Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.


**SUPPORTING INFORMATION FOR**

# Development of novel Gemini-cholesterol analogues for Retinoid-related Orphan Receptor

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## 1. Experimental part

### 1. 1. General procedures (Chemistry)

Solvents were purified and dried by standard procedures before use. The evolution of the reactions was followed by thin layer chromatography (TLC) with Merck 60 $F_{254}$ silica gel plates on aluminium support. The chromatoplates were visualized by exposure to UV light (254 nm) and developed by treatment with a staining solution and subsequent heating. The staining solution used was *p*-anisaldehyde (4.2 mL) in AcOH (3.75 mL), $H_2SO_4$ (12.5 mL) and MeOH (338 mL). For purification by pressure column chromatography was used Merck silica gel 60 (230-400 mesh). The products were previously mixed with silica gel before being introduced into the column.

Optical rotations were obtained using a JASCO P-2000 polarimeter. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker AMX 400 (400 MHz for $^1$H and 100 MHz for $^{13}$C). Chemical shifts (δ) were measured in ppm relative to TMS δ = 0 for $^1$H or to chloroform δ = 77.0 ppm for $^{13}$C as internal standard. Data are reported as follows: chemical shift (integration, multiplicity, coupling constants (*J*) and signal assignment). The infrared spectra were carried out using the ATR technique in a NICOLET 6700. Mass spectra with low- and high-resolution systems were recorded using Bruker FTMS APEXIII and VG AutoSpect M mass spectrometers. Melting points were determined on a STUART SMP20 apparatus.

### 1.2. Materials and Methods (Biological part)

**Chemicals**. 20aHC (Sigma), 25HC (MedChemExpress), T0901317 (Tocris Biosciences) and Gemini ligands **1**, **3**, **5** and **6** were dissolved in absolute ethanol at $10^{-2}$ M. 20epi-cholesterol and Gemini ligand **4** were dissolved in 80% ethanol 20% DMSO at $10^{-2}$M. All ligands were stored at -20 °C until use.

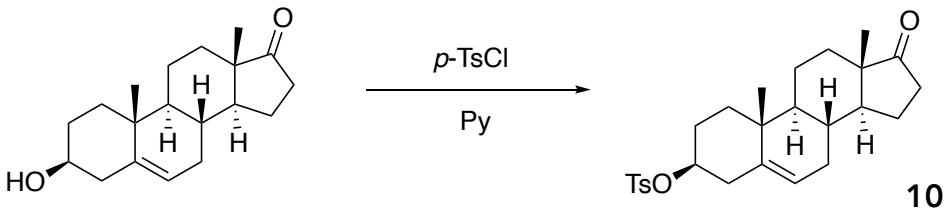
**Expression and purification.** The sequences encoding the His-hROR**γ** (264-518) was inserted into pET15b expression plasmid. The protein was produced in Escherichia coli BL21 DE3 by induction with 1 mM IPTG at an OD600 of ~0.8 and incubation at 22°C for 2h30. Soluble protein was purified by Ni-NTA chromatography followed by size exclusion chromatography on a Superdex 200 (GE) column equilibrated in 20mM Tris-HCl pH7.5, 150mM NaCl, 1mM TCEP. Purity and homogeneity of the hROR**γ** LBD was assessed by SDS-PAGE. The purified protein was concentrated to 0.7 mg/mL with an Amicon Ultra 10 kDa MWCO. The aliquots of purified LBD are incubated with the 5 equivalent ligands were used for thermal stability experiments or crystallization assays.

**Nanoscale Differential Scanning Fluorimetry.** Fluorescence based thermal experiments were performed using Prometheus NT.48 (NanoTemper Technologies, Germany) with capillaries containing 10 µL ROR**γ** LBD with different ligands. The temperature was increased by a rate of 1 °C/min from 20 to 95 °C and the fluorescence at emission wavelengths of 330 nm and 350 nm was measured for 3 technical replicates. NanoTemper

PR.Stability Analysis v1.0.2 was used to fit the data and to determine the melting temperatures Tm. Presented data is the average of 3 biological replicates except for 25HC that correspond to the average of 3 technical replicates.

**Crystallization and structure determination.** Crystals were obtained in 0.8M $NH_4$ acetate, 0.1M Hepes pH = 7.5 at 293K. Protein crystals were mounted in a fiber loop and flash-cooled under a nitrogen flux after cryoprotection with Glycerol 20%. Data collection from a single frozen crystal was performed at 100 K on the ID23-2 at ESRF (France). The raw data were processed with XDS[36] and scaled with AIMLESS[37] programs. The crystals belong to the space group $P6_1$, with two LBD complexes per asymmetric unit. The structure was solved and refined using Phenix[38] and iterative model building using COOT.[45] Crystallographic refinement statistics are presented in Supplementary Table 1. All structural figures were prepared using PyMOL (www.pymol.org/).

1.2. Synthesis of (3*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-10,13-dimethyl-17-oxo-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl 4-methylbenzenesulfonate (10)




dehydroepiandrosterone **10**

To a solution of **dehydroepiandrosterone** (360 mg, 1.25 mmol) in pyridine (7 mL) cooled to 0 °C was added *p*-TsCl (608 mg, 1.25 mmol). The ice bath was removed after 5 minutes and stirring was continued at rt for 5 hours. Saturated $NaHCO_3$ solution (15 mL) was then added and extracted with $CH_2Cl_2$ (2x30 mL). The combined organic phases were dried with $Na_2SO_4$, filtered and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 10% EtOAc/hexane), affording compound **10** (470 mg, 86%).

Compound **10**: white solid; Rf: 0.54 (50% EtOAc/hexane).

**IR (NaCl, $cm^{-1}$):** 2947, 2581, 2362, 1735, 1534, 1455, 1360.

**$[\alpha]^{23}_D$**= -10.79 (c 1.18, $CHCl_3$).

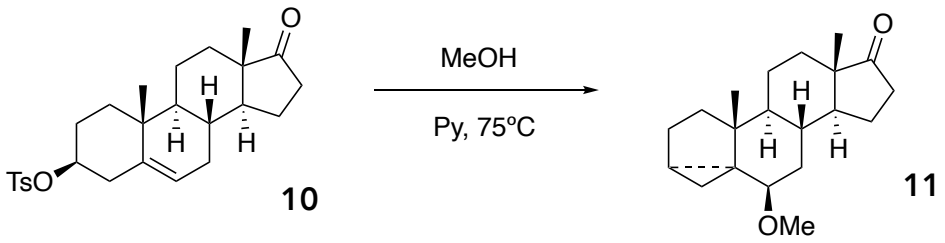
**$^1$H-NMR ($CDCl_3$, δ):** 7.79 (2H, d, *J*=8.3 Hz, Ph), 7.73 (2H, d, *J*=8.0 Hz, Ph), 5.34 (1H, d, *J*=4.7 Hz, H-6), 4.32 (1H, m, H-3), 2.44 (3H, s, $CH_3$-Ts), 2.43 (2H, m), 2.34 (1H, m), 1.93 (2H, m), 1.80 (5H, m), 1.62 (5H, m), 1.25 (3H, m), 1.02 (2H, m), 0.99 (3H, s, $CH_3$-18), 0.86 (3H, s, $CH_3$-19) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 220.6 (C-17), 144.5 (C-Ph), 138.9 (C-Ph), 134.4 (C-5), 129.8 (CH-Ph), 127.5 (CH-Ph), 122.8 (CH-6), 81.9 (CH-3), 51.5 (CH), 49.9 (CH), 47.3 (C-13), 38.8 ($CH_2$), 36.7 ($CH_2$), 36.4 (C-10), 35.7 ($CH_2$), 31.3 ($CH_2$), 31.2 (CH), 30.6 ($CH_2$), 28.4 ($CH_2$), 21.7 ($CH_2$), 21.6 ($CH_3$), 20.2 ($CH_2$), 19.1 ($CH_3$), 13.5 ($CH_3$) ppm.

**MS ($ESI^+$) (m/z, %):** 443.61 ($M^+$+1, 2), 272.57 (22), 271.57 ($M^+$-TsO, 100), 253.58 (6).

**HRMS ($ESI^+$):** 443.2251 calculated for $C_{26}H_{35}O_4S$ and found 443.2251.

1.3. Synthesis of (1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*R*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethyltetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6(1*H*)-one (11)




A solution of ketone **10** (403 mg, 0.91 mmol) and pyridine (0.22 mL, 2.73 mmol) in MeOH (6 mL) was heated at 75 °C for 3 hours. Once the mixture reached rt, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 5% EtOAc/hexane), affording compound **11** (275 mg, 99%).

Compound **11**: colourless oil; Rf: 0.43 (10% EtOAc/hexane).

**IR (NaCl, $cm^{-1}$):** 2930, 2867, 1738, 1469, 1374, 1095, 1014.

**$[\alpha]^{23}_D$**= +81.30 (c 1.00, $CHCl_3$).

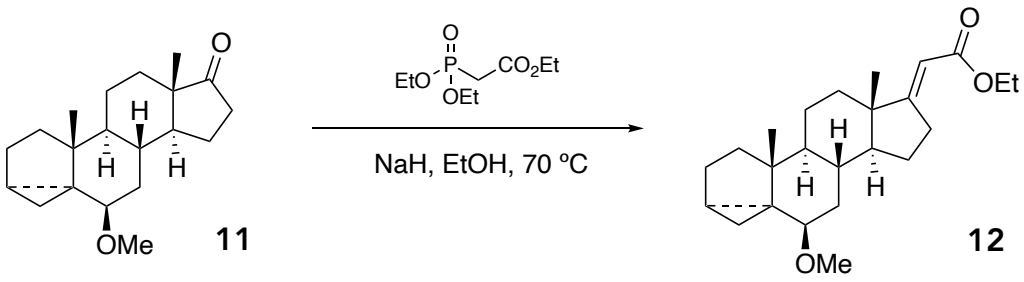
**$^1$H-NMR ($CDCl_3$, δ):** 3.34 (3H, s, MeO), 2.81 (1H, m, H-6), 2.42 (2H, dd, *J*=19.1/8.8 Hz, H-16), 2.15-1.12 (16H, m), 1.03 (3H, s, $CH_3$-18), 0.90 (3H, s, $CH_3$-19), 0.52 (1H, m, H-4), 0.31 (1H, m, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 220.6 (C-17), 81.7 (CH-6), 56.5 ($CH_3$-OMe), 51.3 (CH), 48.1 (CH), 47.8 (C), 43.4 (C), 35.7 ($CH_2$), 34.9 (C-5), 34.1 ($CH_2$), 33.2 ($CH_2$), 31.7 ($CH_2$), 30.0 (CH), 24.8 ($CH_2$), 21.9 ($CH_2$), 21.6 ($CH_2$), 21.1 (CH-3), 19.1 ($CH_3$), 13.8 ($CH_3$), 13.1 ($CH_2$-4) ppm.

**MS ($ESI^+$) (m/z, %):** 303.46 ($M^+$+1, 16), 272.46 ($M^+$-MeO, 100), 253.58 (13).

**HRMS ($ESI^+$):** 303.2319 calculated for $C_{20}H_{31}O_2$ and found 303.2328.

1.4. Synthesis of ethyl (*E*)-2-((1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*S*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethyltetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6(1*H*)-ylidene)acetate (12)




On a mixture of the ketone **11** (1.43 g, 4.73 mmol) and triethyl phosphonoacetate (4.7 mL, 23.7 mmol) was added a suspension of NaH previously washed with hexane (1.14 g, 47.5 mmol) in EtOH (17 mL). The reaction mixture was heated at 70 °C for 16 hours. A saturated NaCl solution (30 mL) was added and extracted with $CH_2Cl_2$ (3x50 mL). The combined organic phases were dried with $Na_2SO_4$, filtered and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 5% EtOAc/hexane), affording compound **12** (1.75 g, 99%).

Compound **12**: colourless oil; Rf: 0.46 (10% EtOAc/hexane).

**IR (NaCl, $cm^{-1}$):** 2931, 2868, 1707, 1650, 1453, 1386, 1260, 1037, 859.

**$[\alpha]^{23}_D$**= +27.35 (c 0.95, $CHCl_3$).

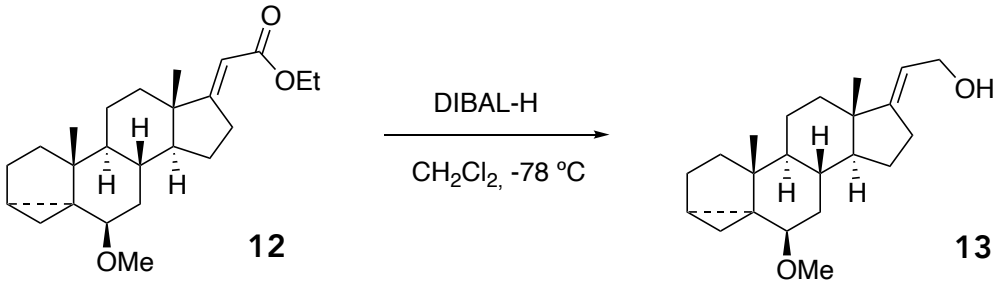
**$^1$H-NMR ($CDCl_3$, δ):** 5.44 (1H, s, H-20), 4.07 (2H, m, $CH_2$-OEt), 3.27 (3H, s, MeO), 2.77 (2H, m, H-16), 2.71 (1H, m, H-6), 1.85 (5H, m), 1.54 (5H, m), 1.12 (2H, m), 0.97 (3H, s, $CH_3$-18), 0.87 (4H, m), 0.79 (3H, s, $CH_3$-19), 0.58 (1H, dd, *J*=4.1/4.0 Hz, H-4), 0.37 (1H, dd, *J*=5.5/7.5 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 176.3 (C-17), 167.3 (C=O), 108.3 (CH-20), 82.0 (CH-6), 59.3 ($CH_2$-OEt), 56.5 ($CH_3$-OMe), 53.6 (CH), 48.1 (CH), 46.4 (C), 43.4 (C), 35.5 ($CH_2$), 35.1 (C-5), 35.0 ($CH_2$), 33.3 ($CH_2$), 30.4 ($CH_2$), 30.2 (CH), 24.8 ($CH_2$), 24.2 ($CH_2$), 22.6 ($CH_2$), 21.3 (CH-3), 19.3 ($CH_3$), 18.6 ($CH_3$), 14.3 ($CH_3$), 13.1 ($CH_2$-4) ppm.

**MS (ESI$^+$) (m/z, %):** 374.24 ($M^+$+2, 23), 373.24 ($M^+$+1, 100), 271.27 ($M^+$-MeO, 4).

**HRMS (ESI$^+$):** 373.2737 calculated for $C_{24}H_{37}O_3$ and found 373.2737.

1.5. Synthesis of (*E*)-2-((1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*S*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethyltetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6(1*H*)-ylidene)ethan-1-ol (13)




To a solution of the ester **12** (2.12 g, 5.7 mmol) in $CH_2Cl_2$ (7 mL) cooled to -78 °C was added a 1 M solution of DIBAL-H in hexane (17 mL, 17.1 mmol) and the resulting mixture was stirred under these conditions for 2 hours. $^tBuOMe$ (10 mL) and $H_2O$ (3 mL) were added and stirring at rt for 30 minutes. Then $Na_2SO_4$ was added, vacuum filtered and washed with AcOEt. After evaporation to dryness of the filtered liquids, the residue was purified by silica gel column chromatography (mobile phase: 20% EtOAc/hexane), affording compound **13** (1.83 mg, 99%).

Compound **13**: colourless oil; Rf: 0.49 (30% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3394, 2930, 2867, 1675,1374, 992, 735.

**$[\alpha]^{24}_D$**= +18.37 (c 1.00, $CHCl_3$).

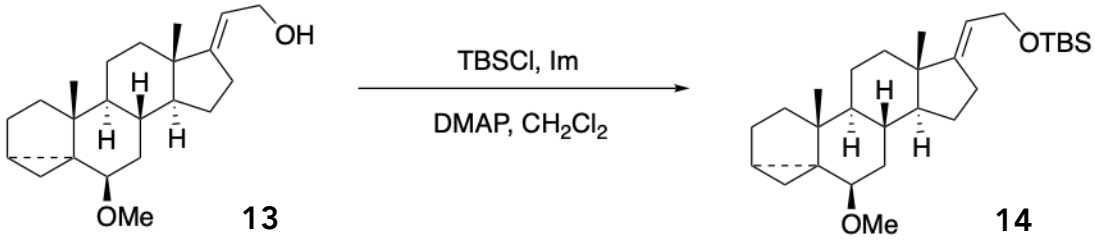
**$^1$H-NMR ($CDCl_3$, δ):** 5.17 (1H, t, *J*=6.7 Hz, H-20), 4.05 (2H, dd, *J*=6.8/12.2 Hz, H-21), 3.29 (3H, s, MeO), 2.75 (2H, m, H-6), 2.62 (1H, s, OH), 2.31 (2H, m, H-16), 1.91 (2H, m), 1.75 (4H, m), 1.48 (3H, m, $CH_3$-OEt), 1.45-1.03 (4H, m), 1.00 (3H, s, $CH_3$-18), 0.82 (3H, m), 0.77 (3H, s, $CH_3$-19), 0.62 (1H, m, H-4), 0.40 (1H, m, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 155.2 (C-17), 115.5 (CH-20), 82.3 (CH-6), 60.0 ($CH_2$-21), 56.5 (MeO), 54.2 (CH), 48.4 (CH), 44.2 (C), 43.5 (C), 36.1 ($CH_2$), 35.1 (C-5), 35.1 ($CH_2$), 33.3 ($CH_2$), 30.3 (CH), 26.2 ($CH_2$), 24.9 ($CH_2$), 24.2 ($CH_2$), 22.6 ($CH_2$), 21.4 (CH-3), 19.3 ($CH_3$), 18.9 ($CH_3$), 13.1 ($CH_2$-4) ppm.

**MS (ESI$^+$) (m/z, %):** 353.24 ($M^+$+$Na^+$, 11), 281.32 (100), 147.34 (44), 145.34 (23).

**HRMS (ESI$^+$):** 353.2451 calculated for $C_{22}H_{34}NaO_2$ and found 353.2446.

1.6. Synthesis of *tert*-butyl((*E*)-2-((1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*S*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethyltetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6(1*H*)-ylidene)ethoxy)dimethylsilane (14)




To a solution of allyl alcohol **13** (3.54 g, 10.94 mmol) in $CH_2Cl_2$ (20 mL), Im (1.5 g, 21.9 mmol), DMAP (cc) and TBSCl (2.15 g, 14.23 mmol) were successively added and the mixture was stirred for 1 hour. $H_2O$ (10 mL) was added and extracted with $CH_2Cl_2$ (3x30 mL). The combined organic phases were washed with a saturated NaCl solution (2x20 mL), dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 1% EtOAc/hexane), affording compound **14** (4.81 g, 99%).

Compound **14**: colourless oil; Rf: 0.76 (10% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 2928, 2853, 1679, 1471, 1374, 1253.

**$[\alpha]^{23}_D$**= +32.00 (c 1.00, $CHCl_3$).

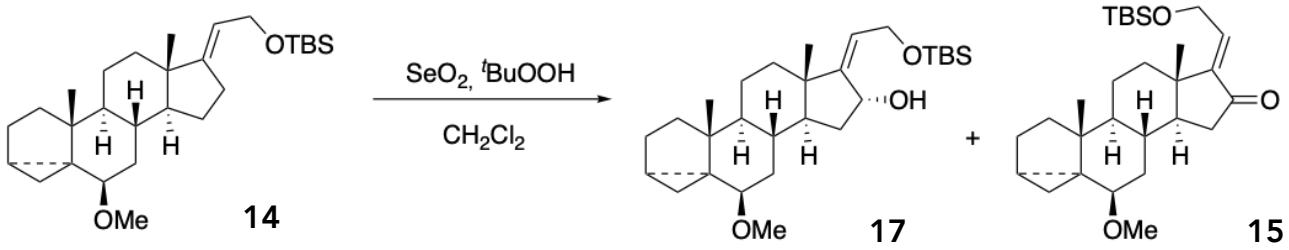
**$^1$H-NMR ($CDCl_3$, δ):** 5.14 (1H, dd, *J*=2.4/8.9 Hz, H-20), 4.16 (2H, m, H-21), 3.34 (3H, s, MeO), 2.79 (1H, t, *J*=2.8 Hz, H-6), 2.41-2.16 (2H, m, H-16), 1.95 (1H, dt, *J*=3.0/13.4 Hz), 1.79 (4H, m), 1.52 (3H, m), 1.50-1.19 (6H, m), 1.13 (1H, m), 1.05 (3H, s, $CH_3$-18), 0.98 (1H, m), 0.91 (9H, s, $CH_3$-$^t$Bu), 0.81 (3H, s, $CH_3$-19), 0.65 (1H, dd, *J*=9.3/13.3 Hz, H-4), 0.44 (1H, dd, *J*=11.5/23.1, H-4), 0.07 (6H, s, $CH_3$-Si) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 152.8 (C-17), 116.4 (CH-20), 82.3 (CH-6), 61.3 ($CH_2$-21), 56.6 (MeO), 54.2 (CH), 48.4 (CH), 44.1 (C), 43.5 (C), 36.1 ($CH_2$), 35.2 (C-5), 35.1 ($CH_2$), 33.4 ($CH_2$), 30.3 (CH), 26.3 ($CH_2$), 26.0 ($CH_3$-$^t$Bu), 24.9 ($CH_2$), 24.3 ($CH_2$), 22.7 ($CH_2$), 21.4 (CH-3), 19.3 ($CH_3$), 18.9 ($CH_3$), 18.4 (C-$^t$Bu), 13.1 ($CH_2$-4), -4.8 ($CH_3$-Si), -4.9 ($CH_3$-Si) ppm.

**MS (ESI$^+$) (m/z, %):** 444.32 ($M^+$, 2), 443.33 ($M^+$-1, 2), 413.29 ($M^+$-MeO, 9), 281.32 (100).

**HRMS (ESI$^+$):** 443.3334 calculated for $C_{28}H_{47}O_2Si$ and found 443.3334.

1.7. Synthesis of (1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*R*,10*R*,10a*R*,*E*)-6-(2-((*tert*-butyldimethylsilyl)oxy)ethylidene)-10-methoxy-3a,5a-dimethyltetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-7(1*H*)-one (15) and (1a*R*,3a*R*,3b*S*,5a*S*,7*R*,8a*S*,8b*R*,10*R*,10a*R*,*Z*)-6-(2-((*tert*-butyldimethylsilyl)oxy)ethylidene)-10-methoxy-3a,5a-dimethylhexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-7-ol (17)




To a suspension of $SeO_2$ (24 mg, 0.21 mmol) in $CH_2Cl_2$ (2 mL) cooled to 0 °C was added a 70% aqueous solution $^tBuOOH$ (120 µl, 0.86 mmol). The mixture was stirred for 1 hour and then a solution of compound **14** (190 mg, 0.427 mmol) in $CH_2Cl_2$ (2 mL) was added. The stirring continued for 36 hours at rt and a 3 M solution of NaOH (4 mL) and $H_2O$ (4 mL) were added. The aqueous aphase was extracted with $CH_2Cl_2$ (3x20 mL) and the combined organic extracts were dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 5% EtOAc/hexane), affording the ketone **15** (42 mg, 21%) and the allylic alcohol **17** (120 mg, 61%).

Compound **15**: colourless oil; Rf: 0.40 (20% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3443, 2953, 2928, 2854, 1471, 1373, 1254, 777.

**$[\alpha]^{27}_D$**= -33.52 (c 1.00, $CHCl_3$).

**$^1$H-NMR (CDCl3, δ):** 6.42 (1H, m, H-20), 4.42 (2H, m, H-21), 3.35 (3H, s, MeO), 2.80 (1H, m, H-6), 2.24-1.27 (15H, m), 1.18 (1H, m), 1.06 (3H, s, $CH_3$-18), 0.90 (9H, s, $CH_3$-$^t$Bu), 0.89 (3H, s, $CH_3$-19), 0.68 (1H, m, H-4), 0.47 (1H, m, H-4), 0.07 (6H, s, $CH_3$-Si) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 206.2 (C-16), 146.0 (C-17), 133.5 (CH-20), 81.9 (CH-6), 59.2 ($CH_2$-21), 56.7 (MeO), 50.0 (CH), 47.8 (CH), 43.6 (C), 43.6 (C), 38.1 ($CH_2$), 36.5 ($CH_2$), 35.4 ($CH_2$), 34.9 (C), 33.1 ($CH_2$), 29.5 (CH), 25.9 ($CH_3$-$^t$Bu), 24.9 ($CH_2$), 22.3 ($CH_2$), 21.2 (CH), 19.2 ($CH_3$), 17.7 ($CH_3$), 18.3 (C-$^t$Bu), 13.2 ($CH_2$-4), -5.2 ($CH_3$-Si) ppm.

**MS ($ESI^+$) (m/z, %):** 499.32 ($M^+$+K, 25), 481.31 ($M^+$+Na, 4), 459.32 ($M^+$+1, 100)

**HRMS ($ESI^+$):** 459.3289 calculated for $C_{28}H_{47}O_3Si$ and found 459.3281.

Compound **17**: colourless oil; Rf: 0.38 (20% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3443, 2953, 2928, 2854, 1471, 1373, 1254, 777.

**$[\alpha]^{23}_D$**= +20.25 (c 0.75, $CHCl_3$).

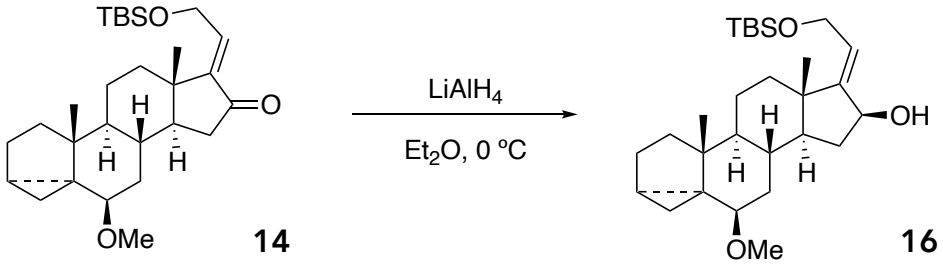
**$^1$H-NMR (CDCl3, δ):** 5.35 (1H, m, H-20), 4.86 (1H, m, H-16), 4.37 (1H, dd, *J*=5.6/13.4 Hz, H-21), 4.26 (1H, dd, *J*=5.6/13.4 Hz, H-21), 3.54 (1H, s, OH), 3.38 (3H, s, MeO), 2.82 (1H, m, H-6), 1.99-1.13 (16H, m), 1.05 (3H, s, $CH_3$-18), 0.90 (9H, s, $CH_3$-$^t$Bu), 0.83 (3H, s, $CH_3$-19), 0.69 (1H, dd, *J*=8.2/12.6 Hz, H-4), 0.47 (1H, dd, *J*=5.1/8.0 Hz, H-4), 0.12 (6H, s, $CH_3$-Si) ppm.

**13C-NMR (CDCl3, δ):** 159.9 (C-17), 118.6 (CH-20), 82.3 (CH-6), 70.8 (CH-16), 61.1 ($CH_2$-21), 56.6 (MeO), 51.3 (CH), 48.3 (CH), 45.2 (C), 43.5 (C), 36.7 ($CH_2$), 35.1 (C-5), 35.1 ($CH_2$), 34.6 ($CH_2$), 33.3 ($CH_2$), 29.8 (CH), 25.9 ($CH_3$-$^t$Bu), 24.9 ($CH_2$), 22.7 ($CH_2$), 21.3 (CH), 20.3 ($CH_3$), 19.3 ($CH_3$), 18.3 (C-$^t$Bu), 13.2 ($CH_2$-4), -5.3 ($CH_3$-Si), -5.4 ($CH_3$-Si) ppm.

**MS (ESI$^+$) (m/z, %):** 483.34 ($M^+$+Na, 20), 443.37 ($M^+$-OH, 100), 429.35 ($M^+$-OMe, 3)

**HRMS (ESI$^+$):** 483.3265 calculated for $C_{28}H_{48}NaO_3Si$ and found 483.3276.

1.8. Synthesis of (1a*R*,3a*R*,3b*S*,5a*S*,7*S*,8a*S*,8b*R*,10*R*,10a*R*,*E*)-6-(2-((*tert*-butyldimethylsilyl)oxy)ethylidene)-10-methoxy-3a,5a-dimethylhexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-7-ol (16)




A solution of the ketone **14** (70 mg, 0.153 mmol) in $Et_2O$ (1.5 mL) was added dropwise to a suspension of $LiAlH_4$ (58 mg, 1.53 mmol) in $Et_2O$ (2.5 mL) cooled to 0 °C. After the addition was complete, the cold bath was removed and the reaction mixture was stirred at rt for 16 hours. $H_2O$ (5 mL) was added and the aqueous solution was extracted with $Et_2O$ (4x15 mL). The combined organic phases were dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 25% EtOAc/hexane), affording the allylic alcohol **16** (56 mg, 80%).

Compound **16**: white solid (mp: 129-131 °C); Rf: 0.28 (20% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3264, 2925, 2855, 1469, 1058, 834, 775.

**$[\alpha]^{27}_D$**= +63.12 (c 1.00, $CHCl_3$).

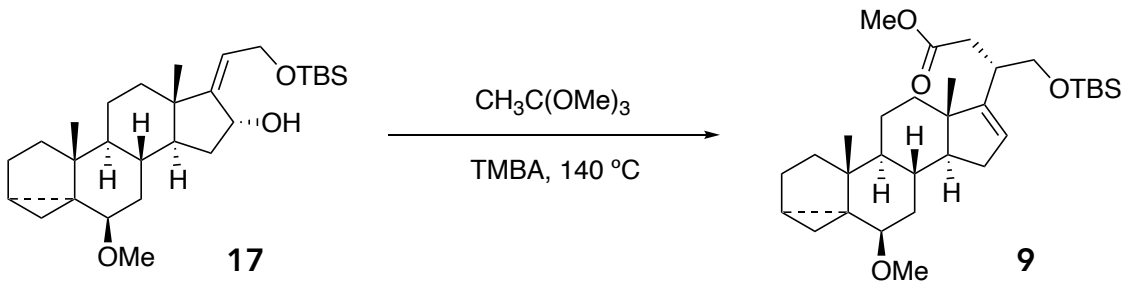
**$^1$H-NMR (CDCl3, δ):** 5.57 (1H, m, H-20), 4.42 (2H, m, H-21), 4.34 (1H, m, H-16), 3.37 (3H, s, MeO), 2.82 (1H, m, H-6), 2.23-1.20 (13H, m), 1.11 (3H, s, $CH_3$-18), 1.10 (3H, m), 0.95 (9H, s, $CH_3$-$^t$Bu), 0.92 (3H, s, $CH_3$-19), 0.69 (1H, m, H-4), 0.48 (1H, m, H-4), 0.12 (6H, s, $CH_3$-Si) ppm.

**13C-NMR (CDCl3, δ):** 154.6 (C-17), 124.8 (CH-20), 82.2 (CH-6), 75.1 (CH-16), 59.5 ($CH_2$-21), 56.6 (MeO), 51.4 (CH), 47.9 (CH), 44.2 (C), 43.5 (C), 37.3 ($CH_2$), 35.1 (C-5), 35.0 ($CH_2$), 34.4 ($CH_2$), 33.3 ($CH_2$), 29.5 (CH), 26.0 ($CH_3$-$^t$Bu), 24.9 ($CH_2$), 22.5 ($CH_2$), 21.4 (CH), 19.2 ($CH_3$), 18.6 ($CH_3$), 18.4 (C-$^t$Bu), 13.2 ($CH_2$-4), -5.02($CH_3$-Si), -5.0 ($CH_3$-Si) ppm.

**MS (ESI$^+$) (m/z, %):** 483.32 ($M^+$+Na, 42), 411.31 ($M^+$-49, 15), 279.21 (100).

**HRMS (ESI$^+$):** 483.3265 calculated for $C_{28}H_{48}NaO_3Si$ and found 483.3248.

1.9. Synthesis of methyl (*S*)-4-((*tert*-butyldimethylsilyl)oxy)-3-((1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*R*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethyl-1,1a,2,3,3a,3b,4,5,5a,8,8a,8b,9,10-tetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)butanoate (9)




To a solution of allylic alcohol **17** (480 mg, 1.04 mmol) in $MeC(OMe)_3$ (10 mL) was added TMBA (cat.) and heated in a sealed tube at 140 °C for 24 hours. Once the reaction mixture reached rt, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 3% EtOAc/hexane), affording the compound **9** (490 mg, 91%).

Compound **9**: colourless oil; Rf: 0.80 (20% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 2951, 2927, 2853, 1741, 1471, 1435, 1094, 776.

**$[\alpha]^{22}_D$**= +42.50 (c 0.75, $CHCl_3$).

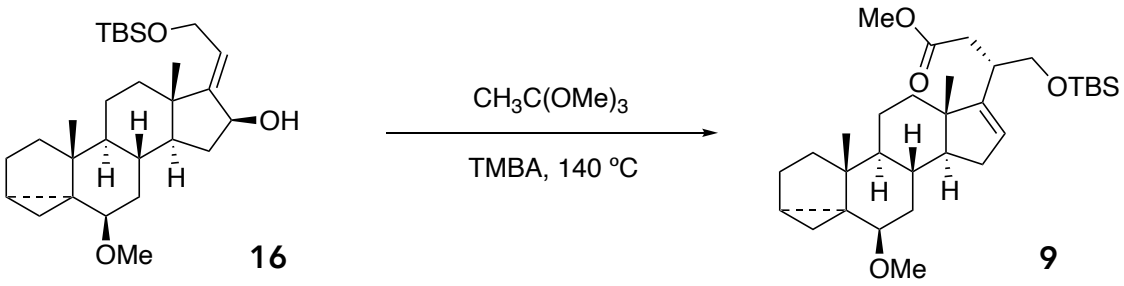
**$^1$H-NMR ($CDCl_3$, δ):** 5.35 (1H, s, H-16), 3.69 (1H, m, H-21), 3.66 (3H, s, $CH_3$-C=O), 3.50 (1H, m, H-21), 3.38 (3H, s, MeO), 2.81 (1H, t, *J*=5.2 Hz, H-6), 2.76 (1H, dd, *J*= 7.2/12.2 Hz, H-20), 2.67 (1H, dd, *J*=6.4/15.0 Hz, H-22), 2.41 (1H, dd, *J*=7.5/15.1 Hz, H-22), 2.28 (1H, m), 2.09 (1H, ddd, *J*=3.2/6.5/14.9 Hz), 2.01-1.70 (5H, m), 1.59-1.42 (4H, m), 1.31 (2H, m), 1.15 (1H, td, *J*=2.6/13.2 Hz), 1.07 (3H, s, $CH_3$-18), 0.94-0.90 (2H, m), 0.89 (9H, s, $CH_3$-$^t$Bu), 0.85 (3H, s, $CH_3$-19), 0.69 (1H, m, H-4), 0.47 (1H, dd, *J*=5.2/7.8 Hz, H-4), 0.06 (6H, s, $CH_3$-Si) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 173.5 (C=O), 155.2 (C-17), 124.2 (CH-16), 82.4 (CH-6), 66.2 ($CH_2$-21), 57.1 (CH-14), 56.6 (MeO), 51.2 ($CH_3$-C=O), 48.6 (CH), 47.3 (C-10), 43.6 (C-13), 37.2 ($CH_2$), 37.0 (CH-20), 35.4 (C-5), 35.1 ($CH_2$), 34.9 ($CH_2$), 33.1 ($CH_2$), 31.3 ($CH_2$), 29.1 (CH), 25.9 ($CH_3$-$^t$Bu), 24.9 ($CH_2$), 22.4 ($CH_2$), 21.4 (CH), 19.2 ($CH_3$), 18.3 (C-$^t$Bu), 17.0 ($CH_3$), 13.1 ($CH_2$-4), -5.4 ($CH_3$-Si), -5.5 ($CH_3$-Si) ppm.

**MS ($ESI^+$) (m/z, %):** 539.37 ($M^+$+Na, 80), 517.37 ($M^+$+1, 100), 485.33 ($M^+$-OMe, 12).

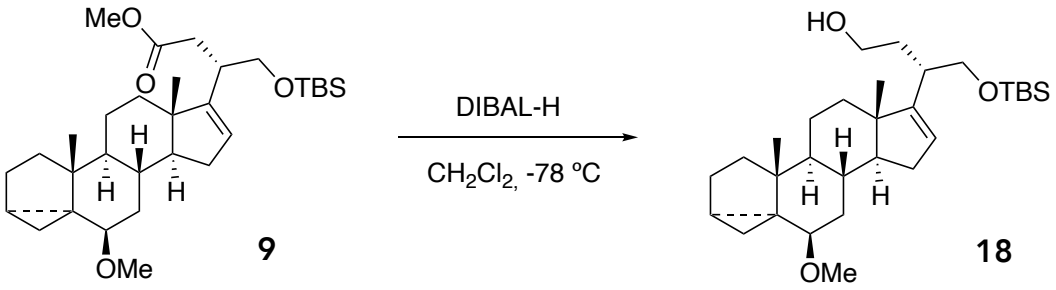
**HRMS ($ESI^+$):** 517.3708 calculated for $C_{31}H_{53}O_4Si$ and found 517.3700.

1.10. Synthesis of methyl (*S*)-4-((*tert*-butyldimethylsilyl)oxy)-3-((1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*R*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethyl-1,1a,2,3,3a,3b,4,5,5a,8,8a,8b,9,10-tetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)butanoate (9)




To a solution of allylic alcohol **16** (20 mg, 0.04 mmol) in $MeC(OMe)_3$ (2 mL) was added TMBA (cat.) and heated in a sealed tube at 140 °C for 14 hours. Once the reaction mixture reached rt, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 3% EtOAc/hexane), affording the compound **9** (17 mg, 85%), whose physical constants and spectroscopic data virtually coincide with those described for this compound in section 1.9.

1.11. Synthesis of (*S*)-4-((*tert*-butyldimethylsilyl)oxy)-3-((1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*R*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethyl-1,1a,2,3,3a,3b,4,5,5a,8,8a,8b,9,10-tetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)butan-1-ol (18)




To a solution of the ester **9** (1.41 g, 2.73 mmol) in $CH_2Cl_2$ (3 mL) cooled to -78 °C was added a 1 M solution of DIBAL-H in hexane (13.6 mL, 13.6 mmol) and the resulting mixture was stirred under these conditions for 15 hours. $^t$BuOMe (10 mL) and $H_2O$ (2 mL) were added and the mixture allowed to reach rt. Stirring was continued till the formation of a white gel before adding $H_2O$ (2 ml) and a 4 M aqueous solution of NaOH (2 mL). Stirring was continued till the formation of a white solid. The solid was separated by filtration. After evaporation to dryness of the filtered liquids, the residue was purified by silica gel column chromatography (mobile phase: 10% EtOAc/hexane), affording the compound **18** (1.03 g, 77%).

Compound **18**: colourless oil; Rf: 0.55 (20% EtOAc/hexane).

**IR (ATR, cm$^{-1}$):** 3410, 2998, 2927, 2853, 1471, 1373, 1254, 1088, 737.

**$[\alpha]^{24}_D$**= +49.20 (c 1.10, $CHCl_3$).

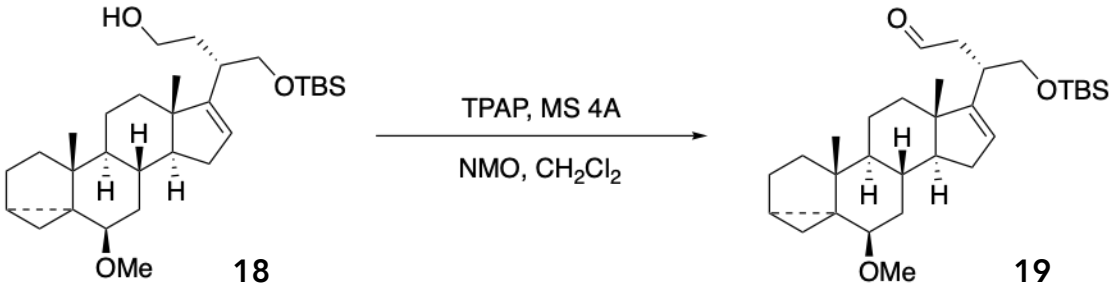
**$^1$H-NMR ($CDCl_3$, δ):** 5.38 (1H, d, *J*=1.1 Hz, H-16), 3.62 (2H, m, H-23), 3.57 (2H, m, H-21), 3.35 (3H, s, MeO), 2.96 (1H, s, OH), 2.79 (1H, t, *J*=2.6 Hz, H-6), 2.39 (1H, s), 2.28-2.25 (2H, m), 2.12-2.04 (2H, m), 1.91 (2H, m), 1.81 (1H, m), 1.73 (2H, m), 1.56-1.47 (4H, m), 1.36-1.28 (3H, m), 1.15 (2H, m), 1.05 (3H, s, $CH_3$-18), 0.90 (9H, s, $CH_3$-$^t$Bu), 0.81 (3H, s, $CH_3$-19), 0.67 (1H, dd, *J*=8.5/13.2 Hz, H-4), 0.45 (1H, dd, *J*= 5.1/8.0 Hz, H-4), 0.07 (6H, s, $CH_3$-Si) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 156.7 (C-17), 123.2 (CH-16), 82.3 (CH-6), 67.6 ($CH_2$-21), 61.6 ($CH_2$-23), 56.9 (CH-14), 56.6 (MeO), 48.7 (CH), 47.6 (C-10), 43.6 (C-13), 38.2 (CH), 37.3 ($CH_2$), 35.3 (C-5), 35.2 ($CH_2$), 34.9 ($CH_2$), 33.1 ($CH_2$), 31.3 ($CH_2$), 29.1 (CH), 25.9 ($CH_3$-$^t$Bu), 24.9 ($CH_2$), 22.4 ($CH_2$), 21.3 (CH-3), 19.2 ($CH_3$-18), 18.3 (C-$^t$Bu), 16.7 ($CH_3$-19), 13.1 ($CH_2$-4), -5.4 ($CH_3$-Si), -5.4 ($CH_3$-Si) ppm.

**MS (ESI$^+$) (m/z, %):** 489.37 ($M^+$+1, 100), 457.33 ($M^+$-OMe, 5).

**HRMS (ESI$^+$):** 489.3758 calculated for $C_{30}H_{53}O_3Si$ and found 489.3772.

1.12. Synthesis of (*S*)-4-((*tert*-butyldimethylsilyl)oxy)-3-((1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*R*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethyl-1,1a,2,3,3a,3b,4,5,5a,8,8a,8b,9,10-tetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)butanal (19)




To a solution of alcohol **18** (1.01 g, 2.07 mmol) in $CH_2Cl_2$ (5 mL) were added 4Å molecular sieves (MS) (600 mg), NMO (726 mg, 6.2 mmol) and TPAP (cat.). The resulting greenish suspension was stirred at rt for 2 h. The solvent was evaporated and the residue was purified by silica gel column chromatography (mobile phase: 10% EtOAc/hexane), affording the compound **19** (540 mg, 54%).

Compound **19**: colourless oil; Rf: 0.75 (20% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 2951, 2927, 2853, 1726, 1470, 1253, 775.

**$[\alpha]^{24}_D$**= +49.10 (c 1.00, $CHCl_3$).

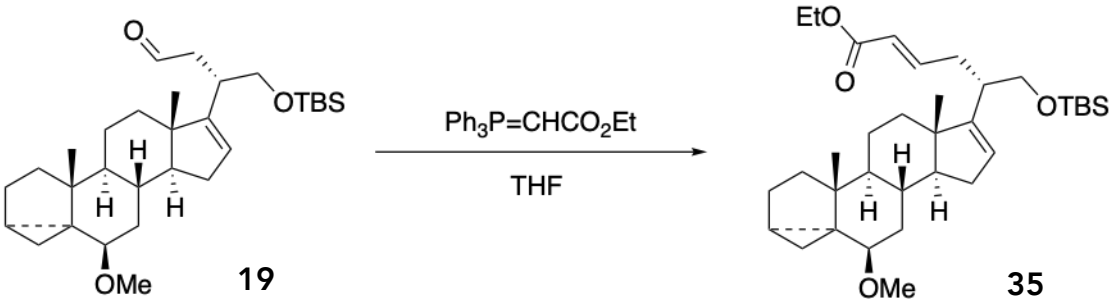
**$^1$H-NMR (CDCl3, δ):** 9.69 (1H, s, H-23), 5.44 (1H, s, H-16), 3.72 (1H, dd, *J*=4.4/9.8 Hz, H-21), 3.48 (1H, t, *J*=9.6 Hz, H-21), 3.36 (3H, s, MeO), 2.88-2.78 (2H, m, H-6 y H-20), 2.63 (1H, ddd, *J*=2.7/6.9/16.0 Hz, H-22), 2.46 (1H, ddd, *J*=2.1/6.8/16.0 Hz, H-22), 2.08 (1H, m), 2.00–1.84 (3H, m), 1.84–1.69 (2H, m), 1.60–1.43 (4H, m), 1.41–1.23 (3H, m), 1.14 (1H, td, *J*=12.0/15.8 Hz), 1.05 (3H, s, $CH_3$-18), 0.99-0.86 (2H, m), 0.88 (9H, s, $CH_3$-$^t$Bu), 0.85 (3H, s, $CH_3$-19), 0.66 (1H, m, H-4), 0.46 (1H, dd, *J*=5.1/7.8 Hz, H-4), 0.03 (6H, s, $CH_3$-Si) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 202.9 (CH-23), 154.7 (C-17), 125.2 (CH-16), 82.3 (CH-6), 66.6 ($CH_2$-21), 57.1 (CH-14), 56.7 (MeO), 48.6 (CH), 47.4 (C-10), 47.2 ($CH_2$), 43.6 (C-13), 35.8 (CH), 35.3 (C-5), 35.1 ($CH_2$), 35.1 ($CH_2$), 33.1 ($CH_2$), 31.3 ($CH_2$), 29.1 (CH), 25.9 ($CH_3$-$^t$Bu), 24.9 ($CH_2$), 22.4 ($CH_2$), 21.3 (CH-3), 19.2 ($CH_3$-18), 18.3 (C-$^t$Bu), 17.0 ($CH_3$-19), 13.1 ($CH_2$-4), -5.4 ($CH_3$-Si), -5.5 ($CH_3$-Si) ppm.

**MS (ESI$^+$) (m/z, %):** 487.35 ($M^+$+1, 11), 456.33 (44), 455.39 ($M^+$-OMe, 100).

**HRMS (ESI$^+$):** 487.3602 calculated for $C_{30}H_{51}O_3Si$ and found 487.3600.

1.13. Synthesis of ethyl (*S*,*E*)-6-((*tert*-butyldimethylsilyl)oxy)-5-((1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*R*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethyl-1,1a,2,3,3a,3b,4,5,5a,8,8a,8b,9,10-tetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)hex-2-enoate (35)




To a solution of aldehyde **19** (516 mg, 1.06 mmol) in THF (10 mL) was added $Ph_3P{=}CHCO_2Et$ (740 mg, 2.12 mmol) and the resulting mixture was stirred at rt for 16 hours. The solvent was evaporated and the residue was purified by silica gel column chromatography (mobile phase: 5% EtOAc/hexane), affording the compound **35** (589 mg, 95%).

Compound **35**: colourless oil; Rf: 0.77 (20% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 2951, 2927, 2852, 1720, 1103, 838.

**$[\alpha]^{24}_D$**= +93.98 (c 1.00, $CHCl_3$).

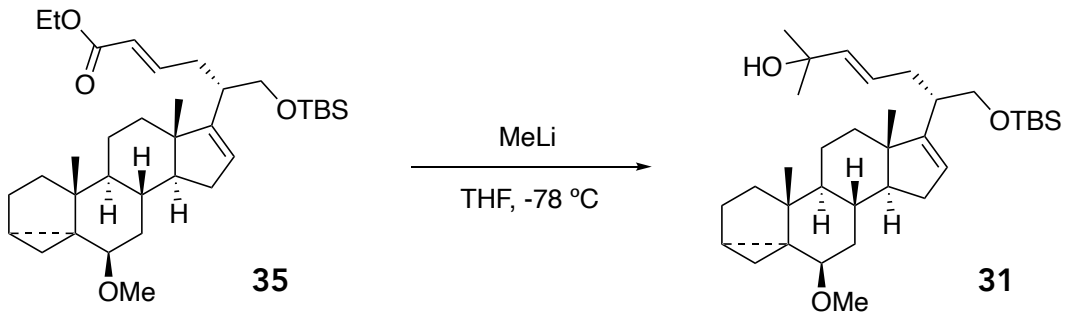
**$^1$H-NMR ($CDCl_3$, δ):** 6.92 (1H, m, H-23), 5.78 (1H, d, *J*=15.5 Hz, H-24), 5.38 (1H, s, H-16), 4.18 (2H, q, *J*=7.1 Hz, $CH_2$-OEt), 3.59 (1H, dd, *J*=9.9/4.3 Hz, H-21), 3.48 (1H, dd, *J*=9.9/8.3 Hz, H-21), 3.35 (3H, s, MeO), 2.79 (1H, m, H-6), 2.52 (1H, m), 2.33 (2H, m), 2.10 (1H, m), 1.92 (3H, m), 1.73 (2H, m), 1.51 (4H, m), 1.32 (3H, m), 1.28 (3H, t, *J*=7.1Hz, $CH_3$-OEt), 1.18 (1H, m), 1.05 (3H, s, $CH_3$-18), 0.89 (9H, s, $CH_3$-$^t$Bu), 0.87 (2H, m), 0.81 (3H, s, $CH_3$-19), 0.66 (1H, dd, *J*=5.1/3.7 Hz, H-4), 0.45 (1H, dd, *J*=8.0/5.1 Hz, H-4), 0.04 (6H, s, $CH_3$-Si) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 166.5 (C=O), 154.8 (C-17), 148.2 (CH-23), 124.1 (CH-24), 122.3 (CH-16), 82.3 (CH-6), 66.0 ($CH_2$-21), 59.9 ($CH_2$-OEt), 56.68 (MeO), 56.6 (CH-14), 48.6 (CH-20), 47.4 (C-10), 43.6 (C-13), 39.4 (CH), 35.3 (C-5), 35.1 ($CH_2$), 35.0 ($CH_2$), 34.9 ($CH_2$), 33.07 ($CH_2$), 31.3 ($CH_2$), 29.1 (CH), 25.9 ($CH_3$-$^t$Bu), 24.8 ($CH_2$), 22.3 ($CH_2$), 21.3 (CH-3), 19.2 ($CH_3$-18), 18.2 (C-$^t$Bu), 16.7 ($CH_3$-19), 14.2 ($CH_3$-OEt), 13.1 ($CH_2$-4), -5.4 ($CH_3$-Si), -5.5 ($CH_3$-Si) ppm.

**MS (ESI$^+$) (m/z, %):** 579.38 ($M^+$+Na, 7), 557.40 ($M^+$+1, 22), 525.38 ($M^+$-OMe, 100).

**HRMS (ESI$^+$):** 557.4021 calculated for $C_{34}H_{57}O_4Si$ and found 557.4022.

1.14. Synthesis of (*S*,*E*)-7-((*tert*-butyldimethylsilyl)oxy)-6-((1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*R*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethyl-1,1a,2,3,3a,3b,4,5,5a,8,8a,8b,9,10-tetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)-2-methylhept-3-en-2-ol (31)




To a solution of ester **35** (503 mg, 0.9 mmol) in THF (5 mL) cooled to -78 ºC was added a 1.5 M solution of MeLi·LiBr in $Et_2O$ (3.0 mL, 4.52 mmol) and the resulting mixture was stirred in these conditions for 2 hours. $H_2O$ (5 mL) was added and the aqueous solution was extracted with $CH_2Cl_2$ (3x15 mL). The combined organic phases were dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 8% EtOAc/hexane), affording the compound **31** (306 mg, 62%).

Compound **31**: colourless oil; Rf: 0.63 (20% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3352, 2952, 2927, 2853, 1473, 1357, 834, 777.

**$[\alpha]^{24}_D$**= +24.30 (c 1.00, $CHCl_3$).

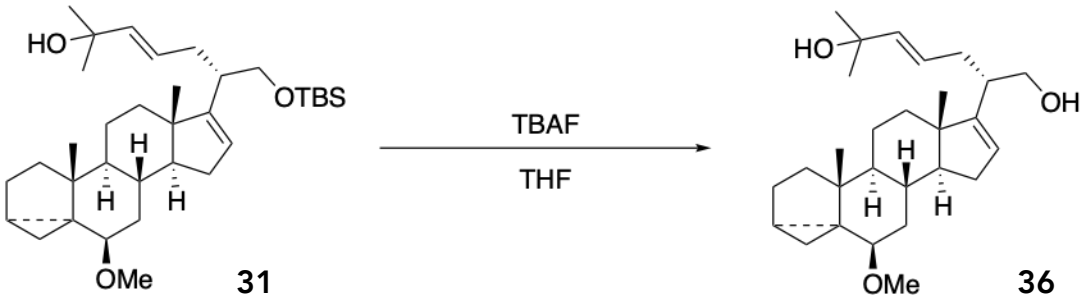
**$^1$H-NMR ($CDCl_3$, δ):** 5.58 (2H, m, H-23/H-24), 5.33 (1H, m, H-16), 3.54 (2H, m, H-21), 3.36 (3H, s, MeO), 2.81 (1H, m, H-6), 2.28 (2H, m), 2.13 (2H, m), 1.92 (3H, m), 1.73 (2H, m), 1.51 (5H, m), 1.33 (2H, m), 1.31 (6H, s, $CH_3$-26/$CH_3$-27), 1.19 (1H, m), 1.07 (3H, s, $CH_3$-18), 0.91 (9H, s, $CH_3$-$^t$Bu), 0.89 (2H, m), 0.82 (3H, s, $CH_3$-19), 0.68 (1H, m, H-4), 0.46 (1H, dd, *J*=8.0/5.1 Hz, H-4), -0.05 (6H, s, $CH_3$-Si) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 155.5 (C-17), 139.5 (CH-24), 125.4 (CH), 123.3 (CH), 82.4 (CH-6), 70.7 (C-25), 65.8 ($CH_2$-21), 56.9 (CH-14), 56.6 (MeO), 48.8 (CH-20), 47.4 (C-10), 43.6 (C-13), 40.0 (CH), 35.4 (C-5), 35.2 ($CH_2$), 35.0 ($CH_2$), 34.5 ($CH_2$), 33.1 ($CH_2$), 31.3 ($CH_2$), 29.9 ($CH_3$), 29.8 ($CH_3$), 29.1 (CH), 25.9 ($CH_3$-$^t$Bu), 24.9 ($CH_2$), 22.4 ($CH_2$), 21.4 (CH-3), 19.2 ($CH_3$-18), 18.3 (C-$^t$Bu), 16.6 ($CH_3$-19), 13.1 ($CH_2$-4), -5.4 ($CH_3$-Si) ppm.

**MS (ESI$^+$) (m/z, %):** 565.40 ($M^+$+Na, 12), 525.41 ($M^+$-OH, 8), 493.38 ($M^+$-49, 100).

**HRMS (ESI$^+$):** 565.4047 calculated for $C_{34}H_{58}NaO_3Si$ and found 565.4063.

1.15. Synthesis of (*S*,*E*)-2-((1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*R*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethyl-1,1a,2,3,3a,3b,4,5,5a,8,8a,8b,9,10-tetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)-6-methylhept-4-ene-1,6-diol (36)




To a solution of **31** (306 mg, 0.564 mmol) in THF (3 mL) was added a 1 M solution of TBAF in THF (1.7 mL, 1.7 mmol) and the resulting mixture was stirred at rt for 13 hours. A saturated aqueous solution of $NH_4Cl$ (3 mL) was added and the aqueous solution was extracted with EtOAc (3x15 mL). The combined organic phases were dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 50% EtOAc/hexane), affording the compound **36** (240 mg, 99%).

Compound **36**: colourless oil; Rf: 0.10 (30% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3373, 2926, 2867, 2847, 1372, 1087, 970.

**$[\alpha]^{22}_D$**= +32.54 (c 1.00, $CHCl_3$).

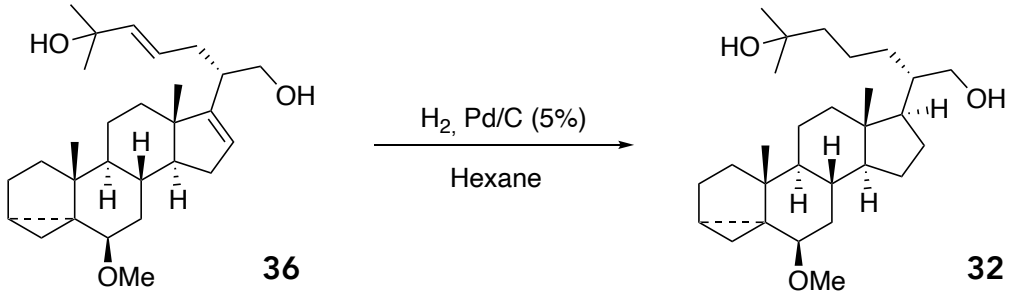
**$^1$H-NMR ($CDCl_3$, δ):** 5.59 (2H, m, H-23/H-24), 5.42 (1H, m, H-16), 3.58 (2H, d, *J*=6.4 Hz, H-21), 3.33 (3H, s, MeO), 2.78 (1H, m, H-6), 2.35 (2H, m), 2.13 (2H, m), 1.92 (3H, m), 1.73 (2H, m), 1.51 (5H, m), 1.33 (2H, m), 1.28 (6H, s, $CH_3$-26/$CH_3$-27), 1.14 (1H, m), 1.04 (3H, s, $CH_3$-18), 0.86 (9H, s, $CH_3$-$^t$Bu), 0.86 (2H, m), 0.83 (3H, s, $CH_3$-19), 0.65 (1H, m, H-4), 0.43 (1H, dd, *J*=8.0/5.1 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 155.5 (C-17), 139.9 (CH-24), 124.8 (CH), 124.2 (CH), 82.3 (CH-6), 70.6 (C-25), 64.5 ($CH_2$-21), 57.2 (CH-14), 56.6 (MeO), 48.6 (CH-20), 47.4 (C-10), 43.6 (C-13), 40.3 (CH), 35.3 (C-5), 35.1 ($CH_2$), 35.0 ($CH_2$), 34.8 ($CH_2$), 33.1 ($CH_2$), 31.3 ($CH_2$), 29.8 ($CH_3$-26/$CH_3$-27), 29.1 (CH), 24.9 ($CH_2$), 22.3 ($CH_2$), 21.3 (CH-3), 19.2 ($CH_3$-18), 16.7 ($CH_3$-19), 13.1 ($CH_2$-4) ppm.

**MS (ESI$^+$) (m/z, %):** 451.31 ($M^+$+Na, 13), 379.29 ($M^+$-49, 100).

**HRMS (ESI$^+$):** 451.3183 calculated for $C_{28}H_{44}NaO_3$ and found 451.3173.

1.16. Synthesis of (2*S*)-2-((1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*S*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethylhexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)-6-methylheptane-1,6-diol (32)




To a suspension of alcohol **36** (76 mg, 0.178 mmol) and Pd/C (5%) (cat.) in hexane (2 mL) was stirred at rt under atmosfera of $H_2$ for 3 hours. The mixture was then filtered through and the filtered liquids was concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 70% EtOAc/hexane), affording the alcohol **32** (53 mg, 71%).

Compound **32**: colourless oil; Rf: 0.28 (50% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3363, 2926, 2859, 2842, 1342, 1008, 943.

**$[\alpha]^{24}_D$**= +17.65 (c 1.00, $CHCl_3$).

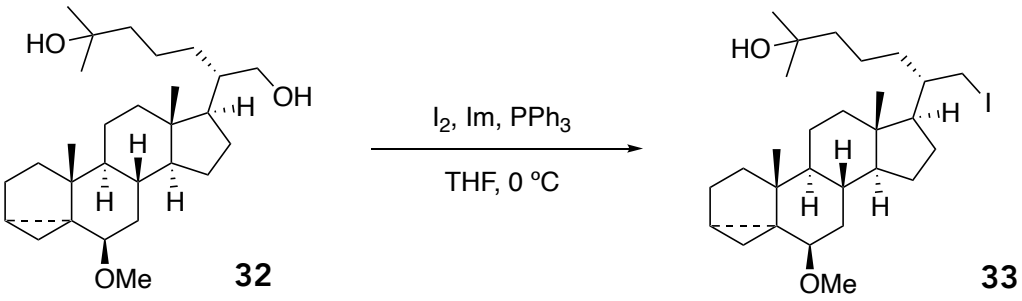
**$^1$H-NMR ($CDCl_3$, δ):** 3.71 (1H, dd, *J*=11.0/2.9 Hz, H-21), 3.53 (1H, dd, *J*=11.0/5.3 Hz, H-21), 3.33 (3H, s, MeO), 3.15 (1H, s, OH), 2.78 (1H, s, H-6), 1.83 (2H, m), 1.77 (3H, m), 1.47 (15H, m), 1.12 (6H, s, $CH_3$-26/$CH_3$-27), 1.10 (2H, m), 1.02 (3H, s, $CH_3$-18), 0.89 (2H, m), 0.74 (3H, s, $CH_3$-19), 0.65 (1H, m, H-4), 0.44 (1H, m, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 82.7 (CH-6), 71.5 (C-25), 63.6 ($CH_2$-21), 56.8 (MeO), 56.5 (CH-14), 50.5 (CH-17), 48.3 (CH-20), 44.3 ($CH_2$), 43.7 (C-10), 43.1 (C-13), 42.6 CH), 40.3 ($CH_2$), 35.5 (C-5), 35.3 ($CH_2$), 33.6 ($CH_2$), 30.8 (CH), 29.9 ($CH_3$), 29.6 ($CH_2$), 29.5 ($CH_3$), 27.8 ($CH_2$), 25.2 ($CH_2$), 24.4 ($CH_2$), 23.1 ($CH_2$), 21.8 (CH-3), 20.6 ($CH_2$), 19.5 ($CH_3$-18), 13.4 ($CH_2$-4), 12.7 ($CH_3$-19) ppm.

**MS (ESI$^+$) (m/z, %):** 455.35 ($M^+$+Na, 18), 415.35 ($M^+$-OH, 33), 383.33 ($M^+$-49, 100).

**HRMS (ESI$^+$):** 455.3496 calculated for $C_{28}H_{48}NaO_3$ and found 455.3498.

1.17. Synthesis of (6*S*)-7-iodo-6-((1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*S*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethylhexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)-2-methylheptan-2-ol (33)




To a solution of diol **32** (126 mg, 0.315 mmol) in THF (4 mL) were added sequentially $PPh_3$ (125 mg, 0.473 mmol) and imidazole (65 mg, 0.945 mmol). After cooling the mixture to 0 °C, $I_2$ (112 mg, 0.441 mmol) was added and stirring continued at rt for 20 minutes. The reaction was quenched with an aqueous saturated solution of $NaHCO_3$ (5 mL) and the product extracted with EtOAc (3x10 mL). The combined organic phase was washed with a 10% aqueous solution of $Na_2S_2O_3$ (10 mL), dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 20% EtOAc/hexane), affording the compound **33** (149 mg, 93%).

Compound **33**: colourless oil; Rf: 0.85 (50% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3393, 2986, 2928, 2867, 1457, 947, 721.

**$[\alpha]^{22}_D$**= +7.28 (c 1.00, $CHCl_3$).

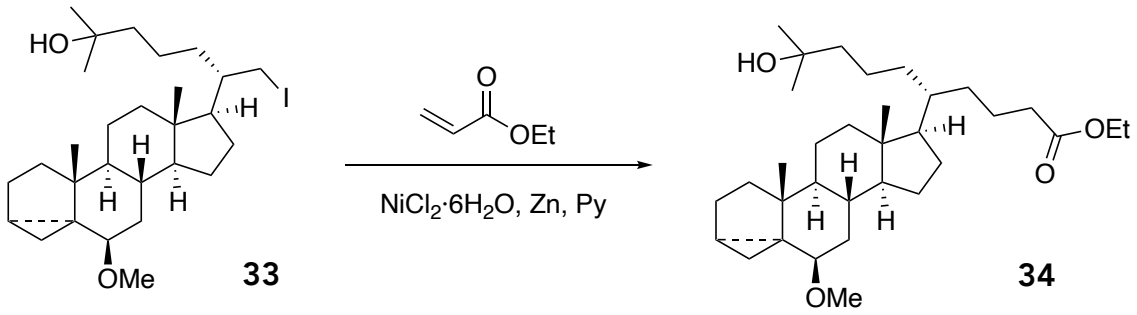
**$^1$H-NMR ($CDCl_3$, δ):** 3.43 (1H, dd, *J*=9.9/2.9 Hz, H-21), 3.32 (3H, s, MeO), 3.25 (1H, dd, *J*=9.9/4.2 Hz, H-21), 2.77 (1H, s, H-6), 1.92 (3H, m), 1.71 (4H, m), 1.45 (8H, m), 1.25 (6H, m), 1.22 (6H, s, $CH_3$-26/27), 1.12 (2H, m), 1.02 (3H, s, $CH_3$-18), 0.88 (3H, m), 0.77 (3H, s, $CH_3$-19), 0.65 (1H, dd, *J*=5.1/3.6 Hz, H-4), 0.44 (1H, dd, *J*=8.1/5.1 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 82.4 (CH-6), 71.0 (C-25), 56.6 (MeO), 56.3 (CH-14), 53.8 (CH-17), 47.9 (CH-20), 43.8 ($CH_2$), 43.4 (C-10), 42.6 (C-13), 40.5 (CH), 40.1 ($CH_2$), 35.2 (C-5), 35.0 ($CH_2$), 33.4 ($CH_2$), 32.7 ($CH_2$), 30.5 (CH), 29.4 ($CH_3$), 29.3 ($CH_3$), 27.5 ($CH_2$), 24.9 ($CH_2$), 23.9 ($CH_2$), 22.8 ($CH_2$), 21.5 (CH-3), 20.5 ($CH_2$), 19.3 ($CH_3$-18), 18.2 ($CH_2$-21), 13.2 ($CH_2$-4), 13.1 ($CH_3$-19) ppm.

**MS (ESI$^+$) (m/z, %):** 565.25 ($M^+$+Na, 5), 511.24 ($M^+$-OMe, 12), 493.23 ($M^+$-49, 100).

**HRMS (ESI$^+$):** 565.2513 calculated for $C_{28}H_{47}INaO_2$ and found 565.2519.

1.18. Synthesis of ethyl (5*R*)-9-hydroxy-5-((1a*R*,3a*R*,3b*S*,5a*R*,8a*S*,8b*S*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethylhexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)-9-methyldecanoate (34)




To a suspension of Zn (330 mg, 5.05 mmol) in pyridine (7 mL) was added $NiCl_2 \cdot 6H_2O$ (240 mg, 1.01 mmol) and ethyl acrylate (0.55 mL, 5.05 mmol) and the resulting mixture was stirred at 65 °C. It was observed that the suspension acquires a reddish-brown colour. After 30 minutes the mixture was cooled to 0 °C and was added a solution of the iodide **33** (186 mg, 0.336 mmol) in pyridine (4 mL) and it was stirred under these conditions for 90 minutes. Once the reaction mixture reaches rt, EtOAc (10 mL) was added and the resulting suspension was filtered over celite. The filtered liquids were washed with a 10% solution of $CuSO_4$ (3x20 mL), $H_2O$ (2x20 mL) and a saturated solution of NaCl (15 mL). The organic phase was dried with $Na_2SO_4$, filtered and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 20% EtOAc/hexane), affording the compound **34** (146 mg, 84%).

Compound **34**: colourless oil; Rf: 0.83 (50% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3447, 2954, 2931, 2860, 1738, 1251, 1164.

**$[\alpha]^{24}_D$**= +28.19 (c 1.00, $CHCl_3$).

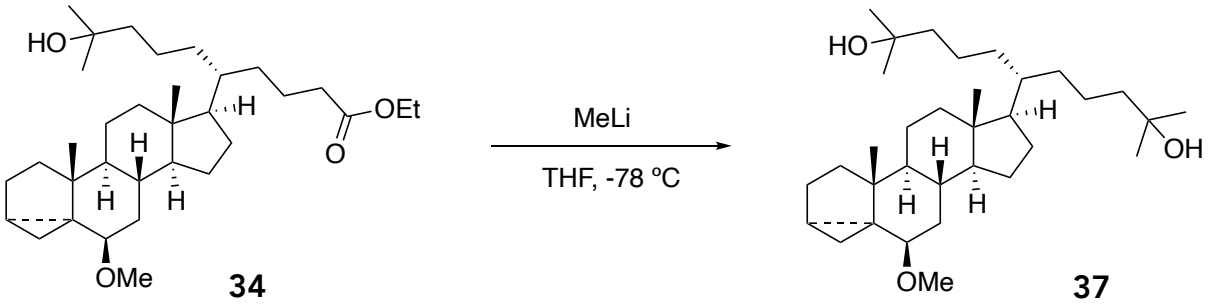
**$^1$H-NMR ($CDCl_3$, δ):** 4.12 (2H, q, *J*=7.1 Hz, $CH_2$-OEt), 3.32 (3H, s, MeO), 2.77 (1H, s, H-6), 2.27 (2H, m, $CH_2$-2'), 1.91 (3H, m), 1.74 (2H, m), 1.61 (2H, m), 1.42 (15H, m), 1.26 (3H, t, *J*=7.1 Hz, $CH_3$-OEt), 1.22 (6H, s, $CH_3$-26/27), 1.12 (4H, m), 1.02 ($CH_3$-18), 0.85 (4H, m), 0.71 (3H, s, $CH_3$-19), 0.65 (1H, m, H-4), 0.43 (1H, dd, *J*=8.0/5.1 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 173.9 (C=O), 82.4 (CH-6), 71.0 (C-25), 60.2 ($CH_2$-2'), 56.5 (MeO), 56.5 (CH-14), 52.5 (CH-17), 48.0 (CH-20), 44.4 ($CH_2$), 43.4 (C-10), 42.8 (C-13), 40.0 ($CH_2$), 39.0 (CH), 35.3 (C-5), 35.0 ($CH_2$), 34.8 ($CH_2$), 33.3 ($CH_2$), 31.0 ($CH_2$), 30.5 (CH), 30.3 ($CH_2$), 29.3 ($CH_3$), 29.3 ($CH_3$), 27.8 ($CH_2$), 25.0 ($CH_2$), 24.1 ($CH_2$), 22.8 ($CH_2$), 21.5 (CH-3), 21.0 ($CH_2$), 19.8 ($CH_2$), 19.3 ($CH_3$-18), 14.3 ($CH_3$-OEt), 13.1 ($CH_2$-4), 12.3 ($CH_3$-19) ppm.

**MS ($ESI^+$) (m/z, %):** 539.40 ($M^+$+Na, 35), ($M^+$-49, 100).

**HRMS ($ESI^+$):** 539.4071 calculated for $C_{33}H_{56}NaO_4$ and found 539.4080.

1.19. Synthesis of 6-((1a*R*,3a*R*,3b*S*,5a*R*,8a*S*,8b*S*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethylhexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)-2,10-dimethylundecane-2,10-diol (37)




To a solution of compound **34** (118 mg, 0.228 mmol) in THF (2 mL) cooled to -78 ºC was added a 1.5 M solution of MeLi·LiBr in $Et_2O$ (0.76 mL, 1.14 mmol) and the resulting mixture was stirred in these conditions for 2 hours. $H_2O$ (10 mL) was added and the aqueous solution was extracted with $CH_2Cl_2$ (3x15 mL). The combined organic phases were dried with $Na_2SO_4$, filtered and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 50% EtOAc/hexane), affording the diol **37** (93 mg, 82%).

Compound **37**: colourless oil; Rf: 0.45 (50% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3427, 2964, 2931, 2874, 1387, 835, 774.

**$[\alpha]^{24}_D$**= +18.72 (c 1.00, $CHCl_3$).

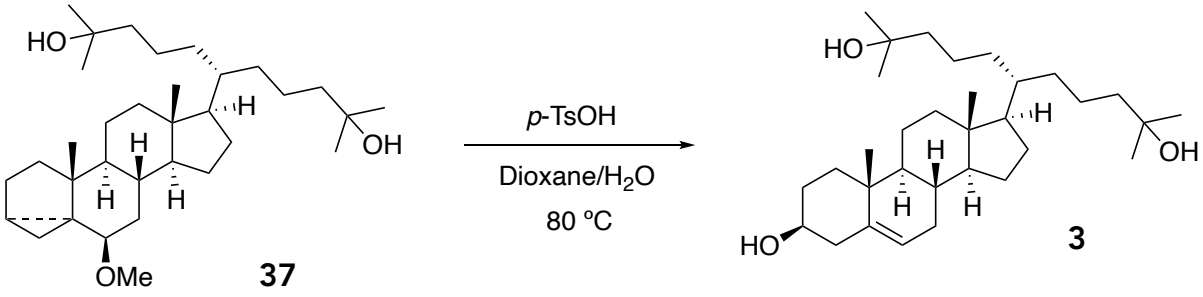
**$^1$H-NMR ($CDCl_3$, δ):** 3.33 (3H, s, MeO), 2.77 (1H, s, H-6), 1.91 (3H, m), 1.74 (3H, m), 1.42 (18H, m), 1.21 (12H, s, $CH_3$-26/27/4'/5'), 1.07 (3H, m), 1.03 (3H, s, $CH_3$-18), 0.88 (4H, m), 0.72 (3H, s, $CH_3$-19), 0.65 (1H, m, H-4), 0.43 (1H, dd, *J*=8.0/5.1 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 82.4 (CH-6), 71.1 (C-25/C-3'), 56.5 (MeO), 56.5 (CH-14), 52.7 (CH-17), 48.0 (CH-20), 44.5 ($CH_2$), 44.4 ($CH_2$), 43.9 (C-10), 42.8 (C-13), 40.0 ($CH_2$), 39.1 (CH), 35.3 (C-5), 35.1 ($CH_2$), 33.3 ($CH_2$), 31.5 ($CH_2$), 31.2 ($CH_2$), 30.5 (CH), 29.3 ($CH_3$), 29.3 ($CH_3$), 29.2 ($CH_3$), 29.2 ($CH_3$), 27.9 ($CH_2$), 25.0 ($CH_2$), 24.1 ($CH_2$), 22.8 ($CH_2$), 21.5 (CH-3), 20.2 ($CH_2$), 19.7 ($CH_2$), 19.3 ($CH_3$-18), 13.1 ($CH_2$-4), 12.7 ($CH_3$-19) ppm.

**MS (ESI$^+$) (m/z, %):** 525.42 ($M^+$+Na, 83), 472.42 ($M^+$-MeO, 6), 453.41 ($M^+$-49, 68), 435.39 ($M^+$-67, 100).

**HRMS (ESI$^+$):** 525.4278 calculated for $C_{33}H_{58}NaO_3$ and found 525.4285.

1.20. Synthesis of 6-((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2,10-dimethylundecane-2,10-diol (3)




To a solution of diol **37** (51 mg, 0.101 mmol) in dioxane (2 mL) and $H_2O$ (0.5 mL) was added *p*-TsOH (cat.) and the resulting mixture was stirred at 80 °C for 3 hours. $H_2O$ (5 mL) was and the aqueous solution was extracted with $CH_2Cl_2$ (3x15 mL). The combined organic phases were dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 70% EtOAc/hexane), affording the triol **3** (48 mg, 99%).

Compound **3**: white solid (mp: 197-199 °C); Rf: 0.26 (50% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3294, 2961, 2938, 2897, 2882, 1371, 1064, 908.

**$[\alpha]^{20}_D$**= +6.40 (c 1.00, $CHCl_3$).

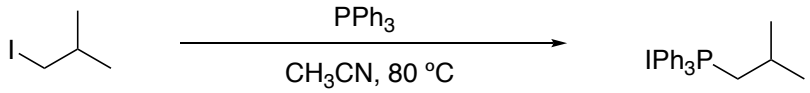
**$^1$H-NMR ($CDCl_3$, δ):** 5.37 (1H, s, H-6), 3.54 (1H, m, H-3), 2.30 (3H, m), 1.98 (3H, m), 1.85 (3H, m), 1.46 (19H, m), 1.24 (12H, s, $CH_3$-26/27/4'/5'), 1.09 (3H, m), 1.03 (3H, s, $CH_3$-18), 0.95 (3H, m), 0.70 (3H s, $CH_3$-19) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 140.7 (C-5), 121.6 (C-6), 71.7 (CH-3), 71.0 (C-25/C-3'), 56.7 (CH-14), 52.4 (CH-17), 50.1 (CH-20), 44.5 ($CH_2$), 44.4 ($CH_2$), 42.3 ($CH_2$), 42.2 (C-13), 39.4 ($CH_2$), 39.1 (CH), 37.2 ($CH_2$), 36.5 (C-10), 31.9 (CH), 31.9 ($CH_2$), 31.6 ($CH_2$), 31.4 ($CH_2$), 31.1 ($CH_2$), 29.3 ($CH_3$), 29.3 ($CH_3$), 29.2 ($CH_3$), 27.7 ($CH_2$), 24.1 ($CH_2$), 21.1 ($CH_2$), 20.1 ($CH_2$), 19.7 ($CH_2$), 19.3 ($CH_3$-18), 11.9 ($CH_3$-19) ppm.

**MS (ESI$^+$) (m/z, %):** 511.41 ($M^+$+Na, 33), 453.40 (13), 394.43 (100).

**HRMS (ESI$^+$):** 511.4122 calculated for $C_{32}H_{56}NaO_3$ and found 511.4127.

1.21. Synthesis of iodo(isobutyl)triphenyl-$\lambda^5$-phosphane (38)




1-iodo-2-methylpropane **38**

To a solution of **1-iodo-2-methylpropane** (3.1 g, 16.85 mmol) in $CH_3CN$ (15 mL) was added $PPh_3$ (6.63 g, 25.31 mmol) and the resulting mixture was stirred at 80 ºC for 22 hours. Then it was allowed to reach rt and the solvent was removed by vacuum distillation. The residue was purified by silica gel column chromatography (mobile phase: 5% MeOH/$CH_2Cl_2$), affording the compound **38** (6.05 g, 80%).

Compound **38**: white solid (mp: 176-180 ºC); Rf: 0.10 (2% MeOH/$CH_2Cl_2$).

**IR (ATR, $cm^{-1}$):** 2959, 2867, 1586, 1482, 1435, 1316, 744.

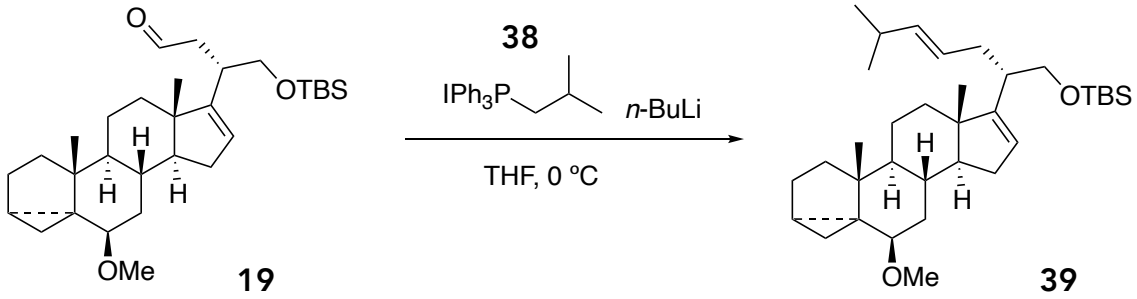
**$^1$H-NMR ($CDCl_3$, δ):** 7.75 (15H, m, Ph), 3.35 (2H, m, $CH_2$), 2.10 (1H, m, CH), 1.04 (6H, s, $CH_3$) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 135.2 (CH-Ph), 133.7 (CH-Ph), 130.7 (CH-Ph), 118.9 (C-Ph), 31.0 ($CH_2$), 24.6 (CH), 24.5 ($CH_3$), 24.4($CH_3$) ppm.

**MS ($ESI^+$) (m/z, %):** 321.16 ($M^+$+2, 2), 320.16 ($M^+$+1, 22), 319.16 ($M^+$, 100).

**HRMS ($ESI^+$):** 319.1610 calculated for $C_{22}H_{24}P$ and found 319.1605.

1.22. Synthesis of *tert*-butyl(((*S*,*E*)-2-((1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*R*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethyl-1,1a,2,3,3a,3b,4,5,5a,8,8a,8b,9,10-tetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)-6-methylhept-4-en-1-yl)oxy)dimethylsilane (39)




To a suspension of phosphonium salt **38** (1.58 g, 3.55 mmol) in THF (5 mL) cooled to 0 ° C was added a 2.5 M solution of *n*-BuLi in hexane (1.33 mL, 3.3 mmol), observing that the mixture of reaction turns orange. After 30 minutes, a solution of the aldehyde **19** (540 mg, 1.11 mmol) in THF (5 mL) was added and the resulting mixture was stirred at rt for 13 hours. A saturated aqueous solution of $NH_4Cl$ (3 mL) was added and the aqueous solution was extracted with EtOAc (2x10 mL). The combined organic phases were dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 2% EtOAc/hexane), affording the alkene **39** (410 mg, 72%).

Compound **39**: colourless liquid; Rf: 0.88 (20% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3853, 3743, 2955, 2928, 2854, 1987, 1967, 1457, 837.

**$[\alpha]^{22}_D$**= +48.30 (c 0.65, $CHCl_3$).

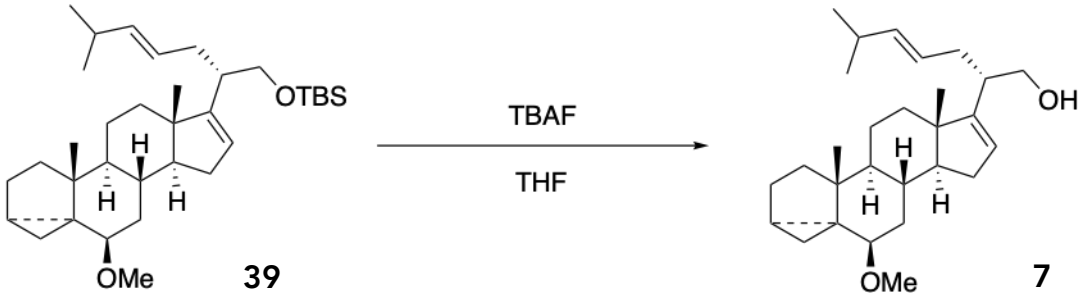
**$^1$H-NMR ($CDCl_3$, δ):** 5.36 (2H, m, CH-16/CH-24), 5.23 (1H, dd, *J*=5.7/10.9 Hz, CH-23), 3.58 (1H, dd, *J*=5.1/9.8 Hz, H-21), 3.51 (1H, dd, *J*=7.8/15.9 Hz, H-21), 3.37 (3H, s, MeO), 2.82 (1H, m, H-6), 2.61 (1H, dd, *J*= 7.4/14.1 Hz), 2.38 (1H, m), 2.28-2.02 (4H, m), 2.01–1.83 (3H, m), 1.83–1.59 (3H, m), 1.59–1.42 (2H, m), 1.41–1.25 (3H, m), 1.23–1.12 (1H, m), 1.04 (3H, s, $CH_3$-18), 1.01 (2H, m), 0.98 (3H, d, *J*=1.2 Hz, $CH_3$), 0.96 (3H, d, *J*=1.3 Hz, $CH_3$), 0.91 (9H, s, $CH_3$-$^t$Bu), 0.79 (3H, s, $CH_3$-19), 0.66 (1H, m, H-4), 0.47 (1H, dd, *J*=5.1/8.0 Hz, H-4), 0.05 (6H, s, $CH_3$-Si) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 155.9 (C-17), 138.2 (CH-24), 125.5 (CH-16), 123.1 (CH-23), 82.4 (CH-6), 66.3 ($CH_2$-21), 56.8 (CH-14), 56.7 (MeO), 48.7 (CH), 47.4 (C-10), 43.6 (C-13), 40.3 (CH), 35.4 (C-5), 35.2 ($CH_2$), 35.0 ($CH_2$), 33.1 ($CH_2$), 31.4 ($CH_2$), 29.8 ($CH_2$), 29.1 (CH), 26.5 (CH-25), 26.0 ($CH_3$-$^t$Bu), 24.9 ($CH_2$), 23.2 ($CH_3$-26/27), 22.4 ($CH_2$), 21.4 (CH-3), 19.3 ($CH_3$-18), 18.3 (C-$^t$Bu), 16.8 ($CH_3$-19), 13.1 ($CH_2$-4), -5.3 ($CH_3$-Si), -5.3 ($CH_3$-Si) ppm.

**MS ($ESI^+$) (m/z, %):** 527.42 ($M^+$+1,11), 495 ($M^+$-MeO, 100).

**HRMS ($ESI^+$):** 527.4279 calculated for $C_{34}H_{58}O_2Si$ and found 527.4274.

1.23. Synthesis of (*S*,*E*)-2-((1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*R*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethyl-1,1a,2,3,3a,3b,4,5,5a,8,8a,8b,9,10-tetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)-6-methylhept-4-en-1-ol (7)




To a solution of alkene **39** (410 mg, 0.779 mmol) in THF (5 mL) was added a 1 M solution of TBAF in THF (2.5 mL, 2.34 mmol) and the resulting mixture was stirred at rt for 13 hours. A saturated aqueous solution of $NH_4Cl$ (3 mL) was added and the aqueous solution was extracted with EtOAc (3x15 mL). The combined organic phases were dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 10% EtOAc/hexane), affording the compound **7** (321 mg, 99%).

Compound **7**: colourless liquid; Rf: 0.50 (20% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3479, 2954, 2926, 2852, 1460, 1376, 1095, 812.

**$[\alpha]^{22}_D$**= +7.07 (c 0.40, $CHCl_3$).

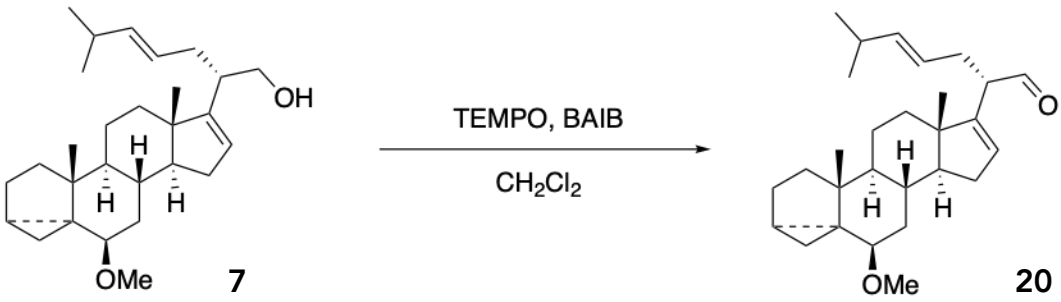
**$^1$H-NMR ($CDCl_3$, δ):** 5.48-5.15 (3H, m, CH-16/23/24), 3.58 (2H, d, *J*=6.1 Hz, H-21), 3.37 (3H, s, MeO), 2.78 (1H, m, H-6), 2.55 (1H, dd, *J*=7.4/14.3 Hz, H-22), 2.31-1.12 (17H, m), 1.04 (3H, s, $CH_3$-18), 1.03–0.90 (9H, m), 0.88 (3H, s, $CH_3$-19), 0.65 (1H, m, H-4), 0.44 (1H, dd, *J*=5.1/8.0 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 155.9 (C-17), 138.9 (CH-24), 124.9 (CH-16), 124.1 (CH-23), 82.3 (CH-6), 64.9 ($CH_2$-21), 57.3 (CH-14), 56.7 (MeO), 48.7 (CH), 47.4 (C-10), 43.6 (C-13), 40.7 (CH), 35.4 (C-5), 35.2 ($CH_2$), 35.0 ($CH_2$), 33.1 ($CH_2$), 31.3 ($CH_2$), 30.2 ($CH_2$), 29.2 (CH), 26.6 (CH-25), 24.9 ($CH_2$), 23.1 ($CH_3$-26/27), 23.1 ($CH_3$-26/27), 22.4 ($CH_2$), 21.4 (CH-3), 19.3 ($CH_3$-18), 16.8 ($CH_3$-19), 13.1 ($CH_2$-4) ppm.

**MS ($ESI^+$) (m/z, %):** 413.34 ($M^+$+1,13), 381.33 ($M^+$-MeO, 100).

**HRMS ($ESI^+$):** 413.3414 calculated for $C_{28}H_{45}O_2$ and found 413.3412.

1.24. Synthesis of (*S*,*E*)-2-((1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*R*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethyl-1,1a,2,3,3a,3b,4,5,5a,8,8a,8b,9,10-tetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)-6-methylhept-4-enal (20)




To a solution of alcohol **7** (85 mg, 0.206 mmol) in $CH_2Cl_2$ (3 mL) was added BAIB (100 mg, 0.31 mmol) and TEMPO (cat.) and the resulting mixture was stirred at rt for 3 hours. The solvent was rotatory evaporated to afford a residue which was taken up in $^t$BuOMe. The resulting solution was washed with 15% aqueous $Na_2S_2O_3$ (2 x10 mL) then with a saturated aqueous solution of $NaHCO_3$ (2x10 mL). The organic phase was dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 5% EtOAc/hexane), affording the compound **20** (65 mg, 78%).

Compound **20**: colourless liquid; Rf: 0.85 (20% EtOAc/hexane).

**IR (ATR, cm$^{-1}$):** 2953, 2926, 2871, 1737, 1521, 1281, 777.

**$[\alpha]^{21}_D$**= +8.32 (c 1.00, $CHCl_3$).

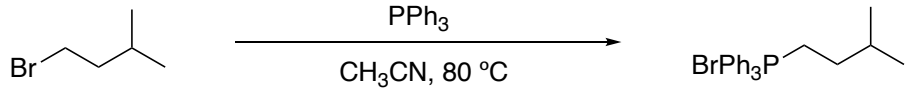
**$^1$H-NMR ($CDCl_3$, δ):** 9.43 (1H, s, H-21), 5.55 (1H, m, H-16), 5.22 (2H, m, H-23/24), 3.36 (3H, s, MeO), 2.97 (1H, m, H-20), 2.81 (1H, s, H-6), 2.53 (2H, m), 2.28 (2H, m), 1.95 (3H, m), 1.75 (2H, m), 1.54 (3H, m), 1.30 (3H, m), 1.06 (3H, s, $CH_3$-18), 0.95 (3H, s, $CH_3$-26/27), 0.93 (3H, s, $CH_3$-26/27), 0.87 (3H, m), 0.82 (3H, s, $CH_3$-19), 0.68 (1H, m, H-4), 0.47 (1H, dd, *J*=8.0/5.0 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 200.1 (CH-21), 150.1 (C-17), 139.2 (CH-24), 127.7 (CH), 123.4 (CH), 82.1 (CH-6), 56.7 (CH), 56.6 (MeO), 51.9 (CH), 48.5 (CH), 47.3 (C-10), 43.5 (C-13), 35.2 (C-5), 35.1 ($CH_2$), 34.6 ($CH_2$), 33.0 ($CH_2$), 31.5 ($CH_2$), 29.0 (CH), 27.4 ($CH_2$), 26.5 (CH-25), 24.8 ($CH_2$), 22.9 ($CH_3$-26/27), 22.8 ($CH_2$), 22.2 ($CH_3$-26/27), 21.2 (CH-3), 19.1 ($CH_3$-18), 16.3 ($CH_3$-19), 13.0 ($CH_2$-4) ppm.

**MS (ESI$^+$) (m/z, %):** 433.31 ($M^+$+Na, 4), 411.32 ($M^+$+1, 10), 379.30 ($M^+$-MeO, 100).

**HRMS (ESI$^+$):** 411.3258 calculated for $C_{28}H_{43}O_2$ and found 411.3262.

### 1.25. Synthesis of bromo(isobutyl)triphenyl-$\lambda^5$-phosphane (40)




1-bromo-2-methylpropane **40**

To a solution of **1-bromo-2-methylpropane** (3.78 g, 25.04 mmol) in $CH_3CN$ (20 mL) was added $PPh_3$ (9.85 g, 37.6 mmol) and the resulting mixture was stirred at 80 °C for 24 hours. Then it was allowed to reach rt and the solvent was removed by vacuum distillation. The residue was purified by silica gel column chromatography (mobile phase: 15% MeOH/$CH_2Cl_2$), affording the compound **40** (6.59 g, 64%).

Compound **40**: white solid (mp: 114-117 °C); Rf: 0.10 (5% MeOH/$CH_2Cl_2$).

**IR (ATR, $cm^{-1}$):** 3478, 3411, 2962, 2910, 2876, 1438, 1109, 995, 756.

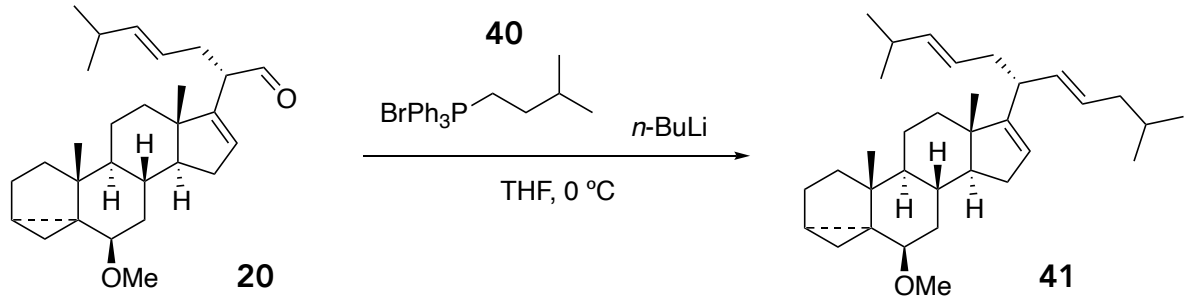
**$^1$H-NMR ($CDCl_3$, δ):** 7.78 (15H, m, Ph), 3.63 (2H, m, $CH_2$-P), 1.96 (1H, m, CH), 1.49 (2H, m, $CH_2$), 0.98 (6H, s, $CH_3$) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 135.1 (CH-Ph), 133.7 (CH-Ph), 130.6 (CH-Ph), 118.7 (C-Ph), 31.1 ($CH_2$-P), 28.9 (CH), 22.19 ($CH_3$), 21.4 ($CH_2$) ppm.

**MS ($ESI^+$) (m/z, %):** 335.17 ($M^+$+2, 3), 334.17 ($M^+$+1, 28), 333.17 ($M^+$, 100).

**HRMS ($ESI^+$):** 333.1767 calculated for $C_{23}H_{26}P$ and found 333.1765.

1.26. Synthesis of (1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*R*,10*R*,10a*R*)-6-((R,3*E*,7*E*)-2,10-dimethylundeca-3,7-dien-6-yl)-10-methoxy-3a,5a-dimethyl-1,1a,2,3,3a,3b,4,5,5a,8,8a,8b,9,10-tetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalene (41)




To a suspension of phosphonium salt **40** (180 mg, 0.43 mmol) in THF (2 mL) cooled to 0 °C was added a 2.5 M solution of *n*-BuLi in hexane (0.16 mL, 0.4 mmol), observing that the mixture of reaction turns orange. After 30 minutes, a solution of the aldehyde **20** (55 mg, 0.134 mmol) in THF (2 mL) was added and the resulting mixture was stirred at rt for 1 hour. A saturated aqueous solution of $NH_4Cl$ (3 mL) was added and the aqueous solution was extracted with EtOAc (3x12 mL). The combined organic phases were washed with $H_2O$ (20 mL) and a saturated NaCl solution (30 mL), dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 1% EtOAc/hexane), affording the alkene **41** (39 mg, 63%).

Compound **41**: colourless liquid; Rf: 0.95 (10% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 2954, 2923, 2850, 1463, 1375, 1095, 966.

**$[\alpha]^{23}_D$**= -7.26 (c 0.5, $CHCl_3$).

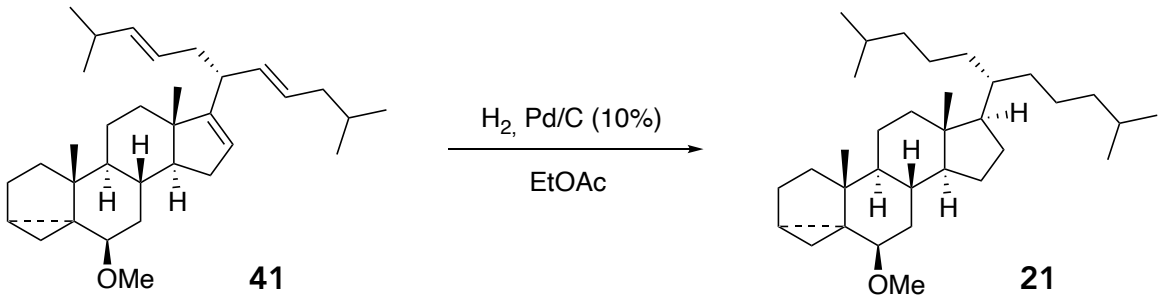
**$^1$H-NMR ($CDCl_3$, δ):** 5.43 (1H, s, H-16), 5.34 (2H, m, H-23/24/21/1'), 5.22 (2H, m, H-23/24/21/1'), 3.38 (3H, s, MeO), 3.06 (1H, m, H-20), 2.82 (1H, s, H-6), 2.59 (1H, m), 2.31 (1H, m), 2.10 (2H, m), 1.96 (5H, m), 1.79 (2H, m), 1.58 (6H, m), 1.37 (3H, m), 1.18 (2H, m), 1.09 (3H, s, $CH_3$-18), 0.95 (6H, d, $CH_3$-26/27), 0.93 (6H, s, $CH_3$-4'/5'), 0.86 (3H, s, $CH_3$-19), 0.69 (1H, t, *J*=4.5 Hz, H-4), 0.48 (1H, dd, *J*=8.0/5.1 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 158.6 (C-17), 138.0 (CH-24), 134.6 (CH), 127.2 (CH), 125.7 (CH), 122.3 (CH), 82.4 (CH-6), 57.4 (CH), 56.6 (MeO), 48.7 (CH), 47.4 (C-10), 43.6 (C-13), 36.7 ($CH_2$), 36.6 (CH), 35.5 (C-5), 35.4 ($CH_2$), 35.1 ($CH_2$), 33.2 ($CH_2$), 33.2 ($CH_2$), 31.2 ($CH_2$), 29.0 (CH), 28.7 (CH), 26.6 (CH-25), 25.0 ($CH_2$), 23.2 ($CH_3$-26/27), 23.2 ($CH_3$-26/27), 22.6 ($CH_3$-4'/5'), 22.5 ($CH_3$-4'/5'), 22.4 ($CH_2$), 21.5 (CH), 19.3 ($CH_3$-18), 17.0 ($CH_3$-19), 13.1 ($CH_2$-4) ppm.

**MS (ESI$^+$) (m/z, %):** 463.39 ($M^+$-H, 3), 433.38 ($M^+$-MeO, 100).

**HRMS (ESI$^+$):** 463.3934 calculated for $C_{33}H_{51}O$ and found 463.3930.

1.27. Synthesis of (1a*R*,3a*R*,3b*S*,5a*R*,8a*S*,8b*S*,10*R*,10a*R*)-6-(2,10-dimethylundecan-6-yl)-10-methoxy-3a,5a-dimethylhexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalene (21)




To a suspension of alkene **41** (38 mg, 0.081 mmol) and Pd/C (10%) (cat.) in EtOAc (3 mL) was stirred at rt under atmosfera of $H_2$ for 14 hours. The mixture was then filtered through and the filtered liquids was concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 1% EtOAc/hexane), affording the compound **21** (35 mg, 93%).

Compound **21**: colourless liquid; Rf: 0.95 (10% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 2953, 2924, 2853, 1464, 1379, 1099, 966.

**$[\alpha]^{22}_D$**= +4.02 (c 0.5, $CHCl_3$).

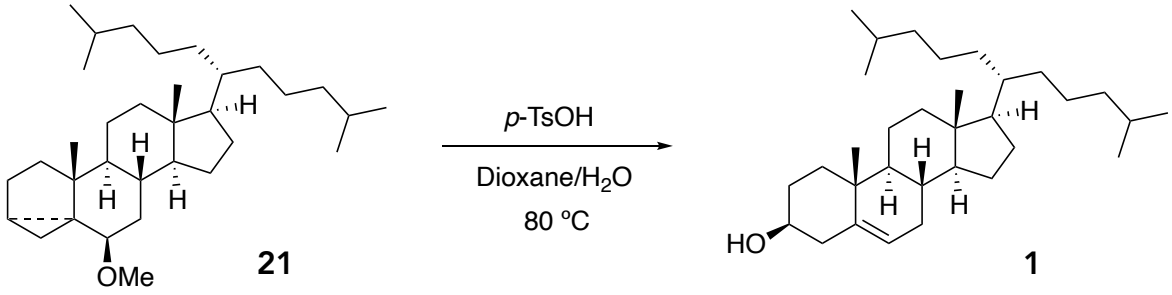
**$^1$H-NMR ($CDCl_3$, δ):** 3.34 (3H, s, MeO), 2.79 (1H, m, H-6), 1.94 (2H, m), 1.77 (3H, m), 1.55 (6H, m), 1.44 (3H, m), 1.32 (6H, m), 1.05 (3H, s, $CH_3$-18), 0.90 (6H, s, $CH_3$-26/27), 0.88 (6H, s, $CH_3$-4'/5'), 0.87 (4H, m), 0.67 (1H, dd, *J*=5.1/3.7 Hz, H-4), 0.45 (1H, dd, *J*=8.0/5.0 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 82.5 (CH-6), 56.5 (MeO), 52.8 (CH), 48.1 (CH), 43.4 (C-10), 42.8 (C-13), 40.0 ($CH_2$), 39.7 ($CH_2$), 39.6 ($CH_2$), 39.3 (CH), 35.4 (C-5), 35.1 ($CH_2$), 33.4 ($CH_2$), 31.1 ($CH_2$), 31.0 ($CH_2$), 30.5 (CH), 28.0 (CH), 27.9 (CH), 27.8 ($CH_2$), 25.0 ($CH_2$), 24.1 ($CH_2$), 23.2 ($CH_2$), 22.9 ($CH_2$), 22.8 ($CH_2$), 22.8 ($CH_3$-26/27/4'/5'), 22.7 ($CH_3$-26/27/4'/5'), 22.7 ($CH_3$-26/27/4'/5'), 22.6 ($CH_3$-26/27/4'/5'), 21.6 (CH), 19.3 ($CH_3$-18), 13.1 ($CH_2$-4), 12.4 ($CH_3$-19) ppm.

**MS ($ESI^+$) (m/z, %):** 439.43 ($M^+$-MeO, 100), 437.41 (25).

**HRMS ($ESI^+$):** 439.4298 calculated for $C_{32}H_{55}$ and found 439.4296.

1.28. Synthesis of (3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-(2,10-dimethylundecan-6-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ol (1)




To a solution of compound **21** (34 mg, 0.072 mmol) in dioxane (2 mL) and $H_2O$ (0.5 mL) was added *p*-TsOH (cat.) and the resulting mixture was stirred at 80 °C for 3 hours. $H_2O$ (5 mL) was and the aqueous solution was extracted with $CH_2Cl_2$ (3x15 mL). The combined organic phases were dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 20% EtOAc/hexane), affording the alcohol **1** (32 mg, 99%).

Compound **1**: colourless liquid; Rf: 0.18 (10% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3360, 2955, 2921, 2850, 1462, 1377, 1187, 969.

**$[\alpha]^{23}_D$**= -23.43 (c 1.00, $CHCl_3$).

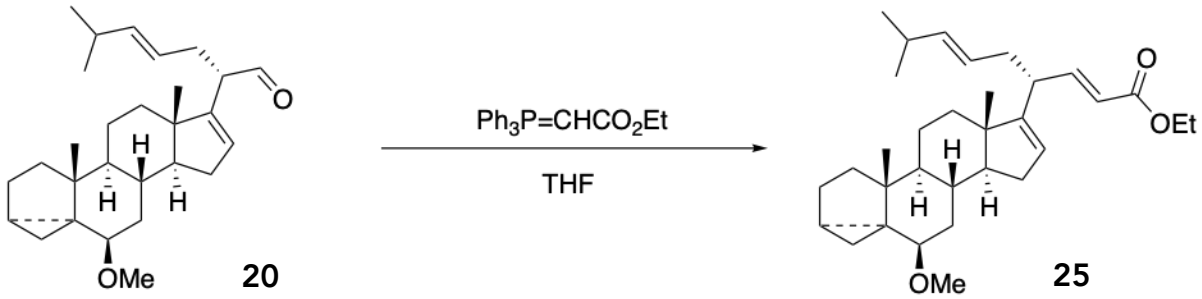
**$^1$H-NMR ($CDCl_3$, δ):** 5.38 (1H, s, H-6), 3.55 (1H, m, H-3), 2.25 (2H, m), 1.97 (2H, m), 1.85 (2H, m), 1.79 (1H, m), 1.72-1.07 (25H, m), 1.03 (3H, s, $CH_3$-18), 0.95 (3H, m), 0.90 (6H, s, $CH_3$-26/27/4′/5′), 0.88 (6H, s, $CH_3$-26/27/4′/5′), 0.69 (3H, s, $CH_3$-19) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 140.8 (C-5), 121.7 (CH-6), 71.8 (CH-3), 56.8 (CH), 52.7 (CH), 50.2 (CH), 42.4 (C-10), 42.3 ($CH_2$), 39.7 ($CH_2$), 39.6 ($CH_2$), 39.5 ($CH_2$), 39.3 (CH), 37.3 ($CH_2$), 36.5 (C-13), 32.0 (CH), 31.9 ($CH_2$), 31.7 ($CH_2$), 31.1 ($CH_2$), 31.0 ($CH_2$), 28.0 (CH), 27.9 (CH), 27.8 ($CH_2$), 24.2 ($CH_2$), 23.2 ($CH_2$), 22.9 ($CH_2$), 22.8 ($CH_3$-26/27/4′/5′), 22.7 ($CH_3$-26/27/4′/5′), 22.7 ($CH_3$-26/27/4′/5′), 22.6 ($CH_3$-26/27/4′/5′), 21.2 ($CH_2$), 19.4 ($CH_3$-18), 12.0 ($CH_3$-19) ppm.

**MS (ESI$^+$) (m/z, %):** 439.43 ($M^+$-OH, 100).

**HRMS (ESI$^+$):** 439.4298 calculated for $C_{32}H_{55}$ and found 439.4294.

1.29. Synthesis of ethyl (*R*,2*E*,6*E*)-4-((1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*R*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethyl-1,1a,2,3,3a,3b,4,5,5a,8,8a,8b,9,10-tetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)-8-methylnona-2,6-dienoate (25)




To a solution of aldehyde **20** (82 mg, 0.2 mmol) in THF (3 mL) was added $Ph_3P{=}CHCO_2Et$ (140 mg, 0.4 mmol) and the resulting mixture was stirred at rt for 19 hours. The solvent was evaporated and the residue was purified by silica gel column chromatography (mobile phase: 3% EtOAc/hexane), affording the ester **25** (78 mg, 82%).

Compound **25**: colourless liquid; Rf: 0.82 (20% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 2955, 2923, 2851, 1722, 1462, 1374, 1262, 1161, 1107, 967.

**$[\alpha]^{20}_D$**= +8.12 (c 1.00, $CHCl_3$).

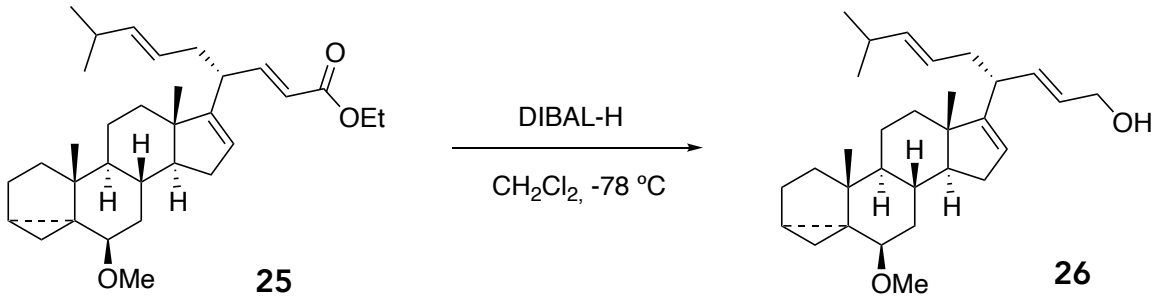
**$^1$H-NMR ($CDCl_3$, δ):** 6.87 (1H, dd, *J*=5.6/8.9 Hz, H-21), 5.78 (1H, dd, J=15.6/1 Hz, H-1'), 5.48 (1H, s, H-16), 5.23 (2H, m, H-23/24), 4.19 (2H, q, *J*=6 Hz, $CH_2$-OEt), 3.36 (3H, s, MeO), 2.88 (1H, m, H-20), 2.81 (1H, s, H-6), 2.56 (1H, m), 2.30 (2H, m), 2.11 (1H, m), 1.92 (3H, m), 1.73 (2H, m), 1.54 (4H, m), 1.38 (2H, m), 1.30 (3H, 3H, t, *J*=7.1Hz, $CH_3$-OEt), 1.14 (1H, m), 1.06 (3H, s, $CH_3$-18), 0.95 (3H, d, *J*=3.4 Hz, $CH_3$-26/27), 0.93 (3H, d, *J*=3.5 Hz, $CH_3$-26/27), 0.91 (3H, m), 0.82 (3H, s, $CH_3$-19), 0.68 (1H, dd, *J*=5.1/3.7 Hz, H-4), 0.47 (1H, dd, *J*=8.1/5.1 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 166.7 (C=O), 155.6 (C-17), 152.0 (CH-21), 138.9 (CH-16), 124.5 (CH), 124.3 (CH), 120.2 (CH-1'), 82.3 (CH-6), 60.2 ($CH_2$-OEt), 57.2 (CH), 56.7 (MeO), 48.6 (CH), 47.6 (C-10), 43.6 (C-13), 41.6 ($CH_2$), 35.4 (C-5), 35.1 ($CH_2$), 35.0 ($CH_2$), 33.1 ($CH_2$), 32.2 ($CH_2$), 31.3 ($CH_2$), 29.0 (CH), 26.7 (CH-25), 24.9 ($CH_2$), 23.1 ($CH_3$-26/27), 23.0 ($CH_3$-26/27), 22.3 ($CH_2$), 21.4 (CH), 19.2 ($CH_3$-18), 16.8 ($CH_3$-19), 14.3 ($CH_3$-OEt), 13.1 ($CH_2$-4) ppm.

**MS ($ESI^+$) (m/z, %):** 503.35 ($M^+$+Na, 40), 449.34 ($M^+$-OMe, 100).

**HRMS ($ESI^+$):** 503.3496 calculated for $C_{32}H_{48}NaO_3$ and found 503.3485.

1.30. Synthesis of (*R*,2*E*,6*E*)-4-((1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*R*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethyl-1,1a,2,3,3a,3b,4,5,5a,8,8a,8b,9,10-tetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)-8-methylnona-2,6-dien-1-ol (26)




To a solution of the ester **25** (78 mg, 0.16 mmol) in $CH_2Cl_2$ (3 mL) cooled to -78 °C was added a 1 M solution of DIBAL-H in hexane (0.65 mL, 0.65 mmol) and the resulting mixture was stirred under these conditions for 22 hours. $^t$BuOMe (1 mL) and $H_2O$ (0.5 mL) were added and the mixture allowed to reach rt. Stirring was continued till the formation of a white gel before adding $H_2O$ (0.5 ml) and a 4 M aqueous solution of NaOH (0.5 mL). Stirring was continued till the formation of a white solid. The solid was separated by filtration. After evaporation to dryness of the filtered liquids, the residue was purified by silica gel column chromatography (mobile phase: 20% EtOAc/hexane), affording alcohol **26** (52 mg, 74%)

Compound **26**: colourless liquid; Rf: 0.23 (20% EtOAc/hexane).

**IR (ATR, cm$^{-1}$):** 3072, 2956, 2922, 2853, 1462, 1377, 1187, 1080, 965.

**$[\alpha]^{20}_D$**= +12.35 (c 1.00, $CHCl_3$).

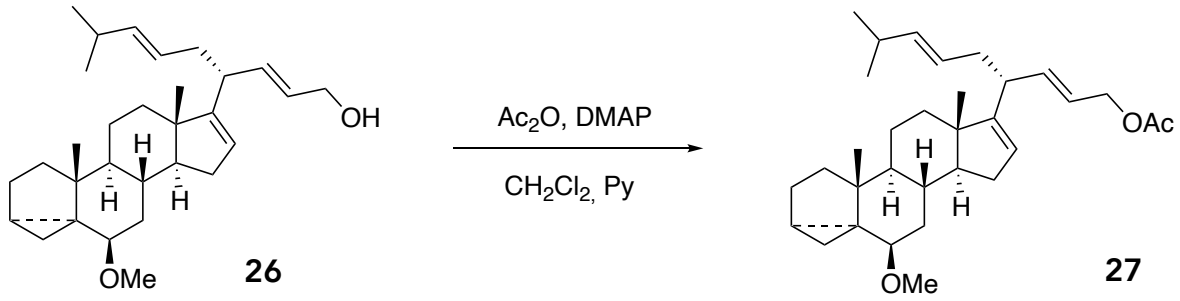
**$^1$H-NMR ($CDCl_3$, δ):** 5.62 (2H, dd, *J*=4.8/2.0 Hz, H21/1'), 5.42 (1H, s, H-16), 5.21 (2H, m, H-23/24), 4.12 (2H, s, H-2'), 3.37 (3H, s, MeO), 2.81 (1H, s, H-6), 2.76 (1H, m, H-20), 2.57 (1H, m), 2.31 (1H, m), 2.10 (2H, m), 1.95 (4H, m), 1.77 (3H, m), 1.54 (5H, m), 1.35 (2H, m), 1.17 (1H, m), 1.07 (3H, s, $CH_3$-18), 0.96 (3H, s, $CH_3$-26/27), 0.94 (3H, s, $CH_3$-26/27), 0.89 (3H, m), 0.84 (3H, s, $CH_3$-19), 0.68 (1H, t, *J*=4.3 Hz, H-4), 0.47 (1H, dd, *J*=8.0/5.0 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 157.4 (C-17), 138.2 (CH), 136.7 (CH), 128.1 (CH), 125.3 (CH), 123.0 (CH), 82.4 (CH-6), 63.7 ($CH_2$-2'), 57.4 (CH), 56.7 (MeO), 48.7 (CH), 47.5 (C-10), 43.6 (C-13), 41.7 ($CH_2$), 35.4 (C-5), 35.2 ($CH_2$), 33.1 ($CH_2$), 32.7 ($CH_2$), 31.2 ($CH_2$), 29.0 (CH), 26.7 (CH), 24.9 ($CH_2$), 23.1 ($CH_3$-26/27), 23.1 ($CH_3$-26/27), 22.4 ($CH_2$), 21.4 (CH), 19.3 ($CH_3$-18), 17.0 ($CH_3$-19), 13.1 ($CH_2$-4) ppm.

**MS (ESI$^+$) (m/z, %):** 407.33 ($M^+$-OMe, 83).

**HRMS (ESI$^+$):** 407.3308 calculated for $C_{29}H_{43}O$ and found 407.3305.

1.31. Synthesis of (*R*,2*E*,6*E*)-4-((1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*R*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethyl-1,1a,2,3,3a,3b,4,5,5a,8,8a,8b,9,10-tetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)-8-methylnona-2,6-dien-1-yl acetate (27)




To a solution of allylic alcohol **26** (52 mg, 0.118 mmol) in $CH_2Cl_2$ (2 mL) was added pyridine (29 µL, 0.36 mmol), acetic anhydride (35 µL, 5.76 mmol) and DMAP (cat.). The resulting mixture was stirred at rt for 1 hour. $H_2O$ (5 mL) was added and the aqeous phase was extracted with $CH_2Cl_2$ (2 x 25 mL). The combined organic phases were washed with 10% HCl solution (5 mL), dried with $Na_2SO_4$, filtered and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 5% EtOAc/hexane), affording compound **27** (51 mg, 91%).

Compound **27**: colourless liquid; Rf: 0.43 (10% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 2956, 2923, 2853, 1745, 1462, 1377, 1229, 1081, 967.

**$[\alpha]^{20}_D$**= +15.14 (c 1.00, $CHCl_3$).

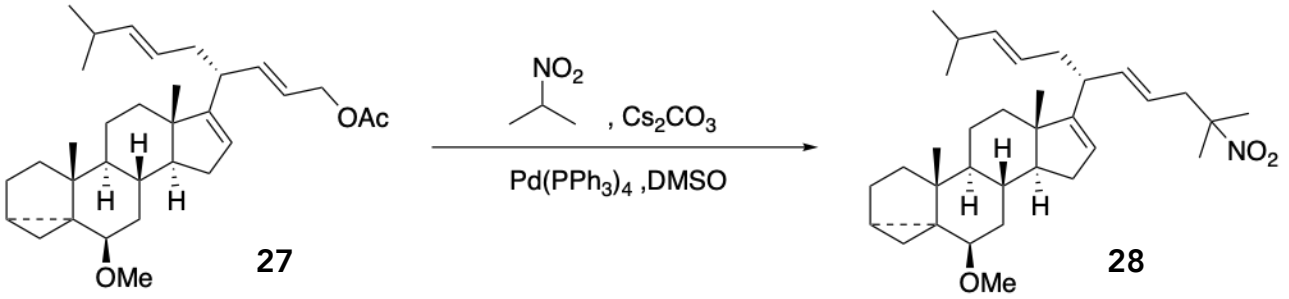
**$^1$H-NMR ($CDCl_3$, δ):** 5.66 (1H, m, H-1'), 5.56 (1H, m, H-21), 5.41 (1H, m, H-16), 5.19 (2H, m, H-23/24), 4.52 (2H, dd, *J*=6.3/1.1 Hz, H-2'), 3.36 (2H, s, MeO), 2.80 (1H, m, H-6), 2.75 (1H, m, H-20), 2.55 (1H, m), 2.29 (1H, m), 2.11 (2H, m), 2.06 (3H, s, H-4'), 1.94 (3H, m), 1.75 (2H, m), 1.53 (3H, m), 1.35 (2H, m), 1.16 (1H, m), 1.06 (3H, s, $CH_3$-18), 0.95 (3H, s, $CH_3$-26/27), 0.93 (3H, s, $CH_3$-26/27), 0.89 (4H, m), 0.82 (3H, s, $CH_3$-19), 0.67 (1H, dd, *J*=5.1/3.7 Hz, H-4), 0.46 (1H, dd, *J*=8.0/5.1 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 170.8 (C=O), 157.1 (C-17), 139.6 (CH), 138.2 (CH), 125.1 (CH), 123.2 (CH), 123.0 (CH), 82.3 (CH-6), 65.0 ($CH_2$-2'), 57.4 (CH), 56.6 (MeO), 48.6 (CH), 47.5 (C-10), 43.6 (C-13), 41.7 ($CH_2$), 35.4 (C-5), 35.1 ($CH_2$), 33.1 ($CH_2$), 32.4 ($CH_2$), 31.2 ($CH_2$), 29.0 (CH), 26.6 (CH-25), 24.9 ($CH_2$), 23.1 ($CH_3$-26/27), 23.0 ($CH_3$-26/27), 22.7 ($CH_2$), 22.4 ($CH_2$), 21.4 (CH), 21.0 ($CH_3$-4'), 19.3 ($CH_3$-18), 16.9 ($CH_3$-19), 13.1 ($CH_2$-4) ppm.

**MS ($ESI^+$) (m/z, %):** 520.32 ($M^+$+K, 13), 503.35 ($M^+$+Na, 13), 449.34 ($M^+$-OMe, 95), 421.34 ($M^+$-OAc, 23).

**HRMS ($ESI^+$):** 503.3496 calculated for $C_{32}H_{48}NaO_3$ and found 503.3492.

1.32. Synthesis of (1a*R*,3a*R*,3b*S*,5a*S*,8a*S*,8b*R*,10*R*,10a*R*)-6-((*R*,3*E*,7*E*)-2,10-dimethyl-10-nitroundeca-3,7-dien-6-yl)-10-methoxy-3a,5a-dimethyl-1,1a,2,3,3a,3b,4,5,5a,8,8a,8b,9,10-tetradecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalene (28)




To a solution of $Pd(PPh_3)_4$ (12 mg, 0.42 mmol), $Cs_2CO_3$ (137 mg, 0.42 mmol) and 2-nitropropane (38 µL, 0.42 mmol) in DMSO (2 mL) was added the solution of acetate **27** (632 mg, 1.6 mmol) in DMSO (1 mL). The resulting mixture was stirred at rt for 25 hours. A saturated aqueous solution of $NH_4Cl$ (8 mL) was added and the aqueous solution was extracted with $^t$BuOMe (3x20 mL). The combined organic phases were dried with $Na_2SO_4$, filtered and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 3% EtOAc/hexane), affording compound **28** (40 mg, 75%).

Compound **28**: colourless liquid; Rf: 0.32 (5% EtOAc/hexane).

**IR (ATR, cm$^{-1}$):** 2955, 2922, 2852, 1541, 1463, 1372, 1095, 970.

**[α]$^{20}_D$**= +16.25 (c 1.00, $CHCl_3$).

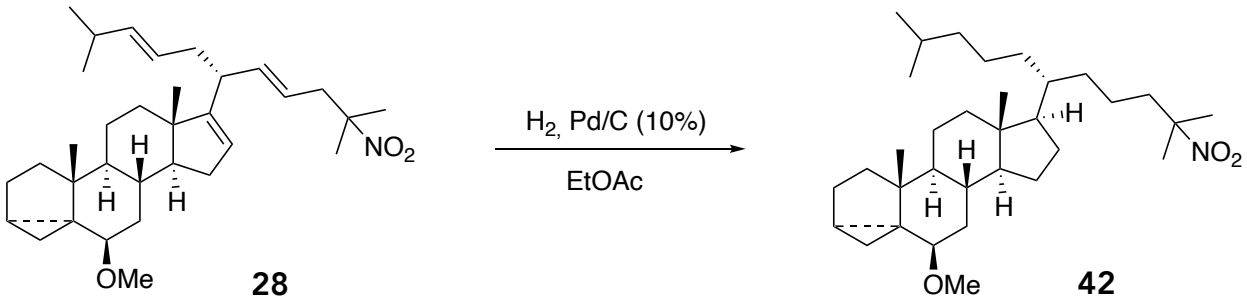
**$^1$H-NMR ($CDCl_3$, δ):** 5.47 (1H, m), 5.39 (1H, s, H-16), 5.21 (3H, m), 3.36 (3H, s, MeO), 2.81 (1H, s, H-6), 2.72 (1H, m, H-20), 2.58 (3H, m, H25/H-2'), 2.28 (1H, m), 2.09 (2H, m), 1.94 (2H, m), 1.76 (2H, m), 1.57 (6H, s, H-4'/5'), 1.51 (3H, m), 1.33 (3H, m), 1.17 (1H, m), 1.07 (3H, s, $CH_3$-18), 0.96 (3H, d, *J*=2.1 Hz, $CH_3$-26/27), 0.93 (3H, d, *J*=2.0 Hz, $CH_3$-26/27), 0.91 (3H, m), 0.82 (3H, s, $CH_3$-19), 0.68 (1H, dd, *J*=5.1/3.7 Hz, H-4), 0.47 (1H, dd, *J*=8.0/5.1 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 157.5 (C-17), 140.4 (CH), 138.1 (CH), 125.4 (CH), 122.9 (CH), 121.6 (CH), 88.1 (C-3'), 82.4 (CH-6), 57.3 (CH), 56.6 (MeO), 48.6 (CH), 47.5 (C-10), 43.9 ($CH_2$), 43.6 (C-13), 42.0 (CH), 35.4 (C-5), 35.1 ($CH_2$), 33.1 ($CH_2$), 32.7 ($CH_2$), 31.2 ($CH_2$), 29.0 (CH), 26.7 (CH-25), 25.6 ($CH_3$-4'/5'), 25.5 ($CH_3$-4'/5'), 24.9 ($CH_2$), 23.1 ($CH_3$-26/27), 23.0 ($CH_3$-26/27), 22.3 ($CH_2$), 21.4 (CH), 19.3 ($CH_3$-18), 16.9 ($CH_3$-19), 13.1 ($CH_2$-4) ppm.

**MS (ESI$^+$) (m/z, %):** 478.36 ($M^+$-OMe, 100).

**HRMS (ESI$^+$):** 478.3680 calculated for $C_{32}H_{48}NO_2$ and found 478.3673.

1.33. Synthesis of (1a*R*,3a*R*,3b*S*,5a*R*,8a*S*,8b*S*,10*R*,10a*R*)-6-((*R*)-2,10-dimethyl-2-nitroundecan-6-yl)-10-methoxy-3a,5a-dimethylhexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalene (42)




To a suspension of compound **28** (40 mg, 0.078 mmol) and Pd/C (10%) (cat.) in EtOAc (2 mL) was stirred at rt under atmosfera of $H_2$ for 16 hours. The mixture was then filtered through and the filtered liquids was concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 2% EtOAc/hexane), affording the compound **42** (36 mg, 90%).

Compound **42**: colourless liquid; Rf: 0.62 (10% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 2950, 2922, 2852, 1541, 1463, 1375, 1099, 721.

**$[\alpha]^{20}_D$**= +13.84 (c 1.00, $CHCl_3$).

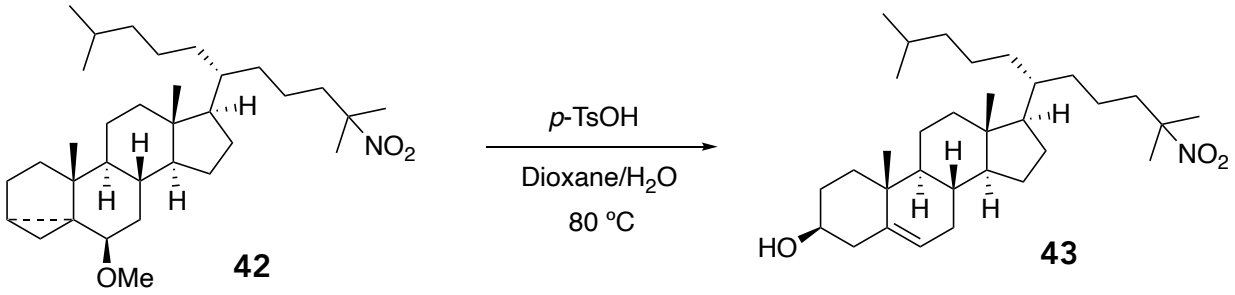
**$^1$H-NMR ($CDCl_3$, δ):** 3.34 (3H, s, MeO), 2.79 (1H, s, H-6), 1.92 (4H, m), 1.76 (3H, m), 1.59 (6H, s, $CH_3$-4'/5'), 1.53 (5H, m), 1.41 (5H, m), 1.28 (7H, m), 1.13 (9H, m), 1.04 (3H, s, $CH_3$-18), 0.91 (2H, m), 0.89 (3H, s, $CH_3$-26/27), 0.88 (3H, s, $CH_3$-26/27), 0.72 (3H, s, $CH_3$-19), 0.66 (1H, dd, *J*=5.1/3.7 Hz, H-4), 0.45 (1H, dd, *J*=8.0/5.0 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 88.3 (C-3'), 82.4 (CH-6), 56.6 (MeO), 56.5 (CH), 52.6 (CH), 48.1 (CH), 43.4 (C-10), 42.9 (C-13), 41.6 ($CH_2$), 40.0 ($CH_2$), 39.5 ($CH_2$), 39.0 (CH), 35.3 (C-5), 35.0 ($CH_2$), 33.4 ($CH_2$), 30.8 ($CH_2$), 30.8 ($CH_2$), 30.5 (CH), 28.0 (CH), 27.8 ($CH_2$), 26.0 ($CH_3$-4'/5'), 25.8 ($CH_3$-4'/5'), 25.0 ($CH_2$), 24.1 ($CH_2$), 22.9 ($CH_2$), 22.8 ($CH_2$), 22.7 ($CH_3$-26/27), 22.7 ($CH_3$-26/27), 21.5 (CH), 20.1 ($CH_2$), 19.3 ($CH_3$-18), 13.1 ($CH_2$-4), 12.4 ($CH_3$-19) ppm.

**MS ($ESI^+$) (m/z, %):** 484.41 ($M^+$-OMe, 100).

**HRMS ($ESI^+$):** 484.4149 calculated for $C_{32}H_{54}NO_2$ and found 484.4141.

1.34. Synthesis of (3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-((*R*)-2,10-dimethyl-2-nitroundecan-6-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ol (43)




To a solution of compound **42** (35 mg, 0.068 mmol) in dioxane (2 mL) and $H_2O$ (0.5 mL) was added *p*-TsOH (cat.) and the resulting mixture was stirred at 80 °C for 3 hours. $H_2O$ (5 mL) was and the aqueous solution was extracted with $CH_2Cl_2$ (3x15 mL). The combined organic phases were dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 30% EtOAc/hexane), affording the alcohol **43** (33 mg, 97%).

Compound **43**: colourless liquid; Rf: 0.10 (10% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3340, 2950, 2923, 2886, 1539, 1463, 1375, 1055.

**$[\alpha]^{23}_D$**= -21.31 (c 0.5, $CHCl_3$).

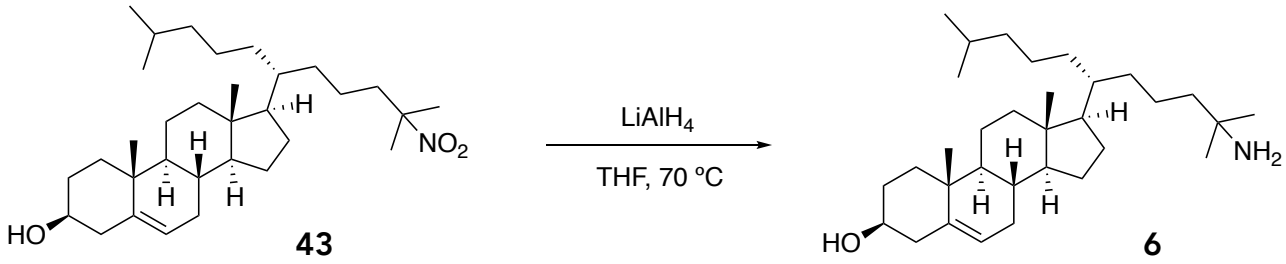
**$^1$H-NMR ($CDCl_3$, δ):** 5.36 (1H, m, H-6), 3.54 (1H, m, H-3), 2.29 (2H, m), 1.97 (2H, m), 1.84 (3H, m), 1.72 (2H, m), 1.59 (6H, s, $CH_3$-4'/5'), 1.51 (3H, m), 1.41 (3H, m), 1.27 (6H, m), 1.13 (6H, m), 1.02 (3H, s, $CH_3$-18), 0.92 (2H, m), 0.89 (3H, s, $CH_3$-26/27), 0.88 (3H, s, $CH_3$-26/27), 0.68 (3H, s, $CH_3$-19) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 140.8 (C-5), 121.7 (CH-6), 88.3 (C-3'), 71.8 (CH-3), 56.7 (MeO), 52.4 (CH), 50.1 (CH), 42.4 (C-13), 42.3 ($CH_2$), 41.6 ($CH_2$), 39.5 ($CH_2$), 39.5 ($CH_2$), 39.0 (CH), 37.3 ($CH_2$), 36.5 (C-10), 31.9 (CH), 31.9 ($CH_2$), 31.6 ($CH_2$), 30.8 ($CH_2$), 30.8 ($CH_2$), 27.9 (CH), 27.8 ($CH_2$), 25.9 ($CH_3$-4'/5'), 25.8 ($CH_3$-4'/5'), 24.2 ($CH_2$), 22.8 ($CH_2$), 22.7 ($CH_3$-26/27), 22.6 ($CH_3$-26/27), 21.1 ($CH_2$), 20.0 ($CH_2$), 19.4 ($CH_3$-18), 12.0 ($CH_3$-19) ppm.

**MS (ESI+) (m/z, %):** 484.41 ($M^+$-OH, 100).

**HRMS ($ESI^+$):** 484.4149 calculated for $C_{32}H_{54}NO_2$ and found 484.4140.

1.35. Synthesis of (3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-((*R*)-2-amino-2,10-dimethylundecan-6-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ol (6)




To a solution of compound **43** (30 mg, 0.065 mmol) in THF (2 mL) was added $LiAlH_4$ (10 mg, 0.263 mmol). The resulting mixture was stirred at 70 ºC for 24 hours. 4 M aqueous solution of NaOH (5 mL) was added and the aqueous was extracted with $Et_2O$ (4x15 mL), The combined organic phases were dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 70% EtOAc/hexane), affording the compound **6** (6 mg, 20%).

Compound **6**: colourless liquid; Rf: 0.10 (30% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3379, 2954, 2923, 2853, 1640, 1463, 1377, 1037.

**$[\alpha]^{23}_D$**= -31.43 (c 0.5, $CHCl_3$).

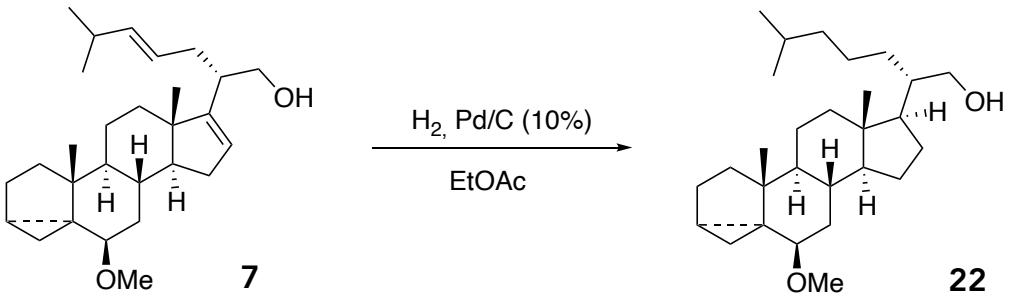
**$^1$H-NMR ($CDCl_3$, δ):** 5.34 (1H, m, H-6), 3.51 (1H, m, H-3), 2.27 (2H, m), 1.94 (2H, m), 1.82 (2H, m), 1.75 (2H, m), 1.59-1.09 (23H, m), 1.08 (6H, s, H-4'/5'), 1.00 (3H, s, $CH_3$-18), 0.86 (3H, s, $CH_3$-26/27), 0.84 (3H, s, $CH_3$-26/27), 0.65 (3H, s, $CH_3$-19) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 140.8 (C-5), 121.7 (CH-6), 71.8 (CH-3), 68.3 (C-3'), 56.7 (MeO), 52.6 (CH), 50.2 (CH), 42.4 (C-13), 42.3 ($CH_2$), 41.3 ($CH_2$), 39.7 ($CH_2$), 39.5 ($CH_2$), 39.2 (CH), 37.3 ($CH_2$), 36.5 (C-10), 31.9 (CH), 31.9 ($CH_2$), 31.7 ($CH_2$), 31.6 ($CH_2$), 31.0 ($CH_2$), 28.0 (CH), 27.8 ($CH_2$), 24.7 ($CH_3$-4'/5'), 24.6 ($CH_3$-4'/5'), 24.2 ($CH_2$), 22.8 ($CH_2$), 22.8 ($CH_3$-26/27), 22.7 ($CH_3$-26/27), 21.1 ($CH_2$), 19.6 ($CH_2$), 19.4 ($CH_3$-18), 12.0 ($CH_3$-19) ppm.

**MS ($ESI^+$) (m/z, %):** 530.45 (100), 472.45 ($M^+$+1, 19).

**HRMS ($ESI^+$):** 472.4513 calculated for $C_{32}H_{58}NO$ and found 472.4505.

1.36. Synthesis of (*S*)-2-((1a*R*,3a*R*,3b*S*,5a*S*,6*R*,8a*S*,8b*S*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethylhexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)-6-methylheptan-1-ol (22)




To a suspension of compound **7** (125 mg, 0.3 mmol) and Pd/C (10%) (cat.) in EtOAc (3 mL) was stirred at rt under atmosfera of $H_2$ for 14 hours. The mixture was then filtered through and the filtered liquids was concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 1% EtOAc/hexane), affording the compound **22** (92 mg, 74%).

Compound **22**: colourless liquid; Rf: 0.84 (50% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3325, 2924, 2923, 2849, 1473 1181, 1121, 724.

**$[\alpha]^{23}_D$**= -79.89 (c 0.25, $CHCl_3$).

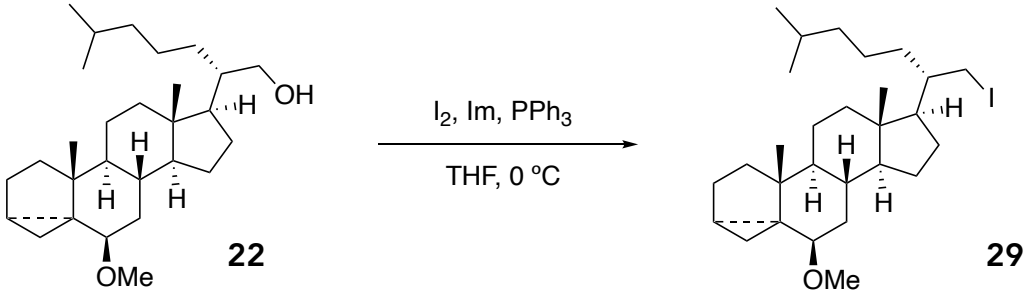
**$^1$H-NMR ($CDCl_3$, δ):** 3.70 (1H, dd, *J*=10.9/2.7 Hz, H-21), 3.53 (1H, dd, *J*=10.9/4.5 Hz, H-21), 3.32 (3H, s, MeO), 2.77 (1H, m, H-6), 1.92 (3H, m), 1.75 (3H, m), 1.52 (4H, m), 1.41 (6H, m), 1.18 (8H, m), 1.03 (3H, s, $CH_3$-18), 0.88 (3H, s, $CH_3$-26/27), 0.87 (3H, s, $CH_3$-26/27), 0.83 (3H, m), 0.74 (3H, s, $CH_3$-19), 0.65 (1H, dd, *J*=5.1/3.7 Hz, H-4), 0.43 (1H, dd, *J*=8.0/5.1 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 82.4 (CH-6), 63.5 ($CH_2$-21), 56.5 (MeO), 56.3 (CH-14), 50.3 (CH), 48.0 (CH), 43.4 (C-10), 42.8 (C-13), 42.4 (CH), 40.1 ($CH_2$), 39.5 ($CH_2$), 35.3 (C-5), 35.1 ($CH_2$), 33.4 ($CH_2$), 30.6 (CH), 29.4 ($CH_2$), 28.0 (CH), 27.5 ($CH_2$), 25.0 ($CH_2$), 24.1 ($CH_2$), 23.8 ($CH_2$), 22.8 ($CH_2$), 22.7 ($CH_3$-26/27), 22.7 ($CH_3$-26/27), 21.5 (CH), 19.3 ($CH_3$-18), 13.1 ($CH_2$-4), 12.5 ($CH_3$-19) ppm.

**MS (ESI$^+$) (m/z, %):** 385.34 ($M^+$-OMe, 100).

**HRMS (ESI$^+$):** 385.3465 calculated for $C_{27}H_{45}O$ and found 385.3464.

1.37. Synthesis of (1a*R*,3a*R*,3b*S*,5a*S*,6*R*,8a*S*,8b*S*,10*R*,10a*R*)-6-((*S*)-1-iodo-6-methylheptan-2-yl)-10-methoxy-3a,5a-dimethylhexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalene (29)




To a solution of diol **22** (72 mg, 0.173 mmol) in THF (43mL) were added sequentially $PPh_3$ (69 mg, 0.26 mmol) and imidazole (36 mg, 0.52 mmol). After cooling the mixture to 0 ºC, $I_2$ (62 mg, 0.242 mmol) was added and stirring continued at rt for 20 minutes. The reaction was quenched with an aqueous saturated solution of $NaHCO_3$ (5 mL) and the product extracted with EtOAc (3x10 mL). The combined organic phase was washed with a 10% aqueous solution of $Na_2S_2O_3$ (10 mL), dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 1% EtOAc/hexane), affording the compound **29** (90 mg, 99%).

Compound **29**: colourless liquid; Rf: 0.85 (10% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 2952, 2924, 2850, 1462, 1183, 1119, 721, 540.

**$[\alpha]^{20}_D$**= +15.80 (c 1.00, $CHCl_3$).

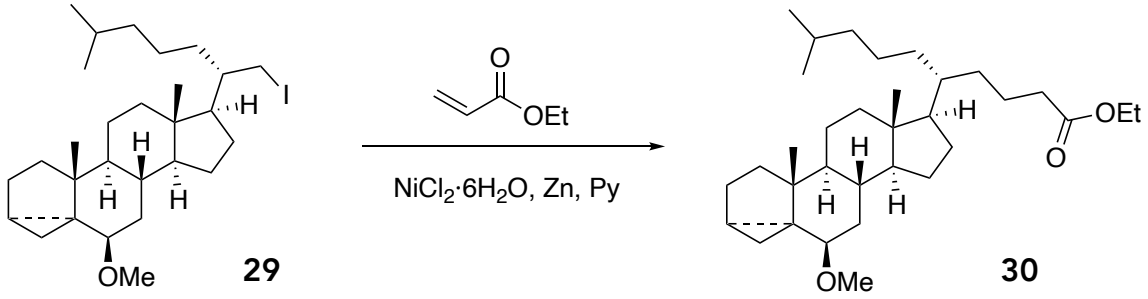
**$^1$H-NMR ($CDCl_3$, δ):** 3.46 (1H, dd, *J*=9.9/2.8 Hz, H-21), 3.36 (3H, s, MeO), 3.28 (1H, dd, *J*=9.9/4.1 Hz, H-21), 2.81 (1H, m, H-6), 1.95 (4H, m), 1.79 (2H, m), 1.69 (2H, m), 1.57 (5H, m), 1.46 (2H, m), 1.22 (10H, m), 1.07 (3H, s, $CH_3$-18), 0.93 (6H, d, *J*=6.6 Hz, $CH_3$-26/27), 0.87 (3H, m), 0.82 (3H, s, $CH_3$-19), 0.69 (1H, dd, *J*=5.1/3.6 Hz, H-4), 0.48 (1H, dd, *J*=8.0/5.1 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 82.4 (CH-6), 56.6 (MeO), 56.4 (CH-14), 53.9 (CH), 48.0 (CH), 43.4 (C-10), 42.7 (C-13), 40.6 (CH), 40.2 ($CH_2$), 39.0 ($CH_2$), 35.3 (C-5), 35.1 ($CH_2$), 33.4 ($CH_2$), 32.5 ($CH_2$), 30.6 (CH), 28.0 (CH), 27.5 ($CH_2$), 25.0 ($CH_2$), 24.0 ($CH_2$), 23.7 ($CH_2$), 22.85 ($CH_3$-26/27), 22.6 (CH), 21.5 (CH), 19.3 ($CH_3$-18), 18.5 ($CH_2$-21), 13.3 ($CH_3$-19), 13.2 ($CH_2$-4) ppm.

**MS (ESI$^+$) (m/z, %):** 557.18 ($M^+$+OMe, 100), 495.25 ($M^+$-OMe, 40).

**HRMS (ESI$^+$):** 495.2482 calculated for $C_{27}H_{44}I$ and found 495.2489.

1.38. Synthesis of ethyl (*R*)-5-((1a*R*,3a*R*,3b*S*,5a*R*,6*R*,8a*S*,8b*S*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethylhexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)-9-methyldecanoate (30)




To a suspension of Zn (167 mg, 2.55 mmol) i n pyridine (4 mL) was added $NiCl_2·6H_2O$ (121 mg, 0.51 mmol) and ethyl acrylate (0.28 mL, 2.55 mmol) and the resulting mixture was stirred at 65 °C. It was observed that the suspension acquires a reddish-brown colour. After 30 minutes the mixture was cooled to 0 °C and was added a solution of the iodide **29** (90 mg, 0.17 mmol) in pyridine (2 mL) and it was stirred under these conditions for 90 minutes. Once the reaction mixture reaches rt, EtOAc (10 mL) was added and the resulting suspension was filtered over celite. The filtered liquids were washed with a 10% solution of $CuSO_4$ (3x20 mL), $H_2O$ (2x20 mL) and a saturated solution of NaCl (15 mL). The organic phase was dried with $Na_2SO_4$, filtered and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 7% EtOAc/hexane), affording the compound **30** (69 mg, 82%).

Compound **30**: colourless liquid; Rf: 0.41 (10% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 2950, 2927, 2867, 1737, 1460, 1373, 1163, 1098.

**$[\alpha]^{22}_D$**= +14.93 (c 0.5, $CHCl_3$).

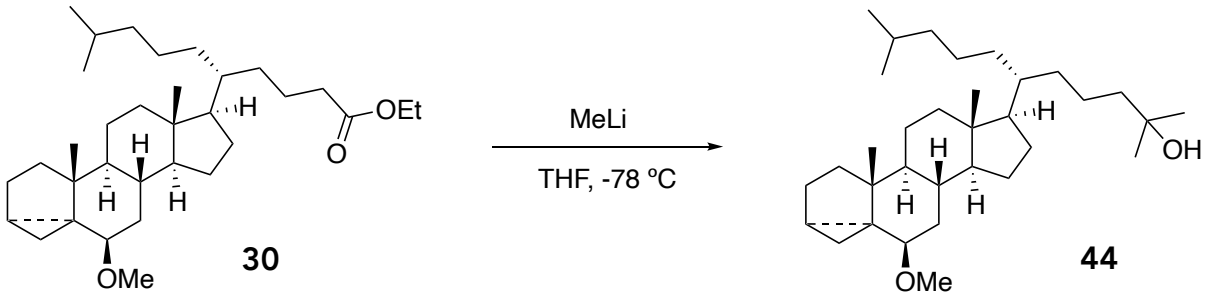
**$^1$H-NMR ($CDCl_3$, δ):** 4.14 (2H, q, *J*=7.5 Hz, $CH_2$-OEt), 3.33 (3H, s, MeO), 2.77 (1H, m, H-6), 2.26 (2H, m, H-2'), 1.92 (2H, m), 1.75 (3H, m), 1.61 (2H, m), 1.52 (4H, m), 1.42 (5H, m), 1.31 (5H, m), 1.26 (3H, t, *J*=7.5 Hz, $CH_3$-OEt), 1.14 (7H, m), 1.03 (3H, s, $CH_3$-18), 0.87 (6H, d, *J*=6.6 Hz, $CH_3$-26/27), 0.85 (3H, m), 0.71 (3H, s, $CH_3$-19), 0.65 (1H, dd, *J*=5.1/3.7 Hz, H-4), 0.43 (1H, dd, *J*=8.1/5.1 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 173.9 (C=O), 82.4 (CH-6), 60.1 ($CH_2$-OEt), 56.5 (MeO), 56.5 (CH-14), 52.6 (CH), 48.1 (CH), 43.4 (C-10), 42.8 (C-13), 40.0 ($CH_2$), 39.5 ($CH_2$), 39.1 (CH), 35.3 (C-5), 35.0 ($CH_2$), 34.9 ($CH_2$), 33.4 ($CH_2$), 30.8 ($CH_2$), 30.5 (CH), 30.4 ($CH_2$), 28.0 (CH), 27.8 ($CH_2$), 25.0 ($CH_2$), 24.1 ($CH_2$), 23.0 ($CH_2$), 22.8 ($CH_2$), 22.7 ($CH_3$-26/27), 22.7 ($CH_3$-26/27), 21.5 ($CH_2$), 21.0 (CH), 19.3 ($CH_3$-18), 14.3 ($CH_3$-OEt), 13.1 ($CH_2$-4), 12.3 ($CH_3$-19) ppm.

**MS (ESI$^+$) (m/z, %):** 469.40 ($M^+$-OMe, 100), 427.35 (10).

**HRMS (ESI$^+$):** 469.4040 calculated for $C_{32}H_{53}O_2$ and found 469.4041.

1.39. Synthesis of (*R*)-6-((1a*R*,3a*R*,3b*S*,5a*R*,6*R*,8a*S*,8b*S*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethylhexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)-2,10-dimethylundecan-2-ol (44)




To a solution of compound **30** (69 mg, 0.137 mmol) in THF (2 mL) cooled to -78 °C was added a 1.5 M solution of MeLi·LiBr in $Et_2O$ (0.46 mL, 0.69 mmol) and the resulting mixture was stirred in these conditions for 14 hours. $H_2O$ (10 mL) was added and the aqueous solution was extracted with $CH_2Cl_2$ (3x15 mL). The combined organic phases were dried with $Na_2SO_4$, filtered and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 10% EtOAc/hexane), affording the alcohol **44** (56 mg, 86%).

Compound **44**: colourless liquid; Rf: 0.20 (10% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3374, 2951, 2925, 2866, 1465, 1378, 1098.

**$[\alpha]^{20}_D$**= +13.11 (c 1.00, $CHCl_3$).

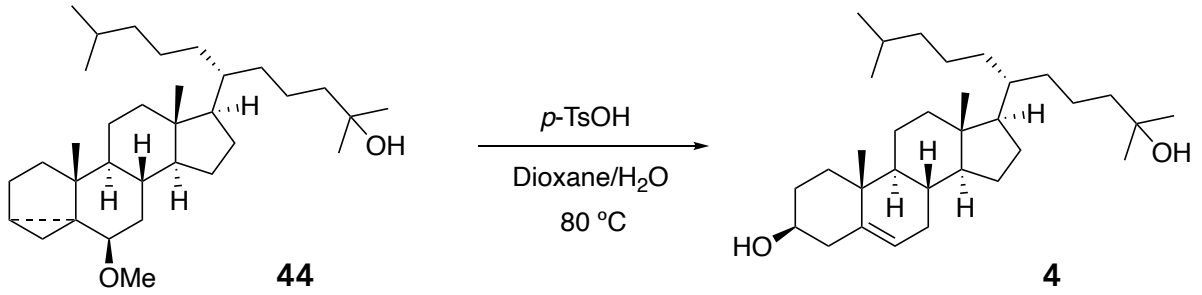
**$^1$H-NMR ($CDCl_3$, δ):** 3.33 (3H, s, MeO), 2.78 (1H, m, H-6), 1.92 (3H, m), 1.75 (4H, m), 1.53 (5H, m), 1.43 (7H, m), 1.31 (6H, m), 1.22 (6H, s, $CH_3$-4'/5'), 1.13 (5H, m), 1.04 (3H, s, $CH_3$-18), 0.88 (6H, d, *J*=6.6 Hz, $CH_3$-26/27), 0.85 (3H, m), 0.72 (3H, s, $CH_3$-19), 0.66 (1H, dd, *J*=5.1/3.7 Hz, H-4), 0.44 (1H, dd, *J*=8.0/5.1 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 82.4 (CH-6), 71.1 (C-3'), 56.5 (MeO), 56.5 (CH-14), 52.7 (CH), 48.1 (CH), 44.6 ($CH_2$), 43.4 (C-10), 42.9 (C-13), 40.0 ($CH_2$), 39.6 ($CH_2$), 39.2 (CH), 35.3 (C-5), 35.1 ($CH_2$), 33.4 ($CH_2$), 31.5 ($CH_2$), 30.9 ($CH_2$), 30.5 (CH), 29.3 ($CH_3$-4'/5'), 29.2 ($CH_3$-4'/5'), 28.0 (CH), 27.9 ($CH_2$), 25.0 ($CH_2$), 24.1 ($CH_2$), 22.9 ($CH_2$), 22.8 ($CH_2$), 22.8 ($CH_3$-26/27), 22.7 ($CH_3$-26/27), 21.5 (CH), 20.2 ($CH_2$), 19.3 ($CH_3$-18), 13.1 ($CH_2$-4), 12.4 ($CH_3$-19) ppm.

**MS (ESI$^+$) (m/z, %):** 509.43 ($M^+$+Na, 1), 455.42 ($M^+$-OMe, 25), 437.41 (100).

**HRMS (ESI$^+$):** 509.4329 calculated for $C_{33}H_{58}NaO_2$ and found 509.4337.

1.40. Synthesis of (3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-((*R*)-2-hydroxy-2,10-dimethylundecan-6-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ol (4)




To a solution of compound **44** (56 mg, 0.115 mmol) in dioxane (2 mL) and $H_2O$ (0.5 mL) was added *p*-TsOH (cat.) and the resulting mixture was stirred at 80 °C for 3 hours. $H_2O$ (5 mL) was and the aqueous solution was extracted with $CH_2Cl_2$ (3x15 mL). The combined organic phases were dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 30% EtOAc/hexane), affording the diol **4** (33 mg, 94%).

Compound **4**: white solid (mp: 146-151 °C); Rf: 0.46 (30% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3289, 2929, 2883, 2864, 1464, 1364, 1190, 939.

**$[\alpha]^{23}_D$**= -39.19 (c 1.00, $CHCl_3$).

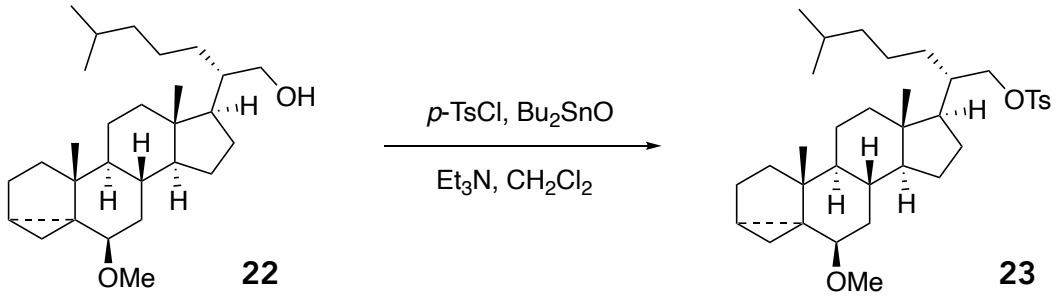
**$^1$H-NMR ($CDCl_3$, δ):** 5.36 (1H, m, H-6), 3.54 (1H, m, H-3), 2.28 (2H, m), 1.97 (2H, m), 1.86 (2H, m), 1.78 (1H, m), 1.69-1.25 (24H, m), 1.23 (6H, s, $CH_3$-4'/5'), 1.15 (5H, m), 1.02 (3H, s, $CH_3$-18), 0.88 (6H, d, *J*=6.6 Hz, $CH_3$-26/27), 0.69 (3H, s, $CH_3$-19) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 140.8 (C-5), 121.7 (CH-6), 71.8 (CH-3), 71.1 (C-3'), 56.7 (MeO), 52.6 (CH), 50.2 (CH), 44.6 ($CH_2$), 42.4 (C-10), 42.3 ($CH_2$), 39.6 ($CH_2$), 39.5 ($CH_2$), 39.2 (CH), 37.3 ($CH_2$), 36.5 (C-13), 32.0 (CH), 31.9 ($CH_2$), 31.7 ($CH_2$), 31.4 ($CH_2$), 30.9 ($CH_2$), 29.3 ($CH_3$-4'/5'), 29.2 ($CH_3$-4'/5'), 28.0 (CH), 27.8 ($CH_2$), 24.2 ($CH_2$), 22.9 ($CH_2$), 22.8 ($CH_3$-26/27), 22.7 ($CH_3$-26/27), 21.1 ($CH_2$), 20.1 ($CH_2$), 19.4 ($CH_3$-18), 12.0 ($CH_3$-19) ppm.

**MS (ESI$^+$) (m/z, %):** 495.42 ($M^+$+Na, 1), 455.43 ($M^+$-OH, 100), 437.41 (60).

**HRMS (ESI$^+$):** 495.4172 calculated for $C_{32}H_{56}NaO_2$ and found 495.4267.

1.41. Synthesis of (*S*)-2-((1a*R*,3a*R*,3b*S*,5a*S*,6*R*,8a*S*,8b*S*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethylhexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)-6-methylheptyl 4-methylbenzenesulfonate (23)




To a solution of compound **22** (54 mg, 0.129 mmol) in $CH_2Cl_2$ (2 mL) was added *p*-TsCl (75 mg, 0.39 mmol), *n*-$BuSnO_2$ (cat.) and $Et_3N$ (0.11 mL, 0.78 mmol). The resulting mixture was stirred at rt for 2 hours. Then *p*-TsCl (0.39 mmol) and $Et_3N$ (0.78 mmol) was added again and was stirred for 10 days. $H_2O$ (10 mL) was added and the aqueous phase was extracted with $CH_2Cl_2$ (3x15 mL). The combined organic phases were dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 10% EtOAc/hexane), affording the compound **23** (57 mg, 78%).

Compound **23**: colourless liquid; Rf: 0.67 (20% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 2952, 2917, 2848, 1463, 1177, 1097, 944.

**$[\alpha]^{24}_D$**= -38.63 (c 0.5, $CHCl_3$).

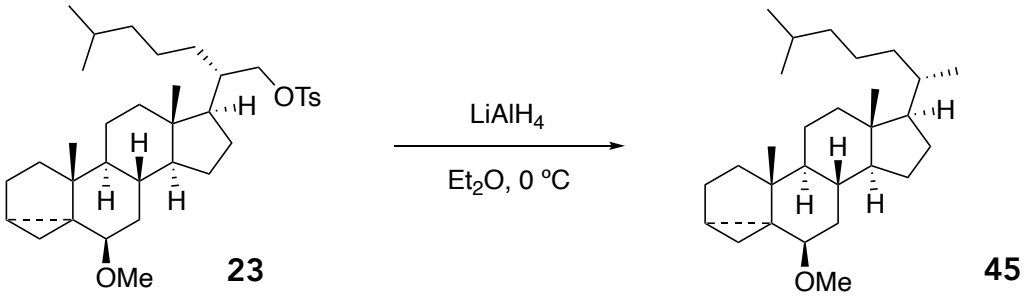
**$^1$H-NMR ($CDCl_3$, δ):** 7.80 (2H, dd, *J*=8.3 Hz, H-Ts), 7.36 (2H, dd, *J*=8.5 Hz, H-Ts), 4.05 (1H, dd, *J*=9.5/2.9 Hz, H-21), 3.92 (1H, dd, *J*=9.4/4.8 Hz, H-21), 3.33 (3H, s, MeO), 2.78 (1H, s, H-6), 2.46 (3H, s, $CH_3$-Ts), 1.88 (2H, m), 1.72 (3H, m), 1.54 (5H, m), 1.41 (3H, m), 1.28 (2H, m), 1.07 (6H, m), 1.02 (3H, s, $CH_3$-18), 0.89 (6H, m), 0.82 (6H, dd, *J*=6.6/2.9 Hz, $CH_3$-26/27), 0.68 (3H, s, $CH_3$-19), 0.66 (1H, m, H-4), 0.44 (1H, dd, *J*=8.1/5.1 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 144.6 (C-OTs), 133.0 (C-Ts), 129.7 (CH-Ts), 127.9 (CH-Ts), 82.3 (CH-6), 71.7 ($CH_2$-21), 56.6 (MeO), 56.2 (CH), 49.9 (CH), 47.9 (CH), 43.4 (C-10), 42.8 (C-13), 42.0 ($CH_2$), 40.3 (CH), 39.9 ($CH_2$), 39.1 ($CH_2$), 35.2 (C-5), 35.0 ($CH_2$), 33.4 ($CH_2$), 30.6 (CH), 29.3 ($CH_2$), 27.9 (CH), 27.3 ($CH_2$), 24.9 ($CH_2$), 24.0 ($CH_2$), 23.5 ($CH_2$), 22.8 ($CH_2$), 22.6 ($CH_3$-26/27), 22.5 ($CH_3$-26/27), 21.6 (CH), 21.5 (CH), 19.3 ($CH_3$-18), 14.2 ($CH_3$-Ts), 13.1 ($CH_2$-4), 12.3 ($CH_3$-19) ppm.

**MS (ESI$^+$) (m/z, %):** 593.36 ($M^+$+Na, 1), 539.35 ($M^+$-OMe, 50), 399.36 ($M^+$-OTs, 1).

**HRMS (ESI$^+$):** 593.3635 calculated for $C_{35}H_{54}NaO_4S$ and found 593.3635.

1.42. Synthesis of (1a*R*,3a*R*,3b*S*,5a*R*,6*R*,8a*S*,8b*S*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethyl-6-((*S*)-6-methylheptan-2-yl)hexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalene (45)




To a solution of compound **23** (20 mg, 0.035 mmol) in $Et_2O$ (1 mL) cooled to 0 ºC was added dropwise a solution of $LiAlH_4$ (20 mg, 0.53 mmol) in $Et_2O$ (1 mL). The resulting mixture was stirred at rt for 16 hours. $H_2O$ (5 mL) was added and the aqueous was extracted with $Et_2O$ (4x15 mL), The combined organic phases were dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 1% EtOAc/hexane), affording the compound **45** (10 mg, 75%).

Compound **45**: colourless liquid; Rf: 0.95 (20% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 2955, 2917, 2849, 1462, 1378, 1098, 966, 720.

**$[\alpha]^{23}_D$**= -17.92 (c 1.00, $CHCl_3$).

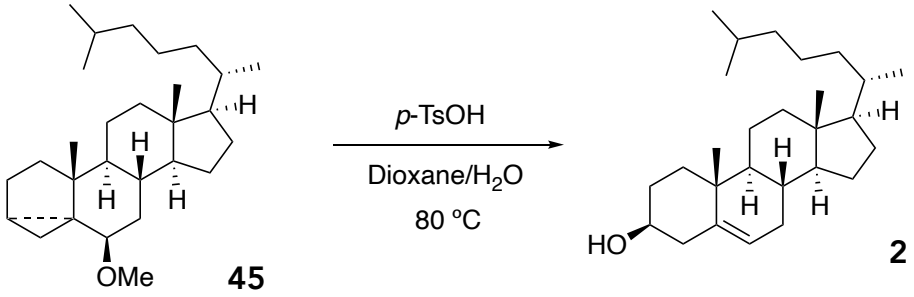
**$^1$H-NMR ($CDCl_3$, δ):** 3.34 (3H, s, MeO), 2.79 (1H, s, H-6), 1.94 (2H, m), 1.75 (3H, m), 1.54 (6H, m), 1.43 (5H, m), 1.31 (4H, m), 1.15 (7H, m), 1.04 (3H, s, $CH_3$-18), 0.89 (6H, d, *J*=6.6 Hz, $CH_3$-26/27), 0.84 (3H, d, *J*=6.5 Hz, $CH_3$-21), 0.74 (3H, s, $CH_3$-19), 0.67 (1H, m, H-4), 0.45 (1H, dd, *J*=8.0/5.1 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 82.5 (CH-6), 56.6 (MeO), 56.6 (CH), 55.9 (CH), 48.1 (CH), 43.4 (C-10), 42.8 (C-13), 40.2 ($CH_2$), 39.5 ($CH_2$), 35.6 ($CH_2$), 35.2 (C-5), 35.1 ($CH_2$), 33.4 ($CH_2$), 30.5 (CH), 28.1 ($CH_2$), 28.1 (CH), 25.0 ($CH_2$), 24.1 ($CH_2$), 24.0 ($CH_2$), 22.8 ($CH_2$), 22.8 (CH), 22.7 (CH), 21.6 (CH), 19.3 ($CH_3$-18), 18.7 ($CH_3$-21), 13.1 ($CH_2$-4), 12.5 ($CH_3$-19) ppm.

**MS (ESI$^+$) (m/z, %):** 369.35 ($M^+$-OMe, 100).

**HRMS (ESI$^+$):** 369.3516 calculated for $C_{27}H_{45}$ and found 369.3514.

1.43. Synthesis of (3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*S*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ol (2)




To a solution of compound **45** (10 mg, 0.115 mmol) in dioxane (1 mL) and $H_2O$ (0.25 mL) was added *p*-TsOH (cat.) and the resulting mixture was stirred at 80 °C for 3 hours. $H_2O$ (5 mL) was and the aqueous solution was extracted with $CH_2Cl_2$ (3x15 mL). The combined organic phases were dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 10% EtOAc/hexane), affording the diol **2** (10 mg, 99%).

Compound **2**: white solid (mp: 142-149 °C); Rf: 0.20 (10% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 3252, 2955, 2920, 2850, 1462, 1376, 1080, 968.

**$[\alpha]^{24}_D$**= -79.84 (c 0.5, $CHCl_3$).

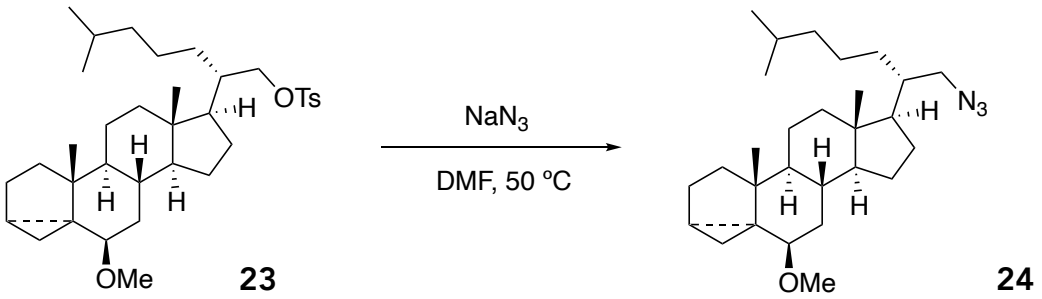
**$^1$H-NMR ($CDCl_3$, δ):** 5.38 (1H, s, H-6), 3.55 (1H, m, H-3), 2.30 (2H, m), 2.02 (2H, m), 1.85 (3H, m), 1.59 (10H, m), 1.29 (3H, m), 1.15 (7H, m), 1.03 (3H, s, $CH_3$-18), 0.95 (1H, m), 0.89 (6H, d, *J*=6.6 Hz, $CH_3$-26/27), 0.84 (3H, d, *J*=6.6 Hz, $CH_3$-21), 0.70 (3H, s, $CH_3$-19) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 140.8 (C-5), 121.7 (CH-6), 71.8 (CH-3), 56.8 (CH), 55.8 (CH), 50.2 (CH), 42.4 (C-13), 42.3 ($CH_2$), 39.7 ($CH_2$), 39.5 ($CH_2$), 37.3 ($CH_2$), 36.5 (CH), 35.7 ($CH_2$), 35.3 (CH), 31.9 (C-10), 31.7 (CH), 28.1 (CH), 28.1 ($CH_2$), 24.2 ($CH_2$), 23.9 ($CH_2$), 22.8 (CH), 22.8 ($CH_3$-26/27), 21.1 ($CH_2$), 19.4 ($CH_3$-18), 18.7 ($CH_3$-21), 12.1 ($CH_3$-19) ppm.

**MS ($ESI^+$) (m/z, %):** 369.35 ($M^+$-OH, 100).

**HRMS ($ESI^+$):** 369.3516 calculated for $C_{27}H_{45}$ and found 369.3505.

1.44. Synthesis of (1a*R*,3a*R*,3b*S*,5a*S*,6*R*,8a*S*,8b*S*,10*R*,10a*R*)-6-((*S*)-1-azido-6-methylheptan-2-yl)-10-methoxy-3a,5a-dimethylhexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalene (24)




To a solution of compound **23** (31 mg, 0.054 mmol) in DMF (2 mL) was added $NaN_3$ (35 mg, 0.543 mmol). The resulting mixture was stirred at 50 ºC for 3 hours. $H_2O$ (5 mL) was added and the aqueous phase was extracted with EtOAc (3x10mL). The combined organic phases were dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 5% EtOAc/hexane), affording the azide **24** (17 mg, 71%).

Compound **24**: colourless liquid; Rf: 0.69 (10% EtOAc/hexane).

**IR (ATR, $cm^{-1}$):** 2953, 2916, 2848, 2095, 1462, 1264, 1098, 735.

**$[\alpha]^{23}_D$**= +7.88 (c 1.00, $CHCl_3$).

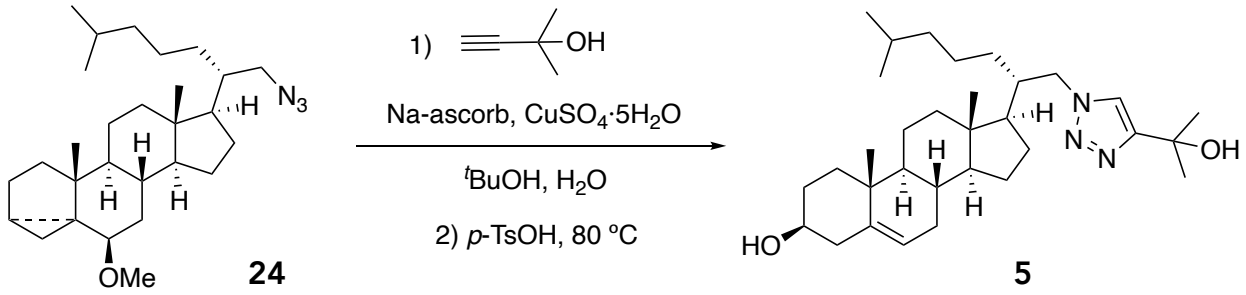
**$^1$H-NMR ($CDCl_3$, δ):** 3.48 (1H, dd, *J*=12.3/3.1 Hz, H-21), 3.35 (3H, s, MeO), 3.24 (1H, dd, *J*=12.3/5.6 Hz, H-21), 2.79 (1H, s, H-6), 1.93 (2H, m), 1.76 (2H, m), 1.65 (1H, m), 1.56 (6H, m), 1.37 (7H, m), 1.18 (6H, m), 1.05 (3H, s, $CH_3$-18), 0.90 (6H, d, *J*=6.6 Hz, $CH_3$-26/27), 0.85 (3H, m), 0.75 (3H, s, $CH_3$-19), 0.67 (1H, dd, *J*=5.0/3.8 Hz, H-4), 0.46 (1H, dd, *J*=8.0/5.1 Hz, H-4) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 82.4 (CH-6), 56.6 (MeO), 56.4 (CH-14), 53.9 (CH), 48.0 (CH), 43.4 (C-10), 42.7 (C-13), 40.6 (CH), 40.2 ($CH_2$), 39.0 ($CH_2$), 35.3 (C-5), 35.1 ($CH_2$), 33.4 ($CH_2$), 32.5 ($CH_2$), 30.6 (CH), 28.0 (CH), 27.5 ($CH_2$), 25.0 ($CH_2$), 24.0 ($CH_2$), 23.7 ($CH_2$), 22.9 ($CH_3$-26/27), 22.6 (CH), 21.5 (CH), 19.3 ($CH_3$-18), 18.5 ($CH_2$-21), 13.3 ($CH_3$-19), 13.2 ($CH_2$-4) ppm.

**MS (ESI$^+$) (m/z, %):** 410.35 ($M^+$-OMe, 100), 382.34 (80).

**HRMS (ESI$^+$):** 410.3530 calculated for $C_{27}H_{44}N_3$ and found 410.3520.

1.45. Synthesis of (3*S*,8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-((*S*)-1-(4-(2-hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)-6-methylheptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ol (5)




To a solution of azide **24** (17 mg, 0.038 mmol) in $^t$BuOH (2 mL) and $H_2O$ (1 mL) was added $CuSO_4 \cdot 5H_2O$ (cat.), an aqueous solution of 1 M sodium ascorbate (10 µl, 0.007 mmol) and 2-methyl-3-butyn-2-ol (5 µl, 0.04 mmol). The resulting mixture was stirred at rt for 5 hours. Then *p*-TsOH (cat.) was added and heated at 80 °C for 3 hours. $H_2O$ (3 mL) was added and the aqueous phase was extracted with $CH_2Cl_2$ (3x15 mL). The combined organic phases were dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (mobile phase: 50% EtOAc/hexane), affording the diol **5** (11 mg, 60%).

Compound **5**: colourless solid (mp: 232-236 °C); Rf: 0.10 (30% EtOAc/hexane).

**IR (ATR, cm$^{-1}$):** 3401, 2956, 2923, 2853, 1463, 1378, 1187, 967.

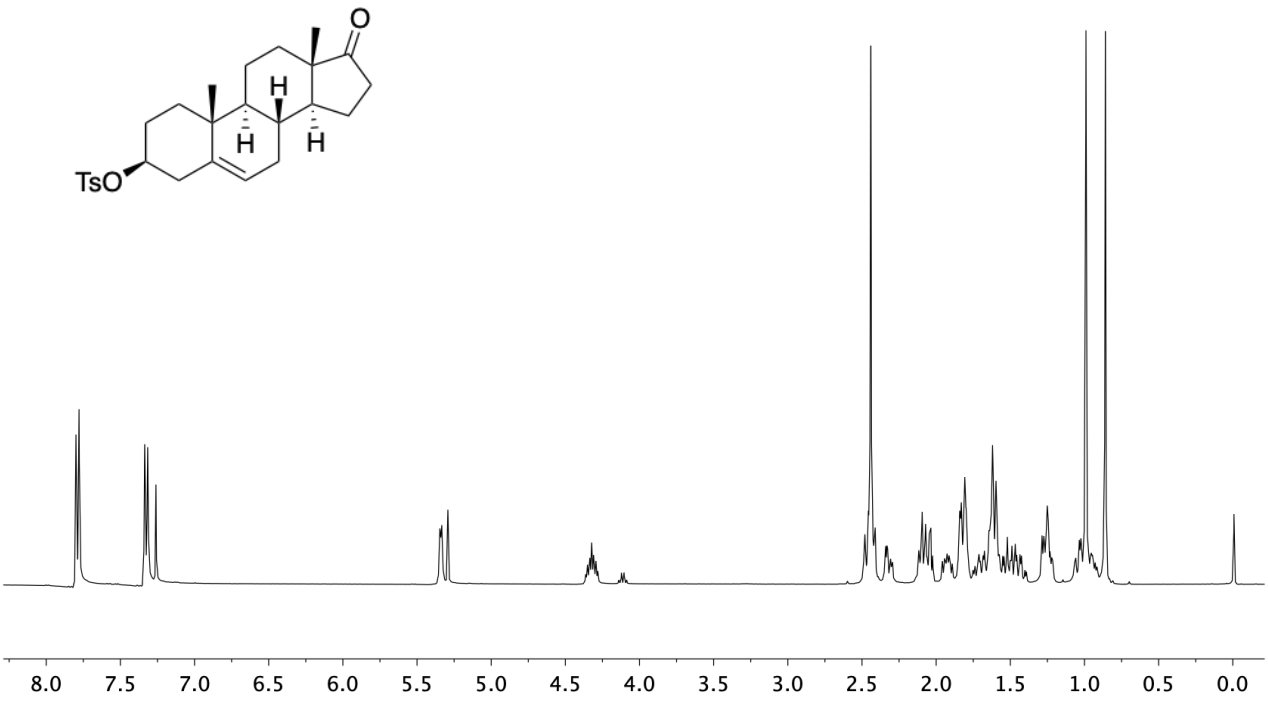
**[α]$^{24}_D$**= -29.85 (c 1.00, $CHCl_3$).

**$^1$H-NMR ($CDCl_3$, δ):** 7.36 (1H, s, H-1'), 5.35 (1H, s, H-6), 4.32 (1H, m, H-21), 4.23 (1H, m, H-21), 3.52 (1H, m, H-3), 2.26 (3H, m), 1.94 (6H, m), 1.83 (5H, m), 1.48 (8H, m), 1.27 (5H, m), 1.23 (6H, d, *J*=9.2 Hz, $CH_3$-4'/5'), 1.06 (3H, m), 1.00 (3H, s, $CH_3$-18), 0.84 (6H, d, *J*=6.6 Hz, $CH_3$-26/27), 0.73 (6H, s, $CH_3$-19) ppm.

**$^{13}$C-NMR ($CDCl_3$, δ):** 140.7 (C-5), 128.8 (C-4''), 121.5 (CH-6), 112.4 (C-5''), 77.2 (C-1'), 71.7 (CH-3), 56.4 (CH-14), 52.3 ($CH_2$-21), 50.6 (CH), 50.0 (CH), 42.7 (C-13), 42.2 ($CH_2$), 41.7 (CH), 39.2 ($CH_2$), 39.2 ($CH_2$), 37.2 ($CH_2$), 36.5 (C-10), 31.9 (CH), 31.8 ($CH_2$), 31.6 ($CH_2$), 30.6 ($CH_3$-2'/3'), 30.5 ($CH_3$-2'/3'), 29.3 ($CH_2$), 27.9 ($CH_2$), 27.8 (CH), 24.3 ($CH_2$), 22.7 ($CH_3$-26/27), 22.5 ($CH_3$-26/27), 22.4 ($CH_2$), 21.1 ($CH_2$), 19.4 ($CH_3$-18), 12.1 ($CH_3$-19) ppm.

**MS (ESI$^+$) (m/z, %):** 534.40 ($M^+$+Na, 10), 512.42 ($M^+$+1, 100), 494.41 ($M^+$-OMe, 31).

**HRMS (ESI$^+$):** 512.4211 calculated for $C_{32}H_{54}N_3O_2$ and found 512.4206.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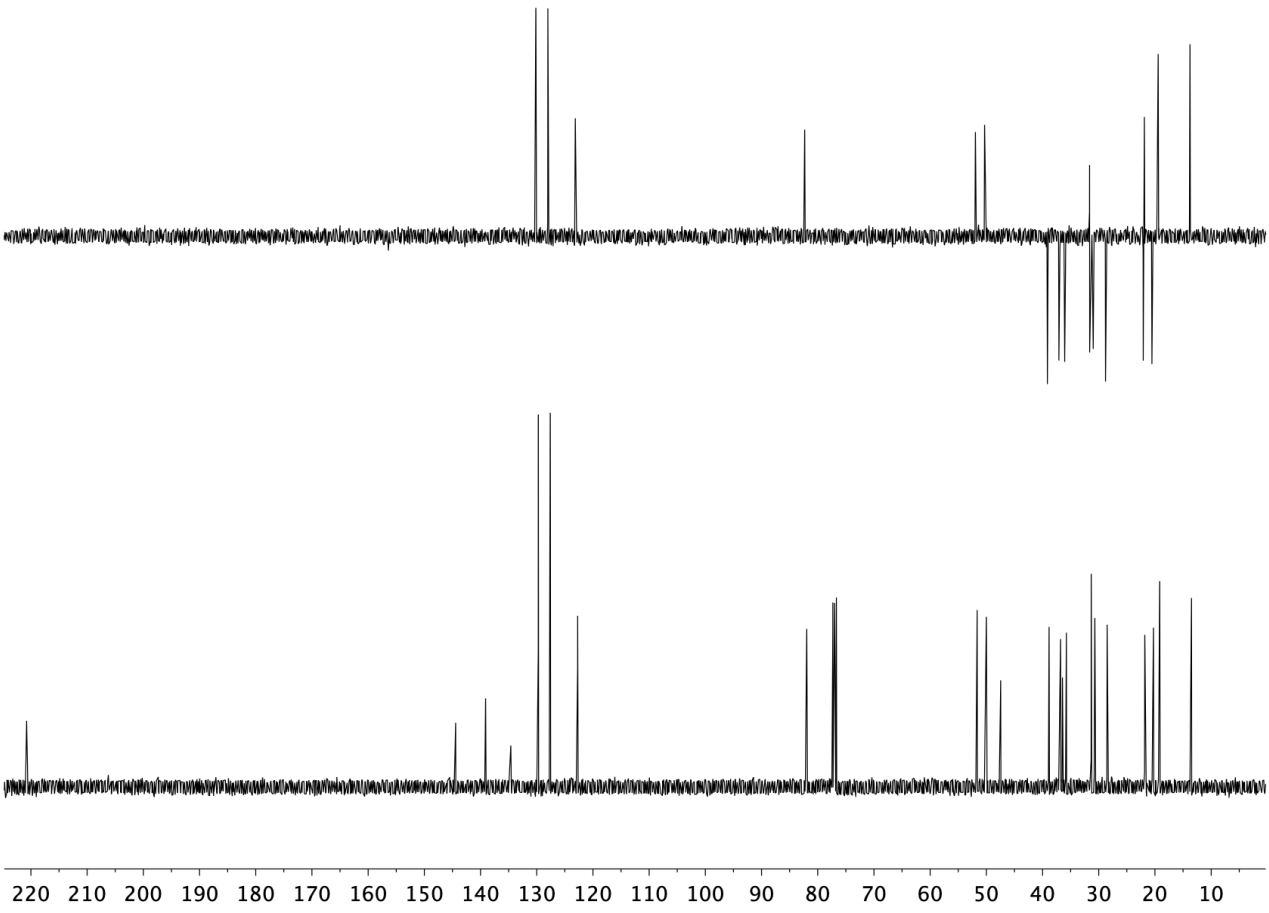
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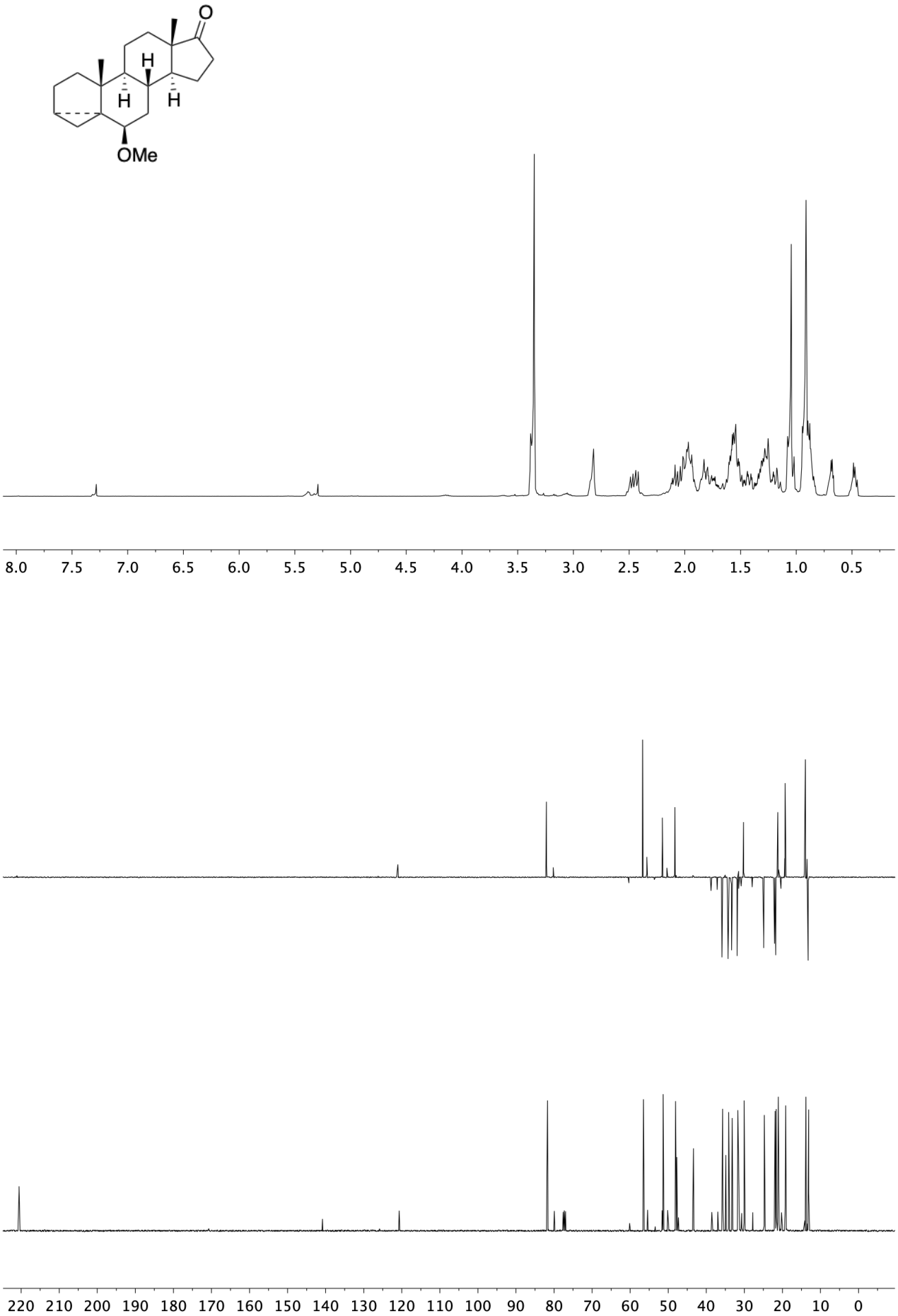
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H
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OMe
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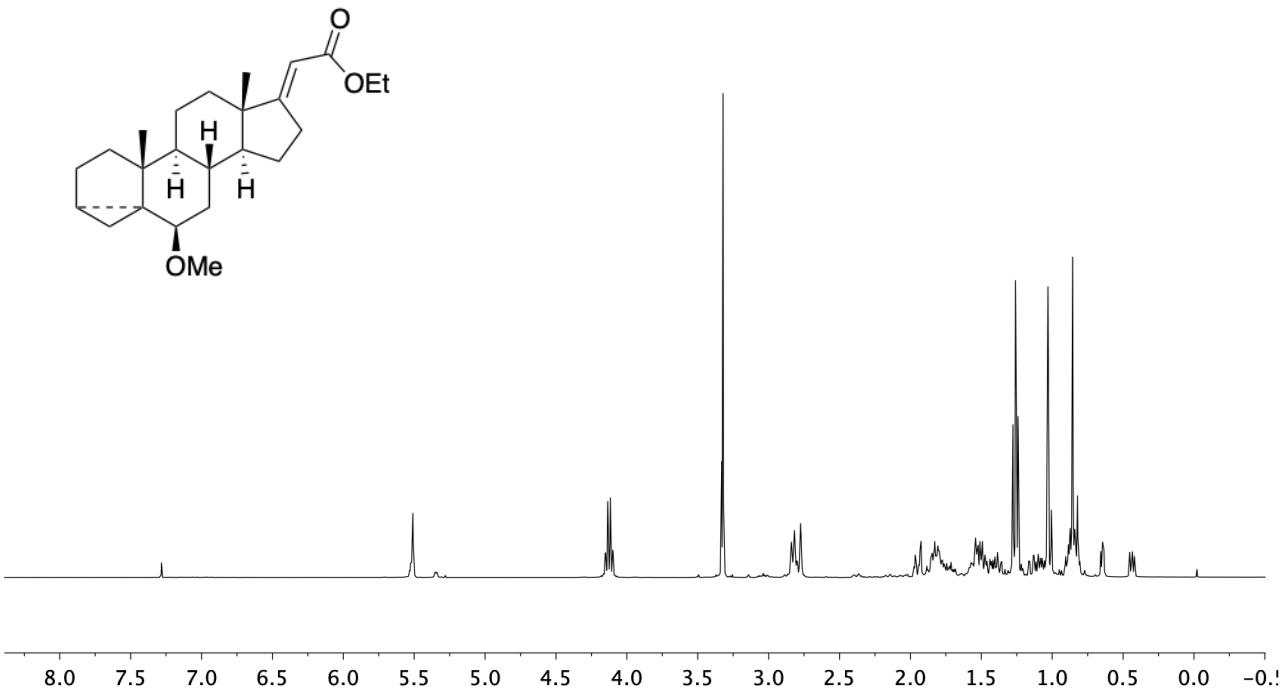
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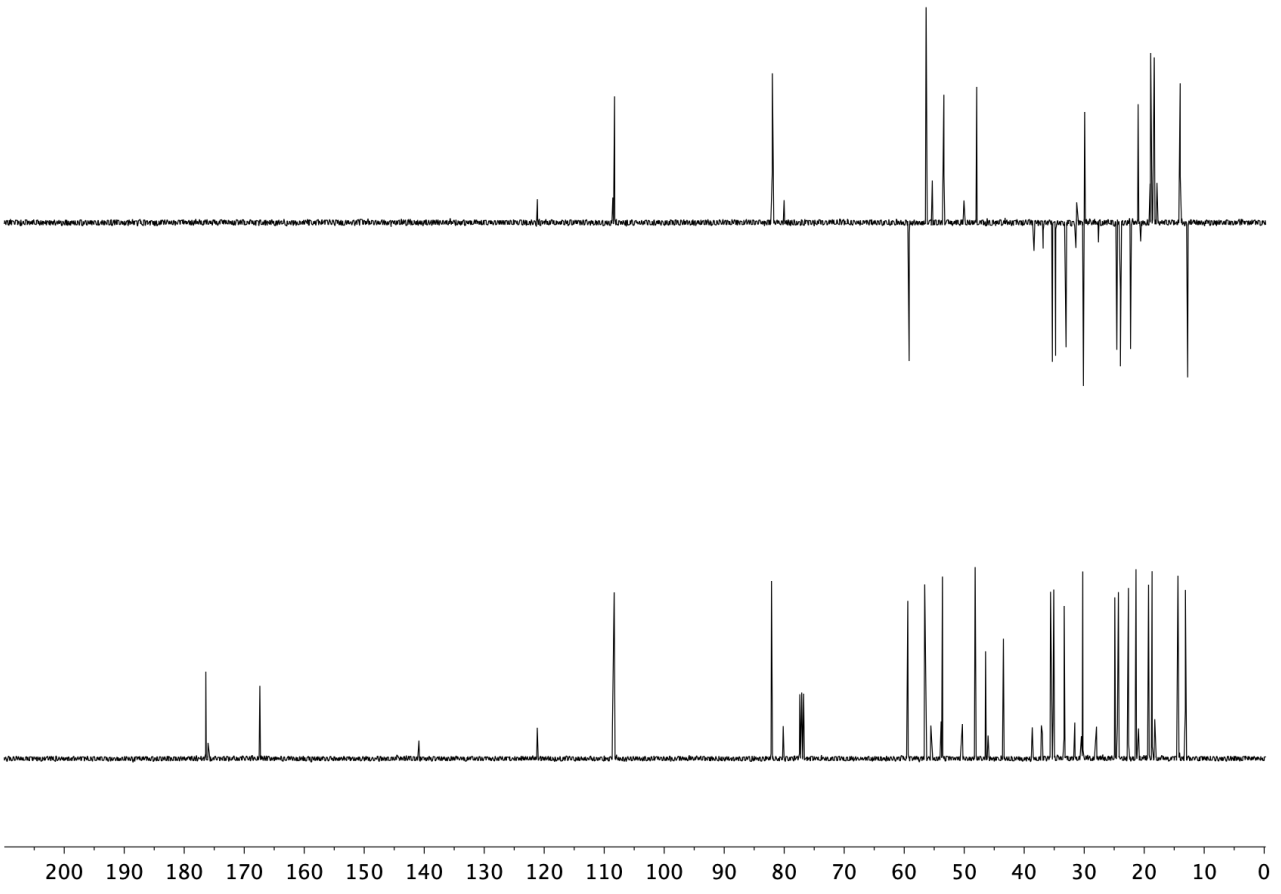
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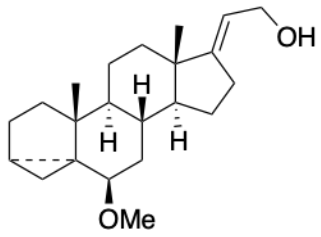
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H
H
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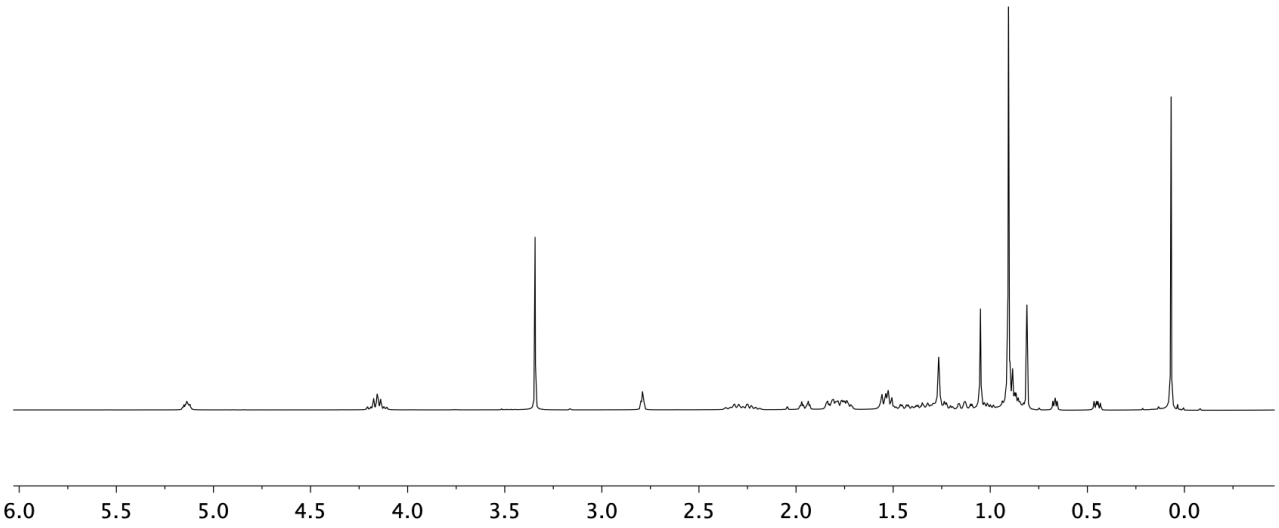
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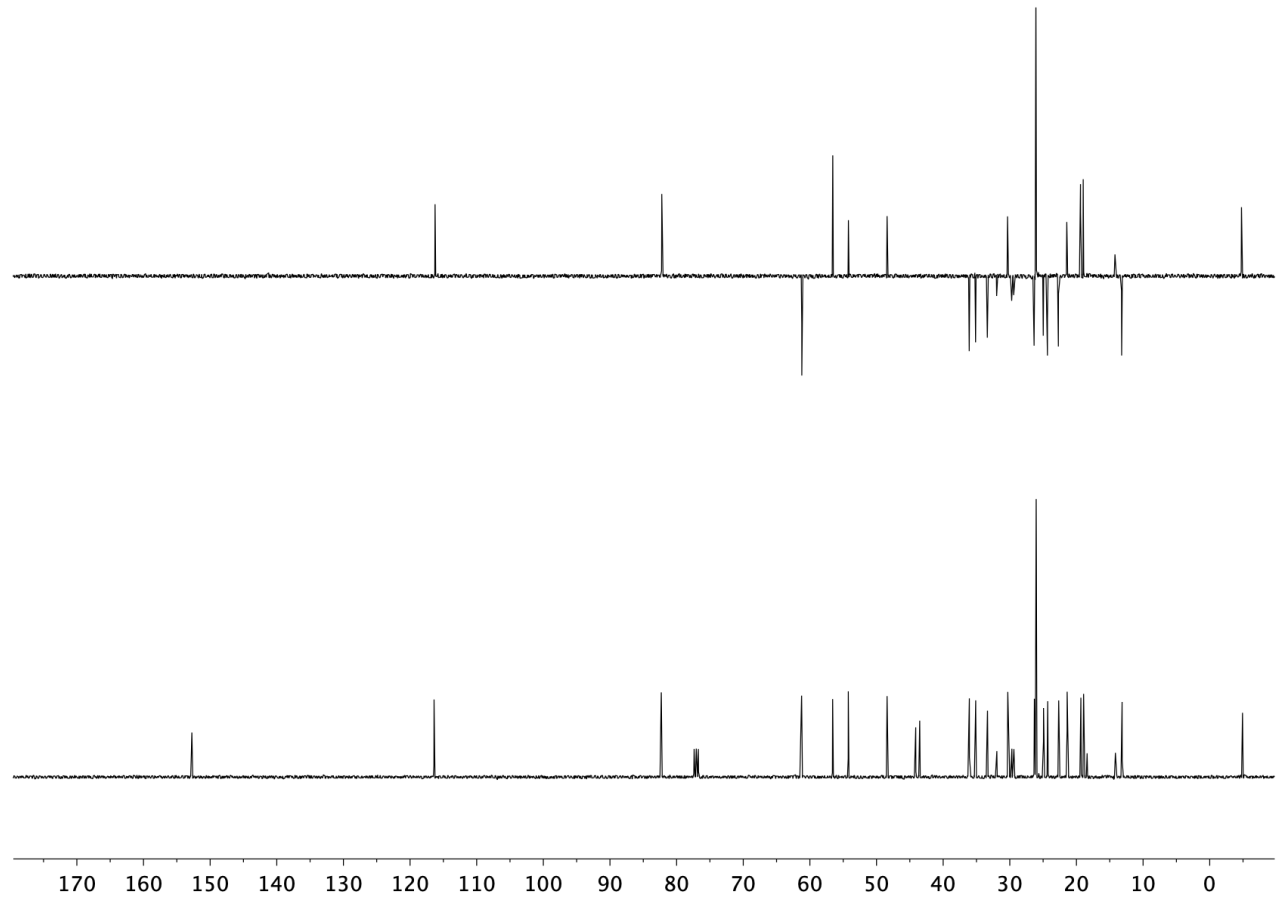
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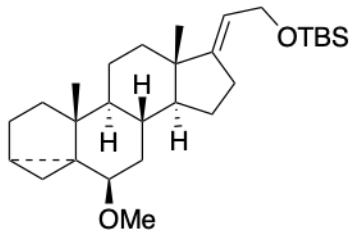
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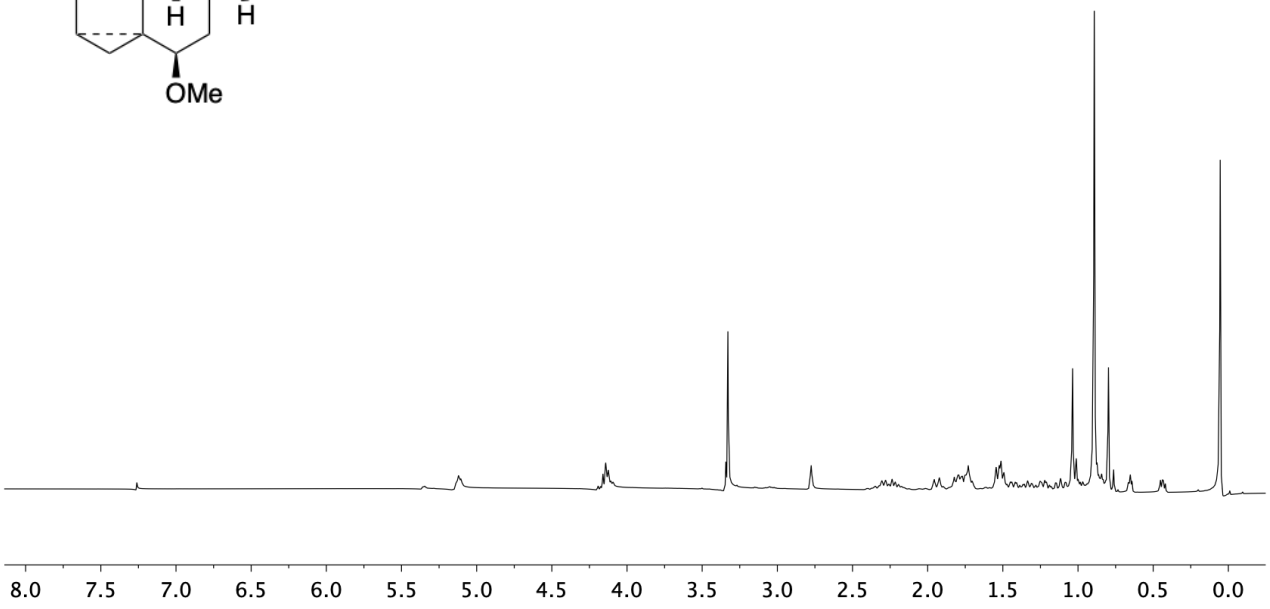
OMe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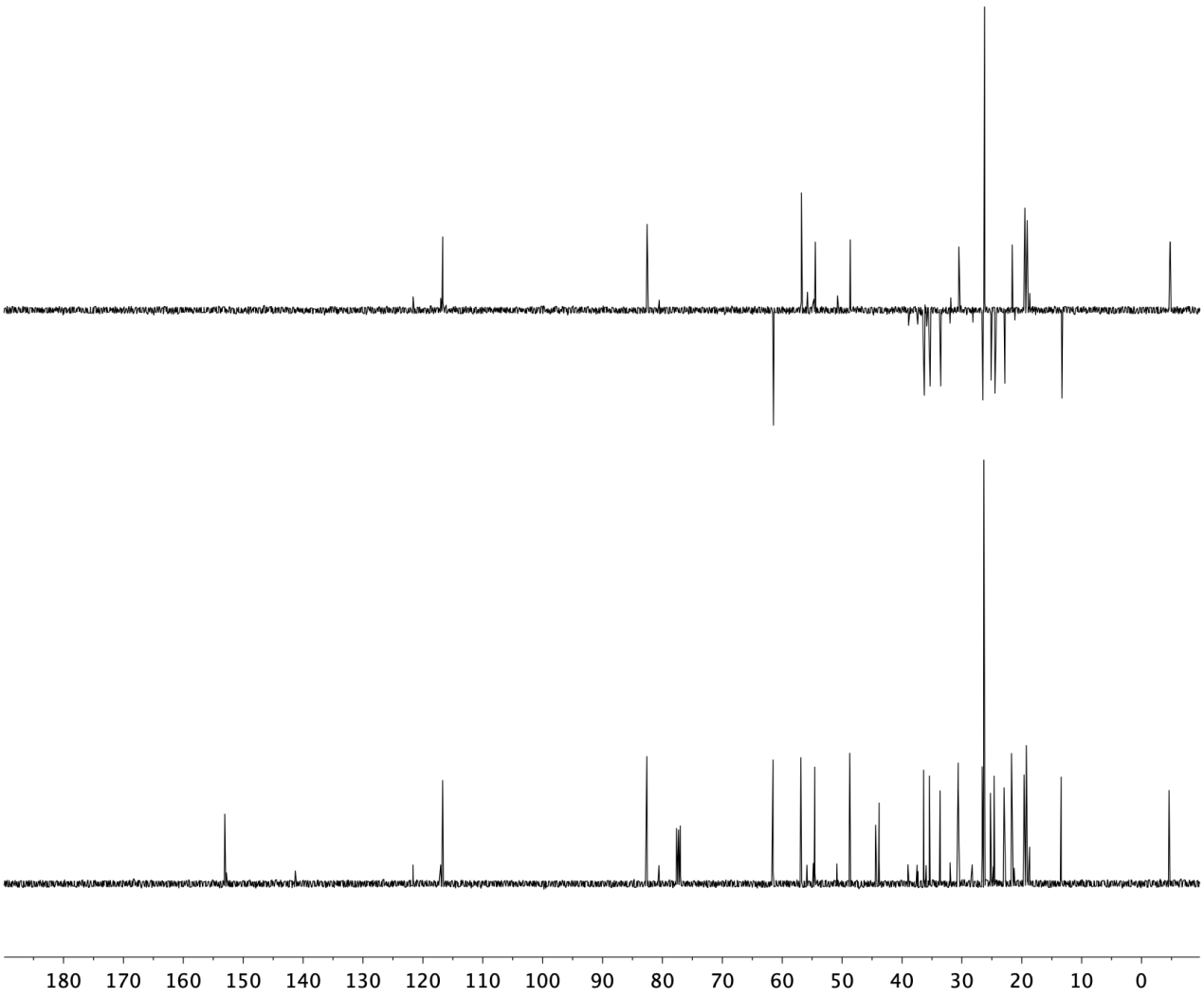
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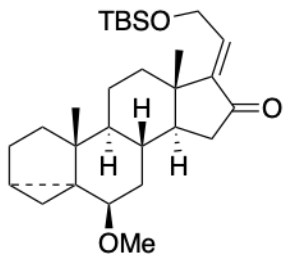
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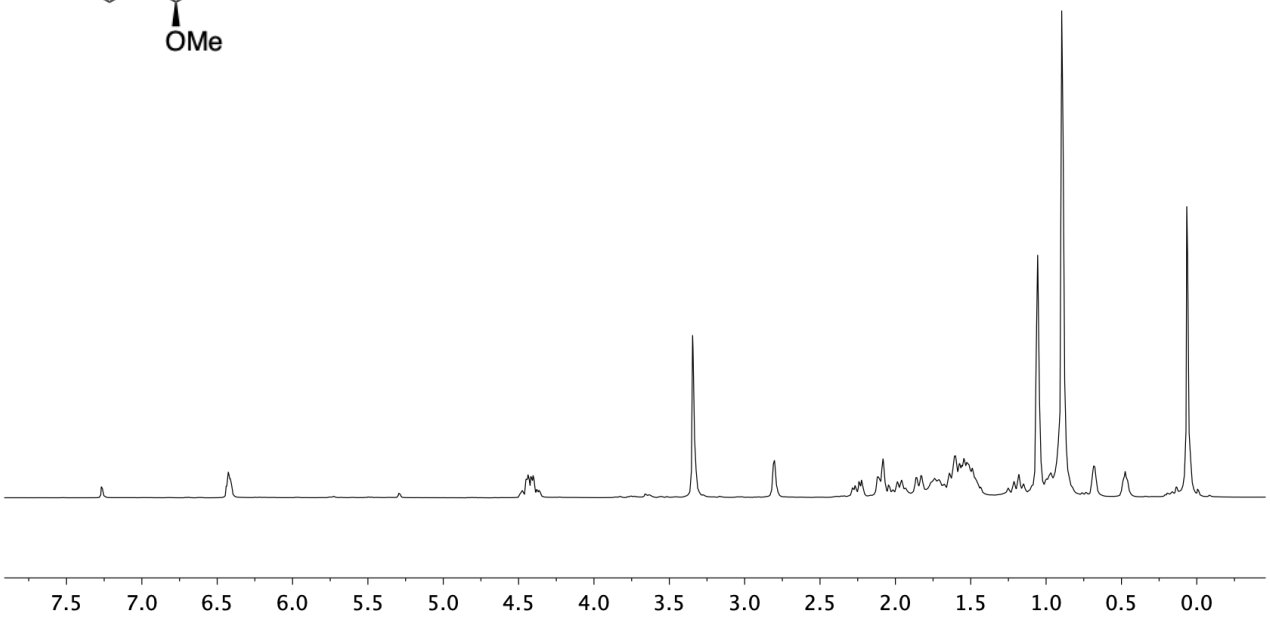
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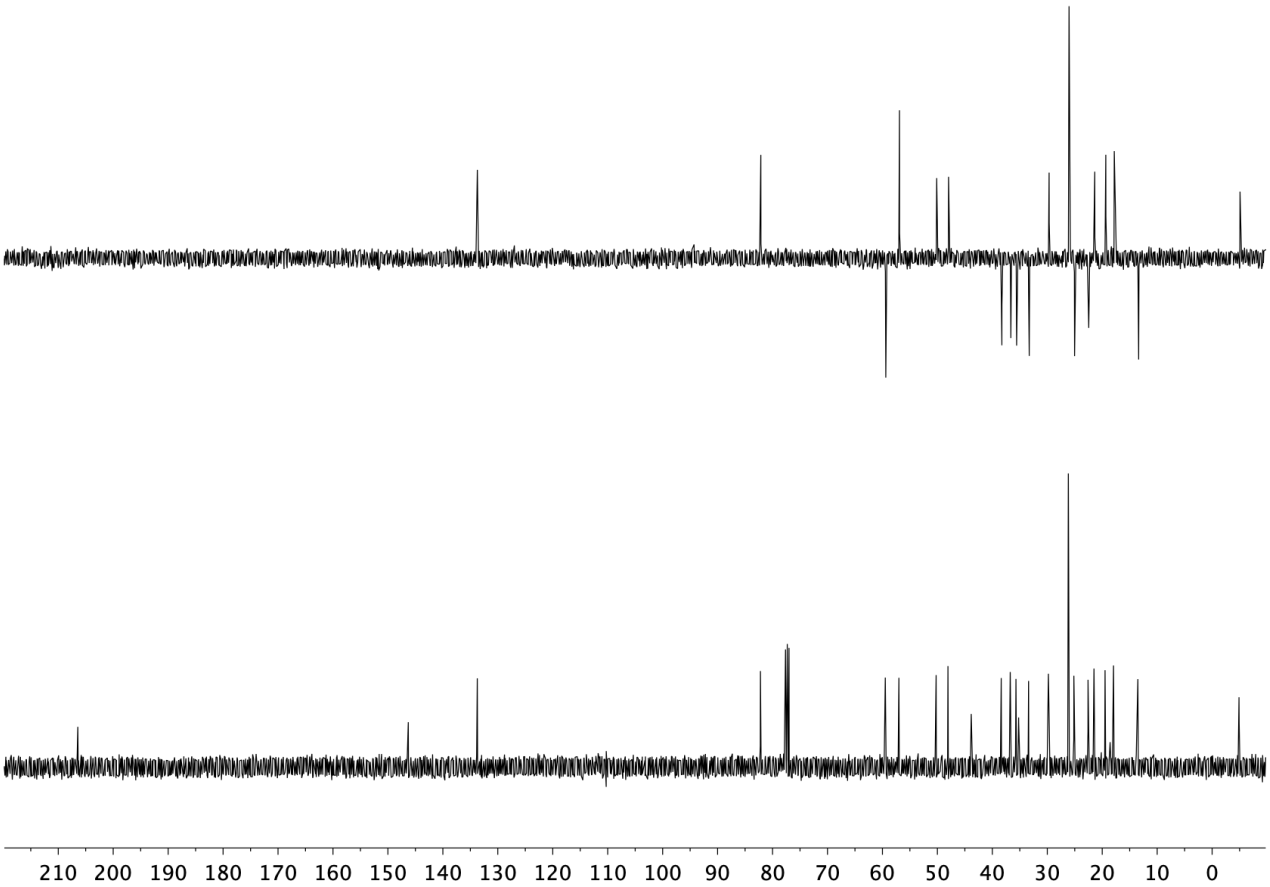
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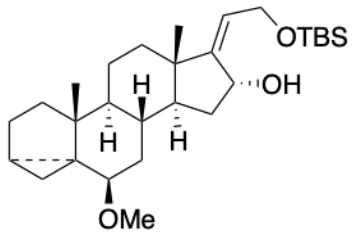
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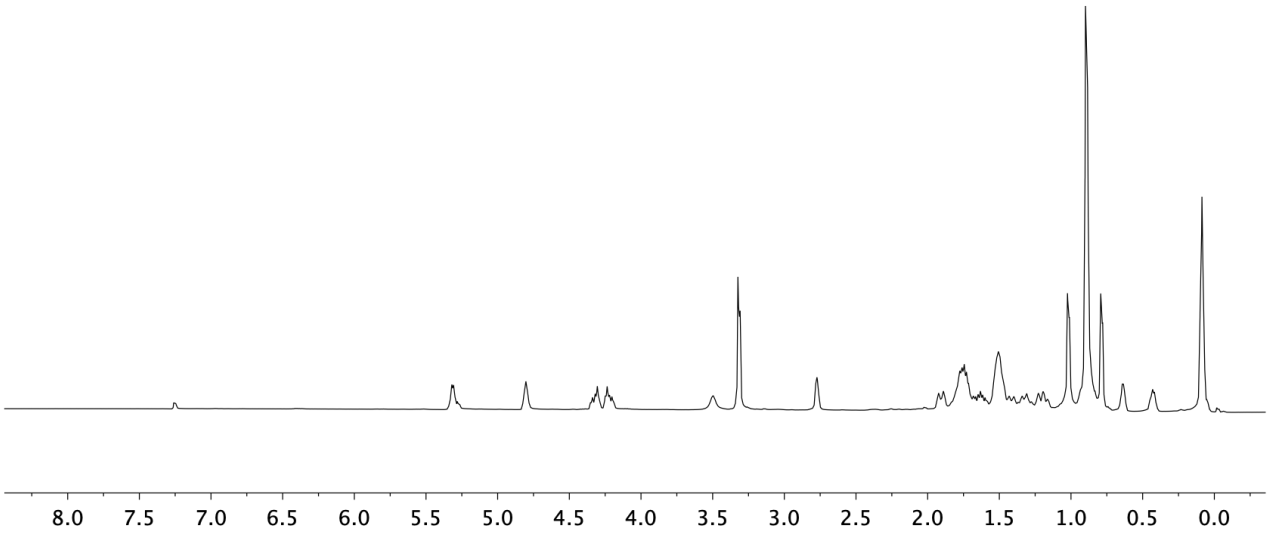
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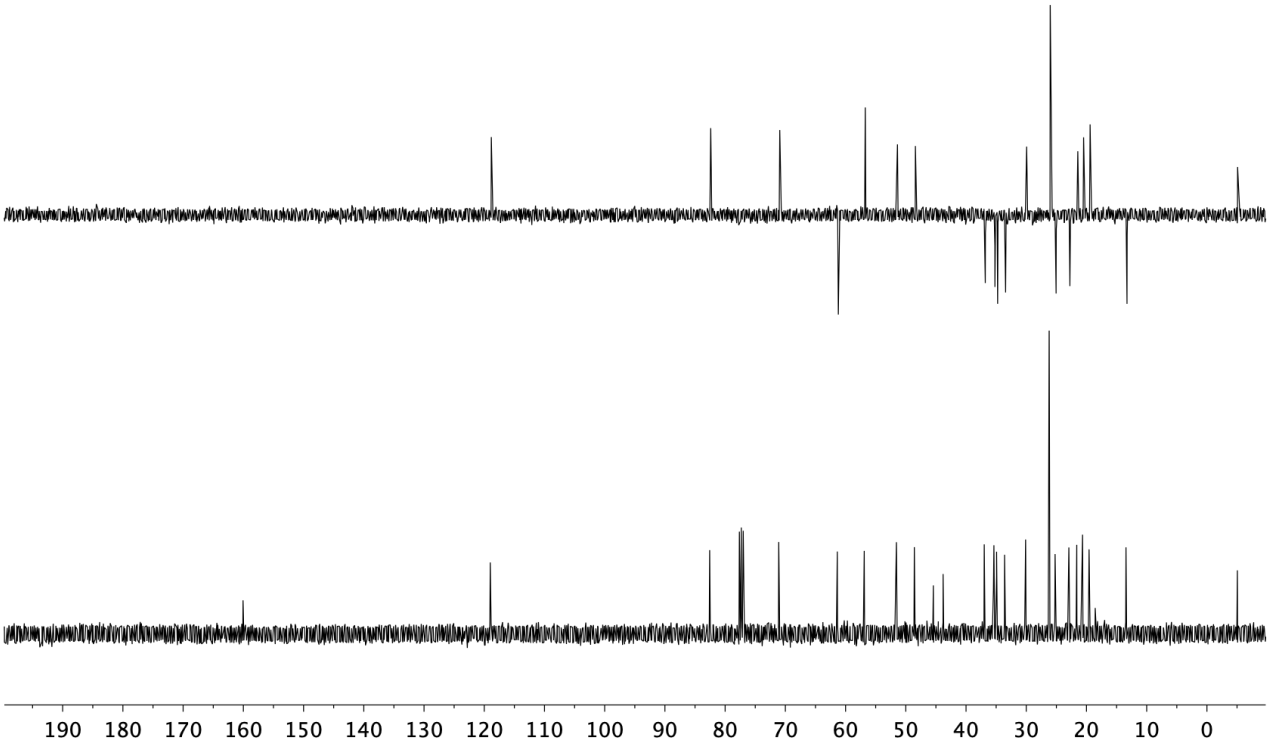
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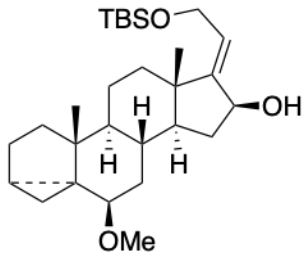
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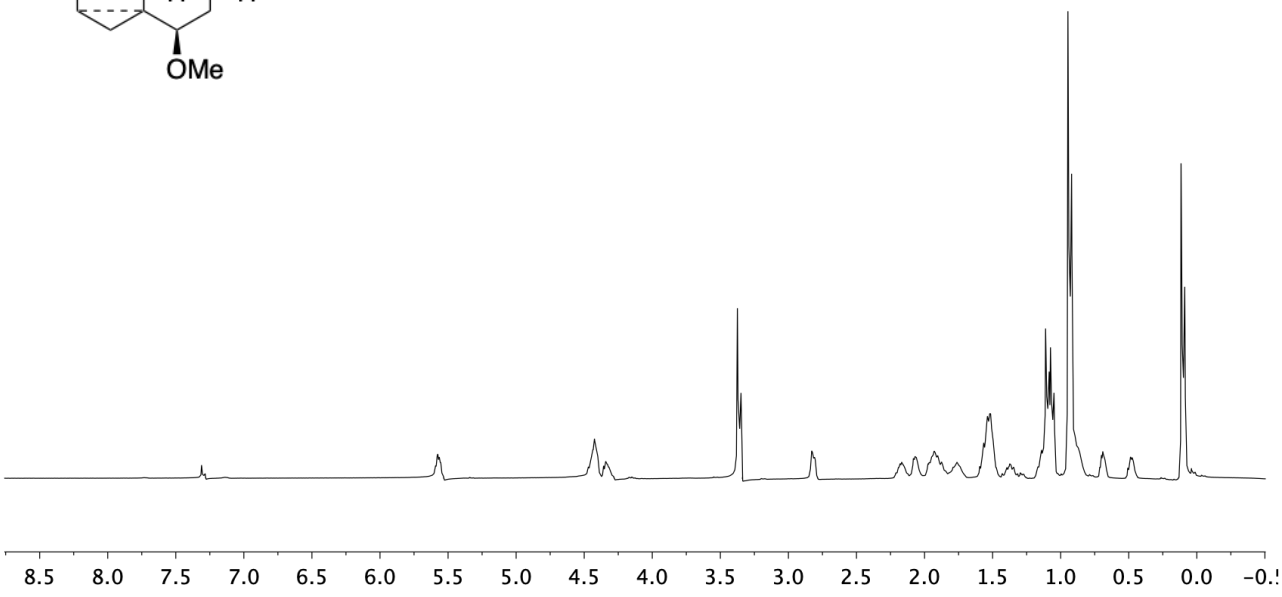
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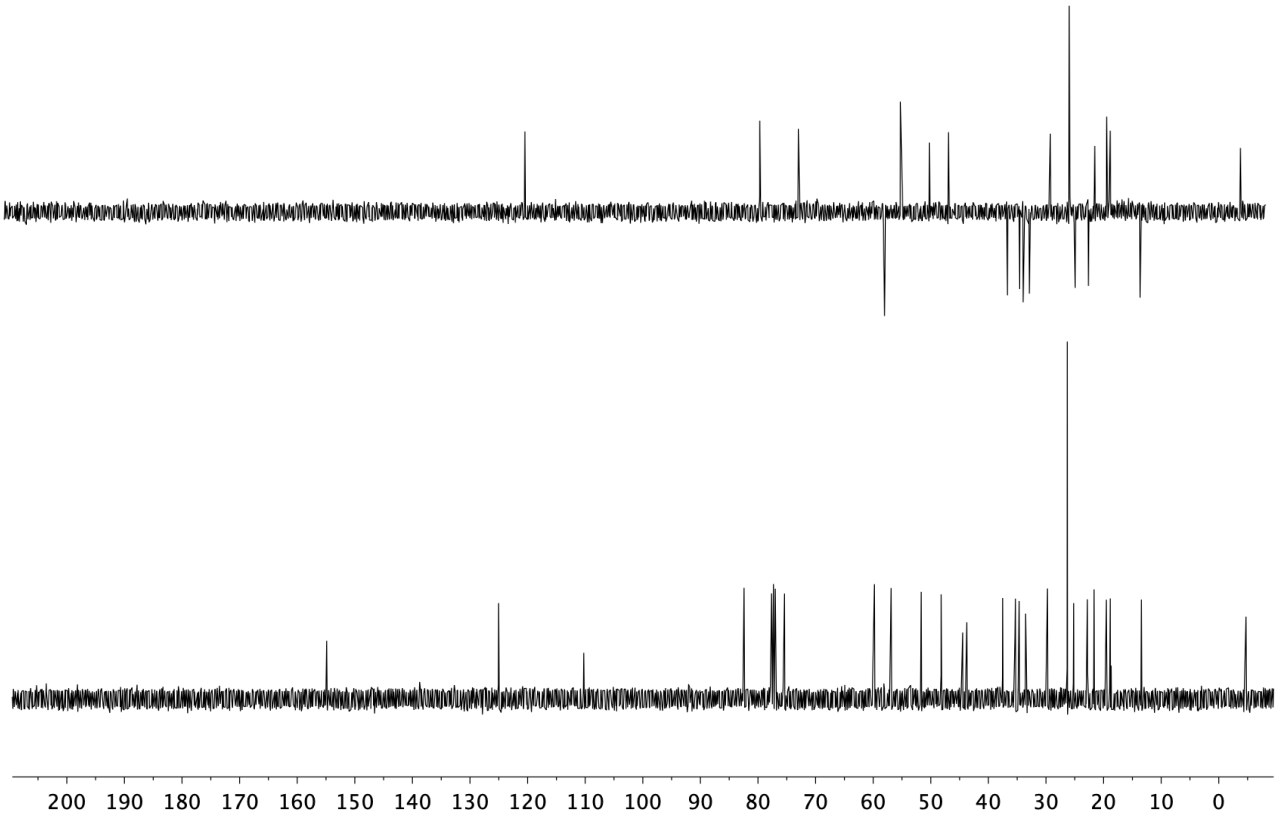
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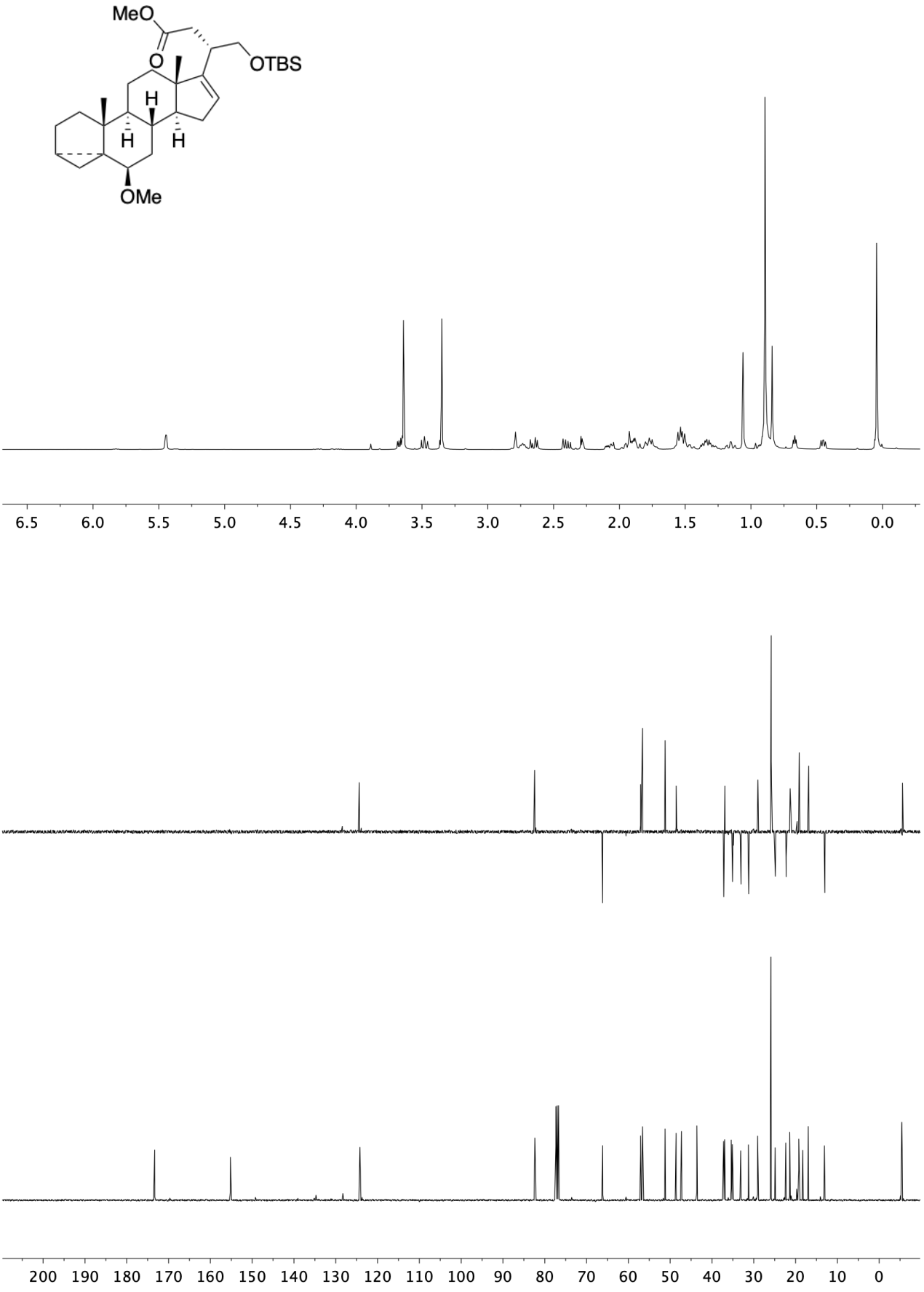
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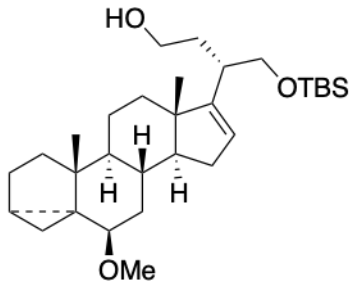
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H
OMe


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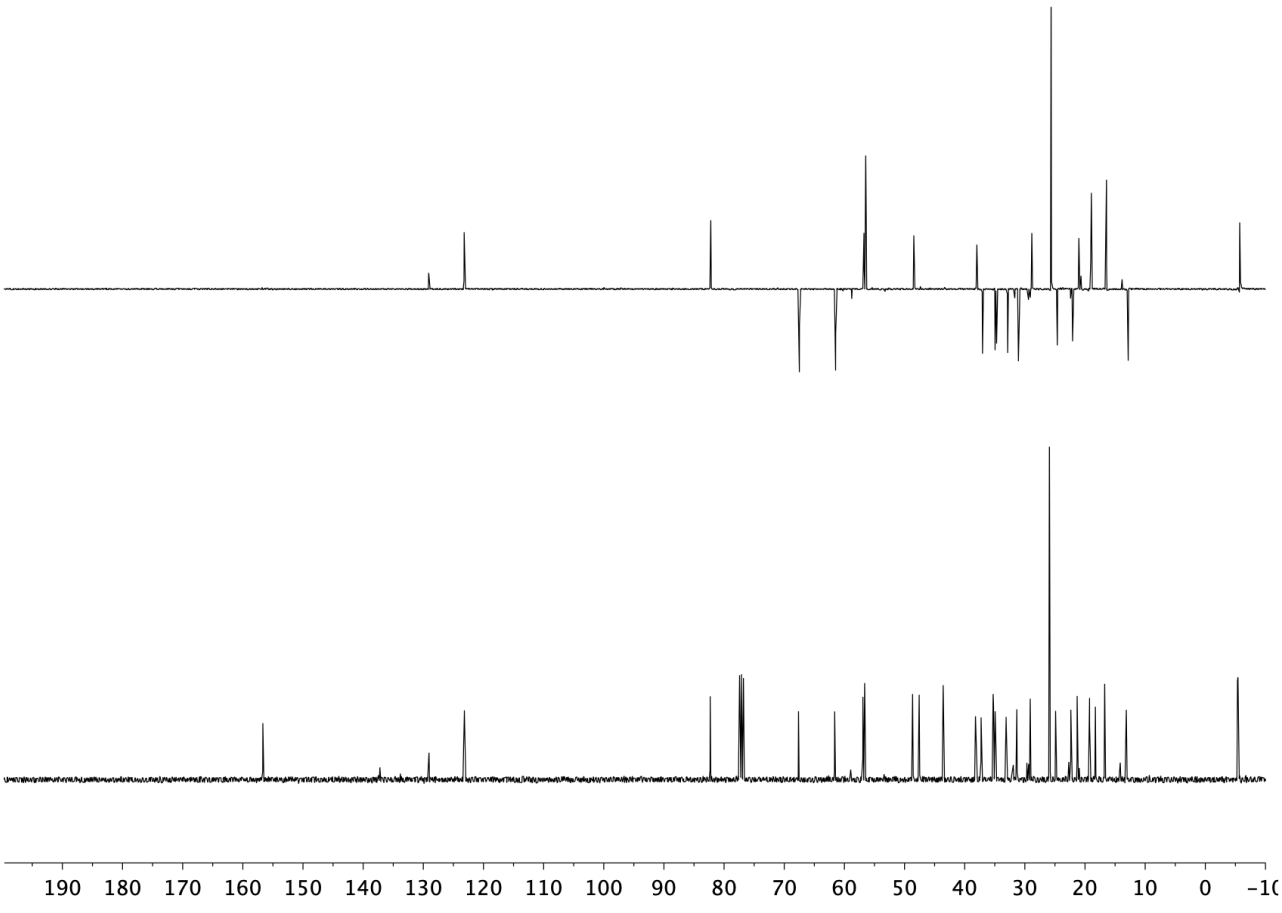
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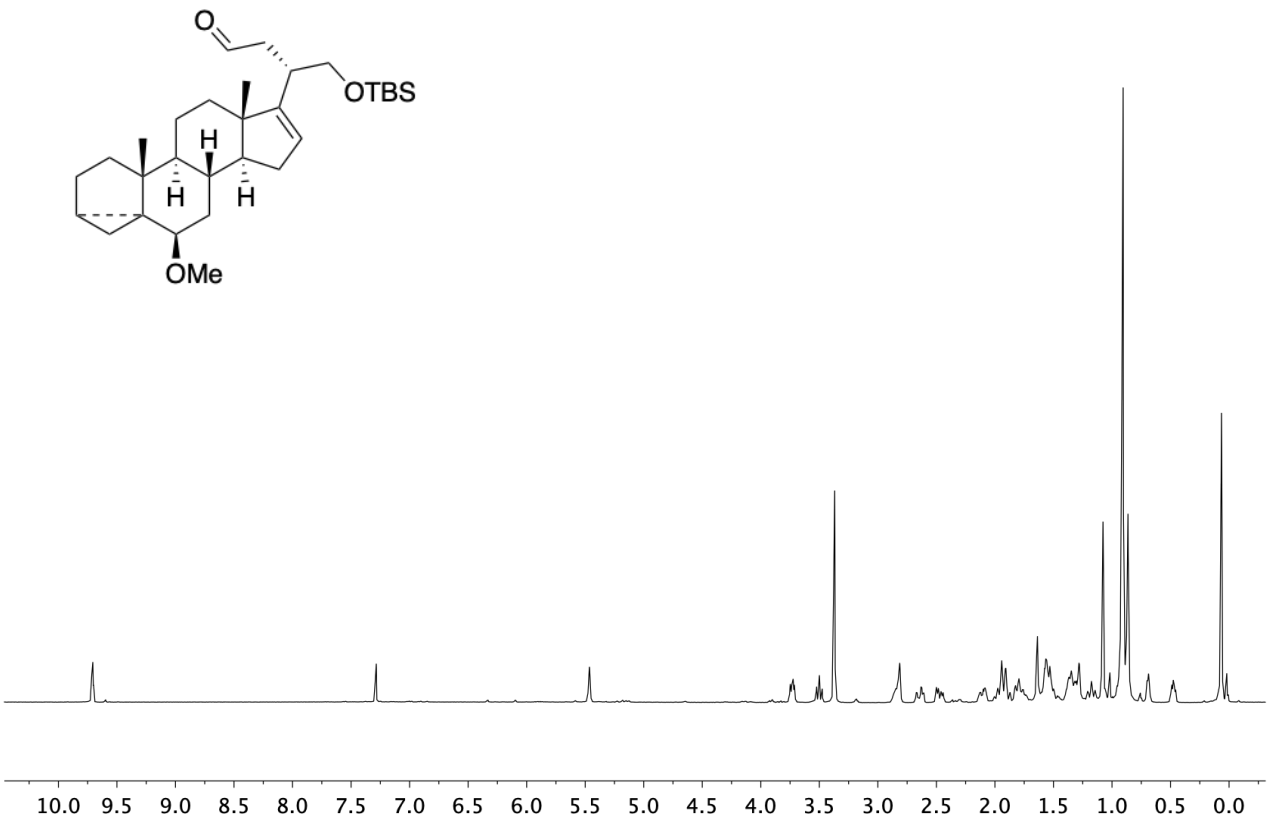
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OMe
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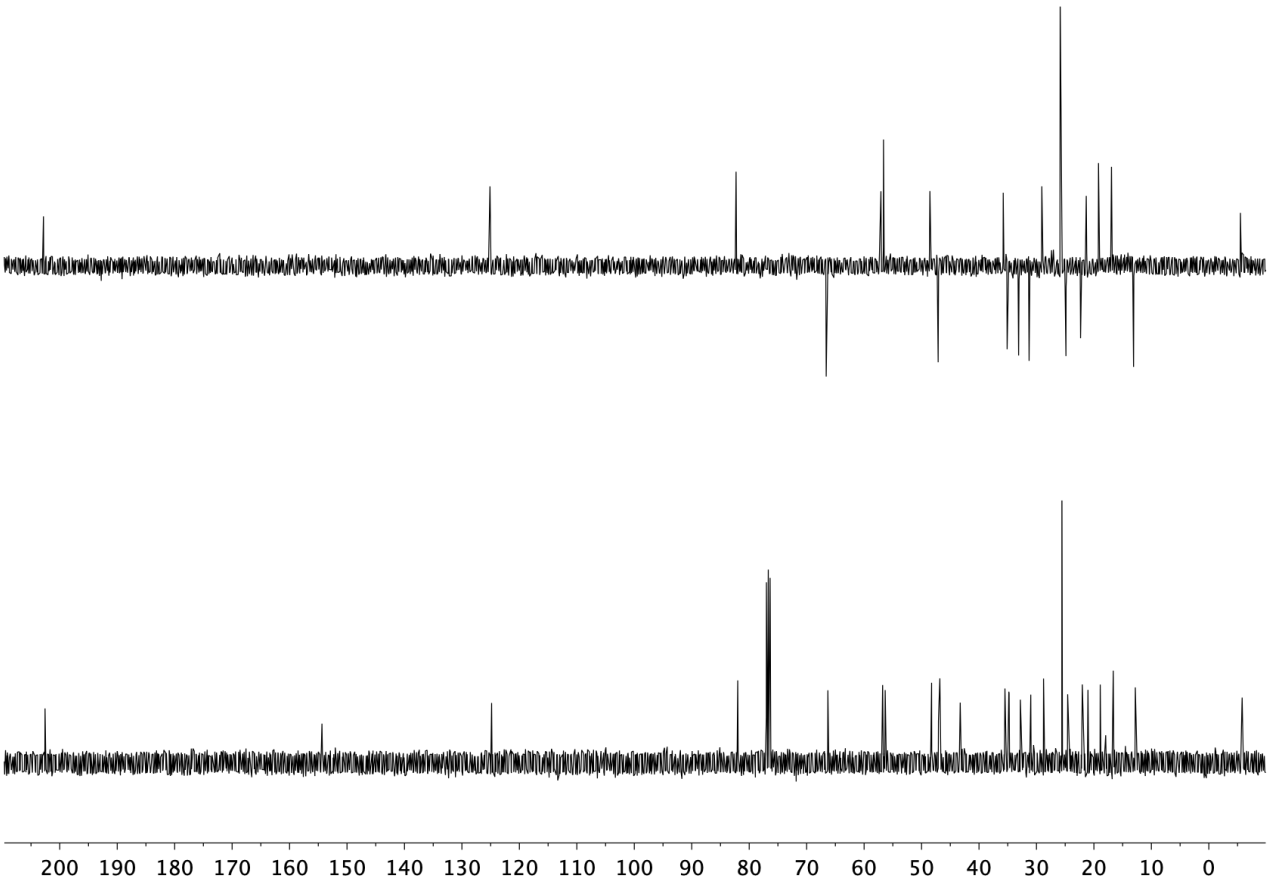
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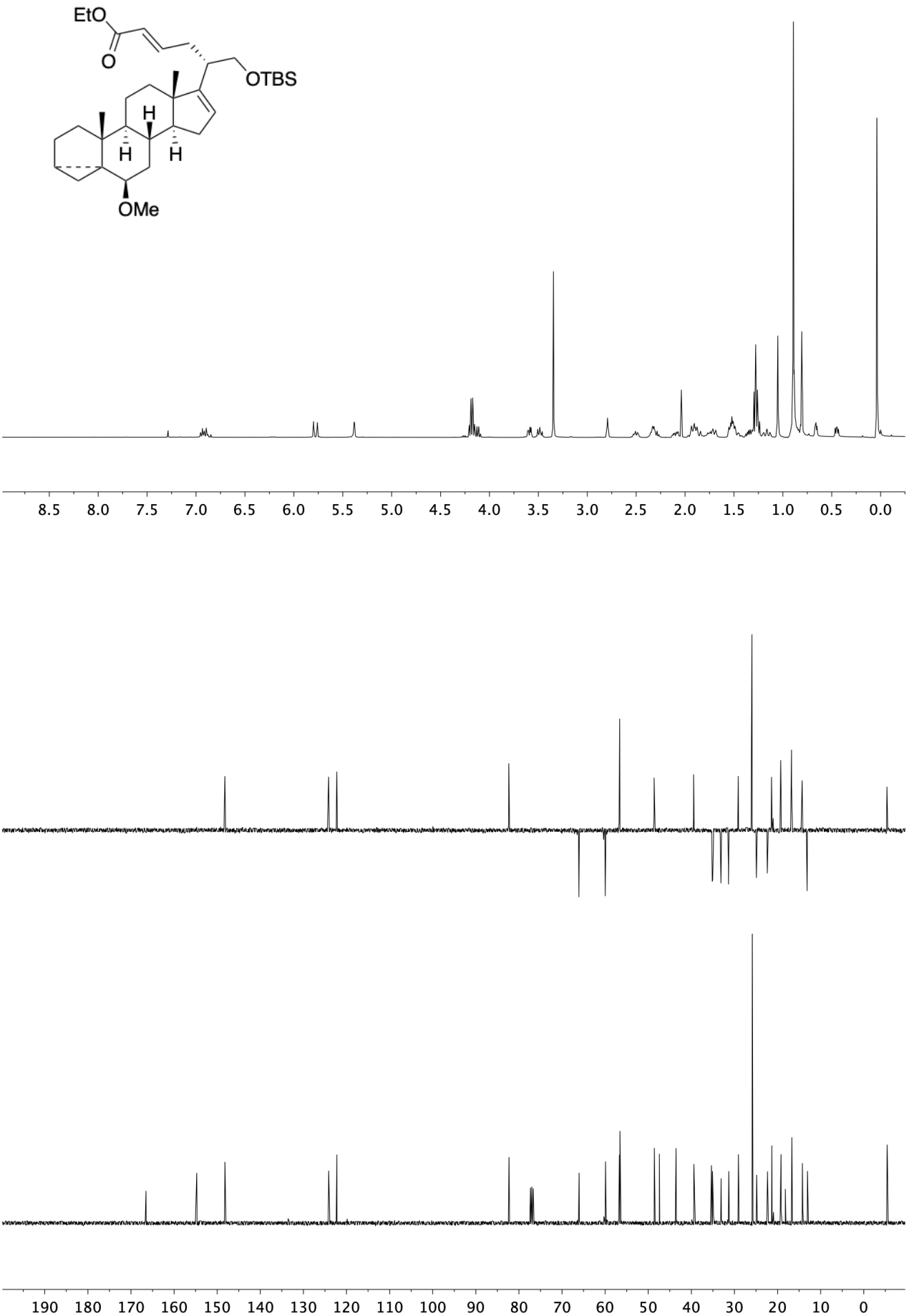
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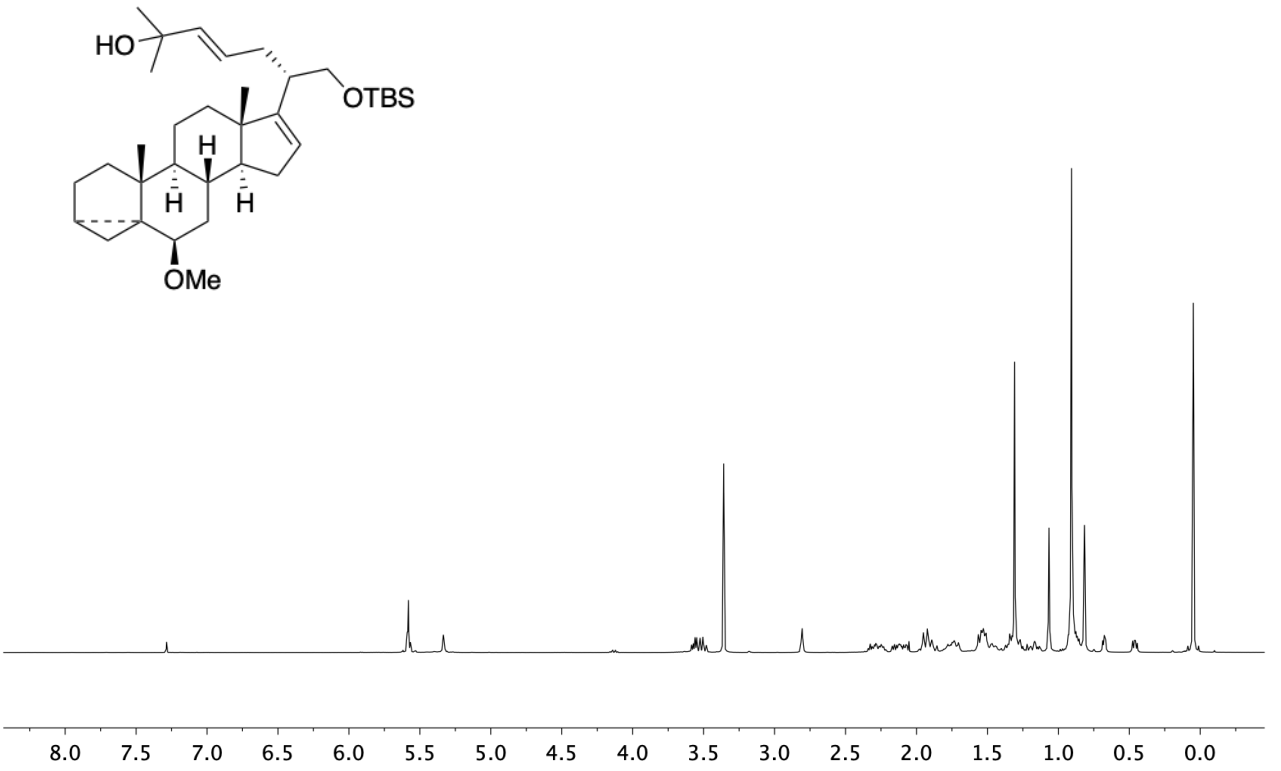
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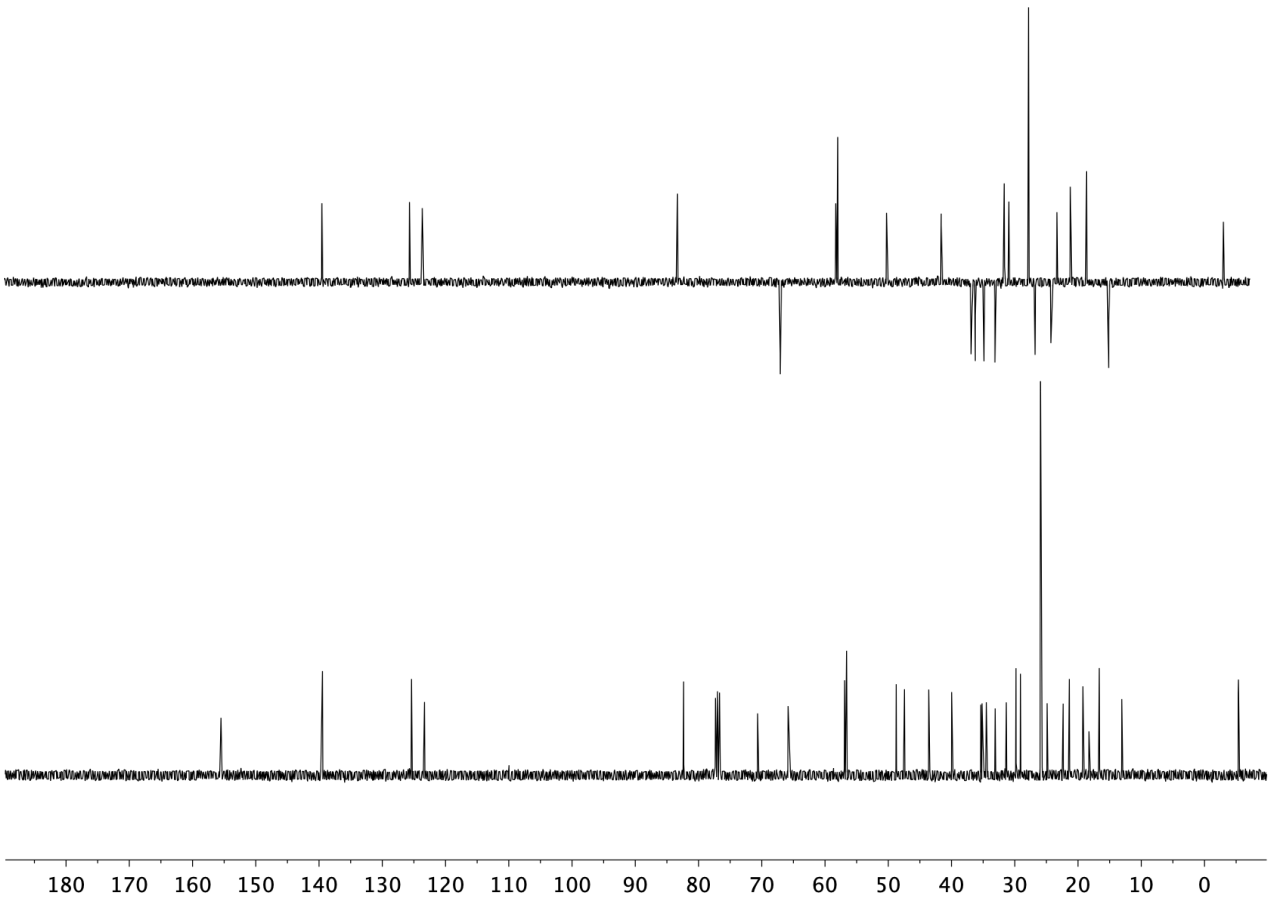
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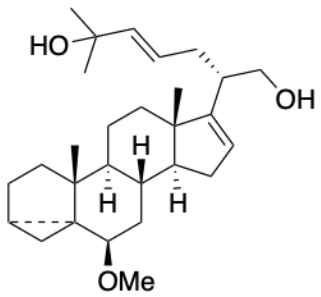
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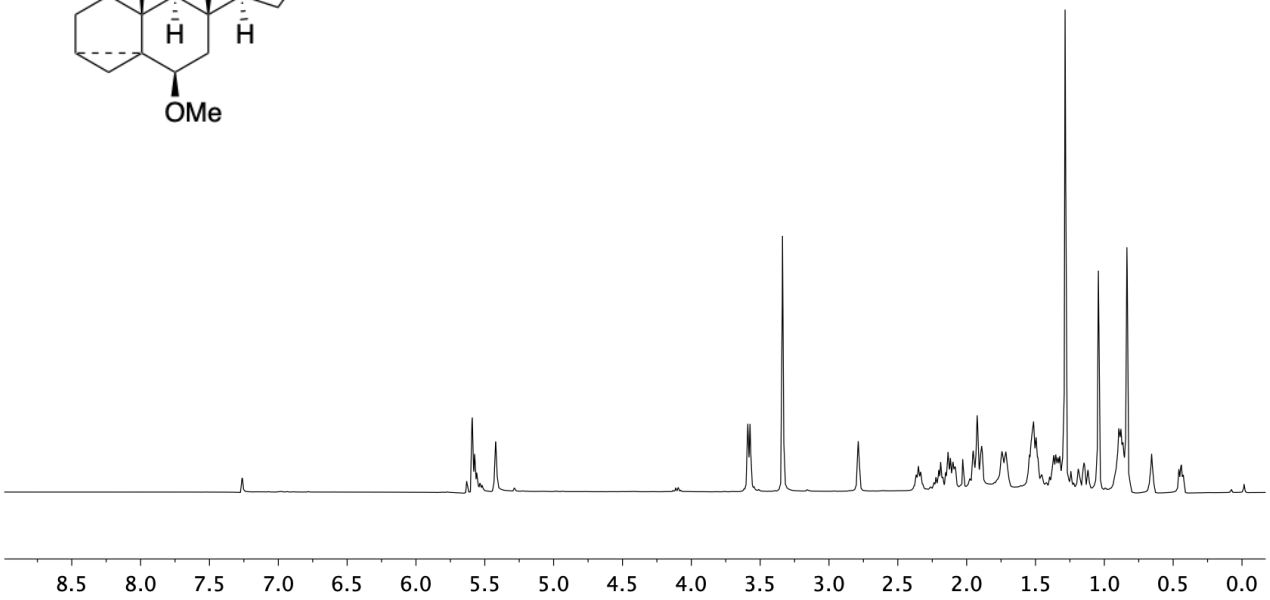
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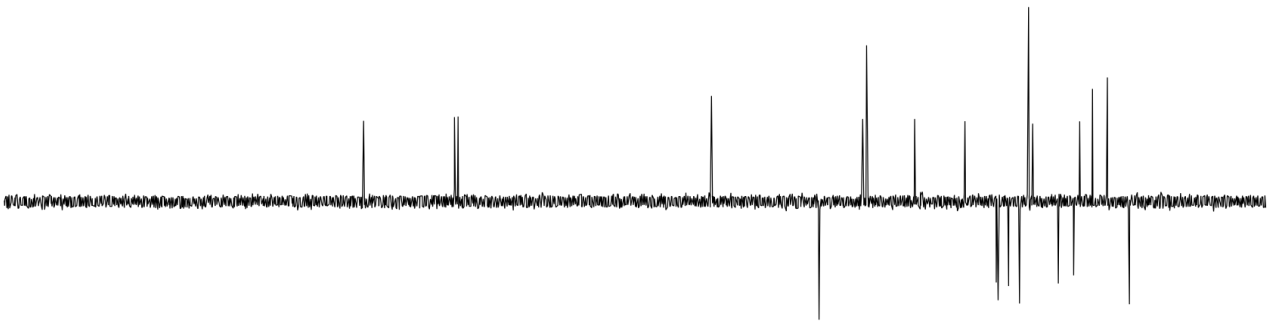

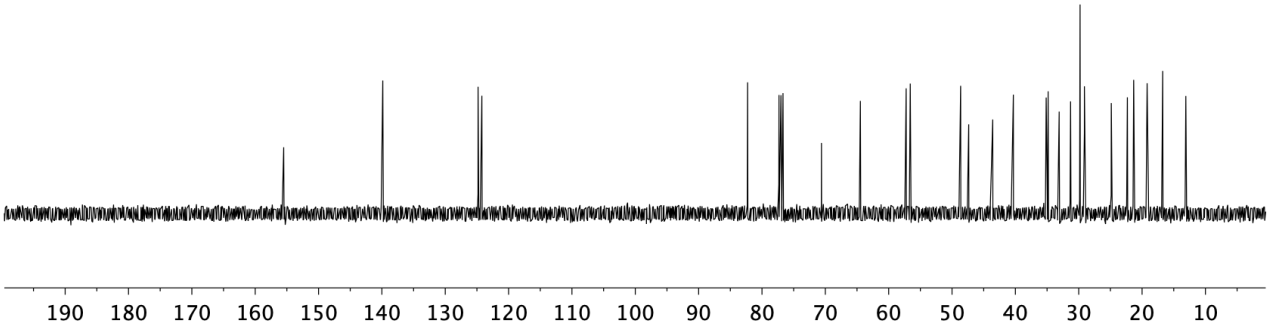
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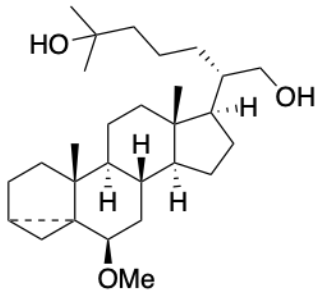
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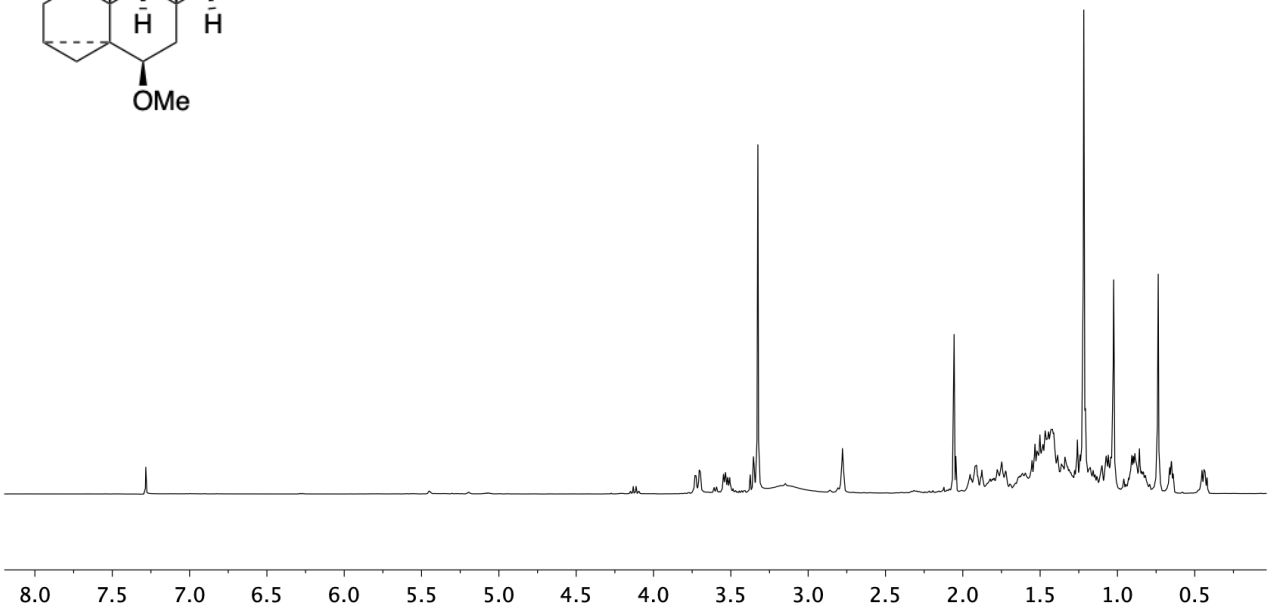
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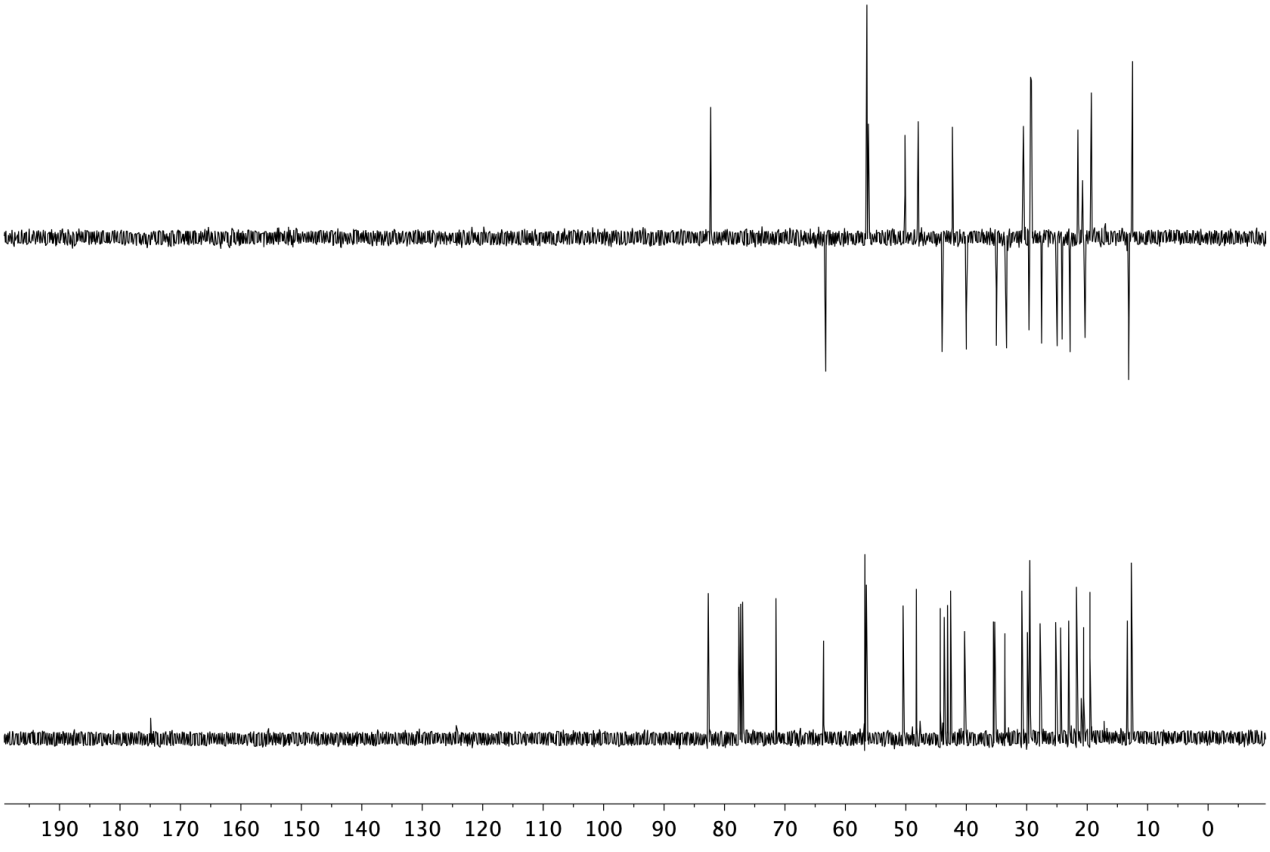
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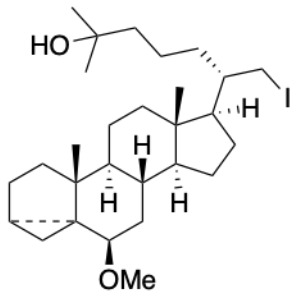
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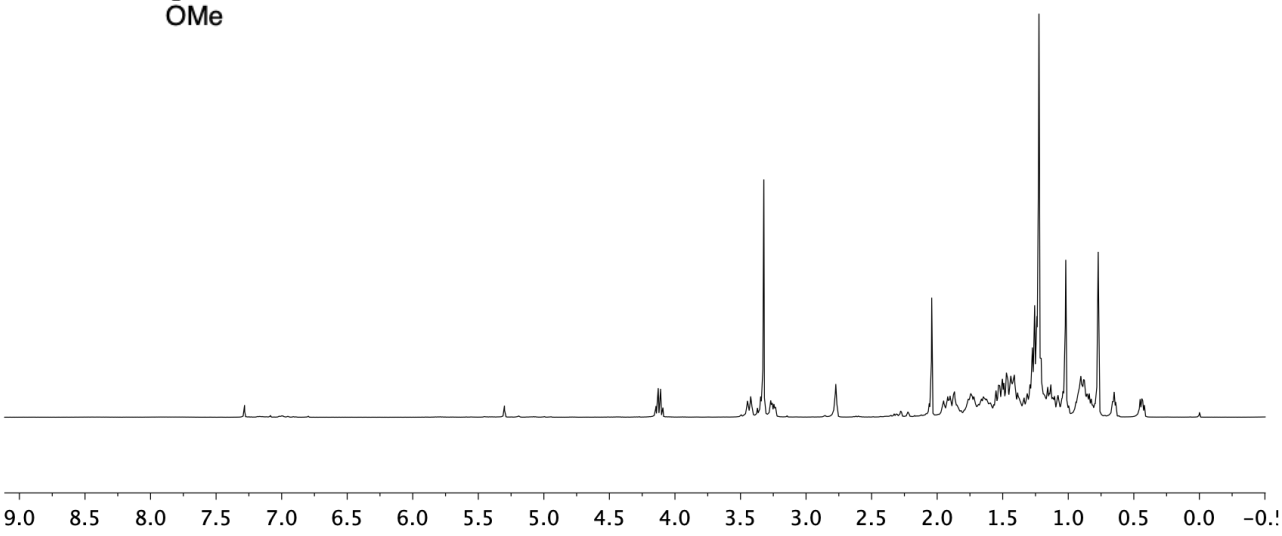
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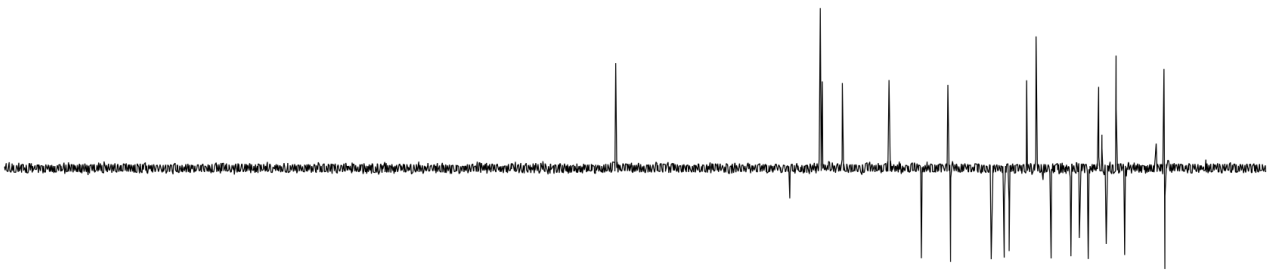

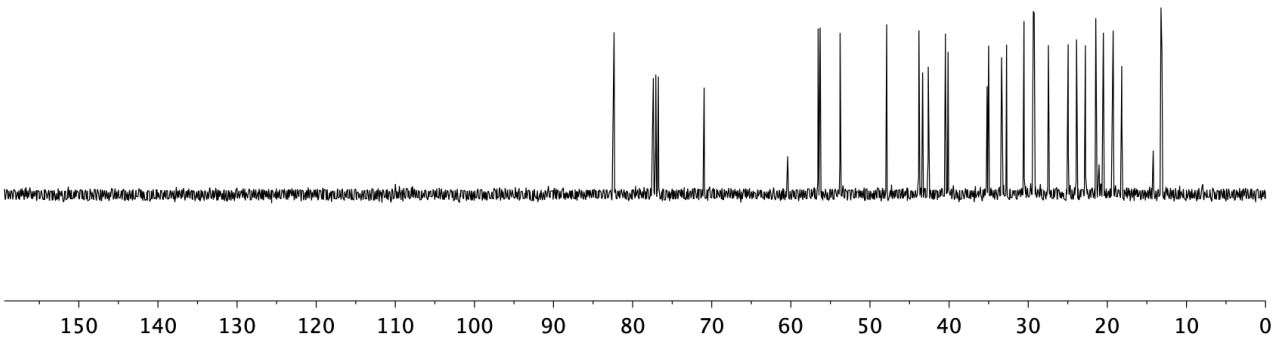
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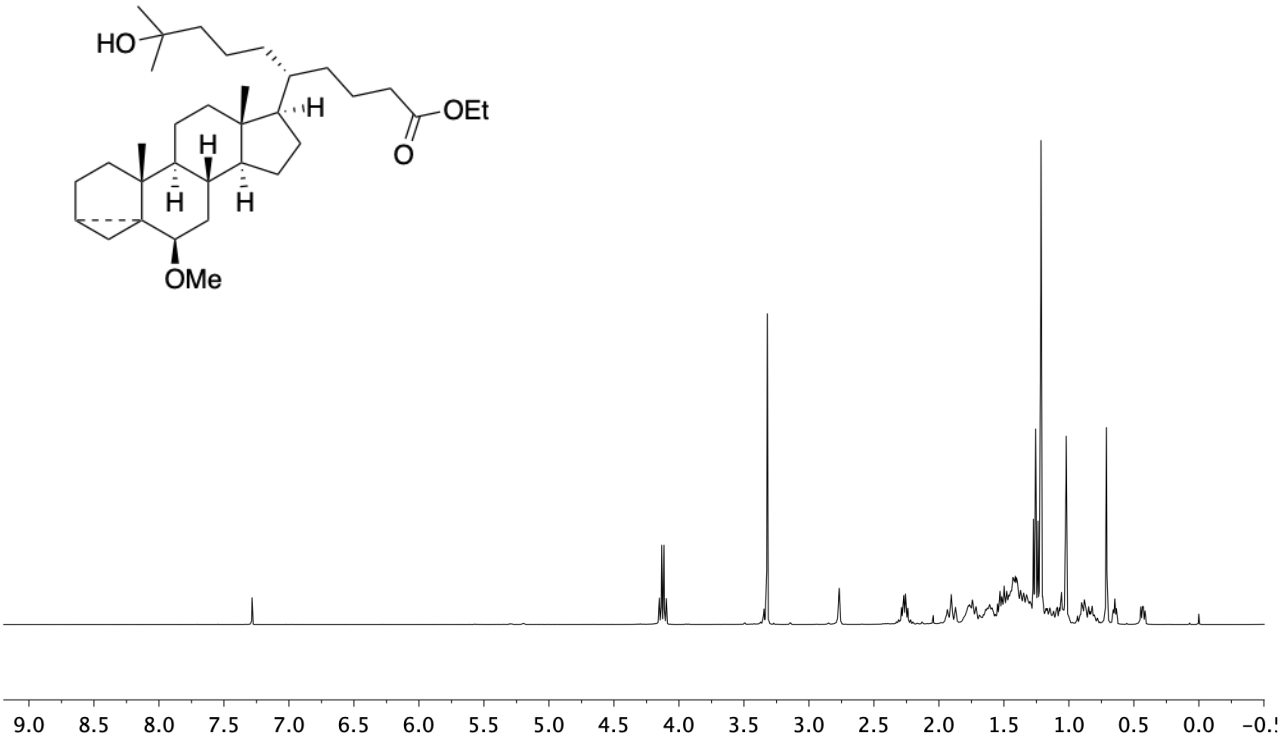
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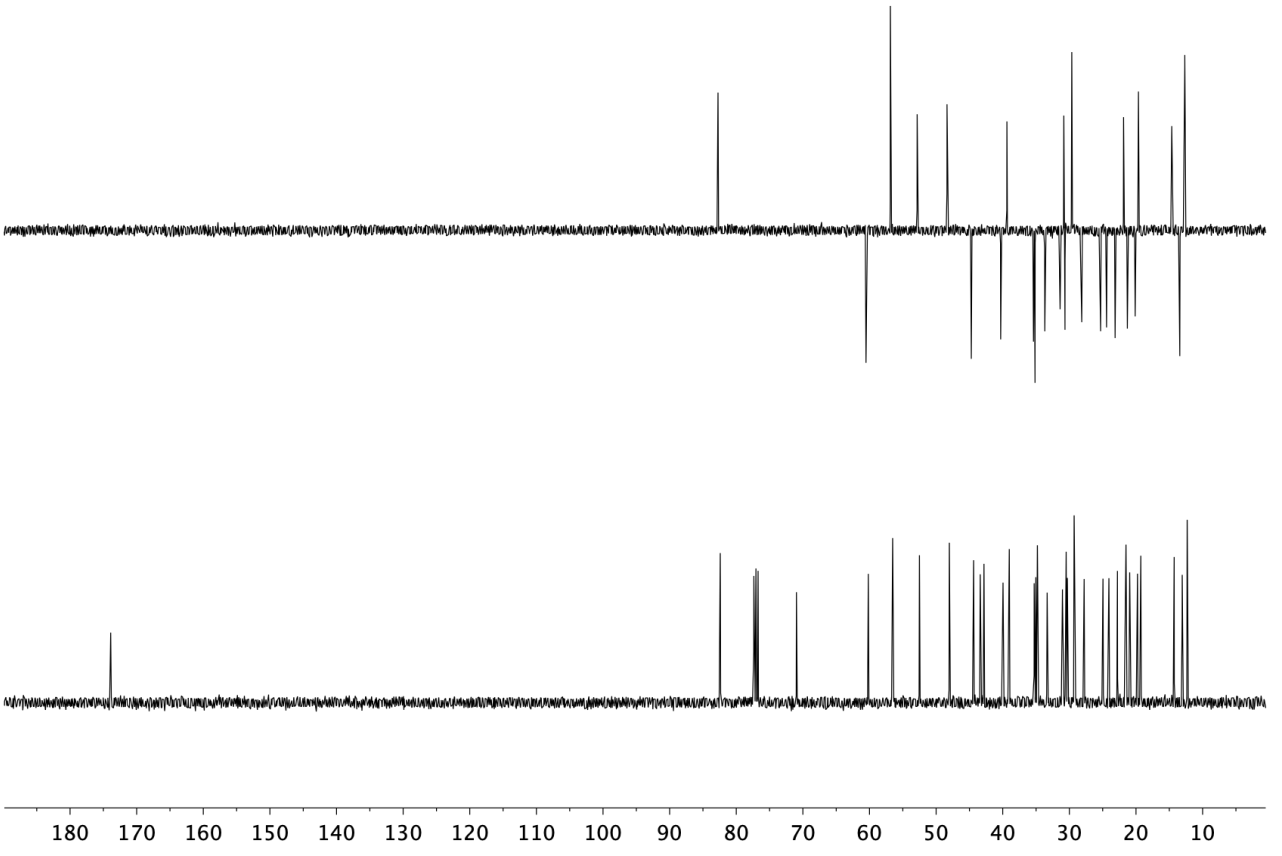
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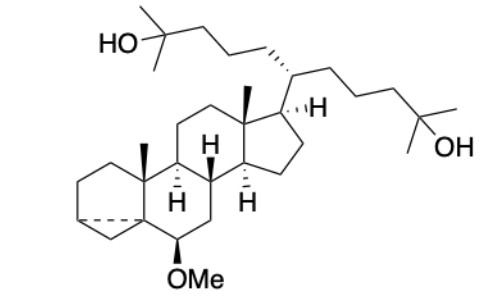
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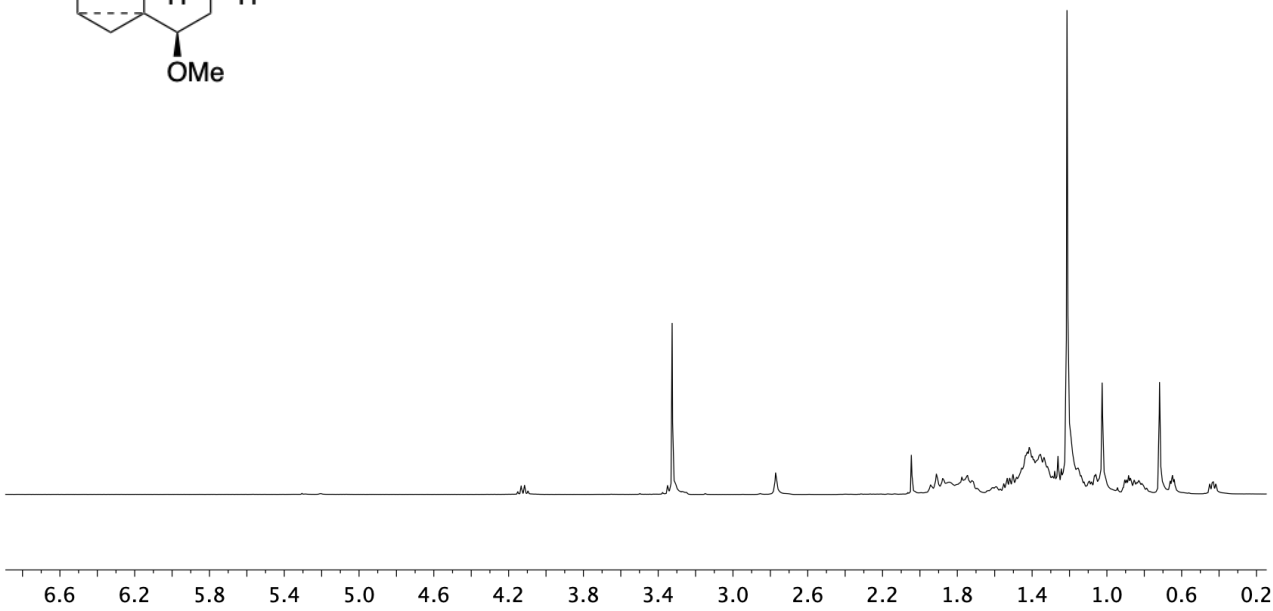
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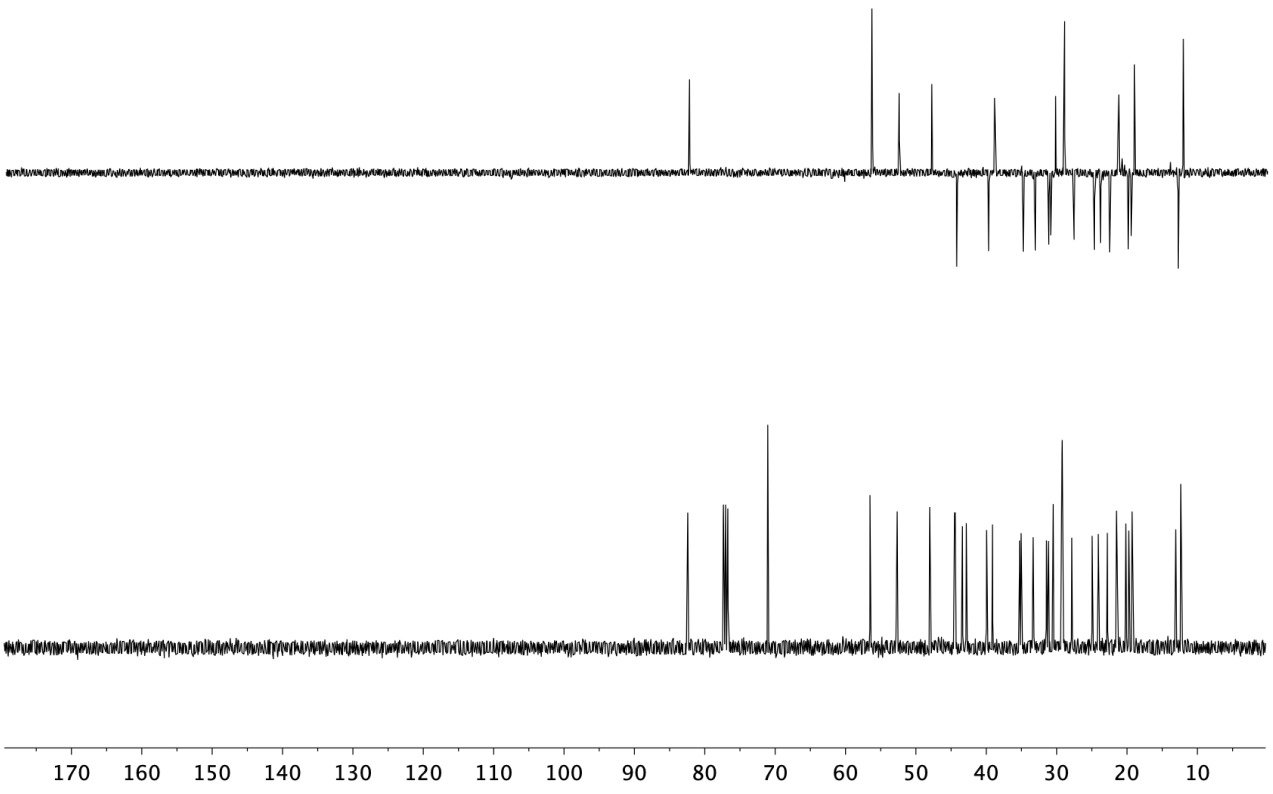
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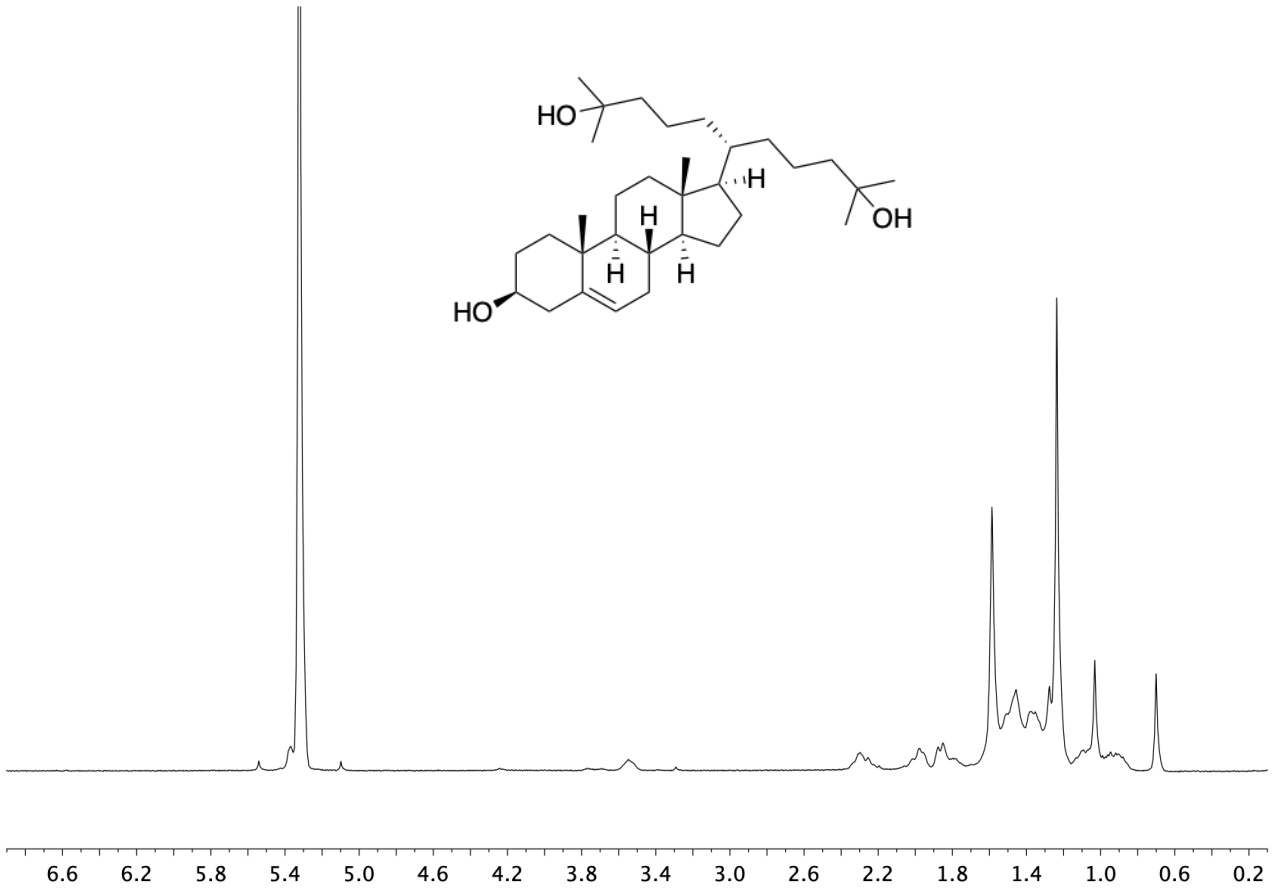
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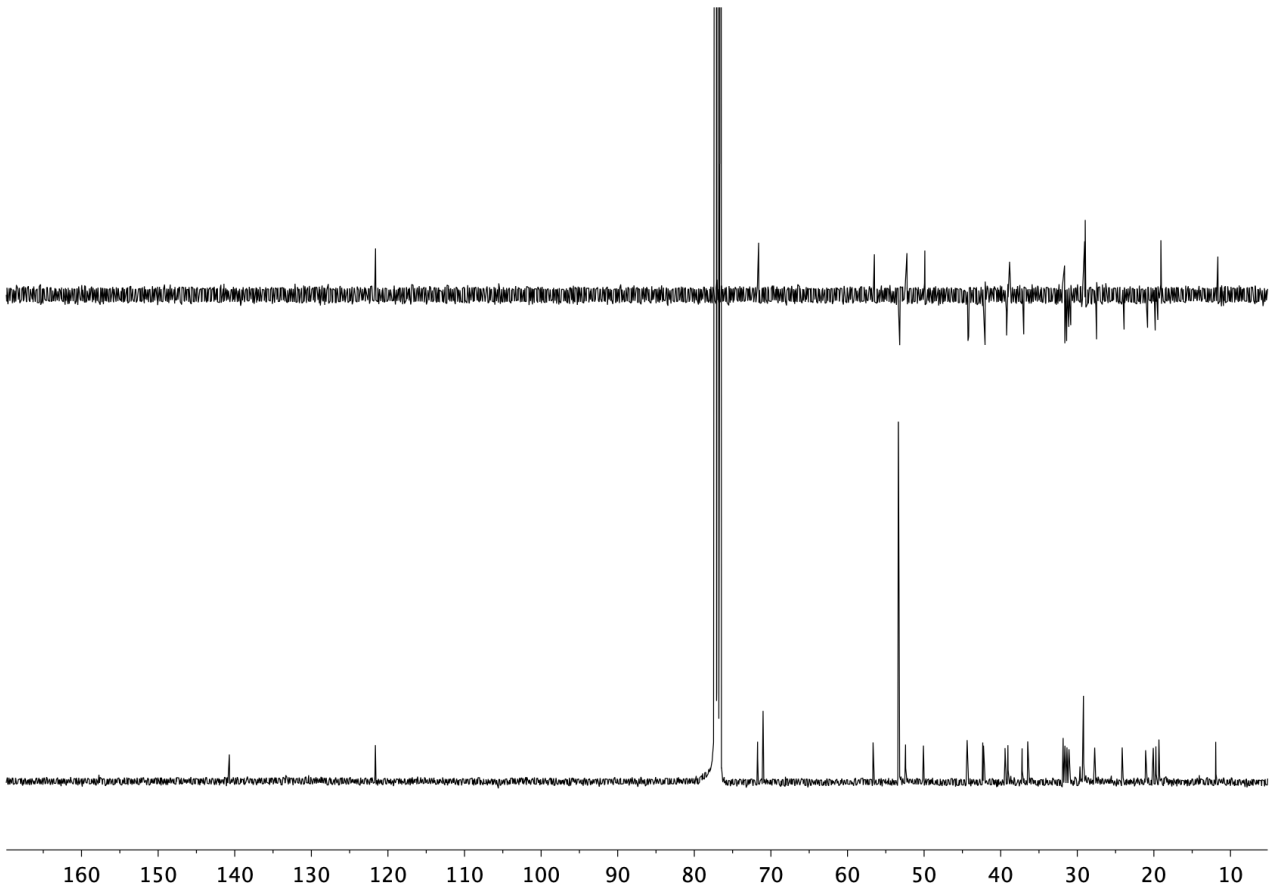
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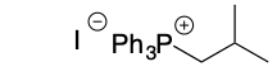
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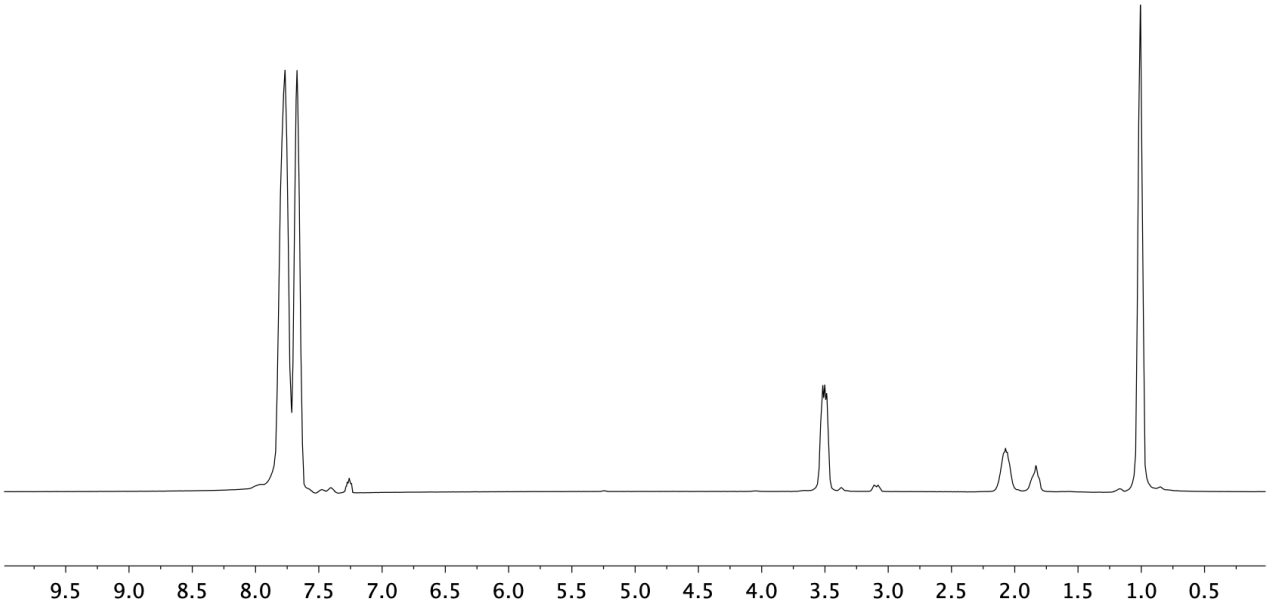
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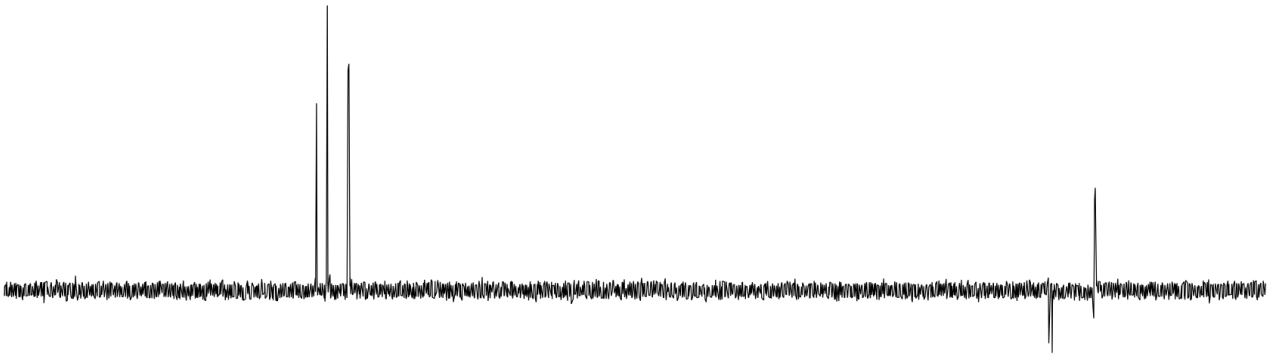

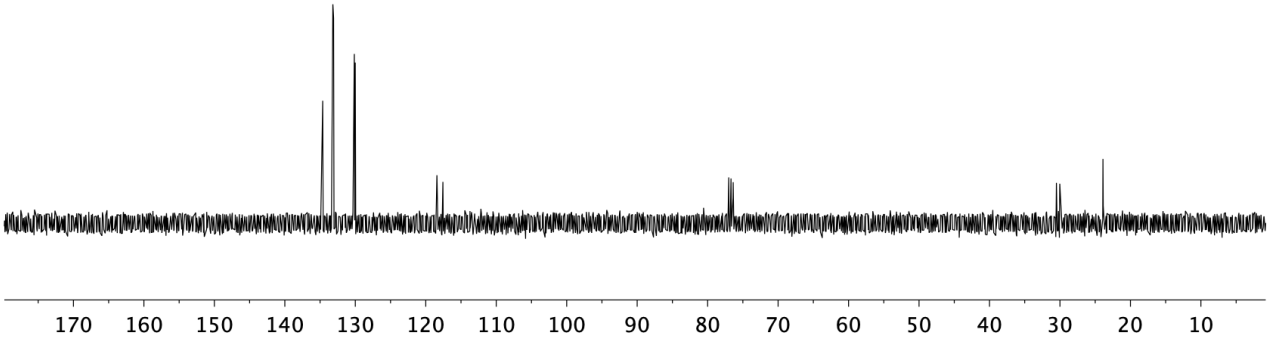
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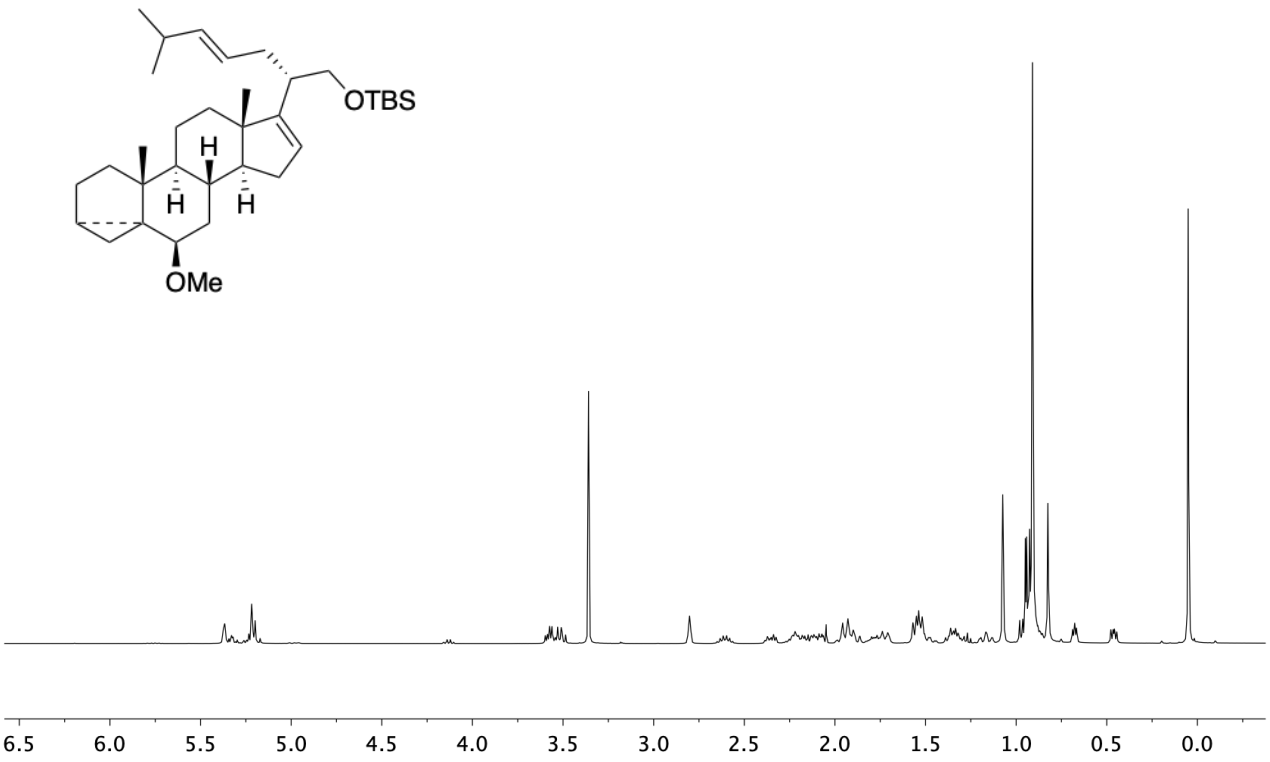
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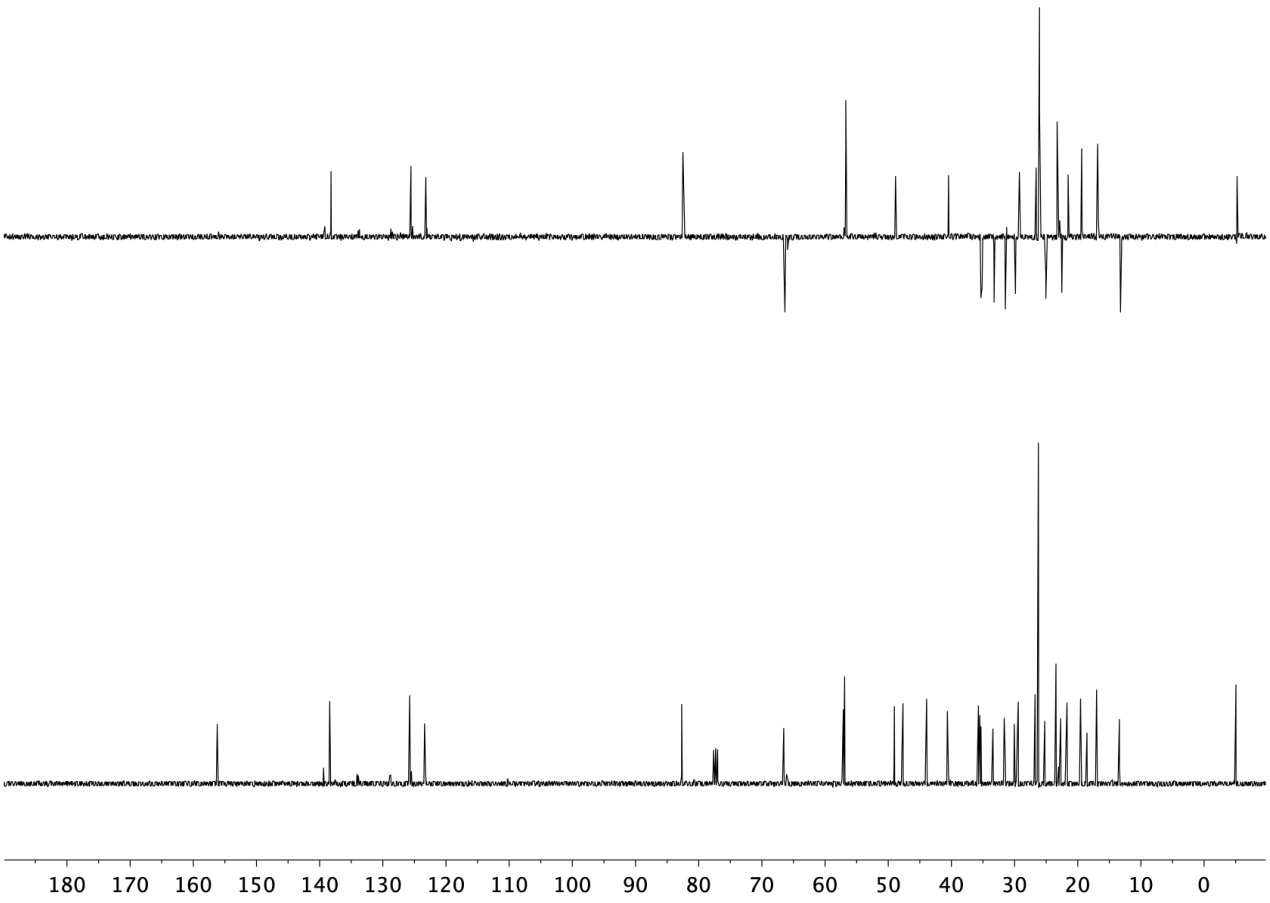
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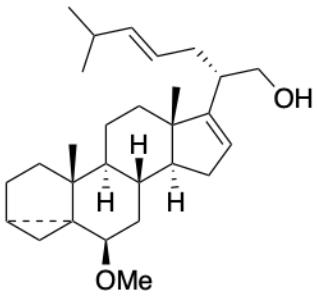
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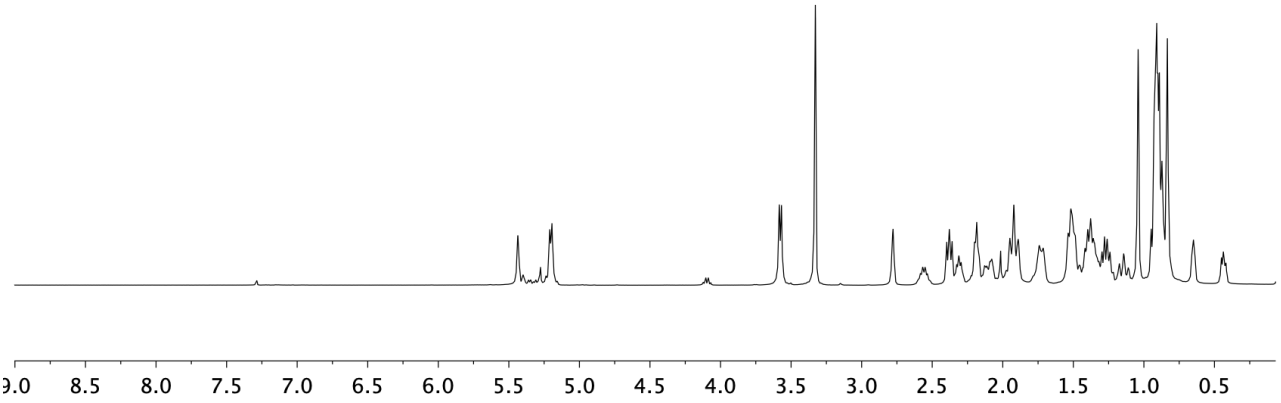
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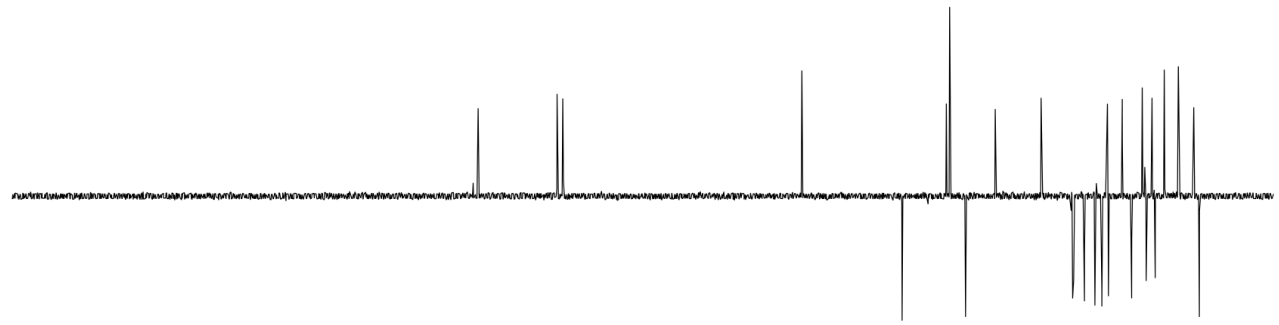

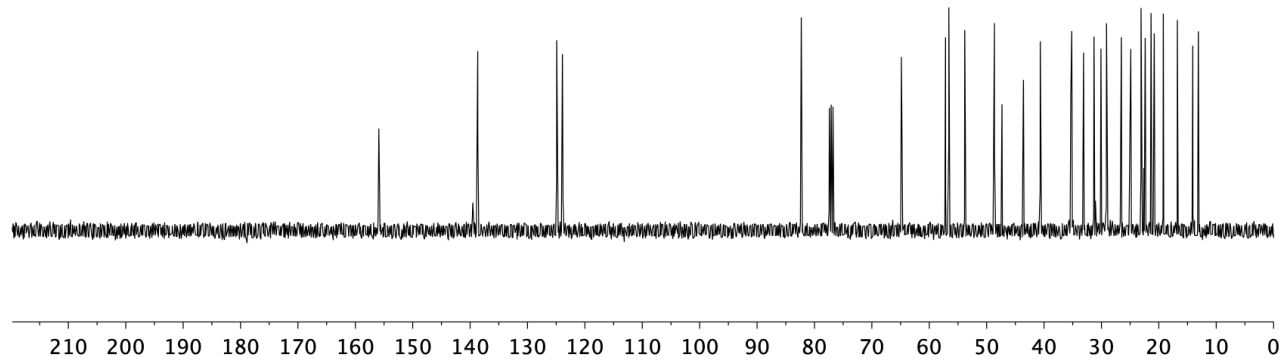
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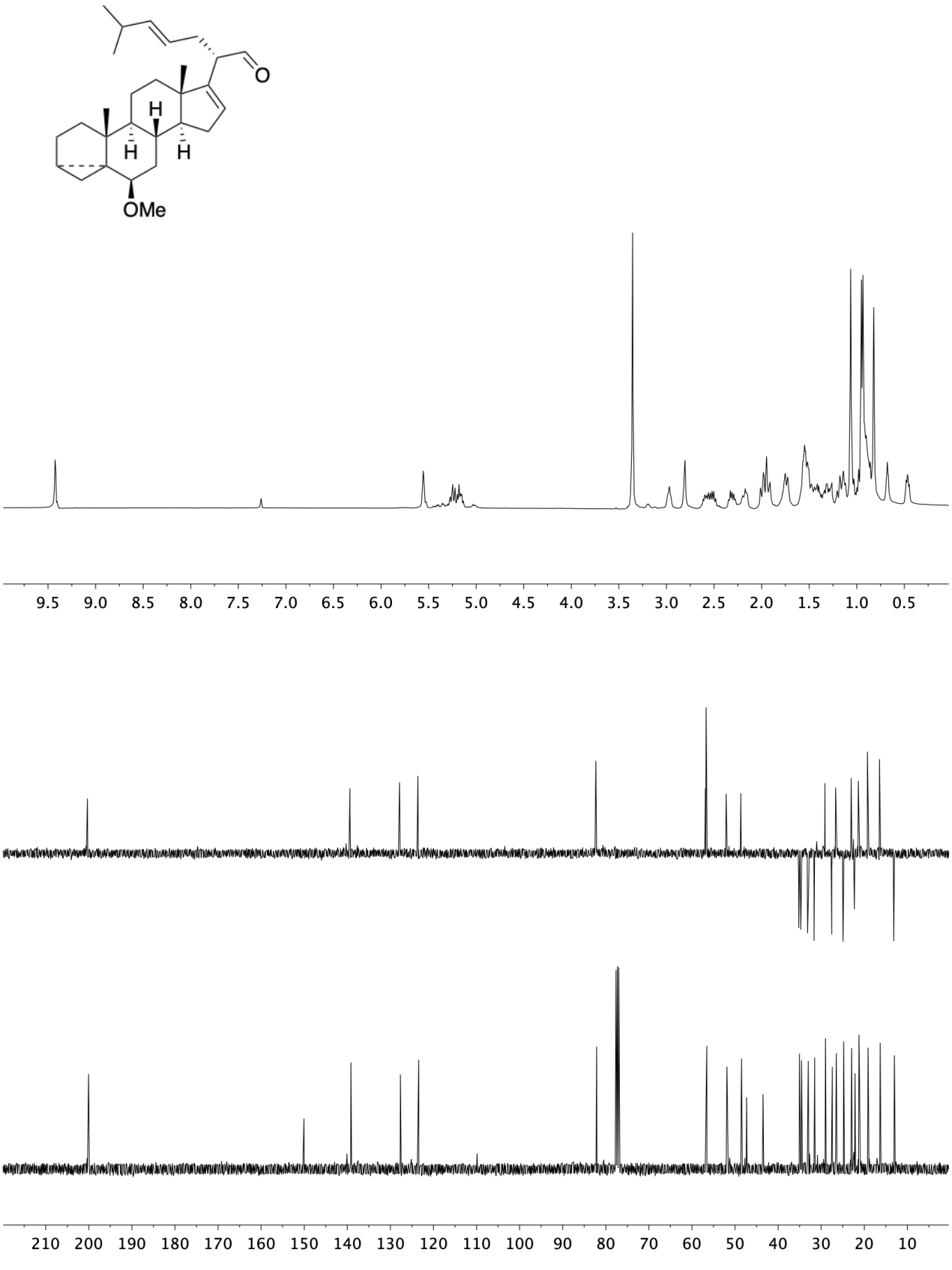
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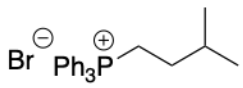
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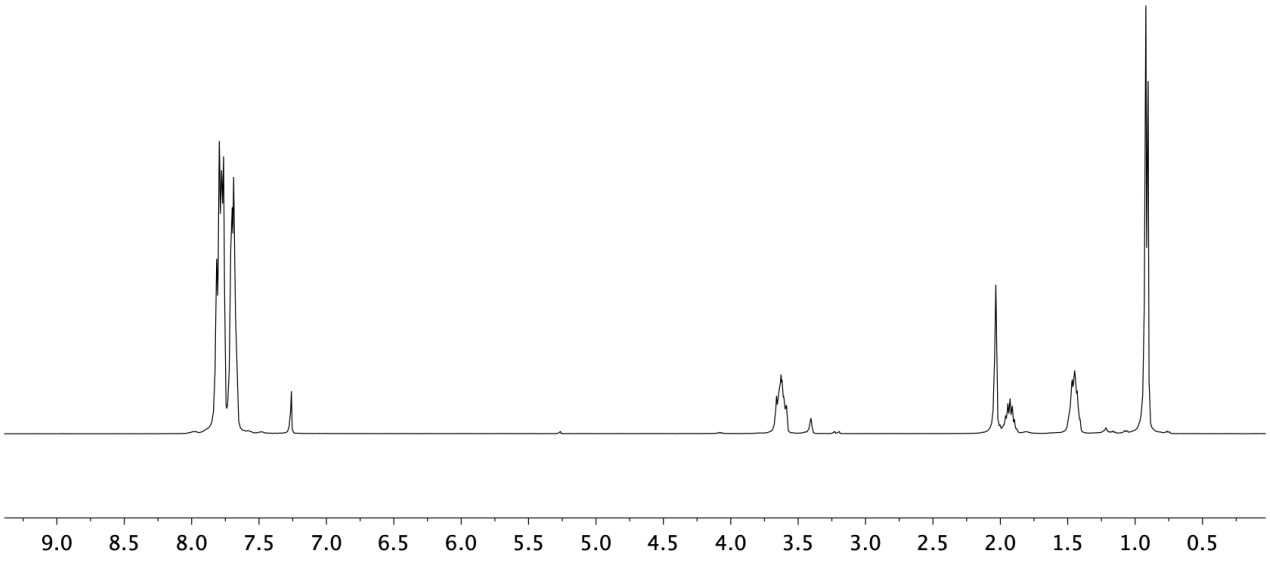
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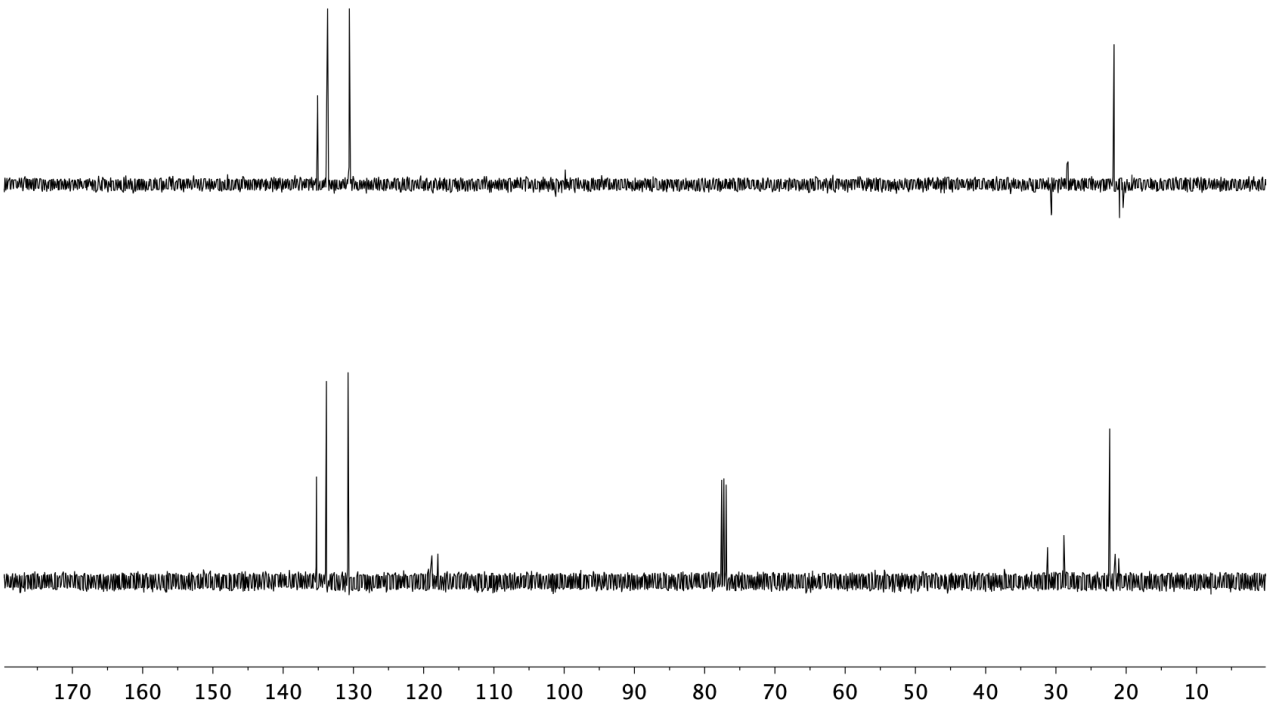
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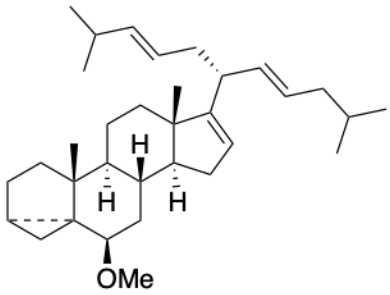
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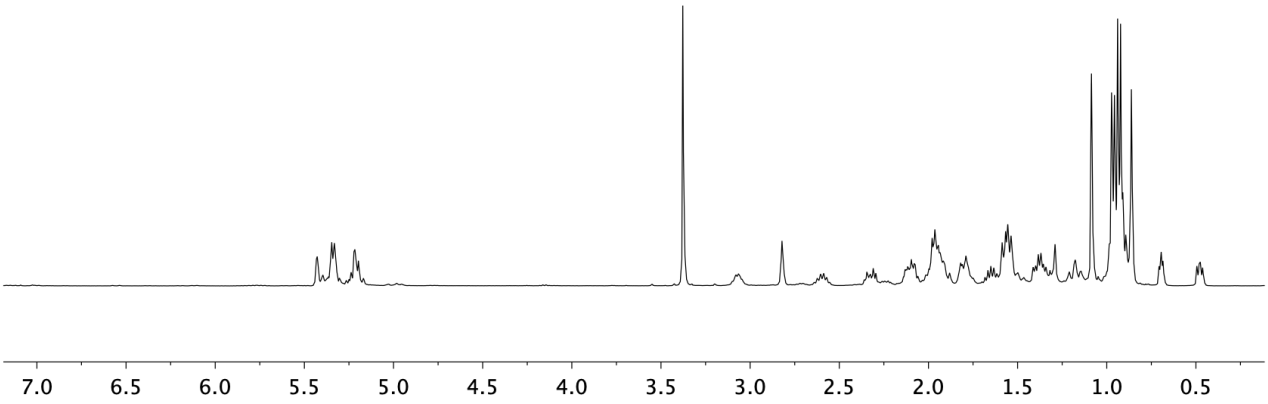
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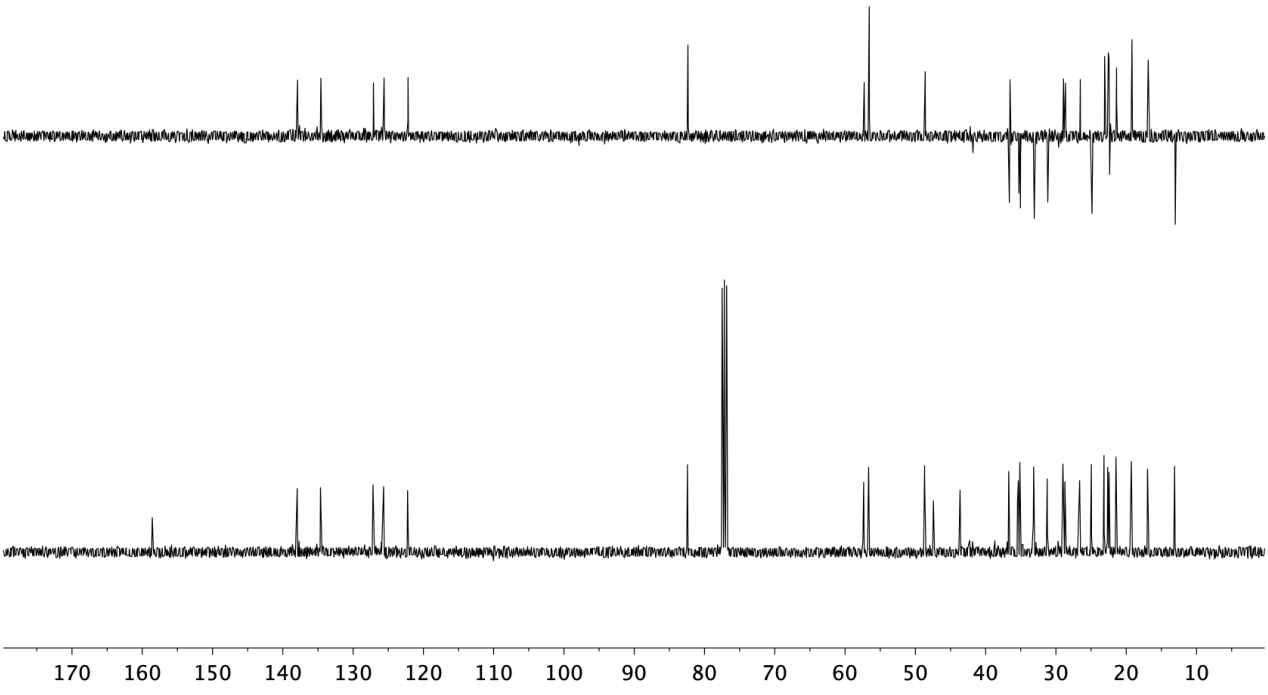
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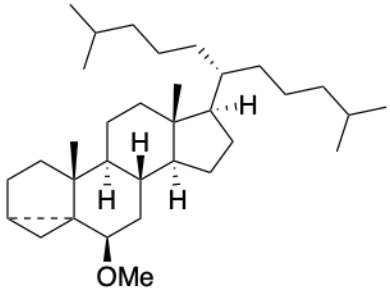
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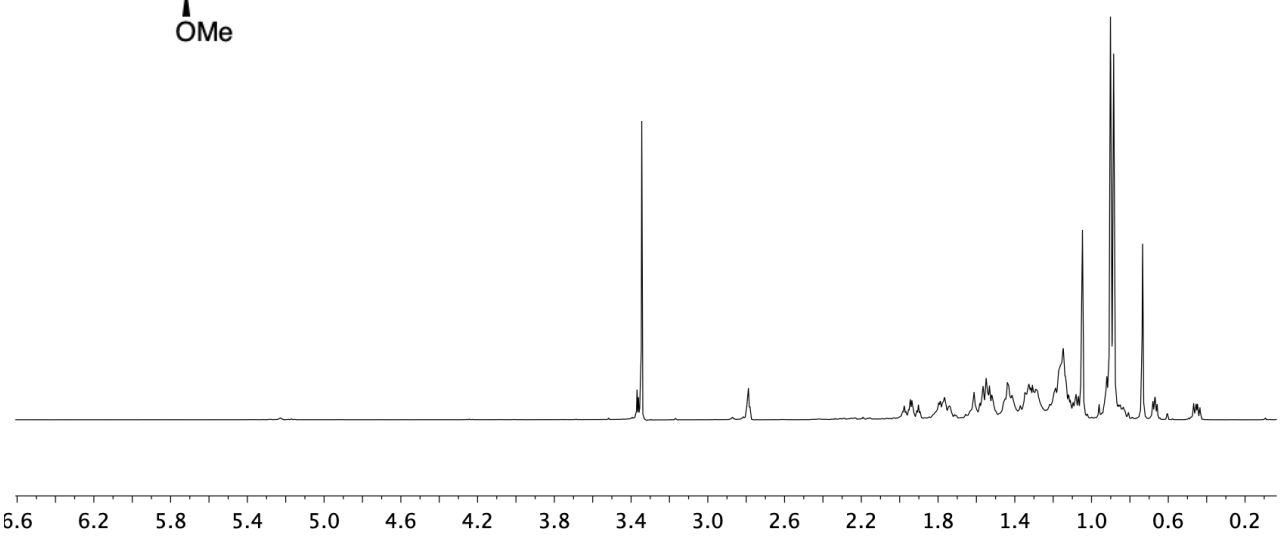
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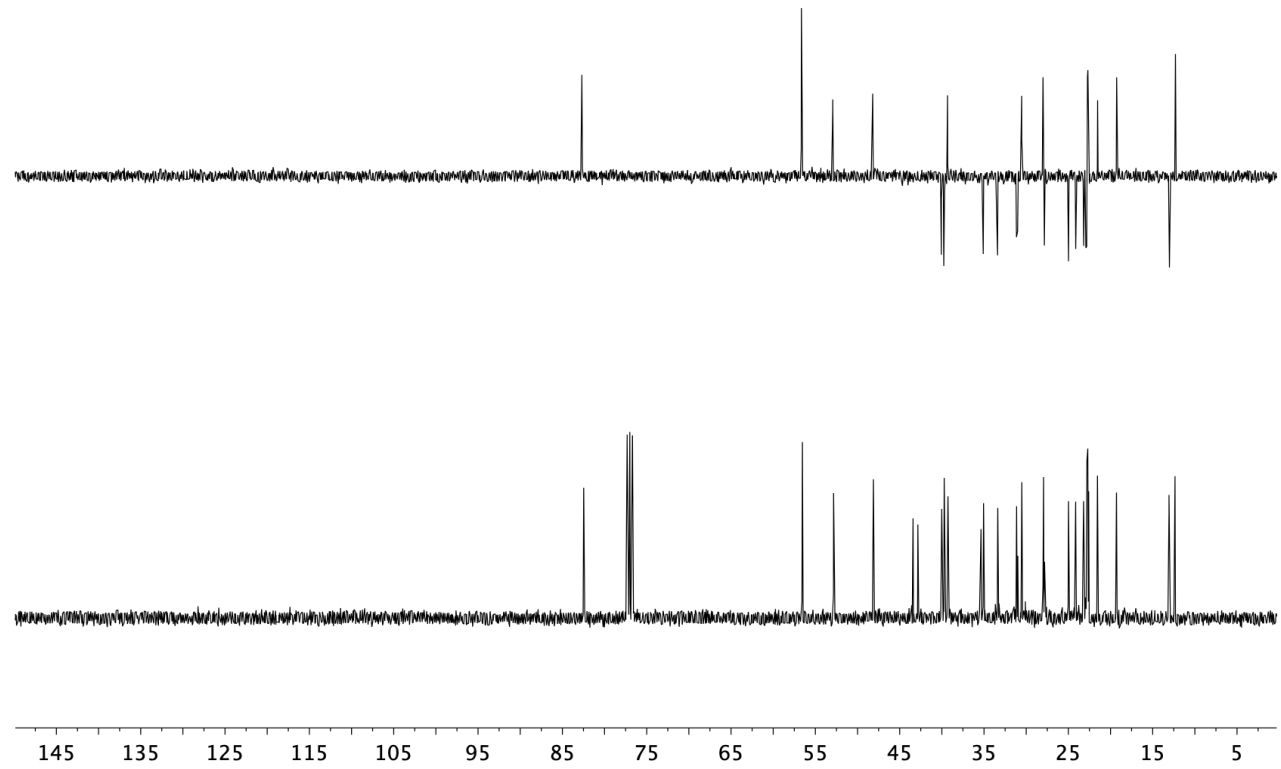
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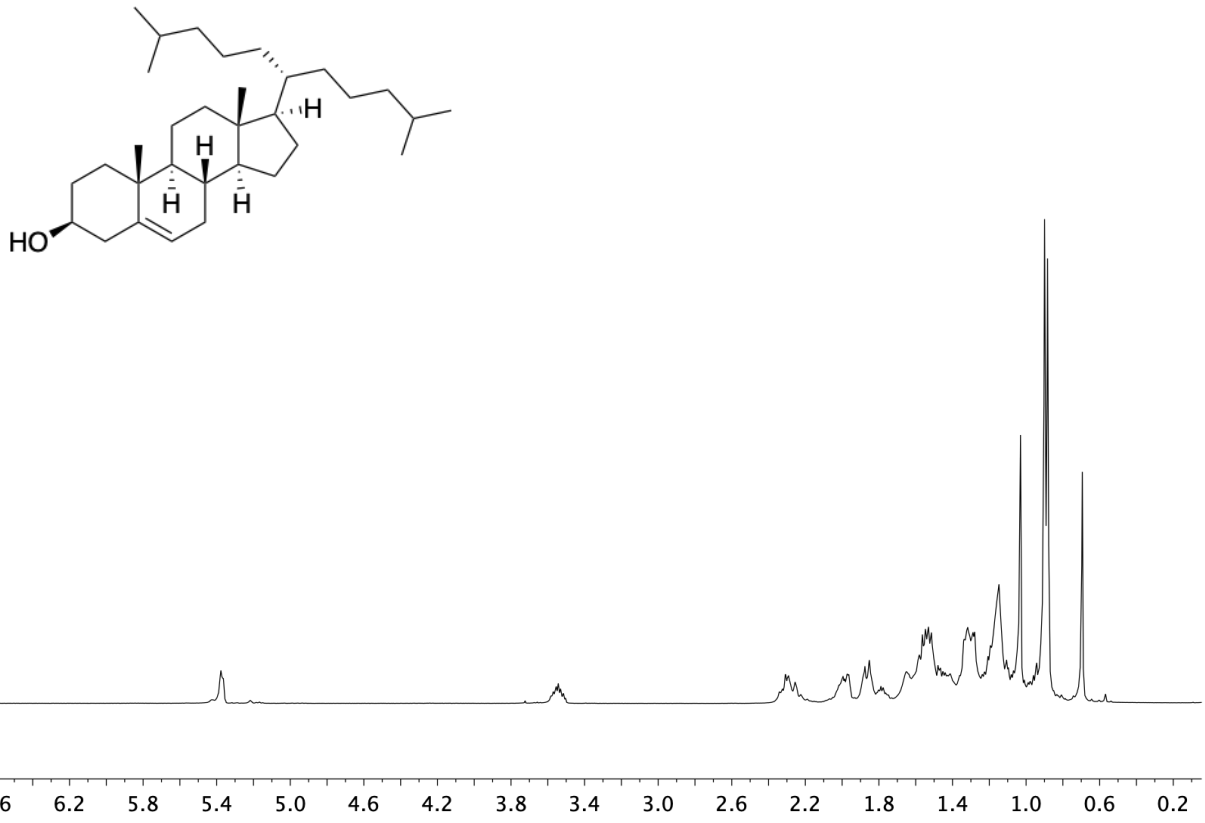
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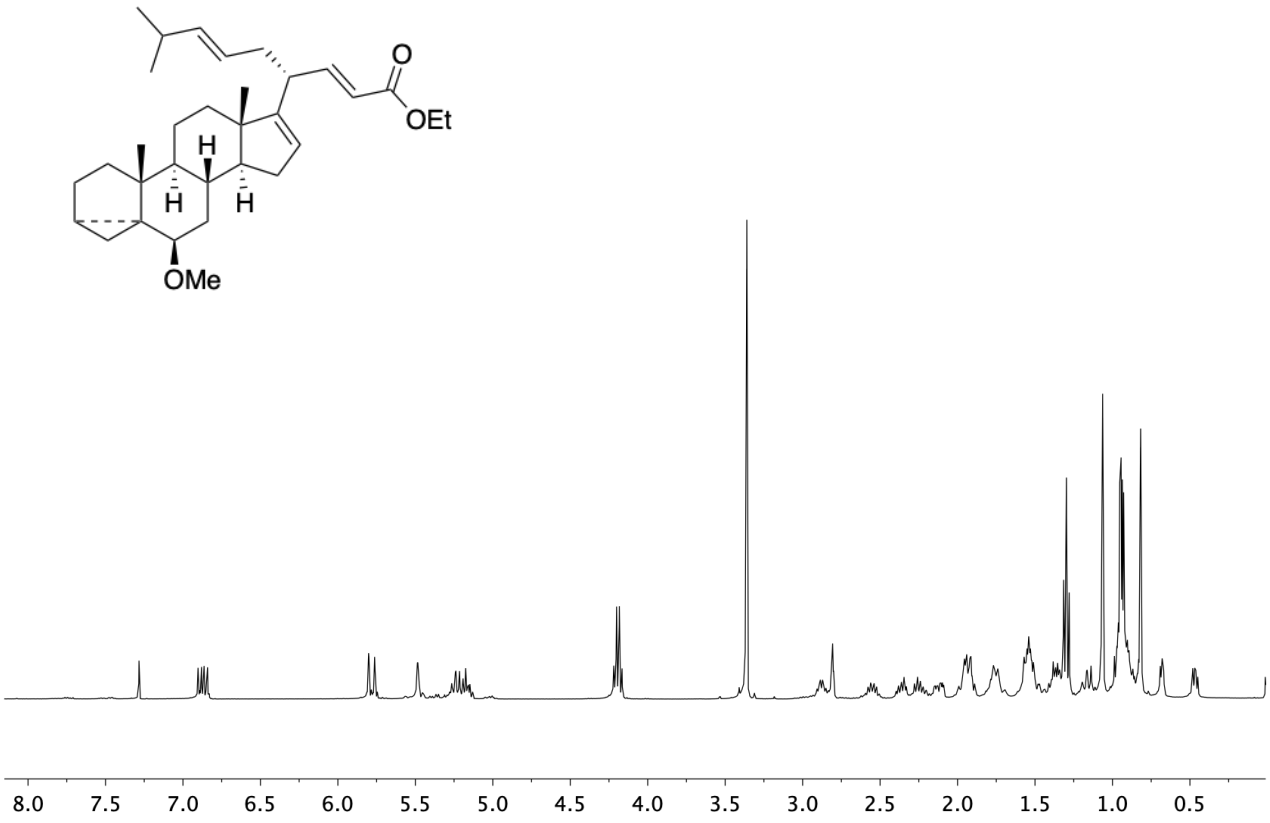
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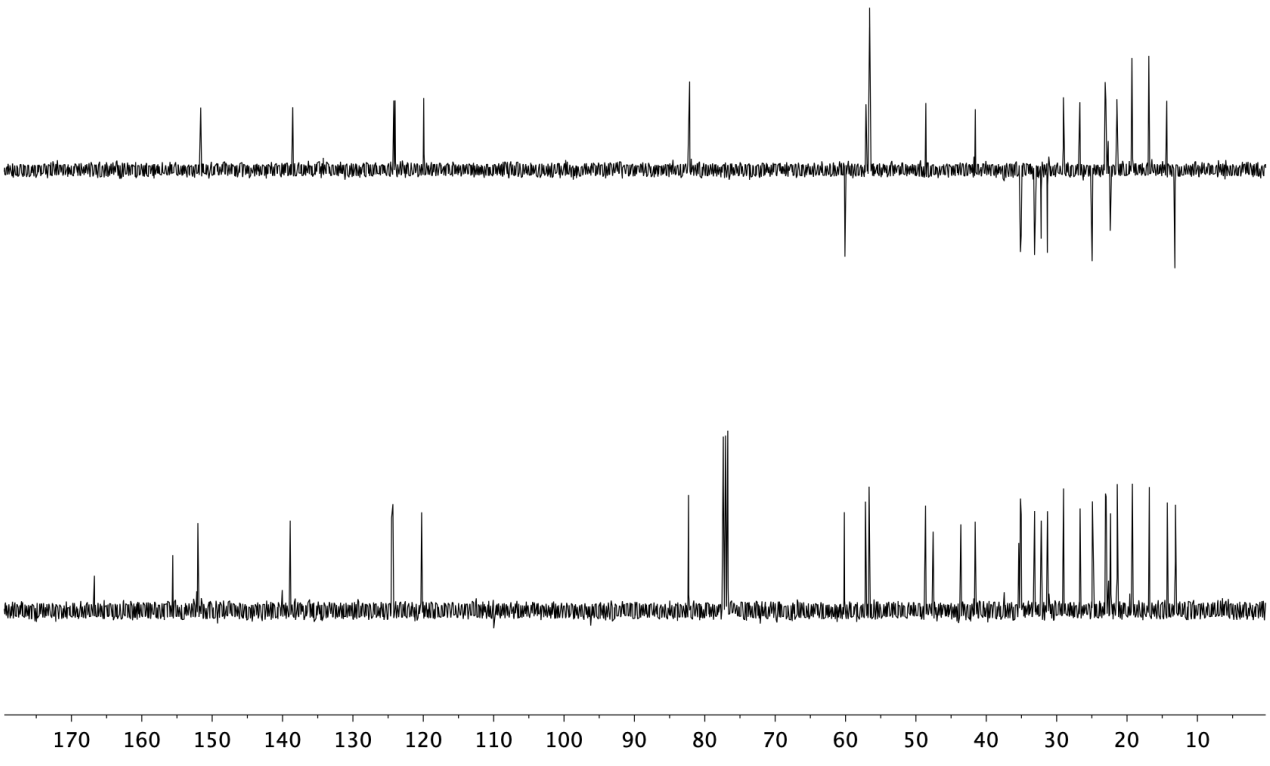
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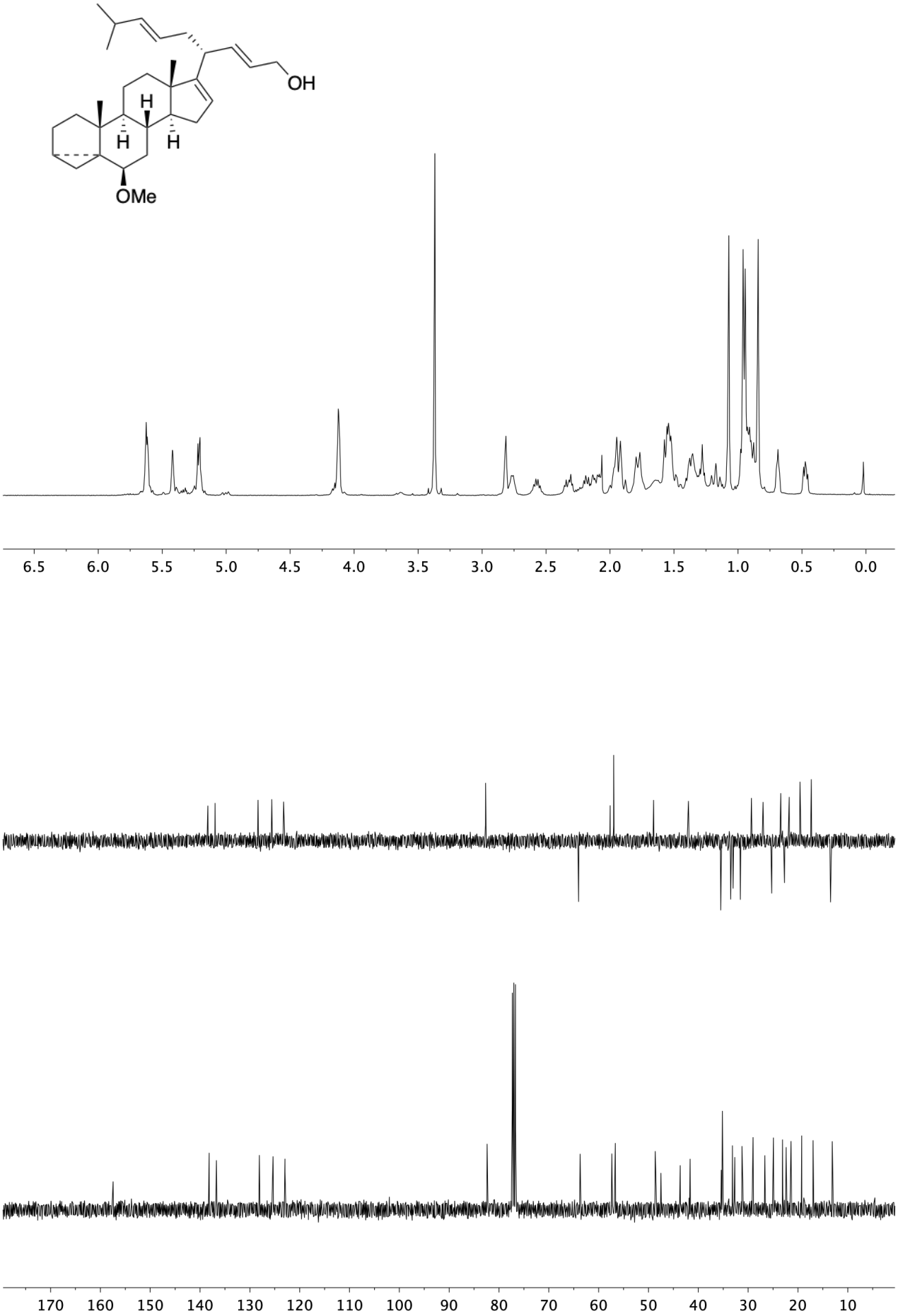
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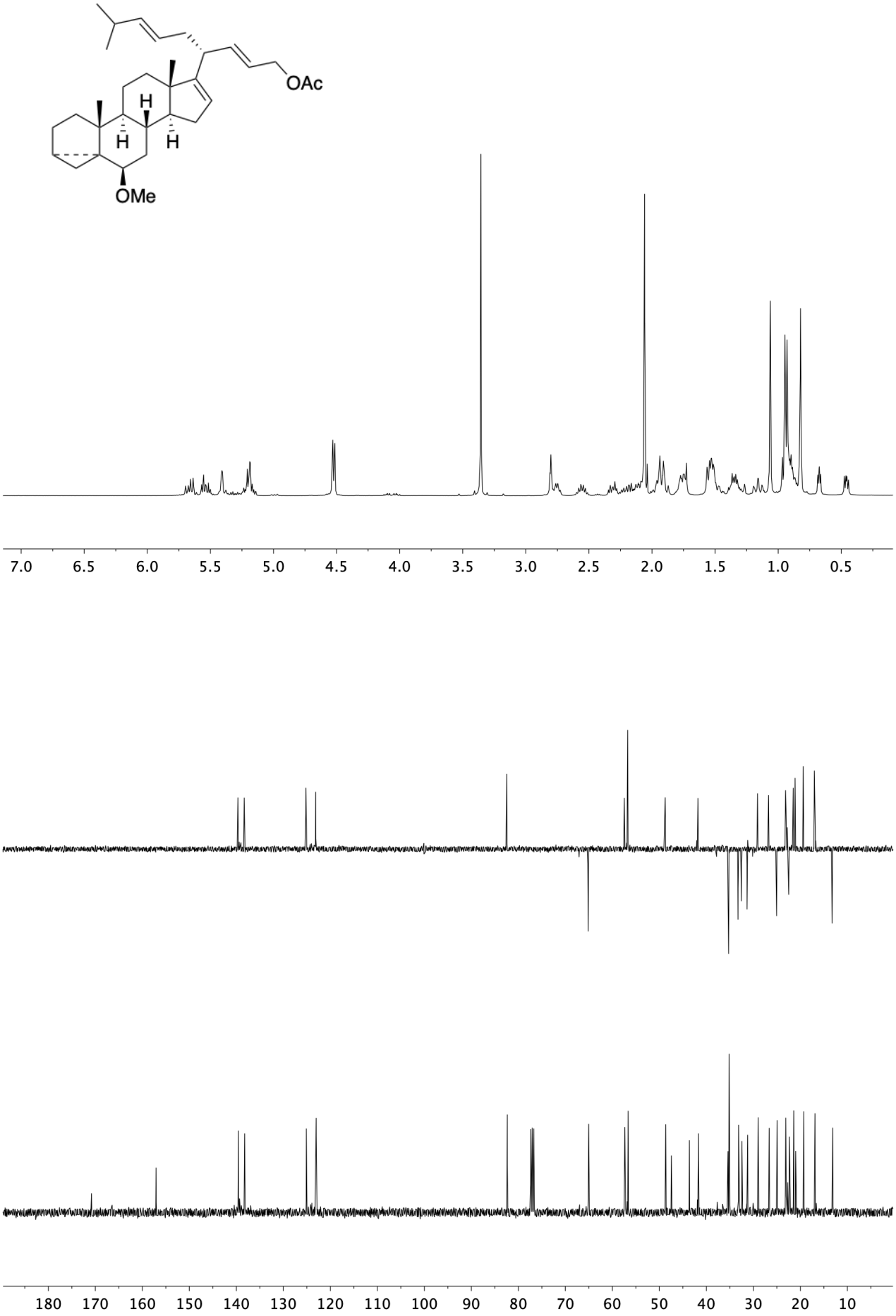
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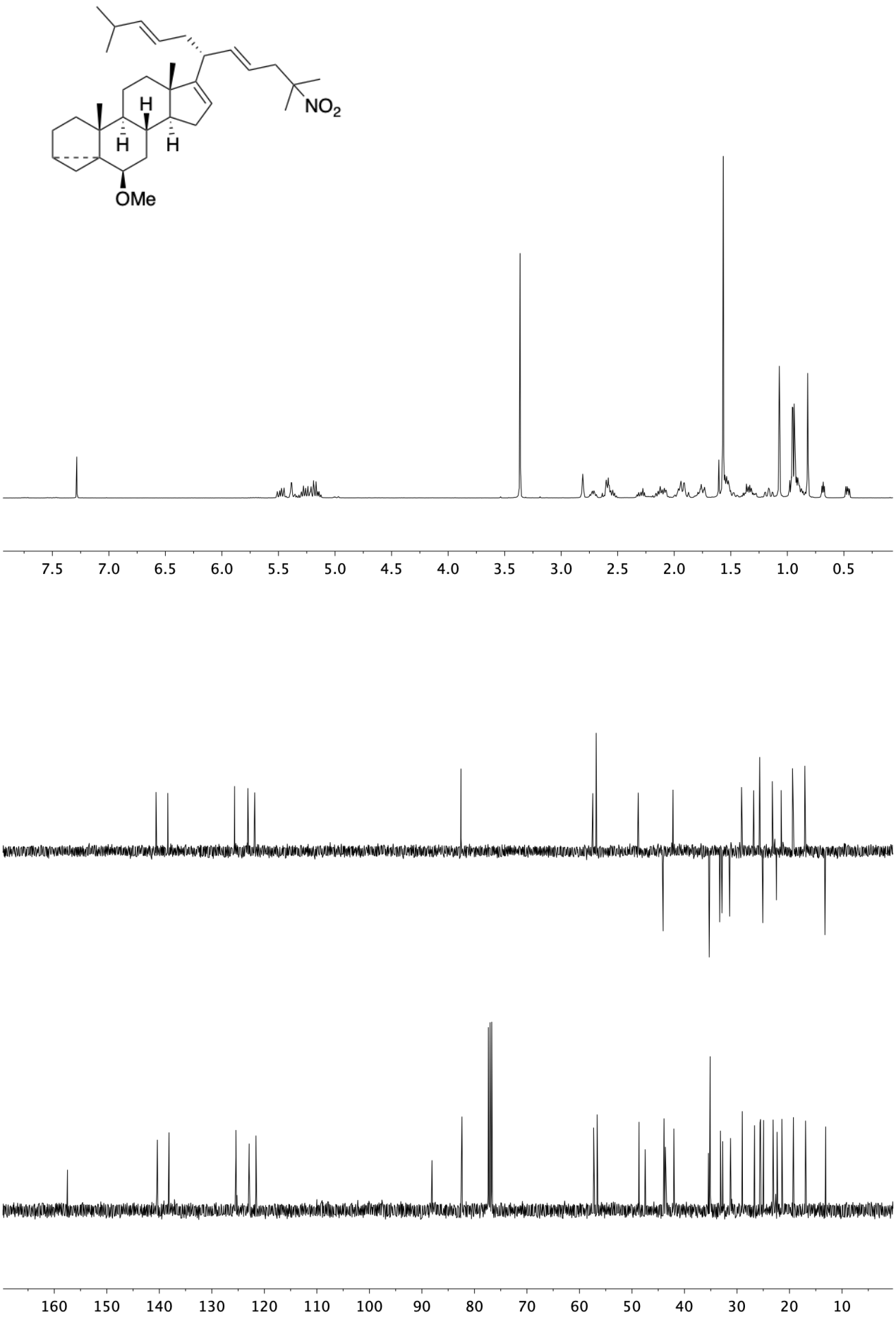
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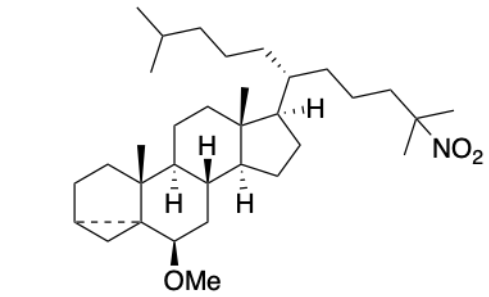
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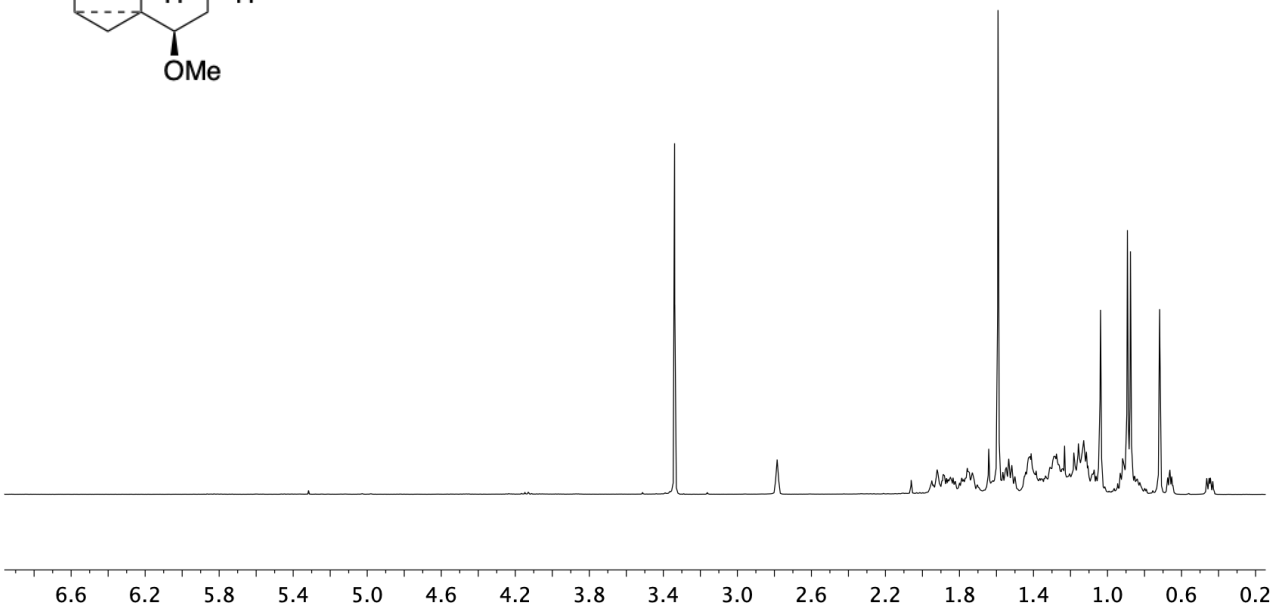
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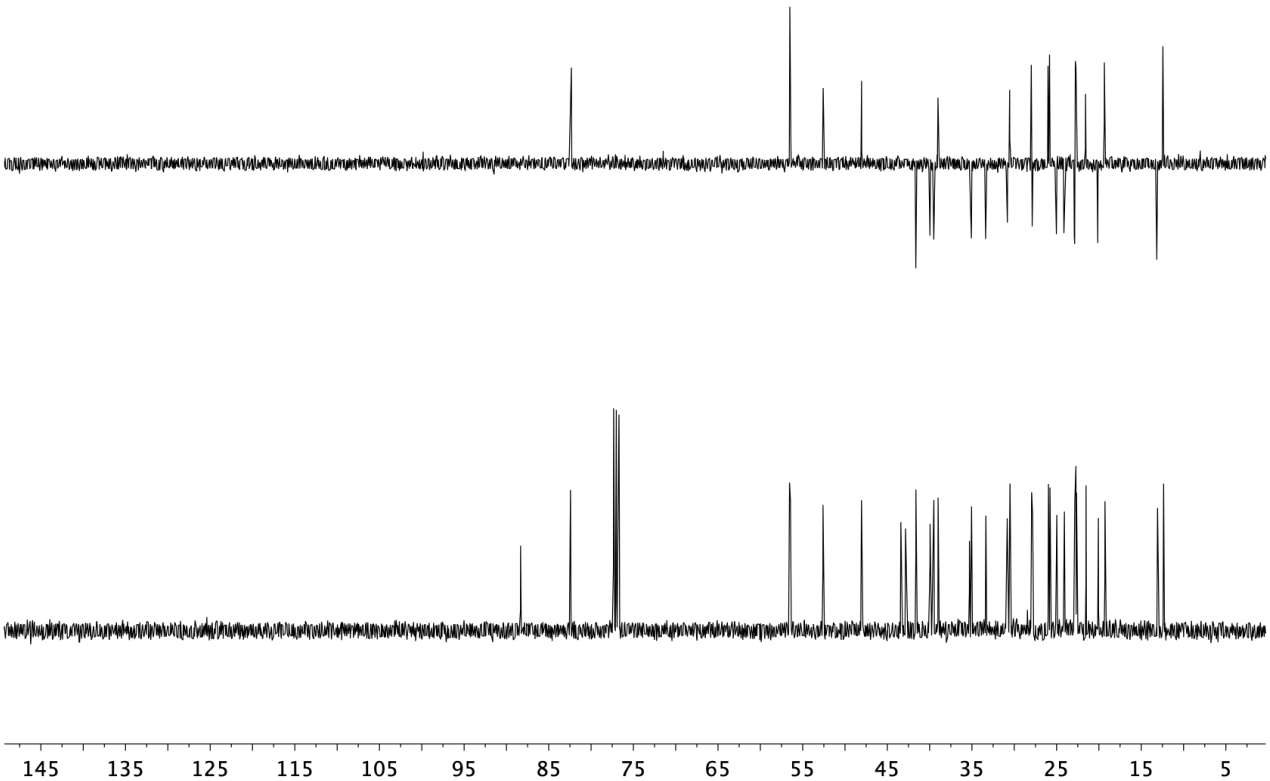
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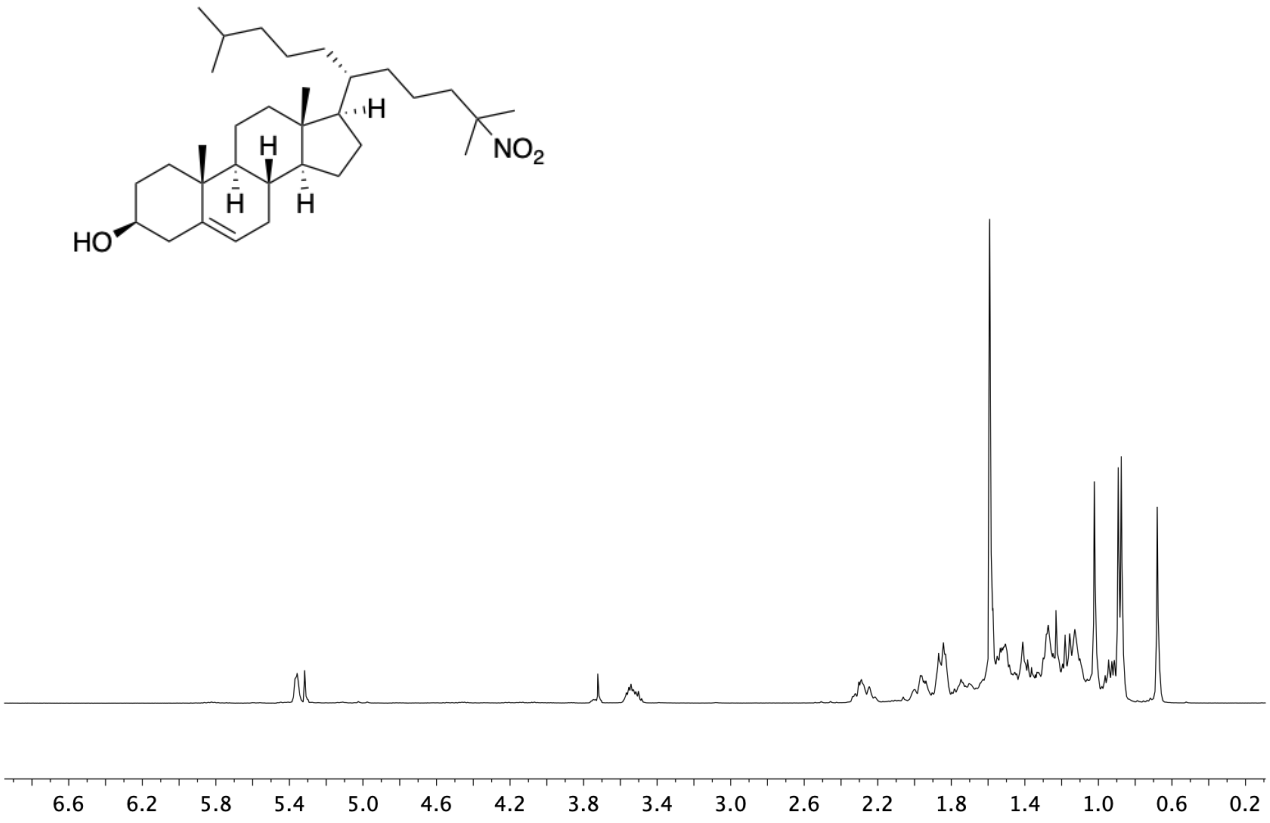
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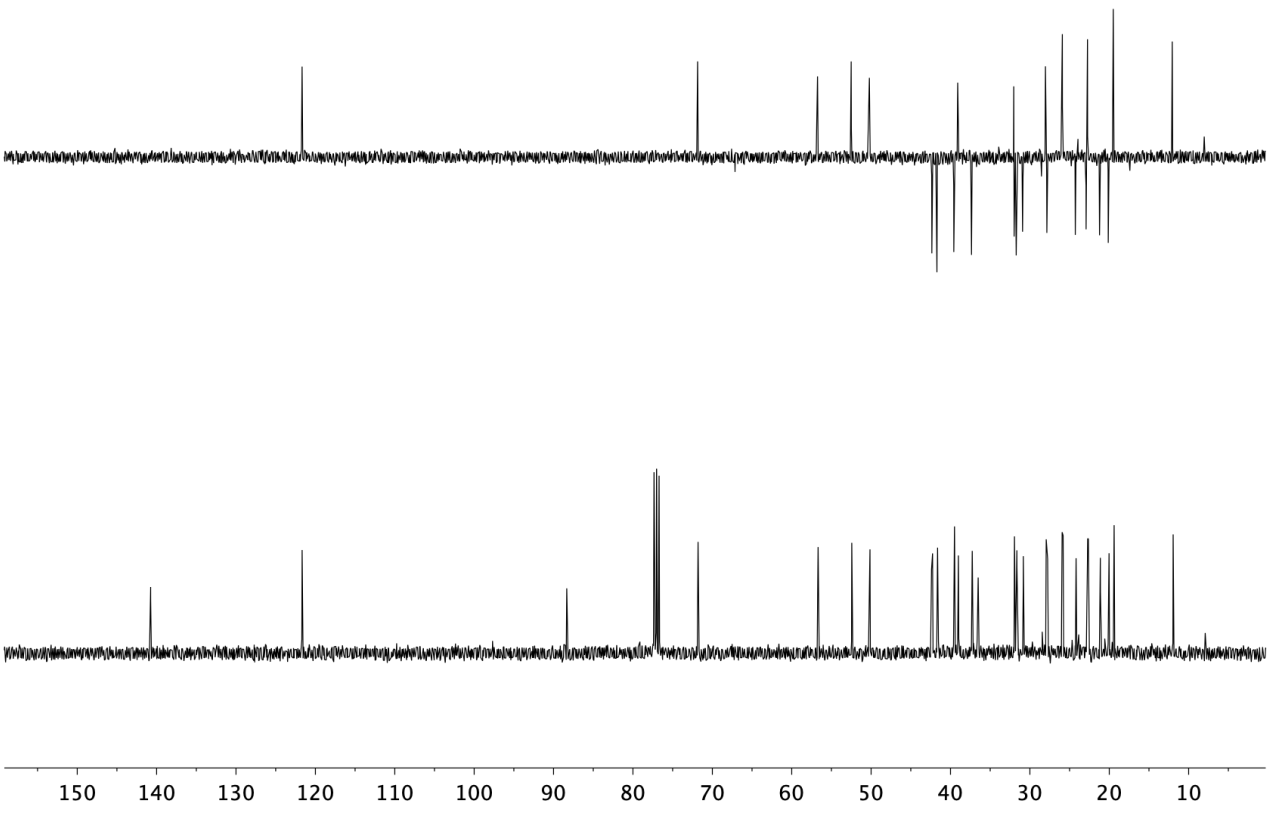
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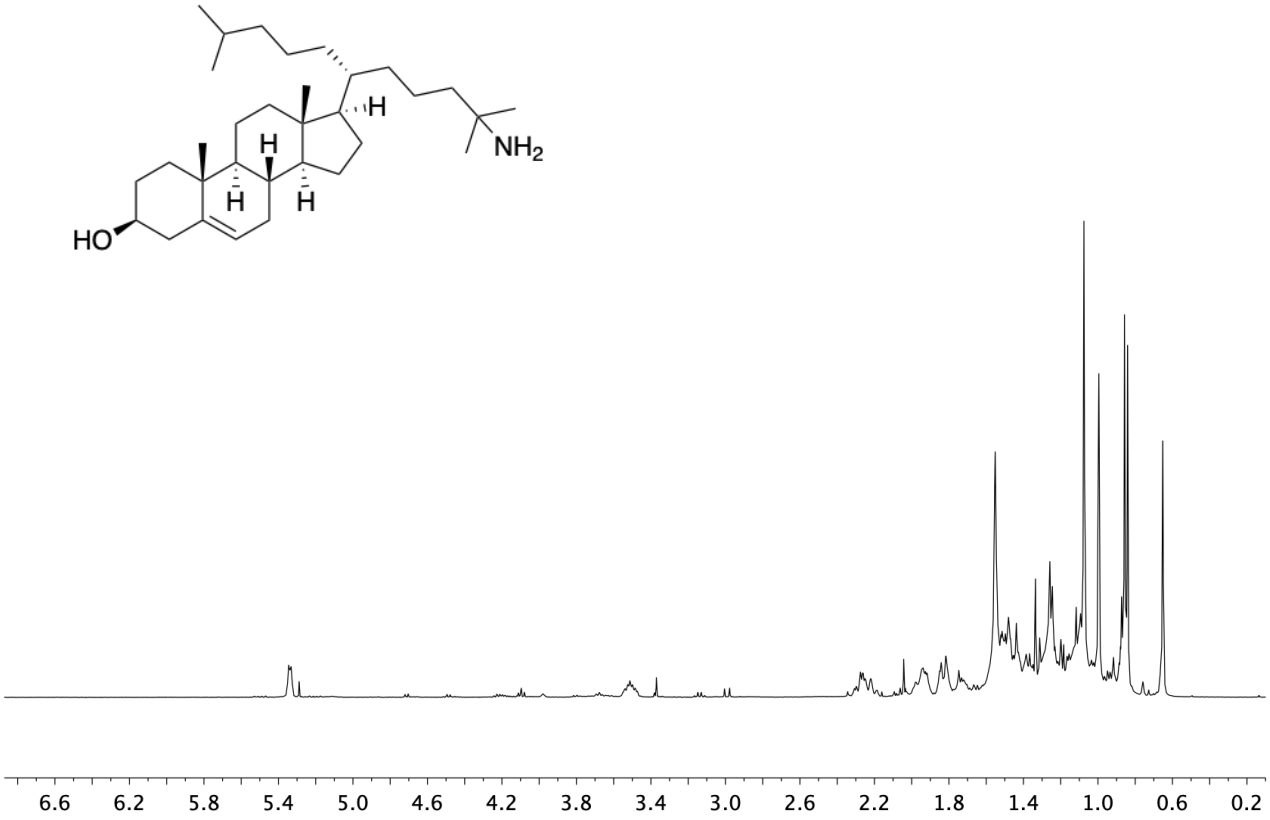
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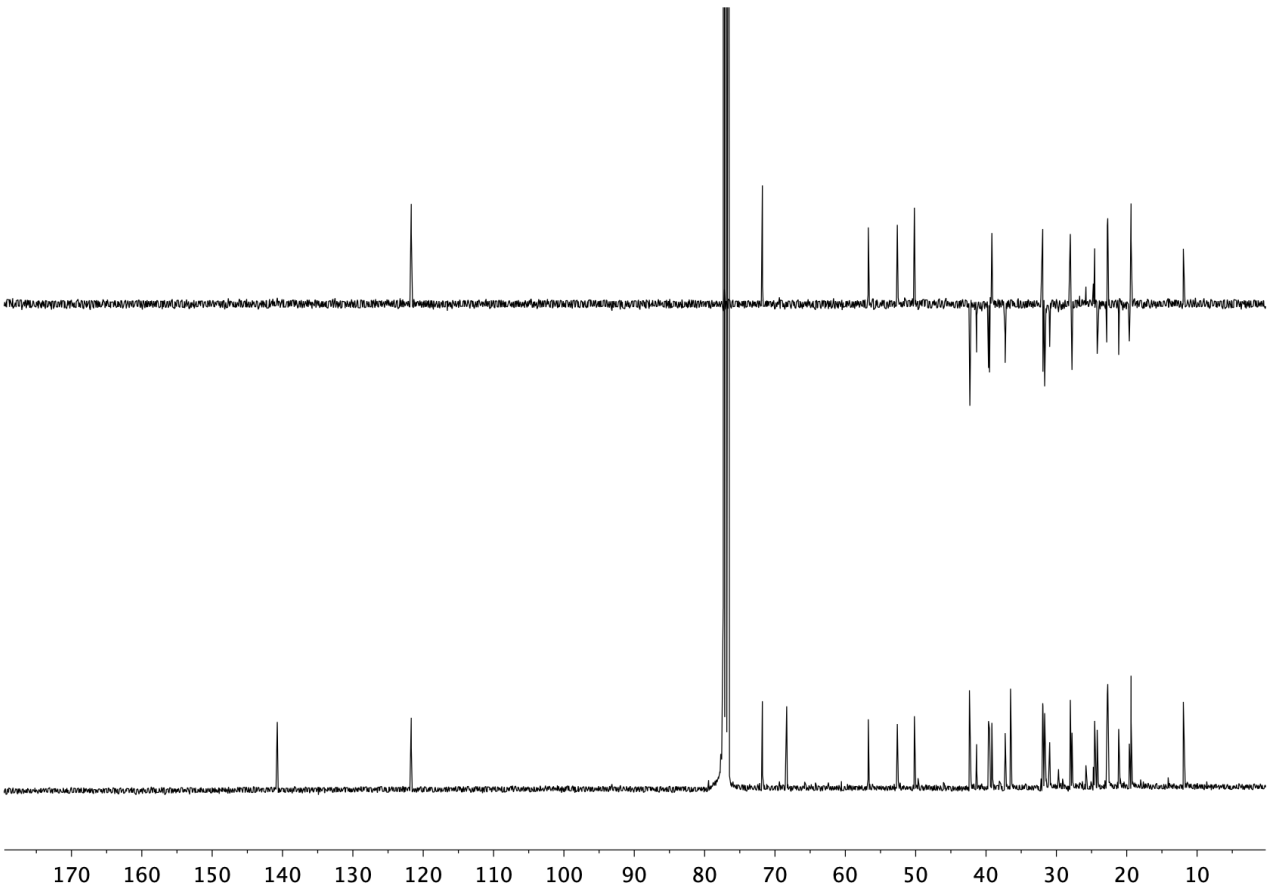
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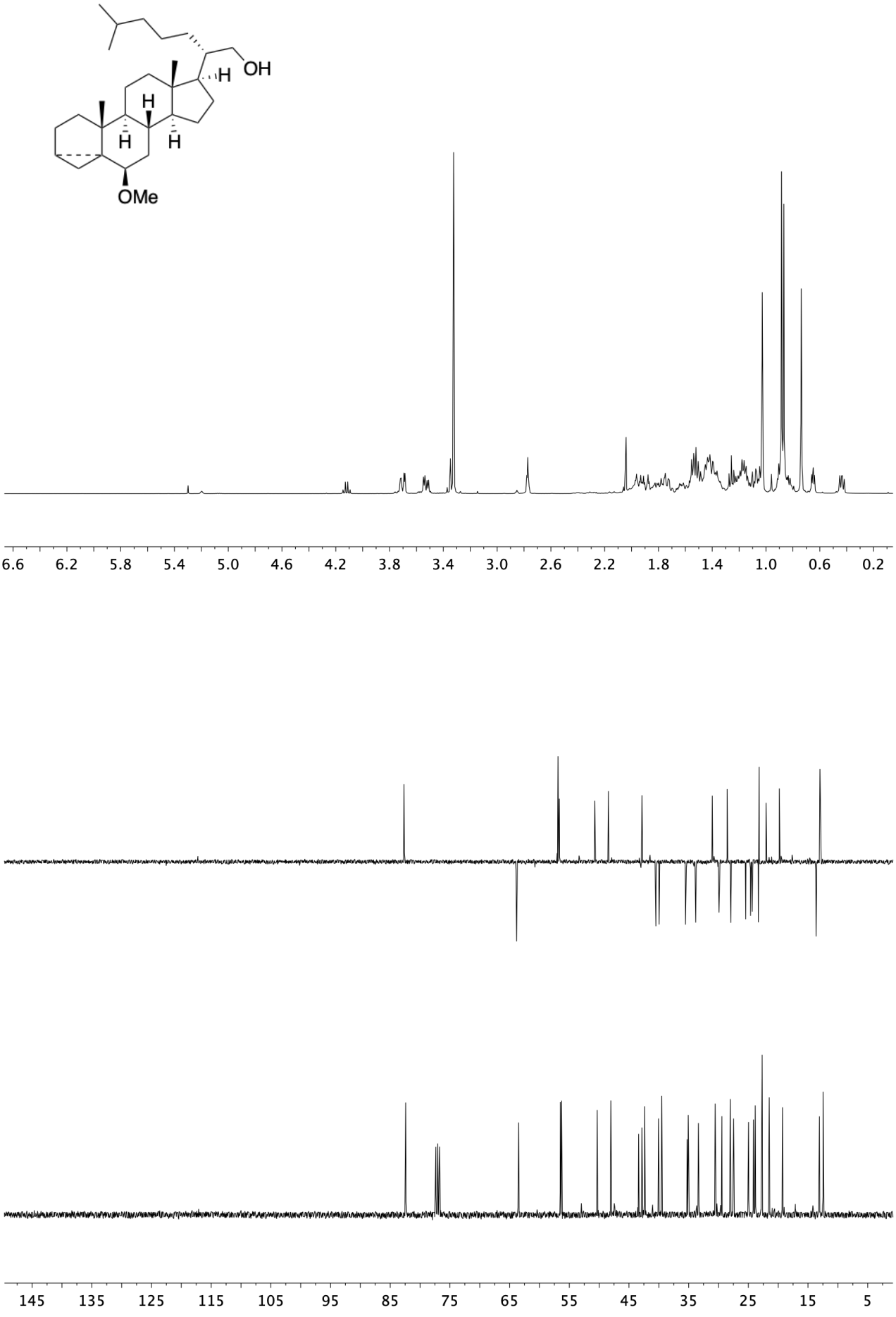
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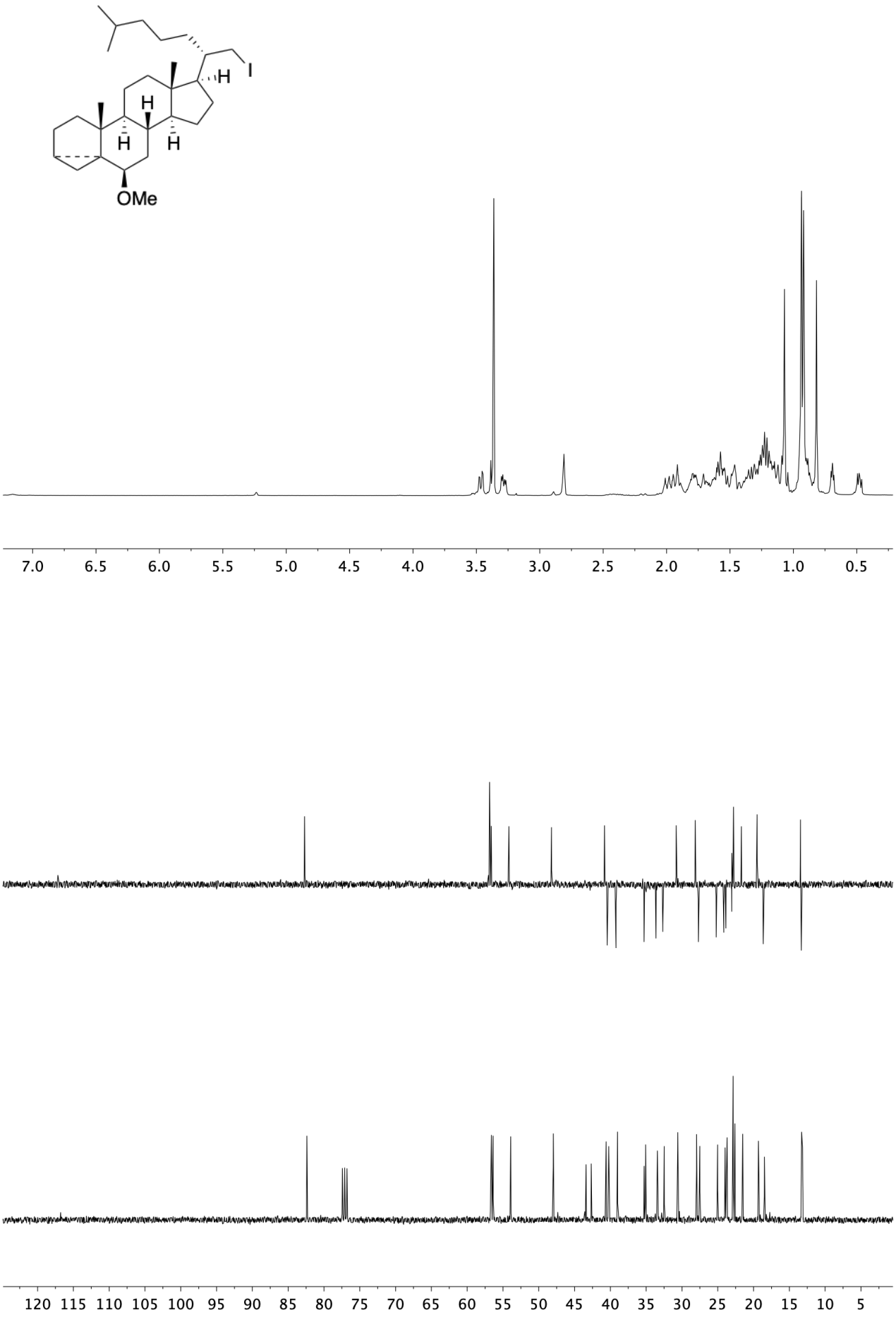
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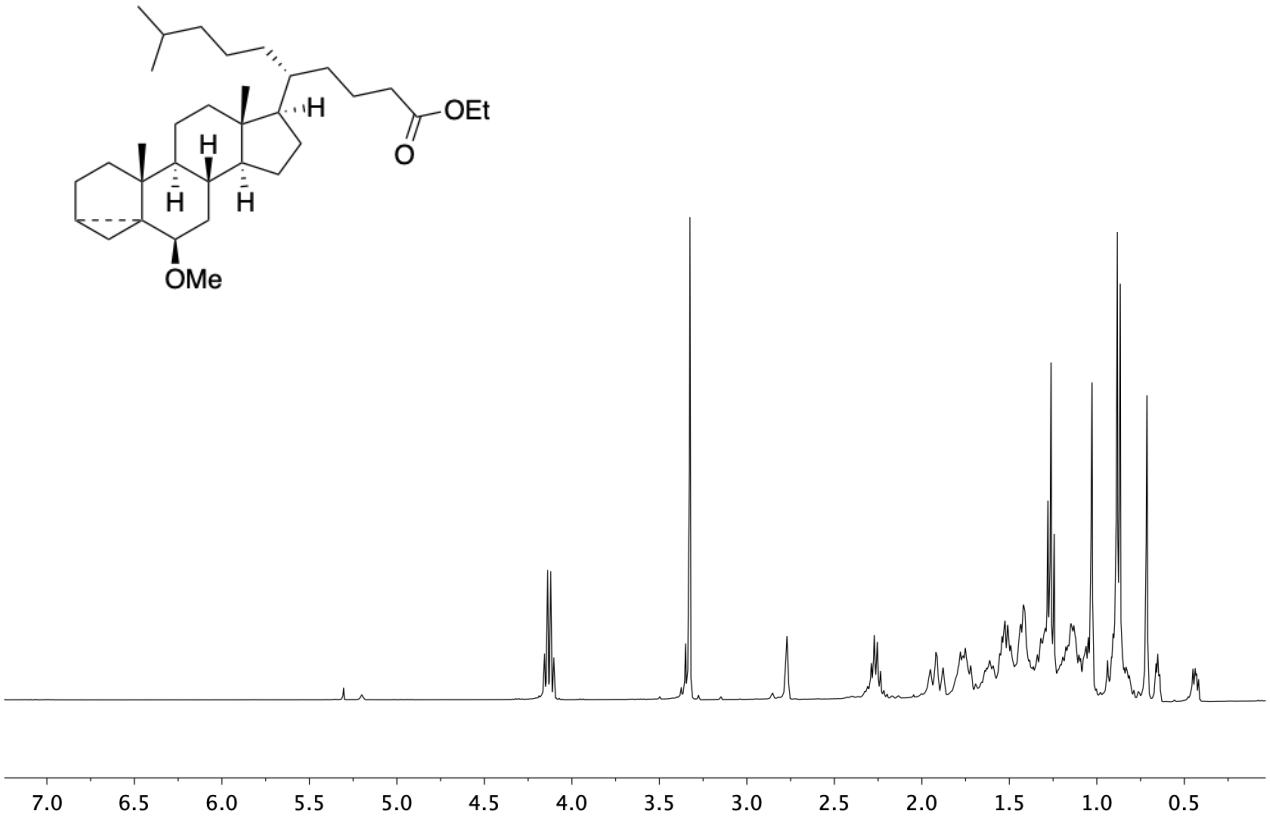
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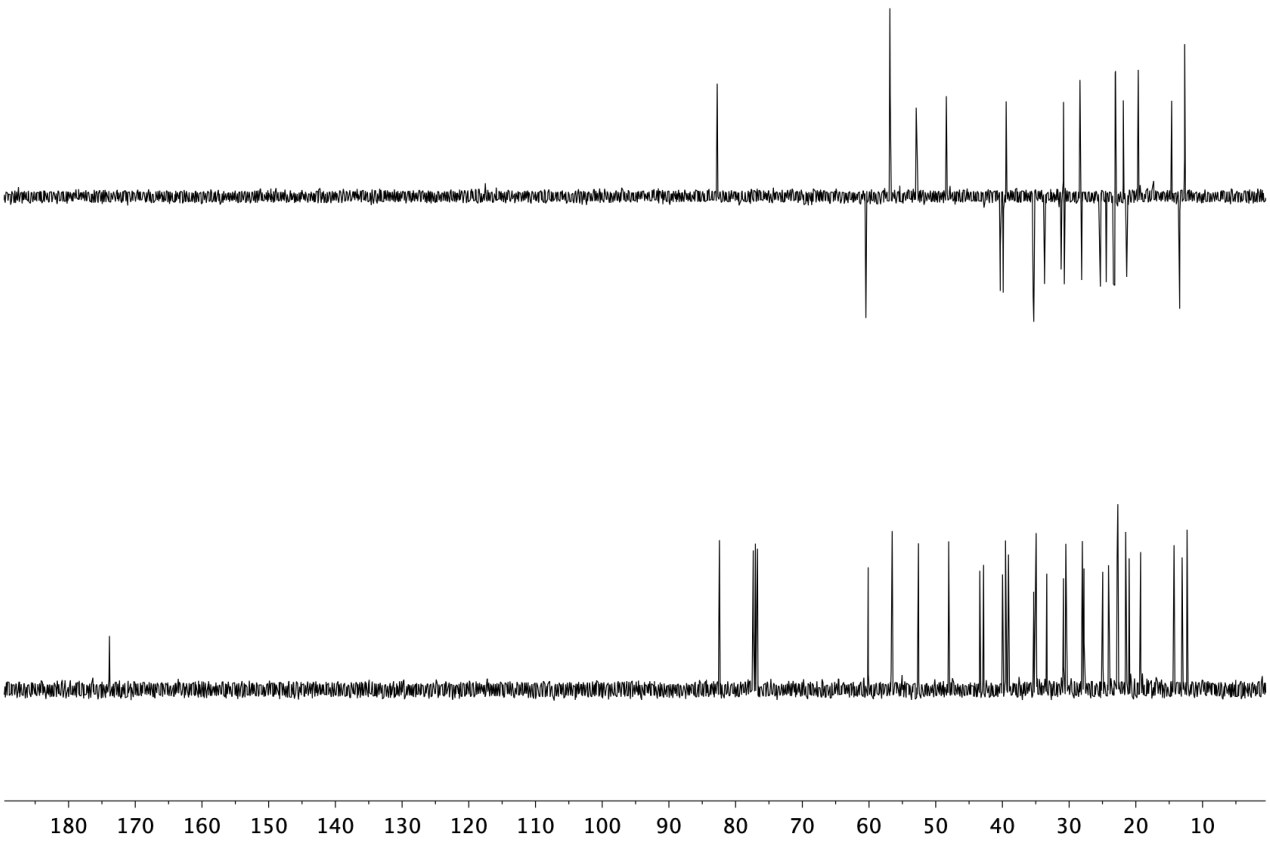
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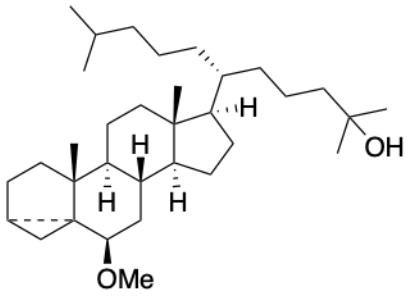
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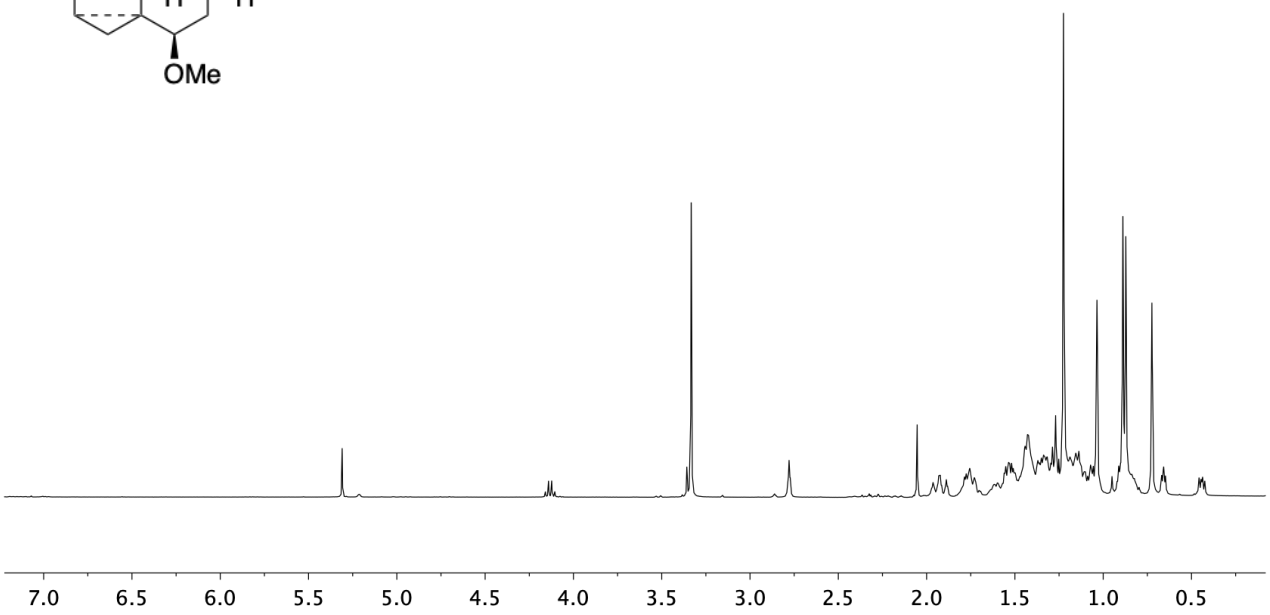
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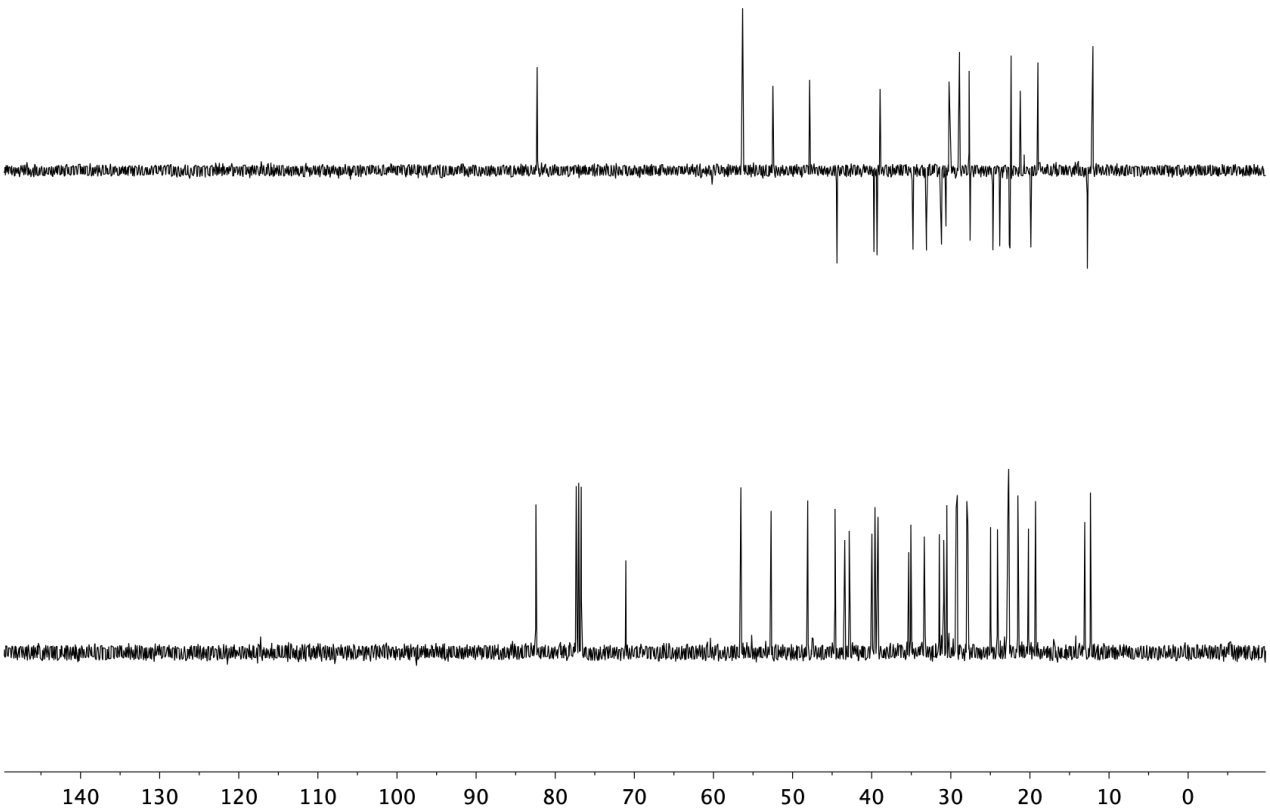
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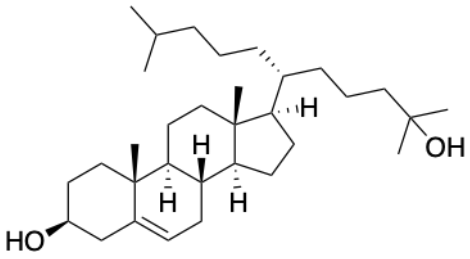
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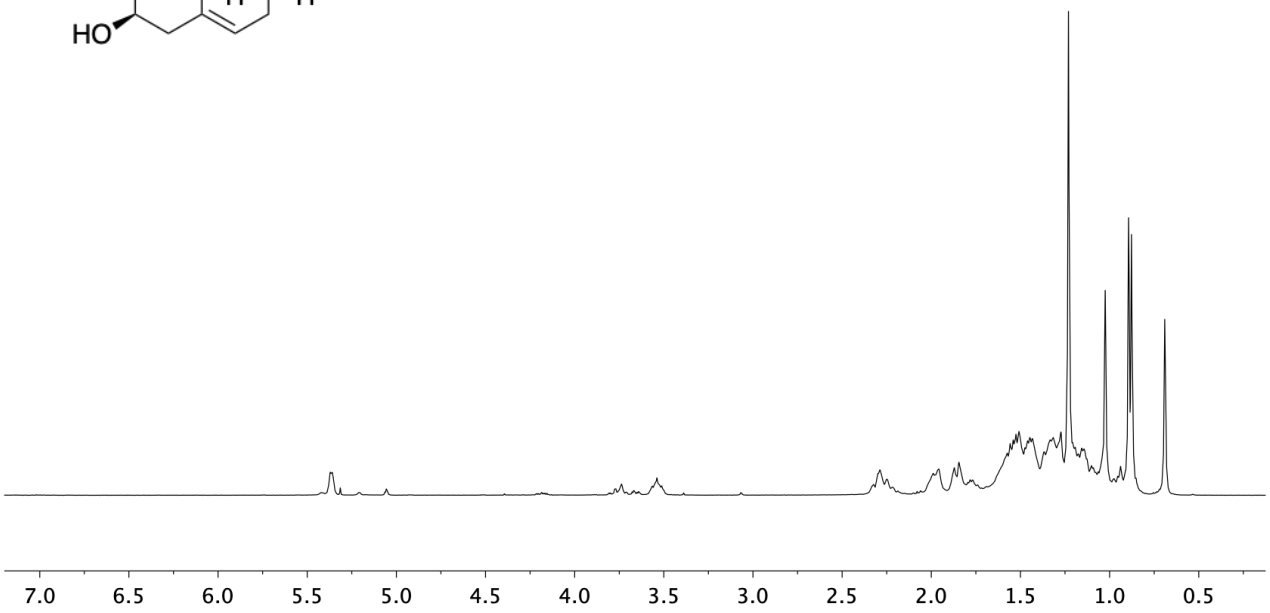
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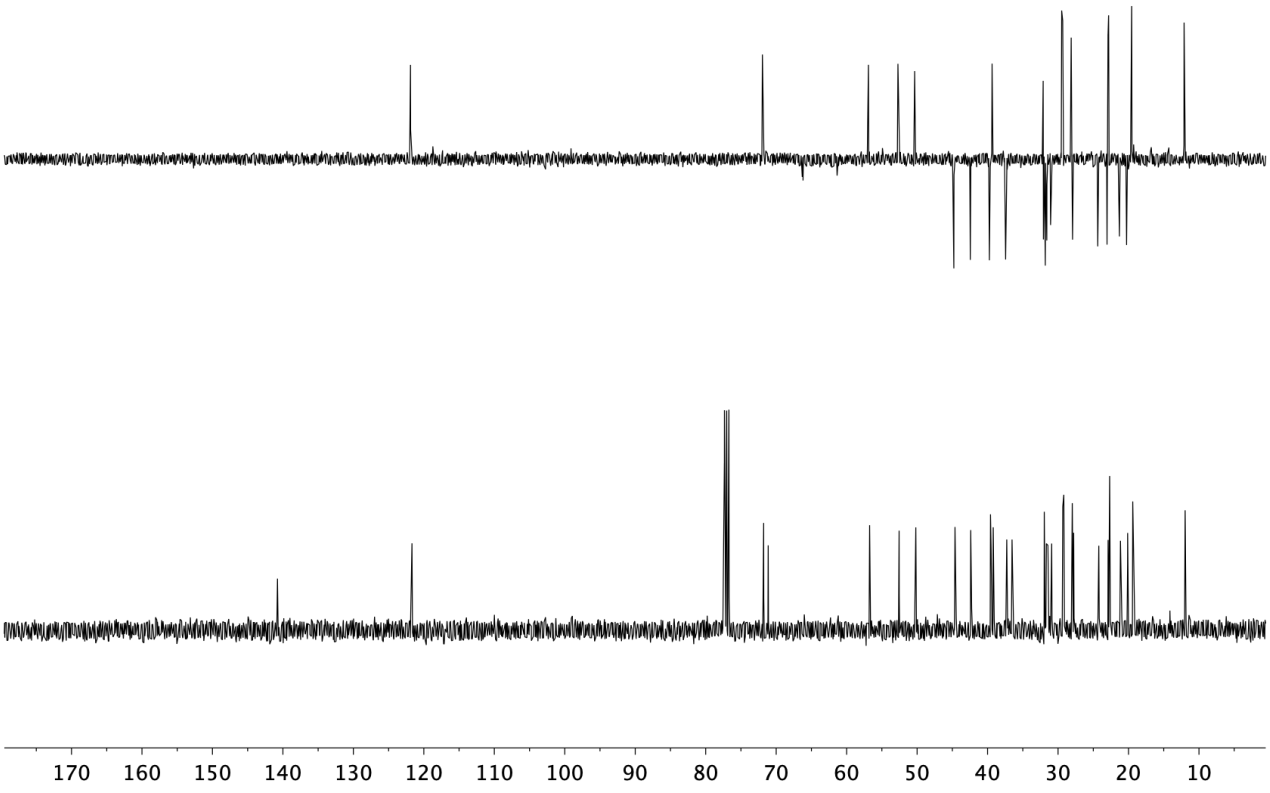
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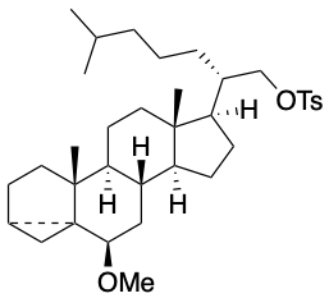
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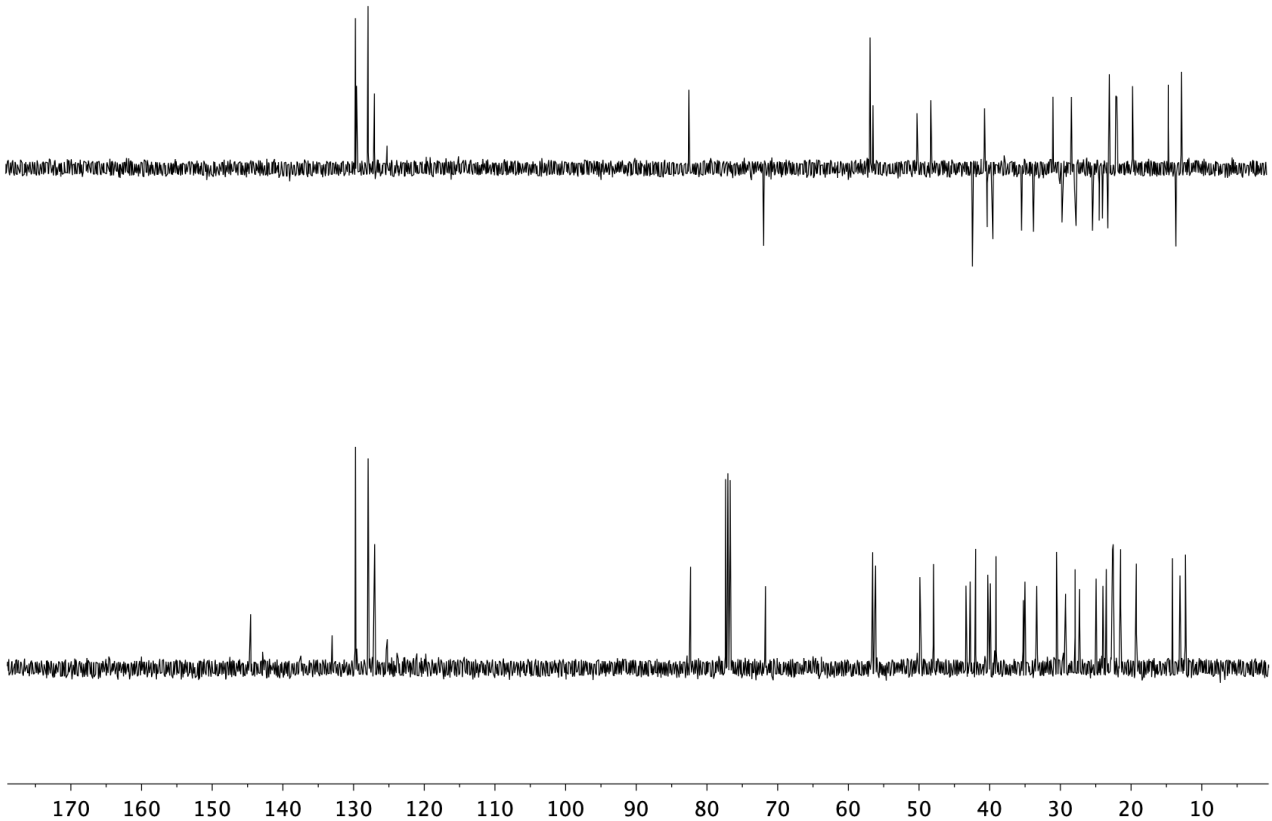
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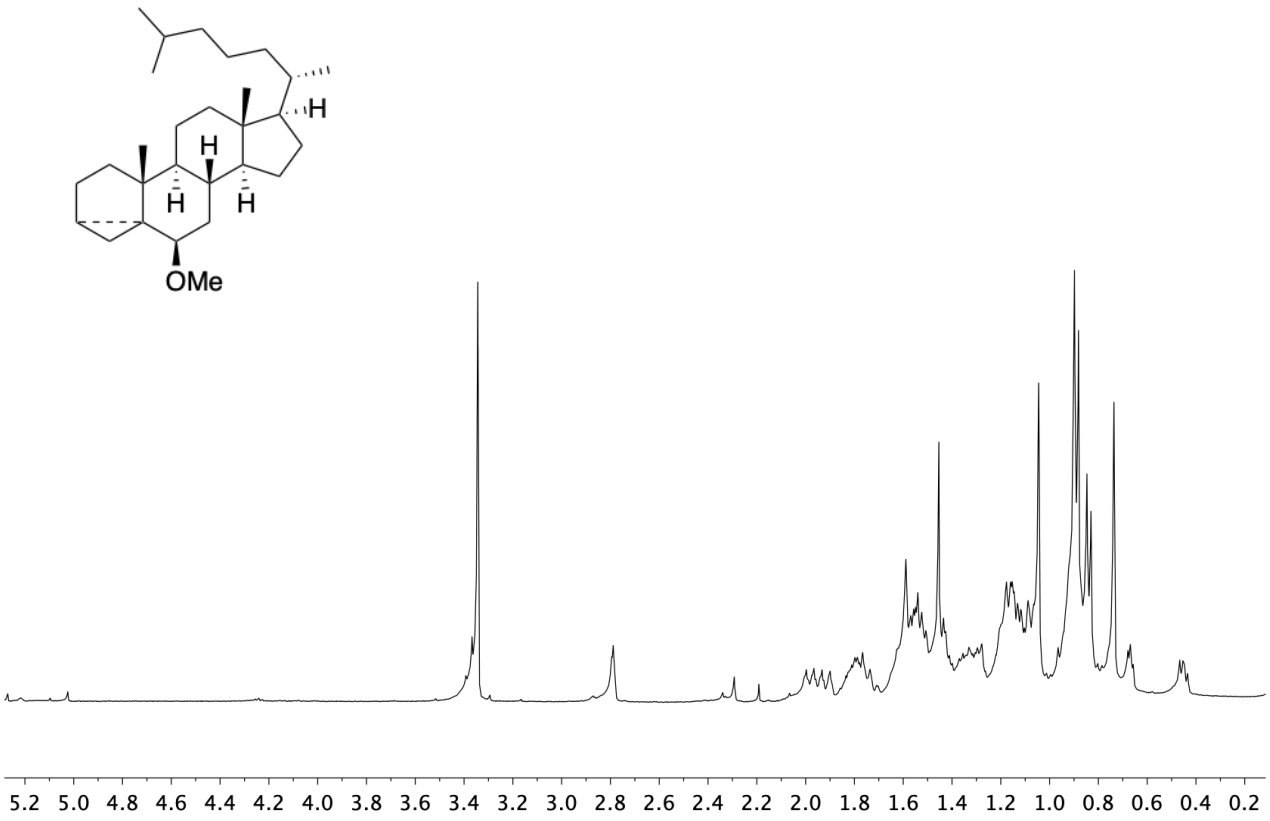
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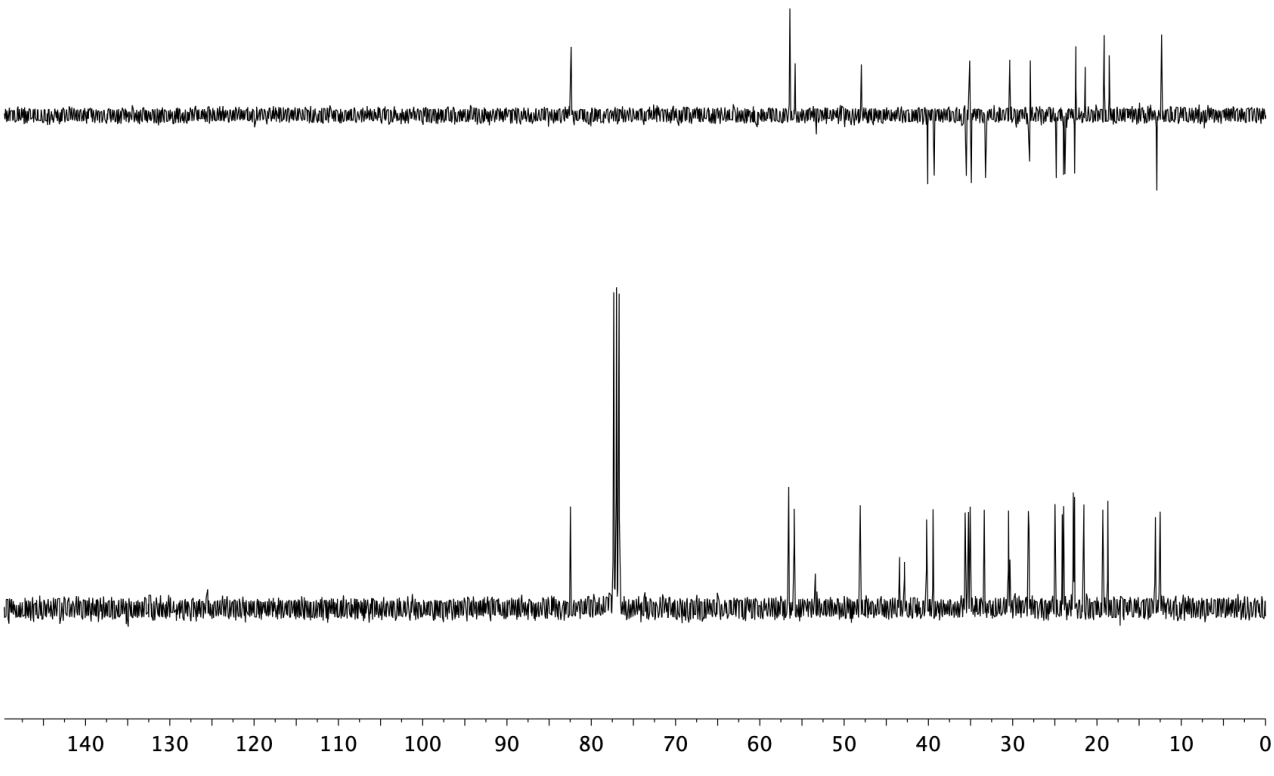
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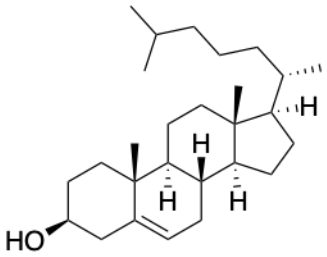
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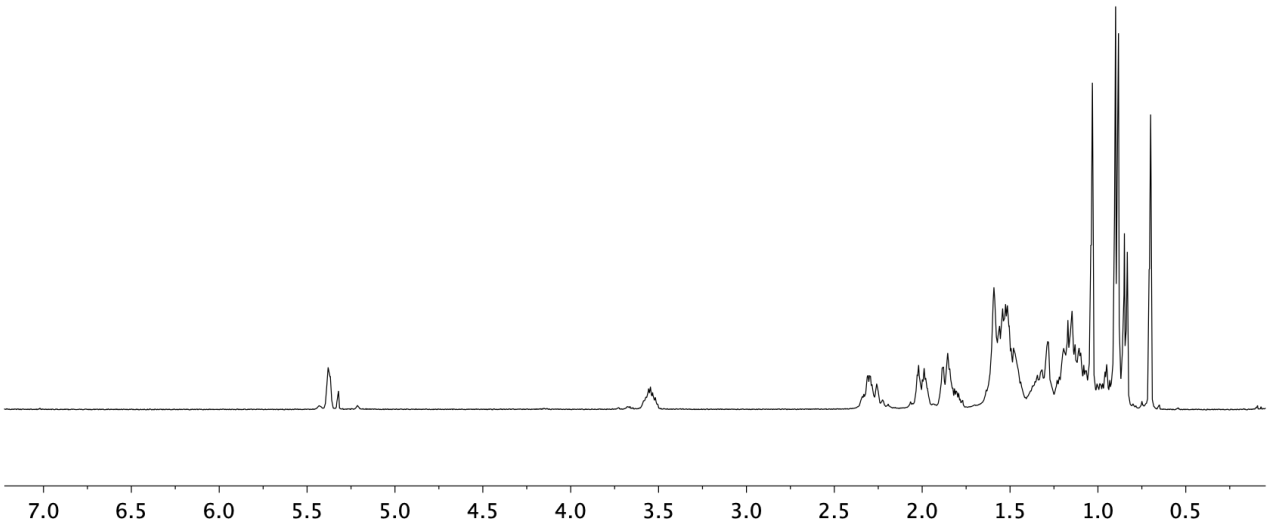
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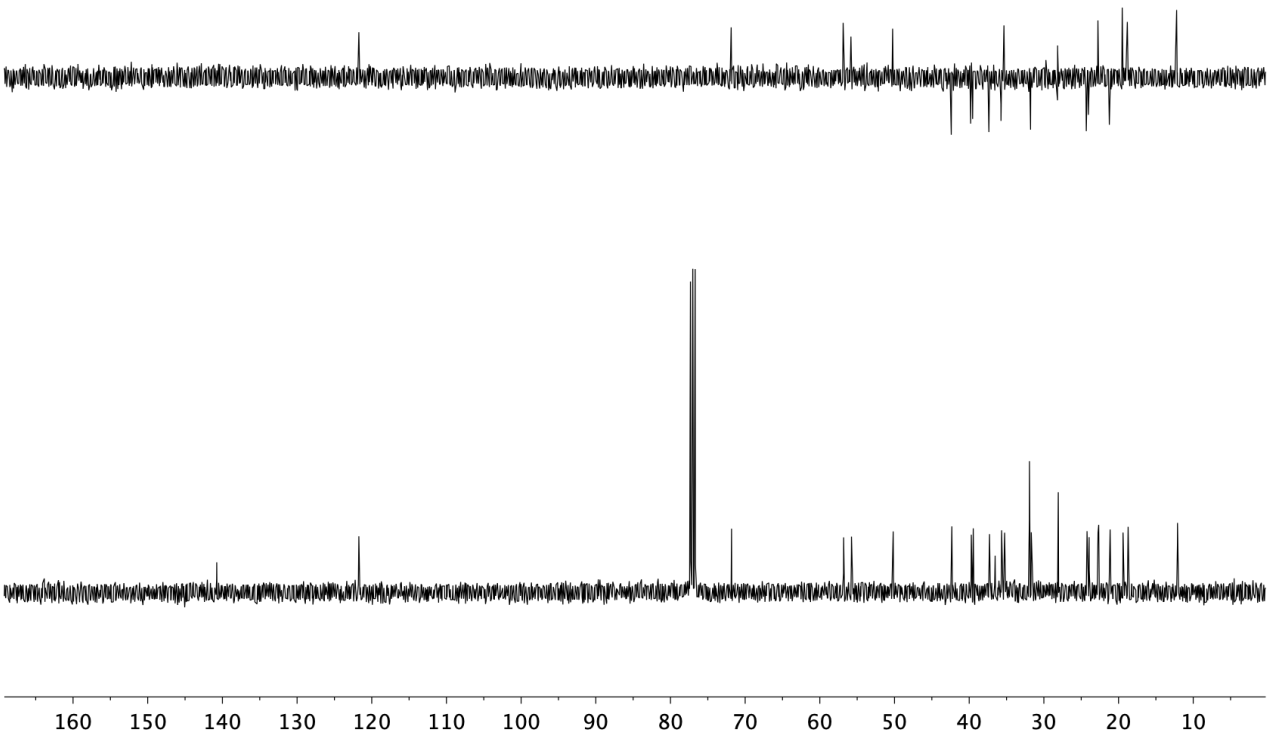
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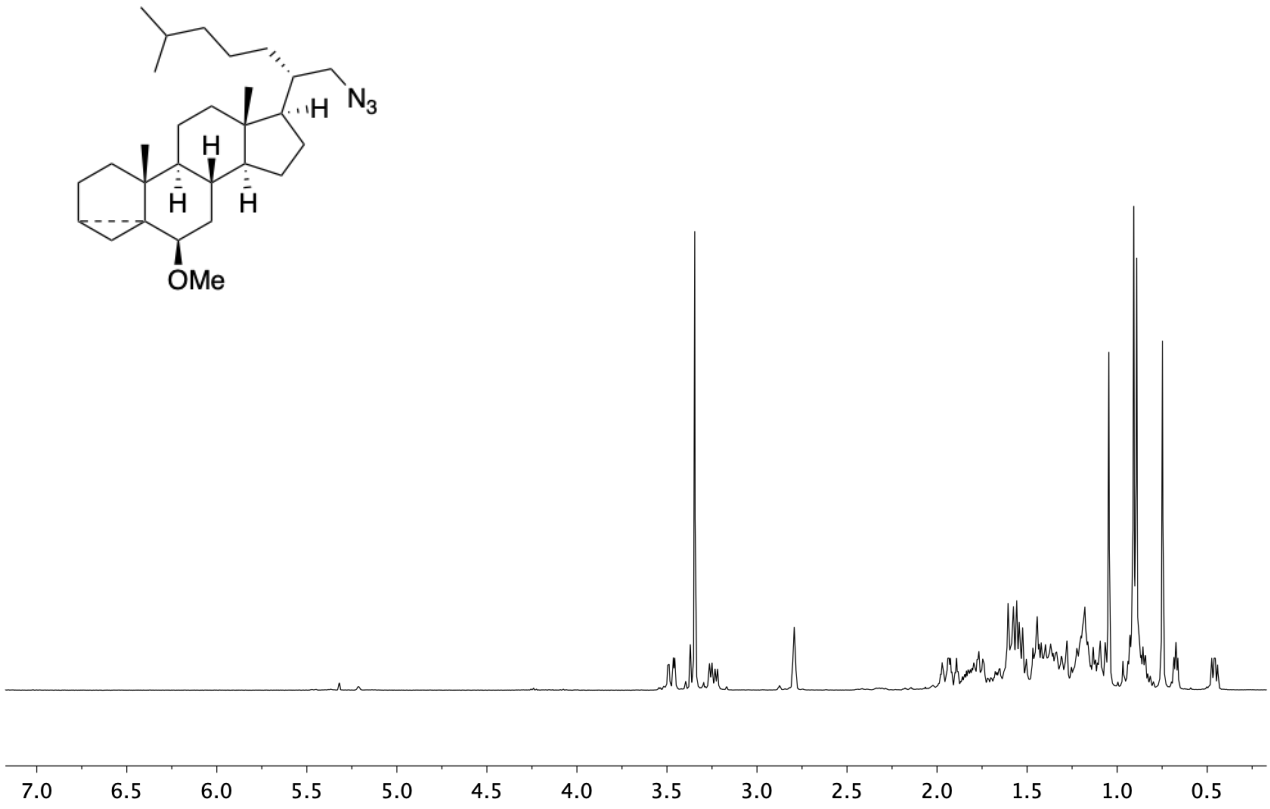
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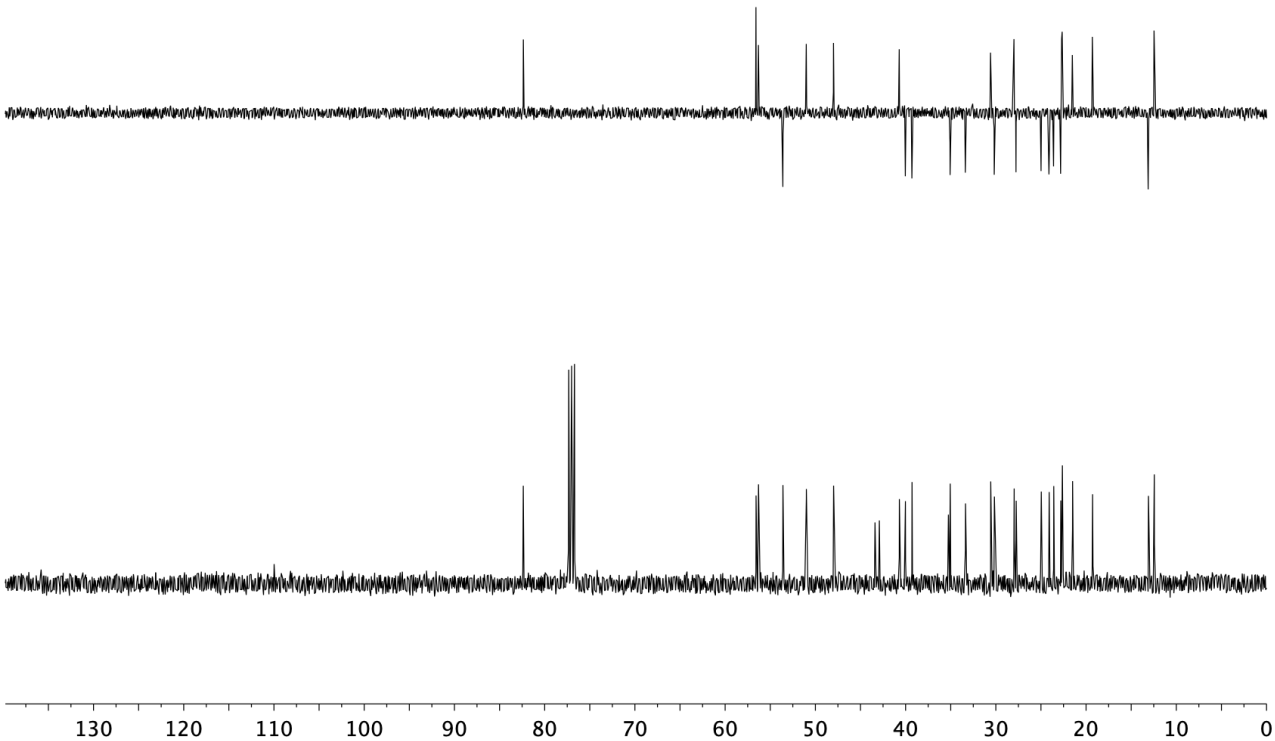
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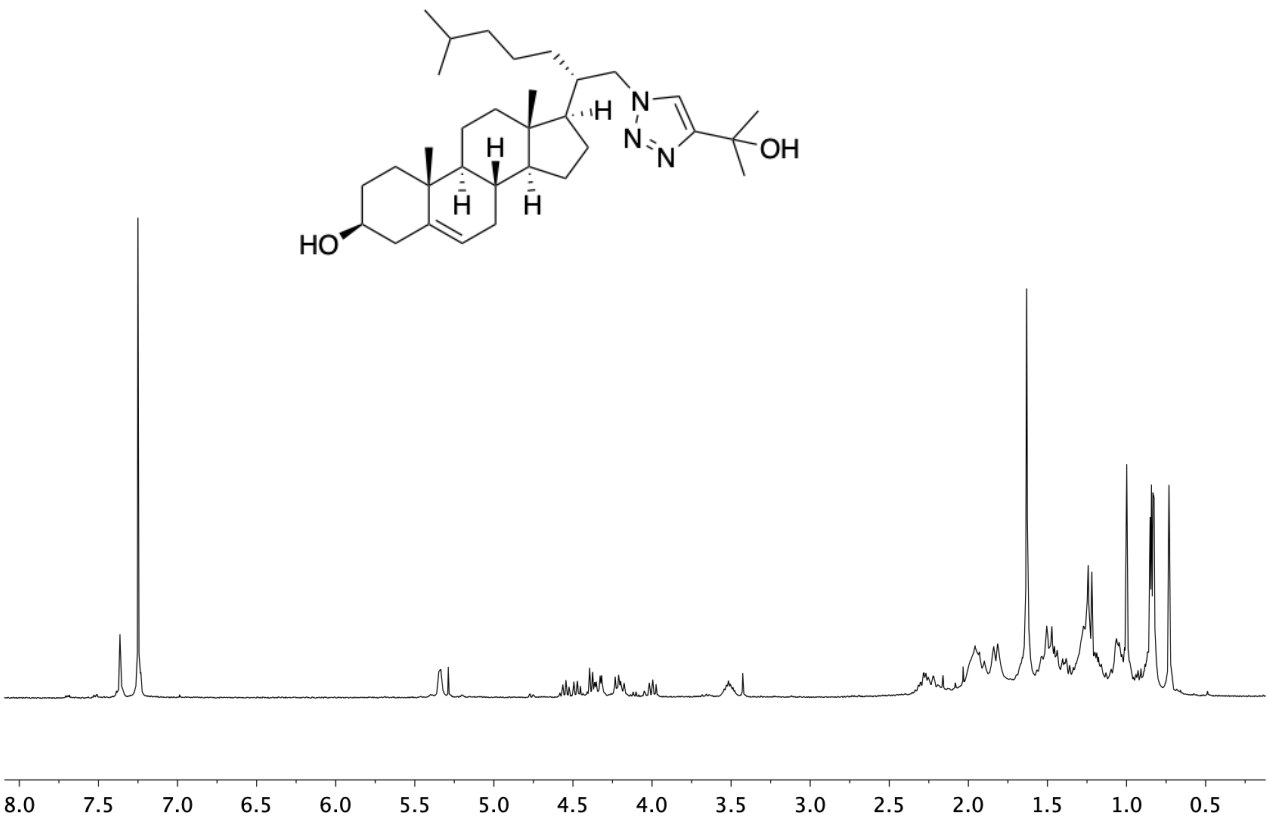
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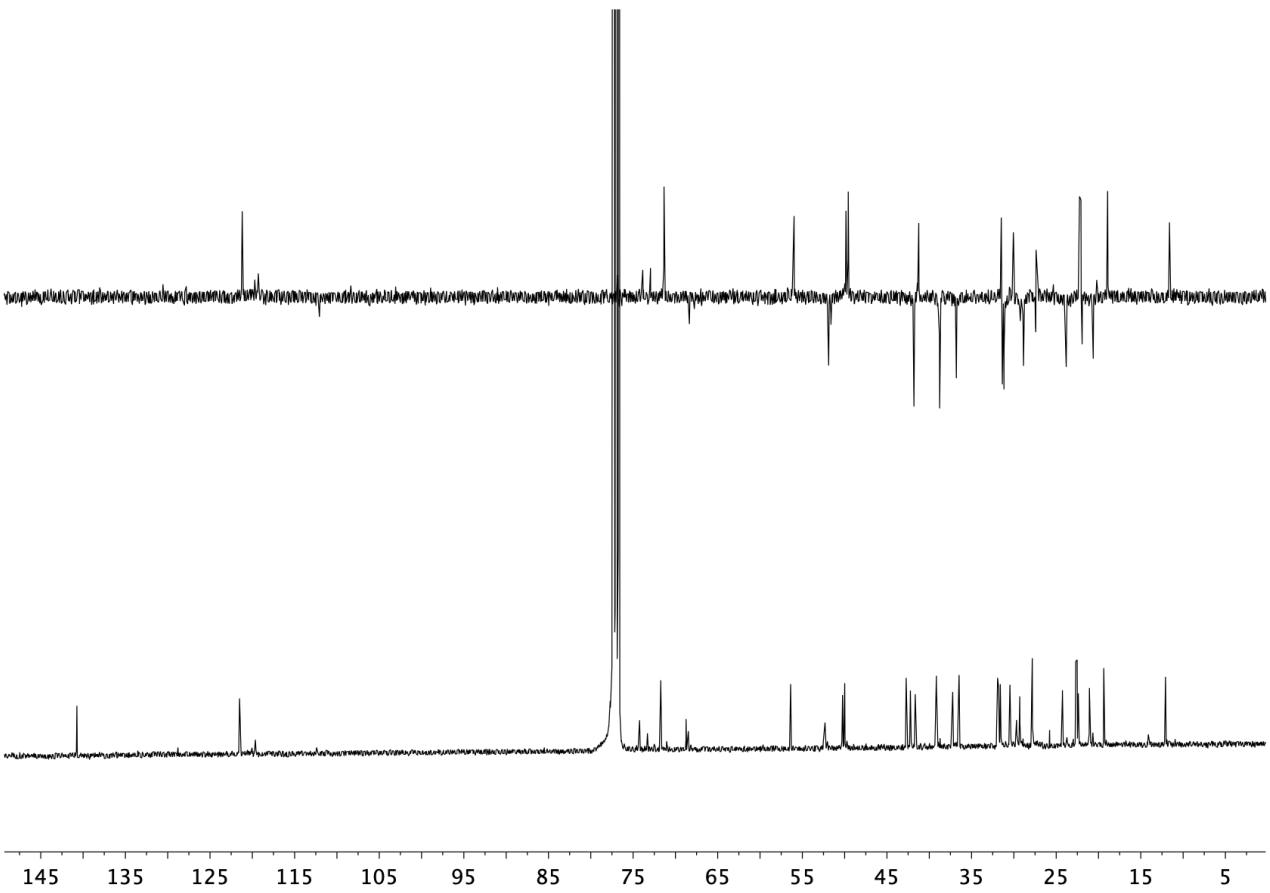
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## 3. X-Ray Spectra

### 3.1. Compound 8

A single crystal of **8** was (Figure 1) analysed by X-ray diffraction and a summary of the crystallographic data and the structure refinement parameters is reported in Table 1. Crystallographic data were collected at room temperature using a Bruker Smart 6000 CCD detector and Cu-Kα radiation (λ = 1.54178 Å) generated by a Incoatec microfocus source equipped with Incoatec Quazar MX optics. The software APEX3 was used for collecting frames of data, indexing reflections, and the determination of lattice parameters, SAINT for integration of intensity of reflections, and SADABS for scaling and empirical absorption correction. The structure was solved by dual-space methods using the program SHELXT. All non-hydrogen atoms were refined with anisotropic thermal parameters by full-matrix least- squares calculations on $F^2$ using the program SHELXL-2014. Hydrogen atoms were inserted at calculated positions and constrained with isotropic thermal parameters except for the hydrogen atom soft the hydroxyl groups. Drawings were produced with PLATON.

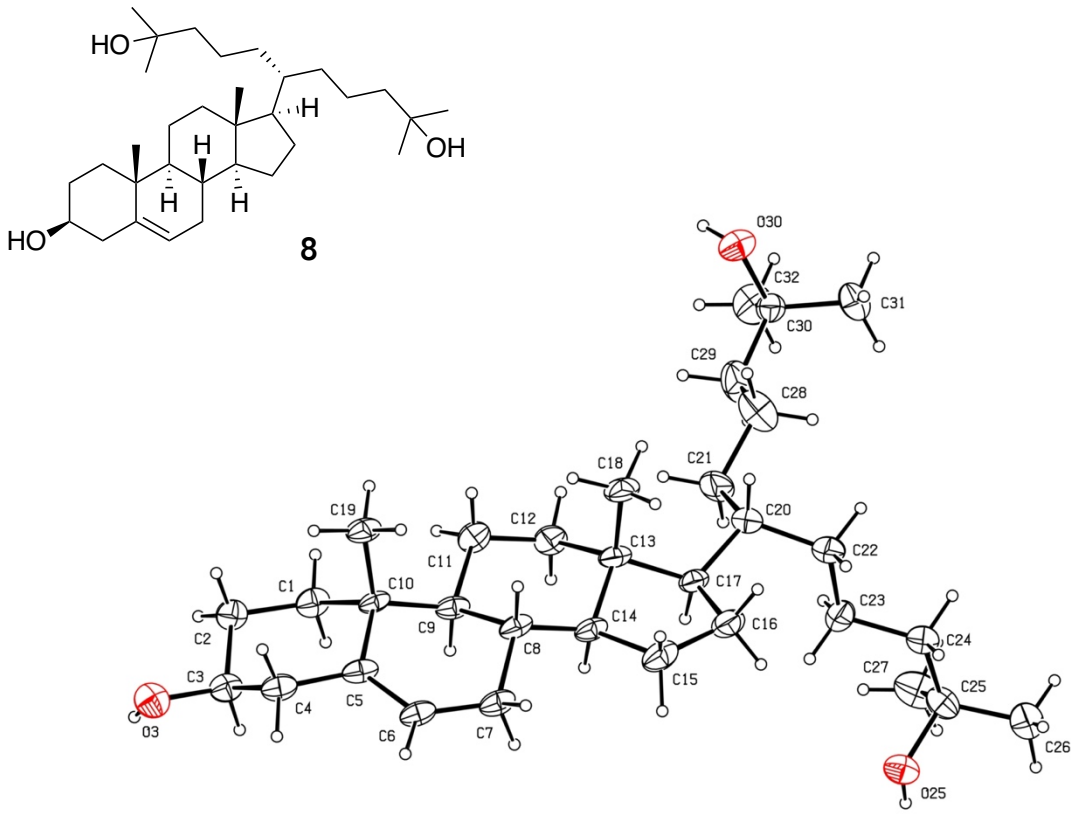



**Figure 1.** Balls and sticks structure for **8**

| | | |
|---|---|---|
| Empirical formula | C32 H56 O3 | |
| Formula weight | 488.76 | |
| Temperature | 296(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Monoclinic | |
| Space group | $P2_1$ | |
| Unit cell dimensions | a = 11.6603(7) Å | a= 90° |
| | b = 6.3016(4) Å | b= 91.932(5)° |
| | c = 20.6766(13) Å | g= 90° |
| Volume | 1518.42(16) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.069 Mg/m3 | |
| Absorption coefficient | 0.504 mm-1 | |
| F(000) | 544 | |
| Crystal size | 0.276 x 0.051 x 0.022 mm3 | |
| Theta range for data collection | 2.138 to 50.561° | |
| Index ranges | -11<=h<=11, -6<=k<=6, -20<=l<=20 | |
| Reflections collected | 8868 | |
| Independent reflections | 3165 [R(int) = 0.1098] | |
| Completeness to theta = 50.561° | 99.8 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.7500 and 0.5978 | |
| Refinement method | Full-matrix least-squares on F2 | |
| Data / restraints / parameters | 3165 / 4 / 331 | |
| Goodness-of-fit on F2 | 0.991 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0900, wR2 = 0.2254 | |
| R indices (all data) | R1 = 0.1229, wR2 = 0.2573 | |
| Absolute structure parameter | -0.1(10) | |
| Extinction coefficient | n/a | |
| Largest diff. peak and hole | 0.482 and -0.195 e.Å-3 | |

**Table 1.** Crystal data and structure refinement for **8**

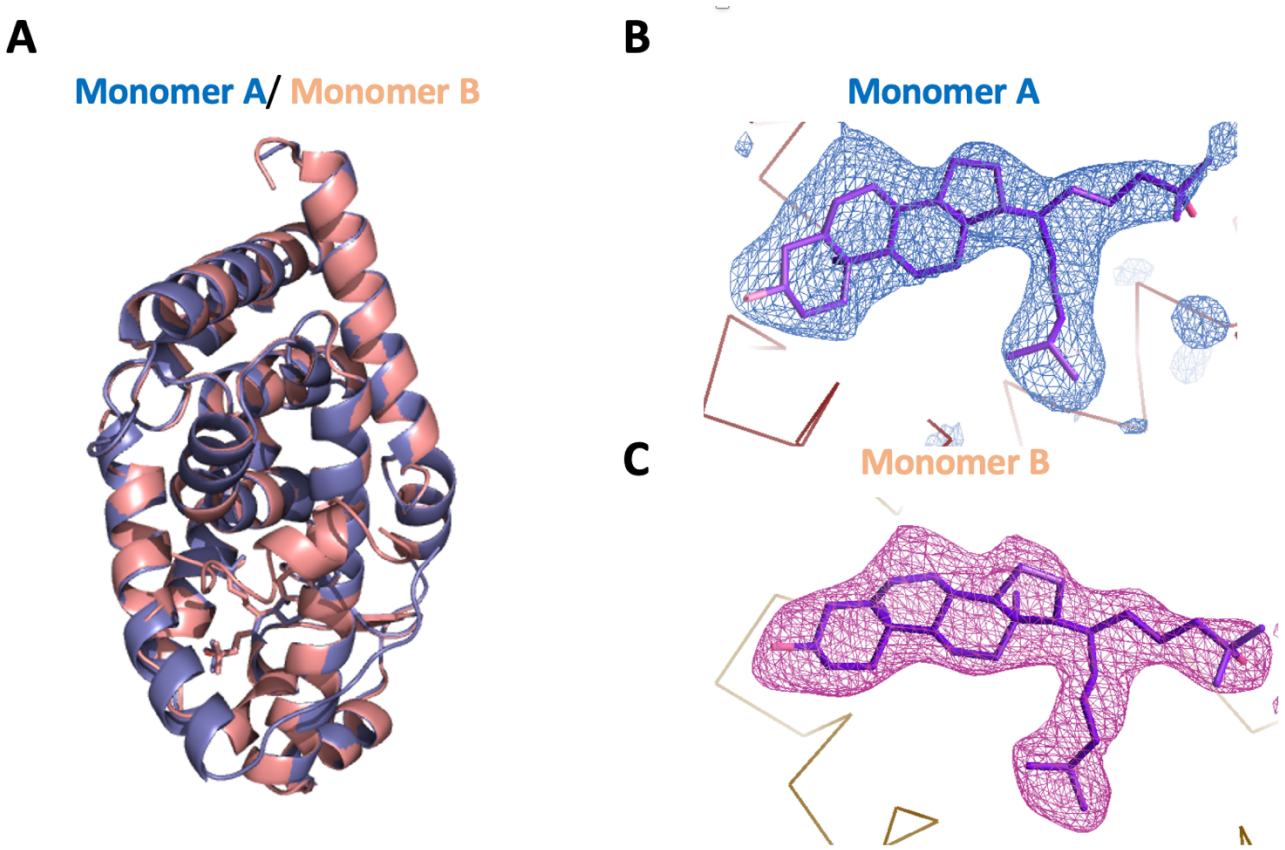
### 3.1. hRORγ LBD - 4

| | hRORγ LBD - 4 |
|---|---|
| **Data Processing** | |
| X-ray source | ESRF ID23-2 |
| Resolution (Å) | 40.83-2.3 |
| Crystal space group | $P6_1$ |
| Unit cell (a, b, c (Å), α, β, γ (°)) | 99,381, 99.381, 129.308, 90, 90, 120 |
| Unique reflections | 32145 |
| Mean redundancy | 9.7 |
| Completeness (%) | 99.17 |
| Mean I/σ | 8.18 |
| $CC_{1/2}$ | 0.97 |
| **Refinement** | |
| N° reflections | 31889 |
| Rwork (%) | 18.33 |
| Rfree (%) | 24.06 |
| N° of non H-atoms | |
| Macromolecules | 3853 |
| Ligands | 84 |
| Water | 195 |
| R.m.s.d. bond length (Å) | 0.007 |
| R.m.s.d. bond angles (°) | 0.85 |
| B-factor | |
| Macromolecules | 67.15 |
| Ligands | 81.35 |
| Water | 68.43 |

Table 2. Data collection and refinement statistics

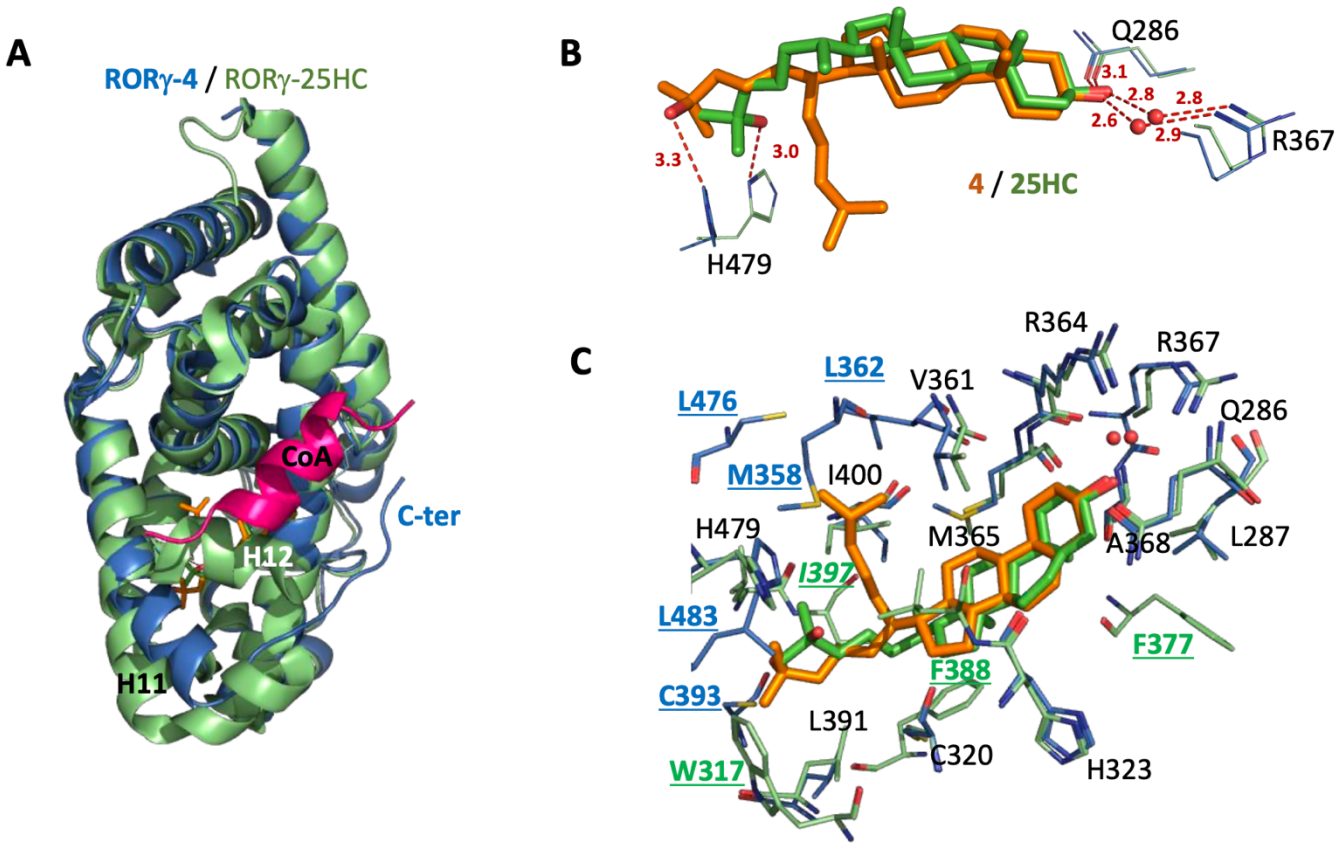
4. Supplementary figures

4.1. Supplementary figure 1



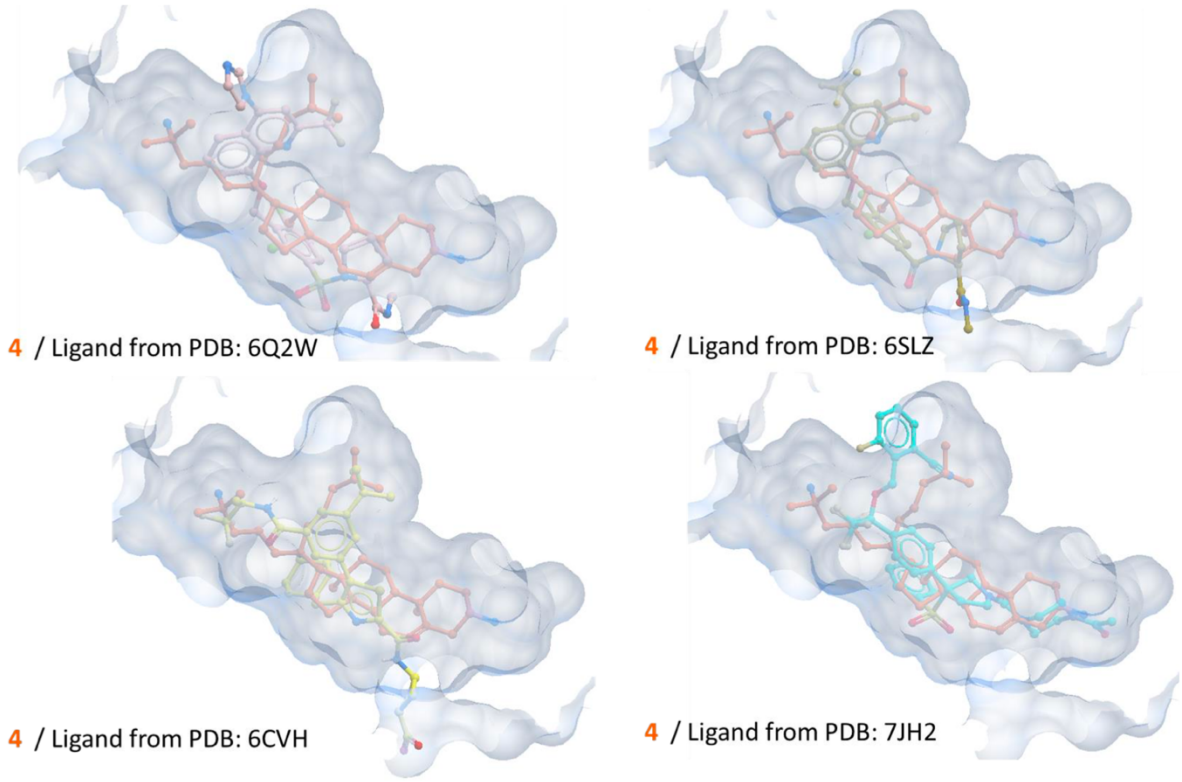

(**A**) Superposition of the two monomers of ROR$\gamma$-**4**. Ligand **4** of monomer A (**B**) and of monomer B (**C**) modelled into the unbiased omit Polder map contoured at 3.0 **σ**.

4.2. Supplementary figure 2




(A) Superimposition of the structures of hRORγ-**4** (blue) to the hRORγ LBD-25HC-SRC2-2 CoA (RORg in green and CoA in pink). (B) Overlay of 4 (in orange) and 25HC (in green) within RORg LBPs. Residues forming hydrogen bonds (red dashed lines) are shown and labeled. Indicated distances are in Å. Red spheres correspond to water molecules. (C) Details of interactions between LBP and **4** in blue and between LBP and 25HC in green at 4.0 Å cut-off. Amino acids (C393, L483, L476, M358 and L362) forming specific interactions with **4** compared to 25HC are underlined in blue. Amino acids forming stronger (F377, F388, I397) or specific interaction (W317) interactions with 25HC compared to **4** are underlined in green.

4.3. Supplementary figure 3




Superposition of the ligands in the **4**-bound LBP. Ligands are shown in stick representation with compound **4** in orange.