REGIO AND STEREOSPECIFIC SYNTHESIS OF 11β-SUBSTITUTED 19-NORSTEROIDS

Influence of 11β-substitution on progesterone receptor affinity - (1)

A. Bélanger (2), D. Philibert and G. Teutsch*

Centre de Recherches Roussel-UCLAF
93230 Romainville, France

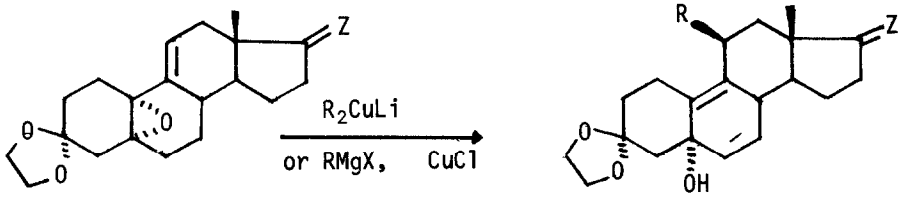
Received 10-29-80

ABSTRACT

The convenient synthesis of a series of 11β-substituted 17-ethynyl-17β-hydroxy-4,9-estradien-3-ones and their corresponding estradiols is reported. Relative affinities for the progestin and estrogen receptors showed very specific interactions between the progesterone receptor and the unsaturated substituents in the 11β-position of the steroid.

INTRODUCTION

In a preliminary paper we reported a new and general method for the synthesis of 11β-substituted 19-norsteroids (3), using the conjugate opening of allylic epoxides by organo-copper reagents (Scheme 1).

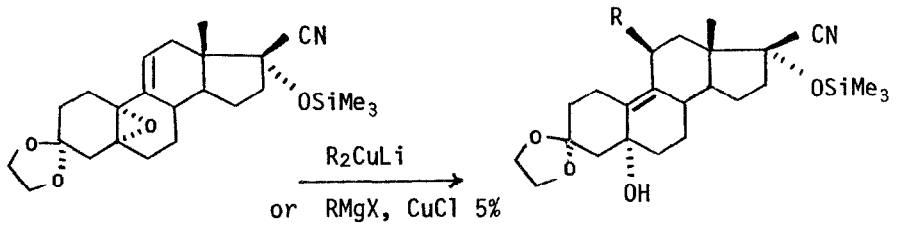


Scheme 1

In the present paper we describe the application of our scheme to the synthesis of a variety of novel 11β-substituted steroidal dienones illustrated by the general formula A. These dienones, besides their inherent interest, represent convenient intermediates to enones of type B, and to the aromatic steroids C.

In the present paper we shall describe the ethynylation which, in fact, proceeds in two discrete steps (the reaction may be stopped at the intermediate 17-ketone stage).

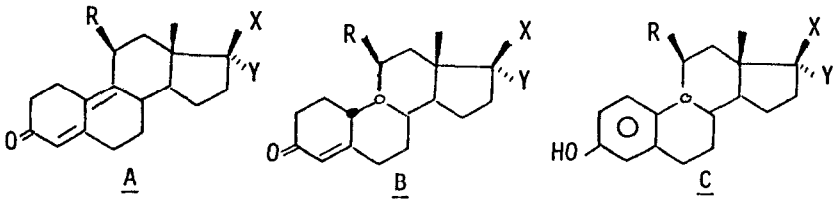
When I was treated with the organo-copper lithium reagents R_2CuLi or, in most instances, more conveniently, with the corresponding organo-magnesium halides in the presence of a catalytic amount of copper I chloride, the 11β substituted steroids II were obtained in, generally, excellent yields (see experimental section). The reaction only failed with allylmagnesium chloride, but could be accomplished satisfactorily with diallylcopper lithium. Perhaps the best illustration of the ease of this type of epoxide opening reaction is the surprisingly successful introduction of an 11β-tertiary butyl group, using di-t-butyl-copper lithium. The reaction, although much slower than with smaller groups, gave a quantitative yield. Only in the case of the 2,6 dimethylphenyl group did the reaction fail.



I

II (a to q)
cf : formulas V and VI

From these results it can be seen that the method is quite general and can accommodate a large variety of substituents, ranging from saturated and unsaturated alkyl groups to aromatic or heterocyclic ones. In this respect, it should nevertheless be mentioned that the introduction of nitrogen-containing substituents, such as pyridines or pyrroles, failed completely. That a 13-ethyl group did not hinder the reactions, as was reported for the 11-keto pathway (6b), was shown by the straightforward introduction of an 11β-vinyl group on a 13-ethyl steroid by our method (transformation III → IV).

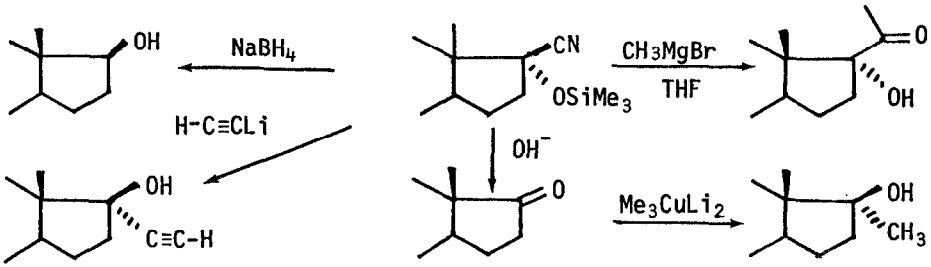


It is clear that our synthesis is of considerable utility in view of the high biological activity of 17α-acetoxy - 11β-methyl-19-norprogesterone (4) and of some 11β-alkylestradiols (5), coupled with the inefficiency of previously available synthetic pathways to these compounds (6). Moreover, it allowed us to prepare a homogenous series of steroids bearing various substituents in the 11β position, and to demonstrate the unexpected importance of this region of the steroid molecule as a binding site for the progesterone receptor.

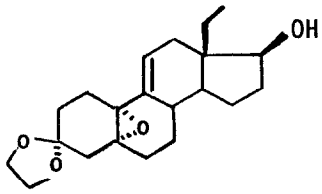
CHEMISTRY

a) *Epoxide opening*

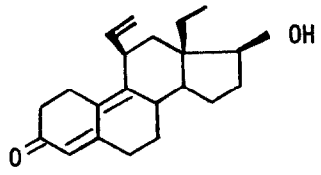
We chose epoxide I as the most convenient starting material (7) since the protected cyanohydrin side chain can be easily transformed at an appropriate stage into a variety of functionalities (Scheme 2).



Scheme 2



III



IV

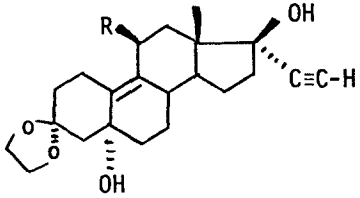
The configuration of substituents was determined by NMR, as already stated in the preliminary paper (3). To sum up, the β nature of the aromatic substituents is clear from the expected large shielding effect they produce on the 18-methyl group. Alkyl and alkenyl groups produce the expected slight deshielding, a point which was confirmed by our recent synthesis of an 11α-methyl steroid (8). The mean value of this shift, taking the 11α-methyl steroid as a reference, is 0.1 ppm. Apart from these general observations, another stereochemical problem deserves comment.

From the quasi-axial orientation of the 11β-substituents and the relatively high steric crowding, it is expected that for branched groups or aromatics, free rotation around the 11β single bond should be unlikely.

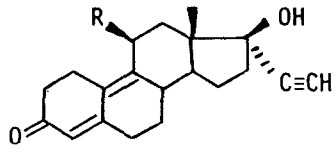
In practice, however, there is no evidence of any non-homogeneity in the NMR of the reaction products. Only in the o-methoxyphenyl case is there the suspicion of the exclusive formation of one atropisomer, having the methoxy substituent directed away from the steroid, as the 2,6-dimethylphenyl group could not be introduced (vide supra). In the case of isopropenyl and 2-thienyl substituents it seemed reasonable to assume that both atropisomers could be formed, but that symmetry considerations in the vicinity of the angular methyl group did not allow differentiation in the NMR spectrum. However, preliminary X-ray data on the derived dienone VIn (see below) show that there is, in this case, a unique atropisomer having the sulfur directed outwards (9).

b) Formation of the dienones

A number of intermediates of type II described in the previous section were treated with lithium acetylide-ethylenediamine complex in ethylenediamine solution at 40°C, affording the 17α-ethynyl steroids V. Refluxing these compounds, generally without further purification, in aqueous ethanol in the presence of a sulfonic resin (Redex CF) yielded dienones VI, by concomitant deketalization and dehydration. In some instances the whole reaction sequence starting from epoxide I has been performed without purification of the intermediates, giving high yields of the final dienones (see preparation of VIb).



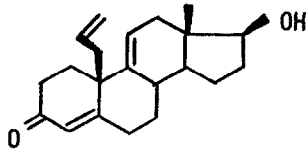
V (b,c,d,e,f,g,h, i,j,k,l,n,o)



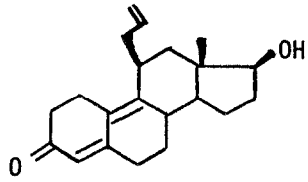
VI (b,c,d,e,f,g,h, i,j,k,l,n,o)

a) R = H
b) R = Et
c) R = Pr
d) R = i-Pr
e) R = n-decyl
f) R = vinyl
g) R = isopropenyl
h) R = allyl
i) R = phenyl
j) R = p-methoxyphenyl
k) R = o-methoxyphenyl
l) R = p-fluorophenyl
m) R = p-CF_3-phenyl
n) R = 2-thienyl
o) benzyl
p) t-butyl
q) 1-methoxyvinyl

That the β orientation of the substituent is maintained in the dienones is again confirmed by NMR which shows the expected shifts of the 18-methyl frequencies relative to the unsubstituted dienone VI. These results are summarized in Table 1. Finally we accomplished an independent and stereospecific synthesis of the 11β-allyl steroid VIII by thermal rearrangement of the known 10β-allyl steroid VII (10). The 18-Me shift induced by the 11β-allyl substituent (0.09 ppm) is in agreement with that observed for compound VIh.



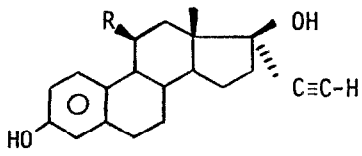
VII



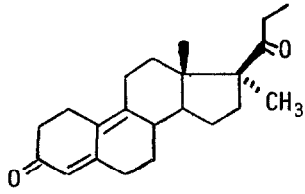
VIII

c) Aromatization of ring A

Dienones VIb, c, d, e, f, h, j, k, n, and o were aromatized by acetyl bromide in acetic anhydride followed by treatment with base according to a known procedure (11), yielding the corresponding compounds IX.



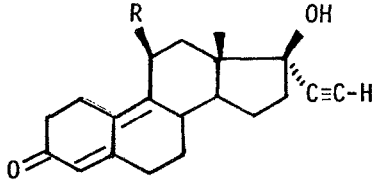
IX (c,d,e,g,h, j,k,n,o)



X RU 5020

TABLE 1

18-Me shifts in the ^{1}H-NMR spectra of 11β-substituted dienones



R	δ ppm	R	δ ppm
H	1.02	phenyl	0.53
Et	1.07	p-methoxyphenyl	0.55
Pr	1.07	o-methoxyphenyl	0.69
iPr	1.09	p-fluorophenyl	0.525
n-$C_{10}H_{21}$	1.07	2-thienyl	0.68
vinyl	0.98	benzyl	1.21
isopropenyl	0.98		
allyl	1.09		

BIOLOGY

Competitive binding studies on the progestin receptor of the rabbit uterus

Immature female New Zealand rabbits were used. They were pretreated with one topical application of 25 µg of estradiol-17β in ethanolic solution on the dorsal skin and killed 5 days after priming. The uteri were excised, weighed, pooled and homogenized in 3 volumes of 10 mM Tris HCl (pH 7.4), 0.25M sucrose buffer in an ice cooled Teflon glass homogenizer. Cytosol (supernatant) was prepared by centrifuging the homogenate at 105,000g for 90 min at 4°C.

Cytosol (250 µl, 1/50 wt/vol) was incubated with 2.5 nM ^{3}H 17α, 21-dimethyl-19-norpregna-4,9-dien-3,20-dione (R 5020), with increasing concentrations (1 - 2500 nM) of unlabelled R 5020, progesterone or competitor for 2 hrs and 24 hrs at 0°C.

Bound radioactivity was measured by dextran-coated charcoal adsorption, and the relative binding affinity (RBA) was determined as previously described (12-13). The RBA of progesterone was taken arbitrarily as equal to 100.

Competitive binding studies on the estrogen receptor of the immature mouse uterus

Immature female Swiss - SPF mice (17-19 days old) were used. The uteri were excised, weighed, minced and homogenized in 10 nM Tris-HCl (pH 7.4), 0.25M sucrose buffer (final dilution 1/50 wt/vol) with an ice cooled Teflon glass homogenizer and centrifuged for 90 min at 105,000g at 4°C. Aliquots of supernatant were incubated at 0-4°C for 24 hrs or at 25°C for 5 hrs with 5nM ^{3}H-estradiol-17β in the presence of increasing concentrations of unlabelled estradiol-17β or competitor (test compound). The bound ^{3}H-estradiol-17β was measured as described above. The RBA of estradiol was taken arbitrarily as equal to 100.

RESULTS AND DISCUSSION

As can readily be seen from Table 2, with regard to saturated substituents, the affinity of the dienones for the progesterone receptor decreases regularly with the increasing size of the substituent, demonstrating the adverse effect of steric hindrance on binding. However, the introduction of unsaturation into the substituent unexpectedly increases the relative binding affinity. Thus, changing the group from ethyl (VIb) to vinyl (VIf) increases the affinity from 39 to 172

and this takes place in the two-hour incubation experiment. After 24 hours of incubation, the difference is even more marked (25 versus 535). The same increase is found when the group is changed from isopropyl to isopropenyl (VId and VIg).

Other types of unsaturation also boost affinity for the receptor, as can be deduced from the values of phenyl (VIi), thienyl (VIn) or p-methoxyphenyl groups (VIj). This comes somewhat as a surprise considering the steric requirements of such substituents.

TABLE 2

Relative binding affinities of various 11β-substituted 17α-ethynyl-17β-hydroxy-estra-4,9-dien-3-ones for the cytoplasmic uterine progestin receptor (average of at least 3 determinations).

	RU N°	R	2 hrs	24 hrs
VI a		H	43	34
VI b	23 813	Et	39	25
VI c	25 057	nPr	18	12
VI d	24 848	iPr	2.3	1.3
VI e	25 336	n decyl	3.6	
VI f	24 850	vinyl	172	535
VI g	24 896	i-propenyl	76	94
VI h	25 258	allyl	49	44
VI i	25 597	phenyl	20	64
VI j	25 056	p-methoxyphenyl	130	335
VI k	25 594	o-methoxyphenyl	1.1	0.7
VI l	25 593	p-fluorophenyl	38	36
VI n	25 055	thienyl	70	85
VI o	24 849	benzyl	0	0

That the position of the unsaturation in the carbon chain is highly important is evident from the comparison between allyl (VIh) and vinyl (VIf) and benzyl (VIo) and phenyl (VIi). Thus, shifting the unsaturation by one carbon atom practically eliminates the affinity.

These results clearly indicate that there must be a very specific bonding interaction of the 11β-unsaturated substituent with part of the progesterone receptor. Suitable possibilities for such an interaction would be hydrogen bonding between a part of the receptor protein

and the electron-rich unsaturation, or a π - π interaction. In support of this, a large difference in affinity is observed between the electron-rich p-methoxyphenyl substituent (VIj) and the depleted p-fluorophenyl substituent (VIl). Even phenyl (VIi) fits into this scheme, being intermediate in electron density.

Another interesting observation is that affinities of steroids possessing desirable unsaturated substituents increase between the 2 hour and 24 hour measurements, whereas for the others they remain constant or slightly decrease. This suggests that the compounds of high affinity dissociate less readily than the marker compound (RU 5020) which, in turn, is known to dissociate much less readily than progesterone (12).

TABLE 3

Relative affinities of various 11β-substituted 17α-ethynyl-1,3,5-estratriene-3,17β-diols for the cytoplasmic estrogen and progestin receptors (average of at least 3 determinations).

	RU N°	R	Estrogen 2hrs 0°C	Estrogen 5hrs 25°C	Progestin 2hrs	Progestin 24hrs
IX a	3 600	H	112	245	21	10
IX c	24 895	n-Pr	95	730*	7.2	3.3
IX d	25 335	i-Pr	84	710	8.0	4.7
IX e	25 058	n-decyl	0.0		0.0	
IX f	24 894	vinyl	91	415	60	77
IX h	25 257	allyl	93	555	17.5	10
IX j	25 338	p-methoxyphenyl	61	66	34	48
IX k	25 599	o-methoxyphenyl	15	8.5	0.7	1.3
IX n	25 053	2-thienyl	76	91*	22	17
IX o	24 897	benzyl	77	53	0.4	0.1

* Only one determination

These findings demonstrate very strikingly the influence of electronic factors which, in this case, override clearly the steric factors.

In the aromatic series (Table 3) it is surprising to see that unsaturated substituents in the 11β-position confer on these compounds a significant affinity for the progesterone receptor, which is especially striking in the case of vinyl (IXf) and p-methoxyphenyl IXj) substituents, confirming the very privileged interaction of this type

of substituents with the progesterone receptor. However, the values do not change significantly during incubation, whereas the RBA's for the estradiol receptor increase considerably and independently of unsaturation (compare IXc and IXf). However, this discovery should make it possible, in principle, to design a molecule with the appropriate ratio of affinities for the progestin and the estrogen receptors required by a potential contraceptive, a goal which had been pursued unsuccessfully by steroid chemists in the past.

It should be mentioned that compound IXf has been tested in vivo and a high potency in the Rubin test was confirmed (about 10 times ethynylestradiol). Efforts to demonstrate a progestational effect in vivo have so far failed.

EXPERIMENTAL PART

Elemental analyses were performed by the Analytical Department of Roussel-Uclaf. Melting points were taken on a Kofler hot stage and are uncorrected. Optical rotations were measured with a Roussel-Jouan Digital micropolarimeter.

NMR spectra were taken with a Varian A 60A or Brucker WP60DS spectrometer. Chemical shifts are in ppm and were measured in $CDCl_3$ solution unless otherwise stated, with TMS as an internal standard. For chronological reasons the epoxide opening reactions are presented in the following sequence: use of lithium cuprates (IIi, b, h, p, q), use of copper catalyzed Grignard reagents (IIf, n, c, d, e, g, i, j, k, l, m, o).

3,3-ethylenedioxy-5-hydroxy-11β-phenyl-17-trimethylsilyloxy-5α-estr-9-ene-17β-carbonitrile IIi

A solution of diphenylcopperlithium was prepared by addition at 0°C of 0.7M phyllithium in ether (7 ml) to a stirred suspension of copper iodide (477 mg) in ether (2.5 ml).

3,3-ethylenedioxy-5,10α-oxido-17-trimethylsilyloxy-5α-estr-9(11)-ene-17β-carbonitrile (860 mg) was added and the reaction was stirred at 0°C under nitrogen overnight. The reaction mixture was poured into aqueous ammonium chloride and extracted with ether. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The crude residue was recrystallized twice from isopropyl ether affording 690 mg of the desired 11β phenyl steroid. Chromatography of the mother liquors through silicagel (Merck H) afforded a further 267 mg of the same compound (combined yield = 98.6 %).

MP 186°C $[\alpha]_D^{20}$ -12.5 ± 2° (0.6 % in $CHCl_3$)

δ ppm 0.54 (18-Me) H_{11} centered at 4.26.

3,3-ethylenedioxy-11β-ethyl-5-hydroxy-17-trimethylsilyloxy-5α-estr-9-ene-17β-carbonitrile IIb

Operating as in example IIi and using 3.6 mM of Et_2CuLi in ether (20 ml) and 2.5 mmol of epoxide I at -20°C for 2 hrs, we isolated 1.16 g (100 %) of the non crystalline 11β-ethyl steroid homogeneous by TLC.

$[\alpha]_D^{20}$ -61° ± 2.5° (0.5 % in $CHCl_3$)

δ ppm 1.06 (18-Me) 0.91 t,7Hz (CH_3 of Et)

3,3-ethylenedioxy-11β-allyl-5-hydroxy-17-trimethylsilyloxy-5α-estr-9-ene-17β-carbonitrile IIh

Allyllithium in Et_2O : THF (tetrahydrofuran) 2:3 (83 ml of 1.23M strength, from allylphenyl ether and Li) was added slowly at -78°C to a stirred suspension of copper bromide dimethylsulfide complex (5.15 g) (14) in THF (20 ml). After 15 min a solution of 4.13 g of the steroidal epoxide I in THF (20 ml) was added and the reaction mixture was stirred at -78°C for 1 hr (after 10 min TLC showed complete disappearance of the starting material). Usual work up followed by chromatography through silicagel afforded 2.43 g (54 %) of the desired 11β-allyl steroid.

$[\alpha]_D^{20}$ -52° ± 2° (0.6 % in $CHCl_3$)

δ ppm 0.22 ($SiMe_3$) 1.07 (18-Me) 3.97 (ketal)
= $\underline{CH_2}$ centered at 4.93 and -$\underline{CH}$=CH_2 centered at 5.67.

Analysis : Calculated for $C_{27}H_{41}O_4NSi$ C 68.74 % H 8.76 % N 2.96 %
Found C 68.5 % H 9.1 % N 3.0 %

3,3-ethylenedioxy-11β-t-butyl-5-hydroxy-17-trimethylsilyloxy-5α-estr-9-ene-17β-carbonitrile IIp

A 1.35M commercial solution of t-BuLi in hexane (6.0 ml) was added dropwise at -50°C to a stirred suspension of copper bromide-dimethylsulfide complex (810 mg) in THF (15 ml). After 15 min at -50°C a solution of the epoxide I (840 mg) in THF (10 ml) was added dropwise and the reaction mixture was stirred for 30 min at -40°C. As the reaction was not completed (TLC), it was left overnight at -25°C.

Extraction as in the previous examples and drying of the crude product to constant weight afforded 942 mg (100 %) of the desired non-crystalline 11β-t-butyl steroid.

$[\alpha]_D^{20}$ -58° ± 3° (0.3 % in $CHCl_3$)

δ ppm 0.22 ($SiMe_3$) 0.98 (tBu) 1.08 (18-Me) 4.00 (ketal).

Analysis : Calculated for $C_{28}H_{45}O_4NSi$ C 68.96 H 9.30 N 2.87
Found C 69.1 H 9.4 N 2.7

3,3-ethylenedioxy-5-hydroxy-11β-(1'methoxyvinyl)-17-trimethylsilyloxy-5α-estr-9-ene-17β-carbonitrile IIq

Bis-(methoxyvinyl) copper lithium (15) was prepared from a THF-hexane solution of methoxyvinyllithium (13 mM) and Me_2S, CuBr (1.4 g) suspended in THF (5 ml) at -40°C.

A solution of the steroidal eppxide I (1.3 g) in THF (5 ml) was added. The reaction mixture was stirred 30 min at -40°C, 1 hr at -20°C and 1.5 hrs at -10°C. Usual work up followed by chromatography through silicagel afforded 1.3 g (88.4 %) of the desired noncrystalline compound.

$[\alpha]_D^{20}$ -56.5° ± 2° (0.4 % in $CHCl_3$)

δ ppm 0.94 (18-Me) 3.53 (OMe)

Analysis : Calculated for $C_{27}H_{41}O_5NSi$ C 66.49 % H 8.47 % N 2.87 %
Found C 66.7 % H 8.8 % N 2.6 %

3,3-ethylenedioxy-5-hydroxy-17-trimethylsilyloxy-11β-vinyl-5α-estr-9-ene-17β-carbonitrile IIf

Copper I chloride (200 mg) was added to a 1.3M solution of vinylmagnesium bromide in THF (60 ml) at -25°C.

After stirring 15 min a solution of the steroidal epoxide I (8.4 g) in THF (40 ml) was added dropwise and the stirring was continued at -10°C overnight (the reaction is essentially complete after 1 hr). Usual work up afforded 9.1 g (quantitative yield) of the crude (homogeneous by TLC) desired 11β-vinyl steroid.

Recrystallization from isopropyl ether afforded an 88 % yield of the analytical material.

MP 213°C $[\alpha]_D^{20}$ -60° ± 2° (0.8 % in $CHCl_3$)

δ ppm 0.13 ($SiMe_3$) 0.95 (18-Me), 11α-H centered at 3.67.

Analysis : Calculated for $C_{26}H_{39}O_4NSi$ C 68.22 % H 8.58 % N 3.05 %
Found C 68.3 % H 8.4 % N 3.0 %

3,3-ethylenedioxy-5-hydroxy-11β-(2-thienyl)-17-trimethylsilyloxy-5α-estr-9-ene-17β-carbonitrile IIn

Copper I chloride (40 mg) was added to a 0.85M solution of 2-thienylmagnesium bromide in THF (12 ml) at -30°C. After stirring at this temperature for 10 min, a solution of the steroidal epoxide I (2.0 g) in THF (12 ml) was added dropwise and the reaction was stirred at -35°C overnight. As there was some unchanged starting material left (TLC) the temperature was raised to -10°C for 2 hrs. The reaction mixture was poured into aqueous ammonium chloride and extracted with ether. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. Chromatography through silicagel of the crude extract afforded 2.34 g (97 %) of the desired compound.

MP 145°C (from petroleum ether) $[\alpha]_D^{20}$ +34° ± 2.5° (0.4% in $CHCl_3$)

δ ppm 0.24 ($SiMe_3$) 0.66 (18-Me), 11αH centered at 4.50 thiophene protons from 6.67 to 7.17

Analysis : Calculated for $C_{28}H_{39}O_4SNSi$	C 65.45 %	H 7.65 %	N 2.72 %
Found	C 65.9 %	H 7.8 %	N 2.7 %

In the same way we prepared :

3,3-ethylenedioxy-5-hydroxy-11β-propyl-17-trimethylsilyloxy-5α-estr-9 ene-17β-carbonitrile IIc

n-Propylmagnesium bromide (30 ml of 1.07M strength in THF) and 150 mg CuCl, left at -25°C overnight with 6.2 g of epoxide I yielded 6.5 g (95 %) of the desired compound after chromatography through silica gel (Merck H 60)

$[\alpha]_D^{20}$ -58.5° ± 1.5° (0.5 % in $CHCl_3$)

δ ppm 0.21 ($SiMe_3$) 1.05 (18-Me) 0.88 (t,7Hz) (Me of n-propyl).

Analysis : Calculated for $C_{27}H_{43}O_4NSi$	C 68.45 %	H 9.14 %	N 2.95 %
	C 68.5 %	H 9.4 %	N 2.9 %

3,3-ethylenedioxy-5-hydroxy-11β-isopropyl-17-trimethylsilyloxy-5α-estr-9-ene-17β-carbonitrile IId

Isopropylmagnesium bromide (30 ml of 0.94M strength in THF) and 135 mg CuCl, left at -15°C overnight with 6 g of epoxide I afforded 5.68 g (86 %) of the desired compound after chromatography.

$[\alpha]_D^{20}$ -70° ± 3° (0.5 % in $CHCl_3$)

δ ppm 1.08 (18-Me) 0.77 (d,7Hz) 1.02 (d,7Hz)(isopropyl).

Analysis : Calculated for $C_{27}H_{43}O_4NSi$	C 68.45 %	H 9.14 %	N 2.95 %
	C 68.7 %	H 9.2 %	N 2.9 %

3,3-ethylenedioxy-11β-decyl-5-hydroxy-17-trimethylsilyloxy-5α-estr-9-ene-17β-carbonitrile IIe

n-Decylmagnesium bromide (40 ml of 0.4M strength in THF) and 80 mg CuCl, left at -10°C overnight with 3 g of epoxide I yielded 3.7 g (93 %) of the desired compound after chromatography.

$[\alpha]_D^{20}$ -45.5° ± 1.5° (0.7 % in $CHCl_3$)

δ ppm 0.88 t, 7Hz (Me of n-decyl) 1.05 (18-Me)

Analysis : Calculated for $C_{34}H_{57}O_4NSi$	C 71.40 %	H 10.04 %	N 2.44 %
Found	C 71.1 %	H 10.0 %	N 2.3 %

3,3-ethylenedioxy-5-hydroxy-11β-isopropenyl-17-trimethylsilyloxy-5α-estr-9-ene-17β-carbonitrile IIg

Isopropenylmagnesium bromide (6.5 ml of 0.92M strength in THF) and 30 mg CuCl left at -30°C for 1 hr (reaction was complete after

5min according to TLC) with 1.3 g of the epoxide I afforded 1.09 g (76 %) of the desired compound after chromatography.

MP 136°C (from Et_2O-Petroleum ether)
$[\alpha]_D^{20}$ -58° ± 2.5°[2] (0.4 % in $CHCl_3$)

δ ppm 0.97 (18-Me) 1.83 (Me of isopropenyl) 11α-H centered at 3.47
Analysis : Calculated for $C_{27}H_{41}O_4NSi$ C 68.73 % H 8.76 % N 2.96 %
Found C 68.9 % H 8.9 % N 2.8 %

3,3-ethylenedioxy-5-hydroxy-11β-phenyl-17-trimethylsilyloxy-5α-estr-9-ene-17β-carbonitrile IIi

Phenylmagnesium bromide (1.1 ml of 1.17M strength in THF) and 5 mg CuCl, left at 0°C for 1.5 hrs with 430 mg of epoxide I afforded a quantative yield of the desired crude compound which was recrystallized from isopropyl ether to yield 369 mg (73 %) of pure material identical to the one obtained previously.

MP 186°C

3,3-ethylenedioxy-5-hydroxy-11β-p-methoxyphenyl-17-trimethylsilyloxy-5α-estr-9-ene-17β-carbonitrile IIj

p-Methoxyphenylmagnesium bromide (7.5 ml of 0.79M strength in THF) and 30 mg CuCl, left for 1 hr at -30°C with 1.3 g of epoxide afforded 1.48 g (91 %) of the desired compound after chromatography.

MP 210°C (from isopropyl ether)
$[\alpha]_D^{20}$ -12° ± 2° (0.4 % in $CHCl_3$)

δ ppm 0.53 (18-Me) 3.77 (O Me), 11α-H centered at 4.25
Analysis : Calculated for $C_{31}H_{43}O_5NSi$ C 69.23 % H 8.05 % N 2.60 %
Found C 69.2 % H 8.4 % N 2.5 %

3,3-ethylenedioxy-5-hydroxy-11β-o-methoxyphenyl-17-trimethylsilyloxy-5α-estr-9-ene-17β-carbonitrile IIk

o-Methoxyphenylmagnesium bromide (25 ml of 1.2M strength in THF) and 100 mg CuCl, left at -10°C for 1 hr with 4.2 g of epoxide I afforded 4.54 g (87 %) of the desired 11β-o-methoxyphenyl steroid (noncrystalline).

$[\alpha]_D^{20}$ -16.5° ± 1° (0.5 % in $CHCl_3$)

δ ppm (18-Me) 3.65 (O Me) 11α-H centered at 4.52
Analysis : Calculated for $C_{31}H_{43}O_5NSi$ C 69.23 % H 8.05 % N 2.60 %
Found C 69.4 % H 7.9 % N 2.4 %

3,3-ethylenedioxy-5-hydroxy-11β-p-fluoro(phenyl)-17-trimethylsilyloxy-5α-estr-9-ene-17β-carbonitrile IIl

p-Fluorophenylmagnesium bromide (20 ml of 0.7M strength in THF)

and 60 mg CuCl, left at -15°C for 30 min. with 2.94 g of the epoxide I afforded a combined 3.31 g (90 %) of the desired compound (from direct crystallization and chromatography of the mother liquors).

MP 166°C (from isopropryl ether)
$[\alpha]_D^{20}$ -7.5° ± 2° (0.5 % in $CHCl_3$)

δ ppm 0.52 ppm (18-Me) 3.65 (O Me) 11α-H centered at 4.33
Analysis for $C_{30}H_{40}O_4NFSi$

Calculated	C 68.53 %	H 7.67 %	N 2.66 %	F 3.64 %
Found	C 68.8 %	H 7.7 %	N 2.6 %	F 3.7 %

3,3-ethylenedioxy-5-hydroxy-11β-p-trifluoromethyl(phenyl)-17-trimethylsilyloxy-5α-estr-9-ene-17β-carbonitrile IIm

p-Trifluoromethylphenylmagnesium bromide (5 ml of 0.45M strength in THF) and 10 mg CuCl at -20°C for 30 min with 430 mg of epoxide I afforded 472 mg (82 %) of the desired compound after chromatography.

MP 193-195°C (from isopropyl ether)
$[\alpha]_D^{20}$ -9.5° ± 1.5° (0.8 % in $CHCl_3$)

δ ppm 0.50 (18-Me) 11α-H centered at 4.42
Analysis for $C_{31}H_{40}O_4NF_3Si$

Calculated	C 64.67 %	H 7.0 %	N 2.43 %	F 9.9 %
Found	C 64.6 %	H 6.9 %	N2.3 %	F 10.0 %

3,3-ethylenedioxy-11β-benzyl-5-hydroxy-17-trimethylsilyloxy-5α-estr-9-ene-17β-carbonitrile IIo

Benzylmagnesium bromide (8.60 ml of 0.7M strength in THF) and 22 mg CuCl, left at -30°C overnight with 1.3 g of epoxide I afforded 1.02 g of the desired compound by direct crystallization from isopropyl ether. Chromatography of the mother liquors afforded an additional 550 mg (combined yield 99.5 %).
MP 152°C (from isopropyl ether)
$[\alpha]_D^{20}$ -86° ± 3° (0.3 % in $CHCl_3$)

δ ppm 1.17 (18-Me) benzylic CH_2 centered at 2.73
Analysis : Calculated for $C_{31}H_{43}O_4NSi$ C 71.35 % H 8.30 % N 2.68 %
Found C 71.0 % H 8.4 % N 2.6 %

13β-ethyl-17β-hydroxy-11β-vinyl-4,9-gonadien-3-one IV

The epoxide III (1.5 g) was reacted with vinylmagnesium bromide-CuCl as in the previous examples (-30°C overnight). After the usual work up, the crude extract was dissolved in 95° EtOH and refluxed in the presence of Redex CF sulfonic resin for 1 hr. Evaporation of the solvent and purification by chromatography, afforded 810 mg (60 %) of the desired dienone, as a resin.

M^+ 312 (required : 312)
$[\alpha]_D^{20}$ -43.5 ± 2.5° (0.5 % in $CHCl_3$)
δ ppm 1.08 (t, J = 7) C = CH_2 (from 4.67 to 5.17)

and $H\rangle C=C$ (from 5.67 to 6.33) H_4 at 5.70
λ max 302 nm (17400).

Ethynylation procedure is illustrated by the preparation of :

3,3-ethylenedioxy-11β-ethyl-17-ethynyl-5α-estr-9-en-5,17β-diol Vb

3,3-ethylenedioxy-11β-ethyl-5-hydroxy-17-trimethylsilyloxy-5α-estr-9-ene-17β-carbonitrile IIb (2.3 g) was dissolved in ethylenediamine (50 ml). Lithium acetylide-ethylenediamine complex (4.5 g) was added and the reaction mixture was heated at 45-50°C for 2 hrs. The work up was performed by pouring into ice-water and extracting with ether, affording 1.95 g of the crude product. Generally this compound was used as such, without further characterization in the next step.

The physical data of the isolated compounds follow :

3,3-ethylenedioxy-17-ethynyl-11β-propyl-5α-estr-9-ene-5,17β-diol Ve

MP 170°C (from ethyl ether)
$[\alpha]_D^{20}$ - 116.5° ± 3.5° (0.35 % in $CHCl_3$)
δ ppm 18-Me 1.00
Analysis : Calculated for $C_{25}H_{36}O_4$ C 74.96 % H 9.05 %
C 74.7 % H 9.3 %

3,3-ethylenedioxy-17-ethynyl-11β-isopropyl-5α-estr-9-ene-5,17β-diol Vd

MP 175°C (from petroleum ether-ethyl acetate 9:1)
$[\alpha]_D^{20}$ -133° ± 3.5° (0.5 % in $CHCl_3$)
δ ppm 18-Me 1.04
Analysis : Calculated for $C_{25}H_{36}O_4$ C 74.96 % H 9.05 %
C 74.7 % H 9.0 %

3,3-ethylenedioxy-17-ethynyl-11β-vinyl-5α-estr-9-ene-5,17β-diol Vf

MP 160°C (from isopropyl ether)
$[\alpha]_D^{20}$ -100° ± 3° (0.5 % in $CHCl_3$)
δ ppm 18-Me 0.89
Analysis : Calculated for $C_{24}H_{32}O_4$ C 74.96 % H 8.39 %
C 75.0 % H 8.5 %

3,3-ethylenedioxy-17-ethynyl-11β-isopropenyl-5α-estr-9-ene-5,17β-diol Vg

MP 193°C (from isopropyl ether)

$[\alpha]_D^{20}$ -84° ± 3° (0.5 % in $CHCl_3$)

δ ppm 18-Me 0.92

Analysis : Calculated for $C_{25}H_{34}O_4$ C 75.34 % H 8.59 %
Found C 75.0 % H 8.3 %

3,3-ethylenedioxy-17-ethynyl-11β-p-methoxyphenyl-5α-estr-9-ene-5, 17β-diol Vj

MP = 150°C (from isopropyl ether)
$[\alpha]_D^{20}$ -41° ± 2.5° (0.5 % in $CHCl_3$)

δ ppm 18-Me 0.475

Analysis : Calculated for $C_{29}H_{36}O_5$ C 74.96 % H 7.81 %
Found C 74.8 % H 7.7 %

3,3-ethylenedioxy-17-ethynyl-11β-(2-thienyl)-5α-estr-9-ene-5,17β-diol

MP 140°C (from ether-chloroform)
$[\alpha]_D^{20}$ -17.5° ± 2° (0.5 % in $CHCl_3$)

δ ppm 18-Me 1.14

Analysis : Calculated for $C_{29}H_{36}O_4$ C 77.64 % H 8.08 %
Found C 77.4 % H 8.3 %

Deketalization-dehydration procedure is exemplified by the preparation of :

11β-ethyl-17-ethynyl-17β-hydroxy-4,9-estradien-3-one VIb

1.95 g of the crude product Vb was dissolved in 95 % ethanol (100 ml). Sulfonic resin "Redex CF" (1.95 g) was added and the mixture was refluxed for 30 min. The beads were removed by filtration, washed with 10 ml chloroform and the filtrate was evaporated to dryness, yielding 1.59 g (98 % overall from IIb) of the crystalline dienone VIb. Recrystallization from isopropyl ether afforded the pure sample (60 % yield), of the dienone VIb.

MP 177°C
$[\alpha]_D^{20}$ -202° ± 4° (0.5 % in $CHCl_3$)

δ ppm 18-Me 1.07

Analysis : Calculated for $C_{22}H_{28}O_2$ C 81.44 % H 8.70 %
Found C 81.2 % H 8.8 %

The following compounds were obtained in the same way :

17-ethynyl-17β-hydroxy-11β-propyl-4,9-estradien-3-one VIc

Yield : 97 % from Vc
MP 185°C (from isopropyl ether)
$[\alpha]_D^{20}$ -151.5° ± 3.5°
λ max 304 nm (20300)

δ ppm 18-Me 1.07
Analysis : Calculated for $C_{23}H_{30}O_2$ C 81.61 % H 8.93 %
Found C 81.6 % H 8.9 %

17-ethynyl-17β-hydroxy-11β-isopropyl-4,9-estradien-3-one VId

Yield : 93 % from Vd after chromatography
MP 178°C (from isopropyl ether)
$[\alpha]_D^{20}$ -165.5° ± 4° (0.4 % in $CHCl_3$)
λ max 304 nm (16500)
δ ppm 18-Me 1.09
Analysis : Calculated for $C_{23}H_{30}O_2$ C 81.61 % H 8.93 %
Found C 81.6 % H 8.9 %

11β-decyl-17-ethynyl-17β-hydroxy-4,9-estradien-3-one VIe

Yield : 50 % from crude Ve after chromatography
Noncrystalline compound
$[\alpha]_D^{20}$ -103° ± 3° (0.5 % in $CHCl_3$)
λ max 305 nm (18900)
δ ppm 18-Me 1.07
Analysis : Calculated for $C_{30}H_{44}O_2$ C 82.51 % H 10.15 %
Found C 82.5 % H 10.3 %

17-ethynyl-17β-hydroxy-11β-vinyl-4,9-estradien-3-one VIf

Yield : 85 % from Vf after chromatography
MP 125°C (from isopropyl ether)
$[\alpha]_D^{20}$ -94° ± 3° (0.5 % in $CHCl_3$)
λ max 301 nm (20200)
δ ppm 18-Me 0.98
Analysis : Calculated for $C_{22}H_{26}O_2$ C 81.94 % H 8.12 %
Found C 81.9 % H 8.1 %

17-ethynyl-17β-hydroxy-11β-isopropenyl-4,9-estradien-3-one VIg

Yield : 56 % from Vg after chromatography and recrystallization from $CHCl_3$-isopropyl ether.
MP 190°C
$[\alpha]_D^{20}$ -110° ± 2.5° (0.5 % in $CHCl_3$)
λ max 302-303 nm (20200)
δ ppm 18-Me 0.98
Analysis : Calculated for $C_{23}H_{28}O_2$ C 82.10 % H 8.38 %
Found C 82.1 % H 8.1 %

11β-allyl-17-ethynyl-17β-hydroxy-4,9-estradien-3-one VIh

Yield : 76 % from IIh after chromatography

MP 167°C (from isopropyl ether)
$[\alpha]_D^{20}$ -137.5° ± 3° (0.5 % in $CHCl_3$)
λ max 304 nm (20500)
δ ppm 18-Me 1.09

17-ethynyl-17β-hydroxy-11β-phenyl-4,9-estradien-3-one VIi

Yield undertermined (from mother liquors of IIi)
Due to the small amount of material available, the structure was only secured by the NMR spectrum.
δ ppm 0.53 (18-Me) 2.63 (C≡C-H)H-11α centered at 4.45 H-4 at 5.77 and aromatic protons centered at 7.22
$[\alpha]_D^{20}$ +47.5° ± 2° (0.45 % in $CHCl_3$)

17-ethynyl-17β-hydroxy-11β-p-methoxyphenyl-4,9-estradien-3-one VIj

Yield : 97 % from Vj after chromatography
MP 200°C (from isopropyl ether)
$[\alpha]_D^{20}$ +101.5° ± 3° (0.3 % in $CHCl_3$)
λ max 302 nm (19300)
λ max 228-229 nm (14700)
δ ppm 18-Me 0.55
Analysis : Calculated for $C_{27}H_{30}O_3$ C 80.56 % H 7.51 %
Found C 80.4 % H 7.5 %

17-ethynyl-17β-hydroxy-11β-o-methoxyphenyl-4,9-estradien-3-one VIk

Yield : 74 % from IIk after chromatography
MP 235°C (from isopropyl ether)
$[\alpha]_D^{20}$ -28° ± 1.5° (0.45 % in $CHCl_3$)
λ max 307 nm (19700)
Other absorptions at 217 nm (E_1^1=308) 240 nm (E_1^1=116) and 282 nm (E_1^1=285).
δ ppm 18-Me 0.69
Analysis : Calculated for $C_{27}H_{30}O_3$ C 80.56 % H 7.51 %
Found C 80.3 % H 7.7 %

17-ethynyl-17β-hydroxy-11β-p-fluorophenyl-4,9-estradien-3-one VIl

Yield : 63 % analytical sample from IIl after chromatography and recrystallization (isopropyl ether).
MP 222°C
$[\alpha]_D^{20}$ +53.5° ± 2.5° (0.6 % in $CHCl_3$)
λ max 300-301 nm (20200)
Other absorptions (inflex.) at 215 nm (E_1^1=260) 236 nm (E_1^1=115) 269 nm (E_1^1=184) and 275 nm (E_1^1=253)
δ ppm 18-Me 0.525
Analysis : Calculated for $C_{26}H_{27}O_2F$ C 79.97 % H 6.97 % F 4.87 %
Found C 80.0 % H 7.2 % F 4.6 %

17-ethynyl-17β-hydroxy-11β-(2-thienyl)-4,9-estradien-3-one VIn

Yield : 67 % from Vn after chromatography and recrystallization (isopropyl ether).
MP 210°C
$[\alpha]_D^{20}$ +94.5° ± 3° (0.5 % in $CHCl_3$)
λ max 237-238 nm (11900)
λ max 300 nm (19800)
δ ppm 18-Me 0.68

Analysis :	Calculated for $C_{24}H_{26}O_2S$	C 76.15 %	H 6.92 %	S 8.47 %
	Found	C 76.1 %	H 6.7 %	S 8.3 %

11β-benzyl-17-ethynyl-17β-hydrox-4,9-estradien-3-one VIo

Yield : 73 % from Vo after chromatography
MP 179°C (from ethyl acetate-petroleum ether)
$[\alpha]_D^{20}$ -185° ± 3° (0.3 % in $CHCl_3$)
λ max 304 nm (16700)
δ ppm 18-Me 1.21

Analysis :	Calculated for $C_{27}H_{30}O_2$	C 83.89 %	H 7.82 %	
	Found	C 83.6 %	H 7.9 %	

11β-allyl-17β-hydroxy-4,9-estradien-3-one VIII by rearrangement of 10β-allyl-17 -hydroxy-4,9(11)-estradien-3-one VII

A solution of VII (60 mg in xylene (2 ml) was refluxed for 6 hrs under nitrogen. Chromatographic separation of the crude mixture afforded 9.5 mg (16 %) of recovered starting material, 25 mg (41.5%) of 4-allyl-17β-hydroxy-5(10),9(11)estradien-3-one (determined by IR, UV and NMR) and 8.5 mg (14 % of the desired 11β-allyl-17β-hydroxy-4,9-estradien-3-one VIII.

δ ppm 0.98 (18-Me) 5.69 (H-4)
(δ 18-Me = 0.89 in the unsubstituted analog)
ν cm^{-1} 3600, 1650 (broad), 1601, 990 and 911.

The aromatization procedure is illustrated by the preparation of :

11β-ethyl-17-ethynyl-1,3,5(10)-estratriene 3, 17β-diol IXb

230 mg of VIb were dissolved in methylene chloride (1.5 ml). The solution was cooled to 0°C and acetic anhydride (0.25 ml) followed by acetyl bromide (0.125 ml) was added. After 1 hr at 0°C the reaction mixture was poured into aqueous sodium bicarbonate and extracted with chloroform. The solvent was removed under reduced pressure and the residue was dissolved in methanol (12.5 ml). A 10N sodium hydroxide solution (1 ml) was added and the reaction mixture was kept at room temperature for 2 hrs. Acidification by diluted sulfuric acid and chloroform extraction afforded the crude product, which was purified by chromatography yielding 175 mg (76 %) of

pure compound.
MP 178°C (from petroleum ether)
$[\alpha]_D^{20}$ +85° ± 2° (0.5 % in $CHCl_3$), δ ppm 18-Me 1.02
Δε 275 nm (+0.11) max 232 nm (+1.5) max 206 nm (-2) max 197 (+7)
Analysis : Calculated for $C_{22}H_{28}O_2$ C 81.44 % H 8.70 %
Found C 81.1 % H 8.9 %

The following compounds were obtained in the same way :

17-ethynyl-11β-propyl-1,3,5(10)-estratriene-3,17 -diol IXc
Yield : 70 % after chromatography
MP 120°C
$[\alpha]_D^{20}$ +81.5° ± 2° (0.4 % in $CHCl_3$), δ ppm 18-Me 1.02
Analysis : Calculated for $C_{23}H_{30}O_2$ C 81.61 % H 8.93 %
Found C 81.6 % H 9.0 %

17-ethynyl-11β-isopropyl-1,3,5(10)-estratrien-3,17β-diol IXd
Yield: 36 % After chromatography
M^+ 338 (required : 338)
MP 184°C (from petroleum ether-methylene chloride)
$[\alpha]_D^{20}$ +60.5° ± 2.5° (0.3 % in $CHCl_3$)
δ ppm 18-Me 1.08, iPr 0.35 d, J = 6 and 0.97 d, J = 6
Analysis : Calculated for $C_{23}H_{30}O_2$ C 81.61 % H 8.93 %
Found C 81.2 % H 9.0 %

11β-decyl-17-ethynyl-1,3,5(10)-estratriene-3,17β-diol IXe
Yield: 75 % After chromatography
MP 144°C (from petroleum ether)
$[\alpha]_D^{20}$ +54° ± 2.5) (0.5 % in $CHCl_3$), δ ppm 18-Me 1.02
Analysis : Calculated for $C_{30}H_{44}O_2$ C 82.51 % H 10.15 %
Found C 82.5 % H 10.3 %

17-ethynyl-11β-vinyl-1,3,5(10)-estratriene-3,17β-diol IXf
Yield: 67 % after chromatography
MP 112°C (from petroleum ether)
$[\alpha]_D^{20}$ 0° (in $CHCl_3$)
Analysis : Calculated for $C_{22}H_{26}O_2$ C 81.94 % H 8.12 %
Found C 81.8 % H 8.2 %

11β-allyl-17-ethynyl-1,3,5(10)-estratriene-3,17β-diol IXj
Yield : 50 % after chromatorgraphy
MP 263°C (from $CHCl_3$ - MeOH)
$[\alpha]_D^{20}$ -142°± 2.5° (0.3 % in $CHCl_3$), δ ppm 18-Me 0.45
Analysis : Calculated for $C_{27}H_{30}O_3$ C 80.56 % H 7.51 %
C 80.3 % H 7.6 %

17-ethynyl-11β-o-methoxyphenyl-1,3,5(10)-estratriene-3,17β-diol IXk
Yield : 67 % after chromatography
MP 248°C (from isopropyl ether)
$[\alpha]_D^{20}$ -144° ± 3° (0.5 % in $CHCl_3$), δ ppm 18-Me 0.54
Analysis : Calculated for $C_{27}H_{30}O_3$ C 80.56 % H 7.51 %
Found C 80.4 % H 7.7 %

17-ethynyl-11β-(2-thienyl)-1,3,5(10)-estratriene-3,17β-diol IXn
Yield : 68% by direct recrystallization and chromatography of the mother liquors. The product is solvated by 1 mole $CHCl_3$.
MP 154°C (from $CHCl_3$-isopropyl ether)

$[\alpha]_D^{20}$ -56° ± 2.5° (0.6 % in $CHCl_3$), δ ppm 18-Me 0.58

Analysis for $C_{24}H_{26}O_2,CHCl_3$

Calculated	C 60.30 %	H 5.47 %	S 6.44 %	Cl 21.36 %
Found	C 60.0 %	H 5.5 %	S 6.5 %	Cl 21.5 %

11β-benzyl-17-ethynyl-1,3,5(10)-estratriene-3,17β-diol IXo

Yield : 81 % after chromatography

MP 152°C (from isopropyl ether)

$[\alpha]_D^{20}$ -46° ± 2) (0.6 % in $CHCl_3$), δ ppm 18-Me 1.12

Analysis : Calculated for $C_{27}H_{30}O_2$ C 83.89 % H 7.82 %

Found C 83.7 % H 7.8 %

REFERENCES

1) Presented in part at the Vth International Congress on Hormonal Steroids, New Dehli 1978.
2) Post Doctoral Fellow 1975 - 1976.
3) G. Teutsch and A. Bélanger, Tetrahedron Lett., 2051 (1979).
4) D. E. Wishart, J. Reprod. Fert., 30, 333 (1972).
5) J. S. Baran, Intra Science Chem. Repts., 3, 57 (1969).
6) a - J. S. Baran, D. D. Langford, I. Laos and C. D. Liang, Tetrahedron, 33, 609 (1977).
   b - R. B. Garland, J. R. Palmer and R. Pappo, J. Org; Chem., 41, 531 (1976).
7) J. C. Gasc and L. Nédélec, Tetrahedron Lett., 2005 (1971).
8) G. Costerousse, A. Farcilli and G. Teutsch, unpublished results.
9) J. P. Mornon, personal communication.
10) G. Nominé, R. Bucourt and A. Pierdet, C.R. Acad. Sci., 254, 1823 (1962).
11) C. Snozzi and B. Goffinet, French Patent 1290 876 (1976).
12) D. Philibert, T. Ojasoo and J. P. Raynaud, Endocrinology, 10 1850 (1977)
13) J. P. Raynaud, T. Ojasoo, M. M. Bouton and D. Philibert, in E. J. Ariens (ed), Drug Design, Vol VIII, Academic Press Inc., New York (1979) pp 169-214.
14) H. O. House, C. Y. Chu, J. M. Wilkins and M. J. Umen, J. Org. Chem., 40 1460 (1975).
15) C. H. Heathcock and C. G. Chavdarian, J. Amer, Chem; Soc;, 97 3822 (1975).