Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting information

Synthesis and Characterization of Potential Stereoisomeric and Degradation Impurities of Ulipristal Acetate

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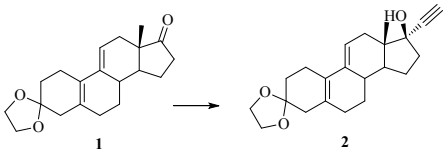
1. General information

All reactions were carried out under a nitrogen atmosphere. Most chemicals and solvents were analytical grade and used without further purification except dichloromethane (DCM) which was dehydrated by phosphorus (V) oxide. TLC was performed using precoated silica gel 60F-254 (0.2 mm) produced by Merck, while column chromatography was performed using silica gel (100-200 mesh and 200-300mesh) produced by Qingdao sea company. ^{1}H NMR and ^{13}C NMR spectra data were recorded in $CDCl_3$ on a Bruker Avance 300 MHz spectrometer (300 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR). Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane (TMS) using the residual solvent resonance ($CDCl_3$: 7.25 ppm for ^{1}H NMR. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = traplet, q = quartet, m = multiplet). Mass spectra were recorded on a LC/MSD TOF HR-MS Spectrum. Melting points were determined on a Mel-TEMP II melting point apparatus without correction. HPLC analysis was carried out on an Agilent 1260 infinity eluded with gradient eluting mixed by CH_3OH and H_2O at a flow rate of 1 mL/min and at λ = 254 nm. Optical rotation data were tested on SGW-2 polarimeter at λ = 589 nm in dichloromethane.

2. Synthesis of the key intermediate (12)

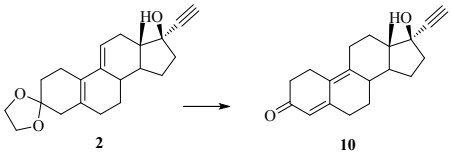
3,3-(Ethylene-dioxy)-17a-ethynyl-17b-hydroxyestr-5(10),9(11)-diene ***(2)***



1 **2**

Potassium tert-butoxide (75.0 g, 0.6696 mol) was dissolved in dry tetrahydrofuran (500 mL) at room temperature. The mixture was stirred for 1 h at the atmosphere of acetylene then cooled to 0 °C and **1** (100.0 g, 0.3183 mol) was added. After that, the reaction mixture was stirred for another 1 h. Saturated ammonium chloride solution (500 mL) was added and the mixture was stirred for 30 minutes. The organic layer was separated and the aqueous phase was extracted by tetrahydrofuran (150 mL × 3). The organic layers were combined, washed by water and concentrated to a volume of 100 mL. The residue was poured into ice water (500 mL) slowly and the precipitated crystals were filtered off and dried at 50 °C.

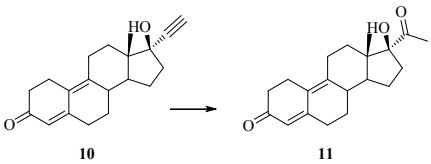
17α-Ethynyl-17β-hydroxyestra-4,9-diene-3-one ***(10)***



2 **10**

2 (30.0 g, 0.0882 mol) was dissolved in acetic acid (300 mL) at room temperature. Then perchloric acid (12 mL, 0.1323 mol) was added dropwise while keeping the reaction temperature was under 30 °C. The reaction mixture was stirred for 1 h, then, poured into water (600 mL) slowly. The precipitated crystals were filtered off, recrystallized by (petroleum ether/ethyl acetate 3:1) and dried at 50 °C.

17β-Hydroxy-19-norpregna-4,9-diene-3,20-dione ***(11)***

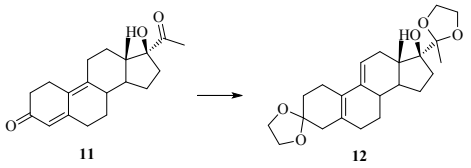


10 **11**

10 (10.0 g, 0.0338 mol) was dissolved in tetrahydrofuran (100 mL), then, 30% sulfuric acid (30 mL), mercuric sulfate (2.0 g, 0.0071 mol) was added to the above mixture. The reaction mixture was stirred for 1 h at 60 °C. After

neutralizing with saturated sodium bicarbonate, the mixture was extracted by dichloromethane (100 mL × 3). The organic layer was separated, combined, dried over sodium sulfate and concentrated under reduced pressure to give yellow oil. The oil was purified via column chromatography (petroleum ether/ethyl acetate 4:1).

3,3,20,20-Bis(ethylene-dioxy)-17β-hydroxy-19-norpregna-5(10),9(11)-diene ***(12)***

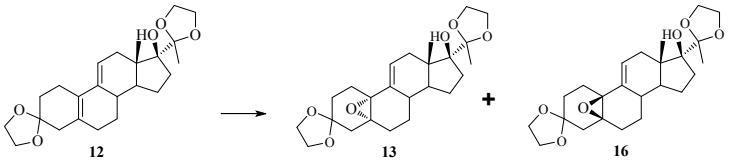


11 **12**

11 (2.0 g, 0.0064 mol), indium trichloride (1.0 g, 0.0045 mol) were dissolved in cyclohexane (20 mL), then ethylene glycol (2 mL) was added. The mixture was heat to reflux and stirred for 3 h. After neutralizing with saturated sodium bicarbonate, the mixture was extracted by dichloromethane (20 mL × 3). The organic layer was separated, combined, dried over sodium sulfate and concentrated under reduced pressure to give white oil. The oil was purified via column chromatography (petroleum ether/ethyl acetate 5:1).

3. Synthesis of 11β,17β-isomer (U-1) and 11α,17β-isomer (U-2)

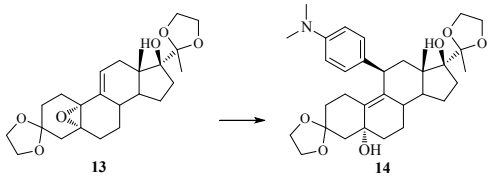
3,3,20,20-Bis(ethylene-dioxy)-17β-hydroxy-5α,10α-epoxy-19-norpregna-9(11)-ene ***(13)*** *and 3,3,20,20-bis(ethylene-dioxy)-17β-hydroxy-5β,10β-epoxy-19-norpregna-9(11)-ene* ***(16)***



12 **13** **16**

30% aqueous hydrogen peroxide (10 mL, 0.3409 mol) and sodium phosphate dibasic dodecahydrate (5.5 g, 0.0155 mol) were added to a solution of hexachloroacetone (1 mL, 0.0066 mol) in dichloromethane (50 mL). The mixture was stirred for 1 h at 0 °C. **12** (5.0 g, 0.0124 mol) was added to above mixture. The reaction mixture was stirred for another 36 h at the same temperature. Then, it was poured into a mixture of dichloromethane (50 mL) and ice. A solution of sodium thiosulphate (11.9 g, 0.0752 mol) in water (100 mL) was added to the mixture to destroy the excess of hydrogen peroxide. After separation and extraction, the organic fraction was washed with water (30 mL × 3) and dried over sodium sulfate. The solvent was removed in vacuo to give product, which was a mixture of the 5α,10α- and 5β,10β-epoxides (80: 20) showed by TLC. The 5α,10α-epoxides was separated through recrystallization by (petroleum ether/ethyl acetate 5:1). The 5β,10β-epoxides was purified via column chromatography (petroleum ether/ethyl acetate 4:1).

3,3,20,20-Bis(ethylene-dioxy)-11β-(4-N, N-dimethylaminophenyl)-5α-hydroxy-17β-hydroxy-19-norpregna-9(10)-ene ***(14)***

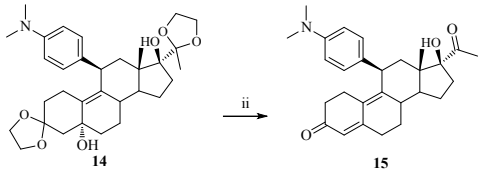


13 **14**

Magnesium (2.9 g, 0.1217 mol), 4-bromo-*N, N*-dimethylaniline (2.0 g, 0.0101 mol), and one crystal of iodine were dissolved in dry tetrahydrofuran (20 mL). The mixture was heat to 50 °C to start the reaction. After the reaction was started, 4-bromo-*N, N*-dimethylaniline (20.0 g, 0.1005 mol) dissolved in dry tetrahydrofuran (200 mL) was added to

the mixture slowly and the temperature of the reaction should be controlled under 35 °C. The grignard reagent was prepared after stirring for 2 h. **13** (8.6 g, 0.0206 mol), copper (I) chloride (0.8 g, 0.0027 mol) was dissolved in dry tetrahydrofuran (10 mL) and cooled to 0 °C while the grignard reagent was added dropwise. The reaction mixture was stirred for 4 h, then, poured into 10% ammonium chloride (200 mL) solution and the organic phase was separated, the residue was extracted with dichloromethane (100 mL × 5). The combined organic fractions were washed with water (200 mL × 3), dried over sodium sulfate, filtered, and concentrated in vacuo to give brown oil. The oil was purified via column chromatography (petroleum ether/ethyl acetate 8:1).

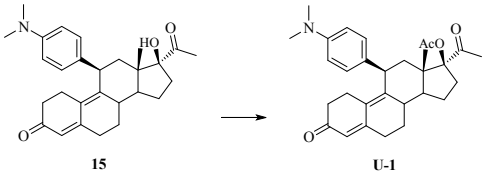
11β-(4-N, N-Dimethylaminophenyl)-17β-hydroxy-19-norpregna-4, 9-diene-3, 20-dione ***(15)***



14 **15**

14 (2.1 g, 0.0039 mol), potassium bisulfate (1.1 g, 0.0078 mol) were dissolved in ice water (20 mL) then cooled to 0 °C. The mixture was stirred for 2 h at 0 °C. After neutralizing with saturated sodium bicarbonate, the mixture was extracted by dichloromethane (30 mL × 3). The organic layer was separated, combined, dried over sodium sulfate and concentrated under reduced pressure to give brown oil. The oil was purified via column chromatography (petroleum ether/ethyl acetate 3:1).

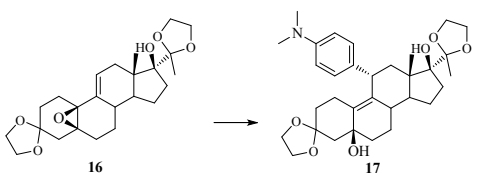
11β,17β-Isomer of UPA ***(U-1)***



15 **U-1**

Perchloric acid (1.5 mL, 0.0163 mol) was added to acetic anhydride (5 mL, 0.0530 mol) by dropwise at -10 °C. The obtained solution was stirred for 1 h, then, cooled to -25 °C and the solution of **15** (1.0 g, 0.0023 mol) in dry dichloromethane (10 mL) was added slowly to keep the temperature between -10 °C and -25 °C. The reaction mixture was stirred at -15 °C for 2 h. After neutralizing with saturated sodium bicarbonate, the organic layer was separated and the residue was extracted by dichloromethane (20 mL × 3), then, the organic layer was combined, dried over sodium sulfate and concentrated under reduced pressure to give yellow oil. The oil was purified via column chromatography (petroleum ether/ethyl acetate 4:1).

3,3,20,20-Bis(ethylene-dioxy)-11α-(4-N, N-dimethylaminophenyl)-5β-hydroxy-17β-hydroxy-19-norpregna-9(10)-ene ***(17)***

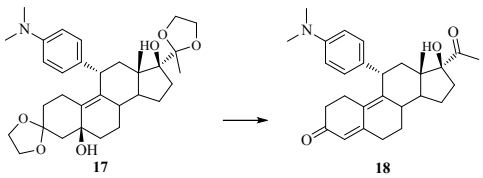


16 **17**

Magnesium (9.2 g, 0.3828 mol), 4-bromo-*N, N*-dimethylaniline (3.8 g, 0.0191 mol), and one crystal of iodine were dissolved in dry tetrahydrofuran (40 mL). The mixture was heat to 50 °C to start the reaction. After the reaction was started, 4-bromo-*N, N*-dimethylaniline (38.1 g, 0.1914 mol) dissolved in dry tetrahydrofuran (400 mL) was added to the mixture slowly and the temperature of the reaction should be controlled under 35 °C. The grignard reagent was

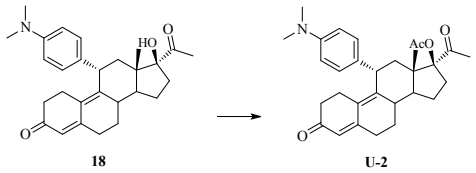
prepared after stirring for 2 h. **16** (10.0 g, 0.0239 mol), copper (I) chloride (4.8 g, 0.0478 mol) was dissolved in dry tetrahydrofuran (20 mL) and cooled to 5 °C while the grignard reagent was added dropwise. The reaction mixture was stirred for 4 h, then, poured into 10% ammonium chloride (400 mL) solution and the organic phase was separated, the residue was extracted with dichloromethane (150 mL × 5). The combined organic fractions were washed with water (150 mL × 3), dried over sodium sulfate, filtered, and concentrated in vacuo to give brown oil. The oil was purified via column chromatography (petroleum ether/ethyl acetate 8:1).

11α-(4-N, N-Dimethylaminophenyl)-17β-hydroxy-19-norpregna-4, 9-diene-3, 20-dione ***(18)***



17 (1.5 g, 0.0278 mol), potassium bisulfate (3.1 g, 0.0223 mol) were dissolved in ice water (30 mL) then cooled to 0 °C. The mixture was stirred for 2 h at 0 °C. After neutralizing with saturated sodium bicarbonate, the mixture was extracted by dichloromethane (50 mL × 3). The organic layer was separated, combined, dried over sodium sulfate and concentrated under reduced pressure to give brown oil. The oil was purified via column chromatography (petroleum ether/ethyl acetate 3:1).

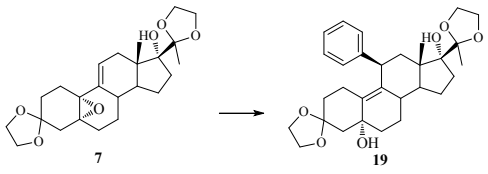
11α,17β-Isomer of UPA ***(U-2)***



Perchloric acid (0.1 mL, 0.0016 mol) was added to acetic anhydride (1.6 mL, 0.0156 mol) by dropwise at -10 °C. The obtained solution was stirred for 1 h, then, cooled to -25 °C and the solution of **18** (0.5 g, 0.0014 mol) in dry dichloromethane (10 mL) was added slowly to keep the temperature between -10 °C and -25 °C. The reaction mixture was stirred at -15 °C for 2 h. After neutralizing with saturated sodium bicarbonate, the organic layer was separated and the residue was extracted by dichloromethane (20 mL × 3), then, the organic layer was combined, dried over sodium sulfate and concentrated under reduced pressure to give yellow oil. The oil was purified via column chromatography (petroleum ether/ethyl acetate 4:1).

4. Synthesis of demethylation impurity (U-3)

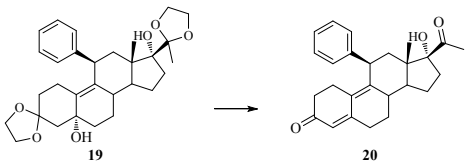
3,3,20,20-Bis(ethylene-dioxy)-11β-(4-phenyl)-5α-hydroxy-17α-hydroxy-19-norpregna-9(10)-ene ***(19)***



Magnesium (4.5 g, 0.1875 mol), bromobenzene (2.0 g, 0.0128 mol), and one crystal of iodine were dissolved in dry tetrahydrofuran (25 mL). The mixture was heat to 45 °C to start the reaction. After the reaction was started, bromobenzene (20.0 g, 0.1282 mol) dissolved in dry tetrahydrofuran (250 mL) was added to the mixture slowly and the temperature of the reaction should be controlled under 30 °C. The grignard reagent was prepared after stirring for 3 h. **7** (15.0 g, 0.0373 mol), copper (I) chloride (1.5 g, 0.0153 mol) was dissolved in dry tetrahydrofuran (20 mL)

and cooled to 0 °C while the grignard reagent was added dropwise. The reaction mixture was stirred for 6 h, then, poured into 10% ammonium chloride (250 mL) solution and the organic phase was separated, the residue was extracted with dichloromethane (150 mL × 5). The combined organic fractions were washed with water (150 mL × 4), dried over sodium sulfate, filtered, and concentrated in vacuo to give yellow oil. The oil was purified via column chromatography (petroleum ether/ethyl acetate 10:1).

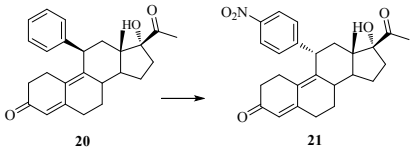
11β-(4-Phenyl)-17α-hydroxy-19-norpregna-4, 9-diene-3, 20-dione ***(20)***



19 **20**

19 was dissolved in ethanol (50 mL), then, 8.5% aqueous sulfuric acid (10 mL) was added. The mixture was stirred for 2 h. After neutralizing with saturated sodium bicarbonate, the mixture was extracted by dichloromethane (60 mL × 3). The organic layer was combined and dried over sodium sulfate, then, concentrated under reduced pressure to give white oil. The oil was purified via column chromatography (petroleum ether/ethyl acetate 6:1).

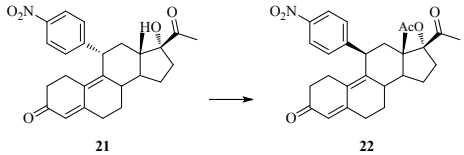
11β-(4-Nitrophenyl)-17α-hydroxy-19-norpregna-4, 9-diene-3, 20-dione ***(21)***



20 **21**

Sulfuric acid (5 mL, 0.0920 mol) was dissolved in nitric acid (10 mL, 0.1511 mol), then, cooled to 10 °C. After stirring for 10 minutes, **20** (5.0 g) was added to the mixture slowly and the temperature should be controlled under 10 °C. The mixture was stirred for 0.5 h and saturated sodium bicarbonate and DCM (50 mL) was added to neutralize. The organic layer was separated, combined and dried over sodium sulfate, then, concentrated under reduced pressure to give orange oil. The oil was purified via column chromatography (petroleum ether/ethyl acetate 3:1).

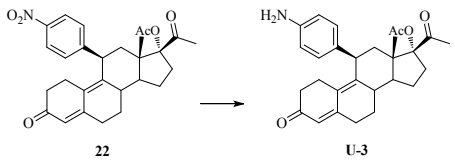
11β-(4-Nitrophenyl)-17α-acetoxy-19-norpregna-4, 9-diene-3, 20-dione ***(22)***



21 **22**

Perchloric acid (3 mL, 0.0326 mol) was added to acetic anhydride (10 mL, 0.1060 mol) by dropwise at -10 °C. The obtained solution was stirred for 1 h, then, cooled to -25 °C and the solution of **21** (2.0 g, 0.0046 mol) in dry dichloromethane (20 mL) was added slowly to keep the temperature between -10 °C and -25 °C. The reaction mixture was stirred at -15 °C for 4 h. After neutralizing with saturated sodium bicarbonate, the organic layer was separated and the residue was extracted by dichloromethane (40 mL × 3), then, the organic layer was combined, dried over sodium sulfate and concentrated under reduced pressure to give yellow oil. The oil was purified via column chromatography (petroleum ether/ethyl acetate 5:1).

Demethylation impurity of UPA ***(U-3)***

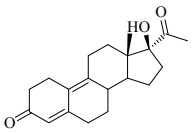


22 **U-3**

22 (0.8 g, 0.0017 mol) was dissolved in dry dichloromethane (10 mL), then, zinc powder (0.2 g, 0.0031 mol) was

added. Acetic acid (1 mL, 0.0171 mol) was added to the mixture by dropwise at room temperature. The obtained solution was stirred for 0.2 h, then, filtrated. After neutralizing with saturated sodium bicarbonate, the organic layer was separated and the residue was extracted by dichloromethane (10 mL × 3), then, the organic layer was combined, dried over sodium sulfate and concentrated under reduced pressure to give orange oil. The oil was purified via column chromatography (petroleum ether/ethyl acetate 3:1).

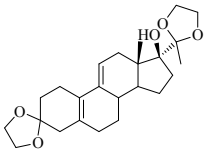
5. Characterization of products



17β-Hydroxy-19-norpregna-4,9-diene-3,20-dione (11): white solid, 50% yield, mp 192-196 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, 3H, –CH_3), 2.30 (s, 3H, –CH_3), 1.26-2.89 (m, 18H), 5.70 (s, 1H, =CH).

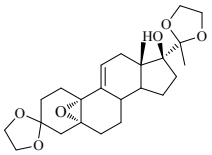
HRMS (ESI$^+$): calcd for $C_{20}H_{27}O_3$ $[M+H]^+$ 315.1955, found 315.1957.



3,3,20,20-Bis(ethylene-dioxy)-17β-hydroxy-19-norpregna-5(10),9(11)-diene (12): white crystalline solid, 40% yield, mp 195-198 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.63 (s, 3H, –CH_3), 0.91-2.68 (m, 19H), 1.29 (s, 3H, –CH_3), 3.69-4.03 (m, 8H, –OCH_2), 5.58 (d, J = 6.0 Hz, 1H, =CH).

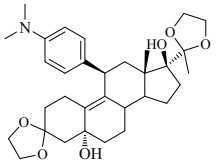
HRMS (ESI$^+$): calcd for $C_{24}H_{35}O_5$ $[M+H]^+$ 403.2479, found 403.2481.



3,3,20,20-Bis(ethylene-dioxy)-17β-hydroxy-5α,10α-epoxy-19-norpregna-9(11)-ene (13): white solid, 60% yield, mp 185-190 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74 (s, 3H, –CH_3), 0.86-2.66 (m, 19H), 1.33 (s, 3H, –CH_3), 3.83-3.93 (m, 8H, –OCH_2), 6.12 (t, J = 3.0 Hz, 1H, =CH).

HRMS (ESI$^+$): calcd for $C_{24}H_{35}O_6$ $[M+H]^+$ 419.2428, found 419.2358.

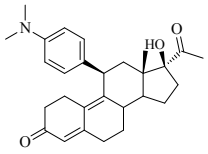


3,3,20,20-Bis(ethylene-dioxy)-11β-(4-*N*, *N*-dimethylaminophenyl)-5α-hydroxy-17β-hydroxy-19-norpregna-9(10)-ene (14): pink powder, 58% yield, mp 193-197 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 3H, –CH_3), 1.11 (s, 3H, –CH_3), 1.21-2.18 (m, 20H), 2.91 (s, 6H, N–CH_3), 3.76-4.08 (m, 8H, –OCH_2), 4.41 (s, 1H, –CH). 6.68 (s, 2H, Ar–H), 7.09 (d, J = 6.0 Hz, 2H, Ar–H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.9, 129.5, 128.5, 121.9, 119.4, 114.9, 111.8, 110.1, 87.3, 65.8, 63.9, 59.9, 51.4, 48.5, 47.9, 46.5, 44.9, 43.7, 40.9, 36.1, 35.9, 34.4, 33.7, 32.0, 31.9, 28.2, 24.3, 22.8, 20.6, 16.2, 15.2, 13.7 ppm.

HRMS (ESI$^+$): calcd for $C_{32}H_{46}NO_6$ $[M+H]^+$ 540.3320, found 540.3320.

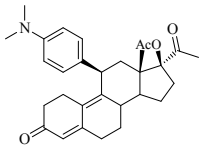


11β-(4-*N, N*-Dimethylaminophenyl)-17β-hydroxy-19-norpregna-4, 9-diene-3, 20-dione (15): light green solid, 60% yield, mp 181-185 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.64 (s, 3H, –CH_3), 1.43-2.71 (m, 17H), 2.31 (s, 3H, –$COCH_3$), 2.92 (s, 6H, N–CH_3), 4.25 (d, J = 9.0 Hz, 1H, –CH). 5.74 (s, 1H, =CH), 6.67 (d, J = 9.0 Hz, 2H, Ar–H), 6.99 (d, J = 9.0 Hz, 2H, Ar–H).

^{13}C NMR (75 MHz, $CDCl_3$): δ =213.9, 199.2, 156.3, 148.0, 145.2, 128.9, 126.9, 122.3, 112.4, 90.6, 48.5, 47.6, 40.2, 39.1, 38.6, 38.5, 36.3, 34.5, 30.6, 27.9, 26.9, 25.3, 23.9, 14.8 ppm.

HRMS (ESI$^+$): calcd for $C_{28}H_{36}NO_3$ $[M+H]^+$ 434.2690, found 434.2609.

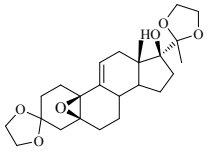


11β,17β-Isomer of UPA (U-1): off-white solid, 700 mg, 60% yield, mp 181-186 °C. $[\alpha]^{20}$= +154.8 (c 1.0, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69 (s, 3H, –CH_3), 1.15-2.58 (m, 17H), 2.08 (s, 3H, –$COCH_3$), 2.12 (s, 3H, –$COCH_3$), 2.93 (s, 6H, N–CH_3), 4.27 (d, J = 9.0 Hz, 1H, –CH). 5.74 (s, 1H, =CH), 6.69 (d, J = 9.0 Hz, 2H, Ar–H), 7.02 (d, J = 9.0 Hz, 2H, Ar–H).

^{13}C NMR (75 MHz, $CDCl_3$): δ =208.4, 199.6, 171.3, 156.6, 148.6, 145.1, 129.5, 127.4, 122.9, 112.7, 96.4, 47.6, 47.1, 40.6, 39.5, 39.4, 38.6, 36.9, 32.8, 31.1, 27.5, 27.2, 25.8, 24.9, 21.1, 16.3 ppm.

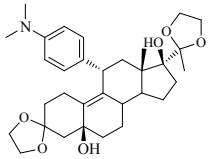
HRMS (ESI$^+$): calcd for $C_{30}H_{38}NO_4$ $[M+H]^+$ 476.2795, found 476.2809.



3,3,20,20-bis(ethylene-dioxy)-17β-hydroxy-5β,10β-epoxy-19-norpregna-9(11)-ene (16): white crystalline solid, 14% yield, mp 180-183 °C.

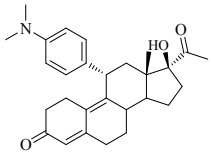
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74 (s, 3H, –CH_3), 0.86-2.66 (m, 19H), 1.33 (s, 3H, –CH_3), 3.83-3.93 (m, 8H, –OCH_2), 5.82 (d, J = 6.0 Hz, 1H, =CH).

HRM S (ESI$^+$): calcd for $C_{24}H_{35}O_6$ $[M+H]^+$ 419.2428, found 419.2358.



3,3,20,20-Bis(ethylene-dioxy)-11α-(4-*N, N*-dimethylaminophenyl)-5β-hydroxy-17β-hydroxy-19-norpregna-9(10)-ene (17): light brown solid, 11% yield, mp 191-193 °C.

HRMS (ESI$^+$): calcd for $C_{32}H_{46}NO_6$ $[M+H]^+$ 540.3320, found 540.3316.

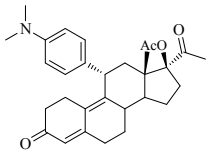


11α-(4-*N, N*-Dimethylaminophenyl)-17β-hydroxy-19-norpregna-4, 9-diene-3, 20-dione (18): green solid, 60% yield, mp 178-182 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.64 (s, 3H, –CH_3), 1.43-2.74 (m, 17H), 2.31 (s, 3H, –$COCH_3$), 2.91 (s, 6H, N–CH_3), 4.25 (d, J = 9.0 Hz, 1H, –CH). 5.74 (s, 1H, =CH), 6.65 (d, J = 9.0 Hz, 2H, Ar–H), 6.99 (d, J = 6.0 Hz, 2H, Ar–H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.9, 199.2, 156.3, 148.1, 145.3, 131.1, 128.9, 126.9, 122.3, 112.3, 90.6, 73.8, 48.6, 47.6, 45.8, 40.1, 39.1, 38.5, 36.3, 35.9, 34.5, 33.9, 30.6, 29.2, 27.8, 26.9, 25.3 ppm.

HRMS (ESI$^+$): calcd for $C_{28}H_{36}NO_3$ $[M+H]^+$ 434.2690, found 434.2685.

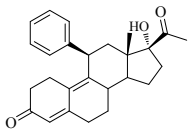


11α,17β-Isomer of UPA (U-2): light yellow powder, 200 mg, 43% yield, mp 182-186 °C, $[\alpha]^{20}$= +117.1 (c 1.0, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69 (s, 3H, –CH_3), 1.16-2.62 (m, 17H), 2.09 (s, 3H, –$COCH_3$), 2.12 (s, 3H, –$COCH_3$), 2.94 (s, 6H, N–CH_3), 4.28 (d, J = 6.0 Hz, 1H, –CH). 5.75 (s, 1H, =CH), 6.71 (s, 2H, Ar–H), 7.04 (d, J = 9.0 Hz, 2H, Ar–H).

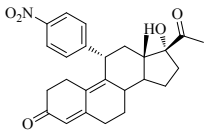
^{13}C NMR (75 MHz, $CDCl_3$): δ =208.4, 199.6, 171.3, 156.6, 148.7, 145.2, 131.4, 129.4, 127.4, 123.0, 112.7, 96.4, 47.6, 47.1, 40.6, 39.5, 39.4, 38.6, 36.8, 32.8, 31.1, 27.5, 27.2, 25.8, 24.9, 21.1, 16.3 ppm.

HRMS (ESI$^+$): calcd for $C_{30}H_{38}NO_4$ $[M+H]^+$ 476.2795, found 476.2813.



11β-(4-Phenyl)-17α-hydroxy-19-norpregna-4, 9-diene-3, 20-dione (20): claret-colored solid, 85% yield, mp 181-185 °C.

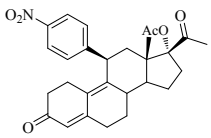
HRMS (ESI$^+$): calcd for $C_{26}H_{31}O_3$ $[M+H]^+$ 391.2268, found 391.2273.



11β-(4-Nitrophenyl)-17α-hydroxy-19-norpregna-4, 9-diene-3, 20-dione (21): dark-yellow solid, 46% yield, mp 189-192 °C.

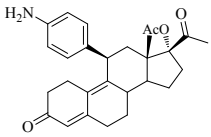
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.33 (s, 3H, –CH_3), 1.16-2.67 (m, 19H), 2.20 (s, 3H, –$COCH_3$), 4.44 (d, J = 7.65 Hz, 1H, –CH). 5.75 (s, 1H, =CH), 7.28 (d, J = 9.0 Hz, 2H, Ar–H), 8.08 (d, J = 9.0 Hz, 2H, Ar–H).

HRMS (ESI$^+$): calcd for $C_{26}H_{30}NO_5$ $[M+H]^+$ 436.2118, found 436.2130.



11β-(4-Nitrophenyl)-17α-acetoxy-19-norpregna-4, 9-diene-3, 20-dione (22): light green solid, 39% yield, mp 183-187 °C.

HRMS (ESI$^+$): calcd for $C_{28}H_{32}NO_6$ $[M+H]^+$ 478.2224, found 478.2235.



Demethylation impurity of UPA (U-3): off-white solid, 500 mg, 60% yield, mp 187-192 °C, $[\alpha]^{20}$= +125.6 (c 1.0, CH_2Cl_2).

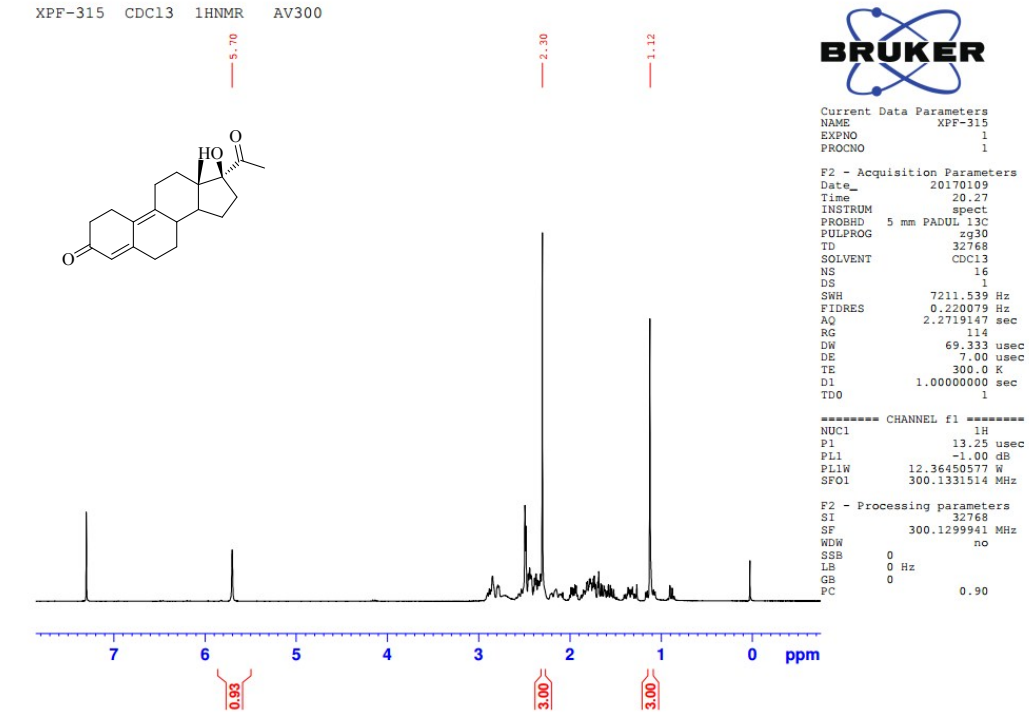
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 3H, –CH_3), 1.19-2.81 (m, 19H), 2.02 (s, 3H, –$COCH_3$), 2.06 (s, 3H, –$COCH_3$), 4.30 (d, J = 6.0 Hz, 1H, –CH). 5.71 (s, 1H, =CH), 6.60 (d, J = 9.0 Hz, 2H, Ar–H), 6.86 (d, J = 6.0 Hz, 2H, Ar–H).

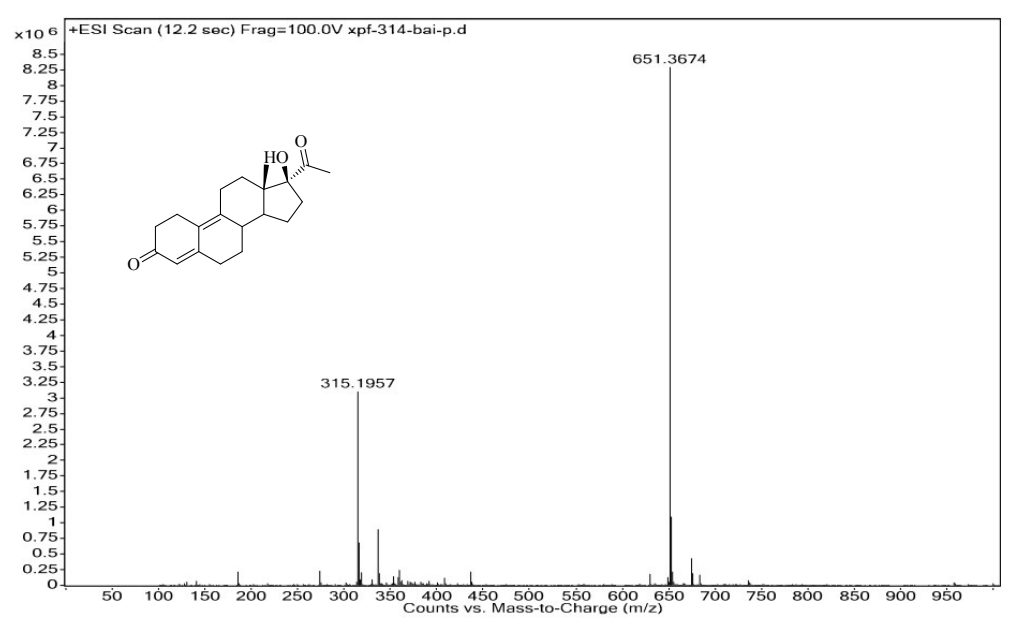
^{13}C NMR (75 MHz, $CDCl_3$): δ =203.9, 199.6, 170.7, 156.6, 148.7, 145.6, 131.5, 129.3, 127.3, 123.0, 112.8, 96.2, 50.9, 47.1, 39.4, 38.4, 36.9, 36.8, 31.1, 30.3, 27.9, 26.9, 25.8, 24.2, 21.3, 15.7 ppm.

HRMS (ESI$^+$): calcd for $C_{28}H_{35}NO_4$ $[M+H]^+$ 448.2482, found 448.2510.

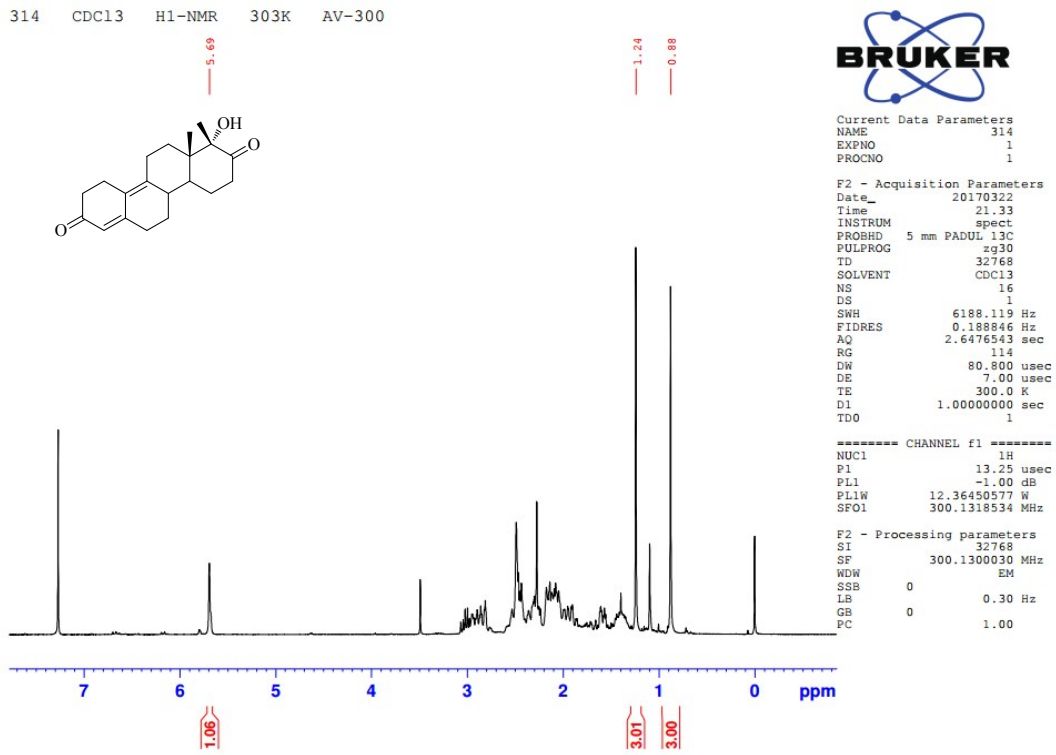
6. NMR spectra

Compound 11

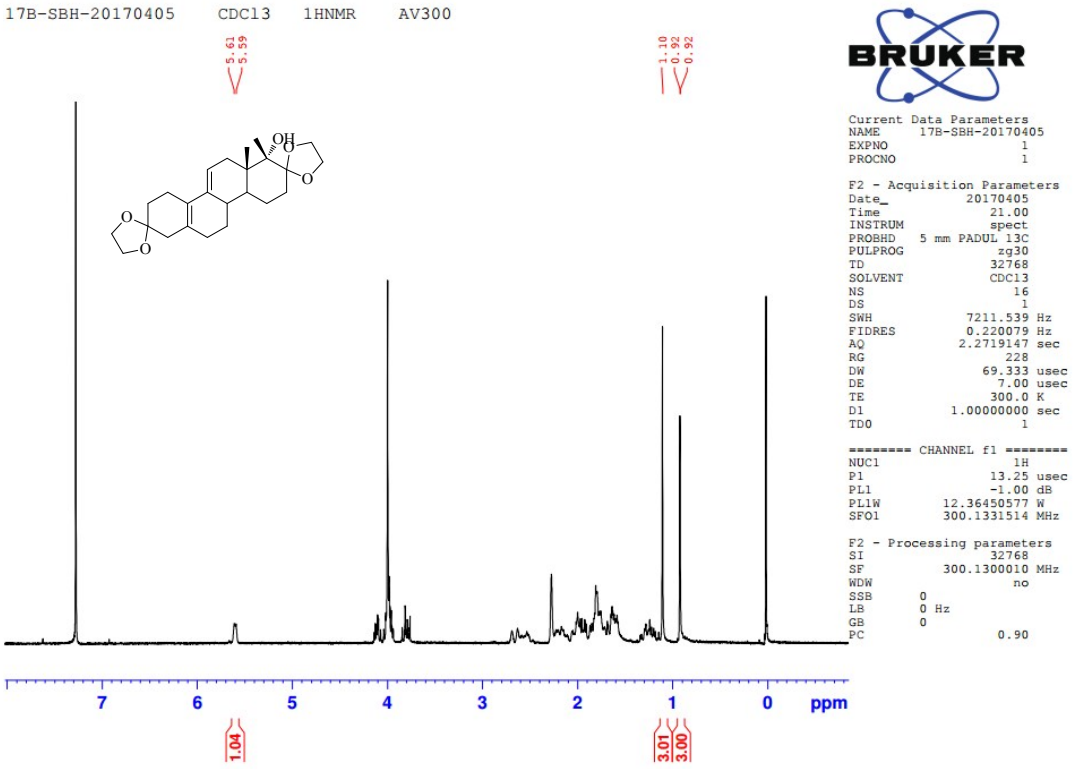




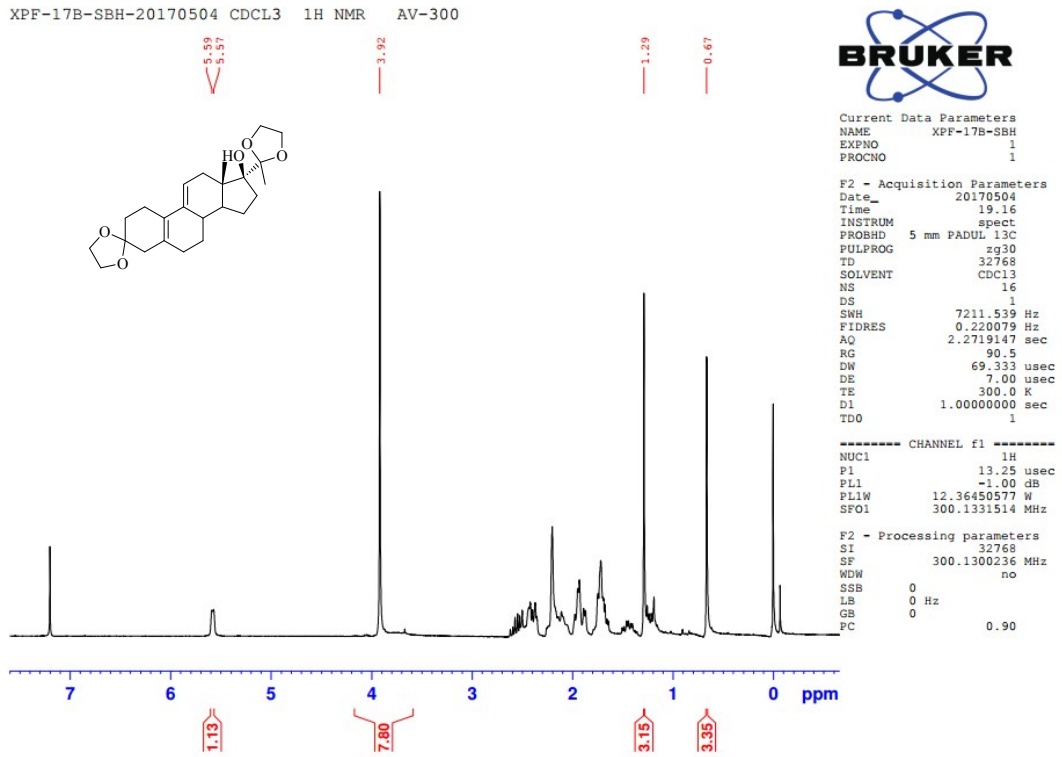
Compound 11-E



Compound Z-1



Compound 12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3.92
1.29
0.67
HO
O
O
O
O
BRUKER
Current Data Parameters
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PROCNO 1
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Time 19.16
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PULPROG zg30
TD 32768
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FIDRES 0.220079 Hz
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DE 7.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
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PL1 -1.00 dB
PL1W 12.36450577 W
SFO1 300.1331514 MHz
F2 - Processing parameters
SI 32768
SF 300.1300236 MHz
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SSB 0
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6
5
4
3
2
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0
ppm
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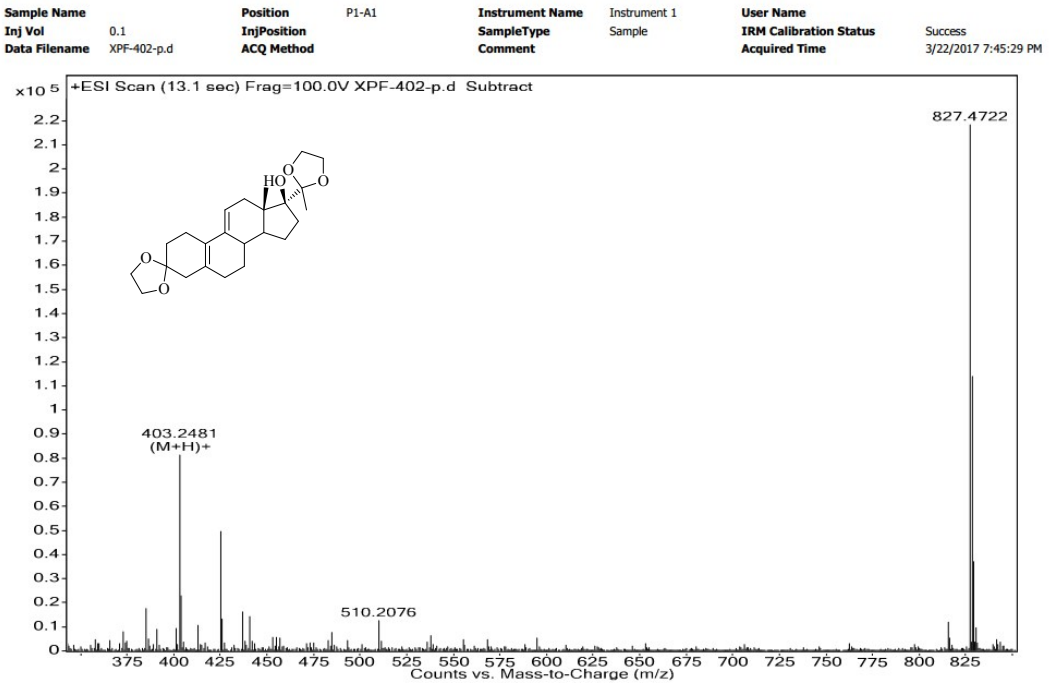
3.35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Instrument Name Instrument 1
User Name
Inj Vol 0.1
InjPosition
SampleType Sample
IRM Calibration Status Success
Data Filename XPF-402-p.d
ACQ Method
Comment
Acquired Time 3/22/2017 7:45:29 PM
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+ESI Scan (13.1 sec) Frag=100.0V XPF-402-p.d Subtract
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(M+H)+
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HO
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O
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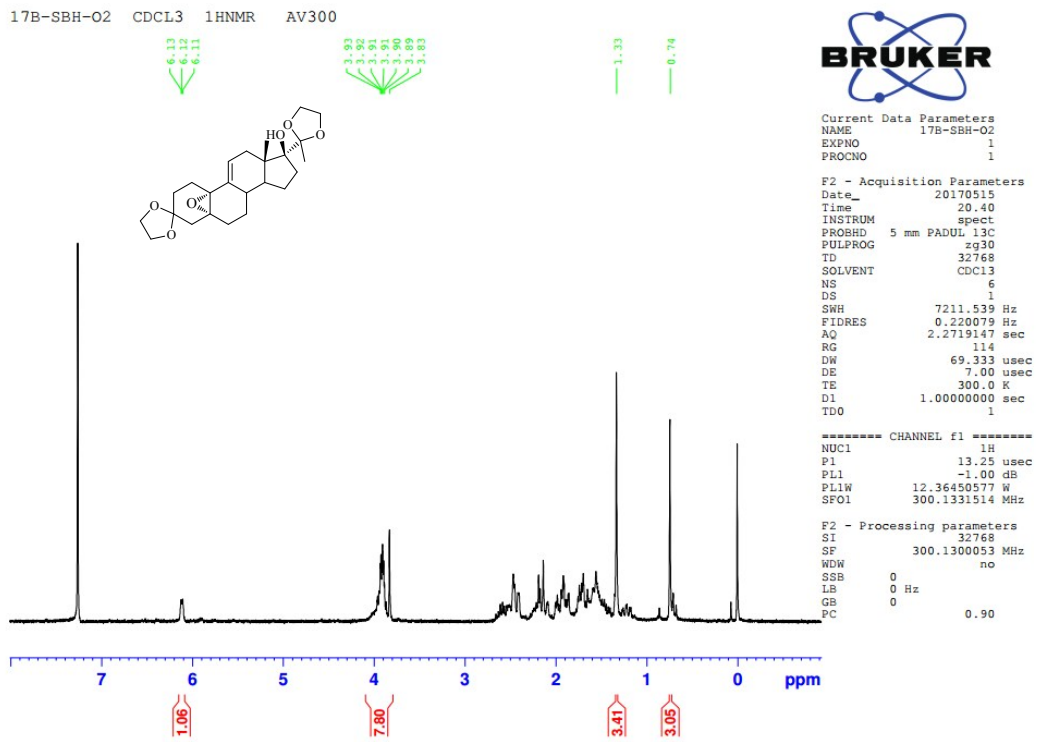
O
Counts vs. Mass-to-Charge (m/z)

Compound 13



Sample Name		**Position**	P1-E2	**Instrument Name**	Instrument 1	**User Name**	
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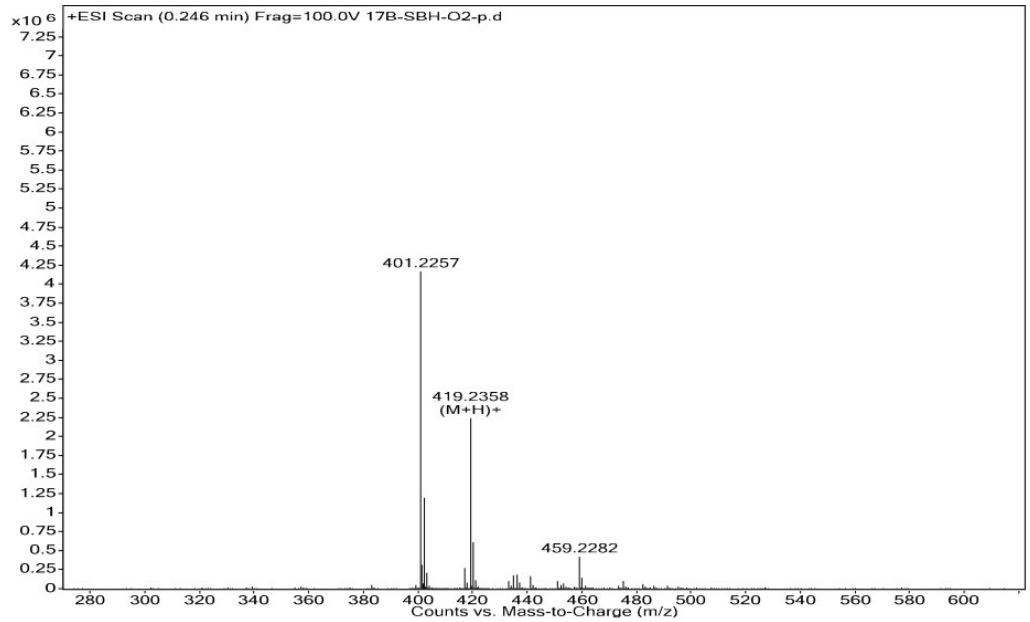
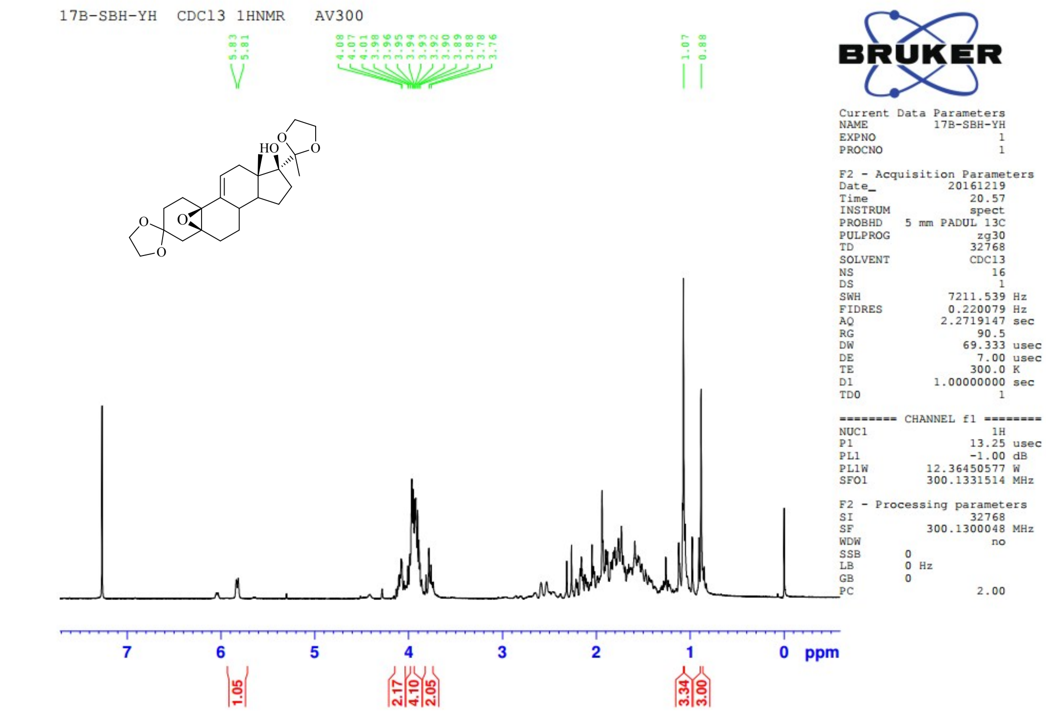
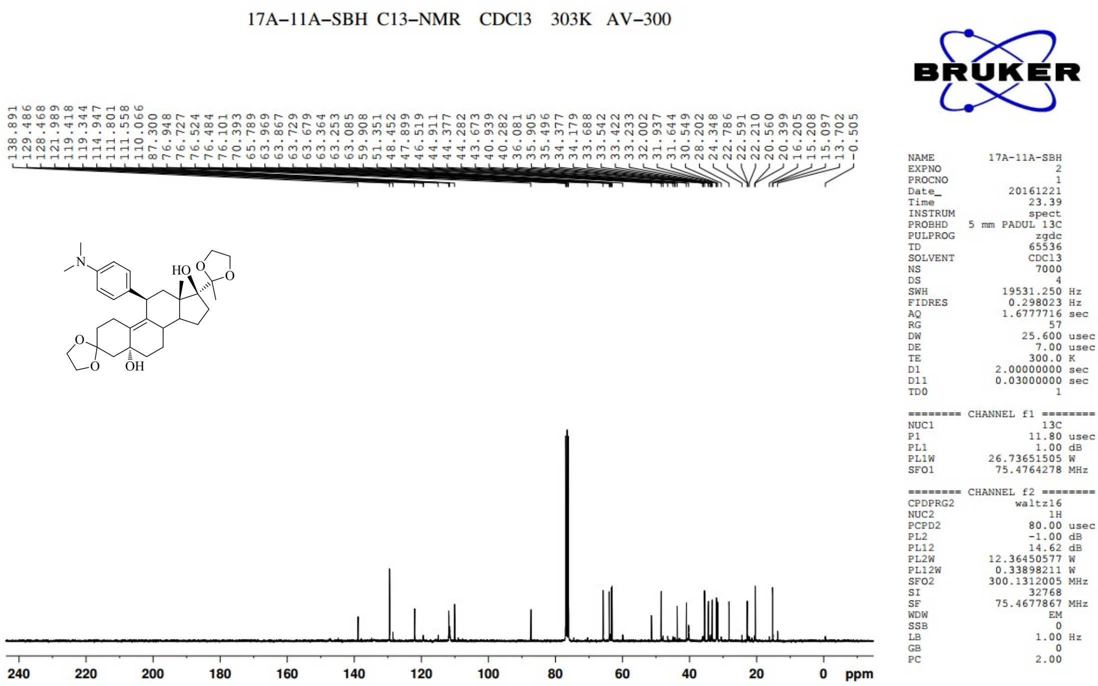


Compound 16


17B-SBH-YH CDCl3 1HNMR AV300

Compound 14


17A-11A-SBH C13-NMR CDCl3 303K AV-300

Sample Name		**Position**	P1-E3	**Instrument Name**	Instrument 1	**User Name**	
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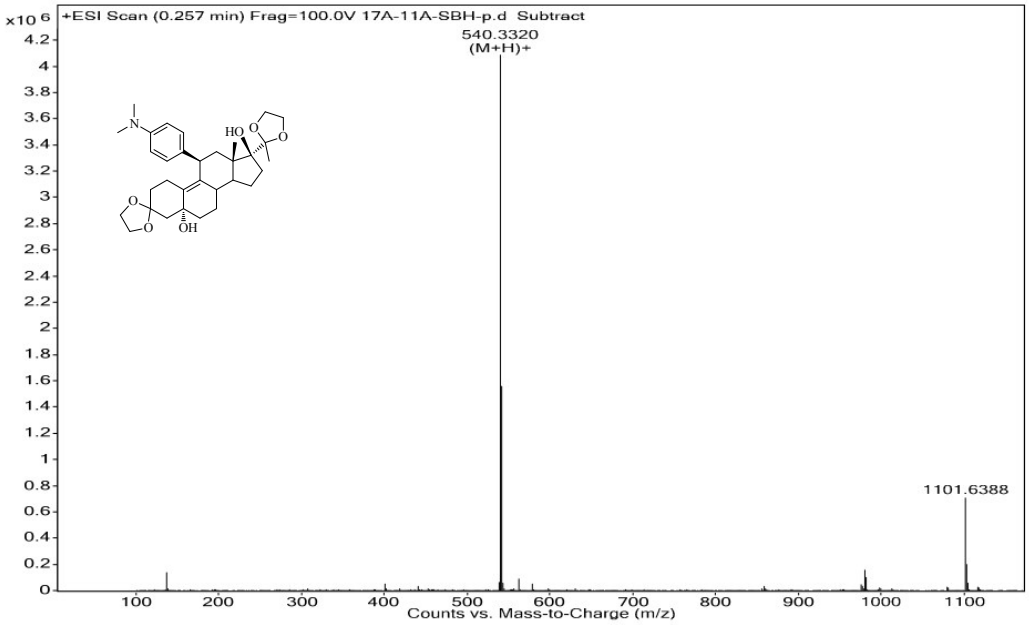
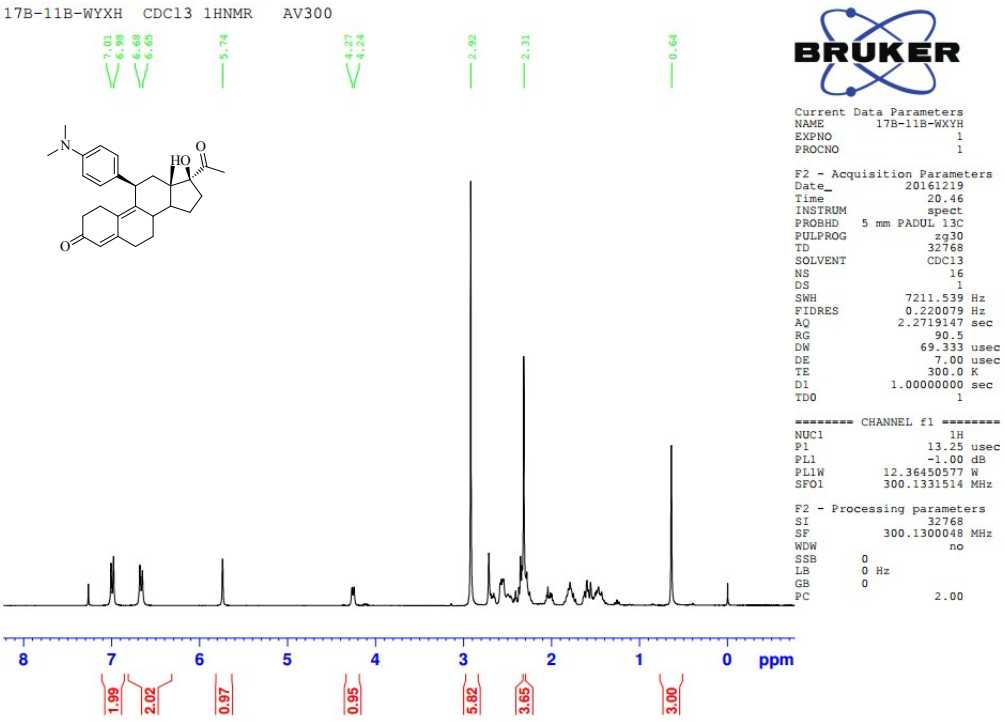
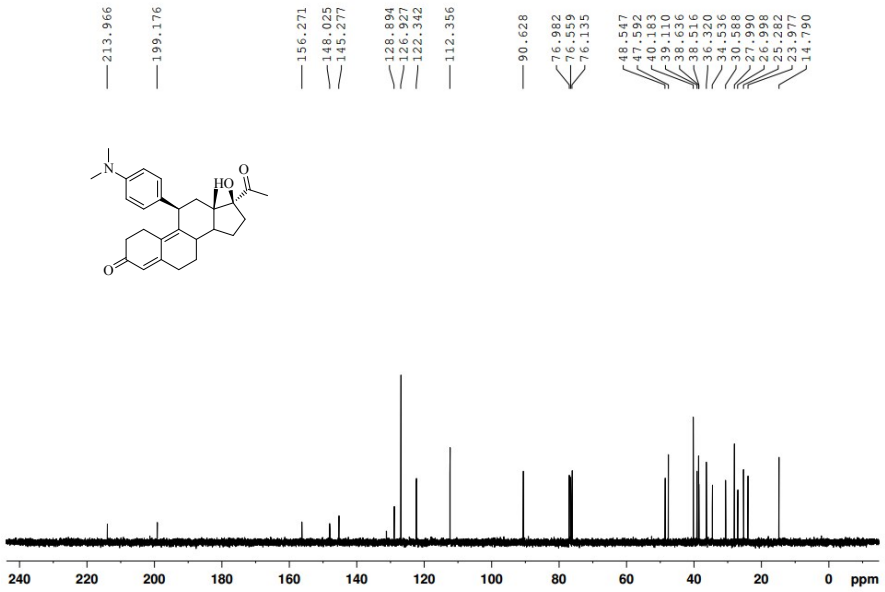


Compound 15



17B-11B-WYXH C13-NMR CDCl3 303K AV-300

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PROCNO                   1
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TD0                      1

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PL1                 1.00 dB
PL1W          26.73651505 W
SFO1           75.4764278 MHz

======== CHANNEL f2 ========
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NUC2                    1H
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PL2                -1.00 dB
PL12               14.62 dB
PL2W          12.36450577 W
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GB                       0
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Sample Name		**Position**	P1-E5	**Instrument Name**	Instrument 1	**User Name**	
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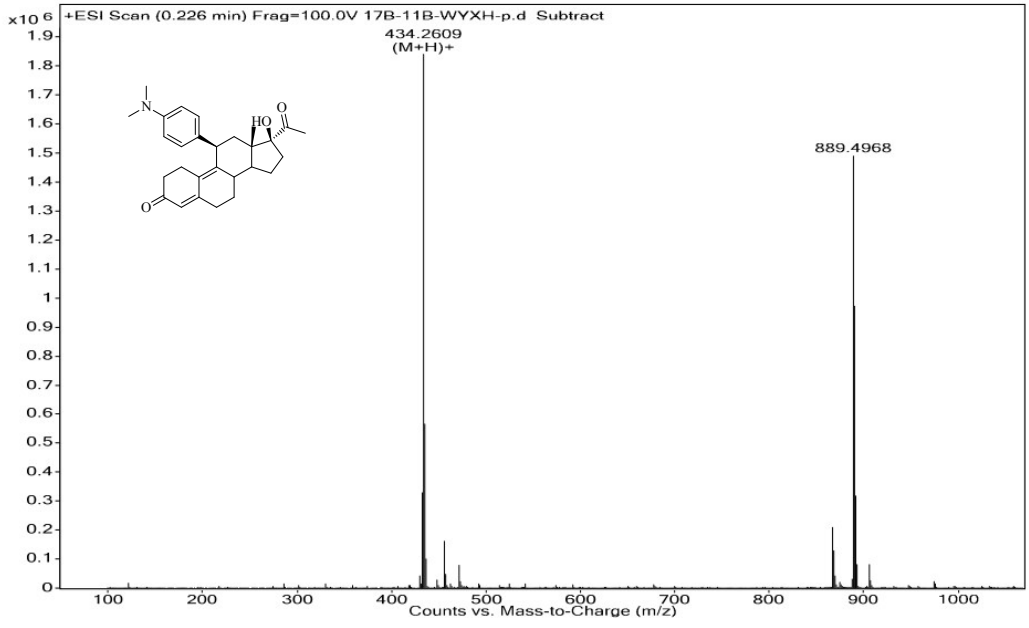
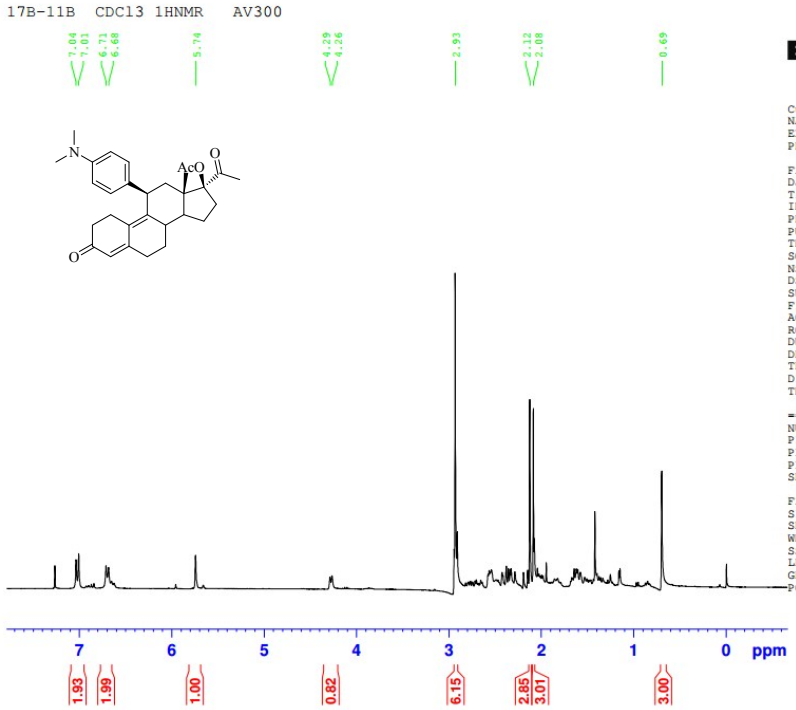


Compound U-1

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PROCNO                      1

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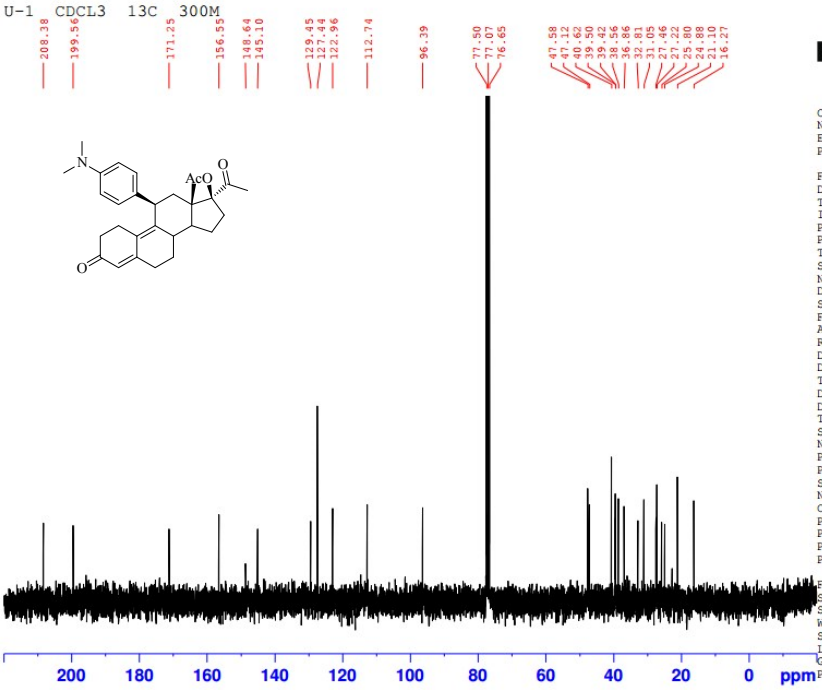


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PROCNO                     10

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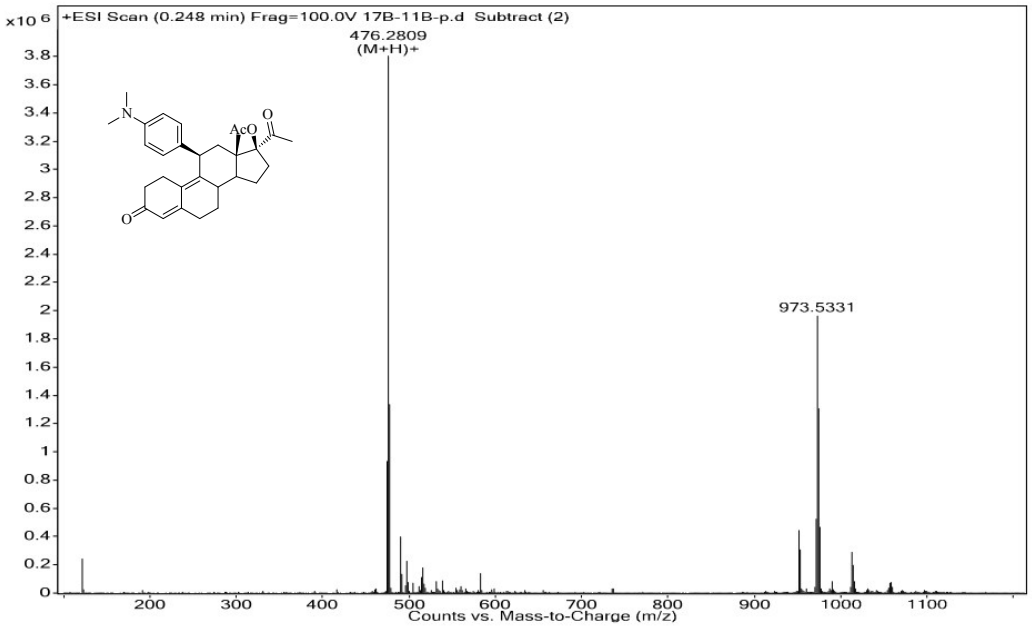
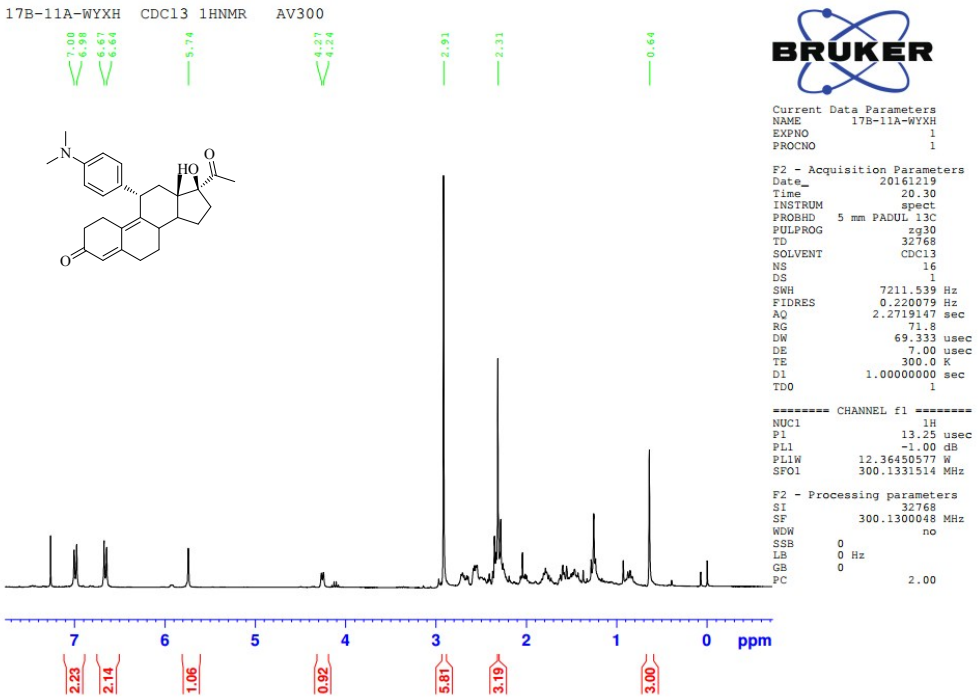
NUC2                    1H
CPDPRG[2             waltz16
PCPD2                 90.00 usec
PLW2           12.00000000 W
PLW12           0.19935000 W
PLW13           0.10027000 W

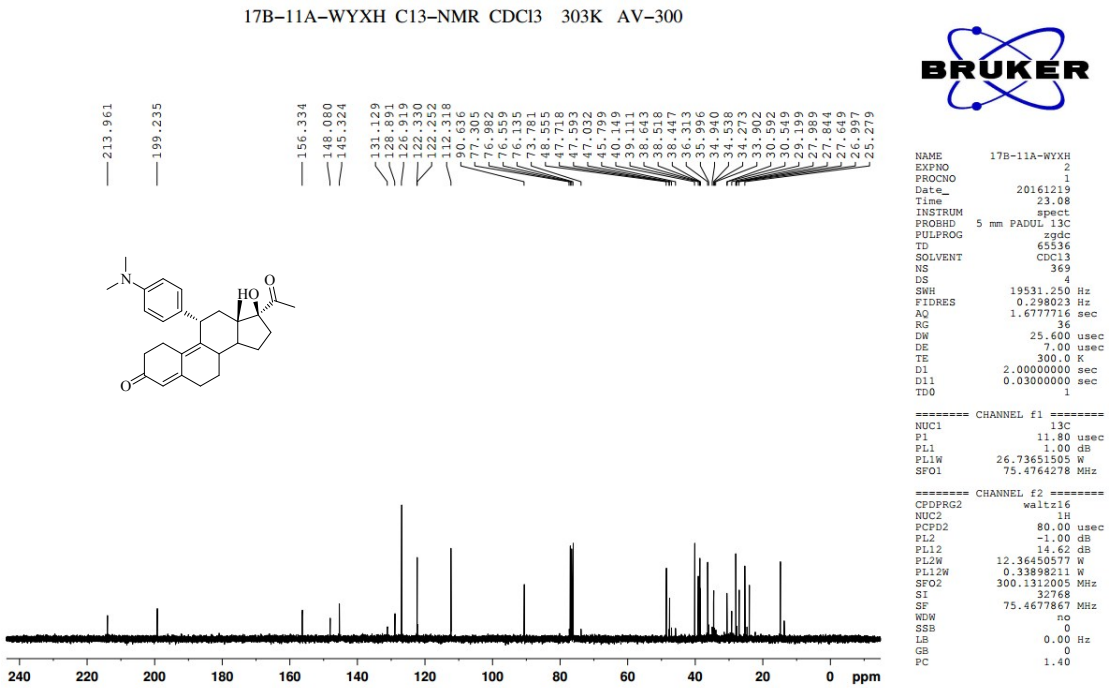
F2 - Processing parameters
SI                    32768
SF             75.4677485 MHz
WDW                      EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```

Sample Name		**Position**	P1-E7	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0.1	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Some Ions Missed
Data Filename	17B-11B-p.d	**ACQ Method**		**Comment**		**Acquired Time**	12/15/2016 8:29:34 PM

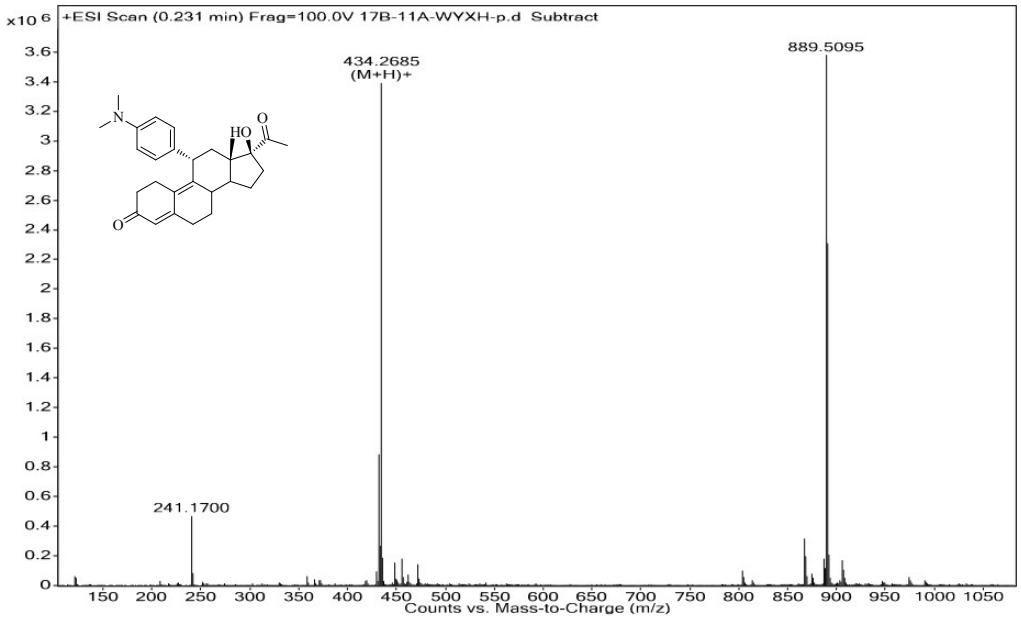


Compound 18

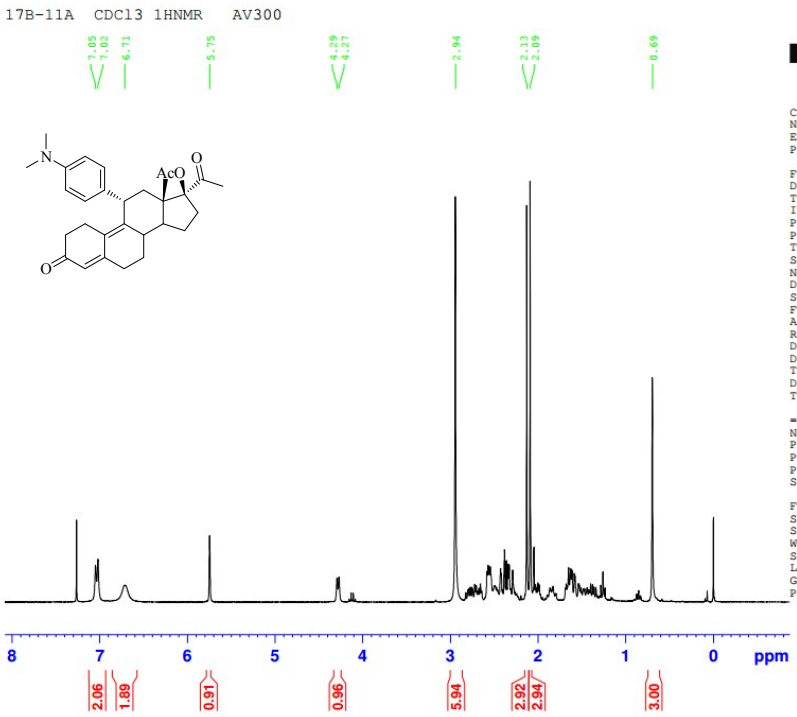




Sample Name		**Position**	P1-F1	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0.1	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	All Ions Missed
Data Filename	17B-11A-WYXH-p.d	**ACQ Method**		**Comment**		**Acquired Time**	12/15/2016 8:37:12 PM



Compound U-2



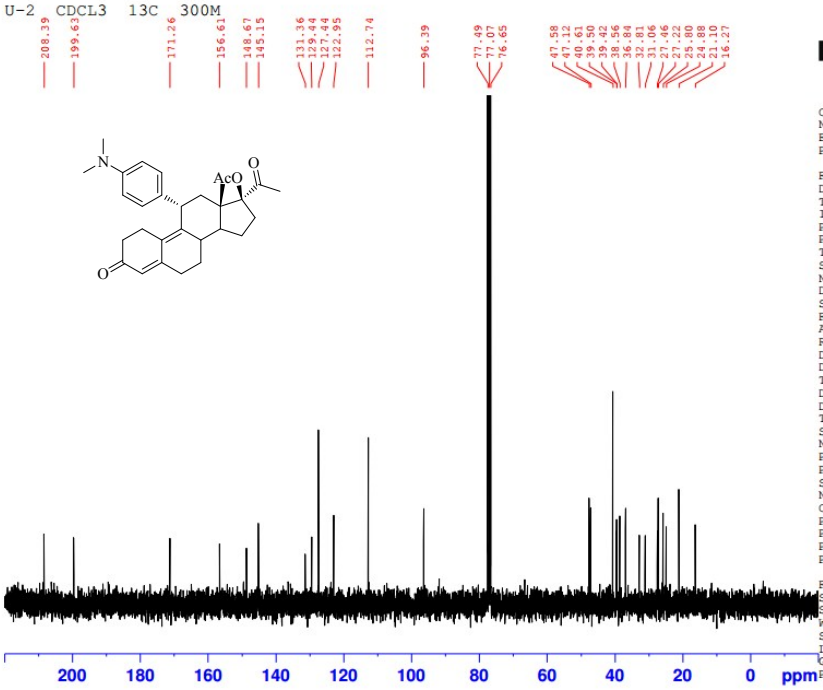
BRUKER

```
Current Data Parameters
NAME                  17B-11A
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20161219
Time                  20.49
INSTRUM               spect
PROBHD   5 mm PADUL 13C
PULPROG                zg30
TD                    32768
SOLVENT               CDCl3
NS                       16
DS                        1
SWH               7211.539 Hz
FIDRES            0.220079 Hz
AQ                2.2719147 sec
RG                     90.5
DW                69.333 usec
DE                   7.00 usec
TE                   300.0 K
D1             1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.25 usec
PL1                    -1.00 dB
PL1W          12.36450577 W
SFO1          300.1331514 MHz

F2 - Processing parameters
SI                    32768
SF            300.1300048 MHz
WDW                      no
SSB          0
LB           0 Hz
GB           0
PC                     2.00
```



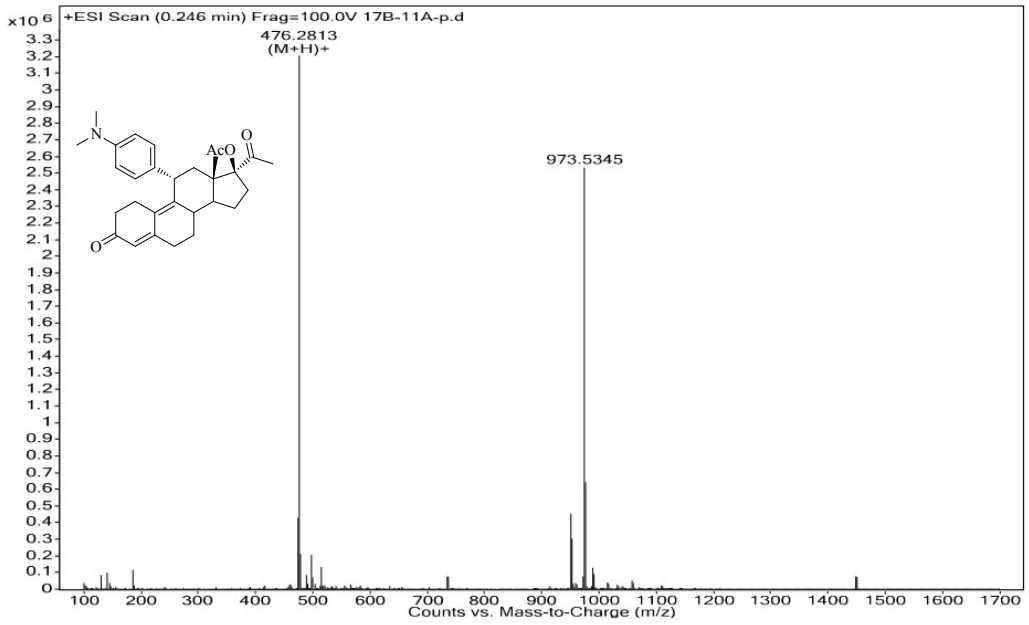
BRUKER

```
Current Data Parameters
NAME                      U-2
EXPNO                       8
PROCNO                     10

F2 - Acquisition Parameters
Date_              20190115
Time                  17.46 h
INSTRUM               spect
PROBHD   Z104275_0384 (
PULPROG              zgpg30
TD                    65536
SOLVENT               CDCl3
NS                      136
DS                        4
SWH              18115.941 Hz
FIDRES            0.552855 Hz
AQ                1.8087935 sec
RG                     6.24
DW                27.600 usec
DE                   6.50 usec
TE                   0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                       1
SFO1          75.4752953 MHz
NUC1                    13C
P1                     9.70 usec
PLW1          39.00000000 W
SFO2          300.1312005 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2                 90.00 usec
PLW2          12.00000000 W
PLW12          0.19935000 W
PLW13          0.10027000 W

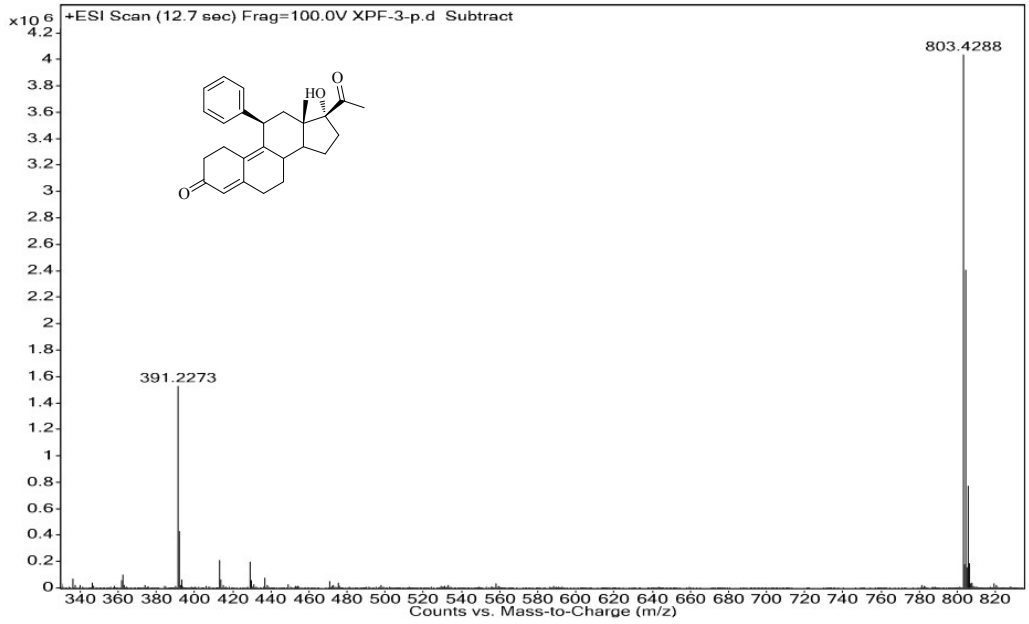
F2 - Processing parameters
SI                    32768
SF            75.4677485 MHz
WDW                      EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```

Sample Name		**Position**	P1-E9	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0.1	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	All Ions Missed
Data Filename	17B-11A-p.d	**ACQ Method**		**Comment**		**Acquired Time**	12/15/2016 8:34:33 PM

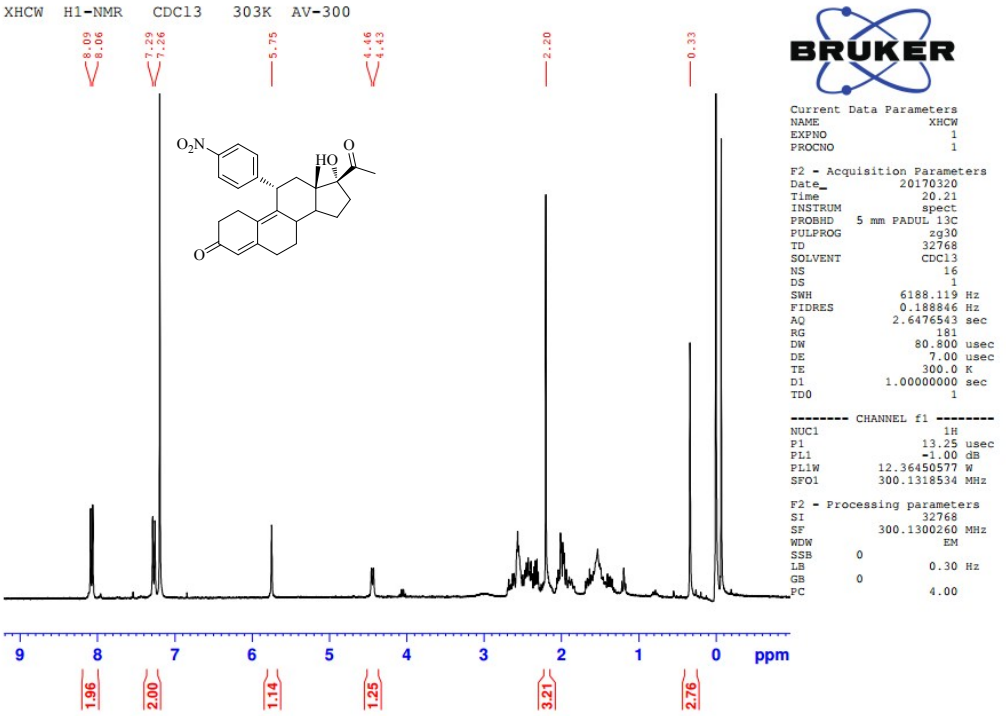


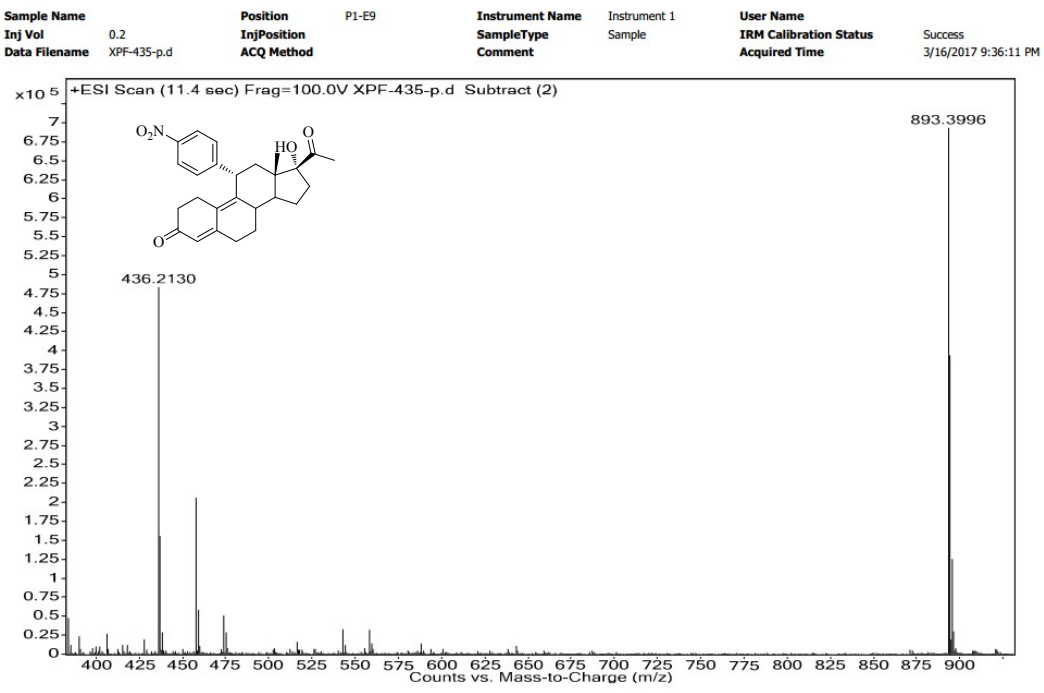
Compound 20

Sample Name		**Position**	P1-C3	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0.1	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	XPF-3-p.d	**ACQ Method**		**Comment**		**Acquired Time**	3/3/2017 8:00:36 PM



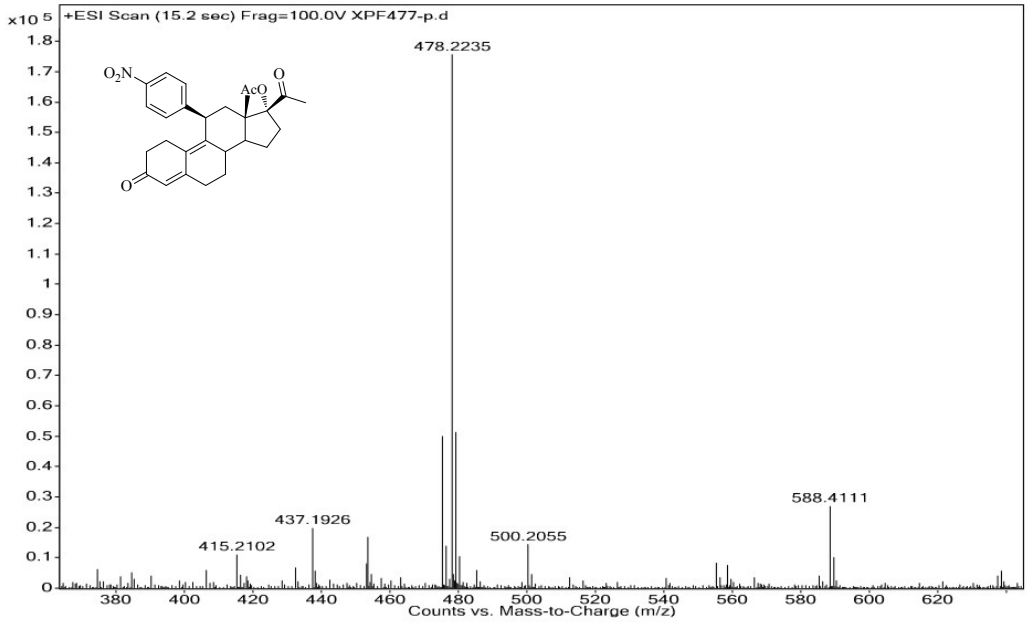
Compound 21


XHCW H1-NMR CDCl3 303K AV-300
8.09
8.06
7.29
7.26
5.75
4.46
4.43
2.20
0.33
BRUKER
Current Data Parameters
NAME XHCW
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170320
Time 20.21
INSTRUM spect
PROBHD 5 mm PADUL 13C
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 1
SWH 6188.119 Hz
FIDRES 0.188846 Hz
AQ 2.6476543 sec
RG 181
DW 80.800 usec
DE 7.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 13.25 usec
PL1 -1.00 dB
PL1W 12.36450577 W
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300260 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
9
8
7
6
5
4
3
2
1
0
ppm
1.96
2.00
1.14
1.25
3.21
2.76

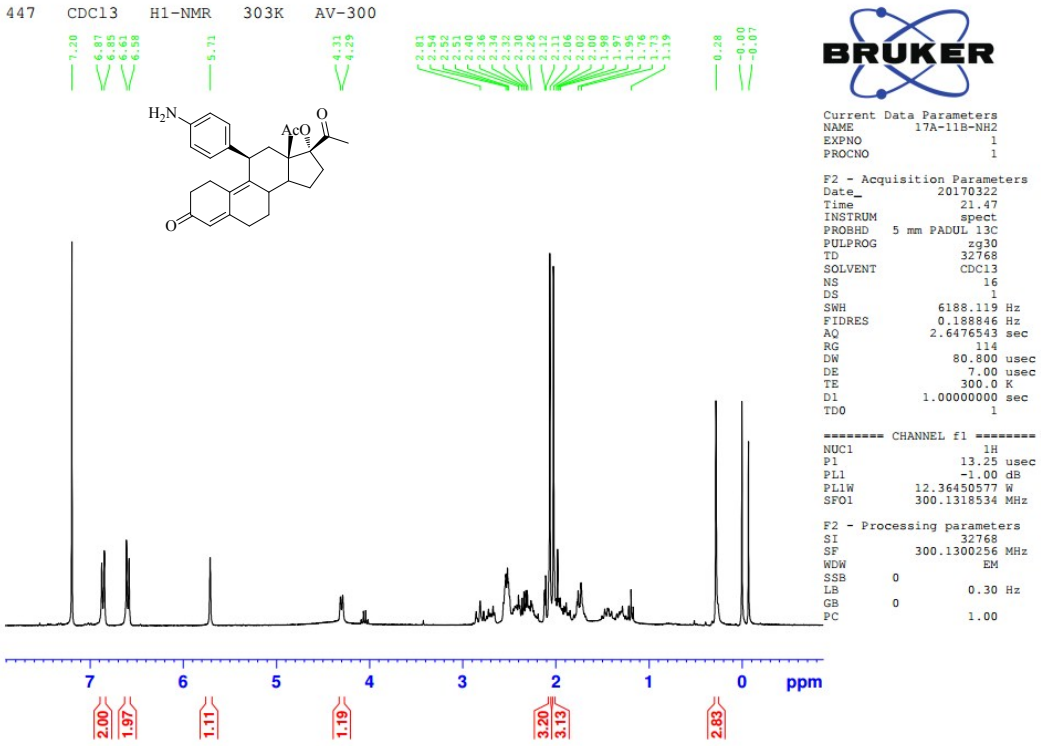

Sample Name
Position P1-E9
Instrument Name Instrument 1
User Name
Inj Vol 0.2
InjPosition
SampleType Sample
IRM Calibration Status Success
Data Filename XPF-435-p.d
ACQ Method
Comment
Acquired Time 3/16/2017 9:36:11 PM
+ESI Scan (11.4 sec) Frag=100.0V XPF-435-p.d Subtract (2)
x10 5
893.3996
436.2130
Counts vs. Mass-to-Charge (m/z)

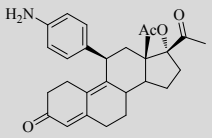
Compound 22

Sample Name		**Position**	P1-F7	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	1	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	XPF477-p.d	**ACQ Method**		**Comment**		**Acquired Time**	3/18/2017 10:11:59 AM

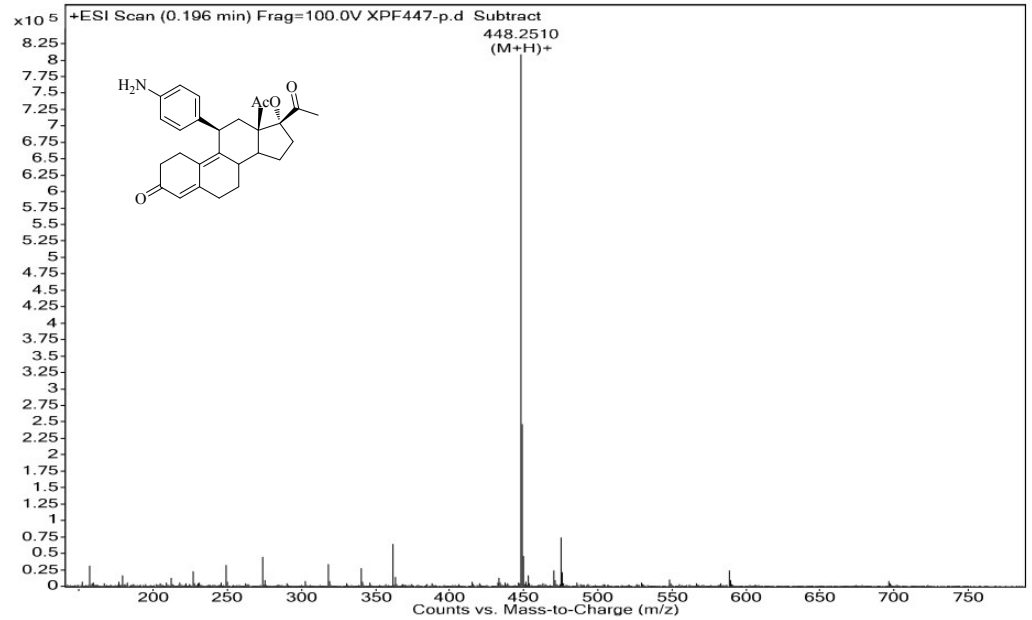


Compound U-3





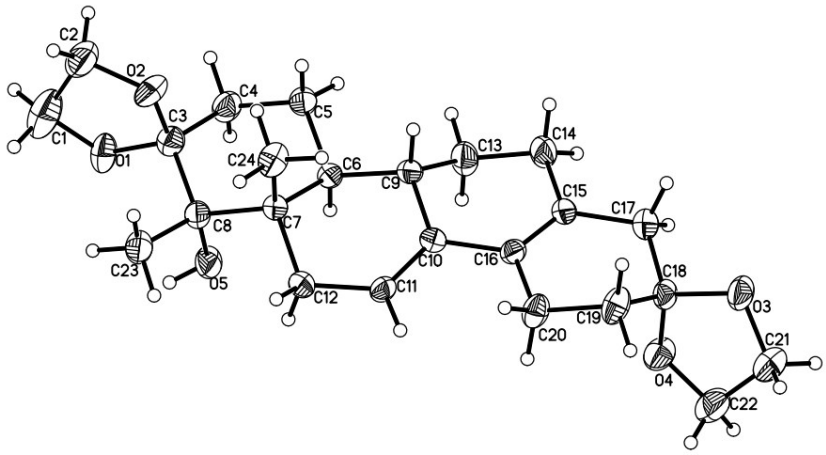
Sample Name		**Position**	P1-D1	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	1	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	XPF447-p.d	**ACQ Method**		**Comment**		**Acquired Time**	3/18/2017 2:34:44 PM



7. X-ray crystal data

The X-ray crystallographic data of Z-1

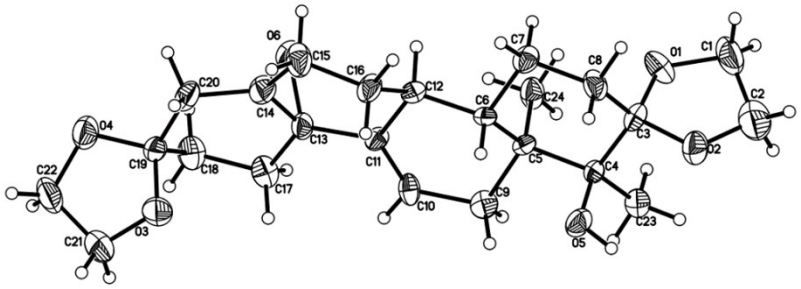
X-ray crystallographic data of **Z-1** were solutions at T=293(2) K: $C_{24}H_{34}O_5$, monoclinic. Space group, P21, a=7.3230(15) Å, b=12.384(3) Å, c=12.233(2) Å, α=90.00°, β=106.42 (3) °, γ=90.00°, V=1064.1(4) $Å^3$, Z=2.



Scheme 2. The X-ray diffraction result of compound **Z-1** drawn with 30% probability thermal ellipsoids

The X-ray crystallographic data of Z-2

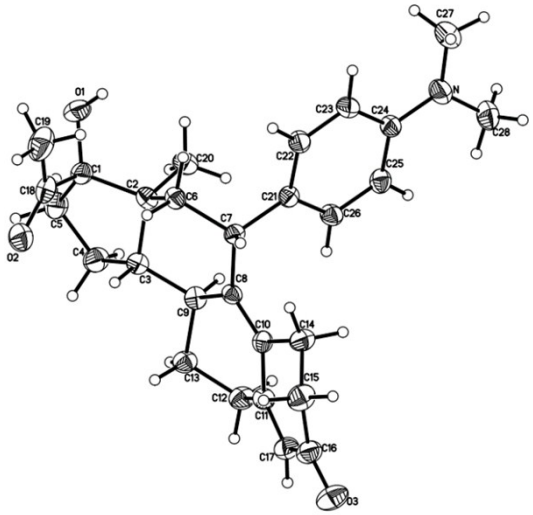
X-ray crystallographic data of **Z-2** were solutions at T=293(2) K: $C_{24}H_{34}O_6$, monoclinic. Space group, P21, a=7.2720(15) Å, b=12.369(3) Å, c=12.296(3) Å, α=90.00°, β=105.99 (3) °, γ=90.00°, V=1063.2(4) $Å^3$, Z=2.



Scheme 2. The X-ray diffraction result of the oxidation product drawn with 30% probability thermal ellipsoids

The X-ray crystallographic data of 15

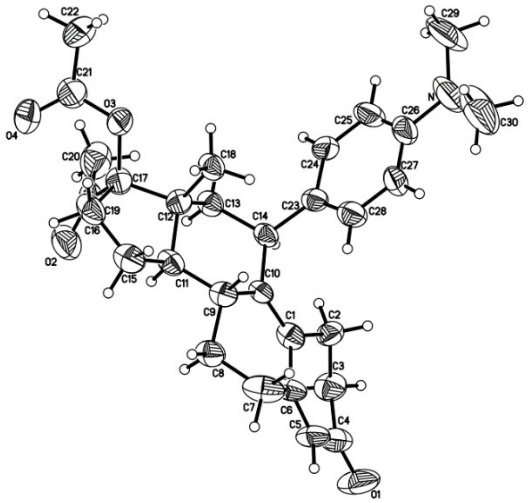
X-ray crystallographic data of **15** were solutions at T=293(2) K: $C_{28}H_{35}NO_3$, orthorhombic. Space group, P212121, a=10.391(2) Å, b=12.429(3) Å, c=18.269(4) Å, α=90.00 °, β=90 °, γ=90.00 °, V=2359.4(8) Å^3, Z=4.



Scheme 5: The X-ray diffraction result of compound **15** drawn with 30% probability thermal ellipsoids

The X-ray crystallographic data of U-1

X-ray crystallographic data of **U-1** were solutions at T=293(2) K: $C_{30}H_{37}NO_4$, hexagonal. Space group, P65, a=17.407(3) Å, b=17.407(3) Å, c=17.977(4) Å, α=90.00°, β=90 °, γ=120.00°, V=4717.6(13) Å^3, Z=6.



Scheme 5: The X-ray diffraction result of compound **U-1** drawn with 30% probability thermal ellipsoids

8. HPLC chromatogram

HPLC Conditions for compound U-1, U-2 and U-3:

Column: ODS-C18, 5 µm, 150 mm x 4.6 mm

Mobile Phase: A = H_2O; B = MeOH

Gradient Profile:

Time (min)	%A	%B
0	60	40
15	5	95
20	5	95
21	60	40
23	60	40

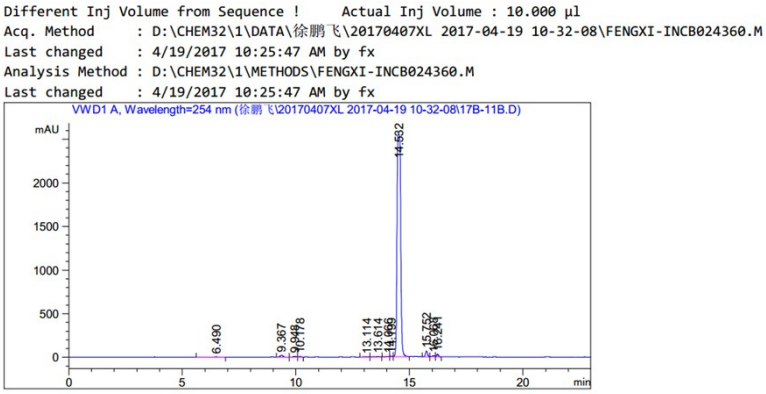
Flow Rate: 1.0mL/min

Column Temperature: 30 °C

Detection: UV @ 254 nm; 1V = 1000 mAU

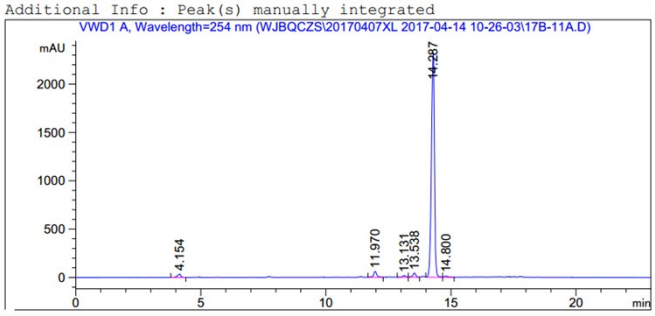
Injection Volume: 10 µL

HPLC chromatogram of compound U-1



HPLC chromatogram of compound U-2

```
Different Inj Volume from Sequence !     Actual Inj Volume : 10.000 µl
Acq. Method      : D:\CHEM32\1\DATA\WJBQCZS\20170407XL 2017-04-14 10-26-03\FENGXI-INCB024360.M
Last changed     : 4/14/2017 10:21:21 AM by 石冰玉
Analysis Method : D:\CHEM32\1\METHODS\FENGXI-INCB024360.M
Last changed     : 4/19/2017 10:25:47 AM by fx
Additional Info : Peak(s) manually integrated
```



HPLC chromatogram of compound U-3

```
Different Inj Volume from Sequence !     Actual Inj Volume : 10.000 µl
Acq. Method      : D:\CHEM32\1\DATA\徐鹏飞\20170504 2017-05-06 14-43-40\FENGXI-INCB024360.M
Last changed     : 5/2/2017 9:09:13 AM
Analysis Method : D:\CHEM32\1\METHODS\FENGXI-INCB024360.M
Last changed     : 5/2/2017 9:09:13 AM
Additional Info : Peak(s) manually integrated
```