Supplementary Materials for

Light–driven reductive cyclization catalyzed by vitamin B_{12}-based artificial photoenzymes

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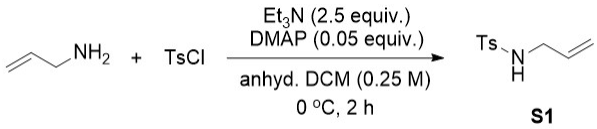
I. Materials and Methods

1. General methods

All chemicals were purchased from Sigma-Aldrich, Alfa Aesar, Combi-Blocks, and Tokyo Chemical Industry, and used as received. In particular, serum albumins were purchased as lyophilized powder from Sigma-Aldrich. Dried solvents (DCM, THF, diethyl ether and MeCN) were drawn from GlassContour Solvent Dispensing System. All reactions requiring anhydrous conditions were carried out under argon atmosphere using oven-dried glassware unless otherwise stated. Reaction progress was monitored using Merck 60 F254, 0.25 µm silica gel plates (TLC plates) and spots were visualized by UV and/or potassium permanganate, and/or ceric ammonium molybdate and/or ninhydrin stain. Flash column chromatography was carried out using Merck 60 F254, 0.040-0.063 µm silica gel. Preparative TLC chromatography was carried out using Merck 60 F254, 0.25 µm silica gel plates. Names of structures were generated using ChemBioDraw Ultra 21.0.0.28. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) were recorded on Bruker AVANCE III 400 MHz with DCH CryoProbe. Chemical shifts are reported in parts per million (ppm) on the delta (δ) scale. Chemical shifts for protons were referenced to residual protium in the NMR solvent ($CDCl_3$: 7.26 ppm; CD_2Cl_2: 5.32 ppm; CD_3OD: 3.31). Chemical shifts for carbon were referenced to the carbon resonances of the NMR solvent ($CDCl_3$: 77.16 ppm; CD_2Cl_2: 53.84 ppm; CD_3OD: 49.0 ppm). NMR spectra were processed using MestReNova 12.0.2. Data is presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentat, dd = doublet of doublets, ddd = doublet of doublets of doublets, td = triplet of doublets, m = multiplet, etc), integration and coupling constants (*J*) in Hertz (Hz). HRMS-ESI (high resolution mass spectrometry-electrospray ionization) spectra were recorded using Agilent 6545B TOF (time-of-flight) mass spectrometer. GC-MS (gas chromatography–mass spectrometry) analyses were obtained on an Agilent 7890A GC equipped with Agilent 5975C Inert XL MSD with Triple-Axis Detector and HP-5ms Ultra Inert column (30 m x 0.25 mm ID x 0.25 µm). Chiral HPLC analyses were obtained on Agilent 1260 Infinity equipped with CHIRALPAK® IE column (250 mm x 4.6 mm ID x 5 µm). ICP-OES (inductively coupled plasma–optical emission spectroscopy) analyses were performed with Perkin Elmer Avio 200 ICP-OES.

2. Preparation of substrates

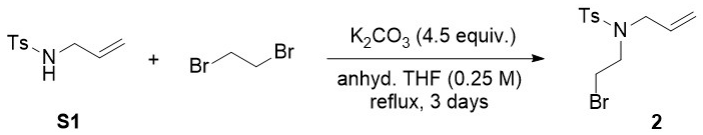
***N*-allyl-4-methylbenzenesulfonamide (S1)**



To a round-bottomed flask (RBF) was added allylamine (3.3 mL, 44.1 mmol, 1.2 equiv.) and anhydrous DCM (147 mL). The flask was cooled to 0°C, followed by the addition of Et_3N (9.3 mL, 91.8 mmol, 2.5 equiv.) and DMAP (224.3 mg, 1.84 mmol, 0.05 equiv.). Tosyl chloride (7.0 g, 36.7 mmol) was subsequently added, and the mixture stirred at 0°C for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution, washed with brine, dried over sodium sulphate, filtered and concentrated *in vacuo* to afford **S1** (7.76 g; 97%) as a crude yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.71 (m, 2H), 7.36 – 7.28 (m, 2H), 5.73 (ddt, *J* = 17.1, 10.2, 5.8 Hz, 1H), 5.17 (dtd, *J* = 17.1, 1.6, 1.1 Hz, 1H), 5.11 (dq, *J* = 10.2, 1.3 Hz, 1H), 4.36 (s, 1H), 3.59 (t, *J* = 5.6 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 137.1, 133.1, 129.9 (2C), 127.3 (2C), 117.9, 46.0, 21.7.

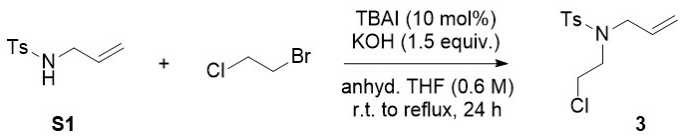
***N*-allyl-*N*-(2-bromoethyl)-4-methylbenzenesulfonamide (2)**



To a 2-neck RBF containing crude *N*-allyl-4-methylbenzenesulfonamide **(S1)** (7.54 g, 35.7 mmol) in anhydrous THF (143 mL) under argon atmosphere, was added K_2CO_3 (14.8 g, 107.1 mmol, 3 equiv.) and 1,2-dibromomethane (18.8 mL, 99.9 mmol, 2.8 equiv.). The mixture was refluxed for 18 h. Additional K_2CO_3 (7.4 g, 53.5 mmol, 1.5 equiv.) and 1,2-dibromomethane (10.06 mL,53.5 mmol, 1.5 equiv.) were added to the flask and the refluxing continued for another 2 days. The reaction mixture was filtered and rinsed down with diethyl ether. The filtered organics was washed twice with saturated NH_4Cl, followed by a brine wash. Then the organic fraction was dried over sodium sulfate, filtered, concentrated in *vacuo*, and azeotroped thrice with toluene. The residue was purified by silica gel flash chromatography (gradient elution from 0:100 to 15:85 with **2** eluting from 7.5:92.5 to 15:85 diethyl ether-hexanes) to afford **2** (9.03 g, 78%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.66 (m, 2H), 7.37 – 7.28 (m, 2H), 5.68 (ddt, *J* = 17.4, 9.8, 6.5 Hz, 1H), 5.24 – 5.19 (m, 1H), 5.18 (t, *J* = 1.3 Hz, 1H), 3.82 (dt, *J* = 6.5, 1.3 Hz, 2H), 3.53 – 3.37 (m, 4H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 136.4, 133.0, 130.0 (2C), 127.3 (2C), 119.9, 52.2, 49.1, 29.4, 21.7. The NMR data were in good agreement with literature.[1, 2]

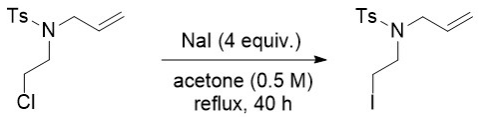
***N*-allyl-*N*-(2-chloroethyl)-4-methylbenzenesulfonamide (3)**



To a sealed tube containing crude *N*-allyl-4-methylbenzenesulfonamide **(S1)** (8 g, 37.9 mmol) in anhydrous THF (63 mL) was added KOH (3.2 g, 56.8 mmol, 1.5 equiv.), 1-bromo-2-chloroethane (1.72 mL, 56.8 mmol, 1.5 equiv.) and TBAI (1.4 g, 3.79 mmol, 10 mol%). The reaction was stirred at r.t. for 16 h, before refluxing for another 8 h. The reaction mixture was cooled to r.t., filtered over celite and rinsed down with diethyl ether. The filtered organics was washed twice with saturated NH_4Cl, followed by a brine wash. Then the organic fraction was dried over sodium sulfate, filtered, and concentrated in *vacuo*. The residue was purified by silica gel flash chromatography (gradient elution from 0:100 to 10:90 with **3** eluting from 8:92 to 10:90 ethyl acetate-hexanes) to afford **3** (10.37 g, 92%, containing ~5% of **2**) as a yellow oil.

^{1}H NMR (400 MHz, $CdCl_3$) δ 7.78 – 7.64 (m, 2H), 7.40 – 7.28 (m, 2H), 5.67 (ddt, *J* = 17.4, 9.7, 6.5 Hz, 1H), 5.21 (dq, *J* = 6.4, 1.3 Hz, 1H), 5.18 (t, *J* = 1.3 Hz, 1H), 3.83 (dt, *J* = 6.5, 1.3 Hz, 2H), 3.62 (dd, *J* = 8.0, 6.8 Hz, 2H), 3.37 (dd, *J* = 8.0, 6.8 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8, 136.5, 133.0, 130.0 (2C), 127.4 (2C), 119.8, 52.3, 48.9, 41.9, 21.7. The NMR data were in good agreement with literature.[3]

***N*-allyl-*N*-(2-iodoethyl)-4-methylbenzenesulfonamide (4)**

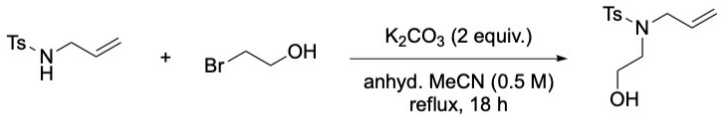


3 4

To a sealed tube containing *N*-allyl-N-(2-chloroethyl)-4-methylbenzenesulfonamide **(3)** (4.5 g, 14.44 mmol) dissolved in acetone (33 mL) was added NaI (9.85 g, 65.8 mmol, 4 equiv.) and refluxed for 40 h. The reaction mixture was cooled to r.t., filtered and concentrated in *vacuo*. The residue was re-suspended in DCM, and washed with saturated NH_4Cl twice, followed by brine, dried over sodium sulfate, filtered and concentrated in *vacuo*. The residue was purified by silica gel flash chromatography (gradient elution from 0:100 to 25:75 with **4** eluting from 15:85 to 25:75 diethyl ether-hexanes) to afford **4** (5.12 g, 85%) as a yellow oil, turning to a yellow solid overtime.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.66 (m, 2H), 7.40 – 7.29 (m, 2H), 5.68 (ddt, *J* = 17.4, 9.9, 6.5 Hz, 1H), 5.21 (dq, *J* = 5.7, 1.3 Hz, 1H), 5.17 (t, *J* = 1.4 Hz, 1H), 3.79 (dt, *J* = 6.5, 1.4 Hz, 2H), 3.49 – 3.38 (m, 2H), 3.28 – 3.18 (m, 2H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8, 136.5, 133.1, 130.0 (2C), 127.3 (2C), 119.8, 51.9, 50.3, 21.7, 2.1. The NMR data were in good agreement with literature.[3]

***N*-allyl-*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide (S2)**



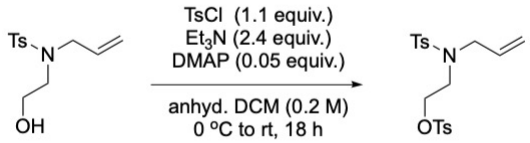
S1 S2

To a sealed tube containing crude *N*-allyl-4-methylbenzenesulfonamide **(S1)** (5 g, 23.7 mmol) dissolved in anhydrous MeCN (47 mL) under argon atmosphere, was added K_2CO_3 (9.8 g, 71.0 mmol, 3 equiv.) and 2-bromoethanol (3.36 mL, 47.3 mmol, 2 equiv.) and the reaction was refluxed for 18 h. The reaction mixture was

cooled to r.t., filtered over celite and rinsed down with diethyl ether. The filtered organics was washed with saturated NH_4Cl twice, followed by brine, dried over sodium sulfate, filtered and concentrated in *vacuo*. The residue was purified by silica gel flash chromatography (gradient elution from 0:100 to 50:50 with **S1** eluting from 20:80 to 25:75 ethyl acetate-hexanes and **S2** eluting from 35:65 to 45:55 ethyl acetate-hexanes) to recover **S1** (2.28 g, 46%) as a yellow solid and to afford **S2** (1.98 g; 33%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.67 (m, 2H), 7.37 – 7.28 (m, 2H), 5.76 – 5.60 (m, 1H), 5.26 – 5.16 (m, 2H), 5.20 – 5.13 (m, 2H), 3.85 (dq, *J* = 6.5, 1.4 Hz, 2H), 3.78 – 3.69 (m, 2H), 3.24 (t, *J* = 5.4 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8, 136.4, 133.2, 130.0 (2C), 127.4 (2C), 119.5, 61.2, 52.4, 49.9, 21.7. The NMR data were in good agreement with literature.[2]

2-((*N*-allyl-4-methylphenyl)sulfonamido)ethyl 4-methylbenzenesulfonate (5)

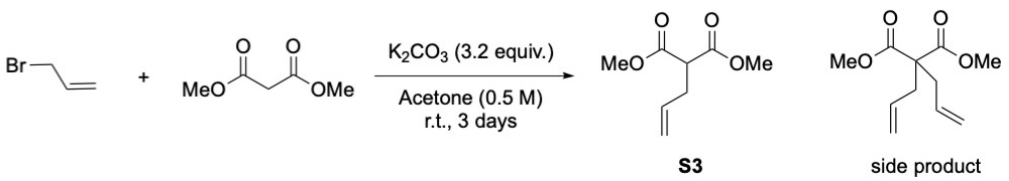


S2 **5**

To a RBF containing *N*-allyl-*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide **(S2)** (1.98 g, 7.7 mmol) in anhydrous DCM (39 mL) was added Et_3N (2.6 mL, 18.6 mmol, 2.4 equiv.) and DMAP (47.4 mg, 0.39 mmol, 0.05 equiv.) and the reaction was cooled to 0 °C. Tosyl chloride (1.63 g, 8.5 mmol, 1.1 equiv.) was then added and stirred for 18 h, allowing the ice-bath to expire. The reaction mixture was quenched with saturated NH_4Cl, washed with brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (gradient elution from 0:100 to 25:75 with **5** eluting from 20:80 to 25:75 ethyl acetate-hexanes) to afford **5** (2.2 g; 69%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.74 (m, 2H), 7.68 – 7.61 (m, 2H), 7.39 – 7.32 (m, 2H), 7.32 – 7.27 (m, 2H), 5.56 (ddt, *J* = 17.5, 9.7, 6.5 Hz, 1H), 5.16 (q, *J* = 1.2 Hz, 1H), 5.14 – 5.10 (m, 1H), 4.13 (t, *J* = 6.3 Hz, 2H), 3.76 (dt, *J* = 6.6, 1.4 Hz, 2H), 3.35 (t, *J* = 6.3 Hz, 2H), 2.46 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2, 143.9, 136.3, 132.7, 132.5, 130.1 (2C), 130.0 (2C), 128.1 (2C), 127.4 (2C), 120.1, 68.4, 52.2, 45.7, 21.8, 21.7. HRMS (ESI-TOF, *m/z*): $[M+Na]^+$ Calcd for $C_{19}H_{23}NNaO_5S_2^+$ *m/z* 432.0910; Found 432.0892; $[M+H]^+$ Calcd for $C_{19}H_{24}NO_5S_2^+$ *m/z* 410.1090; Found 410.1075. IR: 1354, 1176, 1160, 987 cm^{-1}.

Dimethyl 2-allylmalonate (S3) & Dimethyl 2-allyl-2-(2-bromoethyl)malonate (6)

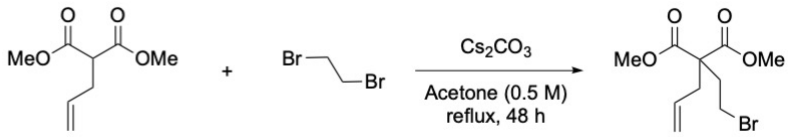


S3 side product

To a RBF containing allyl bromide (5 g, 41.3 mmol) dissolved in acetone (83 mL) was added dimethylmalonate (5.68 mL, 49.6 mmol, 1.2 equiv.) and K_2CO_3 (18.3 g, 132.3 mmol, 3.2 equiv.) and the reaction was stirred at r.t.

for 3 days. The reaction mixture was filtered and concentrated in *vacuo*. The residue was re-suspended in diethyl ether, washed with saturated NH_4Cl twice, followed by brine, dried over sodium sulfate, filtered and concentrated in *vacuo*. The residue was purified twice by silica gel flash chromatography (gradient elution from 0:100 to 8:92 with **S3** eluting from 4:96 to 6:94 diethyl ether-hexanes) to afford **S3** (4.13 g, 58%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.11 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.09 – 5.03 (m, 1H), 3.73 (s, 2 x 3H), 3.46 (t, *J* = 7.6 Hz, 1H), 2.70 – 2.60 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4 (2C), 134.0, 117.8, 52.7 (2C), 51.5, 33.0.

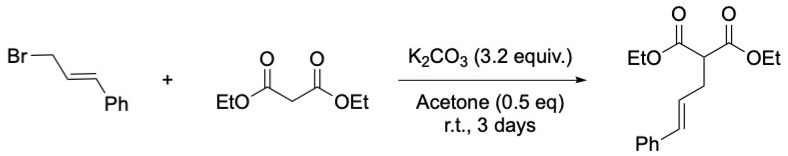


S3 **6**

To a sealed tube containing dimethyl 2-allylmalonate **(S3)** (4.13 g, 24.0 mmol) dissolved in acetone (48 mL) was added Cs_2CO_3 (14.1 g, 43.1 mmol, 1.8 equiv.) and 1,2-dibromomethane (3.1 mL, 35.9 mmol, 1.5 equiv.) and the reaction mixture was refluxed for 24 h. Additional Cs_2CO_3 (3.9 g, 12.0 mmol, 0.5 equiv.) and 1,2-dibromomethane (1.03 mL, 12.0 mmol, 0.5 equiv.) were added and the mixture refluxed for another 24 h. The reaction mixture was filtered through a silica plug and rinsed down twice with diethyl ether. The filtered organics was concentrated in *vacuo*, and azeotroped thrice with toluene. The residue was purified twice by silica gel flash chromatography (gradient elution from 0:100 to 8:92 with **6** eluting from 3:97 to 5:95 diethyl ether-hexanes) to afford **6** (3.11 g, 47%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (ddt, *J* = 17.1, 9.6, 7.4 Hz, 1H), 5.18 – 5.13 (m, 1H), 5.15 – 5.09 (m, 1H), 3.74 (s, 2 x 3H), 3.39 – 3.30 (m, 2H), 2.66 (dt, *J* = 7.4, 1.2 Hz, 2H), 2.49 – 2.40 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (2C), 131.8, 120.0, 57.8, 52.8 (2C), 38.1, 36.4, 27.1. The NMR data were in good agreement with literature.[1]

Diethyl 2-cinnamylmalonate (S4)

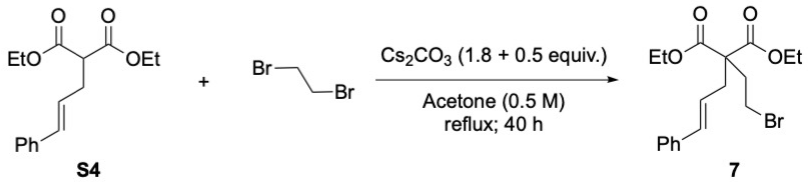


S4

To a RBF containing cinnamyl bromide (4.97 g, 25.23 mmol) dissolved in acetone (50 mL) was added diethylmalonate (5.36 mL, 35.3 mmol, 1.4 equiv.) and K_2CO_3 (11.2 g, 80.7 mmol, 3.2 equiv.) and the reaction was stirred at r.t. for 3 days. The reaction mixture was filtered and concentrated in *vacuo*, and the residue was re-suspended in diethyl ether, washed with saturated NH_4Cl twice, followed by brine, dried over sodium sulfate, filtered and concentrated in *vacuo*. The residue was purified twice by silica gel flash chromatography (gradient elution from 0:100 to 8:92 with **S4** eluting from 4:96 to 6:94 diethyl ether-hexanes) to afford **S4** (2.24 g, 29%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 4H), 7.22 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.48 (dt, *J* = 15.8, 1.5 Hz, 1H), 6.16 (dt, *J* = 15.8, 7.2 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.49 (t, *J* = 7.5 Hz, 1H), 2.80 (td, *J* = 7.4, 1.4 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 2 x 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1 (2C), 137.2, 132.9, 128.6 (2C), 127.5, 126.3 (2C), 125.7, 61.6 (2C), 52.2, 32.4, 14.3 (2C). The NMR data were in good agreement with literature.[4]

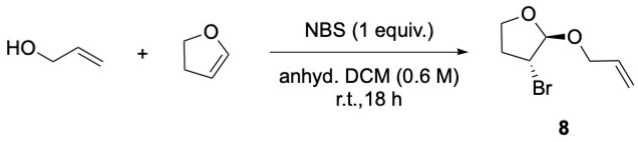
Diethyl 2-(2-bromoethyl)-2-cinnamylmalonate (7)



To a sealed tube containing diethyl 2-cinnamylmalonate **(S4)** (1.47 g, 5.32 mmol) dissolved in acetone (11 mL) was added Cs_2CO_3 (3.12 g, 9.58 mmol, 1.8 equiv.) and 1,2-dibromomethane (688 µL, 7.98 mmol, 1.5 equiv.) and the reaction was refluxed for 16 h. Additional Cs_2CO_3 (867 mg, 2.66 mmol, 0.5 equiv.) and 1,2-dibromomethane (229 µL, 2.66 mmol, 0.5 equiv.) were added and the mixture refluxed for another 24 h. The reaction mixture was filtered through a silica plug and rinsed down twice with diethyl ether. The filtered organics was concentrated in *vacuo*, and azeotroped thrice with toluene. The residue was purified twice by silica gel flash chromatography (gradient elution from 0:100 to 8:92 with **7** eluting from 3:97 to 5:95 diethyl ether-hexanes) to afford **7** (1.59 g, 78%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 4H), 7.25 – 7.19 (m, 1H), 6.47 (dt, *J* = 15.7, 1.4 Hz, 1H), 6.03 (dt, *J* = 15.8, 7.5 Hz, 1H), 4.22 (q, *J* = 7.1, 2H), 4.21 (q, *J* = 7.1, 2H), 3.46 – 3.36 (m, 2H), 2.81 (dd, *J* = 7.5, 1.4 Hz, 2H), 2.55 – 2.45 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 2 x 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (2C), 137.0, 134.6, 128.7 (2C), 127.7, 126.4 (2C), 123.4, 61.8 (2C), 58.1, 37.4, 36.7, 27.3, 14.2 (2C). HRMS (ESI-TOF, m/z): $[M+H]^+$ Calcd for $C_{18}H_{24}BrO_4^+$ m/z 383.0852; Found 383.0834. IR: 2982, 1728, 1446,1261, 1218, 1190, 750 cm^{-1}.

2-(Allyloxy)-3-bromotetrahydrofuran (8)

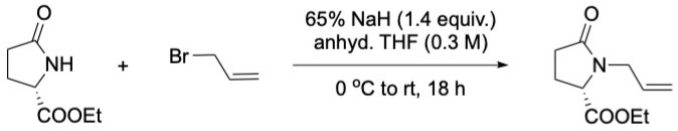


To a RBF containing allyl alcohol (1.45 g, 25.0 mmol) in anhydrous DCM (42 mL) at 0°C, was added 2,3-dihydrofuran (2.27 mL, 30.0 mmol, 1.2 equiv.) and NBS (4.45 g, 25.0 mmol, 1.0 equiv.) and the reaction was stirred at r.t. for 18 h, allowing the ice-bath to expire. The reaction mixture was quenched with saturated NH_4Cl, washed with brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (gradient elution from 0:100 to 3:97 with **8** eluting at 3:97 ethyl acetate-hexanes) to afford **8** (1.37 g; 27%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (dddd, *J* = 17.3, 10.4, 6.2, 5.3 Hz, 1H), 5.34 – 5.23 (m, 2H), 5.19 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.24 (dd, *J* = 5.9, 1.7 Hz, 1H), 4.22 – 4.15 (m, 2H), 4.18 – 4.11 (m, 2H), 4.07 (td, *J* = 8.5, 3.4 Hz, 1H), 3.98 (ddt, *J* = 12.8, 6.2, 1.4 Hz, 1H), 2.66 (dtd, *J* = 14.4, 8.5, 5.9 Hz, 1H), 2.22 (dddd, *J* = 14.0, 7.0, 3.4, 1.7 Hz, 1H). ^{13}C

NMR (101 MHz, $CDCl_3$) δ 134.2, 117.6, 108.1, 68.3, 66.9, 50.2, 34.1. The NMR data were in good agreement with literature.[1]

Ethyl (*S*)-1-allyl-5-oxopyrrolidine-2-carboxylate (S5)

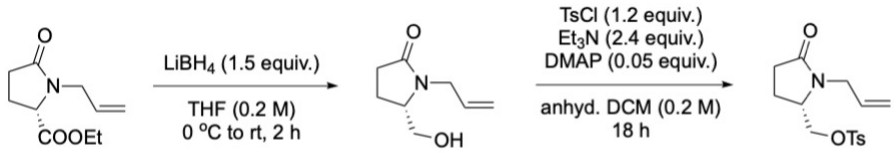


S5

To a heatgun-dried RBF containing ethyl L-pyroglutamate (4.75 g, 30.2 mmol) in anhydrous THF (101 mL) under argon atmosphere at 0 °C, was added 65% NaH (1.52 g, 42.3 mmol, 1.4 equiv.) in small portions and the mixture was stirred for 30 min. Allyl bromide (3.14 g, 36.3 mmol, 1.2 equiv.) was then added and the reaction was stirred at r.t. for 18 h. The reaction mixture was diluted with diethyl ether, quenched with saturated NH_4Cl, washed with brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. The resulting oil was passed through a silica plug with hexanes (discarded), followed by diethyl ether to afford **S5** (1.5 g, 25%) as a colourlesss oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (dddd, *J* = 16.9, 10.3, 7.5, 5.2 Hz, 1H), 5.23 – 5.16 (m, 1H), 5.16 (dq, *J* = 11.1, 1.4 Hz, 1H), 4.35 (ddt, *J* = 15.3, 5.2, 1.6 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.15 (dd, *J* = 9.1, 3.1 Hz, 1H), 3.55 (ddq, *J* = 15.2, 7.5, 1.1 Hz, 1H), 2.61 – 2.46 (m, 1H), 2.45 – 2.24 (m, 2H), 2.14 – 2.02 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 172.1, 132.2, 118.9, 61.6, 59.2, 44.6, 29.7, 23.1, 14.3. The NMR data were in good agreement with literature.[5]

(*S*)-1-allyl-5-(hydroxymethyl)pyrrolidin-2-one (S6) & (*S*)-(1-allyl-5-oxopyrrolidin-2-yl)methyl 4-methylbenzenesulfonate (S7)



S5 **S6** **S7**

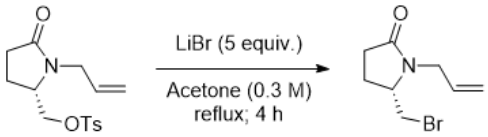
To a RBF containing ethyl (*S*)-1-allyl-5-oxopyrrolidine-2-carboxylate **(S5)** (1.5 g, 7.6 mmol) in anhydrous THF (38 mL) cooled to 0 °C, was added $LiBH_4$ (248 mg, 11.4 mmol, 1.5 equiv.). The mixture was stirred for 2 h, allowing the ice-bath to expire. A solution of HCl (200 µL, 6 N) was added and the mixture stirred until the effervescence ceased. Sodium sulphate was added, and then the mixture was filtered through a pack of celite, rinsed down with 1:1 DCM: EtOAc. The filtrate was further filtered through a 0.45 µm filter and concentrated *in vacuo* to afford crude **S6** (1.18 g, 100%) as a colourlesss oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 – 5.71 (m, 1H), 5.27 – 5.13 (m, 2H), 4.19 (ddt, *J* = 15.5, 5.4, 1.6 Hz, 1H), 3.80 (dd, *J* = 11.7, 3.6 Hz, 1H), 3.77 – 3.65 (m, 2H), 3.60 (dd, *J* = 11.7, 3.4 Hz, 1H), 2.60 – 2.45 (m, 1H), 2.41 – 2.29 (m, 1H), 2.12 (dddd, *J* = 13.1, 10.2, 8.5, 7.2 Hz, 1H), 1.98 (dddd, *J* = 13.0, 10.1, 5.5, 4.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 133.1, 118.1, 62.9, 59.4, 43.9, 30.5, 21.2. The NMR data were in good agreement with literature.[5]

To a RBF containing crude (*S*)-1-allyl-5-(hydroxymethyl)pyrrolidin-2-one **(S6)** (1.18 g, 7.6 mmol) in anhydrous DCM (38 mL) was added Et_3N (2.55 mL, 18.3 mmol, 2.4 equiv.) and DMAP (46.5 mg, 0.38 mmol, 0.05 equiv.) and the mixture was cooled to 0°C. Tosyl chloride (1.74 g, 9.1 mmol, 1.2 equiv.) was added and the mixture stirred for 18 h, allowing the ice-bath to expire. The reaction mixture was quenched with saturated NH_4Cl, washed with brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (gradient elution from 50:50 to 80:20 with **S7** eluting from 60:40 to 80:20 ethyl acetate-hexanes) to afford **S7** (1.9 g, 81%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.74 (m, 2H), 7.41 – 7.34 (m, 2H), 5.62 (dddd, *J* = 17.4, 10.2, 7.4, 5.0 Hz, 1H), 5.16 – 5.04 (m, 2H), 4.20 (ddt, *J* = 15.6, 5.0, 1.7 Hz, 1H), 4.11 – 3.98 (m, 2H), 3.81 (dq, *J* = 7.9, 3.9 Hz, 1H), 3.37 (ddq, *J* = 15.5, 7.4, 1.1 Hz, 1H), 2.46 (s, 3H), 2.46 – 2.37 (m, 1H), 2.38 – 2.25 (m, 1H), 2.21 – 2.08 (m, 1H), 1.87 (dddd, *J* = 13.4, 9.8, 4.7, 3.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 145.5, 132.6, 132.4, 130.2 (2C), 128.1 (2C), 118.5, 69.1, 56.0, 43.6, 29.8, 21.8, 21.4. HRMS (ESI-TOF, m/z): $[M+H]^+$ Calcd for $C_{15}H_{20}NO_4S^+$ m/z 310.1108; Found 310.1097. IR: 3662, 2968, 1686, 1361, 1174, 950, 859, 666 cm^{-1}.

(*S*)-1-allyl-5-(bromomethyl)pyrrolidin-2-one (9)

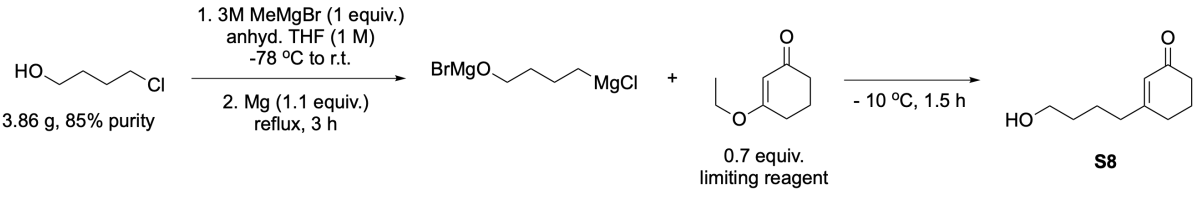


S7 **9**

To a sealed tube containing (*S*)-(1-allyl-5-oxopyrrolidin-2-yl)methyl 4-methylbenzenesulfonate **(S7)** (1.9 g, 6.14 mmol) in acetone (20 mL) was added LiBr (3.34 g, 30.7 mmol, 5 equiv.) and the mixture was refluxed for 4 h. The reaction mixture was cooled to r.t., concentrated in *vacuo*. The residue was re-suspended in 1:1 diethyl ether: DCM, filtered through 2 rounds of celite plug and concentrated in *vacuo*. The residue was purified by silica gel flash chromatography (gradient elution from 50:50 to 0:100 with **9** eluting from 50:50 to 100:0 diethyl ether-hexanes) to afford **9** (1.2 g, 90%) as a yellow glue.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 – 5.67 (m, 1H), 5.24 (dq, *J* = 7.7, 1.4 Hz, 1H), 5.20 (t, *J* = 1.4 Hz, 1H), 4.34 (ddt, *J* = 15.6, 5.0, 1.7 Hz, 1H), 3.90 (ddt, *J* = 8.5, 5.0, 3.6 Hz, 1H), 3.60 – 3.49 (m, 1H), 3.53 – 3.42 (m, 2H), 2.62 – 2.49 (m, 1H), 2.43 – 2.31 (m, 1H), 2.21 (dddd, *J* = 13.3, 10.4, 8.4, 7.2 Hz, 1H), 1.96 (dddd, *J* = 13.3, 10.3, 5.2, 4.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 132.7, 118.5, 57.3, 43.5, 35.1, 29.9, 23.2. HRMS (ESI-TOF, m/z): $[M+H]^+$ Calcd for $C_8H_{13}BrNO^+$ m/z 218.0175; Found 218.0148. IR: 3461, 2962, 1681, 1446, 1414, 1258, 926, 642 cm^{-1}.

3-(4-Hydroxybutyl)cyclohex-2-en-1-one (S8)

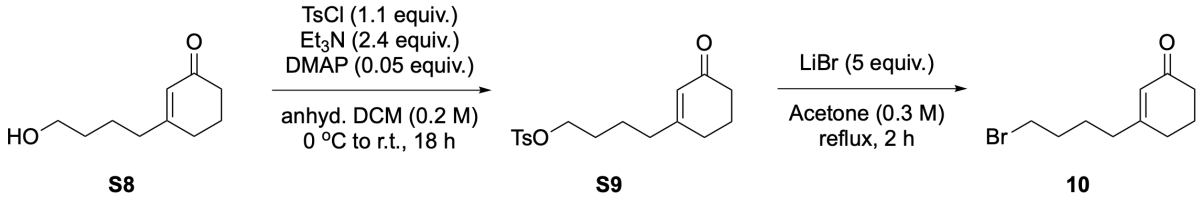


S8

To a heatgun-dried RBF containing 4-chloro-1-butanol (3.86 g, 35.6 mmol, 1.0 equiv.) in anhydrous THF (36 mL) under argon atmosphere cooled to -78 °C, was added 3 M MeMgBr in diethyl ether (11.85 mL, 35.6 mmol, 1.0 equiv.), and the mixture was warmed to r.t.. Mg turnings (0.95 g, 39.1 mmol, 1.1 equiv.) was then added and the reaction mixture refluxed for 3 h. The reaction mixture was cooled to -10 °C and 3-isobutoxycyclohex-2-en-1-one (3.49 g, 24.9 mmol, 0.7 equiv., limiting agent) was added. After stirring at -10 °C for 1.5 h, the reaction mixture was warmed to 0 °C, quenched with 2 N HCl, diluted with diethyl ether, washed with brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography 3 times (gradient elution from 30:70 to 70:30 with **S8** eluting from 45:55 to 50:50 ethyl acetate-hexanes) to afford **S8** (1.12 g, 27%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (t, *J* = 1.4 Hz, 1H), 3.72 – 3.61 (m, 2H), 2.40 – 2.31 (m, 2H), 2.33 – 2.19 (m, 4H), 2.04 – 1.90 (m, 2H), 1.65 – 1.50 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 166.3, 125.9, 62.6, 37.9, 37.5, 32.3, 29.8, 23.3, 22.8. The NMR data were in good agreement with literature.[6]

4-(3-Oxocyclohex-1-en-1-yl)butyl 4-methylbenzenesulfonate (S9) & 3-(4-bromobutyl)cyclohex-2-en-1-one (10)



S8 **S9** **10**

To a RBF containing 3-(4-hydroxybutyl)cyclohex-2-en-1-one **(S8)** (1.12 g, 6.66 mmol) in anhydrous DCM (33 mL) was added Et_3N (2.23 mL, 16.0 mmol, 2.4 equiv.) and DMAP (40.7 mg, 0.33 mmol, 0.05 equiv.), and the flask was cooled to 0°C. Tosyl chloride (1.4 g, 7.32 mmol, 1.1 equiv.) was added and the mixture stirred for 18 h, allowing the ice-bath to expire. The reaction mixture was quenched with saturated NH_4Cl, washed with brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (gradient elution from 10:90 to 40:60 with **S9** eluting from 30:70 to 40:60 ethyl acetate-hexanes) to afford **S9** (2.15 g, 82%) as a colourless oil (not stable; used immediately for next step).

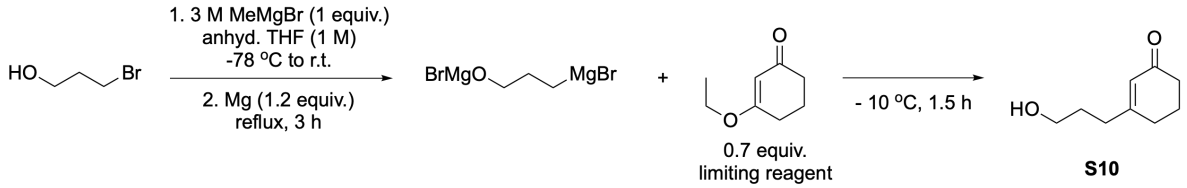
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.74 (m, 2H), 7.39 – 7.31 (m, 2H), 5.79 (t, *J* = 1.4 Hz, 1H), 4.04 (t, *J* = 6.1 Hz, 2H), 2.46 (s, 3H), 2.39 – 2.31 (m, 2H), 2.24 (t, *J* = 5.8 Hz, 2H), 2.17 (t, *J* = 7.5 Hz, 2H), 1.97 (p, *J* = 6.2 Hz, 2H), 1.72 – 1.61 (m, 2H), 1.57 – 1.48 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 165.3, 145.0, 133.2, 130.0 (2C), 128.0 (2C), 126.1, 70.1, 37.4, 37.3, 29.7, 28.5, 22.9, 22.8, 21.8. HRMS (ESI-TOF, m/z): $[M+H]^+$ Calcd for $C_{17}H_{23}O_4S^+$ m/z 323.1312; Found 323.1307.

To a sealed tube containing 4-(3-oxocyclohex-1-en-1-yl)butyl 4-methylbenzenesulfonate **(S9)** (1.76 g, 5.46 mmol) in acetone (18 mL) was added LiBr (2.97 g, 27.3 mmol, 5 equiv.) and the mixture was refluxed for 2 h. The reaction mixture was concentrated in *vacuo*, diluted with diethyl ether, filtered through a celite plug and concentrated in *vacuo*. The residue was purified by silica gel flash chromatography 3 times (gradient elution

from 10:90 to 50:50 with **10** eluting from 30:70 to 50:50 diethyl ether-hexanes) to afford **10** (1.06 g, 84%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (t, *J* = 1.4 Hz, 1H), 3.42 (t, *J* = 6.5 Hz, 2H), 2.36 (dd, *J* = 7.4, 6.0 Hz, 2H), 2.33 – 2.20 (m, 4H), 1.99 (p, *J* = 6.2 Hz, 2H), 1.93 – 1.81 (m, 2H), 1.74 – 1.61 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 165.5, 126.2, 37.5, 37.2, 33.3, 32.2, 29.7, 25.5, 22.8. HRMS (ESI-TOF, m/z): $[M+H]^+$ Calcd for $C_{10}H_{16}BrO^+$ m/z 231.0379; Found 231.0372. IR: 2942, 1664, 1251, 888 cm^{-1}.

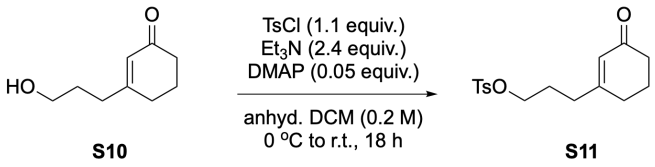
3-(3-Hydroxypropyl)cyclohex-2-en-1-one (S10)



To a heatgun-dried RBF containing 3-bromo-1-propanol (5 g, 36.0 mmol, 1.0 equiv.) in anhydrous THF (45 mL) under argon atmosphere cooled to -78 °C, was added 3 M MeMgBr in diethyl ether (12.0 mL, 36.0 mmol, 1.0 equiv.), and the flask was warmed to r.t.. Mg turnings (1.05 g, 43.2 mmol, 1.2 equiv.) was added and the reaction mixture refluxed for 3 h. The mixture was cooled to -10 °C. 3-Isobutoxycyclohex-2-en-1-one (3.53 g, 25.2 mmol, 0.7 equiv., limiting agent) was then added and the mixture stirred at -10 °C for 1.5 h. The reaction mixture was warmed to 0 °C and quenched with 2 N HCl, diluted with diethyl ether, washed with brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography 3 times (gradient elution from 30:70 to 80:20 with **S10** eluting at 60:40 ethyl acetate-hexanes) to afford **S10** (0.53 g, 14%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (t, *J* = 1.4 Hz, 1H), 3.67 (t, *J* = 6.3 Hz, 2H), 2.39 – 2.27 (m, 2+4H), 2.04 – 1.94 (m, 2H), 1.81 – 1.72 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 166.2, 125.8, 62.2, 37.4, 34.4, 29.9 (2C), 22.8. The NMR data were in good agreement with literature.[7]

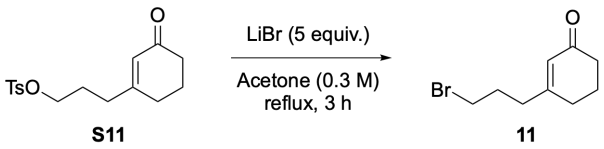
3-(3-Oxocyclohex-1-en-1-yl)propyl 4-methylbenzenesulfonate (S11)



To a RBF containing 3-(3-hydroxypropyl)cyclohex-2-en-1-one **(S10)** (530 mg, 3.44 mmol) in anhydrous DCM (17 mL) was added Et_3N (1.15 mL, 8.25 mmol, 2.4 equiv.) and DMAP (21 mg, 0.17 mmol, 0.05 equiv.) and the flask was cooled to 0°C. Tosyl chloride (721 mg, 8.25 mmol, 1.1 equiv.) was added and the mixture stirred for 18 h, allowing the ice-bath to expire. The reaction mixture was quenched with saturated NH_4Cl, washed with brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (gradient elution from 10:90 to 60:40 with **S11** eluting from 40:60 to 50:50 ethyl acetate-hexanes) to afford **S11** (766 mg, 72%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.71 (m, 2H), 7.40 – 7.31 (m, 2H), 5.78 – 5.72 (m, 1H), 4.04 (t, *J* = 6.1 Hz, 2H), 2.45 (s, 3H), 2.36 – 2.29 (m, 2H), 2.29 – 2.18 (m, 4H), 2.00 – 1.91 (m, 2H), 1.91 – 1.81 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.6, 164.1, 145.1, 133.0, 130.1 (2C), 128.0 (2C), 126.1, 69.5, 37.4, 33.8, 29.8, 26.3, 22.7, 21.8. The NMR data were in good agreement with literature.[8]

3-(3-Bromopropyl)cyclohex-2-en-1-one (11)

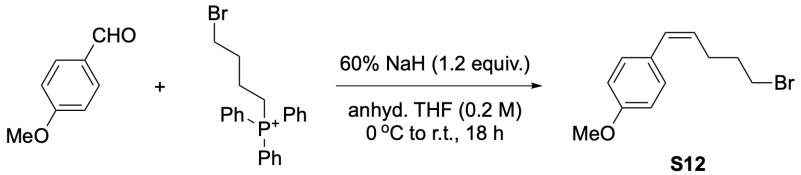


S11 **11**

To a sealed tube containing 3-(3-oxocyclohex-1-en-1-yl)propyl 4-methylbenzenesulfonate **(S11)** (766 mg, 2.48 mmol) in acetone (8 mL) was added LiBr (1.35 g, 12.4 mmol, 5 equiv.) and the mixture was refluxed for 3 h. The reaction mixture was concentrated in *vacuo*, diluted with diethyl ether, filtered through a celite plug and concentrated in *vacuo*. The residue was purified by silica gel flash chromatography (gradient elution from 10:90 to 50:50 with **11** eluting from 30:70 to 50:50 diethyl ether-hexanes) to afford **11** (425 mg, 79%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (p, *J* = 1.4 Hz, 1H), 3.42 (t, *J* = 6.5 Hz, 2H), 2.43 – 2.33 (m, 4H), 2.33 – 2.25 (m, 2H), 2.12 – 2.03 (m, 2H), 2.03 – 1.96 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 164.3, 126.3, 37.4, 36.3, 32.7, 29.9, 29.9, 22.8. HRMS (ESI-TOF, m/z): $[M+H]^+$ Calcd for $C_9H_{14}BrO^+$ m/z 217.0223; Found 217.0216. IR: 2945, 1666, 1257, 889, 753 cm^{-1}.

(*Z*)-1-(5-bromopent-1-en-1-yl)-4-methoxybenzene (S12)

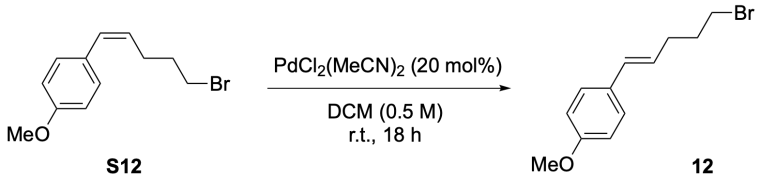


S12

To a heatgun-dried RBF containing (4-bromobutyl)triphenylphosphonium bromide (7.02 g, 17.6 mmol, 1.2 equiv.) in anhydrous THF (73 mL) under argon atmosphere cooled to 0 °C, was added 60% NaH (705 mg, 17.6 mmol, 1.2 equiv.) and the mixture was stirred for 30 min. *p*-Anisaldehyde (2 g, 14.7 mmol) was added and the reaction was stirred at r.t. for 18 h, allowing the ice-bath to expire. The reaction mixture was diluted with diethyl ether, quenched with saturated NH_4Cl, washed with brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (gradient elution from 0:100 to 2:98 with **S12** eluting from 0.5:99.5 to 2:98 diethyl ether-hexanes) to afford **S12** (1.57 g, 42%, *E:Z* ratio of 0.07 : 1) as a volatile colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.17 (m, 2H), 6.92 – 6.85 (m, 2H), 6.41 (dt, *J* = 11.6, 1.9 Hz, 1H), 5.52 (dt, *J* = 11.6, 7.2 Hz, 1H), 3.82 (s, 3H), 3.43 (t, *J* = 6.8 Hz, 2H), 2.48 (qd, *J* = 7.3, 1.8 Hz, 2H), 2.01 (dq, *J* = 8.6, 6.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 130.1, 130.1 (2C), 129.8, 129.1, 113.8 (2C), 55.4, 33.4, 33.2, 27.4. IR: 3006, 2956, 2835, 1607, 1509, 1248, 1175, 1035, 838, 742 cm^{-1}.[9]

(*E*)-1-(5-bromopent-1-en-1-yl)-4-methoxybenzene (12)



To a RBF containing (*Z*)-1-(5-bromopent-1-en-1-yl)-4-methoxybenzene **(S12)** (767 mg, 3.0 mmol) in DCM (6 mL) cooled to 0°C, was added $(MeCN)_2PdCl_2$ (156 mg, 0.6 mmol, 20 mol%) and NBS (4.45 g, 25.0 mmol, 1.0 equiv.) and the mixture was stirred at r.t. for 18 h. The reaction mixture was concentrated *in vacuo* and purified by silica gel flash chromatography (gradient elution from 0:100 to 2:98 with **12** eluting from 0.5:99.5 to 2:98 diethyl ether-hexanes) to afford **12** (684 mg, 89%, *E:Z* ratio of 1 : 0.035) as a volatile colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H), 6.86 – 6.80 (m, 2H), 6.39 (dt, *J* = 15.7, 1.5 Hz, 1H), 6.02 (dt, *J* = 15.8, 7.0 Hz, 1H), 3.80 (s, 3H), 3.46 (t, *J* = 6.7 Hz, 2H), 2.35 (qd, *J* = 7.1, 1.5 Hz, 2H), 2.02 (dq, *J* = 8.0, 6.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 130.8, 130.4, 127.3 (2C), 126.4, 114.1 (2C), 55.4, 33.4, 32.5, 31.4. The NMR data were in good agreement with literature.[9]

3. Preparation of proteins reconstituted with cyanocobalamin

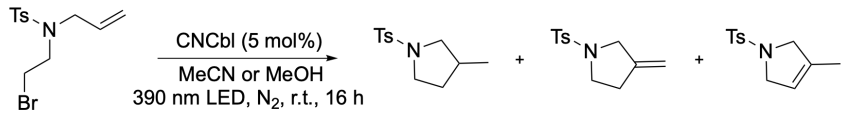
E. coli codon-optimized DNA sequences were synthesized by Twist Biosciences (USA). Subsequently, these genes were inserted into pET28a (+) using Golden Gate assembly and verified by 16S Sanger sequencing (Bio Basic Asia). Transformation of the 6×His tag construct for protein expression was carried out in *E. coli* XJb (DE3) (Zymo Research).

Colonies from the transformations were used to start 4 mL seed cultures in Luria broth (LB), which were shaken at 200 rpm, 37 ˚C overnight. The seed cultures (2 mL) were then used to inoculate 200 mL of LB in 1 L baffled Erlenmeyer flasks (Corning). The flasks were shaken at 200 rpm, 37 ˚C until the OD_{600} reached 0.4, at which point isopropyl β-D-1-thiogalactopyranoside (IPTG) was added to give a final concentration of 0.1 mM. The flasks were then shaken at 200 rpm, 16 ˚C for 16 hours before harvesting. Expression cultures were centrifuged at 5000 x g for 5 min to collect the pellets, which were then resuspended in 10 mL of lysis buffer containing 50 mM sodium phosphate, 150 mM sodium chloride, 0.1% Triton-X, at pH 7.0. The pellets were then lysed by 30 cycles of sonication at 20% amplitude using a 10 sec-on/30 sec-off duty cycle, after which they were centrifuged at 16000 x g for 20 min to pellet cellular debris. The supernatants were then transferred to tubes containing 2 mL of HisPur™ Ni-NTA resin (ThermoFisher) and incubated at 4 ˚C with rotation for 1 hour to allow complete binding of the recombinant proteins to the affinity resin.

Subsequently, the contents of the tubes were poured into Econo-Pac® gravity flow columns (Bio-Rad), and the resin was washed with 20 mL of wash buffer containing 50 mM Na_3PO_4, 150 mM NaCl and 50 mM imidazole, pH 7.0, then eluted in 5mL of elution buffer containing 50 mM Na_3PO_4, 150 mM NaCl and 250 mM imidazole, pH 7.0. The eluted proteins were concentrated, and buffer exchanged into 100 mM Na_3PO_4, pH 8.0 using Amicon

Ultra 15 mL, 10 kDa NMWL centrifugal filters (Merck Millipore), then snap frozen in liquid nitrogen and stored at -80˚C. Separately, a 12.5 mg/mL stock solution of cyanocobalamin (Sigma-Aldrich) in ultrapure water was prepared and stored at -20 ˚C. Immediately before use, the protein and cyanocobalamin solutions were thawed over ice. Once fully thawed, the cyanocobalamin solution was added to the protein to achieve a final protein: cyanocobalamin molar ratio of 1:3.

4. General procedure for reductive cyclization catalyzed by cobalamin in organic solvents



2 **2a** **2b** **2b'**

Procedure (1): A heatgun-dried glass vial containing cyanocobalamin (5.0 mol%), $NaBH_4$ (6.0 equiv.), $NaHCO_3$ (1.2 equiv.) and a stir bar, was evacuated and backfilled with argon thrice. Degassed acetonitrile (2 mL) containing **2** (0.2 mmol) and internal standard (1,3,5-trimethoxybenzene, 0.1 mmol) was added via microsyringe. The sealed vial was exposed to blue light (390 nm) and stirred at r.t. for 16 h. The reaction mixture was quenched with DI water, extracted with ethyl acetate (2 mL) thrice, dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was dissolved in $CDCl_3$ for ^1H NMR analysis and the determination of NMR yields of products was described in section I-8.

Procedure (2): A heatgun-dried glass vial containing cyanocobalamin (5.0 mol%), activated Zn (6.0 equiv.), NH_4Cl (3.5 equiv.) and a stir bar, was evacuated and backfilled with argon thrice. Degassed acetonitrile (2 mL) containing **2** (0.2 mmol) and internal standard (1,3,5-trimethoxybenzene, 0.1 mmol) was added via microsyringe. The sealed vial was exposed to blue light (390 nm) and stirred at r.t. for 16 h. The reaction mixture was quenched with DI water, extracted with ethyl acetate (2 mL) thrice, dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was dissolved in $CDCl_3$ for ^1H NMR analysis and the determination of NMR yields of products was described in section I-8.

5. General procedure for reductive cyclization catalyzed by cobalamin-serum albumin conjugates

Preparation of Ti (III) citrate buffer:

Two batches of titanium (III) chloride solution were used to prepare the Ti (III) citrate buffer used in this work. To ensure consistency of results, the concentration of Ti in commercial stock solutions was determined by ICP-OES. To a RBF containing titanium (III) chloride solution and sodium citrate was added ultrapure water, resulting in a final Ti^{3+} concentration of ~469.93 mM. Sodium carbonate was then carefully added, followed by adjustment of the pH to 8 with extra saturated sodium carbonate solution.

Sample Id	ICP-OES Ti 334.940 (mg/L)	$TiCl_3$ solution	Sodium Citrate	Ultrapure water	Sodium carbonate
SHBK 2947 (Sigma Aldrich)	67481.19	15 mL	9.76 g	30 mL	3 g
MKCT0610 (Sigma Aldrich)	40340.37	15 mL	9.76 g	12 mL	1.5 g

Procedure for analytical-scale reaction:

Stock solutions of serum albumin (1 mL, 0.36 mM in 0.1 M NaPi, pH 8) and cyanocobalamin (1 mL, 0.18 mM in 0.1 M NaPi, pH 8) were combined and incubated at 600 rpm for at least 30 min. An aliquot of albumin-cyanocobalamin conjugate (0.4 mL) was transferred to a glass vial and the vial was evacuated and backfilled with argon thrice. Titanium (III) citrate buffer (0.28 mL, 469.93 mM) was diluted with NaPi buffer (0.1 M) of the same pH and degassed, and 1.4 mL of the degassed buffer was added to the vial via syringe. Substrate (0.02 mmol) and internal standard (1,3,5-trimethoxybenzene, 50 mol% w.r.t substrate) were dissolved in degassed acetonitrile (0.2 mL) and added to the vial via microsyringe. The sealed vial was exposed to LED lamp (427 nm) and stirred at r.t. for 16 h. The reaction mixture was extracted with ethyl acetate (2 mL) three times, and the organic fractions were combined and concentrated *in vacuo*. The residue was dissolved in $CDCl_3$ and the mixture dried through a short pad of Na_2SO_4 for ^1H NMR analysis. The determination of NMR yields of products was described in section I-8.

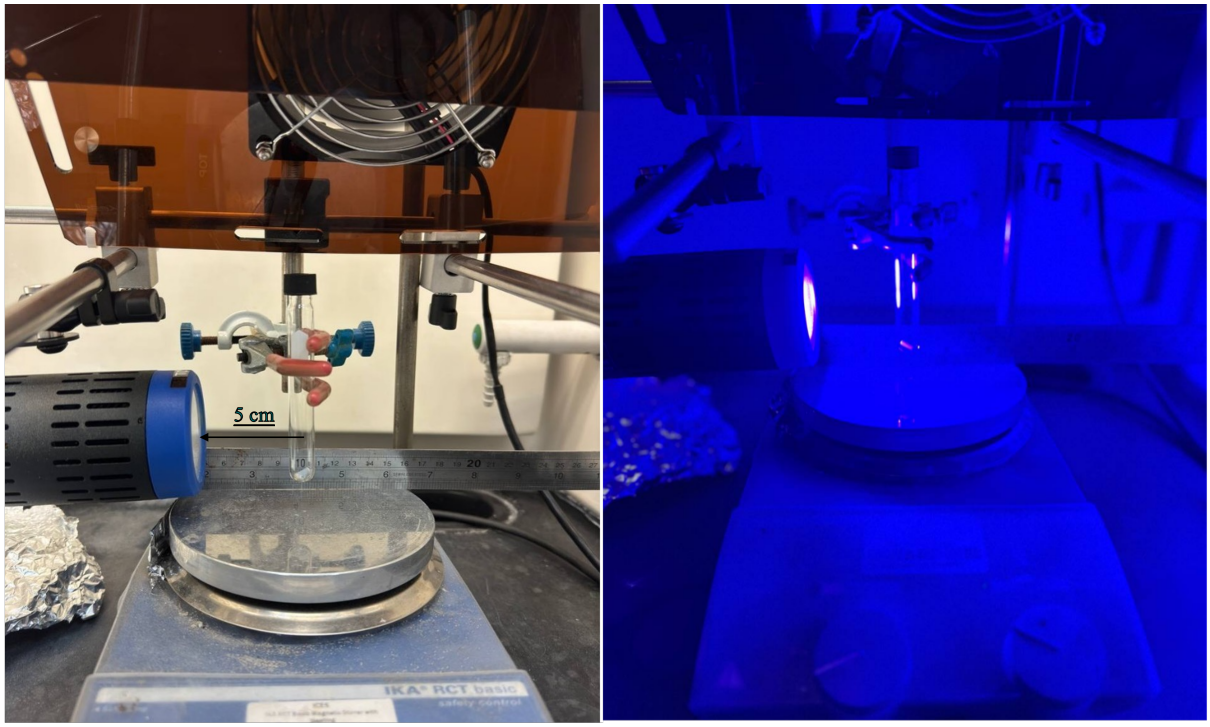


Figure A. Set-up of the analytical-scale photochemical reaction. Kessil LED lamps (PR160L) were used for all of our reactions. The distance between the LED lamp and the reaction vial is 5 cm and the lamp is set at 100% intensity.

Procedure for preparative-scale reaction:

Stock solutions of serum albumin (4 mL, 0.36 mM in 0.1 M NaPi, pH 8) and cyanocobalamin (4 mL, 0.18 mM in 0.1 M NaPi, pH 8) were combined and incubated at 600 rpm for at least 30 min. An aliquot of albumin-cyanocobalamin conjugate (4 mL) was transferred to a quartz tube and the tube was evacuated and backfilled with argon thrice. Titanium (III) citrate buffer (5.6 mL, 469.93 mM) was diluted with NaPi buffer (22.4 mL, 0.1 M, pH 8) and degassed, and 14 mL of the degassed buffer was added to the quartz tube via syringe. Substrate **4** (0.80 mmol) and internal standard (1,3,5-trimethoxybenzene, 50 mol% w.r.t substrate) were dissolved in degassed acetonitrile (4.0 mL) and 2 mL was added to the quartz tube via syringe. The sealed tube was exposed to dual LED lamps (427 nm) and stirred at r.t. for 16 h. This reaction was done in duplicates. The reaction mixture from each quartz tube was extracted with ethyl acetate (20 mL) three times, and the organic fractions were combined and concentrated *in vacuo*. The residue was dissolved in $CDCl_3$ and the mixture was dried through a short pad of anhydrous Na_2SO_4 for ^1H NMR analysis. The product was afforded as a white solid after purification on silica gel through flash chromatography (Hexane/EA, 4/1).

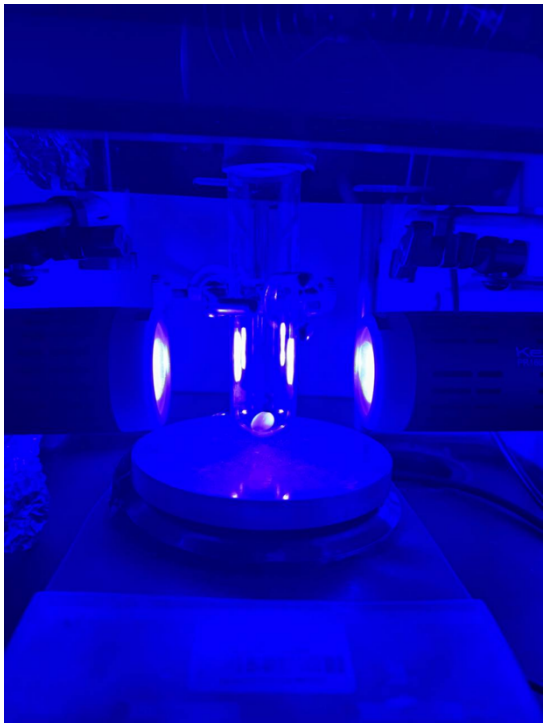


Figure B. Set-up of the preparative-scale photochemical reaction. Two Kessil LED lamps (PR160L) were used, with the Quartz reaction tube placed at the center. Both lamps were set at 100% intensity.

6. General procedure for reductive cyclization catalyzed by reconstituted proteins

A glass vial containing the stock solution of the reconstituted protein (32 nmol in NaPi buffer, with varying concentration and volume) was evacuated and backfilled with argon thrice. Titanium (III) citrate buffer (469.93 mM) was diluted with NaPi buffer (0.1 M, pH 8) and degassed, and the degassed buffer was added to the reaction vial to a final volume of 1.8 mL and a final concentration of 66 mM Ti^{3+}. Substrate (0.02 mmol) and internal

standard (1,3,5-trimethoxybenzene, 50 mol% w.r.t substrate) were dissolved in degassed acetonitrile (0.2 mL) and added to the vial via microsyringe. The sealed vial was exposed to LED lamp (427 nm) and stirred at r.t. for 16 h. The reaction mixture was extracted with ethyl acetate (2 mL) three times, and the organic fractions were combined and concentrated *in vacuo*. The residue was dissolved in $CDCl_3$ and the mixture dried through a short pad of Na_2SO_4 for ^1H NMR analysis. The determination of NMR yields of products was described in section I-8.

7. General procedure for Giese reaction catalyzed by cobalamin-serum albumin conjugates

Stock solutions of serum albumin (1 mL, 0.36 mM in 0.1 M NaPi, pH 8) and cyanocobalamin (1 mL, 0.18 mM in 0.1 M NaPi, pH 8) were combined and incubated at 600 rpm for at least 30 min. An aliquot of albumin-cyanocobalamin conjugate (0.4 mL) was transferred to a glass vial and the vial was evacuated and backfilled with argon thrice. Titanium (III) citrate buffer (0.28 mL, 469.93 mM) was diluted with NaPi buffer (0.1 M) of the same pH and degassed, and 1.4 mL of the degassed buffer was added to the vial via syringe. Substrate (0.02 mmol), methyl acrylate (1, 3 or 10 equiv.) and internal standard (1,3,5-trimethoxybenzene 50 mol% w.r.t substrate) were dissolved in degassed acetonitrile (0.2 mL) and added to the vial via microsyringe. The sealed vial was exposed to LED lamp (427 nm) and stirred at r.t. for 16 h. The reaction mixture was extracted with ethyl acetate (2 mL) three times, and the organic fractions were combined and concentrated *in vacuo*. The residue was dissolved in $CDCl_3$ and the mixture dried through a short pad of Na_2SO_4 for ^1H NMR analysis. The determination of NMR yields of products was described in section I-8.

8. NMR yield determination

NMR yields of the products were averaged from duplicate reactions and calculated using 1,3,5-trimethoxybenzene (50 mol% w.r.t substrate added) as an internal standard. The NMR spectrum obtained after reaction work-up was matched with the reference NMR spectra of the starting material and all its possible products, for identification of non-overlapping distinct peaks of each compound. For the analysis below, only the results from one of the duplicates are presented.

<u>Example of NMR yield determination for model substrate **2**</u>

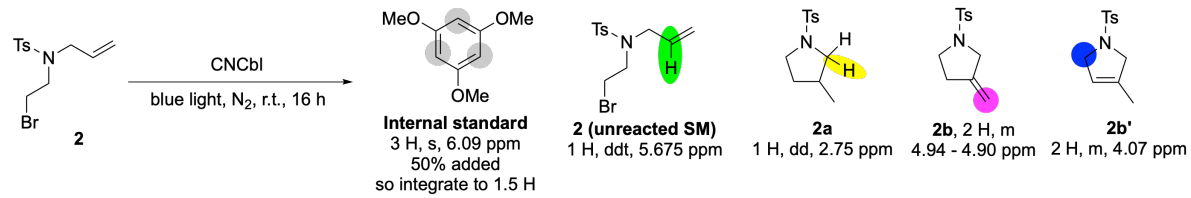
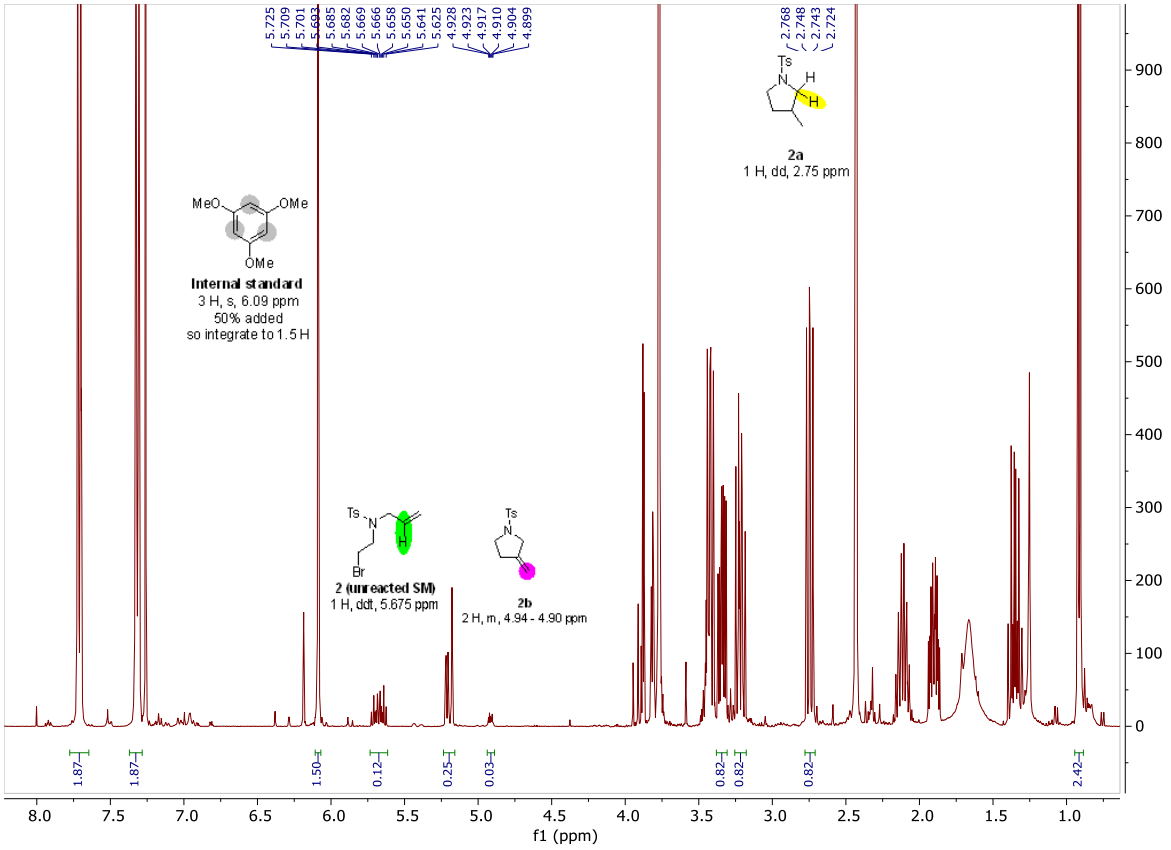


Table 1, Entry 1: Unreacted substrate **2** remained at 12%, while product **2a** and product **2b** were obtained in yields of 82% and 1.5%, respectively. Reference NMR spectra: **2** (section III), **2a** (section III), **2b**[10], **2b'**[11].



NMR yields for the rest of substrates

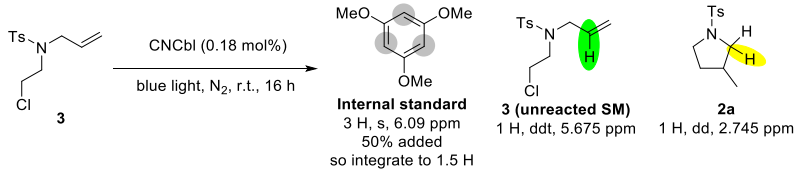


Table 4, Entry 1: Unreacted substrate **3** remained at 96%, while product **2a** was obtained in a yield of 4%. Reference NMR spectra: **3** (section III), **2a** (section III).

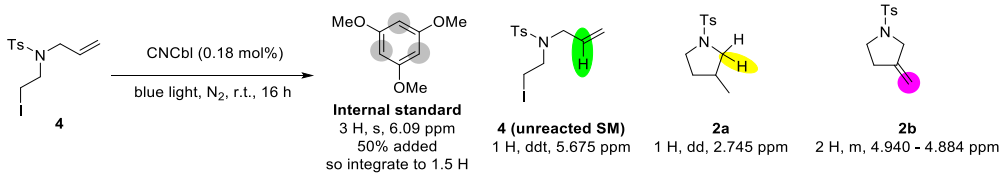


Table 4, Entry 2: Unreacted substrate **4** remained at 6%, while product **2a** and product **2b** were obtained in yields of 89% and 3%, respectively. Reference NMR spectra: **4** (section III), **2a** (section III), **2b**[10].

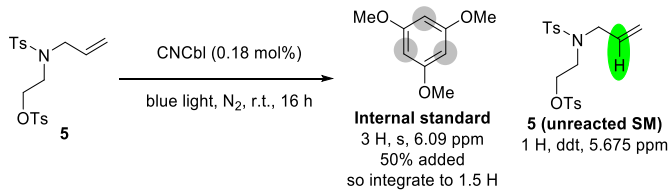


Table 4, Entry 3: Unreacted substrate **5** remained at 100%, with no formation of product **2a** or product **2b**. Reference NMR spectra: **5** (section III).

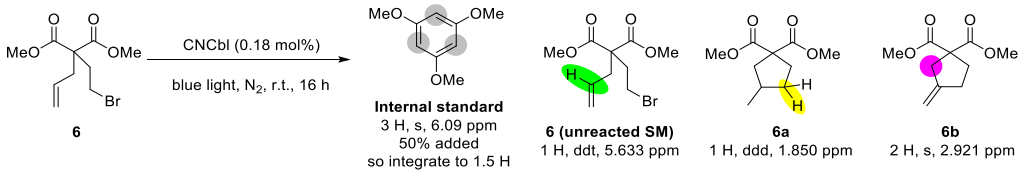


Table 4, Entry 4: Unreacted substrate **6** remained at 37%, while product **6a** and product **6b** were obtained in yields of 56% and 4%, respectively. Reference NMR spectra: **6** (section III), **6a**[12], **6b**[13].

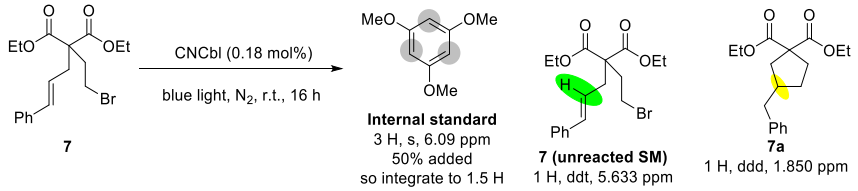


Table 4, Entry 5: Unreacted substrate **7** remained at 74%, while product **7a** was obtained in a yield of 21%. Reference NMR spectra: **7** (section III), **7a**[14].

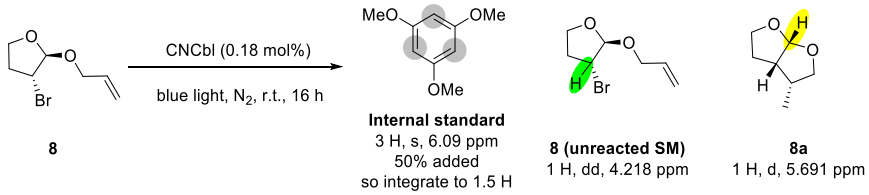


Table 4, Entry 6: Unreacted substrate **8** remained at 21%, while product **8a** was obtained in a yield of 47%. Reference NMR spectra: **8** (section III), **8a**[15].

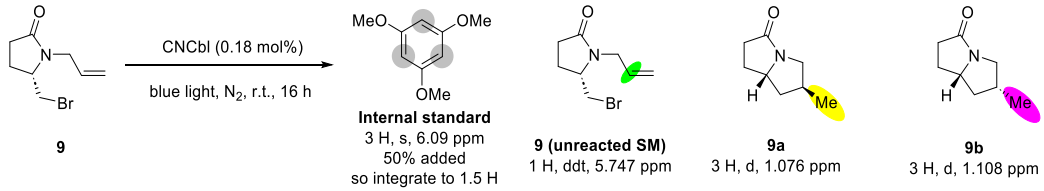


Table 4, Entry 7: Unreacted substrate **9** remained at 49%, while product **9a** and product **9b** were obtained in yields of 31% and 11%, respectively. Reference NMR spectra: **9** (section III), **9a**[16], **9b**[16].

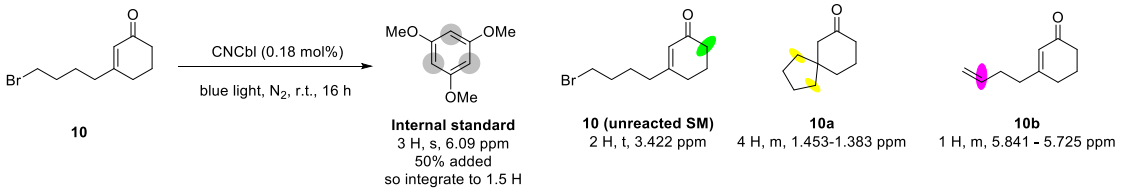


Table 4, Entry 8: Unreacted substrate **10** remained at 23%, while product **10a** and product **10b** were obtained in yields of 60% and 9%, respectively. Reference NMR spectra: **10** (section III), **10a**[19], **10b**[20].

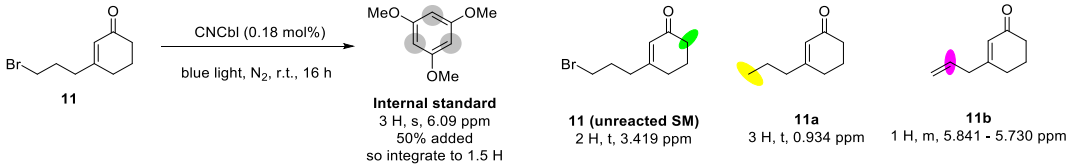


Table 4, Entry 9: Unreacted substrate **11** remained at 2%, while product **11a** and product **11b** were obtained in yields of 79% and 9%, respectively. Reference NMR spectra: **11** (section III), **11a**[21], **11b**[22].

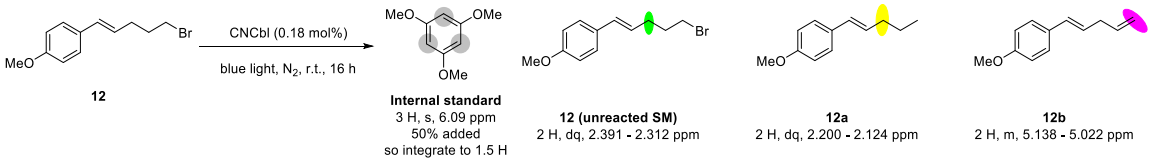
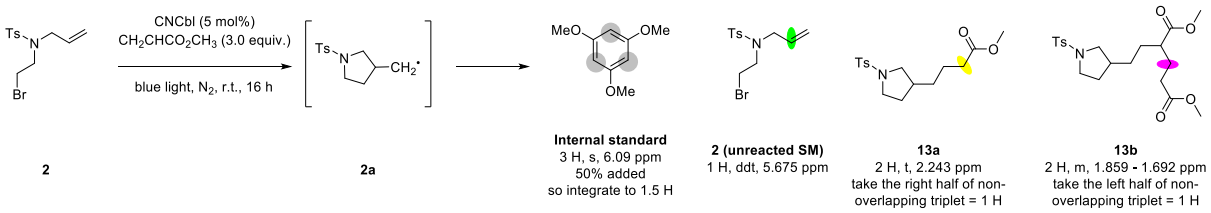


Table 4, Entry 10: Unreacted substrate **12** remained at 68%, while product **12a** and product **12b** were obtained in yields of 19% and 8%, respectively. Reference NMR spectra: **12** (section III), **12a**[17], **12b**[18].

Giese reaction catalyzed by cobalamin-serum albumin conjugates



The reaction was performed in 0.5 mmol scale and purified by silica gel flash chromatography (gradient elution from 30% to 60% with **13a** eluting from 30-35% diethyl ether/hexanes, and **13b** eluting from 40-45% diethyl ether/hexanes) to afford authentic **13a** and **13b** to identify non-overlapping distinct peaks **for NMR yield determination.**

Table 6, Entry 4: Unreacted substrate **2** remained at 61%, while product **13a** and product **13b** were obtained in yields of 20% and 20%, respectively. Reference NMR spectra: **2** (section III), **13a** (section III and ref[23]), **13b** (section III).

Product **13a:**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.65 (m, 2H), 7.38 – 7.27 (m, 2H), 3.64 (s, 3H), 3.46 – 3.38 (m, 1H), 3.32 (ddd, *J* = 9.7, 8.3, 3.5 Hz, 1H), 3.18 (ddd, *J* = 9.7, 8.6, 7.0 Hz, 1H), 2.77 (dd, *J* = 9.8, 7.9 Hz, 1H), 2.43 (s, 3H), 2.24 (t, *J* = 7.4 Hz, 2H), 2.05 – 1.86 (m, 2H), 1.62 – 1.47 (m, 2H), 1.44 – 1.32 (m, 1H), 1.30 – 1.20 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 143.5, 134.0, 129.7, 127.6, 53.2, 51.7, 47.6, 38.7, 34.0, 32.6, 31.4, 23.5, 21.6.

^{1}H NMR (400 MHz, CD_3OD) δ 7.75 – 7.68 (m, 2H), 7.46 – 7.39 (m, 2H), 3.63 (s, 3H), 3.46 – 3.37 (m, 1H), 3.19 (ddd, *J* = 9.9, 8.3, 7.0 Hz, 1H), 2.78 (dd, *J* = 10.0, 7.5 Hz, 1H), 2.45 (s, 3H), 2.24 (t, *J* = 7.3 Hz, 2H), 2.02 – 1.89 (m, 2H), 1.62 – 1.43 (m, 2H), 1.42 – 1.29 (m, 1H), 1.25 – 1.15 (m, 2H). 1 proton is hidden under CD_3OD. ^{13}C NMR (101 MHz, CD_3OD) δ 175.5, 145.2, 135.0, 130.8, 128.7, 54.3, 52.0, 39.8, 34.6, 33.4, 32.3, 24.4, 21.5. 1 carbon peak is hidden under CD_3OD.

HRMS (ESI-TOF, m/z): $[M+H]^+$ Calcd for $C_{16}H_{24}NO_4S^+$ m/z 326.1421 ; Found 326.1406.

Product **13b** (mixture of 2 sets of enantiomers):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.67 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.72 – 3.60 (s, 2 x 3H), 3.46 – 3.37 (m, 1H), 3.38 – 3.27 (m, 1H), 3.23 – 3.12 (m, 1H), 2.75 (ddd, *J* = 10.0, 8.0, 2.2 Hz, 1H), 2.44 (s, 3H), 2.38 – 2.19 (m, 2H + 1H), 2.03 – 1.87 (m, 2H), 1.89 – 1.72 (m, 2H), 1.62 – 1.49 (m, 1H), 1.47 – 1.30 (m, 2H), 1.28 – 1.18 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (175.6, 175.6), (173.3, 173.3), 143.4, (133.8, 133.8), 129.7, 127.5, 53.1, (51.7, 51.7, 51.7 - 2 x OMe), (47.5, 47.5), 44.6, 38.7, 31.6, (31.3, 31.3), (30.7, 30.6, 30.6 - 2C - 4 isomers), (27.1, 27.0), 21.5.

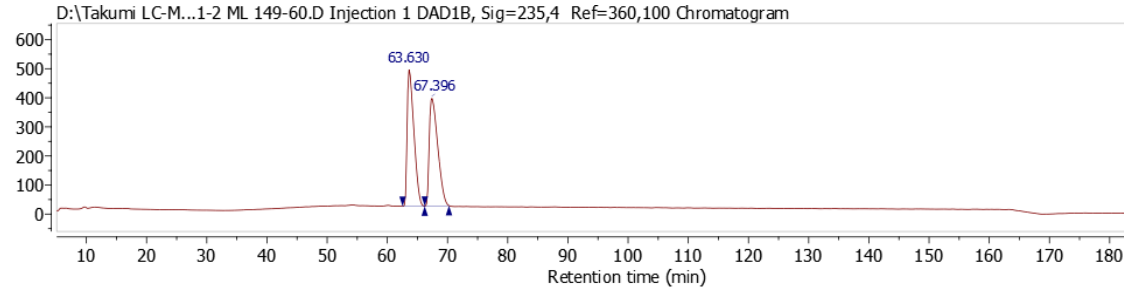
^{1}H NMR (400 MHz, CD_3OD) δ 7.74 – 7.68 (m, 2H), 7.45 – 7.39 (m, 2H), 3.67 – 3.58 (s 2 x 3H), 3.44 – 3.37 (m, 1H), 3.20 – 3.10 (m, 1H), 2.76 (dt, *J* = 10.0, 7.1 Hz, 1H), 2.45 (s, 3H), 2.37 – 2.22 (m, 2H + 1H), 2.01 – 1.87 (m, 2H), 1.86 – 1.66 (m, 2H), 1.59 – 1.46 (m, 1H), 1.44 – 1.32 (m, 2H), 1.22 – 1.07 (m, 2H). 1 proton is hidden under CD_3OD. ^{13}C NMR (101 MHz, CD_3OD) δ 176.0, 173.7, 143.8, 133.6, 129.5, 127.3, 52.9, 50.7, (44.5, 44.4), 38.5, 31.0, (30.8, 30.8), (30.2, 30.2, 30.2, 30.1 – 2 carbons), (26.9, 26.8), 20.1. 1 carbon peak is hidden under CD_3OD.

HRMS (ESI-TOF, m/z): $[M+H]^+$ Calcd for $C_{20}H_{30}NO_6S^+$ m/z 412.1788; Found 412.1776.

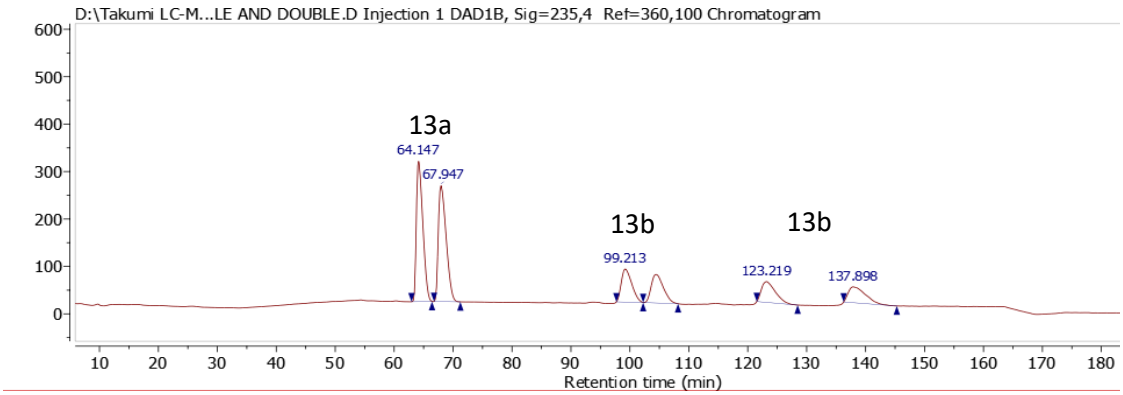
Chiral HPLC analysis was performed on the isolated products of **13a**, and **13b** with CHIRALPAK® IE column (250 mm x 4.6 mm ID x 5 µm) .

Time (min)	Hexane (%)	Isopropanol (%)	Flow (mL/min)
0	85	15	1.2
30	85	15	1.2
50	70	30	1.2
155	70	30	1.2
165	85	15	1.2
180	85	15	1.2

Mono-addition product **13a:** the chromatogram shows 2 enantiomers at 63.6 and 67.4 min.



Mono- and di-addition products **13a + 13b:** the chromatogram shows 2 sets of eneatiomers (4 diasetromers) for product **13b**.



II. Supplementary figures and tables

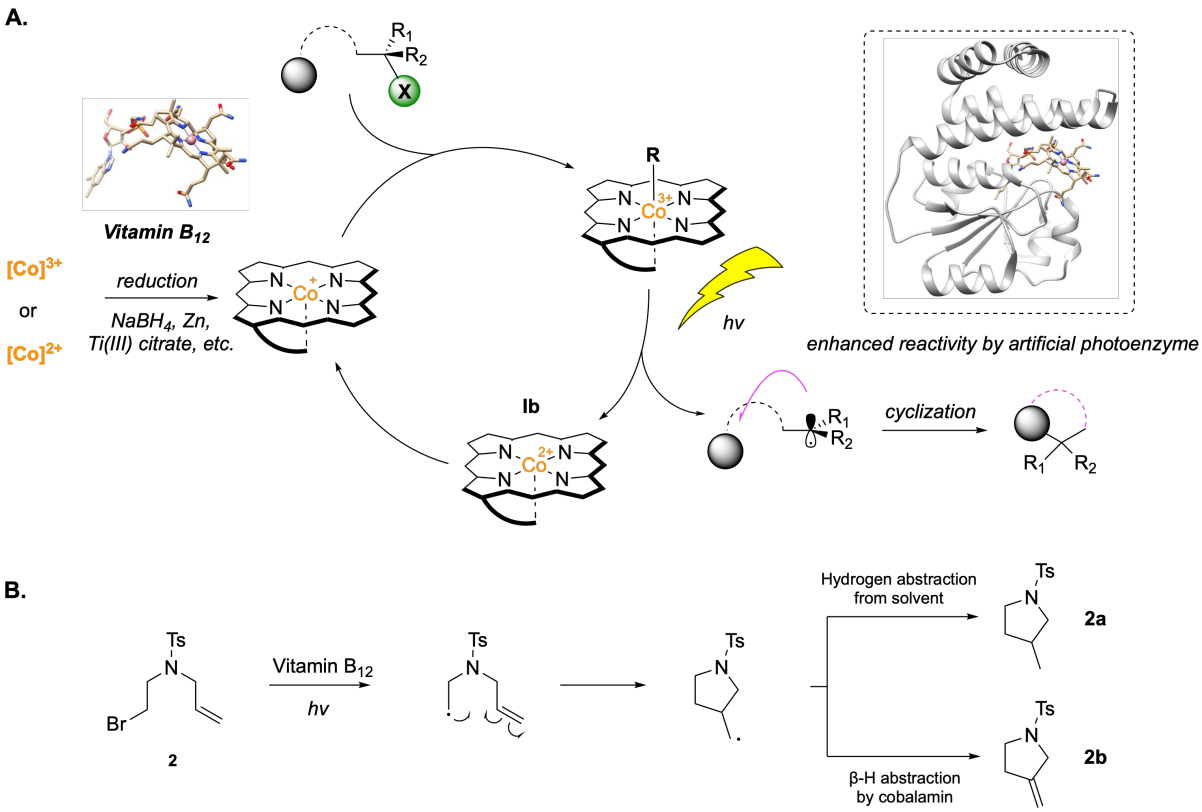
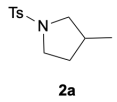
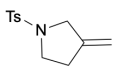
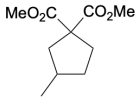
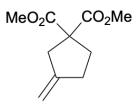
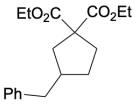


Figure S1. Proposed mechanism for photocyclization catalyzed by cobalamin-serum albumin conjugate.

Table S1. GC-MS methods for identification of reaction products.

Product	Column	Method	Retention Times
 **2a**	HP-5MS (30 m × 0.25 mm × 0.25 µm)	50 °C, 3 min; 50 °C to 280 °C, ramp = 20 °C/min; hold 2 min; 280 °C to 300 °C, ramp = 75 °C/min; hold 3 mins	t = 13.17 min (merged peaks)
 **2b**			
 **6a**			t = 8.74 min
 **6b**			t = 8.84 min
 **7a**			t = 13.34 min

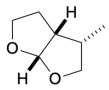
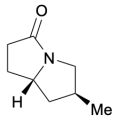
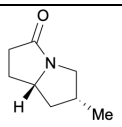
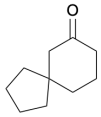
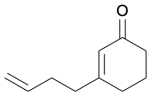
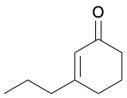
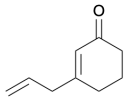
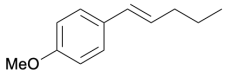
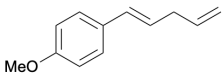
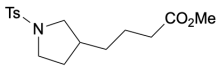
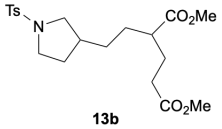
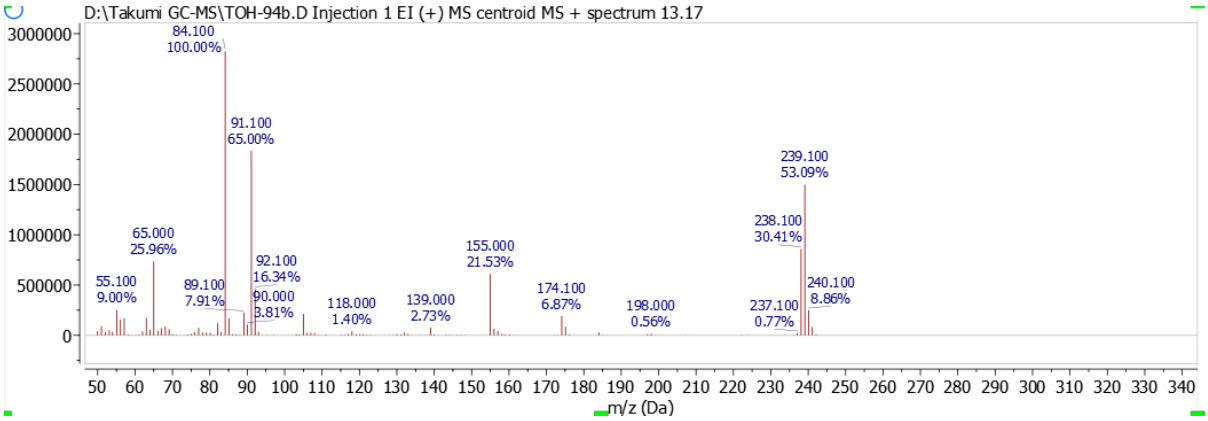
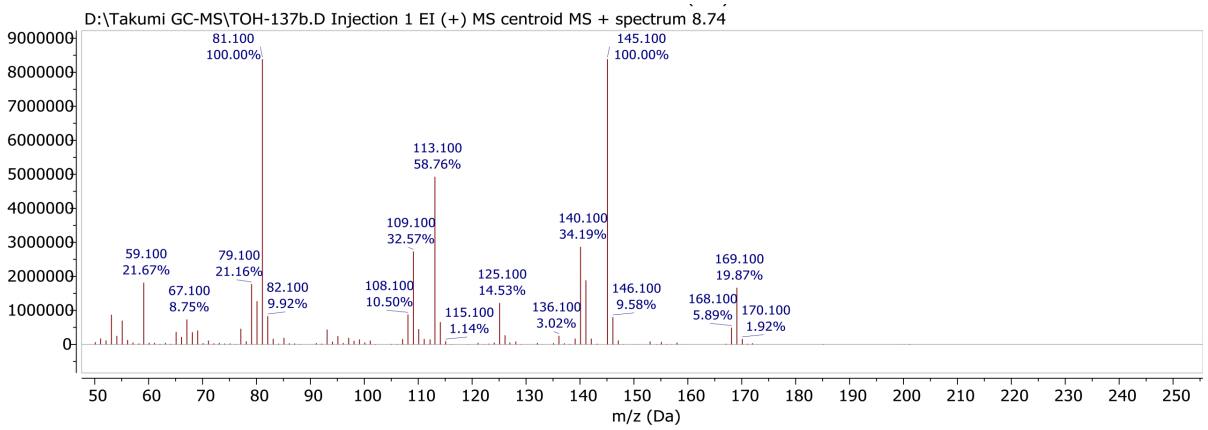
 **8a**		50 °C, 3 min; 50 °C to 280 °C, ramp = 20 °C/min; hold 2 min; 280 °C to 300 °C, ramp = 75 °C/min; hold 3 mins	t = 7.26 min
 **9a**			t = 9.21 min (merged peaks)
 **9b**			
 **10a**			t = 8.83 min
 **10b**			t = 9.25 min
 **11a**			t = 8.59 min
 **11b**			t = 8.43 min
 **12a**			t = 10.19 min
 **12b**			t = 10.15 min
 **13a**			t = 16.35 min
 **13b**			t = 19.49 min

Figure S2. EI-MS spectra for cyclization products from substrates 2-12, 13a and 13b.

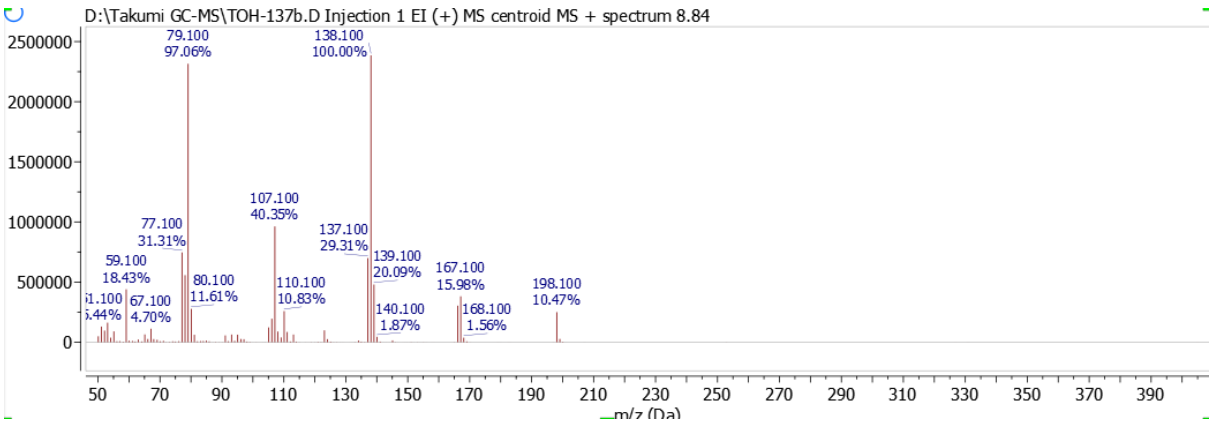
2a: $[M]^+$ 239.1



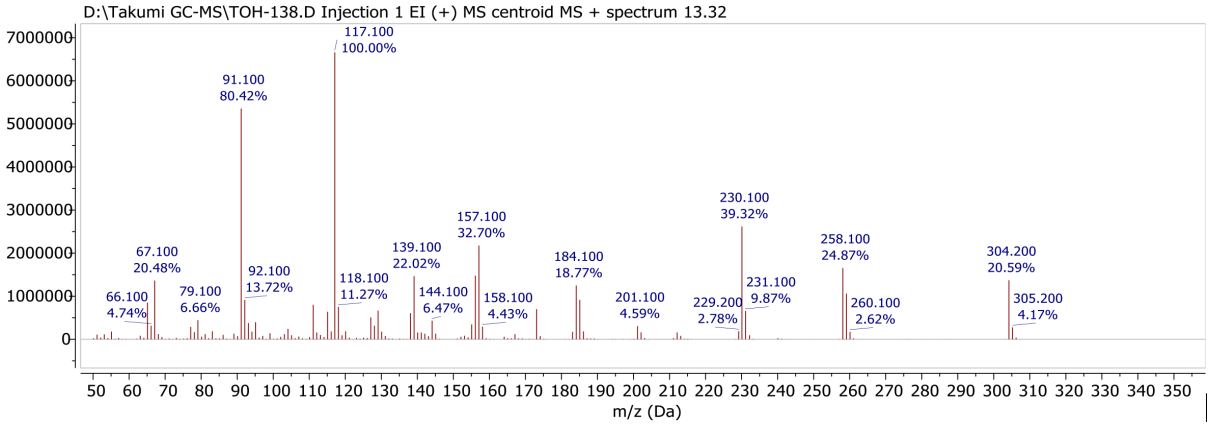
6a: $[M\text{-}OMe]^+$ 169.1



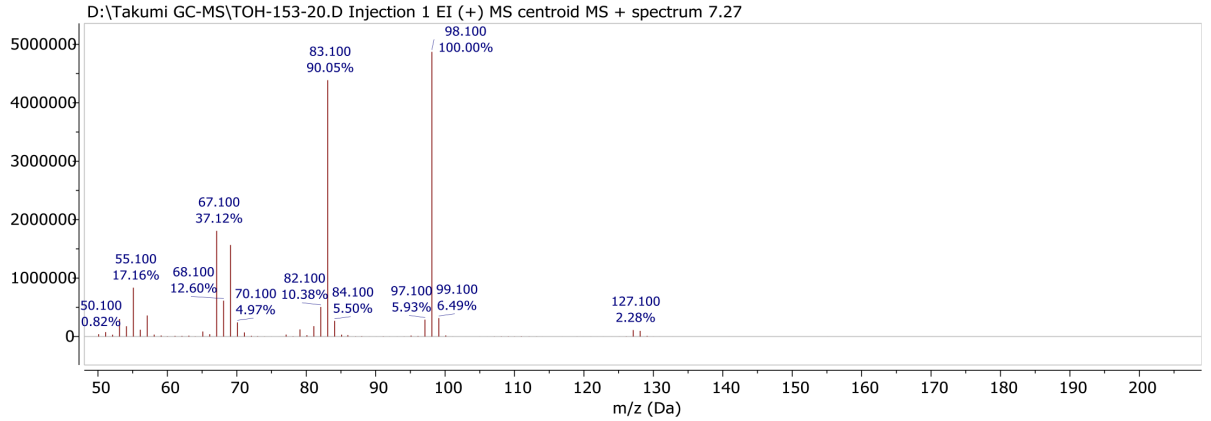
6b: $[M]^+$ 198.1



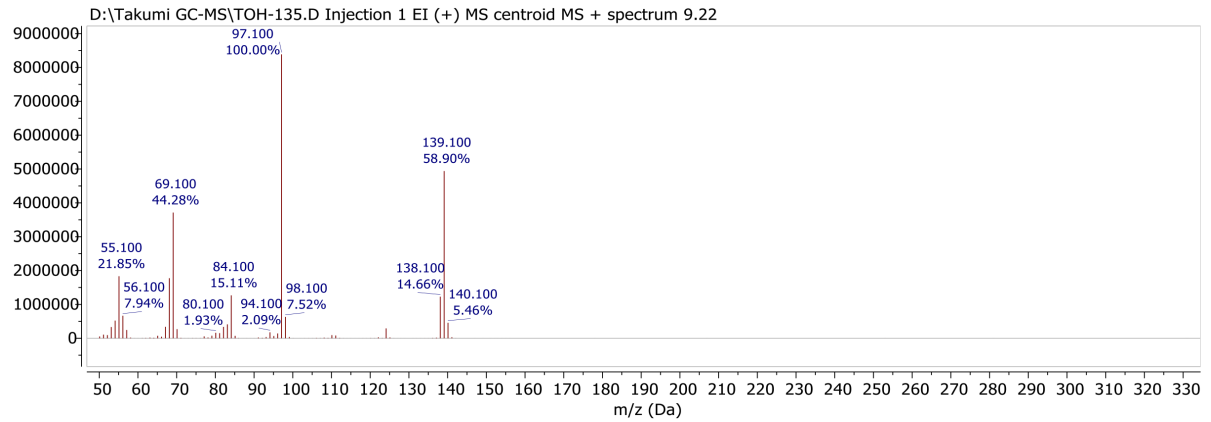
7a: $[M]^+$ 304.2



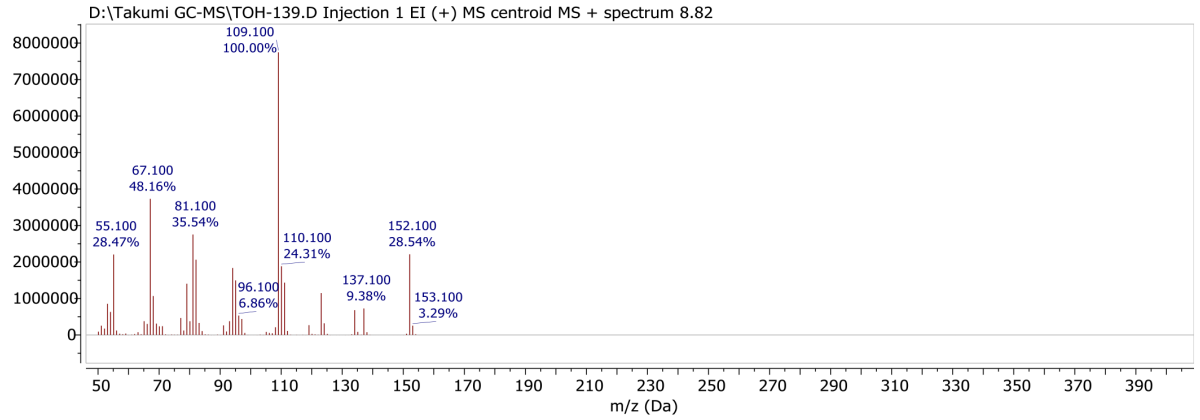
8a: $[M\text{-}H]^+$ 127.1



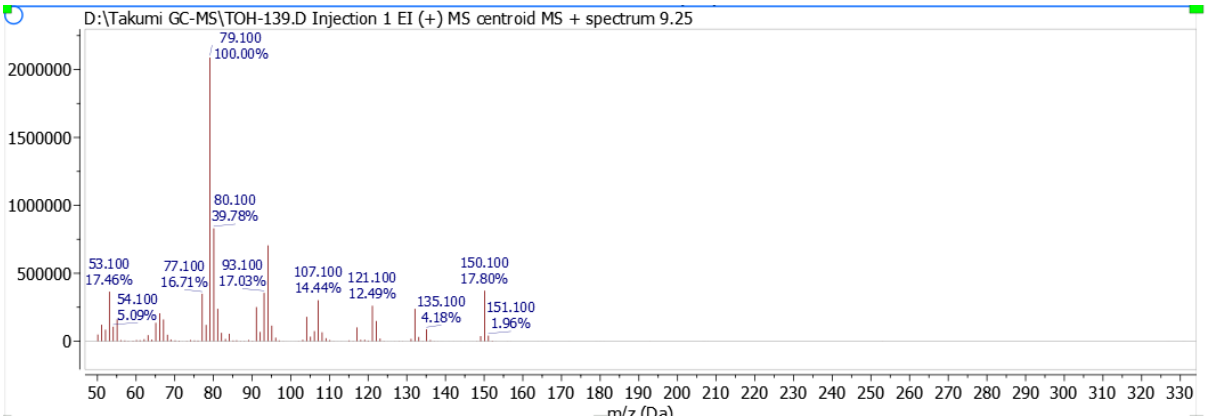
9a/b: $[M]^+$ 139.1



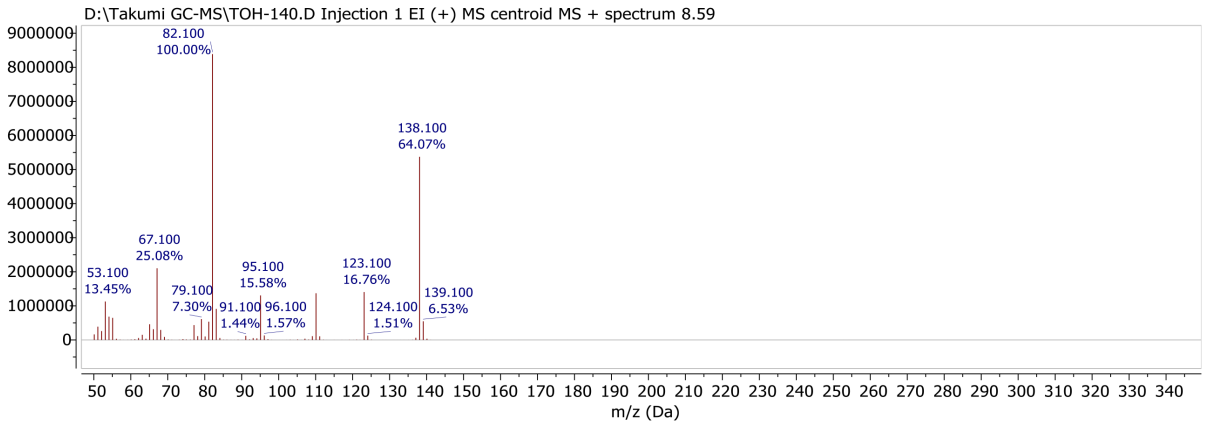
10a: $[M]^+$ 152.1



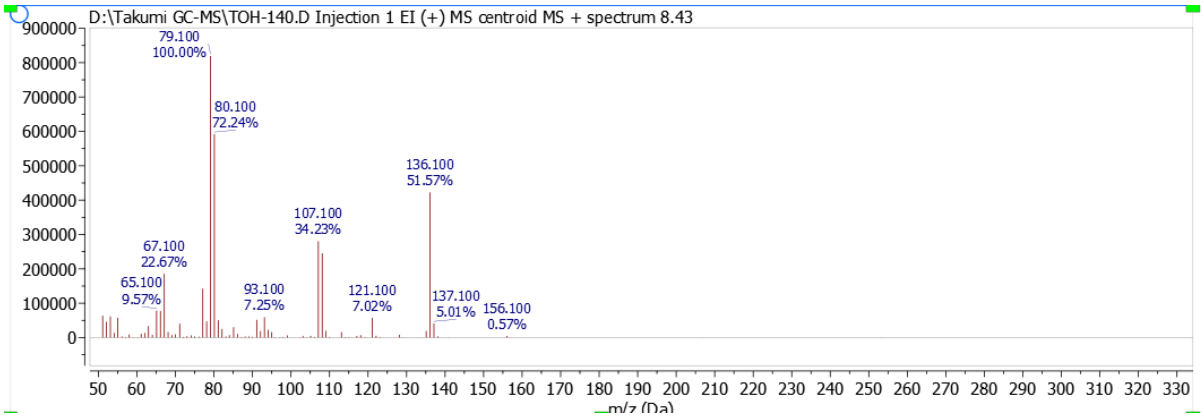
10b: $[M]^+$ 150.1



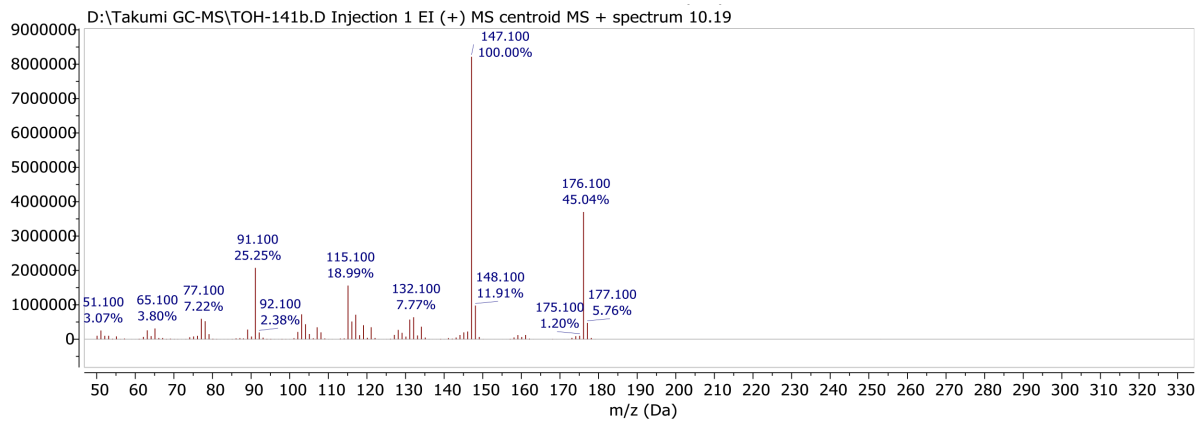
11a: $[M]^+$ 138.1



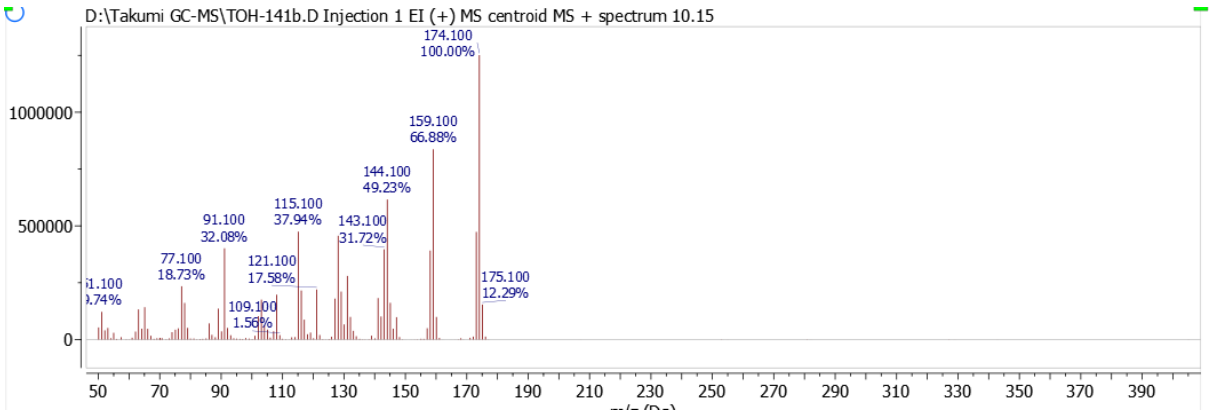
11b: $[M]^+$ 136.1



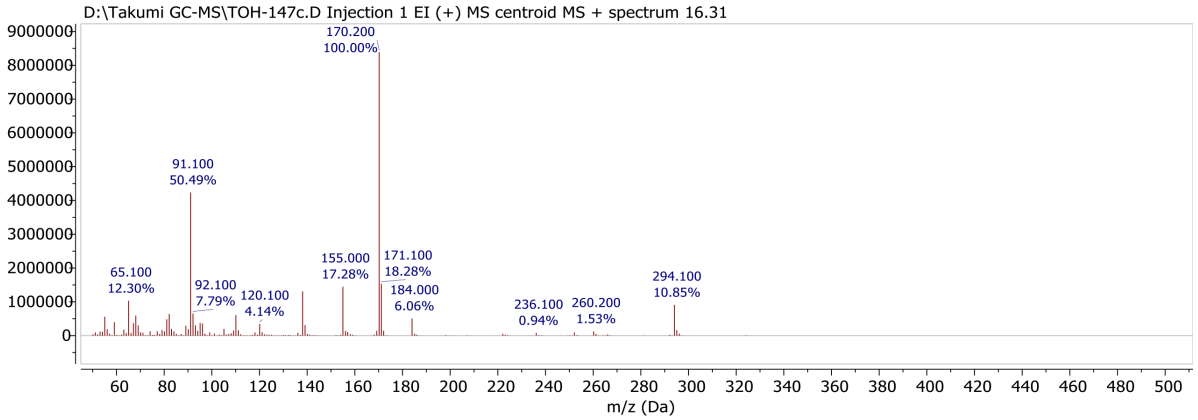
12a: $[M]^+$ 176.1



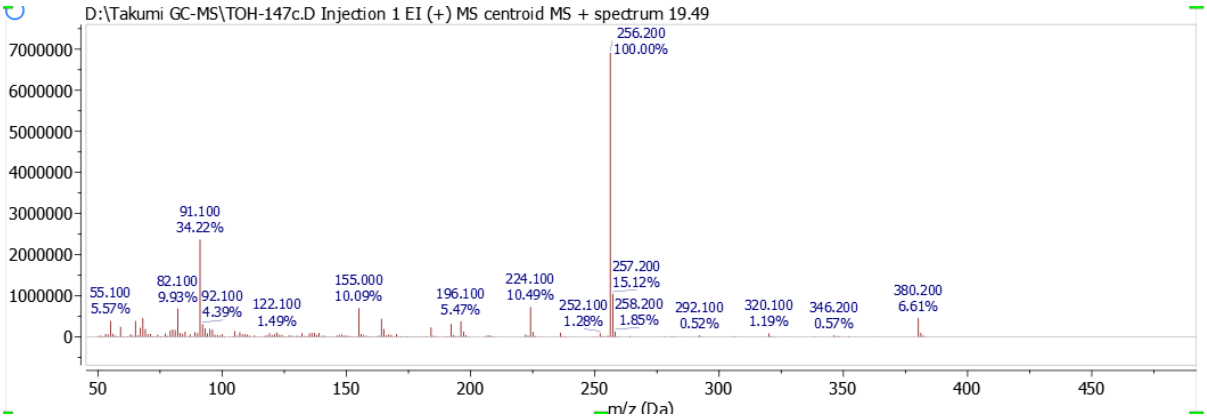
12b: $[M]^+$ 174.1



13a: $[M\text{-}OMe]^+$ 294.1

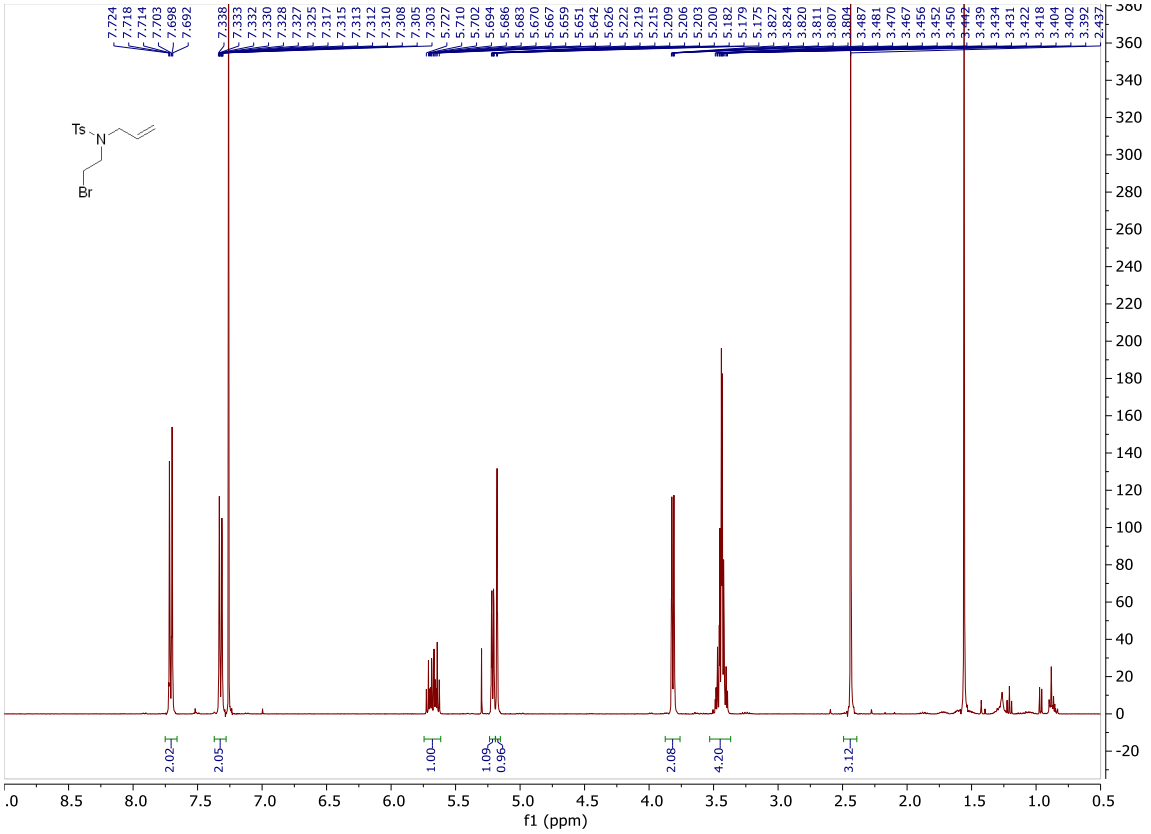


13b: $[M\text{-}OMe]^+$ 380.2

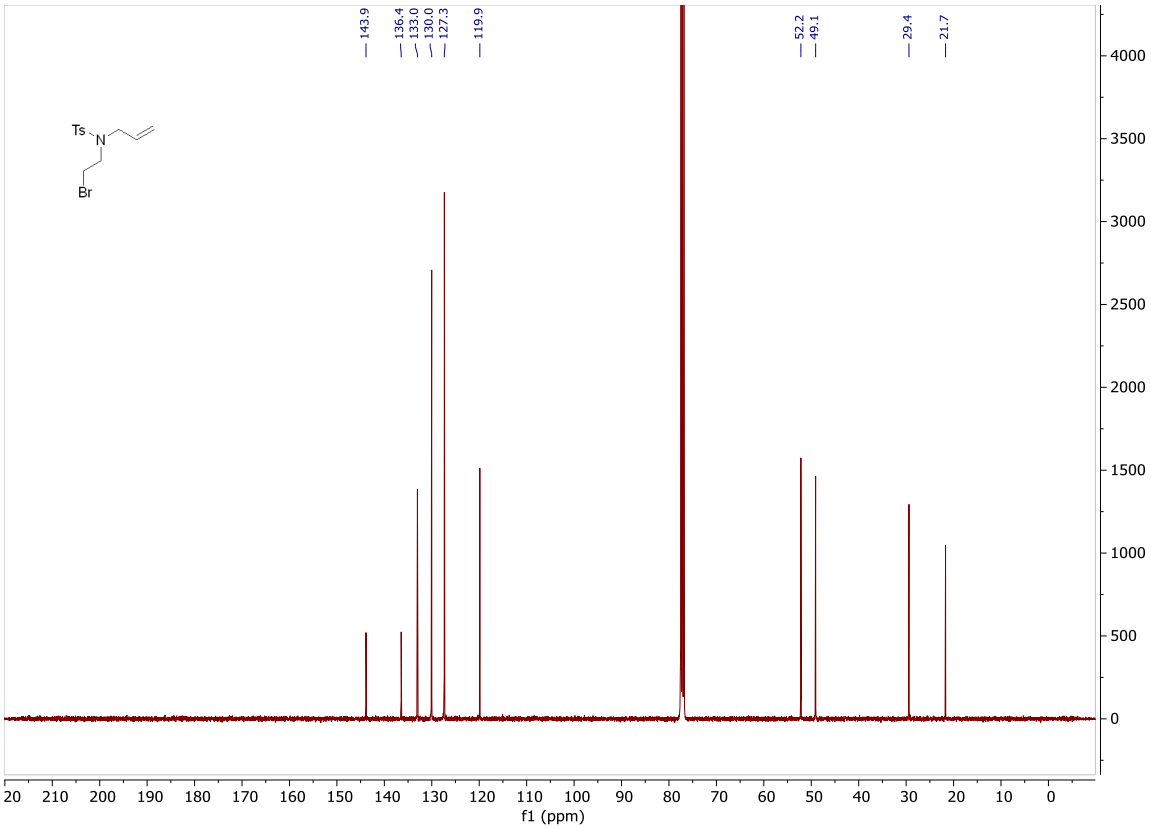


III. NMR spectra of new compounds

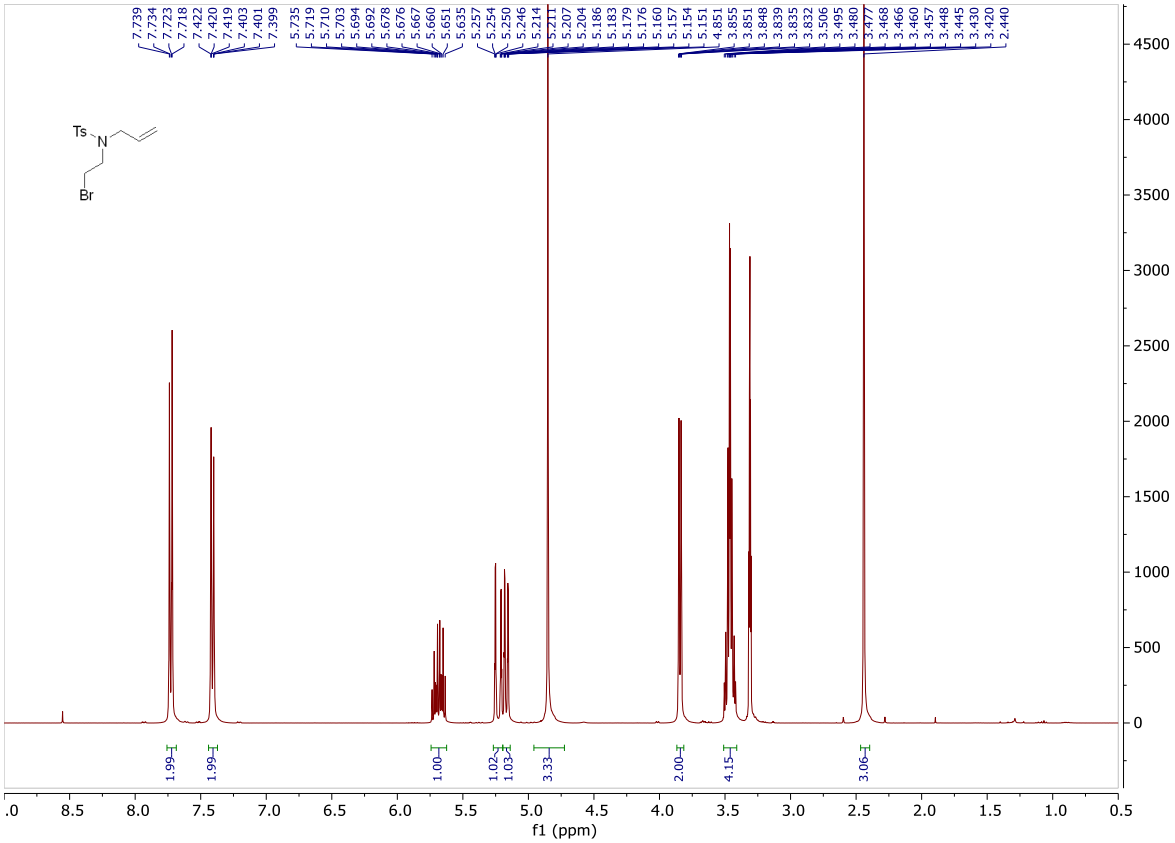
N-allyl-N-(2-bromoethyl)-4-methylbenzenesulfonamide (2), ^{1}H NMR (400 MHz, $CDCl_3$)



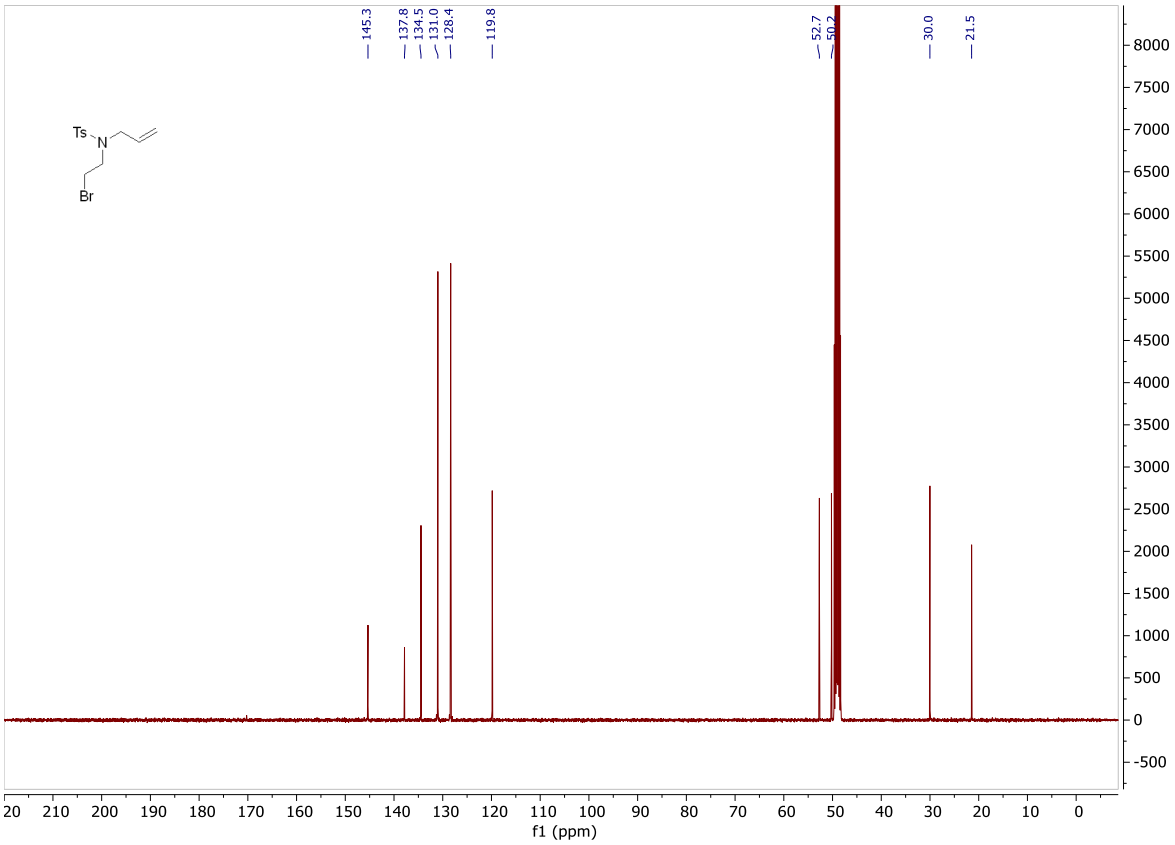
N-allyl-N-(2-bromoethyl)-4-methylbenzenesulfonamide (2), ^{13}C NMR (101 MHz, $CDCl_3$)



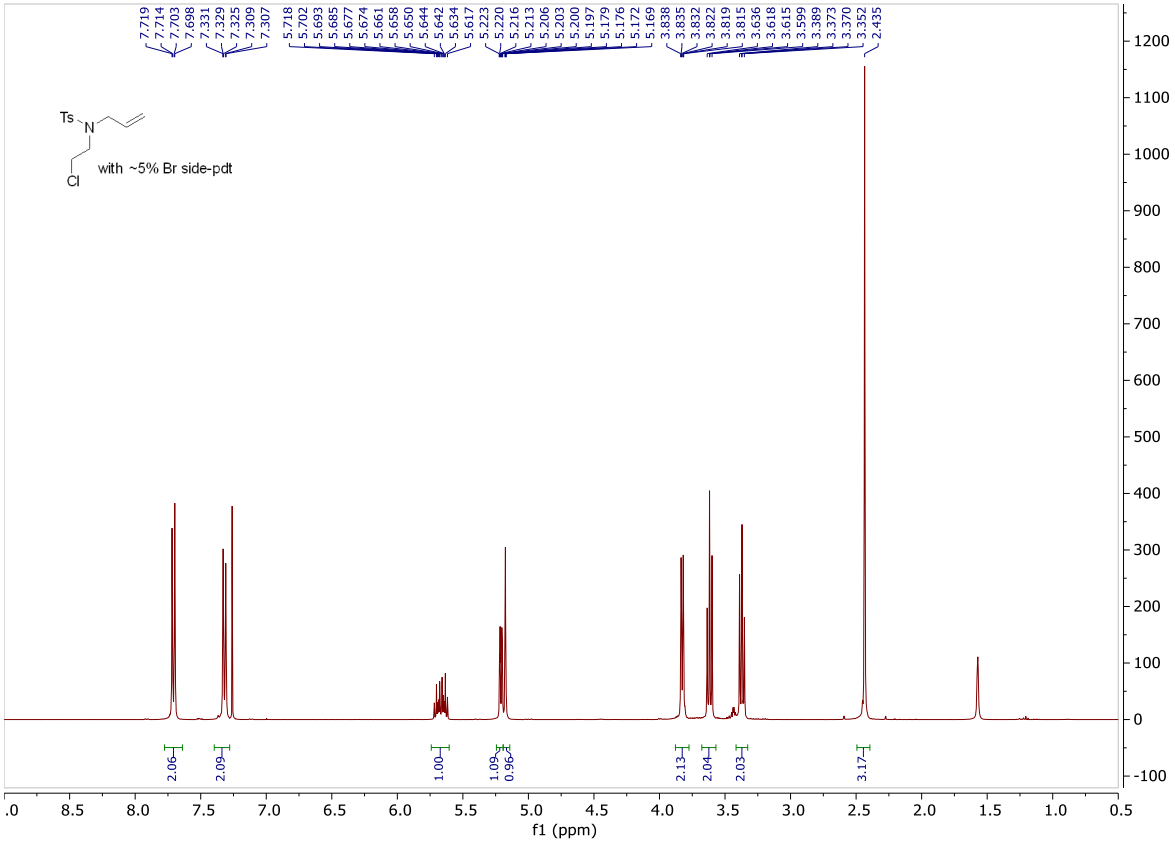
N-allyl-N-(2-bromoethyl)-4-methylbenzenesulfonamide (2), ^{1}H NMR (400 MHz, CD_3OD)



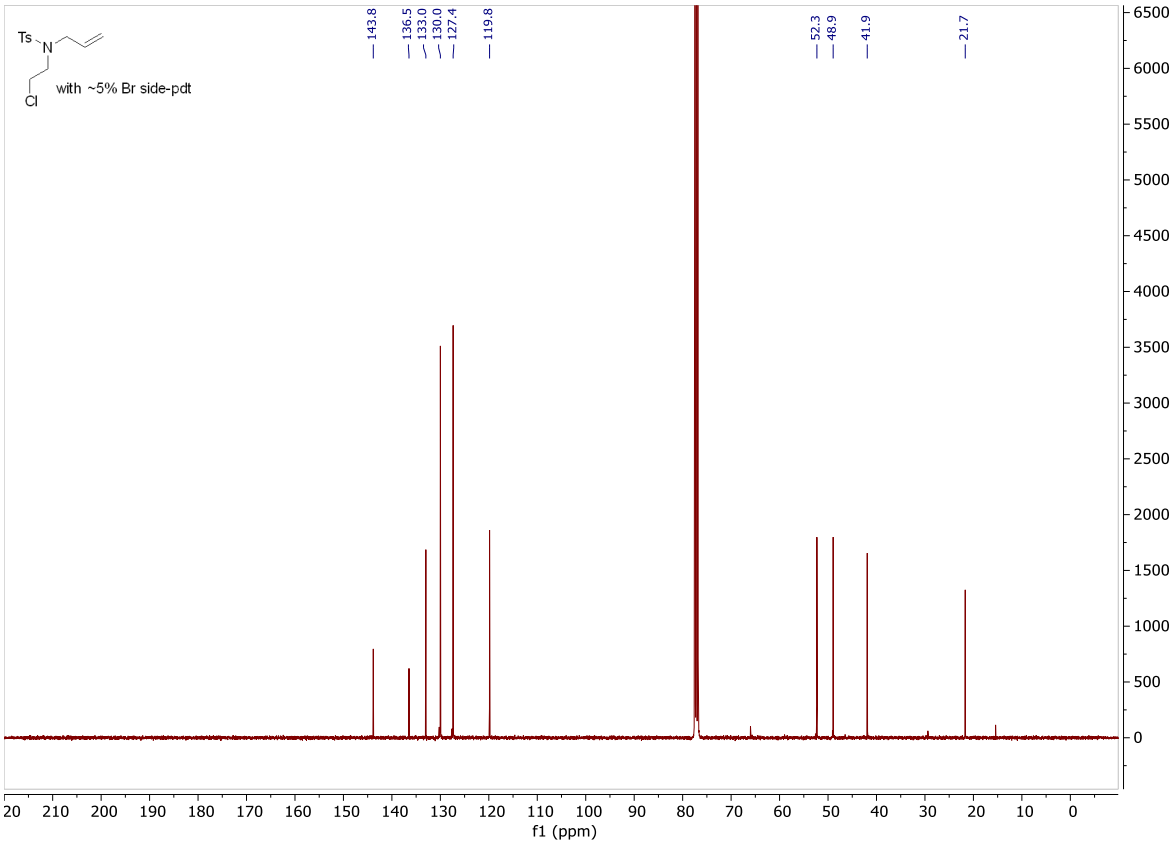
N-allyl-N-(2-bromoethyl)-4-methylbenzenesulfonamide (2), ^{13}C NMR (101 MHz, CD_3OD)



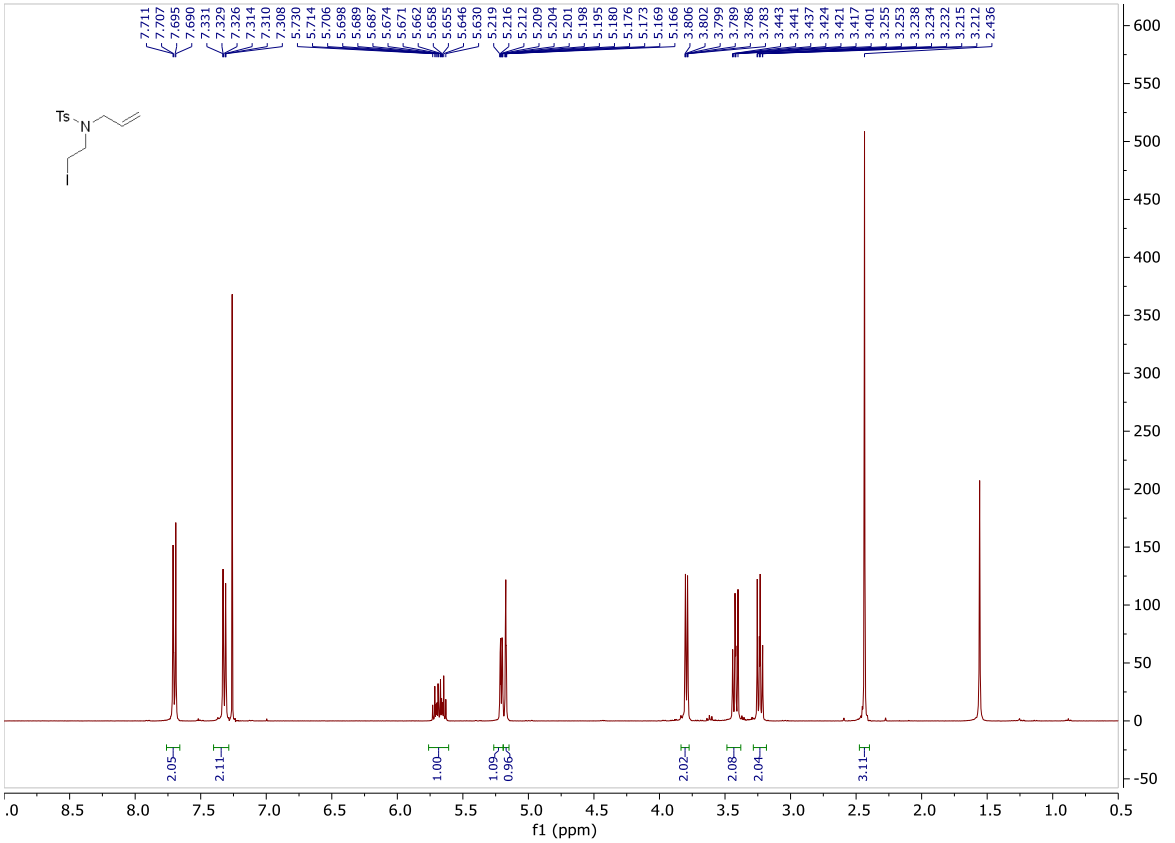
N-allyl-N-(2-chloroethyl)-4-methylbenzenesulfonamide (3), ^{1}H NMR (400 MHz, $CDCl_3$)



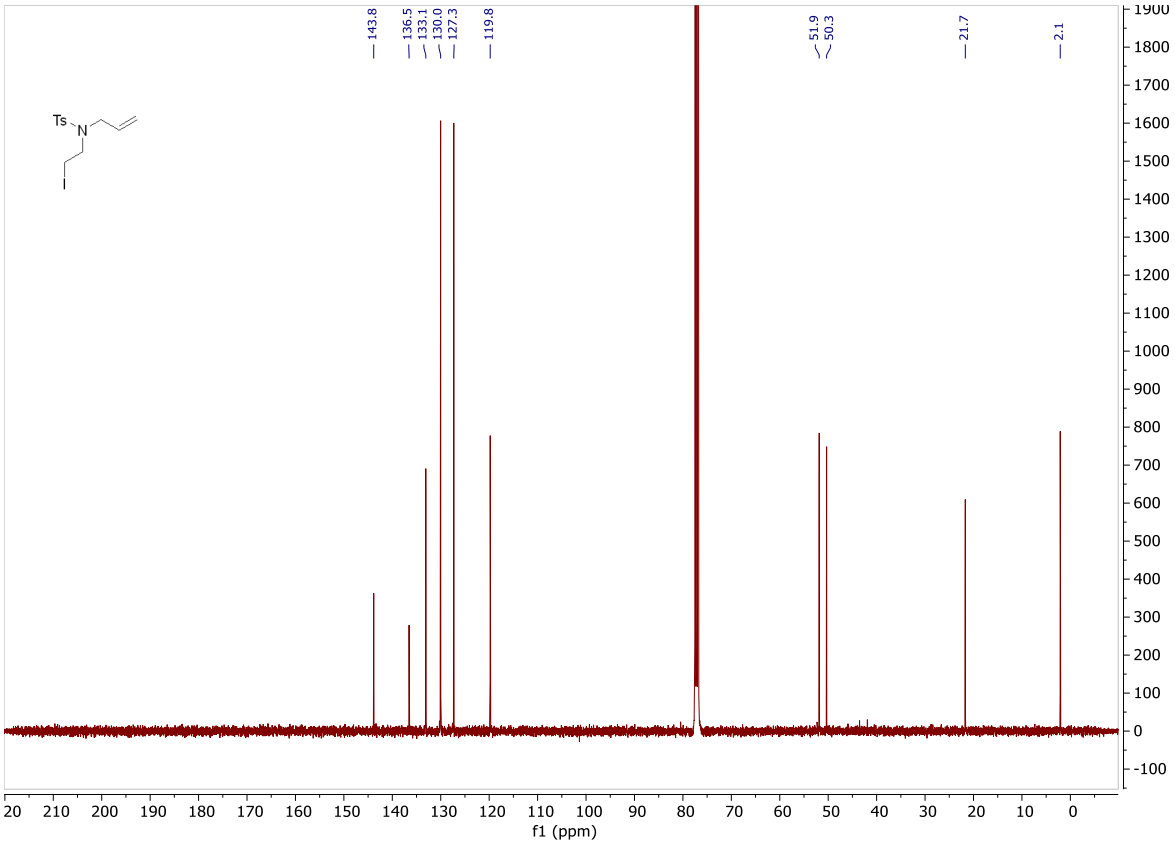
N-allyl-N-(2-chloroethyl)-4-methylbenzenesulfonamide (3), ^{13}C NMR (101 MHz, $CDCl_3$)



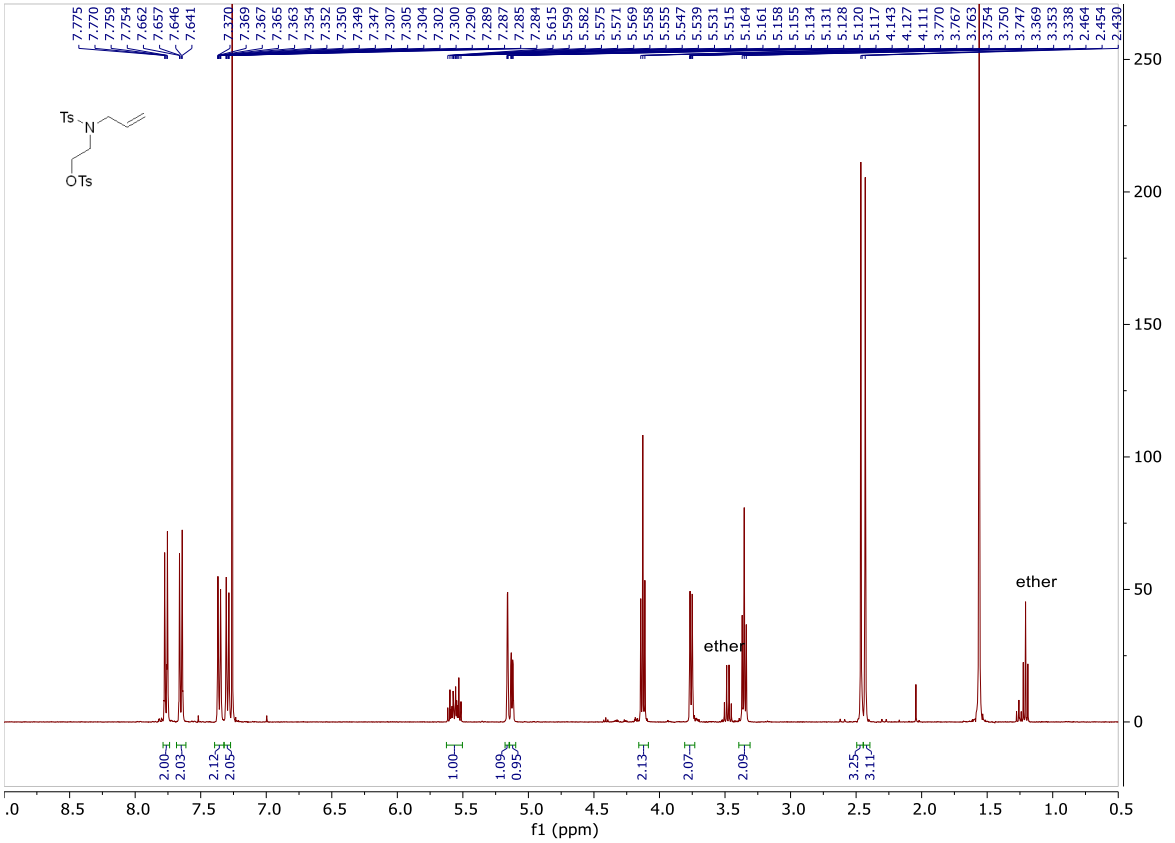
N-allyl-N-(2-iodoethyl)-4-methylbenzenesulfonamide (4), ^{1}H NMR (400 MHz, $CDCl_3$)



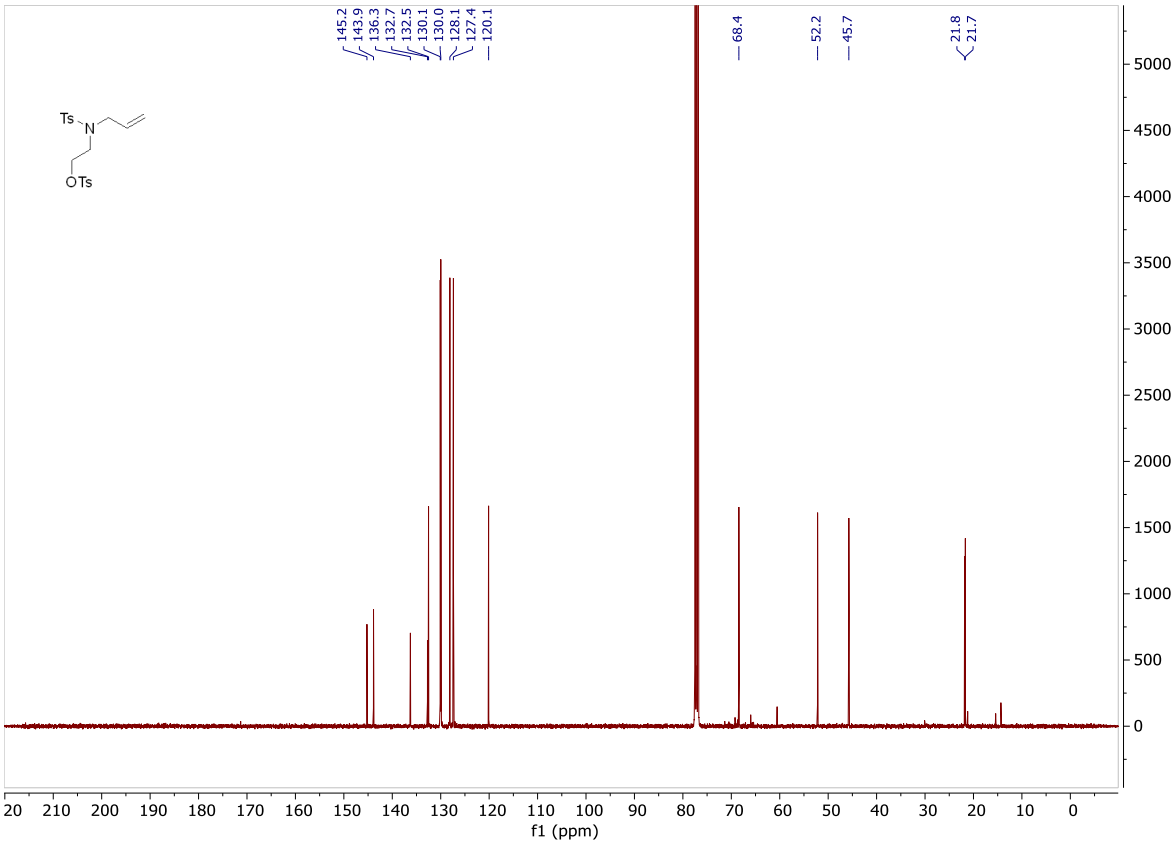
N-allyl-N-(2-iodoethyl)-4-methylbenzenesulfonamide (4), ^{13}C NMR (101 MHz, $CDCl_3$)



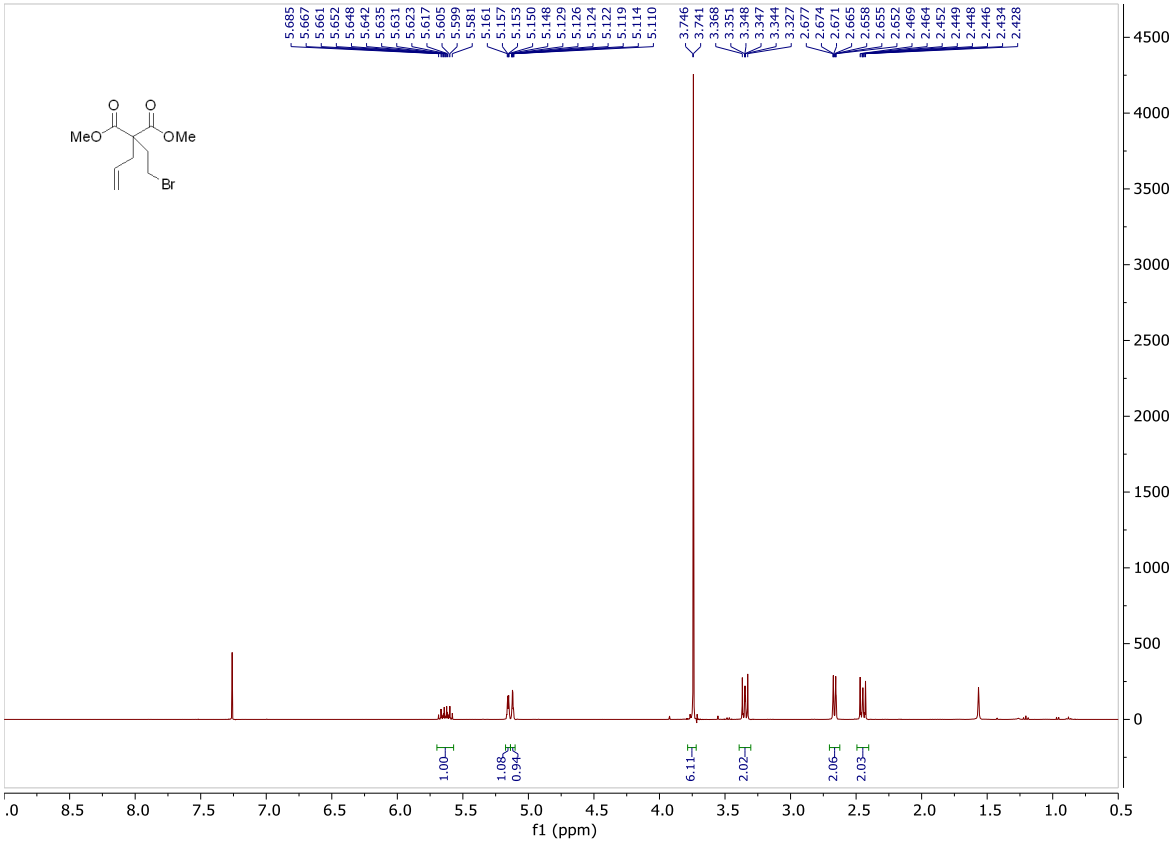
2-((N-allyl-4-methylphenyl)sulfonamido)ethyl 4-methylbenzenesulfonate (5), ^{1}H NMR (400 MHz, $CDCl_3$)



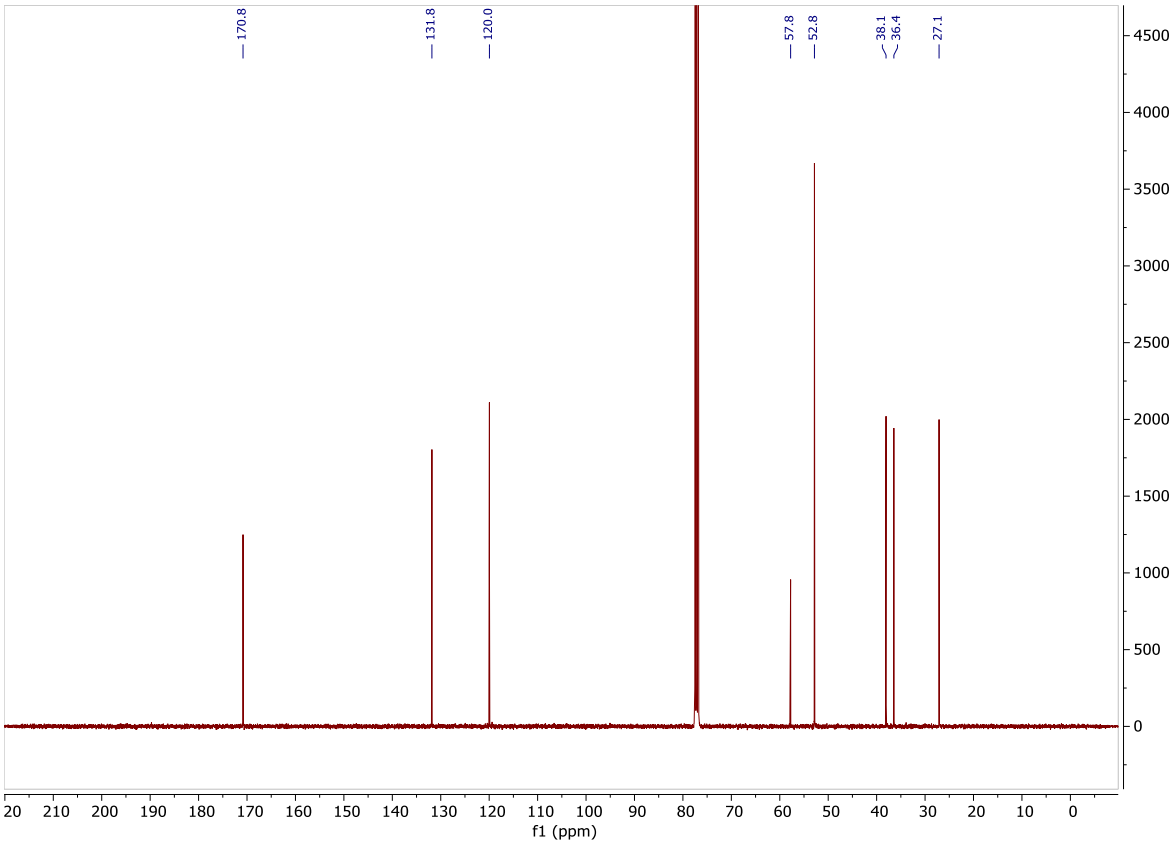
2-((N-allyl-4-methylphenyl)sulfonamido)ethyl 4-methylbenzenesulfonate (5), ^{13}C NMR (101 MHz, $CDCl_3$)



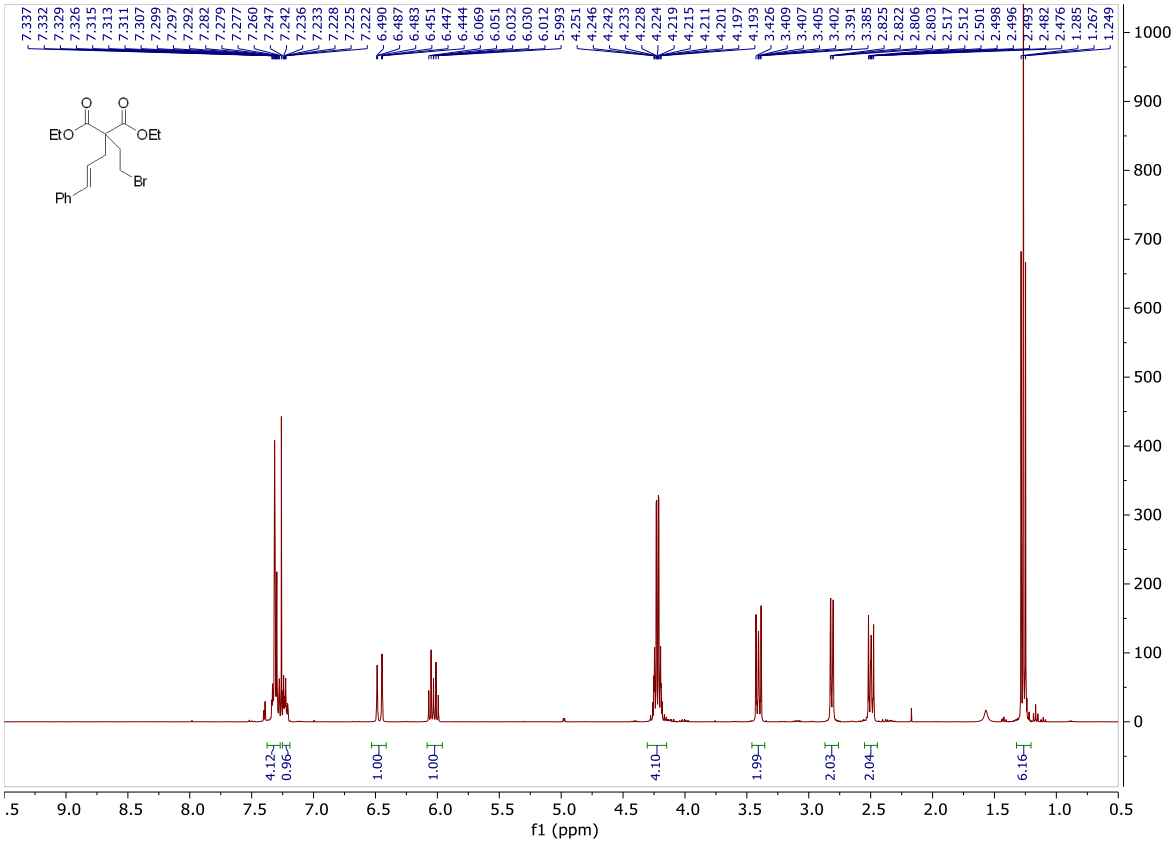
dimethyl 2-allyl-2-(2-bromoethyl)malonate (6), ^{1}H NMR (400 MHz, $CDCl_3$)



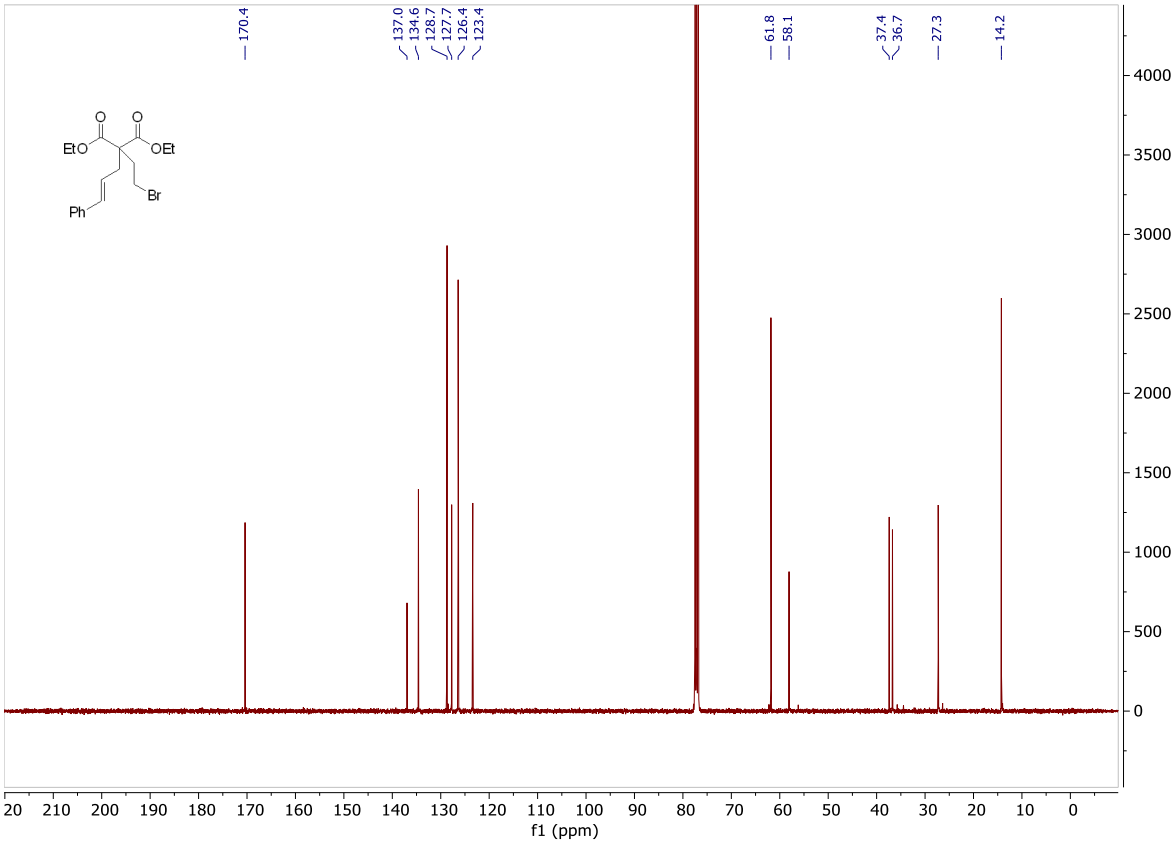
dimethyl 2-allyl-2-(2-bromoethyl)malonate (6), ^{13}C NMR (101 MHz, $CDCl_3$)



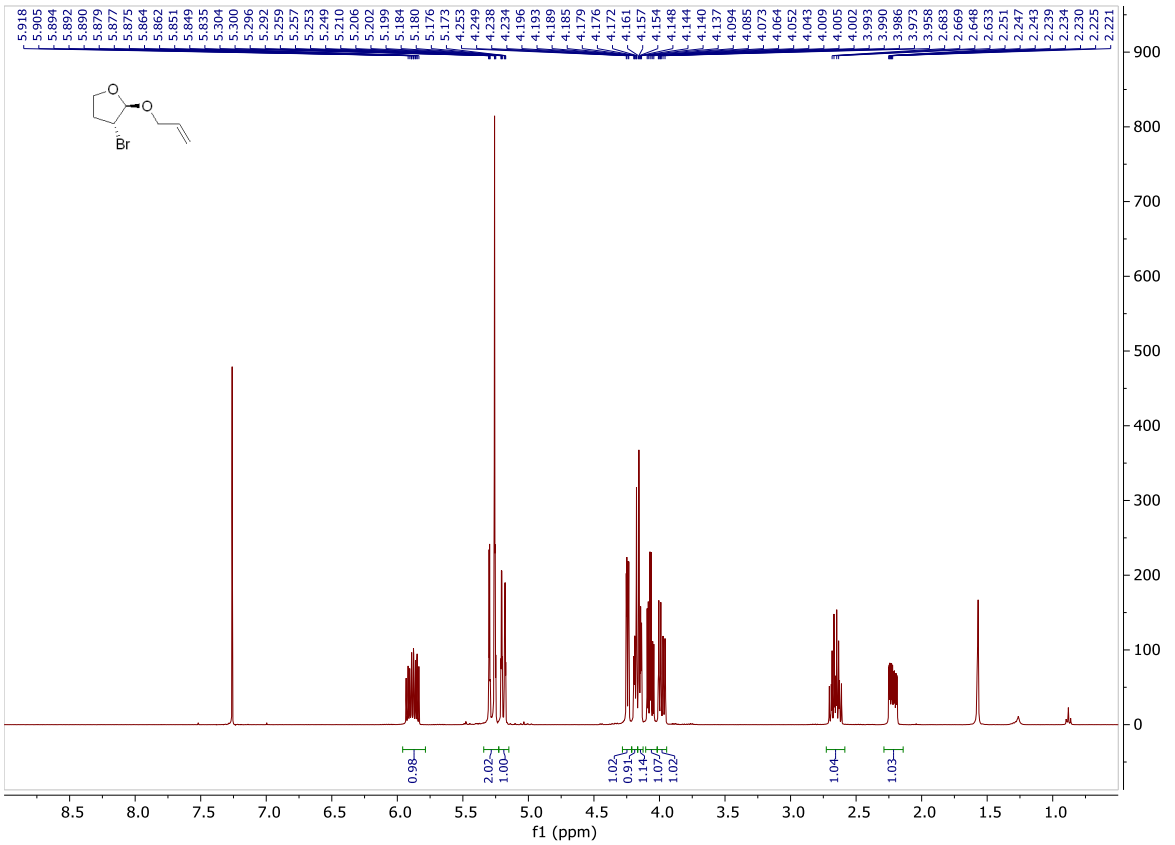
diethyl 2-(2-bromoethyl)-2-cinnamylmalonate (7), ^{1}H NMR (400 MHz, $CDCl_3$)



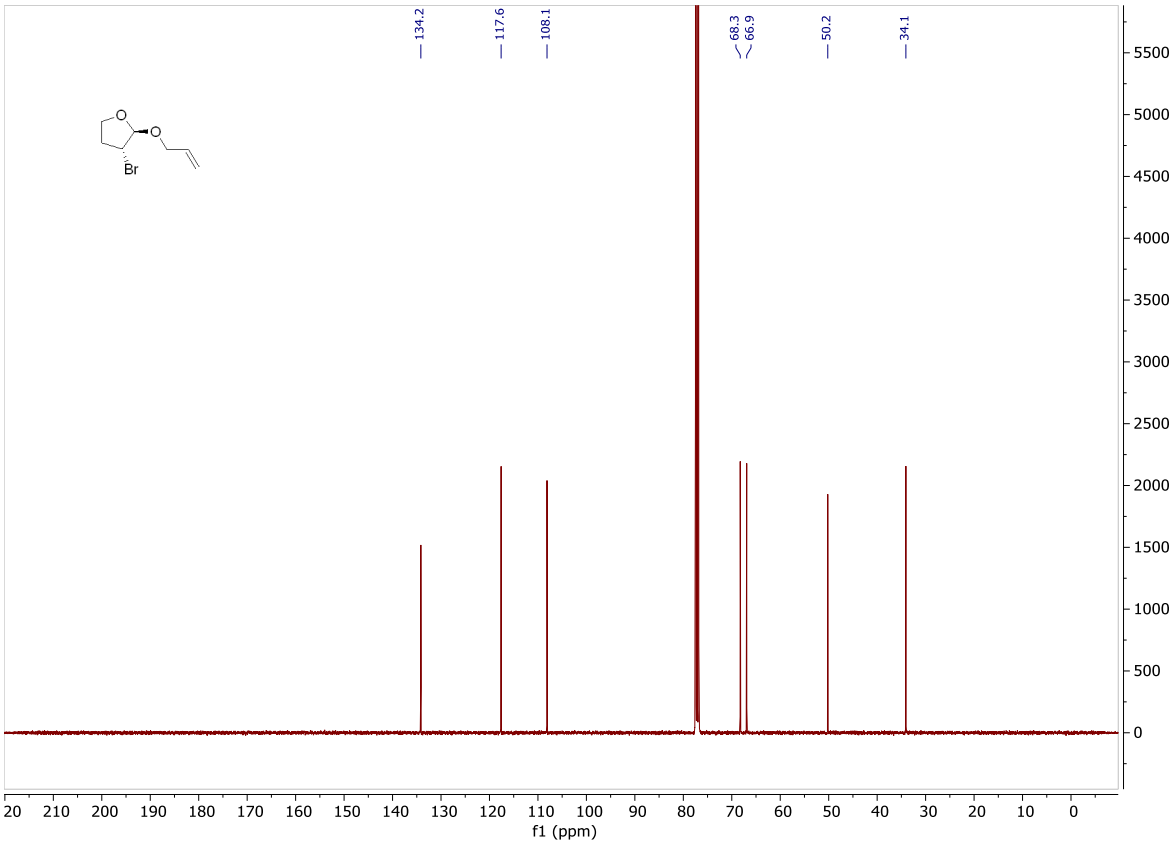
diethyl 2-(2-bromoethyl)-2-cinnamylmalonate (7), ^{13}C NMR (101 MHz, $CDCl_3$)



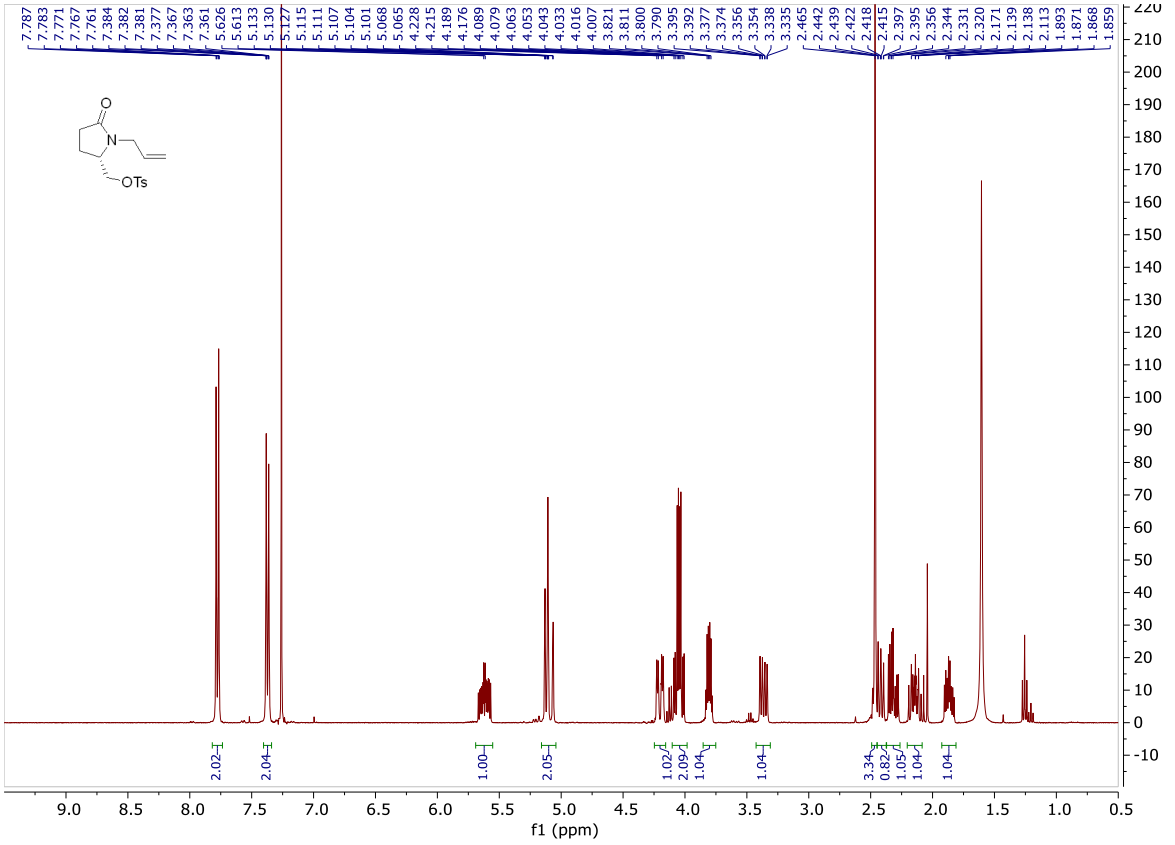
2-(Allyloxy)-3-bromotetrahydrofuran (8), ^{1}H NMR (400 MHz, $CDCl_3$)



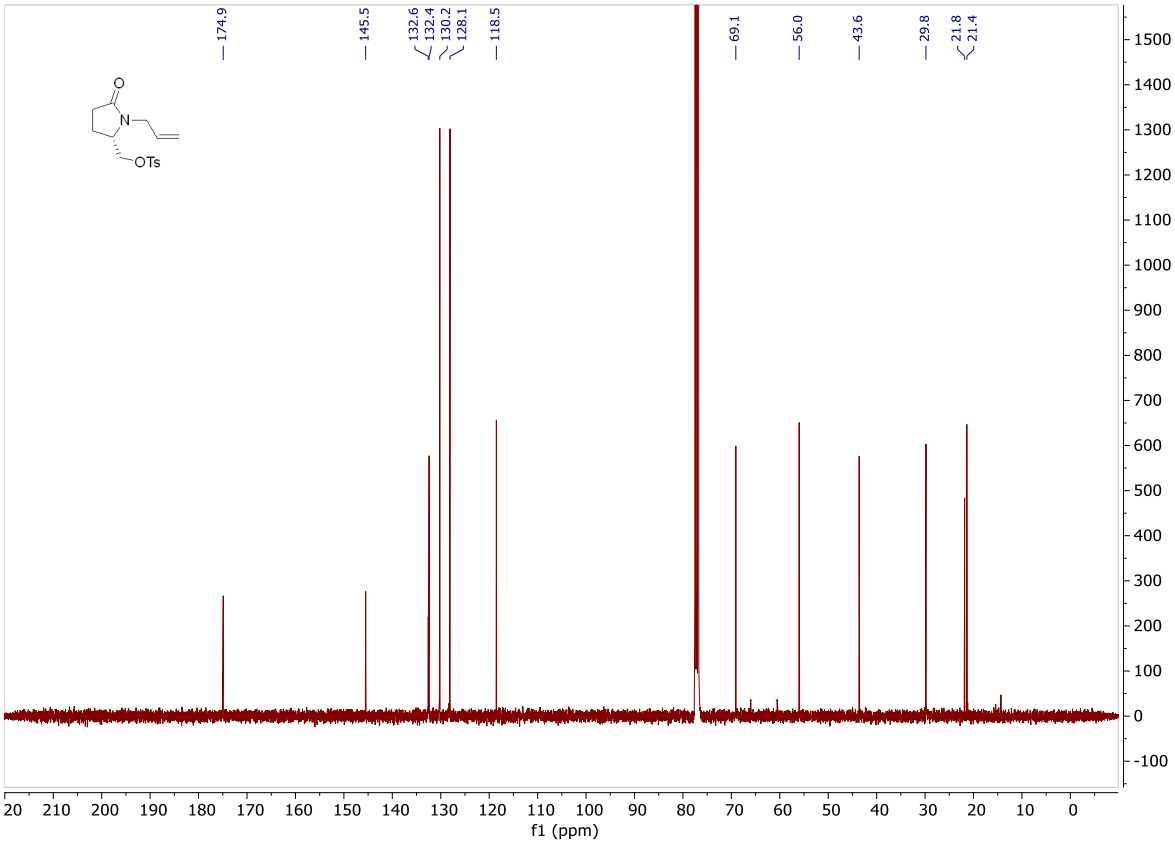
2-(Allyloxy)-3-bromotetrahydrofuran (8), ^{13}C NMR (101 MHz, $CDCl_3$)



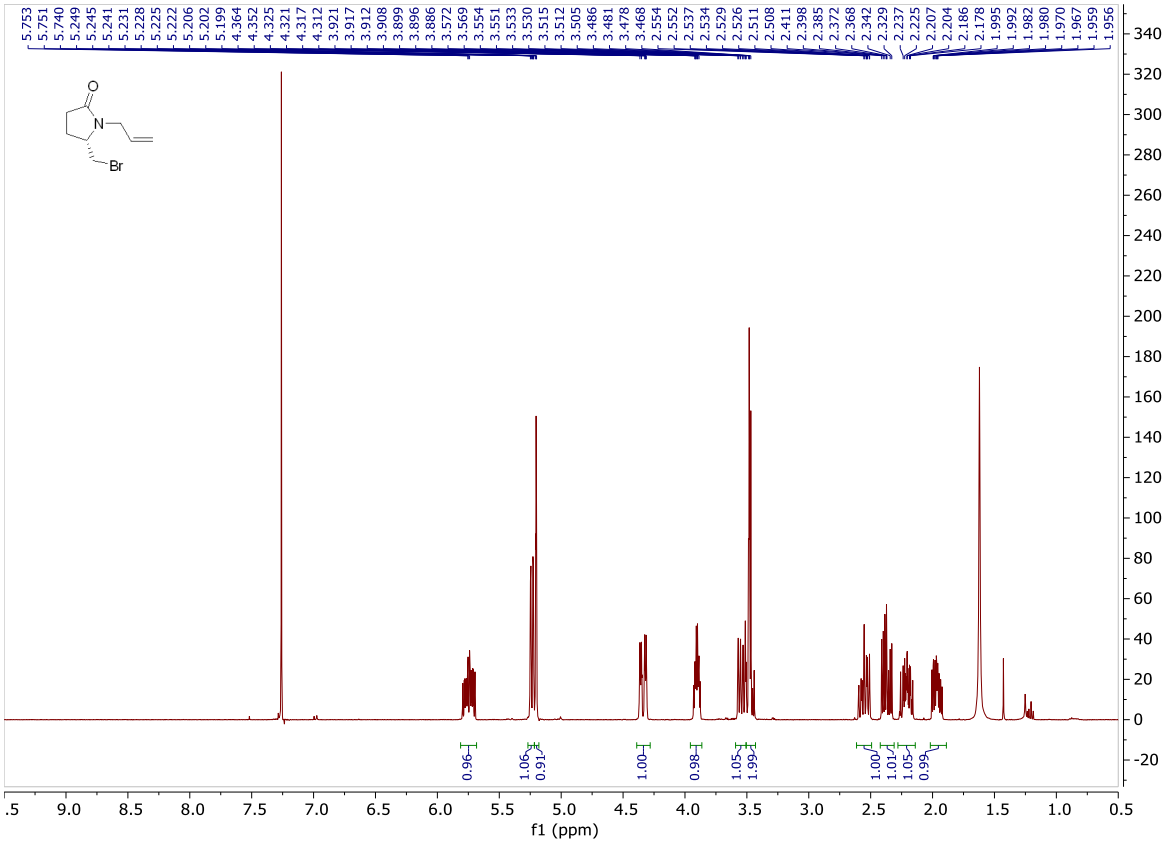
(S)-(1-allyl-5-oxopyrrolidin-2-yl)methyl 4-methylbenzenesulfonate (S7), ^{1}H NMR (400 MHz, $CDCl_3$)



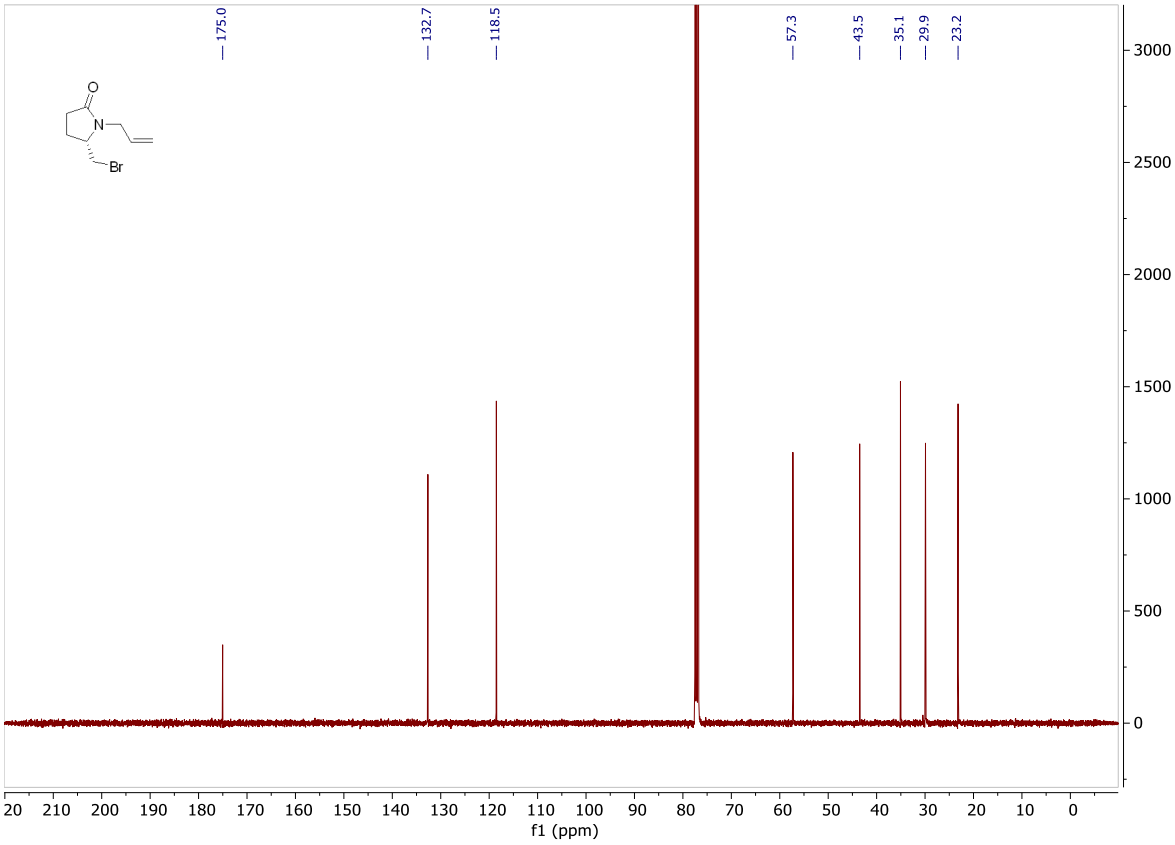
(S)-(1-allyl-5-oxopyrrolidin-2-yl)methyl 4-methylbenzenesulfonate (S7), ^{13}C NMR (101 MHz, $CDCl_3$)



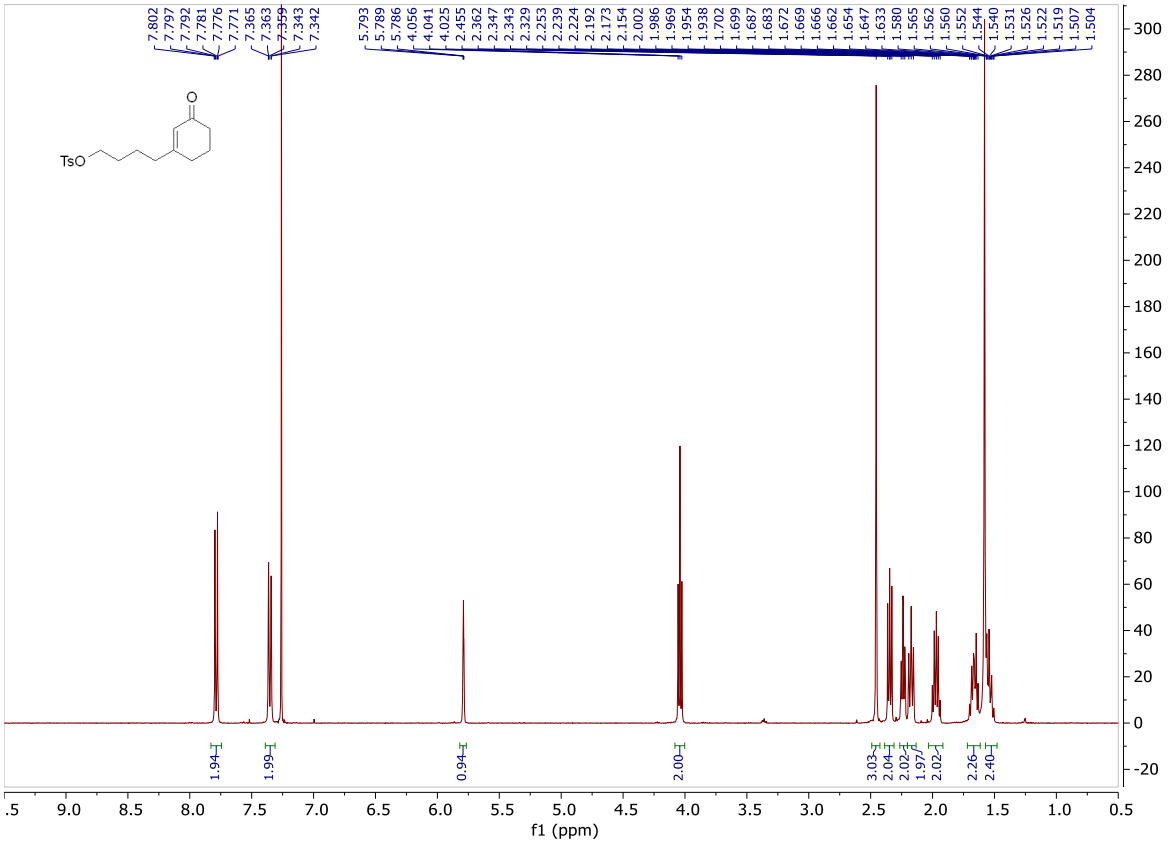
(S)-1-allyl-5-(bromomethyl)pyrrolidin-2-one (9), ^{1}H NMR (400 MHz, $CDCl_3$)



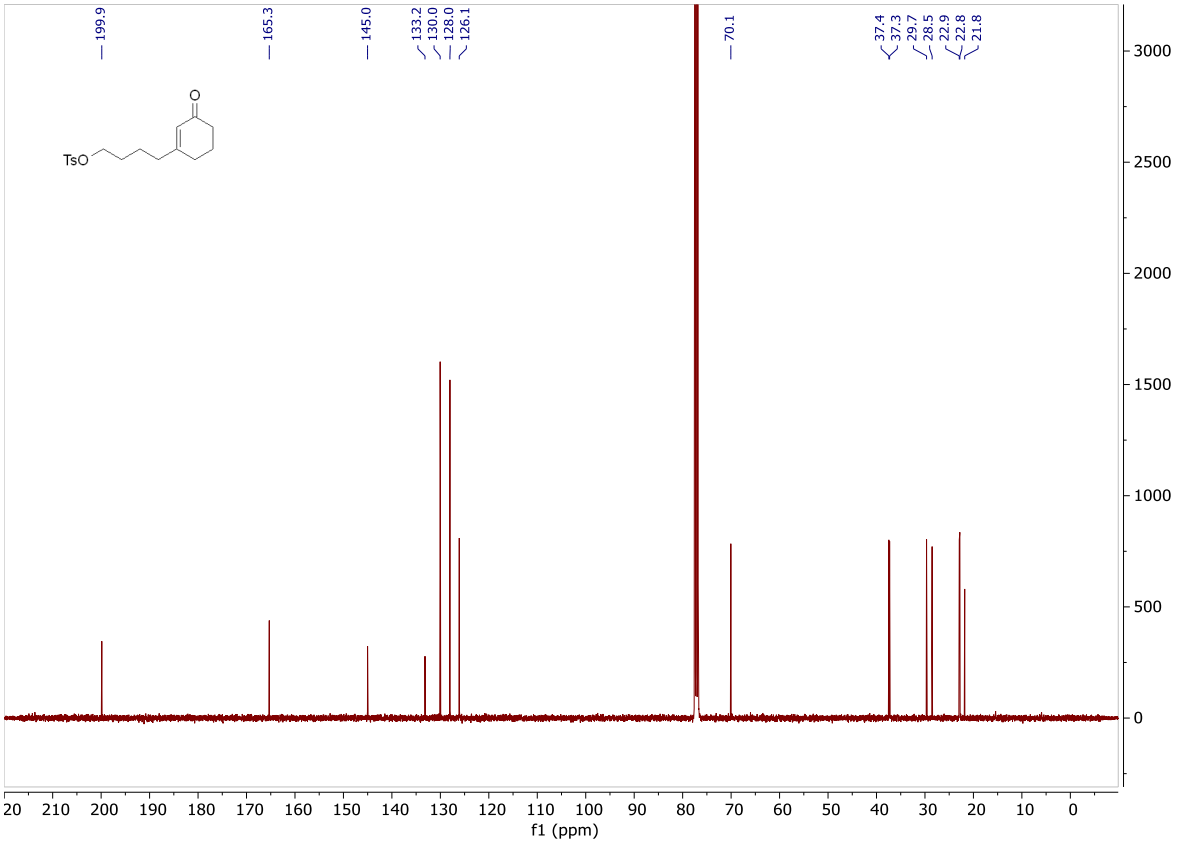
(S)-1-allyl-5-(bromomethyl)pyrrolidin-2-one (9), ^{13}C NMR (101 MHz, $CDCl_3$)



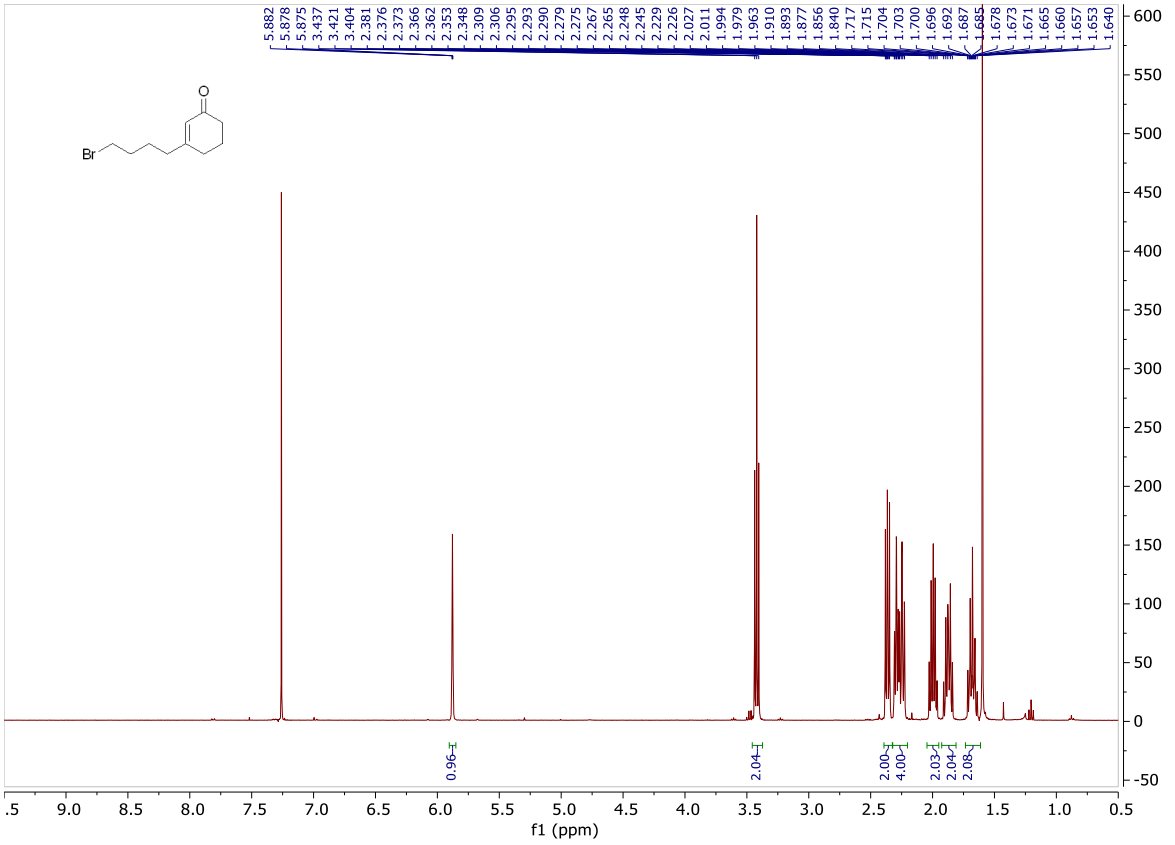
hh4-(3-oxocyclohex-1-en-1-yl)butyl 4-methylbenzenesulfonate (S9), ^{1}H NMR (400 MHz, $CDCl_3$)



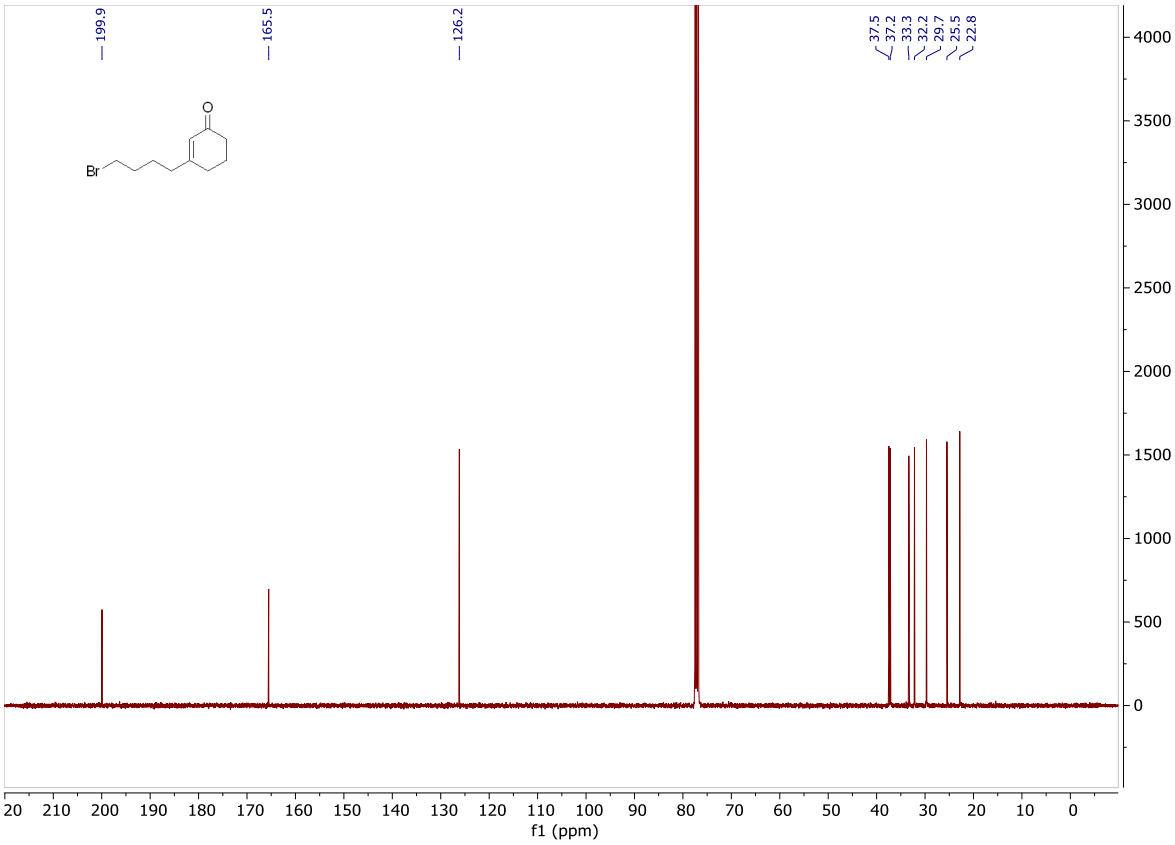
4-(3-oxocyclohex-1-en-1-yl)butyl 4-methylbenzenesulfonate (S9), ^{13}C NMR (101 MHz, $CDCl_3$)



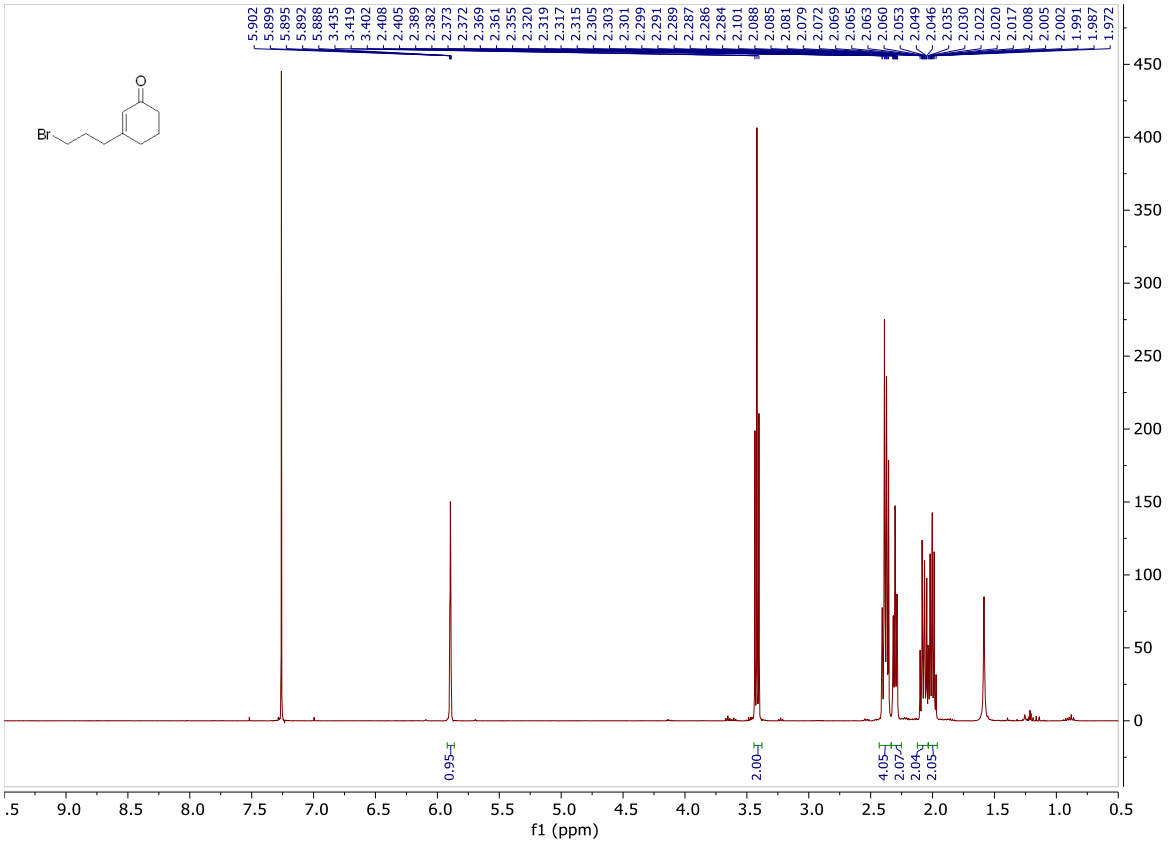
3-(4-bromobutyl)cyclohex-2-en-1-one (10), ^{1}H NMR (400 MHz, $CDCl_3$)



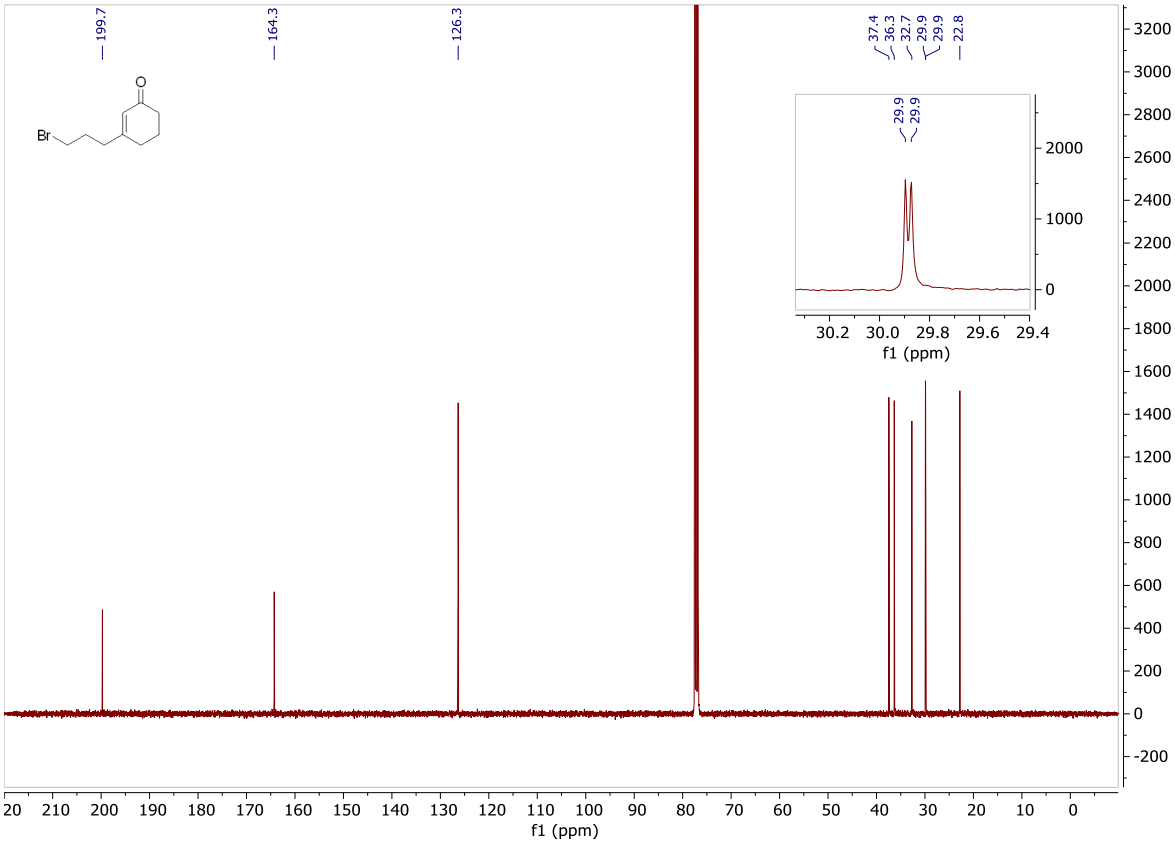
3-(4-bromobutyl)cyclohex-2-en-1-one (10), ^{13}C NMR (101 MHz, $CDCl_3$)



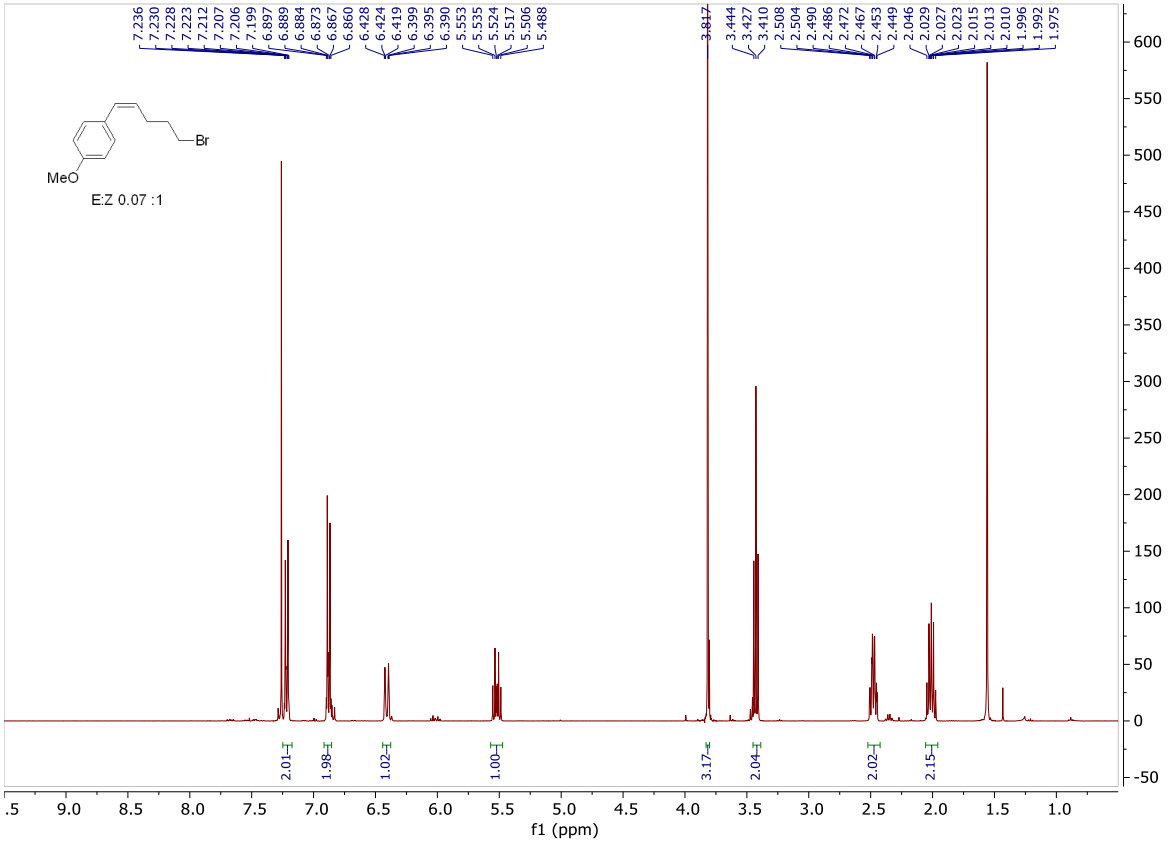
3-(3-bromopropyl)cyclohex-2-en-1-one (11), ^{1}H NMR (400 MHz, $CDCl_3$)



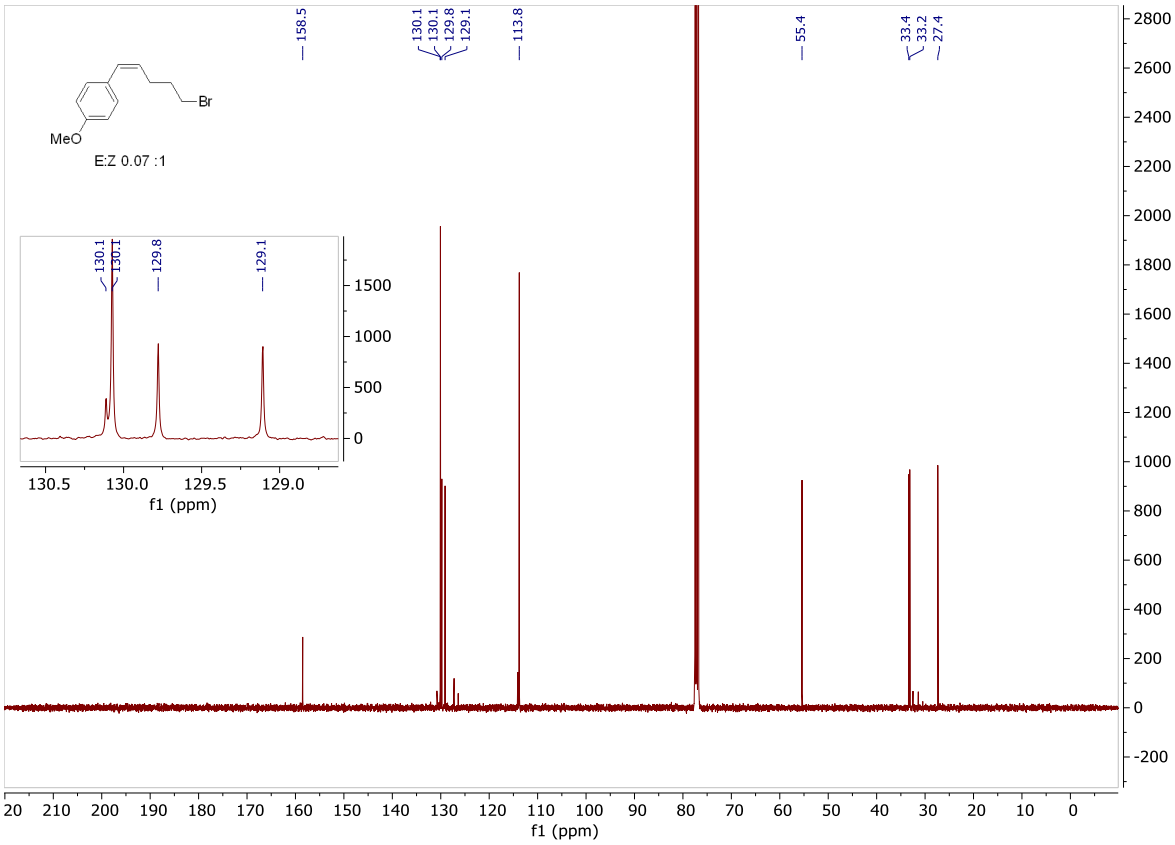
3-(3-bromopropyl)cyclohex-2-en-1-one (11), ^{13}C NMR (101 MHz, $CDCl_3$)



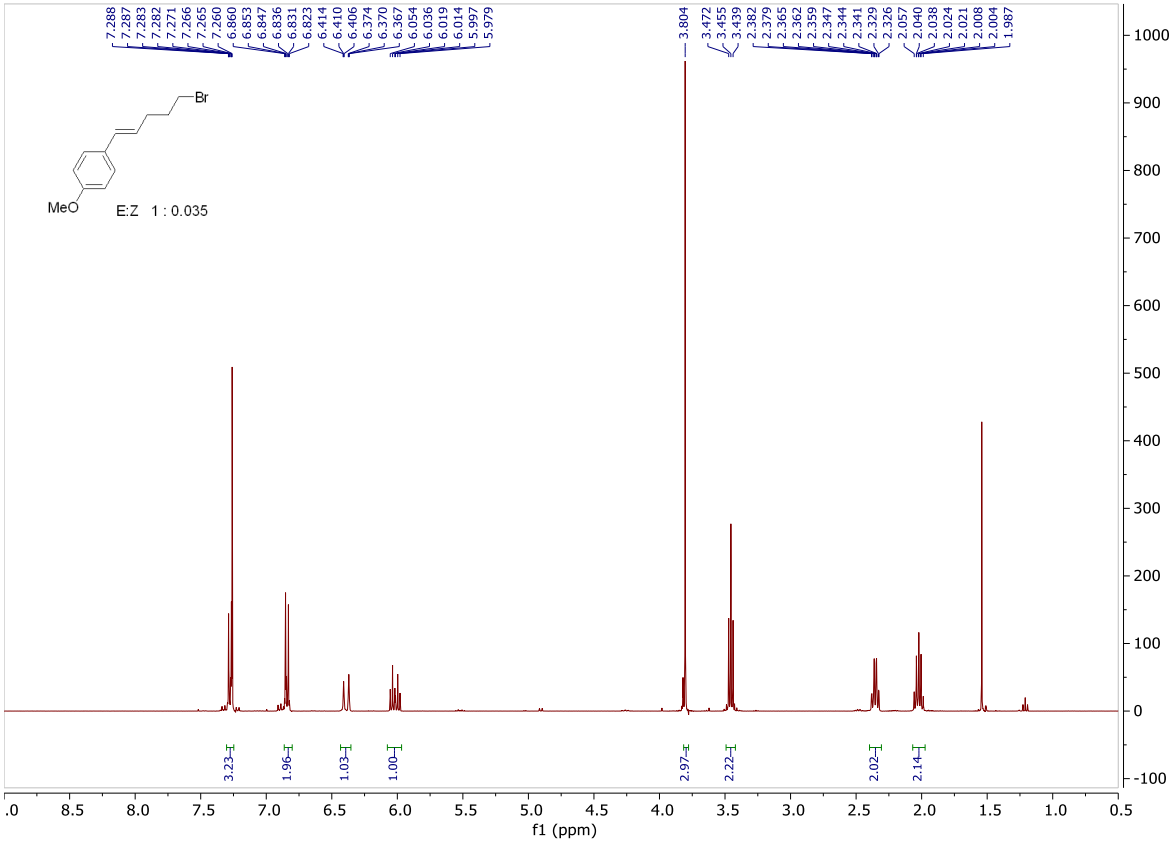
(Z)-1-(5-bromopent-1-en-1-yl)-4-methoxybenzene (S12), ^{1}H NMR (400 MHz, $CDCl_3$)



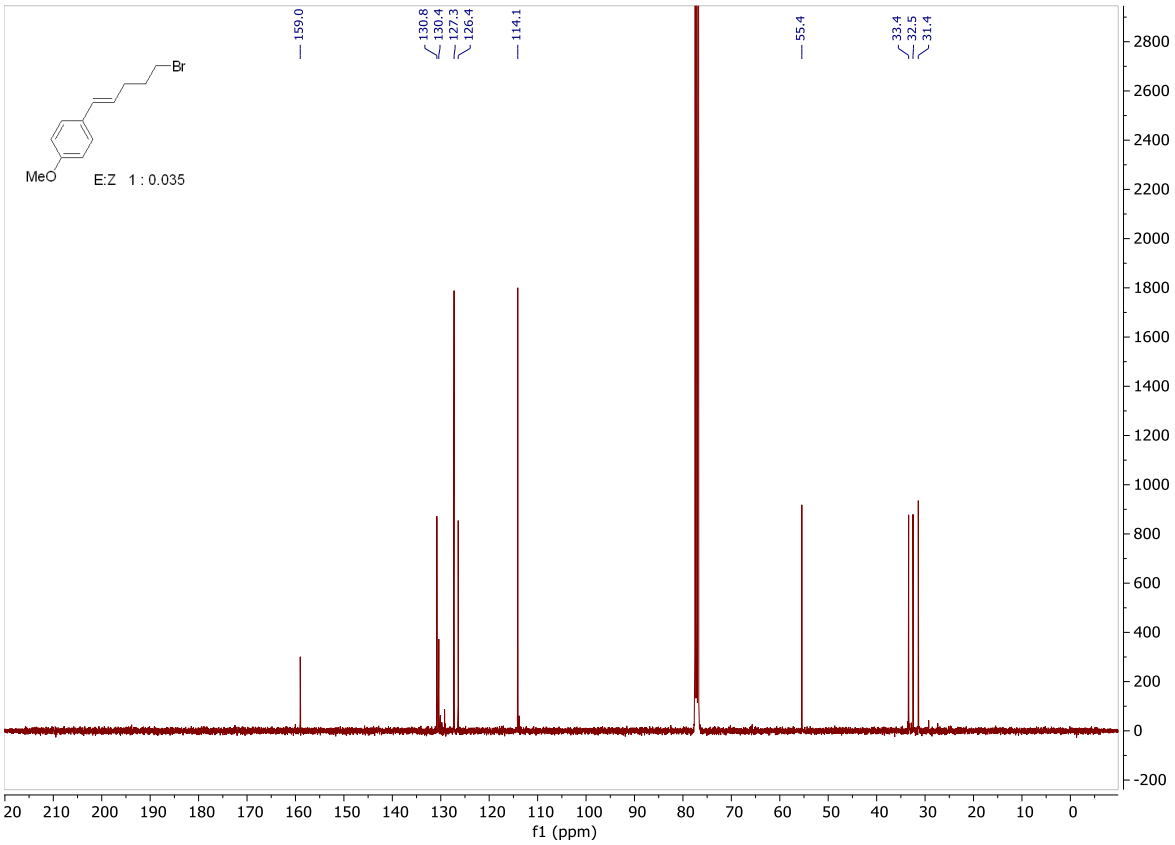
(Z)-1-(5-bromopent-1-en-1-yl)-4-methoxybenzene (S12), ^{13}C NMR (101 MHz, $CDCl_3$)



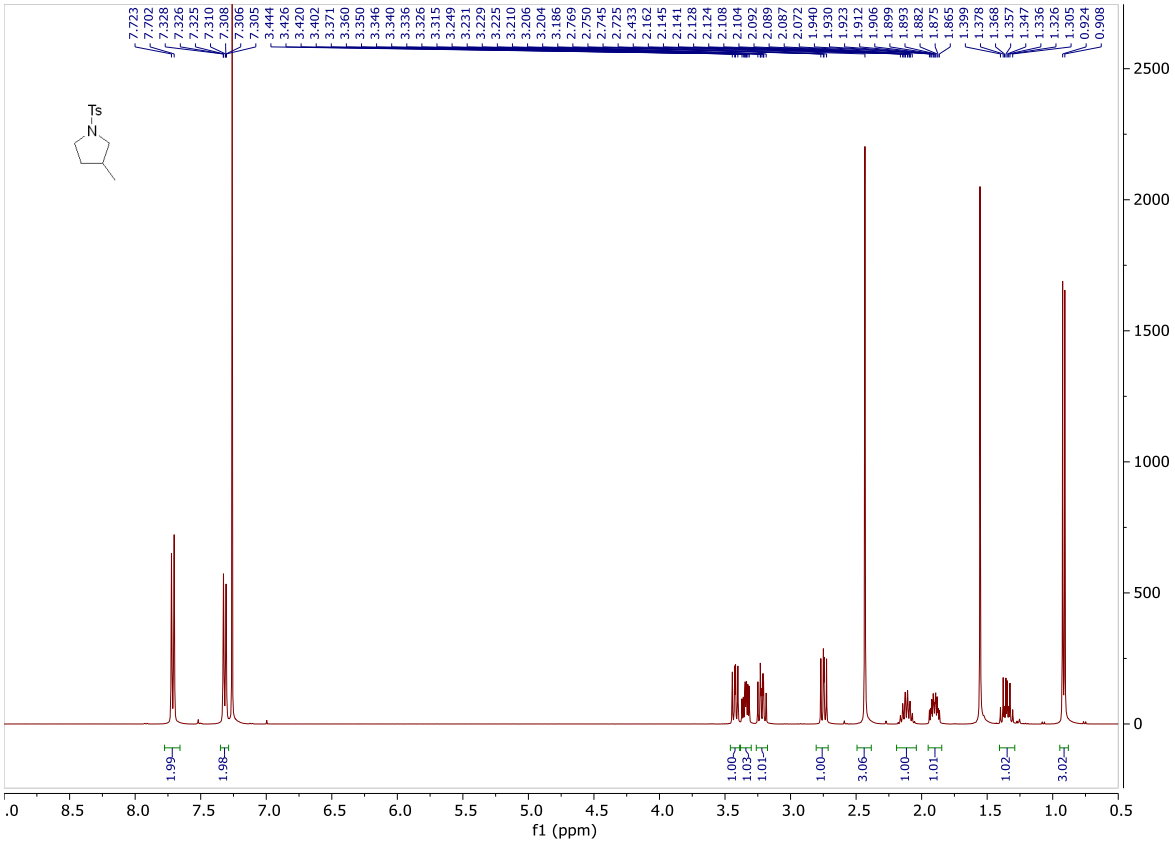
(E)-1-(5-bromopent-1-en-1-yl)-4-methoxybenzene (12), ^{1}H NMR (400 MHz, $CDCl_3$)



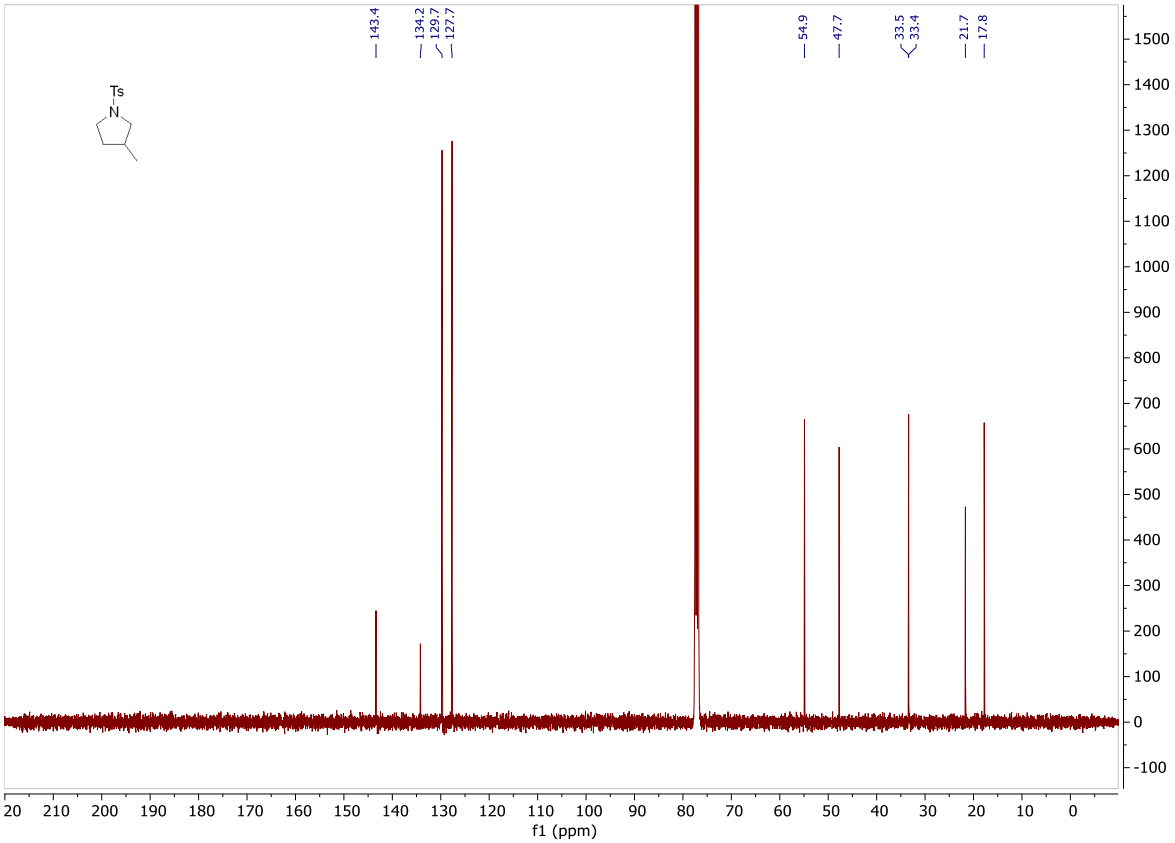
(E)-1-(5-bromopent-1-en-1-yl)-4-methoxybenzene (12), ^{13}C NMR (101 MHz, $CDCl_3$)



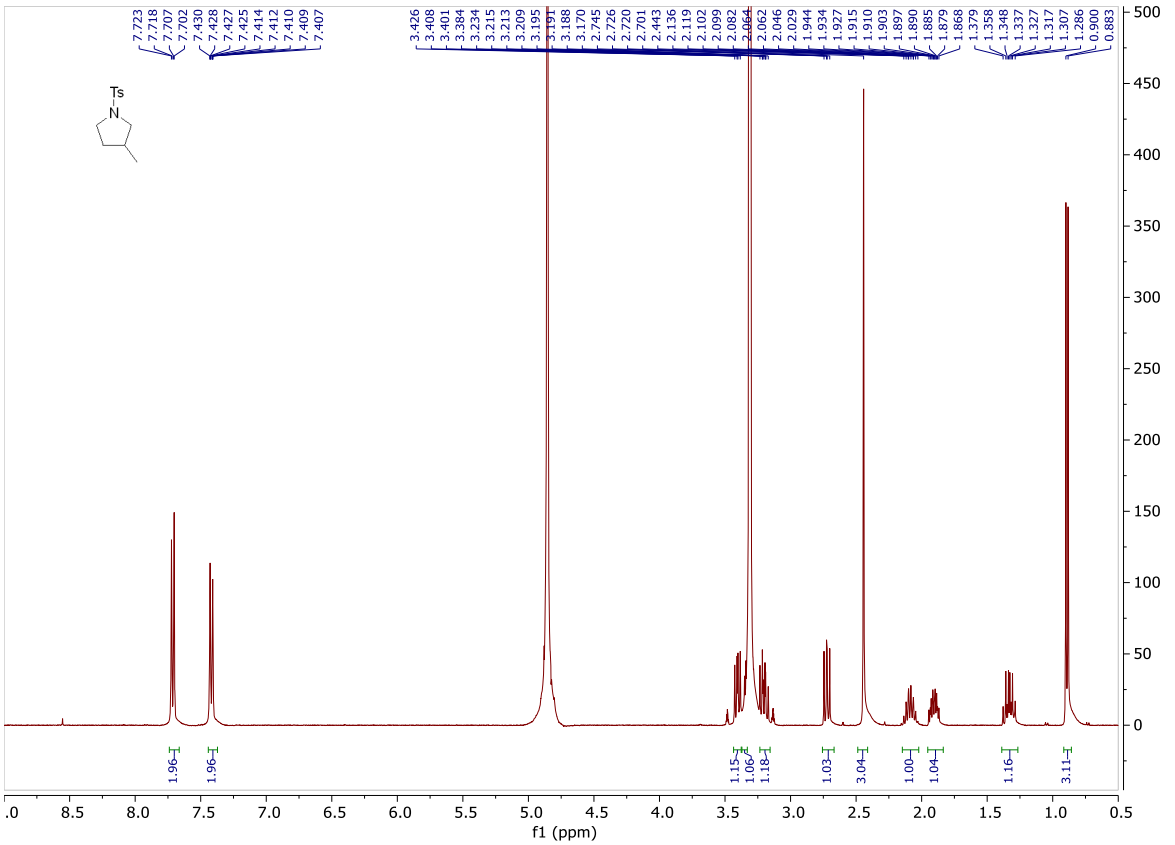
3-methyl-1-tosylpyrrolidine (2a), ^{1}H NMR (400 MHz, $CDCl_3$)



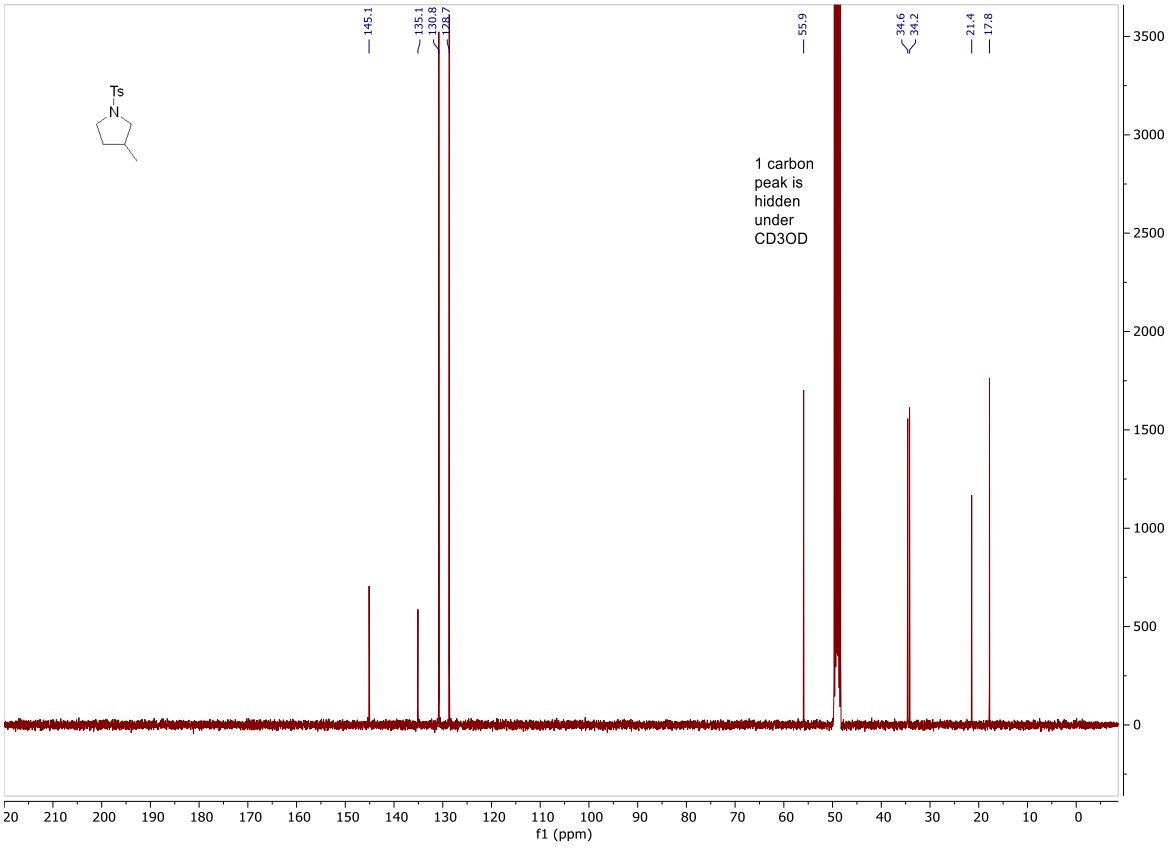
3-methyl-1-tosylpyrrolidine (2a), ^{13}C NMR (101 MHz, $CDCl_3$)



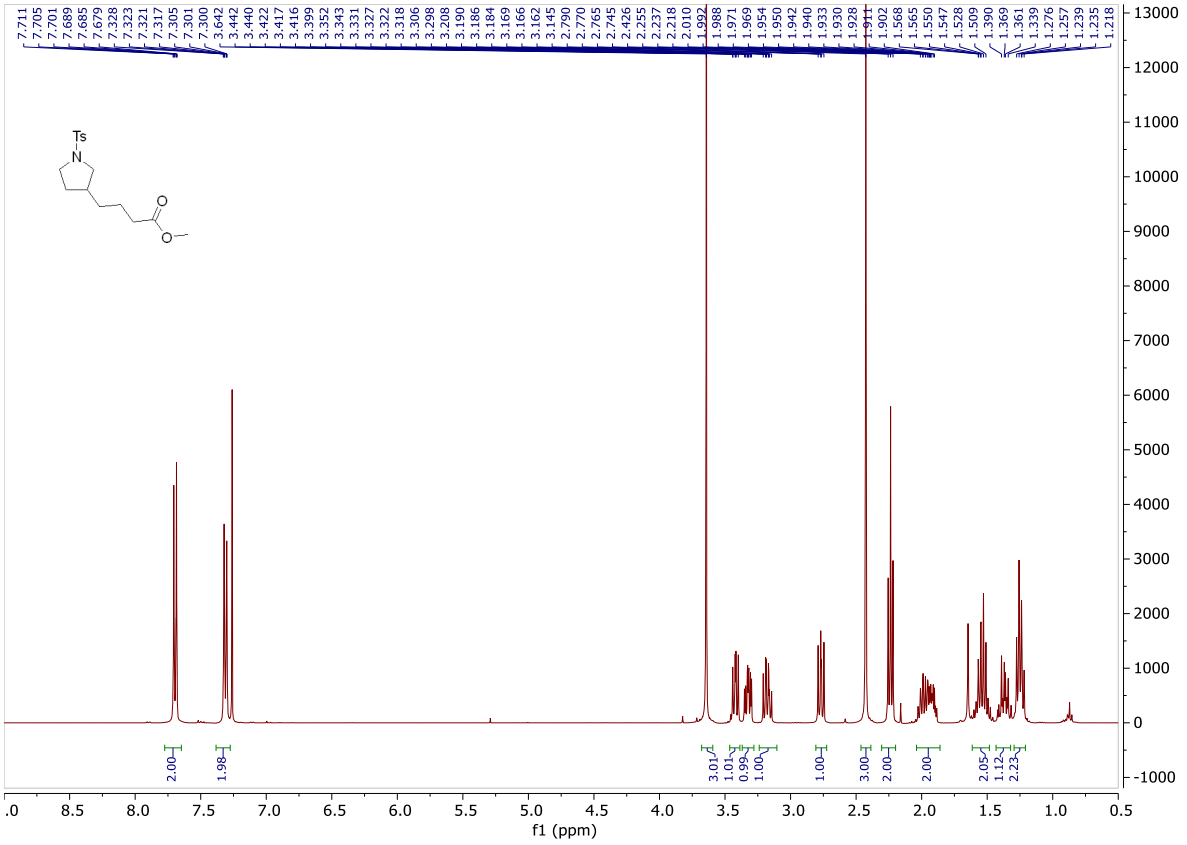
3-methyl-1-tosylpyrrolidine (2a), ^{1}H NMR (400 MHz, CD_3OD)



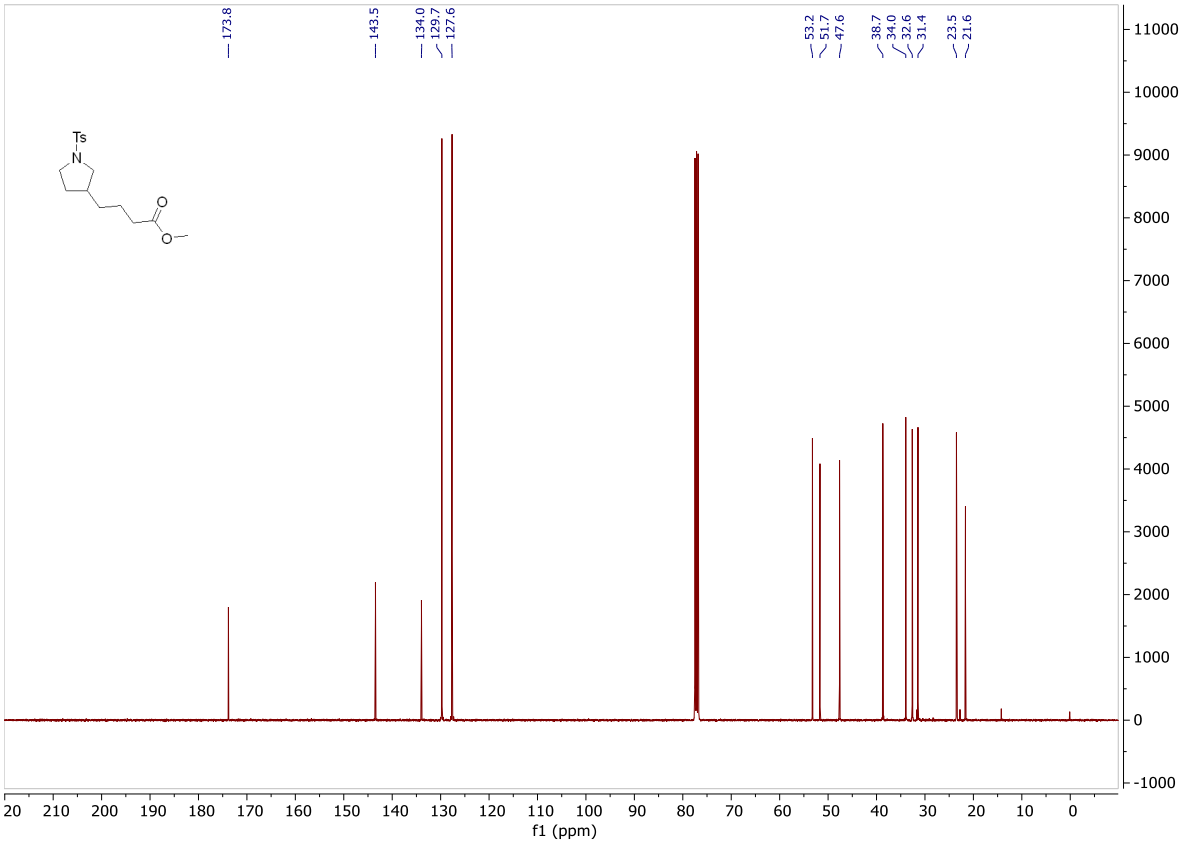
3-methyl-1-tosylpyrrolidine (2a), ^{13}C NMR (101 MHz, CD_3OD)



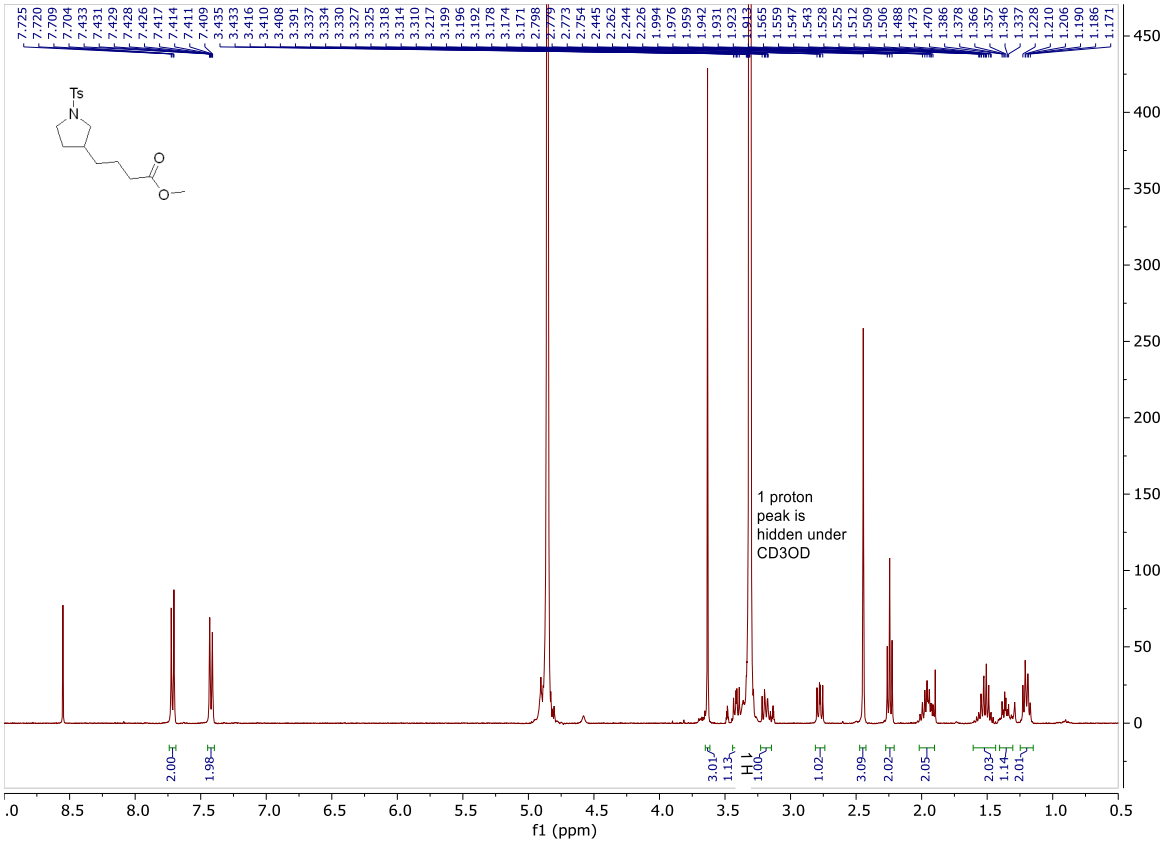
methyl 4-(1-tosylpyrrolidin-3-yl)butanoate (13a) , ^{1}H NMR (400 MHz, $CDCl_3$)



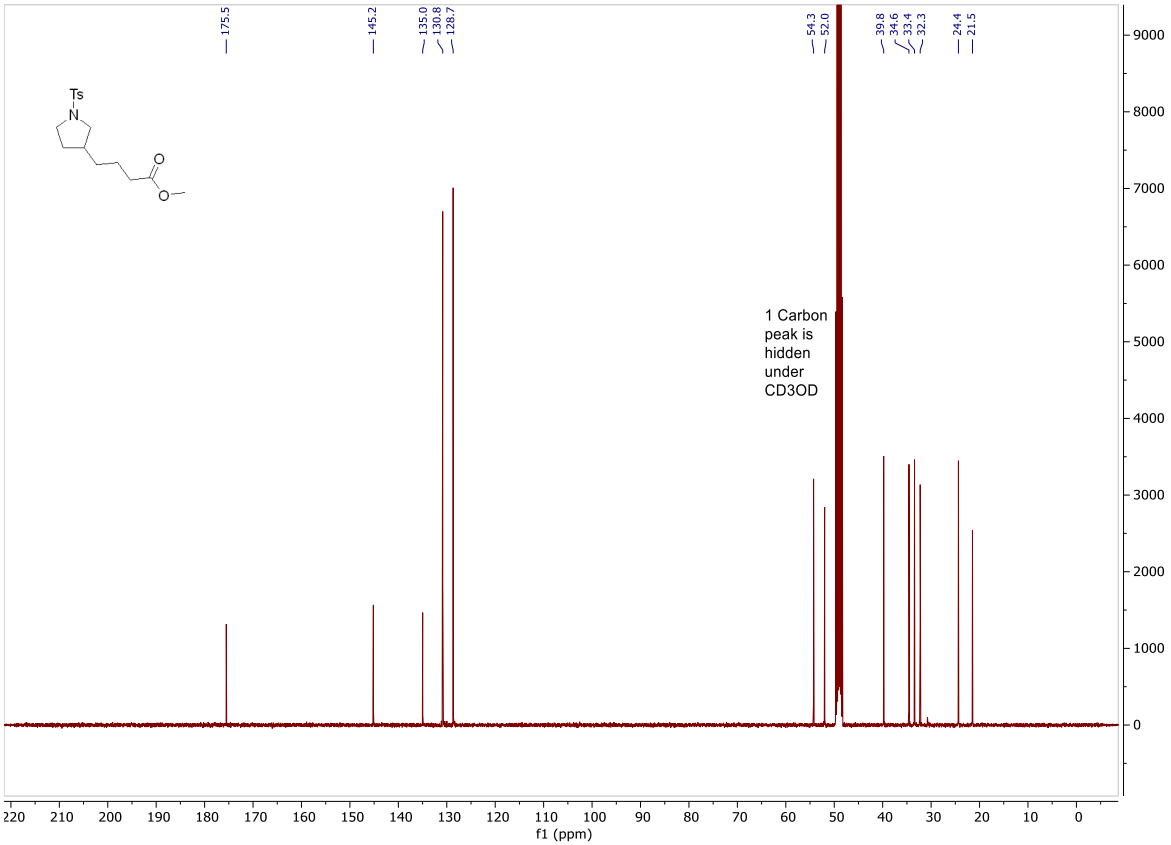
methyl 4-(1-tosylpyrrolidin-3-yl)butanoate (13a), ^{13}C NMR (101 MHz, $CDCl_3$)



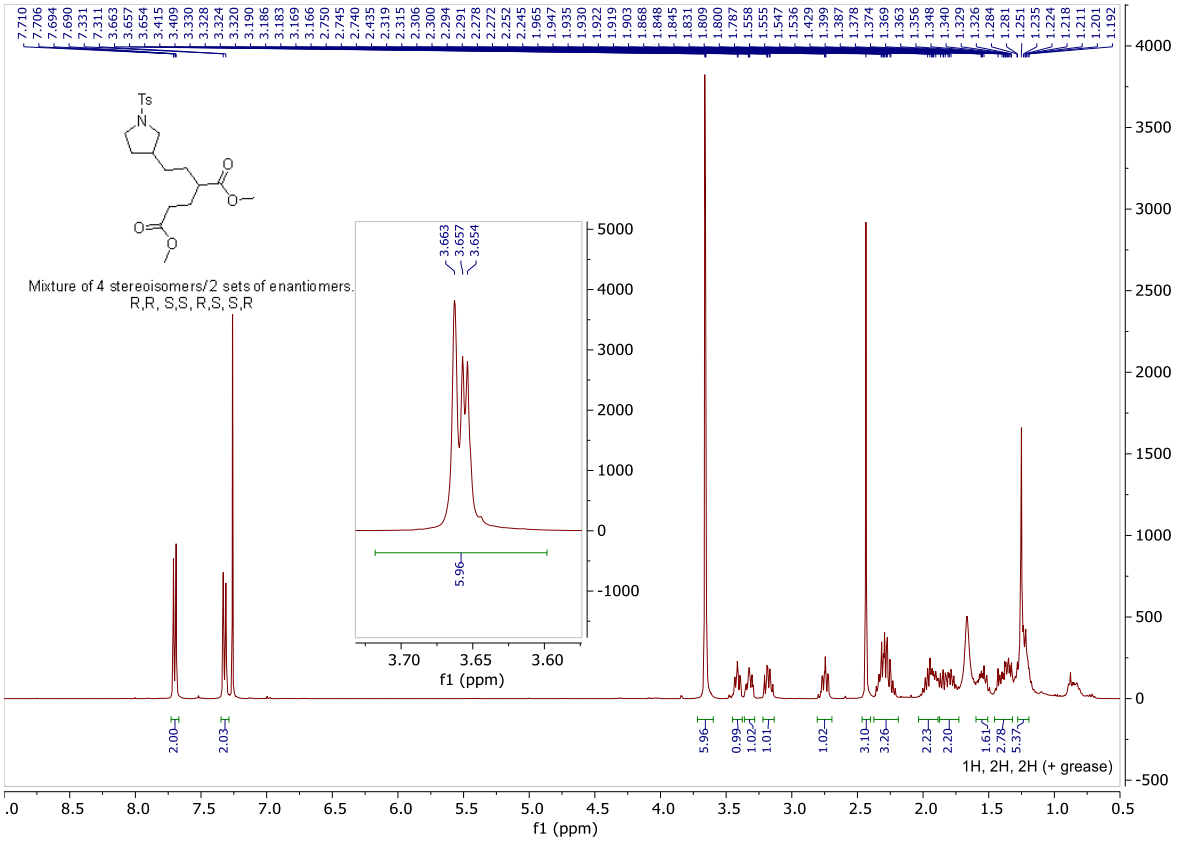
methyl 4-(1-tosylpyrrolidin-3-yl)butanoate (13a) , ^{1}H NMR (400 MHz, CD_3OD)



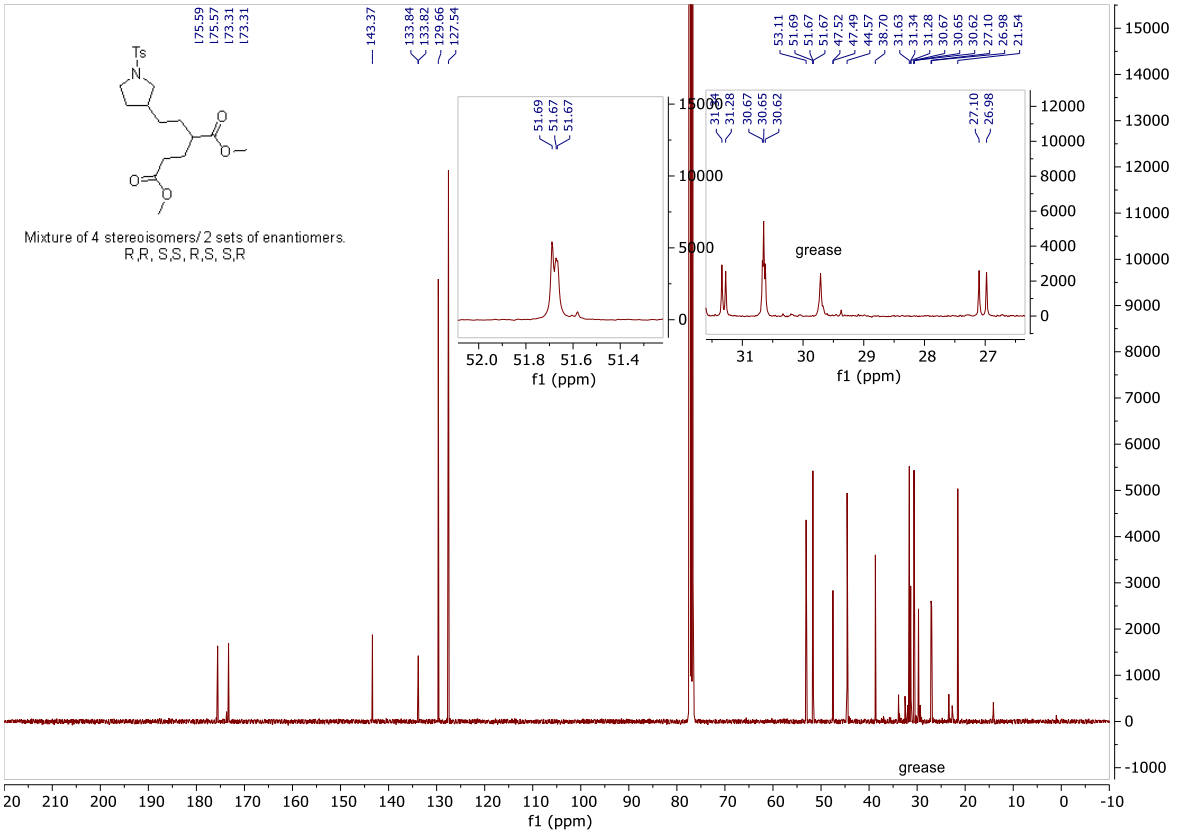
methyl 4-(1-tosylpyrrolidin-3-yl)butanoate (13a), ^{13}C NMR (101 MHz, CD_3OD)



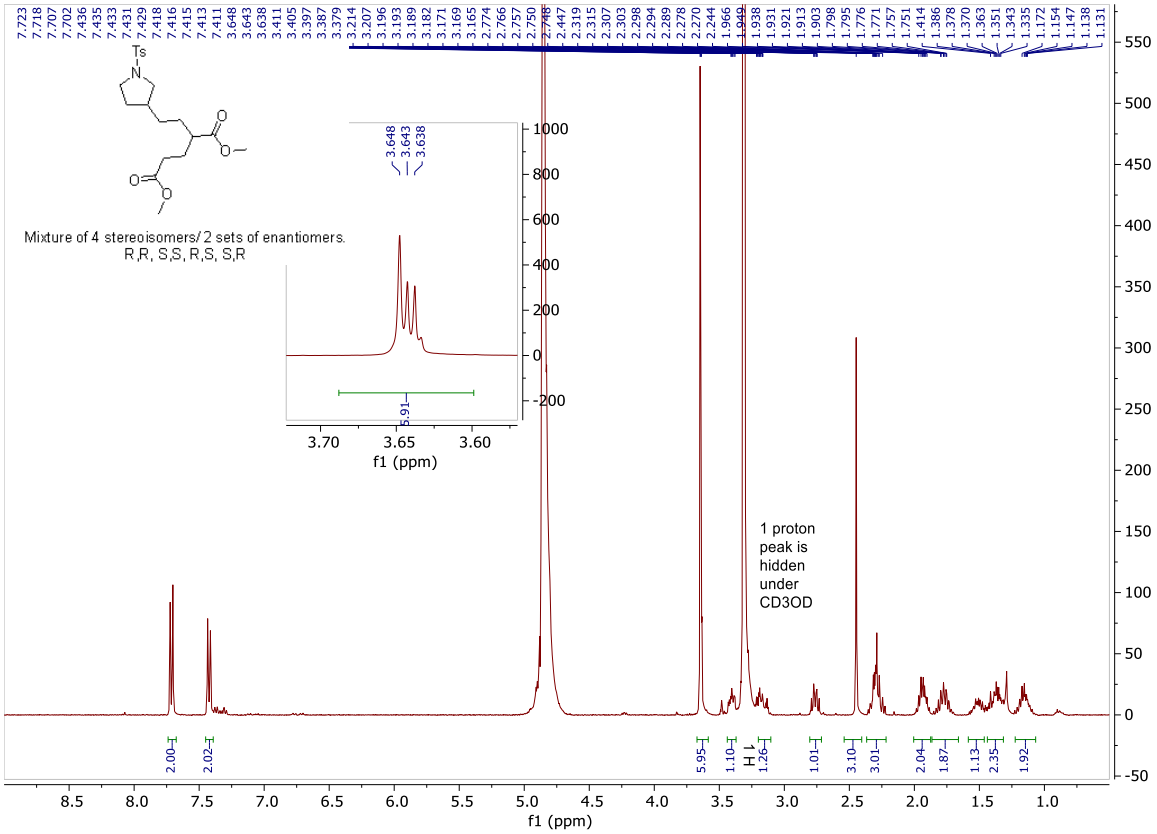
dimethyl 2-(2-(1-tosylpyrrolidin-3-yl)ethyl)pentanedioate (13b), ^{1}H NMR (400 MHz, $CDCl_3$) – 4 isomers



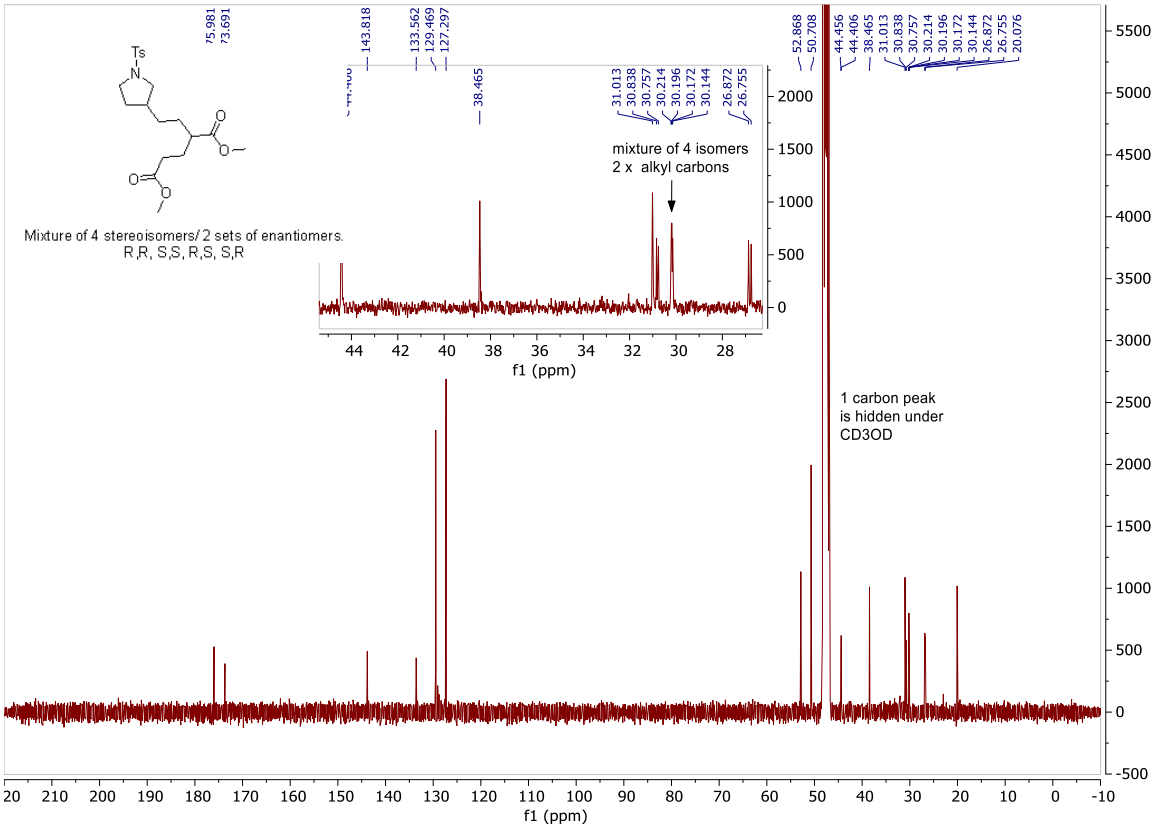
dimethyl 2-(2-(1-tosylpyrrolidin-3-yl)ethyl)pentanedioate (13b), ^{13}C NMR (101 MHz, $CDCl_3$) – 4 isomers



dimethyl 2-(2-(1-tosylpyrrolidin-3-yl)ethyl)pentanedioate (13b), ^{1}H NMR (400 MHz, CD_3OD) 4 isomers



dimethyl 2-(2-(1-tosylpyrrolidin-3-yl)ethyl)pentanedioate (13b), ^{13}C NMR (101 MHz, CD_3OD) 4 isomers



IV. References

1. M. Zidan, T. McCallum, R. Swann and L. Barriault, *Org. Lett.*, 2020, **22**, 8401-8406.
2. X. Dong, R. Sang, Q. Wang, X.-Y. Tang and M. Shi, *Chem. Eur. J.*, 2013, **19**, 16910-16915.
3. S.-H. Ueng, L. Fensterbank, E. Lacôte, M. Malacria and D. P. Curran, *Org. Biomol. Chem.*, 2011, **9**, 3415-3420.
4. G. Giambastiani and G. Poli, *J. Org. Chem.*, 1998, **63**, 9608-9609.
5. P. F. Keusenkothen and M. B. Smith, *Tetrahedron*, 1992, **48**, 2977-2992.
6. H. Liu, L. Huo, B. Yang, Y. Yuan, W. Zhang, Z. Xu, S. Qiu and H. Tan, *Org. Lett.*, 2017, **19**, 4786-4789.
7. D. B. Ushakov and M. E. Maier, *Synlett*, 2013, **24**, 705-708.
8. L. F. Tietze, H. Schirok and M. Wöhrmann, *Chem. Eur. J.*, 2000, **6**, 510-518.
9. I. Colomer, R. C. Barcelos, K. E. Christensen and T. J. Donohoe, *Org. Lett.*, 2016, **18**, 5880-5883.
10. T. Fujioka, T. Nakamura, H. Yorimitsu and K. Oshima, *Org. Lett.*, 2002, **4**, 2257-2259.
11. E. Tosi, K. Spielmann, R. M. de Figueiredo and J.-M. Campagne, *Synlett*, 2021, **32**, 517-520.
12. D. Wei, X. Li, L. Shen, Y. Ding, K. Liang and C. Xia, *Org. Chem. Front.*, 2021, **8**, 6364-6370.
13. C. González-Rodríguez, J. A. Varela, L. Castedo and C. Saá, *J. Am. Chem. Soc.*, 2007, **129**, 12916-12917.
14. S. Kc, P. Basnet, S. Thapa, B. Shrestha and R. Giri, *J. Org. Chem.*, 2018, **83**, 2920-2936.
15. V. B. Phapale, E. Buñuel, M. García-Iglesias and D. J. Cárdenas, *Angew. Chem. Int. Ed.*, 2007, **46**, 8790-8795.
16. S. T. Nguyen, Q. Zhu and R. R. Knowles, *ACS Catal.*, 2019, **9**, 4502-4507.
17. X. Yu, H. Zhao, P. Li and M. J. Koh, *J. Am. Chem. Soc.*, 2020, **142**, 18223-18230.
18. M. Lim, D. Park and J. Yun, *Org. Lett.*, 2023, **25**, 8917-8921.
19. Z. Wu, X. Xu, J. Wang and G. Dong, *Science*, 2021, **374**, 734-740.
20. S. Kehrli, D. Martin, D. Rix, M. Mauduit and A. Alexakis, *Chem. Eur. J.*, 2010, **16**, 9890-9904.
21. F. Scharinger, Á. M. Pálvölgyi, M. Weisz, M. Weil, C. Stanetty, M. Schnürch and K. Bica-Schröder, *Angew. Chem. Int. Ed.*, 2022, **61**, e202202189.
22. S. C. Coote, P. O'Brien and A. C. Whitwood, *Org. Biomol. Chem.*, 2008, **6**, 4299-4314.
23. S. Smoleń, A. Wincenciuk, O. Drapała and D. Gryko, *Synthesis*, 2020, **53**, 1645-1653.