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Synthesis and Spectroscopic Peculiarities of 11β-Aryl-Estra-4,8(14),9-trienes and 11β-Aryl-Estra-5(10),6,8-trienes

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Abstract: A synthetic strategy is disclosed for the introduction of an additional conjugate 8(14) double bond into 11β-arylsubstituted antiprogestins of the RU 486 type. Ring B aromatic analogues are obtained as by-products. Both structural variations markedly affect the rotational behaviour of the 11β-phenyl residue. © 1997 Elsevier Science Ltd.

The classical approach to drug development from a known lead structure remains the systematic variation of substitution pattern and the alteration of stereochemical relationships. The efforts of various groups reported after the discovery of the first progesterone antagonist RU 486 (Mifepristone) can be viewed as a typical example.[1)]

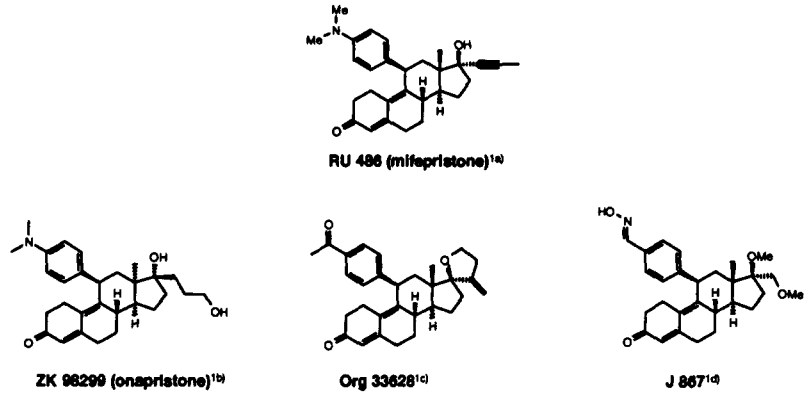


Figure 1: RU 486 (mifepristone) and successor compounds

Besides the more conventional options of structural modification 11β-arylsteroids offer the possibility of addressing the impact of restricted rotation on the biological response.

Despite the unfavourable 1,3-diaxial relationship between the 11β-aryl residue and the angular C-13 methyl group (Figure 2) the phenyl ring of RU 486 can freely rotate around the single bond linking it to the steroid skeleton. In the nmr spectrum the aromatic protons appear as two distinct doublets indicative of equivalent *o,o'*- and *m,m'*-positions.

Recently, we reported on the synthesis of analogues **1**[2)] and **2**.[3)] which by different types of methylene linkages are deprived of rotational freedom freezing either the thermodynamically favoured rotamer (**1**) or the disfavoured orthogonal situation (**2**). The 90° turn of the aromatic ring plane had a dramatic effect on receptor binding and biological activity.

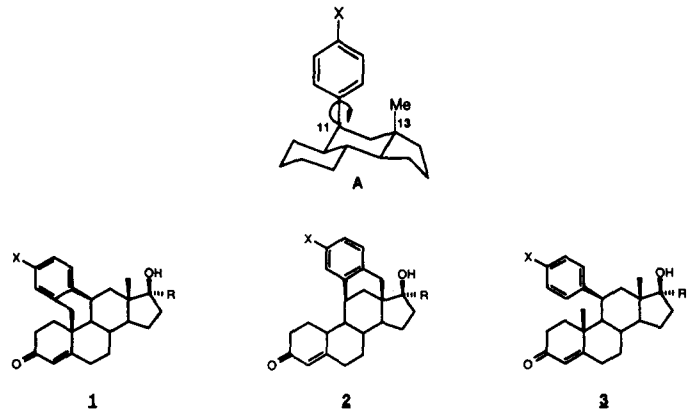


Figure 2: Previous attempts to freeze distinct rotamers

Compound **3** represents a second strategy to induce rotameric preferences. By a rather laborious synthetic sequence a 10β-methyl group was introduced to increase steric strain. Instead of forming a distinct frozen rotamer, however, compound **3** escaped from the unfavourable situation by distorting the steroid skeleton in a way to maintain free rotation for the 11β-phenyl ring.[4]

A third possibility of influencing the rotational behaviour of a 11β-aryl residue was suggested by AM1[5] and MM3[6] computed steroid geometries, which predicted higher barriers to free rotation for derivatives **4** and **5**.

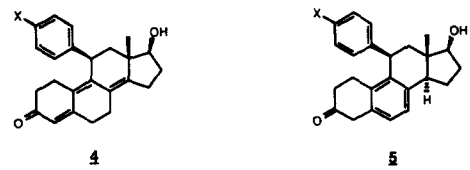
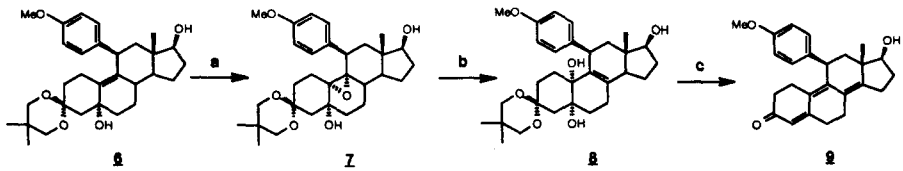


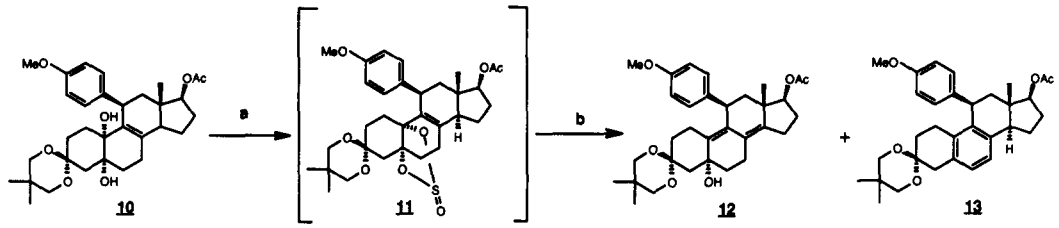
Figure 3.

Since steroids of this substition pattern have not been described before, the necessity arose to devise a viable access. The epoxides of type **7**[7] easily made from the well known allylic alcohols **6**[8] seemed to offer themselves as appropriate starting materials. Not unexpectedly however, the sterically encumbered epoxide moiety turned out to be rather resistant to any kind of nucleophile or base attack. Incidentally, treatment of epoxide **7** with excess lithium aluminum hydride was found to result in a clean reaction with formation of unsaturated triol **8**. As compound **8** maintained the oxidation level of the precursor epoxide, lithium aluminum hydride had exclusively reacted as a base removing proton C-8β, thus initiating epoxide-allylic alcohol rearrangement. No other strong base (K-tert.butylate, LDA, NaH, n-BuLi, t-BuLi) turned out to be suited for this transformation. Lewis acid treatment of triol **8** under aprotic conditions led to clean formation of the desired trienone **9**.[9]



Scheme 1: Synthetic access to estra-4,8(14),9-trienes; a) *m*-chloroperbenzoic acid, CH_2Cl_2, 0°C; b) $LiAlH_4$ (5 molar equiv.), THF, 16 h reflux; c) BF_3-etherate, CH_2Cl_2, -70 to 0°C.

No equally satisfactory solution could be found for the synthesis of type 5 compounds. Triol 8 was protected as its 17β-acetate and treated with thionyl chloride/pyridine to form cyclic sulfite 11 which was visible on the thin layer plate but could not be isolated. Aqueous workup produced a mixture of two components which were separated on silica gel and identified as dienol 12 and the desired B-ring aromatic derivative 13.



Scheme 2: Access to estra-5(10),6,8-trienes; a) $SOCl_2$, pyridine, 0°C, $NaHCO_3$-workup; b) chromatography of crude 11 on silica gel with hexane/ethyl acetate.

Calculation (MM3) had predicted rotational barriers of 9 kcal/mol for the phenyl ring in the RU 486 type of compound and respective values of 12.7 kcal (compound 9) and 15.1 kcal (compound 13). The AM1 computation gave the same relative order but resulted in slightly less pronounced differences (7.9 : 9.6 : 12.5 kcal). Therefore, it was unclear whether the proton nmr spectra would reveal significant effects at room temperature.

The 300 MHz spectra[10] of compounds 9 and 13 soon removed the uncertainty showing marked signs of restricted phenyl rotation. The pair of sharp doublets characteristic for the 11β-(4-substituted)phenyl ring changed into a set of differently shaped signals for compound 9. Whereas the aryl protons H-3 and H-5 remained a clear doublet, the 2,6-resonance lost its fine structure and broadened to an unresolved signal.

An even more striking effect was obtained for derivative 13:[11] The four aromatic protons of the 11-substituent appeared as separate but unresolved signals at ambient temperature and became nicely fine-structured at lower temperatures (Figure 4).[10]

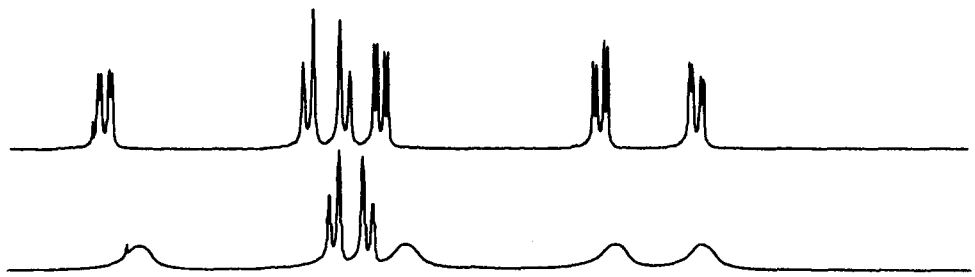


Figure 4: ^{1}H-NMR spectrum (300 MHz, CD_2Cl_2) of compound 13 (aromatic region), temperature dependent changes of 11β-(4-methoxyphenyl)-signals [25°C (lower spectrum) and -55°C].

In conclusion, we have been able to demonstrate restricted rotation in another series of biologically interesting compounds. Furthermore, in contrast to similar studies reported in the 4-aryl-1,4-dihydropyridine series of calcium channel antagonists,[12] force field calculation has been shown to be in fairly good agreement with the experimentally observed result.

The results of biological investigations will be reported elsewhere.

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9. Acid treatment of epoxide **7** gave a complex mixture of A- and B-ring aromatic products.

10. Selected physicochemical characteristics:

8: Colourless oil, $[\alpha]_D^{22}$= –36,0° ($CHCl_3$, c = 0,505), 93,3% yield, **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.85 ppm (s,3H,H-18); 0.92 and 0.94 (2s,3H each,ketal-Me); 3.36-3.55 (m,4H,ketal-CH_2); 3.80 (s,3H,OMe); 3.82 (m,1H,H-17); 6.85 (d,*J* = 10 Hz,2H,arom.H); 7.28 (d,*J* = 10 Hz,2H,arom.H).

9: Yellow oil, $[\alpha]_D^{22}$= +501,2° (MeOH, c = 0,505), 82,1% yield (from **8**), **UV spectrum** (MeOH): λ_{max} 360 nm (ε = 20100), 286 (7560), 280 (8190), 273 (8110), 260 (7560), 228 (13030). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.48 ppm (s,3H,H-18); 3.62 (m,1H,H-17); 3.78 (s,3H,OMe); 4.20 (d,*J* = 6 Hz,1H,H-11); 5.78 (s,1H,H-4); 6.80 (d,J = 10 Hz,2H,arom.H); 7.06 (broad,2H,arom.H).

12: m.p. 127-129°C (diisopropyl ether), $[\alpha]_D^{22}$= +30,0° ($CHCl_3$, c = 0,505), 51,4% yield, **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.48 ppm (s,3H,H-18); 0.87 (s,3H,ketal-Me); 1.05 (s,3H,ketal-Me); 2.01 (s,3H,OAc); 3.39-3.60 (m,4H,ketal-CH_2); 3.78 (s,3H,OMe); 4.06 (d,*J* = 6 Hz,1H,H-11); 4.38 (s,1H,OH); 4.52 (m,1H,H-17); 6.79 (d, *J* = 10 Hz,2H,arom H); 7.09 (broad,2H,arom.H).

13: m.p. 182-184°C, $[\alpha]_D^{22}$= +47,3° ($CHCl_3$, c = 0,515), 23,2% yield, **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.52 ppm (s,3H,H-18); 0.83 (s,3H,ketal-Me); 1.08 (s,3H,ketal-Me); 2.00 (s,3H,OAc); 3.38-3.59 (m,4H,ketal-CH_2); 3.78 (s,3H,OMe); 4.35 (d,*J* = 6 Hz,1H,H-11); 4.72 (m,1H,H-17); 6.49, 6.57, 6.90, 7.28 (broad,1H each,aromatic H); 6.95 and 7.04 (dd,*J* = 8 Hz,1H each,H-6 and H-7).

11. The ketal group of compound **13** could be easily cleaved (aqueous acetic acid) to form a type **5** product, which displayed the same spectroscopic characteristics. However, the deprotected compound turned out to be rather sensitive to oxygen and moisture.

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