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Full Papers

Synthesis of 6β-methyl analogues of mifepristone, new selective antiprogestagens

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Abstract. A new strategy is described to synthesize 19-norsteroids with substituents at C-6, C-11 and C-17. The strategy is applied to the synthesis of 11β-[4-(dimethylamino)phenyl]-6β-methyl-4′,5′—-dihydrospiro[estra-4,9-diene-17,2′-(3′H)-furan]-3-one (**15**, Org 31710) and some related compounds. These compounds have been shown to have potent antiprogestational activity and, compared to previously described 11-aryl-19-norsteroids, much reduced affinity for the glucocorticoid receptor.

Introduction

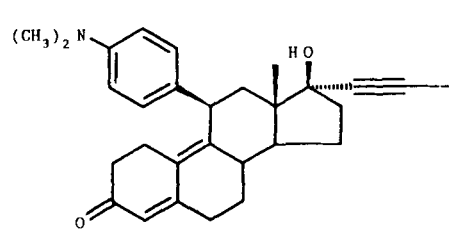
Although 11-aryl-substituted steroids have been known for some time, it is only in the last decade that this class of compounds has been studied intensively. The reason for this is the discovery that these compounds possess strong antihormonal activity[1]. Thus, mifepristone (**1**), the prototype and best studied example, has been shown to have a surprisingly high affinity for the progesterone receptor, but to act as a pure antagonist[2].

Based on its antiprogestational activity, mifepristone was developed as an abortifacient drug for the voluntary termination of pregnancy. For this purpose, mifepristone is administered in conjunction with a small dose of prostaglandin. Despite controversy surrounding its introduction, mifepristone is presently widely used in countries such as France[3]. Mifepristone was shown to hold considerable promise for other therapeutic applications, in particular, for treatment of certain hormone-dependent tumours, such as breast cancer[4]. However, mifepristone is not only an antagonist of progesterone (**2**) but also of the glucocorticoid hormones, such as cortisol (**3**), due to its extremely high affinity for the glucocorticoid receptor. This antiglucocorticoid activity is believed to cause adverse effects (such as nausea, weight loss, etc.) when mifepristone is administered for prolonged periods of time, as is required in cancer therapy. Therefore, we, and others[5,6], have searched for more selective compounds devoid of antiglucocorticoid activity.

The first promising result was our finding that a 6β-methyl substituent, but not a 6α-methyl substituent, caused a substantial reduction in affinity for the glucocorticoid receptor, whereas affinity for the progesterone receptor was unaffected[7]. In order to further improve the dissociation between anti-progestational and antiglucocorticoid activity, modification of the substituent at C-17 was also required. Therefore, a flexible synthesis had to be developed to allow introduction of:

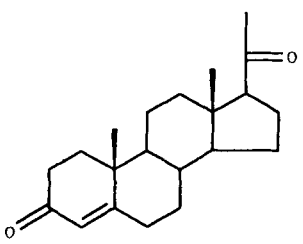
(1) a 6β-methyl group;
(2) an 11β-aryl group;
(3) various 17 substituents.

Ultimately, this led to the discovery of Org 31710 (**15**) as a compound having the desired profile[8]. Independently, a group at Roussel-Uclaf discovered that a spirotetrahydrofuran at C-17 causes a marked increase in the antiprogestational/antiglucocorticoid ratio[6].



1

mifepristone (RU 486)



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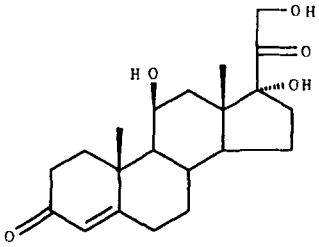

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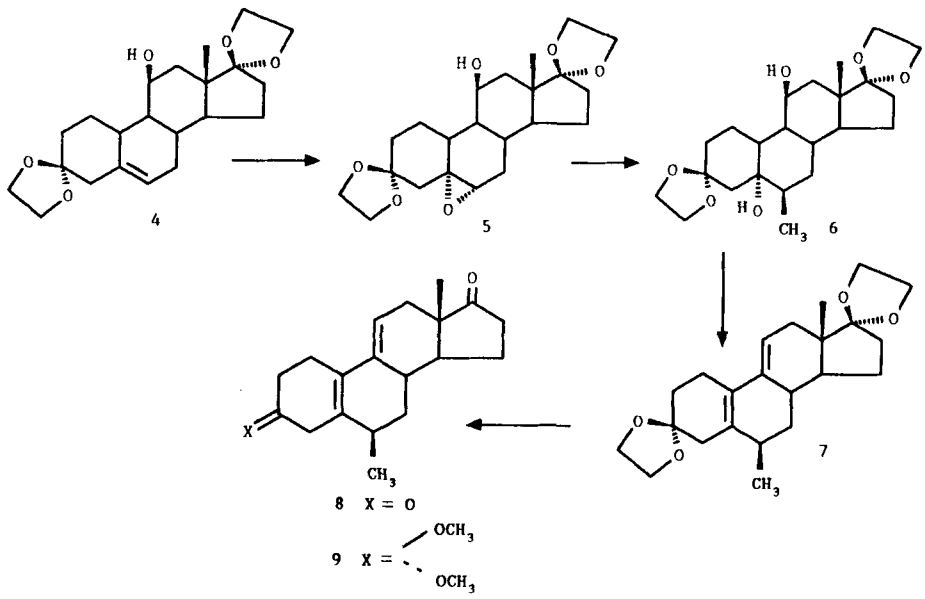


Scheme 1

Results

Synthesis of 6β-methyl intermediate (**9**)

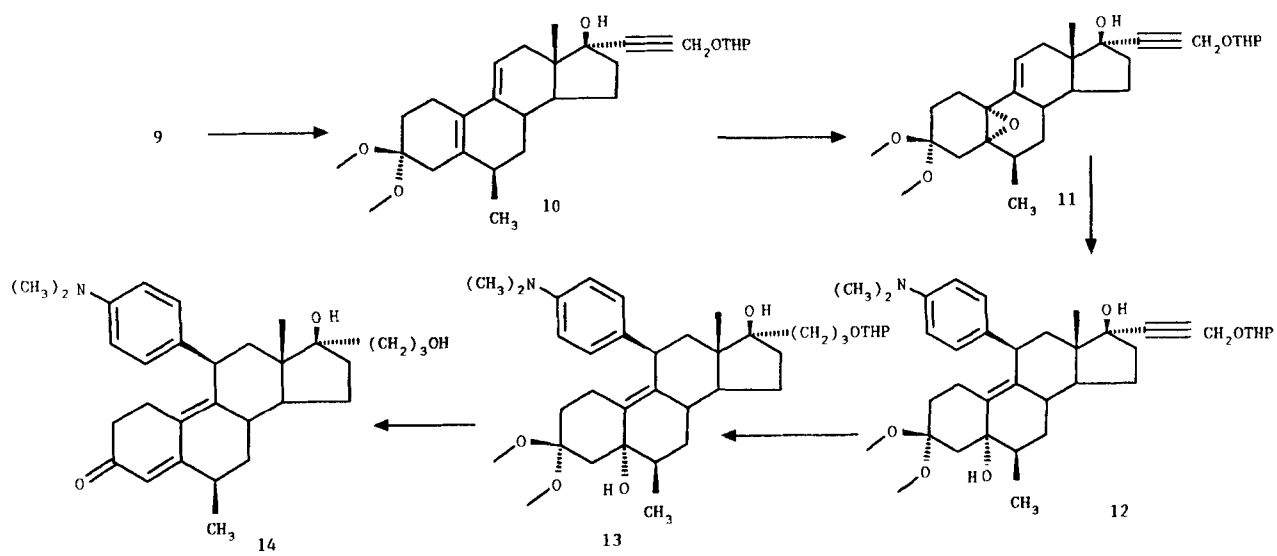
A convenient starting material for our target compounds is the 11β-hydroxy steroid **4**, an intermediate in the synthesis of the widely used progestagen desogestrel[9], which has the proper functional groups for introduction of substituents at C-6 and C-11. Thus, epoxidation of **4** gave the 5α,6α-epoxide **5** as the major product, which upon reaction with methylmagnesium chloride in THF gave the desired 6β-methyl product **6** in high yield[10].

The diol **6** could be dehydrated to the conjugated diene **7** in a single step. After considerable experimentation, best results were obtained with excess of thionyl chloride in pyridine at 10°C which gave **7** in 57% yield as a colourless oil. In order to introduce the 17-substituent monoprotection of the 3-oxo group was required. This was achieved by mild hydrolysis of **7** (70% aqueous acetic acid, 50°C), which gave the unstable deconjugated diketone **8** as a colourless solid. Subsequent reaction of **8** with methanol in the presence of malonic acid (pK_a 2.8) gave selectively the monoacetal **9**, in 68% yield (based on **7**). The monoacetal **9** possesses the proper functional groups to introduce a variety of substituents at C-17 and C-11, as exemplified in the next section.

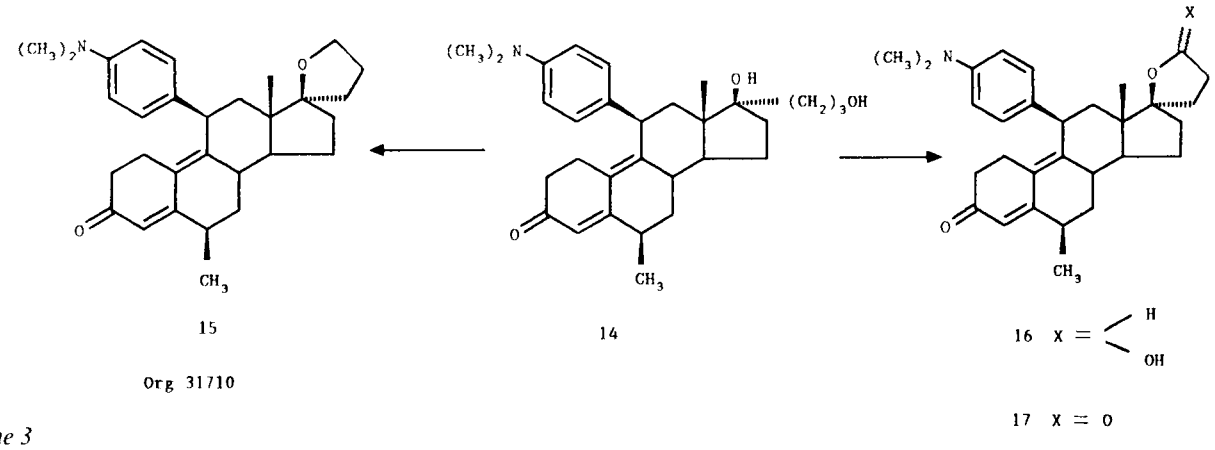
Synthesis of 6β-methyl-11β-aryl steroid (**14–17**)

For the introduction of a 17α-(3-hydroxypropyl) substituent in a steroid, a number of methods have been described, the most straightforward being the reaction of a 17-kerosteroid with the Grignard or lithio reagent derived from 3-bromo-1-propanol, in which the alcohol function is protected as an ether (e.g., ethoxyethyl ether)[11]. In our hands, this gave poor yields when **9** was used as a starting material, probably due to sluggishness of the addition and competing enolization of the 17-ketone. Therefore, we used the more circuitous route described by *Arth* et al.[12]. Thus, when **9** was condensed with the Grignard reagent derived from the 2-tetrahydropyranyl (THP) ether of 2-propyn-1-ol[13], the adduct **10** was obtained in 68% yield.

The substituent at C-11 was then introduced by the methods developed by *Teutsch* et al.[14]. Oxidation of **10** with 3-chloroperoxybenzoic acid gave, as described[15], a mixture of epoxides, predominantly the desired 5α,10α-epoxide **11**, isolated



Scheme 2



Scheme 3

in 47% yield. Subsequent 1,4 addition, using 4-(dimethylamino)phenylmagnesium bromide and CuCl as catalyst, gave the adduct **12** in 71% yield as a yellow amorphous solid. The presence of the 11β-aryl group was clearly demonstrated by the unusual high-field position of the signal of the angular methyl group in the ^{1}H NMR spectrum. This group is located in the shielding cone of the benzene ring causing an upfield shift of approx. 0.3 ppm to δ 0.54 (δ CH_3 in **10** and **11**: 0.88 ppm). At this stage, it was possible to hydrogenate the triple bond without affecting the double bond using 5% $Pd/BaSO_4$ catalyst. Subsequent mild hydrolysis (70% aqueous acetic acid, 50°C) simultaneously removed the THP and acetal protecting groups and caused dehydration, to give the desired product **14** in excellent yield (92%). More vigorous reaction conditions (e.g., HCl/acetone) caused partial epimerization at C-6 to give a mixture of **14** and its 6α-methyl epimer, which were difficult to separate.

Reaction of **14** with 4-toluenesulphonyl chloride in pyridine at room temperature gave, via the putative but undetected tosylate, ring closure to the spirotetrahydrofuran **15** (Org 31710) in 72% yield. Compound **15** was isolated as a colourless solid, m.p. 146–148° (from ethanol). The structure of **15** was confirmed by its spectral data (UV, ^{1}H NMR, ^{13}C NMR) and, more rigorously, by X-ray analysis[16] (see Figure 1).

The lactol and lactone analogues of **15** were obtained by mild oxidation of **14**. Thus, treatment of **14** with pyridinium chlorochromate in CH_2Cl_2 at room temperature gave in modest yield the lactol **16** as a 1 : 1 mixture of the two epimers. Small differences between the two epimers were seen in the ^{1}H NMR spectrum for the signals corresponding to the 13-CH_3 group (δ 0.60 and 0.64, respectively) and the proton at C-11 (doublets with J 6.5 Hz at δ 4.32 and 4.36, respectively). The lactol proton gave rise to a single, unresolved multiplet at δ 5.48. Further oxidation of **16** proved to be troublesome due to the presence of the sensitive aniline moiety, but ultimately oxidation with *Fetizon*'s reagent (silver carbonate/celite)[17] turned out to be successful, giving the lactone **17** in reasonable yield.

Biological data

Compounds **14–17** were screened for their ability to bind to the human progesterone receptor (MCF-7 cells, cytosol) and the glucocorticoid receptor (IM-9 cells) using the reported procedure[18]. From the data summarized in Table I, it can be seen that **15** and **16** have an affinity for the progesterone receptor comparable with mifepristone **1**, but their affinity for the glucocorticoid receptor is reduced by a factor of approx. 15 and 30 times, respectively. Compounds **14** and **17** were somewhat less potent.

Table I Receptor binding (in %).

Compound	Progesterone receptor[a] (MCF-7 cells, cytosol)	Glucocorticoid receptor[b] (IM-9 cells, intact cells)
1	36	366
14	5.4	n.d.[c]
15	32	11.2
16	28	23
17	14	7.3

[a] Reference compound Org 2058[22] = 100%. [b] Reference compound dexamethasone = 100%. [c] Not determined.

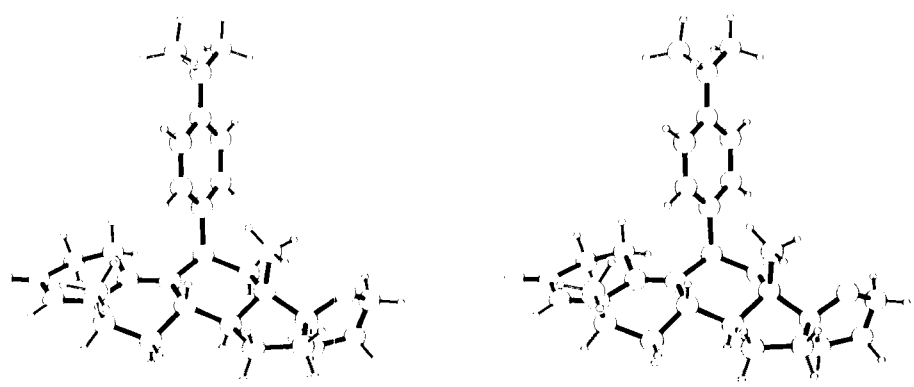


Figure 1. Stereoscopic view of the structure of 15 (Org 31710) as determined by X-ray analysis[16].

The most selective compound **15** (Org 31710) was used for further studies[8]. *In-vivo* studies confirmed its antiprogestational activity, which turned out to be somewhat higher than found for **1**. A reduction of antiglucocorticoid activity, relative to **1**, was also found although *in vivo* this reduction was less pronounced than *in vitro*, resulting, over all, in an 8-fold improvement in the antiprogestational/antiglucocorticoid ratio compared to **1**. Promising results were obtained with **15** in inhibition of the growth of DMBA[a]-induced mammary tumours[19] in rats. In this breast cancer model, **15** showed higher activity than mifepristone (**1**).

Discussion

Progesterone (**2**) is known to bind to its receptor via hydrophobic interactions, involving the steroid skeleton, and by hydrogen bonds to the carbonyl groups at C-3 and C-20. It is estimated that the hydrophobic interactions and hydrogen bonding contribute 6 kcal/mole each, to the binding energy of progesterone to its receptor[20]. Cortisol (**3**) is likely to bind to the glucocorticoid receptor in a similar manner but with formation of additional hydrogen bonds involving the hydroxyl groups at C-11, C-17 and C-21.

It appears, therefore, that the glucocorticoid receptor is more hydrophilic in the area binding the steroid D-ring than the progesterone receptor. Relatively lipophilic, hydrogen-bond accepting substituents at C-17, such as ketones (as in **2**) or ether groups (as in **15**) thus promote binding to the progesterone receptor while binding to the glucocorticoid receptor is less favoured[23]. Hydroxyl groups can either donate or accept hydrogen bonds and, as a result, 17β-hydroxy steroids may have affinity for both the progesterone and glucocorticoid receptor, as found for **1**. In contrast, increase of the polarity of substituents (as in **3**) or the presence of hydroxyl groups, below the steroid D-ring (where the progesterone receptor is believed to possess a hydrophobic pocket[21]) leads to compounds with reduced affinity for the progesterone receptor while the affinity for the glucocorticoid receptor is increased. Dissociation of (anti)progestational and (anti)glucocorticoid activity based on these principles will be investigated further.

Experimental[b]

General remarks

Melting points were measured in capillary tubes on a Büchi 535 instrument. ^{1}H NMR spectra were recorded in $CDCl_3$ solution with TMS (δ 0) as internal standard on a Bruker WP 200 instrument by the Analytical R & D Labs, Organon Scientific Development Group, Oss. Optical rotations were measured in dioxane solution at 10 mg/ml concentration on a Perkin–Elmer 241 polarimeter Microanalyses were carried out by Dr. *W. McMeekin*, Analytical Department, Organon Laboratories, Newhouse, Scotland. For column chromatography, Woelm Silica gel (70–230 mesh, activity grade I) or Merck Lobar^R Fertigsäule was used. Starting materials and reagents were obtained from Diosynth B.V., Oss, or purchased from Aldrich or Janssen Chimica and used without further purification. All reactions were carried out under a dry nitrogen atmosphere.

5α,6α-Epoxy-11β-hydroxyestrane-3,17-dione bis(1,2-ethanediyl acetal) (**5**)

A solution of 44 g (80%, 0.20 mol) of 3-chloroperoxybenzoic acid in 500 ml of dichloromethane was added to a solution of 70 g (0.186 mol) of 11β-hydroxyestr-5-ene-3,17-dione 3,17 bis(1,2-ethanediyl acetal) (**4**)[9] in 1.4 l of dichloromethane at −20°C. The resulting solution was stirred for 2 h at −15°C and then mixed with 1 l of 1 N aqueous NaOH. The organic layer was separated, washed with 500 ml of 5% aqueous Na_2SO_3, 500 ml of 1 N NaOH, water, dried over anhyd. K_2CO_3 and concentrated *in vacuo* to approx. 100 ml. On addition of 200 ml of diisopropyl ether, the product precipated, and was collected by filtration, giving 57 g (78% yield) of **5**, m.p. >265°C. ^{1}H NMR ($CDCl_3$): δ 1.04 (s, 3, 13-CH_3) 2.88 (d, 1, *J* 5 Hz, 6β-H), 3.7–4.1 (m, 8, 2 OCH_2CH_2O), 4.18 (q, 1, *J* 3 Hz, 11α-H).

5α,11β-Dihydroxy-6β-methylestrane-3,17-dione bis(1,2-ethanediyl acetal) (**6**)

Methylmagnesium chloride (1,4M in 350 ml THF) was added to a solution of 57 g (0.145 mol) of the epoxide **5** in 400 ml of dry toluene. The resulting mixture was heated to reflux for 1 h, cooled and poured into 1 l of ice-cold aqueous NH_4Cl. The resulting mixture was extracted with ether (3 × 500 ml). The combined extracts were washed with water, dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The residue was recrystallized from diisopropyl ether, giving 41.3 g (70% yield) of pure **6**, m.p. 188–189°C, $[\alpha]_D^{20}$ −23°. ^{1}H NMR ($CDCl_3$): δ 0.98 (d, *J*, 7 Hz, 3, 6β-CH_3), 1.08 (s, 3, 13-CH_3) 3.75–4.0 (m, 8, 2 OCH_2CH_2O), 4.07 (s, 1, OH), 4.13 (q, 1, *J* 3 Hz, 11α-H).

6β-Methylestra-5(10),9(11)-diene-3,17-dione bis (1,2-ethanediylacetal) (**7**)

Thionyl chloride ($SOCl_2$, 41 ml, 67 g, 0.56 mol) was added dropwise to an ice-cold solution of 41 g (0.10 mol) of the diol **6** in 400 ml of dry pyridine at such a rate that the temperature did not exceed 10°C. The reaction mixture was stirred for 1 h at 10°C and then poured into 700 ml of ice-cold water. The resulting mixture was extracted with ethyl acetate (2 × 250 ml). The combined extracts were washed with water (200 ml), ice-cold (!) 2 N H_2SO_4 and again with water until neutral. Evaporation of the solvents, followed by chromatography of the residue over silica gel (800 g) with hexane/ethyl-acetate (4 : 1) gave 21.3 g (57% yield) of **7** as a colourless oil, $[\alpha]_D^{20}$ +105°. ^{1}H NMR ($CDCl_3$): δ 0.86 (s, 3, 13-CH_3), 1.10 (d, *J* 7 Hz, 3, 6β-CH_3), 3.8–4.05 (m, 8, 2 OCH_2CH_2O), 5.58 (m, 1, 11-H).

6β-Methylestra-5(10),9(11)-diene-3,17-dione (**8**)

The diacetal **7** (21.3 g, 57 mmol) was dissolved in 200 ml of 70% aqueous acetic acid and heated at 50°C for 1 h. The reaction mixture was cooled, diluted with water and extracted with ethyl acetate (3 × 100 ml). The combined extracts were washed with 5% aqueous NaOH, water, dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. This gave 16.0 g (99% yield) of nearly pure **8** as a colourless oil, which solidified on refrigeration, $[\alpha]_D^{20}$ +327°, m.p. 117–119° (from ether), ^{1}H NMR ($CDCl_3$): δ 0.93 (s, 3, 13-CH_3), 1.16 (d, *J*, 7 Hz, 3, 6β-CH_3) 2.78 and 3.12 (each d, *J* 21 Hz, 1, 4-H), 5.63 (m, 1, 11-H)

3,3-Dimethoxy-6β-methylestra-5(10),9(11)-dien-17-one (**9**)

The diketone **8** (16.0 g, 56 mmol) and 8 g (77 mmol) of malonic acid were dissolved in 250 ml of dry methanol. The mixture was stirred for 6 h at room temperature, neutralized with excess saturated aqueous sodium bicarbonate and extracted with hexane (3 × 100 ml). The extracts were washed with water, dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed over silica gel (300 g) with hexane/ethyl-acetate (4 : 1) to give 12.8 g (69% yield) of **9**, m.p. 81–83° (from ethanol), $[\alpha]_D^{20}$ +294°. ^{1}H NMR ($CDCl_3$): δ 0.91 (s, 3, 13-CH_3), 1.14 (d, *J*, 7 Hz, 3, 6β-CH_3) 3.23 and 3.25 (each s, 3, 2 OCH_3), 5.57 (m, 1, 11-H).

3,3-Dimethoxy-6β-methyl-17α-(3-tetrahydropyranyloxy-1-propynyl)-estra-5(10),9(11)-dien-17β-ol (**10**)

Ethylmagnesium bromide (110 ml 1.2M solution in THF) was added dropwise to a solution of 21.0 g (150 mmol) 2-propynol THP ether[13] in 120 ml of dry THF, in 15 min. The mixture was stirred for ½ h at room temperature, and a solution of 10.0 g (30 mmol) of **9** in 90 ml of dry THF was then added dropwise. The resulting mixture was stirred for 3 h and then poured into 500 ml of 10% aqueous NH_4. Extraction with ether (3 × 300 ml), followed by

[a] DMBA = 7,12-dimethylbenz[a]anthracene.

[b] In collaboration with Messrs. *J. A. M. Peters*, *K. H. Schönemann*, *A. I. A. Broess*, *F. A. N. Missler* and *W. J. Schuts*.

washing of the extracts with water, drying over anhyd. Na_2SO_4 and evaporation of the solvents gave an oily residue. This was chromatographed over silica gel with hexane/ethyl-acetate (4 : 1) to give 9.6 g (68% yield) of pure **10** as an oil. ^{1}H NMR ($CDCl_3$): δ 0.88 (d, 3, 13-CH_3), 1.11 (d, *J*, 7 Hz, 3, 6β-CH_3), 3.23 and 3.25 (each s, 3, 2 OCH_3), 3.51 and 3.81 (each m, 1, OCH_2), 4.28 and 4.30 (each d, *J* 16 Hz, ethynyl-CH_2O), 4.79 (m, 1, OCHO), 5.58 (m, 1, 11-H).

3,3-Dimethoxy-5α,10α-epoxy-6β-methyl-17α-(3-tetrahydropyranyloxy--1-propynyl)-estr-9(11)-en-17β-ol (**11**)

Sodium bicarbonate (5.0 g) was added to a solution of 9.4 g (20 mmol) of **10** in 200 ml of CH_2Cl_2, followed at −30 °C, with stirring, by portionwise addition of 5.4 g (80%, 24 mmol) of 3-chloroperoxybenzoic acid. The resulting mixture was stirred at −10° to 0 °C for 3 h, then mixed with 100 ml of 1 N aqueous NaOH. The organic layer was separated, washed with aqueous Na_2SO_3 solution, dried over anhyd. K_2CO_3 and concentrated *in vacuo*. The crude product was chromatographed carefully over silica gel with toluene/ethyl-acetate (9 : 1) to give 4.6 g (47% yield) of **11** as an amorphous solid. ^{1}H NMR ($CDCl_3$): 0.88 (s, 3, 13-CH_3), 1.17 (d, *J* 7 Hz, 3, 6β-CH_3), 3.14 and 3.19 (each s, 3, 2 OCH_3), 4.27 and 4.29 (each d, *J* 15 Hz, ethynyl-CH_2O), 4.78 (m, 1, OCHO), 6.04 (q, *J* 2.3 Hz, 1, 11-H).

3,3-Dimethoxy-11β-[4-(dimethylamino)phenyl]-6β-methyl-17α-(3-tetrahydropyranyloxy-1-propynyl)estr-9-ene-5α,17β-diol (**12**)

Copper(I) chloride (1.23 g) was added at −10 °C to a solution of 4-(dimethylamino)phenylmagnesium bromide [prepared from 40 g (0.20 mol) 4-bromo-*N,N*-dimethylamine and 5.3 g (0.22 mol) of magnesium in 180 ml of dry THF], followed by a solution of 10.1 g (20.8 mmol) of **11** in 120 ml of dry THF. The resulting mixture was stirred at room temperature for 3 h and then poured into 1 l of 10% aqueous NH_4Cl. The mixture thus obtained was extracted with ethyl acetate (3 × 250 ml) and the combined extracts were washed with water, dried over anhyd Na_2SO_4 and concentrated *in vacuo*.

The residue was chromatographed over silica gel (400 g) with hexane/ethyl-acetate (9 : 1 and 7 : 3). Thus, 9.0 g (71% yield) of **12** was obtained as an amorphous solid, still containing some coloured impurities. ^{1}H NMR ($CDCl_3$): δ 0.54 (s, 3, 13-CH_3), 1.08 (d, *J* 7 Hz, 6β-CH_3), 2.90 (s, 6,$(CH_3)_2N$) 3.23 and 3.25 (each s, 3, 2 OCH_3), 3.53 and 3.86 (each m, 1, CH_2O), 4.33 and 4.35 (each d, *J* 15 Hz, 1, ethynyl-CH_2O), 4.15 (t, *J* 3.5 Hz, 1, 11α-H), 4.73 (br. s, 1, 5-OH), 6.65 and 7.06 (each d, *J* 8.6 Hz, 2, aromatic H).

11β-[4(Dimethylamino)phenyl]-17β-hydroxy-17α-(3-hydroxy-1-propyl)--6β-methylestra-4,9-dien-3-one (**14**)

A solution of 10.0 g (16.5 mmol) of **12** in 1 l of toluene/ethanol (1 : 1) was hydrogenated in the presence of 1 g of 5% Pd-$BaSO_4$ catalyst, until two equivalents of hydrogen had been absorbed. The catalyst was removed by filtration and the solvents were evaporated *in vacuo*. The residue was dissolved in 150 ml of 70% aqueous acetic acid and heated at 50 °C for 2 h. The reaction mixture was cooled, diluted with water, neutralized with $NaHCO_3$ and extracted with dichloromethane (4 × 100 ml). The extracts were washed with water, dried over anhyd. K_2CO_3 and concentrated *in vacuo*. The residue was chromatographed over silica gel (200 g) with hexane/ethyl-acetate (9:1) to give 7.0 g (92% yield) of **14** as an amorphous foam, $[\alpha]_D^{20}$ + 153.3°. ^{1}H NMR ($CDCl_3$): δ 0.62 (s, 3, 13-CH_3), 1.29 (d, *J* 7 Hz, 3, 6β-CH_3), 2.91 [s, 6, $(CH_3)_2N$], 3.70 (m, 2, CH_2O), 4.33 (d, *J* 6.4 Hz, 1, 11α-H), 5.78 (br.s, 1, 4-H), 6.65 and 7.00 (each: d, *J* 8.6 Hz, 2, aromatic H's).

11β-[4-(Dimethylamino)phenyl]-6β-methyl-4',5'-dihydrospiro[estra--4,9-diene-17,2'-(3'H)-furan]-3-one (**15**)

4-Toluenesulphonyl chloride (3.1 g, 16 mmol) was added to a solution of 6.2 g (10 mmol) of **14** in 75 ml of dry pyridine. The resulting mixture was stirred for 6 h at room temperature, diluted with 500 ml of water and extracted with ether (3 × 150 ml). The combined extracts were washed thoroughly with water, dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed over 200 g of silica gel with toluene/ethyl-acetate (7 : 3) to give 4.3 g (72% yield) of **15** as an amorphous solid, which crystallized from ethanol/water, m.p. 146–148°, $[\alpha]_D^{20}$ + 177.6°. UV: λ_{max} 303 nm (ε 20500), 261 nm (ε 18400). ^{1}H NMR ($CDCl_3$): δ 0.63 (s, 3, 13-CH_3), 1.27 (d, *J* 7 Hz, 3, 6β-CH_3), 2.90 (s, 6, $(CH_3)_2N$), 3.77 (td, *J* 7 and 1.8 Hz, 2, OCH_2), 4.32 (d, *J* 6.6 Hz), 5.77 (br.s, 1,4-H), 6.65 and 7.00 (each: d, *J* 8.5 Hz, 2, aromatic H's). Anal. $C_{30}H_{39}NO_2$ (445.65) calcd.: C 80.85, H 8.82, N 3.14, O 7.18; found: C 81.12, H 9.04%.

11β-4-(Dimethylamino)phenyl-17β-hydroxy-6β-methyl-17α-(3-oxo--propyl)estra-4,9-dien-3-one cyclic 17β-hemiacetal (**16**)

A solution of 4.6 g (10 mmol) of **14** in 100 ml of dry CH_2Cl_2 was added to a suspension of 7.0 g of pyridinium chlorochromate in 100 ml of dry CH_2Cl_2. The resulting mixture was stirred for 30 min. at room temperature, diluted with 200 ml of ether and filtered over Hyflo. The filtered solution was concertrated *in vacuo* and the residue was chromatographed over 100 g of silica gel. This gave 2.1 g (45% yield) of the corresponding aldehyde, mainly in the form of hemiacetal **16**. ^{1}H NMR ($CDCl_3$): δ 0.60, 0.64 (s, together 3, 13--CH_3) 1.28 (d, *J* 7 Hz, 3, 6β-CH_3), 2.92 (s, 6, $(CH_3)_2N$), 4.32, 4.36 (each d, *J* 6.5 Hz, together 1, 11α-H) 5.48 (m, 1, lactol-H), 5.79 (br.s, 1, 4-H), 6.67 (d, 2, *J* 8.5 Hz, aromatic H's) 7.00, 7.02 (each d, *J* 8.5 Hz, together 2, aromatic H's).

11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-3-oxo-19-nor-17α--pregna-4,9-diene-21-carboxylic acid γ-lactone (**17**)

A solution of 4.6 g (10 mmol) of lactol **16** in 200 ml of toluene was stirred with 45 g of Ag_2CO_3/celite (*Fetizon*'s reagent) at reflux temperature for 5 h. After cooling, 22.5 g of Ag_2CO_3/celite were added and the remaining suspension was refluxed for another 2 h. The reaction mixture was cooled, filtered and concentrated *in vacuo*. The residue was chromatographed over silica gel to give 3.0 g (66% yield) of the lactone **17**, as a yellow amorphous solid, $[\alpha]_D^{20}$ + 144°. ^{1}H NMR ($CDCl_3$): δ 0.68 (s, 3, 13-CH_3), 1.29 (d, *J* 7 Hz, 6β-CH_3), 4.37 (d, *J* 6.5 Hz, 1, 11α-H), 5.80 (br. s, 1, 4-H), 6.66 and 6.98 (each: d, *J* 8.5 Hz, 2 aromatic H's).

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