Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting information

Synthesis and evaluation of radioiodinated estrogens for diagnosis and therapy of male urogenital tumours

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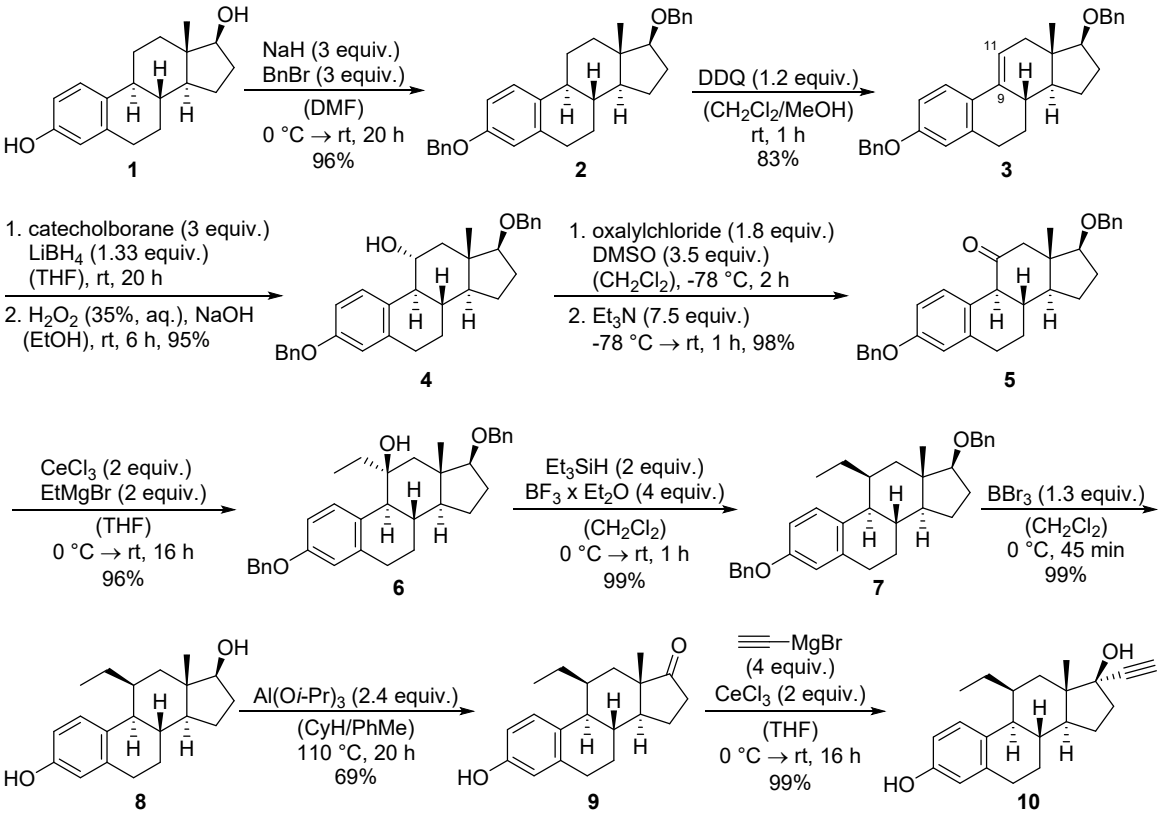
Chemical Syntheses

General direction

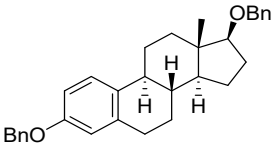
All reactions were carried out under a nitrogen or argon atmosphere with dry solvents under anhydrous conditions unless otherwise mentioned. Anhydrous dimethylformamide (DMF), dimethyl sulfoxide (DMSO), methylene chloride (CH_2Cl_2), and cyclohexane (CH) were purchased from commercial suppliers. Reagents were purchased at commercial quality and used without further purification. TLC was conducted with precoated aluminum sheets (silica gel 60 F254) and visualized by exposure to UV light (254 nm) or stained with ceric ammonium molybdate (CAM), ninhydrin (Ninhydrin) or basic potassium permanganate ($KMnO_4$), and subsequent heating. Flash column chromatography was performed on silica gel (40-60 µm); the eluent used is reported in the respective experiments. IR spectra were measured using ATR-technique in the range of 400-4000 cm^{-1}. ^{1}H NMR spectra were recorded with 600 MHz or 400 MHz instruments from Bruker, ^{13}C NMR spectra at 151 MHz or 101 MHz, and ^{19}F at 376 MHz. Chemical shifts are reported in ppm relative to the solvent signal, coupling constants *J* in Hz. Multiplicities were defined by standard abbreviations. Low-resolution (LRMS) mass spectra were obtained using ESI ionization (positive) on a 6120 quadrupole mass spectrometer with an Agilent Technologies 1260 Infinity liquid chromatograph. High-resolution mass spectra (HRMS) were obtained using ESI ionization (positive or negative) on a Bruker micrOTOF. An Agilent Technologies analytical HPLC system (1200 Series) using Macherey-Nagel chromatography column (EC 250/4.6 NUCLEODUR 100-5 C18ec) was used for method development. Preparative HPLC was performed on an Agilent Technologies system (model 1260 Infinity Series), using a Macherey-Nagel chromatography column (VP 250/21 NUCLEODUR 100-5 C18ec) with a water/acetonitrile mixture as eluent.

Compounds 2-10



Scheme S1: Synthesis of 11β-ethyl-17α-ethinylestradiol **10**. Scheme S1 is identical to Figure 1 of the main text.

(8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(benzyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene (2)

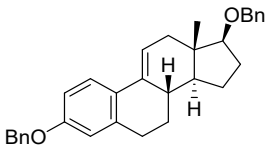


$C_{32}H_{36}O_2$
452.64

17β-estradiol (**1**) (5.00 g, 17.9 mmol, 1 equiv.) was dissolved in DMF (50 mL) and the solution was cooled to 0 °C. Then, NaH (2.16 g, 54.0 mmol, 60% oil dispersion, 3 equiv.) was slowly added to the reaction mixture, which was stirred for 2 h at room temperature. The mixture was then cooled again to 0 °C, BnBr (6.46 mL, 54.0 mmol, 3 equiv.) was added, and the reaction mixture was stirred for 20 h at room temperature. The suspension was added to a methanol/water mixture (3:1, 200 mL) and stirred for 30 minutes. The precipitating colourless solid was filtered off and washed with *n*-hexane (50 mL) and water (30 mL). The solid was dried under high vacuum. Steroid **2** (7.8 g, 17 mmol, 96%) was obtained as a colourless solid. No further purification was necessary.

TLC: R_f (PE/EtOAc 7:3) = 0.67 [UV] [$KMnO_4$]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.49 – 7.28 (m, 10H), 7.23 – 7.17 (m, 1H), 6.78 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.72 (d, *J* = 2.8 Hz, 1H), 5.04 (s, 2H), 4.58 (s, 2H), 3.51 (t, *J* = 8.3 Hz, 1H), 2.96 – 2.75 (m, 2H), 2.35 – 2.25 (m, 1H), 2.19 (ddd, *J* = 15.2, 10.4, 4.4 Hz, 1H), 2.13 – 1.99 (m, 2H), 1.92 – 1.83 (m, 1H), 1.74 – 1.12 (m, 8H), 0.88 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 156.9, 139.5, 138.2, 137.5, 133.2, 128.7, 128.4, 128.0, 127.6, 127.4, 127.4, 126.5, 115.0, 112.4, 88.5, 71.8, 70.1, 50.4, 44.2, 43.6, 38.8, 38.1, 30.0, 28.2, 27.4, 26.6, 23.3, 12.0. The spectroscopical data were identical to those reported in the literature.[3]

(8*S*,13*S*,14*S*,17*S*)-3,17-bis(benzyloxy)-13-methyl-7,8,12,13,14,15,16,17-octahydro-6*H*-cyclopenta[*a*]phenanthrene (3)

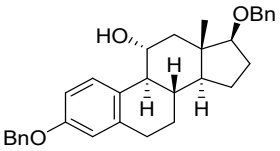


$C_{32}H_{34}O_2$
450.62

Steroid **2** (6.5 g, 14 mmol, 1 equiv.) was dissolved in abs. CH_2Cl_2 (50 mL) and added dropwise to a solution of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 3.9 g, 17 mmol, 1.2 equiv.) in MeOH (80 mL) at room temperature. After stirring for 1 h at room temperature, the mixture was concentrated under reduced pressure and the residue was dissolved in small amount of MeOH. The precipitating colourless solid was filtered off and washed several times with small portions of MeOH. Finally, the solid was dried under a high vacuum to give product **3** (5.38 g, 11.9 mmol, 83%) as a colourless solid.

TLC: R_f (PE/EtOAc 9:1) = 0.42 [UV] [$KMnO_4$]. **^{1}H NMR** (600 MHz, $CDCl_3$): δ [ppm] = 7.53 (d, *J* = 8.8 Hz, 1H), 7.44 – 7.27 (m, 10H), 6.79 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.68 (d, *J* = 2.8 Hz, 1H), 6.12 – 6.10 (m, 1H), 5.05 (s, 2H), 4.65 – 4.53 (m, 2H), 3.59 (t, *J* = 8.6 Hz, 1H), 2.92 – 2.77 (m, 2H), 2.37 (ddd, *J* = 17.7, 5.6, 2.1 Hz, 1H), 2.23 (dt, *J* = 17.8, 3.1 Hz, 1H), 2.14 – 1.99 (m, 3H), 1.87 – 1.78 (m, 1H), 1.73 – 1.63 (m, 1H), 1.48 – 1.29 (m, 3H), 0.89 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 157.7, 139.4, 137.7, 137.3, 135.1, 128.7, 128.4, 128.0, 127.9, 127.6, 127.5, 125.3, 117.9, 114.6, 113.6, 88.6, 71.8, 70.1, 47.8, 41.8, 40.6, 38.7, 30.3, 28.4, 28.3, 24.1, 13.8, 12.0. The spectroscopical data were identical to those reported in the literature.[3]

(8*S*,9*S*,11*R*,13*S*,14*S*,17*S*)-3,17-bis(benzyloxy)-13-methyl-7,8,9,11,12,13,14,15,-16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-11-ol (4)

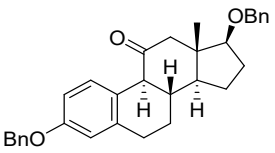


$C_{32}H_{36}O_3$
468.64

Steroid **3** (5.98 g, 13.3 mmol, 1 equiv.) was dissolved in abs. THF (5 mL). After the addition of catecholborane (40 mL, 40 mmol, 1M in THF, 3 equiv.) and $LiBH_4$ (384 mg, 17.6 mmol, 1.33 equiv.), the reaction mixture was stirred for 20 h at room temperature. Then, the reaction mixture was carefully added to a cold solution containing aq. NaOH (18 mL, 33%), EtOH (55 mL), and aq. H_2O_2 (57 mL, 35%). After stirring for 6 h at room temperature, water (100 mL) and EtOAc (100 mL) were added. The aqueous layer was extracted with EtOAc (3×100 mL), and the combined organic layer was washed with water (3×50 mL) and saturated aq. NaCl. The organic layer was dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (PE/EtOAc 95:5 → 85:15). Steroid **4** (5.92 g, 12.6 mmol, 95%) was obtained as a foamy colourless solid.

TLC: R_f (PE/EtOAc 8:2) = 0.31 [UV] [$KMnO_4$]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.86 (d, *J* = 8.7 Hz, 2H), 7.46 – 7.27 (m, 10H), 6.81 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.75 (d, *J* = 2.6 Hz, 1H), 5.05 (s, 2H), 4.65 – 4.52 (m, 2H), 4.32 – 4.16 (m, 1H), 3.53 (t, *J* = 8.3 Hz, 1H), 2.82 (t, *J* = 6.8 Hz, 2H), 2.43 (dd, *J* = 11.9, 5.2 Hz, 1H), 2.19 – 2.02 (m, 2H), 1.93 – 1.82 (m, 1H), 1.74 – 1.56 (m, 2H), 1.46 – 1.40 (m, 2H), 1.37 – 1.25 (m, 3H), 0.86 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ [ppm] = 157.2, 139.3, 137.5, 132.8, 128.7, 128.5, 128.0, 127.6, 127.5, 127.5, 127.5, 114.9, 112.1, 87.8, 71.9, 70.9, 70.1, 50.8, 50.0, 48.6, 44.4, 37.3, 28.9, 28.1, 27.2, 23.2, 12.8. The spectroscopical data were identical to those reported in the literature.[3]

(8*S*,9*S*,13*S*,14*S*,17*S*)-3,17-bis(benzyloxy)-13-methyl-7,8,12,13,14,15,16,17-octahydro-6*H*-cyclopenta[*a*]phenanthren-11(9*H*)-one (5)



$C_{32}H_{34}O_3$
466.62

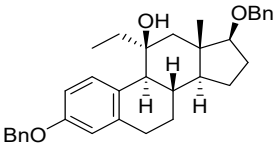
Oxalyl chloride (373 µL, 4.34 mmol, 1.8 equiv.) was dissolved in abs. CH_2Cl_2 (12 mL) at -78 °C. Then, abs. DMSO (600 µL, 8.44 mmol, 3.5 equiv.) was added slowly to the reaction mixture, and the solution was stirred for 30 min at -78 °C. Then, steroid **4** (1.13 g, 2.41 mmol, 1 equiv.) diluted in abs. CH_2Cl_2 (8 mL) was added at -78 °C. The solution was stirred at -78 °C for 1.5 h before Et_3N (2.5 mL, 18 mmol,

7.5 equiv.) was added to the reaction mixture and the mixture was allowed to warm to room temperature over a period of 1 h. After the addition of water (50 mL), the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layer was washed with water (3×50 mL), saturated aq. NH_4Cl and NaCl. The organic layer was dried over Na_2SO_4, and filtered, and the solution was concentrated under reduced pressure. The residue was purified by column chromatography (PE/EtOAc 9:1) to give ketone **5** (1.10 g, 2.36 mmol, 98%) as a colourless solid.

TLC: R_f (PE/EtOAc 8:2) = 0.54 [UV] [$KMnO_4$]. **^{1}H NMR** (600 MHz, $CDCl_3$): δ [ppm] = 7.44 – 7.41 (m, 2H), 7.39 – 7.27 (m, 9H), 6.83 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.70 (d, *J* = 2.7 Hz, 1H), 5.04 (s, 2H), 4.63 – 4.49 (m, 2H), 3.72 (t, *J* = 8.3 Hz, 1H), 3.46 (d, *J* = 11.1 Hz, 1H), 2.88 – 2.80 (m, 1H), 2.76 (ddd, *J* = 16.9, 5.2, 1.9 Hz, 1H), 2.68 (d, *J* = 11.5 Hz, 1H), 2.47 (dt, *J* = 11.8, 1.0 Hz, 1H), 2.25 – 2.15 (m, 1H), 1.97 – 1.83 (m, 3H), 1.83 – 1.76 (m, 1H), 1.74 – 1.67 (m, 1H), 1.53 – 1.44 (m, 2H), 0.87 (d, *J* = 0.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 209.2, 157.4, 138.9, 138.6, 137.4, 131.4, 128.7, 128.5, 128.0, 127.7, 127.5, 127.5, 124.1, 115.0, 112.6, 86.4, 71.8, 70.1, 56.0, 55.3, 50.2, 48.7, 40.4, 30.2, 28.6, 27.7, 22.5, 12.7. The spectroscopical data were identical to those reported in the literature.[3]

[3]

(8*S*,9*S*,11*S*,13*S*,14*S*,17*S*)-3,17-bis(benzyloxy)-11-ethyl-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-11-ol (6)

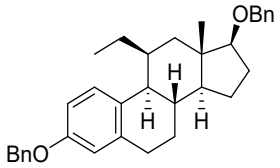


$C_{34}H_{40}O_3$
496.69

Cerium trichloride heptahydrate (902 mg, 2.42 mmol, 2 equiv.) was placed in a Schlenk flask and dried for 1 h at 140 °C in vacuo. Then, abs. THF (6 mL) was added, and the suspension was stirred for 2 h at room temperature. Steroid **5** (566 mg, 1.21 mmol, 1 equiv.) was added at 0 °C and the mixture was stirred for 1 h at room temperature. After dropwise addition of EtMgBr (2.43 mL, 2.43 mmol, 1M in THF, 2 equiv.) at 0 °C, the reaction was stirred for 15 h at room temperature. The reaction was quenched with aq. acetic acid solution (10%). Then, the aqueous layer was extracted with EtOAc (3×20 mL), and the combined organic layer was washed with saturated aq. $NaHCO_3$ and NaCl were dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (PE → PE/EtOAc 9:1). Steroid **6** (580 mg, 1.17 mmol, 96%) was obtained as a colourless solid.

TLC: R_f (PE/EtOAc 8:2) = 0.55 [UV] [CAM]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.79 – 7.55 (m, 1H), 7.46 – 7.26 (m, 10H), 6.91 – 6.65 (m, 2H), 5.05 (s, 2H), 4.57 (s, 2H), 3.49 – 3.43 (m, 1H), 2.79 – 2.62 (m, 2H), 2.28 (d, *J* = 10.5 Hz, 1H), 2.17 – 1.97 (m, 3H), 1.86 – 1.57 (m, 5H), 1.52 – 1.36 (m, 4H), 1.09 (s, 3H), 0.99 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 156.7, 142.4, 139.4, 137.5, 130.6, 128.7, 128.6, 128.4, 128.0, 127.6, 127.5, 115.0, 111.6, 89.6, 76.0, 71.8, 70.1, 51.1, 50.9, 50.2, 43.2, 36.6, 34.6, 29.6, 27.8, 26.4, 24.0, 13.7, 8.9. The spectroscopical data were identical to those reported in the literature.[3]

(8*S*,9*S*,11*S*,13*S*,14*S*,17*S*)-3,17-bis(benzyloxy)-11-ethyl-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene (7)

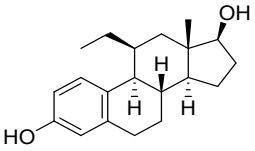


$C_{34}H_{40}O_2$
480.69

Steroid **6** (900 mg, 1.61 mmol, 1 equiv.) was dissolved in abs. CH_2Cl_2 (27 mL) and the mixture was cooled to 0 °C. After adding Et_3SiH (525 µL, 3.22 mmol, 2 equiv.) and $BF_3{\times}Et_2O$ (795 µL, 6.44 mmol, 4 equiv.), the solution was stirred for 1 h at room temperature. The reaction was quenched with saturated aq. $NaHCO_3$ solution. The CH_2Cl_2 was removed under reduced pressure, and the aqueous layer was extracted with EtOAc (3×30 mL). The organic layer was washed with saturated aq. $NaHCO_3$ and NaCl were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (PE/EtOAc 9:1). Steroid **7** (770 mg, 1.60 mmol, 99%) was obtained as a colourless solid.

TLC: R_f (PE/EtOAc 8:2) = 0.71 [$KMnO_4$]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.48 – 7.27 (m, 10H), 7.07 (d, *J* = 8.6 Hz, 1H), 6.79 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.69 (d, *J* = 2.7 Hz, 1H), 5.03 (s, 2H), 4.60 (s, 2H), 3.48 (dd, *J* = 8.8, 7.1 Hz, 1H), 2.82 (td, *J* = 15.0, 13.2, 4.8 Hz, 1H), 2.75 – 2.67 (m, 1H), 2.54 (dd, *J* = 10.8, 4.7 Hz, 1H), 2.38 (dd, *J* = 13.5, 1.9 Hz, 1H), 2.35 – 2.28 (m, 1H), 2.10 – 1.95 (m, 1H), 1.91 – 1.82 (m, 1H), 1.73 – 1.57 (m, 3H), 1.46 – 1.13 (m, 6H), 1.01 (s, 3H), 0.93 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 156.4, 139.5, 139.2, 137.5, 130.9, 128.7, 128.4, 128.0, 127.9, 127.6, 127.5, 127.4, 114.8, 112.9, 89.8, 71.8, 70.1, 52.4, 49.9, 44.0, 39.2, 38.7, 34.4, 30.6, 28.2, 27.2, 23.2, 21.4, 15.2, 13.1. The spectroscopical data were identical to those reported in the literature.[3]

(8*S*,9*S*,11*S*,13*S*,14*S*,17*S*)-11-ethyl-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (8)

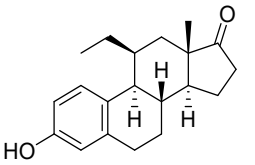


$C_{20}H_{28}O_2$
300.44

Steroid **7** (460 mg, 957 µmol, 1 equiv.) was dissolved in abs. CH_2Cl_2 (10 mL) and the mixture was cooled to -5 °C. A solution of BBr_3 (2.87 mL, 2.87 mmol, 1M in CH_2Cl_2, 3 equiv.) was added dropwise to the solution and stirred at 0 °C for 45 min. The reaction was quenched with water, and the mixture was extracted with EtOAc (3×10 mL). The combined organic layer was washed with saturated aq. $NaHCO_3$ and NaCl, were dried over Na_2SO_4, and filtered. The solvent was evaporated in vacuo and the residue was purified by column chromatography (PE/EtOAc 9:1 → 7:3). Steroid **8** (285 mg, 947 µmol, 99%) was obtained as a beige solid.

TLC: R_f (PE/EtOAc 8.2) = 0.13 [$KMnO_4$]. **^{1}H NMR** (600 MHz, DMSO-d_6): δ [ppm] = 6.91 (d, *J* = 8.4 Hz, 1H), 6.52 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.41 (d, *J* = 2.6 Hz, 1H), 4.46 (s, 1H), 3.49 (t, *J* = 8.3 Hz, 1H), 2.67 (td, *J* = 15.2, 13.5, 4.9 Hz, 1H), 2.60 – 2.54 (m, 1H), 2.42 (dd, *J* = 10.8, 4.5 Hz, 1H), 2.28 – 2.23 (m, 1H), 2.14 (dd, *J* = 13.6, 1.9 Hz, 1H), 1.90 – 1.81 (m, 1H), 1.79 – 1.74 (m, 1H), 1.56 – 1.47 (m, 2H), 1.40 – 1.31 (m, 1H), 1.30 – 1.05 (m, 7H), 0.85 (t, *J* = 7.3 Hz, 3H), 0.79 (s, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6): δ [ppm] = 154.3, 138.1, 128.0, 127.3, 115.0, 113.1, 81.4, 51.4, 49.1, 43.1, 37.6, 37.6, 34.2, 29.8, 29.7, 26.8, 22.8, 20.6, 14.4, 12.7. The spectroscopical data were identical to those reported in the literature.[3]

(8*S*,9*S*,11*S*,13*S*,14*S*)-11-ethyl-3-hydroxy-13-methyl-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17(14*H*)-one (9)



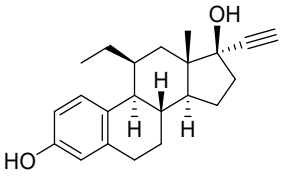
$C_{20}H_{26}O_2$
298.43

Steroid **8** (275 mg, 921 µmol, 1 equiv.) and Al(O*i*-Pr)$_3$ (449 mg, 2.20 mmol, 2.4 equiv.) were dissolved in a cyclohexanone/toluene mixture (2:3, 9 mL) and heated for 20 h under reflux conditions. The reaction mixture was then cooled to room temperature, and the reaction was quenched carefully with HCl solution (1N). The aqueous layer was extracted with EtOAc (3×5 mL), and the combined organic layer was washed with water and saturated aq. NaCl, dried over Na_2SO_4, and filtered. After removing

the solvent under reduced pressure, the residue was purified by column chromatography (PE/EtOAc 9:1 → 8:2). The ketone **9** (189 mg, 633 µmol, 69%) was obtained as a pale yellow solid.

TLC: R_f (PE/EtOAc 8:2) = 0.18 [UV] [CAM]. **^{1}H NMR** (400 MHz, DMSO-d_6): δ [ppm] = 8.97 (s, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 6.54 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.43 (d, *J* = 2.6 Hz, 1H), 2.81 – 2.57 (m, 2H), 2.45 (d, *J* = 8.3 Hz, 1H), 2.39 – 2.29 (m, 1H), 2.07 – 1.83 (m, 4H), 1.77 – 1.64 (m, 1H), 1.63 – 1.16 (m, 6H), 1.15 – 1.01 (m, 1H), 0.94 (s, 3H), 0.86 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6): δ [ppm] = 217.8, 154.5, 138.1, 127.6, 127.3, 115.0, 113.2, 51.5, 48.9, 47.1, 37.5, 34.7, 33.6, 31.7, 29.5, 26.0, 20.8, 20.7, 15.7, 12.6. The spectroscopical data were identical to those reported in the literature.[3]

(8*S*,9*S*,11*S*,13*S*,14*S*,17*R*)-11-ethyl-17-ethinyl-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (10)



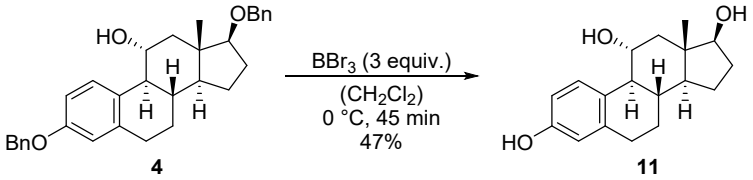
$C_{22}H_{28}O_2$
324.46

Cerium trichloride heptahydrate (168 mg, 904 µmol, 2 equiv.) was placed in a Schlenk flask and dried for 1 h at 140 °C in vacuo. Then, abs. THF (2.3 mL) was added, and the suspension was stirred for 2 h at room temperature. Steroid **9** (135 mg, 452 µmol, 1 equiv.) was added at 0 °C, and the mixture was stirred for 1 h at room temperature. After dropwise addition of ethinylMgBr (3.69 mL, 1.81 mmol, 0.5M in THF, 4 equiv.) at 0 °C, the reaction was stirred for 15 h at room temperature. The reaction was quenched with aq. acetic acid solution (10%). Then, the mixture was extracted with EtOAc (3×20 mL), and the combined organic layers were washed with saturated aq. $NaHCO_3$ and NaCl were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (PE/EtOAc 9:1 → 8:2). Steroid **10** (145 mg, 447 µmol, 99%) was obtained as a colourless solid.

TLC: R_f (PE/EtOAc 8:2) = 0.21 [UV] [CAM]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.03 (d, *J* = 8.3 Hz, 1H), 6.64 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.54 (d, *J* = 2.7 Hz, 1H), 4.69 (s, 1H), 2.84 – 2.64 (m, 2H), 2.63 (s, 1H), 2.59 (dd, *J* = 10.7, 4.8 Hz, 1H), 2.43 – 2.28 (m, 2H), 2.08 – 2.03 (m, 1H), 2.01 (d, *J* = 3.9 Hz, 2H), 1.90 – 1.82 (m, 1H), 1.77 – 1.68 (m, 2H), 1.67 – 1.56 (m, 1H), 1.52 – 1.13 (m, 4H), 1.03 (s, 3H), 0.90 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 153.0, 139.4, 130.5, 128.1, 115.4, 113.3, 87.9, 80.9, 74.7, 51.6, 49.3, 47.8, 39.4, 38.4, 35.2, 33.3, 30.4, 27.1, 22.9, 21.1, 16.0, 13.0. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3356, 3302,

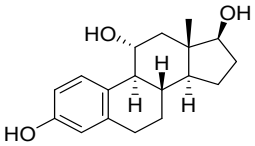
2963, 2875, 1610, 1585, 1448, 1383, 1358, 1287, 1062, 1024, 908, 649, 627. **LRMS** (ESI): *m/z* 342 [M+NH_4^+]. **HRMS** (ESI): *m/z* calculated for $C_{22}H_{28}NaO_2^+$: 347.1982, found 347.1991.

Synthesis of compound 11



Scheme S2: Benzyl deprotection of steroid **4**.

(8*S*,9*S*,11*R*,13*S*,14*S*,17*S*)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,11,17-triol (11)

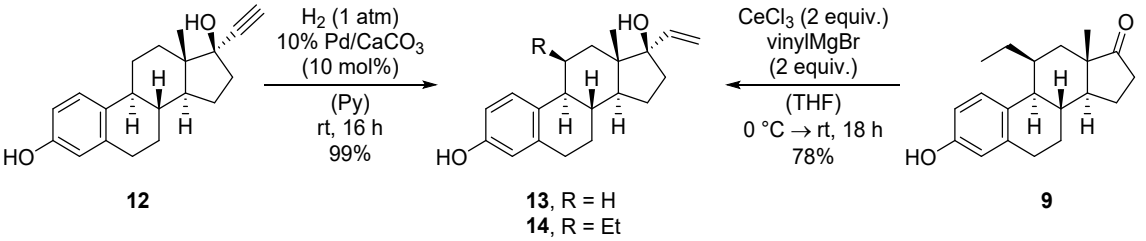


$C_{18}H_{24}O_3$
288.39

Steroid **4** (30 mg, 64 µmol, 1 equiv.) was dissolved in abs. CH_2Cl_2 (0.6 mL) and cooled to 0 °C. Then, a BBr_3 solution (192 µL, 192 µmol, 1M in CH_2Cl_2, 3 equiv.) was added dropwise, and the mixture was stirred at 0 °C for 45 min. After quenching with water, the mixture was extracted with EtOAc (3×10 mL). The organic layer was washed with saturated aq. $NaHCO_3$ and NaCl were dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was purified by column chromatography (PE/EtOAc 1:1 → 2:8) to obtain triol **11** (8.6 mg, 30 µmol, 47%) as a colourless solid.

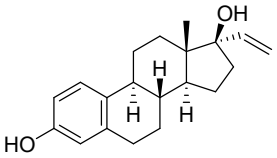
TLC: R_f (PE/EtOAc 3:7) = 0.13 [CAM]. **^{1}H NMR** (400 MHz, DMSO-d_6): δ [ppm] = 7.82 (d, *J* = 8.5 Hz, 1H), 6.46 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.42 (d, *J* = 2.3 Hz, 1H), 4.53 – 4.47 (m, 1H), 3.91 – 3.78 (m, 1H), 3.57 – 3.47 (m, 1H), 2.67 (dd, *J* = 8.2, 5.7 Hz, 2H), 2.09 (dd, *J* = 12.2, 5.0 Hz, 1H), 1.98 (t, *J* = 9.8 Hz, 1H), 1.93 – 1.81 (m, 1H), 1.81 – 1.70 (m, 1H), 1.61 – 1.50 (m, 1H), 1.43 – 1.02 (m, 8H), 0.62 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ [ppm] = 154.8, 137.9, 131.3, 128.0, 114.3, 112.1, 79.7, 69.4, 49.6, 49.1, 47.4, 43.5, 37.3, 29.9, 28.3, 27.0, 22.7, 11.9. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3305, 2919, 2852, 1742, 1463, 1450, 1379, 1352, 1253, 1135, 1077, 1048, 1011, 963, 930, 869, 818, 707, 658, 488, 462. **LRMS** (ESI): *m/z* 287 [M-H^-]. **HRMS** (ESI): *m/z* calculated for $C_{18}H_{23}O_3^-$: 287.1653, found 287.1653.

Synthesis of compounds 13-19



Scheme S3: Synthesis of 17α-vinylestradiols **13** and **14**.

(8*R*,9*S*,13*S*,14*S*,17*R*)-13-methyl-17-vinyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (13)

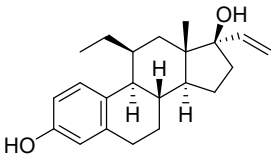


$C_{20}H_{26}O_2$
298.43

Ethinylestradiol **12** (100 mg, 0.34 mmol, 1 equiv.) was dissolved in pyridine (2 mL), $Pd/CaCO_3$ (36 mg, 10 mol%, 10%) was added, and the mixture was stirred for 16 h in a H_2 atmosphere (1 atm). The insoluble parts were filtered off over Celite®, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (CH/EtOAc 7:3) to give steroid **13** (100 mg, 0.34 mmol, 99%) as a colourless solid.

TLC: R_f (PE/EtOAc 7:3) = 0.24 [UV] [CAM]. **^{1}H NMR** (600 MHz, MeOD+$CDCl_3$): δ [ppm] = 7.05 (d, *J* = 8.5 Hz, 1H), 6.55 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.49 (d, *J* = 2.7 Hz, 1H), 6.07 (dd, *J* = 17.3, 10.9 Hz, 1H), 5.14 (d, *J* = 17.2 Hz, 1H), 5.09 (d, *J* = 10.9 Hz, 1H), 2.86 – 2.65 (m, 2H), 2.27 – 2.19 (m, 1H), 2.09 – 2.02 (m, 1H), 1.98 – 1.91 (m, 1H), 1.89 – 1.82 (m, 2H), 1.72 – 1.65 (m, 1H), 1.62 – 1.55 (m, 1H), 1.50 – 1.36 (m, 5H), 1.32 – 1.22 (m, 1H), 0.91 (s, 3H). **^{13}C NMR** (151 MHz, MeOD+$CDCl_3$): δ [ppm] = 155.2, 143.9, 138.6, 132.4, 126.9, 115.8, 113.4, 112.2, 84.7, 49.7, 47.4, 44.6, 40.5, 36.0, 32.9, 30.4, 28.3, 27.1, 23.9, 14.5. **IR** (ATR): $\tilde{u}$ [cm^{-1}] = 3333, 2972, 2935, 2872, 2858, 1617, 1584, 1497, 1473, 1453, 1379, 1357, 1285, 1250, 1157, 1111, 1035, 1016, 1006, 971, 937, 913, 874, 820. **LRMS** (ESI): *m/z* 281 [M-OH^+]. **HRMS** (ESI): *m/z* calculated for $C_{20}H_{26}NaO_2^+$: 321.1825, found 321.1824.

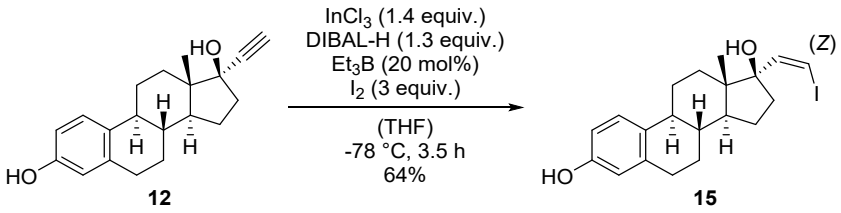
(8*S*,9*S*,11*S*,13*S*,14*S*,17*R*)-11-ethyl-13-methyl-17-vinyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (14)



$C_{22}H_{30}O_2$
326.48

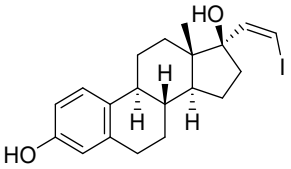
Cerium trichloride heptahydrate (42 mg, 0.11 mmol, 2 equiv.) was placed in a Schlenk flask and dried for 1 h at 140 °C in vacuo. Then, abs. THF (0.3 mL) was added, and the suspension was stirred for 2 h at room temperature. Steroid **9** (17 mg, 57 µmol 1 equiv.) was added at 0 °C, and the solution was stirred for 1 h at room temperature. After the dropwise addition of vinyl MgBr (114 µL, 114 µmol, 1M in THF, 2 equiv.) at 0 °C, the reaction was stirred for 15 h at room temperature. The reaction was quenched with aq. acetic acid (10%). Then, the mixture was extracted with EtOAc (3×5 mL), and the combined organic layer was washed with saturated aq. $NaHCO_3$ and NaCl were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (PE/EtOAc 8:2 → 7:3). Steroid **14** (15 mg, 44 µmol, 78%) was obtained as a colourless solid.

TLC: R_f (PE/EtOAc 8:2) = 0.24 [UV] [CAM]. **^{1}H NMR** (400 MHz, MeOD/$CDCl_3$): δ [ppm] = 6.93 (d, *J* = 8.4 Hz, 1H), 6.57 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.48 (d, *J* = 2.7 Hz, 1H), 6.09 (dd, *J* = 17.2, 10.9 Hz, 1H), 5.14 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.09 – 5.06 (m, 1H), 2.79 – 2.69 (m, 1H), 2.67 – 2.59 (m, 1H), 2.48 – 2.40 (m, 1H), 2.32 – 2.22 (m, 1H), 1.98 – 1.77 (m, 3H), 1.69 – 1.52 (m, 2H), 1.53 – 1.38 (m, 2H), 1.37 – 1.11 (m, 5H), 1.05 (s, 3H), 0.86 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, MeOD): δ [ppm] = 155.4, 145.1, 140.0, 130.3, 128.7, 116.1, 114.1, 112.1, 85.9, 52.3, 50.9, 39.9, 36.7, 36.7, 33.9, 31.4, 28.5, 24.1, 22.2, 18.2, 13.3. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3315, 2918, 1724, 1613, 1582, 1498, 1455, 1376, 1287, 1248, 1117, 1009, 934, 867, 823, 697, 568. **LRMS** (ESI): *m/z* 309 [M-OH^+]. **HRMS** (ESI): *m/z* calculated for $C_{22}H_{30}NaO_2^+$: 349.2138, found 349.2062.



Scheme S4: Stereoselective reduction of ethinylestradiol **12** to (Z)-olefin **15**.

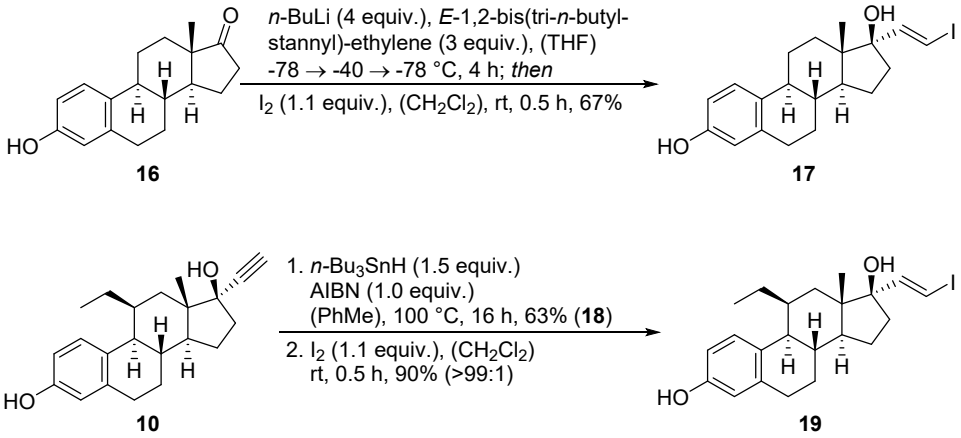
(8*R*,9*S*,13*S*,14*S*,17*R*)-17-((*Z*)-2-iodovinyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (15)



$C_{20}H_{25}IO_2$
424.32

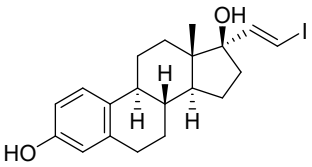
To a suspension of dry $InCl_3$ (50 mg, 0.23 mmol, 1.4 equiv.) in abs. THF (1.7 mL) was added dropwise DIBAL-H (223 µL, 223 µmol, 1M in THF, 1.3 equiv.) at -78 °C. After 30 min at -78 °C, ethinylestradiol (**12**) (50 mg, 0.17 mmol, 1 equiv.) diluted in abs. THF was added, followed by Et_3B (34 µL, 34 µmol, 20 mol%, 1M in hexane). The mixture was stirred for 2.5 h at -78 °C, then iodine (12 mg, 0.51 mmol, 3 equiv.) was added, and the mixture was stirred for 30 min at -78 °C. The reaction mixture was diluted with saturated aq. $NaHCO_3$ and $Na_2S_2O_3$. Then, the aqueous layer was extracted with Et_2O (3×20 mL), the combined organic layer was dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was purified by column chromatography (CH → CH/EtOAc 8:2) to give product **15** as a colourless solid (46.0 mg, 108 µmol, 64%).

TLC: R_f (PE/EtOAc 8:2) = 0.20 [$KMnO_4$] [CAM]. **^{1}H NMR** (400 MHz, MeOD): δ [ppm] = 7.07 (d, *J* = 8.3 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 1H), 6.53 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.47 (d, *J* = 8.6 Hz, 2H), 2.83 – 2.72 (m, 2H), 2.39 – 2.24 (m, 2H), 2.15 – 2.03 (m, 1H), 1.95 – 1.76 (m, 3H), 1.79 – 1.70 (m, 1H), 1.56 (td, *J* = 12.7, 3.8 Hz, 1H), 1.50 – 1.25 (m, 5H), 0.94 (s, 3H). **^{13}C NMR** (101 MHz, MeOD): δ [ppm] = 155.9, 145.2, 138.8, 132.5, 127.2, 116.1, 113.7, 85.3, 77.2, 50.6, 49.3, 45.0, 41.3, 36.8, 33.1, 30.7, 28.8, 27.6, 24.2, 14.8. The spectroscopical data were identical to those reported in the literature.[4]



Scheme S5: Synthesis of vinyl iodine **17** and **19**. The lower part of Scheme S5 is identical to Figure 2 of the main text.

(8*R*,9*S*,13*S*,14*S*,17*R*)-17-((*E*)-2-iodovinyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (17)



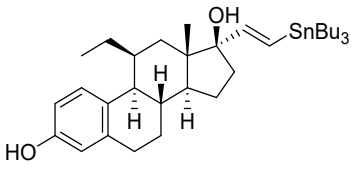
$C_{20}H_{25}IO_2$
424.32

To a solution of estrone (**16**) (40 mg, 0.15 mmol, 1 equiv., prepared from 17β-estradiol in 89% yield) in abs. THF (1.6 mL) was added *n*-BuLi (59 µL, 0.15 mmol, 1 equiv., 2.5M in hexane) dropwise at -78 °C. The reaction mixture was slowly warmed to room temperature for 1 h. In a separate flask, (*E*)-1,2-bis(tri-*n*-butylstannyl)ethylene (234 µL, 444 µmol, 3 equiv.) was diluted in THF (4.2 mL) and cooled to -78 °C followed by dropwise addition of *n*-BuLi (178 µL, 444 µmol, 3 equiv., 2.5M in hexane). The reaction mixture was stirred at -78 °C for 1 h, then warmed to -40 °C and stirred at this temperature for 1 h. Then, the solution was cooled again to -78 °C and added to the estrone solution. The reaction mixture was stirred at -78 °C for 2 h and was diluted with saturated aq. NH_4Cl. The mixture was extracted with CH_2Cl_2 (3×20 mL), and the organic layer was washed with saturated aq. NaCl was dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was purified by column chromatography (CH/EtOAc 8:2) to afford stannane (27 mg, 46 µmol, 31%, 94% brsm) as a colourless solid. The stannane (20 mg, 32 µmol, 1 equiv.) was directly dissolved in abs. CH_2Cl_2 (0.1 mL) and iodine (9 mg, 35 µmol, 1.1 equiv.) dissolved in little amount of CH_2Cl_2 was slowly added to the reaction mixture. After stirring for 0.5 h at room temperature, the reaction was quenched with saturated aq. Na_2SO_3 and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layer was washed with saturated aq. NaCl, dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo.

The residue was purified by column chromatography (PE → PE/EtOAc 6:4) to give steroid **17** (12 mg, 29 µmol, 67%).

TLC: R_f (PE/EtOAc 7:3) = 0.36 [$KMnO_4$]. **^{1}H NMR** (600 MHz, MeOD): δ [ppm] = 7.06 (dd, *J* = 8.6, 1.1 Hz, 1H), 6.81 (d, *J* = 14.4 Hz, 1H), 6.53 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.47 (d, *J* = 2.5 Hz, 1H), 6.29 (d, *J* = 14.4 Hz, 1H), 2.84 – 2.72 (m, 2H), 2.33 – 2.24 (m, 1H), 2.12 – 2.06 (m, 1H), 1.98 – 1.91 (m, 1H), 1.91 – 1.81 (m, 2H), 1.79 – 1.71 (m, 1H), 1.69 – 1.62 (m, 2H), 1.48 – 1.31 (m, 5H), 0.92 (s, 3H). **^{13}C NMR** (151 MHz, MeOD): δ [ppm] = 155.9, 152.8, 138.8, 132.5, 127.2, 116.1, 113.7, 87.8, 74.2, 50.6, 48.3, 45.1, 41.1, 36.5, 33.7, 30.7, 28.7, 27.6, 24.2, 14.6. The spectroscopical data were identical to those reported in the literature.[4]

(8*S*,9*S*,11*S*,13*S*,14*S*,17*R*)-11-ethyl-13-methyl-17-((*E*)-2-(tributylstannyl)vinyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (18)

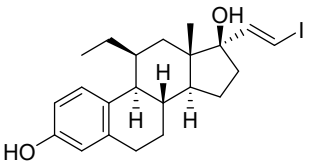


$C_{34}H_{56}O_2Sn$
615.53

A mixture containing steroid **10** (30 mg, 92 µmol, 1 equiv.), AIBN (22.8 mg, 139 µmol, 1 equiv.) and *n*-Bu_3SnH (36.7 µL, 139 µmol, 1.5 equiv.) in abs. toluene (1.4 mL) was heated to 100 °C for 16 h. Then, the reaction solution was concentrated under reduced pressure and the residue was purified by column chromatography (PE/EtOAc 95:5) to give stannane **18** (36 mg, 58 µmol, 63%, (*E*) >99:1) as a colourless solid.

TLC: R_f (PE/EtOAc 6:4) = 0.63 [UV] [CAM]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.02 – 6.95 (m, 1H), 6.62 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.53 (d, *J* = 2.7 Hz, 1H), 6.23 (d, *J* = 19.4 Hz, 1H), 6.07 (d, *J* = 19.3 Hz, 1H), 4.84 (br s, 1H), 2.85 – 2.72 (m, 1H), 2.72 – 2.61 (m, 1H), 2.45 (dd, *J* = 10.7, 4.8 Hz, 1H), 2.37 – 2.25 (m, 1H), 2.10 – 1.94 (m, 1H), 1.93 – 1.82 (m, 3H), 1.73 – 1.60 (m, 3H), 1.57 – 1.43 (m, 8H), 1.36 – 1.21 (m, 12H), 1.10 (s, 3H), 0.96 – 0.85 (m, 15H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 153.0, 153.0, 139.4, 130.5, 128.1, 124.5, 115.4, 113.2, 86.6, 51.2, 49.7, 47.6, 38.6, 36.3, 35.3, 33.0, 30.4, 29.4, 27.4, 27.3, 23.5, 21.3, 17.8, 13.9, 13.1, 9.8. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3358, 2955, 2921, 2870, 2851, 1611, 1586,1499, 1455, 1418, 1376, 1357, 1321, 1286, 1245, 1216, 1194, 1153, 1108, 1071, 1055, 1006, 958, 926, 865, 822, 793, 755, 722, 687, 666, 653, 615, 592, 503. **LRMS** (ESI): *m/z* 599 [M-OH$^+$] **HRMS** (ESI): *m/z* calculated for $C_{34}H_{56}NaO_2Sn^+$: 639.3194, found 639.3207.

(8*S*,9*S*,11*S*,13*S*,14*S*,17*R*)-11-ethyl-17-((*E*)-2-iodovinyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (19)

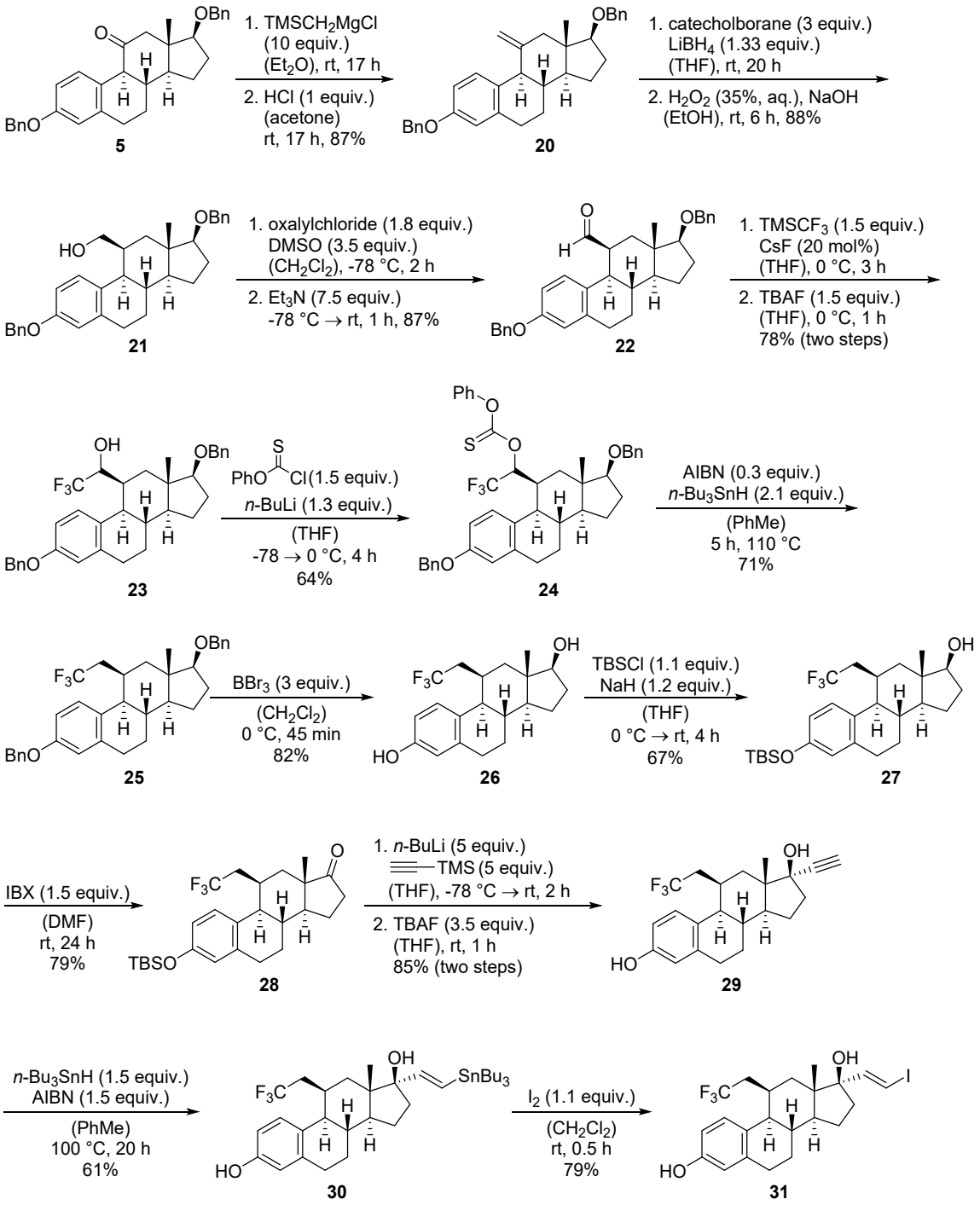


$C_{22}H_{29}IO_2$
452.38

Stannane **18** (25 mg, 43 µmol, 1 equiv.) was dissolved in abs. CH_2Cl_2 (0.1 mL) and iodine (12 mg, 47 µmol, 1.1 equiv.) dissolved in little CH_2Cl_2 was slowly added to the reaction mixture. After stirring for 0.5 h at room temperature, the reaction was quenched with saturated aq. Na_2SO_3 and the aqueous layer were extracted with EtOAc (3×5 mL). The combined organic layer was washed with saturated aq. NaCl was dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was purified by column chromatography (CH/EtOAc 9:1 → 7:3) and chromatographic purification via HPLC (Nucleodur C18 column, MeCN/H_2O 8:2, (*E*) >99:1) to give steroid **19** (13 mg, 29 µmol, 90%) as a colourless solid.

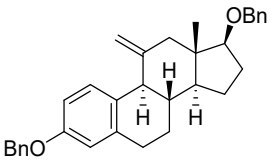
TLC: R_f (PE/EtOAc 6:4) = 0.52 [$KMnO_4$]. **^{1}H NMR** (400 MHz, MeOD): δ [ppm] 6.97 (d, *J* = 8.5 Hz, 1H), 6.83 (d, *J* = 14.4 Hz, 1H), 6.60 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.51 (d, *J* = 2.6 Hz, 1H), 6.32 (d, *J* = 14.4 Hz, 1H), 2.89 – 2.80 (m, 1H), 2.80 – 2.71 (m, 1H), 2.71 – 2.63 (m, 1H), 2.60 – 2.53 (m, 1H), 2.34 – 2.21 (m, 1H), 2.08 – 2.01 (m, 1H), 1.99 – 1.81 (m, 4H), 1.77 – 1.68 (m, 1H), 1.64 – 1.45 (m, 4H), 1.36 – 1.26 (m, 3H), 1.10 (s, 3H). **^{13}C NMR** (151 MHz, MeOD): δ [ppm] = 155.5, 153.2, 140.0, 130.1, 128.8, 116.1, 114.2, 88.7, 74.0, 52.6, 50.9, 49.1, 39.9, 36.8, 36.8, 34.2, 31.4, 28.4, 24.1, 22.2, 18.0, 13.3. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3253, 2956, 2921, 2865, 2851, 2429, 2284, 1619, 1498, 1456, 1378,1246, 1183, 1151, 1109, 1078, 1008, 956, 916, 868, 810, 793, 693, 586. **LRMS** (ESI): *m/z* 453 [M+H$^+$]. **HRMS** (APCI): *m/z* calculated for $C_{22}H_{29}IO_2^+$: 452.1207, found 452.1209.

Synthesis of compound 31



Scheme S6: Synthesis of steroid **31**. Scheme S6 is identical to Figure 3 of the main text.

(8*S*,9*R*,13*S*,14*S*,17*S*)-3,17-bis(benzyloxy)-13-methyl-11-methylen-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene (20)

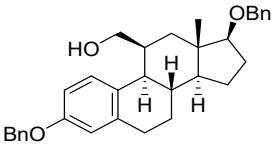


$C_{33}H_{36}O_2$
464.65

To a solution of steroid **5** (147 mg, 315 µmol, 1 equiv.) in abs. Et_2O (4.7 mL) was added $TMSCH_2MgCl$ (3.15 mL, 3.15 mmol, 1M in Et_2O, 10 equiv.). The reaction was stirred at room temperature for 17 h before the reaction was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted with $CHCl_3$ (3×20 mL) and the combined organic layer was washed with water, dried over Na_2SO_4, filtered, and evaporated in vacuo. Then, the resulting colourless solid was dissolved in a mixture of acetone (3.1 mL) and concentrated HCl (8.6 µL, 37%, 1 equiv.) and stirred for 17 h at room temperature. After concentrating the solution under a stream of N_2, the residue was dissolved in EtOAc (20 mL) and washed with saturated aq. $NaHCO_3$ and NaCl. The organic layer was dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (CH/EtOAc 9:1) to give the terminal alkene **20** (127 mg, 273 µmol, 87%) as a colourless solid.

TLC: R_f (PE/EtOAc 8:2) = 0.76 [UV] [$KMnO_4$]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.47 – 7.26 (m, 10H), 6.78 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.72 (d, *J* = 2.8 Hz, 1H), 5.04 (s, 2H), 4.89 – 4.84 (m, 2H), 4.58 (s, 2H), 3.63 – 3.57 (m, 1H), 3.02 (d, *J* = 9.8 Hz, 1H), 2.90 – 2.77 (m, 1H), 2.75 – 2.66 (m, 1H), 2.58 (d, *J* = 11.8 Hz, 1H), 2.15 – 2.07 (m, 2H), 1.86 – 1.78 (m, 1H), 1.73 – 1.59 (m, 2H), 1.52 – 1.27 (m, 5H), 0.85 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 156.8, 148.0, 139.5, 139.4, 137.5, 131.3, 128.7, 128.4, 128.4, 128.0, 127.6, 127.5, 127.5, 114.8, 112.4, 109.7, 87.3, 71.8, 70.1, 51.6, 51.3, 50.0, 46.0, 41.8, 31.0, 28.6, 27.1, 23.0, 12.4. The spectroscopical data were identical to those reported in the literature.[5]

((8*S*,9*R*,11*S*,13*S*,14*S*,17*S*)-3,17-bis(benzyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-11-yl)methanol (21)

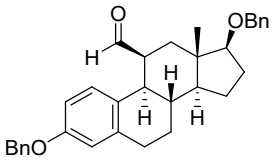


$C_{33}H_{38}O_3$
482.66

Steroid **20** (309 mg, 665 µmol, 1 equiv.) was dissolved in abs. THF (3.3 mL). After addition of catecholborane (2.0 mL, 2.0 mmol, 1M in THF, 3 equiv.) and $LiBH_4$ (19.2 mg, 884 µmol, 1.33 equiv.), the reaction mixture was stirred for 20 h at room temperature. Then, this was carefully added to a solution cooled to 0 °C containing aq. NaOH (888 µL, 33%), ethanol (2.8 mL), and aq. H_2O_2 (2.85 mL, 33.3 mmol, 35%) and stirred for 6 h at room temperature. The reaction was quenched by addition of water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3×20 mL), and the combined organic layer was washed with water (3×20 mL) and saturated aq.NaCl was dried over Na_2SO_4 and filtered. The solvent was evaporated in vacuo to give the primary alcohol **21** as a colourless, foamy solid (284 mg, 588 µmol, 88%).

TLC: R_f (PE/EtOAc 8:2) = 0.22 [UV] [CAM]. **^{1}H NMR** (600 MHz, $CDCl_3$): δ [ppm] = 7.46 – 7.43 (m, 2H), 7.42 – 7.32 (m, 7H), 7.31 – 7.27 (m, 1H), 7.24 (d, *J* = 8.5 Hz, 1H), 6.81 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.71 (d, *J* = 2.7 Hz, 1H), 5.04 (s, 2H), 4.61 (d, *J* = 5.1 Hz, 2H), 3.70 (dd, *J* = 11.2, 5.5 Hz, 1H), 3.57 (dd, *J* = 11.2, 9.3 Hz, 1H), 3.52 (dd, *J* = 8.8, 7.2 Hz, 1H), 2.88 – 2.69 (m, 3H), 2.62 (dd, *J* = 11.1, 5.0 Hz, 1H), 2.51 (dd, *J* = 13.5, 1.8 Hz, 1H), 2.10 – 1.98 (m, 1H), 1.93 – 1.85 (m, 1H), 1.72 – 1.57 (m, 3H), 1.50 (dd, *J* = 13.5, 5.6 Hz, 1H), 1.47 – 1.37 (m, 1H), 1.33 – 1.17 (m, 2H), 1.02 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ [ppm] = 156.7, 139.4, 139.1, 137.4, 129.7, 128.7, 128.4, 128.0, 127.8, 127.6, 127.5, 127.4, 115.1, 113.0, 89.4, 71.8, 70.1, 63.3, 51.9, 47.6, 43.6, 39.7, 39.4, 35.1, 30.5, 28.2, 27.1, 23.2, 15.1. The spectroscopical data were identical to those reported in the literature.[5]

(8*S*,9*R*,11*S*,13*S*,14*S*,17*S*)-3,17-bis(benzyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-11-carbaldehyde (22)

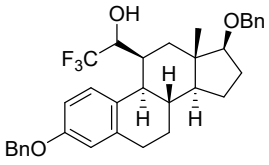


$C_{33}H_{36}O_3$
480.65

Oxalyl chloride (80 µL, 0.93 mmol, 1.8 equiv.) was dissolved in abs. CH_2Cl_2 (2.6 mL) at -78 °C. Then, abs. DMSO (129 µL, 1.81 mmol, 3.5 equiv.) was added dropwise, and the reaction mixture was stirred for 30 min at -78 °C. After that, alcohol **21** (250 mg, 0.52 mmol, 1 equiv.) diluted in abs. CH_2Cl_2 was added to the mixture at -78 °C and stirred for further 1.5 h at this temperature. Et_3N (0.54 mL, 3.9 mmol, 7.5 equiv.) was added to the reaction mixture, and the solution was slowly warmed to room temperature over 1 h. Then, water was added, and the mixture was extracted with EtOAc (3×20 mL). The organic layer was washed with saturated aq. NH_4Cl and NaCl were dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was purified by column chromatography (CH/EtOAc 9:1 → 8:2), and aldehyde **22** (200 mg, 416 µmol, 87%) was isolated as a colourless viscous oil.

TLC: R_f (PE/EtOAc 8:2) = 0.50 [UV] [$KMnO_4$]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 9.71 (d, *J* = 1.5 Hz, 1H), 7.45 – 7.27 (m, 10H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.78 – 6.72 (m, 2H), 5.02 (s, 2H), 4.56 (s, 2H), 3.56 – 3.51 (m, 1H), 3.26 – 3.19 (m, 1H), 3.02 – 2.90 (m, 1H), 2.88 – 2.80 (m, 1H), 2.67 – 2.57 (m, 2H), 2.11 – 2.03 (m, 1H), 2.00 – 1.93 (m, 1H), 1.89 – 1.78 (m, 1H), 1.76 – 1.65 (m, 2H), 1.65 – 1.57 (m, 1H), 1.48 – 1.33 (m, 2H), 1.27 – 1.16 (m, 1H), 0.74 (d, *J* = 0.8 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ [ppm] = 205.8, 157.0, 139.1, 138.8, 137.3, 129.4, 128.7, 128.4, 128.0, 127.6, 127.5, 127.5, 127.0, 115.7, 112.9, 88.1, 71.8, 70.1, 50.3, 48.0, 44.8, 43.6, 41.4, 35.8, 30.1, 28.1, 27.3, 23.2, 15.0. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 2926, 2870, 2854, 1715, 1607, 1499, 1454, 1382, 1279, 1250, 1234, 1158, 1121, 1107, 1074, 1027, 879, 734, 697. **LRMS** (ESI): *m/z* 498 [$M+NH_4^+$]. **HRMS** (ESI): *m/z* calculated for $C_{33}H_{36}NaO_3^+$: 503.2557, found 503.2553.

1-((8*S*,9*R*,11*S*,13*S*,14*S*,17*S*)-3,17-bis(benzyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-11-yl)-2,2,2-trifluoroethan-1-ol (23)

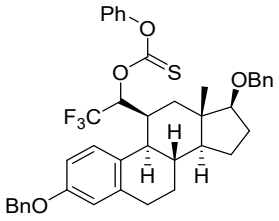


$C_{34}H_{37}F_3O_3$
550.66

Aldehyde **22** (360 mg, 749 µmol, 1 equiv.) was dissolved in abs. THF (5 mL) and CsF (22.8 mg, 150 µmol, 20 mol%), and $TMSCF_3$ (166 µL, 1.12 mmol, 1.5 equiv.) were added successively at 0 °C. The solution was stirred at 0 °C for 3 h, followed by addition of water. The mixture was extracted with EtOAc (3×30 mL), and the combined organic layer was washed with saturated aq. NaCl dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo (crude yield: 420 mg). The residue was redissolved in abs. THF (5 mL), TBAF (1.12 mL, 1.12 mmol, 1M in THF, 1.5 equiv.) was added dropwise at 0 °C and the mixture was stirred for 1 h. Then, the mixture was diluted with water, and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layer was washed with saturated aq. NaCl was dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was purified by column chromatography (CH/EtOAc 95:5 → 9:1) to give alcohol **23** (320 mg, 581 µmol, 78% over two steps) as a colourless oil.

TLC: R_f (PE/EtOAc 8:2) = 0.39 [$KMnO_4$]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.47 – 7.24 (m, 10H), 6.84 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.73 (d, *J* = 2.7 Hz, 1H), 5.08 – 4.97 (m, 2H), 4.58 (d, *J* = 12.1 Hz, 1H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.44 – 4.32 (m, 1H), 3.49 (dd, *J* = 8.8, 6.9 Hz, 1H), 3.11 – 3.00 (m, 1H), 2.96 – 2.80 (m, 1H), 2.78 – 2.59 (m, 2H), 2.24 – 2.16 (m, 1H), 2.13 – 2.00 (m, 2H), 1.97 – 1.88 (m, 1H), 1.76 – 1.60 (m, 4H), 1.13 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 157.3, 139.6, 139.2, 137.1, 129.2, 128.7, 128.5, 128.1, 127.7, 127.6, 127.6, 127.5, 116.1, 113.3, 89.4, 73.7 (q, *J* = 29.2 Hz), 71.8, 70.2, 52.1, 48.1, 44.0, 42.7, 35.7, 35.2, 30.5, 28.0, 27.2, 23.4, 15.6. **^{19}F NMR** (376 MHz, $CDCl_3$): δ [ppm] = -78.79 (d, *J* = 7.5 Hz). **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3525, 2927, 2859, 1607, 1498, 1454, 1254, 1236, 1156, 1137, 1122, 1102, 1084, 1073, 1027, 735, 697. **LRMS** (ESI): *m/z* 586 [$M+NH_4^+$]. **HRMS** (ESI): *m/z* calculated for $C_{34}H_{37}F_3NaO_3^+$: 573.2587, found 573.2595.

***O*-1-((8*S*,9*R*,11*S*,13*S*,14*S*,17*S*)-3,17-bis(benzyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-11-yl)-2,2,2-trifluoroethyl)-*O*-phenylcarbonthioate (24)**

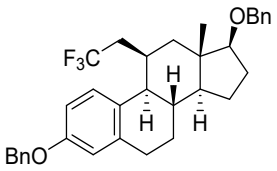


$C_{41}H_{41}F_3O_4S$
686.83

To a solution of alcohol **23** (300 mg, 544 µmol, 1 equiv.) in abs. THF (5.8 mL) was added *n*-BuLi (283 µL, 708 µmol, 2.5M in hexane, 1.3 equiv.) at -78 °C. The resulting mixture was stirred for 0.5 h at -78 °C before *O*-phenylchlorothionoformate (113 µL, 0.82 mmol, 1.5 equiv.) in abs. THF (1.1 mL) was added. The solution was stirred for 3 h at 0 °C followed by quenching with saturated aq. NH_4Cl and EtOAc. The mixture was extracted with EtOAc (3×20 mL), and the combined organic layer was dried over Na_2SO_4, filtered, and the solvent evaporated in vacuo. The residue was purified by column chromatography (CH/EtOAc 95:5) to afford steroid **24** (240 mg, 349 µmol, 64%) as a viscous orange oil.

TLC: R_f (PE/EtOAc 9:1) = 0.23 [$KMnO_4$]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.48 – 7.27 (m, 12H), 7.25 – 7.19 (m, 1H), 6.87 – 6.80 (m, 3H), 6.69 (d, *J* = 2.7 Hz, 1H), 6.62 – 6.53 (m, 1H), 4.94 (s, 2H), 4.58 – 4.56 (m, 2H), 3.52 (dd, *J* = 8.8, 6.8 Hz, 1H), 3.43 – 3.33 (m, 1H), 2.91 – 2.75 (m, 2H), 2.68 – 2.58 (m, 1H), 2.54 (d, *J* = 14.4 Hz, 1H), 2.12 – 1.99 (m, 2H), 1.96 – 1.87 (m, 1H), 1.72 – 1.59 (m, 3H), 1.56 – 1.44 (m, 1H), 1.31 – 1.21 (m, 3H), 1.16 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 194.8, 156.5, 153.6, 139.2, 138.3, 137.4, 129.7, 129.4, 129.3, 128.6, 128.5, 128.0, 127.6, 127.5, 127.5, 126.6, 121.6, 114.9, 112.6, 89.1, 71.9, 70.1, 53.8, 49.5, 43.6, 39.5, 36.0, 35.2, 30.5, 28.4, 27.4, 23.3, 15.9. **^{19}F NMR** (376 MHz, $CDCl_3$): δ [ppm] = -71.75 (d, *J* = 5.8 Hz). **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 2931, 2865, 1608, 1499, 1455, 1354, 1315, 1279, 1250, 1209, 1175, 1137, 1122, 1066, 1026, 1004, 735, 697. **LRMS** (ESI): *m/z* 704 [$M+NH_4^+$]. **HRMS** (ESI): *m/z* calculated for $C_{41}H_{41}F_3NaO_4S^+$: 709.2570, found 709.2574.

(8*S*,9*S*,11*R*,13*S*,14*S*,17*S*)-3,17-bis(benzyloxy)-13-methyl-11-(2,2,2-trifluoroethyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene (25)

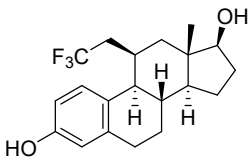


$C_{34}H_{37}F_3O_2$
534.66

To a solution of steroid **24** (172 mg, 250 µmol, 1 equiv.) in abs. toluene (3 mL) *n*-Bu_3SnH (141 µL, 526 µmol, 2.1 equiv.) was added, followed by AIBN (12 mg, 75 µmol, 0.3 equiv.). The mixture was stirred at 110 °C for 5 h, and after cooling to room temperature, the solvent was evaporated in vacuo. The residue was loaded onto silica gel and purified by column chromatography (CH/EtOAc 8:2) to give steroid **25** (95 mg, 0.18 mmol, 71%) as a colourless oil.

TLC: R_f (PE/EtOAc 8:2) = 0.25 [$KMnO_4$]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.48 – 7.27 (m, 10H), 7.08 (d, *J* = 8.6 Hz, 1H), 6.84 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.72 (d, *J* = 2.8 Hz, 1H), 5.05 (s, 2H), 4.59 (s, 2H), 3.57 – 3.46 (m, 1H), 2.87 – 2.68 (m, 3H), 2.61 (dd, *J* = 10.9, 4.9 Hz, 1H), 2.54 – 2.43 (m, 1H), 2.36 – 2.17 (m, 1H), 2.14 – 1.96 (m, 2H), 1.93 – 1.82 (m, 1H), 1.77 – 1.49 (m, 3H), 1.44 – 1.11 (m, 4H), 1.06 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 156.9, 139.4, 139.3, 137.4, 129.2, 128.7, 128.4, 128.1 (q, *J* = 277.4 Hz), 128.0, 127.6, 127.6, 127.5, 127.5, 115.3, 113.4, 89.6, 71.9, 70.1, 51.9, 49.1, 43.6, 40.6, 34.6, 32.7 (q, *J* = 26.7 Hz), 30.8 (d, *J* = 1.8 Hz), 30.4, 28.2, 27.0, 23.3, 16.3. **^{19}F NMR** (376 MHz, $CDCl_3$): δ [ppm] = -63.05 (t, *J* = 11.4 Hz). **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3032, 2955, 2920, 2871, 2853, 1605, 1498, 1455, 1377, 1253, 1127, 1105, 1071, 1025, 960, 880, 734, 694, 596, 508.

(8*S*,9*S*,11*R*,13*S*,14*S*,17*S*)-13-methyl-11-(2,2,2-trifluoroethyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (26)



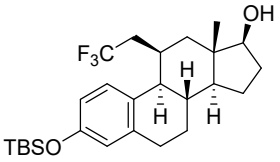
$C_{20}H_{25}F_3O_2$
354.41

Steroid **25** (62 mg, 0.12 mmol, 1 equiv.) was dissolved in abs. CH_2Cl_2 (1.3 mL) and cooled to 0 °C. Then, a BBr_3 solution (348 µL, 348 µmol, 1M in CH_2Cl_2, 3 equiv.) was slowly added to the reaction mixture and stirred at 0 °C for 45 min. The reaction was quenched with water, and the mixture was extracted with EtOAc (3×10 mL). The organic layer was washed with saturated aq. $NaHCO_3$ and NaCl, dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. Column chromatographic purification

(CH/EtOAc 8:2 → 6:4) afforded the 17β-estradiol derivative **26** (34 mg, 95 µmol, 82%) as a colourless solid.

TLC: R_f (PE/EtOAc 6:4) = 0.22 [CAM]. **^{1}H NMR** (400 MHz, MeOD): δ [ppm] = 6.97 (d, *J* = 8.5 Hz, 1H), 6.62 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.53 (d, *J* = 2.7 Hz, 1H), 3.68 (dd, *J* = 9.1, 7.4 Hz, 1H), 2.90 – 2.72 (m, 2H), 2.67 (ddd, *J* = 16.5, 5.0, 2.1 Hz, 1H), 2.58 (dd, *J* = 10.9, 4.8 Hz, 1H), 2.38 (dd, *J* = 13.8, 1.9 Hz, 1H), 2.33 – 2.20 (m, 1H), 2.11 – 2.04 (m, 1H), 2.02 – 1.93 (m, 1H), 1.91 – 1.84 (m, 1H), 1.74 – 1.63 (m, 1H), 1.59 – 1.29 (m, 5H), 1.23 – 1.14 (m, 1H), 0.96 (s, 3H). **^{13}C NMR** (101 MHz, MeOD): δ [ppm] = 156.1, 140.5, 129.2 (q, *J* = 276 Hz), 128.8, 128.3, 116.5, 114.6, 83.7, 52.7, 50.3, 44.4, 40.4, 36.1, 33.41 (q, *J* = 26.7 Hz), 32.02 (q, *J* = 2.2 Hz) 31.1, 30.6, 28.0, 24.0, 16.0. **^{19}F NMR** (376 MHz, $CDCl_3$): δ [ppm] = -64.50 (t, *J* = 11.6 Hz). **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3364, 2924, 2854, 1499, 1451, 1354, 1254, 1156, 1136, 1118, 1096, 1052, 1010. **LRMS** (ESI): *m/z* 353 [M-H$^-$]. **HRMS** (ESI): *m/z* calculated for $C_{20}H_{24}F_3O_2^-$: 353.1734, found 353.1739.

(8*S*,9*S*,11*R*,13*S*,14*S*,17*S*)-3-((*tert*-butyldimethylsilyl)oxy)-13-methyl-11-(2,2,2-trifluoroethyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-17-ol (27)



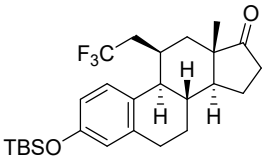
$C_{26}H_{39}F_3O_2Si$
468.68

Steroid **26** (144 mg, 406 µmol, 1 equiv.) was dissolved in abs. THF (0.6 mL) and the solution was cooled to 0 °C followed by addition of NaH (20.0 mg, 488 µmol, 60% oil dispersion, 1.2 equiv.). After stirring the reaction mixture for 0.5 h, TBSCl (80.0 mg, 528 µmol, 1.1 equiv.) was added and the reaction was warmed to room temperature. The reaction mixture was stirred at room temperature for 4 h followed by quenching with water. The mixture was extracted with CH_2Cl_2 (3×30 mL) and the combined organic layer was dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (CH/EtOAc 8:2) to give silyl ether **27** (129 mg, 275 µmol, 67%) as a colourless oil.

TLC: R_f (PE/EtOAc 1:1) = 0.49 [CAM]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.02 – 6.94 (m, 1H), 6.69 – 6.63 (m, 1H), 6.58 – 6.55 (m, 1H), 3.73 (dd, *J* = 9.1, 7.2 Hz, 1H), 2.90 – 2.80 (m, 1H), 2.79 – 2.66 (m, 2H), 2.60 (dd, *J* = 11.0, 4.9 Hz, 1H), 2.40 – 2.31 (m, 1H), 2.26 – 2.06 (m, 2H), 2.04 – 1.96 (m, 1H), 1.93 – 1.84 (m, 1H), 1.75 – 1.64 (m, 1H), 1.55 – 1.46 (m, 3H), 1.41 – 1.30 (m, 2H), 1.24 – 1.14 (m, 1H), 0.98 (s, 9H), 0.96 (s, 3H), 0.19 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 153.5, 139.3, 129.4, 127.9 (q, *J* = 277 Hz), 127.4, 120.5, 118.3, 83.3, 51.8, 49.2, 43.4, 39.4, 34.9, 32.6 (q, *J* = 26.4 Hz), 30.7 (q, *J* = 2.3 Hz), 30.6,

30.2, 27.0, 25.8, 23.3, 18.3, 15.6, -4.2, -4.2. **^{19}F NMR** (376 MHz, $CDCl_3$): δ [ppm] = -63.09 (t, *J* = 11.5 Hz). **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 2926, 1764, 1631, 1445, 1378, 1220, 1112, 1031, 968, 867, 770, 453. **LRMS** (ESI): *m/z* 469 [$M+H^+$]. **HRMS** (ESI): *m/z* calculated for $C_{26}H_{40}F_3O_2S^+$: 469.2744, found 469.2749.

(8*S*,9*S*,11*R*,13*S*,14*S*)-3-((*tert*-butyldimethylsilyl)oxy)-13-methyl-11-(2,2,2-trifluoroethyl)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (28)

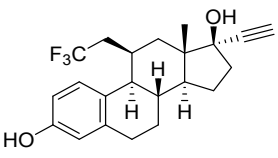


$C_{26}H_{37}F_3O_2Si$
466.66

Silylether **27** (129 mg, 275 µmol, 1 equiv.) was dissolved in DMF (2 mL) and IBX (116 mg, 413 µmol, 1.5 equiv.) was added. The reaction solution was stirred at room temperature for 24 h before CH_2Cl_2 was added and the colourless solid was filtered off over Celite®. The solvent was evaporated in vacuo and the residue was purified by column chromatography (CH/EtOAc 8:2) to give ketone **28** as a yellowish oil (101 mg, 217 µmol, 79%).

TLC: R_f (PE/EtOAc 1:1) = 0.60 [CAM]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 6.99 (dd, *J* = 8.7, 1.0 Hz, 1H), 6.67 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.59 – 6.56 (m, 1H), 2.89 (ddd, *J* = 19.4, 12.4, 4.9 Hz, 1H), 2.83 – 2.69 (m, 2H), 2.66 (dd, *J* = 10.8, 4.9 Hz, 1H), 2.62 – 2.47 (m, 1H), 2.38 – 2.27 (m, 1H), 2.17 – 2.05 (m, 3H), 2.03 – 1.93 (m, 2H), 1.72 – 1.57 (m, 3H), 1.56 – 1.36 (m, 2H), 1.06 (s, 3H), 1.01 – 0.96 (m, 9H), 0.20 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 217.7, 153.7, 139.0, 128.8, 127.8 (q, *J* = 277 Hz), 127.4, 120.6, 118.5, 52.1, 49.2, 47.4, 35.2, 34.4, 33.7, 32.9 (q, *J* = 26.9 Hz), 30.6 (q, *J* = 2.0 Hz), 30.0, 26.3, 25.8, 21.3, 18.3, 16.9, -4.2, -4.3. **^{19}F NMR** (376 MHz, $CDCl_3$): δ [ppm] = -63.07 (t, *J* = 11.2 Hz). **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 2929, 2858, 1741, 1608, 1497, 1389, 1244, 1159, 1129, 1107, 1006, 941, 839, 781. **LRMS** (ESI): *m/z* 484 [$M+NH_4^+$]. **HRMS** (ESI): *m/z* calculated for $C_{26}H_{37}F_3NaO_2Si^+$: 489.2407, found 489.2409.

(8*S*,9*S*,11*R*,13*S*,14*S*,17*R*)-17-ethinyl-13-methyl-11-(2,2,2-trifluorethyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (29)

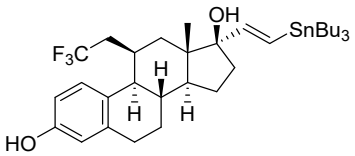


$C_{22}H_{25}F_3O_2$
378.44

TMS acetylene (154 µL, 1.08 mmol, 5 equiv.) was dissolved in abs. THF (1 mL) at -78 °C followed by addition of *n*-BuLi (433 µL, 1.08 mmol, 5 equiv.) and the mixture was stirred at -78 °C for 0.5 h. Then, ketone **28** (101 mg, 216 µmol, 1 equiv.) was added and after further 0.5 h at -78 °C, the solution was stirred for 2 h at room temperature. The reaction was diluted with saturated aq. NH_4Cl and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layer was dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was purified by column chromatography (CH/EtOAc 8:2). The isolated crude material was dissolved in abs. THF (1 mL), then TBAF (758 µL, 758 µmol, 1M in THF, 3.5 equiv.) was added and the solution was stirred for 1 h at room temperature. The reaction was quenched with water and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated in vacuo. The residue was purified by column chromatography (CH/EtOAc 8:2) to give alkyne **29** (70 mg, 18 µmol, 85% over two steps) as a colourless solid.

TLC: R_f (PE/EtOAc 1:1) = 0.55 [CAM]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.16 – 6.95 (m, 1H), 6.69 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.62 – 6.54 (m, 1H), 4.80 (br s, 1H), 2.94 (dd, *J* = 10.2, 4.5 Hz, 1H), 2.83 – 2.72 (m, 2H), 2.71 – 2.64 (m, 2H), 2.45 – 2.32 (m, 1H), 2.31 – 2.10 (m, 4H), 2.05 – 1.95 (m, 1H), 1.93 – 1.85 (m, 1H), 1.81 – 1.66 (m, 3H), 1.57 – 1.40 (m, 2H), 1.08 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 153.5, 139.7, 128.8, 128.1 (q, *J* = 278 Hz), 127.8, 115.8, 113.8, 87.5, 80.8, 75.0, 51.2, 48.6, 47.4, 39.3, 35.4, 35.0, 32.5 (q, *J* = 26.8 Hz), 30.6 (q, *J* = 2.0 Hz), 30.2, 26.9, 23.0, 17.3. **^{19}F NMR** (376 MHz, $CDCl_3$): δ [ppm] = -63.12 (t, *J* = 11.3 Hz). **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3305; 2927, 2876, 1611, 1501, 1447, 1252, 1134, 1036, 924, 634. **LRMS** (ESI): *m/z* 377 [$M\text{-}H^-$]. **HRMS** (ESI): *m/z* calculated for $C_{22}H_{24}F_3O_2^-$: 377.1734, found 377.1738.

(8*S*,9*S*,11*R*,13*S*,14*S*,17*R*)-13-methyl-17-((*E*)-2-(tributylstannyl)vinyl)-11-(2,2,2-trifluoroethyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (30)



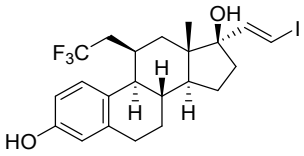
$C_{34}H_{53}F_3O_2Sn$
669.50

Alkyne **29** (21 mg, 55 µmol, 1 equiv.) was dissolved in abs. toluene (350 µL) followed by addition of *n*-Bu_3SnH (22 µL, 82 µmol, 1.5 equiv.) and AIBN (14 mg, 82 µmol, 1.5 equiv.). The reaction mixture was stirred for 20 h at 100 °C. After cooling the reaction mixture to room temperature, the solution was concentrated under reduced pressure. The residue was loaded onto silica and purified by column

chromatography (CH/EtOAc 98:2 → 95:5). The stannane **30** (22 mg, 33 µmol, 61%) was obtained as a pale yellow oil.

TLC: R_f (PE/EtOAc 8:2) = 0.26 [$KMnO_4$]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 6.98 (dd, *J* = 8.5, 1.1 Hz, 1H), 6.65 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.56 (d, *J* = 2.7 Hz, 1H), 6.21 (d, *J* = 19.4 Hz, 1H), 6.09 (d, *J* = 19.3 Hz, 1H), 4.90 (s, 1H), 2.88 – 2.64 (m, 3H), 2.56 – 2.46 (m, 1H), 2.35 – 2.15 (m, 1H), 2.07 – 1.83 (m, 5H), 1.75 – 1.59 (m, 4H), 1.56 – 1.43 (m, 9H), 1.38 – 1.24 (m, 8H), 1.13 (s, 3H), 0.92 – 0.80 (m, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 153.5, 152.5, 139.7, 128.9, 128.2 (q, *J* = 277 Hz), 127.7, 125.3, 115.8, 113.8, 86.6, 50.8, 49.0, 47.2, 36.2, 35.5, 34.6, 32.7 (q, *J* = 26.6 Hz), 30.7 (q, *J* = 2.0 Hz), 30.2, 29.4, 27.4, 27.1, 23.5, 19.0, 13.9, 9.8. **^{19}F NMR** (376 MHz, $CDCl_3$): δ [ppm] = -63.15 (t, *J* = 11.3 Hz). **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3340, 2955, 2923, 2871, 2851, 1611, 1587, 1498, 1456, 1417, 1390, 1353, 1330, 1312, 1289, 1251, 1199, 1166, 1131, 1101, 1071, 1003, 961, 923, 893, 868, 849, 820, 793, 679, 594, 546, 500, 455. **LRMS** (ESI): *m/z* 669 [M-H$^-$]. **HRMS** (ESI): *m/z* calculated for $C_{34}H_{52}F_3O_2Sn^-$: 669.2947, found 669.2951.

(8*S*,9*S*,11*R*,13*S*,14*S*,17*R*)-17-((*E*)-2-iodovinyl)-13-methyl-11-(2,2,2-trifluoroethyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol
(31)



$C_{22}H_{26}F_3IO_2$
506.35

The stannane **30** (20 mg, 32 µmol, 1 equiv.) was dissolved in CH_2Cl_2 (1 mL) and iodine (8.3 mg, 33 µmol, 1.1 equiv.) dissolved in CH_2Cl_2 (1 mL) was added dropwise. The reaction solution was stirred for 0.5 h at room temperature before saturated aq. Na_2SO_3 was added and the mixture was extracted with EtOAc (3×5 mL). The combined organic layer was dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was purified by column chromatography (CH/EtOAc 7:3) and preparative HPLC (C 18, Nucleodur, MeCN/H_2O 9:1) to give vinyl iodide **31** (12 mg, 24 µmol, 79%, (*E*) > 99:1) as a colourless solid.

TLC: R_f (PE/EtOAc 7:3) = 0.36 [$KMnO_4$]. **^{1}H NMR** (400 MHz, MeOD): δ [ppm] = 6.99 (dd, *J* = 8.6, 1.0 Hz, 1H), 6.86 (d, *J* = 14.4 Hz, 1H), 6.62 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.53 (d, *J* = 2.6 Hz, 1H), 6.34 (d, *J* = 14.4 Hz, 1H), 2.91 – 2.82 (m, 1H), 2.82 – 2.74 (m, 1H), 2.73 – 2.65 (m, 1H), 2.62 – 2.55 (m, 1H), 2.37 – 2.24 (m, 1H), 2.11 – 2.04 (m, 1H), 2.02 – 1.84 (m, 4H), 1.79 – 1.70 (m, 1H), 1.66 – 1.48 (m, 4H), 1.38 – 1.28 (m, 1H), 1.12 (s, 3H). **^{13}C NMR** (101 MHz, MeOD): δ [ppm] = 156.1, 152.8, 140.5, 129.0 (q, *J* = 276 Hz), 128.7,

128.4, 116.5, 114.6, 88.6, 74.5, 52.0, 50.0, 48.7, 36.8, 36.8, 35.8, 33.5 (q, *J* = 26.6 Hz), 32.0 (d, *J* = 2.2 Hz), 31.2, 28.2, 24.1, 19.1. **^{19}F NMR** (376 MHz, $CDCl_3$): δ [ppm] = -64.53 (t, *J* = 11.2 Hz). **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3513, 3306, 2912, 1611, 1506, 1448, 1389, 1291, 1245, 1173, 1137, 991, 870, 734. **LRMS** (ESI): *m/z* 505 [$M-H^-$]. **HRMS** (ESI): *m/z* calculated for $C_{22}H_{25}F_3IO_2^-$: 505.0857, found 505.0858.

Sonogashira couplings (A)

The aryl iodide (1 equiv.) was dissolved in Et_3N (0.05M) followed by the addition of $PdCl_2(PPh_3)_2$ (5 mol%) and Cu(I)iodide (5 mol%) and the reaction solution was degassed with N_2 for 30 min. Then, alkyne **12** (1 equiv.) was added, and the mixture was stirred for 16 h at room temperature. The mixture was diluted with water and extracted with EtOAc (3×). The combined organic layer was washed with saturated aq. NaCl, was dried over Na_2SO_4 and filtered. The solvent was evaporated in vacuo, and the residue was purified by column chromatography (PE/EtOAc 9:1 → 1:1).

Boc deprotection with concentrated HCl (B)

The carbamate (1 equiv.) was dissolved in ethanol (0.07M), and concentrated HCl (55 equiv., 37%) was added dropwise at 0 °C. After complete addition, the mixture was warmed to room temperature and stirred for 14 h at ambient temperature. Then, the reaction mixture was diluted with water, and ethanol was evaporated in a vacuo. Finally, the precipitated solid was filtered off, washed with a small amount of water and CH_2Cl_2, and dried under a high vacuum.

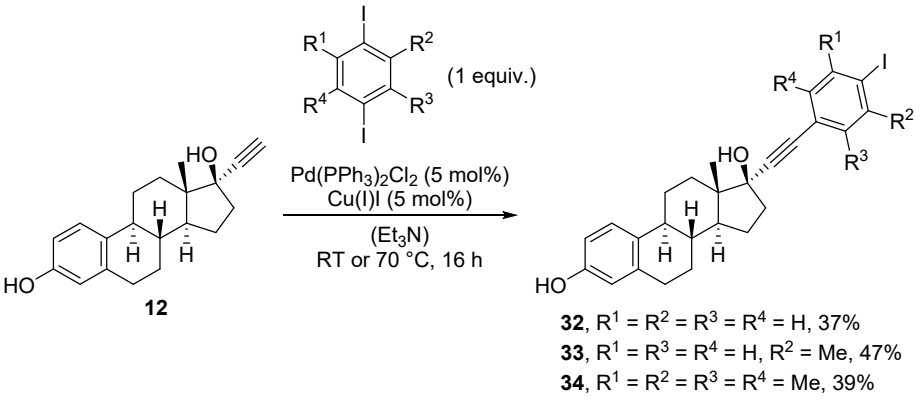
Amide coupling with HATU (C)

The hydrochloride (1 equiv.) was dissolved in DMF (0.3M) and 4-trimethylstannyl-benzoic acid or 4-tri-*n*-butylstannylbenzoic acid (both prepared from 4-iodobenzoic acid in 86%[1] and 91%[2] yield, respectively) were added followed by addition of HATU (2 equiv.). Then, DIPEA (4 equiv.) was added dropwise, stirring the mixture for 16 h at room temperature. The reaction mixture was diluted with water and EtOAc and extracted with EtOAc (3×). The combined organic layer was washed with saturated aq. NaCl, was dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. Finally, the residue was purified by column chromatography (PE → PE/EtOAc 1:1).

Iododestannylation (D)

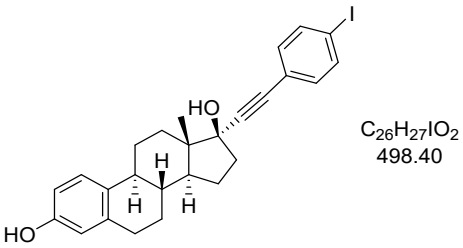
The stannane (1 equiv.) was dissolved in abs. CH_2Cl_2 to a concentration of 0.3M (0.3M) and iodine (1.1 equiv.) dissolved in little abs. CH_2Cl_2 was slowly added to the reaction mixture. After 0.5 h, the reaction was quenched by the addition of saturated aq. Na_2SO_3 solution and the aqueous layer was extracted with EtOAc (3×). The combined organic layer was washed with saturated aq. NaCl solution, dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was purified by column chromatography (PE → PE/EtOAc 6:4).

Synthesis of compounds 32-34



Scheme S7: Synthesis of Aryl iodides **32**-**34** via Sonogashira couplings.

(8*R*,9*S*,13*S*,14*S*,17*S*)-17-((4-iodophenyl)ethynyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (32)

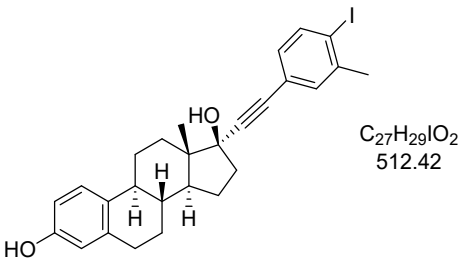


Ethinylestradiol **12** (200 mg, 675 µmol, 1 equiv.) was reacted with 1,4-diodobenzene (223 mg, 675 µmol, 1 equiv.) at room temperature following general procedure **A** to give aryl iodide **32** (126 mg, 253 µmol, 37%) as a gray solid.

TLC: R_f (PE/EtOAc 1:1) = 0.58 [UV] [$KMnO_4$]. **^{1}H NMR** (400 MHz, DMSO-d_6): δ [ppm] = 8.95 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.51 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.43 (d, *J* = 2.6 Hz, 1H), 5.46 (s, 1H), 2.76 – 2.65 (m, 2H), 2.37 – 2.26 (m, 1H), 2.25 – 2.15 (m, 1H), 2.15 – 2.04

(m, 1H), 2.00 – 1.87 (m, 1H), 1.85 – 1.59 (m, 4H), 1.46 – 1.21 (m, 5H), 0.81 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ [ppm] = 154.9, 137.4, 137.1, 133.0, 130.2, 126.0, 122.4, 114.9, 112.7, 96.5, 94.5, 83.2, 78.6, 49.4, 47.2, 43.3, 32.9, 29.2, 26.9, 26.2, 24.1, 22.6, 12.8. The spectroscopical data were identical to those reported in the literature.[6]

(8*R*,9*S*,13*S*,14*S*,17*S*)-17-((4-iodo-3-methylphenyl)ethinyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (33)

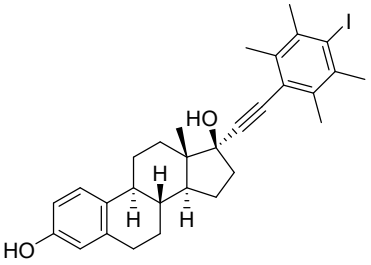


$C_{27}H_{29}IO_2$
512.42

Ethinylestradiol **12** (100 mg, 337 µmol, 1 equiv.) was reacted with 1,4-diodo-2-methylbenzene (116 mg, 337 µmol, 1 equiv., prepared via two-step synthesis from 2-methylaniline in 8% overall yield) at room temperature following general procedure **A** to give aryl iodide **33** (82 mg, 160 µmol, 47%) as a colourless solid.

TLC: R_f (PE/EtOAc 7:3 = 0.28 [CAM] [$KMnO_4$]. **^{1}H NMR** (600 MHz, MeOD): δ [ppm] = 7.75 (d, *J* = 8.1 Hz, 1H), 7.32 (s, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.93 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.54 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.48 (d, *J* = 2.6 Hz, 1H), 2.85 – 2.70 (m, 2H), 2.37 (s, 3H), 2.41 – 2.29 (m, 2H), 2.19 – 2.11 (m, 1H), 2.10 – 2.02 (m, 1H), 2.01 – 1.92 (m, 1H), 1.91 – 1.85 (m, 1H), 1.85 – 1.74 (m, 3H), 1.52 – 1.27 (m, 4H), 0.91 (s, 3H). **^{13}C NMR** (151 MHz, MeOD): δ [ppm] = 155.9, 142.9, 140.2, 138.8, 133.3, 132.5, 131.2, 127.3, 124.9, 116.1, 113.8, 101.2, 95.5, 85.5, 80.9, 51.2, 45.2, 41.2, 39.9, 34.4, 30.7, 28.6, 28.1, 27.8, 23.9, 13.5. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3366, 2929, 2869, 1611, 1585, 1499, 1470, 1453, 1380, 1354, 1287, 1249, 1059, 1046, 1013, 874, 817. **LRMS** (ESI): *m/z* 495 [M-OH$^+$]. **HRMS** (ESI): *m/z* calculated for $C_{27}H_{29}INaO_2^+$: 535.1104, found 535.1123.

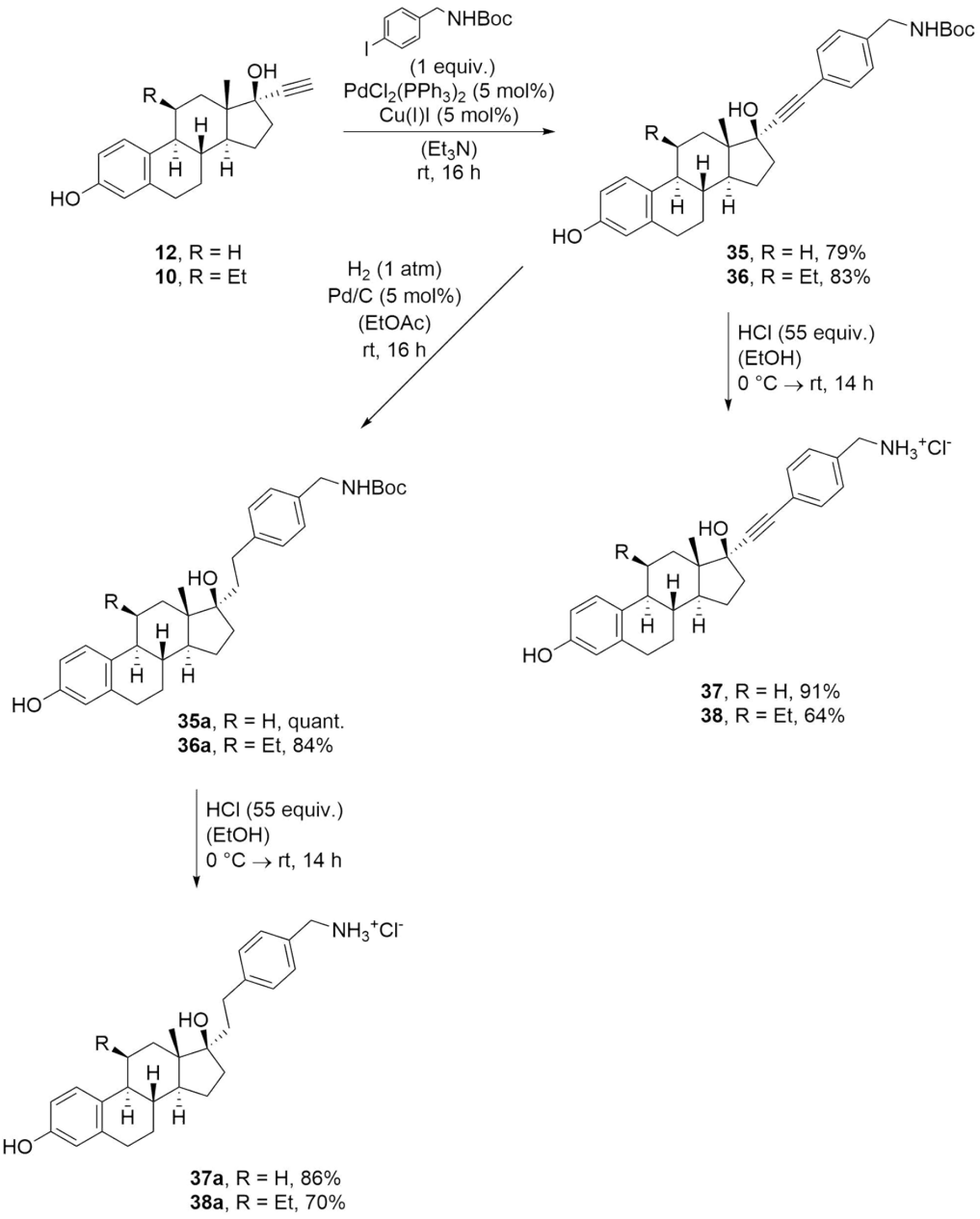
(8*R*,9*S*,13*S*,14*S*,17*S*)-17-((4-iodo-2,3,5,6-tetramethylphenyl)ethynyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (34)



$C_{30}H_{35}IO_2$
554.50

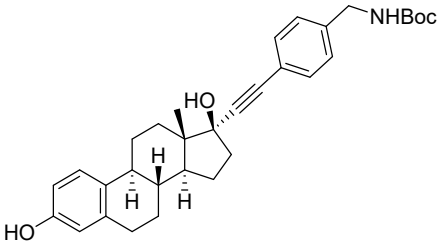
Ethinylestradiol **12** (500 mg, 1.69 mmol, 1 equiv.) was reacted with 1,4-diodo-2,3,5,6-tetramethylbenzene (651 mg, 1.69 µmol, 1 equiv., prepared from durene in 53% yield[7]) at 70 °C following general procedure **A** to give aryl iodide **34** (369 mg, 665 µmol, 39%) as a colourless solid. **TLC**: R_f (PE/EtOAc 7:3) = 0.28 [CAM] [$KMnO_4$]. **^{1}H NMR** (400 MHz, MeOD): δ [ppm] = (d, *J* = 8.4 Hz, 1H), 6.53 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.47 (d, *J* = 2.6 Hz, 1H), 2.81 – 2.71 (m, 2H), 2.49 (s, 6H), 2.42 (s, 6H), 2.40 – 2.28 (m, 2H), 2.16 – 1.99 (m, 3H), 1.92 – 1.74 (m, 4H), 1.51 – 1.23 (m, 4H), 0.92 (s, 3H). **^{13}C NMR** (101 MHz, MeOD): δ [ppm] = 155.9, 138.7, 138.4, 137.1, 132.4, 127.2, 124.9, 116.1, 113.8, 112.1, 103.2, 85.1, 81.4, 51.3, 45.3, 41.1, 40.3, 34.5, 30.7, 28.7, 28.0, 27.7, 23.9, 20.7, 13.5. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3360, 2925, 2869, 1611, 1499, 1447, 1381, 1354, 1286, 1250, 1047, 1016, 912, 871, 736. **LRMS** (ESI): *m/z* 537 [M-OH^+]. **HRMS** (ESI): *m/z* calculated for $C_{30}H_{35}INaO_2^+$: 577.1574, found 577.1587.

Synthesis of compound 35-38 and 35a-38a



Scheme S8: Synthesis of carbamates **35**, 3**6**, **35a**, **36a** and hydrochlorides **37**, **38**, **37a**, **38a**.

***tert*-butyl-4-(((8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)ethynyl)benzylcarbamate (35)**



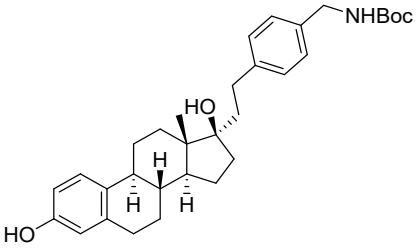
$C_{32}H_{39}NO_4$
501.66

tert-Butyl(4-iodobenzyl)carbamate (303 mg, 911 µmol, 1 equiv., prepared via three-step synthesis from 4-iodobenzyl bromide in 83% overall yield[8]) was dissolved in Et_3N (18 mL), and $PdCl_2(PPh_3)_2$

(32 mg, 46 µmol, 5 mol%) and Cu(I)iodide (8.7 mg, 46 µmol, 5 mol%) were added. After degassing the reaction solution with N_2 for 30 min, ethinylestradiol (**12**) (270 mg, 911 µmol, 1 equiv.) was added in one portion. Then, the mixture was stirred for 16 h at room temperature followed by quenching with water. The mixture was extracted with EtOAc (3×20 mL), and the combined organic layer was washed with saturated aq. NaCl, dried over Na_2SO_4 and filtered. The solvent was evaporated in vacuo and the residue was purified by column chromatography (PE/EtOAc 10:0 → 6:4) to give the desired product **35** (362 mg, 722 µmol, 79%) as pale brown solid.

TLC: R_f (PE/EtOAc 1:1) = 0.54 [UV] [$KMnO_4$]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.41 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 2H), 7.16 (dd, *J* = 8.5, 1.1 Hz, 1H), 6.67 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.59 (d, *J* = 2.7 Hz, 1H), 4.98 (br s, 1H), 4.32 (d, *J* = 6.7 Hz, 2H), 2.86 – 2.78 (m, 2H), 2.49 – 2.33 (m, 2H), 2.28 – 2.18 (m, 1H), 2.18 – 2.08 (m, 1H), 2.05 – 1.94 (m, 1H), 1.92 – 1.74 (m, 4H), 1.48 (s, 9H), 1.55 – 1.30 (m, 4H), 0.95 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 156.2, 153.9, 139.2, 138.2, 132.3, 132.0, 127.4, 126.5, 122.1, 115.5, 112.9, 93.0, 85.8, 80.5, 49.9, 47.8, 43.8, 39.7, 39.2, 33.2, 29.8, 28.5, 27.4, 26.6, 23.1, 13.1. The spectroscopical data were identical to those reported in the literature.[9]

***tert*-butyl-4-(2-((8*R*,9*S*,13*S*,14*S*,17*R*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)ethyl)benzylcarbamate (35a)**

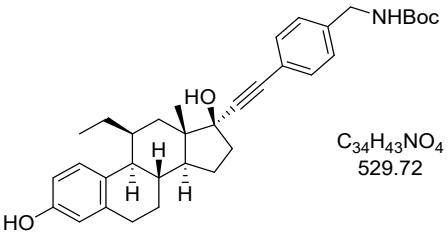


$C_{32}H_{43}NO_4$
505.70

Steroid **35** (300 mg, 598 µmol, 1 equiv.) was dissolved in EtOAc (2 mL) and Pd/C (63 mg, 60 µmol, 10 mol%, 5%) was added. The reaction mixture was stirred under H_2 atmosphere (1 atm) for 16 h, then filtered over Celite® and the filtrate was concentrated in vacuo to give carbamate **35a** (302 mg, 597 µmol, quant.) as a colourless solid.

TLC: R_f (PE/EtOAc 8:2) = 0.33 [UV] [CAM]. **^{1}H NMR** (400 MHz, MeOD): δ [ppm] = 7.18 (s, 4H), 7.05 (d, *J* = 8.5 Hz, 1H), 6.52 (d, *J* = 8.8 Hz, 1H), 6.46 (s, 1H), 4.18 (s, 2H), 2.88 – 2.56 (m, 4H), 2.34 – 2.21 (m, 1H), 2.14 – 2.02 (m, 2H), 1.93 – 1.75 (m, 2H), 1.76 – 1.58 (m, 4H), 1.56 – 1.32 (m, 3H), 1.44 (s, 12H), 0.93 (s, 3H). **^{13}C NMR** (151 MHz, MeOD): δ [ppm] = 155.9, 143.5, 138.8, 132.7, 129.5, 128.3, 127.1, 116.0, 113.7, 84.2, 51.1, 48.2, 45.2, 41.4, 40.6, 34.3, 32.9, 30.9, 30.7, 28.8, 28.8, 27.6, 24.4, 15.2. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3338, 2929, 2869, 1683, 1502, 1452, 1365, 1285, 1248, 1162, 1039, 912, 865, 785, 730, 576. **LRMS** (ESI): *m/z* 523 [M+NH_4^+]. **HRMS** (ESI): *m/z* calculated for $C_{32}H_{43}NNaO_4^+$: 528.3084, found 528.3085.

***tert*-butyl-4-(((8*S*,9*S*,11*S*,13*S*,14*S*,17*S*)-11-ethyl-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)ethynyl)benzylcarbamate (36)**



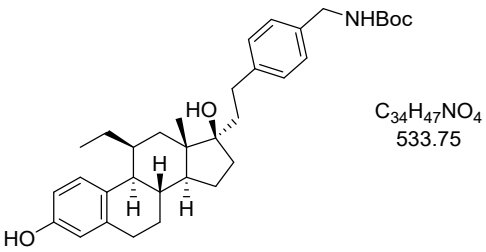
$C_{34}H_{43}NO_4$
529.72

tert-Butyl(4-iodobenzyl)carbamate (171 mg, 514 µmol, 1 equiv., prepared via three-step synthesis from 4-iodobenzyl bromide in 83% overall yield[8]) was dissolved in Et_3N (10 mL) and $PdCl_2(PPh_3)_2$ (18 mg, 26 µmol, 5 mol%) and Cu(I)iodide (5.0, 26 µmol, 5 mol%) were added. After degassing the

reaction solution with N_2 for 30 min, the alkyne **10** (167 mg, 514 µmol, 1 equiv.) was added in one portion. Then, the reaction mixture was stirred for 16 h at room temperature followed by quenching with water. The mixture was extracted with EtOAc (3×10 mL), and the combined organic layer was washed with saturated aq. NaCl, dried over Na_2SO_4 and filtered. The solvent was evaporated in vacuo and the residue was purified by column chromatography (PE/EtOAc 9:1 → 6:4) to give the desired product **36** (226 mg, 427 µmol, 83%) as a foamy colourless solid.

TLC: R_f (PE/EtOAc 8:2) = 0.34 [UV] [CAM]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.41 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.06 (dd, *J* = 8.8, 0.9 Hz, 1H), 6.66 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.56 (d, *J* = 2.9 Hz, 1H), 4.85 (br s, 1H), 4.32 (d, *J* = 6.0 Hz, 2H), 2.89 – 2.67 (m, 2H), 2.66 – 2.57 (m, 1H), 2.49 – 2.37 (m, 2H), 2.20 – 1.98 (m, 4H), 1.96 – 1.76 (m, 3H), 1.48 (s, 9H), 1.41 – 1.19 (m, 4H), 1.09 (s, 3H), 0.94 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 156.0, 153.0, 139.4, 132.0, 130.5, 128.1, 127.5, 122.1, 115.4, 113.3, 93.3, 86.4, 81.3, 52.0, 49.5, 48.3, 39.5, 38.5, 35.3, 33.7, 30.4, 28.6, 27.2, 23.1, 21.1, 16.3, 13.1. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3356, 2965, 2927, 2874, 1688, 1507, 1453, 1392, 1367, 1286, 1248, 1164, 1132, 1060, 1024, 884, 732. **LRMS** (ESI): *m/z* 547 [$M+NH_4^+$]. **HRMS** (ESI): *m/z* calculated for $C_{34}H_{43}NNaO_4^+$: 552.3084, found 552.3105.

***tert*-butyl-(4-(2-((8*S*,9*S*,11*S*,13*S*,14*S*,17*R*)-11-Ethyl-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)ethyl)benzyl)carbamate (36a)**



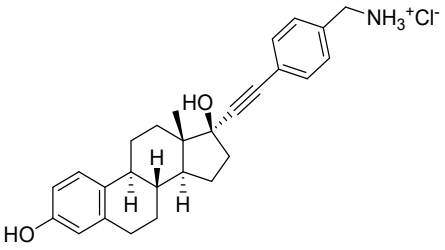
$C_{34}H_{47}NO_4$
533.75

Steroid **36** (26 mg, 49 µmol, 1 equiv.) was dissolved in EtOAc (160 µL) and Pd/C (5.2 mg, 4.9 µmol, 10 mol%, 10%) was added. The reaction mixture was stirred under H_2 atmosphere (1 atm) for 16 h, then filtered over Celite® and the filtrate was concentrated in vacuo to give carbamate **36a** (22 mg, 41 µmol, 84%) as a colourless solid.

TLC: R_f (PE/EtOAc 8:2) = 0.37 [UV] [CAM]. **^{1}H NMR** (600 MHz, $CDCl_3$): δ [ppm] = 7.20 (s, 4H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.62 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.53 (d, *J* = 2.7 Hz, 1H), 4.82 (br s, 1H), 4.31 – 4.26 (m, 2H), 2.88 – 2.63 (m, 4H), 2.51 – 2.43 (m, 1H), 2.37 – 2.27 (m, 1H), 2.17 – 2.08 (m, 1H), 1.96 – 1.82 (m, 3H),

1.78 – 1.53 (m, 6H), 1.46 (s, 9H), 1.30 – 1.14 (m, 4H), 1.07 (s, 3H), 0.88 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ [ppm] = 153.3, 142.3, 139.3, 136.3, 130.1, 128.9, 128.0, 127.8, 115.4, 113.3, 84.5, 51.6, 49.5, 47.5, 39.9, 38.6, 35.6, 34.7, 32.0, 30.4, 30.2, 28.6, 27.3, 23.5, 21.4, 17.7, 13.1. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3390, 2957, 2925, 2872, 2854, 1692, 1611, 1501, 1367, 1249, 1165, 1105, 1021, 906, 864, 800, 729, 647. **LRMS** (ESI): *m/z* 534 [M+H^+]. **HRMS** (ESI): *m/z* calculated for $C_{34}H_{47}NNaO_4^+$: 556.3397, found 556.3409.

(4-(((8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)ethynyl)phenyl)methanaminium chloride (37)

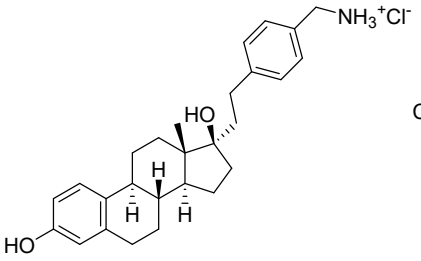


$C_{27}H_{32}ClNO_2$
438.01

Carbamate **35** (120 mg, 239 µmol, 1 equiv.) was deprotected following general procedure **B** to give hydrochloride **37** (95 mg, 220 µmol, 91%) as a colourless solid.

^{1}H NMR (600 MHz, MeOD): δ [ppm] = 7.51 – 7.49 (m, 2H), 7.44 – 7.42 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.54 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.48 (d, *J* = 2.6 Hz, 1H), 4.11 (s, 2H), 2.85 – 2.73 (m, 2H), 2.40 – 2.32 (m, 2H), 2.16 (td, *J* = 11.3, 4.6 Hz, 1H), 2.11 – 2.05 (m, 1H), 1.98 (td, *J* = 13.0, 4.2 Hz, 1H), 1.93 – 1.88 (m, 1H), 1.86 – 1.77 (m, 3H), 1.51 – 1.39 (m, 3H), 1.37 – 1.28 (m, 1H), 0.93 (s, 3H); **^{13}C NMR** (151 MHz, MeOD): δ [ppm] = 156.0, 138.8, 134.2, 133.1, 132.4, 130.1, 127.2, 125.7, 116.1, 113.8, 95.9, 85.5, 80.9, 51.3, 48.9, 45.3, 44.0, 41.2, 40.0, 34.5, 30.7, 28.7, 27.8, 23.9, 13.5. The spectroscopical data were identical to those reported in the literature.[9]

(4-(2-((8*R*,9*S*,13*S*,14*S*,17*R*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)ethyl)phenyl)methanaminium chloride (37a)

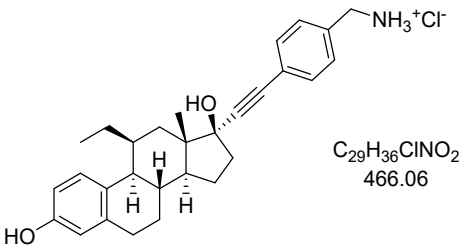


$C_{27}H_{36}ClNO_2$
442.03

Carbamate **35a** (290 mg, 573 µmol, 1 equiv.) was deprotected following general procedure **B** to give hydrochloride **37a** (218 mg, 494 µmol, 86%) as a colourless solid.

^{1}H NMR (600 MHz, MeOD): δ [ppm] = 7.42 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.57 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.52 (d, *J* = 2.6 Hz, 1H), 4.13 (s, 2H), 2.96 – 2.87 (m, 1H), 2.86 – 2.76 (m, 3H), 2.36 – 2.30 (m, 1H), 2.18 – 2.08 (m, 2H), 1.97 – 1.84 (m, 2H), 1.82 – 1.73 (m, 3H), 1.73 – 1.67 (m, 1H), 1.58 – 1.43 (m, 5H), 1.39 – 1.29 (m, 1H), 0.99 (s, 3H). **^{13}C NMR** (151 MHz, MeOD): δ [ppm] = 155.9, 146.3, 138.8, 132.6, 131.6, 130.3, 130.1, 127.1, 116.1, 113.7, 84.1, 51.1, 48.2, 45.2, 44.2, 41.4, 40.5, 34.4, 32.9, 31.0, 30.7, 28.8, 27.6, 24.4, 15.2. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3349, 2926, 2856, 2134, 2114, 1693, 1501, 1446, 1354, 1285, 1224, 1018, 906, 821, 727, 647, 558. **LRMS** (ESI): *m/z* 406 [M-Cl$^+$]. **HRMS** (ESI): *m/z* calculated for $C_{27}H_{36}NO_2^+$: 406.2741, found 406.2741.

(4-(((8*S*,9*S*,11*S*,13*S*,14*S*,17*S*)-11-ethyl-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)ethynyl)phenyl)methanaminium chloride (38)



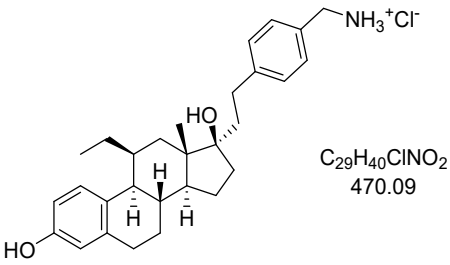
$C_{29}H_{36}ClNO_2$
466.06

Carbamate **36** (50 mg, 94 µmol, 1 equiv.) was deprotected following general procedure **B** to give hydrochloride **38** (28 mg, 60 µmol, 64%) as a colourless solid.

^{1}H NMR (600 MHz, MeOD): δ [ppm] = 7.52 (d, *J* = 8.2 Hz, 2H), 7.47 – 7.43 (m, 2H), 7.01 (d, *J* = 8.6 Hz, 1H), 6.59 (dd, *J* = 8.4, 2.9 Hz, 1H), 6.50 (d, *J* = 2.7 Hz, 1H), 4.13 (s, 2H), 2.83 – 2.75 (m, 1H), 2.72 – 2.64 (m, 1H), 2.57 (dd, *J* = 10.9, 4.7 Hz, 1H), 2.48 – 2.31 (m, 2H), 2.17 (dd, *J* = 13.7, 1.9 Hz, 1H), 2.14 – 2.07

(m, 2H), 1.96 – 1.89 (m, 1H), 1.88 – 1.76 (m, 2H), 1.71 – 1.63 (m, 1H), 1.57 – 1.49 (m, 1H), 1.45 – 1.36 (m, 1H), 1.32 – 1.21 (m, 2H), 1.08 (s, 3H), 0.96 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (151 MHz, MeOD): δ [ppm] = 155.5, 140.0, 134.2, 133.1, 130.1, 130.1, 128.7, 125.7, 116.1, 114.2, 96.2, 86.0, 81.7, 53.3, 50.9, 49.5, 44.0, 40.2, 39.9, 36.6, 34.9, 31.4, 28.4, 23.8, 22.0, 16.8, 13.3. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3256, 2960. 2922, 2872, 1609, 1499, 1453, 1379, 1285, 1245, 1218, 1154, 1117, 1061, 1023, 867, 825, 558. **LRMS** (ESI): *m/z* 430 [M-Cl$^+$]. **HRMS** (ESI): *m/z* calculated for $C_{29}H_{36}NO_2^+$: 430.2741, found 430.2742.

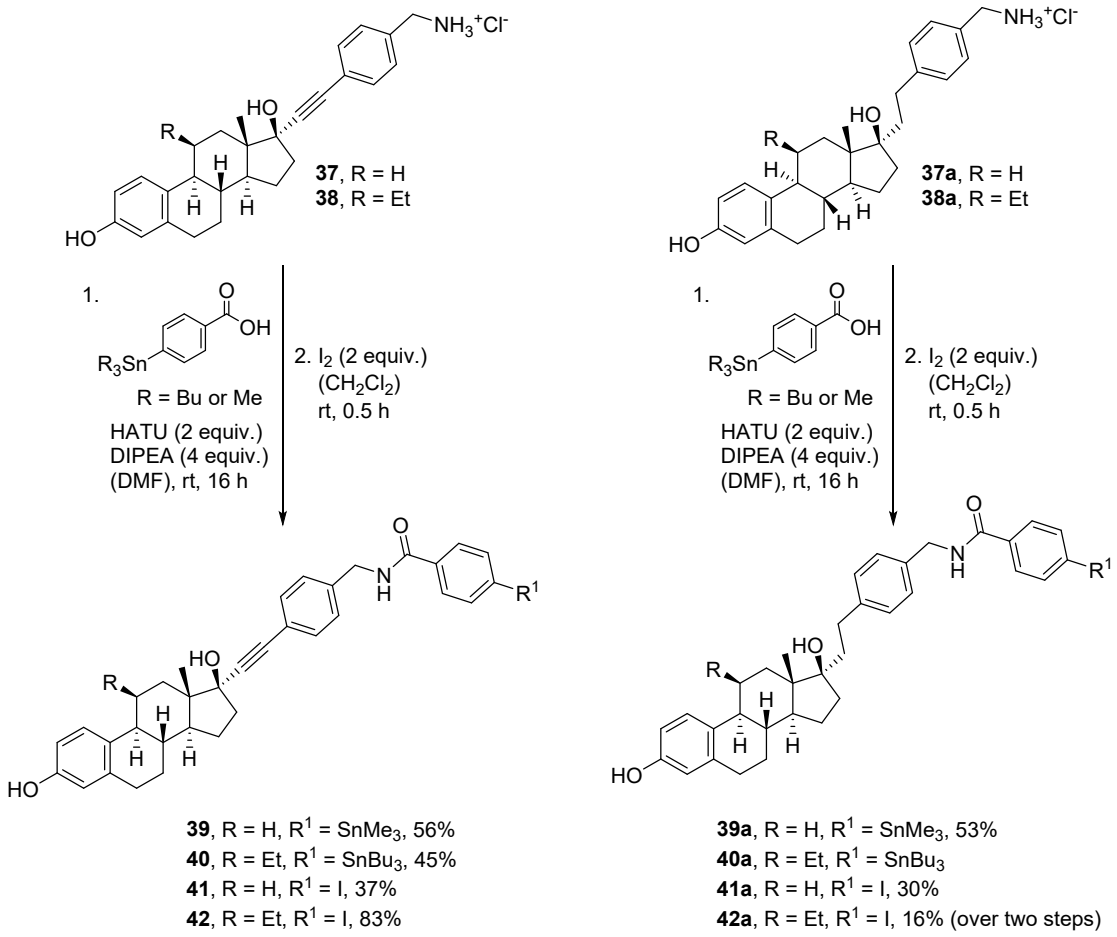
(4-(2-((8*S*,9*S*,11*S*,13*S*,14*S*,17*R*)-11-ethyl-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)ethyl)phenyl)methanaminium chloride (38a)



Carbamate **36a** (110 mg, 206 µmol, 1 equiv.) was deprotected following general procedure **B** to give hydrochloride **38a** (68.0 mg, 145 µmol, 70%) as a colourless solid.

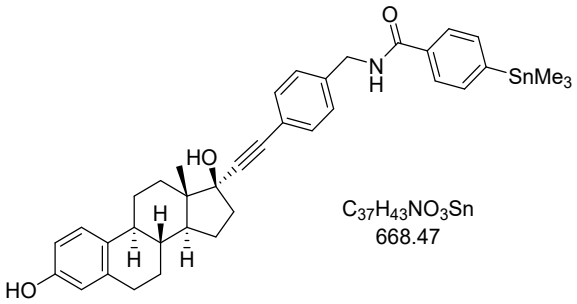
^{1}H NMR (400 MHz, MeOD): δ [ppm] = 7.36 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.53 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.45 (d, *J* = 2.7 Hz, 1H), 4.07 (s, 2H), 2.90 – 2.82 (m, 1H), 2.78 – 2.69 (m, 2H), 2.66 – 2.59 (m, 1H), 2.45 (dd, *J* = 10.9, 4.7 Hz, 1H), 2.38 – 2.31 (m, 1H), 2.11 – 2.03 (m, 1H), 1.97 – 1.91 (m, 1H), 1.90 – 1.83 (m, 2H), 1.76 – 1.56 (m, 5H), 1.53 (dd, *J* = 13.5, 5.9 Hz, 1H), 1.46 – 1.26 (m, 4H), 1.07 (s, 3H), 0.90 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, MeOD): δ [ppm] = 155.5, 146.3, 140.0, 131.5, 130.3, 130.2, 130.1, 128.7, 116.1, 114.1, 84.9, 53.0, 50.8, 44.2, 41.0, 40.0, 36.9, 34.3, 33.1, 31.4, 31.2, 28.5, 24.3, 22.3, 18.6, 13.4. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3019, 2922, 2858, 2837, 1608, 1583, 1499, 1454, 1377, 1349, 1285, 1244, 1209, 1157, 1108, 920, 805, 558. **LRMS** (ESI): *m/z* 434 [M-Cl$^+$]. **HRMS** (ESI): *m/z* calculated for $C_{29}H_{40}NO_2^+$: 434.3054, found 434.3056.

Synthesis of compounds 41, 42 and 41a, 42a



Scheme S9: Synthesis of Aryliodids **41**, **42**, **41a,** and **42a**.

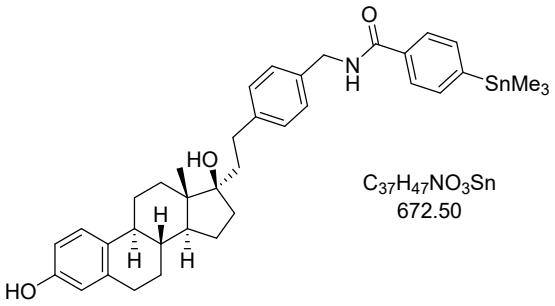
***N*-(4-(((8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)ethynyl)benzyl)-4-(trimethylstannyl)benzamide (39)**



Hydrochloride **37** (55 mg, 126 µmol, 1 equiv.) was reacted with 4-trimethylstannylbenzoic acid (93 mg, 210 µmol, 1.7 equiv.) following general procedure **C** to give stannane **39** (47 mg, 70 µmol, 56%) as a colourless, viscous oil.

TLC: R_f (PE/EtOAc 1:1) = 0.51 [UV] [$KMnO_4$]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.73 (d, *J* = 8.1 Hz, 2H), 7.61 – 7.50 (m, 2H), 7.45 – 7.36 (m, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.13 (dd, *J* = 8.6, 1.1 Hz, 1H), 6.64 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.63 – 6.58 (m, 1H), 6.57 (d, *J* = 2.7 Hz, 1H), 5.89 (br s, 1H), 4.62 (d, *J* = 5.7 Hz, 2H), 2.82 – 2.71 (m, 2H), 2.49 – 2.30 (m, 2H), 2.24 – 2.19 (m, 1H), 2.14 – 2.05 (m, 1H), 1.96 (td, *J* = 13.0, 4.2 Hz, 1H), 1.90 – 1.71 (m, 4H), 1.55 – 1.23 (m, 4H), 0.93 (s, 3H), 0.31 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 168.0, 153.9, 148.0, 138.5, 138.2, 136.2, 133.8, 132.3, 132.1, 127.8, 126.6, 126.2, 122.4, 115.5, 113.0, 93.3, 85.7, 80.5, 50.0, 47.8, 43.9, 43.8, 39.7, 39.2, 33.2, 29.8, 27.4, 26.6, 23.1, 13.1, -9.4. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3317, 2960, 2929, 2870, 1638, 1533, 1506, 1453, 1362, 1287, 1236, 1146, 1048, 1017, 833, 819, 766, 754, 712, 683, 528, 512. **LRMS** (ESI): *m/z* 668 [M+H$^+$]. **HRMS** (ESI): *m/z* calculated for $C_{37}H_{43}NNaO_3Sn^+$: 692.2161, found 692.2179.

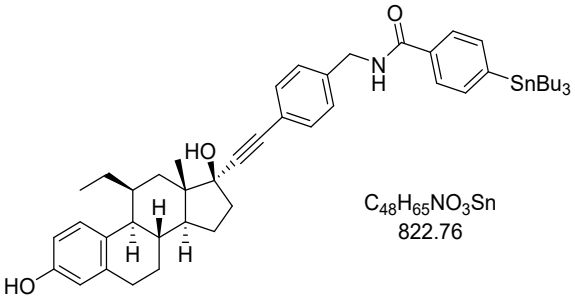
***N*-(4-(2-((8*R*,9*S*,13*S*,14*S*,17*R*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)ethyl)benzyl)-4-(trimethylstannyl)benzamide (39a)**



Hydrochloride **37a** (41 mg, 92 µmol, 1 equiv.) was reacted with 4-trimethylstannylbenzoic acid (24 mg, 84 µmol, 0.9 equiv.) following general procedure **C** to give stannane **39a** (30 mg, 45 µmol, 53%) as a colourless solid.

TLC: R_f (PE/EtOAc 6:4) = 0.35 [UV] [$KMnO_4$]. **^{1}H NMR** (600 MHz, MeOD): δ [ppm] = 7.77 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.22 – 7.18 (m, 2H), 7.03 (d, *J* = 8.7 Hz, 1H), 6.51 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.46 (d, *J* = 2.7 Hz, 1H), 4.53 (s, 2H), 2.88 – 2.65 (m, 4H), 2.30 – 2.21 (m, 1H), 2.13 – 1.97 (m, 2H), 1.89 – 1.78 (m, 2H), 1.74 – 1.66 (m, 3H), 1.65 – 1.57 (m, 1H), 1.50 – 1.40 (m, 4H), 1.33 – 1.21 (m, 2H), 0.91 (s, 3H), 0.29 (s, 9H). **^{13}C NMR** (151 MHz, MeOD): δ [ppm] = 170.4, 155.9, 148.6, 143.8, 138.8, 137.4, 136.9, 135.3, 132.6, 129.6, 128.7, 127.5, 127.1, 116.0, 113.7, 84.1, 51.1, 48.2 45.1, 44.3, 41.3, 40.6, 34.3, 32.9, 31.0, 30.7, 28.8, 27.6, 24.4, 15.2, -10.0. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3333, 2922, 2871, 2855, 1718, 1638, 1531, 1453, 1354, 1285, 1071, 1017, 765, 713, 578, 528. **LRMS** (ESI): *m/z* 674 [M+H$^+$]. **HRMS** (ESI): *m/z* calculated for $C_{37}H_{47}NNaO_3Sn^+$: 696.2476, found 696.2470.

***N*-(4-(((8*S*,9*S*,11*S*,13*S*,14*S*,17*S*)-11-ethyl-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)ethynyl)benzyl)-4-(tributylstannyl)benzamide (40)**

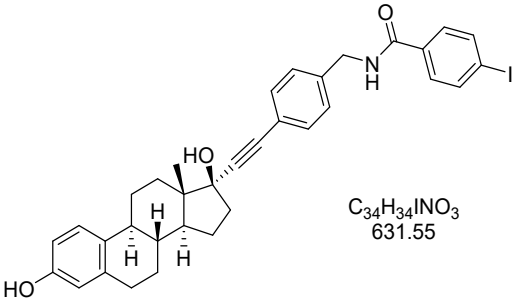


$C_{48}H_{65}NO_3Sn$
822.76

Hydrochloride **38** (20 mg, 43 µmol, 1 equiv.) was reacted with 4-tri-*n*-butylstannyl benzoic acid (21 mg, 52 µmol, 1.2 equiv.) following general procedure **C** to give stannane **40** (15.8 mg, 19.2 µmol, 45%) as a colourless solid.

TLC: R_f (PE/EtOAc 1:1) = 0.38 [UV] [$KMnO_4$]. **^{1}H NMR** (400 MHz, MeOD+$CDCl_3$): δ [ppm] = 7.53 (d, *J* = 8.1 Hz, 2H), 7.38 – 7.30 (m, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.40 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.30 (d, *J* = 2.6 Hz, 1H), 4.36 (s, 2H), 2.64 – 2.33 (m, 3H), 2.26 – 2.10 (m, 2H), 1.91 – 1.82 (m, 2H), 1.71 – 1.50 (m, 3H), 1.48 – 1.18 (m, 9H), 1.17 – 0.98 (m, 8H), 0.90 – 0.83 (m, 4H), 0.83 (s, 3H), 0.74 – 0.59 (m, 15H). **^{13}C NMR** (151 MHz, MeOD+$CDCl_3$): δ [ppm] = 169.4, 154.2, 148.0, 139.3, 139.1, 136.9, 133.9, 132.0, 129.7, 128.1, 127.8, 126.5, 122.7, 115.5, 113.5, 93.9, 85.9, 81.0, 52.2, 49.8, 43.8, 39.5, 38.8, 35.6, 33.9, 30.7, 30.0, 29.4, 27.6, 27.5, 23.2, 21.3, 16.4, 13.8, 13.0, 10.0. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3353, 2956, 2924, 2872, 2853, 1635, 1547, 1499, 1452, 1378, 1356, 1248, 1155, 1068, 1020, 866, 828, 793, 750, 685. **LRMS** (ESI): *m/z* 824 [M+H$^+$]. **HRMS** (ESI): *m/z* calculated for $C_{48}H_{65}NNaO_3Sn^+$: 846.3879, found 846.3938.

***N*-(4-(((8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)ethynyl)benzyl)-4-iodbenzamide (41)**

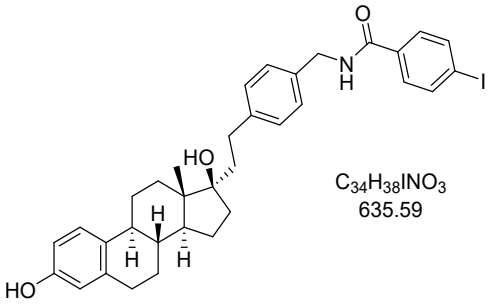


$C_{34}H_{34}INO_3$
631.55

Stannane **39** (50 mg, 75 µmol, 1 equiv.) was reacted following general procedure **D** to give the aryl iodide **41** (17 mg, 27 µmol, 37%) as a colourless solid.

TLC: R_f (PE/EtOAc 1:1) = 0.35 [UV] [$KMnO_4$]. **^{1}H NMR** (400 MHz, MeOD): δ [ppm] = 7.93 – 7.87 (m, 2H), 7.69 – 7.63 (m, 2H), 7.49 – 7.43 (m, 2H), 7.39 – 7.34 (m, 2H), 7.19 – 7.11 (m, 1H), 6.61 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.54 (d, *J* = 2.6 Hz, 1H), 4.61 (s, 2H), 2.91 – 2.80 (m, 2H), 2.48 – 2.35 (m, 2H), 2.26 – 2.09 (m, 2H), 2.07 – 1.99 (m, 1H), 1.98 – 1.79 (m, 4H), 1.60 – 1.34 (m, 4H), 0.98 (s, 3H). **^{13}C NMR** (101 MHz, MeOD): δ [ppm] = 169.3, 155.9, 140.2, 138.9, 138.8, 135.1, 132.6, 132.5, 130.0, 128.6, 127.3, 123.6, 116.1, 113.8, 99.2, 94.4, 86.2, 80.9, 51.2, 48.8, 45.2, 44.3, 41.2, 40.0, 34.4, 30.7, 28.6, 27.8, 23.9, 13.5. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3307, 2927, 2868, 1713, 1640, 1585, 1531, 1504, 1477, 1446, 1412, 1373, 1355, 1285, 1247, 1182, 1143, 1108, 1079, 1045, 1018, 1006, 973, 914, 839, 819, 787, 751, 681, 644, 613, 596, 567, 526, 470, 447, 423. **LRMS** (ESI): *m/z* 632 [M+H$^+$]. **HRMS** (ESI): *m/z* calculated for $C_{34}H_{34}INNaO_3^+$: 654.1476, found 654.1477.

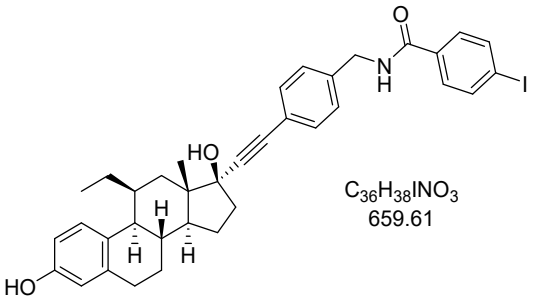
_N_-(4-(2-((8_R_,9_S_,13_S_,14_S_,17_R_)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6_H_-cyclopenta[_a_]phenanthren-17-yl)ethyl)benzyl)-4-iodbenzamide (41a)



Stannane **39a** (20 mg, 30 µmol, 1 equiv.) was reacted following general procedure **D** to give the aryl iodide **41a** (5.6 mg, 8.8 µmol, 30%) as a colourless solid.

TLC: R_f (PE/EtOAc 1:1) = 0.35 [UV] [CAM]. **^{1}H NMR** (600 MHz, MeOD): δ [ppm] = 7.80 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.22 – 7.18 (m, 2H), 7.03 (d, *J* = 8.7 Hz, 1H), 6.51 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.46 (d, *J* = 2.6 Hz, 1H), 4.51 (s, 2H), 2.85 – 2.60 (m, 4H), 2.30 – 2.21 (m, 1H), 2.13 – 2.00 (m, 2H), 1.90 – 1.78 (m, 2H), 1.74 – 1.66 (m, 3H), 1.63 – 1.57 (m, 1H), 1.50 – 1.34 (m, 6H), 0.91 (s, 3H). **^{13}C NMR** (151 MHz, MeOD): δ [ppm] = 169.2, 155.9, 143.8, 138.9, 138.9, 137.2, 135.2, 132.6, 130.3, 130.0, 129.7, 128.7, 127.1, 116.0, 113.7, 84.1, 51.1, 48.2, 45.1, 44.4, 41.3, 40.6, 34.3, 32.9, 30.9, 30.7, 28.8, 27.6, 24.4, 15.2. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3314, 2927, 2861, 1632, 1585, 1557, 1496, 1445, 1416, 1380, 1352, 1284, 1248, 1182, 1060, 1003, 932, 840, 817, 785, 748. **LRMS** (ESI): *m/z* 653 [M+NH_4^+]. **HRMS** (ESI): *m/z* calculated for $C_{34}H_{38}INNaO_3^+$: 658.1789, found 658.1789.

_N_-(4-(((8_S_,9_S_,11_S_,13_S_,14_S_,17_S_)-11-Ethyl-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6_H_-cyclopenta[_a_]phenanthren-17-yl)ethinyl)benzyl)-4-iodbenzamide (42)

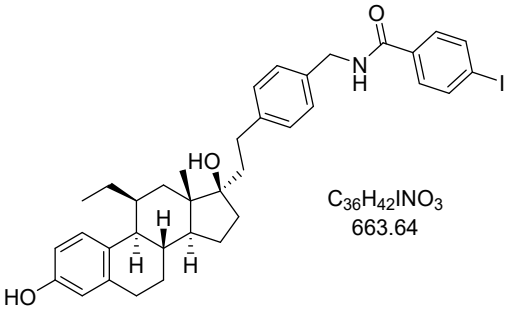


$C_{36}H_{38}INO_3$
659.61

Stannane **40** (11.7 mg, 14 µmol, 1 equiv.) was reacted following general procedure **D** to give the aryl iodide **42** (7.8 mg, 12 µmol, 83%) as a colourless solid.

TLC: R_f (PE/EtOAc 1:1) = 0.43 [UV] [CAM]. **^{1}H NMR** (400 MHz, MeOD): δ [ppm] = = 7.87 – 7.81 (m, 2H), 7.64 – 7.59 (m, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.35 – 7.29 (m, 2H), 7.02 – 6.97 (m, 1H), 6.58 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.49 (d, *J* = 2.6 Hz, 1H), 4.56 (s, 2H), 2.85 – 2.71 (m, 1H), 2.71 – 2.63 (m, 1H), 2.57 (dd, *J* = 10.7, 4.7 Hz, 1H), 2.47 – 2.39 (m, 1H), 2.39 – 2.30 (m, 1H), 2.18 – 2.04 (m, 3H), 1.94 – 1.60 (m, 4H), 1.51 – 1.33 (m, 4H), 1.07 (s, 3H), 0.99 – 0.92 (m, 3H). **^{13}C NMR** (151 MHz, MeOD): δ [ppm] = 169.2, 155.3, 140.0, 139.9, 138.8, 135.0, 132.5, 130.2, 130.0, 128.7, 128.5, 123.5, 116.0, 114.1, 99.2, 94.7, 86.5, 81.6, 53.1, 50.8, 49.4, 44.3, 40.1, 39.8, 36.6, 34.7, 31.3, 28.3, 23.7, 22.0, 16.8, 13.3. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3357, 2957, 2872, 2853, 1535, 1493, 1479, 1392, 1221, 1177, 1150, 1110, 1071, 842. **LRMS** (ESI): *m/z* 660 [M+H$^+$]. **HRMS** (ESI): *m/z* calculated for $C_{36}H_{38}INNaO_3^+$: 682.1789, found 682.1793.

_N_-(4-(2-((8_S_,9_S_,11_S_,13_S_,14_S_,17_R_)-11-Ethyl-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6_H_-cyclopenta[_a_]phenanthren-17-yl)ethyl)benzyl)-4-iodbenzamide (42a)

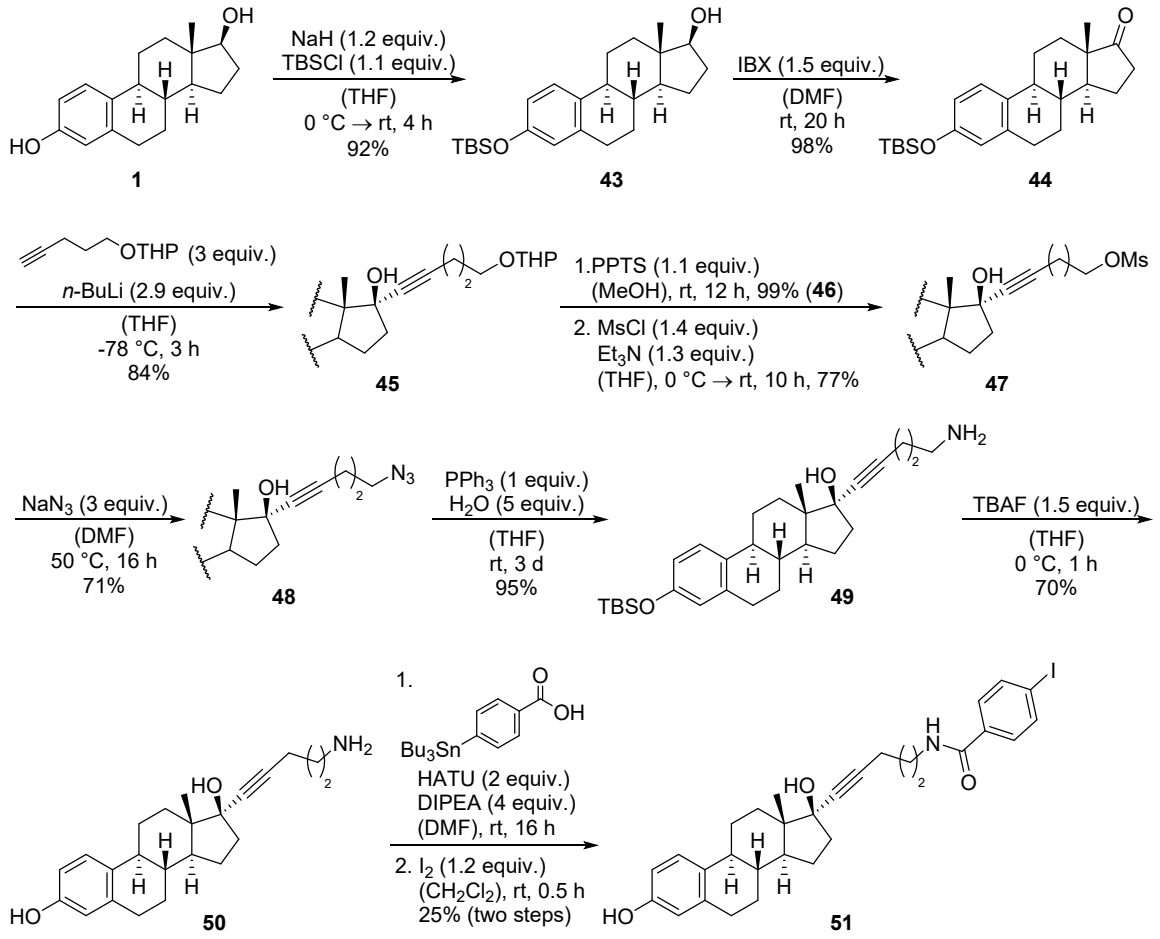


$C_{36}H_{42}INO_3$
663.64

Hydrochloride **38a** (16 mg, 34 µmol, 1 equiv.) was treated with 4-tri-*n*-butylstannyl benzoic acid (17 mg, 41 µmol, 1.2 equiv.) following general procedure **C** to give stannane **40a** (13 mg) as a colourless solid, which was then reacted following general procedure **D** to give the aryl iodide **42a** (3.5 mg, 5.3 µmol, 16% over two steps) as a colourless solid.

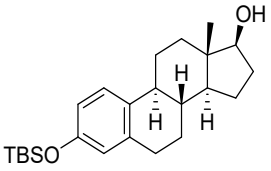
TLC: R_f (PE/EtOAc 1:1) = 0.38 [$KMnO_4$]. **^{1}H NMR** (400 MHz, MeOD): δ [ppm] = 7.82 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 7.9 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 1H), 6.53 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.45 (d, *J* = 2.6 Hz, 1H), 4.52 (s, 2H), 2.89 – 2.56 (m, 4H), 2.51 – 2.41 (m, 1H), 2.40 – 2.26 (m, 1H), 2.12 – 2.03 (m, 1H), 1.96 – 1.80 (m, 3H), 1.76 – 1.49 (m, 6H), 1.49 – 1.18 (m, 4H), 1.06 (s, 3H), 0.90 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, MeOD): δ [ppm] = 169.3, 155.4, 143.9, 140.0, 138.9, 137.2, 135.3, 130.3, 130.0, 129.7, 128.8, 128.7, 116.1, 114.1, 84.9, 53.0, 50.8, 44.4, 41.2, 40.0, 37.0, 34.3, 33.1, 31.4, 31.2, 28.5, 24.4, 22.3, 18.6, 13.4. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3356, 2928, 2871, 1639, 1585, 1561, 1499, 1450, 1376, 1353, 1288, 1248, 1005, 841, 751. **LRMS** (ESI): *m/z* 646 [M-OH^+]. **HRMS** (APCI): *m/z* calculated for $C_{36}H_{43}INO_3^+$: 664.2282, found 664.2288.

Synthesis of compound 51



Scheme S10: Synthesis of steroid **51**.

(8*R*,9*S*,13*S*,14*S*,17*S*)-3-((*tert*-butyldimethylsilyl)oxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-17-ol (43)

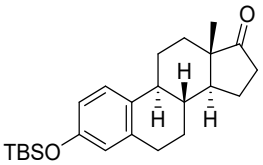


$C_{24}H_{38}O_2Si$
386.65

To 17β-estradiol (**1**) (800 mg, 2.94 mmol, 1 equiv.) dissolved in abs. THF (4.2 mL) NaH (141 mg, 3.52 mmol 60% oil dispersion, 1.2 equiv.) was added at 0 °C and the mixture was stirred at room temperature for 0.5 h. Then, TBSCl (487 mg, 3.23 mmol, 1.1 equiv.) was added, and the mixture was stirred at room temperature for 3 h. The reaction was diluted with water and then extracted with CH_2Cl_2 (3×30 mL). The combined organic layer was dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. Column chromatographic purification (CH/EtOAC 9:1) afforded silyl ether **43** (1.05 g, 2.72 mmol, 92%) as a colourless solid.

TLC: R_f (PE/EtOAc 8:2) = 0.27 [UV] [CAM]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.12 (d, *J* = 8.2 Hz, 1H), 6.61 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 3.77 – 3.68 (m, 1H), 2.86 – 2.75 (m, 2H), 2.35 – 2.24 (m, 1H), 2.23 – 2.05 (m, 2H), 1.99 – 1.89 (m, 1H), 1.92 – 1.81 (m, 1H), 1.76 – 1.63 (m, 1H), 1.57 – 1.12 (m, 7H), 0.98 (s, 9H), 0.78 (s, 3H), 0.19 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 153.5, 138.0, 133.2, 126.3, 120.1, 117.3, 82.1, 50.3, 44.2, 43.4, 39.0, 36.9, 30.8, 29.8, 27.4, 26.4, 25.9, 23.3, 18.3, 11.2, -4.2. The spectroscopical data were identical to those reported in the literature.[10]

(8*R*,9*S*,13*S*,14*S*)-3-((*tert*-butyldimethylsilyl)oxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (44)

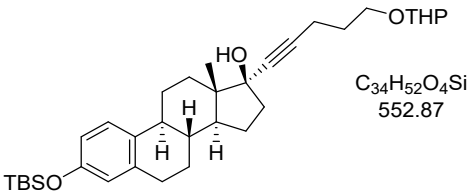


$C_{24}H_{36}O_2Si$
384.64

Steroid **43** (1.00 g, 2.59 mmol, 1 equiv.) was dissolved in abs. DMF (17 mL), IBX (1.09 g, 3.88 mmol, 1.5 equiv.) was added, and the reactants were stirred for 20 h at room temperature. Then, the mixture was concentrated in vacuo, redissolved in CH_2Cl_2, and purified respectively through a short plug of silica gel and Celite®. Finally, the filtrate was concentrated in vacuo to give the estrone derivative **44** (979 mg, 2.55 mmol, 98%) as a colourless solid.

TLC: R_f (PE/EtOAc 9:1) = 0.29 [UV] [CAM]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.12 (d, *J* = 8.3 Hz, 1H), 6.62 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.57 (d, *J* = 2.6 Hz, 1H), 2.90 – 2.81 (m, 2H), 2.56 – 2.44 (m, 1H), 2.43 – 2.33 (m, 1H), 2.30 – 2.18 (m, 1H), 2.17 – 2.07 (m, 1H), 2.06 – 1.95 (m, 2H), 1.70 – 1.35 (m, 7H), 0.98 (s, 9H), 0.91 (s, 3H), 0.19 (s, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ [ppm] = 221.1, 153.7, 137.8, 132.6, 126.3, 120.1, 117.5, 50.7, 48.2, 44.2, 38.5, 36.0, 31.8, 29.6, 26.7, 26.0, 25.9, 21.8, 18.3, 14.0, -4.2. The spectroscopical data were identical to those reported in the literature.[11]

(8*R*,9*S*,13*S*,14*S*,17*S*)-3-((*tert*-butyldimethylsilyl)oxy)-13-methyl-17-(5-((tetrahydro-2*H*-pyran-2-yl)oxy)pent-1-yn-1-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-17-ol (45)

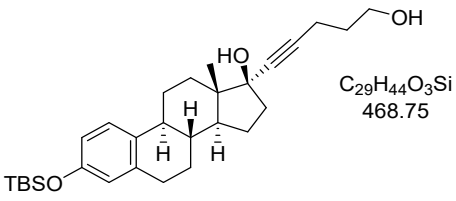


$C_{34}H_{52}O_4Si$
552.87

2-(Pent-4-yn-1-yloxy)tetrahydro-2*H*-pyran (598 mL, 3.44 mmol, 3 equiv., prepared from 4-pentynoic acid in two steps with an overall yield of 45%[12]) was dissolved in abs. THF (8.8 mL) and cooled to -78 °C. Then, *n*-BuLi (1.33 mL, 3.33 mmol, 2.5M in hexane, 2.9 equiv.) was added dropwise and the mixture was stirred at 0 °C for 40 min. Steroid **44** (441 mg, 1.15 mmol, 1 equiv.) was dissolved in abs. THF and then added slowly to the reaction mixture. After stirring for 2 h at -78 °C, the mixture was diluted with 5% aq. $NaHCO_3$ and the aqueous layer were extracted with EtOAc (3×30 mL). The combined organic layer was washed with saturated aq. NaCl and the solvent were evaporated in vacuo. The residue was purified by column chromatography (CH/EtOAc 9:1 → 8:2) to give ether **45** (530 mg, 959 µmol, 84%) as a pale yellow oil.

TLC: Rf (PE/EtOAc 8:2) = 0.19 [UV] [CAM]. **^{1}H NMR** (600 MHz, $CDCl_3$): δ [ppm] = 7.13 (d, *J* = 8.4 Hz, 1H), 6.61 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.55 (d, *J* = 2.6 Hz, 1H), 4.59 – 4.58 (m, 1H), 3.89 – 3.80 (m, 2H), 3.53 – 3.45 (m, 2H), 2.86 – 2.74 (m, 2H), 2.37 (t, *J* = 7.0 Hz, 2H), 2.35 – 2.31 (m, 1H), 2.29 – 2.22 (m, 1H), 2.19 (td, *J* = 11.7, 3.8 Hz, 1H), 2.03 – 1.96 (m, 1H), 1.92 – 1.63 (m, 9H), 1.61 – 1.31 (m, 8H), 0.98 (s, 9H), 0.87 (s, 3H), 0.19 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 153.4, 138.0, 133.2, 126.3, 120.1, 117.3, 99.0, 85.8, 84.3, 80.2, 66.1, 62.5, 49.7, 47.3, 43.9, 39.6, 39.3, 33.1, 30.9, 29.8, 29.2, 27.5, 26.6, 25.9, 25.6, 23.0, 19.8, 18.3, 15.9, 13.0, -4.2. The spectroscopical data were identical to those reported in the literature.[13]

(8*R*,9*S*,13*S*,14*S*,17*S*)-3-((*tert*-butyldimethylsilyl)oxy)-17-(5-hydroxypent-1-yn-1-yl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-17-ol (46)



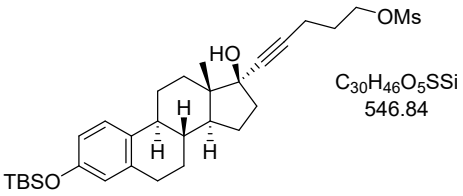
$C_{29}H_{44}O_3Si$
468.75

To a solution of steroid **45** (1.00 g, 1.81 mmol, 1 equiv.) in abs. MeOH (36 mL) was added to PPTS (500 mg, 1.99 mol, 1.1 equiv.). The mixture was stirred for 12 h at room temperature. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (CH/EtOAc 7:3). The diol **46** (842 mg, 1.80 mmol, 99%) was obtained as a colourless oil.

TLC: R_f (PE/EtOAc 6:4) = 0.13 [UV] [CAM]. **^{1}H NMR** (600 MHz, $CDCl_3$): δ [ppm] = 7.16 – 7.11 (m, 1H), 6.61 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.55 (d, *J* = 2.3 Hz, 1H), 3.77 (t, *J* = 6.1 Hz, 2H), 2.87 – 2.73 (m, 2H), 2.38 (t,

J = 6.9 Hz, 2H), 2.36 – 2.31 (m, 1H), 2.29 – 2.22 (m, 1H), 2.19 (td, *J* = 11.5, 3.9 Hz, 2H), 2.02 – 1.95 (m, 1H), 1.89 – 1.81 (m, 2H), 1.82 – 1.76 (m, 2H), 1.72 – 1.61 (m, 2H), 1.53 – 1.30 (m, 4H), 0.98 (s, 9H), 0.87 (s, 3H), 0.19 (s, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ [ppm] = 153.4, 138.0, 133.1, 126.3, 120.1, 117.3, 85.6, 84.6, 80.2, 62.0, 49.8, 47.4, 43.9, 39.6, 39.3, 33.2, 31.7, 29.8, 27.5, 26.5, 25.9, 23.0, 18.3, 15.6, 13.0, -4.2. The spectroscopical data were identical to those reported in the literature.[13]

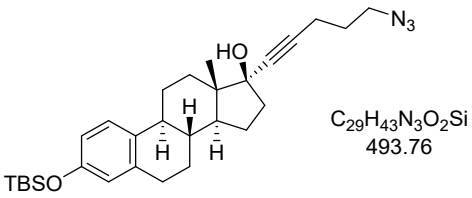
5-((8*R*,9*S*,13*S*,14*S*,17*S*)-3-((*tert*-butyldimethylsilyl)oxy)-17-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)pent-4-yn-1-yl-methanesulfonate (47)



To a solution of steroid **46** (96 mg, 0.20 mmol, 1 equiv.) in abs. THF (1.5 mL) was added Et_3N (37 µL, 0.27 mmol, 1.3 equiv.), and the mixture was cooled to 0 °C. Finally, MsCl (22 µL, 0.29 mmol, 1.4 equiv.) was added, and the reaction mixture was allowed to warm to room temperature and stirred for further 10 h. The reaction was diluted with saturated aq. $NaHCO_3$ and the mixture were extracted with CH_2Cl_2 (3×10 mL). The combined organic layer was washed with saturated aq. NaCl was dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. Column chromatographic purification (CH/EtOAc 7:3) afforded steroid **47** (86 mg, 0.16 mmol, 77%) as a colourless oil.

TLC: R_f (PE/EtOAc 6:4) = 0.27 [UV] [CAM]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.13 (d, *J* = 8.4 Hz, 1H), 6.61 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.55 (d, *J* = 2.6 Hz, 1H), 3.02 (s, 3H), 2.85 – 2.78 (m, 2H), 2.44 (t, *J* = 6.8 Hz, 2H), 2.37 – 2.30 (m, 1H), 2.30 – 2.14 (m, 2H), 2.05 – 1.93 (m, 4H), 1.90 – 1.82 (m, 2H), 1.81 – 1.59 (m, 4H), 1.54 – 1.31 (m, 4H), 0.98 (s, 9H), 0.87 (s, 3H), 0.19 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 153.5, 138.0, 133.1, 126.3, 120.1, 117.3, 85.7, 83.9, 80.2, 68.5, 49.8, 47.3, 43.9, 39.6, 39.3, 37.6, 33.2, 29.8, 28.3, 27.4, 26.5, 25.9, 23.0, 18.3, 15.3, 13.0, -4.2. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3523, 2929, 2857, 1607, 1495, 1471, 1353, 1334, 1287, 1252, 1172, 1006, 970, 956, 932, 910, 878, 837, 779, 729, 527. **LRMS** (ESI): *m/z* 564 [$M+NH_4^+$]. **HRMS** (ESI): *m/z* calculated for $C_{30}H_{46}NaO_5SSi^+$: 569.2727, found 569.2733.

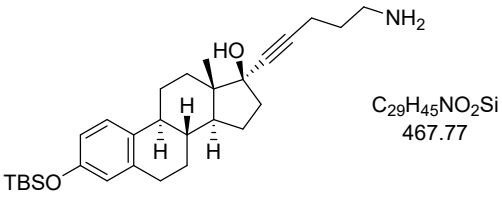
(8*R*,9*S*,13*S*,14*S*,17*S*)-17-(5-azidopent-1-in-1-yl)-3-((*tert*-butyldimethylsilyl)oxy)13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-17-ol (48)



To a solution of steroid **47** (25 mg, 46 µmol, 1 equiv.) in DMF (462 µL), NaN_3 (9.0 mg, 0.14 mmol, 3 equiv.) was added, and the mixture was heated to 50 °C and stirred for 16 h. The reaction was diluted with water, and the mixture was extracted with EtOAc (3×5 mL). The combined organic layer was washed with saturated aq. NaCl, was dried over Na_2SO_4, filtered, and the solvent evaporated in vacuo. The residue was purified by column chromatography (CH/EtOAc 8:2) to give azide **48** (16 mg, 33 µmol, 71%) as a yellow oil.

TLC: R_f (PE/EtOAc 8:2) = 0.36 [UV] [$KMnO_4$]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.13 (d, *J* = 8.3 Hz, 1H), 6.62 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.55 (d, *J* = 2.6 Hz, 1H), 3.43 (t, *J* = 6.6 Hz, 2H), 2.86 – 2.77 (m, 2H), 2.39 (t, *J* = 6.9 Hz, 2H), 2.37 – 2.31 (m, 1H), 2.30 – 2.23 (m, 1H), 2.22 – 2.15 (m, 1H), 2.06 – 1.96 (m, 1H), 1.90 – 1.83 (m, 2H), 1.80 (t, *J* = 6.7 Hz, 2H), 1.77 – 1.61 (m, 3H), 1.51 – 1.31 (m, 4H), 0.98 (s, 9H), 0.88 (s, 3H), 0.19 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 153.5, 138.0, 133.1, 126.3, 120.1, 117.3, 85.2, 84.5, 80.2, 50.5, 49.8, 47.4, 43.9, 39.6, 39.4, 33.2, 29.8, 28.2, 27.5, 26.5, 25.9, 23.0, 18.3, 16.4, 13.0, -4.2. **IR** (ATR): $\tilde{\upsilon}$ [cm^1] = 3446, 2927, 2856, 2096, 1607, 1495, 1471, 1462, 1345, 1287, 1251, 1157, 1128, 1097, 1073, 1045, 1019, 1005, 969, 956, 877, 837, 779. **LRMS** (ESI): *m/z* 511 [M+NH_4^+]. **HRMS** (ESI): *m/z* calculated for $C_{29}H_{43}N_3NaO_2Si^+$: 516.3017, found 516.3021.

(8*R*,9*S*,13*S*,14*S*,17*S*)-17-(5-aminopent-1-yn-1-yl)-3-((*tert*-butyldimethylsilyl)oxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-17-ol (49)

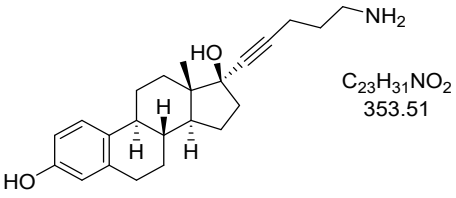


To a solution of azide **48** (480 mg. 972 µmol, 1 equiv.) in abs. THF (3.2 mL) PPh_3 (255 mg, 972 µmol, 1 equiv.) and water (87 µL, 4.9 mmol, 5 equiv.) were added. The reaction mixture was stirred at room temperature for 3 days. Then, the reaction was quenched with EtOAc and water, and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layer was washed with saturated aq. NaCl, dried over Na_2SO_4, filtered, and the solvent was concentrated in vacuo. The residue was purified

by column chromatography (*i*-PrOH/EtOAc 1:1) to give amine **49** (434 mg, 928 µmol, 95%) as a brown solid.

TLC: R_f (*i*-PrOH/EtOAc 6:4) = 0.08 [Ninhydrin]. **^{1}H NMR** (600 MHz, $CDCl_3$+MeOD): δ [ppm] = 7.15 – 7.10 (m, 1H), 6.61 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.54 (d, *J* = 2.7 Hz, 1H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.82 – 2.70 (m, 2H), 2.38 (t, *J* = 6.8 Hz, 2H), 2.36 – 2.30 (m, 1H), 2.30 – 2.21 (m, 1H), 2.21 – 2.11 (m, 1H), 2.04 – 1.95 (m, 1H), 1.90 – 1.60 (m, 7H), 1.51 – 1.29 (m, 4H), 1.01 – 0.94 (m, 9H), 0.86 (s, 3H), 0.18 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$+MeOD): δ [ppm] = 154.2, 138.6, 134.0, 126.9, 120.7, 118.1, 86.4, 83.8, 80.3, 50.6, 48.0, 44.8, 40.5, 39.7, 39.7, 33.9, 30.4, 28.2, 27.6, 27.3, 26.1, 23.5, 18.8, 16.6, 13.3, -4.2. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3389, 2928, 2857, 1495, 1286, 1251, 1156, 1096, 1074, 1048, 1021, 1006, 971, 955, 837, 778, 449. **LRMS** (ESI): *m/z* 468 [$M+H^+$]. **HRMS** (ESI): *m/z* calculated for $C_{29}H_{46}NO_2Si^+$: 468.3292, found 468.3290.

(8*R*,9*S*,13*S*,14*S*,17*S*)-17-(5-aminopent-1-yn-1-yl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (50)

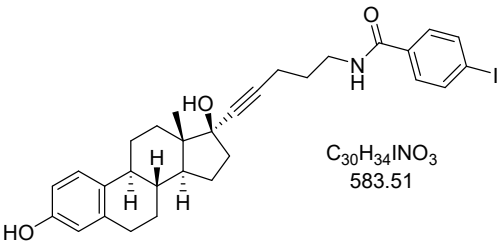


$C_{23}H_{31}NO_2$
353.51

To a solution of amine **49** (100 mg, 213 µmol, 1 equiv.) in abs. THF (1.5 mL) was added TBAF (321 µL, 321 µmol, 1M in THF, 1.5 equiv.) at 0 °C. After stirring for 1 h at 0 °C, the mixture was warmed to room temperature and aq. HCl (1N) and EtOAc were added. The organic layer was extracted with aq. HCl (1N), then the aqueous layer was neutralized with saturated aq. NH_4Cl, and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layer was washed with saturated aq. NaCl, dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. Steroid **50** (53 mg, 15 µmol, 70%) was obtained as a colourless solid and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.07 (d, *J* = 8.5 Hz, 1H), 6.57 (d, *J* = 8.6 Hz, 1H), 6.51 (s, 1H), 2.96 (t, *J* = 7.3 Hz, 2H), 2.80 – 2.71 (m, 2H), 2.35 (t, *J* = 6.7 Hz, 2H), 2.31 – 2.24 (m, 1H), 2.23 – 2.06 (m, 2H), 1.98 – 1.87 (m, 1H), 1.87 – 1.54 (m, 7H), 1.49 – 1.19 (m, 4H), 0.81 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ [ppm] = 154.6, 138.2, 131.8, 126.5, 115.4, 112.9, 85.8, 83.6, 79.8, 49.8, 47.4, 43.9, 39.8, 39.7, 39.1, 33.3, 29.9, 28.0, 27.6, 26.7, 23.0, 16.3, 12.9. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3285, 2927, 2870, 1610, 1584, 1499, 1447, 1378, 1354, 1286, 1249, 1147, 1130, 1074, 1046, 1020, 733. **LRMS** (ESI): *m/z* 354 [M+H$^+$]. **HRMS** (ESI): *m/z* calculated for $C_{23}H_{32}NO_2^+$: 354.2428, found 354.2427.

***N*-(5-((8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)pent-4-yn-1-yl)-4-iodbenzamide (51)**

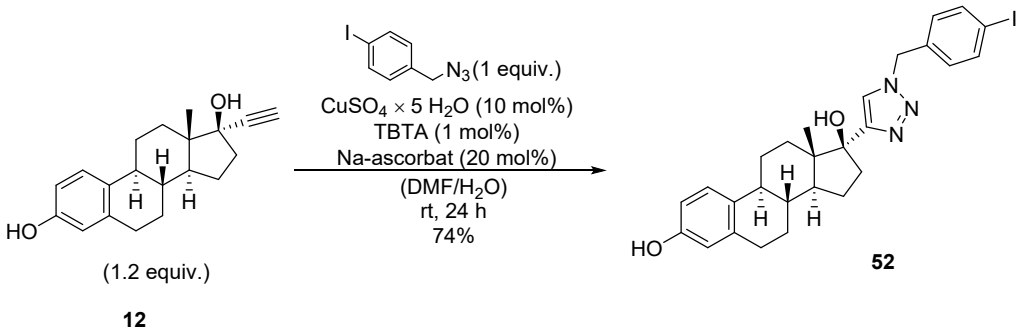


$C_{30}H_{34}INO_3$
583.51

Following general procedures **C** and **D**, steroid **50** (20 mg, 57 µmol) furnished aryl iodide (7 mg, 12 µmol, 25% over two steps) as a colourless solid.

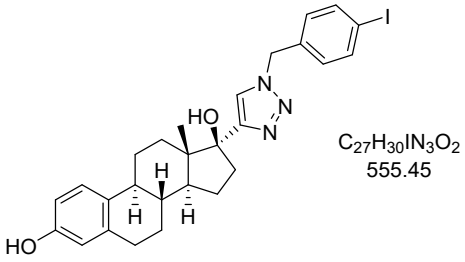
TLC: R_f (PE/EtOAc 6:4) = 0.15 [UV] [CAM]. **^{1}H NMR** (400 MHz, MeOD+$CDCl_3$): δ [ppm] = 7.78 – 7.71 (m, 2H), 7.53 – 7.47 (m, 2H), 7.12 – 7.05 (m, 1H), 6.61 – 6.55 (m, 1H), 6.52 – 6.47 (m, 1H), 3.53 – 3.44 (m, 2H), 2.85 – 2.70 (m, 2H), 2.34 – 2.27 (m, 2H), 2.27 – 2.08 (m, 2H), 2.00 – 1.88 (m, 1H), 1.86 – 1.76 (m, 3H), 1.75 – 1.57 (m, 3H), 1.44 – 1.25 (m, 6H), 0.83 – 0.79 (m, 3H). **^{13}C NMR** (101 MHz, MeOD+$CDCl_3$): δ [ppm] = 154.6, 138.3, 138.0, 132.0, 129.1, 126.6, 115.5, 113.0, 98.5, 85.1, 84.7, 79.9, 49.8, 47.5, 44.0, 39.9, 39.4, 39.2, 33.3, 30.0, 28.5, 28.2, 27.6, 27.1, 26.8, 23.1, 16.6, 13.0.

Synthesis of compound 52 and 55



Scheme S11: Synthesis of compound **52**.

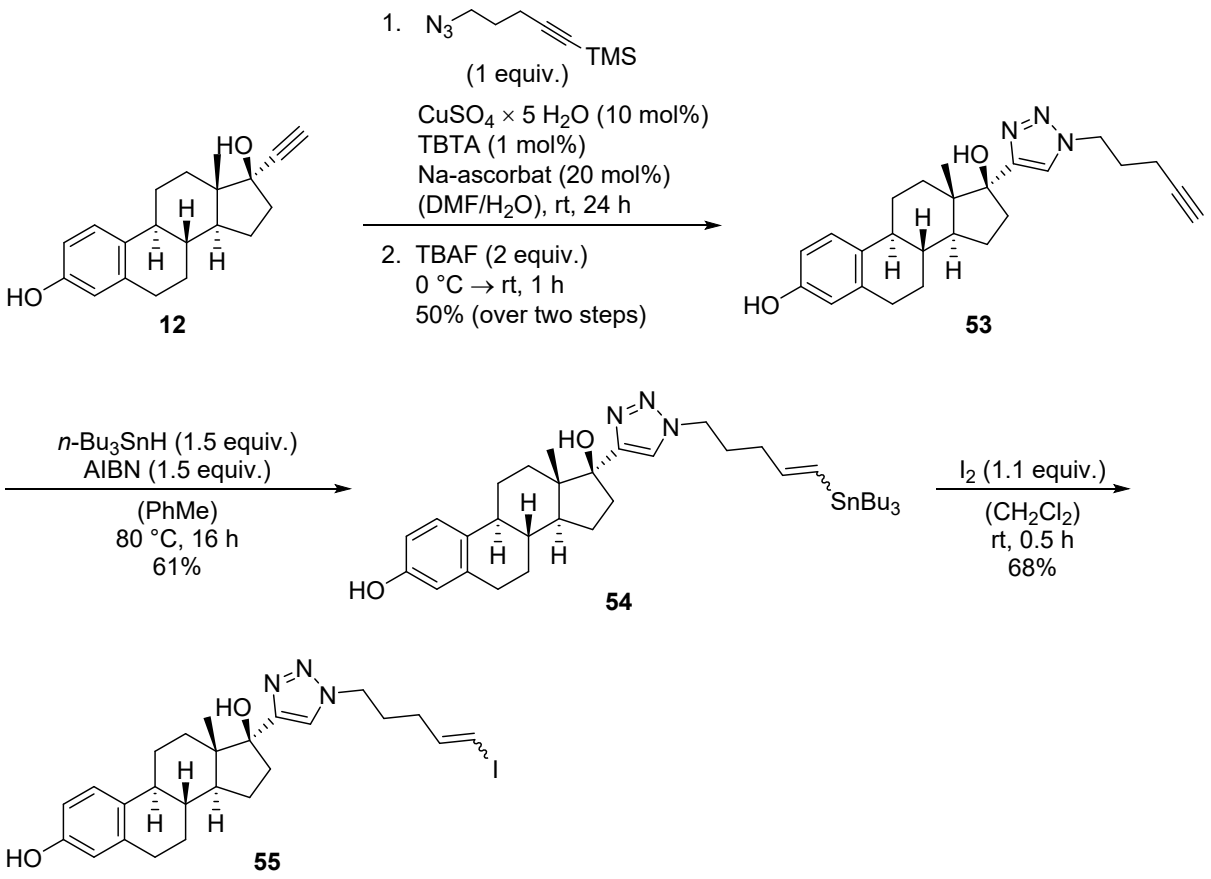
(8*R*,9*S*,13*S*,14*S*,17*S*)-17-(1-(4-Iodbenzyl)-1*H*-1,2,3-triazol-4-yl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (52)



To a solution of 1-(azidomethyl)-4-iodobenzene (87.4 mg, 337 µmol, 1 equiv., quantitatively prepared from 4-iodobenzyl bromide[8]) in abs. DMF (1.1 mL) and water (375 µL) were added ethinylestradiol (**12**) (118 mg, 399 µmol, 1.2 equiv.), $CuSO_4$×5 H_2O (8.4 mg, 34 µmol, 10 mol%), TBTA (1.8 mg, 3.3 µmol, 1 mol%), and (+)-sodium *L*-ascorbate (13 mg, 67 µmol, 20 mol%) and the reaction mixture was stirred for 24 h at room temperature. The mixture was diluted with water and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL), dried over Na_2SO_4, filtered, and the solvent was concentrated in

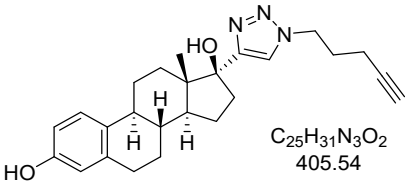
vacuo. The residue was purified by column chromatography (CH/EtOAc 7:3 → 6:4) to give triazole **52** (138 mg, 249 µmol, 74%) as a colourless solid.

TLC: R_f (PE/EtOAc 1:1) = 0.38 [UV] [$KMnO_4$]. **^{1}H NMR** (400 MHz, DMSO-d_6): δ [ppm] = 8.93 (s, 1H), 7.87 (s, 1H), 7.78 – 7.72 (m, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.47 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.41 (d, *J* = 2.6 Hz, 1H), 5.54 (s, 2H), 5.07 (s, 1H), 2.74 – 2.65 (m, 2H), 2.39 – 2.26 (m, 1H), 2.13 – 2.04 (m, 1H), 1.97 – 1.87 (m, 1H), 1.87 – 1.72 (m, 3H), 1.71 – 1.58 (m, 1H), 1.51 – 1.12 (m, 5H), 0.91 (s, 3H), 0.65 – 0.51 (m, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ [ppm] = 154.8, 154.5, 137.5, 137.1, 136.0, 130.4, 130.1, 125.9, 122.8, 114.8, 112.6, 94.2, 81.1, 52.0, 47.5, 46.7, 43.1, 37.2, 32.6, 29.2, 27.2, 26.0, 23.5, 14.3. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3446, 2925, 2867, 1604, 1486, 1445, 1419, 1405, 1259, 1241, 1214, 1138, 1051, 1006, 910, 862, 804, 778. **LRMS** (ESI): *m/z* 556 [M+H$^+$]. **HRMS** (ESI): *m/z* calculated for $C_{27}H_{31}IN_3O_2^+$: 556.1456, found 556.1457.



Scheme S12: Synthesis of steroid **55**.

(8*R*,9*S*,13*S*,14*S*,17*S*)-13-methyl-17-(1-(pent-4-yn-1-yl)-1*H*-1,2,3-triazol-4-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (53)

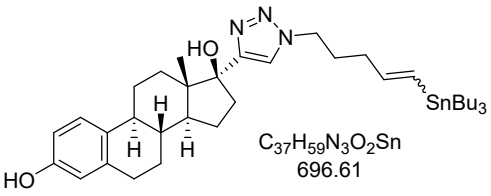


$C_{25}H_{31}N_3O_2$
405.54

(5-Azidopent-1-yn-1-yl)trimethylsilane (100 mg, 551 µmol, 1 equiv., prepared from 4-pentyn-1-ol in three steps with an overall yield of 63%[17-18]) was dissolved in DMF (1.8 mL) and water (0.6 mL). Ethinylestradiol (**12**) (193 mg, 652 µmol, 1.2 equiv.), $CuSO_4 \times 5\ H_2O$ (14 mg, 55 µmol, 10 mol%), TBTA (3.0 mg, 5.5 µmol, 1 mol%) and (+)-sodium *L*-ascorbate (22 mg, 110 µmol, 20 mol%) were added and the reaction mixture was stirred for 16 h at room temperature. The reaction was diluted with water and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layer was washed with water (2×20 mL) and saturated aq. NaCl, dried over Na_2SO_3, filtered, and concentrated under reduced pressure. The residue was used without further purification. For this, the product was dissolved in abs. THF (11 mL) and TBAF (1.1 mL, 1.1 mmol, 1M in THF, 2 equiv.) was added at 0 °C. After the mixture was stirred for 1 h at room temperature, EtOAc and water were added and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated in vacuo. The residue was purified by column chromatography (CH/EtAOc 6:4) to give alkyne **53** (112 mg, 276 µmol, 50% over two steps) as a colourless solid.

TLC: R_f (PE/EtOAc 6:4) = 0.08 [UV] [$KMnO_4$]. **^{1}H NMR** (600 MHz, MeOD+$CDCl_3$): δ [ppm] = 7.70 (s, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.52 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.48 (d, *J* = 2.7 Hz, 1H), 4.50 (t, *J* = 6.9 Hz, 2H), 2.84 – 2.69 (m, 2H), 2.50 – 2.41 (m, 1H), 2.24 – 2.17 (m, 3H), 2.16 – 2.05 (m, 4H), 2.02 – 1.93 (m, 1H), 1.94 – 1.85 (m, 2H), 1.67 – 1.57 (m, 2H), 1.57 – 1.49 (m, 1H), 1.48 – 1.35 (m, 2H), 1.35 – 1.24 (m, 1H), 1.02 (s, 3H), 0.67 (td, *J* = 12.9, 4.2 Hz, 1H). **^{13}C NMR** (151 MHz, MeOD+$CDCl_3$): δ [ppm] = 155.3, 155.0, 138.6, 132.3, 126.9, 123.7, 115.8, 113.4, 82.9, 82.7, 70.8, 49.6, 49.2, 48.0, 44.4, 40.5, 38.1, 33.9, 30.4, 29.6, 28.3, 27.1, 24.3, 16.0, 14.7. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3353, 3293, 2925, 1617, 1579, 1497, 1455, 1436, 1352, 1288, 1253, 1213, 1187, 1144, 1066, 1029, 956, 929, 914, 875, 823, 804, 788, 691, 617, 528, 476, 440. **LRMS** (ESI): *m/z* 406 [M+H$^+$]. **HRMS** (ESI): *m/z* calculated for $C_{25}H_{32}N_3O_2^+$: 406.2489, found 406.2490.

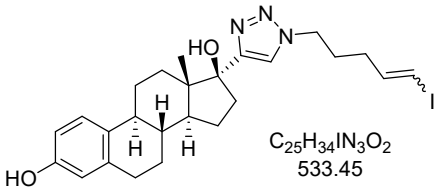
(8*R*,9*S*,13*S*,14*S*,17*S*)-13-methyl-17-(1-(5-(tributylstannyl)pent-4-en-1-yl)-1*H*-1,2,3-triazol-4-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (54)



Alkyne **53** (50 mg, 0.12 mmol, 1 equiv.) was dissolved in abs. toluene (1.8 mL) followed by the addition of *n*-Bu_3SnH (49 µL, 18 µmol, 1.5 equiv.) and AIBN (30 mg, 18 µmol, 1.5 equiv.). The reaction mixture was stirred for 16 h at 80 °C. After cooling the reaction mixture to room temperature, the solution was concentrated under reduced pressure. The residue was loaded onto silica and purified by column chromatography (CH/EtOAc 7:3 → 6:4). The stannane **54** (22 mg, 33 µmol, 61%) was obtained as a pale yellow oil.

TLC: R_f (PE/EtOAc 6:4) = 0.24 [UV] [$KMnO_4$]. **^{1}H NMR** (600 MHz, $CDCl_3$): δ [ppm] = (s, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.59 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.55 (d, *J* = 2.7 Hz, 1H), 6.08 – 5.84 (m, 2H), 5.20 (s, 1H), 4.35 (t, *J* = 7.2 Hz, 2H), 2.88 – 2.72 (m, 3H), 2.45 – 2.32 (m, 1H), 2.19 – 2.10 (m, 4H), 2.07 – 2.00 (m, 2H), 1.95 – 1.85 (m, 3H), 1.69 – 1.40 (m, 12H), 1.35 – 1.26 (m, 8H), 1.04 (s, 3H), 0.91 – 0.84 (m, 12H), 0.67 (td, *J* = 13.0, 4.3 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ [ppm] = 153.6, 146.8, 138.3, 132.6, 130.3, 126.5, 121.3, 115.4, 112.8, 82.5, 77.2, 49.7, 48.7, 47.5, 43.5, 39.6, 38.1, 34.5, 33.1, 29.8, 29.4, 29.3, 29.3, 27.4, 26.4, 23.5, 14.4, 13.9, 9.6. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3155, 2954, 2924, 2870, 2853, 1608, 1502, 1443, 1377, 1287, 1228, 1146, 1054, 1018, 990, 910, 872, 807, 732, 689, 665, 595, 504. **LRMS** (ESI): *m/z* 698 [$M+H^+$]. **HRMS** (ESI): *m/z* calculated for $C_{37}H_{60}N_3O_2Sn^+$: 698.3702, found 698.3687.

(8*R*,9*S*,13*S*,14*S*,17*S*)-17-(1-((E)-5-iodopent-4-en-1-yl)-1*H*-1,2,3-triazol-4-yl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (55)



$C_{25}H_{34}IN_3O_2$
533.45

The steroid **54** (30 mg, 43 µmol, 1 equiv.) was dissolved in CH_2Cl_2 (140 µL), and iodine (12 mg, 47 µmol, 1.1 equiv.) diluted in CH_2Cl_2 was added dropwise to the mixture. After 30 minutes, the reaction was quenched with saturated aq. Na_2SO_3, and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layer was concentrated under reduced pressure and the residue was purified by column chromatography (CH/EtOAc 6:4 → 5:5). Steroid **55** (16 mg, 29 µmol, 68%) was obtained as a colourless solid.

TLC: R_f (PE/EtOAc 6:4) = 0.21 [UV] [$KMnO_4$]. **^{1}H NMR** (600 MHz, MeOD+$CDCl_3$): δ [ppm] = 7.73 (s, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.56 – 6.48 (m, 2H), 6.47 (d, *J* = 2.6 Hz, 1H), 6.21 – 6.11 (m, 1H), 4.39 (t, *J* = 6.8 Hz, 2H), 2.84 – 2.69 (m, 2H), 2.50 – 2.41 (m, 1H), 2.17 – 2.12 (m, 1H), 2.11 – 2.00 (m, 4H), 1.67 – 1.51 (m, 4H), 1.48 – 1.21 (m, 6H), 1.03 (s, 3H), 0.68 (td, *J* = 13.0, 4.2 Hz, 1H). **^{13}C NMR** (151 MHz, MeOD+$CDCl_3$): δ [ppm] = 155.6, 145.5, 138.7, 132.4, 127.0, 123.7, 115.9, 113.5, 83.1, 76.5, 50.1, 48.2, 44.7, 40.8, 38.3, 34.2, 33.5, 30.6, 29.7, 28.5, 27.4, 24.5, 14.8. **IR** (ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3337, 2924, 2868, 2854, 1609, 1498, 1451, 1378, 1355, 1286, 1251, 1222, 1131, 1117, 1056, 1020, 976, 947, 871, 817, 787, 693, 659. **LRMS** (ESI): *m/z* 535 [M+H$^+$]. **HRMS** (ESI): *m/z* calculated for $C_{25}H_{32}IN_3NaO_2^+$: 556.1431, found 556.1437.

Fluorescence anisotropy assay (FAA)

Material and Methods

Binding of estrogens to ERα and ERβ was evaluated by means of two commercial fluorescence anisotropy assays (Thermofisher Scientific), i.e the PolarScreen™ ER Alpha Competitor Assay Kit, Red (A15884, lots: 1847863, 2022570, 2073494, 2100612) and the PolarScreen™ ER Beta Competitor Assay Kit, Red (A15891, lot: 2160721), respectively.[14,15] The assay components were as follows: i) recombinant full-length, untagged, human ERα (140 µg, 3.46-4.82 µM) dissolved in storage buffer (50 mM Tris HCl, pH 8.0, 500 mM KCl, 1 mM EDTA, 1 mM Na_3VO_4, 2 mM DTT, and 10% glycerol) and stored at -80 °C; ii) recombinant full-length, untagged, human ERβ (180 µg, 6.74 µM) dissolved in storage buffer (50 mM Bis-Tris-Propane, pH 9.0, 500 mM KCl, 50% glycerol, 275 mM urea, 0.6% w/v CHAPS, and 2 mM DTT) and stored at -80 °C; iii) Fluormone™ EL Red (285 nM in 20 mM Tris, 90% methanol) stored at -20 °C; iv) ER Red screening buffer (proprietary buffer, pH 8.0, 10% glycerol) stored at room temperature. 17β-Estradiol (**1**, E8875) and diethylstilbestrol (DES, D4628) were commercially obtained from Sigma-Aldrich.

The assays were performed on 96-well plates following the manufacturer's instructions (PolarScreen™ Nuclear Receptor Competitor Assays – Universal Protocol).[16] Briefly, stocks (1-10 mM) of the competitors and the reference estrogen **1** (present in each experiment) were prepared in DMSO and serially diluted in DMSO on a polypropylene 96-well plate with V-bottom (Greiner bio one, 651201). Then, the compounds were further diluted (1:50) in duplicate with ER Red screening buffer to 2x of the final concentration in 100 µL 2% (v/v) DMSO using the same type of plates. Identical volumes (20 µL) of this solution and of mixtures of 2.8 nM Fluormone™ EL Red/ 96-118 nM ERα or 2.8 nM Fluormone™ EL Red/ 276 nM ERβ, both in ER Red screening buffer, were mixed on a black 96-well half-area plate (Corning, 3694) yielding the final concentrations of the competitors and **1**, 1.4 nM Fluormone™ EL Red, 48-59 nM ERα, and 138 nM ERβ in 1% DMSO (v/v), respectively. Maximum and minimum assay controls contained estrogen receptor and Fluormone™ EL Red without and with 10 µM of **1**, respectively. The plates were briefly shaken and incubated for 2 h at 30 °C in the dark in a BioTek Synergy™ 2 multimode microplate reader; then, the parallel and perpendicular fluorescence intensities ($I_{\parallel}$ and $I_{\perp}$, respectively) were measured at λ_{ex} = 540 nm and λ_{em} = 620 nm.

The FA (r) was calculated by the Gen 5 software version 1.11.5 according to the equation $r = (I_{\parallel} - G \times I_{\perp})/(I_{\parallel} + 2G \times I_{\perp}) \times 1000$, with G (preset value of 0.87) correcting "the intrinsic bias of the detector system's response for one plane of polarized light over the other",[17] and plotted versus the

final competitor concentration, [I]. Nonlinear regression according to the equation $r = bottom + ((top - bottom) \times [I]^{nH}/([I]^{nH} + IC_{50}{}^{nH}))$, with bottom and top being the lower and upper plateaus of the dose-response curve, provided the half-maximal inhibitory concentration (IC_{50}) and the Hill slope (nH). Data analysis was done using GraphPad Prism versions 5.03 and 5.04 for Windows (GraphPad Software, San Diego, CA, USA). All values are given as mean value ± standard error of the means (SEM); n represents the number of individual duplicate experiments. Relative binding affinity (RBA) was calculated by dividing the mean IC_{50} value of **1** by that of the competitor, then multiplying the result by 100%.[18]

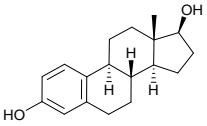
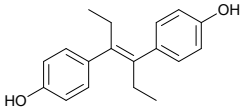
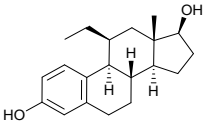
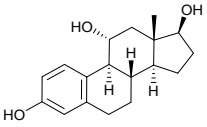
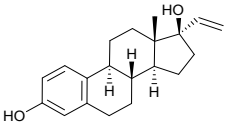
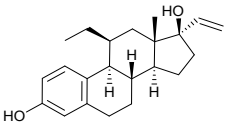
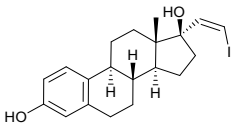
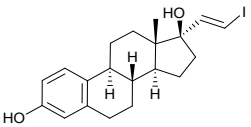
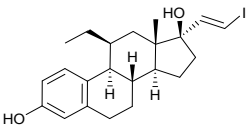
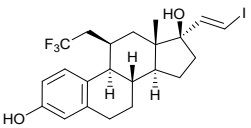
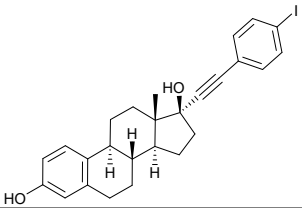
Results and Discussion S1

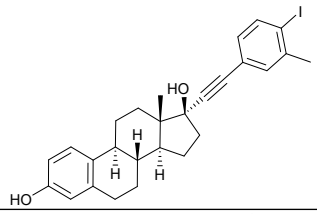
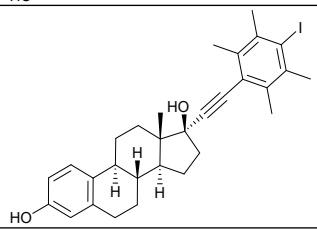
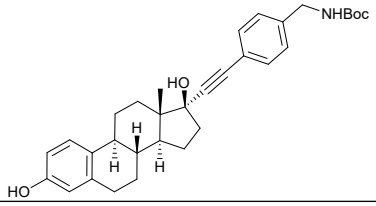
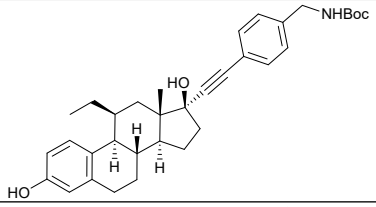
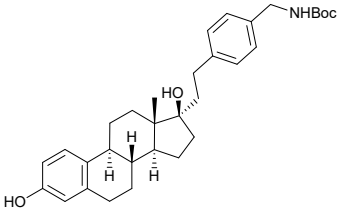
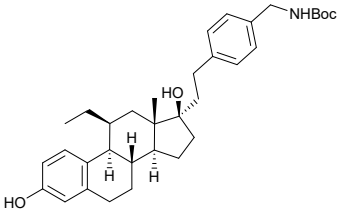
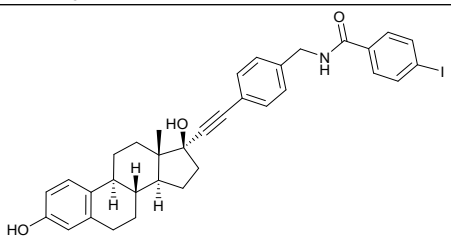
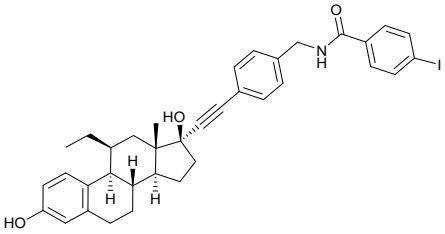
Binding of estrogens to ERα and ERβ was evaluated by following displacement of a fluorescently labelled probe (Fluormone™ EL Red) from the two receptor proteins.[14,15] Values of IC_{50} (Table S1) for the reference estrogen **1** on ERα and ERβ were in line with previous reports using the same assay.[14,15,19–21] In addition, we were able to reproduce the RBA on ERα for the majority of compounds reported in the literature to exhibit a RBA < 100% (**11**, **13**, and **17**). Some small differences could be attributed to different assay systems and sources of ERα. In contrast, ligands whose reported binding affinities far exceeded that of **1** (RBA ≥ 468%), i.e. DES, **8**, **15**, and **19**, were underestimated in their binding properties. This has been observed previously for DES (RBA of 118-130%) in similar fluorescence anisotropy assays with ERα.[22–24] This observation for tight binding competitors is typical for fluorescence anisotropy assays under the given assay conditions, i.e. where the dissociation constant of the probe-receptor complex, K_D, is larger than the probe concentration. In our study, the minimum determinable IC_{50} value was limited by the K_D of Fluormone™ EL Red on ERα (7-14 nM)[14] and on ERβ (14-28 nM)[15], respectively. Therefore, reported IC_{50} values of the investigated tight binding competitors could not be reproduced and differences in potencies disappeared.[25,26] This most probably also applied to the new estrogens **14** and **31**, whose binding affinities on ERα and ERβ were in the range of the K_D value of the respective probe-receptor complex (Table S1). Structure-activity relationships were therefore only concluded for new estrogen derivatives with a RBA < 100% on ERα. An 11β-ethyl substituent increased the ligands' affinities up to 23-fold (**35** vs. **36**, **35a** vs. **36a**, **41** vs. **42**, and **41a** vs. **42a**) which is in accordance with previous reports on **1** vs. **8**[27,28] and **17**[29] vs. **19**[30]. Furthermore, we introduced several linkers in the 17α-position in the search for new iodinated estrogen receptor ligands as starting points for radiotracers. While a 4-iodobenzyl-substituted (**52**) or

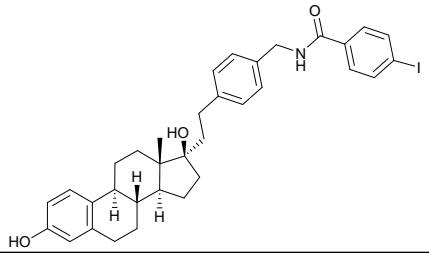
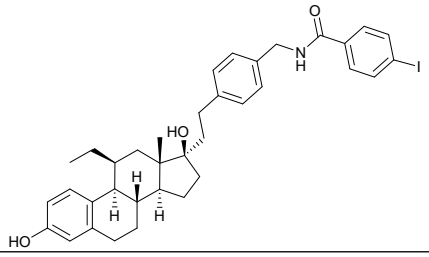
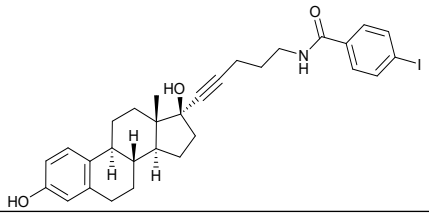
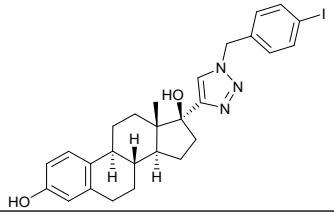
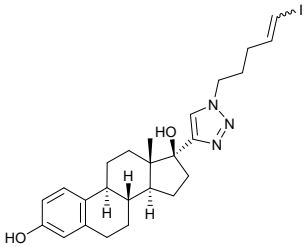
1-iodo-1-penten-5-yl-substituted triazole linker (**55**) led to an almost complete loss of binding to ERα (which is in line with data related to analogous estrogens on ERβ[31]), exchange of these linkers by a (methylated) 4-iodophenylethinyl group resulted in relatively potent ligands (**32**-**34**). The iodine atom was then replaced by an aminomethyl substituent for facile derivatisation, initially investigated on a sub-set of 4-iodobenzoylamides. Here, replacement of the phenylethinyl group by an eth-1-yl-2-ethinyl linker (**41** vs. **51**) or reduction to a phenylethyl moiety (**41** vs. **41a**, **42** vs. **42a**) increased the affinity of the estrogens to ERα by factors of 1.5 and 1.3-3, respectively. The two most promising compounds of this sub-set, i.e. **42** and **42a**, as well as the potent ERα binders **19** and **31** were also investigated on ERβ, where they showed RBAs and differences in potency similar to those on ERα.

The most promising ER ligands of the investigated series were estrogens **19** and **31**, which were selected for radioiodination and further investigation in urothelial carcinoma cells.

Table S1. Binding affinities of estrogens on ERα and ERβ

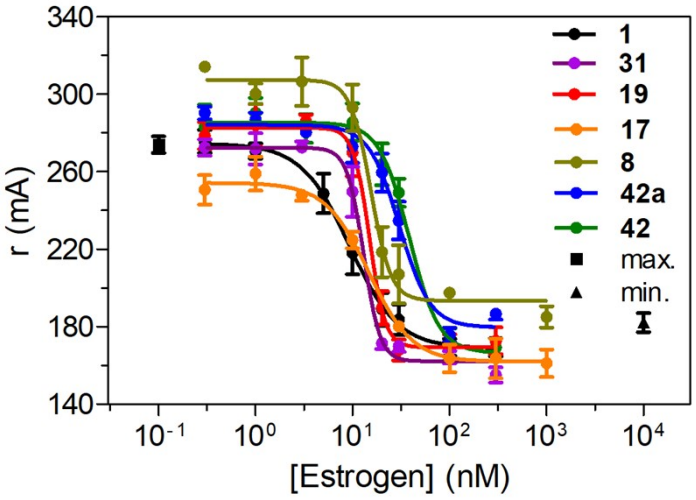
Compd	Structure	ERα: IC_{50} (nM)	ERα: RBA (%)	ERβ: IC_{50} (nM)	ERβ: RBA (%)
1		11.6 ± 1.2[a] (n = 32)	100	39.5 ± 0.7[a] (n = 4)	100
DES		11.9 ± 3.7 (n = 3)	97.5[b]	n.d.[c]	n.d.[c]
8		16.0 ± 1.2 (n = 2)	72.5[b]	n.d.[c]	n.d.[c]
11		>1000[d] (n = 2)	<1.2[b]	n.d.[c]	n.d.[c]
13		24.6 ± 2.7 (n = 3)	47.2[b]	n.d.[c]	n.d.[c]
14		8.37 ± 1.97 (n = 3)	139	n.d.[c]	n.d.[c]
15		7.88 ± 0.36 (n = 3)	147[b]	n.d.[c]	n.d.[c]
17		15.6 ± 3.3 (n = 3)	74.4[b]	n.d.[c]	n.d.[c]
19		14.5 ± 1.9 (n = 3)	80.0[b]	37.6 ± 4.2 (n = 3)	105
31		12.9 ± 0.5 (n = 3)	89.9	26.8 ± 3.0 (n = 3)	147
32		47.9 ± 6.8 (n = 3)	24.2[b]	n.d.[c]	n.d.[c]

33		94.5 ± 22.1 (n = 3)	12.3	n.d.[c]	n.d.[c]
34		48.6 ± 5.8 (n = 3)	23.9	n.d.[c]	n.d.[c]
35		361 ± 138 (n = 3)	3.21[b]	n.d.[c]	n.d.[c]
36		68.2 ± 14.2 (n = 2)	17.0	n.d.[c]	n.d.[c]
35a		132[e] (n = 3)	8.79	n.d.[a]	n.d.[a]
36a		119 ± 8 (n = 3)	9.75	n.d.[c]	n.d.[c]
41		~900[d] (n = 3)	~1.3	n.d.[c]	n.d.[c]
42		38.8 ± 3.4 (n = 3)	29.9	97.7 ± 12.8 (n = 4)	40.4

41a		~300[d] (n = 3)	~3.9	n.d.[c]	n.d.[c]
42a		29.9 ± 2.2 (n = 3)	38.8	75.6 ± 1.7 (n = 2)	52.2
51		~600[d] (n = 4)	~1.9	n.d.[c]	n.d.[c]
52		>1000[d] (n = 4)	<1.2	n.d.[c]	n.d.[c]
55		~1600[d] (n = 4)	~0.73	n.d.[c]	n.d.[c]

[a]Reported IC_{50} values of **1** in the PolarScreen™ Competitor Assay with Fluormone™ EL Red: ERα, 5.9-16 nM; ERβ, 20.8-23 nM.[14,15,19–21] [b]Reported RBAs: DES, 468% (recombinant human ERα),[32] 471% (rat uterine ERα);[33] **8**, 1000, 3000% (rat uterine ERα);[27,28] **11**, 0.31% (human ERα, MCF-7 cells);[34] **13**, 66.7% (rat uterine ERα);[35] **15**, 776% (rat uterine ERα);[30] **17**, 62% (rat uterine ERα);[30] **19**, 890% (lamb uterine ERα);[29] **32**, 4.56% (recombinant human ERα);[6] **35**, 24.1% (calculated from K_i values instead of IC_{50} values, recombinant ERα).[9] [c]n.d., not determined. [d]IC_{50} value was estimated from n duplicate experiments at a single ligand concentration of 1000 nM. [e]IC_{50} value was calculated using mean values of FA from three duplicate experiments. Values of IC_{50} and RBAs of estrogens **1**, **8**, **17**, **19**, **31**, and **42** are also presented in Table 1 of the main text.

a)



b)

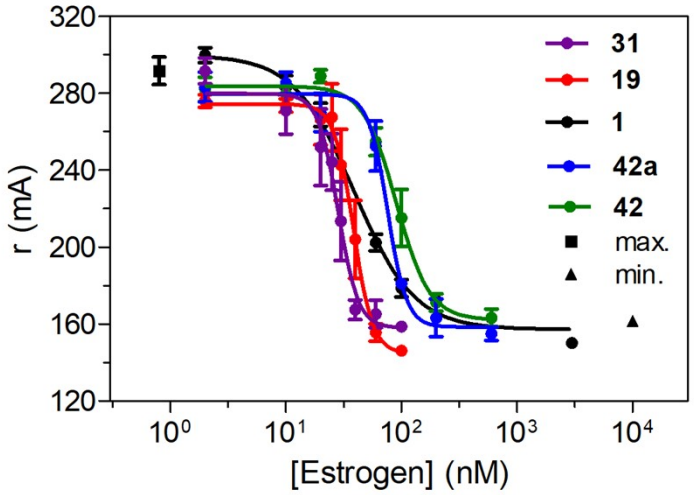


Figure S1. Displacement of Fluormone™ EL Red from ERα (a) and ERβ (b), respectively, by estrogens. Data for candidate estrogens are given as mean values ± SEM from 2-6 single or duplicate experiments. Maximum and minimum assay controls are shown as mean values ± SEM from 11 (ERα) and 4 (ERβ) duplicate to sextuplicate experiments, respectively. IC_{50} value of reference estrogen **1** on ERα (11.1 ± 2.2 nM, n = 11) was calculated from data obtained in experiments with **8**, **17**, **19**, **31**, **42**, and **42a**. All other IC_{50} values on ERα and ERβ are given in Table S1.

Radiosynthesis

On account of the lower specific activity of I-131, with the same radioactivity, the amount of the stannylated precursor used had to be increased compared to I-123. Therefore, the I-131 label was used at 10 µg/µL and for the I-123 label at 0.1 µg/µL. 15 µL of an ACN/stannane solution were mixed with 1 µL of an ACN/N-chlorosuccinimide solution (mg/mL) in a 0.5 mL micro test tube. 1 µL of an alkaline (0.05 M NaOH, 2MBq) sodium radioiodide solution (GE Healthcare) was mixed with 5 µL acetic acid (95%). Both solutions were combined and incubated for 5 min at room temperature. The reaction was stopped with 10 µL of an aqueous sodium bisulfite solution (15 mg/mL). The crude product was purified by HPLC using a C18 column (Macherey, Nagel, NUCLEODOR 5 µm, C18, 110 Å, 250 × 4 mm) and a radio detector (LB 506 C-1, Berthold). An ACN/water mixture was used as the eluent (method: 1.0 mL/min; 0-2 min 40% B; 2-18 min 40-80% B; 18-20 min 100% B; Water: A, acetonitrile: B). After HPLC purification, 1 mL of distilled water and 50 µL of DMSO were added to the product solution. Then the ACN was evaporated to obtain a aqueous DMSO solution of the radio iodinated product.

The radioestrogen solutions used for the experiments had the following properties:

Table S2. Properties of the solutions used for the binding experiments

	^{131}I		^{123}I	
	Ligand 19	Ligand 31	Ligand 19	Ligand 31
Molar activity*	24.3 MBq/nmol	24.3 MBq/nmol	8770 MBq/nmol	8770 MBq/nmol
Radiochemical yield**	83 %	87 %	81 %	85 %
Radiochemical purity***	> 99.9 %	> 99.9 %	> 99.9 %	> 99.9 %

* Radionuclide-related theoretical radioactivity per nmol estrogen ligand **19** ((8S,9S,11S,13S,14S,17R)-11-ethyl-17-((E)-2-iodovinyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol) and **31** ((8*S*,9*S*,11*R*,13*S*,14*S*,17*R*)-17-((*E*)-2-iodovinyl)-13-methyl-11-(2,2,2-trifluoroethyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol)

** related to the radioactivity used for labeling

*** Percentage of desired radioligand based on the total radioactivity of the solution for the binding experiments

Cell culture & Western blot analysis

HTB9, TCam2, LNCap, PC3 and DU145 cells were cultured according to the ATCC recommendation. For HTB9, PC3, TCam2 and LNCap cells RPMI Medium (PAN, P04-16500) was used with 1% Pen/Strep and 10% FCS. DU145 were cultured in DMEM Medium (PAN, P04-03590) with 1% Pen/Strep (PAN, P06-07100), and 10% FBS (PAN, P40-37100). Culturing conditions were 5% CO_2 at constant 37 °C. Before each isolation, cells were serum-starved for 24h and incubated with FBS including medium to have all cells in the same cell cycle step.

All proteins were isolated with RIPA Buffer (Merck, R0278). Briefly, cells were grown until 90% confluency was reached, washed with 1xPBS and incubated on ice with RIPA buffer for at least 30 min. Finally, the cells were centrifuged and the supernatant was stored at -80°C for further usage. Protein quantification was performed with Bradford reagent.

For Western blot analysis, 25 µg of total protein were mixed with 5 µL Laemmli Loading Buffer (Bio-Rad, #1610737), made up to a final volume of 20 µL with distilled water and boiled at 95 °C for 5 min. In addition, a marker for determining protein size (Biometric Pre-Stained Protein Ladder - 5-245 kDa-alpha, Diagnostic Intl. Inc) was used. The electrophoretic separation took place at 15 mA for about 30 min and then at 30 mA for a further 30 min. The transfer process to the blotting membrane took place at 360 mA for 1 h on ice. The membrane (nitrocellulose, 45 micron, Cytiva) was blocked with 5% skin milk powder in Tris Buffered Saline-Tween (20X, with 1% Tween-20, pH 7.4) for 1 hour at room temperature, then incubated first with primary antibodies against ERα (MC-20, 1:500, Santa Cruz) and ERβ (B-3, 1:500, Santa Cruz) and then with secondary antibody (mouse anti-rabbit IgG-HRP, 1:500, Santa Cruz) for 1 hour each at room temperature. Between the steps, the membrane was washed three times with TBST for 5 min each time. UptiLight HRP Blot Chemiluminescent ECL (enhanced chemiluminescence) substrate from Interchim was used for visualization.[36]

Radioligand binding studies

HTB9 cells were cultured in RPMI-1640 (Roswell Park Memorial Institute 1640, Thermofischer) supplemented with 10% estrogen free FBS (Pan Biotech) and 5% antibiotics (penicillin-streptomycin, Thermo Fischer) at 5% CO_2 and 37 °C in a water vapor-saturated atmosphere. The saturation assay was performed on 35 mm 6-well plates (Cellstar, Greiner Bio-One GmbH). The cells (10^6cells/well) were plated and incubated 24 h in hormone-free medium. The cells were then titrated with various concentrations of the radioiodinated ligands in a volume of 1 mL (final concentrations in the well: **19**, 13.5-339.5 pM; **31**, 4.2-346.6 pM). Control wells were treated with hormone-free medium containing no radioligand.

To determine the non-specific binding, another series of experiments was carried out with ER-blocked cells. For this purpose, the cells were incubated with culture medium containing 1 µM 17β-estradiol (Merck) one hour before treatment with radioligands **19** and **31**, respectively. After an incubation time of 24 h, the radioactive medium was removed and the cells were washed three times with 2 mL PBS buffer. Cells were then lysed in 2 mL NaOH (1 M) and collected into measuring tubes. The wells were washed three times with 1 mL acetonitrile. Each wash was collected into the corresponding tube with the cell lysate. The radioactivity of the solution was determined in a borehole measuring station (ISOMED 100, Melit). For the evaluation of the results the software GraphPad Prism version 8.4.3 for Windows (GraphPad Software, San Diego, CA, USA) was used. To obtain "specific binding", "non-specific binding" was subtracted from "total binding". The curve for specific binding was determined via the Marquardt method for performing nonlinear regression. The function $Y = \frac{B_{max} \cdot L}{K_D + L}$ was empirically fitted to the specific binding values by the software to obtain maximal specific saturation, $B_{max,}$ and dissociation constant, K_D. In addition, a linearization was carried out using the Scatchard plot. The maximal specific saturation, B_{max}, was obtained as an amount of specifically accumulated radioactivity per well with 10^6 cells. From this, the number of estrogen receptors per cell was calculated using the following ratio:

$$ER/cell = binding\ sites/cell = \frac{B_{max} \cdot N_a}{A_s}$$

N_a = Avogadro constant = $6.02214076 \times 10^{23}$ mol^{-1}

A_s(I-123) = specific activity (I-123) = 8770.7 MBq/nmol

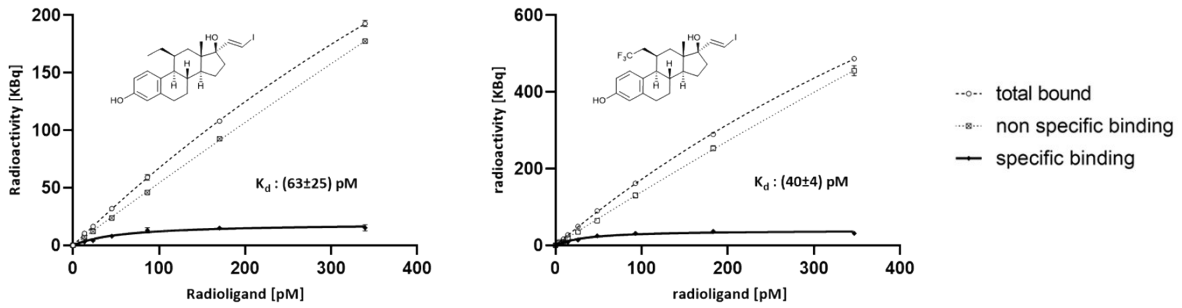


Figure S2: Saturation assays of total, non-specific and specific ER binding of I-123 labelled products **19** (left) and **31** (right). Values of K_D were 63±25 pM for compound **19** and 40±4 pM for compound **31**. To obtain "specific binding", "non-specific binding" was subtracted from "total binding". Maximum specific saturation of activity per cell (B_{max}) was 19.46 - 40.17 kBq, corresponding to 2.2–4.6 fmol and 1375–2840 ER/cell. Wilcoxon Signed Rank Test for the groups "total bound" and "non-specific bound" showed a clear significant difference (P = 0.0313 for compound **19** and 0.0078 for compound **31**).

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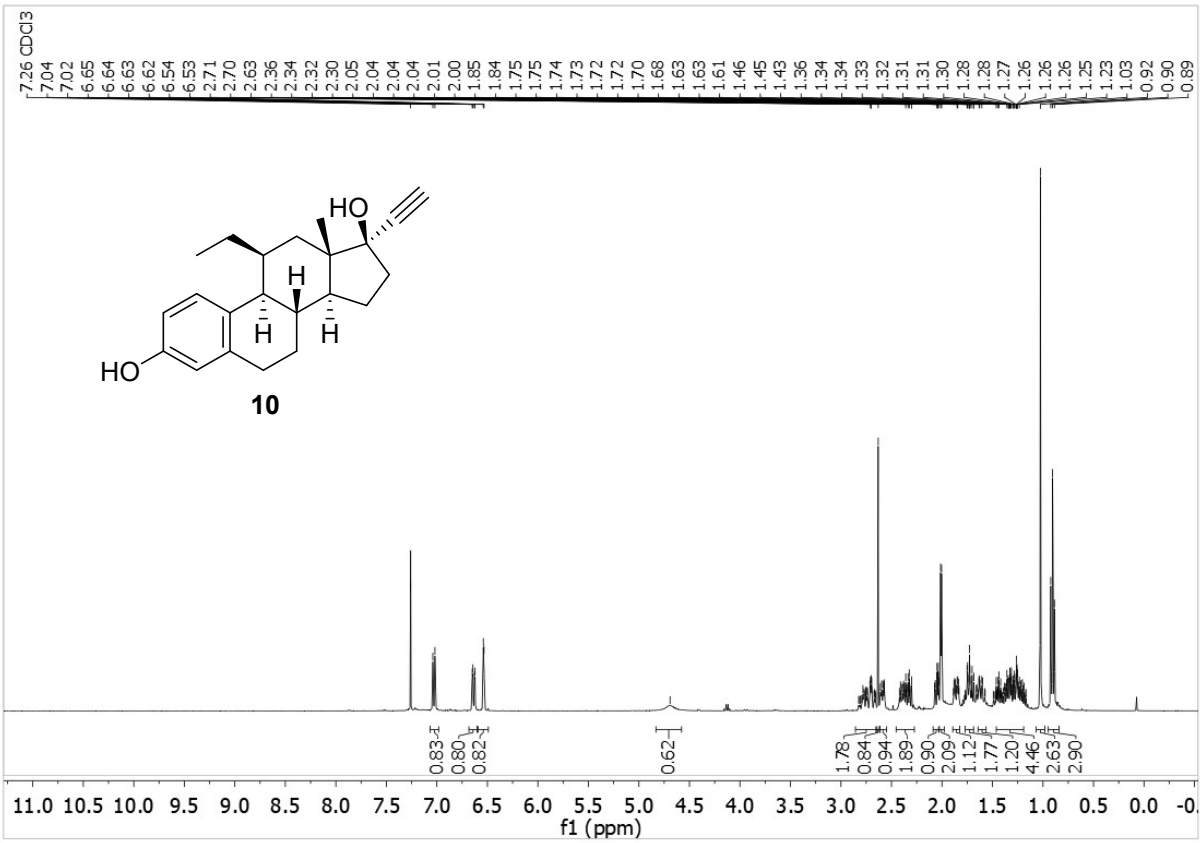
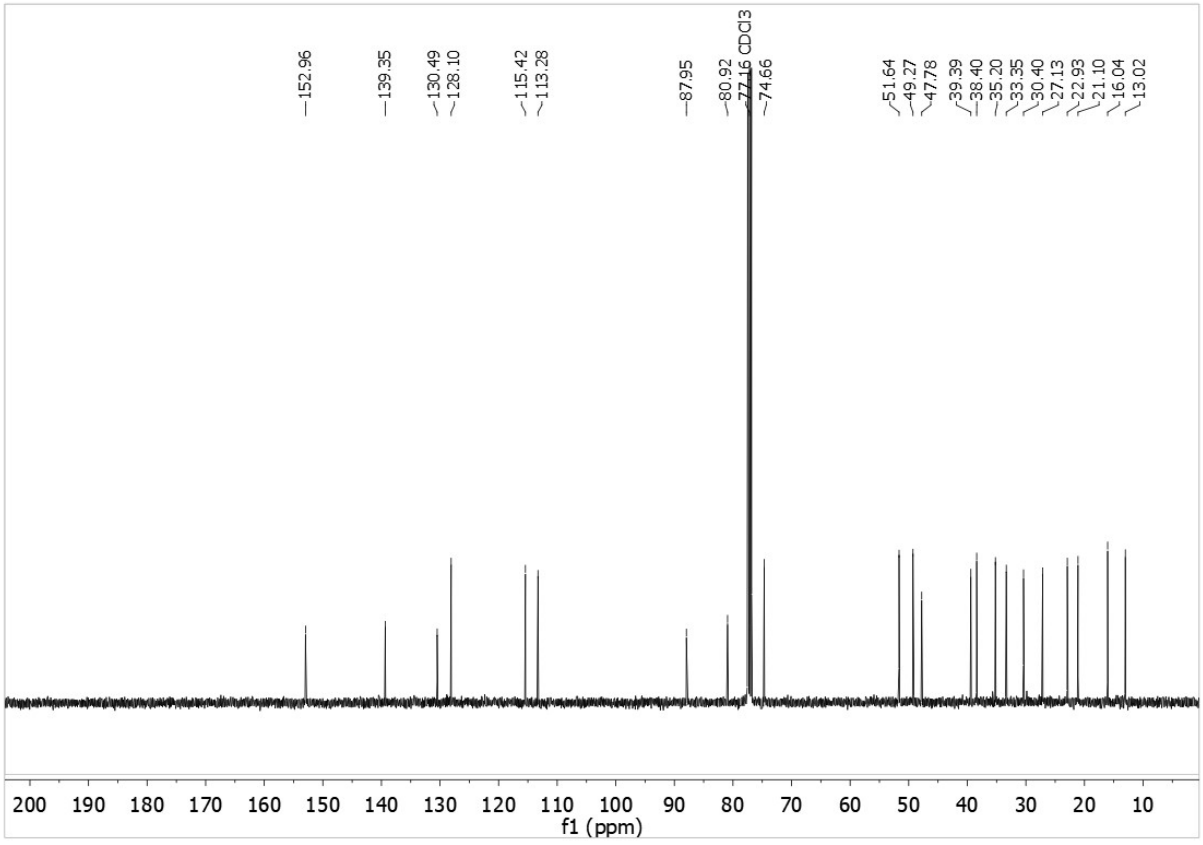
NMR spectra of unknown compounds

^{1}H NMR

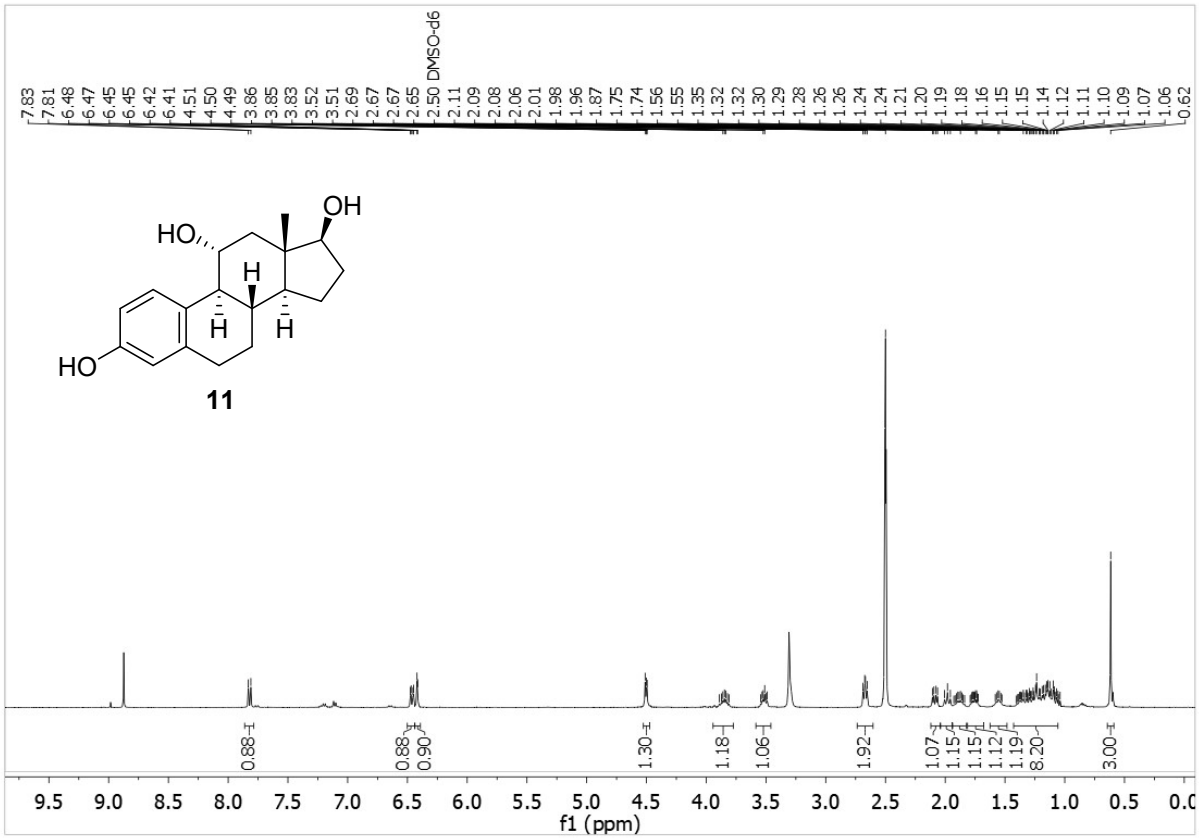


^{13}C NMR

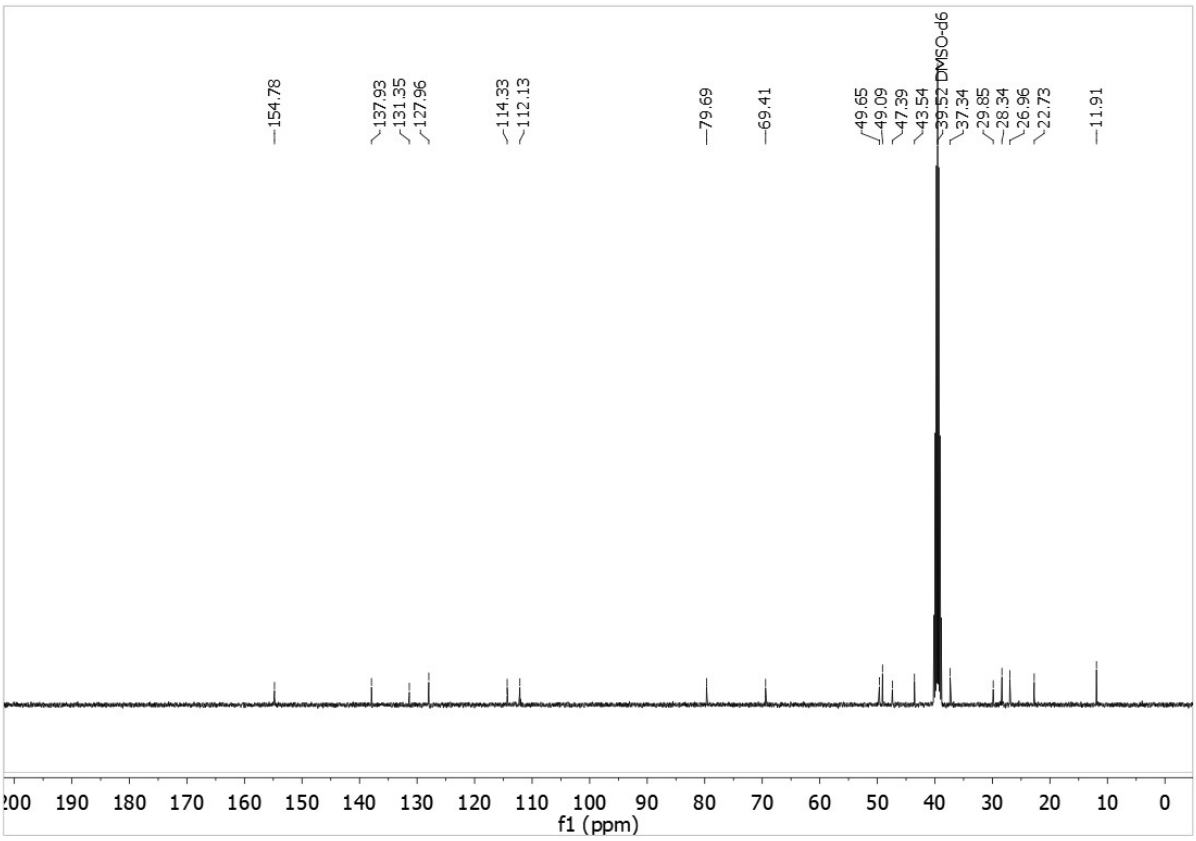


Supporting information

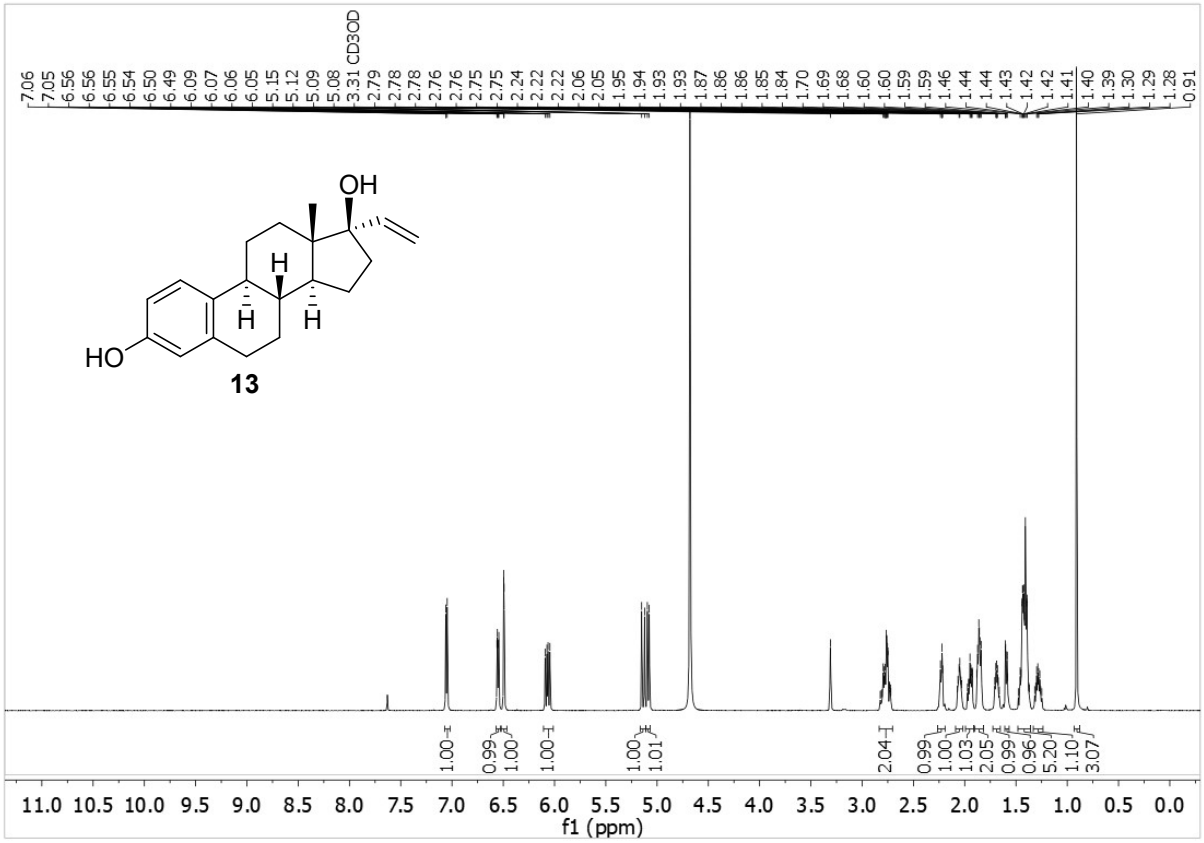
^{1}H NMR



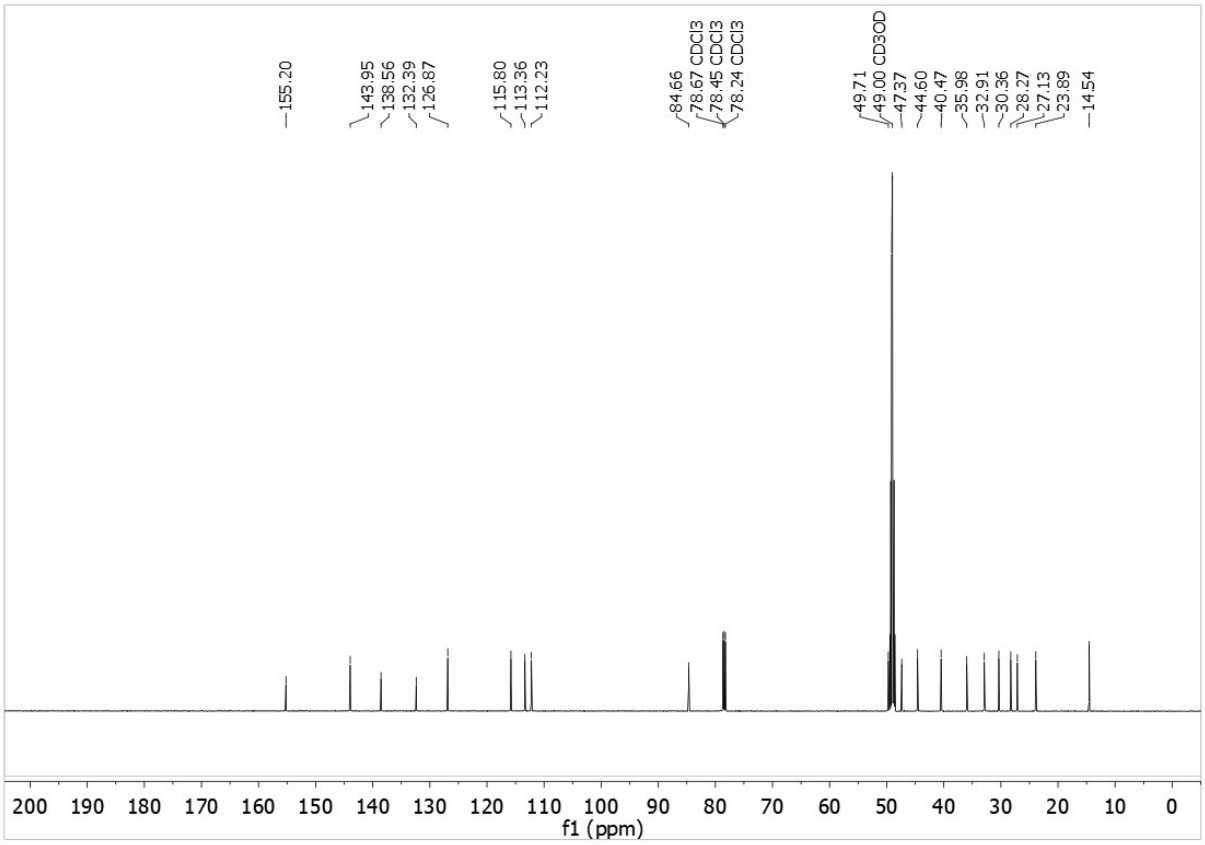
^{13}C NMR



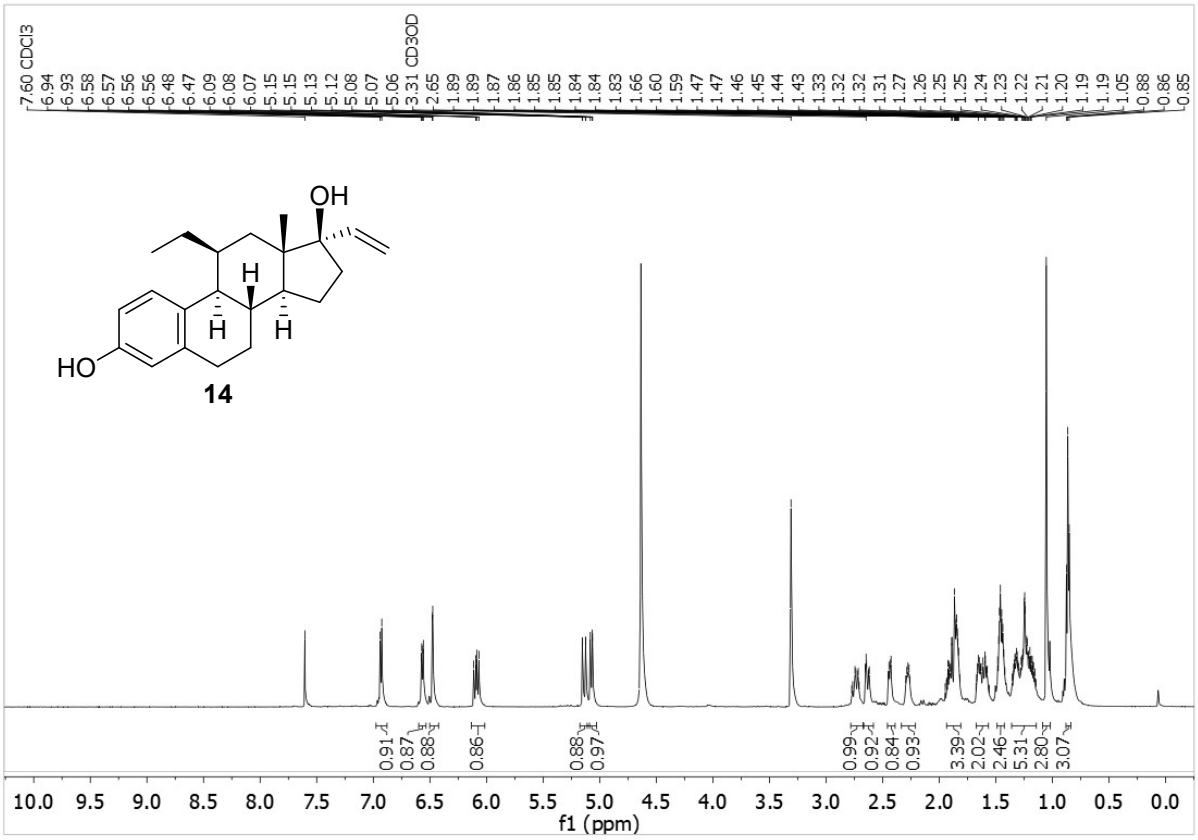
^{1}H NMR



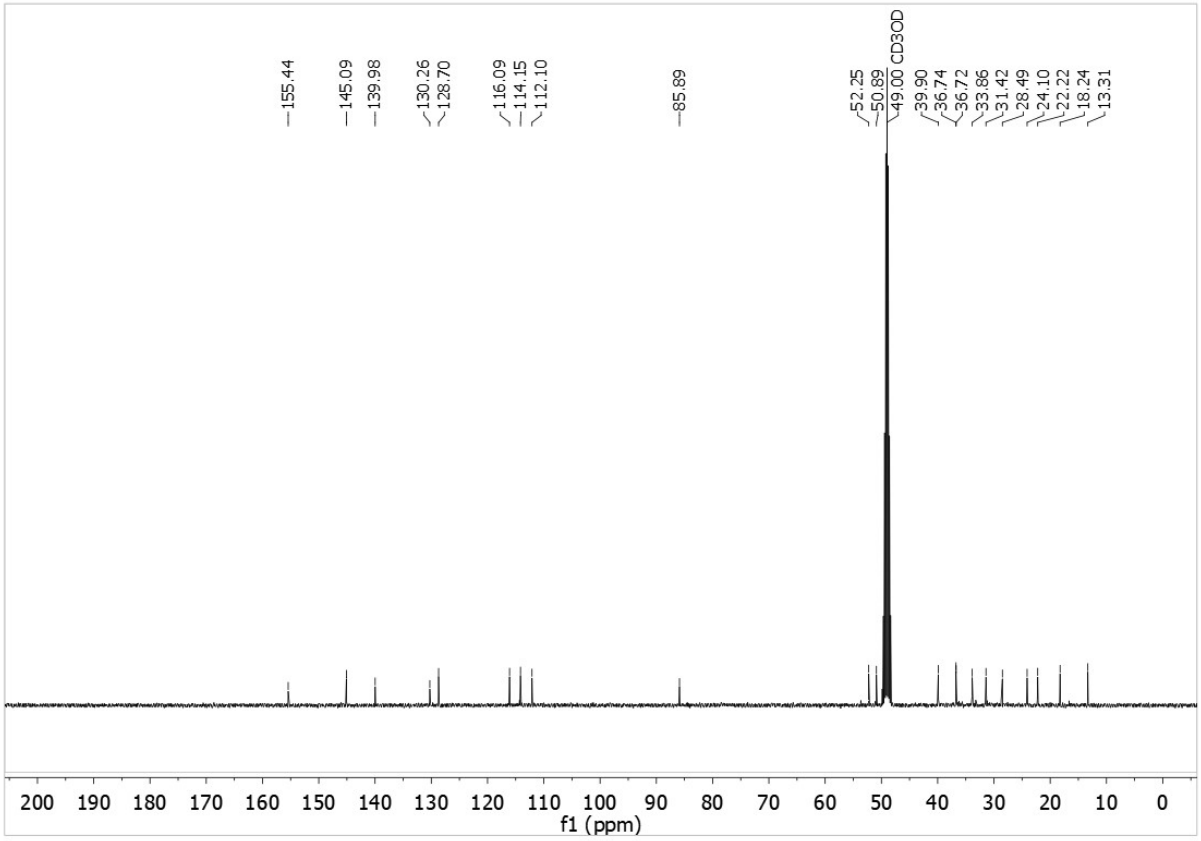
^{13}C NMR



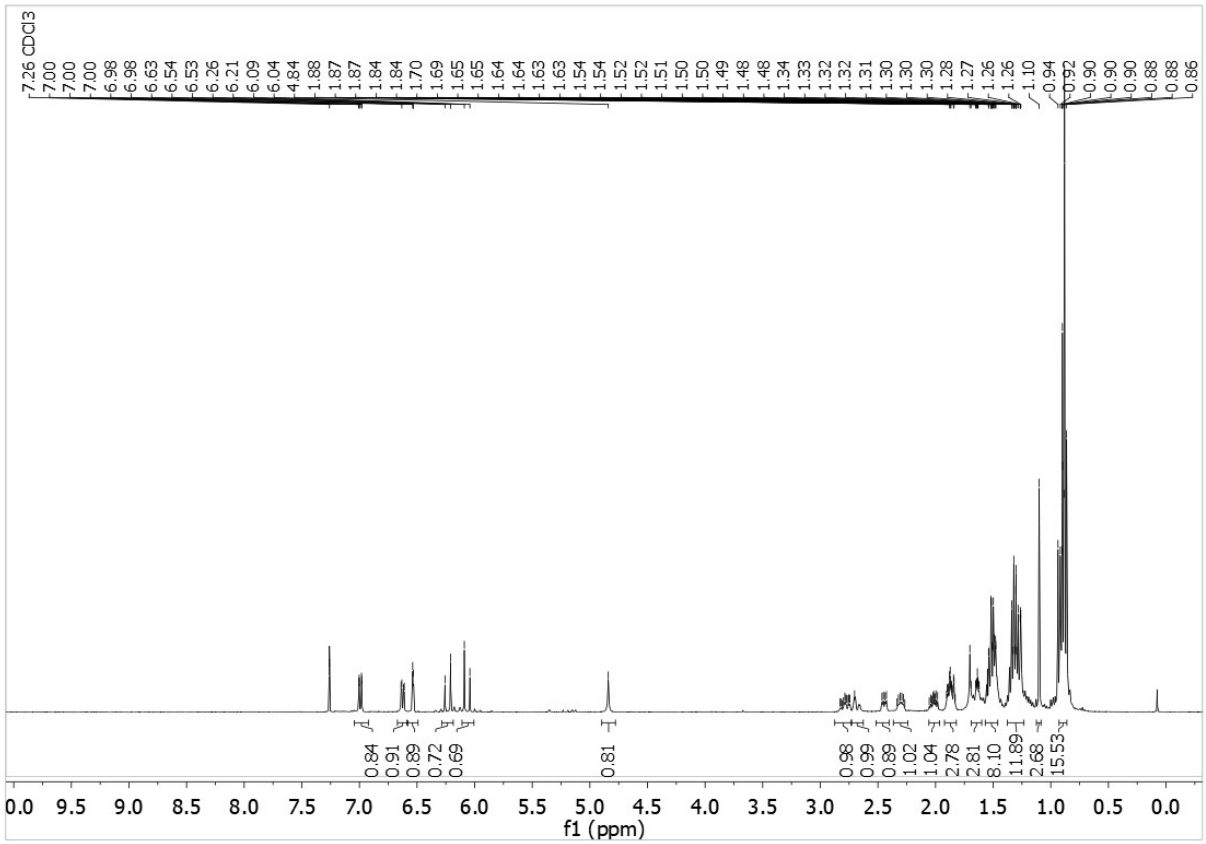
^{1}H NMR



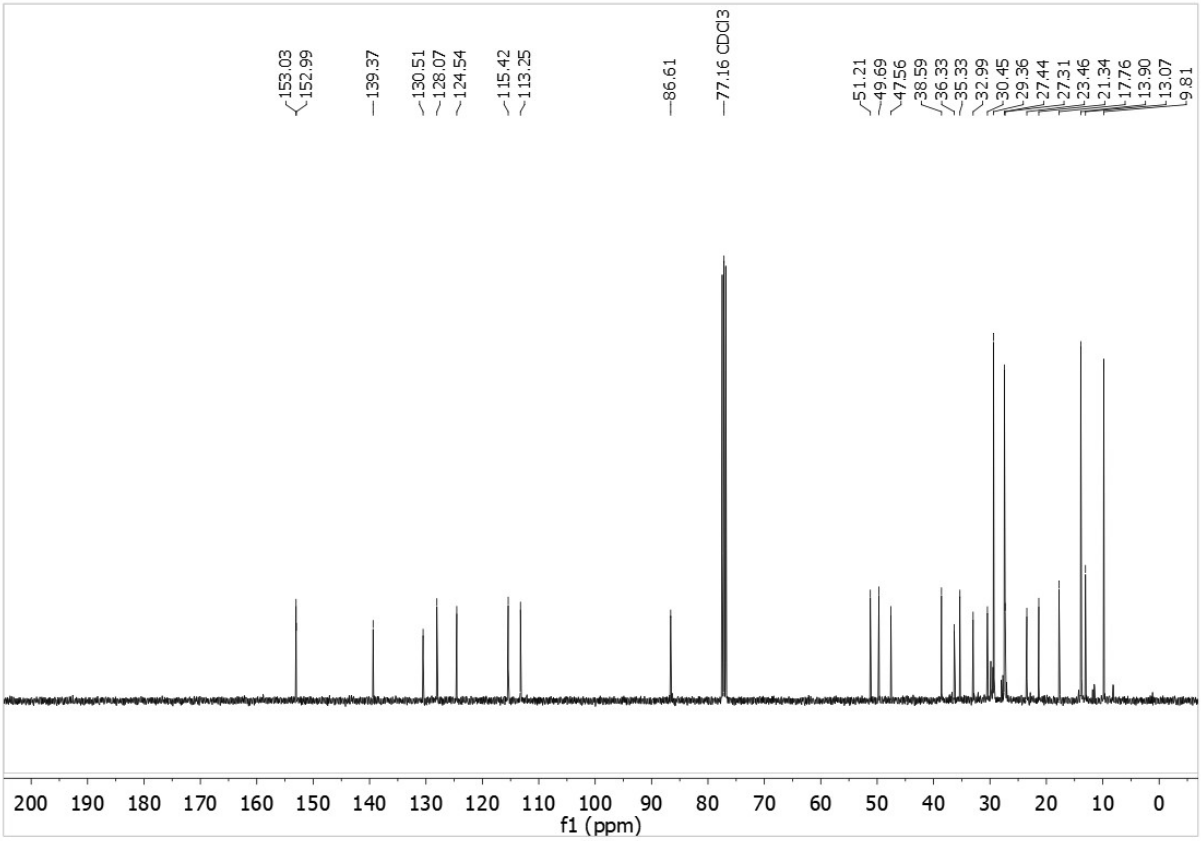
^{13}C NMR



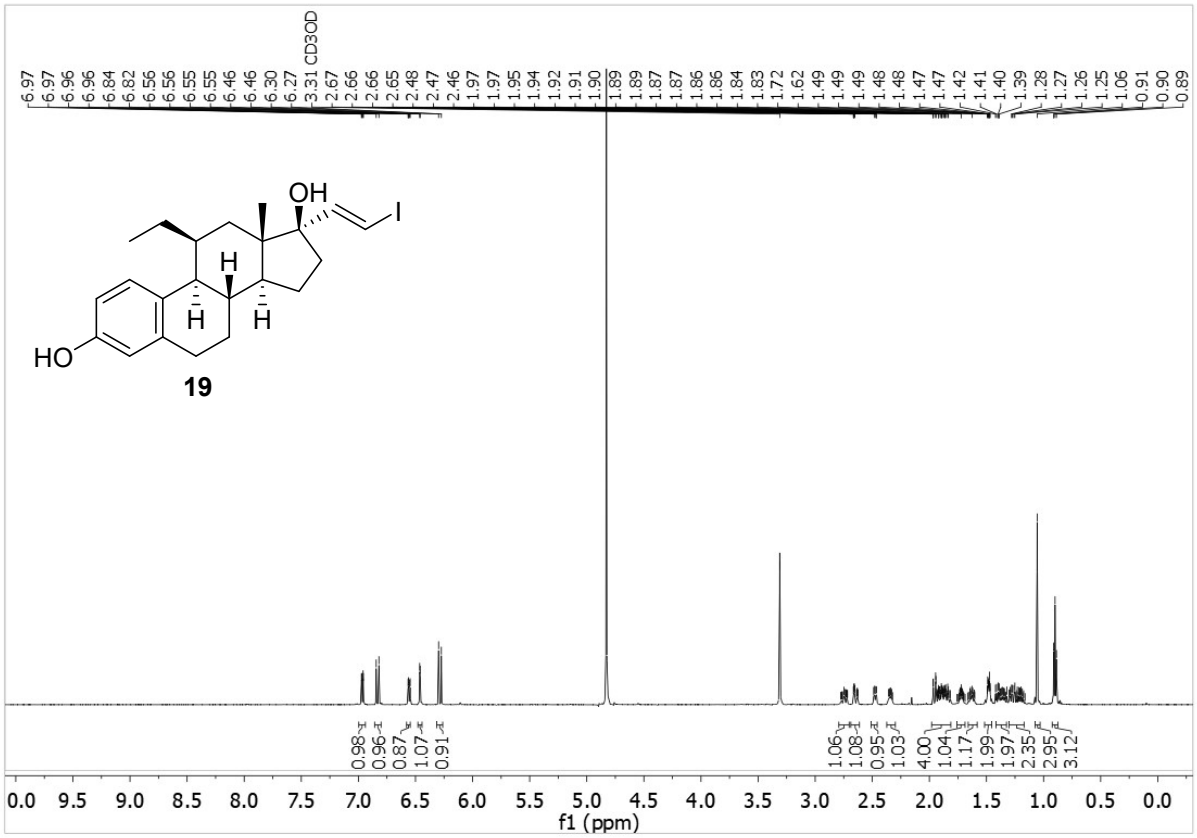
^{1}H NMR



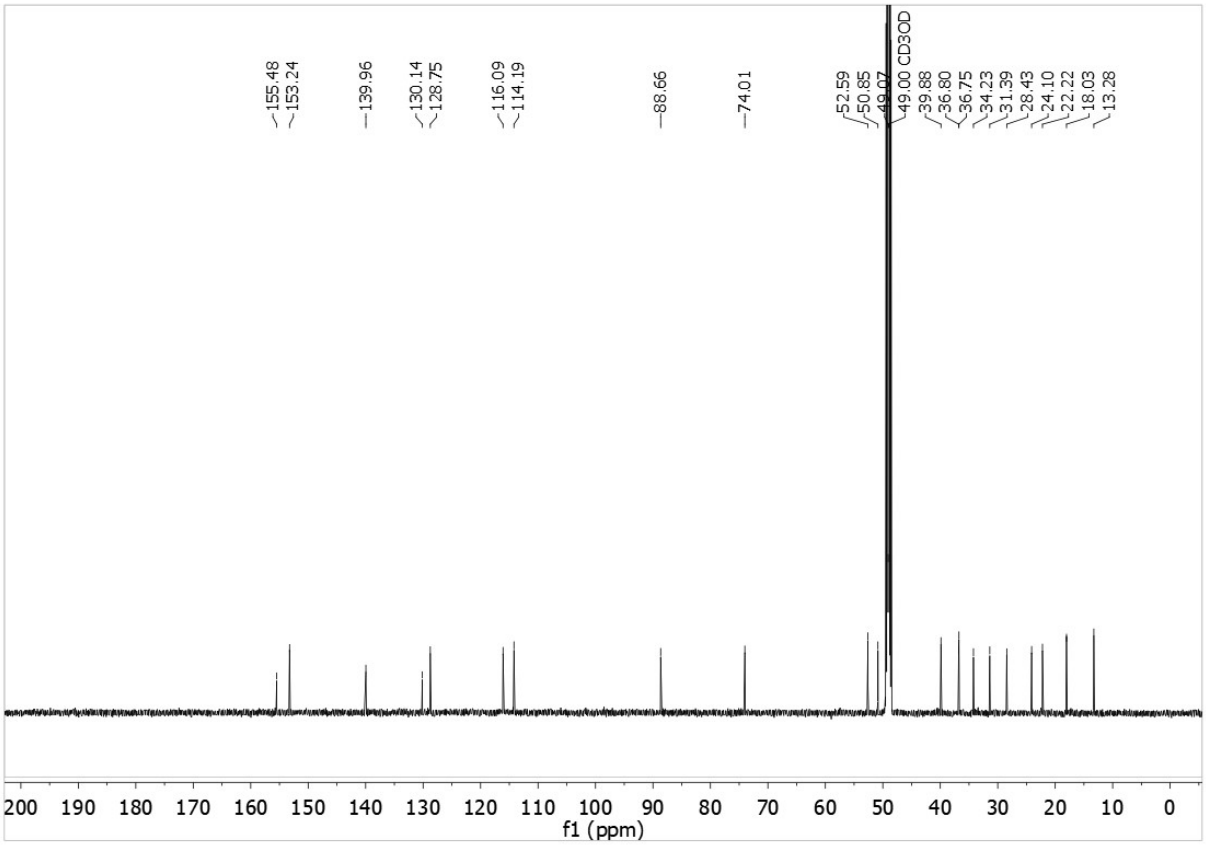
^{13}C NMR


153.03
152.99
139.37
130.51
128.07
124.54
115.42
113.25
86.61
77.16 CDCl3
51.21
49.69
47.56
38.59
36.33
35.33
32.99
30.45
29.36
27.44
27.31
23.46
21.34
17.76
13.90
13.07
9.81
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

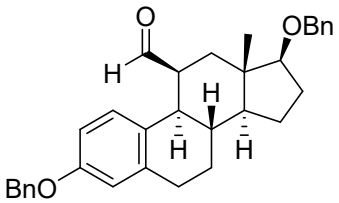
^{1}H NMR


6.97 6.97 6.96 6.96 6.84 6.82 6.56 6.56 6.55 6.55 6.46 6.46 6.30 6.27 3.31 CD3OD 2.67 2.66 2.66 2.65 2.48 2.47 2.46 1.97 1.97 1.95 1.94 1.92 1.91 1.90 1.89 1.89 1.87 1.87 1.86 1.86 1.84 1.83 1.72 1.62 1.49 1.49 1.49 1.48 1.48 1.47 1.47 1.42 1.41 1.40 1.39 1.28 1.27 1.26 1.25 1.06 0.91 0.90 0.89
OH
I
H
H
H
HO
19
0.98 0.96 0.87 1.07 0.91
1.06 1.08 0.95 1.03 4.00 1.04 1.17 1.99 1.97 2.35 2.95 3.12
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

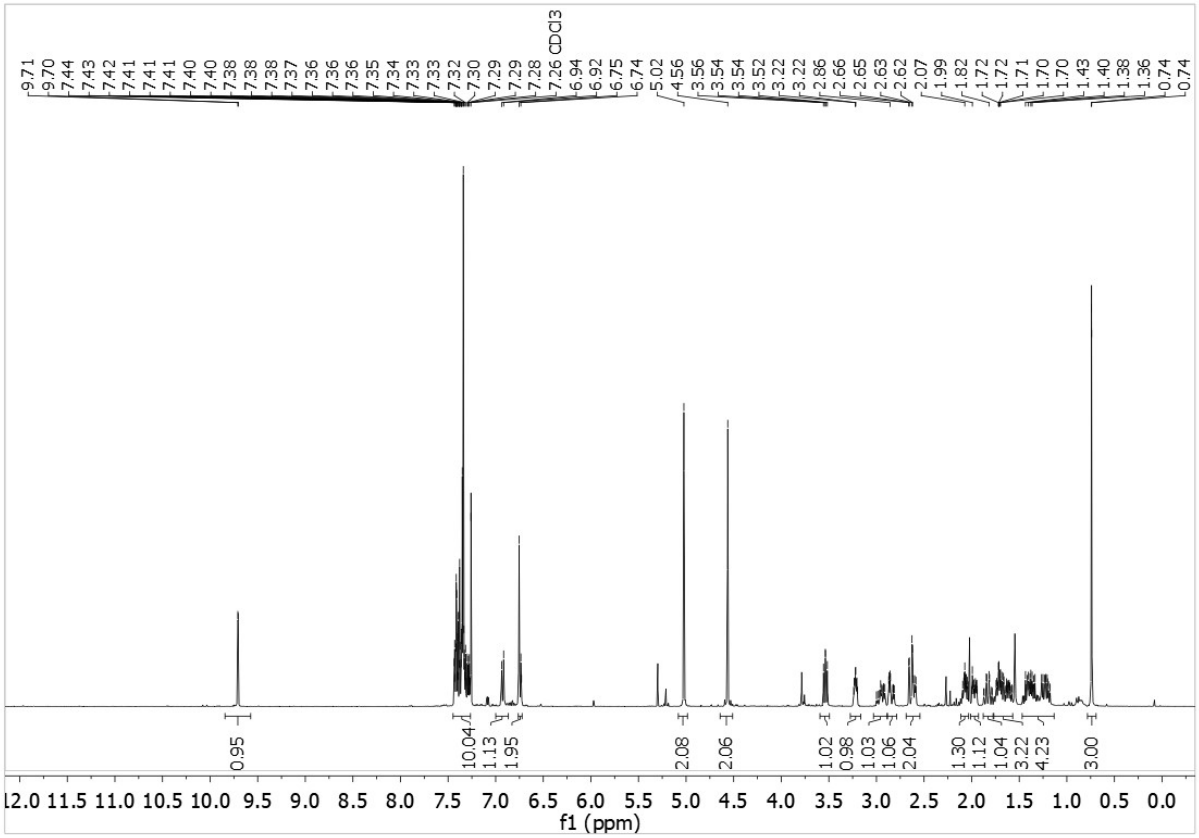
^{13}C NMR



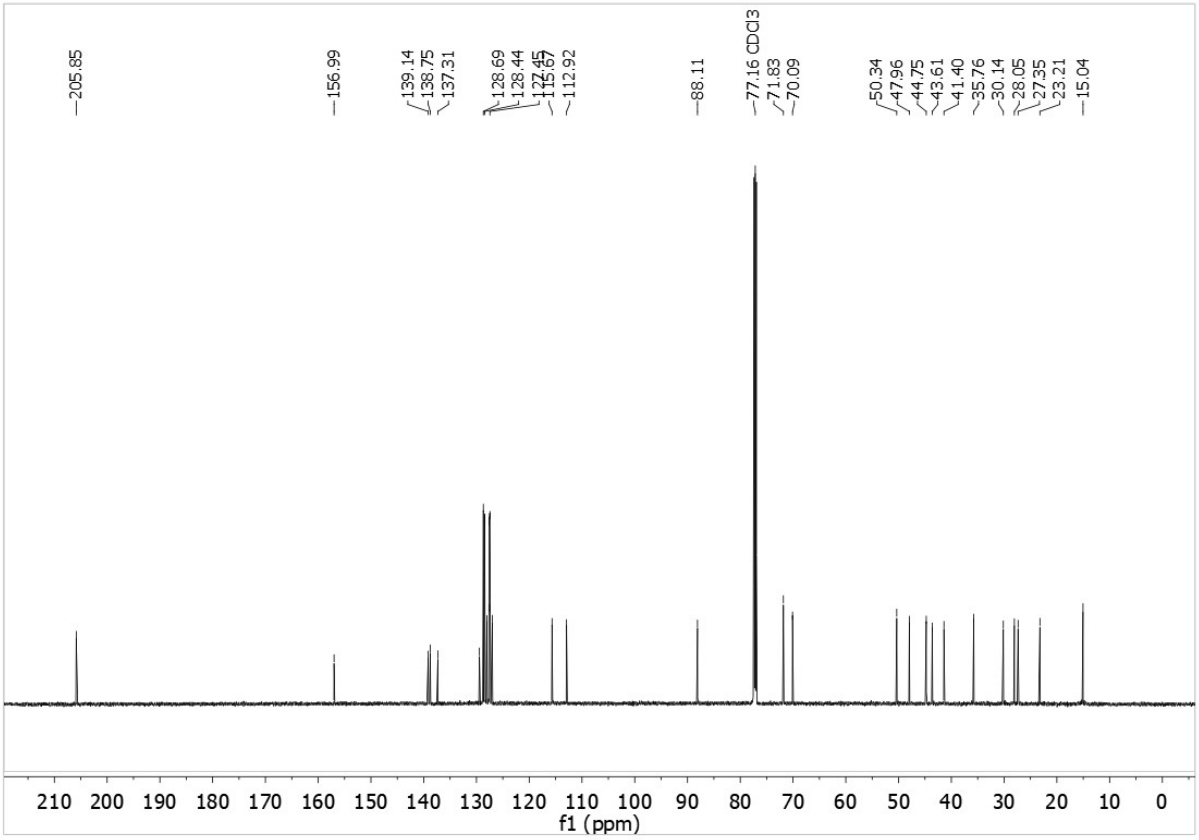
^{1}H NMR



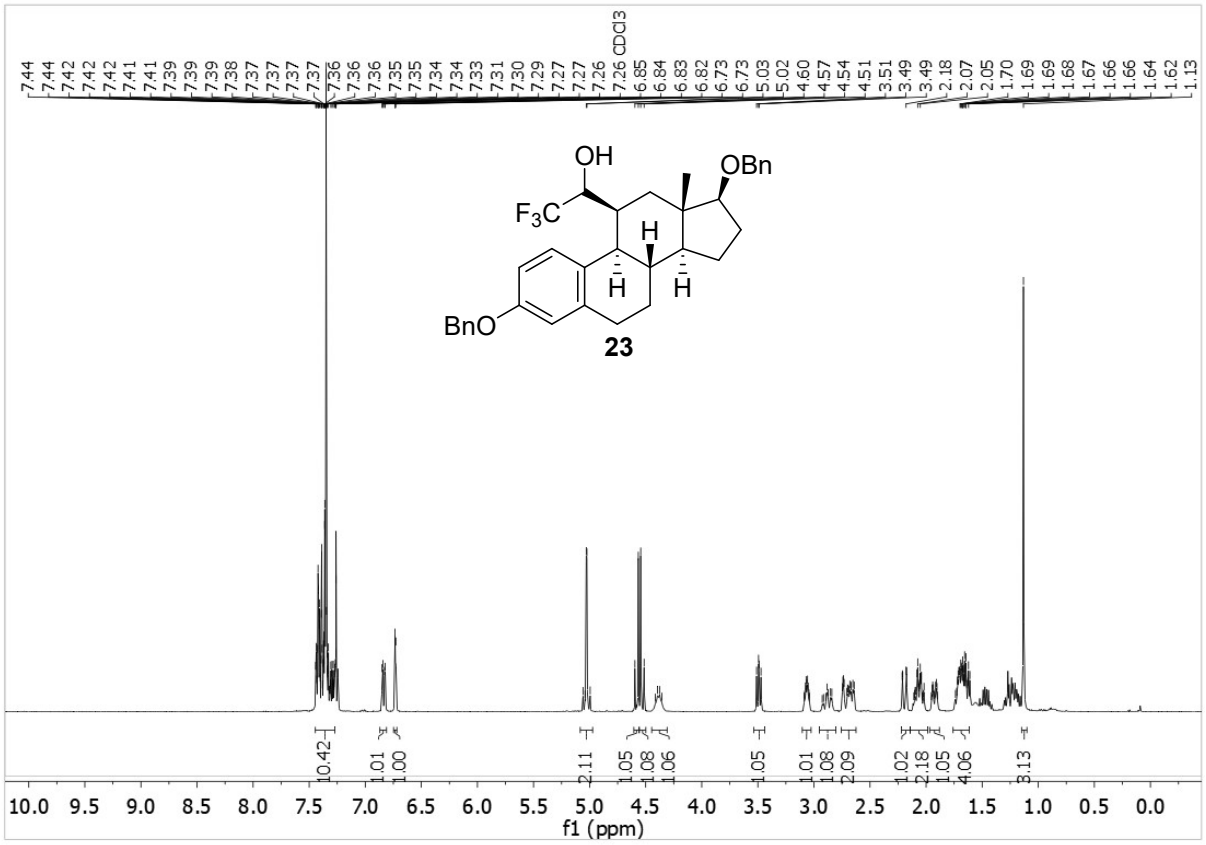
22



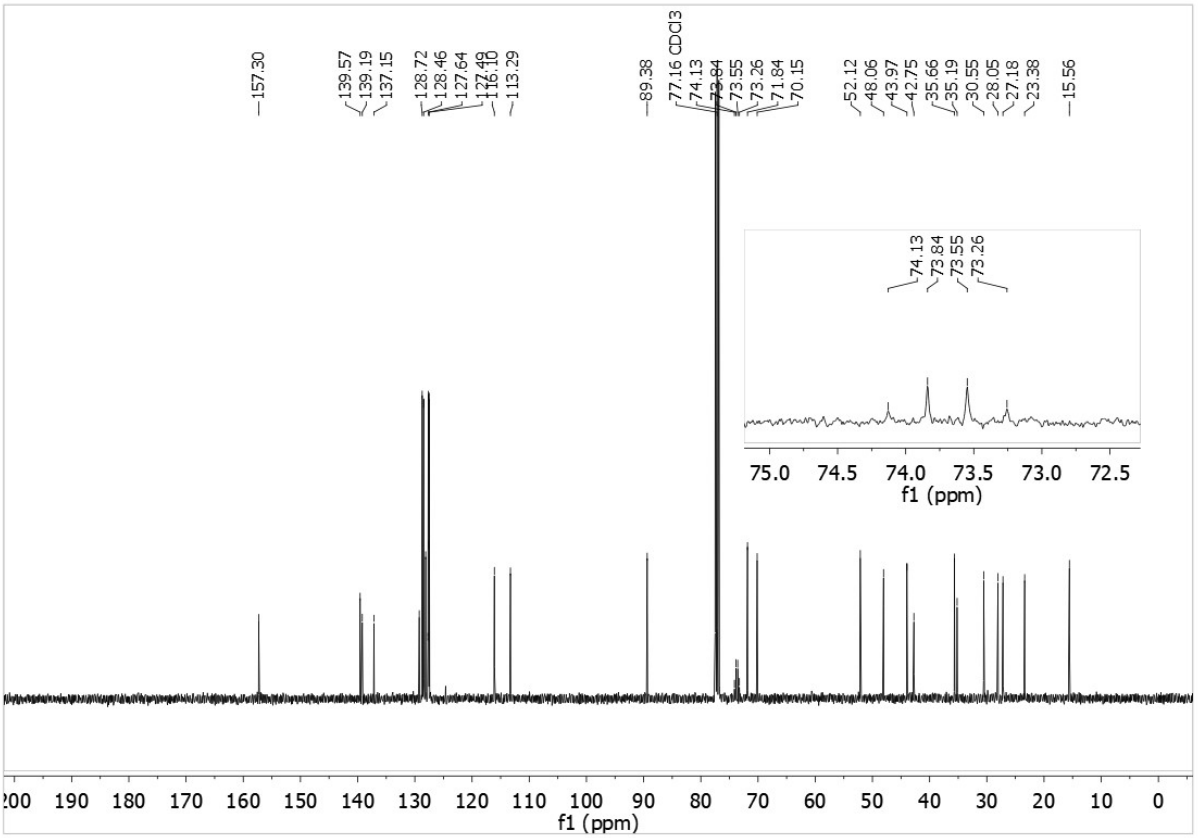
^{13}C NMR



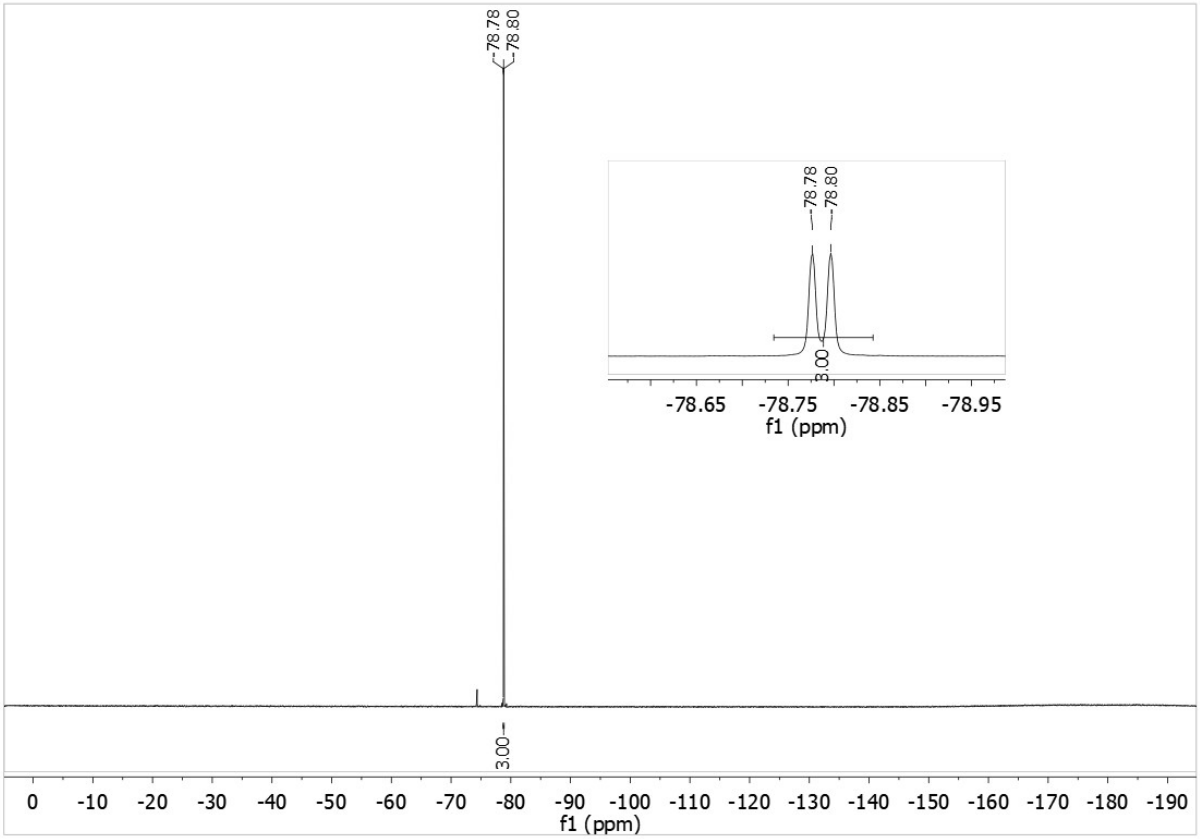
^{1}H NMR



^{13}C NMR



^{19}F NMR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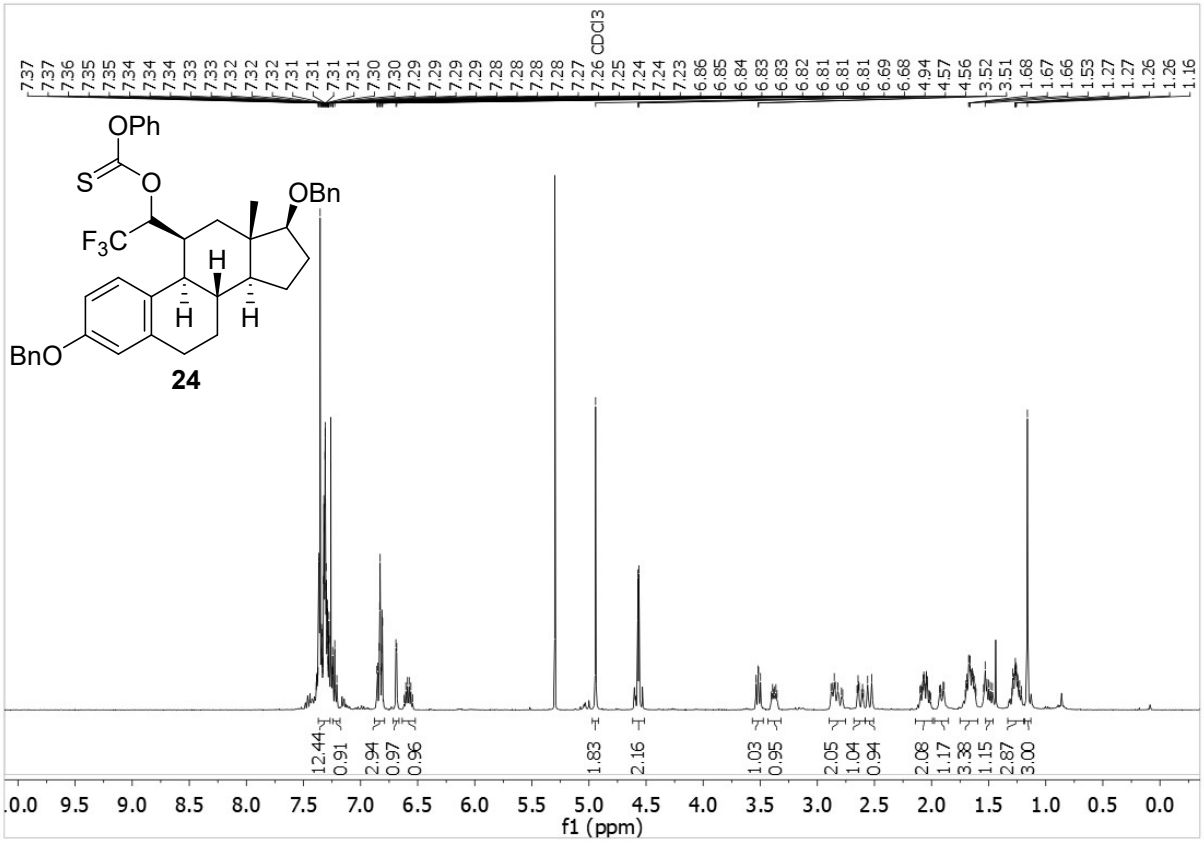
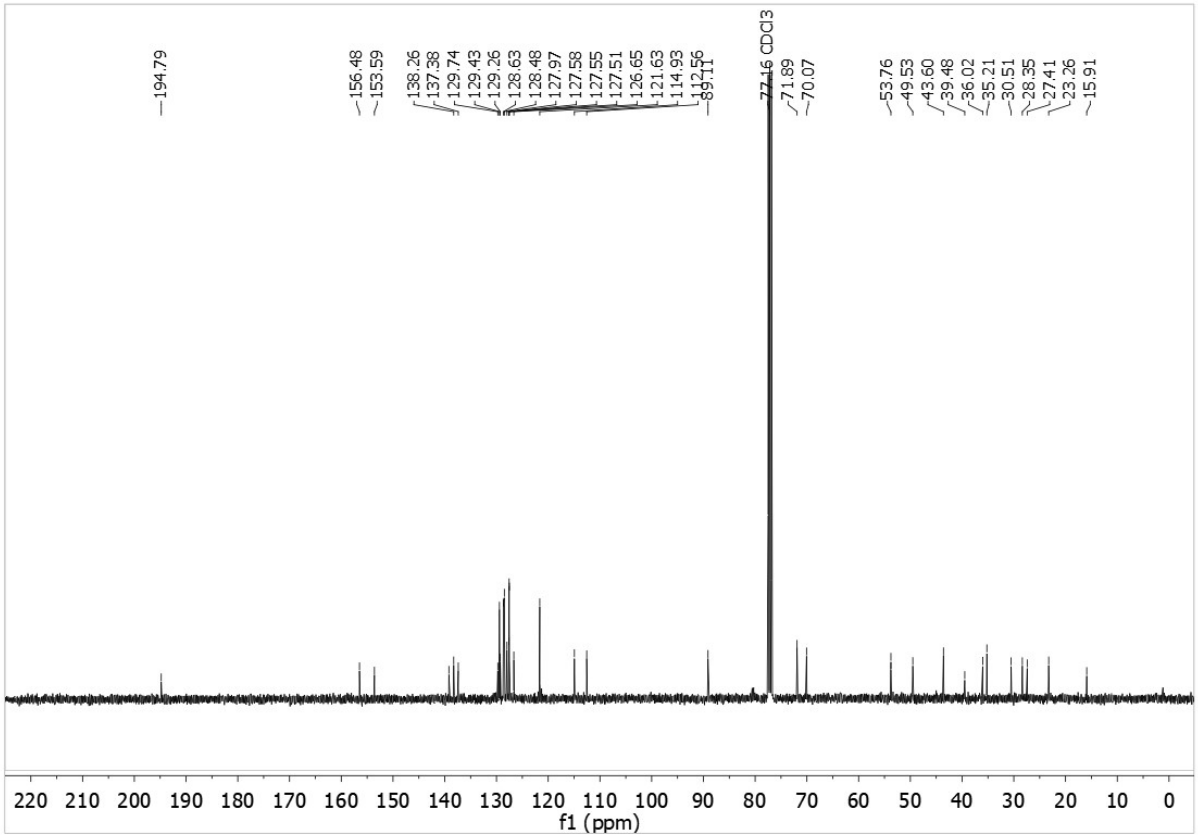
-78.80
3.00
-78.65
-78.75
-78.85
-78.95
f1 (ppm)
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

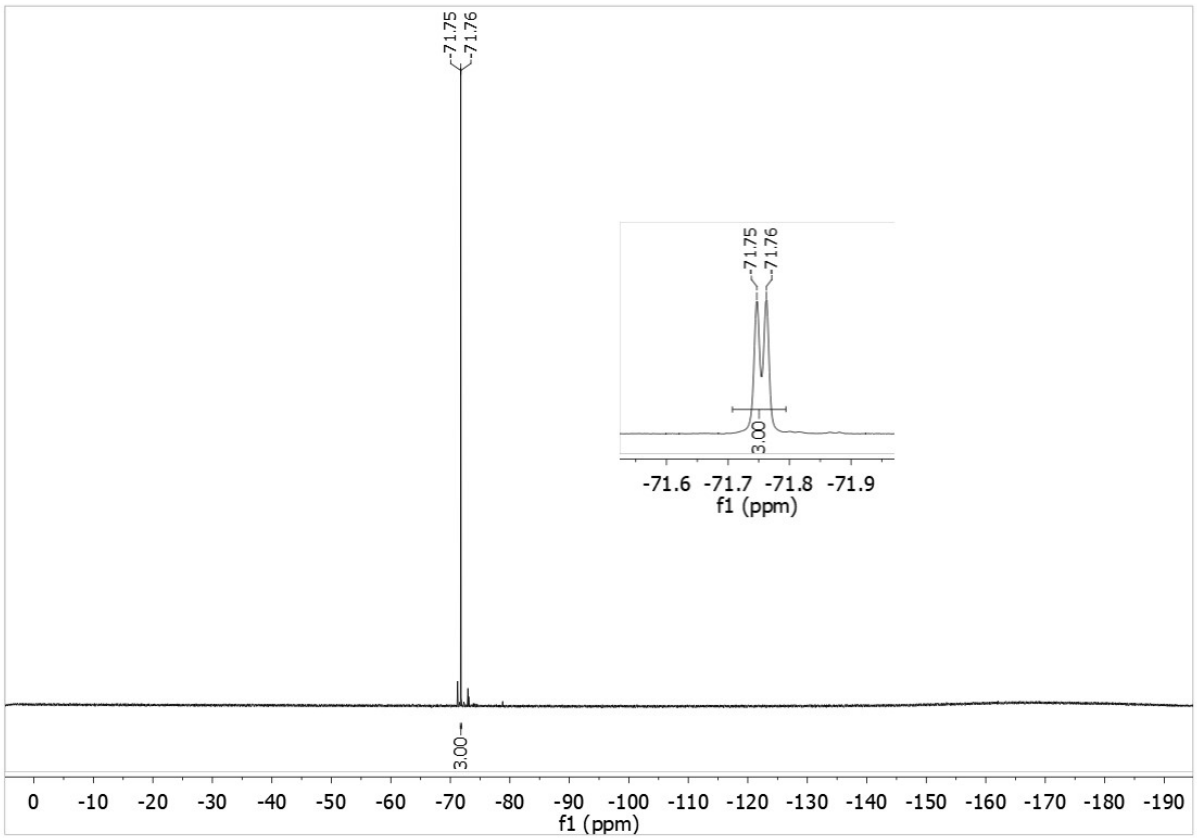
^{1}H NMR



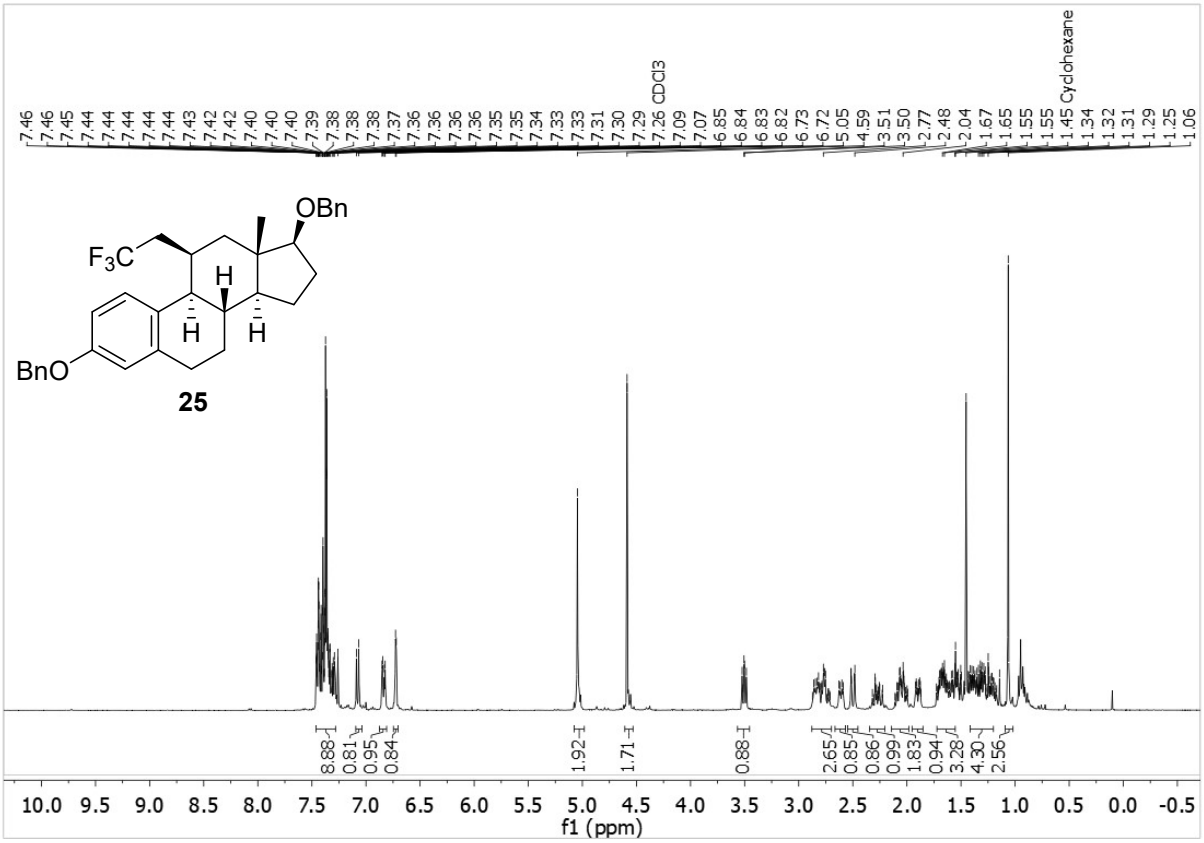
^{13}C NMR


194.79
156.48
153.59
138.26
137.38
129.74
129.43
129.26
128.63
128.48
127.97
127.58
127.55
127.51
126.65
121.63
114.93
112.56
89.11
77.16 CDCl3
71.89
70.07
53.76
49.53
43.60
39.48
36.02
35.21
30.51
28.35
27.41
23.26
15.91
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

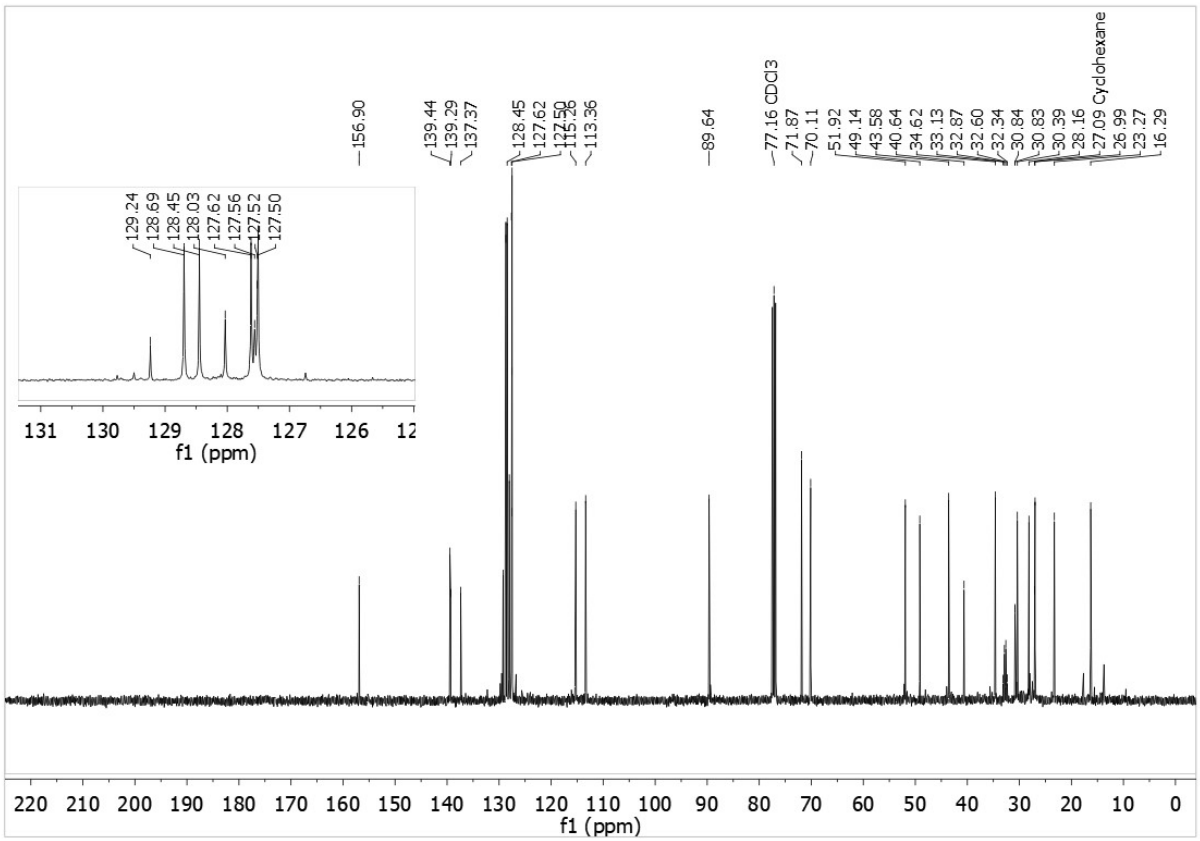
^{19}F NMR


-71.75
-71.76
3.00
-71.6 -71.7 -71.8 -71.9
f1 (ppm)
3.00
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

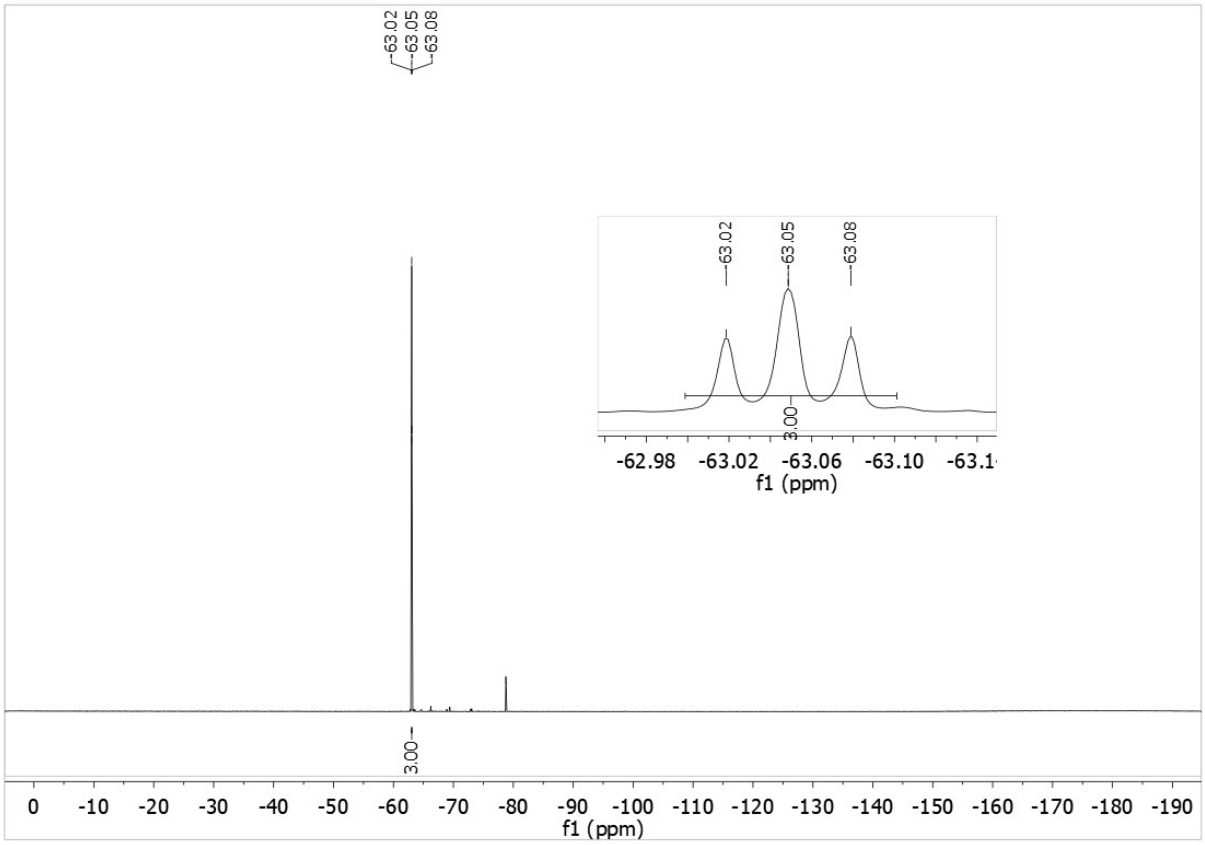
^{1}H NMR



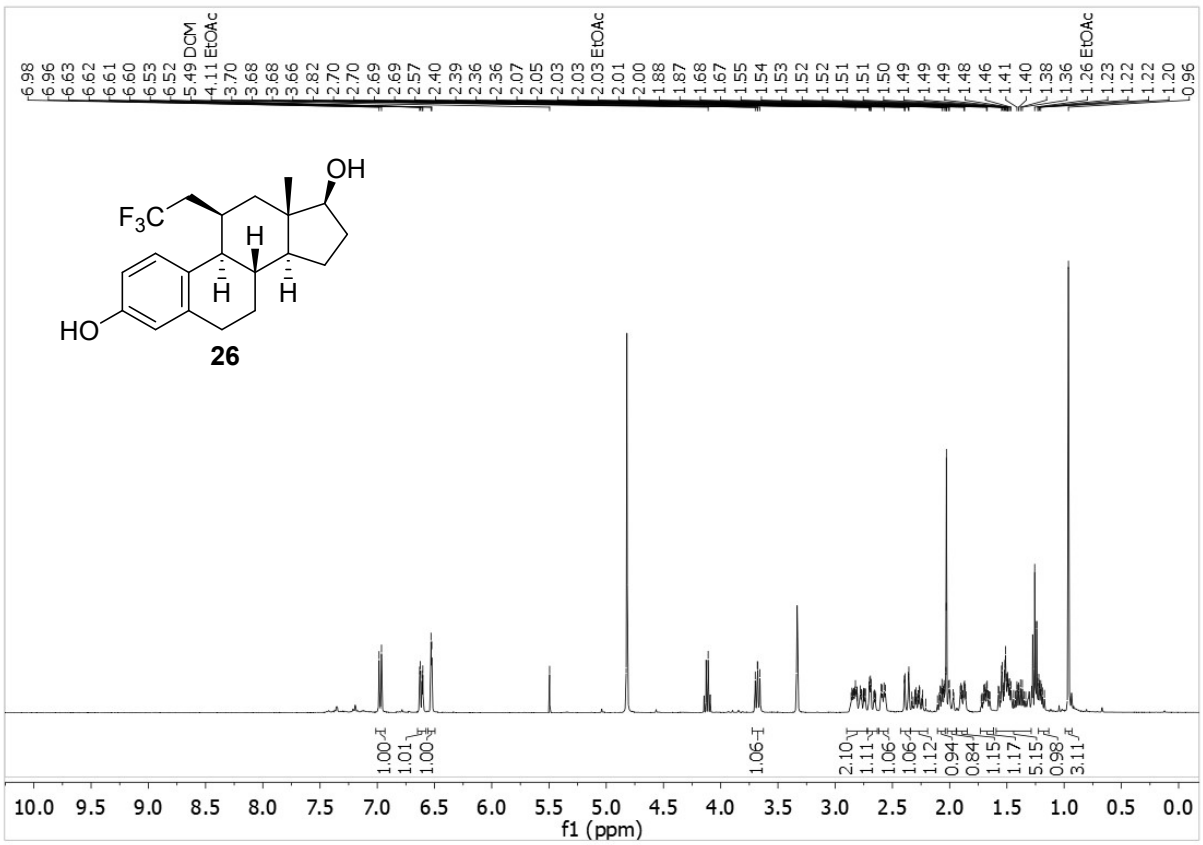
^{13}C NMR


156.90
139.44
139.29
137.37
128.45
127.62
127.50
115.36
113.36
89.64
77.16 CDCl3
71.87
70.11
51.92
49.14
43.58
40.64
34.62
33.13
32.87
32.60
32.34
30.84
30.83
30.39
28.16
27.09 Cyclohexane
26.99
23.27
16.29
129.24
128.69
128.45
128.03
127.62
127.56
127.52
127.50
131 130 129 128 127 126 12
f1 (ppm)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

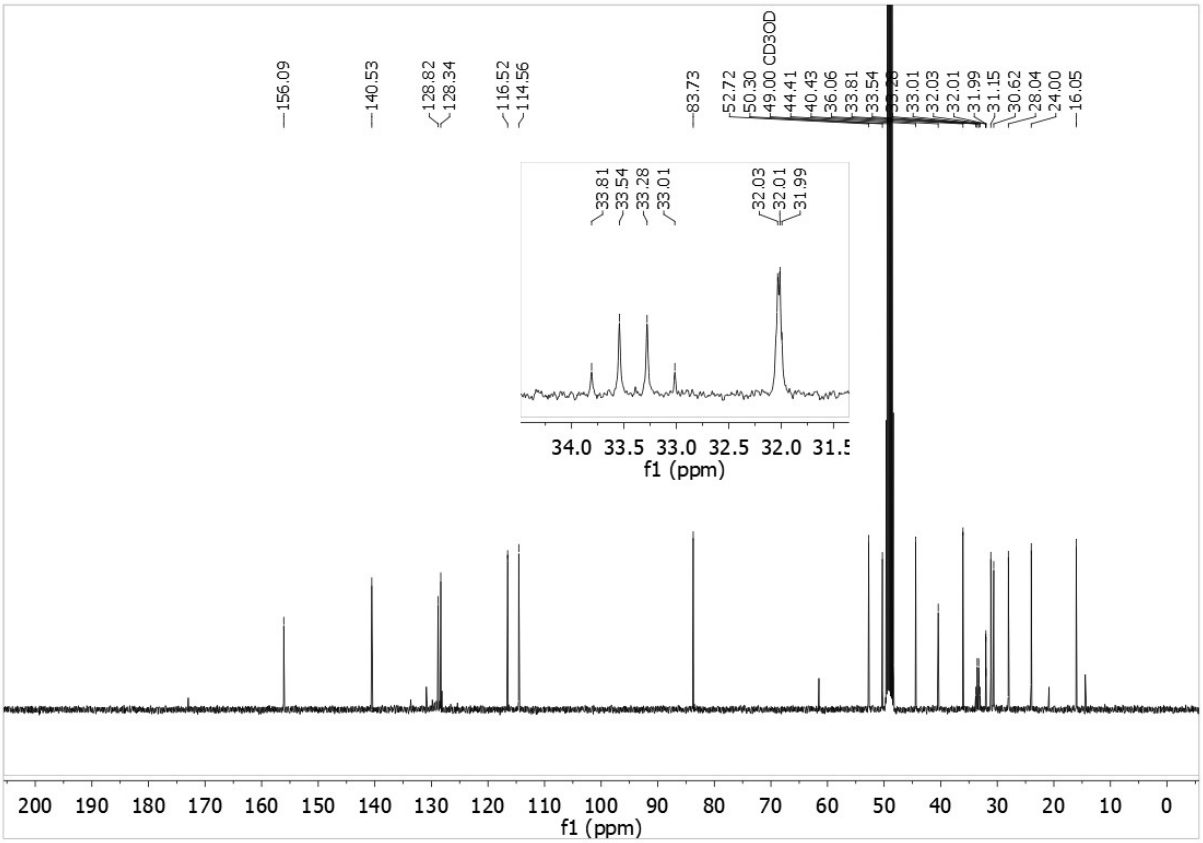
^{19}F NMR


-63.02
-63.05
-63.08
-63.02
-63.05
-63.08
3.00
-62.98 -63.02 -63.06 -63.10 -63.1
f1 (ppm)
3.00
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

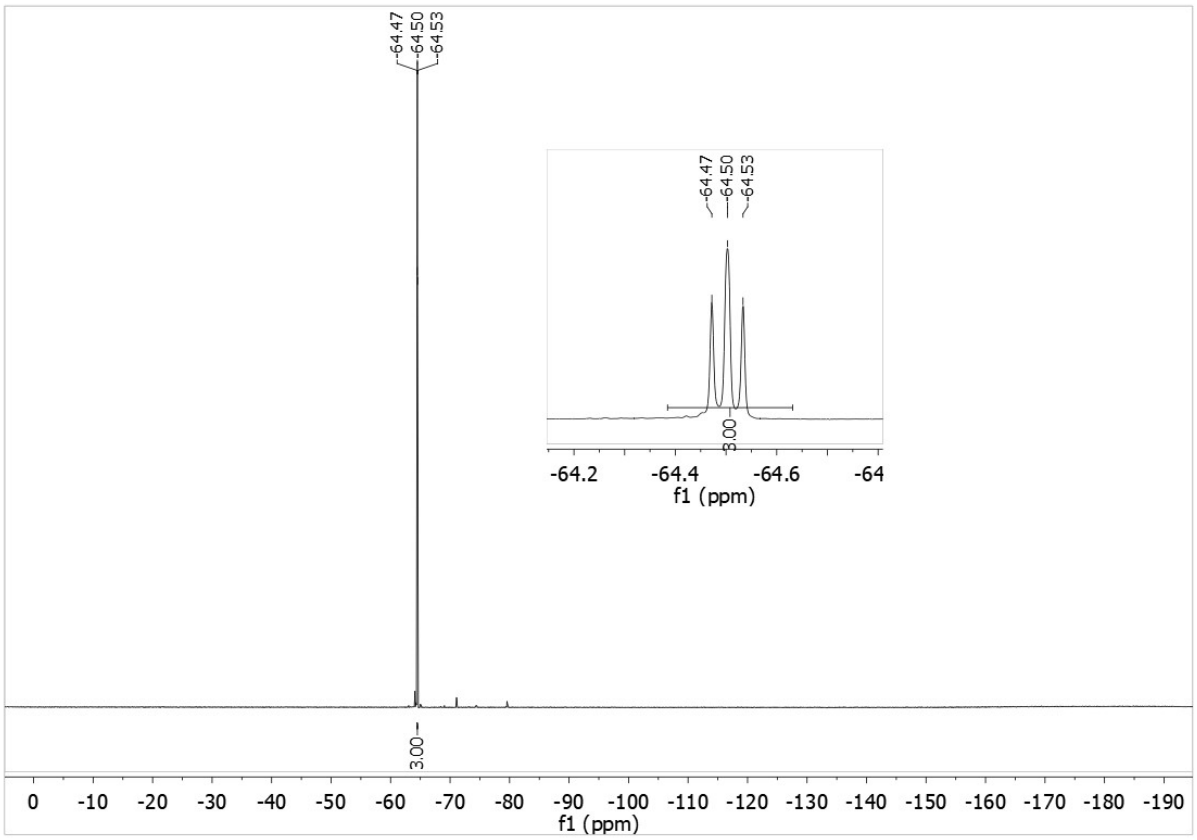
^{1}H NMR



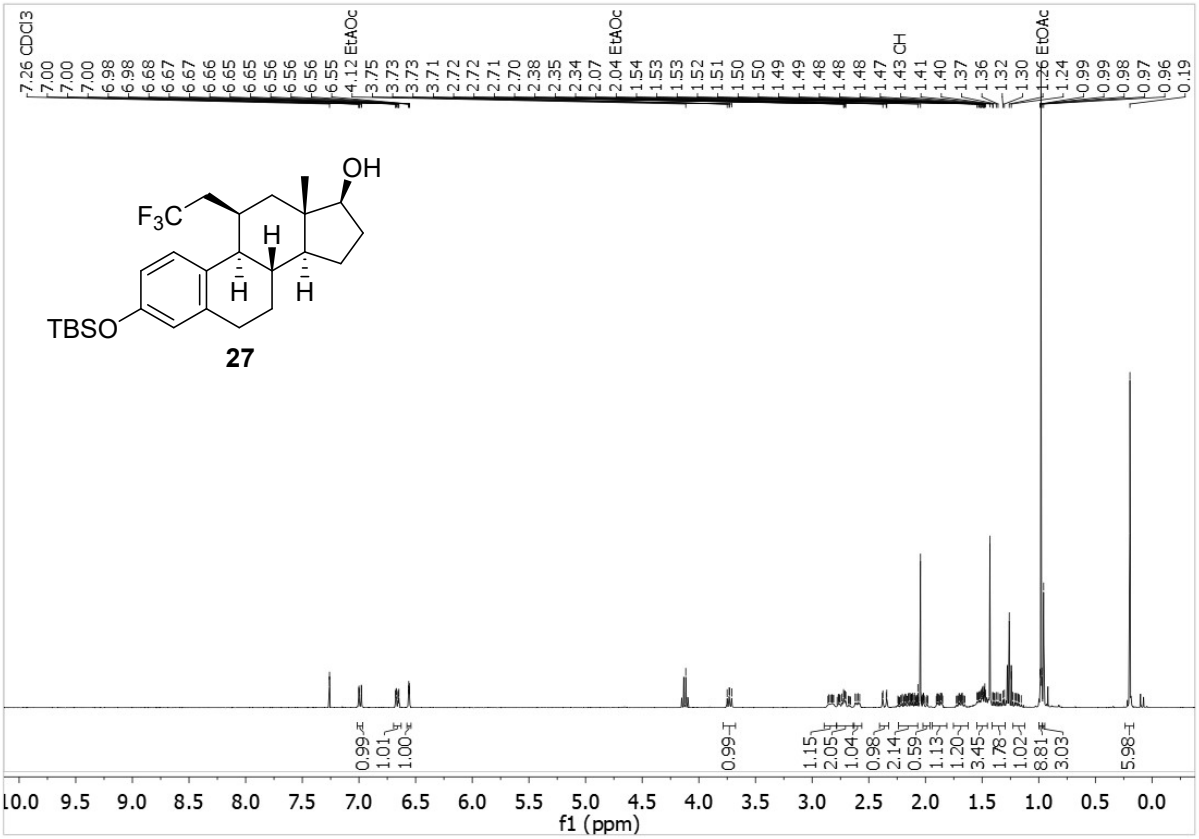
^{13}C NMR


156.09
140.53
128.82
128.34
116.52
114.56
83.73
52.72
50.30
49.00 CD3OD
44.41
40.43
36.06
33.81
33.54
33.01
32.03
32.01
31.99
31.15
30.62
28.04
24.00
16.05
33.81
33.54
33.28
33.01
32.03
32.01
31.99
34.0 33.5 33.0 32.5 32.0 31.5
f1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

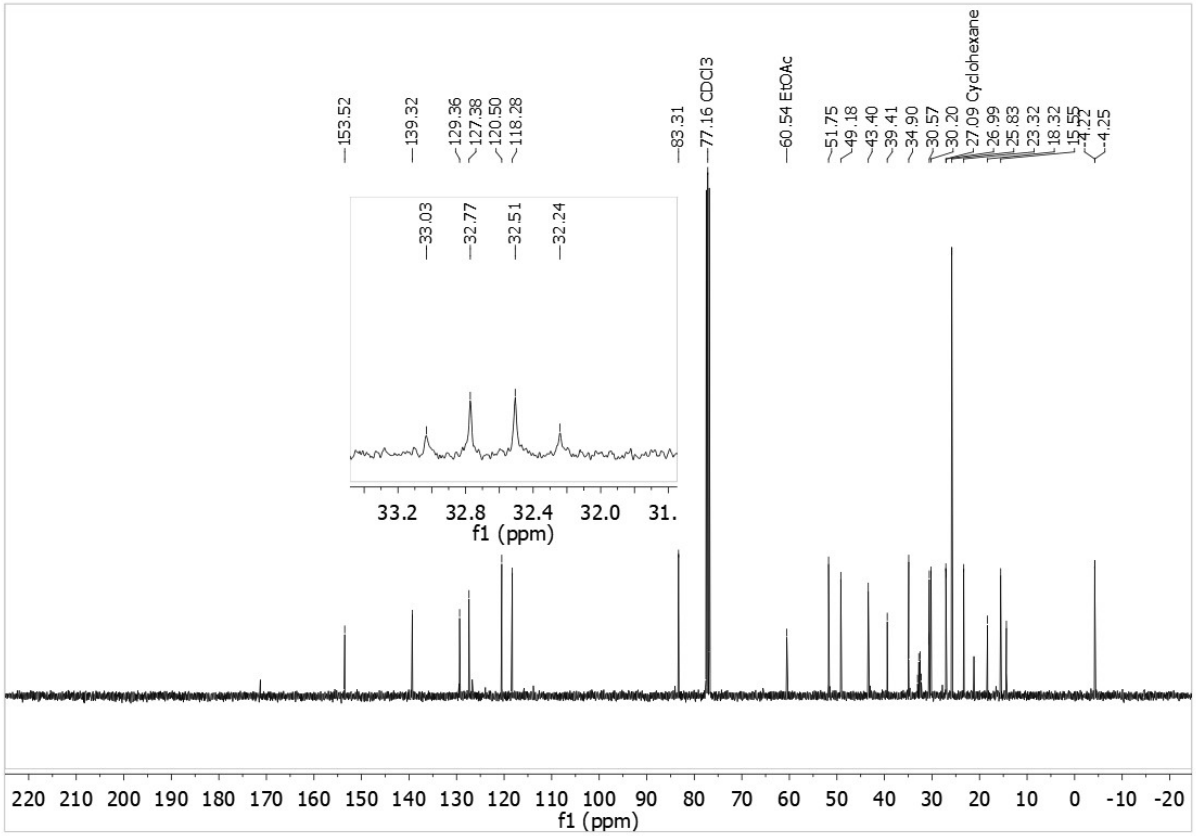
^{19}F NMR


64.47
64.50
64.53
64.47
64.50
64.53
3.00
-64.2 -64.4 -64.6 -64
f1 (ppm)
3.00
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

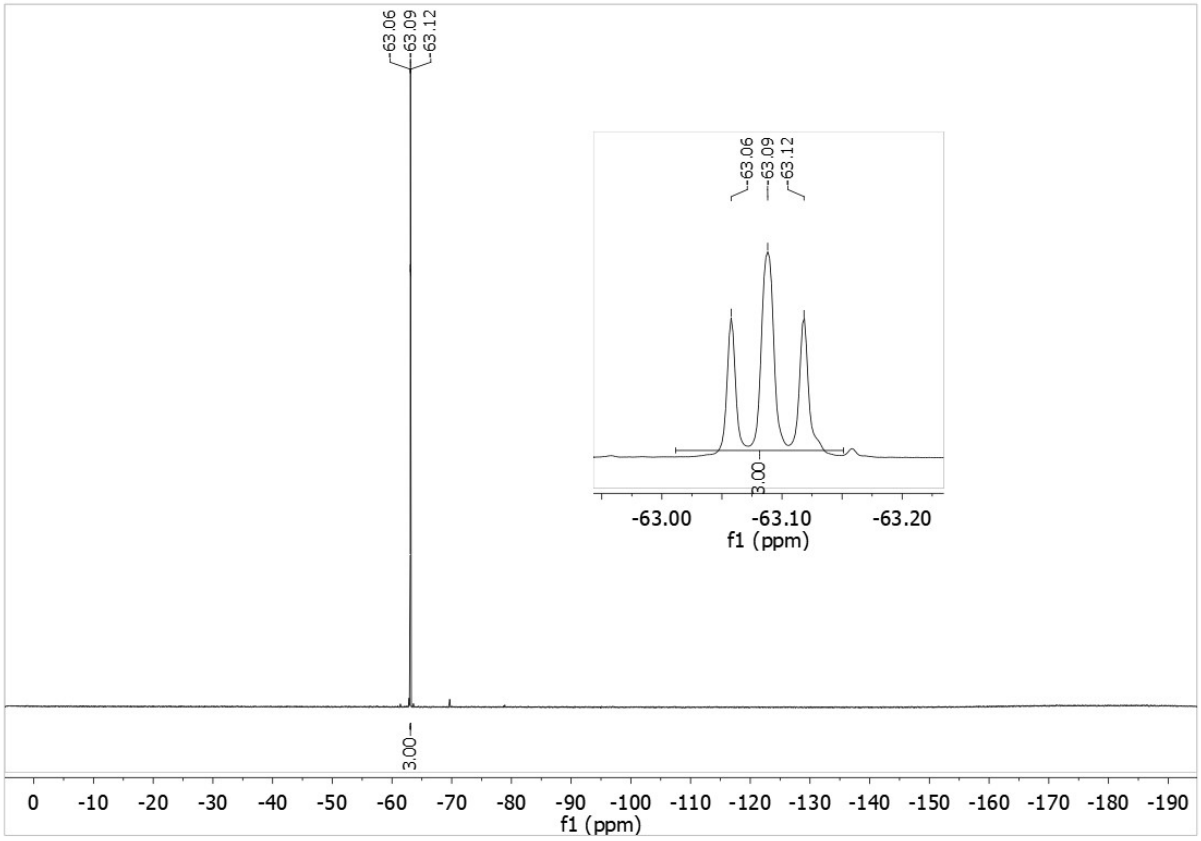
^{1}H NMR



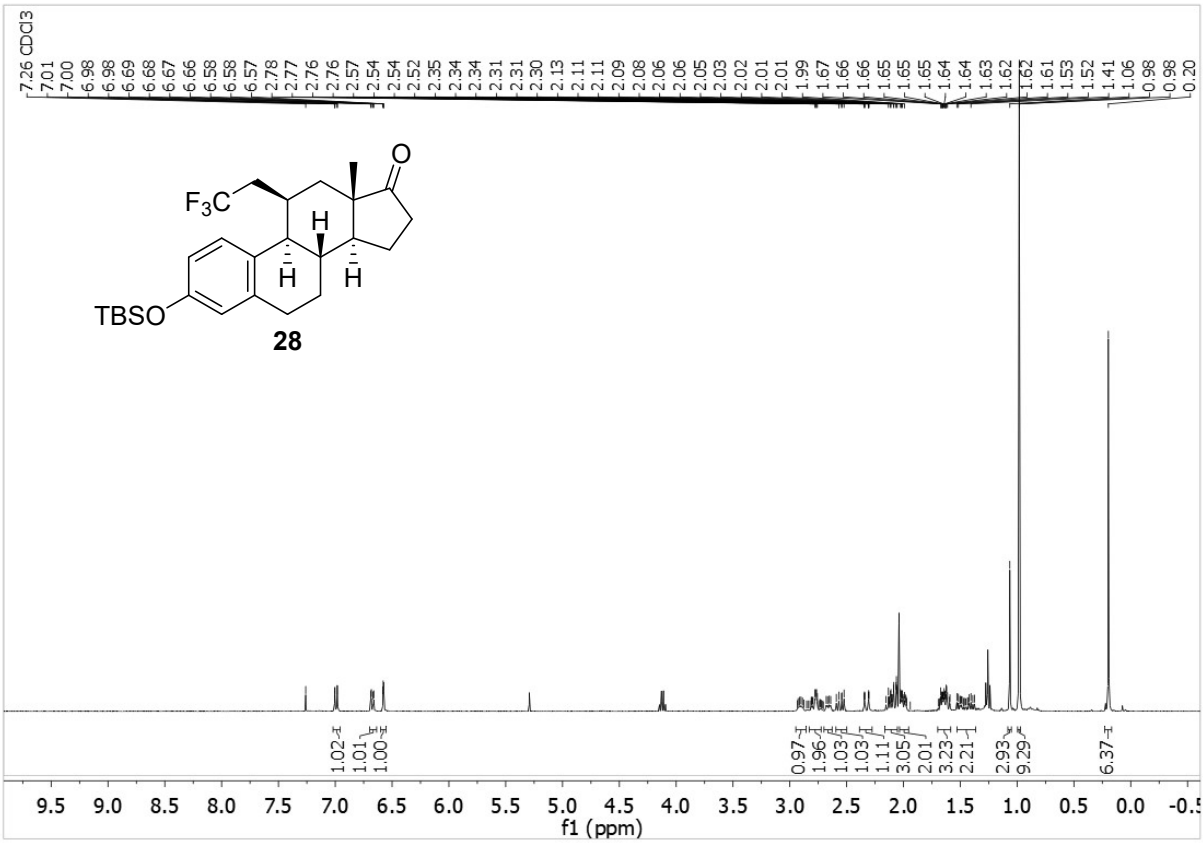
^{13}CNMR



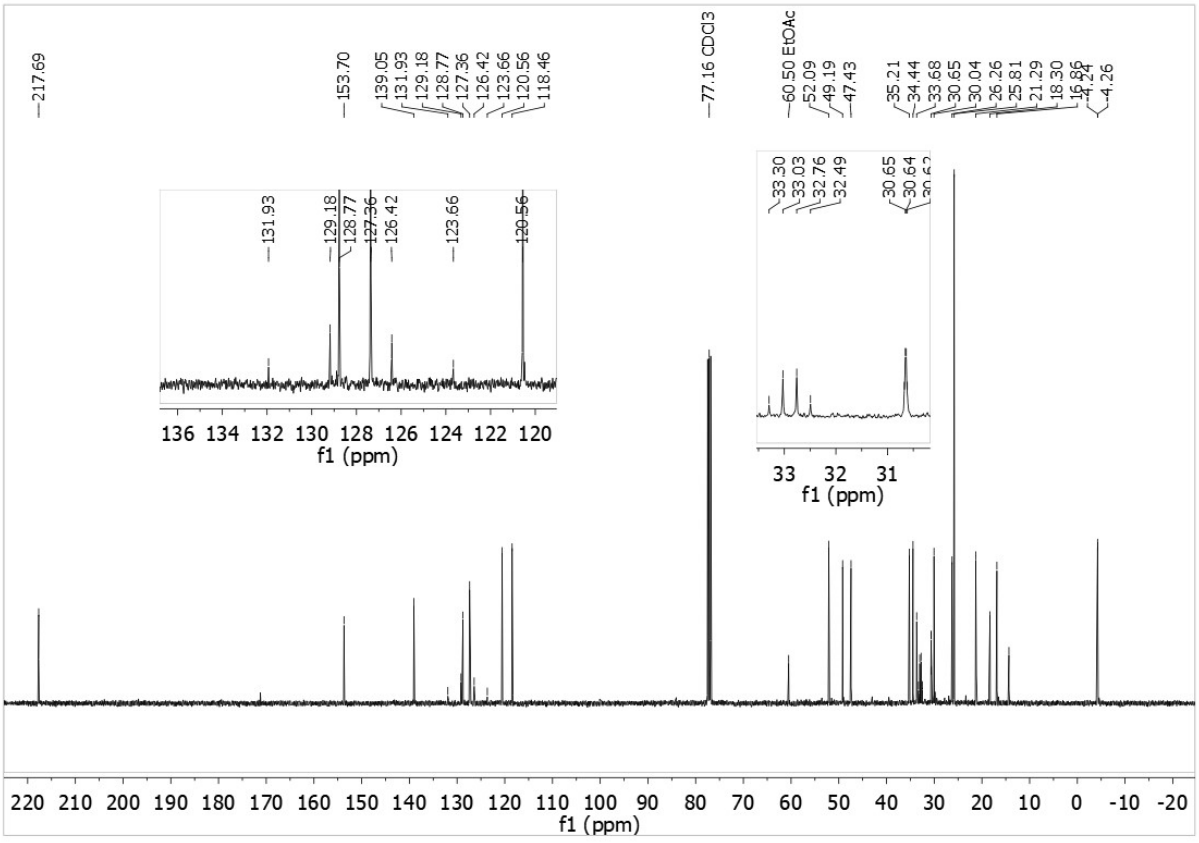
^{19}F NMR


-63.06
-63.09
-63.12
3.00
-63.00
-63.10
-63.20
f1 (ppm)
3.00
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

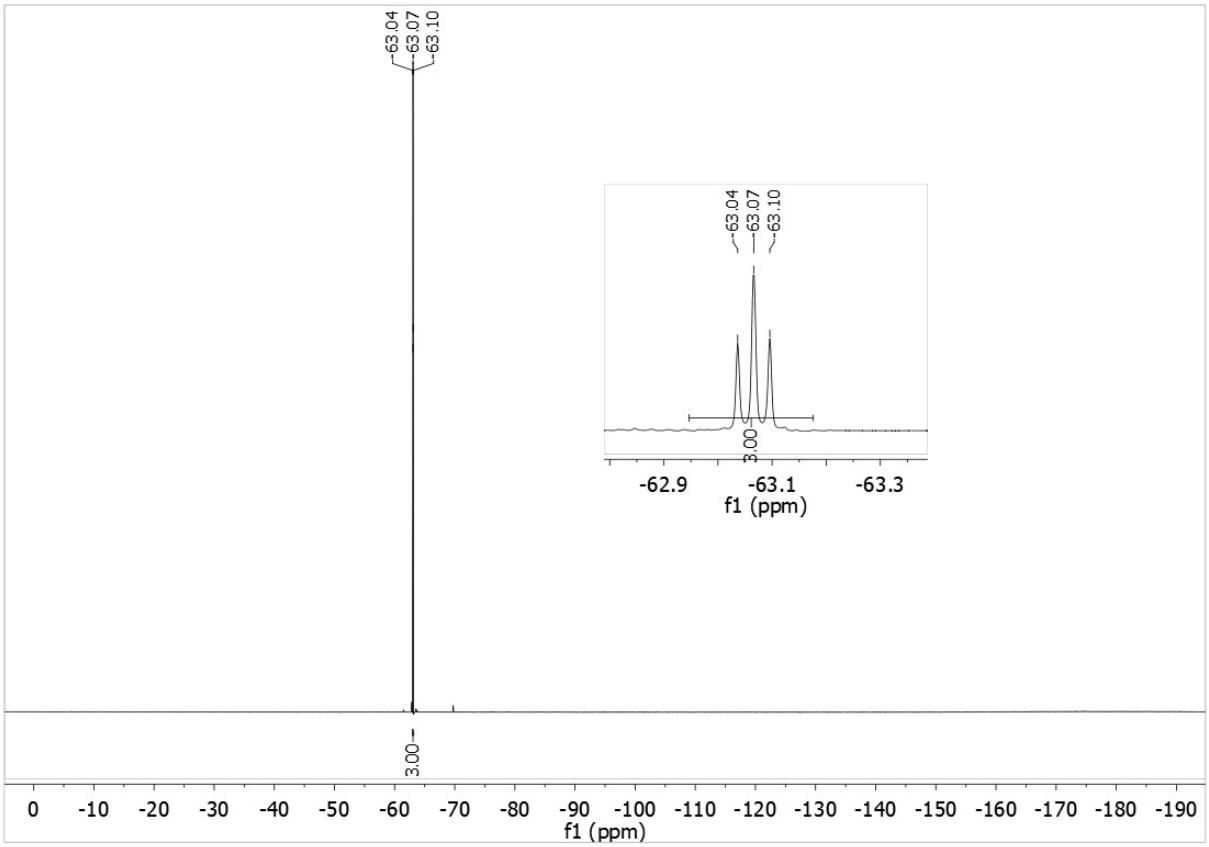
^{1}H NMR



^{13}C NMR



^{19}F NMR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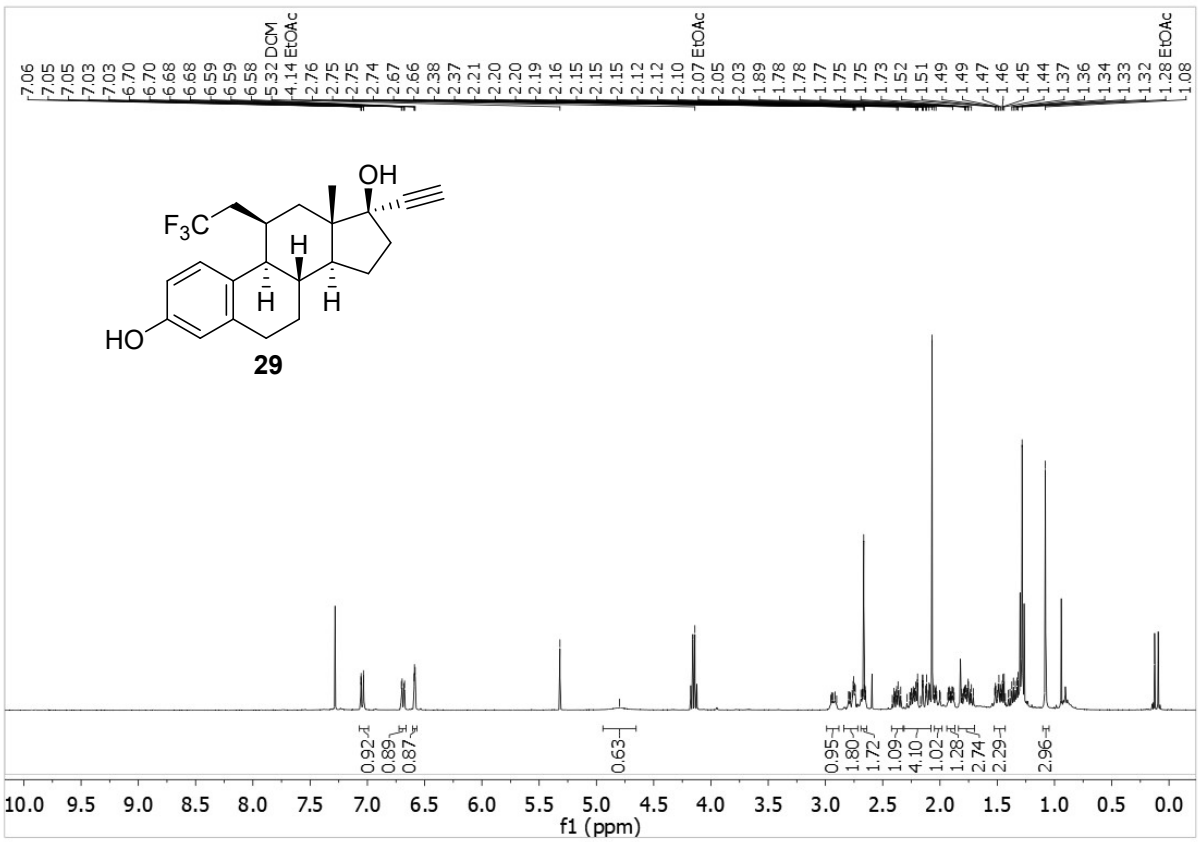
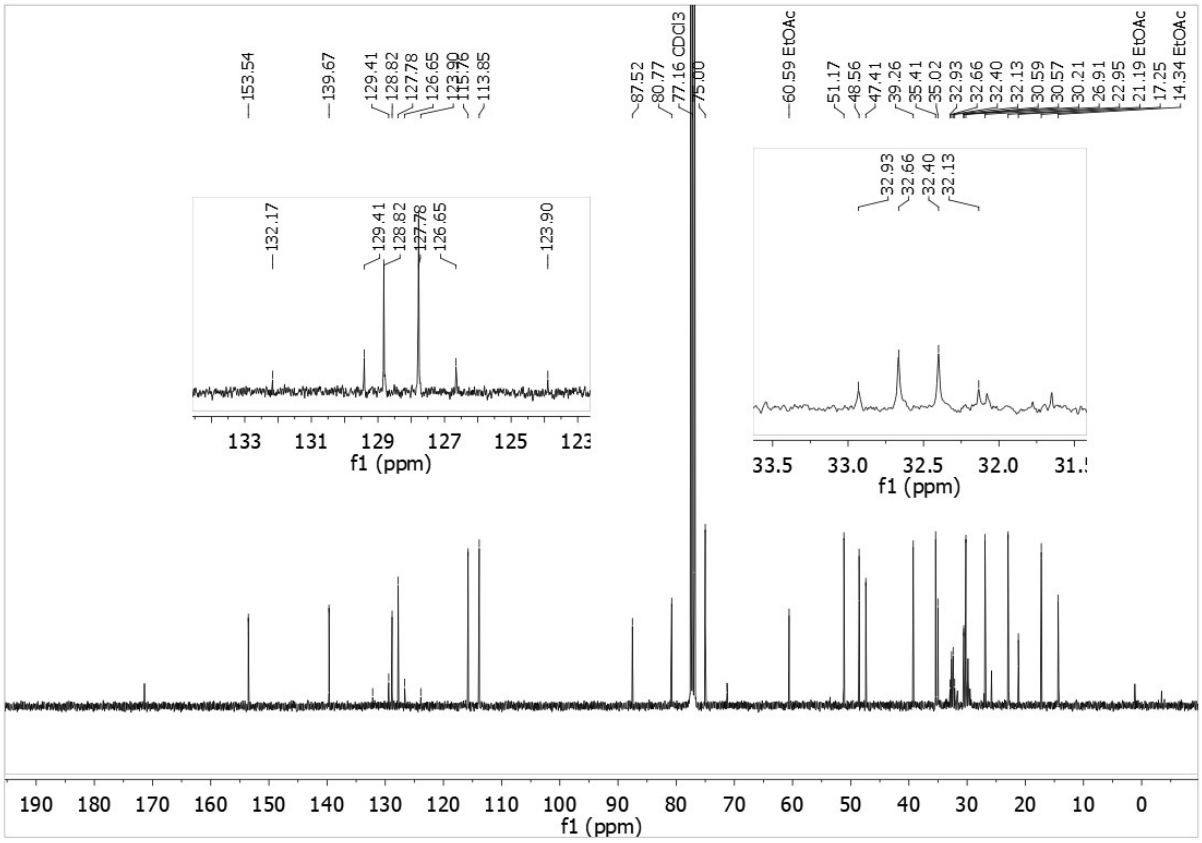
-63.07
-63.10
3.00
-62.9
-63.1
-63.3
f1 (ppm)
3.00
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

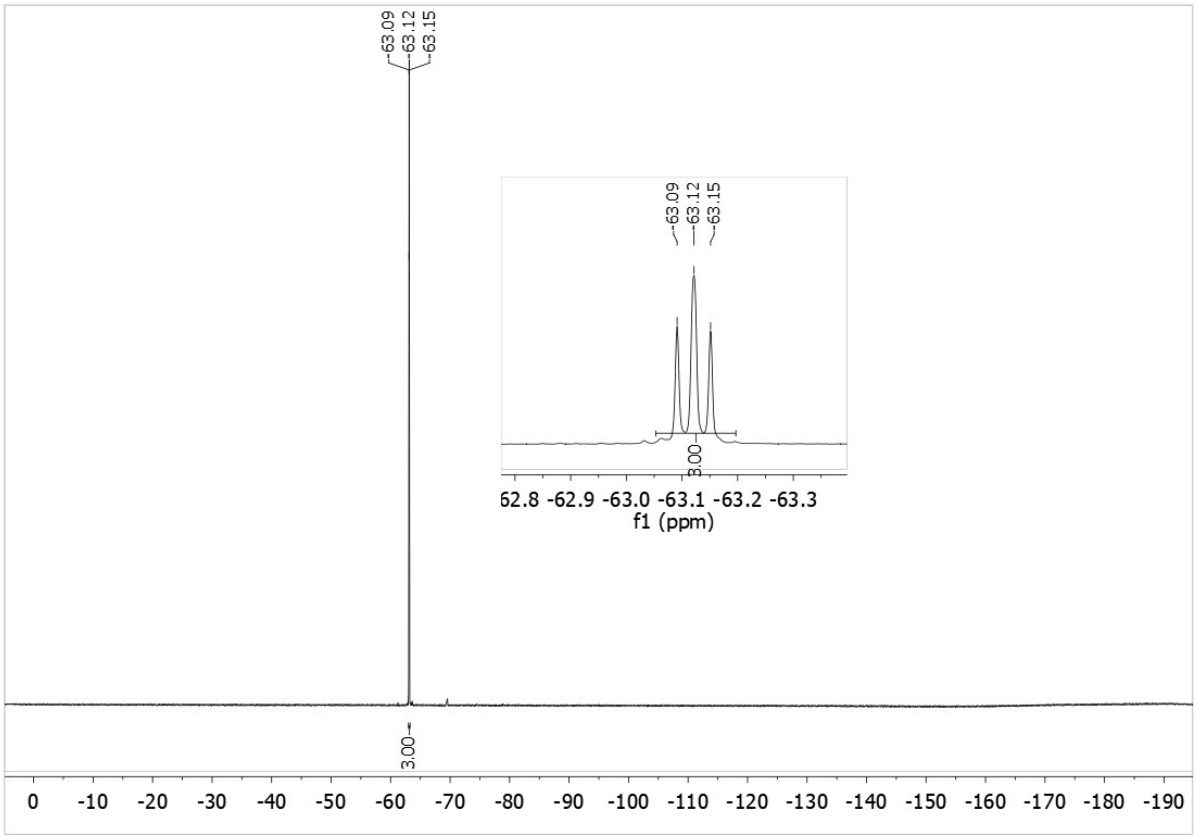
^{1}H NMR



^{13}C NMR

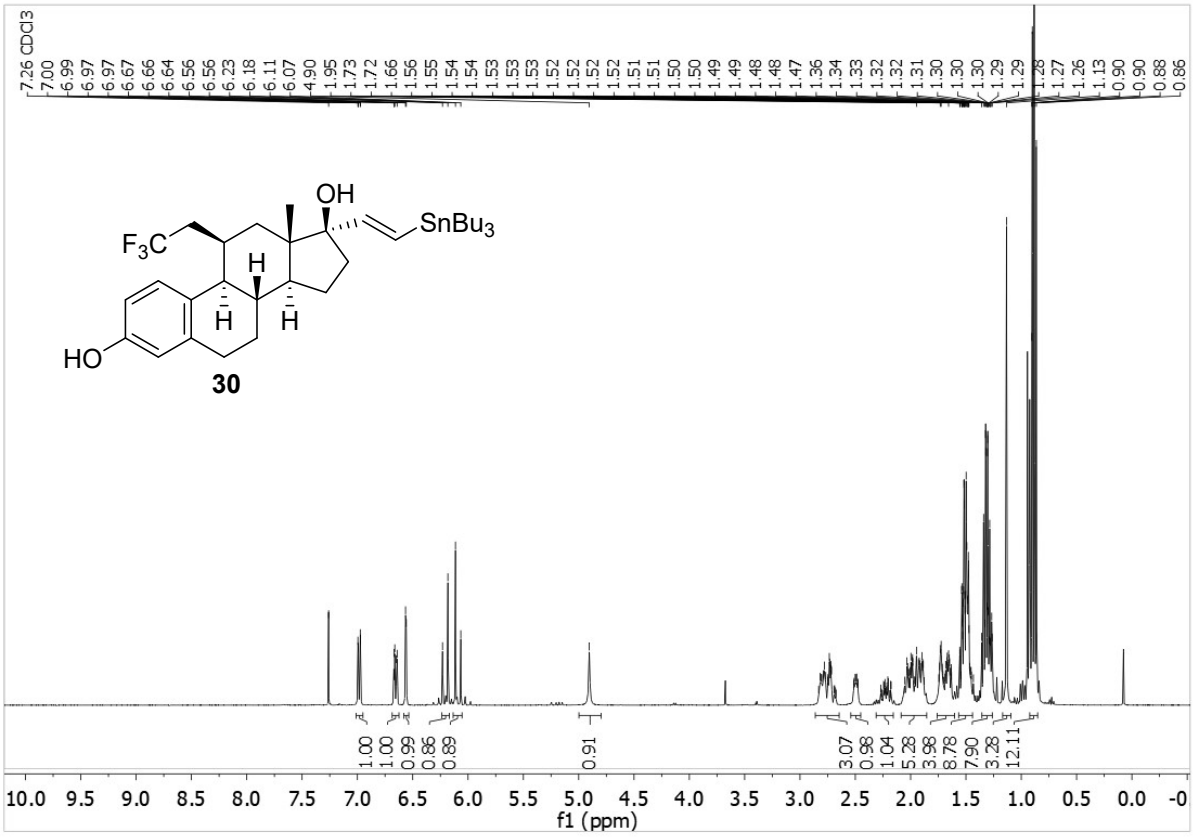

153.54
139.67
129.41
128.82
127.78
126.65
123.90
115.76
113.85
87.52
80.77
77.16 CDCl3
75.00
60.59 EtOAc
51.17
48.56
47.41
39.26
35.41
35.02
32.93
32.66
32.40
32.13
30.59
30.57
30.21
26.91
22.95
21.19 EtOAc
17.25
14.34 EtOAc
f1 (ppm)

^{19}F NMR

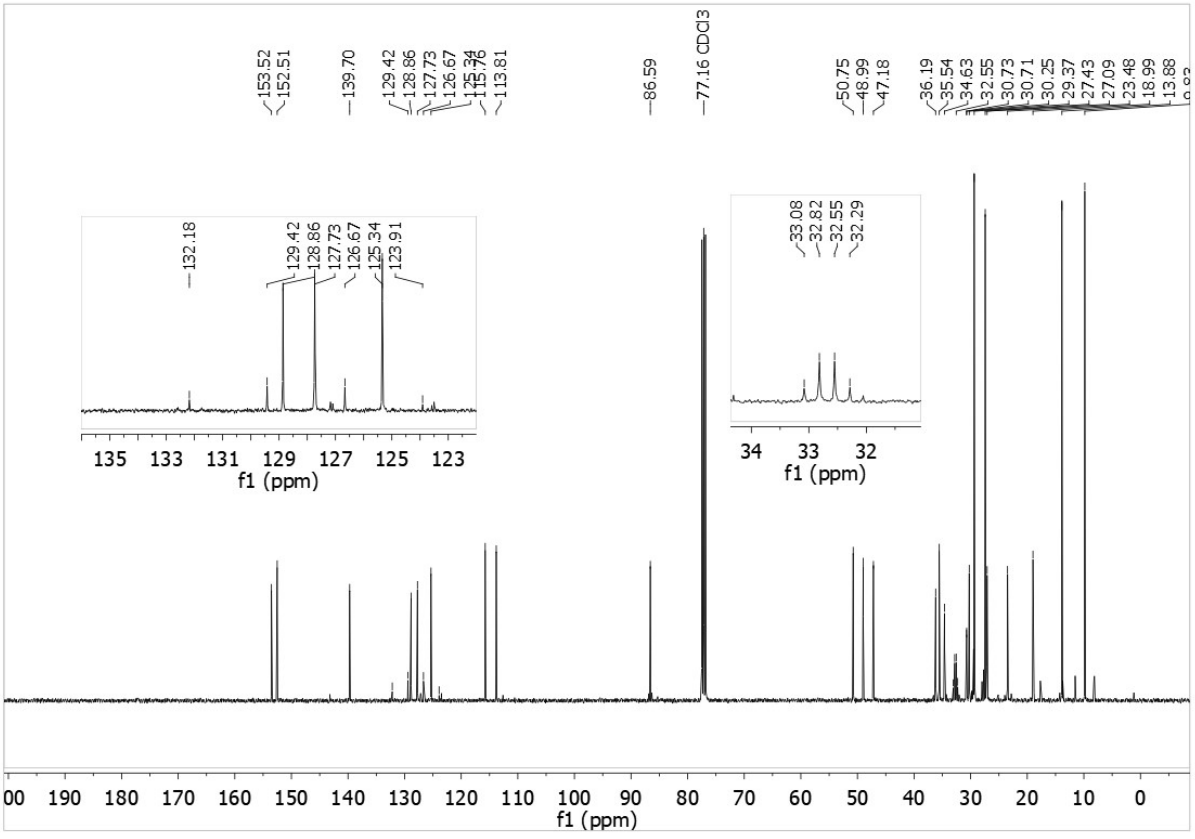

63.09
63.12
63.15
3.00
f1 (ppm)

Supporting information

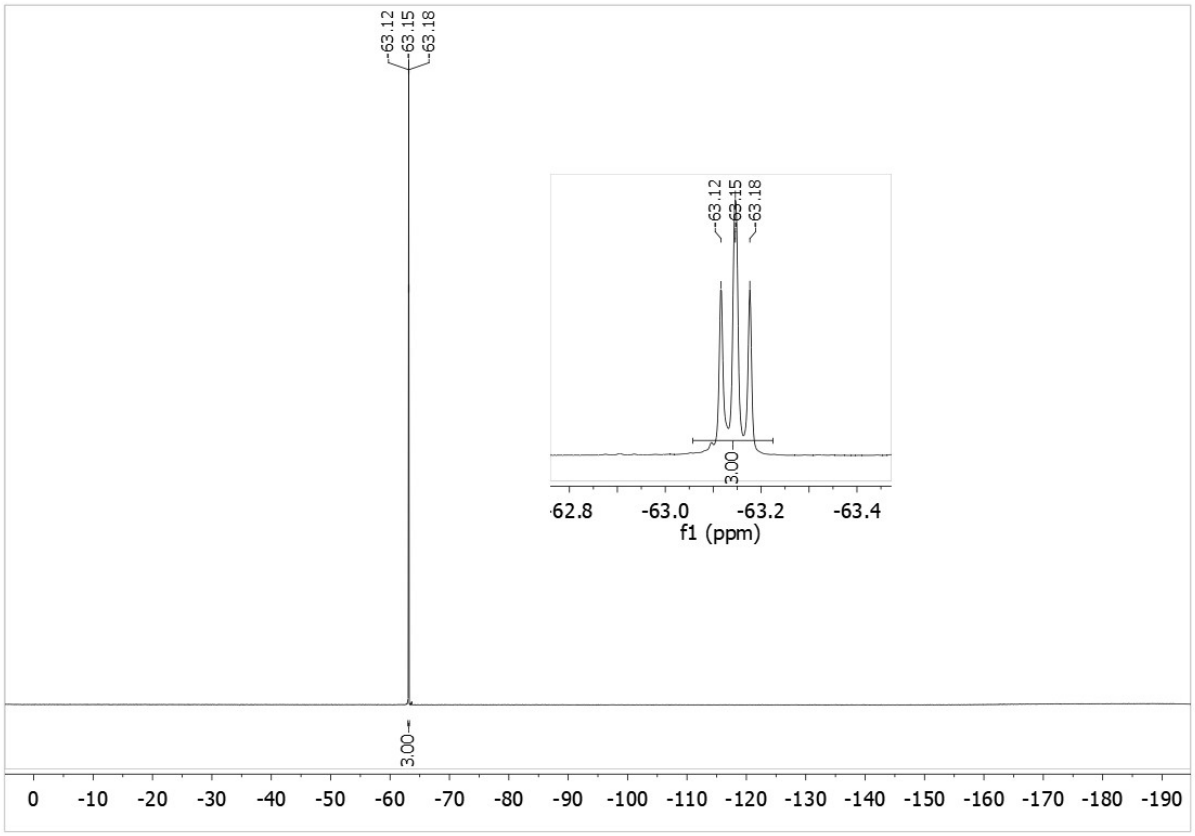
^{1}H NMR



^{13}C NMR



^{19}F NMR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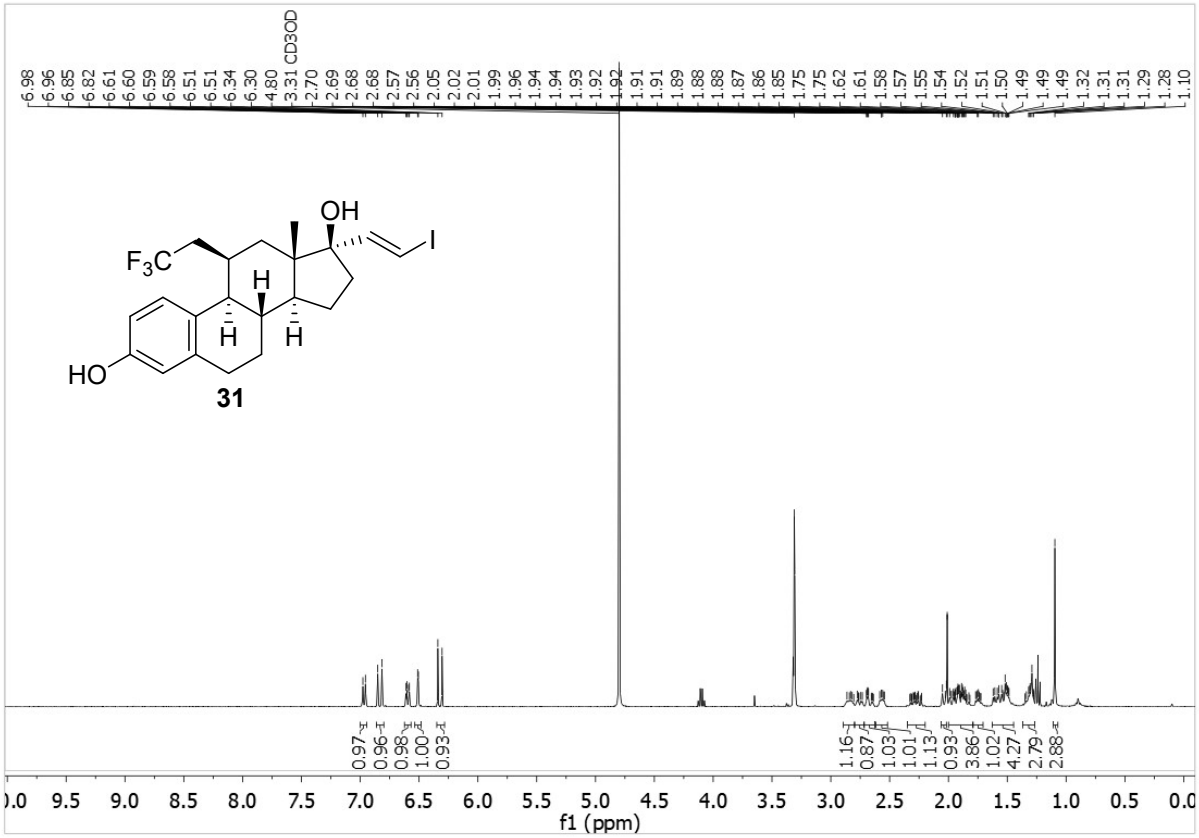
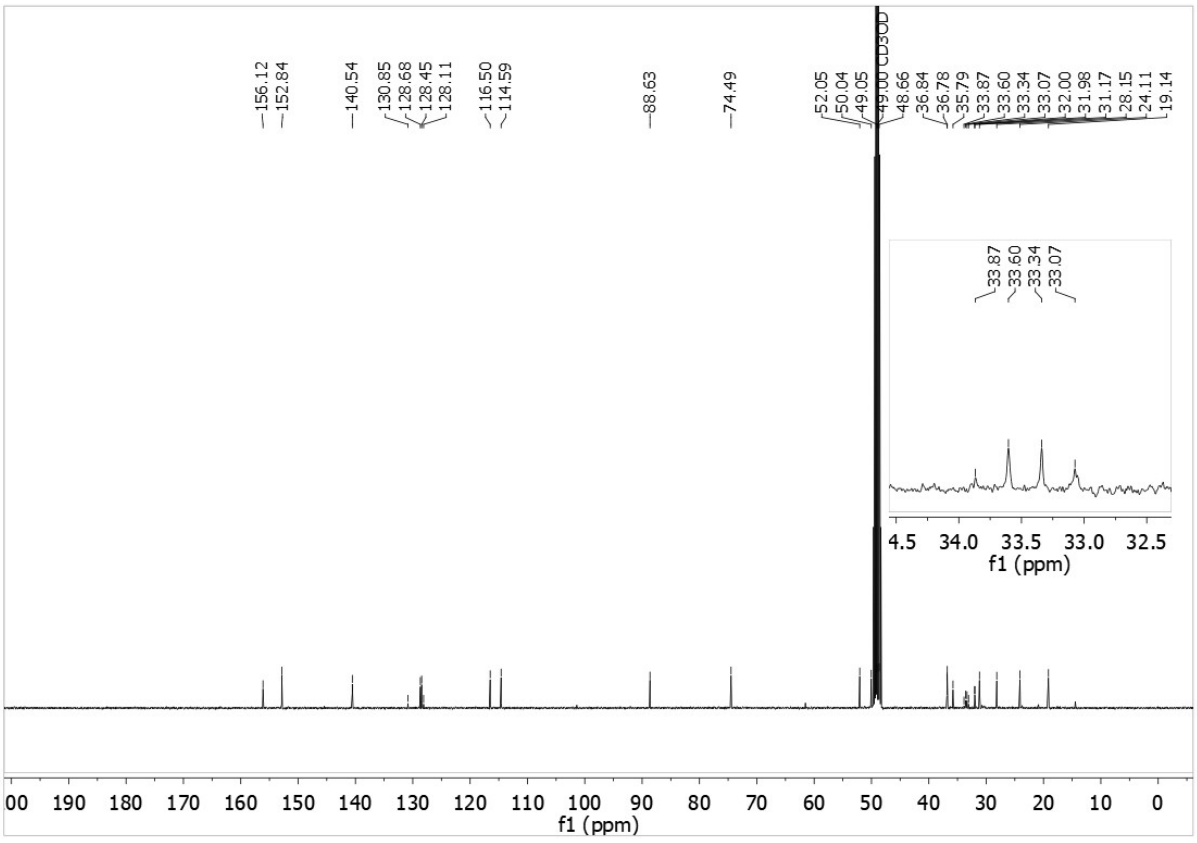
-63.15
-63.18
3.00
-62.8
-63.0
-63.2
-63.4
f1 (ppm)
3.00
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

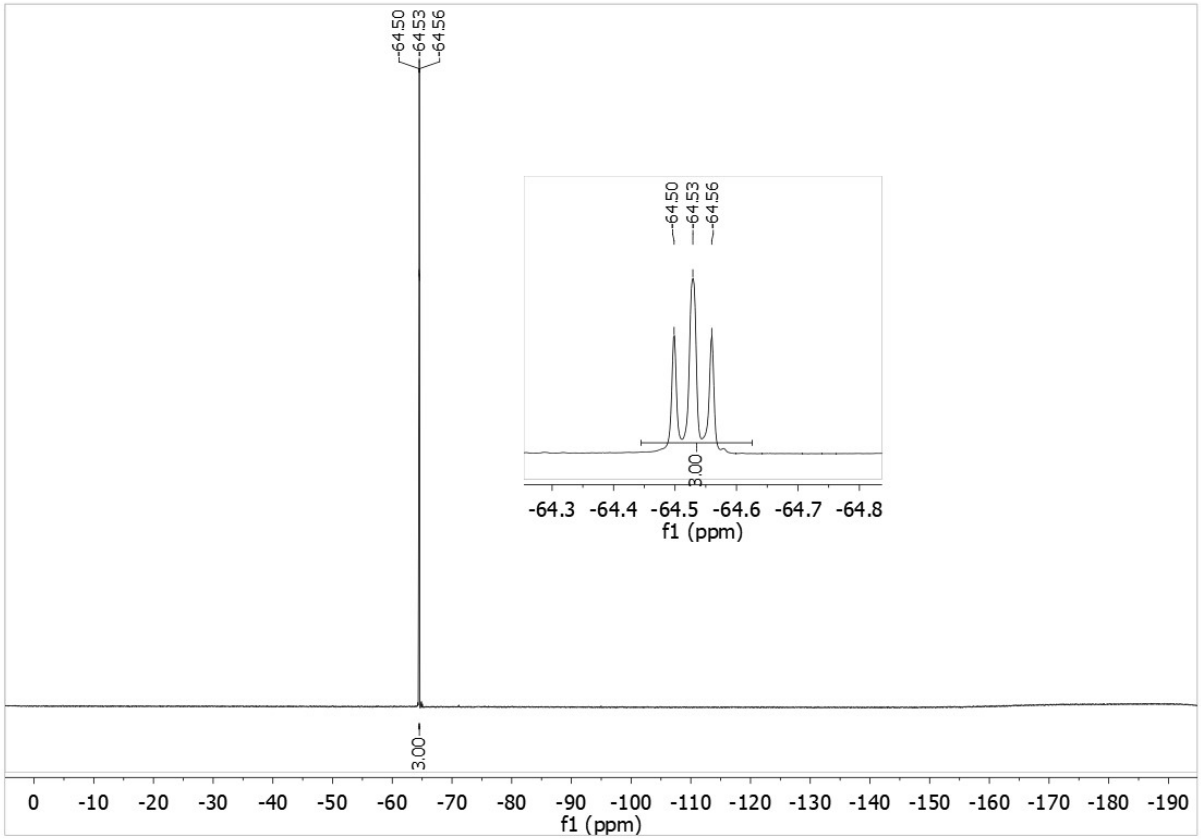
^{1}H NMR



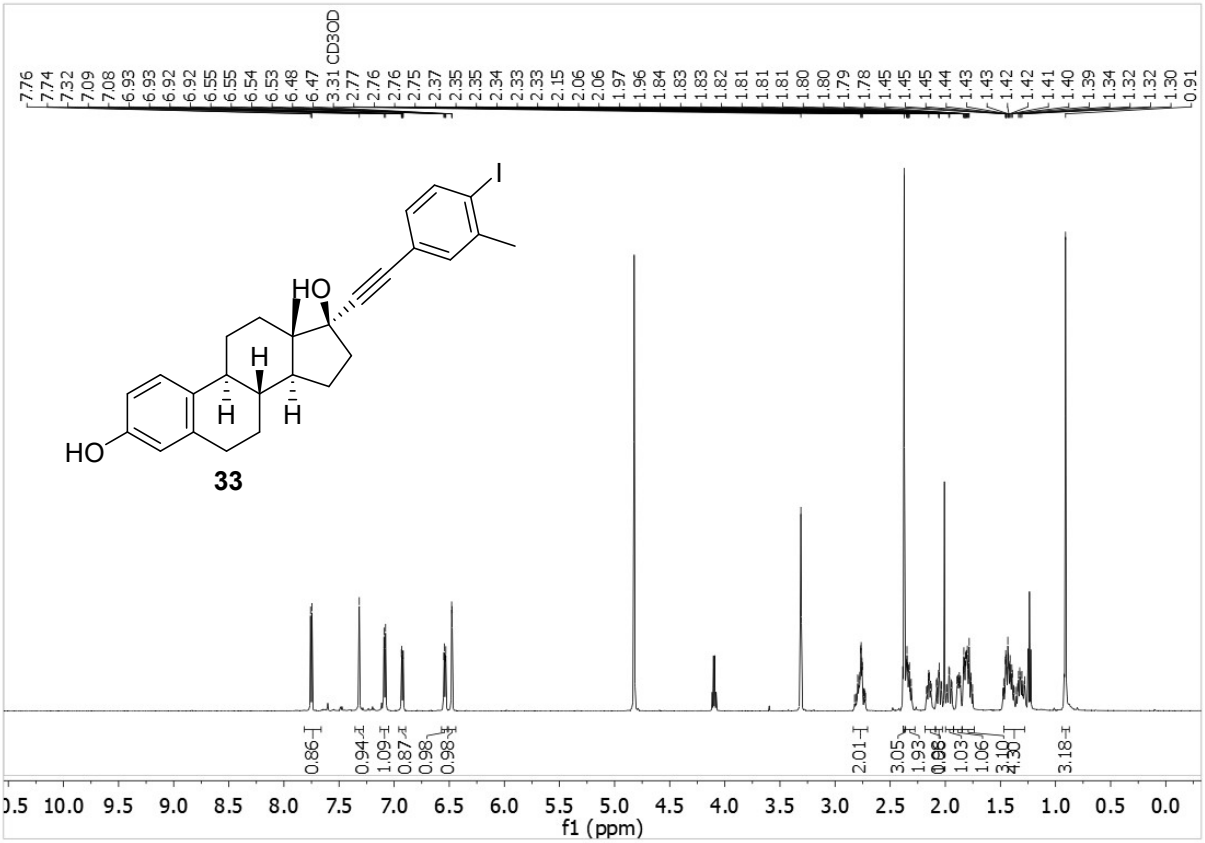
^{13}C NMR



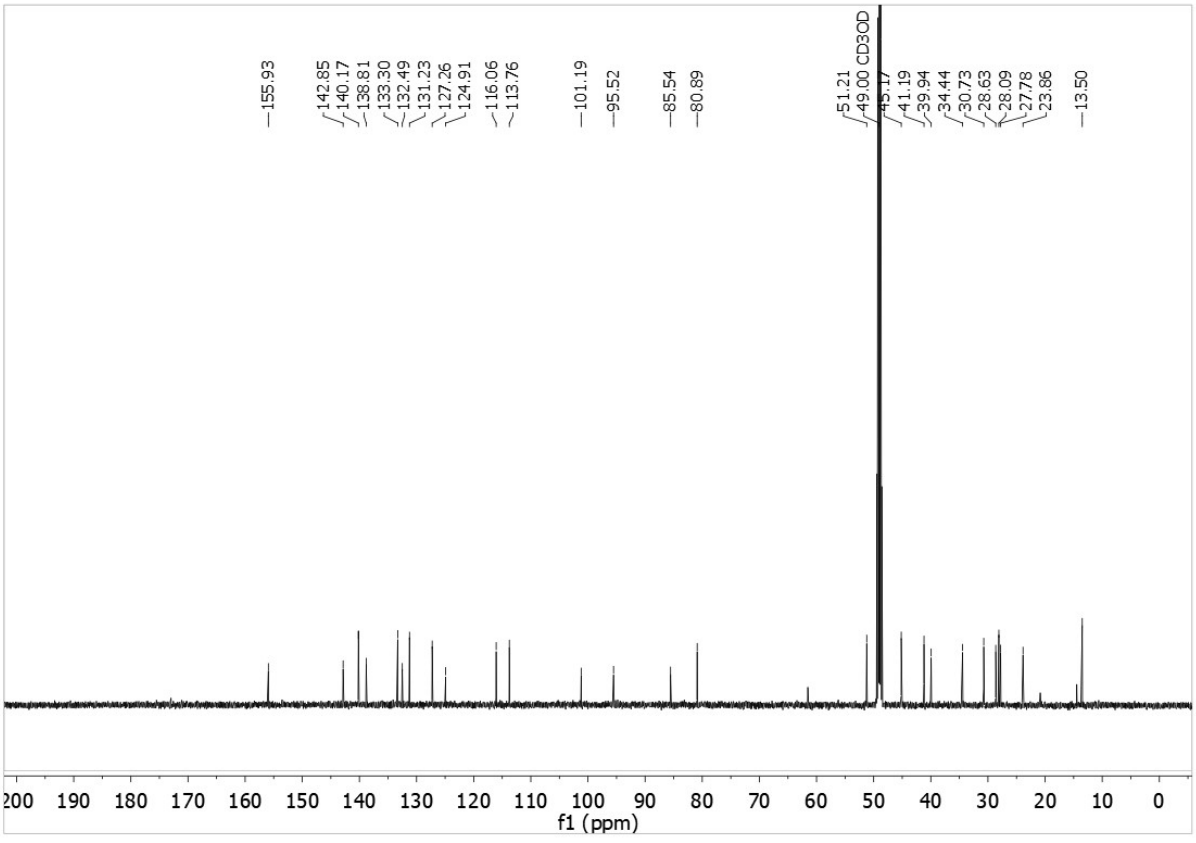
^{19}F NMR


-64.50
-64.53
-64.56
3.00
-64.3 -64.4 -64.5 -64.6 -64.7 -64.8
f1 (ppm)
3.00
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

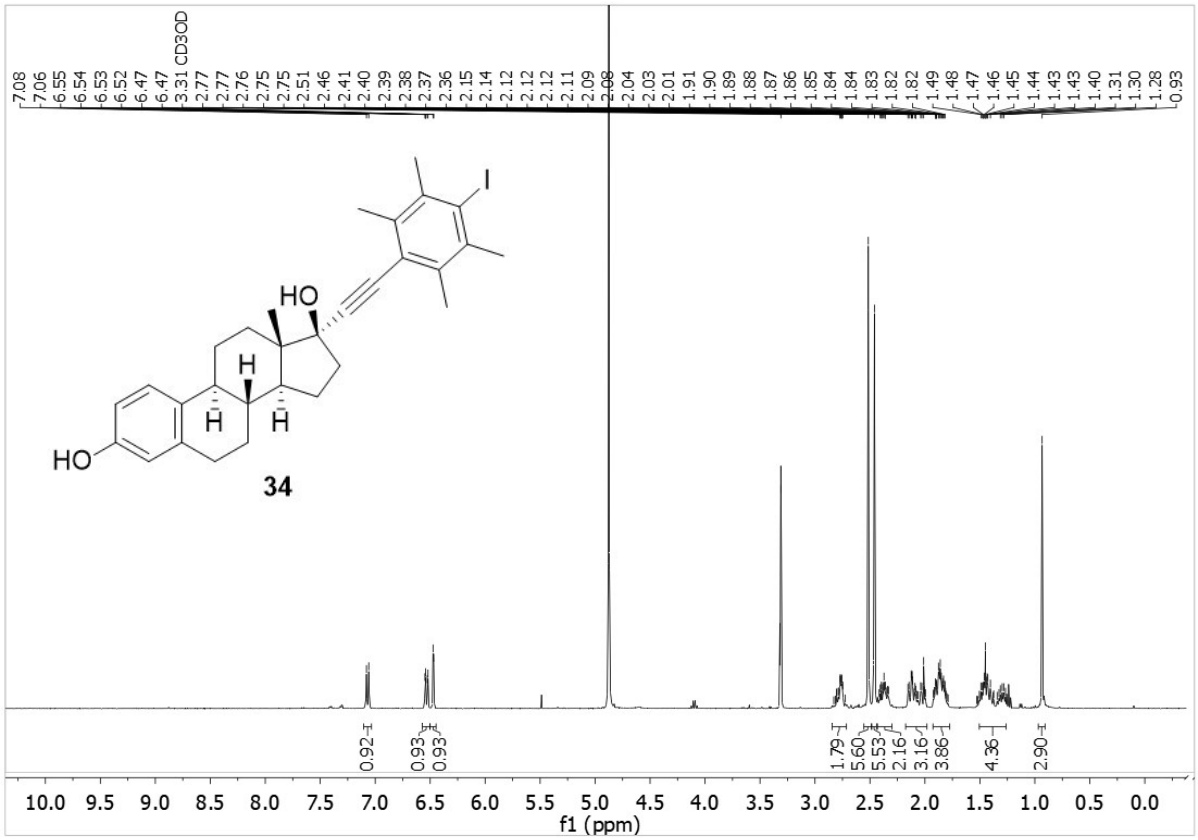
^{1}H NMR



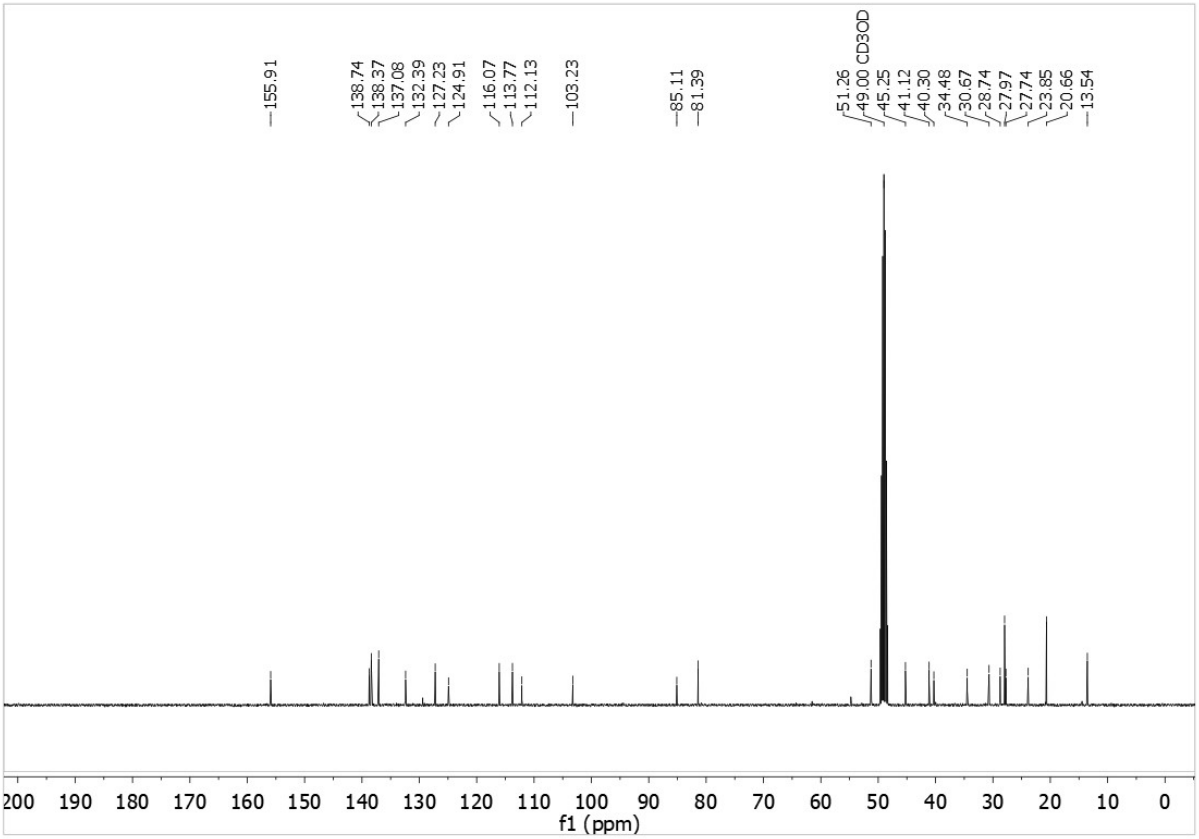
^{13}C NMR



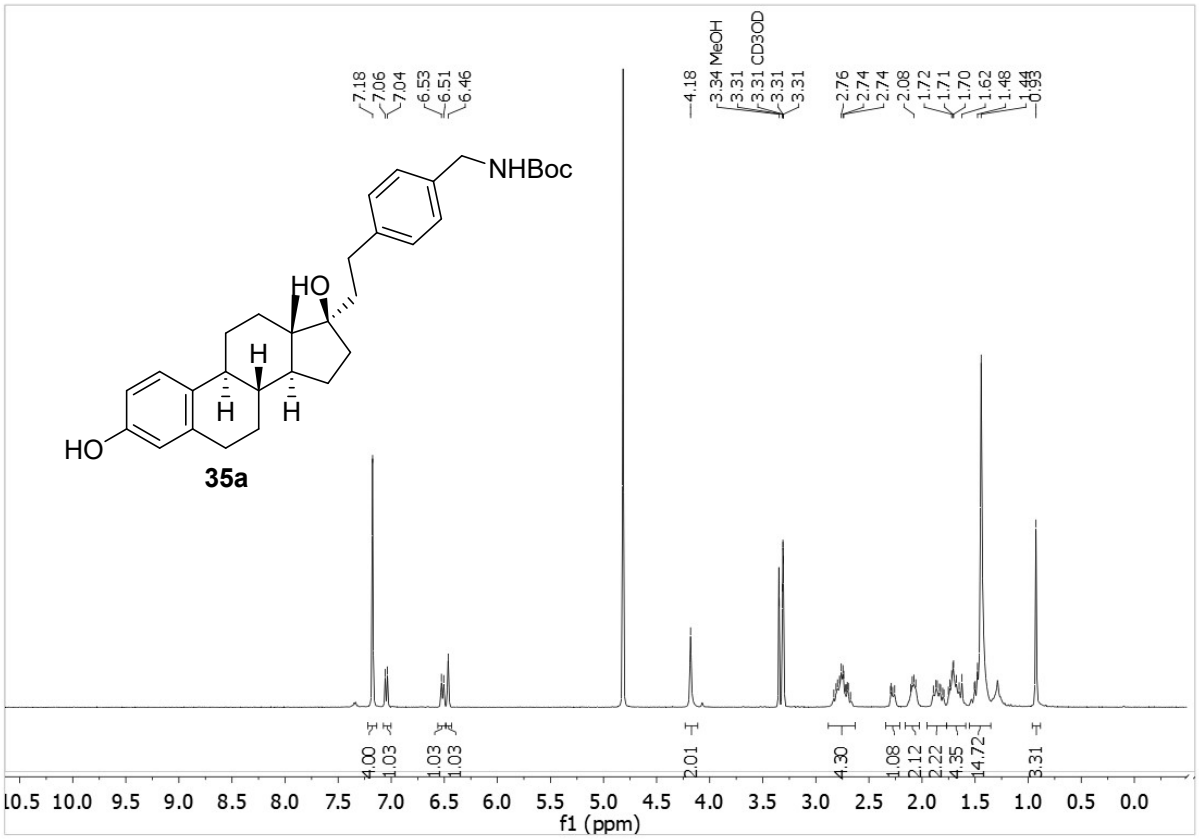
^{1}H NMR



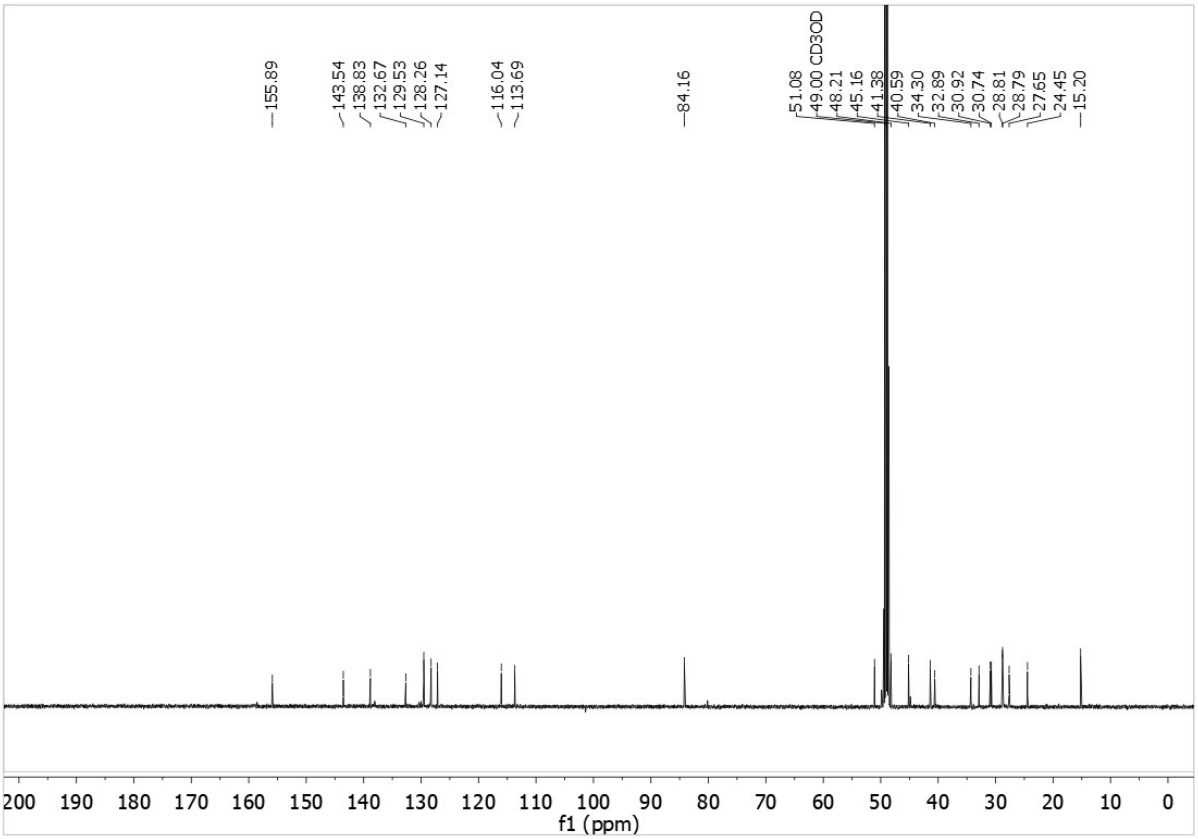
^{13}C NMR



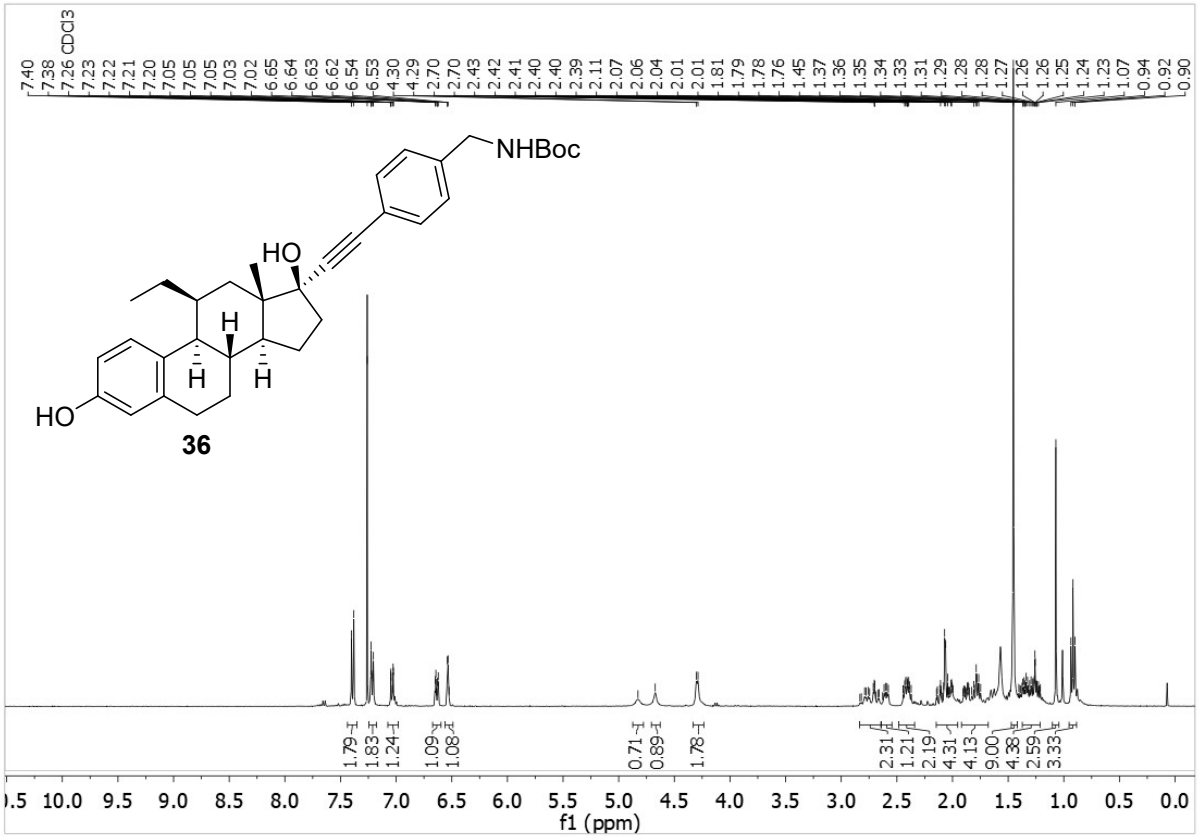
^{1}H NMR



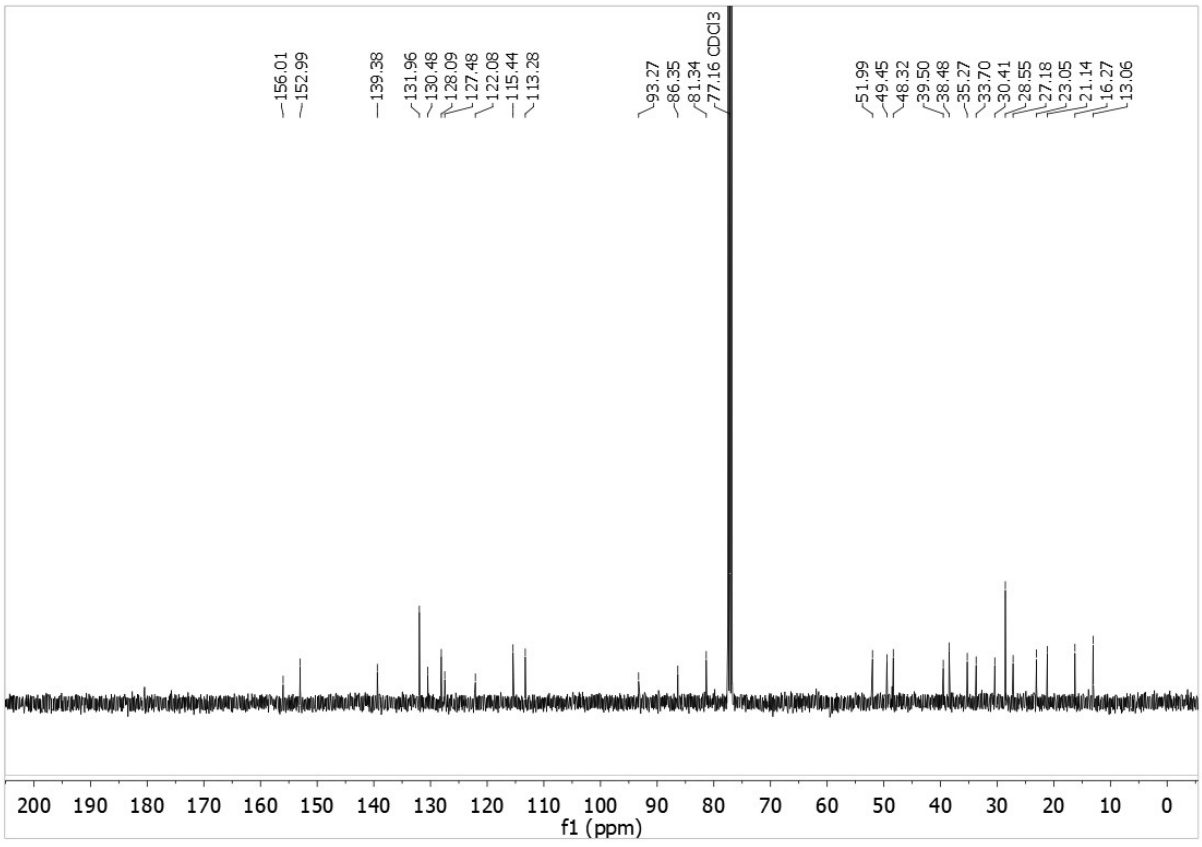
^{13}C NMR


155.89
143.54
138.83
132.67
129.53
128.26
127.14
116.04
113.69
84.16
51.08
49.00 CD3OD
48.21
45.16
41.38
40.59
34.30
32.89
30.92
30.74
28.81
28.79
27.65
24.45
15.20
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

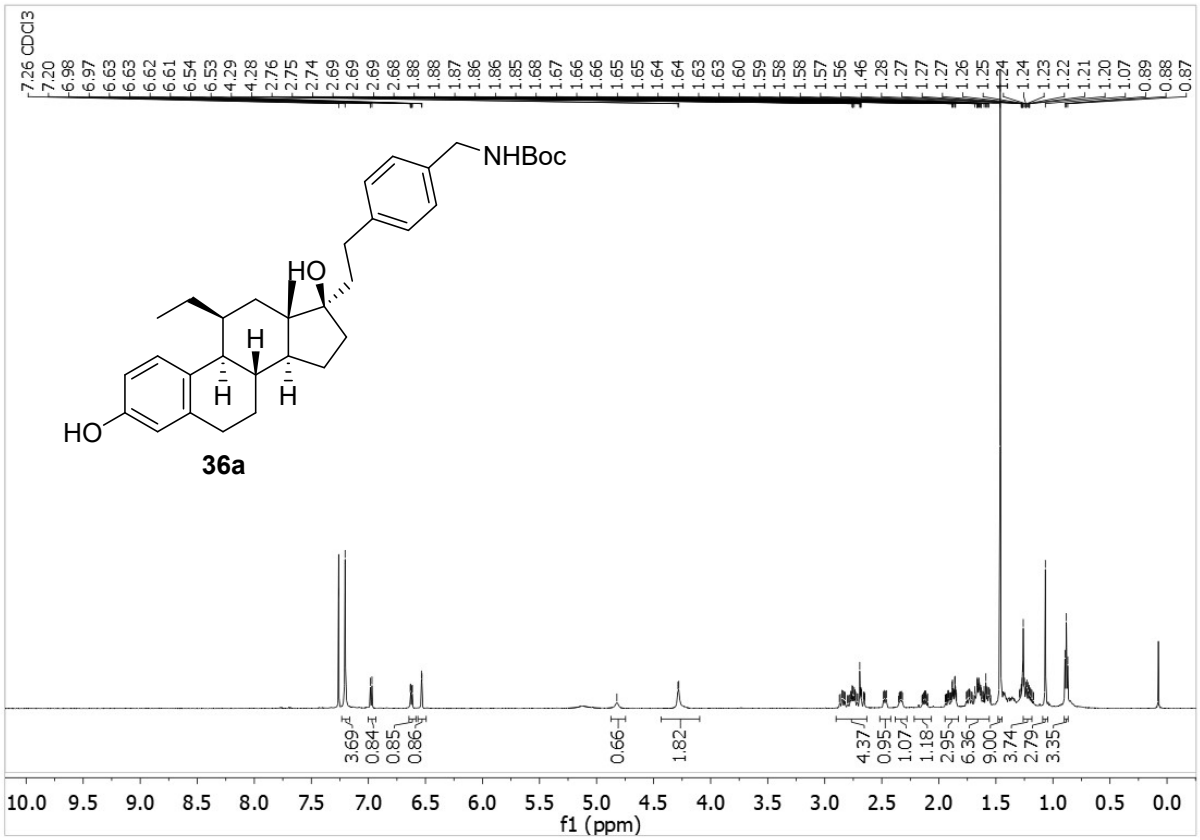
^{1}H NMR



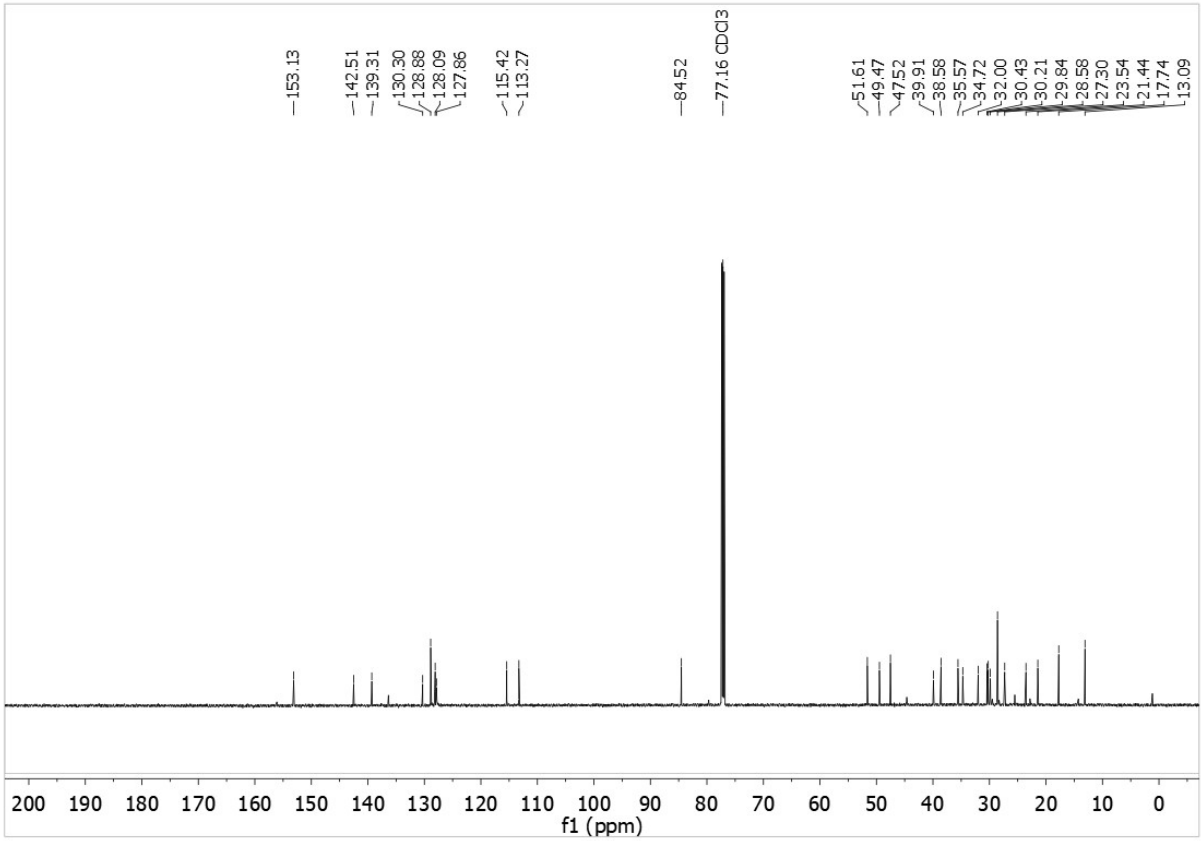
^{13}C NMR



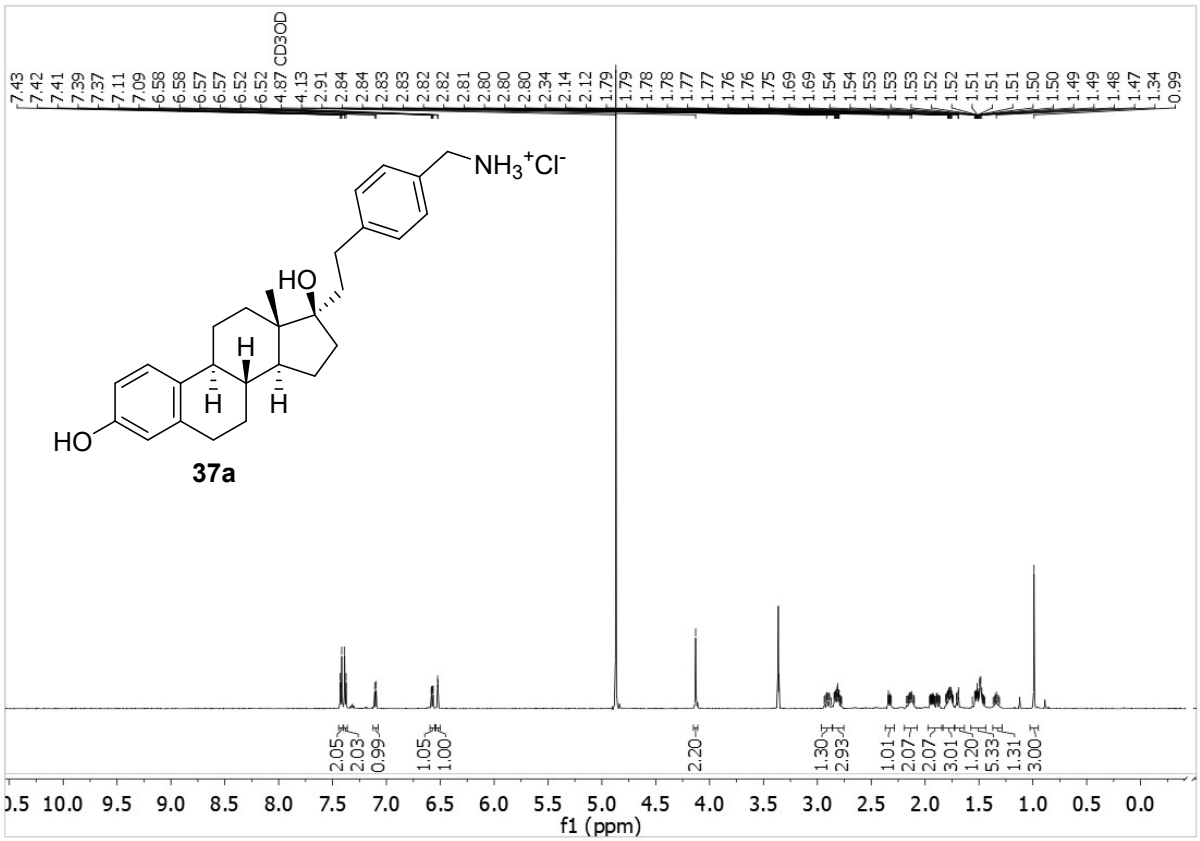
^{1}H NMR



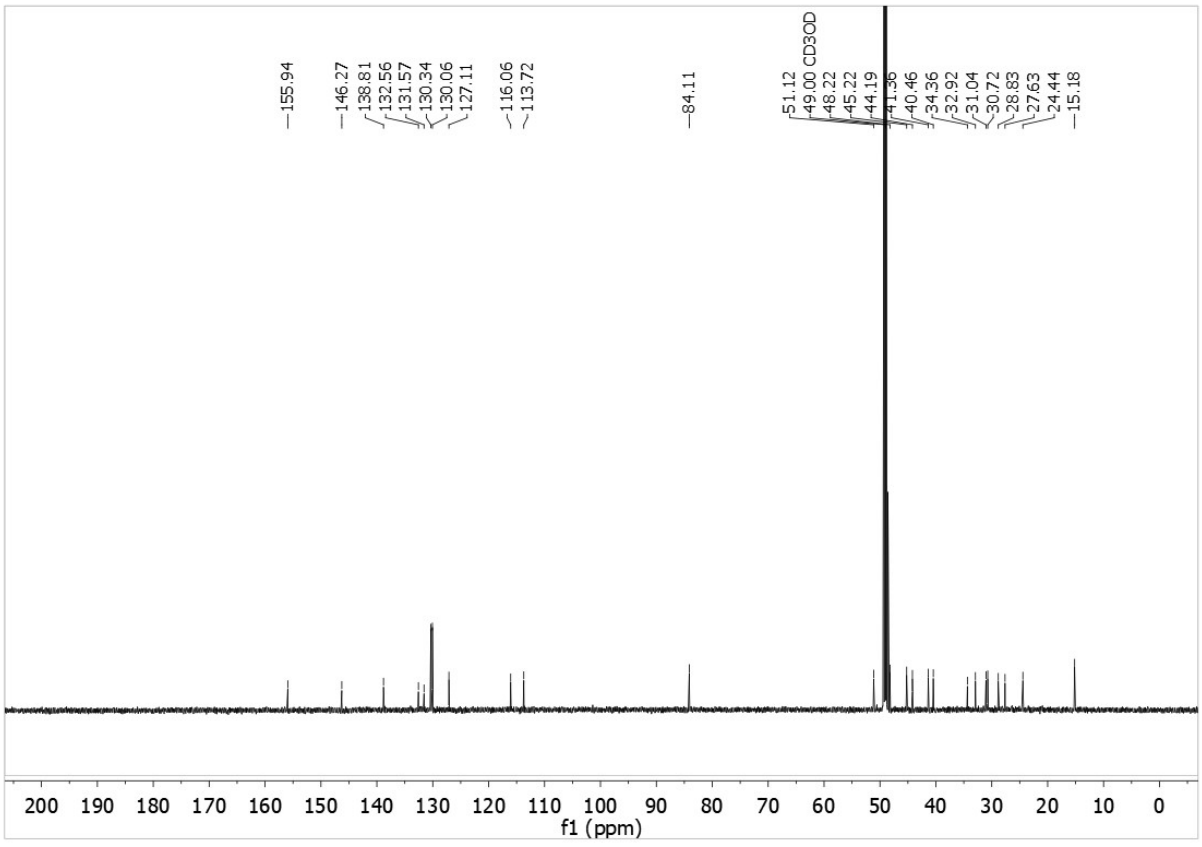
^{13}C NMR



^{1}H NMR

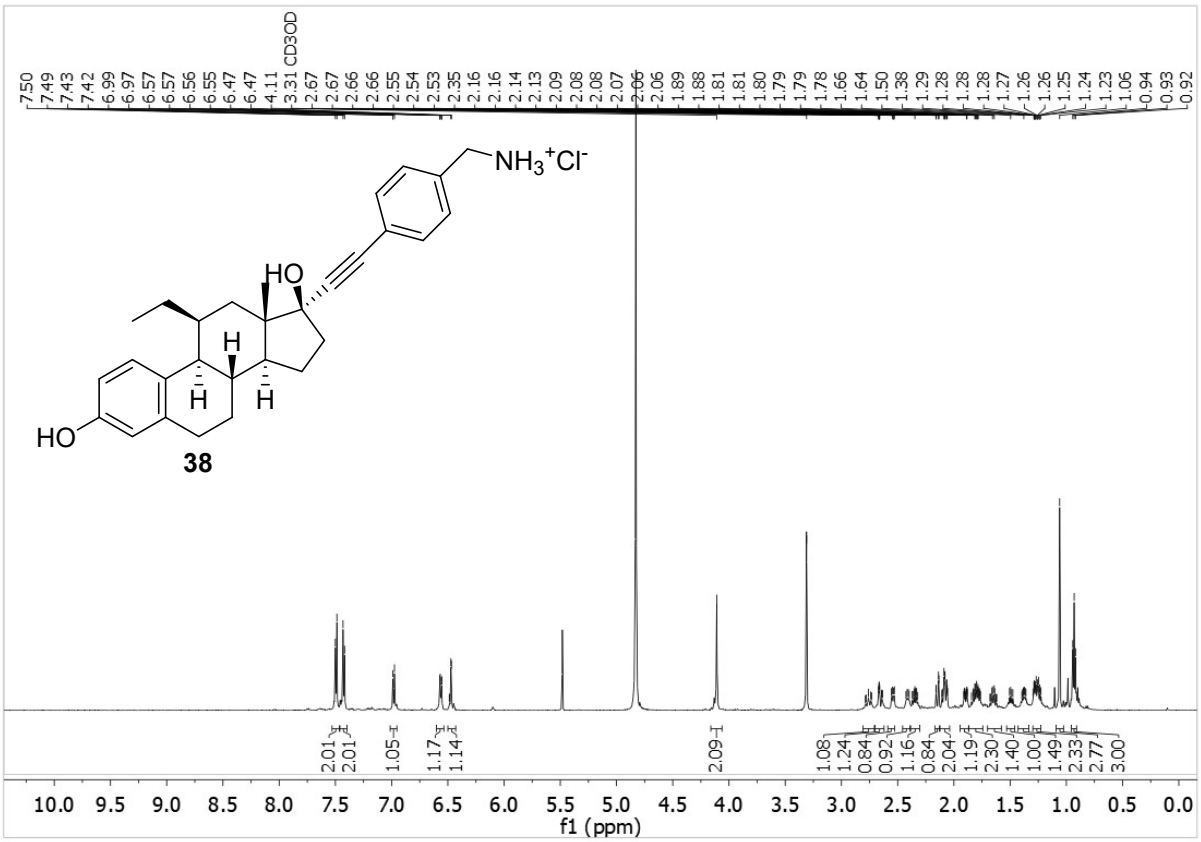


^{13}C NMR

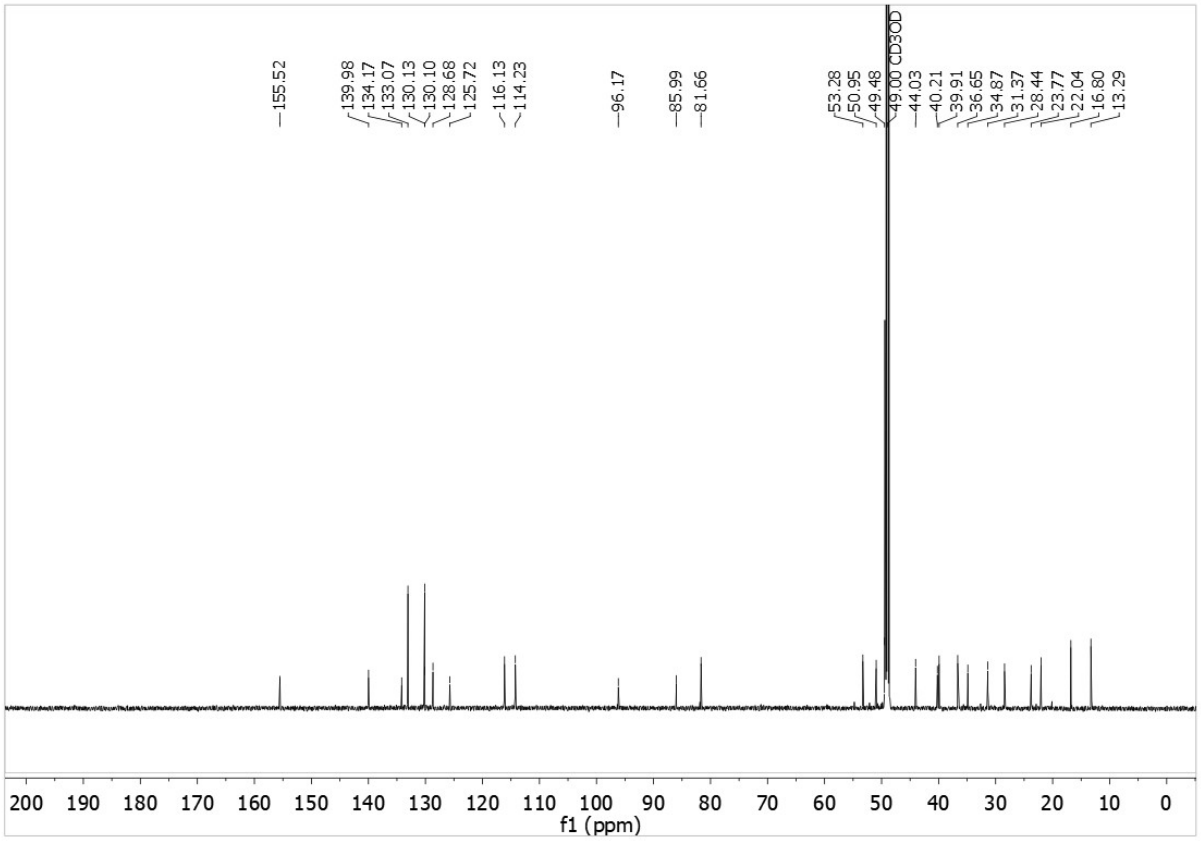


Supporting information

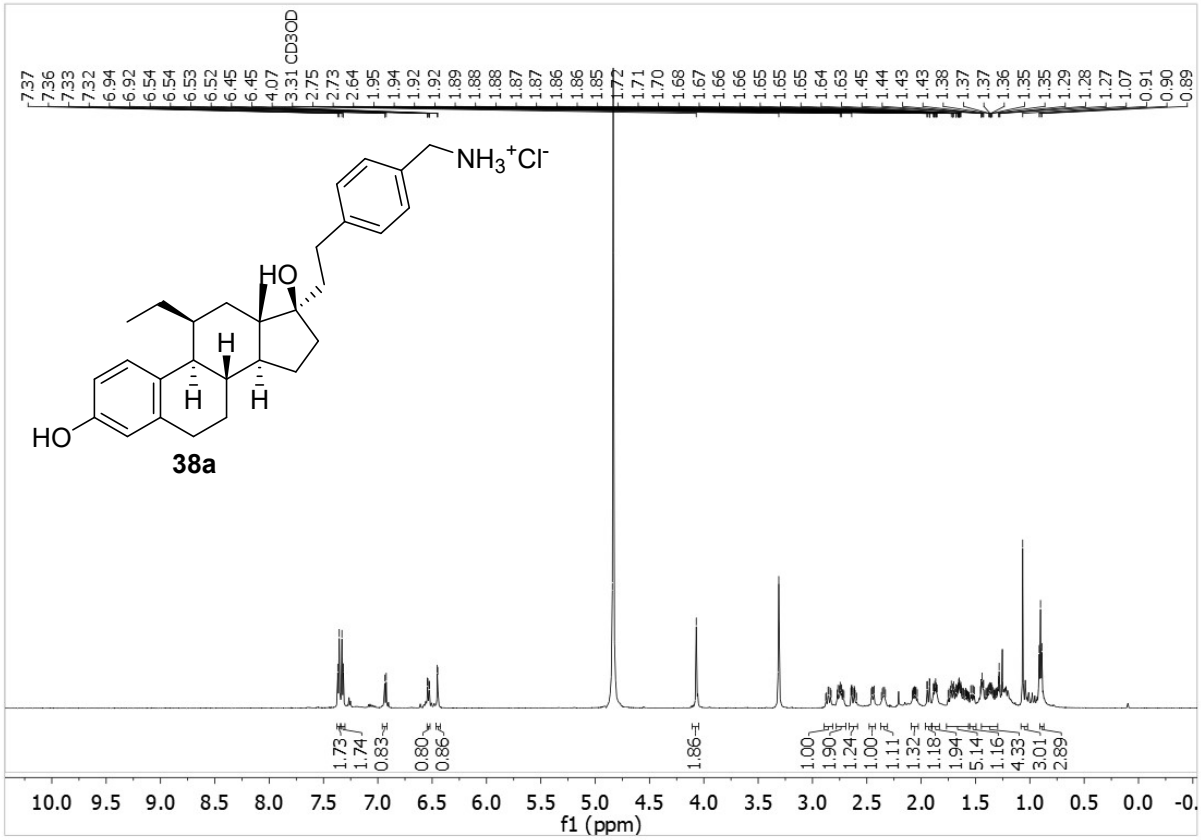
^{1}H NMR



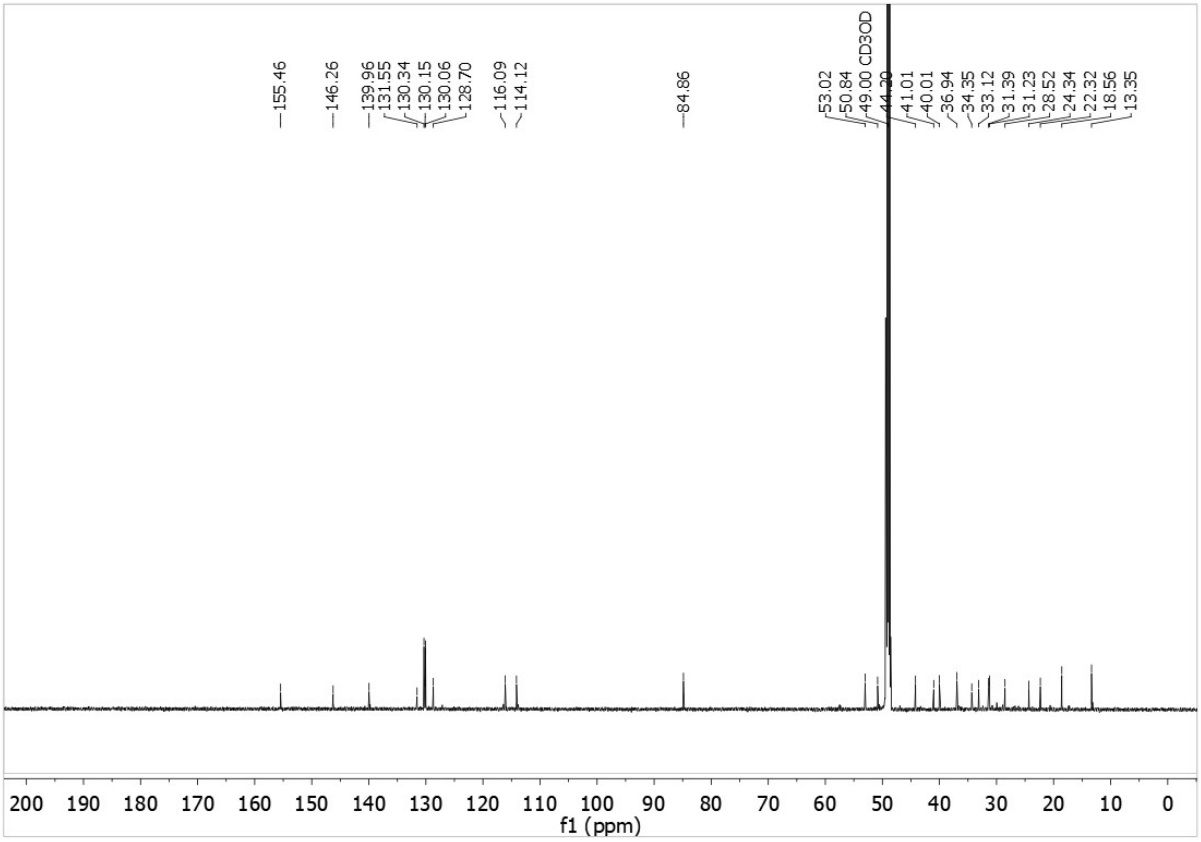
^{13}C NMR



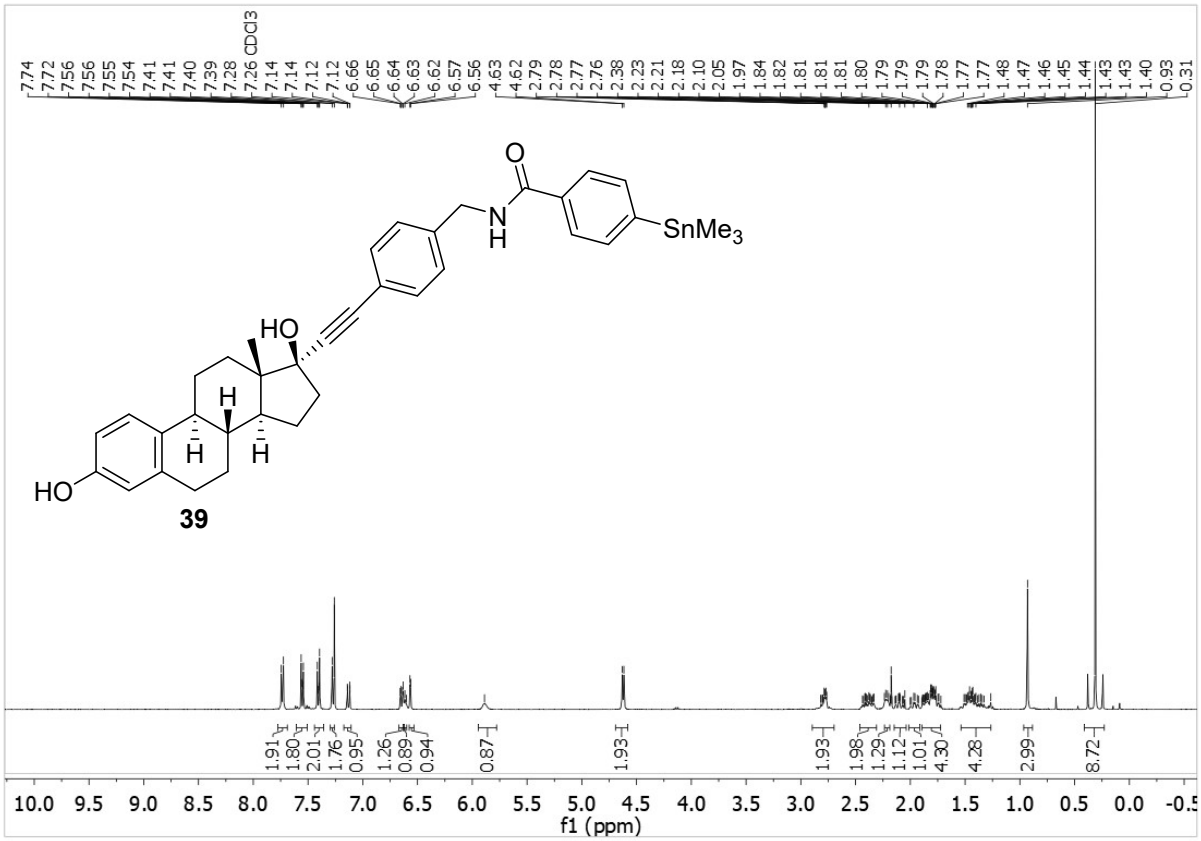
^{1}H NMR



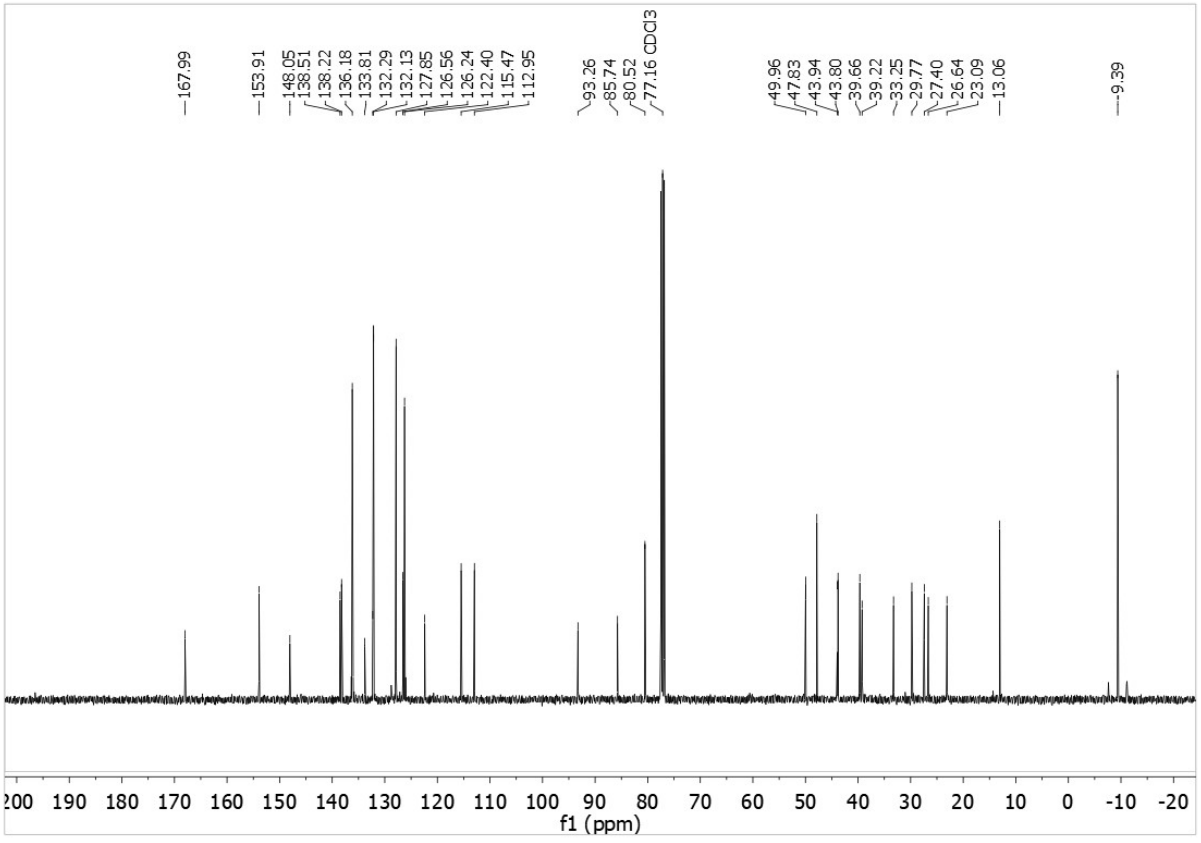
^{13}C NMR



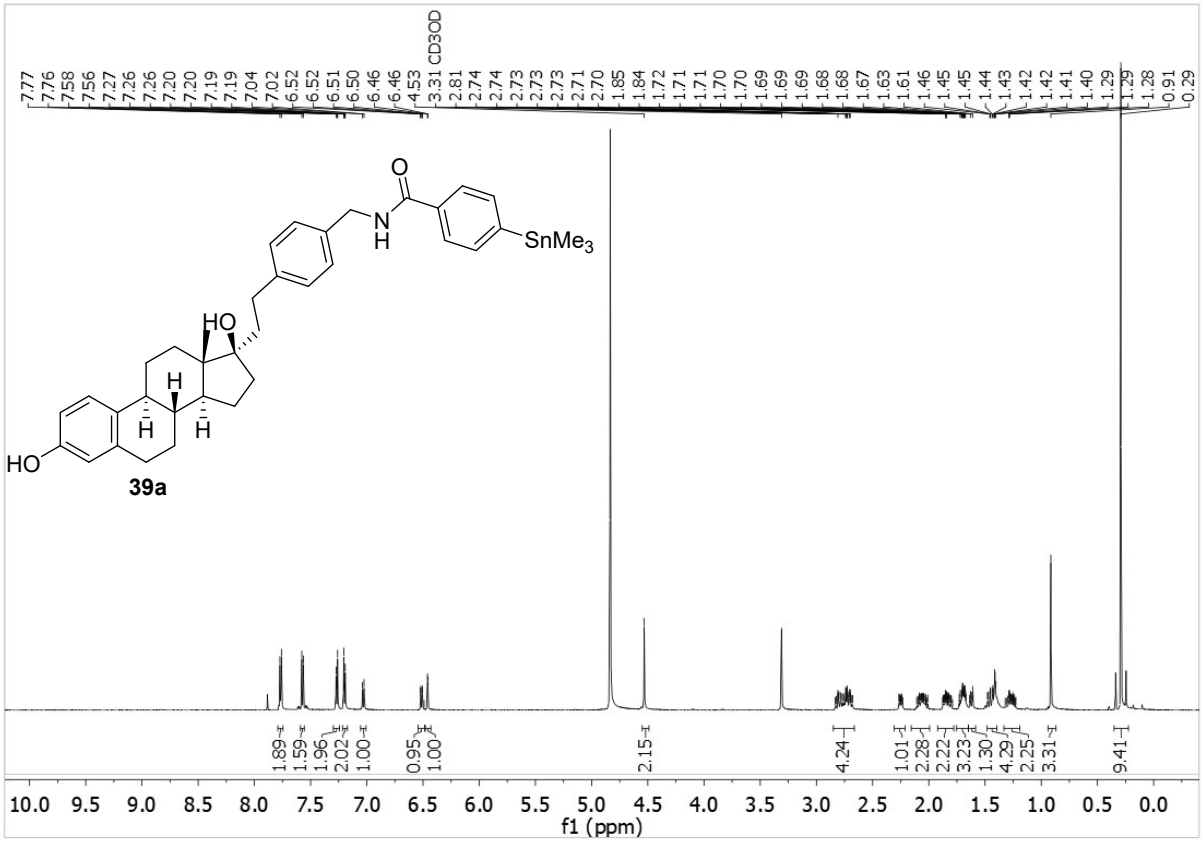
^{1}H NMR



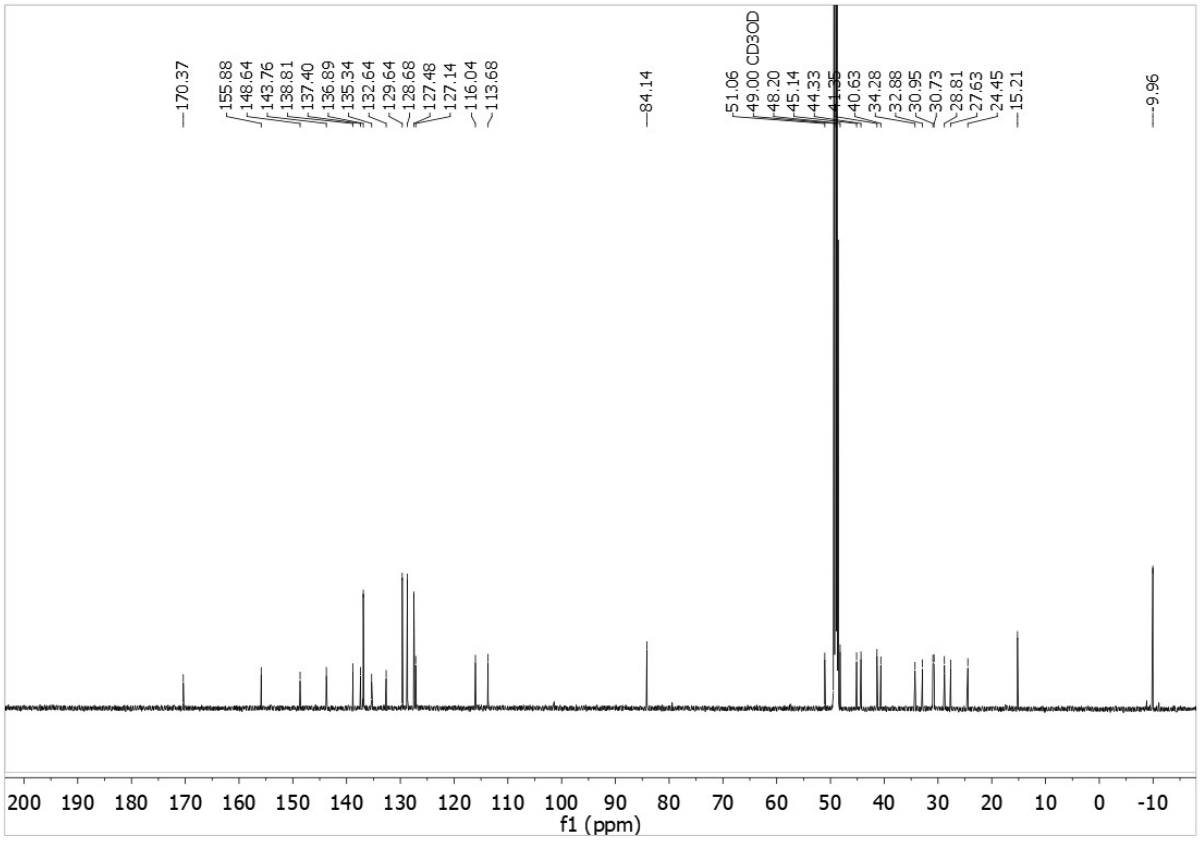
^{13}C NMR



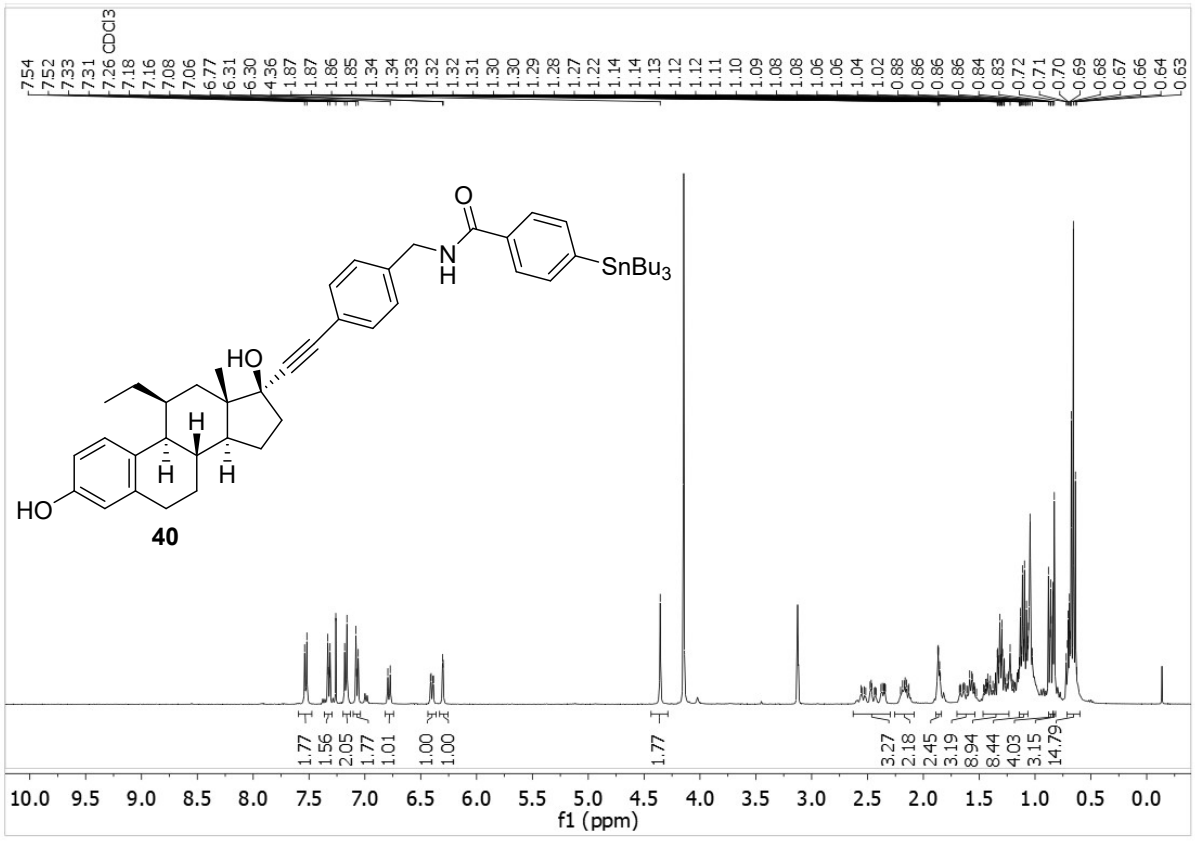
^{1}H NMR



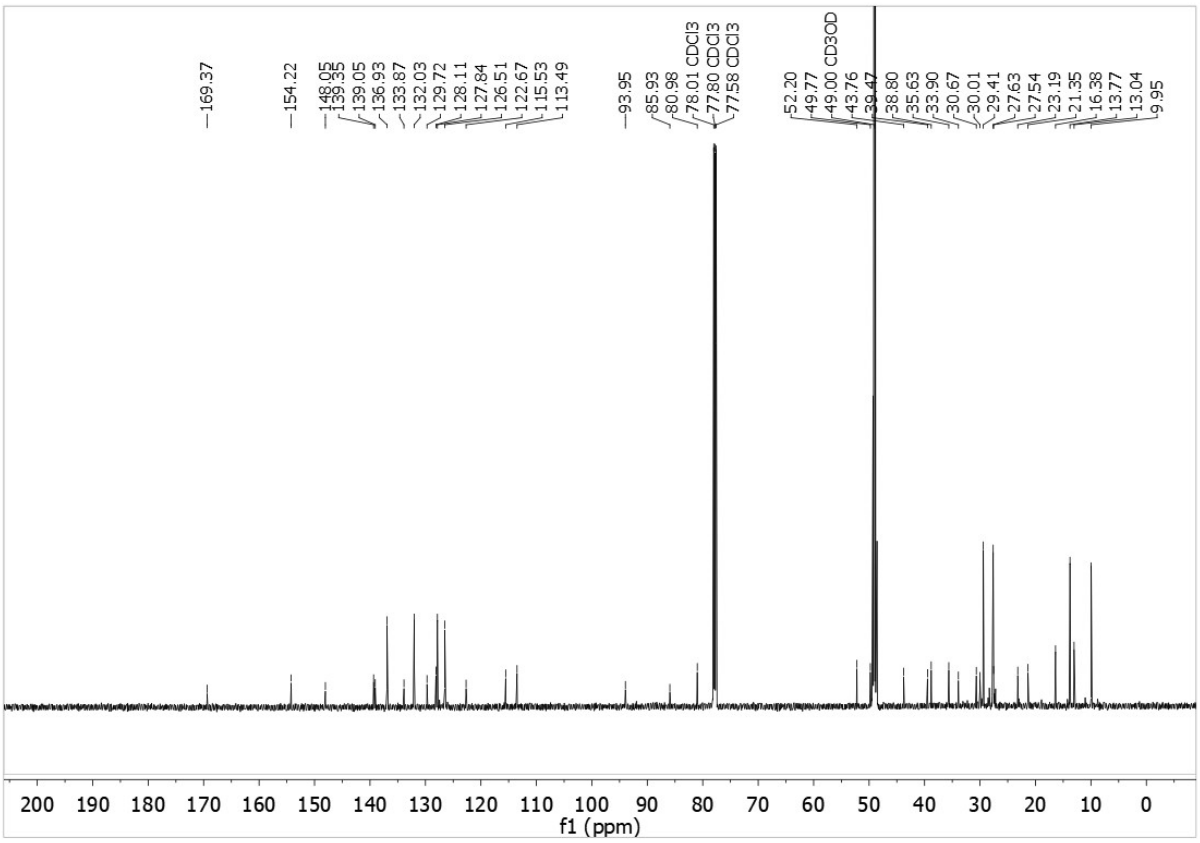
^{13}C NMR



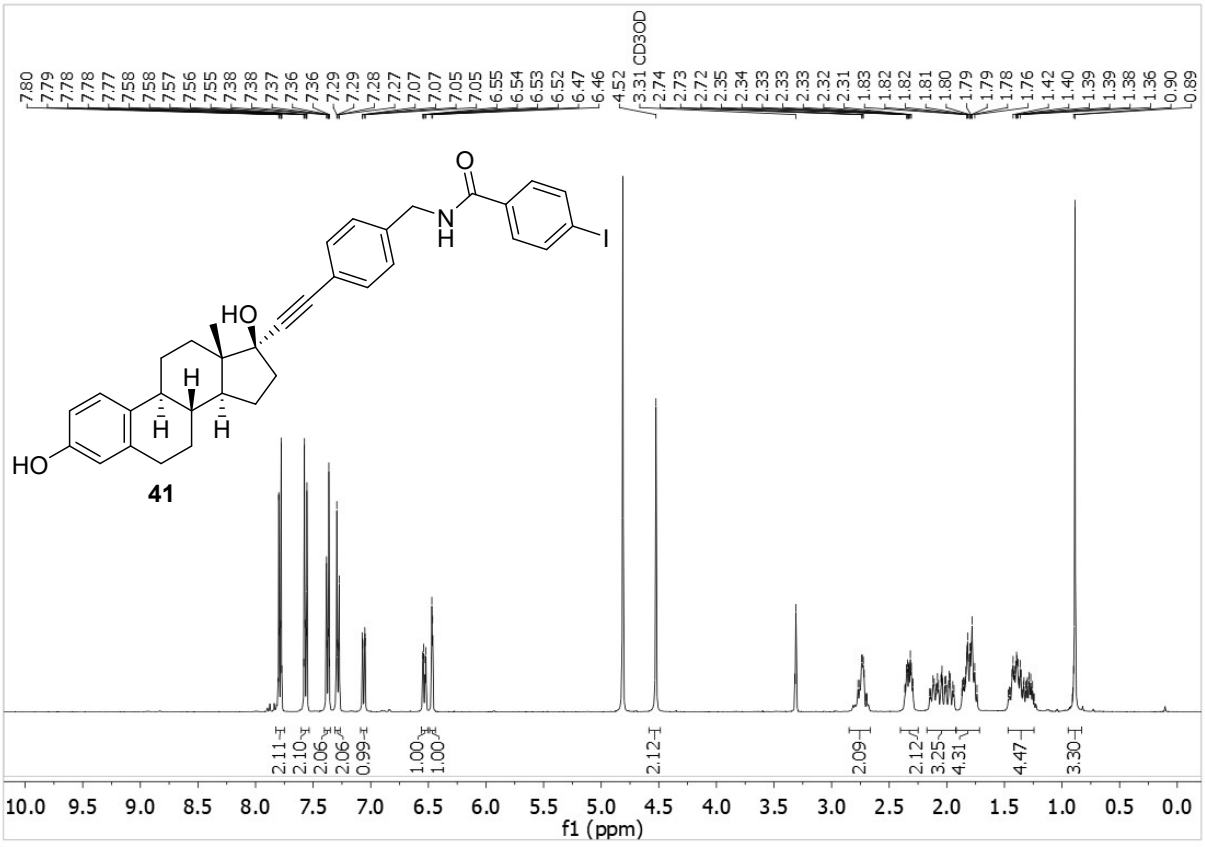
^{1}H NMR



^{13}C NMR



^{1}H NMR



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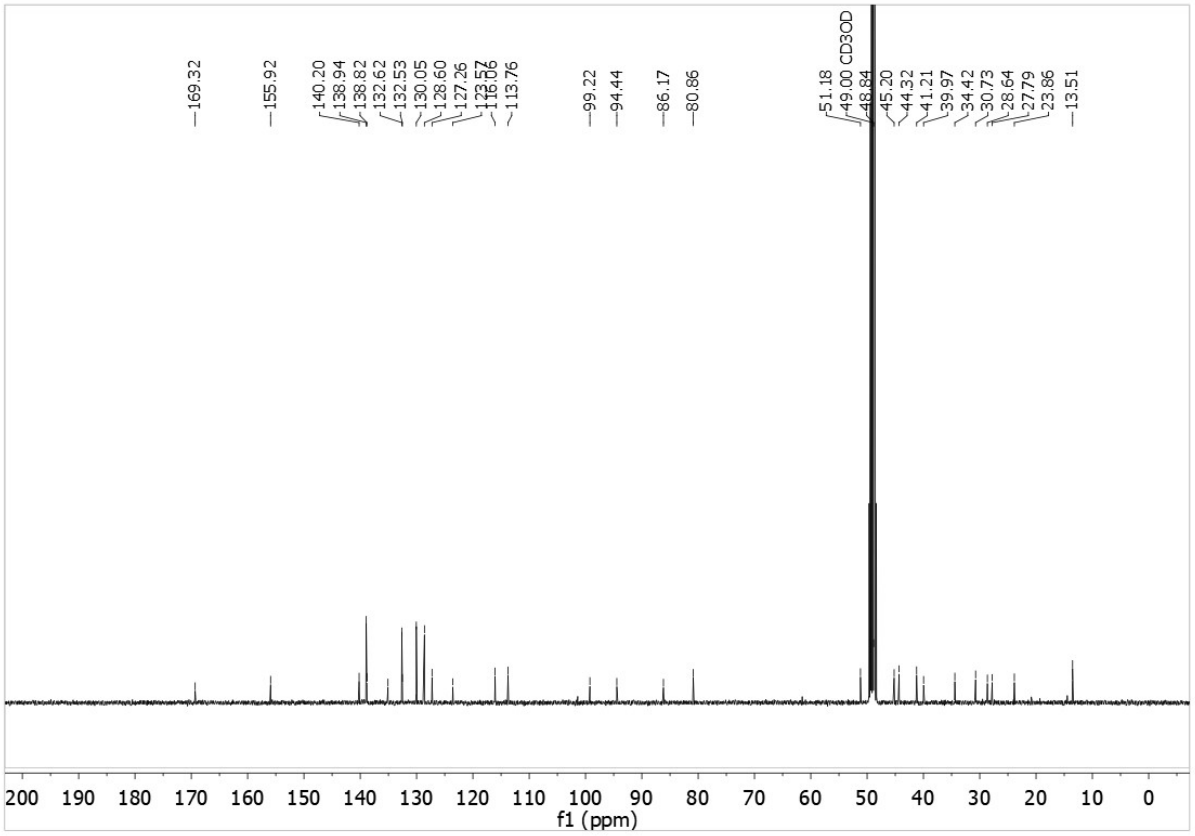
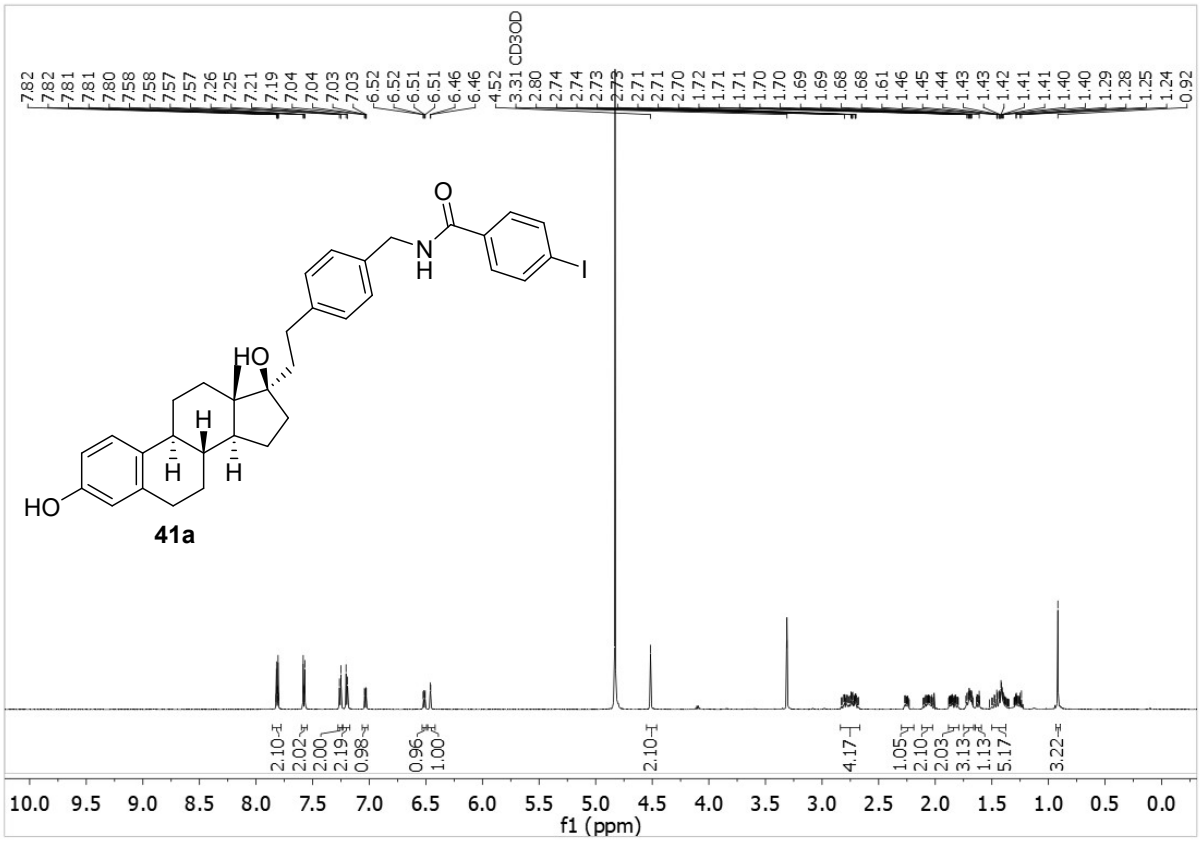


^{1}H NMR



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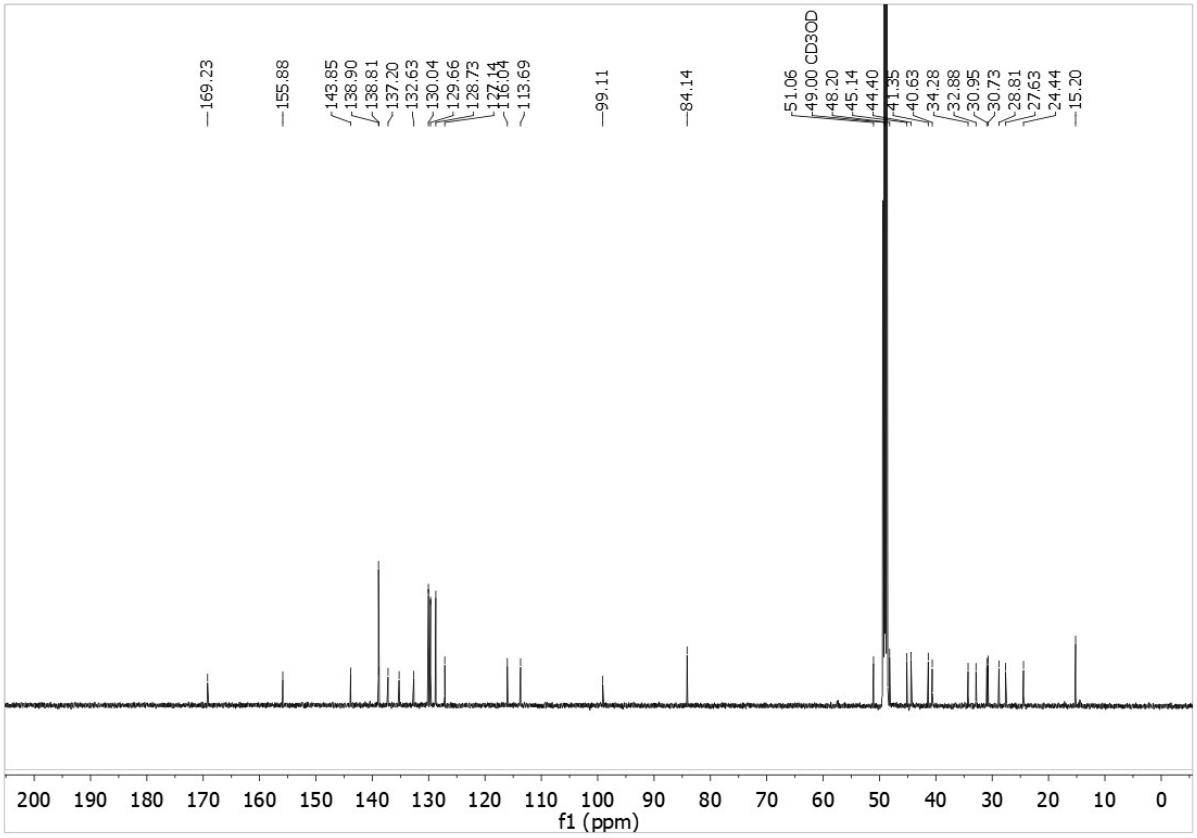
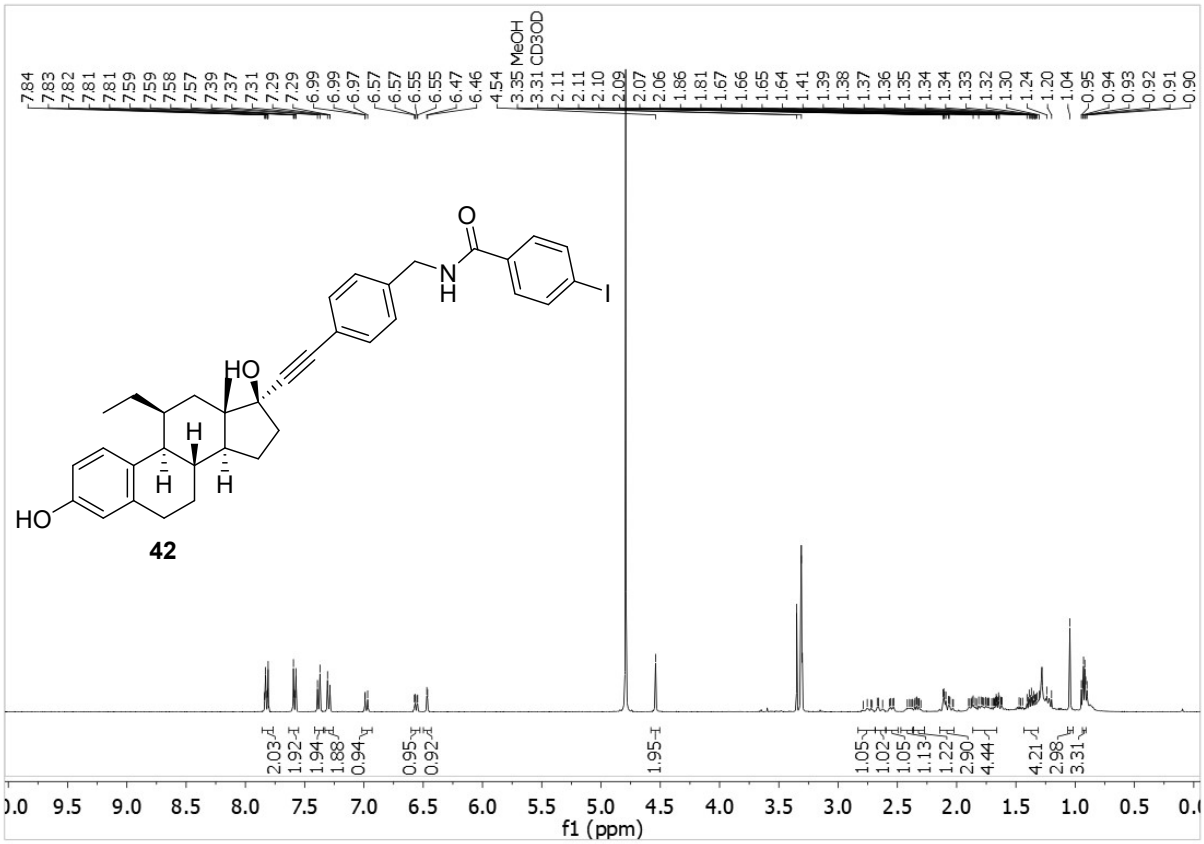
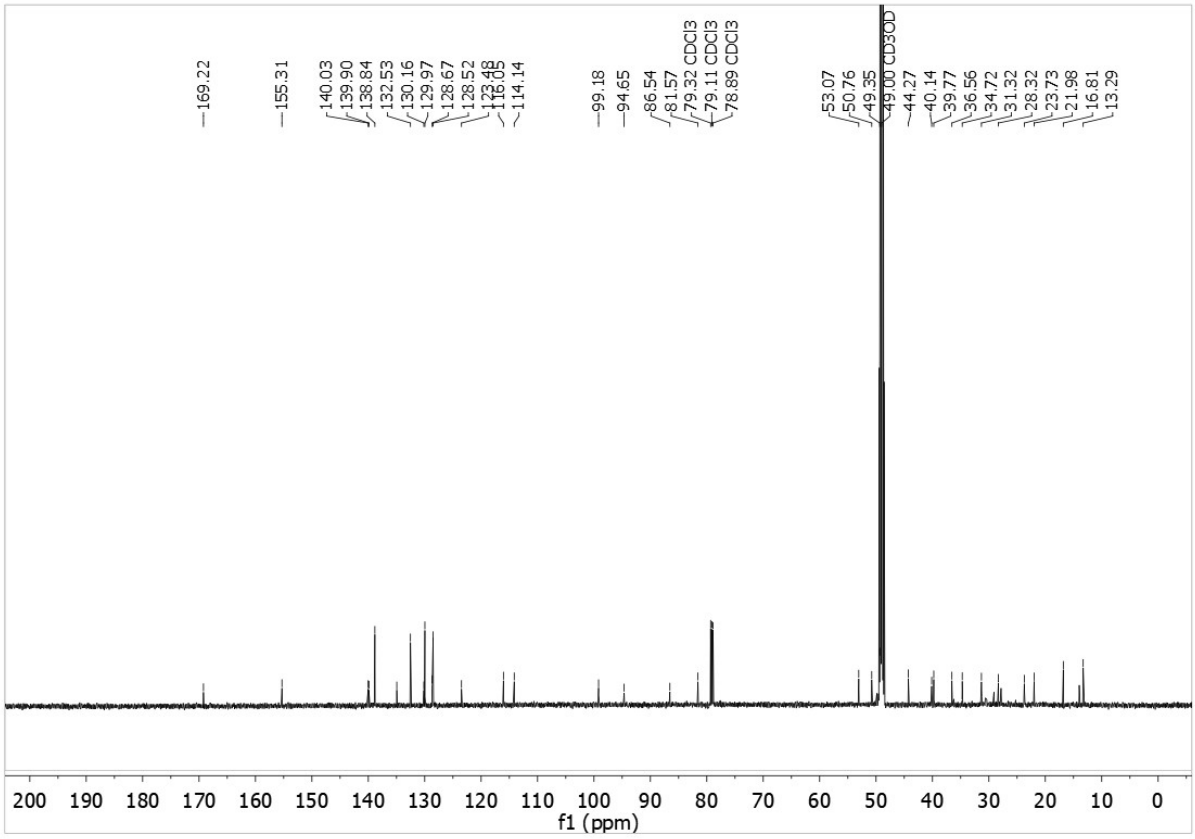

169.23
155.88
143.85
138.90
138.81
137.20
132.63
130.04
129.66
128.73
127.14
116.04
113.69
99.11
84.14
51.06
49.00 CD3OD
48.20
45.14
44.40
41.35
40.63
34.28
32.88
30.95
30.73
28.81
27.63
24.44
15.20
f1 (ppm)

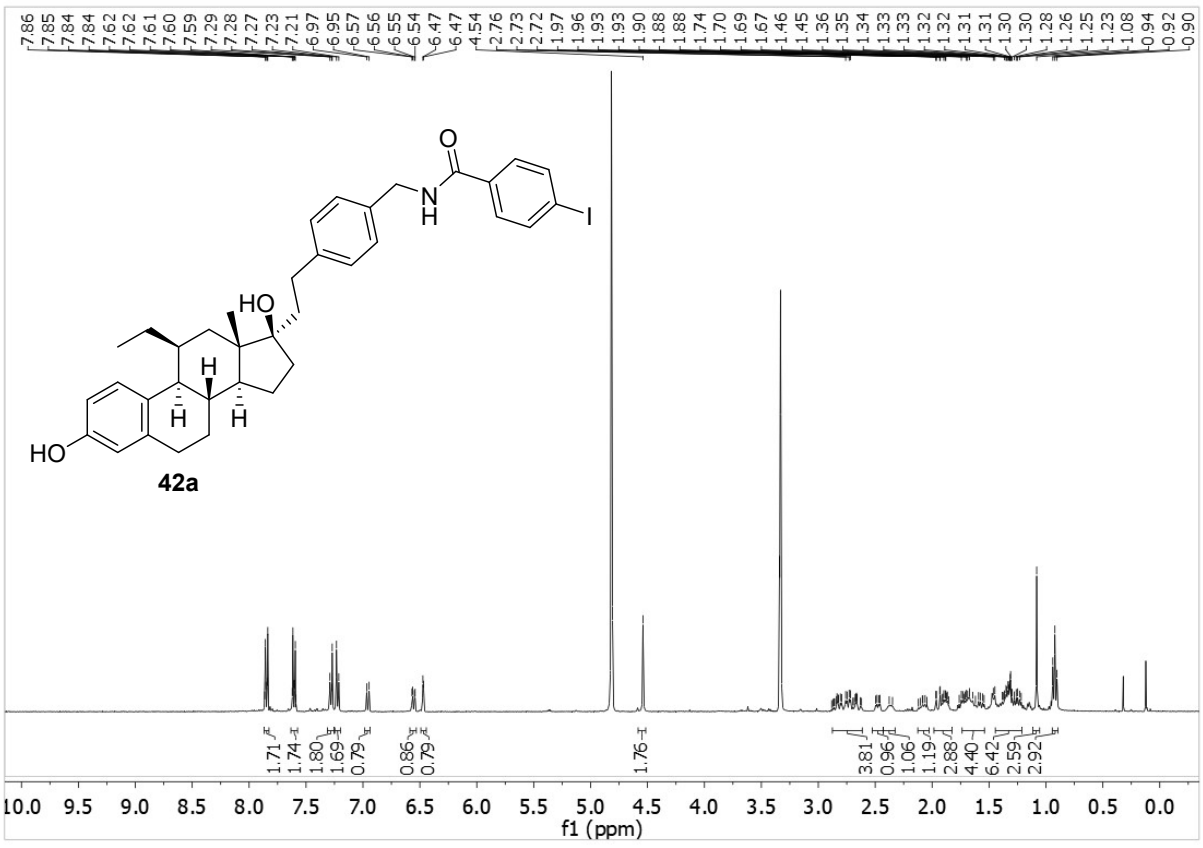
^{1}H NMR


3.35 MeOH
3.31 CD3OD
HO
HO
H
H
H
O
N
H
I
42
f1 (ppm)

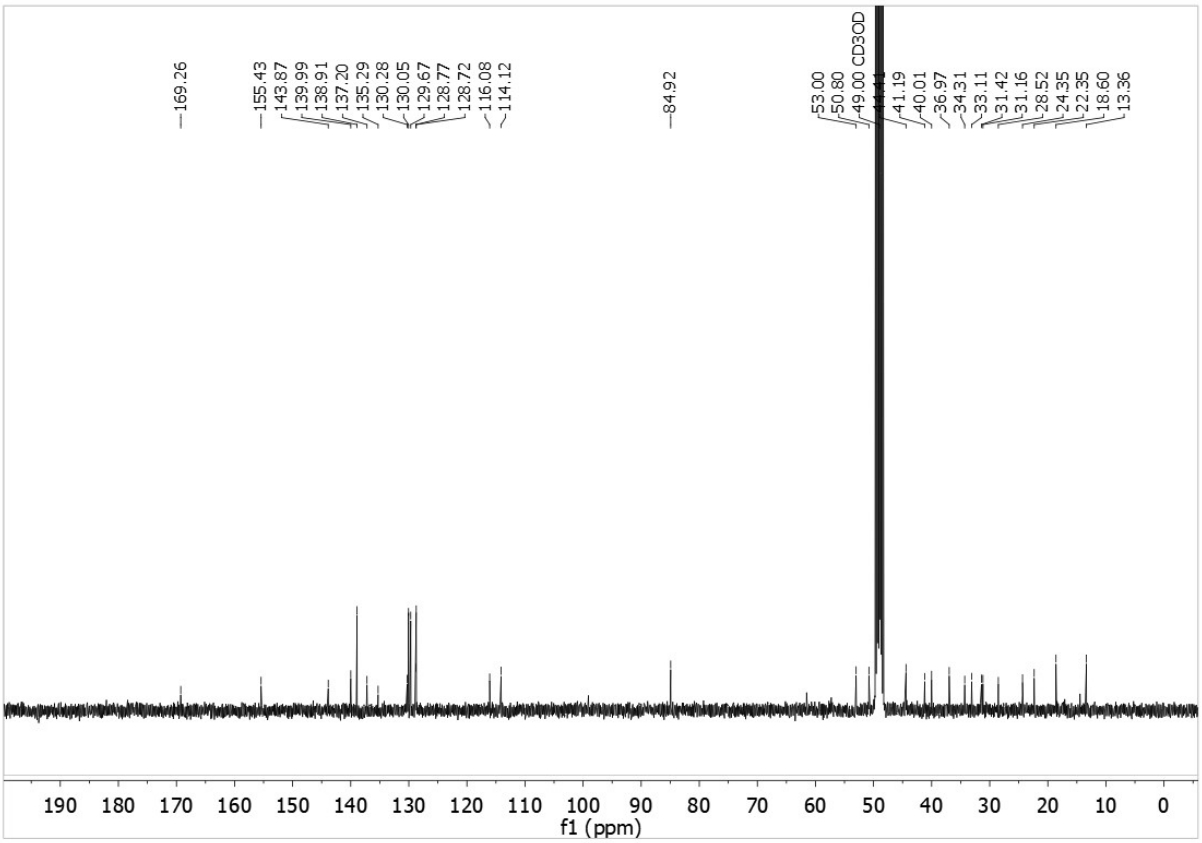
^{13}C NMR



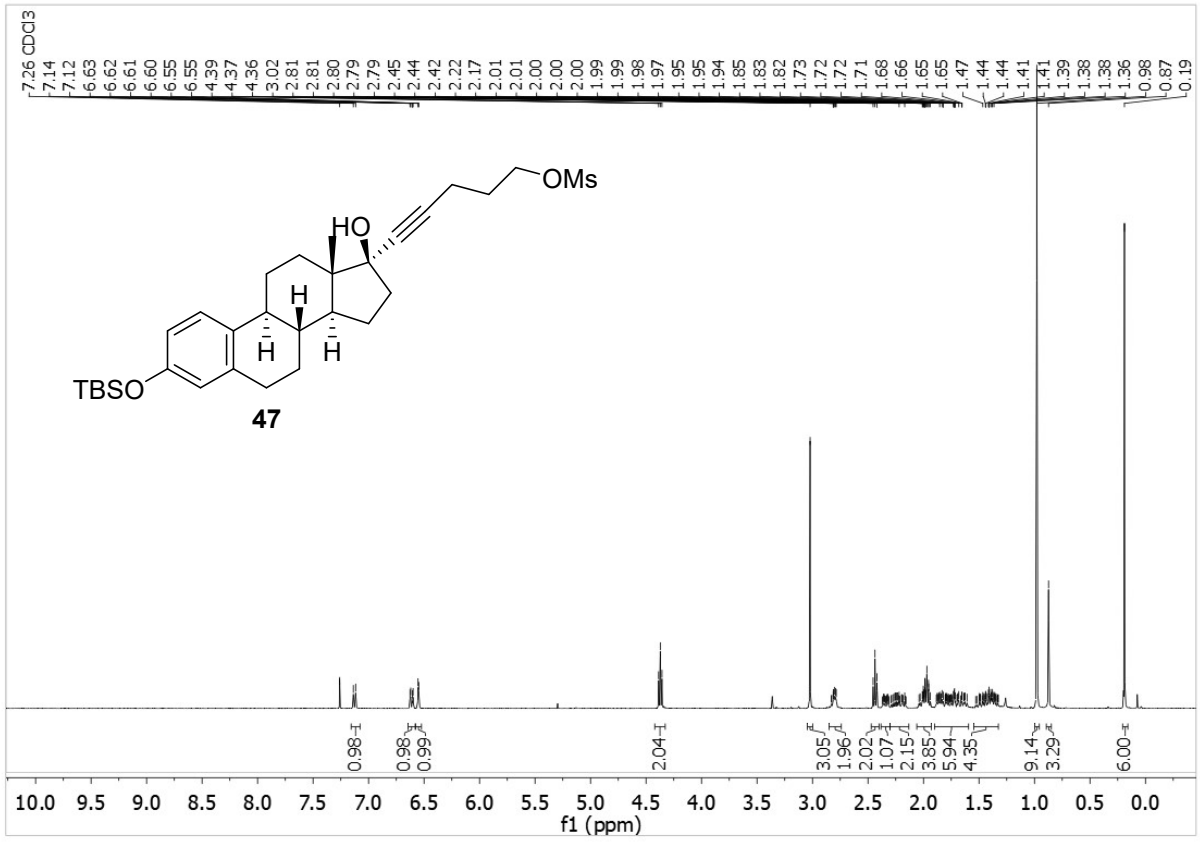
^{1}H NMR



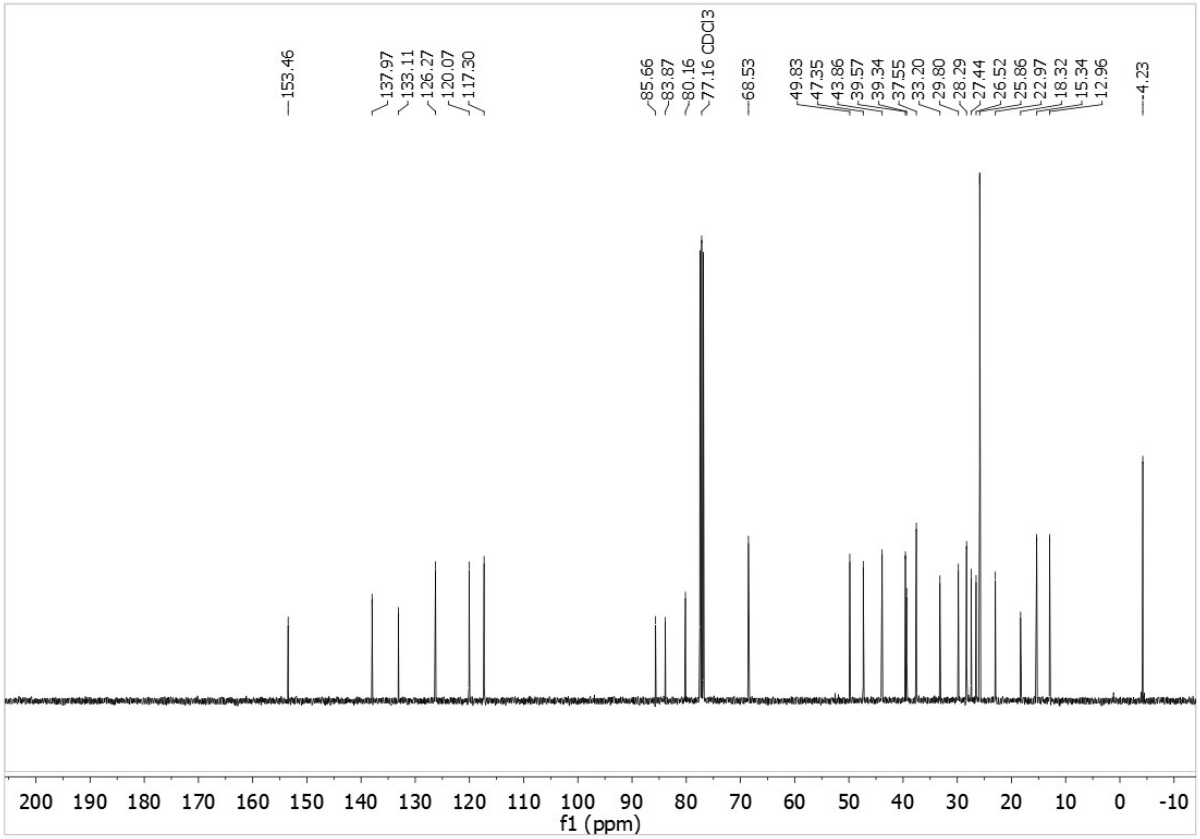
^{13}C NMR



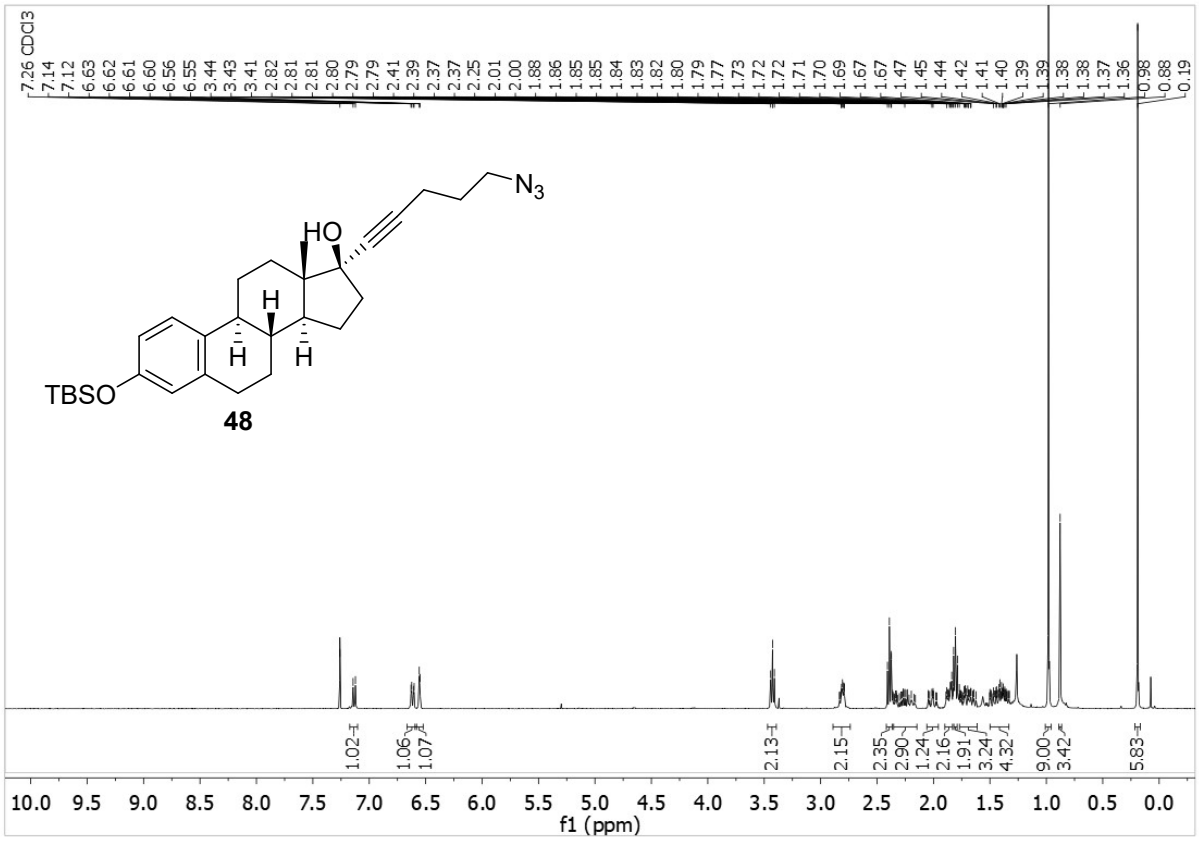
^{1}H NMR



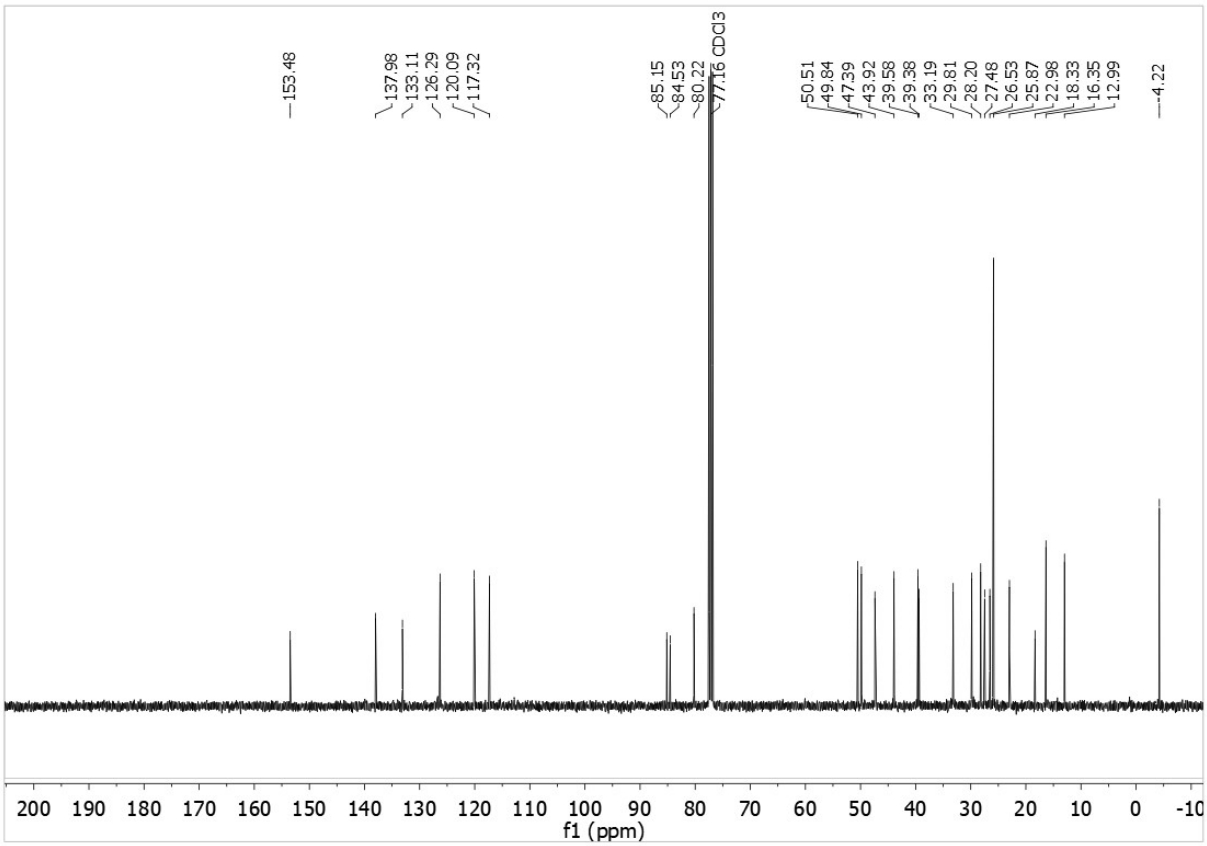
^{13}C NMR



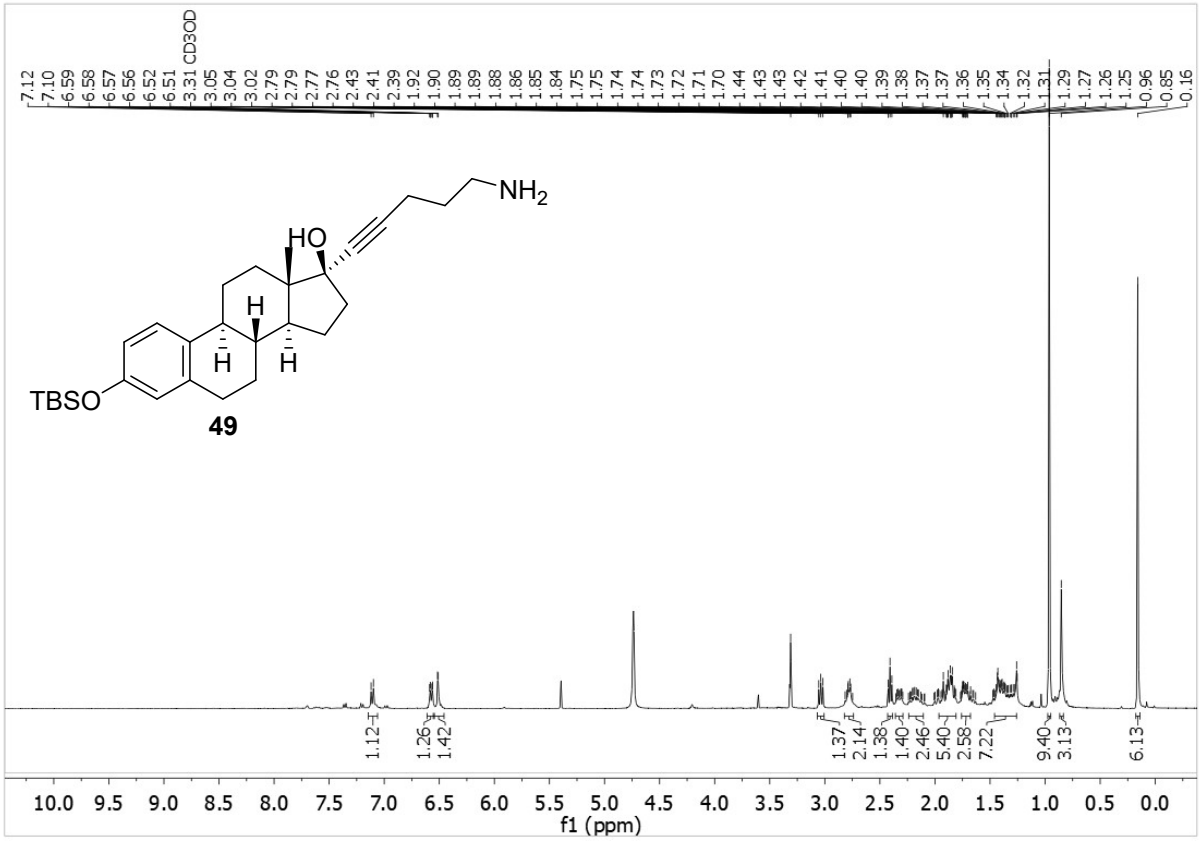
^{1}H NMR



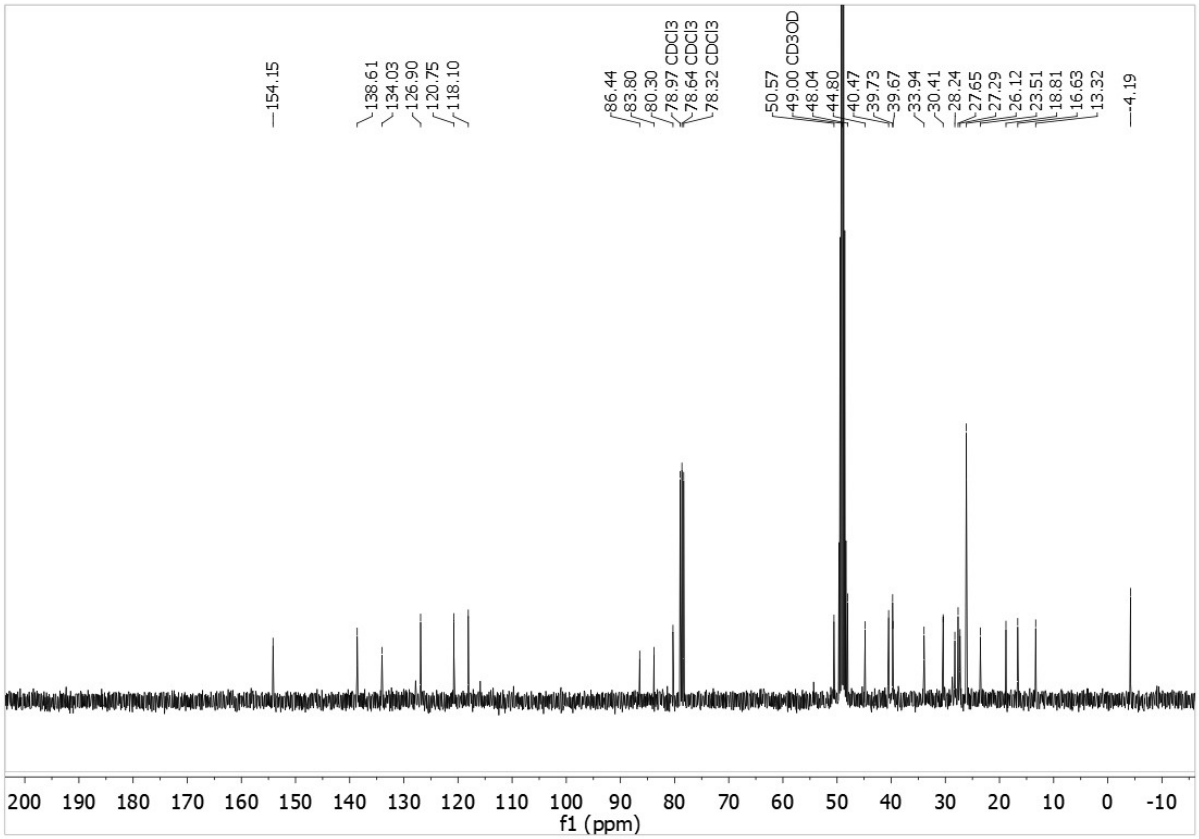
^{13}C NMR



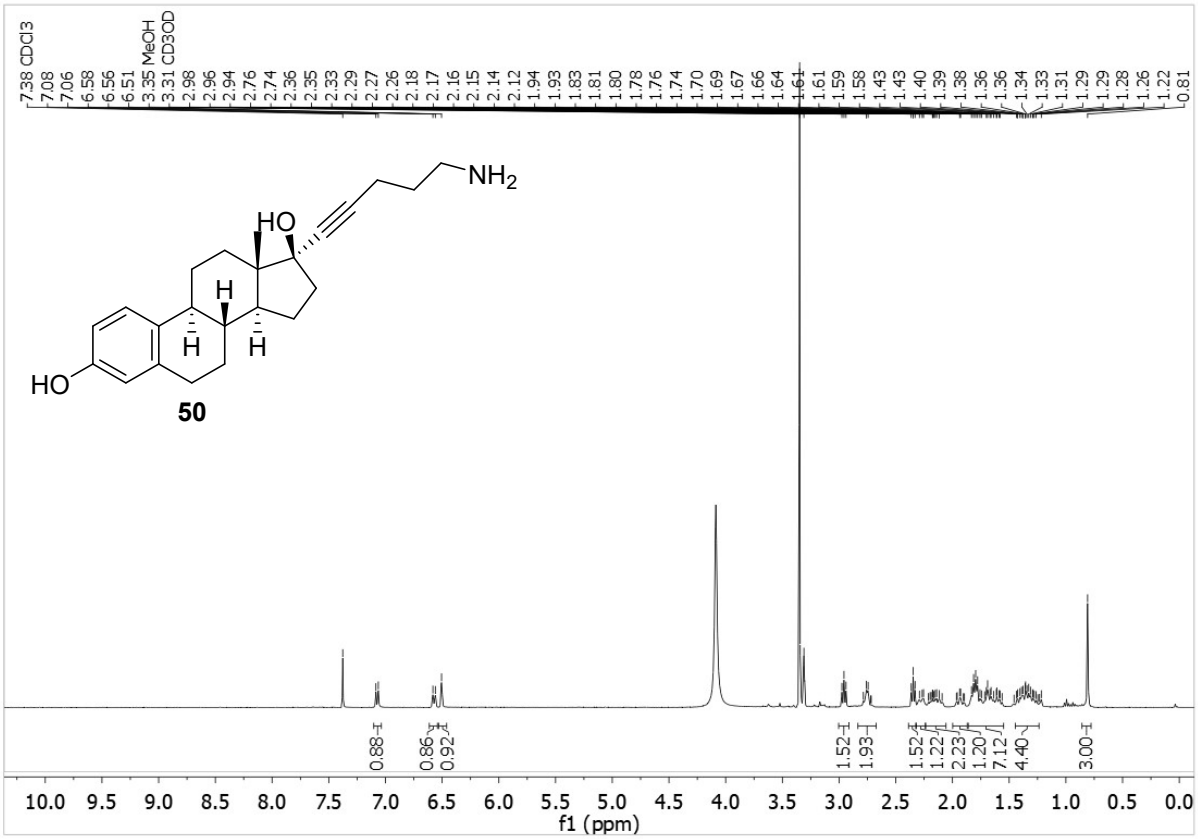
^{1}H NMR



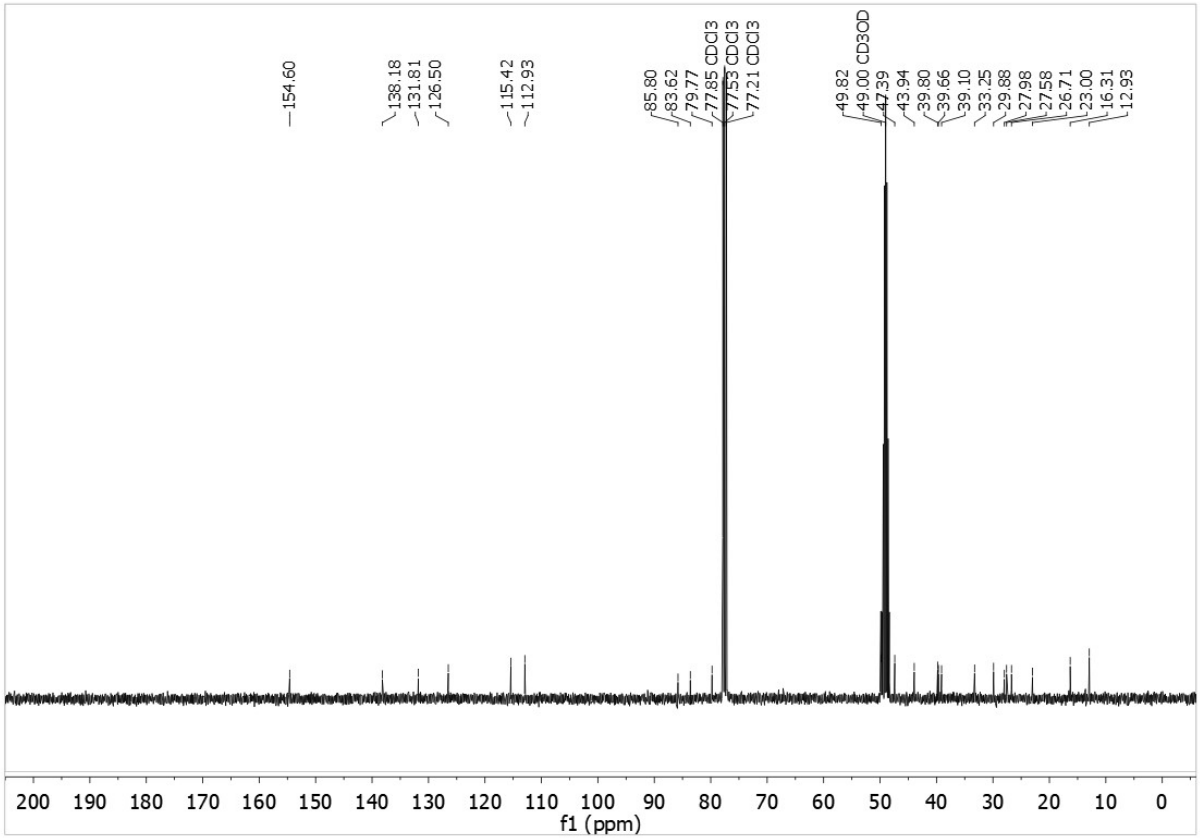
^{13}C NMR



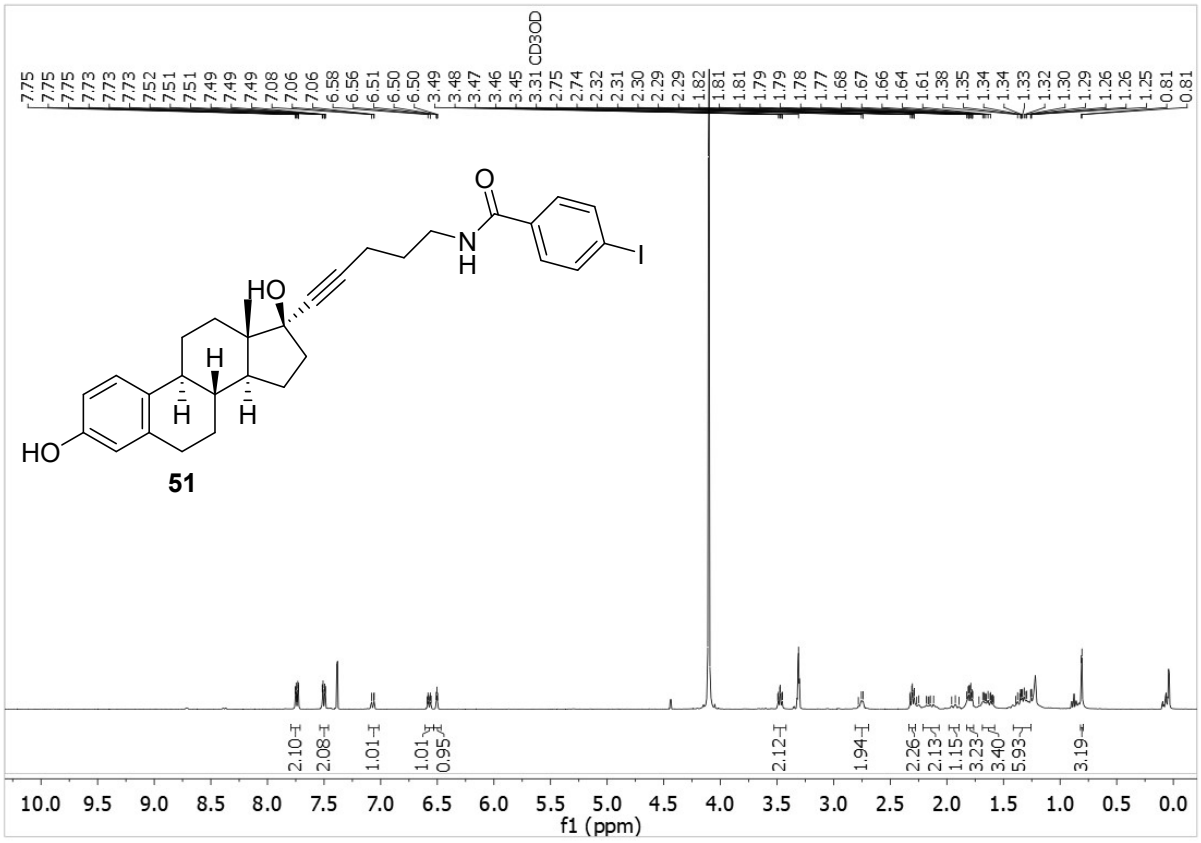
^{1}H NMR



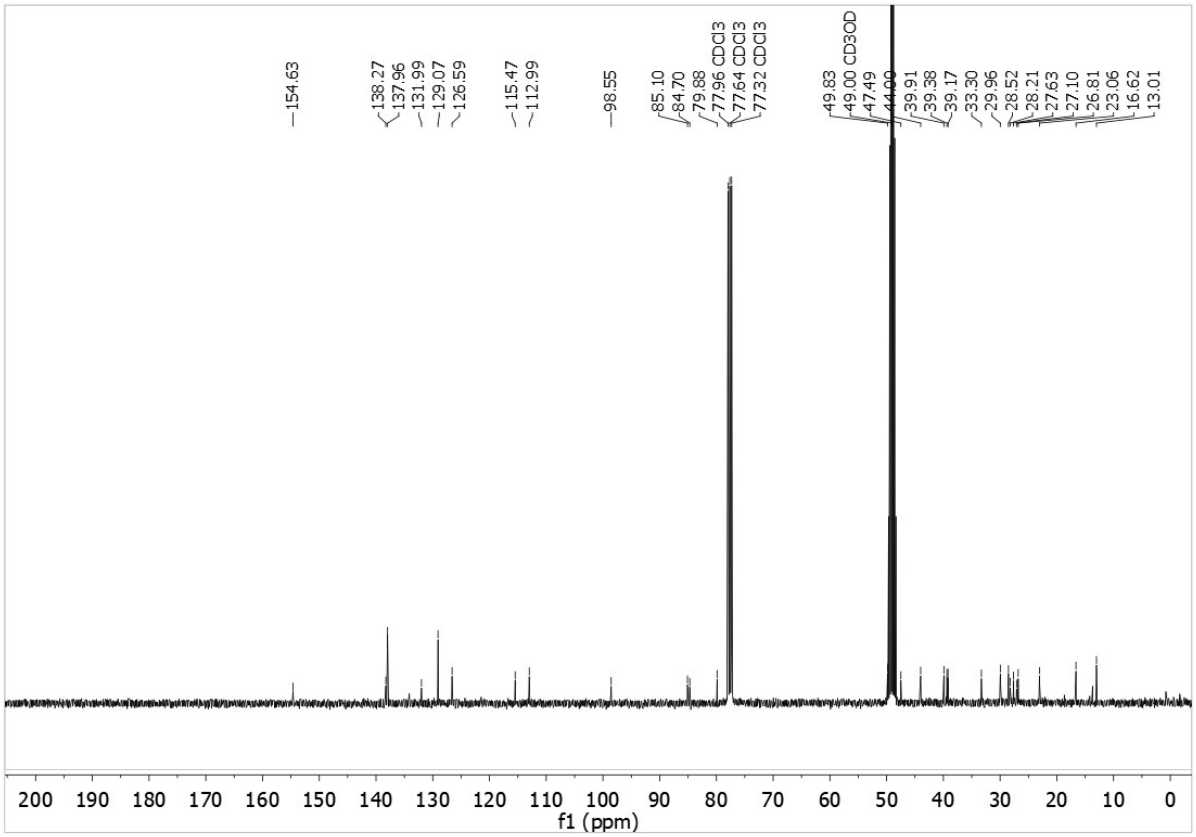
^{13}C NMR



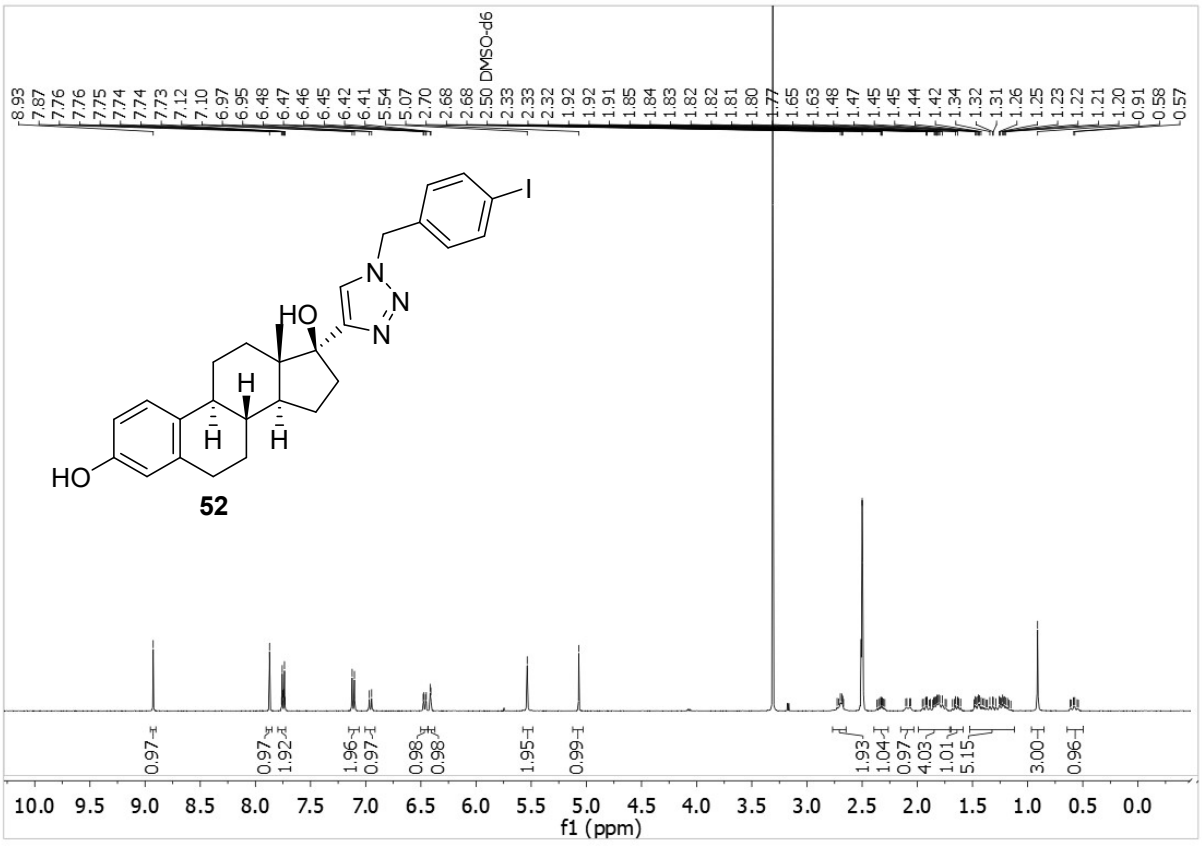
^{1}H NMR



^{13}C NMR



^{1}H NMR



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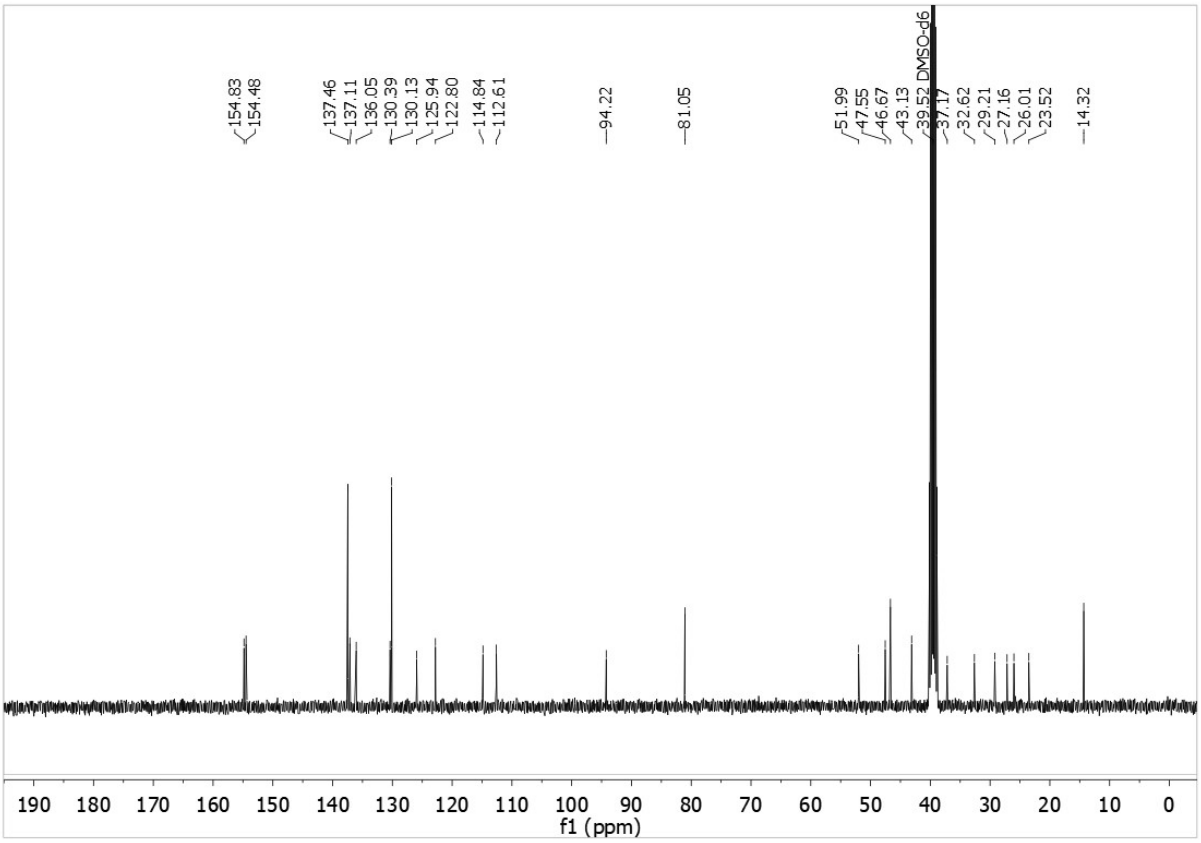
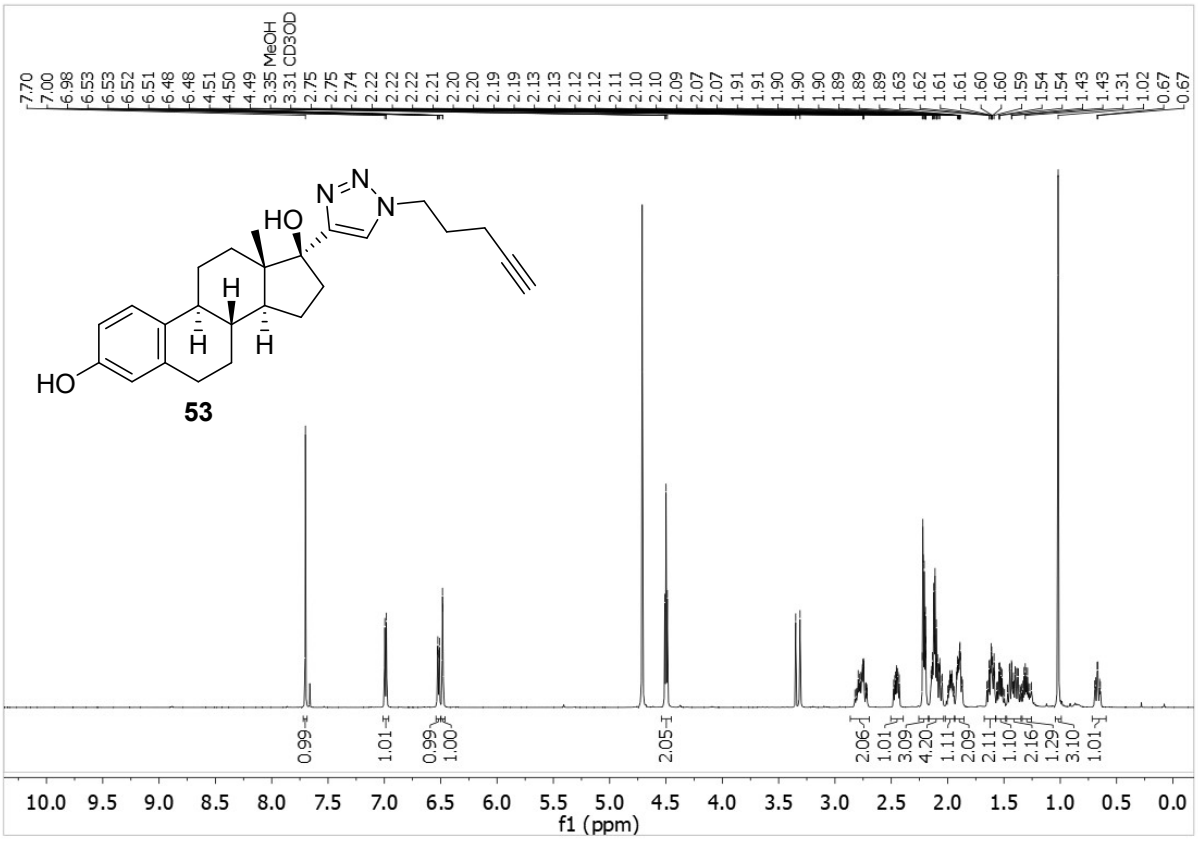
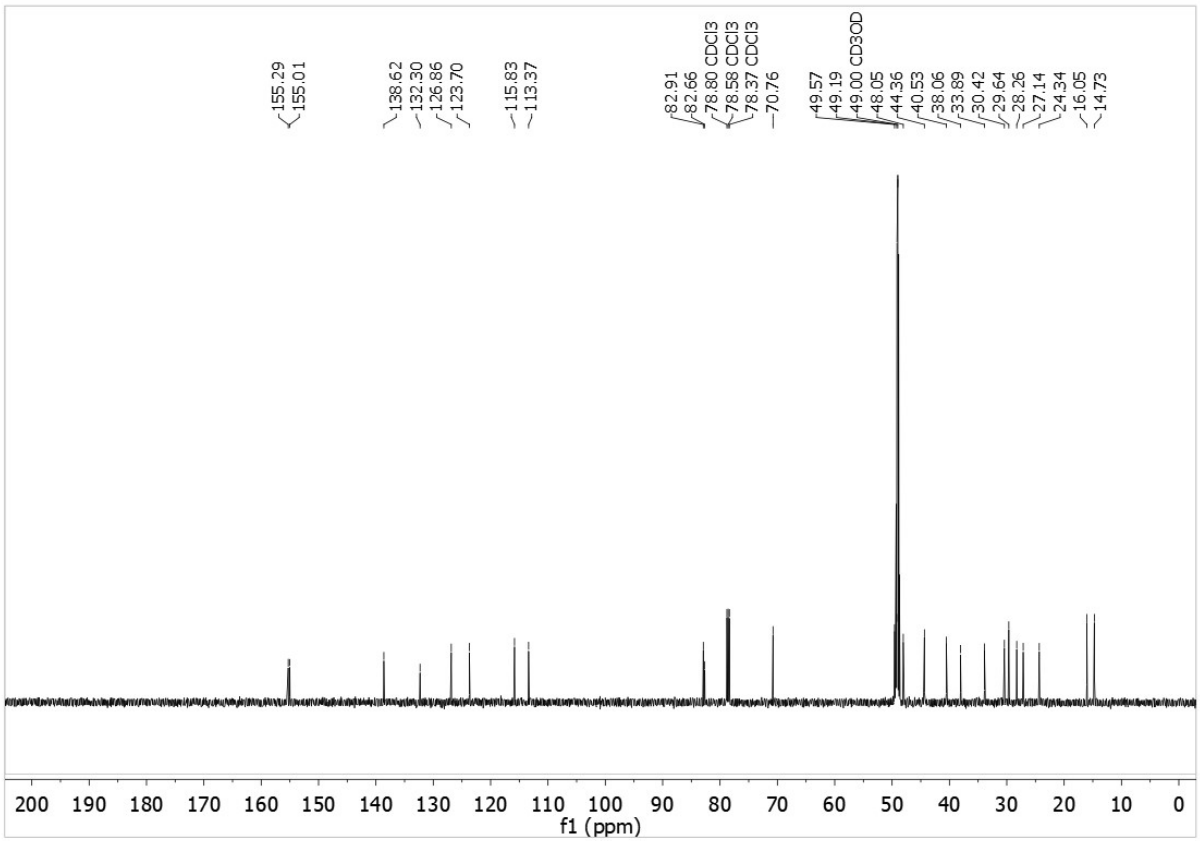


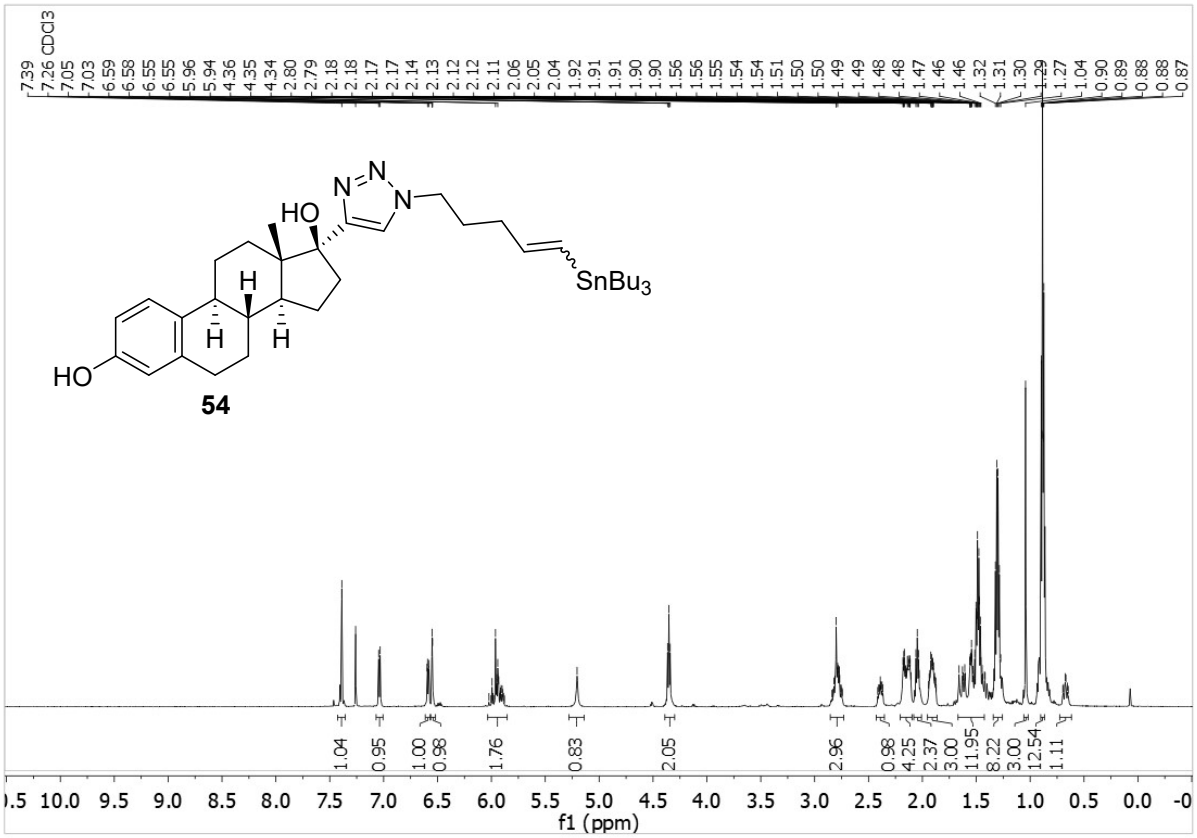
^{1}H NMR


MeOH
CD3OD
HO
N
N
N
H
H
H
HO
53
f1 (ppm)

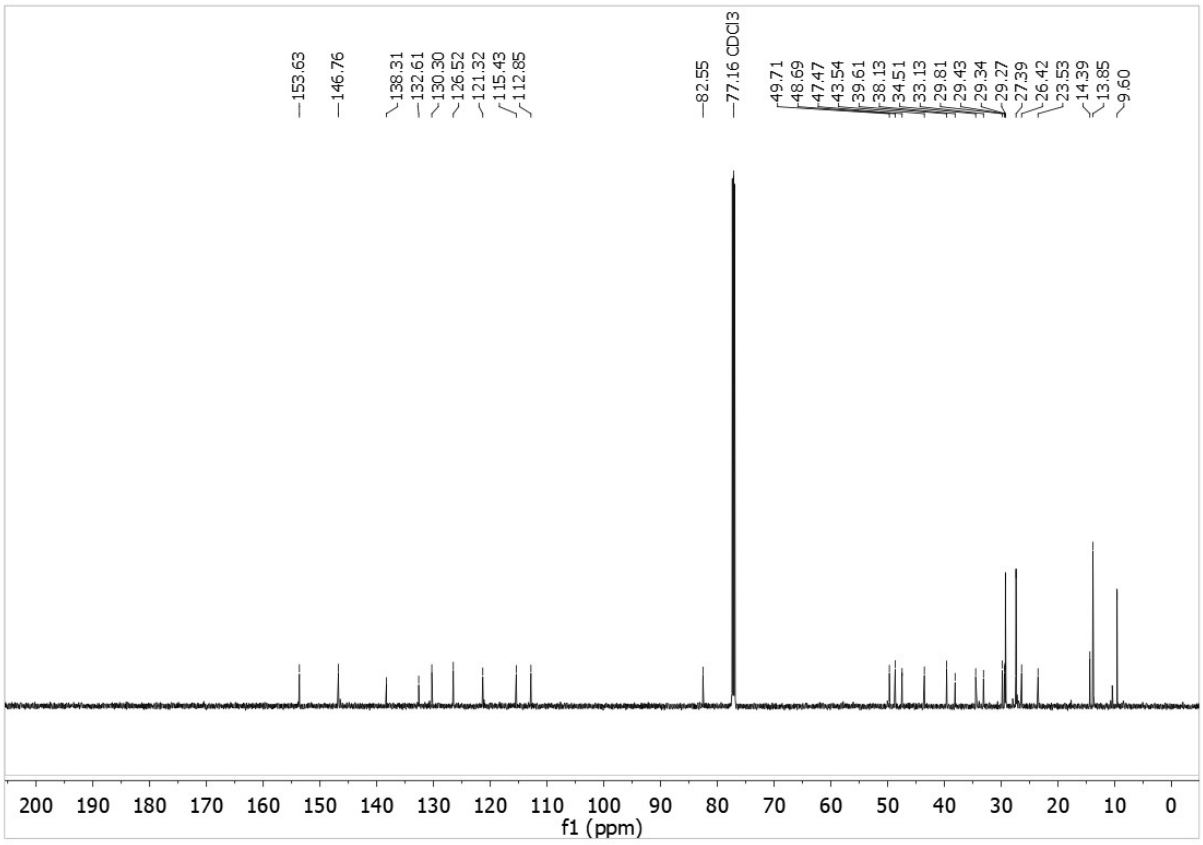
^{13}C NMR


155.29
155.01
138.62
132.30
126.86
123.70
115.83
113.37
82.91
82.66
78.80 CDCl3
78.58 CDCl3
78.37 CDCl3
70.76
49.57
49.19
49.00 CD3OD
48.05
44.36
40.53
38.06
33.89
30.42
29.64
28.26
27.14
24.34
16.05
14.73
f1 (ppm)

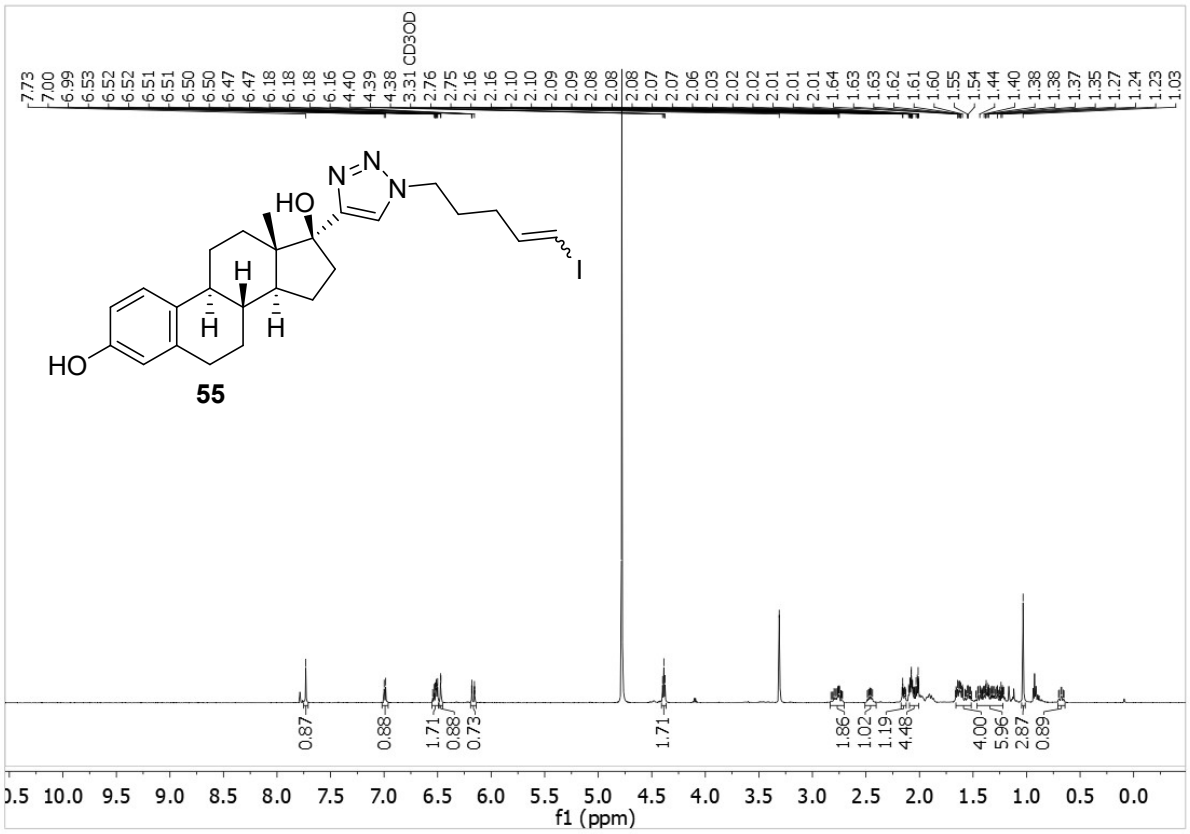
^{1}H NMR



^{13}C NMR



^{1}H NMR



^{13}C NMR