

Novel Steroid Inhibitors of Glucose-6-Phosphate Dehydrogenase

Niall M. Hamilton,^{*,†} Martin Dawson,[§] Emma E. Fairweather,[†] Nicola S. Hamilton,[†] James R. Hitchin,[†] Dominic I. James,[†] Stuart D. Jones,[†] Allan M. Jordan,[†] Amanda J. Lyons,[†] Helen F. Small,[†] Graeme J. Thomson,[†] Ian D. Waddell,[†] Donald J. Ogilvie[†]

Supporting Information

Table of Contents

Summary of purity data:	S2-S4
LC-MS methods and solvent gradients:	S5
Preparative HPLC instrument and solvent gradients:	S6-S7
Preparative methods and spectroscopic data for compounds	
1-4, 8-11, 14a, 14b, 16, 17a, 19, 24 and 27-47:	S8-S24
¹ H NMR spectra of target compounds	S25-S45
References for supporting information:	S46-S48

Summary of purity data

The steroids lack a suitable uv chromophore for easy detection and it is not possible to determine purity using LC-MS with uv detection. Consequently, compound purity was determined by LC-MS with an evaporative light scattering detector (ELSD).

Tabulated results are shown below.

Compound	MW	Purity pH 3 (%)	Mass seen	RT ^a (Min)	Mass		
					Purity pH 10 (%)	seen (ES-)	RT ^a (Min)
1	288.42	100	no peak	1.24	100	no peak	1.24
7c	332.48	100	333.1 (ES+)	1.2	100	331.1	1.18
7d	346.51	100	347.2 (ES+)	1.22	100	345.2	1.22
7e	360.53	100	361.2 (ES+)	1.25	100	359.2	1.25
7f	388.59	100	389.2 (ES+)	1.33	100	387.2	1.31
7g	360.53	100	361.5 (ES+)	1.28	100	no peak	1.27
7h	347.49	100	348.5 (ES+)	1.34	100	no peak	1.33
7i	367.55	100	no peak	1.28	100	366.1	1.26
7j	381.57	100	no peak	1.3	100	380.0	1.29

7k	429.62	70/30	429.1 (ES-)	1.37 / 1.42	63/37	428.1	1.36 / 1.41
7l	368.53	100	367.1 (ES-)	1.23	100	367.1	1.22
9	318.49	no peak	no peak	n/a	no peak	no peak	n/a
14c	360.53	100	361.2 (ES+)	1.27	100	359.0	1.25
14d	388.59	100	389.2 (ES+)	1.36	100	387.2	1.35
14e	375.54	100	376.5 (ES+)	1.44	100	no peak	1.43
14f	395.6	100	no peak	1.36	100	394.1	1.35
14g	409.63	no peak	no peak	n/a	no peak	no peak	n/a
14h	457.67	100	456.2 (ES-)	1.47	100	456.2	1.45
14i	396.59	100	395.1 (ES-)	1.29	100	395.1	1.28
14j	424.64	100	425.1 (ES+)	1.43	100	423.1	1.42
17b	360.53	100	361.1 (ES+)	1.27	100	359.1	1.26
17c	367.55	100	no peak	1.31	100	366.1	1.3

17d	368.53	100	367.1 (ES-)	1.25	100	367.1	1.24
18a	404.59	100	405.1 (ES+)	1.23	82/18	403.1	1.22 / 1.28
18b	391.54	100	392.3 (ES+)	1.32	100	390.3	1.31
18c	411.6	25/75	no peak	1.25 / 1.26	3/9/56/32	410.1 for peaks 3	1.03 / 1.05 / 1.24 /
						and 4	1.25
18d	412.59	100	411.1 (ES-)	1.2	5/95	411.1	1.01 / 1.18
23	332.52	100	no peak	1.42	100	no peak	1.41
25	318.49	100	no peak	1.39	100	no peak	1.38
26	348.52	100	no peak	1.43	33/67	no peak	1.38 / 1.41

^a RT = retention time

LC-MS Methods and Solvent Gradients

LC-MS analyses were performed on a Waters Acquity UPLC system fitted with BEH C18 1.7 μ M columns (2.1 \times 50 mm) and with ELSD detector. Positive and negative mass ion detection was performed using a Waters SQD detector. Analyses were performed with either buffered acidic or basic solvents and gradients as detailed below:

Low pH:

Solvent A – Water + 10mM ammonium formate + 0.1% formic acid

Solvent B – Acetonitrile + 5% water + 0.1% formic acid

High pH:

Solvent A – Water + 10mM ammonium hydrogen carbonate + 0.1% ammonia solution

Solvent B – Acetonitrile + 0.1% ammonia solution

Gradient:

Time	Flow rate (mLmin ⁻¹)	% Solvent A	% Solvent B
0	0.6	95	5
1.2	0.6	5	95
1.7	0.6	5	95
1.8	0.6	95	5

Preparative HPLC instrument and solvent gradients

Some compounds were purified by preparative HPLC on a Waters FractionLynx MS autopurification system, with a Waters XBridge 5 μm C18, 100 mm \times 19 mm i.d. column, running at a flow rate of 20 mLmin^{-1} with UV diode array detection (210–400 nm) and mass-directed collection using both positive and negative mass ion detection.

Purifications were performed using buffered acidic or basic solvent systems as appropriate. Compound retention times on the system were routinely assessed using a 30-50 μL test injection and a standard gradient, and then purified using an appropriately chosen focussed gradient as detailed below, based upon observed retention time.

Low pH:

Solvent A – Water + 10mM ammonium formate + 0.1% formic acid
Solvent B – Acetonitrile + 5% water + 0.1% formic acid

High pH:

Solvent A – Water + 10mM ammonium formate + 0.1% ammonia solution
Solvent B – Acetonitrile + 5% water + 0.1% ammonia solution

Standard Gradient:

Time	Flow rate (mLmin^{-1})	% Solvent A	% Solvent B
0	20	90	10

0.3	20	90	10
8.5	20	2	98
12	20	2	98
12.5	0	2	98

Focussed Gradients:

		% Solvent B				
		Retention time on standard gradient (min.)				
Time	Flow rate (mLmin ⁻¹)	0 – 5.2	4.9 – 6.6	6.3 – 7.5	7.3 – 9.5	9.3 - 12
0	20	10	10	10	10	10
0.25	20	10	10	10	10	10
0.35	20	10	20	35	45	60
10	20	45	55	65	75	98
12	20	98	98	98	98	98
12.5	0	98	98	98	98	98

N-(3 β ,5 α)-17-Oxoandrostan-3-yl]urea **7c** and *N*-(3 β ,5 α)-20-oxopregnan-3-yl]urea

14c were both purified using the high pH standard gradient method.

Preparative Methods and Spectroscopic Data for Compounds 27-47

These compounds have been previously reported in the literature.

(3 β)-3-Hydroxyandrost-5-en-17-one (Dehydroepiandrosterone) 1.¹

^1H NMR (CDCl₃): δ 0.89 (s, 3H), 1.04 (s, 3H), 2.41-2.52 (m, 1H), 3.46-3.60 (m, 1H), 5.36-5.41 (m, 1H); ^{13}C NMR (CDCl₃): δ 13.6, 19.4, 20.4, 21.9, 30.8, 31.4, 31.5, 31.6, 35.9, 36.6, 37.2, 42.2, 47.6, 50.2, 51.8, 71.6, 120.9, 141.1, 221.2; LC-MS no peak; HRMS (ESI) *m/z* [M+Na]⁺ Calcd for C₁₉H₂₈NaO₂: 311.1982. Found: 311.1992.

(3 β ,5 α)-3-Hydroxyandrostan-17-one (Epiandrosterone) 2.²

^1H NMR (CDCl₃): δ 0.85 (s, 3H), 0.88 (s, 3H), 2.40-2.50 (m, 1H), 3.56-3.67 (m, 1H); ^1H NMR (DMSO-*d*₆): δ 0.77 (2 \times s, 2 \times 3H), 2.33-2.42 (m, 1H), 3.29-3.38 (m, 1H), 4.44 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (CDCl₃): δ 11.2, 12.7, 19.4, 20.7, 27.3, 29.8, 30.3, 30.5, 33.9, 34.5, 34.7, 35.8, 37.0, 43.7, 46.7, 50.3, 53.3, 70.0, 220.3.

(3 β ,5 α)-3-Hydroxyandrostan-17-one, cyclic 1,2-ethanediyl acetal 3.³

Epiandrosterone **2** (10 g, 34.4 mmol) was added to a solution of *p*-toluenesulfonic acid monohydrate (0.63 g, 3.67 mmol), ethylene glycol (45.5 g, 733 mmol) and trimethyl orthoformate (38.9 g, 367 mmol) in DCM (100 mL). The mixture was stirred overnight at ambient temperature. The reaction mixture was washed with 2 \times 1M aqueous sodium hydroxide, brine and passed through a hydrophobic frit. The DCM phase was concentrated and the residue chromatographed on silica (100 g SNAP cartridge, ethyl acetate/isohexane gradient elution) and the solvent evaporated to give the product **3** as a white solid (9.68 g, 84%); ^1H NMR (DMSO-*d*₆): δ 0.74 (s,

3H), 0.76 (s, 3H), 3.28-3.39 (m, 1H), 3.72-3.85 (m, 4H), 4.40-4.42 (d, J = 4.71 Hz, 1H).

(3 α ,5 α)-3-Hydroxyandrostan-17-one, cyclic 1,2-ethanediyl acetal 4.⁴

(3 β ,5 α)-3-Hydroxyandrostan-17-one, cyclic 1,2-ethanediyl acetal **3** (12.1 g, 36.1 mmol), triphenyl phosphine (TPP) (10.5 g, 37.9 mmol) and benzoic acid (4.41 g, 36.1 mmol) were dissolved in THF (150 mL) and cooled in an ice bath for 15 min. Diisopropyl azodicarboxylate (DIAD) (7.8 mL, 39.7 mmol) was added slowly via syringe allowing the yellow color to disappear between additions. The mixture was stirred for 2.5 h. All volatiles were evaporated and the residue was mixed with methanol and evaporated again. Methanol (100 mL) was added and the mixture stirred for 30 min. A white solid precipitated - this was filtered off and washed with methanol affording the 3 α -benzoate intermediate as a white solid (12.8 g, 81%); 1 H NMR (CDCl₃): δ 0.87 (s, 3H), 0.88 (s, 3H), 3.86-3.97 (m, 4H), 5.31 (m, 1H), 7.46-7.51 (m, 2H), 7.56-7.62 (m, 1H), 8.06-8.09 (m, 2H).

The 3 α -benzoate intermediate (12.8 g, 29.3 mmol) was dissolved in a mixture of DCM (60 mL) and methanol (60 mL). Sodium methoxide in methanol (25 mL, 135 mmol) was added in portions via syringe and the mixture stirred vigorously overnight. All volatiles were evaporated. The white residue was dissolved in DCM and washed with water, then passed through a hydrophobic frit. The DCM solution was concentrated and isohexane added. The mixture was concentrated and a white solid precipitated. This solid was filtered off and washed with isohexane affording the product **4** as a white solid (7.07 g, 72%); 1 H NMR (CDCl₃): δ 0.80 (s, 3H), 0.86 (s, 3H), 1.94-2.04 (m, 1H), 3.84-3.96 (m, 4H), 4.05-4.06 (m, 1H).

(3 β)-3-Hydroxypregn-5-en-20-one (Pregnenolone) 8.⁵

^1H NMR (CDCl₃): δ 0.65 (s, 3H), 1.02 (s, 3H), 2.14 (m, 1H), 2.51-2.59 (m, 1H), 3.48-3.61 (m, 1H), 5.34-5.39 (m, 1H); ^{13}C NMR (CDCl₃): δ 12.1, 18.3, 20.0, 21.7, 23.4, 30.45, 30.47, 30.6, 30.7, 35.4, 36.1, 37.7, 41.1, 42.9, 48.8, 55.8, 62.6, 70.6, 120.2, 139.6, 208.5.

(3 β ,5 α)-3-Hydroxypregn-20-one 9.⁵

Pregnenolone (15 g, 47.4 mmol) was treated with ethanol (200 mL) and 10% Pd/C (0.66 g). The mixture was stirred vigorously under a hydrogen atmosphere for 5 h. The catalyst was removed by filtration through celite and the filter cake washed with methanol and DCM. The combined filtrates were evaporated affording the product **9** as a white solid (14.7 g, 97%); ^1H NMR (CDCl₃): δ 0.62 (s, 3H), 0.82 (s, 3H), 2.12 (s, 3H), 2.49-2.58 (m, 1H), 3.54-3.67 (m, 1H); ^{13}C NMR (CDCl₃): δ 12.3, 13.5, 21.3, 22.8, 24.4, 28.6, 31.49, 31.53, 32.0, 35.50, 35.51, 37.0, 38.2, 39.1, 44.3, 44.8, 54.2, 56.7, 63.9, 71.3, 209.7; LC-MS no peak.

(5 α)-Pregnane-3,20-dione, cyclic 20-(1,2-ethanediyl acetal) 10.³

Trimethyl orthoformate (50.9 g, 480 mmol) was added to a solution of (3 β ,5 α)-3-hydroxypregn-20-one **9** (15.29 g, 48.0 mmol), *p*-toluenesulfonic acid monohydrate (0.827 g, 4.80 mmol) and ethylene glycol (59.6 g, 960 mmol) in DCM (350 mL). The mixture was stirred overnight at ambient temperature. The reaction mixture was washed with saturated NaHCO₃ solution, 1M NaOH solution, brine and passed through a hydrophobic frit. The solvent was evaporated to give crude (3 β ,5 α)-3-hydroxypregn-20-one, cyclic 1,2-ethanediyl acetal as a white solid (17.63 g, 100%),

used in the next step without further purification; ^1H NMR (CDCl_3): δ 0.77 (s, 3H), 0.82 (s, 3H), 1.31 (s, 3H), 3.56-3.65 (m, 1H), 3.86-4.05 (m, 4H).

To a stirred solution of crude $(3\beta,5\alpha)$ -3-hydroxypregn-20-one, cyclic 1,2-ethanediyl acetal (17.63 g, 48.63 mmol) in DCM (600 mL) at 0 °C under nitrogen was added Dess-Martin periodinane, 15 wt % solution in DCM (68.1 g, 161 mmol). The mixture was allowed to warm to ambient temperature then stirred for 20 h under nitrogen. More Dess-Martin periodinane, 15 wt % solution in DCM (50 mL) was added and the mixture stirred overnight at ambient temperature under nitrogen. The reaction mixture was treated with a 1:1 mixture of saturated NaHCO_3 solution and 10% w/v sodium thiosulfate solution (250 mL). The mixture was stirred vigorously for 1 h and the layers separated. The aqueous phase was extracted twice with DCM. The combined organic liquors were washed with brine then filtered through a hydrophobic frit. Evaporation of the solvent gave a white solid (18.13 g) that was recrystallized from ethanol/pyridine and chromatographed on silica (3 × 100 g SNAP cartridge, isohexane/ethyl acetate/triethylamine gradient elution). Evaporation of the solvent afforded the product **10** as a white solid (7.92 g, 45%); ^1H NMR (CDCl_3): δ 0.80 (s, 3H), 1.03 (s, 3H), 1.31 (s, 3H), 3.85-4.03 (m, 4H).

$(3\alpha,5\alpha)$ -3-Hydroxypregn-20-one, cyclic 1,2-ethanediyl acetal **11.**³

To a stirred solution of (5α) -pregnane-3,20-dione, cyclic 20-(1,2-ethanediyl acetal) **10** (6.47 g, 17.95 mmol) in THF (160 mL) at -78 °C under nitrogen was slowly added K-Selectride® (1.0 M sol. in THF) (18.2 mL, 18.13 mmol) over 15 min. The mixture was stirred at -78 °C for 4 h. Careful addition of a solution of 3N NaOH and 30% hydrogen peroxide solution (29 mL) was exothermic with the temperature rising to -

50 °C. The mixture was allowed to warm to ambient temperature and then stirred for 1 h. The solvent was evaporated to give a solid which was dissolved in DCM and washed with water. The aqueous phase was further extracted with DCM. The combined organic liquors were washed with water, brine and passed through a hydrophobic frit. Evaporation of the solvent gave the product **11** as a white solid (5.92 g, 91%); ¹H NMR (CDCl₃): δ (ppm) 0.68 (s, 3H), 0.71 (s, 3H), 1.22 (s, 3H), 1.93-1.97 (s, 1H), 3.77-3.97 (m, 5H).

(3 β ,5 α)-3-Aminopregnan-20-one **14a.³**

To (3 β ,5 α)-3-aminopregnan-20-one, 20-cyclic 1,2-ethanediyl acetal **13** (100 mg, 0.28 mmol) in DCM (5 mL) was added water (2 mL), MeOH (3 mL) and MeSO₃H (0.4 mL) and the mixture stirred vigorously for 20 min. The reaction mixture was basified with saturated aqueous NaHCO₃ (~10 mL) then 1N NaOH (0.5 mL) and passed through a hydrophobic frit. The aqueous phase was washed with DCM. The combined organic liquors were evaporated and the residue crystallized from diethyl ether to give the product **14a** as a white solid (20 mg, 22%); ¹H NMR (CDCl₃): δ 0.61 (s, 3H), 0.80 (s, 3H), 2.12 (s, 3H), 2.50-2.56 (t, *J* = 9.0 Hz, 1H), 2.68 (m, 1H, w/2 = 23 Hz); ¹³C NMR (DMSO-*d*₆): δ 12.1, 13.1, 20.7, 22.2, 23.9, 28.3, 31.2, 31.6, 32.2, 35.0, 35.2, 37.3, 38.1, 43.5, 45.0, 50.7, 53.7, 55.9, 62.7, 208.5. HRMS (ESI) *m/z* [M+H]⁺ Calcd for C₂₁H₃₆NO: 318.2792; found: 318.2794.

***N*-[(3 β ,5 α)-20-Oxopregnan-3-yl]acetamide **14b**.**

To a stirred solution of (3 β ,5 α)-3-aminopregnan-20-one, 20-cyclic 1,2-ethanediyl acetal **13** (100 mg, 0.28 mmol) and triethylamine (0.08 mL, 0.55 mmol) in DCM (5 mL) at 20 °C under nitrogen was added acetyl chloride (0.02 mL, 0.33 mmol). The

resulting mixture was stirred at ambient temperature for 48 h. The reaction mixture was treated with water (2 mL), MeOH (3 mL) and MeSO₃H (0.4 mL) and stirred vigorously for 15 min. The reaction mixture was basified with saturated NaHCO₃ solution (10 mL) and passed through a hydrophobic frit. The aqueous phase was washed with DCM. The combined organic liquors were evaporated and the residue crystallized from diethyl ether to give product **14b** as a white solid (88 mg, 89%); ¹H NMR (CDCl₃): δ 0.61 (s, 3H), 0.80 (s, 3H), 1.98 (s, 3H), 2.12 (s, 3H), 2.50-2.58 (m, 1H), 3.69-3.84 (m, 1H), 5.50 (br d, *J* = 6.9 Hz, 1H); ¹³C NMR (CDCl₃): δ 11.1, 12.3, 20.0, 21.7, 22.4, 23.3, 27.3, 27.7, 30.4, 30.7, 34.2, 34.33, 34.35, 36.2, 37.9, 43.1, 44.2, 47.9, 53.0, 55.5, 62.7, 168.2, 208.6.

(3 α ,5 α)-3-Aminoandrostan-17-one, cyclic 1,2-ethanediyl acetal 16.³

2-[(3 α ,5 α)-17-Oxoandrostan-3-yl, 17-cyclic 1,2-ethanediyl acetal]-1*H*-isoindole-1,3(2*H*)-dione **15** (5.93 g, 12.8 mmol) was treated with ethanol (180 mL) and hydrazine hydrate (8.0 mL, 164 mmol) and the mixture heated at reflux overnight under a nitrogen atmosphere. The reaction mixture was cooled and the solid precipitate was filtered off. The filtrate was evaporated and the residue partitioned between DCM and water, and then passed through a hydrophobic frit. The DCM phase was evaporated to give the product **16** as a white solid (4.06 g, 95%); ¹H NMR (CDCl₃): δ 0.71 (s, 3H), 0.76 (s, 3H), 1.85-1.94 (m, 1H), 3.01-3.11 (br s, 1H), 3.75-3.87 (m, 4H).

(3 α ,5 α)-3-Aminoandrostan-17-one, hydrochloride (1:1) 17a.³

(3 α ,5 α)-3-Aminoandrostan-17-one, cyclic 1,2-ethanediyl acetal **16** (241 mg, 0.72 mmol) was treated with THF (5 mL), acetone (2 mL) and 2M HCl (5 mL, 10 mmol)

for 48 h. The solution was filtered through a Whatman 0.2 μ M PTFE disc filter. The solvents were evaporated and the residue treated with diethyl ether. The precipitated solid was filtered off, affording the product **17a** as a white hydrochloride salt (203 mg, 87%); 1 H NMR (DMSO- d_6): δ 0.78 (s, 3H), 0.79 (s, 3H), 2.32–2.45 (dd, J = 19.0 and 8.5 Hz, 1H), 3.38 (br s, w/2 = 9 Hz, 1H), 7.92 (br s, 1H); 13 C NMR (DMSO- d_6): δ 11.5, 13.9, 20.1, 21.9, 24.8, 28.1, 30.7, 31.4, 34.4, 31.5, 35.1, 35.9, 36.2, 38.7, 47.8, 51.1, 53.2, 221.1. HRMS (ESI) m/z [M+H] $^+$ Calcd for C₁₉H₃₂NO: 290.2479. Found: 290.2480.

(3 β ,5 α ,17E)-3-[(1,1-Dimethylethyl)dimethylsilyl]oxy]pregn-17(20)-en-21-oic acid, ethyl ester **19⁶**

To a stirred solution of epiandrosterone **2** (1.0 g, 3.44 mmol) in DCM (10 mL) was added pyridine (1 mL) and the solution cooled in an ice bath. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.87 mL, 3.79 mmol) was added in 4 aliquots over 10 min and the ice bath then removed. The mixture was stirred for 3 h, and then saturated ammonium chloride solution was added. After stirring for 10 min, the layers were separated and the aqueous liquors extracted with DCM (20 mL). Evaporation of the solvent gave a white solid that was purified by flash chromatography (isohexane/ethyl acetate gradient elution) to give (3 β ,5 α)-3-[(1,1-dimethylethyl)dimethylsilyl]oxy]androstan-17-one⁷ as a white solid (1.26 g, 3.10 mmol, 90%); 1 H NMR (CDCl₃): δ 0.00 (s, 6H), 0.77 (s, 3H), 0.80 (s, 3H), 0.83 (s, 9H), 2.32–2.44 (m, 1H), 3.44–3.56 (m, 1H).

To a stirred solution of (3 β ,5 α)-3-[(1,1-dimethylethyl)dimethylsilyl]oxy]androstan-17-one (850 mg, 2.1 mmol) in THF (6.5 mL) and ethanol (6.5 mL) was added

triethylphosphonoacetate (4.17 mL, 21 mmol) and then a solution of sodium ethoxide (1429 mg, 21 mmol) in ethanol (14 mL). The mixture was heated at 85 °C for 15 h, then cooled and the solvent evaporated. The residue was partitioned between ethyl acetate and water and the organic layer washed with 2N HCl, saturated sodium bicarbonate and then brine. The solution was dried and evaporated, and the residue was purified by flash chromatography eluting with DCM to give (3 β ,5 α ,17E)-3-[(1,1-dimethylethyl)dimethylsilyl]oxy]pregn-17(20)-en-21-oic acid, ethyl ester **19** (1.06 g, 2.22 mmol, 100%); 1 H NMR (CDCl₃): δ 0.00 (s, 6H), 0.76 (s, 3H), 0.77 (s, 3H), 0.83 (s, 9H), 1.21 and 1.23 (t, J = 7.1 Hz, 3H), 2.73-2.81 (m, 2H), 3.40-3.57 (m, 1H), 4.01 and 4.10 (q, J = 6.9 Hz, 2H), 5.47 (br t, J = 2.4 Hz, 1H).

(3 β ,5 α ,17 β)-Spiro[androstane-17,2'-oxiran]-3-ol 24.

To a stirred solution of epiandrosterone **2** (2.0 g, 6.89 mmol) in THF (10 mL) and DMF (10 mL) were added trimethylsulfonium iodide (5.62 g, 27.5 mmol) and potassium *tert*-butoxide (3.09 g, 27.5 mmol). The reaction mixture was stirred at ambient temperature for 24 h under nitrogen, then poured into ice/water and the precipitated pale yellow solid was filtered off and washed with water. The solid was flash chromatographed on silica (isohexane/ethyl acetate gradient elution) to give the product **24** as a white crystalline solid (1010 mg, 48%); 1 H NMR (CDCl₃): δ 0.83 (s, 3H), 0.89 (s, 3H), 2.61 (d, J = 5.2 Hz, 1H), 2.91 (d, J = 5.2 Hz, 1H), 3.54-3.66 (m, 1H); 13 C NMR (CDCl₃): δ 11.2, 13.3, 19.5, 22.4, 27.4, 27.9, 30.37, 30.39, 32.9, 34.46, 34.51, 35.9, 37.0, 39.0, 43.8, 51.7, 52.5, 53.3, 69.4, 70.1. (3 β ,5 α ,17 β)-3-Methoxyspiro[androstane-17,2'-oxirane] (762 mg, 35%) was isolated as a by-product.

(3 β ,16 α)-16-Bromo-3-hydroxyandrost-5-en-17-one 27.⁸

To copper (II) bromide (8.04 g, 36 mmol) in methanol (175 mL) was added dehydroepiandrosterone **1** (3.46 g, 12 mmol). The reaction mixture was heated at reflux overnight. After cooling the copper salts were removed by filtration and the filtrate was concentrated under reduced pressure. The solution was diluted with diethyl ether and the precipitated solid removed by filtration. Recrystallization from DCM/diethyl ether afforded the product **27** as a white solid (1.24 g, 28%); ¹H NMR (CDCl₃): δ 0.94 (s, 3H), 1.05 (s, 3H), 3.50-3.61 (m, 1H), 4.54-4.58 (m, 1H), 5.37-5.41 (m, 1H); ¹³C NMR (CDCl₃): δ 13.9, 19.4, 20.3, 30.6, 30.8, 31.5, 32.3, 34.2, 36.6, 37.1, 42.2, 46.3, 47.6, 48.3, 50.0, 71.6, 120.6, 141.0, 213.4.

(3 β ,16 α)-3,16-Dihydroxyandrost-5-en-17-one **28⁹**

To (3 β ,16 α)-16-bromo-3-hydroxyandrost-5-en-17-one **27** (184 mg, 0.50 mmol) in 75% aqueous pyridine (7.5 mL) was added sodium hydroxide (24 mg, 0.60 mmol) and the mixture stirred for 1.5 h, then poured into dilute aqueous HCl and extracted with ethyl acetate. The combined extracts were washed with 5% NaHCO₃ solution and water. After evaporation of the solvent the residue was flash chromatographed on silica (isohexane/ethyl acetate gradient elution) and triturated with diethyl ether to give the product **28** as a white solid (56 mg, 37%); ¹H NMR (CDCl₃): δ 1.00 (s, 3H), 1.05 (s, 3H), 3.45-3.62 (m, 1H), 4.37-4.43 (m, 1H), 5.36-5.41 (m, 1H); ¹³C NMR (CDCl₃): δ 13.9, 19.4, 20.0, 30.4, 30.6, 31.2, 31.4, 31.5, 36.6, 37.1, 42.2, 47.5, 48.6, 50.1, 71.3, 71.5, 120.9, 140.9, 219.5.

(3 β ,5 α ,16 α)-16-Bromo-3-hydroxyandrostan-17-one **29¹⁰**

To epiandrosterone **2** (1.74 g, 6.0 mmol) in methanol (125 mL) was added copper (II) bromide (4.02 g, 18 mmol). The reaction mixture was heated at reflux overnight.

After cooling the copper salts were removed by filtration and the filtrate was concentrated under reduced pressure. The solution was diluted with diethyl ether and the precipitated solid removed by filtration. Recrystallization from DCM/diethyl ether afforded the product **29** as a white solid (900 mg, 41%); ¹H NMR (CDCl₃): δ 0.85 (s, 3H), 0.91 (s, 3H), 2.10-2.29 (m, 2H), 3.57-3.69 (m, 1H), 4.52-4.57 (m, 1H); ¹³C NMR (CDCl₃): δ 12.3, 14.2, 20.4, 28.3, 30.7, 31.4, 32.4, 34.1, 34.3, 35.7, 36.9, 38.0, 44.8, 46.4, 47.8, 47.9, 54.2, 71.1, 213.6.

(3 β ,5 α)-3-Hydroxyandrostan-17-one, oxime **30.**

Epiandrosterone **2** (3.0 g, 10 mmol) was treated with ethanol (20 mL), hydroxylamine hydrochloride (754 mg, 10.8 mmol) and triethylamine (1.65 mL, 1.1 m.e.) and heated at reflux for 2 h. The reaction mixture was cooled, diluted with DCM and the volatiles evaporated. The residue was partitioned between water and DCM, passed through a hydrophobic frit and the solvent evaporated to give a white crystalline solid. This solid was partitioned between water and ethyl acetate, and separated. The organic phase was evaporated to give the product **30** as a white crystalline solid (0.99 g, 32%); ¹H NMR (DMSO-*d*₆): δ 0.77 (s, 3H), 0.81 (s, 3H), 2.18-2.40 (m, 2H); 3.27-3.41 (m, 1H), 4.44 (d, *J* = 4.7 Hz, 1H), 10.04 (s, 1H); ¹³C NMR (DMSO-*d*₆): δ 11.2, 16.4, 19.5, 21.9, 23.9, 27.4, 30.3, 30.5, 33.4, 33.6, 34.4, 35.7, 37.3, 42.2, 43.5, 52.6, 53.2, 68.4, 167.0.

(3 β ,17 β)-Spiro[androst-5-ene-17,2'-oxiran]-3-ol **31.¹¹**

To a stirred solution of potassium *tert*-butoxide (3.11 g, 27.7 mmol) in THF (10 mL) and DMF (10 mL) were added dehydroepiandrosterone **1** (2.0 mg, 6.93 mmol) and trimethylsulfonium iodide (5.66 g, 27.7 mmol). The reaction mixture was stirred at

ambient temperature for 5 h under nitrogen. The reaction mixture was poured into ice/water and the precipitated pale yellow solid was filtered off and washed with water. The solid was flash chromatographed on silica (isohexane/ethyl acetate gradient elution) to give the product **31** as a white crystalline solid (1.11 g, 53%); ¹H NMR (CDCl₃): δ 0.92 (s, 3H), 1.04 (s, 3H), 2.63 (d, *J* = 5.1 Hz, 1H), 2.92 (d, *J* = 5.1 Hz, 1H), 3.48-3.61 (m, 1H), 5.36-5.41 (m, 1H); ¹³C NMR (CDCl₃): δ 13.0, 18.3, 19.3, 22.5, 27.9, 30.3, 30.4, 30.9, 32.8, 35.5, 36.1, 38.8, 41.1, 49.1, 52.0, 52.5, 69.4, 70.6, 120.2, 139.8. (3 β ,17 β)-3-Methoxyspiro[androst-5-ene-17,2'-oxirane] (433 mg, 20%) was isolated as a by-product.

(3 β ,17 α)-17,21-Epoxy pregn-5-en-3-ol 32.

To a stirred suspension of trimethylsulfoxonium iodide (439 mg, 2.0 mmol) in *tert*-butanol (5 mL) at 50 °C was added a solution of potassium *tert*-butoxide (224 mg, 2.0 mmol) in *tert*-butanol (5 mL). After 30 min a solution of (3 β ,17 β)-spiro[androst-5-ene-17,2'-oxiran]-3-ol **31** (302 mg, 0.9985 mmol) in *tert*-butanol (5 mL) was added and the mixture heated at reflux for 72 h. The mixture was concentrated to low volume under reduced pressure and diluted with DCM. This solution was washed with water, dried and the solvent evaporated. The solid was flash chromatographed on silica (isohexane/ethyl acetate gradient elution) to give the product **32** as a white crystalline solid (105 mg, 33%); ¹H NMR (CDCl₃): δ 0.80 (s, 3H), 1.04 (s, 3H), 2.75-2.86 (m 1H), 3.45-3.60 (m 1H), 4.28-4.38 (m 1H), 4.41-4.50 (m 1H), 5.33-5.41 (m 1H); ¹³C NMR (CDCl₃): δ 11.8, 19.5, 20.7, 23.3, 30.9, 31.5, 31.6, 32.2, 32.5, 36.6, 37.3, 37.8, 42.3, 44.4, 48.8, 50.0, 64.9, 71.7, 96.7, 121.3, 140.8.

(3 β)-3,21-Dihydroxypregn-5-en-20-one 33.

To a solution of (3 β)-21-(acetyloxy)-3-hydroxypregn-5-en-20-one (500 mg, 1.34 mmol) in methanol (10 mL) and water (1 mL) was added potassium carbonate (185 mg, 1.34 mmol) and the mixture stirred at reflux for 30 min. The reaction mixture was concentrated, diluted with water and extracted with ethyl acetate. The combined extracts were washed with water, dried and the solvent evaporated. The solid was recrystallized from ethyl acetate affording the product **33** as a white solid (164 mg, 37%); ^1H NMR (CDCl_3): δ 0.67 (s, 3H), 1.02 (s, 3H), 2.43-2.52 (m, 1H), 3.48-3.60 (m, 1H), 4.17, 4.25 (ABq, $J_{AB} = 19.0$ Hz, 2H), 5.34-3.39 (m, 1H); ^{13}C NMR (CDCl_3): δ 13.3, 19.4, 21.0, 22.9, 24.6, 31.6, 31.8, 31.9, 36.5, 37.2, 38.6, 42.2, 44.8, 49.9, 57.0, 59.2, 69.4, 71.7, 121.3, 140.8, 210.3.

(3 β ,5 α)-3,21-Dihydroxypregnan-20-one 34.

To a stirred solution of (3 β ,5 α)-21-bromo-3-hydroxypregnan-20-one **37** (1192 mg, 3 mmol) in DMF (100 mL) and water (50 mL) was added sodium hydroxide (144 mg, 3.6 mmol) and the mixture stirred for 30 min. The mixture was then diluted with water and extracted with ethyl acetate. The combined extracts were washed with water, dried, and the solvent evaporated. The residue was chromatographed on silica (isohexane/ethyl acetate gradient elution) and recrystallized from diethyl ether affording the product **34** as a white solid (761 mg, 76%); ^1H NMR (CDCl_3): δ 0.65 (s, 3H), 0.83 (s, 3H), 2.15-2.30 (m, 1H), 2.42-2.50 (m, 1H), 3.27 (br s, 1H) 3.53-3.67 (m, 1H), 4.15, 4.23 (ABq, $J_{AB} = 18.9$ Hz, 2H); ^1H NMR ($\text{DMSO}-d_6$): δ 0.52 (s, 3H), 0.74 (s, 3H), 1.95-2.07 (m, 1H), 2.55 (m, 1H), 4.02 (d, $J = 5.8$ Hz, 2H), 4.42 (d, $J = 4.8$ Hz, 1H), 4.89 (t, $J = 5.8$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 12.3, 13.5, 21.2, 22.9, 24.5, 28.6, 31.5, 32.0, 35.5, 37.0, 38.1, 38.8, 44.8, 45.0, 54.2, 56.8, 59.4, 69.4, 71.2, 77.2, 210.4; HRMS (ESI) m/z [M+Cl] $^-$ Calcd for $\text{C}_{21}\text{H}_{34}\text{ClO}_3$: 369.2201. Found: 369.2211.

(3 β ,5 α)-21-(Acetoxy)-3-hydroxypregnan-20-one 35.

(3 β)-21-(Acetoxy)-3-hydroxypregn-5-en-20-one (0.40 g, 1.07 mmol) was dissolved in ethanol (40 mL) and treated with hydrogen and 10% Pd/C under a nitrogen atmosphere. After stirring overnight the catalyst was removed by filtration through celite and the solvent evaporated. The residue was triturated with diethyl ether and the solid chromatographed on silica (isohexane/ethyl acetate gradient elution) to give the product **35** as a white solid (55 mg, 14%); ^1H NMR (CDCl_3): δ 0.66 (s, 3H), 0.82 (s, 3H), 2.18 (s, 3H), 2.47-2.55 (m, 1H), 3.55-3.68 (m, 1H), 4.54, 4.72 (ABq, $J_{AB} = 16.9$ Hz, 2H); ^{13}C NMR (CDCl_3): δ 11.8, 12.8, 20.0, 20.7, 22.3, 24.0, 28.0, 31.0, 31.5, 35.0, 36.5, 37.6, 38.3, 44.3, 44.4, 53.6, 56.3, 58.9, 60.1, 68.7, 70.7, 169.8, 203.3.

(3 β ,5 α)-21-Chloro-3-hydroxypregnan-20-one 36.

To a stirred solution of (3 β ,5 α)-21-bromo-3-hydroxypregnan-20-one **37** (398 mg, 1.0 mmol) in acetonitrile (15 mL) was added potassium chloride (747 mg, 10.0 mmol) and 18-crown-6 (529 mg, 2 mmol). The mixture was stirred at reflux for 1 h. The reaction mixture was then diluted with water and extracted with DCM. The combined extracts were washed with water, and the solvent evaporated. The residue was chromatographed on silica (isohexane/ethyl acetate gradient elution) and recrystallized from diethyl ether affording the product **36** as a white solid (82 mg, 23%); ^1H NMR (CDCl_3): δ 0.65 (s, 3H), 0.82 (s, 3H), 2.67-2.75 (m, 1H), 3.54-3.67 (m, 1H), 4.07, 4.13 (ABq, $J_{AB} = 15.6$ Hz, 2H); ^{13}C NMR (CDCl_3): δ 11.2, 12.6, 20.1, 22.3, 23.4, 27.4, 30.3, 30.9, 34.4 ($\times 2$), 35.9, 37.0, 37.8, 43.7, 43.9, 48.4, 53.0, 55.6, 59.2, 70.1, 201.2.

(3 β ,5 α)-21-Bromo-3-hydroxypregnan-20-one 37.

To a stirred solution of (3 β ,5 α)-3-hydroxypregnan-20-one **9** (5 g, 15.7 mmol) in methanol (100 mL) at 25 °C was added aqueous HBr (5 drops) and then a solution of bromine (0.89 mL, 17.3 mmol) in methanol (35 mL) was added slowly over 30 min. The mixture was stirred for 1 h then concentrated under reduced pressure, and quenched and precipitated with water. The solid was filtered off, dried and recrystallized from diethyl ether affording the product **37** as a white solid (2.52 g, 40%); 1 H NMR (CDCl₃): δ 0.64 (s, 3H), 0.82 (s, 3H), 2.78-2.87 (m, 1H), 3.54-3.68 (m, 1H), 3.89, 3.94 (ABq, J_{AB} = 13.0 Hz, 2H); 13 C NMR (CDCl₃): δ 12.3, 13.7, 21.2, 23.7, 24.5, 28.5, 31.5, 32.0, 35.51, 35.52, 36.0, 37.0, 38.1, 38.9, 44.8, 45.1, 54.1, 56.6, 60.5, 71.2, 202.1.

(3 β ,5 α)-3-Hydroxypregnan-20-one, oxime 38.

To a stirred suspension of (3 β ,5 α)-3-hydroxypregnan-20-one (300 mg, 0.94 mmol) and hydroxylamine hydrochloride (105 mg, 1.51 mmol) in ethanol (5 mL) under nitrogen was added pyridine (0.15 mL) and the mixture heated at reflux for 2 h. The mixture was diluted with DCM (100 mL), washed with water (25 mL) and the solvent evaporated to give a white solid that was triturated with DCM (20 mL) to give the product **38** as a white solid (105 mg, 33%); 1 H NMR (CDCl₃): δ 0.64 (s, 3H), 0.83 (s, 3H), 1.89 (s, 3H), 2.19-2.27 (m, 1H), 3.55-3.68 (m, 1H), 7.45 (br s, 1H).

(3 α ,5 α)-3-Hydroxyandrostan-17-one 39.¹²

(3 α ,5 α)-3-Hydroxyandrostan-17-one, cyclic 1,2-ethanediyl acetal **4** (335 mg, 1.00 mmol) was treated with water (2 mL), MeOH (3 mL) and MeSO₃H (0.4 mL) and stirred vigorously for 15 min. The reaction mixture was basified with saturated

NaHCO₃ (~10 mL) and passed through a hydrophobic filter. The aqueous phase was washed with DCM. The organic liquors were evaporated affording a residue that was triturated from diethyl ether to give the product **39** as a white solid (165 mg, 57%); ¹H NMR (CDCl₃): δ 0.82 (s, 3H), 0.88 (s, 3H), 2.39-2.50 (m, 1H), 4.04-4.09 (m, 1H); ¹H NMR (DMSO-*d*₆): δ 0.76 (s, 3H), 0.78 (s, 3H), 2.32-2.43 (m, 1H), 3.78-3.84 (m, 1H), 4.18 (d, *J* = 3.1 Hz, 1H); ¹³C NMR (CDCl₃): δ 11.2, 13.8, 20.1, 21.8, 28.3, 29.0, 30.9, 31.6, 32.1, 35.0, 35.8, 35.9, 36.3, 39.1, 47.8, 51.5, 54.4, 66.4, 221.5.

(5α)-Androstan-17-one 40.¹³

Purchased from Interbioscreen; ¹H NMR (DMSO-*d*₆): δ 0.78 (s, 3H), 0.79 (s, 3H), 2.32-2.43 (m, 1H).

(3α,5α)- 3-Hydroxypregn-20-one 41.¹⁴

Purchased from Sigma-Aldrich Chemical Company Ltd; ¹H NMR (CDCl₃): δ 0.62 (s, 3H), 0.80 (s, 3H), 2.13 (s, 1H), 2.50-2.59 (m, 1H), 4.02-4.10 (m, 1H); ¹³C NMR (CDCl₃): δ 11.2, 13.5, 20.8, 22.8, 24.4, 28.5, 29.0, 31.6, 32.0, 32.2, 35.5, 35.9, 36.1, 39.1 (×2), 44.3, 54.2, 56.8, 63.9, 66.5, 209.8.

(3α,5α)-3,21-Dihydroxypregn-20-one 42.

Purchased from Sigma-Aldrich Chemical Company Ltd; ¹H NMR (DMSO-*d*₆): δ 0.52 (s, 3H), 0.73 (s, 3H), 1.95-2.08 (m, 1H), 2.53-2.61 (m, 1H), 3.77-3.84 (m, 1H), 4.03 (d, *J* = 5.9 Hz, 2H), 4.17 (d, *J* = 3.0 Hz, 1H), 4.89 (t, *J* = 5.8 Hz, 1H).

(3β,5α)-3-Hydroxypregnane-11,20-dione 43.

Purchased from Sigma-Aldrich Chemical Company Ltd; ^1H NMR (CDCl_3): δ 0.59 (s, 3H), 0.87 (dt, J = 13.4 and 3.8 Hz, 1H), 1.03 (s, 3H), 2.11 (s, 3H), 2.45-2.62 (m, 3H), 2.69-2.78 (m, 1H), 3.52-3.65 (m, 1H); ^{13}C NMR (CDCl_3): δ 11.0, 13.2, 22.1, 22.8, 26.9, 30.2, 31.5, 34.0, 34.6, 35.5, 36.5, 43.8, 46.1, 54.7, 55.6, 61.1, 63.2, 64.0, 69.8, 207.0, 208.5.

(3 β ,5 α)-3,21-Dihydroxypregnane-11,20-dione 44.

Purchased from Sigma-Aldrich Chemical Company Ltd and tested without NMR spectroscopic analysis.

(3 β ,5 α ,16 α)-16,17-Epoxy-3-hydroxypregn-20-one 45.

(3 β ,16 α)-16,17-Epoxy-3-hydroxypregn-5-en-20-one (500 mg, 1.51 mmol, obtained from Sigma-Aldrich) was dissolved in ethanol (50 mL) and treated with hydrogen and 10% Pd/C under a nitrogen atmosphere. After stirring for 1.5 h the catalyst was removed by filtration through celite and the solvent evaporated. The residue was chromatographed on silica (isohexane/ethyl acetate gradient elution) to give the product **45** as a white crystalline solid (155 mg, 31%); ^1H NMR (CDCl_3): δ 0.83 (s, 3H), 1.03 (s, 3H), 2.04 (s, 3H), 3.54-3.67 (m, 1H), 3.67 (s, 1H); ^1H NMR ($\text{DMSO-}d_6$): δ 0.75 (s, 3H), 0.94 (s, 3H), 1.96 (s, 3H), 3.26-3.41 (m, 1H), 3.91 (s, 1H), 4.43 (d, J = 4.8 Hz, 1H); ^{13}C NMR (CDCl_3): δ 12.3, 15.3, 20.7, 26.0, 27.4, 28.5, 31.46, 31.48, 31.7, 33.2, 35.6, 36.8, 38.1, 41.9, 44.9, 45.2, 54.6, 60.6, 71.0, 71.2, 205.0; ^{13}C NMR ($\text{DMSO-}d_6$): δ 12.8, 15.7, 21.0, 26.5, 27.5, 29.0, 32.0, 32.1, 33.4, 36.0, 37.2, 38.8, 41.9, 45.2, 45.7, 54.9, 60.9, 70.0, 71.0, 205.6.

(3 β ,5 α)-3,17,21-Trihydroxypregn-20-one 46.¹⁵

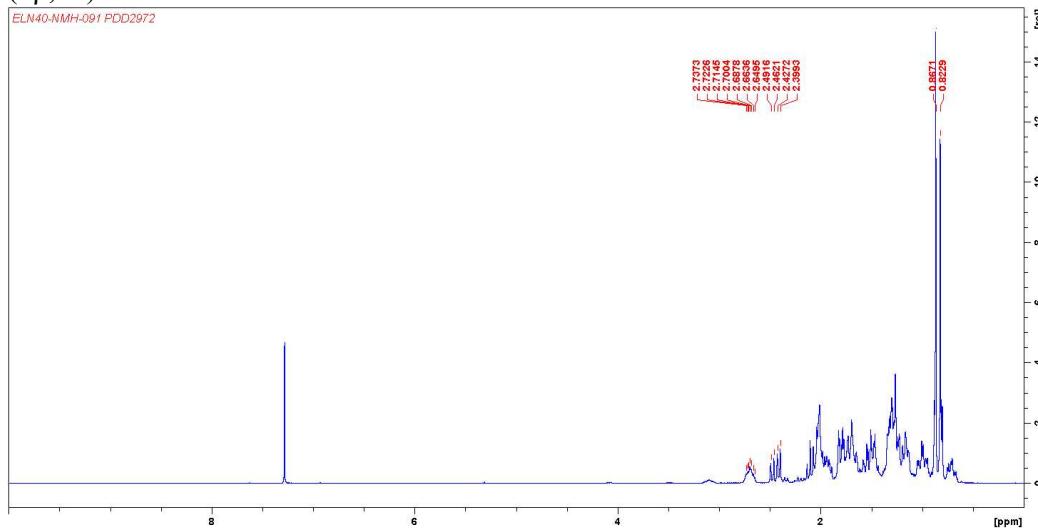
Purchased from Steraloids/Makaira; ^1H NMR (DMSO- d_6): δ 0.48 (s, 3H), 0.74 (s, 3H), 3.35 (m, 1H), 4.05-4.15 (dd, J = 19.0 and 5.5 Hz, 1H), 4.40-4.62 (m, 3H), 5.14 (s, 1H).

(3 β ,5 α)-3,17-Dihydroxypregnane-11,20-dione 47.¹⁶

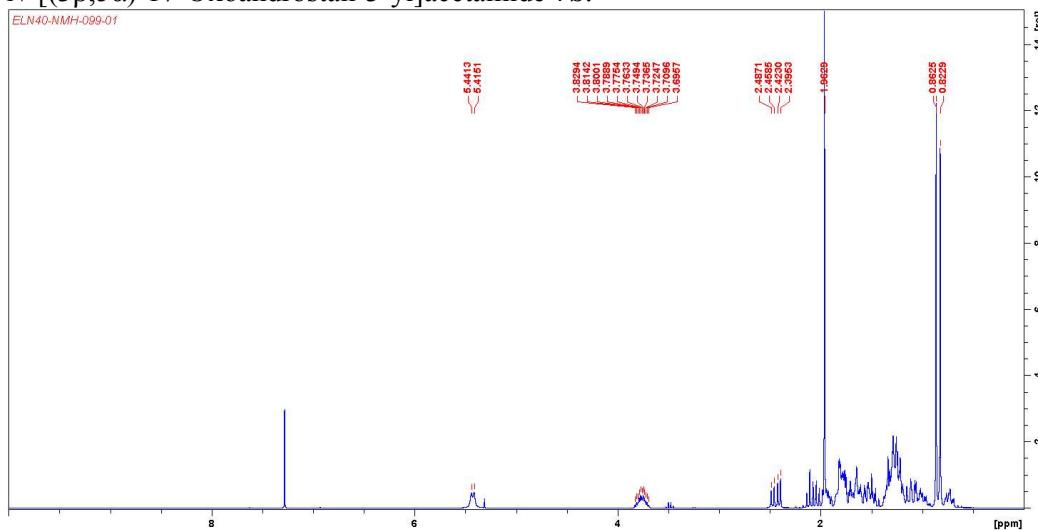
Purchased from Sigma-Aldrich Chemical Company Ltd; ^1H NMR (CDCl₃): δ 0.69 (s, 3H), 1.03 (s, 3H), 1.03 (s, 3H), 2.28 (m, 1H), 2.44-2.54 (m, 1H), 2.68-2.80 (m, 2H), 3.04 (br s, 1H), 3.54-3.66 (m, 1H); ^{13}C NMR (CDCl₃): δ 12.1, 16.4, 23.6, 27.8, 28.0, 31.3, 32.8, 34.0, 35.1, 35.7, 36.2, 37.6, 44.9, 49.8, 50.1, 51.9, 64.1, 71.0, 88.5, 210.83, 210.87.

¹H NMR spectra of target compounds

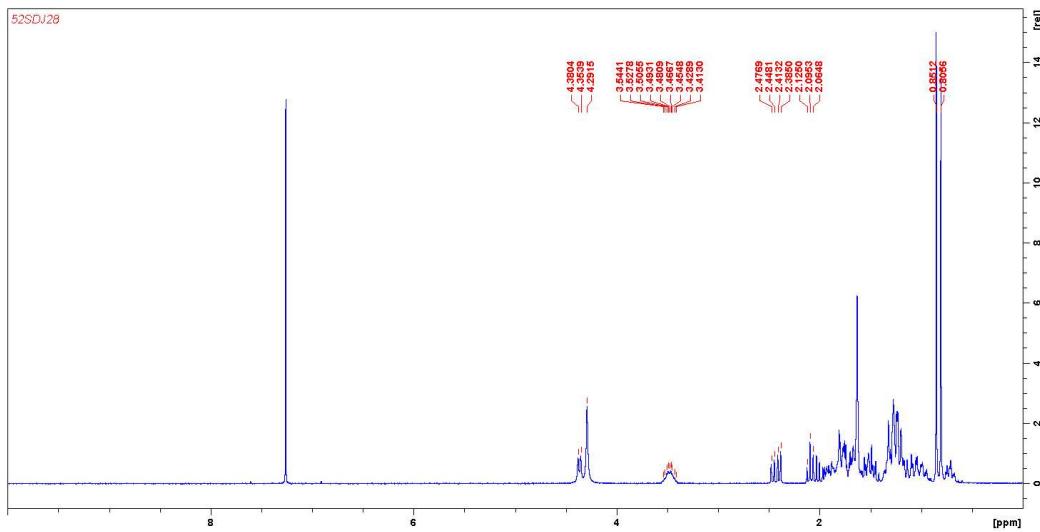
(3 β ,5 α)-3-Aminoandrostan-17-one **7a**.



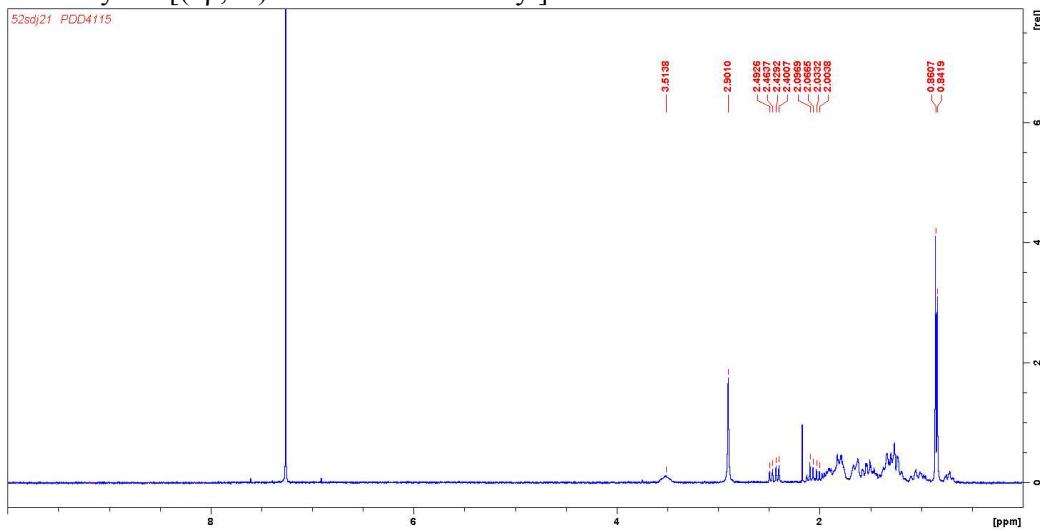
N-[(3 β ,5 α)-17-Oxoandrostan-3-yl]acetamide **7b**.



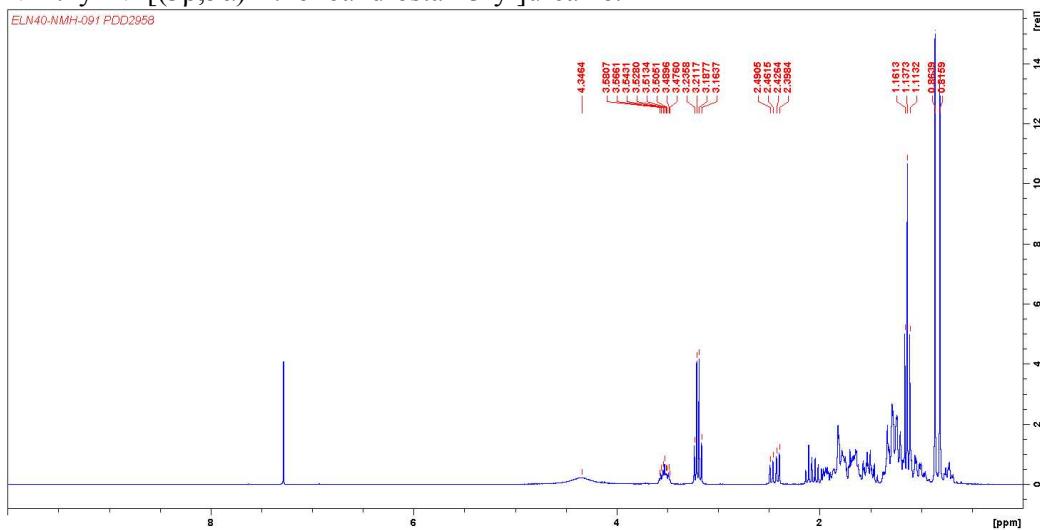
N-[(3 β ,5 α)-17-Oxoandrostan-3-yl]urea **7c**.



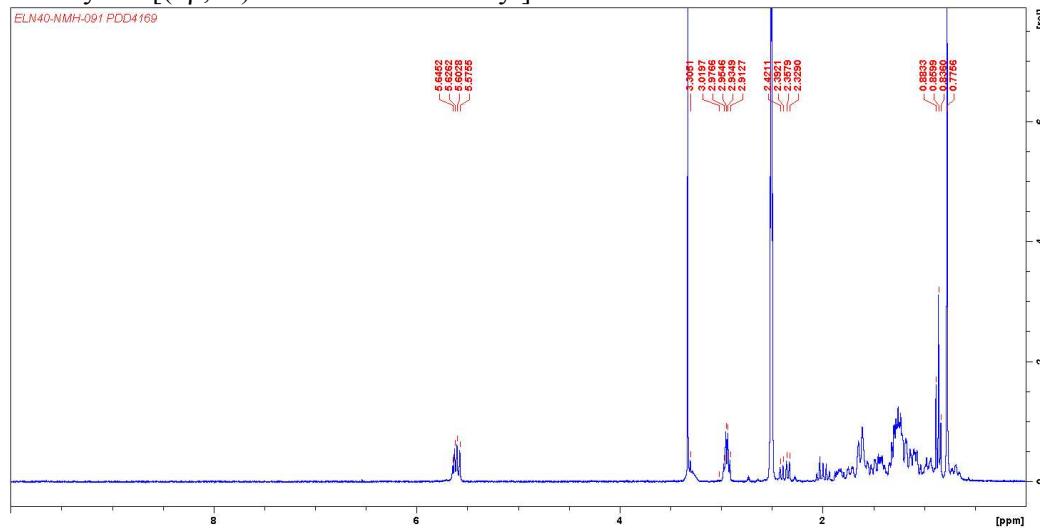
N-Methyl-*N'*-[(3 β ,5 α)-17-oxoandrostan-3-yl]urea **7d**.



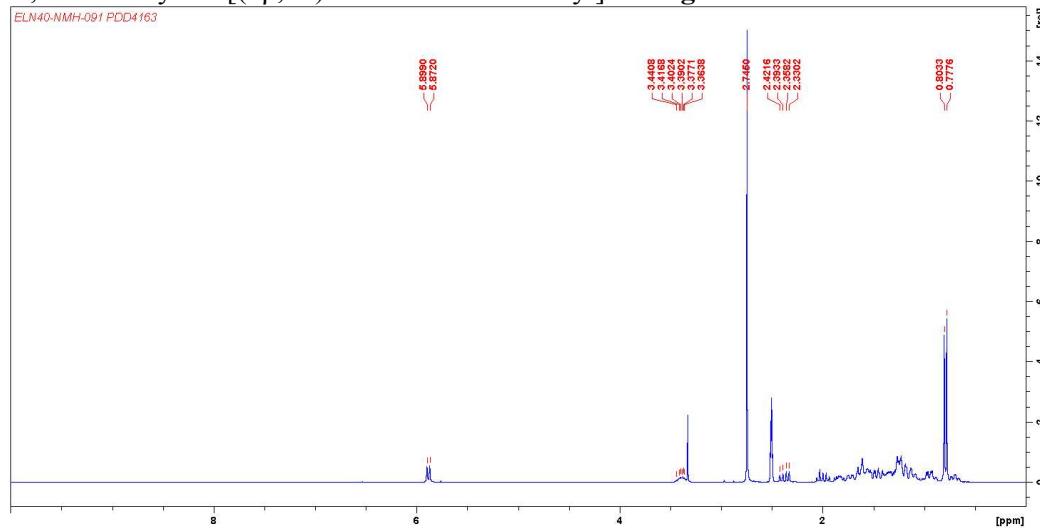
N-Ethyl-*N'*-[(3 β ,5 α)-17-oxoandrostan-3-yl]urea 7e.



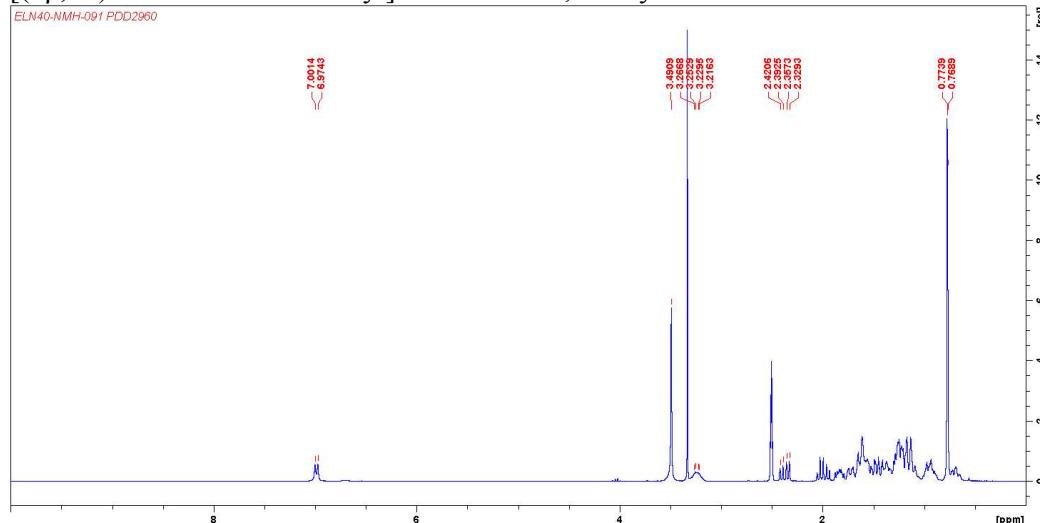
N-Butyl-*N*'-[(3 β ,5 α)-17-oxoandrostan-3-yl]urea **7f**.



N,N-Dimethyl-*N*'-[(3 β ,5 α)-17-oxoandrostan-3-yl]urea **7g**.

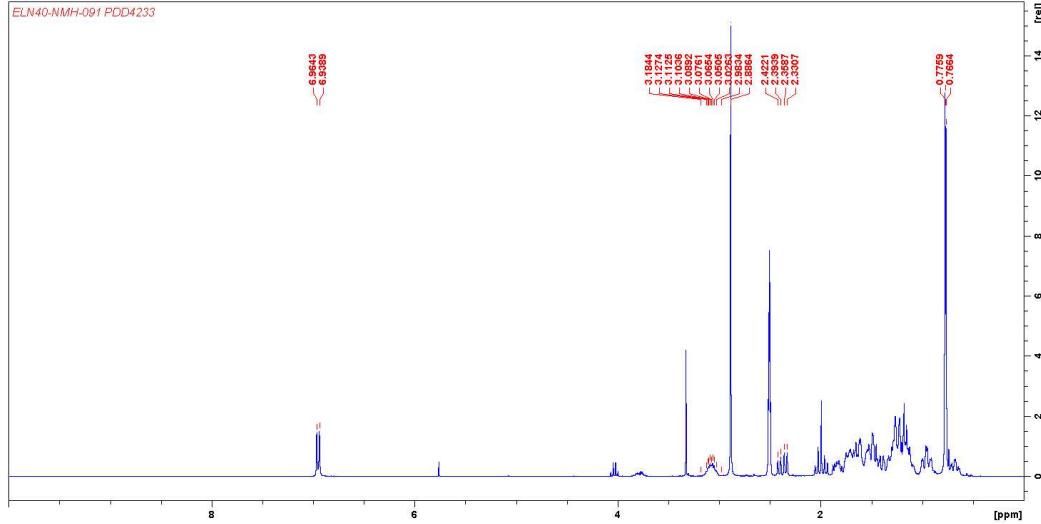


[(3 β ,5 α)-17-Oxoandrostan-3-yl]carbamic acid, methyl ester **7h**.



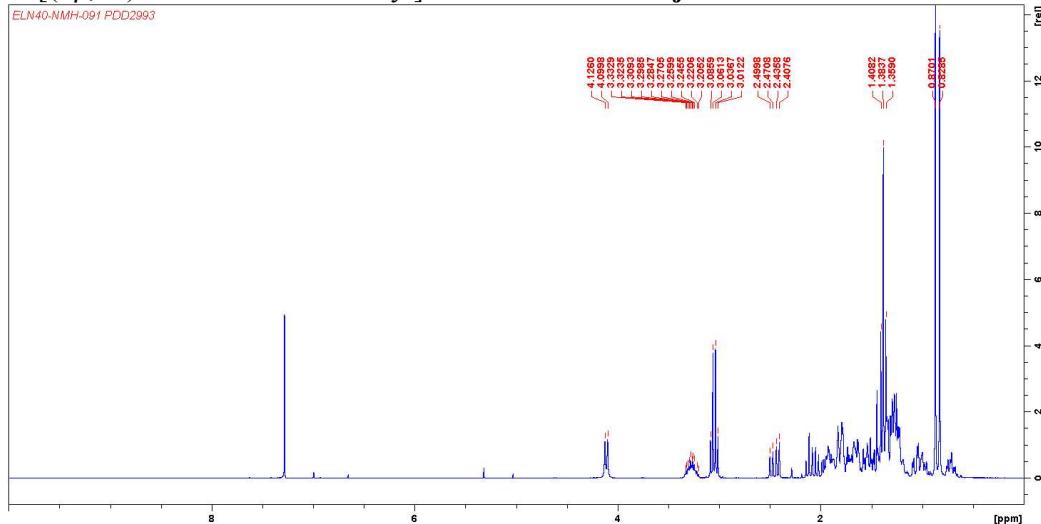
N-[(3 β ,5 α)-17-Oxoandrostan-3-yl]methanesulfonamide **7i**.

EN40-NMH-081 P004233



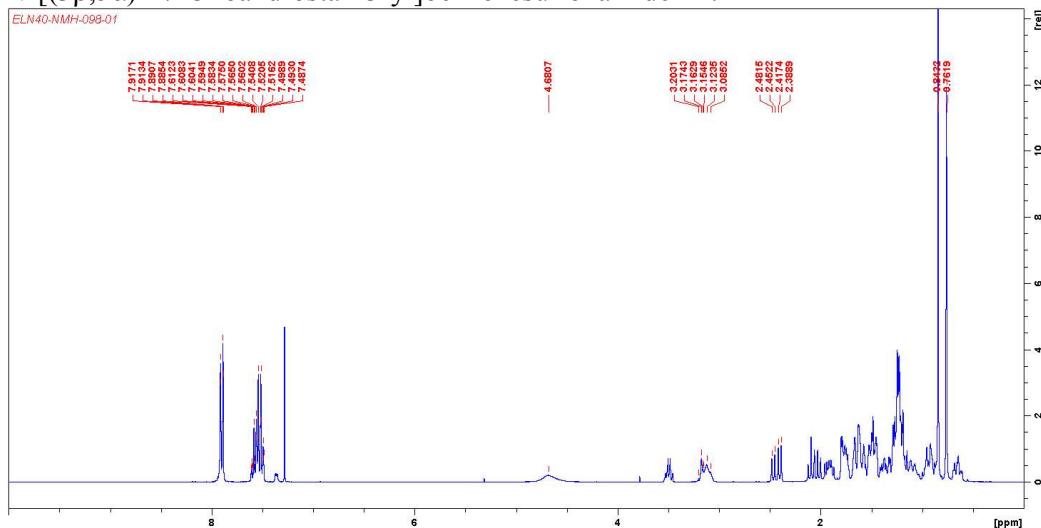
***N*-(3 β ,5 α)-17-Oxoandrostan-3-yl]ethanesulfonamide **7j**.**

ELN40-NMH-091 PDD2993

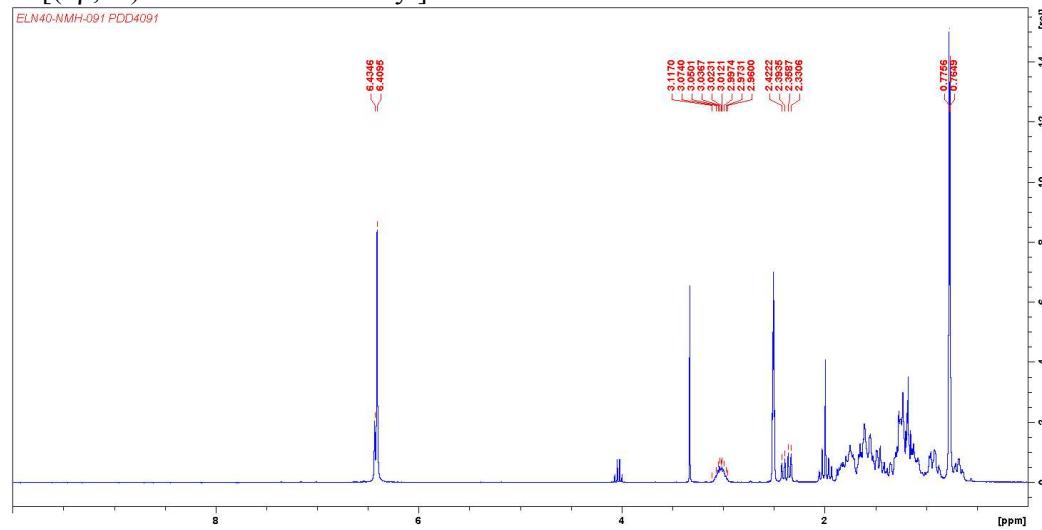


N-[(3 β ,5 α)-17-Oxoandrostan-3-yl]benzenesulfonamide 7k.

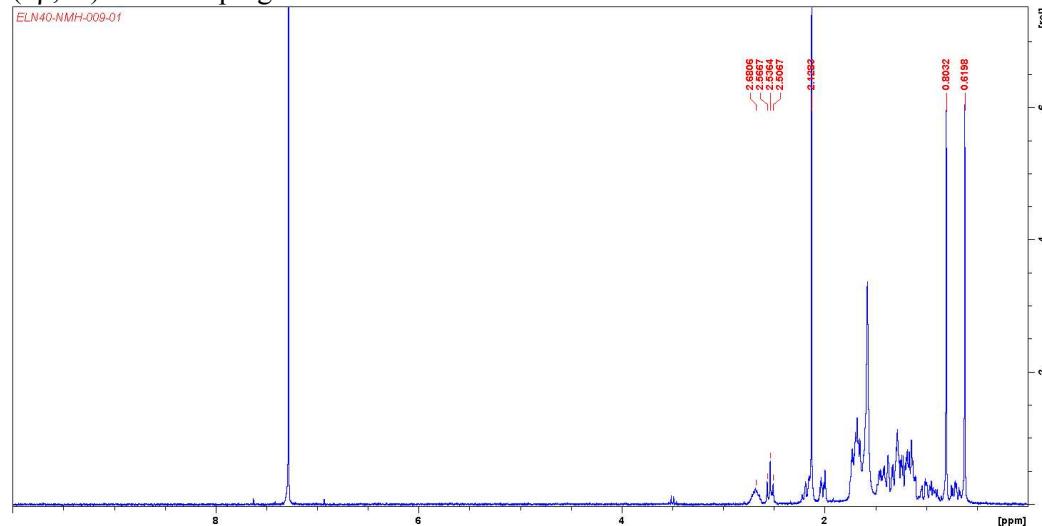
EN40-NMH-098-01



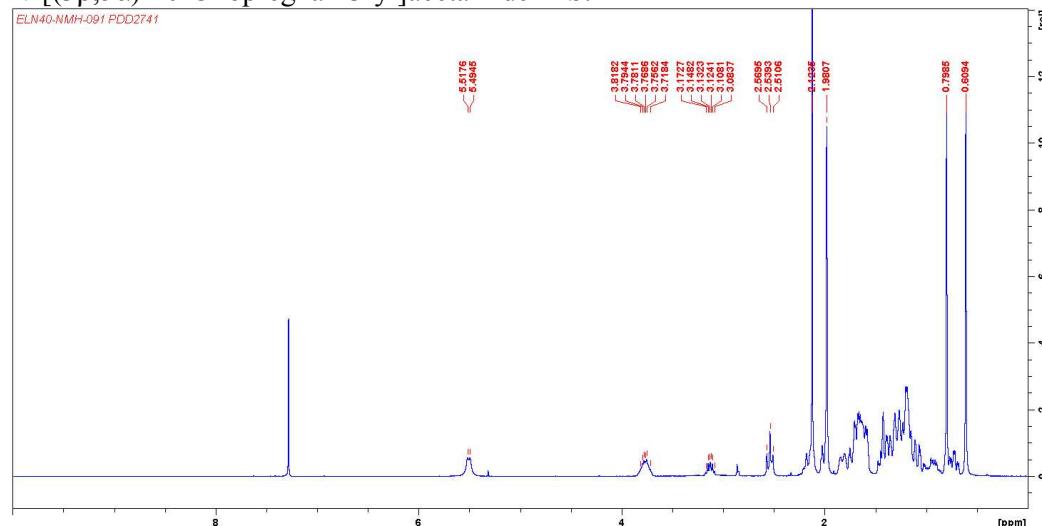
N-[(3 β ,5 α)-17-Oxoandrostan-3-yl]sulfamide **7l**.



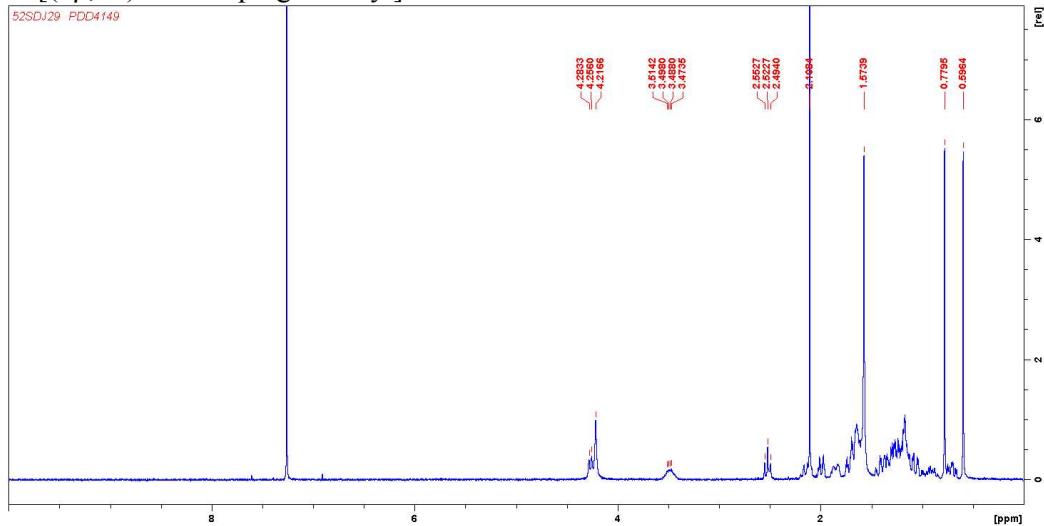
(3 β ,5 α)-3-Aminopregnan-20-one **14a**.



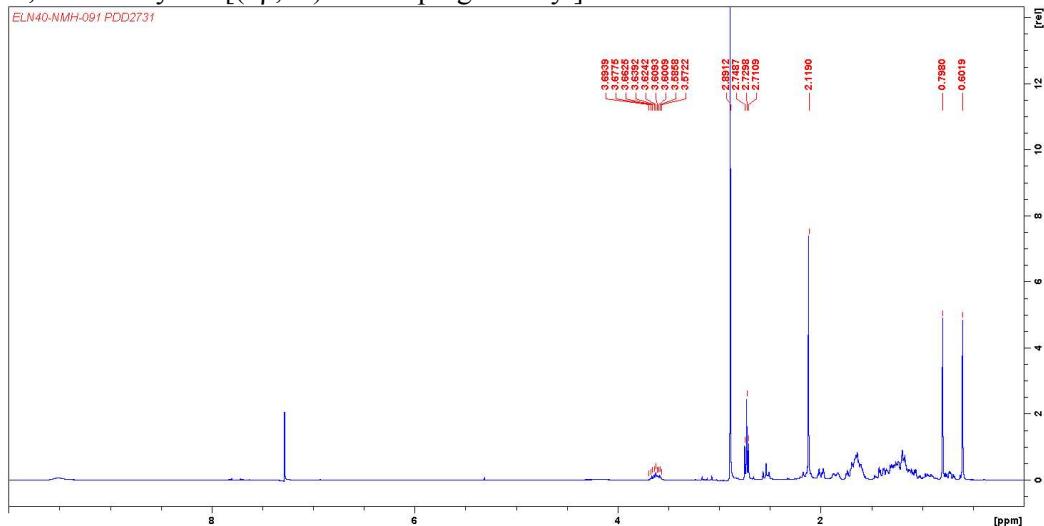
N-[(3 β ,5 α)-20-Oxopregnan-3-yl]acetamide **14b**.



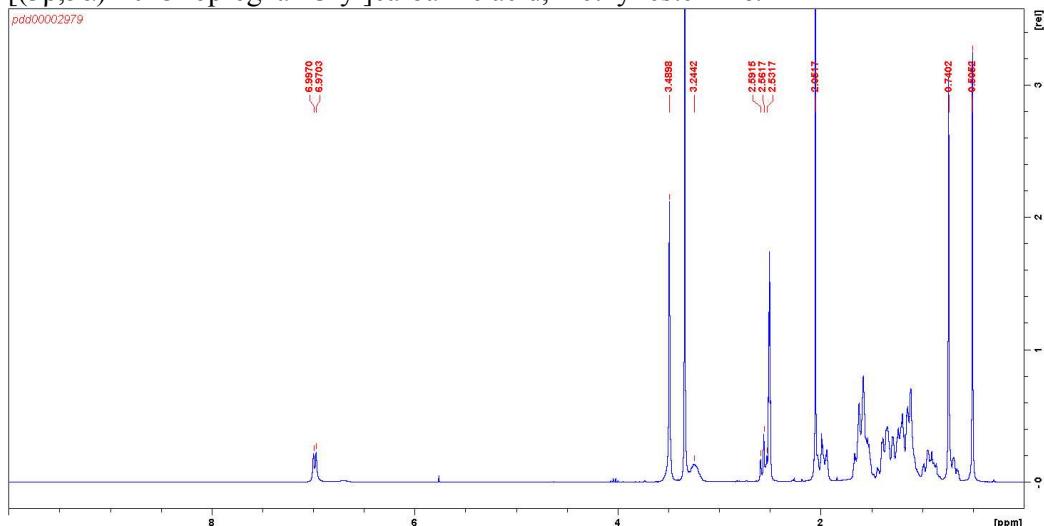
***N*-[(3 β ,5 α)-20-Oxopregnan-3-yl]urea 14c.**



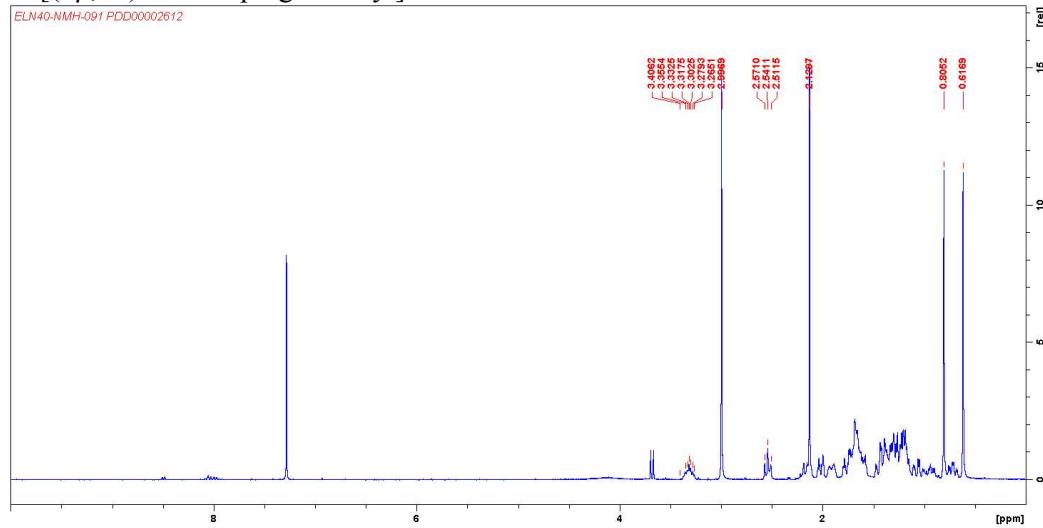
N,N-Dimethyl-*N'*-[(3 β ,5 α)-20-oxopregnan-3-yl]urea 14d.



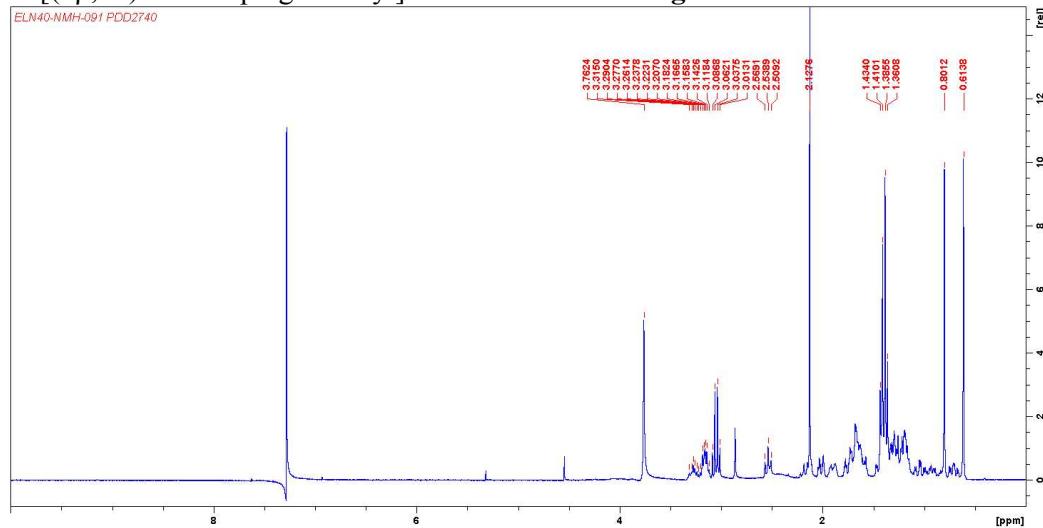
[(3 β ,5 α)-20-Oxopregnan-3-yl]carbamic acid, methyl ester **14e**.



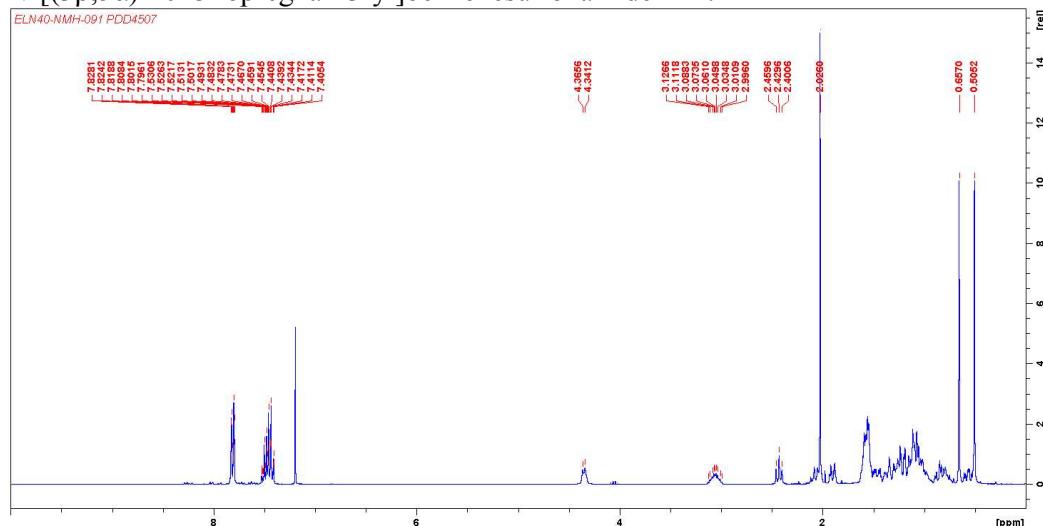
N-[(3 β ,5 α)-20-Oxopregnan-3-yl]methanesulfonamide **14f**.



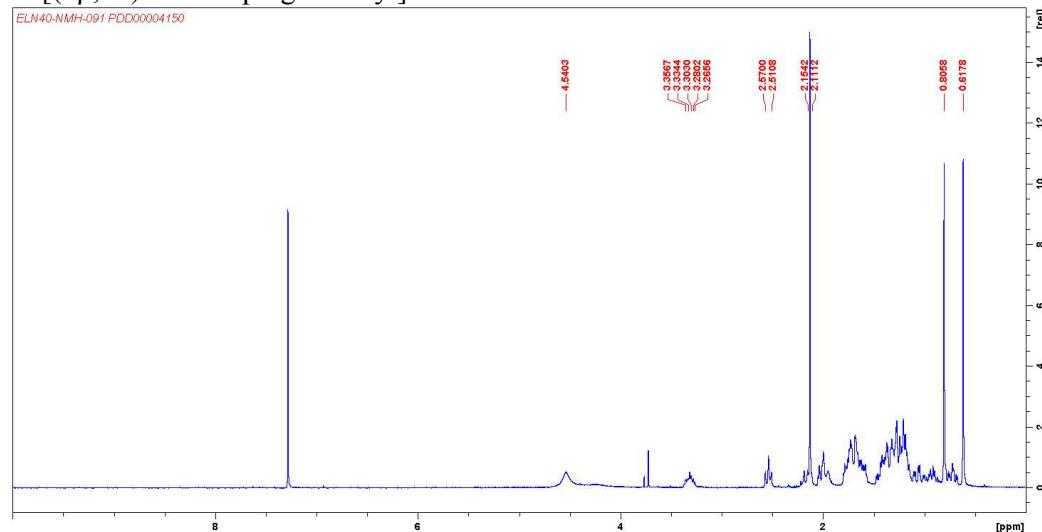
N-[(3 β ,5 α)-20-Oxopregnan-3-yl]ethanesulfonamide **14g**.



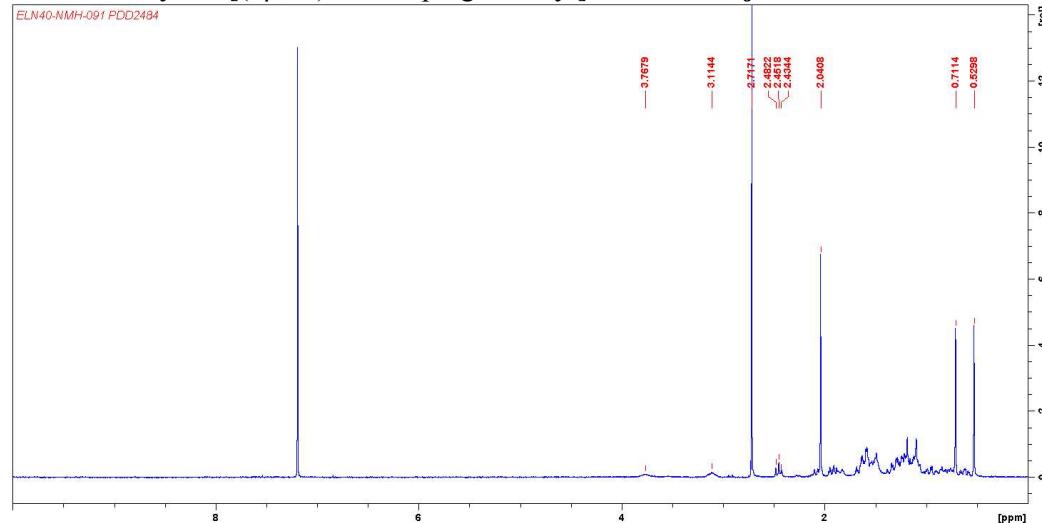
N-[(3 β ,5 α)-20-Oxopregnan-3-yl]benzenesulfonamide **14h**.



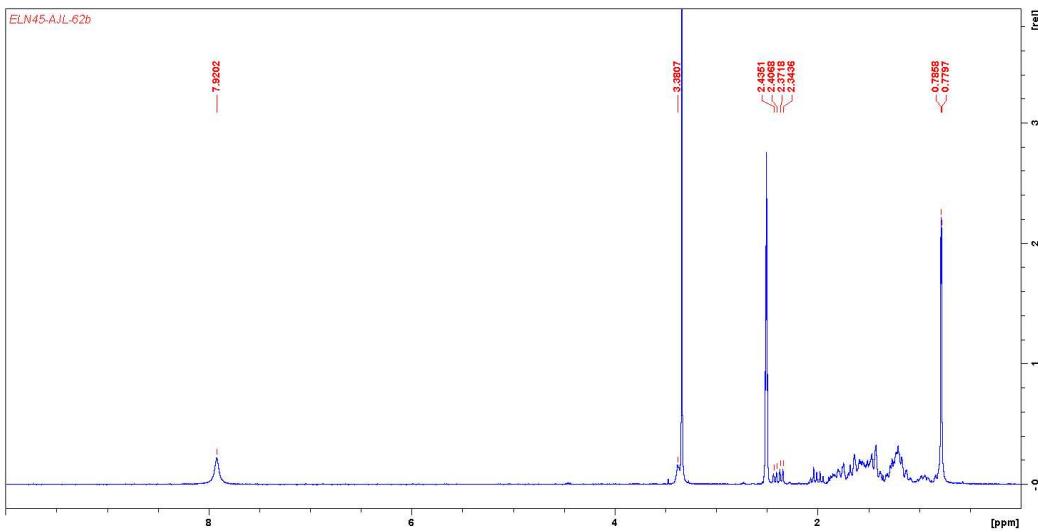
N-[(3 β ,5 α)-20-Oxopregnan-3-yl]sulfamide **14i**.



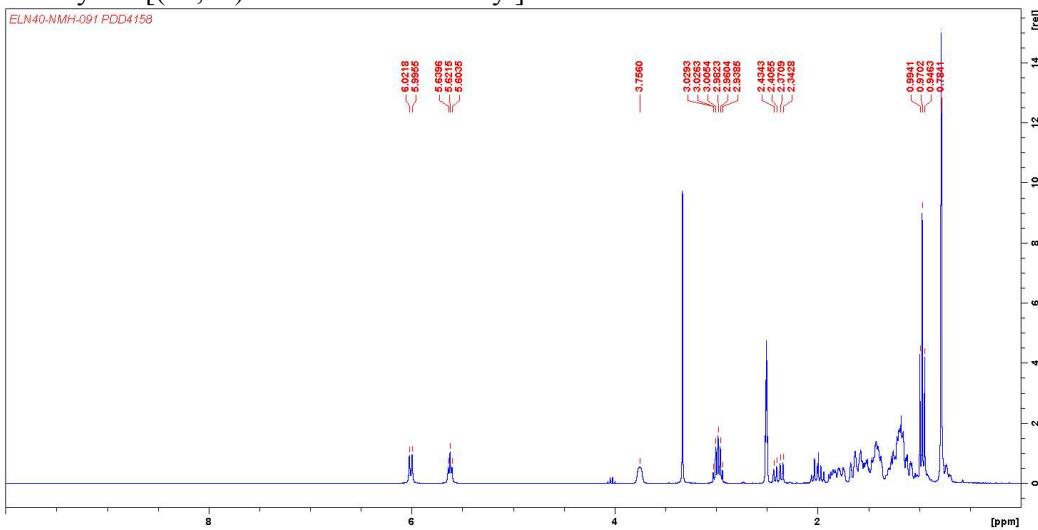
N,N-Dimethyl-*N*-[(3 β ,5 α)-20-oxopregnan-3-yl]sulfamide **14j**.



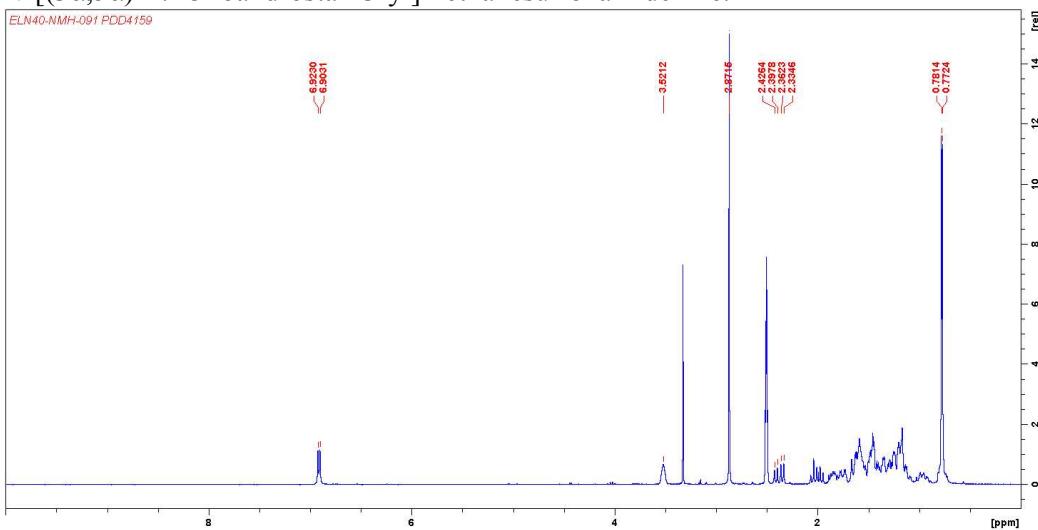
(3 α ,5 α)-3-Aminoandrostan-17-one, hydrochloride (1:1) **17a**.



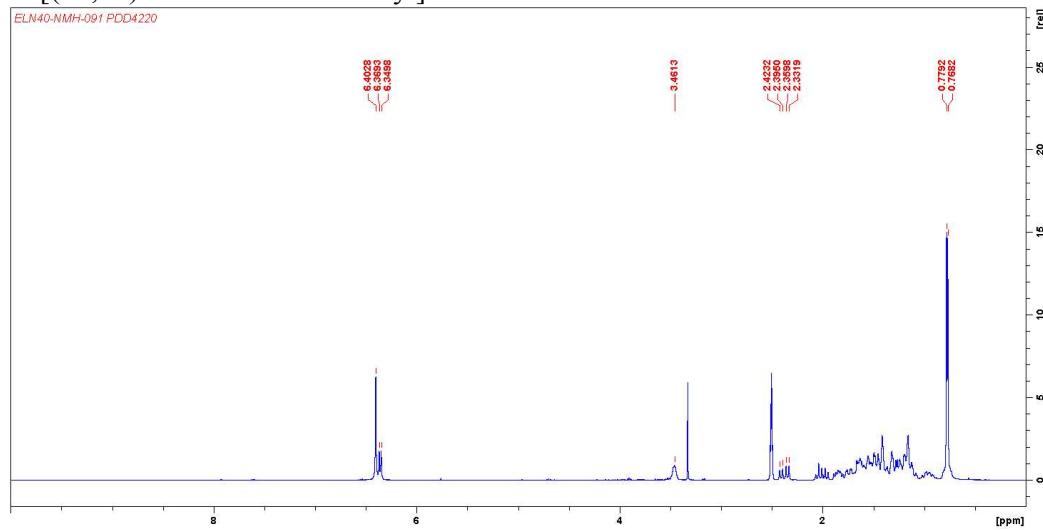
N-Ethyl-*N'*-[(3 α ,5 α)-17-oxoandrostan-3-yl]urea **17b**.



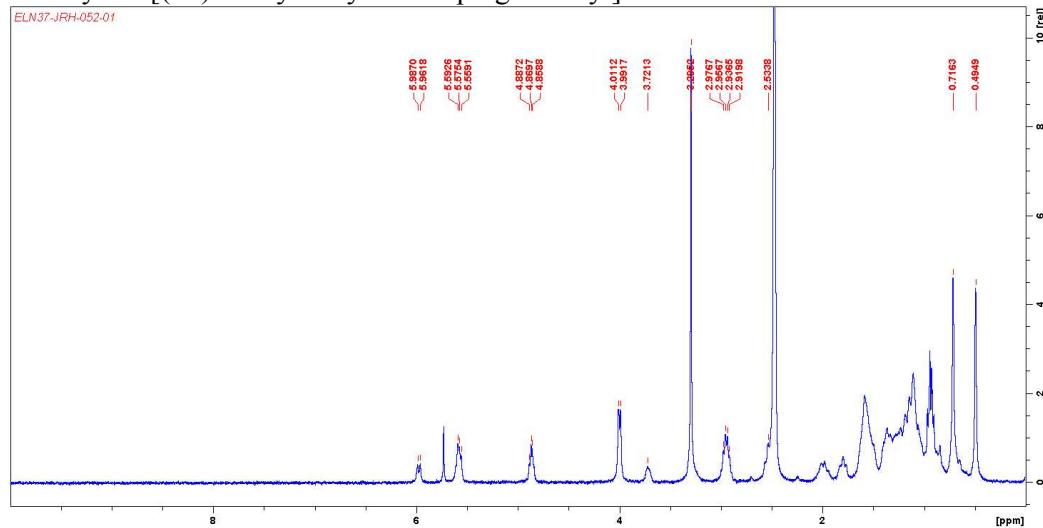
***N*-(3 α ,5 α)-17-Oxoandrostan-3-yl]methanesulfonamide **17c**.**



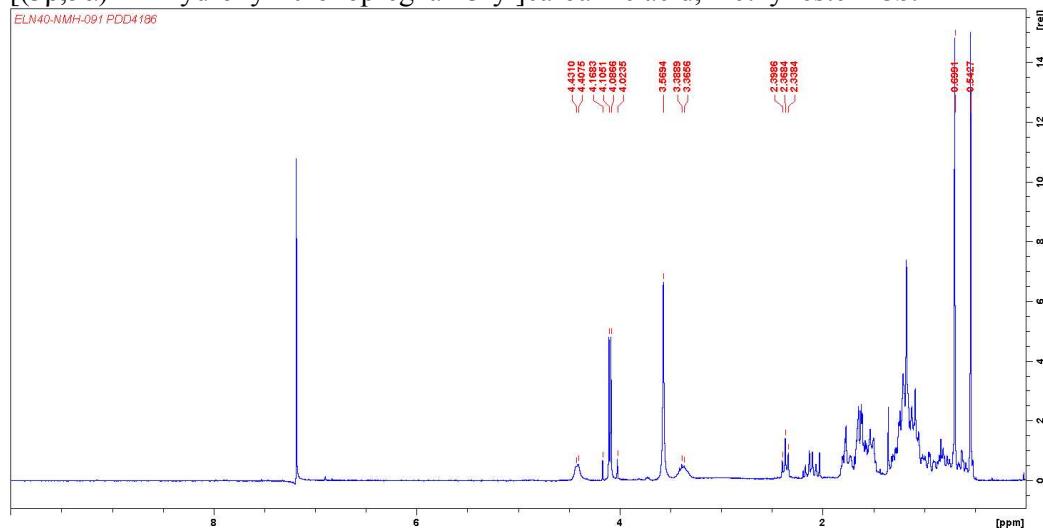
N-[(3 α ,5 α)-17-Oxoandrostan-3-yl]sulfamide **17d**.



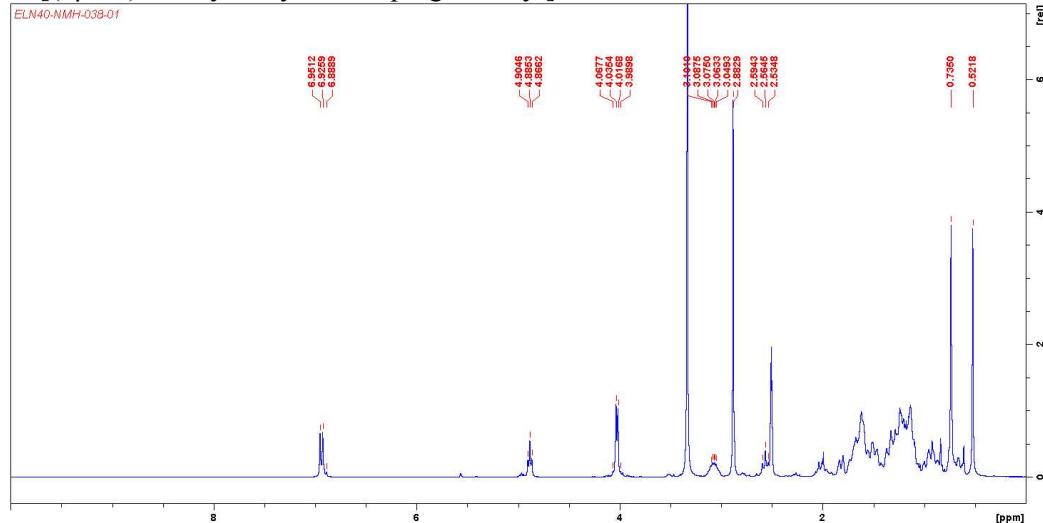
N-Ethyl-*N*-[(5 α)-21-hydroxy-20-oxopregnan-3-yl]urea **18a**.



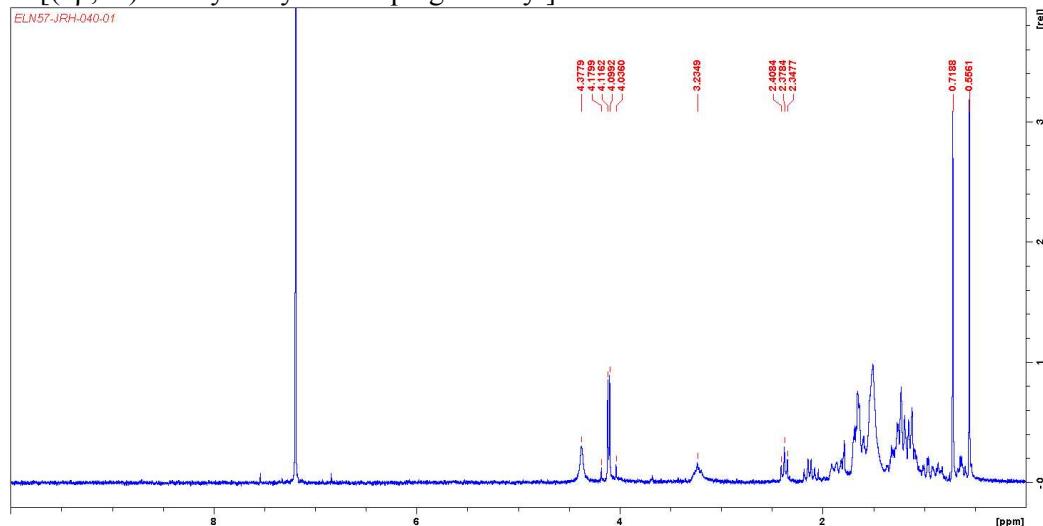
[(3 β ,5 α)-21-Hydroxy-20-oxopregnan-3-yl]carbamic acid, methyl ester **18b**.



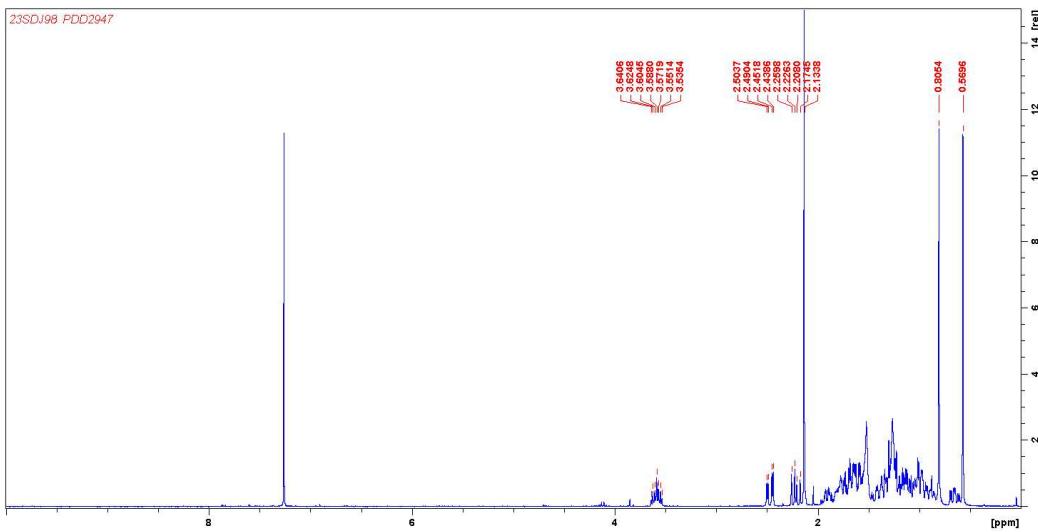
N-[(3 β ,5 α)-21-Hydroxy-20-oxopregnan-3-yl]methanesulfonamide 18c.



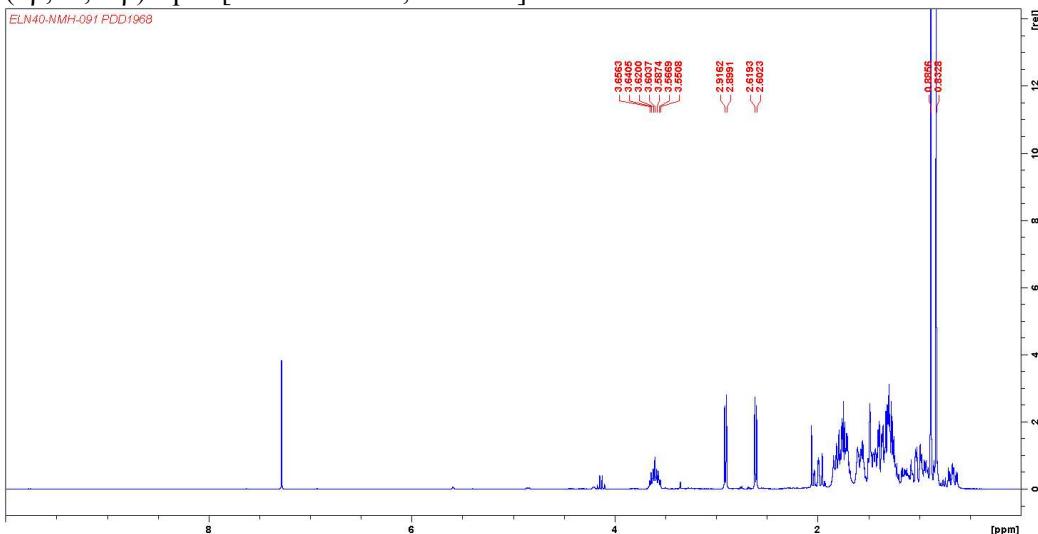
N-[(3 β ,5 α)-21-Hydroxy-20-oxopregnan-3-yl]sulfamide 18d.



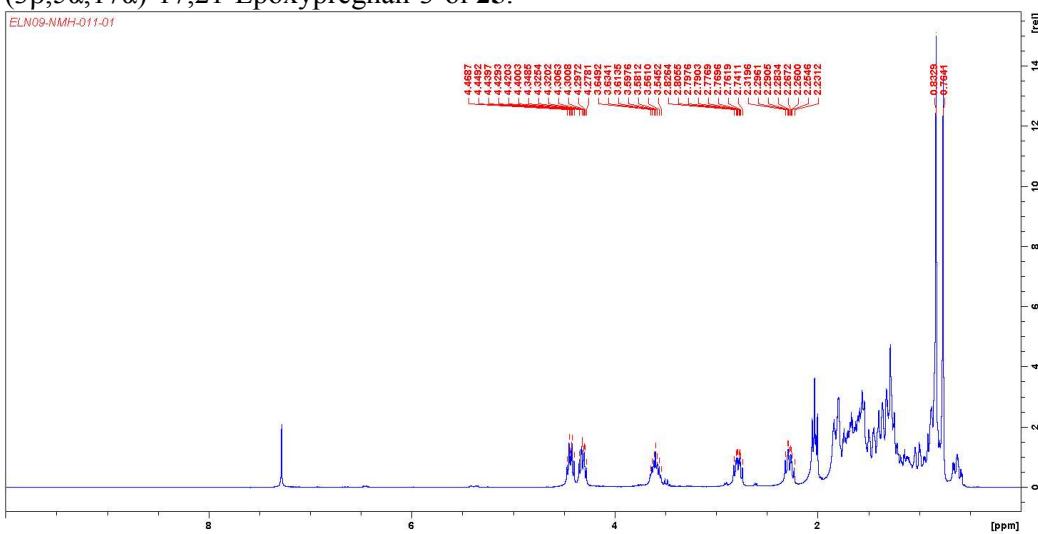
1-[$(3\beta,5\alpha)$ -3-Hydroxyandrostan-17-yl]-2-propanone **23**.



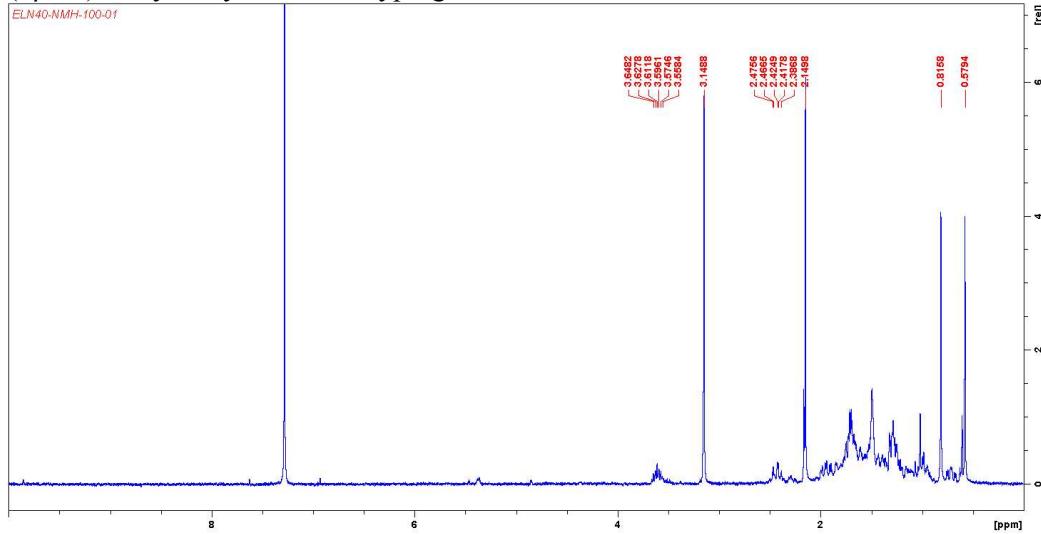
(3 β ,5 α ,17 β)-Spiro[androstane-17,2'-oxiran]-3-ol **24**.



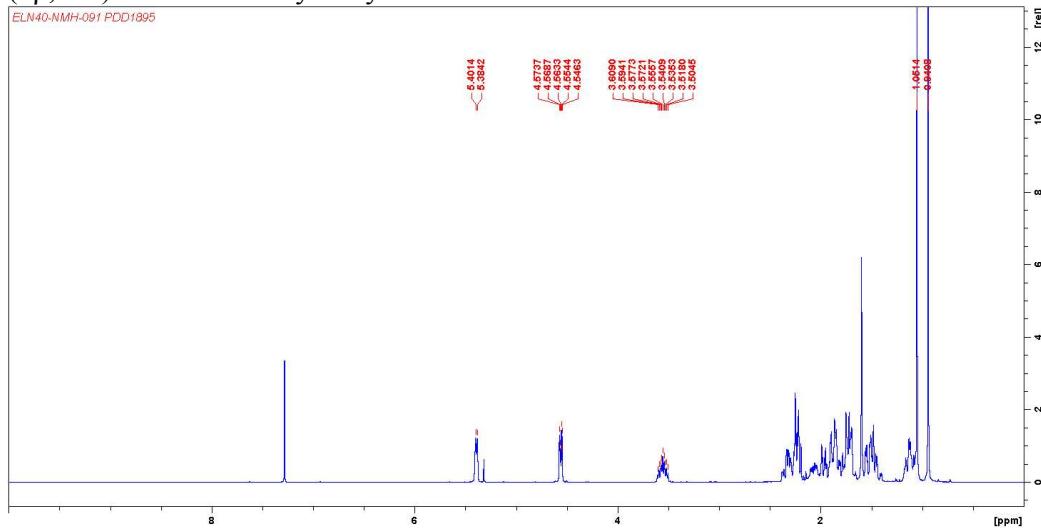
(3 β ,5 α ,17 α)-17,21-Epoxy pregnan-3-ol 25.



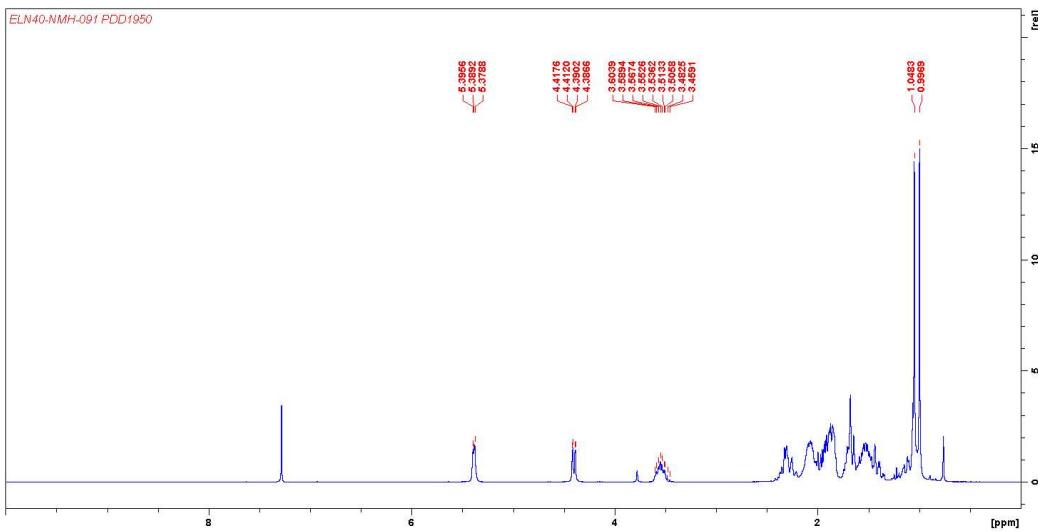
(3 β ,5 α)-3-Hydroxy-17-methoxypregnan-20-one 26.



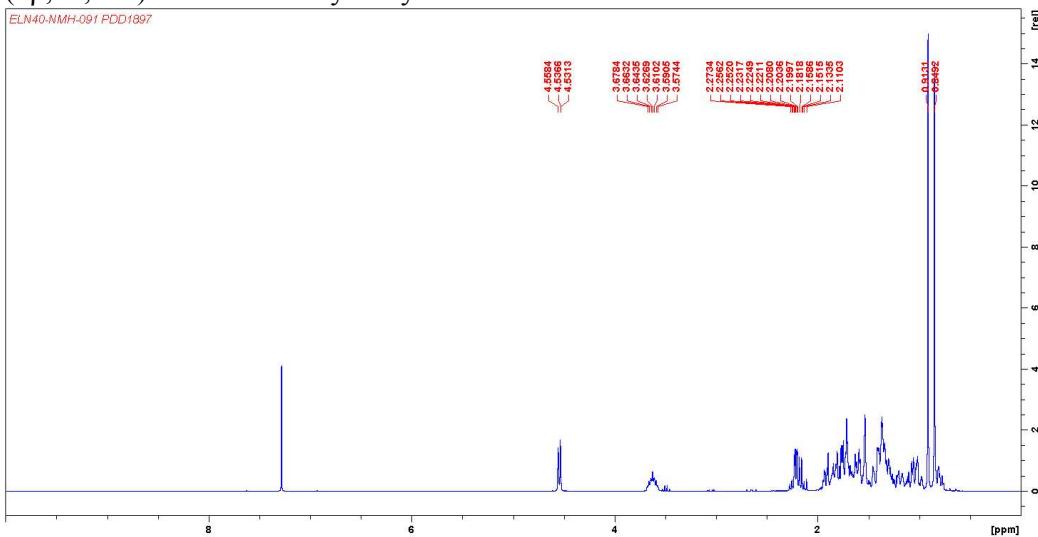
(3 β ,16 α)-16-Bromo-3-hydroxyandrost-5-en-17-one 27.



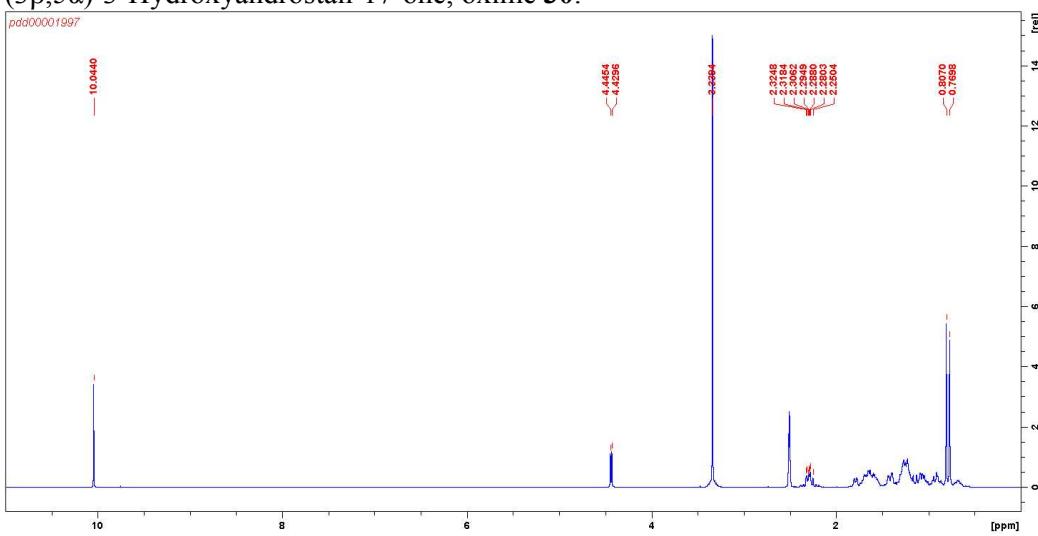
(3 β ,16 α)-3,16-Dihydroxyandrost-5-en-17-one **28.**



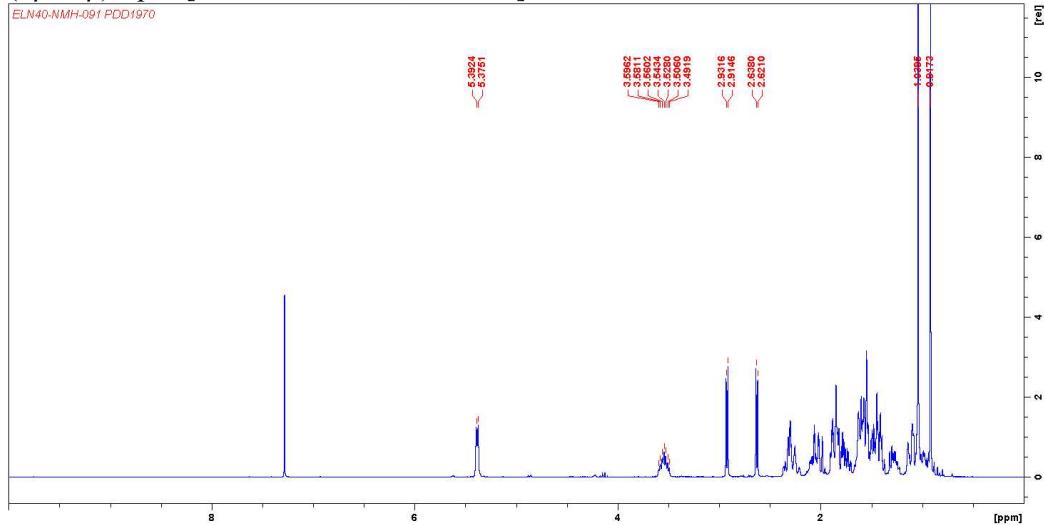
(3 β ,5 α ,16 α)-16-Bromo-3-hydroxyandrostan-17-one 29.



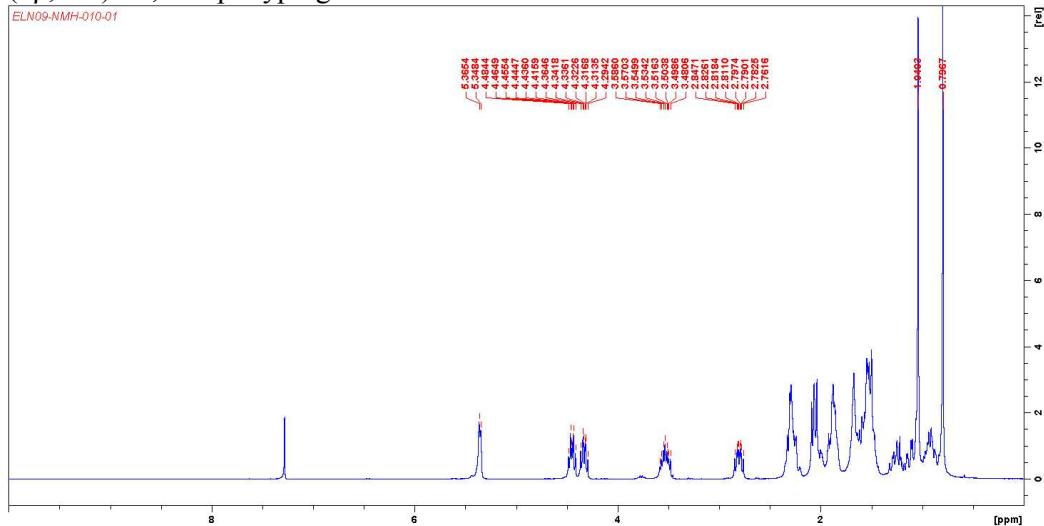
(3 β ,5 α)-3-Hydroxyandrostan-17-one, oxime **30**.



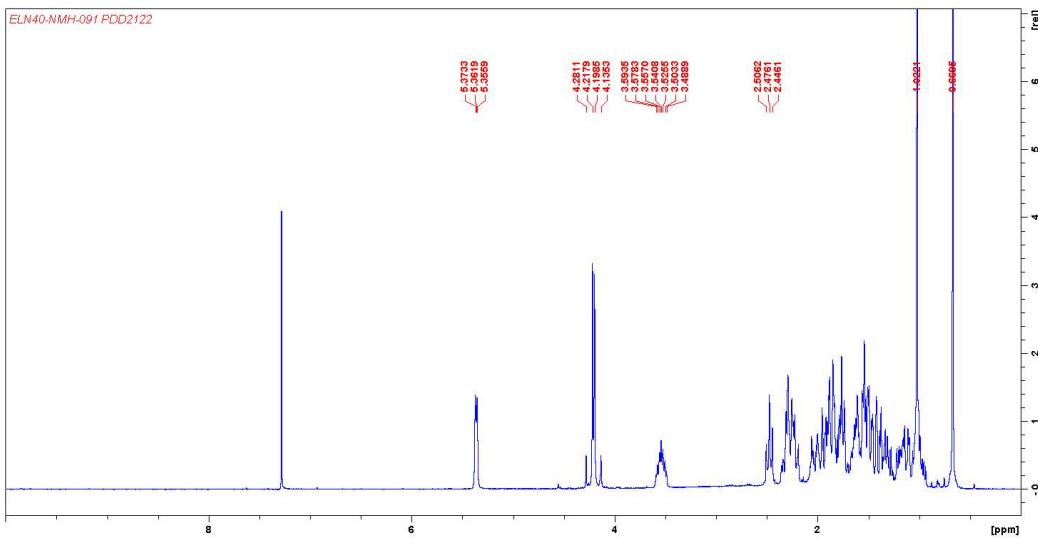
(3 β ,17 β)-Spiro[androst-5-ene-17,2'-oxiran]-3-ol 31.



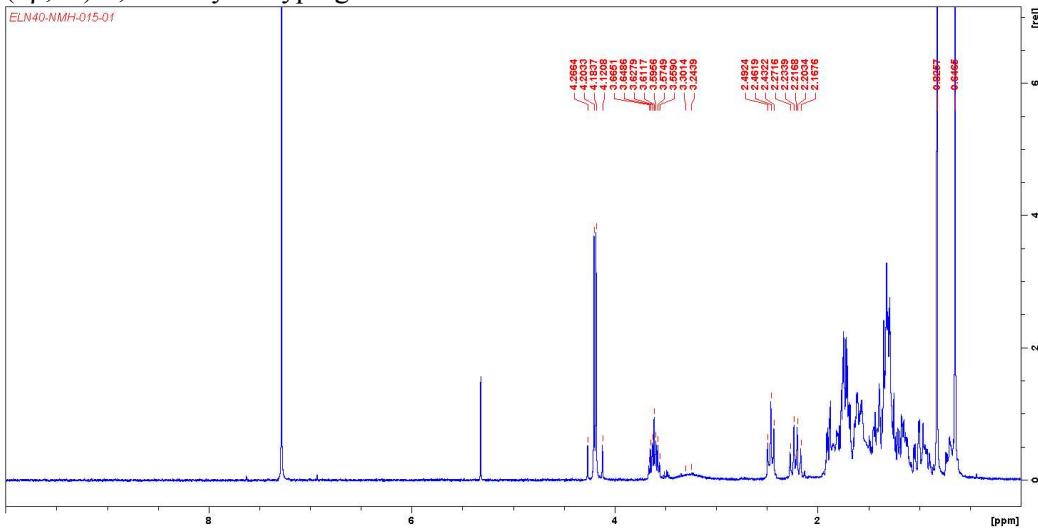
(3 β ,17 α)-17,21-Epoxy pregn-5-en-3-ol 32.



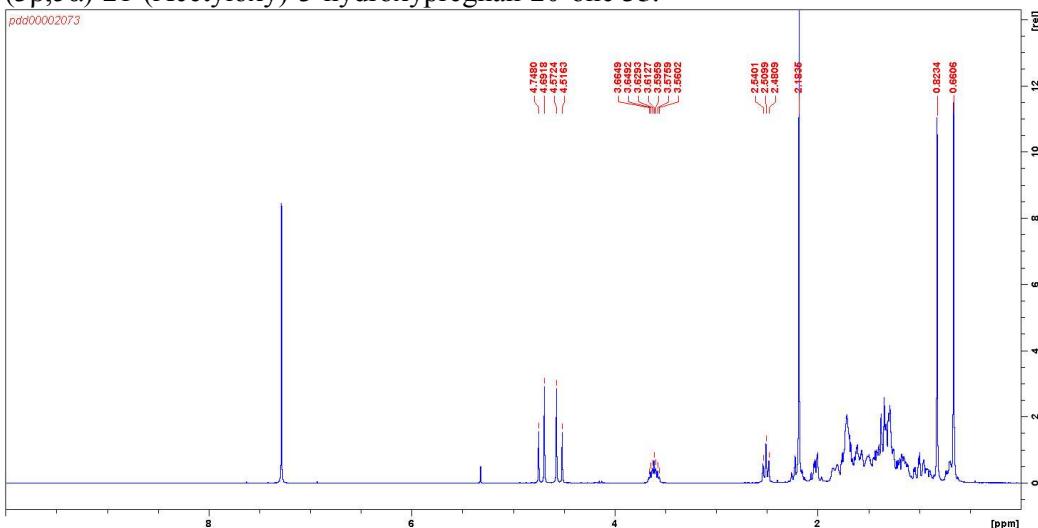
(3 β)-3,21-Dihydroxypregn-5-en-20-one 33.



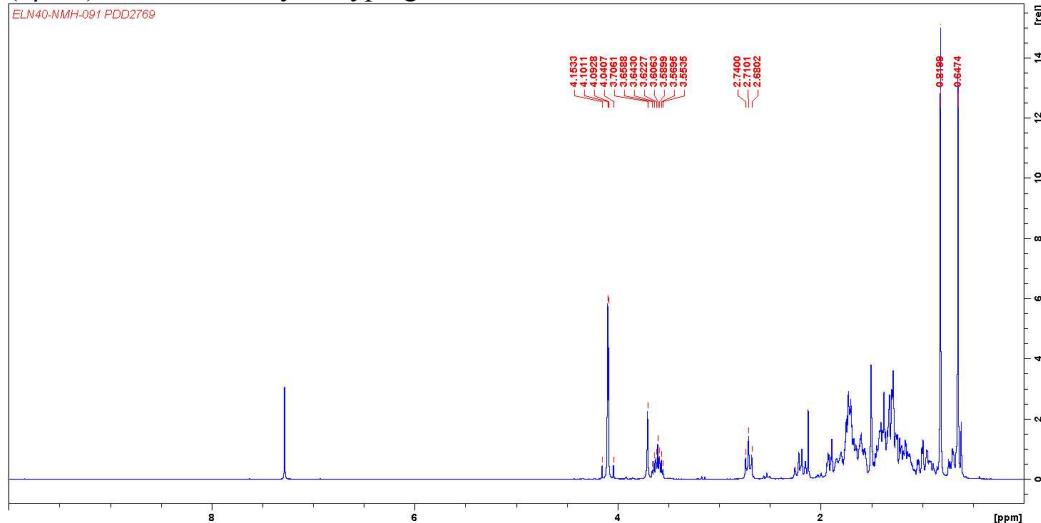
(3 β ,5 α)-3,21-Dihydroxypregnan-20-one **34**.



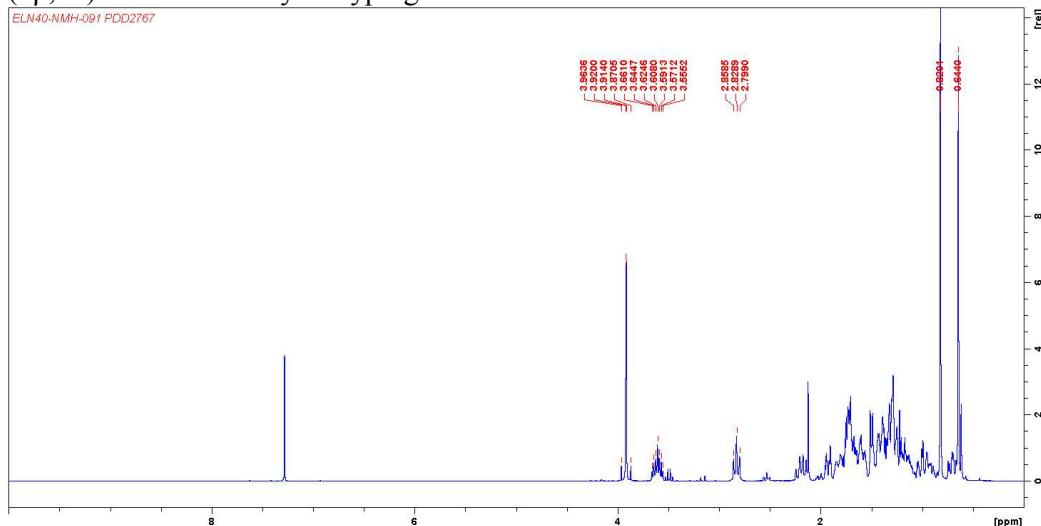
(3 β ,5 α)-21-(Acethoxy)-3-hydroxypregnan-20-one **35**.



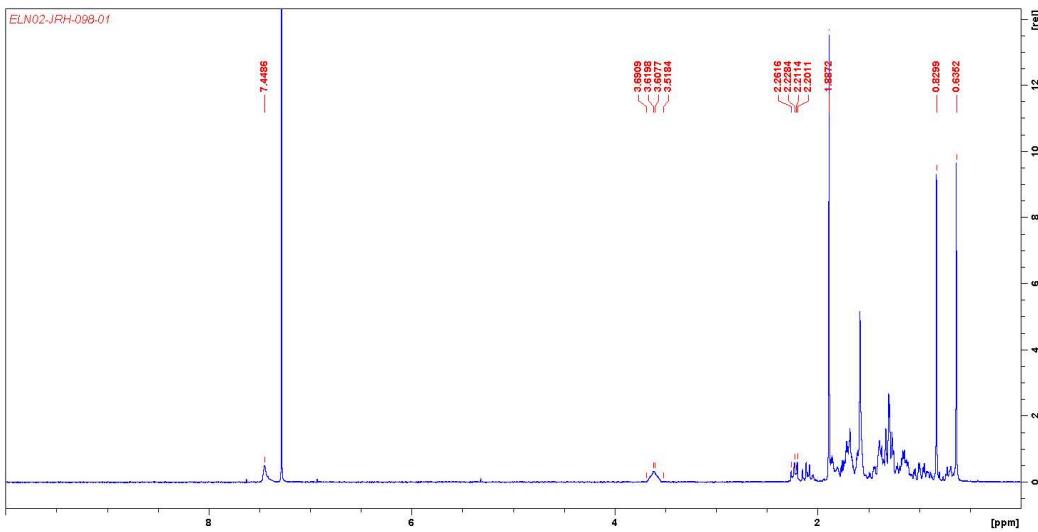
(3 β ,5 α)-21-Chloro-3-hydroxypregnan-20-one 36.



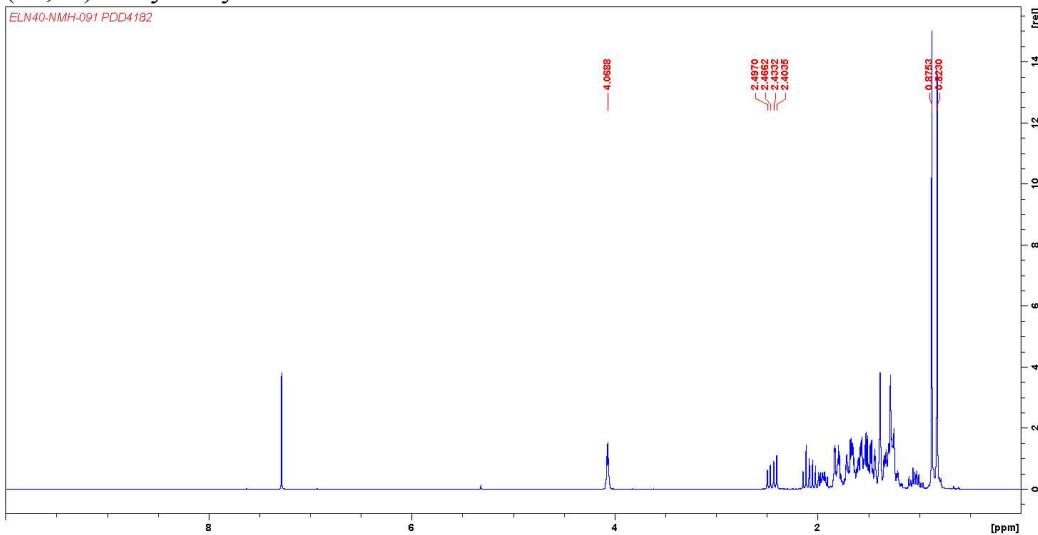
(3 β ,5 α)-21-Bromo-3-hydroxypregnan-20-one 37.



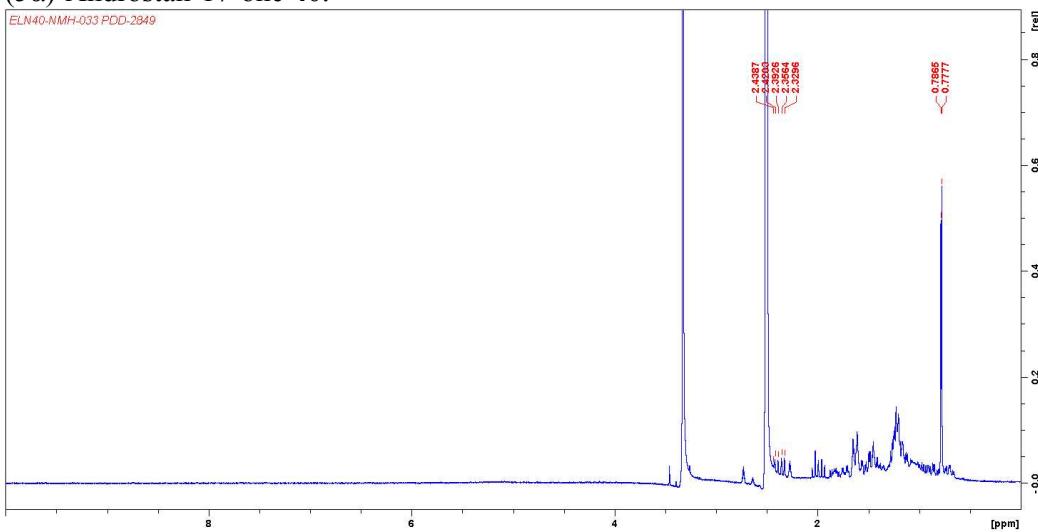
(3 β ,5 α)-3-Hydroxypregnan-20-one, oxime **38**.



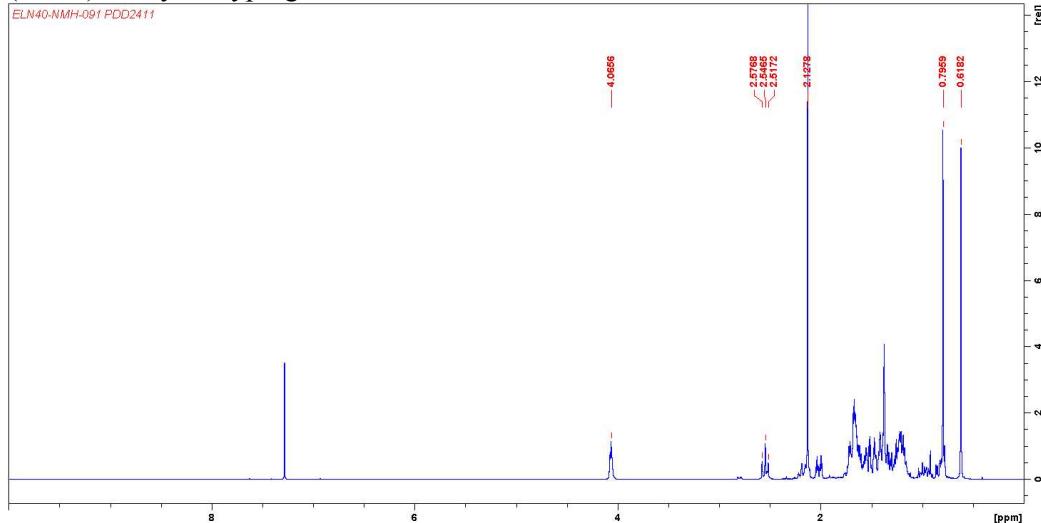
(3 α ,5 α)-3-Hydroxyandrostan-17-one **39**.



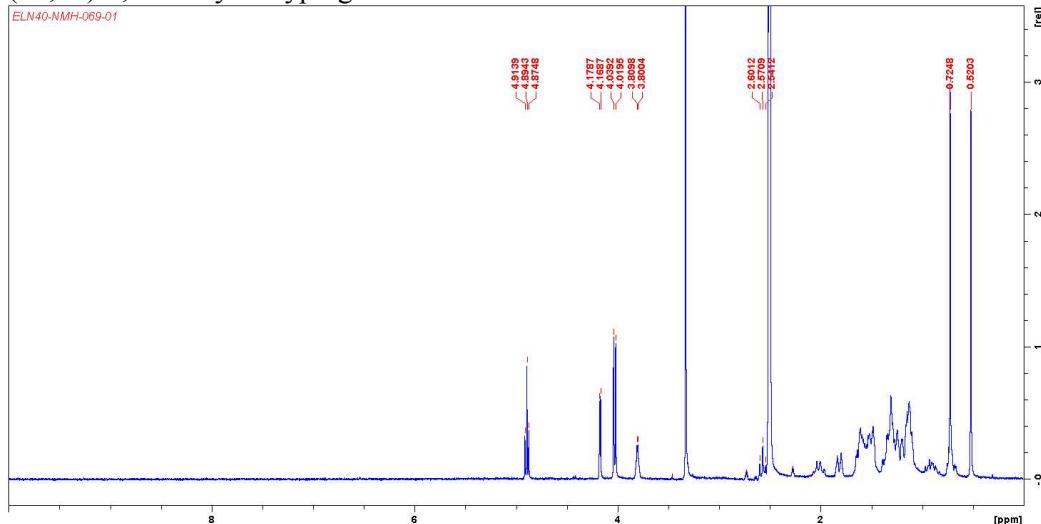
(5 α)-Androstan-17-one **40**.



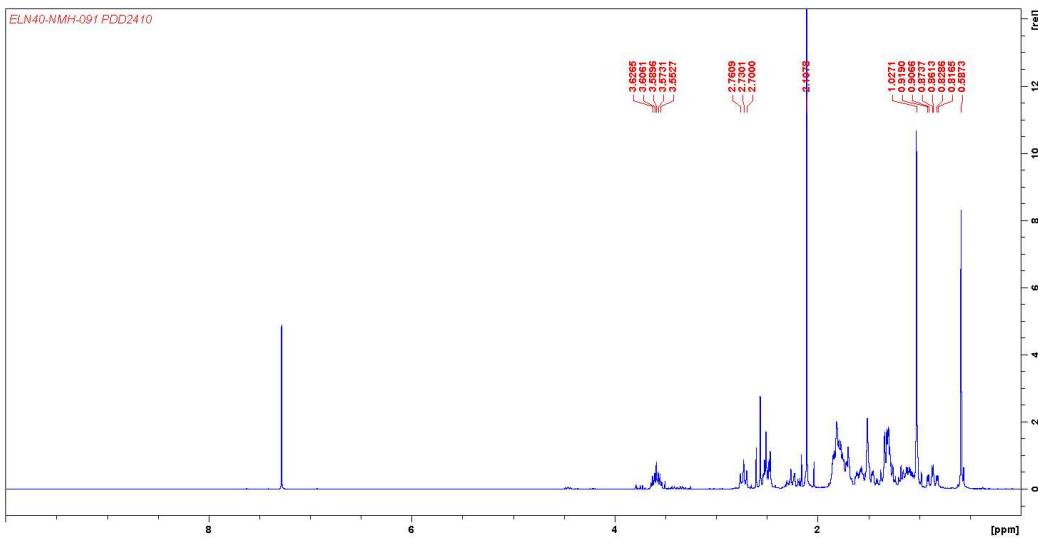
(3 α ,5 α)-3-Hydroxypregn-20-one **41**.



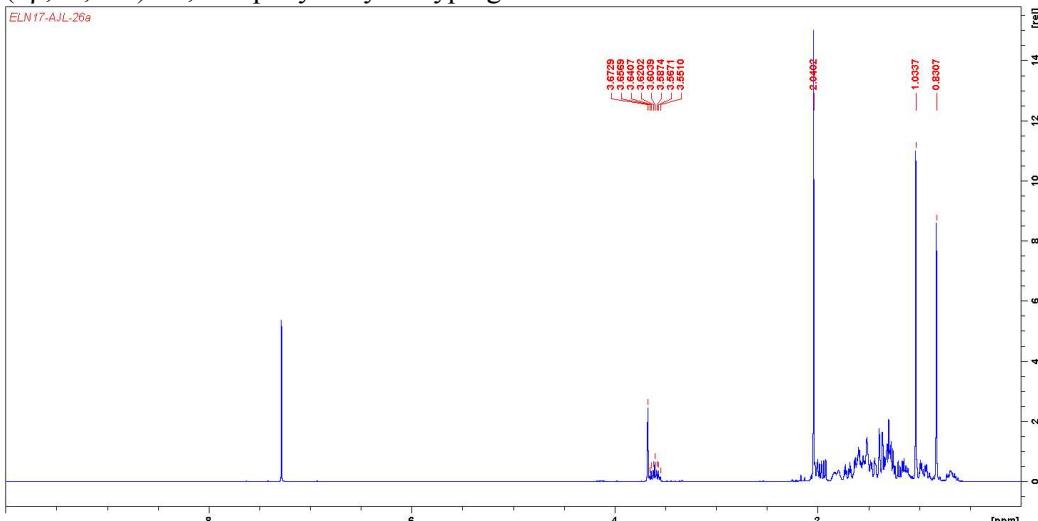
(3 α ,5 α)-3,21-Dihydroxypregn-20-one **42**.



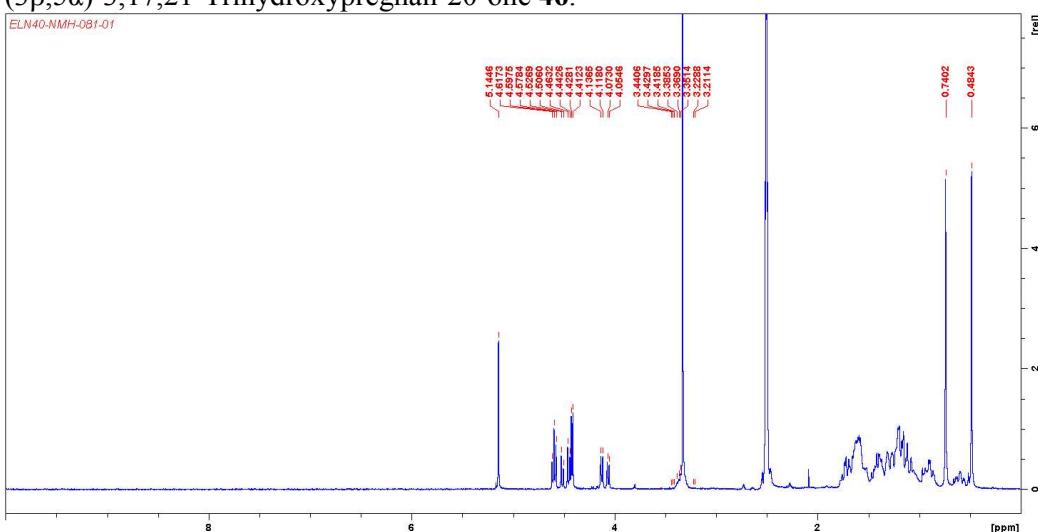
(3 β ,5 α)-3-Hydroxypregnane-11,20-dione **43**.



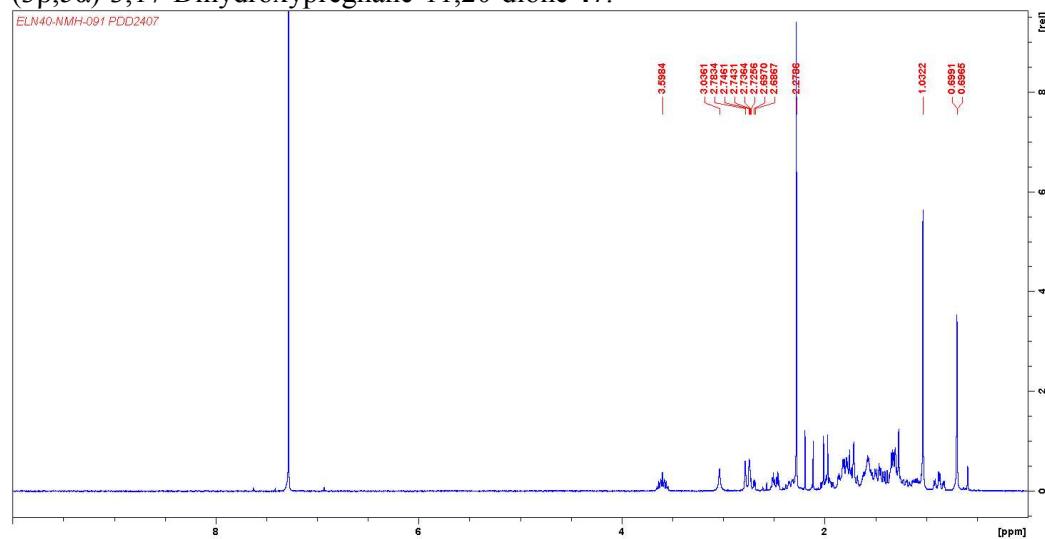
(3 β ,5 α ,16 α)-16,17-Epoxy-3-hydroxypregnan-20-one 45.



(3 β ,5 α)-3,17,21-Trihydroxypregnan-20-one **46**.



(3 β ,5 α)-3,17-Dihydroxypregnane-11,20-dione 47.



References for Supporting Information

- 1 Smuga, D. A.; Smuga, M.; Swizdor, A.; Panek, A.; Wawrzenczyk, C. Synthesis of dehydroepiandrosterone analogues modified with phosphatidic acid moiety. *Steroids* **2010**, *75*(13-14), 1146-1152.
- 2 (a) Nunes, R. M. D.; Peixoto, A. F.; Axet, M. R.; Pereira, M. M.; Moreno, M. J.; Kollar, L.; Claver, C.; Castillon, S. Selective hydrogenation of α,β -unsaturated oxosteroids with homogeneous rhodium catalysts *J. Mol. Catalysis A: Chemical* **2006**, *247*(1-2), 275-282; (b) Kawamorita, S.; Hamasaka, G.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. Hydrogenation of hindered ketones catalyzed by a silica-supported compact phosphine-Rh system. *Org. Lett.* **2008**, *10*(20), 4697-4700.
- 3 Hamilton, N. M.; Hitchin, J. R.; Jordan, A. M.; Lyons, A. J.; Ogilvie, D. A novel scalable and stereospecific synthesis of 3α - and 3β -amino- 5α -androstan-17-ones and 3α - and 3β -amino- 5α -pregnan-20-ones. *Tetrahedron Lett.* **2012**, in press.
- 4 Tchedam Ngatcha, B.; Luu-The, V.; Labrie, F.; Poirier, D. Androsterone 3α -ether- 3β -substituted and androsterone 3β -substituted derivatives as inhibitors of type 3 17β -hydroxysteroid dehydrogenase: Chemical synthesis and structure-activity relationship. *J. Med. Chem.* **2005**, *48*(16), 5257-5268.
- 5 Shingate, B. B.; Hazra, B. G.; Salunke, D. B.; Pore, V. S.; Shirazi, F.; Deshpande, M. V. Stereoselective synthesis and antimicrobial activity of steroidal C-20 tertiary alcohols with thiazole/pyridine side chain. *Eur. J. Med. Chem.* **2011**, *46*(9), 3681-3689.

6 Ibuka, T.; Taga, T.; Shingu, T.; Saito, M.; Nishii, S.; Yamamoto, Y. New stereoselective synthesis of 20S and 20R steroidal side chains. Remarkable stereoselectivity differences between saturated and α,β -unsaturated steroid esters. *J. Org. Chem.* **1988**, *53*(17), 3947-3952.

7 Felzmann, W.; Gmeiner, G.; Gaertner, P. First synthesis of a pentadeuterated 3'-hydroxystanozolol-an internal standard in doping analysis. *Steroids* **2005**, *70*(2), 103-110.

8 Shi, B.; Wu, H.; Yu, B.; Wu, J. 23-Oxa-analogues of OSW-1: efficient synthesis and extremely potent antitumor activity. *Angew. Chem., Int. Ed.* **2004**, *43*(33), 4324-4327.

9 Marwah, P.; Marwah, A.; Lardy, H. A.; Miyamoto, H.; Chang, C. C19-Steroids as androgen receptor modulators: design, discovery, and structure-activity relationship of new steroidal androgen receptor antagonists. *Bioorg. Med. Chem.* **2006**, *14*(17), 5933-5947.

10 Guo, H.; Zhang, G.; Zhang, T.; He, X.; Wu, Z.; Xiao, Y.; Pan, Y.; Qiu, G.; Liu, P.; Hu, X. Synthesis, characterization and biological evaluation of some 16 β -azolyl-3 β -amino-5 α -androstane derivatives as potential anticancer agents. *Eur. J. Med. Chem.* **2011**, *46*(9), 3662-3674.

11 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*(21), 6569-6587.

12 Hunter, A. C.; Collins, C.; Dodd, H. T.; Dedi, C.; Koussoroplis, S-J. Transformation of a series of saturated isomeric steroidal diols by *Aspergillus*

tamarii KITA reveals a precise stereochemical requirement for entrance into the lactonization pathway. *J. Steroid Biochem. Mol. Biol.* **2010**, *122*(5), 352-358.

13 ^{13}C NMR: WSS: Spectral data were obtained from Wiley Subscription Services, Inc. (US), Spectrum ID UWVN006593 (CDCl_3).

14 MacNevin, C. J.; Atif, F.; Sayeed, I.; Stein, D. G.; Liotta, D. C. Development and screening of water-soluble analogues of progesterone and allopregnanolone in models of brain injury. *J. Med. Chem.* **2009**, *52*(19), 6012-6023.

15 Chowdhury, P.; Borah, J. M.; Goswami, P.; Das, A. M. A convenient synthesis of the side chain of loteprednol etabonate - an ocular soft corticosteroid from 20-oxopregnanes using metal-mediated halogenation as a key reaction. *Steroids* **2011**, *76*(5), 497-501.

16 Al-Sanea, M. M.; Abdel-Hafez, A. A.; Omar, F. A.; Youssef, A. F. Biotransformation studies of prednisone using human intestinal bacteria Part II: Anaerobic incubation and docking studies. *J. Enzyme Inhib. Med. Chem.* **2009**, *24*(6), 1211-1219.