Papers

Synthesis and biological activity of 17-chloro-16(17) unsaturated D-homo antiprogestins

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An efficient approach to 17-chloro-16(17) unsaturated D-homo antiprogestins is described. The key steps of the synthesis are a ring-expansion via dichlorocarbene addition to a 17-silyl enol ether and a palladium catalyzed coupling of an 11β-(4-aryltriflate) with tributyl(1-ethoxyethenyl)stannane or diethyl(3-pyridinyl)-borane. The new progesterone antagonists were tested for their biological activities and compared to those of known antiprogestins. (*Steroids* **59**:176–180, 1994)

Keywords: antiprogestins; ring-expansion; six-membered D-ring; palladium catalyzed coupling; sterols

Introduction

The discovery of the first progesterone antagonist RU 38486 (Figure 1) led to extensive investigations of this class of anti-hormones.[1,2] In addition to early pregnancy termination (RU 38486 was approved in 1988 for this indication in France) other potential applications have been studied like induction of parturition, treatment of endometriosis, contraception, and endocrine tumor therapy.

The most prominent structural feature of RU 38486 is the 4-(dimethylamino)phenyl group in the 11β-position. Without this substituent the molecule would be expected to act as an agonist. As part of our investigations in this field we found that the introduction of several other 11β-aryl substituents maintains anti-progestational activity. Replacement of the 4-(dimethyl-amino)phenyl group by, e.g., a 4-acetylphenyl (ZK 112 993, Figure 1)[3] or a 4-(3-pyridinyl)phenyl group (unpublished results) leads to equally or more potent antiprogestins. Earlier work in our laboratories had shown that, depending on the substituents present, D-homo steroids could be highly potent gestagens or antigestagens. Particularly in the field of progesterone agonists 16(17)-unsaturated D-homo derivatives have been found superior to their saturated analogs.[4]

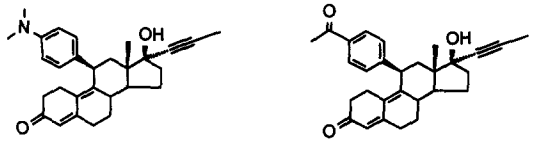
Until now the most frequently used synthetic route to D-homo steroids involves ring-expansion of the five-membered D-rings via the Tiffeneau-Demyanov rearrangement.[5] This concept is dealing with regio-selectivity problems and requires some additional steps for the introduction of the 16,17-double bond.

As an extension of our work in this area we wish to report an efficient approach to D-homo systems which leads directly to 16,17-unsaturated 17-chloro substituted compounds.

Experimental

Chemistry

According to Scheme 1 our synthetic approach starts with the known ketone **1**.[6] Cleavage of the aryl methyl ether, without affecting the other functional groups, was performed by heating **1** with sodium methanethiolate in *N,N*-dimethylformamide under reflux.[7] Compound **2** was protected as its *t*-butyldimethylsilyl ether. To avoid selectivity problems during the addition of dichlorocarbene in the later part of the synthesis it became necessary to protect the 5(6)-double bond. Attempts at a selective reaction of the electron-rich silyl enol ether with dichlorocarbene in the presence of the unprotected 5(6)-double bond failed. For this reason **3** was epoxidized using



RU 38486 ZK 112993

Figure 1 First progesterone antagonist RU 38486.

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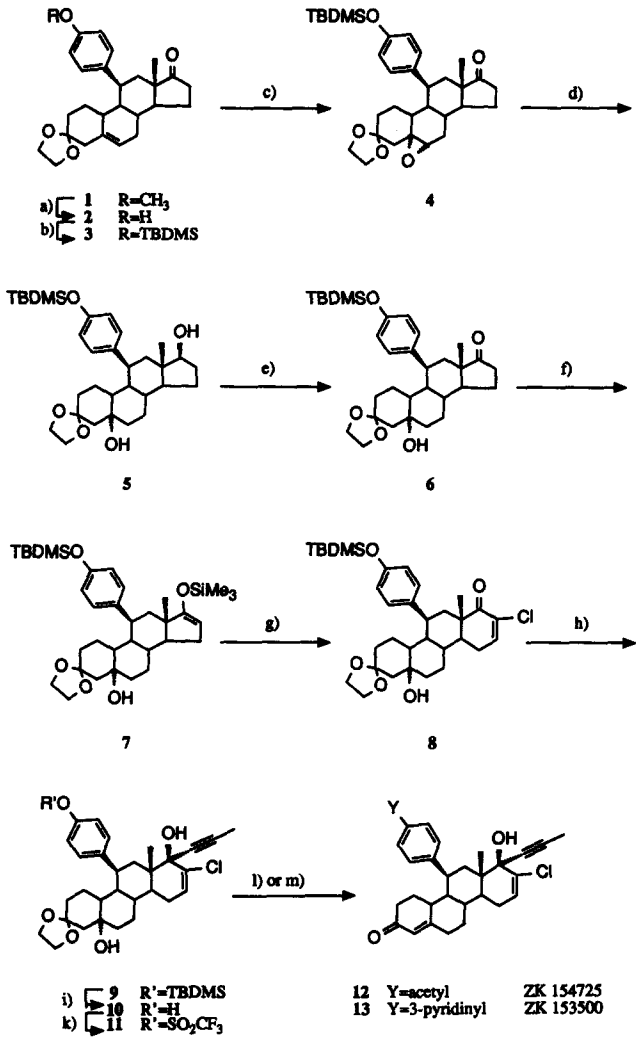

Scheme 1 Reaction conditions: a) CH_3SNa, DMF, reflux, b) TBDMS-Cl, DMF, imidazole, c)- H_2O_2, 2,2,2-trifluoro-1-(3-nitrophenyl)ethanone, CH_2Cl_2, d) $LiAlH_4$, THF, e) CrO_3, pyridine, f) 1. LDA 2. TMS-Cl, g) CCl_3CO_2Na, $CHCl_3$, reflux, h) propyne, n-BuLi, i) Bu_4NF, THF, k) Tf_2O, DMAP, CH_2Cl_2, l) 1. $Pd(PPh_3)_4$, LiCl, tributyl(1-ethoxyethenyl)stannane, dioxane 2. HCl, acetone, m) 1. $Pd(PPh_3)_4$, LiCl, diethyl(3-pyridinyl)borane, ethanol/toluene, 2. HCl, acetone.

m-nitrotrifluoroacetophenone and hydrogen peroxide in dichloromethane.[8] Under these reaction conditions the 5,6α-epoxide **4** was obtained as single isomer in high yield. Epoxidation of compound **3** under standard conditions (peroxy-acids, dichloromethane) led to α,β-mixtures. Reductive cleavage of the epoxide and concomitant reduction of the 17-ketone was achieved by treating **4** with lithium aluminum hydride. Reoxidation of the secondary alcohol function according to Collins' procedure[9] yielded **6**, which was converted to the silyl enol ether **7**. Reaction of **7** with dichlorocarbene, generated from solid sodium trichloroacetate in chloroform in the presence of a phase transfer catalyst as described by Dehmlow and Remmler,[10,11] gave the D-homo-system **8** in 65% yield after aqueous work-up. The initial carbene adduct which was detected on TLC as a new spot with similar polarity as the silyl enol ether **7** was completely converted to compound **8** during aqueous work-up showing higher polarity and UV-activity on TLC. The mild and neutral conditions of Dehmlow's procedure in contrast to other methods for the generation of dichlorocarbene allowed an addition of the carbene to the extremely sensitive silyl enol ether **7** without reconversion to ketone **6** as side reaction. The second best result was obtained by generating dichlorocarbene from sodium trichloroacetate in a 1:3 mixture of 1,2-dimethoxyethane and tetrachloroethylene at 100 C.[12] Under those conditions a mixture of **8** and **6** (3:1, total yield 65%) was isolated. Addition of the propynyl side chain to **8** and cleavage of the silyl ether yielded compound **10**. Aryl triflate **11** was obtained by reaction of **10** with triflic anhydride in methylene chloride in the presence of 4-(dimethylamino)pyridine.[13] Palladium-catalyzed cross-coupling of compound **11** with tributyl(1-ethoxyethenyl)stannane[14] or diethyl(3-pyridinyl)borane[15,16] and subsequent cleavage of the protecting groups by treatment with 4N hydrochloric acid in acetone at 40 C gave **12** and **13**.

General remarks

^1H NMR spectra were obtained using a General Electric QE 300 (tetramethylsilane as internal standard); IR spectra were obtained using Perkin-Elmer PE 621; Mass spectra (MS) were recorded on a Finnigan TSQ 700; and Optical rotations were measured on Perkin-Elmer polarimeter 141. (All solvents were purchased by E. Merck, Darmstadt, Germany.)

Tetrahydrofuran and diethyl ether were distilled over sodium/benzophenone prior to use. All other solvents were purchased as p.a. (pro analysi) quality and dried over molecular sieves. All reactions were run under positive argon pressure. Unless noted otherwise, usual work-up means quenching of the reaction mixture with sodium chloride solution, extraction with ethyl acetate, washing of the organic layer with either sodium bicarbonate solution or dilute hydrochloric acid and sodium chloride solution, drying over sodium sulfate, and evaporation of the solvent. Purification of crude materials was performed by chromatography on silica gel using ethyl acetate/hexane as eluents.

3,3-[1,2-Ethanediylbis(oxy)]-11β-(4-hydroxyphenyl)estr-4-en-17-one (*2*). A solution of 3,3-[1,2-ethanediylbis(oxy)]-11β-(4-methoxyphenyl)estr-5-en-17-on (25 g, 59 mmol) and sodium methanethiolate (16.5 g, 236 mmol) in 440 mL *N,N*-dimethylformamide was heated under reflux for 2 h. Afterwards the reaction mixture was added to 1.5 L ice-water. After stirring overnight the mixture was filtered and the precipitate was washed with water. The crude product (23.6 g, 96%) could be used without further purification. NMR (300 MHz, $CDCl_3$): δ = 7.20 d (J = 9 Hz, 2H, ar), 6.73 d (J = 9 Hz, 2H, ar), 5.56 dbr (J = 5 Hz, 1H, H-6), 3.85–4.00 m (4H, ketal), 3.41 ddbr (J = 7, 5 Hz, 1H, H-11), 0.60 s (3H, C-18).

11β-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]phenyl]-3,3-[1,2-ethanediylbis(oxy)]-estr-5-en-17-one (*3*). A suspension of compound **2** (23 g, 56.3 mmol), *t*-butyldimethylchlorosilane (21.2 g, 141 mmol), and imidazole (19.94 g, 293 mmol) in 250 mL *N,N*-dimethylformamide was stirred overnight at 25 C. The reaction mixture was added to ice-water and worked up as usual. After purification 25 g (85%) **3** was isolated. IR ($CHCl_3$): 2960, 1725, 1600, 1500. NMR (300 MHz, $CDCl_3$): δ = 7.17 d (J = 9 Hz, 2H, ar), 6.73 d (J = 9 Hz, 2H, ar), 5.56 dbr (J = 5 Hz, 1H, H-6), 3.85–4.00 m (4H, ketal), 3.40 ddbr (J = 7, 5 Hz, 1H, H-11), 0.95 s (9H, Si^{t}Bu), 0.58 s (3H, C-18), 0.17 s (6H, $SiMe_2$). MS (EI) m/z: 522 (M^+, 5), 421 (5), 221 (8), 177 (8), 131 (10), 99 (100), 73 (15). $[\alpha]_D^{20}$ = +72.6 (c = 0.515, $CHCl_3$). Analysis

calculated for $C_{32}H_{46}O_4Si$: C 73.52, H 8.87; found: C 73.59, H 8.93.

11β-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]phenyl]-3,3-[1,2-ethanediylbis(oxy)]-5,6α-epoxy-5α-estran-17-one (4). Hydrogen peroxide (19.8 mL of a 30% aqueous solution, 194 mmol) was added slowly to a solution of **3** (25 g, 47.8 mmol), and 2,2,2-trifluoro-1-(3-nitrophenyl)ethanone (5.22 g, 23.8 mmol) in a mixture of 200 mL methylene chloride and 16 mL saturated aqueous sodium bicarbonate at 0 C. The mixture was stirred for 120 h at 25 C. Afterwards the solution was cooled to 0 C and saturated aqueous sodium thiosulfate (80 mL) was added. The layers were separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with 5% aqueous sodium hydroxide and worked-up further as usual. After purification 21.22 g (82.4%) **4** was obtained. IR ($CHCl_3$): 2950, 1730, 1605, 1500. NMR (300 MHz, $CDCl_3$): δ = 7.17 d (J = 9 Hz, 2H, ar), 6.73 d (J = 9 Hz, 2H, ar), 3.80–4.00 m (4H, ketal), 3.24 ddbr (J = 7, 5 Hz, 1H, H-11), 2.96 d (J = 5 Hz, 1H, H-6), 0.97 s (9H, Si^{t}Bu), 0.60 s (3H, C-18), 0.17 s (6H, $SiMe_2$). MS (EI) m/z: 538 (M^+,12), 437 (5), 274 (5), 221 (7), 177 (10), 99 (100), 73 (20) $[\alpha]_D^{20}$ = +30.6 (c = 0.515, $CHCl_3$). Analysis calculated for $C_{32}H_{46}O_5Si$: C 71.33, H 8.61; found C 71.25, H 8.58.

11β-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-phenyl]-3,3-[1,2-ethanediylbis(oxy)]-5α-estrane-5,17β-diol (5). A solution of **4** (21.2 g, 39.3 mmol) in 200 mL THF was added to lithium aluminum hydride (3.73 g, 98.3 mmol) in 100 mL THF at 0 C. After stirring for 1 h the reaction mixture was quenched with 50 mL saturated aqueous ammonium chloride and worked up as usual. Purification of the crude material yielded 18.13 g (85%) **5**. IR ($CHCl_3$): 3480, 2960, 1600, 1510. NMR (300 MHz, $CDCl_3$): 7.22 d (J = 9 Hz, 2H, ar), 6.71 d (J = 9 Hz, 2H, ar), 3.87–3.98 m (4 H, ketal), 3.57 ddbr (J = 7, 6.5 Hz, 1H, H-17), 3.11 m (1H, H-11), 0.97 s (9H, Si^{t}Bu), 0.47 s (3H, C-18), 0.18 s (6H, $SiMe_2$). MS (EI) m/z: 542 (M^+,50), 526 (M^+-H_2O, 10), 370 (25), 261 (25), 221 (30), 177 (25), 99 (100), 73 (40). $[\alpha]_D^{20}$ = +34.5 (c = 0.510, $CHCl_3$). Analysis calculated for $C_{32}H_{50}O_5Si$: C 70.81, H 9.28; found C 70.75, H 9.21.

11β-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]phenyl]-3,3-[1,2-ethanediylbis(oxy)]-5-hydroxy-5α-estran-17-one (6). Chromium(VI)oxide (20 g, 200 mmol) was carefully added to a mixture of 70 mL pyridine and 500 mL methylene chloride at 0 C. After stirring for 20 min a solution of **5** (18.13 g, 33.4 mmol) in 100 mL methylene chloride was added. The reaction mixture was stirred for another 2 h at 0 C. The usual work-up and purification yielded 14.5 g (80%) **6**. IR ($CHCl_3$): 3500, 2960, 1725, 1600, 1500. NMR (300 MHz, $CDCl_3$): δ = 7.23 d (J = 9 Hz, 2H, ar), 6.72 d (J = 9 Hz, 2H, ar), 3.85–3.98 m (4H, ketal), 3.16 m (1H, H-11), 0.96 s (9H, Si^{t}Bu), 0.58 s (3H, C-18), 0.17 s (6H, $SiMe_2$). MS (EI) m/z: 540 (M^+,55), 522 (M^+-H_2O,8), 368 (25), 274 (30), 221 (23), 177 (25), 128(23), 99 (100), 73 (55). $[\alpha]_D^{20}$ = +54.2 (c = 0.500, $CHCl_3$). Analysis calculated for $C_{32}H_{48}O_5Si$: C 71.07, H 8.95; found C 71.12, H 8.99.

11β-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]phenyl]-3,3-[1,2-ethanediylbis(oxy)]-17-[(trimethylsilyl)oxy]-5α-estr-16-en-5-ol (7). Diisopropylamine (9.4 mL, 67 mmol) was dissolved in 200 mL tetrahydrofuran (THF) and cooled to −78 C. Butyllithium (42 mL, 67 mmol, 1.6 M in hexane) was added and the mixture was stirred for 30 min at 0 C. Afterwards it was cooled to −78 C and a solution of **6** (14.5 g, 26.8 mmol) in 100 mL THF was added dropwise. After 1 h of stirring at −78 C chlorotrimethylsilane (8.52 mL, 67.1 mmol) was added. The mixture was warmed to 25 C and stirred for another 30 min. The reaction mixture was added to a saturated aqueous solution of sodium bicarbonate and worked-up further as usual. The crude material (15.6 g) was used for the next step without purification. NMR (300 MHz, $CDCl_3$): δ = 7.16 d (J = 9 Hz, 2H, ar), 6.65 d (J = 9 Hz, 1H, ar), 4.35 m (1H, H-16), 3.85–3.95 m (4H, ketal), 3.08 m (1H, H-11), 0.91 s (9H, Si^{t}Bu), 0.61 s (3H, C-18), 0.15 s (6H, $SiMe_2$), 0.10 s (9H, $SiMe_3$).

17-Chloro-11β-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl]-3,3-[1,2-ethanediyl-bis(oxy)]-5-hydroxy-17a-homo-5α-estr-16-en-17a-one (8). A solution of crude **7** (15.6 g, 25.5 mmol), sodium trichloroacetate (30.2 g, 162.7 mmol) and 700 mg benzyltriethylammonium chloride in 150 mL chloroform was heated under reflux for 4 h. The usual work-up and purification gave 8.99 g (60%) **(8)**. IR ($CHCl_3$): 3500, 2960, 1690, 1600, 1510. NMR (300 MHz, $CDCl_3$): δ = 7.25 d (J = 9 Hz, 2H, ar), 7.00 dd (J = 6, 1.5 Hz, 1H, H-16), 6.72 d (J = 9 Hz, 2H, ar), 3.85–4.00 m (4H, ketal), 3.21 ddbr (J = 7, 5 Hz, 1H, H-11), 2.64 ddd (J = 18, 6, 5 Hz, 1H, H-15α), 2.38 dd (J = 14, 1.5 Hz, 1H, H-12β), 2.11 ddd (J = 18, 10, 2.5 Hz, 1H, H-15β), 1.94 dd (J = 14, 6 Hz, 1H, H-12α), 0.95 s (9H, Si^{t}Bu), 0.73 s (3H, C-18), 0.17 s (6H, $SiMe_2$). MS (EI) m/z: 586/588 (M^+, 25), 568/570 (M^+-H_2O, 3), 485 (5), 414 (5), 235 (15), 221 (18), 177 (20), 141 (17), 128 (23), 99 (100), 73 (35). $[\alpha]_D^{20}$ = −17.6 (c = 0.510, $CHCl_3$). Analysis calculated for $C_{33}H_{47}ClO_5Si$: C 67.49, H 8.07; found C 67.59, H 8.14.

17-Chloro-11β-[4-[[(1,1-dimethylethyl)dimethylsilyl)-oxy]phenyl]-3,3-[1,2-ethanediyl-bis(oxy)]-17aα-(1-propynyl)-17a-homo-5α-estr-16-ene-5,17aβ-diol (9). Tetrahydrofuran (750 mL) was saturated with propyne gas at 0 C. Afterwards butyllithium (95.7 mL, 153.2 mmol, 1.6 M in hexane) was added. After stirring for 30 min at 0 C a solution of **8** (8.99 g, 15.3 mmol) in 150 mL THF was added. The reaction mixture was stirred for another 30 min at 0 C and worked up as usual. After purification 9.1 g (95%) **9** was isolated. IR ($CHCl_3$): 3500, 2950, 1600, 1500. NMR (300 MHz, $CDCl_3$): δ = 7.25 d (J = 9 Hz, 2H, ar), 6.72 d (J = 9, Hz, 2H, ar), 5.39 dd (J = 6, 1.5 Hz, 1H, H-16), 3.85–4.00 m (4H, ketal), 3.20 m (1H, H-11), 2.50 dd (J = 14, 6 Hz, 1H, H-12α), 2.12 dd (J = 14, 1.5 Hz, 1H, H-12β), 1.92 s (3H, propynyl), 0.96 s (9H, Si^{t}Bu), 0.58 s (3H, C-18), 0.15 s (6H, $SiMe_2$). MS (EI) m/z: 626/628 (M^+, 1), 484 (RDA, 5), 379 (10), 258 (16), 234 (18), 221 (20), 196 (20), 177 (15), 99 (100), 73 (40). $[\alpha]_D^{20}$ = −119.8 (c = 0.520, $CHCl_3$). Analysis calculated for $C_{36}H_{51}ClO_5Si$: C 68.93, H 8.19; found C 69.01, H 8.26.

17-Chloro-3,3-[1,2-ethanediylbis(oxy)]-11β-(4-hydroxyphenyl)-17aα-(1-propynyl)-17a-homo-5α-estr-16-en-5,17β-diol (10). A mixture of **9** (9.1 g, 14.5 mmol) and tetrabutylammonium fluoride trihydrate in 150 mL THF was stirred at 25 C for 1.5 h. The reaction mixture was added to an ice-cold saturated aqueous solution of sodium bicarbonate (300 mL) and worked up as usual. After purification 5.58 g (75%) **10** was obtained. IR ($CHCl_3$): 3460, 2940, 1640, 1500. NMR (300 MHz, $CDCl_3$): δ = 7.26 d (J = 9 Hz, 2H, ar), 6.71 d (J = 9 Hz, 2H, ar), 5.30 dd (J = 6, 1.5 Hz, 1H, H-16), 3.85–4.00 m (4H, ketal), 3.20 m (1H, H-11), 2.53 dd (J = 14, 6 Hz, 1H, H-12α), 2.13 dd (J = 14, 1.5 Hz, 1H, H-12β), 1.92 s (3H, propynyl), 0.58 s (3H, C-18). MS (EI) m/z: 494/496 (M^+-H_2O, 5), 353 (80), 232 (23), 141 (20), 99 (100), 73 (25). $[\alpha]_D^{20}$ = −149 (c = 0.515, $CHCl_3$). Analysis calculated for $C_{30}H_{37}ClO_4$: C 70.23, H 7.27; found C 70.29, H 7.32.

17-Chloro-3,3-[1,2-ethanediylbis(oxy)]-17aα-(1-propinyl)-11β-[4-[[(trifluoromethyl)sulfonyl]oxy]phenyl]-17a-homo-5α-estr-16-en-5,17aβ-diol (*11*). To a solution of **10** (5.58 g, 10.88 mmol) and 4-(dimethylamino)pyridine (6.64 g, 54.4 mmol) in 120 mL methylene chloride at −78 C was slowly added triflic anhydride (2.39 mL, 14.25 mmol). After stirring for 1.5 h the reaction mixture was added to 300 mL of saturated aqueous sodium bicarbonate solution. It was stirred for another 30 min at 25 C, extracted with methylene chloride and worked up as usual. Purification gave 5.12 g (73%) **11**. IR ($CHCl_3$): 3460, 2960, 1650, 1500. NMR (300 MHz, $CDCl_3$): δ = 7.50 d (J = 9 Hz, 2H, ar), 7.17 d (J = 9 Hz, 2H, ar), 5.78 dd (J = 6, 1.5 Hz, 1H, H-16), 3.85–4.00 m (4H, ketal), 2.60 dd (J = 14, 6 Hz, 1H, H-12α), 2.15 dd (J = 12, 1.5 Hz, 1H, H-12β), 1.92 s (3H, propynyl), 0.54 s (3H, C-18). MS (EI) m/z: 626/628 (M^+-H_2O, 5), 485/487 (80), 441/443 (10) 423/425 (10), 142/144 (60), 99 (100), 79 (25). $[\alpha]_D^{20}$ = −121.7 (c = 0.515, $CHCl_3$). Analysis calculated for $C_{31}H_{36}ClF_3O_7Si$: C 57.72, H 5.62; found C 57.63, H 5.57.

11β-(4-Acetylphenyl)-17-chloro-17aβ-hydroxy-17aα-(1-propynyl)-17a-homoestra-4,16-dien-3-one (*12*). A solution of **11** (2.59 g, 3.97 mmol), tributyl(1-ethoxyethenyl)stannane (1.79 mL, 5.31 mmol), tetrakis(triphenylphosphine)palladium-(0) (231 mg, 0.2 mmol), lithium chloride (340 mg, 8 mmol) and pyridine (0.46 mL, 5.7 mmol) in dioxane was heated under reflux for 2 h. The solution was filtered through celite. The usual work-up gave the crude coupling product which was diluted with 100 mL of acetone. After addition of aqueous hydrochloric acid (9 mL, 2N) the mixture was stirred for 30 min at 40 C. The reaction mixture was added to 150 mL of saturated aqueous sodium bicarbonate and worked up as usual. Purification yielded 1.20 g (63%) **12**. IR (KBr): 3420, 2950, 1670, 1500. NMR (300 MHz, $CDCl_3$): δ = 7.90 d (J = 9 Hz, 2H, ar), 7.57 d (J = 9 Hz, 2H, ar), 5.89 sbr (1H, H-4), 5.81 dd (J = 6, 1.5 Hz, 1H, H-16), 3.50 ddbr (J = 7, 5 Hz, 1H, H-11), 2.80 m (1H, H-10), 2.61 s (3H, acetyl), 1.92 s (3H, propynyl), 0.62 s (3H, C-18). MS (EI) m/z: 476/478 (M^+, 15), 458/460 (M^+-H_2O, 12), 436 (30), 335 (100), 142 (32), 107 (35), 79 (45). $[\alpha]_D^{20}$ = −88.7 (c = 0.505, $CHCl_3$). Analysis calculated for $C_{30}H_{33}ClO_3$: C 75.53, H 6.97; found C 75.59, H 7.01.

17-Chloro-17aβ-hydroxy-17aα-(1-propynyl)-11β-[4-(3-pyridinyl)phenyl]-17a-homo-estra-4,16-dien-3-one (*13*). A solution of **11** (2.56 g, 3.97 mmol), diethyl(3-pyridinyl)borane (816 mg, 5.55 mmol), tetrakis(triphenylphosphine)palladium(0) (466 mg, 0.40 mmol), lithium chloride (340 mg, 8 mmol) and 2.6 mL of a 2N aqueous sodium carbonate solution in 40 mL toluene and 15 mL ethanol was heated under reflux for 1 h. The usual work-up gave the crude coupling product which was diluted in 100 mL acetone. After addition of aqueous hydrochloric acid (9 mL, 2N) the mixture was stirred for 30 min at 40 C. Afterwards the reaction mixture was added to 150 mL of saturated aqueous sodium bicarbonate solution. The usual work-up and purification gave 1.42 g (70%) **13**. IR (KBr): 3400, 2940, 1670, 1500. NMR (300 MHz, $CDCl_3$): δ = 8.86 sbr (1H, py), 8.57 dd (J = 4, 1.5 Hz, 1H, py), 7.88 dt (J = 7.5, 1.5 Hz, 1H, py), 7.58 d (J = 9 Hz, 2H, ar), 7.50 d (J = 9 Hz, 2H, ar), 7.36 dd (7.5, 4 Hz, 1H, py), 5.90 sbr (1H, H-4), 5.81 dd (J = 6, 1.5 Hz, 1H, H-16), 3.52 ddbr (J = 7, 5 Hz, 1H, H-11), 2.38 m (1H, H-10), 1.92 s (3H, propynyl), 0.68 s (3H, C-18). MS (EI) m/z: 511/513 (M^+,3), 370 (100), 326 (8), 182 (15), 168 (15), 142 (20), 107 (13), 79 (14). $[\alpha]_D^{20}$ = −67.4 (c = 0.525, $CHCl_3$). Analysis calculated for $C_{33}H_{34}ClNO_2$: C 77.40, H 6.69, N 2.74; found C 77.46, H 6.73, N 2.79.

Biological methods

Progesterone receptor preparation. Mature rabbits with 2.5–4 kg body weight were treated 5 times with 10 μmol estradiol benzoate s.c. daily, dissolved in 0.2 mL sesame oil. The animals were killed by decapitation 24 h after the end of treatment, uteri were removed, stripped of fat, and washed with cold saline. All subsequent procedures were carried out at 0–4 C. Uteri were mixed and homogenized with an Ultra-Turrax in 0.01 mmol/L Tris/HCl buffer, pH 7.5, containing 1.5 mmol/L EDTA and 30% glycerol (1:2, w/v). The homogenate was centrifuged for 10 min at 10,000 × g and the supernatant was again spun at 105,000 × g for 90 min. The supernatant was used as cytosol for competition assays.

Competition assay. Cytosol (20 μL) was incubated with 10 μL[^{3}H]progesterone (final concentration 10^{-7} mol/L) and 10 μL unlabeled progesterone for the standard curve or 10 μL of the test substance. The final concentration of unlabeled competitors ranged from 10 nmol/L to 10 μmol/L. Incubations were conducted 2 h at 4 C. After the incubation 460 μL of buffer was added and aliquots of 200 μL were applied to Sephadex G-10 columns for separation of unbound ligand. Bound and unbound ligand were determined by liquid scintillation counting.

For determination of the relative binding affinity of antigestagens the displacement of [^{3}H]progesterone with unlabeled compounds was plotted as percent binding versus log molar concentration. The activity of a compound is indicated as relative binding affinity (RBA) which is defined as the IC_{50} ligand/IC_{50} test compound (IC: inhibitory concentration).

Antiprogestational activity. The progesterone antagonistic activity was tested in the early pregnancy of the rat on day 5 to day 7 post coitum. For the experiments female wistar rats (TZH, Schering AG) were used weighing about 200 g. After successful mating pregnant animals were randomized to treatment and control groups. The beginning of pregnancy was determined by the demonstration of sperms in the vaginal smears on day after mating (= day 1 of pregnancy = d1 p.c.). The animals received the test compound or vehicle (p.o. or s.c.) 1 × daily from day 5 to day 7 p.c.; autopsy was performed on day 9 p.c. The absence of implantation and/or hemorrhagic nidation sites during autopsy were assessed as abortion and used as a parameter for the progesterone-antagonistic activity. The compounds were administered in different doses. Compound **12** was given p.o. in 0.5 mL vehicle (Myri53$^{(R)}$/NaCl) and **13** was given s.c. in 0.2 mL vehicle (benzylbenzoate + castor oil).

Results and discussion

Both compounds **12** (p.o.) and **13** (s.c.) show complete abortion at doses of 0.1 mg/day. Compared to the well studied antigestagens RU 38486 and ZK 112 993 these results mean a visible increase of activity (see Table 1) and confirm the assumption that D-homo steroids bearing a 16(17)-double bond can be highly active antiprogestins.

Cyclopropanation of silyl enol ethers provides an easy access into the series of D-homo steroids. In contrast to the Tiffeneau-Demyanov procedure, this strategy gives only one regioisomer. The resulting 16(17)-double bond in conjunction with the 17-chloro substituent seems to

Table 1 Biological activity of **12**, **13**, RU 38486, and ZK 112 993

		Biological Data		
		Abortive activity in the rat		
			Abortion rate (%)	
Compound	RBA[a]	Dose (mg/day)	p.o.[b]	s.c.[c]
RU 38486	34	1	50	75
ZK 112 993	100	1	100	100
		0.3	0	100
		0.1	0	0
12	29	0.1	100	—
13	40	0.1	—	100

[a] RBA: relative binding affinity.
[b] p.o.: oral application.
[c] s.c.: subcutaneous application.

even enhance the biological activity of D-homo antigestagens.

The cross-coupling of organometallics with triflate **11** offers broad flexibility with respect to aryl substitution and opens the opportunity for extensive structure-activity studies of D-homo antiprogestins.

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