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SYNTHESIS OF NEW INHIBITORS OF ALDOSTERONE BIOSYNTHESIS

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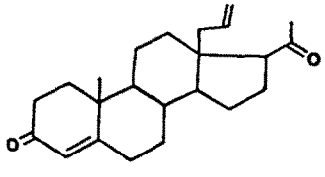
Abstract : The synthesis of 18 vinyl and 18 ethynylprogesterone 1 and 2 is described. The reported data emphasize the decisive role played by the protective group on carbon 3 in the course of reactions taking place at the angular 18 methyl group.
Compounds 1 and 2, designed as kcat inhibitors of aldosterone biosynthesis late step show substantial *in vitro* activity.

Aldosterone is a potent mineralocorticoid which regulates body fluids electrolyte balance by promoting potassium elimination and sodium retention (1). An aldosterone overproduction leads to oedematous diseases and hypertension. These disorders are clinically treated by aldosterone antagonists at the receptor level. The drugs of this therapeutic class currently on the market, belong to the spironolactone series (2). However, their clinical use is often limited because of the side effects attributed to their antiandrogenic and progestational properties (3). Efforts directed to develop aldosterone antagonists devoid of these endocrinal side effects, met with little success.

With a view of developing a novel class of drugs, we investigated the specific inhibition of aldosterone biosynthesis by using the concept of mechanism based (or kcat) inhibitors (4).

Sequential hydroxylations on carbons 21, 11 and 18 by cytochrome P450 dependent monooxygenases constitute the last steps of aldosterone biosynthesis in mammal adrenals (5). It is necessary to intervene at the final step (i.e. to inactivate 18 hydroxylase) to avoid interferences with other hormones biosynthetic pathways. According to literature data on cytochrome P450 inhibition (6) different classes of molecules can be designed as potential kcat inhibitors of that monooxygenase : they are progesterone derivatives substituted on 18 methyl group. We report here the synthesis of derivatives belonging to one of these classes, 18 unsaturated compounds 1 and 2 (Scheme I).



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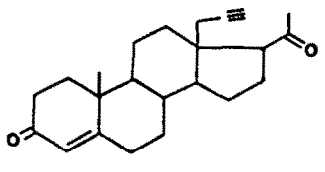
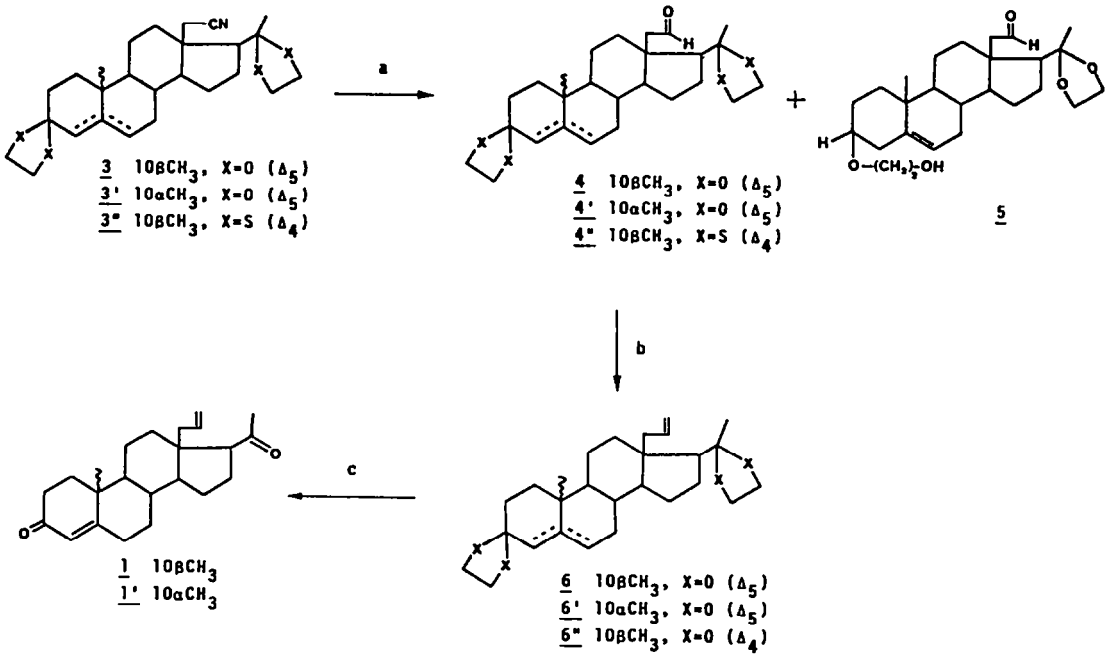


2

Scheme I

Compound 1 has not been reported but the preparation of the corresponding 10α methyl isomer 1' has been described (7) (scheme II). We failed to obtain the 10 β isomer 1 by this route : compound 3 is easily prepared by using the method described by Kalvoda et al. (8) but we could not reduce it into the corresponding aldehyde with a satisfactory yield, as already observed by others (9) : by using DIBAL-H, we isolated some aldehyde 4 (50 %), starting material and also a small amount (6 %) of compound 5 : the reduction of acetals by DIBAL-H, known to occur at high temperature (10) is surprising under the mild conditions (0°C) we used.



a: Dibal-H, toluene ; b: $\Phi_3P{=}CH_2$, THF ; c: H_3O^+

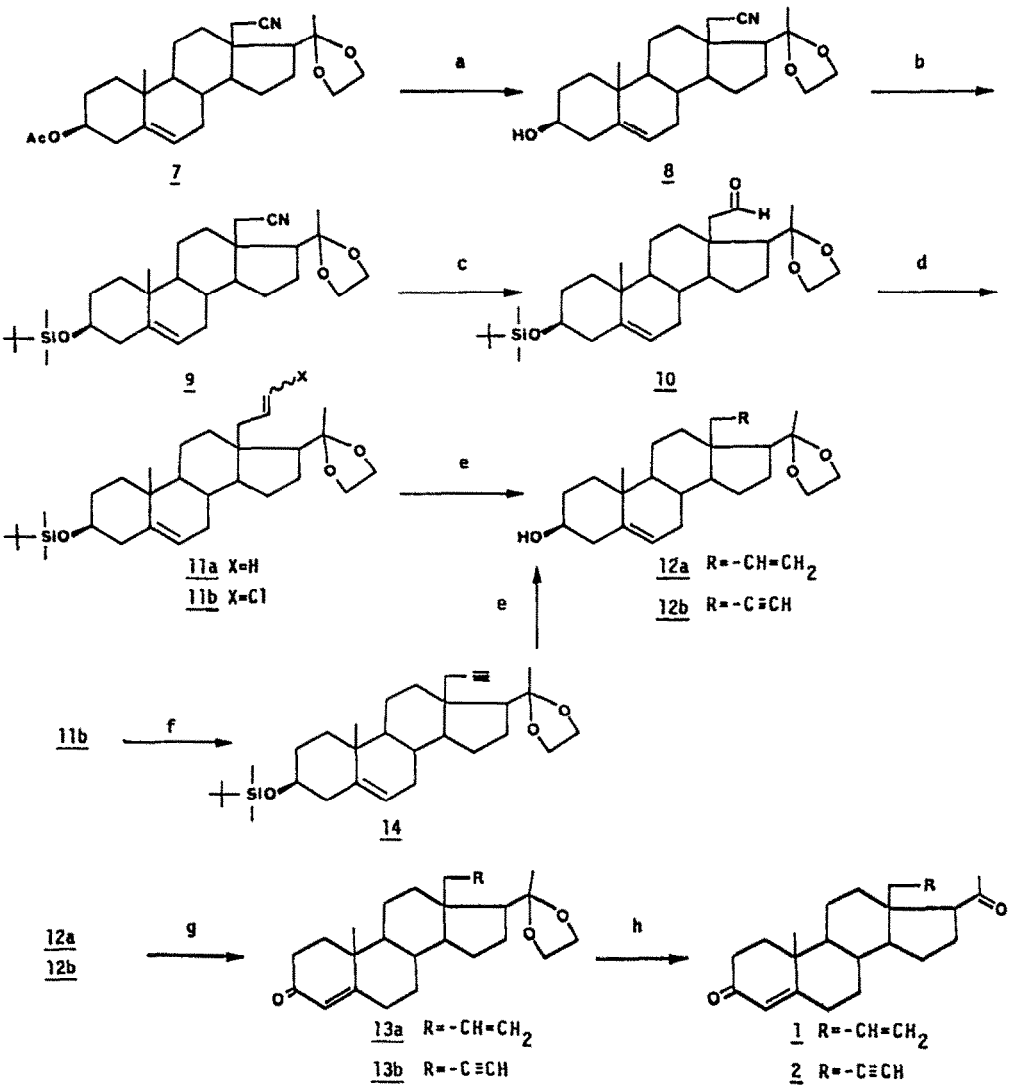
Scheme II

Wittig reaction on compound 4 proceeded with a very low yield (~ 10 %). Use of the lithioylide Φ_3P = CHLi introduced by Corey et al. (11) for highly crowded substrates did not improve this yield. Replacement of the 1,3 dioxolane by the corresponding 1,3 dithiolane derivative allows a quantitative reduction of compound 3" into aldehyde 4". However, Wittig reaction proceeded again in that series with a very poor yield. Since hydrolysis of 1,3 dithiolane raises many difficulties (low yield, oxidation on carbon 6) we had to turn to other protective groups.

The synthesis of derivative 1 was achieved after changing the carbon 3 oxidation state (scheme III). Treatment of compound 7 with DIBAL-H in toluene leads to an unseparable mixture of nitrile 8 and of the corresponding aldehyde, as shown by ^1H and ^{13}C spectroscopy. Finally we saponified the 3-acetyl group and replaced it by a tertiobutyldimethylsilyl group. In that series, reduction of compound 9 proceeds quite well (94 %) and the Wittig reaction leads to the olefin 11a with a satisfying yield.

From these results, it appears that the nature of the protective group on carbon 3 has a decisive importance on reactions taking place at remote positions, such as 18 methyl group. Such long range effects have already been observed in the steroid chemistry field (12). They are poorly understood but they are assumed to be transmitted by conformational distorsions of the polycyclic system. As far as we know, we describe here the first exemple of long range effects transmitted outside of the cyclic system, at an angular methyl group.

Subsequent synthesis of compound 1 (cleavage of the tertiobutyldimethylsilyl ether, Oppenauer oxidation and hydrolysis of the 20 ketal group) proceeded smoothly (scheme III).



Scheme III

The synthesis of the acetylenic derivative **2** was achieved according to a similar pathway. The Merrell Dow Research Group recently described (13, 14) the synthesis of a closely related compound, substituted at the 11 β position by an hydroxyl group : this substitution played a decisive role in the synthesis since it facilitated the 18 cyano group reduction by intramolecular formation of a lactone ring. For preparing compound **2** we used the above described intermediate **10**. With this 3 β tertiobutyldimethylsilyloxy protective group, the Wittig olefination with chloromethyltriphenylphosphonium chloride proceeded with a good yield, leading to the formation of both Z and E isomers **11b**. No reaction occurred when compound **4**, in the 3-ethylenedioxy series, was treated under the same conditions.

We observed a very different behaviour of these E and Z isomers in chloroformic

solution at room temperature. The former compound which exhibits a large coupling constant (J = 15 Hz) between the trans ethylenic protons (characteristic of the E configuration) is quite stable whereas the 20 ketal group of the latter is rapidly hydrolysed leading to the corresponding 20 keto steroid. We have no good explanation for that.

The E compound does not react with lithium diisopropylamide, whereas the Z isomer, in the same conditions, leads to the elimination compound **14**. By using a less hindered base, sodamide, the Z + E mixture was converted to derivative **14** and the synthesis of compound **2** was achieved according to scheme III, using the sequence already described.

Derivatives **1** and **2** have been tested as aldosterone biosynthesis inhibitors, on rat adrenal homogenate. Compounds **1** and **2** inhibit respectively 100 % and 75 % of aldosterone biosynthesis at 0.8 μ M, as reported elsewhere (15). Work is in progress to determine the nature of the inhibition and synthesis of other inhibitors is underway.

ACKNOWLEDGMENTS

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EXPERIMENTAL SECTION

Melting points were determined on a Kofler apparatus and were uncorrected except for compound **1** and **2** (Perkin Elmer DSC2 differential microcalorimeter) (16).

^{13}C and ^{1}H NMR spectra were recorded either on a Jeol FX90Q or on a Bruker AC200 spectrometer in $CDCl_3$. Chemical shifts are reported as values (ppm) relative to TMS.

I.R. spectra were recorded on a Philips SP3-100.

Optical rotations were measured with a Perkin Elmer 241 polarimeter.

3 β-acetoxy-18-cyano-20,20-ethylenedioxy-pregn-5-ene **7**

Ethylene glycol (7.2 ml) and paratoluenesulfonic acid (54 mg) were added to 1.13 g of 3 β-acetoxy 18-cyano pregn-5-ene-20-one (8) dissolved in toluene (72 ml) and the solution was refluxed for 15 hours in a Dean-Stark apparatus. The mixture was neutralized with dilute aqueous sodium bicarbonate and worked up in the usual way. The residue was recrystallized from dichloromethane-diethylether 1:1 to give 1.13 g of **7** (90 %).

mp 185-187°C.

NMR 1.0 (s, 3H, Me19) ; 1.3 (s, 3H, Me21) ; 2.1 (s, 3H, CH_3CO) ; 4.05 (m, 4H, $O-CH_2-CH_2-O$) ; 4.6 (m, 1H, H-3) ; 5.35 (m, 1H, H-6).

3 β-hydroxy-18-cyano-20,20-ethylenedioxy-pregn-5-ene **8**

A 1.5 M solution of potassium carbonate (15 ml) was added to 3 g of **7** in methanol (300 ml) and boiled for 3 hours. The mixture was then concentrated **in vacuo**, the residue dissolved in dichloromethane, washed with water, dried over sodium sulfate and evaporated to dryness yielding 2.46 g of **8** (95 %).

mp 221-222°C.

NMR 1.0 (s, 3H, Me19) ; 1.3 (s, 3H, Me21) ; 3.5 (m, 1H, H-3) ; 4.0 (m, 4H, $O-CH_2-CH_2-O$) ; 5.35 (m, 1H, H-6).

3 β-tertiobutyldimethylsilyloxy-18-cyano-20,20-ethylenedioxy-pregn-5-ene **9**

To a solution of **8** (2.4 g) in dry dichloromethane (65 ml) were added N,N-dimethylaminopyridine (400 mg), tertiobutyldimethylsilyl chloride (1.63 g) and 1.63 ml of anhydrous triethylamine (17). The mixture was stirred at room temperature for 60 hours and extracted with dichloromethane. After usual work-up, **9** was obtained quantitatively.

mp 196-197°C.

NMR 0.05 (s, 6H, Me_2Si) ; 0.9 (s, 9H, tBuSi) ; 1.0 (s, 3H, Me19) ; 1.3 (s, 3H, Me21) ; 3.5 (m, 1H, H-3) ; 3.9 (m, 4H, O-CH_2-CH_2-O) ; 5.3 (m, 1H, H-6).

3 β-tertiobutyldimethylsilyloxy-18-carboxaldehyde-20,20-ethylenedioxy-pregn5-ene **10**

A 1.5 M DIBAL-H solution in toluene (5.56 ml) was added dropwise to a solution of 3.1 g of **9** in dry toluene (115 ml) at 0°C under argon. After stirring for 4 hours at room temperature, the mixture was hydrolysed with 12 ml of 0.05 M hydrochloric acid. The precipitate was filtered off and the filtrate worked up as usual, yielding 2.94 g of **10** (94 %). An analytical sample was obtained after flash chromatography on silica gel (cyclohexane-ethyl acetate 1:1).

mp 198-200°C.

NMR 0.02 (s, 6H, Me_2Si) ; 0.85 (s, 9H, tBuSi) ; 0.96 (s, 3H, Me19) ; 1.26 (s, 3H, Me21) ; 3.45 (m, 1H, H-3) ; 3.85 (m, 4H, O-CH_2-CH_2-O) ; 5.26 (m, 1H, H-6) ; 9.8 (t, 1H, HC = O).

3 β-tertiobutyldimethylsilyloxy-18-vinyl-20,20-ethylenedioxy-pregn-5-ene **11a**

To a suspension of methyltriphenylphosphonium bromide (2.6 g) in 60 ml of anhydrous, freshly distilled THF was added dropwise 4.6 ml of a 1.6 M butyllithium solution in hexane. The red coloured ylide solution was stirred for 1.5 hours at 20°C and then a solution of **10** (750 mg) in 20 ml of anhydrous THF was added at 0°C. After heating at 66°C for 12 hours, the mixture was poured onto ice. The organic layer was washed successively with 1N hydrochloric acid, saturated sodium bicarbonate solution and water. After removal of the solvent in vacuo the residue was flash chromatographied on silica gel (cyclohexane - ethyl acetate 3 %) to yield 567 mg of **11a** containing some triphenylphosphine oxide. 250 mg of **10** was recovered unreacted.

An analytical sample was obtained after chromatography on silica gel (cyclohexane - ethyl acetate 5:1).

mp 124-126°C.

NMR 0.03 (s, 6H, Me_2Si) ; 0.86 (s, 9H, tBuSi) ; 1.0 (s, 3H, Me19) ; 1.33 (s, 3H, Me21) ; 3.45 (m, 1H, H-3) ; 3.95 (m, 4H, O-CH_2-CH_2-O) ; 5.3 (m, 1H, H-6) ; [4.93 (broad s, 1H) ; 5.0 (broad d, 1H) ; 5.95-6.25 (m, 1H) -CH = CH_2].

3 β-hydroxy-18-vinyl-20,20-ethylenedioxy-pregn-5-ene **12a**

520 mg of crude **11a** were dissolved in 8 ml of a 1 M solution of tetrabutylammonium fluoride in THF (18). After stirring overnight at 20°C, the mixture was diluted with dichloromethane and worked up as usual. Chromatography of the residue on silica gel (cyclohexane - ethyl acetate 1:1) yielded 262 mg of **12a**.

mp 156-158°C.

NMR 1.05 (s, 3H, Me19) ; 1.35 (s, 3H, Me21) ; 3.55 (m, 1H, H-3) ; 3.95 (m, 4H, O-CH_2-CH_2-O) ; 5.85 (m, 1H, H-6) ; [4.9 (broad s, 1H) ; 5.05 (broad d, 1H) ; 5.8-6.3 (m, 1H) -CH = CH_2].

18-vinyl-20,20-ethylenedioxy-pregn-4-ene-3-one **13a**

To a solution of **12a** (717 mg) in dry toluene (74 ml) was added N-methyl piperidone (6.1 ml) and the solution was boiled in a Dean Stark apparatus (19). The first condensed fractions (10 ml) were discarded and aluminium isopropoxide (1.2 g) in toluene (6.5 ml) was added under argon. After heating at 110°C for 5 hours, the mixture was diluted with toluene, washed with a 1 % sulfuric acid solution and water to neutrality. The crude product was chromatographied on silica gel (cyclohexane - ethyl acetate 3:1) yielding 502 mg of **13a** (67 %).

mp 153-155°C.

NMR 1.2 (s, 3H, Me19) ; 1.35 (s, 3H, Me21) ; 3.92 (m, 4H, O-CH_2-CH_2-O) ; 5.72 (m, 1H, H-4) ; 4.92 (broad s, 1H) ; [5.1 (broad d, 1H) ; 5.8-6.35 (m, 1H) -CH = CH_2].

18-vinyl-pregn-4-en-3,20-dione **1**

A suspension of **13a** (492 mg) and IRN-77 Amberlite resin (6 g) in acetone (130 ml) was stirred for 24 hours at room temperature (20). The residue was purified by chromatography on silica gel (cyclohexane - ethyl acetate 3:1), recrystallized twice from dichloromethane-isopropylether to yield 260 mg of **1** (59 %).

mp (corrected) 95°C. $[\alpha]_D^{25}$ = +211° (c = 0.46, CH_2Cl_2).

NMR 1.25 (s, 3H, Me19) ; 2.2 (s, 3H, Me21) ; 5.75 (m, 1H, H-4) ; [4,9 (broad s, 1H) ; 4.97 (broad d, 1H) ; 5.2-5.7 (m, 1H) -CH = CH_2].

Anal ($C_{23}H_{32}O_2$) C,H.

3 β-tertiobutyldimethylsilyloxy-18-chlorovinyl-20,20-ethylenedioxy-pregn-5ene **11b**

To a cooled (0°C) suspension of chloromethyltriphenylphosphonium chloride (780 mg) in anhydrous THF (10 ml) were added dropwise 1.75 ml of a 1.6 M butyl lithium solution in hexane and the brownish red solution was stirred at room temperature for 3 hours. 405 mg of **10** in anhydrous THF were then added at 0°C. After stirring overnight at room temperature, the solution was diluted with icewater and THF removed under vacuum. The residue, dissolved in dichloromethane, was worked up in the usual way. The crude product (1.7 g) was purified by flash chromatography on silica gel (cyclohexane - ethyl acetate 9:1) to give 337 mg of the Z and E isomers **11b**, containing some triphenylphosphine oxide. 125 mg of unreacted **10** (31 %) was also recovered.

NMR 0.02 (s, 6H, Me_2Si) ; 0.85 (s, 9H, tBuSi) ; 1.0 (s, 3H, Me19) ; 1.3 (s, 3H, Me21) ; 3.45 (m, 1H, H-3) ; 3.9 (m, 4H, O-CH_2-CH_2-O) ; 5.26 (m, 1H, H-6) ; 5.75-6.25 (m, 2H, CH=CH-Cl).

3 β-tertiobutyldimethylsilyloxy-18-ethynyl-20,20-ethylenedioxy-pregn-5-ene **14**

Sodium (430 mg) was added to 20 ml of condensed, redistilled ammonia at -50°C in the presence of a catalytic amount of ferrous nitrate. After stirring at -50°C for 1 hour, 524 mg of **11b** in 2.7 ml of anhydrous THF was added dropwise and the mixture was allowed to react for 3 hours at -33°C. Ammonia was then removed. Solid ammonium chloride (1.5 g) was added and the solution was diluted with dichloromethane. After addition of aqueous ammonium chloride, the mixture was extracted with dichloromethane and worked up in the usual way, yielding 475 mg (97 %) of the acetylenic compound **14**. An analytical sample was obtained after chromatography (cyclohexane - ethyl acetate 3:1)

mp 170-172°C - IR ($CHCl_3$) 3320 cm^{-1} ($\nu_{C \equiv C-H}$).

NMR 0.05 (s, 6H, Me_2Si) ; 0.9 (s, 9H, tBuSi) ; 1.05 (s, 3H, Me19) ; 1.42 (s, 3H, Me21) ; 3.45 (m, 1H, H-3) ; 3.95 (m, 4H, O-CH_2-CH_2-O) ; 5.29 (m, 1H, H-6).

3 β-hydroxy-18-ethynyl-20,20-ethylenedioxy-pregn-5-ene **12b**

To 500 mg of **14** dissolved in 6 ml of THF was added 3 ml of a 1.0 M tetrabutylammonium fluoride solution in THF and the mixture was stirred overnight at 20°C. After evaporation of the THF, the residue was dissolved in dichloromethane and worked up in the usual way. The crude product was purified by flash chromatography on silica gel (cyclohexane - ethyl acetate 2:1) to yield 270 mg of **12b** (70 %).

mp 198-200°C.

IR ($CHCl_3$) 3320 cm^{-1} ($\nu_{C \equiv CH}$).

NMR 1.0 (s, 3H, Me19) ; 1.45 (s, 3H, Me21) ; 3.5 (m, 1H, H-3) ; 4.0 (m, 4H, O-CH_2-CH_2-O) ; 5.36 (m, 1H, H-6).

18-ethynyl-20,20-ethylenedioxy-pregn-4-en-3-one **13b**

A solution of **12b** (270 mg) and N-methyl piperidone (2.23 ml) in dry toluene (27 ml) was refluxed under argon in a Dean-Stark apparatus. The first 4 ml of the distillate were discarded ; aluminium isopropoxide (370 mg) in toluene (2.3 ml) was added dropwise and refluxing was continued for 5 hours. The mixture was extracted with toluene, washed with a solution of dilute sulfuric acid and water, yielding 210 mg of **13b** (77 %).

NMR 1.2 (s, 3H, Me19) ; 1.4 (s, 3H, Me21) ; 4.0 (m, 4H, O-CH_2-CH_2-O) ; 5.7 (s, 1H, H-4).

18-ethynyl-pregn-4-en-3,20-dione **2**

A suspension of **13b** (210 mg) and IRN-77 amberlite resin (3 g) in acetone (55 ml) was stirred overnight at 20°C. After filtration and concentration of the filtrate the crude product was chromatographied on silica gel (chloroform - acetone 95:5) to give 156 mg of **2** (84 %). High purity sample was obtained by recrystallization in dichloromethane-isopropyl ether.

mp (corrected) 170°C $[\alpha]_D^{25}$ = + 198° (c = 0.3, CH_2Cl_2).

IR ($CHCl_3$) 3320 cm^{-1} ($\nu_{C \equiv CH}$).

^1H NMR 1.16 (s, 3H, Me19) ; 2.24 (s, 3H, Me21) ; 5.72 (s, 1H, H-4).

^{13}C NMR 81.16 C ≡ C-H 71.60 C ≡ C-H.

Anal ($C_{23}H_{30}O_2$) C, H.

3,20-dioxo-pregn-5-ene-18-carboxaldehyde-3,20-bisethylene ketal **4** and 3-(2-hydroxyethyl)oxy-20-oxo-preg-5-ene-18-carboxaldehyde-20-ethylene ketal **5**

To 157 mg of **3** in dry benzene (5 ml) at 10°C under argon, a 1.5 M DIBAL-H solution in toluene (0.3 ml) was added. After stirring for 4 hours at 10°C, the mixture was hydrolysed with 0.05 M hydrochloric acid and worked up as usual. The crude product was chromatographied on silica gel (hexane-ethyl acetate 2:1) to yield 90 mg of a mixture of **3** + **4** and 10 mg (6 %) of **5**.

4 (purified by recristallisation)

mp 163-165°C.

NMR ^{1}H 1.0 (s, 3H, Me19) ; 1.3 (s, 3H, Me21) ; 3.7-4.1 (m, 8H, O-CH_2-CH_2-O) ; 5.35 (m, 1H, H-6) ; 9.85 (t, 1H, HC=O).

NMR ^{13}C 109.3 (C-3) ; 111.1 (C-20) ; 121.6 (C-6) ; 140.3 (C-5) ; 204.6 (CHO).

Mass spectrum (C.I./NH_4^+) : m/z 431 $(M + H)^+$; m/z 448 $(M + NH_4)^+$

5

mp 133-135°C.

NMR ^{1}H 1.0 (s, 3H, Me19) ; 1.3 (s, 3H, Me21) ; 3.5-4.1 (m, 4H, O-CH_2-CH_2-O) ; 5.35 (s broad, 1H, H-6) ; 9.85 (t, 1H, HC=O).

NMR ^{13}C 111.0 (C-20) ; 121.0 (C-6) ; 147.4 (C-5) ; 204.5 (CHO).

Mass spectrum (C.I./NH_4^+) : m/z 433 $(M + H)^+$.

3,3-,20,20-Bis(ethylenedithio)-18-carboxaldehyde-pregn-4-ene **4"**

0.16 ml of a 1.5 M solution of DIBAL-H in toluene was added at 10°C under argon to a 2 ml solution of **3"** (100 mg) in dry benzene and the mixture was stirred at 10°C for 3 hours. Work up was achieved according to the previously described procedure, yielding 10 mg of crude **4"**.

IR ($CHCl_3$) 1710 cm^{-1} ($\nu_{C=O}$).

NMR 1.05 (s, 3H, Me19) ; 1.97 (s, 3H, Me21) ; 3.1-3.5 (m, 8H, S-CH_2-CH_2-S) ; 5.5 (s, 1H, H-4) ; 10.1 (t, 1H, CHO).

3,3-20,20-Bis(ethylenedithio)-18-vinyl-pregn-4-ene **6"**

1.75 ml of a 1.6 M BuLi solution in hexane was added at 0°C under argon to 643 mg of Φ_3PCH_2Br in 10 ml of dry THF. After 2 hours at room temperature, 180 mg of **4"** in 25 ml of dry THF were added dropwise. The mixture was stirred at room temperature for 3 hours and refluxed for 48 nours. The cooled solution was poored into ice. After extraction with a 3:1 ether-methylene chloride mixture, the organic layer was successively washed with cooled 1 N HCl, saturated $NaHCO_3$ solutions and water, yielding 740 mg of crude product. After silica gel chromatography **4"** (45 %) and 24 mg of pure **6"** were recovered.

mp 147-148°C.

NMR 1.0 (s, 3H, Me19) ; 1.95 (s, 3H, Me21) ; 3.1-3.5 (m, 8H, S-CH_2-CH_2-S) ; 5.5 (s, 1H, H-4) ; 5.7-6.3 (m, 1H, CH_2-$\underline{CH}$=CH_2) ; 4.98 (s broad, 1H, CH=$C\underline{H}_2$) ; 5.15 (s broad, 1H, CH=$C\underline{H}_2$).

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