Copper-Catalyzed Cross-Coupling of Alkyl Grignard Reagents and Propargylic Ammonium Salts: Stereospecific Synthesis of Allenes

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Supporting Information

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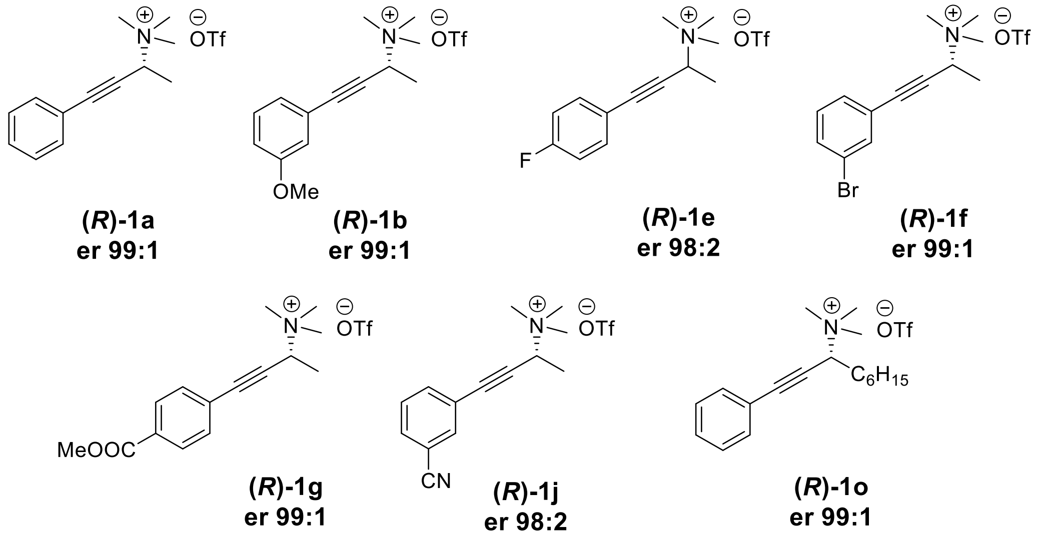
1 GENERAL EXPERIMENTAL DETAILS

Tetrahydrofuran and dichloromethane were purified by passing through a Pure Solv™ column drying system from Innovative Technology, Inc. Additionally, Tetrahydrofuran and dichloromethane were degassed passing Ar through them for 15 min. Diethyl ether was dried using activated 4Å molecular sieves and stored under argon. Unless indicated otherwise, all reactions were conducted under an argon atmosphere using flame-dried glassware with standard vacuum-line techniques. NMR spectra were acquired on a Bruker 300 spectrometer, running at 300, and 75 MHz for ^{1}H and ^{13}C respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals (CDCl$_3$, 7.26 ppm for ^{1}H NMR and 77.2 ppm for ^{13}C NMR respectively). ^{13}C NMR spectra were acquired on a broad band decoupled mode. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet), sept (septuplet), m (multiplet), br (broad). Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or phosphomolybdic acid dip or potassium permanganate dip. Purification of reaction mixtures was carried out by flash chromatography (FC) using silica gel Merck-60. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric ratio (er) of the products was determined by stationary phase SFC, HPLC or GC using chiral columns. Mass Spectrometry (MS) and High-Resolution Mass Spectrometry (HRMS) were registered in a spectrometer GCT Agilent Technologies 6890N using Electronic Impact (E.I.) techniques at 70 eV, Fast Atom Bombardment and electrospray (ESI$^+$ or ESI$^-$).

All ligands and [Cu(CH$_3$CN)$_4$]PF$_6$ were acquired from commercial sources and were used without further purification. Grignard reagents were acquired from commercial sources and were tritrated prior to use.[1] Propargylic ammonium salts were prepared following reported procedures and the enantiomeric ratios are specified in scheme 1.[2]



(*R*)-1a er 99:1

(*R*)-1b er 99:1

(*R*)-1e er 98:2

(*R*)-1f er 99:1

(*R*)-1g er 99:1

(*R*)-1j er 98:2

(*R*)-1o er 99:1

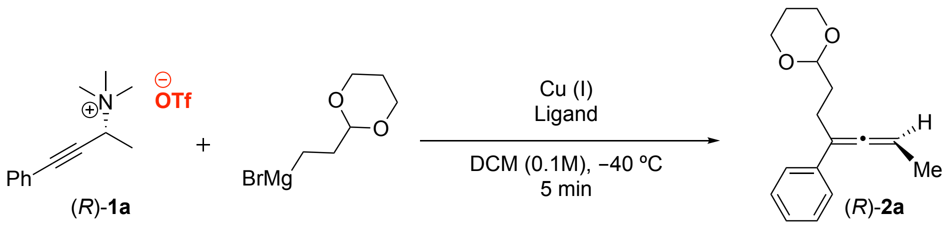
Scheme 1: Enantiomeric ratios of ammonium salts.

2 OPTIMIZATION DETAILS

General procedure for the copper-catalyzed reaction of propargylic ammonium salts and Grignard reagents

An oven-dried vial was charged with Cu(I), the ligand and the corresponding ammonium salt (0.2 mmol) and sealed with a septum. The vial was connected to an argon-vacuum line, evacuated and backfilled with argon (x3). CH_2Cl_2 (2 mL) was added and the mixture was stirred for 5 min at room temperature. The reaction mixture was cooled to –40 ºC and a (1,3-Dioxan-2-ylethyl)magnesium bromide solution in THF (0.3 M, 0.22 mmol) was added dropwise. The mixture was stirred at –40 ºC for 5 minutes. Water (0.1 mL) was added and the solution was filtered through a short pad of $MgSO_4$ and rinsed with CH_2Cl_2. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using *n*-hexane as eluent. The enantiomeric ratio was determined by SFC using Chiralpak-ID column [CO_2/MeOH (98:2)], 1.0 mL/min, τ_{major}= 10.9 min, τ_{minor}= 12.4 min.

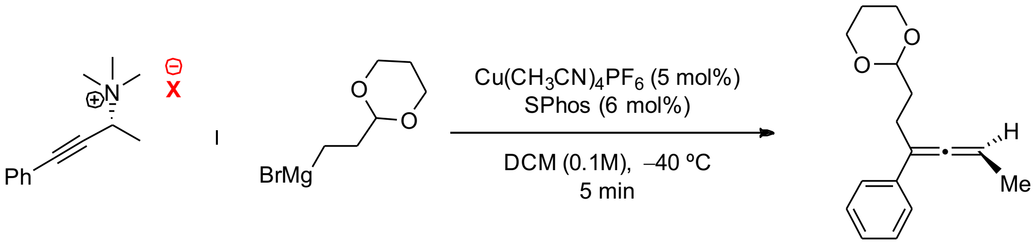
Table S1: Influence of the copper and temperature.



Entry	[Cu] (mol%)	L (mol%)	T (ºc)	Yield[b] (%)	er[c]
2	$Cu(CH_3CN)_4PF_6$ (5)	Sphos (6)	-40	90	98.2
2	$Cu(CH_3CN)_4PF_6$ (5)	Sphos (6)	0	76	95:5
2	$Cu(CH_3CN)_4PF_6$ (5)	Sphos (6)	rt	77	95:5
2	-	-	rt	24	78:22

[a]Reaction conditions: following general procedure. [b]Isolated yield after column chromatography. [c]Determined by chiral SFC.

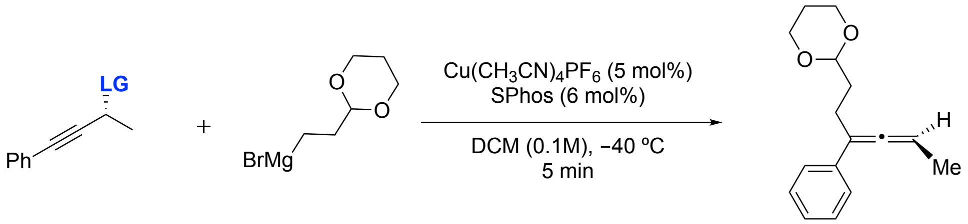
Table S2: Influence of the nature of the counterion.[a]



Entry	X	Yield (%)[b]	α/γ [c]	er[d]
1	**OTf**	90	≥98:2	98:2
2	**OMs**	57	≥98:2	71:29
3	**BF_4**	63	≥98:2	66:34
4	**I**	51	≥98:2	88:12
5	**OTs**	51	≥98:2	65:35

[a] Reaction conditions: following general procedure. [b] Isolated yield after column chromatography. [c] Determined by ^{1}H-NMR. [d] Determined by chiral SFC.

Table S3: Influence of the nature of the leaving group.[a]

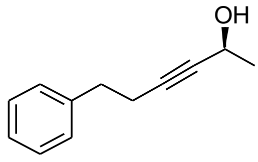


Entry	X	Yield (%)[b]	α/γ [c]	er[d]
1	**NMe_3OTf**	90	≥98:2	98:2
2	**OMs**	55	≥98:2	87:13

[a] Reaction conditions: following general procedure. [b] Yield was determined by isolation. [c] Determined by ^{1}H-NMR. [d] Determined by chiral SFC.

3 SYNTHESIS OF STARTING MATERIALS

3.1 Synthesis of (–)-(*S*)-6-phenylhex-3-yn-2-ol, (*S*)-SI-1z

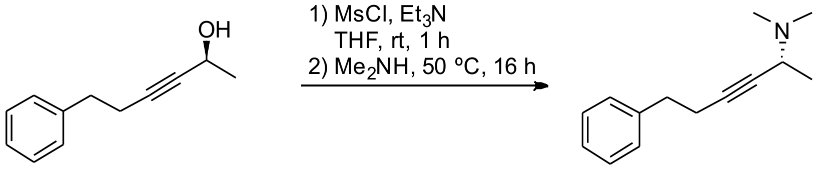


(*S*)-SI-1z

To an oven-dried round bottom flask was added (±)-6-phenylhex-3-yn-2-ol (1.90 g, 10.9 mmol), molecular sieves (0.95 g) and Amano Lipase from Pseudomonas fluorescens (0.95 g). The flask was connected to an argon-vacuum line, evacuated and backfilled with argon (x3). *n*-Hexane (100 mL) and Vinyl acetate (2.7 mL, 33 mmol) were added and the reaction mixture was stirred at room temperature for 2 h. After completion (checked by chiral HPLC) the reaction was filtered and the solvent was removed under reduced pressure. Longer reaction times, results in complete acetylation of the alcohol. Compound **(*S*)-SI-1z** (853 mg, 4.9 mmol) was obtained in 45% yield as a yellowish oil after flash column chromatography (Cy/EtOAc, 90/10).

Compound **(*S*)-SI-1s** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IBN column [CO_2/MeOH (95:5)], 1.0 mL/min, τ_{major}= 11.2 min, τ_{minor}= 6.4 min. ^1H NMR, ^{13}C NMR and MS data were consistent with literature values. [3] **$[\alpha]^{20}_D$**= –33.1 (*c* = 1.0, $CHCl_3$).

3.2 Synthesis of (+)-*N,N*-Dimethyl-6-phenylhex-3-yn-2-amine, SI-2z.

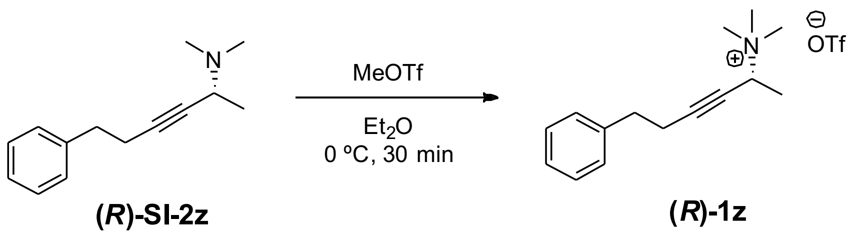


(*S*)-SI-1z **(*R*)-SI-2z**

To a solution of **(*S*)-SI-1z** (800 mg, 4.6 mmol) and triethylamine (3.2 mL, 23 mmol) in THF (12 mL) was added methanesulfonyl chloride (708 µL, 9.2 mmol) at 0 °C. The reaction was stirred for 1 h at room temperature and then, a solution of dimethylamine (12 mL, 2 M in THF, 23 mmol) was added to the mixture. The temperature was raised to 50 °C and the reaction mixture was stirred for 16 h. The reaction mixture was filtered through a short pad of Celite® and rinsed with Et_2O. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (From Cy/EtOAc 2:1 to EtOAc gradient). Compound **(*R*)-SI-2z** (845 mg, 4.2 mmol) was obtained in 91% yield as a yellowish oil.

^1H NMR, ^{13}C NMR and MS data were consistent with literature values. [2] **$[\alpha]^{20}_D$**= +18.4 (*c* = 1.0, $CHCl_3$).

3.3 Synthesis of (+)-(*R*)-*N,N,N*-trimethyl-6-phenylhex-3-yn-2-aminium trifluoromethanesulfonate, (*R*)-1z.



To a solution of **(*R*)-SI-2z** (800 mg, 4 mmol) in Et_2O (8 mL) was added methyl trifluoromethanesulfonate (540 μL, 4.77 mmol) at 0 ºC. The reaction was stirred for 1 h at 0 ºC and a white solid precipitated. The mixture was filtered through a fritted funnel and was washed with cold Et_2O. The white solid was dried under vacuum for 16 h. Compound **(*R*)-SI-2z** (1.35 g, 3.75 mmol) was obtained in 93% yield as a white solid.

^1H NMR, ^{13}C NMR and MS data were consistent with literature values.[2] **$[\alpha]^{20}_D$**= +7.5 (*c* = 1.0, $CHCl_3$).

4 PREPARATION OF (4-PHENYLBUTYL)MAGNESIUM BROMIDE SOLUTION

An oven-dried flask was charged with magnesium (72 mg, 3 mmol, 1 equiv) and a couple of crystals of iodine under Ar atmosphere. Dry THF (6 mL) was added and the mixture was stirred for 2 min. (4-bromobutyl)benzene was added dropwise to the mixture observing a gentle reflux. The mixture was stirred for 2h and then, it was allowed to rest for 24 h. The supernatant was filtered and the solution was tritrated to determine its concentration (0,43M).[1]

5 COPPER-CATALYZED REACTION OF PROPARGYLIC AMMONIUM TRIFLATES WITH ALKYL GRIGNARD REAGENTS.

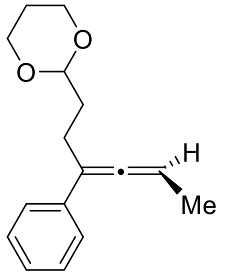
General procedure for the reactions of (±) propargylic ammonium (1) salts with alkylmagnesium halides.

An oven-dried vial was charged with $[Cu(CH_3CN)_4]PF_6$ (3.8 mg, 0.01 mmol) and the correspondent ammonium salt (0.2 mmol) and sealed with a septum. The vial was connected to an argon-vacuum line, evacuated and backfilled with argon (x3). DCM (2 mL) was added and the mixture was stirred for 5 min at room temperature. The reaction mixture was cooled to -40 ºC and the alkyl magnesium bromide solution in THF (0.22 mmol) was added dropwise and the mixture was stirred at -40 ºC for 5 minutes. After total conversion observed by TLC (5 minutes), water (0.1 mL) was added and the solution was filtered through a short pad of $MgSO_4$ and rinsed with DCM. Solvent was removed under reduced pressure and the crude product was purified by flash column chromatography.

General procedure for the reactions of enantiopure propargylic ammonium (1) salts with alkylmagnesium halides.

An oven-dried vial was charged with $[Cu(CH_3CN)_4]PF_6$ (3.8 mg, 0.01 mmol), Sphos (4.9 mg, 0.012 mmol) and the correspondent ammonium salt (0.2 mmol) and sealed with a septum. The vial was connected to an argon-vacuum line, evacuated and backfilled with argon (x3). DCM (2 mL) was added and the mixture was stirred for 5 min at room temperature. The reaction mixture was cooled to -40 ºC and the alkyl magnesium bromide solution in THF (0.22 mmol) was added dropwise and the mixture was stirred at -40 ºC for 5 minutes. After total conversion observed by TLC (5 minutes), water (0.1 mL) was added and the solution was filtered through a short pad of $MgSO_4$ and rinsed with DCM. Solvent was removed under reduced pressure and the crude product was purified by flash column chromatography.

(—)-(*R*)-2-(3-phenylhexa-3,4-dien-1-yl)-1,3-dioxane (2a).



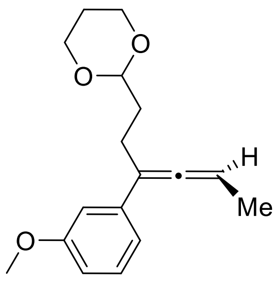
(*R*)-2a

From **(*R*)-1a** (67 mg, 0.2 mmol) and (1,3-Dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-2a** (44 mg, 0.18 mmol) was obtained in 90% yield as a pale yellow oil, after purification by flash column chromatography (cyclohexane/EtOAc 95:5). From **(±)-1a,** following the same procedure without Sphos, compound **(±)-2a** (42 mg, 0.17 mmol) was obtained in 86% yield.

^{1}H NMR, ^{13}C NMR and MS data for **(±)-2a** were consistent with literature values.[4] Compound **(*R*)-2a** was obtained in 98:2 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (98:2)], 1.0 mL/min, τ_{major}= 12.9 min, τ_{minor}= 14.4 min. $[\alpha]^{25}_D$= -64.1 (*c* = 1.0, $CHCl_3$).

The reaction was also carried out in gram scale, from **(*R*)-1a** (1.0 g, 2.96 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (3.3 mmol) affording compound **(*R*)-2a** (614 mg, 2.47 mmol) in 85% yield as a yellow oil and enantiomeric ratio of 98:2.

(–)-(*R*)-2-(3-(3-methoxyphenyl)hexa-3,4-dien-1-yl)-1,3-dioxane (2b).

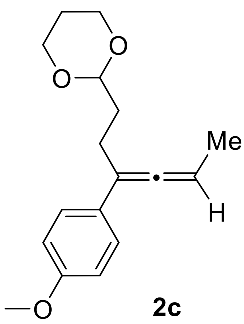


(*R*)-2b

From **(*R*)-1b** (74 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-2b** (51 mg, 0.19 mmol) was obtained in 93% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 97:3). From **(±)-1b,** following the same procedure without SPhos, compound **(±)-2b** (51 mg, 0.19 mmol) was obtained in 93% yield.

^1H NMR, ^{13}C NMR and MS data for **(±)-2b** were consistent with literature values.[4] Compound **(*R*)-2a** was obtained in 98:2 enantiomeric ratio determined by SFC using Chiralpak-IA column [CO_2/MeOH (99:1)], 1.0 mL/min, τ_{major}= 25.5 min, τ_{minor}= 27.3 min. **$[\alpha]^{25}_D$**= -66.7 (*c* = 1.0, $CHCl_3$).

(±)-2-(3-(4-Methoxyphenyl)hexa-3,4-dien-1-yl)-1,3-dioxane (2c).

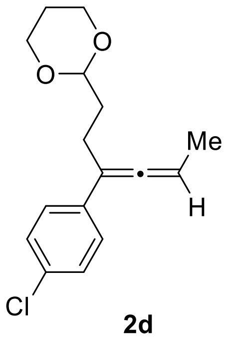


2c

From **1c** (74 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol), following the general procedure described above, compound **2c** (33 mg, 0.12 mmol) was obtained in 60% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 97:3).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 6.88 – 6.82 (m, 2H), 5.53 – 5.41 (m, 1H), 4.62 (t, *J* = 5.2 Hz, 1H), 4.19 – 4.06 (m, 2H), 3.81 – 3.71 (m, 2H), 3.80 (s, 3H), 2.51 – 2.42 (m, 2H), 2.16 – 2.03 (m, 1H), 1.89 – 1.80 (m, 2H), 1.74 (d, *J* = 7.0 Hz, 3H), 1.38 – 1.31 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 204.0, 158.5, 129.8, 127.2, 113.9, 104.3, 102.1, 89.7, 67.1, 55.4, 33.8, 26.0, 24.4, 14.7. **HRMS-(EI)** calculated for $C_{17}H_{21}O_3$ $[M]^+$: 274.1491; Found 274.1495.

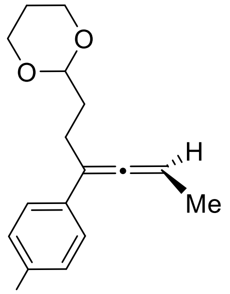
(±)-2-(3-(4-chlorophenyl)hexa-3,4-dien-1-yl)-1,3-dioxane (2d).



2d

From **1d** (74 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **2d** (50 mg, 0.18 mmol) was obtained in 90% yield as a pale yellow oil, after purification by flash column chromatography (cyclohexane/Et_2O 95:5). ^1H NMR, ^{13}C NMR and MS data were consistent with literature values.[4]

(−)-(*R*)-2-(3-(4-fluorophenyl)hexa-3,4-dien-1-yl)-1,3-dioxane (2e).

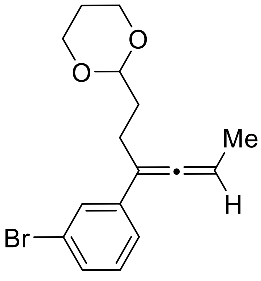


(*R*)-2e

From **(*R*)-1e** (71 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-2e** (50 mg, 0.19 mmol) was obtained in 95% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 97:3). From **(±)-1e,** following the same procedure without SPhos, compound **(±)-2e** (44 mg, 0.17 mmol) was obtained in 84% yield.

Compound **(*R*)-2e** was obtained in 97:3 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (99:1)], 1.0 mL/min, τ_{major}= 18.7 min, τ_{minor}= 20.8 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 2H), 7.03 – 6.92 (m, 2H), 5.49 (qt, *J* = 6.9, 3.2 Hz, 1H), 4.62 (t, *J* = 5.1 Hz, 1H), 4.20 – 4.04 (m, 2H), 3.86 – 3.69 (m, 2H), 2.56 – 2.35 (m, 2H), 2.19 – 2.00 (m, 1H), 1.88 – 1.80 (m, 2H), 1.75 (d, *J* = 7.0 Hz, 3H), 1.40 – 1.30 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 204.3 (d, $J_{C\text{-}F}$ = 2.0 Hz), 161.8 (d, $J_{C\text{-}F}$ = 245.4 Hz), 133.4 (d, $J_{C\text{-}F}$ = 3.2 Hz), 127.6 (d, $J_{C\text{-}F}$ = 7.9 Hz), 115.2 (d, $J_{C\text{-}F}$ = 21.4 Hz), 140.0, 101.9, 90.1, 67.1, 33.7, 26.0, 24.4, 14.5. **HRMS-(EI)** calculated for $C_{16}H_{18}FO_2$ $[M\text{-}H]^+$: 261.1291; Found: 261.0887. **$[\alpha]^{25}_D$**= -68.1 (*c* = 1.0, $CHCl_3$).

(±)-2-(3-(3-Bromophenyl)hexa-3,4-dien-1-yl)-1,3-dioxane (2f).

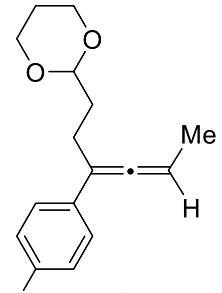


2f

From **1f** (83 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **2f** (58 mg, 0.18 mmol) was obtained in 90% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 95:5).

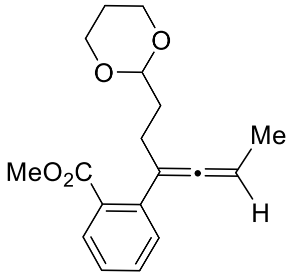
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (t, *J* = 1.9 Hz, 1H), 7.30 (ddt, *J* = 8.0, 5.1, 1.3 Hz, 2H), 7.15 (t, *J* = 7.9 Hz, 1H), 5.53 (qt, *J* = 7.0, 3.3 Hz, 1H), 4.61 (t, *J* = 5.2 Hz, 1H), 4.19 – 4.07 (m, 2H), 3.84 – 3.71 (m, 2H), 2.55 – 2.36 (m, 2H), 2.19 – 2.02 (m, 1H), 1.88 – 1.79 (m, 2H), 1.76 (d, *J* = 7.0 Hz, 3H), 1.40 – 1.30 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 204.7, 140.0, 129.8, 129.4, 129.1, 124.6, 122.7, 104.0, 102.0, 90.5, 67.1, 33.7, 26.0, 24.0, 14.4. **HRMS** (EI) calculated for $C_{16}H_{19}BrO_2$ $[M]^+$: 322.0568; Found: 322.0552.

(±)-Methyl 4-(1-(1,3-dioxan-2-yl)hexa-3,4-dien-3-yl)benzoate (2g).


2g

From **1g** (79 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **2g** (54 mg, 0.17 mmol) was obtained in 89% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 90:10). ^1H NMR, ^{13}C NMR and MS data were consistent with literature values.[4]

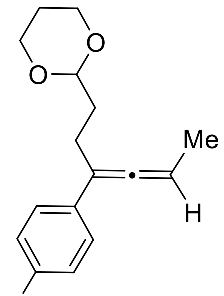
(±)-Methyl 2-(1-(1,3-dioxan-2-yl)hexa-3,4-dien-3-yl)benzoate (2h).


2h

From **1h** (79 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **2h** (30 mg, 0.10 mmol) was obtained in 50% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 90:10).

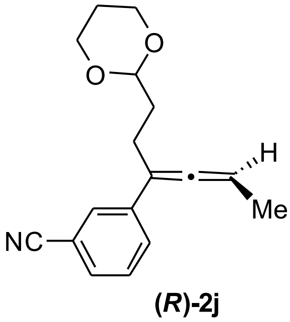
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.45 – 7.37 (m, 1H), 7.33 – 7.26 (m, 2H), 5.25 (qt, *J* = 6.8, 3.2 Hz, 1H), 4.61 (t, *J* = 5.2 Hz, 1H), 4.14 – 4.05 (m, 2H), 3.86 (s, 3H), 3.81 – 3.69 (m, 2H), 2.46 – 2.35 (m, 2H), 2.14 – 2.00 (m, 1H), 1.85 – 1.77 (m, 2H), 1.66 (d, *J* = 7.0 Hz, 3H), 1.37 – 1.28 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 203.2, 168.8, 139.5, 131.1, 130.8, 129.7, 129.28, 126.6, 104.5, 101.8, 87.8, 66.9, 52.0, 33.6, 27.7, 25.9, 14.3. **HRMS** (EI) calculated for $C_{18}H_{22}O_4$ $[M]^+$: 302.1518; Found: 302.1509.

(±)-4-(1-(1,3-Dioxan-2-yl)hexa-3,4-dien-3-yl)benzonitrile (2i).


2i

From **1i** (72 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **2i** (45 mg, 0.17 mmol) was obtained in 84% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 90:10). ^1H NMR, ^{13}C NMR and MS data were consistent with literature values.[4]

(—)-(*R*)-3-(1-(1,3-dioxan-2-yl)hexa-3,4-dien-3-yl)benzonitrile (2j).

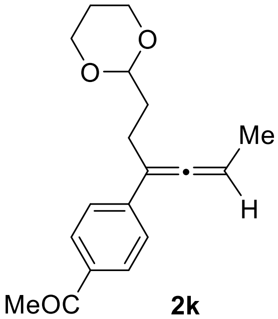


(*R*)-2j

From **(*R*)-1j** (72 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-2j** (50 mg, 0.19 mmol) was obtained in 93% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 90:10). From **(±)-1j,** following the same procedure, compound **(±)-2j** (49 mg, 0.18 mmol) was obtained in 91% yield.

Compound **(*R*)-2j** was obtained in 95:5 enantiomeric ratio determined by SFC using Chiralpak-IB column [CO_2/MeOH (99:1)], 1.0 mL/min, τ_{major}= 28.3 min, τ_{minor}= 26.6 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.65 (t, *J* = 1.8 Hz, 1H), 7.59 (dt, *J* = 7.7, 1.7 Hz, 1H), 7.46 – 7.33 (m, 2H), 5.57 (qt, *J* = 7.0, 3.3 Hz, 1H), 4.61 (t, *J* = 5.1 Hz, 1H), 4.16 – 4.06 (m, 2H), 3.83 – 3.69 (m, 2H), 2.51 – 2.38 (m, 2H), 2.17 – 1.99 (m, 1H), 1.87 – 1.77 (m, 2H), 1.76 (d, J = 7.1 Hz, 3H), 1.39 – 1.30 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 204.8, 139.0, 130.1, 129.8, 129.6, 129.1, 119.2, 112.4, 103.5, 101.6, 91.1, 67.0, 33.5, 25.9, 23.8, 14.2. **HRMS** (ESI) calculated for $C_{17}H_{19}NNaO_2$ [M+Na]$^+$: 292.1313; Found: 292.1318. **[α]$^{25}_{D}$**= -89.3 (*c* = 1.0, $CHCl_3$).

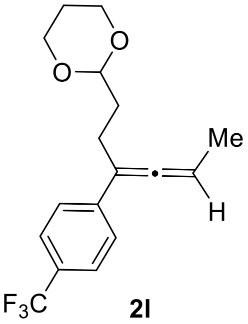
(±)-1-(4-(1-(1,3-Dioxan-2-yl)hexa-3,4-dien-3-yl)phenyl)ethanone (2k).



2k

From **1k** (76 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above (catalytic charge was changed to 0.02 mmol), compound **2k** (23 mg, 0.08 mmol) was obtained in 40% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 80:20). ^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[4]

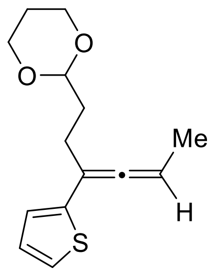
(±)-2-(3-(4-(Trifluoromethyl)phenyl)hexa-3,4-dien-1-yl)-1,3-dioxane (2l).



2l

From **1l** (81 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **2l** (58 mg, 0.19 mmol) was obtained in 93% yield as a pale yellow oil, after purification by flash column chromatography (hexane/AcOEt 95:5). ^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[4]

(±)-2-(3-(Thiophen-2-yl)hexa-3,4-dien-1-yl)-1,3-dioxane (2m).

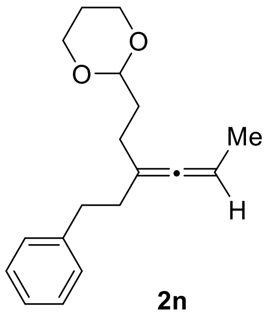


2m

From **1m** (69 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **2m** (40 mg, 0.16 mmol) was obtained in 80% yield as a pale yellow oil, after purification by flash column chromatography (cyclohexane/EtOAc 95:5).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.00 – 6.90 (m, 2H), 5.51 (qt, *J* = 6.9, 3.2 Hz, 1H), 4.62 (t, *J* = 5.2 Hz, 1H), 4.18 – 4.09 (m, 2H), 3.83 – 3.73 (m, 2H), 2.54 – 2.44 (m, 2H), 2.16 – 2.03 (m, 1H), 1.91 – 1.82 (m, 2H), 1.72 (d, *J* = 3.3 Hz, 3H), 1.40 – 1.31 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 203.4, 143.0, 127.4, 124.1, 122.7, 101.9, 100.8, 90.6, 67.1, 33.6, 26.0, 25.5, 14.6. **HRMS** (EI) calculated for $C_{14}H_{17}O_2S$ $[M-H]^+$: 249.0949; Found: 249.0553.

(±)-2-(3-Phenethylhexa-3,4-dien-1-yl)-1,3-dioxane (2n).

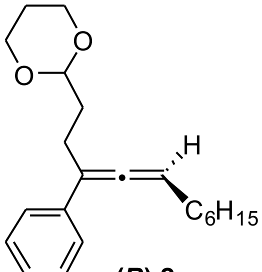


2n

From **1n** (73 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above (temperature was changed to rt), compound **2n** (33 mg, 0.12 mmol) was obtained in 61% yield as a pale yellow oil, after purification by flash column chromatography (cyclohexane/EtOAc 95:5).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 2H), 7.22 – 7.13 (m, 3H), 5.08 (qt, *J* = 7.8, 3.4, 1H), 4.54 (t, *J* = 5.2 Hz, 1H), 4.16 – 4.05 (m, 2H), 3.82 – 3.68 (m, 2H), 2.77 – 2.66 (m, 2H), 2.29 – 2.18 (m, 2H), 2.15 – 1.99 (m, 3H), 1.79 – 1.68 (m, 2H), 1.55 (d, *J* = 7.1 Hz, 3H), 1.39 – 1.29 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.7, 142.5, 128.5, 128.31, 125.8, 102.8, 102.1, 87.9, 67.1, 34.7, 34.2, 33.4, 27.0, 26.0, 15.0. **HRMS** (ESI) calculated for $C_{18}H_{24}NaO_2$ $[M+Na]^+$: 295.1674; Found: 295.1665.

(–)-(*R*)-2-(3-Phenylundeca-3,4-dien-1-yl)-1,3-dioxane (2o).



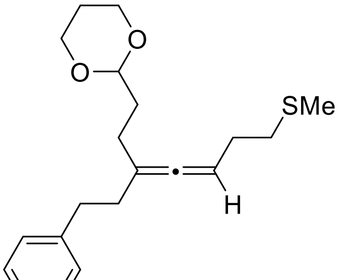
(*R*)-2o

From **(*R*)-1o** (82 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-2o** (48 mg, 0.15 mmol) was obtained in 76% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 95:5). From **(±)-1o,** following the same procedure without SPhos, compound **(±)-2o** (51 mg, 0.16 mmol) was obtained in 81% yield.

Compound **(*R*)-2o** was obtained in 98:2 enantiomeric ratio determined by SFC using Chiralpak-IB column [CO_2/MeOH (99:1)], 1.0 mL/min, τ_{major}= 28.3 min, τ_{minor}= 27.7

min. **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.45 – 7.38 (m, 2H), 7.33 – 7.27 (m, 2H), 7.21 – 7.13 (m, 1H), 5.53 (tt, *J* = 6.6, 3.3 Hz, 1H), 4.63 (t, *J* = 5.2 Hz, 1H), 4.20 – 4.05 (m, 2H), 3.83 – 3.68 (m, 2H), 2.57 – 2.45 (m, 2H), 2.16 – 2.06 (m, 3H), 1.92 – 1.81 (m, 2H), 1.56 – 1.21 (m, 10H), 0.96 – 0.82 (m, 3H). **^{13}C NMR** (76 MHz, CDCl$_3$) δ 203.6, 137.6, 128.4, 126.5, 126.0, 105.2, 102.1, 95.5, 67.1, 33.8, 31.8, 29.4, 29.3, 29.1, 26.0, 24.2, 22.8, 14.2. **HRMS** (EI) calculated for $C_{21}H_{30}O_2$ $[M]^+$: 314.2246; Found: 314.2223. **$[\alpha]^{25}_D$**= -78.2 (*c* = 1.0, CHCl$_3$).

(±)-2-(7-(Methylthio)-3-phenethylhepta-3,4-dien-1-yl)-1,3-dioxane (2p).

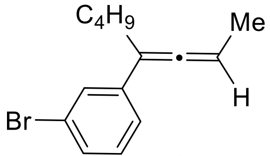


2p

From **1p** (85 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above (temperature was changed to rt), compound **2p** (48 mg, 0.14 mmol) was obtained in 72% yield as a pale yellow oil, after purification by flash column chromatography (cyclohexane/EtOAc 90:10).

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.31 – 7.22 (m, 2H), 7.22 – 7.13 (m, 3H), 5.18 (qt, *J* = 6.2, 3.1 Hz, 1H), 4.54 (t, *J* = 5.1 Hz, 1H), 4.15 – 4.05 (m, 2H), 3.83 – 3.67 (m, 2H), 2.74 (t, *J* = 7.9 Hz, 2H), 2.51 – 2.41 (m, 2H), 2.32 – 2.01 (m, 10H), 1.79 – 1.68 (m, 2H), 1.38 – 1.29 (m, 1H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ 201.0, 142.2, 128.5, 128.3, 125.8, 104.4, 102.0, 91.8, 67.0, 34.6, 34.1, 33.8, 33.4, 29.3, 26.9, 26.0, 15.69. **HRMS** (EI) calculated for $C_{20}H_{28}O_2S$ $[M]^+$: 332.1810; Found: 332.1797.

(±)-1-Bromo-3-(octa-2,3-dien-4-yl)benzene (2q).

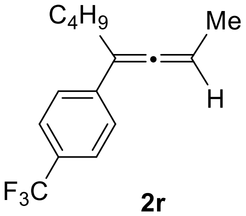


2q

From **1f** (83 mg, 0.2 mmol) and *n*-butylmagnesium chloride solution in THF (0.22 mmol) following the general procedure described above, compound **2q** (30 mg, 0.11 mmol) was obtained in 57% yield as a pale yellow oil, after purification by flash column chromatography (hexane/Et$_2$O 98:2).

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.51 (t, *J* = 1.8 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.16 (dd, *J* = 8.3, 7.4 Hz, 1H), 5.49 (qt, *J* = 6.9, 3.1 Hz, 1H), 2.41 – 2.31 (m, 2H), 1.76 (d, *J* = 0.7 Hz, 3H), 1.58 – 1.34 (m, 4H), 0.93 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ 205.0, 140.3, 129.8, 129.3, 129.2, 124.6, 122.7, 104.3, 89.5, 30.1, 29.6, 22.5, 14.4, 14.1. **HRMS** (EI) calculated for $C_{14}H_{17}Br$ $[M]^+$: 264.0514; Found: 264.0478.

(±)-1-(Octa-2,3-dien-4-yl)-4-(trifluoromethyl)benzene (2r).

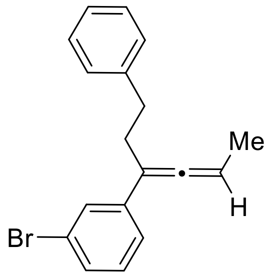


2r

From **1l** (81 mg, 0.2 mmol) and *n*-butylmagnesium bromide chloride solution in THF (0.22 mmol) following the general procedure described above, compound **2r** (42 mg, 0.17 mmol) was obtained in 83% yield as a pale yellow oil, after purification by flash column chromatography (pentane /Et_2O 98:2).

^{1}H NMR (300 MHz, CDCl3) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 5.52 (qt, *J* = 6.8, 3.1 Hz, 1H), 2.45 – 2.35 (m, 2H), 1.78 (d, *J* = 7.0 Hz, 3H), 1.58 – 1.35 (m, 5H), 0.94 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 205.6, 141.7, 128.4 (q, $J_{C\text{-}F}$ = 32.4 Hz), 126.3, 125.3 (q, $J_{C\text{-}F}$ = 3.9 Hz), 124.5 (q, $J_{C\text{-}F}$ = 270.3 Hz), 104.5, 89.6, 30.2, 29.6, 22.5, 14.3, 14.1. **HRMS** (EI) calculated for $C_{15}H_{17}F_3$ $[M]^+$: 254.1282; Found: 254.1279.

(±)-1-Bromo-3-(1-phenylhexa-3,4-dien-3-yl)benzene (2s).

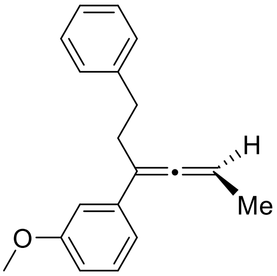


2s

From **(±)-1f** (83 mg, 0.2 mmol) and phenethylmagnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **(±)-2s** (55 mg, 0.18 mmol) was obtained in 88% yield as a pale yellow oil, after purification by flash column chromatography (hexane/Et_2O 98:2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (t, *J* = 1.9 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.24 – 7.14 (m, 4H), 5.51 (qt, *J* = 6.9, 3.1 Hz, 1H), 2.88 – 2.79 (m, 2H), 2.74 – 2.59 (m, 2H), 1.69 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (76 MHz, $CDCl_3$) δ 205.1, 142.0, 139.9, 129.9, 129.5, 129.1, 128.6, 128.5, 126.0, 124.6, 122.8, 103.8, 90.3, 34.2, 31.7, 14.3. **HRMS** (EI) calculated for $C_{18}H_{17}Br$ $[M]^+$: 312.0514; Found: 312.0485.

(—)-(*R*)-1-Methoxy-3-(2-methylhexa-3,4-dien-3-yl)benzene (2t).

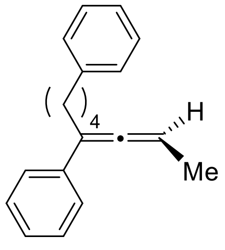


(*R*)-2t

From **(*R*)-1b** (75 mg, 0.2 mmol) and phenethylmagnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-2t** (50 mg, 0.19 mmol) was obtained in 95% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 95:5). From **(±)-1b,** following the same procedure without SPhos, compound **(±)-2t** (52 mg, 0.20 mmol) was obtained in 97% yield.

Compound **(*R*)-2t** was obtained in 96:4 enantiomeric ratio determined by SFC using Chiralpak-IB column [CO_2/MeOH (99:1)], 1 mL/min, τ_{major}= 25.4 min, τ_{minor}= 30.8 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.26 – 7.08 (m, 7H), 6.96 – 6.87 (m, 2H), 6.68 (ddd, *J* = 8.2, 2.5, 1.1 Hz, 1H), 5.39 (qt, *J* = 6.9, 3.0 Hz, 1H), 3.73 (d, *J* = 1.1 Hz, 3H), 2.77 (dd, *J* = 8.2, 5.8 Hz, 2H), 2.69 – 2.57 (m, 2H), 1.61 (dd, J = 7.1, 1.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 205.0, 159.9, 142.3, 139.1, 129.4, 128.7, 128.4, 125.9, 118.7, 112.1, 111.9, 104.7, 89.7, 55.4, 34.4, 31.9, 14.4. **HRMS** (EI) calculated for $C_{19}H_{20}O$ $[M]^+$: 264.1514; Found: 264.1481. **[α]$^{25}_{D}$**= -52.0 (*c* = 1.0, CHCl3).

(—)-(*R*)-Octa-5,6-diene-1,5-diyldibenzene (2u).

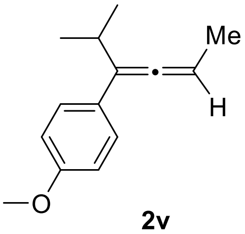


(*R*)-2u

From **(*R*)-1a** (75 mg, 0.2 mmol) and (4-phenylbutyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-2u** (47 mg, 0.18 mmol) was obtained in 90% yield as a pale-yellow oil, after purification by flash column chromatography (hexanes). From **(±)-1a,** following the same procedure, compound **(±)-2u** (46 mg, 0.18 mmol) was obtained in 88% yield.

Compound **(*R*)-2u** was obtained in 98:2 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (99:1)], 1 mL/min, τ_{major}= 11.3 min, τ_{minor}= 12.9 min. ^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[5] **[α]$^{25}_{D}$**= -54.0 (*c* = 1.0, CHCl3).

(±)-1-Methoxy-4-(2-methylhexa-3,4-dien-3-yl)benzene (2v).

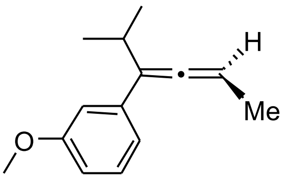


2v

From **1c** (75 mg, 0.2 mmol) and isopropylmagnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **2v** (40 mg, 0.20 mmol) was obtained in 98% yield as a pale-yellow oil, after purification by flash column chromatography (cyclohexane/EtOAc 95:5).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 2H), 6.91 – 6.83 (m, 2H), 5.47 (qd, *J* = 6.9, 2.4 Hz, 1H), 3.81 (s, 3H), 2.87 – 2.66 (m, 1H), 1.76 (dd, *J* = 6.9, 0.7 Hz, 3H), 1.13 (d, *J* = 5.8 Hz, 3H), 1.10 (d, *J* = 5.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 203.4, 158.4, 129.9, 127.7, 113.9, 112.1, 89.8, 55.4, 28.2, 22.7, 22.3, 14.8. **HRMS** (EI) calculated for $C_{14}H_{18}O$ $[M]^+$: 202.1358; Found: 202.1354.

(—)-(*R*)-1-Methoxy-3-(1-phenylhexa-3,4-dien-3-yl)benzene (2w).



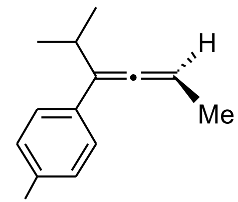
(*R*)-2w

From **(*R*)-1b** (75 mg, 0.2 mmol) and isopropylmagnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-2w** (33 mg, 0.16 mmol) was obtained in 82% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 95:5). From **(±)-1b,** following the same procedure, compound **(±)-2w** (29 mg, 0.14 mmol) was obtained in 71% yield.

Compound **(*R*)-2w** was obtained in 97:3 enantiomeric ratio determined by SFC using Chiralpak-IB column [CO_2/MeOH (99.5:0.5)], 0.5 mL/min, τ_{major}= 26.3 min, τ_{minor}= 24.5 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.8 Hz, 1H), 7.02 – 6.97 (m, 1H), 6.97 –

6.94 (m, 1H), 6.78 – 6.72 (m, 1H), 5.49 (qd, *J* = 6.9, 2.3 Hz, 1H), 3.81 (s, 3H), 2.79 (pd, *J* = 6.7, 2.3 Hz, 1H), 1.76 (d, *J* = 6.9 Hz, 3H), 1.13 (d, *J* = 5.3 Hz, 3H), 1.11 (d, *J* = 5.2 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl3) δ 203.9, 159.8, 139.3, 129.3, 119.2, 112.7, 112.6, 111.6, 90.0, 55.3, 28.1, 22.7, 22.4, 14.6. **HRMS** (EI) calculated for $C_{14}H_{19}O$ [M+H]$^+$: 204.1436; Found: 204.1427. **[α]$^{25}_{D}$**= -47.6 (*c* = 1.0, $CHCl_3$)

(–)-(*R*)-Methyl 4-(2-methylhexa-3,4-dien-3-yl)benzoate (2x).



(*R*)-2x

From **(*R*)-1g** (79 mg, 0.2 mmol) and isopropylmagnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-2x** (39 mg, 0.17 mmol) was obtained in 85% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 97:3). From **(±)-1g,** following the same procedure without SPhos, compound **(±)-2x** (44 mg, 0.19 mmol) was obtained in 95% yield.

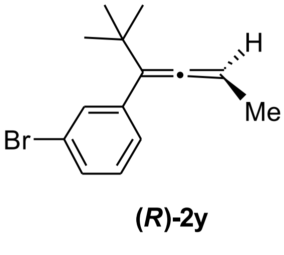
Compound **(*R*)-2x** was obtained in 97:3 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (99:1)], 1 mL/min, τ_{major}= 14.4 min, τ_{minor}= 14.0 min.

Using isopropylmagnesium chloride solution in THF (0.22 mmol) compound **(*R*)-2x** (41 mg, 0.18 mmol) was obtained in 89% yield and 97:3 enantiomeric ratio as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 97:3).

Using isopropylmagnesium chloride solution in Et_2O (0.22 mmol) compound **(*R*)-2x** (12 mg, 0.05 mmol) was obtained in 26% yield and 90:10 enantiomeric ratio as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 97:3). The low yield could be due to a lower solubility of the starting material in the final CH_2Cl_2/Et_2O solution.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 – 7.89 (m, 2H), 7.49 – 7.38 (m, 2H), 5.55 (qd, *J* = 7.0, 2.4 Hz, 1H), 3.90 (s, 3H), 2.82 (septd, *J* = 6.7, 2.4 Hz, 1H), 1.78 (d, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 204.8, 167.2, 142.6, 129.7, 127.9, 126.4, 112.3, 90.6, 52.1, 27.8, 22.6, 22.3, 14.4. **HRMS** (ESI) calculated for $C_{15}H_{18}NaO_2$ [M+Na]$^+$: 253.1204; Found: 253.1198. **[α]$^{25}_{D}$**= -83.7 (*c* = 1.0, $CHCl_3$).

(–)-(*R*)-1-Bromo-3-(2,2-dimethylhexa-3,4-dien-3-yl)benzene (2y).

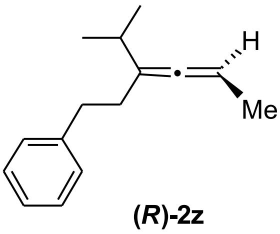


(*R*)-2y

From **(*R*)-1f** (83 mg, 0.2 mmol) and *tert*-butylmagnesium chloride solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-2y** (43 mg, 0.16 mmol) was obtained in 81% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 97:3). From **(±)-1f,** following the same procedure, compound **(±)-2y** (38 mg, 0.14 mmol) was obtained in 72% yield.

Compound **(*R*)-2y** was obtained in 98:2 enantiomeric ratio determined by GC on a Chirasil Dex-CB column (60 ºC, hold 3 min, 60→120 °C @ 10 °C/min, hold 2 min, then →160 °C @ 0.5 °C/min, then →180 °C @ 10 °C/min; flow rate 1.0 mL/min.). τ_{major}= 27.6 min, τ_{minor}= 27.9 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52 – 7.30 (m, 2H), 7.22 – 7.07 (m, 2H), 5.20 (q, *J* = 6.9 Hz, 1H), 1.69 (d, *J* = 6.9 Hz, 3H), 1.12 (s, 9H). **^{13}C NMR** (75 MHz, CDCl3) δ 202.6, 140.6, 132.4, 129.5, 129.3, 128.1, 121.8, 114.1, 86.8, 34.3, 30.0, 14.8. **HRMS** (EI) calculated for $C_{14}H_{17}Br$ $[M]^+$: 264.0514; Found: 264.0506. **$[\alpha]^{25}_D$**= -22.3 (*c* = 1.0, $CHCl_3$).

(*S*)-(3-isopropylhexa-3,4-dien-1-yl)benzene (2z).



(*R*)-2z

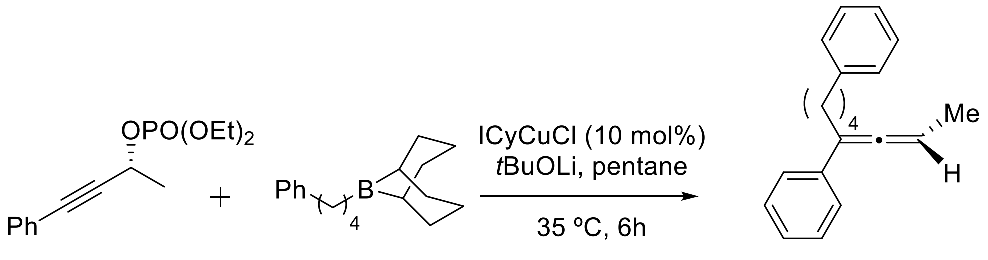
From **(*R*)-1z** (73 mg, 0.2 mmol) and isopropylmagnesium chloride solution in THF (0.22 mmol) following the general procedure described above, compound **(*S*)-2z** (35 mg, 0.18 mmol) was obtained in 88% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 97:3). From **(±)-1z,** following the same procedure, compound **(±)-2z** (33 mg, 0.17 mmol) was obtained in 83% yield.

Compound **(*R*)-2z** was obtained in 98:2 enantiomeric ratio determined by GC on a Chirasil Dex-CB column (60 ºC, hold 3 min, then 60→80 °C @ 10 °C/min, hold 2 min, then →140 °C @ 0.5 °C/min, then →180 °C @ 10 °C/min, hold 3 min; flow rate 1.0 mL/min.). τ_{major}= 68.5 min, τ_{minor}= 70.1 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ7.24 – 7.04 (m, 5H), 5.14 – 4.98 (m, 1H), 2.70 – 2.58 (m, 2H), 2.23 – 2.12 (m, 2H), 2.10 – 1.92 (m, 1H), 1.52 (d, J = 6.8 Hz, 3H), 0.93 (dd, J = 6.8, 1.5 Hz, 6H). **^{13}C NMR** (75 MHz, CDCl3) δ 200.9, 142.8, 128.6, 128.3, 125.8, 110.0, 88.3, 34.5, 32.7, 31.4, 22.0, 21.9, 15.2. **HRMS** (EI) calculated for $C_{15}H_{20}$ $[M]^+$: 200.1565; Found: 200.1573. **$[\alpha]^{25}_D$**= -8.4 (*c* = 1.0, $CHCl_3$).

6 ASSIGNMENT OF ABSOLUTE CONFIGURATION

The absolute configuration was stablished for compound *(R)*-**2u**, by comparison of the sign of the optical rotation with that reported in the literature.[4] The absolute configuration of *(R)*-**2u** reveals an *anti* S_N2' attack of the *in situ* formed cuprate to the ammonium salt. We assumed the same stereochemical outcome for all the enantiomerically enriched compounds prepared.

Previously reported

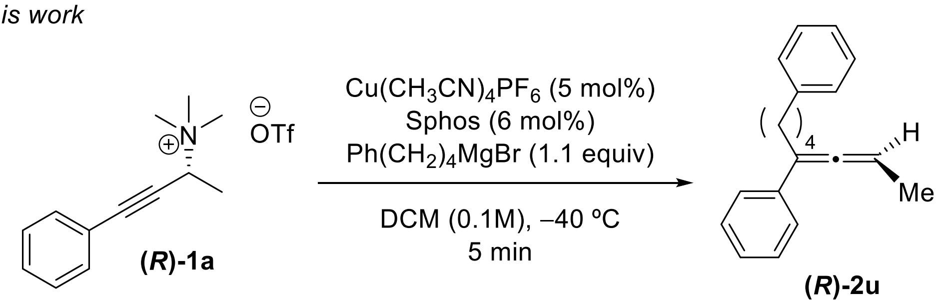


99% ee

(*S*)-3
93%
er 98:2
$[\alpha]^{20}_D$ = +90.6(c 1.4, CH_2Cl_2).

Org. Lett. **2012**, *14*, 362.

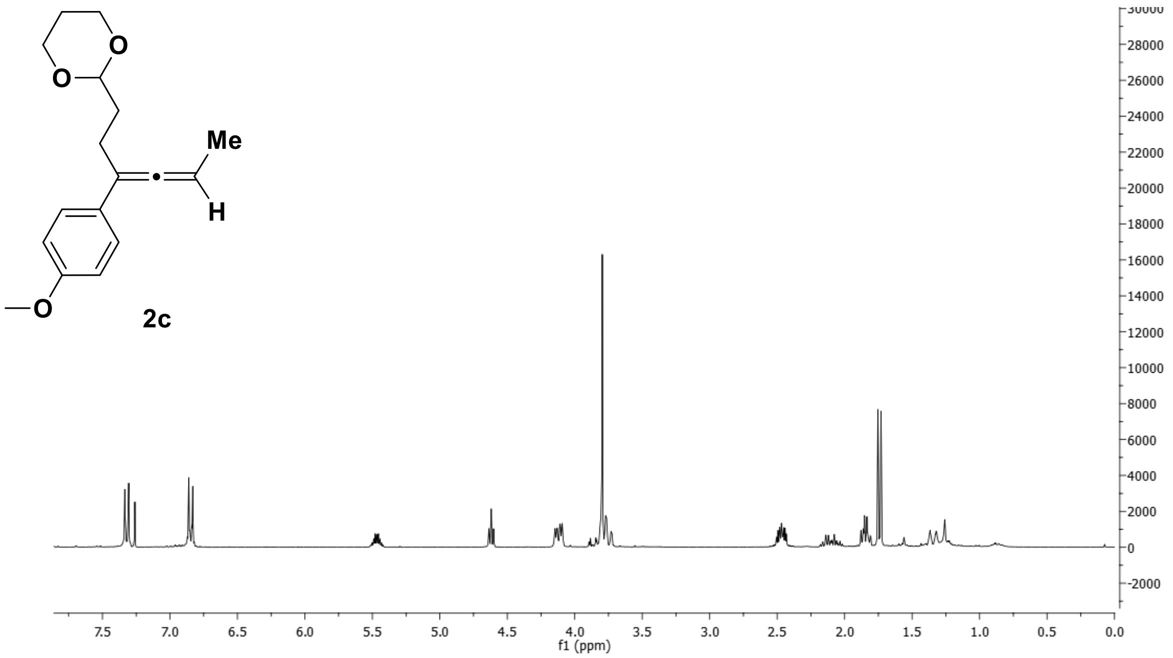
This work



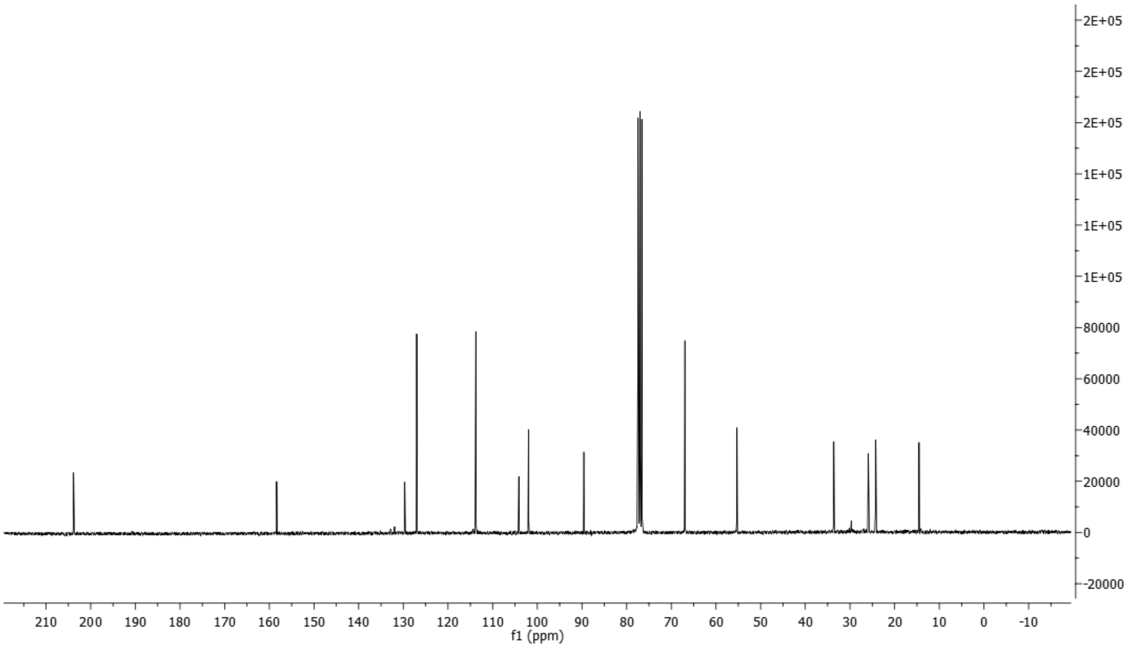
(*R*)-1a

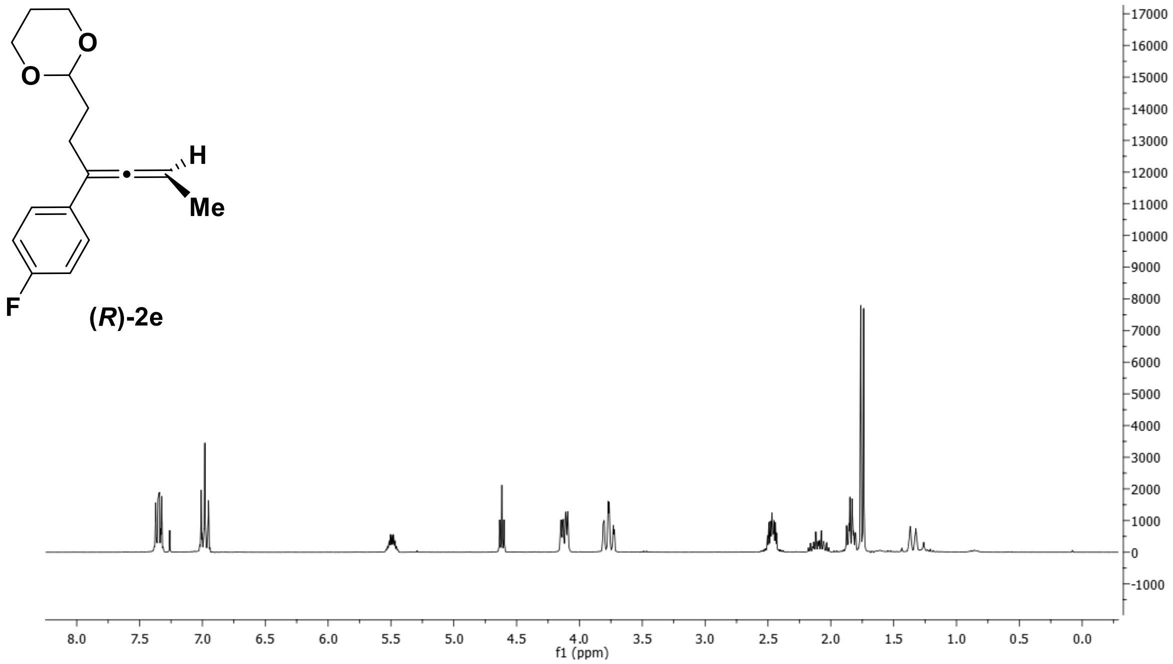
(*R*)-2u
90%
er 98:2
$[\alpha]^{20}_D$= -54.0 (c = 1.0, $CHCl_3$).

7 NMR SPECTRA



2c





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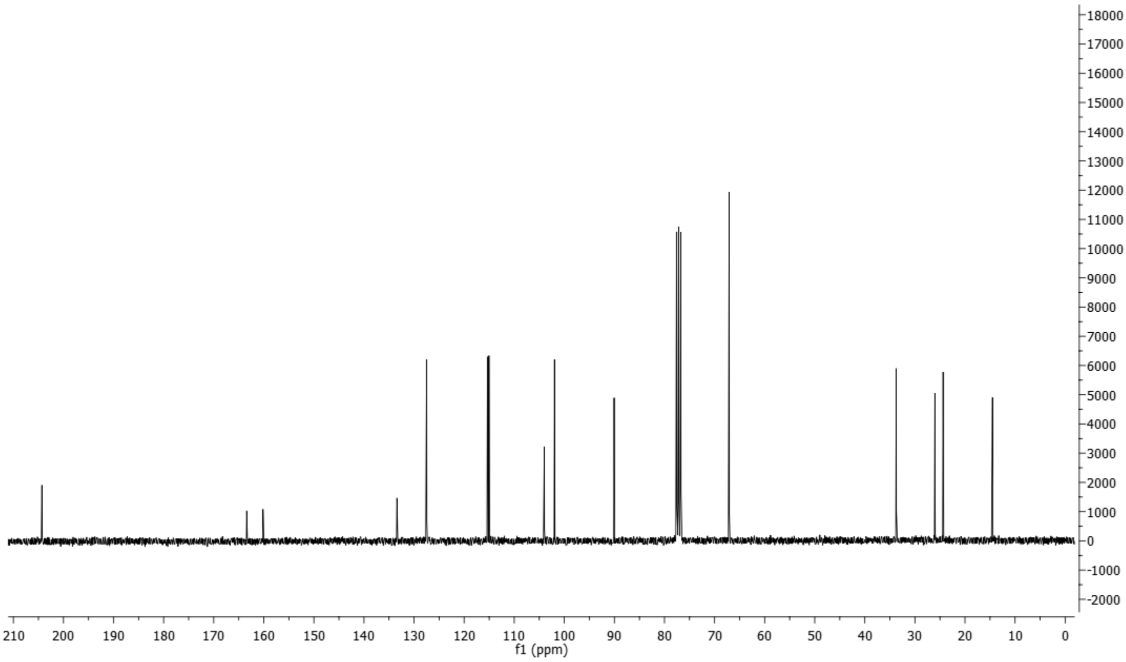
(*R*)-2e



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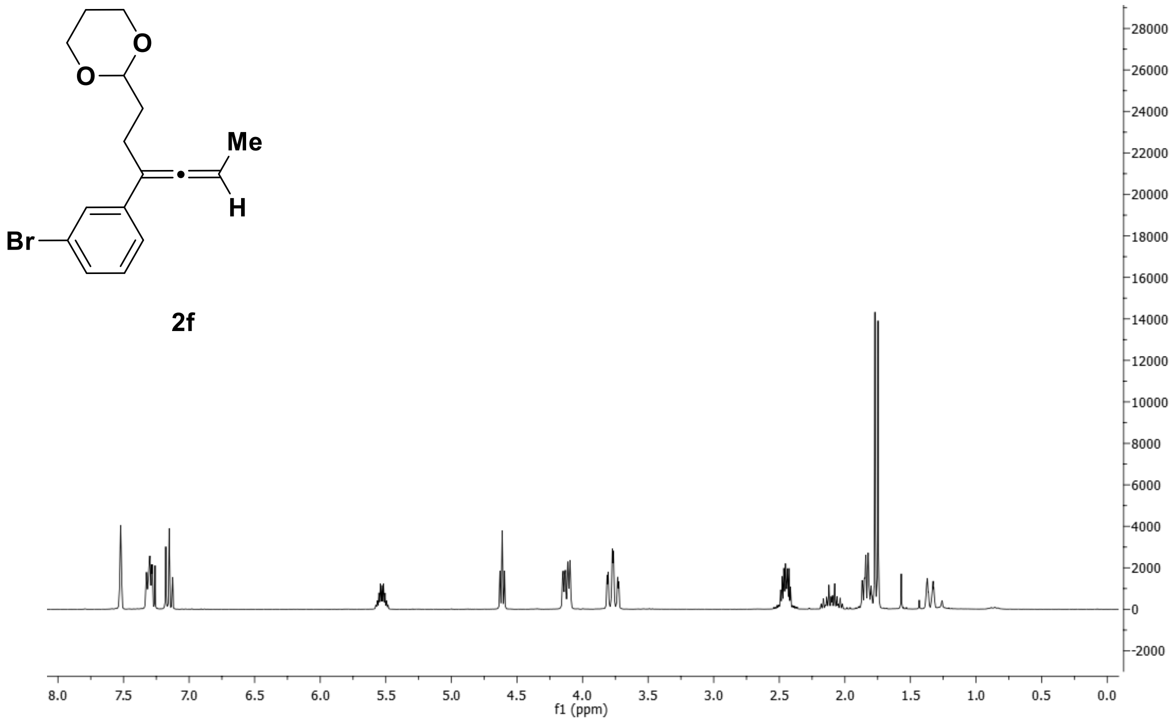
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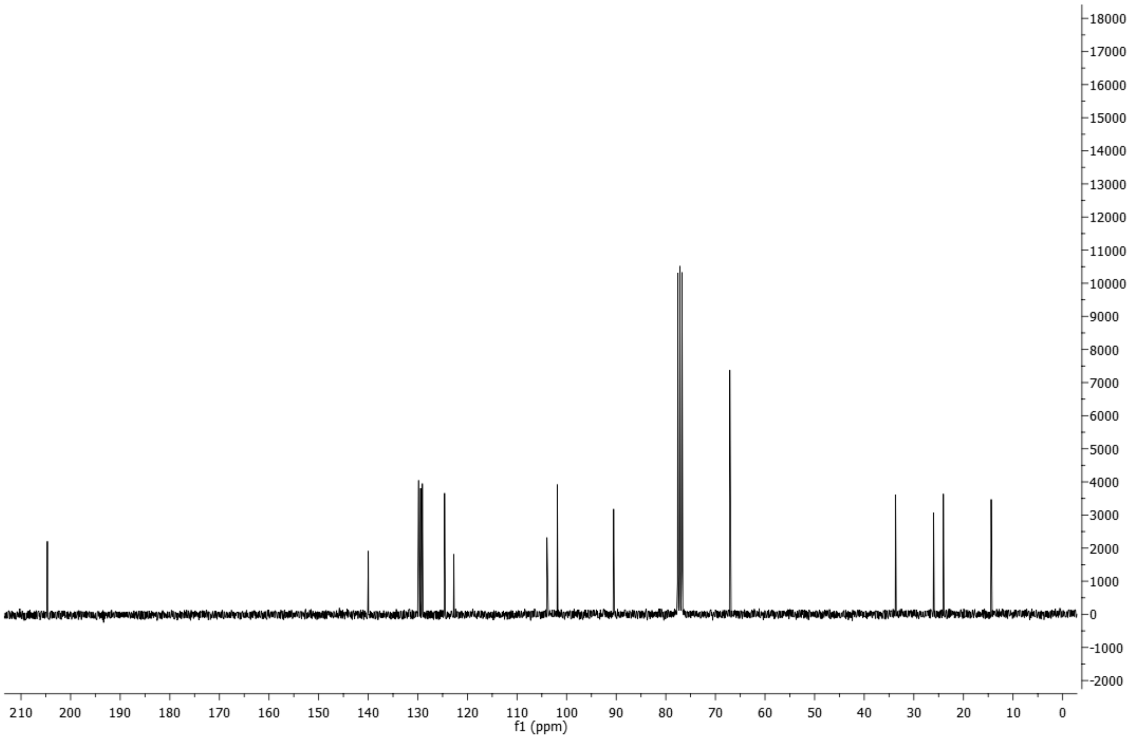
f1 (ppm)

2f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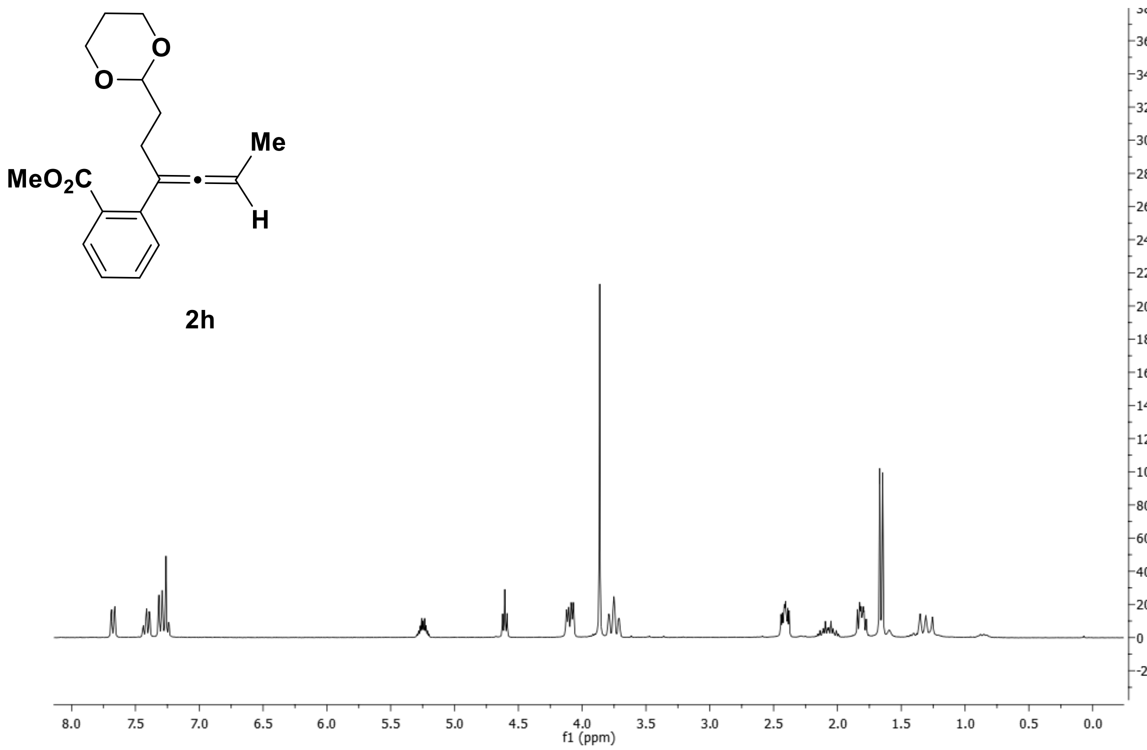

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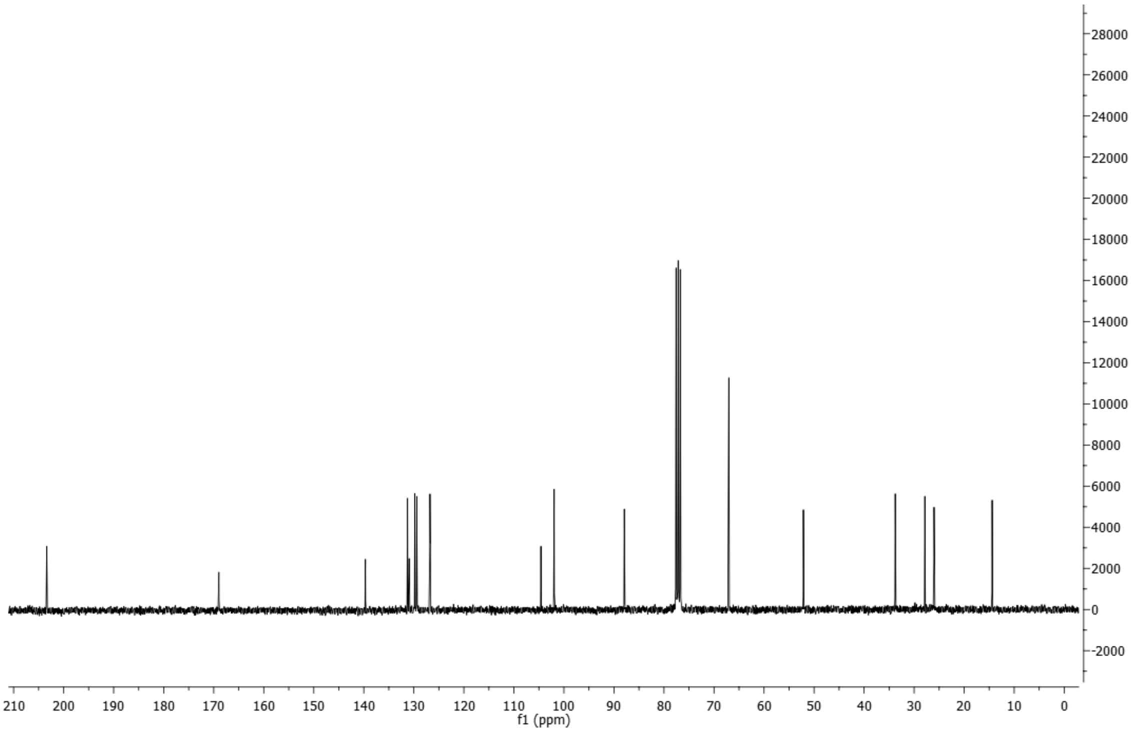
f1 (ppm)

2h



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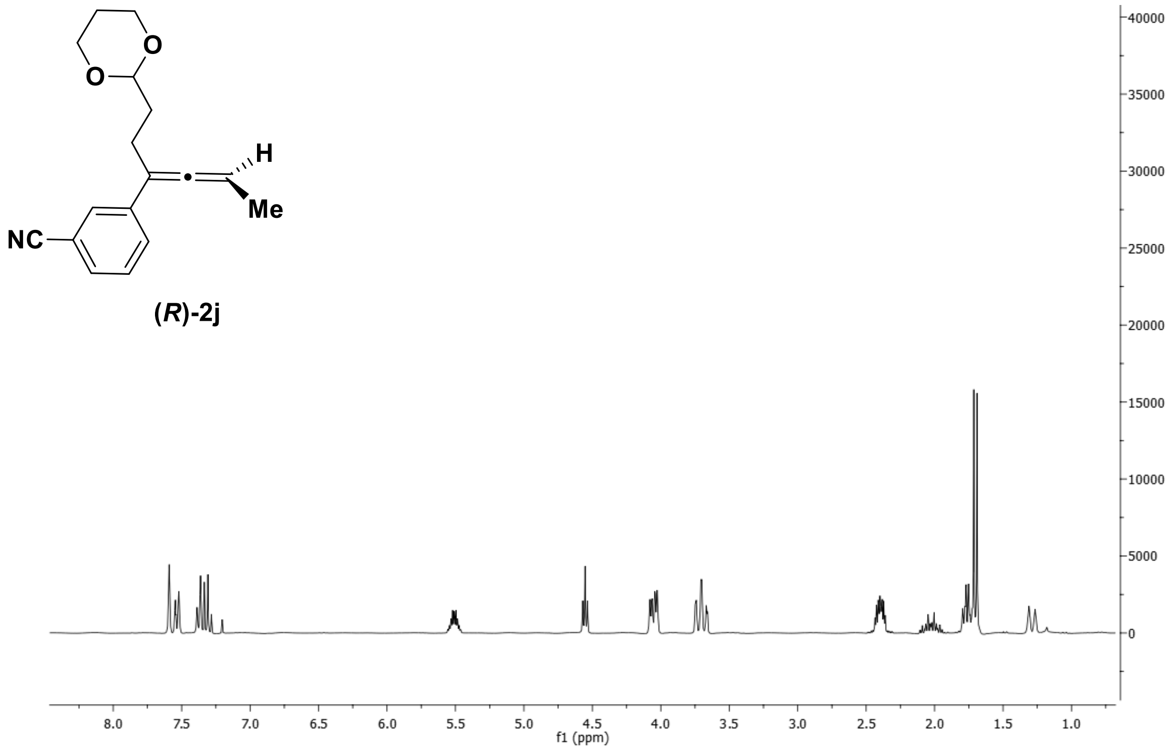
f1 (ppm)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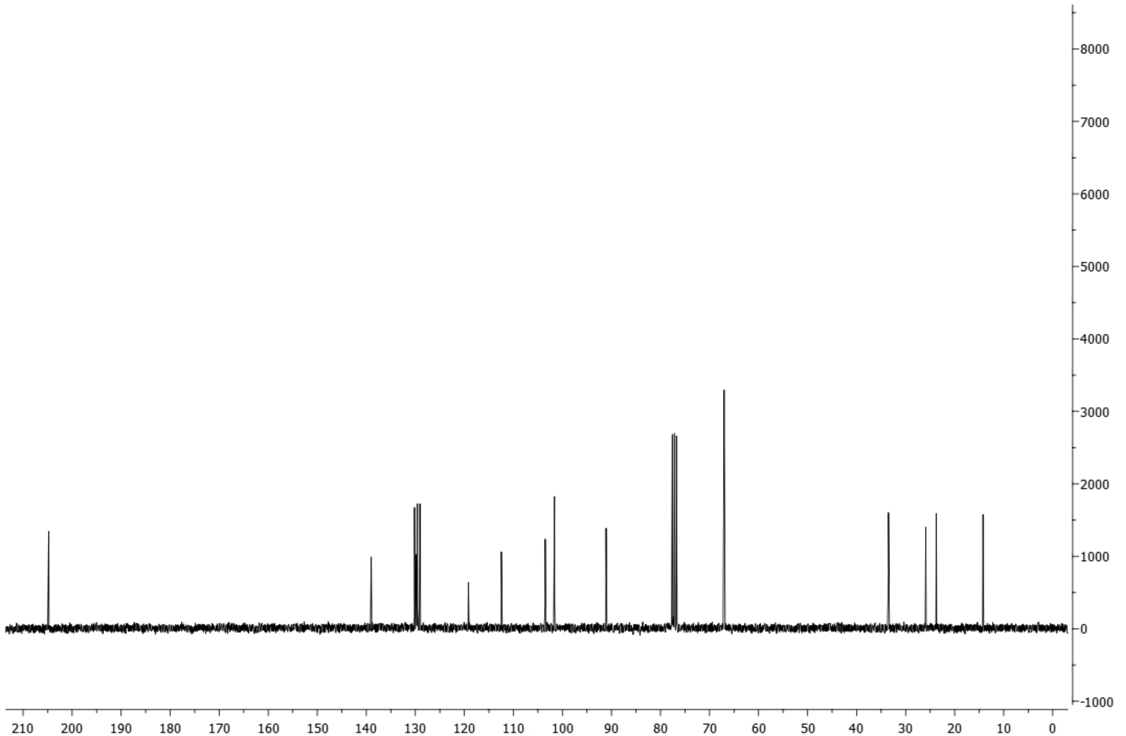
(*R*)-2j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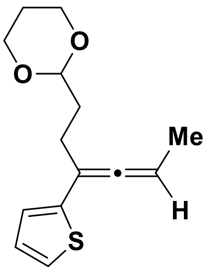
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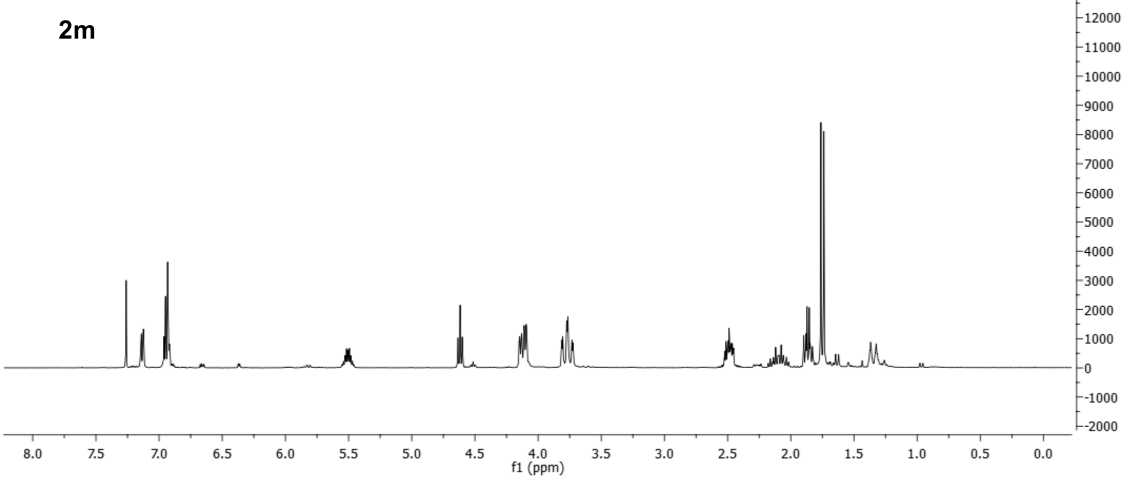
O
Me
H
S

2m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1.0
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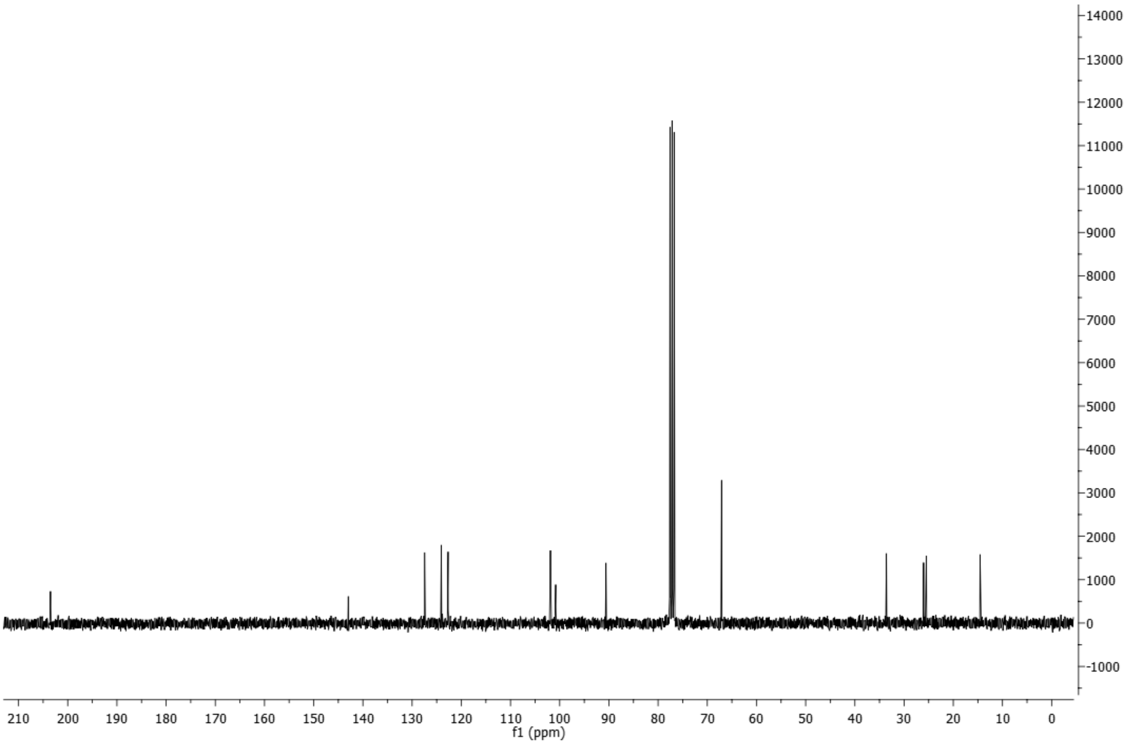
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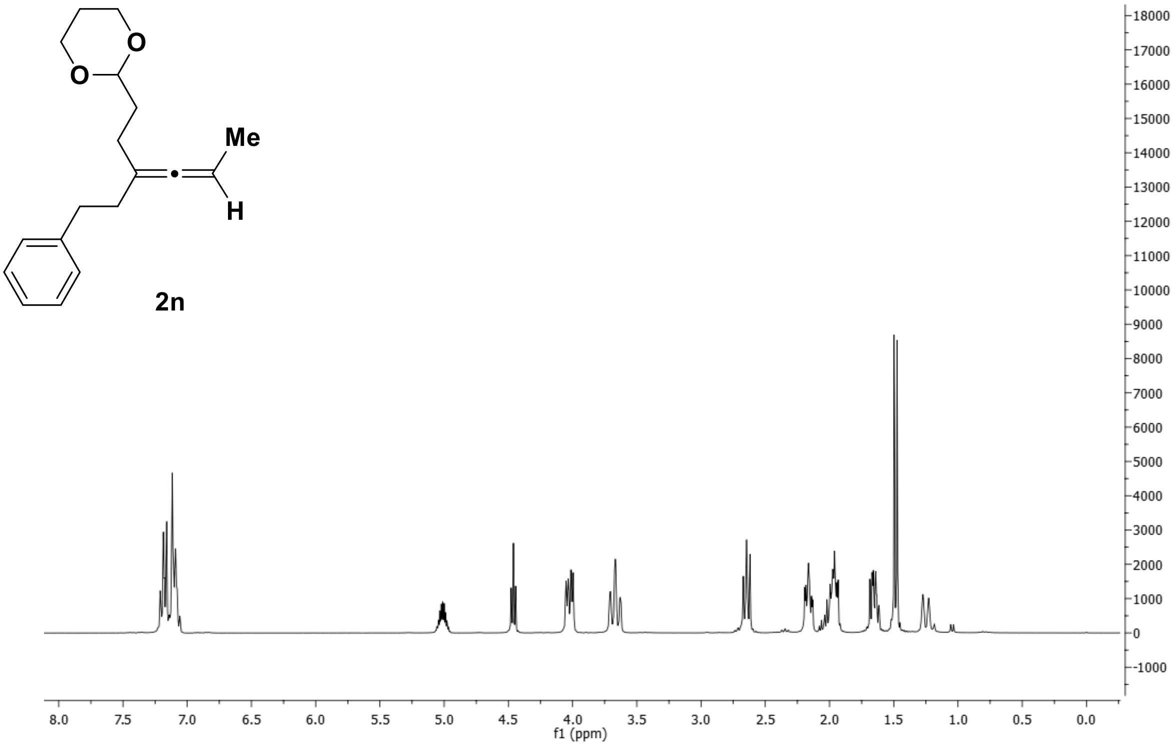
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2n

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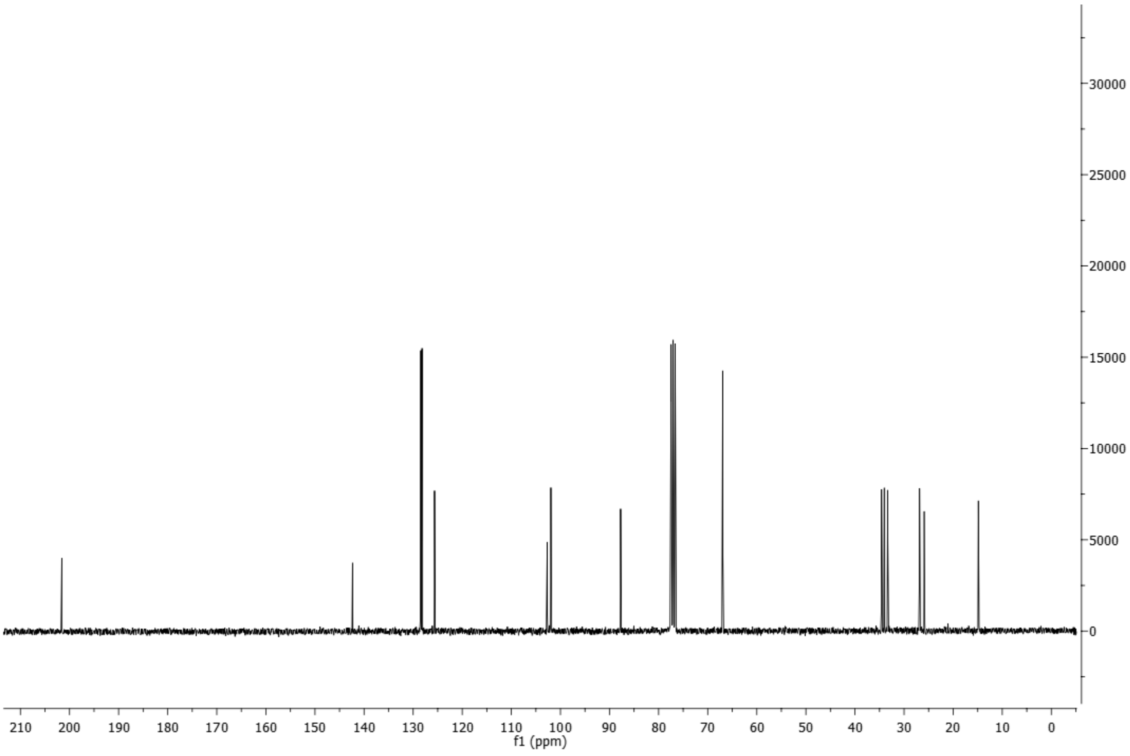
f1 (ppm)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f1 (ppm)

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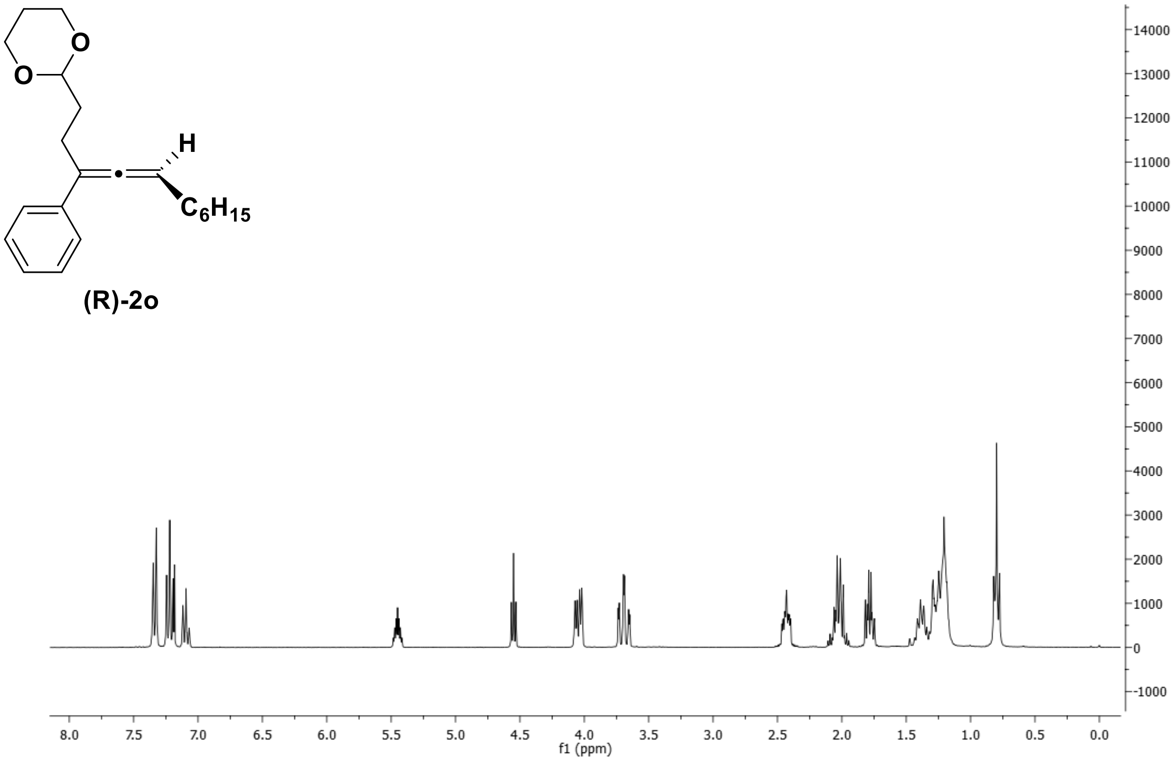
O
H
C6H15

(R)-2o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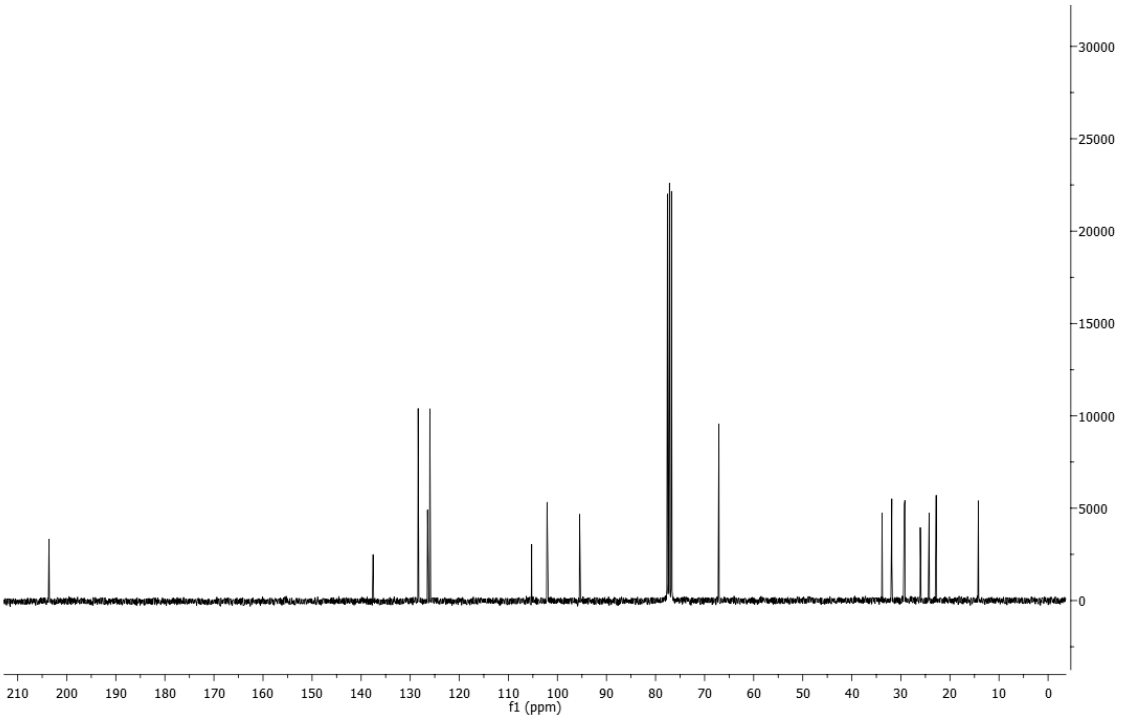
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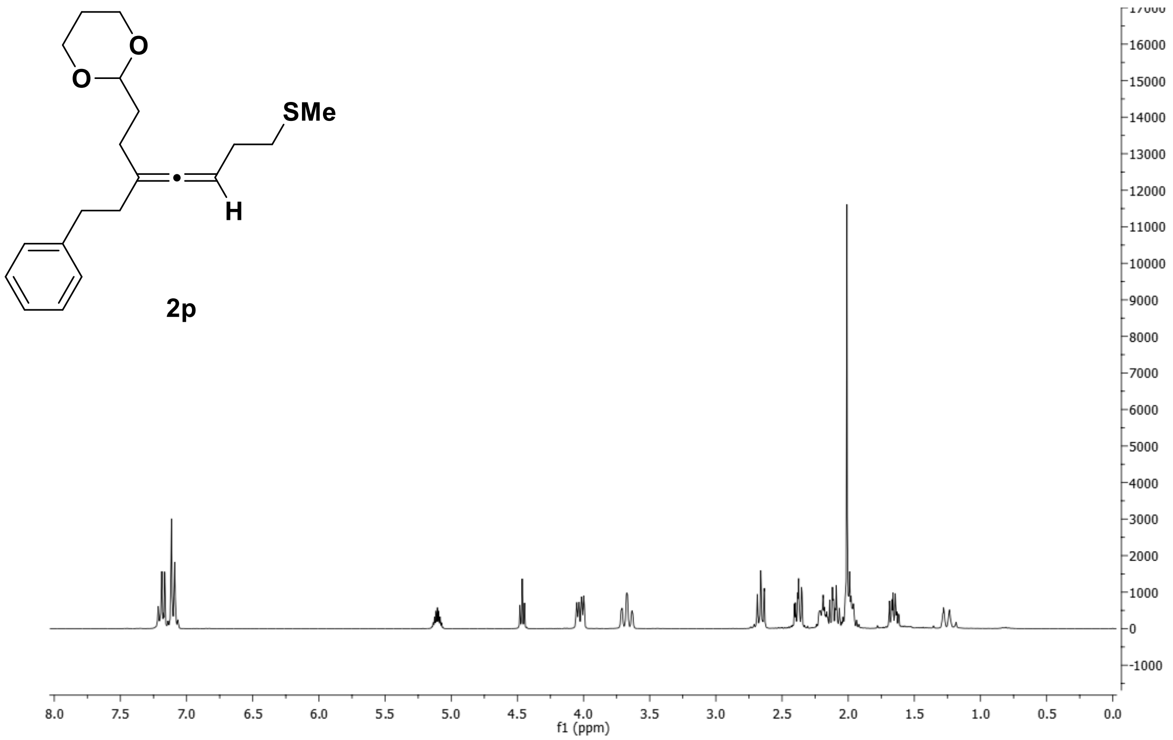
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3.0
2.5
2.0
1.5
1.0
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0.0
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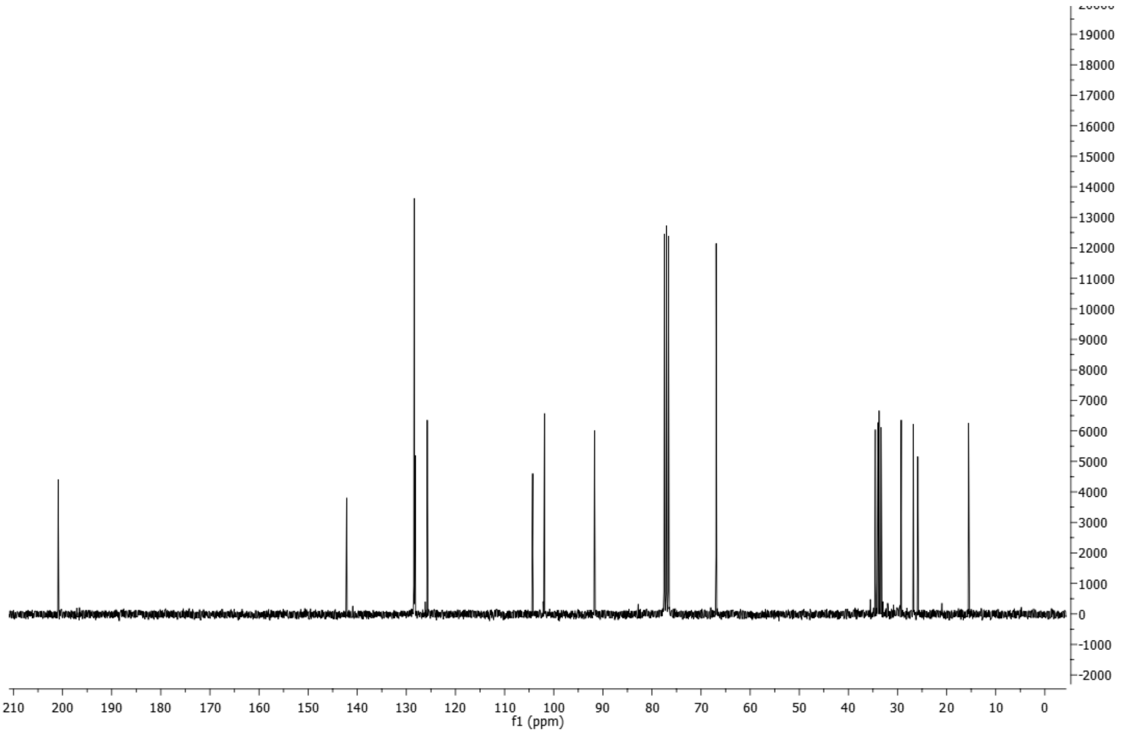
2p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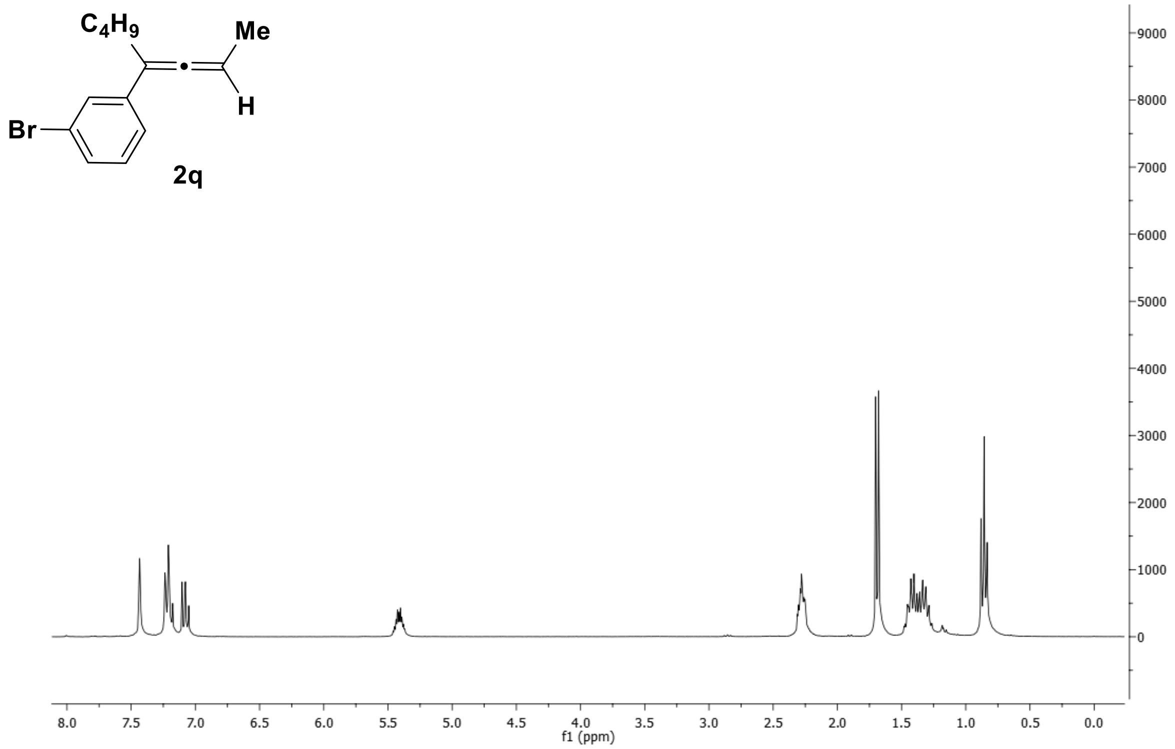
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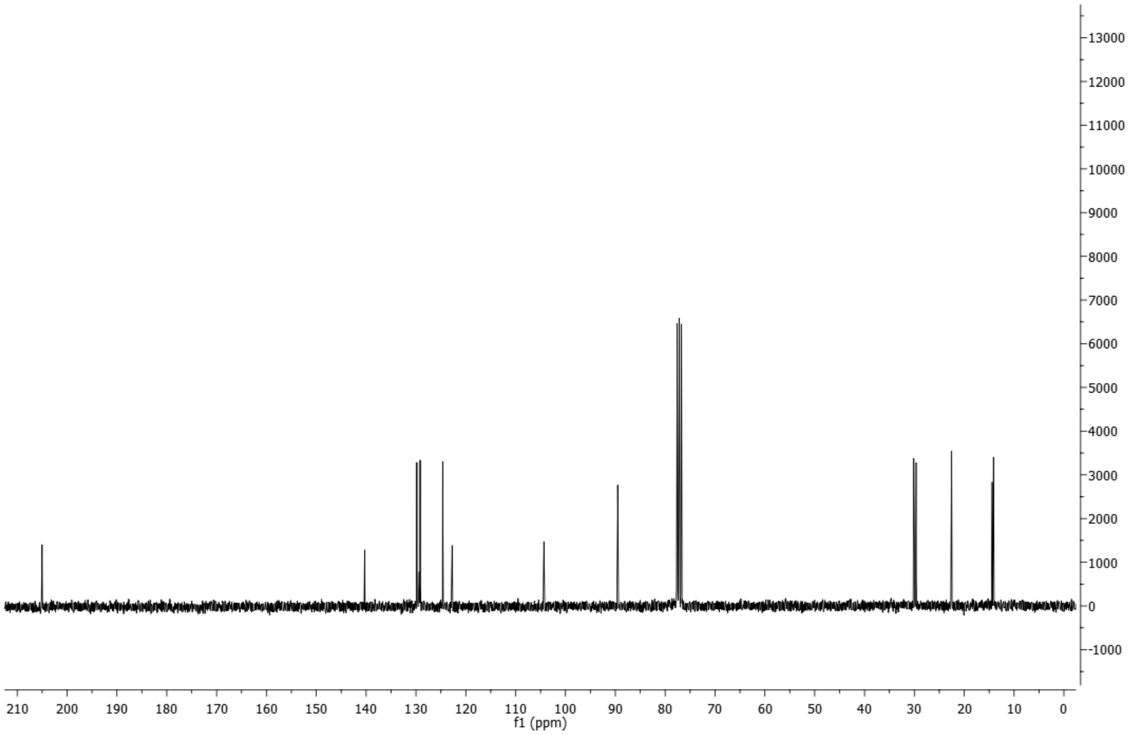
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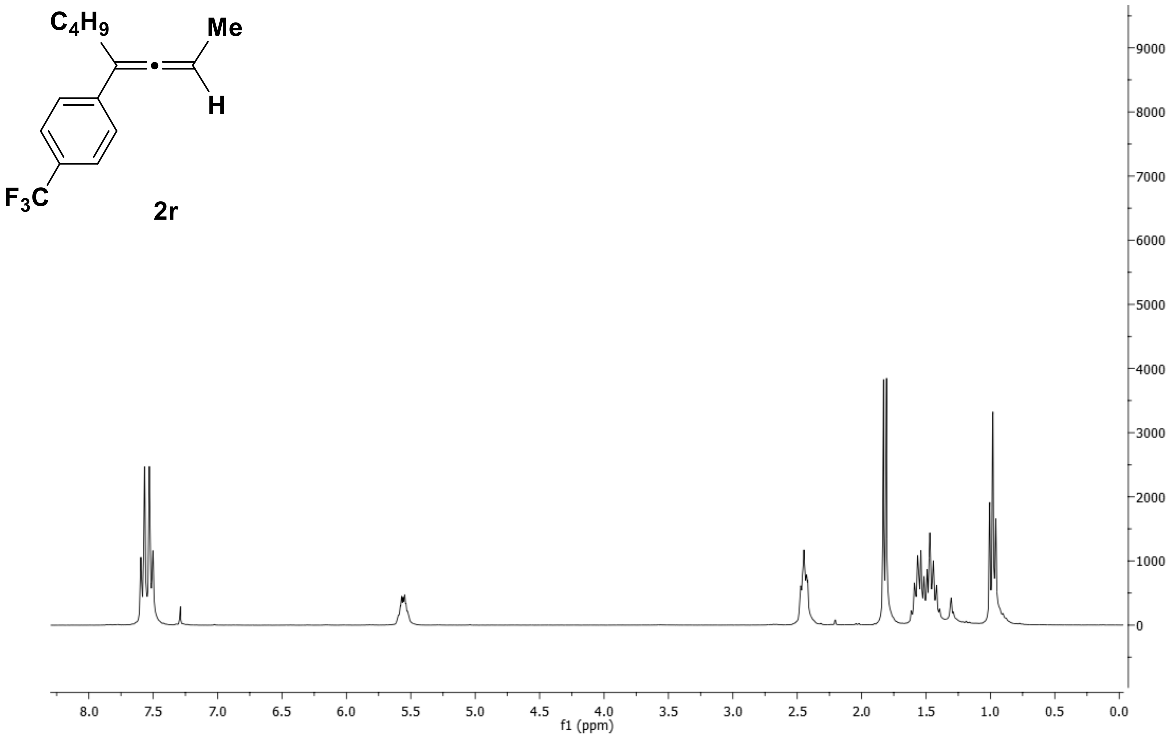

2r

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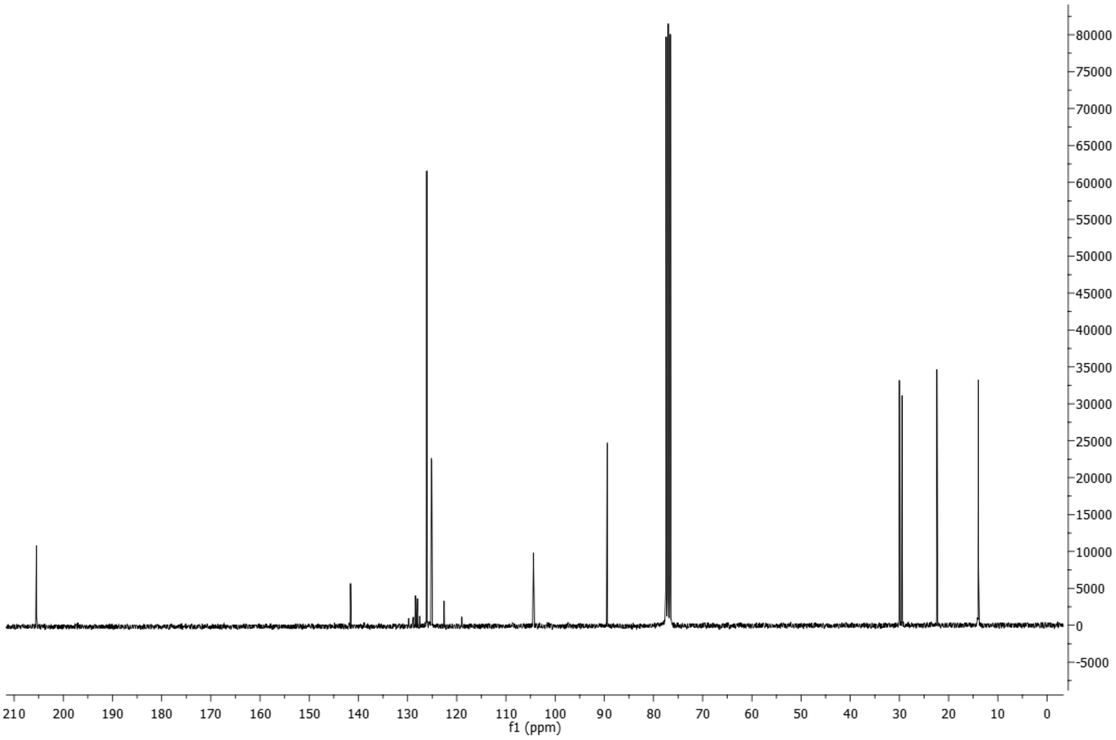

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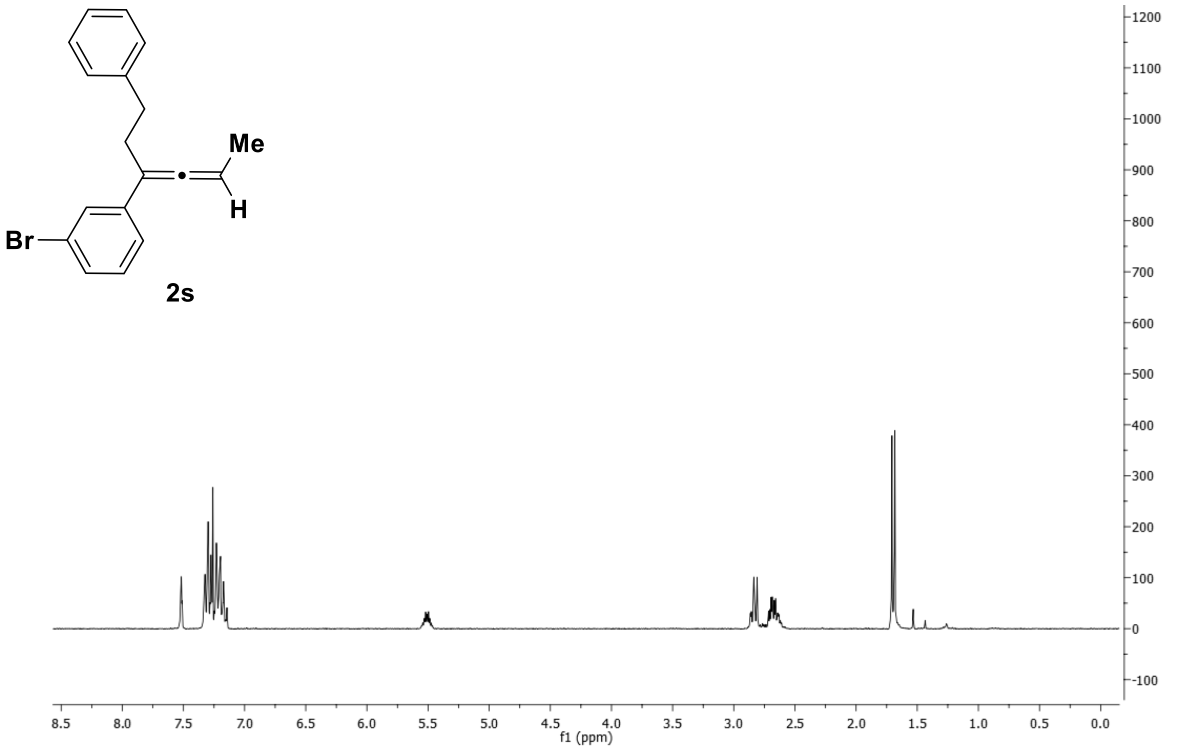
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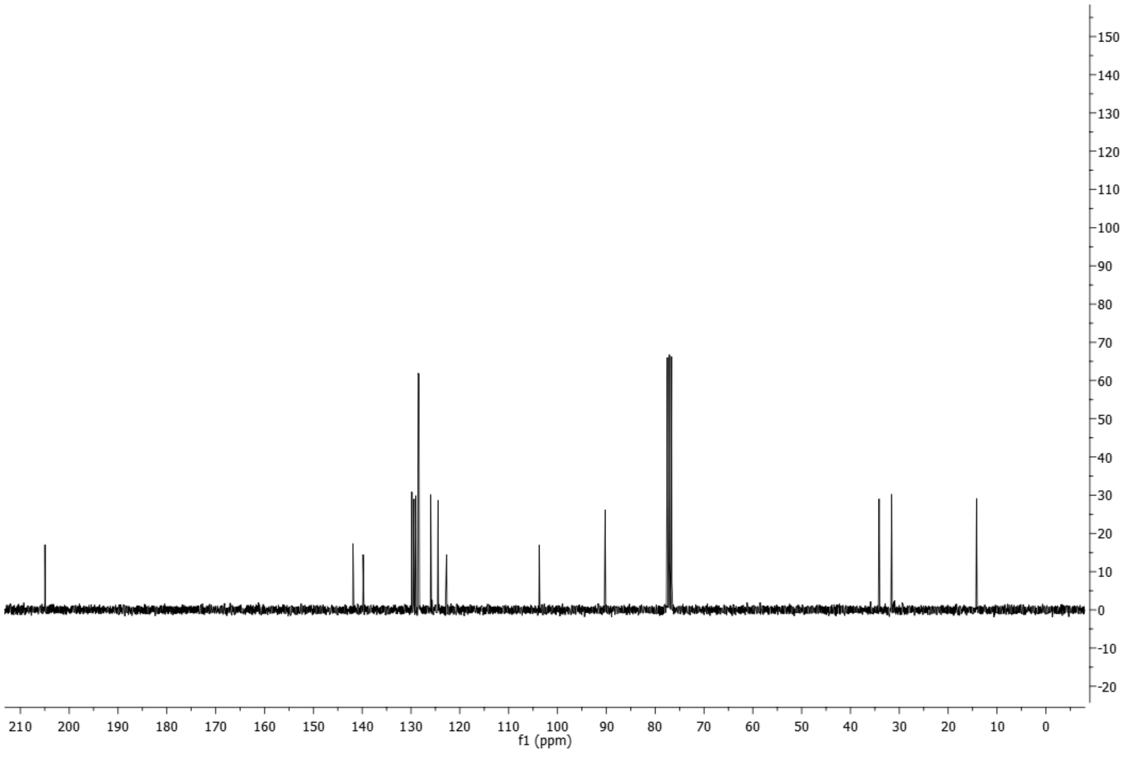
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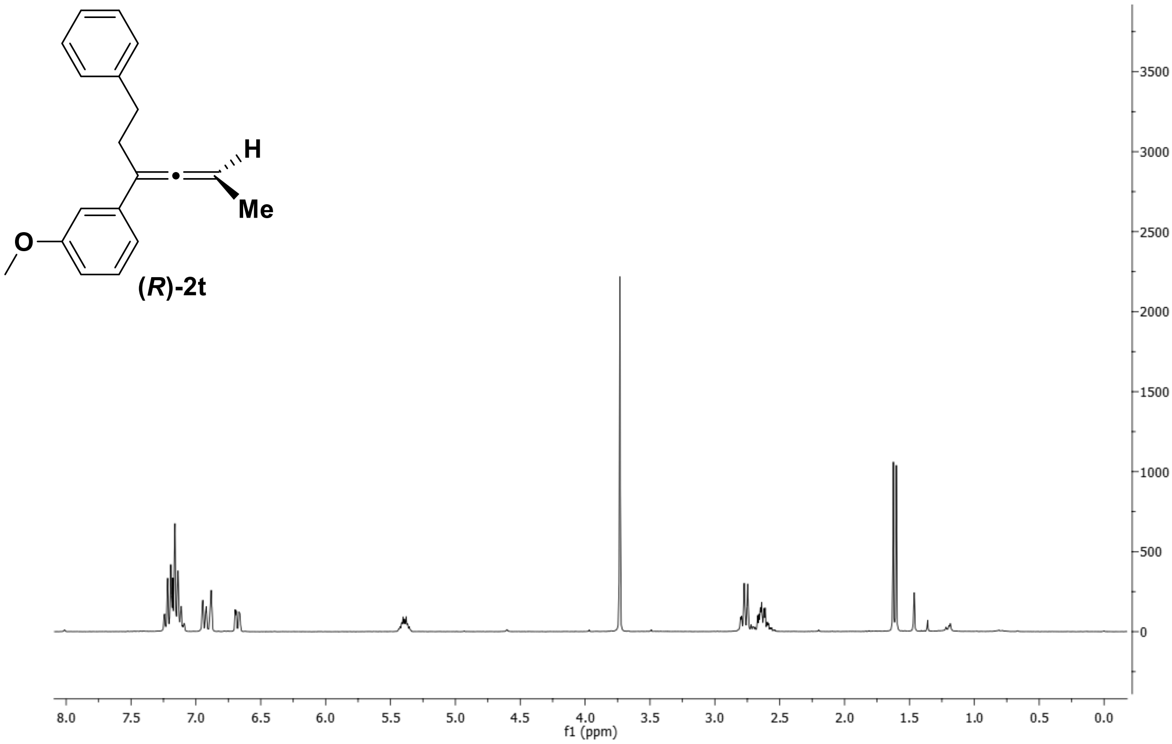
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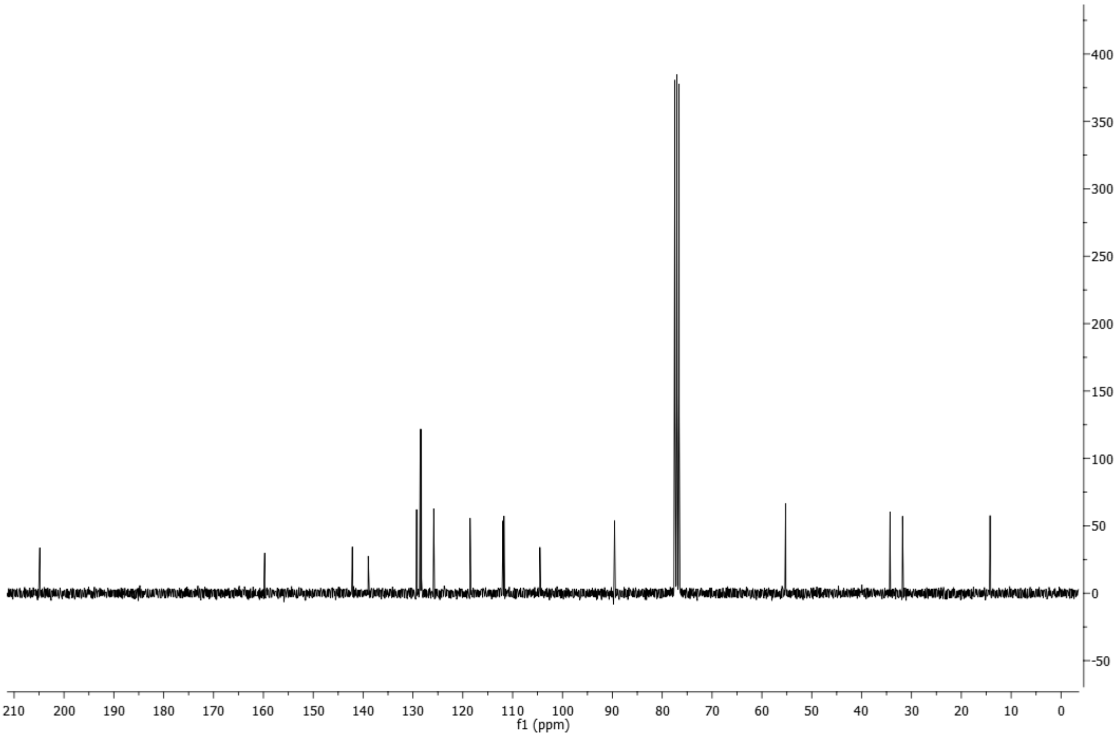
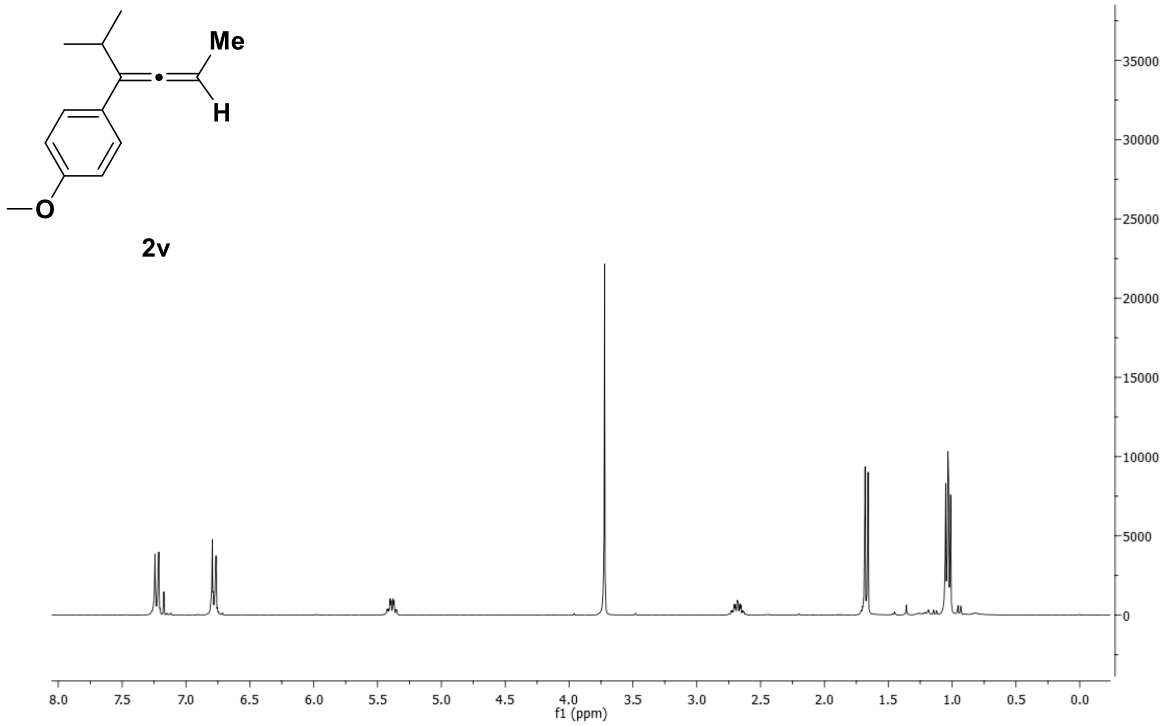
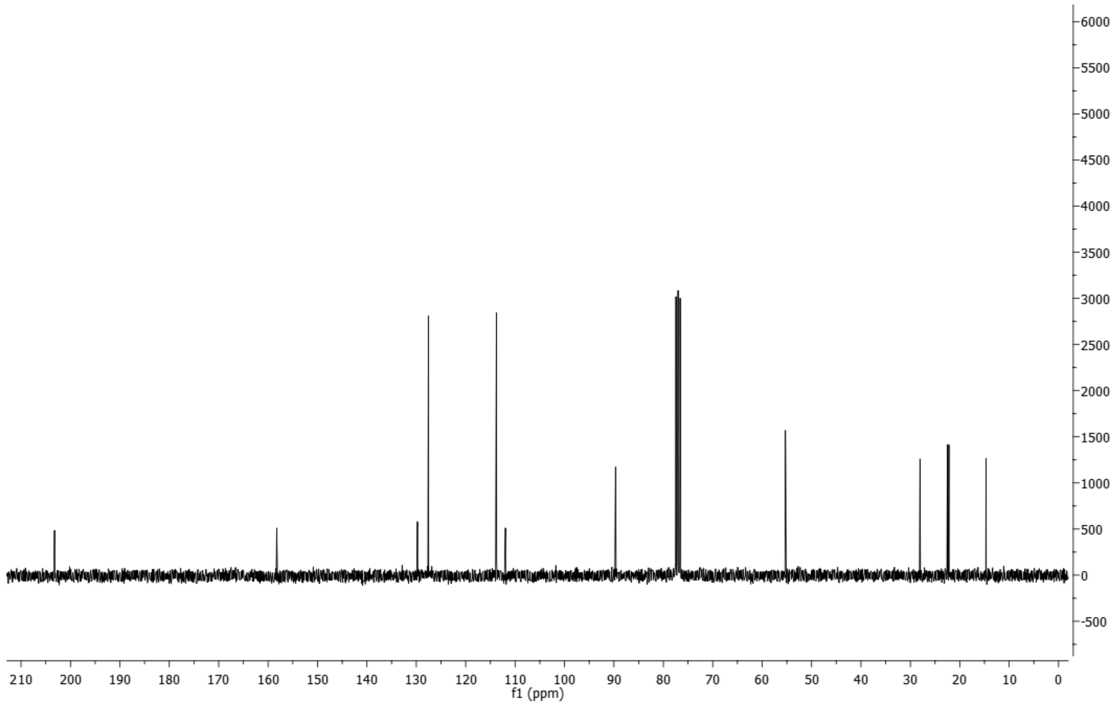
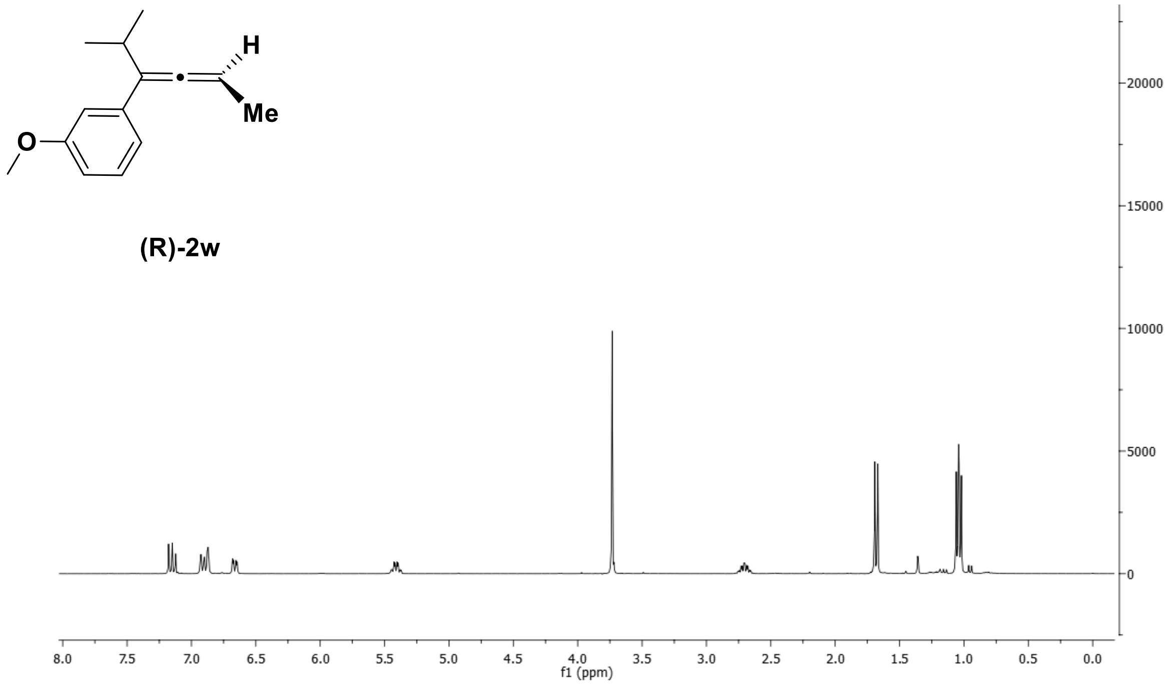
f1 (ppm)

(*R*)-2t

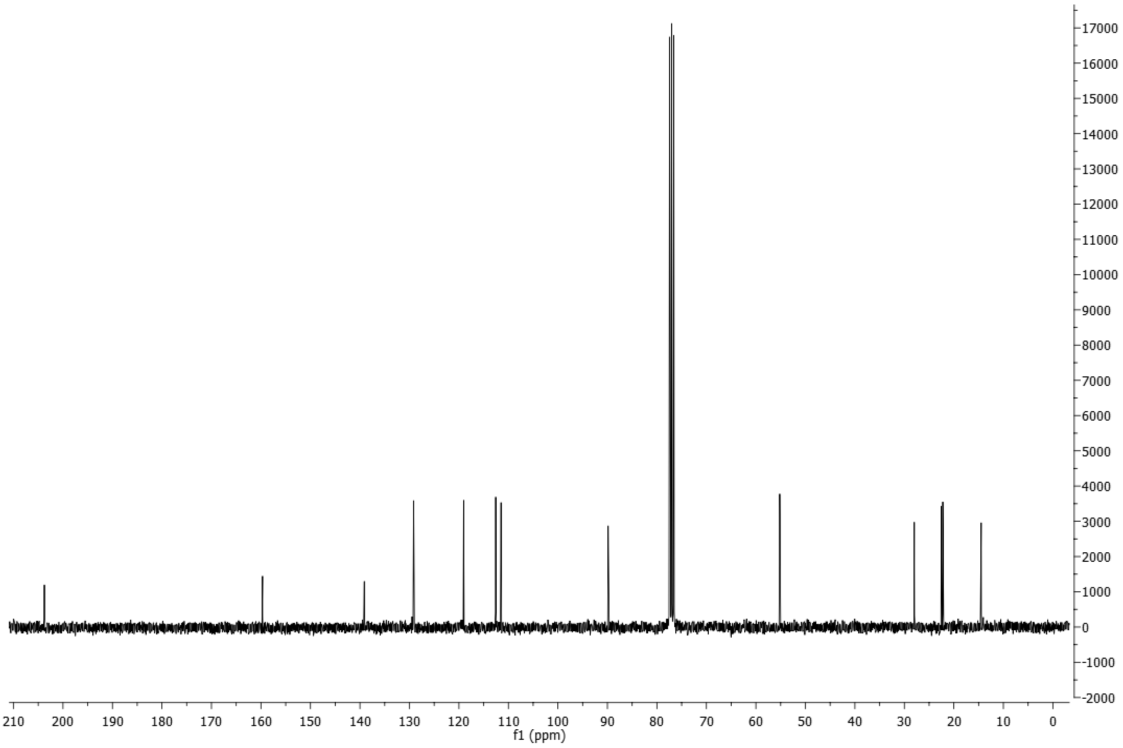

400
350
300
250
200
150
100
50
0
-50
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

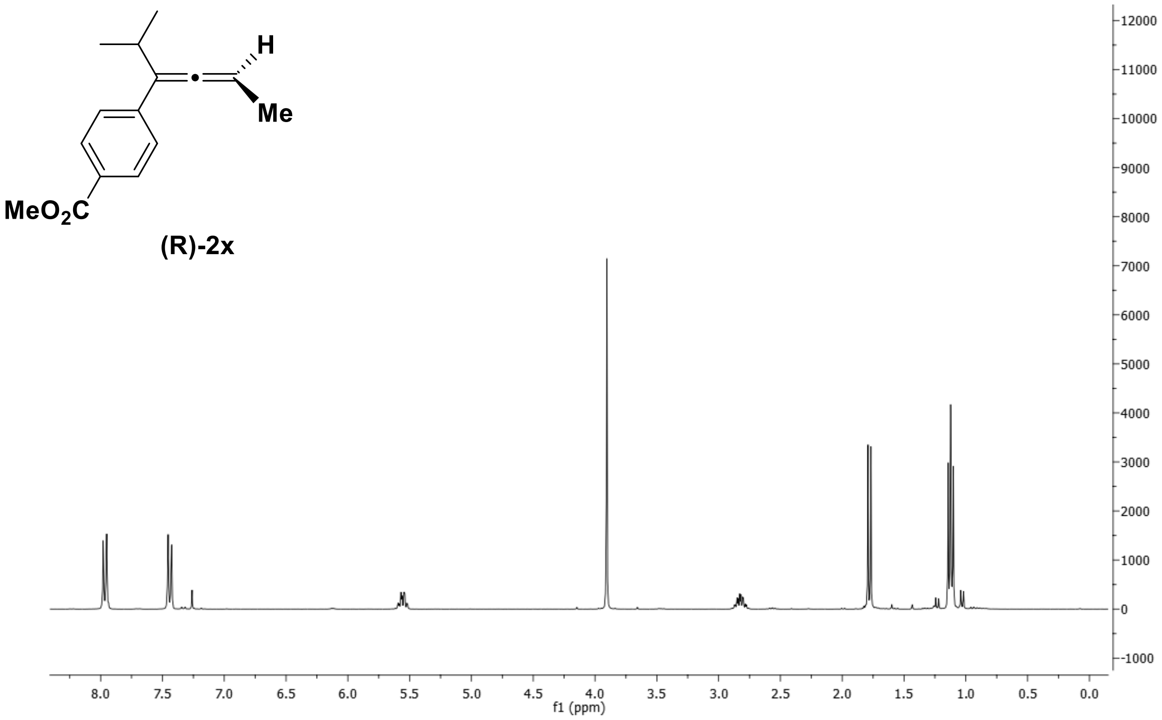

Me
H
O
2v
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
35000
30000
25000
20000
15000
10000
5000
0


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500

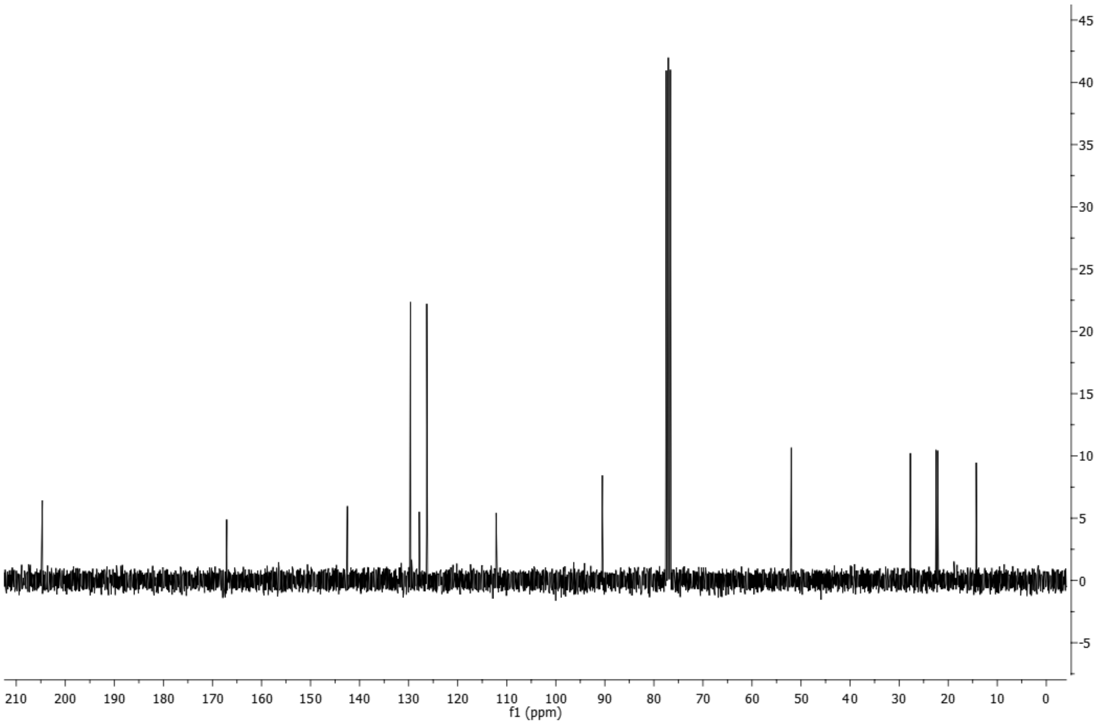

H
Me
O
20000
15000
10000
5000
0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

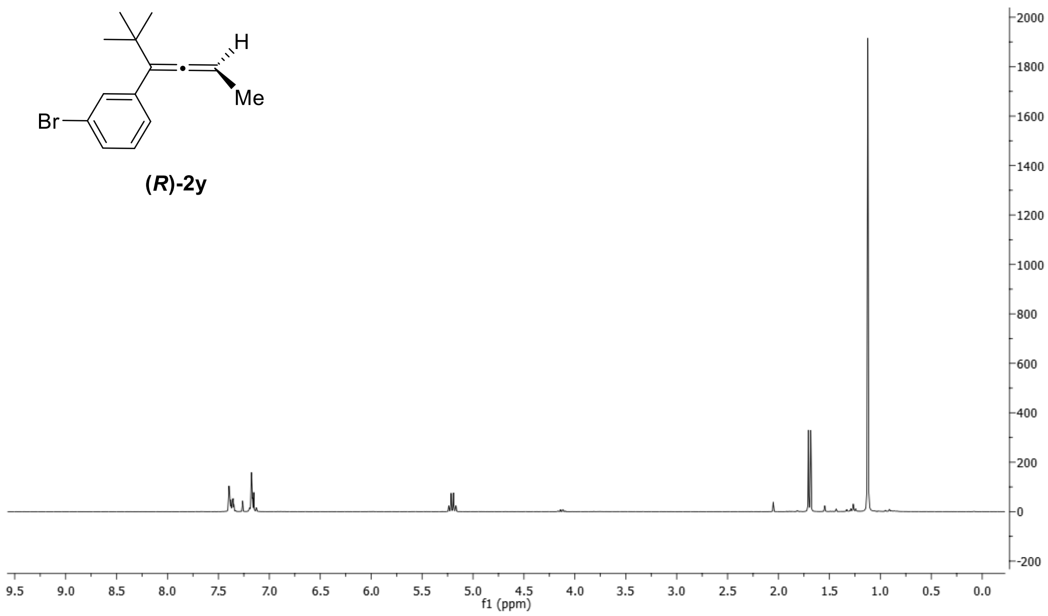
(R)-2w


17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H
Me
MeO2C
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

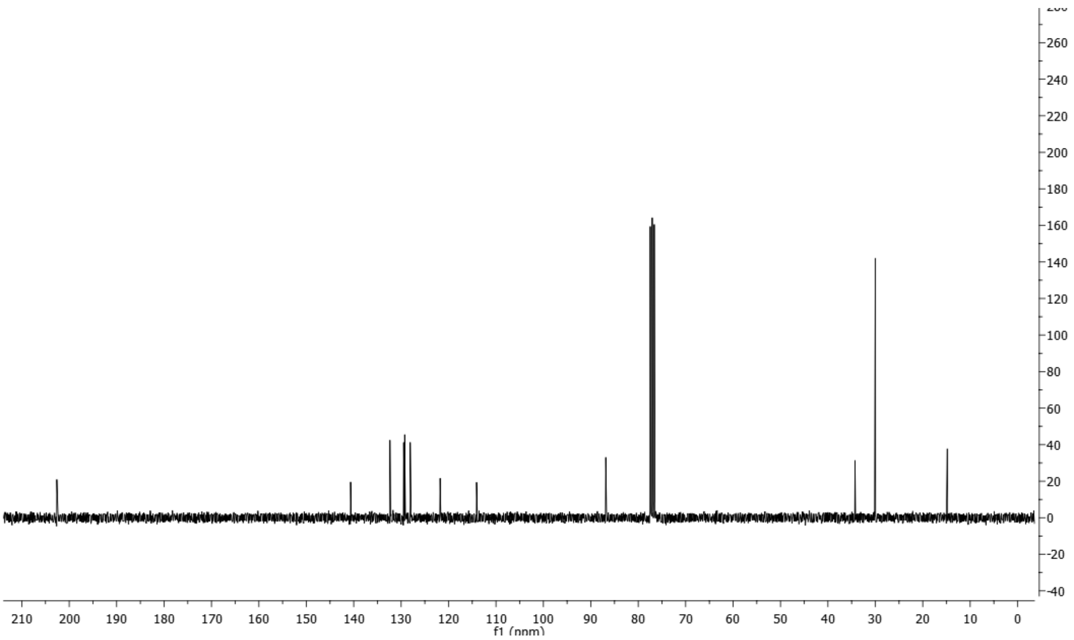
(R)-2x


45
40
35
30
25
20
15
10
5
0
-5
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

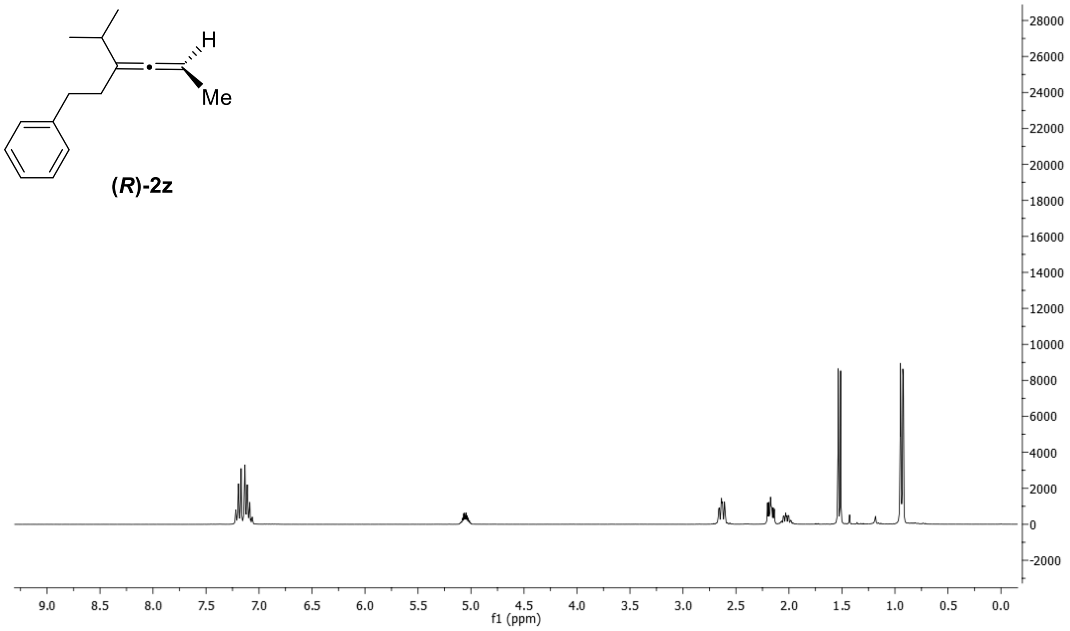


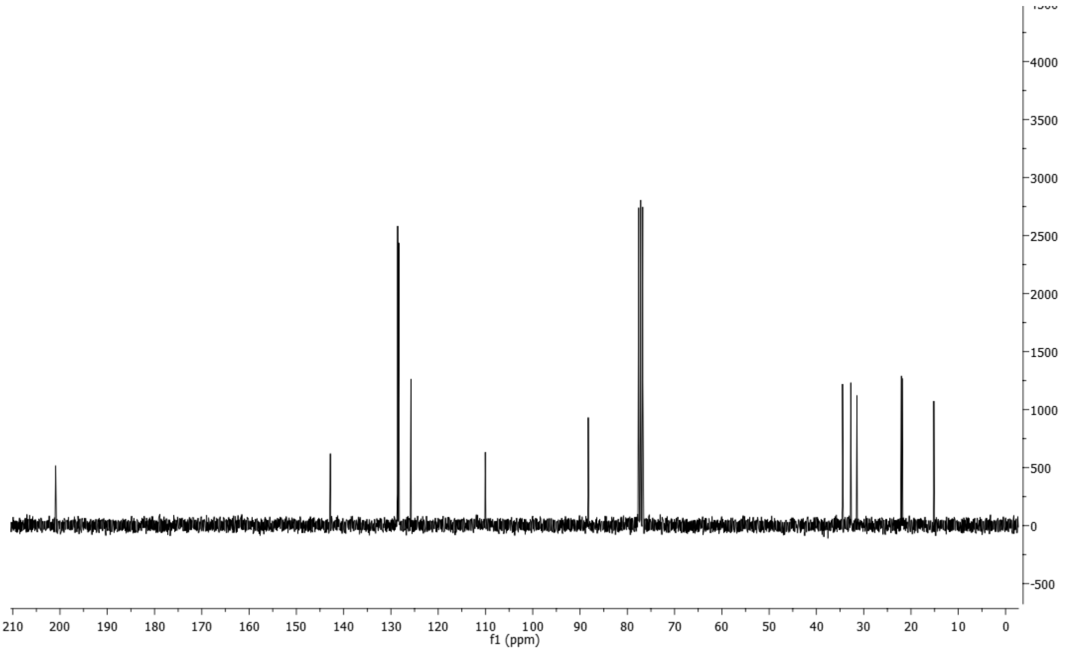
(*R*)-2y

Br
H
Me
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

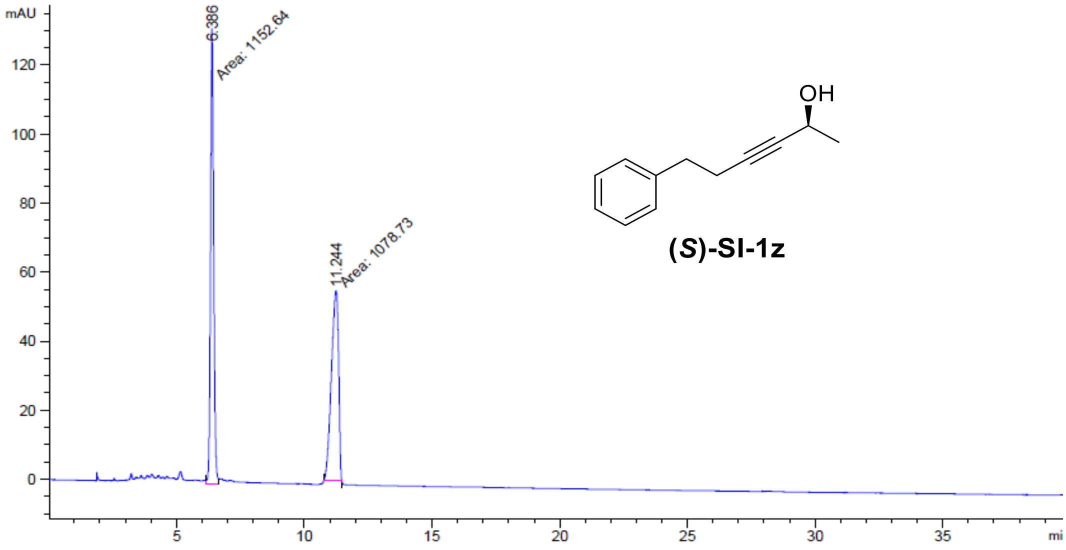


260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


H
Me
(R)-2z
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

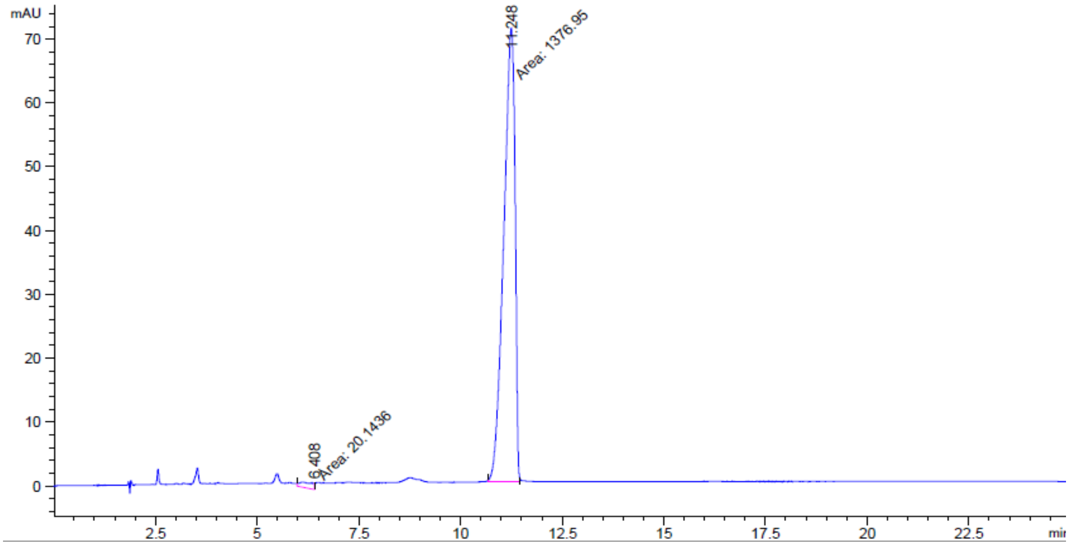

4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

8 SFC CROMATOGRAMS

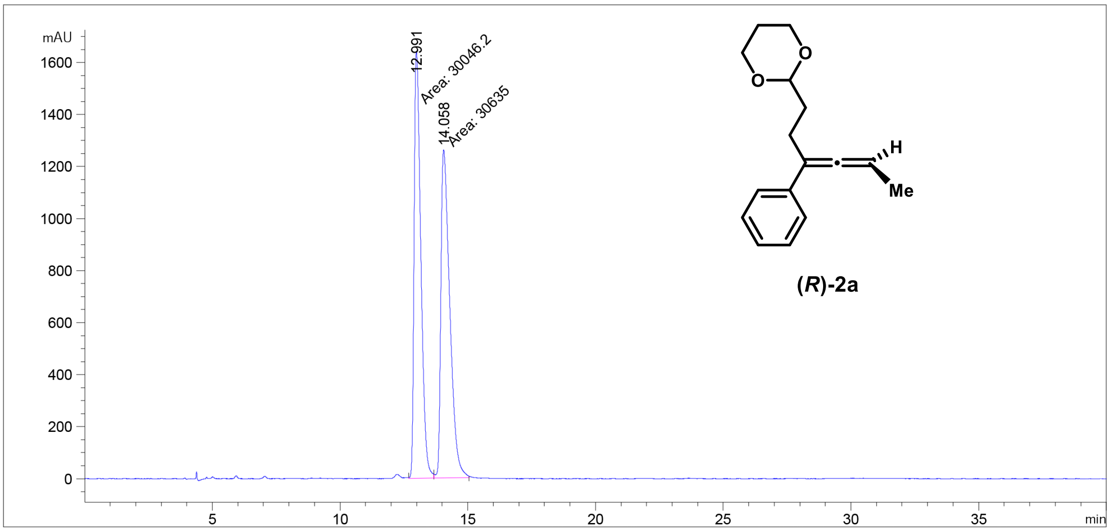


(*S*)-SI-1z

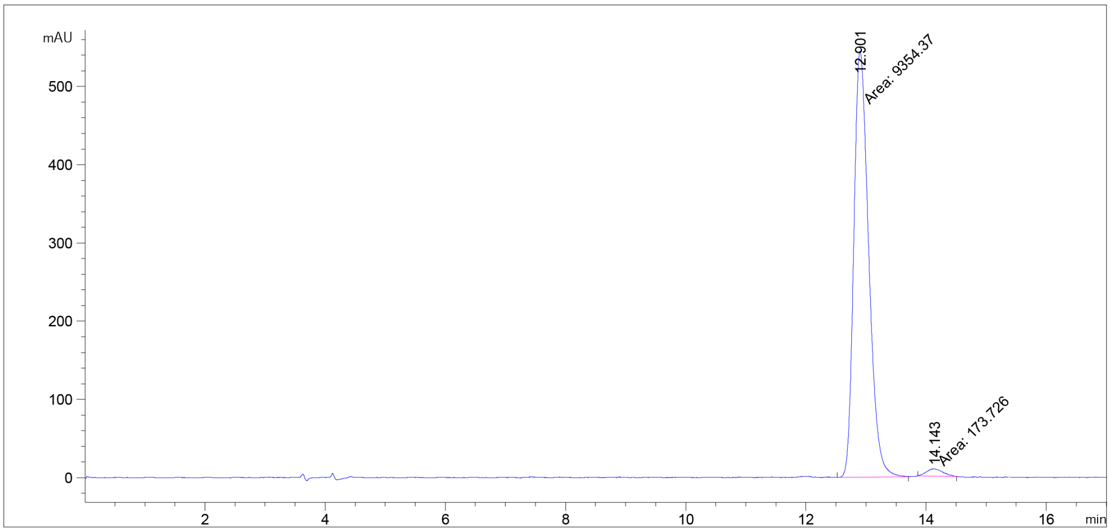
```
Peak RetTime Type  Width     Area      Height     Area  
  #   [min]        [min]   [mAU*s]     [mAU]        %   
----|-------|----|-------|----------|----------|--------|
   1   6.386 MM    0.1454 1152.63916  132.12480 51.6561
   2  11.244 MM    0.3267 1078.72974   55.02945 48.3439
```



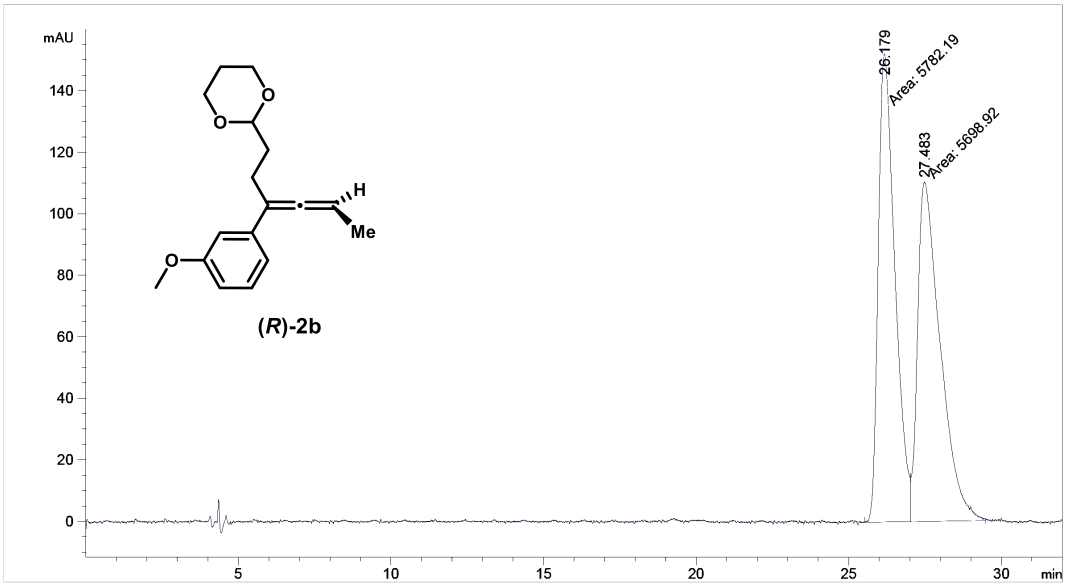
```
Peak RetTime Type  Width     Area      Height     Area  
  #   [min]        [min]   [mAU*s]     [mAU]        %   
----|-------|----|-------|----------|----------|--------|
   1   6.408 MM    0.3209   20.14356    1.04634  1.4418
   2  11.248 MM    0.3226 1376.94812   71.13525 98.5582
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  12.991 MF    0.3050 3.00462e4 1641.93506 49.5148
   2  14.058 FM    0.4047 3.06350e4 1261.52649 50.4852
```

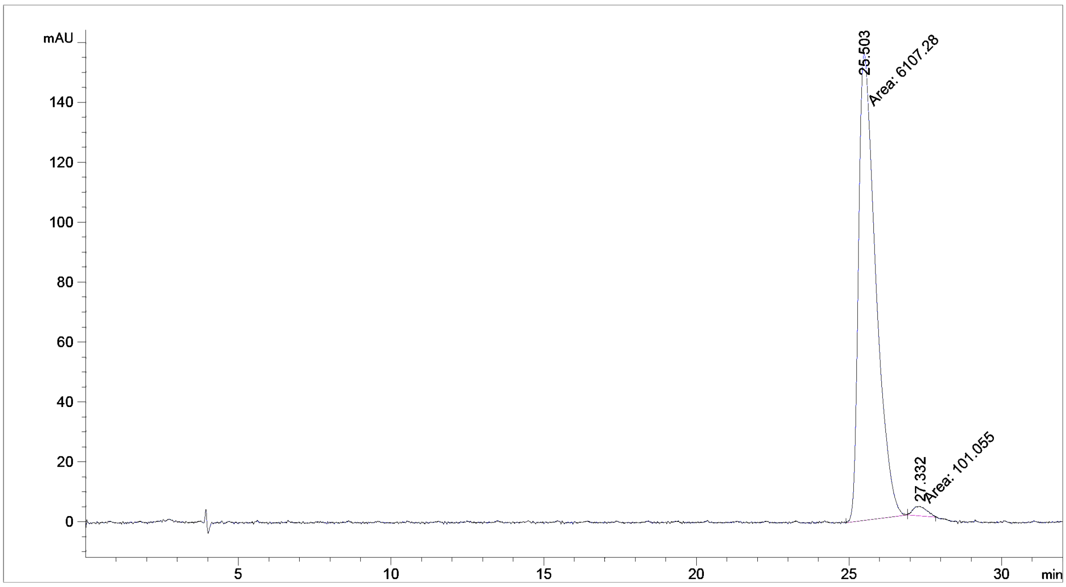


```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  12.901 MM    0.2863 9354.37109  544.54041 98.1767
   2  14.143 MM    0.3158  173.72585    9.16906  1.8233
```

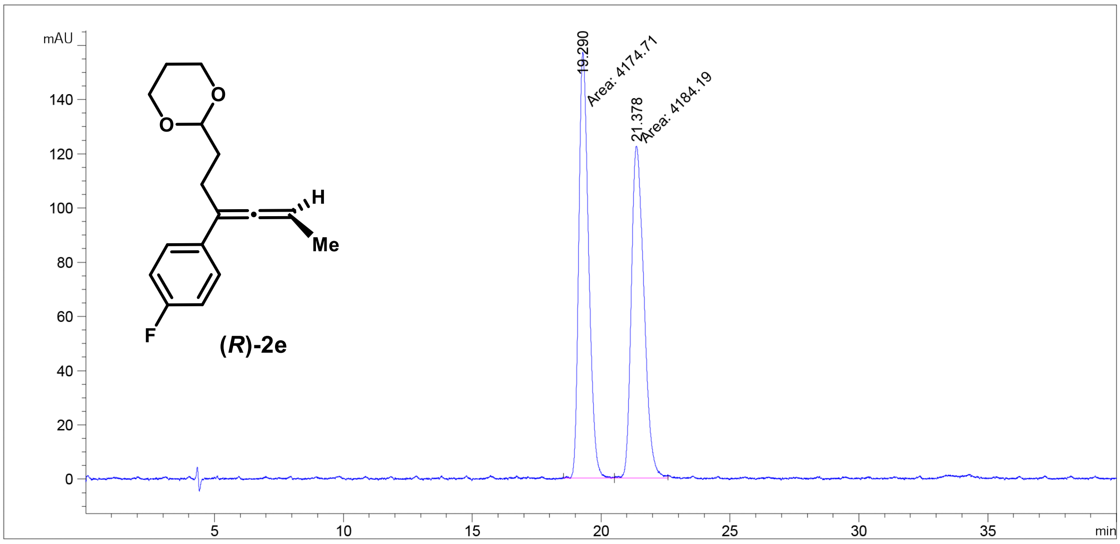


(*R*)-2b

```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  26.179 MF     0.6328 5782.19043  152.28716  50.3626
   2  27.483 FM     0.8602 5698.92236  110.42137  49.6374
```

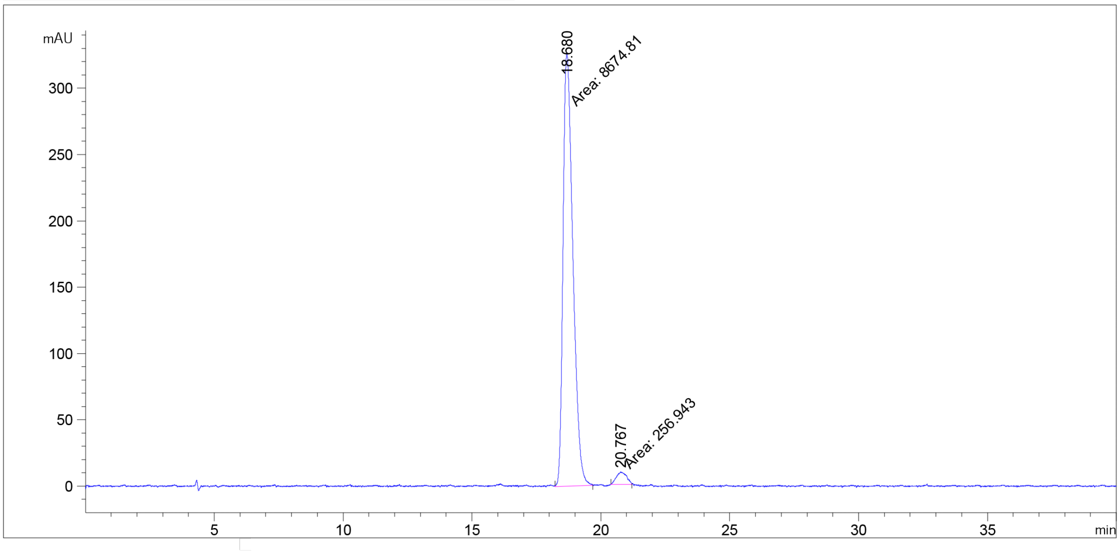


```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  25.503 MM     0.6536 6107.28223  155.73372  98.3723
   2  27.332 MM     0.5117  101.05537    3.29147   1.6277
```

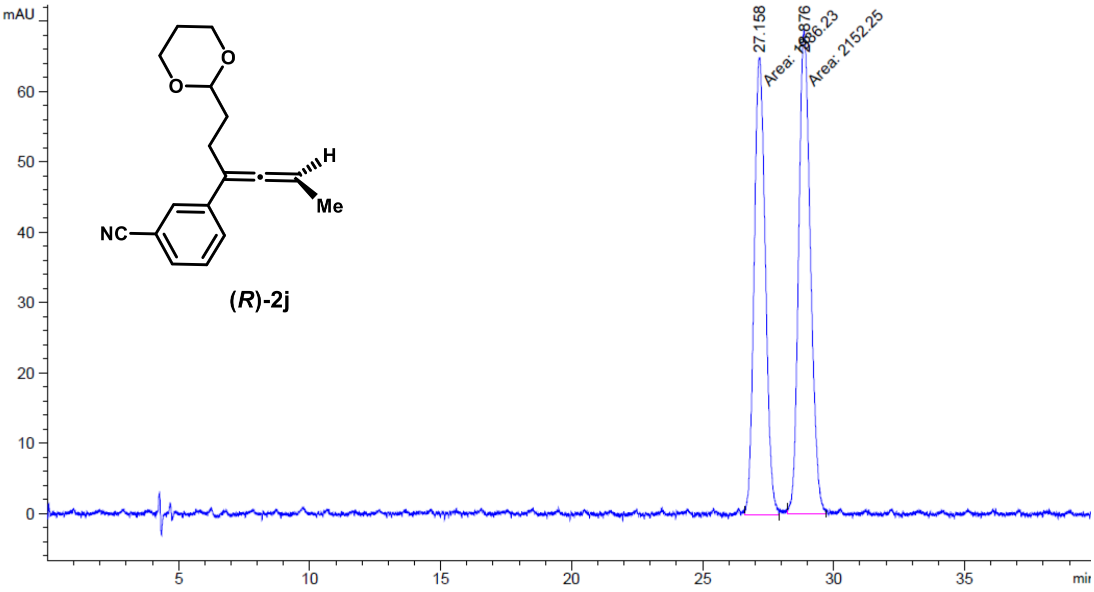


***(R)*-2e**

```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  19.290 MF    0.4431 4174.71191  157.02931  49.9433
   2  21.378 FM    0.5692 4184.19043  122.52728  50.0567
```

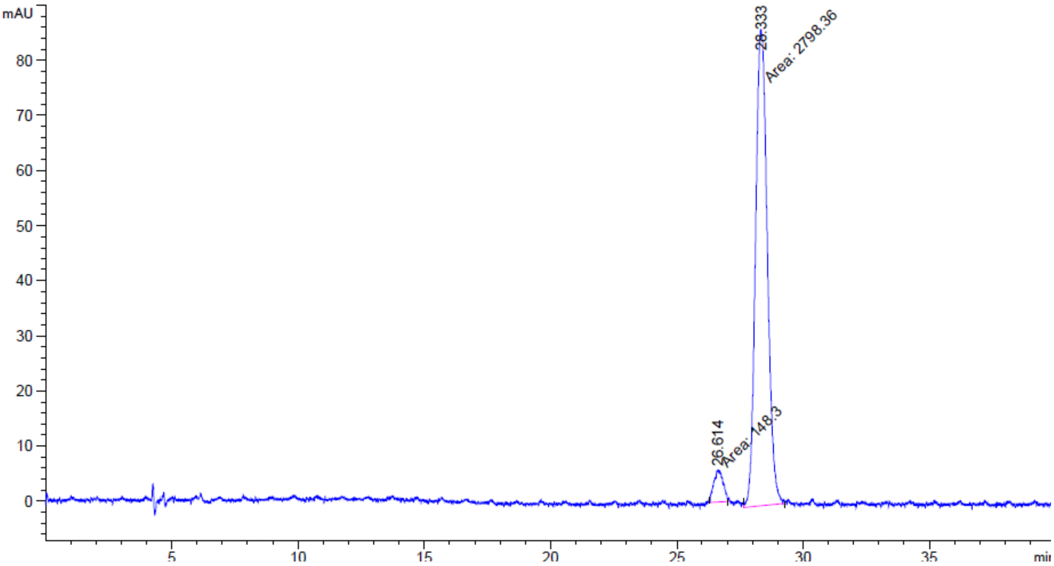


```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  18.680 MM    0.4418 8674.80664  327.22290  97.1233
   2  20.767 MM    0.4559  256.94296    9.39406   2.8767
```

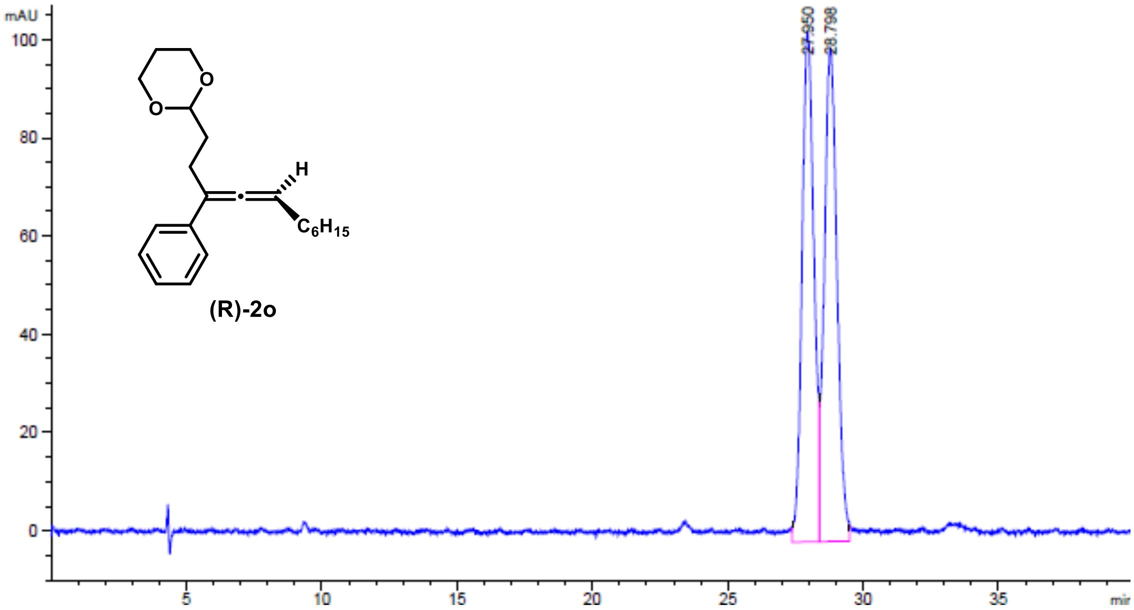


(*R*)-2j

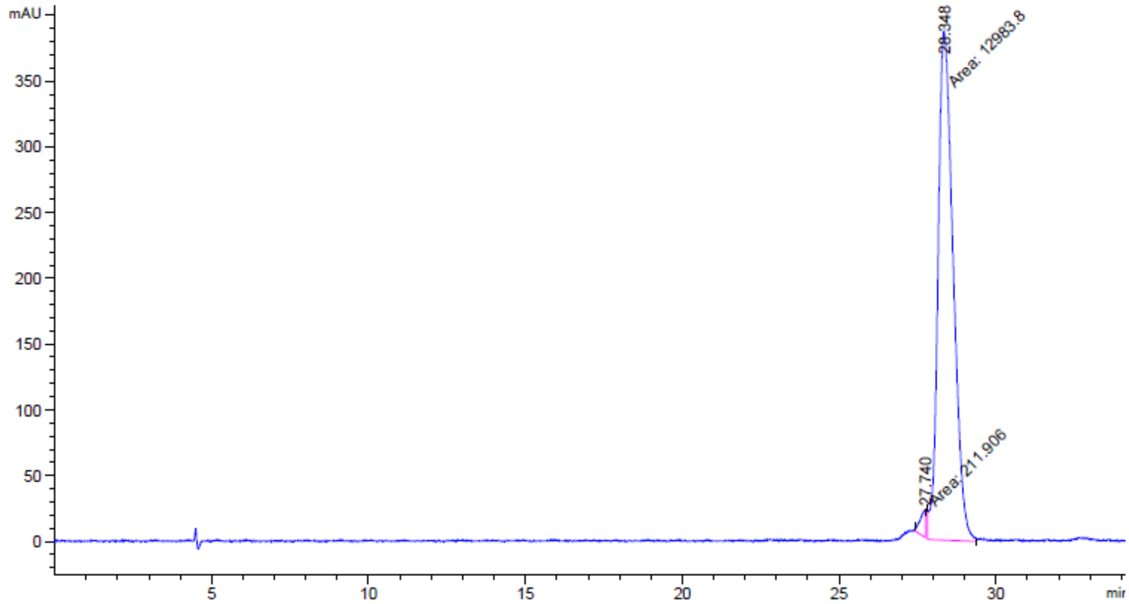
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  27.158 MM    0.4955 1936.23389   65.12766  47.3583
   2  28.876 MM    0.5228 2152.24829   68.60875  52.6417
```



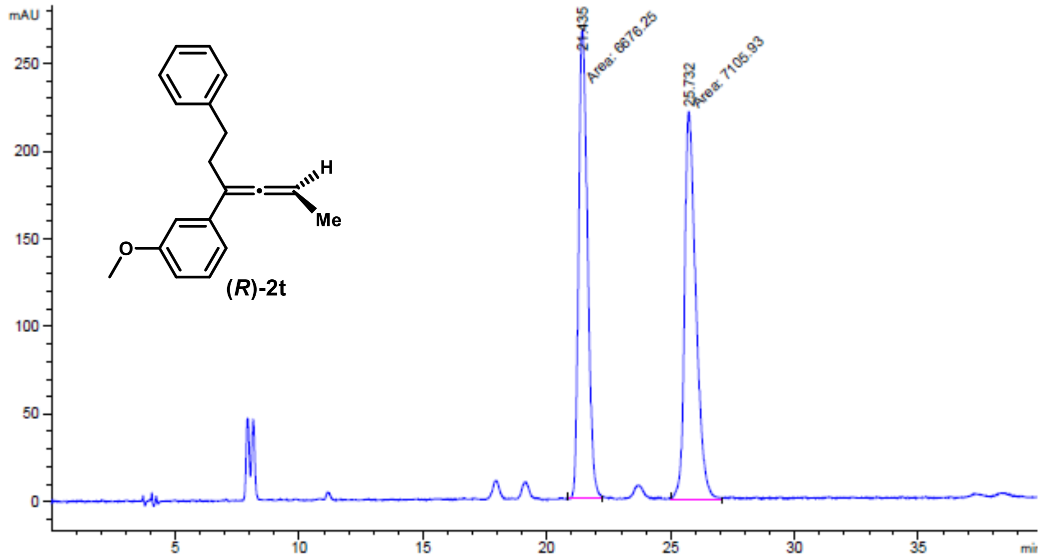
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  26.614 MM    0.4263  148.29996    5.79777   5.0328
   2  28.333 MM    0.5392 2798.36108   86.49338  94.9672
```


(R)-2o

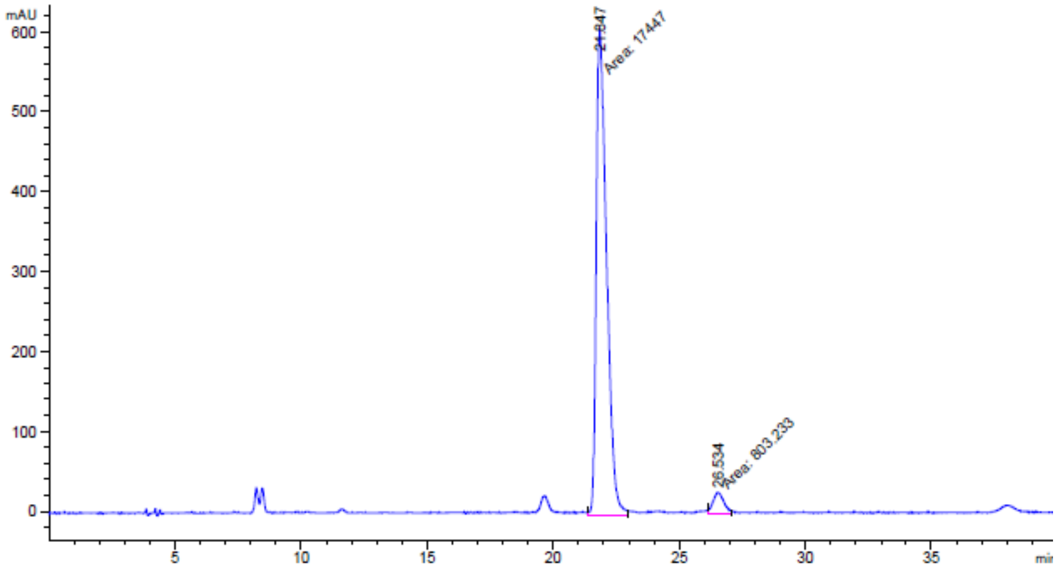
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  27.950 VV    0.3614 3168.53613  103.70884  49.0808
   2  28.798 VV    0.3866 3287.21826  100.50181  50.9192
```



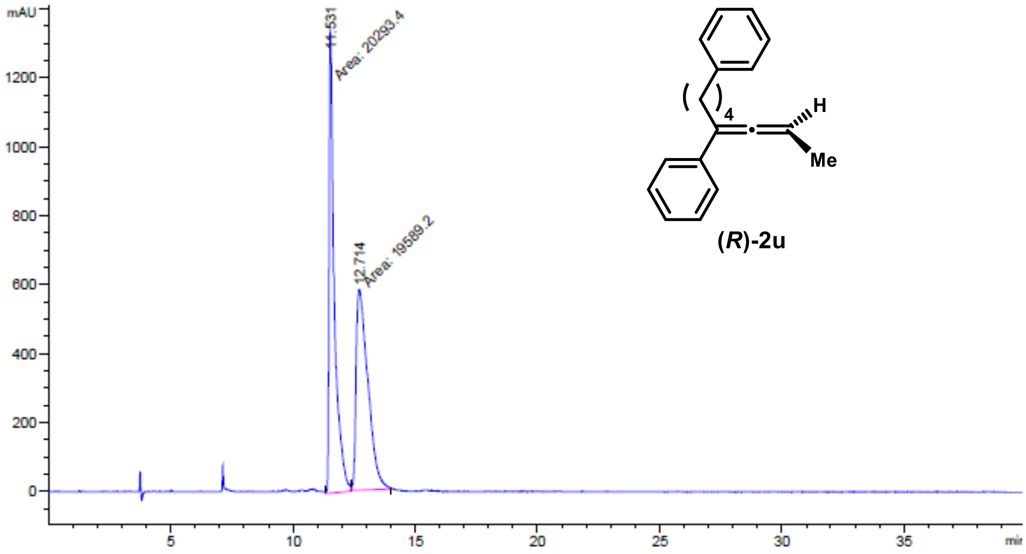
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  27.740 MM    0.1686  211.90648   20.94443   1.6059
   2  28.348 MM    0.5587 1.29838e4   387.30658  98.3941
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  21.435 MM    0.4164 6676.24658  267.22153  48.4412
   2  25.732 MM    0.5333 7105.93164  222.06223  51.5588
```

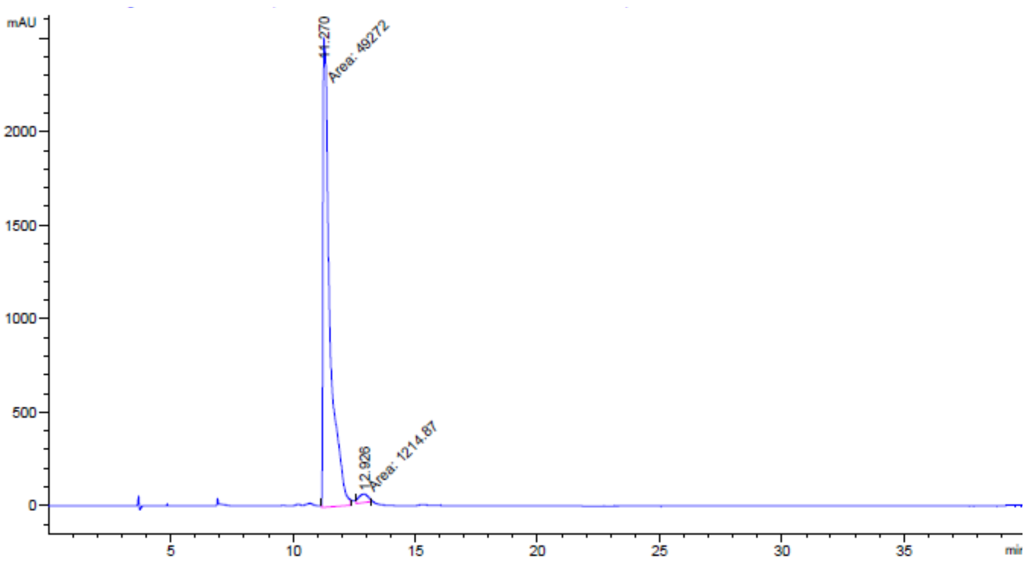


```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  21.847 MM    0.4784 1.74470e4  607.79889  95.5988
   2  26.534 MM    0.5051  803.23254  26.50383   4.4012
```

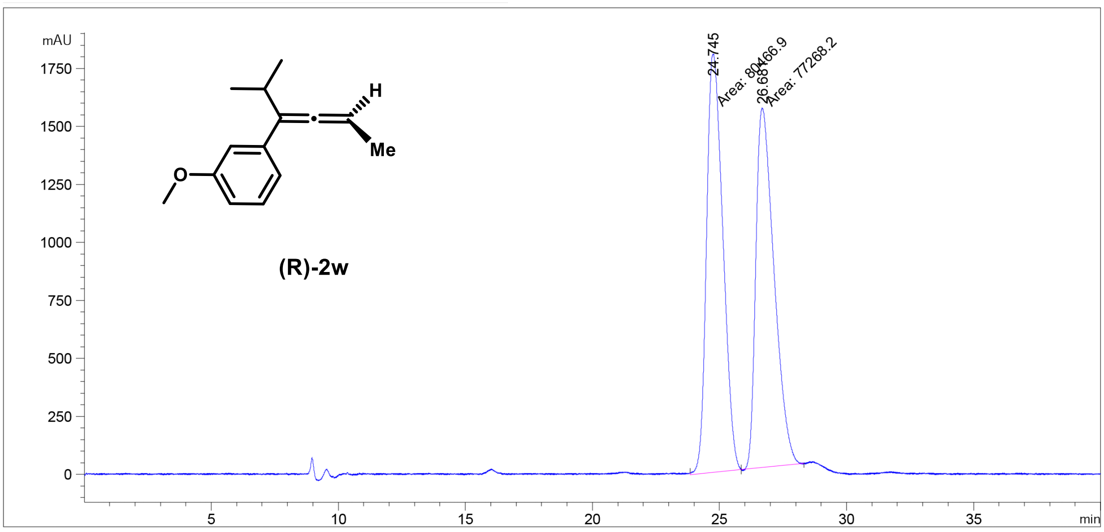


(*R*)-**2u**

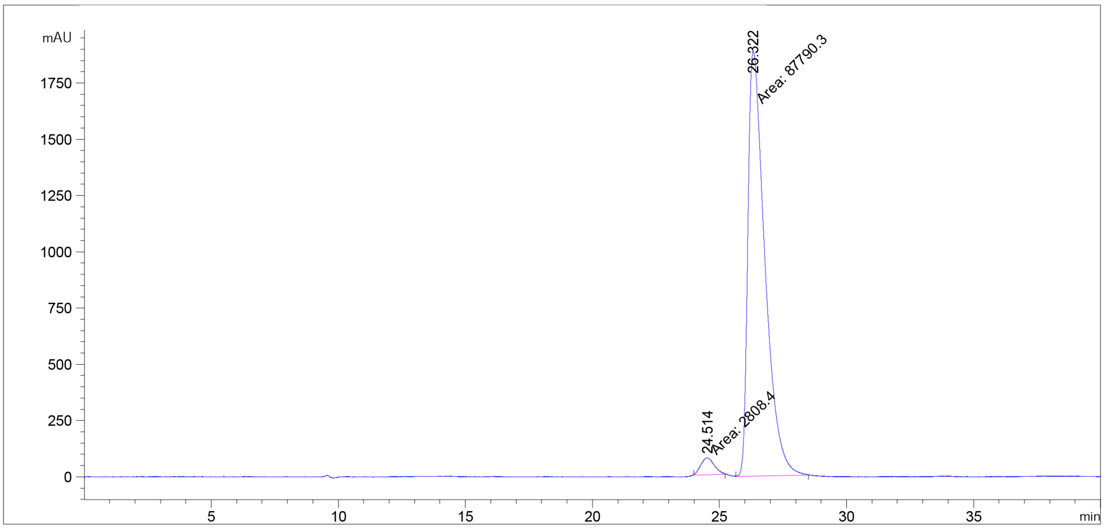
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  11.531 MM    0.2510 2.02934e4 1347.72913 50.8827
   2  12.714 MM    0.5616 1.95892e4  581.32056 49.1173
```



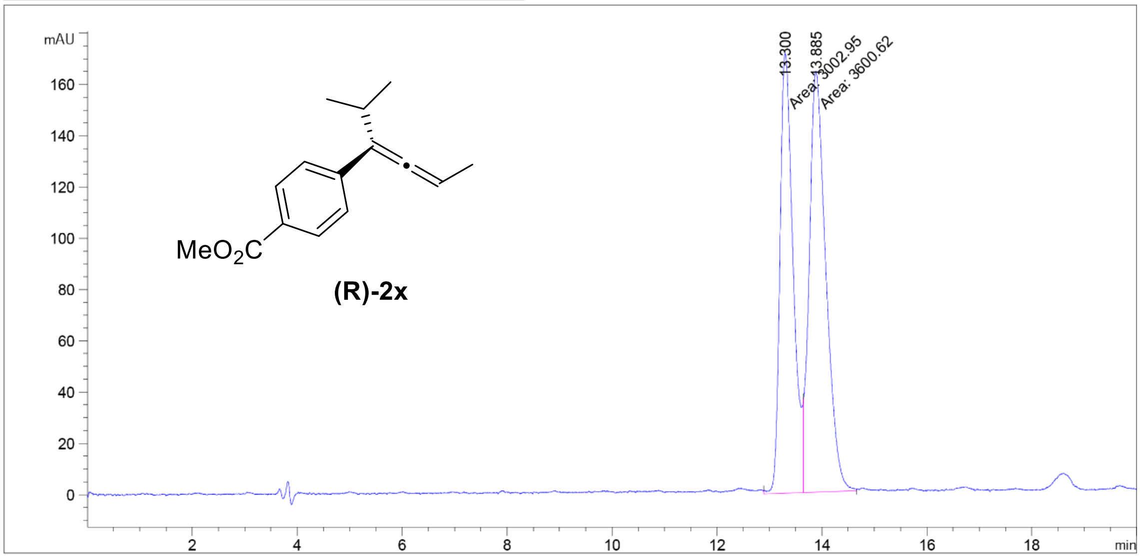
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  11.270 MM    0.3278 4.92720e4 2504.91699 97.5937
   2  12.926 MM    0.4479 1214.87415   45.20641  2.4063
```



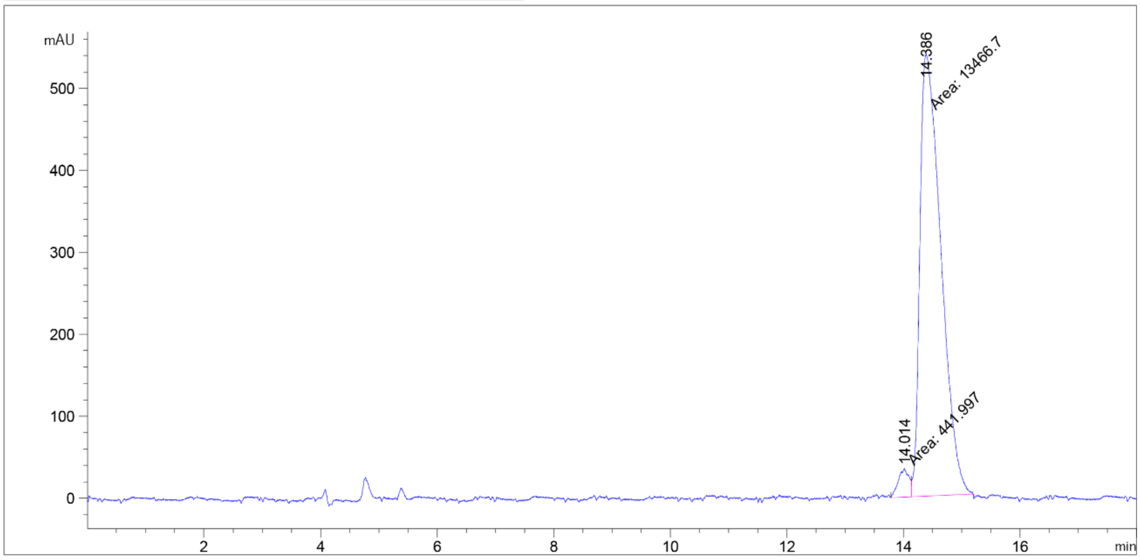
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]         [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1  24.745 MF     0.7434 8.04669e4  1804.02307  51.0139
  2  26.681 FM     0.8309 7.72682e4  1549.91821  48.9861
```



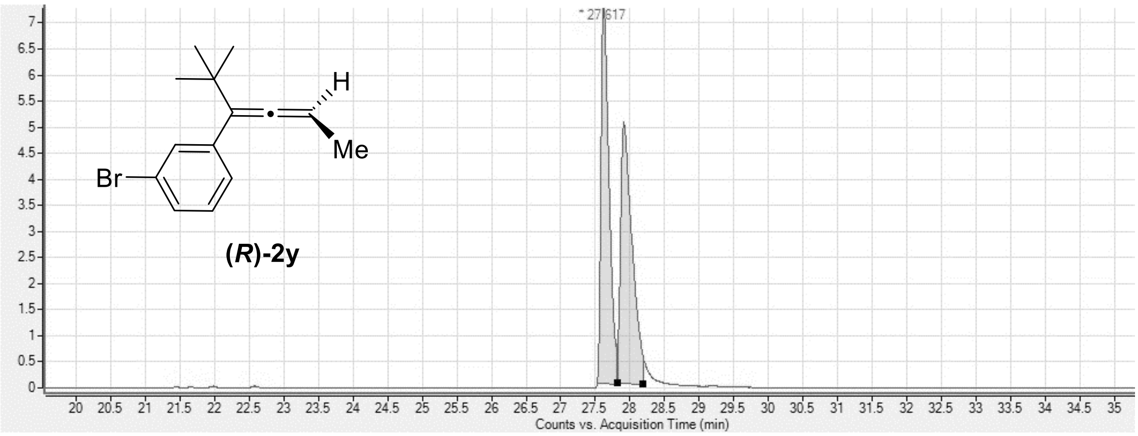
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]         [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1  24.514 MM     0.6154 2808.39893   76.06504   3.0998
  2  26.322 MM     0.7746 8.77903e4  1888.90845  96.9002
```

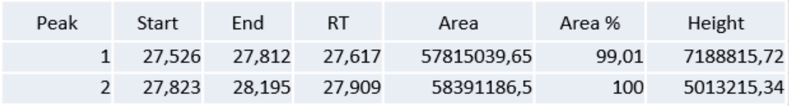


```
Peak RetTime Type  Width      Area       Height      Area
  #    [min]       [min]    [mAU*s]      [mAU]         %
----|-------|----|-------|----------|----------|--------|
   1  13.300 MF    0.2919 3002.95361  171.43990  45.4747
   2  13.885 FM    0.3656 3600.61670  164.14279  54.5253
```

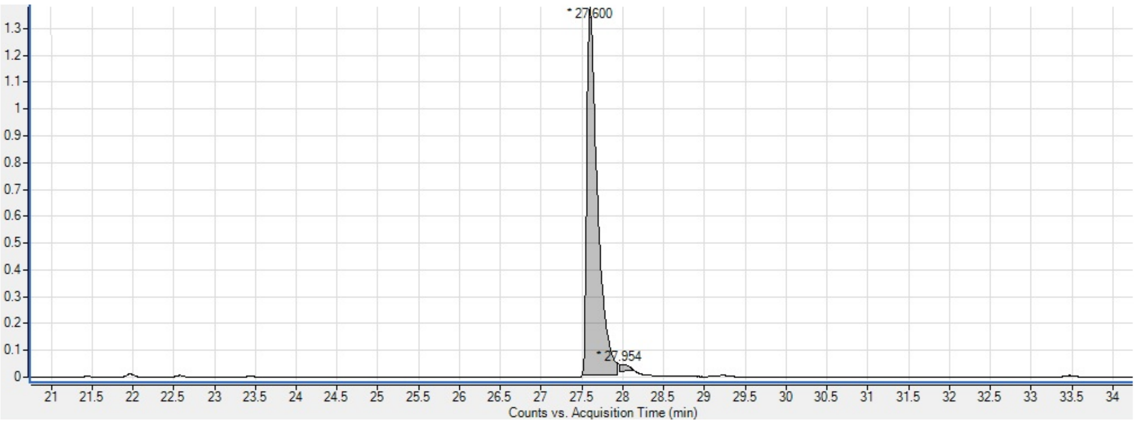


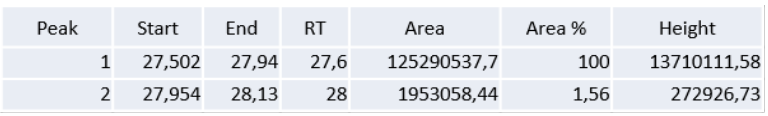
```
Peak RetTime Type  Width      Area       Height      Area
  #    [min]       [min]    [mAU*s]      [mAU]         %
----|-------|----|-------|----------|----------|--------|
   1  14.014 MF    0.2123  441.99741   34.69642   3.1778
   2  14.386 FM    0.4161 1.34667e4  539.39026  96.8222
```



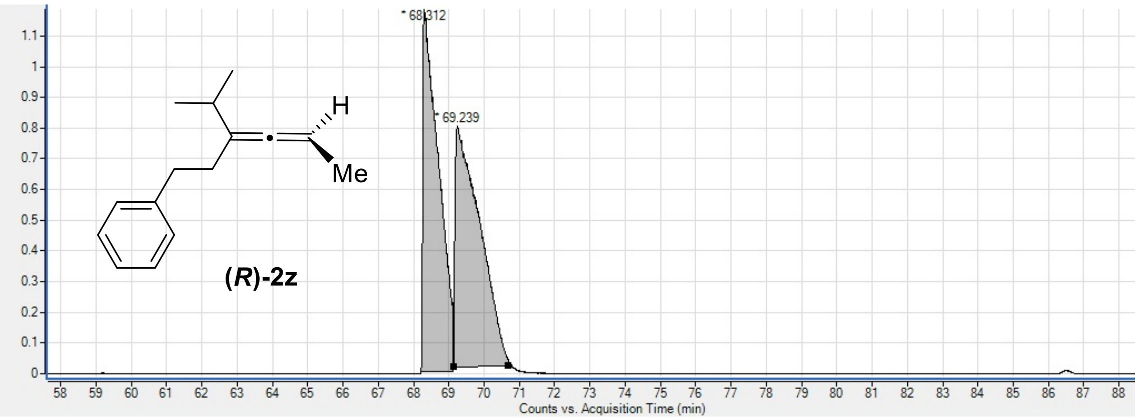


Peak	Start	End	RT	Area	Area %	Height
1	27,526	27,812	27,617	57815039,65	99,01	7188815,72
2	27,823	28,195	27,909	58391186,5	100	5013215,34



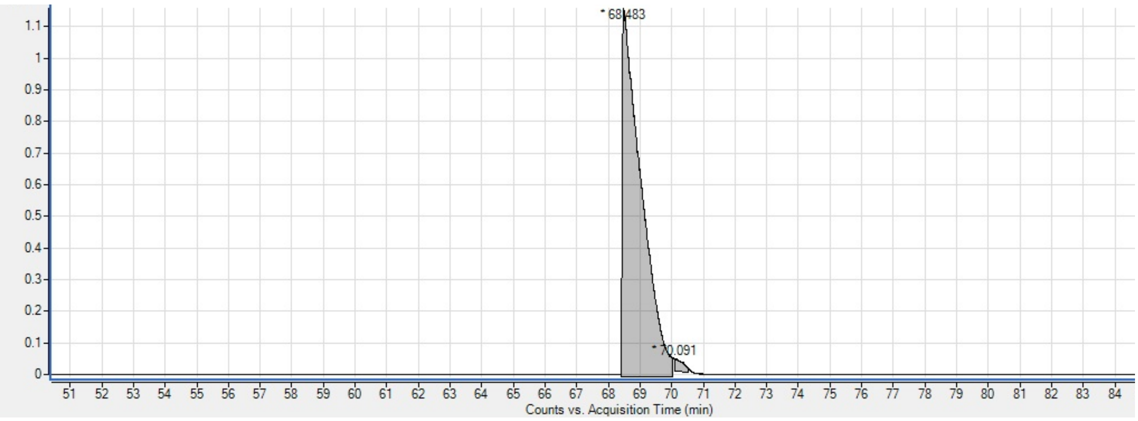


Peak	Start	End	RT	Area	Area %	Height
1	27,502	27,94	27,6	125290537,7	100	13710111,58
2	27,954	28,13	28	1953058,44	1,56	272926,73



(*R*)-2z

Peak	Start	End	RT	Area	Area %	Height
1	68,214	69,124	68,312	36503417,47	95,12	1180333,3
2	69,136	70,686	69,239	38378069,77	100	785301,23



Peak	Start	End	RT	Area	Area %	Height
1	68,426	70,034	68,483	46915341,96	100	1154087,64
2	70,086	70,715	70,091	799440,78	1,7	38877,59

9 REFERENCES

---

[1] Knochel, P. *Synthesis-Stuttgart*, **2006**, *5*, 890.
[2] Guisán-Ceinos, M.; Martín-Heras, V.; Tortosa, M. *J. Am. Chem. Soc.* **2017**, *139*, 8448.
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