Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

Dynamic Trapping as a Selective Route to Renewable Phthalide from Biomass-Derived Furfuryl Alcohol

*Christopher S. Lancefield[+], Bart Fölker[+], Razvan C. Cioc, Katarina Stanciakova, Rosa E. Bulo, Martin Lutz, Marc Crockatt, and Pieter C. A. Bruijnincx**

anie_202009001_sm_miscellaneous_information.pdf

Contents

General Considerations

Chemicals

All reagents were purchased from commercial sources and used as received unless stated otherwise. Acryloyl chloride was purchased from Merck; $Sc(OTf)_3$, $Hf(OTf)_4$, 4-nitrophenol from Acros; hexafluoroisopropanol and trifluoroethyl acrylate from Fluorochem; hexafluoroisopropyl acrylate, acryloyl chloride from TCl; furfuryl alcohol, methyl acrylate, methanesulfonic acid, acetic anhydride, $NaHCO_3$, CH_3CO_2Na, $CHCl_2CO_2Na$, tetrahydrofuran (THF), Celite® Hyflo Supercel, triethylamine (Et_3N), nitrobenzene, acetic acid, 5% Pd/C from Sigma-Aldrich; 2,5-bis(hydroxymethyl)furan from Apollo Scientific; dichloromethane (DCM), chloroform ($CHCl_3$), hexanes, ethyl acetate and toluene from InterCheM; petroleum ether from Biosolve Chimie; acetone from VWR Chemicals; $CDCl_3$, DMSO-d_6 from Euriso-top and toluene-d_8 from Cambridge Isotope Laboratories. 4-nitrophenol acrylate was prepared as previously reported.[1]

Analysis methods

NMR: ^1H and ^{13}C NMR data was 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. Chemical shifts are reported in ppm relative to the residual solvent peak (7.16/77.16 ppm for $CDCl_3$). ^1H, ^{13}C, COSY, HSQC and HMBC experiments used the standard pulse sequences available in VNMRJ 4.2. For quantitative ^1H NMR the relaxation delay was set to 25 seconds and the pulse tip angle to 90°.

GC-MS: measurements were performed on a Shimadzu GC-2010 using a VF5-ms column (30 mm x 0.25 mm, 0.25 µm) and a medium polarity guard column, coupled to a Shimadzu GCMS-QP2010 mass spectrometer. The GC parameters used were as follows: Injector temperature 265 °C. The initial column temperature was 40 °C which was held for 5 mins, then increased to 280 °C with a heating rate of 10 °C/min, and then held at that temperature for 5 mins. All samples were dissolved in chloroform and the injected volume was 0.1 µL.

High resolution ESI TOF-MS$^+$: were measured on a Waters LCT Premier XE KE317 Micromass Technologies spectrometer in acetonitrile at 80 °C; ESI-MS: measured on an Advion Expression CMS spectrometer (acetonitrile).

Single crystal X-ray structure determination: The X-ray diffraction experiment was performed on a Bruker Proteum diffractometer with rotating anode and Helios optics (λ = 1.54184 Å) at a temperature of 150(2) K up to a resolution of $(\sin\theta/\lambda)_{max}$ = 0.59 Å^{-1}. The Eval15 software[2] was used for the intensity

integration. A multiscan absorption correction and scaling was performed with SADABS[3] (correction range 0.59-0.75). The structure was solved with Patterson superposition methods using SHELXT.[4] Least-squares refinement was performed with SHELXL-2018[5] against 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. Geometry calculations and checking for higher symmetry was performed with the PLATON program.[6]

Computational Methods

DFT calculations

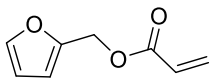
The ADF modeling suite by SCM[7,8] was used for calculating the energies and geometries of the substrates, transition states and products. For all the calculations, the hybrid B3LYP-D3[9,10] XC functional was used together with the TZ2P[11] basis set. This functional and basis set are commonly used for calculations on organic molecules.[12,13] All structures drawn in the graphical user interface were first pre-optimized using the Universal Force Fields (UFF) method,[14] before performing the actual geometry optimization with the above mentioned XC functional and basis set. The optimized geometry was used to calculate the harmonic frequencies in order to obtain the Gibbs free energy of each of the geometries. Frequencies are calculated numerically with the Becke Grid quality set to Good, and thermodynamic corrections were computed at 323 K. All calculations were performed in vacuum. Optimized Cartesian coordinates and energies for investigated structures are given at the end of this document.

Geometry optimization

For calculating the geometry of the global minimum conformer of furfuryl acrylate (**3**), possible conformers of the substrate were generated using the built-in conformer generator. The five conformers with the lowest energy were then geometry optimized, using the appropriate XC functional. The optimised conformer with the lowest electronic internal energy (Uel) was then chosen as the global minimum substrate. The intramolecular DA products of furfuryl acrylate do not have this conformational freedom and thus only require UFF pre-optimization and XC-functional optimization. The geometry of the reactive conformer needed for the intramolecular DA reaction was generated from the corresponding intramolecular DA product by removing/adding the appropriate carbon bonds to reform the substrate. This geometry was than UFF pre-optimized and subsequently XC-functional geometry optimized. In order to find the geometry of the transition state, first an approximate transition state was searched for, using the linear transit method and then optimized by performing a transition state search.[15,16]

Synthesis

Furfuryl acrylate (**3**)

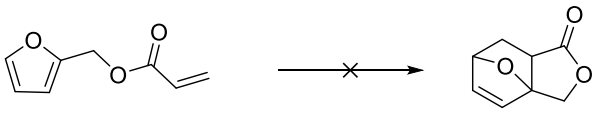


A solution of furfuryl alcohol (**2**)(10.0 g, 102 mmol, 1.00 eq.) and Et_3N (12.9 g, 127 mmol, 1.25 eq.) in DCM (175 mL) was cooled to 0 °C. Acryloyl chloride (10.14 g, 112 mmol, 1.10 eq.) was added dropwise to the solution over 10 mins and then the mixture was stirred for 2 hours before being allowed to warm to RT. The reaction was quenched by the addition of water (200 mL) and brought to pH <7 using 1 M HCl. The organic layer was separated, washed with *aq.* $NaHCO_3$, brine (2 x 200 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield furfuryl acylate (**3**) as an amber liquid (14.7 g, 94%), which was stored at 4 °C before use.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, J = 2.8, 1.9 Hz, 1H), 6.47 – 6.45 (m, 1H), 6.42 (dd, J = 6.0, 2.1 Hz, 1H), 6.38 – 6.34 (m, 1H), 6.19 – 6.09 (m, 1H), 5.84 (dt, J = 10.4, 2.1 Hz, 1H), 5.15 (s, 2H). NMR results were consistent with literature.[17]

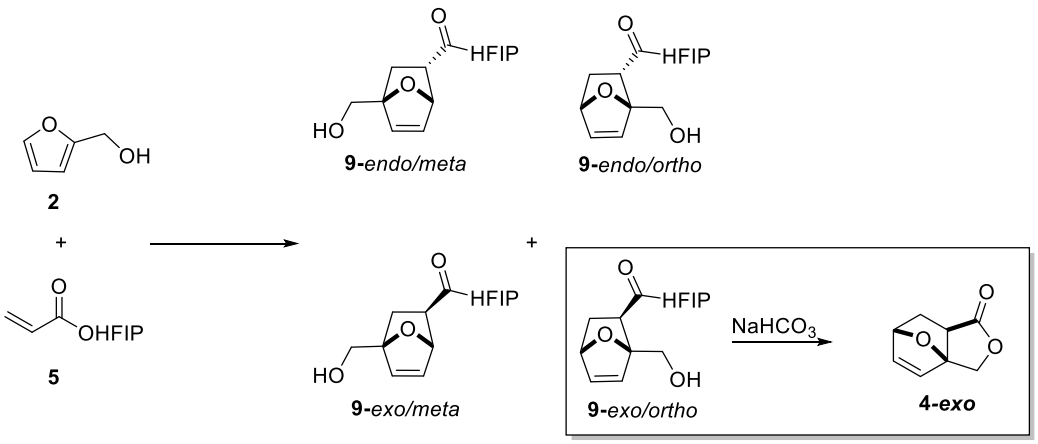
Note: on prolonged storage at RT **3** partially polymerises, apparently via an intermolecular Diels-Alder reaction, as judged by NMR and GPC analysis (data not shown).

Attempted intramolecular Diels-Alder reaction



According to Torosyan *et al.*[18] furfuryl acrylate (**3**) (1.0 g) was precipitated on 'Celite® Hyflo Supercel' (5.0 g) (diatomaceous earth) by dissolving in CH_2Cl_2, slurrying and concentrating under reduced pressure. This powdery mixture was then heated at 80 °C for 56 hours. Extraction of the product with $CDCl_3$ and subsequent NMR analysis indicated that the starting material was recovered unchanged.

Diels-Alder reaction of furfuryl alcohol and HFIP-acrylate to produce DA adduct 9



A solution of furfuryl alcohol (**2**) (4.42 g, 45.0 mmol, 1.00 eq.) and hexafluoroisopropyl acrylate (**5**) (10.0 g, 45.0 mmol, 1.00 eq.) was stirred overnight at RT. The mixture was concentrated under reduced pressure to yield the crude DA products, containing a mixture of 4 Diels-Alder adducts (**9**) and smaller amounts of furfuryl alcohol (**2**), as an amber liquid (7.2 g). Characteristic NMR peaks used for distinguishing the 4 different cycloadducts were: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (ddd, J = 8.8, 4.6, 3.9 Hz, 1H, *endo/meta*), 3.30 (dd, J = 9.2, 3.6 Hz, 1H, *endo/ortho*), 2.76 (dd, J = 8.4, 3.8 Hz, 1H, *exo/meta*), 2.68 (dd, J = 8.1, 4.1 Hz, 1H, *exo/ortho*). The cycloadducts could not be fully separated by column chromatography and underwent retro-Diels-Alder reaction when submitted to GC-MS conditions. To provide further validation for the formation of the 4 expected adducts a portion of the crude mixture was hydrogenated and analysed by GC-MS as follows.

A suspension of Diels-Alder adducts (0.10 g) and Pd/C (1.5 mg, 5 wt% metal on carbon) in THF (5 mL) was degassed under vacuum for 5 min. A H_2 balloon was then attached and the mixture allowed to stir vigorously overnight at RT. The mixture was then filtered, and the filtrate concentrated under reduced pressure. The resulting product was analysed by GC-MS allowing for the identification of 4 characteristic peaks: 14.87 min (m/z = 322), 15.22 min (m/z = 322), 15.65 min (m/z = 322) and 17.72 (m/z = 154) min (Figure S1). A m/z = 322 is consistent with the expected adducts, whilst a m/z = 154 indicates a loss of HFIPOH from one of the adducts (lactonization).

Treatment of a portion of the neat crude product with $NaHCO_3$ (20 mol% assuming pure mixture of cycloadducts) caused the selective conversion of the *exo*/*ortho* isomer into a new product assigned as the lactone **4-exo** (Figure S2) and confirmed by single crystal X-ray diffraction studies (Figure S3).

General Procedures

Optimisation of the preparation of 4-exo (Table 1)

To furfuryl alcohol (**2**) (2 mmol, 1 eq.) and the selected acrylate (2 mmol, 1 eq., unless stated otherwise) in a glass vial (8 mL) was added nitrobenzene (*ca.* 62 mg, 0.5 mmol, 0.25 eq.) as an internal standard (IS). The components were quickly mixed and a sample (20 µL) was taken for immediate quantitative ^{1}H NMR analysis to serve as t=0 hours. The desired base was then added, the vial was tightly sealed, and the reaction mixture heated at the specified temperature, with stirring, in an aluminium heating block. The crude mixture was directly analysed by quantitative ^{1}H NMR after 22 hrs.

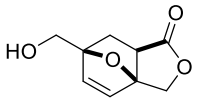
Preparative scale synthesis:

Furfuryl alcohol (**2**) (4.42 g, 45 mmol, 1 eq.), hexafluoroisopropyl acrylate (**5**) (11.0 g, 50.0 mmol, 1.10 eq.) and $NaHCO_3$ (0.04 g, 0.45 mmol, 1 mol %) were stirred at 80 °C for 22 hrs. The crude product was purified by silica gel column chromatography (10-30% EtOAc/hexanes) to give **4-*exo*** as an oil which rapidly crystallised to give off-white crystals (2.53 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 – 6.42 (m, 2H), 5.12 (d, J = 4.6 Hz, 1H), 4.77 (d, J = 11.0 Hz, 1H), 4.68 (d, J = 11.0 Hz, 1H), 2.54 (dd, J = 8.8, 3.4 Hz, 1H), 2.26 (ddd, J = 11.9, 4.4, 3.5 Hz, 1H), 1.69 (dd, J = 11.9, 8.8 Hz, 1H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 176.0, 137.6, 131.8, 92.2, 79.5, 69.1 , 45.0, 29.3. HR-MS (ESI) $C_8H_8O_3$ [2M+Na]+ m/z required 327.0796; found 327.0845.

X-ray crystallographic data for 4-exo: $C_8H_8O_3$, Fw = 152.14, colourless block, 0.36 × 0.23 × 0.10 mm^3, orthorhombic, Pbca (no. 61), a = 8.87439(11), b = 11.6699(3), c = 13.2000(2) Å, V = 1367.04(4) Å^3, Z = 8, D_x = 1.478 g/cm^3, µ = 0.96 mm^{-1}. 13608 Reflections were measured, 1190 Reflections were unique (R_{int} = 0.044), of which 1137 were observed [I>2σ(I)]. 101 Parameters were refined with no restraints. R1/wR2 [I > 2σ(I)]: 0.0348 / 0.0879. R1/wR2 [all refl.]: 0.0356 / 0.0884. S = 1.074. Extinction parameter EXTI = 0.0037(4). Residual electron density between -0.14 and 0.21 e/Å^3. See Figure S3, Table S2, and Table S3.

CCDC 2006649 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Preparation of 12-exo (Table 1)



2,5-Bis(hydroxymethyl)furan (**10**) (640 mg, 5.0 mmol, 1 eq.), hexafluoroisopropyl acrylate (**5**) (1221 mg, 5.5 mmol, 1.10 eq.) and $NaHCO_3$ (4.2 mg, 0.05 mmol, 1 mol %) were stirred at 80 °C for 22 hrs. The crude product was purified by silica gel column chromatography (50-66% EtOAc/petroleum ether) to give **12-*exo*** as a yellow oil (456 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) 6.51 (d, J = 6.0 Hz, 1H), 6.44 (d, J = 6.0 Hz, 1H), 4.74 (d, J = 10.8 Hz , 1H), 4.66 (d, J = 10.8 Hz , 1H), 4.09 (d, J = 12.5 Hz, 1H), 4.00 (d, J = 12.5 Hz , 1H), 2.67 (dd, J = 8.5, 3.5 Hz, 1H), 2.17 (br, 1H), 2.14 (dd, J = 12.0, 3.5 Hz, 1H), 1.69 (dd, J = 12.0, 8.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 138.1, 133.2, 92.5, 92.4, 69.3, 62.4, 47.4, 30.5. MS (ESI) $C_{18}H_{20}O_8$ [2M+Na]+ m/z required 387.1; found 387.1.

Optimisation of the aromatization of 4-exo (Table 2)

Neat reactions and those run with non-deuterated solvents: A solution of **4-*exo*** (33 mg, 0.22 mmol) and nitrobenzene (*ca*. 6.7 mg, 0.06 mmol, 0.25 eq.) in $CDCl_3$ (1 mL) was stirred for 1 min and then the mixture was analysed by quantitative ^{1}H NMR to serve as t=0 hrs. The mixture was then quantitatively transferred to a glass vial and the $CDCl_3$ was evaporated briefly under reduced pressure. Optionally a non-deuterated solvent was then added. The mixture was then cooled to 0 °C and a premixed solution of Ac_2O/acid or just acid was then added, the vial tightly sealed, and the mixture warmed or heated to 20/80 °C as specified. A dark colour quickly developed during the reaction.

Reactions run in deuterated solvents: A solution of **4-*exo*** (33 mg, 0.22 mmol) and nitrobenzene (*ca*. 6.7 mg, 0.06 mmol, 0.25 eq.) in the chosen NMR solvent (1 mL) was stirred for 1 min and then the mixture was analysed by quantitative ^{1}H NMR to serve as t=0 hrs. The mixture was then quantitatively transferred to a glass vial and cooled to 0 °C. The chosen acid was then added, the vial tightly sealed, and the mixture heated to 80 °C as specified. A dark colour quickly developed during the reaction.

Reaction mixtures were analysed by quantitative ^{1}H NMR after 2 hrs at 80 ºC or 22 hrs at 20 °C (RT).

Study of the effect of water: the above procedure was modified as such: water (2 eq.) was added to the solution of **4-*exo*** in the specified solvent prior to the addition of the TfOH (10 mol-%). Reaction mixtures were then stirred at 80 ºC as indicated in the table below and analysed by quantitative ^{1}H NMR.

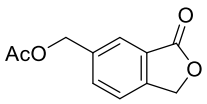
Table S1 Study of the effect of water on the aromatization of **4-*exo***

Entry	Solvent	Time (hrs)	Conversion/Yield (%)		Selectivity (%)	
			Dry	'Wet'[a]	'Wet'[a]	'Wet'[a]
1	$CDCl_3$	1	100/72	94/55	72	59
2	1,4-dioxane	1	90/55	57/13	61	23
	1,4-dioxane	2	98/62	85/21	63	25
	1,4-dioxane	3	100/63	94/27	63	29
3	CH_3COOH	1	100/74	98/40	74	41

[a] Reactions performed in the presence of 2 eq. of water.

Intermediates during the aromatization reaction: A solution of Ac_2O (300 mg, 2.94 mmol, 4.0 eq.) and methanesulfonic acid (MSA) (35 mg, 0.37 mmol, 0.5 eq.) was stirred for 5 min at RT. The mixture was then cooled to 0 °C and **4-*exo*** (112 mg, 0.74 mmol, 1.00 eq.) was added with stirring. After 1 hr at 0 °C the mixture was left to stand in the fridge overnight (4 °C). The reaction was quenched by addition of powdered $NaHCO_3$ (1 g), diluted with $CHCl_3$ (20 mL) and then filtered. The filtrate was washed with water (2 x 20 ml), brine (2 x 20 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The products were partially purified by silica gel column chromatography (5-30% EtOAc/hexanes) to give a mixture of 2 partially aromatized products which were partially characterised by NMR (Figures S12-14).

Aromatization of 12-exo to 13



Methanesulfonic acid (32.6 µL, 0.5 mmol, 0.5 eq.) was added to Ac_2O (378 µL, 4 eq.). This solution was stirred at ambient temperature for 10 min before being added to a mixture of **12-*exo*** (182 mg, 1 mmol, 1 eq.) and Ac_2O (179 µL, 2 eq.). Upon addition, the mixture turned black. Additional Ac_2O (179 µL, 2 eq.) was used as rinse. The mixture was then heated at 80 °C for 17 hours. The reaction was then allowed to cool to ambient temperature and quenched with NEt_3 (35 µL, 0.5 equiv). The crude product was purified by silica gel column chromatography (12-25% acetone/petroleum ether) to give **13** as a white solid (123 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) 7.90 (d, J = 1.6 Hz, 1H), 7.66 (dd, J = 7.5, 1.6 Hz, 1H), 7.49 (d, J = 7.5 Hz, 1H), 5.32 (s, 2H), 5.19 (s, 2H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 170.8, 146.5, 137.8, 133.9, 126.4, 125.1, 122.5, 69.7, 65.3, 21.0.

Supplementary Figures and Tables

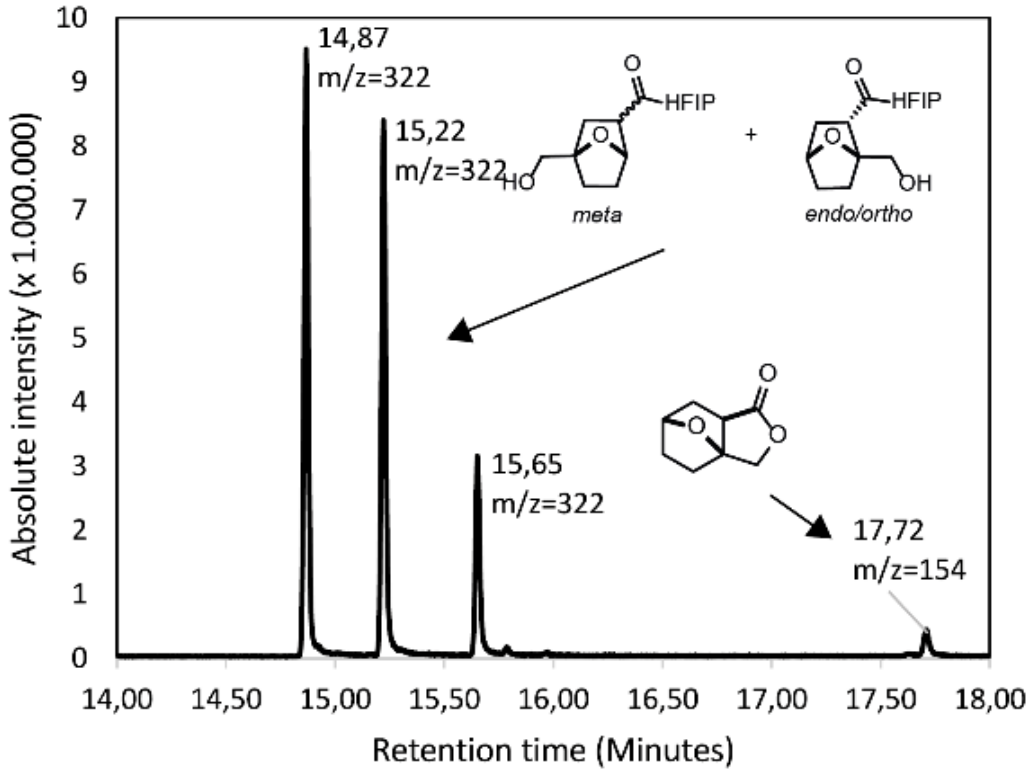


Figure S1 GC-MS analysis of the hydrogenated Diels-Alder adducts obtained from the reaction of furfuryl alcohol and hexafluoroisopropyl acrylate.

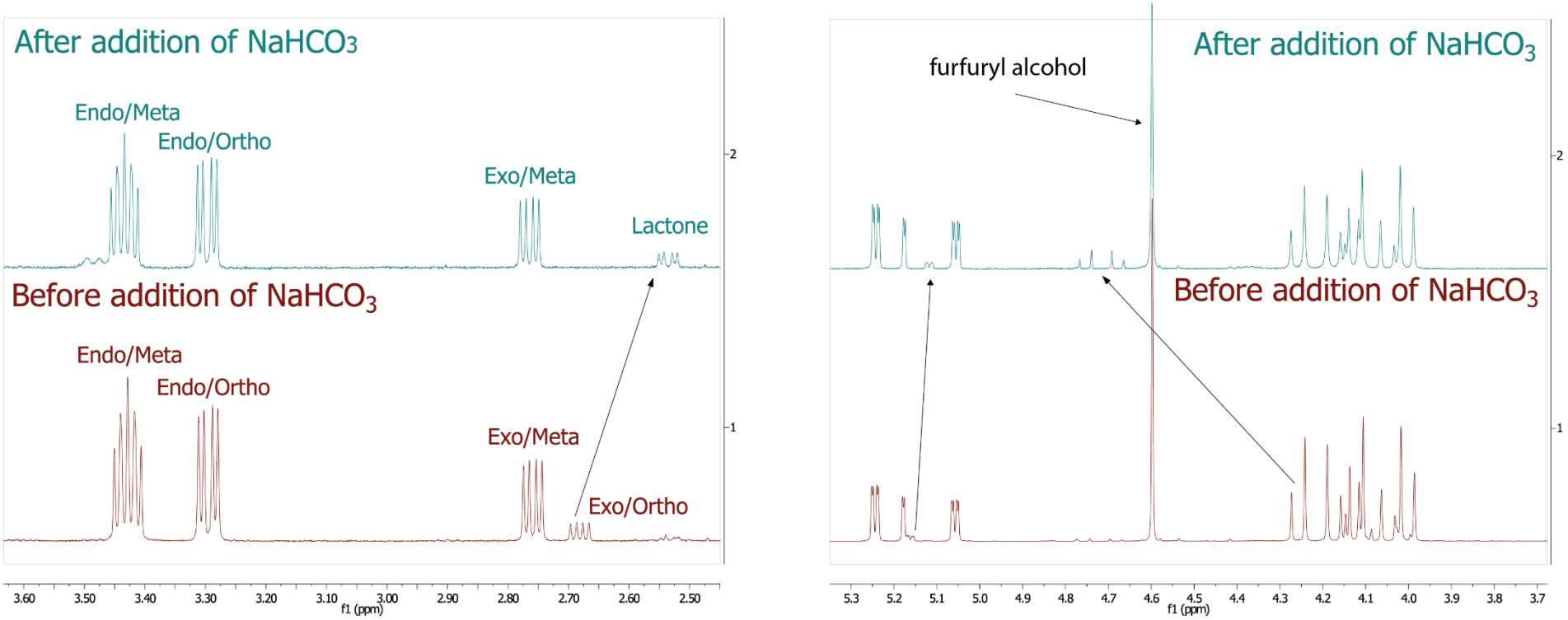


Figure S2 ^{1}H NMR analysis before and after addition of 20 mol% $NaHCO_3$ to the Diels-Alder adducts obtained from the reaction of furfuryl alcohol and hexafluoropropyl acrylate.

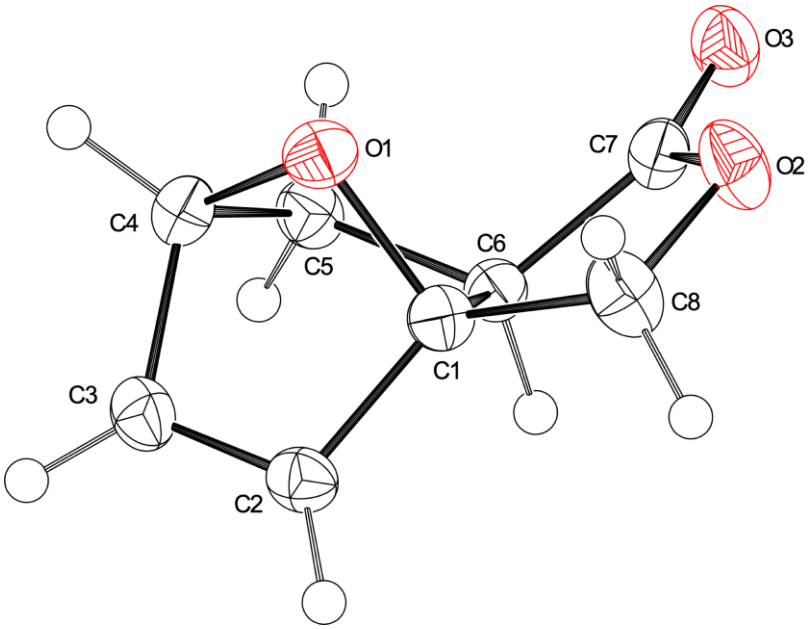
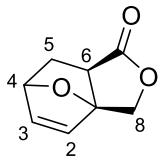


Figure S3 Molecular structure of **4-exo** in the crystal. Displacement ellipsoids are drawn at the 50% probability level. The compound was obtained as a racemate in the centrosymmetric space group Pbca.

Table S2 Comparison of the ^{1}H NMR data reported by Torosyan *et al*. and our ^{1}H NMR data for 4-exo.



Position	Torosyan *et al*.[18]	^{1}H NMR Shift Observed here	^{13}C NMR Shift
1			92.2
2/3	6.50 (m)	6.46 (m)	131.8/137.6
4	5.12 (m)	5.12 (d, *J*=4.6 Hz)	79.5
5	1.10-1.45 (m)	1.69 (dd, *J*=11.9, 8.8 Hz) and 2.26 (ddd, *J*=11.9, 4.4, 3.5 Hz)	29.3
6	-	2.54 (dd, *J*= 8.8, 3.5 Hz)	45.0
7			176.0
8	3.82 (m)	4.68 (d, *J*=11.0 Hz) and 4.77 (d, *J*=11.0 Hz)	69.1

Table S3 Selected bond lengths [Å], angles and torsion angles [°] in the X-ray crystal structure of 4-exo.

C1-O1	1.4442(17	C6-C7-O2	110.23(12)
C4-O1	1.4474(18)	C6-C7-O3	129.64(14)
C7-O2	1.3569(18)	O2-C3-O3	120.13(13)
C8-O2	1.4646(18)	C1-O1-C4	95.04(10)
C7-O3	1.2078(18)	C1-C2-C3	104.77(13)
C1-C2	1.506(2)	C2-C3-C4	106.28(13)
C2-C3	1.324(2)	C3-C4-C5	108.68(12)
C3-C4	1.514(2)	C6-C1-O1-C4	60.84(12)
C4-C5	1.553(2)	C6-C1-C8-O2	28.68(15)
C5-C6	1.5414(19)	C4-C5-C6-C7	-108.78(13)

Table S4 Intermolecular C-H...O hydrogen bonds in the crystal structure of 4-exo

	D-H [Å]	H...A [Å]	D….A [Å]	D-H...A [°]
C3-H3...O3^{i}	0.95	2.60	3.3762(18)	139
C4-H4...O3^{ii}	1.00	2.57	3.5370(18)	162
C6-H6...O3^{iii}	1.00	2.70	3.6339(17)	155

Symmetry codes *i*: 1/2-x, 1-y, z+1/2; *ii*: 1-x, 1-y, 1-z; *iii*: x-1/2, y, 1/2-z.

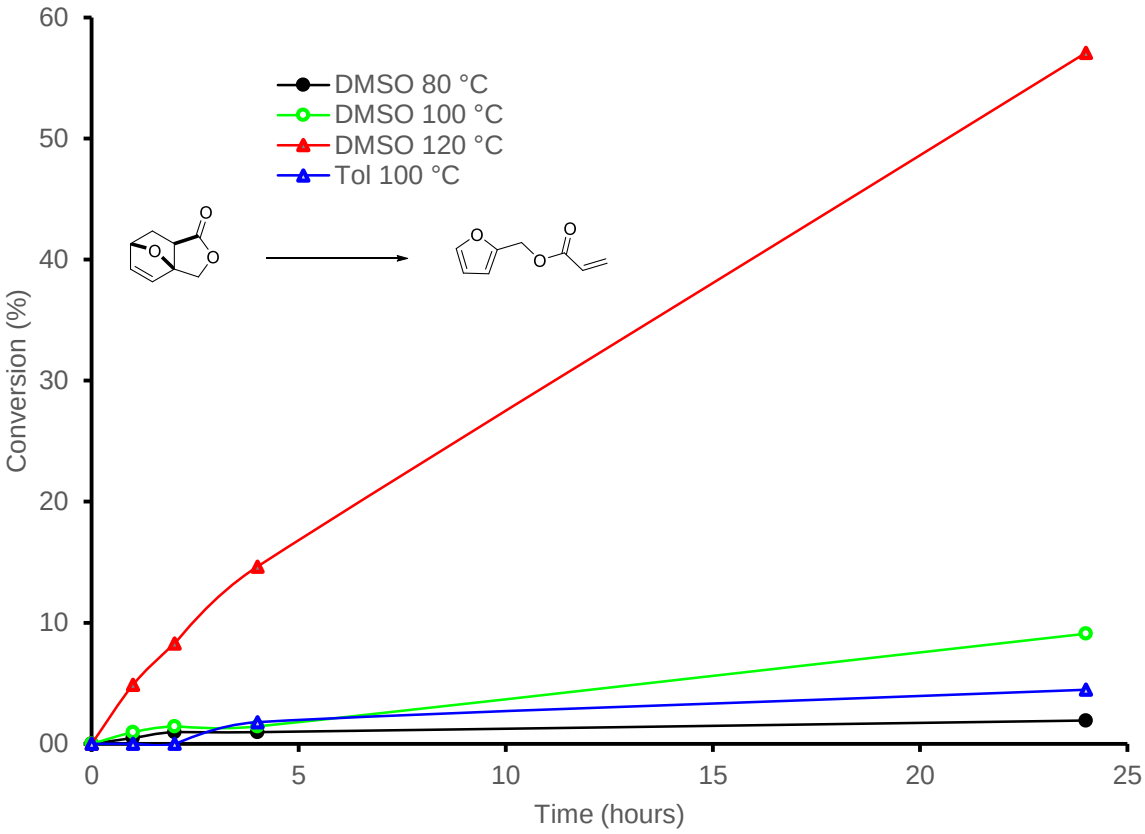


Figure S4 Temperature stability of **4-*exo*** with respect to the retro-Diels-Alder reaction giving furfuryl acrylate (**3**). These experiments were run in an NMR tube with periodic quantitative ^{1}H NMR analysis used to determine conversion. The only product observed was furfuryl acrylate.

NMR Spectra

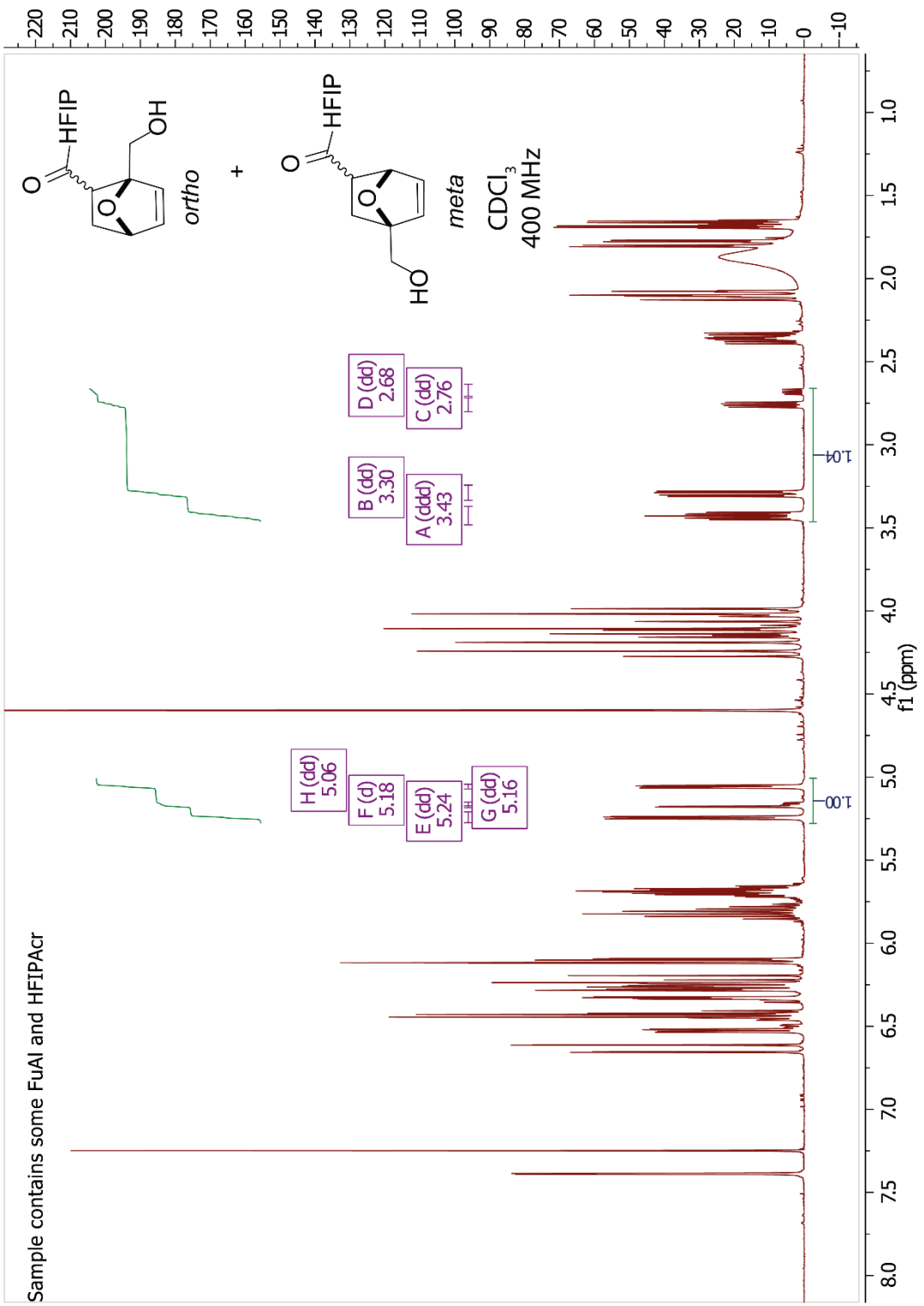


Figure S5 ^{1}H NMR analysis of the crude Diels-Alder adducts obtained from the reaction of furfuryl alcohol and hexafluoroisopropyl acrylate.

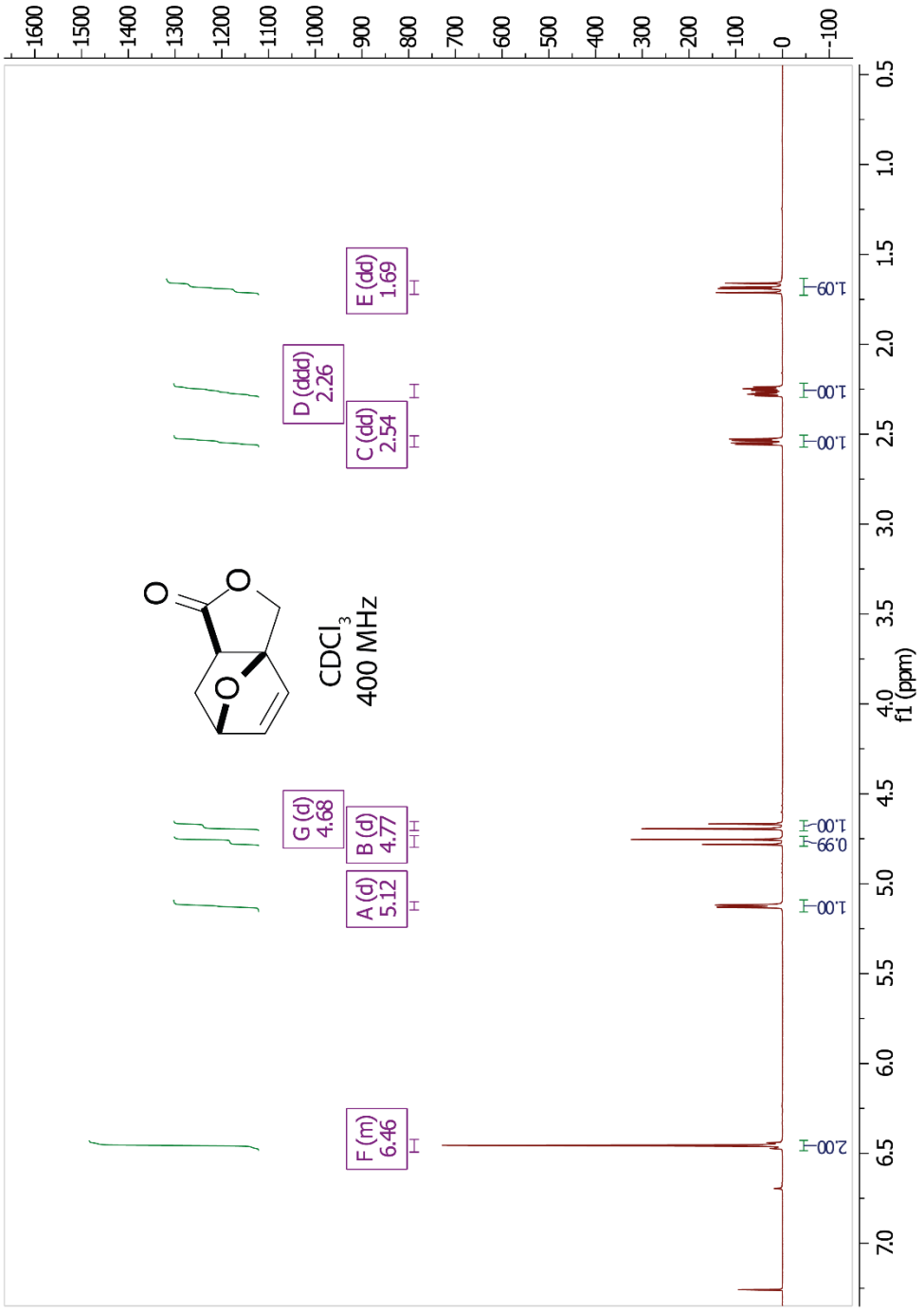


Figure S6 ^{1}H NMR analysis of **4-*exo***.

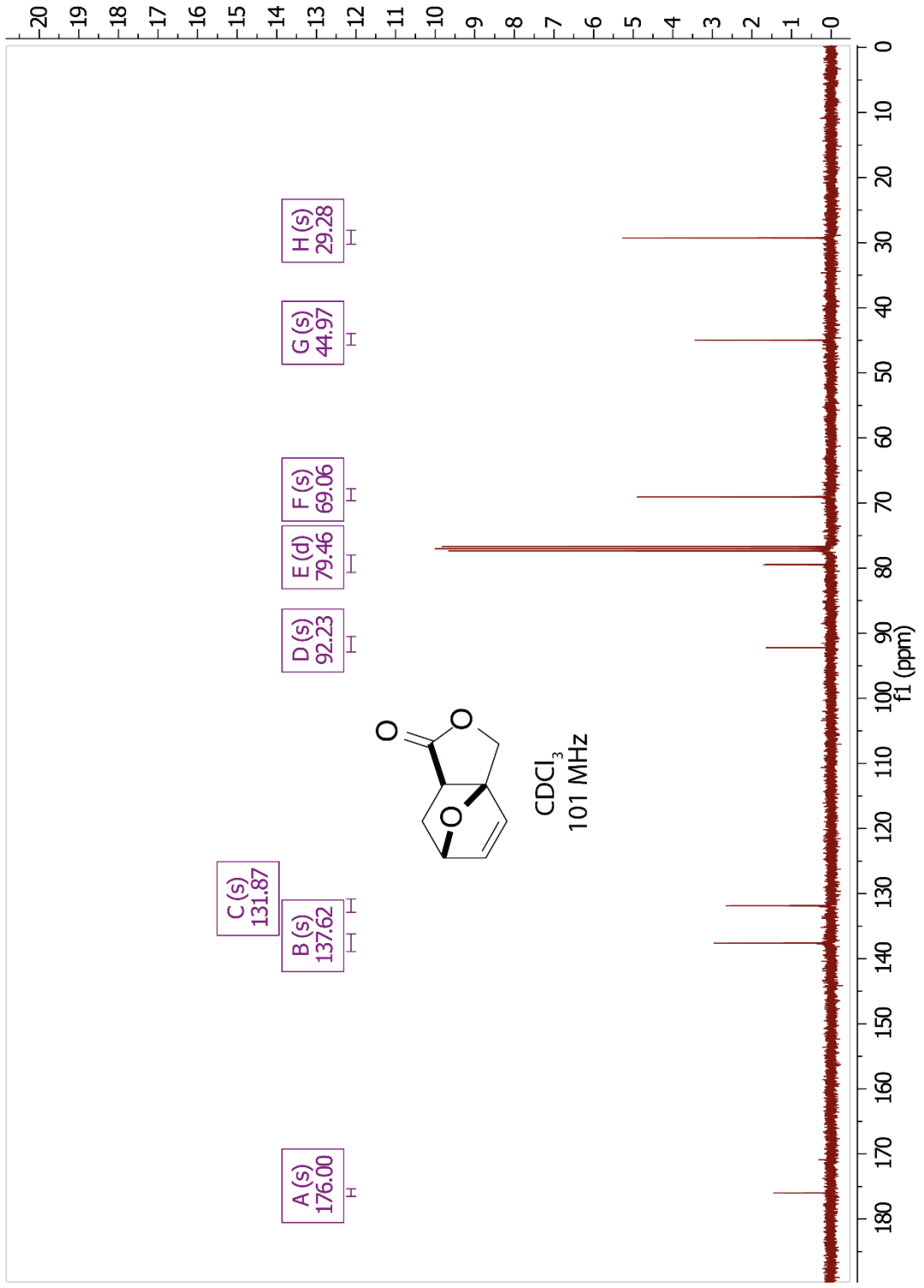


Figure S7 ^{13}C NMR analysis of **4-*exo***.

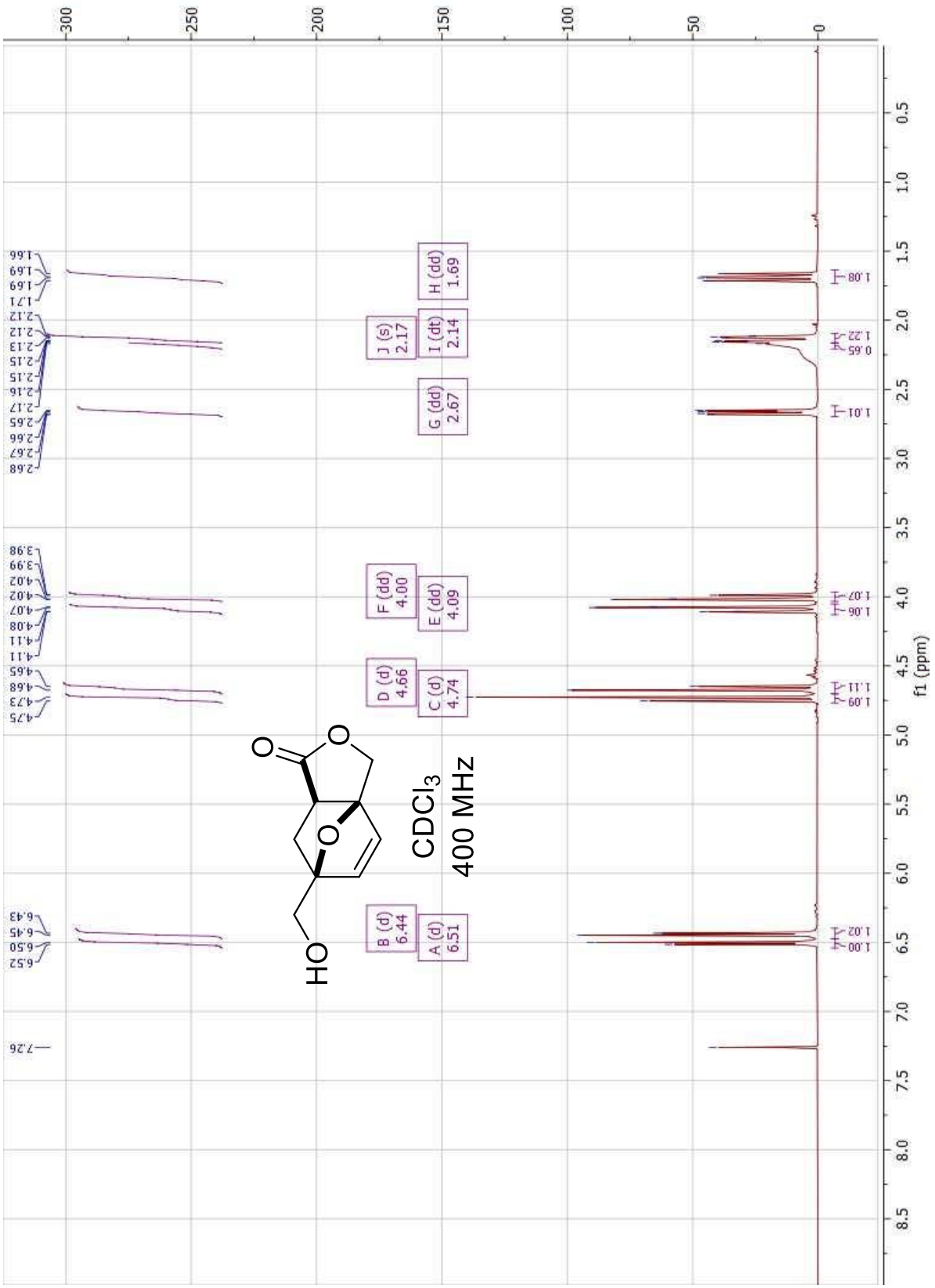


Figure S8 ^{1}H NMR analysis of **12-*exo***.

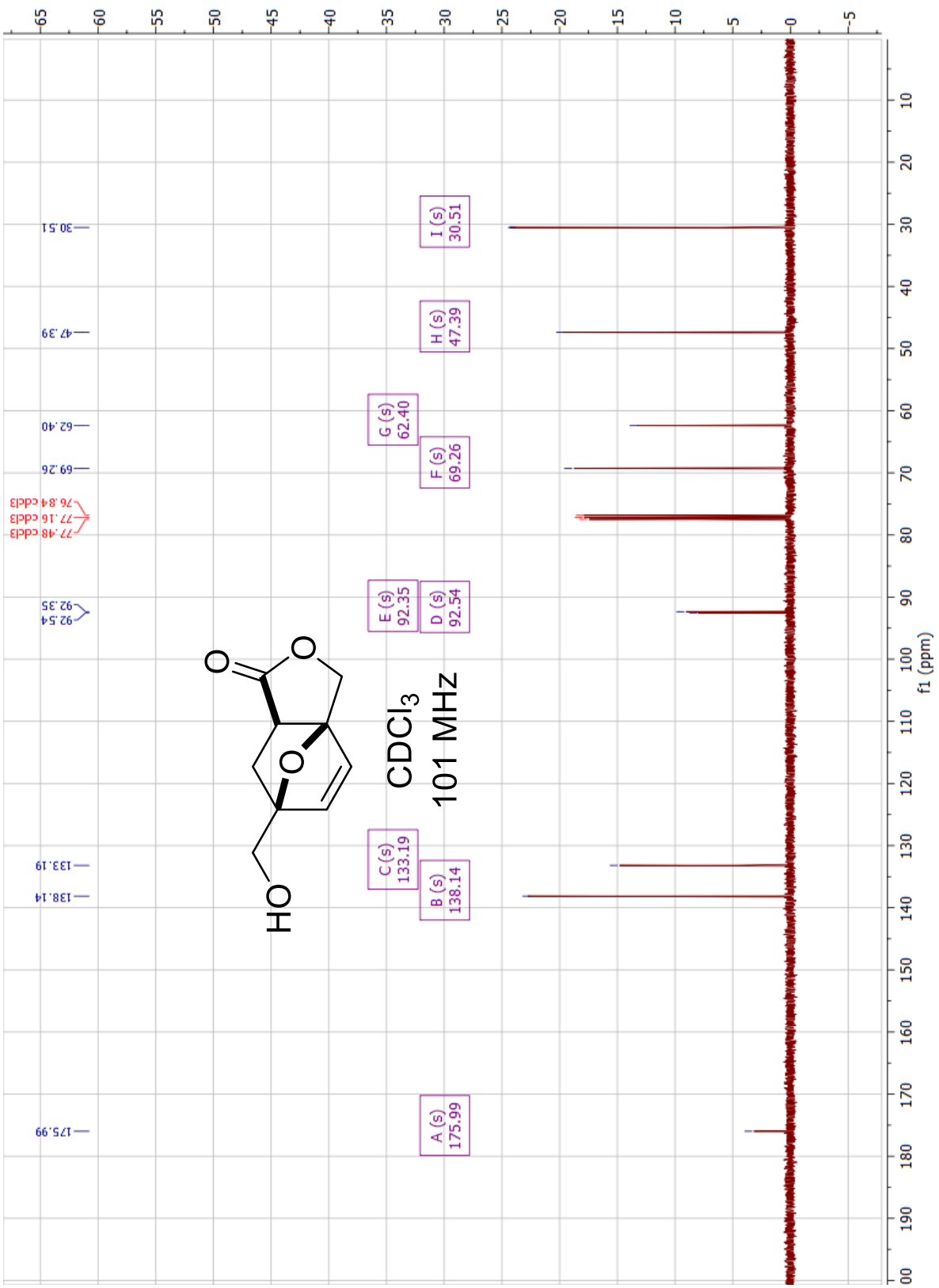


Figure S9 ^{13}C NMR analysis of **12-*exo***.

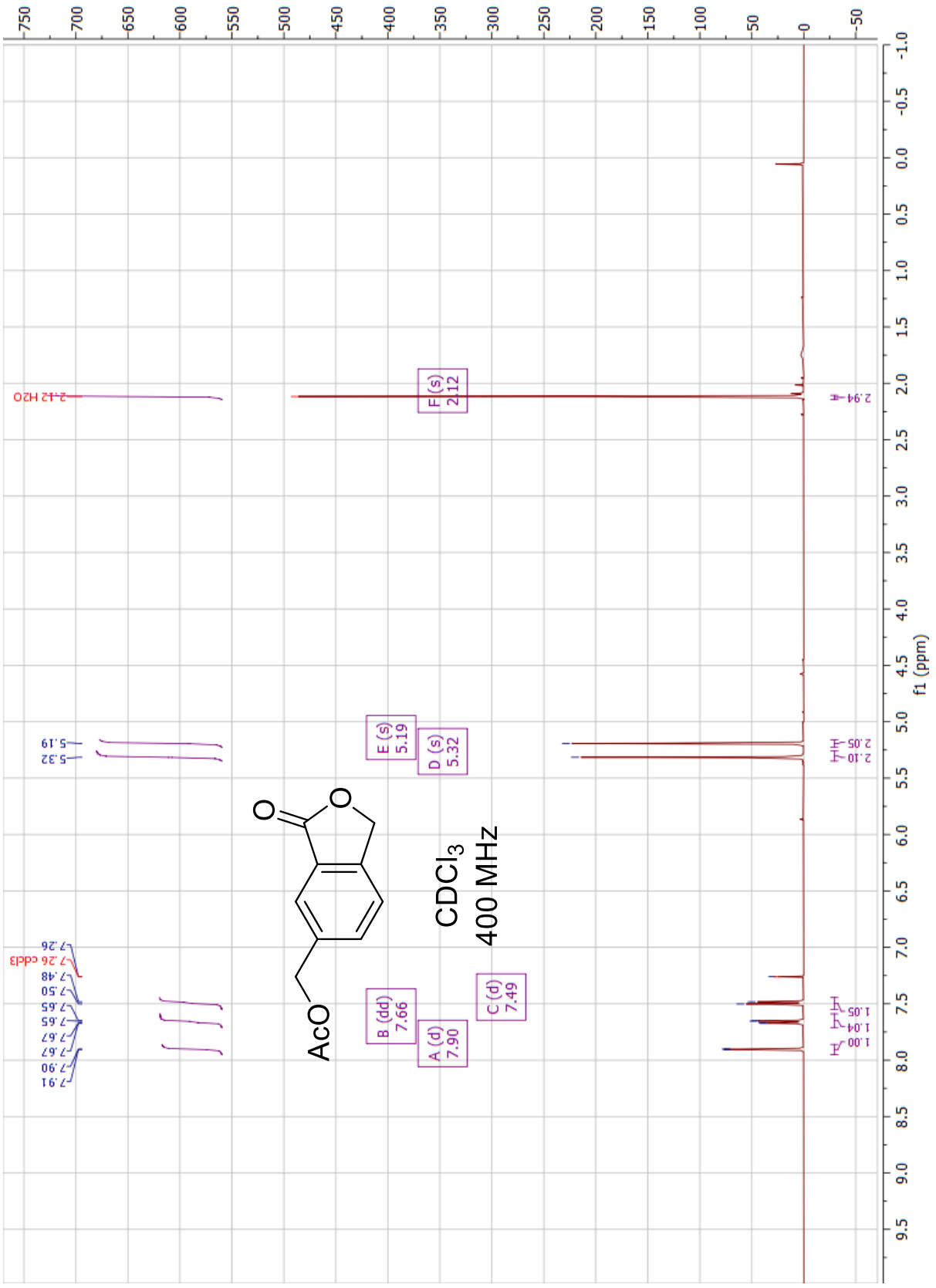


Figure S10 ^{1}H NMR analysis of **13**.

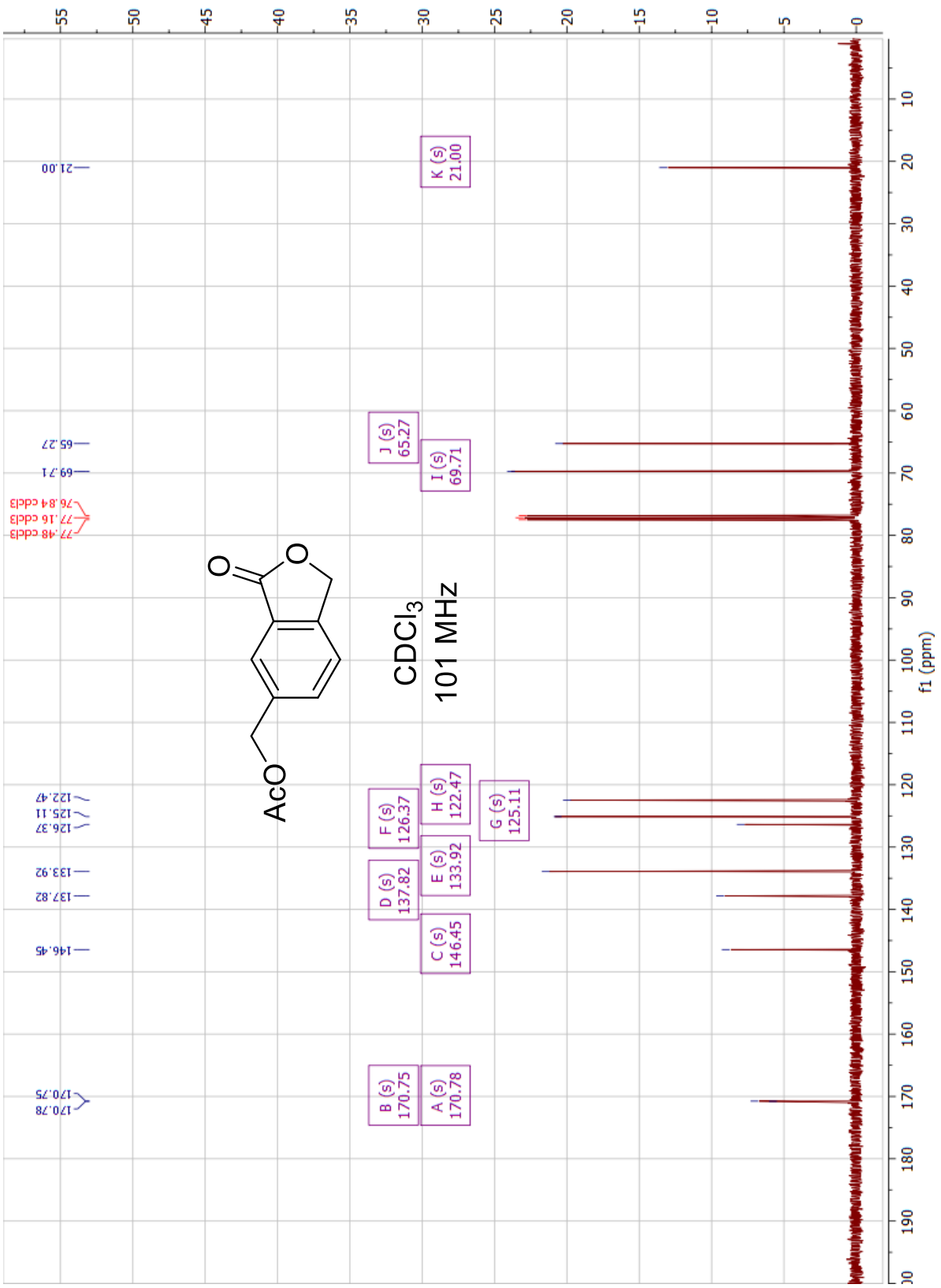


Figure S11 ^{13}C NMR analysis of **13**.

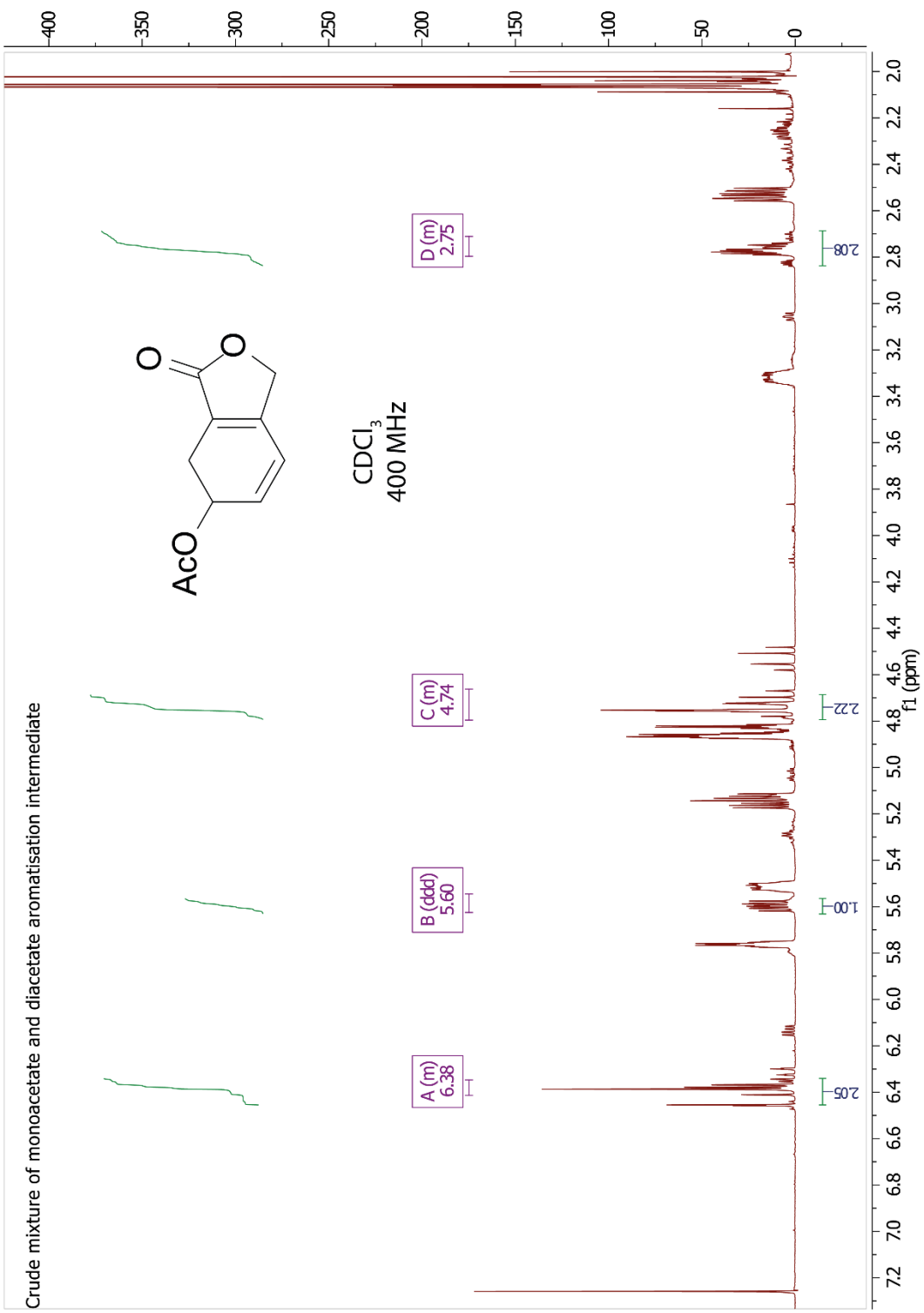


Figure S12 ^{1}H NMR analysis of aromatization intermediates obtained using MSA/Ac_2O at low temperature. Integrals highlight peaks for the compound tentatively assigned as shown.

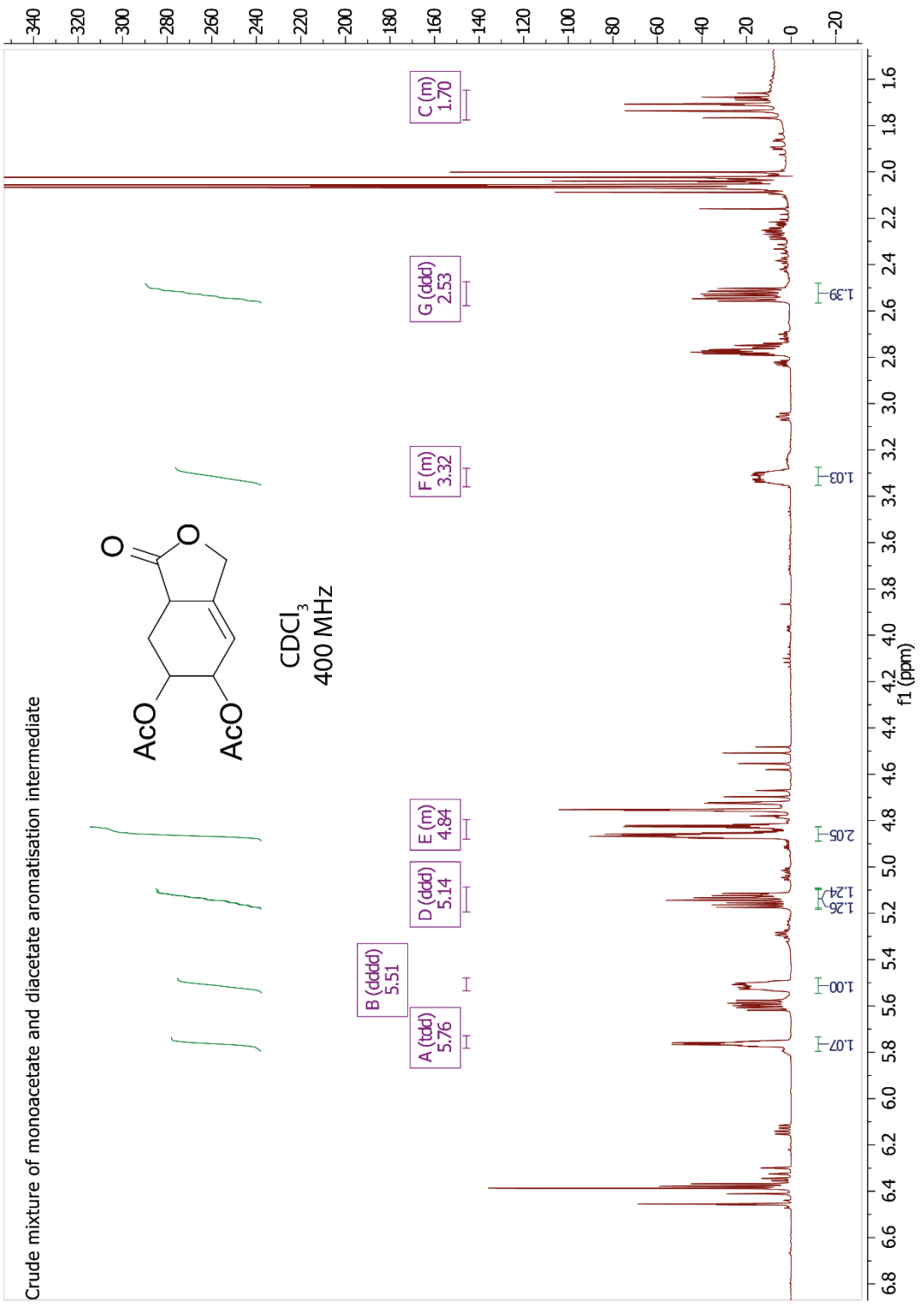


Figure S13 ^{1}H NMR analysis of aromatization intermediates obtained using MSA/Ac_2O at low temperature. Integrals highlight peaks for the compound tentatively assigned as shown.

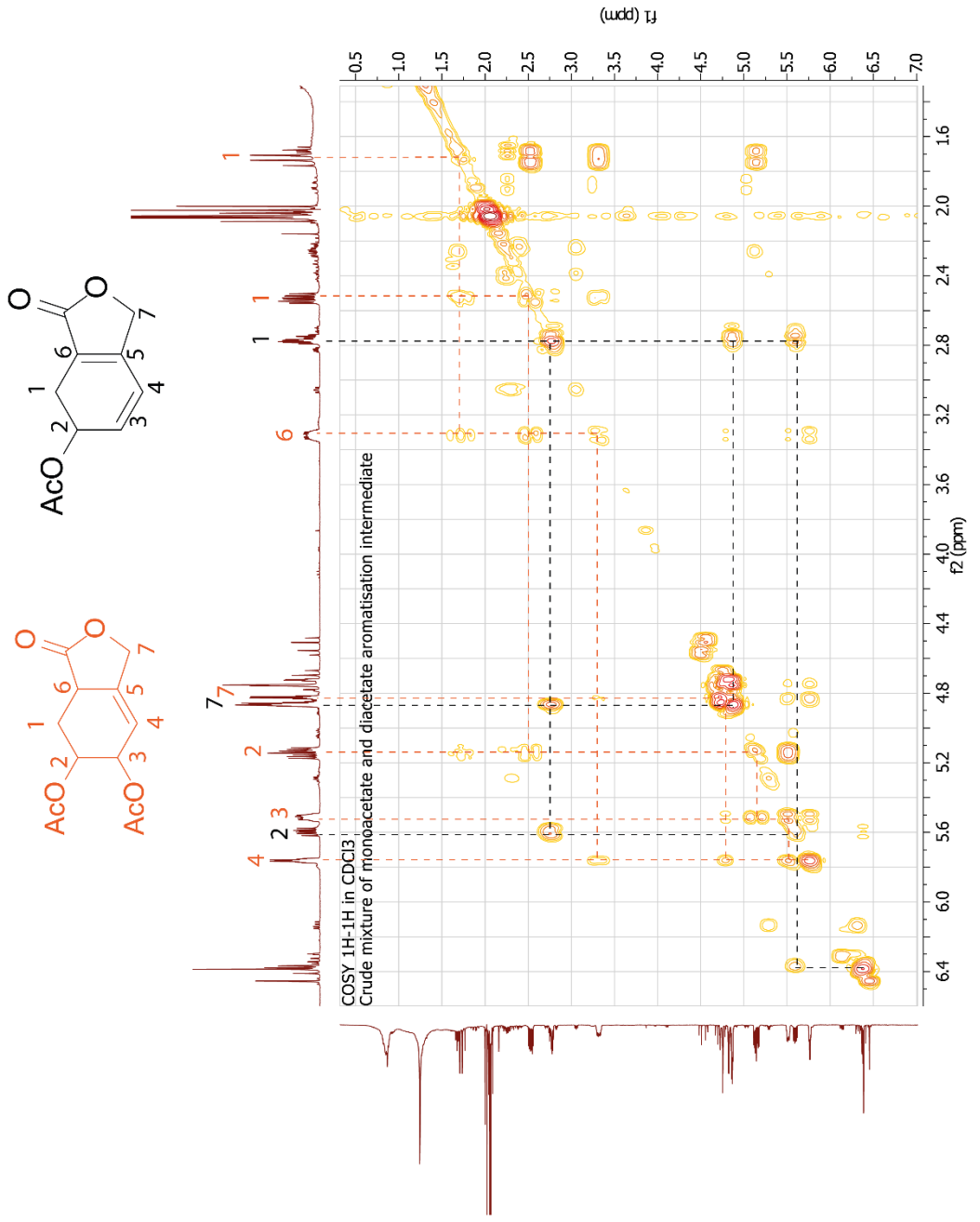


Figure S14 COSY NMR analysis illustrating characteristic couplings used to assign the intermediates.

References

[1] Y. Li, J. Li, X. Zhao, Q. Yan, Y. Gao, J. Hao, J. Hu, Y. Ju, *Chem. - A Eur. J.* **2016**, *22*, 18435–18441.

[2] A. M. M. Schreurs, X. Xian, L. M. J. Kroon-Batenburg, *J. Appl. Crystallogr.* **2010**, *43*, 70–82.

[3] L. Krause, R. Herbst-Irmer, G. M. Sheldrick, D. Stalke, *J. Appl. Crystallogr.* **2015**, *48*, 3–10.

[4] G. M. Sheldrick, *Acta Crystallogr. Sect. A Found. Crystallogr.* **2015**, *71*, 3–8.

[5] G. M. Sheldrick, *Acta Crystallogr. Sect. C Struct. Chem.* **2015**, *71*, 3–8.

[6] A. L. Spek, *Acta Crystallogr. Sect. D Biol. Crystallogr.* **2009**, *65*, 148–155.

[7] G. te Velde, F. M. Bickelhaupt, E. J. Baerends, C. Fonseca Guerra, S. J. A. van Gisbergen, J. G. Snijders, T. Ziegler, *J. Comput. Chem.* **2001**, *22*, 931–967.

[8] C. Fonseca Guerra, J. G. Snijders, G. Te Velde, E. J. Baerends, *Theor. Chem. Acc.* **1998**, *99*, 391–403.

[9] P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623–11627.

[10] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, *132*, 154104.

[11] E. Van Lenthe, E. J. Baerends, *J. Comput. Chem.* **2003**, *24*, 1142–1156.

[12] S. F. Sousa, P. A. Fernandes, M. J. Ramos, *J. Phys. Chem. A* **2007**, *111*, 10439–10452.

[13] J. Tirado-Rives, W. L. Jorgensen, *J. Chem. Theory Comput.* **2008**, *4*, 297–306.

[14] A. K. Rappé, C. J. Casewit, K. S. Colwell, W. A. Goddard, W. M. Skiff, *J. Am. Chem. Soc.* **1992**, *114*, 10024–10035.

[15] L. Versluis, T. Ziegler, *J. Chem. Phys.* **1988**, *88*, 322–328.

[16] L. Fan, T. Ziegler, *J. Am. Chem. Soc.* **1992**, *114*, 10890–10897.

[17] K. Robinson, M. V. De Paz Banez, G. Tustin, T. Jones, *Reversible Polymeric Gelation for Oilfield Applications.*, **2009**, US20080238107 20080925.

[18] G. O. Torosyan, A. A. Akopyan, A. T. Torosyan, A. T. Babayan, *Chem. Heterocycl. Compd.* **1990**, *26*, 390–392.

Optimized Cartesian coordinates and energies

Table S5 Optimized Cartesian coordinates and energies of global minimum conformer of **3**

	Cartesian	(a.u./angstrom)	
Atom	X	Y	Z
O	-2.21807	0.888134	0.499628
C	-1.35404	0.295655	-0.38514
C	-1.68615	-1.01072	-0.5471
C	-2.82493	-1.24833	0.282834
C	-3.10203	-0.06845	0.891188
H	-1.15938	-1.71381	-1.16883
H	-3.36327	-2.17247	0.408063
H	-3.85883	0.24288	1.589271
C	-0.26701	1.138812	-0.92864
H	0.01605	0.794597	-1.92056
H	-0.5729	2.181262	-0.96326
O	0.9141	1.139082	-0.07464
C	1.754045	0.088273	-0.2191
C	2.883024	0.197031	0.738267
H	2.878526	1.055516	1.397076
C	3.840489	-0.72106	0.775137
H	4.66517	-0.64827	1.470919
H	3.812018	-1.56807	0.101486
O	1.591157	-0.80169	-1.01982

Summary of energy terms

	hartree	eV	kcal/mol	kJ/mol
Bond Energy:	-5.08402	-138.343	-3190.27	-13348.1
Internal Energy:	0.157453	4.2845	98.8	413.39
pV/n = RT:	0.001023	0.0278	0.64	2.69
Enthalpy H:	-4.92555	-134.031	-3090.83	-12932
-T*S:	-0.05383	-1.4649	-33.78	-141.34
Gibbs free energy:	-4.97938	-135.496	-3124.61	-13073.4

Table S6 Optimized Cartesian coordinates and energies of the reactive rotamer of **3** leading to **4-*endo***

	Cartesian	(a.u./angstrom)	
Atom	X	Y	Z
C	-0.72867	0.285321	-2.91437
C	1.026884	0.873929	-1.67658
C	0.127621	0.228914	-0.8898
O	-0.95863	-0.14325	-1.64065
H	0.907111	1.345805	-3.87723
C	0.470525	0.910641	-2.99414
H	1.971416	1.28021	-1.35494
H	-1.50024	0.07037	-3.63293
C	0.122628	-0.11567	0.551917
O	-0.66842	0.79364	1.357186
C	-1.93825	0.511389	1.76579
C	-2.65206	-0.6304	1.115651
O	-2.43112	1.204104	2.617372
C	-3.68627	-1.20632	1.718228
H	1.136246	-0.01097	0.934812
H	-0.19732	-1.14533	0.714429
H	-2.32993	-0.95711	0.137609
H	-4.22367	-2.02153	1.251427
H	-4.01598	-0.86874	2.692422

Summary of energy terms

	hartree	eV	kcal/mol	kJ/mol
Bond Energy:	-5.06755	-137.895	-3179.94	-13304.9
Internal Energy:	0.156977	4.2716	98.5	412.14
pV/n = RT:	0.001023	0.0278	0.64	2.69
Enthalpy H:	-4.90955	-133.596	-3080.79	-12890
-T*S:	-0.05386	-1.4655	-33.8	-141.4
Gibbs free energy:	-4.96341	-135.061	-3114.59	-13031.4

Table S7 Optimized Cartesian coordinates and energies of the reactive rotamer of **3** leading to **4-*exo***

		Cartesian	(a.u./angstrom)	
	Atom	X	Y	Z
1	C	-0.1187	-1.69387	-2.51316
2	C	-0.25577	0.445121	-1.91395
3	C	0.046829	-0.30634	-0.82214
4	O	0.139772	-1.62268	-1.17833
5	H	-0.59098	-0.21842	-4.04206
6	C	-0.36219	-0.45937	-3.0176
7	H	-0.38297	1.515237	-1.93525
8	H	-0.09456	-2.67764	-2.94818
9	C	0.319453	0.030024	0.598177
10	O	-0.59047	-0.58988	1.536436
11	C	-1.80679	-0.0701	1.861155
12	C	-2.30917	1.106791	1.087327
13	O	-2.42513	-0.58492	2.755812
14	C	-3.33713	1.817131	1.537983
15	H	0.337428	1.113364	0.721015
16	H	1.291597	-0.36186	0.896964
17	H	-3.72108	2.662866	0.982141
18	H	-3.81589	1.559923	2.474213
19	H	-1.84379	1.354318	0.144638

Summary of energy terms

	hartree	eV	kcal/mol	kJ/mol
Bond Energy:	-5.06623	-137.859	-3179.11	-13301.4
Internal Energy:	0.15697	4.2714	98.5	412.12
pV/n = RT:	0.001023	0.0278	0.64	2.69
Enthalpy H:	-4.90823	-133.56	-3079.96	-12886.6
-T*S:	-0.05389	-1.4665	-33.82	-141.5
Gibbs free energy:	-4.96213	-135.026	-3113.78	-13028.1

Table S8 Optimized Cartesian coordinates and energies of the transition state leading to **4-*endo***

	Cartesian	(a.u./angstrom)	
Atom	X	Y	Z
C	-1.41196	-0.24034	-2.18697
C	-0.3082	1.313081	-1.036
C	-0.19956	0.017304	-0.43953
O	-0.47782	-0.91524	-1.42367
H	-1.51739	1.905541	-2.77727
C	-1.09279	1.146268	-2.13998
H	0.009849	2.234388	-0.57581
H	-1.80261	-0.79293	-3.02744
C	0.564303	-0.2825	0.816666
O	-0.1812	0.386412	1.869442
C	-1.52893	0.553194	1.576408
C	-1.91576	-0.32668	0.439899
O	-2.19196	1.321782	2.210425
C	-2.85883	-0.14973	-0.58783
H	1.565848	0.143701	0.842701
H	0.620223	-1.35753	0.997238
H	-1.70792	-1.36469	0.685567
H	-3.45153	-1.00285	-0.88737
H	-3.33752	0.810086	-0.72037

Summary of energy terms

	hartree	eV	kcal/mol	kJ/mol
Bond Energy:	-5.00928	-136.31	-3143.37	-13151.9
Internal Energy:	0.155084	4.2201	97.32	407.17
pV/n = RT:	0.001023	0.0278	0.64	2.69
Enthalpy H:	-4.85318	-132.062	-3045.41	-12742
-T*S:	-0.04689	-1.2758	-29.42	-123.1
Gibbs free energy:	-4.90006	-133.338	-3074.84	-12865.1

One imaginary frequency was found for the transition state.

Table S9 Optimized Cartesian coordinates and energies of the transition state leading to **4-*exo***

	Cartesian	(a.u./angstrom)	
Atom	X	Y	Z
C	-0.69289	0.447277	-0.98749
C	0.873485	2.019734	-0.75257
C	0.747821	1.220485	0.413328
O	0.113405	0.050602	0.051987
H	-0.358	1.961969	-2.58017
C	-0.05664	1.533965	-1.6377
H	1.449858	2.92748	-0.82994
H	-1.30041	-0.32695	-1.42871
C	1.544283	1.173517	1.671151
O	0.662503	1.002648	2.798713
C	-0.65991	1.286185	2.57701
C	-0.93801	1.98225	1.269659
O	-1.47606	0.991706	3.403934
C	-1.94624	1.535774	0.408067
H	2.107024	2.1022	1.782977
H	2.234936	0.330126	1.692241
H	-2.45883	2.244847	-0.22492
H	-2.51981	0.664231	0.692217
H	-0.69071	3.037299	1.295543

Summary of energy terms

	hartree	eV	kcal/mol	kJ/mol
Bond Energy:	-5.02284	-136.679	-3151.88	-13187.5
Internal Energy:	0.154908	4.2153	97.21	406.71
pV/n = RT:	0.001023	0.0278	0.64	2.69
Enthalpy H:	-4.86691	-132.435	-3054.03	-12778.1
-T*S:	-0.04738	-1.2892	-29.73	-124.39
Gibbs free energy:	-4.91429	-133.725	-3083.76	-12902.5

One imaginary frequency was found for the transition state.

Table S10 Optimized Cartesian coordinates and energies of **4-*endo***

	Cartesian	(a.u./angstrom)	
Atom	X	Y	Z
C	-1.86182	-0.44303	-1.73077
C	-0.18476	0.917295	-1.07586
C	-0.38939	-0.31955	-0.20828
O	-0.82311	-1.29674	-1.1594
H	-1.31934	1.52162	-2.83296
C	-1.08187	0.817893	-2.04957
H	0.50292	1.718865	-0.85361
H	-2.37118	-0.95565	-2.53976
C	0.604941	-0.52929	0.911348
O	0.118307	0.440788	1.898466
C	-1.22282	0.757417	1.704377
C	-1.69412	-0.16937	0.615323
O	-1.77332	1.593336	2.354141
C	-2.76177	-0.04776	-0.47463
H	1.633633	-0.26293	0.681127
H	0.557528	-1.53834	1.325445
H	-1.82474	-1.13518	1.114803
H	-3.56919	-0.76097	-0.32184
H	-3.18405	0.947932	-0.58707

Summary of energy terms

	hartree	eV	kcal/mol	kJ/mol
Bond Energy:	-5.04406	-137.256	-3165.19	-13243.2
Internal Energy:	0.158104	4.3022	99.21	415.1
pV/n = RT:	0.001023	0.0278	0.64	2.69
Enthalpy H:	-4.88493	-132.926	-3065.34	-12825.4
-T*S:	-0.0458	-1.2463	-28.74	-120.25
Gibbs free energy:	-4.93073	-134.172	-3094.08	-12945.6

Table S11 Optimized Cartesian coordinates and energies of **4-*exo***

	Cartesian	(a.u./angstrom)	
Atom	X	Y	Z
C	-1.87588	-0.62553	-1.47541
C	0.014925	0.65683	-1.56616
C	-0.27744	0.029378	-0.21647
O	-0.9019	-1.21388	-0.59335
H	-1.21738	0.573214	-3.35506
C	-0.99338	0.267532	-2.34406
H	0.802913	1.363211	-1.77964
H	-2.46174	-1.38977	-1.97699
C	0.678029	-0.15596	0.934578
O	-0.15567	-0.16849	2.11993
C	-1.42314	0.27782	1.859794
C	-1.49408	0.765046	0.419092
O	-2.28194	0.282856	2.691761
C	-2.66224	0.279262	-0.46319
H	1.388911	0.669058	1.008264
H	1.209071	-1.10437	0.885888
H	-3.20255	1.091921	-0.94412
H	-3.3637	-0.32372	0.109905
H	-1.37827	1.849529	0.429145

Summary of energy terms

	hartree	eV	kcal/mol	kJ/mol
Bond Energy:	-5.06849	-137.921	-3180.53	-13307.3
Internal Energy:	0.158203	4.3049	99.27	415.36
pV/n = RT:	0.001023	0.0278	0.64	2.69
Enthalpy H:	-4.90926	-133.588	-3080.61	-12889.3
-T*S:	-0.04591	-1.2493	-28.81	-120.54
Gibbs free energy:	-4.95518	-134.837	-3109.42	-13009.8