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Studies on modified estrogens: Towards the synthesis of novel 14,15-cyclopropa[a]estra-1,3,5(10),8-tetraenes*

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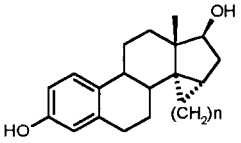
Dedicated to Prof. Dr. Kurt Ponsold, Jena, on the occasion of his 75th birthday

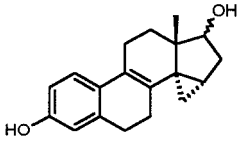
To improve the ratio of non-hormonal to hormonal activity, estrogens **3** and **4** were modified at various molecule positions. Isomerization of the 14α,15α-methylene bridge, controlled 3-methoxy group cleavage with respect to the 14α,15α-methylene bridge stereochemistry, reduction of the 8-double bond, and substitution of the oxyfunctionality at C-17 by a methylene and a difluoromethylene moiety were in the focus. As a result of *in vivo* and *in vitro* tests, compounds **27** and **29** were selected as potential follow-up candidates of lead **3**.

1. Introduction

Insertion of a 14α,15α-methylene bridge into an estrogenic steroid was shown to have considerable effects on the biological profile of the given compound when compared with the "unbridged" parent compound. To give a first example, 14α,15α-methylene estradiol (**2**), in contrast to 17β-estradiol (**1**), was previously shown to be a very strong estrogen for oral administration [1]. Recently, we described 14α,15α-methylene steroids **3** and **4** to have powerful antioxidative potential [2]. Moreover, compound **3** displayed neurotropic or even neuroprotective activity *in vivo* at doses which, unlike 17β-estradiol (**1**), were unable to promote uterine enlargement and hepatic estrogenicity [3]. In addition, compounds **3** and **4**, compared to **1**, showed a much higher potency in total cholesterol lowering activity in rats, at doses which were below those inducing systemic estrogenicity [4]. On the basis of these results compound **3** emerged as a candidate for a non-feminizing drug for gender-independent estrogen replacement therapy in humans. Consequently, follow-up candidates of lead **3** showing an improved ratio of non-feminizing to feminizing activity *versus* compound **3** became highly desirable. To this end, we synthesized novel 14,15-methylene bridged compounds using a recently described cyclopropane ring isomerization process [5, 6] and novel 14α,15α-cyclopropano steroids bearing an additional 17(20)-double bond instead of a C-17-functionality. We report here on our synthetic results in the field and also on initial biological data of the new compounds.



1: n = 0
2: n = 1



3: 17α-OH
4: 17β-OH

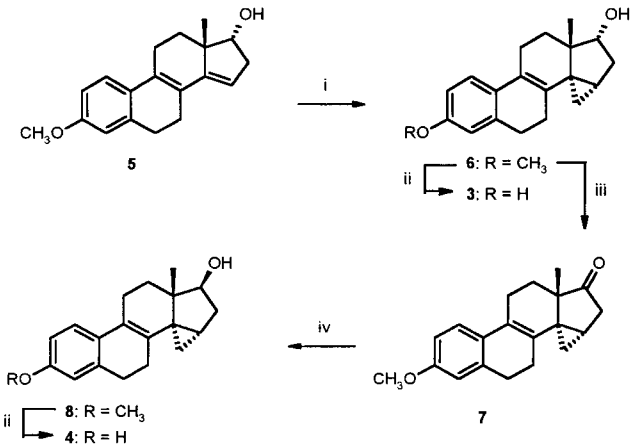
2. Investigations, results and discussion

2.1. Chemistry

2.1.1. Synthesis of leads **3** *and* **4**

Cyclopropano steroid **6**, obtained from pentaene **5** [7] by a sonochemical Simmons Smith reaction [8], gave compound **3** upon methoxy group cleavage with DIBAL-H in refluxing toluene [9] (Scheme 1). Oppenauer oxidation of intermediate **6** provided ketone **7** [10], borane reduction of which yielded a 85 : 15 mixture of alcohols **8** and **6** [11]. Alcohol **8** was isolated by chromatography and provided 17β-hydroxy steroid **4** after demasking of the ether functionality.

Scheme 1

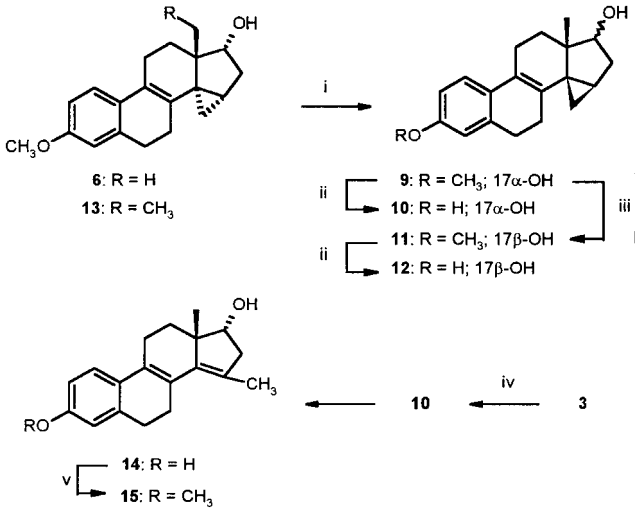


i: Zn, CH_2I_2, THF,))); 80%. ii: DIBAL-H, toluene, reflux; 99 % **3**· 0.5 H_2O, 71 % **4**.
iii: $Al(O/Pr)_3$, cyclohexanone, toluene; 83 %. iv: BH_3, THF; 65 %

2.1.2. Cyclopropane ring isomerization

Recently, stereoisomerization of compound **6** at the 14α,15α-cyclopropane ring by treatment with molecular sieve or trifluoroacetic acid was observed [5, 6]. Extending our investigations into this outstanding property of a 14α,15α-methylen-estra-1,3,5(10),8-tetraene structure, we found that neat 3-methoxy steroid **6**, heated to 180 °C for 8 h, resulted in a clean inversion of the cyclopropane ring too, thus forming 14β,15β-cyclo-propano steroid **9** in a 75% yield (Scheme 2). Compound **9**, treated with DIBAL-H in toluene at reflux, gave species **10** which corresponds to lead **3** with an isomerized cyclopropane ring. The 17β-alcohol **12** resulted from Mitsunobu reaction [12] of compound **9** (yielding **11**) and methoxy group cleavage by DIBAL-H. Attempts to epimerize the 18a-homo steroid **13** by thermic stress gave a complex mixture of compounds. When, instead of methoxy steroid **6**, neat phenol **3** was heated for 2 h at 180 °C, 14β,15β-methylene ster-

Scheme 2



i: 180 °C, 8h; 75 %. ii: DIBAL-H, toluene, reflux; 91 % **10**, 90 % **12** solvate. iii: Diethyl azodicarboxylate, triphenylphosphane, 4-nitrobenzoic acid, toluene; 63 %. iv: 180 °C, 2h; 63 %. v: Me_2SO_4, K_2CO_3, AcMe; 98 %.

oid **10** was formed as an intermediate which gave 15-methyl pentaene **14** by a subsequent cyclopropane/olefin rearrangement. So far, we have no explanation for the different thermic behavior of steroids **3** and **6**.

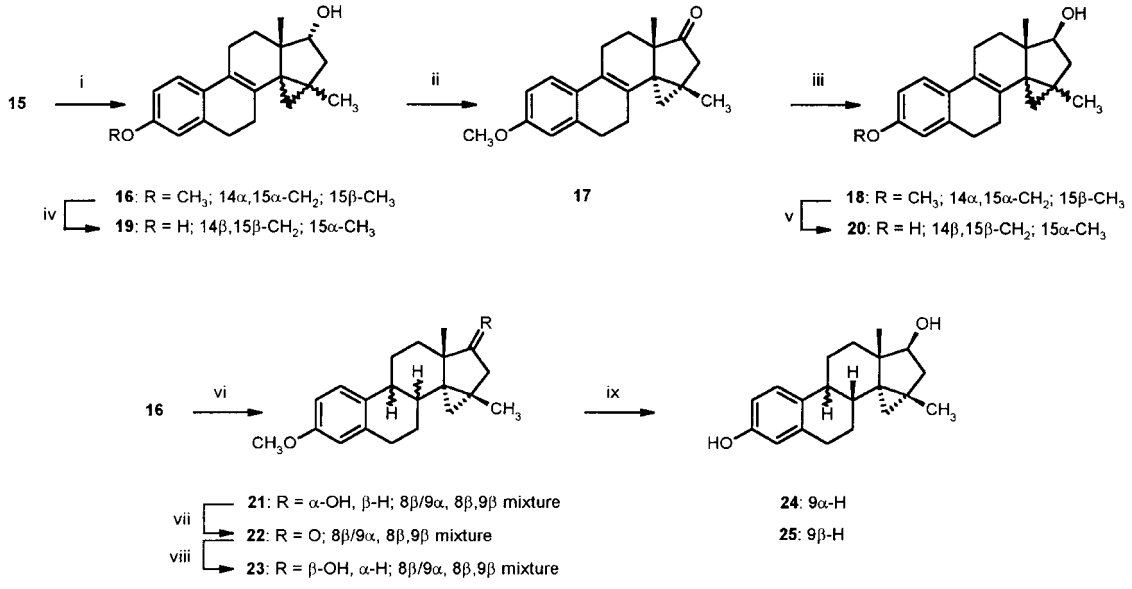
2.1.3. Cyclopropanation of compound **15**

Compound **15**, formed by methylation of phenol **14**, was subjected to sonochemical cyclopropanation and provided compound **16**, albeit in a moderate yield (Scheme 3). To obtain the 17β-hydroxy steroid **18**, ketone **17**, achieved from **16** by Oppenauer oxidation, was reduced with sodium borohydride and the alcohol mixture (**16**, **18**) separated by preparative TLC. Compounds **16** and **18**, on treatment with DIBAL-H in refluxing toluene or with sodium ethanethiolate/potassium *tert*-butoxide [13] in DMSO at 80 °C, gave the 14β,15β-methylene phenols **19** and **20**. Evidently, while methoxy group cleavage of compounds **6** and **8** left the cyclopropane ring stereochemically unchanged, introduction of a 15-methyl group rendered the molecule more susceptible to cyclopropane ring isomerization. Apparently, cyclopropane ring isomerization involves a diradical species [14], formation of which seems to be more favored in case of a ditertiary radical structure.

2.1.4. Synthesis of 8,9-saturated 15-methyl derivatives

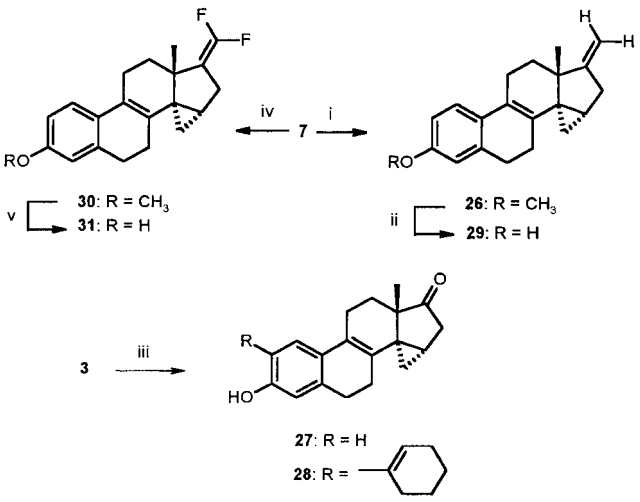
We were now in a position to synthesize 15β-methyl triene **24**, the 15-methyl derivative of lead **2**, for structure-activity studies. To this end, compound **16** was reduced with lithium in liquid ammonia/aniline at −65 °C (Scheme 3). Product **21**, a 4 : 1 mixture of 8,9-diastereomeric trienes by HPLC and ^{1}H NMR, persistently resisted preparative separation by chromatography. The same was true for the following two steps. For this reason, mixture **21** was oxidized with Jones reagent providing the 8,9-diastereomeric ketones **22**. Reduction of **22** with diborane in THF favored the formation of 17β-alcohols **23** by a ratio of 80 : 20. Flash chromatography of this substance allowed isolation of the 8,9-diastereomeric 17β-alcohols **23** which were subjected to methoxy group cleavage with DIBAL-H. Finally, separation of phenols **24** and **25** succeeded by preparative HPLC on a Chiralcel OD-H phase. The ^{1}H NMR spectrum of compound **24** showed a $\Delta\,\delta_{H-1} - \delta_{H-4}$ of 0.65 ppm. This value is in accordance with a $\Delta\delta$ of 0.63 ppm in the spectrum of 3-methoxy-14α,15α-cyclopropa[a]estra-1,3,5(10)-trien-17β-ol [8] and confirms the 8β,9α-configuration of product **24** [15]. For the minor reduction product **25**, a 8β,9β-structure was anticipated. By Molecular Force Field method (MMFF 94) [16], a distance of 2.1 Å from the *exo*-H of the methylene bridge to H-6α for the most preferred conformation of structure **25** was calculated. This distance explains why, in comparison to compound **24**, the *exo*-H of compound **25** is shielded by 0.5 ppm (see Experimental). Accordingly,

Scheme 3



i: Zn, CH_2I_2, toluene,))); 45 %. ii: Al(O*i*Pr)$_3$, cyclohexanone, toluene; 53 %. iii: $NaBH_4$, THF, MeOH; 37 %. iv: NaSEt, KO*t*Bu, DMSO, 80 °C; 43 %. v: DIBAL-H, toluene, reflux; 25 %. vi: Li, NH_3, aniline,THF, -60 °C. vii: CrO_3, H_2SO_4, AcMe. viii: BH_3, THF. ix: DIBAL-H, toluene, reflux, Chiracel OD-H, n-Hx / n-PrOH.

Scheme 4



i: Methyl triphenylphosphonium bromide, NaH, DMSO; 90 %. ii: NaSEt, KO*t*Bu, DMSO, 80 °C; 63 %. iii: $Al(OiPr)_3$, cyclohexanone, toluene; 33 % **28**. iv: *t*BuLi, n-pentane, DME, diethyl difluoromethylphosphonate; 60 %. v: DIBAL-H, toluene, reflux; 83 %.

irradiation of the *exo*-H signal of compound **25** resulted in an NOE at H-6α, thus confirming the 8β,9β-configuration of compound **25**.

2.1.5. Synthesis of 17-methylene derivatives

Recently, 17-difluoromethylene derivatives of estra-1,3,5(10),6-tetraenes were claimed as having antioxidative potency with marginal estrogenicity [17]. We speculated that replacing the 17-hydroxy group of 14α,15α-cyclopropa[a]estra-1,3,5(10),8-tetraenes by a methylene or difluoromethylene moiety should result in compounds with increased antioxidative activity or, at least, reduced estrogenicity. Scheme 4 shows the 17-oxo group methylenation of ketone **7** which gave the 17-methylene species **26** and **30**. Attempts to unmask the methylether of compound **26** with DIBAL-H led to a product which, by NMR analysis, showed the 17-methylene group and the cyclopropane ring to be reductively cleaved. To circumvent the troublesome ether cleavage in the presence of the 17(20)-double bond, olefination of 17-oxo steroid **27** was envisaged. However, Oppenauer oxidation of compound **3** (cyclohexanone/Al-triisopropoxide) led to a mixture consisting of the desired ketone **27** and the C-2 substituted species **28**. Obviously, **28** was formed *via* nucleophilic attack of cyclohexanone by an aluminum coordinated steroid nucleus [18].

Finally, we were pleased to find that treatment of compound **26** with sodium ethanethiolate/potassium *tert*-butoxide in DMSO effected a methoxy group cleavage without cyclopropane ring isomerization providing phenol **29** in 63% yield. Difluoromethylenation of 17-oxo steroid **7** by a Horner Wadsworth Emmons reaction [19] afforded compound **30** in 60% yield. In contrast to 17-methylene steroid **26**, compound **30** reacted cleanly with DIBAL-H in refluxing toluene to give compound **31** in 83% yield. Neither cyclopropane ring isomerization of steroid **30** nor reduction of the 17(20)-double bond or reductive dehalogenation at C-20 was observed.

2.2. Elucidation of the D-ring stereochemistry by ^{1}H NMR

Reportedly, in 17-oxyfunctionalized 14,15-methylene estra-1,3,5(10)-trienes, the chemical shift of the *geminal* H-17 and the splitting of the corresponding signal allows to decide whether the hydroxy group and the methylene bridge are *cis* or *trans* oriented to each other [20]. In particular, the triplet-like signal pattern of H-17 in case of a *trans* position and the doublet-like signal pattern in case of a *cis* position of hydroxy group and methylene bridge allowed easy information on the relative stereochemistry at ring D. ^{1}H NMR spectra measured in pyridine vs. chloroform proved to be another effective tool in this respect. It has previously been demonstrated that in hydroxylic compounds the use of pyridine instead of chloroform results in a paramagnetic solvent shift of protons occupying positions 1,3-diaxial, vicinal, or geminal to the hydroxyl function. In addition, a methyl group vicinally situated to the hydroxyl function was reported to be deshielded depending on the magnitude of the dihedral angle between these two groups [21]. In 14,15-methylen-estra-1,3,5(10),8-tetraene-17β-ols (**8**, **11**) we found a pyridine vs. chloroform induced downfield shift of the 13-methyl group in the range of 0.30 ppm, whereas the *trans* oriented 17α-alcohols (**6**, **9**) showed a negligible or lower effect. In case of a 17-hydroxy group *cis* situated to the 14,15-cyclopropane ring (**6**, **11**), the corresponding *endo* proton of the methylene bridge experienced a downfield shift of 0.65 ppm in pyridine relative to chloroform. When the 17-hydroxy group and the 14,15-cyclopropane ring were in a *trans* position, the downfield shift was 0.15 ppm only. In contrast to the *endo* proton, the *exo* proton of the methylene bridge was much less affected. Table 1 shows these effects exemplarily with compounds **6**, **8**, **9**, and **11**.

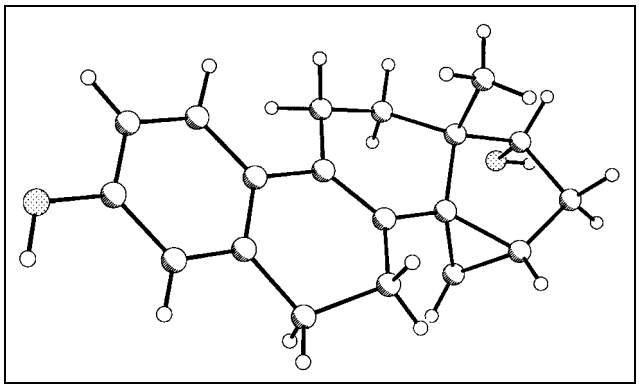


Fig.: X-Ray analysis of compound **3**

Table 1: ^{1}H NMR data (ppm) measured in $CDCl_3$ vs. pyridine-d_5 ($\Delta = \delta_{Py-d5} - \delta_{CDCl_3}$)

Compd.	H-18			14,15-CH_2, endo-H			14,15-CH_2, exo-H		
	δ_{CDCl3}	δ_{Py-d5}	Δ	δ_{CDCl3}	δ_{Py-d5}	Δ	δ_{CDCl3}	δ_{Py-d5}	Δ
8	0.95	1.27	0.32	0.64	0.78	0.14	0.37	0.37	0.00
6	0.92	1.00	0.08	1.28	1.92	0.64	0.47	0.58	0.11
11	1.02	1.32	0.30	1.07	1.62	0.65	1.07	1.20	0.13
9	1.01	1.21	0.20	0.49	0.65	0.16	0.98	1.01	0.03

All used ^{1}H NMR methods primarily led to a relative stereochemistry. However, in connection with the X-ray analysis of compound **3** (Fig.), ^{1}H NMR data immediately provided the absolute stereochemistry of the given molecule.

2.3. Pharmacological results

2.3.1. Estrogenicity

Table 2 shows the *in vivo* and *in vitro* estrogenicity of selected 14,15-methylene bridged estra-1,3,5(10),8-tetraenes. The Allen Doisy test clearly divided the tested steroids into three groups: compounds **2**, **4**, and **19** displayed estrogenicity in the range of β-estradiol (**1**), compounds **3** and **14** showed moderate estrogenic potency, and species **10**, **12**, **29**, and **31** proved to be compounds with minor or negligible estrogenicity. The conspicuous discrepancy between the results of compounds **3** and **12** in the Allen Doisy test and the estrogen receptor α binding assay may be due to partial antiestrogenicity of the compounds. The results of the Allen Doisy test show that an inversion of the 14α,15α-methylene bridge dropped the estrogenicity by one to two orders of magnitude (**3** vs. **10**, **4** vs. **12**). The same was true, when, in the presence of a 14α,15α-methylene bridge, a 17β-hydroxy group was replaced by a 17α-hydroxy group (**4** vs. **3**). Notably, insertion of a 15-methyl group into compound **10** which led to steroid **19**, gave rise to an estrogenicity increased by two orders of magnitude.

2.3.2. Antioxidative potency

The antioxidative potency of various compounds was determined by measuring the lipid peroxidation – inhibiting effect of the test compounds on synaptosomal iron – induced lipid peroxidation. Another test was the inhibitory action of the Fe(II) autoxidation in the presence of rat synaptosomal membrane/lipid fractions (for the methods and the pharmacological background see [2]). In both *in vitro* tests, especially in the first, 17-methylene steroids **29** and **31** showed a comparatively high antioxidative activity (Table 3). Since both steroids simultaneously displayed an outstandingly low estrogenicity *in vitro* and *in vivo* (Table 2), compounds **29** and **31**, in addition to compound **3**, may allow for future *in vivo* studies aiming at gender-independent hormone replacement therapy. The results in this field will be published elsewhere.

Table 2: *In vivo* and *in vitro* estrogenicity of selected compounds

Compd.	Allen Doisy test, s.c. ED_{50} (μg/OVX rat)	ERα binding Rabbit uterus cytosol RBA [%] ± SD*
1	0.19	100
2	0.25	120 ± 8
3	6.5	62 ± 9
4	0.2	55 ± 10
10	55	17 ± 4
12	55	44 ± 4
14	5.5	3.7 ± 0.4
19	0.31	27 ± 8
20		77 ± 9
24		71#
29	1550	6.6 ± 0.9
31	289	3.6 ± 0.3

* Relative molar binding affinity, RBA = 100 × $IC_{50estradiol}/IC_{50compound}$. #Human ERα

Table 3: Antioxidative activity of selected compounds

Compd.	Inhibition of Fe-induced lipid peroxidation IC_{50} (μM)	Fe(II) autoxidation inhibition (%)
3	1.51 ± 0.11	32.5 ± 0.7
4	3.94 ± 0.17	40.9 ± 1.52
12	1.6 ± 0.25	36.7 ± 1.9
14	7.0 ± 0.2	29.5 ± 1.5
29	0.15 ± 0.03	49.7 ± 2.3
31	0.24 ± 0.04	43.9 ± 0.1

3. Experimental

3.1. Reagents and equipment

All reactions were run under argon protection, and, if essential, with strict protection from moisture. Solvents and chemicals (Sigma-Aldrich Chemie GmbH, Deisenhofen/Germany, Merck KGaA, Darmstadt/Germany) were reagent grade or analytical grade and, unless otherwise stated, were used without further purification. Unless otherwise stated, the organic extracts were washed until neutral, dried over anh. Na_2SO_4 or $MgSO_4H_2O$, and evaporated to dryness in a vacuum rotary evaporator. Chromatography (CC) means flash chromatography on Silicagel 60 (Merck-Darmstadt, 0.04 − 0.063 mm), eluents were given in volume proportions. The purity of all final compounds was ≥ 97% area by HPLC or GC. Melting points were measured with a Büchi B-545 and are uncorrected. Optical rotations were taken with a Jasco DIP-1000 polarimeter. Unless otherwise stated, $CHCl_3$ was used as solvent, c = 1 g/100 ml, t = +20 °C. ^{1}H NMR spectra were recorded on a Varian Gemini 300, ^{19}F NMR spectra were taken with a Varian Mercury Vx 400 at 376 MHz. Unless otherwise stated, $CDCl_3$ was used as solvent. Selected samples were allowed to react with TAI (trichloroacetyl isocyanate) to ease the interpretation of spectra [22]. Chemical shifts were reported in ppm downfield from Me_4Si (^{1}H) or $CFCl_3$ (^{19}F) as internal standards, J and Σ (sum of J) were given in Hz. The spectral data were recorded as δ (multiplicities, J or Σ, proton number). Mass spectra (EI) were taken with an MS AMD 402 (BE configuration) of AMD-Intectra, Harpstedt. IR spectra were taken with an ATI Mattson Genesis Series FTIR using KBr pellets. Results of elemental analysis were in an acceptable range for all the compounds synthesized. Abbreviations: MeOH = methanol; EtOH = ethanol; AcOEt = ethyl acetate; AcMe = acetone; n-Hx = n-hexane; CyHx = cyclohexane; Et_2O = diethyl ether; Dx = 1,4-dioxane; Py = pyridine; MeO*t*Bu = methyl *tert*-butyl-ether; THF = tetrahydrofuran; DIBAL-H = diisobutylaluminum hydride; Al(O*i*Pr)$_3$ = aluminium isopropoxide; DMSO = dimethyl sulfoxide; DME = dimethoxyethane; iPrOH = isopropanol; *t*BuLi = *tert*-butyllithium; Me_2SO_4 = dimethylsulfate; NaSEt = sodium ethanethiolate; KO*t*Bu = potassium *tert*-butoxide.

3.2. 14α,15α-Cyclopropa[a]estra-1,3,5(10),8-tetraene-3,17α-diol (3)

A solution of DIBAL-H (46 ml, 0.26 mol) in absolute toluene (104 ml) was added to a cooled (−5 °C) suspension of compound **6** (10 g, 33.7 mmol) in absolute toluene (50 ml) dropwise with stirring, while the temperature was kept between −5 °C and 0 °C. When the DIBAL-H solution had been added completely, the homogeneous mixture was refluxed for 3 h. The mixture was cooled to −20 °C and excess DIBAL-H was very cautiously destroyed by successive addition of EtOH, EtOH/H_2O (1 : 1), and diluted HCl (1 : 2). The organic phase was separated and the aqueous phase extracted two times with AcOEt. The organic solutions were subjected to a water steam distillation until the organic solvents had been completely distilled off. The residual aqueous suspension was stirred for 1 h at 10 °C and filtered off providing a yellow solid. Crystallization from MeOH/H_2O 4 : 1, yielded 9.89 g (99%) of title compound **3** as a solvate containing 5.98% H_2O (monohydrate), estimated by head space GC. Attempts to dry the compound failed due to decomposition. $[\alpha]_D$ −79°. ^{1}H NMR (DMSO-d_6): 0.32 (dd, 7.6, 2.9, 14α,15α-CH), 0.83 (s, H-18), 1.28 ("t", 3.4, 14α,15α-CH), 3.70 (dd, 5.7, 4.3. H-17β), 4.60 (d, 4.3, 17-OH), 6.51 (d, 2.7, H-4), 6.54 (dd, 2.7, 8.4, H-2), 6.96 (d, 8.4, H-1), 9.14 (s, OH). MS: m/z 282.16220 (M^+), 264.15258 (M−H_2O), 249.12980 (264−CH_3), 235.11279 (249−CH_2).
$C_{19}H_{22}O_2$ (282.4)

3.3. 3-Methoxy-14α,15α-cyclopropa[a]estra-1,3,5(10),8-tetraen-17-one (7)

A solution of Al(O*i*Pr)$_3$ (3.75 g, 18.3 mmol) in absolute toluene (85 ml) was added to a distilling solution of alcohol **6** (2.35 g, 7.9 mmol) in toluene (250 ml) and cyclohexanone (35 ml) in such a manner that, as much isopropoxide solution was added as toluene was distilled off. Afterwards,

the reaction mixture was refluxed for 4 h. The solution was now cooled to RT. and aqueous sodium potassium tartrate solution (100 g in 150 ml H_2O) was added with stirring. The organic phase was separated and evaporated *in vacuo*. The oily residue was then steam-distilled for 2 h. The aqueous phase was extracted with CH_2Cl_2. Work-up and crystallization from MeOH gave compound **7** (1.96 g, 83%). M.p. 141–143 °C (MeOH). $[\alpha]_D$ −108°. ^{1}H NMR: 0.16 (dd, 3.1, 5.5, 14α,15α-CH), 0.86 (m, Σ 15.6, 14α,15α-CH), 1.16 (s, H-18), 3.80 (s, 3-OCH_3), 6.69 (d, 2.7, H-4), 6.72 (dd, 2.7, 8.5, H-2), 7.13 (d, 8.2, H-1). MS: m/z 294.16119 (M^+), 266.16958 (M−CO), 251.14410 (266−CH_3). $C_{20}H_{22}O_2$ (294.4)

3.4. 3-Methoxy-14α,15α-cyclopropa[a]estra-1,3,5(10),8-tetraen-17β-ol (**8**)

A borane solution, prepared from $NaBH_4$ (2.95 g, 78 mmol) and BF_3 Et_2O (10.25 ml, 49.6 mmol) in THF (128 ml), was added dropwise to a stirred solution of ketone **7** (8.01 g, 27.2 mmol) in THF (32 ml) at 3 °C. Stirring was continued at 3 °C until TLC control showed the reaction to be complete (1.5 h). The reaction mixture was dropped into H_2O (960 ml) and the precipitate filtered off. The product was a mixture of alcohols **8** and **6** (83% : 10% area by HPLC). CC (CyHx/AcOEt 7 : 3) and crystallization from MeOH provided compound **8** (5.26 g, 65%). M.p. 132–137 °C (MeOH). $[\alpha]_D$ −31°. ^{1}H NMR: 0.37 (dd, 5.1, 7.8, 14α,15α-CH), 0.64 (dd, 3.1, 5.2, 14α,15α-CH), 0.95 (s, H-18), 3.60 (dd, 7.0, 8.8, H-17α) 3.79 (s, 3-OCH_3), 6.68 (d, 2.7, H-4), 6.72 (dd, 2.7, 8.5, H-2), 7.13 (d, 8.5, H-1). MS: m/z 296.17669 (M^+), 281.15439 (M−CH_3), 278.16780 (M−H_2O), 263.14538 (278−CH_3).

3.5. 14α,15α-Cyclopropa[a]estra-1,3,5(10),8-tetraene-3,17β-diol (**4**)

Compound **8** (1.95 g, 6.6 mmol) in absolute toluene (15 ml) was treated with a solution of DIBAL-H (9 ml, 50 mmol) in absolute toluene (29 ml) as described with compound **3**. Work-up gave a crystalline solid (1.61 g) that was subjected to CC (CyHx/AcOEt 7 : 3). Crystallization from MeOH/H_2O afforded compound **4** (1.33 g, 71%). M.p. 105 °C (softening), from 110 °C decomp. $[\alpha]_D$ −29°. ^{1}H NMR: 0.37 ("t", 7.2, 14α,15α-CH), 0.65 (dd, 3.3, 5.5, 14α,15α-CH), 0.96 (s, H-18), 3.62 ("t", 8.7, H-17α), 6.61 (d, 3.4, H-4), 6.64 (dd, 3.3, 7.7, H-4), 7.08 (d, 7.7, H-1). MS: m/z 282.16110 (M^+), 264.15359 (M−H_2O), 249.12959 (264−CH_3).

3.6. 3-Methoxy-14β,15β-cyclopropa[a]estra-1,3,5(10),8-tetraen-17α-ol (**9**)

Cyclopropano steroid **6** (20 g, 67.5 mmol) was heated to 180 °C in a metal bath for 8 h. The melt was cooled, ground, and crystallized from MeOH to give compound **9** (15 g, 75%). M.p. 171–175.5 °C (AcMe/n-Hx). $[\alpha]_D$ +5°. ^{1}H NMR: 0.49 (dd, 6.7, 5.9 14α,15α-CH), 0.98 (dd, 8.0, 5.9, 14α,15α-CH), 1.01 (s, H-18), 3.62 (m, Σ 16.8, H-17), 3.79 (s, 3-OCH_3), 6.67 (d, 2.5, H-4), 6.73 (dd, 8.2, 2.5, H-2), 7.15 (d, 8.2, H-1). MS: m/z 296.17679 (M^+), 278.16870 (M−H_2O), 263.14358 (278−CH_3).
$C_{20}H_{24}O_2$ (296.4)

3.7. 14β,15β-Cyclopropa[a]estra-1,3,5(10),8-tetraene-3,17α-diol (**10**)

Compound **9** (10 g, 33.7 mmol) in absolute toluene (25 ml) was treated with a solution of DIBAL-H (41 ml, 232 mmol) in absolute toluene (91 ml) as described with compound **3**. Work-up gave a solid which was cystallized from AcOEt to afford title compound **10** (8.7 g, 91%). M.p. 232–236 °C (AcOEt). $[\alpha]_D$ −1.5° (Dx); ^{1}H NMR (DMSO-d_6): 0.51 ("t", 5.6, 14β,15β-CH), 0.90 (s, H-18), 3.47 (m, H-17β), 4.48 (d, 5.8. 17-OH), 6.50 (d, 2.2, H-4), 6.56 (dd, 8.4, 2.2. H-2), 6.98 (d, 8.0, H-1), 9.14 (s, 3-OH). MS: m/z 282.16171 (M^+), 264.15188 (M−H_2O), 249.12809 (264−CH_3), 235 (249−CH_2).
$C_{19}H_{22}O_2$ (282)

3.8. 3-Methoxy-14β,15β-cyclopropa[a]estra-1,3,5(10),8-tetraen-17β-ol (**11**)

Diethyl azodicarboxylate (4.63 ml of a 40% solution in toluene, 10.6 mmol) was cautiously added to a stirred mixture of compound **9** (1.0 g, 3.4 mmol), triphenylphosphane (2.67 g, 10.2 mmol), and 4-nitrobenzoic acid (1.70 g, 10.2 mmol) in toluene (50 ml). The mixture was kept at 80 °C for 2 h, then cooled, diluted with H_2O, and extracted three times with AcOEt. After work-up, the product (1.5 g) was allowed to react with K_2CO_3 (9.4 g) in MeOH (250 ml)/H_2O (5 ml) at 50 °C for 3 h. The MeOH was distilled off and the residue diluted with H_2O. The aqueous phase was extracted three times with AcOEt. After evaporation to dryness, the residue was purified by CC (CyHx/AcOEt 3 : 1) yielding compound **11** (0.63 g, 63%). M.p. 162–166 °C (MeOH). $[\alpha]_D$ +47°. UV: 284 (4.3). ^{1}H NMR ($CDCl_3$/TAI): 1.02 (s, H-18), 1.04 (unresolved, 14β,15β-CH), 1.16 ("t", 14.4, 14β,15β-CH), 3.78 (s, 3-OCH_3), 4.99 (d, 6.6, H-17α), 6.65 (d, 2.3, H-4), 6.70 (dd, 2.3, 8.6, H-2), 7.10 (d, 8.6, H-1). MS: m/z 296.17739 (M^+), 281.15439 (M−CH_3), 278.16711 (M−H_2O).

3.9. 14β,15β-Cyclopropa[a]estra-1,3,5(10),8-tetraene-3,17β-diol (**12**)

Methoxy steroid **11** (2.38 g, 8.04 mmol) in absolute toluene (61 ml) was treated with DIBAL-H (9.2 ml, 51.7 mmol) as described with compound **3**. Work-up gave a solid which was cystallized from MeOH to afford title compound **12** (2.05 g, 90%). M.p. 198–215 °C (MeOH solvate). $[\alpha]_D$ +54° (Dx). ^{1}H NMR (DMSO-d_6): 0.90 (s, H-18), 0.95 (dd, 8.3, 5.1, 14β,15β-CH), 1.02 (dd, 5.1, 4.3, 14β,15β-CH), 3.18 (d, 5.3, C*H*$_3$OH), 3.58 (dd, 6.1, 3.9, H-17α), 4.11 (q, 5.3, CH_3O*H*), 4.57 (d, 3.9, 17β-OH), 6.50 (d, 2.4, H-4), 6.55 (dd, 2.4, 8.3, H-2), 6.96 (d, 8.3, H-1), 9.12 (s, 3-OH). MS: m/z 282.16198 (M^+), 264,15139 (M−H_2O), 249.12910 (264−CH_3).

3.10. 15-Methyl-estra-1,3,5(10),8,14-pentaene-3,17α-diol (**14**)

Compound **3** (1.0 g, 3.5 mmol) was heated to 180 °C in a metal bath. The substance immediately became liquid and resolidified after 45 min. After 2 h, the product was cooled to RT., suspended in AcMe (3 ml), and filtered off (630 mg, 63% yield). Crystallization from MeOH gave an analytical sample of compound **14** (99.9% area by HPLC). M.p. from 215 °C (decomp.). $[\alpha]_D$ −369° (Py). ^{1}H NMR (DMSO-d_6): 0.81 (s, H-18), 1.91 (s, 15-CH_3), 3.64 (m, Σ 8.8, H-17β), 4.41 (d, 5.5, 17α-OH), 6.55 (d, 2.3, H-4), 6.57 (dd, 2.3, 8.7, H-2), 7.13 (d, 8.7, H-1), 9.29 (s, 3-OH). MS: m/z 282.16250 (M^+), 264.15341 (M−H_2O), 249.13049 (264−CH_3).
$C_{19}H_{22}O_2$ (282.4)

3.11. 3-Methoxy-15-methyl-estra-1,3,5(10),8,14-pentaen-17α-ol (**15**)

A stirred mixture consisting of compound **14** (2.52 g, 8.9 mmol), K_2CO_3 (2.45 g, 17.7 mmol), Me_2SO_4 (1.67 ml, 17.6 mmol, highly toxic!), and AcMe (100 ml) was refluxed for 14.5 h. The AcMe was evaporated *in vacuo* and the residue partitioned between H_2O (150 ml) and AcOEt (200 ml). The organic phase was separated and worked up. The crude product (2.95 g) was subjected to CC (CyHx/AcOEt 3 : 2) affording compound **15** as a foam (2.60 g, 98% yield). ^{1}H NMR (DMSO-d_6): 0.82 (s, H-18), 1.92 (s, 15-CH_3), 3.64 (d, 5.5, H-17β), 3.73 (s, 3-OCH_3), 4.4 (br, 17α-OH), 6.73 (m, H-2, H-4), 7.23 (d, 9.9, H-1). MS: m/z 296.17739 (M^+), 278.16848 (M−H_2O), 263.14419 (278−CH_3).

3.12. 3-Methoxy-15β-methyl-14α,15α-cyclopropa[a]estra-1,3,5(10),8-tetraen-17α-ol (**16**)

15-Methyl pentaene **15** (1 g, 3.4 mmol) was cyclopropanated according to ref. [8]. Compound **16** (470 mg, 45%) was obtained after CC (CyHx/AcOEt 7 : 2). M.p. 169–174 °C (MeOH); $[\alpha]_D$ −123°. ^{1}H NMR (DMSO-d_6): 0.41 (broad s, 14α,15α-CH), 0.83 (s, H-18), 1.41 (s, 15β-CH_3), 3.57 (m, Σ 9.9, H-17β), 3.71 (s, 3-OCH_3), 4.53 (d, 3.3, 17α-OH), 6.67 (d, 3.3, H-4), 6.69 (dd, 3.3, 7.7, H-2), 7.08 (d, 7.7, H-1). MS: m/z 310.19519 (M^+), 295.16980 (M−CH_3), 292.18380 (M−H_2O); 277.15948 (295−H_2O).

3.13. 3-Methoxy-15β-methyl-14α,15α-cyclopropa[a]estra-1,3,5(10),8-tetraen-17-one (**17**)

Alcohol **16** (5 g, 16 mmol) in toluene (500 ml) was allowed to react with Al(O*i*Pr)$_3$ (5 g, 24.5 mmol) and cyclohexanone (50 ml) in toluene (170 ml) as described with compound **7**. The oily product was purified by CC (CyHx/AcOEt 9 : 1) to give title compound **17** (2.66 g, 53%). M.p. 118–122 °C (CyHx). ^{1}H NMR: 0.41 (d, 5.5, 14α,15α-CH), 0.86 (dd, 5.5, 3.1, 14α,15α-CH), 1.18 (s, H-18), 1.62 (s, 15β-CH_3), 3.81 (s, 3-OCH_3), 6.70 (d, 3.3, H-4), 6.73 (dd, 3.3, 7.7, H-2), 7.16 (d, 7.7, H-1). MS: m/z 308.17800 (M^+), 293.15439 (M−CH_3), 280.18170 (M−CO), 265.15930 (280−CH_3).

3.14. 3-Methoxy-15β-methyl-14α,15α-cyclopropa[a]estra-1,3,5(10),8-tetraen-17β-ol (**18**)

$NaBH_4$ (320 mg, 8.5 mmol) was added to a cooled (0 °C) solution of ketone **17** (400 mg, 1.3 mmol) in a mixture of THF (14 ml) and MeOH (14 ml) portionwise with stirring. After 2 h, AcOH (0.5 ml) was added dropwise until reaching pH 6. The mixture was evaporated to dryness and the residue partitioned between H_2O (80 ml) and AcOEt (80 ml). The organic phase was worked up to yield an oily mixture of alcohols **16** and **18** (ratio 1 : 1). Preparative TLC (CyHx/AcOEt 3 : 2, two developments) gave 17β-alcohol **18** (150 mg, 37%) as a foam. ^{1}H NMR: ($CDCl_3$/TAI): 0.61 (m, Σ 4.4, 14α,15α-CH), 1.07 (s, H-18), 1.50 (s, 15β-CH_3), 3.80 (3-OCH_3), 4.98 (d, 6.6, H-17α), 6.68 (d, 2.2, H-4), 6.72 (dd, 2.2, 7.7, H-2), 7.14 (d, 7.7, H-1), 8.33 (s, NH−CO−CCl_3). MS: m/z 310.19339 (M^+), 295.17010 M−CH_3); 292.18301 (M−H_2O), 277.15921 (292−CH_3).

3.15. 15α-Methyl-14β,15β-cyclopropa[a]estra-1,3,5(10),8-tetraene-3,17α-diol (**19**)

A mixture of methoxy steroid **16** (1.0 g, 3.2 mmol), NaSEt (1.72 g, 20.5 mmol), and KO*t*Bu (2.31 g, 20.6 mmol) in abs. DMSO (30 ml) was stirred for 5 h at 80 °C. After cooling, the solution was diluted with water (150 ml), extracted with Et_2O (150 ml) and two times with AcOEt (100 ml each). After work-up, the product (840 mg) was purified by

preparative TLC (CyHx/AcOEt 3 : 2) affording compound **19** (410 mg, 43%) as an amorphous powder. ^{1}H NMR: 0.68 (d, 5.5, 14α,15α-CH), 0. 90 (d, 5.5, 14α,15α-CH), 0.95 (s, H-18), 1.20 (s, 15-CH_3), 3.54 (t, 8.4, H-17β), 5.03 (3-OH), 6.64 (d, 2.2, H-4), 6.68 (dd, 2.2, 8.8, H-2), 7.16 (d, 8.8, H-1). MS: m/z 296.17800 (M^+), 278.16629 (M−H_2O), 263.14538 (278−CH_3).

3.16. 15α-Methyl-14β,15β-cyclopropa[a]estra-1,3,5(10),8-tetraene-3,17β-diol (**20**)

Methoxy steroid **18** (546 m g, 1.8 mmol) in absolute toluene (8.5 ml) was treated with DIBAL-H (2.5 ml, 14 mmol) as described with compound **3**. Work-up gave a product (290 mg) that was purified by CC (CyHx/AcOEt 3 : 2) yielding title compound **20** (130 mg, 25%) as a foam which solidified with n-Hx. M.p. from 181 °C (decomp.). $[\alpha]_D$ +88° (Dx). ^{1}H NMR (DMSO-d_6): 0.84 (s, H-18), 0.86 (m, 14β,15β-CH), 1.12 (15α-CH_3), 3.34 (s, 3-OCH_3), 3.49 (m, Σ 8.8, H-17α), 4.51 (d, 4.4, 17β-OH), 6.54 (d, 3, H-4), 6.56 (dd, 3, 7.7, H-2), 7.01 (d, 7.7, H-1), 9.16 (s, 3-OH). MS: m/z 296.17770 (M^+), 281.15390 (M−CH_3), 278.16839 (M−H_2O), 263.14489 (278−CH_3).

3.17. 3-Methoxy-15β-methyl-14α,15α-cyclopropa[a]estra-1,3,5(10)-trien-17α-ol and 3-methoxy-15β-methyl-14α,15α-cyclopropa[a]-9β-estra-1,3,5(10)-trien-17α-ol (*mixture* **21**)

A solution of compound **16** (5 g, 16.1 mmol) in a mixture of absolute THF (96 ml) and aniline (5.7 ml), was added to liquid NH_3 (165 ml) at −60 °C. Li (605 mg in small pieces, 87 mmol) was added within 15 min and stirring of the blue solution was continued for another 1 h at −60 °C. The reaction was quenched by addition of NH_4Cl (4.8 g). The NH_3 was allowed to evaporate and the residue was diluted with H_2O. Extraction with Et_2O and work-up gave a yellow oil (5.4 g). Purification by CC (CyHx/AcOEt 9 : 1) afforded mixture **21** (4.98 g) as an oil. ^{1}H NMR ($CDCl_3$/TAI): 0.41 ("d", 5.5, 14α,15α-CH), 0.94 ("d", 5.5, 14α,15α-CH), 1.05 (s, H-18), 1.14 (s, H-18), 1.31 (s, 15β-CH_3), 1.40 (s, 15β-CH_3), 3.78 (s, 3-OCH_3), 4.85 (d, 6.6, H-17β), 4.91 (d, 6.6, H-17β), 6.61 (d, 2.2, H-4), 6.73 (dd, 2.2, 8.8, H-2), 7.08 (d, 8.8, H-1), 7.24 (d, 8.8, H-1), 8.29 (s, HN−$COCCl_3$).

3.18. 3-Methoxy-15β-methyl-14α,15α-cyclopropa[a]estra-1,3,5(10)-trien-17-one and 3-methoxy-15β-methyl-14α,15α-cyclopropa[a]-9β-estra-1,3,5(10)-trien-17-one (*mixture* **22**)

Steroid mixture **21** (4.8 g) was dissolved in AcMe (stabilized against CrO_3, 130 ml) and oxidized with Jones reagent (9.6 ml). Work-up as usual, followed by CC (CyHx/MeO*t*Bu 7 : 3) gave title mixture **22** (2.04 g) as an oil. ^{1}H NMR: 0.28 (m, Σ 7.7, 14α,15α-CH), 0.71 (m, Σ 7.7, 14α,15α-CH), 1.20 (s, H-18), 1.27 (s, H-18), 1.42 (s, 15-CH_3), 1.52 (s, 15-CH_3), 3.78 (s, 3-OCH_3), 3.79 (s, 3-OCH_3), 6.63 (d, 2.2, H-4), 6.74 (dd, 2.2, 8.8, H-2), 7.09 (d, 7.7, H-1), 7.25 (d, 8.8, H-1).

3.19. 3-Methoxy-15β-methyl-14α,15α-cyclopropa[a]estra-1,3,5(10)-trien-17β-ol and 3-methoxy-15β-methyl-14α,15α-cyclopropa[a]-9β-estra-1,3,5(10)-trien-17β-ol (*mixture* **23**)

Mixture **22** (1.87 g) in THF (38 ml) was reduced with a borane solution (38 ml) according to the preparation of compound **8**. The crude product (**23** : **21** nearly 8 : 2) was purified by CC (CyHx/MeO*t*Bu 3 : 2) providing title mixture **23** (770 mg) as a yellowish foam. ^{1}H NMR: 0.24 (d, 5.5, 14α,15α-CH), 0.50 (d, 5.5, 14α,15α-CH), 0.99 (s, H-18), 1.06 (s, H-18), 1.27 (s, 15β-CH_3), 1.37 (s, 15β-CH_3), 3.40 (m, Σ 33.0, H-17α), 3.78 (s, 3-OCH_3), 3.79 (s, 3-OCH_3), 6.62 (d, 3.3, H-4), 6.73 (dd, 3.3, 8.8, H-2), 7.08 (d, 8.8, H-1), 7.26 (d, 7.7, H-1).

3.20. 15β-Methyl-14α,15α-cyclopropa[a]estra-1,3,5(10)-triene-3,17β-diol (24) and 15β-methyl-14α,15α-cyclopropa[a]-9β-estra-1,3,5(10)-triene-3,17β-diol (**25**)

Mixture **23** (710 mg) in abs. toluene (7 ml) was treated with DIBAL-H (12 ml) according to the preparation of compound **3**. CC of the product on LiChrospher Si 60, 12 µm (n-Hx/AcOEt 7 : 3) gave title compounds **24** and **25** as a 79 : 18 mixture by HPLC. The mixture (560 mg) was subjected to a preparative HPLC on Chiracel OD-H (n-Hx/*i*PrOH 85 : 15) providing 8β,9α-isomer **24** (352 mg) and 8β,9β-isomer **25** (40 mg). Compound **24** (350 mg), dissolved in AcMe, was precipitated with n-Hx to give 251 mg crystals. **24**: M.p. 123–124 °C (AcMe/n-Hx). $[\alpha]_D$ +113°. ^{1}H NMR: 0.24 (d, 5.5, 14α,15α-CH), 0.49 (d, 5.5, 14α,15α-CH), 0.99 (s, H-18), 1.36 (s, 15β-CH_3), 3.43 ("t", 7.9, H-17α), 4.91 (3-OH), 6.55 (d, 2.2, H-4), 6.65 (dd, 2.2, 8.8, H-2), 7.2 (d, 8.8, H-1). MS: m/z 298.19320 (M^+), 280.18219 (M−H_2O), 269.15509 (M−CH_2−CH_3), 213.12849 [M−C_5H_9O (D ring)]. **25**: ^{1}H NMR: −0.26 (d, 4.4, 14α,15α-CH), 0.79 (d, 4.4, 14α,15α-CH), 1.06 (s, H-18), 1.27 (s, 15β-CH_3), 3.39 ("t", 8.2, H-17α), 4.77 (s, broad, OH), 6.54 (d, 2.2, H-4), 6.63 (dd, 2.2, 8.8, H-2), 7.03 (d, 8.8, H-1). MS: m/z 298.19351 (M^+), 280.18200 (M−H_2O), 265.15780 (280−CH_3), 254.16560 (280−C_2H_2), 225.12910 (254−CH_2−CH_3).

3.21. 3-Methoxy-17-methylene-14α,15α-cyclopropa[a]estra-1,3,5(10),8-tetraene (**26**)

NaH (0.81 g, 80% in paraffin oil, 33.7 mmol) was added to a mixture of compound **7** (1.0 g, 3.4 mmol) and methyl triphenylphosphonium bromide (10.1 g, 28.3 mmol) in abs. DMSO (34 ml) with stirring. The solution was heated for 2 h at 55 °C, then cooled to RT. and diluted with H_2O (35 ml). The solution was extracted three times with Et_2O. After work-up, the product was purified by CC (CyHx/AcOEt 9 : 1) to give title compound **26** (0.89 g, 90%) as a foam. $[\alpha]_D$ −136°. ^{1}H NMR (DMSO-d_6): 0.18 ("t", 3.3, 14α,15α-CH), 0.48 (dd, 4.4, 6.6, 14α,15α-CH), 0.99 (s, H-18), 3.72 (s, 3-OCH_3), 4.75 (broad s, 17=CH), 4.78 (broad s, 17=CH), 6.70 (d, 3.3, H-4), 6.71 (dd, 3.3, 8.8, H-2), 7.10 (d, 8.8, H-1). MS: m/z 292.18411 (M^+), 277.15820 (M−CH_3), 262.13800 (277−CH_3).

3.22. 2-Cyclohex-1′-enyl-3-hydroxy-14α,15α-cyclo-propa[a]estra-1,3,5(10), 8-tetraen-17-one (**28**)

Compound **3** (1 g, 3.5 mmol) in dry toluene (100 ml) was allowed to react with Al(O*i*Pr)$_3$ (1 g, 4.9 mmol) and cyclohexanone (10 ml) in toluene (33 ml) as described with compound **7**. CC of the product (CyHx/AcOEt 4 : 1) gave title compound **28** (420 mg, 33%) and a mixed fraction containing compounds **27** and **28**. **28**: M.p. 160 °C (softening) 162.5–167 °C (AcMe/n-Hx). $[\alpha]_D$ −93° (Py). ^{1}H NMR: 0.15 (dd, 5.5, 2.7, 14α,15α-CH), 0.86 (m, Σ 15.4, 14α,15α-CH), 1.16 (s, H-18), 1.43 (s, $(CH_2)_4$), 5.58 (3-OH), 5.85 (m, =CH-), 6.71 (s, H-4), 6.94 (s, H-1). MS: m/z 360.20849 (M^+), 345.18499 (M−CH_3), 332.21411 (M−CO), 317.19061 (345−CO or 332−CH_3).

3.23. 17-Methylene-14α,15α-cyclopropa[a]estra-1,3,5(10),8-tetraen-3-ol (**29**)

Methoxy compound **26** (400 mg, 1.4 mmol) was allowed to react with NaSEt (688 mg, 8.2 mmol) and KO*t*Bu (924 mg, 8.2 mmol) in dry DMSO (10 ml) as described with compound **19**. The cooled reaction mixture was then diluted with H_2O (30 ml) and extracted three times with Et_2O. After work-up the product (370 mg) was purified by CC (CyHx/AcOEt 7 : 3) yielding title compound **29** as an amorphous powder (239 mg, 63%). $[\alpha]_D$ −132°. ^{1}H NMR (DMSO-d_6): 0.17 ("t", 3.8, 14α,15α-CH), 0.45 (dd (4.4, 6.6, 14α,15α-CH), 0.98 (s, H-18), 4.74 (broad s, 17=CH), 4.77 (broad s, 17=CH), 6.52 (d, 2.5, H-4), 6.54 (dd, 2.5, 7.7, H-2), 6.98 (d, 7.7, H-1), 9.15 (s, 3-OH). MS: m/z 278.16659 (M^+), 263.14309 (M−CH_3).

3.24. 17-Difluoromethylene-3-methoxy-14α,15α-cyclopropa[a]estra-1,3,5(10),8-tetraene (**30**)

*t*BuLi (1.95 ml of a 1.7 M solution in n-pentane, 3.3 mmol) was added to a −70 °C cold mixture of DME (4.6 ml), n-pentane (0.9 ml), and diethyl difluoromethylphosphonate (0.52 ml, 3.3 mmol) with stirring. Stirring was continued for 15 min and ketone **7** (395 mg, 1.3 mmol), dissolved in DME (6 ml) and n-pentane, was added. The reaction mixture was kept at −70 °C for another 30 min and then slowly distilled in an oil bath of 110 °C until the reaction mixture reached 80 °C. Now, the mixture was refluxed for 4 h, cooled to RT., and diluted with ice water (75 ml). The viscous precipitate was filtered off and subjected to CC (CyHx/MeO*t*Bu 10 : 1) affording title compound **30** (267 mg, 60%). M.p. 115.5–117 °C (CyHx). $[\alpha]_D$ −109°. IR: 1769 cm^{-1} (C=CF_2). ^{1}H NMR: 0.37 (dd, 3.1, 4.7, 14α,15α-CH), 0.51 (m, Σ 13.7, 14α,15α-CH), 1.10 (s, H-18), 3.79 (s, 3-OCH_3), 6.67 (d, 3.1, H-4), 6.70 (dd, 3.1, 8.2, H-2), 7.11 (d, 8.2, H-1). ^{19}F NMR: −91.6 (d, 67), −94.7 (d, 67). MS: m/z 328.16549 (M^+), 313.14199 (M−CH_3), 171.08059 (M−C/D ring).

3.25. 17-Difluoromethylene-14α,15α-cyclopropa[a]estra-1,3,5(10),8-tetraen-3-ol (**31**)

Methoxy steroid **30** (610 mg, 1.8 mmol) in absolute toluene (9.4 ml) was treated with DIBAL-H (2.7 ml, 15.1 mmol) as described with compound **3**. Work-up gave a solid (550 mg) that was triturated in CyHx affording two crops of title compound **31**. Yield: 487 mg (83%). M.p. 156–158 °C (CyHx). $[\alpha]_D$ −115°. IR: 1769 (=CF_2), 3303 (OH). ^{1}H NMR: 0.37 (dd, 3.5, 4.7, 14α,15α-CH), 0.51 (m, Σ 13.7, 14α,15α-CH), 1.10 (s, H-18), 4.70 (s, 3-OH), 6.59 (d, 2.7, H-4), 6.63 (dd, 2.7, 8.2, H-2), 7.06 (d, 8.2, H-1). ^{19}F NMR: −91.6 (d, 67, 17=CF), −94.7 (d, 67, 17=CF). MS: m/z 314.14920 (M^+), 299.12658 (M−CH_3).

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