# Synthetic approaches toward total synthesis of 12β-methyl- and 12-methylene-19-norpregnanes

**Arnold I. A. Broess, Nico P. van Vliet, Marinus B. Groen, and Hans Hamersma**

*Organon International B.V., Scientific Development Group, Oss, The Netherlands*

*The effect of a substituent in the 12-position of progestagens was studied. To this end, various approaches toward the preparation of 12β-alkyl- and 12-alkylidenenorpregnanes were investigated. Eventually, the desired compounds 17β-hydroxy-12β-methyl-18a-homo-19-nor-17α-pregn-4-en-20-yn-3-one* ***(37)*** *and 17β-hydroxy-12-methylene-18a-homo-19-nor-17α-pregn-4-en-20-yn-3-one* ***(38)*** *were obtained in racemic form by total synthesis; they were shown to lack progestagenic activity. (Steroids* **57:**514–521, 1992)

**Keywords:** steroids; total synthesis; 12-methylpregnanes; 12-methylenepregnanes; progestagens

## Introduction

The transposition of a substituent in a biologically active molecule often leads to a change in activity. This change, of course, may either be an increase or a decrease. In this respect, we decided to investigate the influence of shifting the position of the methylene group from position 11 to position 12 in the progestagen 3-ketodesogestrel* **1** or its 13-methyl analogue[1] **2** (Figure 1). In addition, it was our intention to prepare the corresponding 12β-methyl compound, because molecules of this type have been claimed to possess pharmacological activity.[2]

## Experimental

All reactions were performed under an atmosphere of dry nitrogen unless this was clearly unnecessary. All dichloromethane extracts were washed with water and dried over $Na_2SO_4$ before concentration under reduced pressure.

Melting points (mp) were determined on a Büchi 535 melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Bio-Rad Digilab FTS-60 spectrometer. The positions of the signals are expressed as the wave numbers ($cm^{-1}$).

$^1H$ nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC-200. Samples were dissolved in $CDCl_3$, unless indicated otherwise; the positions of the peaks are given in ppm relative to tetramethylsilane as the internal standard. Electron impact (EI) mass spectra were recorded with a Hewlett Packard HP-5989 mass spectrometer using a Wagner Analysen Technik Vertriebs GmbH (WATV) direct insertion probe. Accurate masses were determined with the peak matching technique at a resolution of 7,300 on a Finnigan MAT 90 mass spectrometer (MS) in positive ion fast atom bombardment (FAB) mode using glycerol as the matrix, which produces $MH^+$ rather than $M^+$ molecular ions.

### *3,3 : 17,17-Bisethylenedioxy-11-trimethylsilyloxyestra-5,11-diene* **(4)**

To a solution of 6.44 ml (42 mmol) of diisopropylamine in 84 ml of dry tetrahydrofuran (THF), cooled to −25 C, was added 28 ml of a n-butyllithium solution (15% in hexane). The solution was stirred at this temperature for another hour and then cooled to −75 C. Subsequently, a solution of 13.09 g (35 mmol) of 3,3 : 17,17-bisethylenedioxyestr-5-en-11-one[3] **(3)** in 84 ml of THF was added dropwise, and the mixture stirred for another 3.5 hours. Then, 5.76 ml (45 mmol) of chlorotrimethylsilane was added dropwise, and stirring at −75 C was continued for another 3.5 hours. The reaction mixture was allowed to warm to room temperature overnight, poured into 500 ml of ice-water, and extracted into dichloromethane. Concentration of the extract left a residue of 15.6 g, which was purified by column chromatography over silica gel [dichloromethane/ethyl acetate (19 : 1)]. Yield: 10.64 g (68%) of crystalline material, mp 116–118 C. IR (KBr): 1,640 (C=C), further absorptions at 1,470, 1,370, 1,300, 1,245, 1,110, 1,038, 1,000, 950, 900, 840, and 757 $cm^{-1}$. NMR ($CDCl_3$ + $C_5D_5N$): 5.55 (m, 1H, H-6), 4.95 (t, 1H, H-12), 4.0–3.9 (m, 8H, $OCH_2CH_2O$), 2.8 (m, 1H), 2.1–1.1 (m, 15H), 0.91 (s, 3H, $CH_3$), 0.20 (s, 9H, $CH_3Si$).

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Address reprint requests to Dr. Hans Hamersma, Organon International RL 212, P.O. Box 20, 5340 BH Oss, The Netherlands.

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* Desogestrel (BAN, INN) is 11-methylene-18a-homo-19-nor-17α-pregn-4-en-20-yn-17β-ol; 3-ketodesogestrel (17β-hydroxy-11-methylene-18a-homo-19-nor-17α-pregn-4-en-20-yn-3-one) is its active metabolite.

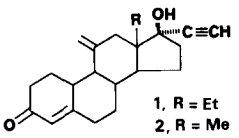



**Figure 1** Structure of the model progestagens.

### *11,12-Epoxy-3,3:17,17-bisethylenedioxy-11-trimethylsilyloxyestr-5-enes* (**5**)

m-Chloroperbenzoic acid (2.6 g, 14 mmol) was dissolved in 50 ml of dichloromethane, and the mixture added dropwise to a solution of 5.0 g (12.5 mmol) of **4** and 900 mg of sodium bicarbonate in 100 ml of dichloromethane, cooled to −70 C. The mixture was allowed to warm to −5 C over 1.5 hours, and stirred at this temperature for another 3 hours. Subsequently, the reaction mixture was poured into 1 L of saturated $NaHCO_3$ solution. The organic layer was separated and concentrated to leave 5.8 g (quantitative yield) of the desired epoxide. The NMR spectrum of this compound showed two signals for H-12 at 2.55 and 2.66 ppm in about a 1 : 1 ratio, indicating a mixture of epimers.

### *12α-Hydroxyestr-4-ene-3,11,17-trione* (**6**)

The epoxides **5** (5.8 g, 12.5 mmol) were dissolved in 100 ml of acetone and 10 ml of 2 N HCl added. The mixture was stirred at room temperature for 1 hour, after which the solution was poured into saturated $NaHCO_3$ solution and extracted with dichloromethane. The extract was concentrated and purified by chromatography over silica gel [hexane/acetone (3 : 2)], which left 2.5 g (66% yield) of the product. IR (KBr): 3,380 (OH), 1,740 (17-C=O), 1,720 (11-C=O), 1,670 and 1,620 (C=C—C=O), further absorptions at 1,460, 1,360, 1,260, 1,060, 890, and 630 $cm^{-1}$. NMR: 5.90 (t, 1H, H-4), 4.17 (s, 1H, H-12), 3.1 (br m, 1H, OH), 2.8–2.0 (m, 12H), 1.8–1.2 (m, 4H), 0.82 (s, 3H, $CH_3$).

### *3,3 : 17,17-Bisethylenedioxy-12α-tetrahydropyranyloxyestr-5-en-11-one* (**7**)

A solution of 1.97 g (6.5 mmol) of **6** and 30 mg of p-toluenesulfonic acid in a mixture of 9 ml of ethylene glycol and 4.5 ml of triethyl orthoformate was stirred at room temperature for 20 hours, after which the reaction mixture was poured into saturated bicarbonate solution. Extraction with ethyl acetate and concentration of the extract left 2.38 g of a residue. This was taken up in 30 ml of dichloromethane, to which, at a temperature of −5 C, 3 ml of dihydropyran and 50 mg of p-toluenesulfonic acid were added. The mixture was stirred at the same temperature for 2 hours and then poured into saturated $NaHCO_3$ solution. Extraction with dichloromethane, concentration of the extract, and purification of the residue by column chromatography over silica gel [hexane/ethyl acetate/pyridine (80 : 20 : 1)] left 2.40 g (78%) of the product as an oil. IR ($CCl_4$): 1,720 (C=O), 1,675 (C=C), further absorptions at 1,440, 1,380, 1,260, 1,110, 1,080, 1,040, 965, 910, and 695 $cm^{-1}$.

### *3,3 : 17,17-Bisethylenedioxyestra-5,11-dien-11-yl N,N,N',N'-tetramethylphosphorodiamidate* (**8**)

To a cooled (−15 C) mixture of 4.80 ml of dry diisopropylamine and 60 ml of dry THF was added dropwise 19.7 ml of a butyllithium solution (1.6 M in hexane). After 0.75 hours, the solution was cooled further to −75 C, and 8.00 g (21.39 mmol) of **3** in 50 ml of THF was added dropwise. The mixture was stirred at the same temperature for a further 3.5 hours, after which 5.18 ml (31.5 mmol) of bis(dimethylamino)phosphorochloridate was added; stirring was continued at −75 C for another 3 hours, after which the mixture was allowed to warm to room temperature overnight. The reaction mixture was then partitioned between water and dichloromethane; the organic layer was concentrated and purified by column chromatography over silica gel [first eluting with dichloromethane/ethyl acetate (9 : 1) to remove unreacted starting material, and subsequently with ethyl acetate/ethanol (9 : 1], leaving 9.12 g of the desired ester (84% yield). NMR: 5.84 (t, J = 1.5 Hz, 1H, H-12), 5.57 (m, 1H, H-6), 4.0–3.9 (m, 8H, $OCH_2CH_2O$), 2.70, 2.67, 2.65, and 2.62 (each an s of 3H, $NCH_3$), 2.3–1.25 (m, 16H), 0.95 (s, 3H, $CH_3$).

### *Estra-4,11-diene-3,17-dione* (**10**)

To 250 ml of liquid ammonia, kept at −33 C, 4.00 g of lithium metal was added in small pieces. After 0.75 hours, the temperature was lowered to −50 C, and a solution of 9.12 g (17.95 mmol) of **8** in 18 ml of isopropanol was added. The reaction mixture was kept at −50 C for 1 hour and at −30 C for 2 hours, and subsequently discolored by addition of ethanol. After evaporation of the ammonia, the residue was taken up in dichloromethane, washed with water, and concentrated. The residue was dissolved in a mixture of 60 ml of acetone and 5 ml of 2 N HCl, and stirred at room temperature for 3 hours. The reaction mixture was poured into 500 ml of water and extracted with dichloromethane. Concentration of the extract and purification by column chromatography [dichloromethane/acetone (19 : 1)] left 2.31 g of the product of mp 107.5–108 C, yield 48%. IR (KBr): 1,740 (17-C=O), 1,680 and 1,620 (C=C—C=O), further absorptions at 1,440, 1,370, 1,340, 1,260, 1,200, 1,050, 1,010, 970, 895, 840, and 730 $cm^{-1}$. NMR: 6.11 (dd, J = 10 and 2.5 Hz, 1H, H-12), 5.89 (t, J = 2 Hz, 1H, H-4), 5.70 (dd, J = 10 and 1.5 Hz, 1H, H-11), 2.70–1.20 (m, 16H), 1.00 (s, 3H, $CH_3$).

### *Ethyl 7-(3-methoxyphenyl)-3-methylsulfinyl-4-oxoheptanoate* (**16**)

To a suspension of 3.81 g (100 mmol) of sodium hydride (6.35 g of a 60% dispersion in mineral oil) in 90 ml of dry THF was added a solution of 24.28 g (96 mmol) of the sulfoxide **15**[4] in 60 ml of dry THF. After the brownish solution had been stirred for 0.75 hours at room temperature, 11.62 ml (105 mmol) of ethyl bromoacetate was added dropwise. After another hour, the reaction mixture was poured into 1 L of ice-water and extracted with dichloromethane. Concentration and chromatography of the residue [hexane/acetone (1 : 1)] afforded 21.84 g (67%) of the adduct as an unstable oil. NMR: 7.20 (m, 1H) and 6.8–6.7 (m, 3H), aromatic protons, 4.35 (dd, J = 9 and 4 Hz, 0.42H), and 4.30 (dd, J = 10 and 4 Hz, 0.58H), methine, 4.14 (q, 2H, $CH_2CH_3$), 3.80 (s, 3H, $OCH_3$), 3.2–2.5 (m, 6H), 2.47 and 2.44 (both s, 1.75H and 1.25H respectively, $CH_3SO$), 2.05–1.9 (m, 2H, $CH_2CH_2CH_2$), 1.24 (t, 3H, $CH_3$).

### *Ethyl 7-(3-methoxyphenyl)-4-oxo-(E)-hept-2-enoate* (**17**)

A solution of 21.84 g (64 mmol) of **16** in 150 ml of dioxane was refluxed for 0.5 hours. After cooling, the solvent was removed under reduced pressure and the residue chromatographed over silica gel [hexane/acetone (4 : 1)] to afford 15.96 g (90% yield) of **17** as an oil. NMR: 7.21 (td, J = 8 and 1 Hz, 1H), and 6.8–6.7 (m, 3H), aromatic protons, 7.03 and 6.63 (each a d of 1 H with J = 16 Hz, CH=CH), 4.25 (q, 2H, $OCH_2CH_3$), 3.79 (s, 3H, $OCH_3$), 2.63 (t, 4H), 1.98 (quintet of d, 2H, J = 7.5 and 1 Hz), 1.32 (t, 3H, $CH_3$).

### *Ethyl 2-(1-ethyl-2,5-dioxocyclopentyl)-7-(3-methoxyphenyl)-3-oxoheptanoate* (**18**)

Ester **17** (15.35 g, 55.6 mmol) and 15.0 g (119 mmol) of 2-ethylcyclopentane-1,3-dione were dissolved in a mixture of 100 ml of ethyl acetate and 5 ml of triethylamine. The mixture was refluxed for 24 hours and then concentrated under reduced pressure. The residue was purified by column chromatography over silica gel [hexane/ethyl acetate (4 : 1)] to afford 19.00 g (85%) of the addition product as an oil. NMR: 7.19 (m, 1H), and 6.80–6.72 (m, 3H), aromatic protons, 4.02 (q, 2H, $CH_2O$), 3.88 (t, 1H, CHCOO), 3.80 (s, 3H, $OCH_3$), 3.0–2.8 (m, 6H), 2.62 (t, 2H, $ArCH_2$), 2.50 (t, 2H, $CH_2CO$), 1.96 (quintet, 2H, $CH_2CH_2CH_2$), 1.15 (t, 3H, $CH_3$), 1.01 (t, 3H, $CH_3$).

### *Ethyl rac-3-methoxy-17-oxo-18a-homoestra-1,3,5(10),8,14-pentaene-12β-carboxylate* (**19**)

Trione **18** (15.20 g, 37.8 mmol) was dissolved in 75 ml of dichloromethane. The mixture was cooled in an ice bath and 20 ml of methanesulfonic acid was added. Stirring at 0 C was continued for 8 hours. The reaction mixture was partitioned between ice-water and dichloromethane, the organic layer washed with ice-cold bicarbonate solution and water, and the extracts concentrated to afford the crude product, which consisted of a 9 : 1 mixture of epimers as was indicated by the ratio of the methoxy signals in the NMR at 3.80 and 3.95 ppm, respectively. The major component could be isolated by chromatography over silica gel [hexane/ethyl acetate (9 : 1)], giving 11.39 g (82%) of the cyclized product **19** with mp 108–110 C. IR ($CCl_4$): 2,840 (weak, $OCH_3$), 1,750 (keto C=O), 1,730 (ester C=O), further absorptions at 1,603, 1,583, 1,500, 1,247, 1,160, and 1,047 $cm^{-1}$. NMR: 7.20 (d, 1H, H-1), 6.75–6.70 (m, 2H, H-2, and H-4), 6.05 (t, J = 3.5 Hz, 1H, C=CH), 4.30–4.20 (m, 2H, $OCH_2$), 3.80 (s, 3H, $OCH_3$), 3.05–2.95 (m, 3H, H-16, and H-11α), 2.80 (dd, J = 11.5 and 5.5 Hz, 1H, H-12α), 2.84–2.78 (m, 2H, H-6), 2.70–2.60 (m, 2H), 2.40–2.30 (m, 1H), 2.03 and 1.72 (each a degenerate dd of 1H, J = 7 and 10 Hz, $CH_2CH_3$), 1.34 (t, 3H, $CH_3$), 0.71 (t, 3H, $CH_3$).

### *Ethyl rac-17β-hydroxy-3-methoxy-18a-homoestra-1,3,5(10),8,14-pentaene-12β-carboxylate* (**20**)

In a mixture of 108 ml of toluene and 432 ml of methanol was dissolved 11.01 g (30.1 mmol) of **19**. The solution was cooled to 0 C and 2.20 g (58 mmol) of $NaBH_4$ were added. Stirring was continued for another 1.5 hours, after which the reaction mixture was neutralized with glacial acetic acid. The solution was then concentrated under reduced pressure and the residue taken up in dichloromethane. Evaporation of the solvent left 11.00 g (99%) of the product. NMR: 7.27 (d, 1H, H-1), 6.78–6.71 (m, 2H, H-2, and H-4), 5.75 (dd, 1H, H-15), 4.49 (t, 1H, H-17), 4.27 (q, 2H, $CH_2O$), 3.82 (s, 3H, $OCH_3$), 2.9–2.25 (m, 9H), 1.66 and 1.40 (each a dd of 1H, $CH_2CH_3$), 1.60 (br s, 1H, OH), 1.36 (t, 3H, $CH_3$), 0.87 (t, 3H, $CH_3$).

### *Ethyl rac-17β-hydroxy-3-methoxy-18a-homoestra-1,3,5(10),8-tetraene-12β-carboxylate* (**21**)

A suspension of 11.0 g (29.6 mmol) of **20** and 4.0 g 5% Palladium (Pd) on $CaCO_3$ in 180 ml of THF was hydrogenated at ambient temperature for 21 hours, after which the theoretical volume of hydrogen had been absorbed. The reaction mixture was filtered over a Celite pad and the filtrate concentrated to leave 8.73 g (79%) of a solid residue, mp 126.6–127.8 C. IR (KBr): 3,505 (OH), 2,840 (weak, $OCH_3$), 1,705 (C=O), further absorptions at 1,610, 1,500, 1,450, 1,430, 1,370, 1,300, 1,255, 1,130, 1,050, and 1,040 $cm^{-1}$. NMR ($C_6D_6$): 7.21 (d, 1H, H-1), 6.78 (d, 1H, H-4), 6.71 (dd, 1H, H-2), 4.55 (d, 1H, OH), 4.31 (m, 1H, H-17), 3.98–3.87 (m, 2H, $OCH_2$), 3.39 (s, 3H, $OCH_3$), 2.88–2.83 (m, 2H, H-12, and H-11α), 2.70–2.50 (m, 2H, H-6), 2.33–2.20 (m, 2H, H-16, and H-11β), 2.10–2.08 (m, 1H, H-14), 2.06–1.94 (m, 3H, H-7, and H-16), 1.70–1.60 and 1.50–1.40 (each an m of 1H, together $CH_2CH_3$), 1.45–1.25 (m, 2H, H-15), 1.14 (t, 3H, $CH_3$), 0.94 (t, 3H, $CH_3$).

### *rac-17β-Hydroxy-3-methoxy-18a-homoestra-1,3,5(10)-triene-12β-carboxylic acid* (**23**)

Ester **21** (8.73 g, 23.6 mmol) was dissolved in 400 ml of a 0.4 N solution of KOH in methanol. The mixture was refluxed for 2 hours, after which the methanol was removed under reduced pressure. The residue was acidified with diluted HCl with cooling, and the resulting precipitate (8.10 g, quantitative yield) of the acid **22** collected and washed with water, dried, and dissolved in 200 ml of dry THF. This solution was added dropwise to 1 L of liquid ammonia. Small pieces of lithium metal were added until the blue color persisted. After 2 hours, the reaction mixture was discolored by the addition of $NH_4Cl$. The ammonia and most of the THF were evaporated, and the residue acidified by addition of 2 N HCl. A precipitate formed, which was shown to consist of a 3 : 1 mixture of epimers (9α : 9β). Recrystallization from methanol afforded 4.64 g (57%) of the 9α-epimer (**23**), mp 237.5–239.5 C. IR (KBr): 3,360 (weak, OH), 3,200–2,600 (COOH bridged with 17-OH), 1,685 (C=O), further absorptions at 1,610, 1,505, 1,470, 1,310, 1,240, 1,130, 1,050 $cm^{-1}$. NMR ($C_6D_6$ + $CD_3OD$): 7.38 (d, 1H, H-1), 6.78 (dd, 1H, H-2), 6.72 (d, 1H, H-4), 4.07 (t, 1H, H-17), 3.45 (s, 3H, $OCH_3$), 2.83 (d of t, J = 13.5 and 4 Hz, 1H, H-11α), 2.72 (dd, J = 9 and 4 Hz, 1H, H-12), 2.2–2.05 (m, 1H), 2.03–1.93 (m, 2H), 1.85–1.0 (m, 12H), 1.11 (t, 3H, $CH_3$). The mass spectrum showed prominent peaks at m/z 344 ($M^+$), 326 ($M^+ - H_2O$), 297 ($M^+ - C_2H_5$), 285 ($M^+ - C_3H_7O$), 174 ($C_{12}H_{14}O^+$), 160 ($C_{11}H_{12}O^+$), 147 ($C_{10}H_{11}O^+$). An accurate mass determination of $MH^+$ gave 345.205978; $C_{21}H_{29}O_4$ would require 345.20659.

### *Methyl rac-17β-hydroxy-3-methoxy-18a-homo-9β-estra-1,3,5(10)-triene-12β-carboxylate* (**24**)

The mother liquor of the preparation of **23** was concentrated to leave 3.4 g of solid material, which was taken up in a mixture of 20 ml of THF, 100 ml of methanol, and 1.5 ml of concentrated HCl, and refluxed for 48 hours. After cooling, the reaction mixture was poured into 250 ml of water and extracted into dichloromethane. After evaporation of the solvent, the residue was chromatographed over silica gel [hexane/ethyl acetate (9 : 1)] to give 0.93 g of the 9β-epimer as an oil. IR ($CCl_4$): 3,595 (weak, free OH), 3,520 (OH, bridged), 1,740 (C=O unbridged ester), 1,715 (C=O bridged ester), further absorptions at 1,610, 1,500, 1,465, 1,435, 1,340, 1,245, 1,220, and 1,050 $cm^{-1}$. NMR: 7.24 (d, 1H, H-1), 6.72 (dd, 1H, H-2), 6.61 (d, 1H, H-4), 4.27 (d, 1H, OH), 3.97 (t, 1H, H-17), 3.77 (s, 3H, $OCH_3$), 3.72 (s, 3H, $OCH_3$), 3.09–3.03 (m, 1H, H-9), 2.81–2.61 (m, 3H, H-11α, and H-6), 2.2–1.25 (m, 12H), 0.93 (t, 3H, $CH_3$).

### *Methyl rac-17β-hydroxy-3-methoxy-18a-homoestra-1,3,5(10)-triene-12β-carboxylate* (**25**)

Esterification of 3.50 g (10.17 mmol) of **23** was performed as described earlier. After cooling, the reaction mixture was poured into 250 ml of water and the resulting precipitate collected, washed with water, and dried. Yield: 3.57 g, 98%. NMR: 7.27 (d, 1H, H-1), 6.73 (dd, 1H, H-2), 6.64 (d, 1H, H-4); 4.36 (br s,

1H, OH), 4.20 (t, 1H, H-17), 3.78 (s, 3H, $OCH_3$), 3.77 (s, 3H, $OCH_3$), 2.88 (dd, J = 9 and 5 Hz, 2H), 2.75 (d of t, J = 14 and 4 Hz, 1H, H-11α), 2.36 (dd, J = 12.5 and 3 Hz, 1H), 2.2 (m, 2H), 1.9 (m, 1H), 1.8–1.2 (m, 9H), 0.89 (t, 3H, $CH_3$).

### *rac-12β-Hydroxymethyl-3-methoxy-17β-tetrahydropyranyloxy-18a-homoestra-1,3,5(10)-triene* (**27**)

A solution of 3.57 g (9.97 mmol) of **25** in a mixture of 71 ml of dichloromethane and 4.0 ml of dihydropyran was cooled in an ice bath, and 36 mg of p-toluenesulfonic acid was added. The mixture was stirred at 0 C for a further 4.5 hours, and then poured into a solution of 1 g of $NaHCO_3$ in 100 ml of ice-water. The product was extracted into dichloromethane and the extract concentrated. Boiling hexane was added to the residue, whereupon a precipitate was formed of mp 144–146 C. This product was dissolved in 70 ml of dry THF, and 0.80 g (21 mmol) of lithium aluminum hydride was added portionwise. The reaction mixture was stirred at room temperature for a further 2 hours; the excess $LiAlH_4$ was then destroyed by the addition of saturated $Na_2SO_4$ solution, and the mixture filtered over a Celite pad. The filtrate was concentrated and the residue recrystallized from methanol, giving 2.68 g (65%) of crystalline material of mp 156.4–158.2 C. IR (KBr): 3,544, 3,442 (OH), 2,830 ($OCH_3$), further absorptions at 1,604, 1,580, 1,500, 1,199, 1,107, 1030, 967 $cm^{-1}$. NMR: 7.17 (d, J = 9 Hz, 1H, H-1), 6.69 (dd, J = 9 and 3 Hz, 1H, H-2), 6.63 (d, J = 3 Hz, 1H, H-4), 4.75 (m, 1H, OCHO), 4.0–3.4 (m, 5H, H-17 and $CH_2O$), 3.77 (s, 3H, $OCH_3$), 2.92–2.82 (m, 2H, H-6), 2.35–1.0 (m, 21H), 1.17 (t, 3H, $CH_3$).

### *rac-3-Methoxy-17β-tetrahydropyranyloxy-12β-tosyloxymethyl-18a-homoestra-1,3,5(10)-triene* (**28**)

A solution of 3.45 g (18 mmol) of tosyl chloride in 14 ml of pyridine was added dropwise to an ice-cooled solution of 2.57 g (6.2 mmol) of **27** in 26 ml of pyridine. After the addition was complete, stirring was continued for 9 hours at 0 C and overnight at room temperature. The mixture was then poured into 500 ml of ice-water; the resulting precipitate was collected and dried, leaving 3.56 g (quantitative yield) of solid product with mp 132–132.4 C. NMR: 7.82 (d, 2H) and 7.37 (d, 2H), $C_6H_4SO_2$, 7.11 (d, 1H, H-1), 6.70 (dd, 1H, H-2), 6.62 (d, 1H, H-4), 4.53 (dd, J = 10 and 3 Hz, 1H, OCHO), 4.48 (t, 1H, H-17), 3.97 (dd, J = 9.5 and 11.5 Hz, 1H, $CH_2OSO_2$), 3.85 (m, 1H, $CH_2O$), 3.78 (s, 3H, $OCH_3$), 3.62 (t, J = 9.5 Hz, 1H, $CH_2OSO_2$), 3.5 (m, 1H, $CH_2O$), 2.85 (dd, J = 9 and 4 Hz, 2H, H-6), 2.47 (m, 1H, H-9), 2.46 (s, 3H, $ArCH_3$), 2.25–2.1 (m, 2H), 1.9–1.15 (m, 17H), 0.97 (t, 3H, $CH_3$).

### *rac-3-Methoxy-12-methylene-18a-homoestra-1,3,5(10)-trien-17β-ol* (**30**)

Tosylate **28** (3.2 g, 5.6 mmol) was dissolved in 50 ml of 2,4,6-collidine, and the mixture refluxed for 21 hours. After cooling, the mixture was poured into ice-cold diluted HCl. A precipitate, weighing 1.82 g, was formed; chromatography over silica gel [hexane/ethyl acetate (7 : 3)] afforded 1.56 g of the pure product (88%), mp 126.4–128.6 C. IR (KBr): 3,595 (OH), 3,488 (OH), 3,070 (=$CH_2$), 1,638 (C=C), further absorptions at 1,609, 1,574, 1,494, 1,254, 1,130, 1,071, 1,050, 900, 883, and 806 $cm^{-1}$. NMR: 7.20 (d, 1H, H-1), 6.72 (dd, 1H, H-2), 6.64 (d, 1H, H-4), 4.97 and 4.89 (both t of 1H with J = 2 Hz, =$CH_2$), 4.31 (dd, J = 9 and 8 Hz, 1H, H-17), 3.78 (s, 3H, $OCH_3$), 2.92–2.80 (m, 3H, H6, and H-11α), 2.28 (td, J = 11, 11, and 4 Hz, 1H, H-9α), 2.08 (dm, 1H, H-15α), 2.0–1.8 (m, 2H, H-7α, and H-11β), 1.7–1.2 (m, 9H), 0.87 (t, 3H, $CH_3$).

### *rac-3-Methoxy-12β-mesyloxymethyl-17β-tetrahydropyranyloxy-18a-homoestra-1,3,5(10)-triene* (**31**)

Mesylate **31** was prepared from 0.66 g (1.59 mmol) of **27** and 0.6 ml of methanesulfonyl chloride as described for tosylate **28**. Yield: 0.70 g, 90%. NMR: 7.08 (d, J = 9 Hz, 1H, H-1), 6.72 (dd, J = 9 and 3 Hz, 1H, H-2), 6.61 (d, J = 3 Hz, 1H, H-4), 4, 72 (m, 1H, OCHO), 4.48 (dd, J = 9.5 and 6 Hz, 1H, $CH_2OSO_2$), 4.02 (dd, J = 9.5 and 8 Hz, 1H, $CH_2OSO_2$), 4.0–3.5 (m, 3H, H-17, and $CH_2O$), 3.78 (s, 3H, $CH_3O$), 3.02 (s, 3H, $CH_3SO_2$), 2.8–2.65 (m, 2H), 2.35–2.2 (m, 1H), 2.1–1.4 (m, 19H), 1.15 (t, 3H, $CH_3$).

### *rac-17β,12β-Epoxymethano-3-methoxy-18a-homoestra-1,3,5(10)-triene* (**32**)

To a solution of 0.25 g (0.6 mmol) of **31** in 12 ml of dimethylformamide (DMF) were added 170 mg of lithium bromide and 300 mg of calcium carbonate. The mixture was heated to 130 C for 2 hours and, after cooling, poured into 100 ml of ice-cold water. Extraction with ethyl acetate and concentration of the extract afforded 0.2 g of the crude product, which, as NMR indicated, consisted mainly of the bridged compound **32**: 7.12 (d, J = 8.5 Hz, 1H, H-1), 6.73 (dd, J = 8.5 and 3 Hz, 1H, H-2), 6.61 (d, J = 3 Hz, 1H, H-4), 3.97 (dd, J = 10 and 8 Hz, 1H, $OCH_2$), 3.91 (d, J = 10 Hz, 1H, $OCH_2$), 3.77 (s, 3H, $OCH_3$), 3.17 (t, J = 10 Hz, 1H, H-17), 2.8–2.6 (m, 3H), 2.4–1.4 (m, 13H), 1.14 (t, 3H, $CH_3$).

### *rac-3-Methoxy-12β-methyl-18a-homoestra-1,3,5(10)-trien-17β-ol* (**33**)

Lithium aluminum hydride (0.75 g, 19.7 mmol) was added to a suspension of 2.7 g of **28** in 100 ml of dry THF. The mixture was refluxed for 3 hours, after which 3 ml of saturated $Na_2SO_4$-solution were added. The mixture was filtered over a Celite pad and the filtrate concentrated to afford 1.90 g of product, which was suspended in a mixture of 5 ml of THF, 20 ml of methanol and 2 ml of 2 N HCl. This mixture was stirred for 5 hours, after which the reaction mixture was poured into water. Extraction with dichloromethane, concentration of the extract, and purification of the residue by column chromatography [silica gel, eluent hexane/ethyl acetate (7 : 3)] afforded 1.45 g of the hydrolyzed product, yield 92%. NMR: 7.18 (d, 1H, H-1), 6.69 (dd, 1H, H-2), 6.62 (d, 1H, H-4), 3.90 (dd, J = 9.5 and 7.5 Hz, 1H, H-17), 3.78 (s, 3H, $OCH_3$), 2.95–2.85 (m, 2H), 2.32–2.05 (m, 3H), 1.98–1.85 (dm, 1H), 1.7–1.15 (m, 11H), 1.12 (d, J = 6.5 Hz, 3H, 12β-$CH_3$), 1.0 (t, J = 7.5 Hz, 3H, 18-$CH_3$).

### *rac-17β-Hydroxy-12β-methyl-18a-homoestr-4-en-3-one* (**34a**)

Lithium metal (1.2 g) was cut to small pieces, which were dissolved in 75 ml of liquid ammonia. After stirring for 0.75 hour, a solution of 1.45 g (4.5 mmol) of **33** in 20 ml of dry THF was added dropwise. Stirring was continued for 5 hours, after which 12 ml of ethanol was added. After evaporation of the ammonia, the remainder of the reaction mixture was poured into water. Extraction with dichloromethane and concentration under reduced pressure afforded 1.45 g of the crude product. This product was stirred overnight in a mixture of 10 ml THF, 20 ml methanol and 10 ml 2 N HCl. The reaction mixture was poured into water and extracted with dichloromethane. The residue after concentration was purified by column chromatography over silica gel [hexane/ethyl acetate (7 : 3)], affording 0.88 g of the desired product, yield 61% from **33**. NMR: 5.82 (t, J = 2 Hz, 1H, H-4), 3.84 (dd, J = 9 and 7.5 Hz, 1H, H-17), 2.55–1.0 (m, 22H), 1.13 (t, 3H, $CH_2CH_3$), 1.05 (d, 3H, $CH_3$).

### *rac-12β-Methyl-18a-homoestr-4-ene-3,17-dione* (**35a**)

A solution of 0.88 g (2.9 mmol) of **34a** in 6 ml of dichloromethane was added dropwise to a suspension of 2.16 g of pyridinium chlorochromate and 1.38 g of sodium acetate in 30 ml of dichloromethane. After being stirred for 0.75 hour at room temperature, the mixture was filtered through a Celite pad; the filtrate was concentrated, leaving a residue of 0.68 g (77%); an analytical sample was recrystallized from acetone/ether, giving crystals which melted at 175.5–177.5 C. IR (KBr): 1,725 (17-C=O), 1,665, 1,625 (O=C—C=C), further absorptions at 1,455, 1,400, 1,330, 1,260, 1,220, 1,120, 990, and 910 $cm^{-1}$. NMR: 5.84 (t, J = 2 Hz, 1H, H-4), 2.6–0.95 (m, 21H), 1.17 (d, 3H, $CH_3$), 0.89 (t, 3H, $CH_2CH_3$).

### *rac-12-Methylene-18a-homoestr-4-ene-3,17-dione* (**35b**)

Compound **30** (1.5 g, 4.8 mmol) was reduced to **34b** as outlined for **34a**. The yield was 0.9 g of purified product, which was oxydized with 1.08 g of pyridinium chlorochromate as described for **35a**, affording 0.66 g (45% from **30**) of the diketone; after recrystallization from acetone/ether, crystals with mp 165.7–168.2 C were obtained. IR (KBr): 3,100 (=$CH_2$), 1,730 (17-C=O), 1,675, 1,625 (O=C—C=C), 1,647 (C=C), further absorptions at 1,400, 1,360, 1,330, 1,260, 1,202, 980, and 905 $cm^{-1}$. NMR: 5.87 (t, J = 2 Hz, 1H, H-4), 5.45 and 4.93 (both t of 1H with J = 1.5 Hz, =$CH_2$), 2.6–1.0 (m, 20H), 0.77 (t, 3H, $CH_3$).

### *rac-3-Ethoxy-12β-methyl-18a-homoestra-3,5-dien-17-one* (**36a**)

A suspension of 0.66 g (2.2 mmol) of **35a** in a mixture of 2 ml of absolute ethanol and 1 ml of triethyl orthoformate was cooled to 0 C. To this suspension, 10 mg of p-toluenesulfonic acid hydrate was added, and the mixture was stirred at 0 C for a further 5.5 hours. The pH was then adjusted to 9 with triethylamine, and the resulting precipitate collected. The dried product weighed 0.70 g, yield 97%.

### *rac-3-Ethoxy-12-methylene-18a-homoestra-3,5-dien-17-one* (**36b**)

The enol ether was prepared as outlined above from 0.64 g (2.15 mmol) of **35b**, affording 0.70 g of product (quantitative yield). IR ($CCl_4$): 1,735 (C=O), 1,650, 1,615 (C=C), further absorptions at 1,380, 1,235, 1,230, and 1,175 $cm^{-1}$.

### *rac-17β-Hydroxy-12β-methyl-18a-homo-19-nor-17α-pregn-4-en-20-yn-3-one* (**37**)

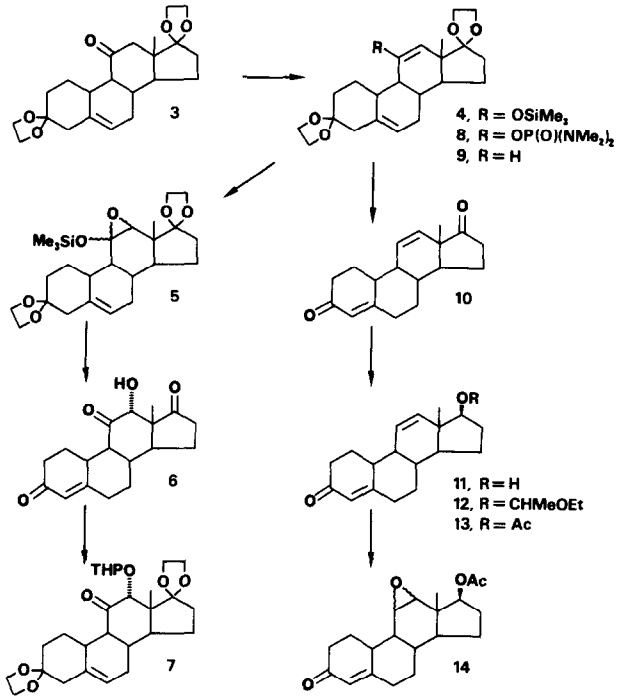
Acetylene gas was passed through a suspension of 0.75 g of potassium-*tert*-butylate in 7.5 ml of dry *tert*-butanol. A solution of 0.35 g (0.93 mmol) of **36a** in 5 ml of dry toluene was added and the mixture stirred at room temperature over 8 hours, acetylene being passed through continually. HCl (2 N) was then added to reach pH 3, and the mixture was poured into water. The aqueous layer was extracted with dichloromethane and the extract concentrated under reduced pressure to afford 0.30 g of the crude product; chromatography over silica gel [hexane/ethyl acetate (7 : 3)] finally gave 190 mg of the desired compound (55%) as an amorphous solid with mp 73–75 C. IR (KBr): 3,440 (OH), 3,300 (C=C), 1,665, 1,620 (O=C—C=C), further absorptions at 1,460, 1,360, 1,260, 1,210, 1,060, and 1,025 $cm^{-1}$. NMR: 5.83 (t, J = 2 Hz, 1H, H-4), 2.58 (s, 1H, H-21), 2.5–1.4 (m, 22H), 1.14 (t, 3H, $CH_3$), 1.02 (d, 3H, $CH_3$). The mass spectrum showed prominent peaks at m/z 326 ($M^+$), 300 (M − $C_2H_2$), 256 (M − $C_4H_6O$), 243 (M − $C_5H_7O$). An accurate mass determination of $MH^+$ gave 327.234500; $C_{22}H_{31}O_2$ would require 327.23241.

### *rac-17β-Hydroxy-12-methylene-18a-homo-19-nor-17α-pregn-4-en-20-yn-3-one* (**38**)

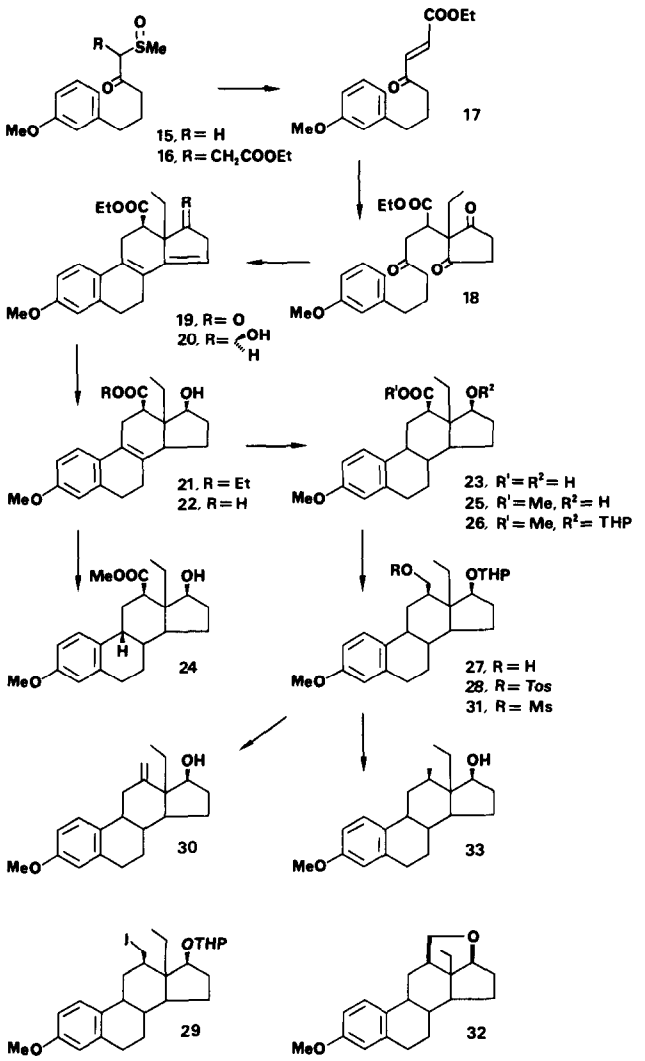
The hydroxy-ethynyl compound was prepared from 0.28 g (0.67 mmol) of **36b** as described for **37**. Chromatography over silica gel [hexane/ethyl acetate (7 : 3)] afforded 0.15 g (54%) of the desired pregnane as an amorphous solid of mp 86–88 C. IR (KBr): 3,410 (OH), 3,285 (C=C), 3,080 (=$CH_2$), 1,665, 1,620 (O=C—C=C), further absorptions at 1,450, 1,360, 1,260, 1,210, 1,130, 1,065, 895, and 865 $cm^{-1}$. NMR: 5.85 (t, J = 2 Hz, 1H, H-4), 5.16 and 5.06 (both t of 1H with J = 1.5 Hz, =$CH_2$), 2.62 (s, 1H, H-21), 2.55–1.0 (m, 21H), 0.91 (t, 3H, $CH_3$). The mass spectrum showed peaks at m/z 324 ($M^+$), 298(M − $H_2O$), 295 (M − $C_2H_5$), 270 (298 − CO), 269 (298 − $C_2H_5$). An accurate mass determination of $MH^+$ gave 325.217853; calculated for $C_{22}H_{29}O_2$, 325.21676.

## Results and discussion

A number of synthetic approaches into 12-alkyl steroids have been published. Thus, Coombs and Danna[5] reported a total synthesis of 12-methylestratrienes, but the steroids produced mainly have the 8α-configuration. Moreover, the 12α:12β ratio found by these investigators is unfavorable for our purposes. The Roussel synthesis[6] depends on the 1,8-addition of a copper Grignard reagent to an estra-4,9,11-trien-3-one; because this route starts with an existing steroid molecule, enantiomerically pure compounds would be produced, but they would mainly possess the 12α-configuration. Moreover, an additional double bond compared with our model progestagens would be present. Initially, therefore, we decided to attempt a partial synthesis from an 11-keto steroid, either through transposition of the keto group, or through α-functionalization and subsequent removal of the 11-carbonyl function. Our synthetic efforts (Scheme 1) started from the 3,17-diketal **3** of the readily available[7] estr-4-ene-3,11,17-trione. Various methods were tried to directly introduce the desired methyl (lithium diisopropylamide/methyl iodide) or methylene[8] substituents into the 12-position, but these attempts met with disappointing results. Consequently, the remaining unprotected keto function of **3** was converted to its silyl enol ether **4**. Attempts toward direct introduction of a substituent, such as methyl,[9] methylene,[10] formyl,[11] or phenylthiomethyl[12] groups into the β-position of the enol ether failed. However, treatment of **4** with m-chloroperbenzoic acid produced the 11-12 epoxide **5**, which was hydrolyzed to a 9 : 1 α : β epimer mixture of the 12-hydroxy compound. The major (12αOH) isomer **6** was identified by the appearance in the NMR spectrum of the H-12 signal as a sharp singlet; if the hydrogen atom had occupied the α-position, a W-coupling with the proton at C-18 would have been expected.[13] Protection of the hydroxy function and two of the carbonyl groups left only the 11-keto group exposed, but the remaining ketone of **7** proved to be quite unreactive toward either hydrazine or sodium borohydride.




**Scheme 1** 12-Functionalized steroids through partial synthesis.




**Scheme 2** 12-Substituted steroids through total synthesis.

In a second approach, we envisaged introduction of the functionality at position 12 through regioselective reduction of the 11,12-epoxide, itself derived from the 11,12-unsaturated steroid. Thus, **3** was converted to **8** by treatment with bis(dimethylamino)phosphorochloridate.[14] A dissolving metal reduction produced the $\Delta^{4,11}$-compound **10**. Contrary to expectations,[15] however, attempted epoxidation of this product mainly gave products from a Baeyer-Villiger-type rearrangement in the D ring. The intermediate **9**, however, in which the two carbonyl groups are protected as ketals, gave a mixture of diepoxides upon treatment with m-CPBA. Partial reduction of **10** gave **11**, but when the latter compound was protected with ethyl vinyl ether the resulting product **12** did not undergo epoxidation. When **11** was protected as the acetate, **13** could be epoxidized selectively at the 11,12-double bond, producing a 3 : 2 mixture of $\alpha$ and $\beta$ epoxides, but when protection of the 3-keto group of **14** as its ethylene ketal was attempted before reduction of the epoxide, none of the desired compound could be produced.

Because our efforts to introduce the required functionality into an existing steroid molecule had failed, we decided to resort to total synthesis. This would enable us to incorporate the 13-ethyl group, which is known[1] to enhance the progestagenic activity, although problems might be envisaged in producing enantiomerically pure compounds. An earlier, related synthesis[16] used a cationic-polyene-type cyclization; however, this led to predominant formation of the 12$\alpha$-alkyl product. Therefore, we decided to use a classical synthesis of estrone[17] in the adaptation described by Kurosawa, Tohma, and coworkers.[18–20] Thus (Scheme 2), the $\beta$-ketosulfoxide **15**[4] was alkylated with ethyl bromoacetate; subsequent thermal elimination led to the $\alpha,\beta$-unsaturated-$\gamma$-ketoester **17** possessing the E configuration exclusively, as indicated by a coupling of the olefinic protons of J = 16 Hz in the NMR spectrum. Michael addition of the anion of ethylcyclopentanedione gave the desired adduct **18**. Treatment of this adduct with methanesulfonic acid in dichloromethane at 0 C gave the racemic steroid **19** as a 1 : 9 12$\alpha$/12$\beta$ epimer mixture. The use of other acids, such as p-toluenesulfonic acid or hydrochloric acid, resulted in a less favorable epimer ratio or a lower yield. Attempts to effect a stereoselective cyclization by chiral induction through the addition of optically pure substances, e.g., phenylalanine,[21] did not give the desired effect, only products resulting from a retro-Michael reaction being observed.

After reduction of the 17-keto group, the $\Delta^{14}$ double bond was hydrogenated over palladium/calcium carbonate. The 14$\alpha$ configuration was confirmed by NMR spectroscopy, where the COSY spectrum showed a

long-range (homoallylic) coupling[13] between H-14 and one of the protons at position 11. The configurational conditions for such a coupling could be met by an axial 14$\beta$ proton combined with a boat conformation of the C ring; however, an additional W-coupling between H-12$\alpha$ and H-18 that was also observed is incompatible with such a conformation. As the ester group of **21**, but not the corresponding carboxylic acid, had been reported to be epimerizable to the 12$\alpha$-position under the conditions used to effect hydrogenation of the $\Delta^8$ double bond,[18] the ester was hydrolyzed to **22** before the reduction. Conversion to **23** was then effected by reduction with lithium/ammonia; these conditions afforded a 3 : 1 9$\alpha$/9$\beta$ mixture, from which the pure 9$\alpha$-epimer was obtained in 57% overall yield (76% based on **23** present). The configuration of H-9 could not be determined directly, because its NMR signal was obscured by other peaks in a number of solvents; however, an unequivocal assignment of signals was possible later in the synthesis (vide infra). From the mother liquors of **23**, an amount of the 9$\beta$-epimer was obtained that could be characterized as its methyl ester **24**; this compound showed, in the NMR, a broad multiplet for H-9, indicative for the $\beta$-position.

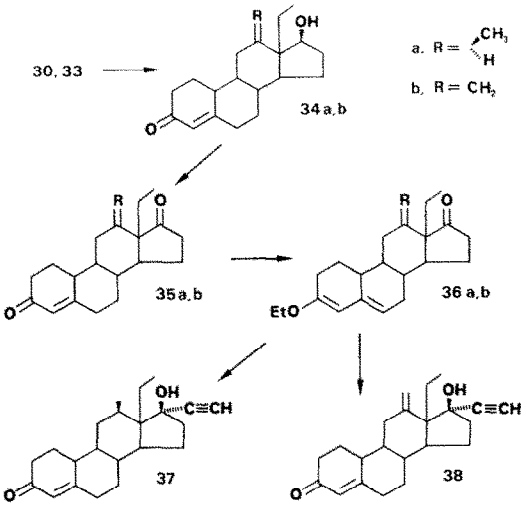
As the protection of the alcohol function in **23** as its THP-ether gave a mixture of products, the carboxylic acid **22** had to be re-esterified to **25** first. The ester group of the protected alcohol **26** was then reduced to the corresponding primary alcohol **27**. Tosylation/dehydrotosylation gave the desired methylene compound **30**.† The NMR spectrum of this compound showed H-9 at 2.28 ppm as a triplet of doublets with J = 11, 11, and 4 Hz, in addition to very small benzylic couplings; the two large couplings point to diaxial interactions and hence to a 9$\alpha$-configuration.

The corresponding mesylate **31**, when treated under basic conditions, gave a mixture of products, in which the interesting epoxymethano compound **32** could be identified as the major component. Finally, reductive detosylation of **28** afforded, after hydrolysis, the 12$\beta$-methyl compound **33**. Both 12-substituted steroids were converted (Scheme 3) to the corresponding 3-keto-$\Delta^4$-compounds, which were, after oxidation of the 17-hydroxy groups to the ketones, converted to the hydroxyethynyl analogues in the usual manner.[22]

Thus, the desired pregnenynes **37** and **38** were obtained as racemates in an overall yield from **15** of 1.1% and 2.2% respectively.

## *Biological results*

To assess the influence of the substituent at position 12, both compounds were screened in the normal test battery for progestagenic compounds. Both the relative binding affinity for the progesterone receptor[23] and the in vivo activity (Clauberg-McPhail test[24]) were established. In either test, the 12-methylene compound **38** was shown to be much less active than the 11-methylene compound desogestrel **1**. The 12-methyl compound **37**, whose corresponding 11$\beta$-methyl analogue **2** is known[25] to be an active progestagen, was also shown to be devoid of progestagenic activity. Thus, the transposition of the substituent from the 11- to the 12-position is demonstrated to be detrimental for the progestagenic activity.




**Scheme 3** Synthesis of the final products in the methyl (**33** → **34a** → **35a** → **36a** → **37**) and methylene (**30** → **34b** → **35b** → **36b** → **38**) series.

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† When the tosylate was first converted to the iodide **29** and this compound treated with base, **30** was also obtained, but in a lower overall yield.

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