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TETRAHEDRON

7α,15α-Ethano Bridged Steroids. Synthesis and Progesterone Receptor Interaction

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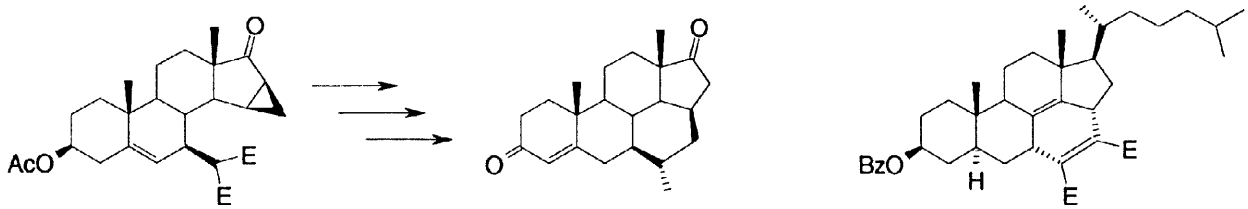
Abstract: The synthesis of 7α,15α-ethano bridged steroids is described. Diels-Alder reaction of 3-methoxyestra-1,3,5(10),7,14-pentaen-17-one **4** with ethylene under high pressure provides efficient synthetic access to this class of steroids. Compounds **15** and **17** were tested for their binding affinities to the progesterone receptor (PR). Two low energy conformations **17a** and **17b** could be identified by force field calculations of compound **17**. Both conformations were analysed in complex with the ligand binding domain of the human progesterone receptor (hPR LBD).

INTRODUCTION

A decade ago K. Nickisch et al. described the synthesis of pentacyclic 7β,15β-ethano androstene derivatives (Figure 1).[1] Key step in their synthetic approach was an intramolecular opening of a 15β,16β-methylene-17-oxo moiety by a 7β-malonyl ester function which was unexpectedly observed under decarboxylation conditions. Several additional steps were required to remove the diester function from the bridge. Compound **2** was tested for its binding affinity to the androgen receptor and for aromatase inhibition *in vitro*. However only weak effects were observed.

Some years later W. Chong et al. claimed 7,15-bridged compounds with antihypercholesterolemic activity in a patent application.[2] They installed this bridge using a Diels-Alder reaction. The focus of their activities lies on aromatic bridges bearing heteroatoms. Nevertheless, they also described compounds bridged by carbon moieties like **3** which were obtained by cycloaddition of diethyl acetylenedicarboxylate. Compounds with an unsubstituted etheno or ethano bridge are part of the patent claims but were not described experimentally. Obviously, for the preparation of these unsubstituted bridges several steps are necessary to remove the ester functionalities.



1 E=CO_2Et **2** **3**

Figure 1

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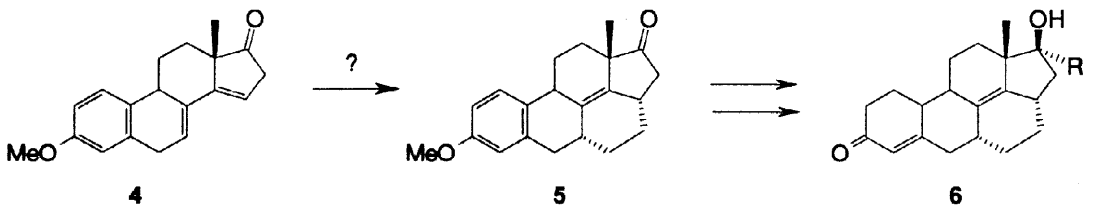
In the course of an ongoing drug finding program, we planned to study the influence of 7α,15α-ethano bridged structures of type **6** upon progestational activity.

As shown in Figure 2 we planned the installation of the 7α,15α-ethano bridge via Diels-Alder reaction of ethylene to 3-methoxyestra-1,3,5(10),7,14-pentaen-17-one **4**.[3] The compounds derived from this cycloaddition strategy exhibit a double bond between C-8 and C-14. It is known, that the progesterone receptor (PR) tolerates small substituents at the positions 7α and 15α as well as the incorporation of an 8(14) double bond.[4,5,6] Therefore, the question arose whether the desired 7α,15α-ethano bridged compounds which formally combine these three structural elements would still exhibit high binding affinity.



4 **5** **6**

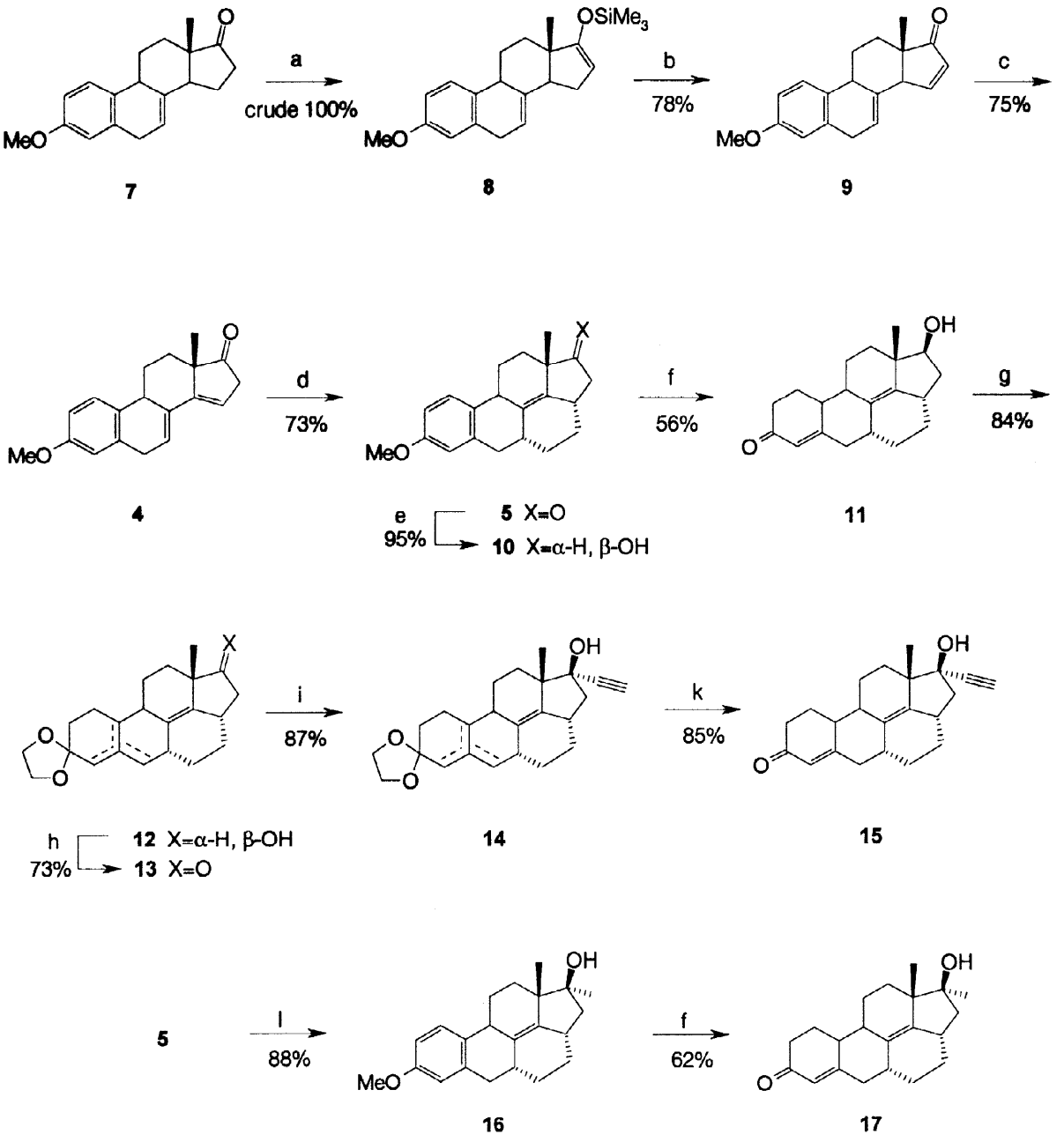
Figure 2

RESULTS AND DISCUSSION

As shown in Scheme 1 the synthetic approach to 7α,15α-bridged compound **15** starts with known equilin 3-methyl ether **7**.[7] The 15-unsaturated derivative **9** was prepared via modified Saegusa oxidation of the corresponding silyl enol ether **8** using one equivalent of palladium(II) acetate in acetonitrile.[8] Deconjugation of the 15-double bond was achieved by stirring **9** with triethylamine and silica gel in a mixture of hexane and ethyl acetate.[9] Initial studies carried out upon compound **4** revealed that [4+2]cycloaddition of ethylene in a pressure vessel proceeds very slowly at 120°C under high pressure (200-300 bar). Attempts to optimize this cycloaddition by conducting it at elevated temperatures led to significant improvement. Diels-Alder reaction in benzene at 160°C under 300 bar pressure was almost complete after 60 h. Under these reaction conditions the bridged compound **5** was obtained in a satisfactory yield of 73 % together with 10 % recovered starting material. Extended reaction time did not afford a higher yield. Further increase of the temperature caused considerable darkening of the reaction mixture and decomposition of compound **4**. The attack of ethylene proceeded from the less hindered α-face of the steroid exclusively. The configuration at C-7 and C-15 was assigned by 2D NMR techniques (COSY and NOESY, NOE between H-18 and H-15, no effect between H-9α and H-7) and as described later confirmed by X-ray crystal structure determination of compound **17**. The 17-ketone **5** was reduced to the alcohol **10** with sodium borohydride. Birch reduction of **10** followed by cleavage of the generated enol ether under acidic conditions yielded the Δ^4-3-ketone **11**. This two step procedure was considerably more efficient than direct Birch reduction of ketone **5**. Protection of ketone **11** as ethylene ketal gave **12** as mixture of three double bond isomers. Oxidation of the 17-hydroxy group was performed using Swern conditions.[10] Addition of ethynyl lithium followed by cleavage of the 3-ketal yielded compound **15**.

Since we were not able to obtain appropriate crystals, X-ray crystal structure determination of compound **15** could not be performed. Therefore, the corresponding 17α-methyl analog **17** was prepared. In contrast to the 17α-ethynyl derivative aromatic ring A could be reduced after introduction of the 17α-side chain.

Both compounds **15** and **17** exhibit only weak affinity to PR (≈ 1% of the natural hormone progesterone).[11]



reaction conditions: a: 1. LDA, THF, -78°C, 2. TMS-Cl, THF, 25°C, b: $Pd(OAc)_2$, CH_3CN, 25°C, c: silica gel, NEt_3, ethyl acetate/hexane, 25°C, d: ethylene, benzene, 300 bar, 160°C, e: $NaBH_4$, THF/MeOH, 25°C, f: 1. Li, NH_3, -78°C, 2. 4N HCl, acetone, 25°C, g: ethylene glycol, $CH(OMe)_3$, p-TosOH, CH_2Cl_2, 25°C, h: 1. oxalic chloride, DMSO, CH_2Cl_2, -78°C, 2. NEt_3, -20°C, i: ethyne, n-BuLi, THF, 0°C, k: 4N HCl, acetone, 25°C, l: MeLi, Et_2O/THF, 0°C.

Scheme 1

Suitable crystals of **17** for X-ray crystal structure determination were obtained by recrystallization from methylene chloride/methanol. The constitution of **17** was confirmed as shown in Figure 3.

The crystal structure is representing a roughly even distribution of two conformations: An optimum fit of experimental data was obtained in the refinement procedure considering a 50/50 occupancy factor for the differences in the A and E (defined by the 7,15 ethano anellation) ring regions, respectively. As a consequence, however, an assignment of the electron densities in these two isolated parts of the crystal structure to unique conformations was not possible due to combinatorial unambiguities. Therefore, force field calculations utilising the programme SYBYL[12] were conducted in order two explore the conformational space for A and E ring distortions. Two low energy conformations could be identified which are in agreement with the experimental data. The energy difference between these two conformations, **17a** and **17b**, is only 0.7 kcal/mol in favour of **17a**. As shown in the superposition (Figure 4), the E-ring in conformation **17a** adopts a 'sofa' form. In conformation **17b**, a boat form is established in the E ring resulting in an orientation of the 3-keto group above the A ring plane of conformation **17a**. The superposition nicely reflects the experimental findings, indicating major differences between to be the two conformations expected only in the A and E ring moieties.

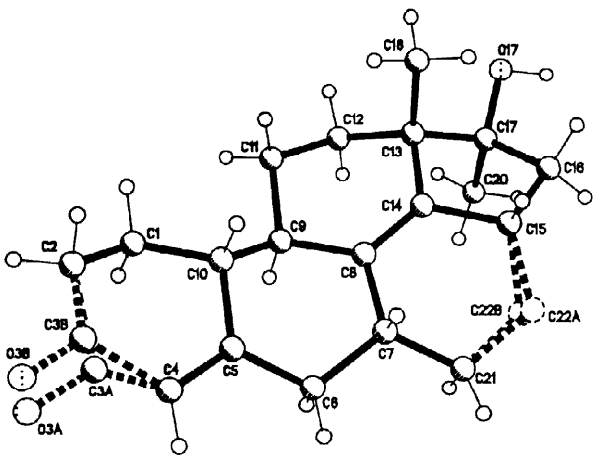


Figure 3 — X-ray crystal structure of **17**

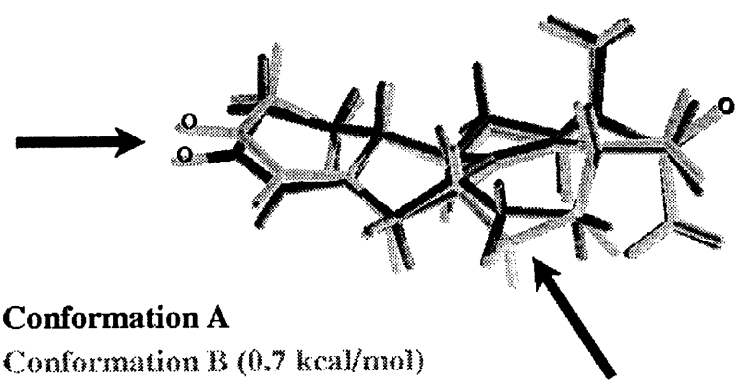


Figure 4 — Superposition of low-energy conformations **17a** and **17b**

Both conformations were further analysed in complex with the ligand binding domain of the human progesterone receptor (hPR LBD), published recently.[13] The compounds were fitted into the binding pocket such that those hydrogen-bonds observed in the crystal structure of the hPR LBD / progesterone complex were conserved. The energy of the protein-ligand complexes were relaxed with standard minimisation techniques utilising the programme DISCOVER.[14]

In these calculations, **17a** and **17b** were forced to the low energy conformations predicted by SYBYL applying a set of torsional constraints. However, during the course of energy minimisation of the protein-ligand complexes, **17a** and **17b** were severely distorted: A root-mean-square deviation (RMSD) between the starting low-energy conformations **17a** and **17b** and their final structures after minimisation in the protein ligand complex is 0.29 Å and 0.57 Å, respectively. It is known that the A ring position is fixed in the crystal structures of hPR LBD and other nuclear receptor LBDs, i.e. the A ring determines the orientation of the entire ligand in the binding niche. If the A rings of the starting and final structures of **17a** and **17b** are superimposed, large deviations particularly arise in the D rings which may be seen as a result of the following unfavourable interactions: The close vicinity of the angular methyl group in position 13 to the polar ASN719 side chain (distance C_{18}-OD1: 3.4Å), the E ring atoms (**17b** only) to the carbonyl oxygen of LEU887, and a very short van-der-Waals distance of C16 atoms to the side chain of CYS891 (distance C16-CB: 3.3 Å(**17a**) and 2.5 Å(**17b**), respectively) as exemplified for **17a** in Figure 5.

Hence, the reduced PR binding affinity of **17** may be explained in terms of steric hindrance in the ligand binding niche.

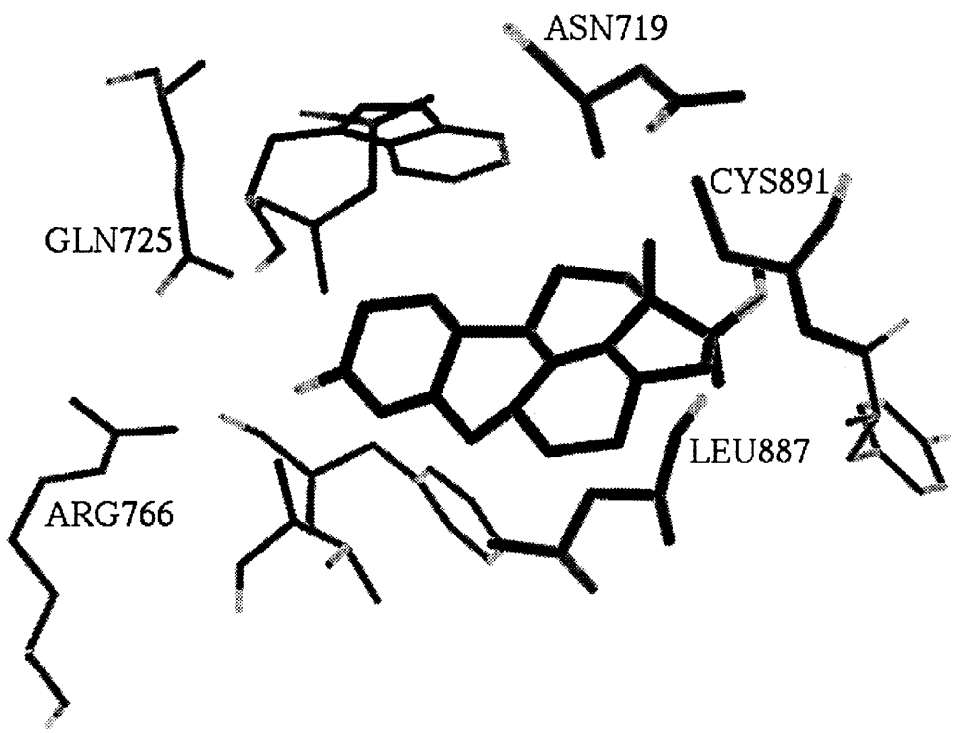


Figure 5 — Energy-minimised complex of **17** and hPR LBD. For clarity, only relevant amino acid residues are displayed. Amino acid residues involved in hydrogen-bonds are labelled as well as those causing steric hindrance.

EXPERIMENTAL SECTION

Spectral data were obtained as follows: ^1H NMR: Bruker AC 300 (300 MHz/75 MHz) spectrometer; δ in ppm relative to TMS as internal standard. IR: Bruker FT-IFS 25 spectrometer. MS: Fisons Instruments VG 70-70 E spectrometer; recorded at 70 eV ionizing voltage; NH_3 was used for chemical ionization (CI). Optical rotations: Perkin Elmer polarimeter 241. Melting points were determined on either a Mettler FP62 melting point instrument or a Kofler hot plate apparatus and are uncorrected. Microanalytical data were provided by Schering analytical department. TLC analyses were performed on Merck F_{254} silica gel plates. Spots were visualized by soaking plates with a diethyl ether solution containing vanillin (2.5‰) and sulfuric acid (5%) and heating by means of a heat gun. 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 atmosphere.

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 (Merck silica gel 60, 70-230 mesh) using ethyl acetate/hexane as eluents.

3-Methoxy-17-[(trimethylsilyl)oxy]estra-1,3,5(10),7,16-pentaene (8): Butyllithium (19.1 ml, 47.75 mmol, 2.5 M in hexane) was added to a solution of diisopropylamine (6.7 ml, 47.8 mmol) in 120 ml tetrahydrofuran (THF) at -78°C. The reaction mixture was stirred for 30 min at 0°C. Afterwards it was cooled to -78°C and a solution of 5.4 g (19.12 mmol) **7** in 60 ml THF was added dropwise. After 1 h of stirring at -78°C chlorotrimethylsilane (8.45 ml, 66.90 mmol) was added. The mixture was warmed to 25°C and stirred for another 30 min. Then the reaction mixture was poured into saturated sodium bicarbonate solution and further worked-up as usual. The crude silyl enol ether (6.78 g, 100%) was used without purification.

3-Methoxyestra-1,3,5(10),7,15-pentaen-17-one (9): Compound **8** (6.775 g, 19.12 mmol) was dissolved in 80 ml acetonitrile. Palladium(II) acetate (4.72 g, 21.03 mmol) was added and the solution was stirred at 25°C for 1 h. Afterwards the reaction mixture was filtered through Celite®. Evaporation and purification yielded 4.179 g (78%) **9** as white foam. **IR** ($CHCl_3$, cm^{-1}): 3013, 2946, 2837, 1708, 1611. **^1H NMR** (300 MHz, $CDCl_3$): δ=7.63 dd (J=6, 1 Hz, 1H, H-15), 7.18 dbr (J=9 Hz, 1H, H-1), 6.80 dd (J=9, 2 Hz, 1H, H-2), 6.68 dbr (J=2 Hz, 1H, H-4), 6.11 dd (J=6, 3 Hz, 1H, H-16), 5.54 m (1H, H-7), 3.79 s (3H, OMe), 3.50 m (2H, H-6), 3.28 m (2H, H-9, H-14), 0.96 s (3H, H-18). **MS** (EI) m/z: 280 (M^+, 100), 265 (30), 237 (25), 209 (25), 171 (40), 158 (60), 115 (30). $[\alpha]_D^{22}$= +199.0° (c=0.515, $CHCl_3$). **$C_{19}H_{20}O_2$** (280.37) calcd. C 81.40, H 7.19; found C 81.44, H 7.20%.

3-Methoxyestra-1,3,5(10),7,14-pentaen-17-one (4): Compound **9** (4.1 g, 14.6 mmol) was dissolved in 800 ml of a 9:1 mixture of ethyl acetate and hexane. Triethylamine (80 ml) and silica gel (350 g) were added. The reaction mixture was stirred for 20 h at 25°C. After filtration, evaporation and purification 3.075 g (75%) **4** was isolated. **IR** ($CHCl_3$, cm^{-1}): 3013, 2940, 1739, 1612, 1504. **^1H NMR** (300 MHz, $CDCl_3$): δ=7.21 dbr (J=9 Hz, 1H, H-1), 6.80 dd (J=9, 2 Hz, 1H, H-2), 6.66 dbr (J=2 Hz, 1H, H-4), 5.91 m (1H, H-15), 5.80 m (1H, H-7), 3.80 s (3H, OMe), 3.50 m (2H, H-6), 3.19 m (1H, H-9), 3.13 dbr (J= 22 Hz, 1H, H-16), 2.92 dd (J=22, 3 Hz, 1H, H-16'), 1.10 s (3H, H-18). **MS** (EI) m/z: 280 (M^+, 100), 252 (50), 237 (35), 223 (20), 209 (20), 184 (15), 171 (25). $[\alpha]_D^{22}$= -35.2° (c=0.505, $CHCl_3$). **$C_{19}H_{20}O_2$** (280.37) calcd. C 81.40, H 7.19; found C 81.48, H 7.23%.

3-Methoxy-5',6',8β,15β-tetrahydrobenzo[7,8,14,15]estra-1,3,5(10)-trien-17-one (5): In a pressure vessel a solution of 3 g (10.70 mmol) **4** in 60 ml benzene was reacted with ethylene at 300 bar and 160°C. After 60 h reaction time the solvent was evaporated. Purification of the crude material gave 2.41 g (73%) **5** and 300 mg (10%) starting material as white foams. **IR** (KBr, cm^{-1}): 2920, 2860, 1740, 1620, 1490. **^1H NMR** (300 MHz, $CDCl_3$): δ=7.12 dbr (J=10Hz, 1H, H-1), 6.78 m (2H, H-2, H-4), 3.80 s (3H, OMe), 3.11 m (1H, H-9α), 2.94 m (1H, H-15β), 2.75 dd (J=14, 5 Hz, 1H, H-6β), 2.64 dd (J=18, 9 Hz, 1H, H-16β), 2.43 t (J=14 Hz, 1H, H-6α), 2.33 m (1H, H-11α), 2.04 dd (J=18, 10 Hz, 1H, H-16α), 1.97-2.05 m (2H, H-7β, H-12β), 1.85-1.95 m (2H, H-11β, H-15a), 1.74-1.85 m (2H, H-7aβ, H-15a'), 1.68 m (1H, H-12α), 1.31 m (1H, H-7aα), 1.17 s (3H, H-18). **MS** (EI) m/z: 308 (M^+, 100), 280 (35), 265 (25), 223 (25), 209 (20). **$C_{21}H_{24}O_2$** (308.42) calcd. C 81.78, H 7.84; found C 81.73, H 7.79%.

3-Methoxy-5',6',8β,15β-tetrahydrobenzo[7,8,14,15]estra-1,3,5(10)-trien-17β-ol (10): Sodium borohydride (166 mg, 4.39 mmol) was added to a solution of compound **5** (1.2 g, 3.89 mmol) in a mixture of 20 ml THF and 3 ml methanol. It was stirred for 1 h at 25°C. Then the reaction mixture was poured into saturated ammonium chloride solution and further worked-up as usual. After purification 1.149 g (95%) **10** was obtained as white foam. **IR** ($CHCl_3$, cm^{-1}): 3610, 3010, 2933, 2862. **^1H NMR** (300 MHz, $CDCl_3$): δ=7.15 dbr (J=10 Hz, 1H, H-1), 6.78 m (2H, H-2, H-4), 3.80 m (1H, H-17), 3.79 s (3H, OMe), 3.10 m (1H, H-9α) 2.75 dd (J=13, 5 Hz, 1H, H-6β), 2.31-2.55 m (3H, H-6α, H-11α, H-

15β), 1.00 s (3H, H-18). **MS** (EI) m/z: 310 (M^+, 100), 292 (M^+-H_2O, 20), 277 (55), 165 (20). $[\alpha]_D^{22}$= -122.3° (c=0.510, $CHCl_3$). **$C_{21}H_{26}O_2$** (310.44) calcd. C 81.25, H 8.44; found C 81.24, H 8.42%.

17β-Hydroxy-5',6',8β,15β-tetrahydrobenzo[7,8,14,15]estr-4-en-3-one (11): A solution of compound **10** (1.10 g, 3.54 mmol) in 20 ml THF was added to 40 ml liquid ammonia at -78°C. Lithium wire (0.4 g, 57.63 mmol) was added portionwise. It was stirred for 2 h at -78°C. Afterwards 5 ml ethanol was added. Then the reaction mixture was quenched with water. After evaporation of the ammonia it was worked-up as usual. The crude product was dissolved in 50 ml acetone. Hydrochloric acid (2.5 ml, 4 N) was added. It was stirred for another 15 min at 25°C. Then the reaction mixture was poured into saturated sodium bicarbonate solution. It was extracted with methylene chloride and further worked-up as usual. After purification 592 mg (56%) **11** was obtained. **IR** ($CHCl_3$, cm^{-1}): 3609, 3012, 2933, 2861, 1660. **^{1}H NMR** (300 MHz, $CDCl_3$): δ=5.88 sbr (1H, H-4), 3.71 t (J=9 Hz, 1H, H-17), 1.02 s (3H, H-18). **MS** (EI) m/z: 298 (M^+, 100), 280 (M^+-H_2O, 20), 254 (55), 240 (20), 145 (30), 110 (25). $[\alpha]_D^{22}$= -125.7° (c=0.520, $CHCl_3$). **$C_{20}H_{26}O_2$** (298.43) calcd. C 80.50, H 8.78; found C 80.56, H 8.81%.

17β-Hydroxy-5',6',8β,15β-tetrahydrobenzo[7,8,14,15]estren-3-one cyclic 1,2-ethanediyl acetal (12): A solution of compound **11** (540 mg, 1.81 mmol), ethylene glycol (1 ml, 17.93 mmol), trimethoxymethane (0.59 ml, 5.42 mmol) and a catalytic amount of p-toluenesulfonic acid in methylene chloride (15 ml) was stirred 4 h at 25°C. Afterwards the reaction mixture was poured into saturated sodium bicarbonate solution and further worked-up as usual. After purification compound **12** was obtained as mixture of 3 double bond isomers (521 mg, 84%). **IR** ($CHCl_3$, cm^{-1}): 3609, 3013, 2933. **^{1}H NMR** (300 MHz, $CDCl_3$): δ=5.48 m (1H/Δ^5 compound, H-6), 5.43 m (1H/Δ^4 compound, H-4), 3.90-4.10 m (4H, ketal), 3.80 m (1H, H-17), 1.03+1.00 s (3H, H-18). **MS** (EI) m/z: 342 (M^+, 90), 324 (M^+-H_2O, 10), 298 (15), 280 (40), 239 (35), 99 (100).

5',6',8β,15β-Tetrahydrobenzo[7,8,14,15]estrene-3,17-dione cyclic 3-(1,2-ethanediyl acetal) (13): To a solution of oxalic chloride (0.25 ml, 2.90 mmol) in 20 ml dichloromethane was added a solution of dimethylsulfoxide (0.41 ml, 5.77 mmol) in 1 ml dichloromethane at -78°C. The mixture was stirred for 3 min at this temperature. Then a solution of **12** (500 mg, 1.46 mmol) in 15 ml dichloromethane was added. Stirring was continued for 15 min at -78°C. Afterwards a solution of triethylamine (1.20 ml, 8.66 mmol) in 3 ml dichloromethane was added. After stirring for another 15 min at -20°C the reaction mixture was poured into saturated sodium bicarbonate solution. It was extracted with dichloromethane and further worked-up as usual. After purification 363 mg (73%) **13** was obtained. **IR** ($CHCl_3$, cm^{-1}): 3013, 2931, 1734. **^{1}H NMR** (300 MHz, $CDCl_3$): δ=5.49 m (1H/Δ^5 compound, H-6), 5.44 m (1H/Δ^4 compound, H-4), 3.95-4.05 m (4H, ketal), 1.17+1.15+1.12 s (3H, H-18). **MS** (EI) m/z: 340 (M^+, 95), 312 (25), 278 (20), 250 (20), 236 (25), 211 (35), 99 (100), 87 (40).

17α-Ethynyl-17β-hydroxy-5',6',8β,15β-tetrahydrobenzo[7,8,14,15]estren-3-one cyclic 1,2-ethanediyl acetal (14): Tetrahydrofuran (18 ml) was saturated with ethyne gas at 0°C. Butyllithium (6.43 ml, 10.29 mmol, 1.6 M in hexane) was added. After stirring for 30 min at 0°C a solution of **13** (350 mg, 1.03 mmol) in 15 ml THF was added. The reaction mixture was stirred for another 30 min at 0°C and worked-up as usual. After purification 328 mg (87%) **14** were obtained. **IR** ($CHCl_3$, cm^{-1}): 3599, 3306, 3013, 2937, 2863. **^{1}H NMR** (300 MHz, $CDCl_3$): δ=5.48 m (1H/Δ^5 compound, H-6), 5.42 m (1H/Δ^4 compound, H-4), 3.95-4.05 m (4H, ketal), 2.54 s (1H, ethyne), 1.11+0.98+0.97 s (3H, H-18). **MS** (EI) m/z: 366 (M^+, 15), 348 (M^+-H_2O, 15), 298 (15), 212 (25), 99 (100), 57 (40).

17α-Ethynyl-17β-hydroxy-5',6',8β,15β-tetrahydrobenzo[7,8,14,15]estr-4-en-3-one (15): Hydrochloric acid (0.8 ml, 4 N) was added to a solution of **14** (310 mg, 0.85 mmol) in 10 ml acetone. It was stirred for 1 h at 25°C. Afterwards, the reaction mixture was poured into saturated sodium bicarbonate solution and worked-up as usual. After purification 232 mg (85%) **15** was obtained. **IR** ($CHCl_3$, cm^{-1}): 3558, 3305, 3012, 2938, 2863, 1659. **^{1}H NMR** (300 MHz, $CDCl_3$): δ=5.89 sbr (1H, H-4), 2.56 s (1H, ethyne), 1.13 s (3H, H-18). **MS** (EI) m/z: 322 (M^+, 65), 254 (100), 240 (40), 145 (40), 91 (30). $[\alpha]_D^{22}$= -169.0° (c=0.530, $CHCl_3$). **$C_{22}H_{26}O_2$** (322.45) calcd. C 81.95, H 8.13; found C 81.99, H 8.15%.

3-Methoxy-17α-methyl-5',6',8β,15β-tetrahydrobenzo[7,8,14,15]estra-1,3,5(10)-trien-17β-ol (16): A solution of compound **5** (1.0 g, 3.24 mmol) in 25 ml THF was added to a solution of methyllithium in diethylether (10 ml, 16 mmol, 1.6 M) at 0°C. It was stirred for 1 h at 0°C. Afterwards the reaction mixture was poured into a saturated ammonium chloride solution and further worked-up as usual. After purification 926 mg (88%) **16** was obtained. **IR** ($CHCl_3$, cm^{-1}): 3610, 3013, 2937, 2865. **^{1}H NMR** (300 MHz, $CDCl_3$): δ=7.15 dbr (J=10 Hz, 1H, H-1), 6.76 m (2H, H-2, H-4), 3.80 s (3H, OMe), 3.10 m (1H, H-9α), 2.74 dd (J=14, 5 Hz, 1H, H-6β), 2.26-2.48 m (3H, H-6α, H-11α, H-15β), 1.22 s (3H, 17α-methyl), 1.00 s (3H, H-18). **MS** (EI) m/z: 324 (M^+, 30), 306 (M^+-H_2O, 10), 291 (25), 266 (100), 224 (20), 131 (20). $[\alpha]_D^{22}$= -135.6° (c=0.525, $CHCl_3$). **$C_{22}H_{28}O_2$** (324.46) calcd. C 81.44, H 8.70; found C 81.52, H 8.76%.

17β-Hydroxy-17α-methyl-5',6',8β,15β-tetrahydrobenzo[7,8,14,15]estr-4-en-3-one (17): The procedure used for the preparation of compound **17** was the same as described for **11**: Compound **16** (875 mg, 2.70 mmol) was reacted with lithium wire (300 mg, 43.22 mmol) in liquid ammonia. The crude enol ether was cleaved with hydrochloric acid in acetone. After chromatography 522 mg (62%) **17** was obtained. **IR** ($CHCl_3$, cm^{-1}): 3610, 3012, 2937, 2864, 1660. **^1H NMR** (300 MHz, $CDCl_3$): δ=5.89 sbr (1H, H-4), 1.18 s (3H, 17α-methyl), 1.13 s (3H, H-18). **MS** (EI) m/z: 312 (M^+, 35), 254 (100), 239 (20), 145 (35), 129 (20). $[\alpha]_D^{22}$= -129.5° (c=0.515, $CHCl_3$). **$C_{21}H_{28}O_2$** (312.43) calcd. C 80.73, H 9.03; found C 80.77, H 9.05%.

Crystal data of 17: $C_{21}H_{28}O_2$, M = 312.43 g/mol, yellow, platelet-shaped crystals from methylene chloride/methanol, 0.45 x 0.45 x 0.1 mm^3, monoclinic, space-group $P2_1$, a = 9.970(9), b = 8.497(4), c = 11.025(8) Å, β = 111.39(5)°, V = 870(1) $Å^3$, Z = 2, D_{calc} = 1.193 g/cm^3, μ = 0.578 mm^{-1}, F(000) = 340, graphite monochromated CuKα radiation from a fine focus sealed tube (λ = 1.54178 Å), 2834 reflections measured ($3° \le 2\theta \le 120°$, $-10 \le h \le 10$, $-1 \le k \le 9$, $-11 \le l \le 11$), 1442 unique reflections (R_{int} = 10.8%), 1262 observed reflections ($F \le 4.0\ \sigma(F)$). The data collected on a Siemens P4 four-circle diffractometer were corrected for Lorentz and polarisation effects. Three standard reflections measured every 97 reflections revealed no decay due to radiation damage.

Structure Analysis and Refinement:[15] The crystal quality was only moderate: Most of the reflection profiles were broad or - in some cases - even split. Nevertheless, data could be collected up to a reasonable resolution. All calculations were performed using the Siemens SHELXTL+ program.[16] The structure was solved by direct methods which yielded all of the carbon and oxygen positions. The hydrogen atom at O17 was located from a Difference Fourier map, the other hydrogens were included in calculated positions. A riding model was used to refine the isotropic displacement coefficients for the hydrogen atoms, except for the hydrogen of the hydroxyl group which was refined independently. Convergence for the full-matrix least-squares refinement using anisotropic displacement coefficients for all ordered carbon and oxygen atoms was achieved at R = 7.3% (wR2 = 18.9%, data-to-parameter ratio = 6.0:1). For three of the atoms (C3, O3 and C22, see Fig. 3) disordering was observed. The site occupancy factors for these atoms were set to 0.5 resulting in comparable displacement coefficients for the equivalent atomic positions. Interestingly, intermolecular hydrogen bonds between the hydroxyl group and both of the disordered positions of O3 are possible with comparable geometries.

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