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SYNTHESIS OF 18-SUBSTITUTED ANDROST-4-EN-3-ONE DERIVATIVES AS POTENTIAL INHIBITORS OF ALDOSTERONE BIOSYNTHESIS

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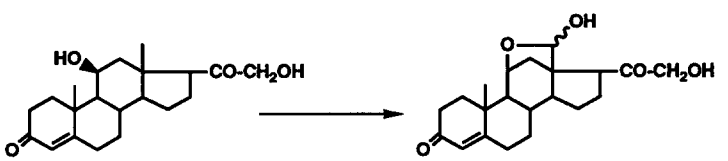
Abstract

Androst-4-en-3-one derivatives substituted at the 18-methyl group bearing a 17-keto or 17-spirolactone function have been synthesized and tested *in vitro* as inhibitors of aldosterone biosynthesis

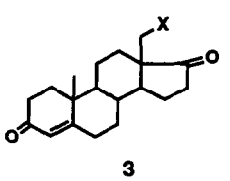
Aldosterone is a potent mineralocorticoid which regulates body fluids electrolyte balance by promoting potassium elimination and sodium retention[1] An aldosterone overproduction leads to oedema formation and hypertension With a view of developing a new class of antihypertensive drugs we are now investigating the specific inhibition of aldosterone biosynthesis We are therefore designing and synthesizing kcat inhibitors[2] of the final steps, the hydroxylation of the C-18 methyl group of corticosterone **1**



1 **2**

This transformation is catalyzed by a cytochrome P450 monooxygenase
According to literature data on cytochrome P450 inhibition[3], different classes of molecules can be designed as potential kcat inhibitors of that monooxygenase they are substrate analogues substituted on the 18-methyl group We have already described the synthesis of various C-18 modified progesterones[4,5] We wish to report here the results obtained in the androstene-3,17-dione and spirolactone series Previous results[6] indicated that androstenedione **3**(X = H) can also be hydroxylated at C-18 by the cytochrome P-450 involved in the corticosterone transformation

This prompted us to develop androstenedione analogues **3** substituted at the 18-methyl group in the hope that synthesis in that case should be easier than in the progesterone series In addition spirolactones **4** should be easily obtained from the androstenediones **3** using Sturtz reagent[7] Spironolactone **4a**, an antagonist of aldosterone, is the most widely used antimineralocorticoid[8] The targeted spirolactones **4** could be both inhibitors of aldosterone biosynthesis and antagonists at the receptor level



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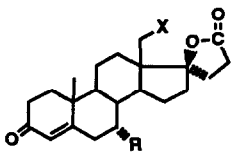
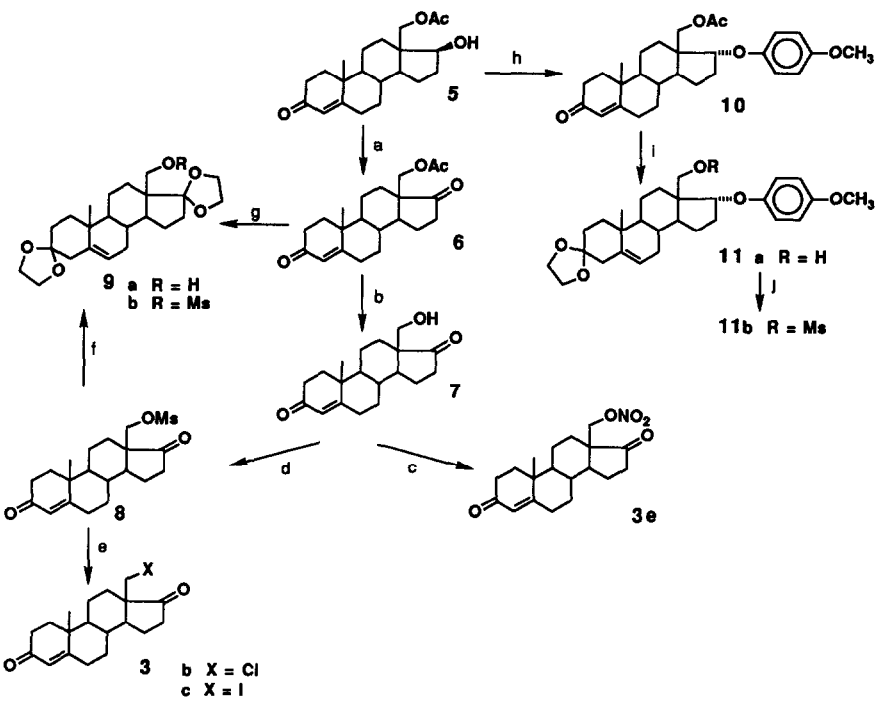


4 R = H
4a R = $SCOCH_3$
X = H

We first attempted to prepare 18-halogenated androstenediones since we had already shown that 18-halogenated progesterones inhibit the 18-hydroxylase, as 19-substituted androstenediones inhibit aromatase[9]

The synthesis of 18-chloro and 18-iodo androstenediones **3b** and **3c** is given in Scheme 1



Scheme 1

a) PCC, CH_2Cl_2 , b) HCl, CH_3OH , c) NO_3H, $(CH_3CO)_2O$, d) CH_3SO_2Cl, $(C_2H_5)_3N$, e) $(C_4H_9)_4N^+Cl$ or $(C_4H_9)_4N^+I$, HMPA, f) $HOCH_2$-CH_2OH, pTosOH, C_6H_6 , g) $HOCH_2$-CH_2OH, pTosOH, C_6H_6 , K_2CO_3, CH_3OH , h) 4-OH anisol, $(C_6H_5)_3P$, DEAD , i) $HOCH_2$-CH_2OH, pTosOH, C_6H_6 , K_2CO_3, CH_3OH , j) CH_3SO_2Cl, $(C_2H_5)_3N$

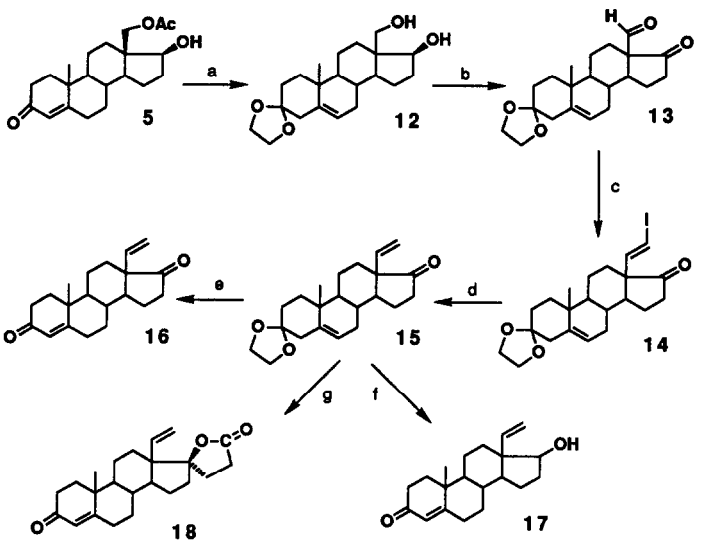
Compound **5** was prepared in 8 steps starting from the commercially available pregnenolone according to already described methods[10-14] After oxidation of the 17-hydroxyl group with pyridinium chlorochromate (PCC), the acetate group was hydrolysed under acidic conditions to avoid any retroaldolisation[12,15] The mesylate **8** was then obtained quantitatively Treated with tetrabutylammonium chloride, it yielded the chlorocompound **3b** (43 %) Using tetrabutylammonium iodide under the same conditions we could prepare **3c** but with lower yield (30 %) We failed in displacing the mesylate using tetrabutylammonium fluoride in HMPA The 18-nitrate analogue **3e** was prepared directly from **7** by treatment with nitric acid in acetic anhydride[14]

The direct nucleophilic substitution by cyanide was not attempted on the diketone **8** since we anticipated that the expected intermediate 18-cyano-17-cyanhydrine could transform spontaneously into a 5-membered lactone[16] We first tried to prepare the mesylate **9b** from the hydroxy derivative **9a** However it turned out that **9a** was a very unstable compound, difficult to isolate and to characterize because of the spontaneous hydrolysis of the ketal groups **9b** could be obtained by ketalization of the two carbonyls of **8** using conventional procedure However we were not successful in displacing the 18-mesylate group of **9b** by most of the nucleophiles that we tried (I^-, CN^-,) We only succeeded in displacing it by Cl^-, leading after hydrolysis to the already obtained product **3b**

We reasoned that these failures might be due to steric hindrance and tried to protect the 17β-hydroxyl group in **5** by transforming it into a 17α-ether **10** according to Fukuyama et al [17] (Scheme 1)

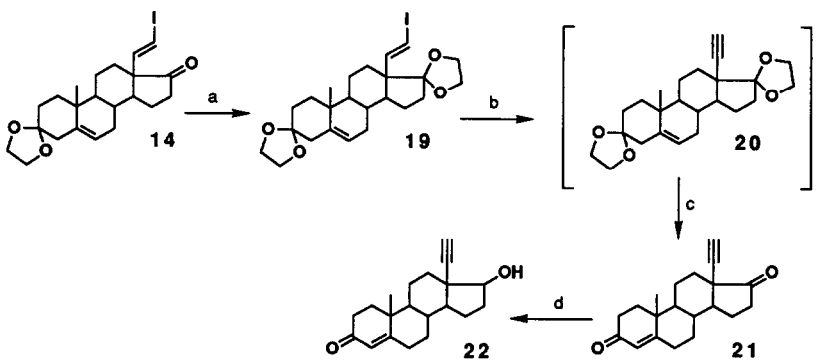
Compound **10** was transformed into **11a** and **11b** All attempts to substitute the mesylate group by CN^- (for instance 90 h in HMPA at 110°, with crown ether) led only to starting material

We turned then to the synthesis of 18-unsaturated androstene This was achieved according to Scheme 2 and Scheme 3 The 18-aldehyde **13** was easily obtained from **5** This compound was then treated with the organochromium reagent prepared from $CrCl_2$ and iodoform, according to K Takai[18] which selectively transformed the aldehyde into the iodomethylidene compound **14** Treatment with a Zn-Cu couple[19] afforded the methylidene derivative **15** which was transformed into the diketone **16**, ketoalcool **17** or lactone **18**, with the dianion of allyltetramethylphosphorodiamidate, according to Sturtz et al [20] (Scheme 2) After protection of the 17-keto group of **14**, HI elimination with $NaNH_2$ yielded the methylidyne derivative **20** This compound was easily hydrolyzed into the diketone **21** Selective reduction of the saturated 17-keto group by $NaBH_4$ at -60°C in a 50-50 CH_3OH-CH_2Cl_2 mixture according to Ward et al [21] afforded the 17-hydroxy compound **22**[22] (Scheme 3)



Scheme 2

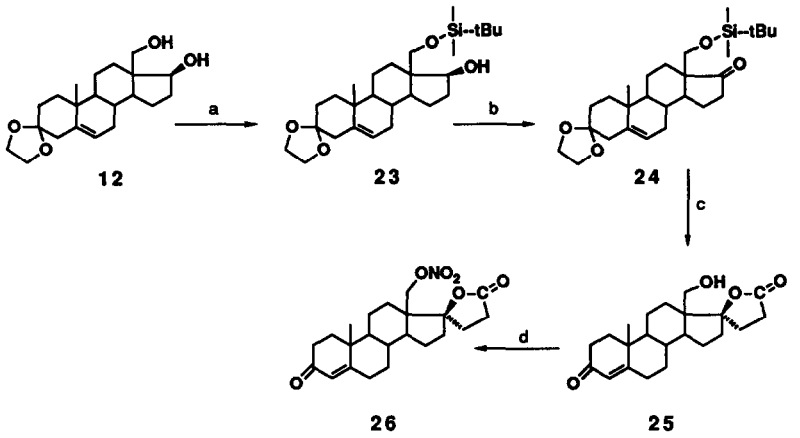
a) $HOCH_2$-CH_2OH, pTosOH, C_6H_6 , K_2CO_3, CH_3OH , b) $(ClCO)_2$, DMSO, CH_2Cl_2 , c) $CrCl_2$, CHI_3, THF , d) Zn, HCl , e) Amberlite, acetone , f) $NaBH_4$, C_2H_5OH , g) $(Me_2N)_2$-P(O)-CH=CH-CH_2^-, $2Li^+$, HCl, H_2O, CH_3OH



Scheme 3

a) $HOCH_2$-CH_2OH, pTosOH, C_6H_6 , b) $NaNH_2$, THF , c) HCl 1N, C_2H_5OH , d) $NaBH_4$, CH_3OH / CH_2Cl_2

The synthesis of another 18-modified spirolactone is described in Scheme 4 Treatment of the diol **12** with t-butyldimethylsilyl chloride under carefully controlled conditions (2 eq , short reaction time) led to preferential formation of the monoether **23** in spite of the neopentylic nature of the primary alcohol After oxidation of the 17-hydroxyl group, lactonisation was achieved according to the Sturtz procedure[19] leading to the hydroxy compound **25** Nitration was carried out under usual conditions[14]



Scheme 4

a) $tBuMe_3SiCl$, DMAP, CH_2Cl_2, b) PDC, CH_2Cl_2, c) $(Me_2N)_2$-P(O)-$\underset{O^-}{CH}$=CH_2, $2Li^+$, d) NO_3H, $(CH_3CO)_2O$

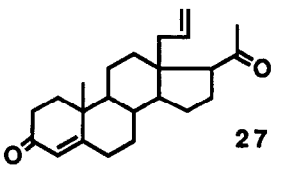
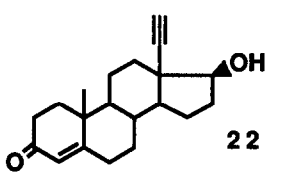
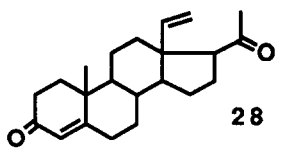
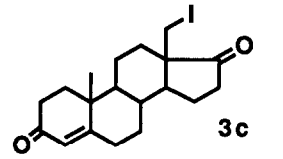
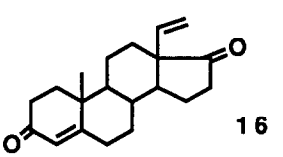
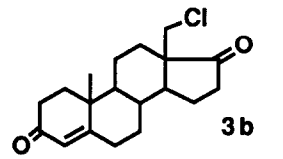
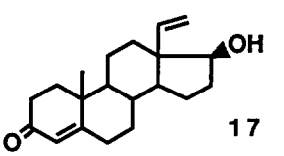
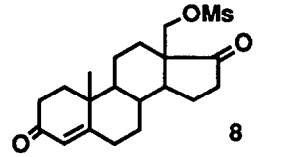
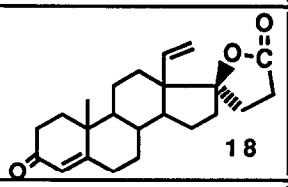
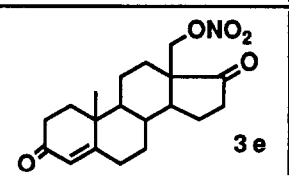
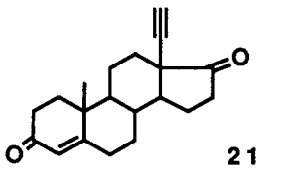
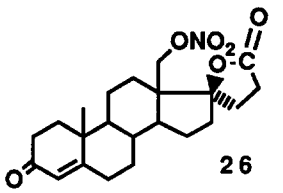
II - BIOLOGICAL ASSAYS

These newly synthesized compounds were tested according to the already described procedure[4] as aldosterone biosynthesis inhibitors The results are given in Table 1 along with those already obtained with 18-vinyl progesterone **27** and 18-methylidene progesterone **28**[4,5] Compound **27** which remains the most active of all the derivatives that we have prepared is taken as a reference

18-unsaturated compounds which are designed to bind to the porphyrin part of the enzyme[3] are more potent than compounds with a good leaving group at C-18 and supposed to bind with the protein Comparison of results obtained with **16**, **17** and **28** shows that the substitution at C-17 does not influence the inhibiting potency

Studies are in progress to determine the effect of these newly synthesized products on the different steroid receptors in the hope that their relatively low power in inhibiting biosynthesis could be compensated by an antagonistic action at the mineralocorticoid receptor level and (or) a negligible affinity to the other receptors

Table 1

Compound	% inhibition of aldosterone biosynthesis (conc, μM)	Compound	% inhibition of aldosterone biosynthesis (conc, μM)
 27	100 (0 8)	 22	85 (13)
 28	50 (11)	 3c	0 (81)
 16	50 (10)	 3b	35 (10)
 17	60 (10)	 8	0 (4 5)
 18	70 (8 7)	 3e	35 (4 5)
 21	80 (12)	 26	30 (8)

ACKNOWLEDGMENTS

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EXPERIMENTAL SECTION

Melting points (mp) were determined on a Kofler apparatus and are uncorrected. ^{13}C and ^{1}H NMR spectra were recorded either on a Jeol FX 90 Q or on a Brucker AC 200 spectrometer in $CDCl_3$ Chemical shifts are expressed in ppm relative to TMS and coupling constants in Hz A first order analysis has been carried out for the methylidene compounds **14** through **19** in order to assign ^{1}H chemical shifts. IR spectra were recorded on a Perkin Elmer 1420 spectrometer Optical rotations were measured with a Perkin Elmer 241 polarimeter IC (NH_3) mass spectra were obtained with a RIBER MAG R 10 10 and high resolution mass spectra on a KRATOS MS 50 spectrometer Analytical samples were prepared by recristallization in a methylene chloride-isopropyl ether mixture Microanalyses were carried out by the "Centre de Microanalyse de l'Université Paris VI" Starting material (pregnenolone) was a gift of the ROUSSEL-UCLAF Company

17β-Hydroxy-18-acetoxy-androst-4-ene-3-one 5

This compound was prepared according to already described methods[10]

mp 170-172° (lit 170-175°)[10]

18-Acetoxy-androst-4-ene-3,17-dione 6

Pyridinium chlorochromate (2 g, 5 3 mmol) was added to 200 mg (0 58 mmol) of **5** dissolved in dry methylene chloride (20 mL) and the mixture was stirred at room temperature for 4 h Ethyl ether was then added, the mixture was filtered on celite, washed with water and concentrated Purification was achieved by thin layer chromatography (cyclohexane / ethylacetate 3 7) yielding 180 mg of pure **6** (90 %)

mp 127-128° (lit 128-129°)[10]

^{1}H NMR (200 MHz) 1 20 (s, 3H, Me19) , 2 05 (s, 3H, CH_3CO) , 4 15, 4 35 (AB, 2H, J = 12 4, CH_2OAc) , 5 70 (s, 1H, H-4)

Anal Calcd for $C_{21}H_{28}O_4$ C, 73 25 , H, 8 13 Found C, 73 05 , H, 8 35

18-Hydroxy-androst-4-ene-3,17-dione 7

2 8 mL of 12N HCl were added to 160 mg (0 46 mmol) of **6** dissolved in methanol (40 mL) and the mixture was refluxed for 1 h The solvent was then concentrated, the residue was extracted with ethyl acetate and treated in the usual way to afford quantitatively **7** (95 %)

mp 200-202°

^{1}H NMR (90 MHz) 1 20 (s, 3H, Me19) , 3 55, 3 90 (AB, 2H, J = 11 2, CH_2-OH) , 5 70 (s, 1H, H-4)

18-(Methylsulfonyloxy)-androst-4-ene-3,17-dione 8

Mesyl chloride (50 µL, 0 76 mmol) was added slowly under argon to a cold (-15°C) mixture of 115 mg (0 38 mmol) of **7** and triethylamine (130 µL, 1 14 mmol) in dry methylene chloride After 1 h at room temperature, 7 mL of a saturated solution of ammonium chloride were added and after conventional work-up 135 mg of crude **8** were obtained (93 %)

mp 180-182°

^{1}H NMR (200 MHz) 1 20 (s, 3H, Me19) , 3 00 (s, 3H, SO_2CH_3) , 4 40 (s, 2H, CH_2-OMs) , 5 75 (s, 1H, H-4)

18-Chloro-androst-4-ene-3,17-dione 3b

Mesylate **8** (38 mg, 0 1 mmol) dissolved in 3 mL of dry HMPA was added to tetrabutylammonium chloride (570 mg, 2 mmol) dried according to Cox et al [23] for 24 h at 45°C under a 0 05 mm Hg vacuum The mixture was then heated under argon at 90°C for 20 h, solid K_2CO_3 was added and conventional work-up (ethyl acetate) followed by chromatography (ethyl acetate / hexane 1/1) yielded pure **3b** (13 5 mg, 43 %)

An analytical sample was obtained after cristallisation in a methylene chloride-isopropyl ether mixture

mp 244-246°

^{1}H NMR (200 MHz) 1 20 (s, 3H, Me19) , 3 35, 3 80 (AB, 2H, J = 12 4, CH_2-Cl) , 5 72 (s, 1H, H-4)

$[\alpha]_D^{20}$ = +168° (c = 0 14, $CHCl_3$)

High resolution mass spectrum calcd for $C_{19}H_{25}O_2{}^{35}Cl$ 320,15431 , found 320,1542

18-Iodo-androst-4-ene-3,17-dione 3c

Mesylate **8** was treated with previously dried tetrabutylammonium iodide according to the above described procedure After 48 h at 90°C, the crude mixture was worked up and chromatography (ethyl acetate / cyclohexane 1/1) yielded 50 % of unreacted mesylate **8** and 30 % of the 18-iodo compound **3c**

mp 189-190°

^{1}H NMR (200 MHz) 1 25 (s, 3H, Me19) , 3 20, 3 45 (AB, 2H, J = 10 5, CH_2I) , 5 72 (s, 1H, H-4)

$[\alpha]_D^{20}$ = +46° (c = 0 13, $CHCl_3$)

High resolution mass spectrum calcd for M-I $C_{19}H_{25}O_2$ 285,1854 , found 285,1851

3,17-Dioxo-androst-4-en-18-yl nitrate 3e

Compound **7** (20 mg, 0 06 mmol) was added slowly to 150 µL of nitric acid in 1 5 mL of acetic anhydride and stirred for 1 h at -5°C The mixture was then poured in iced water, extracted with ethyl acetate, washed with saturated sodium bicarbonate, yielding after evaporation 22 mg of **3e** (96 %)

mp 158-159°

IR 1280 (-ONO_2)

$[\alpha]_D^{20}$ = +130° (c = 0 13, $CHCl_3$)

^{1}H NMR (200 MHz) 1 20 (s, 3H, Me19) , 4 60, 4 61 (AB, 2H, J = 5 2, CH_2-ONO_2) , 5 78 (s, 1H, H-4)

High resolution mass spectrum calcd for $C_{19}H_{25}O_5$ N 347, 1733 , found 347,1727

3,3,17,17-Bis(ethylenedioxy)-androst-5-en-18-ol 9a

A mixture of **6** (490 mg, 1 4 mmol) dissolved in 30 mL of dry benzene, 3 mL of ethyleneglycol and 11 mg of paratoluenesulfonic acid were refluxed for 17 h in a Dean-Stark apparatus

Extraction and usual work-up yielded 546 mg of crude product which was then dissoved in methanol (60 mL) and refluxed with K_2CO_3 (600 mg) and water (0 6 mL) for 4 h

After extraction (ethyl acetate) and work-up, the crude mixture was purified by flash chromatography on silica gel (ethyl acetate / cyclohexane 1/1) yielding 313 mg of pure **9a** (63 %) which was unstable upon recristallization

^{1}H NMR (90 MHz) 0 95 (s, 3H, Me19) , 3.65 (s, 2H, CH_2-OH) , 3 85-3 90 (2s, 8H, O-CH_2-CH_2-O) , 5 25 (m, 1H, H-6)

3,3,17,17-Bis(ethylenedioxy)-18-(methylsulfonyloxy)-androst-5-ene 9b

Mesylate **8** (56 mg, 0 16 mmol) in benzene (6 mL) was refluxed for 14 h with paratoluenesulfonic acid (6 mg) in a Dean-Stark apparatus After conventional work-up and chromatography of the crude mixture on silica gel (cyclohexane / ethyl acetate 3/5), 13 mg of pure **9c** (20 %) were obtained

mp 56 58° (decomp)

^{1}H NMR (90 MHz) 0.98 (s, 3H, Me19) , 2 95 (s, 3H, SO_2CH_3) , 3 90 (bs, 4H, O-CH_2-CH_2-O), 4 05, 4 35 (AB, 2H, J = 10 0, CH_2-OMs) , 5 35 (m, 1H, H-6)

High resolution mass spectrum calcd for $C_{24}H_{36}O_7S$ 468,21817 , found 468,2182

18-Acetoxy-17α-(4-methoxyphenoxy)-androst-4-en-3-one 10

A mixture of **5** (800 mg, 2 31 mmol) dissolved in anhydrous toluene (10 mL), of 4-hydroxyanisol (860 mg, 6 94 mmol), of triphenylphosphine (788 mg, 3 01 mmol) and ethyl azodicarboxylate (474 µL, 3 01 mmol) were refluxed for 18 h After extraction and washing with a saturated solution of sodium hydrogenocarbonate and water, the crude product was chromatographed on silica gel (cyclohexane / ethylacetate 1/1) yielding 845 mg (80 %) of **10**

^{1}H NMR (200 MHz) 1 20 (s, 3H, Me19) , 2 12 (s, 3H, CO-CH_3) , 3 75 (s, 3H, OCH_3) , 3 75, 4 35 (AB, 2H, J =12 3, CH_2OH) , 4 47 (d, 1H, J = 6 7, H-17β) , 5 20 (s, 1H, H-4) , 6 78 (m, 4H, Ar)

3,3-(Ethylenedioxy)-17α-(4-methoxyphenoxy)-androst-5-en-18-ol 11a

The ketone **10** (120 mg, 0 26 mmol) dissolved in 7 5 mL of dry benzene, ethyleneglycol (0 75 mL) and paratoluenesulfonic acid (3 mg) were refluxed for 17 h in a Dean-Stark apparatus After conventional work up the crude mixture was dissolved in methanol (12 mL) and refluxed with K_2CO_3 (150 mg) and water (1 5 mL) for 2 h After extraction the crude mixture was purified by chromatography on silica gel (cyclohexane / ethyle acetate 1/1) yielding 84 mg (77 %) of **11a**

An analytical sample of the compound was obtained by recristallization in a methylene chloride-isopropyl ether mixture

mp 188-190°

^{1}H NMR (200 MHz) 1 02 (s, 3H, Me19) , 3 10, 3 85 (AB, 2H, J = 12 3, CH_2OH) , 3 72 (s, 3H, OCH_3) , 3 95 (s, 4H, O-CH2-CH2-O) , 4 65 (d, 1H, J = 6 1, H-17β) , 5 32 (m, 1H, H-6) , 6 80 (s, 4H, Ar)

3,3-(Ethylenedioxy)-17α-(4-methoxyphenoxy)-18-(methylsulfonyloxy)-androst-5-ene 11b

11a (50 mg, 0 10 mmol) in dry methylene chloride (3 mL) triethylamine (46 µL) and mesyl chloride (17 µL) was stirred at room temperature for 4 h A conventional work up yields 64 mg (99 %) of a crude product which was purified by silica gel chromatography (cyclohexane ethyl acetate 2/1)

mp 85° (decomp)

^{1}H NMR (90 MHz) 1 05 (s, 3H, Me19) , 3.00 (s, 3H, SO_2CH_3) , 3 75 (s, 3H, O-CH_3) , 3 85, 4 45 (AB, 2H, J = 10, CH_2OMs) , 3 90 (s, 4H, O-CH_2-CH_2-O) , 4 50 (d, 1H, J = 5 7, H-17β) , 5 35 (m, 1H, H-6) , 6 75 (s, 4H, Ar)

3,3-(Ethylenedioxy)-androst-5-en-17β,18-diol 12

Compound **5** (1 78 g, 5 1 mmol) was dissolved in dry benzene (200 mL) and refluxed with ethyleneglycol (4 5 mL) and paratoluenesulfonic acid (100 mg) for 15 h After conventional work up the crude mixture of the 18-hydroxy and 18-acetoxy compounds was dissolved in methanol (85 mL) and refluxed for 1 h with K_2CO_3 (1 g) in water (3 mL) Methanol was then evaporated and the residue extracted with ethyl acetate, washed with water and dried under vacuum Crystallization from ethyl ether gave 1 53 g of **12** still containing 20 % of unprotected 3-ketone

^{1}H NMR (90 MHz) 1 00 (s, 3H, Me19) , 3 65-3 90 (m, 7H, CH_2-OH + H-17α + O-CH_2-CH_2-O) , 5 36 (m, 1H, H-6)

3,3-(Ethylenedioxy)-17-oxo-androst-5-en-18-al 13

Oxalyl chloride (2 mL, 21 5 mmol) in CH_2Cl_2 (40 mL) was cooled to -60° under argon and then DMSO (4 mL, 35 mmol) in CH_2Cl_2 (15 mL) was added dropwise After 30 min at -60° **12** (520 mg, 1 5 mmol) in CH_2Cl_2 (20 mL) was added and the mixture was stirred for another 30 min at -60° After addition of triethylamine (15 mL) at -60° and stirring for 2 h at room temperature the mixture was poured in water (200 mL) and 1N HCl was added until neutrality Extraction (CH_2Cl_2) and washing (saturated NH_4Cl and water) afforded crude **13** which was purified by flash chromatography (cyclohexane / ethyl acetate 3/1) yielding 400 mg of pure aldehyde **13** (75 %)

mp 170-172°

^{1}H NMR (90 MHz) 0 95 (s, 3H, Me19) , 3 92 (s, 4H, O-CH_2-CH_2-O) , 5 32 (m, 1H, H-6) , 9 55 (d, 1H, J = 2 8, CHO)

3,3-(Ethylenedioxy)-18a-iodo-18a-homoandrost-5,18(18a)-dien-17-one 14

Iodoform (1 2 g, 2 90 mmol) and aldehyde **13** (500 mg, 1 45 mmol) in anhydrous THF were added slowly at 10° under argon to $CrCl_2$ (1 2 g, 9 86 mmol) in THF The mixture was then stirred for 5 h at room temperature, poured into a saturated $NaHCO_3$ solution (300 mL), extracted with ethyl acetate, washed with water to neutrality and evaporated yielding crude **14** Flash chromatography (cyclohexane / ethyle acetate 4/1) afforded pure **14** (60 %)

mp 162-163°

^{1}H NMR (200 MHz) 1 02 (s, 3H, Me19) , 3 94 (bs, 4H, O-CH_2-CH_2-O) , 5 45 (m, 1H, H-6) , 6 27 (d, 1H, J = 15 4, C=CHI) , 6 68 (d, 1H, J = 15 4, -CH=C)

3,3-(Ethylenedioxy)-18a-homoandrost-5,18(18a)-dien-17-one 15

Zinc powder (4 8 g) in a 10 % HCl suspension was stirred for 15 min at room temperature and then filtered, washed with HCl 10 %, water and then acetone, before being dried under high vacuum CH_3CO_2Cu (480 mg) dissolved in acetic acid (24 mL) was briefly refluxed under argon before addition of the activated zinc powder After a 2-3 min reflux, the coloration disappeared, the powder was filtered under argon, washed with acetic acid, water, acetone and finally ether
Iodo compound **14** (938 mg, 2 mmol) in THF (40 mL) and water (500 µL) were then added under argon and the mixture refluxed for 24 h After filtration on celite, washings with ethyl acetate, 800 mg of crude **15** were obtained Purification was achieved by flash chromatography (cyclohexane / ethyl acetate 2/1) affording 487 mg of pure **15** (71 %)
mp 148-150°
^{1}H NMR (200 MHz) 1 00 (s, 3H, Me19) , 4 00 (bs, 4H, O-CH_2-CH_2-O) , 5 18 (d, 1H, J = 17 9, -C=CH) , 5 28 (d, 1H, J = 12 3, -C=CH) , 5 39 (m, 1H, H-6) , 5 96 (m, 1H, -CH=C)

18-a-Homoandrost-4,18(18a)-dien-3,17-dione 16

Ethylenic compound **15** (50 mg, 0 14 mmol) in acetone (20 mL) was stirred with Amberlite (800 mg) for 24 h After filtration and concentration, crude **16** (47 mg) was obtained and purified by thin layer chromatography ($CHCl_3$ / acetone 1 %) yielding 36 mg (84 %) of pure **16**
mp 150-152°
$[\alpha]_D^{20}$ = +33° (c = 0 43, $CHCl_3$)
^{1}H NMR (200 MHz) 1 15 (s, 3H, Me19) , 5 19 (d, 1H, J = 17 0, -C=CH) , 5 31 (d, 1H, J = 13 2, -C=CH) , 5 72 (bs, 1H, H-4) , 6 01 (m, 1H, -CH=C-)
High resolution mass spectrum calcd for $C_{20}H_{26}O_2$ 298,1933 , found 298,1937

17β-Hydroxy-18a-homoandrost-4,18(18a)-dien-3-one 17

Sodium borohydride (50 mg) was added to 60 mg (0 17 mmol) of crude **15** in ethanol (3 mL) and the mixture was stirred for 90 min at room temperature After addition of 10 % HCl at 0° a conventional work up (ethyl acetate extraction) yielded 78 mg of crude hydroxy compound which was chromatographed on silica gel (cyclohexane / ethyl acetate 1/1) yielding 42 mg of pure hydroxy compound (69,5 %)
^{1}H NMR (200 MHz) 0 95 (s, 3H, Me19) , 3 60 (m, 1H, H-17α) , 3 95 (bs, 4H, O-CH_2-CH_2-O) , 5 28 (d, 1H, J = 17 0, -C=CH) , 5 33 (m, 1H, H-6) , 5 68 (d, 1H, J = 11 2, -C=CH) , 5 71 (m, 1H, -CH=C)
The hydroxycompound was treated with amberlite (500 mg) in acetone (20 mL) for 24 h yielding **17** (36 mg) (98 %)
mp 136-138°
$[\alpha]_D^{20}$ = +124° (c = 0 29, $CHCl_3$)
^{1}H NMR (200 MHz) 1 10 (s, 3H, Me19) , 3 62 (m, 1H, H-17α) , 5 27 (d, 1H, J = 17 0, -C=C-H) , 5 54 (d, 1H, J = 12 9, -C=CH) , 5 72 (m, 2H, H-4 + -CH=C)
High resolution mass spectrum calcd for $C_{20}H_{28}O_2$ 300,2089 , found 300,2088

3-Oxo-17α-homopregn-4,18(18a)-dien-21,17-carbolactone 18

A 1 6 M solution of nBuLi in hexane (10 mL) was cooled at -60° in an acetone-dry ice bath and 2 mL of Sturtz reagent prepared according to Blankenship et al [19] in THF (3 mL) were added

dropwise The temperature was raised to -20° and the dark red solution stirred for another hour 2 mL of this solution were then added under inert atmosphere onto 112 mg (1 06 mmol) of 1,4-diazabicyclo (2 2 2) octane (DABCO) followed by 0 15 mmol (51 3 mg) of **15** The mixture was stirred at 80° for 8 h, then poured in a cold saturated ammonium chloride solution, neutralized with 1N HCl Work up with CH_2Cl_2 afforded 140 mg of crude 3,3-ethylenedioxy compound which was hydrolyzed to the corresponding ketone by treatment for 1 h in ethanol (5 mL) containing 1N HCl (1 mL) After neutralization with a saturated $NaHCO_3$ solution, evaporation of the solvent and extraction with CH_2Cl_2, 65 mg of a yellow oil were obtained Silica gel chromatography (cyclohexane / ethyle acetate 2/1) afforded 10 mg of pure **18** (20 %)

mp 184-188°

IR 1770 (lactone)

$[\alpha]_D^{20}$ = +52° (c = 1 0, $CHCl_3$)

^{1}H NMR (200 MHz) 1 12 (s, 3H, Me19) , 5 20 (d, 1H, J = 18, -C=CH) , 5 42 (d, 1H, J = 11, -C=CH) , 5 65-5 81 (m, 2H, H-4 + -CH=C)

^{13}C NMR (200 MHz) 199 (C-3) , 178 (C-21') , 170 (C-5) , 146 (C-18) , 125 (C-4) , 120 (C-18') , 95 (C-17)

High resolution mass spectrum calcd for $C_{23}H_{30}O_3$ 354,2194 , found 354,2200

3,3,17,17-Bis(ethylenedioxy)-18a-iodo-18a-homoandrost-5,18(18a)-diene 19

A mixture of 14 (400 mg, 0 94 mmol), ethyleneglycol (2 5 mL) and paratoluene sulfonic acid (20 mg) in benzene (25 mL) was refluxed in a Dean Stark apparatus for 24 h After addition of a saturated solution of sodium bicarbonate conventional work up (ethyl acetate) yielded 1 1 g of an oily compound which was purified by chromatography in cyclohexane / ethyl acetate 5/1 containing 2 % of triethylamine 432 mg (90 %) of pure **19** were obtained

mp 162-163°

^{1}H NMR (200 MHz) 0 98 (s, 3H, Me19) , 3 85 (m, 4H, O-CH_2-CH_2-O) , 3 94 (m, 4H, O-CH_2-CH_2-O) , 5 35 (m, 1H, H-6) , 6 24 (d, 1H, J = 15,4, C=CHI) , 6 47 (d, 1H, J = 15,4, CH=C)

18a-Homoandrost-4-en-18(18a)-yne-3,17-dione 21

A catalytic amount of $Fe(NO_3)$ was added to dry liquid ammonia (10 mL) at -50° followed by 10 mg of sodium After 15 min at -50° 140 mg of sodium were added and the dark blue solution stirred for 45 min at -50° After addition of **19** (60 mg, 0 12 mmol) in THF (3 mL) the mixture was kept under refluxing ammonia (-33°) for 3 h After evaporation of the remaining ammonia, ammonium chloride was added, first as a solid and then as a saturated solution, the mixture was neutralized with 1N HCl A conventional work up (CH_2Cl_2) yielded 100 mg of crude **20** which was treated without purification by 1N HCl (1 mL) in ethanol (5 mL) for 4 h After addition of $NaHCO_3$, ethanol was evaporated, the mixture extracted with CH_2Cl_2 yielding an oily product which was purified by silica gel chromatography in cyclohexane / ethyl acetate 3/1 30 mg of pure **21** were then obtained (50 %)

mp 150-152°

IR 3300 (C≡C-H)

^{1}H NMR (200 MHz) 1 20 (s, 3H, Me19) , 2 35 (s, 1H, C≡C-H) , 5 75 (s, 1H, H-4)

^{13}C NMR (200 MHz) 76 32 (C≡C-H) , 80 (-C≡C-H)

High resolution mass spectrum calcd for $C_{20}H_{24}O_2$ 296,1776 , found 296,1780

17β-Hydroxy-18a-homoandrost-4-en-18(18a)-yn-3-one 22

Compound **21** (70 mg, 0 23 mmol), dissolved in 95 mL of a 50/50 CH_3OH/CH_2Cl_2 mixture, was cooled to -60° After addition of sodium borohydride (38 mg) the mixture was stirred for 3 h at -60° The reaction was stopped by addition of acetone and extraction afforded crude **22** (97 mg) which was purified by thin layer chromatography (cyclohexane / ethyl acetate 1/1) yielding 45 mg (64 %) of pure **22**

mp 150-152°

IR 3300 (C≡C-H)

$[\alpha]_D^{20}$ = +116° (c = 0 13, $CHCl_3$)

^1H NMR (90 MHz) 1 10 (s, 3H, Me19) , 3 65 (m, 1H, H-17α) , 5 65 (s, 1H, H-4)

High resolution mass spectrum calcd for $C_{20}H_{26}O_2$ 298, 1933 , found 298,1934

3,3-(Ethylenedioxy)-18-(dimethylterbutylsilyloxy)-androst-5-en-17β-ol 23

A solution of dimethyltertiobutylsilyl chloride (500 mg, 3 08 mmol) and dimethylamino-pyridine (85 mg, 0 56 mmol) in CH_2Cl_2 (8 mL) was added to compound **12** (500 mg, 1 4 mmol) dissolved in CH_2Cl_2 (20 mL) and triethylamine (850 µL, 5 6 mmol) at 0° and the mixture was stirred at room temperature for 1h30 1N HCl was then added until neutrality Extraction (CH_2Cl_2), and washing (saturated NH_4Cl) afforded a crude mixture which was chromatographed on silica gel (cyclohexane / ethyl acetate 7/3) affording 150 mg of the 17,18 bissilyloxy compound, 485 mg of the 18-monosilyloxy derivative **23** (83 %) and 100 mg of the starting compound **12**

mp 80-85° (decomp)

^1H NMR (200 MHz) 0 08 (s, 6H, $SiMe_2$) , 0 9 (s, 9H, SitBu) , 1 02 (s, 3H, Me19) , 3 75 (m, 1H, H-17α) , 3 85 (s, 2H, CH_2-OSi) , 3 93 (s, 4H, O-CH_2-CH_2-O) , 5 35 (m, 1H, H-6)

3,3-(Ethylenedioxy)-18-(dimethylterbutylsilyloxy)-androst-5-en-17-one 24

Pyridinium dichromate (PDC) (3 5 g, 1 mmol) was added to **23** (450 mg, 0 1 mmol) in CH_2Cl_2 (50 mL) and the mixture was stirred at room temperature for 24 h Ether (300 mL) was then added and the suspension was filtered on celite The organic phases were washed with water to neutrality, evaporated and the residue (445 mg) chromatographed in chloroform containing acetone (3 ‰ v/v) yielding **24** (350 mg, 80 %)

mp 122-124°

^1H NMR (200 MHz) 0 08 (s, 6H, $SiMe_2$) , 0 8 (s, 9H, SitBu) , 1 02 (s, 3H, Me19) , 3 65, 3 80 (AB, 2H, J = 9, CH_2-OSi) , 3 90 (s, 4H, O-CH_2-CH_2-O) , 5 35 (m, 1H, H-6)

18-Hydroxy-3-oxo-17α-pregn-4-ene-21,17-carbolactone 25

The reaction was performed as described before for compound **18** with 178 mg of **24** (0 37 mmol) yielding 240 mg of an orange oil which was purified by flash chromatography on silica gel in a chloroform-acetone 8/2 mixture yielding 20 mg of the 17-keto compound and 50 mg of **25** (38 %)

IR 1775 (lactone)

^1H NMR (200 MHz) 1 15 (s, 3H, Me19) , 3 8 (m, 2H, CH_2-OH) , 5 7 (s, 1H, H-4)

18-Hydroxy-3-oxo-17α-pregn-4-en-21,17-carbolactone, 18-nitrate 26

Nitric acid (200 µL) in acetic anhydride (1 5 mL) were added to a cold (-5°) solution of **25** (50 mg, 0 14 mmol) in acetic anhydride (2 5 mL) The mixture was stirred for 2 h at -5° and poured into an iced $NaHCO_3$ solution After extraction with methylene chloride, a yellow oily product was obtained which was chromatographied in a 9-1 mixture of chloroform and acetone, yielding 20 mg (35 %) of **26** as an oil

IR 1770 (lactone), 1280 (-ONO_2)

^1H NMR (200 MHz) 1 20 (s, 3H, Me19) , 4 62, 4 67 (AB, 2H, J = 8, CH_2-ONO_2) , 5 74 (s, 1H, H_4)

High resolution mass spectrum calcd for $C_{22}H_{29}O_6N$ 403,1995 , found 403,2001

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