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

Supporting Information

Synthetic Studies on the Indane SHIP1 Agonist AQX-1125

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Contents

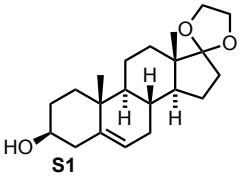
Synthesis of AQX-1125 and Analogs

General Methods: All anhydrous reactions were run under a positive pressure of argon. All syringes, needles, and reaction flasks required for anhydrous reactions were dried in an oven and cooled under an N_2 atmosphere or in a desiccator. Dichloromethane and THF were dried by passage through an alumina column following the method of Grubbs (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996,** *15*, 1518). Hexanes, ethyl acetate (EA) and all other reagents and solvents were purchased from commercial sources and used without further purification.

Analysis and Purification. Analytical thin layer chromatography (TLC) was performed on precoated glass backed plates (silica gel 60 F_{254}; 0.25 mm thickness). The TLC plates were visualized by UV illumination and by staining. Solvents for chromatography are listed as volume:volume ratios. Flash column chromatography was carried out on silica gel (40-63 μm).

Identity. Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded at 300 or 400 MHz and 75 or 100 MHz respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. Coupling constants are reported in hertz (Hz). Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; td = triplet of doublets; tt = triplet of triplets; qd = quartet of doublets; ddd = doublet of doublet of doublets; br s = broad singlet). Where applicable, the number of protons attached to the corresponding carbon atom was determined by DEPT 135 NMR. Infrared (IR) spectra were obtained using an FTIR equipped with an attenuated total reflection (ATR) attachment. Melting points were recorded using an electrothermal melting point apparatus and are uncorrected. Molecular formula information was supported by combustion analysis. In cases where combustion analysis was difficult to obtain due to the small quantitates of compound prepared, high resolution mass spectrometry (HRMS) was used to determine the molecular formula. HRMS data was obtained using positive-ion and negative-ion mode electrospray ionization with an Apollo II ion source on a Bruker 10 Tesla APEX -Qe FTICR-MS at Old Dominion University.

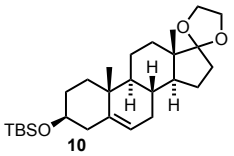
Purity. Compound homogeneity was determined via ^{1}H and ^{13}C NMR spectra after silica gel chromatography, a copy of the spectra for new compounds is included in the supporting information. In most cases purity was supported by combustion analysis, with elemental analytical values for carbon and hydrogen (and nitrogen, if present) agreeing with calculated values within 0.4%. Elemental analyses were performed on an elemental analyzer with a thermal conductivity detector and 2 meter GC column maintained at 50 °C.



S1

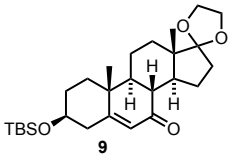
5-Androsten-3β-ol-17-ethylene ketal (S1). (This compound has been previously reported, see: Calogeropoulou, T.; Avlonitis, N.; Minas, V.; Alexi, X.; Pantzou, A.; Charalampopoulos, I.; Zervou, M.; Vergou, V.; Katsanou, E. S.; Lazaridis, I.; Alexis, M. N.; Gravanis, A. "Novel Dehydroepiandrosterone Derivatives with Antiapoptotic, Neuroprotective Activity." *J. Med. Chem.* **2009**, *52*, 6569.)
Dehydroepiandrosterone (5.00 g, 17.3 mmol) was added to a flame dried round-bottom flask. 50 mL of dry benzene was added. *p*-Toluene sulfonic acid monohydrate (0.114 g, 0.66 mmol) and ethylene glycol (5.00 mL) were then added to the reaction. This reaction mixture was heated to reflux using a Dean-Stark trap for 24 h under argon. The mixture was then removed from heat and allowed to cool to rt. The excess benzene was removed under reduced pressure with a rotary evaporator. The remaining residue was diluted with diethyl ether (150 mL) and washed successively with sat. aq. $NaHCO_3$ (2 × 75 mL) and sat. aq. NaCl

(1 x 75 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (30% EA/70% hexanes) provided ketal **S1** as a white colored solid (0.553 g, 96%). mp = 73-74 °C; TLC R_f = 0.28 (30% EA/70% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40-5.32 (m, 1H), 3.99-3.81 (m, 4H), 3.61-3.46 (m, 1H), 2.39-2.17 (m, 2H), 2.09-1.95 (m, 2H), 1.92-1.76 (m, 3H), 1.75-1.66 (m, 1H), 1.65-1.57 (m, 2H), 1.51-1.36 (m, 6H), 1.34-1.18 (m, 2H), 1.13-1.03 (m, 1H), 1.01 (s, 3H), 0.99-0.93 (m, 1H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 121.5, 119.5, 71.7, 65.2, 64.6, 50.6, 50.0, 45.7, 42.3, 37.3, 36.6, 34.2, 32.2, 31.6, 31.2, 30.6, 22.8, 20.5, 19.4, 14.2. Anal calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70;. Found: C, 75.90; H, 9.85.



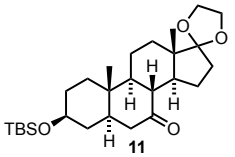
10

5-Androsten-3β-ol-17-ethylene ketal tert-butyldimethylsilyl ether (10). Ketal **S1** (5.00 g, 15.0 mmol) was added to a flame dried round-bottom flask. 27 mL of DMF and 27 mL of DCM were added to dissolve the ketal. Imidazole (2.51 g, 36.8 mmol) and *tert*-butyl (chloro) dimethylsilane (3.51 g, 23.3 mmol) were then added. This reaction mixture was allowed to stir at rt for 20 h under argon. The excess solvent was then removed under reduced pressure. The remaining contents were diluted with diethyl ether (150 mL) and washed successively with 5% aq. HCl (2 × 75 mL), saturated $NaHCO_3$ (2 × 75 mL) and saturated aq. NaCl (75 mL). The organic layer was then dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to yield silyl ether **10** as a white colored solid (6.53 g, 97%). TLC R_f = 0.74 (30% EA/70% hexanes); IR (neat) 2928, 1471, 1460, 1254, 1077, 834, 772 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32-5.30 (m, 1H), 3.98-3.82 (m, 4H), 3.52-3.44 (m, 1H), 2.29-2.10 (m, 2H), 2.00-1.95 (m, 2H), 1.87-1.66 (m, 3H), 1.63-1.53 (m, 3H), 1.53 (s, 3H), 1.52-1.36 (m, 4H), 1.35-1.19 (m, 1H), 1.07-1.04 (m, 1H), 1.01 (s, 3H), 0.89 (s, 9H), 0.86 (s, 3H), 0.06 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 120.9, 119.6, 72.5, 65.1, 64.5, 50.6, 50.0, 45.7, 42.8, 37.3, 36.6, 34.2, 32.2, 32.0, 31.2, 30.6, 25.9, 22.7, 20.4, 19.4, 18.2, 14.2, -4.5. Anal calcd for $C_{27}H_{46}O_3Si$: C,72.59; H. 10.38;. Found: C, 72.33; H, 10.24.



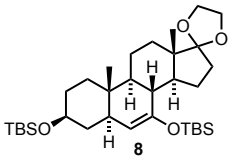
9

5-Androsten-7-one-3β-ol 17-ethylene ketal tert-butyldimethylsilyl ether (9). tert-Butyldimethylsilyl ether **10** (6.00 g, 13.4 mmol) was added to a flame dried round-bottom flask. 24 mL of cyclohexane and 3 mL of water were added to dissolve the ketal. Ruthenium trichloride trihydrate (0.022 g, 0.084 mmol, 0.6 mol %) was added followed by the dropwise addition of 70% *tert*-butyl hydroperoxide solution (aq., 14 mL, 102 mmol). This reaction stirred for 22 h under argon. The mixture was then diluted with EA (100 mL) and filtered through celite. The filtrate was washed successively with 25% aq. Na_2SO_3 (2 × 75 mL) and sat. aq. NaCl (75 mL). The organic layer was then dried with anhydrous Na_2SO_4, filtered and concentrated. The residue was recrystallized from EA to provide the unsaturated ketone **9** as a pale-yellow solid (3.34 g, 54%). mp = 183-184 °C; TLC R_f = 0.21 (10% EA/90% hexanes); IR (neat) 2979, 2857, 1727, 1656, 1625, 1470, 1459, 1351, 1092 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (s, 1H), 3.99-3.74 (m, 4H), 3.68-3.55 (m, 1H), 2.56-2.43 (m, 3H), 2.29-2.18 (m, 1H), 2.06-1.88 (m, 2H), 1.87-1.73 (m, 3H), 1.69-1.59 (m, 2H), 1.54-1.38 (m, 5H), 1.23-1.15 (m, 4H), 0.89 (s, 9H), 0.86 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 166.1, 125.8, 118.7, 71.2, 65.2, 64.4, 49.9, 46.1, 45.3, 44.3, 42.5, 38.3, 36.4, 34.1, 31.7, 29.6, 25.8, 25.1, 20.6, 18.1, 17.3, 14.4, -4.6, -4.7. Anal calcd for $C_{27}H_{44}O_4Si$: C, 70.39; H, 9.63;. Found: C, 70.00; H, 9.29.



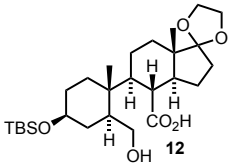
11

5-Androsta-7-one-3β-ol 17-ethylene ketal tert-butyldimethylsilyl ether (11). Enone **9** (2.13g, 4.62 mmol) was dissolved in 140 mL of EA and 10% Pd/C (0.45 g, 0.42 mmol, 9 mol %) was added. The mixture was then placed under vacuum and the atmosphere inside the flask replaced with hydrogen using a hydrogen balloon. The reaction mixture was stirred under a hydrogen atmosphere for 20 h at rt. The reaction was then filtered through celite with EA and concentrated under reduced pressure to yield ketone **11** as a white colored solid (2.02 g, 94%). mp = 198-200 °C; TLC R_f = 0.30 (10% EA/90% hexanes); IR (ATR) 2979, 1698, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 3.98-3.78 (m, 4H), 3.61-3.48 (m, 1 H), 2.33 (t, J = 11.8 Hz, 2H), 2.29-2.18 (m, 1H), 2.04-1.56 (m, 7H), 1.53-1.29 (m, 6H), 1.24-1.09 (m, 2H), 1.07 (s, 3H), 1.05-0.92 (m, 2H), 0.87 (s, 9H), 0.83 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.4, 118.7, 71.4, 65.2, 64.4, 55.3, 50.1, 46.6, 45.9, 45.7, 43.4, 38.4, 36.3, 35.9, 34.1, 31.5, 29.7, 25.8, 23.8, 21.3, 18.2, 14.4, 11.8, -4.7. Anal calcd for $C_{27}H_{46}O_4Si$: C, 70.08; H, 10.02;. Found: C, 69.70; H, 9.93.



8

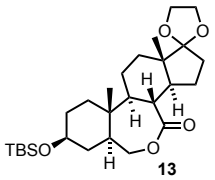
5-Androsta-7-tert-butyldimethyl oxysilane-3β-ol 17-ethylene ketal tert-butyldimethylsilyl enol ether (8). Ketone **11** (3.30 g, 7.13 mmol) was dissolved in 65 mL of DCM. The reaction was then cooled to 0 °C and triethylamine (38.8 mL, 278 mmol) was added dropwise. After 15 min at 0 °C, *tert*-butyldimethylsilyl trifluoromethanesulfonate (9.80 mL, 42.8 mmol) was then added to the reaction with the temperature being maintained at 0 °C. This reaction mixture was then allowed to warm to rt and allowed to stir for 20 h under argon. The mixture was then re-cooled to 0 °C and isopropyl alcohol (1.1 mL) was added. The reaction was then diluted with DCM (150 mL) and saturated $NaHCO_3$ (150 mL). The organic phase was separated and the aqueous phase was extracted 2x with DCM (100 mL). The combined organic layers were then washed with sat. aq. $NaHCO_3$ (1 × 100 mL) and sat. aq. NaCl (1 × 100 mL). The organic extracts were then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (10% EA/90% hexanes) to yield silyl enol ether **8** as a pale-yellowish solid (3.40 g, 83%). TLC R_f = 0.58 (10% EA /90% hexanes); IR (neat) 2927, 2854, 1655, 1470, 1103, 1082, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.38 (s, 1H), 3.96-3.79 (m, 4H), 3.58 (sep, J = 5.2 Hz, 1H), 1.99-1.85 (m, 4 H), 1.82-1.57 (m, 6 H), 1.52-1.45 (m, 2H), 1.42-1.15 (m, 4H), 1.12-0.97 (m, 2H), 0.91 (s, 9 H), 0.88 (s, 12 H), 0.74 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 118.7, 108.4, 72.1, 65.2, 64.5, 53.9, 48.6, 47.5, 43.4, 42.0, 37.3, 34.9, 34.5, 34.3, 31.9, 30.8, 26.1, 25.9, 25.7 (2C), 20.9, 18.3, 18.2, 18.1, 14.7, 11.3, -2.9 (2C), -3.9, -4.2, -4.55, -4.56. Anal calcd for $C_{21}H_{32}O_3$: C, 68.69; H, 10.48; Found: C, 68.39; H, 10.62.



12

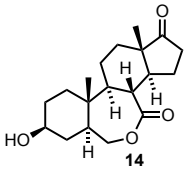
(7a'S)-5'-((1R,4S)-4-((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl)-1-methylcyclohexyl)-7a'-methyloctahydrospiro[[1,3]dioxolane-2,1'-indene]-4'-carboxylic acid (12). Silyl enol ether **8** (4.41 g, 7.64 mmol) was dissolved in methanol (122 mL) and DCM (122 mL) and cooled to -78 ° C. Ozone gas was then bubbled through this solution until a blue color was observed. The excess ozone was then removed by purging with argon gas, the blue color dissipated. The reaction mixture was then allowed to

warm to 0 °C and sodium borohydride (0.866 g, 22.9 mmol) was added. The reaction mixture was then allowed to warm to rt and allowed to stir for 20 h. More $NaBH_4$ (0.288 g, 7.6 mmol) was added and the mixture stirred for another 3 h. Most of the solvent was removed on a rotary evaporator, and DCM was added (150 mL) followed by water (150 mL). The solution foamed from the evolution of H_2 gas so 10% HCl was added drop wise until the foaming stopped. The DCM layer was separated and the aqueous layer extracted with DCM (3 × 75 mL). The combined organic extracts were washed with sat. aq. NaCl (2 × 75 mL). The organic layer was then dried with anhydrous Na_2SO_4, filtered and concentrated. Purification by silica gel chromatography (10% MeOH/ 90% DCM)) provided carboxylic acid **12** as a cream colored solid (2.39 g, 63%). TLC R_f = 0.47 (10% MeOH/ 90% DCM); IR (neat) 3404, 1701, 1053 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.57 (bs, 1H), 3.96-3.77 (m, 4H), 3.71 (d, *J* = 9.2 Hz, 1H), 3.49 (bs, 1H), 3.25 (s, 1H), 2.29 (t, *J* = 10.8 Hz, 1H), 2.04-1.82 (m, 4H), 1.81-1.69 (m, 3H), 1.68-1.45 (m, 4H), 1.44-1.18 (m, 7H), 0.86 (s, 12H), 0.79 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.1, 118.7, 71.0, 65.2, 64.6, 62.6, 47.5, 45.5, 45.1, 45.0, 42.1, 37.7, 34.4, 33.6, 31.2, 29.9, 25.9 (2C), 22.9, 20.7, 19.3, 18.2, 13.7, -4.6. Anal calcd for $C_{18}H_{28}O_4$: C, 65.28; H, 9.74 Found: C, 65.25; H, 9.76.



13

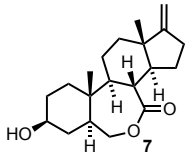
(2'*R*,5'*S*,16'*S*)-5'-((tert-butyldimethylsilyl)oxy)-2',16'-dimethylspiro[1,3-dioxolane-2,15'-[9]oxatetracyclo[9.7.0.0^{2,7}.0^{12,16}]octadecan]-10'-lactone (13). Carboxylic acid **12** (1.50 g, 3.02 mmol) was dissolved in 45 mL of DCM and DMAP (0.074 g, 0.604 mmol) was added. After stirring for 5 min, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.94 g, 6.04 mmol) was then added. This was allowed to stir at rt for 24 h. The reaction was diluted with DCM (150 mL) and washed successively with sat. aq. $NaHCO_3$ (2 × 50 mL), 10% aq. HCl (2 × 50 mL), and sat. aq. NaCl (50 mL). The organic layer was then dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. This was subjected to silica gel chromatography using (20% EA/80% hexanes) to yield lactone **13** as a white solid (1.39 g, 96%). mp = 200-201 °C; TLC R_f = 0.51 (20% EA /80% hexanes); IR (neat) 2979, 1716, 1095, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.31 (dd, *J* = 12.7, 7.2 Hz, 1H), 3.98-3.80 (m, 4H), 3.60 (d, *J* = 12.7 Hz, 1H), 3.57-3.46 (m, 1H), 2.56 (t, *J* = 11.1 Hz, 1H), 2.36-2.21 (m, 1H), 2.00-1.76 (m, 5H), 1.75-1.58 (m, 3H), 1.56-1.48 (m, 2H), 1.45-1.24 (m, 4H), 1.23-1.05 (m, 2H), 1.03 (s, 3H), 0.88 (s, 9H), 0.84 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 118.7, 70.9, 68.2, 65.2, 64.5, 47.2, 46.6, 44.7, 44.0, 42.3, 38.6, 37.6, 37.3, 33.5, 31.3, 29.2, 25.7, 24.7, 21.5, 18.2, 12.9, 13.4, -4.7. Anal calcd for $C_{27}H_{46}O_5Si$: C, 67.74; H, 9.69 Found: C, 67.55; H, 9.52.



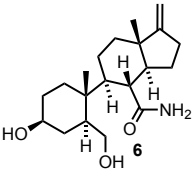
14

((2*R*,5*S*,16*S*)-5-Hydroxy-2,16-dimethyl-9-oxatetracyclo[9.7.0.0^{2,7}.0^{12,16}]octadecane-15-one-10'-lactone (14). Acetal **13** (0.200 g, 0.42 mmol) was suspended in 10 mL of methanol and 6.0 mL of 10% aq. HCl was added. This reaction mixture was allowed to stir at rt for 4 h. The reaction mixture was then concentrated and the residue diluted with EA (75 mL) and water (75 mL). The aqueous layer was extracted with EA (2 × 50 mL) and the combined organic layers were washed successively with sat. aq. $NaHCO_3$ (2 × 50 mL) and NaCl (1 × 50 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by silica gel chromatography (80% EA/20% hexanes) yielded ketone **14** as a white solid (0.11 g, 82%). mp = 194-197 °C; TLC R_f = 0.34 (100% EA); IR (neat) 3478, 1739, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.37 (q, *J* = 7.8 Hz, 1H),

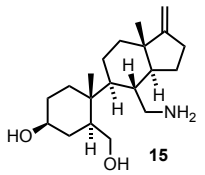
3.67 (d, J = 13.1 Hz, 1H), 3.64-3.56 (m, 1H), 2.74 (t, J = 10.7 Hz, 1H), 2.51-2.38 (m, 1H), 2.26-2.00 (m, 3H), 1.99-1.86 (m, 2H), 1.86-1.72 (m, 3H), 1.66-1.56 (m, 2H), 1.51-1.22 (m, 6H), 1.13-1.02 (m, 1H), 1.06 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.7, 175.9, 69.9, 68.3, 47.2, 46.4, 45.9, 45.8, 41.6, 38.8, 37.2, 36.6, 35.4, 30.7, 30.3, 23.6, 21.6, 13.22, 13.19; Anal calcd for $C_{18}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.26; H, 8.64.



(2*R*,5*S*,16*S*)-5-Hydroxy-2,16-dimethyl-15-methylene-9- oxatetracyclo[9.7.0.0^{2,7}.0^{12,16}]octadecan-10'-lactone (7). Methyltriphenylphosphonium bromide (10.6 g, 29.6 mmol) was suspended in 56.7 mL dry THF under argon. n-BuLi (11.2 mL, 2.5 M, 28 mmol) was added dropwise to the stirring solution to generate the ylide. This stirred for 15 min at rt before being heated to 40˚C. Ketone **14** (1.90 g, 5.93 mmol) was dissolved in 69.3 mL dry THF and added dropwise into the stirring reaction. The temperature was then increased to reflux. After 24 h the mixture was allowed to cool down to rt before water (75 mL) was added dropwise to quench the reaction. EA (100 mL) and more water (75 mL) were added and the layers separated. The aqueous phase was extracted with EA (2 × 100 mL). The combined organic extracts were washed with water (2 × 75 mL) and sat. aq. NaCl (2 × 75 mL), dried with anhydrous $MgSO_4$, filtered and concentrated. The residue was subjected to silica gel chromatography using (25% Et_2O/75% EA) to yield alkene **6** as a white solid (1.28 g, 67%). TLC R_f = 0.51 (100% EA); IR (neat) 3510, 3074, 1701, 1675 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65 (d, J = 8.9 Hz, 2H), 4.33 (dd, J = 12.6, 7.8 Hz, 1H), 3.68-3.50 (m, 2H), 2.59 (t, J = 10.8 Hz, 1H), 2.52-2.39 (m, 1H), 2.37-2.22 (m, 1H), 2.11-2.01 (m, 1H), 1.98-1.67 (m, 7H), 1.66-1.46 (m, 2H), 1.44-1.12 (m, 5H), 1.03 (s, 4H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 160.0, 101.8, 69.9, 68.2, 48.4, 47.1, 46.5, 42.0, 41.7, 38.7, 37.3, 36.6, 34.2, 30.7, 28.8, 26.1, 22.0, 17.9, 13.2. HRMS (ESI+) calcd for $C_{20}H_{31}O_3$ $(M+H)^+$: 319.2273. Found: 319.2266.

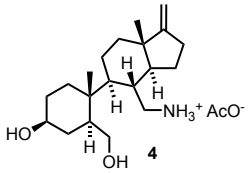


(3a*S*,4*R*,5*S*,7a*S*)-5-[(1*R*,2*S*,4*S*)-4-Hydroxy-2-(hydroxymethyl)-1-methylcyclohexyl]-7a-methyl-1-methylene-2,3,3a,4,5,6,7,7a-octahydroindene-4-carboxamide (6). A solution of ammonia in THF (5.3 mL, 0.5 M, 2.65 mmol) was cooled to -78˚C. n-BuLi (1.0 mL, 2.5 M, 2.5 mmol) was added dropwise and allowed to stir for 30 min. Lactone **7** (0.169 g, 0.53 mmol) was dissolved in a solution of 2.0 mL dry THF and added dropwise into the reaction before allowing the reaction to warm to rt. The reaction continued for 24 h. The reaction was diluted with NH_4Cl (50 mL) and extracted successively with EA (2 × 75 mL). The combined organic extracts were washed with sat. aq. NaCl (2 × 50 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated. The residue was subjected to silica gel chromatography using (10% MeOH/90% EA) to yield amide **6** as a white solid (0.101 g, 57%). TLC R_f = 0.51 (20% MeOH/80% EA); IR (neat) 3430, 3333, 3197, 2959, 2928, 1690, 1643, 1615, 1387, 1236, 1040, 1004 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 4.69 (s, 2 H), 3.77 (dd, J = 10.7, 3.1 Hz, 1 H), 3.55-3.39 (m, 1 H), 3.12 (t, J = 10.7 Hz, 1 H), 2.59-2.46 (m, 1 H), 2.41 (t, J = 10.4 Hz, 1 H), 2.34-2.07 (m, 2 H), 2.03-1.95 (m, 1H), 1.94-1.74 (m, 4H), 1.73-1.55 (m, 3H), 1.54-1.30 (m, 6H), 0.97 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, MeOD) δ 181.2, 162.0, 102.5, 71.4, 62.6, 52.9, 46.1, 46.0, 44.3, 43.9, 39.0, 36.6, 35.1, 31.9, 31.5, 30.0, 26.2, 22.4, 19.9, 18.5. Anal calcd for $C_{20}H_{33}NO_3$: C, 71.60; H, 9.92; N, 4.18. Found: C, 71.20; H, 9.63; N, 4.28.



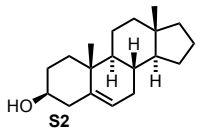
15

(1*S*,3*S*,4*R*)-4-[(3a*S*,4*R*,5*S*,7a*S*)-4-(aminomethyl)-7a-methyl-1-methylene-2,3,3a,4,5,6,7,7a-octahydroinden-5-yl]-3-(hydroxymethyl)-4-methylcyclohexanol (15). Amide **6** (0.350 g, 1.25 mmol) was dissolved in 12.0 mL of THF and cooled to 0 ˚C. A solution of $LiAlH_4$ (25.0 mL, 1.0 M in THF, 25 mmol) was added dropwise to the stirring solution. The temperature was increased to reflux for 20 h. The reaction was then cooled to rt and diluted with THF before being cooled to 0˚C. The reaction was then diluted with ethyl ether (50 mL) and quenched by the stepwise addition of 1 mL of water followed by 1 mL of 15% aq. NaOH followed by 3 mL of water. The white suspension was then filtered through celite, dried with $MgSO_4$, filtered and concentrated. Purification of the residue via silica gel chromatography (10% MeOH/89% EA/1% sat. aq. NH_4OH) yielded the amine **15** as a white gum (0.164 g, 49%). TLC R_f = 0.23 (89% EA/10% MeOH/1% sat. aq. NH_4OH); ^1H NMR (300 MHz, CD_3OD) δ 4.65 (s, 2H), 3.75 (dd, *J* = 10.8, 2.2 Hz, 1H), 3.56-3.39 (m,1H), 3.25-3.00 (m, 2H), 2.74 (d, *J* = 14.4 Hz, 1H), 2.63-2.43 (m, 1H), 2.42-2.24 (m, 1H), 2.32-2.10 (m, 1H), 1.94-1.74 (m, 5H), 1.74-1.21 (m, 10H), 1.11 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 101.2, 70.2, 62.8, 49.9, 43.3, 41.9, 38.7, 37.1, 35.9, 34.4, 31.1, 30.7, 29.7, 29.1, 24.7, 23.2, 21.1, 18.3, 14.1.



4

(1*S*,3*S*,4*R*)-4-[(3a*S*,4*R*,5*S*,7a*S*)-4-(aminomethyl)-7a-methyl-1-methylene-2,3,3a,4,5,6,7,7a-octahydroinden-5-yl]-3-(hydroxymethyl)-4-methylcyclohexanol ammonium acetate AQX-1125 (4). Amine **15** (0.100 g, 0.311 mmol) was dissolved in 5 mL 80% acetic acid and heated to 40 °C while stirring for 90 min. The reaction was then cooled to rt and 10 mL toluene was added. The solution was concentrated down 3 times with toluene and the residue was washed with diethyl ether 3× to yield amine salt **4** as a white solid (0.052 g, 43%). ^1H NMR (300 MHz, CD_3OD) δ 4.69 (s, 2H), 3.73 (dd, *J* = 11.0, 2.6 Hz, 1H), 3.59-3.42 (m, 1H), 3.17 (t, *J* = 10.4 Hz, 1H), 3.06 (dd, *J* = 13.9, 2.8 Hz, 1H), 2.69-2.50 (m, 1H), 2.45-2.27 (m, 1H), 2.26-2.13 (m, 1H), 1.99-1.94 (m, 1H), 1.93 (s, 3H), 1.92-1.79 (m, 5H), 1.68-1.56 (m, 2H), 1.55-1.38 (m, 4H), 1.37-1.21 (m, 4H), 1.19 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 176.1, 161.7, 102.4, 71.0, 62.8, 51.2, 45.8, 45.0, 44.8, 42.6, 38.3, 37.3, 36.8, 35.2, 32.0, 30.0, 25.5, 24.1, 22.0, 21.4, 18.6. HRMS (ESI+) calcd for $C_{20}H_{36}NO_2$ 322.2741; Found 322.2740. Anal calcd for $C_{22}H_{39}NO_4$: C, 69.25; H, 10.30; N, 3.61. Found: C, 69.28; H, 10.25; N, 3.30.

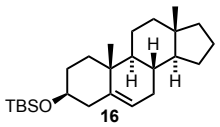


S2

5-Androsten-3β-ol (S2). (This compound has been previously reported, see: Mori, K.; Nakayama, T.; Sakuma, M., Synthesis of some analogues of blattellastanoside A, the steroidal aggregation pheromone of the German cockroach. *Bioorg. Med. Chem.* **1996,** *4*, 401-408.)

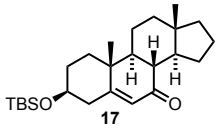
Potassium hydroxide (4.90 g, 86.7 mmol) was added to 25 mL diethylene glycol and heated until dissolved with a heat gun. Once the solution of KOH in diethylene glycol had cooled to rt, dehydroepiandrosterone (5.00 g, 17.3 mmol) and hydrazine hydrate (3.4 mL, 69.3 mmol) were added. With a reflux condenser attached the flask the solution was heated to 245˚C and refluxed for 24 h. The condenser was then removed and a short path distillation head was attached. The diethylene glycol was then mostly removed by

distillation. The reaction was then allowed to cool to rt and 100 mL MTBE and 100 mL sat. aq. NaCl were added. The mixture stirred overnight. The aqueous phase was then separated and extracted with MTBE (10 × 60 mL). The combined organic extracts were washed with sat. aq. NaCl (5 × 60 mL), dried with sodium sulfate, filtered and concentrated. Silica gel chromatography (30% EA/70% hexanes) yielded alcohol **S2** as a white colored solid (4.59 g, 96%). mp = 117-120 °C; TLC R_f = 0.24 (30% EA /70% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38-5.37 (m, 1H), 3.58-3.50 (m, 1H), 2.35-2.21 (m, 2H), 2.08-1.99 (m, 1H), 1.90-1.82 (m, 2H), 1.79-1.73 (m, 1H), 1.72-1.38 (m, 10H), 1.24-1.05 (m, 4H), 1.04 (s, 3H), 1.01-0.88 (m, 2H), 0.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 121.7, 71.8, 54.9, 50.4, 42.3, 40.6, 40.3, 38.7, 37.4, 36.7, 32.2, 32.1, 231.7, 25.6, 21.1, 20.5, 19.4, 17.3.



16

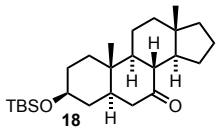
5-Androsten-3β-ol- tert-butyldimethylsilyl ether (16). Alcohol **S2** (3.64 g, 13.3 mmol) was added to a 250 mL flame dried round-bottom flask. 44 mL of DMF and 44 mL of DCM were added to dissolve the alcohol. Imidazole (2.21 g, 32.5 mmol) and tert-butyl(chloro)dimethylsilane (3.10 g, 20.6 mmol) were then added to the reaction. This reaction mixture was allowed to stir at rt for 20 h under argon. The excess solvent was then removed under reduced pressure. The remaining contents were diluted with diethyl ether (150 mL) and washed successively with 5% aq. HCl (2 × 75 mL), sat. aq. $NaHCO_3$ (2 × 75 mL) and sat. aq. NaCl (75 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and concentrated to yield the silyl ether **16** as a white colored solid (4.67 g, 91%). mp = 118-119 °C; TLC R_f = 0.89 (10% EA/90% hexanes); IR (neat) 2952, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (d, J = 5.1, 1H), 3.48 (sep, J = 4.6 Hz, 1H), 2.32-2.22 (m, 1H), 2.17 (ddd, J = 13.1, 4.9, 2.1 Hz, 1H), 2.06-1.96 (m, 1H), 1.82 (dt, J = 16.7, 3.5 Hz, 1H), 1.78-1.62 (m, 4H), 1.61-1.55 (m, 2H), 1.54-1.50 (m, 2H), 1.49-1.34 (m, 3H), 1.27-1.10 (m, 3H), 1.09-1.03 (dd, J = 13.6, 3.7, 1H), 1.01 (s, 3H), 0.99-0.92 (dd, J = 11.8, 5.2, 1H), 0.91-0.86 (m, 10H), 0.71 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 121.2, 72.7, 54.9, 50.5, 42.8, 40.6, 40.3, 38.8, 37.5, 36.8, 32.3, 32.2, 32.1, 25.9, 25.6, 21.1, 20.5, 19.5, 18.3, 17.3, -4.6. Anal calcd for $C_{25}H_{44}OSi$: C, 77.25; H, 11.41. Found: C, 76.91, H, 11.54.



17

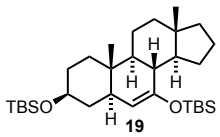
5-Androsten-7-one-3β-ol tert-butyldimethylsilyl ether (17). Alkene **16** (0.250 g, 0.64 mmol) was added to an oven dried test tube along with bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (0.005 g, 0.0064 mmol). The solids were dissolved in n-heptanes (2 mL) and 70 wt % tert-butyl hydroperoxide (0.40 mL, 3.2 mmol) was added slowly. The test tube was equipped with a purge needle and allowed to stir at room temperature for 16 h. After stirring for 16 h the reaction mixture was diluted with EA (5 mL) and was quenched with a sat. aq. sodium thiosulfate solution (10 mL). The organic layer was separated and subsequently washed with deionized water (2 × 5 mL). The combined aqueous layers were extracted once more with EA (5 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (10% EA/hexanes) provided enone **17** as a white solid (0.124 g, 48% yield). mp = 147-149 °C; TLC R_f = 0.89 (100% hexanes); IR (ATR) 2938, 1656, 1058 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (d, J = 1.34, 1H), 3.60 (sep, J = 15.8, 10.3, 5.5, 1H), 2.57-2.31 (m, 3H), 2.19 (t, J = 11.2, 1H), 1.92 (dt, J = 13.7, 3.5 Hz, 1H), 1.86-1.78 (m, 1H), 1.74 (dt, J = 13.0, 3.3 Hz, 1H), 1.69-1.64 (m, 2H), 1.63-1.57 (m, 3H), 1.55-1.47 (m, 2H), 1.46-1.28 (m, 2H), 1.27-1.21 (m, 1H), 1.19 (s, 3H), 1.17-1.07 (m, 2H), 0.89 (s, 9H), 0.72 (s, 3H), 0.66 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 166.2, 125.7, 71.3, 50.3, 48.1, 45.8, 42.6, 41.3, 39.2, 38.5, 37.8, 36.5, 31.8, 27.6,

25.8, 21.3, 20.6, 18.1, 17.3, 17.2, -4.6. Anal calcd for $C_{25}H_{42}O_2Si$: C, 74.57; H, 10.51. Found: C, 74.62; H, 10.42.



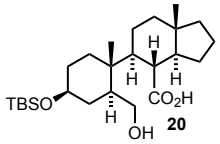
18

5-Androsta-7-one-3β-ol tert-butyldimethylsilyl ether (18). Enone **17** (2.25 g, 5.58 mmol) was dissolved in 154 mL of EA. 10% Pd/C (0.26 g, 0.244 mmol, ~4 mol %) was added to the reaction. The atmosphere above the suspension was removed and replaced with hydrogen gas from a balloon. This was allowed to stir for 20 h at rt. The reaction was then filtered through celite, rinsing with EA. Concentration under reduced pressure provided ketone **18** as a white solid (2.14 g, 95%). mp = 104-105 °C; TLC R_f = 0.67 (15% EA/85% hexanes); IR (neat) 2929, 1707, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 3.55 (septet, J = 15.1, 10.5, 4.2 Hz, 1H), 2.44-2.18 (m, 3H), 2.07-1.95 (m, 1H), 1.78-1.68 (m, 3H), 1.67-1.57 (m, 3H), 1.54-1.37 (m, 6H), 1.36-1.21 (m, 2H), 1.20-1.10 (m, 2H), 1.08 (s, 3H), 1.07-0.92 (m, 2H), 0.88 (s, 9H), 0.68 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 71.5, 55.8, 50.4, 47.0, 46.9, 46.1, 40.8, 39.4, 38.5, 37.8, 36.3, 36.1, 31.6, 26.3, 25.9, 21.9, 20.6, 18.2, 17.4, 11.9, -4.6. Anal calcd for $C_{25}H_{44}O_2Si$: C, 74.20; H, 10.96. Found: C, 74.08; H, 10.84.



19

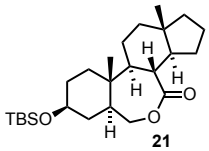
5-Androsta-7–tert-butyldimethyl oxysilane-3β-ol tert-butyldimethylsilyl ether (19). Ketone **18** (0.76 g, 1.87 mmol) was dissolved in 15.3 mL of DCM. The solution was cooled to 0 °C and triethylamine (10.2 mL, 74.0 mmol) was added. The mixture was allowed to stir at this temperature for 15 min. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (2.15 mL, 9.37 mmol) was then added to the reaction, maintaining the temperature at 0 °C. This reaction mixture was then allowed to warm to rt and stirred for 20 h under argon. The mixture was re-cooled to 0°C and isopropyl alcohol (1.1 mL) was then added. DCM (100 mL) and sat. aq. $NaHCO_3$ (50 mL) were then added, and the organic phase was separated. The aqueous phase was extracted 2× with DCM (100 mL) and the combined organics washed with sat. aq. $NaHCO_3$ (1 × 50 mL) followed by sat. aq. NaCl (1 × 50 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated. Purification by silica gel chromatography (1% EA/99% hexanes) gave silyl enol ether **19** as a pale yellow colored solid (0.85 g, 87%). mp = 105-109 °C; TLC R_f = 0.58 (1% EA/99% hexanes); IR (neat) 2928, 1082 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.41 (s, 1H), 3.59 (septet, J = 15.3, 10.5, 5.3 Hz, 1H), 1.98-1.78 (m, 3H), 1.77-1.68 (m, 2H), 1.67-1.56 (m, 3H), 1.52-1.45 (m, 2H), 1.44-1.18 (m, 5H), 1.17-0.96 (m, 5H), 0.92 (s, 9H), 0.89 (s, 9H), 0.74 (s, 3H), 0.73 (s, 3H), 0.13 (s, 3H), 0.11 (s, 3H), 0.06 (bs, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 108.5, 72.2, 54.6, 52.4, 43.6, 42.5, 42.3, 39.8, 39.4, 37.4, 34.9, 34.3, 31.9, 28.5, 26.0, 25.9, 21.5, 20.8, 18.2, 18.0, 11.3, -3.9, -4.2, -4.5 (2C). HRMS (ESI+) calcd for $C_{31}H_{58}O_2Si_2+H^+$ [M+H^+]: 519.4054; Found 519.4050.



20

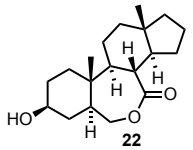
(7a*S*)-5-[(1*R*,4*S*)-4-((tert-butyldimethylsilyl)oxy)-1-methylcyclohexyl]-7a-methylperhydro-1*H*-indene-4-carboxylic acid (20). Silyl enol ether **19** (1.30 g, 2.50 mmol) was dissolved in methanol (40 mL) and DCM (40 mL). The solution was cooled to -78 °C and O_3 gas was bubbled through the solution until it turned blue. After purging with argon, the blue color dissipated. The mixture was warmed to 0 °C and sodium borohydride (0.38 g, 10.0 mmol) was added. The reaction mixture was then allowed to warm

to rt and stirred for 20 h. More $NaBH_4$ (0.38 g, 10.0 mmol) was then added. After 3 h the solvent was mostly removed on a rotary evaporator. DCM was added (50 mL) and water (50 mL) were then added to the residue. The DCM layer was separated and the aqueous layer extracted with DCM (3 × 50 mL). The organic layers were combined and washed with sat. aq. NaCl (2 × 50 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated to provide acid **20** as a cream colored foam (0.659 g, 60%). mp = 140-143 °C; TLC R_f = 0.49 (10% MeOH/ 90% DCM); IR (neat) 3314, 2932, 1669, 1245, 1209, 1100, 1067, 960, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.75 (dd, *J* = 10.8, 3.2 Hz, 1H), 3.58-3.48 (m, 1H), 3.09 (t, *J* = 10.4 Hz, 1H), 2.24 (t, *J* = 11.2 Hz, 1H), 2.09-2.05 (m, 1H), 1.96-1.89 (m, 1H), 1.79-1.38 (m, 13H), 1.34-1.18 (m, 4H), 0.90 (s, 12H), 0.72 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 71.6, 61.0, 51.5, 46.0, 44.8, 42.3, 39.6, 39.4, 38.0, 37.2, 34.3, 31.2, 30.0, 25.8, 25.0, 20.9, 19.6, 18.3, 17.6, 15.6, -5.8. HRMS (ESI+) calcd for $C_{25}H_{46}NaO_4Si$ 461.3057; Found: 461.3053.



21

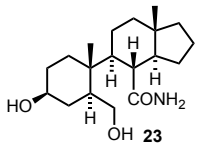
(2*R*,5*S*,16*S*)-5-((tert-butyldimethylsilyl)oxy)-2,16-dimethyl-9-oxatetracyclo[9.7.0.0^{2,7}.0^{12,16}] octadecan-10-lactone (21). Carboxylic acid **20** (0.27 g, 0.62 mmol) was dissolved in 9.2 mL of DCM followed by the addition of DMAP (0.015 g, 0.12 mmol). After stirring for 5 minutes, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.19 g, 1.23 mmol) was then added. This was allowed to stir at rt for 24 h. The reaction was diluted with DCM (75 mL) and washed successively with sat. aq. $NaHCO_3$ (2 x 25 mL), 10% aq. HCl (2 × 25 mL), and sat. aq. NaCl (25 mL). The organic layer was dried with anhydrous $MgSO_4$ and solvent removed under reduced pressure. This was subjected to silica gel chromatography using (20% EA/80% hexanes) to yield protected lactone **21** as a white solid (0.24 g, 92%). TLC R_f = 0.42 (10% EA/90% hexanes); IR (neat) 2972, 1732, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.33 (dd, *J* = 12.9, 7.5 Hz, 1H), 3.61 (d, *J* = 12.8 Hz, 1H), 3.53 (septet, *J* = 15.4, 10.7, 4.7 Hz, 1H), 2.50 (t, *J* = 11.1 Hz, 1H), 1.95-1.83 (m, 2H), 1.82-1.74 (m, 2H), 1.73-1.60 (m, 5H), 1.52-1.15 (m, 8H), 1.12-1.05 (m, 1H), 1.03 (s, 3H), 1.02-0.97 (m, 1H), 0.87 (s, 9H), 0.71 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 70.9, 68.3, 48.5, 47.4, 46.7, 41.9, 39.8, 38.7, 38.7, 37.5, 37.3, 37.2, 31.3, 27.5, 25.9, 22.2, 19.9, 18.2, 16.7, 13.3, -4.7. HRMS (ESI+) calcd for $C_{25}H_{44}O_3Si$:420.3060; Found: 420.3054.



22

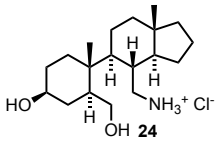
(2*R*,5*S*,16*S*)-5-Hydroxy-2,16-dimethyl-9-oxatetracyclo[9.7.0.0^{2,7}.0^{12,16}]octadecan-10-one (22). Lactone **21** (0.19 g, 0.19 mmol) was added to a 100 mL flame dried round-bottom flask. 5.0 mL of methanol and 6.0 mL of 10% aq. HCl was added to reaction. The reaction mixture was allowed to stir at rt for 4 h. The solution was concentrated down and the contents diluted with EA (50 mL) and water (50 mL). The aqueous phase was extracted with EA (2 × 50 mL) and the collected organic was washed successively with sat. aq. $NaHCO_3$ (2 × 25 mL) and sat. aq. NaCl (1 × 25 mL). The organic layer was then dried with anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification through silica gel chromatography (80% EA/ 20% hexanes) yielded lactone **22** as a white colored solid (0.123 g, 89%). mp = 126-129 °C; TLC R_f = 0.42 (50% EA/ 50% hexanes); IR (neat) 3276, 1733, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.34 (dd, *J* = 12.9, 7.9 Hz, 1H), 3.67-3.49 (m, 2 H), (t, *J* = 10.6 Hz, 1H), 1.96-1.86 (m, 2H), 1.85-1.72 (m, 5H), 1.70-1.58 (m, 4H), 1.53-1.41 (m, 2H), 1.40-1.13 (m, 6H), 1.13-1.10 (m, 1H), 1.07 (s, 3 H), 0.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 70.1, 68.2, 48.5, 47.2, 46.5, 41.8,

39.8, 38.7 (2C), 37.3, 37.2, 36.7, 30.8, 27.5, 22.2, 19.9, 16.7, 13.2. HRMS (ESI+) calcd for $C_{19}H_{30}O_3$ 306.2195; Found: 306.2195.



23

(7a*S*)-5-[(1*R*,4*S*)-4-Hydroxy-2-(hydroxymethyl)-1-methylcyclohexyl]-7a-methylperhydro-1*H*-indene-4-carboxamide (23). A solution of ammonia in THF (9.12 mL, 0.5 M) was cooled to -78˚C in a dry ice / acetone bath. n-BuLi (1.7 mL, 2.5 M) was added dropwise and allowed to stir for 30 min. Lactone **22** (0.350 g, 1.14 mmol) was dissolved in a solution of 5 mL THF and added dropwise into the reaction before allowing the reaction to warm to rt The reaction continued for 24 h. The reaction was diluted with sat. aq. NH_4Cl (20 mL) and extracted successively with EA (2 × 25 mL) The collected organic extracts were washed with saturated NaCl (25 mL). The organic layer was dried with anhydrous $MgSO_4$ and solvent removed under reduced pressure. This was subjected to silica gel chromatography using (90% EA/10% MeOH) to yield amide **23** as a white solid (0.195 g, 53%). TLC R_f = 0.45 (90% EA /10% MeOH); IR (neat) 3333, 3196, 1651 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 3.65 (d, *J* = 10.8 Hz, 1H), 3.37-3.28 (m, 1H), 3.00 (t, *J* = 10.2 Hz, 1H), 2.16 (t, *J* = 10.5 Hz, 1H), 2.02 (d, *J* = 13.2 Hz, 1H), 1.82-1.91 (m, 1H), 1.68-1.06 (m, 17H), 0.84 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.9, 69.9, 61.1, 51.2, 44.7, 44.6, 42.4, 39.8, 39.4, 38.1, 37.4, 33.5, 30.4, 29.9, 26.1, 21.0, 19.6, 18.3, 15.8. HRMS (ESI+) calcd for $C_{19}H_{33}NO_3$: 323.2460; Found 323.2456.



24

(1*S*,4*R*)-4-[(7a*S*)-4-(Aminomethyl)-7a-methylperhydro-1*H*-inden-5-yl]-3-(hydroxymethyl)-4-methylcyclohexanol ammonium chloride (24). Amide **23** (0.100 g, 0.31 mmol) was dissolved in 3.0 mL of dry THF and cooled to 0˚C. $LiAlH_4$ (4.64 mL, 1.0 M in THF) was added dropwise to the stirring solution. The temperature was increased to reflux for 20 h. The reaction was cooled to rt and diluted with THF before being cooled to 0 ˚C. Fieser method was used to work up the reaction. The filtered product was dried with $MgSO_4$ and concentrated down to give the crude amine. Purification through silica gel chromatography (9% methanol: 90% EA: 1% NH_4OH) yield the amine **S3** as a clear oil (0.033 g). This was dissolved in 3.0 mL of Et_2O and HCl (g) was bubbled into the solution at rt for 15 min. The solution was then concentrated and the residue was washed with diethyl ether (2×) to yield the amine hydrochloride salt **24** as a white solid (0.019 g, 29%). IR (neat) 3310, 2929, 1612, 1378, 1036, 1003, 951, 732 cm^{-1}; ^1H NMR (300 MHz, MeOD) δ 3.71 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.45-3.35 (m, 1H), 3.21-3.00 (m, 2H), 2.15 (d, *J* = 12.3 Hz, 1H), 1.91-1.67 (m, 8H), 1.63-1.38 (m, 6H), 1.36-1.18 (m, 6H), 1.07 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (75 MHz, MeOD) δ 70.8, 62.6, 51.0, 45.6, 46.6, 43.0, 41.6, 41.2, 39.6, 38.1, 37.4, 35.0, 31.9, 26.8, 24.0, 21.9, 21.1, 17.3, 15.4. HRMS (ESI+) calcd for $C_{19}H_{35}NO_2$: 309.2668; Found: 309.2671.

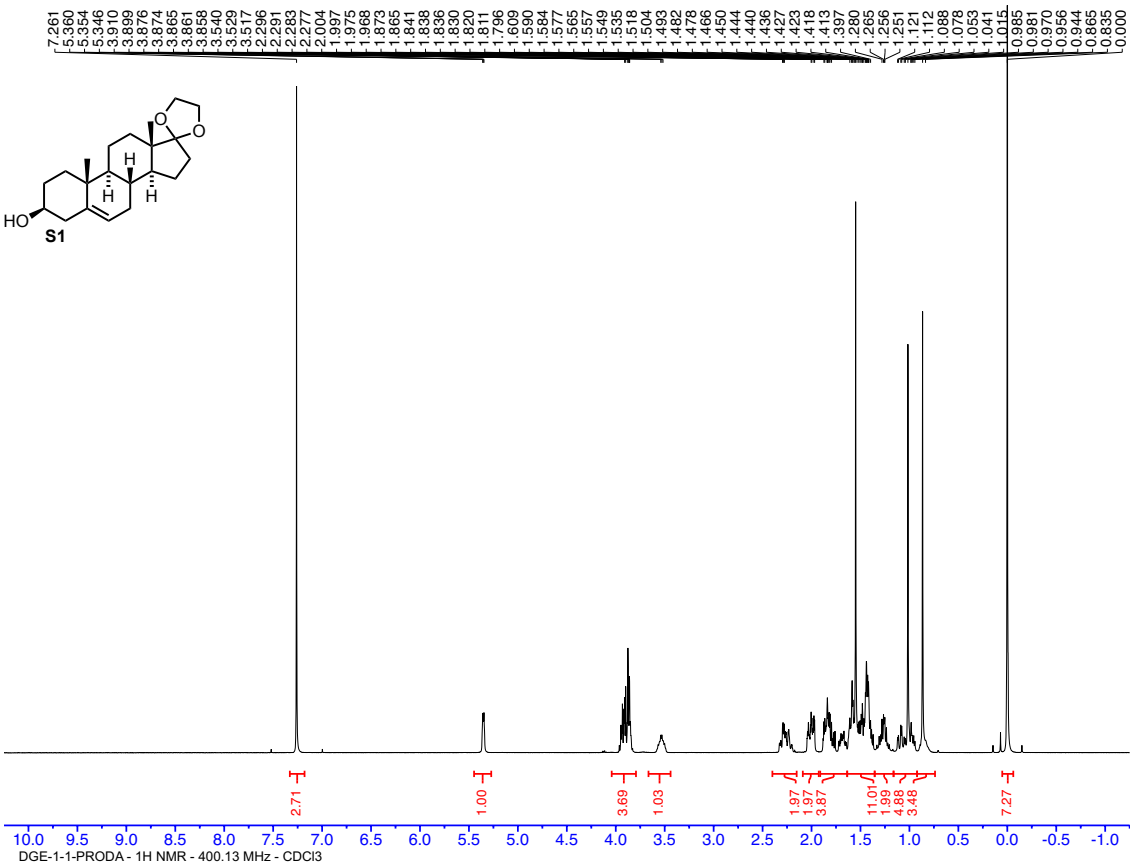
<u>Malachite Green Phosphatase Release Assays.</u>

Malachite Green Phosphatase Release Assays (Echelon Biosciences) were performed with recombinant human truncated SHIP1 (tSHIP1)(see Brooks, R.; Iyer, S.; Akada, H.; Neelam, S.; Russo, C. M.; Chisholm, J. D.; Kerr, W. G. *Stem Cells* **2015,** *33*, 848-58. doi:10.1002/stem.1902). Briefly, serial dilutions of the compounds dissolved in DMSO were added to the recombinant enzymes diluted in reaction buffer Rx (50mM Hepes pH 7.4, 150mM NaCl, 1mM $MgCl_2$, 0.25mM EDTA) in triplicate reactions in 96-well plates. Reactions were incubated at 37 ˚C for 30 min. 2.5 mL of 1mM Phosphatidylinositol 3,4,5-trisphosphate diC8 (PI(3,4,5)P_3diC8) (Echelon Biosciences) was added to each

reaction to a final concentration of 100µM in a final volume of 25 mL /well. Following 20 min incubation at 37˚C, 100µL of Malachite Green Solution (Echelon Biosciences) was added to each well and plates were incubated at room temperature in the dark for 15 min. Plates were then read at 620nm on a plate reader (Synergy 2, BioTek). Mean ± SEM of enzymatic activity is expressed at % of solvent alone control (5% DMSO). Data was pooled from triplicate wells from 4 independent experiments.

Cell Viability Assay

OPM-2 cells (DSMZ) were seeded $4x10^5$cells/ml in media (10%FBS:DMEM) in 96-well plates and incubated with dilutions of 3AC (in 1% EtOH final) or AQX-1125 (in DMSO 1% final) at 37 °C, 5% CO_2. After 24 h incubation, 10ul of Cell Counting Kit-8 solution (CCK-8, Dojindo Molecular Technologies, Inc.) was added, incubation was continued for 2h at 37˚C and O.D.450nm was measured on a Bio-Tek Synergy 2 plate reader. Cell viability is expressed as % of vehicle treated cells (compound concentration 0). Data were pooled from at least 4-well replicates from 3 independent experiments, and were analyzed with 1-way Analysis of Variance (ANOVA) in GraphPad Prizm 9.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2.277
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H
O
O
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1.00
3.69
1.03
1.97
1.97
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4.88
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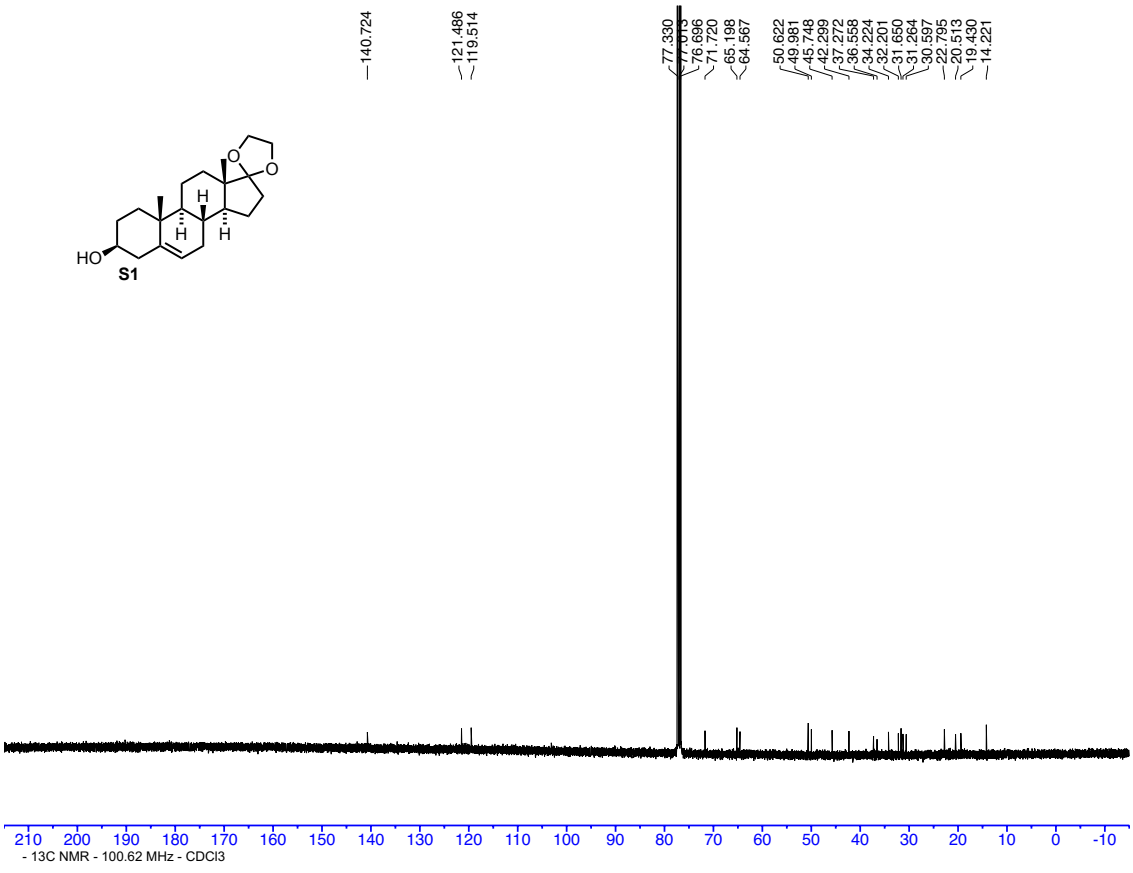
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
DGE-1-1-PRODA - 1H NMR - 400.13 MHz - CDCl3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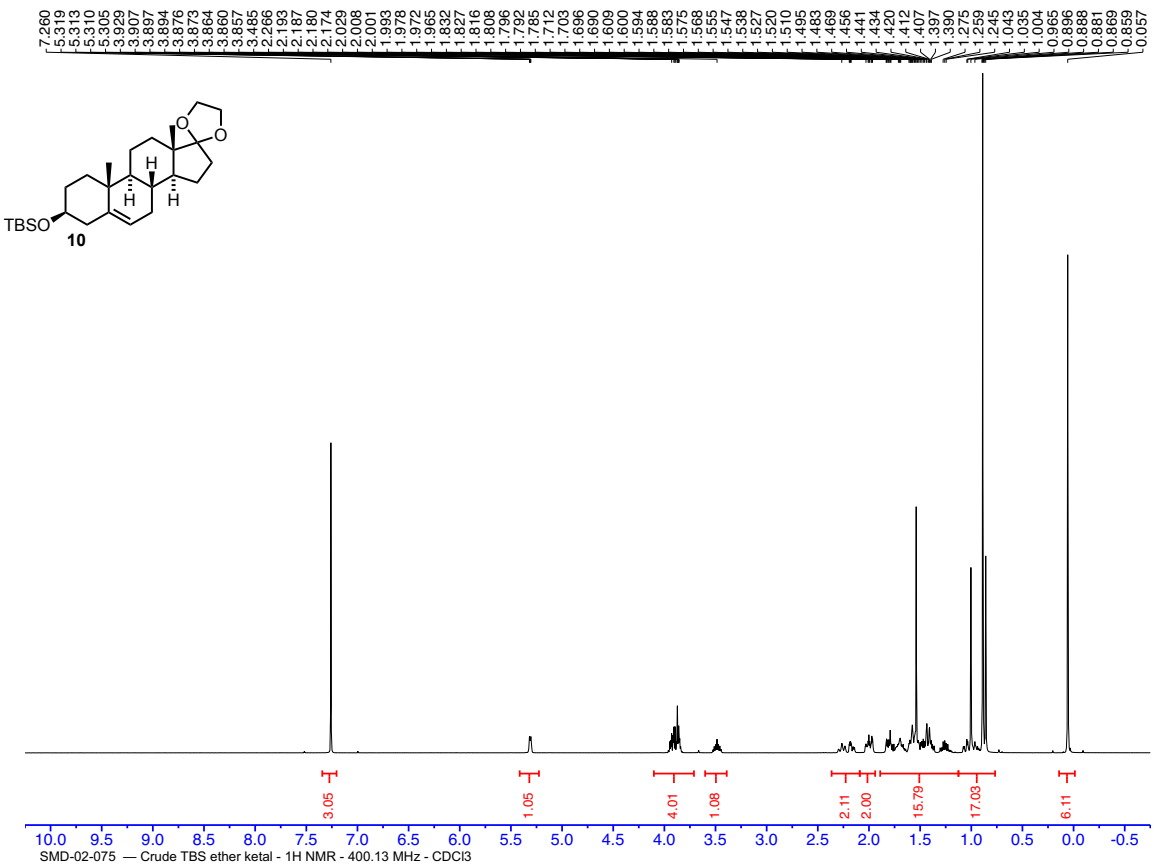
- 13C NMR - 100.62 MHz - CDCl3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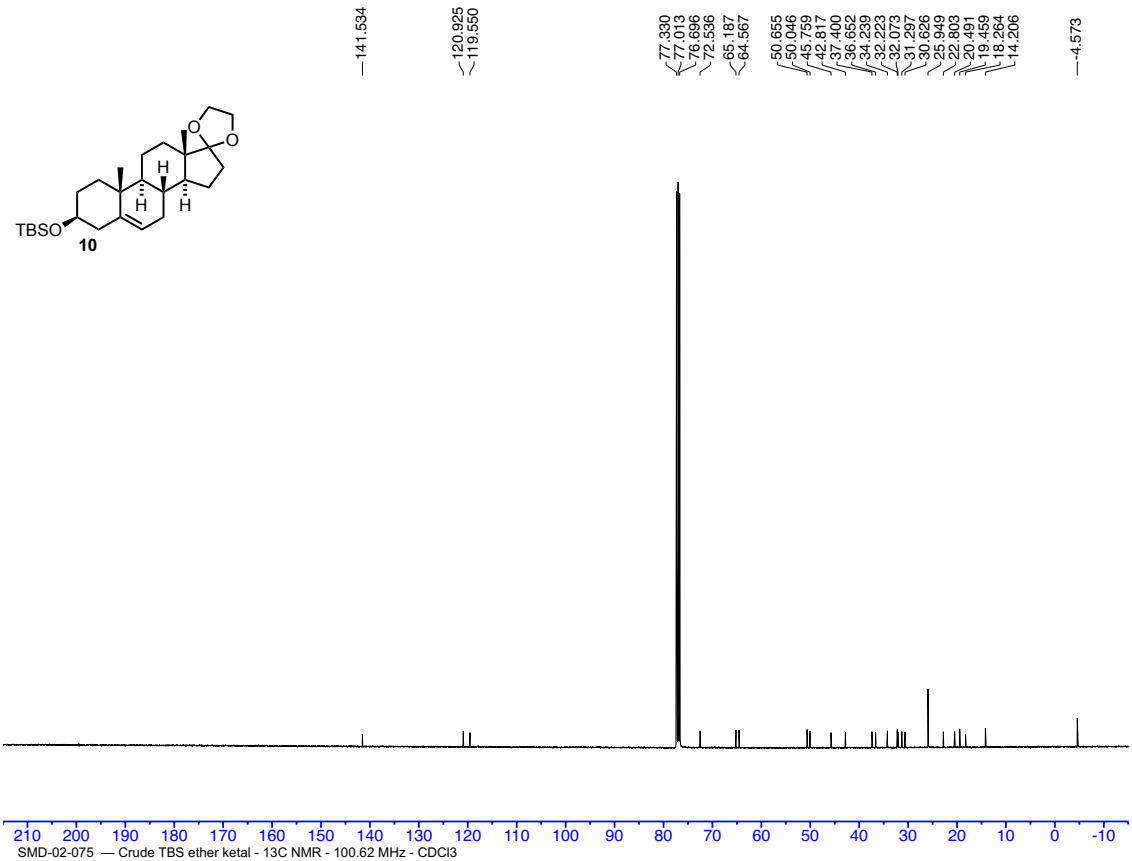
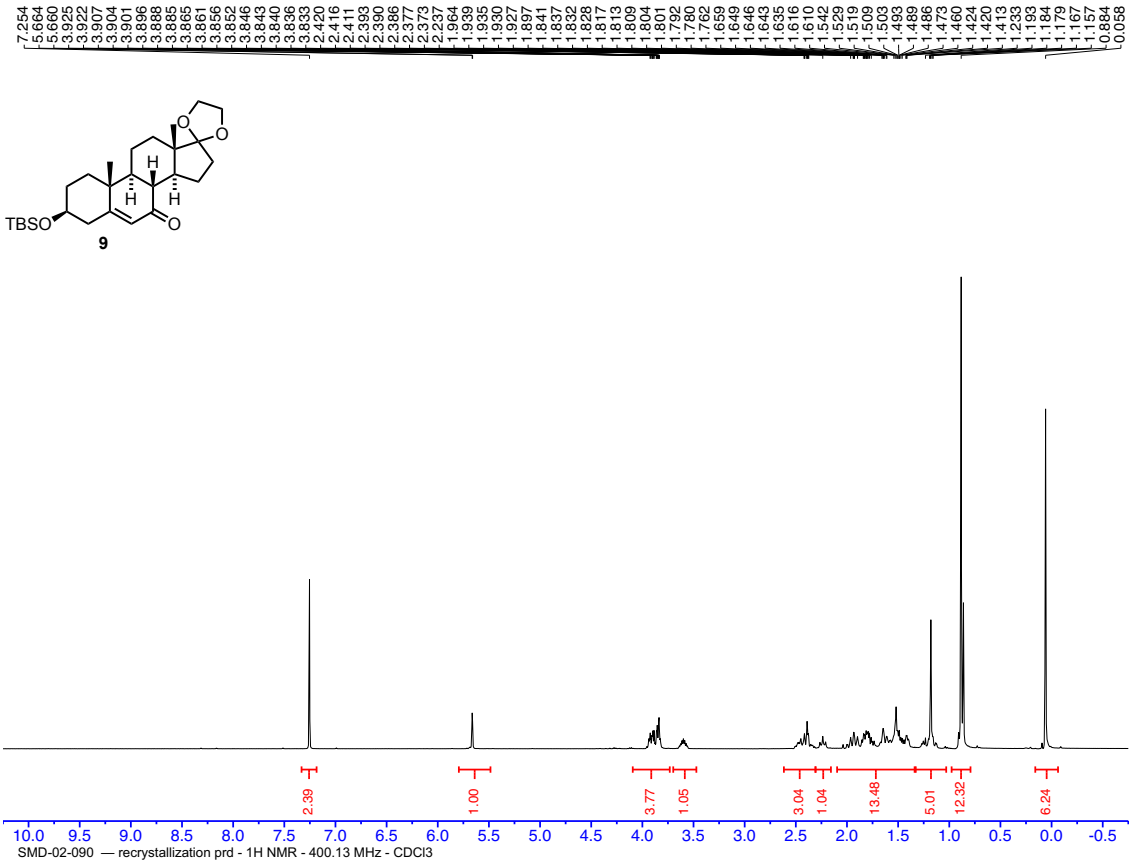
SMD-02-075 — Crude TBS ether ketal - 1H NMR - 400.13 MHz - CDCl3


TBSO
10
SMD-02-075 — Crude TBS ether ketal - 13C NMR - 100.62 MHz - CDCl3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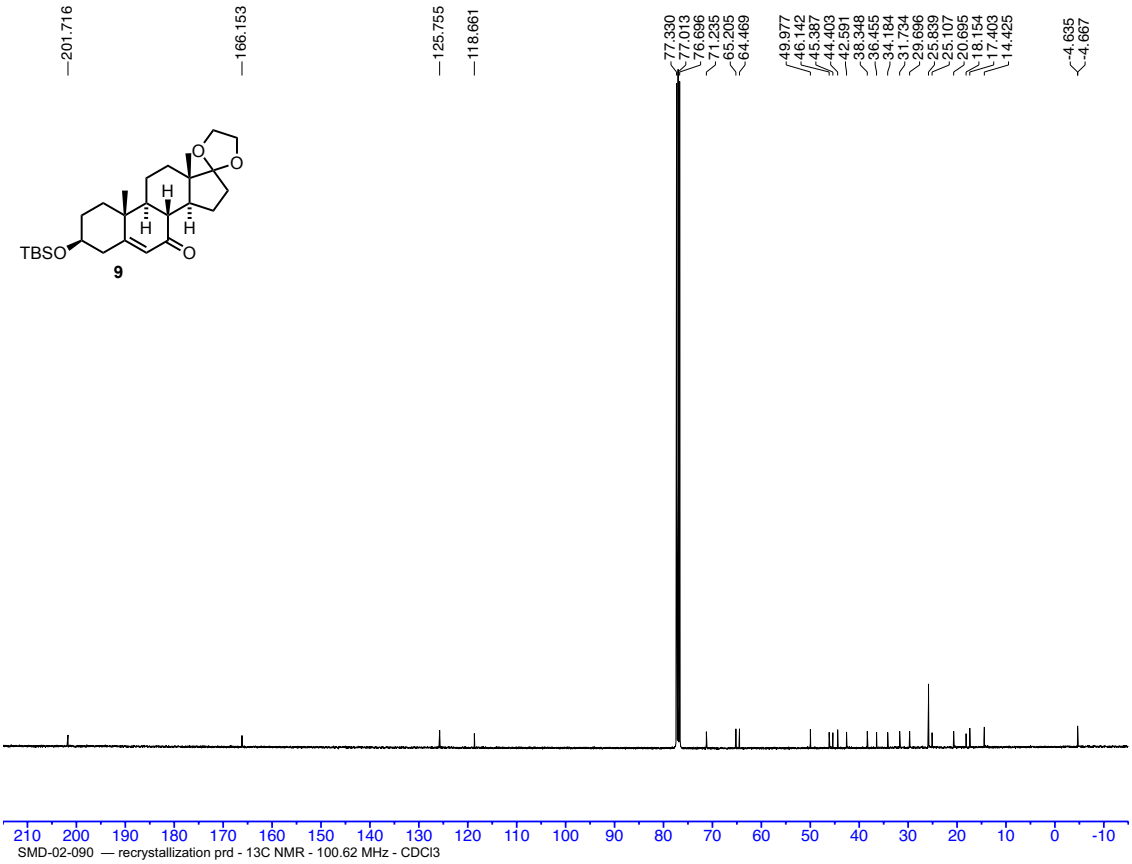
SMD-02-090 — recrystallization prd - 1H NMR - 400.13 MHz - CDCl3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H
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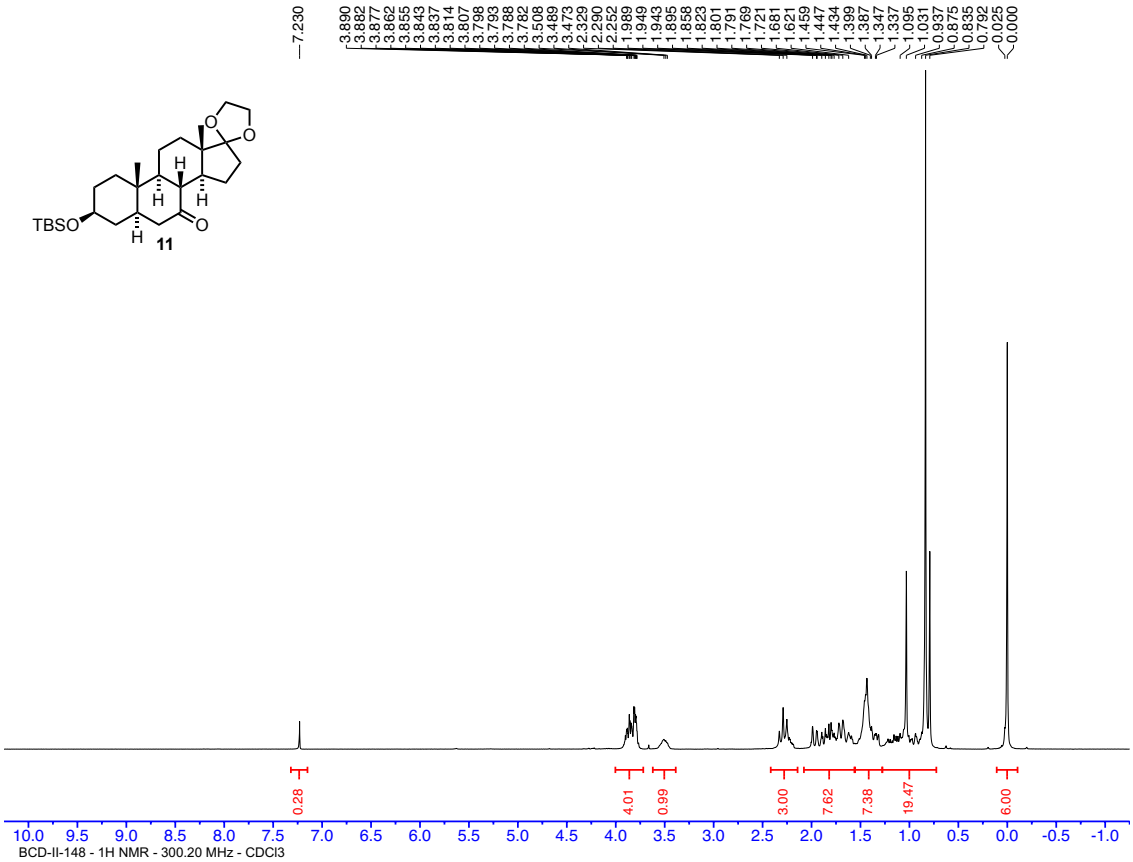
SMD-02-090 — recrystallization prd - 13C NMR - 100.62 MHz - CDCl3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7.38
19.47
6.00
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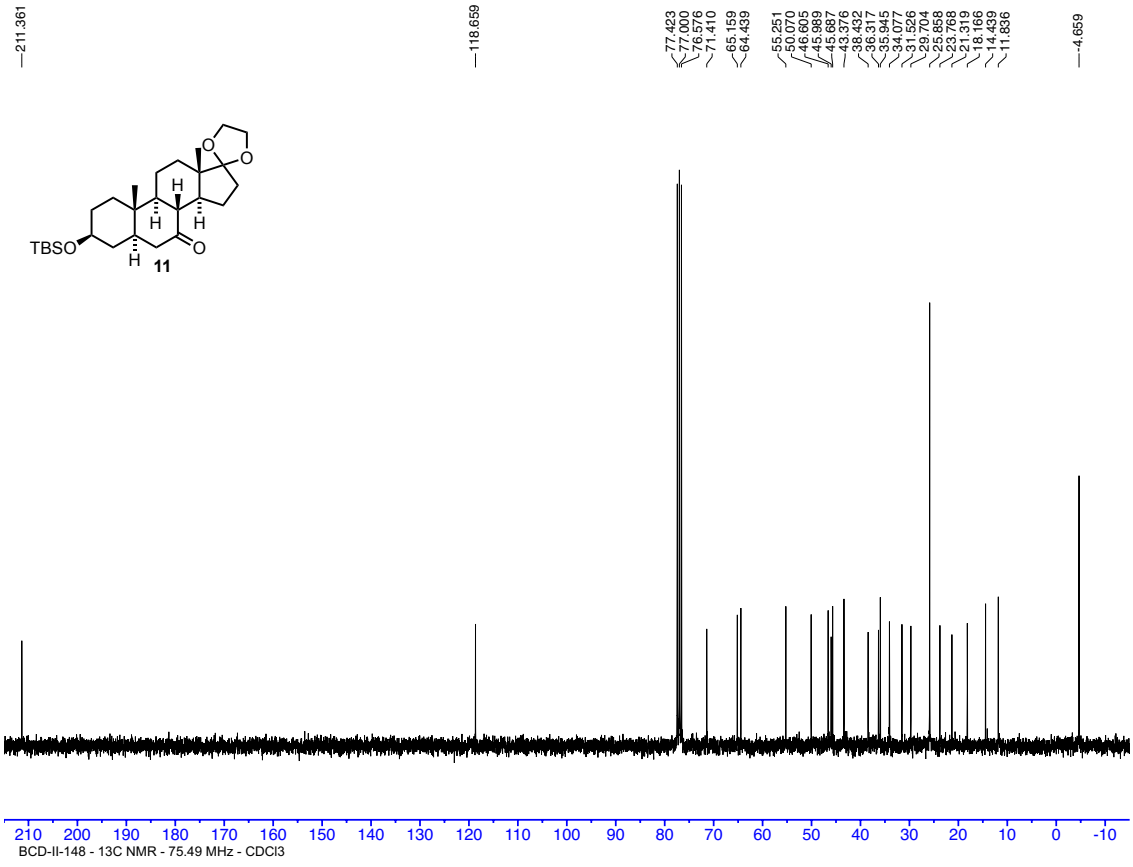
BCD-II-148 - 1H NMR - 300.20 MHz - CDCl3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H
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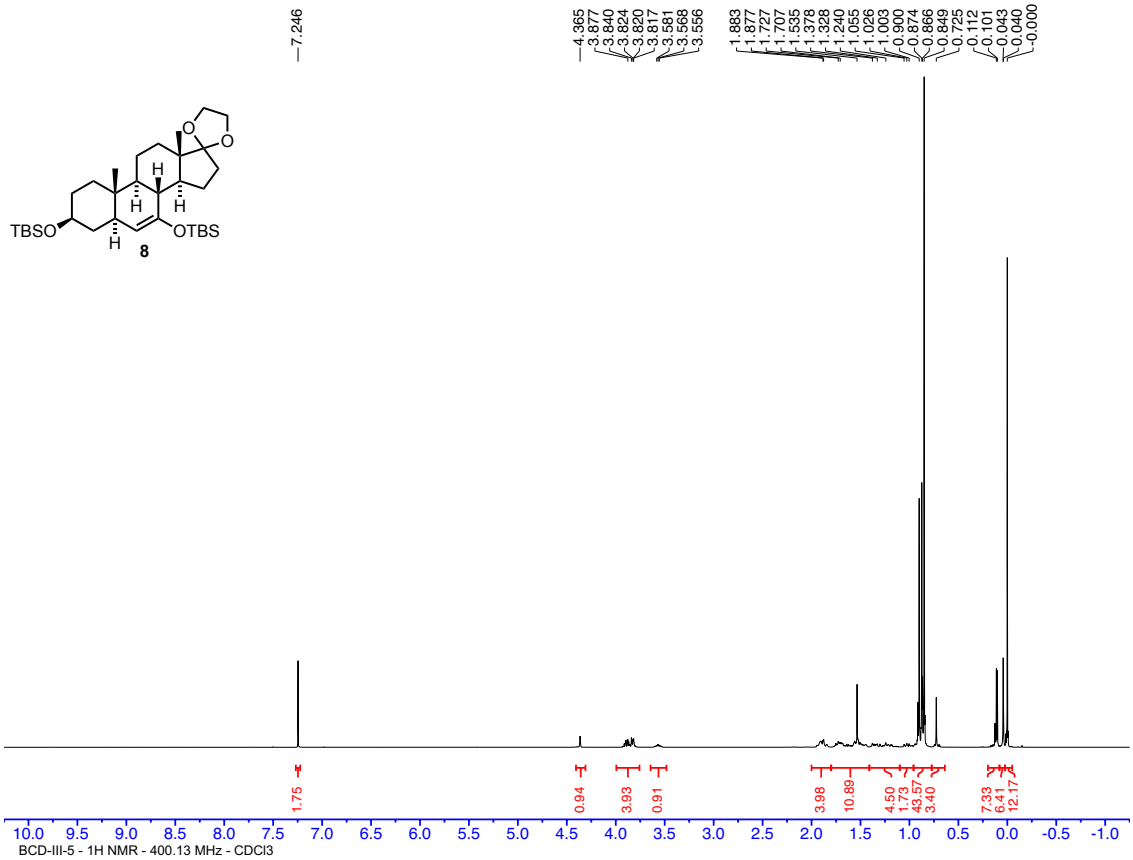
BCD-II-148 - 13C NMR - 75.49 MHz - CDCl3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0.101
0.043
0.040
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0.91
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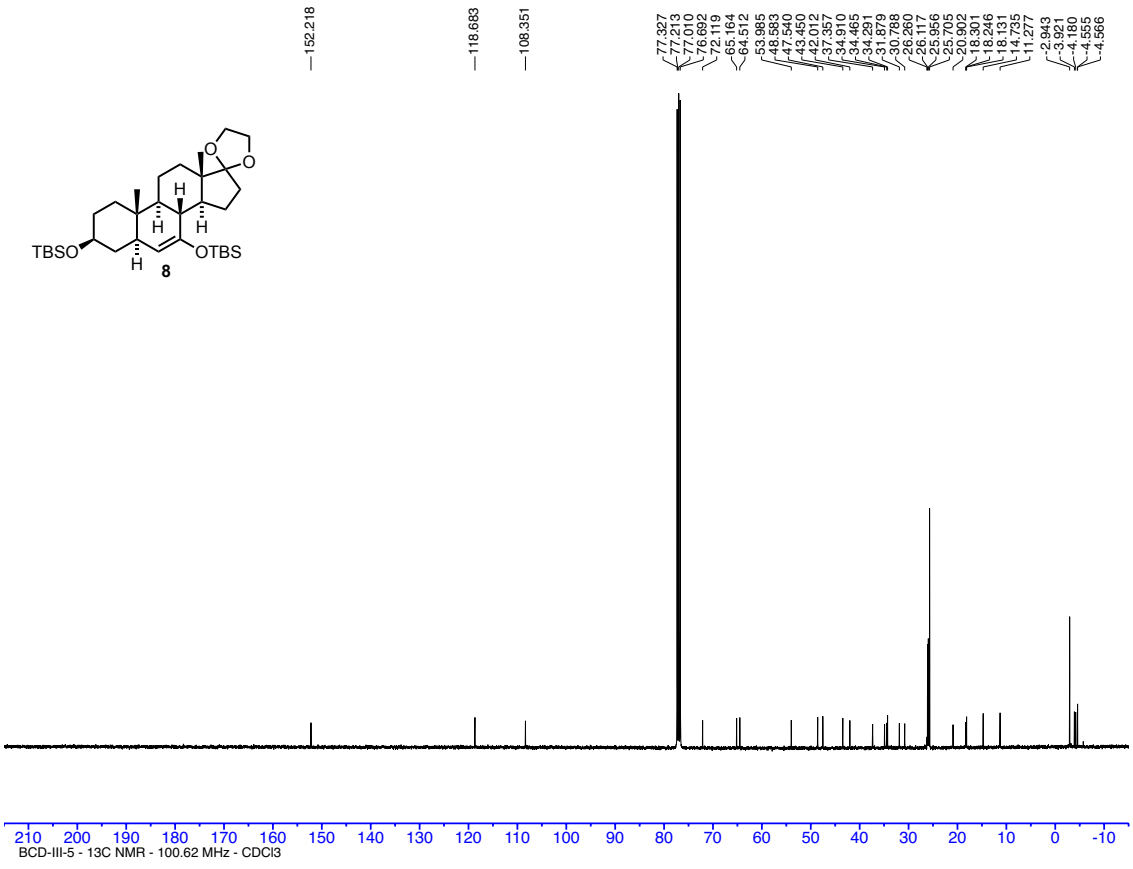
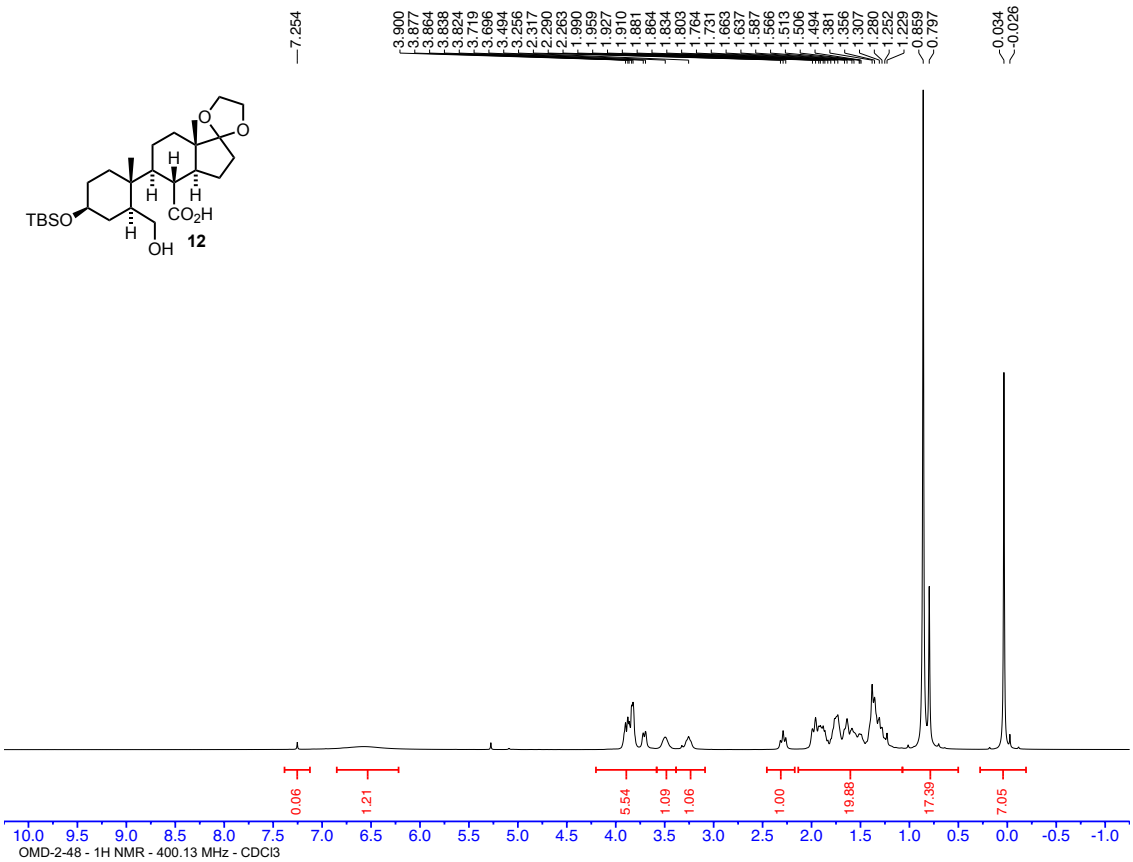
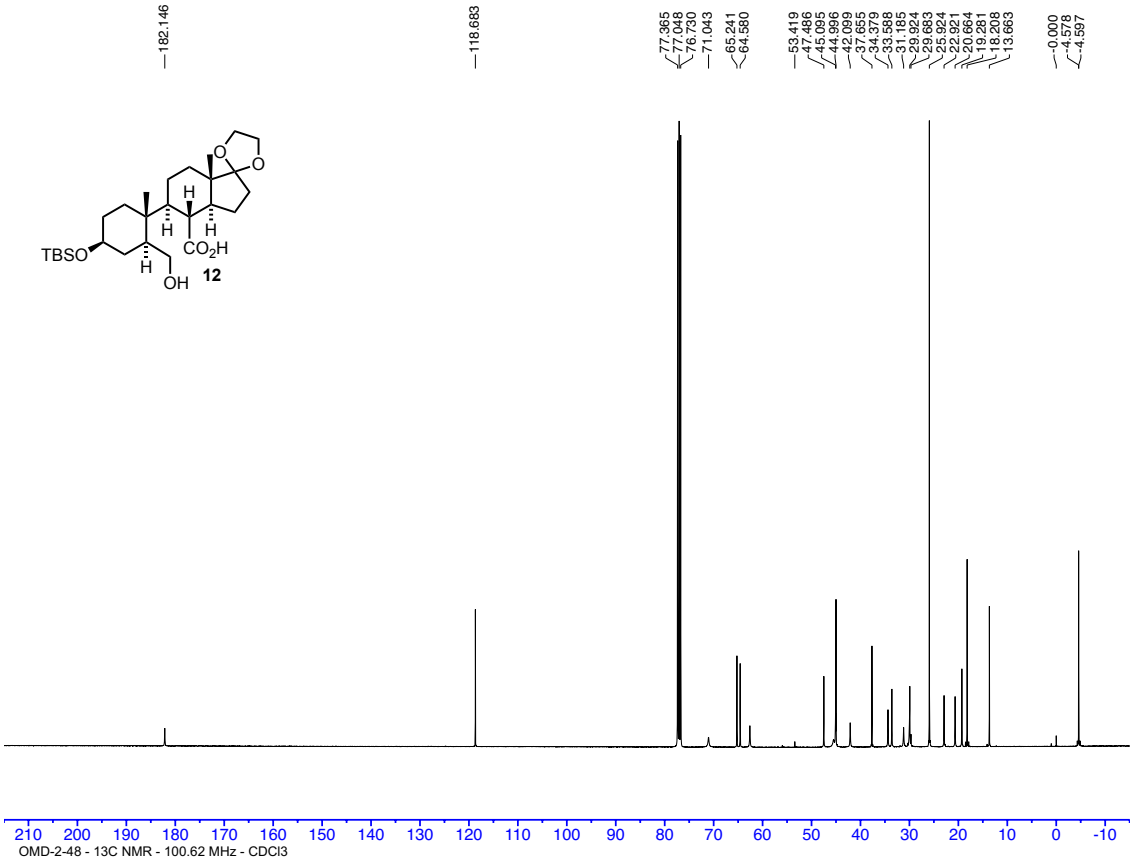
10.89
4.50
1.73
43.57
3.40
7.33
6.41
12.17
BCD-III-5 - 1H NMR - 400.13 MHz - CDCl3


152.218
118.683
108.351
77.327
77.213
77.010
76.692
72.119
65.164
64.512
53.985
48.583
47.540
43.450
42.012
37.357
34.910
34.465
34.291
31.879
30.788
26.260
26.117
25.956
25.705
20.902
18.301
18.246
18.131
14.735
11.277
-2.943
-3.921
-4.180
-4.555
-4.566
TBSO
OTBS
8
BCD-III-5 - 13C NMR - 100.62 MHz - CDCl3


7.254
3.900
3.877
3.864
3.838
3.824
3.719
3.696
3.494
3.256
2.317
2.290
2.263
1.990
1.959
1.927
1.910
1.881
1.864
1.834
1.803
1.764
1.731
1.663
1.637
1.587
1.566
1.513
1.506
1.494
1.381
1.356
1.307
1.280
1.252
1.229
0.859
0.797
0.034
-0.026
TBSO
H
H
H
CO2H
H
OH
12
0.06
1.21
5.54
1.09
1.06
1.00
19.88
17.39
7.05
10.0 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 -0.5 -1.0
OMD-2-48 - 1H NMR - 400.13 MHz - CDCl3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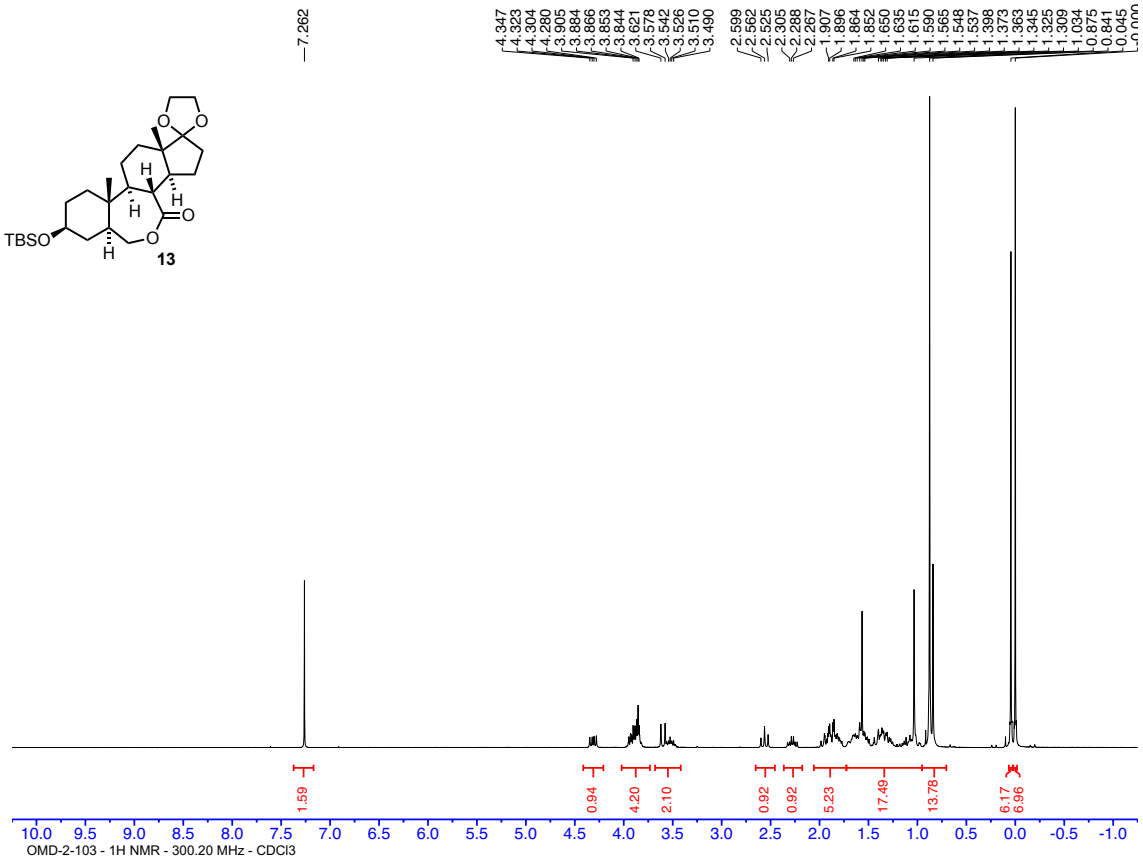
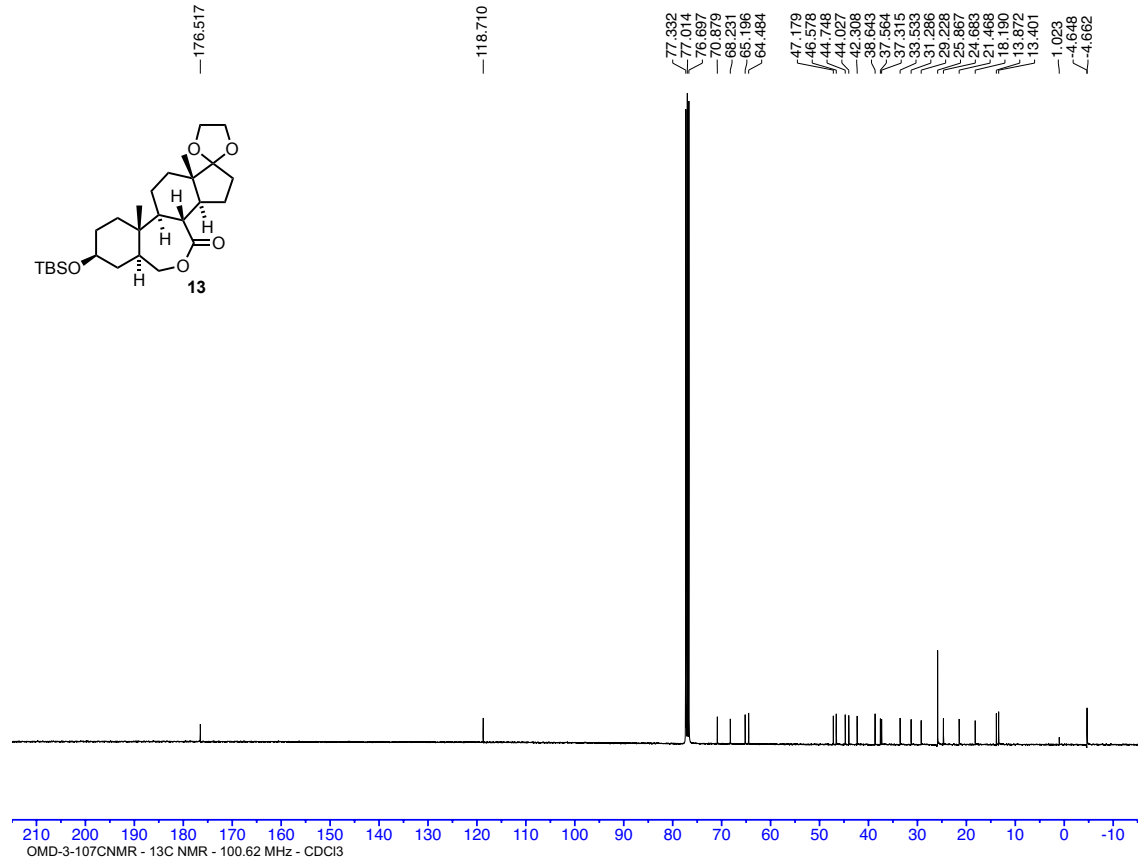
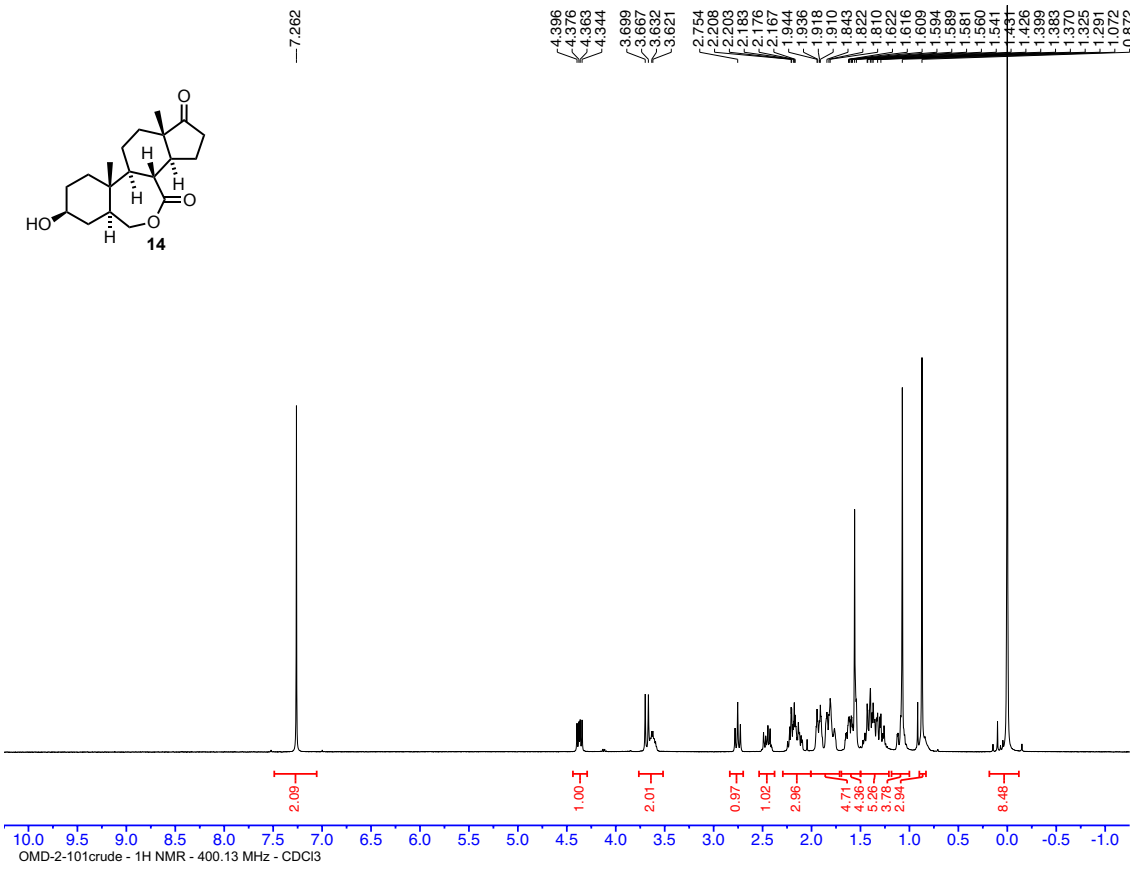
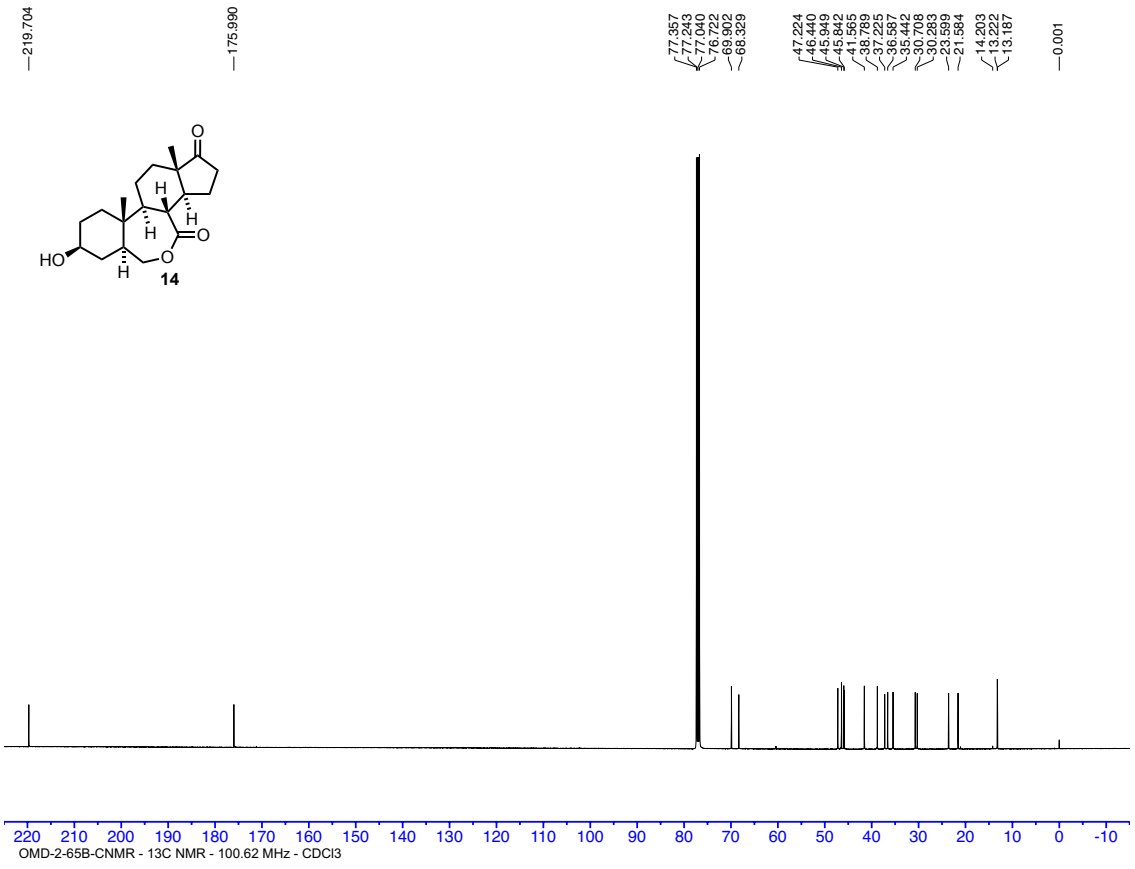
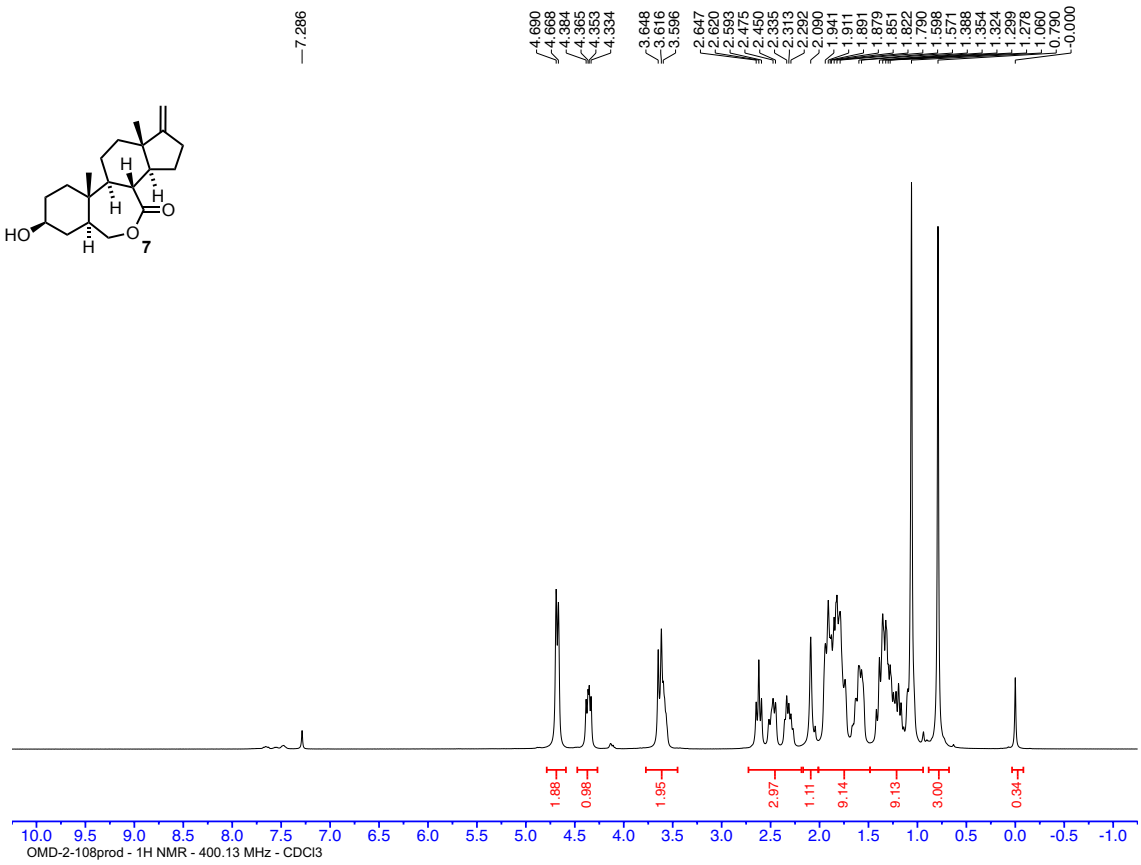
118.683
77.365
77.048
76.730
71.043
65.241
64.560
53.419
47.486
45.095
44.996
42.099
37.655
34.379
33.588
31.185
29.924
29.683
25.924
22.921
20.664
19.281
18.208
13.663
0.000
-4.578
-4.597
TBSO
H
H
H
CO2H
H
OH
12
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
OMD-2-48 - 13C NMR - 100.62 MHz - CDCl3

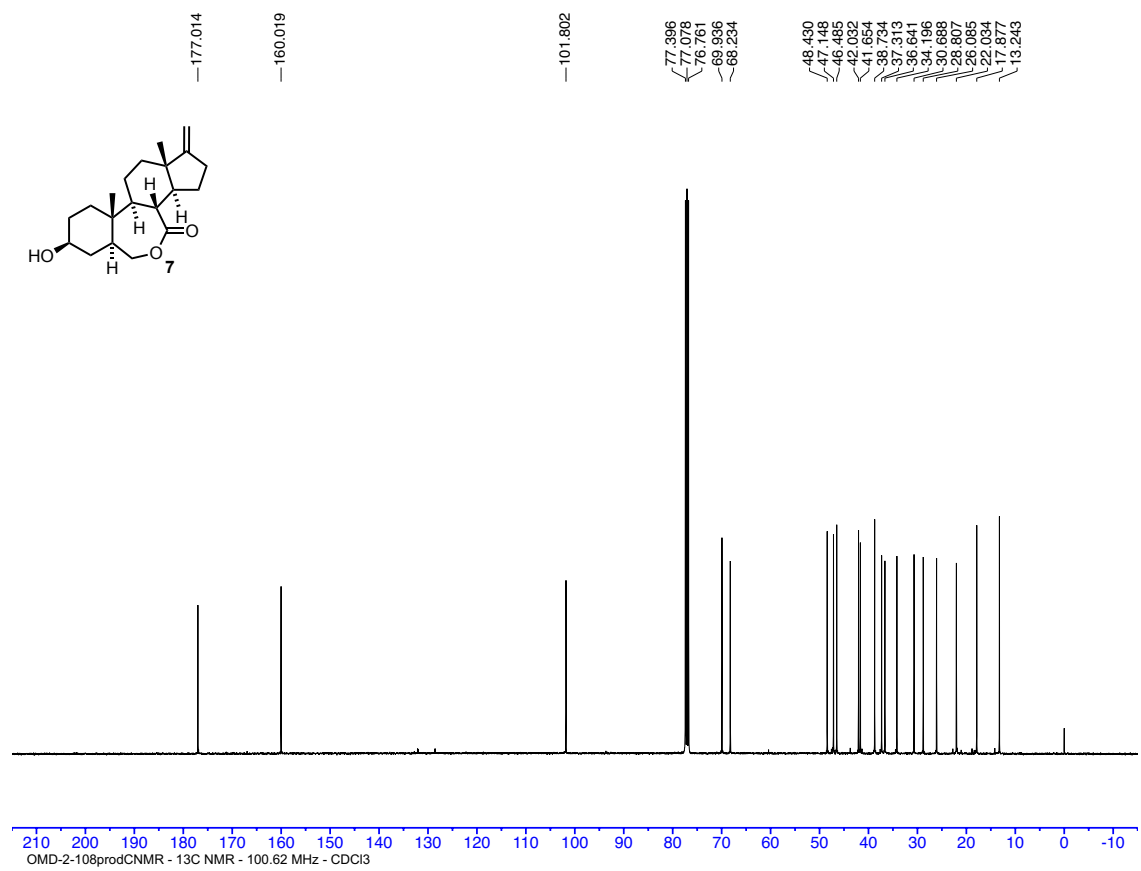

7.262
4.347
4.323
4.304
4.280
3.905
3.884
3.866
3.853
3.844
3.621
3.578
3.542
3.526
3.510
3.490
2.599
2.562
2.525
2.305
2.288
2.267
1.907
1.896
1.864
1.852
1.650
1.635
1.615
1.590
1.565
1.548
1.537
1.398
1.373
1.363
1.345
1.325
1.309
1.034
0.875
0.841
0.045
TBSO
13
1.59
0.94
4.20
2.10
0.92
0.92
5.23
17.49
13.78
6.17
6.96
10.0 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 -0.5 -1.0
OMD-2-103 - 1H NMR - 300.20 MHz - CDCl3

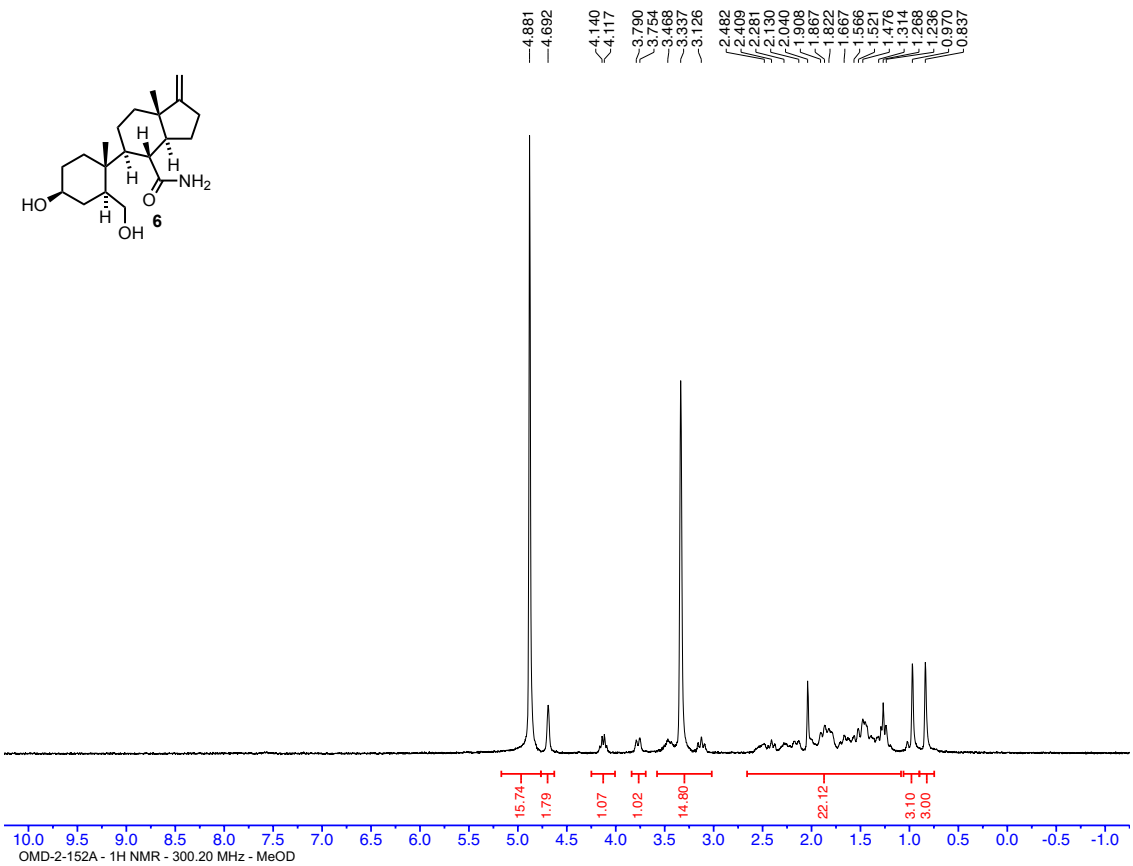

176.517
118.710
77.332
77.014
76.697
70.879
68.231
65.196
64.484
47.179
46.578
44.748
44.027
42.308
38.643
37.564
37.315
33.533
31.286
29.228
25.867
24.683
21.468
18.190
13.872
13.401
1.023
-4.648
-4.662
TBSO
13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
OMD-3-107CNMR - 13C NMR - 100.62 MHz - CDCl3

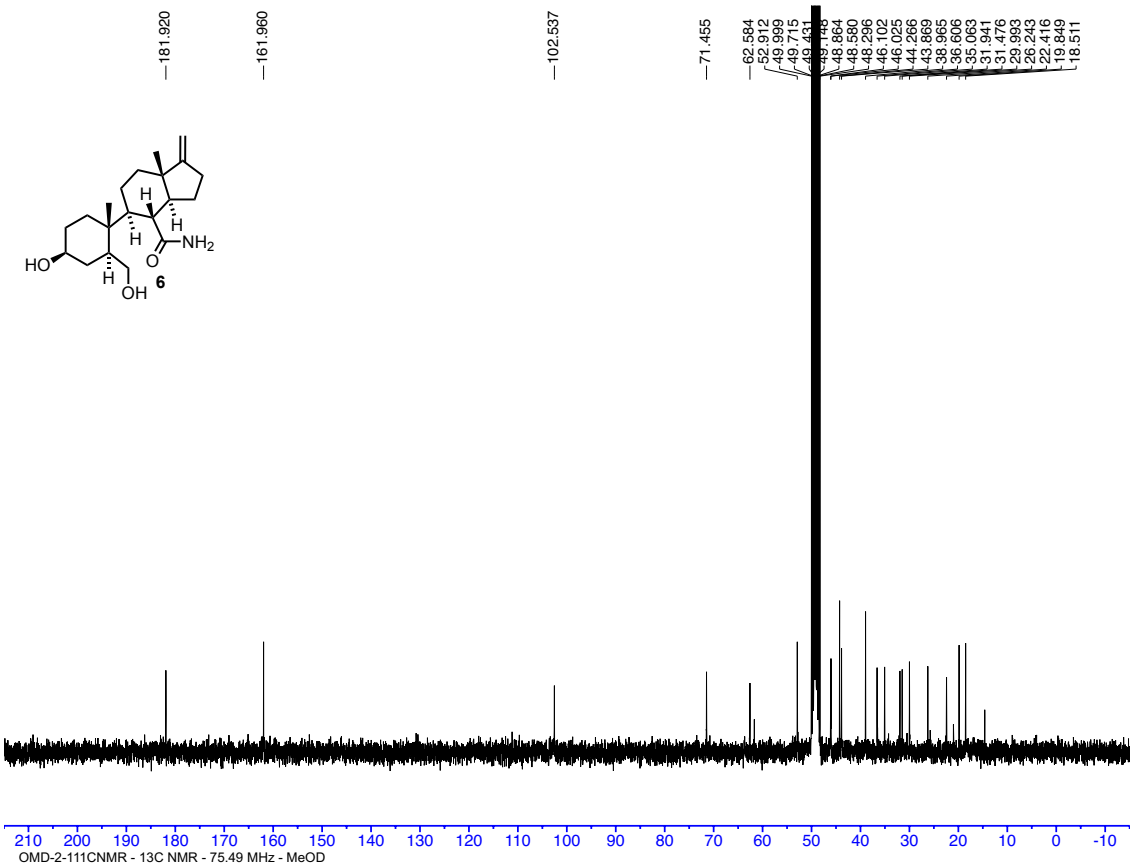

7.262
4.396
4.376
4.363
4.344
3.699
3.667
3.632
3.621
2.754
2.208
2.203
2.183
2.176
2.167
1.944
1.936
1.918
1.910
1.843
1.822
1.810
1.622
1.616
1.609
1.594
1.589
1.581
1.560
1.541
1.431
1.426
1.399
1.383
1.370
1.325
1.291
1.072
2.09
1.00
2.01
0.97
1.02
2.96
4.71
4.36
5.28
3.78
2.94
8.48
10.0 9.5 9.0 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 -0.5 -1.0
OMD-2-101crude - 1H NMR - 400.13 MHz - CDCl3

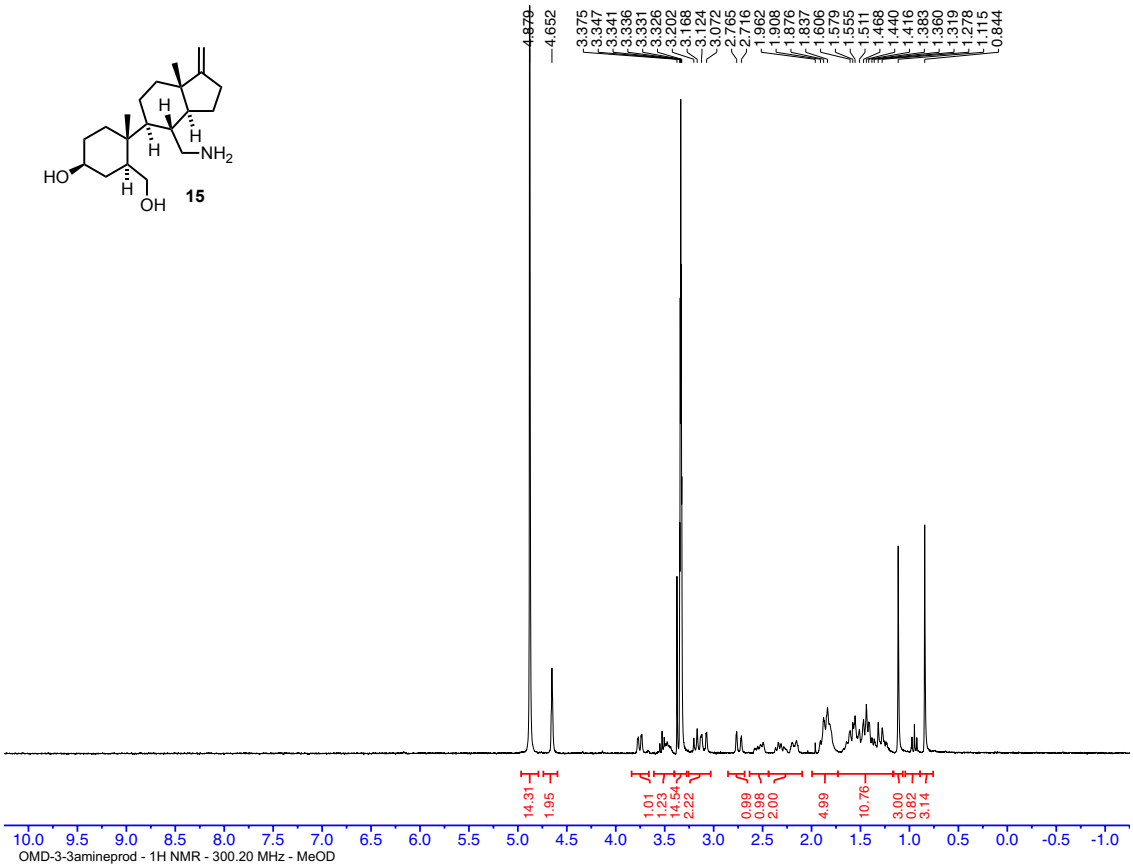

219.704
175.990
77.357
77.243
77.040
76.722
69.902
68.329
47.224
46.440
45.949
45.842
41.565
38.789
37.225
36.587
35.442
30.708
30.283
23.599
21.584
14.203
13.222
13.187
0.001
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
OMD-2-65B-CNMR - 13C NMR - 100.62 MHz - CDCl3

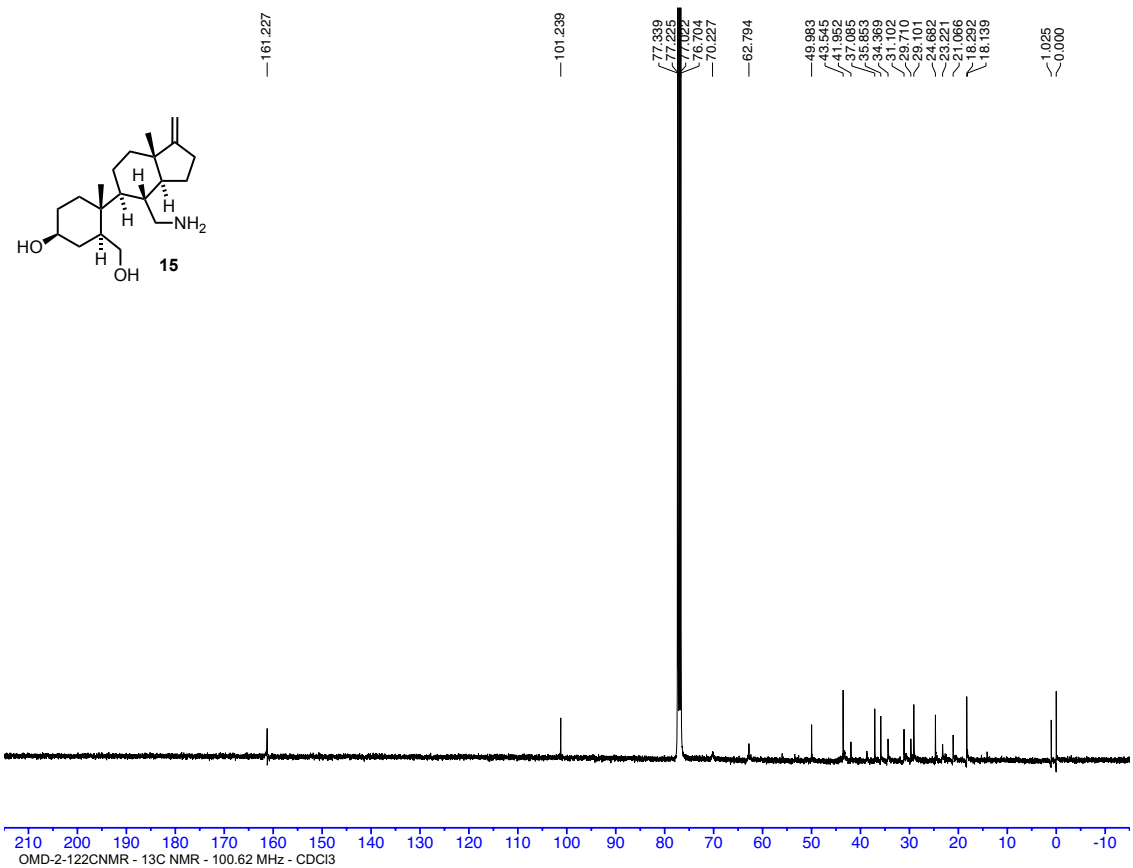

7.286
4.690
4.668
4.384
4.365
4.353
4.334
3.648
3.616
3.596
2.647
2.620
2.593
2.475
2.450
2.335
2.313
2.292
2.090
1.941
1.911
1.891
1.879
1.851
1.822
1.790
1.598
1.571
1.388
1.354
1.324
1.299
1.278
1.060
0.790
-0.000
HO
H
H
H
O
O
7
1.88
0.98
1.95
2.97
1.11
9.14
9.13
3.00
0.34
10.0 9.5 9.0 8.5 8.0 7.5 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 -0.5 -1.0
OMD-2-108prod - 1H NMR - 400.13 MHz - CDCl3

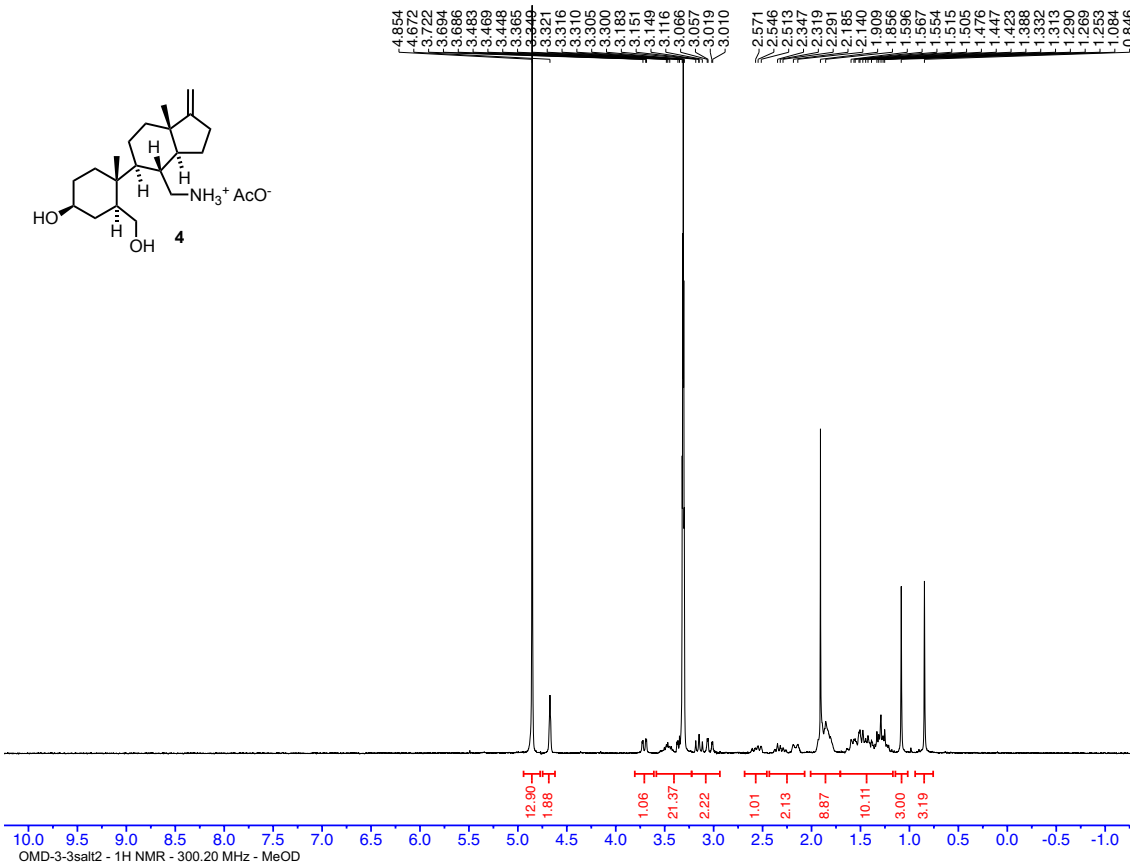

177.014
160.019
101.802
77.396
77.078
76.761
69.936
68.234
48.430
47.148
46.485
42.032
41.654
38.734
37.313
36.641
34.196
30.688
28.807
26.085
22.034
17.877
13.243
HO
H
H
H
O
O
7
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
OMD-2-108prodCNMR - 13C NMR - 100.62 MHz - CDCl3

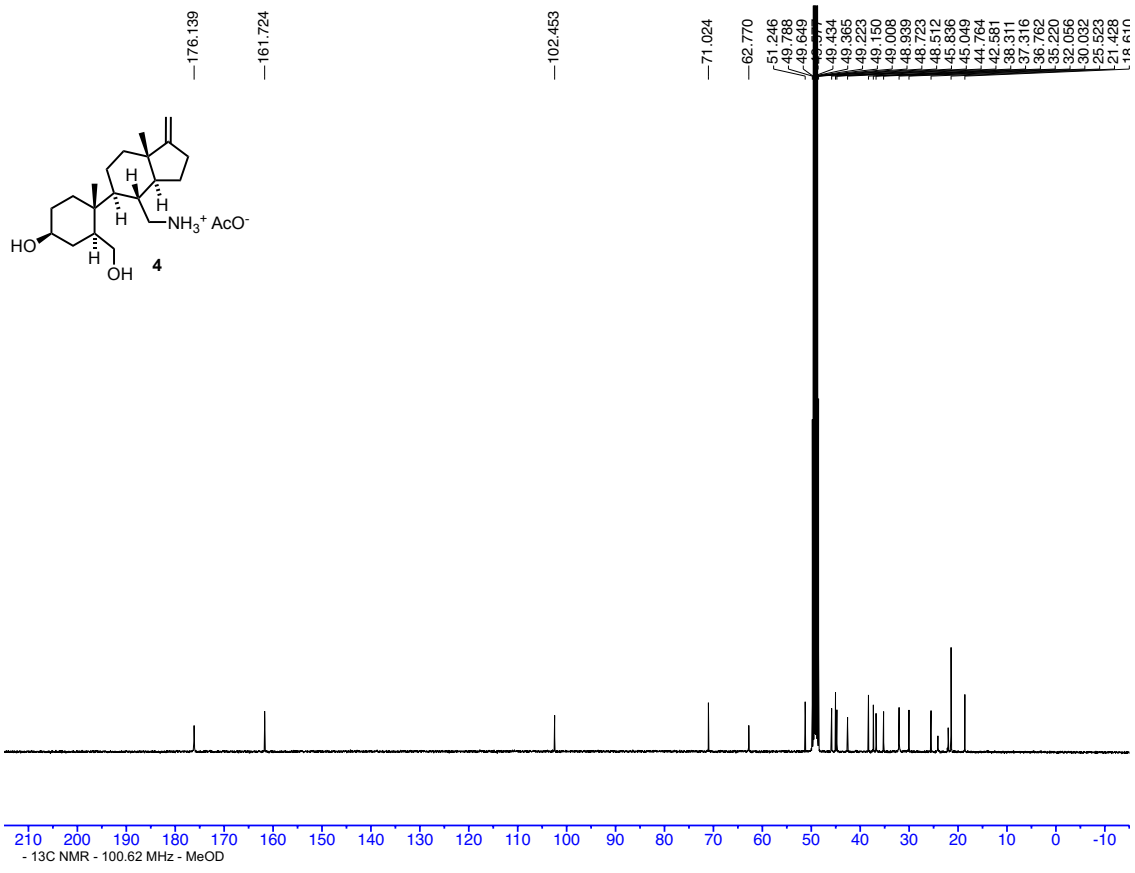

4.881
4.692
4.140
4.117
3.790
3.754
3.468
3.337
3.126
2.482
2.409
2.281
2.130
2.040
1.908
1.867
1.822
1.667
1.586
1.521
1.476
1.314
1.268
1.236
0.970
0.837
HO
H
H
H
NH2
O
H
OH
6
15.74
1.79
1.07
1.02
14.80
22.12
3.10
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
OMD-2-152A - 1H NMR - 300.20 MHz - MeOD

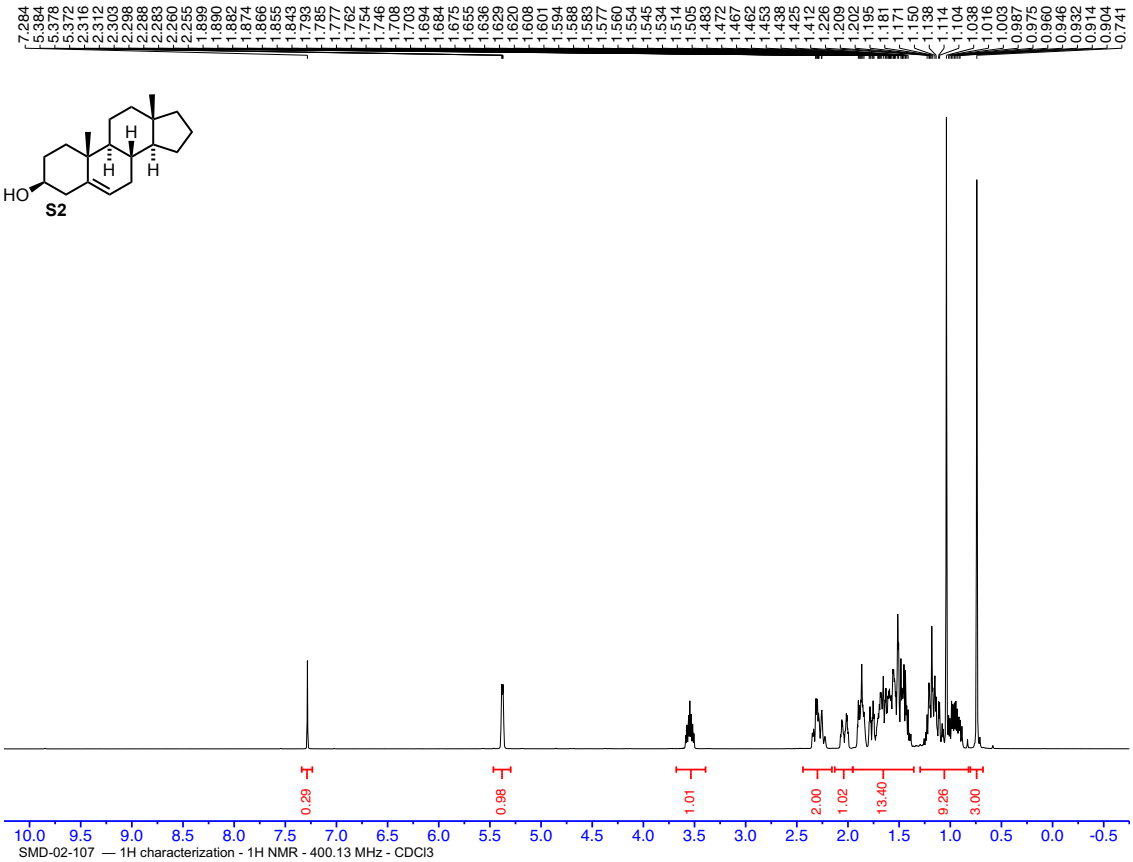

181.920
161.960
102.537
71.455
62.584
52.912
49.999
49.715
49.431
49.148
48.864
48.580
48.296
48.012
46.102
46.025
44.266
43.869
38.965
36.606
35.063
31.941
31.476
29.993
26.243
22.416
19.849
18.511
HO
H
H
H
NH2
O
H
OH
6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
OMD-2-111CNMR - 13C NMR - 75.49 MHz - MeOD

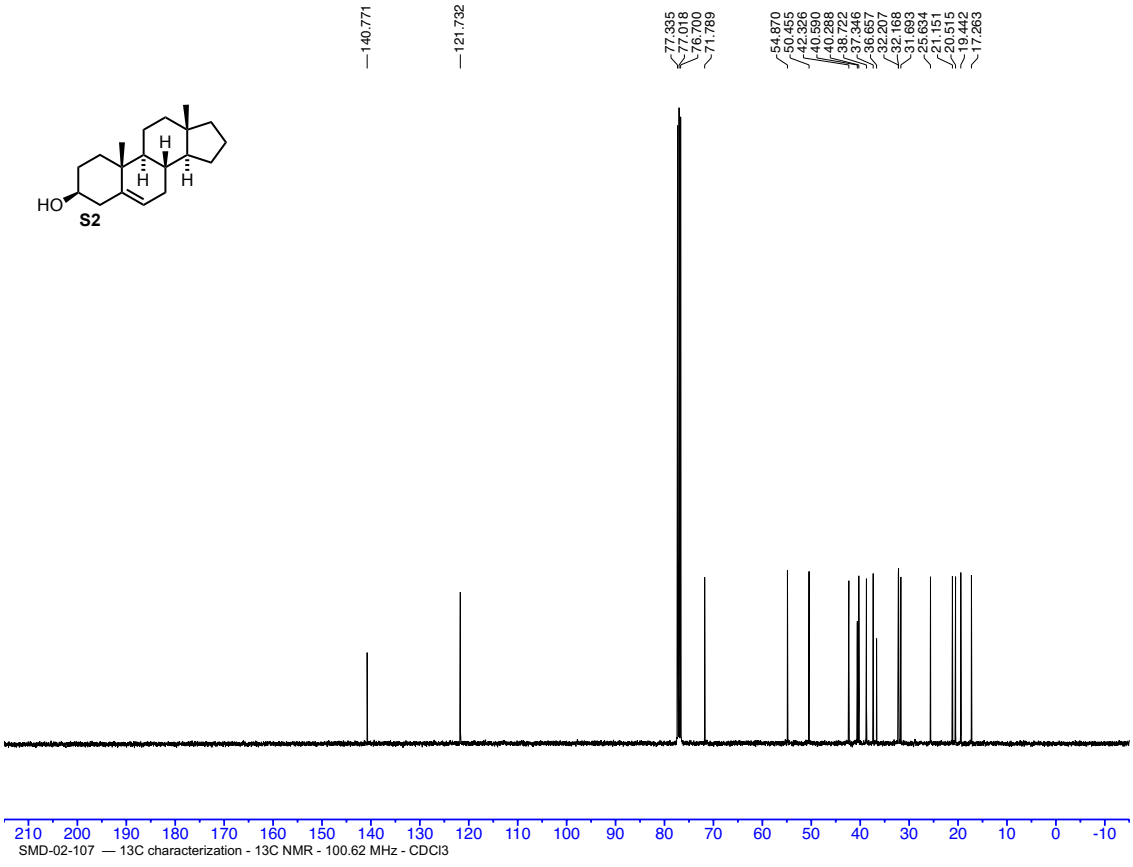

HO
H
H
H
NH2
H
OH
15
4.879
4.652
3.375
3.347
3.341
3.336
3.331
3.326
3.202
3.168
3.124
3.072
2.765
2.716
1.962
1.908
1.876
1.837
1.606
1.579
1.555
1.511
1.468
1.440
1.416
1.383
1.360
1.319
1.278
1.115
0.844
14.31
1.95
1.01
1.23
14.54
2.22
0.99
0.98
2.00
4.99
10.76
3.00
0.82
3.14
10.0 9.5 9.0 8.5 8.0 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 -0.5 -1.0
OMD-3-3amineprod - 1H NMR - 300.20 MHz - MeOD

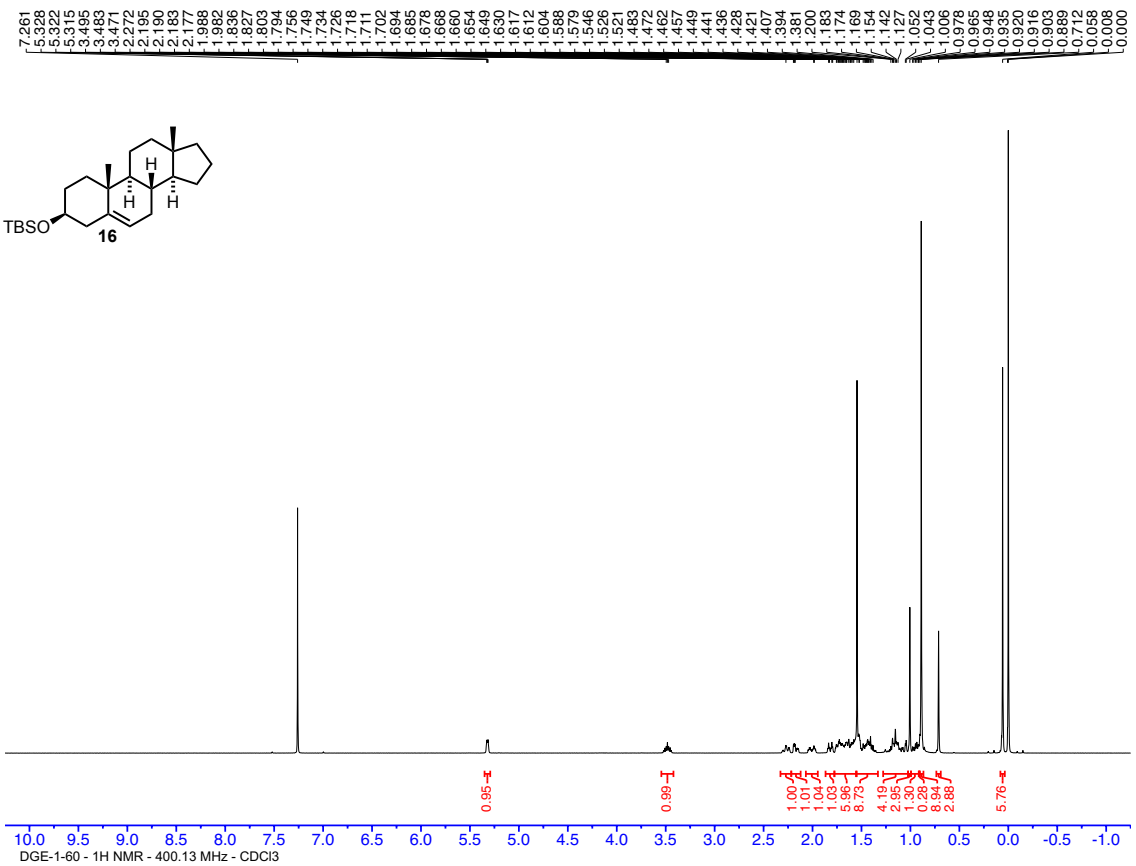

HO
H
H
H
NH2
H
OH
15
161.227
101.239
77.339
77.225
77.022
76.704
70.227
62.794
49.983
43.545
41.952
37.085
35.853
34.369
31.102
29.710
29.101
24.682
23.221
21.066
18.292
18.139
1.025
0.000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
OMD-2-122CNMR - 13C NMR - 100.62 MHz - CDCl3

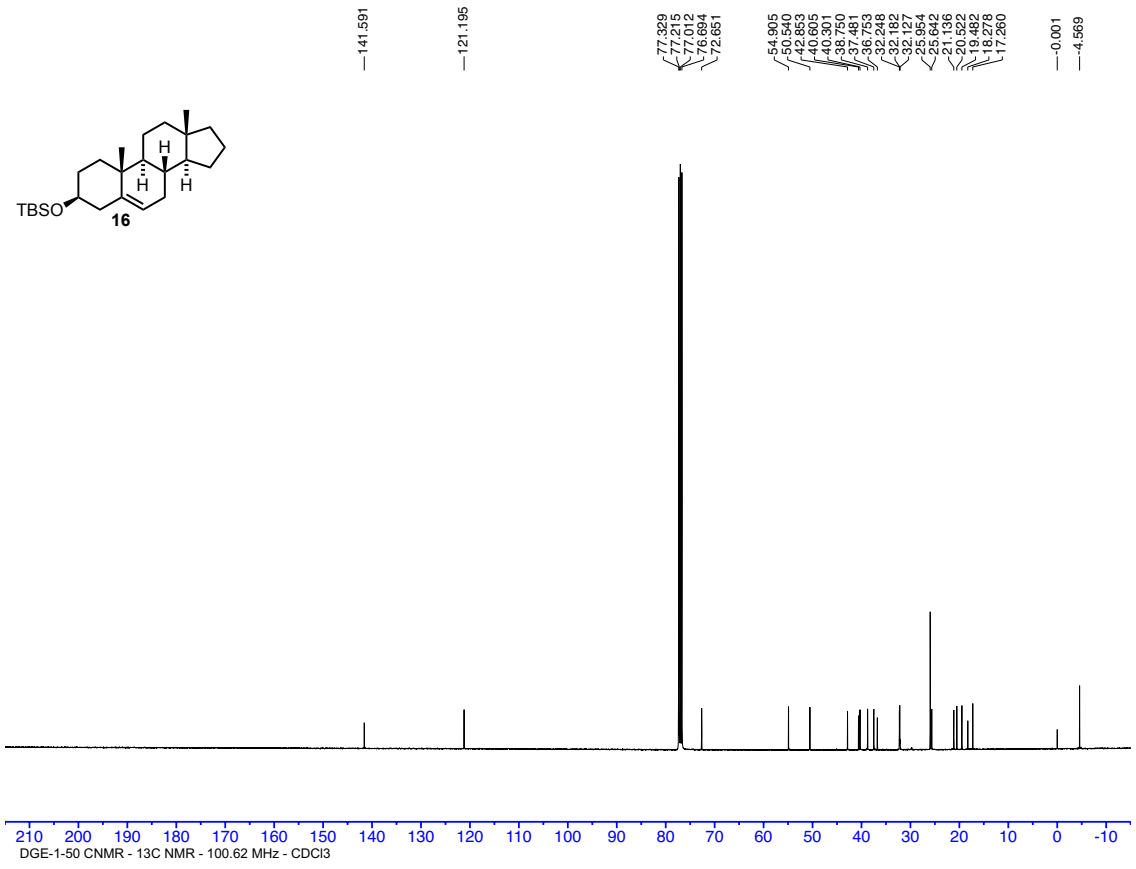

4.854
4.672
3.722
3.694
3.686
3.483
3.469
3.448
3.365
3.349
3.321
3.316
3.310
3.305
3.300
3.183
3.151
3.149
3.116
3.066
3.057
3.019
3.010
2.571
2.546
2.513
2.347
2.319
2.291
2.185
2.140
1.909
1.856
1.596
1.567
1.554
1.515
1.505
1.476
1.447
1.423
1.388
1.332
1.313
1.290
1.269
1.253
1.084
HO
H
H
H
NH3+ AcO-
H
OH
4
12.90
1.88
1.06
21.37
2.22
1.01
2.13
8.87
10.11
3.00
3.19
10.0 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 -0.5 -1.0
OMD-3-3salt2 - 1H NMR - 300.20 MHz - MeOD

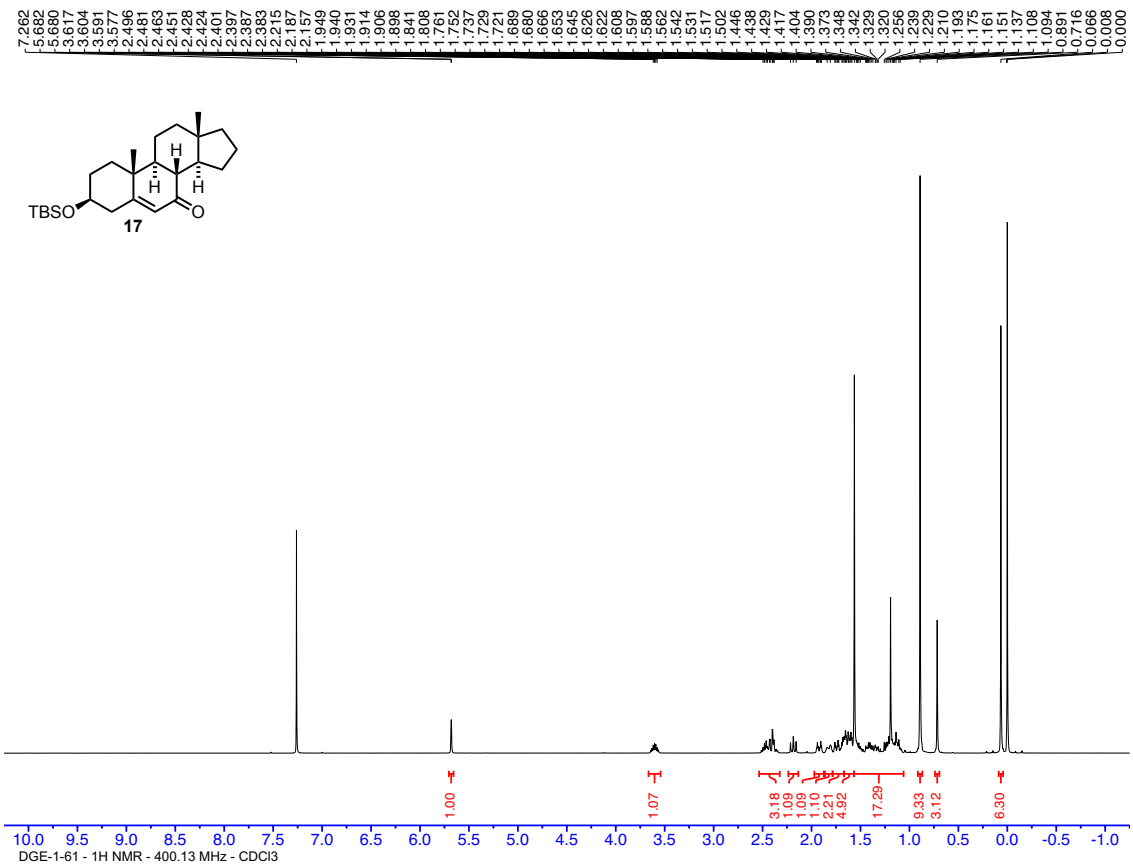

176.139
161.724
102.453
71.024
62.770
51.246
49.788
49.649
49.434
49.365
49.223
49.150
49.008
48.939
48.723
48.512
45.836
45.049
44.764
42.581
38.311
37.316
36.762
35.220
32.056
30.032
25.523
21.428
HO
H
H
H
NH3+ AcO-
H
OH
4
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
- 13C NMR - 100.62 MHz - MeOD

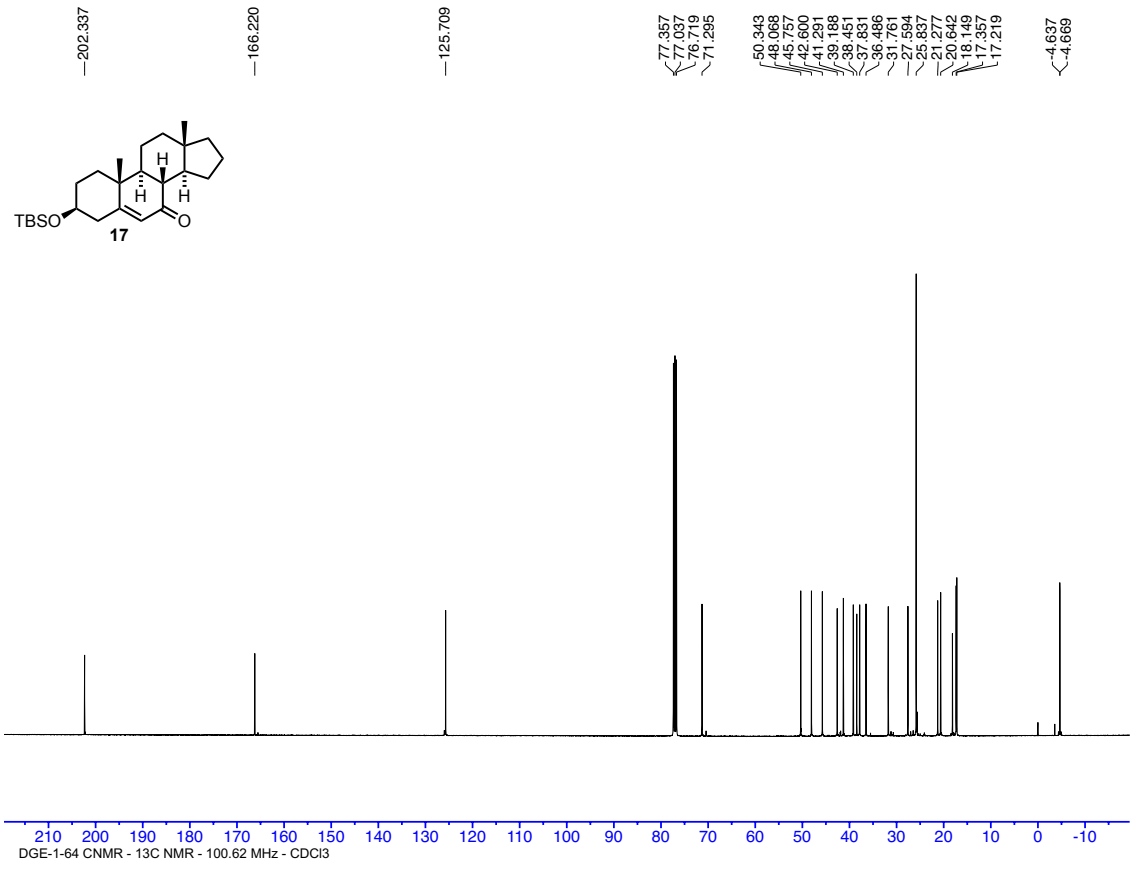

HO
S2
SMD-02-107 — 1H characterization - 1H NMR - 400.13 MHz - CDCl3

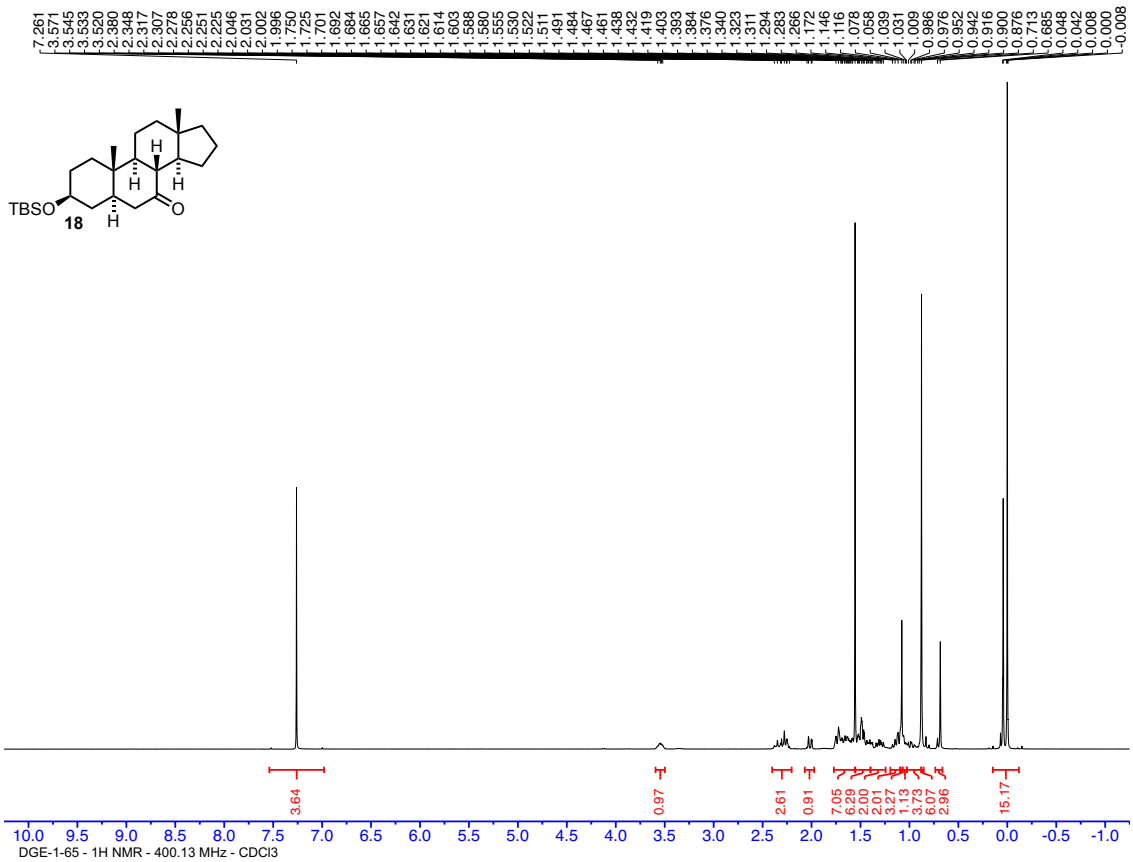

HO
S2
SMD-02-107 — 13C characterization - 13C NMR - 100.62 MHz - CDCl3

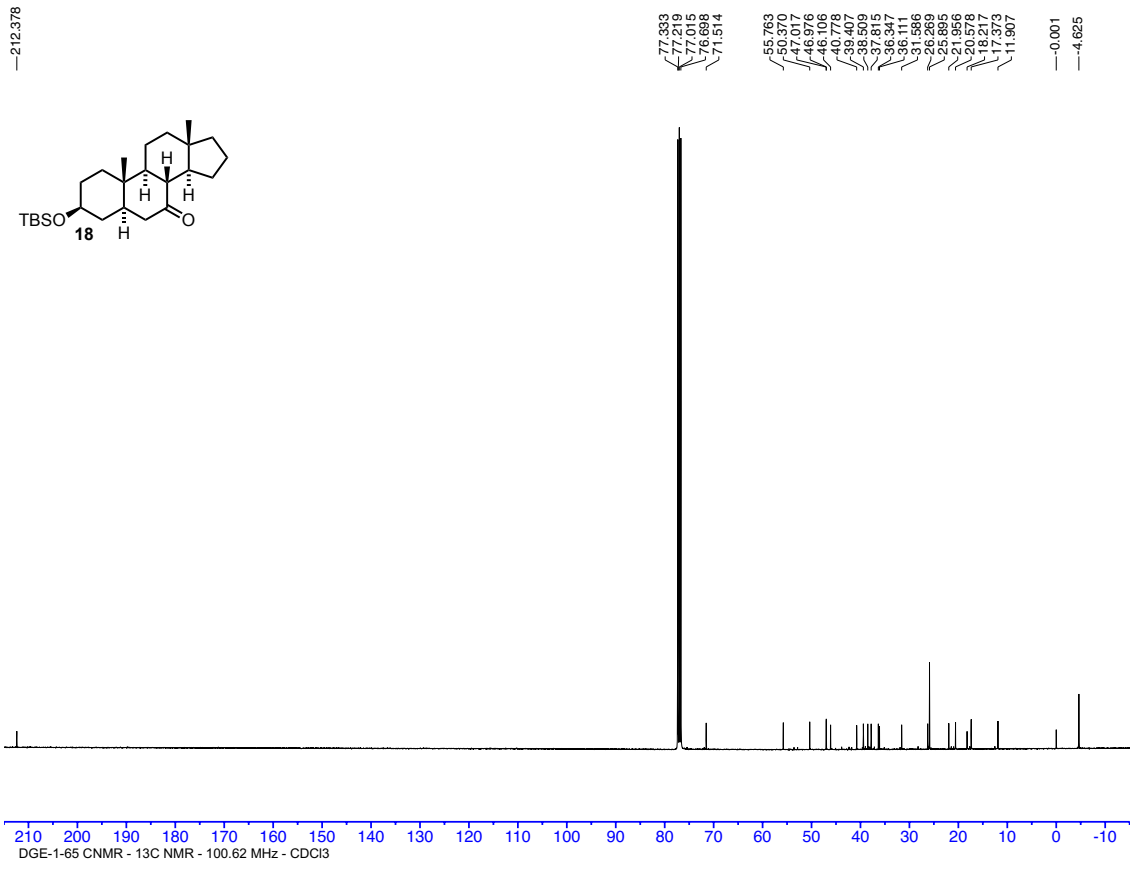

TBSO
16
DGE-1-60 - 1H NMR - 400.13 MHz - CDCl3

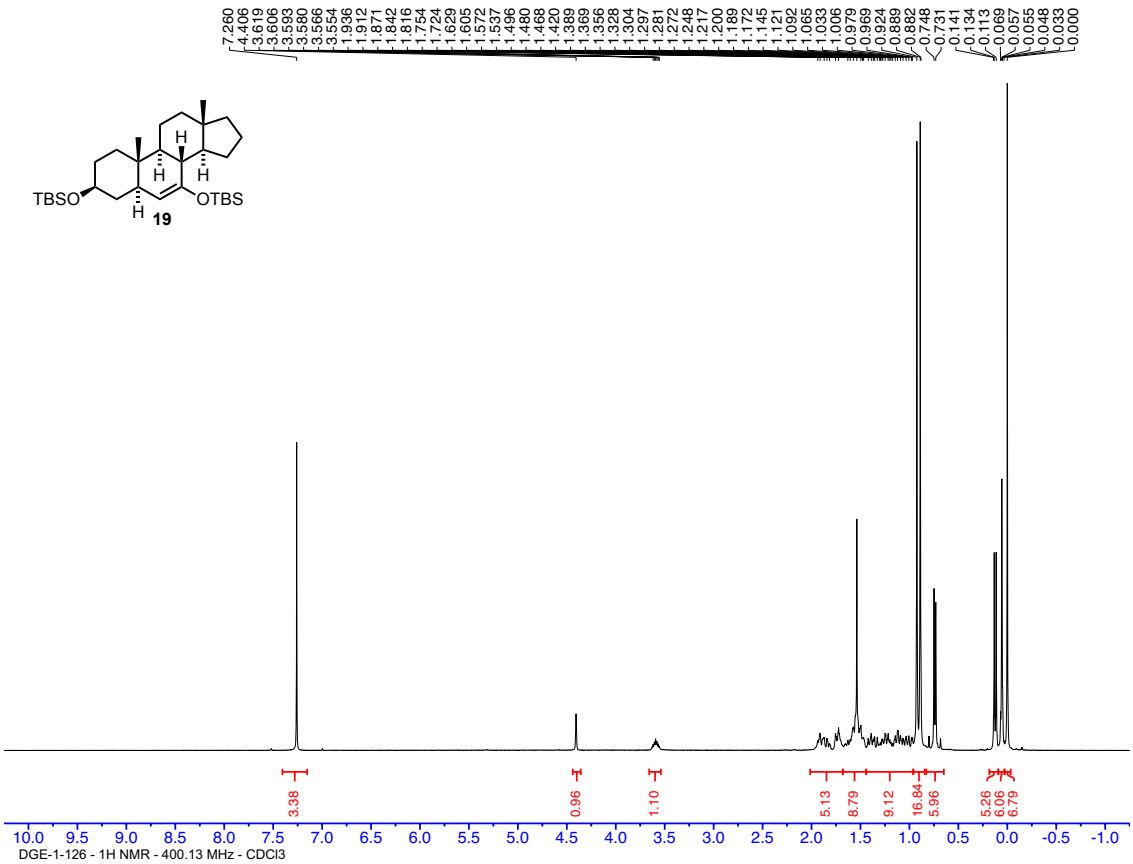

TBSO
16
DGE-1-50 CNMR - 13C NMR - 100.62 MHz - CDCl3

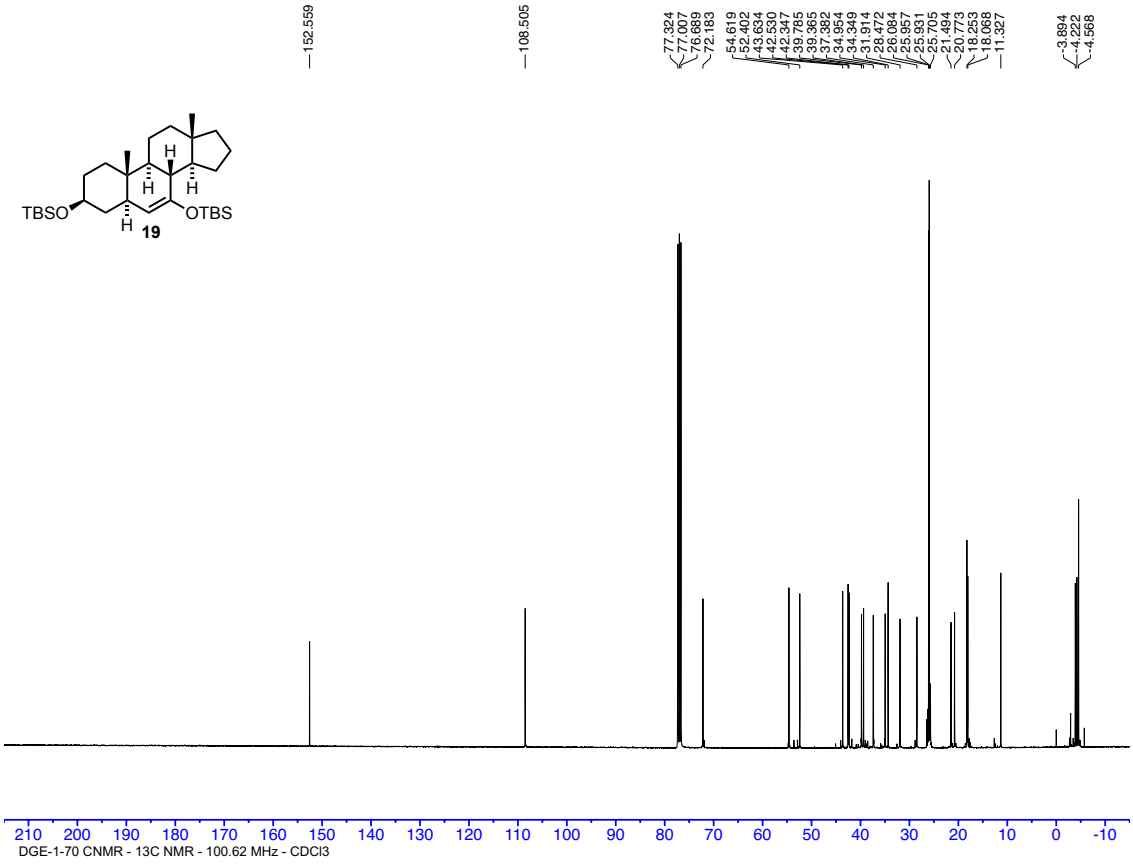

TBSO
17
DGE-1-61 - 1H NMR - 400.13 MHz - CDCl3

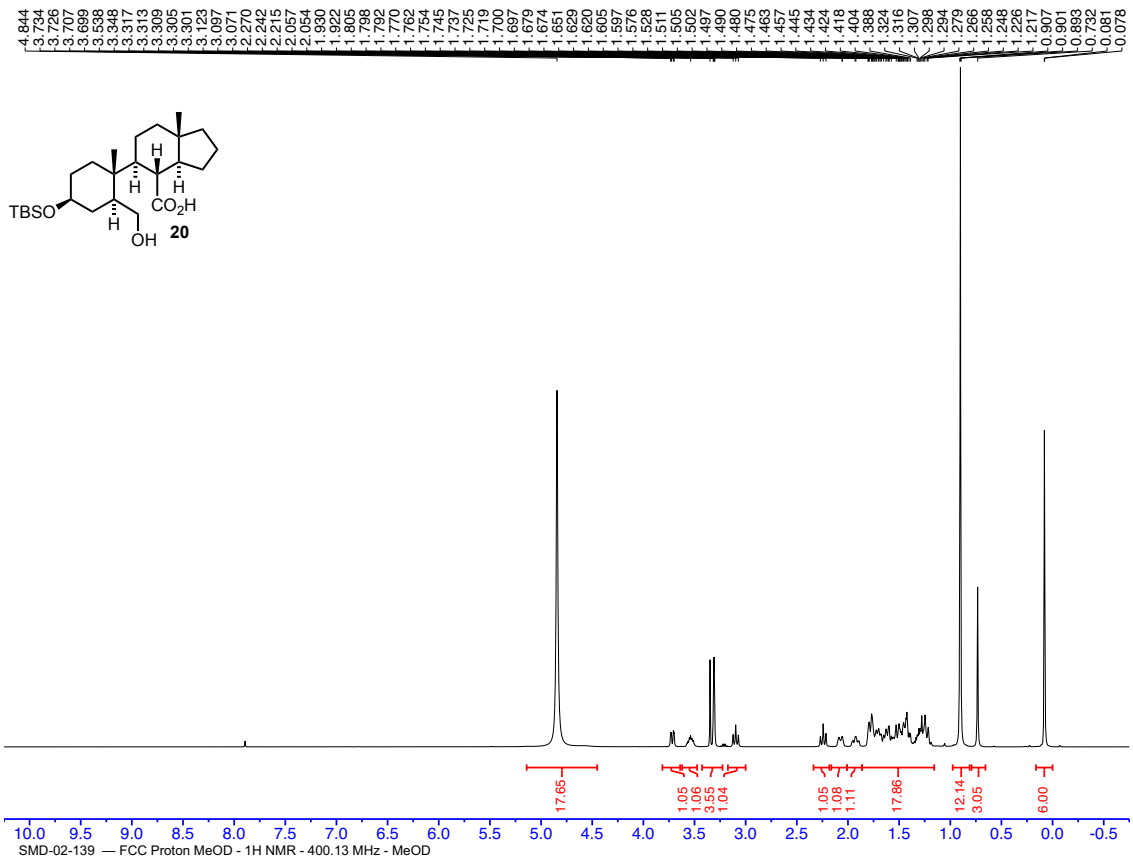

TBSO
17
DGE-1-64 CNMR - 13C NMR - 100.62 MHz - CDCl3

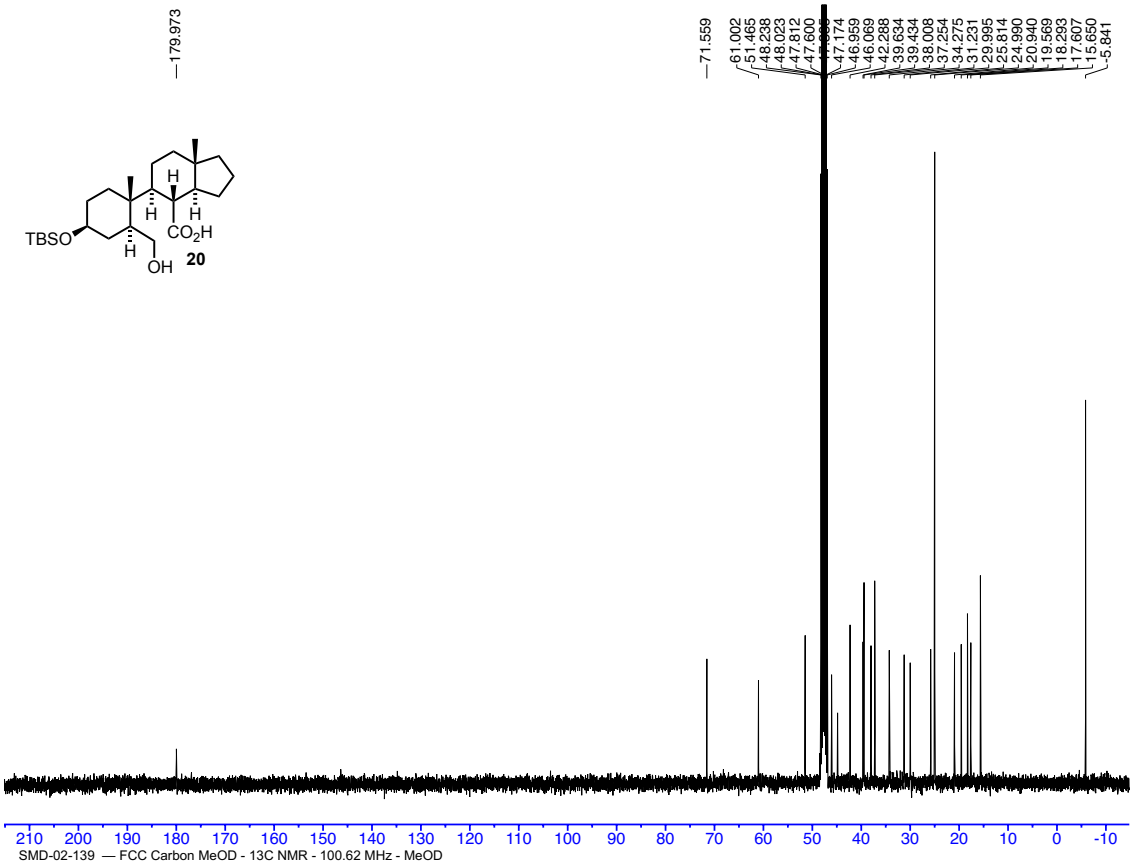

TBSO
18
DGE-1-65 - 1H NMR - 400.13 MHz - CDCl3

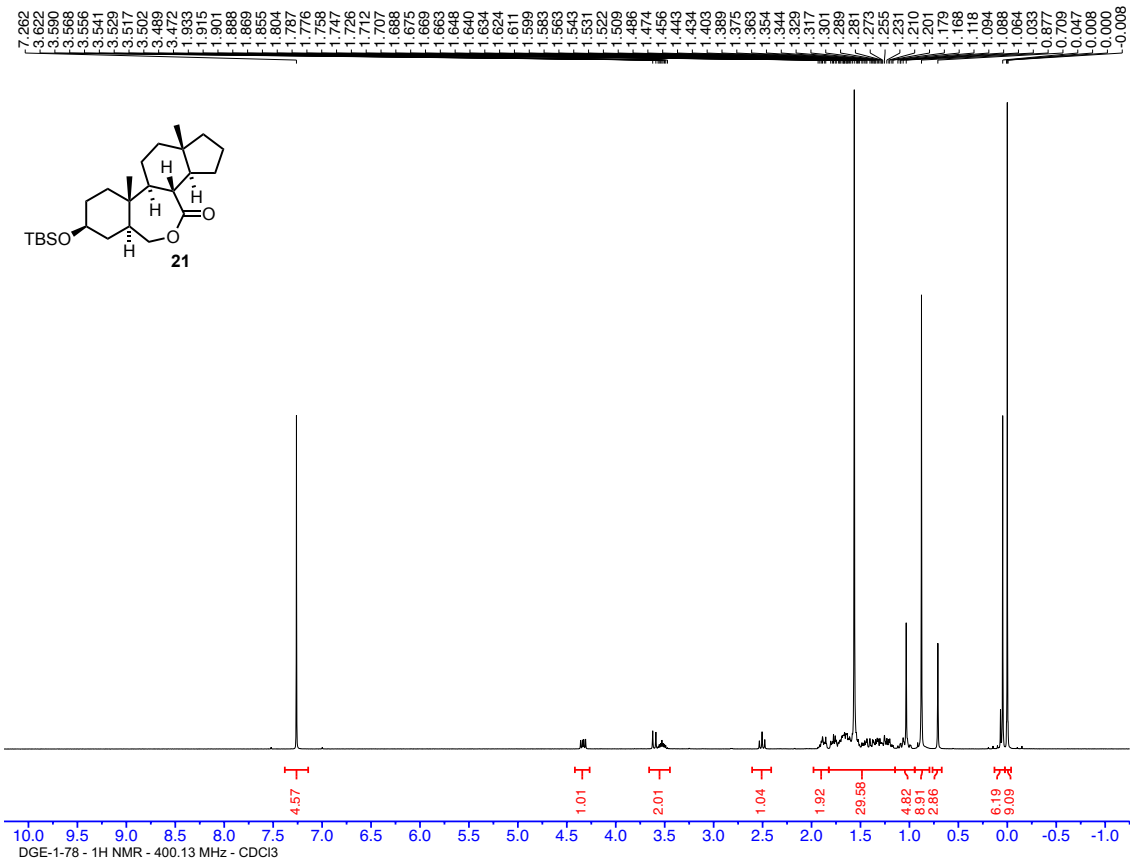

TBSO
18
DGE-1-65 CNMR - 13C NMR - 100.62 MHz - CDCl3

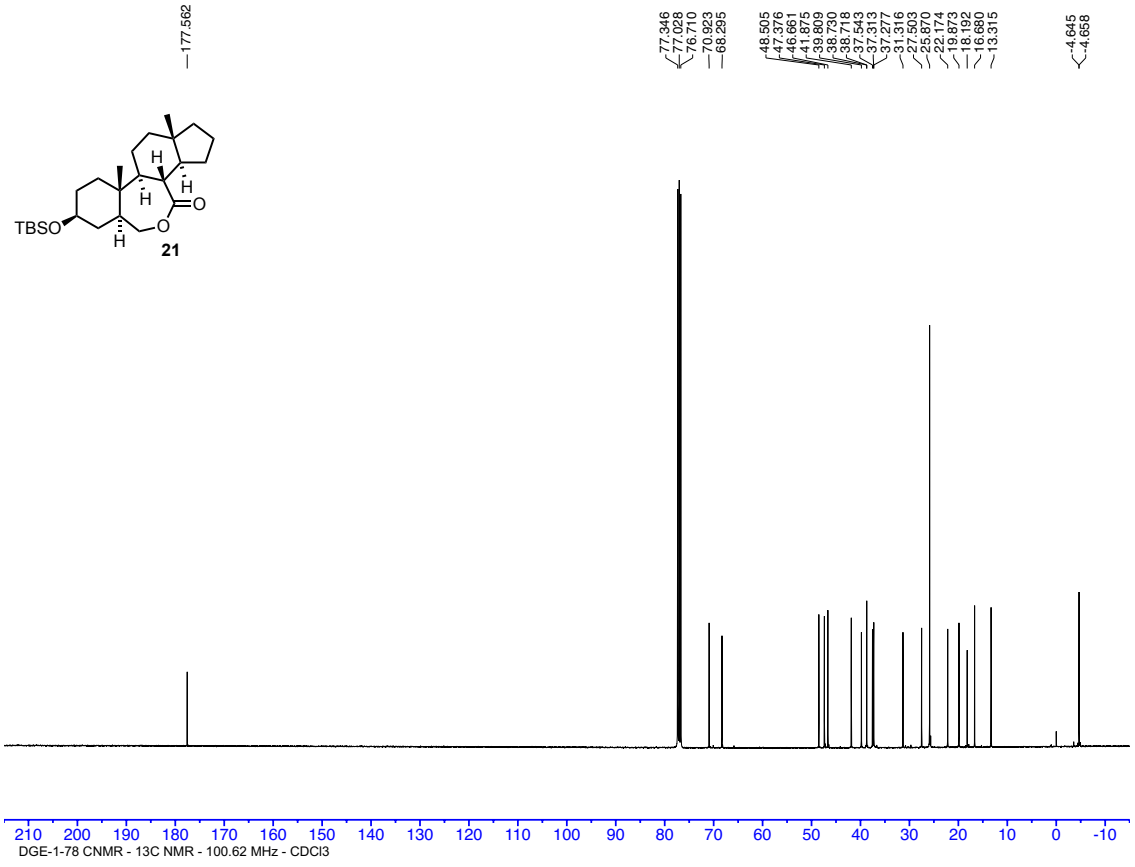

TBSO
OTBS
H
19
DGE-1-126 - 1H NMR - 400.13 MHz - CDCl3

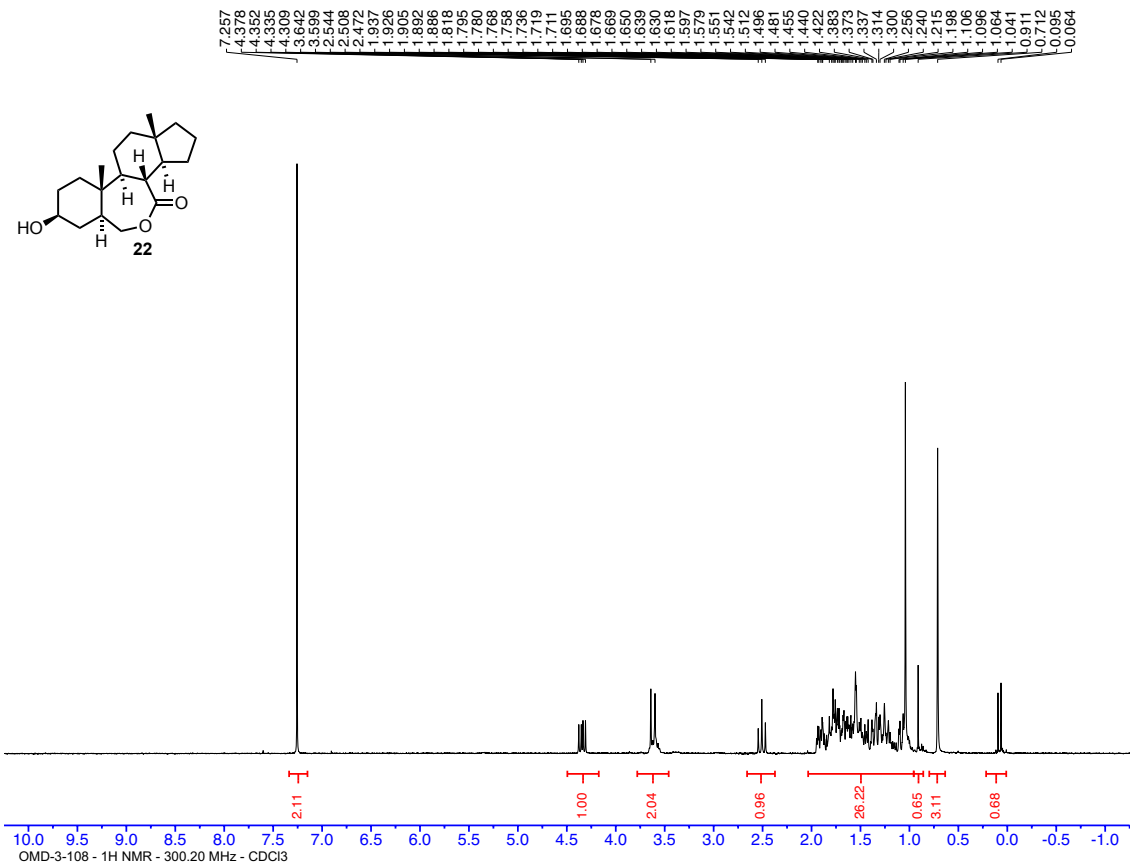

TBSO
OTBS
H
19
DGE-1-70 CNMR - 13C NMR - 100.62 MHz - CDCl3

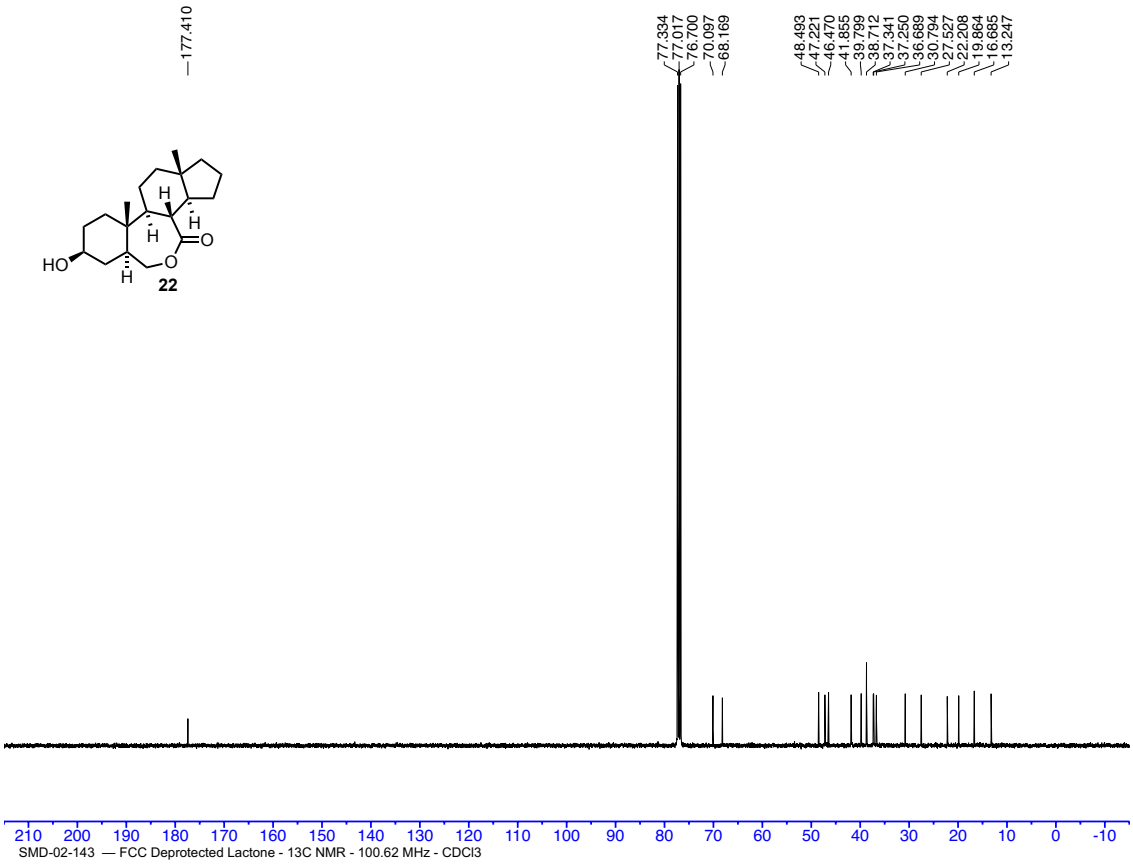

TBSO
H
H
H
CO2H
H
OH
20
SMD-02-139 — FCC Proton MeOD - 1H NMR - 400.13 MHz - MeOD

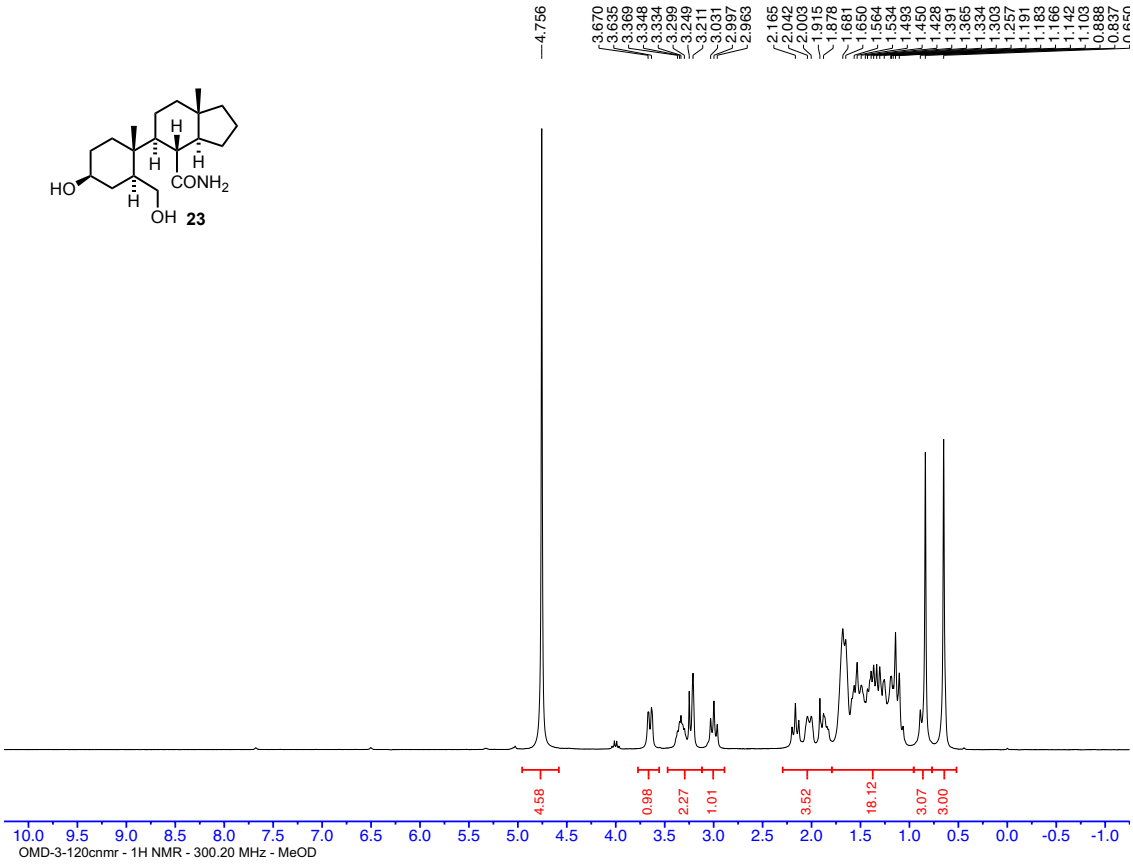

TBSO
H
H
H
CO2H
H
OH
20
SMD-02-139 — FCC Carbon MeOD - 13C NMR - 100.62 MHz - MeOD

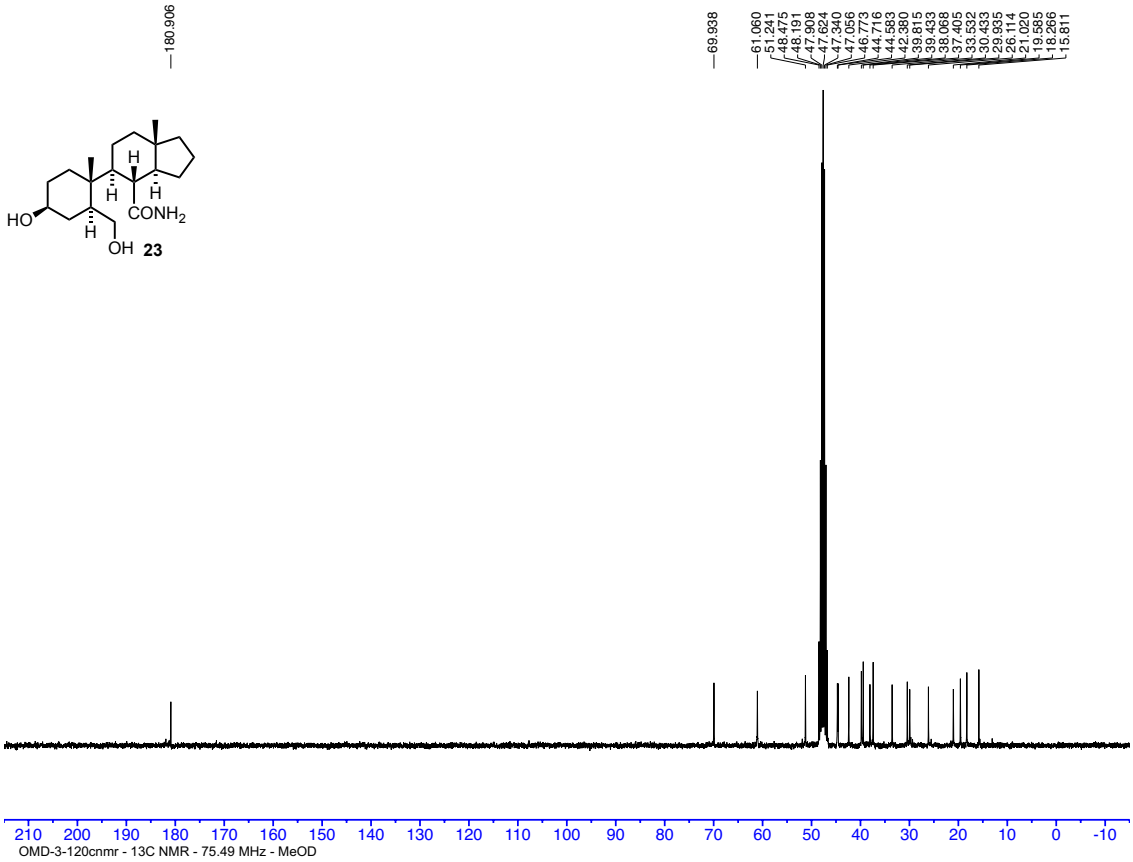

TBSO
21
4.57
1.01
2.01
1.04
1.92
29.58
4.82
8.91
2.86
6.19
9.09
DGE-1-78 - 1H NMR - 400.13 MHz - CDCl3

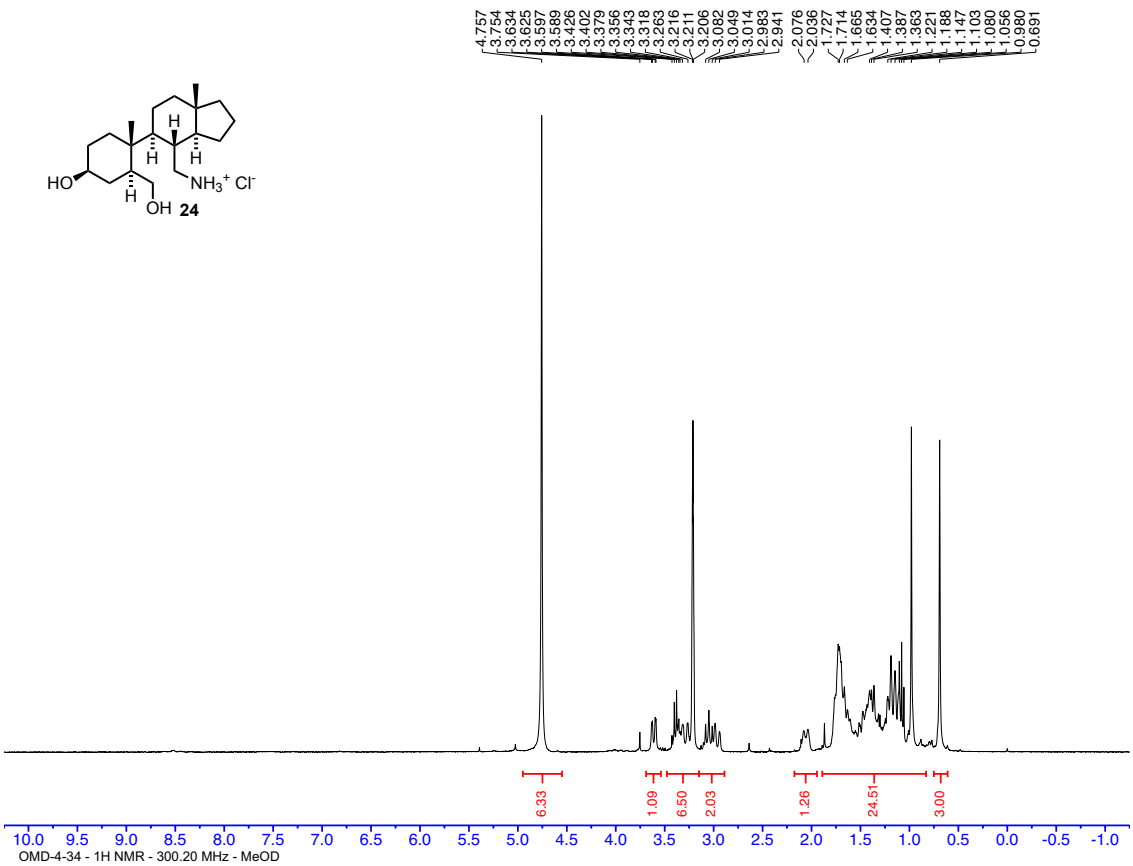

177.562
77.346
77.028
76.710
70.923
68.295
48.505
47.376
46.661
41.875
39.809
38.730
38.718
37.543
37.313
37.277
31.316
31.503
25.870
22.174
19.873
18.192
16.680
13.315
-4.645
-4.658
TBSO
21
DGE-1-78 CNMR - 13C NMR - 100.62 MHz - CDCl3

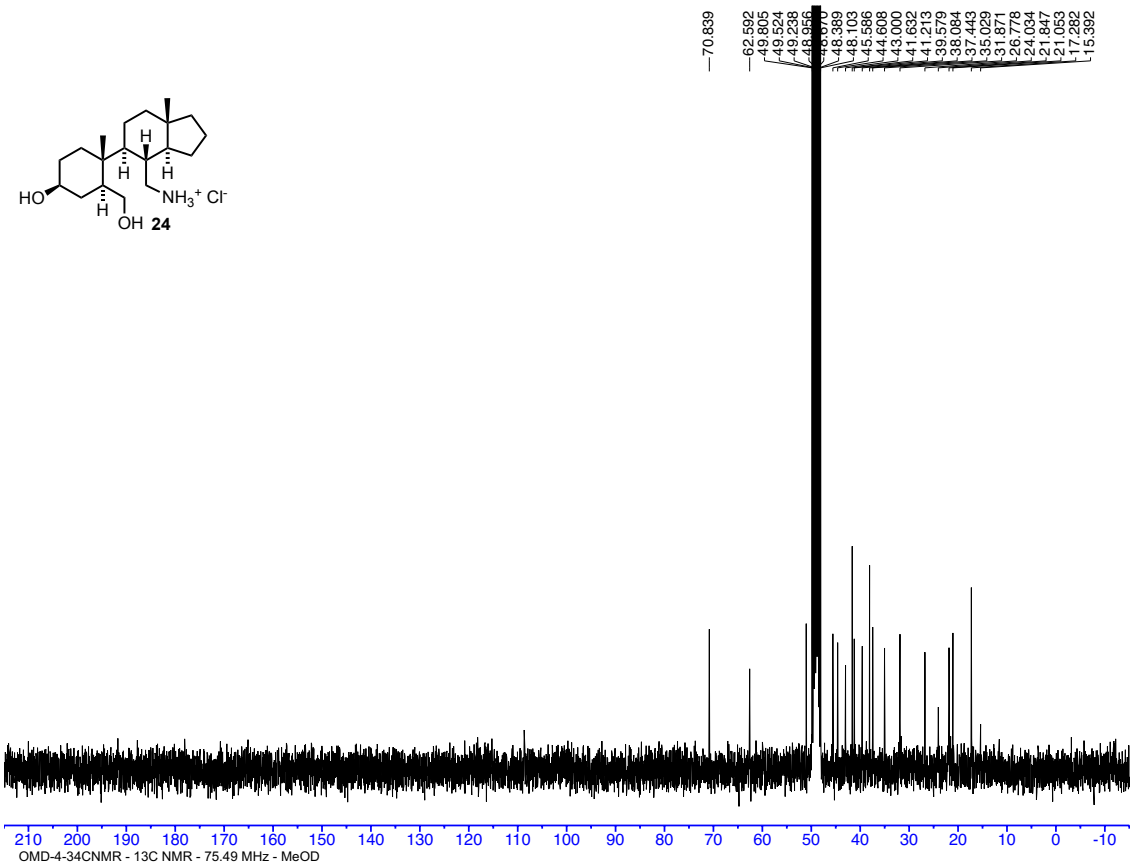

7.257
4.378
4.352
4.335
4.309
3.642
3.599
2.544
2.508
2.472
1.937
1.926
1.905
1.892
1.886
1.818
1.795
1.780
1.768
1.758
1.736
1.719
1.711
1.695
1.688
1.678
1.669
1.650
1.639
1.630
1.618
1.597
1.579
1.551
1.542
1.512
1.496
1.481
1.455
1.440
1.422
1.383
1.373
1.337
1.314
1.300
1.256
1.240
1.215
1.198
1.106
1.096
1.064
1.041
0.911
0.712
0.095
0.064
HO
H
H
H
O
O
H
22
2.11
1.00
2.04
0.96
26.22
0.65
3.11
0.68
10.0 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 -0.5 -1.0
OMD-3-108 - 1H NMR - 300.20 MHz - CDCl3


177.410
77.334
77.017
76.700
70.097
68.169
48.493
47.221
46.470
41.855
39.799
38.712
37.341
37.250
36.689
30.794
27.527
22.208
19.864
16.685
13.247
HO
H
H
H
O
O
H
22
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
SMD-02-143 — FCC Deprotected Lactone - 13C NMR - 100.62 MHz - CDCl3


4.756
3.670
3.635
3.369
3.348
3.334
3.299
3.249
3.211
3.031
2.997
2.963
2.165
2.042
2.003
1.915
1.878
1.681
1.650
1.564
1.534
1.493
1.450
1.428
1.391
1.365
1.334
1.303
1.257
1.191
1.183
1.166
1.142
1.103
0.888
0.837
HO
H
H
H
CONH2
H
OH
23
4.58
0.98
2.27
1.01
3.52
18.12
3.07
3.00
10.0 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 -0.5 -1.0
OMD-3-120cnmr - 1H NMR - 300.20 MHz - MeOD


180.906
69.938
61.060
51.241
48.475
48.191
47.908
47.624
47.340
47.056
46.773
44.716
44.583
42.380
39.815
39.433
38.068
37.405
33.532
30.433
28.935
26.114
21.020
19.585
18.266
15.811
HO
H
H
H
CONH2
H
OH
23
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
OMD-3-120cnmr - 13C NMR - 75.49 MHz - MeOD


4.757
3.754
3.634
3.625
3.597
3.589
3.426
3.402
3.379
3.356
3.343
3.318
3.263
3.216
3.211
3.206
3.082
3.049
3.014
2.983
2.941
2.076
2.036
1.727
1.714
1.665
1.634
1.407
1.387
1.363
1.221
1.188
1.147
1.103
1.080
1.056
0.980
0.691
HO
H
H
H
NH3+ Cl-
H
OH 24
6.33
1.09
6.50
2.03
1.26
24.51
3.00
10.0 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 -0.5 -1.0
OMD-4-34 - 1H NMR - 300.20 MHz - MeOD


70.839
62.592
49.805
49.524
49.238
48.956
48.670
48.389
48.103
45.586
44.608
43.000
41.632
41.213
39.579
38.084
37.443
35.029
31.871
26.778
24.034
21.847
21.053
17.282
15.392
HO
H
H
H
NH3+ Cl-
H
OH 24
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
OMD-4-34CNMR - 13C NMR - 75.49 MHz - MeOD