Supporting Information

Amphidynamic Crystals of a Steroidal Bicyclo[2.2.2]octane Rotor: A High Symmetry Group that Rotates Faster than Smaller Methyl and Methoxy Groups

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General Information. All reactions were carried out under an inert atmosphere of argon in oven or flame-dried glassware, unless the reaction procedure states otherwise. All chemicals were purchased from commercial suppliers and used as received. Mestrone (**4**) and Ethynylestradiol (**9**) are commercially available and bicyclo[2.2.2]octane-1,4-dimethanol (**6**) was synthesized following the procedure reported in reference (2). Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone in a continuous still under an atmosphere of argon. Dichloromethane was distilled from calcium hydride in a still under an atmosphere of argon. Room temperature reactions were carried out between 20-25 °C, reactions at 0 °C were performed using a water-ice bath and reactions at -78 °C were carried out in an acetone-dry ice bath. Analytical thin-layer chromatography (TLC) was performed using pre-coated TLC plates with Silica Gel 60 F254 and visualized using combinations of UV, potassium permanganate ($KMnO_4$), and cerium molybdate (CAM) staining. Flash column chromatography was performed using silica gel (230-400 mesh) as the stationary phase. Proton magnetic resonance spectra were recorded at 500 MHz, and carbon-13 magnetic resonance spectra were recorded at 125 MHz, respectively. All chemical shifts are reported in ppm on the δ-scale relative to TMS (δ 0.0) using residual solvent as reference ($CDCl_3$ δ 7.26 and δ 77.16 for proton and carbon, respectively). Coupling constants *J* are reported in Hz. Multiplicities are reported as broad (br), singlet (s), doublet (d), triplet (t), quartet (q), quintet (qnt), sextet (sxt), septuplet (spt) and multiplet (m). Uncorrected melting points were recorded on a melting point apparatus using open glass capillaries. IR spectral data were obtained using an Attenuated Total Reflectance (ATR) spectrometer as the neat compound and the units are stated in cm^{-1}. Optical Rotations were measured on a polarimeter with a sodium lamp and a light wavelength of 589 nm (the sodium D line). High resolution mass spectrometric data were collected using Electrospray Ionization technique with a Time-of-Flight detector (ESI-TOF) mass spectrometer and a Liquid Introduction Field Desorption Ionization mass spectrometer with a Time-of-Flight detector (LIFDI-TOF).

X-ray single crystal analysis. A colorless prism of compound **3** grown from slow evaporation of hexanes/ethyl acetate (4:1), with approximate dimensions of 0.30 mm x 0.10 mm x 0.05 mm, was used for intensity data. The diffraction data were measured at 100(2) K on a X-ray diffractometer system equipped with Mo-Kα radiation (λ = 0.71073 Å) and area detector. The structure was solved and refined using the SHELXTL software package. The absolute

configuration of the compound was fixed based on the known chiral centers. All atoms were refined anisotropically, and hydrogen atoms were placed at calculated positions.

X-Ray powder diffraction. Compounds **3** and **3-d_6** were obtained as crystalline solids from slow evaporation of hexanes/ethyl acetate (4:1) and mestranol-d_3 was recrystallized from ethanol. Analyses were carried out on using Cu-$K_{\alpha 1}$ = 1.5406 Å radiation. Data were collected at room temperature in the range of 2Θ = 4-50° (step of 0.016°, step time 125 s).

Thermal analysis. Compound **3** was obtained as a crystalline solid from slow evaporation of hexanes/ethyl acetate (4:1). Differential scanning calorimetry was carried out on a DSC analyzer under nitrogen atmosphere, using a cycle from 25 to -50 °C and from -50 °C to 350 °C with a cooling/heating rate of 10 °C/min. Thermogravimmetric analysis was obtained on a thermoanalyzer under argon atmosphere using a temperature interval from 50 to 400 °C with a heating rate of 10 °C/min.

Solid state NMR spectrometer. ^{13}C CPMAS solid state NMR spectra of compound **3** was obtained on a ^{1}H 300 MHz spectrometer at ^{13}C frequency of 75.47 MHz, with ^{1}H broadband decoupler in a 4 mm broadband probe. Spinning frequency of 10 kHz was used for the removal of spinning sidebands, and cross polarization contact times of 5 or 0.5 ms were used. Dipolar dephasing experiments (^{13}C CPMAS NQS) were carried out with a delay of 60 μs before turning the ^{1}H decoupler on.

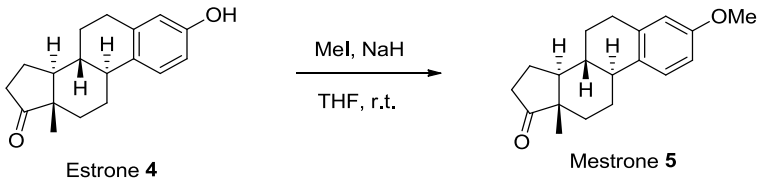
Solid state NMR samples for ^{13}C CPMAS. Compound **3** was obtained as a crystalline solid from slow evaporation of hexanes/ethyl acetate (4:1). Approximately 110 mg of the crystalline solid were gently ground using mortar and pestle and packed in a 4 mm wide ZrO_2 rotor with a KelF cap.

Spin lattice relaxation experiments (T_1, NMR). ^{1}H T_1, NMR relaxation was measured on polycrystalline samples of compound **3** and **3-d_3** recrystallized from hexanes/ethyl acetate and polycrystalline samples of commercial mestranol and mestranol-d_3 recrystallized from ethanol. The experiments were carried out with a static wideline probe using solid-state spectrometer operating at a ^{1}H Larmor frequency of 300 MHz. The saturation recovery sequence used contains a saturation pulse comb followed by a time τ' (τ' values taken from the variable delay list) with a

π/2 pulse p1. For each measurement, an acquisition time of 2.0985 ms was used. The ^{1}H spin-lattice relaxation experiments were determined for T=165 - 395 K.

Synthetic procedures

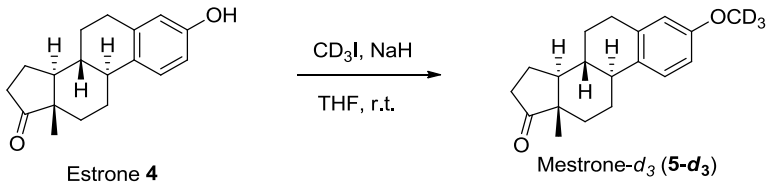
Scheme S1. *Synthesis of mestrone (compound **5**).*



Estrone **4** → Mestrone **5**

Synthesis of mestrone (compound 5). Sodium hydride 60% dispersion in mineral oil (48 mg, 1.21 mmol, 1.1 equiv) was added to a solution of Estrone (**4**) (297 mg, 1.01 mmol, 1.0 equiv) in dry THF (8.0 mL), this mixture was stirred until no gas evolution was observed and then iodomethane (0.2 mL, 468 mg, 3.29 mmol, 3.0 equiv) was added. After stirring for 8 h at room temperature and under argon atmosphere more iodomethane (0.4 mL, 936 mg, 6.58 mmol, 6.0 equiv) was added. The resulting mixture was stirred for 12 h, then poured into brine (20 mL) and extracted with ethyl acetate (3 x 20mL). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness. The crude product was purified by flash column chromatography (10% EtOAc-hexanes) yielding Mestrone **5** (295 mg, 94%) as a white powder. m.p. 170.3-173.5 °C (lit.: 168-169 °C). The spectral data matched those previously reported.[1]

Scheme S2. *Synthesis of mestrone-d_3 (compound **5-d_3**)*

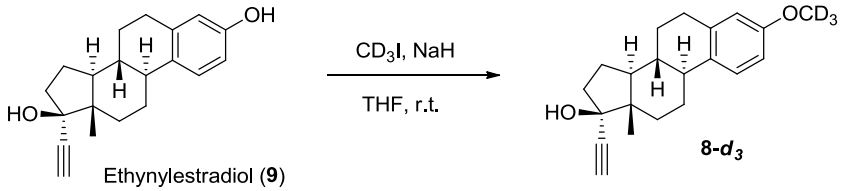


Estrone **4** → Mestrone-d_3 (**5-d_3**)

Synthesis of mestrone-d_3 (compound 5-d_3). Sodium hydride 60% dispersion in mineral oil (88 mg, 2.21 mmol, 1.1 equiv) was added to a solution of Estrone (**4**) (543 mg, 2.01 mmol, 1.0 equiv) in dry THF (6.0 mL), the resulting mixture was stirred until no gas evolution was observed and then iodomethane (1.12 mL, 2.62 g, 18.06 mmol, 9.0 equiv) was added. After stirring for 24 h at room temperature and under argon atmosphere, the mixture was poured into brine (30 mL) and extracted with ethyl acetate (3 x 30mL). The combined organic layers were

dried over Na_2SO_4 and concentrated to dryness. The crude product was purified by flash column chromatography (10% EtOAc-hexanes) yielding Mestrone-d_3 **5-d_3** (518 mg, 90%) as a white powder. TLC R_f = 0.57 (20% EtOAc-hexanes) m.p. 174.4-175.3 °C. IR (neat) ν_{max}: 2915, 2849, 2242, 2068, 1736, 1501, 1315, 1254, 1109, 843, 821 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (1H, d, *J* = 8.5 Hz, H-1), 6.72 (1H, dd, *J* = 8.5, 2.7 Hz, H-2), 6.65 (1H, d, *J* = 2.7 Hz, H-4), 2.97-2.85 (2H, m, H-6), 2.51 (1H, dd, *J* = 18.7, 8.5 Hz, H-16a), 2.43-2.37 (1H, m, H-11a), 2.26 (1H, td, *J* = 10.5, 4.3 Hz, H-9), 2.15 (1H, dt, *J* = 18.7, 8.9 Hz, H-16b), 2.10-1.98 [2H, (m, H-15a), (m, H-7a)] 1.98-1.91 (1H, m, H12a), 1.70-1.39 [6H, (m, H-15b), (m, H-8), (m, H-14), (m, H-11b), (H-7b), (H-12b)] 0.91 (3H, s, H-18). ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.1 (C-17), 157.7 (C-3), 137.9 (C-5), 132.1 (C-10), 126.5 (C-1), 114.0 (C-4), 111.7 (C-2), 54.50 (spt, J_{CD} = 21.9 Hz, C-19), 50.5 (C-14), 48.1 (C-13), 44.1 (C-9), 38.5 (C-8), 36.0 (C-16), 31.7 (C-12), 29.8 (C-6), 26.7 (C-7), 26.0 (C-11), 21.7 (C-15), 14.0 (C-18). HRMS(ESI) calcd. for $[C_{19}H_{21}D_3O_2+H]^+$: 288.2043, found: 288.2043.

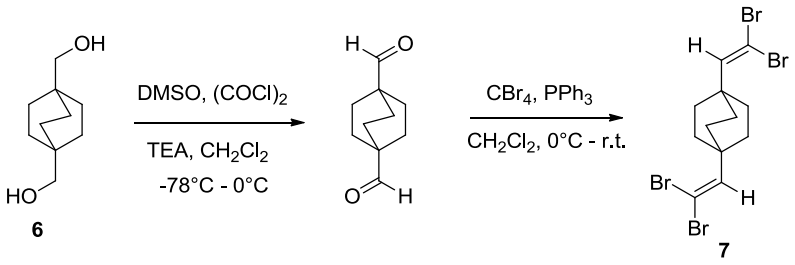
Scheme S3. *Synthesis of mestranol-d_3 (compound **8-d_3**).*



Synthesis of mestranol-d_3 (compound 8-d_3). Sodium hydride 60% dispersion in mineral oil (85 mg, 2.13 mmol, 1.0 equiv) was added to a solution of Ethynylestradiol (**9**) (633 mg, 2.13 mmol, 1.0 equiv) in dry THF (6.3 mL), the resulting mixture was stirred until no gas evolution was observed and then iodomethane (0.8 mL, 1.86 g, 12.81 mmol, 16.0 equiv) was added. The reaction mixture was stirred at room temperature and under argon atmosphere for 1 h and quenched with methanol (0.5 mL). The mixture was diluted with ethyl acetate (30 mL), washed with brine (30 mL) and the aqueous phase was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness. The residue was purified by flash column chromatography (20% EtOAc-hexanes) yielding **8-d_3** (634 mg, 95%) as a white crystalline powder. TLC R_f = 0.67 (30% EtOAc-hexanes) m.p. 156.4-157.5 °C. IR (neat) ν_{max}: 3518, 3476, 3288, 3247, 2932, 2237, 2067, 1611, 1503, 1256, 1109, 999, 842, 832 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (1H, d, *J* = 8.6 Hz, H-1), 6.72 (1H, dd, *J* = 8.6, 2.7 Hz, H-2),

6.64 (1H, d, *J* = 2.7 Hz, H-4), 2.93-2.80 (2H, m, H-6), 2.61 (1H, s, H-21), 2.42-2.30 [2H, (m, H-11a), (m, H-16a)] 2.24 (1H, td, *J* = 11.4, 4.2 Hz, H-9a), 2.03 (1H, ddd, *J* = 13.6, 12.2, 3.9 Hz, H-16b), 1.98 (1H, br, OH), 1.92 (1H, td, *J* = 13.0, 4.2 Hz, H-12a), 1.91-1.85 (1H, m, H-7b), 1.84-1.67 [3H, (m, H-15a), (m, H-12b), (m, H-14a)], 1.55-1.32 [4H, (m, H-11b), (m, H-15b), (m, H-7a), (m, H-8b)], 0.89 (3H, s, H-18). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5 (C-3), 138.1 (C-5), 132.6 (C-10), 126.5 (C-1), 113.9 (C-4), 111.6 (C-2), 87.6 (C-20), 80.0 (C-17), 74.2 (C-21), 54.5 (spt, J_{CD} = 21.9 Hz, C-19), 49.6 (C-14), 47.2 (C-13), 43.6 (C-9), 39.5 (C-8), 39.1 (C-16), 32.9 (C-12), 30.0 (C-6), 27.4 (C-7), 26.5 (C-11), 22.9 (C-15), 12.8 (C-18). HRMS(ESI) calcd. for $[C_{21}H_{23}D_3O_2$ - OH$]^+$: 296.2094, found: 296.2085.

Scheme S4. *Synthesis of compound **7**.*



Synthesis of compound 7.

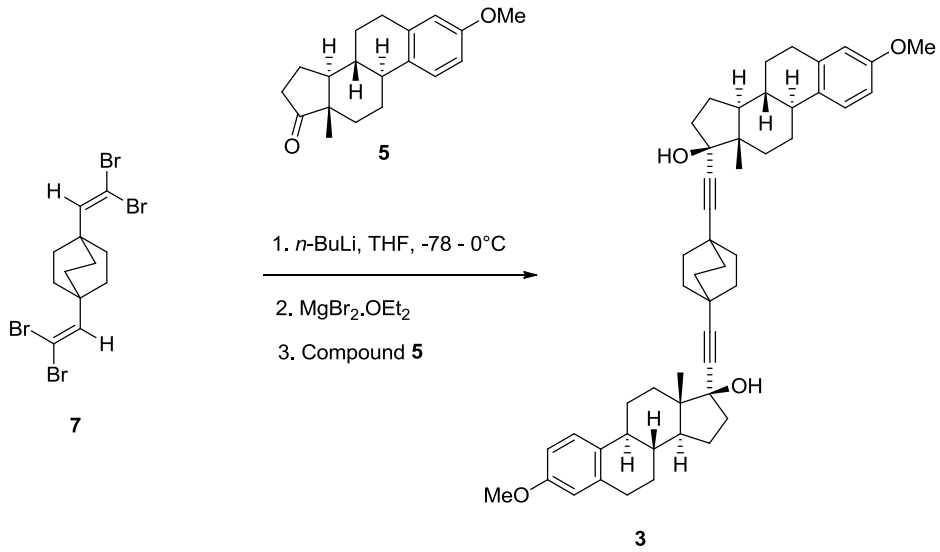
Step 1. Synthesis of dialdehyde. To a stirred solution of dry DMSO (1.33 mL, 1.46 g, 18.74 mmol, 4.7 equiv) in dry CH_2Cl_2 (20 mL) at -78 °C was added slowly oxalyl chloride (2.0M in CH_2Cl_2, 4.2 mL, 8.37 mmol, 2.1 equiv), the reaction mixture was stirred under Argon atmosphere for 15 min at -78 °C, then was added dropwise a solution of of diol **6**[2] (679 mg, 3.99 mmol, 1.0 equiv) in a mixture of CH_2Cl_{2anh}-$DMSO_{anh}$ 4:1 (8 mL, washed 1 x 2 mL), the reaction mixture was stirred for 35 min at -78 °C, then dry triethylamine (6.1 mL, 4.44 g, 43.87 mmol, 11.0 equiv) was added, the mixture was stirred 5 min at -78 °C, then warmed to 0 °C and stirred for 1 h. Afterward, 20 mL of water was added, the CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined and washed successively with 1% HCl (1 x 50 mL), 5% Na_2CO_3 (1 x 50 mL), water (1 x 50 mL) and brine (1 x 50 mL). After drying over $MgSO_4$ most of the solvent was removed *in vacuo*, then the flask was fitted with a septum cap, flushed with argon and the residue was dissolved in dry CH_2Cl_2 (5

mL), this solution containing dialdehyde was kept under argon atmosphere and used in the next step with any further purification.

Note: Decomposition of the dialdehyde occurs when concentrated to dryness.

*Step 2. Synthesis of compound **7**.* In a round-bottom flask, a solution of carbon tetrabromide (6.61 g, 19.94 mmol, 5.0 equiv) in dry CH_2Cl_2 (40 mL) was cooled down to 0 °C, then triphenylphosphine (10.46 g, 39.88 mmol, 10.0 equiv) was added and immediately after the solution of the freshly prepared dialdehyde was added with cannula. The mixture was stirred for 1 h at 0 °C and 2 h at room temperature. The reaction mixture was quenched with 40 mL of water and extracted with CH_2Cl_2 (3 x 50 mL), the combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography (4% diethyl ether-hexanes) affording bis-dibromoalkene **7** as white crystals (1.82 g, 95% two steps). m.p. 112.0-113.0 °C (lit.: 109 °C). The spectral data matched those previously reported.[3]

Scheme S5. *Synthesis of bicyclo[2.2.2]octane-mestranol rotor (compound **3**)*.



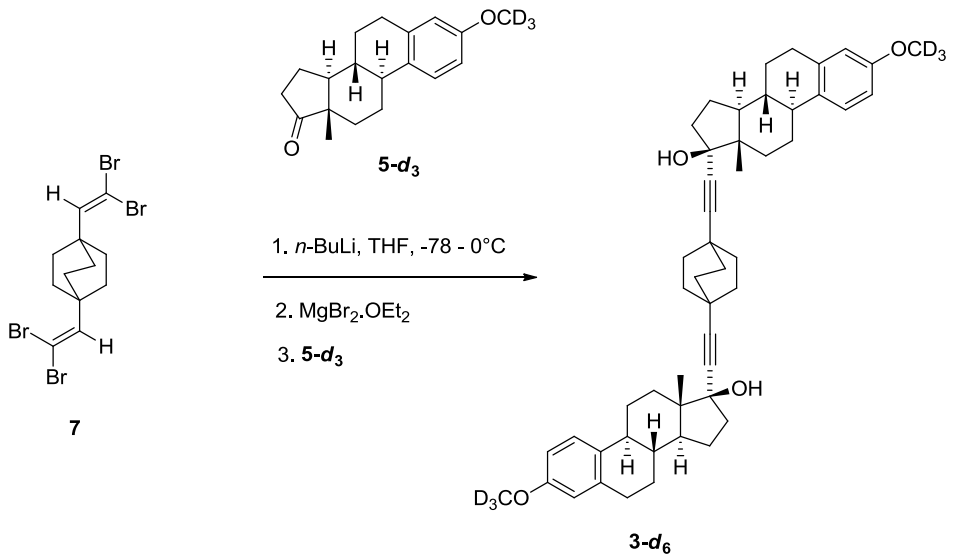
Synthesis of* bicyclo[2.2.2]octane-mestranol *rotor (compound 3).

Step 1. Preparation of $MgBr_2{\cdot}OEt_2$. Some drops of 1,2-dibromoethane were added to a mixture of Magnesium turnings (50 mg, 2.05 mmol, 4.0 equiv) and dry diethyl ether (3.0 mL). The mixture was heated until reflux started, then the remaining 1,2-dibromoethane (0.18 mL (total), 386 mg,

2.05 mmol, 4.0 equiv) was added dropwise. The mixture was allowed to stir at room temperature for 1 h after completion of the addition.

Step 2. *n*-BuLi (1.6M in hexanes, 1.76 mL, 2.82 mmol, 5.5 equiv) was added dropwise to a solution of bis-dibromoalkene **7** (245 mg, 0.51 mmol, 1.0 equiv) in dry THF (3.6 mL) at -78 °C, the reaction mixture was stirred at this temperature under argon atmosphere for 1.5 h and 30 min at 0 °C. The resulting mixture was cooled again to -78 °C and the previously prepared $MgBr_2 \cdot OEt_2$ mixture was added by syringe. Afterwards, mestrone **5** (292 mg, 1.03 mmol, 2.0 equiv) was added dissolved in dry diethyl ether (2.7 mL) and dry CH_2Cl_2 (2.7 mL). Then the dry ice bath was replaced by a 0 °C ice bath and the reaction mixture was stirred 15 h, allowing the mixture reach room temperature slowly. Then, the mixture was cooled to -78 °C, and aqueous saturated solution of NH_4Cl (6.0 mL) was added, the mixture was stirred at room temperature and after separation of the layers, brine was added (6 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (20% ethyl acetate-hexanes) to afford compound **3** (170 mg, 46%) as a white solid. TLC R_f = 0.20 (20% EtOAc-hexanes) m.p. 252-253 °C. $[\alpha]_D^{23}$ = -19.0 (c 0.4, $CHCl_3$). IR (neat) ν_{max}: 3532, 3468, 2941, 2866, 1610, 1498, 1257, 1041, 868, 817, 781 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (2H, d, *J* = 8.6 Hz, H-1), 6.71 (2H, dd, *J* = 8.6, 2.8 Hz, H-2), 6.63 (2H, d, *J* = 2.8 Hz, H-4), 3.78 (6H, s, OCH_3), 2.93-2.78 (4H, m, H-6), 2.34 (2H, m, H-11a), 2.21 (2H, ddd, *J* = 13.5, 9.5, 5.5 Hz, H-16a), 2.16 (2H, m, H-9), 1.97 (2H, td, *J* = 13.5, 3.8 Hz, H-16b), 1.92-1.68 [6H, (m, H-7a), (m, H-12a), (m, H-15a)], 1.76 (12H, s, H-23), 1.68-1.57 [4H, (m, H-12b), (m, H-14)], 1.52-1.28 [8H, (m, H-11b), (m, H-8), (m, H-7b), (m, H-15b)], 0.85 (6H, s, H-18). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5 (C-3), 138.1 (C-5), 132.6 (C-10), 126.5 (C-1), 113.9 (C-4), 111.6 (C-2), 92.7 (C-20), 83.9 (C-21), 79.8 (C-17), 55.3 (C-19), 49.7 (C-14), 47.4 (C-13), 44.0 (C-9), 39.6 (C-8), 39.2 (C-16), 33.0 (C-12), 32.1 (C-23), 30.0 (C-6), 27.5 (C-7), 26.6 (C-11), 26.4 (C-22), 22.9 (C-15), 13.0 (C-18). HRMS (LIFDI) calcd. for $[C_{50}H_{62}O_4]^+$: 726.4648, found: 726.4670.

Scheme S6. *Synthesis of bicyclo[2.2.2]octane-mestranol rotor (compound **3-d$_6$**)*



Synthesis of bicyclo[2.2.2]octane-mestranol rotor (compound 3-d$_6$)

Step 1. Preparation of $MgBr_2 \cdot OEt_2$. Some drops of 1,2-dibromoethane were added to a mixture of Magnesium turnings (73 mg, 3.00 mmol, 4.0 equiv)and dry diethyl ether (9.0 mL). The mixture was heated until reflux started, then the remaining 1,2-dibromoethane (0.26 mL (total), 563 mg, 3.00 mmol, 4.0 equiv) was added dropwise. The mixture was allowed to stir at room temperature for 1 h after completion of the addition.

Step 2. n-BuLi (1.6M in hexanes, 2.6 mL, 4.12 mmol, 5.5 equiv) was added dropwise to a solution of bis-dibromoalkene **7** (358 mg, 0.75 mmol, 1.0 equiv) in dry THF (5.4 mL) at -78 °C, the reaction mixture was stirred at this temperature under argon atmosphere for 1.5 h and 30 min at 0 °C. The resulting mixture was cooled to -78 °C and the recently prepared $MgBr_2 \cdot OEt_2$ mixture was added by syringe. Afterwards, mestrone **5-*d*$_3$** (431 mg, 1.50 mmol, 2.0 equiv) was added dissolved in dry diethyl ether (4.0 mL) and dry CH_2Cl_2 (8.0 mL). Then the dry ice bath was replaced by a 0 °C ice bath and the reaction mixture was stirred 15 h, during this time the mixture is allowed to reach room temperature slowly. The mixture was cooled to -78 °C, then aqueous saturated solution of NH_4Cl (15 mL) was added and the mixture was stirred at room temperature. After separation of the layers, brine was added (15.0 mL), then the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated *in*

vacuo. The crude product was purified by flash column chromatography (20% ethyl acetate-hexanes) to afford compound **3-*d*$_6$** (295 mg, 53%) as a white solid. TLC R_f = 0.18 (20% EtOAc-hexanes) m.p. 251.6-253.0 °C. IR (neat) ν_{max}: 3532, 3464, 2942, 2865, 2243, 2212, 2066, 1609, 1495, 1288, 1257, 1110, 1000, 867, 817 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* = 8.6 Hz, H-1), 6.71 (2H, dd, *J* = 8.6, 2.7 Hz, H-2), 6.63 (2H, d, *J* = 2.7 Hz, H-4), 2.93-2.78 (4H, m, H-6), 2.34 (2H, m, H-11a), 2.21 (2H, ddd, *J* = 13.5, 9.5, 5.5 Hz, H-16a), 2.16 (2H, m, H-9), 1.97 (2H, td, *J* = 13.5, 3.8 Hz, H-16b), 1.92-1.68 [6H, (m, H-7a), (m, H-12a), (m, H-15a)], 1.77 (12H, s, H-23), 1.68-1.57 [4H, (m, H-12b), (m, H-14)], 1.52-1.28 [8H, (m, H-11b), (m, H-8), (m, H-7b), (m, H-15b)], 0.86 (6H, s, H-18). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5 (C-3), 138.1 (C-5), 132.6 (C-10), 126.5 (C-1), 113.9 (C-4), 111.6 (C-2), 92.6 (C-20), 83.9 (C-21), 79.8 (C-17), 54.5 (spt, J_{CD} = 21.8 Hz, C-19), 49.6 (C-14), 47.3 (C-13), 44.0 (C-9), 39.6 (C-8), 39.2 (C-16), 33.0 (C-12), 32.1 (C-23), 30.0 (C-6), 27.4 (C-7), 26.6 (C-11), 26.4 (C-22), 22.9 (C-15), 13.0 (C-18). HRMS(ESI) calcd. for $[C_{50}H_{56}D_6O_4 - OH]^+$: 715.4997, found: 715.5006.

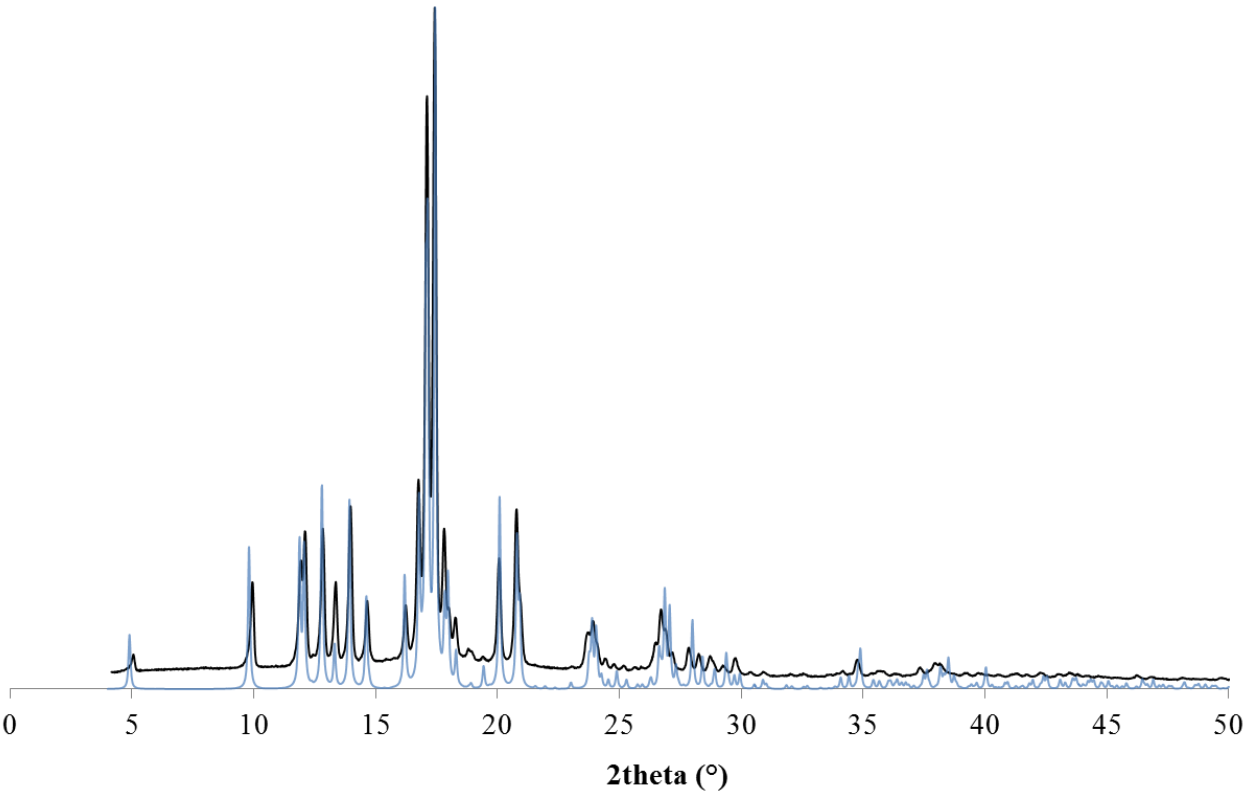


Figure S1. Comparison between calculated (blue line, bottom) and experimental (black line, top) powder X-ray diffraction patterns of rotor **3** samples from hexanes/ethyl acetate.

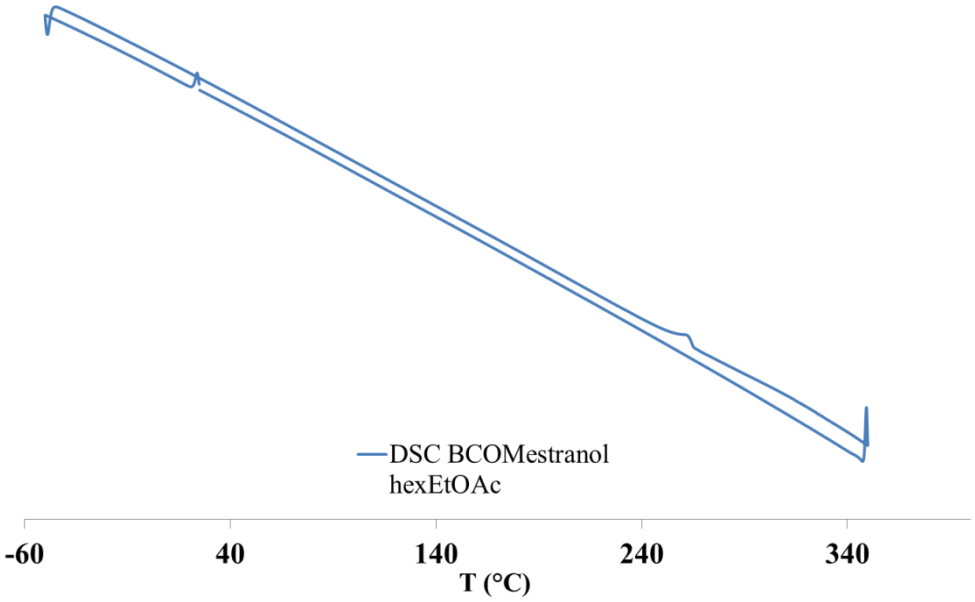


Figure S2. Differential scanning calorimetry trace from -50 °C to 350 °C of rotor **3**. Sample recrystallized from hexanes/ethyl acetate. The irreversible endothermic transition occurring in the 251-253 °C range corresponds to the melting point, as confirmed by visual determination.

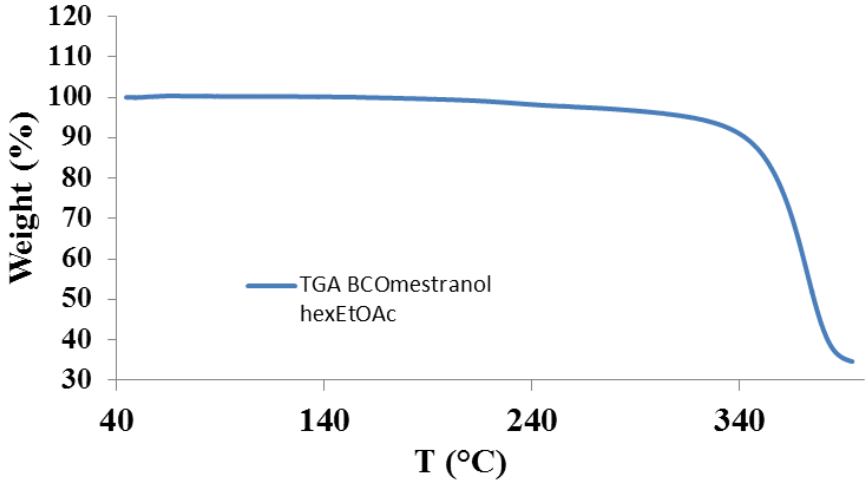


Figure S3. Thermogravimetric analysis of rotor **3**. Sample recrystallized from hexanes/ethyl acetate showing the rapid decomposition of the melted sample at 323 °C.

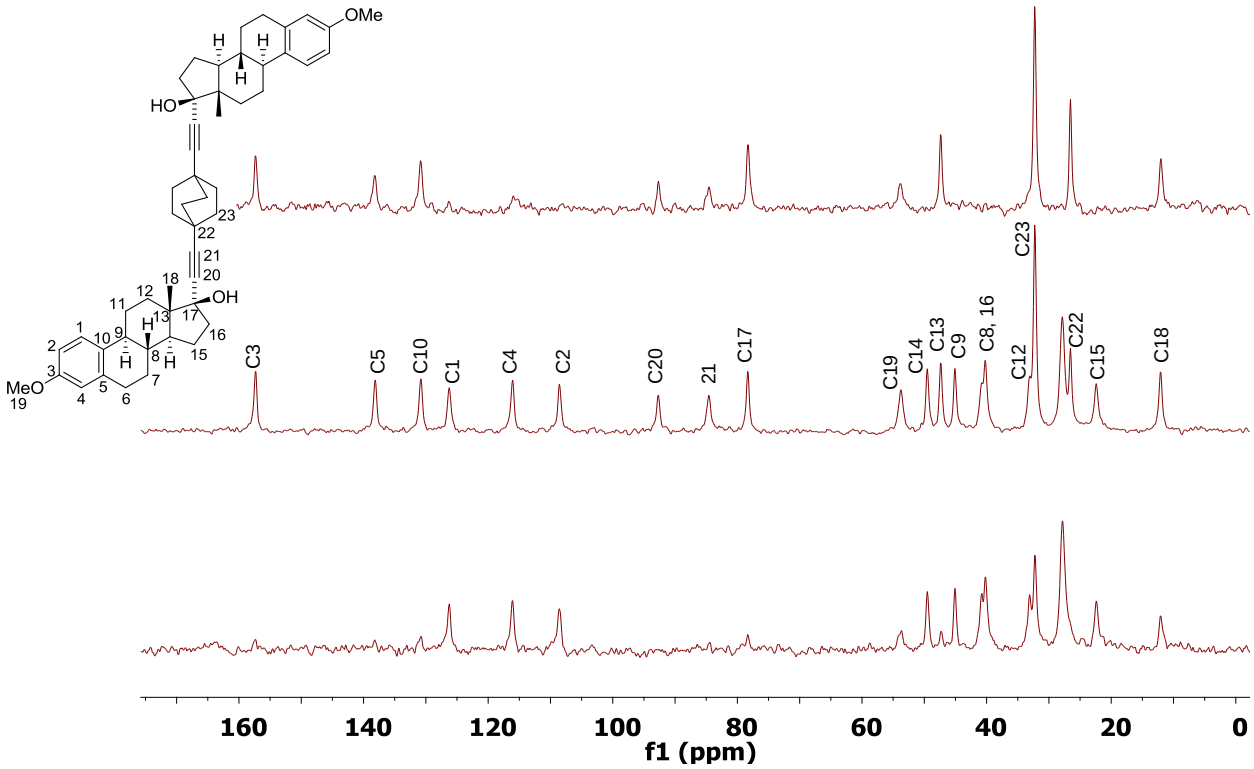


Figure S4. ^{13}C NMR CPMAS spectra of compound **3** recrystallized from hexanes/ethyl acetate at room temperature. Center: Spectrum showing all carbon atom signals using a contact time of 5 ms. Top: Dipolar dephasing experiment highlighting quaternary and protonated, highly mobile carbon atoms, including the bicyclo[2.2.2]octane methylene carbons (C23). Bottom: Contact time of 0.1 ms, showing only protonated carbon atoms. Assignments are based on chemical shifts and by comparison with solution experiments.

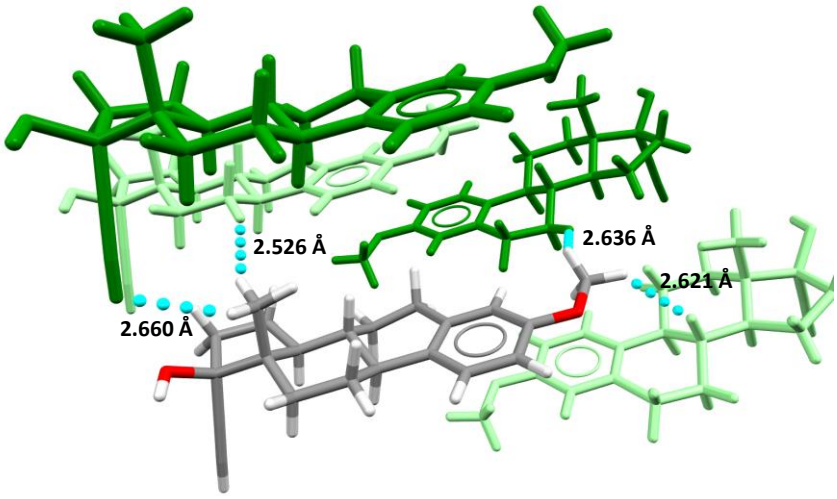


Figure S5. Diagram illustrating the neighboring molecules of compound **8** with distances of 2.621 and 2.636 Å.

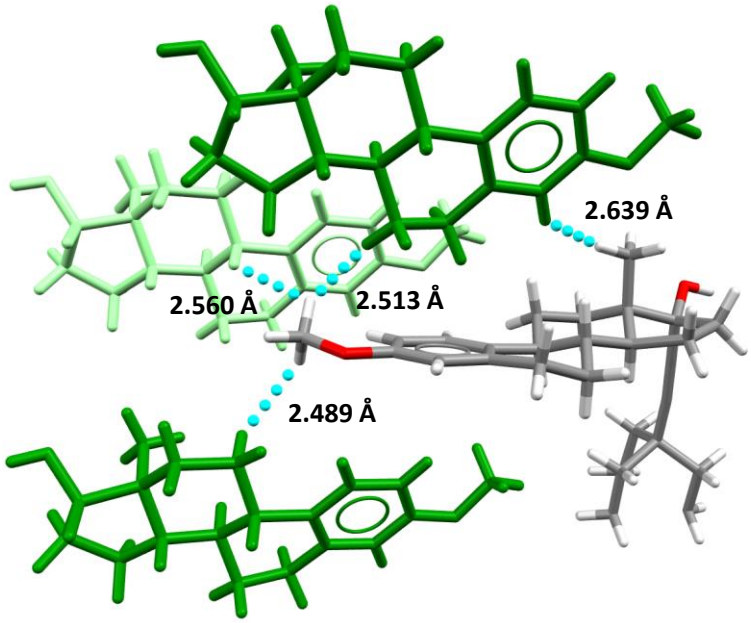


Figure S6. Diagram illustrating the neighboring molecules of compound **3** with distances of 2.489, 2.513 and 2.560 Å.

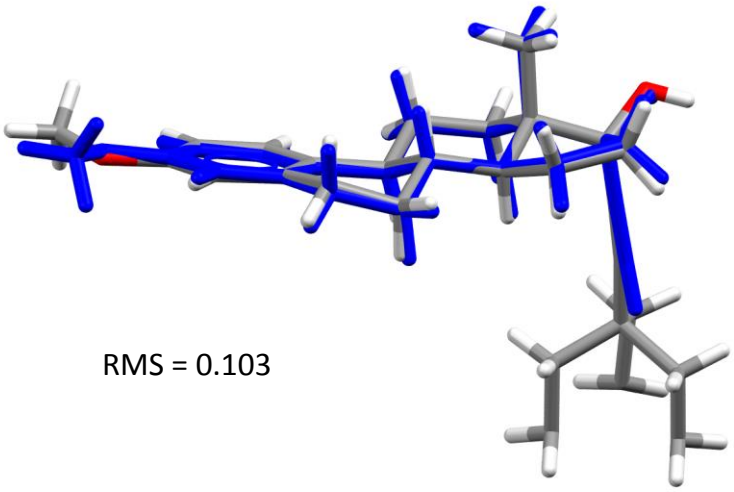


Figure S7. Overlay of the steroidal fragments of compound **3** and **8**. The root-mean-square value highlights the similarity between the structures.

Table 1. Selected crystallographic parameters of compound 3

Formula	C50 H62 O4
MW/g mol^{-1}	727.00
Crystal system	Tetragonal
Space group	$P4_32_12$
a/Å	7.4876(7)
b/Å	7.4876(7)
c/Å	72.129(10)
α(°)	90.00
β(°)	90.00
γ(°)	90.00
V/$Å^3$	4043.9(8)
Z	4
Z’	0.5
ρc/g cm^{-3}	1.194
Collected Refl.	51185
Ind. Refl. (Rint)	3118
Observed Refl.	2692
$R[F^2 > 2\sigma(F^2)]$	0.0569
R_w (all data)	0.1526
Δρmax/e $Å^3$	0.318
Δρmin/e $Å^3$	-0.345
T (K)	100(2)

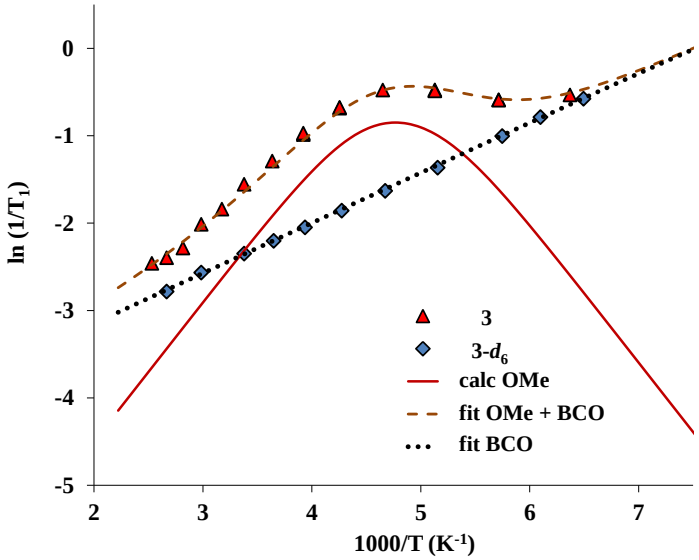


Figure S8. Fit of the ^{1}H spin-lattice relaxation experiments to the Kubo-Tomita expression of compounds **3** (filled triangles) and **3-*d*$_6$** (filled squares) The dashed line is the result of adding the calculated contribution of the OMe (solid line) and the experimental contribution of the BCO (dotted line) groups.

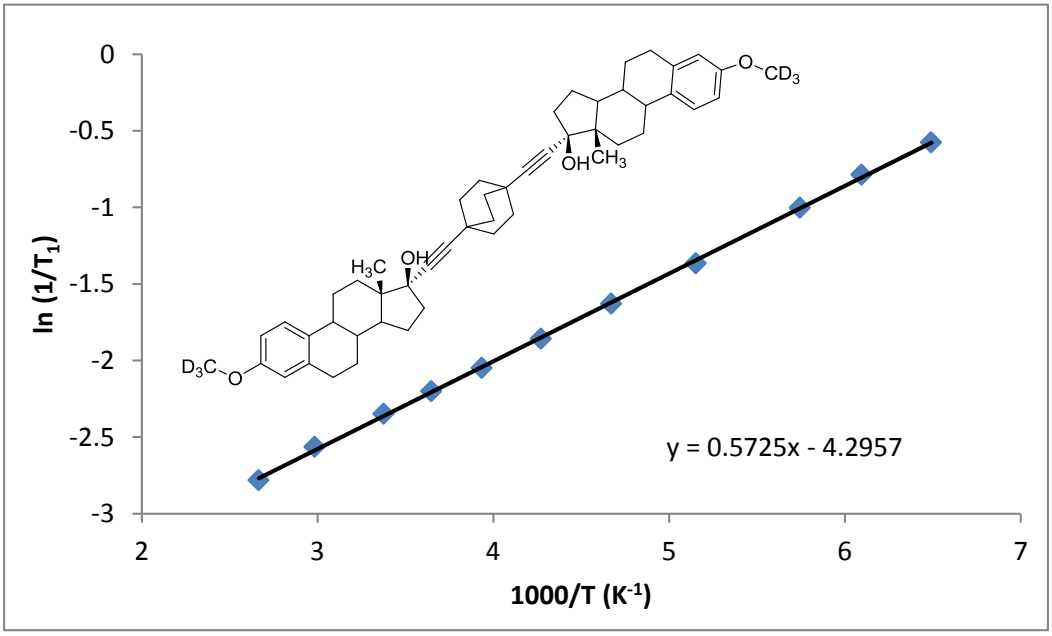


Figure S9. Kubo-Tomita fit for the T_1 values from the ^{1}H spin-lattice relaxation experiments of compound **3**-d_6.

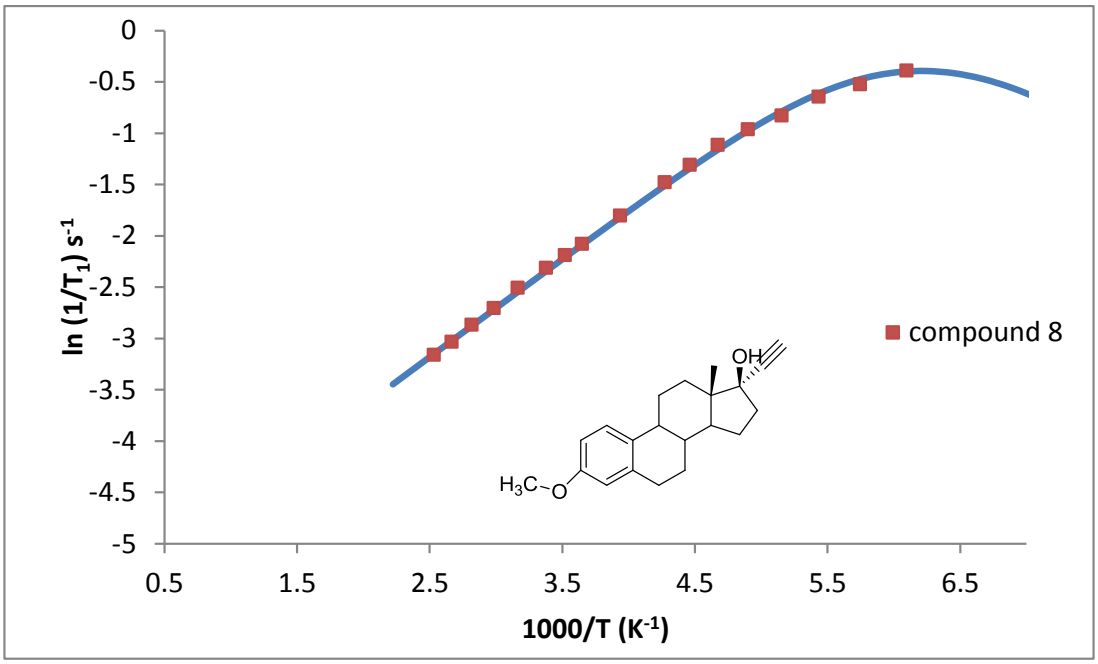


Figure S10. Kubo-Tomita fit for the T_1 values from the ^{1}H spin-lattice relaxation experiments of compound **8**.

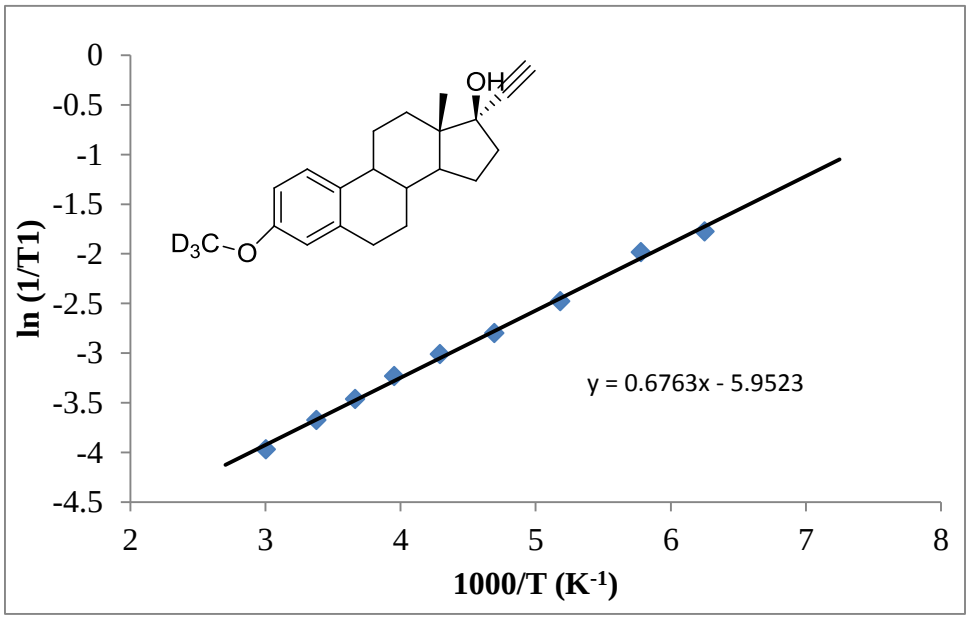


Figure S11. Linear regression fit for the T_1 values from the ^{1}H spin-lattice relaxation experiments of compound **8**-d_3.

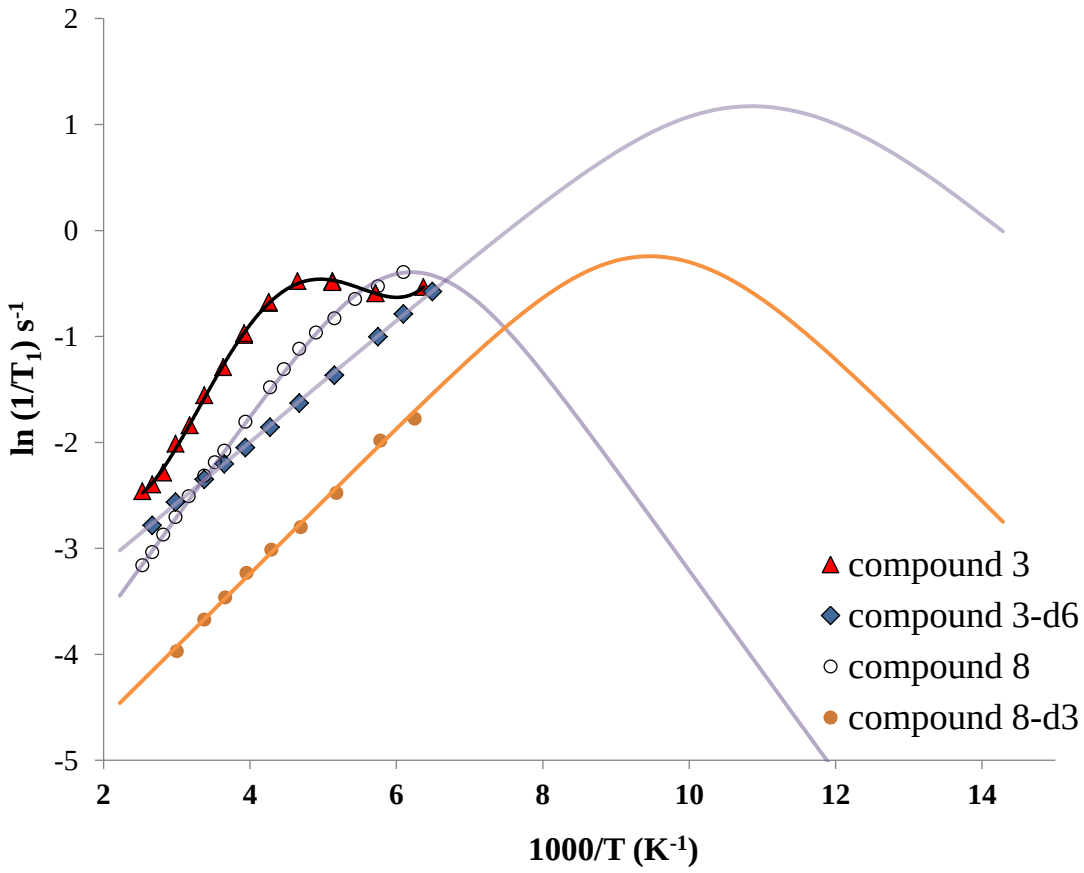


Figure S12. Comparison of the measured spin lattice relaxation rates, $1/T_1$, and the corresponding Kubo-Tomita fit of compounds studied in this paper. In compound **3** both the BCO and MeO groups dominate the relaxation process (triangles), contrasting with methoxy-deuterated **3-*d*$_6$** where the BCO group is the main responsible of the relaxation (filled squares). Similarly, the MeO group causes the relaxation in mestranol **8** (open circles) whereas the Me group is the responsible of the relaxation in methoxy-deuterated mestranol **8-*d*$_3$** (solid circles).

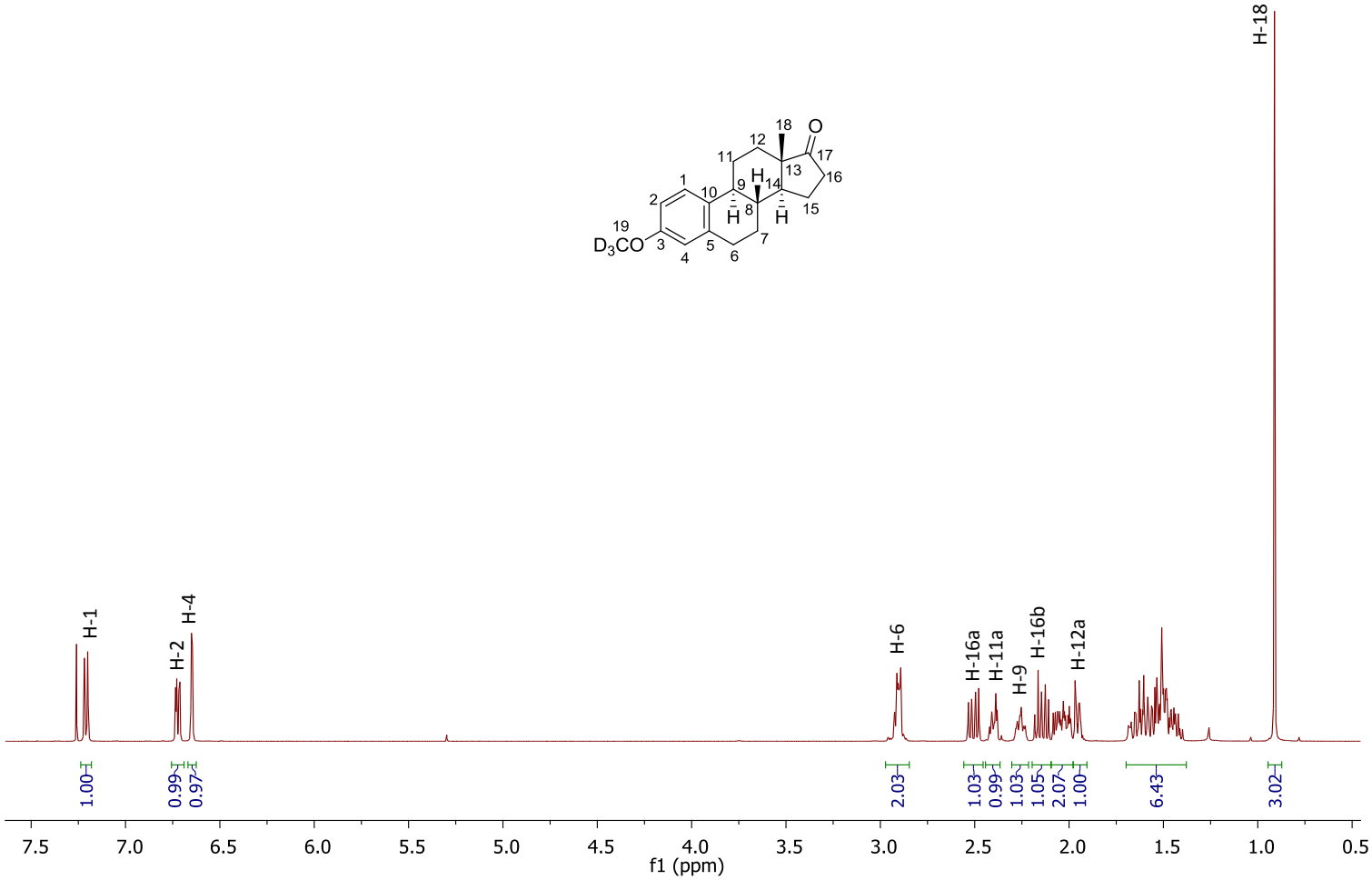


Figure S13. ^{1}H NMR of compound **5-*d*$_3$** in $CDCl_3$ at 500 MHz

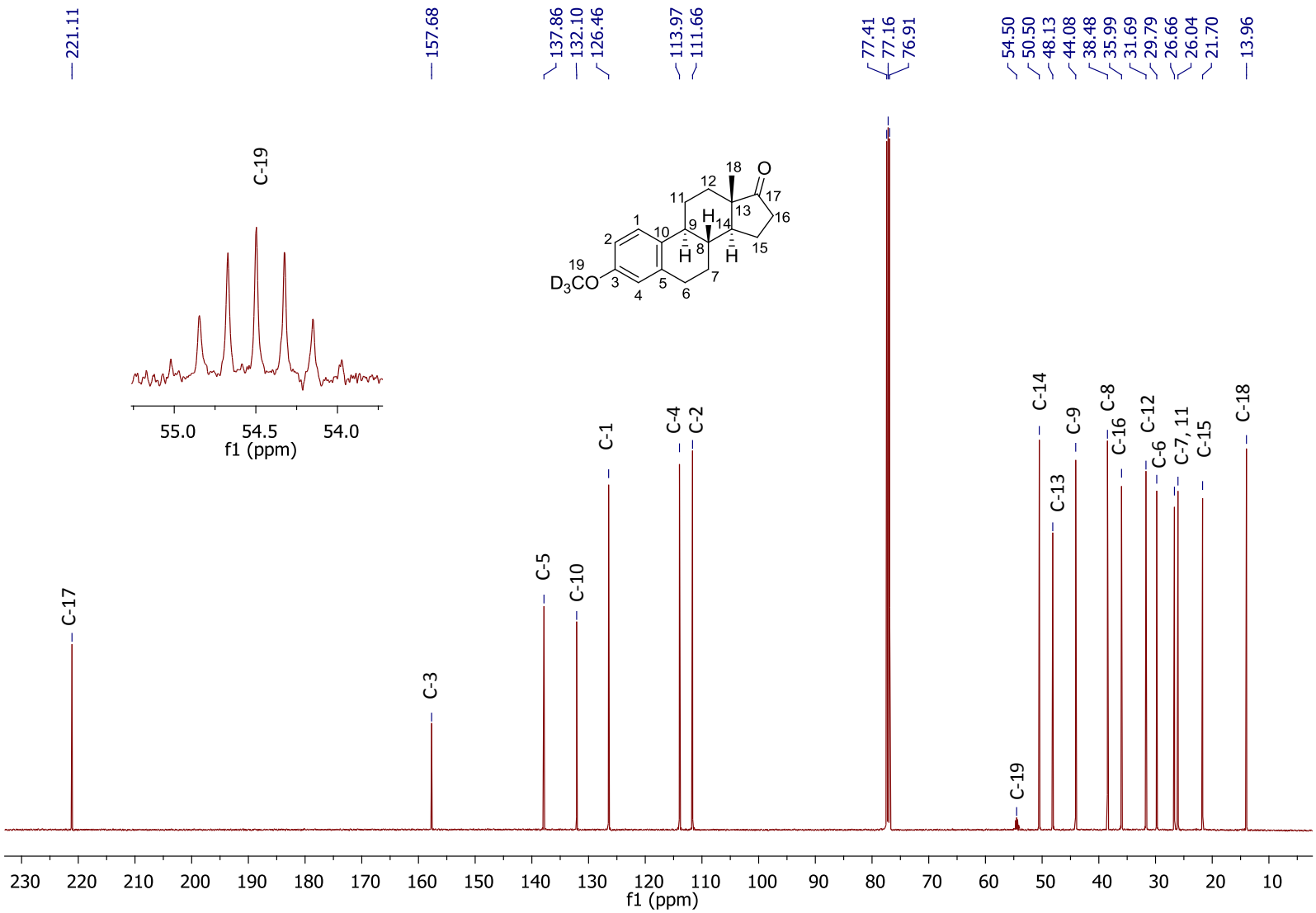


Figure S14. ^{13}C NMR of compound **5-*d*$_3$** in $CDCl_3$ at 125 MHz

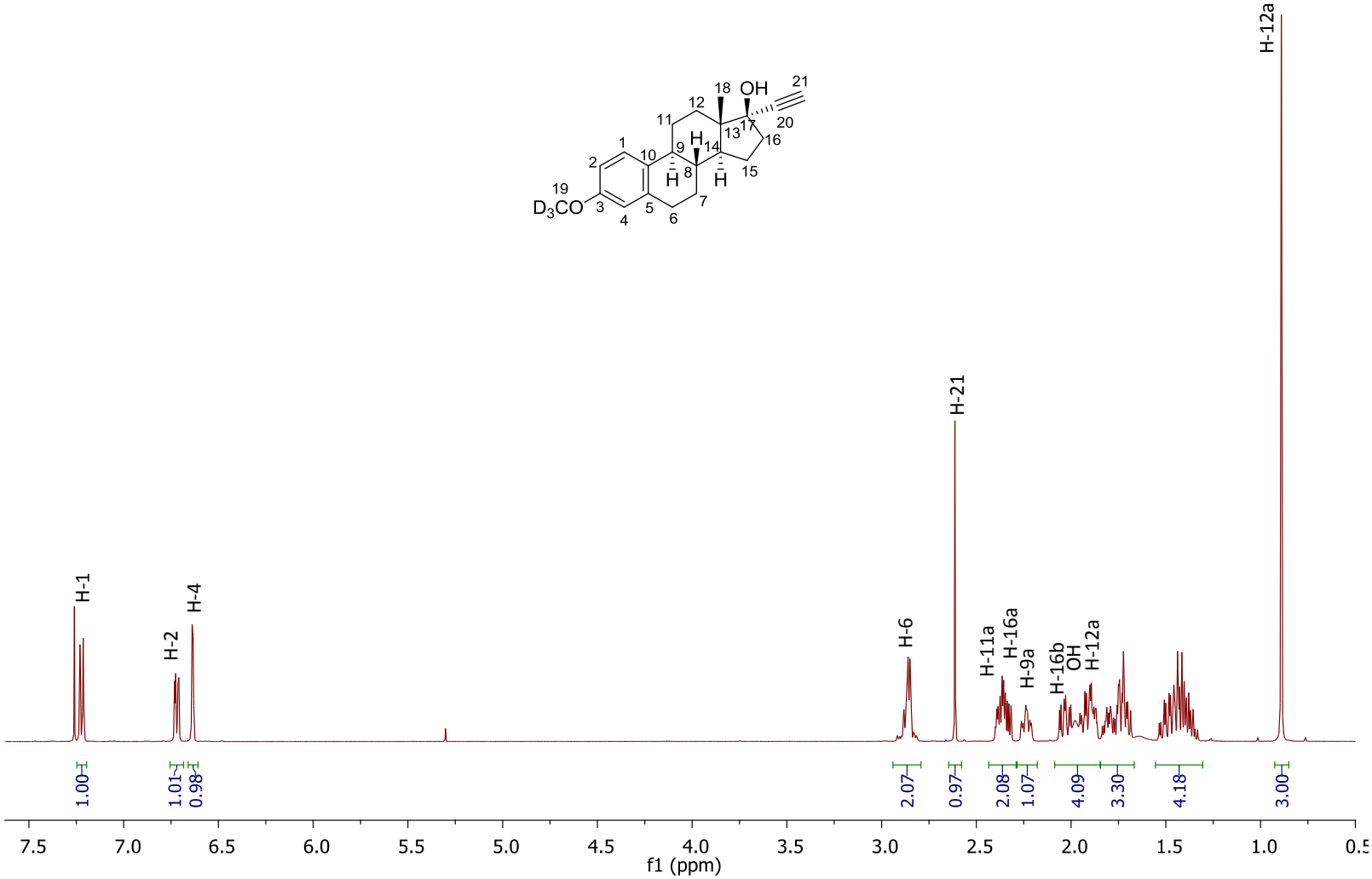


Figure S15. ^{1}H NMR of **8-*d*$_3$** in $CDCl_3$ at 500 MHz

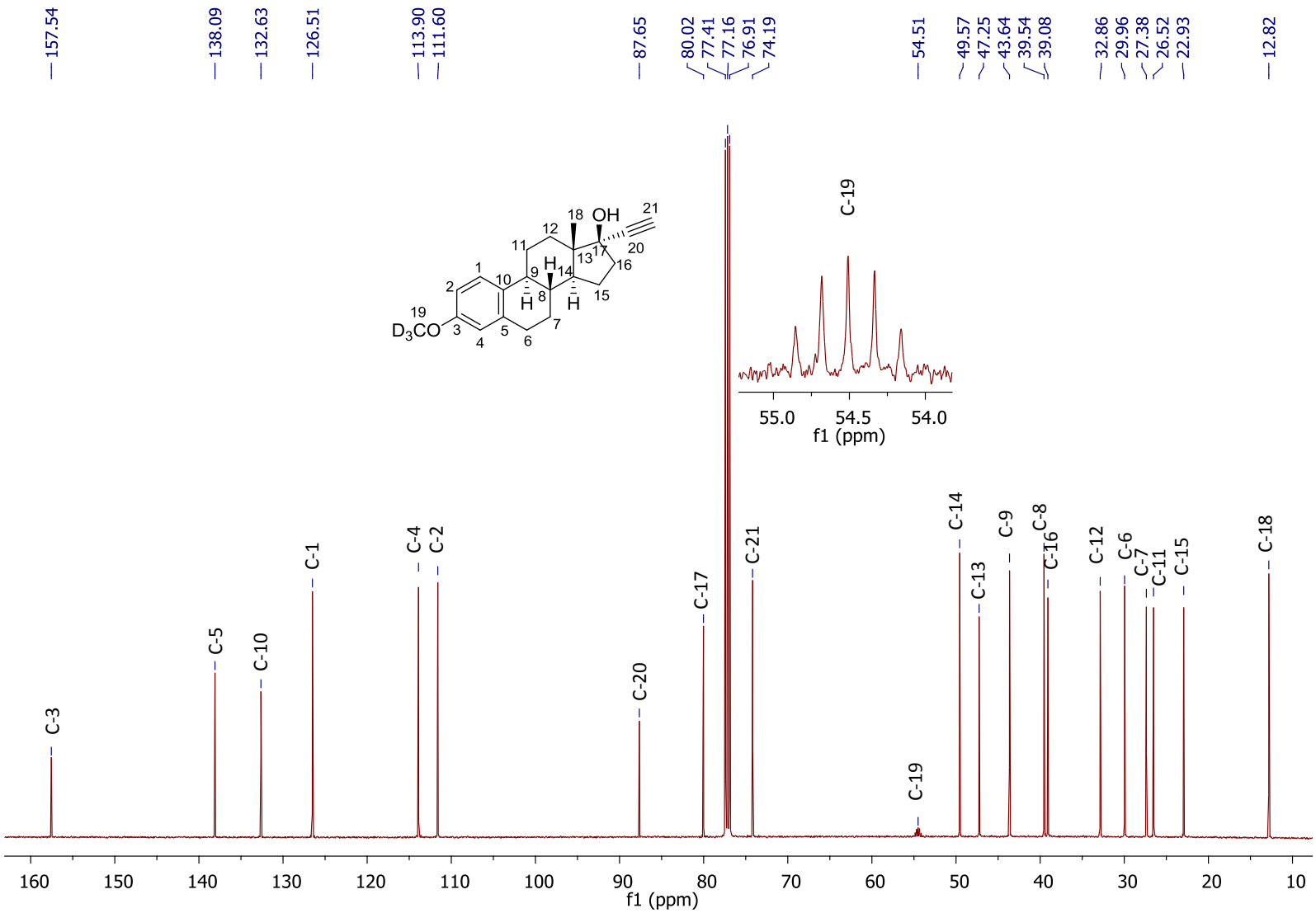


Figure S16. ^{13}C NMR of **8-*d*$_3$** in $CDCl_3$ at 125 MHz

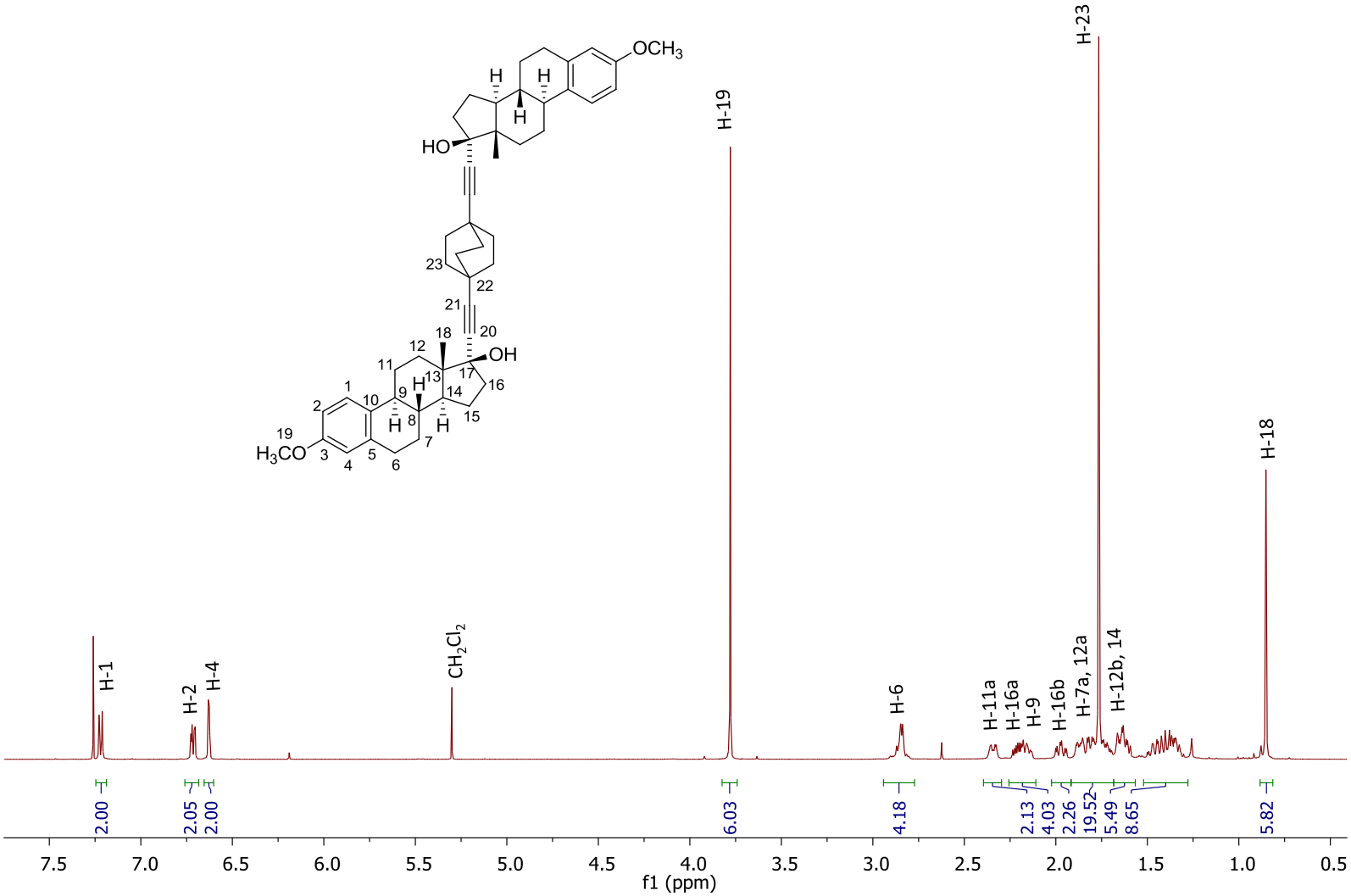


Figure S17. ^{1}H NMR of compound **3** in $CDCl_3$ at 500 MHz

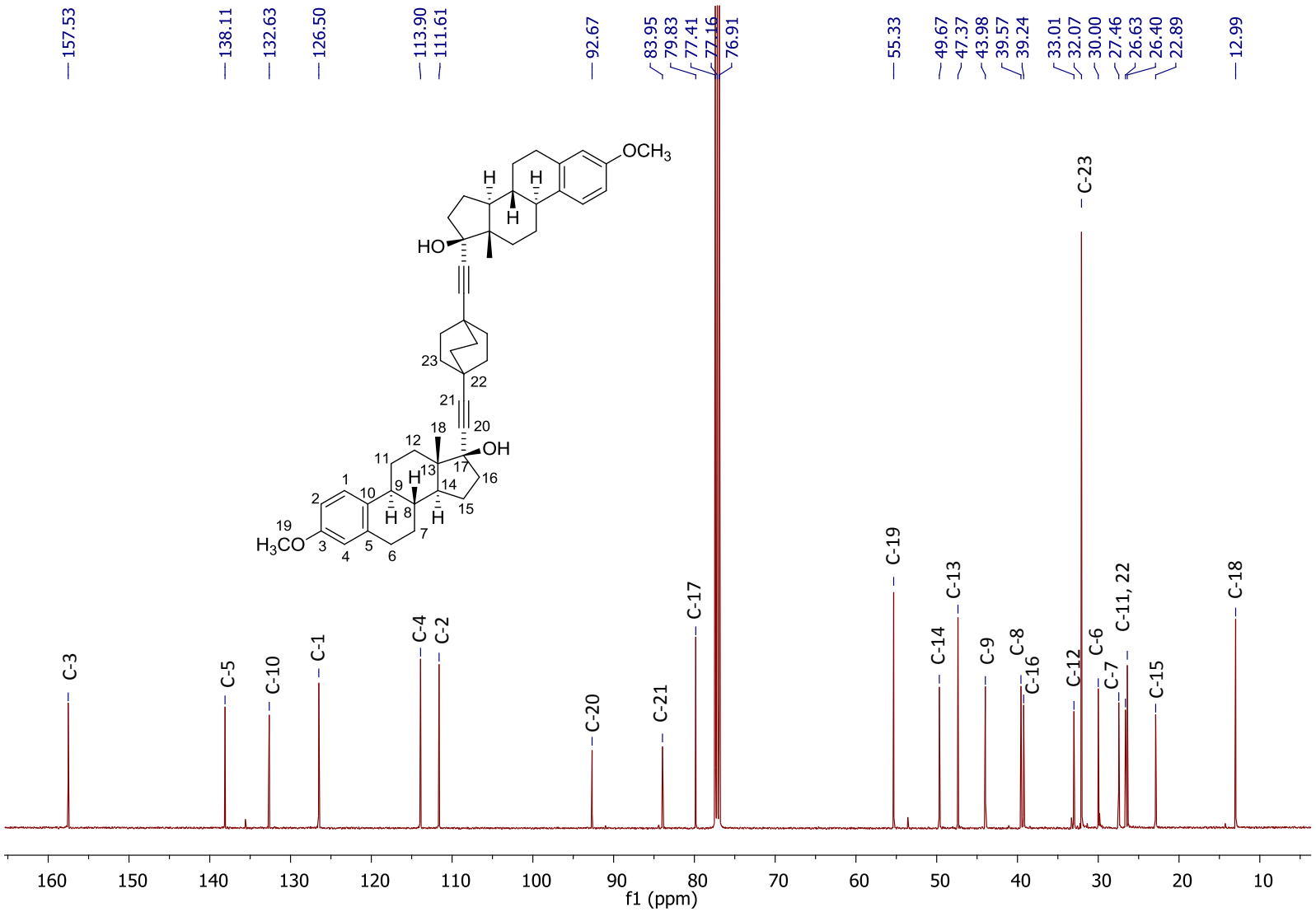


Figure S18. ^{13}C NMR of compound **3** in $CDCl_3$ at 125 MHz

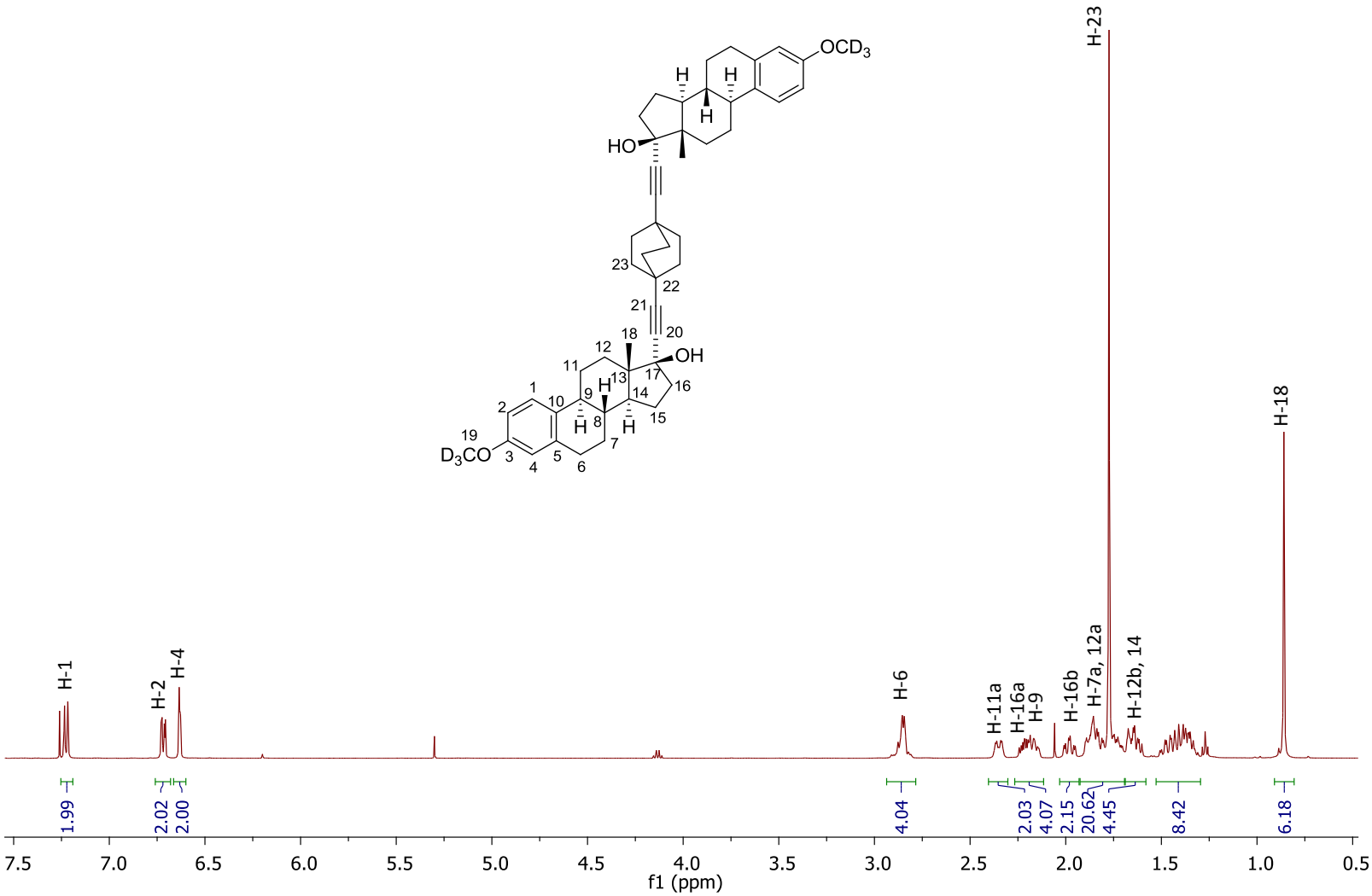


Figure S19. ^{1}H NMR of compound **3-*d*$_3$** in $CDCl_3$ at 500 MHz

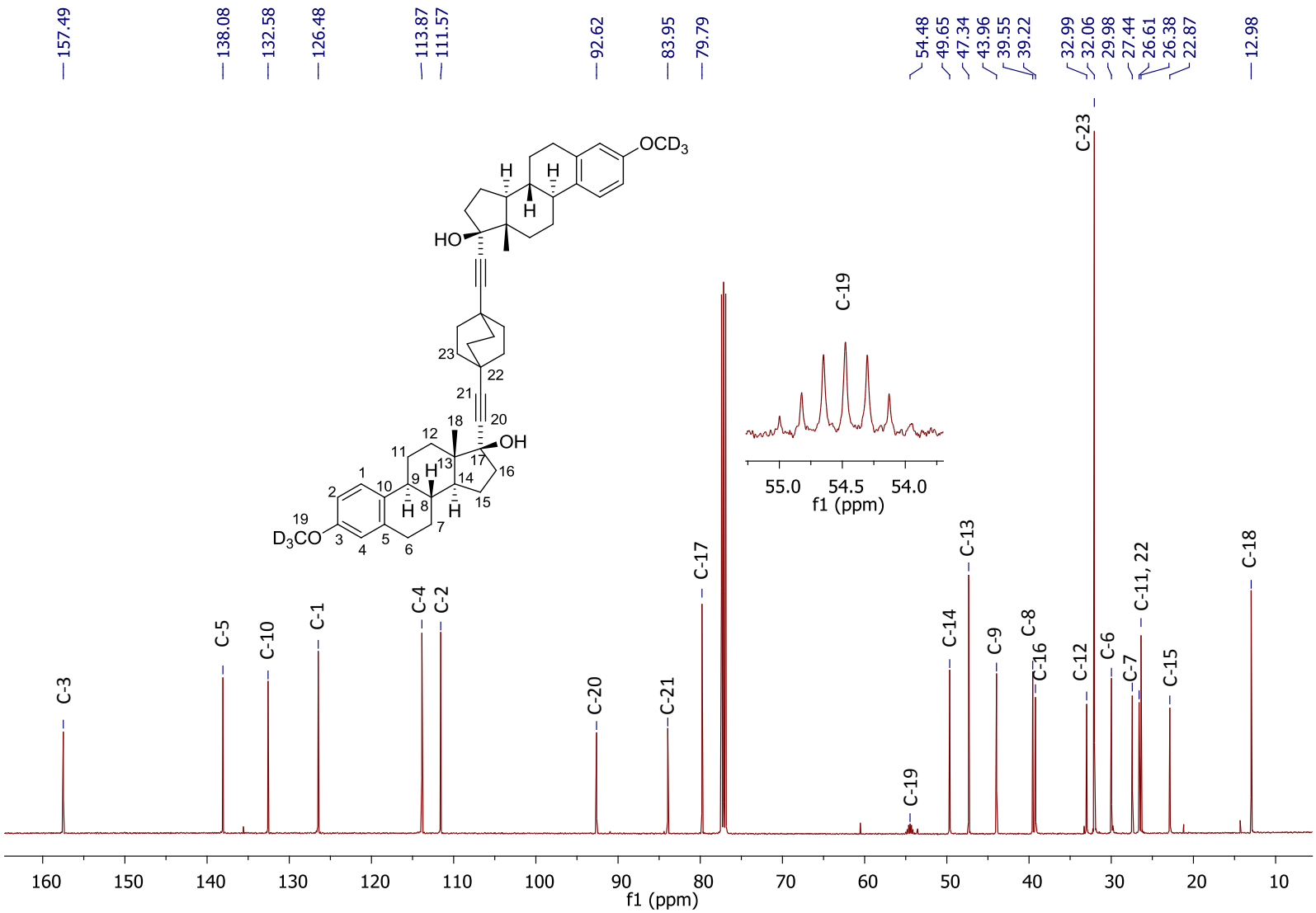


Figure S20. ^{13}C NMR of compound **3-*d*$_3$** in $CDCl_3$ at 125 MHz

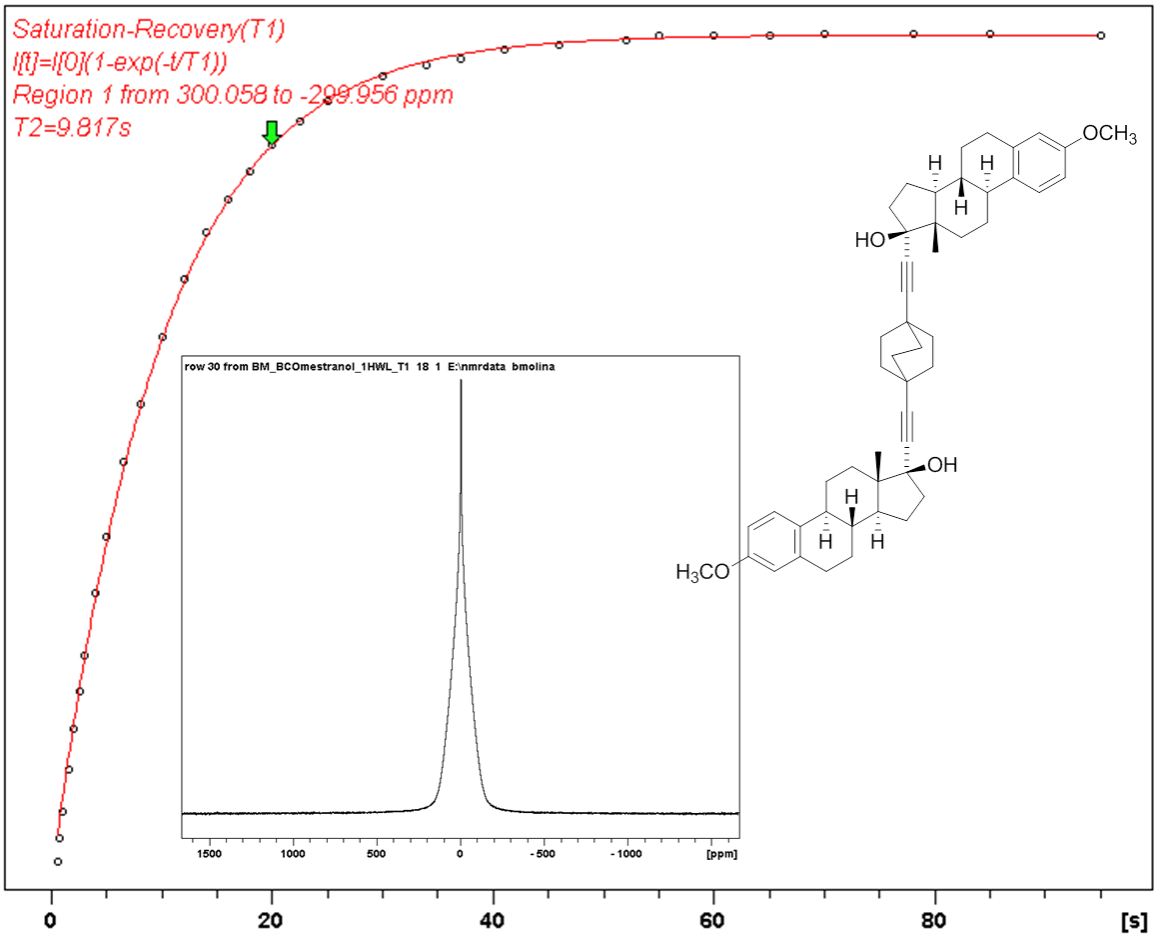


Figure S21. Representative example of the mono-exponential fit to representative ^{1}H wideline spin-lattice relaxation (T_1) inversion recovery data of compound **3** at T= 355 K (T_1 = 9.817 s) with τ' values of 0.5s, 0.75s, 1s, 1.5s, 2s, 2.5s, 3s, 4s, 5s, 6.5s, 8s, 10s, 12s, 14s, 16s, 20s, 22.5s, 25s, 30s, 34s, 37s, 41s, 46s, 52s, 55s, 60s, 65s, 70s, 78s, 85s and 95s. The insert shows the recovery of the signal at 52 s.

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2. (a) Kumar, K.; Wang, S. S.; Sukenik, C. N.; *J. Org. Chem.* **1984**, *49*, 665. (b) Goldmisth, R. H.; Vura-Weis, J.; Scott, A. M.; Scott, A. M.; Borkar, S; Sen, A.; Ratner, M. A.; Wasielewski, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 7659.

3. Lemouchi, C.; Vogelsberg, C. S.; Zorina, L.; Simonov, S.; Batail, P.; Brown, S.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **2011**, *133*, 6371-6379.