Pergamon

Tetrahedron, Vol. 52, No. 5, pp. 1529-1542, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)00983-3

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

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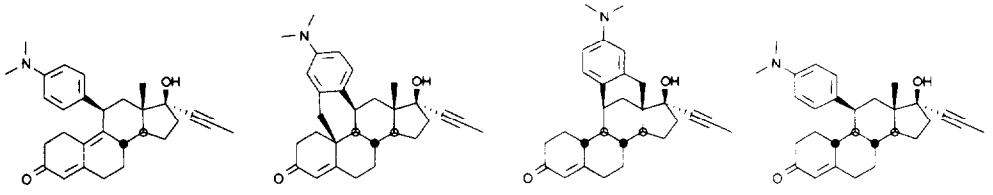
Abstract: The syntheses of 11β-arylandrost-4-en-3-one **24** and the corresponding 9β,19-cyclo derivative **8** are described. Steric interaction between C-19 and the aryl residue effects conformational changes of the steroid ring system that result in reduced affinity for the progesterone receptor.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

INTRODUCTION

One of the primary structural features of antiprogestational steroids is the 11β-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 11β-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 antiprogestins 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 10β-H compound would have been expected to have a reduced PR affinity, as well. AM1 calculations[5] showed, however, that the phenyl torsions in the minimum structures of 10β-H species and $\Delta^{4,9}$-systems like RU 38 486 are very similar.[6] Indeed, 10β-H compounds turned out to be highly active antiprogestins *in vitro* and *in vivo*.[7]



RU 38 486
RBA 100 (2h)
250 (24h)

ZK 118 561
RBA 38 (2h)
71 (24h)

ZK 135 617
RBA 5 (2h)
6 (24h)

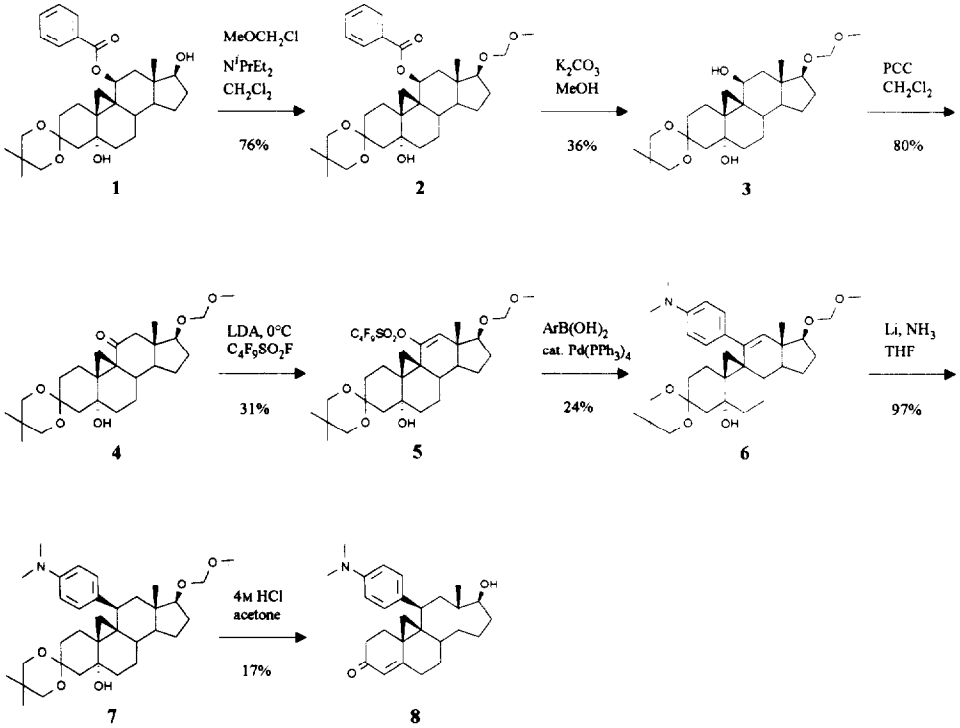
ZK 135 660
RBA 125 (2h)
227 (24h)

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

The question arises whether an unbridged 11β-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 9β,19-cyclo derivatives and the corresponding 10β-methyl analogues. Receptor data are given and discussed in comparison to known 11β-aryl steroids.

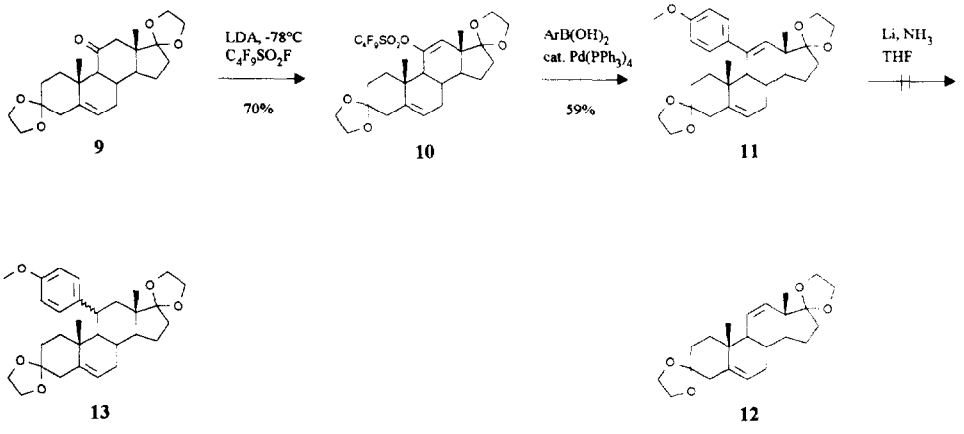
RESULTS AND DISCUSSION

To put compatibility of C-19 with 11β-aryl to the test, we envisaged the synthesis of a 9β,19-cycloandrostene derivative. In this case, the steric demand of C-19 would be restricted, hopefully allowing for an 11β-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 $LiAlH_4$ 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 5α-OH in compound **4** failed as it is sterically congested and prone to rearrangements. Under the best conditions found for the free 5α-hydroxy-11-ketone **4**, enol nonaflate **5** was obtained in 31% yield. Suzuki cross-coupling[11] 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. 11β-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**.



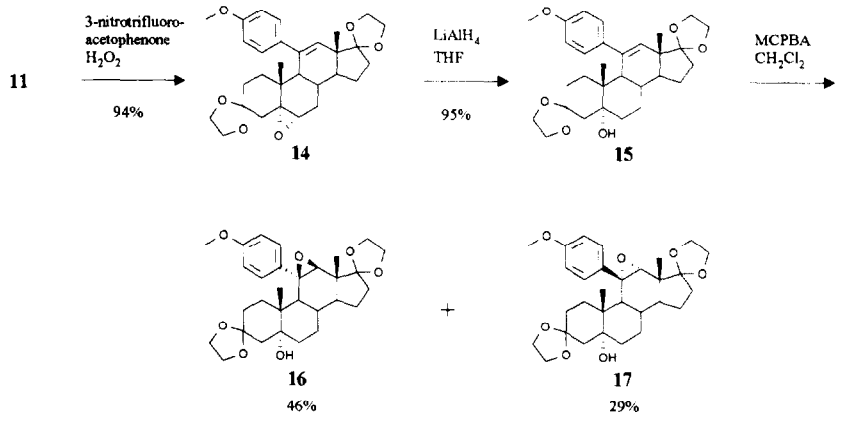
Scheme 1.

The above aryl introduction protocol appeared to be suitable for the 10β-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.

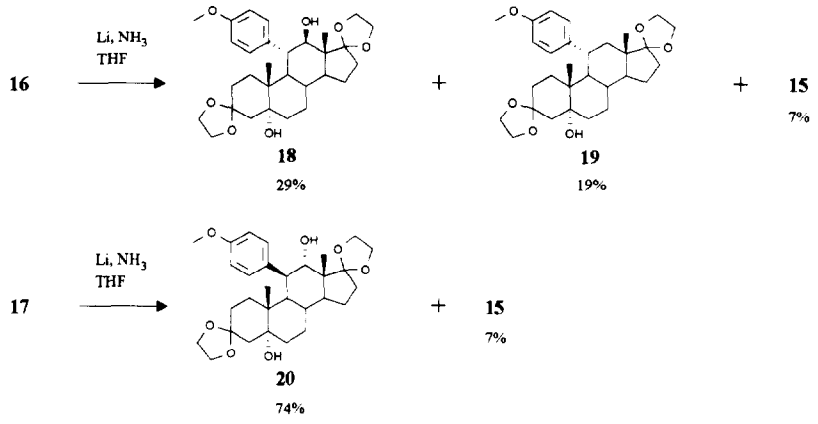
In order to disencumber the steric constraint at C-11, we decided to prepare an 11,12-epoxide. The 5-double bond was protected by regio- and stereoselective α-epoxidation followed by reduction to 5α-hydroxy derivative **15**. Oxidation of Δ^{11} with *m*-chloroperoxybenzoic acid (MCPBA) proceeded slowly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



Scheme 3.

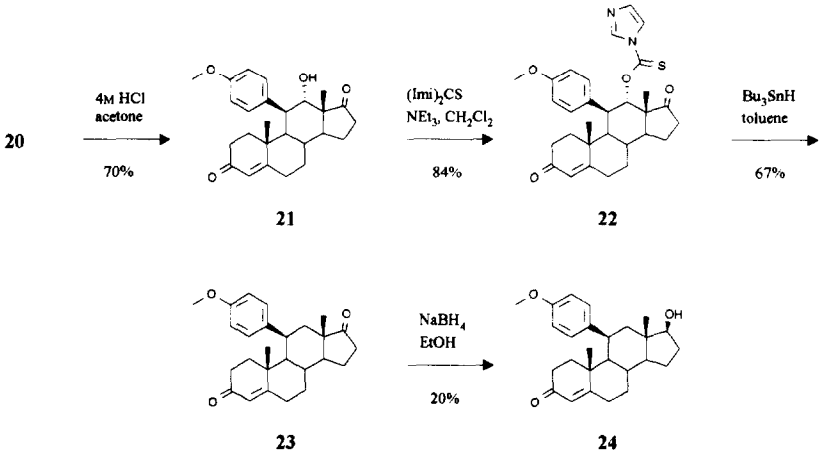
Applying Birch conditions to β-epoxide **16** gave benzyl reduction product **18**, deoxygenation product **19** and a minor amount of olefin **15**, which had probably been formed by elimination of water from **18** (Scheme 4). Interestingly, the reduction took place with complete retention of stereochemistry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

17 under the same conditions furnished 11β-arylandrostane **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 12α-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 11β-aryltestosterone **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 11β-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 ^{1}H NMR in $CDCl_3$, 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). 10β-Methyl is even less shielded (δ 0.99). The three bulky β-substituents force the tetracyclic steroid system to adopt a β-convex conformation.

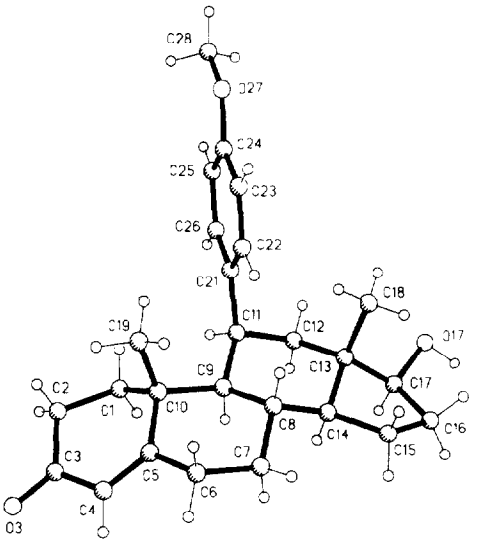
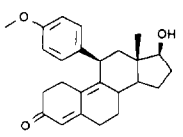


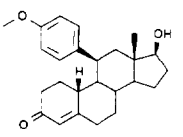
Fig. 2. — X-ray crystal structure of **24**.

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 17α-substituent binding affinities of derivatives **29** - **31** are generally lower than those of the 17α-propynyl analogues shown in Figure 1. Whereas 4,9-dien-3-one **29**, 10β-H-compound **30**, and bridged derivative **31** display comparable RBAs, changing to 10β-methyl practically abolishes PR binding.

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



29



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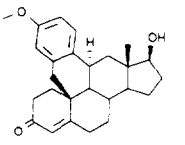

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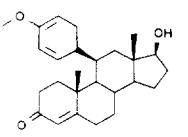


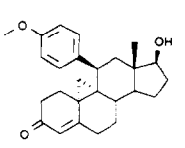
24

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

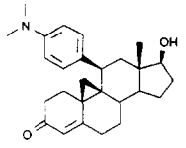
In the 9,19-cycloandrostene series, stereochemistry of C-19 has a critical influence on binding affinity: while 9,10α-methylene derivative **32**[13] still binds fairly good to the PR, 9,10β-methylene compound **8** is almost devoid of PR affinity (Table 2). Although compounds **32** and **8** have different 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 11β-Aryl-9,10-methylene Steroids. (Rabbit uterus, incubation time 2 h, 6°C, progesterone =100).

Compound	**32**	**8**
RBA (2 h)	13	0.2



32



8

The low affinity of systems with 11β-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.

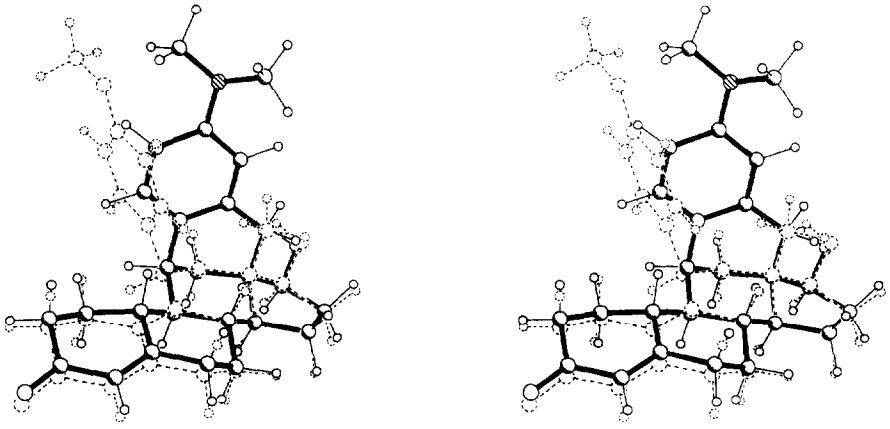


Fig. 3. — Stereoscopic representation of the superposition of optimized **29** (dashed lines) and bridged 17α-H analogue of ZK 135 617.

Can we understand the low PR affinity of the new 11β-arylandrostenes 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 10β-methyl-11β-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 10β-methyl group and the 11β-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.

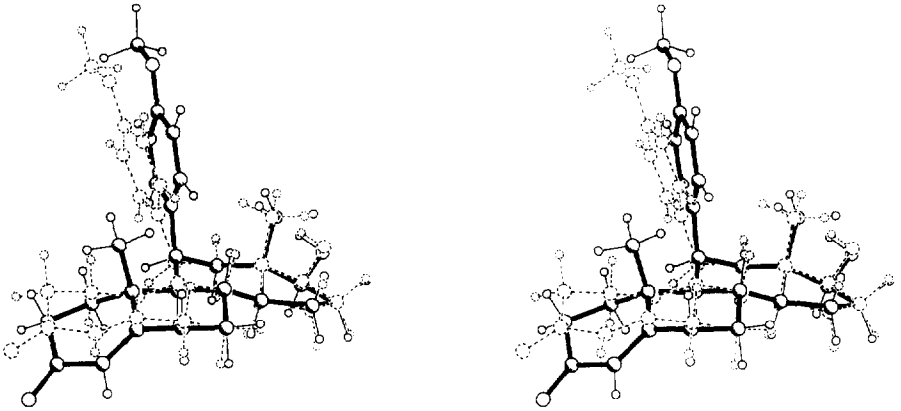


Fig. 4. — Stereoscopic representation of the superposition of optimized **29** (dashed lines) and **24** in the putatively bioactive aryl conformation.

For 9β,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.

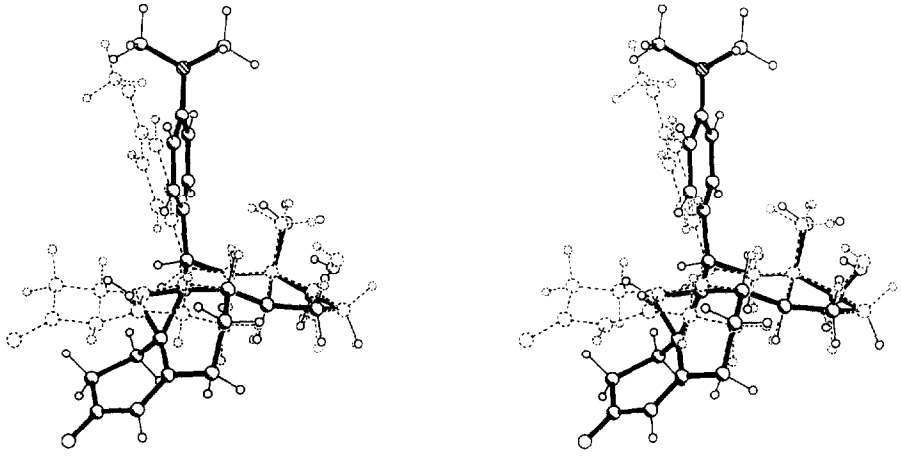


Fig. 5. — Stereoscopic representation of the superposition of optimized **29** (dashed lines) and **8**.

In contrast, 9α,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° for compound **32**. According to our calculations, the energy needed to adopt the putatively bioactive orientation of 21° is 0.4 kcal/mol, only.

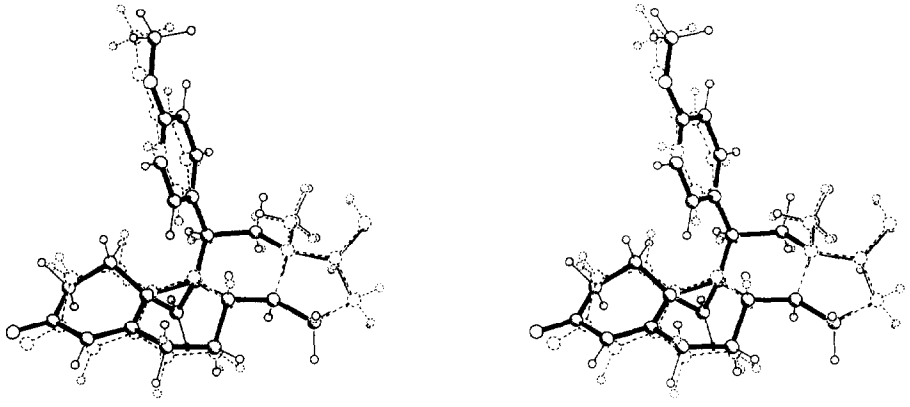


Fig. 6. — Stereoscopic representation of the superposition of optimized **29** (dashed lines) and **32**.

CONCLUSION

In conclusion, we have shown that 11β-arylandrostenes are synthetically accessible. While the preparation of 9β,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 11β-aryl moiety causes distortions of the steroid system accounting for the observed effects.

EXPERIMENTAL SECTION

Spectral data were obtained as follows: ^{1}H 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.

11β-(Benzoyloxy)-5-hydroxy-17β-(methoxymethoxy)-9,19-cyclo-5α,9β-androstan-3-one cyclic 2,2-dimethyl-1,3-propanediyl acetal (2): 11β-(Benzoyloxy)-5,17β-dihydroxy-9,19-cyclo-5α,9β-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 Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give **2** (7.54 g, 76%): **^{1}H NMR** (300 MHz, $CDCl_3$): 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'); **$C_{33}H_{46}O_7$** (554.7) calcd. C 71.45, H 8.36; found C 71.42, H 8.33%.

5,11β-Dihydroxy-17β-(methoxymethoxy)-9,19-cyclo-5α,9β-androstan-3-one cyclic 2,2-dimethyl-1,3-propanediyl acetal (3): Benzoate **2** (6.58 g, 11.86 mmol) and K_2CO_3 (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 Na_2SO_4, filtered, and evaporated. Column chromatography gave the following products in order of increasing polarity: 5-hydroxy-17β-(methoxymethoxy)-9,19-cyclo-5α,9β-androst-11-en-3-one cyclic 2,2-dimethyl-1,3-propanediyl acetal **27** (302 mg, 6%) {**^{1}H NMR** (300 MHz, $CDCl_3$): 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'); **$C_{26}H_{40}O_5$** (432.6) calcd. C 72.19, H 9.32; found C 72.05, H 9.31%}; 5-hydroxy-11β-methoxy-17β-(methoxymethoxy)-9,19-cyclo-5α,9β-androstan-3-one cyclic 2,2-dimethyl-1,3-propanediyl acetal **26** (411 mg, 8%) {**^{1}H NMR** (300 MHz, $CDCl_3$): 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); **$C_{27}H_{44}O_6$** (464.7) calcd. C 69.79, H 9.55; found C 69.79, H 9.51%}; 5-hydroxy-11α-methoxy-17β-(methoxymethoxy)-9,19-cyclo-5α,9β-androstan-3-one cyclic 2,2-dimethyl-1,3-propanediyl acetal **25** (980 mg, 19%) {**^{1}H NMR** (300 MHz, $CDCl_3$): 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'); **$C_{27}H_{44}O_6$** (464.7) calcd. C 69.79, H 9.55; found C 69.72, H 9.52%}; 5,19-dihydroxy-17β-(methoxymethoxy)-5α-androst-9(11)-en-3-one cyclic 2,2-dimethyl-1,3-propanediyl acetal **28** (322 mg, 6%) {**^{1}H NMR** (300 MHz, $CDCl_3$): 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); **$C_{26}H_{42}O_6$** (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); $[\alpha]_D^{22}$= +3.4° (c=0.500, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): 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'); **$C_{26}H_{42}O_6$** (450.6) calcd. C 69.30, H 9.39; found C 69.08, H 8.94%.

5-Hydroxy-17β-(methoxymethoxy)-9,19-cyclo-5α,9β-androstane-3,11-dione cyclic 3-(2,2-dimethyl-1,3-propanediyl acetal) (4): 11β-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); $[\alpha]_D^{22}$= +37.6° (c=0.500, $CHCl_3$); **IR** (KBr, cm^{-1}): ν 3500 (OH), 1668 (C=O); **^{1}H NMR** (300 MHz, $CDCl_3$): 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); **$C_{26}H_{40}O_6$** (448.6) calcd. C 69.61, H 8.99; found C 69.27, H 8.80%.

5-Hydroxy-17β-(methoxymethoxy)-11-[[(1,1,2,2,3,3,4,4,4-nonafluorobutyl)sulfonyl]oxy]-9,19-cyclo-5α,9β-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-butanesulfonyl fluoride (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}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'); **$C_{30}H_{36}F_9O_8S$** (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-17β-(methoxymethoxy)-9,19-cyclo-5α,9β-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-17β-(methoxymethoxy)-9,19-cyclo-5α,9β-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%, $[MH]^+$), 551 (100%, $M^{+\cdot}$), 534 (56%, $[MH-H_2O]^+$); **^{1}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'); **$C_{34}H_{49}NO_5$** (551.8) calcd. C 74.01, H 8.95, N 2.54; found C 73.95, H 8.78, N 2.49%.

11β-[4-(Dimethylamino)phenyl]-5-hydroxy-17β-(methoxymethoxy)-9,19-cyclo-5α,9β-androstan-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 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 water and with brine, dried over Na_2SO_4, filtered, and evaporated. Column chromatography gave 11β-arylsteroid **7** (112 mg, 97%): **^{1}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%, $[MH]^+$), 536 (41%, $[MH-H_2O]^+$); **$C_{34}H_{51}NO_5$** (553.8) calcd. C 73.74, H 9.28, N 2.53; found C 73.73, H 9.20, N 2.51%.

11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-9,19-cyclo-9β-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}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%, $M^{+\cdot}$), 283 (54%), 270 (62%); **$C_{27}H_{35}NO_2$** (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]androsta-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-butanesulfonyl fluoride (40.99 ml, 228.6 mmol, 3 equiv.) and allowed to warm to room temperature over night. 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); $[\alpha]_D^{22}$= –30.6° (c=0.500, $CHCl_3$); **^{1}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%, $[MH+NH_3]^+$), 671 (27%, $[MH]^+$); **$C_{27}H_{31}F_9O_7S$** (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 Na_2CO_3 solution (2 M, 200 ml) in toluene (800 ml) and ethanol (400 ml) for 48 h. The reaction mixture was poured into saturated $NaHCO_3$ 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 Na_2SO_4, filtered, and evaporated. Column chromatography of the residue afforded 11-arylsteroid **10** (15.02 g, 59%): **mp** 177.2°C (diisopropyl ether); $[\alpha]_D^{22}$= +44.0° (c=0.500, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): 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); **$C_{30}H_{38}O_5$** (478.6) calcd. C 75.28, H 8.00; found C 75.28, H 7.98%.

11-(4-Methoxyphenyl)-5,6α-epoxy-5α-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 H_2O_2 (30%, 12.8 ml), and saturated $NaHCO_3$ solution (14 ml) in dichloromethane (300 ml) for 6 d at ambient temperature. The mixture was washed with saturated $Na_2S_2O_3$ solution to destroy excess of H_2O_2 and the aqueous layer was extracted with dichloromethane. The organic fractions were washed with saturated $NaHCO_3$ solution and with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography gave α-epoxide **14** (14.51 g, 94%): **mp** 180.4°C (diisopropyl ether); $[\alpha]_D^{22}$= +53.2° (c=0.520, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): 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); **$C_{30}H_{38}O_6$** (494.6) calcd. C 72.85, H 7.74; found C 72.69, H 7.65%.

5-Hydroxy-11-(4-methoxyphenyl)-5α-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 $LiAlH_4$ (1.10 g, 28.9 mmol, 1 equiv.) in THF (300 ml) for 1 h at room temperature. At 0°C, saturated NH_4Cl 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; $[\alpha]_D^{22}$= +101.3° (c=0.505, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): 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); **$C_{30}H_{40}O_6$** (496.6) calcd. C 72.55, H 8.12; found C 72.06, H 8.11%.

5-Hydroxy-11α-(4-methoxyphenyl)-11β,12β-epoxy-5α-androstane-3,17-dione cyclic bis(1,2-ethanediyl acetal) (16) and 5-hydroxy-11β-(4-methoxyphenyl)-11α,12α-epoxy-5α-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 Na_2SO_4, 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); $[\alpha]_D^{22}$= +29.9° (c=0.515, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): 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%, $[MH+NH_3]^+$), 513 (100%, $[MH]^+$), 495 (36%, $[MH-H_2O]^+$); **$C_{30}H_{40}O_7$** (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); $[\alpha]_D^{22}$= +9.5° (c=0.515, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): 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%, $[MH+NH_3]^+$), 513 (100%, $[MH]^+$), 495 (33%, $[MH-H_2O]^+$), 477 (14%, $[MH-2H_2O]^+$); **$C_{30}H_{40}O_7$** (512.6) calcd. C 70.29, H 7.86; found C 70.19, H 7.87%.

5-Hydroxy-11α-(4-methoxyphenyl)-5α-androstane-3,17-dione cyclic bis(1,2-ethanediyl acetal) (19) and 5,12β-dihydroxy-11α-(4-methoxyphenyl)-5α-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}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%, $[MH]^+$), 481 (100%, $[MH-H_2O]^+$); **$C_{30}H_{42}O_6$** (498.7) calcd. C 72.26, H 8.49; found C 72.30, H 8.49%}; and 12β-alcohol **18** (364 mg, 29%): $[\alpha]_D^{22}$= +0.8° (c=5.075, $CHCl_3$); **^{1}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%, $[MH]^+$), 497 (78%, $[MH-H_2O]^+$), 479 (100%, $[MH-2H_2O]^+$); **$C_{30}H_{42}O_7$** (514.7) calcd. C 70.01, H 8.23; found C 69.85, H 8.23%.

5,12α-Dihydroxy-11β-(4-methoxyphenyl)-5α-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 12α-alcohol **20** (2.55 g, 74%): **^{1}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%, $[MH]^+$), 497 (72%, $[MH-H_2O]^+$), 479 (100%, $[MH-2H_2O]^+$); **$C_{30}H_{42}O_7$** (514.7) calcd. C 70.01, H 8.23; found C 69.92, H 8.12%.

12α-Hydroxy-11β-(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%): $[\alpha]_D^{22}$= +239.6° (c=0.505, $CHCl_3$); **IR** (KBr, cm^{-1}): ν 3460 (OH), 1740 (C=O), 1665 (C=O); **^{1}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 2Hz, 1H, H-11), 0.99 (s, 3H, H-19), 0.84 (s, 3H, H-18); **MS** (EI, *m/z*): 408 (58%, $M^{+\cdot}$), 121 (100%); **$C_{26}H_{32}O_4$** (408.5) calcd. C 76.44, H 7.90; found C 76.49, H 7.91%.

12α-[(1*H*-Imidazol-1-yl)thioxomethoxy]-11β-(4-methoxyphenyl)androst-4-ene-3,17-dione (22): 12α-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°C (ethyl acetate); $[\alpha]_D^{22}$= +120.1° (c=0.505, $CHCl_3$); **IR** (KBr, cm^{-1}): ν 1740 (C=O), 1662 (C=O); **^{1}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%, $M^{+\cdot}$), 390 (100%); **$C_{30}H_{34}N_2O_4S$** (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%.

11β-(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%): $[\alpha]_D^{22}$= +223.4° (c=0.520, $CHCl_3$); **^{1}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); **$C_{26}H_{32}O_3$** (392.5) calcd. C 79.56, H 8.22; found C 79.51, H 8.21%.

17β-Hydroxy-11β-(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°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); $[\alpha]_D^{22}$= +209.8° (c=0.500, $CHCl_3$); **IR** (KBr, cm^{-1}): ν 3435 (OH), 1664 (C=O); **^{1}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 5Hz, 1H, H-11), 0.99 (s, 3H, H-19), 0.77 (s, 3H, H-18); **^{13}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 $C_{26}H_{34}O_3$ 394.2508, obsd. 394.2516; **$C_{26}H_{34}O_3$** (394.6) calcd. C 79.15, H 8.69; found C 79.17, H 8.68%.

Crystal data of 24: $C_{26}H_{34}O_3$, M = 394.6 g/mol, colourless, needle-shaped crystals from 2-propanol, 0.5 x 0.15 x 0.08 mm^3, monoclinic, space-group C2, a = 20.37(1), b = 9.178(4), c = 23.93(1) Å, β = 99.57(4)°, V = 4410(4) $Å^3$, Z = 8, D_c = 1.188 g/cm^3, μ = 0.076 mm^{-1}, F(000) = 1712, graphite monochromated MoKα radiation from a fine focus sealed tube (λ = 0.71073 Å), 6433 reflections measured ($3° \le 2\theta \le 45°$, $-18 \le h \le 16$, $-9 \le k \le 9$, $-25 \le l \le 25$), 5299 unique reflections (R_{int} = 2.49%), 3219 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:[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.

Acknowledgement. We are grateful to Mrs. Andrea Nork and Mr. Helmut Morack for technical assistance.

REFERENCES AND NOTES

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

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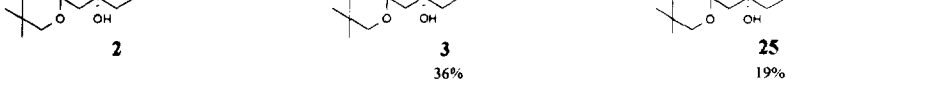
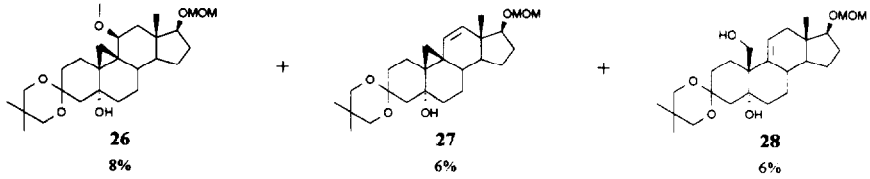
9. The following products were characterized (see Experimental Section):



2 → **3** (36%) + **25** (19%) +



26 8% + **27** 6% + **28** 6%

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

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(*Received in Germany* 27 *September* 1995; *accepted* 31 *October* 1995)