SUPPLEMENTARY INFORMATION

β-Hydroxy-γ-lactones as nucleophiles in the Nicholas reaction for the synthesis of oxepene rings. Enantioselective formal synthesis of (–)-isolaurepinnacin and (+)-rogioloxepane A

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Table of Contents

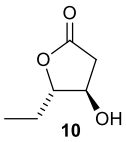
1. Materials and methods S3
2. Experimental details for the preparation of compounds **10**, *syn*-**12**, *anti*-**12**, *syn*-**6**, *anti*-**6**, *cis*-**13**, *cis*-**5**, *trans*-**13**, *trans*-**5**, **14**, **15**, **16**, **17**, **18**, **19**, **3**, **4** S3-S13
3. ^{1}H NMR and ^{13}C NMR spectra of **10** in $CDCl_3$.....S14
4. ^{1}H NMR spectra of (*S*)-Mosher's ester derivative from compound **10** in $CDCl_3$.....S15
5. ^{1}H NMR and ^{13}C NMR spectra of uncomplexed alkyne derivative from compound *syn*-**12** in $CDCl_3$ S16
6. ^{1}H NMR and ^{13}C NMR spectra of terminal alkene derivative from *syn*-**12** in $CDCl_3$.....S17
7. ^{1}H NMR and ^{13}C NMR spectra of *syn*-**6** in $CDCl_3$ S18
8. ^{1}H NMR and ^{13}C NMR spectra of uncomplexed alkyne derivative from compound *anti*-**12** in $CDCl_3$ in $CDCl_3$ S19
9. ^{1}H NMR and ^{13}C NMR spectra of terminal alkene derivative from *anti*-**12** in $CDCl_3$.....S20
10. ^{1}H NMR and ^{13}C NMR spectra of *anti*-**6** in $CDCl_3$ S21
11. ^{1}H NMR and ^{13}C NMR spectra of *cis*-**5** in $CDCl_3$ S22
12. COSY and NOESY spectra of *cis*-**5** in $CDCl_3$.....S23
13. ^{1}H NMR and ^{13}C NMR spectra of *trans*-**5** in $CDCl_3$ S24
14. NOESY spectra of *trans*-**5** in $CDCl_3$.....S25
15. ^{1}H NMR and ^{13}C NMR spectra of **14** in $CDCl_3$.....S26
16. ^{1}H NMR and ^{13}C NMR spectra of **15** in $CDCl_3$.....S27
17. ^{1}H NMR and ^{13}C NMR spectra of propargylic alcohol derivative from **14** in $CDCl_3$ S28
18. ^{1}H NMR and ^{13}C NMR spectra of **16** in $CDCl_3$.....S29
19. ^{1}H NMR and ^{13}C NMR spectra of propargylic alcohol derivative from **15** in $CDCl_3$ S30

20. ^{1}H NMR in C_6D_6 and ^{13}C NMR spectra of **17** in $CDCl_3$.....S31
21. ^{1}H NMR and ^{13}C NMR spectra of major epoxy alcohol derivative from **16** in $CDCl_3$.....S32
22. ^{1}H NMR and ^{13}C NMR spectra of minor epoxy alcohol derivative from **16** in $CDCl_3$.....S33
23. ^{1}H NMR and ^{13}C NMR spectra of **18** in $CDCl_3$.....S34
24. ^{1}H NMR and ^{13}C NMR spectra of major epoxy alcohol derivative from **17** in $CDCl_3$.....S35
25. ^{1}H NMR and ^{13}C NMR spectra of minor epoxy alcohol derivative from **17** in $CDCl_3$.....S36
26. ^{1}H NMR and ^{13}C NMR spectra of **19** in $CDCl_3$.....S37
27. ^{1}H NMR and ^{13}C NMR spectra of **3** in $CDCl_3$.....S38
28. ^{1}H NMR and ^{13}C NMR spectra of **4** in $CDCl_3$.....S39

Materials and methods.

^{1}H NMR spectra were recorded at 500, 400 or 300 MHz, ^{13}C NMR spectra were recorded at 75 or 100 MHz, and chemical shifts are reported in ppm and referenced to the solvent peak. The temperature was calibrated with methanol and ethylene glycol standards. Melting points were taken on a capillary melting point apparatus and are uncorrected. Optical rotations were determined for solutions in chloroform. Column chromatographies were performed on silica gel, 60Å and 0.2-0.5mm. Compounds were visualized by use of UV light, 2.5% phosphomolybdic acid in ethanol or vanillin with acetic and sulfuric acid in ethanol with heating. All solvents were purified by standard techniques.[1] Reactions requiring anhydrous conditions were performed under nitrogen. Anhydrous magnesium sulfate was used for drying solutions.

Preparation of the (4*R*,5*S*)-5-Ethyl-4-hydroxydihydrofuran-2(3H)-one (10).



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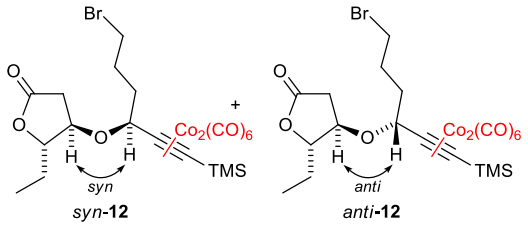
To a solution of commercially available methyl *trans*-3-hexenoate (15 mL, 13.7 g, 104.7 mmol) in acetonitrile (1.2 L) at 0ºC was added buffer solution [600 mL of aqueous solution 0.05 M $Na_2B_4O_7{\cdot}10H_2O$ and $4{\cdot}10^{-4}$ M in Na_2(EDTA)], tetrabutylammoniun hydrogen sulfate (1.5 g, 4.2 mmol) and the commercially available Shi's ketone **9** (13.8 g, 52.4 mmol). Immediately, two solutions were added simultaneously dropwise (with the aid of syringe pump): Oxone® [96.6 g, 157.1 mmol, dissolved in 390 mL of aqueous $4{\cdot}10^{-4}$ M Na_2(EDTA)] and K_2CO_3 (92.1 g, 659.6 mmol, dissolved in 390 mL of water) in a period of 1.5 h. After this time, the reaction mixture was diluted with hexane and water, and extracted with hexane (3 x 600 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated (with several portions of acetone to obtain an azeotrope) to yield the crude epoxide as an oil, which was used without further purification.

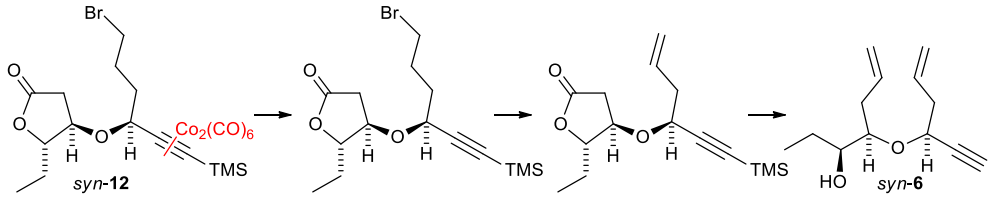
A solution of the above crude epoxide in 3% H_2SO_4 aqueous (1000 mL) was stirred at room temperature until TLC showed complete conversion (ca. 45 minutes). After this time, the reaction mixture was carefully neutralized with powder $NaHCO_3$ until pH = 7. Then, the reaction mixture was saturated with NaCl and extracted CH_2Cl_2 (3 x 500 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography with silica gel (hexane/ethyl acetate = 1/2) and subsequent distillation at 120ºC and 2 mmHg yielding *trans*-β-hydroxy-γ-lactone (**10**) (11.1 g, 81 % yield) as a colorless oil: $[\alpha]^{25}_{D}$ – 18.6 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.5 Hz, 3H), 1.60 (m, 2H), 2.45 (dd, *J* = 18.1, 3.4 Hz, 1H), 2.76 (dd, *J* = 18.1, 6.6 Hz, 1H), 3.91(s, 1H), 4.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.6 (q), 26.1 (t), 37.7 (t), 71.1 (d), 89.6 (d), 176.2 (s); IR (film NaCl plates) (cm^{-1}) 3434, 2973, 2941, 1770, 1191; HRMS (ESI) *m/z* calcd for $C_6H_{10}O_3Na$ $[M+Na]^+$: 153.0528, found: 153.0526.

Preparation of the (4*R*,5*S*)-4-(((*S*)-6-Bromo-1-(trimethylsilyl)hex-1-yn-3-yl)oxy)-5-ethyldihydrofuran-2(3H)-one hexacarbonyl dicobalt complex (*syn*-12) and (4*R*,5*S*)-4-(((*R*)-6-Bromo-1-(trimethylsilyl)hex-1-yn-3-yl)oxy)-5-ethyldihydrofuran-2(3H)-one hexacarbonyl dicobalt complex (*anti*-12).



To a solution of cobalt complex **9** (300 mg, 0.56 mmol) and γ-lactone **10** (360 mg, 2.77 mmol) in dry CH_2Cl_2 (1.2 mL) at 0ºC under argon was added $BF_3{\cdot}OEt_2$ (82 µL, 0.66 mmol). After 2 hours the reaction was quenched adding a saturated solution of $NaHCO_3$, followed by extraction with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. This procedure was repeated 35 times in a carousel.[1] The crude was purified by column chromatography with silica gel (hexane/ethyl acetate = 9/1) to yield *syn*-**12** (4.45 g, 35 % yield) and *anti*-**12** (4.45 g, 35 % yield) both of them as a slurry red oil.

Preparation of the (3*S*,4*R*)-4-(((*S*)-Hex-5-en-1-yn-3-yl)oxy)hept-6-en-3-ol (*syn*-6).



To a solution of *syn*-**12** (4.40 g, 6.80 mmol) in acetone (23 mL) at 0ºC was added ceric ammonium nitrate (13.31 g, 23.8 mmol) portionwise. Then the reaction mixture was stirred at room temperature until TLC showed complete conversion (ca. 1 h), and then was poured into 30 mL of water and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and the crude was purified by column chromatography with silica gel (hexane/ethyl acetate = 6/1) to yield the uncomplexed alkyne (2.38 g, 97 % yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 9H), 1.01 (t, *J* = 7.4 Hz, 3H), 1.68 (m, 2H), 1.82 (m, 2H), 1.98 (m, 2H), 2.44 (dd, *J* = 18.0, 3.8 Hz, 1H), 2.75 (dd, *J* = 17.9, 7.0 Hz, 1H), 3.40 (t, *J* = 6.5 Hz, 2H), 4.07 (t, *J* = 6.1 Hz, 1H), 4.26 (m, 1H), 4.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.1 (q), 9.5 (q), 26.4 (t), 28.4 (t), 33.3 (t), 34.3 (t), 35.0 (t), 68.3 (d), 76.3 (d), 86.9 (d), 92.2 (s), 103.2 (s), 174.7 (s); IR (film NaCl plates) (cm^{-1}) 2966, 2941, 2171, 1784, 1251; HRMS (ESI) *m/z* calcd for $C_{15}H_{25}{}^{79}BrO_3SiNa$ $[M+Na]^+$: 383.0654, found: 383.0644.

To a solution of *o*-NO_2PhSeCN (1.80 g, 4.98 mmol) in EtOH (50 mL) at 0ºC under argon was added $NaBH_4$ (250 mg, 6.47 mmol). The mixture was stirred for 15 minutes and then the uncomplexed alkyne obtained before (1.8 g, 4.98 mmol) was added. After 15 minutes, the reaction mixture was warmed to room temperature and stirred for 3 h. Then, the reaction mixture was poured into 40 mL of water and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to yield a crude oil which was used in the next step without purification. The previous crude was dissolved in 60 mL of dry THF at 0ºC was added H_2O_2 35 wt. % solution in H_2O (0.51 mL, 5.98 mmol). After 15 minutes at 0ºC, the reaction mixture was warmed to room temperature and stirred for 3 h. Then, the reaction mixture was poured into 60 mL of water and extracted with CH_2Cl_2 (3 x 60 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification by column chromatography with silica gel (hexane/ethyl acetate = 9/1) afforded the terminal alkene (1.39 g, quantitative) as a slightly yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.17 (s, 9H), 1.03 (t, *J* = 7.4 Hz, 3H), 1.70 (m, 2H), 2.43 (t, *J* = 6.7 Hz, 2H), 2.48 (dd, *J* = 18.1, 3.9 Hz, 1H), 2.76 (dd, *J* = 18.0, 7.0 Hz, 1H), 4.04 (t, *J* = 6.5 Hz, 1H), 4.28 (m, 1H),

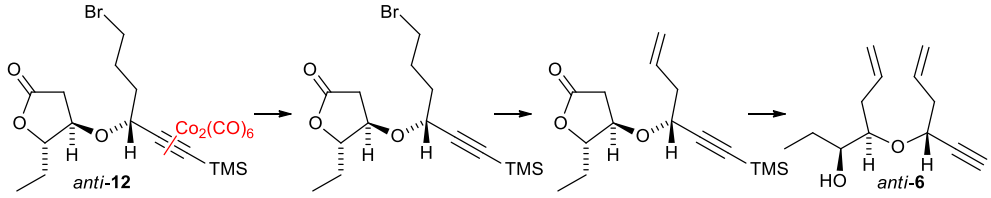
1.- This reaction can be run in a multigram scale, however, we observed a detriment in the yield of about 10%.

4.43 (m, 1H), 5.11 (m, 2H), 5.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.1 (q), 9.5 (q), 26.4 (t), 35.1 (t), 40.3 (t), 68.9 (d), 76.3 (d), 87.0 (d), 92.1 (s), 103.4 (s), 118.3 (t), 133.0 (d), 174.9 (s); IR (film NaCl plates) (cm^{-1}) 3081, 2967, 2172, 1783, 1251; HRMS (ESI) *m/z* calcd for $C_{15}H_{24}O_3SiNa$ $[M+Na]^+$: 303.1392, found: 303.1396.

To a solution of the terminal alkene obtained before (1.20 g, 4.28 mmol) in dry Et_2O (43 mL) at −85ºC under argon atmosphere it was added a DIBAL-H solution (4.70 mL, 1 M in heptane). The reaction was monitored by TLC and quenched adding 0.5 mL of H_2O. After gel formation, it was added $MgSO_4$ and filtered over a pad of Celite and washed several times with EtOAc. The solvent was removed under reduced pressure and the crude obtained was used without any further purification.

To a suspension of methyltriphenylphosphonium bromide (3.91 g, 10.7 mmol) in dry THF (40 mL) at 0ºC under argon was added *n*-BuLi (0.94 mL of solution 10 M in hexane, 9.42 mmol) dropwise and the reaction mixture was stirred for 30 minutes. Then, this solution was added over a solution of the lactol obtained above in dry THF (30 mL) at −17ºC under argon. The reaction was kept at such temperature until TLC showed complete conversion (ca. 24 h), and then quenched adding 40 mL of H_2O and the reaction mixture was warmed to room temperature and stirred for 1/2 h. After this time, the reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by column chromatography with silica gel (hexane/ethyl acetate: 9/1) to give the diene *syn*-**6** (796 mg, 89 % yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (td, *J* = 7.4, 2.0 Hz, 3H), 1.48 (m, 2H), 2.05 (m, 1H), 2.25 (m, 1H), 2.35 (m, 1H), 2.46 (br, 3H), 3.65 (m, 2H), 4.18 (m, 1H), 5.10 (m, 4H), 5.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5 (q), 25.1 (t), 33.9 (t), 40.5 (t), 68.5 (d), 74.2 (d), 74.3 (d), 80.9 (d), 83.2 (d), 117.3 (t), 118.0 (t), 133.4 (d), 135.2 (d); IR (film NaCl plates) (cm^{-1}) 3458, 3304, 3079, 2967, 1080; HRMS (ESI) *m/z* calcd for $C_{13}H_{20}O_2Na$ $[M+Na]^+$: 231.1361, found: 231.1362.

Preparation of the (3*S*,4*R*)-4-(((*R*)-Hex-5-en-1-yn-3-yl)oxy)hept-6-en-3-ol (*anti*-6).



To a solution of *anti*-**12** (4.45 g, 6.87 mmol) in acetone (23 mL) at 0ºC was added ceric ammonium nitrate (13.45 g, 24.0 mmol) portionwise. Then the reaction mixture was stirred at room temperature until TLC showed complete conversion (ca. 1 h), and then was poured into 30 mL of water and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and the crude was purified by column chromatography with silica gel (hexane/ethyl acetate = 6/1) to yield the uncomplexed alkyne (2.38 g, 96 % yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.17 (s, 9H), 1.02 (t, *J* = 7.4 Hz, 3H), 1.66 (m, 2H), 1.84 (m, 2H), 2.00 (m, 2H), 2.67 (dd, *J* = 18.2, 3.6 Hz, 1H), 2.87 (dd, *J* = 18.2, 7.0 Hz, 1H), 3.42 (t, *J* = 6.5 Hz, 2H), 4.17 (m, 2H), 4.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.1 (q), 9.6 (q), 26.6 (t), 28.5 (t), 33.3 (t), 34.4 (t), 36.1 (t), 68.5 (d), 77.0 (d), 85.8 (d), 92.6 (s), 103.3 (s), 175.1 (s); IR (film NaCl plates) (cm^{-1}) 2965, 2882, 2171, 1784, 1251; HRMS (ESI) *m/z* calcd for $C_{15}H_{25}{}^{79}BrO_3SiNa$ $[M+Na]^+$: 383.0654, found: 383.0660.

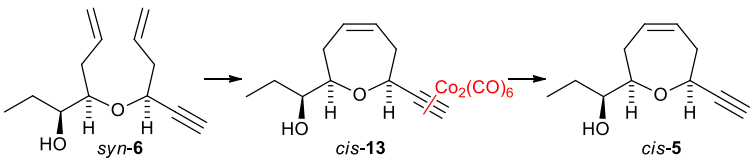
To a solution of *o*-$NO_2PhSeCN$ (1.80 g, 4.98 mmol) in EtOH (50 mL) at 0ºC under argon was added $NaBH_4$ (250 mg, 6.47 mmol). The mixture was stirred for 15 minutes and then the uncomplexed alkyne obtained before (1.8 g, 4.98 mmol) was added. After 15 minutes, the reaction mixture was warmed to room temperature and stirred for 3 h. Then, the reaction mixture was poured into 40 mL of water and extracted

with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to yield a crude oil which was used in the next step without purification. The previous crude was dissolved in 60 mL of dry THF at 0ºC was added H_2O_2 35 wt. % solution in H_2O (0.51 mL, 5.98 mmol). After 15 minutes at 0ºC, the reaction mixture was warmed to room temperature and stirred for 3 h. Then, the reaction mixture was poured into 60 mL of water and extracted with CH_2Cl_2 (3 x 60 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification by column chromatography with silica gel (hexane/ethyl acetate = 9/1) afforded the terminal alkene (1.39 g, quantitative) as a slightly yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 9H), 1.02 (t, *J* = 7.4 Hz, 3H), 1.66 (p, J = 7.3 Hz, 2H), 2.43 (br, 2H), 2.68 (dd, *J* = 18.3, 3.8 Hz, 1H), 2.86 (dd, *J* = 18.2, 7.1 Hz, 1H), 4.14 (t, *J* = 6.5 Hz, 1H), 4.19 (m, 1H), 4.30 (m, 1H), 5.11 (m, 2H), 5.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.1 (q), 9.6 (q), 26.6 (t), 36.1 (t), 40.3 (t), 69.1 (d), 77.0 (d), 85.8 (d), 92.5 (s), 103.5 (s), 118.3 (t), 133.0 (d), 175.2 (s); IR (film NaCl plates) (cm^{-1}) 3081, 2967, 2172, 1790, 1252; HRMS (ESI) *m/z* calcd for $C_{15}H_{24}O_3SiNa$ $[M+Na]^+$: 303.1392, found: 303.1389.

To a solution of the terminal alkene obtained before (1.20 g, 4.28 mmol) in dry Et_2O (43 mL) at −85ºC under argon atmosphere it was added a DIBAL-H solution (4.70 mL, 1 M in heptane). The reaction was monitored by TLC and quenched adding 0.5 mL of H_2O. After gel formation, it was added $MgSO_4$ and filtered over a pad of Celite and washed several times with EtOAc. The solvent was removed under reduced pressure and the crude obtained was used without any further purification.

To a suspension of methyltriphenylphosphonium bromide (3.91 g, 10.7 mmol) in dry THF (40 mL) at 0ºC under argon was added *n*-BuLi (0.94 mL of solution 10 M in hexane, 9.42 mmol) dropwise and the reaction mixture was stirred for 30 minutes. Then, this solution was added over a solution of lactol obtained above in dry THF (30 mL) at −17ºC under argon. The reaction was kept at such temperature until TLC showed complete conversion (ca. 24 h), and then quenched adding 40 mL of H_2O and the reaction mixture was warmed to room temperature and stirred for 1/2 h. After this time, the reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by column chromatography with silica gel (hexane/ethyl acetate: 9/1) leading to the diene *anti*-**6** (796 mg, 89 % yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.4 Hz, 3H), 1.47 (m, 2H), 1.98 (br, 1H), 2.26 (m, 1H), 2.41 (m, 2H), 2.48 (m, 2H), 3.64 (m, 2H), 4.22 (td, *J* = 6.5, 2.0 Hz, 1 H), 5.11 (m, 4H), 5.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6 (q), 25.0 (t), 33.8 (t), 40.6 (t), 68.0 (d), 73.2 (d), 74.0 (d), 80.7 (d), 83.0 (d), 116.6 (t), 118.4 (t), 133.6 (d), 135.5 (d); IR (film NaCl plates) (cm^{-1}) 3468, 3305, 3079, 2967, 2939, 1078; HRMS (ESI) *m/z* calcd for $C_{13}H_{20}O_2Na$ $[M+Na]^+$: 231.1361, found: 231.1362.

Preparation of the (*S*)-1-((2*R*,7*S*)-7-Ethynyl-2,3,6,7-tetrahydrooxepin-2-yl)propan-1-ol (*cis*-5).



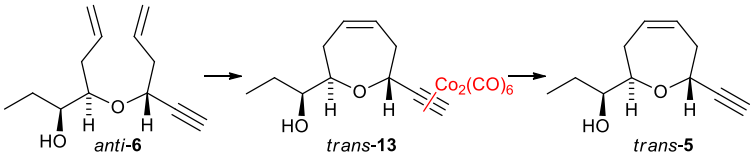
To a solution of the diene *syn*-**6** (500 mg, 2.40 mmol) in CH_2Cl_2 (24 mL) under argon at room temperature was added $Co_2(CO)_8$ (1.10 g, 2.88 mmol). The reaction mixture was stirred for 2 h. and then concentrated and purified by column chromatography with silica gel (hexane/ethyl acetate = 19/1) to give the hexacarbonyl dicobalt complex (1.19 g, quantitative) as a slurry red oil.

To a solution of the above cobalt complex (1.19 g, 2.40 mmol) in dry and degassed CH_2Cl_2 (600 mL) under argon was added 2nd Generation Grubbs Catalyst (610 mg, 0.72 mmol). The mixture was stirred and refluxed

overnight. After this time, the reaction mixture was concentrated and purified by column chromatography with silica gel (hexane/ethyl acetate = 9/1) to give *cis*-**13** (940 mg, 84 % yield) as a slurry red oil.

To a solution of *cis*-**13** (900 mg, 1.87 mmol) in acetone (10 mL) at 0ºC was added ceric ammonium nitrate (3.70 g, 6.55 mmol) portionwise. Then the reaction mixture was stirred at room temperature until TLC showed complete conversion (ca. 1 h), and then was poured into 10 mL of water and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and the crude was purified by column chromatography with silica gel (hexane/ethyl acetate = 6/1) to yield *cis*-**5** (320 mg, 95 % yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.4 Hz, 3H), 1.50 (m, 2H), 2.08 (br, 1H), 2.24 (ddd, *J* = 16.6, 8.1, 1.3 Hz, 1H), 2.42 (m, 3H), 2.66 (m, 1H), 3.36 (ddd, *J* = 10.4, 4.0, 1.6 Hz, 1H),3.56 (m, 1H), 4.19 (dt, *J* = 10.5, 2.0 Hz, 1H), 5.72 (m, 1H), 5.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.4 (q), 25.4 (t), 31.5 (t), 38.5 (t), 70.4 (d), 72.3 (d), 75.7 (d), 83.4 (d), 83.7 (s), 128.3 (d), 130.6 (d); IR (film NaCl plates) (cm^{-1}) 3427, 3296, 3024, 2966, 2934, 1101; HRMS (ESI) *m/z* calcd for $C_{11}H_{16}O_2Na$ $[M+Na]^+$: 203.1048, found: 203.1045.

Preparation of the (*S*)-1-((2*R*,7*R*)-7-Ethynyl-2,3,6,7-tetrahydrooxepin-2-yl)propan-1-ol (*trans*-5).

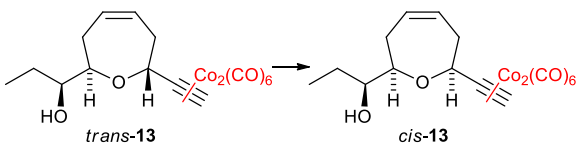


To a solution of the diene *anti*-**6** (500 mg, 2.40 mmol) in CH_2Cl_2 (24 mL) under argon at room temperature was added $Co_2(CO)_8$ (1.10 g, 2.88 mmol). The reaction mixture was stirred for 2 h. and then concentrated and purified by column chromatography with silica gel (hexane/ethyl acetate = 19/1) to give the hexacarbonyl dicobalt complex (1.19 g, quantitative) as a slurry red oil.

To a solution of the above cobalt complex (1.19 g, 2.40 mmol) in dry and degassed CH_2Cl_2 (600 mL) under argon was added 2nd Generation Grubbs Catalyst (610 mg, 0.72 mmol). The mixture was stirred and refluxed overnight. After this time, the reaction mixture was concentrated and purified by column chromatography with silica gel (hexane/ethyl acetate = 9/1) to give *trans*-**13** (940 mg, 84 % yield) as a slurry red oil.

The same procedure to obtain the cycle *cis*-**5** was applied to compound *trans*-**13**. Thus, the procedure for decomplexation afforded the oxepene *trans*-**5** (320 mg, 95 % yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.4 Hz, 3H), 1.49 (m, 2H), 2.24 (ddd, *J* = 16.6, 7.4, 1.5 Hz, 1H), 2.38 (m, 1H), 2.45 (d, *J* = 2.2 Hz, 1H), 2.50 (m, 1H), 2.62 (m, 1H), 2.91 (br, 1H), 3.54 (dt, *J* = 8.4, 4.0 Hz, 1H), 4.03 (ddd, *J* = 10.5, 3.8, 1.7, 1H), 4.82 (m, 1H), 5.72 (m, 1H), 5.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.4 (q), 25.3 (t), 30.8 (t), 35.7 (t), 66.4 (d), 74.4 (d), 75.3 (d), 76.0 (d), 82.3 (s), 127.1 (d), 130.9 (d); IR (film NaCl plates) (cm^{-1}) 3427, 3296, 3028, 2967, 2934, 1097; HRMS (ESI) *m/z* calcd for $C_{11}H_{16}O_2Na$ $[M+Na]^+$: 203.1048, found: 203.1052.

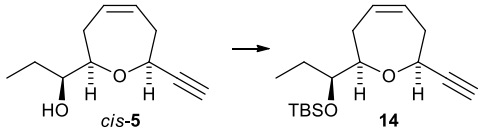
Isomerization of cycle-complex *trans*-13 to cycle-complex *cis*-13.



To a solution of *trans*-**13** (100 mg, 0.21 mmol) in dry CH_2Cl_2 (43 mL) at 0ºC under argon atmosphere was added $BF_3{\cdot}OEt_2$ (30 µL, 0.25 mmol). The reaction was kept at such temperature until TLC showed complete

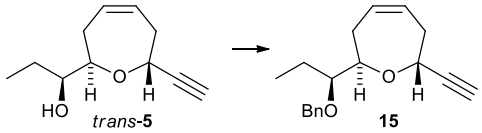
conversion (ca. 1 h). After this time, the reaction was quenched adding a saturated solution of $NaHCO_3$, followed by extraction with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography with silica gel (hexane/ethyl acetate = 9/1) afforded *cis*-**13** (94 mg, 94 % yield).

Preparation of the *tert*-Butyl((*S*)-1-((2*R*,7*S*)-7-ethynyl-2,3,6,7-tetrahydrooxepin-2-yl)propoxy)dimethylsilane (14).



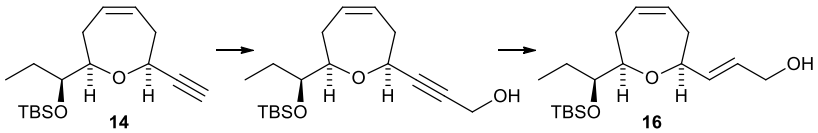
To a solution of alcohol *cis*-**5** (300 mg, 1.66 mmol) in dry CH_2Cl_2 (3 mL) and under argon atmosphere, it was added triethylamine (0.95 mL, 6.64 mmol) and TBSOTf (0.78 mL, 3.32 mmol) at room temperature. The mixture was stirred and refluxed overnight. Then, the mixture was poured into a saturated aqueous $NaHCO_3$ (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with a 5 % HCl aqueous solution (15 mL) and finally with brine (15 mL), dried over $MgSO_4$, filtered, concentrated and the crude was purified by chromatographic column with silica gel and 2 % EtOAc/Hexane to give **14** (450 mg, 92 % yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (d, *J* = 8.0 Hz, 6H), 0.89 (s, 9H), 0.90 (t, *J* = 7.4 Hz, 3H), 1.49 (m, 1H), 1.66 (m, 1H), 2.26 (m, 1H), 2.42 (m, 3H), 2.63 (m, 1H), 3.25 (ddd, *J* = 10.2, 5.9, 1.7 Hz, 1H), 3.62 (q, *J* = 5.6, 1H), 4.14 (dt, *J* = 10.5, 2.1 Hz, 1H), 5.71 (m, 1H), 5.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.3 (q), -4.1 (q), 9.0 (q), 18.4 (s), 26.1 (q), 26.9 (t), 32.7 (t), 38.7 (t), 70.3 (d), 71.8 (d), 75.9 (d), 82.6 (d), 83.8 (s), 128.2 (d), 130.9 (d); IR (film NaCl plates) (cm^{-1}) 3314, 3025, 2959, 2932, 1110; HRMS (ESI) *m/z* calcd for $C_{17}H_{30}O_2SiNa$ $[M+Na]^+$: 317.1913, found: 317.1912.

Preparation of the (2*R*,7*R*)-2-((*S*)-1-(Benzyloxy)propyl)-7-ethynyl-2,3,6,7-tetrahydrooxepine (15).



To a solution of alcohol *trans*-**5** (300 mg, 1.66 mmol) in dry THF (8 mL) at 0ºC under argon was added sodium hydride (73 mg of 60 % dispersion in mineral oil, 1.83 mmol), benzyl bromide (0.24 mL, 1.99 mmol) and TBAI (cat.). The mixture was stirred and refluxed at 70ºC until TLC showed complete conversion (ca. 10 h). Then, the mixture was quenched with saturated aqueous NH_4Cl (8 mL) and extracted with Et_2O (3 x 15 mL). The combined organic phases were dried over $MgSO_4$, filtered, concentrated and the crude was purified by column chromatography with silica gel (2 % EtOAc/Hexane) yielding **15** (390 mg, 87 % yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.4 Hz, 3H), 1.65 (m, 2H), 2.35 (m, 1H), 2.46 (m, 3H), 2.65 (m, 1H), 3.33 (q, *J* = 5.4 Hz, 1H), 4.11 (m, 1H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.65 (d, *J* = 11.4 Hz, 1H), 4.84 (m, 1H), 5.74 (m, 1H), 5.90 (m, 1H), 7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.6 (q), 23.4 (t), 32.2 (t), 36.1 (t), 66.1 (d), 72.3 (t), 74.1 (d), 74.4 (d), 82.4 (s), 83.0 (d), 127.3 (d), 127.5 (d), 128.0 (d), 128.4 (d), 131.3 (d), 139.0 (s); IR (film NaCl plates) (cm^{-1}) 3293, 3029, 2933, 2877, 1100; HRMS (ESI) *m/z* calcd for $C_{18}H_{22}O_2Na$ $[M+Na]^+$: 293.1517, found: 293.1512.

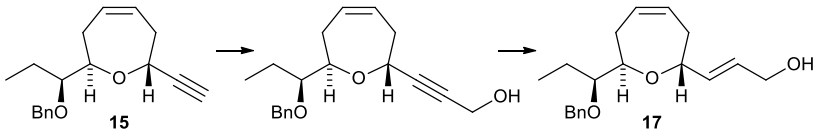
Preparation of the (*E*)-3-((2*S*,7*R*)-7-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propyl)-2,3,6,7-tetrahydrooxepin-2-yl)prop-2-en-1-ol (16).



To a solution of alkyne **14** (360 mg, 1.22 mmol) in dry THF (6 mL) at −20ºC under argon atmosphere, it was added *n*-BuLi (0.13 mL of solution 10 M in hexane, 1.3 mmol), and the reaction mixture was stirred for 15 minutes. To this mixture it was added paraformaldehyde (54 mg, 1.71 mmol) and the reaction mixture was warmed at room temperature and stirred overnight. After this time, the mixture was poured into a saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by column chromatography with silica gel (hexane/ethyl acetate = 4/1) to give the propargylic alcohol (370 mg, 93 % yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06 (d, *J* = 7.1 Hz, 6H), 0.88 (m, 12H), 1.48 (m, 1H), 1.65 (m, 1H), 2.06 (br, 1H), 2.21 (m, 1H), 2.41 (td, *J* = 16.2, 8.1 Hz, 2H), 2.60 (m, 1H), 3.25 (m, 1H), 3.59 (m, 1H), 4.16 (dd, *J* = 10.5, 1.4 Hz, 1H), 4.27 (br, 2H), 5.70 (m, 1H), 5.82 (m,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.3 (q), -4.2 (q), 8.9 (q), 18.3 (s), 26.1 (q), 26.7 (t), 32.9 (t), 38.7 (t), 51.2 (t), 70.5 (d), 75.7 (d), 82.2 (s), 82.5 (d), 85.7 (s), 128.2 (d), 130.9 (d); IR (film NaCl plates) (cm^{-1}) 3359, 3023, 2932, 2858, 1108; HRMS (ESI) *m/z* calcd for $C_{18}H_{32}O_3SiNa$ $[M+Na]^+$: 347.2018, found: 347.2024.

To a solution of the compound obtained before (250 mg, 0.77 mmol) in dry THF (8 mL) at room temperature under argon, it was added $LiAlH_4$ (46 mg, 1.16 mmol). The reaction was monitored by TLC and quenched adding a drop of water. After gel formation, it was added $MgSO_4$ and filtered over a pad of Celite and washed several times with EtOAc. The solvent was removed under reduced pressure and the crude obtained was purified by column chromatography with silica gel (hexane/ethyl acetate = 4/1) leading to the desired allylic alcohol **16** (230 mg, 92 % yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (d, *J* = 4.4 Hz, 6H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.89 (s, 9H), 1.38 (br, 1H), 1.49 (m, 1H), 1.69 (m, 1H), 2.27 (m, 3H), 2.42 (m, 1H), 3.30 (m, 1H), 3.60 (q, *J* = 5.2, 1H), 3.91 (m, 1H), 4.14 (d, *J* = 5.0 Hz, 1H), 5.80 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.2 (q), -4.2 (q), 8.7 (q), 18.3 (s), 26.1 (q), 26.7 (t), 33.3 (t), 37.8 (t), 63.4 (t), 76.0 (d), 79.6 (d), 81.9 (d), 128.8 (d), 128.8 (d), 130.4 (d), 133.5 (d); IR (film NaCl plates) (cm^{-1}) 3352, 3021, 2932, 2859, 1105; HRMS (ESI) *m/z* calcd for $C_{18}H_{34}O_3SiNa$ $[M+Na]^+$: 349.2175, found: 349.2177.

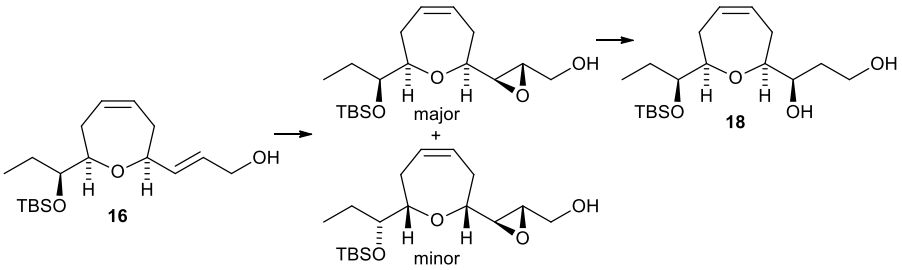
Preparation of the (*E*)-3-((2*R*,7*R*)-7-((*S*)-1-(Benzyloxy)propyl)-2,3,6,7-tetrahydrooxepin-2-yl)prop-2-en-1-ol (17).



The same sequence of reactions to obtain the allylic alcohol **14** was applied to compound **15** (300 mg, 1.11 mmol). Thus, the procedure for homologation afforded the propargylic alcohol (313 mg, 94 % yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.4 Hz, 3H), 1.64 (m, 2H), 1.86 (br. s, 1H), 2.40 (m, 3H), 2.63 (m, 1H), 3.33 (m, 1H), 4.08 (m, 1H), 4.26 (br, 2H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H),4.86 (m, 1H), 5.71 (m, 1H), 5.86 (m, 1H), 7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.5 (q), 23.3 (t), 32.3 (t), 36.1 (t), 51.1 (t), 66.3 (d), 72.3 (t), 74.1 (d), 83.0 (d), 84.4 (s), 84.5 (s), 127.4 (d), 127.6 (d), 127.9 (d), 128.4 (d), 131.1 (d), 139.0 (s); IR (film NaCl plates) (cm^{-1}) 3412, 3029, 2931, 2877, 1097; HRMS (ESI) *m/z* calcd for $C_{19}H_{24}O_3Na$ $[M+Na]^+$: 323.1623, found: 323.1624. And the alkyne reduction yielded the allylic alcohol **17** (300 mg, 95 % yield) as a colorless oil: ^{1}H NMR (400 MHz, C_6D6) δ 0.98 (td, *J* = 7.4, 1.7 Hz, 3H), 1.56 (m, 1H), 1.73 (m, 1H), 2.05 (dd, *J* = 17.4, 5.2 Hz, 1H), 2.38 (m, 2H), 2.51 (m, 1H), 3.35 (m,

1H), 3.84 (d, *J* = 3.8 Hz, 2H), 4.16 (m, 1H), 4.50 (d, *J* = 11.7 Hz, 1H), 4.55 (d, *J* = 11.7 Hz, 1H), 4.61 (br, 1H), 5.57 (m, 1H), 5.71 (m, 3H), 7.11 (m, 1H), 7.19 (m, 2H), 7.35 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.7 (q), 23.8 (t), 30.5 (t), 35.1 (t), 63.3 (t), 72.6 (t), 75.0 (d), 76.2 (d), 83.0 (d), 127.6 (d), 127.9 (d), 128.1 (d), 128.4 (d), 129.4 (d), 129.6 (d), 133.1 (d), 139.1 (s); IR (film NaCl plates) (cm^{-1}) 3407, 3024, 2926, 2877, 1098; HRMS (ESI) *m/z* calcd for $C_{19}H_{26}O_3Na$ $[M+Na]^+$: 325.1780, found: 325.1783.

Preparation of the (*R*)-1-((2*S*,7*R*)-7-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propyl)-2,3,6,7-tetrahydrooxepin-2-yl)propane-1,3-diol (18).

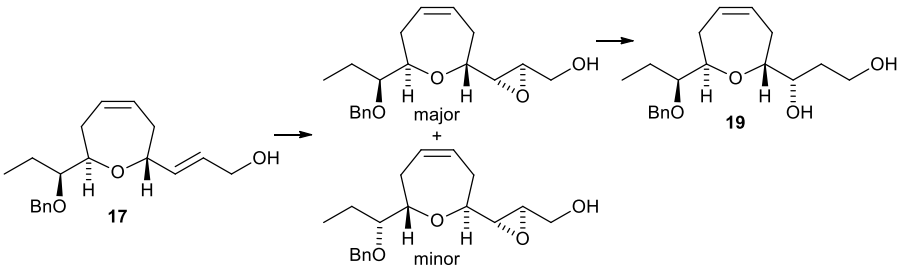


A mixture of powdered commercially activated 4Å molecular sieves (40 mg) and 3 mL of CH_2Cl_2 was cooled to –20ºC. Then, *L*-(+)-Diethyl tartrate (0.14 mL, 0.81 mmol) and Ti(OPr-*i*)$_4$ (0.21 mL, 0.70 mmol) were added sequentially. After 15 minutes it was added compound **16** (190 mg, 0.58 mmol). The reaction was kept at such temperature and stirred for an additional 30 min. and then TBHP (0.21 mL of solution 5.0 M in isooctane, 1.04 mmol) was added dropwise. After 8 h, a 15 % tartaric acid aqueous solution (5 mL) was added and the reaction mixture was warmed at room temperature and stirred vigorously for 30 minutes. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were concentrated and diluted in Et_2O (10 mL) and treated with solution of NaOH at 15 % (10 mL, at 0ºC) for 2 minutes. Finally, the aqueous layer was extracted with Et_2O (3 x 10 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated and the crude was purified by column chromatography with silica gel (hexane/ethyl acetate = 4/1) to yield 167 mg of the major epoxide (84 % yield) and 24 mg of the minor epoxide (12 % yield). Major epoxide: $[\alpha]^{25}_D$ – 22.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (d, *J* = 3.5 Hz, 6H), 0.87 (t, *J* = 7.5 Hz, 3H), 0.89 (s, 9H), 1.45 (m, 1H), 1.63 (m, 1H), 1.86 (br, 1H), 2.22 (m, 1H), 2.37 (m, 3H), 2.96 (m, 1H), 3.14 (m, 1H), 3.24 (dd, *J* = 10.0, 5.9 Hz, 1H), 3.30 (m, 1H), 3.59 (m, 2H), 3.92 (d, *J* = 12.5 Hz, 1H), 5.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.3 (q), -4.2 (q), 8.9 (q), 18.3 (s), 26.1 (q), 26.7 (t), 32.9 (t), 34.3 (t), 57.2 (d), 57.5 (d), 61.7 (t), 76.0 (d), 79.2 (d), 81.8 (d), 128.1 (d), 130.4 (d); IR (film NaCl plates) (cm^{-1}) 3443, 3021, 2931, 2858, 1254, 1118; HRMS (ESI) *m/z* calcd for $C_{18}H_{34}O_4SiNa$ $[M+Na]^+$: 365.2124, found: 365.2128. Minor epoxide: $[\alpha]^{25}_D$ – 7.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (d, *J* = 4.5 Hz, 6H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.89 (s, 9H), 1.48 (m, 1H), 1.64 (m, 1H), 1.79 (br, 1H), 2.23 (m, 2H), 2.38 (m, 2H), 3.07 (dd, *J* = 5.1, 2.2 Hz, 1H), 3.13 (m, 1H), 3.23 (ddd, *J* = 10.1, 5.8, 1.4 Hz, 1H), 3.35 (ddd, *J* = 10.5, 5.1, 1.5 Hz, 1H), 3.63 (m, 2H), 3.93 (d, *J* = 12.6 Hz, 1H), 5.74 (m, 1H), 5.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.3 (q), -4.2 (q), 8.9 (q), 18.3 (s), 26.1 (q), 26.7 (t), 32.8 (t), 33.8 (t), 55.8 (d), 58.0 (d), 61.5 (t), 76.0 (d), 79.5 (d), 82.2 (d), 128.2 (d), 130.5 (d); IR (film NaCl plates) (cm^{-1}) 3447, 3022, 2931, 2858, 1255, 1115; HRMS (ESI) *m/z* calcd for $C_{18}H_{34}O_4SiNa$ $[M+Na]^+$: 365.2124, found: 365.2117.

To a solution of major epoxide (140 mg, 0.41 mmol) in dry THF (4 mL) at 0ºC under argon was added Red-Al® (0.20 ml of solution 60 % in toluene, 0.62 mmol). The reaction was kept at such temperature until TLC showed complete conversion (ca. 8h). Then, the reaction mixture was quenched adding a drop of water. After gel formation, it was added $MgSO_4$ and filtered over a pad of Celite and washed several times with EtOAc. The solvent was removed under reduced pressure and the crude obtained was purified by column chromatography with silica gel (hexane/ethyl acetate = 6/4) leading to the desired diol **18** (126 mg, 90 %

yield) as a colorless oil: $[\alpha]^{25}_D$ – 3.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (d, *J* = 3.3 Hz, 6H), 0.90 (m, 12H), 1.48 (m, 1H), 1.61 (m, 1H), 1.74 (m, 1H), 2.26 (m, 4H), 2.71 (br, 1H), 2.86 (br, 1H), 3.32 (m, 1H), 3.37 (m, 1H), 3.56 (dd, *J* = 10.4, 4.5 Hz, 1H), 3.79 (m, 1H), 3.85 (t, *J* = 5.5 Hz, 1H), 5.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.3 (q), -4.1 (q), 9.6 (q), 18.3 (s), 26.1 (q), 26.1 (t), 32.3 (t), 32.8 (t), 33.9 (t), 61.6 (t), 74.2 (d), 76.4 (d), 82.9 (d), 82.9 (d), 129.1 (d), 129.8 (d); IR (film NaCl plates) (cm^{-1}) 3383, 3022, 2931, 2859, 1254, 1104; HRMS (ESI) *m/z* calcd for $C_{18}H_{36}O_4SiNa$ $[M+Na]^+$: 367.2281, found: 367.2276.

Preparation of the (*S*)-1-((2*S*,7*R*)-7-((*S*)-1-(Benzyloxy)propyl)-2,3,6,7-tetrahydrooxepin-2-yl)propane-1,3-diol (19).

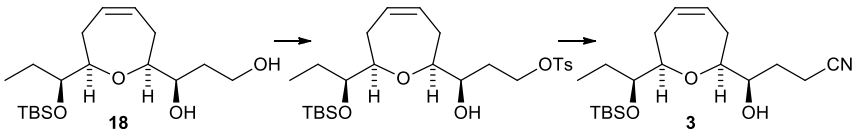


A mixture of powdered commercially activated 4Å molecular sieves (40 mg) and 3 mL of CH_2Cl_2 was cooled to –20ºC. Then, *D*-(–)-Diethyl tartrate (0.13 mL, 0.78 mmol) and Ti(OPr-*i*)$_4$ (0.20 mL, 0.68 mmol) were added sequentially. After 15 minutes it was added compound **17** (170 mg, 0.56 mmol). The reaction was kept at such temperature and stirred for an additional 30 min. and then TBHP (0.20 mL of solution 5.0 M in isooctane, 1.00 mmol) was added dropwise. After 8 h, a 15 % tartaric acid aqueous solution (5 mL) was added and the reaction mixture was warmed at room temperature and stirred vigorously for 30 minutes. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were concentrated and diluted in Et_2O (10 mL) and treated with solution of NaOH at 15 % (10 mL, at 0ºC) for 2 minutes. Finally, the aqueous layer was extracted with Et_2O (3 x 10 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated and the crude was purified by column chromatography with silica gel (hexane/ethyl acetate = 3/1) to yield 150 mg of the major epoxide (84 % yield) and 21 mg of the minor epoxide (12 % yield). Major epoxide: $[\alpha]^{25}_D$ + 10.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D6) δ 0.96 (t, *J* = 7.4, 3H), 1.61 (m, 2H), 1.99 (br, 1H), 2.42 (m, 4H), 2.98 (dd, *J* = 5.5, 2.0 Hz, 1H), 3.10 (m, 1H), 3.36 (m, 1H), 3.62 (m, 1H), 3.86 (d, *J* = 12.6, 1H), 3.97 (m, 1H), 4.13 (m, 1H), 4.60 (br, 2H), 5.70 (m, 2H), 7.28 (m, 1H), 7.34 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.7 (q), 23.6 (t), 30.3 (t), 31.7 (t), 57.3 (d), 57.4 (d), 61.6 (t), 72.6 (t), 75.0 (d), 77.0 (d), 82.7 (d), 127.5 (d), 127.6 (d), 127.9 (d), 128.4 (d), 129.3 (d), 140.0 (s); IR (film NaCl plates) (cm^{-1}) 3422, 3026, 2929, 1456, 1097; HRMS (ESI) *m/z* calcd for $C_{19}H_{26}O_4Na$ $[M+Na]^+$: 341.1729, found: 341.1724. Minor epoxide: $[\alpha]^{25}_D$ + 9.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D6) δ 0.96 (t, *J* = 7.3, 3H), 1.62 (m, 2H), 1.89 (br, 1H), 2.21 (dd, *J* = 17.2, 6.2, 1H), 2.37 (m, 1H), 2.53 (m, 2H), 3.07 (m, 1H), 3.15 (br, 1H), 3.39 (m, 1H), 3.63 (dd, *J* = 12.5, 3.2, 1H), 3.90 (d, *J* = 12.5, 1H), 4.12 (m, 2H), 4.62 (m, 2H), 5.69 (m, 2H), 7.28 (m, 1H), 7.33 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.8 (q), 23.9 (t), 30.2 (t), 31.3 (t), 55.9 (d), 58.1 (d), 61.3 (t), 72.7 (t), 74.4 (d), 76.9 (d), 82.8 (d), 127.2 (d), 127.6 (d), 127.9 (d), 128.4 (d), 129.4 (d), 139.1 (s); IR (film NaCl plates) (cm^{-1}) 3429, 3026, 2929, 1455, 1108; HRMS (ESI) *m/z* calcd for $C_{19}H_{26}O_4Na$ $[M+Na]^+$: 341.1729, found: 341.1724.

To a solution of major epoxide (100 mg, 0.31 mmol) in dry THF (3 mL) at 0ºC under argon was added Red-Al® (0.15 ml of solution 60 % in toluene, 0.47 mmol). The reaction was warmed at room temperature and stirred for 3h. Then, the reaction mixture was quenched adding a drop of water. After gel formation, it was added $MgSO_4$ and filtered over a pad of Celite and washed several times with EtOAc. The solvent was removed under reduced pressure and the crude obtained was purified by column chromatography with silica gel (hexane/ethyl acetate = 6/4) leading to the desired diol **19** (94 mg, 93 % yield) as a colorless oil:

$[\alpha]^{25}_{D}$ – 9.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.4, 3H), 1.64 (m, 4H), 2.22 (m, 2H), 2.49 (m, 2H), 2.88 (br, 1H), 3.23 (br, 1H), 3.34 (dt, *J* = 7.1, 4.2 Hz, 1H), 3.82 (m, 3H), 4.05 (m, 1H), 4.27 (ddd, *J* = 10.4, 4.2, 1.4 Hz, 1H), 4.60 (m, 2H), 5.69 (m, 2H), 7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1 (q), 23.2 (t), 28.3 (t), 30.6 (t), 33.9 (t), 61.6 (t), 72.6 (t), 74.5 (d), 76.5 (d), 78.5 (d), 83.2 (d), 127.8 (d), 128.0 (d), 128.1(d), 128.5 (d), 128.9 (d), 138.6 (s); IR (film NaCl plates) (cm^{-1}) 3393, 3025, 2930, 1455, 1066; HRMS (ESI) *m/z* calcd for $C_{19}H_{28}O_4Na$ $[M+Na]^+$: 343.1885, found: 343.1884.

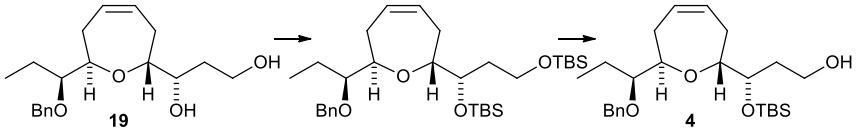
Preparation of the (*R*)-4-((2*S*,7*R*)-7-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propyl)-2,3,6,7-tetrahydrooxepin-2-yl)-4-hydroxybutanenitrile (3).



To a solution of diol **18** (37 mg, 0.11 mmol) in dry CH_2Cl_2 (2 mL) at 0ºC under argon atmosphere, it was added triethylamine (22 µL, 0.16 mmol), DMAP (cat.) and *p*-TsCl (26 mg, 0.13 mmol). The reaction mixture was warmed to room temperature and stirred for 5 h. After this time, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution and the mixture was dilutes with CH_2Cl_2. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The organic layer was washed with brine, dried over Mg_2SO_4, filtered, and concentrated. Purification by column chromatography with silica gel with 20 % EtAcO/Hexane afforded the tosylate (54 mg, quantitative).

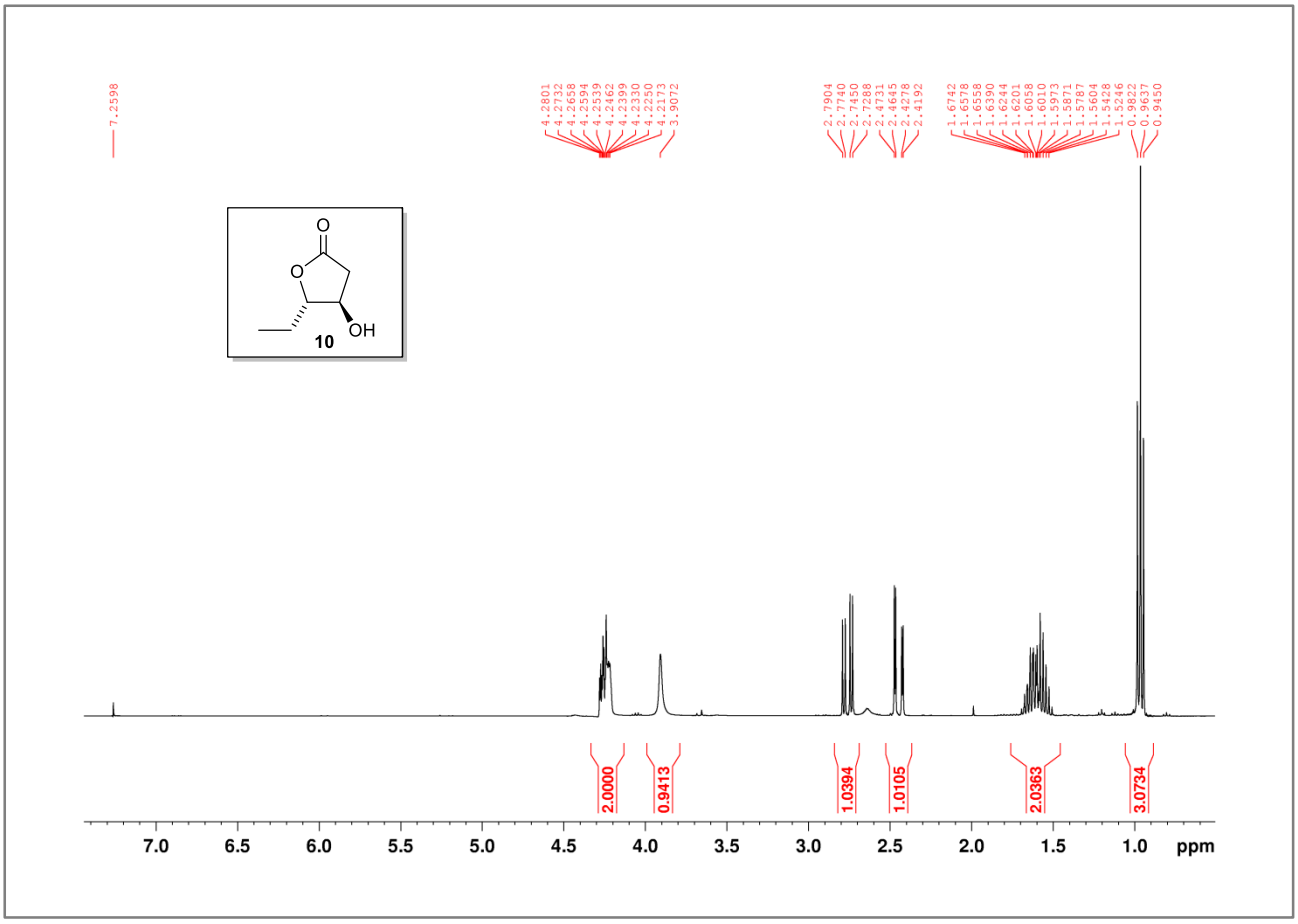
To a solution of the compound obtained before (54 mg, 0.11 mmol) in acetonitrile (0.55 mL) under argon, it was added NaI (17 mg, 0.11 mmol) and NaCN (33 mg, 0.66 mmol). The reaction mixture was stirred and refluxed until TLC showed complete conversion (ca. 36 h), then poured into water (5 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with water (2 x 5 mL) and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (hexane/ethyl acetate = 4/1) affored nitrile **3** (30 mg, 80 % yield) as a colorless oil: $[\alpha]^{25}_{D}$ – 4.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (d, 6H), 0.90 (s, 9H), 0.91 (t, *J* = 7.5 Hz, 3H), 1.54 (m, 3H), 1.81 (m, 2H), 2.13 (m, 1H), 2.27 (m, 3H), 2.53 (m, 2H), 3.32 (m, 1H), 3.43 (m, 1H), 3.55 (dt, *J* = 6.7, 4.1 Hz, 1H), 3.61 (dt, *J* = 9.9, 3.3 Hz, 1H), 5.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.3 (q), -4.1 (q), 9.8 (q), 14.0 (t), 18.3 (s), 25.9 (t), 26.1 (q), 28.1 (t), 32.4 (t), 32.8 (t), 72.4 (d), 76.4 (d), 82.3 (d), 83.2 (d), 120.0 (s), 128.7 (d), 130.1 (d); IR (film NaCl plates) (cm^{-1}) 3487, 3022, 2930, 2857, 1254, 1110; HRMS (ESI) *m/z* calcd for $C_{19}H_{35}NO_3SiNa$ $[M+Na]^+$: 376.2284, found: 376.2275.

Preparation of the (*S*)-1-((2*R*,7*R*)-7-((*S*)-1-(Benzyloxy)propyl)-2,3,6,7-tetrahydrooxepin-2-yl)-3-((*tert*-butyldimethylsilyl)oxy)propan-1-ol (4).



To a solution of diol **19** (50 mg, 0.16 mmol) in CH_2Cl_2 (1.6 mL) at room temperature under argon atmosphere was added Imidazole (22 mg, 0.32 mmol), triethylamine (0.13 mL, 0.96mmol) and TBSOTf (0.12 mL, 0.48 mmol). The reaction mixture was stirred and refluxed until TLC showed complete conversion (ca. 18 h), then poured into a 5 mL of water and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to yield the crude bis-silyl ethers as an oil, which was uses without further purification.

To a solution of above crude oil in a mixture tetrahydrofuran-water 1:1 (0.8 mL/0.8mL) at 0ºC, it was added trifluoroacetic acid (15 µL, 0.19 mmol). The reaction was monitored by TLC until complete conversion was observed. Then, the reaction was quenched with by addition of saturated aqueous $NaHCO_3$ solution and the mixture was dilutes with Et_2O. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography with silica gel with 15 % EtAcO/Hexane afforded **4** (58 mg, 86 % yield after 2 steps) as a colorless oil: $[\alpha]^{25}_D$ – 10.8 (*c* 1.92, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (d, *J* = 4.5 Hz, 6H), 0.89 (s, 9H), 0.94 (t, *J* = 7.4, 3H), 1.59 (m, 2H), 1.77 (m, 1H), 1.90 (m, 1H), 2.38 (m, 5H), 3.37 (dt, *J* = 6.5, 4.5 Hz, 1H), 3.78 (m, 3H), 4.11 (m, 2H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 5.71 (m, 2H), 7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.3 (q), -4.2 (q), 10.0 (q), 18.2(s), 23.9 (t), 26.0 (q), 29.5 (t), 30.2 (t), 36.1 (t), 59.5 (t), 72.7 (t), 73.8 (d), 77.5 (d), 78.3 (d), 83.1 (d), 126.7 (d), 127.9 (d), 128.4(d), 128.8 (d), 129.2 (d), 139.1 (s); IR (film NaCl plates) (cm^{-1}) 3426, 3024, 2931, 2858, 1253, 1104; HRMS (ESI) *m/z* calcd for $C_{25}H_{42}O_4SiNa$ $[M+Na]^+$: 457.2750, found: 457.2758.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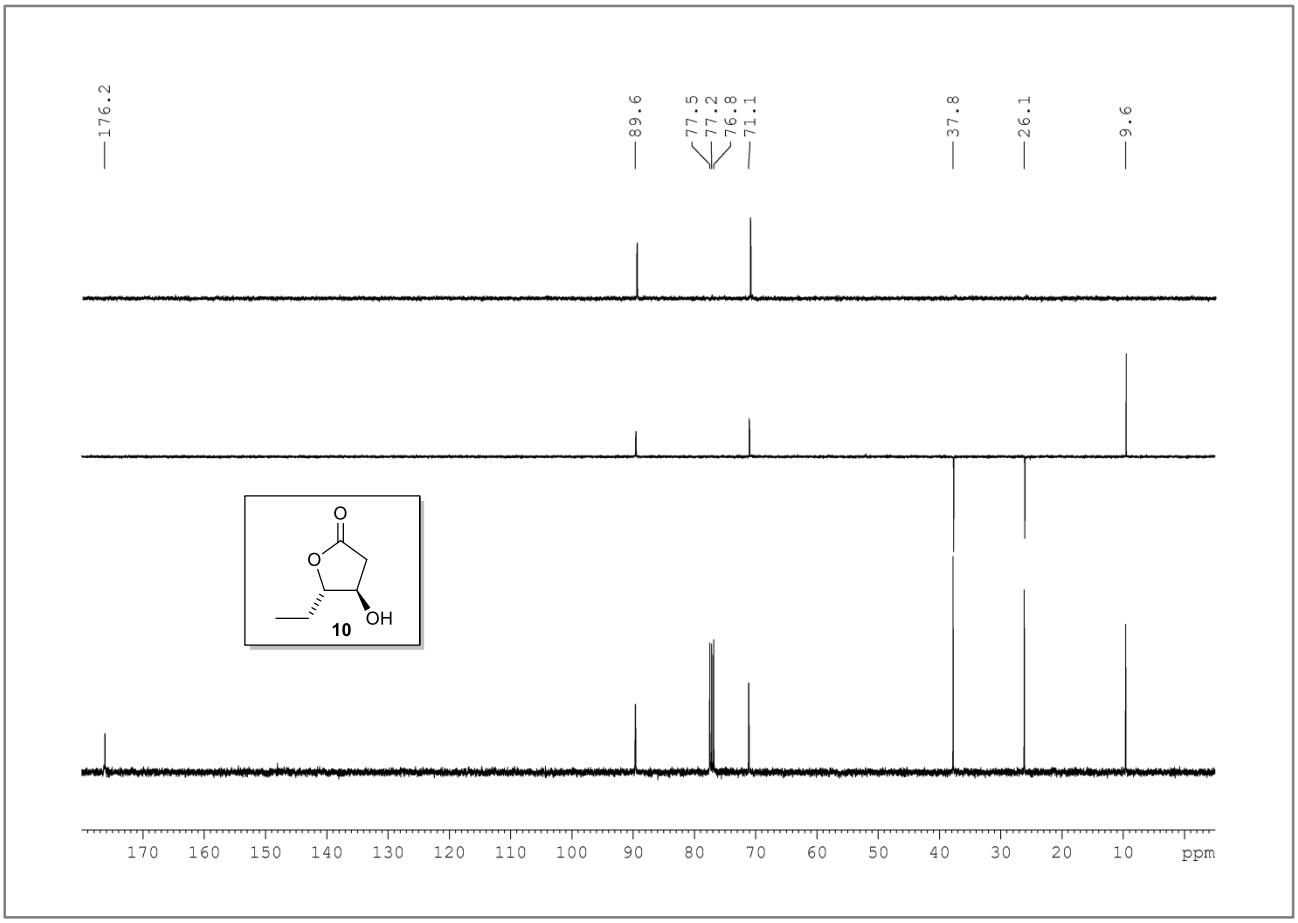
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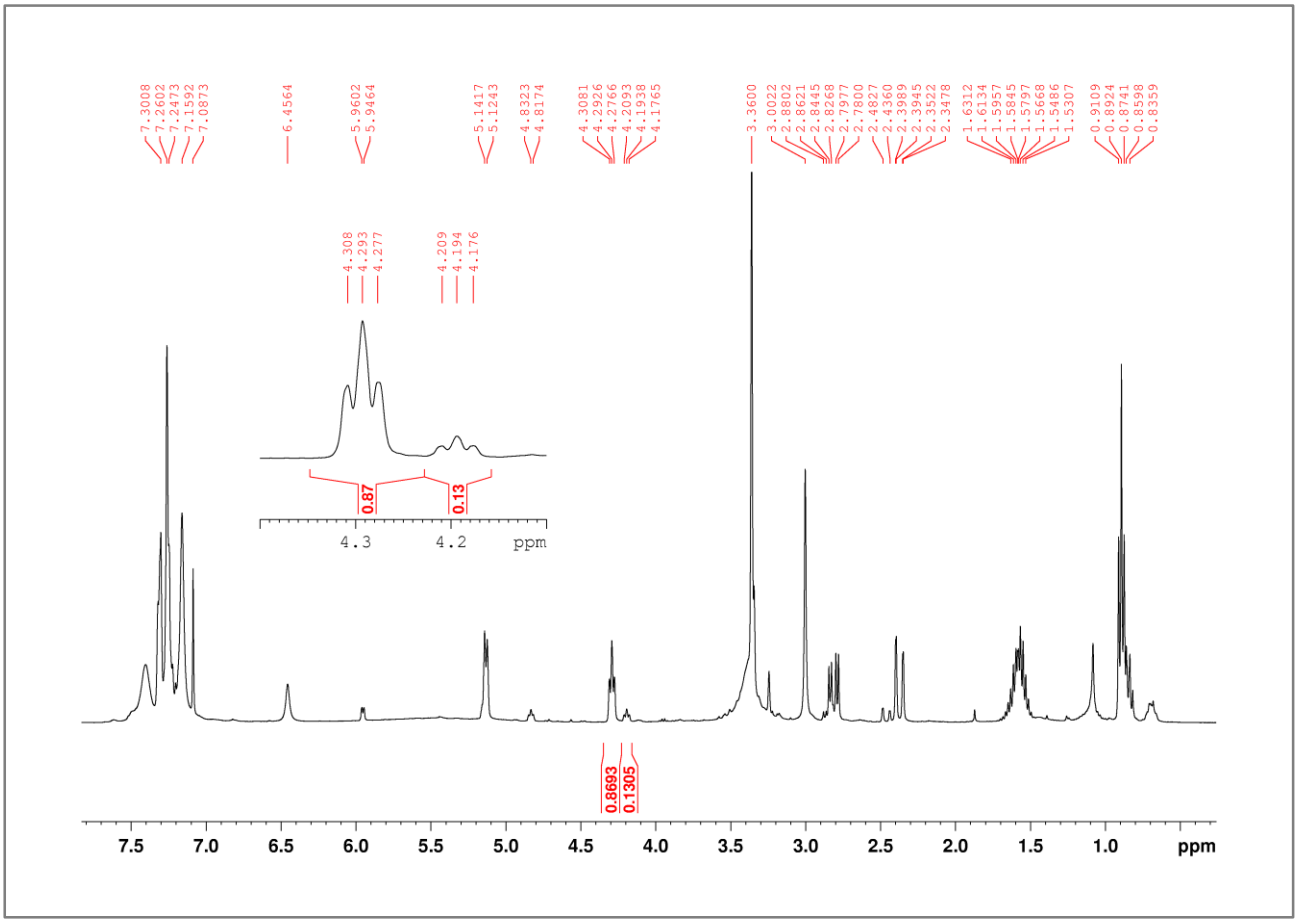
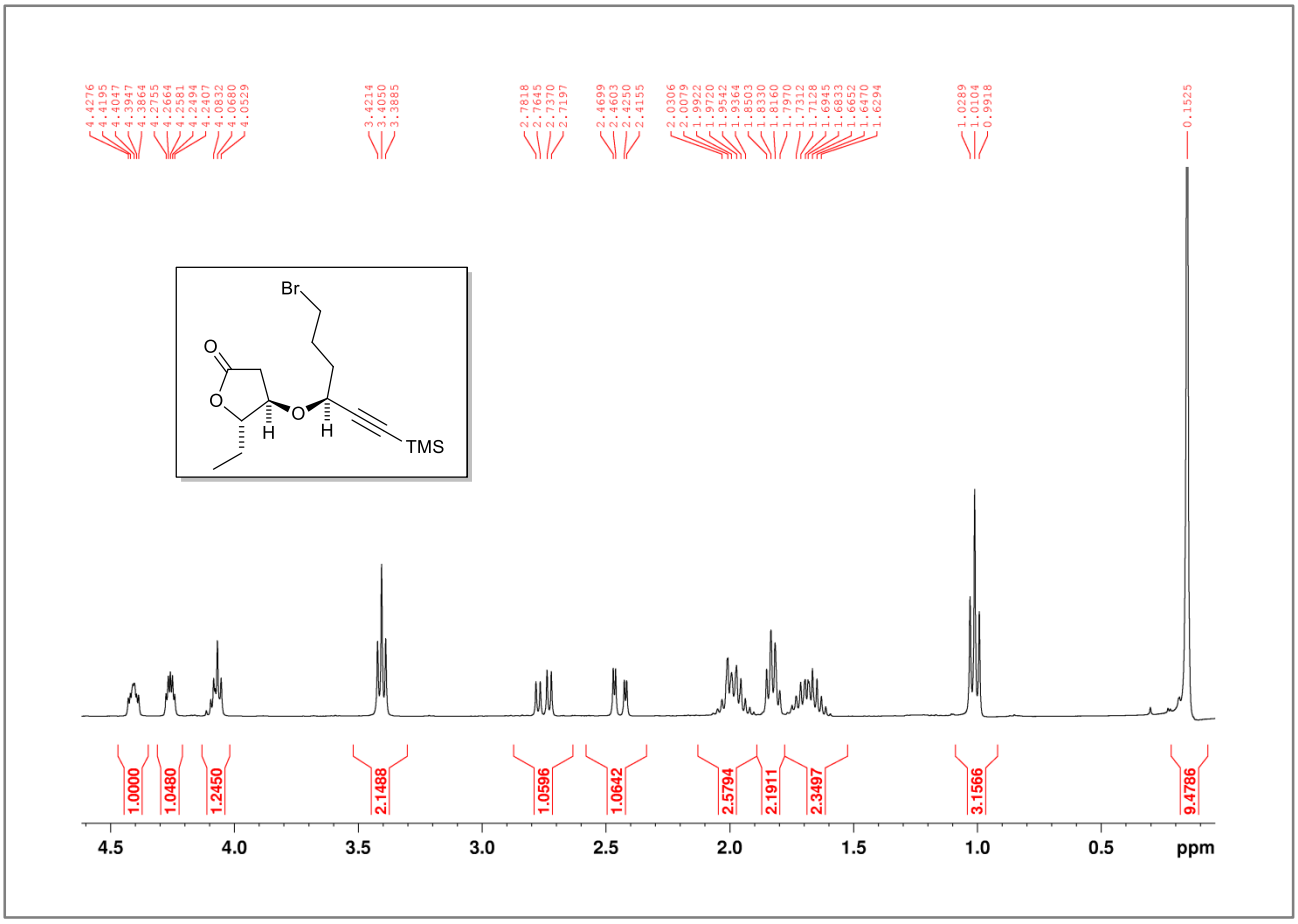
^{1}H NMR spectra of (*S*)-Mosher's ester derivative from compound **10** in $CDCl_3$

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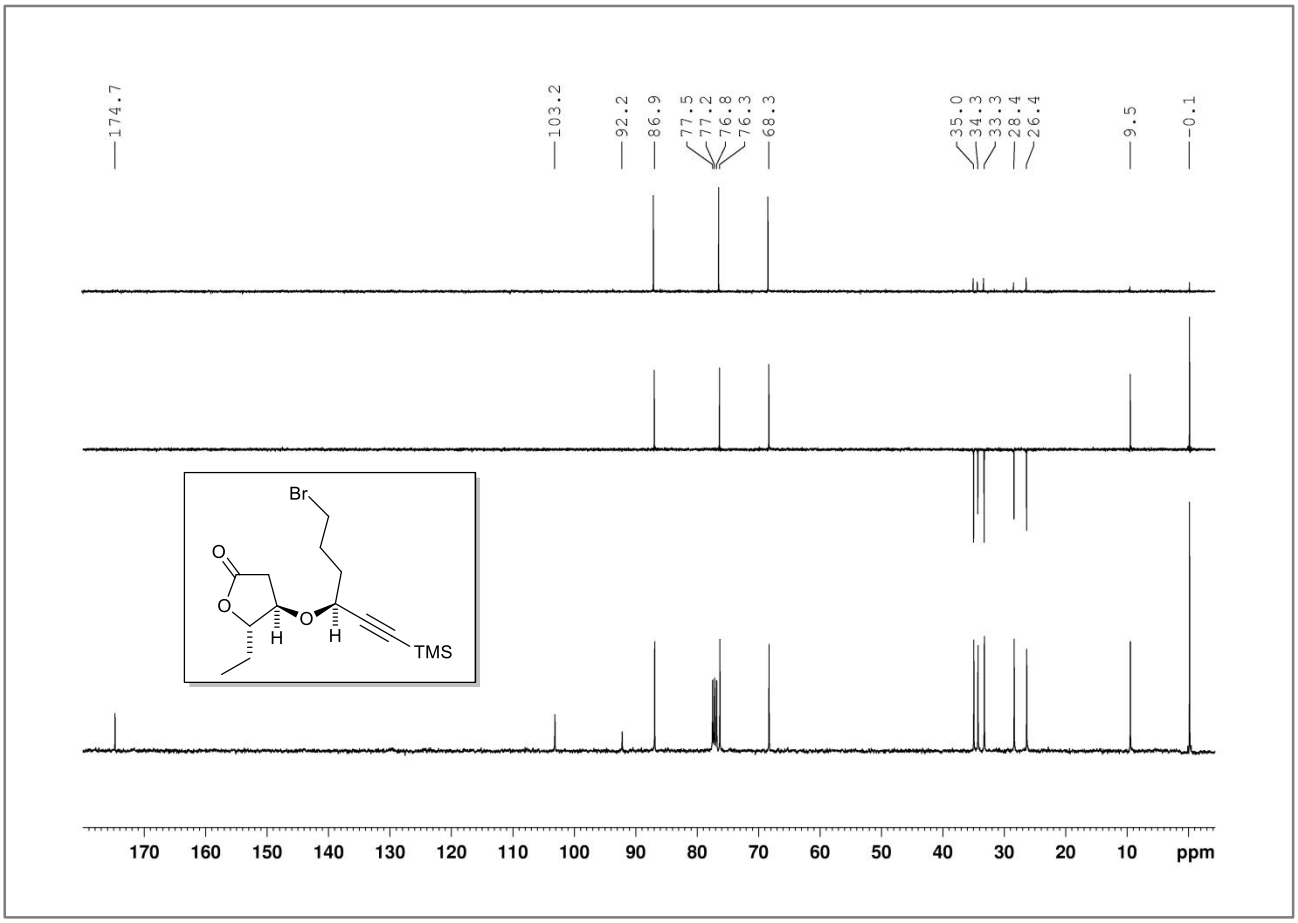
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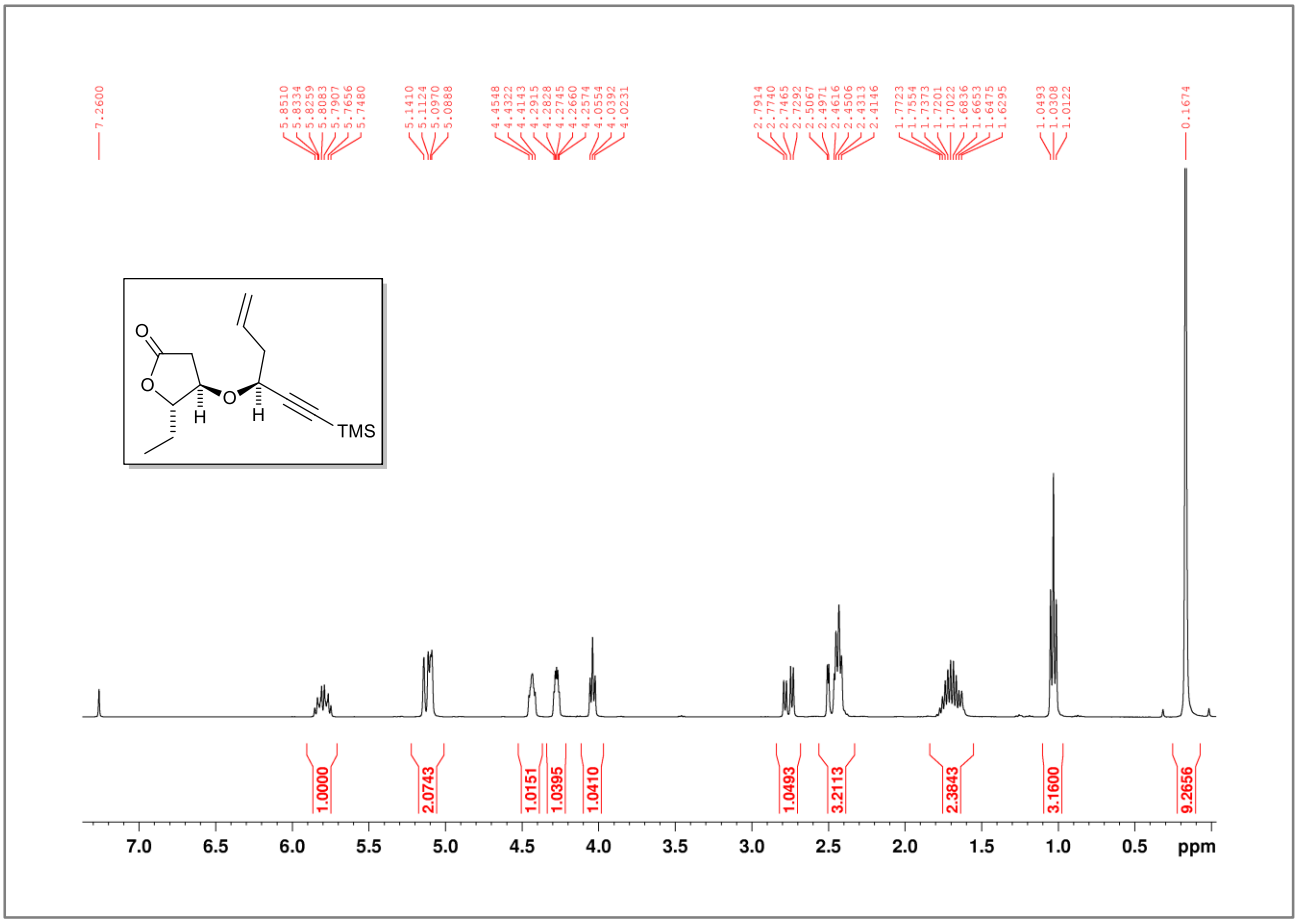
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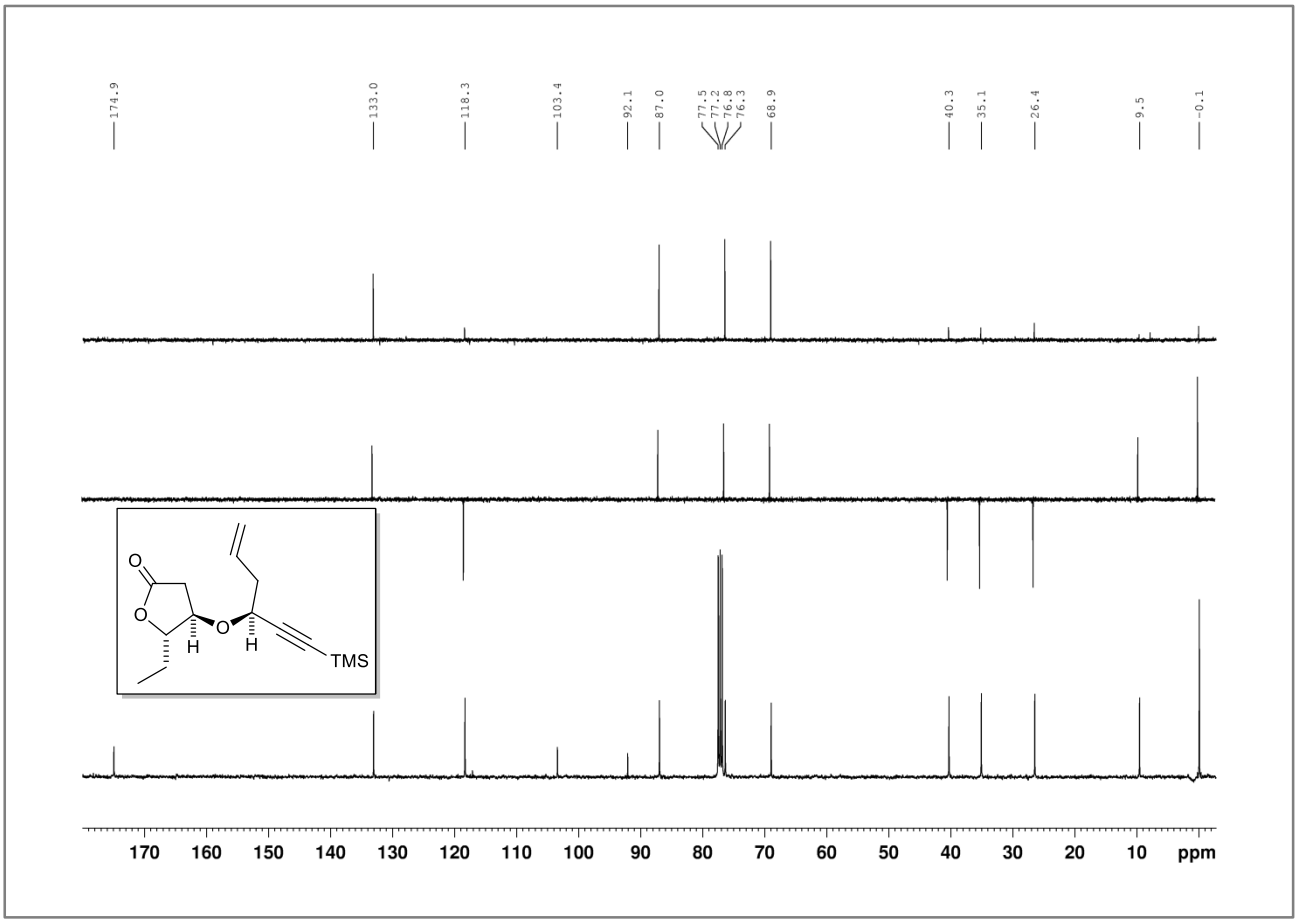
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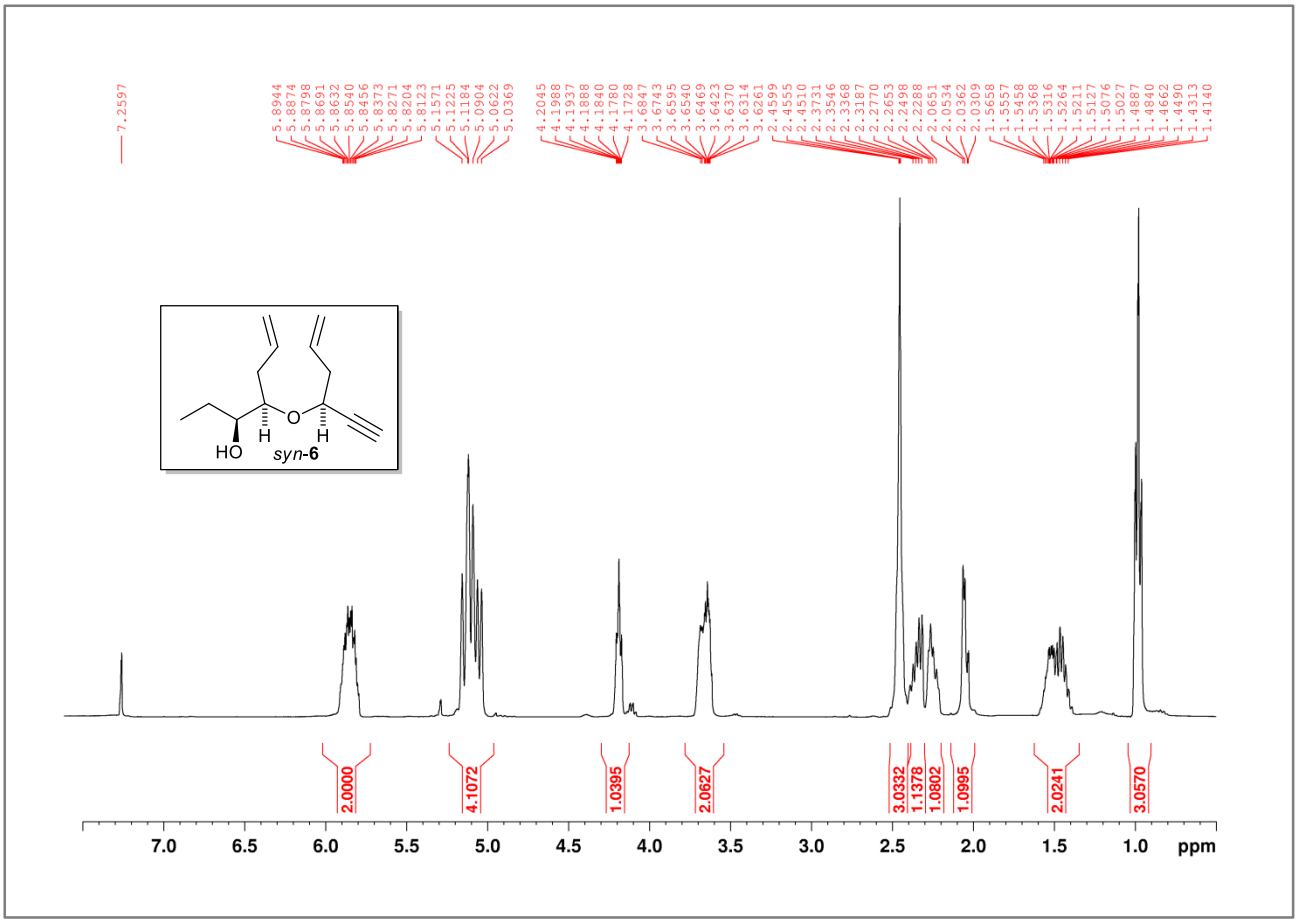
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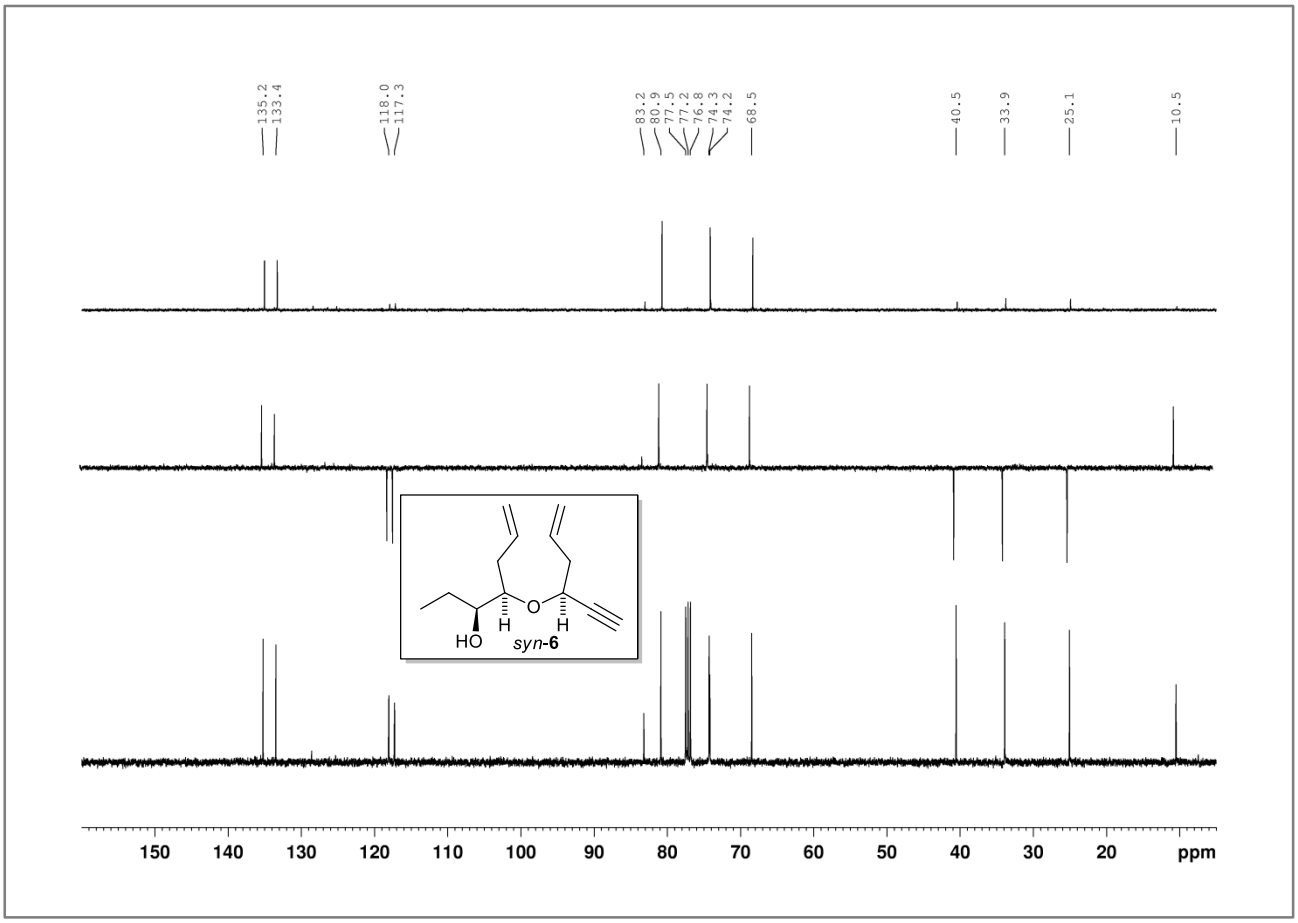
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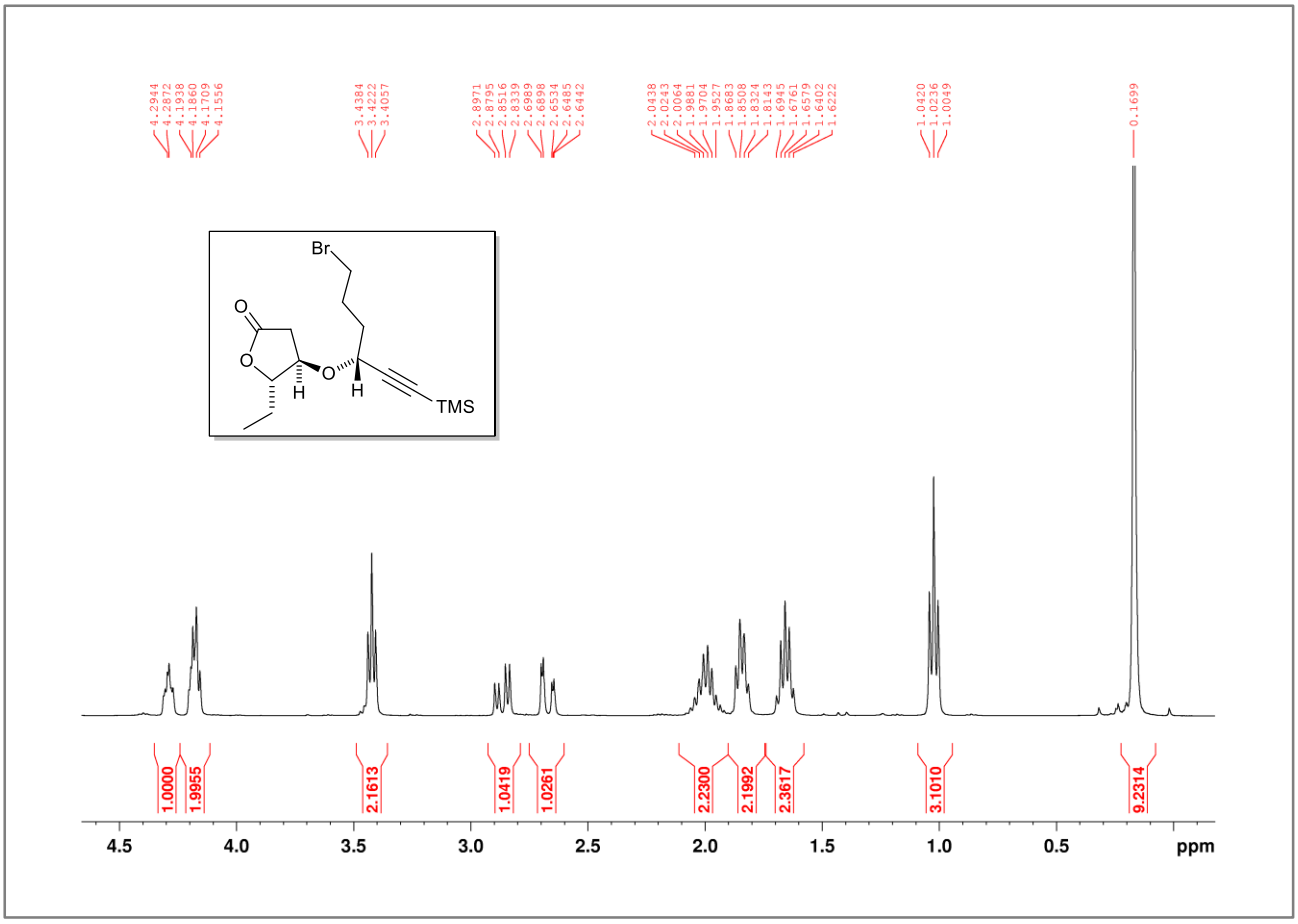
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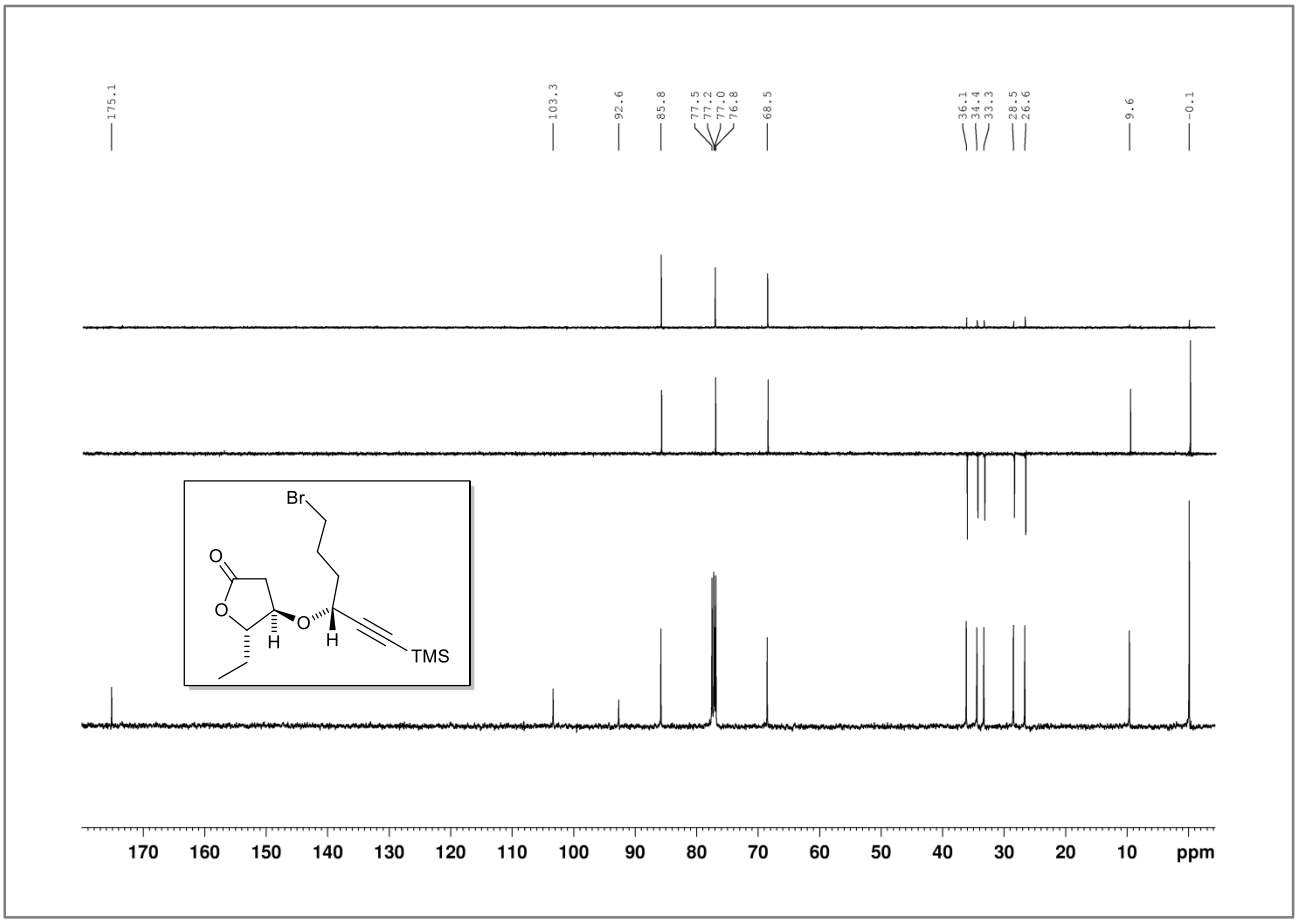
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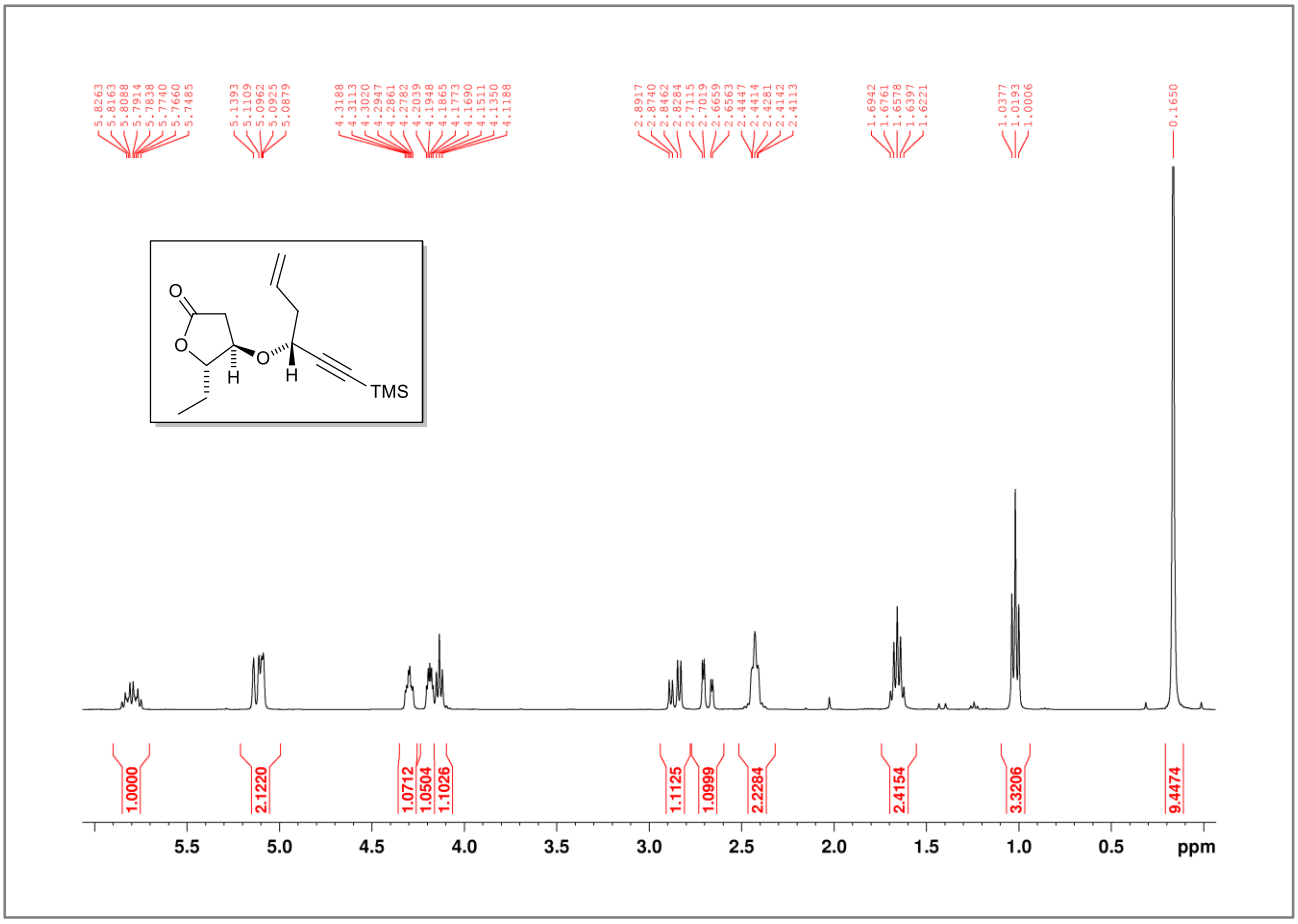
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5.7838
5.7740
5.7660
5.7485
5.1393
5.1309
5.0962
5.0925
5.0879
4.3188
4.3113
4.3020
4.2947
4.2861
4.2782
4.2039
4.1948
4.1865
4.1773
4.1690
4.1511
4.1350
4.1188
2.8917
2.8740
2.8462
2.8284
2.7115
2.7019
2.6659
2.6563
2.4447
2.4414
2.4281
2.4142
2.4113
1.6942
1.6761
1.6578
1.6397
1.6221
1.0377
1.0193
1.0006
0.1650
O
O
O
H
H
TMS
1.0000
2.1220
1.0712
1.0504
1.1026
1.1125
1.0999
2.2284
2.4154
3.3206
9.4474
5.5
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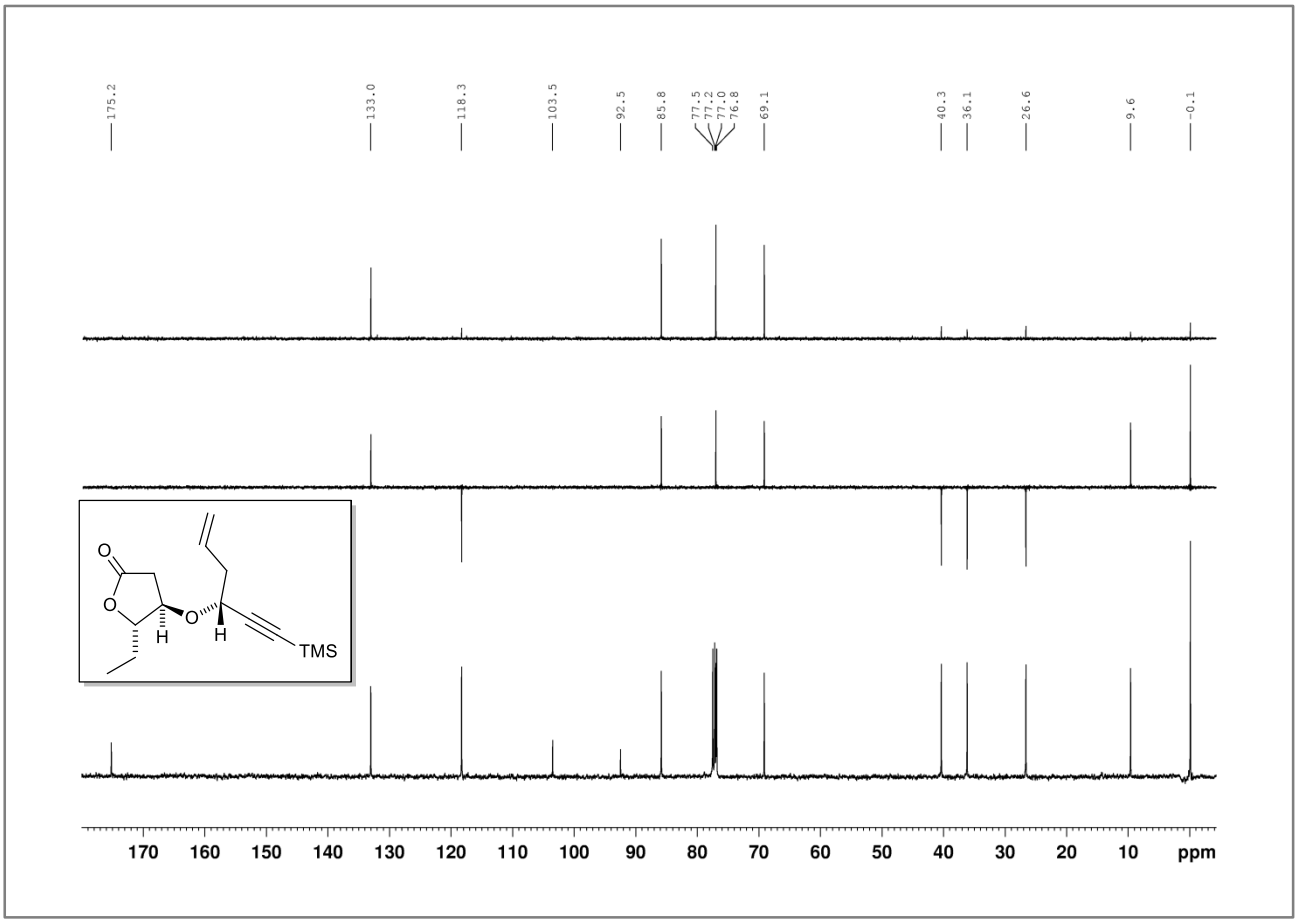
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm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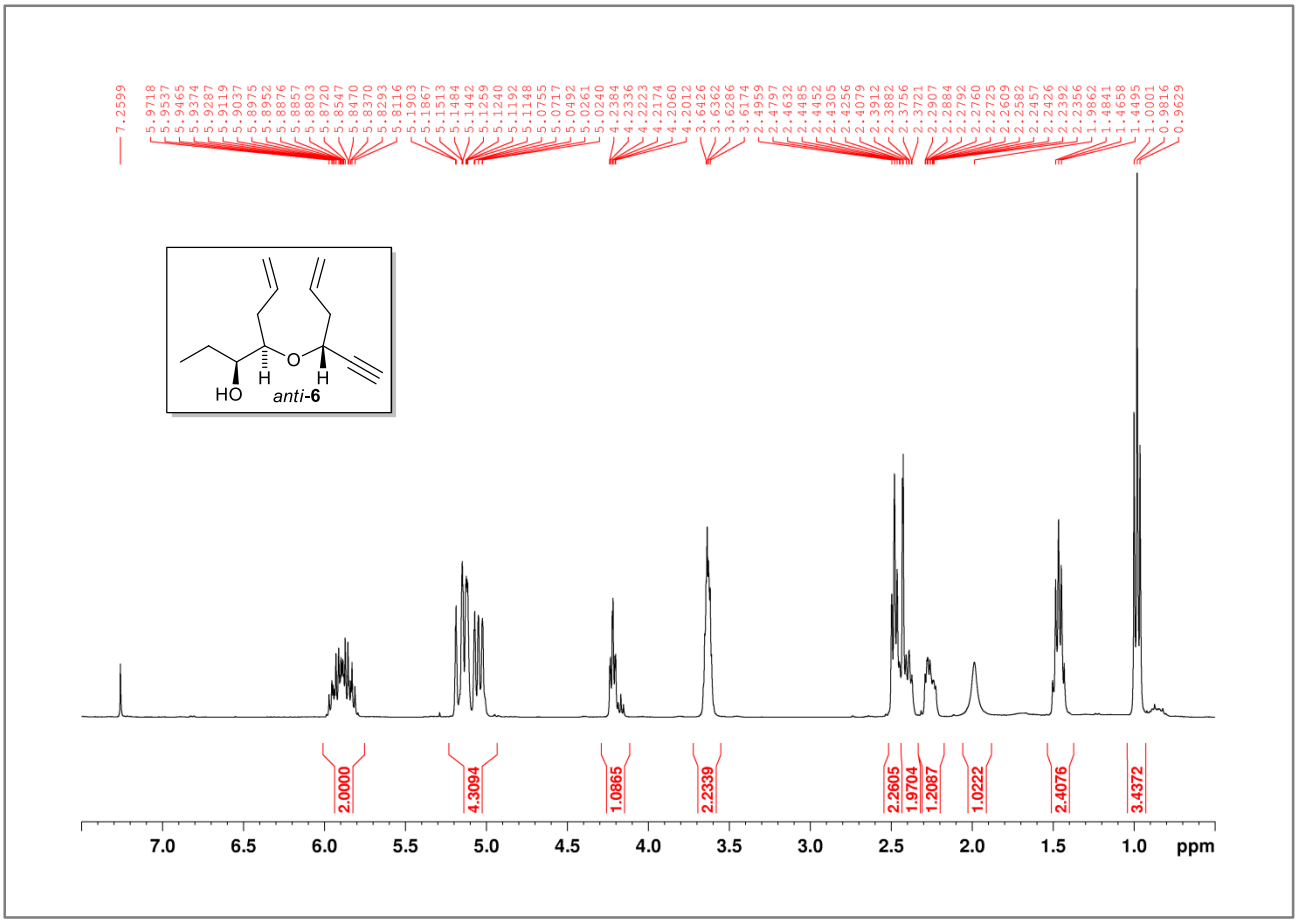
133.0
118.3
103.5
92.5
85.8
77.5
77.2
77.0
76.8
69.1
40.3
36.1
26.6
9.6
-0.1
O
O
O
H
H
TMS
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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5.9718
5.9537
5.9465
5.9374
5.9287
5.9119
5.9037
5.8975
5.8952
5.8876
5.8857
5.8803
5.8720
5.8547
5.8470
5.8370
5.8293
5.8116
5.1903
5.1867
5.1513
5.1484
5.1442
5.1259
5.1240
5.1192
5.1148
5.0755
5.0717
5.0492
5.0261
5.0240
4.2384
4.2336
4.2223
4.2174
4.2060
4.2012
3.6426
3.6362
3.6286
3.6174
2.4959
2.4797
2.4632
2.4485
2.4452
2.4305
2.4256
2.4079
2.3912
2.3882
2.3756
2.3721
2.2907
2.2884
2.2792
2.2760
2.2725
2.2609
2.2582
2.2457
2.2426
2.2392
2.2356
1.9862
1.4841
1.4658
1.4495
1.0001
0.9816
0.9629
HO
H
O
H
anti-6
2.0000
4.3094
1.0865
2.2339
2.2605
1.9704
1.2087
1.0222
2.4076
3.4372
7.0
6.5
6.0
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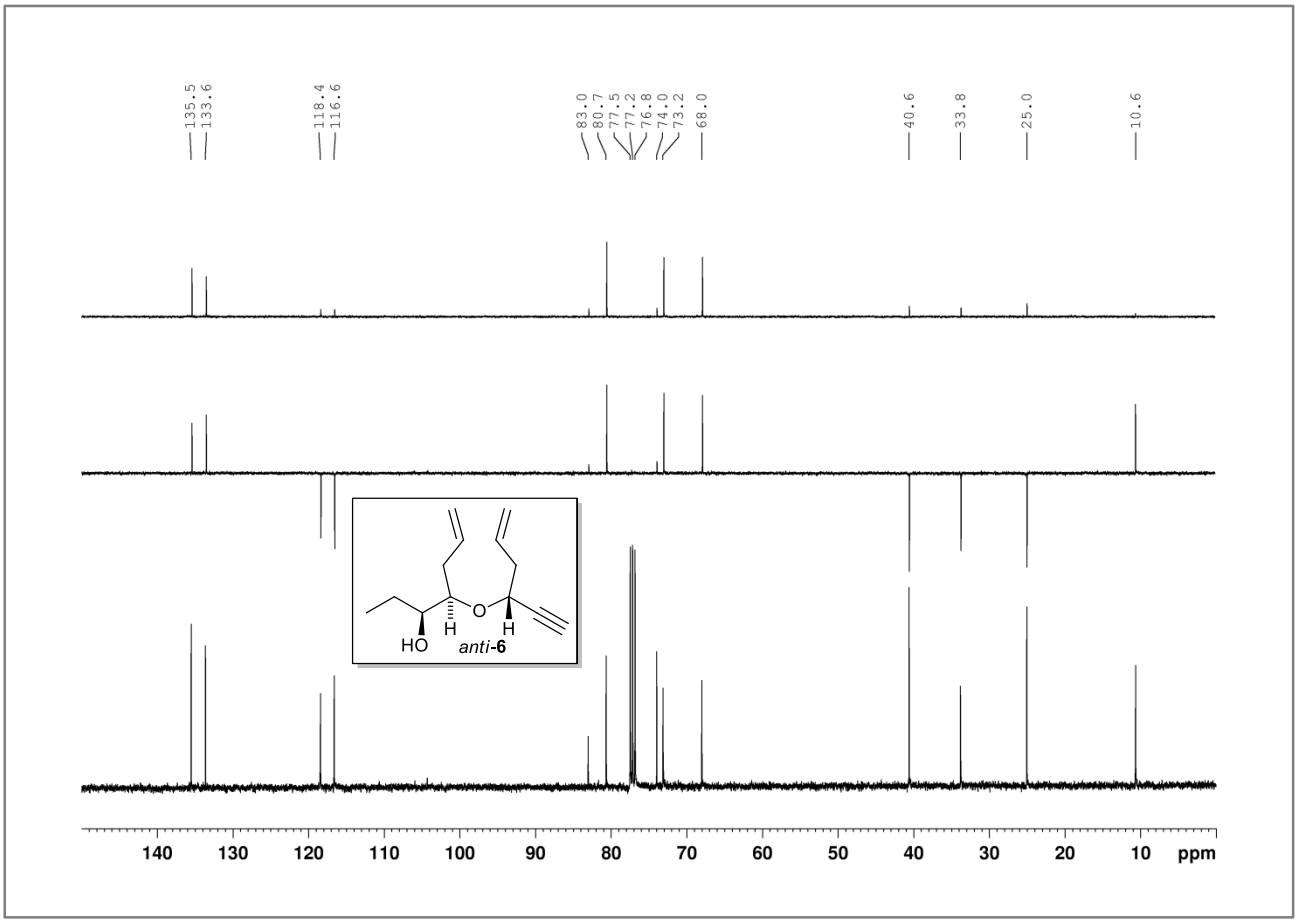
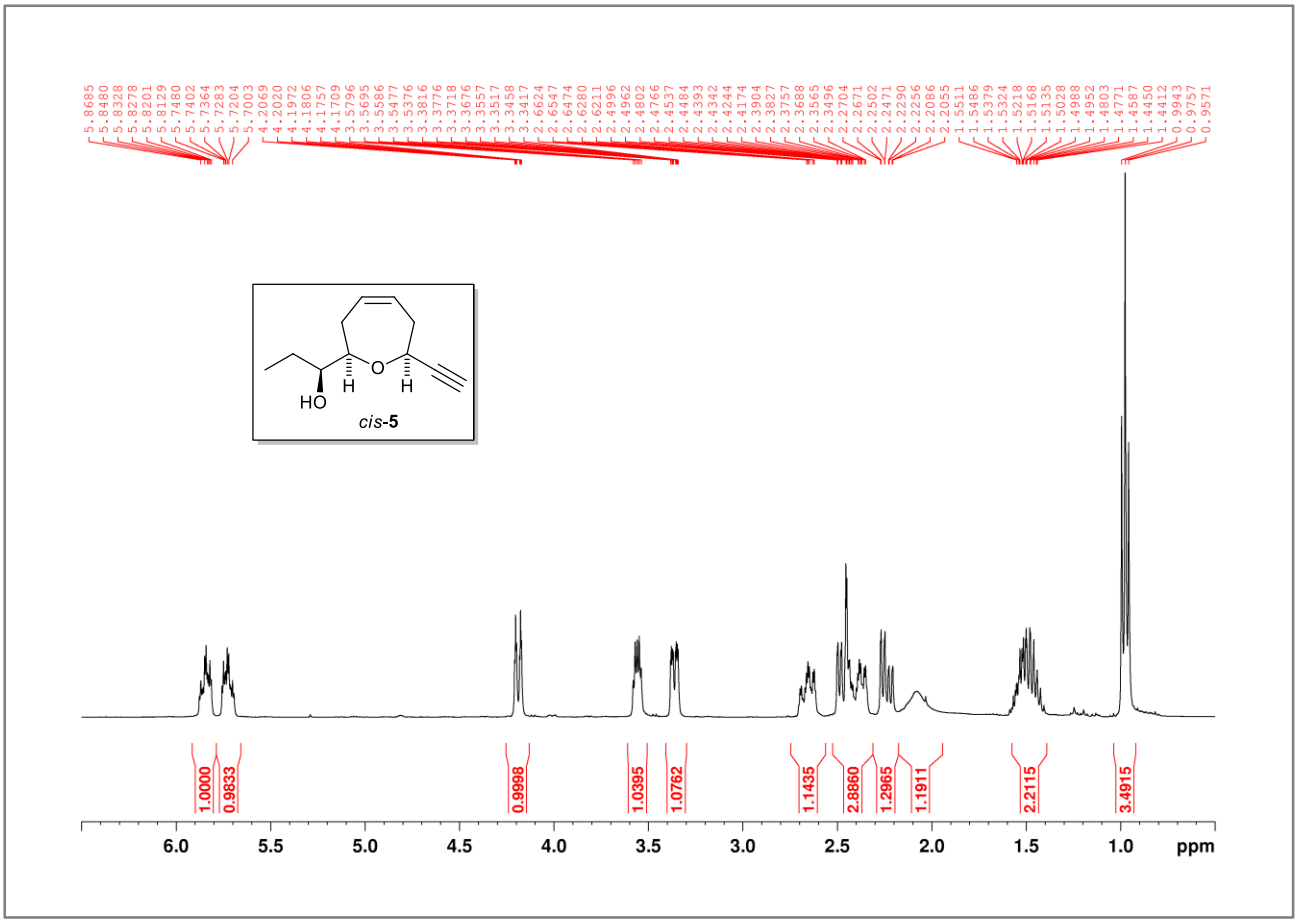
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


135.5
133.6
118.4
116.6
83.0
80.7
77.5
77.2
76.8
74.0
73.2
68.0
40.6
33.8
25.0
10.6
HO
H
O
H
anti-6
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


cis-5
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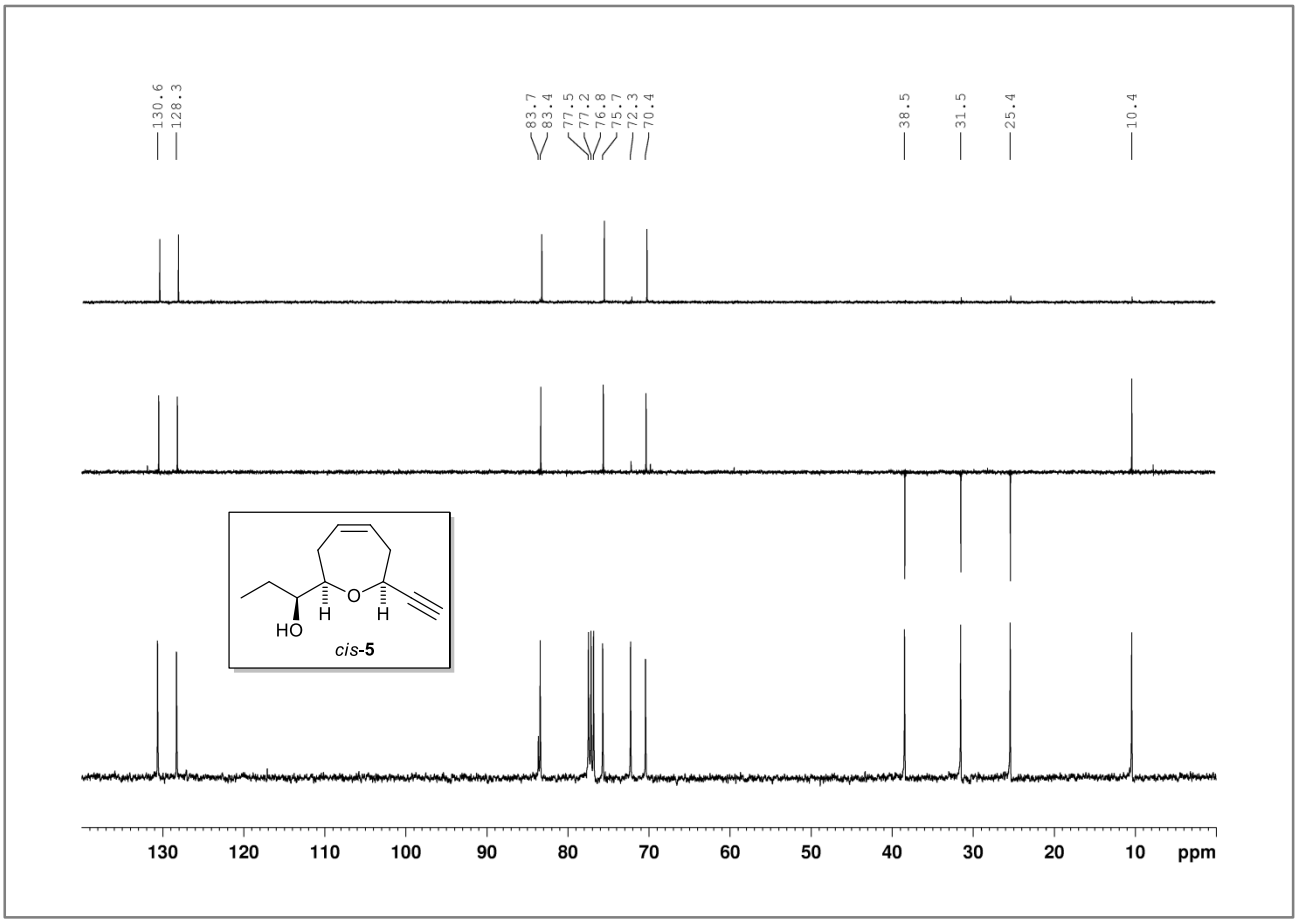
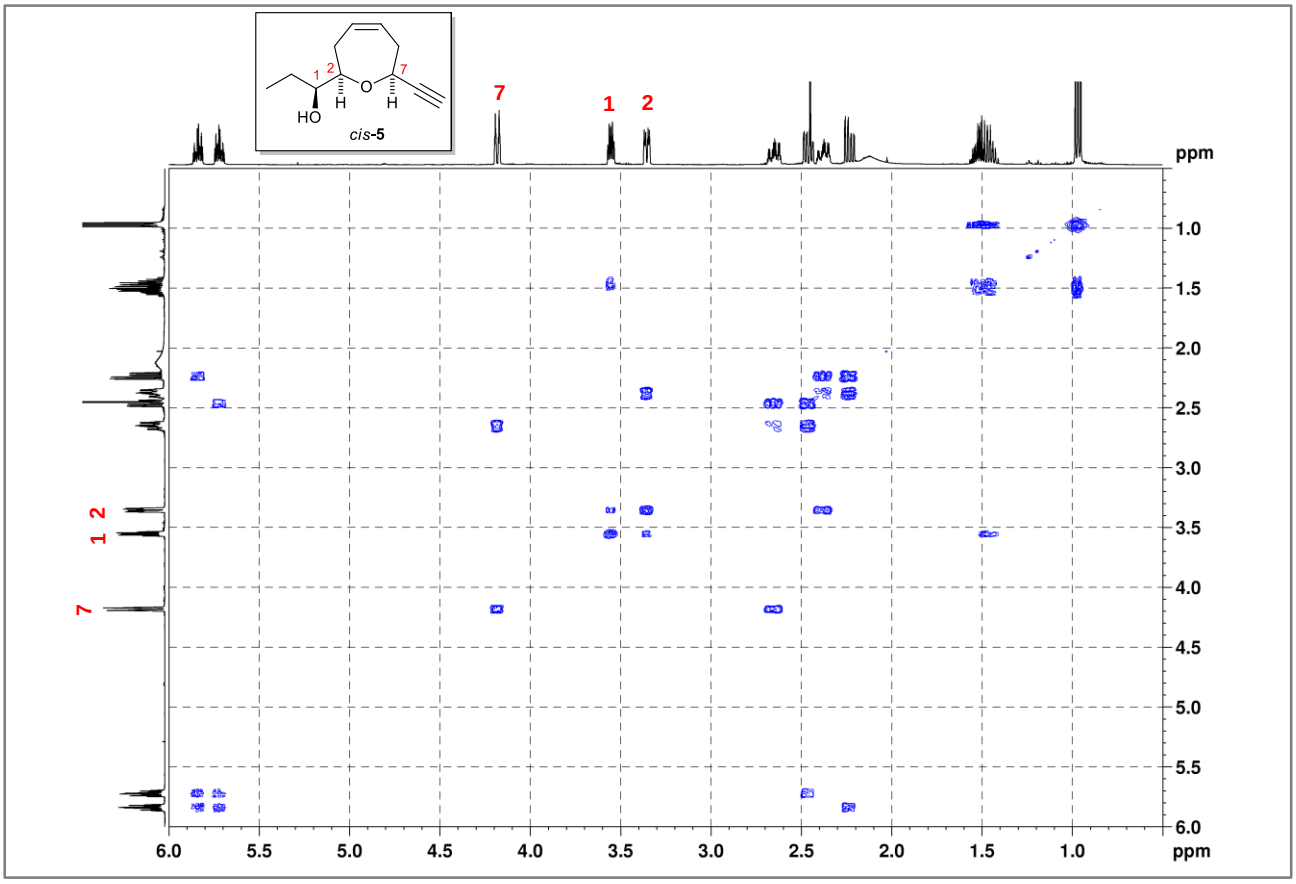
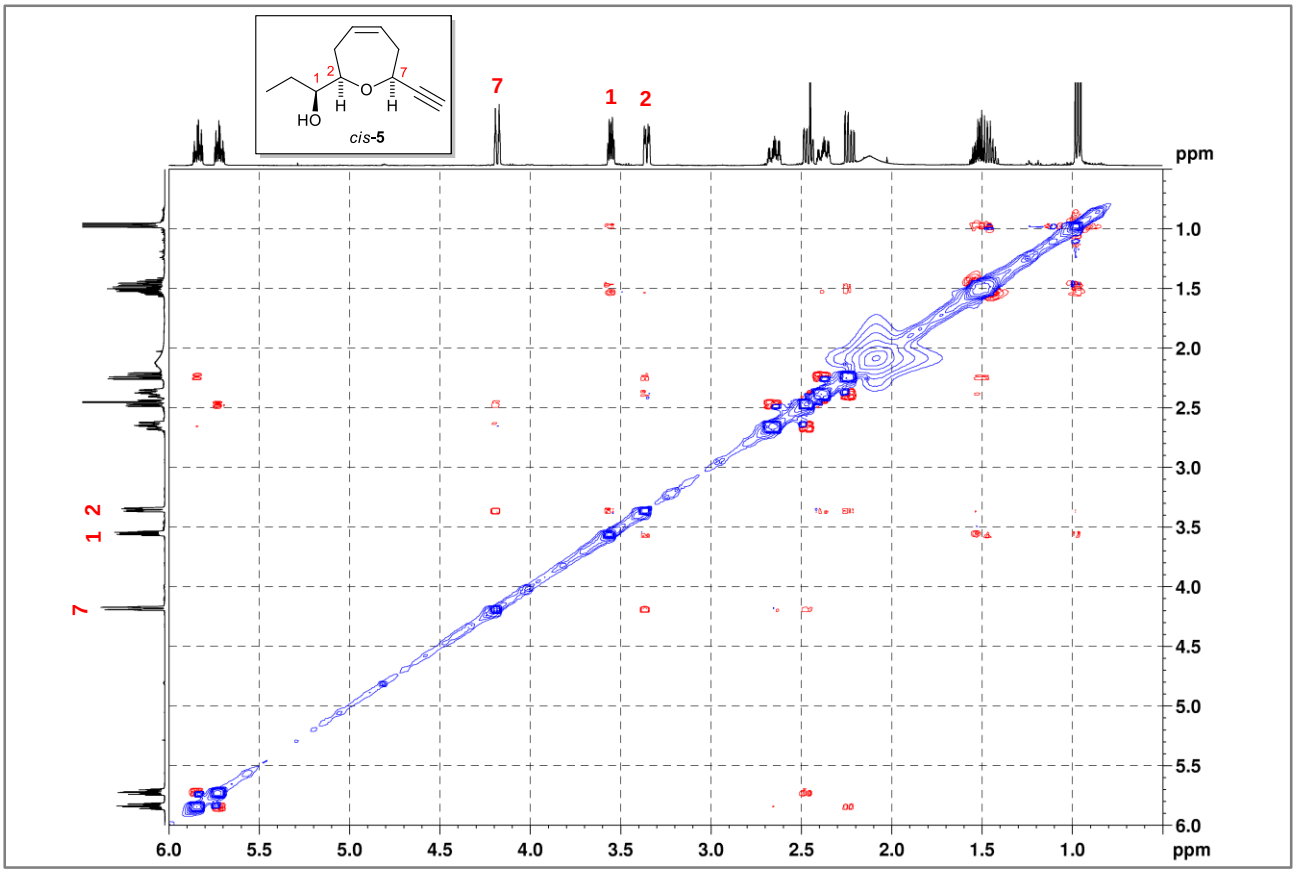
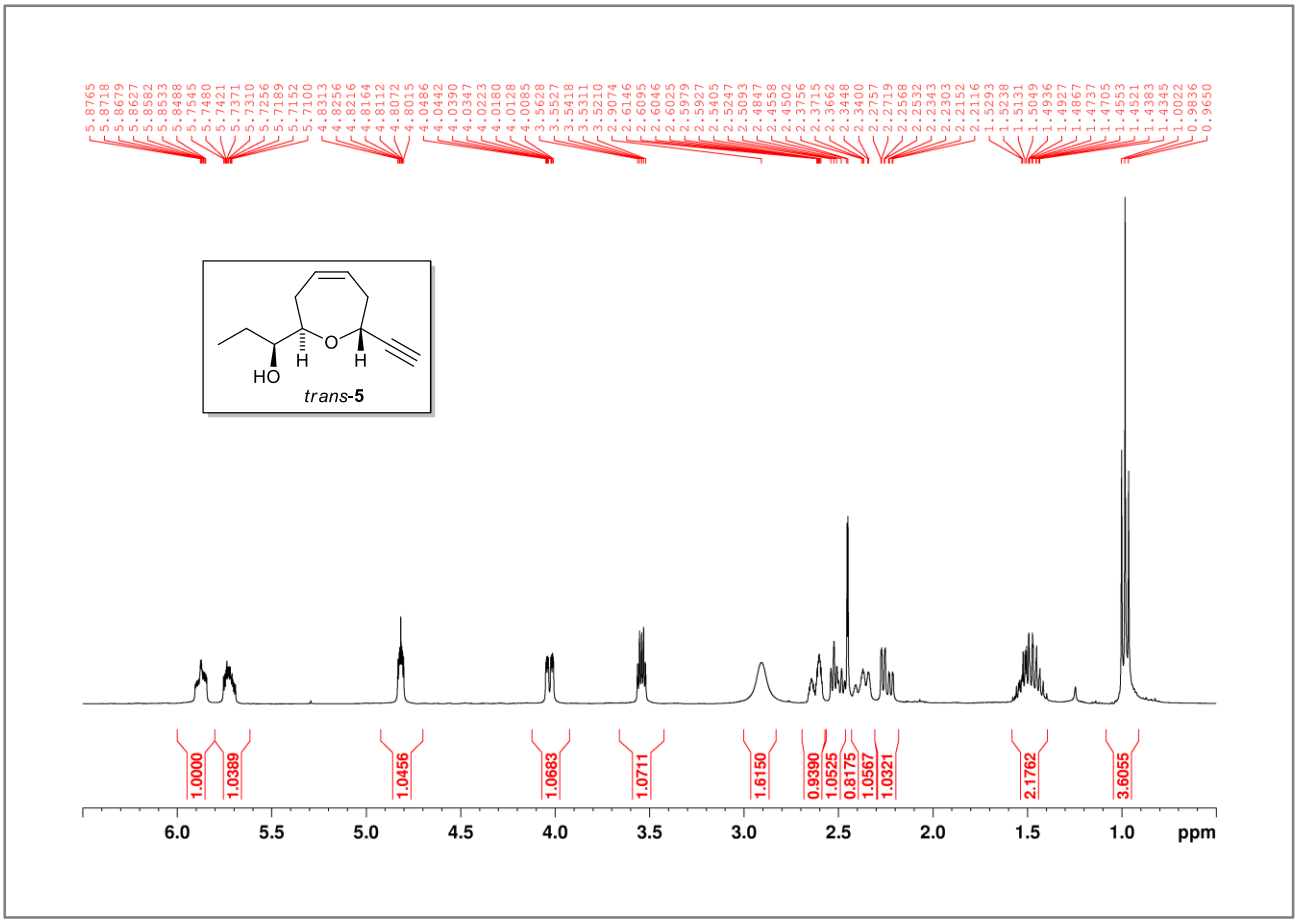
0.9998
1.0395
1.0762
1.1435
2.8860
1.2965
1.1911
2.2115
3.4915
ppm

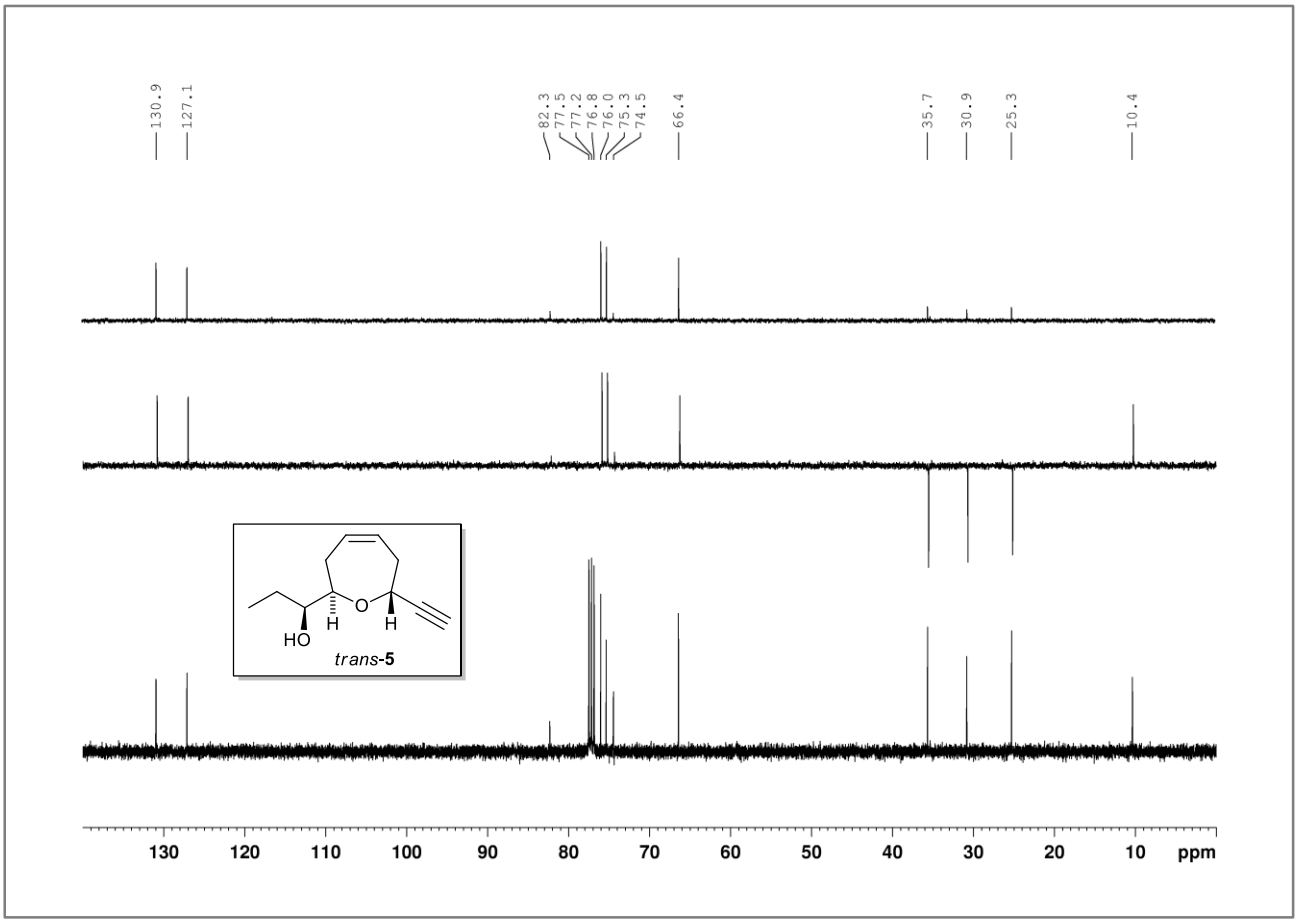

130.6
128.3
83.7
83.4
77.5
77.2
76.8
75.7
72.3
70.4
38.5
31.5
25.4
10.4
cis-5
ppm

COSY and NOESY spectra of *cis*-**5** in $CDCl_3$

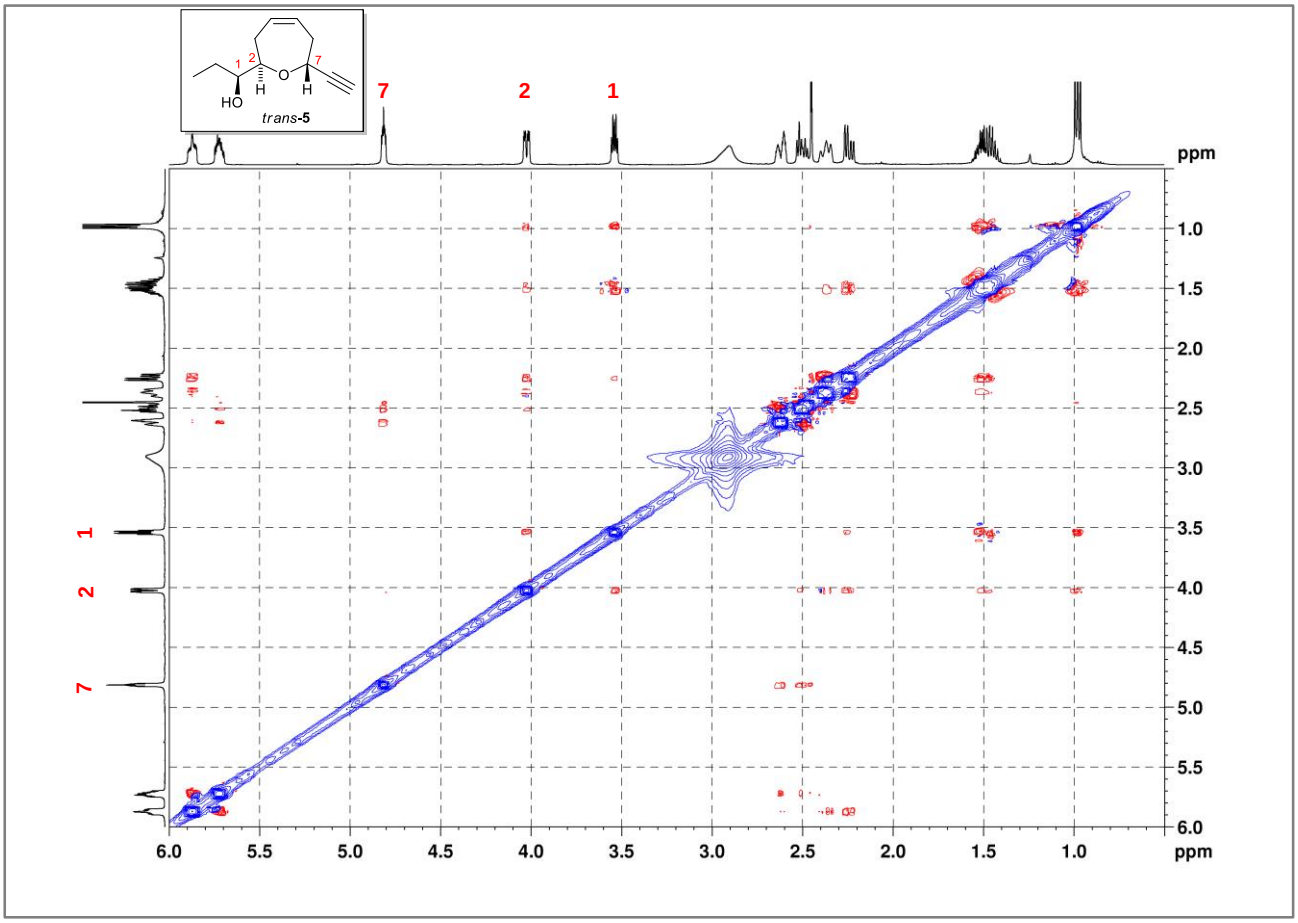


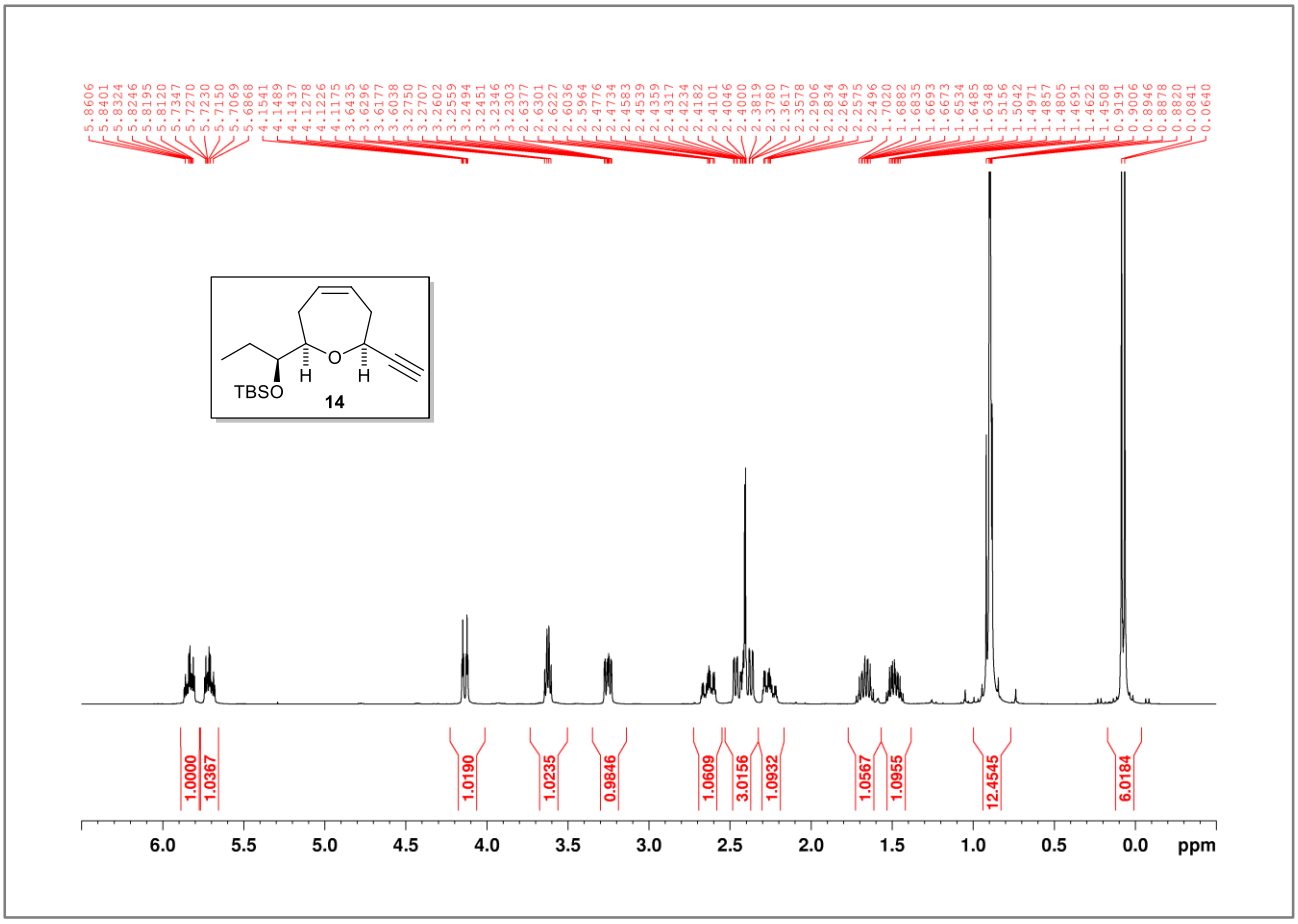


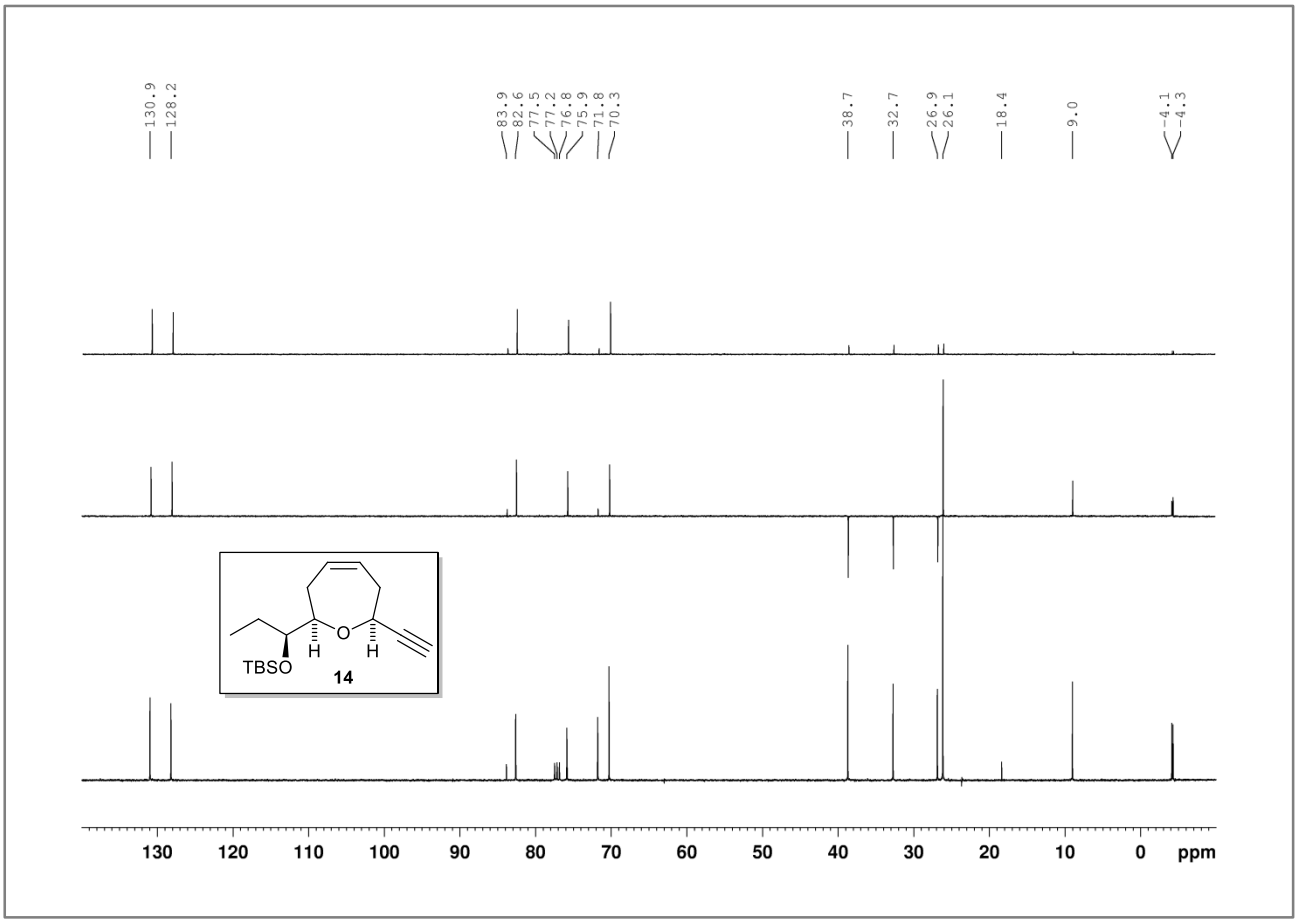

HO
H
O
H
trans-5
1.0000
1.0389
1.0456
1.0683
1.0711
1.6150
0.9390
1.0525
0.8175
1.0567
1.0321
2.1762
3.6055
ppm

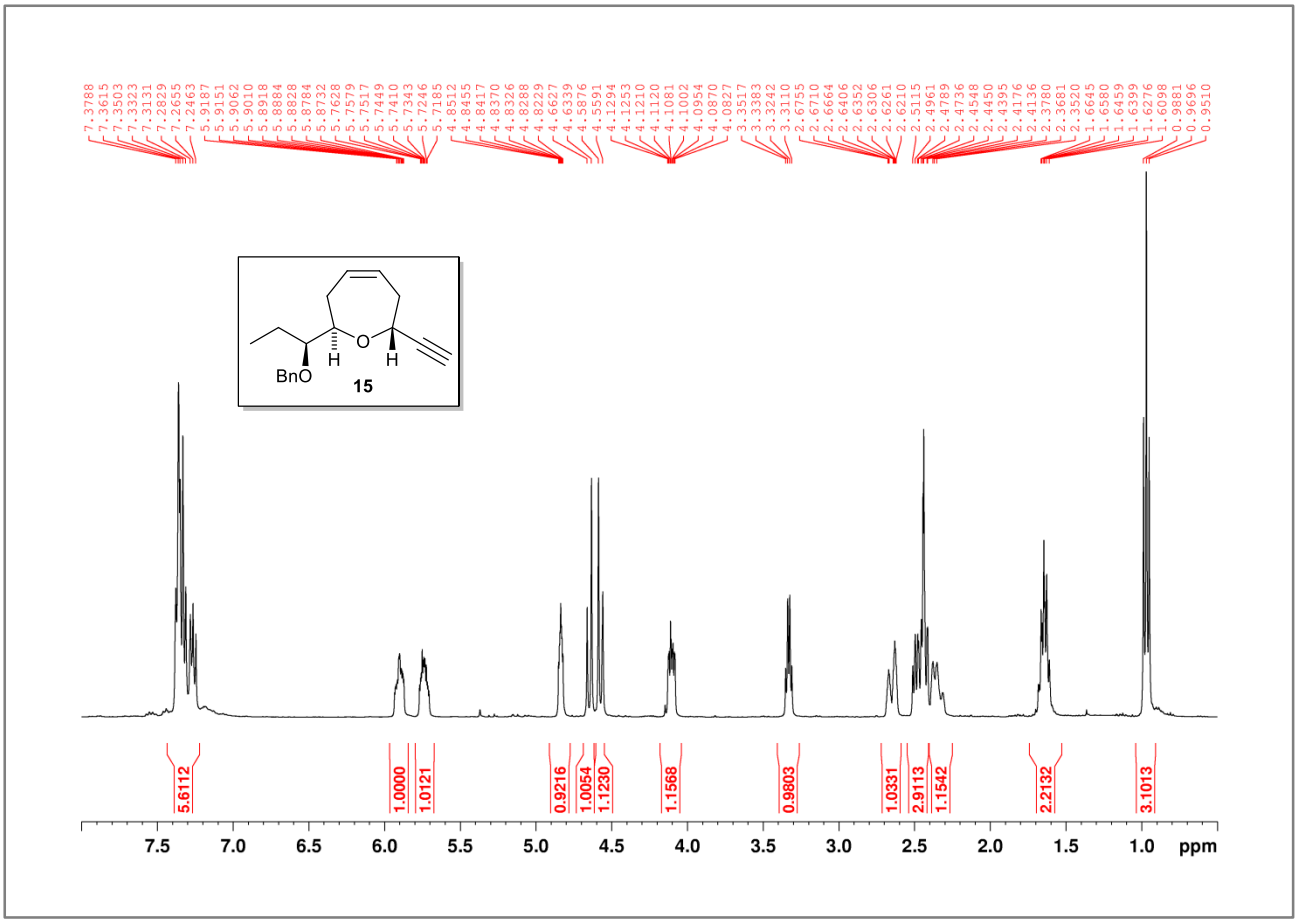

130.9
127.1
82.3
77.5
77.2
76.8
76.0
75.3
74.5
66.4
35.7
30.9
25.3
10.4
HO
H
O
H
trans-5
ppm

NOESY spectra of *trans*-**5** in $CDCl_3$




TBSO
H
O
H
14
1.0000
1.0367
1.0190
1.0235
0.9846
1.0609
3.0156
1.0932
1.0567
1.0955
12.4545
6.0184
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
ppm


130.9
128.2
83.9
82.6
77.5
77.2
76.8
75.9
71.8
70.3
38.7
32.7
26.9
26.1
18.4
9.0
-4.1
-4.3
TBSO
H
O
H
14
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


BnO
H
O
H
15
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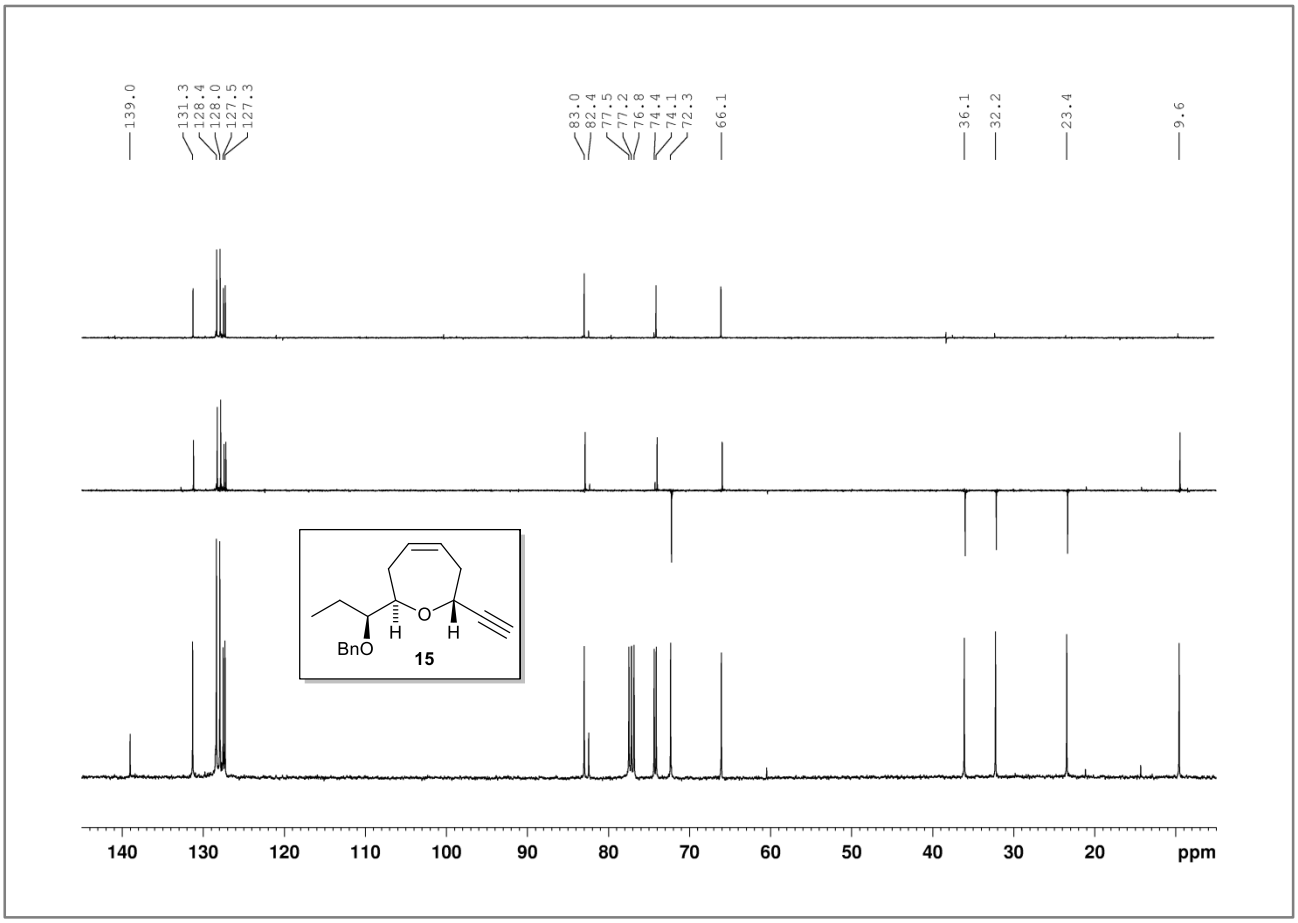
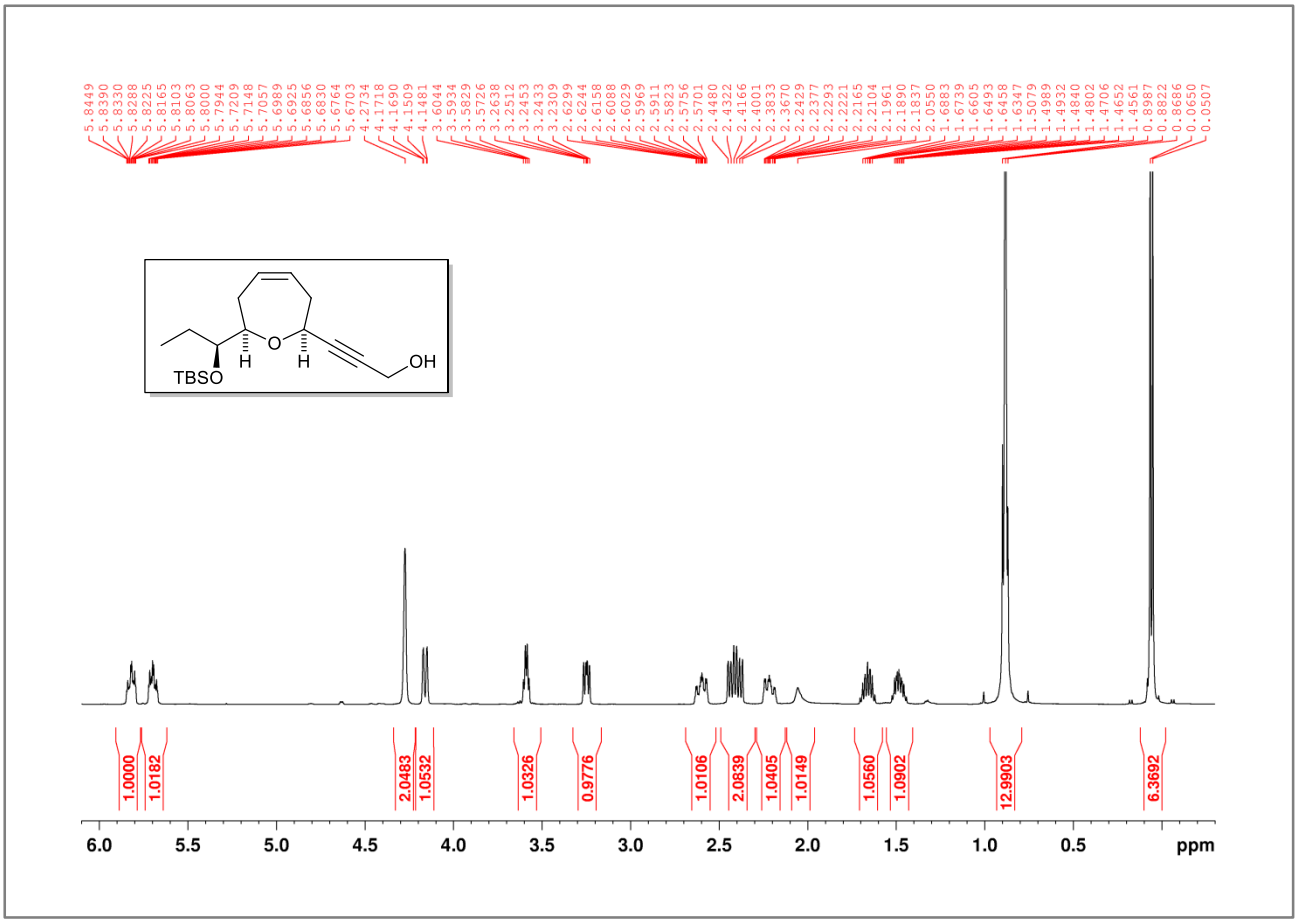
1.0000
1.0121
0.9216
1.0054
1.1230
1.1568
0.9803
1.0331
2.9113
1.1542
2.2132
3.1013
ppm


139.0
131.3
128.4
128.0
127.5
127.3
83.0
82.4
77.5
77.2
76.8
74.4
74.1
72.3
66.1
36.1
32.2
23.4
9.6
BnO
H
O
H
15
ppm


TBSO
H
O
H
OH
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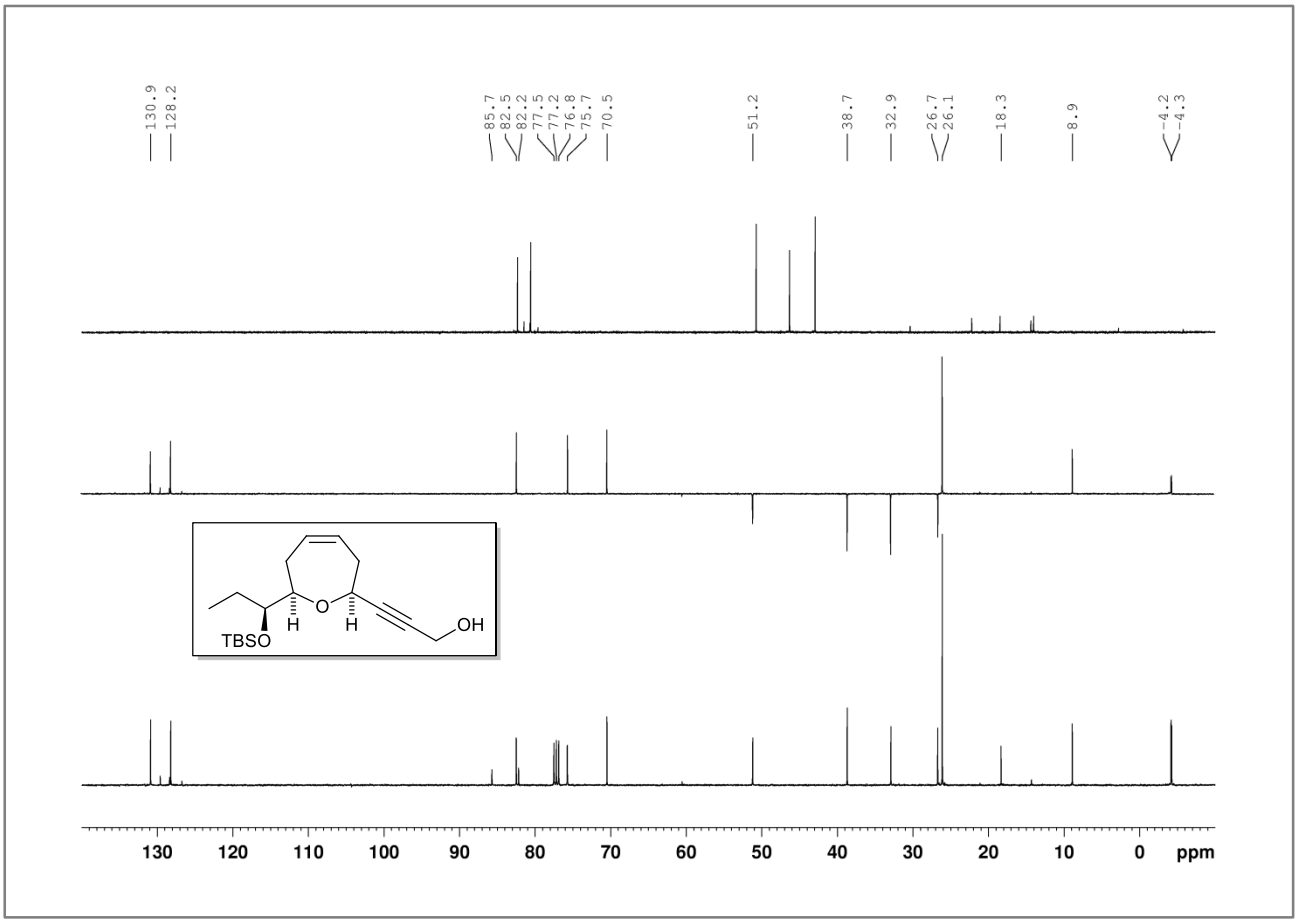
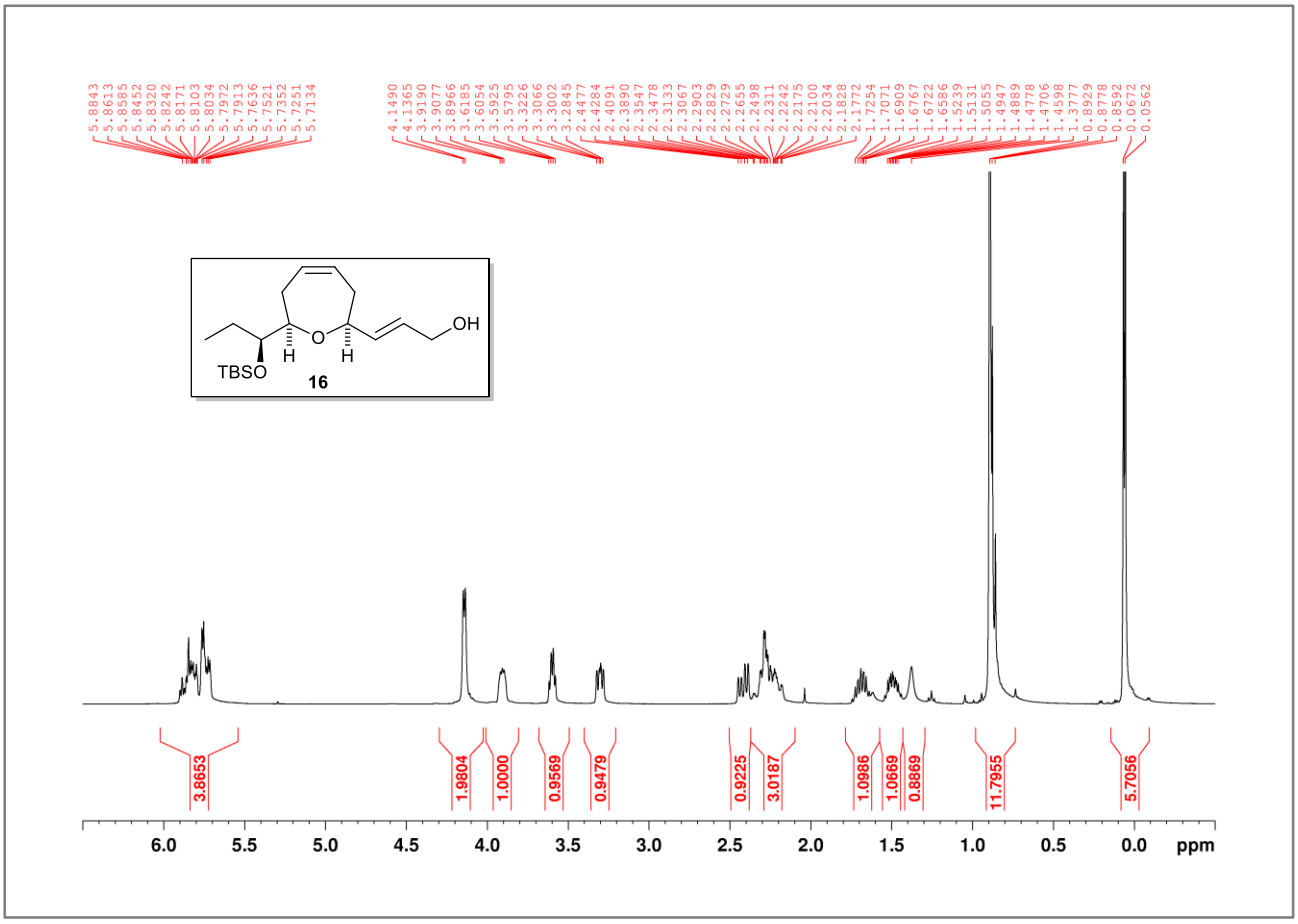
2.0483
1.0532
1.0326
0.9776
1.0106
2.0839
1.0405
1.0149
1.0560
1.0902
12.9903
6.3692
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


130.9
128.2
85.7
82.5
82.2
77.5
77.2
76.8
75.7
70.5
51.2
38.7
32.9
26.7
26.1
18.3
8.9
-4.2
-4.3
TBSO
H
O
H
OH
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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5.8320
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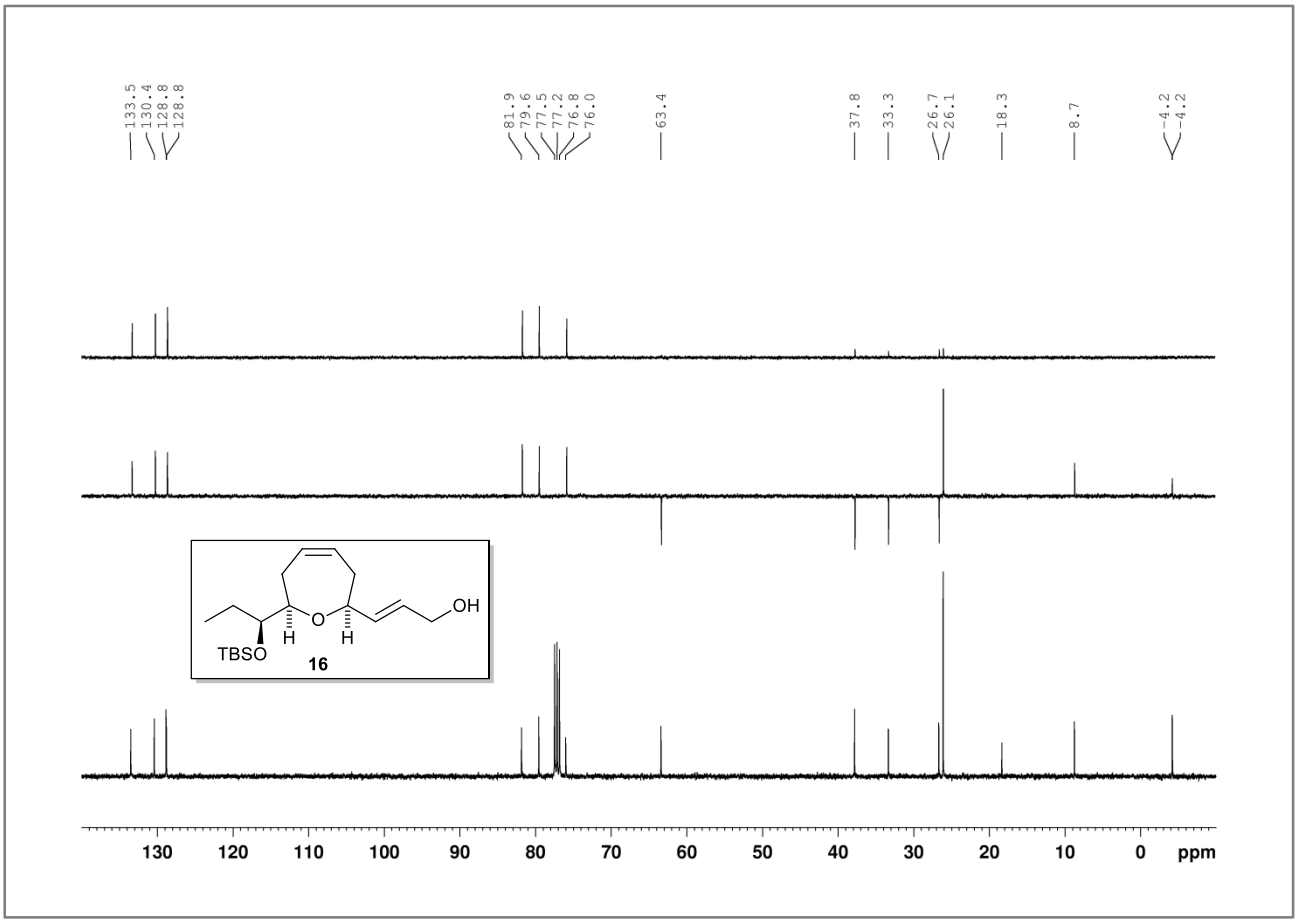
5.8171
5.8103
5.8034
5.7972
5.7913
5.7636
5.7521
5.7352
5.7251
5.7134
4.1490
4.1365
3.9190
3.9077
3.8966
3.6185
3.6054
3.5925
3.5795
3.3226
3.3066
3.3002
3.2845
2.4477
2.4284
2.4091
2.3890
2.3647
2.3478
2.3333
2.3067
2.2903
2.2829
2.2729
2.2655
2.2498
2.2311
2.2242
2.2175
2.2100
2.2034
2.1828
2.1772
1.7254
1.7071
1.6909
1.6767
1.6722
1.6586
1.5239
1.5131
1.5055
1.4947
1.4889
1.4778
1.4706
1.4598
1.3777
1.3599
0.8929
0.8778
0.8592
0.0672
0.0562
OH
O
H
H
TBSO
16
3.8653
1.9804
1.0000
0.9569
0.9479
0.9225
3.0187
1.0986
1.0669
0.8869
11.7955
5.7056
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
ppm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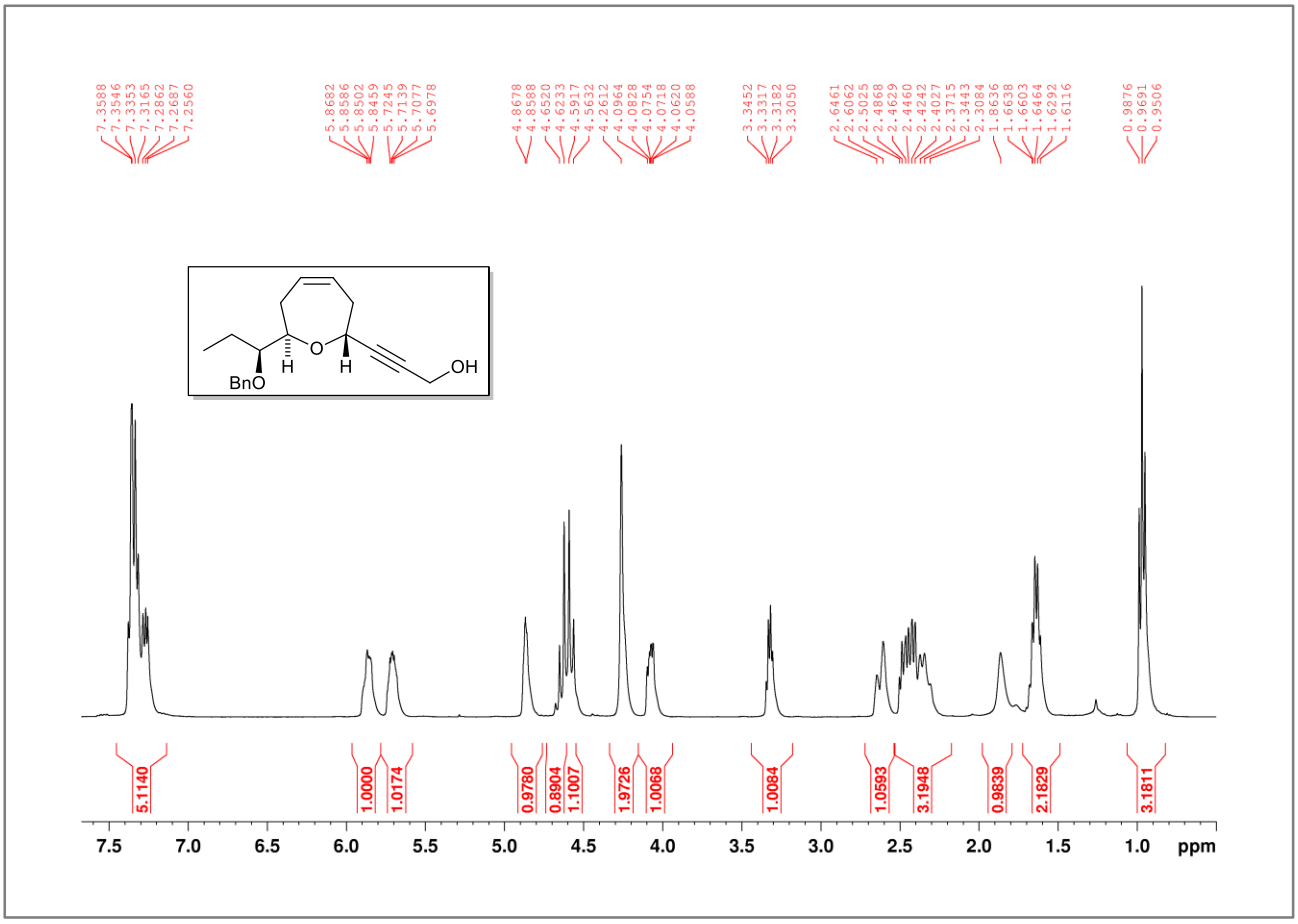
130.4
128.8
128.8
81.9
79.6
77.5
77.2
76.8
76.0
63.4
37.8
33.3
26.7
26.1
18.3
8.7
-4.2
-4.2
OH
O
H
H
TBSO
16
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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7.3546
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7.3165
7.2862
7.2687
7.2560
5.8682
5.8586
5.8502
5.8459
5.7445
5.7139
5.7077
5.6978
4.8678
4.8588
4.6520
4.6233
4.5917
4.5632
4.2612
4.0964
4.0828
4.0754
4.0718
4.0620
4.0588
3.3452
3.3317
3.3182
3.3050
2.6461
2.6062
2.5025
2.4868
2.4629
2.4460
2.4242
2.4027
2.3715
2.3443
2.3084
1.8636
1.6638
1.6603
1.6464
1.6292
1.6116
0.9876
0.9691
0.9506
BnO
H
O
H
OH
5.1140
1.0000
1.0174
0.9780
0.8904
1.1007
1.9726
1.0068
1.0084
1.0593
3.1948
0.9839
2.1829
3.1811
7.5
7.0
6.5
6.0
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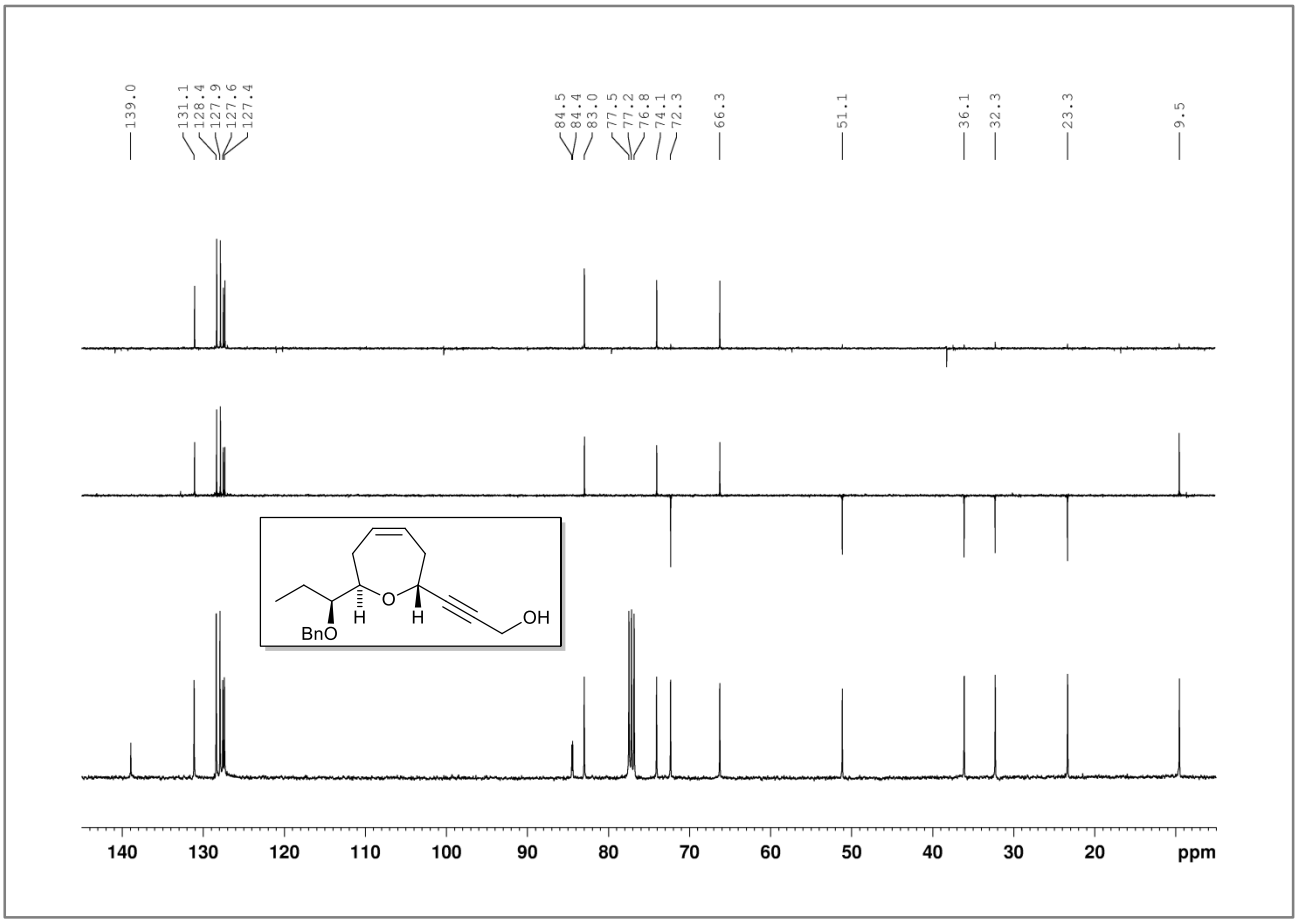
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm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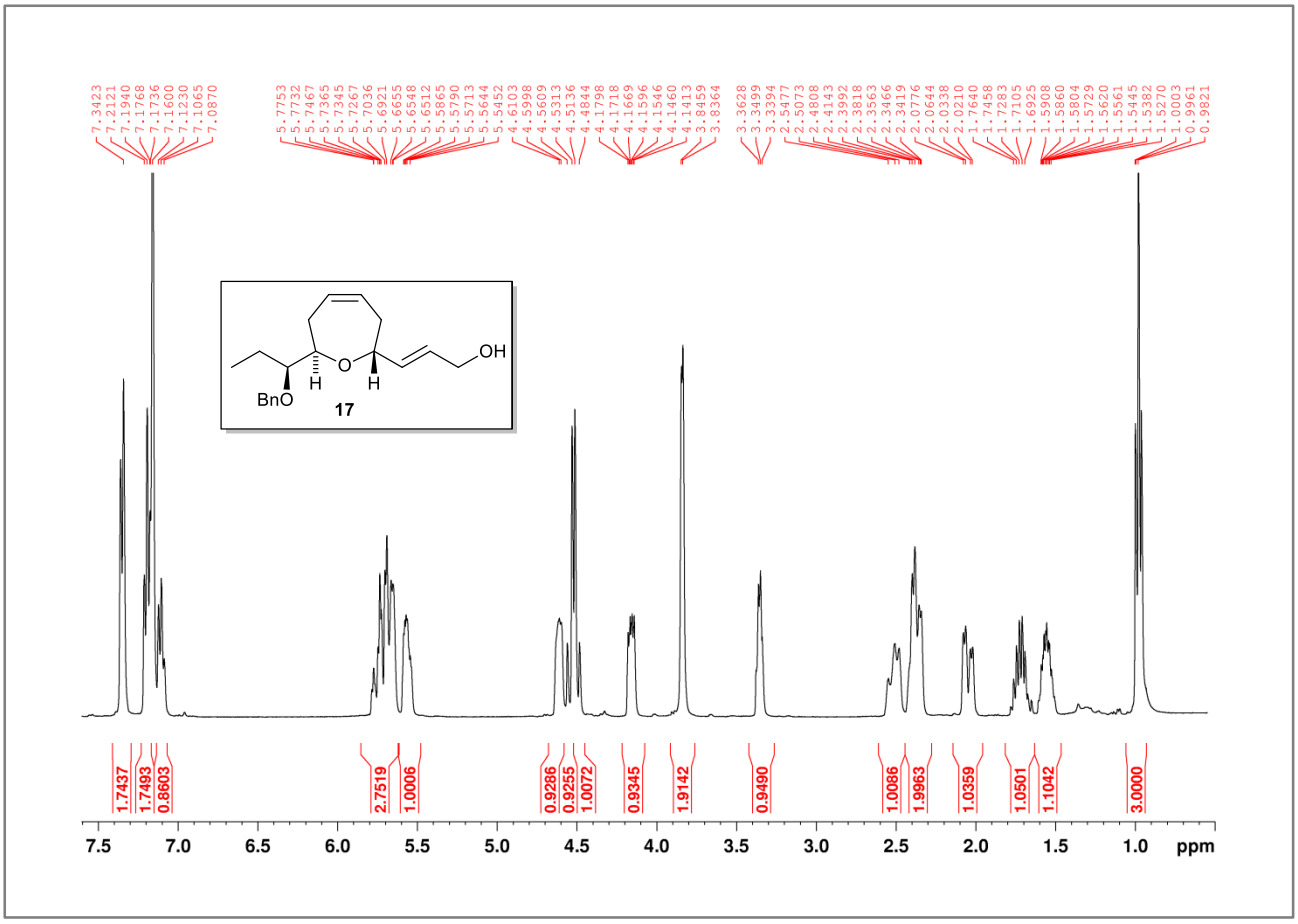
127.9
127.6
127.4
84.5
84.4
83.0
77.5
77.2
76.8
74.1
72.3
66.3
51.1
36.1
32.3
23.3
9.5
BnO
H
O
H
OH
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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7.1940
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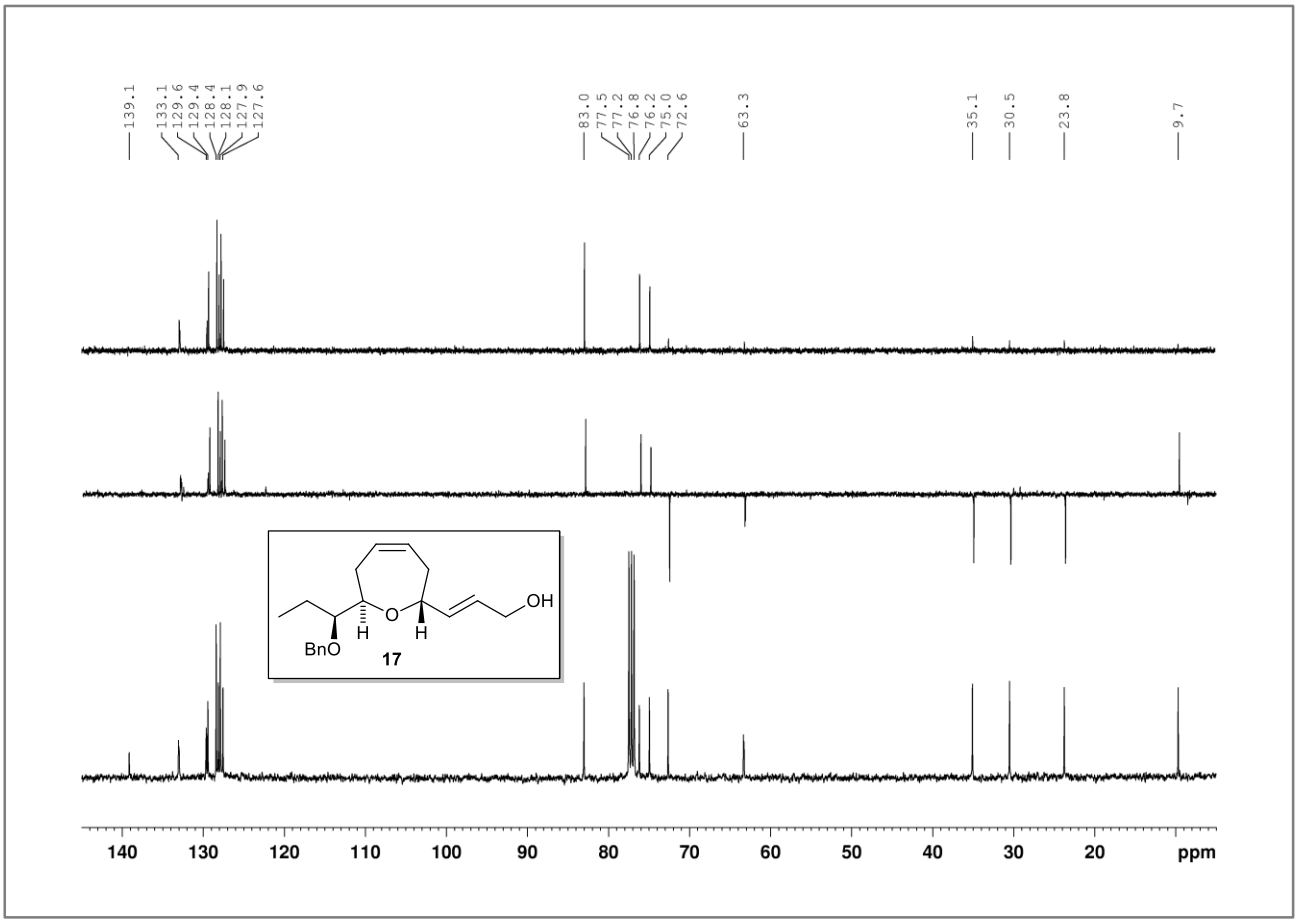
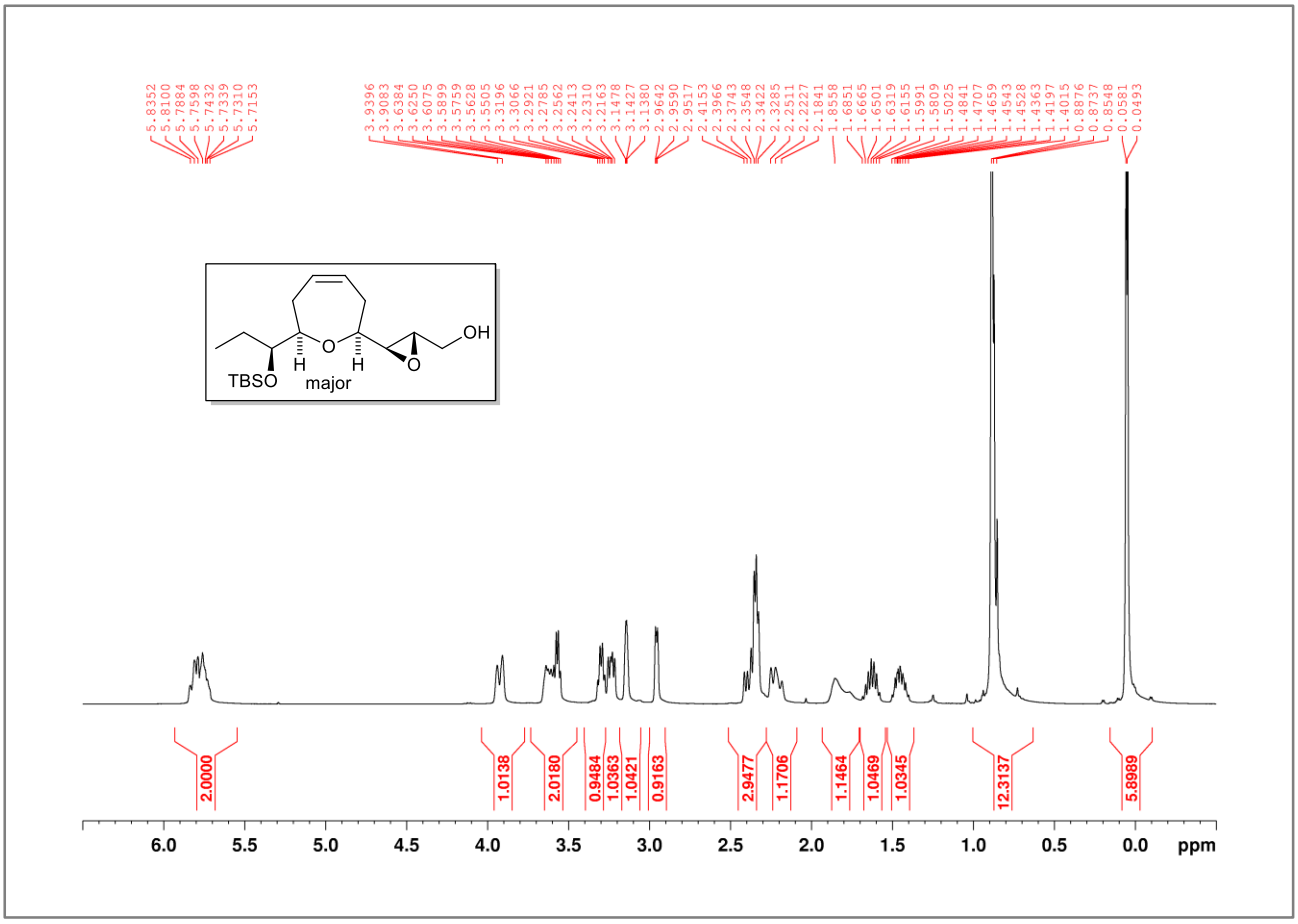
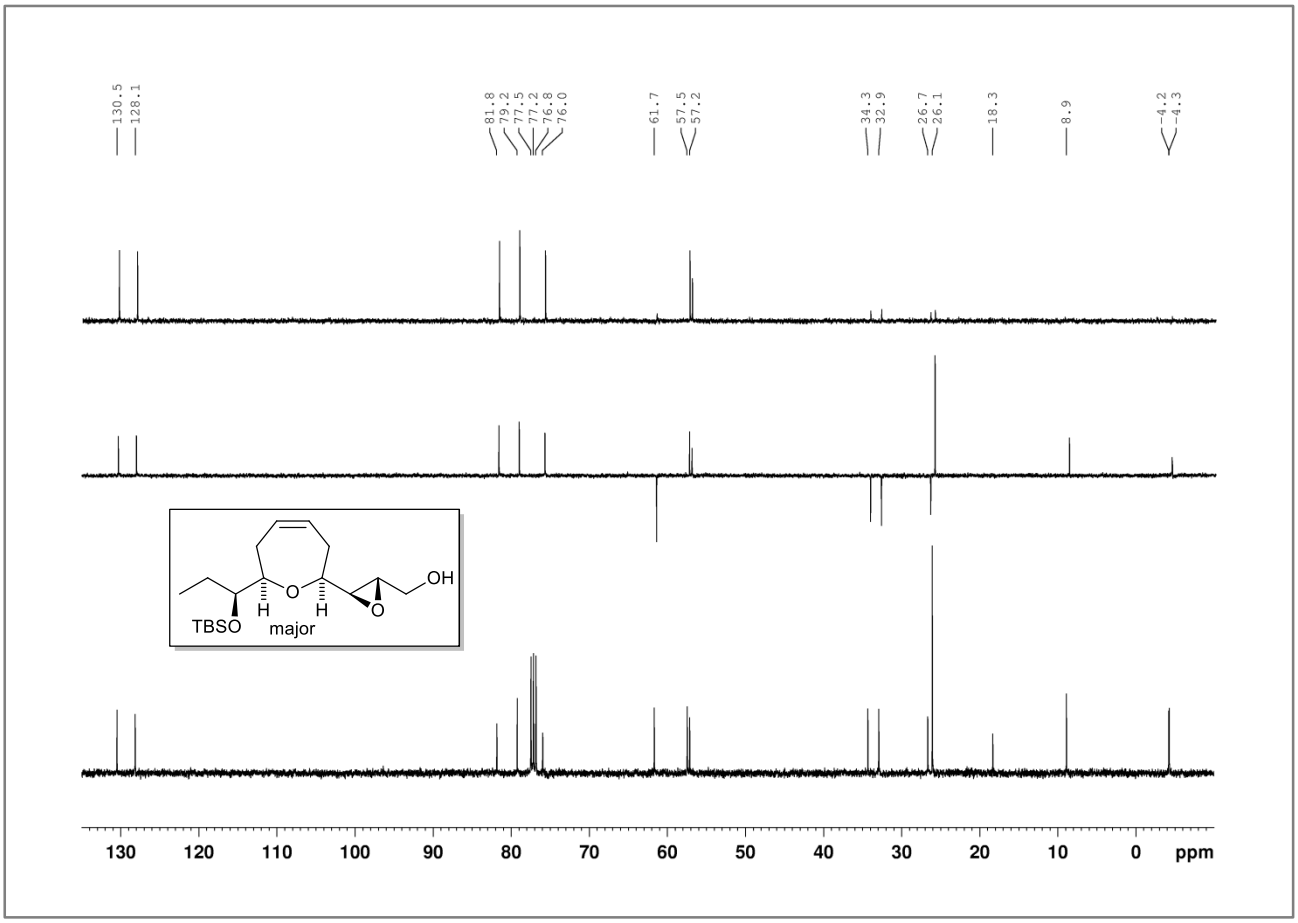
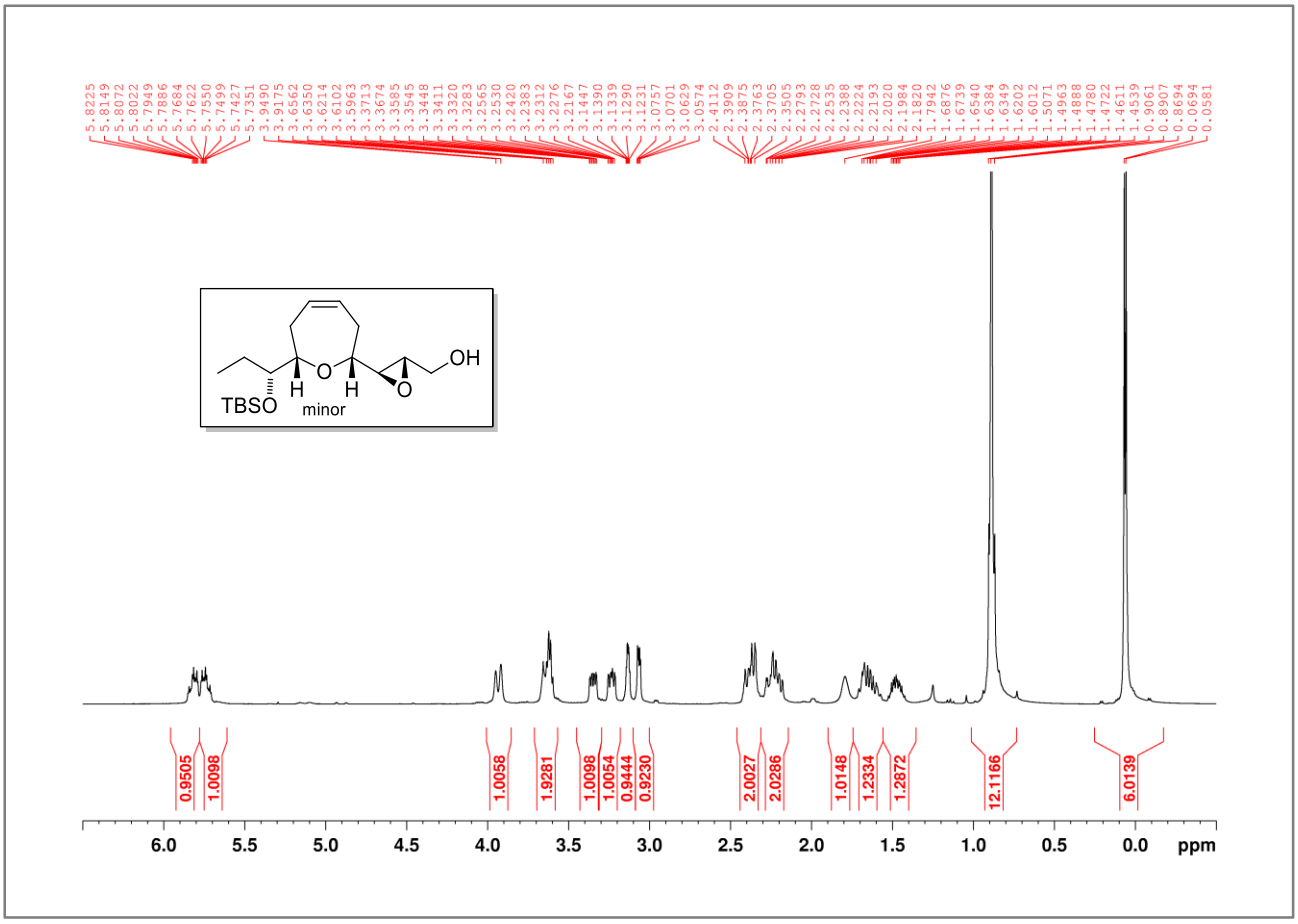
7.1600
7.1230
7.1065
7.0870
5.7753
5.7732
5.7467
5.7365
5.7345
5.7267
5.7036
5.6921
5.6655
5.6548
5.6512
5.5865
5.5790
5.5713
5.5644
5.5452
5.5403
4.6003
4.5998
4.5609
4.5313
4.5136
4.4944
4.1798
4.1718
4.1669
4.1596
4.1546
4.1460
4.1413
3.8459
3.8364
3.3628
3.3499
3.3394
2.5477
2.5073
2.4808
2.4143
2.3992
2.3818
2.3563
2.3466
2.3419
2.0776
2.0644
2.0338
2.0210
1.7640
1.7458
1.7283
1.7105
1.6925
1.5908
1.5860
1.5804
1.5729
1.5620
1.5561
1.5445
1.5382
1.5270
1.0003
0.9961
0.9821
OH
O
H
H
BnO
17
1.7437
1.7493
0.8603
2.7519
1.0006
0.9286
0.9255
1.0072
0.9345
1.9142
0.9490
1.0086
1.9963
1.0359
1.0501
1.1042
3.0000
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
ppm


139.1
133.1
129.6
129.4
128.4
128.1
127.9
127.6
83.0
77.5
77.2
76.8
76.2
75.0
72.6
63.3
35.1
30.5
23.8
9.7
OH
O
H
H
BnO
17
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


TBSO
major
OH
ppm


TBSO
major
OH
ppm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0.9230
2.0027
2.0286
1.0148
1.2334
1.2872
12.1166
6.0139
6.0
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4.0
3.5
3.0
2.5
2.0
1.5
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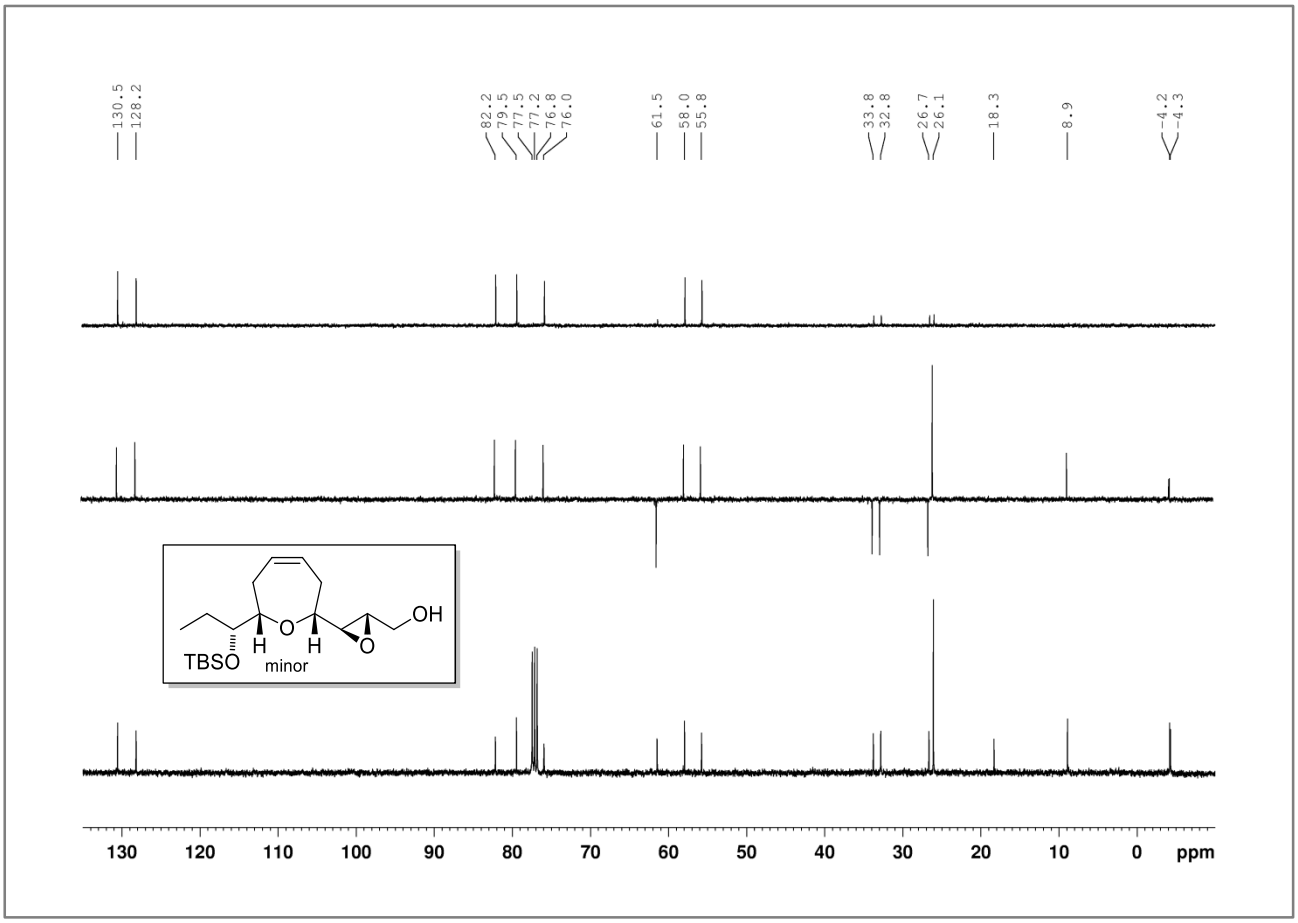
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82.2
79.5
77.5
77.2
76.8
76.0
61.5
58.0
55.8
33.8
32.8
26.7
26.1
18.3
8.9
-4.2
-4.3
TBSO
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O
H
O
OH
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110
100
90
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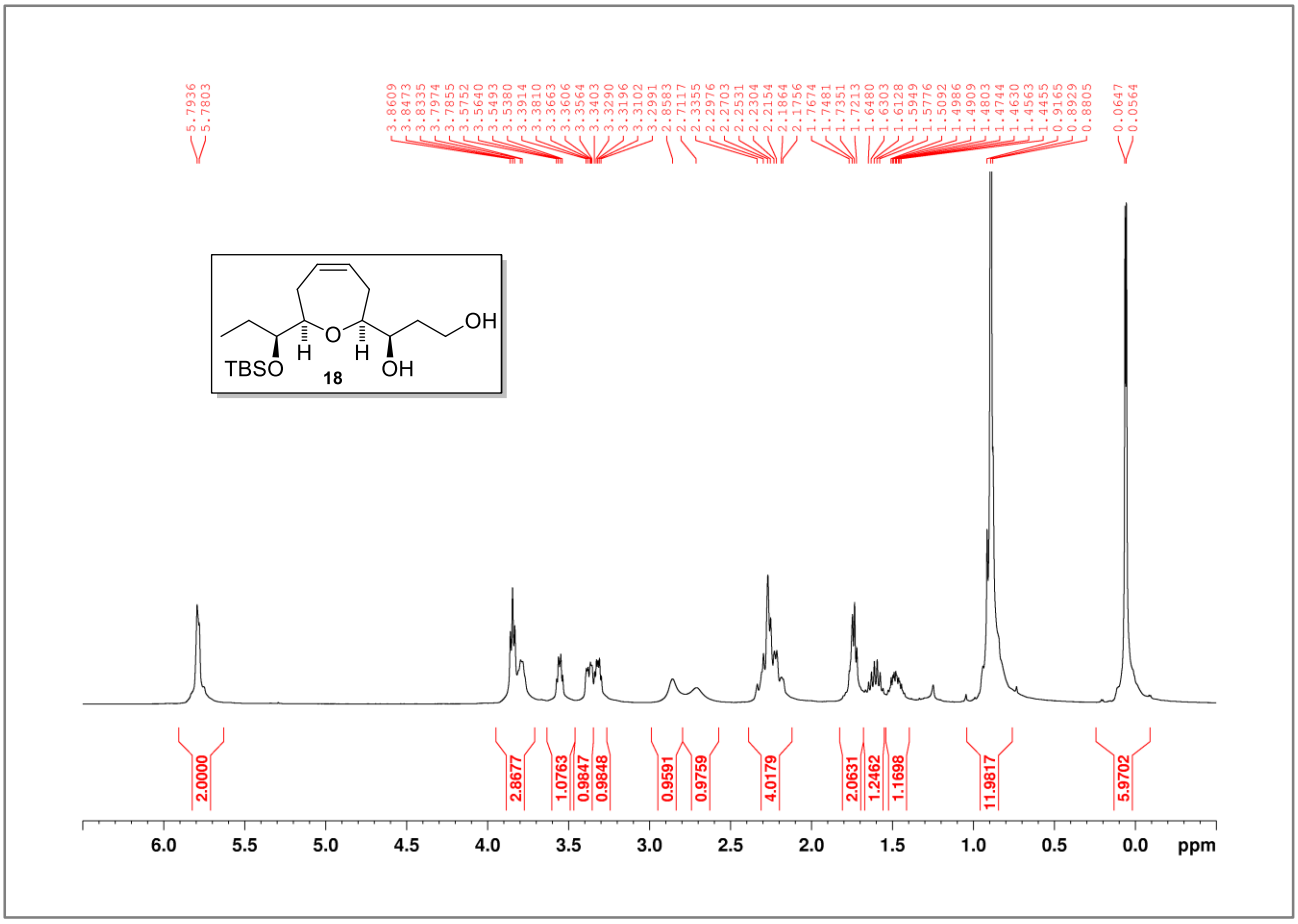
60
50
40
30
20
10
0
ppm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3.3914
3.3810
3.3663
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3.3564
3.3403
3.3290
3.3196
3.3102
3.2991
3.2883
2.7117
2.3355
2.2976
2.2703
2.2531
2.2304
2.2154
2.1864
2.1756
1.7674
1.7481
1.7351
1.7213
1.6480
1.6303
1.6128
1.5949
1.5776
1.5092
1.4986
1.4909
1.4803
1.4744
1.4630
1.4563
1.4455
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0.8929
0.8805
0.0647
0.0564
TBSO
H
O
H
OH
OH
18
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0.9591
0.9759
4.0179
2.0631
1.2462
1.1698
11.9817
5.9702
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4.0
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3.0
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1.5
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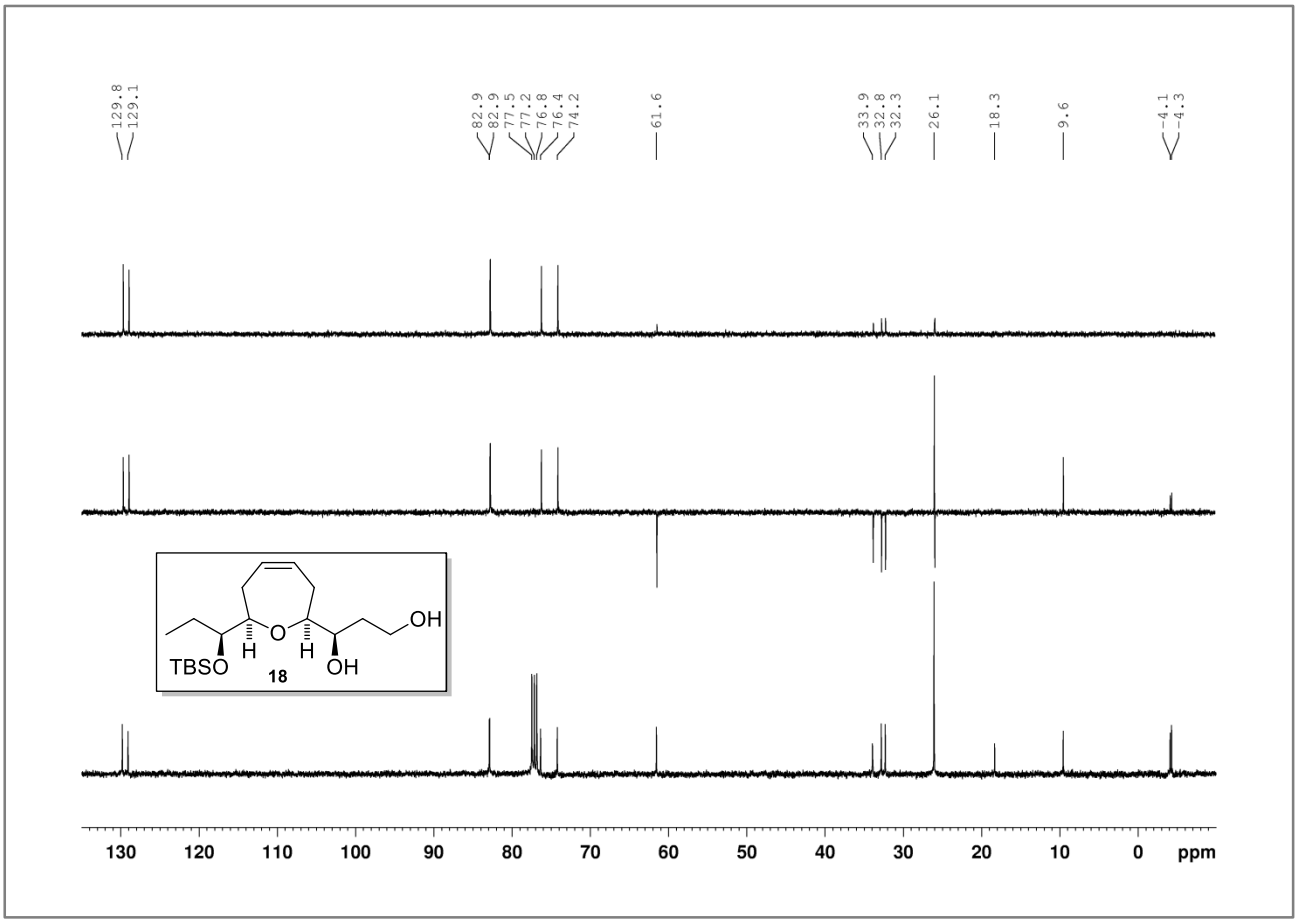
0.0
ppm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76.4
74.2
61.6
33.9
32.8
32.3
26.1
18.3
9.6
-4.1
-4.3
TBSO
H
O
H
OH
OH
18
130
120
110
100
90
80
70
60
50
40
30
20
10
0
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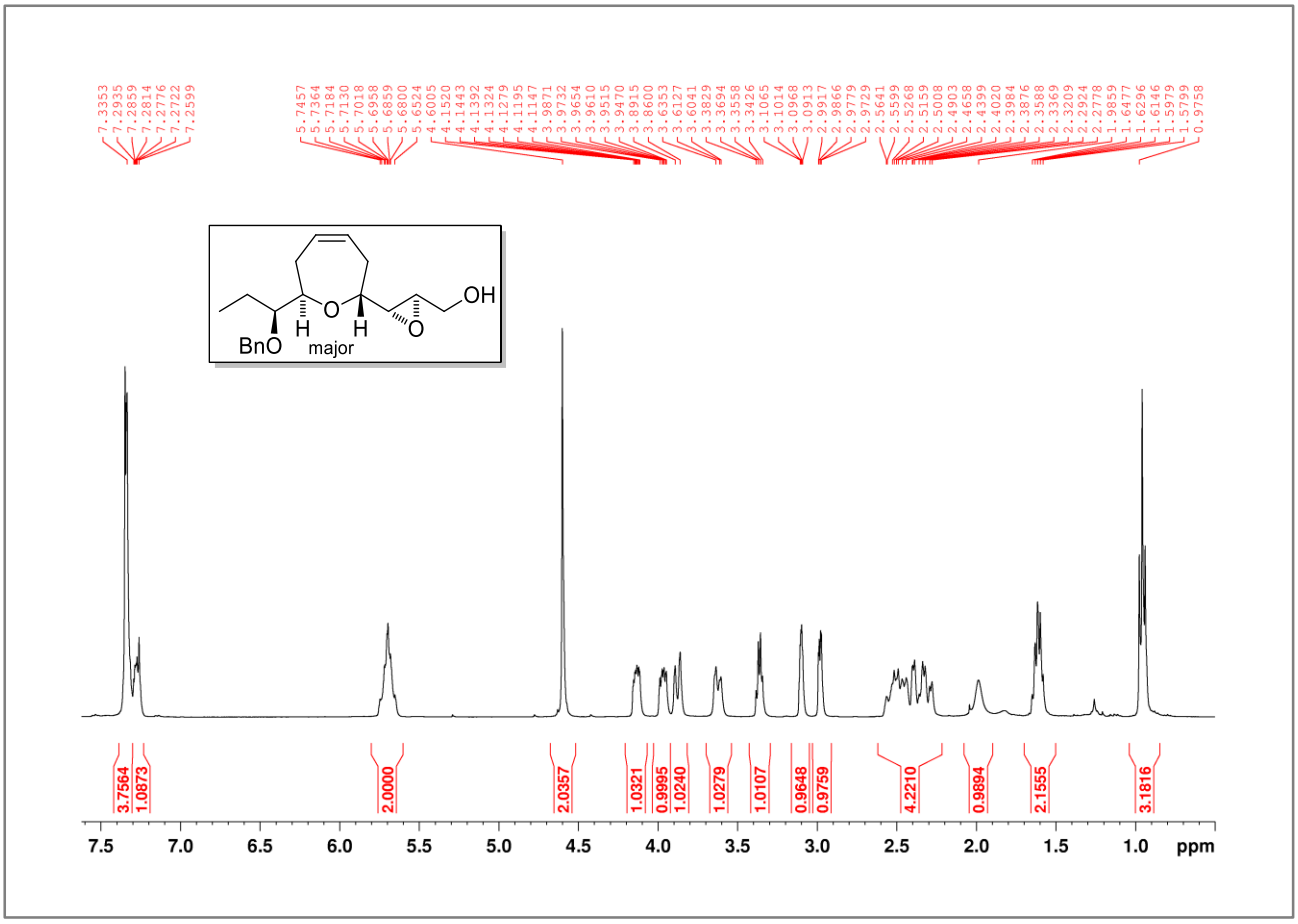
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1.0107
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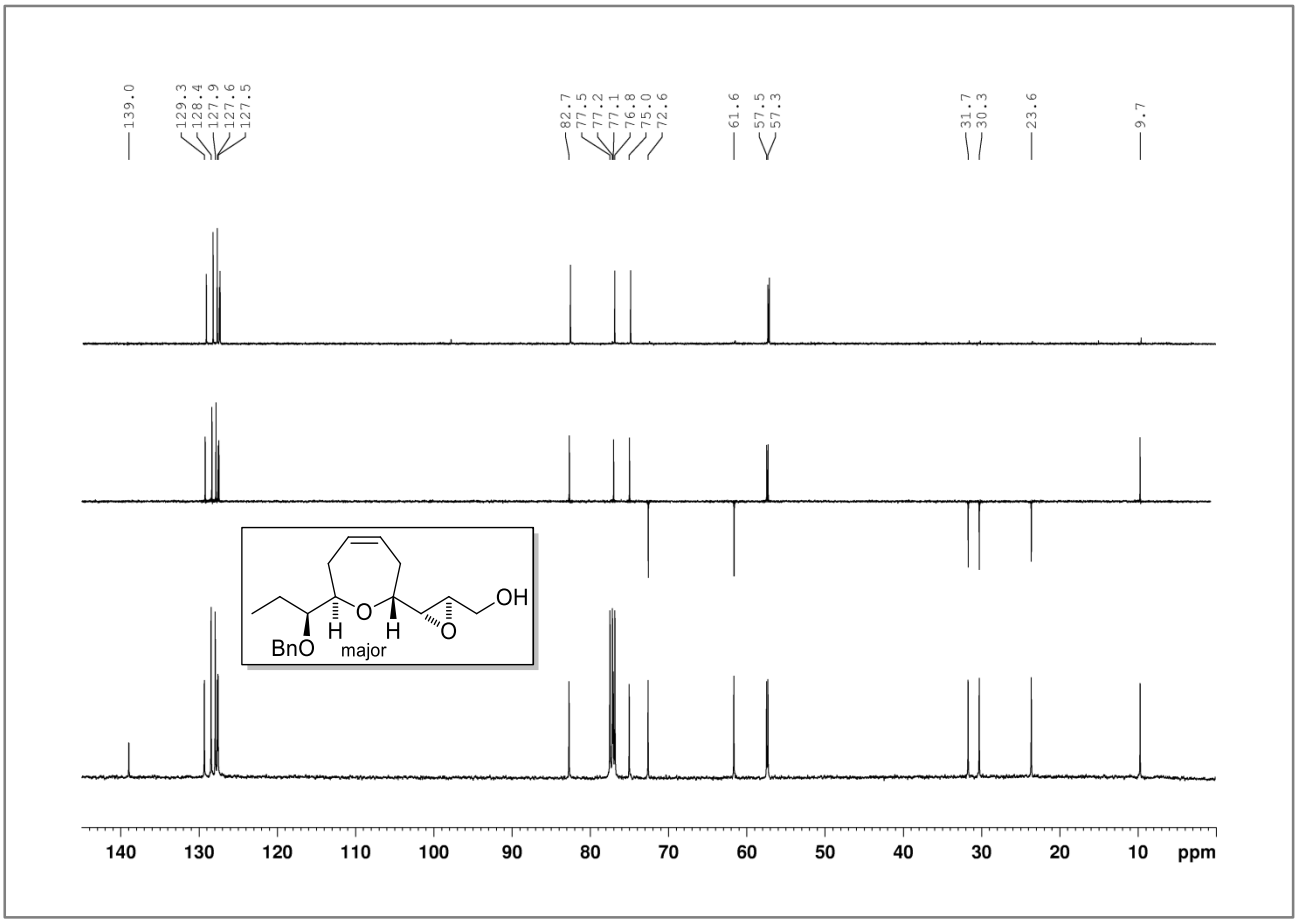
3.1816
ppm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O
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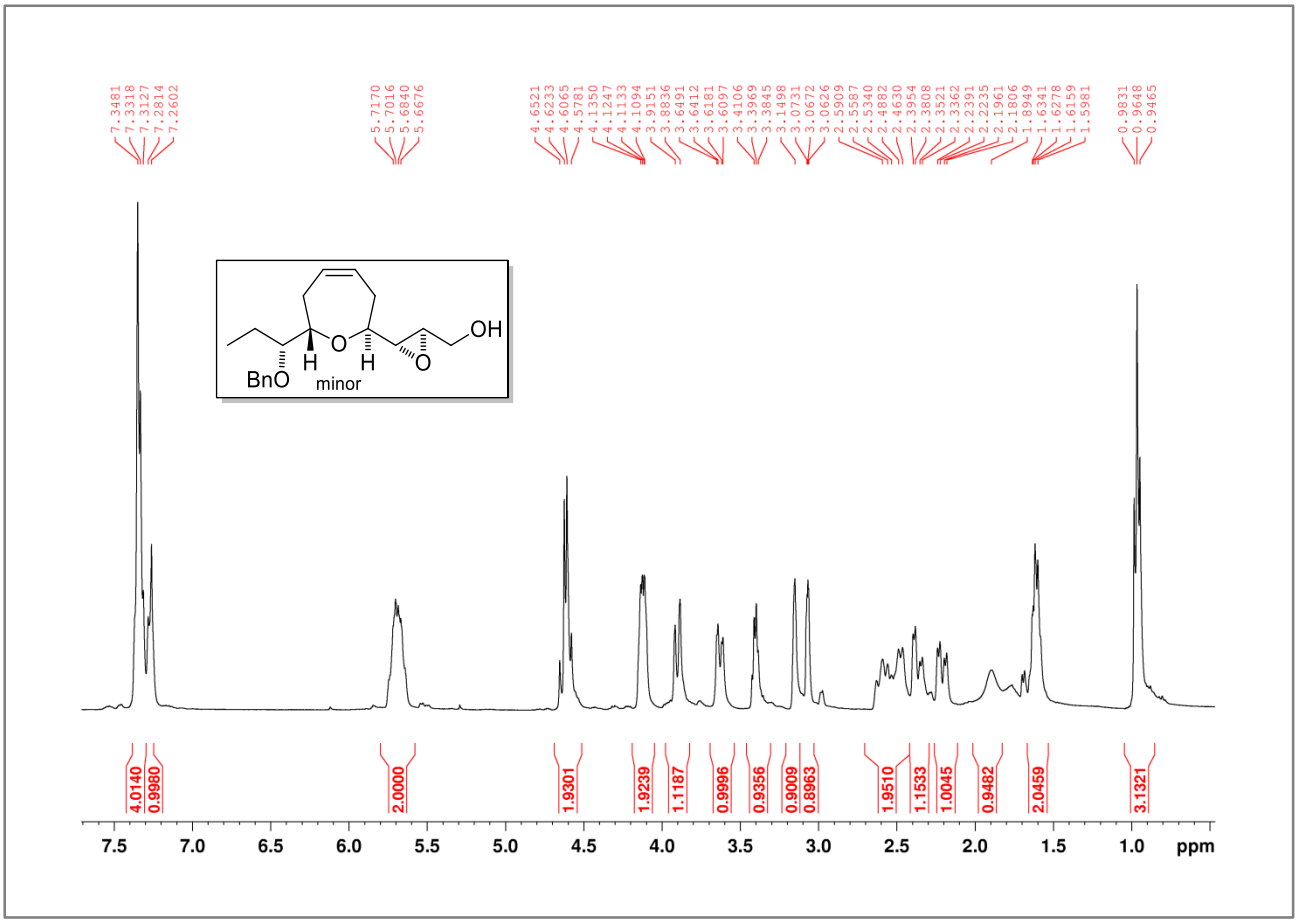
major
ppm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5.6676
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4.6233
4.6065
4.5781
4.1350
4.1247
4.1133
4.1094
3.9151
3.8836
3.6491
3.6412
3.6181
3.6097
3.4106
3.3969
3.3845
3.1498
3.0731
3.0672
3.0626
2.5909
2.5587
2.5340
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2.3954
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2.3362
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2.2235
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1.6159
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H
O
BnO
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0.9482
2.0459
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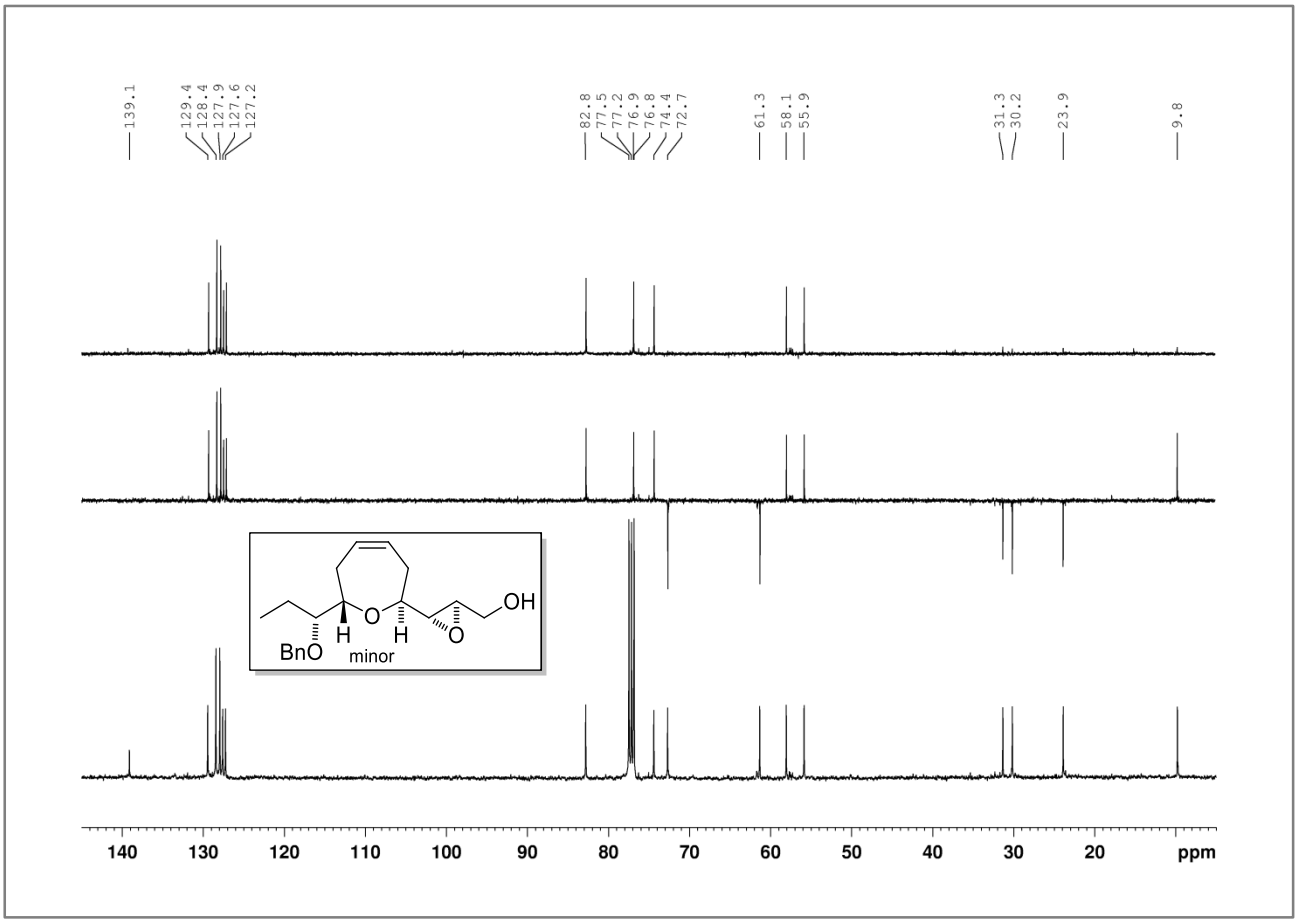
ppm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127.6
127.2
82.8
77.5
77.2
76.9
76.8
74.4
72.7
61.3
58.1
55.9
31.3
30.2
23.9
9.8
OH
O
H
H
O
BnO
minor
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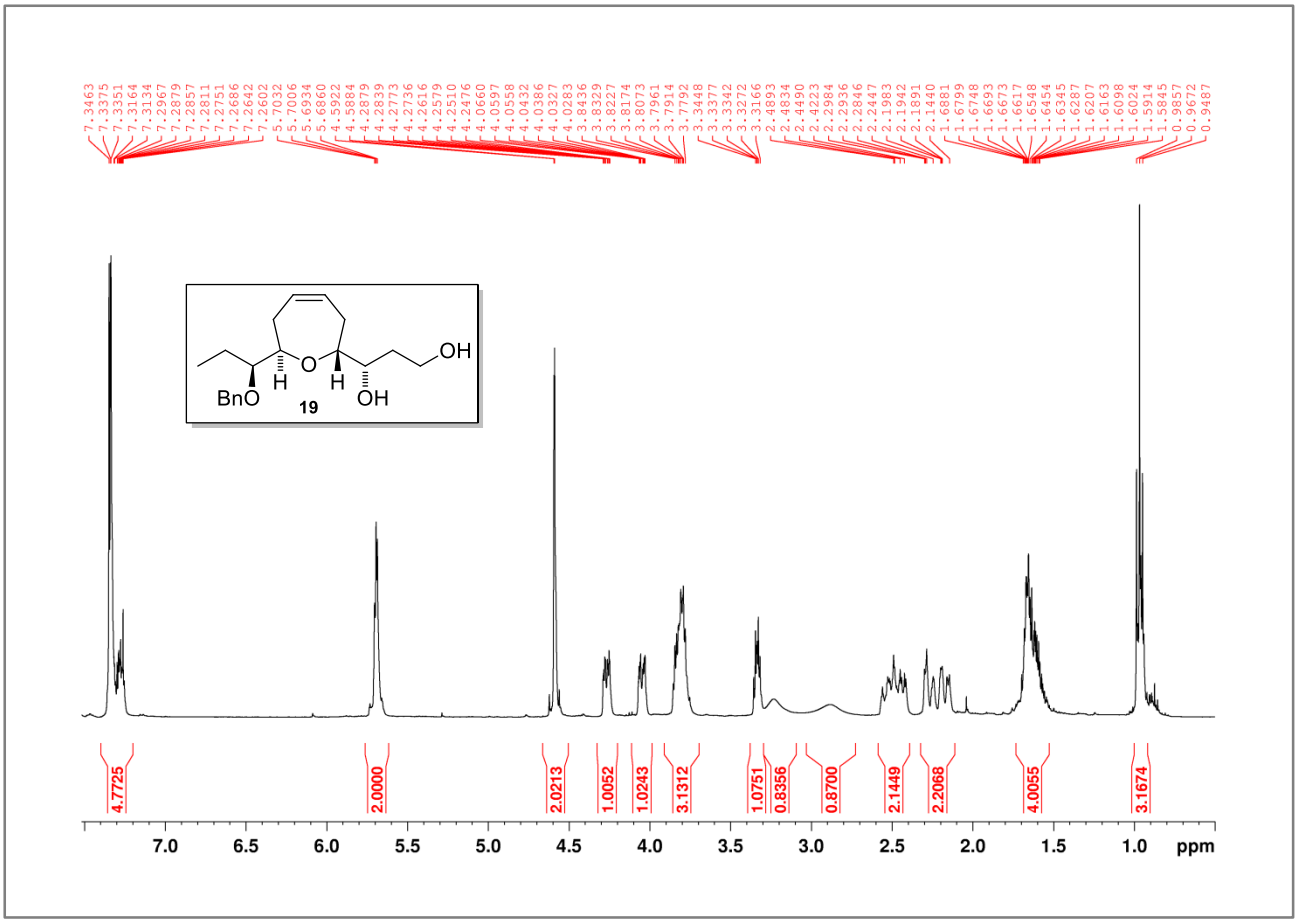
130
120
110
100
90
80
70
60
50
40
30
20
ppm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7.2602
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5.6934
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4.5922
4.5884
4.2879
4.2839
4.2773
4.2736
4.2616
4.2579
4.2510
4.2476
4.0660
4.0597
4.0558
4.0432
4.0386
4.0327
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H
BnO
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1.0052
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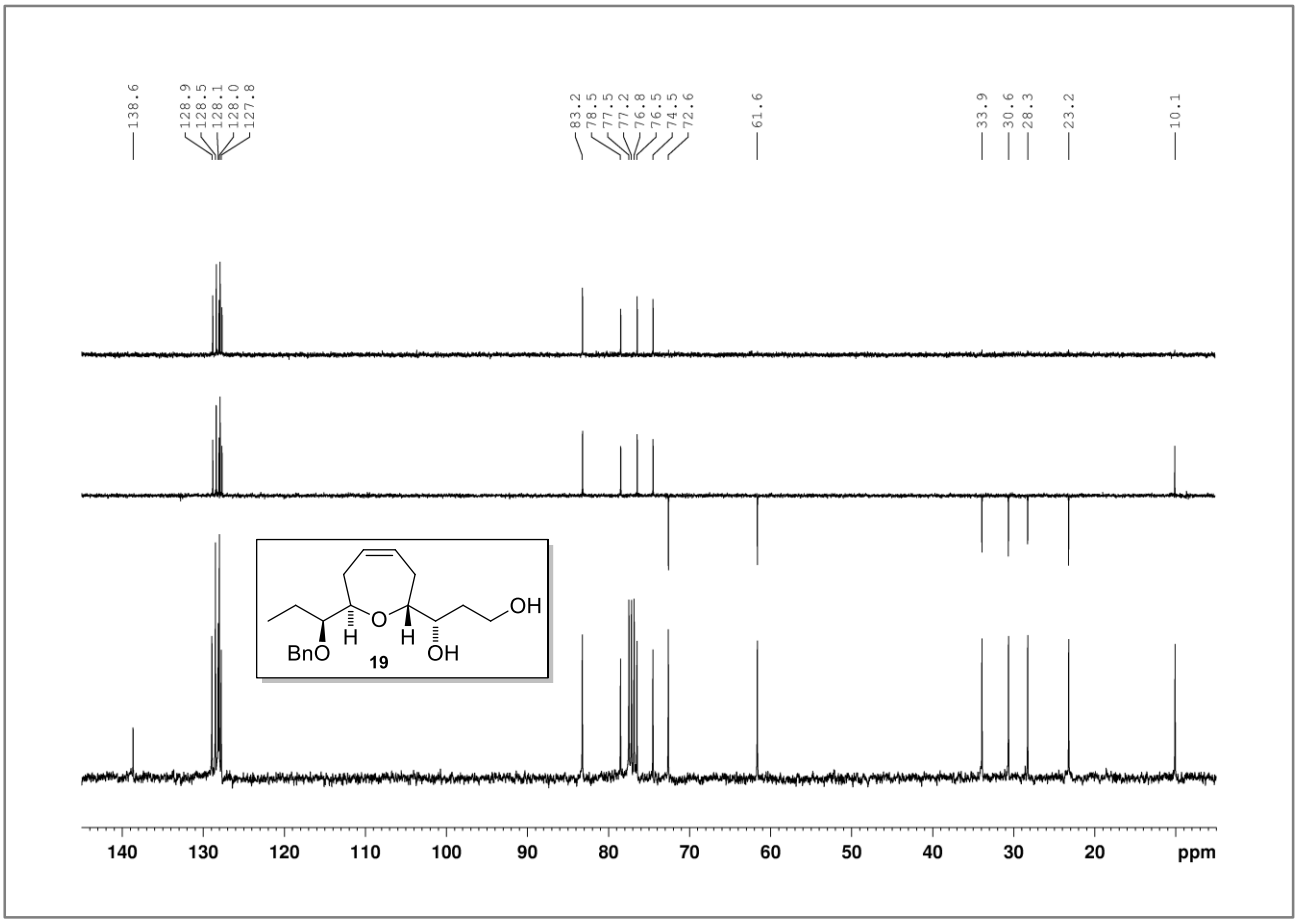
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83.2
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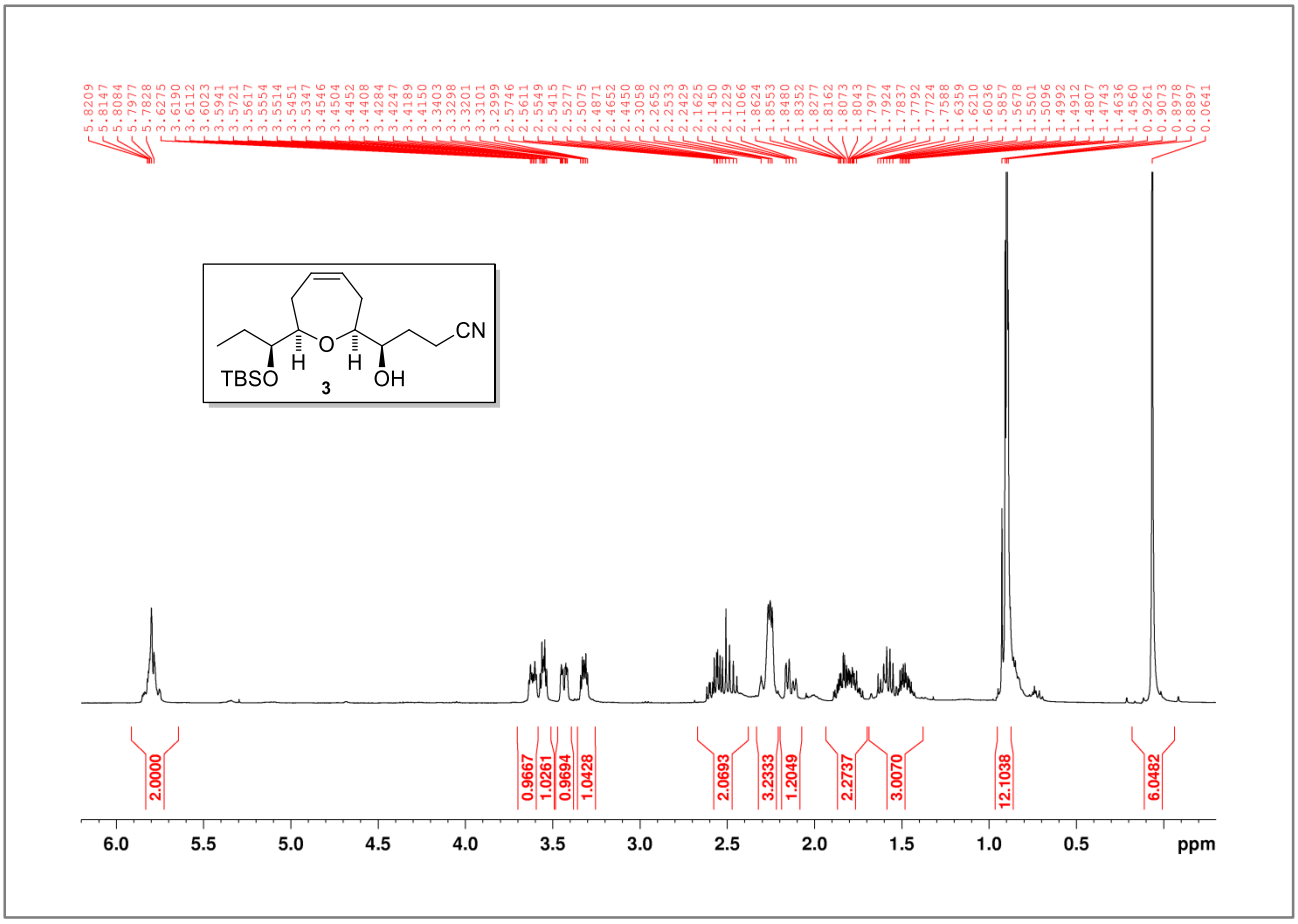
77.5
77.2
76.8
76.5
74.5
72.6
61.6
33.9
30.6
28.3
23.2
10.1
OH
O
H
H
BnO
OH
19
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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H
OH
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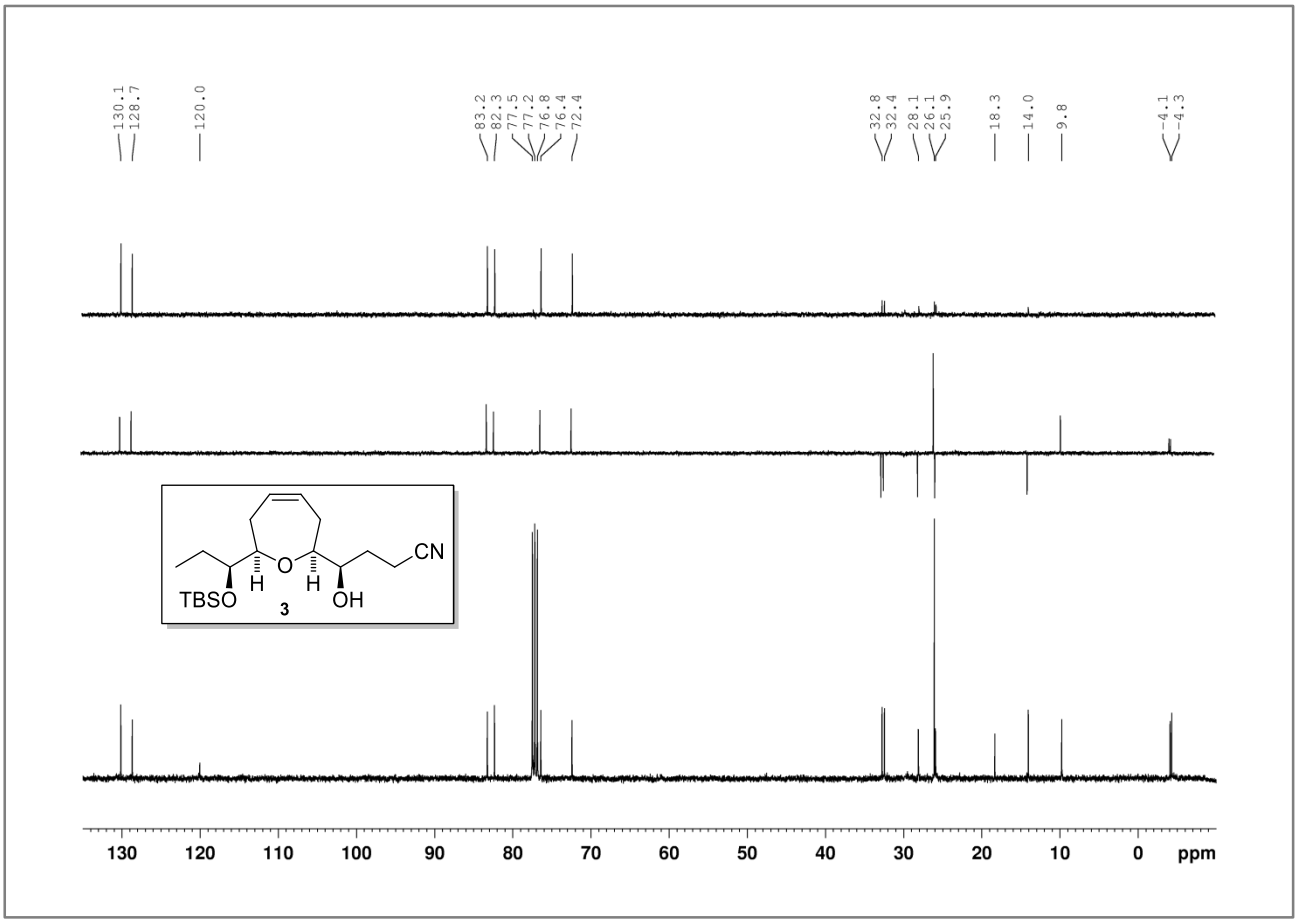
ppm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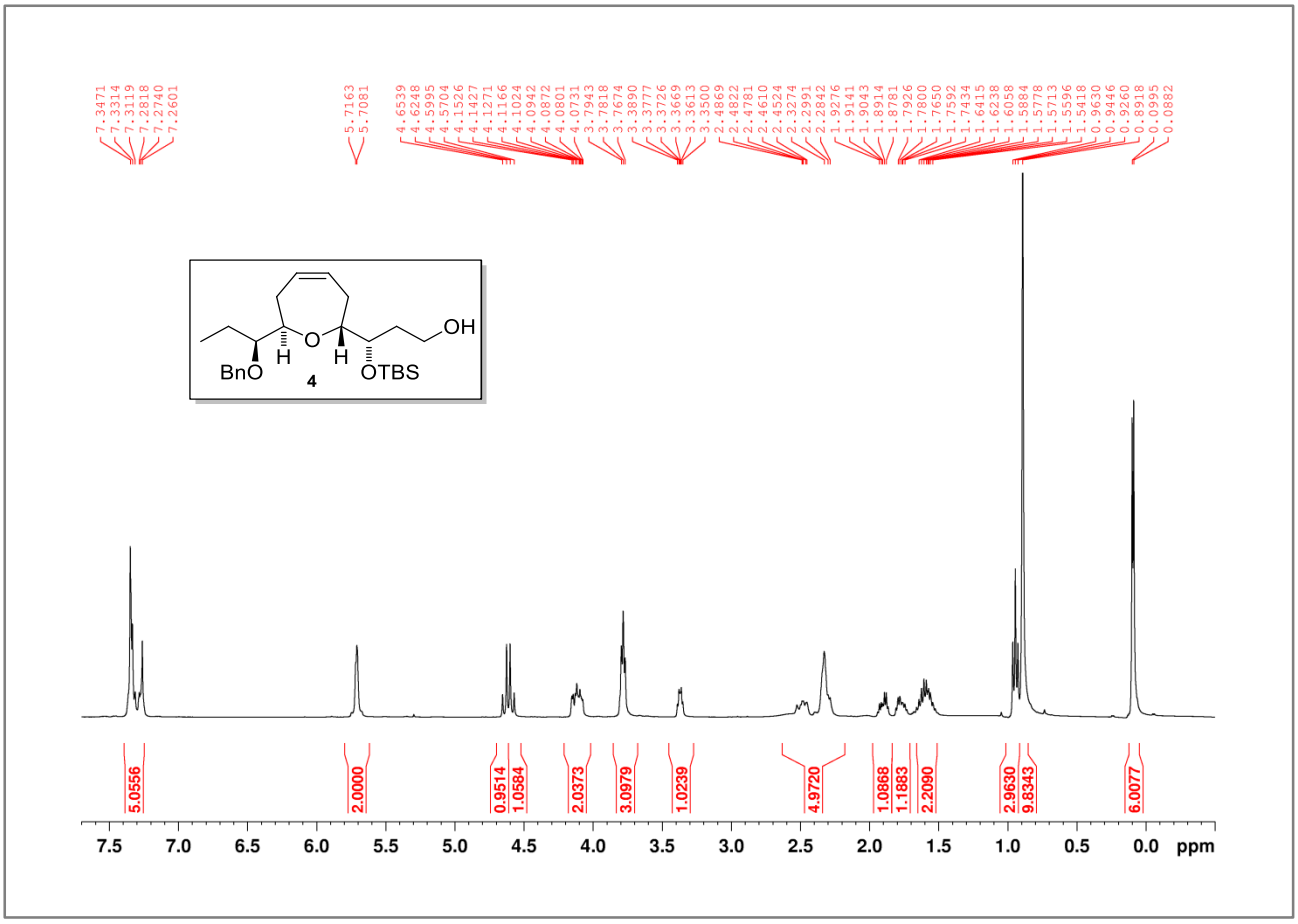
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4.1526
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4.1166
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4.0801
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0.9260
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OH
BnO
H
O
H
OTBS
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1.1883
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2.9630
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6.0
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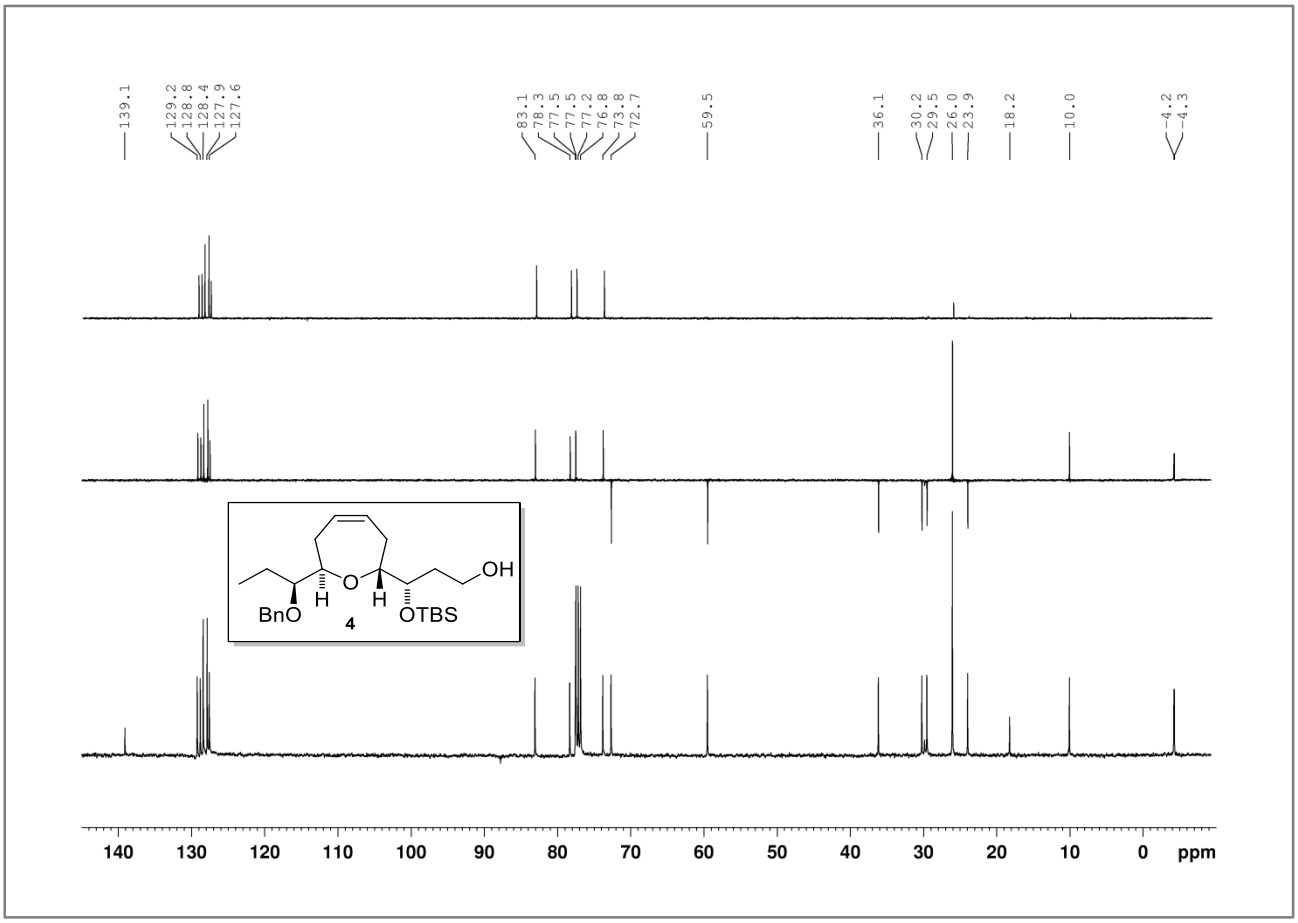
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127.6
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77.5
77.2
76.8
73.8
72.7
59.5
36.1
30.2
29.5
26.0
23.9
18.2
10.0
-4.2
-4.3
OH
BnO
H
O
H
OTBS
4
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm