



11 β -Aryl Steroids in the Androstene Series. The Role of the 11 β -Region in Steroid Progesterone Receptor Interaction

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Abstract: The syntheses of 11 β -arylandrost-4-en-3-one **24** and the corresponding 9 β ,19-cyclo derivative **8** are described. Steric interaction between C-19 and the aryl residue effects conformational changes of the steroid ring system that result in reduced affinity for the progesterone receptor. The conformation of 11 β -arylandrostenes is discussed in comparison with known antiprogesterone steroids.

INTRODUCTION

One of the primary structural features of antiprogesterone steroids is the 11 β -aryl moiety. It was found to be essential for antagonistic action at the progesterone receptor (PR). Teutsch et al. showed that a lipophilic pocket of the receptor protein fits very well for flat unsaturated 11 β -substituents such as vinyl or phenyl.¹ On the other hand, saturated substituents reduce receptor affinity with increasing steric demand. It was also demonstrated that the planes of unsaturated residues nearly eclipse the steroidal C-9–C-11 single bond in the X-ray crystal structure of *estra-4,9-dien-3-ones*.² Fixing the aryl residue in the eclipsed conformation by bridging it to C-19 retains receptor affinity (Figure 1).³ This suggests that the biologically active and the energetically favoured conformations of unbridged antiprogesterone steroids are closely related. Forcing the phenyl ring into a position orthogonal to the optimum conformation by installing a bridge to C-18 drastically reduces binding affinity.⁴ Due to steric interactions with the ortho-phenyl position, a 10 β -H compound would have been expected to have a reduced PR affinity, as well. AM1 calculations⁵ showed, however, that the phenyl torsions in the minimum structures of 10 β -H species and $\Delta^{4,9}$ -systems like RU 38 486 are very similar.⁶ Indeed, 10 β -H compounds turned out to be highly active antiprogesterone steroids *in vitro* and *in vivo*.⁷

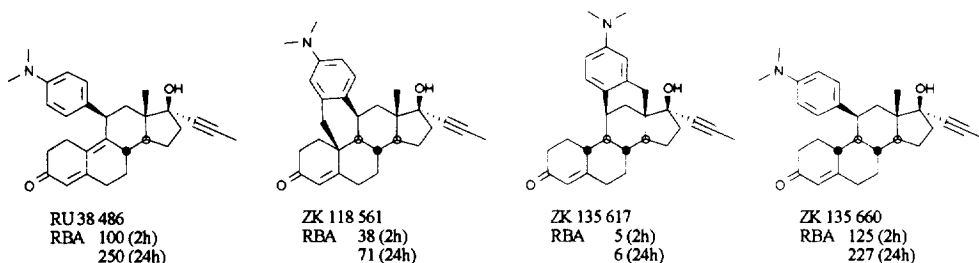
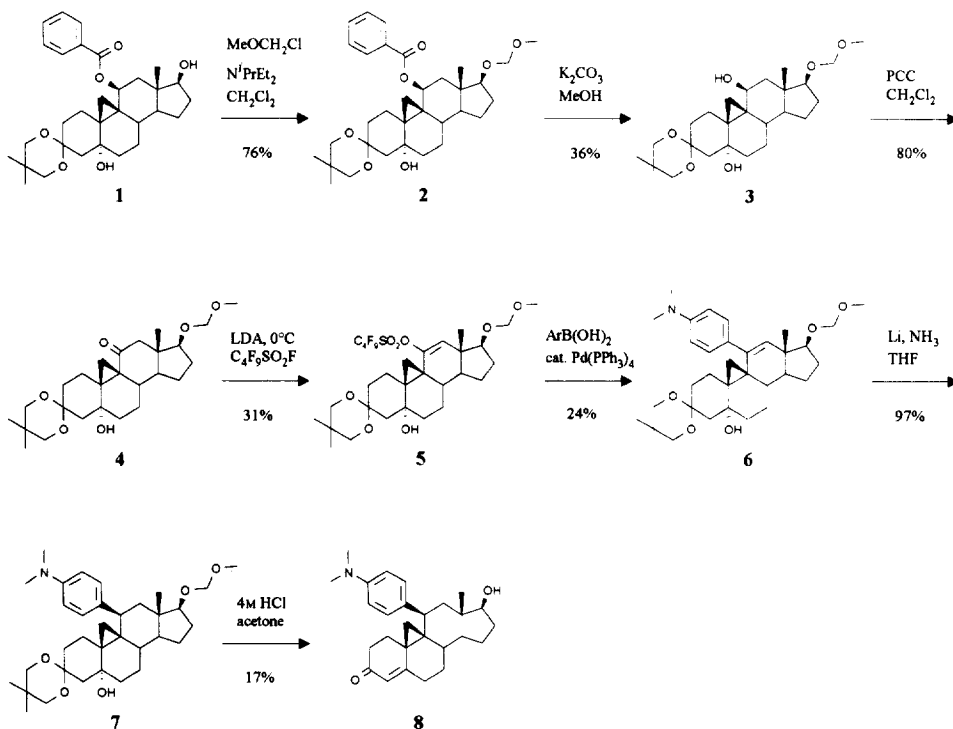


Fig. 1. — Relative binding affinities (RBA) of 11 β -aryl steroids to the PR.
(Rabbit uterus, incubation times 2 h and 24 h, 6°C, progesterone = 100).

The question arises whether an unbridged 11 β -aryl steroid of the androstene series possessing C-19 would still be able to bind to the PR. Herein we report synthetic routes to this sterically congested compound class represented by 9 β ,19-cyclo derivatives and the corresponding 10 β -methyl analogues. Receptor data are given and discussed in comparison to known 11 β -aryl steroids.

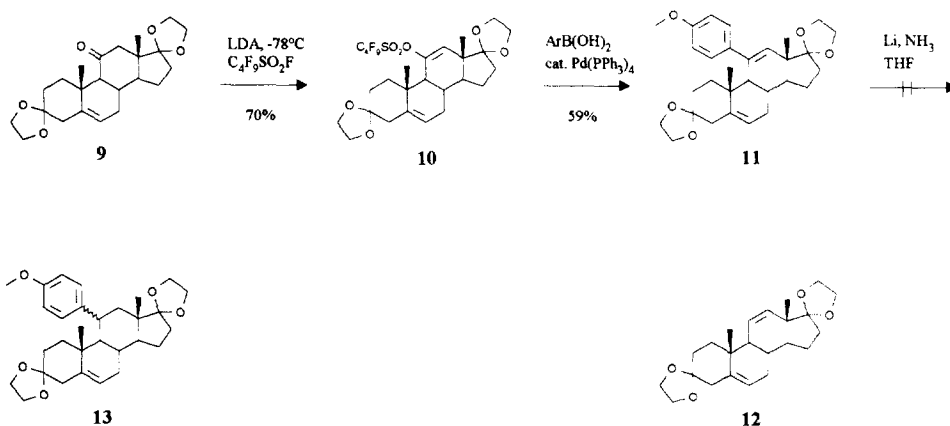
RESULTS AND DISCUSSION

To put compatibility of C-19 with 11 β -aryl to the test, we envisaged the synthesis of a 9 β ,19-cycloandrostene derivative. In this case, the steric demand of C-19 would be restricted, hopefully allowing for an 11 β -phenyl to be established. Known compound **1**⁸ proved to be a suitable starting material (Scheme 1). After having protected 17-hydroxy, benzoate hydrolysis of **2** under various conditions afforded only a moderate yield of 11-alcohol **3** and a variety of products resulting from an intermediate cyclopropylmethyl cation.⁹ Reductive benzoate cleavage with DIBAL and LiAlH₄ gave comparable or lower yields of **3**. Oxidation of **3** to 11-ketone **4** went smoothly with pyridinium chlorochromate (PCC). Previously, we had experienced with steroidal ketones of different series that conversion into enol perfluoroalkylsulfonates is inhibited by the presence of free hydroxy groups in the molecule.¹⁰ However, all attempts to protect 5 α -OH in compound **4** failed as it is sterically congested and prone to rearrangements. Under the best conditions found for the free 5 α -hydroxy-11-ketone **4**, enol nonaflate **5** was obtained in 31% yield. Suzuki cross-coupling¹¹ of **5** with [4-(dimethylamino)phenyl]boronic acid was dominated by reduction of the enol nonaflate to olefin **27**⁹ (61%). Reduction of the styrene double bond in **6** using Birch conditions proceeded almost quantitatively without affecting the three membered ring. 11 β -Aryl derivative **7** was obtained exclusively. Due to the acid sensitivity of the cyclopropane moiety hydrolysis of the protecting groups yielded only 17% target compound **8**.



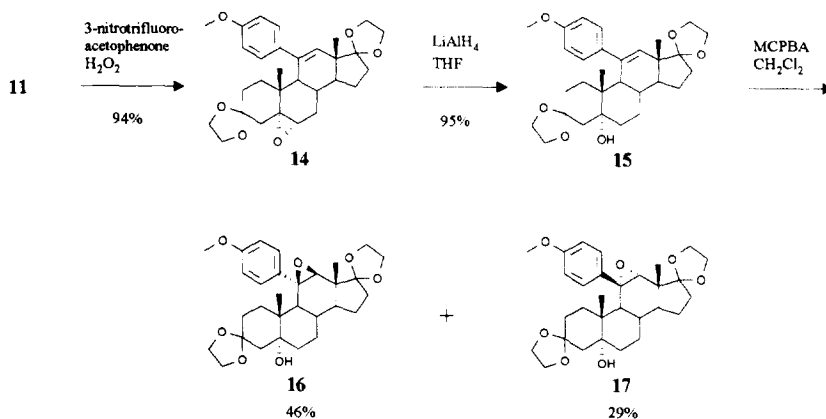
Scheme 1.

The above aryl introduction protocol appeared to be suitable for the 10 β -methyl series as well. Attempts to convert known 11-ketone **9**¹² into the thermodynamically controlled enol triflate or nonaflate resulted in yields below 10%, while the kinetically controlled enol nonaflate **10** was obtained in reasonable yield. To suppress simple reduction of **10**, a tenfold excess of (4-methoxyphenyl)boronic acid had to be employed in the cross-coupling step. Using only 1.3 equivalents boronic acid, after 19 h at reflux the major product isolated was compound **12** (43%), along with 48% starting material **10** and 6% of the desired product **11**. Reduction of the 11-double bond in **11** was effected neither by dissolved metal in liquid ammonia nor by hydrogenation.



Scheme 2.

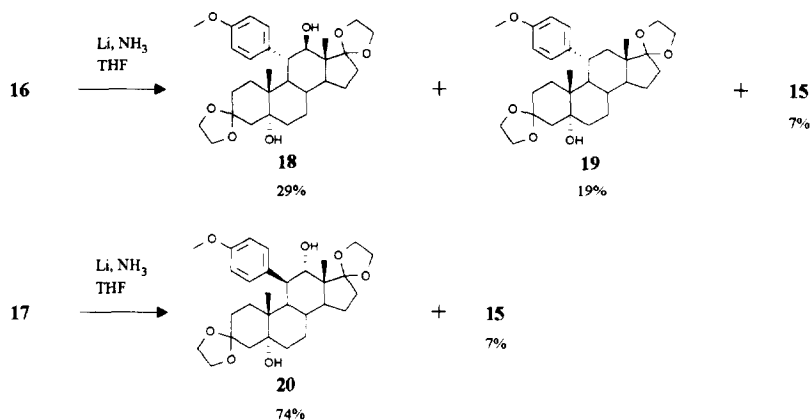
In order to disencumber the steric constraint at C-11, we decided to prepare an 11,12-epoxide. The 5-double bond was protected by regio- and stereoselective α -epoxidation followed by reduction to 5 α -hydroxy derivative **15**. Oxidation of Δ^{11} with *m*-chloroperoxybenzoic acid (MCPBA) proceeded slowly yielding a 3:2 mixture of β - and α -epoxides **16** and **17**.



Scheme 3.

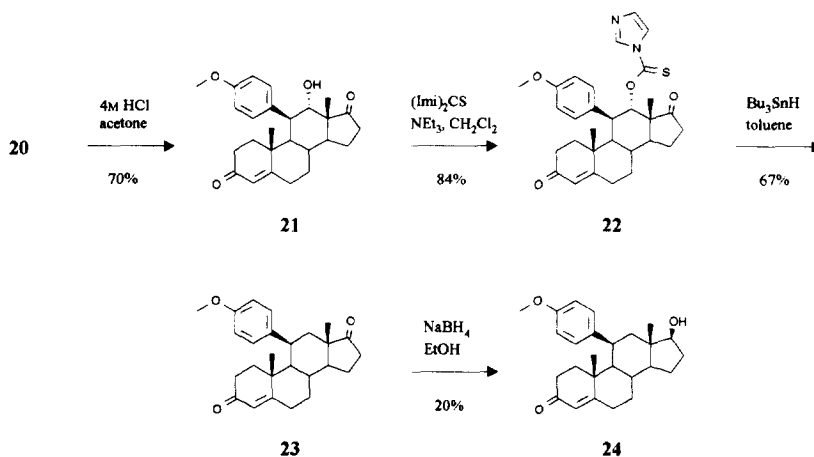
Applying Birch conditions to β -epoxide **16** gave benzyl reduction product **18**, deoxygenation product **19** and a minor amount of olefin **15**, which had probably been formed by elimination of water from **18** (Scheme 4). Interestingly, the reduction took place with complete retention of stereochemistry at C-11. Reacting α -epoxide

17 under the same conditions furnished 11 β -arylndrostane **20** in good yield. In this case, no deoxygenation was observed. Olefin **15** was the only by-product found. Again, stereochemistry at C-11 was retained.



Scheme 4.

To obtain a substitution pattern relevant for the PR assay, we had to remove the 12 α -hydroxy function of **20**. This was effected after deprotection of both carbonyl groups by conversion of **21** into the 1*H*-imidazole-1-carbothioate *O*-ester **22** and successive radical deoxygenation (Scheme 5). Due to steric hindrance the formation of **22** proceeded very slowly and required the presence of a base. Boranate reduction of **23** to 11 β -arylttestosterone **24** displayed only low 3,17-selectivity.



Scheme 5.

The constitution of **24** was confirmed by X-ray crystal structure determination (Figure 2 and experimental section). As expected, the double 1,3-diaxial relationship between 11 β -aryl and both C-18 and C-19 causes a significant distortion of the steroid ring system. The phenyl substituent and the methyl groups attempt to escape from steric pressure by twisting out of their axial positions. This is also evident in ¹H NMR in CDCl₃, where the phenyl shielding effect on H-18 is decreased (δ 0.77) compared to the analogous 4,9-dien-

3-one **29** (δ 0.44). 10 β -Methyl is even less shielded (δ 0.99). The three bulky β -substituents force the tetracyclic steroid system to adopt a β -convex conformation.

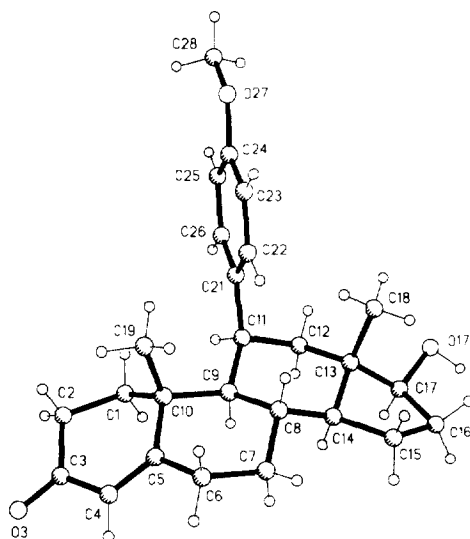
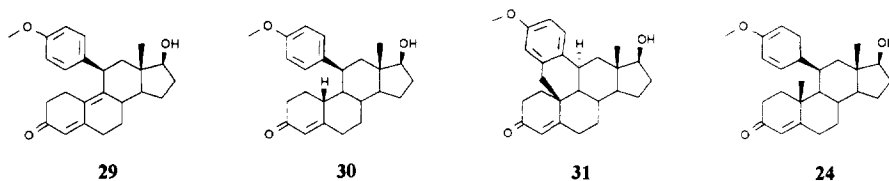


Fig. 2. — X-ray crystal structure of **24**.

Relative binding affinities (RBA) of the two new androstenes **24** and **8** to the PR are compared to the RBAs of secondary 17-alcohols of known antiprogestational series in Table 1. Due to the absence of a 17 α -substituent binding affinities of derivatives **29** - **31** are generally lower than those of the 17 α -propynyl analogues shown in Figure 1. Whereas 4,9-dien-3-one **29**, 10 β -H-compound **30**, and bridged derivative **31** display comparable RBAs, changing to 10 β -methyl practically abolishes PR binding.

Table 1. — Relative Binding Affinities (RBA) of 11 β -Aryl Steroids. (Rabbit uterus, incubation times 2 h and 24 h, 6°C, progesterone =100).

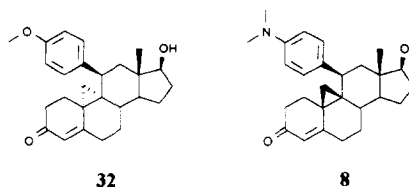


Compound	29	30	31	24
RBA (2 h)	4	5	1	< 0.1
RBA (24 h)	9	10	3	< 0.1

In the 9,19-cycloandrosterone series, stereochemistry of C-19 has a critical influence on binding affinity: while 9,10 α -methylene derivative **32**¹³ still binds fairly good to the PR, 9,10 β -methylene compound **8** is almost devoid of PR affinity (Table 2). Although compounds **32** and **8** have different aryl substituents, the RBAs observed correlate directly to the antiprogestational quality of the steroid system. Dimethylamino is known to be an equally or even more potent structural element of antiprogestins compared to methoxy.¹

Table 2. — Relative Binding Affinities (RBA) of 11 β -Aryl-9,10-methylene Steroids. (Rabbit uterus, incubation time 2 h, 6°C, progesterone =100).

Compound	32	8
RBA (2 h)	13	0.2



The low affinity of systems with 11 β -aryl substituents linked to position 18 such as ZK 135 617 (see Figure 1) can be explained reasonably in terms of an unfavourable orientation of the phenyl ring plane as all other structural features of the steroid system correspond quite well to those of the active analogue **29** (Figure 3). Using semiempirical AM1 calculations,¹⁴ the dihedral angles ϕ (C-9-C-11-C-21-C-22, according to the atom labelling scheme in Figure 2) have been calculated to be 21° in 4,9-dien-3-one **29** but 88° in bridged structure ZK 135 617, respectively.

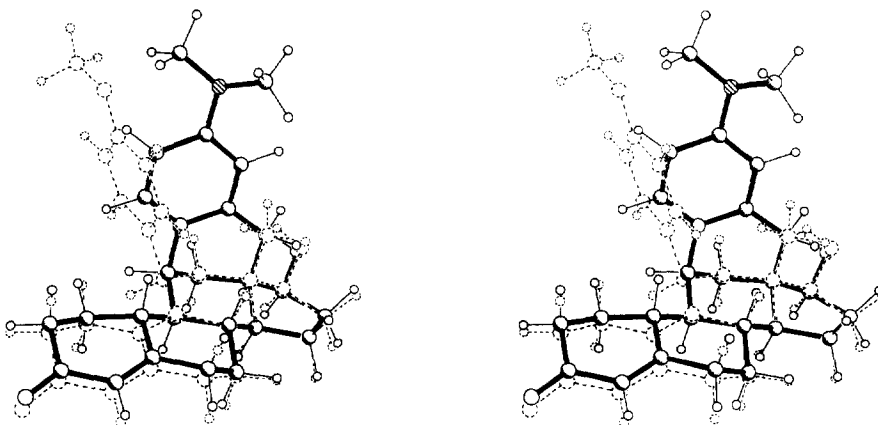


Fig. 3. — Stereoscopic representation of the superposition of optimized **29** (dashed lines) and bridged 17 α -H analogue of ZK 135 617.

Can we understand the low PR affinity of the new 11 β -aryl androstrenes in similar terms? In order to get an idea about the energies required to adopt a phenyl conformation similar to that in **29**, we calculated 10 β -methyl-11 β -aryl compound **24**. A comparison of the AM1 minimum structures **29** and **24**, again, reveals a difference in the phenyl torsions which is, however, less pronounced compared to the bridged derivative. The respective dihedral angle ϕ in **24** has been calculated to be 44°. Twisting the phenyl ring of **24** back into the putatively bioactive orientation of 21° represented by **29**, surprisingly, requires less than 1 kcal/mol which,

therefore, cannot explain the weak affinity of **24**. However, as a consequence of the steric interaction between the 10 β -methyl group and the 11 β -aryl moiety, ring A of **24** is bent downwards relative to its corresponding moiety in **29** when using C-7, C-11 and O-17 as anchor positions, as shown in Figure 4. This effect is already present in the minimum structure but is even more pronounced in the slightly distorted conformation. Following the assumption that the two polar groups at C-3 and C-17 and the phenyl planes ought to fit at the same time to provide a tight binding to the receptor site, the misplacement of the carbonyl function in **24** has to be made responsible for low affinity.

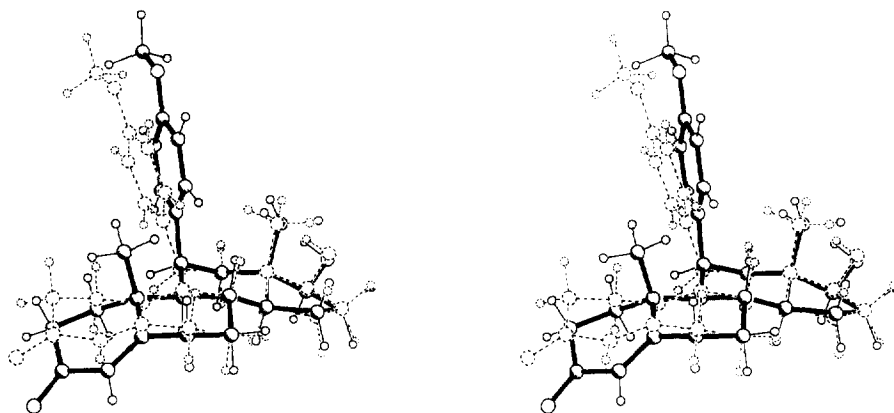


Fig. 4. — Stereoscopic representation of the superposition of optimized **29** (dashed lines) and **24** in the putatively bioactive aryl conformation.

For 9 β ,19-cyclo compound **8**, the β -cyclopropane moiety gives rise to an even more pronounced bending of the A ring in the low energy conformations. According to Figure 5, the overall shape of the steroid system is detrimental to PR binding.

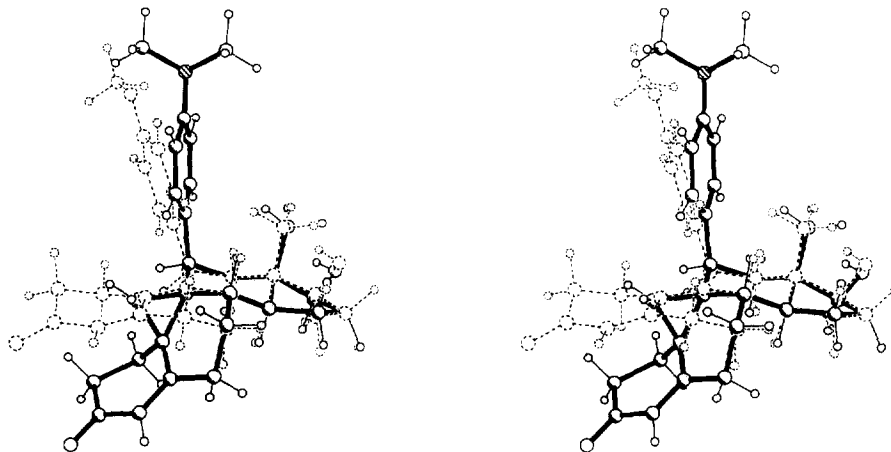


Fig. 5. — Stereoscopic representation of the superposition of optimized **29** (dashed lines) and **8**.

In contrast, 9 α ,19-cyclo derivative **32** allows for an appropriate superposition with structure **29** as shown in Figure 6, revealing an inverted conformation of ring A in the global minimum structure. The dihedral angle ϕ of the aryl moiety is calculated to be 9 $^\circ$ for compound **32**. According to our calculations, the energy needed to adopt the putatively bioactive orientation of 21 $^\circ$ is 0.4 kcal/mol, only.

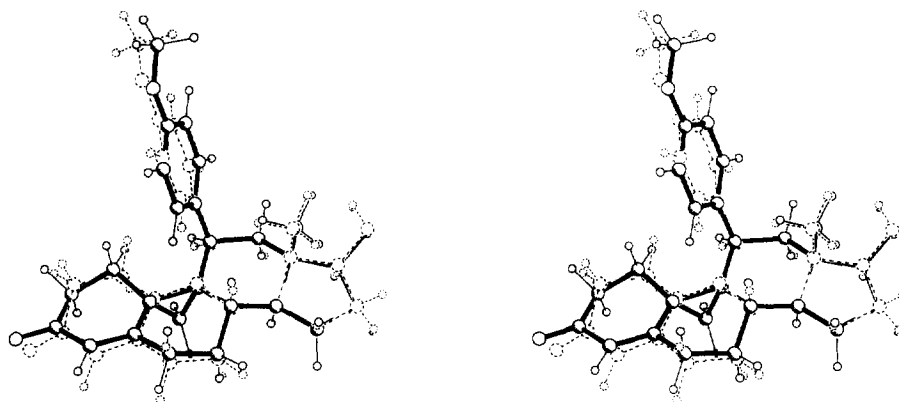


Fig. 6. — Stereoscopic representation of the superposition of optimized **29** (dashed lines) and **32**.

CONCLUSION

In conclusion, we have shown that 11 β -arylandrostenes are synthetically accessible. While the preparation of 9 β ,19-cyclo compound **8** proceeded in a straightforward fashion, establishing the desired stereochemistry at C-11 in 11-arylandrosta-5,11-diene **11** proved to be a problem requiring an unconventional approach. Both new compounds, **8** and **24** displayed very weak PR affinity. In either case, interaction of C-19 with the 11 β -aryl moiety causes distortions of the steroid system accounting for the observed effects.

EXPERIMENTAL SECTION

Spectral data were obtained as follows: ^1H and ^{13}C 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. Column chromatography was carried out on Merck silica gel 60, 70-230 mesh, using ethyl acetate/hexane as eluent. Reactions were run under nitrogen atmosphere. Solvents were reagent grade and dried prior to use. Boronic acids were prepared according to the literature procedure.¹⁵ 2,2,2-Trifluoro-1-(3-nitrophenyl)ethanone was prepared by nitration of 2,2,2-trifluoro-1-phenylethanone.¹⁶ All other reagents were purchased from commercial suppliers and were used as received.

11 β -(Benzoyloxy)-5-hydroxy-17 β -(methoxymethoxy)-9,19-cyclo-5 α ,9 β -androstan-3-one cyclic 2,2-dimethyl-1,3-propanediyl acetal (2): 11 β -(Benzoyloxy)-5,17 β -dihydroxy-9,19-cyclo-5 α ,9 β -androstan-3-one cyclic 2,2-dimethyl-1,3-propanediyl acetal **1** (9.09 g, 17.8 mmol) was dissolved in dichloromethane (90 ml), treated with ethyldiisopropylamine (9.3 ml, 53.4 mmol, 3 equiv.) and chloromethyl methyl ether (3.94 ml, 53.4 mmol, 3 equiv.), and stirred at ambient temperature for 5 h. The reaction mixture was poured into ice/water and the organic layer was separated. The aqueous layer was extracted with dichloromethane, and the organic portions were combined, washed with water and with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give **2** (7.54 g, 76%): ¹H NMR (300 MHz, CDCl₃): δ 8.08 (d, *J*=8 Hz, 2H, aryl), 7.57 (dd, *J*=8 Hz and 8 Hz, 1H, aryl), 7.46 (dd, *J*=8 Hz and 8 Hz, 2H, aryl), 5.28 (m, 1H, H-11), 4.61 (d, *J*=6 Hz, 1H, MOM), 4.59 (d, *J*=6 Hz, 1H, MOM), 4.34 (d, *J*=1 Hz, 1H, 5-OH), 3.64 (dd, *J*=8 Hz and 8 Hz, 1H, H-17), 3.32 (s, 3H, MOM), 1.07 (s, 3H, ketal), 0.99 (s, 3H, ketal), 0.98 (s, 3H, H-18), 0.80 (d br, *J*=5 Hz, 1H, H-19), 0.43 (d br, *J*=5 Hz, 1H, H-19'); C₃₃H₄₆O₇ (554.7) calcd. C 71.45, H 8.36; found C 71.42, H 8.33%.

5,11 β -Dihydroxy-17 β -(methoxymethoxy)-9,19-cyclo-5 α ,9 β -androstan-3-one cyclic 2,2-dimethyl-1,3-propanediyl acetal (3): Benzoate **2** (6.58 g, 11.86 mmol) and K₂CO₃ (6.56 g, 47.44 mmol, 4 equiv.) were stirred overnight in methanol (330 ml) at 60°C. The reaction mixture was diluted with dichloromethane, washed with water and with brine, dried over Na₂SO₄, filtered, and evaporated. Column chromatography gave the following products in order of increasing polarity: 5-hydroxy-17 β -(methoxymethoxy)-9,19-cyclo-5 α ,9 β -androst-11-en-3-one cyclic 2,2-dimethyl-1,3-propanediyl acetal **27** (302 mg, 6%) {¹H NMR (300 MHz, CDCl₃): δ 6.07 (d, *J*=10 Hz, 1H, H-12), 5.19 (d, *J*=10 Hz, 1H, H-11), 4.68 (d, *J*=6 Hz, 1H, MOM), 4.66 (d, *J*=6 Hz, 1H, MOM), 4.47 (d, *J*=1 Hz, 1H, 5-OH), 3.69 (dd, *J*=8 Hz and 8 Hz, 1H, H-17), 3.38 (s, 3H, MOM), 0.99 (s, 3H, ketal), 0.97 (s, 3H, ketal), 0.89 (s, 3H, H-18), 0.68 (dd, *J*=5 Hz and 1.5 Hz, 1H, H-19), 0.48 (d, *J*=5 Hz, 1H, H-19'); C₂₆H₄₀O₅ (432.6) calcd. C 72.19, H 9.32; found C 72.05, H 9.31%}; 5-hydroxy-11 β -methoxy-17 β -(methoxymethoxy)-9,19-cyclo-5 α ,9 β -androstan-3-one cyclic 2,2-dimethyl-1,3-propanediyl acetal **26** (411 mg, 8%) {¹H NMR (300 MHz, CDCl₃): δ 4.64 (m, 2H, MOM), 4.26 (d, *J*=1 Hz, 1H, 5-OH), 3.58 (dd, *J*=8 Hz and 8 Hz, 1H, H-17), 3.38 (s, 3H, MOM), 3.30 (s, 3H, OMe), 3.08 (m, 1H, H-11), 0.99 (s, 3H, H-18), 0.99 (s, 3H, ketal), 0.96 (s, 3H, ketal), 0.41 (d, *J*=5 Hz, 1H, H-19); C₂₇H₄₄O₆ (464.7) calcd. C 69.79, H 9.55; found C 69.79, H 9.51%}; 5-hydroxy-11 α -methoxy-17 β -(methoxymethoxy)-9,19-cyclo-5 α ,9 β -androstan-3-one cyclic 2,2-dimethyl-1,3-propanediyl acetal **25** (980 mg, 19%) {¹H NMR (300 MHz, CDCl₃): δ 4.67 (m, 2H, MOM), 4.43 (d, *J*=1 Hz, 1H, 5-OH), 3.72 (dd, *J*=8 Hz and 8 Hz, 1H, H-17), 3.38 (s, 3H, MOM), 3.19 (s, 3H, OMe), 2.94 (dd br, *J*=5.5 Hz and 2.5 Hz, 1H, H-11), 0.99 (s, 3H, ketal), 0.96 (s, 3H, H-18), 0.89 (s, 3H, ketal), 0.56 (d, *J*=5 Hz, 1H, H-19), 0.45 (d br, *J*=5 Hz, 1H, H-19'); C₂₇H₄₄O₆ (464.7) calcd. C 69.79, H 9.55; found C 69.72, H 9.52%}; 5,19-dihydroxy-17 β -(methoxymethoxy)-5 α -androst-9(11)-en-3-one cyclic 2,2-dimethyl-1,3-propanediyl acetal **28** (322 mg, 6%) {¹H NMR (300 MHz, CDCl₃): δ 5.46 (m, 1H, H-11), 4.65 (d, *J*=6 Hz, 1H, MOM), 4.62 (d, *J*=6 Hz, 1H, MOM), 4.56 (d, *J*=1 Hz, 1H, 5-OH), 3.70 (d br, *J*=11 Hz, 1H, H-19), 3.62 (dd, *J*=8 Hz and 8 Hz, 1H, H-17), 3.47 (d, *J*=11 Hz, 1H, H-19), 3.36 (s, 3H, MOM), 0.99 (s, 3H, ketal), 0.92 (s, 3H, ketal), 0.73 (s, 3H, H-18); C₂₆H₄₂O₆ (450.6) calcd. C 69.30, H 9.39; found C 69.18, H 9.31%}; and the desired product **3** (1.91 g, 36%): mp 183.2°C (diisopropyl ether); [α]_D²⁵ = +3.4° (c=0.500, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 4.63 (s, 2H, MOM), 4.28 (d, *J*=2 Hz, 1H, 5-OH), 3.68 (s br, 1H, H-11), 3.58 (dd, *J*=8 Hz and 8 Hz, 1H, H-17), 3.37 (s, 3H, MOM), 1.06 (s, 3H, ketal), 0.97 (s, 3H, ketal), 0.97 (s, 3H, H-18), 0.81 (dd, *J*=5 Hz and 2 Hz, 1H, H-19), 0.37 (d, *J*=5 Hz, 1H, H-19'); C₂₆H₄₂O₆ (450.6) calcd. C 69.30, H 9.39; found C 69.08, H 8.94%.

5-Hydroxy-17 β -(methoxymethoxy)-9,19-cyclo-5 α ,9 β -androstan-3,11-dione cyclic 3-(2,2-dimethyl-1,3-propanediyl acetal) (4): 11 β -Alcohol **3** (1.80 g, 3.99 mmol) was stirred with PCC (1.29 g, 5.99 mmol, 1.5 equiv.) in dichloromethane (100 ml) at ambient temperature. After 1 h the slurry was filtered over silica gel and evaporated. Column chromatography afforded 11-ketone **4** (1.43 g, 80%): mp 123.8°C (diisopropyl ether); [α]_D²⁵ = +37.6° (c=0.500, CHCl₃); IR (KBr, cm⁻¹): ν 3500 (OH), 1668 (C=O); ¹H NMR (300 MHz, CDCl₃): δ 4.64 (d, *J*=6 Hz, 1H, MOM), 4.59 (d, *J*=6 Hz, 1H, MOM), 4.52 (d, *J*=1 Hz, 1H, 5-OH), 3.70 (dd, *J*=8 Hz and 8 Hz, 1H, H-17), 3.34 (s, 3H, MOM), 2.67 (d, *J*=14 Hz, 1H, H-12), 2.16 (d br, *J*=14 Hz, 1H, H-12'), 1.02 (s, 3H, ketal), 0.92 (s, 3H, ketal), 0.80 (s, 3H, H-18), 0.65 (d br, *J*=4 Hz, 1H, H-19); C₂₆H₄₀O₆ (448.6) calcd. C 69.61, H 8.99; found C 69.27, H 8.80%.

5-Hydroxy-17 β -(methoxymethoxy)-11-[(1,1,2,2,3,3,4,4,4-nonafluorobutyl)sulfonyl]oxy-9,19-cyclo-5 α ,9 β -androst-11-en-3-one cyclic 2,2-dimethyl-1,3-propanediyl acetal (5): To a solution of diisopropylamine (4.22 ml, 30.1 mmol, 10 equiv.) in THF (30 ml) was added butyl lithium (1.6 M in hexane, 18.4 ml, 9.8 equiv.) at 0°C. After 0.5 h stirring at that temperature, a solution of **4** (1.35 g, 3.01 mmol) in THF (30 ml) was added slowly. The reaction mixture was stirred at 0°C for 15 min, treated with 1,1,2,2,3,3,4,4,4-nonafluoro-1-butanefluoride (5.41 ml, 30.1 mmol, 10 equiv.) and allowed to warm to room temperature. After 6.5 h, water was carefully added at 0°C, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate, and the organic portions were combined, washed with

water and with brine, dried over Na_2SO_4 , filtered, and evaporated. Column chromatography of the residue furnished nonaflate **5** (680 mg, 31%): $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 6.25 (s, 1H, H-12), 4.65 (d, $J=6$ Hz, 1H, MOM), 4.61 (d, $J=6$ Hz, 1H, MOM), 4.56 (d, $J=1$ Hz, 1H, 5-OH), 3.73 (dd, $J=8$ Hz and 8 Hz, 1H, H-17), 3.37 (s, 3H, MOM), 1.10 (d, $J=5.5$ Hz, 1H, H-19), 1.04 (s, 3H, ketal), 0.98 (s, 3H, ketal), 0.93 (s, 3H, H-18), 0.86 (d br, $J=5.5$ Hz, 1H, H-19); $\text{C}_{30}\text{H}_{36}\text{F}_9\text{O}_8\text{S}$ (730.7) calcd. C 49.31, H 5.38, F 23.40, S 4.39; found C 49.38, H 5.30, F 23.42, S 4.36%.

11-[4-(Dimethylamino)phenyl]-5-hydroxy-17 β -(methoxymethoxy)-9,19-cyclo-5 α ,9 β -androst-11-en-3-one cyclic 2,2-dimethyl-1,3-propanediyl acetal (6): Enol nonaflate **5** (668 mg, 0.91 mmol) was heated at reflux with lithium chloride (78 mg, 1.83 mmol, 2 equiv.), [4-(dimethylamino)phenyl]boronic acid (194 mg, 1.19 mmol, 1.3 equiv.), tetrakis(triphenylphosphine)palladium(0) (32 mg, 0.027 mmol, 0.03 equiv.), and aqueous Na_2CO_3 solution (2 M, 1.21 ml) in toluene (20 ml) and ethanol (10 ml) for 4 h. The reaction mixture was filtered over Celite[®], the solid was rinsed with ethyl acetate, and the filtrate was washed with water. The aqueous layer was extracted with ethyl acetate, and the organic portions were combined, washed with water and with brine, dried over Na_2SO_4 , filtered, and evaporated. Column chromatography of the residue afforded the following two products in the order of increasing polarity: 5-hydroxy-17 β -(methoxymethoxy)-9,19-cyclo-5 α ,9 β -androst-11-en-3-one cyclic 2,2-dimethyl-1,3-propanediyl acetal **27** (240 mg, 61%) and 11-arylsteroid **6** (121 mg, 24%): MS (FAB, m/z): 552 (23%, $[\text{MH}]^+$), 551 (100%, M^+), 534 (56%, $[\text{MH}-\text{H}_2\text{O}]^+$); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 6.92 (d, $J=9$ Hz, 2H, aryl), 6.62 (d, $J=9$ Hz, 2H, aryl), 5.83 (s, 1H, H-12), 4.65 (s, 2H, MOM), 4.37 (s, 1H, 5-OH), 3.80 (dd, $J=8$ Hz and 8 Hz, 1H, H-17), 3.34 (s, 3H, MOM), 2.93 (s, 6H, NMe_2), 0.96 (s, 3H, ketal), 0.90 (s, 3H, ketal), 0.87 (s, 3H, H-18), 0.71 (m, 1H, H-19), 0.67 (m, 1H, H-19); $\text{C}_{34}\text{H}_{49}\text{NO}_5$ (551.8) calcd. C 74.01, H 8.95, N 2.54; found C 73.95, H 8.78, N 2.49%.

11 β -[4-(Dimethylamino)phenyl]-5-hydroxy-17 β -(methoxymethoxy)-9,19-cyclo-5 α ,9 β -androst-3-one cyclic 2,2-dimethyl-1,3-propanediyl acetal (7): A solution of **6** (115 mg, 0.208 mmol) in THF (3 ml) was added to liquid ammonia (approx. 3 ml) at -78°C . Then, lithium wire (6 mg, 0.864 mmol, 4 equiv.) was added. After 3 h at -78°C the mixture was cautiously treated with water until decoloration occurred, the ammonia was evaporated, the residue was diluted with water, and the aqueous layer was extracted with ethyl acetate. The organic portions were combined, washed with water and with brine, dried over Na_2SO_4 , filtered, and evaporated. Column chromatography gave 11 β -arylsteroid **7** (112 mg, 97%): $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.31 (d, $J=9$ Hz, 2H, aryl), 6.71 (d, $J=9$ Hz, 2H, aryl), 4.63 (s, 2H, MOM), 4.35 (s, 1H, 5-OH), 3.65 (dd, $J=8$ Hz and 8 Hz, 1H, H-17), 3.36 (s, 3H, MOM), 2.92 (s, 6H, NMe_2), 2.87 (d br, $J=4.5$ Hz, 1H, H-11), 0.99 (s, 3H, ketal), 0.97 (s, 3H, ketal), 0.35 (s, 3H, H-18), 0.23 (d, $J=5$ Hz, 1H, H-19); MS (CI, m/z): 554 (100%, $[\text{MH}]^+$), 536 (41%, $[\text{MH}-\text{H}_2\text{O}]^+$); $\text{C}_{34}\text{H}_{51}\text{NO}_5$ (553.8) calcd. C 73.74, H 9.28, N 2.53; found C 73.73, H 9.20, N 2.51%.

11 β -[4-(Dimethylamino)phenyl]-17 β -hydroxy-9,19-cyclo-9 β -androst-4-en-3-one (8): Compound **7** (105 mg, 0.190 mmol) was deprotected by stirring with aqueous HCl (4 M, 0.5 ml) in acetone (4 ml) for 4 h at 40°C . The reaction mixture was poured into saturated NaHCO_3 solution, the aqueous layer was extracted with ethyl acetate, the organic portions were combined, washed with water and with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by repeated column chromatography to yield **8** (13 mg, 17%): IR (KBr, cm^{-1}): ν 3420 (OH), 1660 (C=O); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.32 (m, 2H, aryl), 6.78 (m, 2H, aryl), 5.94 (s, 1H, H-4), 3.69 (dd, $J=8$ Hz and 7 Hz, 1H, H-17), 3.03 (d, $J=5.5$ Hz, 1H, H-11), 2.94 (s, 6H, NMe_2), 0.96 (d, $J=5$ Hz, 1H, H-19), 0.38 (s, 3H, H-18), 0.38 (d, $J=5$ Hz, 1H, H-19); MS (EI, m/z): 405 (100%, M^+), 283 (54%), 270 (62%); $\text{C}_{27}\text{H}_{35}\text{NO}_2$ (405.6) calcd. C 79.96, H 8.70, N 3.40; found C 79.97, H 8.69, N 3.35%.

11-[[[(1,1,2,2,3,3,4,4,4-Nonafluorobutyl)sulfonyl]oxy]androst-5,11-diene-3,17-dione cyclic bis(1,2-ethanediyl acetal) (10): To a solution of diisopropylamine (44.28 ml, 311 mmol, 4.1 equiv.) in THF (1.4 l) was added butyl lithium (1.6 M in hexane, 194.5 ml, 4.1 equiv.) at -78°C . After 0.5 h stirring at that temperature, a solution of androst-5-ene-3,11,17-trione cyclic 3,17-bis(1,2-ethanediyl acetal) **9** (29.6 g, 76.29 mmol) in THF (300 ml) was slowly added. The reaction mixture was stirred at -78°C for 0.5 h, treated with 1,1,2,2,3,3,4,4,4-nonafluoro-1-butanefluorobutyl sulfonate (40.99 ml, 228.6 mmol, 3 equiv.) and allowed to warm to room temperature overnight. The reaction mixture was poured into saturated NH_4Cl solution, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate, and the organic portions were combined, washed with water and with brine, dried over Na_2SO_4 , filtered, and evaporated. Column chromatography of the residue furnished nonaflate **10** (35.90 g, 70%): mp 127.1°C (diisopropyl ether); $[\alpha]_D^{25} = -30.6^\circ$ ($c=0.500$, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 6.05 (s, 1H, H-12), 5.51 (d br, $J=5.5$ Hz, 1H, H-6), 4.02-3.81 (m, 8H, ketal), 2.39 (d, $J=7$ Hz, 1H, H-9), 1.16 (s, 3H, H-19), 1.01 (s, 3H, H-18); MS (CI, m/z): 688 (100%, $[\text{MH}+\text{NH}_3]^+$), 671 (27%, $[\text{MH}]^+$); $\text{C}_{27}\text{H}_{31}\text{F}_9\text{O}_7\text{S}$ (670.6) calcd. C 48.36, H 4.66, F 25.50, S 4.78; found C 48.88, H 4.65, F 26.21, S 4.95%.

11-(4-Methoxyphenyl)androsta-5,11-diene-3,17-dione cyclic bis(1,2-ethanediyl acetal) (11): Enol nonaflate 10 (35.68 g, 53.2 mmol) was heated at reflux with lithium chloride (4.51 g, 106.4 mmol, 2 equiv.), (4-methoxyphenyl)boronic acid (80.84 g, 532 mmol, 10 equiv.), tetrakis(triphenylphosphine)palladium(0) (2.46 g, 2.13 mmol, 0.04 equiv.), and aqueous Na₂CO₃ solution (2 M, 200 ml) in toluene (800 ml) and ethanol (400 ml) for 48 h. The reaction mixture was poured into saturated NaHCO₃ solution, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate, and the organic portions were combined, washed with brine, dried over Na₂SO₄, filtered, and evaporated. Column chromatography of the residue afforded 11-arylsteroid 10 (15.02 g, 59%): mp 177.2°C (diisopropyl ether); [α]_D²⁵ = +44.0° (c=0.500, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.10 (d br, *J*=9 Hz, 1H, aryl), 7.06 (d br, *J*=9 Hz, 1H, aryl), 6.81 (d br, *J*=9 Hz, 1H, aryl), 6.74 (d br, *J*=9 Hz, 1H, aryl), 5.78 (d, *J*=1.5 Hz, 1H, H-12), 5.52 (d br, *J*=5.5 Hz, 1H, H-6), 4.01-3.76 (m, 8H, ketal), 3.80 (s, 3H, OMe), 2.56 (d br, *J*=6 Hz, 1H, H-9), 1.05 (s, 3H, H-19), 1.05 (s, 3H, H-18); C₃₀H₃₈O₅ (478.6) calcd. C 75.28, H 8.00; found C 75.28, H 7.98%.

11-(4-Methoxyphenyl)-5,6 α -epoxy-5 α -androst-11-ene-3,17-dione cyclic bis(1,2-ethanediyl acetal) (14): Compound 11 (15 g, 31.3 mmol) was stirred with 2,2,2-trifluoro-1-(3-nitrophenyl)ethanone (3.43 g, 15.67 mmol, 0.5 equiv.), aqueous H₂O₂ (30%, 12.8 ml), and saturated NaHCO₃ solution (14 ml) in dichloromethane (300 ml) for 6 d at ambient temperature. The mixture was washed with saturated Na₂S₂O₃ solution to destroy excess of H₂O₂ and the aqueous layer was extracted with dichloromethane. The organic fractions were washed with saturated NaHCO₃ solution and with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by column chromatography gave α -epoxide 14 (14.51 g, 94%): mp 180.4°C (diisopropyl ether); [α]_D²⁵ = +53.2° (c=0.520, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.13 (m, 1H, aryl), 7.01 (m, 1H, aryl), 6.77 (m, 2H, aryl), 5.78 (d, *J*=2 Hz, 1H, H-12), 4.00-3.73 (m, 8H, ketal), 3.80 (s, 3H, OMe), 3.00 (d, *J*=5 Hz, 1H, H-6), 2.77 (dd, *J*=10 Hz and 2 Hz, 1H, H-9), 1.11 (s, 3H, H-19), 1.00 (s, 3H, H-18); C₃₀H₃₈O₆ (494.6) calcd. C 72.85, H 7.74; found C 72.69, H 7.65%.

5-Hydroxy-11-(4-methoxyphenyl)-5 α -androst-11-ene-3,17-dione cyclic bis(1,2-ethanediyl acetal) (15): Epoxide 14 (14.3 g, 28.9 mmol) was reduced by stirring with LiAlH₄ (1.10 g, 28.9 mmol, 1 equiv.) in THF (300 ml) for 1 h at room temperature. At 0°C, saturated NH₄Cl solution was cautiously added until the entire alanate had reacted. The slurry was filtered over Celite[®], and rinsed thoroughly with ethyl acetate. After evaporation of the filtrate, the residue was purified by recrystallization from diisopropyl ether to yield 15 (13.63 g, 95%): mp 201.6°C; [α]_D²⁵ = +101.3° (c=0.505, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.16 (dd br, *J*=9 Hz and 2 Hz, 1H, aryl), 7.00 (dd br, *J*=9 Hz and 2 Hz, 1H, aryl), 6.78 (dd br, *J*=9 Hz and 2 Hz, 1H, aryl), 6.75 (dd br, *J*=9 Hz and 2 Hz, 1H, aryl), 5.69 (d, *J*=2 Hz, 1H, H-12), 4.26 (s, 1H, 5-OH), 3.98-3.73 (m, 8H, ketal), 3.79 (s, 3H, OMe), 3.18 (dd br, *J*=10 Hz and 2 Hz, 1H, H-9), 1.02 (s, 3H, H-19), 1.00 (s, 3H, H-18); C₃₀H₄₀O₆ (496.6) calcd. C 72.55, H 8.12; found C 72.06, H 8.11%.

5-Hydroxy-11 α -(4-methoxyphenyl)-11 β ,12 β -epoxy-5 α -androstane-3,17-dione cyclic bis(1,2-ethanediyl acetal) (16) and 5-hydroxy-11 β -(4-methoxyphenyl)-11 α ,12 α -epoxy-5 α -androstane-3,17-dione cyclic bis(1,2-ethanediyl acetal) (17): Compound 15 (11.7 g, 23.6 mmol) was reacted with MCPBA (50%, 32.5 g, 94.2 mmol, 4 equiv.) in dichloromethane (235 ml) for 1 d at ambient temperature. The reaction mixture was treated with aqueous NaOH (2 M, 100 ml), diluted with water, and extracted with dichloromethane. The organic portions were combined, washed with brine, dried over Na₂SO₄, filtered, and evaporated in vacuo. Column chromatography afforded the following products in order of increasing polarity: β -epoxide 16 (5.59 g, 46%) [mp 153.3°C (diisopropyl ether); [α]_D²⁵ = +29.9° (c=0.515, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.38 (d br, *J*=9 Hz, 1H, aryl), 7.24 (d br, *J*=9 Hz, 1H, aryl), 6.83 (d br, *J*=9 Hz, 1H, aryl), 6.80 (d br, *J*=9 Hz, 1H, aryl), 4.19 (s, 1H, 5-OH), 3.99-3.76 (m, 8H, ketal), 3.79 (s, 3H, OMe), 2.93 (d, *J*=10 Hz, 1H, H-9), 2.53 (s, 1H, H-12), 1.21 (s, 3H, H-19), 1.00 (s, 3H, H-18); MS (CI, *m/z*): 530 (8%, [MH+NH₃]⁺), 513 (100%, [MH]⁺), 495 (36%, [MH-H₂O]⁺); C₃₀H₄₀O₇ (512.6) calcd. C 70.29, H 7.86; found C 69.99, H 7.74%]; and α -epoxide 17 (3.50 g, 29%): mp 174.4°C (diisopropyl ether); [α]_D²⁵ = +9.5° (c=0.515, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.41 (dd br, *J*=9 Hz and 2 Hz, 1H, aryl), 7.09 (dd br, *J*=9 Hz and 2 Hz, 1H, aryl), 6.80 (dd br, *J*=9 Hz and 2 Hz, 1H, aryl), 6.75 (dd br, *J*=9 Hz and 2 Hz, 1H, aryl), 4.19 (s, 1H, 5-OH), 4.00-3.75 (m, 8H, ketal), 3.79 (s, 3H, OMe), 2.80 (s, 1H, H-12), 2.68 (d, *J*=10 Hz, 1H, H-9), 1.12 (s, 3H, H-19), 1.06 (s, 3H, H-18); MS (CI, *m/z*): 530 (17%, [MH+NH₃]⁺), 513 (100%, [MH]⁺), 495 (33%, [MH-H₂O]⁺), 477 (14%, [MH-2H₂O]⁺); C₃₀H₄₀O₇ (512.6) calcd. C 70.29, H 7.86; found C 70.19, H 7.87%.

5-Hydroxy-11 α -(4-methoxyphenyl)-5 α -androstane-3,17-dione cyclic bis(1,2-ethanediyl acetal) (19) and 5,12 β -dihydroxy-11 α -(4-methoxyphenyl)-5 α -androstane-3,17-dione cyclic bis(1,2-ethanediyl acetal) (18): A solution of 16 (1.25 g, 2.44 mmol) in THF (25 ml) was added to liquid ammonia (approx. 25 ml) at -78°C. Then, lithium wire (68 mg, 9.75 mmol, 4 equiv.) was added. After 2 h at -78°C the mixture was cautiously treated with water until decolouration occurred, the ammonia was evaporated, the residue was diluted with water, and the aqueous layer was extracted with

ethyl acetate. The organic portions were combined, washed with brine, dried over Na_2SO_4 , filtered, and evaporated. Column chromatography yielded the following products in order of increasing polarity: Δ^{11} -derivative **15** (82 mg, 7%), deoxygenation product **19** (231 mg, 19%) ($^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.27 (dd br, $J=9$ Hz and 2 Hz, 1H, aryl), 6.95 (dd br, $J=9$ Hz and 2 Hz, 1H, aryl), 6.85 (dd br, $J=9$ Hz and 2 Hz, 1H, aryl), 6.73 (dd br, $J=9$ Hz and 2 Hz, 1H, aryl), 4.01 (s, 1H, 5-OH), 4.00-3.67 (m, 8H, ketal), 3.78 (s, 3H, OMe), 2.74 (ddd, $J=12$ Hz and 12 Hz and 5 Hz, 1H, H-11), 2.18 (dd br, $J=12$ Hz and 9 Hz, 1H, H-9), 1.06 (s, 3H, H-19), 0.95 (s, 3H, H-18); MS (CI, m/z): 499 (19%, $[\text{MH}]^+$), 481 (100%, $[\text{MH}-\text{H}_2\text{O}]^+$); $\text{C}_{30}\text{H}_{42}\text{O}_6$ (498.7) calcd. C 72.26, H 8.49; found C 72.30, H 8.49%; and 12 β -alcohol **18** (364 mg, 29%): $[\alpha]_D^{25} = +0.8^\circ$ ($c=5.075$, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.34 (dd br, $J=9$ Hz and 2 Hz, 1H, aryl), 7.02 (dd br, $J=9$ Hz and 2 Hz, 1H, aryl), 6.92 (dd br, $J=9$ Hz and 2 Hz, 1H, aryl), 6.76 (dd br, $J=9$ Hz and 2 Hz, 1H, aryl), 4.03 (s, 1H, 5-OH), 3.96-3.76 (m, 8H, ketal), 3.79 (s, 3H, OMe), 3.72 (dd, $J=9.5$ Hz and 2 Hz, 1H, H-12), 2.59 (dd, $J=11$ Hz and 9.5 Hz, 1H, H-11), 2.26 (dd, $J=11$ Hz and 10 Hz, 1H, H-9), 1.06 (s, 3H, H-19), 1.00 (s, 3H, H-18); MS (CI, m/z): 515 (4%, $[\text{MH}]^+$), 497 (78%, $[\text{MH}-\text{H}_2\text{O}]^+$), 479 (100%, $[\text{MH}-2\text{H}_2\text{O}]^+$); $\text{C}_{30}\text{H}_{42}\text{O}_7$ (514.7) calcd. C 70.01, H 8.23; found C 69.85, H 8.23%.

5,12 α -Dihydroxy-11 β -(4-methoxyphenyl)-5 α -androstane-3,17-dione cyclic bis(1,2-ethanediyl acetal) (20): Reduction of α -epoxide **17** (3.45 g, 6.73 mmol) as described for β -epoxide **16** and column chromatography gave the following products in the order of increasing polarity: Δ^{11} -derivative **15** (225 mg, 7%) and 12 α -alcohol **20** (2.55 g, 74%): $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.32 (m, 2H, aryl), 6.72 (d br, $J=9$ Hz, 2H, aryl), 4.09 (s, 1H, 5-OH), 4.01-3.80 (m, 8H, ketal), 3.88 (m 1H, H-12), 3.78 (s, 3H, OMe), 3.12 (d br, $J=5.5$ Hz, 1H, H-11), 2.88 (dd, $J=12$ Hz and 5.5 Hz, 1H, H-9), 0.94 (s, 3H, H-19), 0.76 (s, 3H, H-18); MS (CI, m/z): 515 (22%, $[\text{MH}]^+$), 497 (72%, $[\text{MH}-\text{H}_2\text{O}]^+$), 479 (100%, $[\text{MH}-2\text{H}_2\text{O}]^+$); $\text{C}_{30}\text{H}_{42}\text{O}_7$ (514.7) calcd. C 70.01, H 8.23; found C 69.92, H 8.12%.

12 α -Hydroxy-11 β -(4-methoxyphenyl)androst-4-ene-3,17-dione (21): Compound **20** (2.28 g, 4.43 mmol) was deprotected by stirring with aqueous HCl (4 M, 2.2 ml) in acetone (45 ml) for 1 d at room temperature. The reaction mixture was poured into saturated NaHCO_3 solution, the aqueous layer was extracted with ethyl acetate, the organic portions were combined, washed with water and with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by column chromatography to yield **21** (1.27 g, 70%): $[\alpha]_D^{25} = +239.6^\circ$ ($c=0.505$, CHCl_3); IR (KBr, cm^{-1}): ν 3460 (OH), 1740 (C=O), 1665 (C=O); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.40 (m, 2H, aryl), 6.78 (d br, $J=9$ Hz, 2H, aryl), 5.69 (d, $J=1.5$ Hz, 1H, H-4), 4.03 (m, 1H, H-12), 3.80 (s, 3H, OMe), 3.38 (dd, $J=5$ Hz and 2 Hz, 1H, H-11), 0.99 (s, 3H, H-19), 0.84 (s, 3H, H-18); MS (EI, m/z): 408 (58%, M^+), 121 (100%); $\text{C}_{26}\text{H}_{32}\text{O}_4$ (408.5) calcd. C 76.44, H 7.90; found C 76.49, H 7.91%.

12 α -[(1*H*-Imidazol-1-yl)thioxomethoxy]-11 β -(4-methoxyphenyl)androst-4-ene-3,17-dione (22): 12 α -Alcohol **21** (1.26 g, 3.08 mmol) was stirred with 1,1'-carbonothioylbis[1*H*-imidazole] (1.65 g, 9.24 mmol, 3 equiv.) and triethylamine (430 μl , 3.08 mmol, 1 equiv.) in dichloromethane (30 ml) at ambient temperature for 6 d, during which time one further equivalent of 1,1'-carbonothioylbis[1*H*-imidazole] (549 mg, 3.08 mmol) was added daily. The reaction mixture was poured into aqueous HCl (1 M, 20 ml) and the organic layer was separated. The aqueous fraction was extracted with dichloromethane, the organic portions were combined, washed with brine, dried over Na_2SO_4 , filtered, and evaporated. Column chromatography of the residue gave **22** (1.34 g, 84%): mp 178.7 $^\circ\text{C}$ (ethyl acetate); $[\alpha]_D^{25} = +120.1^\circ$ ($c=0.505$, CHCl_3); IR (KBr, cm^{-1}): ν 1740 (C=O), 1662 (C=O); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.17 (s, 1H, imi), 7.60 (m, 2H, aryl), 7.49 (s br, 1H, imi), 7.02 (s br, 1H, imi), 6.84 (m, 2H, aryl), 5.81 (d, $J=2$ Hz, 1H, H-12), 5.70 (d, $J=1.5$ Hz, 1H, H-4), 3.82 (s, 3H, OMe), 3.77 (dd, $J=5.5$ Hz and 2 Hz, 1H, H-11), 2.55 (dd, $J=18$ Hz and 9 Hz, 1H, H-16), 1.05 (s, 3H, H-18), 0.97 (s, 3H, H-19); MS (EI, m/z): 518 (12%, M^+), 390 (100%); $\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_4\text{S}$ (518.7) calcd. C 69.47, H 6.61, N 5.40, S 6.18; found C 69.47, H 6.55, N 5.36, S 6.02%.

11 β -(4-Methoxyphenyl)androst-4-ene-3,17-dione (23): A solution of tributylstannane (1.39 ml, 5.17 mmol, 2 equiv.) in toluene (50 ml) was heated at reflux. Compound **22** (1.34 g, 2.58 mmol), dissolved in toluene (25 ml) was added and reflux was continued for 2 h. The mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by column chromatography to provide **23** (679 mg, 67%): $[\alpha]_D^{25} = +223.4^\circ$ ($c=0.520$, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.30 (m, 2H, aryl), 6.78 (d br, $J=9$ Hz, 2H, aryl), 5.69 (d, $J=1.5$ Hz, 1H, H-4), 3.80 (s, 3H, OMe), 3.44 (dd br, $J=6$ Hz and 5 Hz, 1H, H-11), 0.99 (s, 3H, H-19), 0.88 (s, 3H, H-18); $\text{C}_{26}\text{H}_{32}\text{O}_3$ (392.5) calcd. C 79.56, H 8.22; found C 79.51, H 8.21%.

17 β -Hydroxy-11 β -(4-methoxyphenyl)androst-4-en-3-one (24): Diketone **23** (600 mg, 1.53 mmol) was stirred with sodium borohydride (29 mg, 764 mmol, 0.5 equiv.) in ethanol (15 ml) for 5 h at RT. At 0 $^\circ\text{C}$, water was slowly added and the organic layer was separated. The aqueous fraction was extracted with ethyl acetate, the organic portions were

combined, washed with brine, dried over Na_2SO_4 , filtered, and evaporated. Column chromatography gave **24** (122 mg, 20%): mp 182°C (2-propanol); $[\alpha]_D^{25} = +209.8^\circ$ ($c=0.500$, CHCl_3); IR (KBr, cm^{-1}): ν 3435 (OH), 1664 (C=O); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.32 (m, 2H, aryl), 6.77 (d br, $J=9$ Hz, 2H, aryl), 5.67 (s br, 1H, H-4), 3.80 (s, 3H, OMe), 3.54 (dd br, $J=9$ Hz and 6 Hz, 1H, H-17), 3.38 (dd br, $J=6$ Hz and 5 Hz, 1H, H-11), 0.99 (s, 3H, H-19), 0.77 (s, 3H, H-18); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 199.3 (s, C-3), 172.5 (s, C-4'), 157.6 (s, C-5), 136.8 (s, C-1'), 132.8 (d, C-4), 122.0 (d), 112.4 (d), 83.2 (d, C-17), 57.1 (d), 55.1 (q, OMe), 54.4 (d), 47.6 (t), 42.1 (s), 40.9 (d), 39.9 (s), 35.8 (t), 33.8 (d), 33.7 (t), 33.4 (t), 32.0 (t), 30.0 (t), 23.4 (t), 22.4 (q), 14.2 (q); HRMS: calcd. for $\text{C}_{26}\text{H}_{34}\text{O}_3$ 394.2508, obsd. 394.2516; $\text{C}_{26}\text{H}_{34}\text{O}_3$ (394.6) calcd. C 79.15, H 8.69; found C 79.17, H 8.68%.

Crystal data of 24: $\text{C}_{26}\text{H}_{34}\text{O}_3$, $M = 394.6$ g/mol, colourless, needle-shaped crystals from 2-propanol, $0.5 \times 0.15 \times 0.08$ mm³, monoclinic, space-group C2, $a = 20.37(1)$, $b = 9.178(4)$, $c = 23.93(1)$ Å, $\beta = 99.57(4)^\circ$, $V = 4410(4)$ Å³, $Z = 8$, $D_c = 1.188$ g/cm³, $\mu = 0.076$ mm⁻¹, $F(000) = 1712$, graphite monochromated MoK α radiation from a fine focus sealed tube ($\lambda = 0.71073$ Å), 6433 reflections measured ($3^\circ \leq 2\theta \leq 45^\circ$, $-18 \leq h \leq 16$, $-9 \leq k \leq 9$, $-25 \leq l \leq 25$), 5299 unique reflections ($R_{\text{int}} = 2.49\%$), 3219 observed reflections ($F \leq 4.0 \sigma(F)$). 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.

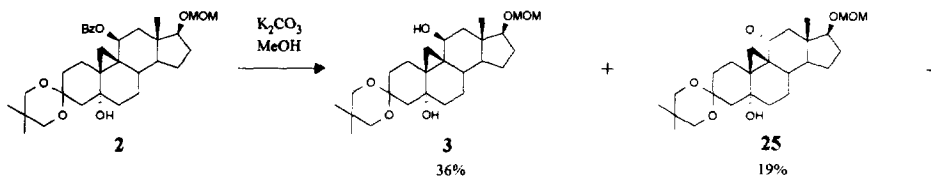
Structure Analysis and Refinement:¹⁷ All calculations were performed using the Siemens SHELXTL+ (VMS) program. The structure was solved by direct methods which yielded only about 60% of the carbon and oxygen positions and by subsequent Fourier techniques. The hydrogen atoms belonging to the hydroxyl groups were located from difference Fourier maps and the remaining hydrogens were included in calculated positions. One overall temperature factor was refined for all hydrogen atoms. Convergence for the full-matrix least-squares refinement using anisotropic displacement coefficients for all carbon and oxygen atoms was achieved at $R = 3.99\%$ ($R_w = 4.11\%$, data-to-parameter ratio = 6.2:1). There are two independent molecules in the asymmetric unit adopting similar conformations. The crystal packing is stabilized by intermolecular hydrogen bonds.

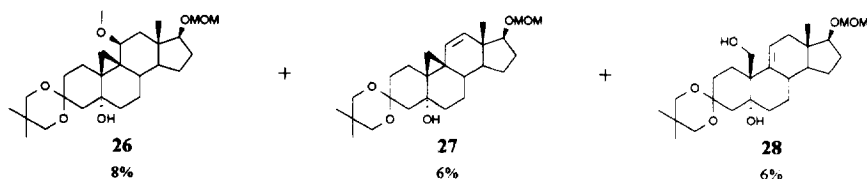
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REFERENCES AND NOTES

This paper is dedicated to Professor Helmut Vorbrüggen on the occasion of his 65th birthday.

- Teutsch, G.; Ojasoo, T.; Raynaud, J. P. *J. Steroid Biochem.* **1988**, *31*, 549-565.
- Herrmann, C.; Hoyer, G.-A.; Neef, G.; Schomburg, D.; Wiechert, R. *Liebigs Ann. Chem.* **1986**, 1317-1326.
- Neef, G.; Ottow, E.; Scheidges, C.; Scholz, S.; Wiechert, R. New Developments in the Field of Anti-Progestational Steroids. In *Trends in Medicinal Chemistry*; van der Goot, H.; Domány, G.; Pallos, L.; Timmerman, H. Eds.; Elsevier Science Publishers B. V.; Amsterdam, **1989**; pp. 581-597.
- Ottow, E.; Beier, S.; Elger, W.; Fritzeimer, K.-H.; Neef, G.; Wiechert, R. *Steroids* **1994**, *59*, 185-189.
- Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902-3909.
- The phenyl torsions of the minimum structures have been calculated to be 27° for the 10 β -H compound ZK 135 660 and 21° for RU 38 486, respectively.
- Neef, G.; Sauer, G.; Wiechert, R. *Tetrahedron Lett.* **1983**, *24*, 5205-5208; Schering AG (Cleve, A.; Scheidges, C.; Neef, G.; Ottow, E.; Elger, W.; Beier, S.; Inv.) *Eur. Pat. Appl.* EP 404,283 (27.12.1990) [*Chem. Abstr.* **1991**, *114*, P 164625f].
- For preparation of compound **1** see: Schering AG (Neef, G.; Vierhufe, H.; Ast, G.; Inv.) *Ger. Offen.* DE 3,842,646 (14.12.1988) [*Chem. Abstr.* **1991**, *114*, P 62494v].
- The following products were characterized (see Experimental Section):





Using alcohol free conditions, e.g. dil. NaOH/THF, increased the relative amounts of 27 and 28.

10. Cleve, A. unpublished results.
11. For a review on triflate/nonaflate reactions, see: Ritter, K. *Synthesis* **1993**, 735-762.
12. For preparation of compound 9 see: Schering AG (Bittler, D.; Hofmeister, H.; Brumby, T.; Kroll, J.; Künzer, H.; Sauer, G.; Fritzemeier, K.-H.; Michna, H.; Inv.) *PCT Int. Appl.* WO 93/13,122 (22.12.1991) [*Chem. Abstr.* **1993**, 119, P 250245s].
13. Prepared by Simmons-Smith cyclopropanation of 5,17 β -dihydroxy-11 β -(4-methoxyphenyl)-5 α -estr-9-en-3-one cyclic 2,2-dimethyl-1,3-propanediyl acetal as described in: Neef, G.; Cleve, G.; Ottow, E.; Seeger, A.; Wiechert, R. *J. Org. Chem.* **1987**, *52*, 4143-4146.
14. AM1 structures have been proven to be in reasonable agreement with the X-ray crystal structures such as 24: Considering all non-hydrogen atoms of the steroid skeleton, a rms deviation of 0.14 Å has been calculated.
15. Staab, H. A.; Meissner, B. *Liebigs Ann. Chem.* **1971**, *753*, 80-91.
16. Smitsman, E. E.; Li, J. P.; Israïli, Z. H. *J. Org. Chem.* **1968**, *33*, 4231-4236.
17. The atomic co-ordinates and anisotropic displacement coefficients for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this publication.

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