Asymmetric Synthesis of Functionalized *trans*-Cyclopropoxy Building Block for Grazoprevir

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Supporting Information

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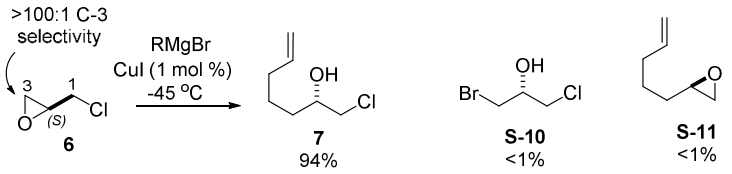
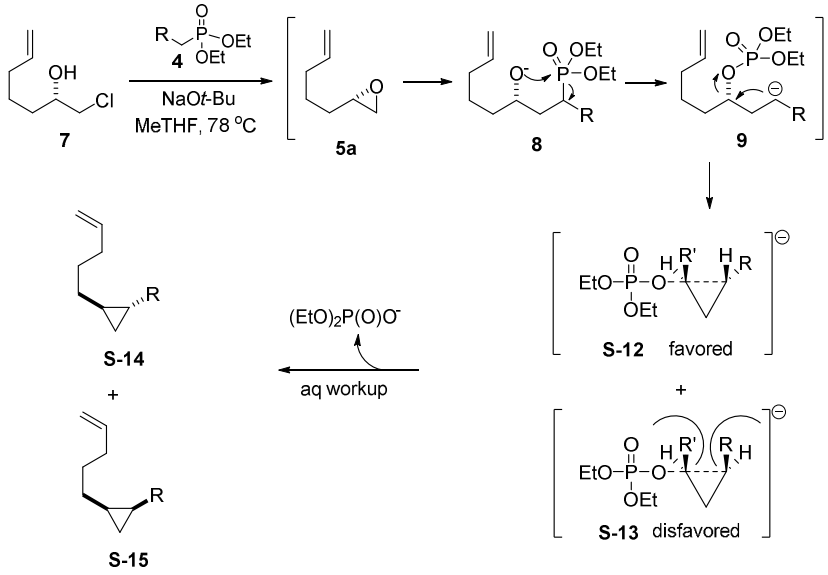
1. Reaction temperature and addition rate effects on epichlorohydrin opening



The temperature effect and addition rate of 3-butenyl magnesium bromide on epichlorohydrin opening were studied. Treatment of (*S*)-epichlorohydrin (**6**) with 3-butenyl magnesium bromide in the presence of 1 mol % CuI afforded chlorohydrin **7** in >94% yield with >100:1 regioselectivity (C-3 vs. C-1 attack on epichlorohydrin), as the C-1 attack gave the corresponding epoxide **S-11**. In the absence of CuI, the formation of 2-bromo-3-chloro-propanol (**S-10**) became the major product, which is presumably promoted by Mg^{2+} salt acting as a Lewis acid. Further studies showed the formation of **S-10** was reliant on temperature and addition rate of Grignard reagent. For example, addition of 3-butenyl magnesium bromide over 15 h at -10 °C resulted in formation of ~10% of **S-10**. As the Grignard reagent in the reaction mixture starved due to the prolonged slow addition, the competition of the Br^- opening pathway became significant. However, this side reaction was easily suppressed to <1% by maintaining the reaction temperature at -45 °C even with extended slow addition of Grignard reagent, because the Br^- opening pathway was much slower than the desired Cu(I) promoted Grignard addition at low temperature.

2. Diastereoselectivity of cyclopropanation



entry	phosphonate **4**	yield (%)	trans/cis
1	R = MeCO	45[a]	>97:3[b]
2	R = CN	28[a]	3:1[a]
3	R = CO_2Et	71[a]	>97:3[b]
4	R = $CONMe_2$	87[c]	>200:1[c]

[a]Determined by GC analysis. [b]Determined by ^1H NMR analysis. [c]Determined by HPLC analysis.

The diastereoselectivity of cyclopropanation can be affected by the steric bulkiness of the R group in phosphonate **4**. Presumably, the bulky size of the *N.N*-dimethyl carbonyl in intermediate **9** (entry 4, R = $CONMe_2$), which could be derived from intermediate **8** through a [1,3]-phosphorus–Brook rearrangement,[7,8] played a key role to distinguish the sterically favored intramolecular S_N2 displacement intermediate **S-12** vs. the disfavored intermediate **S-13**, resulting the desired *trans* isomer **S-14** in high selectivity. In contrast, a smaller nitrile group in intermediate **9** (entry 2, R = CN) results in less steric hindrance/repulsion in intermediate **S-13** and therefore reduces the energy difference with **S-12** to give lower cis/trans selectivity on cyclopropanation.[s1]

3. Analytical HPLC and GC conditions

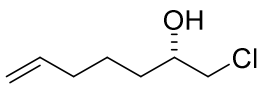
GC method conditions: Restek RTX-35 Amine column, 30 m x 0.32 mm, 1µm df or equivalent, injector temperature: 180 ^oC, detector temperature: FID at 220 ^oC; Carrier Gas: Helium, column flow: 2.0 mL/min.

HPLC method conditions: Atlantis DC18 column, 3µm particle size, 150 × 4.6 mm; mobile phase: 0.1% H_3PO_4 in water / acetonitrile, 1.8 ml/min flow rate, 30 °C, detection at 210 nm.

Chiral GC method conditions for amide **10** and alcohol **14**: Restek Rt-βDEXsa column, 30 m x 0.25 mm, 0.25µm film, injector temperature: 220 ^oC , detector: FID at 230 ^oC; Carrier Gas: Helium, column flow: 1.8 mL/min.

Chiral HPLC method conditions for ketone **11**: AD-RH column, 5µm particle size, 150 × 4.6 mm; mobile phase: isocratic 0.05% CF_3CO_2H in water / acetonitrile, 0.5 ml/min flow rate, 25 °C, detection at 210 nm.

4. Experimental procedure for the preparation of building block 2[s2]



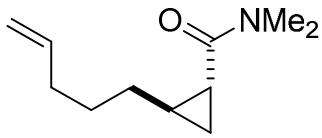
(*S*)-1-Chlorohept-6-en-2-ol (7). 4-Butenyl magnesium bromide is commercially available and can also be prepared as follows: To a 1-L three-neck round-bottom flask equipped with an overhead stirrer, a condenser, an additional funnel, and a N_2 inlet were charged 2-MeTHF (290 mL) and magnesium turnings (9.0 g, 0.37 mol), followed by iodine (0.45 g, 0.002 mol). The mixture was heated to 70 °C and agitated for 1.5 h. 4-Bromo-1-butene (47.5 g, 0.352 mol) was added dropwise over 1.5 h at 70 °C. The mixture was aged 6 h at 70 °C, and then cooled to ambient temperature.

To a mixture of (*S*)-(+)-epichlorohydrin (25.0 g, 0.27 mol) in 2-MeTHF (150 mL) and CuI (2.56 g, 0.013 mol) at -45 – -50 °C was added the above Grignard reagent dropwise, while maintaining the reaction temperature between -45 – -50 °C. The reaction mixture was aged for

[s1] Xu, F.; Murry, J. A.; Simmons, B.; Corley, E.; Filtch K.; Karady, S.; Tschaen, D. *Org. Lett.* **2006**, *17*, 3885–3888.
[s2] The entire process for the preparation of compound **2** has been scaled up on large scale (>100 Kg).

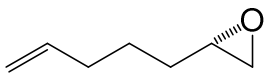
additional 1 – 2 h at -45 °C. Then, the reaction mixture was transferred to a solution of aqueous NH_4Cl (5 M, 375 mL). The quenched mixture was agitated at ambient temperature for additional 30 min. The separated organic phase was washed with aqueous NH_4Cl (5 M, 150 mL) followed by NaCl solution (10%, 100 mL). The organic phase was azeotropically solvent switched to 2-MeTHF under vacuum to a volume of 150 mL. The solution was assayed for 37.7 g of the desired product **7**. 94% assay yield. The solution of chlorohydrin **7** in 2-MeTHF was used directly for the subsequent reaction.

An analytically pure sample of chlorohydrin **7**[13a] could be obtained through silica gel column purification eluting with a mixture of EtOAc and hexane. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (m, 1 H), 5.03 (d, *J* = 17.1 Hz, 1 H), 4.98 (d, *J* = 10.1 Hz, 1 H), 3.82 (m, 1 H), 3.64 (dd, *J* = 11.1, 3.2 Hz, 1 H), 3.48 (dd, *J* = 11.1, 7.1 Hz, 1 H), 2.18 (s, br, 1 H), 2.10 (m, 2 H), 1.59 (m, 1 H), 1.55 (m, 2 H), 1.48 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 115.2, 71.5, 50.7, 33.8, 33.7, 25.0.

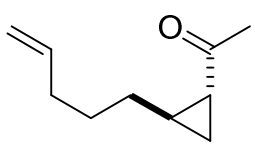


(1*R*,2*R*)-*N*,*N*-dimethyl-2-(pent-4-en-1-yl)cyclopropane-1-carboxamide (10). To a solution of sodium *tert*-butoxide (61.9 g, 0.644 mol) in 2-MeTHF (600 mL) was added a solution of chlorohydrin **7** in 2-MeTHF (36.9 g assay, 0.248 mol, ~150 mL) followed by diethyl[2-(dimethylamino)-2-oxoethyl] phosphonate (**4**, R = $CONMe_2$; 69.0 g assay, 0.309 mol), while maintaining the internal temperature below 20 °C. The reaction solution was heated to 78 °C and agitated for 20 h. The reaction solution was cooled to ambient temperature, and water (370 mL) was added dropwise, while the internal temperature was maintained at < 25 °C with external cooling. The separated organic phase was washed with 10% NaCl solution (100 mL x 3). The organic phase was azeotropically distilled under vacuum below 30 °C to a volume of ~150 mL. The organic phase was assayed (HPLC) for 39.0 g of cyclopropyl amide **10**. 87% assay yield. The dried solution of cyclopropyl amide **10** in 2-MeTHF was directly used in the subsequent reaction without further purification.

An analytically pure sample of amide **10** could be obtained through silica gel column purification eluting with a mixture of EtOAc and hexane. ^{1}H NMR (500 MHz, d_4-MeOH) δ 5.81 (m, 1 H), 5.00 (m, 1 H), 4.93 (m, 1 H), 3.20 (s, 3 H), 2.94 (s, 3 H), 2.09 (m, 2 H), 1.67 (m, 1 H), 1.52 (m, 2 H), 1.37 (m, 1 H), 1.25 (m, 1 H), 1.07 (m, 1 H), 0.67 (m, 1 H). ^{13}C NMR (125 MHz, d_4-MeOH) δ 175.8, 140.0, 115.2, 38.0, 36.4, 34.6, 33.7, 29.9, 23.2, 19.7, 15.5. HRMS calc'd for $C_{11}H_{19}NO$ $[M+H]^+$ 182.1545; found 182.1549.

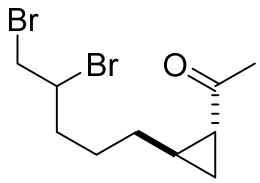


(*S*)-2-(pent-4-en-1-yl)oxirane (5a). Epoxide **5a** was formed during the preparation of amide **10**, which could be obtained by quenching the reaction with water after **7** was mixed with sodium *tert*-butoxide and stirred at ambient temperature for several hours. An analytically pure sample of epoxide **5a**[13] could be obtained through silica gel column purification eluting with a mixture of EtOAc and hexane. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (m, 1 H), 5.04 (d, *J* = 17.3 Hz, 1 H), 4.98 (d, *J* = 10.2 Hz, 1 H), 2.93 (m, 1 H), 2.76 (m, 1 H), 2.48 (m, 1 H), 2.13 (m, 2 H), 1.57 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 115.0, 52.4, 47.3, 33.6, 32.1, 25.4.



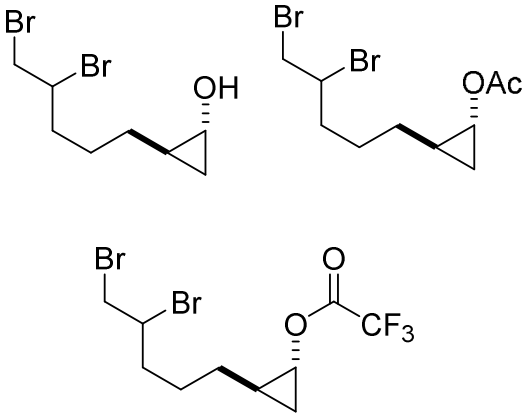
1-((1*R*,2*R*)-2-(pent-4-en-1-yl)cyclopropyl)ethan-1-one (11). To a solution of MeMgCl in THF (3 M, 135 mL, 0.405 mol) at 55 °C was added a solution of cyclopropyl amide **10** in 2-MeTHF (36.6 g assay, 0.202 mol, ~200 mL) over 2.5 h. After addition, the reaction solution was agitated at 55 – 60 °C for additional 1 h. The reaction mixture was quenched to a mixture of 5 M aqueous NH_4Cl (460 mL) and hexanes (425 mL), while the internal temperature was maintained <5 °C with external cooling. The quenched mixture was stirred at ambient temperature for additional 1 h. The separated organic phase was washed with 1 N HCl (100 mL) followed by 10% NaCl solution (100 mL). The organic phase was azeotropically distilled under vacuum at a volume of ~60 mL, while maintaining the internal temperature at <15°C. The organic phase was assayed (HPLC) for 29.2 g of cyclopropyl methyl ketone **11**. 95% assay yield. The crude stream of ketone **11** was used directly in the subsequent step without further purification.

An analytically pure sample of methyl ketone **11** could be obtained through silica gel column purification eluting with a mixture of EtOAc and hexane. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (m, 1 H), 5.00 (d, *J* = 17.1 Hz, 1 H), 4.94 (d, *J* = 9.92 Hz, 1 H), 2.21 (s, 3 H), 2.06 (m, 2 H), 1.69 (m, 1 H), 1.48 (m, 2 H), 1.38 (m, 1 H), 1.34 (m, 2 H), 1.32 (m, 1 H), 1.23 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4, 138.7, 114.8, 33.5, 32.8, 30.4, 29.4, 28.6, 25.9, 18.2. HRMS calc'd for $C_{10}H_{16}O$ $[M+H]^+$ 153.1279; found 153.1281.



1-((1*R*,2*R*)-2-(4,5-dibromopentyl)cyclopropyl)ethan-1-one (12). To a solution of methyl ketone **11** in hexane (10 g assay, 65.7 mmol, ~50 wt%) were added MeCN (30 mL) and pyridine (2.6 g, 32.85 mmol). The batch was cooled to -5 – 5 °C. A solution of pyridinium tribromide (25.2 g, 79 mmol) in MeCN (50 mL) was added dropwise over several hours, while maintaining the batch temperature between -5 – 5 °C. After aging the reaction slurry for additional 30 min, a solution of 10% $Na_2S_2O_3$ in 5% NaCl aqueous (30 mL) was slowly charged, while maintaining the internal temperature <10 °C. The batch was agitated at ambient temperature for at least 30 min. EtOAc (60 mL) followed by 0.5N HCl (40 mL) was charged. The separated organic phase was washed with 15% NaCl (20 mL). The organic phase was aezotropically dried and solvent-switched to EtOAc at a final volume of ~80 mL in vacuum, while maintaining the internal temperature <20 °C. The organic phase was assayed (HPLC) for 19.7 g of bromide **12**. 96% assay yield. The crude stream of bromo ketone **12** was used directly in the subsequent step without further purification.

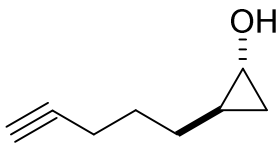
An analytically pure sample of dibromide **12** could be obtained through silica gel column purification eluting with a mixture of EtOAc and hexane. The bromide product was a mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16 (m, 1 H), 3.85 (m, 1 H), 3.62 (m, 1 H), 2.23 and 2.20 (s, 3 H), 2.18 (m, 1 H), 1.81 (m, 1 H), 1.73 (m, 2 H), 1.53 (m, 1 H), 1.38 (m, 3 H), 1.26 (m, 1 H), 0.77 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.17, 208.15, 52.82, 52.79, 36.30, 36.27, 35.71, 35.67, 32.50, 32.47, 30.50, 30.45, 29.24, 29.12, 26.61, 26.53, 25.48, 25.41, 18.16, 18.05. HRMS calc'd for $C_{10}H_{16}Br_2O$ $[M+H]^+$ 310.9646; found 310.9648.



(1R,2R)-2-(4,5-dibromopentyl)cyclopropan-1-ol (13a), (1R,2R)-2-(4,5-dibromopentyl)cyclopropyl acetate (13b), and (1R,2R)-2-(4,5-dibromopentyl)cyclopropyl 2,2,2-trifluoroacetate (13c). To a mixture of urea hydrogen peroxide (24.1 g, 256.4 mmol) in EtOAc (80 mL) at 0 °C under nitrogen was added a solution of bromide **12** (20.0 g assay, 64.1 mmol) in EtOAc (140 mL). $(CF_3CO)_2O$ (55.2 g, 262.8 mmol) was then added at 0 °C dropwise over 3 h. The resulting mixture was stirred overnight at 0°C. The reaction mixture was pH adjusted to 7 – 8 by addition of 20% Na_2CO_3 (~140 mL, 265 mmol) at <5 °C with external cooling. The organic phase was separated. The aqueous layer was extracted with EtOAc (100 mL). The combined organic phase was washed with 10% $Na_2S_2O_3$ in 5% NaCl aqueous (60 mL) followed by 10% NaCl aqueous (60 mL). The organic layer was azeotropically dried and solvent-switched to hexanes (100 mL), while maintaining the internal temperature <25 °C. The slurry was agitated at 20 °C for additional 1 h and the solid was removed through filtration. The wet cake was washed with hexanes (20 mL x 3). The combined filtrate was concentrated and solvent-switched to 2-MeTHF to a volume of ~50 mL, while maintaining the internal temperature <25 °C. 91% assay yield of products **13a-c**. The crude stream of products **16a-c** was used directly in the subsequent step without further purification.

The bromide acetate product is a mixture of diastereomers. An analytically pure sample of dibromide **13a-c** could be obtained through silica gel column purification eluting with a mixture of EtOAc and hexane. Dibromide **13b** was the major product as a mixture of diasteromers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18 (m, 1 H), 3.87 (m, 1 H), 3.84 (m, 1 H), 3.65 (m, 1 H), 2.19 (m, 1 H), 2.03 (s, 3 H), 1.83 (m, 1 H), 1.73 (m, 1 H), 1.58 (m, 1 H), 1.36 (m, 1 H), 1.29 (m, 1 H), 1.04 (m, 1 H), 0.86 (m, 1 H), 0.57 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 54.53, 54.47, 53.0, 36.49, 36.46, 35.87, 35.82, 30.8, 30.7, 26.20, 26.12, 21.14, 18.40, 18.37, 12.21, 12.12. HRMS calc'd for $C_{10}H_{16}Br_2O_2$ $[M+H]^+$ 326.9595; found 326.9590.

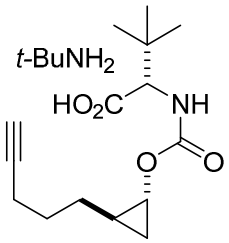
The minor bromide alcohol **13a** was a mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.39 (m, 1 H), 3.89 (m, 1 H), 3.86 (m, 1 H), 3.65 (m, 1 H), 3.24 (m, 1 H), 2.19 (m, 1H), 1.84 (m, 2 H), 1.69 (m, 1 H), 1.54 (m, 1 H), 1.30 (m, 1 H), 1.18 (m, 1 H), 0.95 (m, 1 H), 0.74 (m, 1 H), 0.36 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.11, 53.06, 52.9, 52.8, 36.5, 35.9, 35.8, 31.1, 31.0, 26.44, 26.38, 20.81, 20.78, 14.8, 14.7.



(1*R*,2*R*)-2-(pent-4-yn-1-yl)cyclopropan-1-ol (14). To a solution of *N',N'*-diethylethylene-1,2-diamine (2.43 Kg, 20.9 mol) in 2-MeTHF (10.5 L) was added *n*-BuLi (2.7 M in hexanes, 5.95 L, 16.1 mol) dropwise, while maintaining the internal temperature below -25 °C. The resulting solution was agitated at -15 °C for 2 – 3 h. A solution of bromides **13a-c** in 2-MeTHF (0.753 Kg assay of combined **13a-c**, 2.30 mol, 1.5 L) was added dropwise over 2 – 4 h, while maintaining the batch temperature at -15 °C. The batch was agitated at -15 °C for additional 2 – 4 h. Then, the batch was added to a solution of water (3 L)

and 2-MeTHF (1.5 L) slowly, while maintaining the internal temperature below 5 °C. The reaction solution was agitated at 0 °C for 12 h. Citric acid aqueous (40%, ~6.6 L) was added until the batch pH was 6.0 – 6.5, while maintaining the internal temperature below 5 °C. The batch was warmed to 20 °C. The organic phase was separated and washed with water (3 L x 2), 5% $NaHCO_3$ (3 L) and water (3 L). The organic phase was azeotropically dried and solvent-switched to 2-MeTHF at a final volume of ~1.5 L under vacuum, while maintaining the internal temperature below 20 °C. The organic phase was assayed (HPLC) for 0.266 Kg of **14**. 93% assay yield. The crude stream of alcohol **14** was used directly in the subsequent step without further purification.

An analytically pure sample of alcohol **14** could be obtained through silica gel column purification eluting with a mixture of EtOAc and hexane. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.20 (m, 1 H), 2.31 (s, br, 1 H), 2.21 (m, 2 H), 1.92 (t, *J* = 2.6 Hz, 1 H), 1.60 (m, 2 H), 1.33 (m, 1 H), 1.21 (m, 1 H), 0.89 (m, 1 H), 0.68 (m, 1 H), 0.32 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 84.7, 68.6, 52.7, 30.7, 28.0, 20.4, 18.2, 14.5.

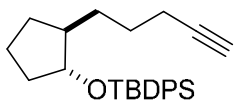


(*S*)-3,3-dimethyl-2-((((1*R*,2*R*)-2-(pent-4-yn-1-yl)cyclopropoxy)carbonyl)amino)butanoic acid *tert*-butylamine salt (2). To a mixture of CDI (1.68 Kg, 10.05 mol) in 2-MeTHF (9.6 L) was added a solution of alcohol **14** in 2-MeTHF (0.96 Kg assay, 7.73 mol, 3.5 L) at 0 °C over 2 – 5 h. The reaction solution was agitated for additional 1 – 2 h. Water (4.8 L) was added, while maintaining the internal temperature < 10 °C. The reaction solution was then agitated at 5 °C for additional 1 – 2 h. Heptane (7.7 L) was added. The organic phase was separated, and the aqueous layer was extracted with 2-MeTHF/heptane (1:1, 2.9 L) at <10 °C. The combined organic phase was washed with water (4.8 L) <10 °C. The organic phase was azeotropically dried and solvent-switched to 2-MeTHF at a final volume of ~3 L. *N*-Methylpyrrolidinone (16.8 L) followed by *tert*-L-leucine (1.254 Kg, 9.27 mol) and 2-hydroxypyridine *N*-oxide (0.35 Kg, 3.10 mol) was added. The reaction mixture was agitated between 60 – 65 °C for 10 – 18 h. MTBE (14.4 L) and water (14.4 L) were added at ambient temperature. The batch was pH adjusted with 5 N HCl (~1.5 L) to pH = 1.5 – 2.5. The organic phase was separated, and the aqueous layer was extracted with MTBE (14.4 L). The combined organic phase was washed with water (9.6 L x 2). The organic phase was extracted with NaOH aqueous (1 N, 11.5 L). The separated aqueous phase was washed with MTBE (9.6 L x 2). MTBE (11.5 L) was added, and the batch was pH adjusted with 5 N HCl (~2.45 L) to pH = 1.5 – 2.5. The separated organic phase was washed with water (4.8 L). MTBE was added to the separated organic phase to a final volume of ~33.5 L. A solution of *t*-$BuNH_2$ (0.744 Kg, 10.07 mol) in MTBE (0.95 L) was added dropwise at 40 °C. After ~35% of the above *t*-$BuNH_2$ solution was added, the batch was seeded. The remaining *t*-$BuNH_2$ solution was added dropwise over 2 – 4 h. After aging at 40 °C for additional 2 h, the batch was cooled to ambient temperature and filtered. The wet cake was washed wet MTBE (containing 1wt% water, 9.5 L x 2). Vacuum oven dry at 30 – 35 °C with nitrogen sweep gave 2.22 Kg of product **2** *t*-$BuNH_2$ salt. 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, br, 3 H), 6.04 (d, *J* = 8.4 Hz, 1 H), 3.60 (m, 1 H), 3.45 (d, *J* = 8.4 Hz, 1 H), 2.72 (t, J = 2.7 Hz, 1 H), 2.18 (td, *J* = 7.1, 2.7 Hz, 2 H), 1.54 (m, 2 H), 1.26 (m, 2 H), 1.22 (s, 9 H), 0.89 (m, 1 H), 0.88 (s, 9 H), 0.76 (m, 1 H), 0.44

(m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 156.1, 84.4, 71.2, 64.2, 53.5, 50.0, 34.0, 29.7, 27.7, 27.18, 27.15, 17.6, 17.3, 11.3. HRMS calc'd for $C_{15}H_{23}NO_4$ $[M+H]^+$ 282.1700; found 282.1692.

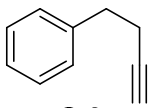
General procedure for the bromination of mono-alkene substrates (Table 3, entries 1, 3, 4, 5, and 6): To a solution of a mono-alkene substrate (5.0 mmol) and pyridine (6.0 mmol, 0.485 mL) in MeCN (15 mL) at -5 – 5 °C was added a solution of 90 wt% of pyridinium tribromide (6.0 mmol, 2.14 g) in acetonitrile (5 mL) dropwise. After addition, the reaction mixture was stirred at -5 – 5 °C for additional 0.5 h. MTBE (25 mL) was added. Then, 10% $Na_2S_2O_3$ in 5% NaCl aqueous (10 mL) was slowly added, maintaining the internal temperature at <10 °C. The organic layer was separated and washed with 0.5 N HCl (15 mL) followed by brine (15 mL). The organic layer was dried over anhydrous Mg_2SO_4. The crude product obtained upon concentration in vacuum was dissolved in 2-MeTHF (7.5 mL) and directly used for the elimination.

General procedure for the elimination of dibromo intermediates (Table 3, entries 1, 3, 4, 5, 6, 7 and 8): To a dried 100 mL three-neck round-bottom flask equipped with an overhead stirrer, a thermocouple probe, and a nitrogen inlet were charged 2-MeTHF (16 mL) and diethyl ethylenediamine (26.0 mmol, 3.63 mL). The reaction mixture was cooled to -30 – -20 °C. *n*-BuLi in hexanes (2.5 M, 20.0 mmol, 8.0 mL) was slowly added over 1 – 2 h at -30 to -20 °C through a syringe pump. After addition, the reaction mixture was stirred at -30 – -20 °C for additional 2 h. A solution of a dibromo compound (5.0 mmol, Table 2, entries 1, 3, 4, 5, 6 and 8) or the bromoalkene (5.0 mmol, Table 2, entry 7) in 2-MeTHF (7.5 mL) was added slowly, while maintaining the temperature at -20 – -10 °C. The resulting reaction solution was stirred at -20 – -10 °C for additional 2 h, then warmed to 0 – 5 °C, and stirred at 0 – 5 °C until the reaction was completed. Citric acid aqueous (40%, 10 mL) was added slowly, while maintaining the internal temperature at 0 – 5 °C. The separated aqueous layer was extracted with MTBE (25 mL). The combined organic layer was washed with 5 N HCl (15 mL x 2) followed by brine (15 mL). The crude product obtained upon concentration in vacuum was purified through silica gel column chromatography eluting with EtOAc/hexanes to afford the desired product.

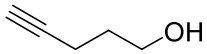


S-1

***tert*-Butyl(((1*R*,2*R*)-2-(pent-4-yn-1-yl)cyclopentyl)oxy)diphenylsilane (S-1, Table 3, entry 1):** Compound **S-1** was isolated as an oil in 82% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (m, 4 H), 7.40 (m, 6 H), 3.83 (m, 1 H), 2.04 (m, 2 H), 1.89 (m, 2 H), 1.80 (m, 1 H), 1.70 (m, 1 H), 1.57 (m, 2 H), 1.48 (m, 1 H), 1.35 (m, 3 H), 1.06 (m, 10 H), 0.96 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.9, 134.8, 134.6, 129.4, 127.4, 84.6, 80.2, 68.1, 47.7, 34.4, 32.7, 29.2, 27.0, 21.9, 19.2, 18.5. HRMS calcd for $C_{26}H_{34}OSi$ $[M+H]^+$ 391.2452; found 391.2451.

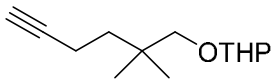

S-3

But-3-yn-1-ylbenzene (S-3, Table 3, entry 3): Compound **S-3** (commercial available) was isolated as an oil in 87% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (m, 2 H), 7.23 (m, 3 H), 2.86 (t, J = 7.6 Hz, 2 H), 2.50 (td, J = 7.6, 2.6 Hz, 2 H), 1.98 (t, J = 2.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.4, 128.4, 126.3, 83.8, 68.9, 34.9, 20.6.



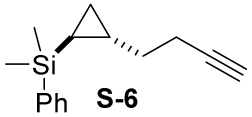
S-4

Pent-4-yn-1-ol (S-4, Table 3, entry 4): Compound **S-4** (commercial available) was isolated as an oil in 88% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.71 (t, *J* = 6.2 Hz, 2 H), 2.32 (br s, 1 H), 2.28 (dt, *J* = 7.1, 2.7 Hz, 2 H), 1.95 (t, *J* = 2.7 Hz, 1 H), 1.74 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 83.8, 68.7, 61.2, 30.9, 14.6.



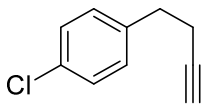
S-5

2-((2,2-Dimethylhex-5-yn-1-yl)oxy)tetrahydro-2H-pyran (S-5, Table 3, entry 5): Compound **S-5** was isolated as an oil in 88% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.53 (t, *J* = 3.4 Hz, 1 H), 3.81 (ddd, *J* = 11.4, 8.8, 3.0 Hz, 1 H), 3.49 (m, 1 H), 3.44 (d, *J* = 9.3 Hz, 1 H), 2.97 (d, *J* = 9.3 Hz, 1 H), 2.16 (m, 2 H), 1.91 (t, *J* = 2.7 Hz, 1 H), 1.80 (m, 1 H), 1.67 (m, 1 H), 1.55 (m, 6 H), 0.90 (s, 3H), 0.89 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 99.0, 85.4, 76.0, 67.7, 61.8, 38.3, 34.2, 30.6, 25.5, 24.3, 24.2, 19.3, 13.6. HRMS calcd for $C_{13}H_{22}O$ $[M+H]^+$ 211.1698; found 211.1690.



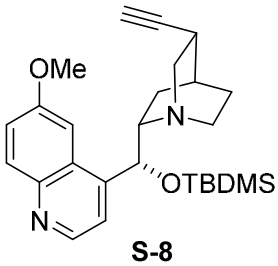
S-6

Dimethyl(phenyl)((1S,2S)-2-(prop-2-yn-1-yl)cyclopropyl)silane (S-6, Table 3, entry 6): Compound **S-6** was isolated as an oil in 85% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (m, 2 H), 7.36 (m, 3 H), 2.26 (m, 2 H), 1.95 (t, *J* = 2.6 Hz, 1 H), 1.66 (m, 1 H), 1.42 (m, 1 H), 0.83 (m, 1 H), 0.48 (m, 2 H), 0.23 (s, 3 H), 0.20 (s, 3 H), -0.39 (dt, *J* = 9.7, 6.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.1, 133.7, 128.9, 127.6, 84.6, 68.2, 34.9, 18.8, 15.2, 9.0, 3.4, -3.7, -4.0. HRMS calcd for $C_{14}H_{18}Si$ $[M+H]^+$ 229.1407; found 229.1406.



S-7

1-(But-3-yn-1-yl)-4-chlorobenzene (S-7, Table 3, entry 7): Compound **S-7** (commercial available) was isolated as an oil in 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26 (m, 2 H), 7.15 (m, 2 H), 2.80 (t, *J* = 7.4 Hz, 2 H), 2.45 (td, *J* = 7.4, 2.6 Hz, 2 H), 1.96 (t, *J* = 2.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.8, 132.2, 129.8, 128.5, 83.3, 69.2, 34.1, 20.4.

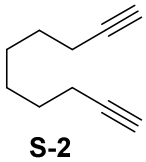


S-8

(1S,2S,4S,5S)-2-((R)-((tert-Butyldimethylsilyl)oxy)(6-methoxyquinolin-4-yl)methyl)-5-ethynylquinuclidine (S-8, Table 3, entry 8): Compound **S-8**[s3] was isolated as an oil in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.76 (d, *J* = 4.5 Hz, 0.67 H), 8.64 (d, *J* = 4.2 Hz, 0.33 H), 8.02 (d, *J* = 9.2 Hz, 0.67 H), 7.98 (d, *J* = 9.2 Hz, 0.33 H), 7.90 (d, *J* = 2.4 Hz, 0.33 H), 7.57 (d, *J* = 4.5 Hz, 0.67 H), 7.36 (dd, *J* = 9.2, 2.5 Hz, 0.67 H), 7.32 (dd, *J* = 9.2, 2.5 Hz, 0.33 H), 7.21 (d, *J* = 2.3 Hz, 0.67 H), 7.12 (d, *J* = 4.2 Hz, 0.33 H), 5.61 (, d, *J* = 4.7 Hz, 0.67 H), 4.94 (d, *J* = 9.6 Hz, 0.33 H), 3.94 (s, 2.01 H), 3.92 (s, 0.99 H), 3.44 (m, 1 H), 2.96 (m, 2 H), 2.81 (td, *J* = 9.2, 3.2 Hz, 0.67 H), 2.64 (dt, *J* = 13.4, 8.7 Hz, 0.67 H), 2.50 (m, 1.67 H), 2.28 (m, 0.67 H), 2.16

[s3] Braje, W. M.; Frackenpohl, J.; Schrake, O.; Wartchow, R.; Beil, W.; Hoffmann, H. M. R. *Helvetica Chimica Acta* **2000**, *83*, 777–792.

(dd, *J* = 15.2, 2.1 Hz, 1 H), 2.10 (dd, *J* = 13.6, 8.1 Hz, 0.33 H), 1.98 (m, 1 H), 1.84 (m, 0.33 H), 1.53 (m, 0.33 H), 1.43 (m, 1.67 H), 1.28 (m, 0.67 H), 0.93 (s, 6 H), 0.83 (s, 3 H), 0.13 (s, 3 H), -0.33 (s, 2.10 H), -0.39 (s, 0.99 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.8, 156.6, 148.3, 147.6, 147.2, 147.0, 145.5, 144.4, 131.9, 131.5, 127.0, 126.5, 121.4, 121.2, 121.1, 119.0, 104.8, 100.5, 87.9, 87.5, 79.4, 72.3, 69.2, 69.1, 61.5, 60.6, 55.6, 55.4, 50.4, 50.0, 49.3, 49.2, 28.3, 28.2, 28.2, 27.8, 26.7, 26.0, 25.7, 25.2, 25.1, 22.4, 18.1, 18.0, -4.6, -4.7, -4.9, -5.2.

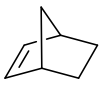


S-2

Deca-1,9-diyne (S-2, Table 3, entry 2): To a solution of di-alkene (5.0 mmol), pyridine (12.0 mmol, 0.97 mL) in MeCN (30 mL) at -5 – 5 °C was added a solution of 90 wt% of pyridinium tribromide (12.0 mmol, 4.28 g) in acetonitrile (10 mL) dropwise. The reaction mixture was stirred at -5 – 5 °C for additional 0.5 h. MTBE (50 mL) was added. Then, 10% $Na_2S_2O_3$ in 5% NaCl aqueous (20 mL) was slowly added, maintaining the internal temperature at <10 °C. The organic layer was separated and washed with 0.5 N HCl (30 mL) followed by brine (30 mL). The organic layer was dried over anhydrous Mg_2SO_4. The crude product obtained upon concentration in vacuum was dissolved in 2-MeTHF (7.5 mL).

To a dried 100 mL three-neck round-bottom flask equipped with an overhead stirrer, a thermocouple probe, and a nitrogen inlet were charged 2-MeTHF (28 mL) and diethyl ethylenediamine (45.5 mmol, 6.35 mL). The reaction mixture was cooled to -30 – -20 °C. *n*-BuLi in hexanes (2.5 M, 35.0 mmol, 14.0 mL) was slowly added over 1 – 2 h at -30 to -20 °C through a syringe pump. The reaction mixture was stirred at -30 – -20 °C for additional 2 h. The above solution of tetrabromo intermediate in 2-MeTHF (7.5 mL) was added slowly, while maintaining the temperature at -20 – -10 °C. The resulting reaction solution was stirred at -20 – -10 °C for additional 2 h, then warmed to 0 – 5 °C and stirred at 0 – 5 °C until the reaction was completed. Citric acid aqueous (40%, 20 mL) was added slowly, while maintaining the temperature at 0 – 5 °C. The separated aqueous layer was extracted with MTBE (25 mL). The combined organic layer was washed with 5 N HCl (15 mL x 2) followed by brine (15 mL). By gas chromatography analysis, 90% assay yield.

The product **S-2** is volatile. An analytically pure sample of deca-1,9-diyne **(S-2**) could be obtained through silica gel column purification eluting with a mixture of EtOAc and hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.17 (m, 4 H), 1.92 (br s, 2 H), 1.52 (m, 4 H), 1.40 (m, 4 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 84.4, 68.2, 28.2, 28.1, 18.3.



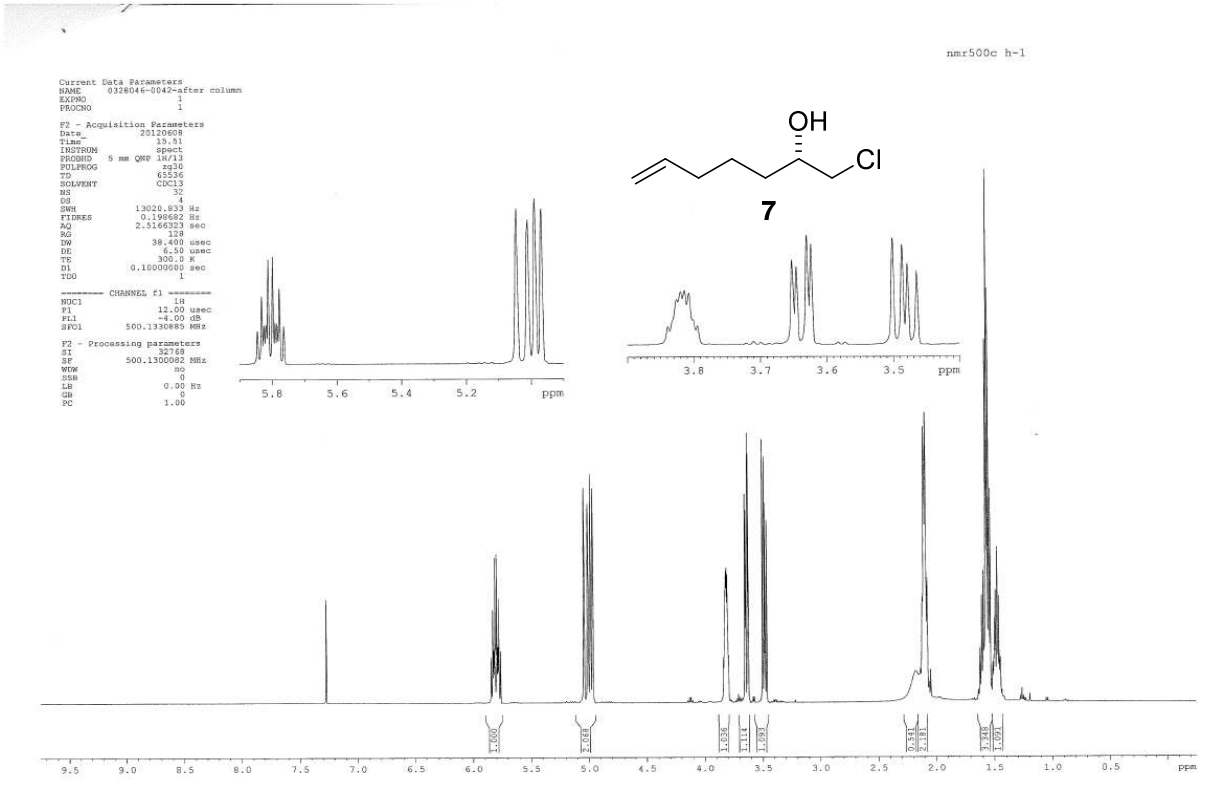
S-9

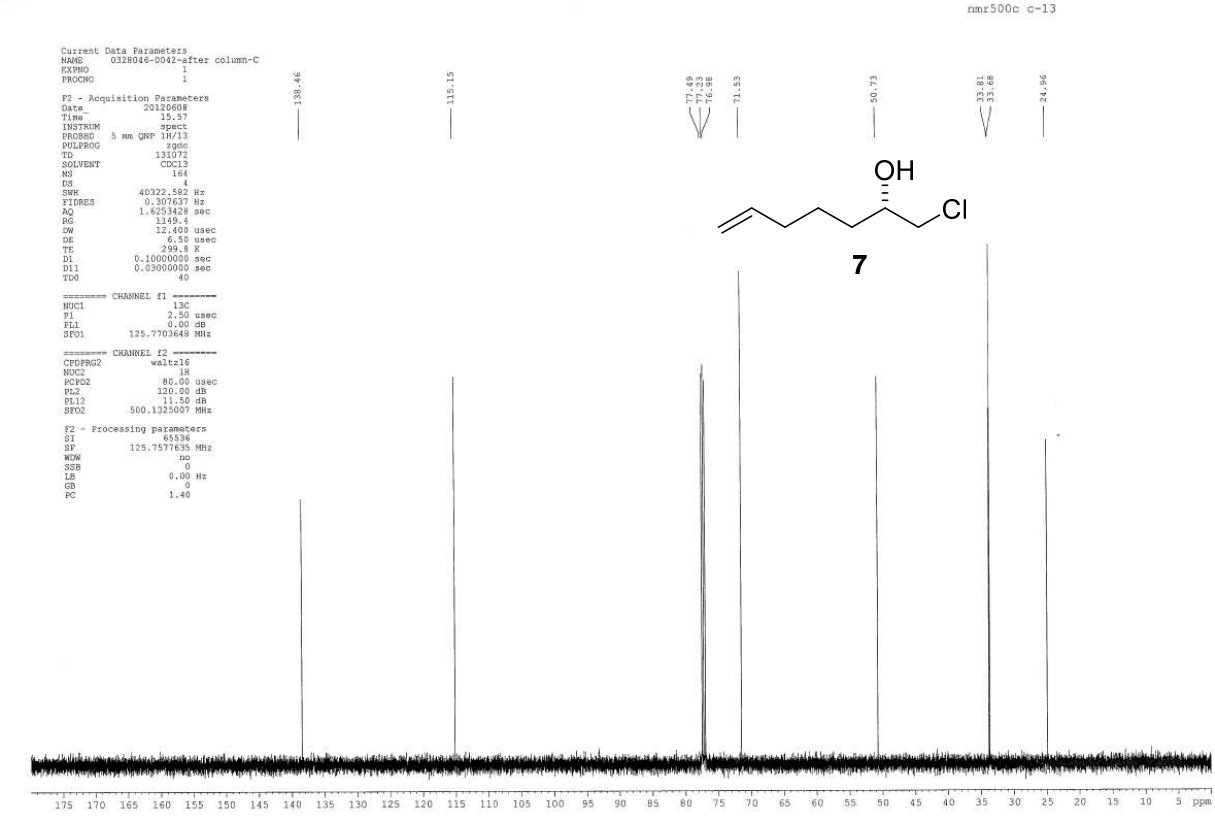
Bicyclo[2.2.1]hept-2-ene (S-9, Table 3, entry 9): To a dried 100 mL three-neck round-bottom flask equipped with an overhead stirrer, a thermocouple probe, and a nitrogen inlet were charged THF (16 mL) and diethyl ethylenediamine (16.25 mmol, 2.27 mL). The reaction mixture was cooled to -30 – -20 °C. *n*-BuLi in hexanes (2.5 M, 12.5 mmol, 5.0 mL) was slowly added over 1 – 2 h at -30 to -20 °C through a syringe pump. The reaction mixture was stirred at -30 – -20 °C for additional 2 h. A solution of exo-2-bromonorbornane (5.0 mmol) in THF (2.5 mL) was added slowly, while maintaining the temperature at -20 – -10 °C. The resulting reaction solution was stirred at -20 – -10 °C for additional 2 h, then warmed to 0 – 5 °C and stirred at 0 – 5 °C until the reaction was completed. Citric acid aqueous (40 wt%, 10 mL) was added slowly, while maintaining the temperature at 0 –

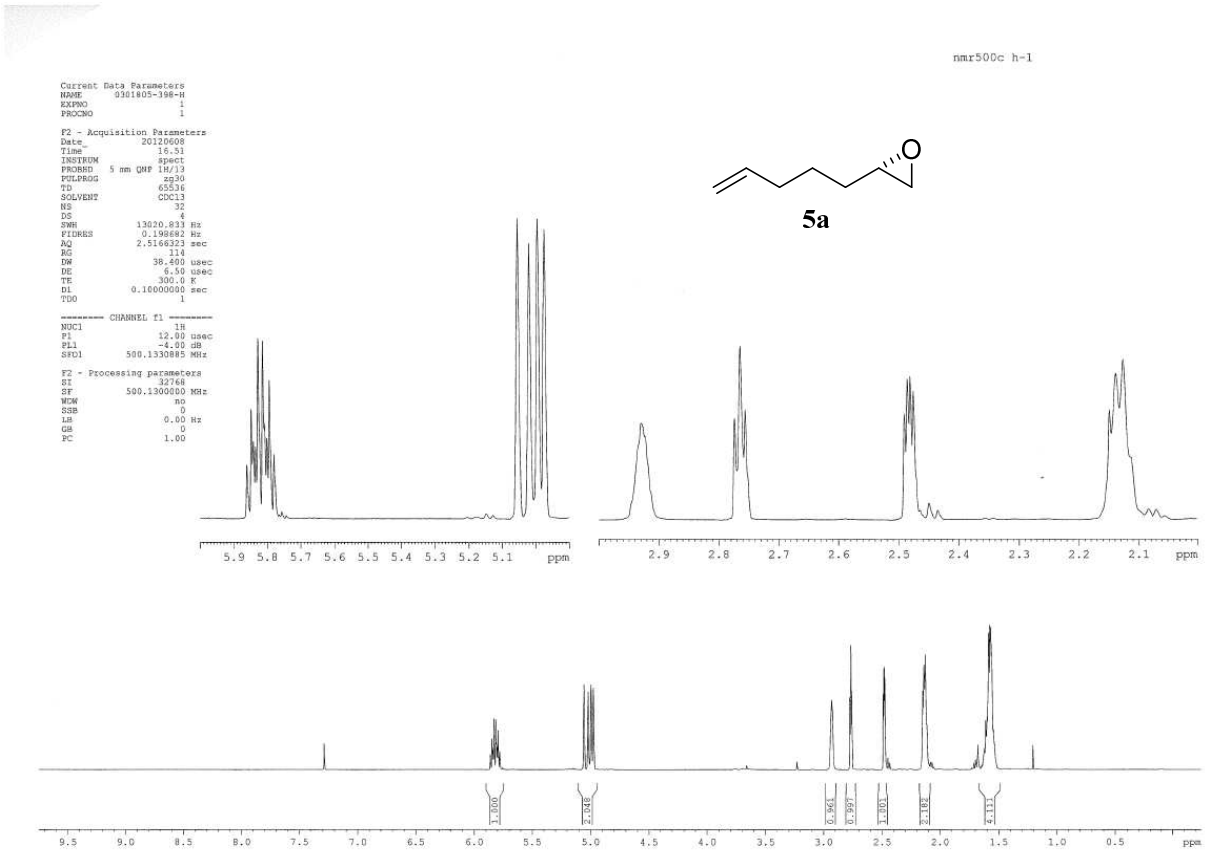
5 °C. The separated aqueous layer was extracted with hexanes (10 mL). The combined organic layer was washed with 5 N HCl (15 mL x 2) followed by brine (15 mL). By HPLC analysis, 98% assay yield.

An analytically pure sample of bicyclo[2.2.1]hept-2-ene (**S-9**) could be obtained by distillation at 1 atmosphere pressure. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.99 (t, J = 1.8 Hz, 2 H), 2.85 (m, 2 H), 1.61 (m, 2 H), 1.32 (m, 1H), 1.08 (d, J = 8.0 Hz, 1 H), 0.96 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.3, 48.5, 41.8, 24.6.

5. ^{1}H and ^{13}C NMR spectra



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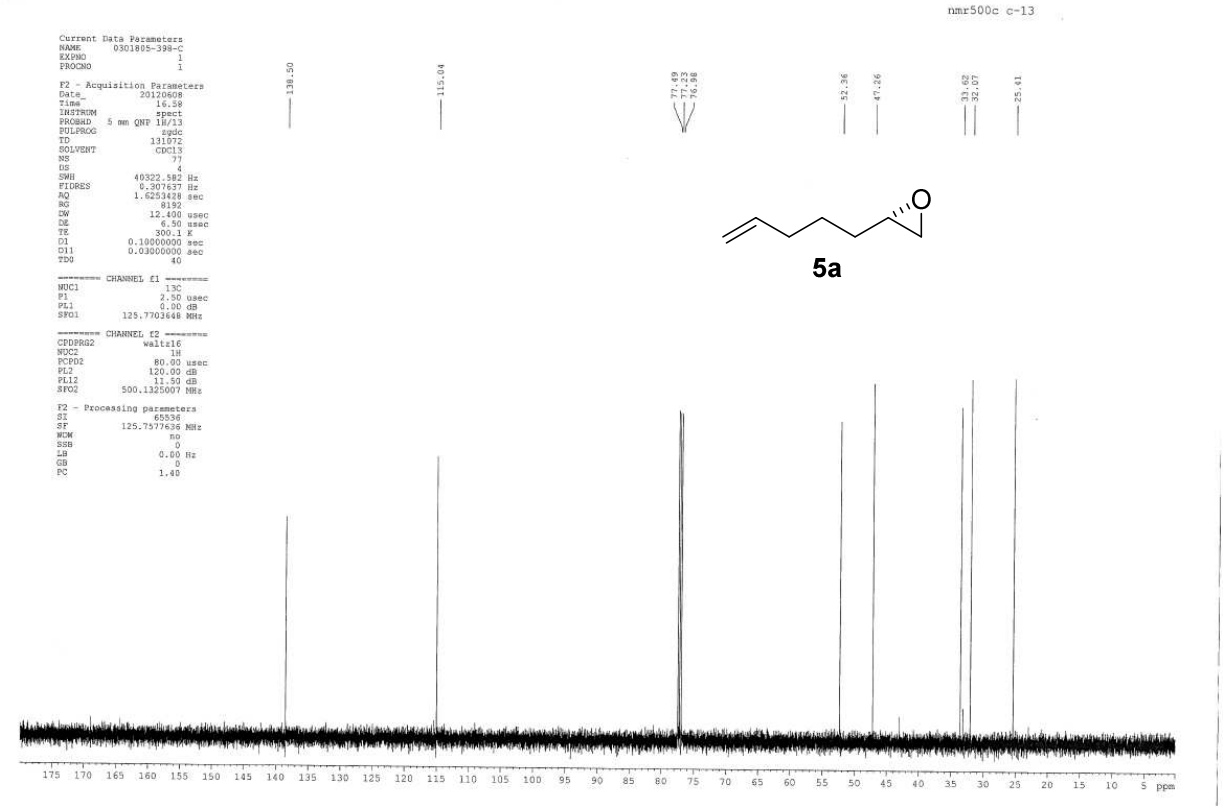
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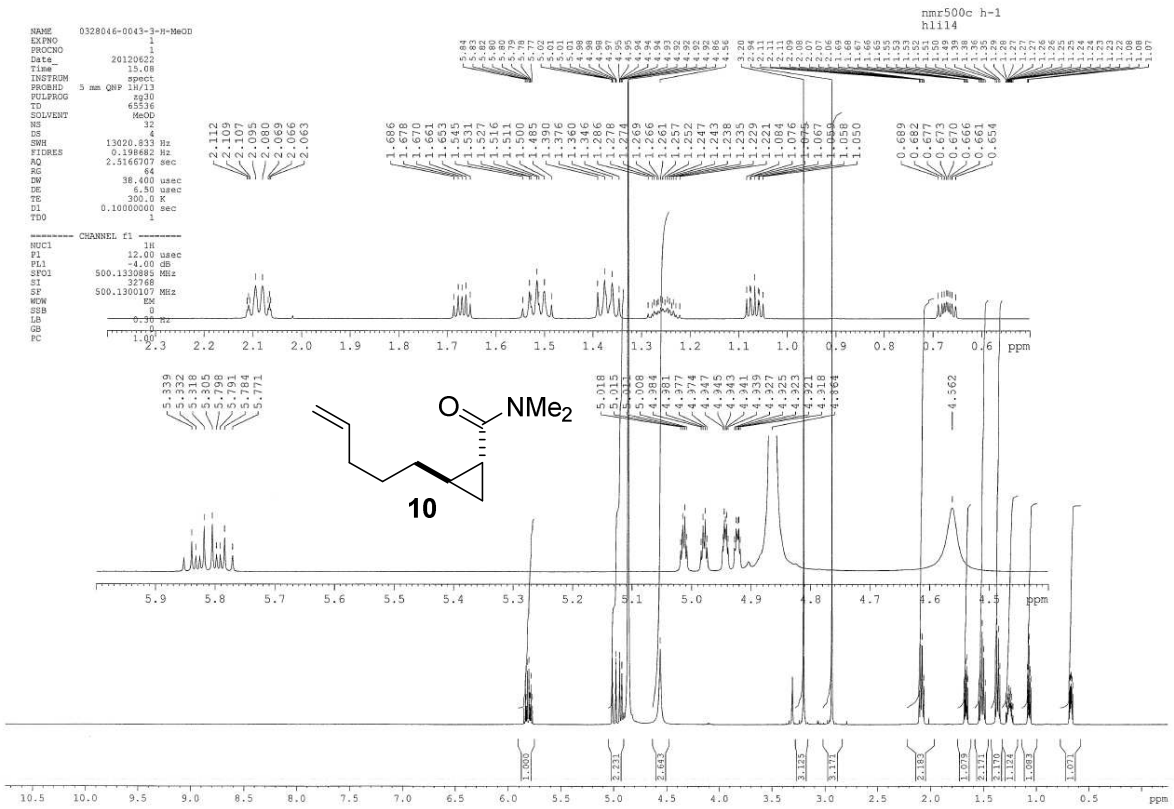
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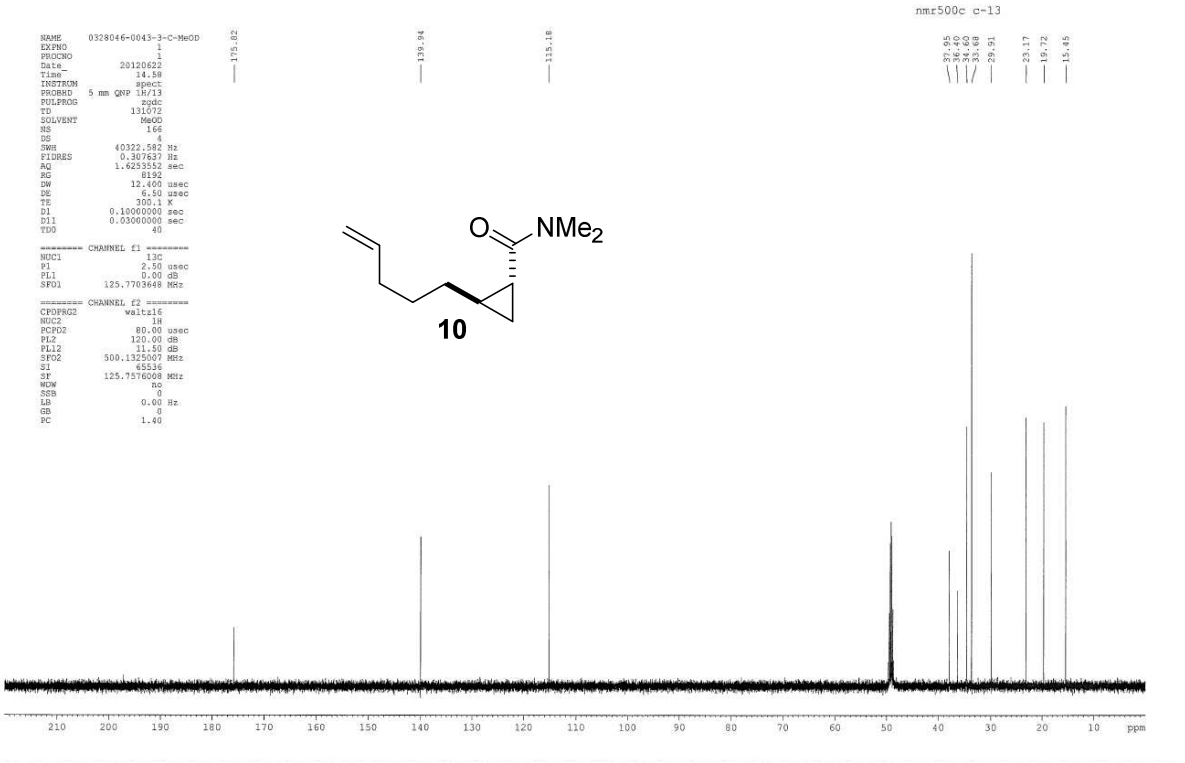
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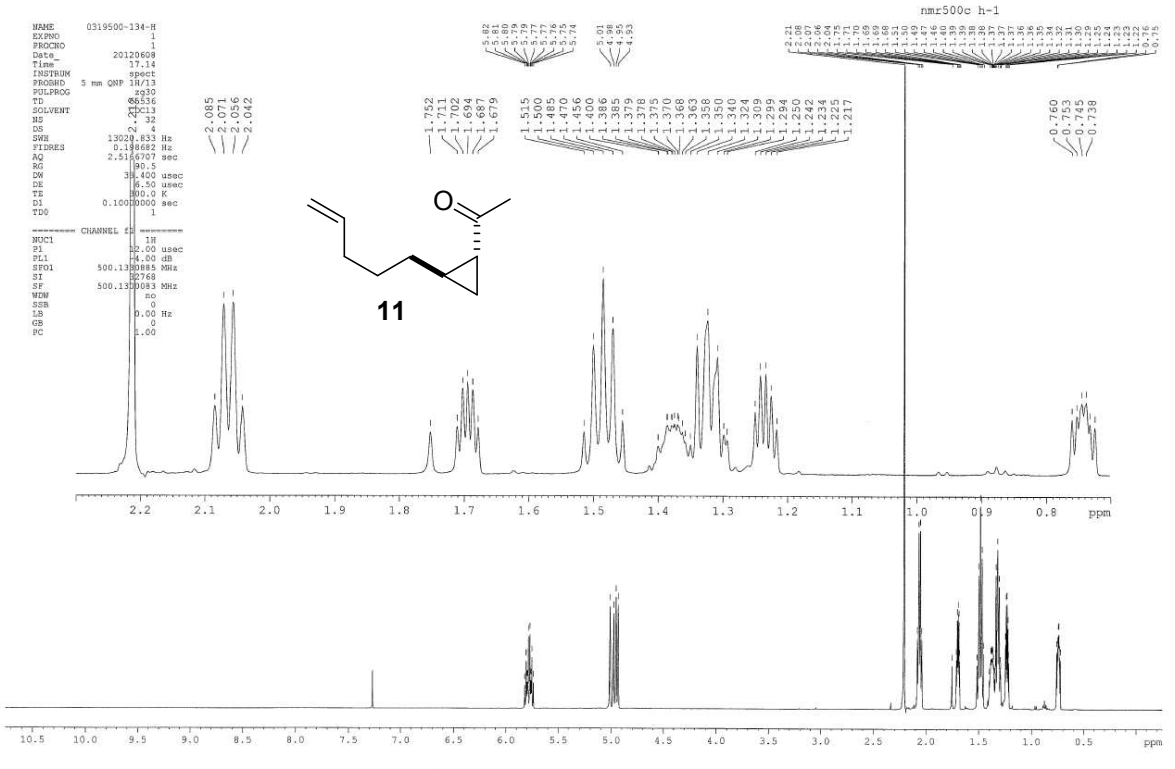
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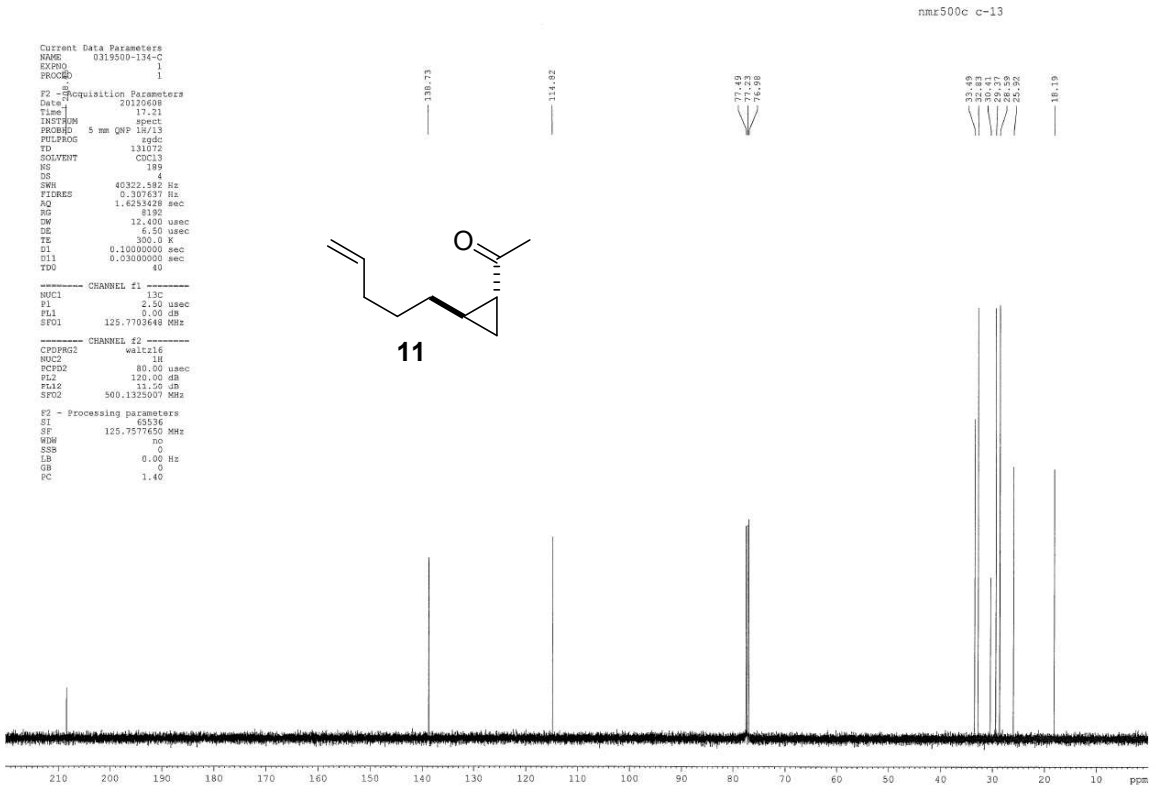
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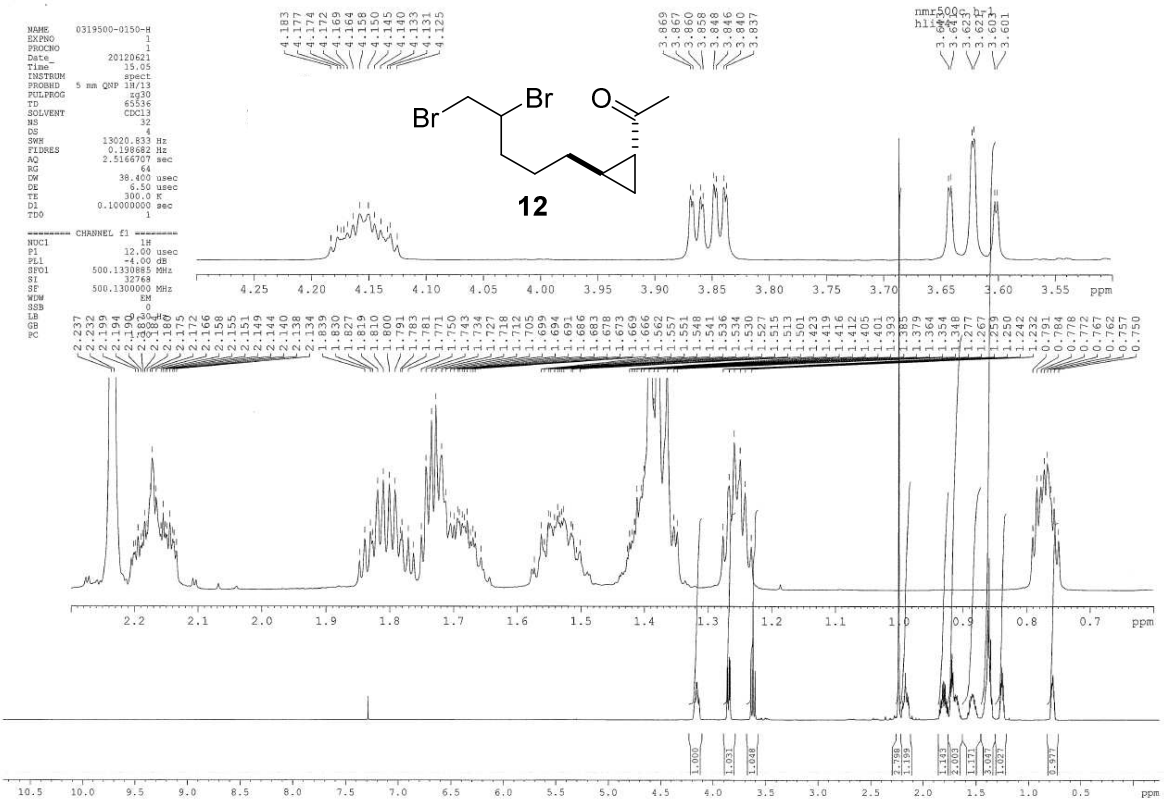
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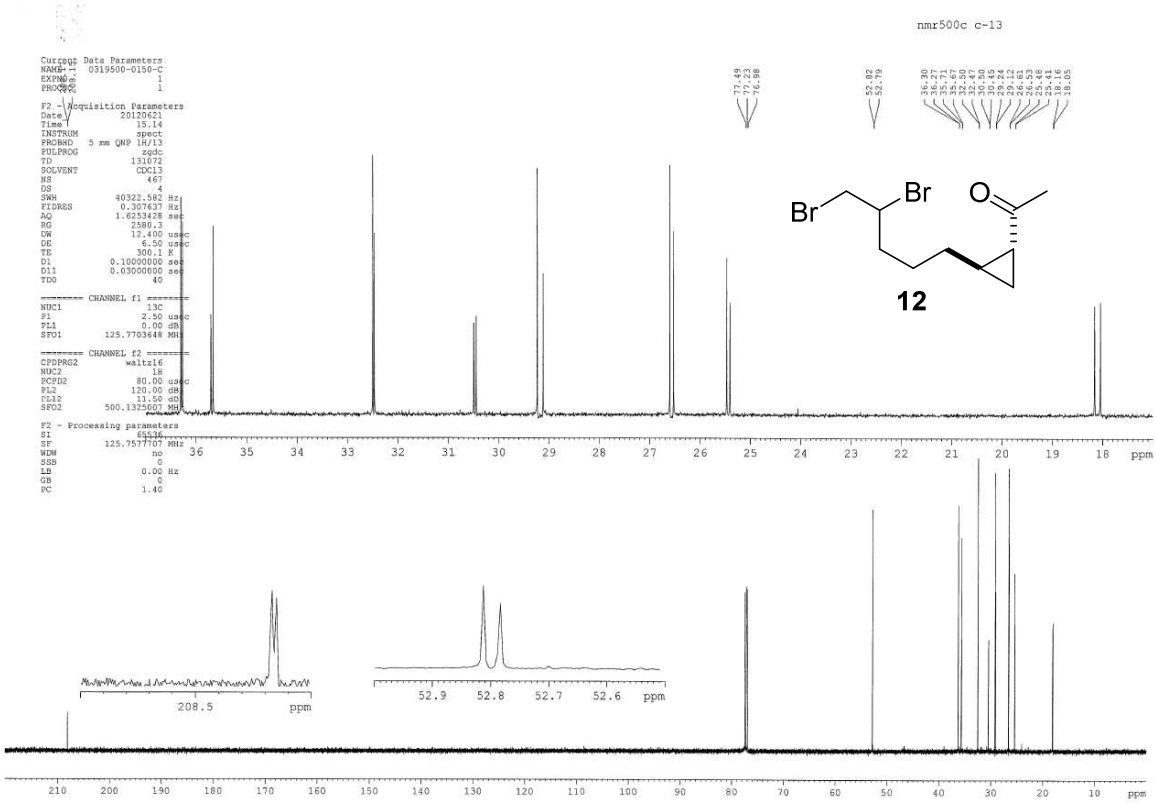
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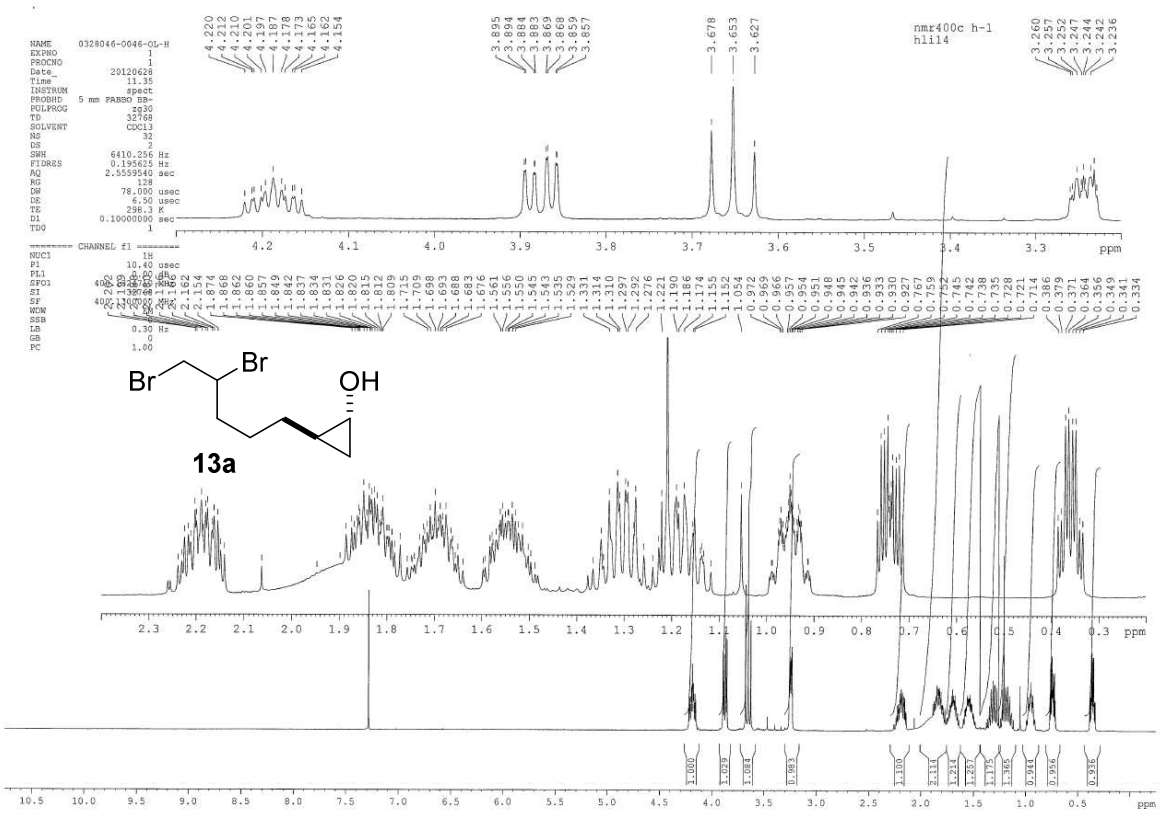
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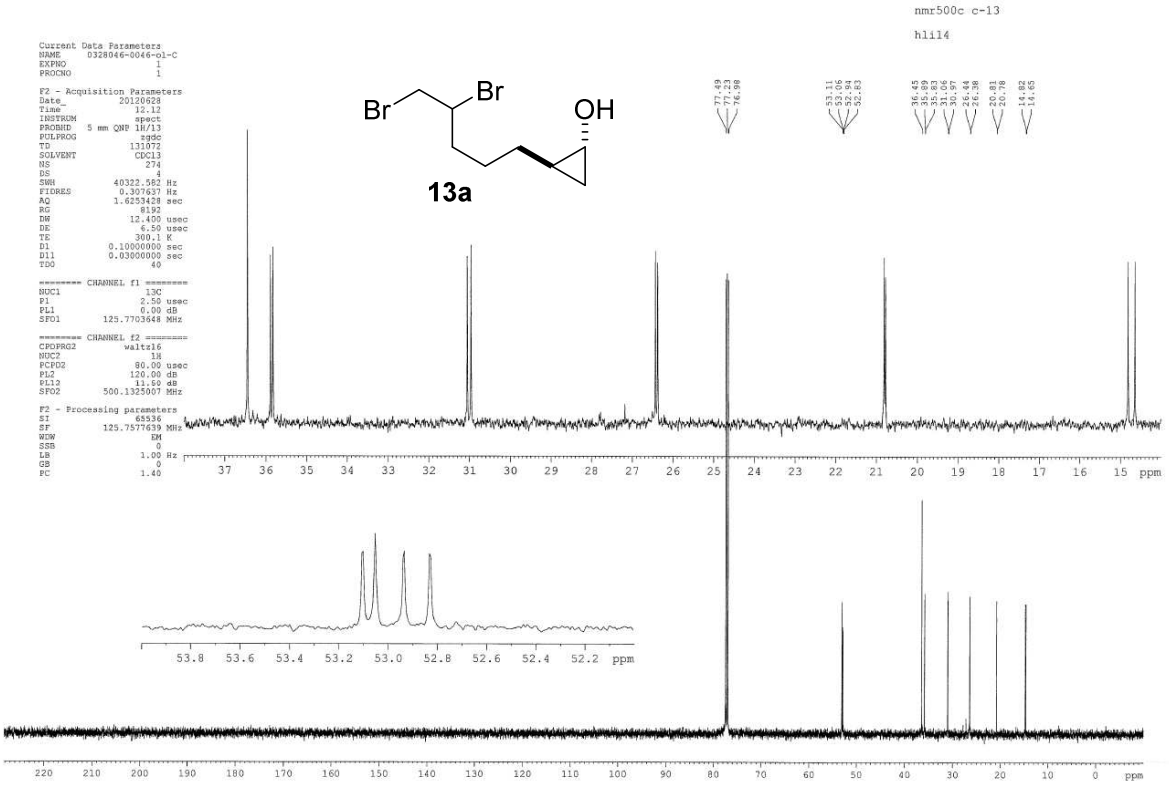
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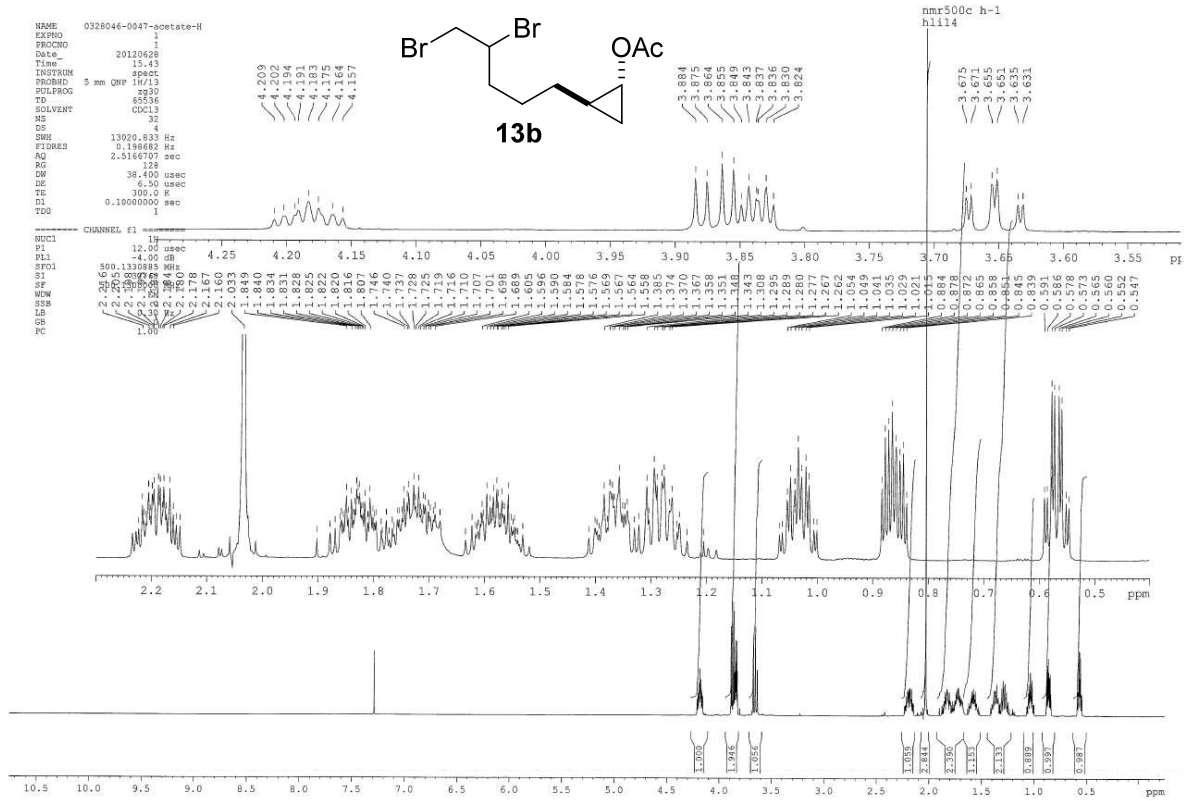
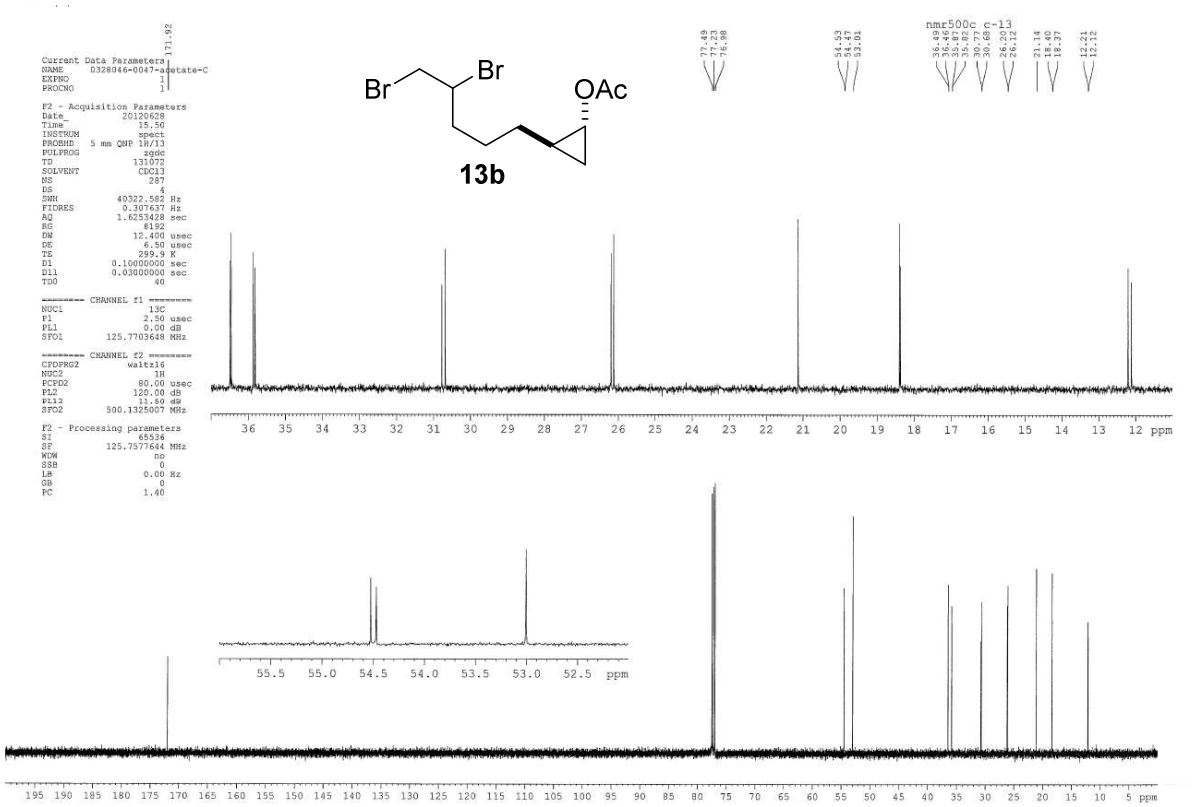
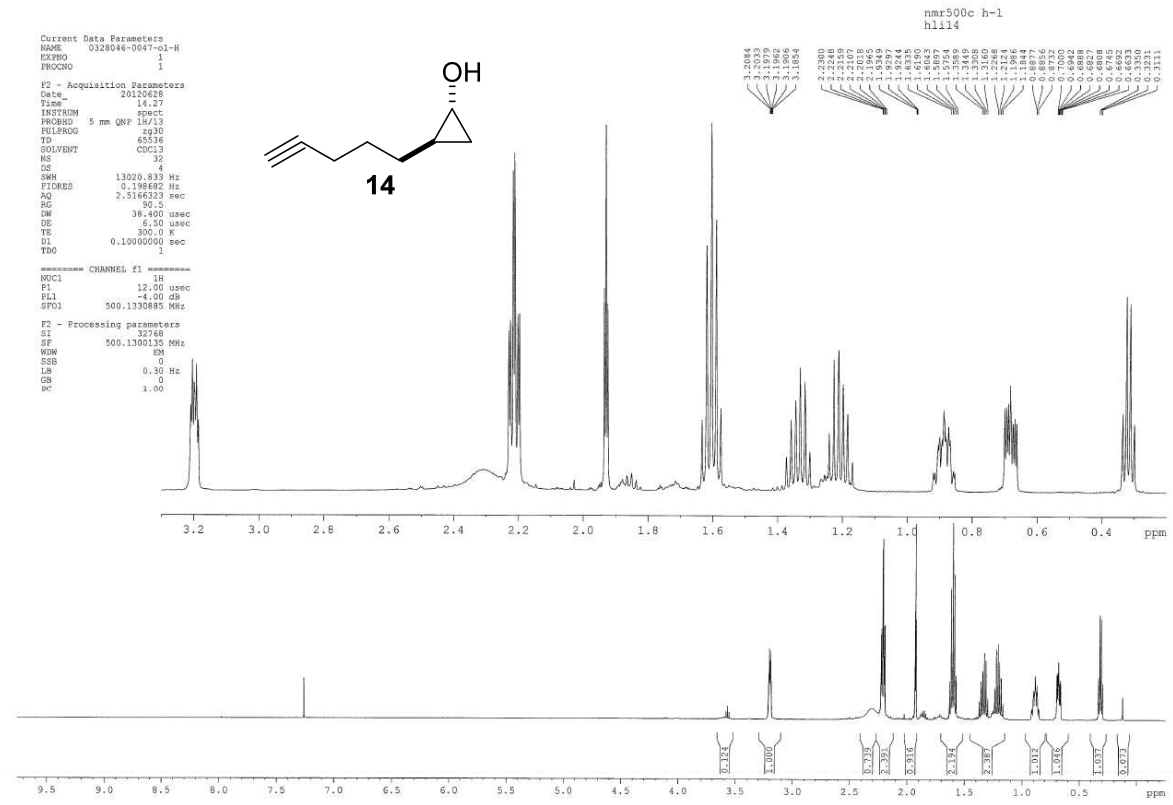
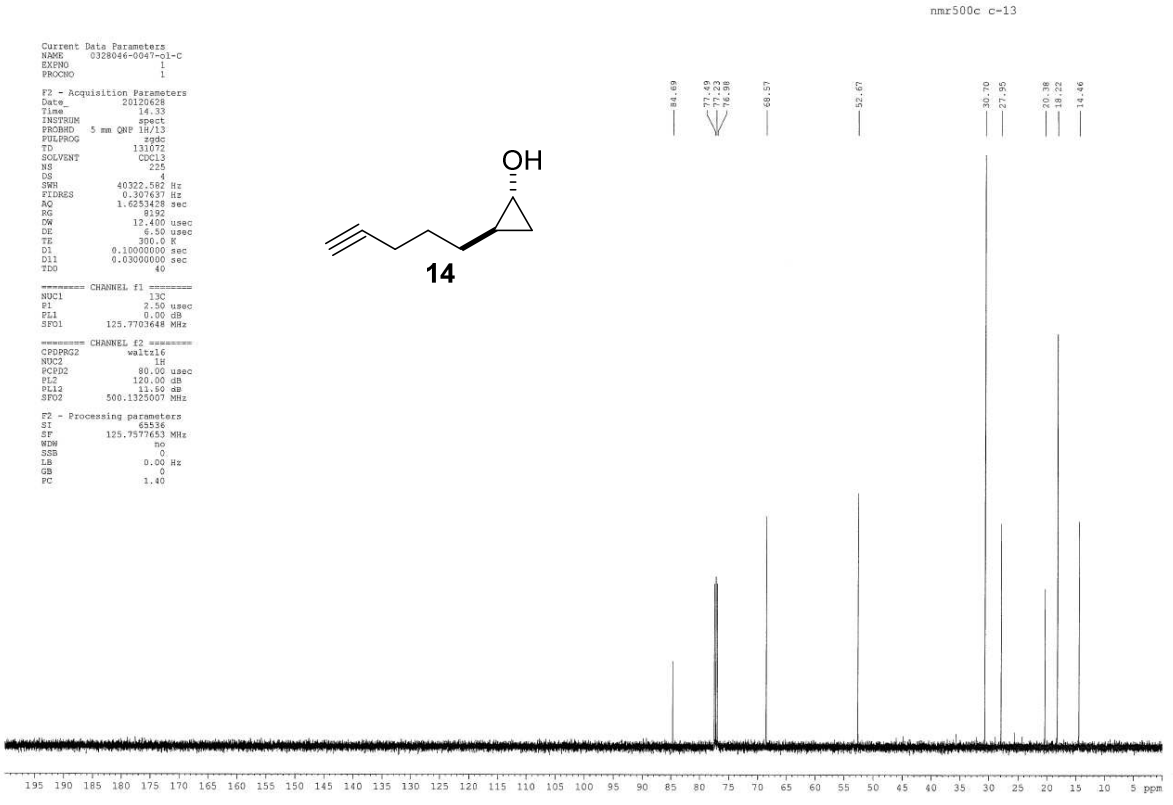
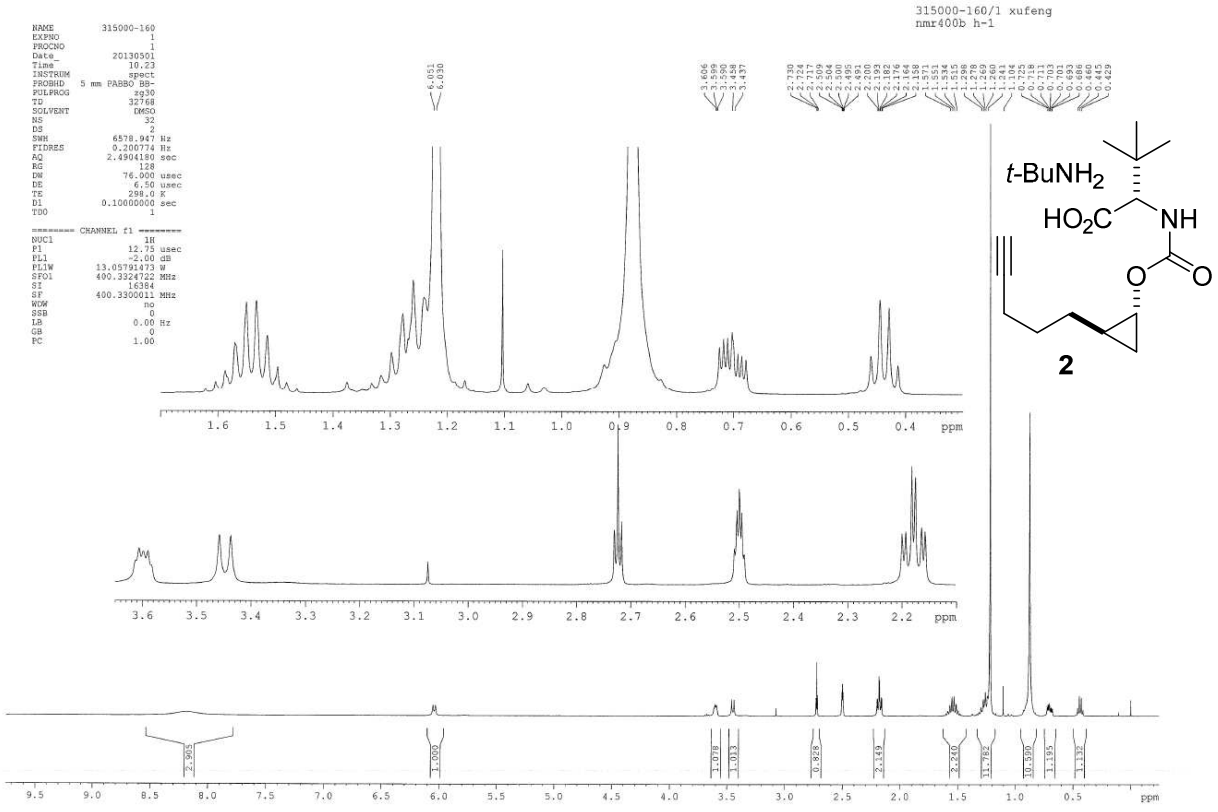
OH
13a

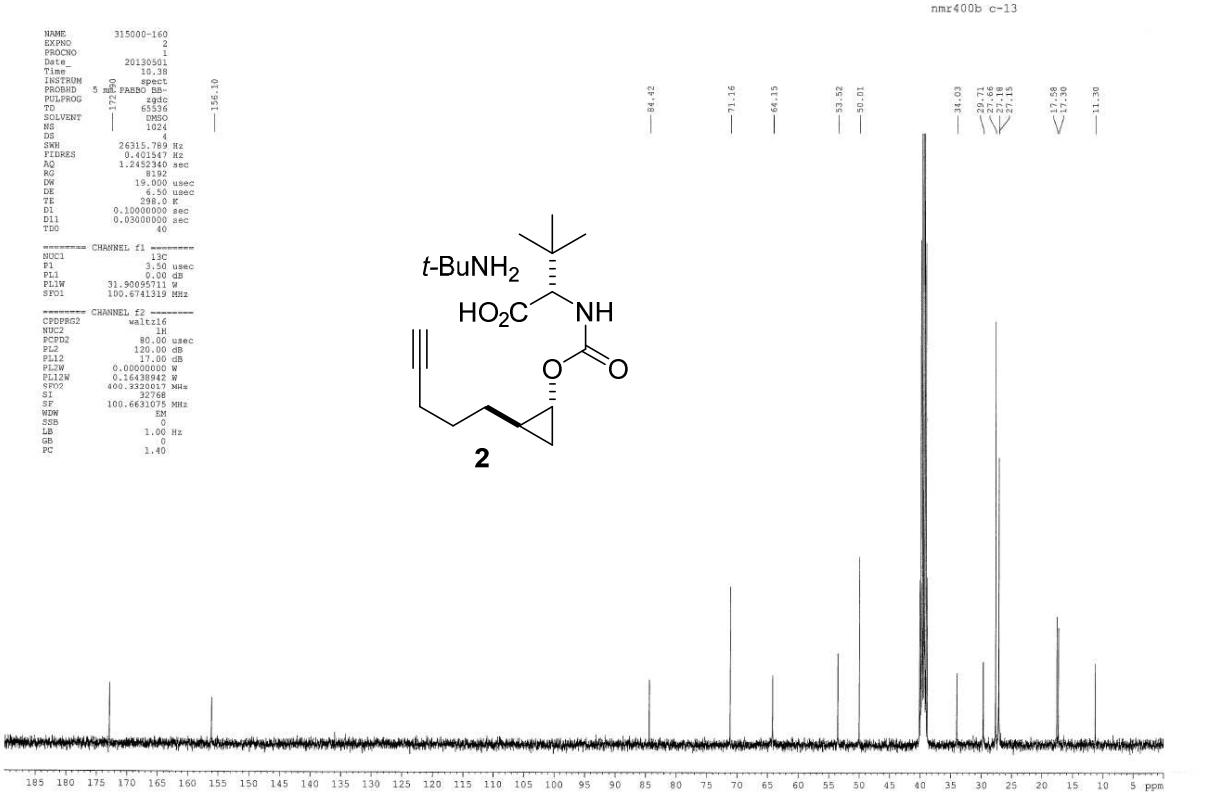

Br
Br
OAc
13b
nmr500c h-1
hli14

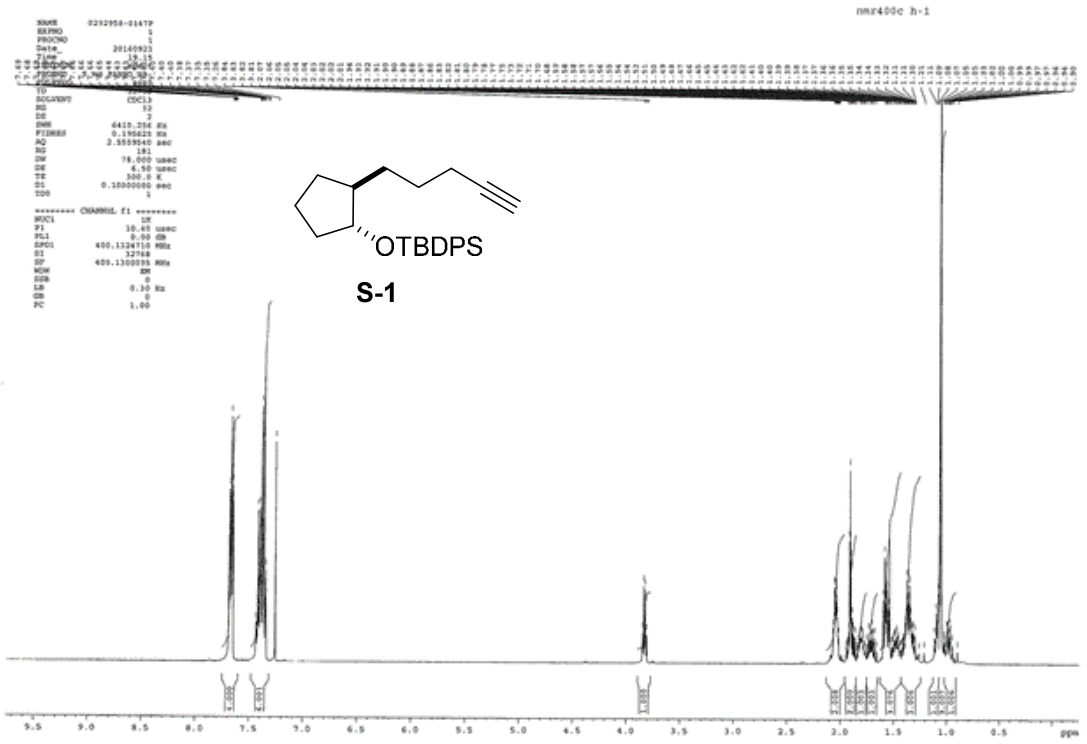

Br
Br
OAc
13b
nmr500c c-13


nmr500c h-1
hli14
OH
14
ppm


nmr500c c-13
OH
14
ppm

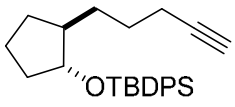

315000-160/1 xufeng
nmr400b h-1
t-BuNH2
HO2C
NH
O
O
2
ppm


nmr400b c-13
t-BuNH2
HO2C
NH
O
O
2
ppm

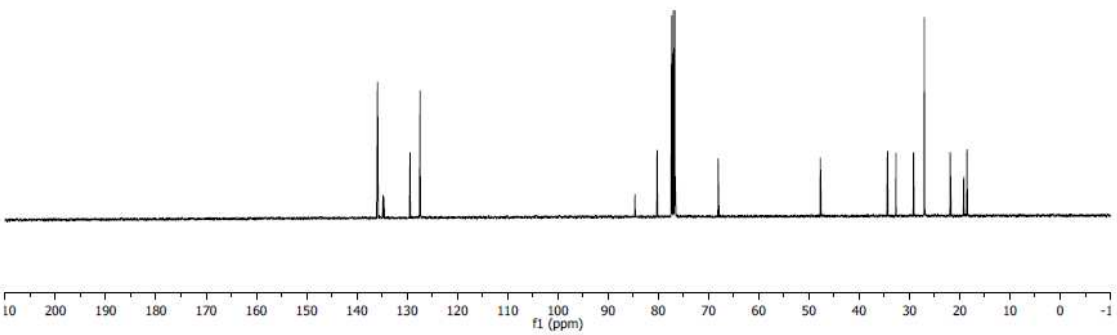

nmr400c h-1
OTBDPS

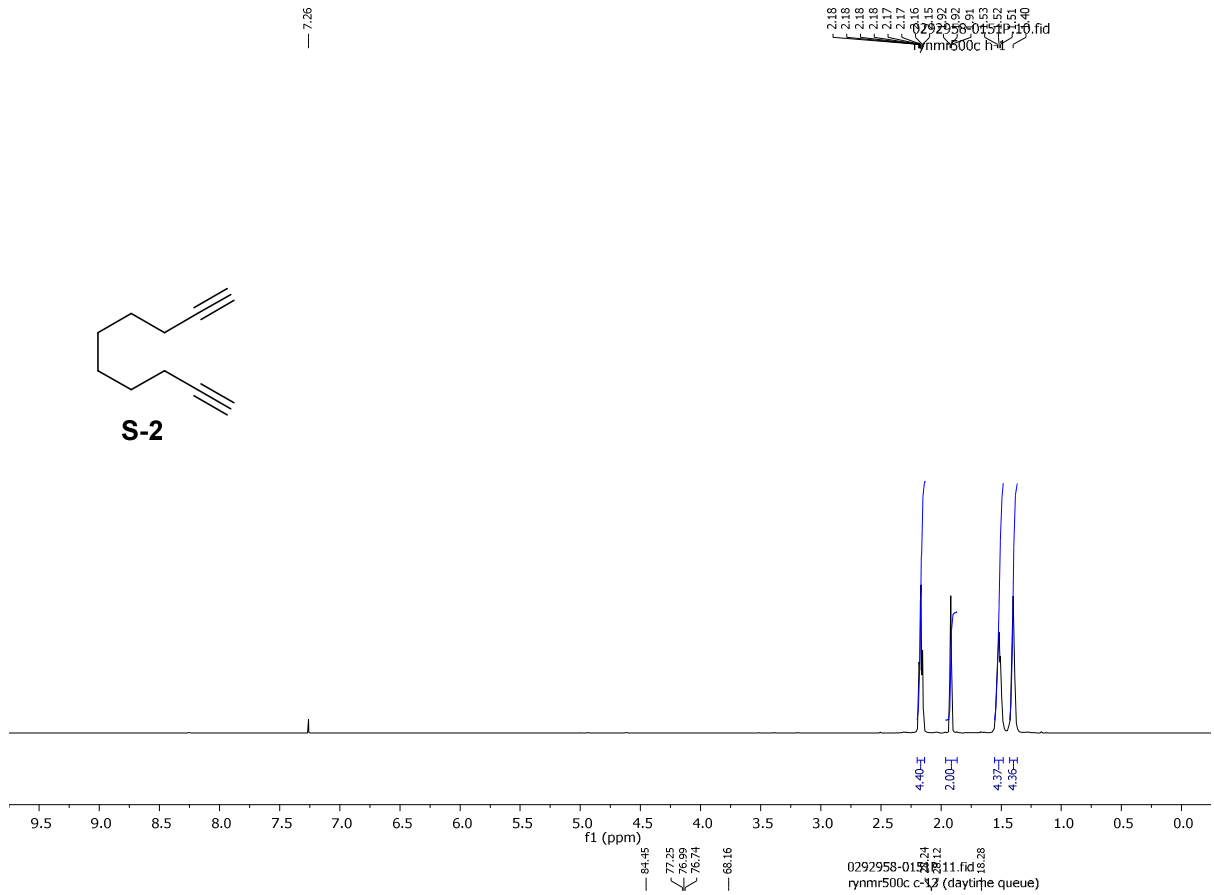
S-1

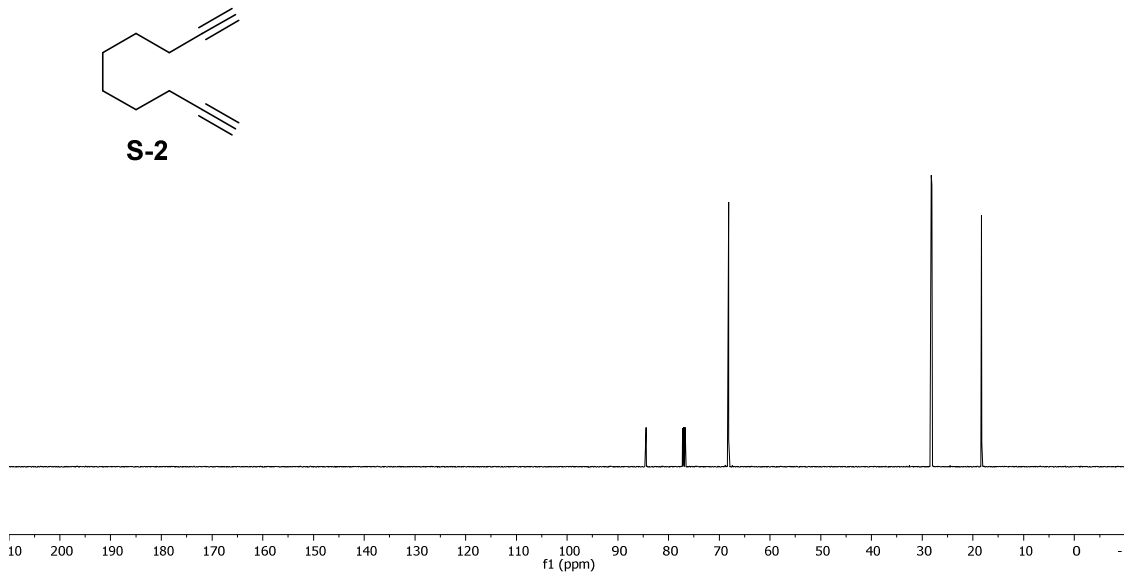

135.89
135.86
134.77
134.61
129.44
129.39
127.46
127.41
84.64
80.22
77.31
76.99
76.68
68.07
47.72
nmr400c c-13


OTBDPS

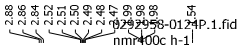
S-1

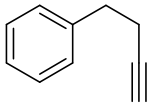

f1 (ppm)


7.26
2.18
2.18
2.18
2.18
2.17
2.17
2.16
2.15
2.92
2.92
2.91
2.53
2.52
2.51
2.40
0292958-0151P-1H.fid
rynmr500c h-1
S-2
4.40
2.00
4.37
4.36
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)
84.45
77.25
76.99
76.74
68.16
rynmr500c c-13 (daytime queue)

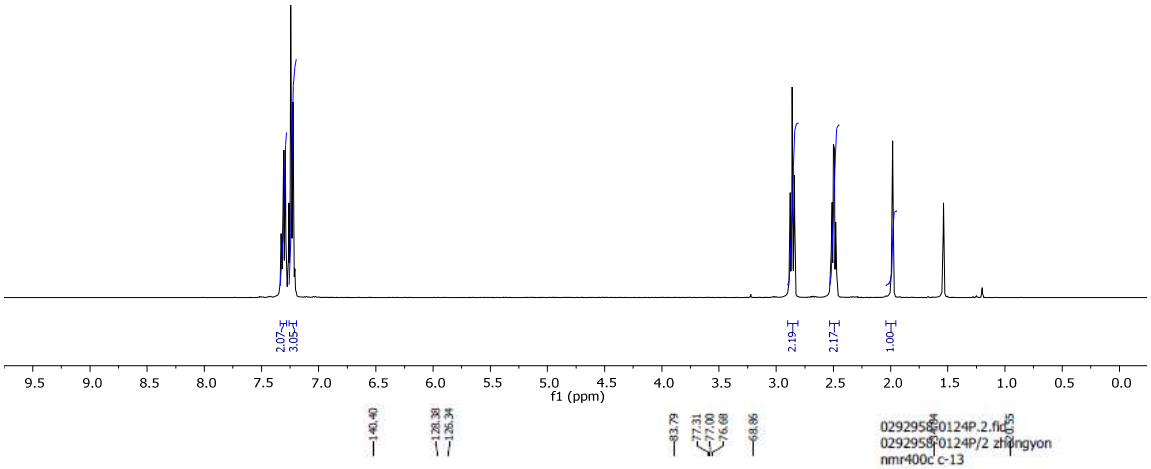

S-2
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

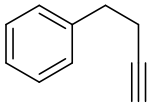

7.33
7.31
7.31
7.30
7.29
7.26
7.24
7.23
7.21
7.21


2.88
2.86
2.84
2.52
2.51
2.50
2.49
2.48
2.47
0292958-0124P.1.fid
nmr400c h-1

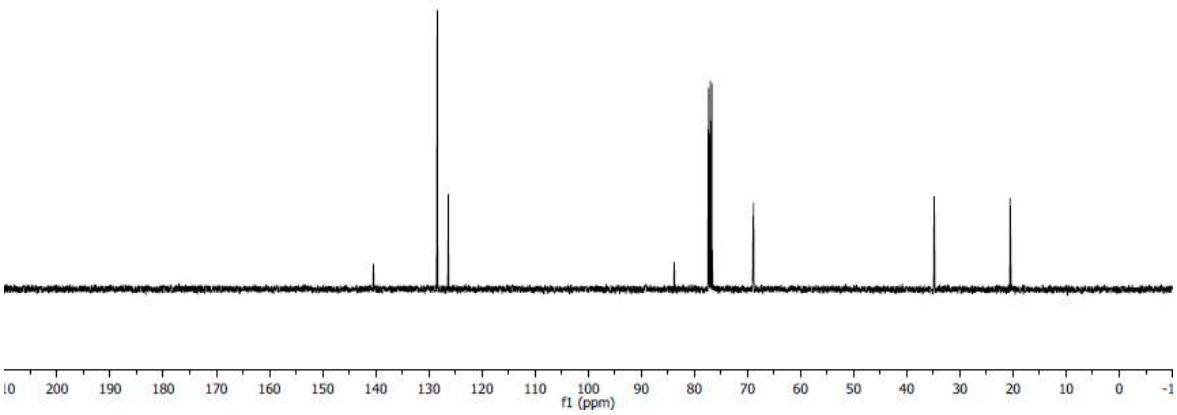


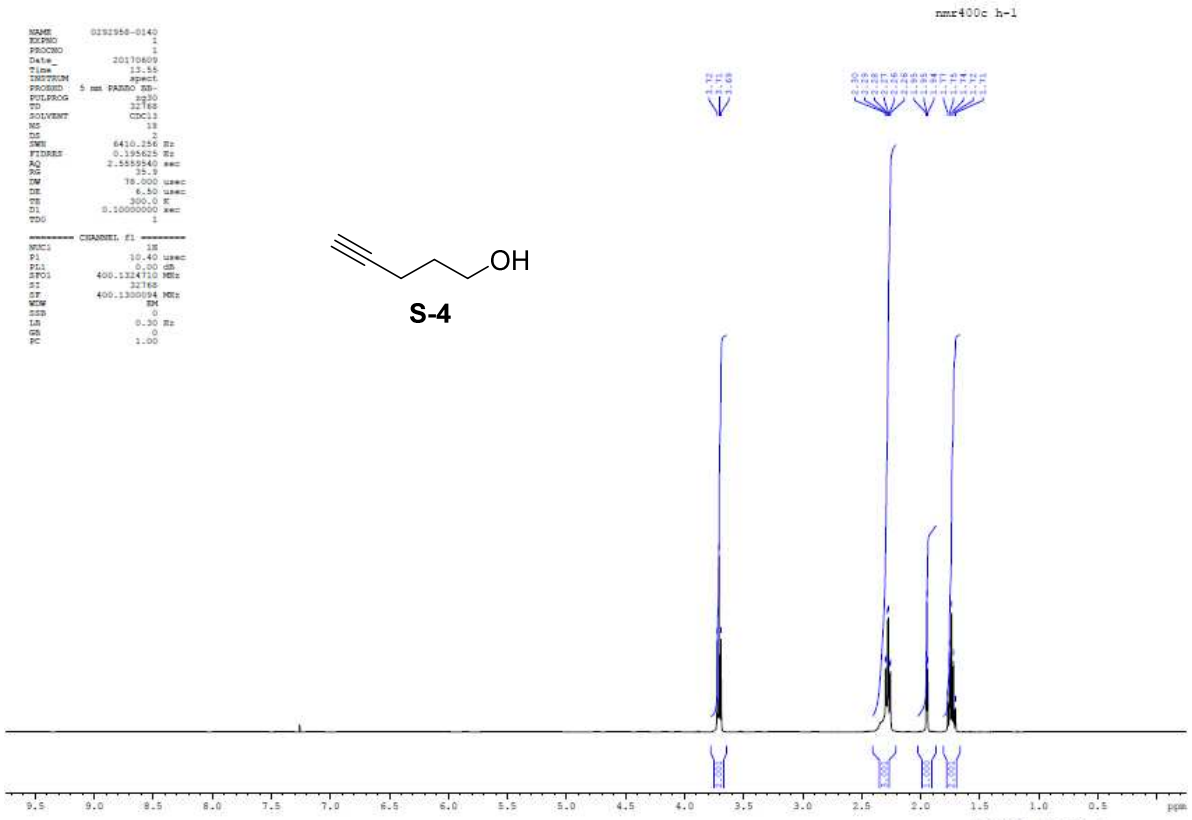
S-3

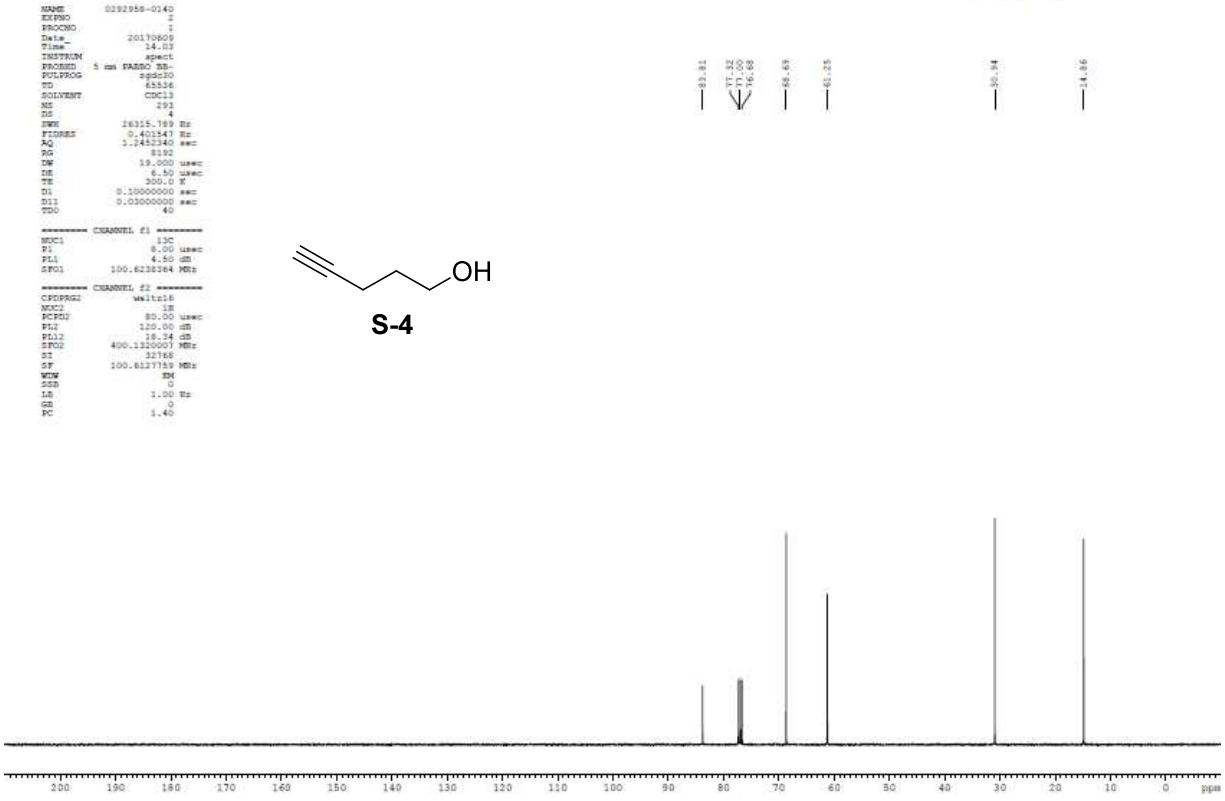

2.07
3.05
2.19
2.17
1.00
f1 (ppm)
140.40
128.38
126.34
83.79
77.31
77.00
76.68
68.86
0292958-0124P.2.fid
0292958-0124P/2 zhangyon
nmr400c c-13

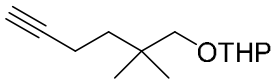


S-3


f1 (ppm)

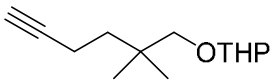

nmr400c h-1
OH
S-4


0292958-0140/2 zhongyon
nmr400c c-13
OH
S-4

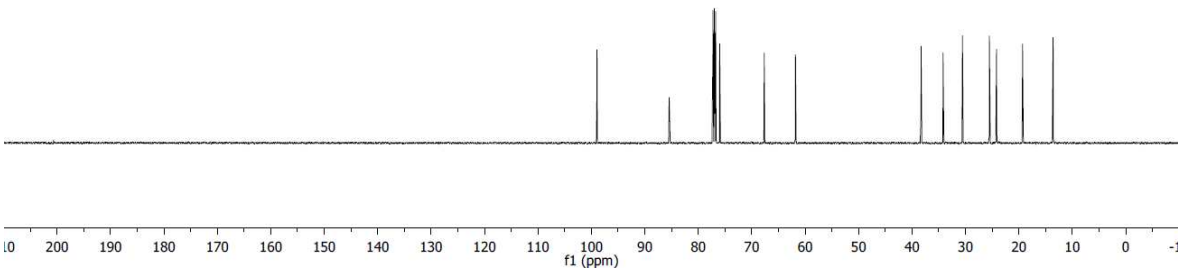

OTHP

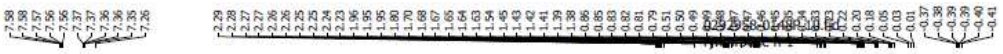
S-5

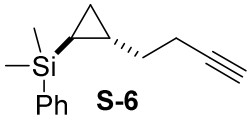
1.00
1.03
1.01
1.07
1.04
2.04
0.92
1.03
1.07
6.20
3.03
3.09
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
98.95
85.44
77.25
77.00
76.74
75.99
67.65
61.81
13.59


OTHP

S-5

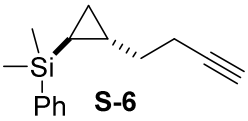

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



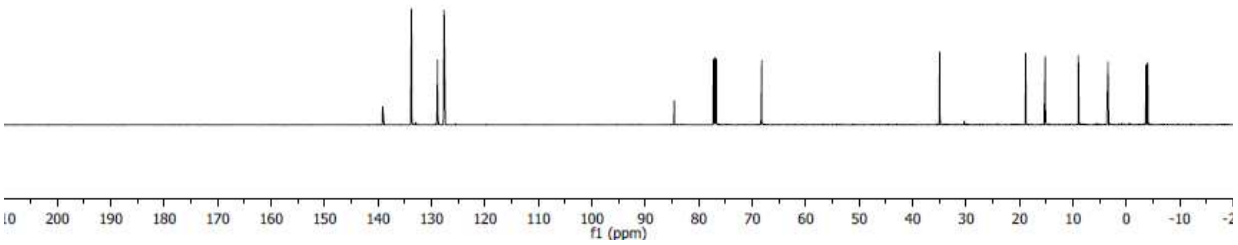

Si
Ph

S-6

1.98
2.94
2.00
0.91
1.03
1.04
0.99
2.05
2.94
3.05
0.95
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 -0.5
f1 (ppm)
139.13
133.73
128.85
127.65
84.57
77.25
77.00
76.74
68.22
0292958-0148
nynmr500c c-13 (right, 2.5 hr, nst=5120)

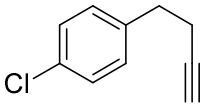

Si
Ph

S-6

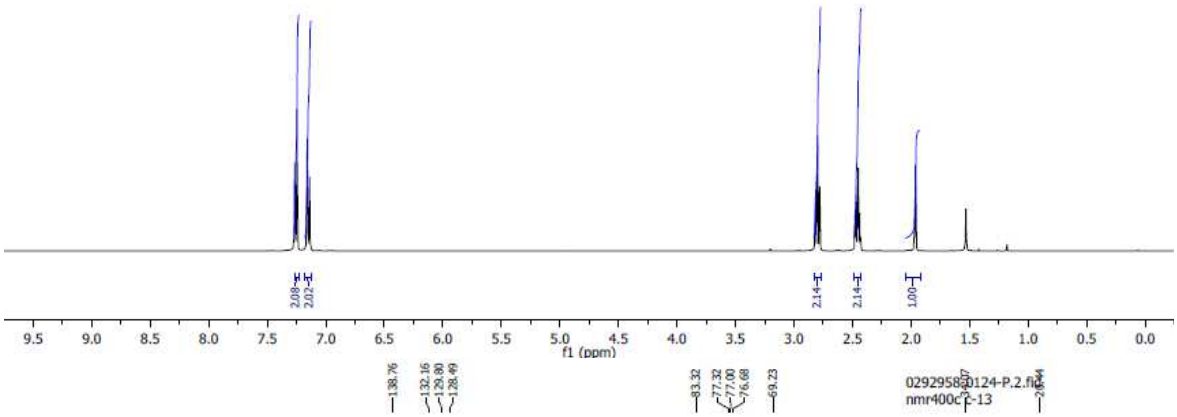

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

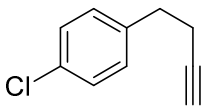

7.27
7.27
7.26
7.24
7.24
7.16
7.15
7.14


2.82
2.80
2.78
2.48
2.47
2.46
2.45
2.44
2.43
2.07
2.06
2.06
02929580-0524-P.1.fid
nmr400c h-1

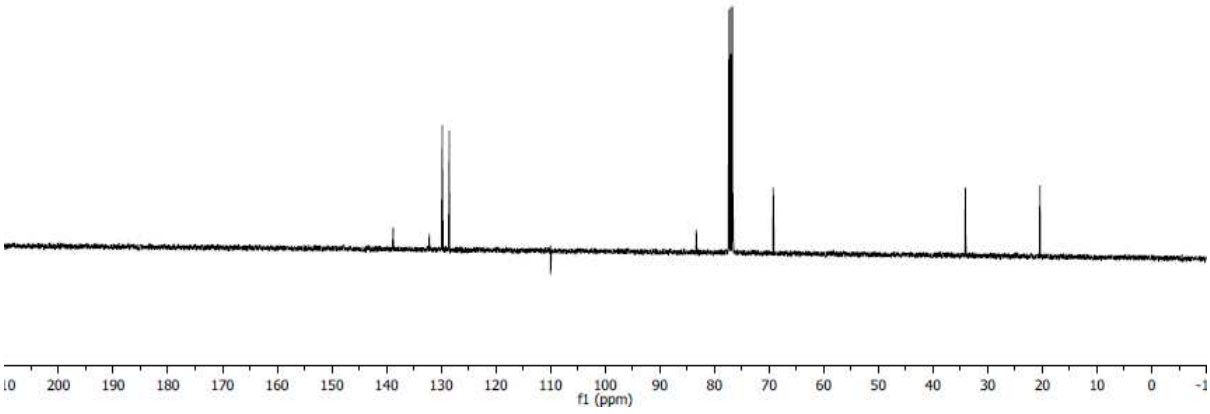

Cl

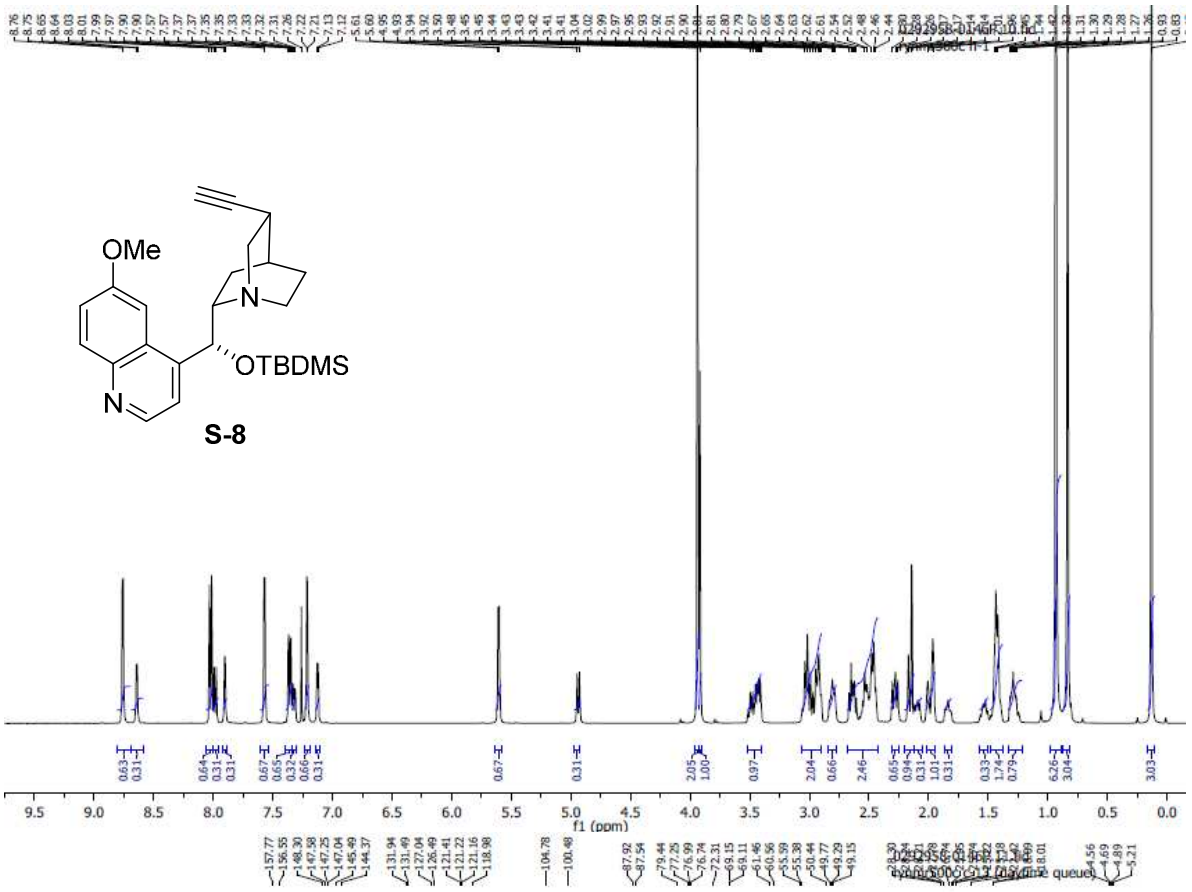
S-7


2.09
2.02
2.14
2.14
1.00
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)
138.76
132.16
129.80
128.49
83.32
77.32
77.00
76.68
69.23
02929580-0124-P.2.fid
nmr400c c-13
20.44

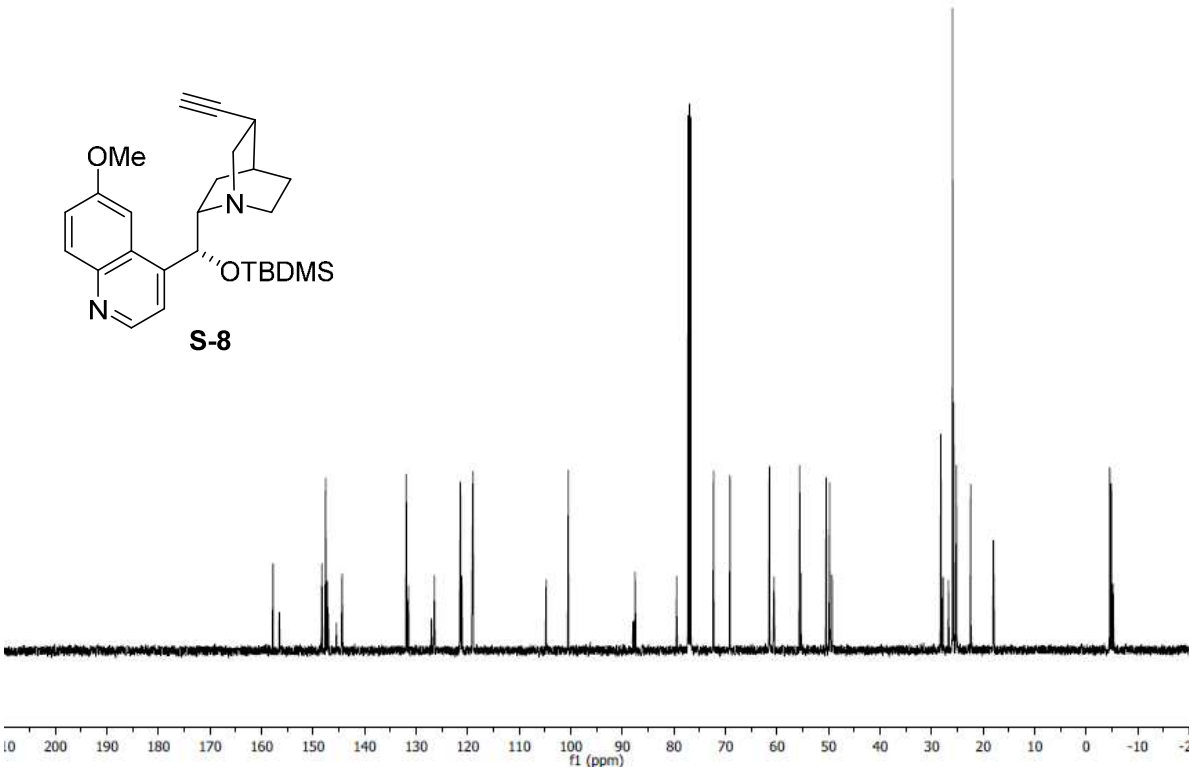

Cl

S-7


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

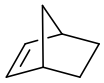


S-8

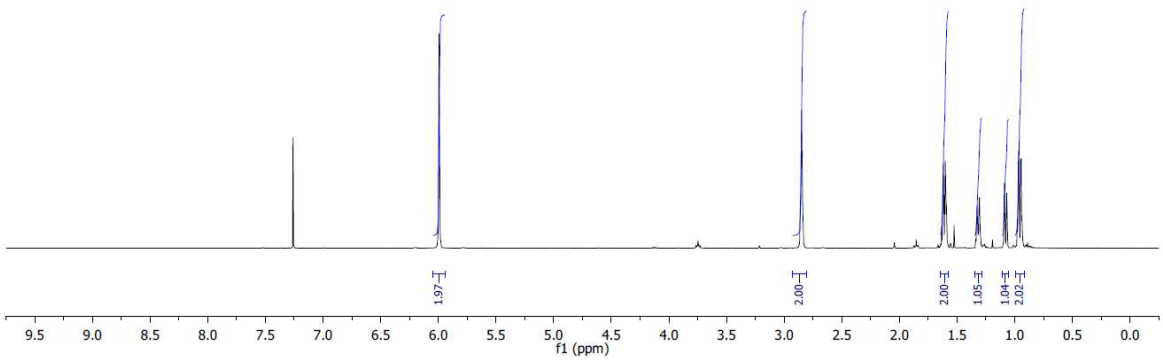


S-8

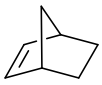

7.26
6.00
5.99
5.99
0292958-0167-P2-10.fid
0292958-0167-P2-10 zhongyon



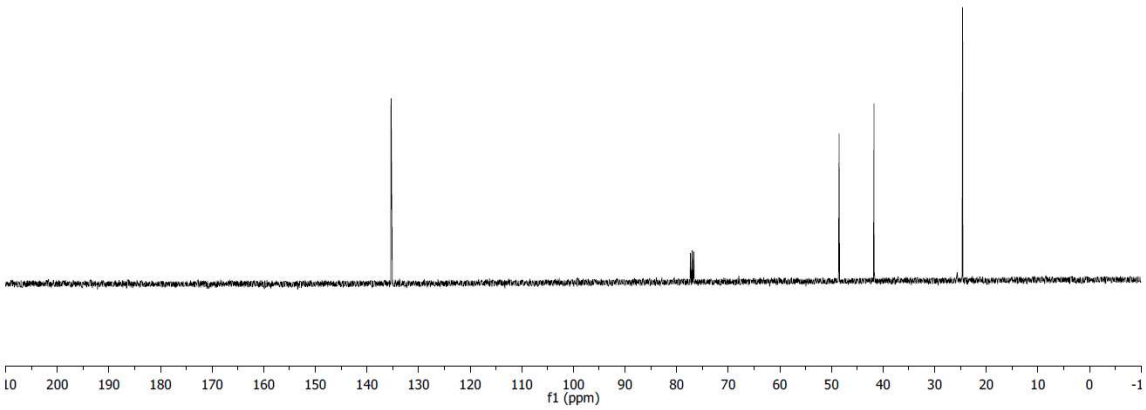
S-9


1.97
2.00
2.00
1.05
1.04
2.02
f1 (ppm)


135.32
77.32
77.00
76.68
48.52
0292958-0167-P2-20.fid
0292958-0167-P2-20 zhongyon



S-9

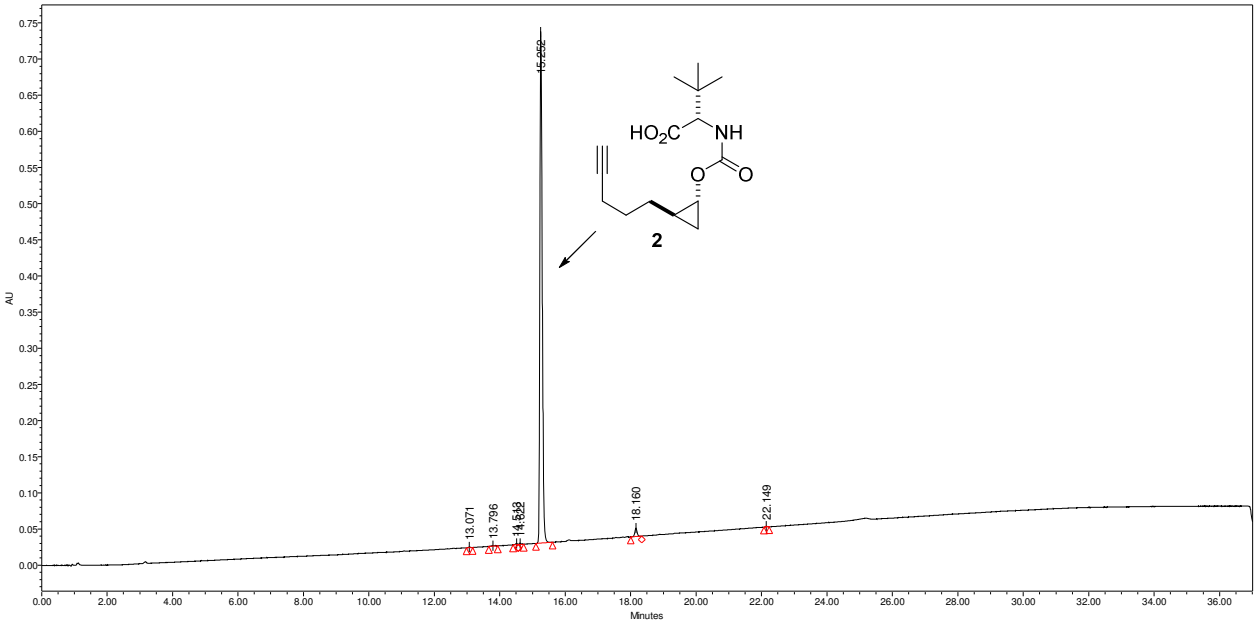

f1 (ppm)

6. HPLC and chiral HPLC chromatograms of compound 2

Column:	Ascentis Express C18 Column, 10 cm x 4.6 mm, 2.7 µm particle size
Detector:	UV at 195 nm
Temperature:	40 °C
Flow rate:	1.0 mL/min
Mobile Phase:	A: 0.1% Phosphoric acid in water B: Acetonitrile

Mobile Phase Program:

Time (min)	%B
0	10
30	85
35	95
35.1	10
40	10

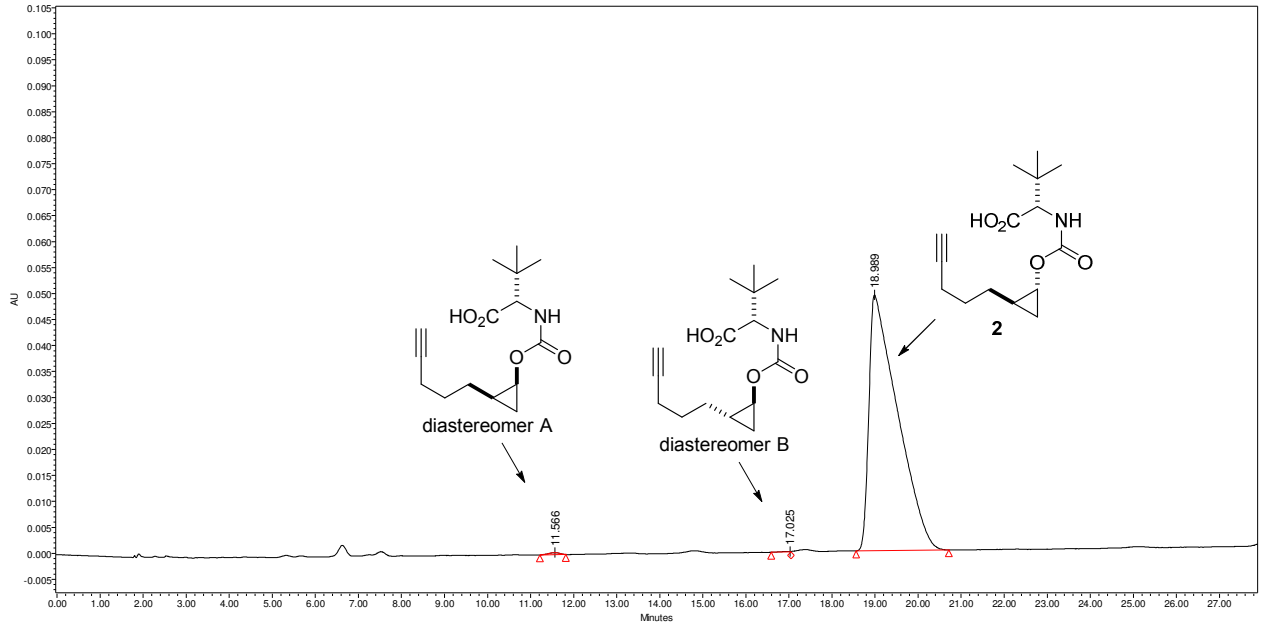


Name	RT(min)	RRT	% Area
	13.07	0.86	0.10
	13.80	0.90	0.15
	14.51	0.95	0.19
	14.62	0.96	0.19
Cmpd **2**	15.25	1.00	97.78
	18.16	1.19	1.48
	22.15	1.45	0.11

Column:	Chiralcel OJ-RH Column, 4.6 cm x 150 mm, 5 µm particle size
Detector:	UV at 210 nm
Temperature:	40 °C
Flow rate:	1.0 mL/min
Mobile Phase:	A: 0.1% Phosphoric acid in water
	B: 75:25 v/v% = Acetonitrile:Methanol

Mobile Phase Program:

Time	B%
0	30
25	35
32	85
32.1	30
40	30



	RT (min)	RRT	Area%
Diastereomer A	11.59	0.61	0.11
Diastereomer B	17.03	0.90	0.06
2	18.98	1.00	99.83