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Synthesis of 13-Ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17-ol (Desogestrel) and its Main Metabolite 3-Oxo Desogestrel [1]

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Abstract: A synthesis of the steroid hormone desogestrel (**25**) from the 18a-homo steroid **1** is described. **25** was transformed into 3-oxo desogestrel (**28**) by allyl oxidation.

INTRODUCTION

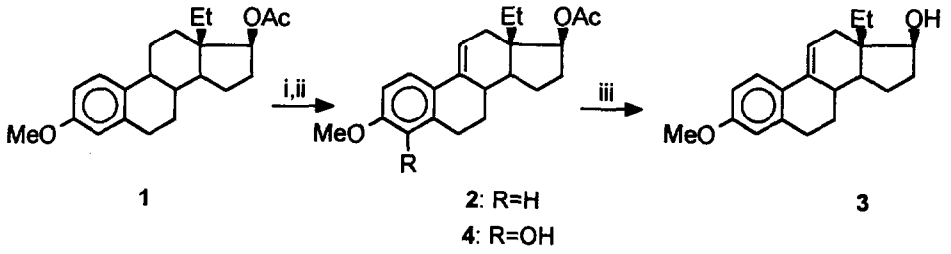
13-Ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17-ol (desogestrel) (**25**) is a powerful progestogen and widely used in oral contraceptives [2].

Recently a partial synthesis of **25** has been described, starting with an estrane derivative and applying intramolecular hypoiodite reaction as key step towards the homologization of the angular 18-methyl group [3].

We report here an alternative approach to the preparation of title compounds **25** and **28** from 18a-homosteroid **1**, readily available by total synthesis [4].

RESULTS AND DISCUSSION

Initially the starting material **1** was subjected to oxyfunctionalization with *in situ* generated dimethyldioxirane [5] affording the 9-hydroxy derivative of **1** [6]. Water elimination upon treatment with sulfuric acid provided 9(11)-dehydro acetate **2** [7], which was saponified to afford alcohol **3** (70% from **1**). To a minor degree the aromatic nucleus is attacked by the oxidizing agent, since the 4-hydroxy derivative **4** was found as a by-product (Scheme1).

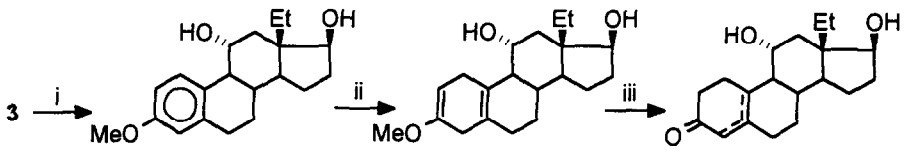


(i) dimethyldioxirane (ii) H_2SO_4, CH_2Cl_2 *(iii)* KOH, MeOH

Scheme 1

This dimethyldioxirane approach, very recently used for the preparation of 9α-hydroxy and 9(11)-dehydro estra-1,3,5(10)-trienes [8,9], has proved to be the method of choice for the introduction of a 9(11)-double bond into the 18a-homosteroid **1** under mild conditions. In the past numerous methods were described for introducing a 9(11)-double bond into aromatic steroids, but many of them suffer from low yields, are sensitive to the nature of the substituents at positions 3 and 17 or use toxic reagents, e.g. quinones [10]. Total synthetic pathways to 9(11)-dehydro derivatives of aromatic 18a-homosteroids have also been reported [11,12], however, at present these routes seem to be technically less effective.

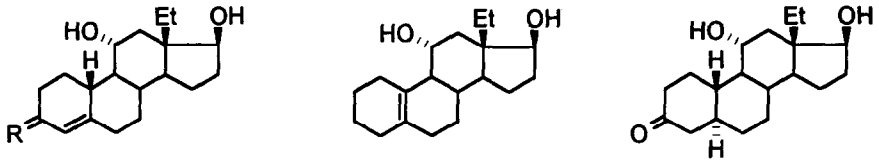
Compound **3** was subjected to hydroboration / alkaline hydrogen peroxide oxidation [13] affording 11α-hydroxy compound **5** [14] in 75% yield. *Birch* reduction of **5** gave the 1,4-dihydro derivative **6**, which provided enone **8** in acidic medium *via* the unconjugated ketone **7** [14] (72% yield from **5**) (Scheme 2).



(i) B_2H_6, H_2O_2, NaOH (ii) Li, liqu.NH_3, i-PrOH, THF (iii) HCl, acetone

Scheme 2

Detailed investigation of this *Birch* process showed that the 3-deoxy compounds **9** and **10**, the hydrogenated ketone **11**, and the allyl ether **12** were formed as by-products in small amounts [15] (Scheme 3).



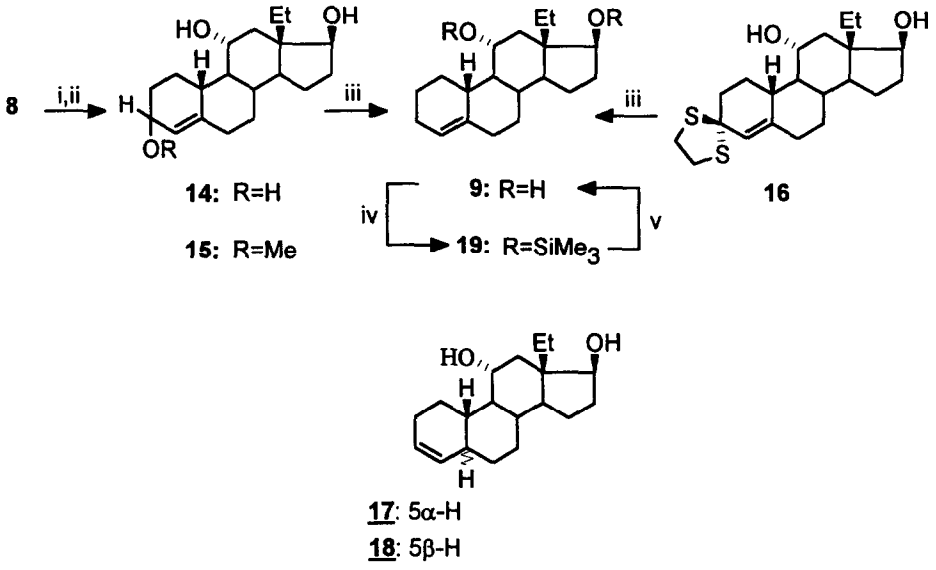
9: R = H, H
12: R = α-H, β-OMe

10

11

Scheme 3

Obviously, conjugated dienes are partially involved in the *Birch* reaction [16], undergoing further reduction including hydrogenolytic cleavage of the 3-methoxy group. Noticeably, the acid - promoted isomerization of **7** to **8** was accompanied by formation of 10α-*H* enone **13**. Numerous attempts to yield **8** without concomitant formation of **13** failed. Although **6** and **7** were allowed to react with various acids under variable conditions (solvents, temperature), **13** was formed in any case up to 7%. On the other hand, when applying the same protocol to the 11-deoxy analog of **7**, no 10α-*H* compound was detected [17]. The structure of **13** was confirmed by CD measurement in the range between 300 nm and 400 nm. Compared with the negative circular dichroism of **8** the CD curve of **13** proved unchanged in sign but displayed a higher intensity. This is in agreement with the structure of a 10α-*H* 4-en-3-oxo steroid [18] and excludes a *retro* steroid structure (10α-*H*, 9ß-*H*), which would show a strong positive circular dichroism [19].
Reductive elimination of the 3-oxo group of **8** to obtain **9** was the next goal (Scheme 4).



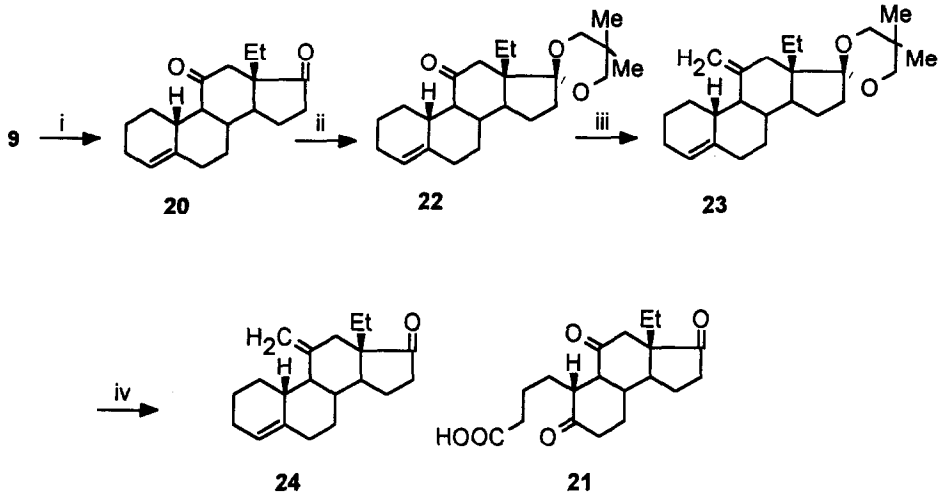
14: R=H
15: R=Me
9: R=H
19: R=SiMe$_3$
16
17: 5α-H
18: 5β-H

i) $NaBH_4$, $CeCl_3$ (ii) MeOH, p-TosOH (iii) Li, $EtNH_2$, THF (iv) $(Me_3Si)_2NH$, DMF (v) H_2SO_4, MeOH

Scheme 4

Compound **8** was converted into allyl methyl ether **15** by *Luche* reduction [20] and subsequent treatment of the triol **14** formed with methanol / p-toluenesulfonic acid. The reductive cleavage of **15**, which consists of a 6 : 4 mixture of 3ß- and 3α- isomers, was performed with lithium in ethylamine [21] and provided diol **9**. Alternatively the thioacetal **16** gave diol **9** on reaction with lithium in liquid ammonia [22] or in ethylamine. In each case diol **9** was contaminated by the double bond isomers **17** and **18** [23]. Strongly dependent on various reaction parameters (e.g. alkali metal, solvent, temperature) the 3-ene isomers were formed in a proportion ranging from less than 3% to more than 15%. Purification of **9** on a small scale was effected by crystallization of the silyl ether **19**, obtained from crude **9**.

Oxidation of diol **9** to the diketone **20** was the next step (Scheme 5).



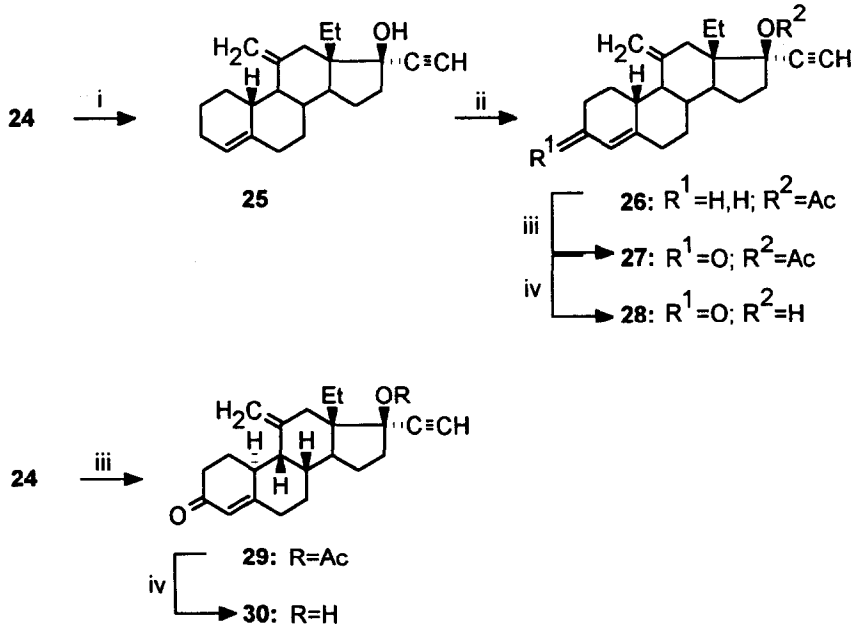
(i) DMSO, Py·SO_3, NEt_3 (ii) $HC(OEt)_3$, $Me_2C(CH_2OH)_2$, p-TosOH (iii) $Ph_3P{=}CH_2$, DMSO,))) (iv) p-TosOH, acetone

Scheme 5

Various attempts to oxidize **9** with chromium (VI) reagents suffered from low yields of **20**. This was due to a concomitant oxidative scission of the C-C double bond, which resulted in the formation of trioxo acid **21** [24]. Oxidation by dimethyl sulfoxide / sulfur trioxide pyridine complex [25] was successful and provided **20** in 80% yield.

Compound **20** was then subjected to selective protection of the 17-oxo group. Whereas the transformation of estr-4-ene-11,17-dione into the 17-ethylenedioxy derivative was reported to proceed smoothly in a high yield [26], the analogous reaction of the 18a-homo compound **20** proved to be unsatisfactory. However, the 2,2-dimethyl-propane-1,3-dioxy derivative **22** was formed in an 85% yield.

The subsequent introduction of the 11-methylene group was accomplished by *Wittig* olefination [27] of **22** with methylene triphenylphosphorane. Previous reports have shown that 11-oxo-17-ethylene acetals of 19-norsteroids, which lack functionality at position 3, react slowly and give moderate yields only [26]. In agreement with these results the methylene acetal **23** was obtained from **22** with insufficient yield and purity even after treatment with 8 equivalents of ylide and a reaction time of more than 24 h at 80 °C. The result was dramatically improved, when the reaction was allowed to run under sonification [28]: the olefination was finished after 10 to 12 h at 80 °C with 3.15 equivalents of ylide and provided **23** in an 85% yield [29]. The synthesis of the title compound **25** was completed by deprotection of methylene acetal **23** to give 17-oxo steroid **24** nearly quantitatively, which was allowed to react with lithium acetylide / ethylene-diamine affording desogestrel (**25**) in 85% yield (Scheme 6).



(i) Li, ethylenediamine, C_2H_2 (ii) Ac_2O, $HClO_4$ (iii) $(t\text{-}BuO)_2CrO_2$, Ac_2O, AcOH, CCl_4
(iv) NaOH, MeOH

Scheme 6

Besides the synthesis of desogestrel (**25**) we have been studying an approach to the 3-oxo derivative **28** [26], the main metabolite of **25** [30], which we needed for a radioimmunoassay development. It seemed to us that allyl oxidation of acetate **26** might be a short and convenient approach to **28**. After several attempts the oxidation of **26** with tert. butyl chromate was found to give satisfactory results. Flash chromatography [31] of the crude reaction product and subsequent hydrolysis of intermediate **27** yielded the desired 3-oxo desogestrel (**28**) in a moderate yield. As a second compound *retro* steroid **30** was formed *via* **29**, probably by enolization during the oxidation process. The *retro* structure of **30** followed from chiroptical data: **30** shows a positive circular dichroism between 280 nm and 380 nm, whereas **25** displays a negative one in the same wavelength range [19].

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Varian 300 (300 MHz for ^1H and 75.4 MHz for ^{13}C). Deuteriochloroform was used as solvent and chemical shifts were reported as δ values in ppm downfield from tetramethylsilane as internal standard. Mass spectra were taken with a double focusing mass spectrometer AMD 402 (AMD-Intectra, Harpstett / Bremen). GC and GC - MS measurements were run with a Shimadzu GC 14A and an HP 5890 Series II / HP MSD 5971. Melting points were measured with a Mettler FP 90 / FP 81 HT. UV spectra were taken with a Zeiss Specord M 40 in methanolic solutions, λ_{max} in nm (log ε). IR spectra were taken with a Nicolet 205 instrument, υ_{max} in cm^{-1}, KBr pellets. Optical rotations were measured with the Polamat A (Carl Zeiss Jena), solvent chloroform (unless otherwise stated), c = 1g / 100 ml, t = 20 °C. Chromatography means flash chromatography [31], which was performed on Kieselgel 60 (Merck A. G. Darmstadt, 0.04 - 0.063 mm). For reversed phase chromatography Kieselgel 60, Dimethylsilan-Derivat (Merck A. G., 0.063 - 0.2 mm) was used. Work-up of the extract includes: the organic phase was washed with brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to give the crude product. Sonification was performed in a Sonorex cleaning bath at a frequency of 35 kHz.

3-Methoxy-18a-homo-estra-1,3,5,9(11)-tetraen-17ß-ol (3).

To a stirred solution of **1** (10 g; 29 mmol) in a mixture of dichloromethane (1500 ml), acetone (130 ml), and water (150 ml) was added sodium hydrogen carbonate (30 g, 357 mmol). This mixture was cooled to +5 °C and potassium monopersulfate (2 $KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$; 70 g; 114 mmol) was added within 3 h. Stirring was continued at 15 °C for another 4 h. The organic phase was then separated and worked up. The product (13 g), was dissolved in dichloromethane and the solution treated with sulfuric acid (70%) at 0 °C for 2 h. Saturated aqueous sodium hydrogen carbonate solution was added and, upon work-up of the organic phase, crude **2** obtained was purified by chromatography (eluent: toluene / ethyl acetate 10:1) followed by crystallization from methanol to yield pure **2**: mp. 79 - 82.5 °C; $[\alpha]_D$ + 84; ^1H NMR 0.93 (t, J = 7.7 Hz, $-CH_2-CH_3$), 1.06 (td, J = 13.0 Hz, 3.2 Hz, H-6), 2.06 (s, $-CO-CH_3$), 2.53 (dd, J = 17.6 Hz, 5.9 Hz, H-12), 2.86 (m, H-6), 3.78 (s, $-OCH_3$), 4.82 (dd, J = 8.7 Hz, 8.7 Hz, H-17), 6.07 (m, H-11), 6.59 (d, J = 2.8 Hz, H-4), 6.71 (dd, J = 8.8 Hz, 2.8 Hz, H-2), 7.50 (d, J = 8.2 Hz, H-1); ^{13}C NMR 171.1 ($-CO-CH_3$), 158.4 (C-3), 137.3 (C-5), 135.4 (C-10), 127.6 (C-9), 125.2 (C-1), 117.6 (C-11), 113.2 (C-4), 112.6 (C-2), 84.2 (C-17), 55.2 ($-OCH_3$), 48.6 (C-14), 43.1 (C-13), 38.7 (C-8), 35.1 (C-12), 30.0 (C-6), 28.5 (C-16), 27.8 (C-7), 23.7 (C-15), 21.3 ($-CO-CH_3$), 18.6 ($-CH2-CH_3$), 10.2 ($-CH2-CH_3$); UV 263 (4.30); IR 1735 (vs, C=O), 1626 (w, -CH=C<), 1605 (s), 1567 (w), 1497 (s) (arom.), 1250 - 1230 (-O-CO); MS m/z 340.20300 (M^+); $C_{22}H_{28}O_3$ (340.46) calcd. C, 77.61 H, 8.29 found C, 77.61 H, 8.30. Under argon the crystallized **2** was dissolved in methanol (133 ml), potassium hydroxide (6.65 g, 118.5 mmol) was added and the solution stirred at + 40 °C for 4 h. The methanol was distilled off *in vacuo* and the resulting solution was neutralized with 1N hydrochloric acid. On addition of water (300 ml) the precipitated crystals were filtered off, washed with water, dried and recrystallized from methanol, affording **3** (6.1 g, 70 % yield from **1**).

3 proved to be moderately stable at room temperature and should be used in the next step without delay; ^1H NMR 0.99 (t, J=7.6 Hz, $-CH_2-CH_3$), 3.78 (s, $-OCH_3$), 3.90 (t, J=8.7 Hz, H-17), 6.11 (H-11), 6.59 (s, H-4), 6.71 (d, J=8,8 Hz, H-2), 7.51 (d, J=8.8 Hz, H-1); ^{13}C NMR 158.33 (C-3), 137.36 (C-5), 135.77 (C-10), 127.69 (C-9), 125.21 (C-1), 117.70 (C-11), 113.27 (C-4), 112.58 (C-2), 84.14 (C-17), 55.22 ($-OCH_3$); UV 263 (4.28); IR 3441 (OH), 1625 (-CH=C<), 1607, 1572 (arom.), 1233 (Ph-O-C).

The mother liquor from crystallization of **2** was evaporated to dryness and the product subjected to chromatography (eluent: toluene), yielding **4**: ^1H NMR 0.92 (t, J = 7.5 Hz, $-CH_2-CH_3$), 2.06 (s, CH_3COO), 3.87 (s, CH_3O), 4.84 (dd, J = 8.7 Hz, 8.7 Hz, 17-H), 6.10 (m, 11-H), 6.71 (d, J = 8.7 Hz, 2-H); 7.11 (d, J = 8.7 Hz, 1-H); MS m/z 356.19668 (M^+), 296.17679 (M - CH_3COOH), 267.13791 (296 - C_2H_5).

3-Methoxy-18a-homo-estra-1,3,5(10)-triene-11α,17ß-diol (5).

To a stirred suspension of **3** (10.0 g; 33.5 mmol) and sodium borohydride (1.4 g; 37 mmol) in 1,2-dimethoxyethane (50 ml) was added dropwise boron trifluoride diethyl ether (9.65 ml; 76.8 mmol) under an argon blanket. The mixture was heated for 1 h at 50 °C, then cooled to +10 °C and carefully quenched with water (5 ml). A cold solution of sodium hydroxide (4.8 g; 120 mmol) and hydrogen peroxide (30%; 20 ml) in water (40 ml) was added and the resulting mixture was stirred at room temperature for 1 h.

The solution was then neutralized with aqueous hydrochloric acid, 1,2-dimethoxyethane was distilled off *in vacuo* , and the resulting aqueous mixture was extracted several times with ethyl acetate. Work-up of the combined organic phases and recrystallization of the product from ethyl acetate gave **5** (7.95 g; 75%): mp. 160.1 - 160.7 °C; $[\alpha]_D$ -87°; ^{1}H NMR 1.06 (t, J=7.4 Hz, -CH_2-CH_3), 2.58 (dd, J=8.1, 4.8 Hz, H-9), 3.80 (s, -OCH_3), 3.84 (dd, J = 8.4Hz, 8.4 Hz, H-17), 4.08 (dt, J=5.1, 10.2 Hz, H-11), 6.66 (d, J=2.6 Hz, H-4), 6.73 (dd, J =8.7, 2.7 Hz, H-2), 7.85 (d, J=8.8 Hz, H-1); ^{13}C NMR 157.69 (C-3), 139.05 (C-10), 132.53 (C-5), 127.14 (C-1), 113.75 (C-4), 110.96 (C-2), 83.18 (C-17), 70.51 (C-11), 55.19 (-OCH_3); IR 3508, 3455 (-OH), 1611, 1576 (Ph), 1250 (Ph-O-C); UV 277 (3.26); MS m/z 316.20629 (M^+); $C_{20}H_{28}O_3$ (316.44) calcd. C, 75.91 H, 8.92 found C, 75.87 H, 8.87.

3-Methoxy--18a-homo-estra-2,5(10)-diene-11α,17ß-diol (6).

To liquid ammonia (110 ml) was added at -48 °C a solution of **5** (10 g; 32 mmol) in a mixture of tetrahydrofuran (90 ml) and propan-2-ol (10 ml; 130 mmol) under an argon blanket. Sodium (2.9 g; 0.126 g-atom) was added during 1.5 h with stirring, while the temperature was maintained between -45 °C and -48 °C. Stirring was continued at -48 °C for an additional hour. After the reaction had been quenched by addition of ammonium chloride .

(6.7 g; 125 mmol), the ammonia was allowed to distill off. The resulting solution was diluted with water and the organic layer was separated, washed twice with concentrated aqueous potassium hydroxide solution and evaporated *in vacuo* to give a product (9.8 g) which was recrystallized from toluene, affording **6** (7.55 g; 75%): mp.185 °C (decomp.); $[\alpha]_D$ + 20°; ^{1}H NMR 1.04 (t, J = 7.2 Hz, -CH_2-CH_3);), 2.49 (dd, J = 12.3, 4.8 Hz, H-12), 2.59 (m, H-9), 3.55 (s, -OCH_3), 3.75 (dt, J = 4.8, 10.6 Hz, H-11), 3.80 (dd, J = 8.6 Hz, 8.6 Hz, H-17),4.67 (t, J = 3.4 Hz, H-2); ^{13}C NMR 151.7 (C-3), 128.2 (C-5), 126.3 (C-10), 91.2 (C-2), 83.4 (C-17), 70.2 (C-11), 53.8 (-OCH_3), 51.9 (C-14), 50.3 (C-9), 45.3 (C-13), 44.7 (C-12), 37.4 (C-8), 18.5 (-CH_2-CH_3), 9.8 (CH_2-CH_3); IR 3521, (s), 3487, (s), 1075-1025, (m, R-OH), 2826, (s), 1210, (s), (C-O-CH_3), 1657, (w, >C=C<); MS m/z 318.22100 (M^+); $C_{20}H_{30}O_3$ (318.46) calcd. C, 75.43 H, 9.50 found C, 75.09 H, 9.50.

11α,17ß-Dihydroxy-18a-homo-estr-4-en-3-one (8).

To a stirred suspension of **6** (10 g; 31.4 mmol) in acetone (40 ml) was added a mixture of hydrochloric acid (2 ml), water (5 ml), and acetone (33 ml). Stirring was continued until the enol ether cleavage was complete (TLC). The solution was then neutralized with saturated aqueous sodium hydrogen carbonate solution (3.5 ml), concentrated *in vacuo*, and diluted with water to give crystals of **8** which were collected, washed with water and dried. Yield: 8.8 g; 92%. Recrystallization from acetone gave a pure sample: mp. 201.1 - 201.9 °C; $[\alpha]_D$ -37°; ^{1}H NMR 1.08 (t, J=7.9 Hz, -CH_2-CH_3), 3.7 (m, H-11, H-17), 5.83 (s, H-4); ^{13}C NMR 213.19 (C-3), 167.22 (C-5), 124.54 (C-4), 83.07 (C-17), 71.93 (C-11); IR 3450-3260 (-OH), 1655 (>C=O), 1624 (C=C), 1075-1044 (>CH-OH); UV 242 (4.21); MS m/z 304.20251 (M^+); $C_{19}H_{28}O_3$ (304.43) calcd. C, 74.96 H, 9.27 found C, 74.98 H, 9.21.

11α,17ß-Dihydroxy-18a-homo-5α-estran-3-one (11) and 11α,17ß-dihydroxy-18a-homo-10α-estr-4-en-3-one (13).

The mother liquor from crystallization of **8** was evaporated to dryness, the residue dissolved in ethyl acetate and subjected to chromatography. On elution with the same solvent, **11**, additional **8**, and **13** were eluated in turn. **11**: mp.160 - 162 °C (methanol); $[\alpha]_D$ + 4°; ^{1}H NMR 3.78 (dd, J = 8.5 Hz, 8.5 Hz, H-17), 3.69 (m, H-11), 1.07 (t, J = 7.4 Hz, CH2-CH3); ^{13}C NMR 211.8 (C-3), 83.3 (C-17), 71.7 (C-11), 54.3 (C-14), 50.3 (C-9), 48.9 (C-12), 22.7 (C-15), 18.6 (CH2-CH3), 9.8 (CH2-CH3); IR 3466, 3444, (s, OH), 1704, (vs, CO), 1043, (s, C-O); MS m/z 306.21850 (M^+); $C_{19}H_{30}O_3$ (306.45) calcd. C, 74.47 H, 9.87 found C, 74.35 H, 9.80. **13**: mp. 218 - 222 °C (methanol); $[\alpha]_D$ -212° (dioxan); CD (dioxan) 334.60 nm, $\Delta\varepsilon_{max}$ -1.766, 347.20 nm, $\Delta\varepsilon_{max}$ -1.7525; ^{1}H NMR 1.04 (t, J = 6.4, -CH_2-CH_3), 2.44 (dd, J = 11.8, 4.4 Hz, H-12), 2.98 (m, H-10), 3.79 (m, H-11, 17), 5.88 (s, H-4); ^{13}C NMR 199.9 (C-3), 170.4 (C-5), 125.5 (C-4), 83.0 (C-17), 67.5 (C-11), 53.3, 47.4 (C-9,14), 45.4 (C-13), 42.1 (C-12), 38.0 (C-16), 37.7 (C-10), 30.9 (C-8), 30.4, 30.0, 28.9, 24.6 (C-1,2,6,7), 22.3 (C-15), 18.4 (CH_2-CH_3), 9.5 (CH_2-CH_3); IR 3500 - 3260, (s, OH), 1655, (vs, >C=C-C=O), 1619, (m, >C=C-C=O), 1070 - 1000, m (C-O), 878, m (=CH); UV 243 (4.21); MS m/z 304.20529 (M^+); $C_{19}H_{28}O_3$ (304.43) calcd. C, 74.96 H, 9.27 found C, 74.43 H, 9.20;

3-Methoxy-18a-homo-estr-4-ene-11α,17ß-diol (15).
8 (5.0 g; 16.4 mmol) and $CeCl_3.7H_2O$ (6.13 g; 16.4 mmol) were dissolved in methanol (200 ml). The solution was cooled to 0 °C and sodium borohydride (3.13 g; 82.7 mmol) was added slowly. When the reduction was complete (TLC), acetic acid (2 ml) was added and the methanol distilled off *in vacuo*. Dilution with water (50 ml), extraction with ethyl acetate and work-up of the combined extracts gave **14** as a mixture of the 3α- and 3β-epimers. This mixture (3.5 g; 11.4 mmol) was dissolved in methanol (30 ml), p-toluenesulfonic acid hydrate (20 mg; 0.105 mmol) was added, and the reaction mixture set aside for 1 h. Neutralization with saturated aqueous sodium hydrogen carbonate solution, evaporation of the methanol, extraction with ethyl acetate, and work-up of the combined organic phases gave **15** (3.7 g) as a mixture of the 3β- and the 3α-epimers (6 : 4 by Gc), which were used for the next step without separation.
To obtain a reference sample of the 3ß-methoxy compound **12**, the mixture **15** was subjected to chromatography (eluent: ethyl acetate). **12**: mp. 100 - 106 °C (ethyl acetate /n-hexane); $[\alpha]_D$ -27°; ^{1}H NMR 0.78 (t, 9.2 Hz, $-CH_2-CH_3$), 3.36 (s, $-OCH_3$), 3.64 - 3.82 (m, H-3/11/17), 5.51 (s, H-4); ^{13}C NMR 143.2 (C-5), 122.4 (C-4), 83.3 (C-17), 75.5 (C-11), 72.4 (C-3), 55.6 ($-OCH_3$), 55.5 (C-14), 50.3 (C-9), 44.9 (C-13), 44.5 (C-12), 43.5 (C-8), 39.9 (C-10), 35.7 (C-6), 31.5 (C-7), 30.9 (C-16), 27.8, 26.8 (C-1/2), 18.6 ($-CH_2-CH_3$), 9.9 ($-CH_2-CH_3$); IR 3550 - 3150, (s, -OH), 3000 - 2800, (s, CH), 1656, (w, >C=CH), 1100 - 1040 (>CH-O-); MS m/z 320.23471 (M^+); $C_{20}H_{32}O_3$ (320.48) calcd. C, 74.96 H, 10.07 found C, 74.24 H, 10.36.

3,3-Ethylenedithio-18a-homo-estr-4-ene-11α,17ß-diol (16).
8 (10 g; 32.8 mmol) was dissolved in methanol (45 ml) and ethanedithiol (4.1 ml; 49 mmol). While this solution was stirred at room temperature, boron trifluoride diethyl ether (2.5 ml; 20 mmol) was added dropwise. The mixture was stirred for another hour and then poured into saturated aqueous sodium hydrogen carbonate solution (1.5 l). The precipitated crystals were filtered off, washed with water (3 x 50 ml) and dried. Yield: 12.5 g; nearly 100%. A pure sample of **16** was obtained by chromatography (eluent toluene/ethyl acetate 10 : 1 v/v) and recrystallization from ethyl acetate: mp. 158.5 - 160.0 °C ; $[\alpha]_D$ + 48°; ^{1}H NMR 1.06 (t, J = 7.5 Hz, $-CH_2-CH_3$), 3.4-3.2 (m, $S-CH_2-CH_2-S$), 3.66 (dt, Jd = 4.5 Hz, Jt = 10.2 Hz, 11-H), 3.76 (dd, J = 8.6 Hz, 8.6 Hz, 17-H), 5.61 (s, 4-H); ^{13}C NMR 141.9 (5-C), 125.8 (4-C), 83.2 (17-C), 72.5 (11-C), 65.6 (3-C), 55.1 (14-C), 50.2 (9-C), 44.8 (13-C), 42.3 (8-C), 39.8 (10-C), 18.6 ($-CH_2-CH_3$), 9.9 ($-CH_2-CH_3$); IR 3550 - 3100, (s, OH), 3000 - 2820, (vs, alkyl), 1490 - 1350, (m, alkyl), 1160 - 980, (s, R_2CH-OH), 847, (m, CR'R"=CHR); MS m/z 380.187 (M^+).

18a-Homo-estr-4-ene-11α,17ß-diol (9).
(a) Under an argon blanket ethylamine (1.35 l), dried over potassium hydroxide, was condensed at -30° C. Lithium (7.68 g; 1.11 g-atom) was added to the amine and subsequently a solution of **15** (156.8 g; 0.49 mol) in tetrahydrofuran (400 ml) and another portion of lithium (7.68 g; 1.11 g-atom) were added, carefully avoiding the blue colour of the reaction mixture to disappear. The reaction was allowed to proceed for another additional 0.5 h at -30 °C to -35 °C and then quenched with ammonium chloride (117 g; 2.2 mol). Ethylamine was distilled off as completely as possible, water was added and the two phases formed were separated. The organic layer was washed twice with concentrated aqueous potassium hydroxide solution and evaporated *in vacuo* to give a product which was crystallized from toluene yielding **9** (120.8 g; 85%).
To obtain an analytical sample, the product (1 g; 3.44 mmol) was allowed to react with hexamethyldisilazane (1.0 ml) in dimethylformamide (10 ml) at room temperature. When the etherification was complete (TLC), the precipitate formed was filtered off and recrystallized from methanol containing a trace of triethylamine.
The silyl ether **21** was transformed into **9** by hydrolysis in methanolic sulfuric acid: mp. 119 - 121 °C (toluene); $[\alpha]_D$ + 16°; ^{1}H NMR 1.06 (t, J = 7.4 Hz, $-CH_3$), 2.44 (dd, J = 4.6, 12.1 Hz, H-12), 3.69 (dt, J = 4.8, 10.1 Hz, H-11), 3.77 (dd, J = 8.5 Hz, 8.5 Hz; H-17), 5.44 (s, broad, H-4); ^{13}C NMR 140.2 (C-5), 121.1 (C-4), 83.4 (C-17), 72.6 (C-11), 55.7 (C-9), 50.4 (C-14), 44.9 (C-13), 44.5 (C-12), 43.5 (C-8), 40.2 (C-10), 36.1 (C-16), 22.0 (C-15), 18.7 (CH2-CH3), 9.9 (CH2-CH3); IR 3435, (s) 1085 - 990, (m, R-OH); MS m/z 290.22509 (M+); $C_{19}H_{30}O_2$ (290.45) calcd., C, 78.57 H, 10.41 found C, 78.54 H, 10.39.
(b) According to protocol (a) **16** (10 g; 26.3 mmol) in tetrahydrofuran (50 ml) was reductively cleaved with lithium (0.85 g and 0.425 g; 0.18 g-atom) in ethylamine (200 ml) to give **9** (6.6 g; 87%), identical in all aspects with the product obtained above.

18a-Homo-estr-4-ene-11,17-dione (20).
9 (10 g; 34.4 mmol) was dissolved in triethylamine (40 ml; 288 mmol) and dimethyl sulfoxide (34.7 ml; 488 mmol). Sulfur trioxide pyridine complex (20 g; 126 mmol) was added at room temperature with stirring. The mixture was stirred for another 3 h at room temperature and then diluted with water (250 ml). The solution was extracted with toluene (3 x 50 ml) and the combined organic phases were worked up to give **20** (8.38 g; 85%). To obtain a pure sample the product was subjected to chromatography (eluent: toluene) and crystallized from methanol: mp. 154.2 - 154.8 °C ; $[\alpha]_D$ +222°; ^{1}H NMR 0.82 (t, J = 7.2 Hz, -CH2-CH$_3$), 1.26 (q, J = 7.2 Hz, -CH$_2$-CH$_3$), 2.26 (d, J = 12.2 Hz, H-12), 2.51 (dd, J = 8.2 Hz, H-16), 2.70 (d, J = 12.2 Hz, H-12), 5.50 (s, broad, H-4); ^{13}C NMR 215.9 (C-17), 210.3 (C-11), 137.8 (C-5), 122.7 (C-4), 61.3 (C-14), 55.0 (C-13), 51.0 (C-9), 45.9 (C-12), 40.7 (C-8), 36.1 (C-16), 35.3 (C-10), 20.6 (C-15), 19.3 (-CH$_2$-CH$_3$), 7.5 (-CH2-CH$_3$); IR 1733, (vs, 17-C=O), 1698, (vs, 11-C=O); MS m/z 286.19360 (M$^+$); $C_{19}H_{26}O_2$ (286.41) calcd. C, 79.68 H, 9.15 found C, 79.65 H, 9.15.

17,17-[(2,2-Dimethyl)propane-1,3-dioxy]-18a-homo-estr-4-en-11-one (22).
A mixture of **20** (10 g; 34.9 mmol), 2,2-dimethyl-propane-1,3-diol (20 g; 192 mmol), triethylorthoformate (20 ml; 120 mmol), and p-toluenesulfonic acid hydrate (0.6 g; 3.15 mmol) was stirred for 3 h at +40 °C. The solution was then diluted with toluene (250 ml) and washed with saturated aqueous sodium hydrogen carbonate solution (50 ml). The organic phase was worked up to yield **22** as crude material. An analytical sample was obtained by chromatography (eluent: toluene) and subsequent crystallization from ethanol: mp. 130 - 134 °C ; $[\alpha]_D$ + 121°; ^{1}H NMR 0.71 (s, -CH$_3$), 1.01 (t, J = 7.3 Hz, CH$_2$-CH$_3$), 1.08 (s, -CH$_3$), 2.53 (d, J = 11.7 Hz, H-12), 2.76 (d, J = 11.7 Hz, H-12), 3.36 (q, J = 10.9 Hz, -OCH$_2$C-), 3.63 (d, J = 11.1 Hz, -OCH$_2$C-), 5.45 (s, broad, H-4); ^{13}C NMR 213.4 (C-11), 138.8 (C-5), 122.0 (C-4), 108.5 (C-17), 72.2 (-OCH$_2$-), 70.6 (-OCH$_2$-), 61.0 (C-9), 54.0 (C-13), 49.2 (C-14), 44.4 (C-12), 41.7 (C-8), 35.4 (C-10), 35.1 (C-16), 32.1 (C-6), 30.3 (-C(CH$_3$)2), 29.0, 28.1 (C-1,7), 25.6 (C-3), 22.5 (-CH$_3$), 22.1 (-CH$_3$), 21.82 (C-2), 21.78 (C-15), 21.6 (-CH$_2$-CH$_3$), 9.3 (-CH$_2$-CH$_3$); IR 1708, (vs, >C=O); MS m/z 372.26568 (M$^+$); $C_{24}H_{36}O_3$ (372.55) calcd. C, 77.38 H, 9.74 found C, 77.53 H, 9.68.

11-Methylene-17[(2,2-dimethyl)-propane-1,3-dioxy]-18a-homo-estr-4-ene (23).
Under an argon blanket sodium hydride (5.04 g; 210 mmol) and methyl triphenylphosphonium iodide (88.9 g; 220 mmol) were allowed to react in dry dimethyl sulfoxide (120 ml) under sonification at 80 °C. Ylide formation was complete after 1 to 1.5 h. A solution of **22** (24.8 g; 66.6 mmol) in toluene (30 ml) was then slowly added with stirring, and sonification was continued at 80 °C for 10 to 12 h. After this most of the toluene and dimethyl sulfoxide was distilled off *in vacuo* and water (2 ml) was added with cooling to give a mixture which was intensively stirred with cyclohexane (5 x 250 ml). The combined cyclohexane phases were washed with brine, concentrated *in vacuo*, filtered through silica gel 60 (Merck, 63 - 200 µm) and evaporated to dryness *in vacuo*.
The product obtained was crystallized from acetone to yield **23** (21 g; 85%): mp. 100.5 - 104.5 °C ; $[\alpha]_D$ + 74°; ^{1}H NMR 0.72 (s, -CH$_3$), 1.00 (t, J = 7.1 Hz, -CH2-CH$_3$), 1.12 (s, -CH$_3$), 2.32 (d, J = 12.3 Hz, H-12), 2.46 (d, J = 12.3 Hz, H-12), 3.36 (q, J = 10.7 Hz, -OCH$_2$C-), 3.60 (d, J = 11.7 Hz, -OCH$_2$C-), 4.87 (s, =CH$_2$), 4.96 (s, =CH$_2$), 5.45 (s, broad, H-4); ^{13}C NMR 148.5 (C-11), 140.2 (C-5), 121.1 (C-4), 109.6 (C-17), 108.0 (=CH$_2$), 72.1 (-OCH$_2$-), 70.4 (-OCH$_2$-), 54.9 (C-9), 50.9 (C-13), 50.4 (C-14), 42.2 (C-8), 37.6 (C-12), 36.7 (C-10), 35.7 (C-16), 31.8 (C-6), 30.4 (-C(CH$_3$)$_2$), 22.6 (-CH$_3$), 22.2 (-CH$_3$), 22.0 (C-15), 20.8 (C-18), 8.9 (-CH$_2$-CH$_3$); IR 3080, (w, =CH$_2$), 1638,(m, =CH$_2$); MS m/z 370.28839 (M+); $C_{25}H_{38}O_2$ (370.58) calcd. C, 81.03 H, 10.34 found C, 81.18 H, 10.28.

11-Methylene- 18a-homo-estr-4-en-17-one (24).
A solution of **23** (6 g; 16.2 mmol) and p-toluenesulfonic acid hydrate (0.6 g; 3.1 mmol) in acetone (50 ml) was stirred for 12 h at room temperature. To the mixture was then added aqueous sodium hydrogen carbonate solution (50 ml). The acetone was distilled off *in vacuo* and the crystals formed were collected, washed with water, and dried, to give **24** (4.55 g; nearly 100%). To obtain an analytical sample, the product was recrystallized from methanol: mp. 101.0 - 102.5 °C (lit. [26] 96 - 99 °C); $[\alpha]_D$ +174° (lit. [26] +166°); ^{1}H NMR 0.76 (t, J = 7.5 Hz, -CH2-CH$_3$), 2.58 (d, J = 12.3 Hz, H-12), 4.84 (s, =CH$_2$), 4.93 (s, =CH$_2$), 5.49 (s, broad, H-4); ^{13}C NMR 218.8 (C-17), 146.1 (C-11), 139.4 (C-5), 121.7 (C-4), 110.0 (=CH$_2$), 55.1 (C-9),

53.0 (C-13), 52.4 (C-14), 41.6 (C-8), 39.6 (C-12), 36.6 (C-10), 36.1 (C-16), 35.3 (C-6), 20.8 (C-15), 18.1 (CH2-CH3), 7.2 (-CH2-CH_3); IR 3086 (>C=CH_2), 1732 (C=O), 1643, 907 (>C=CH_2, >C=CH-); MS m/z 284.21380 (M+); $C_{20}H_{28}O$ (284.45) calcd. C, 84.45 H, 9.92 found C, 84.45 H, 9.91.

13-Ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17-ol (25; desogestrel).
Ethine was passed into a solution of lithium (10g; 1.44 g-atom) in ethylenediamine (200 ml) over a period of 2 h. Then a solution of **24** (10 g; 35 mmol) in tetrahydrofuran (100 ml) was added and the resulting reaction mixture stirred for 2 h at +25 °C, with the ethine flow being maintained . The solution was diluted with ethyl acetate (250 ml) and neutralized with sulfuric acid (20%) with cooling .
Work-up of the organic phase gave **25**, which was subjected to chromatography (eluent: dichloromethane) and subsequently to recrystallization from n-hexane (9.28 g; 85%): mp. 109.0 - 111.0 °C (lit. [26] 109 -110°C); $[\alpha]_D$ +56 °C (lit. [32] +55 °C); ^{1}H NMR 1.04 (t, J = 7.5 Hz,-CH2-CH3), 1.44 (q, J = 7.5 Hz, -CH_2-CH_3), 2.60 (s, -C≡CH), 2.61 (d, J = 12.4 Hz, H-12), 4.78 (s, =CH_2), 4.98 (s, =CH_2), 5.46 (s, broad, H-4); ^{13}C NMR 147.4 (C-11), 139.9 (C-5), 121.4 (C-4), 108.6 (=CH_2), 88.9 (-C≡CH), 81.2 (C-17), 74.1 (-C≡CH), 54.7 (C-9), 52.5 (C-14), 50.4 (C-13), 42.6 (C-8), 40.7 (C-12), 39.8 (C-16), 36.6 (C-10), 35.6 (C-6), 31.7 (C-7), 29.1, 25.7, 21.94, 21.91 (C-1,2,3,15), 19.9 (-CH2-CH3), 9.2 (-CH2-CH3); IR 3541, (s, OH), 3285, (s, ≡CH), 3091, (w), 1640, (m), 898, 910 (=CH_2), 2105 (w, C≡C), 1033, 1042 (C-O); MS m/z 310.22821 (M^+); $C_{22}H_{30}O$ (310.48) calcd. C, 85.11 H, 9.74 found C, 85.19 H, 9.68.
The X-ray crystallographic data of **25** (measured by G. Reck) are in accordance with lit. [33].

13-Ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one (28; 3-Oxo desogestrel) and 13-Ethyl-17-hydroxy-11-methylene 18,19-dinor-9β,10α, 17α-pregn-4-en-20-yn-3-one (30).
25 (10 g; 32.2 mmol) was dissolved in toluene (100 ml) and acetic acid anhydride (12 ml). Perchloric acid (85%; 0.1 ml) was added and the mixture allowed to react for 1 h at room temperature. The solution was neutralized with saturated aqueous sodium hydrogen carbonate solution and worked up, to yield **26**. To **26**, dissolved in tetrachloromethane (100 ml), was added a solution of tert. butyl chromate in tetrachloromethane (160 ml; 185 g CrO_3 / l), acetic acid (46 ml), and acetic acid anhydride (17 ml) . The reaction mixture was refluxed for 5 h, subsequently cooled to room temperature, and reduced by dropwise addition of aqueous sodium hydrogen sulfite solution. The organic phase was washed with saturated aqueous sodium hydrogen carbonate solution and water and worked up. The product obtained was subjected to chromatography (eluent: toluene/ethyl acetate 10 : 1 v/v) yielding **27** (1 g) and **29** (3 g). **27** (1 g; 2.7 mmol) was dissolved in methanol (100 ml). Methanolic sodium hydroxide solution (1%; 2 ml) was added and the mixture was kept for 3 h at room temperature. The solution was neutralized with acetic acid (1% in methanol) and evaporated *in vacuo*. The resulting **28** was dissolved in toluene and purified by chromatography (eluent: toluene/ethyl acetate 10 : 1 v/v) and subsequently by crystallization from ethyl acetate/n-hexane; yield : 0.55 g (62%): mp. 195.8-196.5 °C (lit. [26] 198 -199 °C); $[\alpha]_D$ + 85° (lit. [26] + 84°); ^{1}H NMR 1.06 (t, J = 7 Hz, -CH2-CH_3), 2.63 (s, ≡CH), 4.83 (=CH_2), 5.07 (=CH_2), 5.88 (s, -CO-CH=C<, H-4); ^{13}C NMR 200.1 (-CH_2-CO-CH=, C-3), 166.6 (-CO-CH=C< C-5), 146.3 (>C=, C-11),125.6 (-CO-CH=C<, C-4), 108.8 (=CH_2), 87.6 (-C≡), 80.8 (>C<, C-17), 74.3 (≡CH), 9.1 (-CH_2CH_3); IR 3400, (s, -OH), 3270, (s), 2100, (w, C≡CH), 3075, (w, >C=CH_2), 2820-3000, (vs, alkanes), 1690-1600, (s, >C=CH_2, C=C-C=O-), 1140-1000, (s, C-O) 897, (m, >C=CH2); UV 240 (4.22); MS m/z 324.21051 (M^+); **29** (3 g) was saponified using the same protocol to give **30** (1.6 g; 60%). mp. 177.5 - 181.5 °C (ethyl acetate/n-hexane); $[\alpha]_D$ -34°; CD (dioxan) 335.6 nm, $\Delta\varepsilon_{max}$ +3,56, ^{1}H NMR 0.95 (m, H-16), 1.03 (t, J = 7.4 Hz, -CH2-CH_3), 1.44, 1.25 (q, J = 7.4 Hz, -CH_2-CH_3), 2.60 (s, ≡CH), 2.66 (d, J = 12.8 Hz, H-12), 4.94 (s, =CH_2), 5.07 (s, =CH_2), 5.79 (s, H-4); ^{13}C NMR 201.5 (C-3), 163.7 (C-5), 145.4 (C-11), 123.7 (C-4), 109.9 (=CH_2), 87.5 (-C≡CH), 80.5 (C-17), 74.3 (-C≡CH), 50.2 (C-13), 49.2 (C-9), 48.2 (C-14), 46.2 (C-8), 40.1 (C-10), 40.0 (C-12), 39.9 (C-16), 35.9 (C-2), 34.9 (C-6), 27.7 (C-7), 25.7 (C-1), 23.8 (C-15), 19.8 (-CH_2-CH_3), 8.8 (-CH2-CH_3); IR 3440, (s, R-OH), 3304, (m, ≡CH), 3094, (m), 1673, (m), 1630, (m), 897, (m, >C=CH-C=O-), 1000-1140, (s, C-O); UV 238 (4.15); MS m/z 324.21011 (M^+); $C_{22}H_{28}O_2$ (324.47) calcd. C, 81.44 H, 8.70 found C, 81.30 H, 8.79.

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17. Obviously, the 11α-hydroxy group gives rise to an intrinsic configurational instability at C_{10}, which may lead to a partial inversion of this center whenever 10β-*H* gets the opportunity for abstraction. This is confirmed by our finding that acetalization of **8** provides a 1:1 mixture of 10β-*H* and 10α-*H* ethylene acetals, whereas the 11-deoxy derivative of **8** yields solely the 10β-*H* acetal (unpublished).
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24. Mp.143 - 145 °C (ethyl acetate); ^{1}H NMR 0.84 (t, J = 7.4 Hz, -CH_2-CH_3), 2.76 (d, 12.3 Hz, 12-H), 10.15 (s, br., COOH); ^{13}C NMR 215.0 (C-17), 210.9 (C-11), 208.1 (C-5), 179.3 (C-4), 58.9 (C-9), 54.9 (C-13), 50.3 (C-14), 47.9 (C-8), 45.2 (C-11), 40.7 (C-6), 39.8 (C-10), 35.9 (C-16), 34.0 (C-3), 29.9 (C-2), 26.8, 22.7 (C-7/C-1), 20.6 (C-15), 19.4 (-CH_2-CH_3), 7.4 (-CH2-CH_3); MS 334.17779 (M^+), 316.16949 (M - H_2O), 248.14059 (M - CH_2=CH-CH_2-COOH).
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