Available online at www.sciencedirect.com
SCIENCE DIRECT®
Steroids 68 (2003) 739–749
Steroids
www.elsevier.com/locate/steroids

Hydrolytic behavior of 5α-hydroxy-11β- and 5β-hydroxy-11α-substituted 19-norsteroids

Erzsébet Francsics-Czinege*, Zoltán Tuba, Csaba Molnár, Judit Horváth, János Csörgei, György Visky, Gábor Balogh, Marianna Mák, Béla Hegedűs, Mária Magyari, János Horváth

Department of Steroid Research, Gedeon Richter Ltd., P.O. Box 27, Budapest, 1475, Hungary

Received 28 April 2003; received in revised form 8 July 2003; accepted 21 July 2003

Abstract

Teutsch G. and Bélanger A. treated 5α,10α epoxides with Grignard-reagents catalyzed by copper(I) ions. The reaction with steroidal epoxides proceeded with complete regio- and stereospecificity, leading exclusively to the 11β-substituted compounds. According to our synthetic strategy, the 5,10 epoxide isomers were not separated; instead, the pure 11β, and in some cases, 11α-substituted molecules were isolated after the conjugate addition of the Grignard-reagents, followed by deketalization and dehydration. Surprisingly, appearance of a third compound was generally observed beside the expected deprotected products, and this compound turned out to have a 3-keto-5(10),9(11) structural unit. Starting from pure 3-ethylenedioxy-5α,10α-epoxy-estr-9(11)-ene-17-one and 3-ethylenedioxy-5β,10β-epoxy-estr-9(11)-ene-17-one, four model compounds were synthesized (11α- and 11β-{4-[1,1-(ethylenedioxy)-ethyl]phenyl}-estra-, as well as 11α- and 11β-cyclohexyl-estra-derivatives) to study the process of deprotection and dehydration. 3-keto-5(10),9(11)-derivatives were found to form after deketalization and dehydration only from 11α-substituted derivatives, while 11β-derivatives resulted in only the expected 3-keto-5,9-diene structure. After observing this remarkable difference between the behavior of 11α-, 11β-substituted isomers we decided to take a closer look at the processes of deketalization and dehydration. In order to carry out the hydrolysis under mild conditions, pyridinium paratoluenesulfonate, a weakly acidic salt, was applied. All the intermediate products observed by TLC were isolated. The outcome of the deprotection and elimination reactions can be rationalized by two factors: conjugation of olefins (with the 3-oxo-group or the 11-phenyl group) and orientation of groups to be eliminated.

Keywords: Steroid; Hydrolysis; 11α-Substituted steroids; 11β-Substituted steroids; 11-Substituted-5(10),9(11) steroids

1. Introduction

The initial breakthrough in finding compounds with progesterone antagonist activity was purely chemical, with the discovery of a general access to 11β-substituted 19-norsteroids. Teutsch G. and Bélanger A. treated 5α,10α epoxides with Grignard-reagent catalyzed by copper(I) ions [1]. The reaction with steroidal epoxides proceeded with complete regio- and stereospecificity, leading exclusively to the 11β-substituted compounds (**2**). It is well-known that compounds of type **2** can be deketalized and concomitantly dehydrated by acids yielding molecules with a 3-keto-4,9-diene-system (**3**) (Scheme 1).

A great number of 11β-substituted compounds with antiprogestational and/or antiglucocorticoid activity were synthesized by Teutsch's method [2–5]. To complete the study of the conjugate addition of Grignard-reagent into epoxides, Teutsch proved that 5β,10β epoxides afforded 11α-substituted compounds [6].

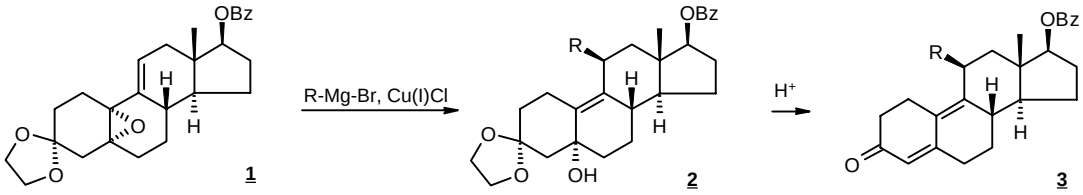
According to our synthetic strategy, the new 5,10 epoxide isomers were not separated; instead, the pure 11β, and in some cases, 11α-substituted molecules were isolated after the conjugate addition of the Grignard-reagent, deketalization, and dehydration. Surprisingly, the appearance of a third compound was generally observed besides the expected deprotected products. In this article, we describe two examples of the isolated compounds and give an explanation for our results by examining the dehydration and deketalization of model compounds.

2. Experimental

Melting points were determined on a BÜCHI-510 apparatus and are uncorrected. The NMR spectra were recorded on

* Corresponding author. Tel.: +36-1431-5414; fax: +36-1260-0349.
E-mail address: e.francsics@richter.hu (E. Francsics-Czinege).

0039-128X/$ – see front matter © 2003 Elsevier Inc. All rights reserved.
doi:10.1016/j.steroids.2003.07.003



R= ethyl, phenyl, etc.

Scheme 1.

either a Varian ^{Unity}INOVA-300 or a Varian ^{Unity}INOVA-500 spectrometer, applying $CDCl_3$ or DMSO-d_6 as a solvent. Infrared spectra were recorded on a Perkin–Elmer Spectrum 1000 FT-IR instrument with spectral resolution of 4 cm^{-1}, using a KBr matrix. Electron ionization mass spectral analyses were carried out by a VG-TRIO-2 quadrupole mass spectrometer at 70 eV with direct introduction and at an ion source temperature of 250 °C. The "fast atom bombardment" (FAB) and the "daughter ion" spectra were performed with a Finnigan MAT 95SQ hybrid tandem mass spectrometer. The Cs^+ gun was used at 20 kV, and the matrix applied was glycerin or 3-nitrobenzyl alcohol. High resolution mass measurements (HRMS) were performed by Finnigan MAT 95SQ mass spectrometer, and the accuracy of the peak matching was ±1 ppm. Column chromatography was performed on 63–230 μM silica gel obtained from Merck Co, Darmstadt, Germany. TLC analyses were carried out on silica gel 60 F_{254} aluminum sheets (20 cm × 20 cm with 250 μM layer). Analytical HPLC was conducted using a reverse phase column Nucleosil 120 C-18 7 μm (250 × 4) and acetonitrile:methanol:water 35:35:30 as a mobile phase, the UV detector (SPD-6A) was set at 205, 260 or 320 nm.

All reactions were carried out under a nitrogen atmosphere. Most chemicals and solvents were analytical grade and used without further purification.

2-Prop-2-ynyloxy-tetrahydro-pyran was prepared according to the procedure of Jones et al. [7] 4-bromoacetophenone ethylene ketal was synthesized according to Neville's method [8]. Pyridinium *p*-toluenesulfonate was synthesized starting from pyridine and *p*-toluenesulfonic acid [9].

2.1. 3-Ethylenedioxy-5,10-epoxy-18a-homo-estr-9(11)-ene-17-one (5)

Hexachloroacetone (1.2 ml, 8 mmol) and 70% aqueous hydrogen peroxide (6.9 ml, 0.18 mol) was added to a solution of **4** (11.2 g, 0.034 mol) in methylene chloride (75 ml) at 0 °C. The reaction mixture was stirred for 3 h at the same temperature. Then, it was poured into a mixture of methylene chloride (340 ml) and ice (160 g). A solution of sodium thiosulphate (31.6 g, 0.2 mol) in water (140 ml) was added dropwise to the mixture to destroy the excess of hydrogen peroxide. After separation, the organic fraction was washed with water (2 × 100 ml) and dried on sodium sulphate. The solvent was removed in vacuo, and the residue was crystallized from diisopropyl ether to give a mixture of 5α,10α and 5β,10β isomers of the epoxides. The epoxide ratio was determined by HPLC and by ^{1}H NMR. Yield: 10.4 g (89%); 5α,10α/5β,10β epoxide ratio 57.9/42.1 (HPLC); MS: (*m*/*z*) 344 (M^+); IR: 2967, 2938, 2878, 1730, 1637, 1117, 1072, 1057, 1006 cm^{-1}. Analysis calculated for $C_{21}H_{28}O_4$: C 73.22, H 8.19; found: C 73.09, H 8.12. ^{1}H NMR {300 MHz, $CDCl_3$ (TMS), δ (ppm), 59:41 rates mixture of two isomers (5α,10α-epoxy/5β,10β-epoxy)}: 0.80/0.76 (3H, t, –CH_2–**CH_3**); 3.83–4.00 (4H, m, ethylenedioxy); 6.03/5.83 (1H, m, H-11).

2.2. 3-Ethylenedioxy-5,10-epoxy-17β-hydroxy-17α-[3-(tetrahydro-2H-pyran-2-yloxy)-1-propynyl]-18a-homo-estr-9(11)-ene (7)

A 1.65 mol solution of butyl lithium in *n*-hexane (550 ml, 0.88 mol butyl lithium) was added to a solution of 2-[(prop-2-ynyl)oxy]-tetrahydropyran (**6**) (141 ml, 0.97 mol) in dry tetrahydrofuran (650 ml), and the mixture was stirred for 30 min at the same temperature. Compound **5** (0.15 mol), dissolved in dry tetrahydrofuran (80 ml), was slowly added at 0 °C, and the solution was stirred for 30 min, and then poured into saturated aqueous ammonium chloride solution (730 ml). After separation, the aqueous fraction was extracted with tetrahydrofuran (2 × 250 ml). The combined organic fractions were dried over sodium sulfate and concentrated in vacuo to give an oil. The excess reagent was removed via column chromatography (in cyclohexane), and after evaporating of the solvent in vacuo, **7** was retrieved as a foam. Yield: 59.5 g (85%); 5α,10α/5β,10β epoxide ratio 63.9/36.1 (HPLC); IR: 3450, 2940, 2878, 2237, 1643, 1119, 1065, 1024, 970, 902 cm^{-1}. HPLC assay: 97.9%; HRMS: calculated for $C_{29}H_{39}O_5$ $[MH-18]^+$: 467.2798, found: 467.2808. ^{1}H NMR {500 MHz, $CDCl_3$ (TMS), δ (ppm), 62:38 ratio for rates mixture of 2 isomers (5α,10α-epoxy/5β,10β-epoxy)}: 0.96/0.90 (3H, t, –CH2–**CH_3**); 3.47–4.38 (8H, m, –O–CH_2–); 4.77 (1H, m, –O–CH–O–); 6.08/5.90 (1H, m, H-11).

2.2.1. Procedure for synthesis of compounds *10a*, *11*, and *12a*

Under anhydrous conditions, dry tetrahydrofuran (6 ml) was added to magnesium (3.14 g, 0.13 mol). A portion

(8 ml) of a solution of 4-bromo-*N*,*N*-dimethylaniline (23.8 g, 0.119 mol) in dry tetrahydrofuran (94 ml) and a drop of dibromoethane was added at 50 °C. After evidence of reaction was observed, the entire amount of the reagent was added dropwise at 15–20 °C. The Grignard-reagent was added dropwise to a suspension of **7** (11.6 g, 0.024 mol) and copper (I) chloride (0.5 g, 0.005 mol) in dry methylene chloride (60 ml) at 10–15 °C. The reaction mixture was stirred for 2 h and then, it was poured into 10% ammonium chloride solution (360 ml) and extracted with methylene chloride (3 × 50 ml). The combined organic fractions were washed with water (4 × 80 ml), dried over sodium sulfate, filtered, and concentrated in vacuo to give a dark oil (40 g). Purification via column chromatography (cyclohexane) gave the product in the form of a foam, which was hydrolyzed.

2.2.1.1. Hydrolysis. The protected product (0.01 mol) was added to a solution of potassium hydrogensulfate (5.8 g, 0.042 mol) in water (46 ml) under a nitrogen atmosphere. The reaction mixture was stirred for 2 h. After neutralizing with 10% potassium hydroxide solution, the mixture was diluted with water (20 ml) and extracted with methylene chloride (3 × 40 ml). The organic fractions were washed with water (2 × 16 ml), dried over sodium sulfate, and concentrated in vacuo. The oily residue was crystallized in acetonitrile to give **10a**. The acetonitrile mother liquor was concentrated in vacuo, and **11** as well as **12a** were isolated by column chromatography (cyclohexane–acetone 9:1).

*11β-(4′-dimethyl-amino-phenyl)-17β-hydroxy-17-(3-hydroxy-1-propynyl)-18a-homo-estra-4,9-diene-3-one (**10a**).* Yield: 1.25 g (25%); mp: 127–131 °C; MS: (*m*/*z*) 459 (M^+); IR: 3363, 2940, 2858, 1691, 1593, 1515, 1445, 1308, 1214, 1135, 1044, 822, 611 cm^{-1}. Analysis calculated for $C_{30}H_{37}NO_3$: C 78.39, H 8.11, N 3.06; found: C 78.51, H 8.03, N 3.11. ^{1}H NMR {500 MHz, DMSO-d_6 (TMS), δ (ppm)}: 0.22 (3H, t, –CH_2–**CH_3**), 2.83 (6H, s, –N–CH_3), 4.13 (2H, d, –**CH_2**–OH), 4.31 (1H, m, H-11), 5.10 (1H, t, –CH_2–**OH**), 5.16 (1H, s, 17-OH), 5.61 (1H, br, H-4), 6.62 (2H, m, H-3′,5′), 7.03 (2H, m, H-2′,6′).

*1α-(4′-Dimethyl-amino-phenyl)-17β-hydroxy-17-(3-hydroxy-1-propynyl)-18a-homo-estra-4,9-diene-3-one (**11**).* Yield: 0.58 g (12%); mp: 167–72 °C; MS: (*m*/*z*) 459 (M^+); IR: 3369, 3298, 2931, 2873, 1637, 1617, 1597, 1068, 1019, 812. Analysis calculated for $C_{30}H_{37}NO_3$: C 78.39, H 8.11, N 3.06; found: C 78.15, H 8.14, N 3.14. ^{1}H NMR {300 MHz, $CDCl_3$ (TMS), δ (ppm)}: 1.11 (3H, t, –CH_2–**CH_3**), 2.91 (6H, s, –N–CH_3), 3.72 (1H, m, H-11), 4.61 (2H, s, **CH_2**–OH), 5.62 (1H, br, H-4), 6.65 (2H, m, H-3′,5′), 6.96 (2H, m, H-2′,6′).

*11-(4′-Dimethyl-amino-phenyl)-17β-hydroxy-17-(3-hydroxy-1-propynyl)-18a-homo-estra-5(10),9(11)-diene-3-one (**12a**).* Yield: 0.87 g (18%); mp: 203–206 °C; MS: (*m*/*z*) 459 (M^+); IR: 3411, 3361, 3314, 2930, 2877, 1701, 1607, 1517, 1071, 1017, 843, 824. Analysis calculated for $C_{30}H_{37}NO_3$: C 78.39, H 8.11, N 3.06; found: C 78.52, H 8.07, N 3.01. ^{1}H NMR {500 MHz, $CDCl_3$ (TMS), δ (ppm)}: 1.11 (3H, t, –CH_2–**CH_3**), 2.95 (6H, s, –N–CH_3), 4.23 (2H, s, **CH_2**–OH), 6.68 (2H, br, H-3′,5′), 7.09 (2H, br, H-2′,6′).

*2.2.2. Procedure for synthesis of compounds **10b** and **12b***

Under anhydrous conditions, dry tetrahydrofuran (3 ml) was added to magnesium (1.25 g, 0.052 mol). A portion (4 ml) of a solution of 4-bromoacetophenone ethylene ketal (12.2 g, 0.05 mol) in dry tetrahydrofuran (50 ml) and a drop of dibromoethane was added at 50 °C. After evidence of reaction was observed, the entire amount of the reagent was added dropwise. The reaction mixture was stirred for an additional 2 h while it was cooling to room temperature. The mixture was then added dropwise to a suspension of **7** (4.67 g, 0.01 mol) and copper (I) chloride (0.3 g, 0.003 mol) in dry methylene chloride (30 ml) at 10–15 °C. The reaction mixture was stirred for 1 h, and then it was poured into 10% ammonium chloride (70 ml) solution and extracted with methylene chloride (3 × 40 ml). The combined organic fractions were washed with water (4 × 70 ml), dried over sodium sulfate, filtered, and concentrated in vacuo to give a yellow oil (9.7 g). Purification via column chromatography (cyclohexane/acetone 9:1) gave a yellowish oil (4.3 g), which was hydrolyzed.

2.2.2.1. Hydrolysis. 2N hydrochloric acid (12 ml) was added to a solution of the mixture of protected product (4.14 g, 0.009 mol) in methanol (90 ml). The reaction mixture was stirred for 20 min. After neutralizing with 5% sodium hydrogencarbonate solution, the mixture was diluted with water (50 ml) and extracted with methylene chloride (3 × 50 ml). The organic fractions were washed with water (2 × 40 ml), dried over sodium sulfate, and concentrated in vacuo. The oily residue was crystallized in acetonitrile to give **10b**, while **12b** was isolated by column chromatography (methylene chloride/ethyl acetate 1:1).

*11β-(4′-Acetyl-phenyl)-17β-hydroxy-17-(3-hydroxy-1-propynyl)-18a-homo-estra-4,9-diene-3-one (**10b**).* Yield: 1.3 g (24%); mp: 132–34 °C; IR: 2914, 1701, 1679, 1579, 1597, 1400, 1358, 1265, 1179, 1073, 951, 837, 598 cm^{-1}; MS: (*m*/*z*) 458 (M^+). Analysis calculated for $C_{30}H_{34}O_4$: C 78.57, H 7.47; found: C 78.38, H 7.41. ^{1}H NMR {300 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.24 (3H, t, –CH_2–**CH_3**), 2.58 (3H, s, –CO–CH_3), 4.36 (2H, s, **CH_2**–OH), 4.45 (1H, m, H-11), 5.76 (1H, br, H-4), 7.30 (2H, m, H-2′,6′), 7.87 (2H, m, H-3′,5′).

*11-(4′-Acetyl-phenyl)-17β-hydroxy-17-(3-hydroxy-1-propynyl)-18a-homo-estra-5(10),9(11)-diene-3-one (**12b**).* Yield: 0.8 g (17%); mp: 197–201 °C; MS: (*m*/*z*) 458 (M^+); IR: 3480, 3320, 2250, 1672, 1633, 1598, 1271, 1025, 837. Analysis calculated for $C_{30}H_{34}O_4$: C 78.57, H 7.47; found: C 78.76, H 7.39. ^{1}H NMR {500 MHz, $CDCl_3$ (TMS), δ

(ppm)}: 1.14 (3H, t, –CH_2–**CH_3**), 2.59 (3H, s, –CO–CH_3), 2.79 & 2.86 (2H, d & d, H-4), 4.23 (2H, s, **CH_2**-OH), 7.32 (2H, br, H-2′,6′), 7.88 (2H, m, H-3′,5′).

*2.3. 3-Ethylenedioxy-5α-hydroxy-11β-{4′-[1′,1′-(ethylenedioxy)-ethyl]phenyl}-estra-9-ene-17-one (**16a**)*

Under anhydrous conditions, dry tetrahydrofuran (3 ml) was added to magnesium (1.25 g, 0.052 mol). A portion (4 ml) of a solution of 4-bromoacetophenone ethylene ketal (12.2 g, 0.05 mol) in dry tetrahydrofuran (50 ml) and a drop of dibromoethane was added at 50 °C. After evidence of reaction was observed, the entire amount of the reagent was added dropwise. The reaction mixture was stirred for an additional 2 h while it was cooling to room temperature. The mixture was then added dropwise to a suspension of **14** (3.14 g, 0.01 mol) and copper (I) chloride (0.3 g, 0.003 mol) in dry methylene chloride (30 ml) at 0 °C. The reaction mixture was stirred for 1 h, and then, it was poured into 10% ammonium chloride (70 ml) solution and extracted with methylene chloride (3 × 40 ml). The combined organic fractions were washed with water (4 × 70 ml), dried over sodium sulfate, filtered, and concentrated in vacuo to give a yellow oil (9.7 g). Purification via column chromatography (methylene chloride–ethyl acetate 1:1) followed by trituration in diisopropyl ether gave **16a**. Yield: 2.56 g (52%); mp: 183–88 °C (lit. 190–91 °C); MS: (*m*/*z*) 494 (M^+); IR: 3561, 3533, 2935, 2890, 1733, 1691, 1610, 1169, 1125, 1084, 1045, 950, 831, 819. Analysis calculated for $C_{30}H_{38}O_6$: C 72.85, H 7.74; found: C 72.68, H 7.60. ^{1}H NMR {500 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.47 (3H, s, H-18), 1.63 (3H, s, –CH_3), 3.77 & 4.02 (4H, m, ethylenedioxy), 3.89–4.06 (4H, m, 3-ethylenedioxy), 4.31 (1H, m, H-11), 4.34 (1H, br, 5-OH), 7.19 (2H, m, H-2′,6′), 7.35 (2H, m, H-3′,5′).

*2.4. 3-Ethylenedioxy-5α-hydroxy-11β-cyclohexyl-estra-9-ene-17-one (**16b**)*

16b was synthesized from **14** (3.14 g, 0.01 mol) according to the procedure given for the synthesis of **16a**. The Grignard-reagent (**14**) was prepared from cyclohexyl bromide (6.2 ml, 0.05 mol) without dibromoethane. The product was isolated by crystallization from diisopropyl ether to give 1.70 g (40%) of **16b**; mp: 152–154 °C; MS: (*m*/*z*) 414 (M^+); IR: 3519, 2930, 1739, 1447, 1182, 1138, 1107, 978, 840. Analysis calculated for $C_{26}H_{38}O_4$: C 75.32, H 9.24; found: C 75.48, H 9.31. ^{1}H NMR {500 MHz, $CDCl_3$ (TMS), δ (ppm)}: 1.03 (3H, s, H-18), 1.38 (1H, m, H-1′), 2.59 (1H, m, H-11), 3.94–4.08 (4H, m, ethylenedioxy), 4.34 (1H, d, 5-OH).

*2.5. 11β-(4′-Acetyl-phenyl)-estra-4,9-diene-3,17-dione (**17a**)*

2 N hydrochloric acid (1 ml) was added to a suspension of **16a** (1.0 g, 0.002 mol) in methanol (10 ml) and the reaction mixture was stirred at room temperature for 20 min. Meanwhile, the starting material dissolved, and then, the solution turned into a suspension. The crystals were filtered off, washed with methanol and water, and dried in vacuo over potassium hydroxide to yield **17a** (0.59 g, 76%); mp: 180–82 °C; MS: (*m*/*z*) 388 (M^+); IR: 2948, 2873, 1731, 1675, 1657, 1600, 1563, 839. Analysis calculated for $C_{26}H_{28}O_3$: C 80.38, H 7.26; found: C 80.21, H 7.19. ^{1}H NMR {500 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.54 (3H, s, H-18), 2.58 (3H, s, –CO–CH_3), 4.48 (1H, m, H-11), 5.82 (1H, br, H-4), 7.32 (2H, m, H-2′,6′), 7.89 (2H, m, H-3′,5′).

*2.6. 11β-Cyclohexyl-estra-4,9-diene-3,17-dione (**17b**)*

17b was synthesized from **16b** (0.8 g, 0.002 mol) according to the procedure given for synthesis of **17a**. Yield: 0.74 g (85%); mp: 205–207 °C; MS: (*m*/*z*) 352 (M^+); IR: 2931, 2848, 1735, 1658, 1605, 1441, 1383, 1242, 1033, 862. Analysis calculated for $C_{24}H_{32}O_2$: C 81.77, H 9.15; found: C 81.91, H 9.08. ^{1}H NMR {500 MHz, $CDCl_3$ (TMS), δ (ppm)}: 1.10 (3H, s, H-18), 1.52 (1H, m, H-1′), 2.72 (1H, m, H-11), 5.70 (1H, br, H-4).

*2.7. 3-Ethylenedioxy-5β-hydroxy-11α-{4′-[1′,1′-(ethylenedioxy)-ethyl]phenyl}-estra-9-ene-17-one (**19a**)*

19a was synthesized from **18** (3.14 g, 0.01 mol) according to the procedure given for synthesis of **16a**. The reaction time of **18** with the Grignard-reagent **8b** was 4 h.

Yield: 1.45 g (30%); mp: 160–62 °C; MS: (*m*/*z*) 478 ([M-18]$^+$); IR: 3507, 2932, 2876, 1731, 1681, 1660, 1607, 1188, 1160, 1115, 1039, 945, 844, 826. Analysis calculated for $C_{30}H_{38}O_6$: C 72.85, H 7.74; found: C 73.02, H 7.81. ^{1}H NMR {500 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.98 (3H, s, H-18), 1.62 (3H, s, –CH_3), 3.69–4.05 (8H, m, ethylenedioxy), 3.88 (1H, m, H-11), 4.53 (1H, br, 5-OH), 7.07 (2H, m, H-2′,6′), 7.35 (2H, m, H-3′,5′).

*2.8. 3-Ethylenedioxy-5β-hydroxy-11α-cyclohexyl-estra-9-ene-17-one (**19b**)*

19b was synthesized from **18** (3.14 g, 0.01 mol) according to the procedure given for the synthesis of **16b**. The reaction time of **18** with the Grignard-reagent **15** was 4 h. Purification was carried out by column chromatography (*n*-hexane–ethyl acetate 1:1) to yield **19b** (2.14 g, 52%); mp: 184–85 °C; MS: (*m*/*z*) 396 ([M-18]$^+$); IR: 3500, 2924, 1736, 1449, 1269, 1187, 1105, 993, 839. Analysis calculated for $C_{26}H_{38}O_4$: C 75.32, H 9.24; found: C 75.53, H 9.18. ^{1}H NMR {500 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.86 (3H, s, H-18), 1.51 (1H, m, H-1′), 2.78 (1H, m, H-11), 3.93–4.07 (4H, m, ethylenedioxy), 4.47 (1H, s, 5-OH).

*2.8.1. Procedure for synthesis of **20a** and **21a***

2N hydrochloric acid (1 ml) was added to a suspension of **19a** (1.0 g, 0.002 mol) in methanol (10 ml) and the reaction

mixture was stirred at room temperature for 30 min. After neutralizing with 5% aqueous sodium hydrogencarbonate solution, the mixture was diluted with water (50 ml) and extracted with methylene chloride (3 × 50 ml). The organic fractions were washed with water (3 × 35 ml), dried over sodium sulfate, and concentrated in vacuo. The resulted oily residue was purified by column chromatography (*n*-hexane–ethyl acetate 1:1) to yield **20a** and **21a** as white crystals.

*2.8.1.1. 11α-(4′-Acetyl-phenyl)-estra-4,9-diene-3,17-dione (**20a**).* Yield: 0.20 g (26%); mp: 176–178 °C; MS: (*m*/*z*) 388 (M^+); IR: 2932, 2874, 1738, 1680, 1660, 1603, 1582, 831. Analysis calculated for $C_{26}H_{28}O_3$: C 80.38, H 7.26; found: C 80.57, H 7.19. ^{1}H NMR {500 MHz, $CDCl_3$ (TMS), δ (ppm)}: 1.04 (3H, s, H-18), 2.57 (3H, s, –CO–CH_3), 4.18 (1H, m, H-11), 5.73 (1H, br, H-4), 7.17 (2H, m, H-2′,6′), 7.87 (2H, m, H-3′,5′).

*2.8.1.2. 11-(4′-Acetyl-phenyl)-estra-5(10),9(11)-diene-3,17-dione (**21a**).* Yield: 0.42 g (54%); mp: 114–116 °C; MS: (*m*/*z*) 388 (M^+); IR: 2919, 2856, 1738, 1717, 1681, 1601, 1557, 839. Analysis calculated for $C_{26}H_{28}O_3$: C 80.38, H 7.26; found: C 80.55, H 7.21. ^{1}H NMR {500 MHz, $CDCl_3$ (TMS), δ (ppm)}: 1.05 (3H, s, H-18), 2.60 (3H, s, –CO–CH_3), 2.80 & 2.89 (2H, d & d, H-4), 7.29 (2H, m, H-2′,6′), 7.88 (2H, m, H-3′,5′).

*2.8.2. Procedure for synthesis of **20b** and **21b***

20b and **21b** were prepared from **19b** (0.8 g, 0.002 mol) according to the procedure given for the synthesis of **20a** and **21a**. The reaction mixture was stirred for 40 min.

*2.8.2.1. 11α-Cyclohexyl-estra-4,9-diene-3,17-dione (**20b**).* **20b** was isolated as a white foam (0.36 g, 52%); IR: 2926, 2950, 1739, 1660, 1590, 1449, 1373, 1219, 1064, 873. HPLC: 97.4%; HRMS: calculated for $C_{24}H_{32}O_2$ 352.24023, found: 352.24045. ^{1}H NMR {500 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.90 (3H, s, H-18), 1.62 (1H, m, H-1′), 3.06 (1H, m, H-11), 5.74 (1H, br, H-4).

*2.8.2.2. 11-Cyclohexyl-estra-5(10),9(11)-diene-3,17-dione (**21b**).* **21b** was isolated as a white foam (0.09 g, 13%); IR: 2929, 2952, 1739, 1719, 1669, 1593, 1450, 1367, 1226, 1061, 1013. HPLC: 96.9%; HRMS: calculated for $C_{24}H_{32}O_2$ 352.24023, found: 352.24039. ^{1}H NMR {500 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.86 (3H, s, H-18), 2.37 (1H, m, H-1′), 2.81 & 2.96 (2H, m, H-4).

*2.8.3. Procedure for preparation of the intermediates **22**, **23***

16a (1.0 g, 2 mmol) was added to a solution of pyridinium *p*-toluenesulfonate (0.2 g, 0.8 mmol) in ethanol (30 ml). The reaction mixture was stirred at 20 °C and and slowly turned into a solution. The reaction was monitored by TLC (*n*-hexane–ethyl acetate 1:1), and the intermediates were isolated when they reached their maximum concentration in the reaction mixture.

2.8.3.1. Work-up and isolation. The reaction mixture was poured into 5% sodium hydrogencarbonate (100 ml), and after stirring for 30 min, the precipitate was collected on a filter washed with water and dried over potassium hydroxide. The crude product was purified by column chromatography (*n*-hexane–ethyl acetate 1:1).

*2.9. 3-Ethylenedioxy-5α-ethoxy-11β-{4′-[1′,1′-(ethylenedioxy)-ethyl]phenyl}-estr-9-ene-17-one (**21**)*

21 was isolated after working up the reaction mixture after 20 min. Yield: 0.26 g (27%); IR: 1739, 1682, 1610, 1245, 1197, 1123, 1091, 1040, 833. HPLC: 97.8%; HRMS: calculated for $[M-46]^+$ $C_{30}H_{36}O_5$ 476.25627, found: 476.25608. ^{1}H NMR {500 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.46 (3H, s, H-18), 1.21 (3H, t, –CH_2–**CH_3**), 1.63 (3H, s, –CH_3), 3.35 & 3.53 (2H, m, –**CH_2**–CH_3), 3.73–4.05 (8H, m, ethylenedioxy), 4.32 (1H, m, H-11), 7.19 (2H, m, H-2′,6′), 7.35 (2H, m, H-3′,5′).

*2.10. 3-Ethylenedioxy-5α-ethoxy-11β-(4′-acetyl-phenyl)-estr-9-ene-17-one (**23**)*

23 was isolated by working up the reaction mixture after 60 min. Yield: 0.17 g (20%); IR: 1739, 1691, 1603, 1270, 1186, 1120, 1063, 832. HPLC: 96.9%; HRMS: calculated for $[M-46]^+$ $C_{28}H_{32}O_4$ 432.23006, found: 432.22997. ^{1}H NMR {500 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.47 (3H, s, H-18), 1.21 (3H, t, –CH_2–CH_3), 2.57 (3H, s, –CO–**CH_3**), 3.36 & 3.54 (2H, m, –**CH_2**–CH_3), 3.74–3.97 (4H, m, ethylenedioxy), 4.38 (1H, m, H-11), 7.35 (2H, m, H-2′,6′), 7.87 (2H, m, H-3′,5′).

*2.11. 3-Ethylenedioxy-5α-hydroxy-11β-(4′-acetyl-phenyl)-estr-9-ene-17-one (**24**)*

24 was prepared from **16a** in 90% ethanol according to the procedure given for **22** by working up the reaction mixture after 3.5 h. TLC monitoring and column chromatography was carried out in *n*-hexane–methylene chloride 1:1. Yield: 0.39 g (40%); IR: 3535, 1678, 1601, 1565, 1269, 1134, 1121, 1051, 838. HPLC: 97.8%; HRMS: calculated for $[M-18]^+$ $C_{28}H_{32}O_4$ 432.23006, found: 432.23015. ^{1}H NMR {500 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.48 (3H, s, H-18), 2.57 (3H, s, –CO–CH_3), 3.87–4.06 (4H, m, ethylenedioxy), 4.35 (1H, d, 5-OH), 4.37 (1H, m, H-11), 7.34 (2H, m, H-2′,6′), 7.86 (2H, m, H-3′,5′).

*2.12. 3-Ethylenedioxy-11-{4′-[1′,1′-(ethylenedioxy)-ethyl]phenyl}-estra-5(10),9(11)-diene-17-one (**25**)*

25 was prepared from **19a** in 90% ethanol according to the general procedure given for **22** by working up the reaction

mixture after 10 min. TLC monitoring and column chromatography was carried out in *n*-hexane–ethyl acetate 1:1.

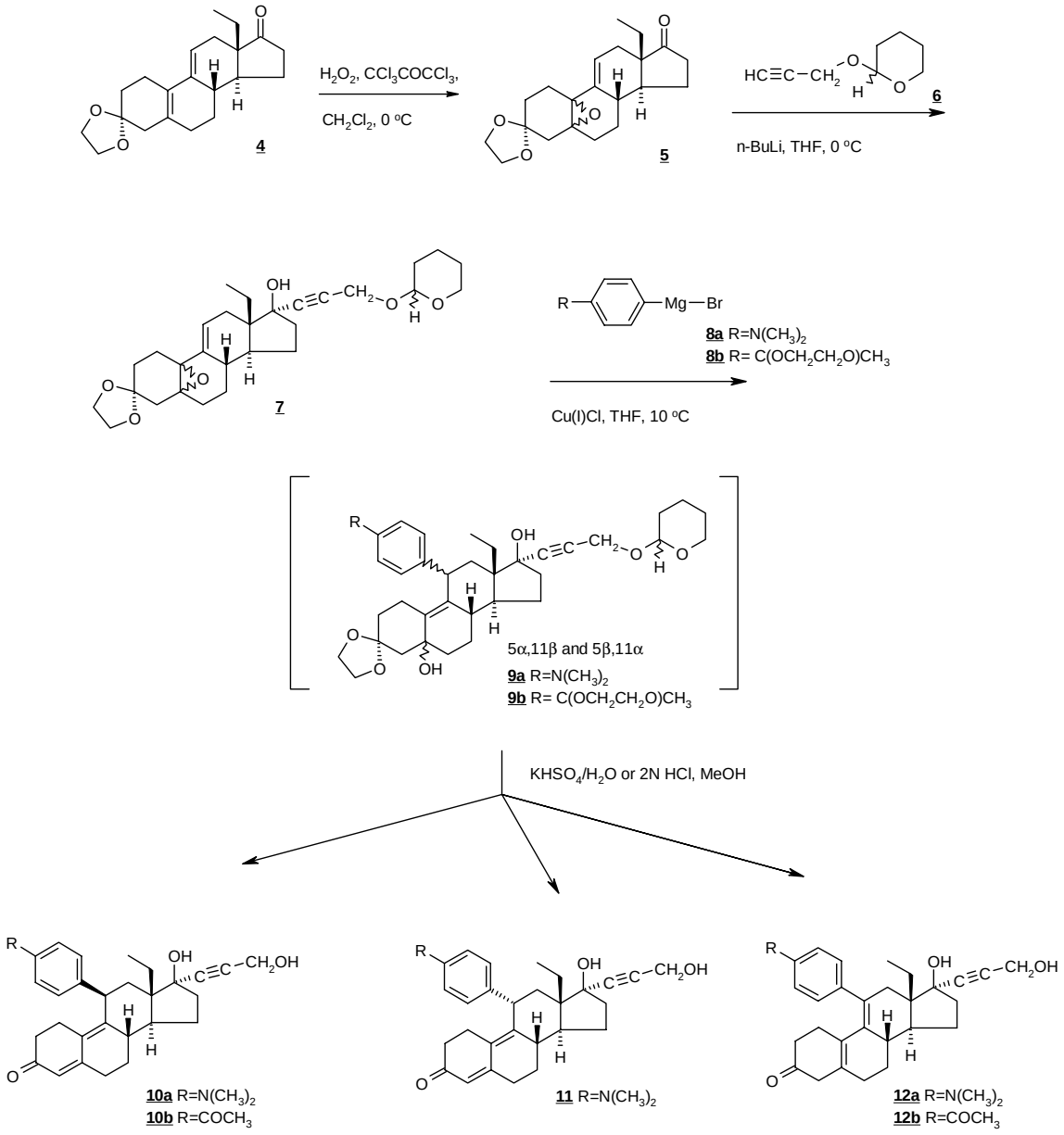
Yield: 0.26 g (27%); IR: 1739, 1604, 1253, 1199, 1111, 1037, 869, 836. HPLC: 97.5%; HRMS: calculated for $C_{30}H_{36}O_5$ 476.25627, found: 476.25623. ^{1}H NMR {500 MHz, $CDCl_3$ (TMS), δ (ppm)}: 1.01 (3H, s, H-18), 1.67 (3H, s, $-CH_3$), 3.73–4.07 (8H, m, ethylenedioxy), 7.14 (2H, m, H-2′,6′), 7.37 (2H, m, H-3′,5′).

2.13. 3-Ethylenedioxy-11-(4′-acetyl-phenyl)-estra-5(10), 9(11)-diene-17-one (**26**)

26 was prepared from **19a** in 90% ethanol according to the general procedure given for **22** by working up the reaction mixture after 30 min. TLC monitoring and column chromatography was carried out in *n*-hexane–ethyl acetate 1:1. Yield: 0.21 g (24%); IR: 1738, 1691, 1602, 1558, 1269, 1112, 1056, 836. HPLC: 97.8%; HRMS: calculated for $C_{28}H_{32}O_4$ 432.23006, found: 432.23019. ^{1}H NMR {500 MHz, $CDCl_3$ (TMS), δ (ppm)}: 1.02 (3H, s, H-18), 2.60 (3H, s, $-CO-CH_3$), 3.80–3.96 (4H, m, ethylenedioxy), 7.28 (2H, m, H-2′,6′), 7.87 (2H, m, H-3′,5′).

3. Results

A mixture of epoxides (**5**, 5α,10α/5β,10β ratio 58:42) was prepared from 3-ethylenedioxy-13β-ethyl-gona-5(10),



Scheme 2.

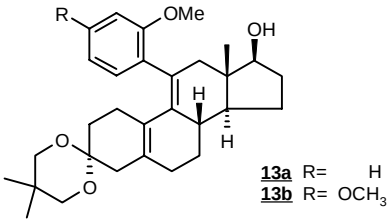
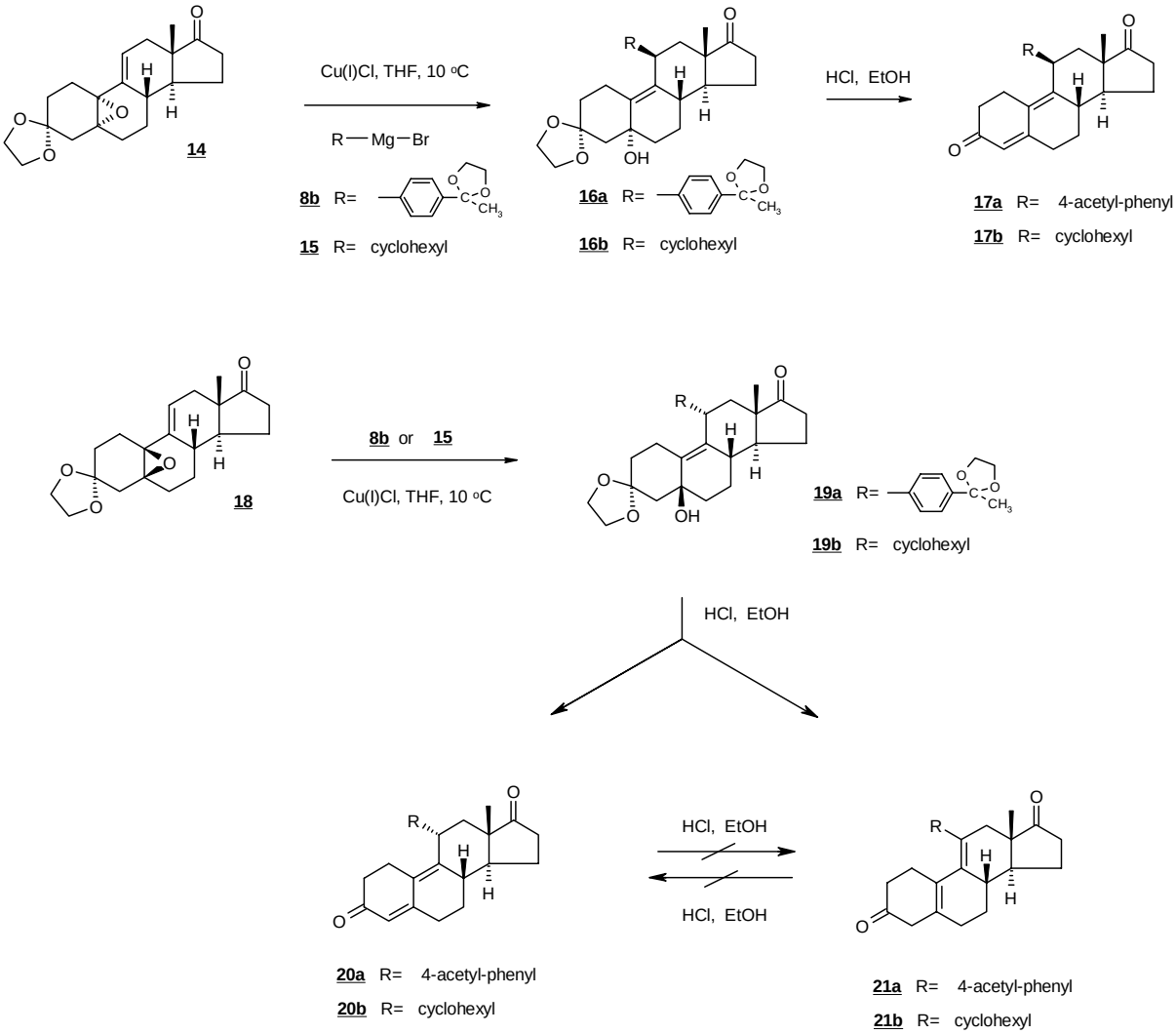


Fig. 1. Known conjugated 5(10),9(11)-diene system.

9(11)-diene-17-one [10] with hexachloroacetone and 70% hydrogen peroxide according to the procedure of Teutsch et al. Nucleophilic addition of 2-[(prop-2-ynyl)oxy]-tetrahydro-pyran (**6**) in the presence of *n*-butyl lithium generated the 17α-propynyl side chain with a protected hydroxy group (**7**). Conjugate addition of **8a** or **8b** Grignard-reagents afforded the protected intermediates **9a** and **9b**, which were hydrolyzed with $KHSO_4$ in water (**9a**) or with 2N HCl (**9b**). Products **10a** and **10b** were isolated by crystallization, while **11**, **12a**, and **12b** were isolated by column chromatography (Scheme 2). The stereoposition of the C(11) substituent was verified, along with some characteristic chemical shift data in NMR spectra, with NOE measurements: for an α substituent the C(18) methyl group exhibited an NOE connection with the H_β-11 proton, while for a β substituent, it showed NOE into the aromatic protons.

To the best of our knowledge, no 11α-substituted compound in the 13β-series prepared by Teutsch's method was published, and the only example in the literature to demonstrate the formation of a 5(10),9(11)-diene system was described by Wiechert and coworkers [11] (**13a-b**)(Fig. 1). **13a-b** were formed during the dehydration of pure 11β-substituted 5α-hydroxy intermediates. Their formation was explained by steric factors due to ortho-substitution on the phenyl ring.

After observing the formation of the unexpected products of type **12**, the hydrolysis and dehydration were studied on model compounds to decide whether the by-products could be formed only from one of the isomers (5α,11β or 5β,11α) or from both of them with a different ratio. Model



Scheme 3.

compounds with 11-aromatic and 11-cyclohexyl substitutions were chosen to investigate the role of the conjugation of the 5(10),9(11)-diene system with the 11-phenyl group during formation of compounds type **12**.

Model compounds **16a** [5], **16b**, **19a**, and **19b** were prepared by conjugate addition of Grignard-reagents (**8b**, **15**) with the epoxides starting from both pure 5α,10α (**14**) [12] and 5β,10β epoxide isomers (**18**) [13] (Scheme 3). **14** and **18** were isolated from a mixture of epoxides in a ratio of α/β 67:33. The 5α,10α is°mer (**14**) was separated by repeated crystallization from diisopropyl ether, while the 5β,10β isomer (**18**) was isolated by column chromatography, followed by crystallization from diisopropyl ether. Taking advantage of the selectivity of the copper(I) ion-catalyzed addition of the Grignard-reagent at position 11 of the steroid skeleton, protection of the 17-keto group was omitted.

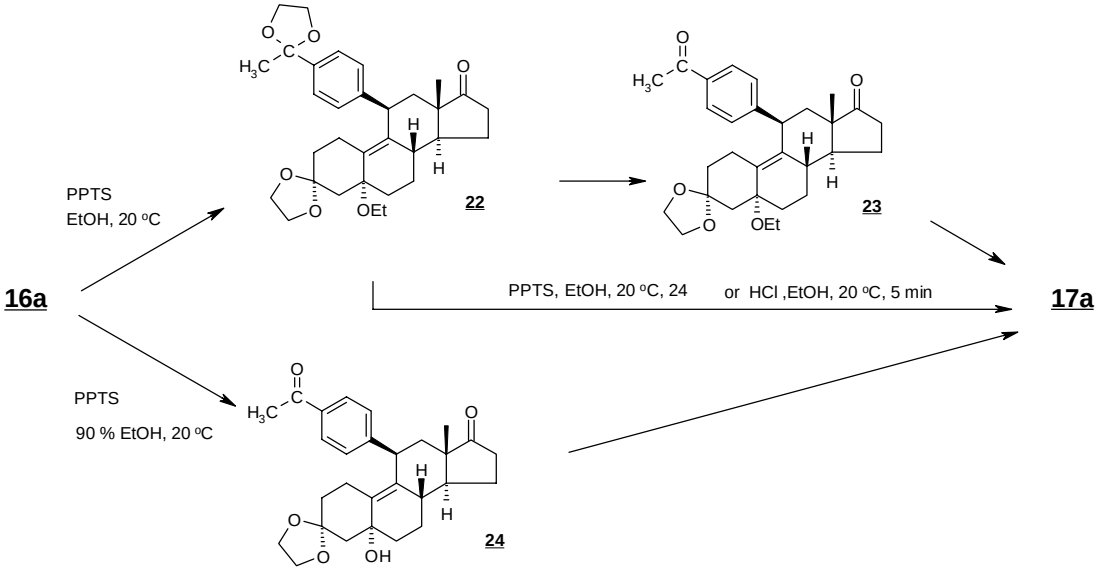
As a matter of the rate of reactions, a marked difference was observed between the epoxides **14** and **18** in the Grignard-reaction. 5β,10β-Epoxide (**18**) reacted with the Grignard-reagents (**8b** and **15**) much slower than the 5α,10α-epoxide (**14**). After carrying out the conjugate addition with the Grignard-reagents, all the protected intermediates (**16a**, **16b**, **19a**, and **19b**) were isolated in crystal form.

The stereoposition of the C(11) substituent was verified, along with some characteristic chemical shift data in the NMR spectra, with NOE measurements: for an α substituent, the C(18) methyl group exhibited a NOE connection with the H_β-11 proton, while for a β substituent, it showed NOE into the aromatic protons. Surprisingly, while **16a** was found to be stable, **19a** was slowly decomposing, affording compounds more apolar than **19a** itself. Decomposition of **19a** was observed by TLC, and a remarkable difference between **16a** and **19a** was found by MS. In the EI mass spectrum of **16a**, *m*/*z* 494 was detected, while for **19a**, only 476 was found due to immediate H_2O elimination. A similar behavior was observed in the case of compounds **16b** and **19b**.

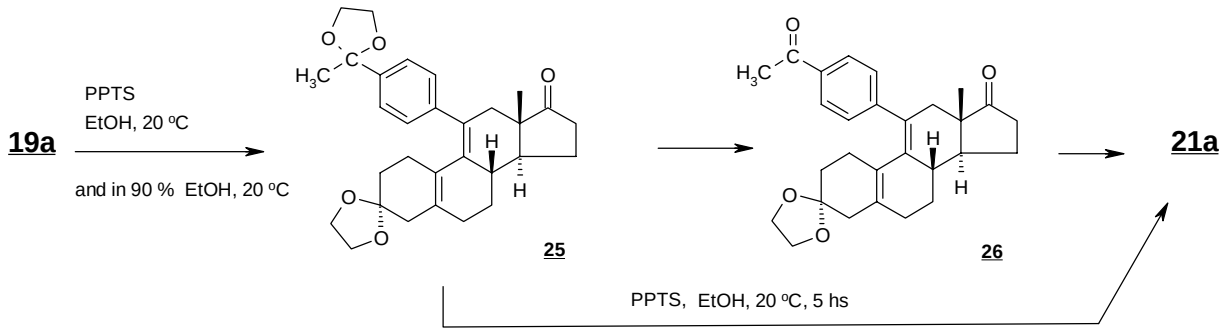
All protected isomers (**16a**, **16b**, **19a**, and **19b**) were deprotected and dehydrated according to the general practice by HCl in methanol. Hydrolysis of both **16a** and **16b** afforded an only product, **17a** and **17b**, respectively, which was expected from Teutsch's procedure. However, both 11α-isomers **19a** and **19b** resulted in two products following hydrolysis. **20a** and **21a** were obtained from **19a** at a ratio of 35:65, while **19b** yielded **20b** and **21b** at a ratio of 85:15. **20a** and **21a** could not be converted into each other by HCl in methanol; both of them proved to represent a final stage of hydrolysis. Both 11-cyclohexyl and 11-acetyl-phenyl substituted model compounds led to the same type of dehydrated and deprotected products. The fact that **21b** was formed only at a yield of 15% versus **21a** (65%) indicates the possibility of spread delocalization of the Π-electrons in the 5(10),9(11)-double bonds; the 11-phenyl-group does play an important role in the formation of the product (**21a**).

After observing the remarkable difference between the behavior of 11α (**19a** and **19b**) and 11β isomers (**16a** and **16b**), we decided to take a closer look at the process of deketalization and dehydration and to explore the pathways leading to the formation of both the expected and unexpected products. No intermediate could be isolated under general hydrolytic circumstances (e.g. HCl in methanol); therefore, milder conditions were necessary to investigate the chosen 11-(4-acetyl-phenyl)-derivatives **16a** and **19a**.

Carrying out the hydrolysis under mild conditions, pyridinium *p*-toluenesulfonate (PPTS), a weakly acidic salt was applied in 90% ethanol and pure ethanol at 20 °C. The process, monitored by TLC, was observed to be a series of consecutive steps. All the intermediates were isolated when they reached their maximum concentration in the reaction mixture. Thus, **24**, the only intermediate from **16a** in 90%



Scheme 4.



Scheme 5.

ethanol, was isolated from the reaction mixture after 3.5 h of reaction time, whereas PPTS in ethanol afforded two new compounds **22** (after 20 min) and **23** (after 1 h) from **16a** (Scheme 4). After a long reaction time (24 h) the starting material (**16a**) and the intermediates (**22** and **23**) disappeared, forming **17a**. In addition, both isolated **22** and **24** were converted into **17a** under the conditions described before.

In the case of **19a**, the route leading to the formation of major product **21a** was mapped (Scheme 5) by TLC monitoring and intermediate isolation. Both reaction conditions provided the intermediates **25** (after 10 min in ethanol) and **26** (after 30 min in ethanol). Hydrolysis of **25** by PPTS in ethanol yielded pure **21a**, indicating that whenever the 5(10),9(11)-diene system conjugated with the 11-aryl group formed no appearance of 3-keto-4,9-diene system could be detected.

A remarkable distinction can be declared in the dehydration and deketalization of 5α-hydroxy-11β-, and 5β-hydroxy-11α-substituted 19-norsteroids indicated by the different products. Moreover, **17a**, the only product from **16a**, and **21a**, the major product from **19a**, were observed to be formed by different pathways. The selectivity of the reaction conditions was proved by the differentiation of the hydrolysis of the two ketals within the molecules. Despite the selective conditions, elimination of the 5α-hydroxy group and hydrolysis of 3-ethylene ketal could not be distinguished in **16a**, showing that these steps proceeded concomitantly. Conditions in abs. ethanol made it possible to form ethyl ether from the relatively stable 5α-hydroxy group, rather than eliminate it.

However, under the same conditions **19a** was compelled to eliminate the 5β-hydroxy group, mainly in vinylogous syn-elimination with the periplanar 11β-hydrogen first. This elimination preceded not only the hydrolysis of the 3-ethylene-ketal, but of the one on the 11β-(4-acetyl-phenyl) substituent, which proved to be the fastest step in the formation **17a**.

4. Discussion

Relying upon the above results, we assume that the outcome of the elimination and deprotection reactions can be rationalized by two crucial factors: possibility of conjugation of olefins (with the 3-oxo group or the 11-phenyl group) and the orientation of the groups to be eliminated. Studies of elimination in a variety of systems show that the orientation of groups to be eliminated determines reactivity in the following order: anti-coplanar > syn-coplanar > nonplanar [14]. It is obvious that in case of 11β-derivatives (**16a**, **16b**), both the conjugation of the 4,9-diene system with the 3-oxo group and the anticoplanar orientation of the 5α-OH group with the axial H at position 4, which is regarded to be the most favorable for elimination, yielded only one type of product **17a** and **17b**, respectively.

Table 1
Torsion angles of the hydrogens at positions 4 and 11 with respect to the 5βOH–5C bond

Compounds	Torsion angles (°)		
	5βOH–5C–4C–4βH_{ax}	5βOH–5C–4C–4αH_{ekv}	5βOH–5C–11C–11βH_{ekv}
19a	39.8	76.0	8.1
19b	45.1	71.0	0.2

As the orientation of the eliminating groups was not evident in the 11α-subsituted isomers, the three-dimensional structures of the molecules **19a** and **19b** were modeled by "Hyperchem™ Release 4 for Windows Molecular Modeling System." The geometry was optimized using the AM1 molecular approximation procedure and MM+ method, and the torsion angles of the appropriate groups were measured (Table 1). To confirm our explanation for the 11β-derivatives, **16a** and **16b** were also modeled (Table 2). Figs. 2 and 3 show the three-dimensional structures of **16a** and **19a** to demonstrate the difference in geometry between the 11α- and 11β-isomers.

Table 2
Torsion angles of the hydrogens at positions 4 and 11 with respect to the 5αOH–5C bond

Compounds	Torsion angles		
	5αOH–5C–4C–4βH_{ax} (°)	5αOH–5C–4C–4αH_{ekv}	5αOH–5C–11C–11αH_{ekv}
16a	5.1	58.2	39.0
16b	5.3	58.6	71.8

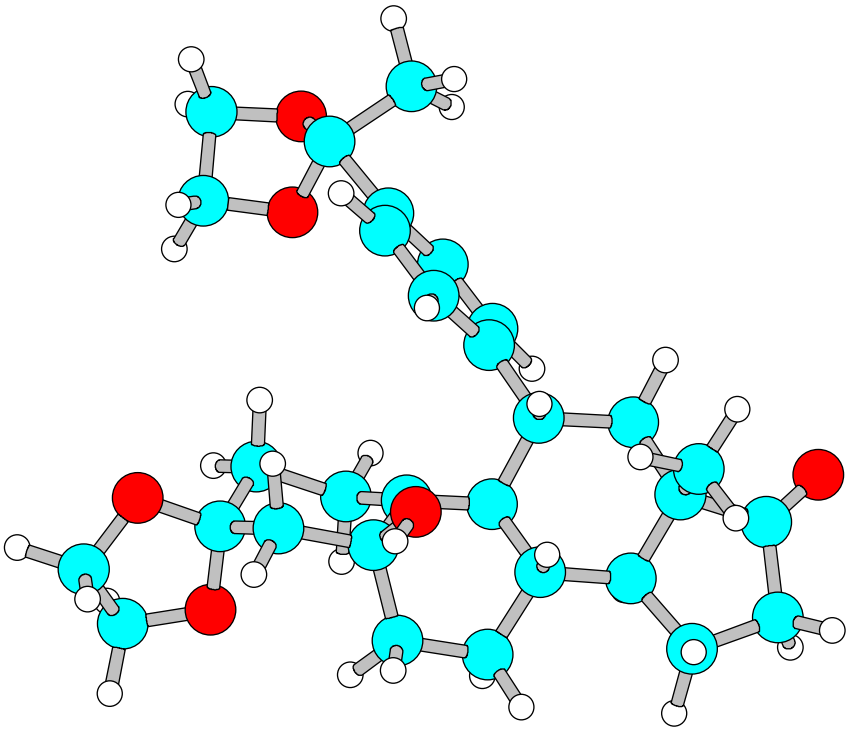


Fig. 2. The three-dimensional structure of **19a** optimized by Hyperchem™ Release 4.

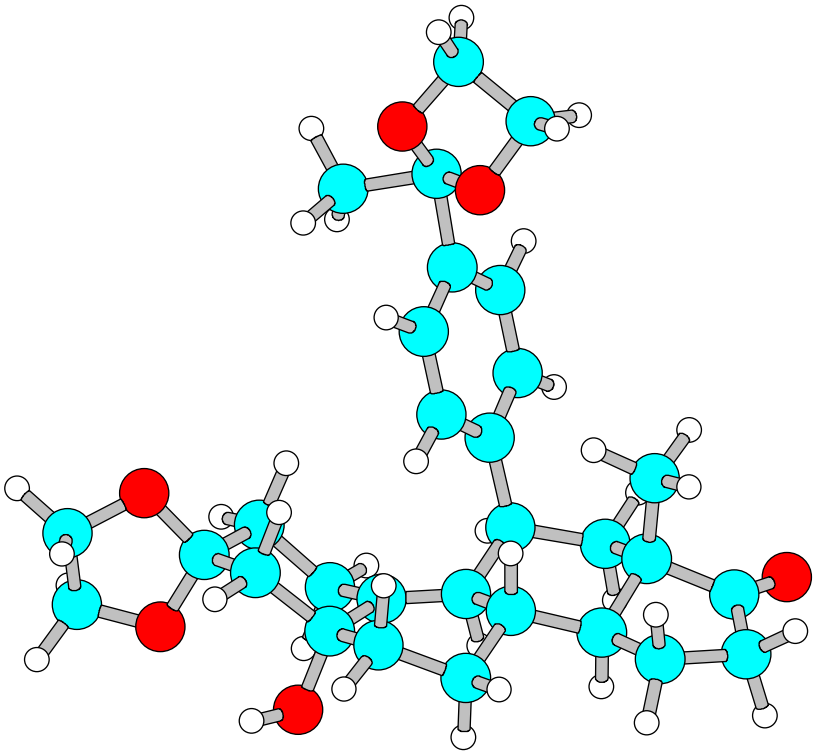


Fig. 3. The three-dimensional structure of **16a** optimized by Hyperchem™ Release 4.

On the basis of the torsion angles measured in the three-dimensional structures of **19a** and **19b**, it was obvious that in these molecules the orientation of the 11βH and 5βOH groups is syn-coplanar; consequently, the overlap of the orbitals was favorable for syn-elimination and was more favorable, than for any of the hydrogens at position 4, which were nonplanar. In the case of **19a**, the forming 5(10),9(11)-diene-system was stabilized by conjugation with the 11-(4-acetyl-phenyl)-group, resulting in a thermodynamically stable compound **21a**. Despite the favorable orientation of 11βH and 5βOH in **19b** for syn-elimination, the product containing the 5(10),9(11)-diene-system was only a minor component, as there was no possibility for conjugation with the 11-substitution. The major product **20b**, stabilized by the 3-keto-4,9-diene system was more stable thermodynamically.

References

[1] Bélanger A, Philibert D, Teutsch G. Regio and stereospecific synthesis of 11β-substituted 19-norsteroids. Steroids 1981;37:361–82.

[2] Teutsch G, Philibert D. History and perspectives of antiprogestins from the chemist's point of view. Human Reprod 1994;9:12–31.

[3] Cook CE, Lee YW, Wani MC, Fail PA, Petrow V. Effects of D-ring substituents on antiprogestational (antagonist) and progestational (agonist) activity of 11β-aryl steroids. Human Reprod 1994;9: 32–9.

[4] Rao PN, Cessac JW, Blye RP, Kim HK. 11β-Substituted 13β-ethyl gonane derivatives exhibit reversal of antiprogestational activity. Steroids 1998;63:50–7.

[5] Rao PN, Wang Z, Cessac JW, Rosenberg RS, Jenkins DJA, Diamandis EP. New 11β-aryl substituted steroids exhibit both progestational and antiprogestational activity. Steroids 1998;63:523–30.

[6] Teutsch G, Bélanger A. Regio and stereospecific synthesis of 11β-substituted 19 norsteroids. Tetrahedron Lett 1979;22:2051–4.

[7] Jones RG, Mann MJ. New methods of synthesis of β-aminoethylpyrazoles. J Am Chem Soc 1953;75:4048–52.

[8] Neville RG. Synthesis of 4-acetylphenylmethylsilanes using 2-(4-bromophenyl)-2-methyl-1,3-dioxolane. J Org Chem 1959;24:111–2.

[9] Miyashita M, Yoshikoshi A, Grisco PA. Pyridinium *p*-toluenesulfonate. A mild and efficient catalyst for tetrahydropyranylation of alcohols. J Org Chem 1977;42:3772–4.

[10] Teichmüller G, Müller G, Krahmer S, Streibhardt G, Wentzke M. Preparation of 17 alpha-cyanomethyl-17 beta-hydroxy steroids. (Jenapharm, Germany) Ger. (East) DD 296495 A5 1991125 6pp (German). APPLICATION: DD 90-342604 19900709. CA 116:129375.

[11] Cleve A, Ottow E, Neef G, Wiechert R. Synthesis of oxygen-bridged antigestagens. Tetrahedron 1993;49:2217–26.

[12] Faraj H, Claire M, Rondot A, Aumelas A, Auzou G. Synthesis of new steroidal 11β-substituted spirolactones. J Chem Soc Perkin Trans 1 1990;11:3045–8.

[13] Zhang TY, Lee YW, Fang QC, Xiao R, Ito Y. Preliminary applications of cross-axis syncronous flow-through coil planet centrifuge for large-scale preparative counter-current chromatography. J Chromatogr 1988;454:185–93.

[14] Kirk DN, Harsthorn MP. Steroid reaction mechanism In: Eaborn C, editor. Reaction mechanism in organic chemistry. A series of monographs (monograph 7). Amsterdam: Chapman NB; 1968. p. 101–27.