# Supplementary Information

# Ruthenium-Catalyzed Intermolecular Alkene-Alkyne Couplings in biologically relevant media

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## Contents

## General information

The synthesis of precursors and complexes were performed under an atmosphere of dry nitrogen using vacuum-line and standard Schlenk techniques. Dry solvents were directly purchased from Sigma Aldrich or Acros Organics and used without further purification. Water used in the catalytic reactions was fresh Mili-Q grade. The abbreviation "rt" corresponds to approximately 23 ºC. All reactions were stirred using Teflon-coated magnetic stirring bars. Flash chromatography was carried out on Merck Geduran Si 60 (40 – 63 µm) silica gel (normal phase) or by reversed-phase high- performance liquid chromatography (RP-HPLC) otherwise stated. $MgSO_4$ were used as drying agents. Reactions carried out with temperature control were performed using either Thermo watch-controlled silicone oil baths or heating blocks for heating or the corresponding bath for cooling (water-ice for 0 ºC or acetone-dry ice for -78 ºC).

$^1H$, $^{13}C$ NMR spectra were collected on a 300 MHz (Varian), 400 MHz (Varian), 400 MHz (Bruker) or 500 MHz (Bruker and Varian) in $CDCl_3$. Carbon types and structure assignments were determined from DEPT-NMR. NMR spectra were analyzed using MestreNova© NMR data processing software (www.mestrelab.com). Abbreviations to denote the multiplicity of the signals are s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet), m (multiplet) and their corresponding combinations.

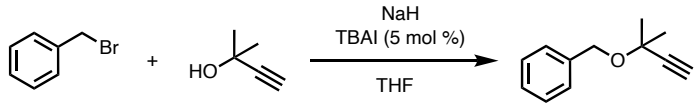
All peptide synthesis reagents and amino acid derivatives were purchased from Sigma Aldrich and Iris Biotech; amino acids were purchased as protected Fmoc amino acids with the standard side chain protecting scheme:, Fmoc-Phe-OH, Fmoc-Ile-OH, FmocTyr-OH, Fmoc-Pro-OH Fmoc-His(Trt)-OH, Fmoc-Val-OH, Fmoc-propargylGly-OH, Boc-propargylGly-OH. All other chemicals were purchased from Aldrich. All solvents were dry and synthesis grade, unless specifically noted.

## Synthesis of reaction precursors

### Alkynes

Alkynes **2b**, **2f**, **2h**, **2i**, **2j**, **2l**, **2m**, **2n**, **2o** are commercially available and were used without further purification.

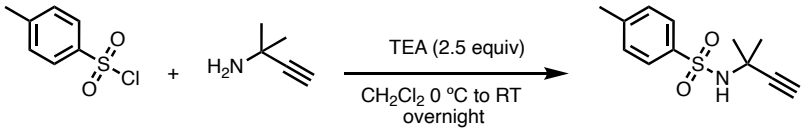
### (((2-Methylbut-3-yn-2-yl)oxy)methyl)benzene (2a)




The synthesis of **2a** was carried out according to a reported procedure:[1]

In a dried round bottom flask under nitrogen, 2-methyl-3-butyn-2-ol (1.2 mL, 11.8 mmol, 1.0 equiv) was added to an heterogeneous mixture of NaH (60% in mineral oil, 0.594 g, 14.9 mmol, 1.25 equiv) in anhydrous THF (80 mL). After stirring the mixture for 1h at rt, tetrabutylammonium iodide (TBAI, 0.220 g, 0.60 mmol, 0.050 equiv) and benzyl bromide (1.8 mL, 14.9 mmol, 1.25 equiv) were sequentially added and the mixture was stirred for 18 h. Then, the reaction mixture was diluted with $Et_2O$ (100 mL), washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered. The organic phases were concentrated under reduced pressure and the resulting residue was purified by flash column chromatography (FCC) in silica gel using Hexanes:$Et_2O$ (98:2) as eluent, to afford **2a** as a colorless oil (1.49 g, 8.56 mmol, 72% yield). The NMR data is in accordance with that previously reported.[1] **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.46 – 7.19 (m, 6H), 4.67 (s, 2H), 2.50 (s, 1H), 1.58 (s, 6H).

### *N*-(1,1-Dimethylprop-2-ynyl)-*p*-toluenesulfonamide (2b)

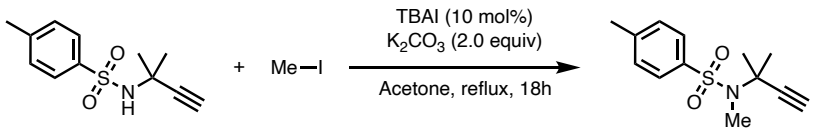



The synthesis of **2b** was carried out according to a reported procedure:[2]

2-Methylbut-3-yn-2-amine (1.9 mL, 18.0 mmol, 1.0 equiv), $Et_3N$ (6.3 mL, 45.1 mmol, 2.5 equiv) and $CH_2Cl_2$ (36 mL) were added to a two neck round bottom flask under nitrogen atmosphere. The mixture was cool down in an ice-water bath for 15 min and tosyl

chloride (3.44 g, 18.0 mmol, 1.0 equiv) was added in one portion. The mixture was allowed to warm to rt and was stirred overnight. The reaction was quenched by the addition of HCl (15 mL, 1M) and the aqueous phase was extracted with $CH_2Cl_2$ (2x10 mL). The organic phase was then washed with $NaHCO_3$ (aq, 15 mL), brine (15 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford compound **2b** as a white off powder (3.22g, 13.5 mmol, 75% yield). No further purification was required. The NMR data is in accordance with that previously reported. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.90 (s, 1H), 2.44 (s, 3H), 2.12 (s, 1H), 1.57 (s, 6H).

***N*-Methyl-N-(1,1-dimethylprop-2-ynyl)-p-toluenesulfonamide (2c)**

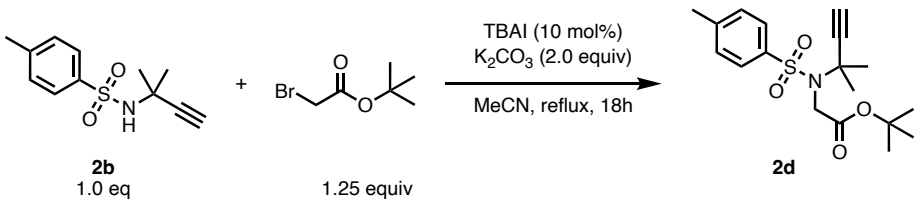



**2c**

The synthesis of **2c** was carried out according to a reported procedure:[3]

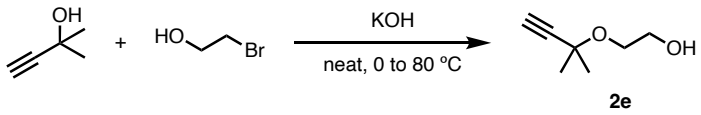
N-(1,1-dimethylprop-2-ynyl)-*p*-toluenesulfonamide, **2b**, (474 mg, 2.0 mmol, 1.0 equiv) was dissolved in acetone (10 mL), in a 50 mL Schlenk under nitrogen atmosphere. $K_2CO_3$ (567 mg, 4.0 mmol, 2.0 equiv), tetrabutylammonium iodide (TBAI, 74 mg, 0.2 mmol, 0.10 equiv) and MeI (250 $\mu$L, 4.0 mmol, 2.0 equiv) were sequentially added and the resulting mixture was refluxed for 18 h. Then, the solvent was removed under reduced pressure and the resulting residue was dissolved in EtOAc (15 mL), and sequentially washed with water (10 mL) and brine (10 mL). The organic phase was then dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give a residue which was purified by FCC in silica gel with Hexanes:EtOAc (8:2) as eluent to afford **2c** as a white off solid (410 mg, 1.6 mmol, 82% yield). The NMR data is in accordance with that previously reported. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 3.08 (s, 3H), 2.41 (s, 3H), 2.23 (s, 1H), 1.67 (s, 6H).

***tert*-Butyl N-(2-methylbut-3-yn-2-yl)-N-tosylglycinate (2d)**




N-(1,1-Dimethylprop-2-ynyl)-*p*-toluenesulfonamide, **2b** (1.0 g, 4.2 mmol, 1.0 equiv) was dissolved in acetonitrile (13.3 mL) in a 50 mL Schlenk tube under nitrogen atmosphere. $K_2CO_3$ (1.2g, 8.4 mmol, 2.0 equiv), tetrabutylammonium iodide (TBAI, 155 mg, 0.42 mmol, 0.10 equiv) and *tert*-butyl 2-bromoacetate (780 $\mu$L, 5.3 mmol, 1.25 equiv) were sequentially added to this solution. The resulting mixture was refluxed for 18 h, filtered through a celite plug and the solvent was removed under reduced pressure. The resulting crude residue was purified by FCC in silica gel using Hexanes: EtOAc (7:3) as eluent to afford **2d** as a white off solid (1.4 g, 4.0 mmol, 96% yield). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.9 (d, *J* = 7.6 Hz, 2H), 7.3 (d, *J* = 8.1 Hz, 2H), 4.3 (s, 2H), 2.4 (s, 3H), 2.3 (s, 1H), 1.7 (s, 6H), 1.5 (s, 9H).

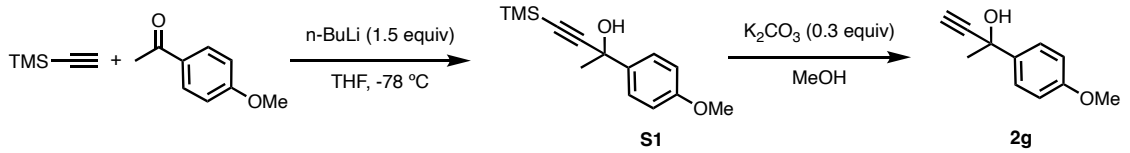
**2-((2-Methylbut-3-yn-2-yl)oxy)ethan-1-ol (2e)**




The synthesis of **2e** was carried out according to a reported procedure:[4]

In a 10 mL round bottom flask, crushed KOH pellets (2.7g, 47.5 mmol, 2.0 equiv) and 2-methylbut-3-yn-2-ol (2.0 g, 23.7 mmol, 1.0 equiv) were mixed for 15 min. 2-Bromoethanol (1.7 mL, 23.7 mmol, 1.0 equiv) was then added and the resulting reaction mixture was heated to 80 ºC overnight. After being cooled down to rt, the mixture was diluted with $Et_2O$, filtered through a celite plug and the solvent was removed under reduced pressure to give a crude residue which was purified by FCC in silica gel with pentane:$Et_2O$ (6:4) to afford **2e** as a clear oil (450 mg, 3.50 mmol, 15% yield). The NMR data is in accordance with that previously reported. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 3.80 – 3.59 (m, 4H), 2.47 – 2.39 (m, 1H), 1.54 – 1.51 (m, 3H), 1.48 (t, *J* = 0.9 Hz, 3H).

***p*-(4-Methoxyphenyl)but-3-yn-2-ol (2g)**



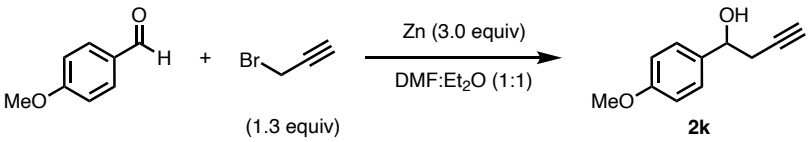

The synthesis of **2g** was carried out according to a reported procedure:[5]

i) In a 250 mL two neck round bottom flask under nitrogen atmosphere trimethylsilylacetylene (4.0 mL, 28.2 mmol, 1.6 equiv) was dissolved in THF (80 mL) and cooled down to -78 °C. After 15 min, *n*-BuLi (10.6 mL, 2.5 M in hexanes, 1.5 equiv) was added dropwise and the reaction mixture was allowed to stir at -78 ºC for 15 min. A solution of 2-acetophenone (3.0 g, 17.6 mmol) in THF (10 mL) was then added dropwise, the mixture was stirred at -78 °C for 15 min and then allowed to warm up to rt. After being stirred for 1 h, $NaHCO_3$ (aq, 100 mL), and EtOAc (100 mL) were added. The aqueous phase was extracted with EtOAc (2 x 50 mL) and the combined organic layers were washed with brine (40 mL), dried over anhydrous $Mg_2SO_4$ and concentrated under reduced pressure. The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (8:2) as eluent, to afford compound **S1** as a colorless oil (5.60 g, 22.5 mmol, 90% yield). The NMR data is in accordance with that previously reported. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 8.2 Hz, 2H), 3.82 (s, 3H), 1.74 (s, 3H), 0.21 (s, 9H).

ii) In a 25 mL round bottom flask under nitrogen atmosphere the trimethylsilyl protected alkyne **S1** (1.0 g, 4.0 mmol, 1.0 equiv) was dissolved in MeOH (8.0 mL) and $K_2CO_3$ (167.0 mg, 1.21 mmol, 0.3 equiv) was added to this solution. The mixture was stirred at rt until TLC indicated complete consumption of the starting material (1 h aprox.). The solvent was then removed under reduced pressure, the residue was resuspended in $NH_4Cl$ (sat, 15 mL) and $Et_2O$ (15 mL). The phases were separated, and the aqueous phase was extracted with $Et_2O$ (2 x 10 mL). The combined organic phases were washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting residue was purified by FCC in silica gel using Hexanes:EtOAc (8:2) as eluent to afford **2g** as a colorless oil (210.0 mg, 1.2 mmol, 30% yield). The NMR data is in accordance with that previously

reported. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.2 Hz, 2H), 3.82 (s, 3H), 2.67 (s, 1H), 1.78 (s, 3H).

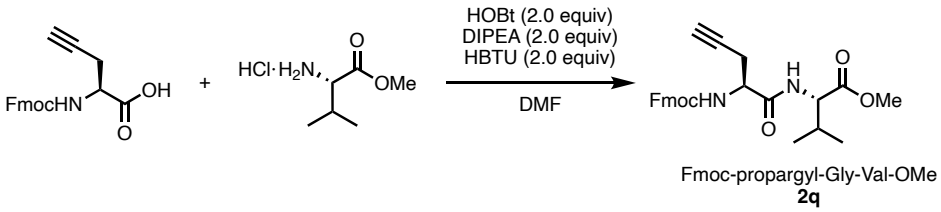
**1-(4-Methoxyphenyl)but-3-yn-1-ol (2k)**




The synthesis of **2k** was carried out according to a reported procedure:[6]

Freshly activated Zn (2.0 g, 30 mmol, 3.0 equiv) was added over the period of 10 min to a 250 mL round-bottom flask connected to a reflux condenser, containing a solution of *p*-anisaldehyde (1.2 mL, 10 mmol, 1.0 equiv) and propargyl bromide (80% in toluene, 1.4 mL, 13 mmol, 1.3 equiv) in $Et_2O$:DMF (1:1, 100 mL). The reaction mixture was stirred at rt for 18h. After the indicated time, the reaction was quenched by slow addition of $NH_4Cl$ (sat), the aqueous phase was extracted with $Et_2O$ (3 x 30 mL) and the resulting organic fraction was washed with brine (3 x 50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (8:2) as eluent to afford **2k** as a colorless oil (1.1 g, 6.2 mmol, 62% yield). The NMR data is in accordance with that previously reported **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 2H), 6.94 – 6.84 (m, 2H), 4.83 (td, *J* = 6.5, 3.4 Hz, 1H), 3.80 (s, 3H), 2.98 – 2.84 (m, 3H), 2.67 – 2.58 (m, 2H).

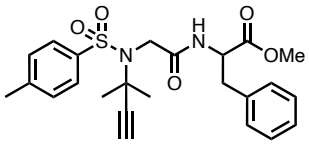
**Methyl Fmoc-L-2-propargylglycyl-*L*-valinate (2q)**




In a 10 mL round bottom flask under nitrogen, Fmoc-propargyl-Gly-OH (75.8 mg, 0.36 mmol, 1.05 equiv), HBTU (217.4 mg, 0.68 mmol, 2.0 equiv), HOBt (103.7 mg, 0.68 mmol, 2.0 equiv) and DIPEA (118 $\mu$L, 0.68 mmol, 2.0 equiv) were mixed in DMF (3.4 mL) and cooled down to 0 ºC. After 10 min at this temperature, methyl L-valinate hydrochloride (61.5 mg, 0.34 mmol, 1.0 equiv) was added, the mixture was allowed to warm to rt and stirred overnight. The solvent was removed by vacuum distillation, the

residue was redissolved in $CH_2Cl_2$ (10 mL) and washed with aqueous $NaHCO_3$ (10% , 10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$ and removed under reduced pressure to give a crude residue which was purified by FCC in silica gel using $CH_2Cl_2$:*i*-PrOH (98:2) as eluent to afford **2q** as colorless sticky oil (140 mg, 0.31 mmol, 92% yield). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.61 (d, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 1H), 5.85 – 5.76 (m, 1H), 4.65 – 4.55 (m, 1H), 4.53 – 4.38 (m, 3H), 4.25 (t, *J* = 7.1 Hz, 1H), 3.73 (s, 3H), 2.82 (d, *J* = 17.1 Hz, 1H), 2.73 – 2.58 (m, 1H), 2.27 – 2.15 (m, 1H), 2.15 – 2.08 (m, 1H), 1.00 – 0.88 (m, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 171.9, 169.9, 156.0, 143.8, 143.8, 141.4, 127.8, 127.2, 125.1, 120.1, 79.3, 72.0, 67.5, 57.5, 53.4, 52.2, 47.1, 31.3, 22.7, 19.0, 17.9. **HRMS** (ESI+) for $C_{26}H_{29}N_2O_5$ $[M+H]^+$ 449.2071found 449.2070.

**Methyl *N*-(2-methylbut-3-yn-2-yl)-*N*-tosylglycylphenylalaninate (2p)**



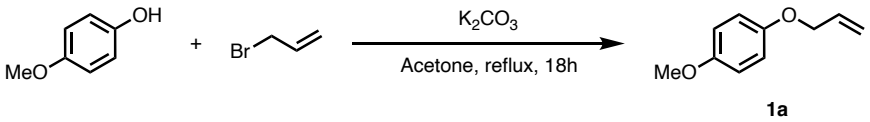

Tos-Prop-Gly-Phe-OMe
**2p**

Prepared according to the previously described procedure for the synthesis of **2q,** using *N*-(2-methylbut-3-yn-2-yl)-*N*-tosylglycine and D/L-phenylalaninate hydrochloride (76.7 mg, 0.34 mmol, 1.0 equiv). The resulting crude residue was purified by FCC in silica gel using $CH_2Cl_2$: *i*-PrOH (98:2) as eluent to afford **2p** as a yellow oil (114 mg, 0.25 mmol, 74% yield). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.38 – 7.17 (m, 6H), 6.99 (d, *J* = 8.3 Hz, 1H), 4.86 (q, *J* = 6.2 Hz, 1H), 4.05 (q, *J* = 17.9 Hz, 2H), 3.72 (s, 3H), 3.22 – 3.06 (m, 2H), 2.42 (s, 3H), 2.10 (s, 1H), 1.56 (d, *J* = 7.0 Hz, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 171.6, 169.4, 144.1, 137.1, 135.8, 129.7, 129.5, 128.8, 128.1, 127.3, 84.5, 72.6, 57.1, 53.2, 52.3, 51.7, 37.9, 30.6, 30.1, 21.6. **HRMS** (ESI+) for $C_{24}H_{29}N_2O_5S$ $[M+H]^+$ 457.1786 found 457.1792.

**Alkenes**

Alkene **1d** is commercially available and was used without further purification.

**1-(Allyloxy)-4-methoxybenzene (1a)**

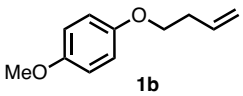



**1a**

The synthesis of **1a** was carried out according to a reported procedure:[7]

In a dried 100 mL round bottom flask under nitrogen atmosphere, 4-methoxyphenol (2.0 mL, 16.1 mmol, 1.0 equiv) was dissolved in acetone (40 mL). $K_2CO_3$ (4.4 g, 32.2 mmol, 2.0 equiv) and allyl bromide (1.7 mL, 19.3 mmol, 1.2 equiv) were added, the mixture was refluxed for 18 h, filtered through a celite plug and the volatiles were removed under reduced pressure. The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (9:1) as eluent to afford **1a** as colorless oil (2.5 g, 15.2 mmol, 94% yield). The NMR data is in accordance with that previously reported. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 6.91 – 6.78 (m, 4H), 6.05 (ddt, *J* = 15.9, 10.5, 5.3 Hz, 1H), 5.40 (d, *J* = 17.2 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 4.49 (d, *J* = 5.1 Hz, 2H), 3.77 (s, 3H).

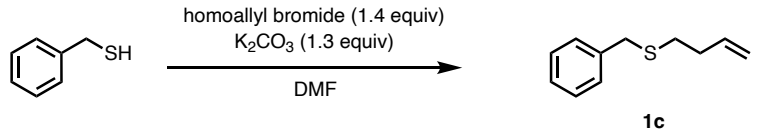
**1-(But-3-en-1-yloxy)-4-methoxybenzene (1b)**




**1b**

Prepared according to the previously described procedure for the synthesis of **1a**, using homoallyl bromide instead of allyl bromide. The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (9:1) as eluent to afford **1b** as colorless oil (1.70 g, 10.0 mmol, 62% yield). The NMR data is in accordance with that previously reported[8].**$^1$H NMR** (300 MHz, $CDCl_3$) δ 6.89 – 6.76 (m, 4H), 5.91 (ddt, *J* = 13.4, 10.1, 6.7 Hz, 1H), 5.25 – 4.98 (m, 2H), 3.97 (t, *J* = 6.7 Hz, 2H), 3.77 (s, 3H), 2.52 (q, *J* = 6.5 Hz, 2H).

**Benzyl(but-3-en-1-yl)sulfane (1c)**

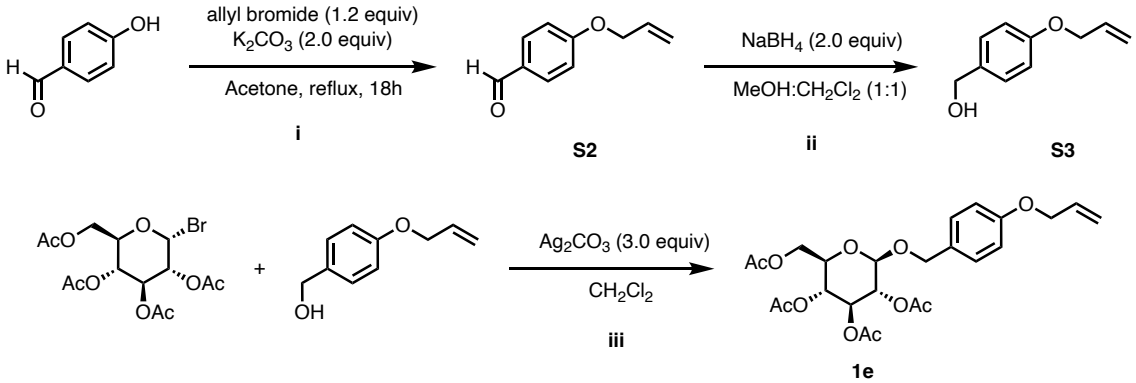



**1c**

The synthesis of **1c** was carried out according to a reported procedure:[9]

$K_2CO_3$ (3.0 g, 22.1 mmol, 1.3 equiv) and homoallyl bromide (1.3 mL, 23.9 mmol, 1.4 equiv) were added to a 100 mL round bottom flask containing a solution of benzyl mercaptan (2.0 mL, 17.1 mmol, 1.0 equiv) in DMF (40 mL), under nitrogen. The reaction mixture was stirred for 18 h, poured into water (200 mL) and extracted with $Et_2O$ (2x15 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried over $MgSO_4$ and filtered. The organic phase was concentrated under reduced pressure to give a crude residue which was purified by FCC in silica gel using Hexanes:EtOAc (98:2) as eluent to afford **1c** as a colorless oil (2.10 g, 12.0 mmol, 70% yield). The NMR data is in accordance with that previously reported. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 15.8 Hz, 5H), 5.82 (ddt, *J* = 16.9, 10.3, 6.6 Hz, 1H), 5.19 – 4.91 (m, 2H), 3.75 (s, 2H), 2.51 (t, *J* = 7.3 Hz, 2H), 2.33 (q, *J* = 7.2 Hz, 2H).

**(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-((4-(allyloxy)benzyl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (1e)**

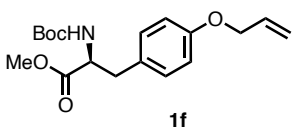



i) 4-(Allyloxy)benzaldehyde (**S2**) was prepared according to the previously described procedure for the synthesis of **1a**. The crude residue was purified by FCC in silica gel using Hexanes:EtOAc (9:1) as eluent. (2.24 g, 13.8 mmol, 85% yield, colorless oil). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.83 (d, *J* = 6.8 Hz, 2H), 7.02 (d, *J* = 6.8 Hz, 2H), 6.15 – 5.96 (m, 1H), 5.43 (d, *J* = 17.3 Hz, 1H), 5.33 (d, *J* = 10.6 Hz, 1H), 4.67 – 4.58 (m, 2H).

ii) In a dried 100 mL Schlenk tube, 4-(allyloxy)benzaldehyde (**S2,** 1.0 g, 6.20 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$:MeOH (1:1, 60 mL). The mixture was cooled down to 0 ºC for 15 min and $NaBH_4$ (467 mg, 12.3 mmol, 2.0 equiv) was added portion wise. After 30 min, the reaction was allowed to warm to rt and stirred overnight. Then, it was quenched by addition of HCl (1.0 M, 10 mL), the organic phase was removed under reduced pressure and the resulting aqueous mixture was extracted with $CH_2Cl_2$ (2x20 mL). The combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude residue that was purified by FCC in silica gel using Hexanes:EtOAc (8:2) as eluent to afford (4-(allyloxy)phenyl)methanol (**S3**) as colorless oil (732 mg, 4.46 mmol, 72% yield). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.36 – 7.22 (m, 2H), 6.98 – 6.87 (m, 2H), 6.08 (ddt, *J* = 17.2, 10.5, 5.3 Hz, 1H), 5.43 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.31 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.64 (s, 2H), 4.57 (dt, *J* = 5.3, 1.5 Hz, 2H).

iii) In a dried 10 mL Schlenk tube, (4-(allyloxy)phenyl)methanol (**S3**, 150 mg, 0.36 mmol, 1.0 equiv) was dissolved in dry $CH_2Cl_2$ (2.0 mL) over 4 A MS. $Ag_2CO_3$ (302 mg, 1.1 mmol, 3.0 equiv) and a crystal of iodine were added to the solution. After being stirred for 15 min, a solution of the bromo-sugar ((2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-(bromomethyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate) (180 mg, 1.1 mmol, 3.0 equiv in 1.5 mL of $CH_2Cl_2$) was added to the mixture, the tube was shielded from light and the mixture was stirred overnight. Then, the reaction mixture was diluted with EtOAc and filtered through a celite plug and the solvent was removed under reduced pressure to give a crude residue which was purified by FCC in silica gel using Hexanes:EtOAc (7:3 to 1:1) as eluent to afford **1e** as colorless sticky oil (120 mg, 0.24 mmol, 66% yield). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.24 – 7.12 (m, 2H), 6.94 – 6.81 (m, 2H), 6.03 (ddt, *J* = 17.1, 10.5, 5.2 Hz, 1H), 5.46 – 5.32 (m, 1H), 5.27 (dt, *J* = 10.4, 1.5 Hz, 1H), 5.21 – 4.95 (m, 3H), 4.79 (d, *J* = 11.9 Hz, 1H), 4.58 – 4.43 (m, 4H), 4.25 (dd, *J* = 12.3, 4.7 Hz, 1H), 4.14 (dd, *J* = 12.3, 2.5 Hz, 1H), 3.64 (m, 1H), 2.08 (s, 3H), 1.98 (d, *J* = 6.8 Hz, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 170.7, 170.3, 169.5, 169.4, 158.6, 133.2, 129.6, 128.8, 117.8, 114.8, 99.0, 72.9, 71.9, 71.4, 70.5, 68.9, 68.5, 62.1, 20.8, 20.7, 20.7. **HRMS** (ESI+) for $C_{24}H_{31}O_{11}$+ $[M+H]^+$ 495.1861 found 495.1855.

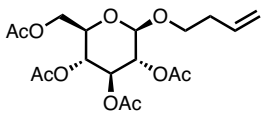
**Methyl (*S*)-3-(4-(allyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate. Boc- Tyr(Allyl)-OMe. (1f)**



**1f**

Prepared according to the previously described procedure for the synthesis of **1a**. No further purification was required after extraction. Compound **1f** was isolated as white off powder (566 mg, 1.70 mmol, 99%). The NMR data is in accordance with that previously reported.[10] **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.04 (d, *J* = 7.7 Hz, 2H), 6.91 – 6.81 (m, 2H), 6.14 – 5.96 (m, 1H), 5.54 – 5.39 (m, 1H), 5.30 (dd, *J* = 10.4, 2.2 Hz, 1H), 4.97 (d, *J* = 8.3 Hz, 1H), 4.60 – 4.48 (m, 2H), 3.76 – 3.69 (m, 3H), 3.05 (d, *J* = 6.1 Hz, 2H), 1.44 (s, 9H).

**(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(but-3-en-1-yloxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (1g)**



**1g**

Prepared according the previously described procedure for the synthesis of **1e**, using ((2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-(bromomethyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate) (150 mg, 365 µmol, 1.0 equiv), but-3-en-1-ol (94 µL, 1095 µmol, 3.0 equiv) and $Ag_2CO_3$ (302 mg, 1095 µmol, 3.0 equiv). The crude residue was purified by FCC in silica gel using Hexanes:EtOAc (7:3 to 1:1) as eluent to afford **1g** as white solid (75.5 mg, 187 µmol, 51% yield). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.17 (t, *J* = 9.4 Hz, 1H), 5.10 – 4.90 (m, 4H), 4.48 (d, *J* = 7.9 Hz, 1H), 4.24 (dd, *J* = 12.3, 4.7 Hz, 1H), 4.10 (dd, *J* = 12.3, 2.5 Hz, 1H), 3.89 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.67 (ddd, *J* = 9.9, 4.8, 2.5 Hz, 1H), 3.51 (dt, *J* = 9.5, 6.9 Hz, 1H), 2.39 – 2.24 (m, 2H), 2.10 – 1.91 (m, 12H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 170.7, 170.3, 169.5, 169.3, 134.5, 116.8, 100.9, 72.9, 71.9, 71.3, 69.4, 68.6, 62.1, 33.9, 20.8, 20.7, 20.7. **HRMS** (ESI+) for $C_{18}H_{26}O_{10}$+ $[M+H]^+$ 403.1599 found 403.1603.

Synthesis of peptides **2r** and **2s**

The peptides **Boc-NH-G(Prop)-V-G-W-A-CONH$_2$** (**2r**) and **Ac-NH-F-G-G(Prop)-V-G-W-A-CONH$_2$** (**2s**) were synthesized following the usual Solid Phase Peptide Synthesis (SPPS) protocol. Peptide syntheses was performed using Fmoc strategy on a Rink-amide-ChemMatrix (0.5 mmol/g) using DIC as activator, oxyma (ethyl(hydroxyimino)cyanoacetate) as base, and DMF as solvent. The removal of the temporal Fmoc protecting groups was performed by treating the resin with piperidine (20%) in DMF.

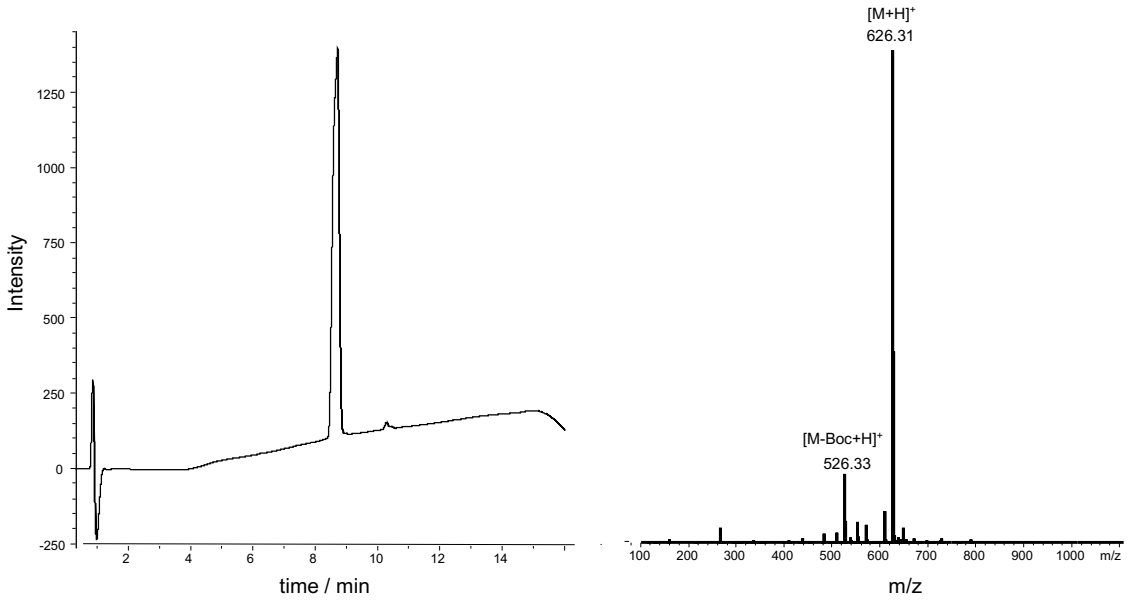
Acetylation of the *N*-terminus was carried out by treatment of the resin with 10 mL of an acetylation cocktail (1.6 ml $Ac_2O$ and 4 mL of DIPEA and 6.4 mL DMF) for 2h, followed by thoroughly washing with DMF (3 x 7 mL).

For cleavage of the peptide from the resin and deprotection of the side chains, 8 mL of deprotection cocktail (90 : 5 : 2.5 : 2.5 : 2.5, TFA : $CH_2Cl_2$ : $H_2O$ : TIPS) were added and the mixture was stirred for 2 h under $N_2$ bubbling. The solution was drained and collected, and the resin washed with 2 x 2 mL of the cocktail followed by 4 mL of $CH_2Cl_2$. The solvent was evaporated with a $N_2$ stream to a final volume of 2-3 mL.

The crude peptide was precipitated by addition of 45 mL of cold $Et_2O$. The mixture was homogenized by vortexing, kept at 0 ºC for 10 min, centrifuged and the supernatant decanted. $Et_2O$ (45 mL) were added again, and the process repeated twice.

For protection of the *N*-terminus with Boc group, the resulting crude solid was treated with di-tert-butyl decarbonate (5 mL, 0.2M in DMF) and DIPEA (5 mL, 0.2 M in DMF) for 4h. Then the solvent was removed under reduced pressure and the residue was purified by preparative HPLC (from 20 to 75% MeCN in water in 15 min), yielding peptide **2r** as a yellow fluffy solid.

**a)** **Boc-NH-G(Prop)-V-G-W-A-CONH$_2$ (2r)**




**b)** **Ac-NH-F-G-G(Prop)-V-G-W-A-CONH$_2$ (2s)**

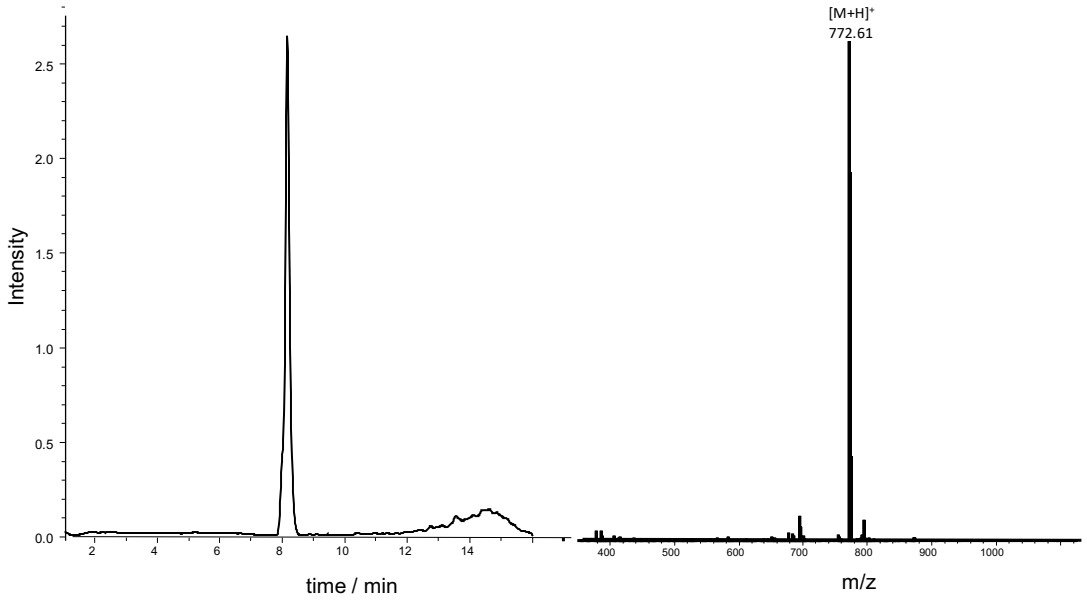
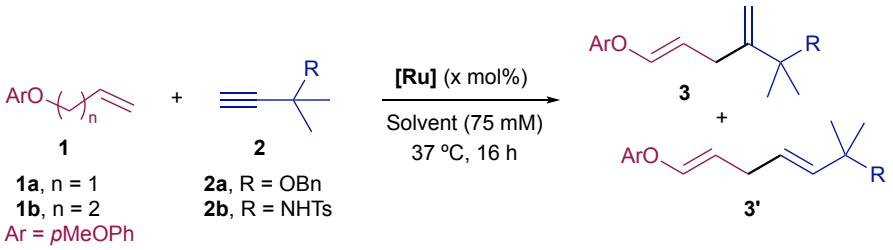



**Figure S1. a)** MS profile of A Boc-NH-G(Prop)-V-G-W-A-CONH$_2$ Calculated mass for $C_{31}H_{44}N_7O_7$: 626.3. Found: 626.3 $[M+H]^+$; 526.3 $[M-Boc+H]^+$**. b)** MS profile of Ac-NH-F-G-G(Prop)-V-G-W-A-CONH$_2$. Calculated mass for $C_{39}H_{50}N_9O_8$: 772.6. Found: 772.4 $[M+H]^+$.

## Ruthenium catalyzed alkene-alkyne coupling

### Table S1. Preliminary screening under aqueous conditions.[a]

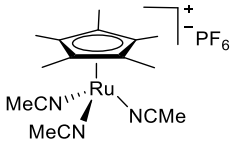



**1a**, n = 1
**1b**, n = 2
Ar = *p*MeOPh

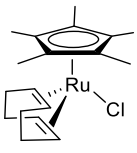
**2a**, R = OBn
**2b**, R = NHTs

| entry | 1 | 2 | solvent | [Ru] (x mol%) | regio (3:3') | 3, % yield |
|---|---|---|---|---|---|---|
| 1 | **1a** | **2a** | THF | **Ru1**, 10 | > 9:1 | **3aa**, 32 |
| 2 | **1a** | **2a** | Acetone | **Ru1**, 10 | > 9:1 | **3aa**, 30 |
| 3 | **1a** | **2a** | $CH_2Cl_2$ | **Ru1**, 10 | > 9:1 | **3aa**, 40 |
| 4 | **1a** | **2a** | $H_2O$ | **Ru1**, 10 | > 9:1 | **3aa**, 36 |
| 5 | **1a** | **2a** | $H_2O$/THF (8:2) | **Ru1**, 10 | > 9:1 | **3aa**, 70[b] |
| 6 | **1a** | **2a** | $H_2O$/THF (8:2) | **Ru2**, 10 | > 9:1 | **3aa**, 0 |
| 7 | **1a** | **2a** | $H_2O$/THF (9:1) | **Ru1**, 5 | > 9:1 | **3aa**, 56 |
| 8 | **1a** | **2b** | $H_2O$/THF (8:2) | **Ru1**, 5 | > 9:1 | **3ab**, 99 |
| 9 | **1a** | **2b** | $H_2O$/THF (9:1) | **Ru1**, 5 | > 9:1 | **3ab**, 68 |
| 10 | **1a** | **2b** | $H_2O$/EtOH (8:2) | **Ru1**, 5 | 5:1 | **3ab**, 88 |
| 11 | **1a** | **2b** | $H_2O$/$^t$BuOH (8:2) | **Ru1**, 5 | > 9:1 | **3ab**, 77 |
| 12 | **1a** | **2b** | $H_2O$/DMSO (8:2) | **Ru1**, 5 | > 9:1 | **3ab**, 45 |
| 13 | **1a** | **2b** | $H_2O$/DMF (8:2) | **Ru1**, 5 | > 5:1 | **3ab**, 57 |
| 14 | **1a** | **2b** | $H_2O$/$CH_3CN$ (8:2) | **Ru1**, 5 | - | **3ab**, 0 |
| 15 | **1a** | **2b** | $H_2O$ | **Ru1**, 10 | > 9:1 | **3ab**, 53 |
| 16[c] | **1a** | **2b** | $H_2O$/THF (8:2) | **Ru1**, 10 | > 9:1 | **3ab**, 97 |
| 17[d] | **1a** | **2b** | $H_2O$/THF (8:2) | **Ru1**, 10 | > 9:1 | **3ab**, 78 |
| 18[e] | **1b** | **2b** | $H_2O$/THF (8:2) | **Ru1**, 20 | > 9:1 | **3ab**, 98 |
| 19[f] | **1b** | **2b** | $H_2O$/THF (8:2) | **Ru1**, 50 | > 9:1 | **3ab**, 96 |
| 20[g] | **1b** | **2b** | $H_2O$/THF (8:2) | **Ru1**, 50 | > 9:1 | **3ab**, 14 |
| 21 | **1a** | **2a** | $H_2O$/THF (8:2) | **Ru3**, 10 | 1: 6 | **3aa'**, 40[h] |
| 22 | **1a** | **2b** | $H_2O$/THF (8:2) | **Ru3**, 10 | 1:7 | **3ab'**, 99[i] |

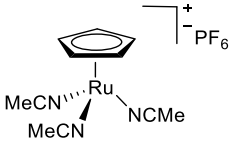
[a] Conditions: Alkene 1a (0.075 mmol), alkyne 2 (0.075 mmol), the degassed solvent (1.0 mL, ) and the [Ru] catalyst (x mol%) were stirred under $N_2$ at 37 ºC for 16 h, under otherwise noted; Yields and branched to linear (**3**:**3'**) ratios determined by $^1$H-NMR using dimethylsulfone as internal standard. [b] 61% isolated yield. [c] Carried out with non-degassed solvents. [d] Carried out under air and non-degassed solvents [e] Carried out at 1mM. [f] Carried out at 500µM. [g] Carried out at 250µM. [h]33% isolated yield. [i]78% isolated yield




**Ru1**

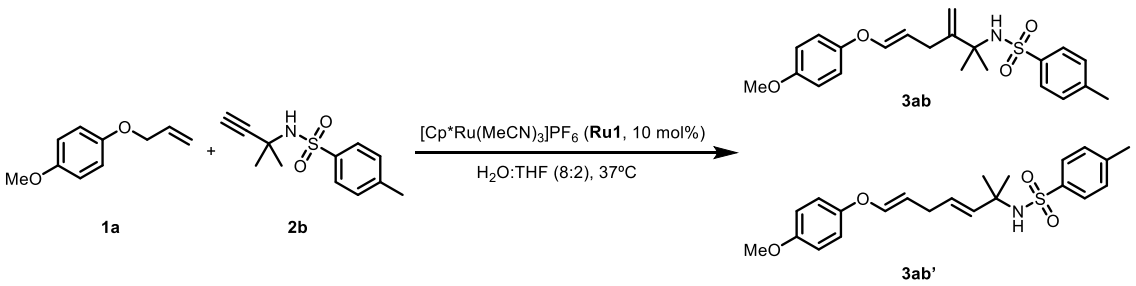



**Ru2**



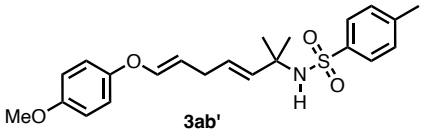

**Ru3**

**General procedure for the coupling catalyzed by Ru1.** Exemplified for the reaction between **1a** and **2b** to give (*E*)-*N*-(7-(4-methoxyphenoxy)-2-methyl-3-methylenehept-5-en-2-yl)-4-methylbenzenesulfonamide (**3ab**).




$[Cp^*Ru(MeCN)_3]PF_6$ (**Ru1** 7.6 mg, 10 mol%) was added to a stirred solution of **1a** (24.6 mg, 150 $\mu$mol) and **2b** (37.7 mg, 150 $\mu$mol) in degassed $H_2O$:THFmixture (8:2, 2 mL), under $N_2$ at 37 ºC. The reaction mixture was stirred at this temperature for 16 h and subsequently extracted with $CH_2Cl_2$ (5 x 1 mL). The extract was filtered through a florisil plug (in a 3 mL syringe) directly into a vial and the solvent was removed under reduced pressure. Then, 700 $\mu$L of a stock solution of $DMSO_2$ (0.71 mM in $CDCl_3$) were added and the crude residue was analyzed by NMR, which allowed to determine the formation of (*E*)-*N*-(7-(4-methoxyphenoxy)-2-methyl-3-methylenehept-5-en-2-yl)-4-methyl benzenesulfonamide (**3ab**) and its linear isomer (*Z*)-*N*-(7-(4-methoxyphenoxy)-2-methyl-3-methylenehept-5-en-2-yl)-4-methyl benzenesulfonamide (**3ab'**) in a combined 99% yield). The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (87.5:12.5 to 82.5:17.5) as eluent to afford a 9:1 mixture of **3ab** : **3ab'** (60.0 mg, 149 $\mu$mol, 99% yield). NMR data of **3ab** (deduced from this 9:1 mixture of **3ab** : **3ab'**): **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 6.97 – 6.82 (m, 4H), 6.30 (dt, *J* = 12.1, 1.2 Hz, 1H), 5.15 – 5.02 (m, 2H), 5.00 (s, 1H), 4.94 (s, 1H), 3.80 (s, 3H), 2.70 (d, *J* = 7.5, 2H), 2.41 (s, 3H), 1.39 (s, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 155.4, 151.8, 151.2, 144.5, 143.1, 140.1, 129.5, 127.3, 118.0, 114.8, 111.8, 109.6, 59.6, 55.8, 28.9, 27.8, 21.6. **HRMS** (ESI+) $C_{22}H_{28}NO_4S$ $[M+H]^+$ calc 402.1734 found 402.1734.

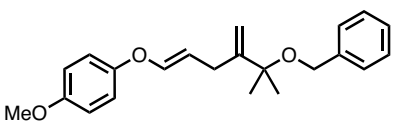
**((3*E*,6*E*)-7-(4-Methoxyphenoxy)-2-methylhepta-3,6-dien-2-yl)-4-methylbenzenesulfonamide (3ab')**



**3ab'**

Prepared according to the abovementioned general procedure from **1a** (24.5 mg, 150 $\mu$mol) and **2b** (35.6 mg, 234 $\mu$mol) but using $[CpRu(MeCN)_3]PF_6$ (**Ru3**, 6.5 mg, 10 mol%) instead of **Ru1**. **NMR Yield** = 99% (**3ab** : **3ab'** = 1:7). The resulting crude residue was purified by FCC in silica gel (fine silica, particle ⌀ = 25 – 40 µm) using Hexanes:EtOAc (8:2) as eluent to afford to afford a 1:8 mixture **3ab** : **3ab**' as a colorless oil (47 mg, 117 $\mu$mol, 78% yield). NMR data of **3ab'** (deduced from this 1:8 mixture of **3ab** : **3ab'**): **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.78 – 7.67 (m, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.99 – 6.78 (m, 4H), 6.35 – 6.22 (m, 1H), 5.50 (dt, *J* = 15.7, 5.9 Hz, 1H), 5.40 – 5.26 (m, 1H), 5.13 – 4.93 (m, 1H), 4.88 (s, 1H), 3.77 (d, *J* = 0.9 Hz, 3H), 2.61 – 2.47 (m, 2H), 2.38 (s, 3H), 1.28 (s, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 155.4, 151.2, 143.9, 142.9, 140.3, 136.0, 129.5, 127.5, 127.3, 117.9, 114.8, 109.3, 56.8, 55.8, 29.9, 28.5, 21.6. **HRMS** (ESI+) $C_{22}H_{28}NO_4S$ $[M+H]^+$ calc 402.1734 found 402.1734.

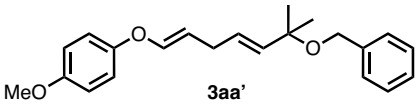
**(*E*)-1-((5-(Benzyloxy)-5-methyl-4-methylenehex-1-en-1-yl)oxy)-4-methoxybenzene (3aa).**



**3aa**

Prepared according to the abovementioned general procedure from **1a** (24.6 mg, 150 $\mu$mol), **2a** (24.5 mg, 150 $\mu$mol) and $[Cp^*Ru(MeCN)_3]PF_6$ (**Ru1**, 7.6 mg, 10 mol%). **NMR Yield** = 70% (**3aa** : **3aa'** = 9:1). The resulting crude residue was purified by FCC in silica gel using Hexanes: EtOAc (95:5) as eluent to afford **3aa** as a colorless oil (30 mg, 88.5 $\mu$mol, 61% yield, **3aa** : **3aa'** >20:1). **3aa**: **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 23.1, 4.8 Hz, 5H), 6.88 – 6.69 (m, 4H), 6.29 (d, *J* = 12.1 Hz, 1H), 5.23 (dt, *J* = 12.1, 7.6 Hz, 1H), 5.08 (s, 1H), 5.02 (s, 1H), 4.19 (s, 2H), 3.69 (s, 3H), 2.76 (d, *J* = 7.7 Hz, 2H), 1.35 (s, 6H). **$^{13}$C NMR** (75 MHz, $CDCll_3$) δ 155.5, 152.3, 151.5, 144.3, 139.6, 128.5, 127.5, 127.4, 118.0, 114.9, 112.4, 110.2, 64.9, 55.7, 28.1, 26.1. **HRMS** (ESI+) for $C_{22}H_{26}NaO_3$ $[M+Na]^+$ calc 361.1774 found 361.1777.

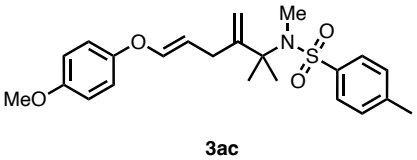
**1-(((1*E*,4*E*)-6-(Benzyloxy)-6-methylhepta-1,4-dien-1-yl)oxy)-4-methoxybenzene (3aa')**



**3aa'**

Prepared according to the abovementioned general procedure from **1a** (24.5 mg, 150 $\mu$mol) and **2a** (26.1 mg, 234 $\mu$mol), but using $[CpRu(MeCN)_3]PF_6$ (**Ru3**, 6.5 mg, 10 mol%) instead of **Ru1**. **NMR Yield** = 40% (**3aa** : **3aa'** = 1:6). The resulting crude residue was purified by FCC in silica gel (fine silica, particle ⌀ = 25 – 40 μm) using Hexanes:$Et_2O$ (95:5) as eluent to afford **3aa'** as a colorless oil (17 mg, 50 $\mu$mol, 33% yield, **3aa** : **3aa'** >1:20). **3aa'**: **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.41 – 7.18 (m, 5H), 6.97 – 6.88 (m, 2H), 6.87 – 6.78 (m, 2H), 6.39 (d, *J* = 12.1 Hz, 1H), 5.75 – 5.55 (m, 2H), 5.29 (dt, *J* = 12.4, 7.3 Hz, 1H), 4.38 (s, 2H), 3.78 (s, 3H), 2.78 (t, *J* = 6.2 Hz, 2H), 1.37 (s, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 155.5, 151.4, 143.9, 140.0, 136.8, 128.6, 128.5, 128.4, 127.5, 127.2, 118.0, 114.8, 110.0, 5.4, 65.0, 55.8, 30.3, 26.7, 1.2. **HRMS** (ESI+) for $C_{22}H_{26}NaO_3$ $[M+Na]^+$ calc 361.1774 found 361.1777.

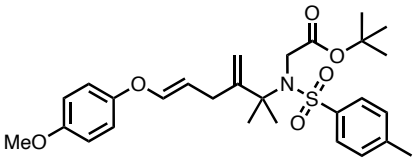
**(*E*)-*N*-(7-(4-methoxyphenoxy)-2-methyl-3-methylenehept-5-en-2-yl)-N,4-dimethyl-benzenesulfonamide (3ac)**



**3ac**

Prepared according to the abovementioned general procedure with **1a** (24.6 mg, 150 $\mu$mol), **2c** (37.7 mg, 150 $\mu$mol) $[Cp^*Ru(MeCN)_3]PF_6$ (**Ru1**, 7.6 mg, 10 mol%). **NMR Yield** = 99% (**3ac** : **3ac'** = 7:1). The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (from 87.5:12.5 to 82.5: 17.5) eluent to afford a 9:1 mixture **3ac** and **3ac'** as a colorless oil (47.0 mg, 112 $\mu$mol, 75% yield). NMR data of **3ac** (deduced from this 9:1 mixture of **3ac** : **3ac'**): **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.81 – 7.69 (m, 2H), 7.36 – 7.25 (m, 2H), 7.00 – 6.82 (m, 4H), 6.38 (dt, *J* = 12.1, 1.3 Hz, 1H), 5.34 – 5.17 (m, 1H), 5.06 (s, 1H), 5.02 (s, 1H), 3.81 (s, 3H), 2.86 (s, 3H), 2.76 (dt, *J* = 7.7, 1.2 Hz, 2H), 2.44 (s, 3H), 1.43 (s, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 155.5, 153.8, 151.3, 144.4, 143.0, 139.9, 129.7, 127.2, 118.0, 114.8, 111.3, 109.8, 65.0, 55.8, 33.5, 28.5, 25.6, 21.6. **HRMS** (ESI+) for $C_{23}H_{30}NO_4S$ $[M+H]^+$ calc 418.1890 found 418.1885.

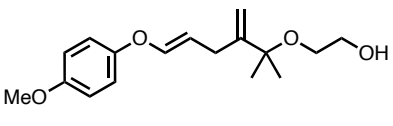
***tert*-Butyl (*E*)-*N*-(6-(4-methoxyphenoxy)-2-methyl-3-methylenehex-5-en-2-yl)-*N*-tosyl glycinate (3ad)**



**3ad**

Prepared according to the abovementioned general procedure from **1a** (23.8 mg, 145 $\mu$mol), **2d** (51.0 mg, 145 mol) and $[Cp^*Ru(MeCN)_3]PF_6$ (**Ru1**, 7.3 mg, 10 mol%). **NMR Yield** = 70% (**3ad** : **3ad'** = 7:1). The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (9:1) as eluent to afford a 9:1 mixture of **3ad** and **3ad'** as a colorless oil (50.5 mg, 98 $\mu$mol, 67% yield). NMR data of **3ad** (deduced from this 9:1 mixture of **3ad** : **3ad'**): **$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 2H), 7.44 – 7.20 (m, 2H), 7.02 – 6.78 (m, 4H), 6.33 (d, *J* = 12.1 Hz, 1H), 5.14 (s, 1H), 5.05 (s, 1H), 3.92 (s, 2H), 3.80 (s, 3H), 2.80 (d, *J* = 7.6 Hz, 2H), 2.51 – 2.33 (m, 3H), 1.50 (s, 9H), 1.41 (6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 169.5, 155.3, 153.4, 151.1, 144.4, 143.2, 140.7, 129.4, 129.3, 128.1, 127.8, 127.7, 118.2, 117.9, 114.8, 114.7, 112.4, 109.6, 81.5, 65.6, 55.7, 48.2, 29.6, 28.2, 28.1, 28.0, 28.0, 25.6, 21.5. **HRMS** (ESI+) for $C_{28}H_{38}NO_6S$ $[M+H]^+$ calc. 516.2414 found 516.2419.

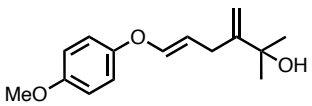
**(*E*)-2-((6-(4-Methoxyphenoxy)-2-methyl-3-methylenehex-5-en-2-yl)oxy)ethan-1-ol (3ae)**



**3ae**

Prepared according to the repr abovementioned general esentative procedure from **1a** (25.4mg, 150 $\mu$mol), **2e** (19.8 mg, 155 $\mu$mol) and $[Cp^*Ru(MeCN)_3]PF_6$ (**Ru1**, 7.8 mg, 10 mol%). **NMR Yield** = 66% (**3ae** : **3ae' =** 9:1). The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (8:2) as eluent to afford **3ae** as a colorless oil (21 mg, 72 $\mu$mol, 46% yield, **3ae** : **3ae'** >20:1). **3ae**: **$^1$H NMR** (300 MHz, $CDCl_3$) δ 6.97 – 6.88 (m, 2H), 6.88 – 6.78 (m, 2H), 6.39 (d, *J* = 12.1 Hz, 1H), 5.28 (dt, *J* = 12.1, 7.6 Hz, 1H), 5.09 (s, 1H), 5.04 (s, 1H), 3.78 (s, 3H), 3.69 (p, *J* = 4.9 Hz, 2H), 3.30 (t, *J* = 4.7 Hz, 2H), 2.77 (d, *J* = 7.7 Hz, 2H), 1.35 (s, 6H).**$^{13}$C NMR** 126 MHz, $CDCl_3$) δ 155.4, 151.8, 151.3, 144.2, 117.9, 114.8, 112.3, 110.0, 63.6, 62.4, 55.8, 31.0, 28.1, 26.0. **HRMS** (ESI+) for $C_{17}H_{24}NaO_4$ $[M+Na]^+$ calc 315.1567 found 315.1567.

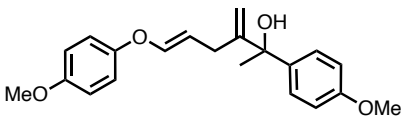
**(*E*)-6-(4-Methoxyphenoxy)-2-methyl-3-methylenehex-5-en-2-ol (3af).**



**3af**

Prepared according to the abovementioned general procedure from **1a** (58.6 mg, 355 $\mu$mol), **2f** (30.0 mg, 355 $\mu$mol) and [Cp*Ru(MeCN)$_3$]PF$_6$ (**Ru1**, 9.0 mg, 5 mol%) in 4.7 mL of degassed H$_2$O:THF (8:2). **NMR Yield** = 99% (**3af** : **3af'** = 6:1). The resulting crude residue was purified by FCC in silica gel using Hexanes: EtOAc (9:1) as eluent to afford **3af** as colorless oil (63.2 mg, 254 $\mu$mol, 71% yield, **3af** : **3af'** > 20:1). **3af**: **$^1$H NMR** (500 MHz, CDCl$_3$) δ 6.96 – 6.90 (m, 2H), 6.88 – 6.81 (m, 2H), 6.41 (dt, *J* = 12.1, 1.3 Hz, 1H), 5.30 (dt, *J* = 12.1, 7.6 Hz, 1H), 5.15 (q, *J* = 0.9 Hz, 1H), 4.88 (td, *J* = 1.5, 1.0 Hz, 1H), 3.78 (s, 3H), 2.83 (dtd, *J* = 7.6, 1.5, 1.0 Hz, 2H), 1.38 (s, 6H). **$^{13}$C NMR** (126 MHz, CDCl$_3$) δ 155.4, 155.2, 151.3, 144.3, 118.0, 114.8, 110.1, 108.9, 73.4, 55.8, 29.4, 29.3. **HRMS** (ESI+) for $C_{15}H_{20}NaO_3$ $[M+Na]^+$ calc 271.1310 found 271.1313.

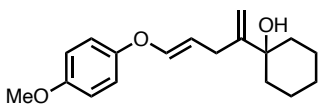
**(*E*)-6-(4-Methoxyphenoxy)-2-(4-methoxyphenyl)-3-methylenehex-5-en-2-ol (3ag).**



**3ag**

Prepared according to the abovementioned general procedure from **1a** (24.6 mg, 150 $\mu$mol) and **2g** (24.5 mg, 150 $\mu$mol) and [Cp*Ru(MeCN)$_3$]PF$_6$ (**Ru1**, 7.6 mg, 10 mol%). **NMR Yield** = Not determined (**3ag** : **3ag'** = 8:1). The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (8:2) as eluent to afford **3ag** as a colorless oil (37mg, 114 $\mu$mol, 76% yield, **3ag** : **3ag'** >20:1). **$^1$H NMR** (300 MHz, CDCl$_3$) δ 7.43 – 7.30 (m, 2H), 6.85 (ddt, *J* = 12.4, 9.1, 3.8 Hz, 7H), 6.26 (dd, *J* = 12.2, 1.4 Hz, 1H), 5.34 (s, 1H), 5.25 – 5.13 (m, 1H), 5.07 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 2.59 (qd, *J* = 16.8, 7.7 Hz, 2H), 1.70 (s, 3H). **$^{13}$C NMR** (75 MHz, CDCl$_3$) δ 158.7, 155.4, 153.9, 151.3, 144.2, 138.2, 129.4, 126.7, 118.0, 114.8, 113.7, 110.6, 109.9, 55.8, 55.4, 32.5, 29.5, 29.3. **HRMS** (ESI+) for $C_{22}H_{28}NO_4S$ $[M+H]^+$ calc 402.1734 found 402.1734.

**(*E*)-1-(5-(4-Methoxyphenoxy)penta-1,4-dien-2-yl)cyclohexan-1-ol (3ah)**

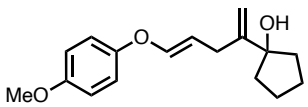


**3ah**

Prepared according to the abovementioned general procedure from **1a** (25.4 mg, 155 $\mu$mol), **2h** (19.2 mg, 155 mol) and [Cp*Ru(MeCN)$_3$]PF$_6$ (**Ru1**, 7.8 mg, 10 mol%). **NMR Yield** = 93% (**3ah** : **3ah'** = 7:1). The resulting crude residue was purified by FCC in

silica gel using Hexanes:EtOAc (9:1) as eluent to afford **3ah** as a colorless oil (37.9 mg, 131 $\mu$mol, 85% yield, **3ah** : **3ah'** > 20:1). **3ah**: **$^1$H NMR** (300 MHz, $CDCl_3$) δ 6.93 (dd, *J* = 9.1, 2.0 Hz, 2H), 6.88 – 6.79 (m, 2H), 6.39 (d, *J* = 12.2 Hz, 1H), 5.30 (dtd, *J* = 12.0, 7.5, 1.9 Hz, 1H), 5.15 (s, 1H), 4.92 (s, 1H), 3.78 (s, 3H), 2.83 (d, *J* = 7.5 Hz, 2H), 1.64 (q, *J* = 8.0 Hz, 10H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 155.4, 151.3, 144.2, 118.0, 116.2, 114.8, 110.5, 109.7, 74.0, 55.8, 36.4, 31.1, 25.8, 22.1. **HRMS** (ESI+) for $C_{18}H_{24}NaO_3$ $[M+Na]^+$ calc 311.1618 found 311.1613.

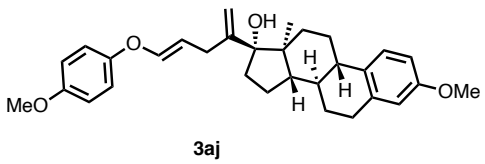
**(*E*)-1-(5-(4-Methoxyphenoxy)penta-1,4-dien-2-yl)cyclopentan-1-ol (3ai)**



**3ai**

Prepared according to the abovementioned general procedure from **1a** (25.4 mg, 150 $\mu$mol), **2i** (17.1 mg, 155 µmol) and $[Cp^*Ru(MeCN)_3]PF_6$ (**Ru1**, 7.8 mg, 10 mol%). **NMR Yield** = 99% (**3ai** : **3ai'** = 7:1). The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (9:1) as eluent to afford **3ai** as a colorless oil (38.4 mg, 140 $\mu$mol, 90% yield, **3ai** : **3ai'** > 20:1). **3ai**: **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.01 – 6.89 (m, 2H), 6.92 – 6.82 (m, 2H), 6.43 (dq, *J* = 12.2, 1.4 Hz, 1H), 5.42 – 5.26 (m, 1H), 5.18 (dd, *J* = 1.9, 1.0 Hz, 1H), 4.93 (q, *J* = 1.4 Hz, 1H), 3.80 (s, 3H), 2.87 (dt, *J* = 7.6, 1.3 Hz, 2H), 1.99 – 1.63 (m, 8H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 155.5, 153.2, 151.4, 144.4, 118.1, 114.9, 110.2, 109.5, 84.6, 55.8, 38.8, 29.9, 23.5. **HRMS** (ESI+) for $C_{17}H_{22}NaO_3$ $[M+Na]^+$ calc 297.1461 found 297.1461.

**(8*R*,9*S*,13*S*,14*S*,17*R*)-3-Methoxy-17-((*E*)-5-(4-methoxyphenoxy)penta-1,4-dien-2-yl)-13-methyl-7,8,9, 11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol (3aj)**

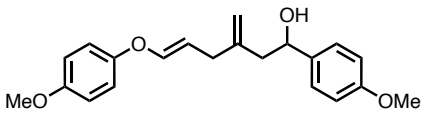


**3aj**

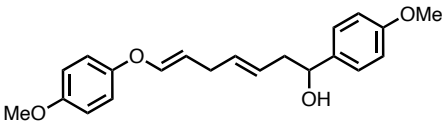
Prepared according to the abovementioned general procedure from **1a** (24.6 mg, 150 $\mu$mol), **2j** (46.6 mg, 150 mol) and $[Cp^*Ru(MeCN)_3]PF_6$ (**Ru1**, 7.6 mg, 10 mol%). **NMR Yield** = 62% (**3aj** : **3aj'** = not determined). The resulting crude residue was purified by FCC in silica gel (particle ⌀ = 25 – 40 µm) using Hexanes:$Et_2O$ (6:4) as eluent to afford **3aj** as a white off solid (43.2 mg, 91 $\mu$mol, 60% yield, **3aj** : **3aj'** >20:1). **3aj**: **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.6 Hz, 1H), 6.97 – 6.91 (m, 2H), 6.89 – 6.82 (m, 2H), 6.70 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.63 (d, *J* = 2.5 Hz, 1H), 6.42 (d, *J* = 12.1 Hz, 1H), 5.36 (ddd, *J* = 12.1, 8.4, 6.6 Hz, 1H), 5.17 (s, 1H), 4.88 (s, 1H),

3.81 – 3.72 (m, 6H), 3.01 – 2.94 (m, 1H), 2.90 – 2.79 (m, 2H), 2.29 – 2.16 (m, 2H), 2.11 (td, *J* = 11.5, 4.1 Hz, 1H), 1.96 – 1.85 (m, 2H), 1.80 – 1.64 (m, 3H), 1.63 – 1.54 (m, 1H), 1.53 – 1.40 (m, 3H), 1.39 – 1.17 (m, 3H), 0.98 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 157.57, 155.38, 153.64, 151.39, 144.12, 138.09, 132.80, 126.37, 117.93, 114.82, 113.93, 113.32, 111.57, 111.10, 87.85, 55.82, 55.33, 47.51, 47.30, 43.61, 39.66, 39.19, 33.81, 31.25, 29.99, 27.55, 26.64, 23.64, 14.52. **HRMS** (ESI+): for $C_{31}H_{38}NaO_4$ calc 497.2662 $[M+Na]^+$ found 497.2658.

**(*E*)-7-(4-Methoxyphenoxy)-1-(4-methoxyphenyl)-3-methylenehept-5-en-1-ol (3ak) and (3*E*,6*E*)-7-(4-methoxyphenoxy)-1-(4-methoxyphenyl)hepta-3,6-dien-1-ol (3ak')**



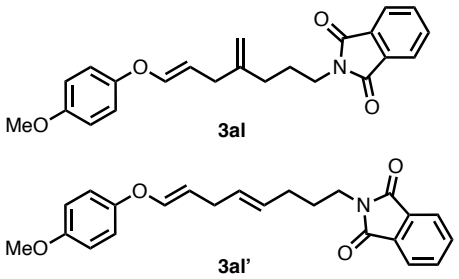

**3ak**




**3ak'**

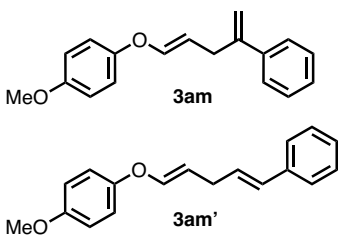
Prepared according to the abovementioned general procedure from **1a** (41.9 mg, 255 $\mu$mol), **2k** (45.0 mg, 255 µmol) and $[Cp^*Ru(MeCN)_3]PF_6$ (**Ru1**, 12.9 mg, 10 mol%). **NMR yield** = Not determined (**3ak** : **3ak'** = 3:1) The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (85:15) as eluent to afford a 3:1 mixture of **3ak** and **3ak'** as a colorless oil (57.1 mg, 116 $\mu$mol, 66% yield). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.22 (m, 2H), 6.99 – 6.79 (m, 6H), 6.45 – 6.30 (m, 1H), 5.65 – 5.40 (m, 0.5 H), 5.33 – 5.17 (m, 1H), 5.00 (d, 0.75 H), 4.94 (s, 0.75 H), 4.79 (t, *J* = 6.7 Hz, 0.75H), 4.65 (t, *J* = 6.5 Hz, 0.25H), 3.83 – 3.75 (m, 6H), 2.78 – 2.67 (m, 2H), 2.52 – 2.40 (m, 2H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) reδ 159.06, 155.34, 151.07, 145.35, 144.50, 143.67, 136.21, 132.48, 127.04, 126.78, 117.95, 117.87, 114.69, 113.82, 113.76, 113.67, 109.92, 108.81, 73.27, 71.59, 55.67, 55.27, 46.12, 42.50, 34.04, 30.33, 29.71. **HRMS** (ESI+): for $C_{21}H_{24}NO_4$ calc 363.1567 $[M+H]^+$ found 363.1559.

**(E)-2-(8-(4-Methoxyphenoxy)-4-methyleneoct-6-en-1-yl)isoindoline-1,3-dione (3al) and 2-((4*E*,7*E*)-8-(4-methoxyphenoxy)octa-4,7-dien-1-yl)isoindoline-1,3-dione (3al')**



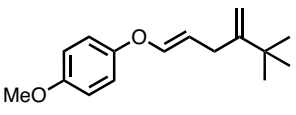

Prepared according to the abovementioned general procedure from **1a** (19.1 mg, 116 $\mu$mol), **2l** (25.0 mg, 116 mol) and [Cp*Ru(MeCN)$_3$]PF$_6$ (5.9 mg, 10 mol%). **NMR yield** = Not determined (**3al** : **3al'** = 3:1). The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (8:2) as eluent to afford 3:1 mixture of **3al** : **3al'** as a colorless oil (36.7 mg, 97 $\mu$mol, 83%, **3al** : **3al'** = 3:1). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.75 – 7.63 (m, 2H), 6.96 – 6.75 (m, 4H), 6.35 (m, 1H), 5.48 (m, 0.5H), 5.22 (m, 1H), 4.86 – 4.78 (m, 1.5H), 3.79 - 374 (m, 3H), 3.72-3.63 (m, 2H), 2.68 (m, 2H), 2.18 – 2.01 (m, 2H), 1.93 – 1.68 (m, 2H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 168.52, 155.38, 155.32, 151.35, 151.25, 147.35, 144.28, 143.58, 134.00, 132.27, 129.76, 129.54, 123.29, 117.98, 114.78, 110.58, 110.34, 109.33, 55.78, 37.86, 37.77, 34.08, 33.14, 30.34, 29.93, 28.22, 26.47. **HRMS** (ESI+): for $C_{23}H_{24}NO_4$ calc 378.1700 $[M+H]^+$ found 378.1696.

**(*E*)-1-Methoxy-4-((4-phenylpenta-1,4-dien-1-yl)oxy)benzene (3am) and 1-methoxy-4-(((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)oxy)benzene (3am')**




Prepared according to the abovementioned general procedure from **1a** (24.6 mg, 150 $\mu$mol), with excess of **2m** (23.0 mg, 225 $\mu$mol) and [Cp*Ru(MeCN)$_3$]PF$_6$ (**Ru1**, 7.6 mg, 10 mol%). **NMR yield** = Not determined (**3am** : **3am'** = 1.2:1). The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (9:1) as eluent to afford 1.2:1mixture of **3am** and **3am'** as a yellow oil (32.8 mg, 123 $\mu$mol, 83% yield). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.52 – 7.15 (m, 5H), 6.98 – 6.77 (m, 4H), 6.52 – 6.33 (m, 1.6H), 6.33-6.15 (m, 0.4H), 5.47 – 5.27 (m, 1.4H), 5.17 (m, 0.6H), 3.79 (m, 3H), 3.21 (dq, *J* = 7.3, 1.2 Hz, 1.2H), 2.94 (ddt, *J* = 7.6, 6.4, 1.4 Hz, 0.8H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 155.9, 155.8, 151.8, 151.8, 147.6, 145.1, 144.7, 141.6, 138.1, 131.1, 129.4, 129.1, 128.9, 128.1, 127.6, 126.6, 118.5, 118.3, 116.3, 115.3, 115.2, 113.6, 110.0, 110.0, 56.2, 33.6, 31.2, 1.6. **HRMS** (ESI+): $C_{18}H_{19}O_2$ $[M+H]^+$ calc 267.1380 found 267.1369.

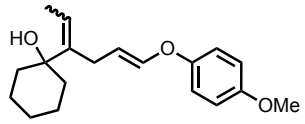
**(*E*)-1-((5,5-Dimethyl-4-methylenehex-1-en-1-yl)oxy)-4-methoxybenzene (3an)**




**3an**

Prepared according to the abovementioned general procedure with **1a** (24.6 mg, 150 $\mu$mol), **2n** (18.5 mg, 225 $\mu$mol) and [Cp*Ru(MeCN)$_3$]PF$_6$ (**Ru1**, 7.6 mg, 10 mol%). **NMR Yield** = 55% (**3an** : **3an'** >20:1). The resulting crude residue was purified by FCC in silica gel using Hexanes:Et$_2$O (9:1) as eluent to afford **3an** as a colorless oil (14.5 mg, 60 $\mu$mol, 40% yield, **3an** : **3an'** >20:1). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 6.94 (d, *J* = 8.8 Hz, 2H), 6.88 – 6.81 (m, 2H), 6.37 (d, *J* = 12.1 Hz, 1H), 5.30 (dt, *J* = 12.3, 7.7 Hz, 1H), 4.92 (s, 1H), 4.79 (s, 1H), 3.78 (s, 3H), 2.76 (d, *J* = 7.6 Hz, 2H), 1.10 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 157.3, 155.4, 151.5, 143.8, 118.0, 114.8, 111.1, 107.9, 55.8, 36.2, 29.4. **HRMS** (ESI+): Calculated for $C_{16}H_{23}O_2$ $[M+H]^+$ 247.1693found 247.1686.

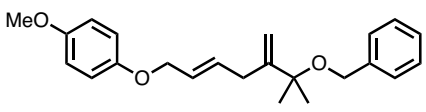
**1-((5*E*)-6-(4-Methoxyphenoxy)hexa-2,5-dien-3-yl)cyclohexan-1-ol (3ao)**




**3ao**

Prepared according to the abovementioned general procedure from **1a** (24.6 mg, 150 $\mu$mol), **2o** (20.7 mg, 155 mol) and [Cp*Ru(MeCN)$_3$]PF$_6$ (**Ru1**, 7.6 mg, 10 mol%). **NMR yield:** Not determined (**3ao** : **3ao'** = 6:1) The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (9:1) as eluent to afford a 14:1 mixture **3ao** and **3ao'**as a colorless oil (25.7 mg, 85 µmol, 57% yield). NMR data of **3ao** (deduced from this 14:1 mixture of **3ao** : **3ao'**): **$^1$H NMR** (300 MHz, $CDCl_3$) δ 6.97 – 6.79 (m, 4H), 6.37 (d, *J* = 12.2 Hz, 1H), 5.36 (s, 1H), 5.32 – 5.16 (m, 1H), 3.77 (d, *J* = 1.5 Hz, 3H), 2.64 (d, *J* = 7.6 Hz, 2H), 1.90 (s, 3H), 1.70 – 1.52 (m, 5H), 1.50 – 1.29 (m, 5H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 155.4, 151.3, 144.1, 137.5, 131.9, 117.9, 114.8, 110.1, 71.9, 55.8, 40.3, 39.5, 38.8, 29.8, 25.6, 22.7, 17.6. **HRMS (ESI+):** for $C_{19}H_{26}NaO_3$ calc 325.1774 $[M+Na]^+$ found 325.1774.

**(*E*)-1-((6-(Benzyloxy)-6-methyl-5-methylenehept-2-en-1-yl)oxy)-4-methoxybenzene (3ba)**

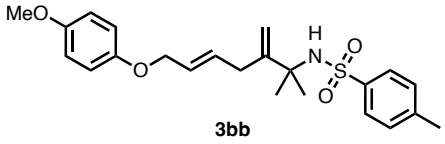



**3ba**

Prepared according to the abovementioned general procedure from **1b** (26.7 mg, 150 $\mu$mol) **2a** (26.1 mg, 150 $\mu$mol) and [Cp*Ru(MeCN)$_3$]PF$_6$ (**Ru1**, 7.6 mg, 10 mol%). **NMR Yield** = 77% (**3ba** : **3ba'** = 9:1). The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (9:1) as eluent to afford **3ba** as a

colorless oil (27.2 mg, 77 $\mu$mol, 55% yield, **3ba** : **3ba'** > 20:1). **3ba**: **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.39 – 7.22 (m, 5H), 6.91 – 6.80 (m, 4H), 5.88 (dt, *J* = 13.6, 6.6 Hz, 1H), 5.75 (dt, *J* = 15.4, 5.6 Hz, 1H), 5.17 (s, 1H), 5.02 (s, 1H), 4.48 (d, *J* = 5.7 Hz, 2H), 4.28 (s, 2H), 3.79 (s, 3H), 2.96 (d, *J* = 6.6 Hz, 2H), 1.43 (s, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 153.9, 152.9, 151.3, 139.5, 133.2, 128.5, 127.5, 127.31, 127.3, 115.9, 114.7, 112.6, 69.3, 64.9, 55.8, 33.5, 26.1. **HRMS** (ESI+) for $C_{23}H_{28}O_3Na$ $[M+Na]^+$ calc 375.1931 found 375.1944.

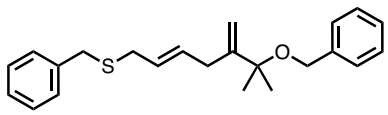
**(*E*)-*N*-(7-(4-methoxyphenoxy)-2-methyl-3-methylenehept-5-en-2-yl)-4-methylbenzenesulfonamide (3bb)**



**3bb**

Prepared according to the abovementioned general procedure from **1b** (13.4 mg, 75 $\mu$mol) **2b** (17.8 mg, 75 $\mu$mol) and $[Cp^*Ru(MeCN)_3]PF_6$ (**Ru1**, 3.8 mg, 10 mol%). **NMR Yield** = 72% (**3bb** : **3bb'** = 9:1). The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (9:1) as eluent to afford **3bb** as a colorless oil (21.7 mg, 52 $\mu$mol, 70% yield, **3bb** : **3bb'** > 20:1). **3bb**: **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 2H), 7.22 – 7.15 (m, 2H), 6.82 – 6.74 (m, 4H), 5.65 – 5.52 (m, 2H), 5.48 – 5.35 (m, 1H), 5.24 (dd, *J* = 13.0, 4.1 Hz, 1H), 4.55 (s, 1H), 4.34 (d, *J* = 4.7 Hz, 2H), 3.72 – 3.67 (m, 3H), 1.23 (s, 2H), 2.58 (d, *J* = 7.0 Hz, 2H), 2.33 (s, 3H).**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 154.01, 152.88, 142.96, 140.28, 136.60, 132.34, 129.49, 127.40, 126.62, 126.53, 115.85, 114.76, 69.25, 56.93, 55.86, 34.86, 28.48, 21.62. **HRMS** (ESI+) for $C_{23}H_{29}NO_4SNa$ $[M+Na]^+$ calc 438.1710 found 438.1722.

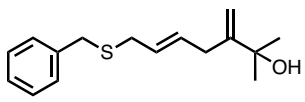
**(*E*)-Benzyl(6-(benzyloxy)-6-methyl-5-methylenehept-2-en-1-yl)sulfane (3ca).**




Prepared according to the abovementioned general procedure from **1c** (25.1 mg, 140 $\mu$mol) **2a** (24.5 mg, 140 $\mu$mol) and $[Cp^*Ru(MeCN)_3]PF_6$ (**Ru1**, 7.1 mg, 10 mol%). **NMR Yield** = 97% (**3ca**:**3ca'** = 9:1, *E*/*Z* = 9:1). The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (8:2) as eluent to afford **3ca** as a colorless oil (39.1 mg, 111 $\mu$mol, 79%, **3ca** : **3ca'** = 20>1, *E*/*Z* = 9:1). *E*-**3ca**: **$^1$H NMR** (750 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 8H), 7.31 – 7.25 (m, 2H), 6.16 (d, *J* = 11.7 Hz, 1H), 5.63 (ddd, *J* = 11.7, 7.7, 6.2 Hz, 1H), 5.31 (s, 1H), 5.07 (s, 1H), 4.34 (s, 2H), 3.74 (s, 2H), 2.54 (dtd, *J* = 8.6, 6.9, 1.7 Hz, 2H), 2.51 – 2.46 (m, 2H), 1.43 (s, 6H). **$^{13}$C NMR** (189 MHz, $CDCl_3$) δ 148.7, 139.5, 138.5, 131.1, 129.0, 128.9, 128.6, 128.4, 127.6, 127.3, 127.1, 114.3, 65.0,

36.4, 31.5, 28.7, 26.4. **HRMS** (ESI+) for $C_{23}H_{28}NaOS$ $[M+Na]^+$ calc 375.1753 found 375.1750.

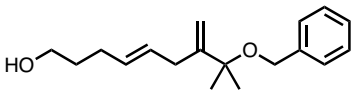
**(*E*)-7-(Benzylthio)-2-methyl-3-methylenehept-5-en-2-ol (3cf)**




**3cf**

Prepared according to the abovementioned general procedure from **1c** (26.7 mg, 150 $\mu$mol) **2f** (12.6 mg, 150 $\mu$mol) and $[Cp^*Ru(MeCN)_3]PF_6$ (**Ru1**, 7.6 mg, 10 mol%). **NMR Yield** = 72% (**3cf** : **3cf'**= 9:1, 8:1 E/Z). The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (9:1) as eluent to afford **3cf** as a colorless oil (13.0 mg, 55 $\mu$mol, 33% yield, **3cf** : **3cf'** > 20:1, 8:1 E/Z). *E*-**3cf**: **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 4.4 Hz, 4H), 7.19 – 7.14 (m, 1H), 6.00 (d, *J* = 10.2 Hz, 1H), 5.57 – 5.48 (m, 1H), 5.22 (d, *J* = 1.6 Hz, 1H), 4.74 (t, *J* = 1.5 Hz, 1H), 3.64 (s, 2H), 2.41 – 2.35 (m, 4H), 1.27 (s, 6H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 151.7, 138.4, 131.4, 128.9, 128.9, 128.5, 127.0, 110.8, 72.8, 36.3, 31.3, 29.1, 28.1. **HRMS** (ESI+): for $C_{16}H_{22}NaOS$ $[M+Na]^+$ calc 285.1285 found 285.1284.

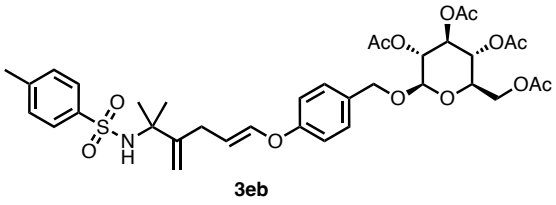
**(*E*)-8-(Benzyloxy)-8-methyl-7-methylenenon-4-en-1-ol (3da)**




**3da**

Prepared according to the abovementioned general procedure from **1d** (15 mg, 150 $\mu$mol), **2a** (26.1 mg, 150 $\mu$mol). **NMR Yield** = 66% (**3da** : **3da**' = 9:1). The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (82.5:17:5). as eluent to afford a 14:1 mixture of **3da** and **3ab'** as a colorless oil (25.6 mg, 82 $\mu$mol, 59% yield). NMR data of **3ab** (deduced from this 14:1 mixture of **3da** : **3da'**): **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.41 – 7.24 (m, 5H), 5.54 – 5.46 (m, 2H), 5.15 (s, 1H), 5.02 (s, 1H), 4.28 (s, 2H), 3.67 (t, *J* = 6.5 Hz, 2H), 2.86 (d, *J* = 4.6 Hz, 2H), 2.14 (q, *J* = 6.7 Hz, 2H), 1.74 – 1.60 (m, 2H), 1.43 (s, 6H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 151.0, 138.5, 130.5, 128.0, 127.3, 126.3, 126.1, 110.9, 76.6, 63.8, 61.5, 32.5, 31.4, 27.8, 25.0. **HRMS** (ESI+): for $C_{18}H_{26}NaO_2$ $[M+Na]^+$ calc 297.1825 found 297.18.

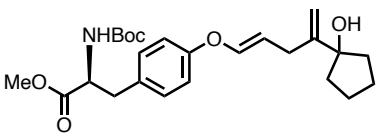
**(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-((4-(((*E*)-5-methyl-4-methylene-5-((4-methylphenyl)sulfonamido)hex-1-en-1-yl)oxy)benzyl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (3eb).**



**3eb**

Prepared according to the abovementioned general procedure from **1e** (37.1 mg, 175 $\mu$mol), **2b** (17.8 mg, 75 $\mu$mol) and $[Cp^*Ru(MeCN)_3]PF_6$ (**Ru1**, 3.8 mg, 10 mol%). The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (1:1) as eluent to afford a 10:1 mixture of **3eb** and **3eb'** as a white off solid (38.5 mg, 53 $\mu$mol, 86% yield). NMR data of **3eb** (deduced from this 10:1 mixture of **3eb** : **3eb'**): **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.7 Hz, 2H), 7.34 – 7.16 (m, 4H), 6.94 (d, *J* = 8.2 Hz, 2H), 6.46 – 6.28 (m, 1H), 5.26 – 4.97 (m, 5H), 4.99 – 4.59 (m, 2H), 4.64 – 4.47 (m, 3H), 4.33 – 4.05 (m, 3H), 3.66 (s, 1H), 2.72 (d, *J* = 7.6 Hz, 2H), 2.39 (s, 3H), 2.19 – 1.93 (m, 13H) 1.37 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 170.7, 170.3, 169.4, 169.3, 157.1, 151.5, 143.1, 142.9, 139.9, 130.7, 129.7, 129.4, 129.4, 127.2, 116.3, 115.3, 111.8, 111.3, 99.1, 72.8, 71.8, 71.3, 70.3, 68.4, 62.0, 59.6, 29.7, 28.8, 27.6, 21.5, 20.7, 20.7, 20.6. **HRMS** (ESI+) for C36H46NO13S $[M+H]^+$ calc 732.2684 found 732.2680

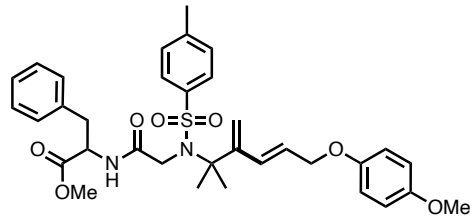
**Methyl (*S*,*E*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-((4-(1-hydroxycyclopentyl) -1,4-dien-1-yl)oxy)phenyl)propanoate (3fi)**



**<**Prepared according to the abovementioned general procedure from **1f** (50 mg, 150 $\mu$mol), with excess of **2i** (24.5 mg, 234 $\mu$mol) and $[Cp^*Ru(MeCN)_3]PF_6$ (**Ru1**, 7.6 mg, 10 mol%). **NMR yield** = not determined (**3fi** : **3fi'** = 4:1). The resulting crude residue was purified by FCC in silica gel using Hexanes:EtOAc (8:2) to afford **3fi** as a white off solid (41 mg, 93 $\mu$mol, 62% yield, **3fi** : **3fi'** > 20:1). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.5 Hz, 2H), 6.96 – 6.83 (m, 2H), 6.50 – 6.38 (m, 1H), 5.41 (dt, *J* = 12.1, 7.6 Hz, 1H), 5.17 (s, 1H), 4.97 (d, *J* = 8.1 Hz, 1H), 4.91 (d, *J* = 1.5 Hz, 1H), 4.54 (d, *J* = 7.0 Hz, 1H), 3.71 (s, 3H), 3.06 (dt, *J* = 15.2, 6.9 Hz, 2H), 2.91 – 2.78 (m, 4H), 1.99 – 1.63 (m, 4H), 1.41 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 172.3, 156.4, 155.0, 152.8, 142.8, 130.4, 130.1, 116.5,

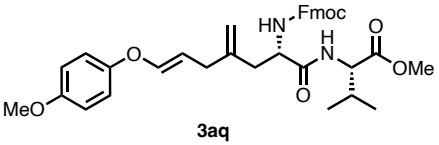
111.5, 109.4, 84.4, 80.0, 54.5, 52.2, 38.7, 37.6, 29.8, 28.3, 23.5. **HRMS** (ESI+) for $C_{25}H_{35}NNaO_6$ $[M+Na]^+$ calc 468.2357 found 468.2365.

**_N_-Methyl (_E_)-_N_-(6-(4-methoxyphenoxy)-2-methyl-3-methylenehex-4-en-2-yl)-_N_-tosylglycylphenylalaninate (3ap)**



Prepared according to the abovementioned general procedure from **1a** (12.9 mg, 79 $\mu$mol), **2p** (36 mg, 79 $\mu$mol) and $[Cp^*Ru(MeCN)_3]PF_6$ (4.0 mg, 10 mol%). FCC in fine silica (particle ⌀ = 25 – 40 μm) using Hexanes:EtOAc (8:2 to 7:3) as eluent to afford **3ap** as whit solid (20 mg, 32 $\mu$mol, 40%, >9:1 branched : linear). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.9 Hz, 2H), 7.37 – 7.14 (m, 7H), 6.97 – 6.80 (m, 3H), 6.72 (d, *J* = 7.9 Hz, 1H), 6.29 (d, *J* = 12.1 Hz, 1H), 5.16 (dt, *J* = 12.9, 7.5 Hz, 1H), 5.09 (s, 1H), 5.03 (s, 1H), 4.91 (q, *J* = 6.5 Hz, 1H), 3.92 (dd, *J* = 17.0, 13.0 Hz, 2H), 3.80 (s, 3H), 3.73 (s, 3H), 3.17 (d, *J* = 5.8 Hz, 2H), 2.79 – 2.56 (m, 2H), 2.43 (s, 3H), 1.37 (s, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 171.6, 169.4, 155.3, 152.6, 151.2, 144.3, 143.7, 139.1, 135.7, 129.6, 129.6, 129.4, 128.7, 128.1, 127.2, 117.8, 114.7, 112.5, 109.7, 66.1, 55.7, 53.4, 52.3, 49.9, 37.9, 28.6, 26.3, 25.7, 21.5. **HRMS** (ESI+) for $C_{34}H_{40}N_2NaO_7S$ $[M+Na]^+$ 643.2448 found 643.2431.

**Methyl ((_S_,_E_)-2-((((9_H_-fluoren-9-yl)methoxy)carbonyl)amino)-7-(4-methoxyphenoxy)-4-methylenehept-5-enoyl)-_L_-valinate (3aq).**



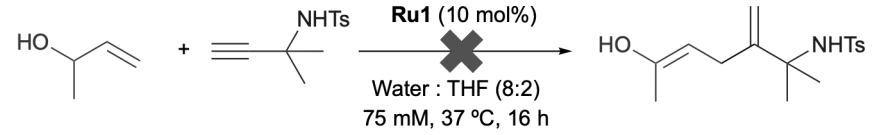
3aq

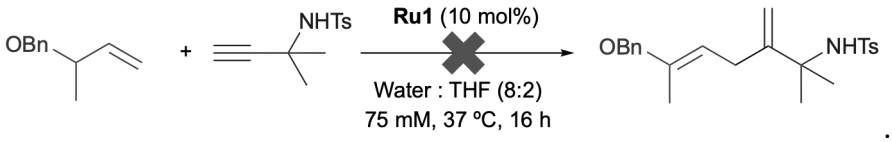
Prepared according to the abovementioned general procedure from **1a** (19.4 mg, 118 $\mu$mol), **2q** (35.4 mg, 79 $\mu$mol) and $[Cp^*Ru(MeCN)_3]PF_6$ (4.0 mg, 10 mol%). FCC in fine silica (particle ⌀ = 25 – 40 μm) using Hexanes:EtOAc (8:2) as eluent to afford a 3:1 mixture of **3aq** and **3aq'** as white solid (45 mg, 73 $\mu$mol, 93%, 3:1 branched : linear). A 20 mg fraction of the branched compound was isolated and characterized. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.5 Hz, 2H), 7.59 (d, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 6.98 – 6.89 (m, 2H), 6.88 – 6.80 (m, 2H), 6.55 (d, *J* = 8.7 Hz, 1H), 6.46 (d, *J* = 12.2 Hz, 1H), 5.39 – 5.17 (m, 2H), 5.02 (s, 1H), 4.94 (s, 1H), 4.54 (dd, *J* = 8.7, 4.9 Hz, 1H), 4.42 (t, *J* = 7.4 Hz, 3H), 4.24 (t, *J* = 7.0 Hz, 1H), 3.77 (d, *J* = 1.6 Hz, 3H), 3.73 (s, 3H), 2.76 (s, 2H), 2.64 (dd, *J* = 14.6,

6.2 Hz, 1H), 2.48 (s, 1H), 2.17 (dp, *J* = 13.6, 6.9 Hz, 1H), 0.93 (t, *J* = 7.6 Hz, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 171.2, 155.4, 151.1, 144.8, 143.9, 143.7, 141.3, 127.8, 127.1, 125.0, 120.0, 117.9, 114.7, 114.4, 108.3, 67.3, 57.3, 55.7, 53.3, 52.2, 47.1, 38.7, 33.6, 31.3, 18.9, 17.8. **HRMS** (ESI+) for $C_{36}H_{40}N2NaO_7$ $[M+Na]^+$ 635.2728 found 635.2726.

**Reactions with alkenes (1) bearing substituents at the allylic position.**

Preliminary results with but-3-en-2-ol and ((but-3-en-2-yloxy)methyl)benzene suggest that the presence of additional substituents in the allylic carbon of the alkene partner (**1**) hamper the process.



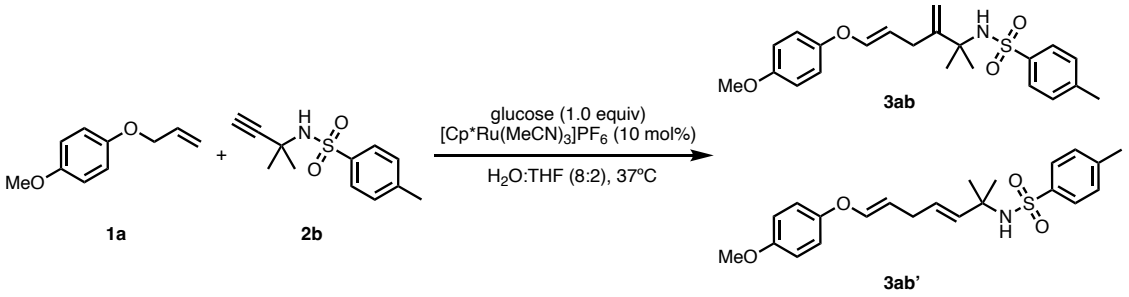
## Bioorthogonality assays

**Bioorthogonality of the Ru-catalyzed coupling in the presence of different biological media.**

Reactions were carried out following the representative procedure of the previous section changing the aqueous media for the corresponding degassed biological milieu.

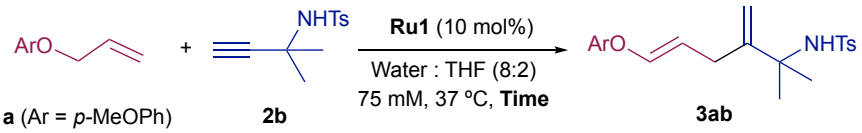
**Bioorthogonality of the Ru-catalyzed coupling in the presence of different relevant biomolecules.**

Representative Procedure for the addition of glucose (1.0 equiv)



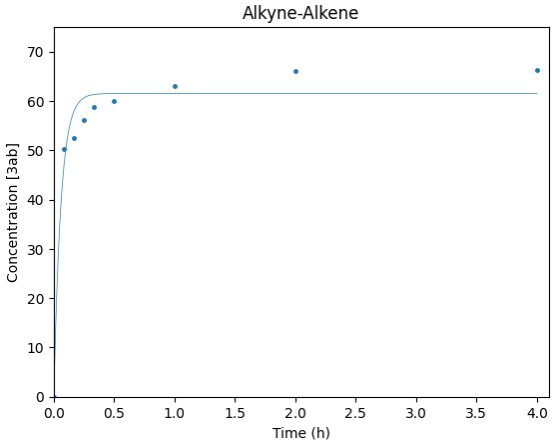

$[Cp^*Ru(MeCN)_3]PF_6$ (**Ru1** 7.6 mg, 10 mol%) was added to a stirred solution of **1a** (24.6 mg, 150 $\mu$mol), **2b** (37.7 mg, 150 $\mu$mol) and glucose (13.5 mg, 75 µmol, 1.0 equiv) in degassed $H_2O$:THFmixture (8:2, 2 mL), under $N_2$ atmosphere, at 37 ºC. The reaction mixture was stirred at this temperature for 16 h and subsequently extracted with $CH_2Cl_2$ (5 x 1 mL). The extract was filtered through a florisil plug (in a 3 mL syringe) directly into a vial and the solvent was removed under reduced pressure. Then, 700 $\mu$L of a stock solution of $DMSO_2$ (0.71 mM in $CDCl_3$) were added and the mixture was analyzed by NMR, which allowed to determine the formation of (*E*)-*N*-(7-(4-methoxyphenoxy)-2-methyl-3-methylenehept-5-en-2-yl)-4-methyl benzenesulfonamide (**3ab**) and its linear isomer (*Z*)-*N*-(7-(4-methoxyphenoxy)-2-methyl-3-methylenehept-5-en-2-yl)-4-methyl benzenesulfonamide (**3ab'**) in a combined 99% yield and a branched (**3ab**) : linear (**3ab'**) ratio of 9:1.

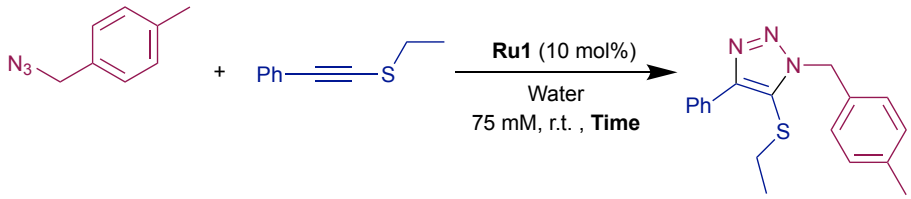
## Comparative rates of the Ru-catalyzed alkyne-alkene coupling and the Ru-azide-thioalkyne cycloaddition (RuAtAC)



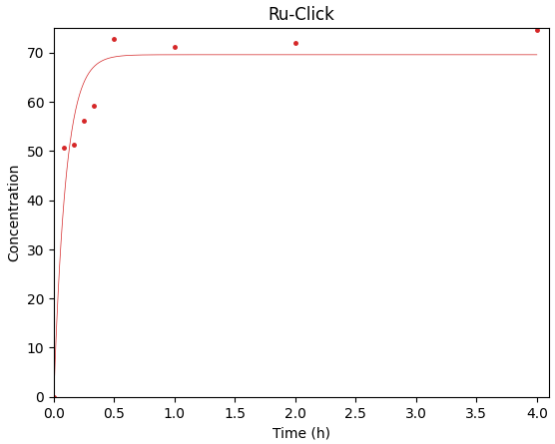

**1a** (Ar = *p*-MeOPh) **2b** **3ab**

| Time h | Yield (%) | [3ab] |
|---|---|---|
| 0 | 0 | 0 |
| 0.08 | 67 | 50.25 |
| 0.16 | 70 | 52.5 |
| 0.25 | 75 | 56.25 |
| 0.33 | 78.5 | 58.875 |
| 0.5 | 80 | 60 |
| 1 | 84 | 63 |
| 2 | 88 | 66 |
| 4 | 88.5 | 66.375 |



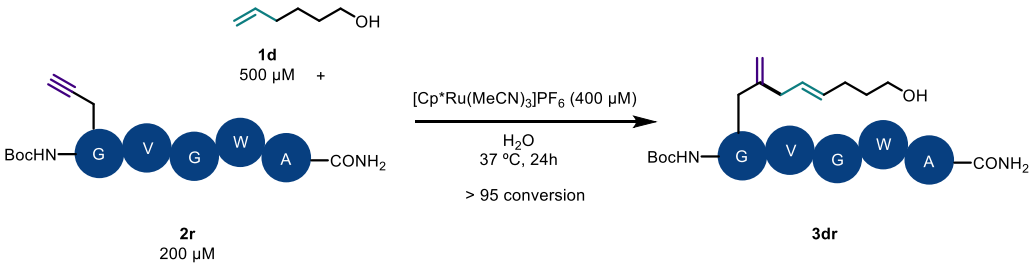




| Time h | Yield (%) | [3ab] |
|---|---|---|
| 0 | 0 | 0 |
| 0.08 | 67.5 | 50.62 |
| 0.16 | 68.5 | 51.37 |
| 0.25 | 75 | 56.25 |
| 0.33 | 79 | 59.25 |
| 0.5 | 97 | 72.75 |
| 1 | 95 | 71.25 |
| 2 | 96 | 72 |
| 4 | 99.5 | 74.62 |



## Ruthenium catalyzed alkene alkyne coupling with peptides

Exemplified with the modification of peptide **2r** with alkene **1d**:

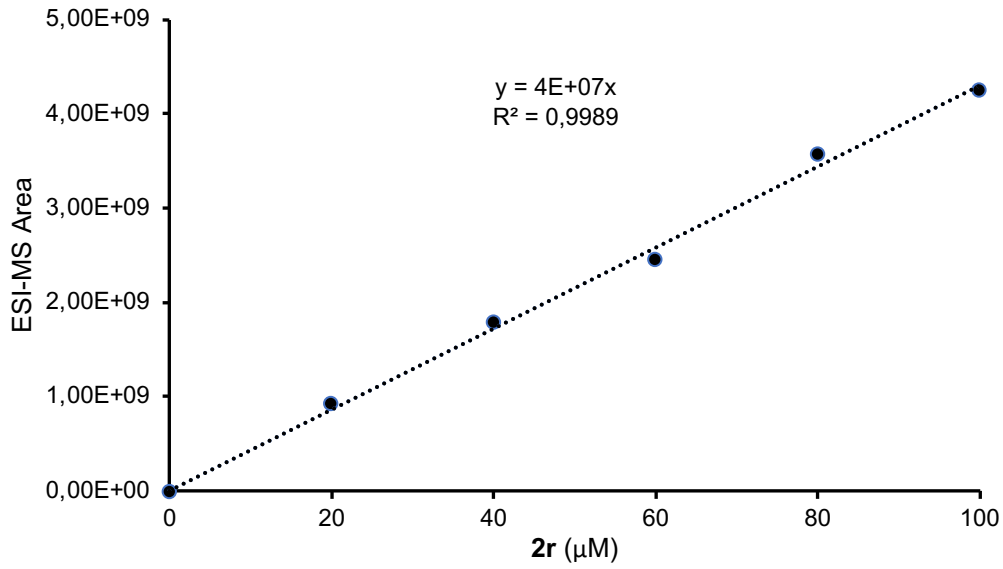


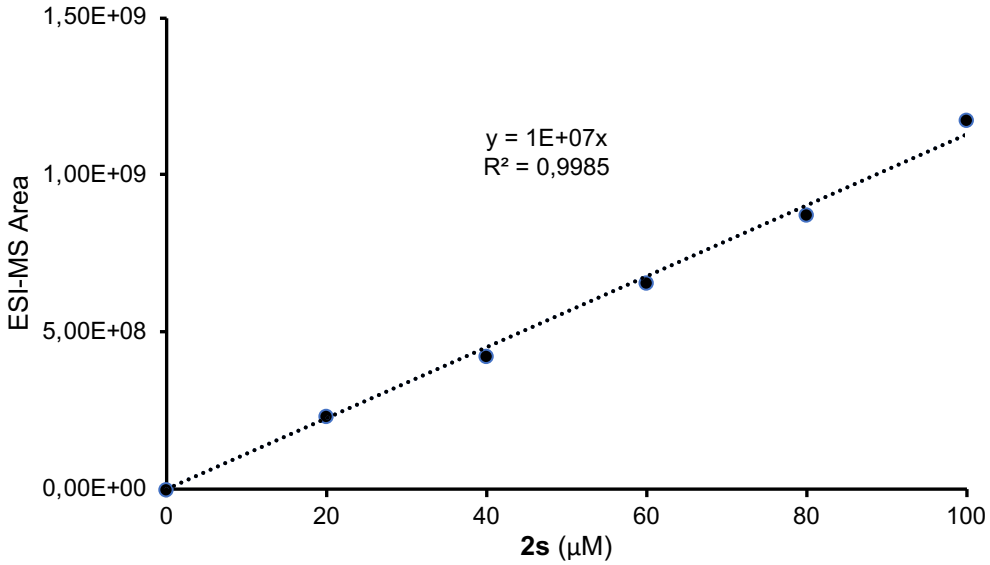

In a 500 µL Eppendorf vial, water (97 µL) peptide (**2r**, 1 µL, 20 mM stock solution in DMSO), alkene (**1d,** 1 µL, 80 mM stock solution in DMSO) and $[Cp^*Ru(MeCN)_3]PF_6$ (**Ru1**, 1 µL, 40.0 mM stock solution in DMSO), were sequentially added. The resulting mixture was shaken at 700 rpm at 37 ºC for 6h, diluted with MeOH (100 µL) and analyzed by HPLC-MS (from 5% to 95 % MeCN in 12 min, with + 0.1 formic acid).

Conversions of the peptide **2** towards the product **3** could be determined based on the following calibration curves. Values are based on MS data. Below, we include MS data for each peak (extracted ion chromatogram and exact mass). As can be deduced from the clean HPLC traces, reactions are generally very efficient [only original peptide (**2r** or **2s**), product peptide (**3**) and ruthenium catalytic species are detected]

### Calibration curves for 2r and 2s

20 mM stock solution of **2r** and **2s** in DMSO, were used for the calibration curves, and diluted with $H_2O$:MeOH (1:1) to the desired concentration.




1,50E+09
1,00E+09
5,00E+08
0,00E+00
ESI-MS Area
y = 1E+07x
R² = 0,9985
0
20
40
60
80
100
2s (μM)

Peptide **3dr**

Prepared according to the representative example using alkene **1d** (500 µM), peptide **2r** (200 µM) and **Ru1** (400 µM).

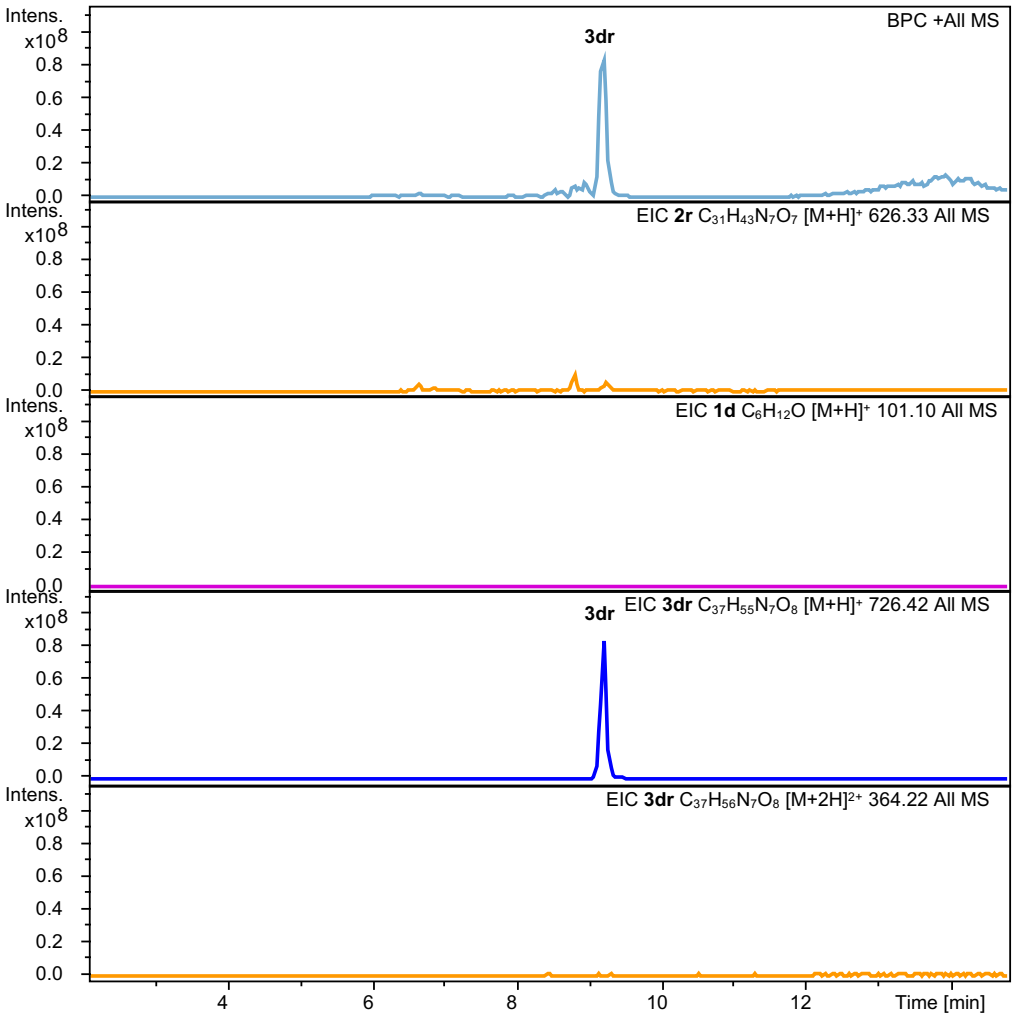



**Figure S2.** ESI-MS Chromatogram for the reaction of **1d** and **2r.** Extracted ion chromatogram (EIC) for **2r** $[M+H]^+$, **1d** $[M+H]^+$, **3dr** $[M+H]^+$ and **3dr** $[M+2H]^{2+}$. **2r** not detected in the reaction crude (100% conversion)

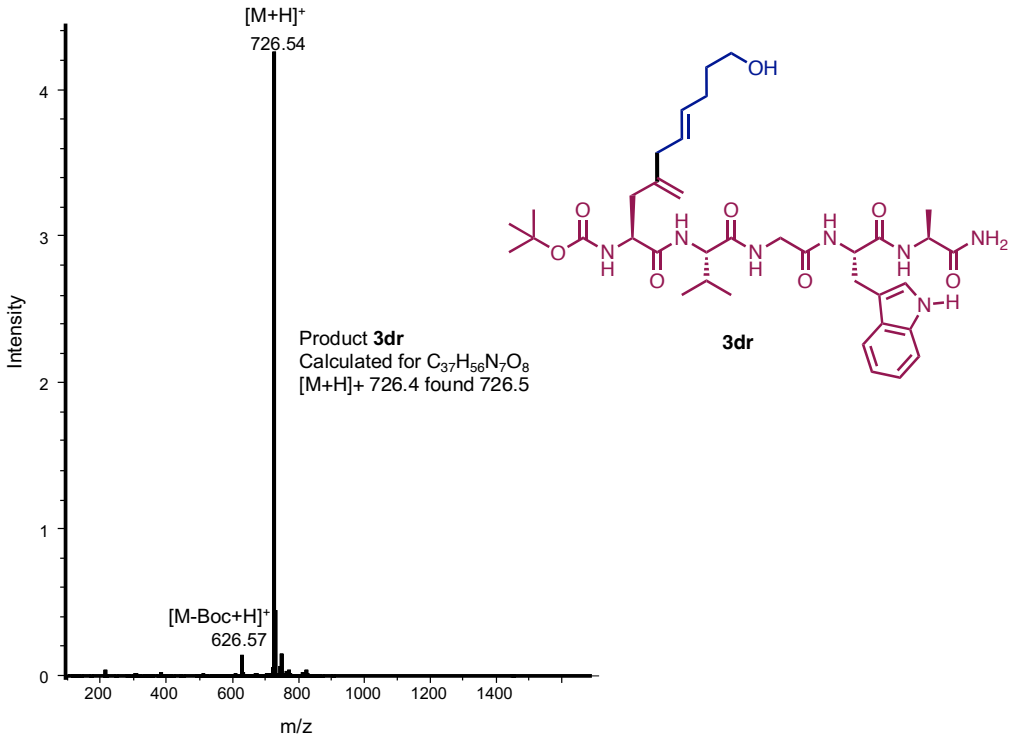



**Figure S3.** Calculated mass for $C_{37}H_{56}N_7O_8$ [M+H]+ 726.4 found 726.5

Peptide **3fr**

Prepared according to the representative example using alkene **1f** (500 µM), peptide **2r** (200 µM) and **Ru1** (400 µM).

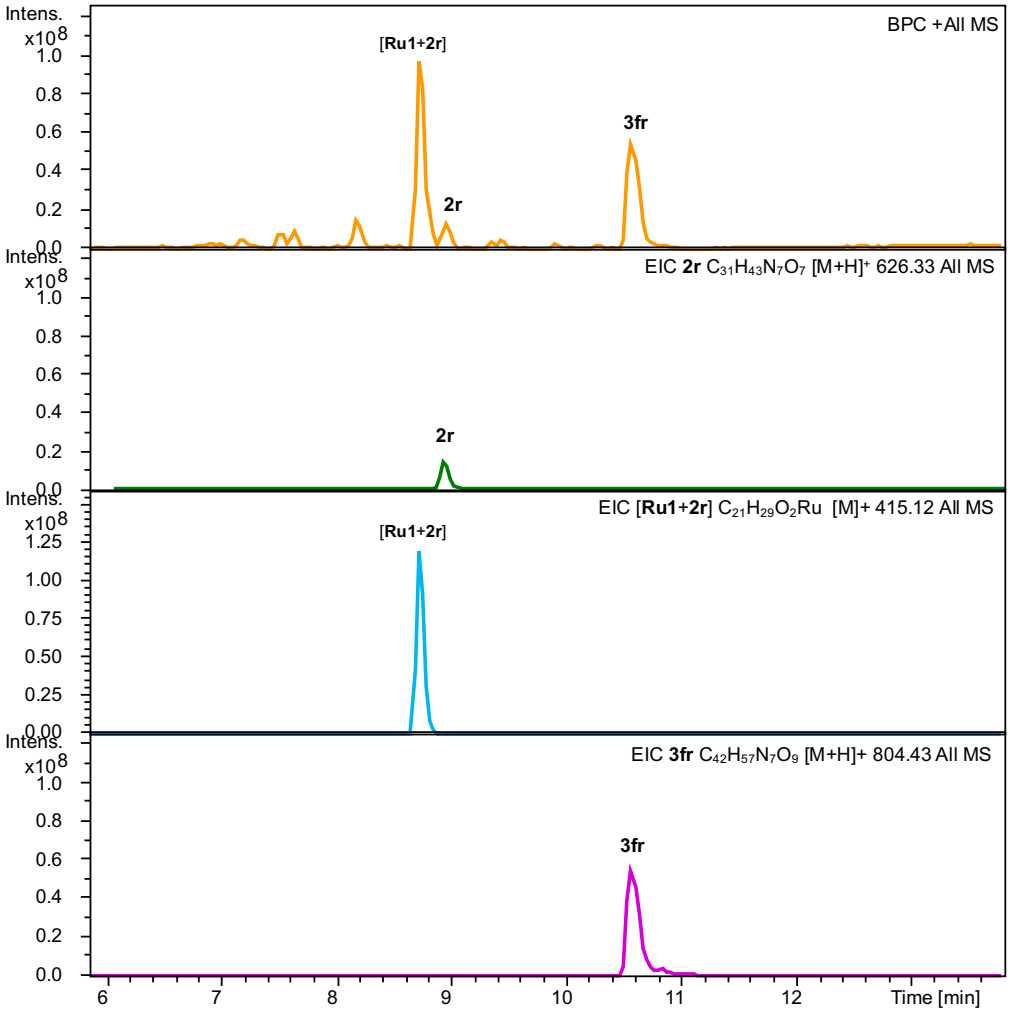



**Figure S4.** ESI-MS Chromatogram for the reaction of **1f** and **2r** and EIC for **2r** $[M+H]^+$, [**Ru1**+**1f**] $[M]^+$ and **3fr** $[M+H]^+$. Conversion of **2r** over 95 % (area of **2r** < $2.0 \cdot 10^8$, concentration of **2r** < 5.0 µM, conversion > 97.5%)

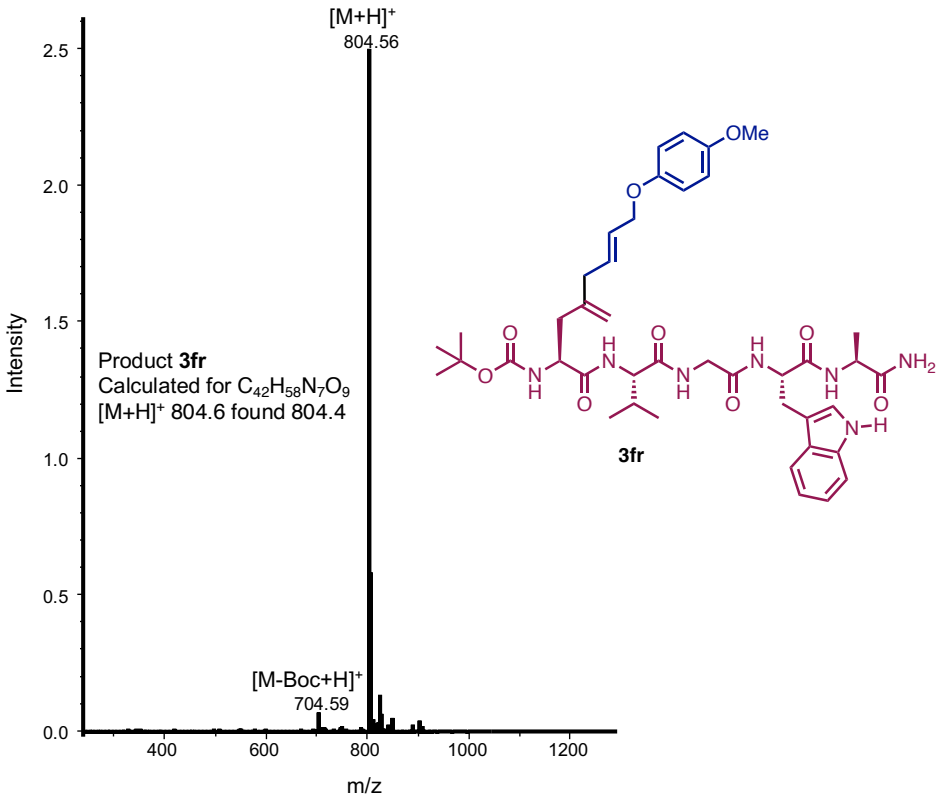



**Figure S5.** Calculated mass for $C_{42}H_{58}N_7O_9$ [M+H]+ 804.6 found 804.4

Peptide **3cr**

Prepared according to the representative example using alkene **1c** (500 µM), peptide **2r** (200 µM) and **Ru1** (400 µM).

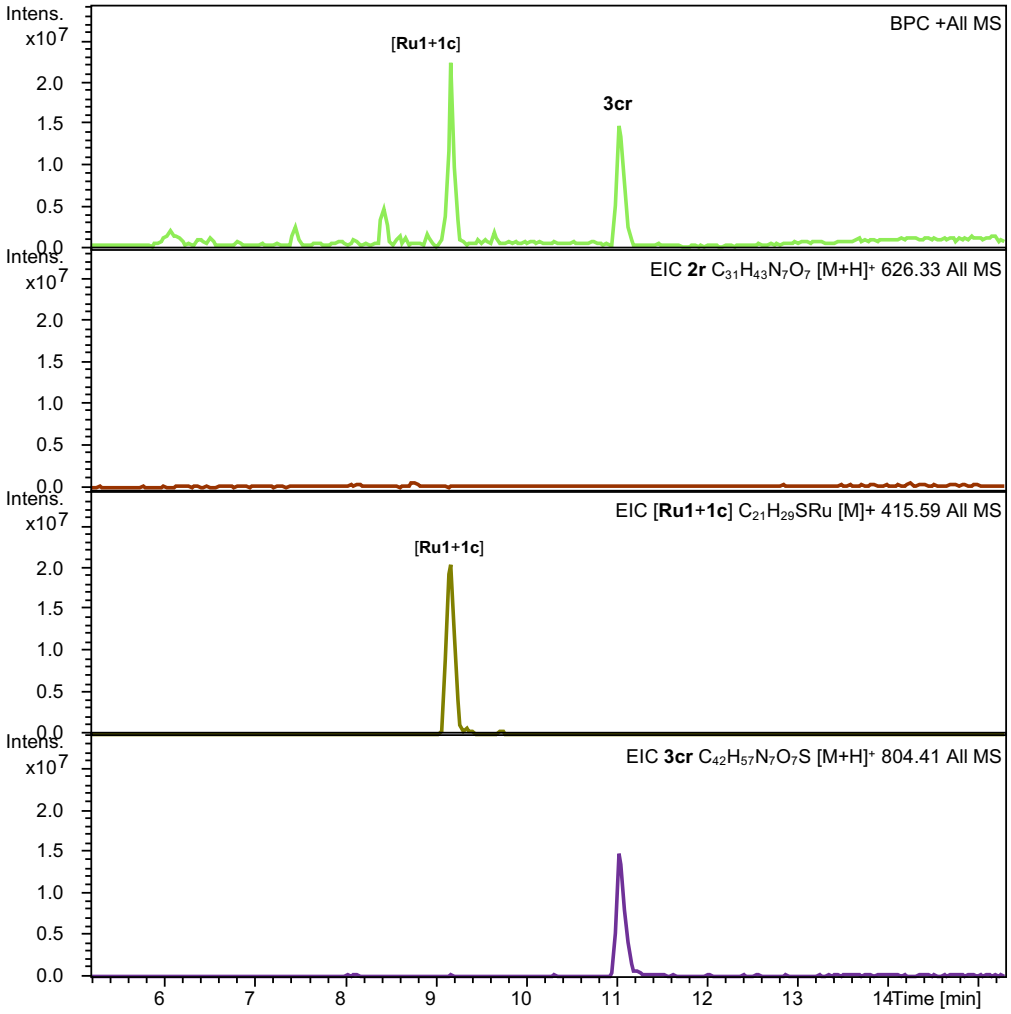



**Figure S6.** ESI-MS Chromatogram for the reaction of **1c** and **2r.** EIC for **2r** $[M+H]^+$, [**Ru1**+**1c**] $[M]^+$ and **3cr** $[M+H]^+$. **2r** not detected in the reaction crude (100% conversion).

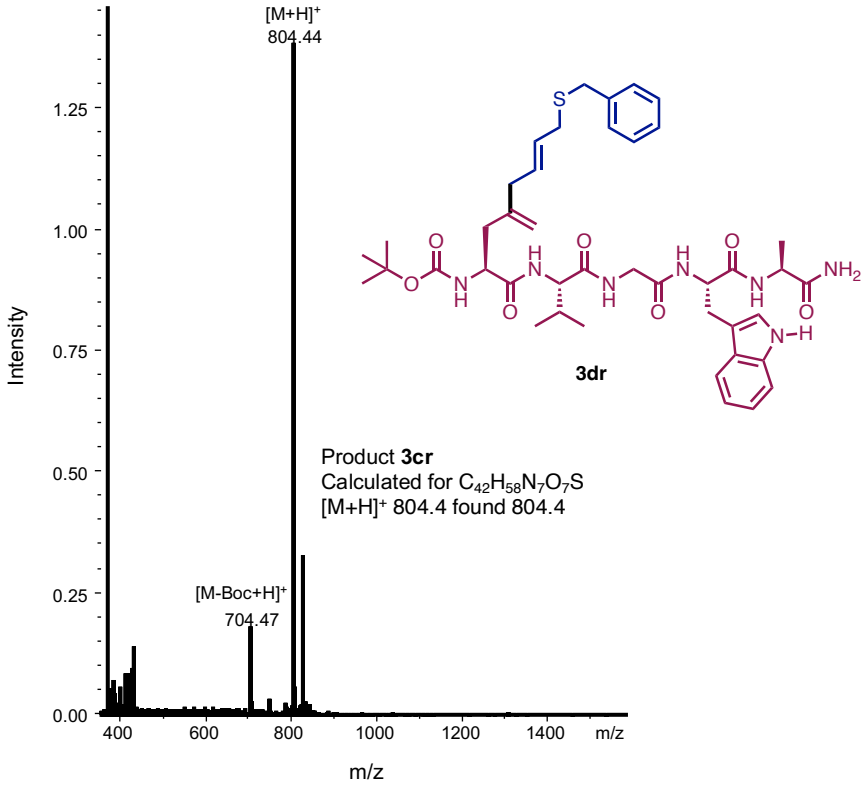



**Figure S7.** Calculated mass for $C_{42}H_{58}N_7O_7S$ [M+H]+ 804.4 found 804.4

Peptide **3gr**

Prepared according to the representative example using alkene **1g** (500 µM), peptide **2r** (200 µM) and **Ru1** (400 µM).

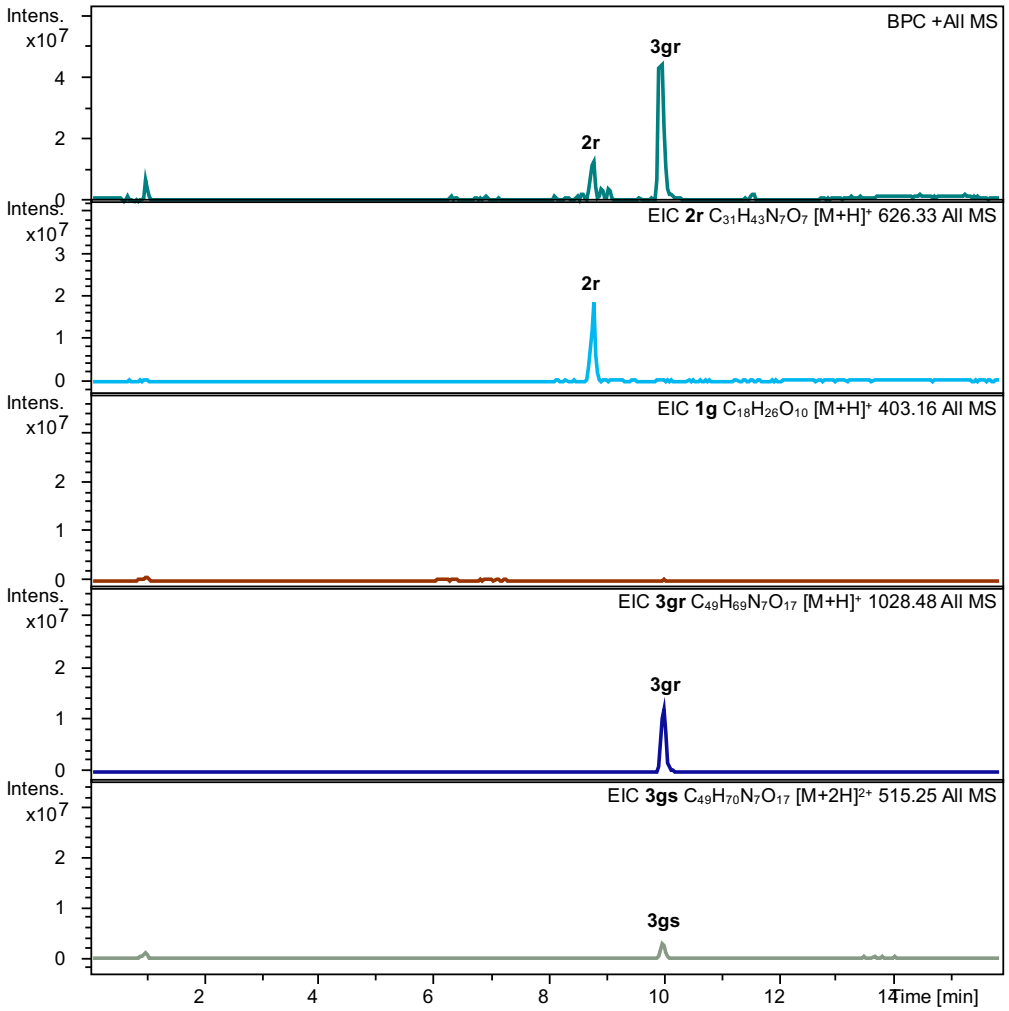



**Figure S8.** ESI-MS Chromatogram for the reaction of **1g** and **2r.** EIC for **2r** $[M+H]^+$, **2g** $[M+H]^+$, **3gr** $[M+H]^+$ and **3gr** $[M+2H]^{2+\cdot}$ Conversion of **2r** over 95 % (area of **2r** < $2.0 \cdot 10^8$, concentration of **2r** < 5.0 µM, > 97.5% conversion)

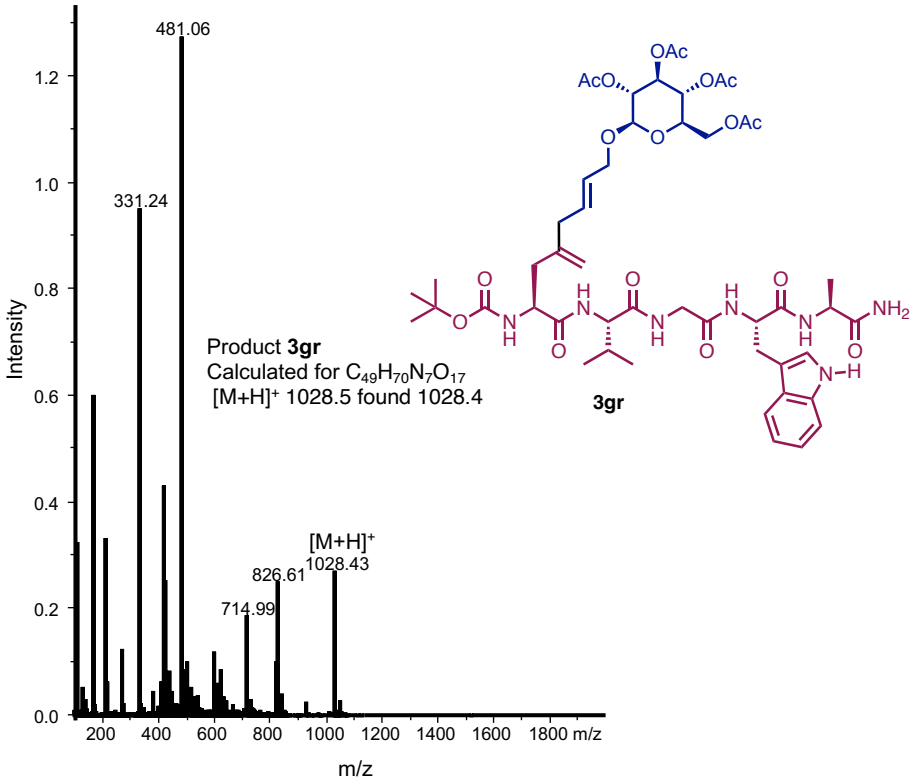



**Figure S9.** Calculated mass for $C_{49}H_{70}N_7O_{17}$ [M+H]+ 1028.5 found 1028.4

Peptide **3cs**

Prepared according to the representative example using alkene **1c** (500 µM), peptide **2s** (200 µM) and **Ru1** (400 µM).

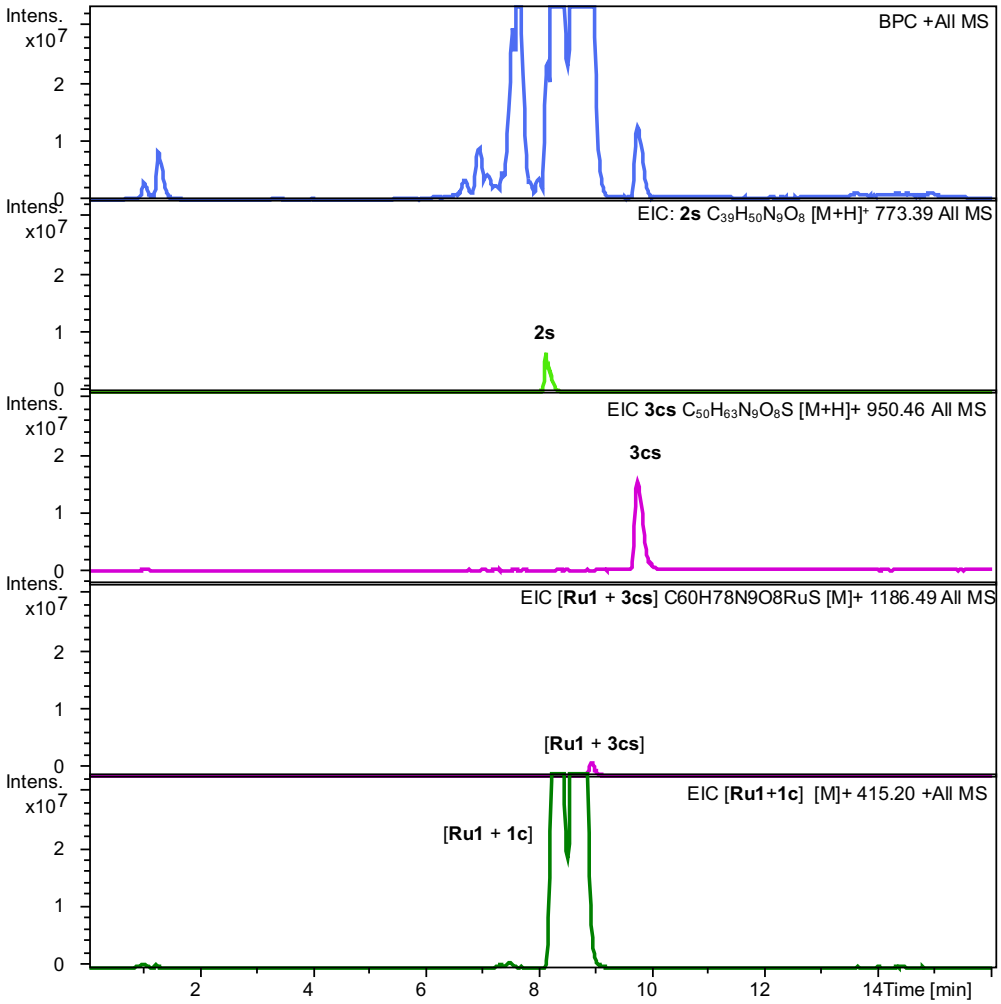



**Figure S10.** ESI-MS Chromatogram for the reaction of **1c** and **2s.** EIC for **2s** $[M+H]^+$, **3cs** $[M+H]^+$, [**Ru1** + **3cs**] $[M]^+$ and [**Ru1** + **1c**] $[M]^{+\cdot}$ Conversion of **2s** 95 % (area of **2s** < $5.6 \cdot 10^7$, concentration of **2** < = 5.0 µM, >97.5% conversion).

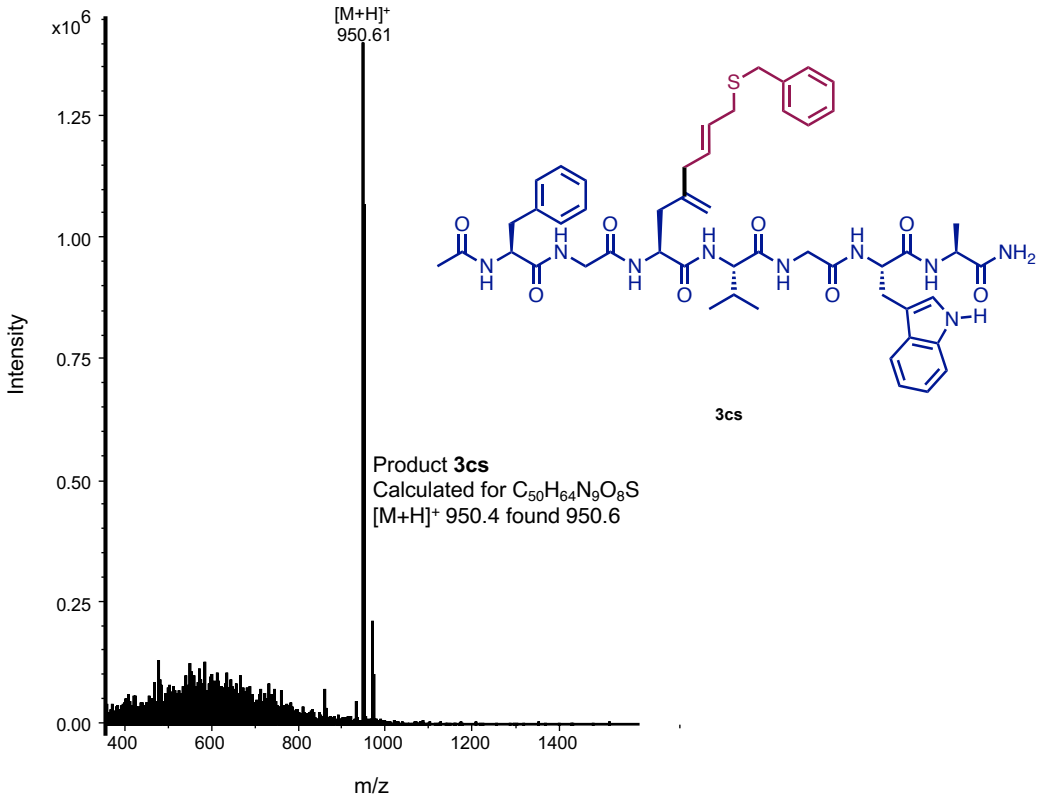



**Figure S11**. Calculated mass for $C_{50}H_{64}N_9O_8S$ [M+H]+ 950.4 found 950.6

Peptide **3fs**

Prepared according to the representative example using alkene **1f** (500 µM), peptide **2s** (200 µM) and **Ru1** (400 µM).

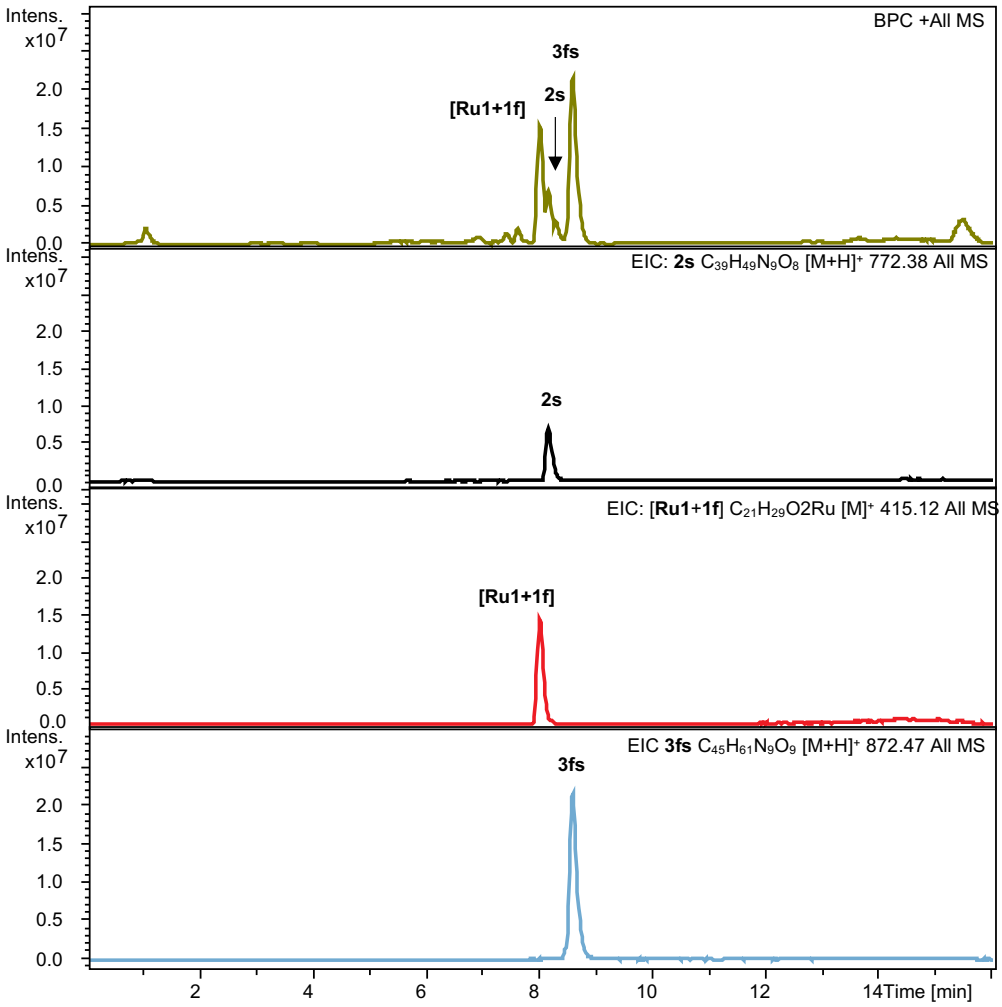



**Figure S12.** ESI-MS Chromatogram for the reaction of **1f** and **2s.** EIC for **2s** $[M+H]^+$, **[Ru1+1f]** $[M]^+$ and **3fs** $[M+H]^+$. Conversion of **2s** 95 % (area of **2s** = $5.6 \cdot 10^7$, concentration of **2s** = 5.0 µM, 97.5% conversion).

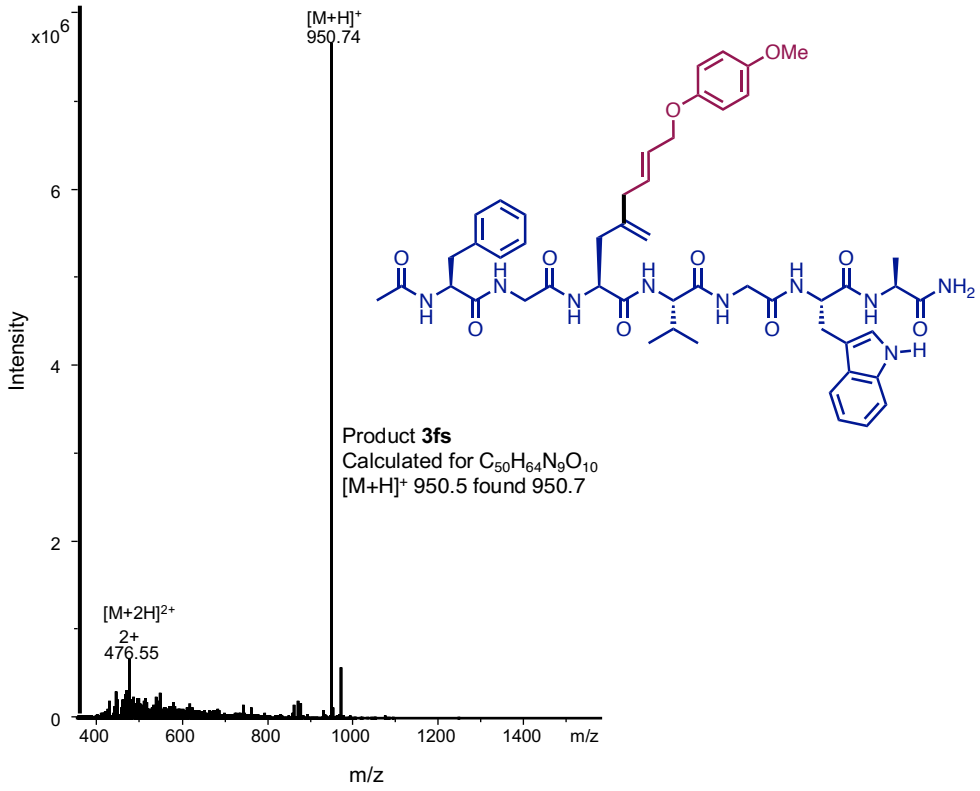



**Figure S13.** Calculated mass for $C_{50}H_{64}N_9O_{10}$ [M+H]+ 950.5 found 950.7

Peptide **3ds**

Prepared according to the representative example using alkene **1d** (500 µM), peptide **2s** (200 µM) and **Ru1** (400 µM).

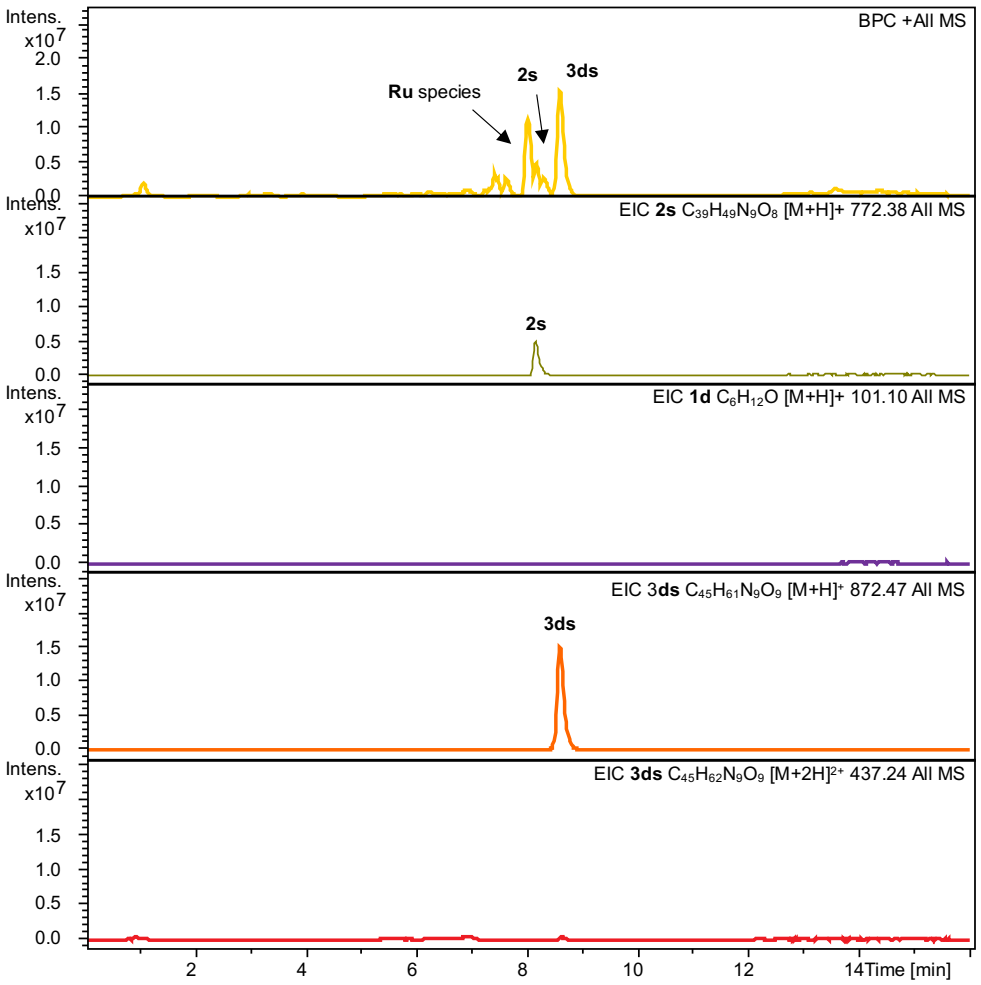



**Figure S14.** ESI-MS Chromatogram for the reaction of **1d** and **2s.** EIC for **2s** $[M+H]^+$, **1d** $[M+H]^+$, **3ds** $[M+H]^+$ and **3ds** $[M+2H]^{2+}$. Conversion of **2s** 95 over % (area of **2s** < $5.6 \cdot 10^7$, concentration of **2s** < 5.0 µM, 97.5% conversion).

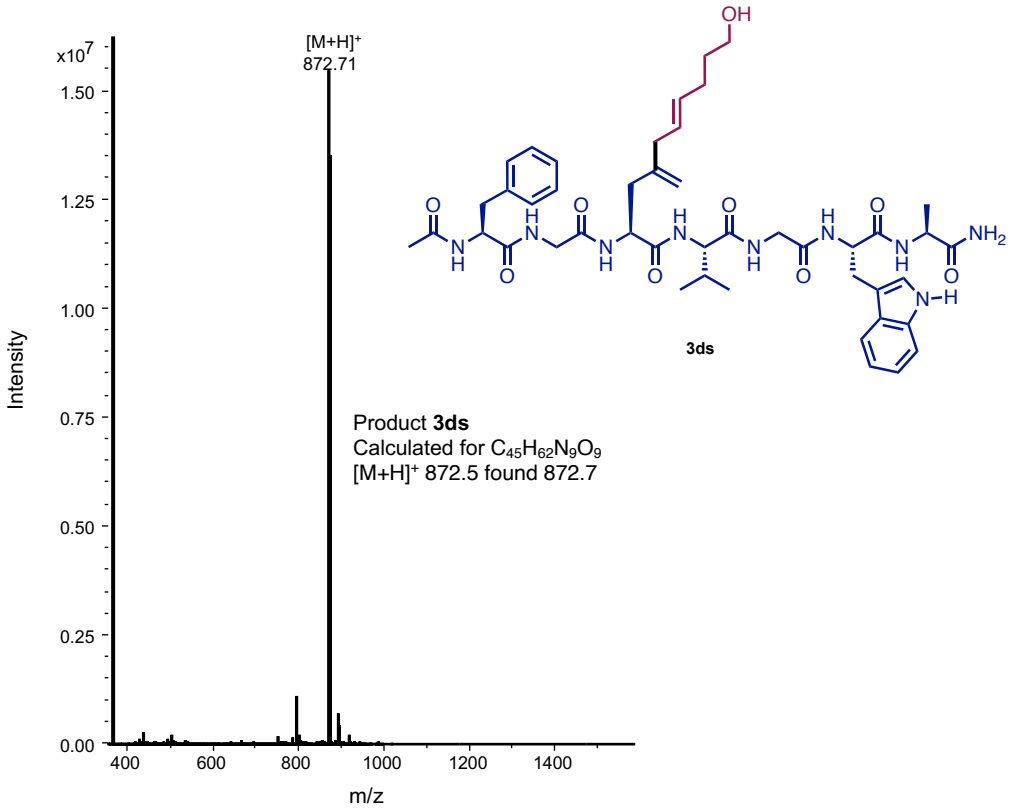
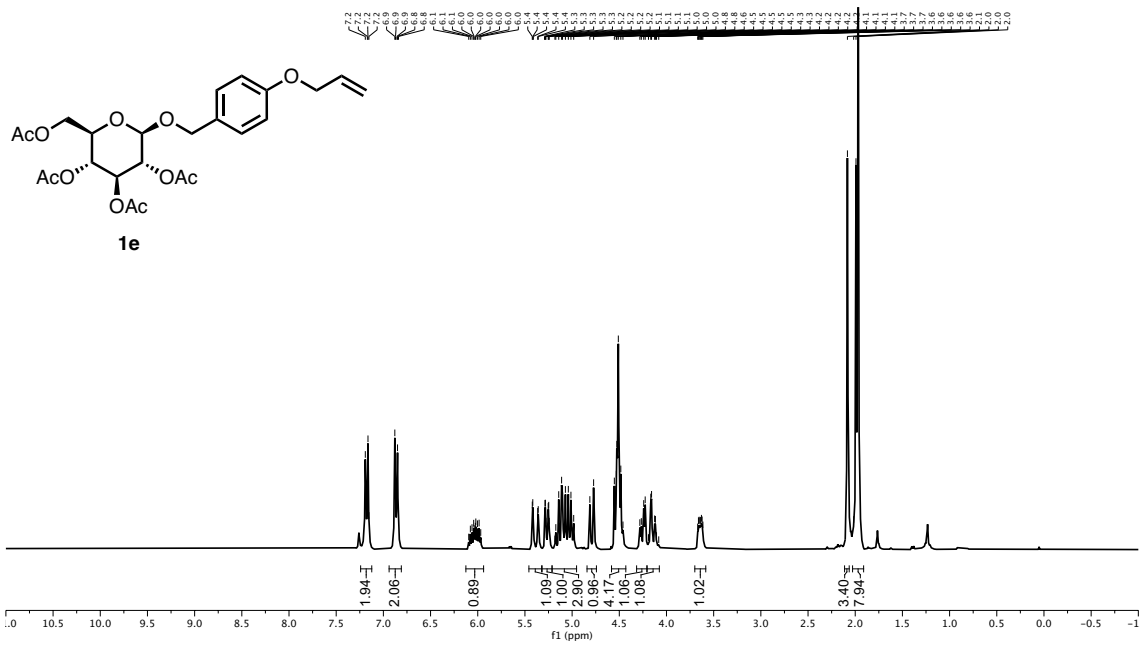



**Figure S15.** Calculated mass for $C_{45}H_{62}N_9O_9$ [M+H]+ 872.5 found 872.7.

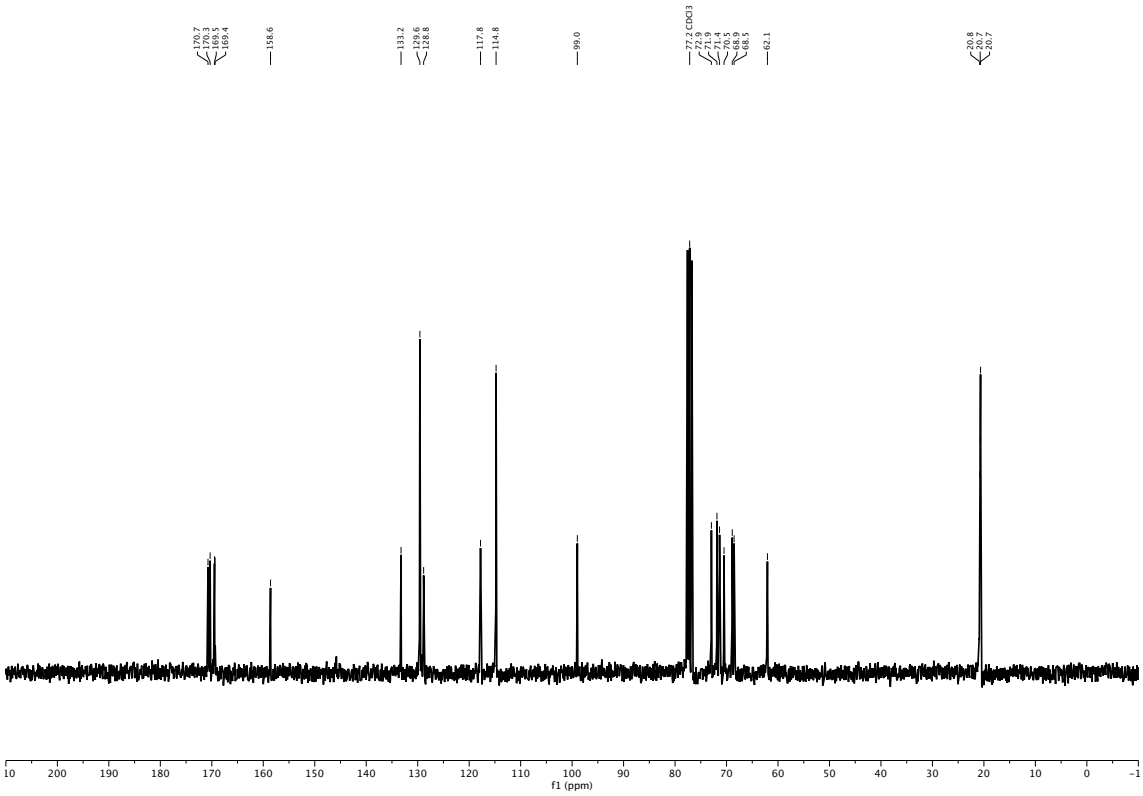
## NMR spectra

### 2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-((4-(allyloxy)benzyl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (1e)

**$^{1}$H NMR** (300 MHz, $CDCl_3$)

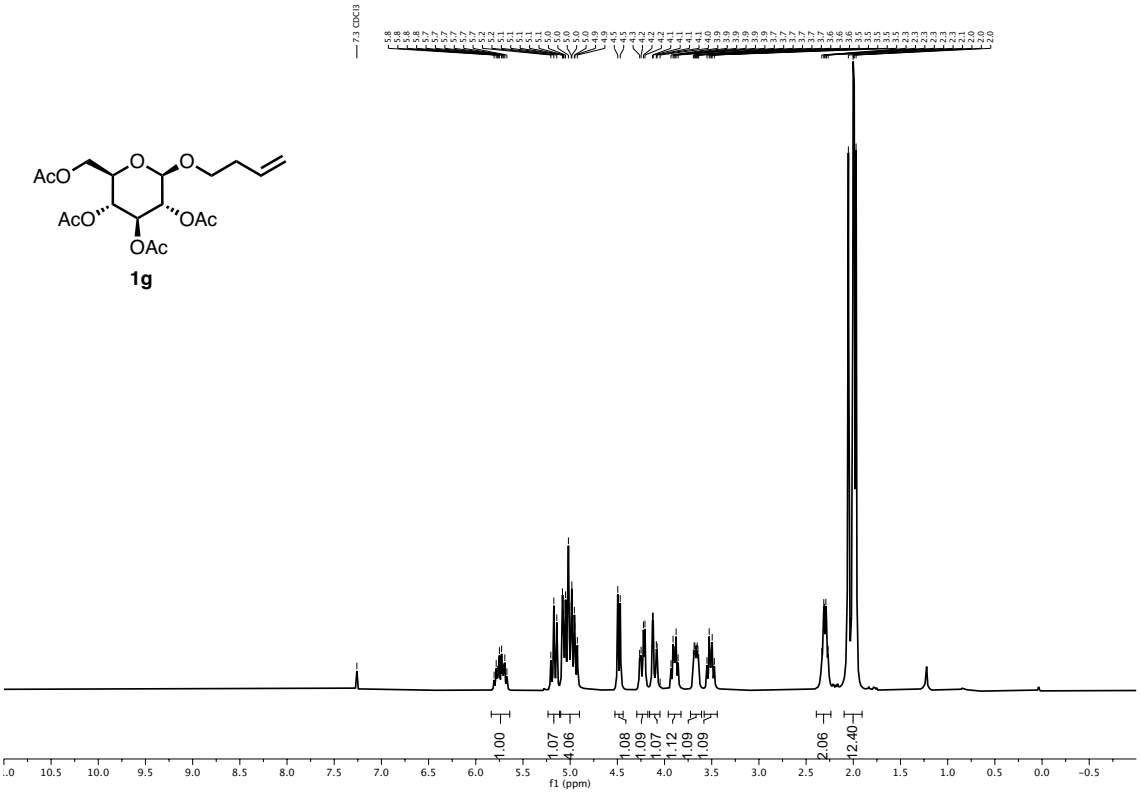



**$^{13}$C NMR** (75 MHz, $CDCl_3$)

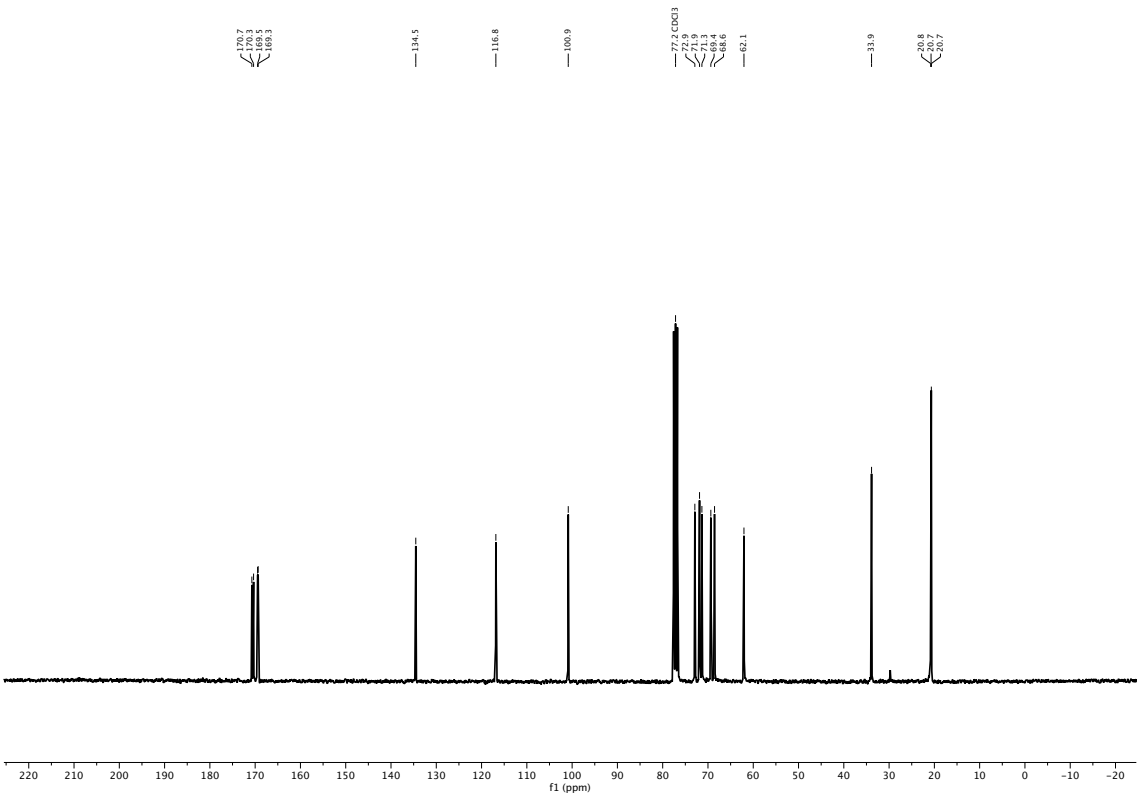


**(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(but-3-en-1-yloxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate**

**$^{1}$H NMR** (300 MHz, $CDCl_3$)

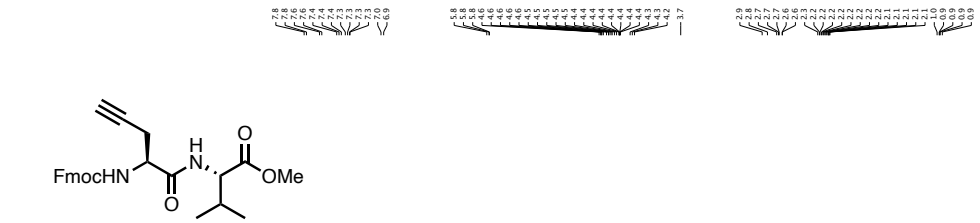



**$^{13}$C NMR** (75 MHz, $CDCl_3$)



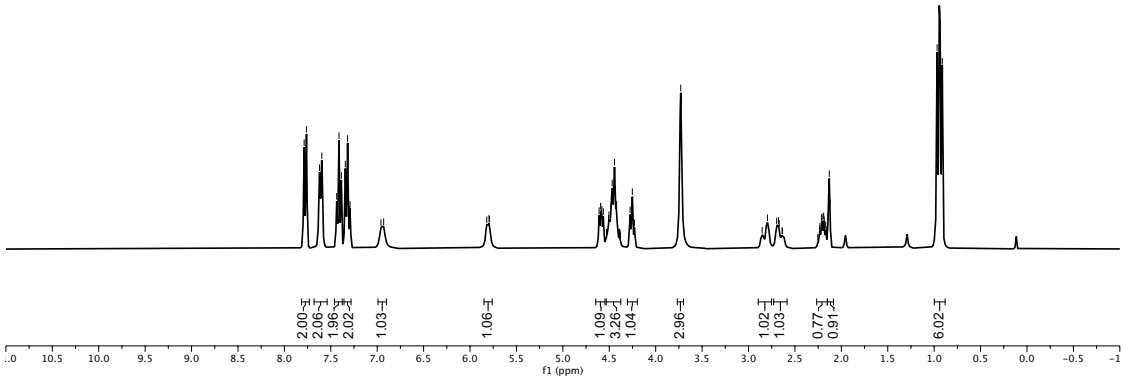
## Methyl Fmoc-L-2-propargylglycyl-*L*-valinate (2q)

**$^{1}$H NMR** (300 MHz, $CDCl_3$)

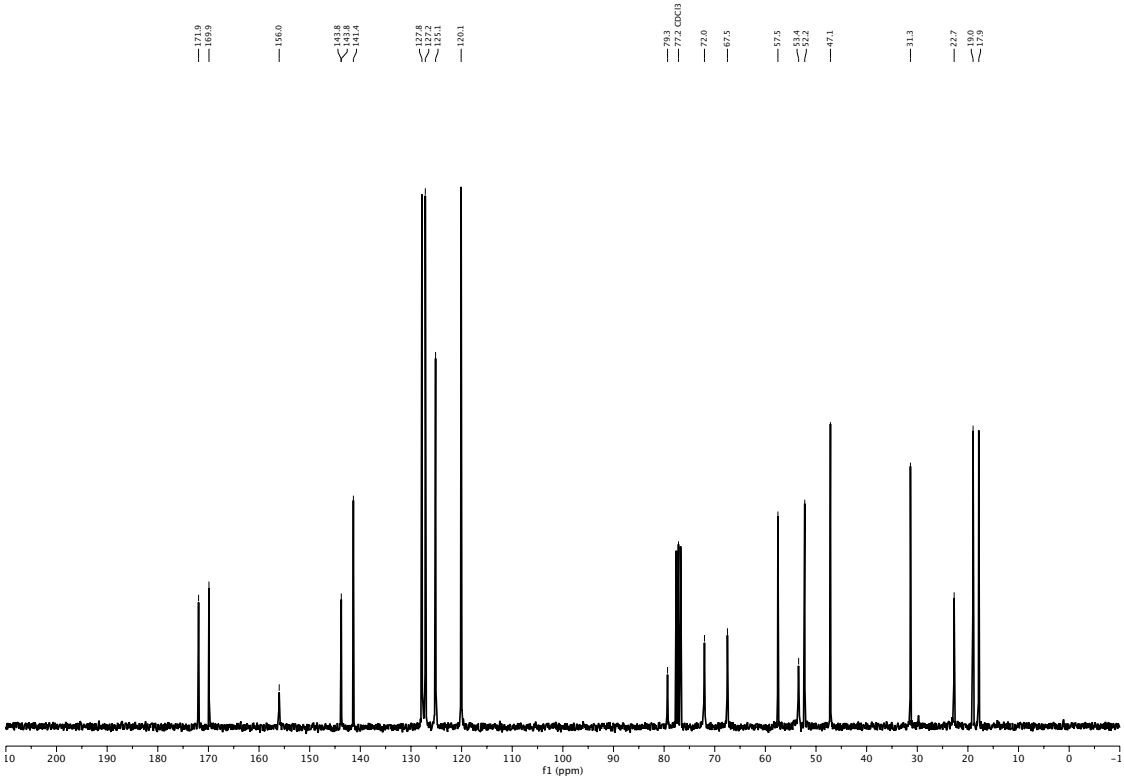





Fmoc-propargyl-Gly-Val-OMe
**2q**

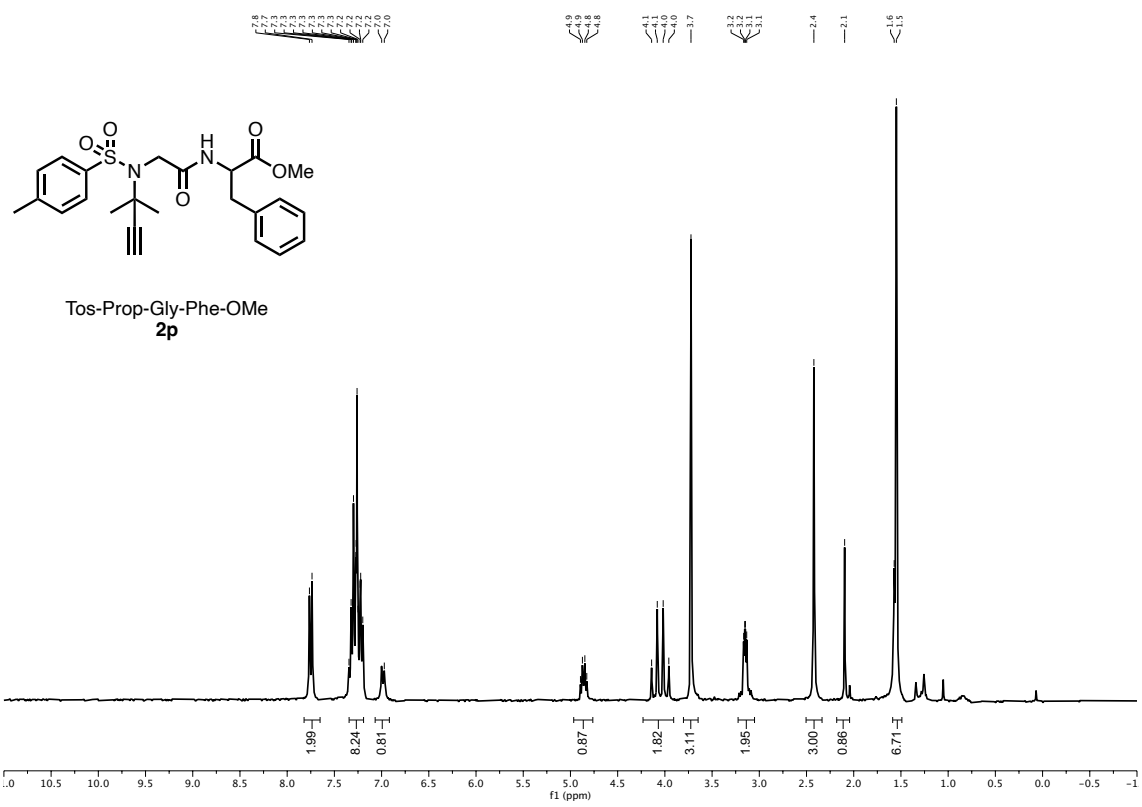



**$^{13}$C NMR** (75 MHz, $CDCl_3$)

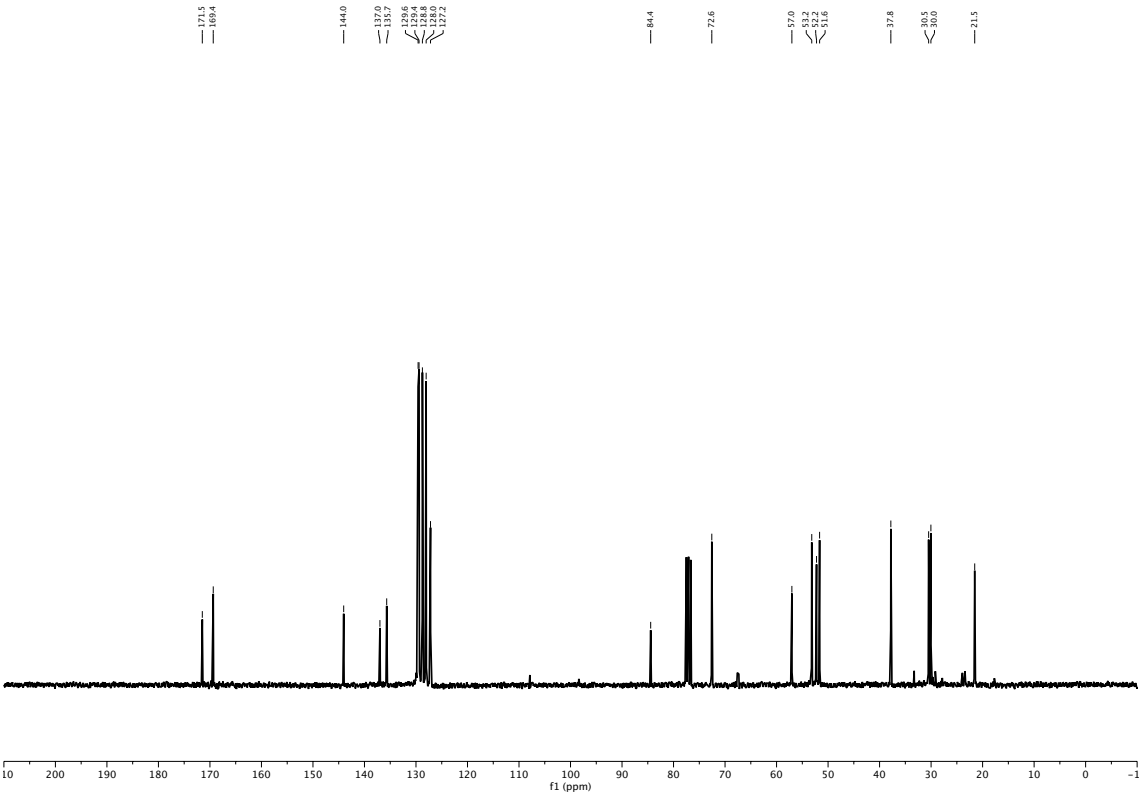


## Methyl *N*-(2-methylbut-3-yn-2-yl)-*N*-tosylglycylphenylalaninate (2p)

**$^1$H NMR** (300 MHz, $CDCl_3$)

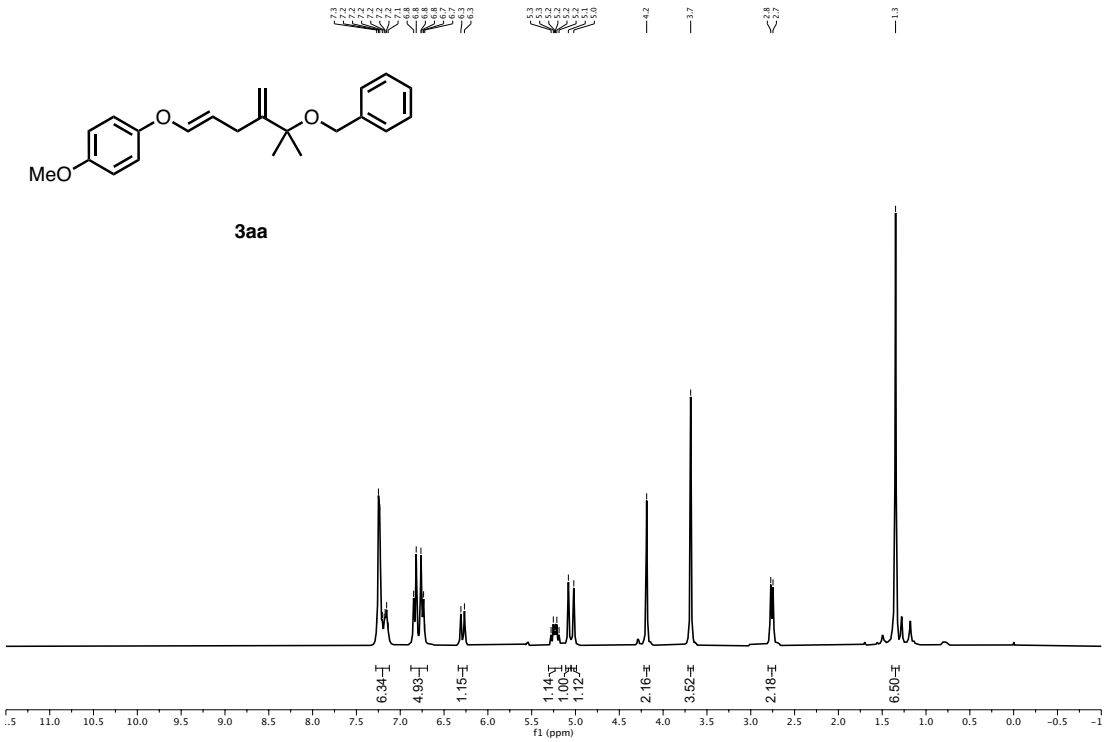



**$^{13}$C NMR** (75 MHz, $CDCl_3$)

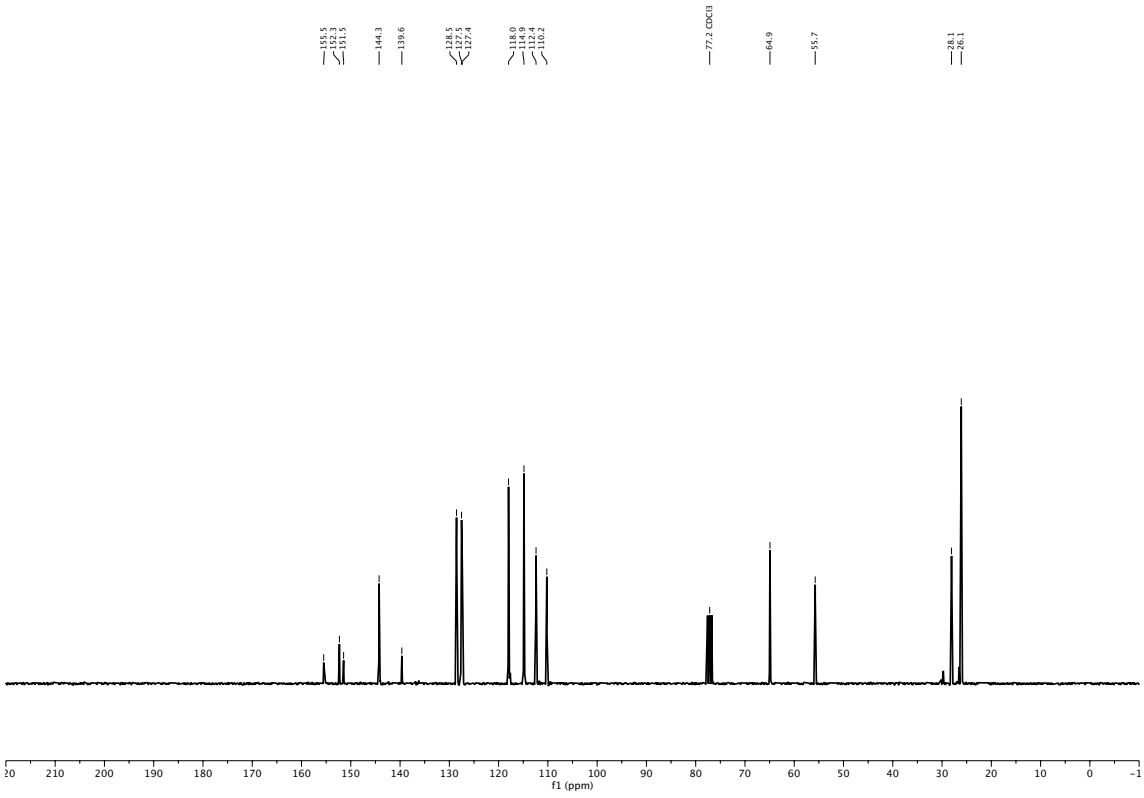


**(*E*)-1-((5-(Benzyloxy)-5-methyl-4-methylenehex-1-en-1-yl)oxy)-4-methoxybenzene (3aa)**.

**$^{1}$H-NMR** (300 MHz, $CDCl_3$)

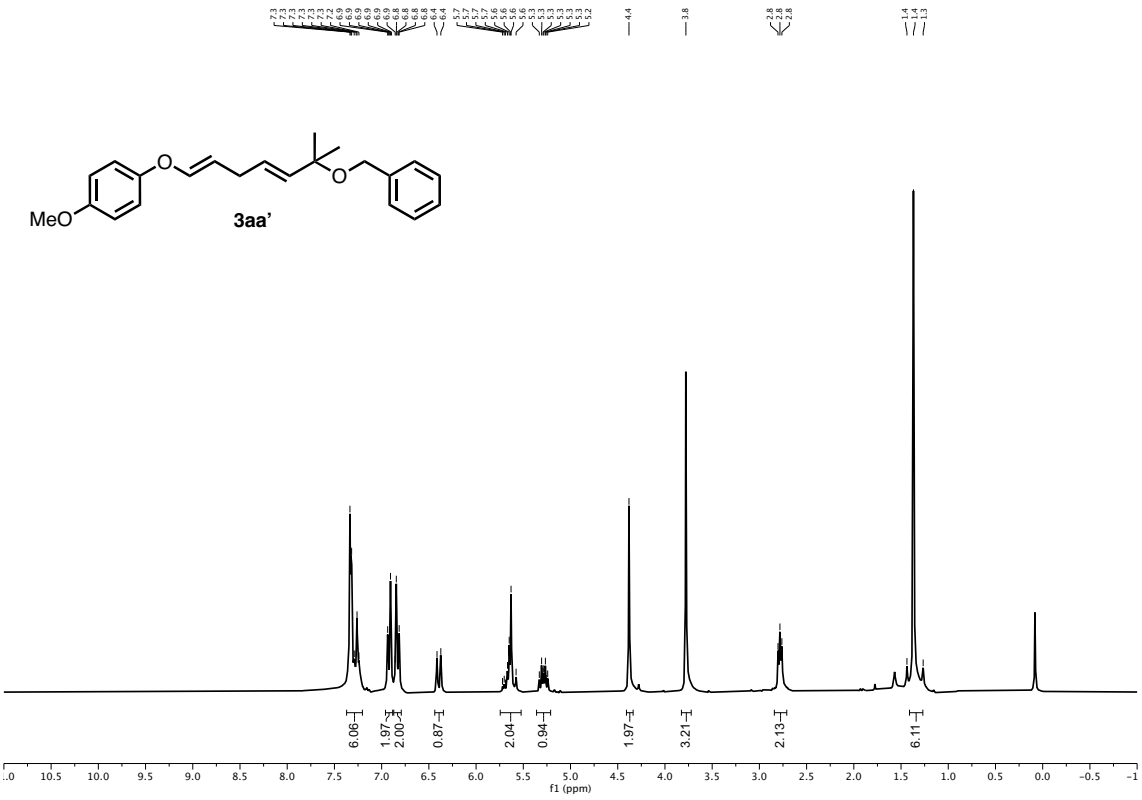



**$^{13}$C-NMR** (75 MHz, $CDCl_3$)

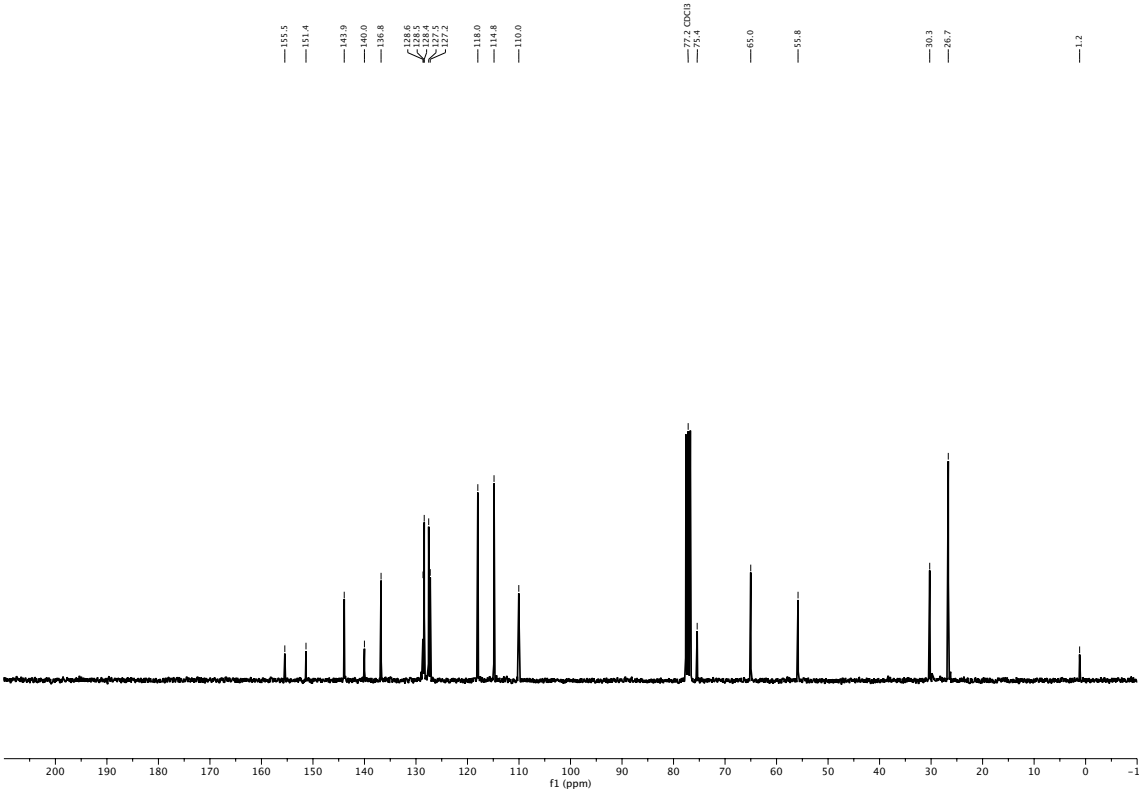


**1-(((1*E*,4*E*)-6-(benzyloxy)-6-methylhepta-1,4-dien-1-yl)oxy)-4-methoxybenzene (3aa')**

**$^{1}$H-NMR** (300 MHz, $CDCl_3$)

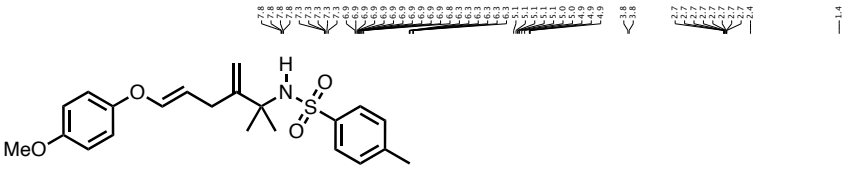



**$^{13}$C-NMR** (75 MHz, $CDCl_3$)

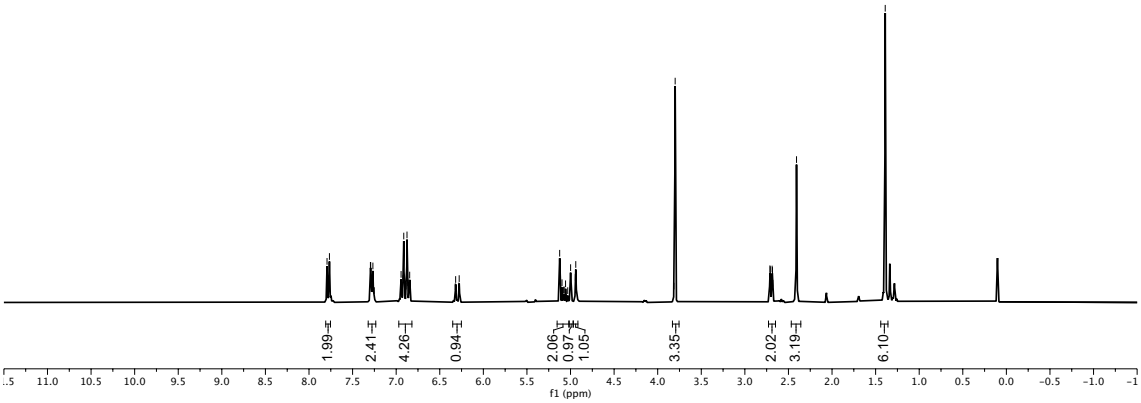


**(E)-N-(7-(4-Methoxyphenoxy)-2-methyl-3-methylenehept-5-en-2-yl)-4-methylbenze nesulfonamide (3ab).**

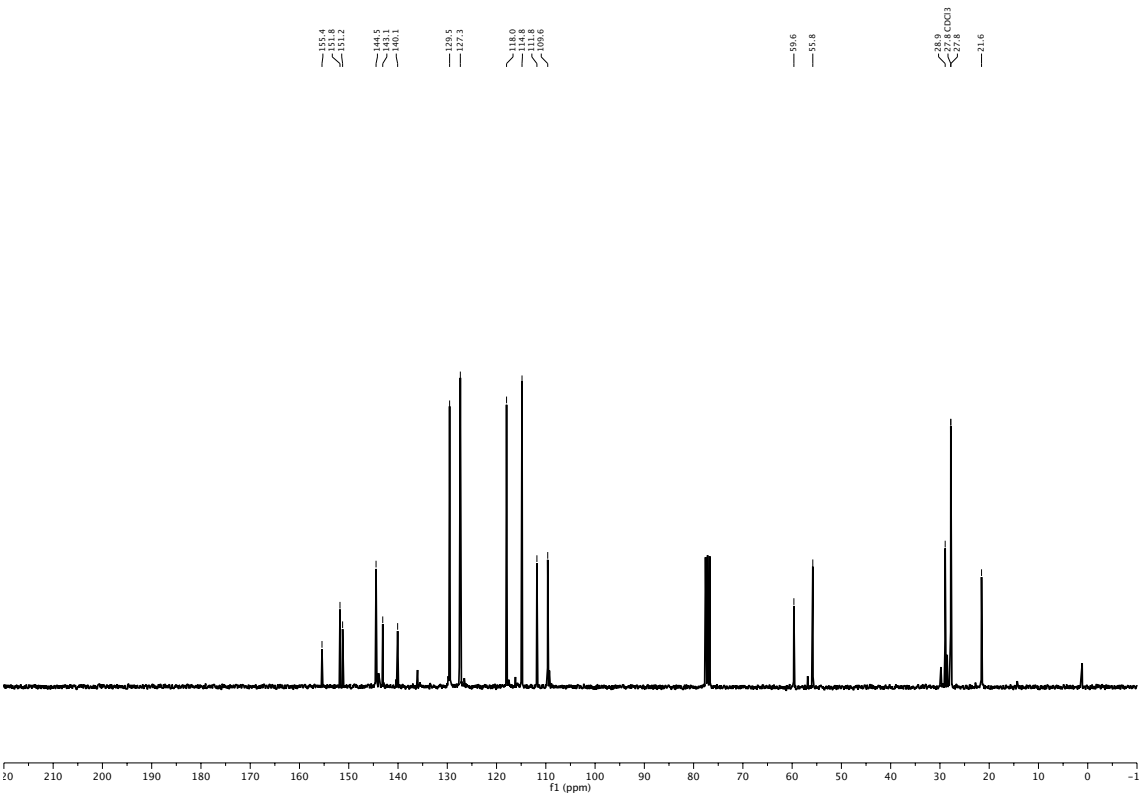
**$^{1}$H-NMR** (300 MHz, $CDCl_3$)




**3ab**

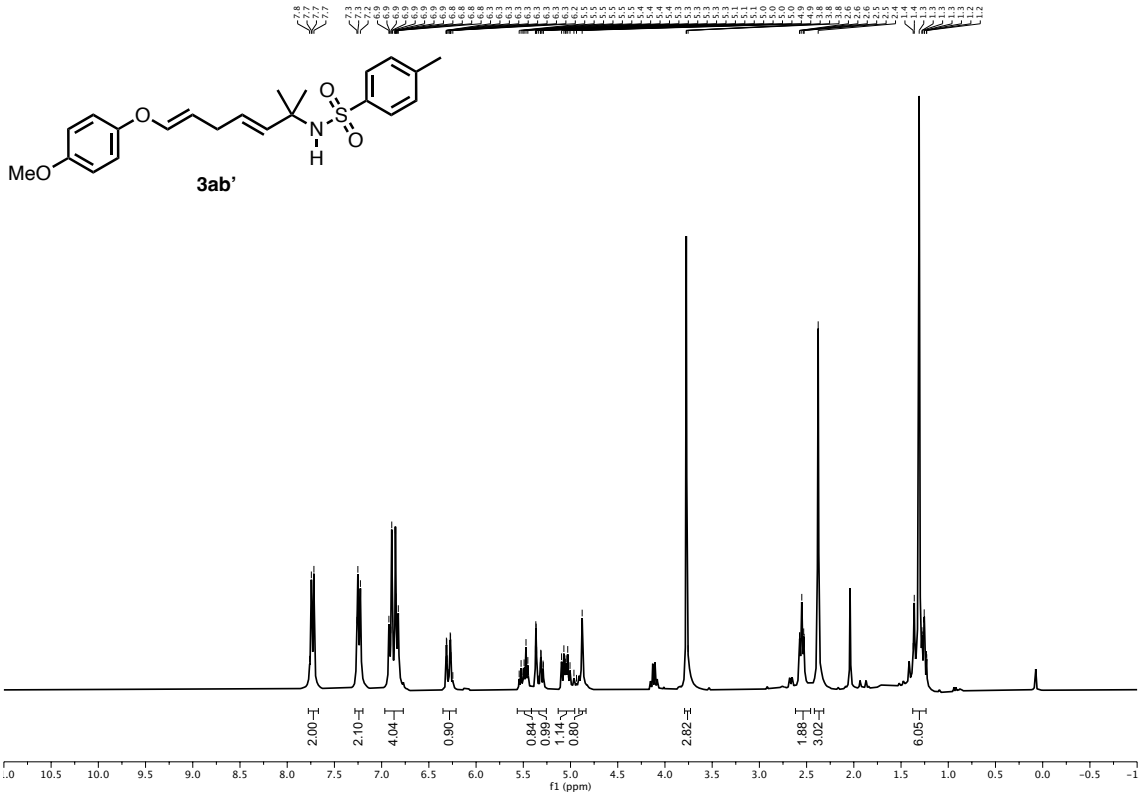



**$^{13}$C-NMR** (75 MHz, $CDCl_3$)

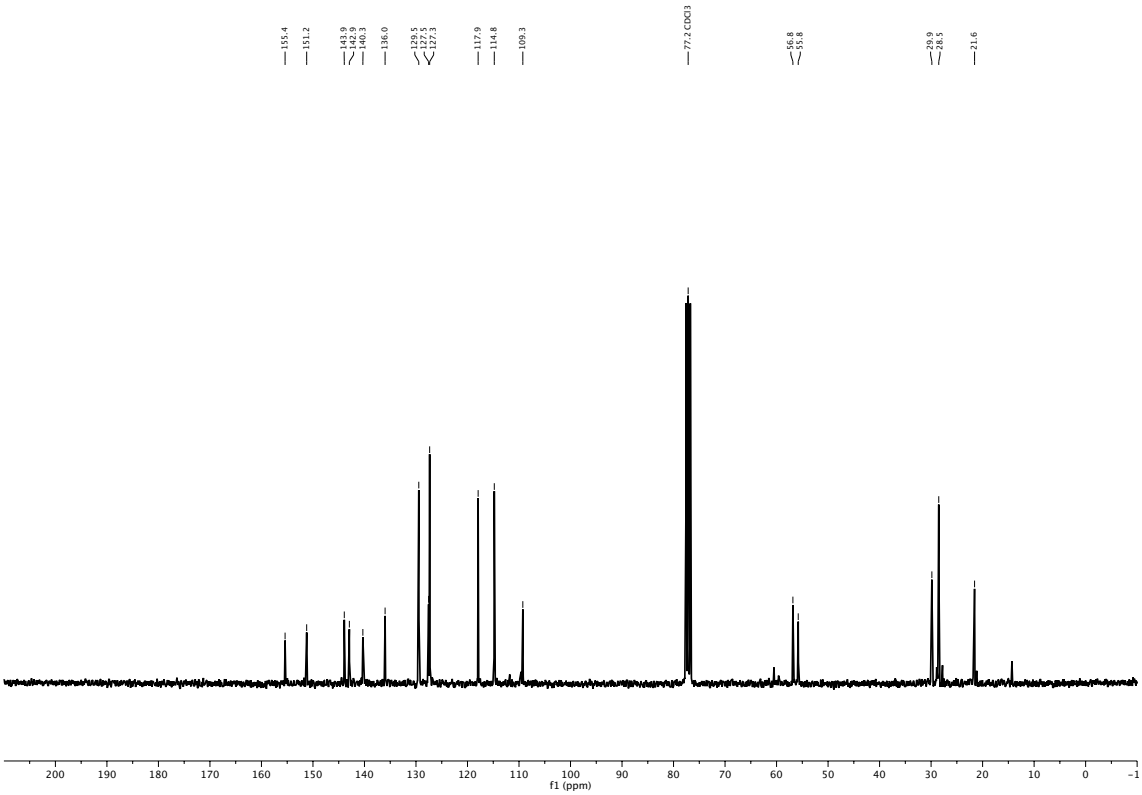


**((3*E*,6*E*)-7-(4-Methoxyphenoxy)-2-methylhepta-3,6-dien-2-yl)-4-methylbenzene sulfonamide (3ab')**

**$^{1}$H-NMR** (300 MHz, $CDCl_3$)

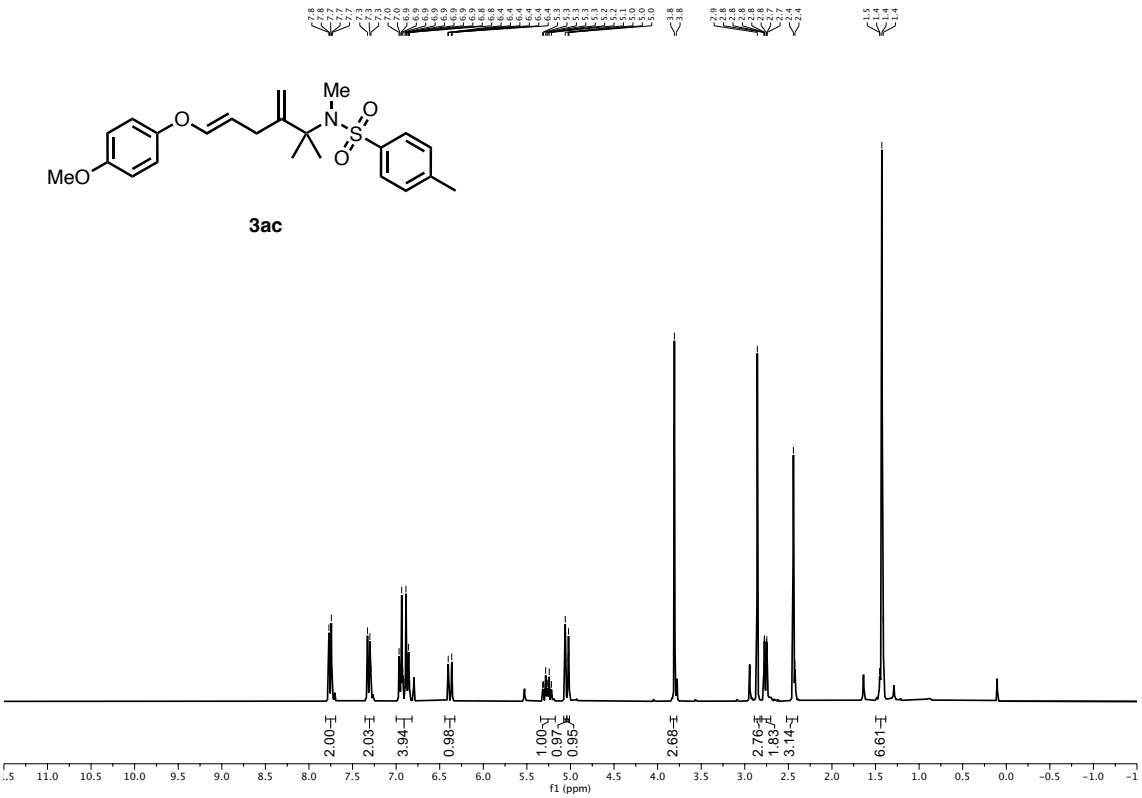



**$^{13}$C-NMR** (75 MHz, $CDCl_3$)

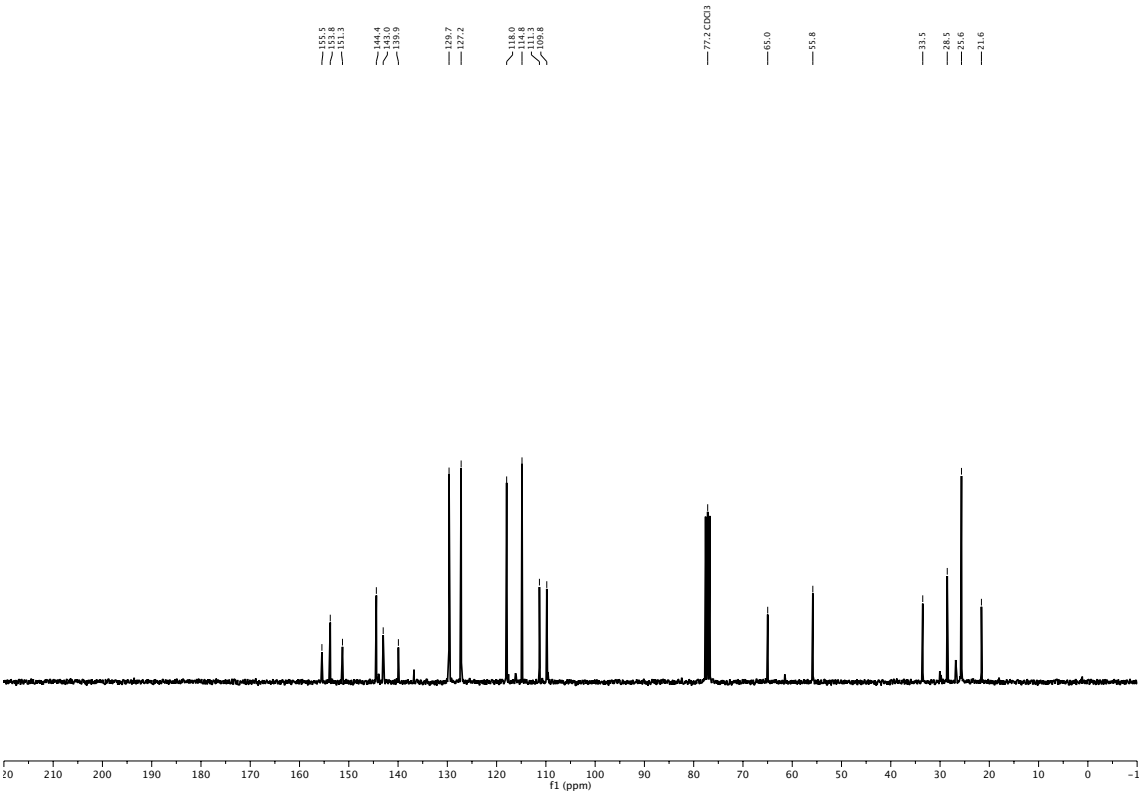


**(E)-N-(7-(4-Methoxyphenoxy)-2-methyl-3-methylenehept-5-en-2-yl)-N,4-dimethyl-benzenesulfonamide (3ac)**

**$^{1}$H-NMR** (300 MHz, $CDCl_3$)

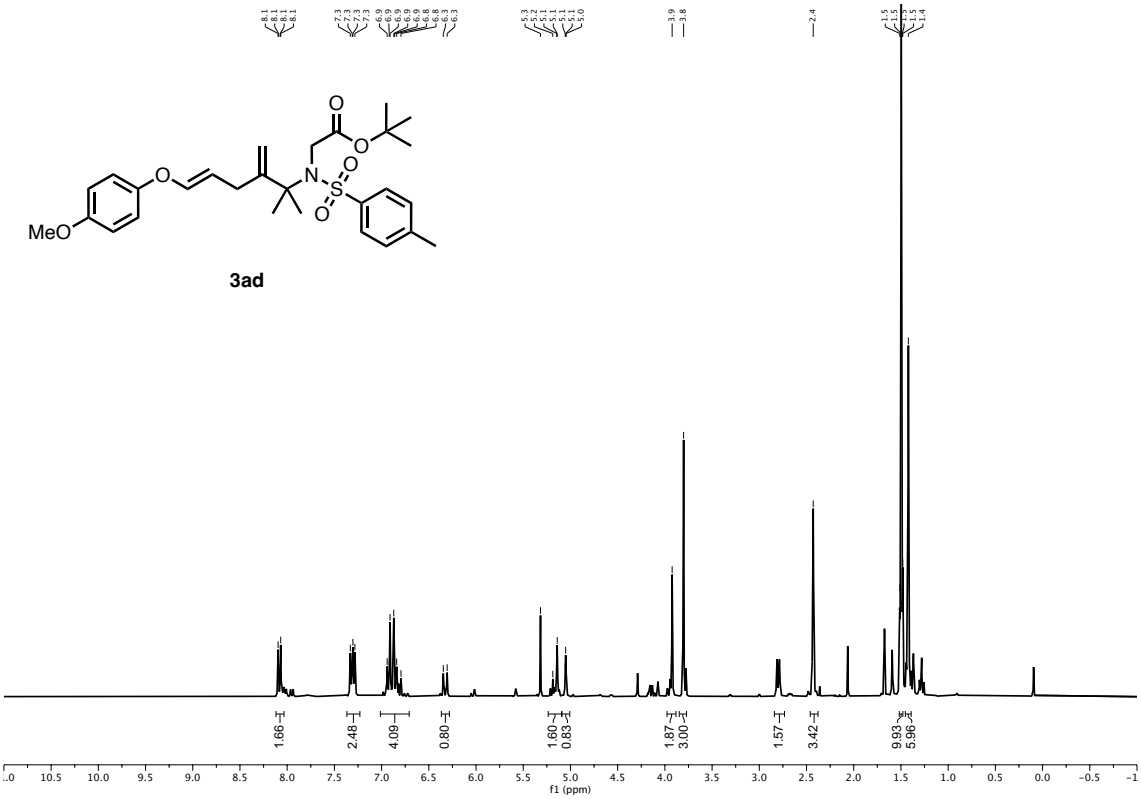



**$^{13}$C-NMR** (75 MHz, $CDCl_3$)

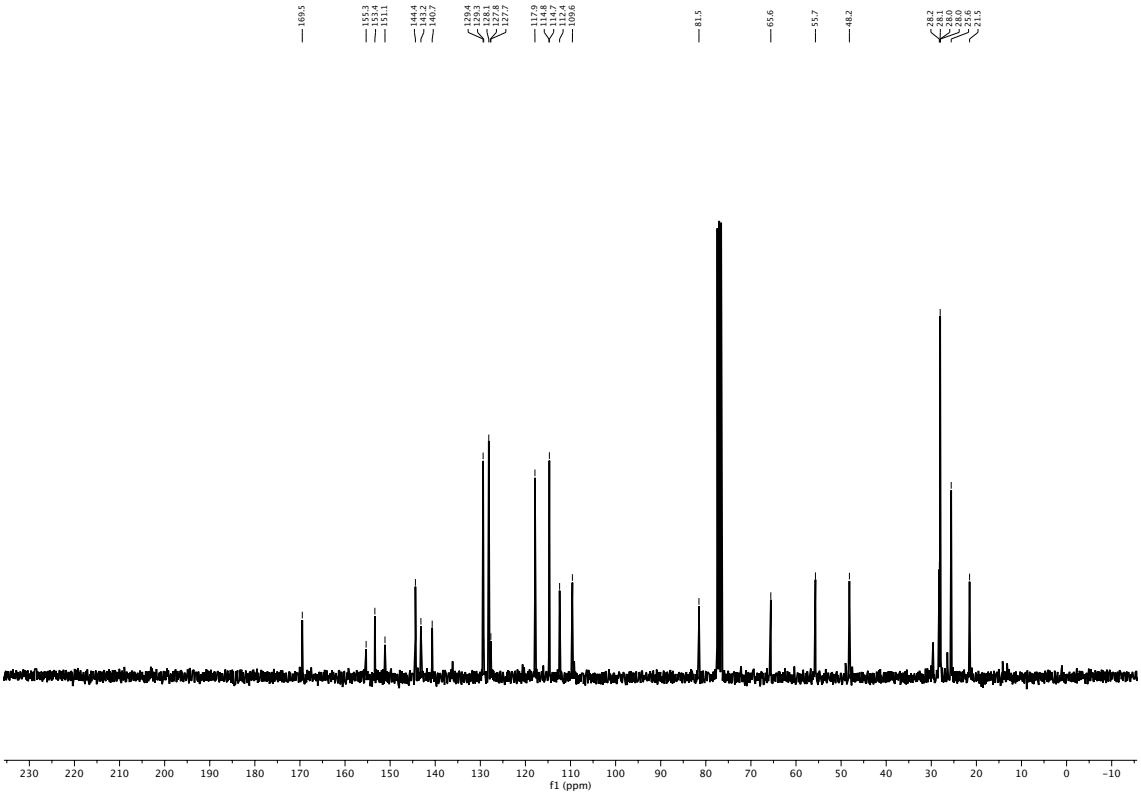


**(*E*)-*N*-(6-(4-Methoxyphenoxy)-2-methyl-3-methylenehex-5-en-2-yl)-*N*-tosylglycinate (3ad)**

**$^{1}$H NMR** (300 MHz, $CDCl_3$)

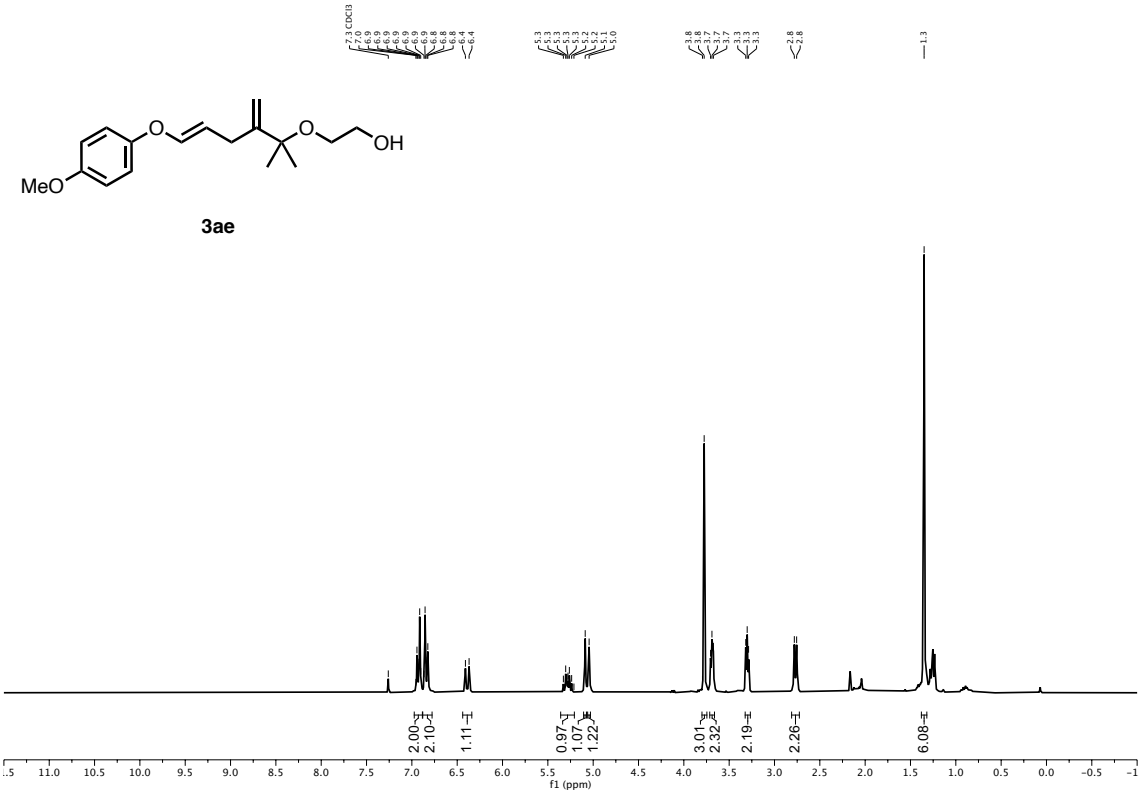



**$^{13}$C NMR** (75 MHz, $CDCl_3$)

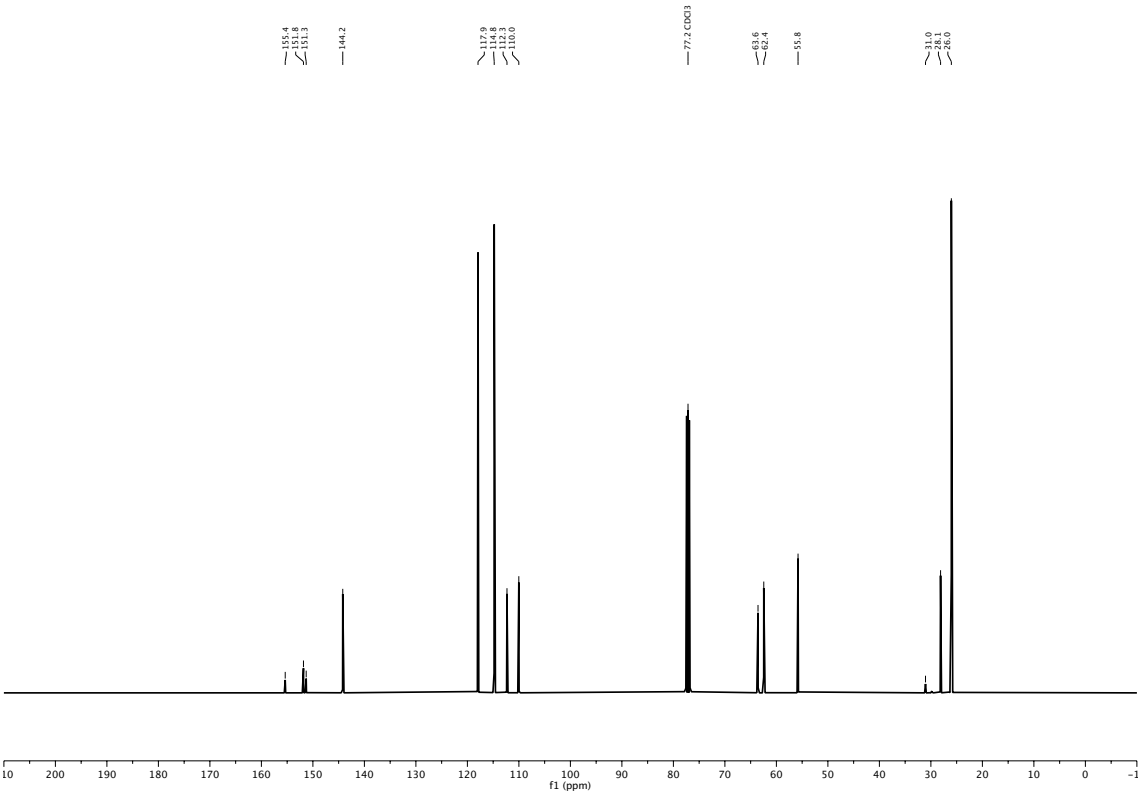


**(*E*)-2-((6-(4-methoxyphenoxy)-2-methyl-3-methylenehex-5-en-2-yl)oxy)ethan-1-ol (3ae)**

**$^{1}$H-NMR** (300 MHz, $CDCl_3$)

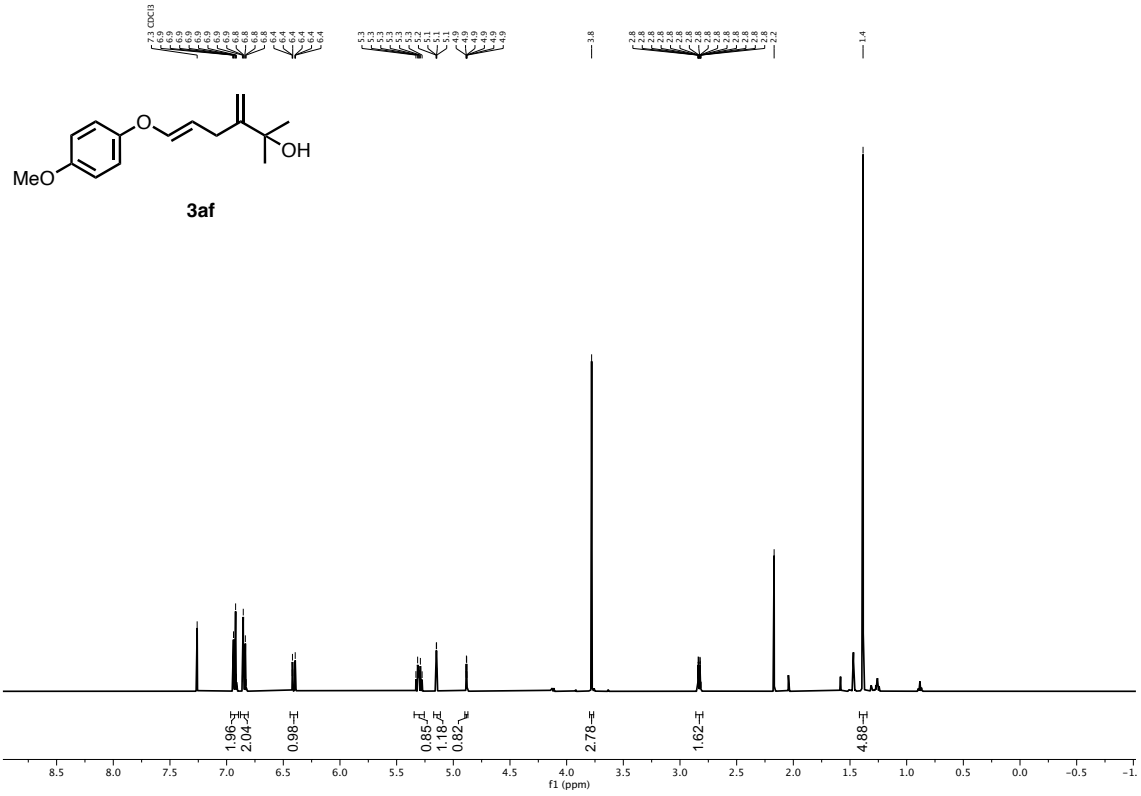



**$^{13}$C-NMR** (75 MHz, $CDCl_3$)

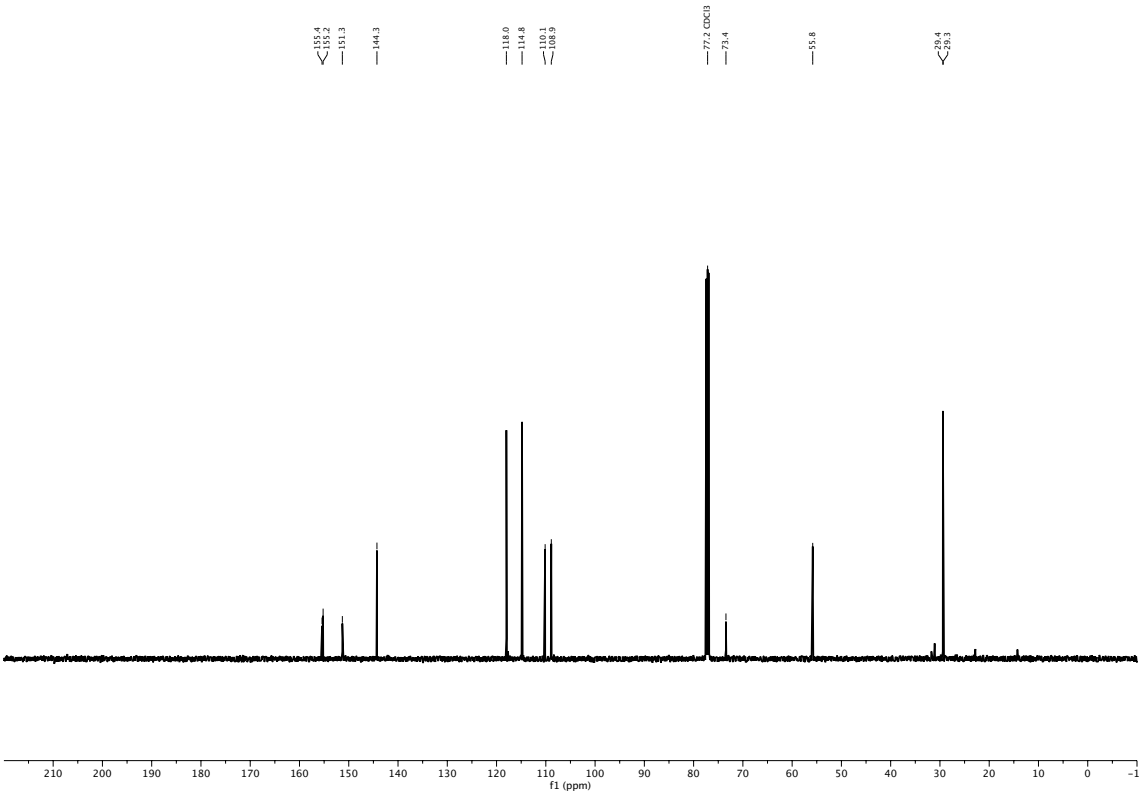


**(E)-6-(4-Methoxyphenoxy)-2-methyl-3-methylenehex-5-en-2-ol (3af).**

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

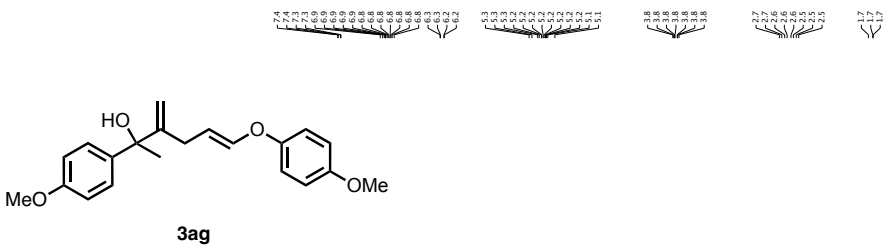



**$^{13}$C-NMR** (126 MHz, $CDCl_3$)

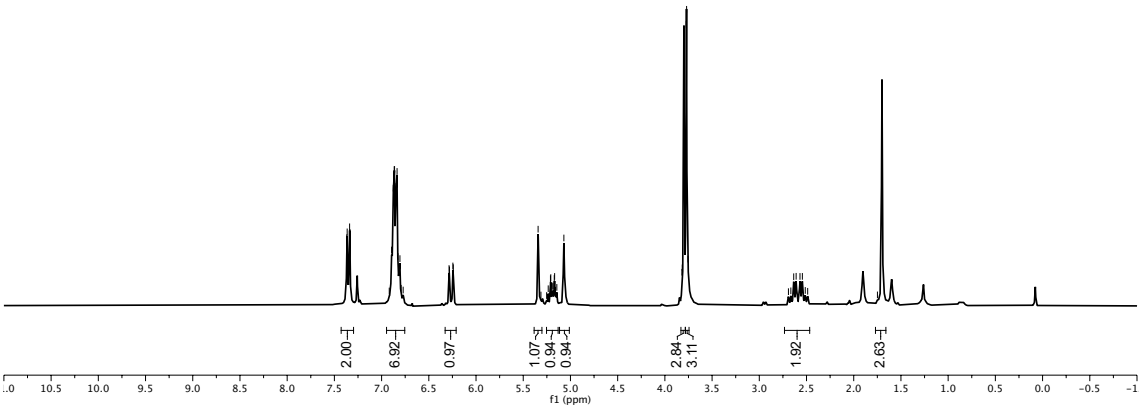


## (*E*)-6-(4-Methoxyphenoxy)-2-(4-methoxyphenyl)-3-methylenehex-5-en-2-ol (3ag)

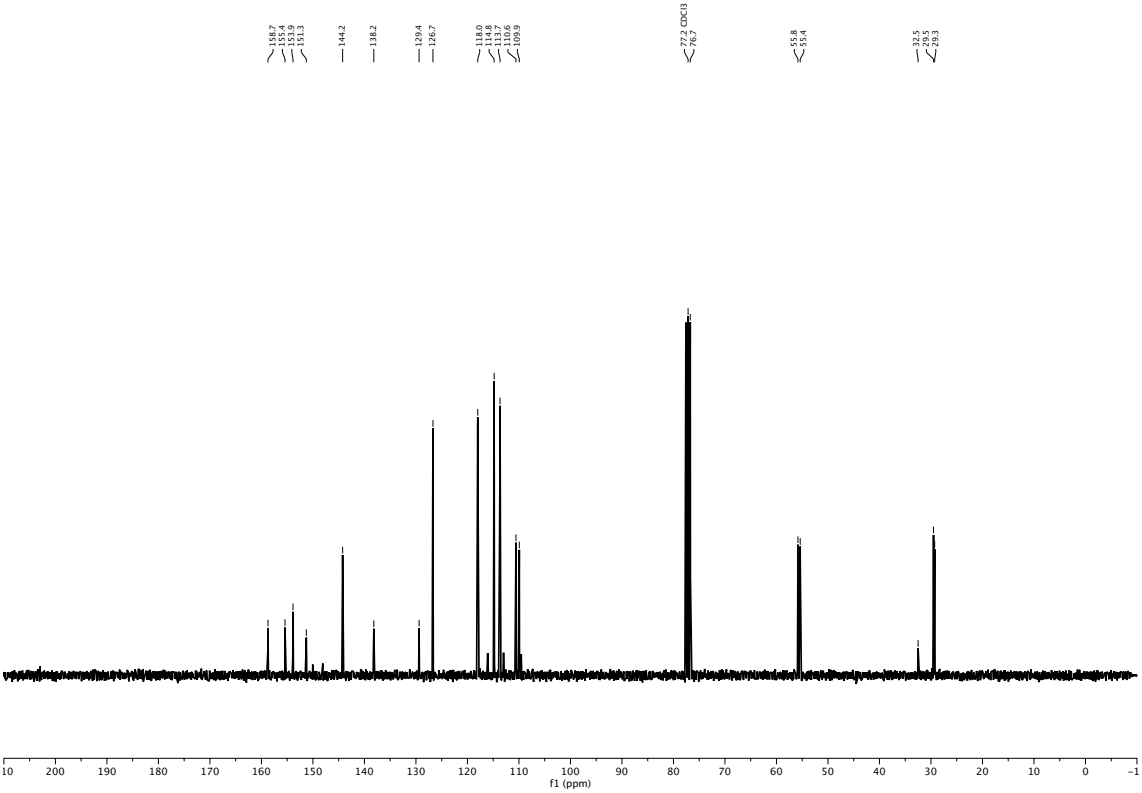
**$^{1}$H-NMR** (300 MHz, $CDCl_3$)




**3ag**

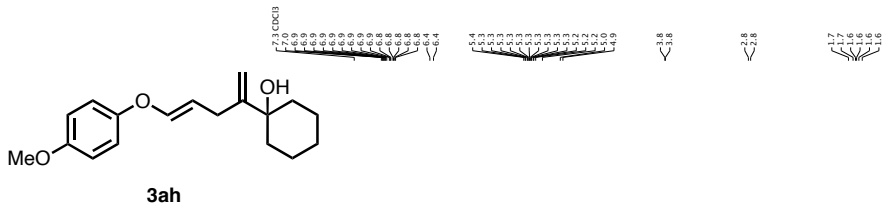



**$^{13}$C-NMR** (75 MHz, $CDCl_3$)

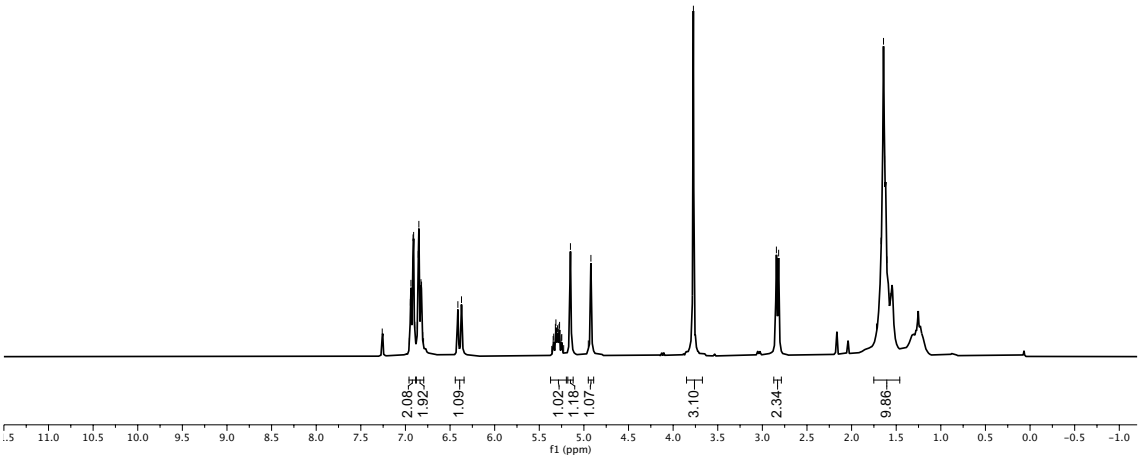


***tert*-Butyl (*E*)-*N*-(6-(4-methoxyp (*E*)-1-(5-(4-methoxyphenoxy)penta-1,4-dien-2-yl)cyclohexan-1-ol (3ah)**

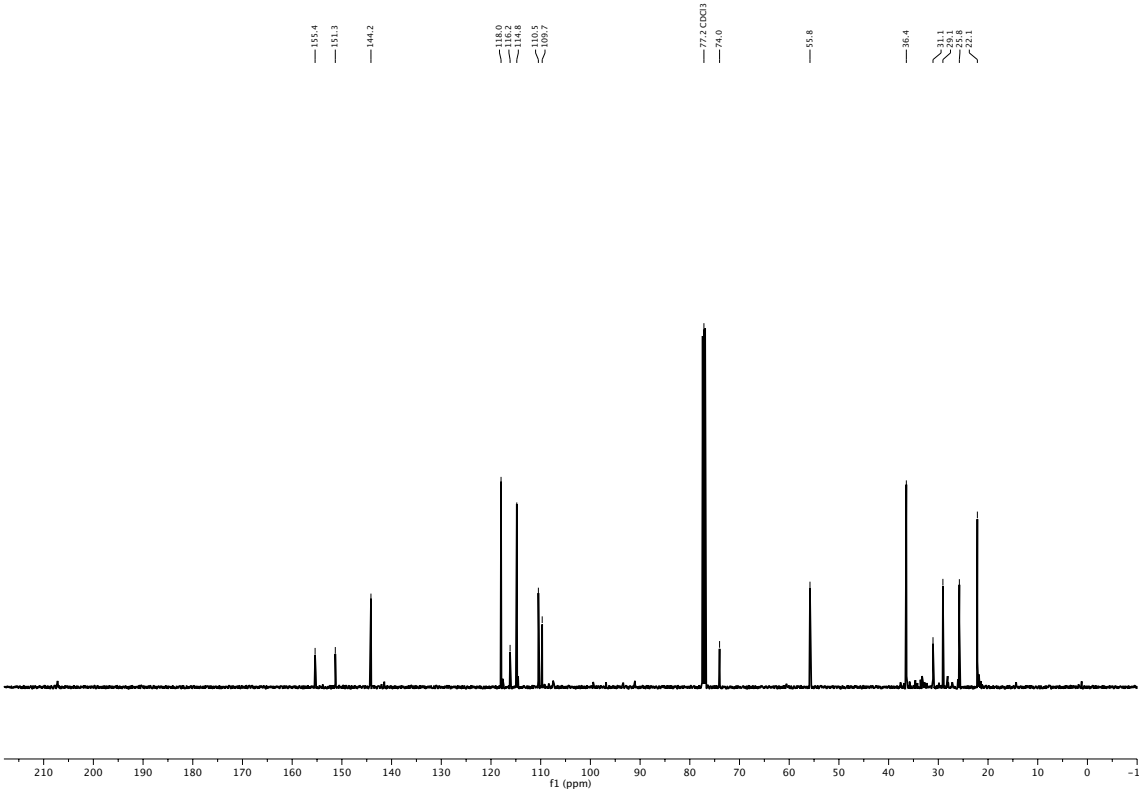
**$^{1}$H-NMR** (500 MHz, $CDCl_3$)




**3ah**

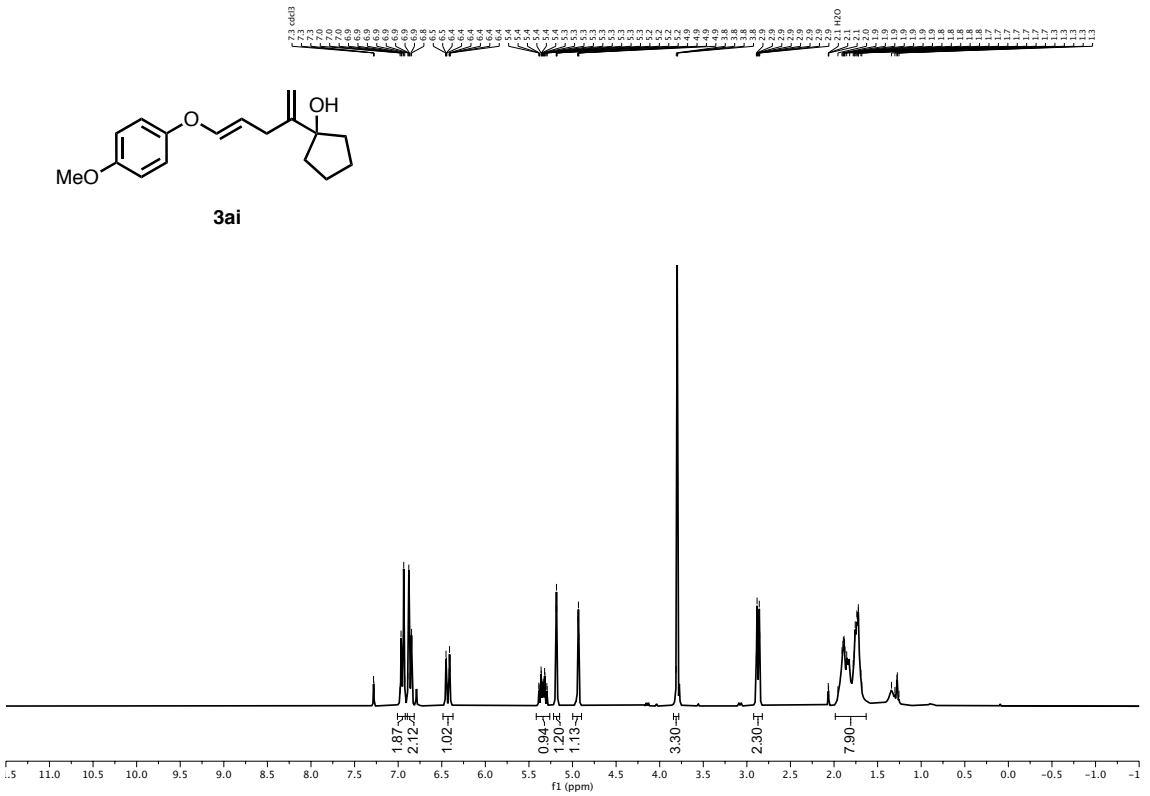



**$^{13}$C-NMR** (126 MHz, $CDCl_3$)

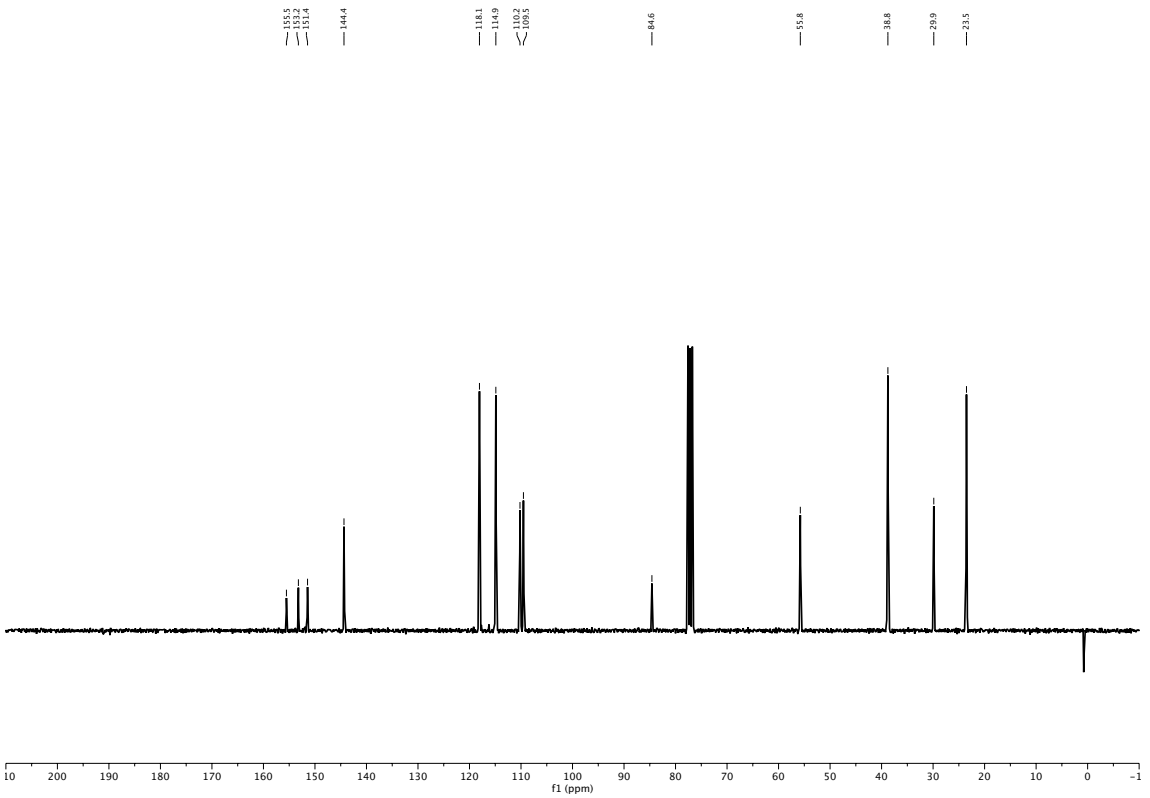


## (*E*)-1-(5-(4-Methoxyphenoxy)penta-1,4-dien-2-yl)cyclopentan-1-ol (3ai)

**$^{1}$H-NMR** (300 MHz, $CDCl_3$)

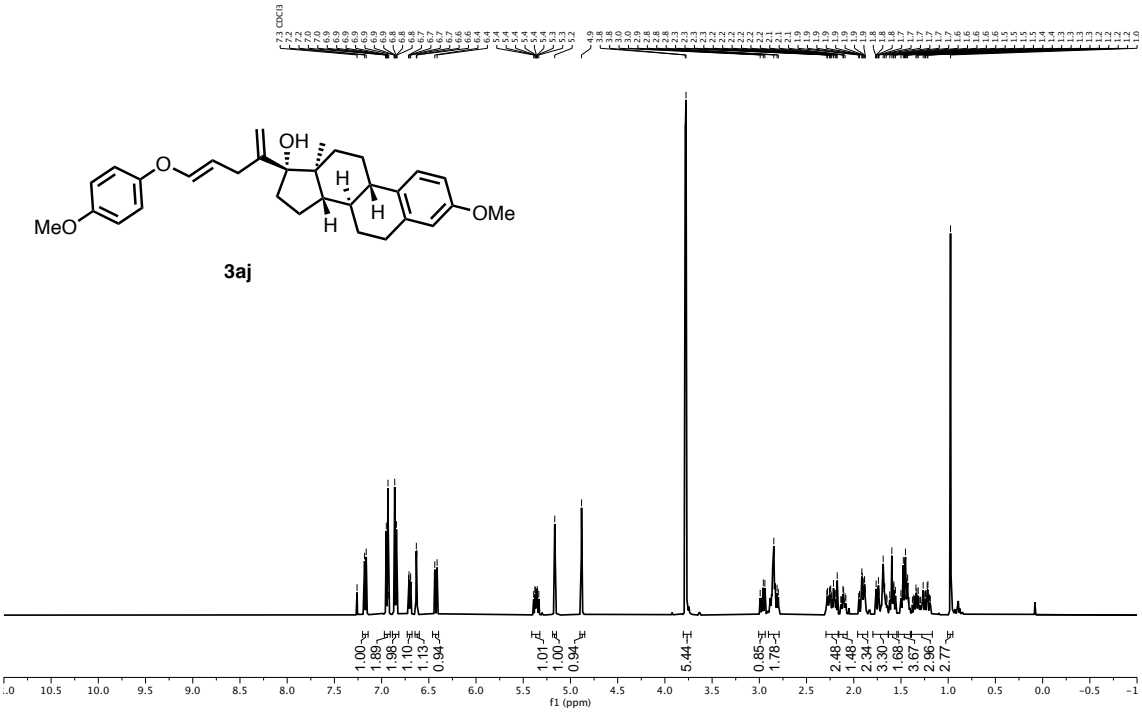



**$^{13}$C-NMR** (75 MHz, $CDCl_3$)

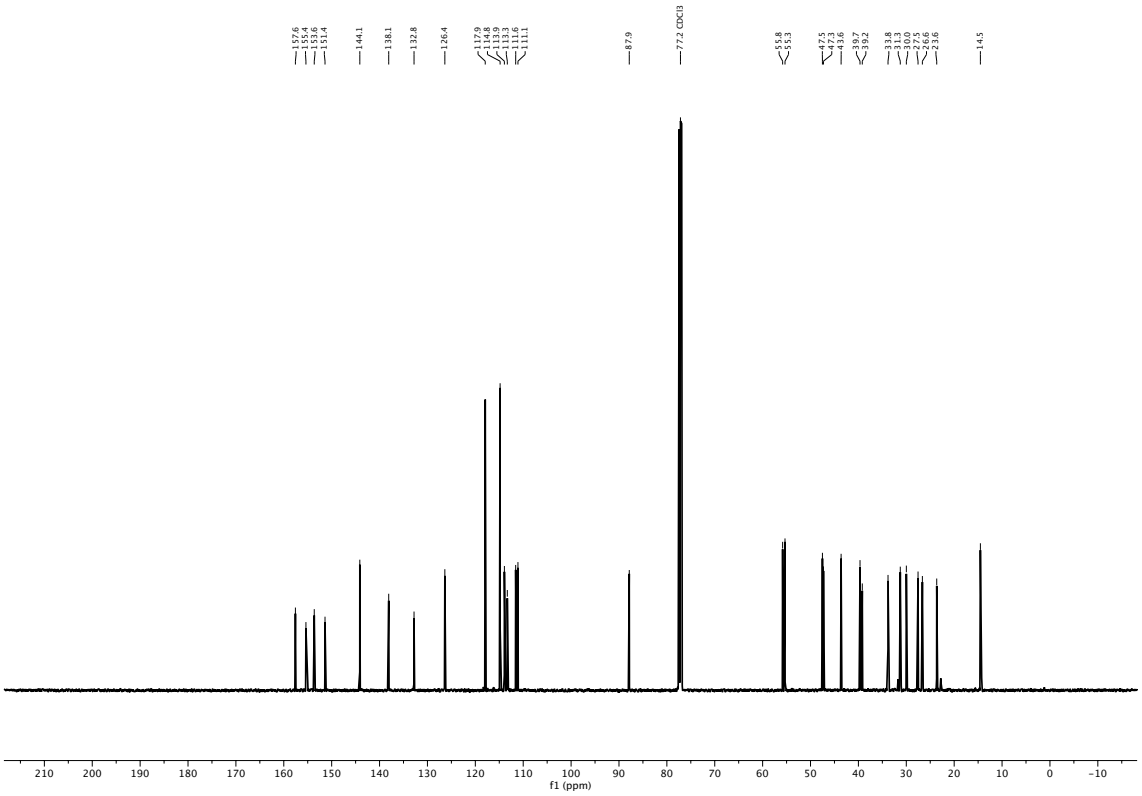


**(8*R*,9*S*,13*S*,14*S*,17*R*)-3-Methoxy-17-((*E*)-5-(4-methoxyphenoxy)penta-1,4-dien-2-yl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol (3aj).**

**$^{1}$H NMR** (500 MHz, $CDCl_3$)

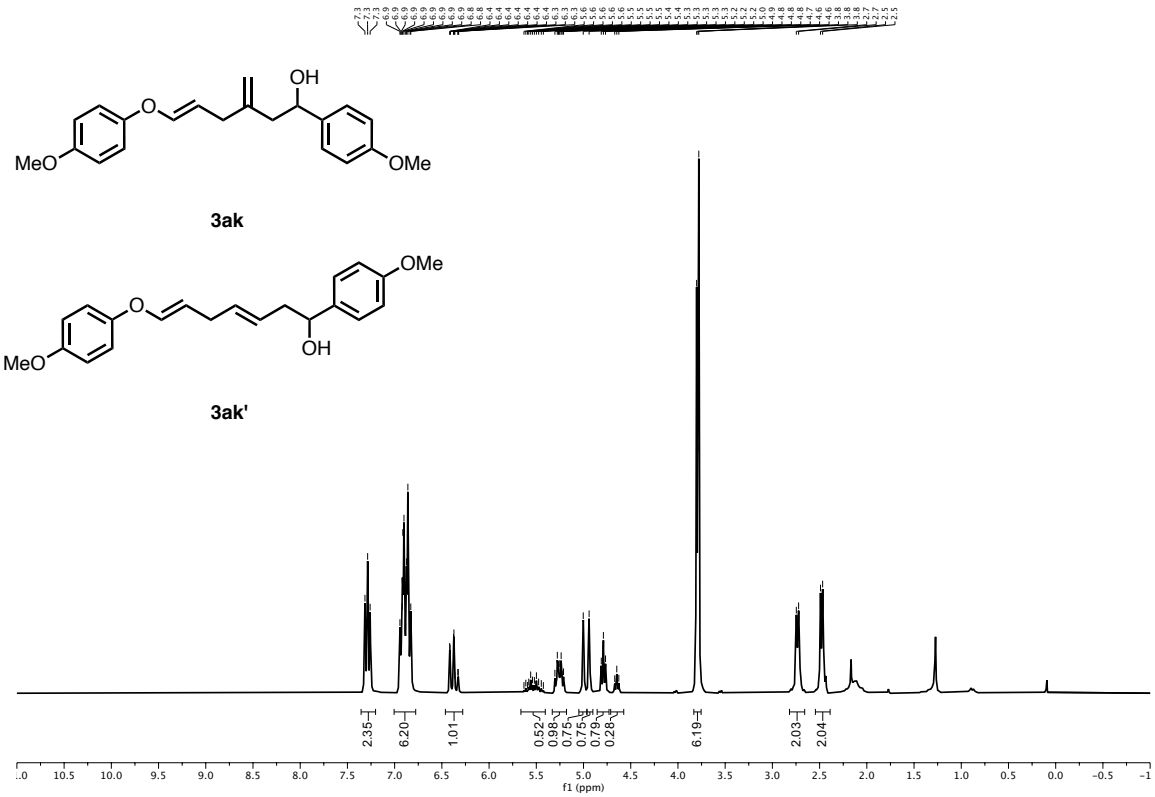



**$^{13}$C NMR** (126 MHz, $CDCl_3$)

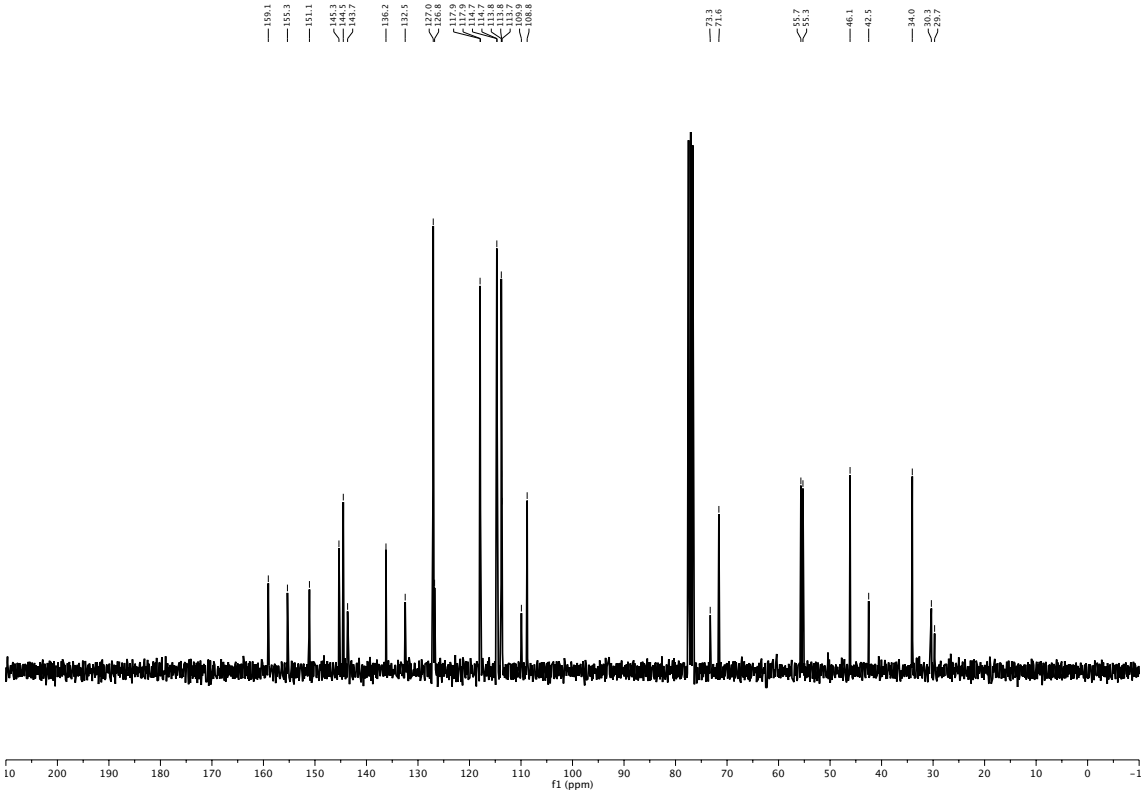


**(*E*)-7-(4-Methoxyphenoxy)-1-(4-methoxyphenyl)-3-methylenehept-5-en-1-ol (3ak) & (3*E*,6*E*)-7-(4-methoxyphenoxy)-1-(4-methoxyphenyl)hepta-3,6-dien-1-ol (3ak')**

**$^{1}$H NMR** (300 MHz, $CDCl_3$)

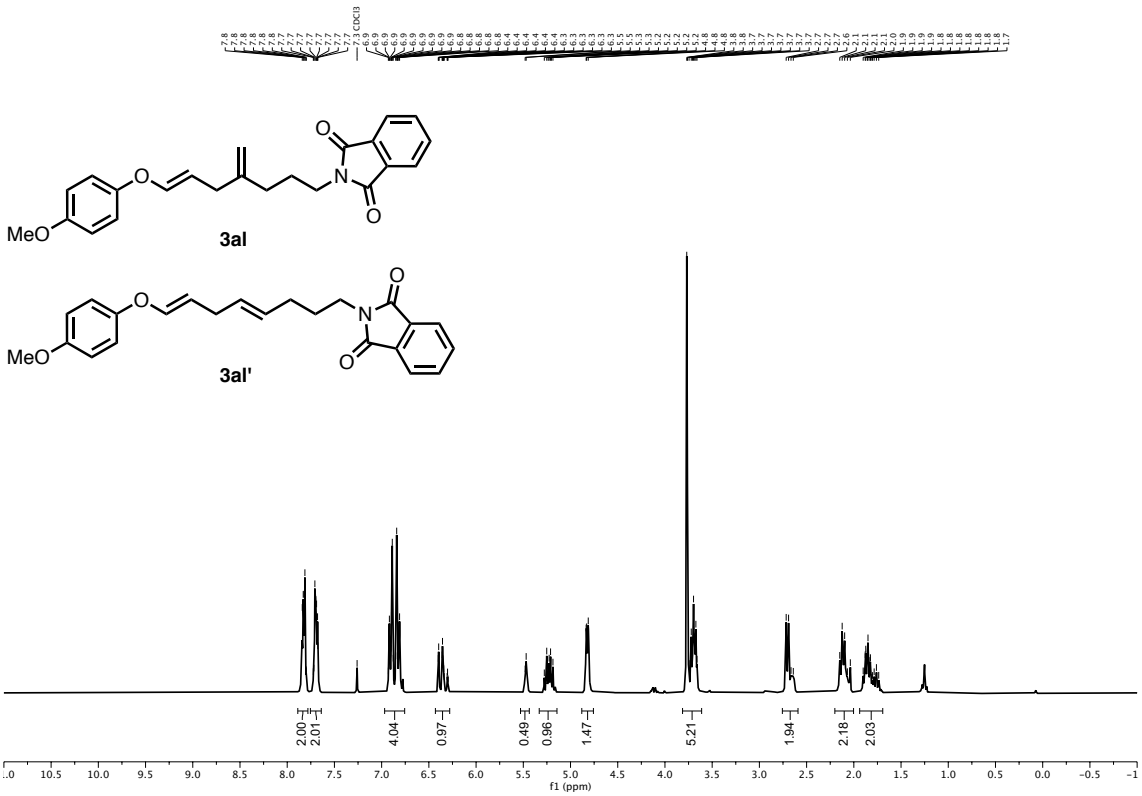



**$^{13}$C NMR** (75 MHz, $CDCl_3$)

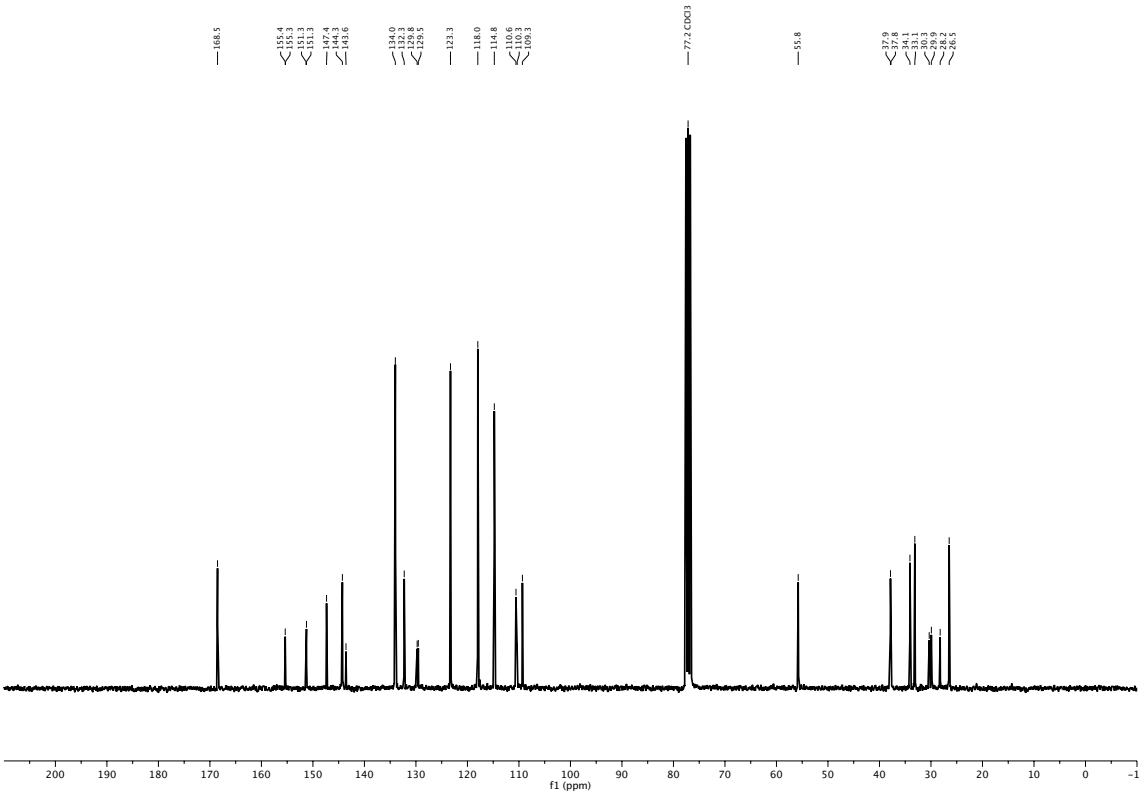


**(E)-2-(8-(4-Methoxyphenoxy)-4-methyleneoct-6-en-1-yl)isoindoline-1,3-dione (3al) and 2-((4*E*,7*E*)-8-(4-methoxyphenoxy)octa-4,7-dien-1-yl)isoindoline-1,3-dione (3al')**

**$^{1}$H NMR** (300 MHz, $CDCl_3$)

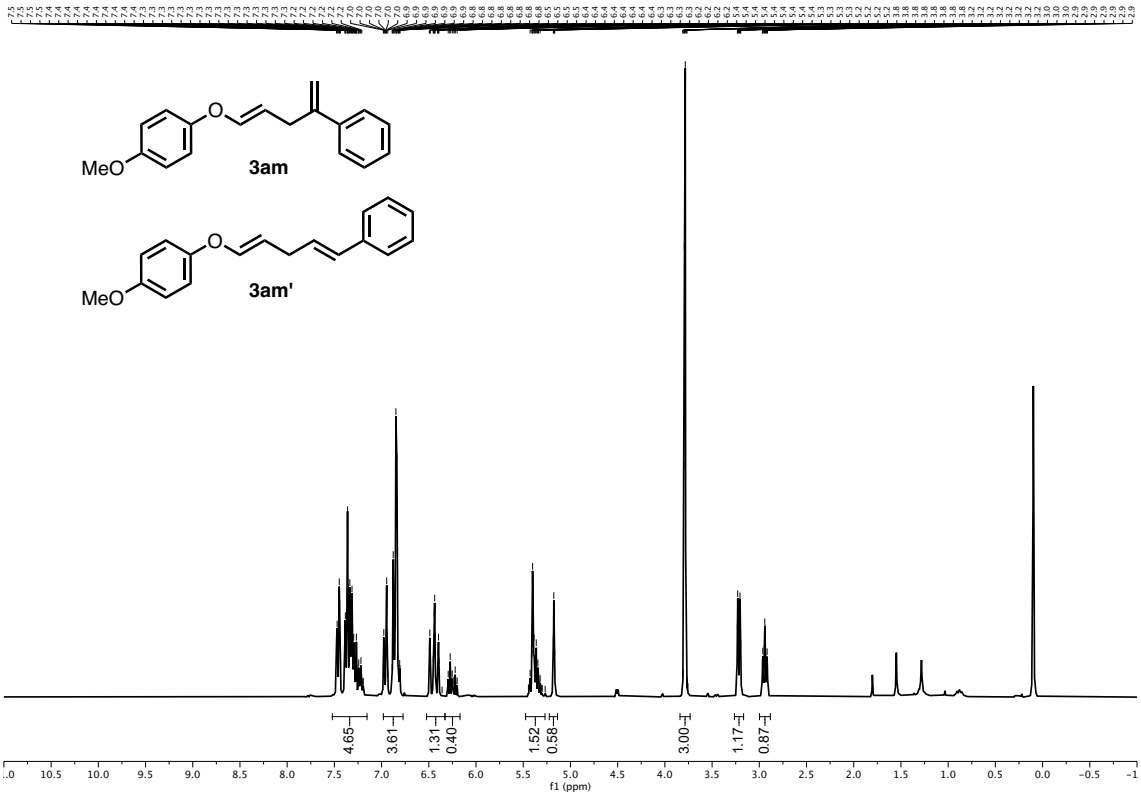



**$^{13}$C NMR** (75 MHz, $CDCl_3$)

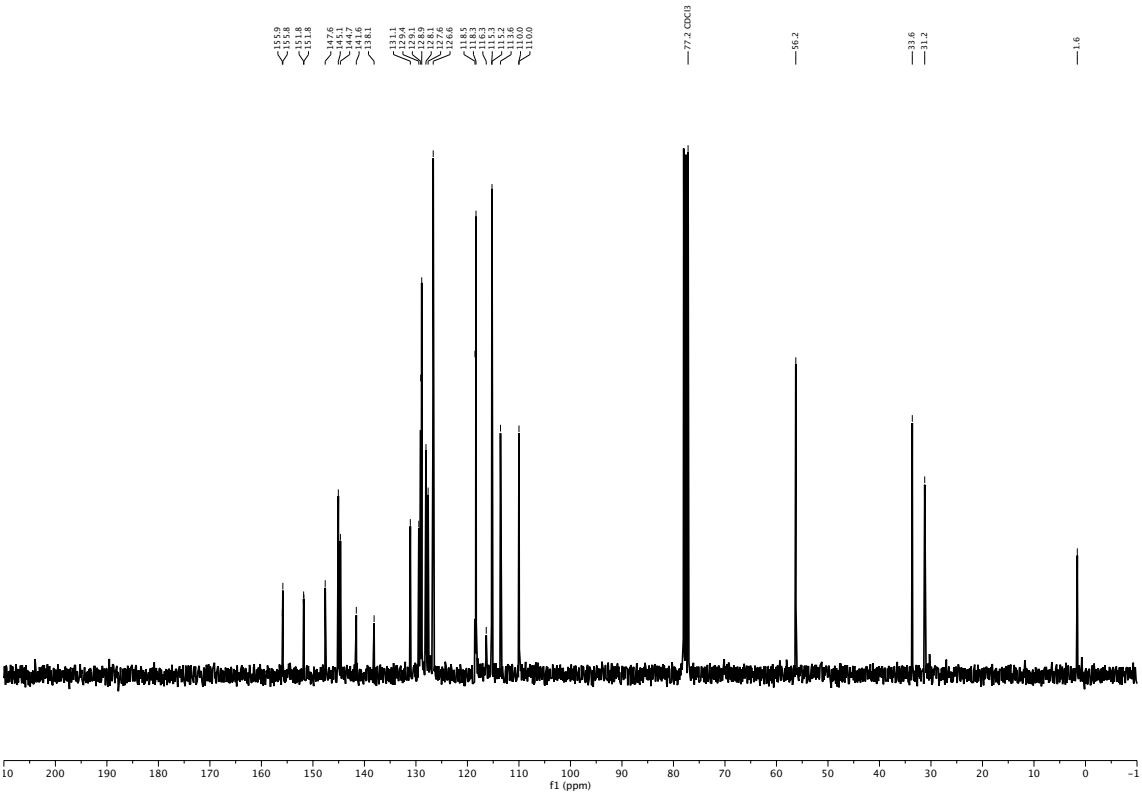


**(*E*)-1-Methoxy-4-((4-phenylpenta-1,4-dien-1-yl)oxy)benzene (3am) and 1-Methoxy-4-(((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)oxy)benzene (3am')**

**$^{1}$H NMR** (300 MHz, $CDCl_3$)

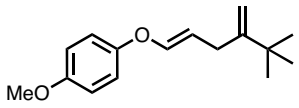



**$^{13}$C NMR** (75 MHz, $CDCl_3$)

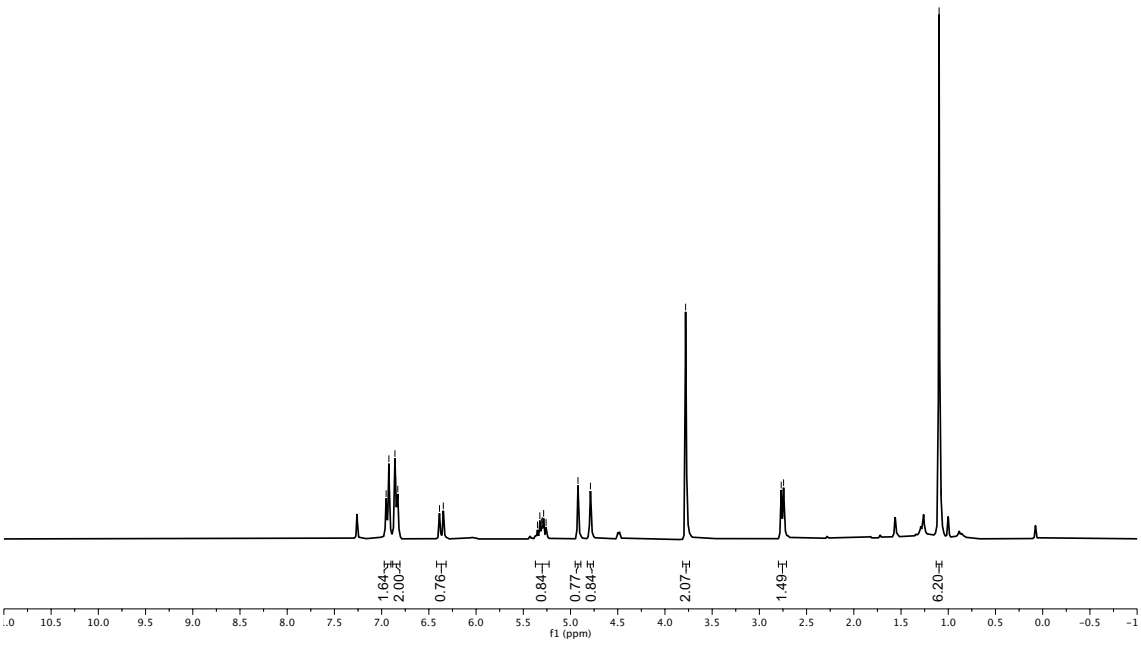


## (*E*)-1-((5,5-Dimethyl-4-methylenehex-1-en-1-yl)oxy)-4-methoxybenzene (3an)

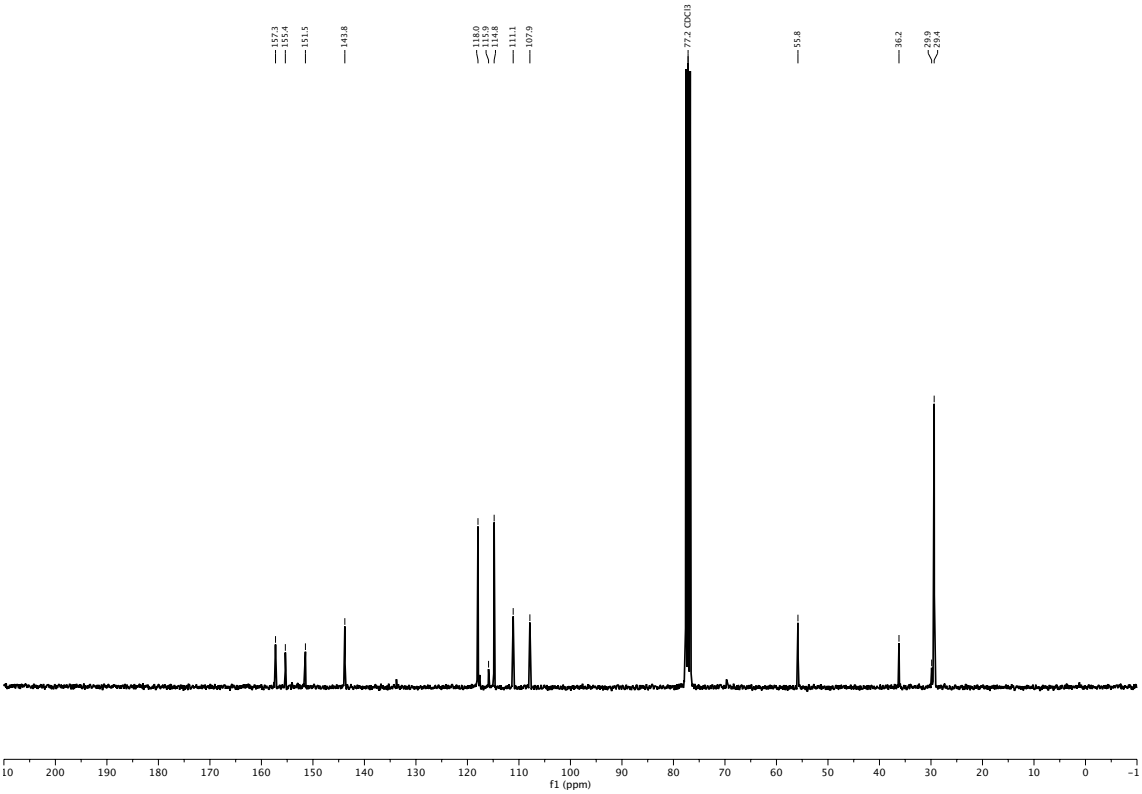
**$^1$H NMR** (300 MHz, $CDCl_3$)




**3an**

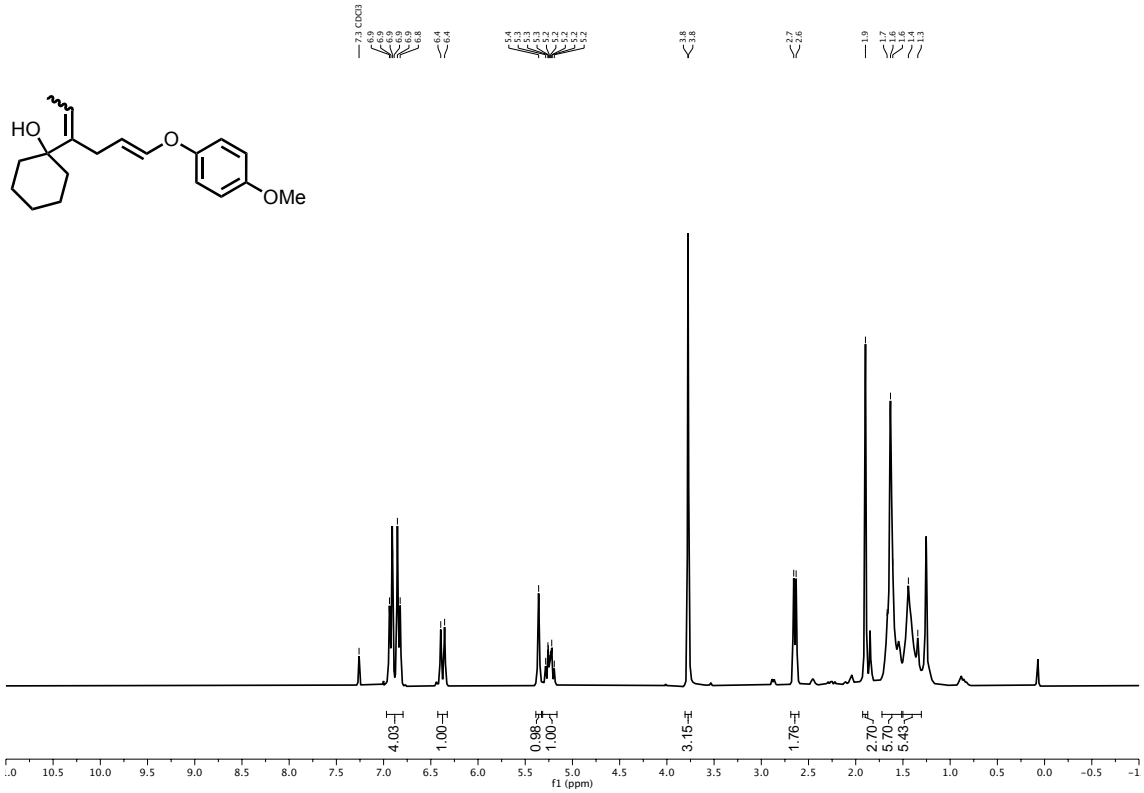



**$^{13}$C NMR** (75 MHz, $CDCl_3$)

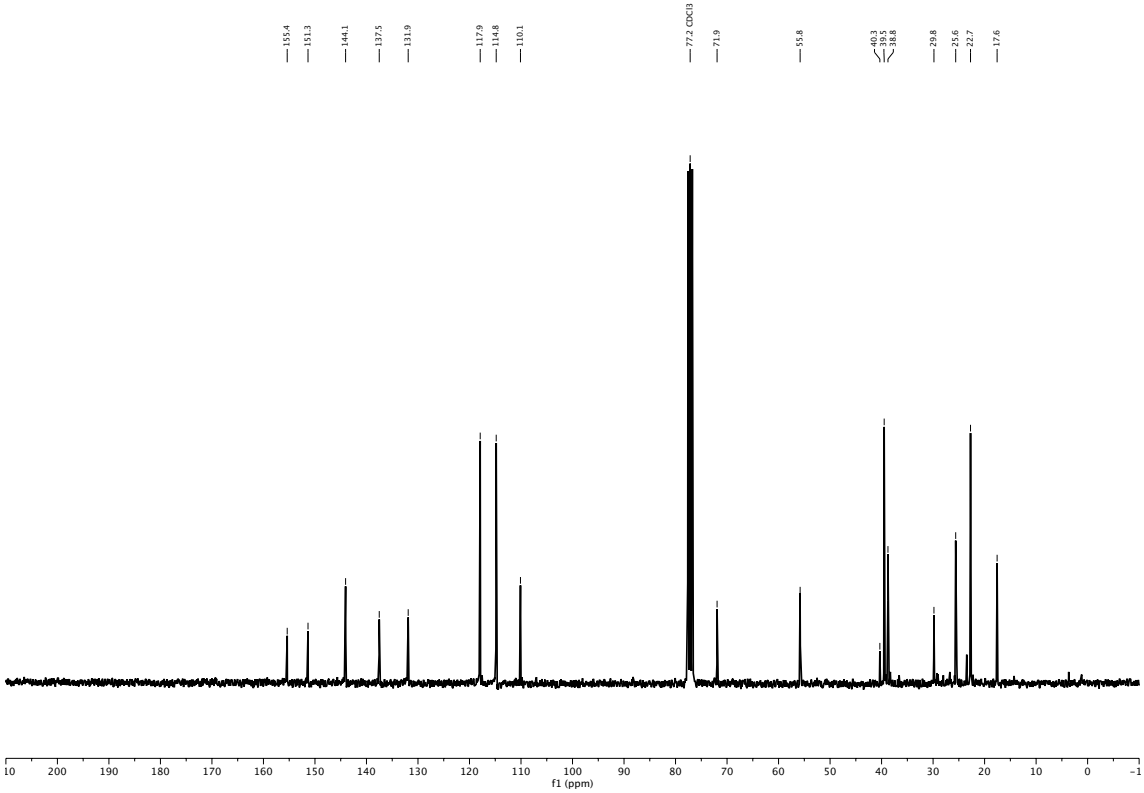


## 1-((5*E*)-6-(4-methoxyphenoxy)hexa-2,5-dien-3-yl)cyclohexan-1-ol (3ao)

**$^{1}$H NMR** (300 MHz, $CDCl_3$)

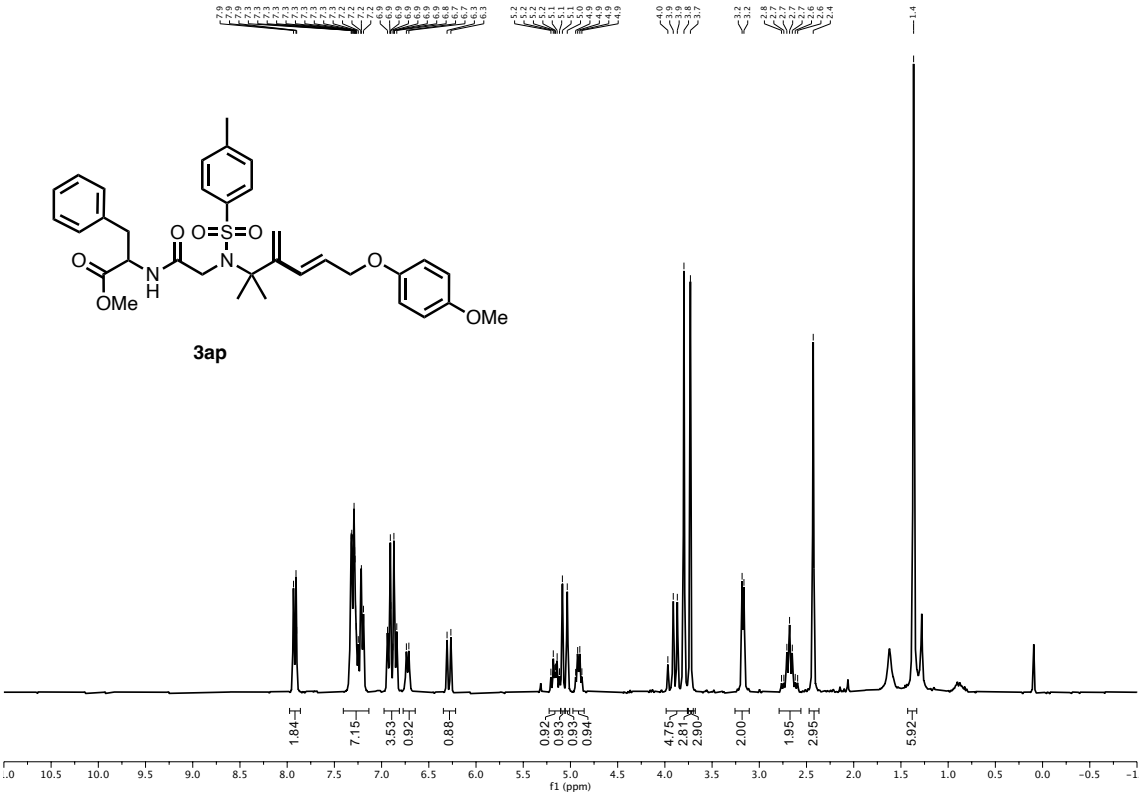



**$^{13}$C NMR** (75 MHz, $CDCl_3$)

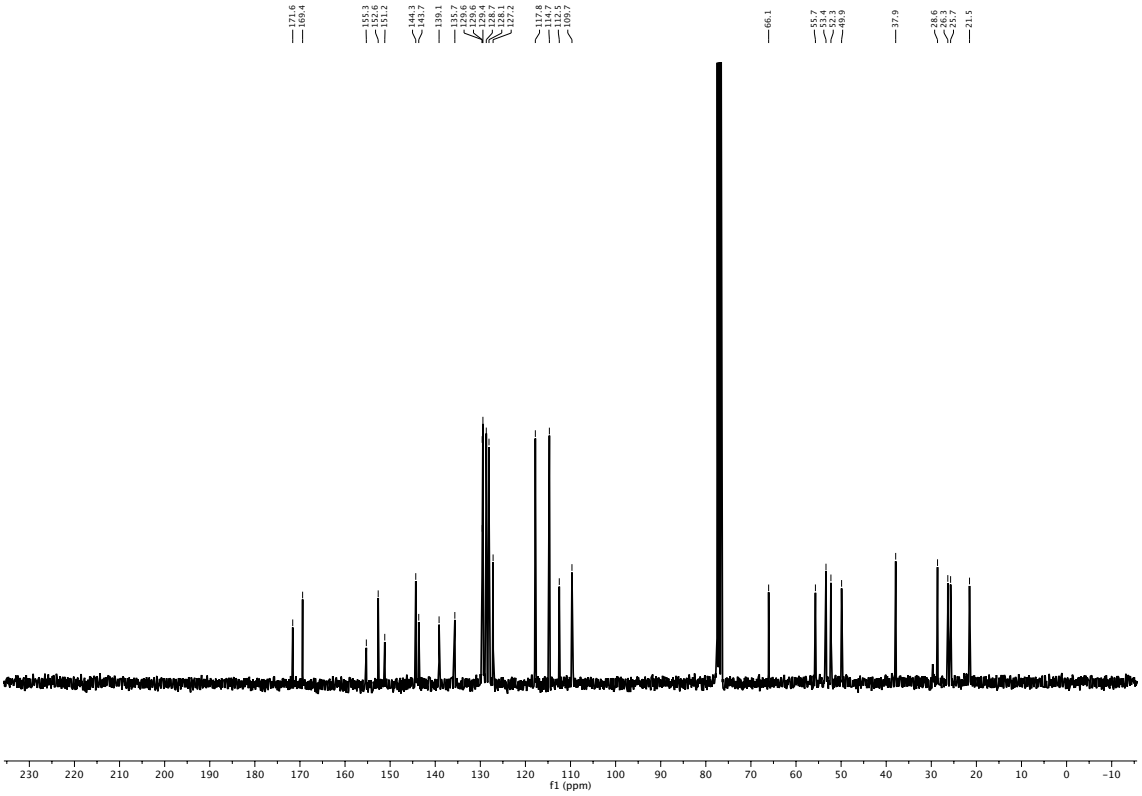


**Methyl (*E*)-*N*-(6-(4-methoxyphenoxy)-2-methyl-3-methylenehex-4-en-2-yl)-*N*-tosylglycylphenylalaninate (3ap)**

**$^1$H NMR** (300 MHz, $CDCl_3$)

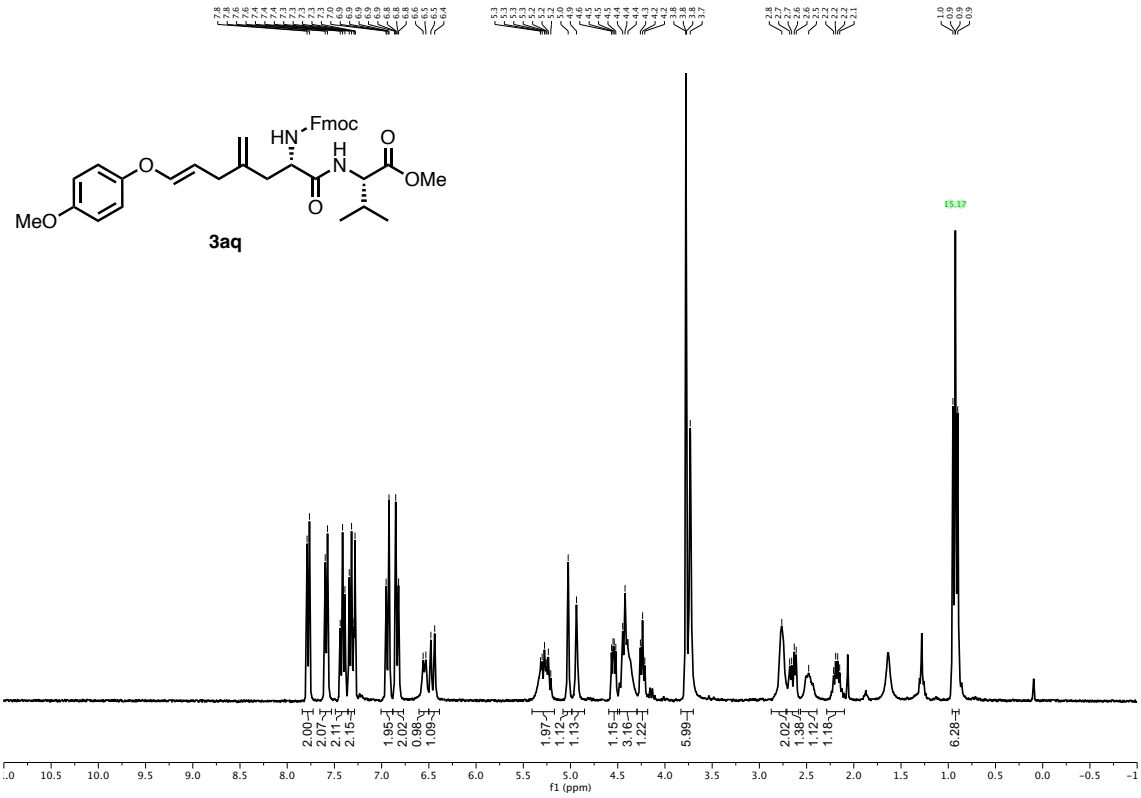



**$^{13}$C NMR** (75 MHz, $CDCl_3$)

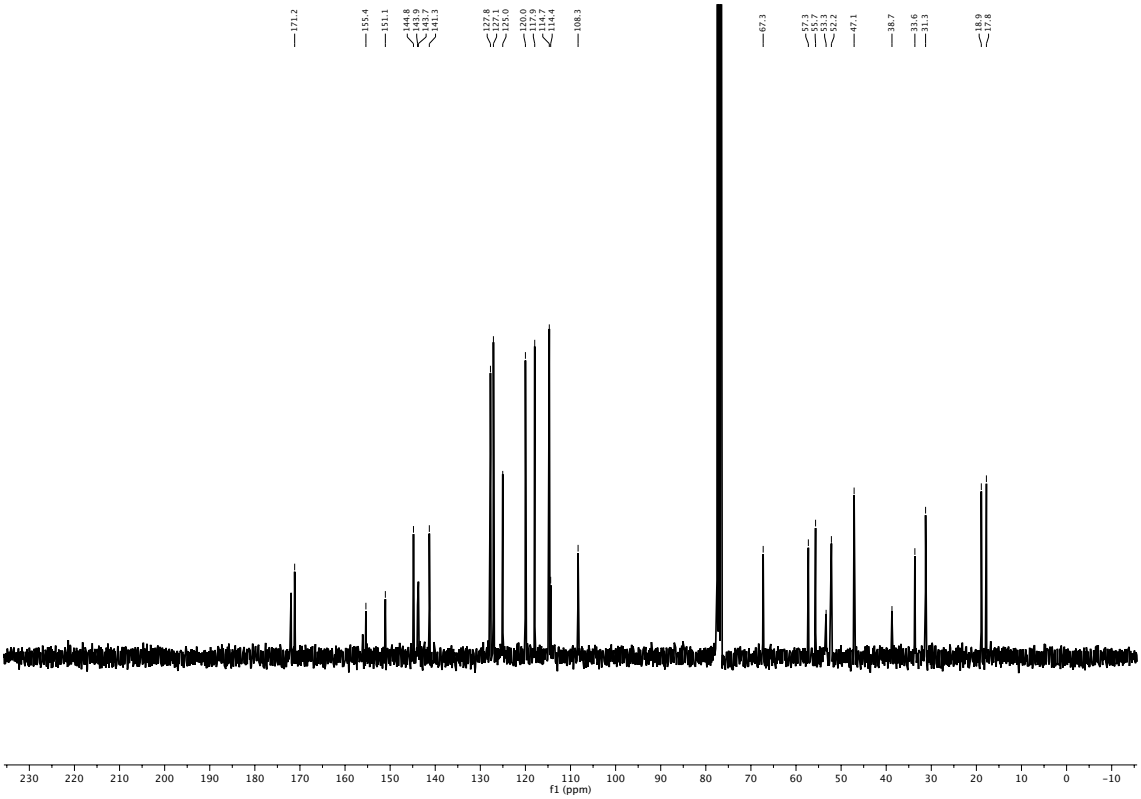


**Methyl ((*S*,*E*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-7-(4-methoxyphenoxy)-4-methylenehept-5-enoyl)-*L*-valinate (3aq).**

**$^{1}$H NMR** (300 MHz, $CDCl_3$)

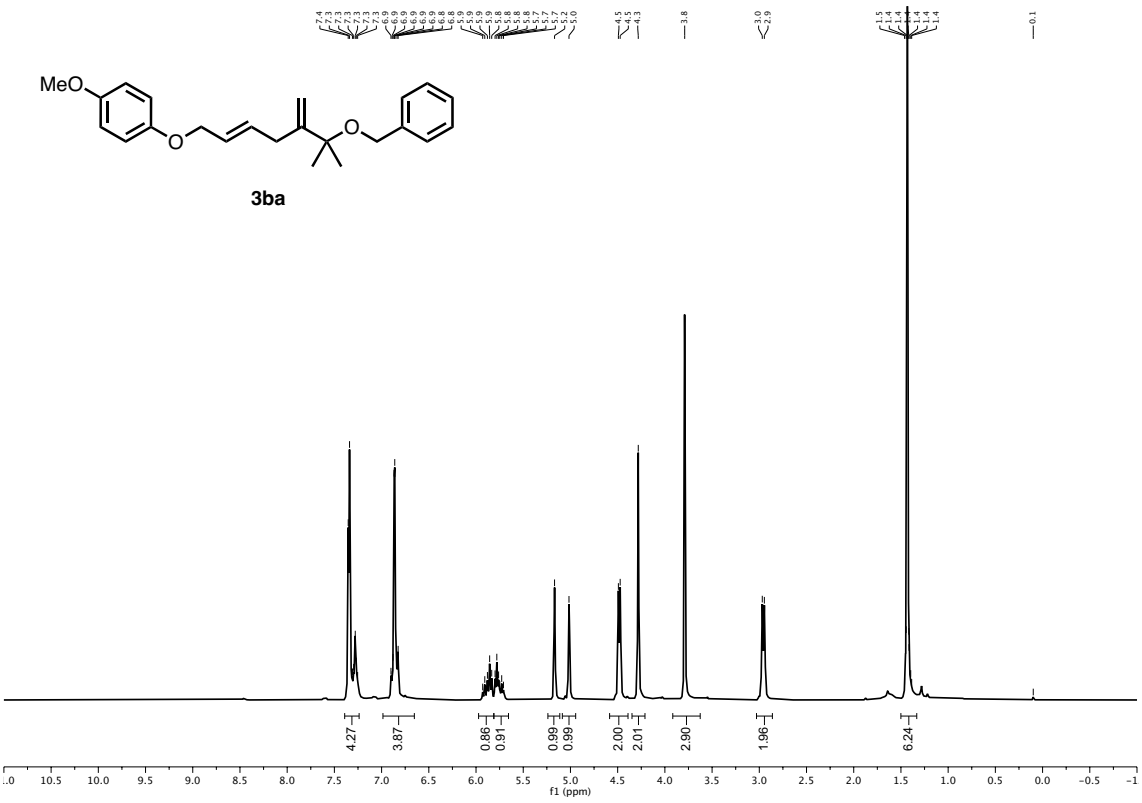



**$^{13}$C NMR** (75 MHz, $CDCl_3$)

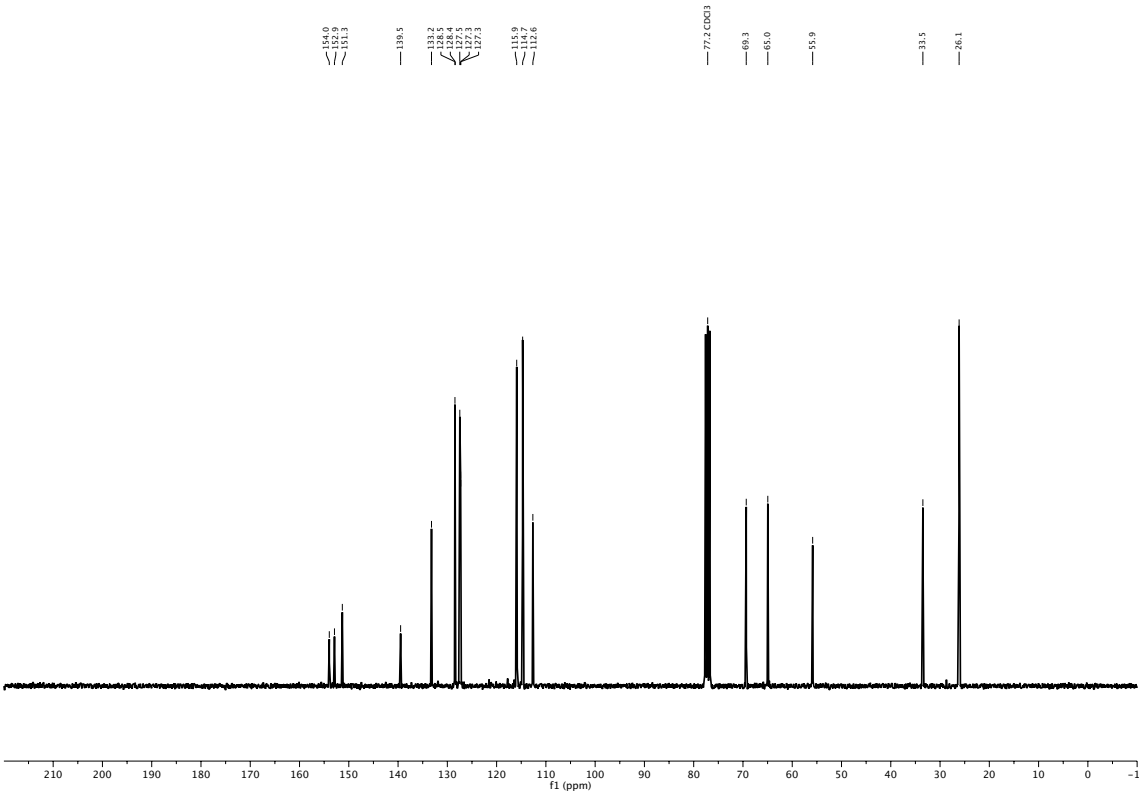


**(*E*)-1-((6-(Benzyloxy)-6-methyl-5-methylenehept-2-en-1-yl)oxy)-4-methoxybenzene (3ba)**

**$^{1}$H-NMR** (300 MHz, $CDCl_3$)

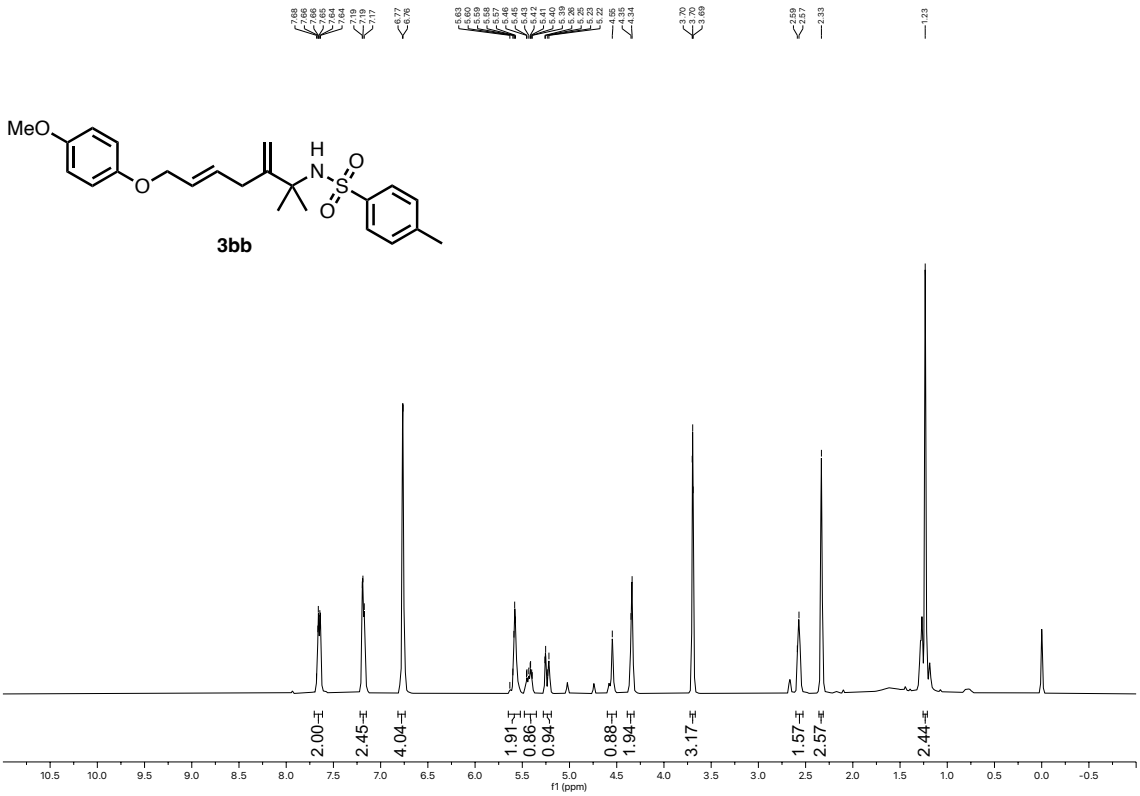



**$^{13}$C-NMR** (75 MHz, $CDCl_3$)

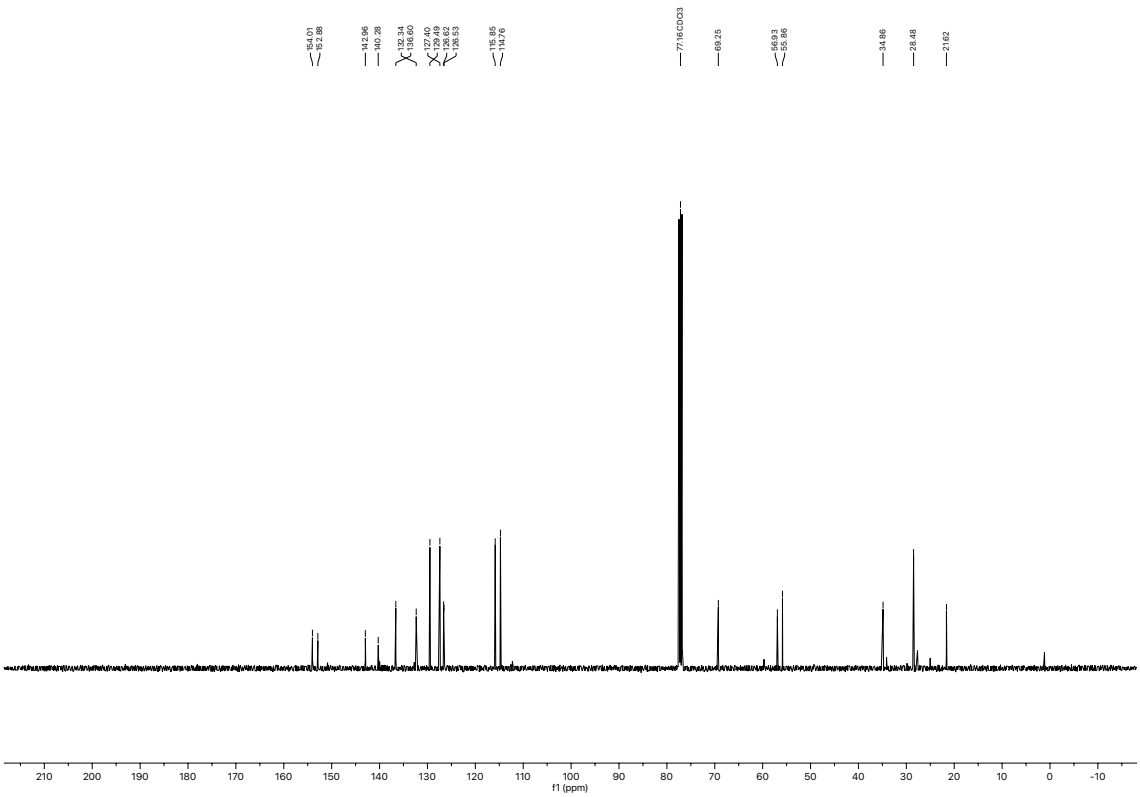


**(*E*)-*N*-(7-(4-methoxyphenoxy)-2-methyl-3-methylenehept-5-en-2-yl)-4-methylbenzenesulfonamide (3bb)**

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

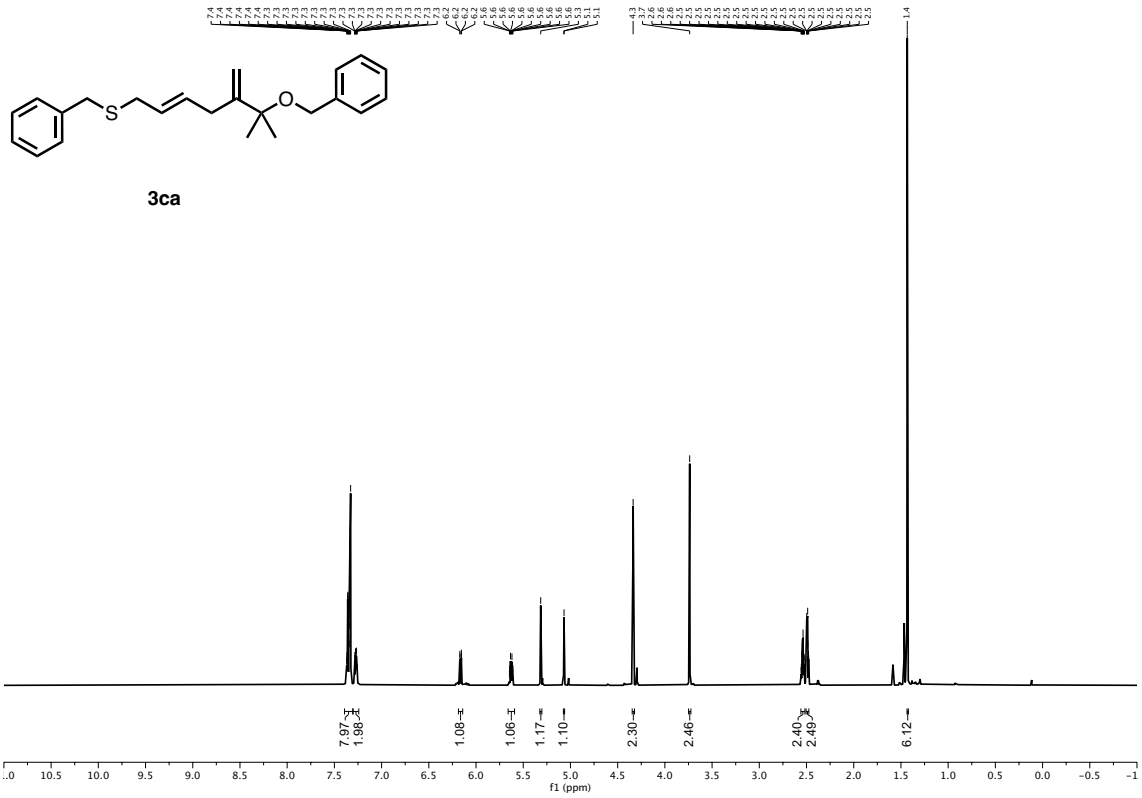



**$^{13}$C-NMR** (101 MHz, $CDCl_3$)

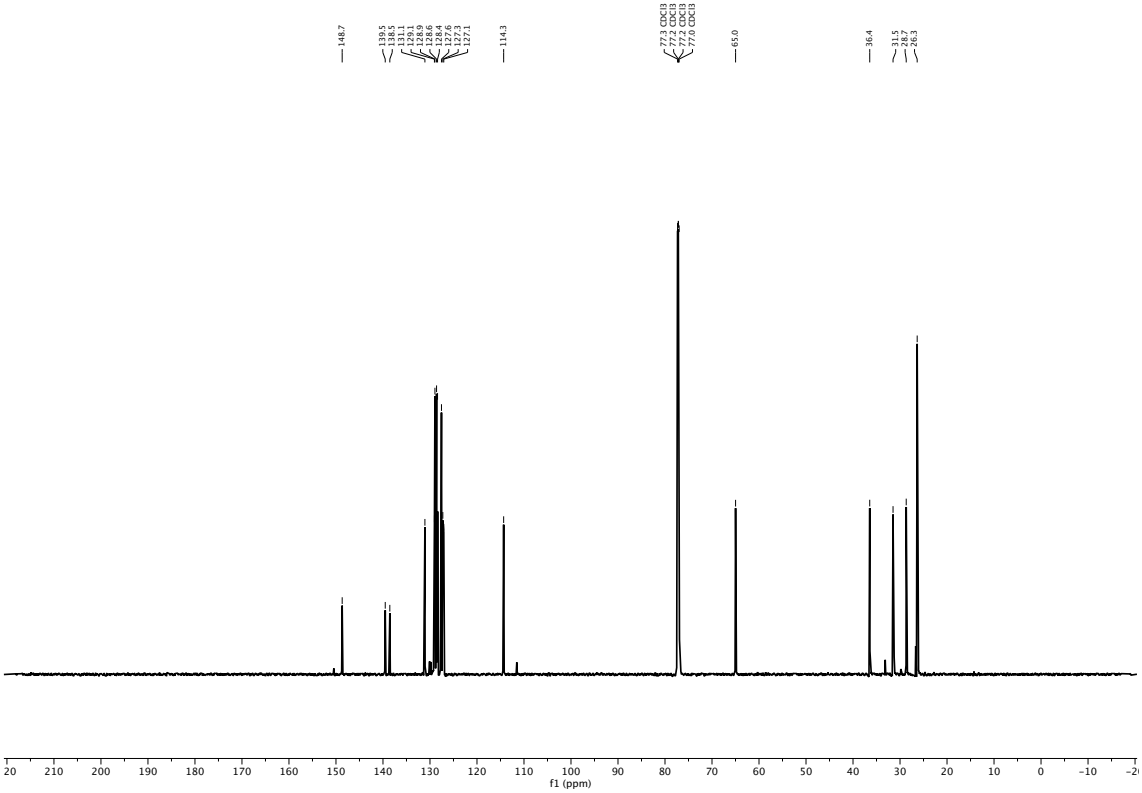


## (*E*)-Benzyl(6-(benzyloxy)-6-methyl-5-methylenehept-2-en-1-yl)sulfane (3ca)

**$^{1}$H NMR** (750 MHz, $CDCl_3$)

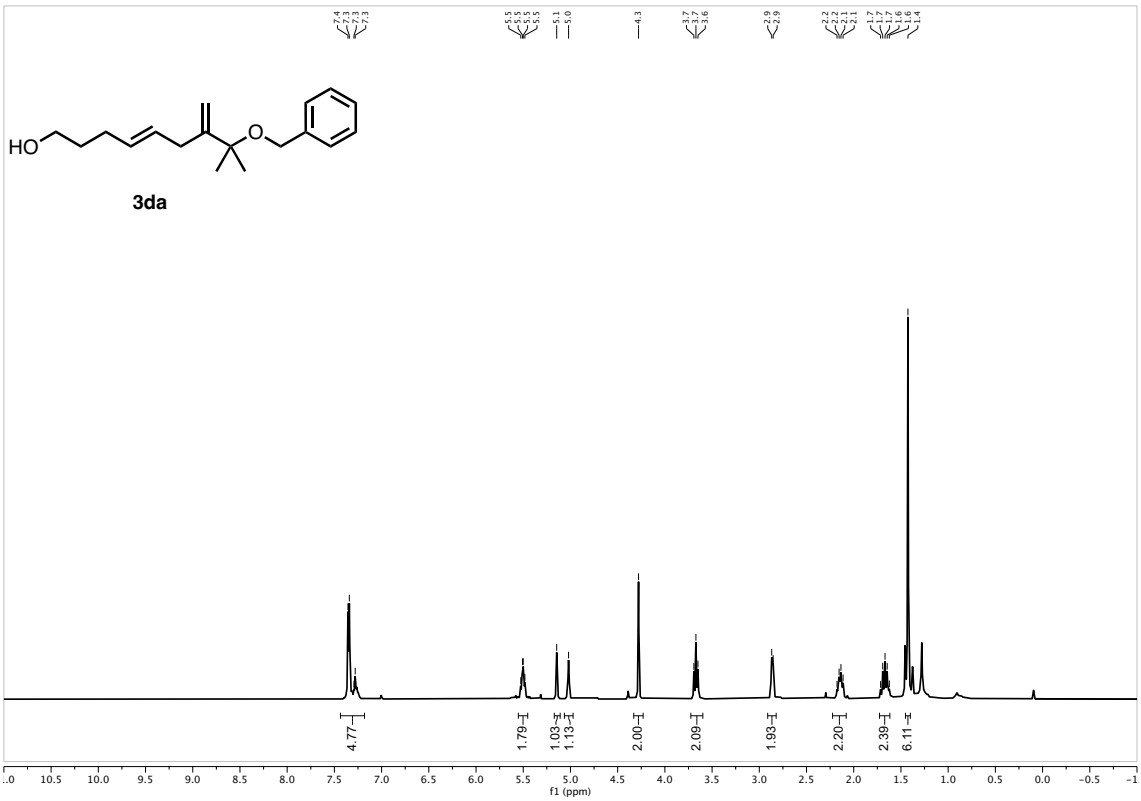



**$^{13}$C NMR** (189 MHz, $CDCl_3$)

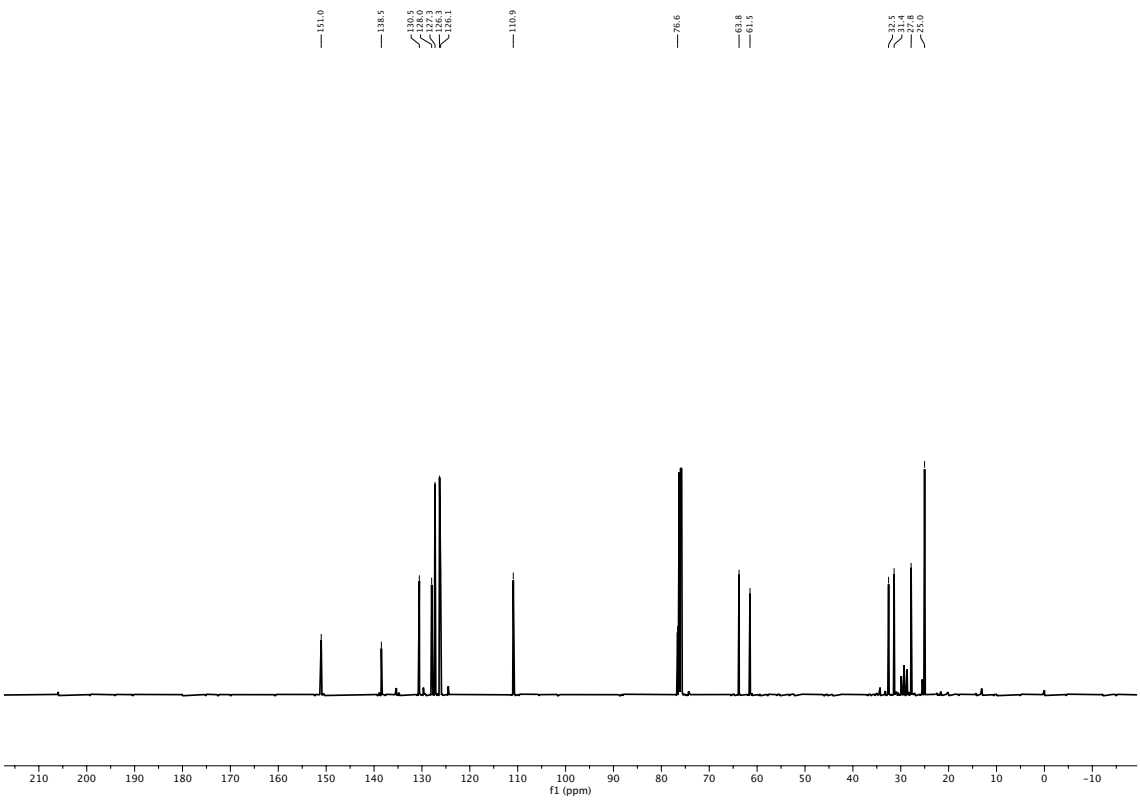


## (*E*)-8-(Benzyloxy)-8-methyl-7-methylenenon-4-en-1-ol (3da)

**$^{1}$H NMR** (300 MHz, $CDCl_3$)

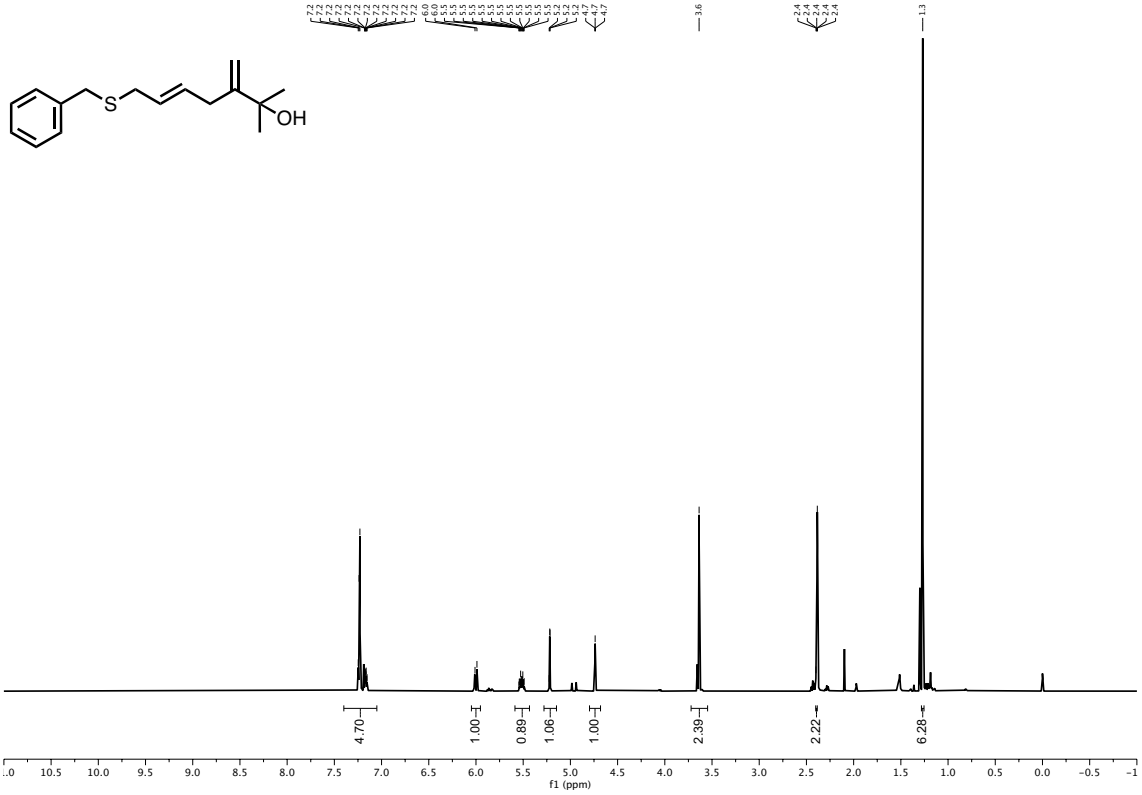



**$^{13}$C NMR** (126 MHz, $CDCl_3$)

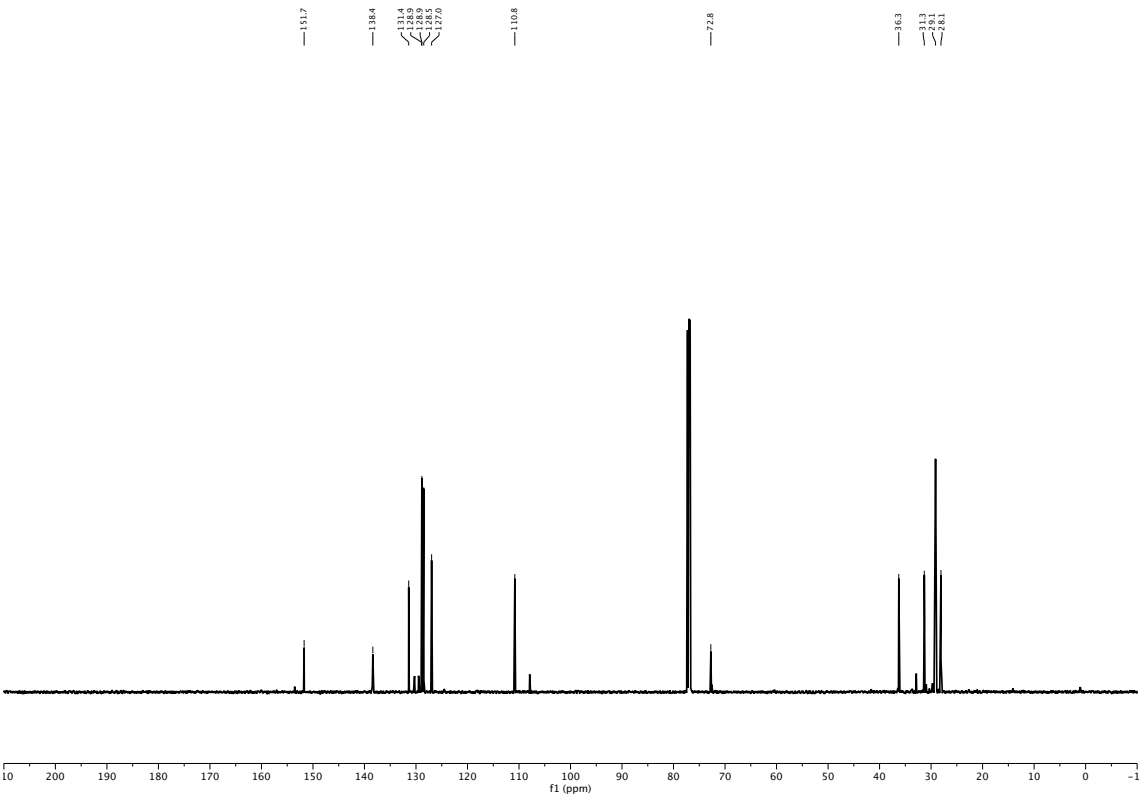


## (*E*)-7-(Benzylthio)-2-methyl-3-methylenehept-5-en-2-ol (3cf)

**$^{1}$H NMR** (500 MHz, $CDCl_3$)

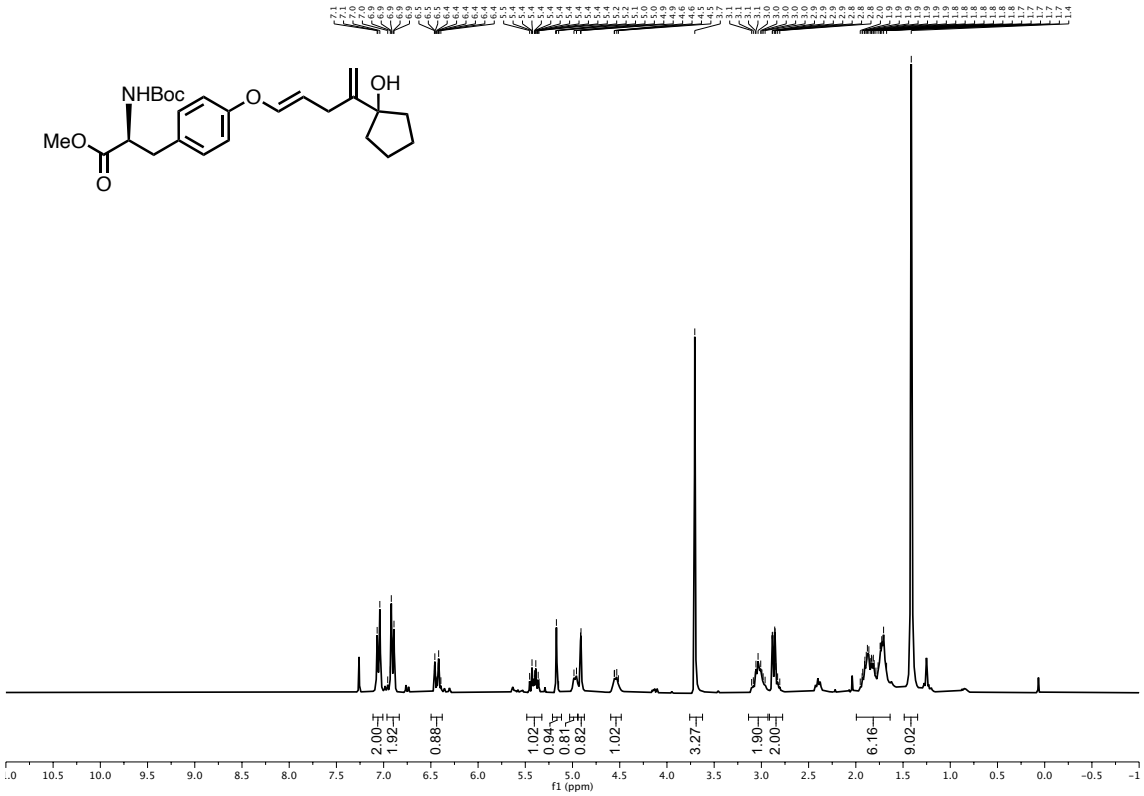



**$^{13}$C NMR** (126 MHz, $CDCl_3$)

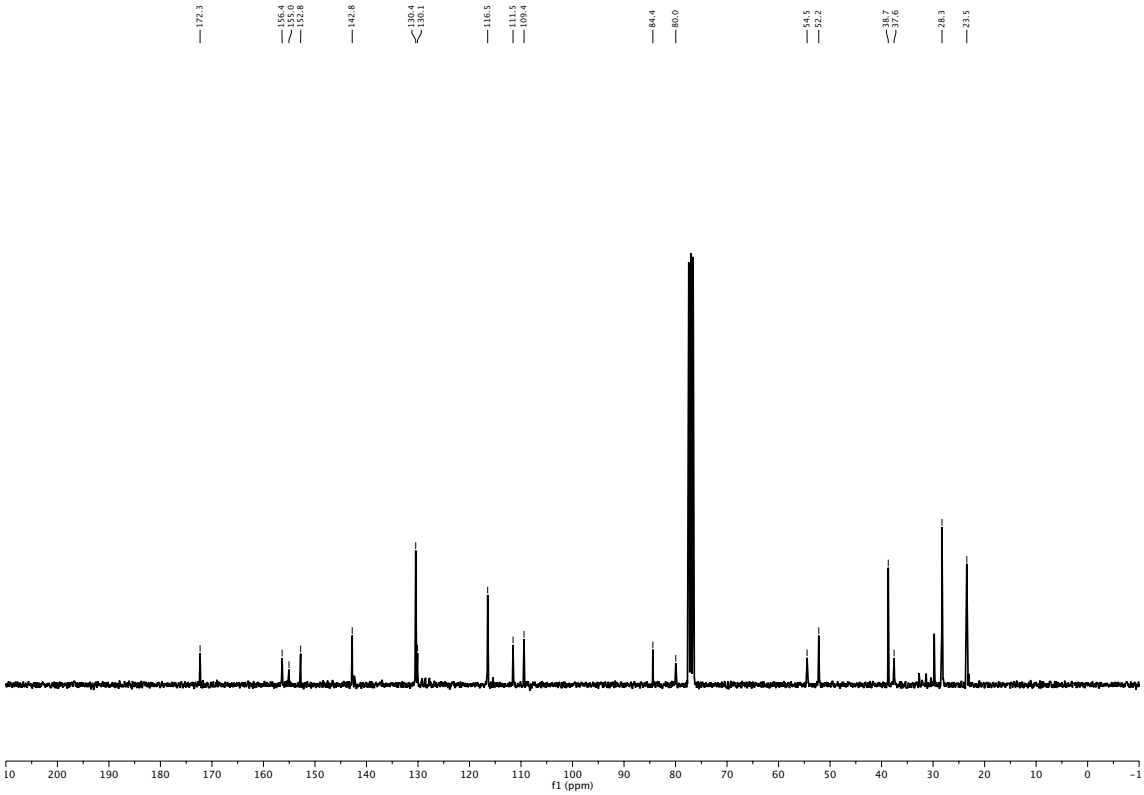


**Methyl (*S*,*E*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-((4-(1-hydroxycyclopentyl) penta-1,4-dien-1-yl)oxy)phenyl)propanoate (3fi).**

**$^{1}$H NMR** (300 MHz, $CDCl_3$)

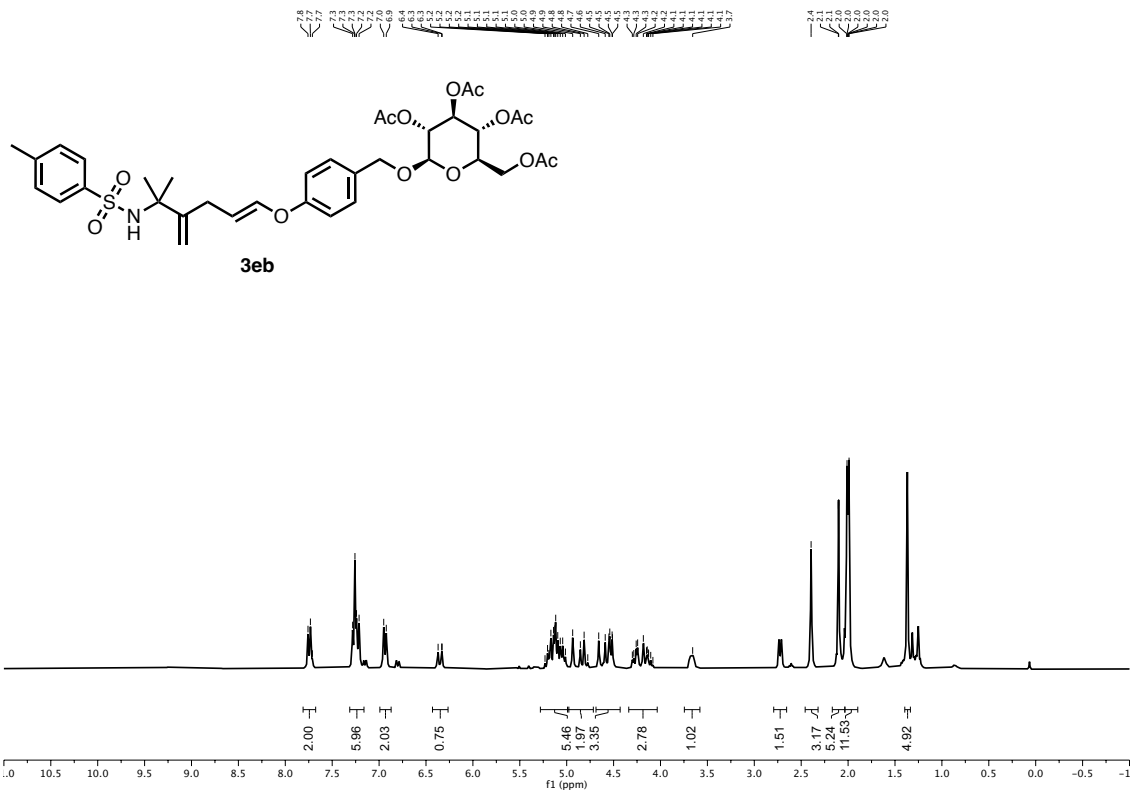



**$^{13}$C NMR** (75 MHz, $CDCl_3$)

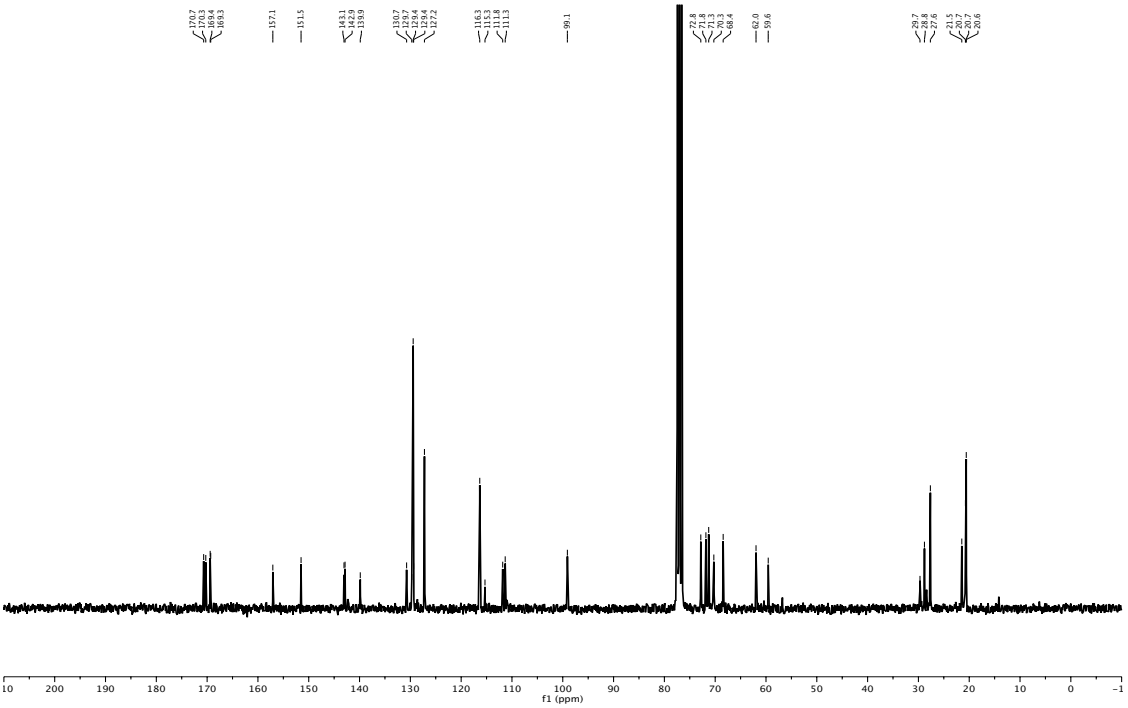


**(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-((4-(((*E*)-5-methyl-4-methylene-5-((4-methylphenyl)sulfonamido)hex-1-en-1-yl)oxy)benzyl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (3eb).**

**$^{1}$H NMR** (300 MHz, $CDCl_3$)




**$^{13}$C NMR** (75 MHz, $CDCl_3$)



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