# Steroids 48. Synthesis of 16α-ethyl-21-hydroxy-19-norpregn-4-ene-3,20-dione from 17-substituted 3-methoxyestradiols

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*A new synthesis of 16α-ethyl-21-hydroxy-19-norpregn-4-ene-3,20-dione is described, starting from 17-cyano- and 17α-ethynyl-3-methoxyestra-1,3,5(10)-trien-17-ols.* (*Steroids* **58**:185–189, 1993)

**Keywords:** steroids; synthesis; 19-norpregnenes; A-aromatic pregnenes

## Introduction

The importance of the synthesized 16α-ethyl-21-hydroxy-19-norpregn-4-ene-3,20-dione (**15b**) lies in its use in the determination of progesterone receptors.[2] Its synthesis was reported in 1985 by Organon, starting from 3β-acetoxypregna-5,16-dien-20-one (pregnadienolone acetate).[3] The process involved 12 steps, some of which gave only poor yields. The restricted availability of pregnadienolone, which is a transformed derivative of natural steroidal saponins or alkaloids, also prompted us to look for other starting materials.

3-Methoxyestra-1,3,5(10)-trien-17-one (estrone methyl ether) can be prepared synthetically,[4,5] so we chose its derivatives as starting materials. On the route to 16-substituted-19-norpregnenes, two main problems arise: the synthesis of the 16α-substituted-17β-acetyl system and the formation of the 4-unsaturated-3-ketone system. The former can be solved by the transformation of the known 17-cyanoestradiol- and 17α-ethynylestradiol methyl ethers. The aromatic ring A can be reduced in the appropriate step of the reaction sequence by the Birch method.[6]

## Experimental

Estrone 3-methyl ether and 17α-ethynylestradiol 3-methyl ether (mestranol) were kindly provided by the Gedeon Richter Chemical Works Ltd. (Budapest). The neutral alumina used for column chromatography was of activity grade III–IV (Brockman), silica gel was of 230–400 mesh. Melting points (mp) were determined on a Kofler block and are uncorrected. Optical rotations were measured with a Polamat-A (Zeiss) polarimeter, in chloroform solution. The reactions were monitored on thin-layer chromatography [Merck 5554 layer, developing solvent system methanol/benzene (5:95), visualization by spraying with concentrated $H_2SO_4$]. Infrared (IR) spectra were recorded in KBr pellets on a UNICAM SP 200 instrument. Proton nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ solution on a Bruker AM 400 FT-NMR instrument; chemical shifts are given as δ values (ppm), with tetramethylsilane as internal standard.

### *3-Methoxyestra-1,3,5(10),16-tetraene-17-carbonitrile (2)*

17α,β-Hydroxy-3-methoxyestra-1,3,5(10)-triene-17α,β-carbonitrile (**1**)[7] (0.6 g) in dry pyridine (4.4 ml) was heated at reflux temperature with $POCl_3$ (0.75 ml) for 15 minutes. To the cooled solution, water (50 ml) was added and the precipitated material was filtered off and washed with 2 N HCl and then with water. After drying at 100 C, the crude product (0.42 g, 74%) was chromatographed on alumina (24 g). Elution with benzene/petroleum ether (4:1) and evaporation afforded a solid, which was recrystallized from dichloromethane/methanol. mp, 171–173 C (ref.[8]: mp, 168–170 C); IR: 2,220 (C≡N), 1,610 (aromatic CH), 1,585 (conjugated C=C), 1,510 (aromatic CH) $cm^{-1}$; $^1H$ NMR δ: 0.91 (s, 3 H, 18-$H_3$), 3.76 (s, 3 H, $OCH_3$), 5.68 (m, 1 H, 16-H), 6.68, 6.80, 7.15 (each s, 1 H each, aromatic hydrogens) ppm. Analysis calculated for $C_{20}H_{20}NO$ (293.4): C, 81.87; H, 7.90; N, 4.77. Found: C, 81.67; H, 7.93; N, 4.62%.

### *17α,β-Cyano-3-methoxy-2,4-dinitroestra-1,3,5(10)-trien-17α,β-yl nitrate (5)*

To a stirred, cold (−20 C) suspension of cyano compound **1** (1 g) in acetic anhydride (10 ml), concentrated nitric acid (1.5 ml) was added dropwise within 10 minutes. The mixture was further stirred at the same temperature for 1 hour, becoming a solution, and it was then poured into ice-water (100 ml). On standing overnight, the oily organic layer was transformed into yellow crystals, which were filtered off, washed with water until neutral, and dried in a desiccator over phosphorus pentoxide.

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For additional material, see *Steroids* **58**:115–118, 1993.

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Recovery was 1.3 g (91%); mp, 103–106 C. IR: 1,665 (very strong (v.s.), $ONO_2$), 1,545 (v.s., Ar-$NO_2$), 1,350 ($ONO_2$), 1,295 (Ar-$NO_2$), 840 ($ONO_2$) $cm^{-1}$; $^1H$ NMR δ: 1.02 (s, 3 H, 18-$H_3$), 2.83 (m, 2 H, 16-$H_2$), 3.98 (s, 3 H, $OCH_3$), 8.01 (s, 1 H, 1-H) ppm. Analysis calculated for $C_{20}H_{22}N_4O_8$ (446.4): C, 53.80; H, 4.97; N, 12.55. Found: C, 54.13; H, 4.87; N, 12.45%.

### *3-Methoxy-2-nitro-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-17β-yl nitrate (6)*

Mestranol (**3**) (1.00 g) was treated as **1** in the previous experiment. Yellow crystals were obtained (1.25 g, 97%); mp, 162–164 C. IR: 3,380 (C≡C), 1,650 (v.s., $ONO_2$), 1,535 (v.s., Ar-$NO_2$), 1,350 ($ONO_2$), 1,300 (strong (s), Ar-$NO_2$), 858 ($ONO_2$) $cm^{-1}$; $^1H$ NMR δ: 0.93 (s, 3 H, 18-$H_3$), 2.64 (s, 1 H, C≡CH), 2.80 (m, 2 H, 16-$H_2$), 3.81 (s, 3 H, $OCH_3$), 6.71 (s, 1 H, 4-H), 7.76 (s, 1 H, 1-H) ppm. Analysis calculated for $C_{21}H_{24}N_2O_6$ (400.4): C, 62.98; H, 6.04; N, 6.99. Found: C, 63.29; H, 6.03; N, 6.71%.

### *3-Methoxy-19-norpregna-1,3,5(10),16-tetraen-20-one (7)*

**From 2.** To a solution of 16-unsaturated nitrile **2** (1.25 g, 4.3 mmol) in dry benzene (4 ml), methylmagnesium iodide, prepared freshly from methyl iodide (2.48 g, 0.02 mol) and magnesium (0.4 g, 0.02 g atom) in dry ether (25 ml), was added. The mixture was heated at reflux temperature for 6 hours, then poured into a mixture of acetic acid (75 ml) and water (25 ml). The organic solvents were distilled out in vacuum and the separated yellow material was collected by filtration, washed with water until neutral, and dried at 110 C. The crude product (0.97 g, 74%) was dissolved in hot dichloromethane, and methanol was added until turbidity. After standing at 5 C for 24 hours, the separated white crystals were filtered off and dried at 110 C. Recovery was 0.8 g; mp, 193–195 C (ref.[8]: 192–194 C). IR: 1,680 (C=O), 1,590 (conjugated C=C), 1,620, 1,520 (aromatic bonds) $cm^{-1}$; $^1H$ NMR δ: 0.95 (s, 3 H, 18-$H_3$), 2.30 (s, 3 H, 21-$H_3$), 3.85 (s, 3 H, $OCH_3$), 6.70–7.50 (m, 4 H, 1-H, 2-H, 4-H, 16-H) ppm. Analysis calculated for $C_{21}H_{26}O_2$ (310.4): C, 81.25; H, 8.44. Found: C, 80.96; H, 8.24%.

**From 4.** A solution of unsaturated ethynyl compound **4**[9] (12.3 g) in formic acid (96%, 500 ml) was refluxed for 30 minutes, then cooled, mixed with ice-water (1,000 ml) and left to stand overnight at 5 C. The separated material was collected by filtration and washed with water until neutral. After drying at 110 C, the light brown powder (12.4 g, 95%) was recrystallized from dichloromethane/methanol. Recovery was 5.85 g; mp, 193–194 C. The mother liquor was evaporated to dryness and the residue was chromatographed on alumina (50 g). Elution with benzene/hexane (1 : 4) afforded a further 3.08 g of **7** with the same purity as from recrystallization. The spectroscopic data on the material were identical to those on the compound obtained from **2**.

### *Pregna-4,16-diene-3,20-dione (9)*

A formic acid (3 ml) solution of pregnenyne **8**[10] (0.5 g) was heated at reflux temperature for 30 minutes. After cooling, the brown solution was mixed with cold water (25 ml), and was extracted with diethyl ether (3 × 20 ml). The combined organic fractions were washed with water, dried ($Na_2SO_4$), and evaporated. The residue (0.42 g, 81%) was crystallized twice from methanol; mp, 189–191 C (ref.[11]: mp, 190–192 C). $[\alpha]_D^{23}$ = +132° (c = 1) (ref.[12]: $[\alpha]_D^{23}$ = +134.5°); $^1H$ NMR δ: 0.92 (s, 3 H, 18-$H_3$), 1.18 (s, 3 H, 19-$H_3$), 2.17 (s, 3 H, 21-$H_3$), 5.73 (s, 1 H, 4-H), 6.17 (s, 1 H, 16-H) ppm.

### *19-Norpregna-4,16-dien-20-yn-3-one (10)*

Norethisterone (1 g) was dissolved in dry pyridine (5 ml), and freshly distilled phosphorus oxychloride (0.52 ml) was added. The solution was gently boiled for 1.5 hours, then poured onto ice (100 g), acidified with concentrated HCl to pH 5. The water slurry was extracted with diethyl ether (3 × 25 ml), the combined ethereal parts washed with 10% $Na_2CO_3$ solution and with water. It was dried ($Na_2SO_4$), evaporated, and the residue chromatographed on silica gel (20 g). Benzene eluted 0.53 g (56%) of **10**; mp, 159–161 C; $[\alpha]_D^{23}$ = +105° (c = 0.2). IR: 3,220 (C≡CH), 1,665 (3-C=O), 1,610 (conjugated C=C) $cm^{-1}$; $^1H$ NMR δ: 0.92 (s, 3 H, 18-$H_3$), 3.08 (s, 1 H, C≡CH), 5.84 (s, 1 H, 4-H), 6.11 (tr, 1 H, 16-H) ppm. Analysis calculated for $C_{20}H_{24}O$ (280.4): C, 85.67; H, 8.63. Found: C, 85.43; H, 8.52%.

### *19-Norpregna-4,16-diene-3,20-dione (11)*

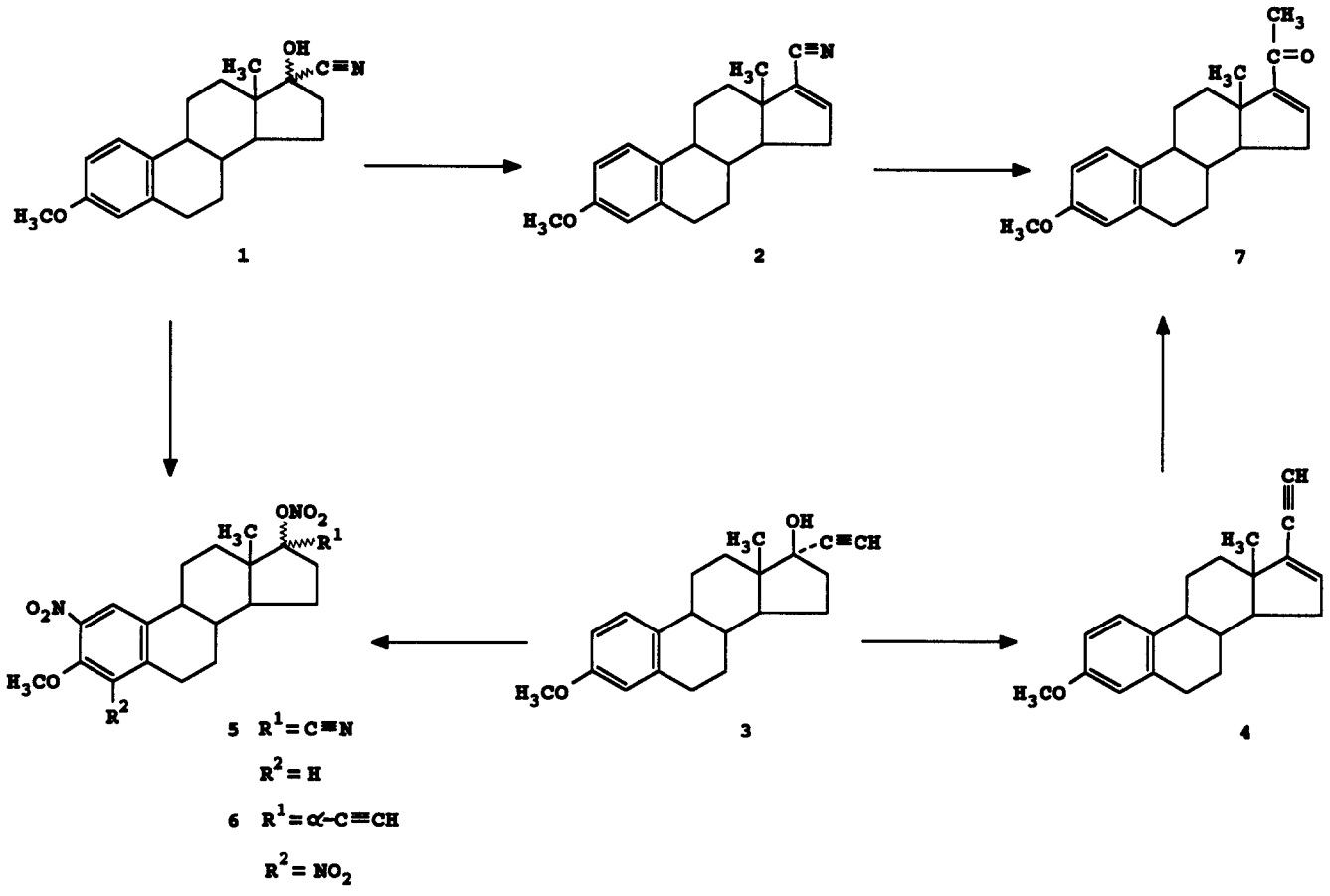
19-Norpregna-4,16-dien-20-yn-3-one (**10**; 0.5 g) was boiled in formic acid (20 ml) for 30 minutes. The reddish brown solution was poured onto ice (50 g) and left to stand for 2 hours. The slurry was then extracted with diethyl ether (4 × 15 ml), and the combined organic fractions washed with water and dried ($Na_2SO_4$). After evaporation the remaining oil (0.38 g, 91%) was purified by flash chromatography on silica gel (10 g). Elution with petroleum ether/dichloromethane (1 : 9) afforded pure **11**. It was recrystallized from methanol; mp, 178–180 C; $[\alpha]_D^{23}$ = +126° (c = 0.3). IR: 1,670, 1,660 (two conjugated C=O), 1,615, 1,587 (two conjugated C=C) $cm^{-1}$; $^1H$ NMR δ: 0.95 (s, 3 H, 18-$H_3$), 2.27 (s, 3 H, 21-$H_3$), 5.84 (s, 1 H, 4-H), 6.71 (s, 1 H, 16-H) ppm. Analysis calculated for $C_{20}H_{26}O_2$ (298.4): C, 80.49; H, 8.78. Found: C, 80.20; H, 8.79%.

### *16α-Ethyl-3-methoxy-19-norpregna-1,3,5(10)-trien-20-one (12)*

Grignard reagent was prepared from magnesium (2 g, 82 mmol) and ethyl iodide (12.8 g, 82 mmol) in diethyl ether (60 ml). Tetrahydrofuran (150 ml) was added, the diethyl ether was distilled out, and freshly prepared cuprous chloride (0.2 g, 2 mmol) was added to the tetrahydrofuran solution. A solution of **7** (5.2 g, 17 mmol) in tetrahydrofuran (150 ml) was added dropwise to the former dark blue solution at room temperature during stirring. The mixture was left to stand for 24 hours and poured into ice-water (200 ml) saturated with ammonium chloride. The brown slurry was decolorized with $Na_2S_2O_3$ solution and the light blue solution was extracted with diethyl ether (3 × 100 ml). The combined ethereal fractions were dried ($CaCl_2$) and evaporated in vacuum. The sticky residue (6.8 g) was purified on an alumina column (70 g). Elution with benzene/petroleum ether (1 : 5) afforded first a small amount of an apolar material, and then **12** (4.2 g, 73%) as an oil. IR: 1,740 (20-C=O), 1,610, 1,510 (aromatic bonds) $cm^{-1}$; $^1H$ NMR δ: 0.70 (s, 3 H, 18-$H_3$), 0.81 (tr, 3 H, Me of Et), 2.16 (s, 3 H, 21-$H_3$), 3.73 (s, 3 H, $OCH_3$), 6.65, 6.79, 7.11 (each s, 1 H each, aromatic hydrogens) ppm.

### *16α-Ethyl-19-norpregn-4-ene-3,20-dione (13)*

To cooled (−70 C) and stirred liquid ammonia (350 ml) under nitrogen, lithium (3 g) was added in portions. Stirring was continued for 1 hour and then a tetrahydrofuran (60 ml) solution of ethylated **12** (4 g) was added dropwise to the deep blue solution. After stirring for 90 minutes at reflux temperature (10–15 C), the mixture was cooled to 0 C and dry ethanol (40 ml) was added dropwise. The colorless solution was stirred for 30 minutes at 0 C and it was then left to warm to room temperature, the ammonia being allowed to evaporate. After 20 hours, the remaining jellylike mixture was mixed with water (100 ml), saturated with




**Scheme 1**

ammonium chloride, and extracted with diethyl ether (3 × 75 ml). The combined ether extracts were dried ($CaCl_2$) and evaporated to dryness. The residue (4.3 g) was dissolved in methanol (200 ml) and heated with concentrated HCl (10 ml) at reflux temperature for 2 hours. After standing for 10 hours, the solution was poured into ice-water (100 ml) and the resulting suspension was extracted with diethyl ether (3 × 75 ml). The combined organic fractions were dried ($CaCl_2$) and evaporated to dryness. The residue (4.5 g) was dissolved in dry acetone (200 ml), and freshly prepared Jones reagent[13] (6 ml) was added. After 2 hours at room temperature, the solution was poured into ice-water (100 ml) and the slurry was extracted with diethyl ether (3 × 50 ml). The combined ethereal fractions were dried ($Na_2SO_4$) and evaporated to dryness. The 3.9 g product was chromatographed on alumina (80 g). Elution with petroleum ether/benzene (1 : 4) afforded 2.4 g (63%) pure **13**. After recrystallization from acetone/water (95 : 5); mp, 128–130 C. IR: 1,740 (20-C=O), 1,680 (3-C=O), 1,620 (conjugated C=C) $cm^{-1}$; $^1H$ NMR δ: 0.70 (s, 3 H, 18-$H_3$), 0.81 (tr, 3 H, Me of Et), 2.16 (s, 3 H, 21-$H_3$), 5.79 (s, 1 H, 4-H) ppm.

## *21-Acetoxy-16α-ethyl-19-norpregn-4-ene-3,20-dione (15a)*

19-Norpregnene derivative **13** (2.4 g) was dissolved in dry methanol (50 ml) under nitrogen, and freshly distilled pyrollidine (3 ml) was added. The solution was stirred under nitrogen at 60 C for 1 hour, then cooled to 5 C. The separated yellow crystals were filtered off and dried in a desiccator over $P_2O_5$. Yield 1.28 g. A further amount of **14** (0.61 g, together 68%) was obtained by concentration of the mother liquor; mp, 118–126 C.

Enamine (**14**) (1 g) was dissolved in abs. ethanol (50 ml) containing dry HCl (0.5 g), and ethanolic bromine solution (10 ml, prepared freshly at −60 C, containing 0.66 g, 1.5 moleq bromine) was added dropwise over 20 minutes. The mixture was evaporated to 5 ml and diethyl ether (50 ml) was added when an oily material separated. The diethyl ether solution was decanted and the remaining oily residue was dissolved in ethanol (20 ml) and treated with a water (25 ml) solution of $KHCO_3$ (1 g) at room temperature. After 10 hours, the turbid solution was extracted with dichloromethane (3 × 50 ml). The combined fractions were washed successively with 2 N HCl solution, with 2 N $KHCO_3$ solution, and with water. The dried ($Na_2SO_4$) solution was evaporated to dryness in vacuum. The remaining material (0.88 g) was boiled with potassium acetate (3 g) in acetone (70 ml) for 4 hours. After cooling, the solution was extracted with dichloromethane (3 × 30 ml). The combined dichloromethane fractions were dried ($Na_2SO_4$) and evaporated to dryness. The remaining light brown oil (**15a**; 0.83 g, 82%) crystallized in a few drops of ethanol. After recrystallization from ethanol; mp, 135–136 C. IR: 1,760 (acetyl), 1,740 (20-C=O), 1,685 (3-C=O), 1,630 (conjugated C=C) $cm^{-1}$; $^1H$ NMR δ: 0.72 (s, 3 H, 18-$H_3$), 0.80 (tr, 3 H, Me of Et), 2.20 (s, 3 H, acetyl), 4.60–4.96 (dd, 2 H, 21-$H_2$), 5.80 (s, 1 H, 4-H) ppm. Analysis calculated for $C_{24}H_{34}O_4$ (386.5): C, 74.57; H, 8.87. Found: C, 74.29; H, 9.09%.

### *16α-Ethyl-21-hydroxy-19-norprogesterone (15b)*

21-Acetoxy derivative (**15a**) (0.5 g) was hydrolyzed in a saturated methanolic solution of $K_2CO_3$ (5 ml) at room temperature for 3 hours. The solution was poured into ice-water (50 ml). The precipitated white powder was collected by filtration, washed with water until neutral, and dried at 110 C. The crude product (0.42 g, 94%) was recrystallized from acetone; mp, 133–134 C (ref.[3]: mp, 134–135 C); $[\alpha]_D^{23} = +97°$ (c = 1) ref.[3]: $[\alpha]_D^{23} = +99°$). IR: 3,490 (21-OH), 1,715 (20-C=O), 1,685 (3-C=O), 1,625 (conjugated C=C) $cm^{-1}$; $^1H$ NMR δ: 0.73 (s, 3 H, 18-$H_3$), 0.81 (tr, 3 H, Me of Et), 3.28 (m, 1 H, 21-OH), 3.93 (d, 2 H, 21-$H_2$), 5.84 (s, 1 H, 4-H) ppm. Analysis calculated for $C_{22}H_{32}O_3$ (344.5): C, 76.70; H, 9.36. Found: C, 76.70; H, 9.45%.

## Results and discussion

Cyanohydrin (**1**) is dehydrated with phosphorus oxychloride, when the desired 16-unsaturated compound (**2**) is obtained. The yield does not exceed 75%. We attribute the loss to stereoisomerism on C-17, and the resulting difficulty of elimination of the 17β-hydroxy group.

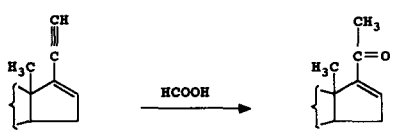
The Schering group applied the isomerization of nitrate esters in the case of pregnyne and 19-norpregnyne derivatives, in connection with hydration of the triple bond.[14] Formation of nitrate esters from estradiols **1** or **3** is accompanied by nitration of the aromatic ring A at positions 2 and 4, resulting in **5** and **6** (Scheme 1). These ring A–substituted derivatives are useful for the preparation of amino derivatives. This part of the work will be published separately.

From the products of the direct dehydrations (75% of **2** from **1**, and 65% of **4** from **3**), we form the 16-unsaturated-17-acetyl system, which is the key intermediate for target substance **15b**.

The transformation of the unsaturated carbonitrile (**2**) can be realized on alkylation with methylmagnesium iodide, to give **7**.[8,15]

For hydration of the triple bond in **4**, we apply successfully a simple boiling with formic acid. This reaction gives a nearly quantitative yield, and the reagent is permitted even in the large-scale preparation of pharmaceuticals and diagnostics, because it satisfies the criteria of a "good manufacturing process," whereas oxide or salts of mercury(II), which are widely used in hydration reactions with sulfuric or acetic acid,[10,16–19] must be avoided.

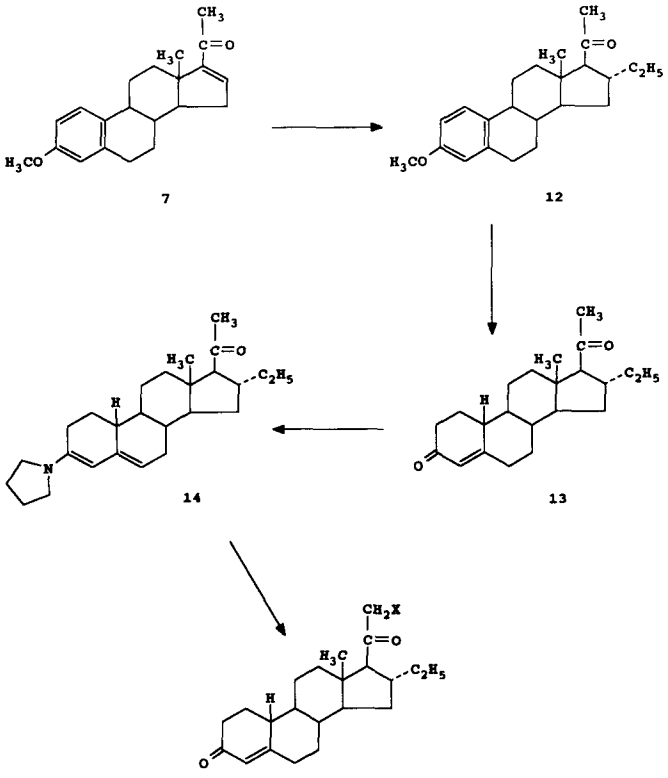
Our hydration method is also applicable to 16-unsaturated-ethynyl derivatives of testosterone (**8**)[20] and 19-nortestosterone (**10**).[11] The corresponding 17-acetyl




8 Pregn-4-en-3-ones 9

10 19-Norpregn-4-en-3-ones 11

**Scheme 2**




**Scheme 3**

compounds (**9**[12,21] and **11**) are obtained in excellent yield (Scheme 2).

The next step of the synthesis is the 1,4-addition[22] of ethylmagnesium iodide to the key intermediate (**7**). With a fivefold molar amount of the reagent, the 16α-ethyl compound (**12**) is transformed in the Birch reduction, followed by reoxidation at C-20[23] to the norpregnene derivative (**13**).

21-Hydroxylation or acetoxylation is generally achieved through a 21-halogen compound.[24–26] These methods do not give good results for our substances, and we therefore apply bromination[27] of the pyrrolidine enamine (**14**). After elimination of the protecting group at the ring A ketone, the 21-bromo compound (**15**) is transformed with potassium acetate in acetone solution to the desired 21-acetoxy derivative (**15a**) and by basic hydrolysis to the end-product (**15b**) (Scheme 3).

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