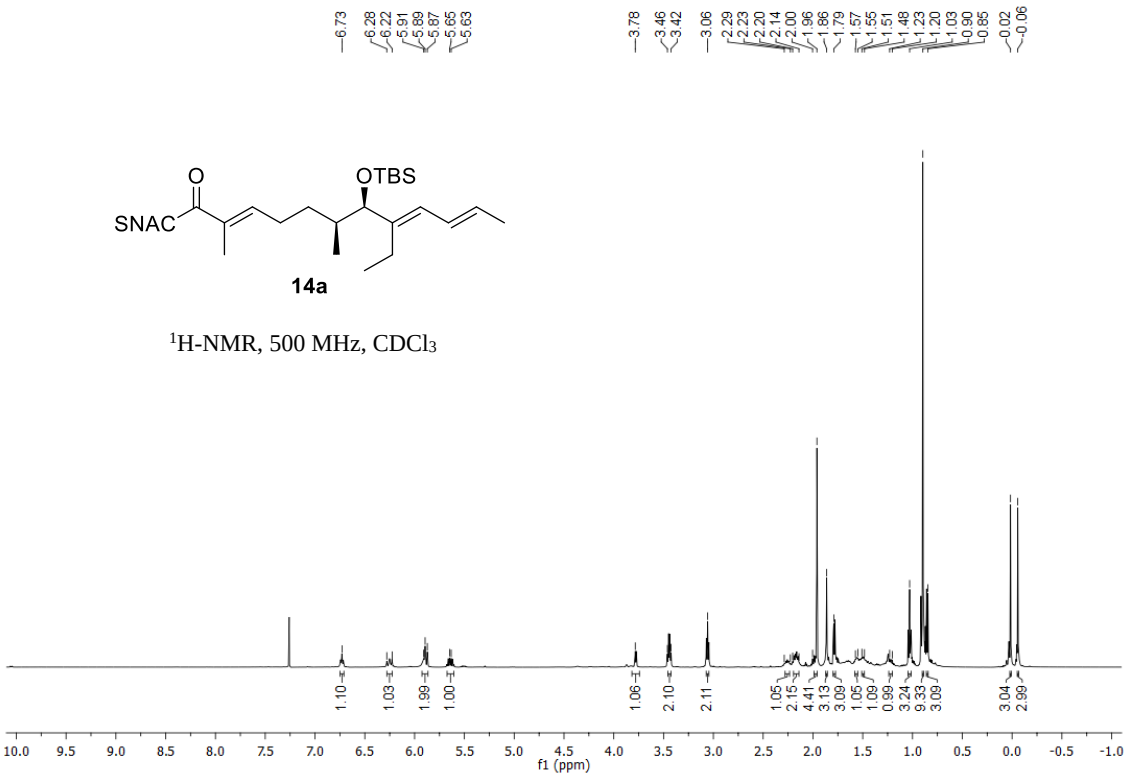
^{1}H-NMR, 500 MHz, $CDCl_3$

Figure **S31**: ^{1}H-NMR-spectrum of silyl ether **13a** in $CDCl_3$.



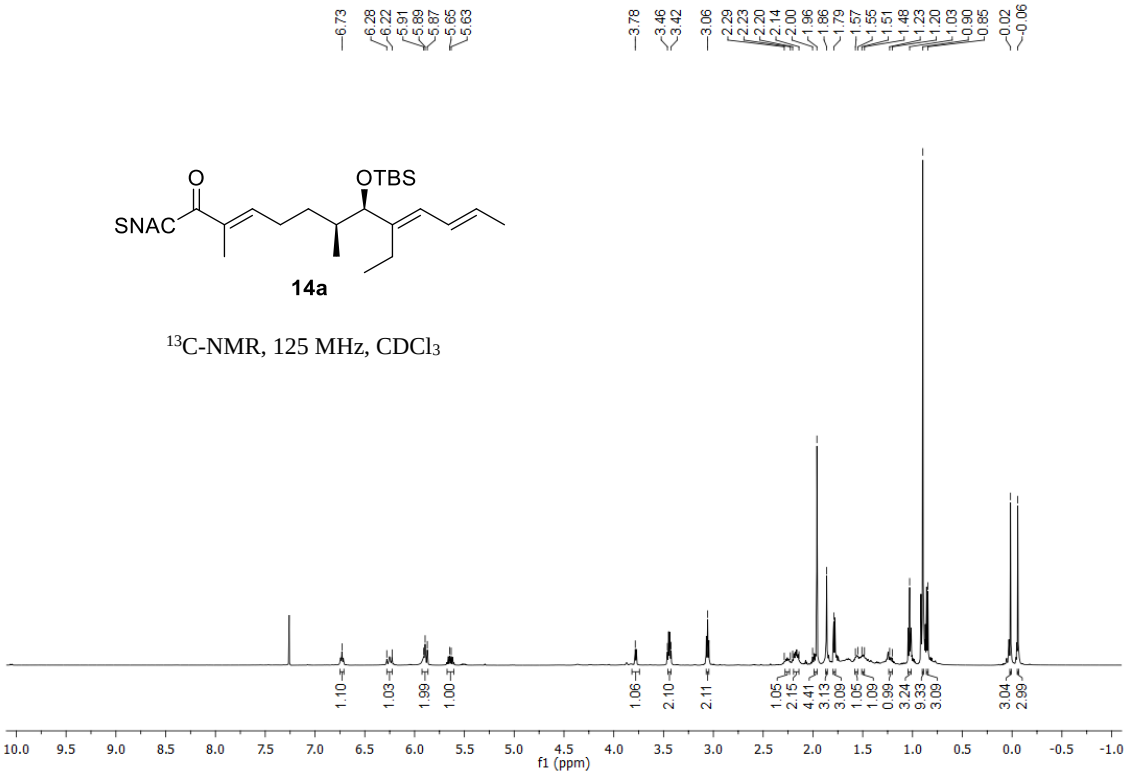
^{13}C-NMR, 125 MHz, $CDCl_3$

Figure **S32**: ^{13}C-NMR-spectrum of silyl ether **13a** in $CDCl_3$.



^{1}H-NMR, 500 MHz, $CDCl_3$

Figure **S33**: ^{1}H-NMR-spectrum of α,β-unsaturated thioester **14a** in $CDCl_3$.



^{13}C-NMR, 125 MHz, $CDCl_3$

Figure **S34**: ^{13}C-NMR-spectrum of α,β-unsaturated thioester **14a** in $CDCl_3$.

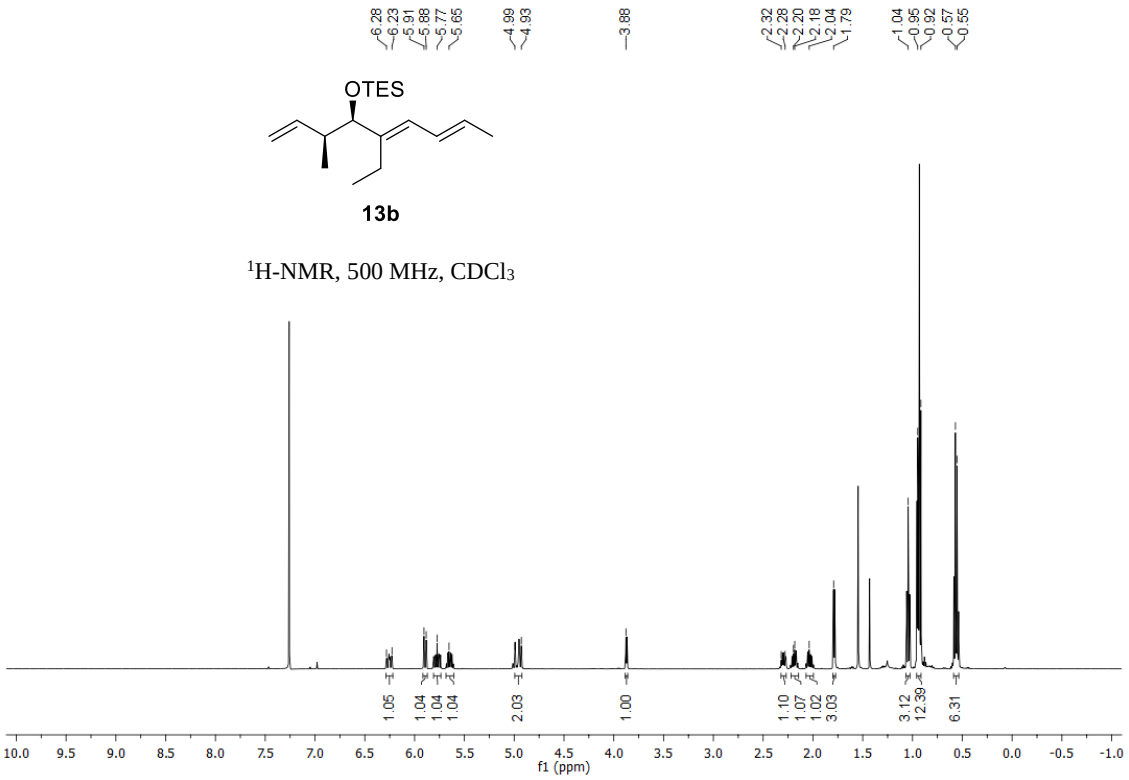


Figure **S35**: ^{1}H-NMR-spectrum of silyl ether **13b** in $CDCl_3$.

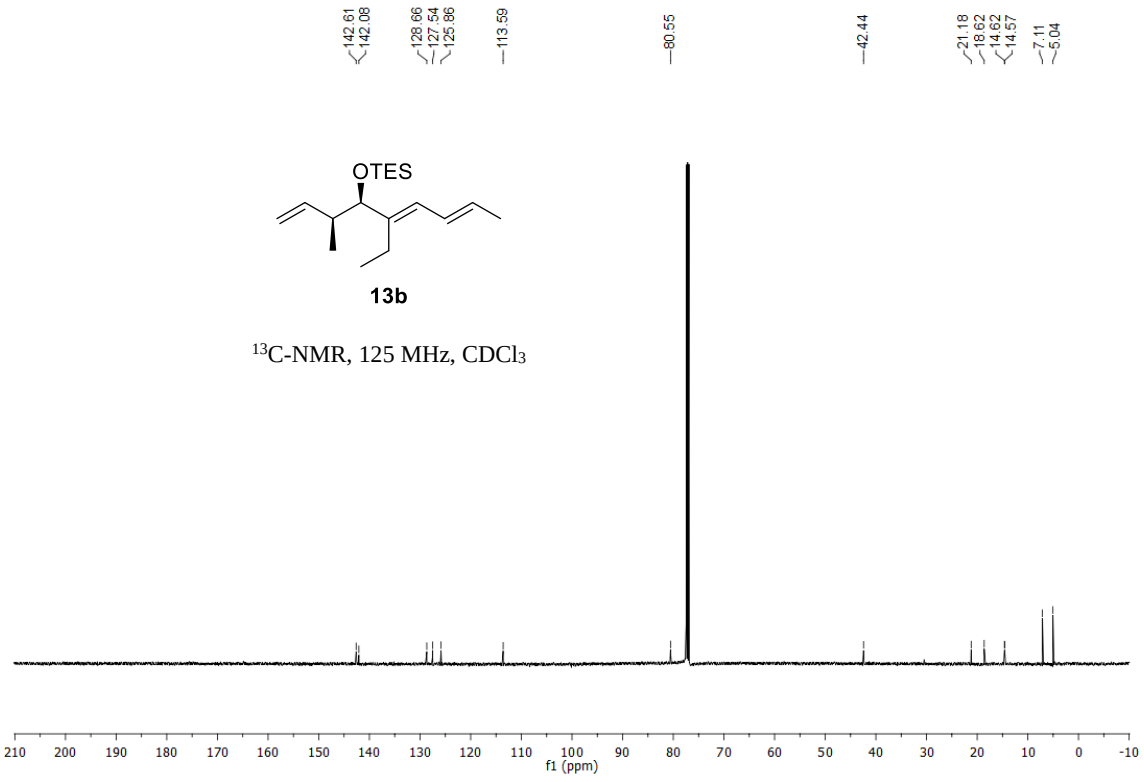


Figure **S36**: ^{13}C-NMR-spectrum of silyl ether **13b** in $CDCl_3$.

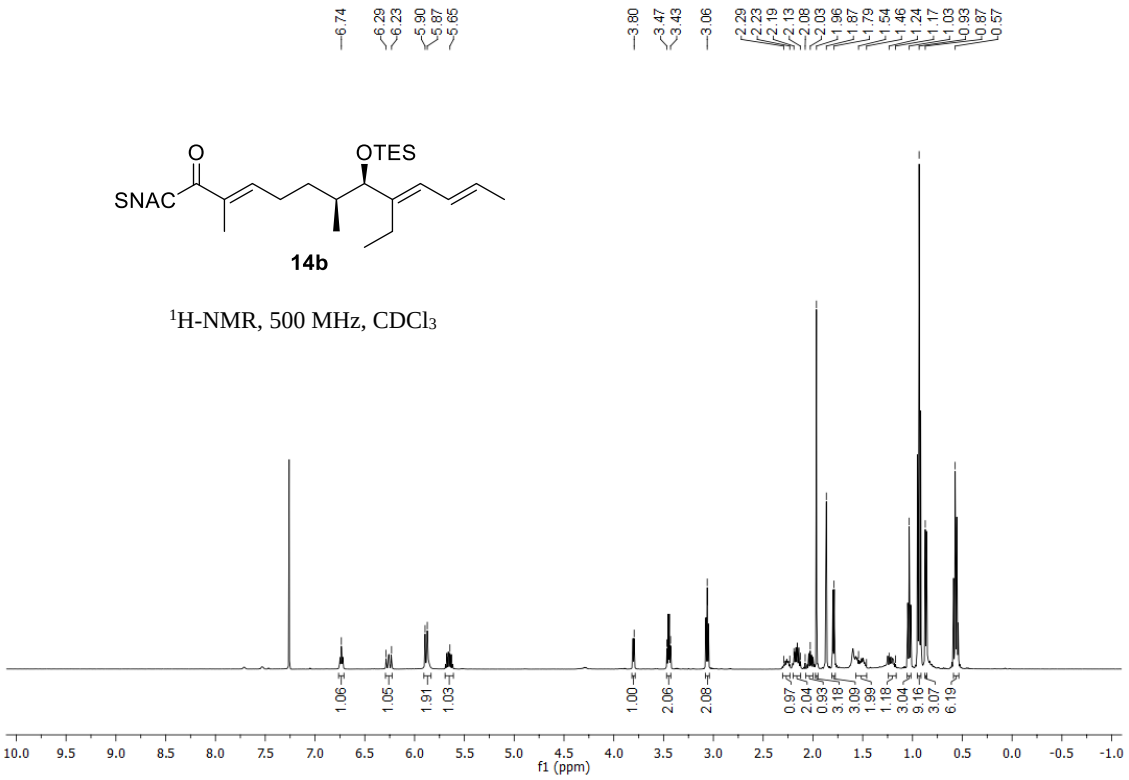


Figure **S37**: ^{1}H-NMR-spectrum of α,β-unsaturated thioester **14b** in $CDCl_3$.

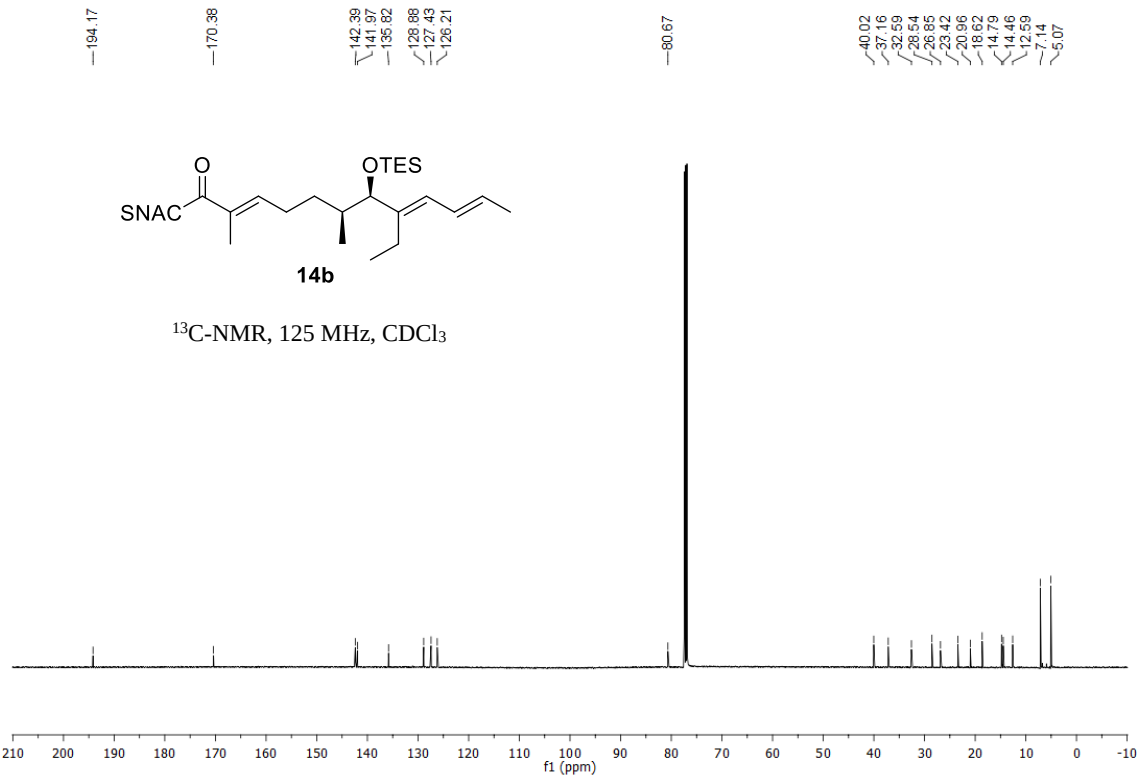
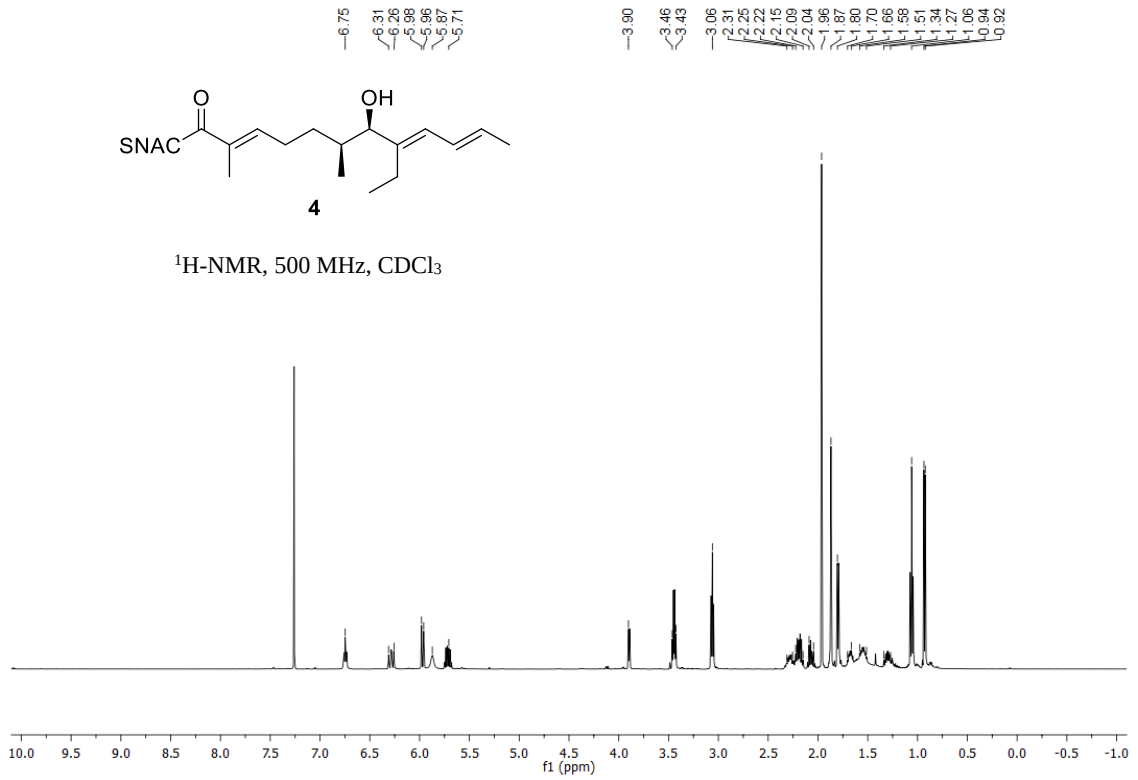
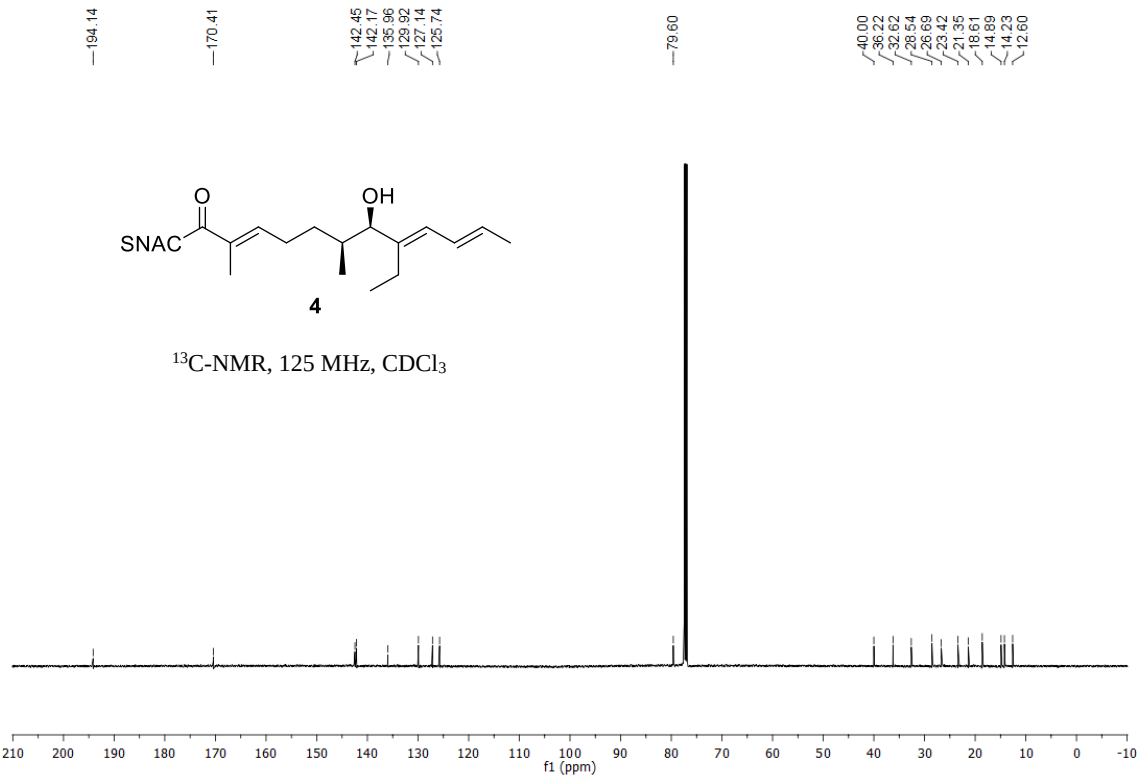


Figure **S38**: ^{13}C-NMR-spectrum of α,β-unsaturated thioester **14b** in $CDCl_3$.



^{1}H-NMR, 500 MHz, $CDCl_3$

Figure **S39**: ^{1}H-NMR-spectrum of α,β-unsaturated thioester **4** in $CDCl_3$.



^{13}C-NMR, 125 MHz, $CDCl_3$

Figure **S40**: ^{13}C-NMR-spectrum of α,β-unsaturated thioester **4** in $CDCl_3$.