ELECTRONIC SUPPORTING INFORMATION

Efficient Synthesis of Fully Renewable, Furfural-Derived Building Blocks via Formal Diels-Alder Cycloaddition of Atypical Addends

Răzvan C. Cioc,*[a,#] Eva Harsevoort,[a,#] Martin Lutz,[b] and Pieter C. A. Bruijnincx*[a]

a Dr. R. C. Cioc, E. Harsevoort, Prof. Dr. P. C. A. Bruijnincx
Organic Chemistry and Catalysis, Institute for Sustainable and Circular Chemistry, Faculty of Science, Utrecht University
Universiteitsweg 99, 3584 CG, Utrecht (The Netherlands)
E-mail: r.c.cioc@uu.nl, p.c.a.bruijnincx@uu.nl

b Dr. M. Lutz
Structural Biochemistry, Bijvoet Centre for Biomolecular Research, Faculty of Science, Utrecht University
Universiteitsweg 99, 3584 CG Utrecht (The Netherlands)

General information

Chemicals

Unless stated otherwise, all solvents and commercially available reagents were used as purchased. Molecular sieves were activated thermally prior use (250 °C, several days).

Diethylamine was purchased from Antonides C.V.; KOH from Boom B.V.; 5-(hydroxymethyl)-2-furaldehyde from Apollo Scientific; acetone, HCl (30%), ethanol, methanol, ethyl acetate, acetonitrile, toluene, dichloromethane (DCM), NaCl from VWR Chemicals; Petroleum ether 40-60°C from Biosolve Chimie; DMSO-d_6 from Cambridge Isotope Laboratories; triethylamine (NEt_3), acetyl chloride, $NaHCO_3$, hydroxylamine hydrochloride, sodium borohydride, acetic acid (AcOH), CuBr, N-methylimidazole (NMI), iodine, potassium phosphate monobasic (KH_2PO_4), sodium hypochlorite, sodium thiosulfate pentahydrate, thionyl chloride, mesitylene, allyl bromide, acetic anhydride (Ac_2O), 4-dimethylaminopyridine (DMAP), $MgSO_4$, $NaHCO_3$, silicagel (0.060-0.200 nm) from Acros; allyl alcohol, furfural, 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO), amberlyst 15H, methanesulfonic acid, 2,2-bipyridine (bipy), 1-Hydroxytetraphenylcyclopentadienyl-(tetraphenyl-2,4-cyclopentadien-1-one)-μ-hydrotetracarbonyldiruthenium(II) (Shvo catalyst), sodium chlorite, 5-bromo-2-furaldehyde, trifluoroacetic acid (TFA), Pd/C 10%, 5-methylfurfural, furfuryl alcohol, 5-(ethoxymethyl)furan-2-carboxaldehyde, celite® Hyflo Supercel, $CDCl_3$ from Merck.

Furfuryl allyl ether **2a** was prepared as previously reported in literature (Engel, et al. *Eur. J. Inorg. Chem.* **2015**, 1226–1232). Molecular sieves were activated thermally prior use (250 °C, several days).

Analysis

Nuclear magnetic resonance (NMR) spectra were recorded on an Agilent MRF 400 equipped with a OneNMR probe and Optima Tune system or a Varian VNMR-S-400 equipped with a PFG probe. Resonances were referenced to residual solvent peaks (^{1}H: δ 7.26 ppm, ^{13}C{^{1}H}: δ 77.16 ppm for $CDCl_3$, ^{1}H: δ 2.50 ppm, ^{13}C{^{1}H}: δ 39.52 ppm for DMSO) Chemical shifts (δ) are given in ppm and coupling constants (*J*) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), br (broad singlet) and m (multiplet) or combinations thereof. Electrospray Ionization (ESI) mass spectrometry was carried out using an Agilent technologies 6560 ion mobility Q-TOF instrument; ionization was found to be difficult for some of the products, elemental analysis was performed instead in such cases. Elemental analysis was done by MEDAC Ltd. (United Kingdom).

Experimental procedures and characterization of novel products

Profile of one-pot acetalization/DA reaction
Furfural **1b** (48.1 mg, 0.50 mmol, 1 equiv), allyl alcohol (680 µL, 10 mmol, 20 equiv), 3Å molecular sieves (100 mg, 200 mg/mmol) and mesitylene (internal standard, 23.3 mg, 0.193 mmol, 0.386 equiv) were stirred in a glass vial. TFA (3.8 µL, 0.05 mmol, 10 mol-%) was added and the closed vial was heated to 100 °C in an oil bath. Samples (100 µL) taken from the reaction mixture at the indicated times were dissolved in $CDCl_3$ and filtered to determine the conversion and yield by quantitative NMR.

Notes:
- 20 equiv allyl alcohol were used instead of 10 equiv as employed on preparative scale.
- at longer reaction times, the mass balance is over 100%. This may be due to the escape of a small amount of the internal standard from the system.

General procedure scope evaluation
5-substituted furfural (1 equiv) was dissolved in allyl alcohol (10 equiv) and trifluoroacetic acid (10 mol-%) and 3Å molecular sieves (300 mg/mmol) were added. The mixture was stirred at 100 °C for 24 h and allowed to cool to rt. The mixture was filtered; the solids were washed with toluene and the filtrate was concentrated *in vacuo* and stripped with toluene. Conversion, stereoselectivity and crude yield were determined by quantitative ^{1}H NMR analysis of an aliquot sample using an external standard. The *anti*-adduct was isolated by silicagel flash column chromatography.

Notes:
- quenching trifluoroacetic acid during the workup protocol was not necessary; this was only performed in the reaction with **1d**.
- the *anti*/*syn* diastereoisomers are well resolved but coelution with residual aldehyde was observed in some cases.

Large scale synthesis
Furfural **1b** (11.03 g, 114 mmol, 1 equiv) was diluted with allyl alcohol (78.0 mL, 1.14 mol, 10 equiv). TFA (0.878 mL, 11.4 mmol, 10 mol-%) and 3Å molecular sieves (34 g, 300 g/mol) were added to the light-brown solution and the mixture was heated to 100 °C. After 24 h the mixture was allowed to cool to rt. The brown suspension was filtered, and the residue was washed with toluene (2 x 50 mL). The filtrate was concentrated *in vacuo* and stripped with toluene (50 mL). The resulting crude (30.65 g) contains the starting material **1b** (6.5 mmol, 5.7% recovery), acetal intermediate **2b** (8.7 mmol, 7.6% yield) and the DA adduct **3b** (89 mmol, 78% yield) as determined by quantitative NMR using an external standard. The adduct is formed in a diastereomeric ratio of 95:5. Mass balance: 91%.

To this crude mixture was added water (331 mL) and 4M HCl (58 mL, 2 equiv). The light orange, almost homogeneous mixture was then heated to 50 °C for 17 h. The mixture was cooled on an ice bath and the reaction was quenched with solid KOH (13.8 g, 246 mmol, 2.2 equiv) until pH ~ 7, and concentrated *in vacuo* at 60 °C. The light-brown slurry was partitioned between water (50 mL) and ethyl acetate (100 mL), and NaCl (10 g) was added to improve the layer separation. The aqueous layer was extracted in ethyl acetate (6 x 100 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The product was precipitated from the crude light-yellow liquid (13.54 g) by addition of cold diethyl ether (20 mL). After stirring vigorously on an ice bath for 1 h the suspension was filtered; the solids were washed with cold diethyl ether (10 mL).

4b was obtained as a light-yellow powder (12.37 g, (11.97 g corrected), 77.65 mmol, 87% yield) in 97% purity as determined by quantitative NMR using an external standard. The orange filtrate (0.698 g) contains an additional 2.65 mmol product (2.9% yield). Mass balance: 90%.

Stability and storage

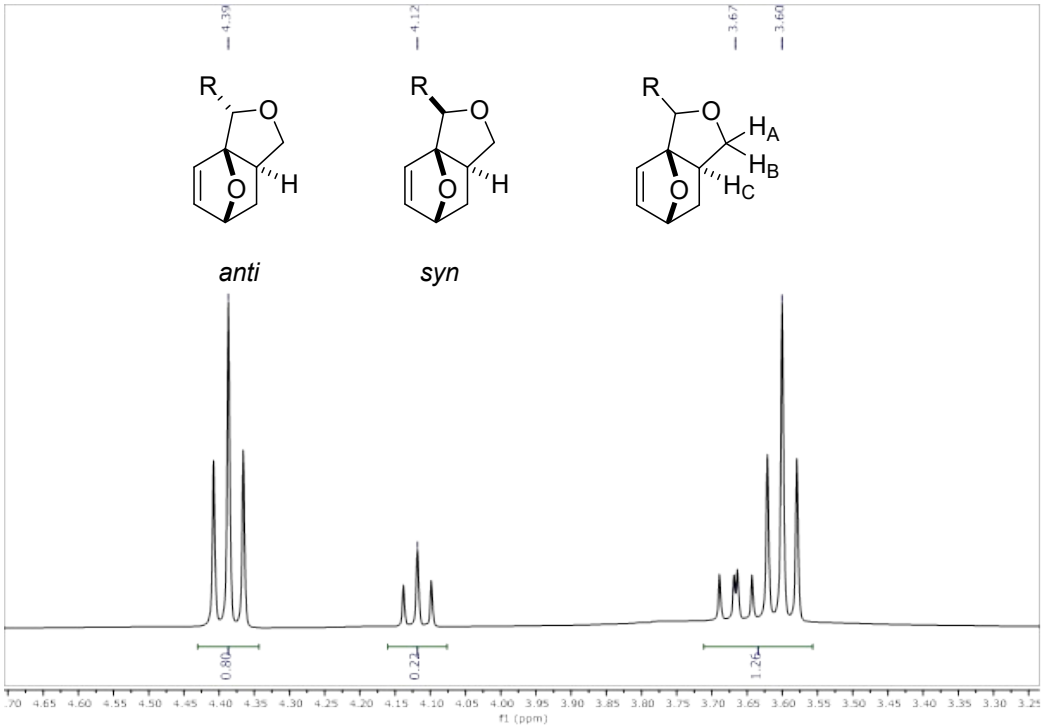
The compounds described herein are generally stable at ambient temperature. Upon storage for prolonged times (several months), a low extent of retro Diels-Alder reaction was observed for some adducts, particularly the oils and especially **3a**. Storage in the freezer (<-20 °C) of these samples is recommended.

Stereochemistry

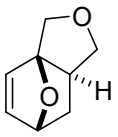
The one pot acetalization/Diels-Alder reaction leads to a pair of *anti*/*syn* diastereoisomers; generally, the *anti*-isomer (R = OAllyl, substituent pointing in the opposite direction with respect to the oxabridge) is formed with >95:5 stereopreference. The deprotected adduct **4b** was obtained as the *anti*-diastereoisomer in solid state, but was found to be in a solvent-dependent *anti*/*syn* equilibrium in solution, with the *anti*-isomer generally being the major isomer. Derivatization of **4b** at the hemiacetal position generally afforded again the *anti*-isomer with high stereoselectivity (*e.g.* in **6**, **7**).

Upon workup and purification, in all these cases, the diastereoisomers were well resolved; isolated yields refer to the pure *anti*-diastereoisomer only (the less polar, first eluting isomer). The minor *syn* diastereoisomer was generally not collected nor thoroughly characterized (except for *syn*-**3f**)**.**

In ^{1}H NMR, the two anti/syn isomers can be distinguished by several elements, for instance the splitting patterns of the -CH_2O- protons H_A and H_B. Thus, in the *anti*-isomer, $^{3}J_{HA,HC} = {}^{3}J_{HB,HC} = {}^{2}J_{HA,HB}$, leading to triplet resonances for both H_A and H_B. In the *syn*-isomer, these signals appear as a triplet and a doublet of doublets respectively, as depicted below:



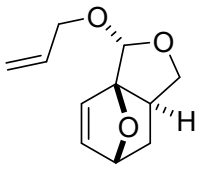
Section of the ^{1}H NMR spectrum of **4b** ($CDCl_3$), highlighting diagnostic signals for the *anti* and *syn* isomers



Diels-Alder adduct 3a

Furfuryl allyl ether **1b** (3.25 g, 23.5 mmol, 1 eq) was stirred at 80 °C under neat conditions for 24 h. The resulting orange liquid was allowed to cool to rt and the adduct was separated from the unreacted starting material **2a** by silicagel flash column chromatography (2 to 10 v/v % ethyl acetate in petroleum ether), affording the recovered starting material (2.16 g, 15.6 mmol, 67% yield) and the product as a light-yellow oil (345 mg, 2.56 mmol, 11% yield).

TLC (ethyl acetate/petroleum ether, 5/95 v/v) R_f = 0.55; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.42 (d, J = 5.8 Hz, 1H), 6.38 (dd, J = 5.8, 1.7 Hz, 1H), 5.09 (dd, J = 4.4, 1.7 Hz, 1H), 4.21 (d, J = 10.8 Hz, 1H), 4.17 (t, J = 7.9 Hz, 1H), 4.06 (d, J = 10.8 Hz, 1H), 3.39 (dd, J = 10.2, 8.1 Hz, 1H), 2.16-2.07 (m, 1H), 1.74 (ddd, J = 11.6, 4.5, 3.0 Hz, 1H), 1.37 (dd, J = 11.6, 7.6 Hz, 1H), ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.0, 134.2, 98.3, 80.8, 73.2, 68.0, 45.3, 29.2, ppm; **IR** (ATR): $\tilde{\nu}$ = 2945 (s), 2871 (s), 1737 (w), 1322 (m), 1107 (m), 1053 (m), 992 (s), 873 (s), 700 (s), 567 (w) cm^{-1}; **ESI-MS**: *m/z* [*M*+Na]$^+$ calculated for $C_8H_{10}NaO_2$: 161.0573, found: 161.0593.

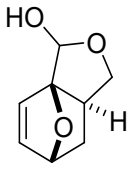


Diels-Alder adduct 3b

Furfural diallyl acetal **2b** (1.392 g, 7.17 mmol) was stirred at 80 °C under neat conditions for 24 h. The resulting yellow liquid was allowed to cool to rt. ^{1}H NMR analysis of the crude reaction mixture indicated a ratio of approx. 1:1:10 between **1b**, unreacted **2b** and adduct **3b**; **3b** was formed as a mixture of two diastereomers in approx. 95:5 ratio (*anti*/*syn)*. The adducts were separated from the unreacted starting materials by silicagel flash column chromatography (5 to 10 v/v % ethyl acetate in petroleum ether), affording the *anti*-isomer as a light-yellow oil (0.921 g, 4.74 mmol, 66% yield).

As benchmark in the substrate scope evaluation, **3b** was also prepared according to the general procedure starting from furfural **1b** (276 mg, 2.87 mmol). Flash column chromatography (5 to 14 v/v % ethyl acetate in petroleum ether) afforded *anti*-**3b** as a light-yellow oil (53% yield).

TLC (ethyl acetate/petroleum ether, 10/90 v/v) R_f = 0.40; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.54 (d, J = 5.8 Hz, 1H), 6.37 (dd, J = 5.8, 1.7 Hz, 1H), 6.02-5.90 (m, 1H), 5.32 (dq, J = 17.2, 1.7 Hz, 1H), 5.23 (s, 1H), 5.20 (dq, J = 10.4, 1.5 Hz, 1H), 5.10 (dd, J = 4.5, 1.7 Hz, 1H), 4.37-4.27 (m, 2H), 4.12 (ddt, J = 13.1, 5.9, 1.5 Hz, 1H), 3.62 (t, J = 8.2 Hz, 1H), 2.32 (qd, J = 8.2, 3.0 Hz, 1H), 1.80 (ddd, J = 11.5, 4.5, 3.0 Hz, 1H), 1.53 (dd, J = 11.6, 7.7 Hz, 1H), ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.4, 134.5, 133.7, 117.1, 100.2, 98.6, 80.3, 73.2, 68.5, 41.3, 32.2, ppm; **IR** (ATR): $\tilde{\nu}$ = 2965 (m), 2890 (m), 1450 (w), 1305 (w), 1245 (w), 1078 (m), 1051 (m), 995 (s), 866 (m), 690 (m) cm^{-1}; **ESI-MS**: *m/z* [*M*-OAllyl]$^+$ calculated for $C_8H_9O_2$: 137.0597, found: 137.0603.



Diels-Alder adduct hemiacetal 4b

4b was prepared as described above (large scale synthesis).

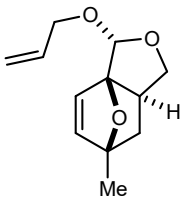
TLC (ethyl acetate/petroleum ether, 50/50 v/v) R_f = 0.30; *anti*/*syn* ratio in **$CDCl_3$**, approx. 80:20.

Anti isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.55 (d, J = 5.8 Hz, 1H), 6.39 (dd, J = 5.8, 1.7 Hz, 1H), 5.56 (s, 1H), 5.12 (dd, J = 4.5, 1.6 Hz, 1H), 4.39 (t, J = 8.4 Hz, 1H), 3.60 (t, J = 8.4 Hz, 1H), 2.37 (qd, J = 8.4, 2.9 Hz, 1H), 1.80 (ddd, J = 11.5, 4.5, 2.9 Hz, 1H), 1.52 (dd, J = 11.6, 7.7 Hz, 1H), ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.5, 133.6, 99.0, 95.6, 80.4, 73.3, 41.0, 31.8, ppm.

Syn-isomer: **^{1}H NMR** (400 MHz, $CDCl_3$), 6.50 (d, J = 5.8 Hz, 1H), 6.43 (dd, J = 5.8, 1.7 Hz, 1H), 5.73 (s, 1H), 5.21 (dd, J = 4.4, 1.7 Hz, 1H), 4.12 (t, J = 7.9 Hz, 1H), 3.67 (dd, J = 10.3, 8.3 Hz, 1H), 2.24 (dtd, J = 10.4, 7.6, 2.9 Hz, 1H), 1.88 (ddd, J = 11.7, 4.5, 2.9 Hz, 1H), 1.40 (dd, J = 11.7, 7.6 Hz, 1H), ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.1, 133.4, 97.4, 95.2, 81.0, 72.0, 44.8, 30.0, ppm.

anti/*syn* ratio in **DMSO-d6**, 97:3. *Anti*-isomer: **^{1}H NMR** (400 MHz, DMSO-d6) δ 6.66 (d, J = 5.5 Hz, 1H), 6.43 (d, J = 5.8 Hz, 1H), 6.40 (dd, J = 5.8, 1.6 Hz, 1H), 5.25 (d, J = 5.4 Hz, 1H), 5.04 (dd, J = 4.5, 1.6 Hz, 1H), 4.17 (t, J = 8.3 Hz, 1H), 3.34 (t, J = 8.3 Hz, 1H), 2.19 (qd, J = 8.4, 2.9 Hz, 1H), 1.65 (ddd, J = 11.5, 4.5, 2.9 Hz, 1H), 1.39 (dd, J = 11.5, 7.6 Hz, 1H), ppm; **^{13}C NMR** (101 MHz, DMSO-d6) δ 136.5, 133.5, 98.8, 94.6, 79.5, 71.9, 40.6, 31.3, ppm.

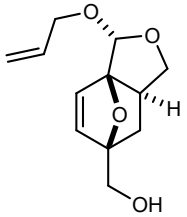
IR (ATR): $\tilde{\nu}$ = 3399 (br), 3017 (w), 2904 (m), 2943 (m), 1303 (w), 1104 (m), 1050 (m), 977 (s), 944 (s), 863 (s), 695 (m), 547 (w) cm^{-1}; **Elemental analysis** calcd for $C_8H_{10}O_3$: C 62.33, H 6.54, found: C 61.78, H 6.58.



Diels-Alder adduct 3c

Prepared from 5-methylfurfural **1c** (489 mg, 4.44 mmol) according to the general procedure. Flash column chromatography (2 to 35 v/v % ethyl acetate in petroleum ether) afforded a mixture of the *anti*-**3c** contaminated with furfural **1c** (454 mg, 85 wt-% adduct) as a yellow oil. A second purification by flash column chromatography (20 v/v % petroleum ether in dichloromethane to 20 v/v % ethyl acetate in dichloromethane) allowed the isolation of the pure *anti*-**3c** as a yellow oil (41% yield).

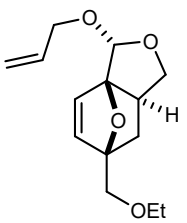
TLC (ethyl acetate/petroleum ether, 5/95 v/v) R_f = 0.40, (dichloromethane/petroleum ether, 80/20 v/v) R_f = 0.40; **^{1}H NMR** (400 MHz, DMSO-d6) δ 6.45 (d, J = 5.6 Hz, 1H), 6.30 (d, J = 5.7 Hz, 1H), 5.93 (dddd, J = 17.2, 10.5, 5.6, 4.9 Hz, 1H), 5.29 (dq, J = 17.3, 1.8 Hz, 1H), 5.16 (ddt, J = 10.5, 2.1, 1.5 Hz, 1H), 5.08 (s, 1H), 4.25-4.14 (m, 2H), 4.06 (ddt, J = 13.5, 5.6, 1.6 Hz, 1H), 3.49 (t, J = 8.2 Hz, 1H), 2.27 (qd, J = 8.5, 3.0 Hz, 1H), 1.57 (dd, J = 11.4, 7.5 Hz, 1H), 1.55 (s, 3H), 1.44 (dd, J = 11.5, 3.0 Hz, 1H), ppm; **^{13}C NMR** (101 MHz, DMSO-d6) δ 140.0, 134.8, 133.3, 116.4, 99.3, 97.5, 88.0, 72.5, 67.4, 44.1, 37.9, 18.7, ppm; **IR** (ATR): $\tilde{\nu}$ = 3675 (w), 2972 (s), 2891 (s), 1402 (w), 1329 (w), 1074 (s), 995 (s), 808 (m), 706 (m) cm^{-1}; **ESI-MS**: *m/z* $[M+Na]^+$ calculated for $C_{12}H_{16}NaO_3$: 231.0992, found: 231.0998.



Diels-Alder adduct 3d

Prepared from 5-hydroxymethylfurfural **1d** (340 mg, 2.70 mmol) according to the general procedure. Flash column chromatography (30 to 40 v/v % ethyl acetate in petroleum ether) afforded *anti*-**3d** as a yellow oil that solidifies at rt; **1d** and the product were found to coelute, the product is contaminated with approx. 10 wt-% of **1d** (31% yield, corrected).

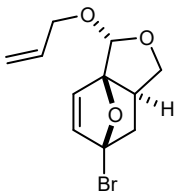
TLC (ethyl acetate/petroleum ether, 40/60 v/v) R_f = 0.30; **^{1}H NMR** (400 MHz, DMSO-d6) δ 6.46 (d, J = 5.7 Hz, 1H), 6.40 (d, J = 5.8 Hz, 1H), 5.93 (dddd, J = 17.2, 10.5, 5.5, 4.9 Hz, 1H), 5.29 (dq, J = 17.3, 1.8 Hz, 1H), 5.17 (dq, J = 10.5, 1.6 Hz, 1H), 5.10 (s, 1H), 4.95 (t, J = 5.9 Hz, 1H), 4.26-4.14 (m, 2H), 4.07 (ddt, J = 13.5, 5.5, 1.6 Hz, 1H), 3.86-3.73 (m, 2H), 3.47 (t, J = 8.3 Hz, 1H), 2.26 (qd, J = 8.4, 2.9 Hz, 1H), 1.60 (dd, J = 11.5, 2.9 Hz, 1H), 1.43 (dd, J = 11.4, 7.6 Hz, 1H), ppm; **^{13}C NMR** (101 MHz, DMSO-d6) δ 137.8, 134.8, 133.3, 116.4, 99.3, 97.7, 92.6, 72.4, 67.4, 61.0, 43.2, 33.0, ppm; **IR** (ATR): $\tilde{\nu}$ = 3426 (br), 2965 (m), 2919 (m), 1364 (m), 1282 (w), 1061 (m), 984 (w), 725 (w), 551 (w) cm^{-1}; **ESI-MS**: *m/z* $[M-OH]^+$ calculated for $C_{12}H_{15}O_3$: 207.1017, found: 207.1016.



Diels-Alder adduct 3e

Prepared from 5-ethoxymethylfurfural **1e** (363 mg, 2.35 mmol) according to the general procedure. Flash column chromatography (2 to 10 v/v % ethyl acetate in petroleum ether) afforded *anti*-**3e** as a light-yellow oil; **1e** and the product were found to coelute, the product is contaminated with approx. 8 wt-% of **1e** (60% yield, corrected).

TLC (ethyl acetate/petroleum ether, 5/95 v/v) R_f = 0.25; **^{1}H NMR** (400 MHz, DMSO-d6) δ 6.47 (d, J = 5.7 Hz, 1H), 6.38 (d, J = 5.8 Hz, 1H), 6.00-5.87 (m, 1H), 5.29 (dq, J = 17.3, 1.8 Hz, 1H), 5.17 (ddt, J = 10.5, 2.1, 1.5 Hz, 1H), 5.10 (s, 1H), 4.24-4.15 (m, 2H), 4.07 (ddt, J = 13.5, 5.6, 1.6 Hz, 1H), 3.84 (d, J = 11.5 Hz, 1H), 3.77 (d, J = 11.5, 1H), 3.50 (q, J = 7.0 Hz, 2H), 3.46 (t, J = 8.2 Hz, 1H), 2.25 (qd, J = 8.4, 2.9 Hz, 1H), 1.60 (dd, J = 11.5, 2.9 Hz, 1H), 1.46 (dd, J = 11.4, 7.6 Hz, 1H), 1.11 (t, J = 7.0 Hz, 3H), ppm; **^{13}C NMR** (101 MHz, DMSO-d6) δ 137.6, 134.8, 133.3, 116.5, 99.3, 97.9, 91.2, 72.4, 69.4, 67.5, 66.2, 42.9, 33.3, 15.1, ppm; **IR** (ATR): $\tilde{\nu}$ = 2974 (m), 2888 (m), 1683 (m), 1521 (w), 1334 (w), 1088 (m), 995 (s), 915 (m), 709 (w) cm^{-1}; **ESI-MS**: *m/z* [*M*+Na]$^+$ calculated for $C_{14}H_{20}NaO_4$: 275.1254, found: 275.1270.



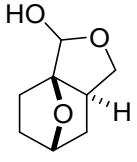
Diels-Alder adduct 3f

Prepared from 5-bromofurfural **1f** (308 mg, 1.76 mmol) according to the general procedure. Flash column chromatography (2 to 25 v/v % ethyl acetate in petroleum ether) afforded respectively *anti*-**3f** (56% yield) and *syn*-**3f** (12% yield), both as colorless oils; *anti*-**3f** was found to crystallize into a white solid in the freezer.

Anti-isomer: **TLC** (ethyl acetate/petroleum ether, 2/98 v/v) R_f = 0.25; (ethyl acetate/petroleum ether, 10/90 v/v) R_f = 0.80, **^{1}H NMR** (400 MHz, DMSO-d6) δ 6.62-6.55 (m, 2H), 6.01-5.86 (m, 1H), 5.30 (dq, J = 17.3, 1.8, 1H), 5.21-5.13 (m, 2H), 4.27-4.16 (m, 2H), 4.14-4.04 (m, 1H), 3.63 (t, J = 8.2 Hz, 1H), 2.39 (qd, J = 8.1, 3.1 Hz, 1H), 2.19 (dd, J = 11.6, 7.4 Hz, 1H), 2.09 (dd, J = 11.7, 3.1 Hz, 1H), ppm; **^{13}C NMR** (101 MHz, DMSO-d6) δ 140.3, 134.6, 134.2, 116.7, 98.6, 96.3, 90.1, 72.0, 67.7, 44.3, 43.1, ppm;

Syn-isomer: **TLC** (ethyl acetate/petroleum ether, 10/90 v/v) R_f = 0.25; **^{1}H NMR** (400 MHz, DMSO-d6) δ 6.72 (d, J = 5.5 Hz, 1H), 6.53 (d, J = 5.5 Hz, 1H), 5.97-5.83 (m, 1H), 5.53 (s, 1H), 5.25 (dq, J = 17.3, 1.8 Hz, 1H), 5.16 (dq, J = 10.4, 1.5 Hz, 1H), 4.18 (ddt, J = 13.0, 5.3, 1.6 Hz, 1H), 4.10-3.98 (m, 2H), 3.57 (dd, J = 10.3, 8.2 Hz, 1H), 2.33 (dtd, J = 10.6, 7.4, 3.3 Hz, 1H), 2.05 (dd, J = 11.7, 3.3 Hz, 1H), 1.99 (dd, J = 11.6, 7.3 Hz, 1H), ppm; **^{13}C NMR** (101 MHz, DMSO-d6) δ 140.1, 135.7, 134.8, 117.3, 99.5, 94.9, 91.3, 71.8, 69.6, 48.6, 40.5, ppm;

IR (ATR): $\tilde{\nu}$ = 3098 (w), 2993 (w), 2894 (m), 1557 (w), 1299 (m), 1126 (m), 1058 (m), 985 (s), 920 (s), 712 (m), 563 (w) cm^{-1}. **ESI-MS**: *m/z* [*M*+Na]$^+$ calculated for $C_{11}H_{13}BrNaO_3$: 294.9942, found: 294.9940.



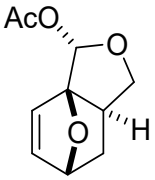
Hydrogenated hemiacetal 5

Under inert atmosphere, Pd/C (10 wt-%) (293 mg, 0.27 mmol Pd, 0.7 mol-%) was added to ethyl acetate (77 mL) while stirring. Adduct **4b** (6.15 g, 39.9 mmol, 1 equiv) was added and a hydrogen balloon was attached, which was refreshed after 6 h. After stirring at rt for a total of 22 h, the mixture was filtered over celite, and the filter was washed with ethyl acetate (2 x 10 mL). The filtrate was concentrated *in vacuo*, affording a light yellow, viscous oil (6.23 g, 39.9 mmol, 100% yield). In solution ($CDCl_3$) the product is a mixture of diastereomers (*dr anti/syn*) 2:1.

Anti-isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.56 (s, 1H), 4.69 (t, J = 4.7 Hz, 1H), 4.31 (t, J = 8.6 Hz, 1H), 3.51 (t, J = 8.0 Hz, 1H), 2.60 (qd, J = 8.2, 3.8 Hz, 1H), 1.94-1.45 (m, 6H), ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 98.0, 96.5, 78.3, 74.4, 44.9, 38.7, 29.4, 27.4, ppm.

Syn-isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.41 (d, J = 11.1 Hz, 1H), 4.78 (t, J = 4.7 Hz, 1H), 3.95 (t, J = 8.2 Hz, 1H), 3.60 (br, 1H), 3.58 (dd, J = 9.9, 8.3 Hz, 1H), 2.49 (dtd, J = 9.8, 7.8, 4.1 Hz, 1H), 1.94-1.45 (m, 6H), ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 97.0, 94.2, 79.3, 71.8, 48.0, 36.5, 30.2, 28.4, ppm;

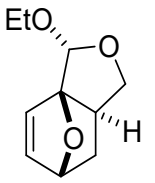
IR (ATR): $\tilde{\nu}$ = 3349 (s), 2989 (m), 2958 (s), 2892 (m), 1447 (w), 1287 (m), 1208 (m), 1049 (m), 982 (s), 961 (s), 897 (m), 849 (m), 538 (w) cm^{-1}; **ESI-MS**: *m/z* $[2M+Na-H2O]^+$ calculated for $C_{16}H_{22}NaO_5$: 317.1359, found: 317.1362.



Acetylated adduct 6

Hemiacetal **4b** (175 mg, 1.13 mmol, 1 equiv) was dissolved in dichloromethane (4.5 mL). The light-yellow solution was cooled on an ice bath and triethylamine (221 µL, 1.59 mmol, 1.4 equiv) and acetyl chloride (113 µL, 1.59 mmol, 1.4 equiv) were added. The mixture was allowed to warm to room temperature and two additional portions of both triethylamine and acetyl chloride (both 0.2 equiv) were added after 1.5 h and 3 h respectively. After 2 additional hours of stirring, 1M HCl (5 mL) was added. The organic layer was washed subsequently with 1M HCl (5 mL), sat $NaHCO_3$ (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford a light-orange oil. The crude contains two diastereomers (*dr anti*/*syn* 94:6), based on ^{1}H NMR spectroscopy. Purification by silicagel flash column chromatography (2 to 20 v/v % ethyl acetate in petroleum ether) affords the *anti*-adduct as a light-yellow oil (181 mg, 0.92 mmol, 82% yield).

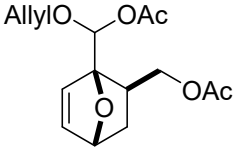
Anti-isomer **TLC** (ethyl acetate/petroleum ether, 30/70 v/v) R_f = 0.80; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.38-6.31 (m, 2H), 6.28 (s, 1H), 5.06 (d, J = 4.5, 1H), 4.30 (t, J = 8.5 Hz, 1H), 3.56 (t, J = 8.5 Hz, 1H), 2.26 (qd, J = 8.5, 2.7 Hz, 1H), 2.05 (s, 3H), 1.75 (ddd, J = 11.6, 4.5, 2.9 Hz, 1H), 1.47 (dd, J = 11.7, 7.6 Hz, 1H), ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.5, 136.7, 132.4, 98.0, 94.4, 80.5, 74.2, 40.9, 31.5, 21.0, ppm; **IR** (ATR): $\tilde{\nu}$ = 2971 (w), 2898 (w), 1741 (s), 1371 (m), 1233 (s), 1214 (s), 1093 (w), 1004 (s), 957 (s), 865 (m), 688 (w), 540 (w) cm^{-1}; **ESI-MS**: *m/z* $[M+Na]^+$ calculated for $C_{10}H_{12}NaO_4$: 219.0628, found: 219.0639.



Acetal adduct 7

Hemiacetal **4b** (350 mg, 2.27 mmol, 1 equiv) was dissolved in ethanol (5 mL). Amberlyst 15(H) (104 mg, 4.7 mmol/g, 20 mol-%) was added and the mixture was heated to 30 °C. After 20 h TLC analysis showed full conversion and the Amberlyst was filtered off. The filtrate was dried over Na_2SO_4 and concentrated *in vacuo*. The orange crude oil (436 mg) was purified by silicagel flash column chromatography (20 to 50 v/v % ethyl acetate in petroleum ether), affording the product as a light-yellow oil (370 mg, 2.03 mmol, 89% yield) as a single (*anti*) diastereoisomer.

TLC (ethyl acetate/petroleum ether, 50/50 v/v) R_f = 0.90; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.51 (d, J = 5.8 Hz, 1H), 6.36 (dd, J = 5.8, 1.7 Hz, 1H), 5.18 (s, 1H), 5.10 (dd, J = 4.5, 1.7 Hz, 1H), 4.30 (t, J = 8.5 Hz, 1H), 3.86 (dq, J = 9.7, 7.1 Hz, 1H), 3.66-3.54 (m, 2H), 2.29 (qd, J = 8.4, 3.0 Hz, 1H), 1.79 (ddd, J = 11.5, 4.5, 3.0 Hz, 1H), 1.52 (dd, J = 11.5, 7.7 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H), ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.3, 133.8, 100.8, 98.6, 80.3, 73.0, 63.6, 41.4, 32.1, 15.4, ppm; **IR** (ATR): $\tilde{\nu}$ = 2975 (m), 2889 (m), 1382 (w), 1305 (w), 1102 (m), 1077 (m), 995 (s), 866 (m), 689 (w) cm^{-1}; **ESI-MS**: *m/z* $[M-OEt]^+$ calculated for $C_8H_9O_2$: 137.0597, found: 137.0596.



Ring-opened product 8

Methane sulfonic acid (3.4 µL, 0.052 mmol, 0.1 equiv) was added to acetic anhydride (2 mL) and stirred for 10 min. This mixture was added to

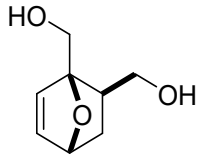
the adduct **3b** (102 mg, 0.52 mmol, 1 equiv) and heated to 50 °C for 2 h. The mixture was purified by silicagel flash column chromatography (2 to 30 v/v % ethyl acetate in petroleum ether) affording the product as a white solid (133 mg, 0.448 mmol, 86% yield) as a mixture of two diastereomers (*dr* 2:1).

TLC (ethyl acetate/petroleum ether, 15/85 v/v) R_f = 0.30;

Major isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.40-6.28 (m, 2H), 6.27 (s, 1H), 6.00-5.78 (m, 1H), 5.28 (dq, J = 17.2, 1.7 Hz, 1H) 5.15 (dq, J = 10.5, 1.4 Hz, 1H), 4.92 (dd, J = 4.3, 1.5 Hz, 1H), 4.30-4.07 (m, 4H), 2.10-2.00 (m, 1H), 2.06 (s, 3H), 2.02 (s, 3H), 1.63-1.47 (m, 2H), ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.0, 170.7, 136.4, 134.3, 133.5, 117.5, 94.1, 89.6, 78.4, 70.8, 65.5, 38.4, 32.2, 21.2, 21.0, ppm.

Minor isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.39-6.27 (m, 2H), 6.22 (s, 1H), 5.95-5.81 (m, 1H), 5.27 (dq, J = 17.2, 1.6 Hz, 1H), 5.15 (dq, J = 8.4, 1.4 Hz, 1H), 4.95 (dd, J = 4.5, 1.6 Hz, 1H), 4.29-4.12 (m, 3H), 3.99 (dd, J = 11.1, 7.5 Hz, 1H), 2.11 (s, 3H, minor), 2.10-2.00 (m, 1H), 1.98 (s, 3H), 1.62-1.46 (m, 2H), ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.0, 170.6, 137.0, 134.6, 133.6, 118.0, 94.1, 89.7, 78.4, 71.6, 65.9, 38.1, 32.3, 21.2, 21.0, ppm.

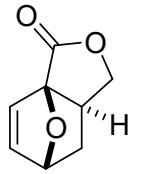
IR (ATR): $\tilde{\nu}$ = 2952 (w), 1737 (s), 1367 (m), 1223 (s), 1010 (m), 943 (m), 713 (w) cm^{-1}; **ESI-MS**: *m/z* $[M+Na]^+$ calculated for $C_{15}H_{20}NaO_6$: 319.1152, found: 319.1164.



Diol 9

A solution of hemiacetal **4b** (161 mg, 1.04 mmol, 1 equiv) in methanol (5 mL) was cooled on an ice bath. Sodium borohydride (64 mg, 1.63 mmol, 1.6 equiv) was added during 10 min. After stirring for 5 min, the solution was allowed to warm to rt. The reaction was quenched with AcOH (387 µL, 6.5 eq) after 2 h and the resulting solution was evaporated to dryness. The resulting oil solidifies at room temperature; this crude product was suspended in ethyl acetate (10 mL) and filtered. Saturated sodium bicarbonate (4 mL) was added the layers were separated. NaCl was added to the aqueous layer until saturation and the product was extracted in ethyl acetate (6 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*, affording the product as a clear oil which solidifies into a white solid upon storage in the freezer (134 mg, 0.86 mmol, 83% yield).

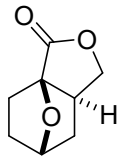
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39-6.31 (m, 2H), 4.89 (dd, J = 4.6, 1.4 Hz, 1H), 4.12 (d, J = 11.8 Hz, 1H), 4.07 (d, J = 11.8 Hz, 1H), 3.78 (dd, J = 10.8, 3.8 Hz, 1H), 3.68 (t, J = 10.3 Hz, 1H), 3.00 (br, 1H), 2.48 (br, 1H), 1.95 (ddt, J = 9.8, 8.0, 3.9 Hz, 1H), 1.59 (dd, J = 11.5, 8.2 Hz, 1H), 1.32 (dt, J = 11.5, 4.3 Hz, 1H), ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.54, 136.46, 89.9, 77.8, 64.1 61.3, 40.7, 31.0, ppm; **IR** (ATR): $\tilde{\nu}$ = 3368 (br), 3000 (w), 2936 (m), 2874 (m), 1449 (w), 1324 (w), 1034 (s), 975 (m), 877 (w), 751 (m), 714 (m) cm^{-1}; **Elemental analysis** calcd for $C_8H_{12}O_3$: C 61.52, H 7.74, found: C 61.29, H 7.79.



Unsaturated lactone 10

Hemiacetal **4b** (154 mg, 1 mmol, 1 equiv) and CuBr (7.2 mg, 0.05 mmol, 0.05 equiv) were dissolved in acetonitrile (2 mL). TEMPO (8 mg, 0.05 mmol, 0.05 equiv), 2,2'-bipyridine (8 mg, 0.05 mmol, 0.05 equiv) and *N*-methyl imidazole (8 µL, 0.1 mmol, 0.1 equiv) were then added, leading to an orange solution. The mixture was stirred at ambient temperature under an air balloon for 2 days; the color turned turquoise. The solution was concentrated and the crude product was purified by silicagel flash column chromatography (20 to 33 v/v % ethyl acetate in petroleum ether) affording pure **10** as a white solid (106 mg, 0.7 mmol, 70% yield).

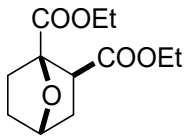
TLC (ethyl acetate/petroleum ether, 33/66 v/v) R_f = 0.36; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.55 (d, J = 5.8 Hz, 1H), 6.51 (dd, J = 5.8, 1.2 Hz, 1H), 5.27 (dd, J = 4.3, 1.2 Hz, 1H), 4.63 (t, J = 8.7 Hz, 1H), 4.14 (t, J = 8.7 Hz, 1H), 2.56 (qd, J = 7.5, 2.5 Hz, 1H), 2.00 (ddd, J = 11.5, 4.0, 2.6 Hz, 1H), 1.58 (dd, J = 11.5, 7.5 Hz, 1H), ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.4, 138.2, 132.0, 88.9, 82.6, 74.4, 42.7, 31.4, ppm; **IR** (ATR): $\tilde{\nu}$ = 3090 (w), 2997 (w), 1765 (s), 1475 (w), 1377 (s), 1250 (m), 1101(m), 973 (m), 722 (m), 641 (w) cm^{-1}; **Elemental analysis** calcd for $C_8H_8O_3$: C 63.15, H 5.30, found: C 63.18, H 5.29.



Saturated lactone 11

Under inert atmosphere, hemiacetal **4b** (5.72 g, 36.6 mmol, 1 equiv) was dissolved in degassed acetone (52 mL). The solution was degassed for another 30 min before Shvo's catalyst (22 mg, 0.02 mmol, 0.05 mol-%) was added. The yellow solution was stirred at 50 °C for 4 days. The solution was concentrated *in vacuo* and the crude (5.9 g) was purified by silicagel flash column chromatography (20 to 30 v/v % ethyl acetate in petroleum ether, staining with I_2) affording the product as an off-white solid (5.34 g). The product was then triturated with diethyl ether (18 mL) and the solids were washed with cold diethyl ether (2 x 5 mL). The solids were dried *in vacuo,* yielding pure **11** as a white solid (4.15 g, 26.9 mmol, 74% yield).

TLC (ethyl acetate/petroleum ether, 20/80 v/v) R_f = 0.20; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.88 (td, J = 4.6, 1.2 Hz, 1H), 4.44 (t, J = 8.7 Hz, 1H), 3.94 (t, J = 9.0 Hz, 1H), 2.83-2.72 (m, 1H), 2.12 (ddd, J = 11.4, 10.8, 4.1 Hz, 1H), 2.12-1.90 (m, 1H), 1.90-1.80 (m, 2H), 1.83-1.68 (m, 1H), 1.63 (dt, J = 7.0, 4.8 Hz, 1H), ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.5, 86.2, 81.3, 73.1, 45.8, 37.9, 29.6, 28.5, ppm; **IR** (ATR): $\tilde{\nu}$ = 3016 (w), 2963 (w), 2885 (w), 1766 (s), 1470 (w), 1376 (w), 1206 (m), 1088 (m), 966 (m), 722 (m), 565 (w) cm^{-1}; **Elemental analysis** calcd for $C_8H_{10}O_3$: C 62.33, H 6.54, found: C 62.32, H 6.56.



Bis ethyl ester 12

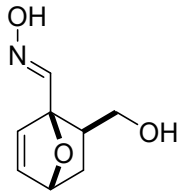
To a suspension of lactone **11** (100 mg, 0.65 mmol, 1 equiv) in ethanol (1.3 mL) was added 4M HCl (40 µL, 0.16 mmol, 25 mol-%). The mixture was stirred at rt, forming a clear solution after 5 min. After stirring for 21 h, $NaHCO_3$ (20 mg) was added, and the mixture was concentrated *in vacuo*. Dichloromethane (4 mL) was added to the resulting white solids with vigorous stirring. The mixture was filtered, and the residue was washed with dichloromethane (2 x 4 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* yielding a colorless oil (126 mg) as the crude hydroxy ethyl ester that was directly used in the next step.

This intermediate was dissolved in acetonitrile (6.5 mL) on an ice bath. To this solution were subsequently added: TEMPO (13.5 mg, 0.086 mmol, 13 mol-%), a solution of KH_2PO_4 (70 mg, 0.51 mmol) in water (5 mL) with pH ~ 6, 80 wt-% sodium chlorite (125 mg, 1.34 mmol, 2.1 equiv) and sodium hypochlorite 10-15 % active chlorine (53 µL, 0.065 mmol, 10 mol-%). The now dark-red solution was allowed to warm to rt and stirred for 20 h, during which it turned light-yellow. Additional TEMPO (7.7 mg), sodium chlorite (72 mg) and sodium hypochlorite (25 µL) were then added and the mixture was stirred for an additional 28 h before complete conversion was reached. Saturated thiosulfate solution (4 mL) was added, and solid NaCl was added until saturation. The product was extracted in ethyl acetate (4 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*, yielding a white solid (156 mg) as the *crude bis carboxylic acid mono ethyl ester* that was used directly in the next step.

This crude intermediate was suspended in ethanol (4.2 mL) and cooled on an ice bath. Thionyl chloride (52 µL, 0.71 mmol, 1.1 equiv) was added and the mixture was allowed to warm to rt

and stirred for 2 h. TLC analysis showed incomplete conversion and another 1.1 equiv of thionyl chloride was then added. After stirring for an additional 19 h, sat $NaHCO_3$ (5 mL) was added and the product was extracted in ethyl acetate (4 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield a crude yellow oil (124 mg) which was purified by silicagel flash column chromatography (5 to 40 v/v % ethyl acetate in petroleum ether) affording the product as a light-yellow oil (91 mg, 0.38 mmol, over three steps: 58% yield).

TLC (ethyl acetate/petroleum ether, 30/70 v/v) R_f = 0.50; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.72 (t, J = 4.9 Hz, 1H), 4.34-4.20 (m, 2H), 4.19-4.01 (m, 2H), 3.03 (dd, J = 9.4, 5.4 Hz, 1H), 2.15-2.06 (m, 1H), 1.99 (dd, J = 12.2, 9.3 Hz, 1H), 1.95-1.86 (m, 3H), 1.64-1.54 (m, 1H, overlaps with water signal), 1.32 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.4, 170.6, 86.5, 76.7, 61.4, 61.0, 50.3, 36.5, 34.6, 30.0, 14.3, 14.2, ppm; **IR** (ATR): $\tilde{\nu}$ = 2983 (m), 1732 (s), 1447 (w), 1371 (m), 1325 (m), 1236 (m), 1186 (m), 1101 (m), 1049 (m), 963 (m), 754 (w) cm^{-1}; **ESI-MS**: *m/z* $[M+H]^+$ calculated for $C_{12}H_{19}O_5$: 243.1227, found: 243.1227.

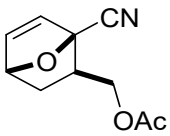


Oxime 13

Hemiacetal **4b** (149 mg, 0.966 mmol, 1 equiv) was dissolved in water (2 mL) and sodium bicarbonate was added (82 mg, 0.976 mmol, 1.01 equiv). To this light-yellow solution hydroxylamine hydrochloride (69 mg, 0.99 mmol, 1.02 equiv) was added in portions. After stirring at room temperature for 17 h the mixture was diluted with water (5 mL) and NaCl was added till saturated. The product was extracted in ethyl acetate (6 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* affording the pure product as a white solid (161 mg, 0.95 mmol, 98% yield). In solution, **13** is a mixture of *syn* and *anti*-isomers (*dr* 91:9) of which only the major isomer is spectroscopically characterized.

TLC (ethyl acetate/petroleum ether, 70/30 v/v) R_f = 0.30; **^{1}H NMR** (400 MHz, DMSO-d6) δ 11.02 (s, 1H), 7.60 (s, 1H), 6.41 (d, J = 5.8 Hz, 1H), 6.37 (ddd, J = 5.7, 1.6, 0.9 Hz, 1H), 4.88 (dd, J = 4.5, 1.7 Hz, 1H), 4.64 (dd, J = 5.6, 4.4 Hz, 1H), 3.46 (ddd, J = 10.7, 8.1, 5.6 Hz, 1H), 3.36 (ddd, J = 10.8, 6.4, 4.5 Hz, 1H), 1.79 (tdd, J = 7.9, 6.3, 3.8 Hz, 1H), 1.45 (dd, J = 11.4, 7.8 Hz, 1H), 1.33 (dt, J = 11.4, 4.2 Hz, 1H), ppm; **^{13}C NMR** (101 MHz, DMSO-d6) δ 146.6, 135.9, 135.1, 87.0, 77.4, 62.6, 44.1, 39.5, 31.1, ppm; **IR** (ATR): $\tilde{\nu}$ = 3185 (br), 3110 (br), 2932 (s), 2816 (m), 1505 (w), 1329 (w), 1223 (w), 1036 (s), 949 (s), 784 (m), 715 (m) cm^{-1}; **Elemental analysis** calcd for $C_8H_{11}O_3N$: C 56.80, H 6.55, N 8.28 found: C 56.96, H 6.64, N 8.00.

Nitrile 14

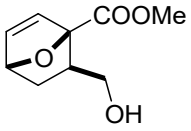


Oxime **13** (338 mg, 2 mmol, 1 equiv) was dissolved in dichloromethane (10 mL). Ac_2O (0.95 mL, 10 mmol, 5 equiv), NEt_3 (0.7 mL, 5 mmol, 2.5 equiv) and DMAP (24 mg, 0.2 mmol, 10 mol-%) were then added and the clear solution was stirred at ambient temperature for 6 days. The volatiles were removed and the product was purified by column chromatography on silicagel (petroleum ether/ethyl acetate 3:1, R_f = 0.18). Product was obtained as a green-yellow oil (123 mg, 0.64 mmol, 32%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (dd, J = 5.8, 2.0 Hz, 1H), 6.34 (d, J = 5.8 Hz, 1H), 5.03 (dd, J = 4.5, 2.0 Hz, 1H), 4.26 (dd, J = 11.5, 8.8 Hz, 1H), 4.15 (dd, J = 11.5, 6.0 Hz, 1H), 2.31-2.22 (m, 1H), 2.09 (s, 3H), 1.61 (dd, J = 11.5, 8.0 Hz, 1H), 1.52 (dt, J = 11.5, 5.0 Hz, 1H), ppm; **^{13}C**

NMR (101 MHz, $CDCl_3$) δ 170.9, 137.7, 133.6, 116.1, 78.9, 77.2, 64.9, 41.3, 29.6, 20.9, ppm; **IR** (ATR): $\tilde{\nu}$ = 3087 (w), 2890 (w), 2252 (w), 1727 (s), 1460 (m), 1244 (s), 1226 (s), 1036 (s), 938 (m), 720 (m), 532 (w) cm^{-1}; **ESI-MS**: A suitable MS spectrum could not be obtained for this compound due to poor ionization/instability.

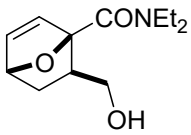
Ester 15



Lactone **10** (600 mg, 3.9 mmol) was dissolved in methanol (6 mL) and AmberlystH (130 mg) was added. The mixture was stirred at ambient temperature for 3 hours; complete conversion was noted in the crude ^{1}H-NMR sample. The solid catalyst was filtered off and the filter was rinsed with methanol. The filtrate was concentrated *in vacuo* leaving the product as an oil of sufficient purity. Product crystallized slowly as an off-white solid (688 mg, 3.74 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (d, J = 5.5 Hz, 1H), 6.38 (dd, J = 5.5, 1.5 Hz, 1H), 4.99 (dd, J = 4.5, 1.5 Hz, 1H), 3.83 (s, 3H), 3.69 (dd, J = 11.0, 5.0 Hz, 1H), 3.62 (t, J = 11.0 Hz, 1H), 2.21-2.07 (m, 2H), 1.57 (dt, J = 11, 4.5 Hz, 1H), 1.51 (dd, J = 11.0, 8.0 Hz, 1H), ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.4, 136.9, 134.8, 88.6, 78.5, 63.6, 52.6, 43.9, 29.6, ppm; **IR** (ATR): $\tilde{\nu}$ = 3490 (s), 2941 (m), 1745 (s), 1442 (m), 1334 (m), 1244 (s), 1088 (m), 1045 (m), 933 (m), 738 (m), 574 (w) cm^{-1}; **ESI-MS**: *m/z* [*M*+Na]$^+$ calculated for $C_9H_{12}NaO_4$: 207.0628, found: 207.0610.

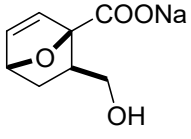
Amide 16



Lactone **10** (76 mg, 0.5 mmol, 1 equiv) was suspended in diethylamine (258 µL, 2.5 mmol, 5 equiv). The mixture was sealed and stirred at ambient temperature overnight. As the reaction progressed, the mixture became a yellow solution. The volatiles were then removed *in vacuo* leaving the product is sufficiently high purity according to ^{1}H NMR. Product was obtained as an orange oil (112 mg, 0.5 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (d, J = 5.5, 1H), 6.31 (dd, J = 5.5, 1.5 Hz, 1H), 4.93 (dd, J = 4.5, 1.5 Hz, 1H), 4.53 (br, 1H), 3.72-3.56 (m, 3H), 3.52-3.28 (m, 3H), 2.21 (sept, J = 4.0 Hz, 1H), 1.58 (dd, J = 11.5, 8.5 Hz, 1H), 1.30 (dt, J = 11.5, 4.5 Hz, 1H), 1.16 (t, J = 7.0 Hz, 3H), 1.10 (t, J = 7.0 Hz, 3H), ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.7, 136.9, 135.3, 91.8, 78.1, 65.0, 44.1, 42.2, 41.8, 31.4, 14.7, 12.7, ppm; **IR** (ATR): $\tilde{\nu}$ = 3600-3100 (br), 2973 (m), 1603 (s), 1436 (m), 1269 (w), 1052 (m), 957 (m), 690 (w) cm^{-1}; **ESI-MS**: *m/z* [*M*+Na]$^+$ calculated for $C_{12}H_{19}NNaO_3$: 248.1257, found: 248.1256.

Carboxylate salt 17



To lactone **10** (76 mg, 0.5 mmol, 1 equiv) was added 1 mL of a 0.5 M methanolic solution of NaOH (prepared by diluting 52 mg, 0.65 mmol of 50 wt-% NaOH in 1.3 mL of methanol) and the resulting solution was stirred overnight. The volatiles were then removed *in vacuo* and the residue was co-evaporated with acetonitrile to remove traces of water. ^{1}H NMR analysis indicated the product was of sufficiently high purity. Product was obtained as a white foam (100 mg, 0.5 mmol, quant.).

^{1}H NMR (400 MHz, D_2O) δ 6.48 (d, J = 6.0, 1H), 6.45 (d, J = 6.0 Hz, 1H), 5.03 (d, J = 4.5 Hz, 1H), 3.78 (dd, J = 10.5, 4.5 Hz, 1H), 3.39 (t, J = 10.5, Hz, 1H), 2.10 (sept, J = 4.5 Hz, 1H), 1.69 (dt, J = 12.0, 4.5 Hz, 1H), 1.61 (dd, J = 12.0, 8.0 Hz, 1H), ppm; **^{13}C NMR** (101 MHz, D_2O) δ 176.2, 136.5, 136.0, 90.7, 78.2, 63.5, 41.7, 30.0, ppm; **IR** (ATR): $\tilde{\nu}$ = 3600-3300 (br), 2945

(w), 1590 (s), 1422 (s), 1177 (w), 1053 (w), 959 (m), 787 (m), 686 (w) cm^{-1}; **ESI-MS**: *m/z* $[M+H]^+$ calculated for $C_8H_{10}NaO_4$: 193.0471, found: 193.0473.

Computational details

Density functional theory (DFT) calculations were performed using the B3LYP functional with all electron 6-311+G(d) basis set on all atoms as implemented in Gaussian 16 C.01 program.[1] Grimme's D3 correction scheme with Becke-Johnson damping was used in all calculations.[2] Nature of the stationary points was confirmed by the vibrational analysis carried out at the same level of theory. All structures corresponding to local minima showed no imaginary frequencies while transition state (TS) structures were characterized by a single imaginary frequency corresponding to the expected reaction coordinate. Bulk solvent effects were accounted for using the SMD solvation model[3] with standard parameters for methanol. Reaction Gibbs free energies (ΔG_{298K}) and activation Gibbs free energies ($\Delta G^{\ddagger}$) were computed using the results of the normal-mode analysis within the ideal gas approximation at a pressure of 1 atm and temperature of 298.15 K. Since the reaction delivers the *anti*-adduct with a strong stereopreference (95:5) the mechanism was only calculated for the pathway towards this stereoisomer; indeed, *syn*-**3b** was found to be approx. 3 kcal/mol higher in energy.

Table S1. Computed energies

Structure	ImFreqs	G (a.u.)	ΔG_{298} (kcal/mol)
DA reaction with furfuryl allyl ether **2a**			
2a (GS)	0	-461.281409	0.0
2a (RC)	0	-461.279347	1.3
TS-**2a**---**3a**	1	-461.237869	27.3
3a	0	-461.277853	2.2
DA reaction with furfuryl diallyl acetal **2b**			
2b (GS)	0	-653.208799	0.0
2b (RC)	0	-653.207087	1.1
TS-**2b**---**3b**	1	-653.167469	25.9
anti-**3b**	0	-653.210191	-0.9
syn-**3b**	0	-653.207050	2.0
Intermolecular reaction **1b** and allyl alcohol (**AA**)			
1b	0	-343.417904	0.0
AA	0	-193.131509	0.0
1b---**AA**	0	-536.540148	5.8
TS-**1b**---**AA**	1	-536.495197	34.0
Inter adduct	0	-536.531877	11.0

GS = ground state; RC = reactive conformation

Ground state furfuryl allyl ether **2a**

O	-1.64381	0.06420	-1.08229
C	-1.20638	-0.57202	0.05881
C	-1.88230	-0.08452	1.13441
C	-2.79432	0.90864	0.63965
C	-2.60568	0.96109	-0.70413
H	-1.74331	-0.39304	2.16031
H	-3.49240	1.50205	1.21169
H	-3.04548	1.54090	-1.50018
C	-0.12846	-1.58063	-0.10219
H	-0.01340	-2.12613	0.84077
H	-0.38025	-2.29461	-0.88897
O	1.12974	-1.01741	-0.49980
C	3.11189	0.16307	0.07466
H	3.77457	-0.68446	-0.09307

C	3.56161	1.40630	-0.08075
H	4.59047	1.60855	-0.36350
H	2.91888	2.26891	0.07758
C	1.71914	-0.17167	0.50012
H	1.73007	-0.71386	1.45620
H	1.12038	0.73574	0.63248

Reactive conformation furfuryl allyl ether **2a**

C	-2.09948	0.61150	0.61807
C	-1.41359	-0.78190	-0.98861
C	-0.59605	-0.91976	0.09287
O	-1.02180	-0.07745	1.09446
H	-3.19047	0.58347	-1.27030
C	-2.38553	0.21497	-0.65130
H	-1.31996	-1.31587	-1.92312
H	-2.55072	1.31269	1.30193
C	0.64311	-1.69874	0.34952
O	1.82186	-1.15926	-0.27337
C	1.42637	1.24259	-0.58251
C	0.82609	2.27751	0.00126
H	0.54809	-2.70339	-0.06339
H	0.80598	-1.77909	1.43007
H	0.34091	3.05637	-0.57921
H	0.80111	2.38810	1.08227
H	1.43013	1.15419	-1.66776
C	2.17401	0.16792	0.15242
H	2.04170	0.26346	1.23616
H	3.24322	0.24926	-0.06563

Transition state **2a**---**3a**

C	-1.78048	0.25527	0.67819
C	-1.04183	-1.19314	-0.86084
C	-0.01884	-0.85552	0.06109
O	-0.63149	-0.32985	1.18778
H	-3.10085	-0.39727	-0.99598
C	-2.16510	-0.50193	-0.46516
H	-0.89005	-1.75199	-1.77386
H	-2.43364	0.69109	1.42165
C	1.38102	-1.32714	0.23986
O	2.32055	-0.29542	-0.14193
C	0.42335	1.10751	-0.66642
C	-0.69151	1.79282	-0.14882
H	1.59449	-2.19291	-0.38698
H	1.54651	-1.59425	1.28918
H	-1.39854	2.24215	-0.83759
H	-0.57857	2.33661	0.78542
H	0.46652	0.93646	-1.73847
C	1.74994	1.01936	0.02628
H	1.64962	1.25507	1.09307
H	2.49265	1.69382	-0.40831

Diels-Alder adduct **3a**

C	-1.65710	0.49924	0.60330
C	-1.10070	-1.30323	-0.68670

C	0.06990	-0.64275	0.00780
O	-0.54639	-0.17781	1.24104
H	-3.18681	-0.66183	-0.69674
C	-2.17124	-0.58676	-0.32958
H	-1.02352	-2.09610	-1.41949
H	-2.34422	0.89740	1.34545
C	1.43002	-1.25300	0.22860
O	2.39397	-0.19889	-0.01059
C	0.33982	0.73090	-0.70104
C	-0.88752	1.55442	-0.25783
H	1.63307	-2.06329	-0.47409
H	1.53478	-1.62871	1.25030
H	-1.48328	1.92476	-1.09245
H	-0.60258	2.40272	0.36793
H	0.41224	0.60458	-1.78181
C	1.70311	1.06797	-0.11207
H	1.60781	1.51651	0.88286
H	2.31416	1.71677	-0.74047

Ground state furfuryl diallyl acetal **2b**

O	-2.20926	-0.99668	-0.86099
C	-1.00786	-1.12308	-0.21180
C	-1.13427	-1.97776	0.83667
C	-2.50474	-2.41215	0.84423
C	-3.10977	-1.79024	-0.19947
H	-0.35322	-2.26487	1.52348
H	-2.96918	-3.09665	1.53872
H	-4.11124	-1.79380	-0.59913
C	0.11817	-0.31305	-0.77120
H	0.31713	-0.58579	-1.81338
O	-0.19106	1.07143	-0.84519
C	-0.51257	3.16283	0.23449
H	0.45895	3.56420	-0.04906
C	-1.54622	3.97913	0.42728
H	-1.44904	5.05545	0.32067
H	-2.52646	3.60098	0.70718
C	-0.57941	1.68110	0.40659
H	0.11259	1.35669	1.19033
H	-1.58906	1.35914	0.67855
O	1.24195	-0.57708	0.02940
C	2.47847	-0.08753	-0.52936
H	2.68576	-0.61442	-1.46694
H	2.37085	0.98055	-0.74646
C	3.56184	-0.30707	0.47436
H	3.40979	0.16132	1.44533
C	4.67182	-0.99904	0.22849
H	4.84497	-1.47697	-0.73260
H	5.45239	-1.10599	0.97581

Reactive conformation furfuryl diallyl acetal **2b**

C	-2.49695	-1.97685	0.58214
C	-1.20740	-1.38413	-1.14742
C	-0.74485	-0.78261	-0.01892
O	-1.52010	-1.14367	1.05311

H	-2.97221	-2.77202	-1.39177
C	-2.34729	-2.16160	-0.75651
H	-0.80026	-1.27099	-2.14114
H	-3.19217	-2.34810	1.31804
C	0.34465	0.19947	0.25741
O	0.23611	1.37102	-0.54968
C	-2.17107	1.86044	-0.44109
C	-3.14352	1.73180	0.45844
H	0.30425	0.49499	1.31444
H	-4.15122	1.44569	0.17255
H	-2.96712	1.90916	1.51662
H	-2.36894	1.66525	-1.49326
C	-0.77436	2.29881	-0.10961
H	-0.66503	2.47684	0.96612
H	-0.53453	3.22587	-0.63620
C	2.72162	0.36022	0.41752
H	2.85381	1.24562	-0.20819
H	2.52908	0.68673	1.44770
O	1.57802	-0.39965	-0.03617
C	3.92112	-0.52766	0.36212
C	5.02419	-0.23691	-0.32367
H	3.86055	-1.44652	0.94278
H	5.88940	-0.89307	-0.31496
H	5.10526	0.67298	-0.91329

Transition state **2b---3b**

C	-3.03832	-0.60327	0.26196
C	-1.15517	-1.70061	-0.26209
C	-0.88493	-0.50168	0.43942
O	-2.03879	-0.11522	1.08913
H	-3.10986	-2.45449	-0.97001
C	-2.52776	-1.76303	-0.37709
H	-0.41740	-2.31679	-0.75395
H	-4.04554	-0.42518	0.61087
C	0.37231	0.11728	0.95252
O	0.23954	1.51795	0.89228
C	-1.18319	0.92150	-1.07441
C	-2.58575	0.87213	-1.18523
H	0.56528	-0.10790	2.00688
H	-3.03573	0.45547	-2.07904
H	-3.17706	1.64603	-0.70461
H	-0.59619	0.47351	-1.86851
C	-0.48280	2.00353	-0.29407
H	-1.18898	2.74162	0.08825
H	0.25343	2.51383	-0.91995
O	1.42079	-0.37959	0.15045
C	2.73237	0.01070	0.60155
H	2.87124	1.08604	0.46076
H	2.81234	-0.21110	1.67396
C	3.74279	-0.77066	-0.17324
H	3.66333	-1.85404	-0.10051
C	4.70803	-0.21547	-0.90223
H	5.44202	-0.81837	-1.42859
H	4.80528	0.86364	-0.99301

Diels-Alder adduct *anti*-**3b**

C	-3.02270	-0.46590	0.19639
C	-1.14254	-1.71988	-0.15591
C	-0.88572	-0.29188	0.26387
O	-2.00827	-0.02460	1.13718
H	-3.07001	-2.65168	-0.57598
C	-2.47418	-1.82463	-0.21167
H	-0.38715	-2.42662	-0.47072
H	-4.00836	-0.43117	0.65257
C	0.39503	0.26429	0.82966
O	0.29278	1.66568	0.63715
C	-1.22713	0.65324	-0.93657
C	-2.77012	0.53513	-0.97630
H	0.53072	0.09484	1.90118
H	-3.14757	0.16225	-1.92868
H	-3.25572	1.48815	-0.75944
H	-0.75275	0.30665	-1.85317
C	-0.61192	1.97590	-0.46873
H	-1.35425	2.67405	-0.07985
H	-0.03564	2.46830	-1.25367
O	1.46011	-0.30579	0.10406
C	2.76373	0.07830	0.58364
H	2.94243	1.13647	0.37420
H	2.78882	-0.06859	1.67151
C	3.78244	-0.78538	-0.08549
H	3.66157	-1.85816	0.05561
C	4.80160	-0.31227	-0.79883
H	5.53916	-0.97281	-1.24488
H	4.94095	0.75454	-0.95614

Diels-Alder adduct *syn*-**3b**

C	2.37241	-1.01869	-0.93759
C	1.70428	-1.18435	1.24173
C	0.93011	-0.18321	0.41441
O	0.93839	-0.80478	-0.89281
H	3.43671	-2.35988	0.62607
C	2.61445	-1.69182	0.40450
H	1.60392	-1.32391	2.31021
H	2.64922	-1.56439	-1.83580
C	-0.41986	0.40404	0.79444
O	-0.34584	1.79885	0.46687
C	1.85684	1.05089	0.14839
C	2.87827	0.45818	-0.84459
H	3.90875	0.52572	-0.49547
H	2.81213	0.93140	-1.82627
H	2.30844	1.40909	1.07393
C	0.82405	2.05038	-0.35436
H	0.57824	1.88678	-1.40774
H	1.09788	3.09460	-0.20535
H	-0.60677	0.34175	1.87061
O	-1.44327	-0.24874	0.09472
C	-2.76895	0.10056	0.54280
H	-2.98679	1.14118	0.28726
H	-2.80326	-0.00306	1.63544

C	-3.74197	-0.83063	-0.10294
H	-3.57226	-1.89139	0.07397
C	-4.77836	-0.42852	-0.83476
H	-4.96542	0.62499	-1.02795
H	-5.48260	-1.13658	-1.26130

Furfural **1b**

C	0.26115	0.27459	-0.00007
C	-0.77734	1.17510	-0.00004
C	-1.97672	0.41460	0.00004
C	-1.59230	-0.89702	0.00005
O	-0.24285	-1.00694	-0.00005
H	-0.67776	2.25075	-0.00014
H	-2.99125	0.78313	0.00023
H	-2.13979	-1.82682	-0.00015
C	1.68144	0.47629	0.00002
O	2.52379	-0.41862	0.00004
H	1.98389	1.53605	0.00006

Allyl alcohol **(AA)**

C	-0.58214	0.44633	0.30963
H	-0.43805	1.41773	-0.17554
H	-0.88126	0.62275	1.35025
C	0.67541	-0.35941	0.26840
H	0.61158	-1.35749	0.69965
C	1.82737	0.08089	-0.23300
H	1.91647	1.07136	-0.67282
H	2.72613	-0.52846	-0.21544
O	-1.62327	-0.29504	-0.36007
H	-2.47252	0.12760	-0.17572

Complex **1b**---**AA**

C	2.11767	0.97300	-0.54603
C	1.56365	-0.17169	1.28166
O	1.38742	-0.09080	-0.95511
H	2.79610	1.70520	1.39898
C	2.26239	0.97235	0.81304
H	1.44693	-0.50125	2.30369
H	2.46564	1.63295	-1.32528
C	-1.74249	1.58929	0.14444
C	-0.92774	2.23744	-0.68446
H	-0.50819	3.20531	-0.42791
H	-0.65950	1.83102	-1.65548
H	-1.99401	2.01961	1.11295
C	-2.39939	0.28488	-0.17163
H	-1.96273	-0.16495	-1.06962
C	1.04085	-0.79523	0.17473
C	0.23745	-1.97839	0.04639
H	0.02200	-2.48186	1.00107
O	-0.18055	-2.43273	-1.01635
H	-3.47033	0.44062	-0.35685
O	-2.24423	-0.59588	0.95642
H	-2.75142	-1.40134	0.79003

Transition state intermolecular reaction

C	1.90532	0.27061	-0.70689
C	1.38947	-0.87624	1.14653
O	0.86209	-0.58024	-1.04374
H	3.31291	0.20032	1.03599
C	2.40350	-0.15603	0.57431
H	1.31831	-1.24719	2.15937
H	2.51556	0.56458	-1.55044
C	-0.27096	1.40974	0.39607
C	0.86623	1.82726	-0.31635
H	1.60672	2.41454	0.21602
H	0.70013	2.16531	-1.33736
H	-0.25771	1.41430	1.48079
C	-1.61492	1.34135	-0.23809
H	-1.57119	0.79005	-1.18785
C	0.35842	-0.97006	0.17542
C	-0.88738	-1.67752	0.21171
H	-1.21571	-1.97760	1.21868
O	-1.56994	-1.93863	-0.78218
H	-1.96802	2.35585	-0.47640
O	-2.53467	0.72434	0.66880
H	-3.39896	0.66134	0.24197

Intermolecular Diels-Alder adduct

C	1.85916	0.35874	-0.70485
C	1.30320	-0.91328	1.10229
O	0.75692	-0.50074	-1.10350
H	3.38471	-0.29935	0.91095
C	2.37222	-0.35667	0.53258
H	1.21018	-1.41881	2.05412
H	2.54487	0.50482	-1.53457
C	-0.16199	0.98309	0.45531
C	1.08592	1.61576	-0.21839
H	1.67583	2.23181	0.45998
H	0.79591	2.22440	-1.07770
H	-0.20464	1.17390	1.52844
C	-1.45462	1.44257	-0.18661
H	-1.47624	1.17061	-1.24695
C	0.13118	-0.55213	0.18801
C	-1.03969	-1.47802	0.23708
H	-1.46224	-1.63896	1.24139
O	-1.48329	-2.05985	-0.73322
H	-1.54146	2.53226	-0.11026
O	-2.54245	0.81246	0.50664
H	-3.34861	0.90385	-0.01714

X-ray structural data

*X-ray crystal structure determination of **3f***

Suitable crystals for XRD were obtained by spontaneous crystallization in the freezer. $C_{11}H_{13}BrO_3$, Fw = 273.12, colourless block, 0.37 × 0.24 × 0.10 mm^3, triclinic, P**Error!** (no. 2), a = 5.8474(4), b = 9.4994(5), c = 11.3086(6) Å, α = 107.710(4), β = 98.149(4), γ = 105.204(4) °, V = 560.42(6) Å^3, Z = 2, D_x = 1.619 g/cm^3, μ = 3.65 mm^{-1}. The diffraction experiment was performed on a Bruker Kappa ApexII diffractometer with sealed tube and Triumph monochromator (λ = 0.71073 Å) at a temperature of 150(2) K up to a resolution of $(\sin\theta/\lambda)_{max}$ = 0.65 Å^{-1}. The intensity integration was done with the Eval15 software.[4] A numerical absorption correction and scaling was performed with SADABS.[5] (correction range 0.37-0.72). A total of 9421 reflections was measured, 2576 reflections were unique (R_{int} = 0.027), 2363 reflections were observed [I>2σ(I)]. The structure was solved with Patterson superposition methods using SHELXT.[6] Structure refinement was performed with SHELXL-2018[7] on F^2 of all reflections. Non-hydrogen atoms were refined freely with anisotropic displacement parameters. All hydrogen atoms were located in difference-Fourier maps and refined with a riding model. 136 Parameters were refined with no restraints. R1/wR2 [I > 2σ(I)]: 0.0240 / 0.0610. R1/wR2 [all refl.]: 0.0276 / 0.0622. S = 1.064. Residual electron density between -0.28 and 0.57 e/Å^3. Geometry calculations and checking for higher symmetry was performed with the PLATON program.[8]

*X-ray crystal structure determination of **4b***

Suitable crystals for XRD were obtained by slow evaporation of a solution of **4b** in Et_2O. $C_8H_{10}O_3$, Fw = 154.16, colourless needle, 0.41 × 0.12 × 0.08 mm^3, monoclinic, $P2_1/c$ (no. 14), a = 10.0582(5), b = 10.1124(6), c = 7.0300(3) Å, β = 90.351(3) °, V = 715.03(6) Å^3, Z = 4, D_x = 1.432 g/cm^3, μ = 0.11 mm^{-1}. The diffraction experiment was performed on a Bruker Kappa ApexII diffractometer with sealed tube and Triumph monochromator (λ = 0.71073 Å) at a temperature of 150(2) K up to a resolution of $(\sin\theta/\lambda)_{max}$ = 0.65 Å^{-1}. The intensity integration was done with the Eval15 software.[4] A multi-scan absorption correction and scaling was performed with SADABS[5] (correction range 0.68-0.75). A total of 13471 reflections was measured, 1636 reflections were unique (R_{int} = 0.027), 1368 reflections were observed [I>2σ(I)]. The structure was solved with Patterson superposition methods using SHELXT.[6] Structure refinement was performed with SHELXL-2018[7] on F^2 of all reflections. Non-hydrogen atoms were refined freely with anisotropic displacement parameters. All hydrogen atoms were located in difference-Fourier maps. The O-H hydrogen atom was refined freely with an isotropic displacement parameter. C-H hydrogen atoms were refined with a riding model. 104 Parameters were refined with no restraints. R1/wR2 [I > 2σ(I)]: 0.0351 / 0.0933. R1/wR2 [all refl.]: 0.0427 / 0.0981. S = 1.064. Residual electron density between -0.18 and 0.31 e/Å^3. Geometry calculations and checking for higher symmetry was performed with the PLATON program.[8]

The crystal structures of **3f** and **4b** have been deposited in the CCDC under the numbers 2126534 en 2126535.

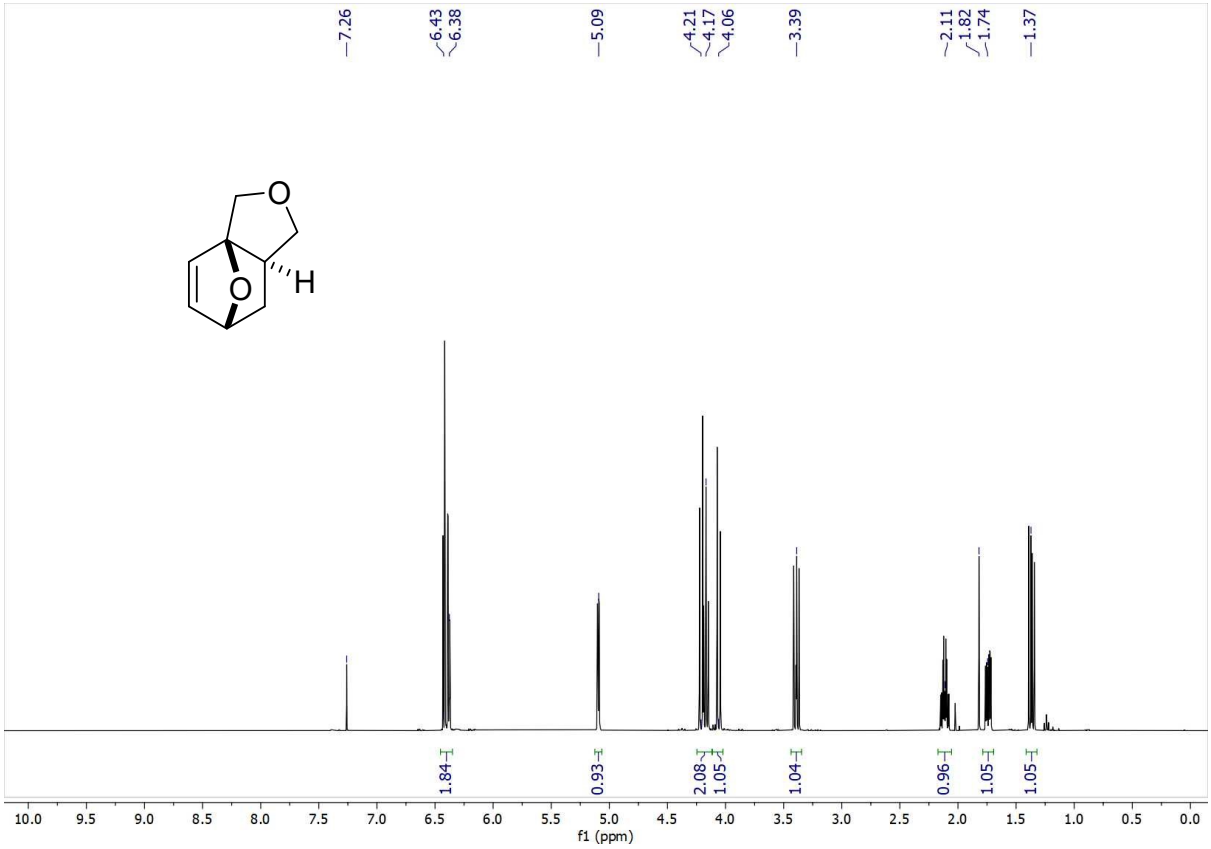
Table S2. Hydrogen bond geometry in compound **4b**

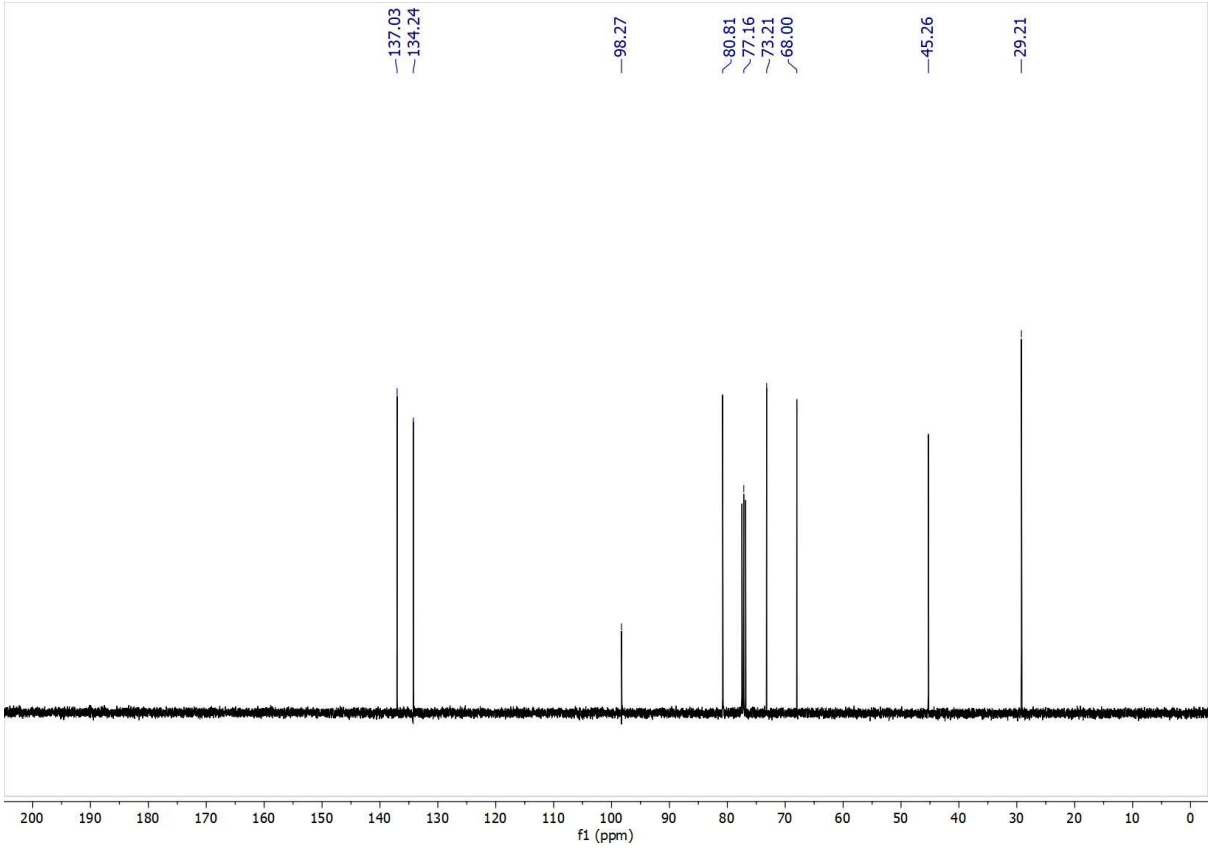
	D-H [Å]	H…A [Å]	D….A [Å]	D-H…A [°]
O2-H2…O1^i	0.877(19)	1.864(19)	2.7408(12)	178.7(18)

Symmetry code *i*: x, ½-y, z+½

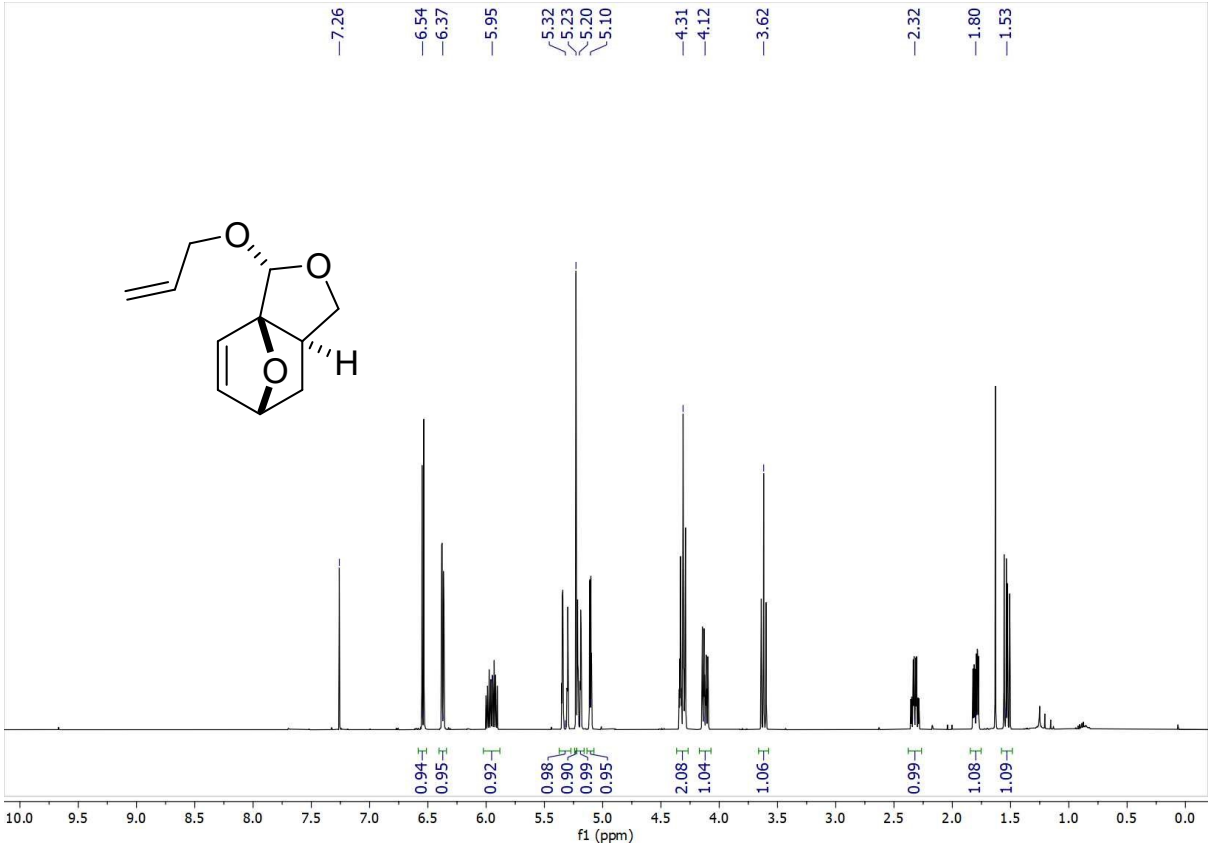
NMR data

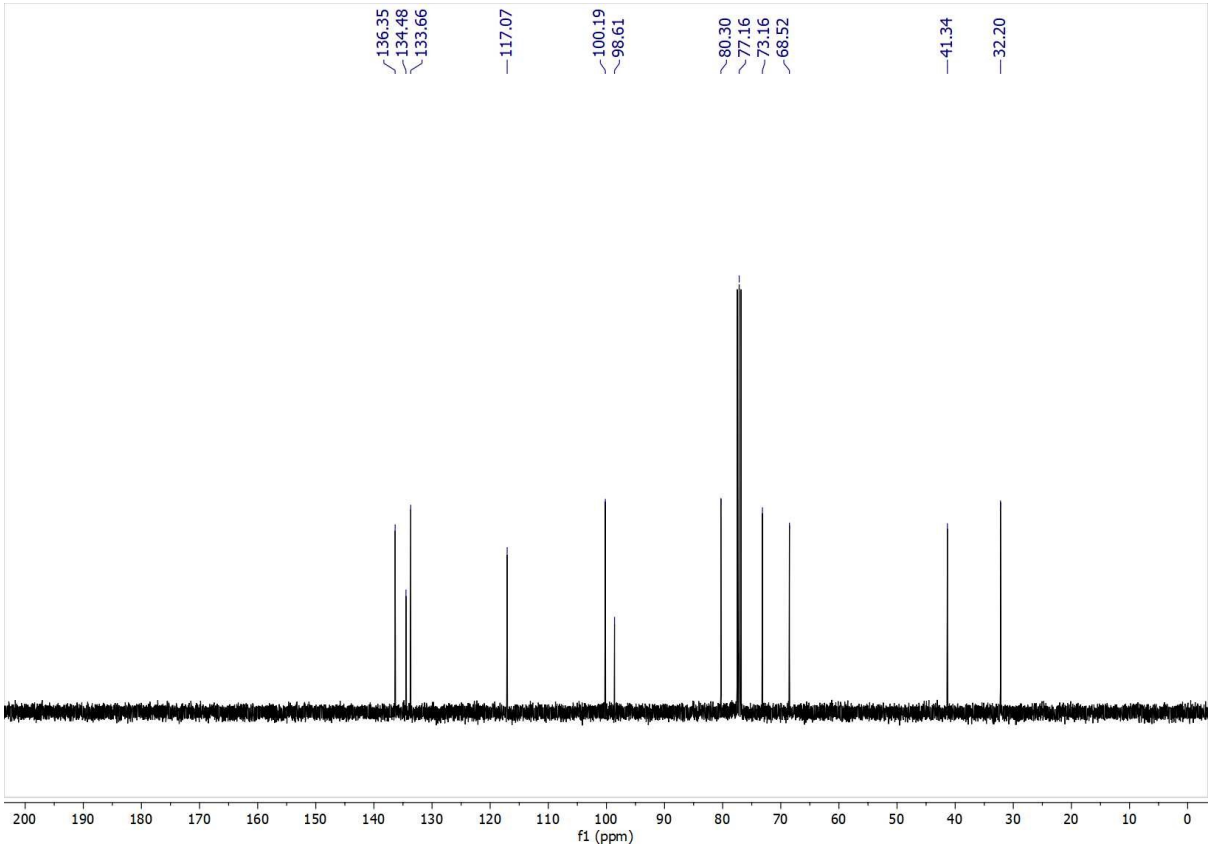
Diels-Alder adduct 3a



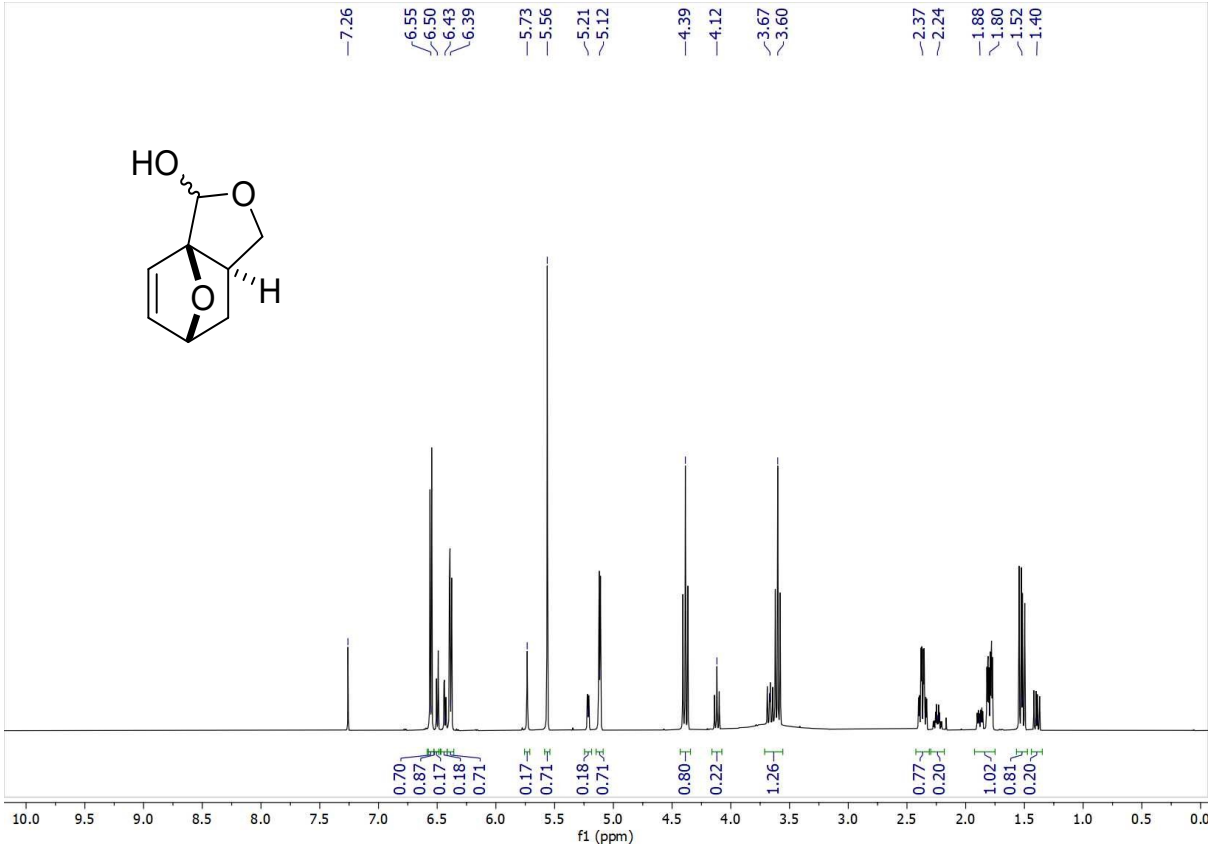


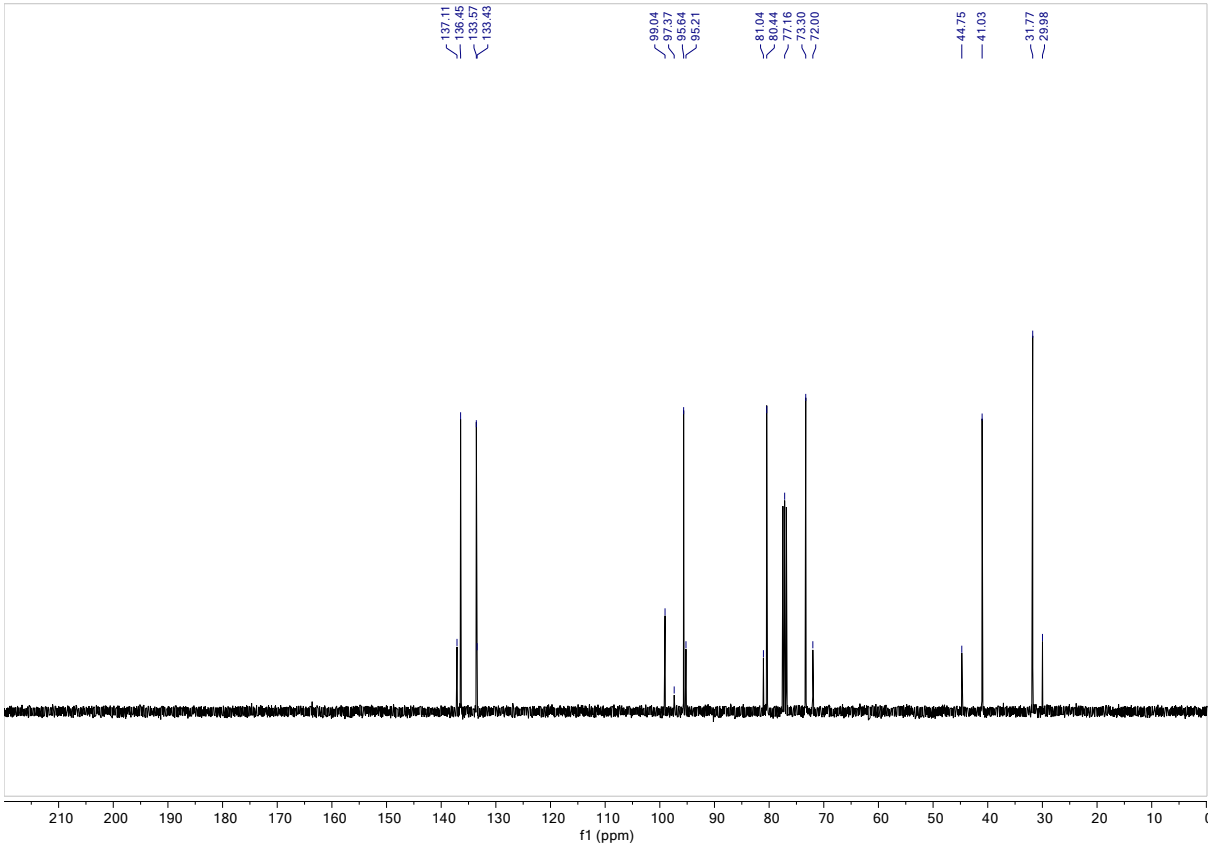
Diels-Alder adduct 3b



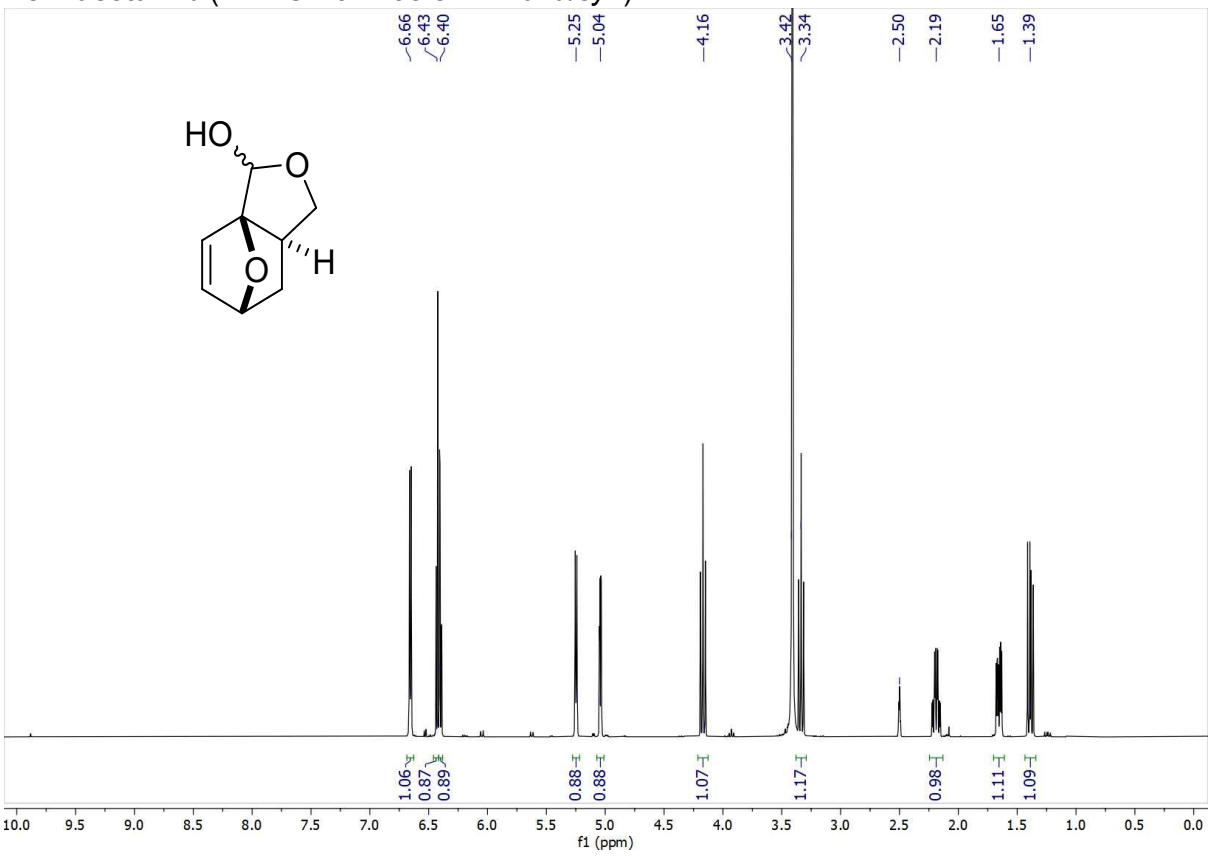


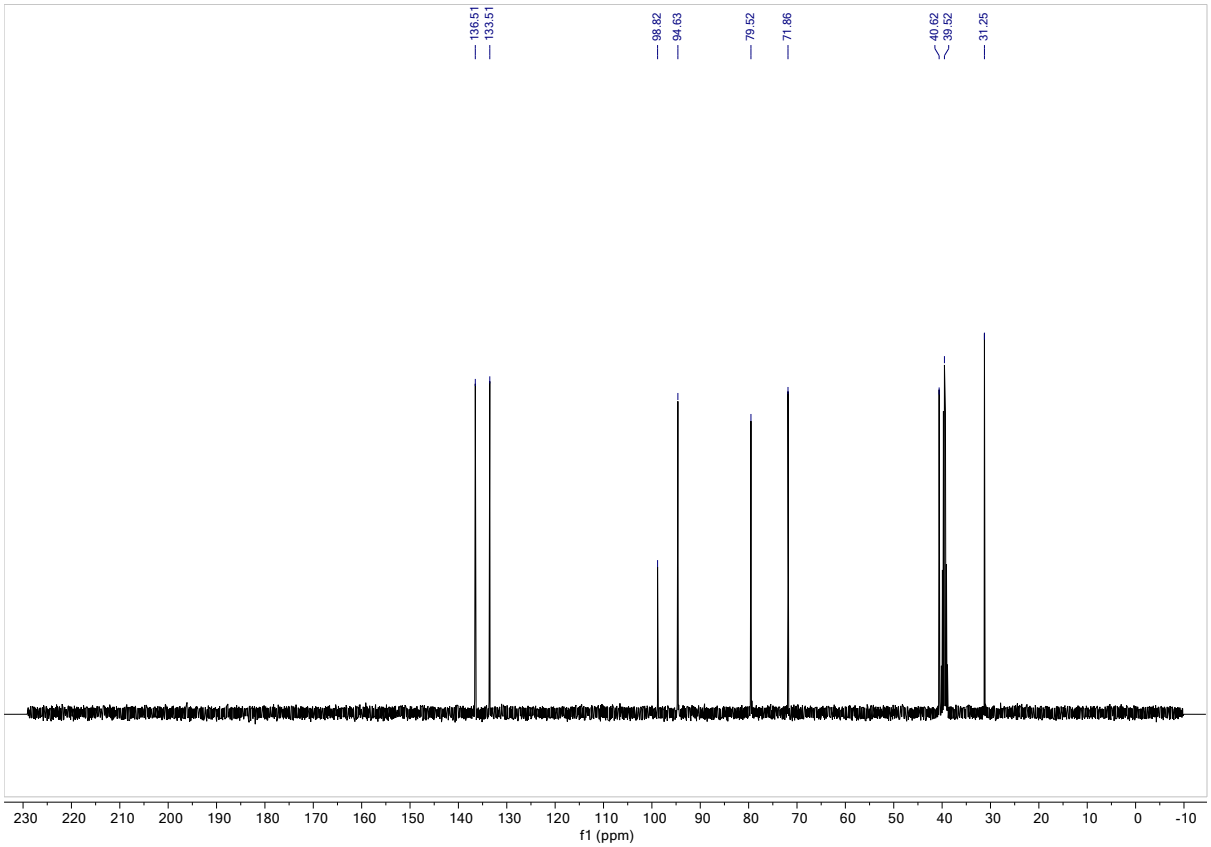
Hemiacetal 4b ($CDCl_3$: 4:1 ratio *anti*/*syn*)



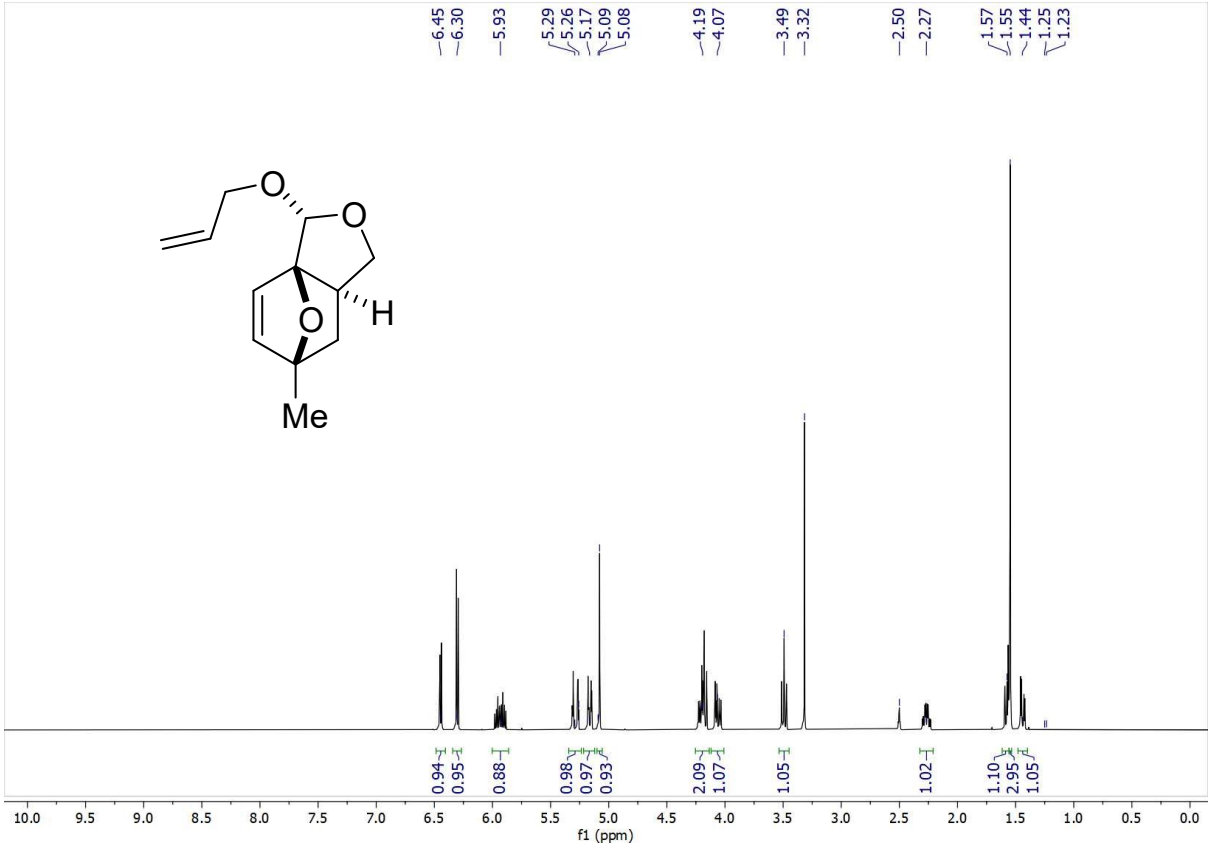


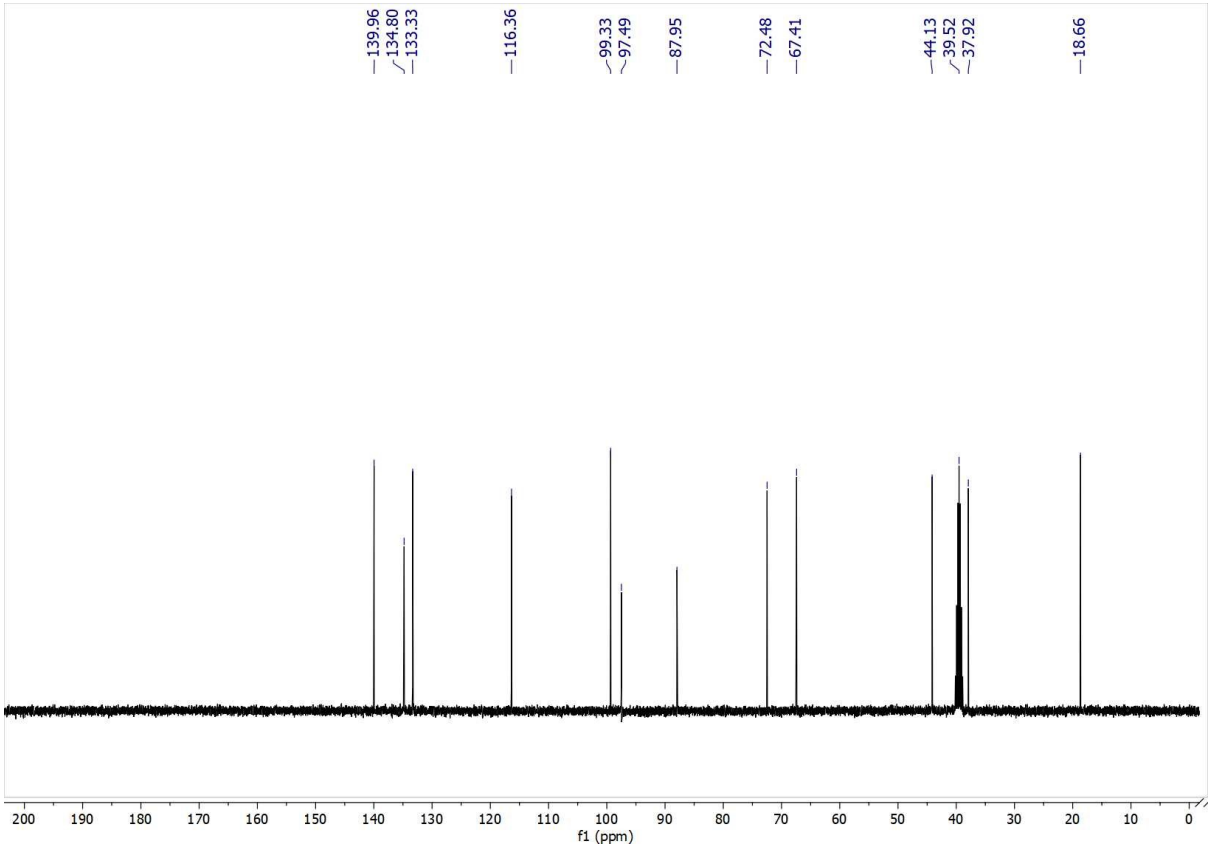
Hemiacetal 4b (DMSO-d6: > 95:5 ratio *anti*/*syn*)



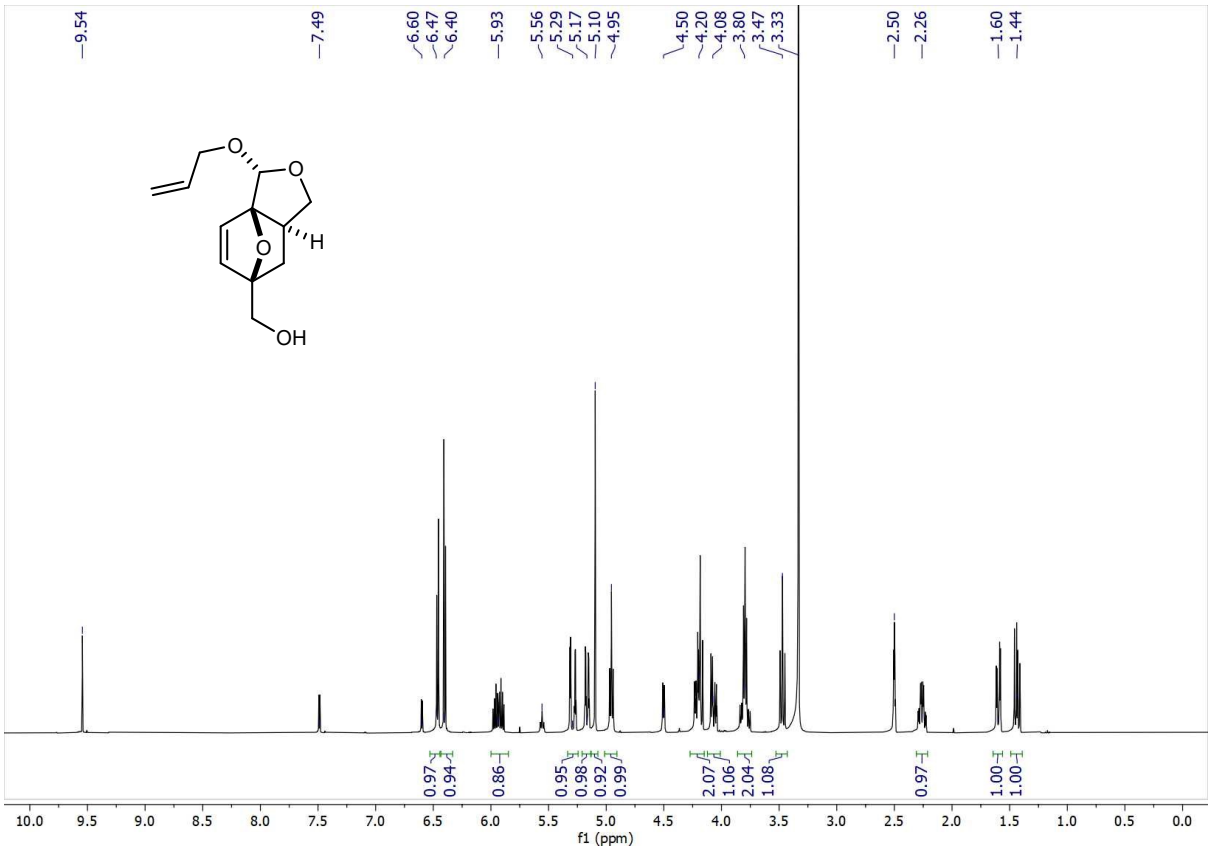


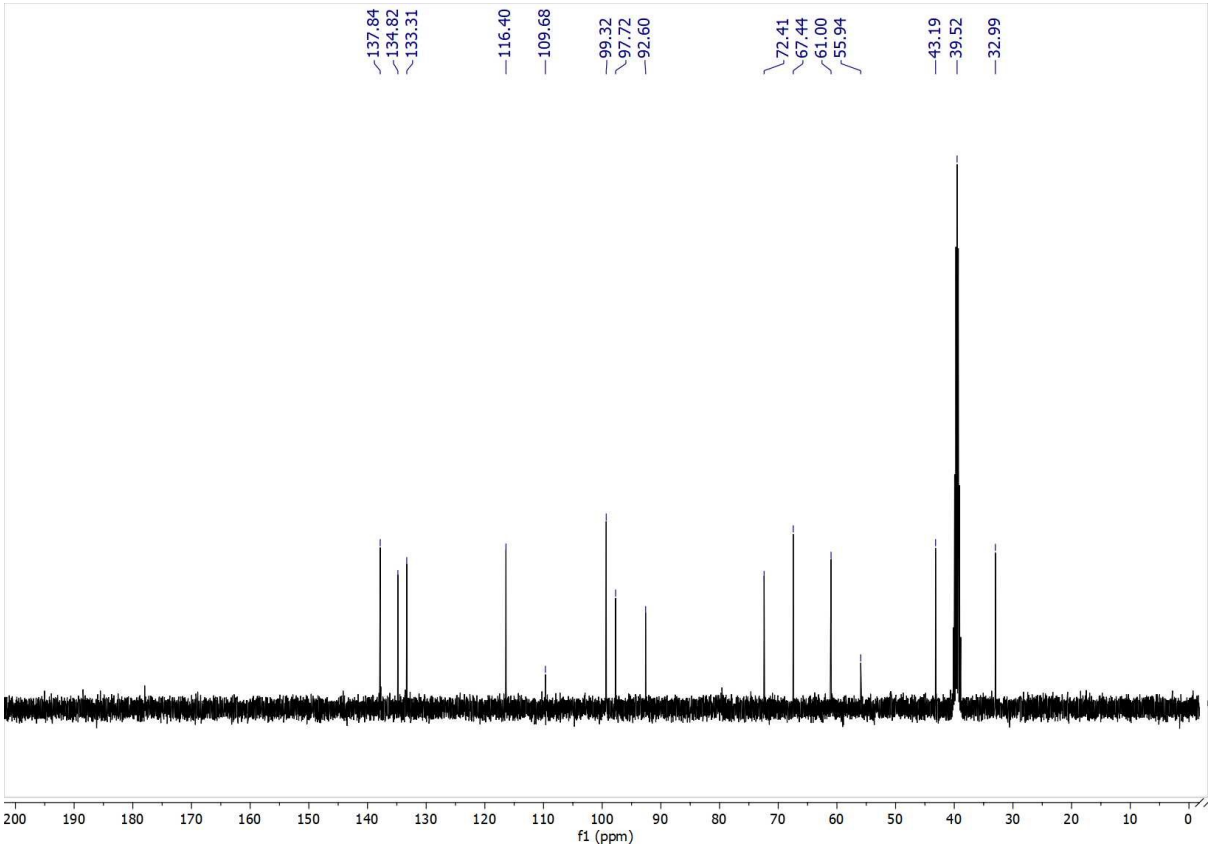
Diels-Alder adduct 3c



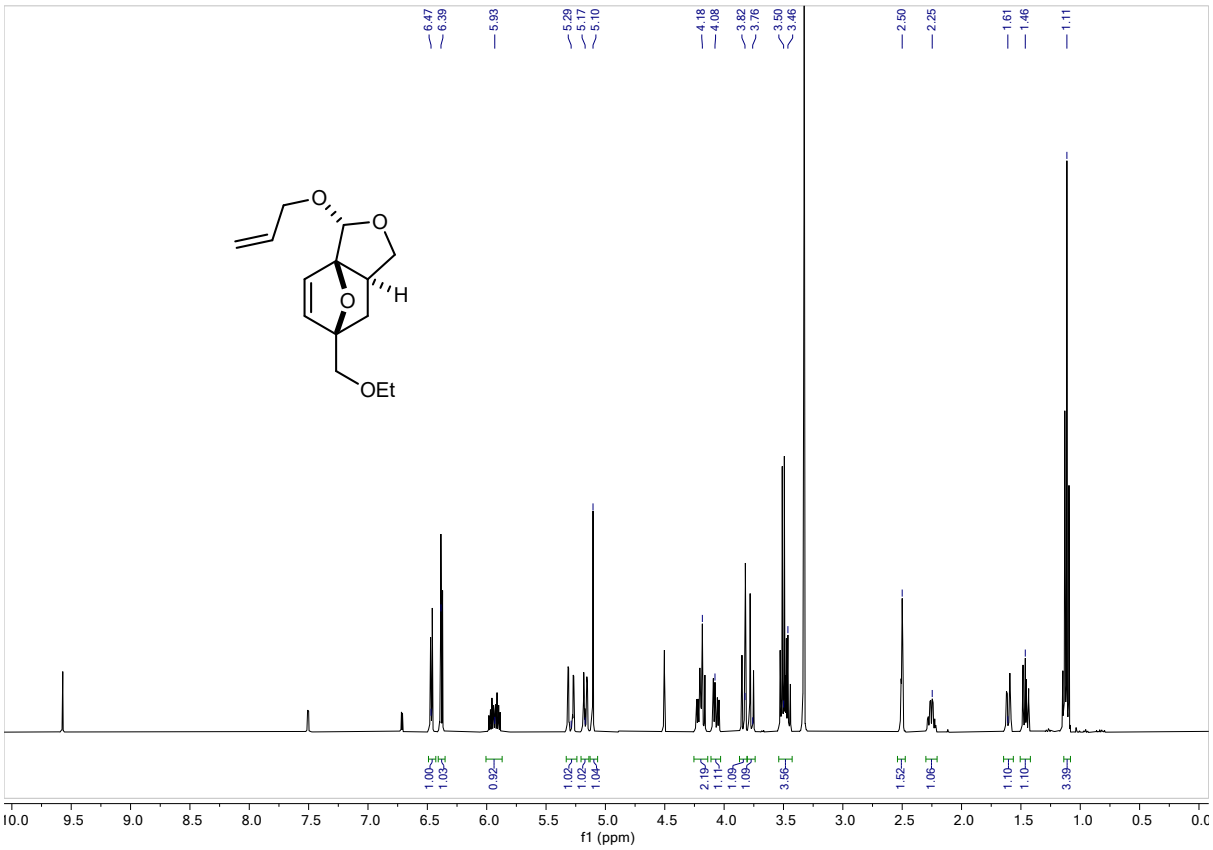


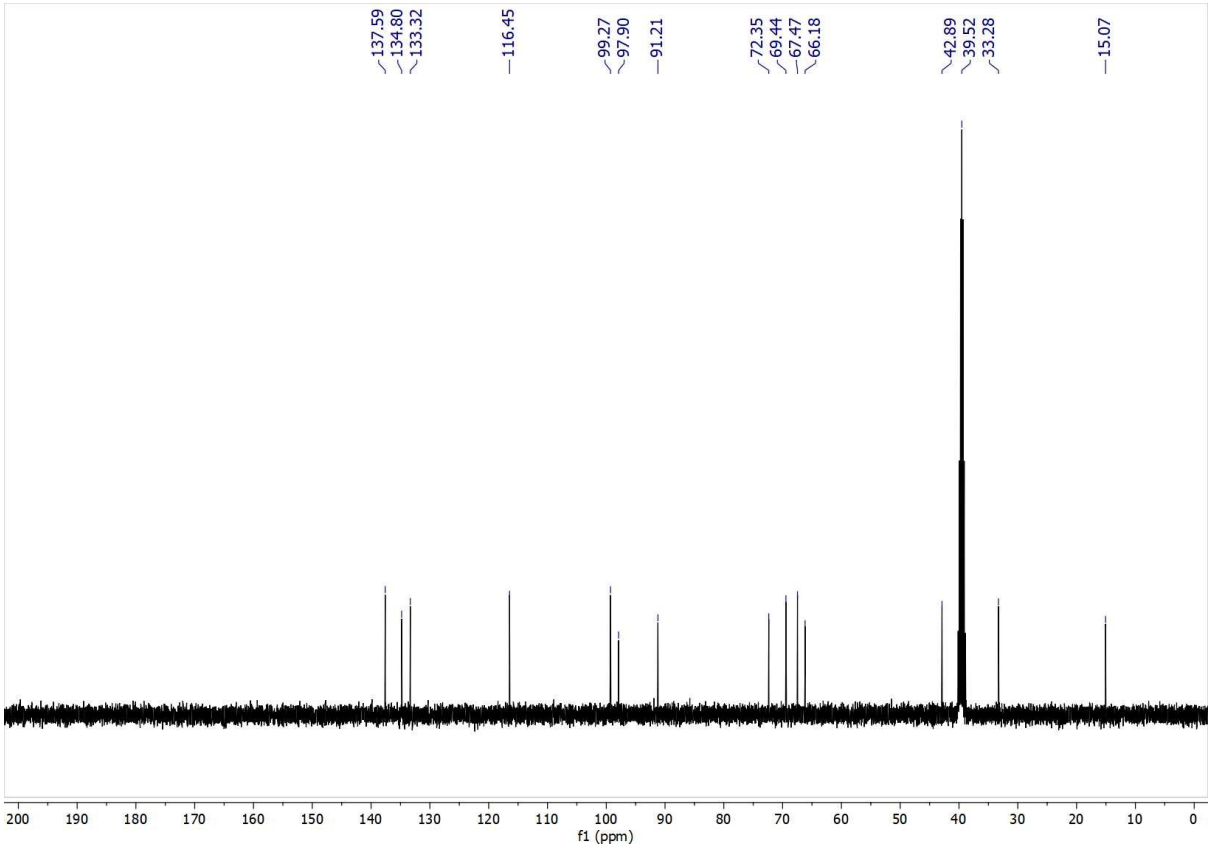
Diels-Alder adduct 3d



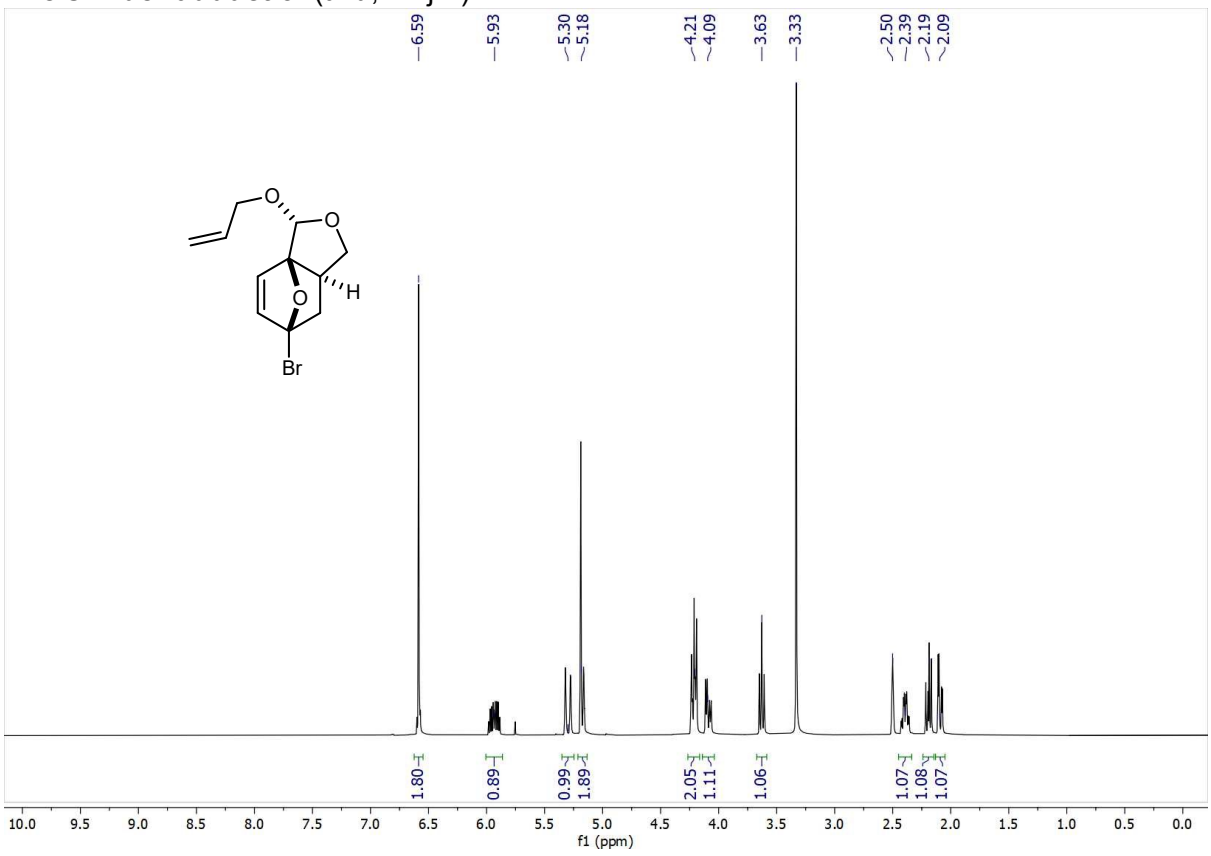


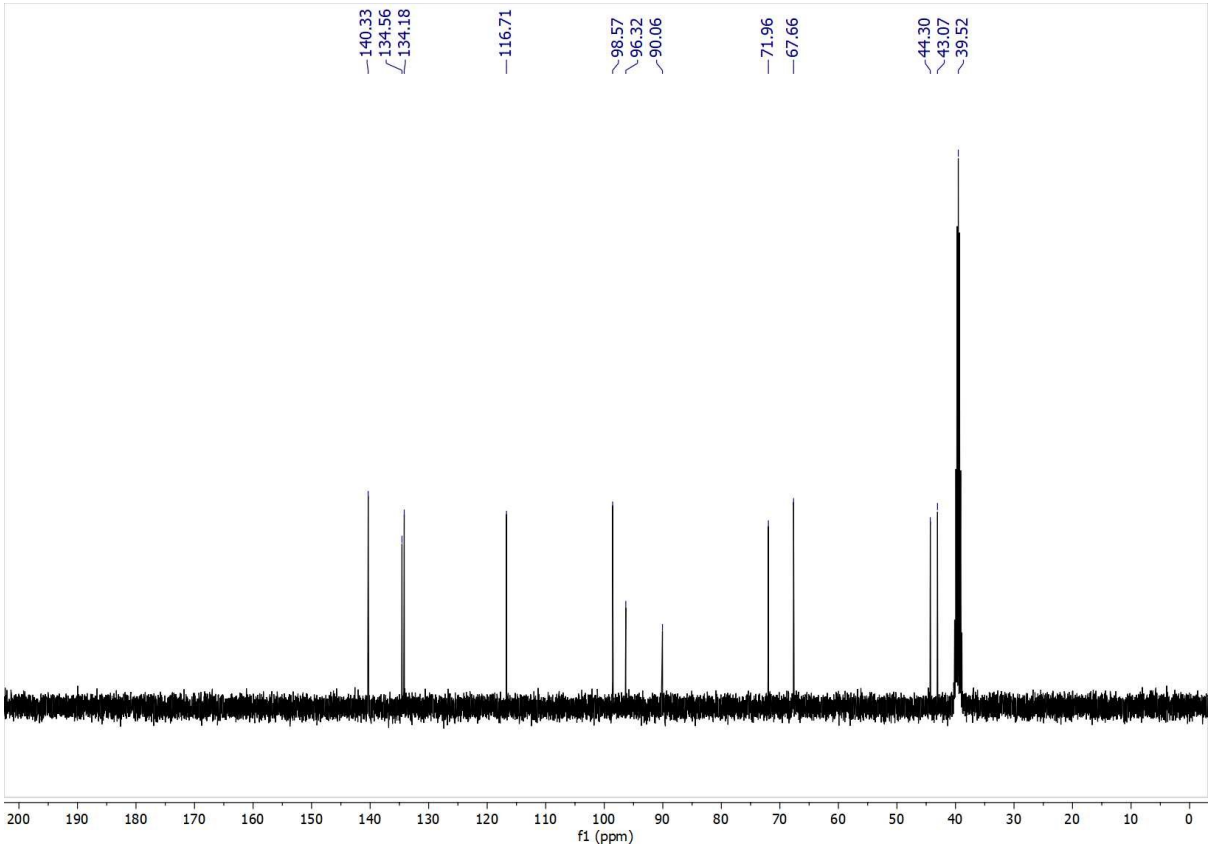
Diels-Alder adduct 3e



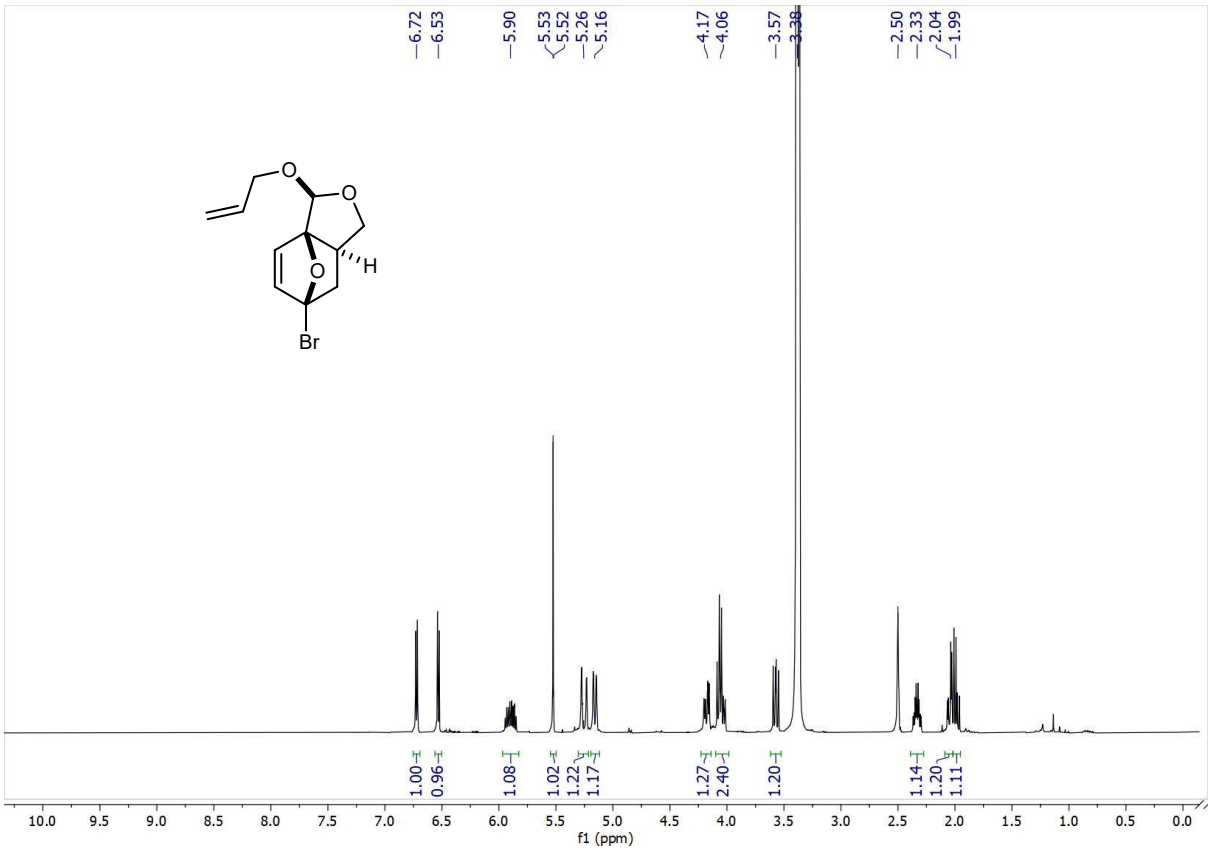


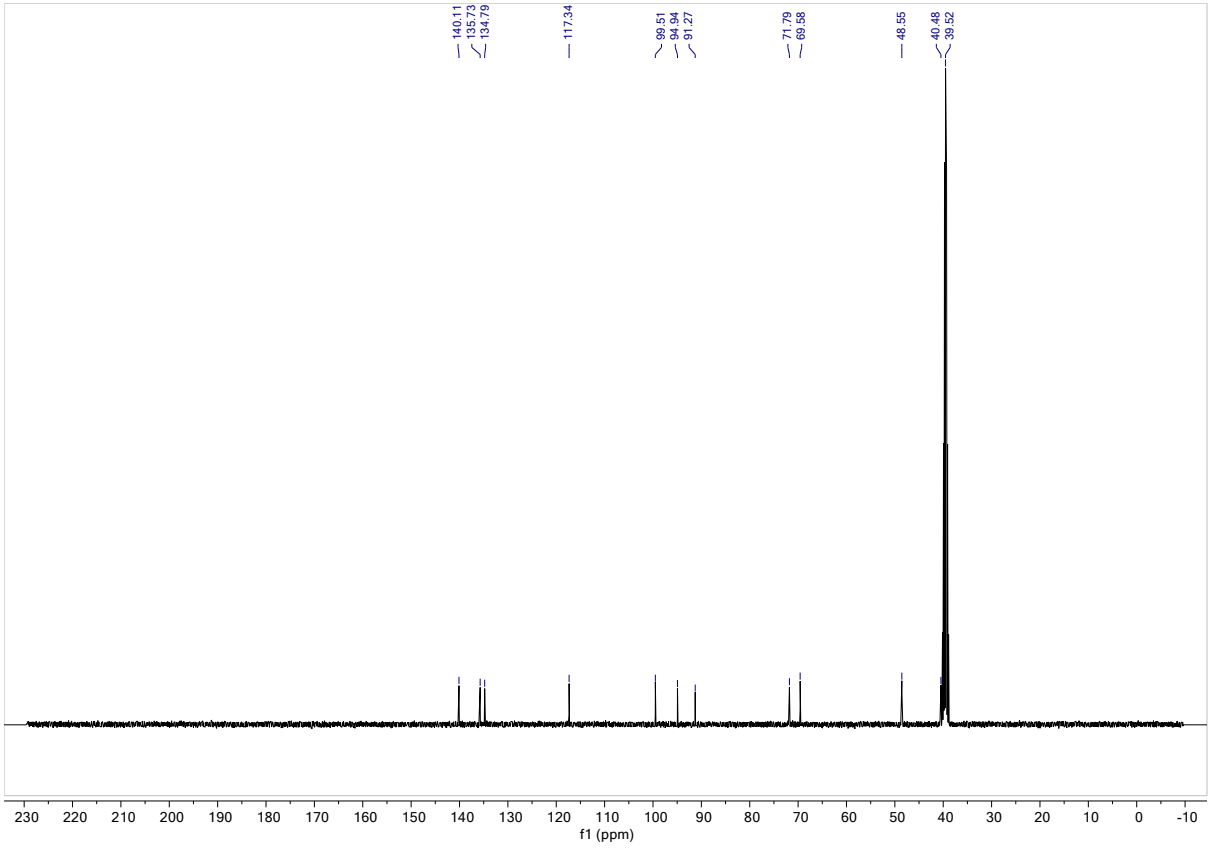
Diels-Alder adduct 3f (*anti*, major)



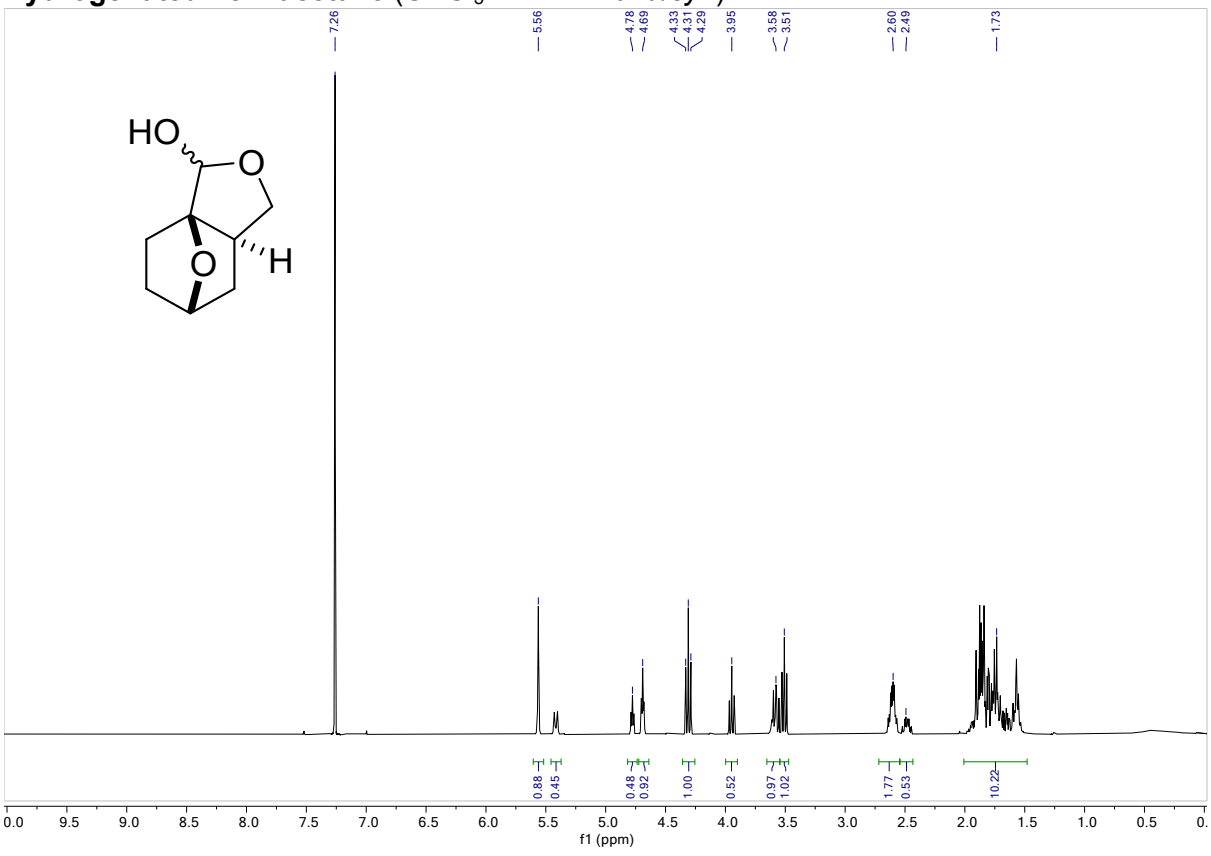


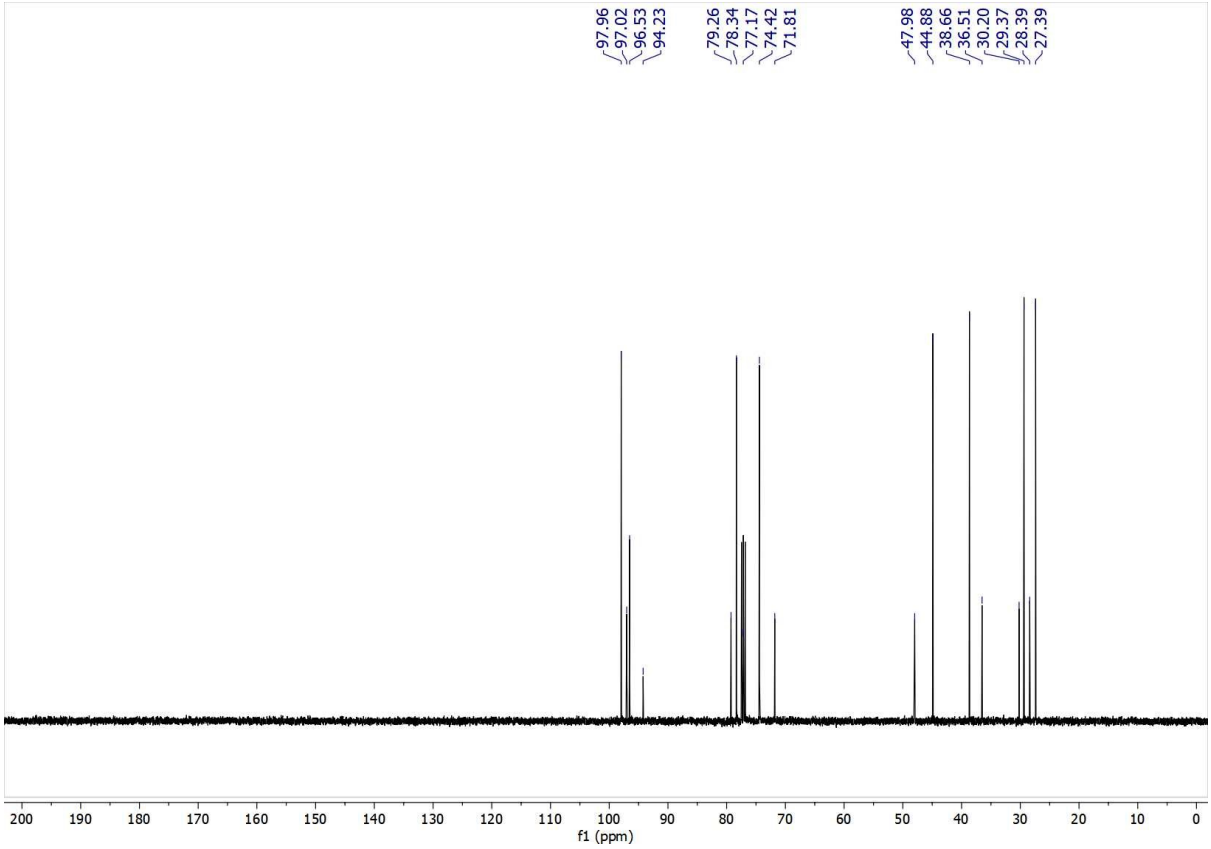
Diels-Alder adduct 3f (*syn*, minor)



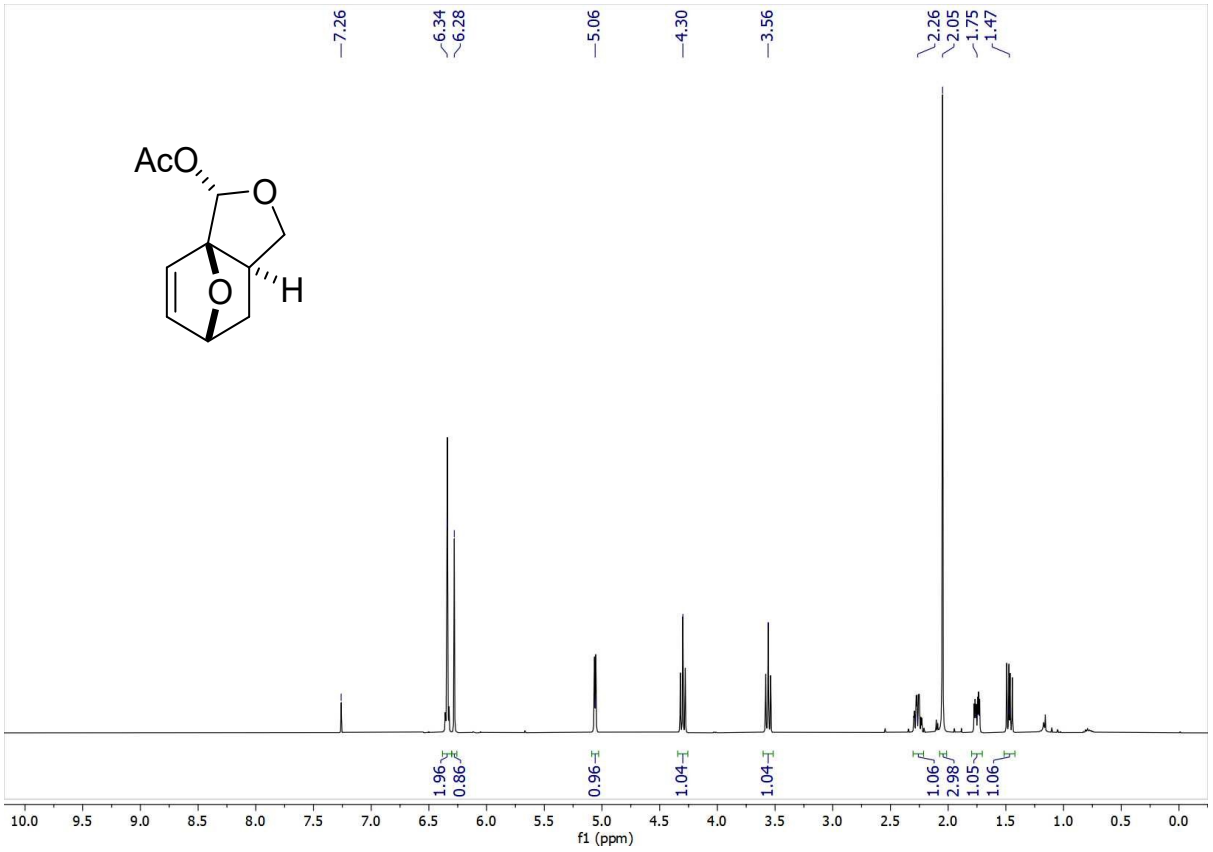


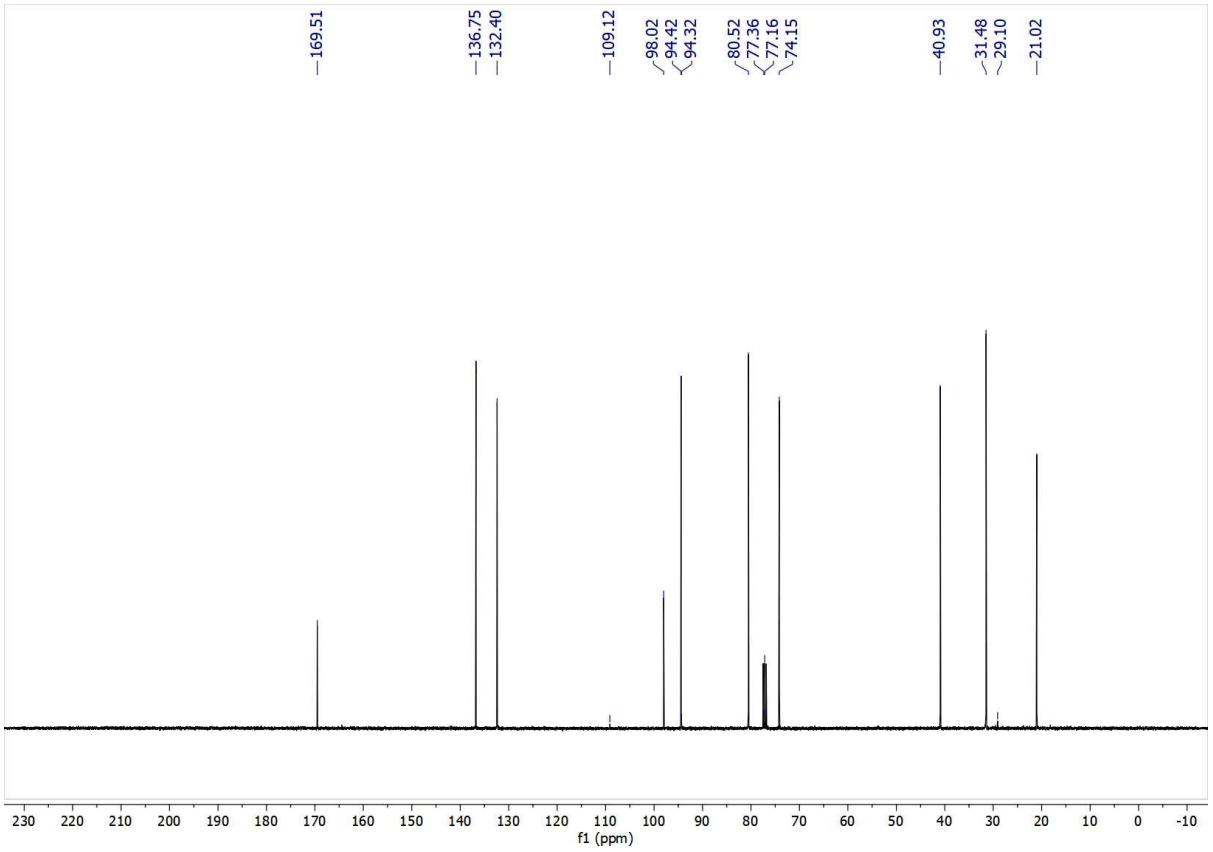
Hydrogenated hemiacetal 5 ($CDCl_3$: 2:1 ratio *anti*/*syn*)



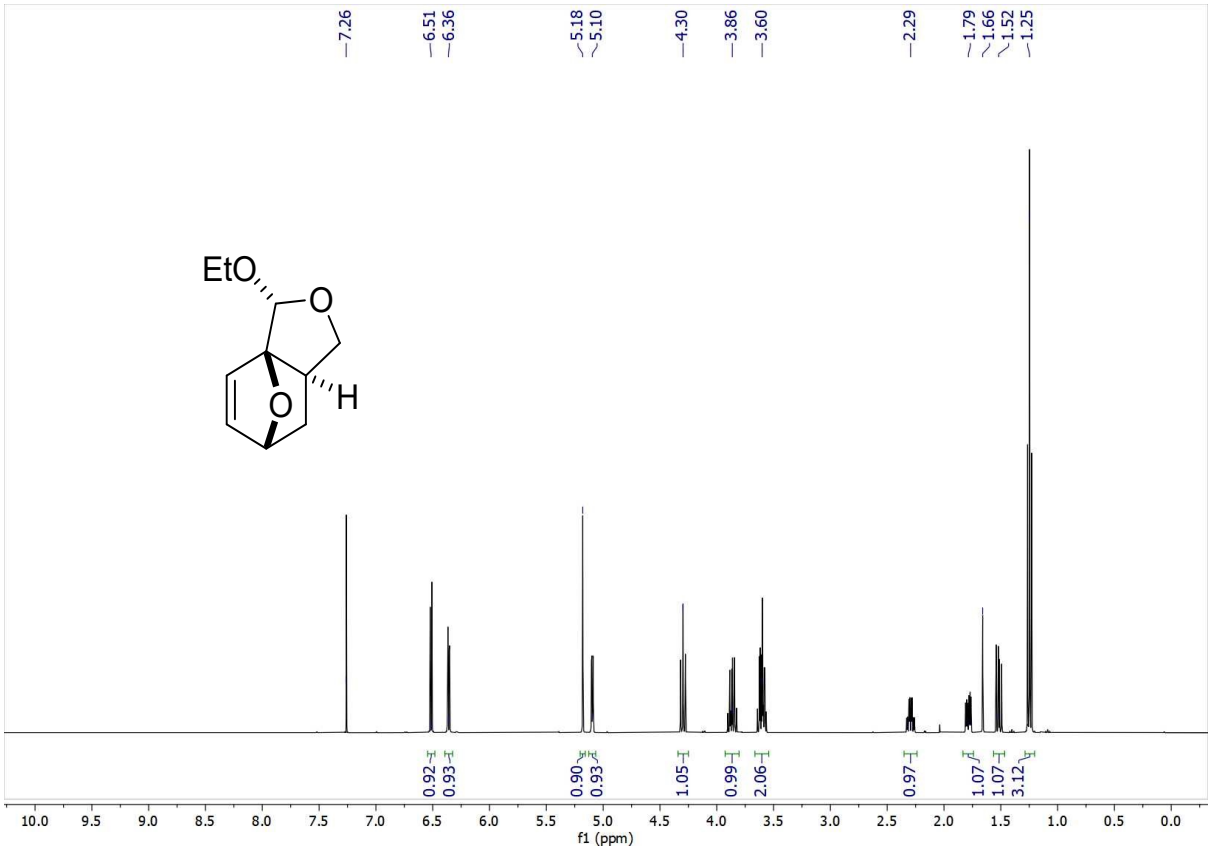


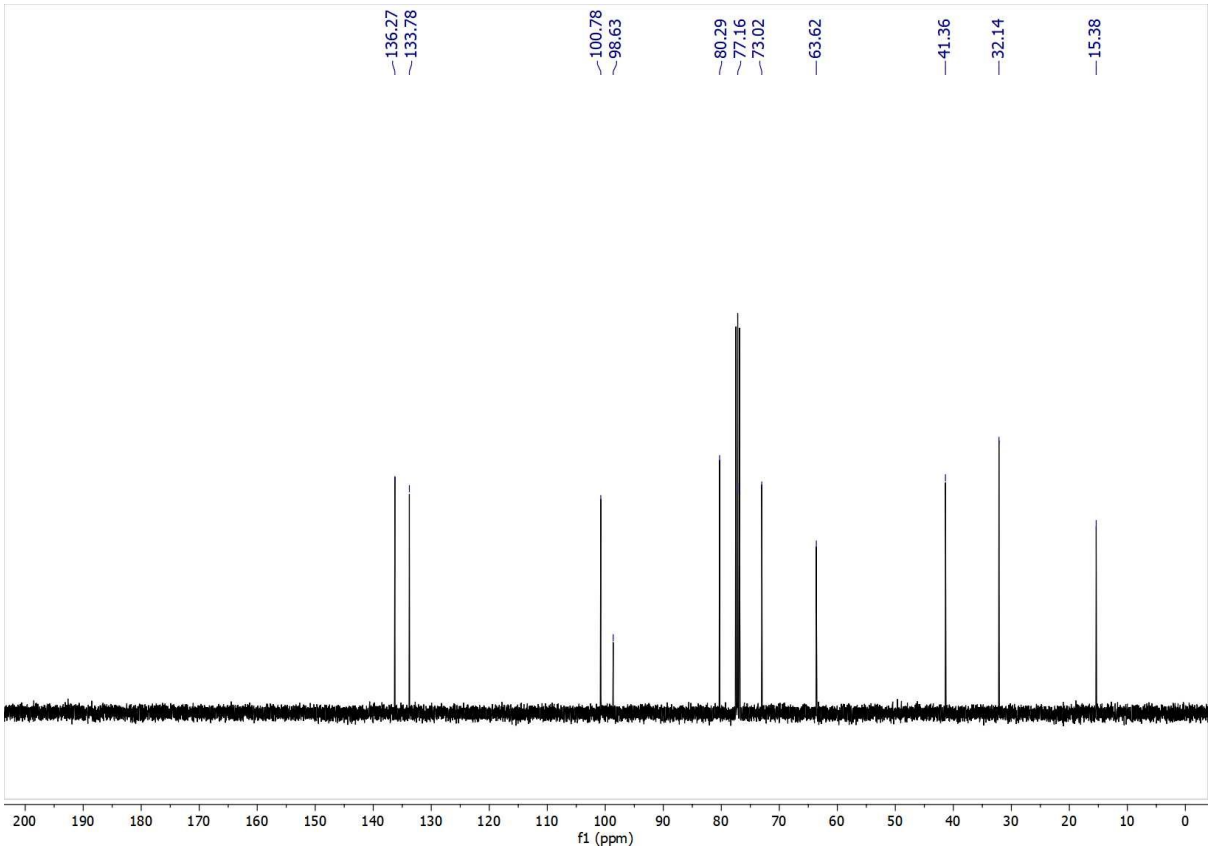
Acetate 6


7.26
6.34
6.28
5.06
4.30
3.56
2.26
2.05
1.75
1.47
AcO
O
O
H
1.96
0.86
0.96
1.04
1.04
1.06
2.98
1.05
1.06
f1 (ppm)


169.51
136.75
132.40
109.12
98.02
94.42
94.32
80.52
77.36
77.16
74.15
40.93
31.48
29.10
21.02
f1 (ppm)

Ether 7


7.26
6.51
6.36
5.18
5.10
4.30
3.86
3.60
2.29
1.79
1.66
1.52
1.25
EtO
O
O
H
0.92
0.93
0.90
0.93
1.05
0.99
2.06
0.97
1.07
1.07
3.12
f1 (ppm)


136.27
133.78
100.78
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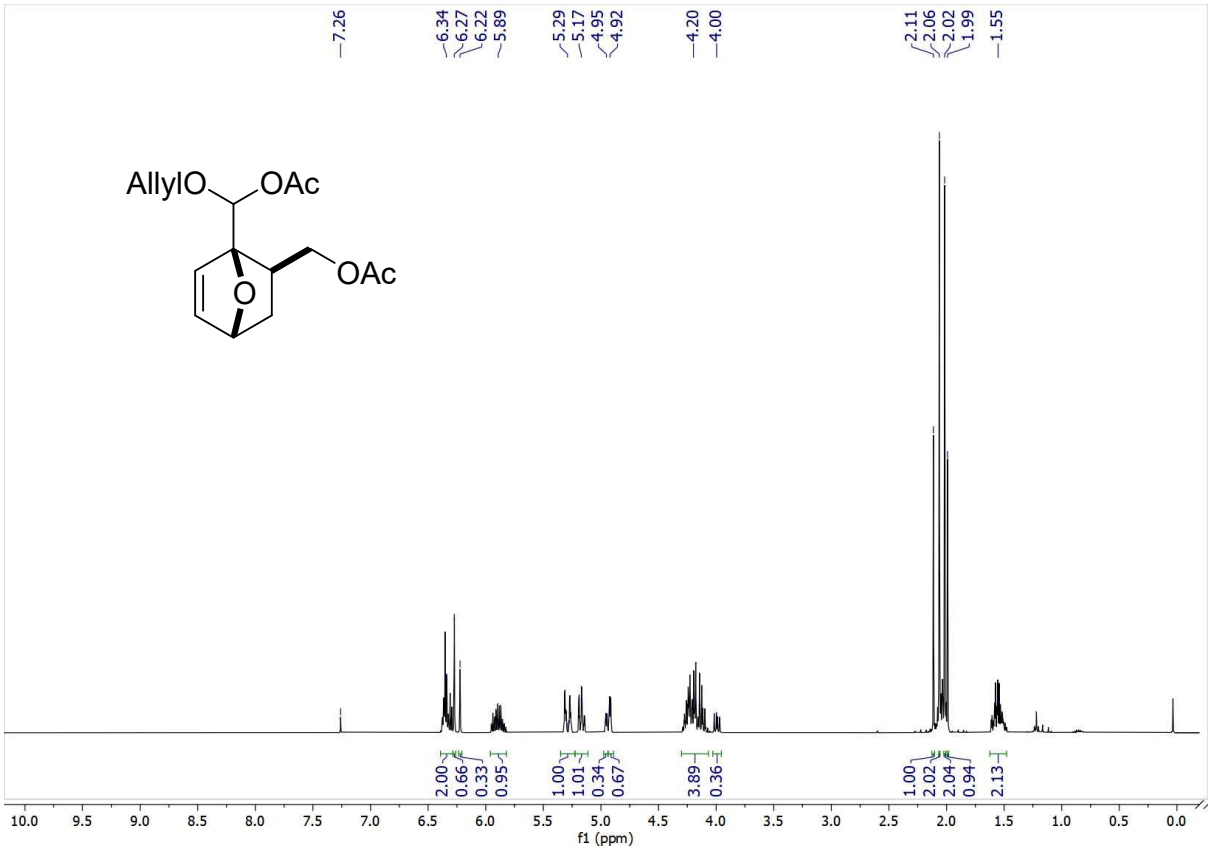
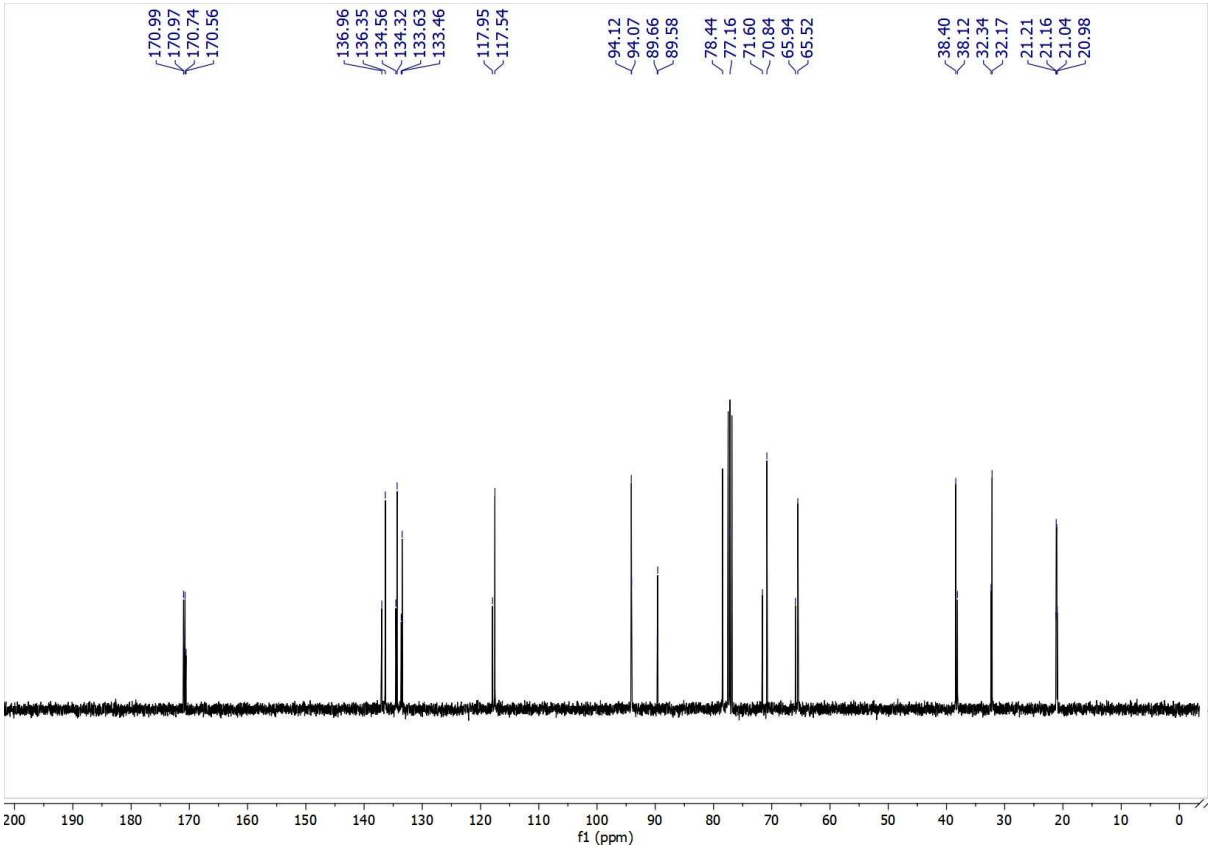
80.29
77.16
73.02
63.62
41.36
32.14
15.38
f1 (ppm)

Acetate 8


7.26
6.34
6.27
6.22
5.89
5.29
5.17
4.95
4.92
4.20
4.00
2.11
2.06
2.02
1.99
1.55
AllylO
OAc
OAc
O
2.00
0.66
0.33
0.95
1.00
1.01
0.34
0.67
3.89
0.36
1.00
2.02
2.04
0.94
2.13
f1 (ppm)


170.99
170.97
170.74
170.56
136.96
136.35
134.56
134.32
133.63
133.46
117.95
117.54
94.12
94.07
89.66
89.58
78.44
77.16
71.60
70.84
65.94
65.52
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32.17
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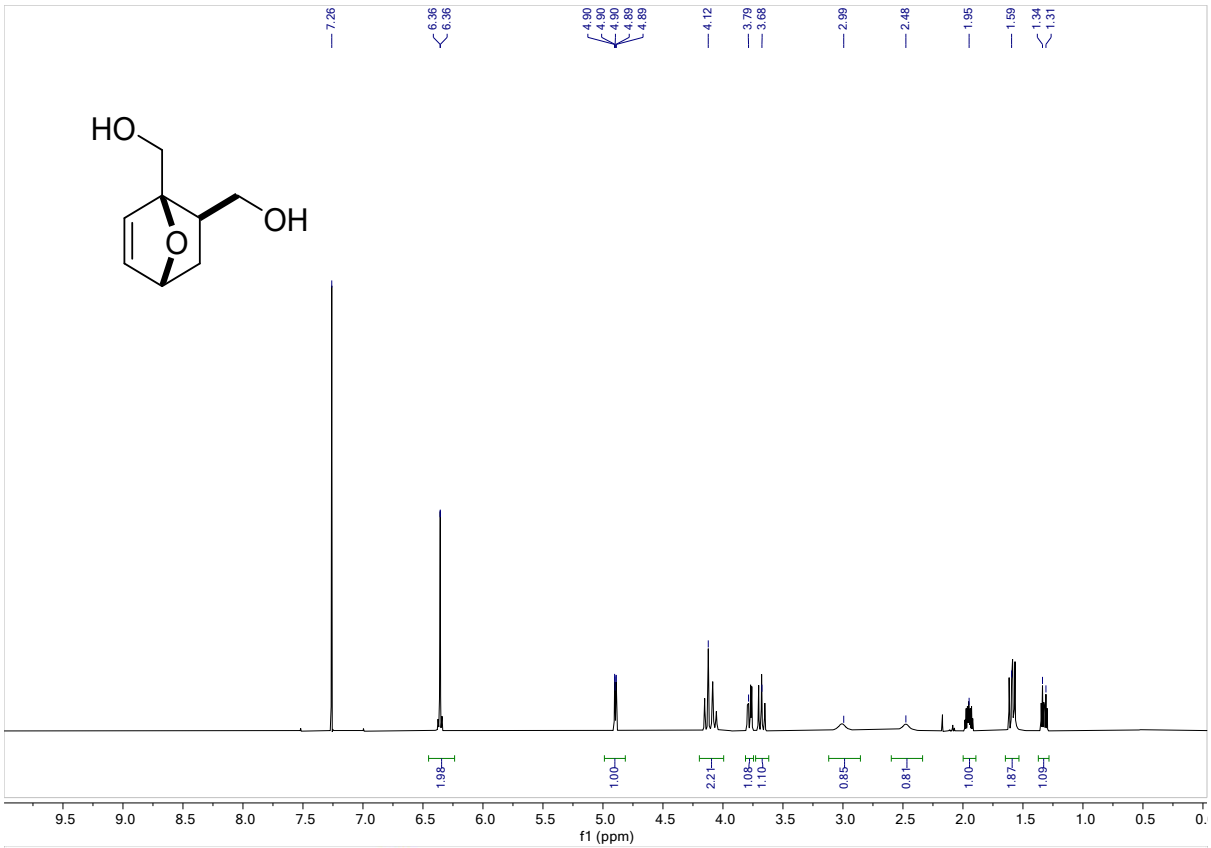
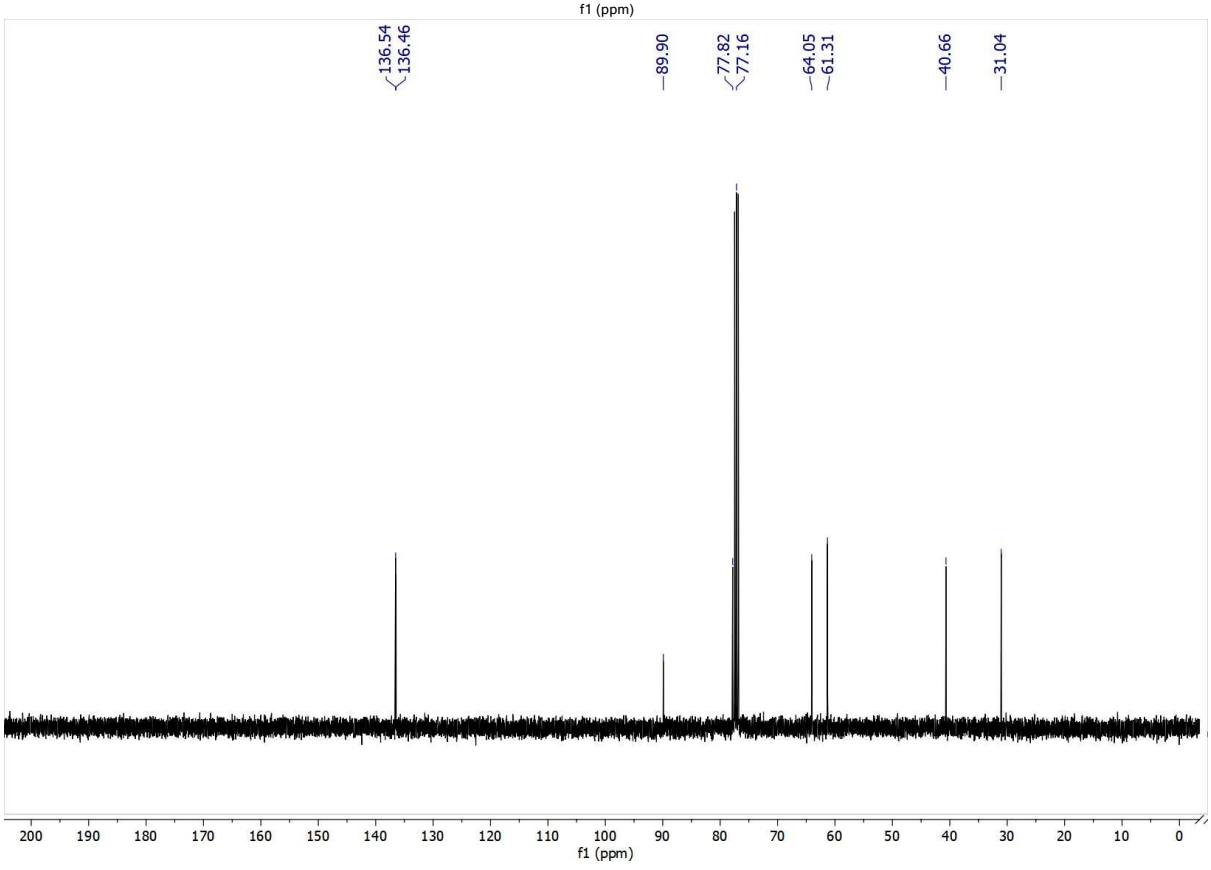
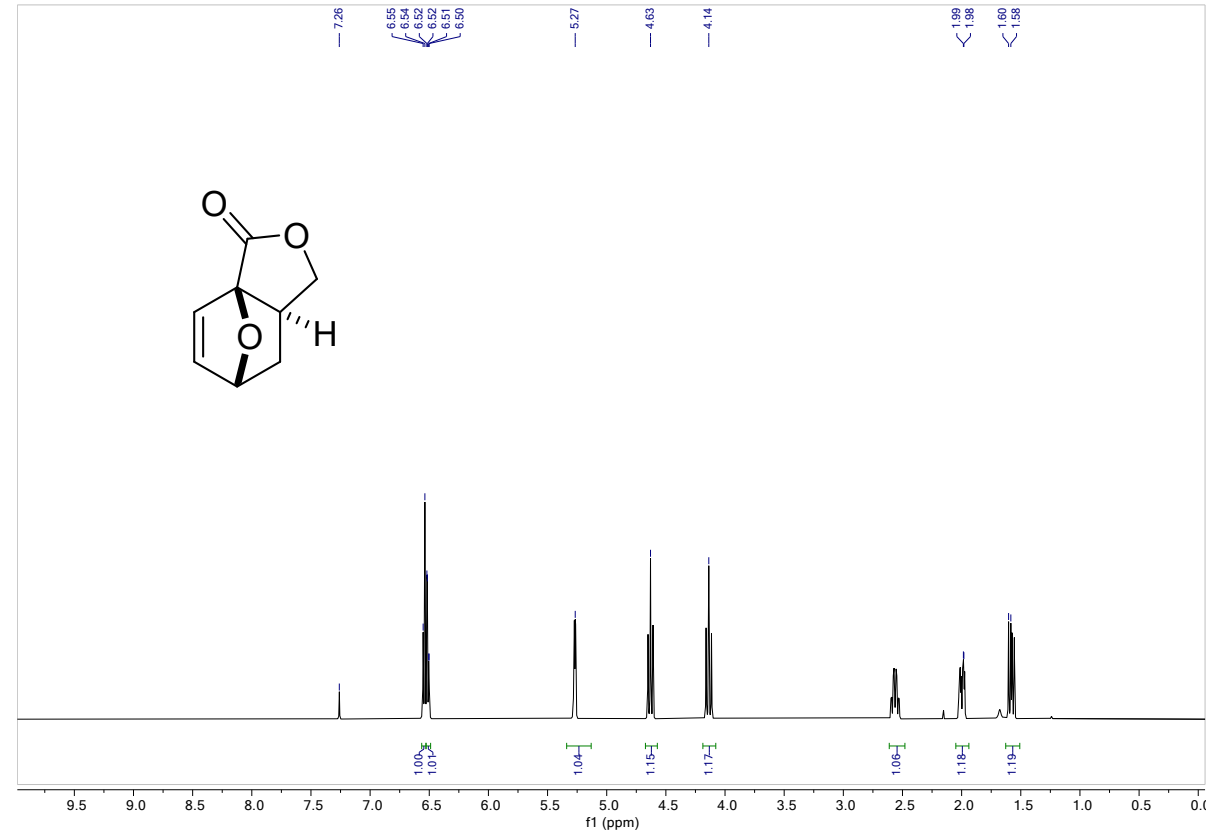
21.16
21.04
20.98
f1 (ppm)

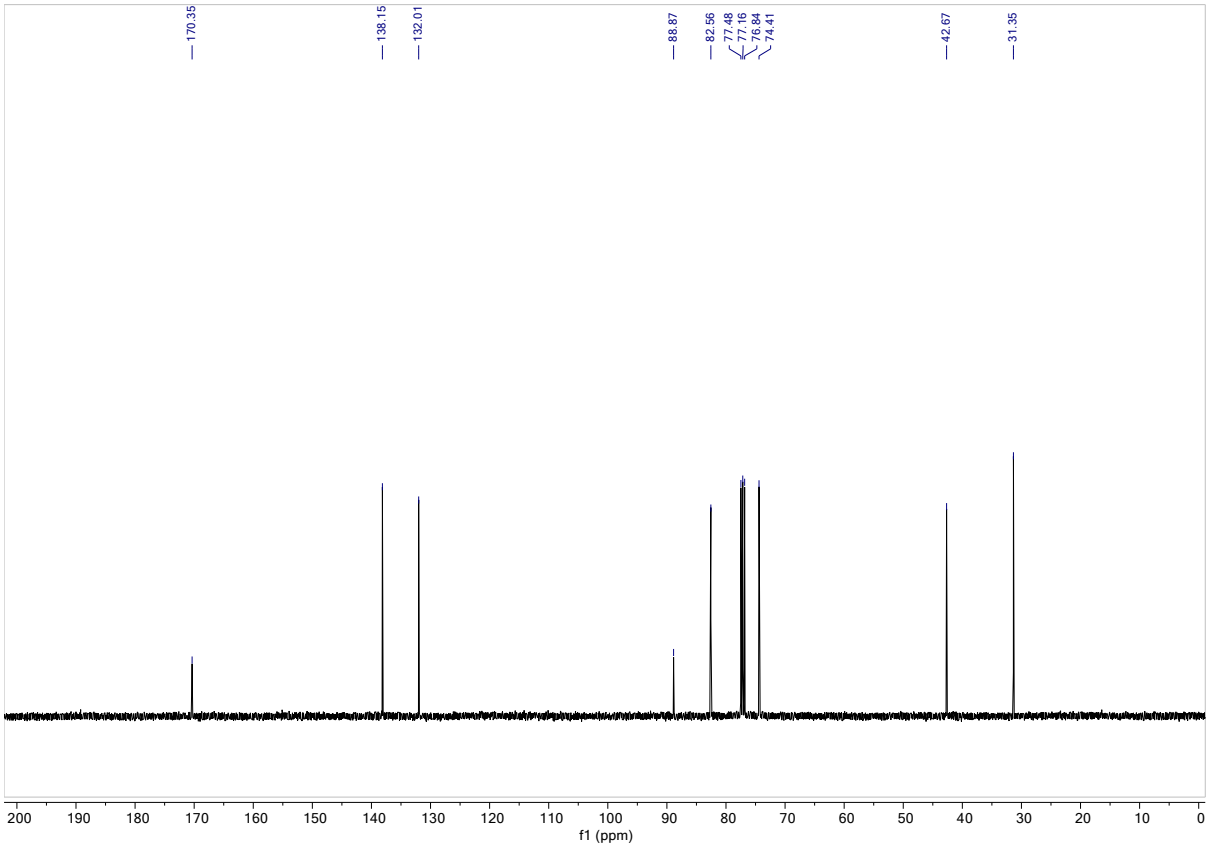
Diol 9


HO
OH
O
7.26
6.36
6.36
4.90
4.90
4.90
4.89
4.89
4.12
3.79
3.68
2.99
2.48
1.95
1.59
1.34
1.31
1.98
1.00
2.21
1.08
1.10
0.85
0.81
1.00
1.87
1.09
f1 (ppm)

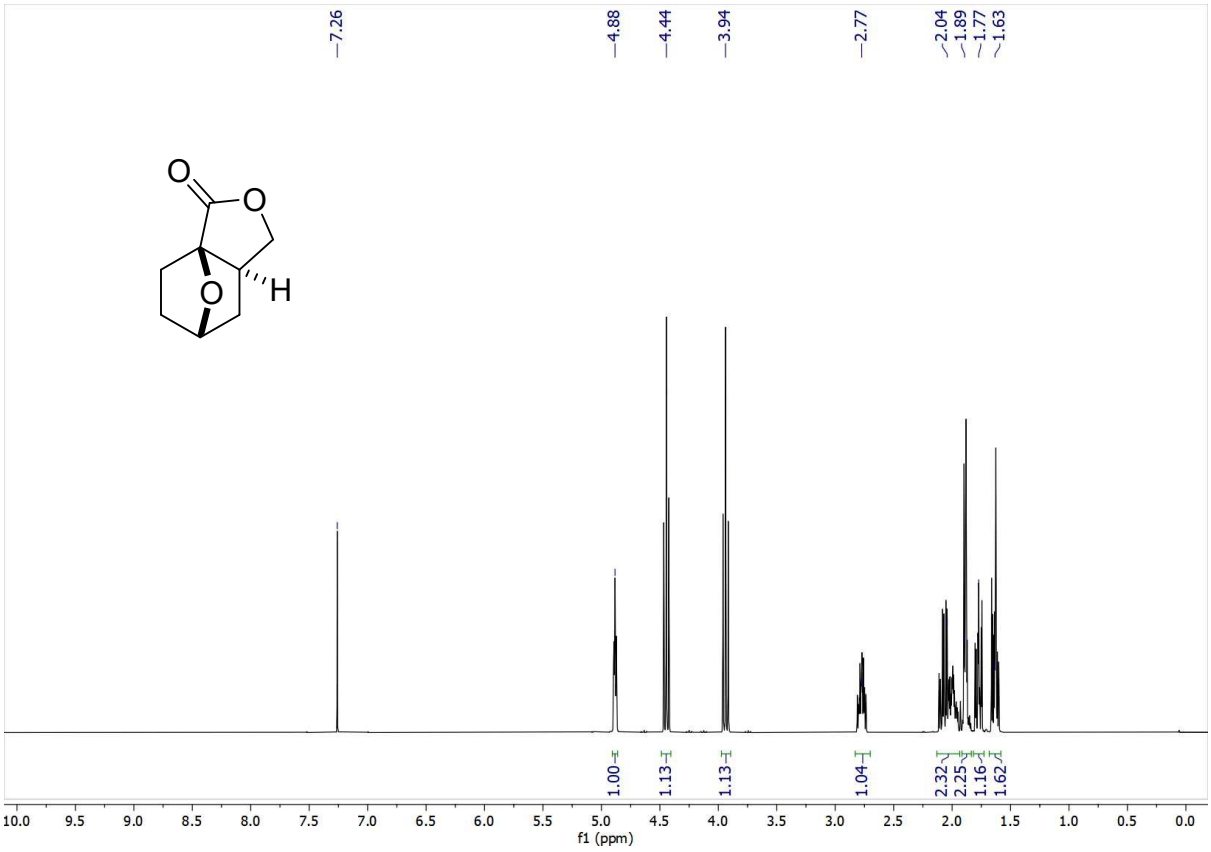

136.54
136.46
89.90
77.82
77.16
64.05
61.31
40.66
31.04
f1 (ppm)

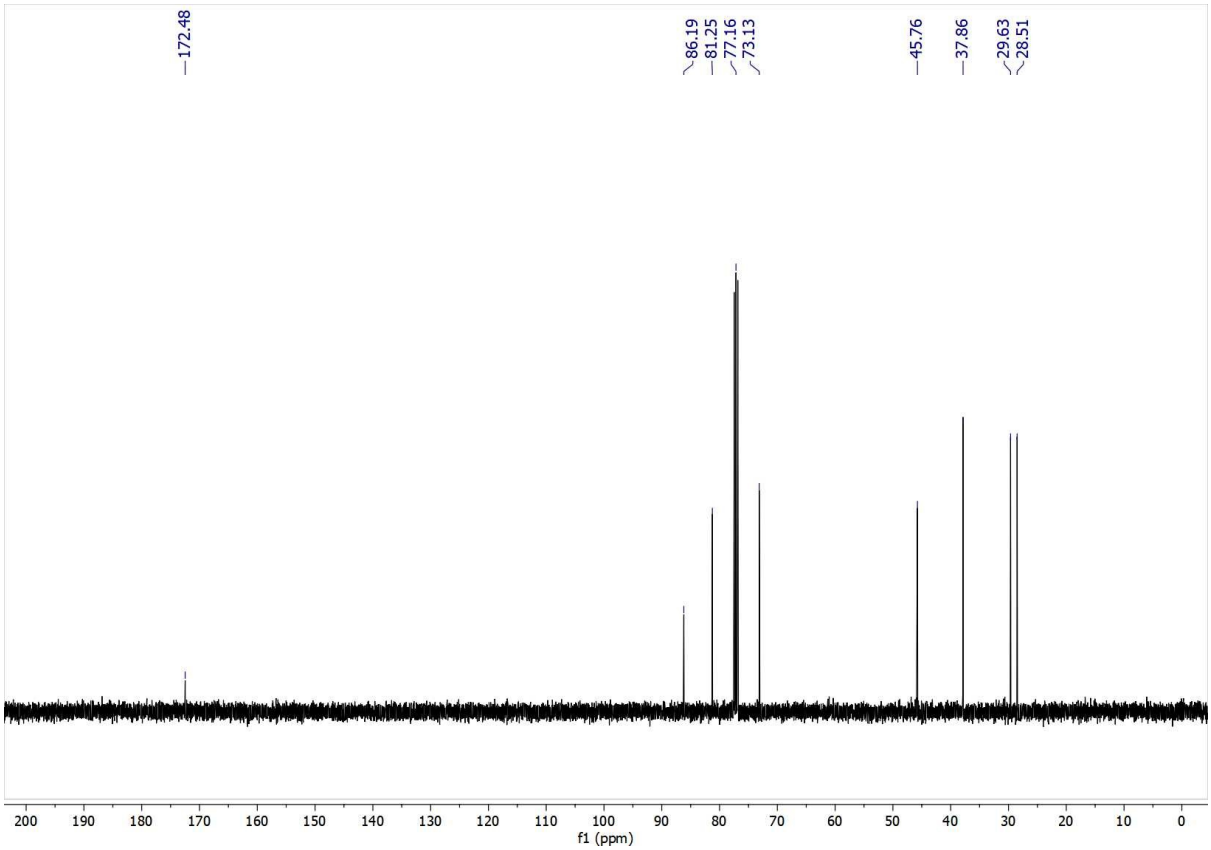
Unsaturated lactone 10



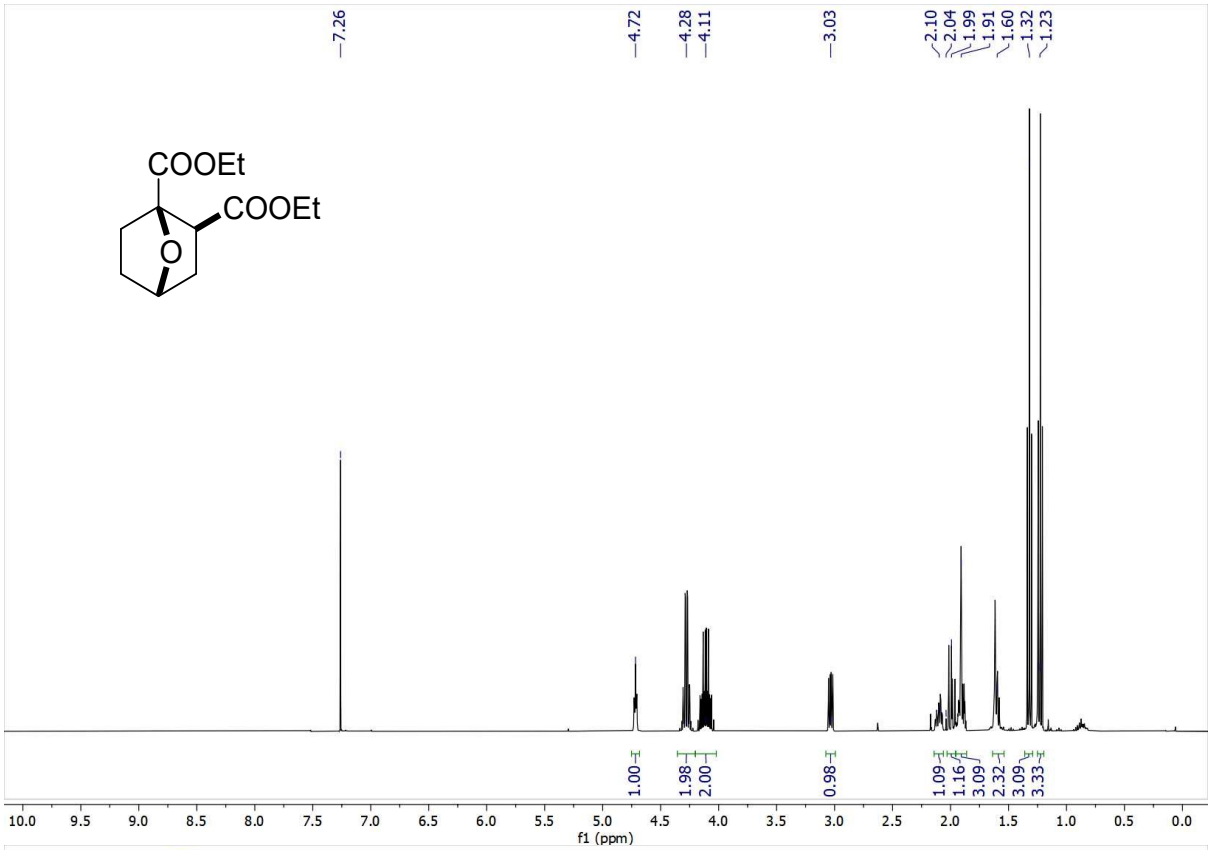


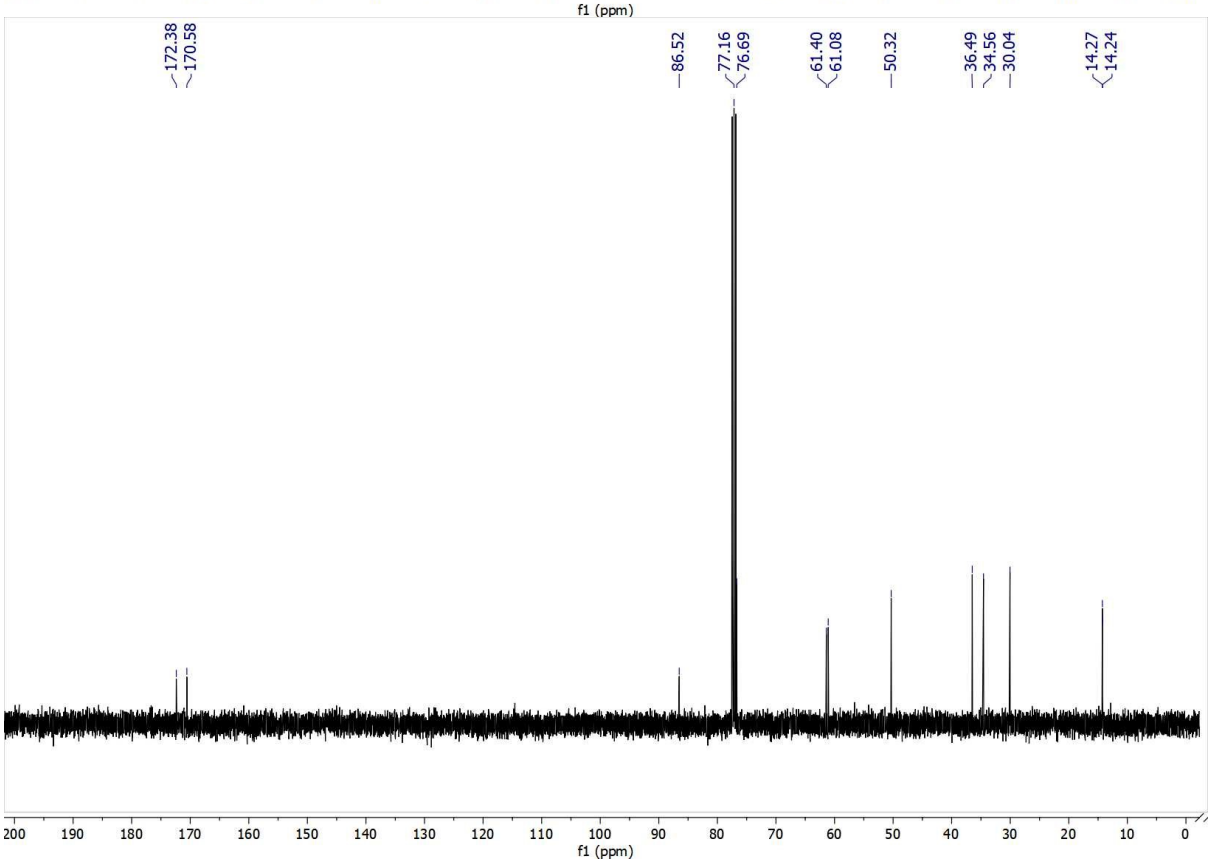
Saturated lactone 11



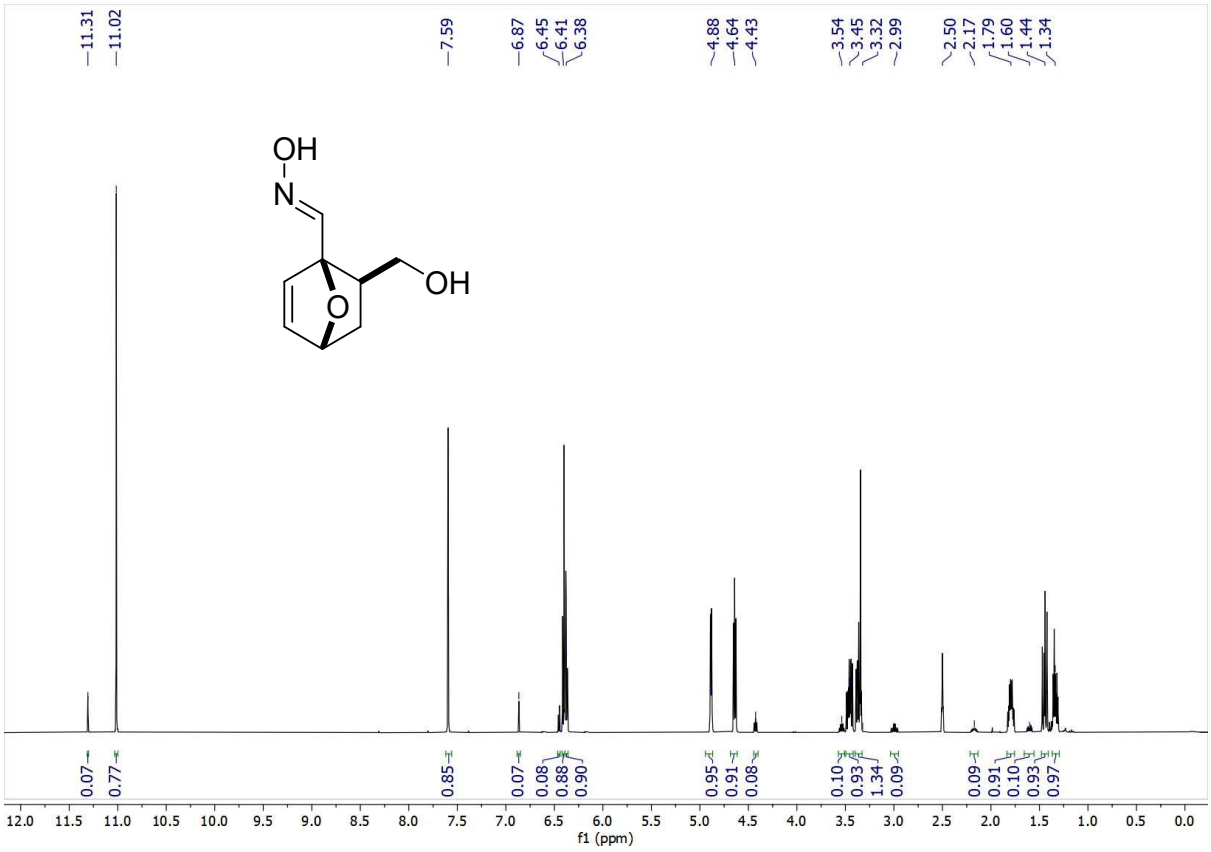


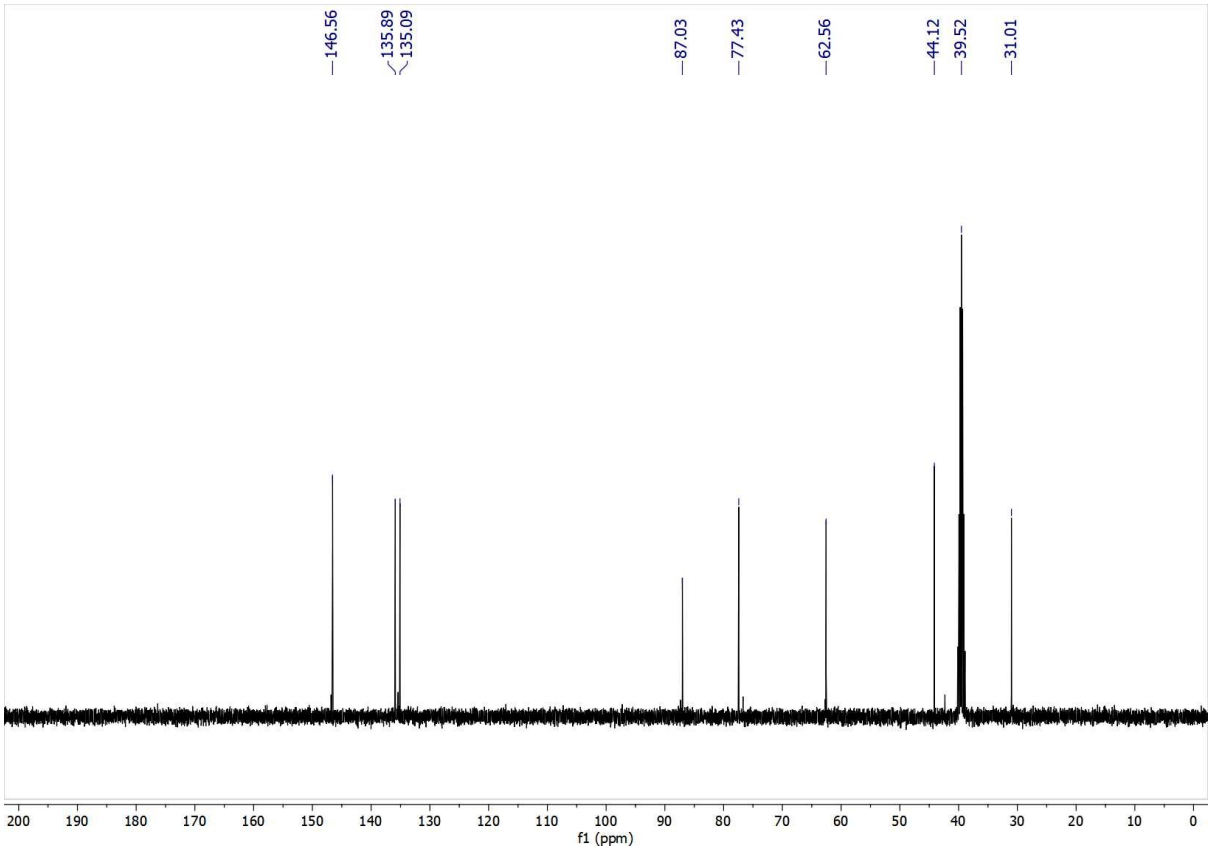
Bisester 12


7.26
4.72
4.28
4.11
3.03
2.10
2.04
1.99
1.91
1.60
1.32
1.23
COOEt
COOEt
O
1.00
1.98
2.00
0.98
1.09
1.16
3.09
2.32
3.09
3.33
f1 (ppm)

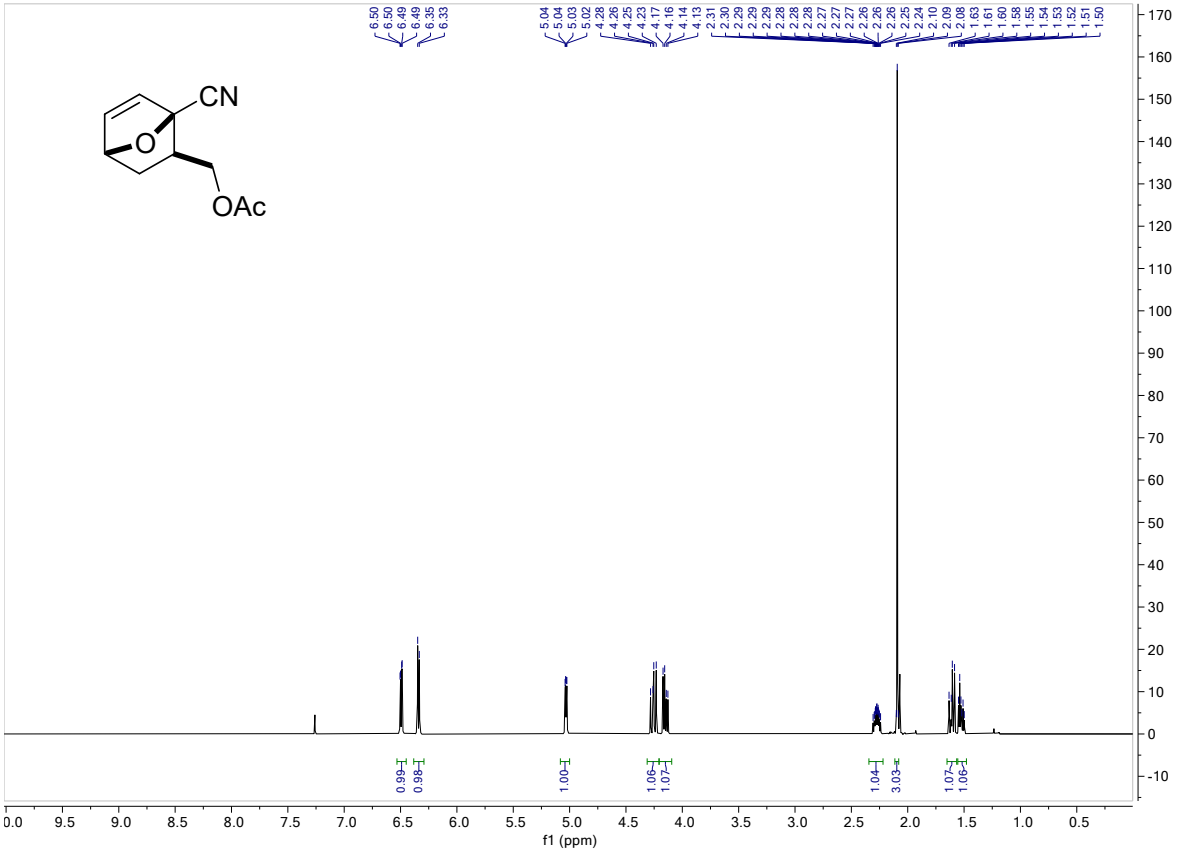

172.38
170.58
86.52
77.16
76.69
61.40
61.08
50.32
36.49
34.56
30.04
14.27
14.24
f1 (ppm)

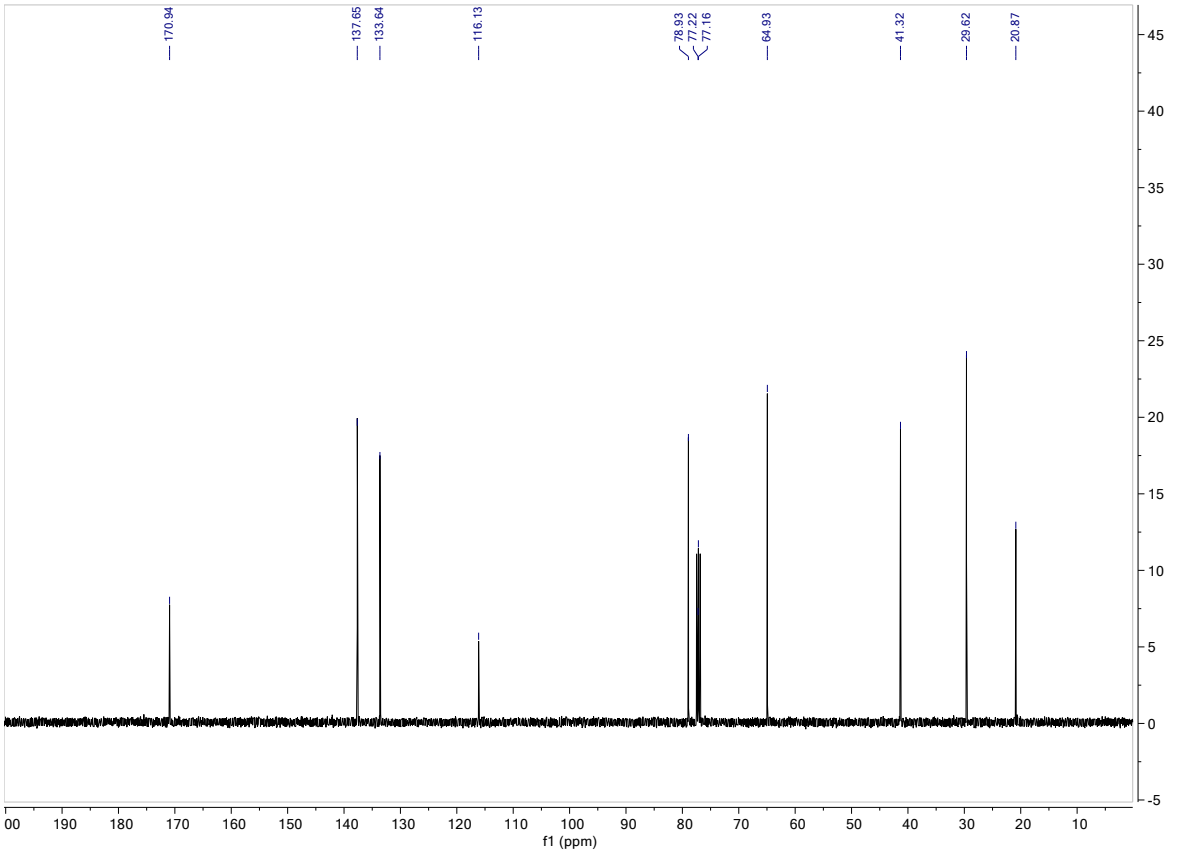
Oxime 13


11.31
11.02
7.59
6.87
6.45
6.41
6.38
4.88
4.64
4.43
3.54
3.45
3.32
2.99
2.50
2.17
1.79
1.60
1.44
1.34
OH
N
OH
O
0.07
0.77
0.85
0.07
0.08
0.88
0.90
0.95
0.91
0.08
0.10
0.93
1.34
0.09
0.09
0.91
0.10
0.93
0.97
f1 (ppm)

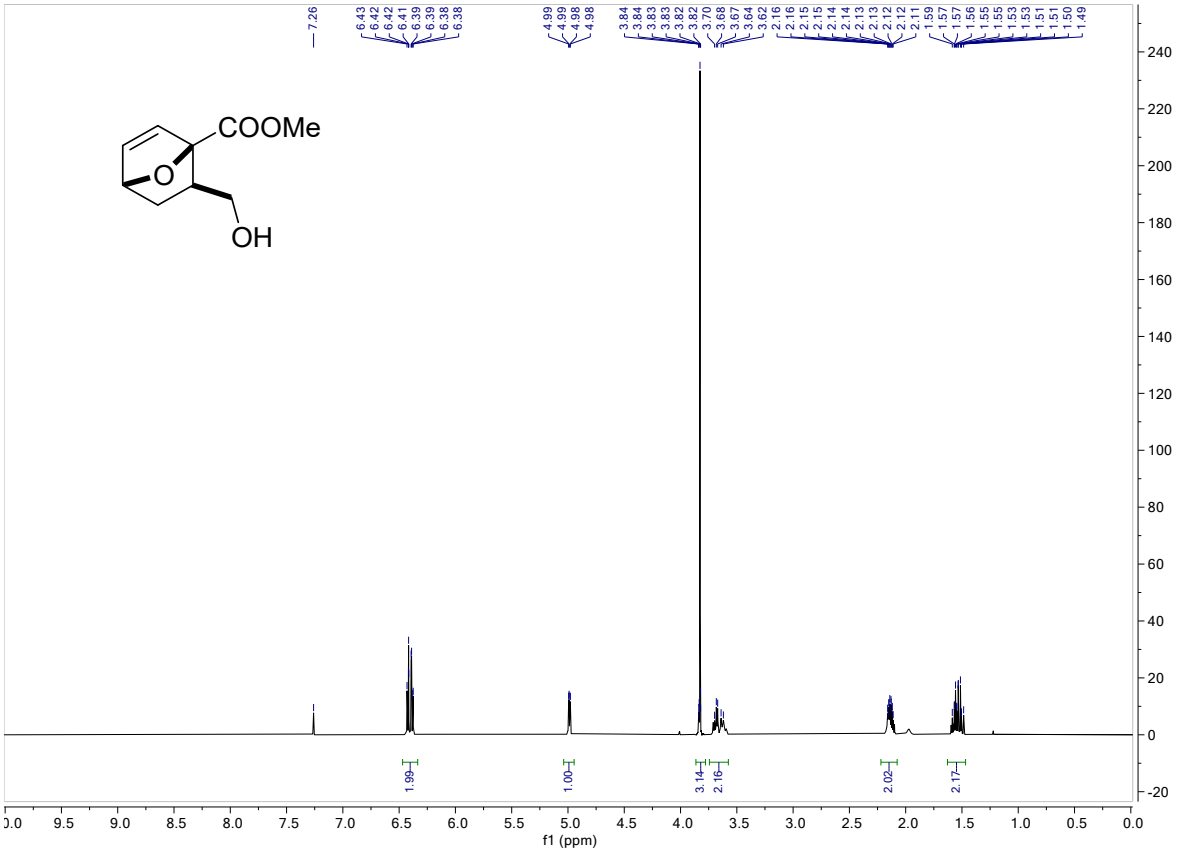

146.56
135.89
135.09
87.03
77.43
62.56
44.12
39.52
31.01
f1 (ppm)

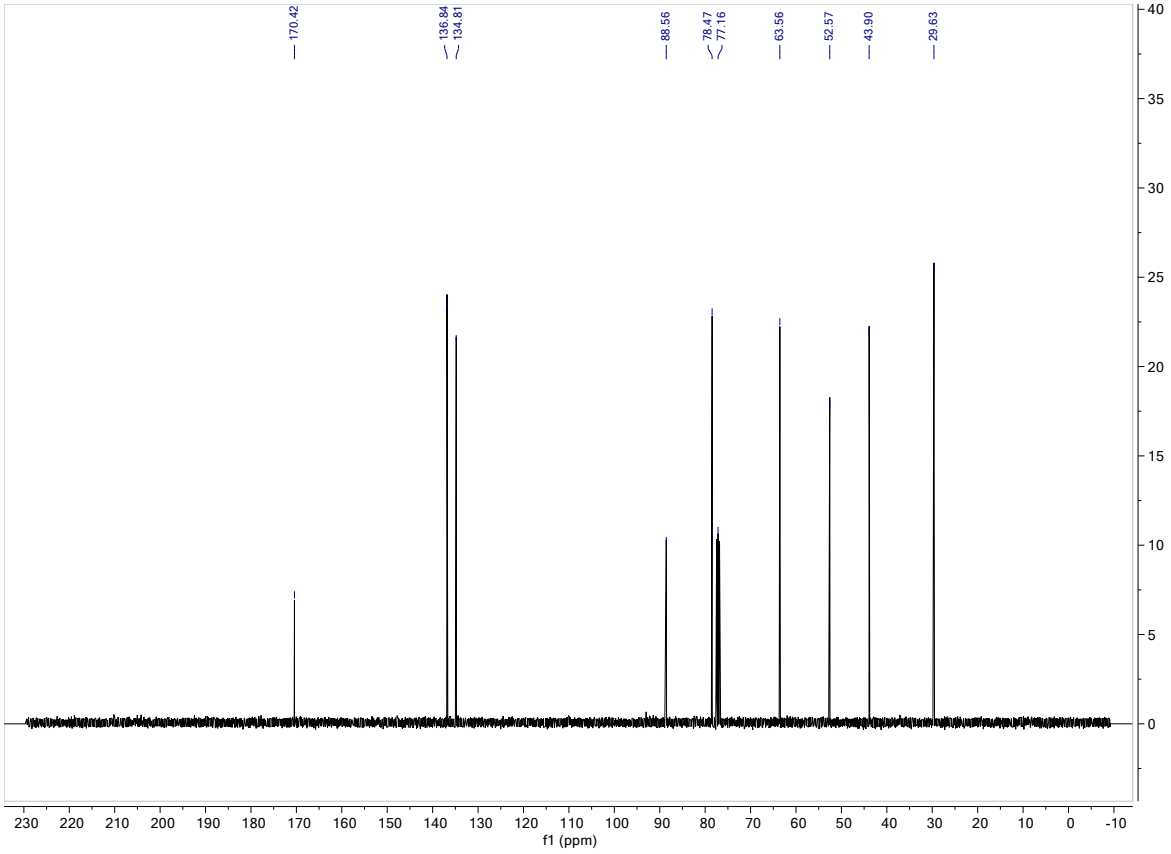
Nitrile 14


CN
O
OAc
f1 (ppm)

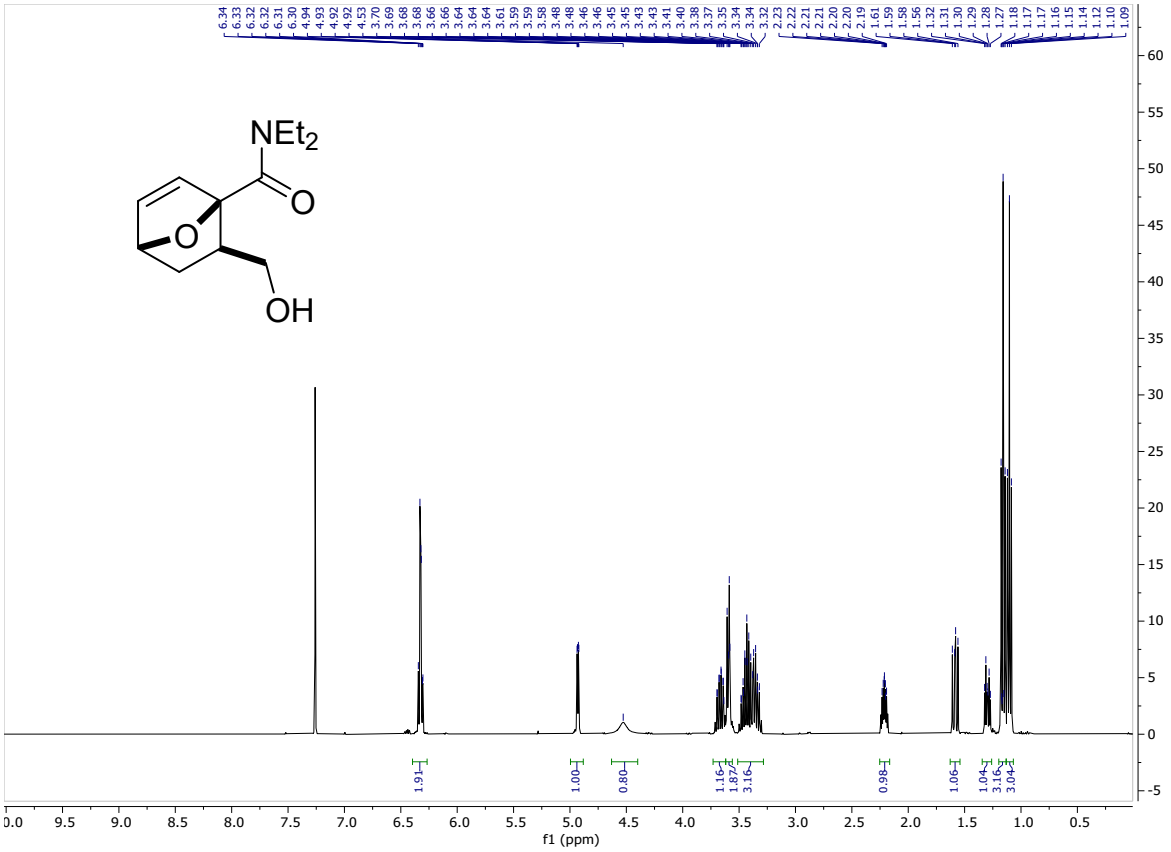

170.94
137.65
133.64
116.13
78.93
77.22
77.16
64.93
41.32
29.62
20.87
f1 (ppm)

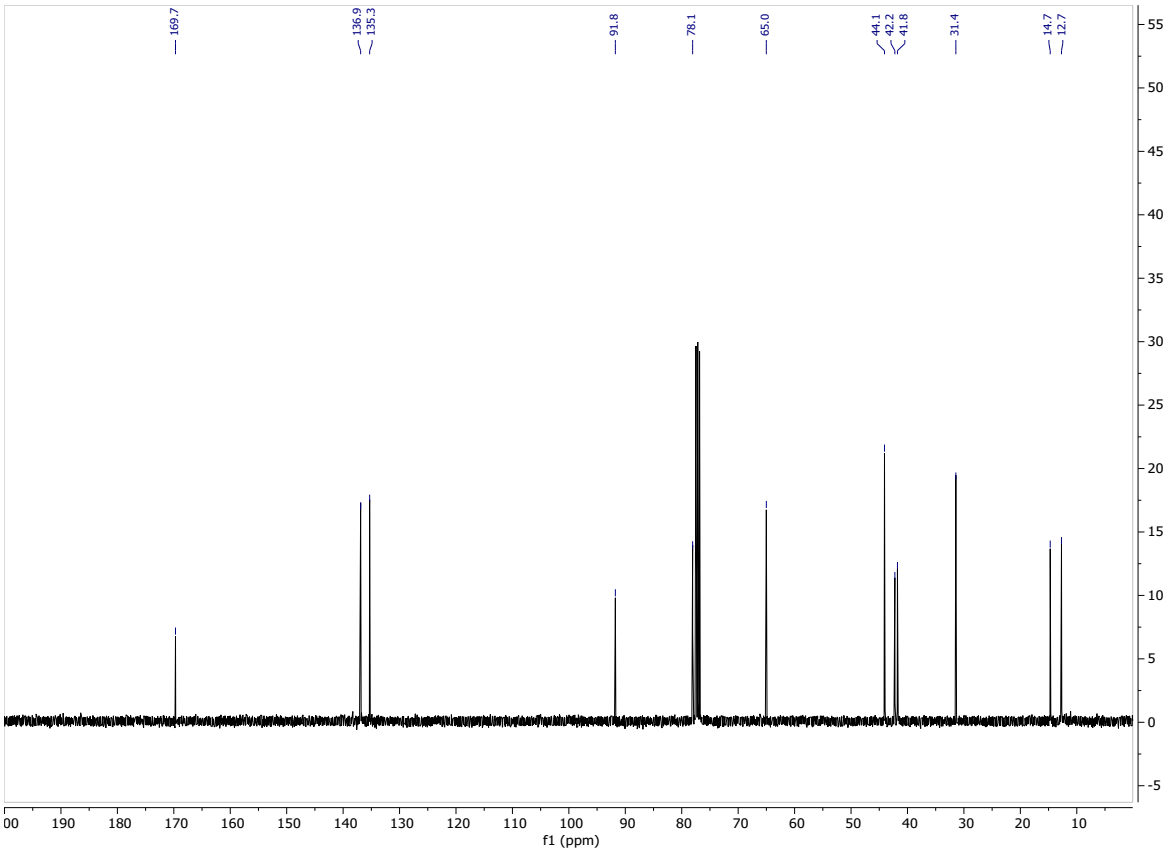
Ester 15


7.26
6.43
6.42
6.42
6.41
6.39
6.39
6.38
6.38
4.99
4.99
4.98
4.98
3.84
3.84
3.84
3.83
3.82
3.82
3.70
3.68
3.67
3.64
3.62
2.16
2.16
2.15
2.15
2.14
2.14
2.13
2.13
2.12
2.12
2.11
1.59
1.57
1.57
1.56
1.55
1.55
1.53
1.53
1.51
1.51
1.50
1.49
COOMe
O
OH
1.99
1.00
3.14
2.16
2.02
2.17
f1 (ppm)

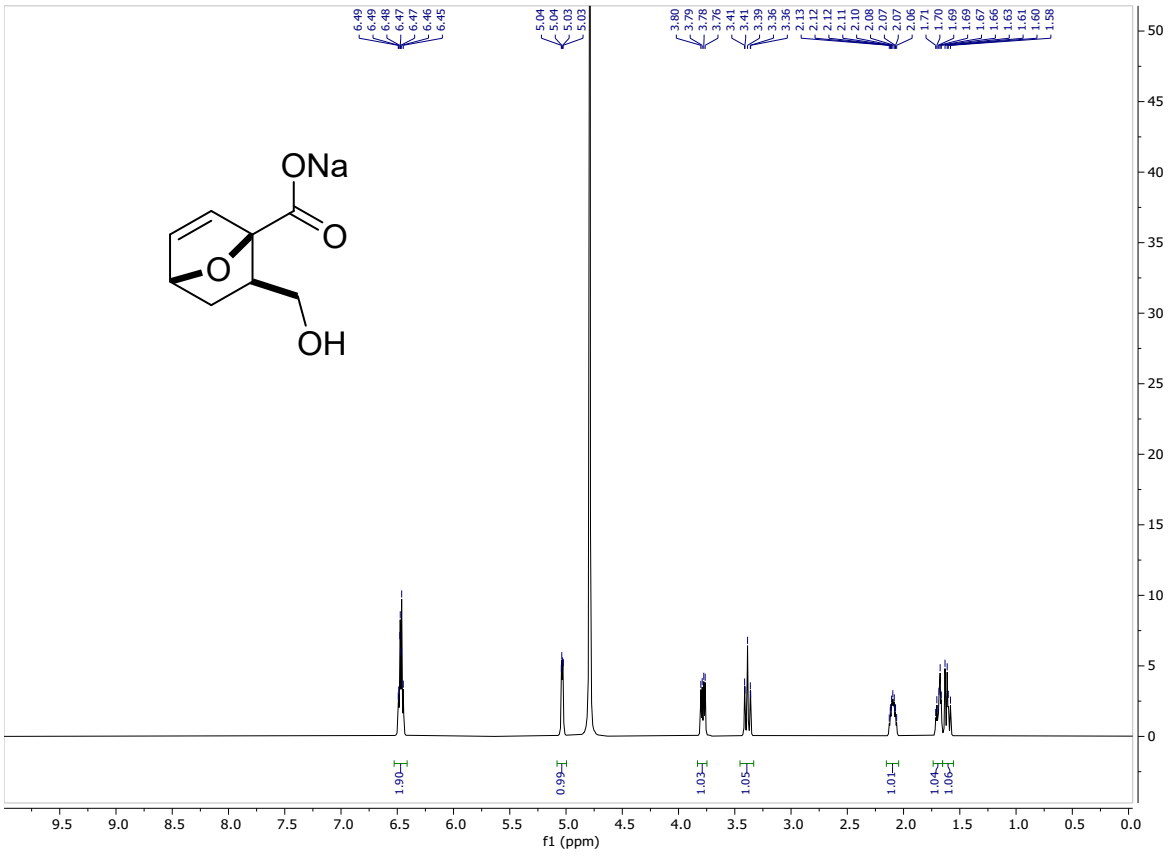


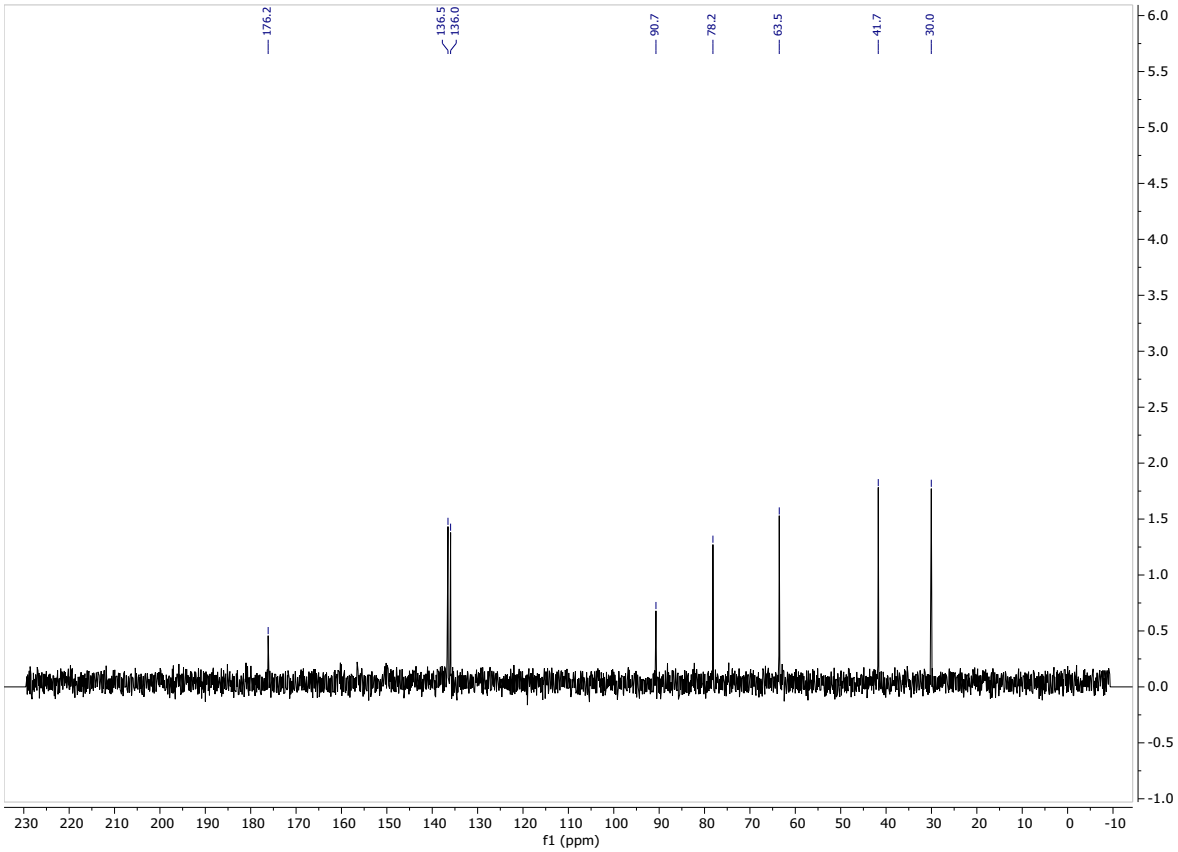
Amide 16


NEt2
O
O
OH
f1 (ppm)


169.7
136.9
135.3
91.8
78.1
65.0
44.1
42.2
41.8
31.4
14.7
12.7
f1 (ppm)

Carboxylate salt 17





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