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SYNTHESIS OF 17β-ESTRADIOL DERIVATIVES WITH N-BUTYL, N-METHYL ALKYLAMIDE SIDE CHAIN AT POSITION 15

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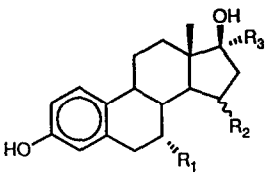
Abstract: New derivatives of 17β-estradiol with N-butyl, N-methyl alkylamide side chains of three different lengths at position 15 have been synthesized from estrone. Compounds **5** and **6** having a shorter alkylamide chain were obtained in eleven steps by introduction of a 15,16 double bond followed by an 1,4 addition of alkylcopper reagent and further transformations including hydrolysis, Jones' oxidation, amidation, reduction and cleavage of the protective group. Compound **7** having the longest alkylamide chain was synthesized by chain lengthening (five additional steps) of an intermediate obtained in the course of synthesis of compound **6**.

Steroidal compounds are essential regulators of a long series of important biological functions. Among them, estradiol (1) controls differentiation, growth and function of female reproductive tissues and is involved in the growth of estrogen-sensitive breast cancer[1,2]. Since estrogens are well known to play such a predominant role in the regulation of human breast cancer growth[1-3], a therapy based on the use of a pure antiestrogen (a compound able to block access to the estrogen receptor with high potency while not exerting by itself any activation of the receptor) seems a logical approach for the treatment of this disease. Unfortunately, so-far, the antiestrogens available, including Tamoxifen, possess mixed agonistic and antagonistic-estrogenic properties[1,2,4,5], thus limiting their potential as blockers of estrogen action. Such a lack of pure antiestrogenic activity could well explain the limited efficacy achieved with Tamoxifen in the therapy of breast cancer in women[3,4].

Since the transformation of estrone into the potent estrogen 17β-estradiol requires the action of the enzyme 17β-hydroxysteroid dehydrogenase[6], another potential site of blockade of estrogens is inhibition of this enzymatic step essential for estradiol formation. Our research efforts have thus been focused on the synthesis of compounds which could act simultaneously as pure blockers of the estrogen receptor and inhibitors of 17β-hydroxysteroid dehydrogenase activity. Based on the finding that 7α-alkylamide derivatives of estradiol (compound 2) possess pure antiestrogenic activity[4,5,7-9], we have already synthesized compound **3** [10], which has its alkylamide side chain at posi-

tion 17α of estradiol instead of 7α (compound 2). We have also synthesized 17α-alkynylamide derivatives of estradiol 4 [11] having side chains of various length (m=0,5,-8,10,11). In the present study, we report the synthesis of new derivatives of estradiol 5-7 having alkylamide chains of three different lengths at position 15.



1 R_1=R_2=R_3=H (Estradiol)
2 R_1=$(CH_2)_{10}$CONBuMe, R_2=R_3=H (ICI 164384)
3 R_1=R_2=H, R_3=$(CH_2)_{10}$CONBuMe
4 R_1=R_2=H, R_3= C≡C$(CH_2)_m$CONBuMe
5-7 R_1=R_3=H, R_2=$(CH_2)_{n-1}$CONBuMe (n=9,11,13)

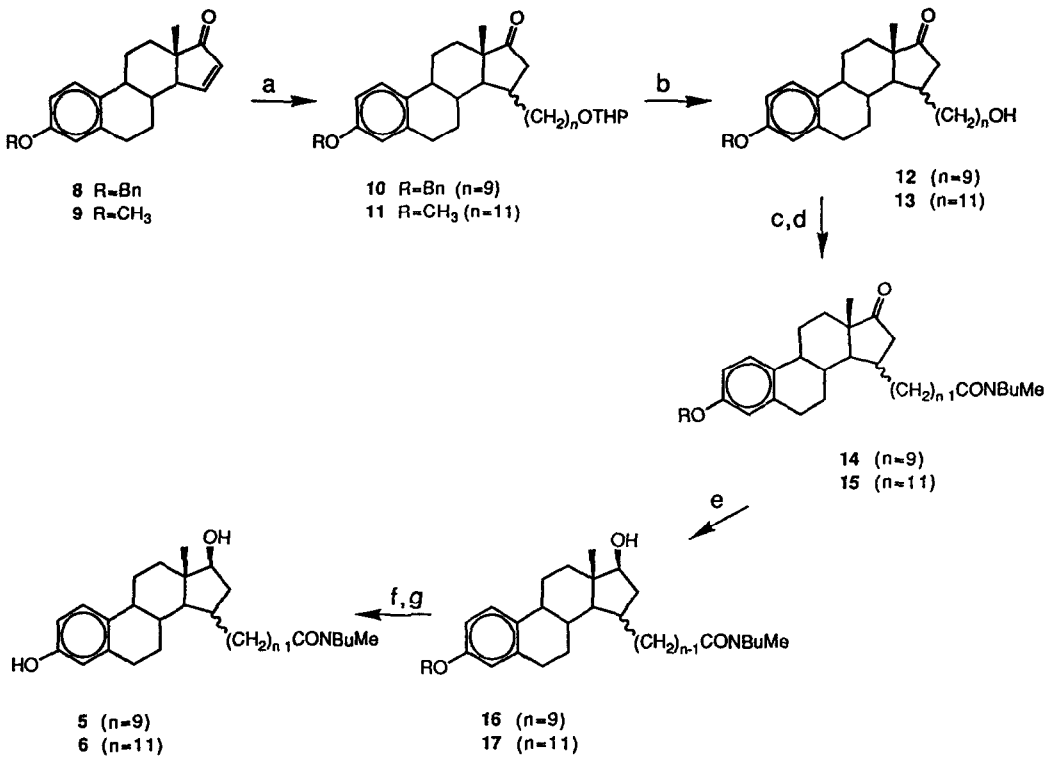
RESULTS AND DISCUSSION

Synthesis of compounds 5 and 6 (scheme 1)

Alkylation at steroidal C-15 position was achieved by 1,4-addition of organocopper reagent on the 15,16-unsaturated ketone. This approach requires the synthesis of an enone intermediate which includes the synthesis of 16-bromo-17-ketal estrone in one step ($PhN(CH_3)_3Br_3$, $HOCH_2CH_2OH$, THF) or two steps (1. p-TSA, $HOCH_2CH_2OH$ 2. pyr.HBr_3), dehydrobromination with potassium t-butoxide in dimethyl sulphoxide or xylene and hydrolysis of the ketal group with p-TSA in aqueous acetone. Using this approach, we have synthesized the 15,16-unsaturated ketones **8** and **9** from estrone. However, for preparation of compound **9**, 16-bromo-17-ketal estrone was obtained by another sequence, namely bromination with $CuCl_2$ in MeOH[15] and subsequent standard ketalyzation.

The first step in the synthesis of alkylamides **5** and **6** (scheme 1) was the introduction of an hydroxyalkyl group at position-15 by 1,4-addition of organocopper reagent ($Cu(CH_2)_nOTHP$, n = 9,11) generated from CuCl and the corresponding Grignard reagent. These Grignard reagents have been obtained from tetrahydropyranyl derivatives of commercially available 9-bromononanol or 11-bromoundecanol. Recently, Horiguchi et al.[16] have reported that copper-catalysed conjugate addition of the Grignard reagent in the presence of Me_3SiCl and HMPA proceeds in much higher yield than the reaction of conventional organocopper reagents and shows very good regio-, stereo-, and chemoselectivities. Using this methodology, we have obtained, after hydrolysis of the silyl enol ether intermediate, the 15-alkylated compounds **10** and **11** as a mixture of two isomers. Following this step, the THP-protective group was cleaved (p-TSA, MeOH) to give the alcohols **12** and **13**. The global yields for the introduction of the hydroxyalkyl group (two steps) were good at 62% and 66%, respectively, for compounds **12** (n = 9) and **13** (n = 11).

Scheme 1

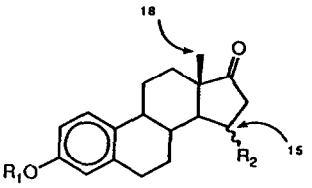


Reagents: **(a)** 1. $BrMg(CH_2)_nOTHP$(n = 9,11), CuCl, THF, HMPA, TMSCl; 2. K_2CO_3, MeOH **(b)** p-TSA, MeOH **(c)** Jones' reagent **(d)** 1. $N(Bu)_3$, ClCOOi-Bu, CH_2Cl_2; 2. HNBuMe **(e)** $NaBH_4$, MeOH **(f)** H_2, Pd/C (10%), AcOEt **(g)** BBr_3, CH_2Cl_2

The proportion of the C-15 (α:β) isomeric mixture was evaluated by NMR-spectroscopy using the intensity of the 18-CH_3-signal (Table 1). We have observed a proportion of about 15% for the minor isomer and 85% for the major isomer. The minor isomer has signals at 0.90 ppm (for THP-derivatives) and 0.96 ppm (for alcohols) while the signal of the major isomer appears at 1.02 ppm for THP or the alcohol derivative. In fact, the β-isomer shows a "pseudo" 1,3-diaxial interaction[17] between the 15β-methylene group and 18-CH_3. This interaction shields the 18-CH_3 signal near 0.90-0.96 ppm while for the α-isomer, this interaction does not exist and the 18-CH_3 signal appears at 1.02 ppm. These observations are in agreement with the analysis of enone 8 or 9 by the Drieding model, which shows that the organocopper-attack is mainly performed on the less hindered α-side instead of the β-steroidal side. Thus, the minor isomer corresponds to 15β-derivatives of estrone while the major isomer corresponds to 15α-derivatives.

Table 1

NMR-chemical shifts of 18-CH_3 for the isomeric mixture at position-15



Compounds	R_1	R_2	δ 18-CH_3 of isomers (ppm) Minor	Major	Proportion 15β:15α
10	Bn	$(CH_2)_9$ OTHP	0.90	1.02	13:87
11	CH_3	$(CH_2)_{11}$OTHP	0.90	1.02	14:86
12	Bn	$(CH_2)_9$ OH	0.96	1.02	12:88
13	CH_3	$(CH_2)_{11}$OH	0.96	1.02	17:83

The mixture of 15α,15β-isomers was used for the additional steps of synthesis without separation. In fact, we have found more practical to obtain, at the end of the chemical sequence, an isomeric mixture of 15α and 15β-alkylamide estradiol, which can be separated to the corresponding isomers. Thus, during the synthesis illustrated in scheme 1, as well as that described in scheme 2, we always obtain a mixture of 15α- and 15β- isomers present in proportions of about 85 and 15%, respectively. Starting from alcohol **12** or **13**, the next step was the formation of amides **14** and **15**. The primary alcohol was firstly oxidized to carboxylic acid (Jones' reagent) which, without purification, was transformed to the corresponding amide as described[18]. In this case, isobutyl chloroformate is used to activate the carboxylic acid by formation of a mixed anhydride. This anhydride, when submitted to the action of methyl butylamine, gives the corresponding amide in good yields (77% and 70% for compounds **14** and **15**, respectively, obtained in two steps). The formation of amide compounds was confirmed in i.r. spectroscopy by the disappearance of the OH-band of the alcohol or acid and by the appearance of a carbonyl band of the amide group (1630 or 1640 cm^{-1}). By NMR spectroscopy (200 MHz), we observed two singlets at 2.91 and 2.97 ppm (N-CH_3, two rotamers) as well as two triplets at 3.25 and 3.36 ppm (N-$\underline{CH_2}CH_2$, two rotamers) which are typical of similar alkylamide compounds[11].

Reduction of ketoamides **14** and **15** by $NaBH_4$ permits to obtain the hydroxyamides **16** and **17** in excellent yield (91-96%). The angular 18-CH_3 group provides excellent facial selectivity for the reduction of 17-keto steroids with an unsubstituted D-ring[19]. However, this selectivity for the 17β-alcohol is not obvious when 16α- or 15α-substituents are present. In fact, 16α-halogeno-17-keto steroids give substantial amounts of 17α-alcohol while other 16α-substituents (ethyl, alkyl, benzyl and alkene or alkyne derivatives) give 17β-acohol[20] For 15β-alkylamide compounds, the 17β-alcohols

are obtained (two groups on β-side of steroid) but for 15α-alkylamide compounds, the result of reduction is less predictable. The methyl group is however closer than the bulky 15α-substituent and its influence will probably be more important. Moreover, analysis of the Drieding model shows that hydride attack will be mainly performed onto the α-side of the 17-ketone leading to the 17β-alcohol. In our case, we observed, after reduction, a 15β and 15α-isomeric mixture (∿ 15: 85) of the 17β-alcohol[21]. By NMR, 18-CH_3 was shielded to 0.80 ppm (minor 15β-isomer) and 0.88 ppm (major 15α-isomer) while a new signal was observed at 3.70 ppm for the 17α-proton.

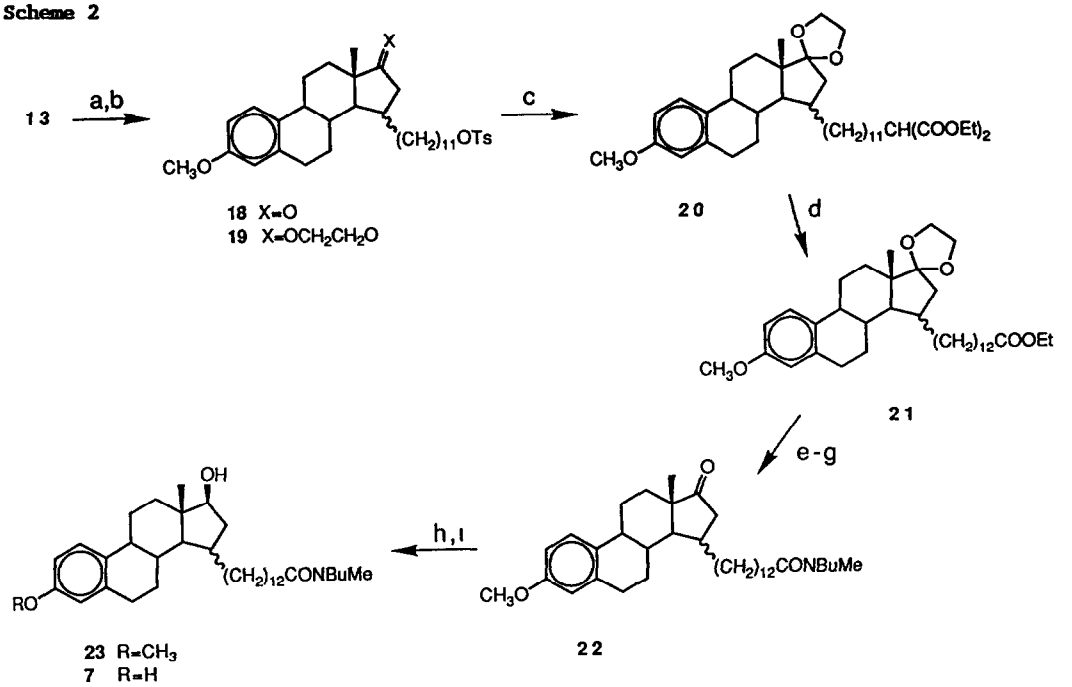
The final step was the cleavage of the protecting group. The benzyl group of compound **16** was removed by catalytic hydrogenation at atmospheric pressure (H_2, Pd/C (10%))[22] to give phenol **5** (n=9) at a yield of 82%. The reaction was slow but complete after 24h. The other alkylamide derivative of E_2 **17** (n=11) was demethylated with BBr_3 at 0°C[23]. Three equivalents of reagent were needed to perform this transformation since two equivalents were chelated by hydroxyl- and amide-groups and were not available for demethylation. The reaction was fast but proceeded at a moderate yield to give 65% of phenol **6**. The 15α-akylamide derivatives of E_2 (**5**,**6**) were characterized by i.r. spectroscopy with an hydroxyl band at 3280 cm^{-1} and a carbonyl band for the amide at 1610 cm^{-1}. By NMR spectroscopy, the 18-CH_3 signals (0.80 and 0.88 ppm) were not affected by cleavage of the distant protecting group at position-3. We observed the characteristic signals of the amide side chain at 2.91 and 2.97 ppm (2s, CH_3NCO) as well as at 3.26 and 3.36 ppm (2t, $CH_2\underline{CH_2}NCO$). The 17α-proton appears at 3.7 ppm as a triplet while a broad signal was seen at 5.10 or 6.15, respectively, for the phenolic proton of compound **5** or **6**. Mass spectral analysis was also in agreement with the indicated chemical structure.

Synthesis of compound 7 (scheme 2)

The compound with the longer alkylamide side-chain **7** has been synthesized by a different route (scheme 2). In fact, bromotridecanol was not commercially available and, instead of synthesizing this starting material, we preferred to use the isomeric mixture of ketoalcohol **13** which was an intermediate previously obtained in the synthesis of compound **6**. The reaction sequence consists in lenghtening the alkyl side chain of two carbon units. Thus, the keto alcohol **13** was tosylated followed by ketalyzation with ethylene glycol to lead compound **19**. The tosylate group was then substituted by diethyl sodium malonate in refluxing THF to give the diethylmalonate derivative **20** with a 90% yield. Decarboalkoxylation of **20** was performed using wet lithium chloride in DMF at reflux[24], thus giving the monoester **21** at a typical yield of 62% for this type of reaction[25].

This sequence of reactions (substitution of the tosylate group and decarboalkoxylation) was also performed without 17-ketone protection. However, in this case, the yields were much lower (51% and 29%, respectively). The formation of ester **21** was supported

Scheme 2



Reagents: (a) $N(Et)_3$, p-TSCl, CH_2Cl_2 (b) p-TSA, $HOCH_2CH_2OH$, $PhCH_3$ (c) $NaCH(COOEt)_2$, THF (d) LiCl, H_2O, DMF (e) KOH (10%, p/v), MeOH (f) 1. $N(Bu)_3$, ClCOOi-Bu, CH_2Cl_2; 2. HNBuMe (g) p-TSA, H_2O, CH_3COCH_3 (h) $NaBH_4$, MeOH (i) BBr_3, CH_2Cl_2

by i.r. and MS data. Moreover, on NMR, the methine proton of the malonate residue (3.30 ppm) was replaced by methylene protons of the ester group (2.29 ppm) and only one ethyl group was observed by NMR integration. The following three steps were KOH hydrolysis of the ester to carboxylic acid, the previously described amide formation, and, finally, hydrolysis of the ketal group. The resulting keto amide 22 was then obtained at a global yield of 88%. The other two steps were the reduction of the ketone to 17β- alcohol[21] with the same selectivity as previously reported and, the final cleavage of the methoxy group to yield phenol 7. The new amide compound 7(n=13) showed the same spectroscopic characteristics than the other amides 5 and 6 (n=9,11) on i r or NMR-spectroscopic analysis but mass spectrometry gave the expected suitable higher mass (565, M^+)

HPLC separation of compounds 5, 6 and 7

As indicated earlier, we then separated the phenolic alkylamides 5, 6 an 7. The 15α,15β-isomeric mixture of these compounds as well as their precursor inter

mediate compounds, show only one spot on usual TLC systems and, consequently, could not be separated by conventional column chromatography. Using HPLC (Table 2), it was possible to separate the isomeric mixture of compounds with longer side-chains **6** and **7** to the corresponding isomers **6a**, **6b** and **7a**, **7b**, while the other isomeric mixtures having a shorter side chain, compound **5**, could not be separated by this approach. We thus observed that side chain length (i.e. number of methylene groups) markedly influences the polarity of the molecule and, consequently, their chromatographic characteristics. In fact, the solvent systems used for the separation of compound **7** (n=13) was not appropriate for the separation of compound **6** (n=11), and the two different solvent systems used for compounds **6** and **7** were not suitable for the separation of compound **5** (n=9). Other solvent systems in normal phase or reverse phase chromatography were also unable to achieve separation of compound **5** to **5a** and **5b**.

Table 2

HPLC separation of 15α,15β-isomeric mixture of phenolic alkylamides **5**, **6** and **7**

Compounds [a]	Eluent system [b,c]	Flow rate ml/min	Retention time (min) major (α)	Retention time (min) minor (β)
5 (n=9)	A or B (unresolved)	--	--	--
6 (n=11)	A	9	72	81
	A	7	140	157
	B (unresolved)	--	--	--
7 (n=13)	B	30	45	51

(a) n= number of methylene groups on alkylamide side chain
(b) HPLC: Waters, column: PrePak μ Porasil (10 μm), UV detection: 280 nm
(c) A: hexane-ethyl acetate-acetonitrile/84:12:4 (v/v/v)
B: hexane-tetrahydrofuran/85:15 (v/v)

In summary, three new compounds with an alkylamide side chain ($(CH_2)_{n-1}CONBuMe$, n=9, 11, 13) at the 15α or 15β position of estradiol have been synthesized in 11 or 16 steps. Following introduction of a 15,16-double bond into the steroidal D-ring, the conjugate addition of organocopper reagent leads to a mixture of two isomers, namely a major 15α-chain (n=9 or 11) (∿ 85%) and a minor 15β-chain (n=9 or 11) (∿15%) Subsequent chemical modification permits to obtain the phenolic amides **5** and **6** with good overall yields. The amide **7** was synthesized by chain lengthening using an intermediate (compound **13**) obtained during the synthesis of compound **6** HPLC was used to resolve the isomeric mixtures of compounds **6** and **7** to isomers **6a**, **6b** and **7a**, **7b**. These new compounds are now under investigation in various systems for assay of biological activity.

EXPERIMENTAL

Chemical reagents were purchased from Aldrich Chemical Company (Milwaukee, WI) or Sigma Chemical Company (St. Louis, MO), while most solvents were obtained from BDH Chemicals (Montréal, Canada). Thin-layer chromatography (TLC) was performed on 0.25 mm Kieselgel $60F_{254}$ plates (E. Merck, Darmstadt, FRG), while 70-230 mesh Kieselgel $60F_{254}$ (E. Merck, Darmstadt, FRG) was used for dry column or column chromatography. Infrared spectra (i.r.) were obtained on a Perkin-Elmer 1310 spectrophotometer while nuclear magnetic resonance spectra (NMR) were recorded with a Varian EM-360A (60 MHz) or Varian XL-20 (200 MHz) spectrometer using tetramethylsilane (TMS) as internal standard. Ultraviolet spectra (u.v.) were obtained on a Beckman DU-6 spectrophotometer with appropriate solven Mass spectra (MS) were recorded with a V.G. Micromass 16F while high resolution mass spectra (HRMS) were provided by Le Centre Régional de Spectrométrie de Masse, Université de Montréal, Montreal, Canada.

SYNTHESIS OF 15,16-UNSATURATED ESTRONES 8 AND 9

Formation of 15,16-unsaturated ketone was performed using a well known methodology[12-14] which is discussed in detail in the Results and Discussion section.

3-Benzyloxy-1,3,5(10),15-estratetraene-17-one (8). White solid from hexane:ethyl acetate, 90:10, v/v, mp 102-104°C; i.r. ν (KBr): 3010 w, 2980-2800, 1685, 1595, 1570 w, 1490, 1225, 1015, 810 cm^{-1}; NMR-200 δ ($CDCl_3$): 1.16 (s, 3H, 18-CH_3), 2.86 (m, 2H,6-CH_2), 5.02 (s, 2H, Ph$\underline{CH_2}$O), 6.21 (dd, J_1=2.3 Hz and J_2=6.3 Hz, 1H, 15-CH), 6.69 (d, J=2.7 Hz, 1H, 4-CH), 6.77 (dd, J_1=3.1 Hz and J_2=8.6 Hz, 1H, 2-CH), 7.08 (d, J=8.6 Hz, 1H, 1-CH), 7.40 (m, 5H, $\underline{Ph}CH_2O$), 7.61 (dd, J_1=2.3 Hz and J_2=6.3 Hz, 1H, 16-CH); u.v. λmax (MeOH): 2 (shoulder), 278 (ε=2250) nm; MS m/e (rel. intensity): 358(M^+,33), 282(4.2), 262(10), 135(100), 91(91); HRMS M^+ calculated for $C_{25}H_{26}O_2$: 358.1933, found: 358.1931.

3-Methoxy-1,3,5(10),15-estratetraene-17-one (9). Colorless needles from hexane: ethyl acetate, 80:20, v/v, mp 178-179°C (Litt. 180-181°C)[26]; i.r. ν (KBr): 2995 w, 2960-2820, 1700, 1605, 1570 w, 1490, 1250, 1035, 815 cm^{-1}; NMR-200 δ ($CDCl_3$): 1.11 (s, 3H, 18-CH_3), 2.96 (m, 2H, 6-CH_2), 3.79 (s, 3H, CH_3O), 6.09 (dd, J_1=2.9 Hz and J_2=6.2 Hz, 1H, 15-CH), 6.67 (d, J=2.6 Hz, 1H, 4-CH), 6.74 (dd, J_1=2.6 Hz and J_2=8.4 Hz, 1H, 2-CH), 7.21 (d, J=8 Hz, 1H, 1-CH), 7.63 (dd, J_1=2.2 Hz and J_2=6.2 Hz, 1H, 16-CH); u.v. λmax (MeOH): 223 (ε=14000), 278 (ε=2200) nm; MS m/e (rel. intensity): 282 (M^+, 100), 267 (7.7), 254 (30), 239 (17), 225 (54); HRMS M^+ calculated for $C_{19}H_{22}O_2$: 282.1620, found: 282.1615.

GENERAL PROCEDURE FOR ADDITION OF ORGANOCOPPER REAGENT TO 15,16-UNSATURATED ESTRONE (SYNTHESIS OF COMPOUNDS 10 AND 11)

A. Preparation of appropriate bromo side chain ($Br(CH_2)_nOTHP$, n=9,11)

Tetrahydropyranyl derivatives of 9-bromononanol or 11-bromoundecanol were obtained according to the procedure described by Bucourt et al.[7]. The products obtained were in agreement with i.r., NMR and MS analysis. Before their use, these bromo side chains wer filtered through neutral alumina (Merck, type I, 70-230 mesh) with hexane as solvent and dried over molecular sieve (4A).

B. Preparation of Grignard reagent (solution stock: ∿ 1.3 mmol/1.0 ml)

Magnesium (16 mmol) was added in a dry three-neck flask under argon atmosphere and activated by iodine and heat. The system was then cooled to 0°C and a solution of bromo side chain (13 mmol, ∿ 4 ml) in dry tetrahydrofuran (6 ml) was added dropwise (about 1 h

The cooling bath was removed and the reaction mixture was allowed to react 2.5 h before its use.

C. Addition of organocopper reagent to conjugated ketone

Grignard reagent from stock solution (3.4 mmol, 2.6 ml) was added in a dry three-neck flask under argon atmosphere and cooled to -40 ± 5°C. Hexamethylphosphoramide (6.8 mmol) and copper chloride (0.17 mmol) were added to Grignard reagent followed by dropwise addition of 15,16 unsaturated estrone over a period of 1.6 h. The enone **8** (304 mg, 0.85 mmol) or **9** was dissolved in dry tetrahydrofuran (8 ml) and chlorotrimethylsilane (1.7 mmol). After standing overnight at room temperature, ammonium chloride 10% (p/v) was added and the reaction mixture was extracted with ethyl acetate, washed with brine and dried over $MgSO_4$ to give the crude 17-trimethylsilyloxy compound. This TMS derivative was hydrolysed by potassium carbonate (0.91 mmol) in methanol (50 ml) for 1 h at room temperature. Then, water was added and methanol was evaporated under reduced pressure before extraction with dichloromethane. The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane-ethyl acetate, 92:8, v/v) to give residual side chain and alkylated compound.

3-Benzyloxy-15(α,β)-{9'[(tetrahydro-2"H-pyran-2"-yl)oxy]-1'-nonanyl}-1, 3,5(10)-estratriene-17-one (10). Colorless oil (345 mg, 69% yield); i.r. ν (neat): 2905, 2830, 1720, 1595, 1560 w, 1480, 1015 cm^{-1}; NMR-200 δ($CDCl_3$): 0.97 and 1.02 (2s, 3H, 18-CH_3) two isomers (15β:15α/13:87), 2.92 (m, 2H, 6-CH_2), 3.45 and 3.80 (2m, 4H, 9'-CH_2 and OCH_2 of THP group), 4.56 (t, J≈2Hz, 1H, 2'-CH of THP group), 5.04 (s, 2H, Ph$\underline{CH_2}$O), 6.76 (s_{app} 1H, 4-CH), 6.79 (dd, J_1=2.6Hz and J_2= 8.4Hz, 1H, 2-CH), 7.21 (d,J=8.1, Hz, 1H, 1-CH), 7.38 (m, 5H, $PhCH_2O$); MS m/e (rel. intensity): 502 (M^+-DHP, 4.1), 484 (0.6), 411 (1.4), 393 (1.7), 91 (100).

3-Methoxy-15(α,β)-{11'-[(tetrahydro-2"H-pyran-2"-yl)oxy]-1'-undecyl}- 1,3,5(10)-estratriene-17-one (11). Colorless oil (2.53 g, 92% yield); i.r. ν (neat): 2910, 2840, 1725, 1600, 1565 w, 1490, 1025 cm^{-1}; NMR-200 δ ($CDCl_3$): 0.90 and 1.02 (2s, 3H, 18-CH_3) two isomers (15β:15α/14:86), 2.92 (m, 2H, 6-CH_2), 3.45 and 3.80 (2m, 4H, 11'-CH_2 and OCH_2 of THP group), 3.78 (s, 3H, CH_3O), 4.58 (t, J≈2Hz, 1H, 2'-CH of THP group), 6.66 (d, J=2.9 Hz, 1H, 4-CH), 6.72 (dd, J_1=2.6 Hz and J_2=8.4 Hz, 1H, 2-CH), 7.20 (d, J=8.4 Hz, 1H, 1-CH); MS m/e (rel. intensity): 539 (M^+, 1.3), 454 (79), 436 (60), 85 (100).

GENERAL PROCEDURE FOR HYDROLYSIS OF THE TETRAHYDROPYRANYL GROUP (SYNTHESIS OF ALCOHOLS 12 AND 13)

The tetrahydropyranyl derivatives **10** (219 mg, 0.37 mmol) or **11** (1.67 g, 3.10 mmol) were dissolved in methanol (50-100 ml) and p-toluenesulfonic acid (0.16-0.53 mmol) was added while the resulting solution was stirred at room temperature When the reaction was completed (1.5-4 h), water was added, methanol was evaporated under reduced pressure and the residue was extracted with ethylacetate. After evaporation of the organic phase, the crude product was purified by column chromatography (hexane-ethyl acetate, 80:20, v/v) to yield the alcohol.

3-Benzyloxy-15(α,β)-(9'-hydroxy-1'-nonanyl)-1,3,5(10)-estratriene-17-one (12). Colorless oil (169 mg, 90% yield); i.r. ν (neat): 3400, 2900, 2830, 1715, 1595, 1560 w, 1485 cm^{-1}; NMR-200 δ ($CDCl_3$): 0.97 and 1.02 (2s, 3H, 18-CH_3) two isomers (15β : 15α/12:88), 2.92 (m, 2H, 6-CH_2), 3.65 (m, 2H, $\underline{CH_2}OH$), 5.04 (s, 2H, Ph$\underline{CH_2}$O), 6.76(s_{app}, 1H,4-CH), 6.80 (dd, J_1=2.6 Hz and J_2= 8.4 Hz, 1H, 2-CH), 7.20 (d,J=8.4 Hz, 1H, 1-CH), 7.38 (m, 5H, $\underline{PH}CH_2O$); MS m/e (rel. intensity): 502 (M^+, 3.5), 484 (0.9), 411 (1.2), 393 (1.5), 91 (100); HRMS M^+ calculated for $C_{34}H_{46}O_3$: 502.3447, found: 502 3426.

3-Methoxy-15(α,β)-(11'-hydroxy-1'-undecyl)-1,3,5(10)-estratriene-17-one (13). Colorless oil (1.01 g, 72% yield); i.r. ν (neat): 3420, 2910, 2840, 1725, 1605, 1570 w, 1495 cm^{-1}; NMR-200 δ ($CDCl_3$): 0.96 and 1.02 (2s, 3H, 18-CH_3) two isomers (15β: 15α/17:83), 2.92 (m, 2H, 6-CH_2), 3.64 (t, J=6.4 Hz, 2H, $\underline{CH_2}OH$), 3.79 (s, 3H, CH_3O), 6.66 (d, J=2.6 Hz 1H, 4-CH), 6.72 (dd, J_1=2.9 Hz and J_2=8.4 Hz, 1H, 2-CH), 7.20 (d, J=8.1 Hz, 1H, 1-CH); MS m/e (rel. intensity): 454 (M^+, 100), 436 (10), 424 (6.0), 409 (2.6), 227 (30), 160 (42); HRMS M^+ calculated for $C_{30}H_{46}O_3$: 454.3447, found: 454.3422.

GENERAL PROCEDURE FOR OXIDATION OF ALCOHOL TO CARBOXYLIC ACID FOLLOWING BY AMIDE FORMATION (SYNTHESIS OF COMPOUNDS 14 AND 15)

To a cooled solution (0°C) of alcohol **12** (163 mg, 0.325 mmol) or **13** in acetone (40 ml), 0.24 ml of Jones' reagent (8N-chromic acid solution) was added dropwise. After 1 h isopropanol (2 ml) was added and the mixture was concentrated under vacuum. Water was added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated to dryness. Without purification, the crude carboxylic acid (i.r. acid band at 1700 and 2400-3600 cm^{-1}) was dissolved in dry dichloromethane (40 ml) and tributylamine (0.39 mmol). After cooling the mixture at -10°C, isobuty chloroformate (0.42 mmol) was added and allowed to react for 40 min. At this time, N-methylbutylamine in excess (3.3 mmol) was added and the cooling bath was removed. After 1.5 h, dichloromethane was added and the organic phase was washed with HCl(1N), saturated $NaHCO_3$ and water. After drying on $MgSO_4$, the solvent was removed and the crude amide was purified by dry column chromatography (hexane-ethyl acetate, 70:30, v/v).

N-butyl, N-methyl-9-(3'-benzyloxy-17'-oxo-1',3',5'(10')-estratrien-15'(α,β)-yl)-nonamide (14). Colorless oil (143 mg, 77% yield); i.r. ν (neat): 2900, 2835, 1720, 1630, 1595, 1560w, 1485 cm^{-1}; NMR-200 δ ($CDCl_3$): 0.92 and 0.95 (2t, J=6.6 Hz, 3H, $CH_2\underline{CH_3}$), 1.02 (s, 18'-CH_3 of major isomer (15'α) i.e. the singulet of minor isomer (15'β) is masqued by triplets of $CH_2\underline{CH_3}$), 2.9 (broad, 2H, 6-CH_2), 2.91 and 2.97 (2s, 3H, CH_3NCO), 3.25 and 3.3 (2t, J=7.3 Hz, 2H, $CH_2\underline{CH_2}NCO$), 5.04 (s, 2H, $Ph\underline{CH_2}O$), 6.76 (s_{app}, 1H, 4'-CH), 6.79 (dd, J_1=2.6 Hz and J_2=8.4 Hz, 1H, 2'-CH), 7.20 (d, J=8.4 Hz, 1H, 1'-CH), 7.38 (m, 5H, $\underline{Ph}CH_2O$); MS m/e (rel. intensity): 585 (M^+, 3.9), 494 (26), 475 (4.6), 459 (1 8), 91 (100); HRMS M calculated for $C_{39}H_{55}O_3N$: 585.4182, found: 585.4190.

N-butyl, N-methyl-11-(3'-methoxy-17'-oxo-1',3',5'(10')-estratrien-15'(α,β)-yl)-undecanamide (15). Colorless oil (285 mg, 70% yield); i.r. ν (neat): 2920, 2345, 1730, 1640, 1605, 1570 w, 1495 cm^{-1}; NMR-200 δ ($CDCl_3$): 0.92 and 0.95 (2t, J=7.0 Hz, 3H, $CH_2\underline{CH_3}$), 1.0 (s, 18'-CH_3 of major isomer (15'α) i.e. the singulet of minor isomer (15'β) is masqued by triplets of $CH_2\underline{CH_3}$), 2.9 (broad, 2H, 6'-CH_2), 2.91 and 2.96 (2s, 3H, CH_3NCO), 3.25 and 3.36 (2t, J=7.3 Hz, 2H, $CH_2\underline{CH_2}NCO$), 3.79 (s, 3H, CH_3O), 6.66 (d, J=2.6 Hz, 1H, 4'-CH), 6.72 (dd, J_1=2.6 Hz and J_2=8.4 Hz, 1H, 2'-CH), 7.20 (d, J=8.4 Hz, 1H, 1'-CH); MS m/e (rel intensity): 537 (M^+, 71), 519 (5.2), 504 (2.7), 424 (9.5), 348 (20); HRMS M^+ calculated for $C_{35}H_{55}O_3N$: 537:4182, found: 537.4142

GENERAL PROCEDURE FOR REDUCTION OF KETONE TO ALCOHOL (SYNTHESIS OF COMPOUNDS 16 AND 17)

A mixture of ketoamide **14** (130 mg, 0.22 mmol) or **15**, methanol (30 ml) and sodium borohydride (0.27 mmol) was stirred at room temperature for 1.5 h. Then, the reaction mixture was acidified (pH ∿ 5) with diluted HCl while and methanol was evaporated under reduced pressure. After extraction with dichloromethane, the organic phase was dried ($MgSO_4$) and the solvent removed. The crude alcohol was purified by dry column chromatography with hexane-ethyl acetate, 70:30, v/v as eluent.

N-butyl, N-methyl-9-(3'-benzyloxy-17'β-hydroxy-1',3',5'(10')- estratriene-15'(α,β)-yl)-nonamide (16). Colorless oil (126 mg, 96% yield); i.r. ν (film): 3400, 2900, 2830, 1615, 1560 w, 1480 cm^{-1}; NMR-200 δ ($CDCl_3$): 0.80 and 0.88 (2s, 3H, 18'-CH_3) two isomers (15'β: 15'α/13:87), 0.92 and 0.95 (2t, J=7.0 Hz, 3H, $CH_2\underline{CH_3}$), 2.88 (m, 2H, 6'-CH_2), 2.91 and 2.97 (2s, 3H, CH_3NCO), 3.26 and 3.37 (2t, J= 7 Hz, 2H, $CH_2\underline{CH_2}NCO$), 3.7 (m, 1H, $\underline{CH}OH$), 5.04 (s, 2H, $Ph\underline{CH_2}O$), 6.74 (d, J= 2.2 Hz, 1H, 4'-CH), 6.78 (dd, J_1= 2.2 Hz and J_2= 8 Hz, 1H, 2'-CH), 7.20 (d, J=8.4 Hz, 1H, 1'-CH), 7.38 (m, 5H, $\underline{Ph}CH_2O$); MS m/e (rel. intensity): 587 (M^+, 0.3), 496 (5.1), 478 (23), 91 (100); HRMS M^+ calculated for $C_{39}H_{57}O_3N$: 587.4338, found: 587.4349.

N-butyl, N-methyl-11-(3'-methoxy-17'β-hydroxy-1',3',5'(10')-estratriene-15'(α,β)-yl)-undecanamide (17). Colorless oil (199 mg, 91% yield); i.r. ν (neat): 3400, 2910, 2840, 1615, 1560 w, 1485 cm^{-1}; NMR-200 δ ($CDCl_3$): 0.80 and 0.88 (2s, 3H, 18'-CH_3) two isomers (15'β: 15'α/16:84), 0.92 and 0.95 (2t, J=7.0 Hz, 3H, $CH_2\underline{CH_3}$), 2.88 (m, 2H, 6'-CH_2), 2.91 and 2.96 (2s, 3H, CH_3NCO), 3.25 and 3.36 (2t, J=7.3 Hz, 2H, $CH_2\underline{CH_2}NCO$), 3.70 (t, J=7.5 Hz, 1H, $\underline{CH}OH$), 3.78 (s, 3H, CH_3O), 6.65 (d, J=2.9 Hz, 1H, 4'-CH), 6.71 (dd, J_1=2.9 Hz and J_2=8.4 Hz, 1H, 2'-CH), 7.20 (d, J=8.8 Hz, 1H, 1'-CH); MS m/e (rel. intensity): 539 (M^+, 29), 521 (100), 505 (19); HRMS M^+ calculated for $C_{35}H_{57}O_3N$: 539.4338, found: 539.4323.

CLEAVAGE OF BENZYLOXY GROUP (SYNTHESIS OF PHENOL 5)

The benzyloxy compound **16** (54 mg, 0.092 mmol) was dissolved in ethyl acetate (30 ml) containing 20 mg of 10% Pd/C. The reaction mixture was then shaken at room temperature under an atmospheric pressure of hydrogen for 25 h, filtered on celite and evaporated under reduced pressure. The crude phenolic compound was purified by column chromatography using hexane-ethyl acetate/70:30 to 50:50, v/v as eluents.

N-butyl, N-methyl-9-(3',17'β-dihydroxy-1',3',5'(10')-estratriene-15'(α,β)-yl)-nonamide (5). Colorless viscous oil (37 mg, 82% yield); i.r. ν (film): 3280, 2910, 2840, 1610 cm^{-1}; NMR-200 δ ($CDCl_3$): 0.80 and 0.88 (2s, 3H, 18'-CH_3) two isomers (15'β: 15'α/12:88), 0.92 and 0.95 (2t, J=7.0 Hz, 3H, $CH_2\underline{CH_3}$), 2.84 (m, 2H, 6'-CH_2), 2.91 and 2.97 (2s, 3H, CH_3NCO), 3.26 and 3.36 (2t, J=7.0 Hz, 2H, $CH_2\underline{CH_2}NCO$), 3.70 (t, J=7 Hz, 1H, $\underline{CH}OH$), 5.10 (s, 1H, OH phenol), 6.59 (d, J=2.9 Hz, 1H, 4'-CH), 6.63 (dd, J_1=2.6 Hz and J_2=8.4 Hz, 1H, 2'-CH), 7.14 (d, J=8.1 Hz, 1H, 1'-CH); MS m/e (rel. intensity): 497 (M^+, 10), 479 (20), 282 (100); HRMS M^+ calculated for $C_{32}H_{51}O_3N$: 497.3869, found: 497.3860.

CLEAVAGE OF METHOXY GROUP (SYNTHESIS OF PHENOL 6)

To a solution of methoxy compound **17** (105 mg, 0.195 mmol) in dry dichloromethane (15 ml) at 0°C, was added with stirring boron tribromide (0.585 mmol). After 2.5 h at 0°C, the reaction mixture was quenched by the addition of water, neutralized with saturated $NaHCO_3$ and extracted with dichloromethane and ethyl acetate. The combined organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude phenolic compound was purified by column chromatography with hexane-ethyl acetate, 70:30, v/v as eluent.

N-butyl, N-methyl-11-(3',17'β-dihydroxy-1',3',5'(10')-estratriene-15'(α,β)-yl)-undecanamide (6). Colorless viscous oil (67 mg, 65% yield); i.r. ν (film): 3280, 2910, 2840, 1610 cm^{-1}; NMR-200 δ ($CDCl_3$): 0.80 and 0.87 (2s, 3H, 18'-CH_3) two isomers (15'β: 15'α/18:82), 0.92 and 0.95 (2t, J=7.0 Hz, 3H, $CH_2\underline{CH_3}$), 2.84 (m, 2H, 6'-CH_2), 2.92 and 2.97 (2s, 3H, CH_3NCO), 3.26 and 3.36 (2t, J=7.3 Hz, 2H, $CH_2\underline{CH_2}NCO$), 3.70 (t, J=8.8 Hz, 1H, $\underline{CH}OH$), 6.15 (broad, 1H, OH phenol), 6.65 (dd, J_1=2.6 Hz and J_2=7.9 Hz, 1H, 2'-CH), 6.67 (s_{app}, 1H,

4'-CH), 7.13 (d, J=9.5 Hz, 1H, 1'-CH); MS m/e (rel. intensity): 525 (M^+, 18), 507 (25), 348 (12), 310 (33), 282 (19), 44 (100); HRMS M^+ calculated for $C_{34}H_{55}O_3N$: 525.4182, found: 525.4158.

SYNTHESIS OF TOXYLATE 18

To a solution of alcohol **13** (525 mg, 1.16 mmol) in dry dichloromethane (60 ml) and dry triethylamine (30 ml) was added p-toluenesulfonyl chloride (11.6 mmol). The reaction mixture was stirred at room temperature for 12 h. Then, water was added and organic solvents were evaporated under reduced pressure. The residue was extracted with ethyl acetate and the organic phase was washed with a solution of $NaHCO_3$ (10%, p/v) and dried with $MgSO_4$. After removal of solvent, the crude tosylate was purified by column chromatography with hexane- ethyl acetate, 90:10, v/v as eluent.

3-Methoxy-15(α,β)-(11'-p-tosyloxy-1'-undecyl)-1,3,5(10)-estratriene-17-one (18). Colorless oil (557 mg, 79% yield); i.r. ν (neat): 2910, 2840, 1725, 1600, 1570 w, 1490, 1355, 1170 cm^{-1}; NMR-200 δ ($CDCl_3$): 0.95 and 1.01 (2s, 3H, 18-CH_3) two isomers (15'β: 15'α/20:80), 2.44 (s, 3H, $\underline{CH_3}Ph$), 2.90 (m, 2H, 6-CH_2), 3.78 (s, 3H, CH_3O), 4.01 (t, J=6.4 Hz, 2H, $CH_2\underline{CH_2}OTs$), 6.65 (d, J=2.6 Hz, 1H, 4-CH), 6.71 (dd, J_1=2.6 Hz and J_2=8.8 Hz, 1H, 2-CH), 7.19 (d, J=8.8 Hz, 1H, 1-CH), 7.33 and 7.78 (2d, J=8.1 Hz, 4H, $CH_3\underline{Ph}$); MS m/e (rel. intensity): 608 (M^+, 72), 590 (3.9), 516 (4.9), 472 (13), 454 (35), 436 (85), 227 (76), 91 (100); HRMS M^+ calculated for $C_{37}H_{52}SO_5$: 608.3536, found: 608.3538.

PROTECTION OF 17-KETONE (SYNTHESIS OF KETAL 19)

To a solution of ketone **18** (557 mg, 0.92 mmol) in dry toluene (120 ml) was added ethylene glycol (12 ml) and p-toluenesulfonic acid (0.53 mmol). The resulting mixture was heated at reflux for 4 days in a Dean Stark apparatus. It was then diluted with a saturated solution of sodium bicarbonate and extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification was done by column chromatography (hexane-ethyl acetate, 90:10, v/v) to obtain 212 mg (38%) of starting material and 303 mg (51%) of ketal **19**.

3-Methoxy-17,17-ethylenedioxy-15(α,β)-(11'-p-tosyloxy-1'-undecyl)-1,3,5(10)-estratriene (19). Colorless oil (303 mg, 51% yield); i.r. ν (neat): 2910, 2840, 1590, 1565 w, 1490, 1350, 1170 cm^{-1}; NMR-200 δ ($CDCl_3$): 0.92 and 0.98 (2s, 3H, 18-CH_3) two isomers (15β: 15α/20:80), 2.44 (s, 3H, $\underline{CH_3}Ph$), 2.86 (m, 2H, 6-CH_2), 3.76 (s, 3H, CH_3O), 3.90 (m, 4H, OCH_2CH_2O), 4.01 (t, J=6.6 Hz, 2H, $CH_2\underline{CH_2}OTs$), 6.64 (d, J=2.6 Hz, 1H, 4-CH), 6.70 (dd, J_1=2.9 Hz and J_2=8.4 Hz, 1H, 2-CH), 7.19 (d, J=8.4 Hz, 1H, 1-CH), 7.33 and 7.78 (2d, J=8.1 Hz, 4H, $CH_3\underline{Ph}$); MS m/e (rel. intensity): 652 (M^+, 2.8), 608 (28), 590 (5.6), 564 (3.1), 436 (4.7), 423 (100); HRMS M^+ calculated for $C_{39}H_{56}SO_6$: 652.3828, found: 652.3798.

DISPLACEMENT OF TOSYLATE WITH SODIUM DIETHYL MALONATE (SYNTHESIS OF COMPOUND 20)

A. Preparation of sodium diethyl malonate (solution stock: 0.75 mmol/ 1.0 ml)

In a flame-dried flask under an argon atmosphere was added diethyl malonate (9.4 mmol, 1.43 ml), dry tetrahydrofuran (10 ml) and sodium hydride (8.6 mmol). The mixture was stirred and kept at room temperature until its use in the next step.

B. Substitution of tosylate by sodium diethyl malonate

To a solution of tosylate **19** (460 mg, 0.7 mmol) in dry tetrahydrofuran (35 ml) was added sodium diethyl malonate (two portions of 2.8 mmol) and the mixture heated at reflux.

The second portion of reagent was added 3 h after the beginning of reflux. After 10 h, ethyl acetate was added to the cooled reaction mixture and the organic phase washed with water and brine. The organic phase was dried ($MgSO_4$), filtered and evaporate under reduced pressure. The crude product was purified by column chromatography (hexane-ethyl acetate, 95:5, v/v) to give the diethyl malonate derivative **20**.

Ethyl-2-(ethoxycarbonyl)-13-(3'-methoxy-17',17'-ethylenedioxy-1',3',5'(10')-estratriene-15'(α,β)-yl)-tridecanoate(20). Light yellow oil (405 mg, 90% yield); i.r. ν (neat): 2910, 2840, 1730, 1600, 1565 w, 1490, 1150, 1035 cm^{-1}; NMR-200 δ ($CDCl_3$): 0.91 and 0.97 (2s, 3H, 18'-CH_3) two isomers (15'β: 15'α/19:81), 1.25 (t, J=7.0 Hz, 6H, $CH_2\underline{CH_3}$), 2.85 (m, 2H, 6-CH_2), 3.30 (t, J=7.0 Hz, 1H, $CH_2\underline{CH}(COOEt)_2$), 3.77 (s, 3H, CH_3O), 3.90 (m, 4H, OCH_2CH_2O), 4.18 (q, 4H, $\underline{CH_2}CH_3$), 6.63 (d, J=2.6 Hz, 1H, 4'-CH), 6.68 (dd, J_1=2.9 Hz and J_2=8.4 Hz, 2'-CH), 7.19 (d, J=8.4 Hz, 1H, 1'-CH); MS m/e (rel. intensity): 640 (M^+, 3.1), 596 (1.7), 578 (4.2), 549 (2.4), 411 (100); HRMS M^+ calculated for $C_{39}H_{60}O_7$: 640.4339, found: 640.4346.

DECARBOALKOXYLATION OF DIETHYL MALONATE DERIVATIVE (SYNTHESIS OF ESTER 21)

Diethyl malonate derivative **20** (400 mg, 0.625 mmol), dimethylformamide (80 ml), water (12.5 mmol) and lithium chloride (12.5 mmol) were stirred and heated at reflux for 12 h. The cooled reaction mixture was diluted with ethyl acetate and washed with HCl (1N) and brine. The organic phase was dried over $MgSO_4$ and solvent was evaporated. The crude ester was purified by column chromatography with hexane-ethyl acetate, 90:10, v/v as eluent.

Ethyl-13-(3'-methoxy-17',17'-ethylenedioxy-1',3',5'(10')-estratriene-15'(α,β)-yl)-tridecanoate (21). Colorless oil (219 mg, 62% yield): i.r. ν (neat): 2910, 2840, 1725, 1600, 1565 w, 1490, 1160, 1040 cm^{-1}; NMR-200 δ ($CDCl_3$): 0.92 and 0.98 (2s, 3H, 18'-CH_3) two isomers (15'β: 15'α/21:79), 1.25 (t, J=7.0 Hz, 3H, $CH_2\underline{CH_3}$), 2.29 (t, J=7.3 Hz, 2H, $CH_2\underline{CH_2}CO$), 2.88 (m, 2H, 6'-CH_2), 3.78 (s, 3H, CH_3O), 3.91 (m, 4H, OCH_2CH_2O), 4.13 (q, J=7.0 Hz, 2H, $\underline{CH_2}CH_3$), 6.65 (d, J=2.6 Hz, 1H, 4'-CH), 6.72 (dd, J_1= 2.6 Hz and J_2= 8.4 Hz, 1H, 2'-CH), 7.21 (d, J=9.2 Hz, 1H, 1'-CH); MS m/e (rel. intensity): 568 (M^+, 4.1), 523 (4.2), 339 (100); HRMS M^+ calculated for $C_{36}H_{56}O_5$: 568.4127, found: 568.4135.

TRANSFORMATION OF KETAL ESTER 21 TO KETONE AMIDE 22 (HYDROLYSIS OF ESTER, FORMATION OF AMIDE AND HYDROLYSIS OF KETAL GROUP)

1. Hydrolysis

To a solution of ester (212 mg, 0.37 mmol) in methanol (45 ml) was added an aqueous solution of KOH 10%, w/v (20 ml) and the mixture was refluxed under an argon atmosphere for 17 h. Thereafter, water was added and methanol was evaporated under reduced pressure. The resulting solution was acidified with HCl and extracted with ethyl acetate. The organic phase was washed with water and brine, dried over $MgSO_4$ and evaporated to give the crude carboxylic acid (i.r. acid bands at 1700 and 2400-3500 cm^{-1}).

2. Formation of amide

Without purification, the crude carboxylic acid (200 mg, 0.37 mmol) was dissolved in dry dichloromethane (50 ml) and tributylamine (0.48 mmol). After cooling, the mixture at -10°C, isobutyl chloroformate (0.52 mmol) was added and allowed to react for 30 min. At this time, N-methylbutylamine in excess (3.0 mmol) was added and the cooling bath was removed. After 3.5 h, dichloromethane was added and the organic phase was washed with HCl (1N) and dried over $MgSO_4$. Before the next step, the crude amide was purified by column chromatography (hexane-ethyl acetate, 70:30, v/v) in order to remove residual amine and urethane side product ($(CH_3)_2CHCH_2OCONBuMe$).

3. Hydrolysis of ketal

The ketal amide (208 mg, 0.34 mmol) was dissolved in acetone (40 ml) and p-toluenesulfonic acid (0.21 mmol dissolved in 4 ml of water) was added. The reaction mixture was stirred at room temperature for 3 days. Then, water was added, and acetone was removed under reduced pressure before extraction with diethyl ether. The organic phase was washed with a saturated solution of $NaHCO_3$ and dried over $MgSO_4$. After evaporation of solvent, the crude ketone amide was purified by dry column chromatography (hexane-ethyl acetate, 70:30, v/v).

N-butyl, N-methyl-13-(3'-methoxy-17'-oxo-1',3',5'(10')-estratriene-15'-(α,β)-yl)-tridecanamide (22), Colorless oil (185 mg, 88% yield); i.r. ν (neat): 2910, 2840, 1725, 1630, 1605, 1570 w, 1490 cm^{-1}; NMR-200 δ ($CDCl_3$): 0.92 and 0.95 (2t, J=7 Hz, 3H, $CH_2\underline{CH_3}$), 1.03 (s, 18'-CH_3 of major isomer (15'α) i.e. the singulet of minor isomer (15'β) is masqued by triplet of $CH_2\underline{CH_3}$), 2.9 (broad, 2H, 6'-CH_2), 2.91 and 2.96 (2s, 3H, CH_3NCO), 3.25 and 3.36 (2t, J=7.3 Hz, 2H, $CH_2\underline{CH_2}NCO$), 3.79 (s, 3H, CH_3O), 6.66 (d, J=2.6 Hz, 1H, 4'-CH), 6.72 (dd, J_1=2.6 Hz and J_2=8.4 Hz, 1H, 2'-CH), 7.20 (d, J=8.4 Hz, 1H, 1'-CH); MS m/e (rel. intensity): 565 (M^+, 29), 547 (6.1), 450 (4.5), 376 (15), 88 (100); HRMS M^+ calculated for $C_{37}H_{59}O_3N$: 565.4495, found: 565.4513.

REDUCTION OF KETONE 22 TO ALCOHOL 23

The general procedure for reduction of ketone described above was used. Purification of crude product was achieved by dry column chromatography with hexane-ethyl acetate, 70:30, v/v as eluent.

N-butyl, N-methyl-13-(3'-methoxy-17'β-hydroxy-1',3',5'(10')-estratriene-15'(α,β)-yl)-tridecanamide (23). Colorless oil (163 mg, 93% yield); i.r. ν (neat): 3400, 2910, 2840, 1620, 1570 w, 1485 cm^{-1}; NMR-200 δ ($CDCl_3$): 0.80 and 0.88 (2s, 3H, 18'-CH_3) two isomers (15'β: 15'α/12:82), 0.92 and 0.95 (2t, J=7 Hz, 3H, $CH_2\underline{CH_3}$), 2.88 (m, 2H, 6'-CH_2), 2.91 and 2.96 (2s, 3H, CH_3NCO), 3.25 and 3.35 (2t, J= 7.3 Hz, 2H, $CH_2\underline{CH_2}NCO$), 3.69 (t, J=8.6 Hz, 1H, $\underline{CH}OH$), 3.77 (s, 3H, CH_3O), 6.64 (d, J= 2.6 Hz, 1H, 4'-CH), 6.70 (dd, J_1= 26 Hz and J_2=8.4 Hz, 1H, 2'-CH), 7.20 (d, J=8.4 Hz, 1'H, 1'-CH); MS m/e (rel. intensity): 567 (M^+, 38), 549 (66), 534(8), 57(100); HRMS M^+ calculated for $C_{37}H_{61}O_3N$: 567.4651, found: 567.4674.

TRANSFORMATION OF METHOXY COMPOUND 23 TO PHENOL 7

The general procedure for methoxy group cleavage described above was used. Purification of crude product was performed by column chromatography with hexane-ethyl acetate, 70:30, v/v as eluent.

N-butyl, N-methyl-13-(3'-17'β-dihydroxy-1',3',5'(10')-estratriene-15'(α,β)-yl)-tridecanamide (7) Colorless oil (69 mg, 73% yield); i.r. ν (film): 3300, 2910, 2840, 1615 cm^{-1}; NMR-200 δ ($CDCl_3$): 0.80 and 0.88 (2s, 3H, 18'-CH_3) two isomers (15'β: 15'α/15:85), 0.92 and 0.95 (2t, J=7.3 Hz, 3H, $CH_2\underline{CH_3}$), 2.85 (m, 2H, 6'-CH_2), 2.93 and 2.98 (2s, 3H, CH_3NCO), 3.26 and 3.37 (2t, J=7.3 Hz, 2H, $CH_2\underline{CH_2}NCO$), 3.71 (t, J=8.6 Hz, 1H, $\underline{CH}OH$), 6.65 (dd, J_1= 2.6 Hz and J_2= 7.7 Hz, 1H, 2'-CH), 6.68 (s_{app}, 1H, 4' CH), 6.8 (broad, 1H, OH phenol), 7.14 (d, J=8.1 Hz, 1H, 1'-CH); MS m/e (rel. intensity): 553 (M^+, 28), 535 (53), 376 (26), 338 (59), 310 (23), 114 (99), 88 (100); HRMS M^+ calculated for $C_{36}H_{59}O_3N$: 553.4495, found: 553.4488.

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REFERENCES AND NOTES

1. Poulin, R.; Labrie, F. Cancer Res. **1986**, 46, 4933-4937.
2. Poulin, R.; Simard, J; Labrie, C.; Petitclerc, L.; Dumont, M.; Lagacé, L.; Labrie, F. Endocrinology **1989**, 125, 392-399.
3. Lippman, M.E.; Dickson, R.B.; Gelmann, E.P.; Rosen, N.; Knabbe, C.; Bates, S.; Bronzert, D.; Huff, K.K.; Kasid, A. J. Steroid Biochem. **1988**, 30, 53-61.
4. Wakeling, A.E.; Bowler, J. J. Steroid Biochem. **1988**, 30, 141-147.
5. Poulin, R.; Mérand, Y.; Poirier, D.; Lévesque, C.; Dufour, J.M.; Labrie, F. Breast Cancer Res. Treatm. **1989**, 14, 65-76.
6. Luu-The, V.; Labrie, C.; Zhao, H.F.; Couët, J.; Lachance, Y.; Simard, J.; Leblanc, G.; Côté, J.; Bérubé, D.; Gagné, R.; Labrie, F. Mol. Endocrinol. **1989**, 3, 1301-1309.
7. Bucourt, R.; Vignau, M.; Torelli, V.; Richard-Foy, H.; Geynet, C.; Secco-Milet, C.; Redeuilh, G.; Baulieu, E.E. J. Biol. Chem. **1978**, 253, 8221-8228.
8. Wakeling, A.E.; Bowler, J. J. Endocr. **1987**, 112, R7-R10.
9. Lévesque, C.; Mérand, Y.; Dufour, J.M.; Labrie, C.; Labrie, F. J. Med. Chem. **1991**, in press.
10. Poirier, D; Labrie, F. Communication presented at CIC Meeting, Halifax, Canada, 15-20 July, **1990**.
11. Poirier, D.; Labrie, C.; Mérand, Y.; Labrie, F. J. Steroid Biochem. **1991**, submitted.
12. Matsui, M.; Kinuyama, Y. J.C.S. Perkin I **1976**, 1429-1432.
13. Rasmusson, G.H.; Arth, G.E. Steroids **1973**, 22, 107-111.
14. Kelly, R.W.; Sykes, P.J. J.C.S. (C) **1968**, 416-421.
15. Kirk, D.N.; Klyne, W.; Peach, C.M.; Wilson, M.A. J.C.S. (C) **1970**, 1454-1460.
16. Horiguchi, Y.; Matsuzawa, S;, Nakamura, E.; Kuwajima, I. Tetrahedron Lett. **1986**, 27, 4025-4028.
17. Drieding model analysis shows a pseudo-1,3-diaxial interaction between 18-CH_3 and 16β- or 15β-alkyl group. Some examples illustrate this shielding effect (∿ 0.1 ppm) for 16-alkyl-17-keto steroid, δ 18-CH_3 (ppm) = 16β-CH_3: 0.84; 16α-CH_3: 0.94 (Neef, G. et al. J. Org. Chem. **1978**, 43, 4679-4680), 16β-allyl: 0.87, 16α-allyl: 0.95 (Fevig, T.L. and Katzenellenbogen, J.A., ref. 20) and others 16β-alkyl: 0.80-0.87, 16α-alkyl: 0.94-0.98 (Goto, G. et al. Tetrahedron **1974**, 30, 2107-2114).
18. Bowler, J.; Lilley, T.J.; Pittam, J.D.; Wakeling, A.E. Steroids **1989**, 54, 71-99.
19. Wheeler, D.M.S.; Wheeler, M.M. In: Fried, J., Edwards, J.A. (eds). Organic Reactions in Steroid Chemistry, Van Nostrand Reinhold: New York. **1972**, vol. 1, p. 61.
20. Fevig, T.L.; Katzenellenbogen, J.A. J. Org. Chem. **1987**, 52, 247-251.

21. The 17β-orientation of the hydroxyl group was confirmed by NOE difference experiments using the major isomer **7a**. In these experiments, irradiation of the 18-CH_3 signal showed no NOE on 17-H and irradiation of the 17-H signal showed no NOE on 18-CH_3. These findings suggest that proton at position 17 is opposed to axial 18-CH_3 (β). Consequently, this proton is at the 17α-position while the hydroxyl group is at the 17β-position.
22. Büchi, G. J. Am. Chem. Soc. **1971**, 93, 746-752.
23. McOmie, J.F.W.; Watts, M.L.; West, D.E. Tetrahedron **1968**, 24, 2289-2292.
24. Krapcho, A.P.; Weimaster, J.F.; Eldridge, J.M.; Jahngen, Jr., E.G.E.; Lovey, A.J.; Stephens, W.P. J. Org. Chem. **1978**, 43, 138-147.
25. Bérubé, G.; Deslongchamps, P. Can. J. Chem. **1990**, 68, 404-411.
26. Johnson, W.S.; Johns, W.F. J. Am. Chem. Soc. **1957**, 79, 2005-2009.