Monatshefte für Chemie 136, 1651–1669 (2005)
DOI 10.1007/s00706-005-0344-5

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Azasteroids. Synthesis by *Diels-Alder* Reaction between Maleimides, Citraconimide, and Triazolindiones and 1-(1-Trialkylsiloxyvinyl)-3,4-dihydronaphthalene Derivatives

Adnan Sultani, Harald Dietrich, Friedrich Richter, and **Hans-Hartwig Otto***

Department of Pharmaceutical/Medicinal Chemistry (PMC), Institute of Pharmacy, Ernst-Moritz-Arndt-University, DE-17487 Greifswald, Germany

Received December 27, 2004; accepted January 3, 2005
Published online July 22, 2005

Summary. 18-Nor-16-azaestrane derivatives with 8β, 13β, and 14β orientation were isolated from *Diels-Alder* reactions between maleimides or citraconimide and 1-(1-siloxyvinyl)naphthalene derivatives. (8*RS*)-13,14,16-Triazaestrane derivatives were synthesized from 1,2,4-triazolin-3,5-diones. The parent 11-oxo derivatives were obtained by desilylation, and they were transformed into 11-hydroxyimino derivatives. 3-Hydroxy derivatives, finally were synthesized by cleavage of the 3-methoxy group with BBr_3. During these transformations the stereochemistry of the steroidal skeleton was not changed. The stereochemistry of these "unnatural" steroids was elucidated by spectroscopic methods, and compared with results from calculations, and with the configuration of natural estrane derivatives. Finally, an improved method for the synthesis of the starting material, 6-methoxy-1-[(1-trialkylsiloxy)-vinyl]-3,4-dihydronaphthalene was developed.

Keywords. 2-Trialkylsiloxy-1,3-diene; Maleimide; Triazolindione; Azasteroid; Cycloaddition.

Introduction

Natural steroids with 8β, 9α, 13β, and 14α configuration, and partially modified derivatives are used as highly potent drugs [1]. During the last decades derivatives with a partial natural configuration but unusual substitution patterns became valuable therapeutics like the 5α-reductase inhibitor finasteride [2] and the antigestagene mifepristone [3]. Whereas the structure of mifepristone shows an unusual substituent, a *para*-dimethylaminophenyl group at position C-11, finasteride

* Corresponding author. E-mail: ottohh@pharmazie.uni-greifswald.de

belongs to the important group of 4-azasteroids [4]. There are many potent syntheses described for those systems containing the nitrogen atom either in ring A or in ring B of the steroid skeleton [5]. We have described *Diels-Alder* reactions between 1-(1-siloxyvinyl)cyclohexene and dienophiles [6] and reactions between cyclopentadiene and maleimides [7]. Here we report about our studies of the reaction between 1-(1-siloxyvinyl)-3,4-dihydronaphthalene derivatives and maleimides and related dienophiles.

Results and Discussion

Synthesis

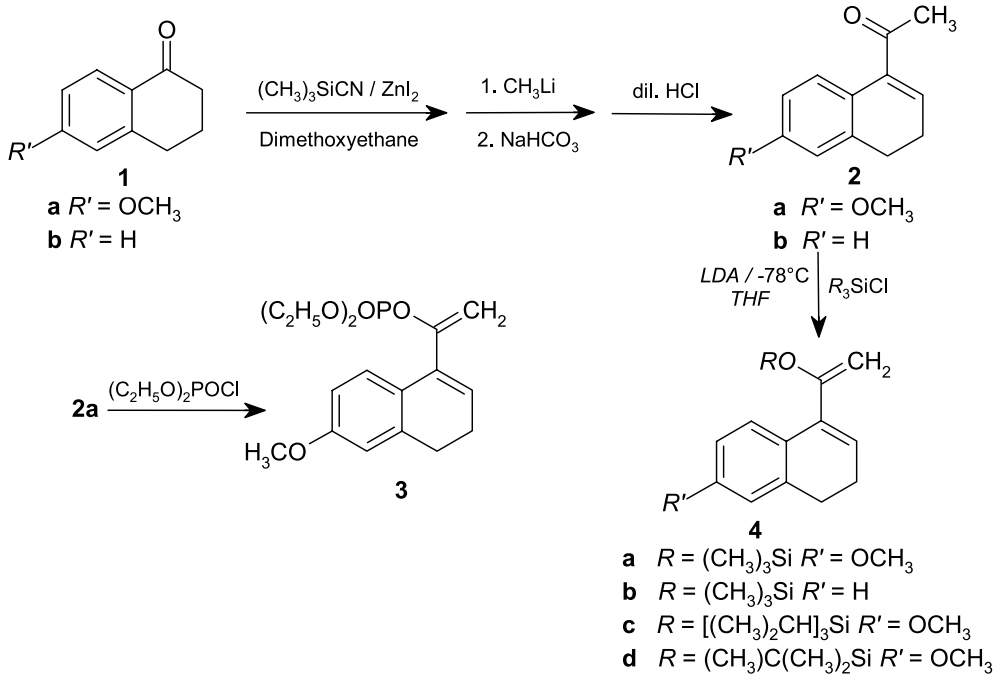
Starting materials for the synthesis of the 1-(1-trialkylsiloxyvinyl)-3,4-dihydronaphthalenes **4a**, **4c**, **4d**, and **4b** were the acetyl derivatives **2a** and **2b** which could be prepared from the tetralones **1a** and **1b** by reaction with sodium acetylide followed by a *Rupe* rearrangement [8, 9], but the reaction needs drastic and dangerous conditions, and the yields of **2a** and **2b** were not satisfying. The *Friedel-Crafts* acylation of 1-trimethylsilyl-3,4-dihydronaphthalenes with acetyl chloride could be an alternative route [10] but yielded a number of by-products. Therefore, we prepared **2a** and **2b** from **1** following Ref. [11] by reaction with Me_3SiCN and ZnI_2 without isolation of the intermediates followed by a reaction with *Me*MgBr, and finally hydrolysis. We modified the reaction conditions, the procedure, and replaced *Me*MgBr by *Me*Li, which allowed working at more convenient temperatures, and improved the yields. Therefore, we give the detailed procedure in the experimental part. The overall yield was in all experiments higher than 65%. The final silylation step was done in the usual way [12, 13] in *THF* at -78°C with *LDA* and $ClSiR_3$. The dienes **4a**–**4d** were isolated as light yellow viscous liquids with yields higher than 90%. They were relatively stable when stored at -20°C under N_2. As known from other experiments, **4d** is the most stable compound of this group, and cleavage of the Si–O bond is extremely difficult because of the bulky silyl moiety [14].

From the reaction between **2a** and diethylchlorophosphate the phosphorylated diene **3** was obtained as a reddish liquid, yield 50%, which was very air-sensitive, whereby we did not use this compound for further reactions.

The IR spectra of the siloxydienes **4a**–**4d** were characterized by two bands at 1625 and 1610 cm^{-1} caused by the asymmetrically substituted olefinic double bond. In the ^1H NMR spectra a triplet from the proton at C-2 of the naphthalene ring, the signals of the silyl group, and two singlets of the olefinic protons at C-2′ confirmed the structure.

The cycloadditions between **4a**–**4c** and maleimides were done by refluxing equivalent amounts in toluene with *TLC* control. After evaporation of the solvent the 11-trialkylsiloxy-16-azasteroids **5a**, **5c**–**5h** were obtained with yields of 40% to >95%. Using these conditions, the yields of reactions between **4d** and maleimides were not satisfying. Therefore, these reactions were done at -78°C in CH_2Cl_2 in the presence of $EtAlCl_2$ yielding compounds **6a**–**6c** with yields up to 65%.

Trialkylsilyl groups used as protecting groups very often can be cleaved by mild methods. We tried to desilylate the cycloaddition products by many different

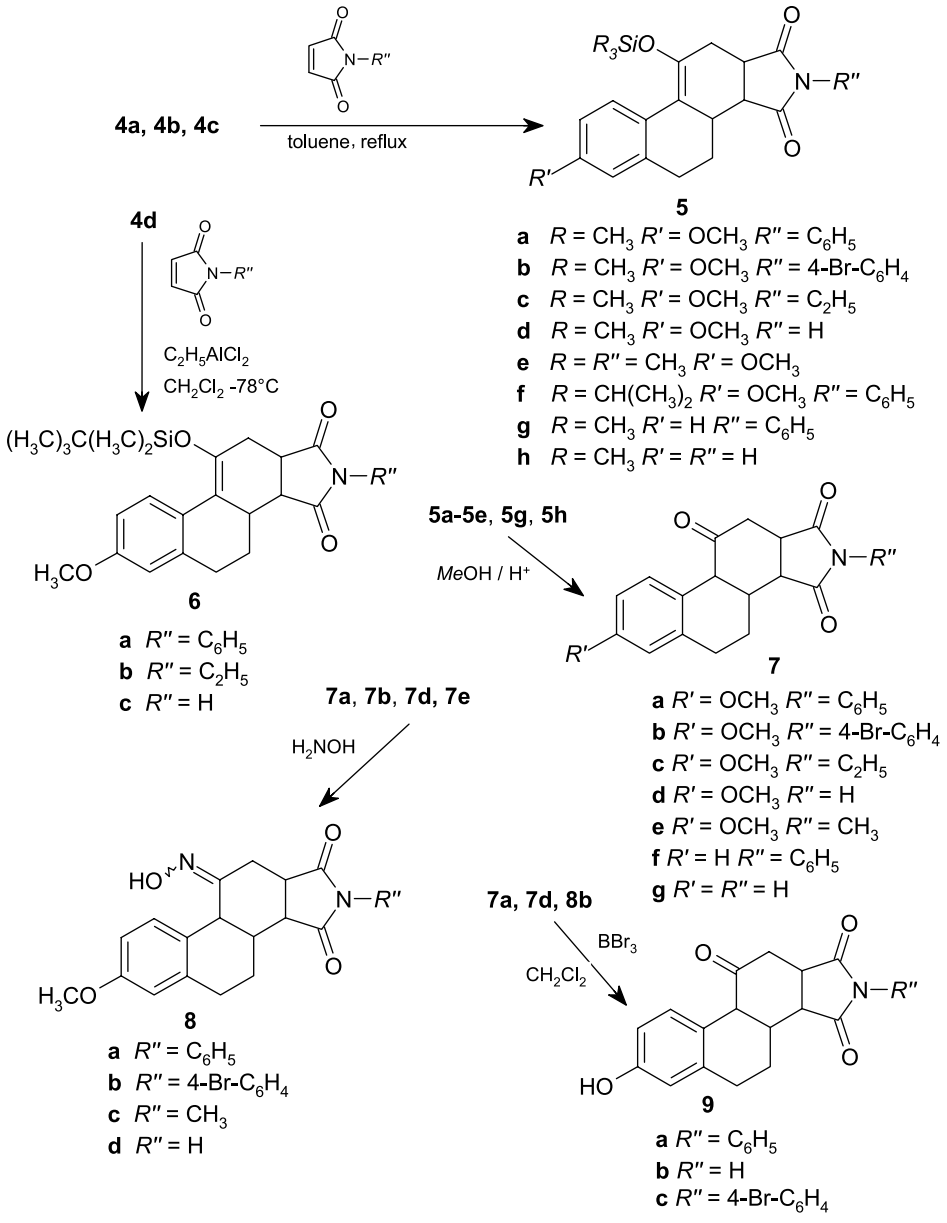


Scheme 1

methods. Finally, short-time refluxing of **5a**–**5e**, **5g**, and **5h** in a mixture of conc. HCl and *Me*OH yielded the crystalline and uniform 11-oxo derivatives **7a**–**7g** with yields of 75–99%. But when we tried to deprotect the other siloxy compounds using these conditions we failed completely. Compounds **6a**–**6c** and **5f** resisted the desilylation, and even other methods like *TBAF* in *THF* with *Ac*OH, or KF, or *TBAF*/SiO_2 were not successful.

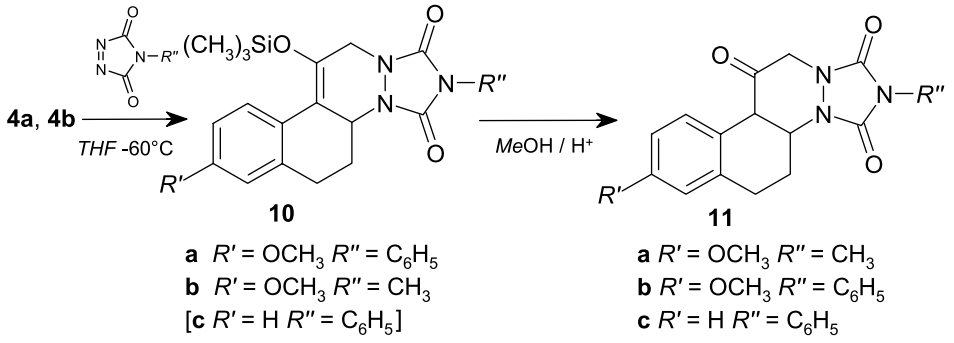
The IR spectra of **7a**–**7g** showed an intensive carbonyl band at 1720 cm^{-1}, and the C=C band around 1620 cm^{-1} was missing in the spectra. **7a**–**7c** and **7f** showed good solubility in $CHCl_3$ and similar solvents, whereas **7d**, **7e**, and **7g** were soluble only in *DMSO* or *DMF*. Finally, 4 derivatives, **7a**, **7b**, **7d**, and **7e** were transformed with $H_2NOH \times HCl$ into the crystalline 11-hydroxyimino derivatives **8a**–**8d** using the standard procedure in *Et*OH with aqueous *Ac*ONa or a modified procedure in *THF* (Scheme 2). An appropriate method to deprotect the 3-hydroxy group was the reaction with BBr_3 in CH_2Cl_2 at 0°C. When we applied this method to **7a** and **7d** the crystalline phenols **9a** and **9b** were isolated with yields of *ca.* 40%. Applying the reaction to the 11-hydroxyimino derivative **8b** not only the methoxy group was deprotected, but even the hydroxyimino group was transformed into the ketone function, and we obtained **9c** with 44% yield. As we deduced from spectroscopic data, the stereochemistry of the starting material was not changed during anyone of the described transformations (Scheme 2).

By the reactions with maleimides one nitrogen atom was introduced into position 16 of the steroid skeleton, whereas reactions between **4a**, **4b** and azadienophiles should give the possibility for the introduction of additional nitrogen atoms into positions 13 and 14. Therefore, we started experiments with the usually highly

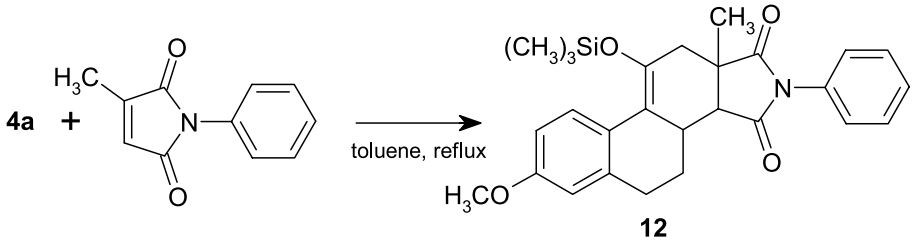


Scheme 2

reactive azodicarboxylates, but we failed completely. Either no product was obtained or the starting materials were reisolated. More successful were reactions between **4a** and **4b** and 4-phenyl- or 4-methyl-1,2,4-triazolin-3,5-diones, but these very reactive dienophiles afforded special reaction conditions. All reactions had to be done under N_2 at $-60°C$ in *THF*. Using these conditions we obtained the siloxy derivatives **10a**–**10c** with yields of *ca.* 75%. As these siloxy derivatives are very air-sensitive, they were immediately, without further purification, hydrolyzed to the 11-oxo derivatives **11a**–**11c**, isolated as colorless crystals with *ca.* 80% yield (Scheme 3).



Scheme 3

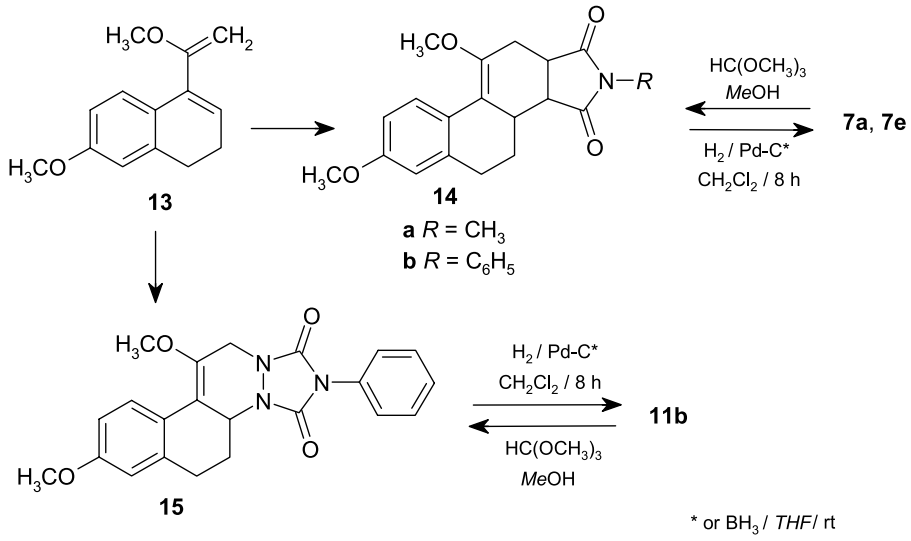


Scheme 4

The IR spectra confirmed the general structures. In the spectra of **10a** and **10b** we detected the C=C band at 1620 cm^{-1}, and in the spectra of **11a**–**11c** the carbonyl band at 1720 cm^{-1} caused by the 11-oxo group was a characteristic element.

The reaction between **4a** and α-methyl-*N*-phenylmaleimide (citraconimide) was successful when we used our standard procedure, refluxing in toluene for 3.5 h, and gave 30% of the starting material **4a**, and about 40% of a crystalline, conform product **12** showing in the MS spectra $m/z = 461$ (M^+). In the ^{1}H NMR spectrum we found one singlet for the methoxy group at $\delta = 3.76$ ppm, and one singlet for a methyl group at $\delta = 1.46$ ppm. These were interpreted as hints for the formation of only one of the two possible regioisomers. The question which one was formed could be answered by the analysis of the ^{1}H NMR spectra. We found an AB system for 8-H and 14-H at $\delta = 2.68$ and 2.86 ppm with a coupling constant $J = 3.4$ Hz, torsion angle $\sim 30°$, and positive N*O*E between 8-H and one 7-H, one 12-H, and 14-H. Considering these results, and the *endo* addition, 8-H should be β-orientated, and the methyl group should be fixed to C-13 in a *pseudoaxial* orientation (β). This result was supported by a calculation of the electron densities and the coefficients of the starting materials explaining the regioselectivity [15]. Comparing the diene **4a** with the analogue vinylnaphthalene, explains the opposite regioselectivity in the reaction between citraconimide and the vinylnaphthalene [15].

Experiments to hydrolyze the silylenol group of **12** by *Me*OH/H^+ at 60°C, or with *TBAF*/*THF*, or by H_2/Pd in CH_2Cl_2 failed. This might be explained by the half-chair conformation of ring B, and the *pseudoaxial* orientation of the methyl group prohibiting an attack of the reagent from the upper side *and* from the downside of the molecule. Furthermore, this result confirmed the proposal that in the hydrolysis of compounds with an H atom at C-13 the attack of the reagent occurred



Scheme 5

from the upper side of the molecule, which was found even in reductions of the 11-oxo and 17-oxo group yielding in all experiments the α-orientated hydroxyl group [15].

Finally, reactions between the 1-(1-methoxyvinyl) derivative **13** [9] and substituted maleimides opened a route to 11-methoxy derivatives, whereby we isolated **14a**, **14b**, and **15** with yields of 50–60%. Reductive demethylation either by H_2/Pd-C or by BH_3/*THF* gave the 11-oxo derivatives **7a**, **7e**, and **11b** with quantitative yields. Furthermore, **14a**, **14b**, and **15** were prepared from the parent 11-oxo derivatives by reaction with methyl orthoformiate in *Me*OH with high yields (Scheme 5).

Stereochemistry and Spectroscopy

Considering the mechanism of the cycloaddition [16] the reaction between the siloxy dienes and maleimides should have occurred as an *endo* addition yielding at least two possible structures for all trialkylsiloxy derivatives: either the relative

Table 1. ^{1}H NMR data of **5a**, **6b**, **5f** (250 MHz), **5d** (200 MHz), and **5e** (300 MHz); $CDCl_3$; δ (ppm)

Proton	**5a**	**6b**	**5f**	**5d**	**5e**
7β	2.10	2.07	2.14	2.04	2.11
7α	2.32	2.21	2.38	2.23	2.31
12β	2.52	2.47	2.50	2.50	2.56
6β	2.62	2.51	2.57	2.52	2.58
8β	2.68	2.59	2.71	2.72	2.68
6α	2.74	2.71	2.71	2.72	2.73
12α	2.92	2.98	2.97	2.79	2.85
14β	3.22	3.10	3.21	3.10	3.12
13β	3.34	3.14	3.36	3.22	3.20

Table 2. ^{1}H NMR data (300 MHz, $CDCl_3$, H,H-COSY) of **5e**

Proton	δ (ppm)	^2J (Hz)	^3J (Hz)
7β	2.11 (dddd)	12.6	5.8, 3.5, 3.5
7α	2.31 (dddd)	12.6	12.6, 12.6, 3.5
12β	2.56 (ddd)	15.4	7.0
6β	2.58 (ddd)	14.6	12.6, 3.5
8β	2.68 (dddd)		12.6, 5.8, 5.8
6α	2.73 (ddd)	14.6	3.5, 3.5
12α	2.85 (dd)	15.4	1.6
14β	3.12 (dd)		8.8, 5.8
13β	3.20 (ddd)		8.8, 7.0, 1.6

structure with 8β, 13β, and 14β orientation, or the relative structure with 8α, 13β, and 14β orientation. As the ^{1}H NMR data of all trialkylsiloxy compounds (Tables 1, and 2, and Exp.) of this reaction showed an analogous pattern of shift values and coupling constants, the structure elucidation is demonstrated for compound **5e** (Table 2).

The signals of 13-H and 14-H in the spectra of **5e** at $\delta = 3.20$ and 3.12 ppm, showed a coupling constant $J = 8.8$ Hz, confirming the *cis* orientation. The signal at $\delta = 2.68$ ppm (8-H) exhibited a coupling with the signal of 14-H, $J = 5.8$ Hz, which agreed with the *cis* orientation.

A further support for this structure was obtained by N*O*E experiments. Irradiation at $\delta = 2.68$ ppm (8-H) caused positive effects on the signals at $\delta = 2.11$ ppm (7-H) and $\delta = 3.12$ ppm (14-H), and irradiation at $\delta = 3.12$ ppm (14-H) caused a positive N*O*E at $\delta = 2.68$ ppm (8-H) and $\delta = 3.20$ ppm (13-H). Both effects should be possible only if 8-H, 13-H, and 14-H are situated at the same side of the molecule. Irradiation on the signal of 13-H enlarged the signals of 14-H, 12-H, and 7β-H, and irradiation at the signal of 7β-H enlarged the signals of 14-H, 8β-H, and 7α-H. All data fit to a structure with *cis-syn-cis*-connection of the rings B, C, and D, and 8β, 13β, and 14β-orientation.

Interpretation of the coupling constants following the *Karplus-Conroy* rules enabled us to construct a favored form of **5e** (under NMR conditions in $CDCl_3$), showing ring C in a flat boot form connected *endo-cis* with ring D, and ring B

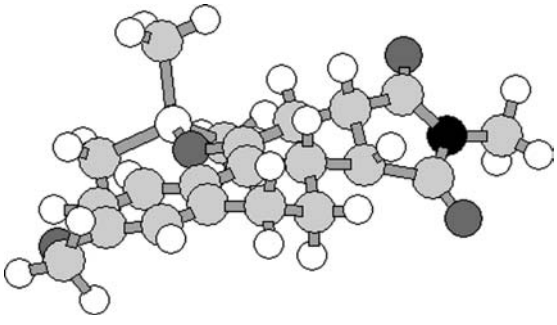


Fig. 1. Calculated structure of **5e** (MM+, HYPERCHEM)

Table 3. ^{1}H NMR data of **7a**, **7c** (300 MHz, $CDCl_3$), **7a** (400 MHz, pyridine-d_5), and **7d**, **7e** (400 MHz, *DMSO*-d_6); shift values, δ (ppm); coupling constants of the proton with the proton in position noted, J (Hz)

Proton	**7a**	**7a***		**7c**		**7d**		**7e**	
		δ	J	δ	J	δ	J	δ	J
7α	1.55	1.70	8β = 15	1.38	8β = 12	1.33	8β = 15	1.26	8β = 15
7β	2.06	2.10		1.84		1.76		1.62	
8β	2.90	3.01	9β = 4.1	2.88	9β = 4.5	2.76	9β = 4.5	2.61	9β = 4
12β	2.90	3.12	13β = 6	2.84	13β = 6	2.67	13β = 6	2.61	13β = 6
12α	2.90	3.30	13β = 2	2.84	13β = 1.5	2.76	13β = 2	2.61	13β = 2
9β	3.46	3.74		3.44		3.52		3.58	
14β	3.46	3.90	8β = 6	3.35	8β = 6	3.50	8β = 6	3.50	8β = 6
13β	3.46	4.00	14β = 9	3.35	14β = 9	3.50	14β = 9	3.50	14β = 9

* In pyridine-d_5

existing in a half-chair conformation. This proposal was in agreement with the result of a MM+ calculation (HYPERCHEM, Fig. 1).

From the shift values of other 11-trialkylsiloxy derivatives like **5a**, **5d**, **5f**, and **6b** (Table 1), and the coupling constants $^3J_{13\beta/14\beta}$ = 8–9 Hz, $^3J_{13\beta/12\beta}$ = 6 Hz, $^3J_{8\beta/14\beta}$ = 6 Hz, and $^3J_{8\beta/7\beta}$ = 6 Hz in these spectra we deduced that all isolated 11-trialkylsiloxy compounds independently from the synthetic route showed the relative structure with the orientation 8β, 13β, and 14β demonstrating that in these examples the cycloaddition strictly had followed the *endo*-rule of *Alder* [17].

An additional stereocenter at C-9 was generated by the desilylation reaction, whereby for the 11-oxo derivatives two isomers could be formed. If 9-H is *cis* related to 8β-H, the structure would show 8β, 9β, 13β, and 14β orientation, and if 9-H is *trans* related to 8β-H, the overall relative structure would be 8β, 9α, 13β, and 14β. Shift values of the ^{1}H NMR spectra of selected 11-oxo derivatives are collected in Table 3. Comparing these values with those of **5e** clearly demonstrated the different structures. Whereas the values of the signals of 8β-H and 12-H are only slightly influenced by the carbonyl group, the signals of 7-H, 13β-H, and 14β-H exhibited greater differences. N*O*E experiments showed that the proton 9-H in $CDCl_3$ solution of the isolated 11-oxo compounds was β-orientated. Irradiation at δ = 2.88 ppm (8β-H, **7c**) showed a positive effect on the signals of 9-H and 14β-H, and *vice versa*. In addition, the coupling constants ^3J = 3 Hz (**7a**, **7d**), and 4.15 Hz (**7c**, torsion angle ~44°) between the signals of 8β-H and 9-H confirmed a *pseudoaxial* orientation of both protons and thereby the relative conformation 8β, 9β, 13β, and 14β with *cis-syn-cis* connection of the rings B, C, and D. The coupling $^3J_{13\beta/14\beta}$ = 9 Hz, torsion angle ~9°, was interpreted as resulting from an *axial*/*axial* orientation, and $^3J_{8\beta/14\beta}$ = $^3J_{12\beta/13\beta}$ = 6 Hz, torsion angle ~30°, and $^3J_{12\alpha/13\beta}$ = 1.5 Hz, torsion angle ~62°, and $^3J_{8\beta/9\beta}$ = 4.5 Hz, torsion angle ~41° were interpreted as the result of a flattened boat conformation of ring C. The stereochemistry of the triaza derivatives **11a**, **10b**, and **11b** was deduced from their ^{1}H NMR data (Table 4) confirming the 8β and 9β orientation, and suggesting that the overall conformation equals that of the other 11-oxo compounds. Characteristic

Table 4. Selected ^{1}H NMR data of **11a**, **10b**, and **11b** (250 MHz, $CDCl_3$); δ (ppm); J (Hz)

	11a	**10b**	**11b**
δ (7α-H)	1.75	2.50	1.92
δ (7β-H)	2.20	1.90	2.35
δ (9β-H)	3.96	–	4.07
δ (12β-H)	4.21	4.00	4.35
δ (12α-H)	4.25	4.40	4.34
δ (8β-H)	4.60	4.46	4.78
J (8β/9β)	6	–	5.5
J (8β/7β)	3	1.5	1.5
J (8β/7α)	12	12	15

for the β orientation seemed to us the couplings $J_{8\beta/7\beta}$, $J_{8\beta/7\alpha}$, and $J_{8\beta/9\beta} = 6.0$ and 5.5 Hz indicating a torsion angle of $\sim 30^\circ$ between 8-H and 9-H.

Comparing the spectroscopic data of the 11-hydroxyimino derivatives and of the 3-hydroxy derivatives allowed us to postulate identical configuration and conformation as deduced for the 11-trialkylsiloxy and 11-oxo derivatives.

The formation of the 9β orientation in the desilylation reaction may be understood by the stereochemistry of the 11-trialkylsiloxy compounds. Considering the deduced stereochemistry (Fig. 1) is correct, the addition of a proton on C-9 occurred kinetically controlled from the downside of the conformative strained and fixed molecule (*anti*) yielding the 9β orientation as an attack from the upper side and thereby formation of the thermodynamically preferred 9α orientation is blocked by the bulky silyloxy substituent at C-11.

Whereas the natural estrogenes like estrone and estradiol are characterized by an all-*trans* connection of the rings B, C, and D [18], our unnatural derivatives show an all-*cis* connection between these rings or a *trans-cis-cis* connection. And whereas the natural estrogenes act as activators in the system of sexual hormons [19], some of the unnatural derivatives act as inhibitors of enzymes of this system like cleaving enzyme, aromatase, and 5α-reductase, and thereby might be starting materials for optimized inhibitor drugs [20].

Experimental

Melting points: *Linström* apparatus; IR spectra (KBr): Perkin-Elmer IR 1310, Nicolet 205, Beckmann IR 4240, IR 33; NMR spectra: ^{1}H: Varian T 60 (60 MHz), Bruker WP 80 (80 MHz), ARX 200 (200 MHz), WP 250 (250 MHz), ARX or WM 300 (300 MHz), AM 400 (400 MHz), ^{13}C: Bruker WH 90 (22.63 MHz), WM 250 (62.80 MHz), AM 400 (100.61 MHz), 27°C, internal *TMS*, $CDCl_3$, values from 250 MHz spectra, $CDCl_3$, if not otherwise noted; MS spectra: Finnigan MAT 44 S, EI, 70 eV; elemental analyses: Pharmazeutisches Institut, University of Freiburg or Pharmazeutisches Institut, University of Greifswald, Perkin Elmer Analyzer 2400 CHN; the results agreed with the calculated values within experimental error. Column chromatography (CC): silica gel 60 Merck 7734. Lithium diisopropylamide (*LDA*) was freshly prepared by mixing of equimolar amounts of diisopropylamine in *THF* and *n*-butyl lithium (*Bu*Li, 1.6 *M* solution in *n*-hexane) at -78°C. Solvents were purified/dried according to literature procedures. Abbreviations: *AcOEt* = ethyl acetate; *al* = aliphatic; *ar* = aromatic; *DME* = dimethoxyethane; *HMPT* = hexamethylphosphortrisamide;

PE = petroleum ether; *TBAF* = tetrabutylammonium fluoride (1 *M* solution in *THF*); TLC = thin layer chromatography (pre-coated silica gel plates 60 F_{254}, Merck 5554 or 5550). Note that all stereochemical notations describe relative stereochemistry.

1-Acetyl-6-methoxy-3,4-dihydronaphthalene (**2a**) [11]
At 60°C, under N_2 and stirring, trimethylsilylcyanide (19 cm^3, 150 mmol) was added to a mixture from a solution of 6-methoxytetralone (22.6 g, 128 mmol) in 50 cm^3 *DME* and 0.8 g ZnI_2. After stirring for 90 min, the mixture was cooled to 0°C, and with vigorous stirring *Me*Li (100 cm^3, 1.6 *M* in Et_2O, 160 mmol) was dropwise added, stirring was continued for 1 h at 0°C, and 12 h at room temperature. Then the mixture was cooled to 0°C, and very slowly hydrolyzed by dropwise adding of a satd. aqueous solution of $NaHCO_3$ (~100 cm^3), and then extracted with 6×50 cm^3 Et_2O. The combined organic layers were dried ($MgSO_4$), and evaporated *in vacuo*. 150 cm^3 HCl (10%) were added to the residue, and the mixture was refluxed for 3 h, cooled to room temperature, and extracted with 8×50 cm^3 Et_2O. The combined organic layers were washed with 250 cm^3 of a satd. aqueous solution of $NaHCO_3$, dried ($MgSO_4$), and evaporated *in vacuo*. The residue crystallized on cooling. Yield 21.4 g (83%); beige crystals; mp 74–76°C (*Me*OH).

1-Acetyl-3,4-dihydronaphthalene (**2b**) [11]
As described for **2a** from α-tetralone (13.5 cm^3, 100 mmol), 0.7 g ZnI_2 in 25 cm^3 *DME*, and trimethylsilylcyanide (15 cm^3, 100 mmol), at 60°C for 3.5 h, *Me*Li (100 cm^3, 160 mmol), and stirring for 12 h. A mixture from 300 cm^3 *Et*OH, and 300 cm^3 dil. HCl was added to the first residue, reflux 3.5 h, and work-up as for **2a**. The final residue was distilled *in vacuo*. Yield 14 g (81%); light yellow air-sensitive liquid; bp 180°C/267 Pa; IR: $\bar{\nu} = 3060$, 3020 (*ar* CH), 2940, 2900, 2840 (*al* CH), 1670 (CO), 1610 (C=C), 1600, 1490, 1450, 1260, 770 (*ar*) cm^{-1}; ^{1}H NMR: $\delta = 2.40$ (m, *Me*, 3-H_{ax}, 3-H_{eq}), 2.75 (m, 4-H_{ax}, 4-H_{eq}), 7.0 (t, $J = 6$ Hz, 2-H), 7.1 (m, 5-H, 6-H, 7-H), 7.72 (t, $J = 9$ Hz, 8-H) ppm; ^{13}C NMR: $\delta = 23.47$ (C-3), 27.28 (C-4), 29.49 (*Me*), 126.26 (C-5), 126.45 (C-7), 127.38 (C-8), 127.49 (C-4a), 130.68 (C-1), 133.21 (C-2), 136.26 (C-8a), 139.13 (C-6), 199.18 (CO) ppm.

1-(α-Diethylphosphoryloxyvinyl)-6-methoxy-3,4-dihydronaphthalene (**3**, $C_{17}H_{23}O_5P$)
Under N_2 and at −78°C, a solution of **2a** (4.1 g, 20 mmol) in 10 cm^3 *THF* was added dropwise and with stirring to a solution of *LDA* (25 mmol) in 10 cm^3 *THF*. After stirring for 20 min diethyl chlorophosphate (6.9 g, 40 mmol) was added in one portion, stirring was continued for 12 h, while the mixture warmed to room temperature. Then, 50 cm^3 of *n*-pentane were added, and the mixture was poured into 50 cm^3 of an aqueous satd. solution of $NaHCO_3$, the organic layer was separated, washed with 100 cm^3 of an aqueous satd. solution of NaCl, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by Kugelrohr distillation. Yield 3.1 g (50%); bp 200°C/133 Pa; IR: $\bar{\nu} = 2980$ (*al* CH), 1610 (C=C), 1500, 1250 (O–P) cm^{-1}; ^{1}H NMR (80 MHz): $\delta = 1.46$ (t, $J = 11$, 4.5 Hz, *Me*), 2.65 (m, 3-H_{ax}, 3-H_{eq}), 2.75 (m, 6-H_{ax}, 6-H_{eq}), 3.75 (s, O*Me*), 4.62 (dt, $J = 11$, 4.5 Hz, 3 Hz, CH_2), 4.59, 5.17 (2 t, $J = 2.5$, 1 Hz, 1 H, CH_{2vinyl}), 6.25 (dd, $J = 5.5$, 3 Hz, 1 H, CH_{2vinyl}), 6.75 (m, 5-H, 7-H), 7.32 (t, $J = 9$, 2 Hz, 8-H) ppm.

1-(α-Trimethylsiloxyvinyl)-6-methoxy-3,4-dihydronaphthalene (**4a**)
See Ref. [21]

1-(α-Trimethylsiloxyvinyl)-3,4-dihydronaphthalene (**4b**, $C_{15}H_{20}OSi$)
A solution of **2b** (3.4 g, 20 mmol) in 10 cm^3 *THF* was dropwise added at −78°C and under N_2 to a solution of *LDA* (25 mmol) in 10 cm^3 *THF*. After 10 min, $ClSi(Me)_3$ (4 cm^3, 32 mmol) was added in one portion. After warming to room temperature (after 12 h), work-up as described for **4a**. Yield 4.4 g (90%); light yellow air-sensitive liquid; bp 280°C/133 Pa; IR: $\bar{\nu} = 3120$, 3000 (*ar* CH), 2940 (*al* CH), 1620 (=C-OSi), 1480, 1450, 1250, 1020, 850 (*ar*) cm^{-1}; ^{1}H NMR: $\delta = 0.2$ (s, SiMe_3), 2.32 (m, 3-H_{ax}, 3-H_{eq}), 2.73 (m, 4-H_{ax}, 4-H_{eq}), 4.50, 4.62 (2s, CH_2), 6.13 (dd, $J = 10$, 3 Hz, 2-H), 7.25 (m, 4 *ar* H) ppm.

1-(α-Triisopropylsiloxyvinyl)-6-methoxy-3,4-dihydronaphthalene (**4c**, $C_{19}H_{28}O_2Si$)
From **2a** (4.1 g, 20 mmol) and chlorotriisopropylsilane (6.0 cm^3, 30 mmol) in 20 cm^3 *HMPT* as described for **4a**, purification by CC (Al_2O_3). Yield 6.5 g (90%); yellow viscous liquid; IR (film): $\bar{\nu} = 2960$ (*al* CH), 1625 (=C-OSi), 1470, 1260, 1050, 890 (*ar*) cm^{-1}; ^1H NMR (80 MHz): $\delta = 1.0$ (s, Si(CH*Me*$_2$)$_3$), 2.2 (m, 3-H_e, 3-H_a), 2.74 (m, 4-H_a, 4-H_e), 3.77 (s, O*Me*), 6.17 (t, $J = 10$ Hz, 2-H), 6.75 (m, 5-H, 7-H), 7.37 (d, $J = 9$ Hz, 8-H) ppm.

1-(α-tert-Butyldimethylsiloxyvinyl)-6-methoxy-3,4-dihydronaphthalene (**4d**, $C_{19}H_{28}O_2Si$)
From **2a** (4.1 g, 20 mmol) and *t*-butylchlorodimethylsilane (6.0 g, 30 mmol) in 15 cm^3 *HMPT* as described for **4a**, purification by CC (Florisil^R, *n*-hexane). Yield 6.3 g (99%); light yellow viscous liquid; IR (film): $\bar{\nu} = 3120$, 3040, 3000 (*ar* CH), 2960, 2940, 2890, 2860, 2840 (*al* CH), 1625, 1610 (=C-OSi), 1570, 1500, 840 (*ar*) cm^{-1}; ^1H NMR (60 MHz): $\delta = 0.1$ (s, Si*Me*$_2$), 0.9 (s, C*Me*$_3$), 2.0–2.9 (m, 3-H, 4-H), 3.80 (s, O*Me*), 4.45, 4.55 (2s, 2′-H), 6.15 (t, $J = 4.5$ Hz, 2-H), 6.7 (m, 5-H, 7-H), 7.35 (m, 8-H) ppm.

General Procedure for the Reaction between α-Trialkylsiloxyvinylcycloalkenes and Maleinimides
Equivalent amounts of the siloxydiene and of the maleimide in toluene were refluxed as noted (TLC control). After cooling to room temperature, the solvent was evaporated *in vacuo*, and the residue was purified as noted.

(8β,13β,14β)-3-Methoxy-16-phenyl-11-trimethylsiloxy-18-nor-16-azaestra-1,3,5(10),9(11)-tetraene-15,17-dione (**5a**, $C_{26}H_{29}NO_4Si$)
From **4a** (1.43 g, 5.1 mmol) and *N*-phenylmaleimide (0.9 g, 5.2 mmol), 30 cm^3 of toluene, 8 h. Yield 1.6 g (72%); colorless crystals; mp 105°C (*PE*); IR: $\bar{\nu} = 3070$, 3050 (*ar* CH), 2960, 2900, 2840 (*al* CH), 1770, 1710 (CO), 1630 (=C-OSi), 1610, 1570, 1490, 1190, 850, 650 (*ar*) cm^{-1}; ^1H NMR: $\delta = 0.15$ (s, Si*Me*$_3$), 2.10 (dddd, $J = 12$, 6, 3, 3 Hz, 7β-H), 2.32 (dddd, $J = 12$, 12, 12, 3 Hz, 7α-H), 2.52 (dd, $J = 15$, 6 Hz, 12β-H), 2.62 (ddd, $J = 15$, 12, 3 Hz, 6β-H), 2.68 (ddd, $J = 12$, 6, 6, 1.5 Hz, 8β-H), 2.74 (ddd, $J = 15$, 3, 3 Hz, 6α-H), 2.92 (dd, $J = 15$, 1.5 Hz, 12α-H), 3.22 (dd, $J = 9$, 6 Hz, 14β-H), 3.34 (ddd, $J = 9$, 6, 1.5 Hz, 13β-H), 3.80 (s, O*Me*), 6.61 (d, $J = 2$ Hz, 4-H), 6.63 (dd, $J = 2$, 9 Hz, 2-H), 7.1 (m, 2 *ar* H), 7.36 (m, 3 *ar* H), 7.81 (d, $J = 9$ Hz, 1-H) ppm; ^{13}C NMR (62.80 MHz): $\delta = 0.67$ (Si*Me*$_3$), 25.17 (C-7), 31.20 (C-6), 31.62 (C-12), 38.52 (C-8), 41.52 (C-13), 43.51 (C-14), 55.07 (O*Me*), 111.43 (C-4), 112.67 (C-2), 113.25 (C-9), 125.58 (C-10), 126.70 (C-2′, C-6′), 128.50 (C-1), 129.05 (C-4′), 129.69 (C-3′, C-5′), 132.09 (C-1′), 139.99 (C-5), 143.98 (C-11), 157.36 (C-3), 176.72 (C-15), 178.34 (C-17) ppm; DEPT 135: $\delta = 0.65$ (Si*Me*$_3$), 25.15 (CH_2, C-7), 31.19 (CH_2, C-6), 31.61 (CH_2, C-12), 38.50 (C-8), 41.51 (C-13), 43.50 (C-14), 55.08 (O*Me*), 111.42 (C-4), 112.66 (C-2), 126.70 (C-2′, C-6′), 128.49 (C-1), 129.05 (C-4′), 129.68 (C-3′, C-5′) ppm; MS: m/z (%) = 447 (62) [M^+], 261 (22), 260 (100), 73 (48), 45 (8).

(8β,13β,14β)-16-(4-Bromophenyl)-3-methoxy-11-trimethylsiloxy-18-nor-16-azaestra-1,3,5(10),9(11)-tetraene-15,17-dione (**5b**, $C_{26}H_{28}BrNO_4Si$)
From **4a** (10.0 g, 37 mmol) and *N*-(4-bromophenyl)maleimide (9.2 g, 37 mmol), 70 cm^3 of toluene, 4.5 h reflux, and stirring for 12 h at room temperature. The precipitate was separated and washed with a few cm^3 of cold *PE*. Yield 11.6 g (60%); colorless needles; mp 172–174°C (toluene); IR: $\bar{\nu} = 3097$, 2956, 2906, 2838 (CH), 1768, 1700 (CO), 1621 (=C-OSi), 1488 (*ar*), 1262 (Si*Me*$_3$) cm^{-1}; ^1H NMR (200 MHz): $\delta = 0.11$ (s, Si*Me*$_3$), 2.11 (dddd, $J = 12.3$, 6.0, 3.0, 3.0 Hz, 7β-H), 2.27 (dddd, $J = 12.2$, 12.2, 12.2, 3.5 Hz, 7α-H), 2.47–2.81 (m, 6α-H, 6β-H, 8β-H, 12β-H), 2.90 (dd, $J = 15.1$, 1.7 Hz, 12α-H), 3.23 (dd, $J = 8.8$, 5.5 Hz, 14β-H), 3.36 (ddd, $J = 8.6$, 6.6, 1.8 Hz, 13β-H), 3.78 (s, O*Me*), 6.63 (d, $J = 2.7$ Hz, 4-H), 6.66 (dd, $J = 8.8$, 2.7 Hz, 2-H), 7.01 (d, $J = 8.8$ Hz, 3′-H, 5′-H), 7.51 (d, $J = 8.6$ Hz, 2′-H, 6′-H), 7.80 (d, $J = 8.4$ Hz, 1-H) ppm; ^{13}C NMR (75 MHz): $\delta = 0.64$ (Si*Me*$_3$), 25.09

(C-7), 31.11 (C-6), 31.58 (C-12), 38.49 (C-8), 41.53 (C-13), 43.52 (C-14), 55.12 (O*Me*), 111.38 (C-4), 112.68 (C-2), 113.19 (C-9), 122.36 (C-4′), 125.41 (C-10), 128.15 (C-2′, C-6′), 129.59 (C-1), 130.92 (C-1′), 132.24 (C-3′, C-5′), 139.94 (C-5), 143.91 (C-11), 157.37 (C-3), 176.42 (C-15), 178.02 (C-17) ppm; DEPT 135: $\delta = 0.64$ (Si*Me*$_3$), 25.08 (CH_2, C-7), 31.10 (CH_2, C-6), 31.57 (CH_2, C-12), 38.48 (C-8), 41.52 (C-13), 43.51 (C-14), 55.11 (O*Me*), 111.37 (C-4), 112.67 (C-2), 128.15 (C-2′, C-6′), 129.57 (C-1), 132.23 (C-3′, C-5′) ppm.

(8β,13β,14β)-3-Methoxy-16-ethyl-11-(trimethylsiloxy)-18-nor-16-azaestra-1,3,5(10),9(11)-tetraene-15,17-dione (**5c**, $C_{22}H_{29}NO_4Si$)

From **4a** (1.4 g, 5.3 mmol) and *N*-ethylmaleimide (0.6 g, 5 mmol), 30 cm^3 of toluene, 4 h. The product was immediately used for the synthesis of **7c**. Yellow liquid; IR: $\bar{\nu} = 2942$, 2838 (*al* CH), 1771, 1698 (CO), 1605 (=C-OSi), 1570, 1408, 1251, 974, 882, 754, 696 (*ar*) cm^{-1}; ^{1}H NMR: $\delta = 0.2$ (s, Si*Me*$_3$), 1.0 (t, $J = 7.5$ Hz, *Me*), 2.60 (m, 9 *al* H), 3.50 (q, $J = 7.5$ Hz, CH_2), 3.75 (s, O*Me*), 6.72 (m, 2-H, 4-H), 7.75 (d, $J = 9$ Hz, 1-H) ppm.

(8β,13β,14β)-3-Methoxy-11-(trimethylsiloxy)-18-nor-16-azaestra-1,3,5(10),9(11)-tetraene-15,17-dione (**5d**, $C_{20}H_{25}NO_4Si$)

From **4a** (7.6 g, 28 mmol) and maleimide (2.7 g, 28 mmol), 130 cm^3 of toluene, 2–3 h. Yield 9.4 g (92%); colorless crystals; mp 221–223°C (*n*-pentane/acetone); IR: $\bar{\nu} = 3180$ (*ar* CH), 2980, 2880, 2820 (*al* CH), 1776, 1701 (CO), 1628 (=C-OSi), 1610, 1570, 1490, 1360, 1250, 850 (*ar*) cm^{-1}; ^{1}H NMR (200 MHz): $\delta = 0.12$ (s, Si*Me*$_3$), 2.04 (dddd, $J = 12.7$, 5.9, 3.3, 3.3 Hz, 7β-H), 2.23 (dddd, $J = 12.3$, 12.3, 12.3, 3.4 Hz, 7α-H), 2.50 (dd, $J = 15.7$, 6.7 Hz, 12β-H), 2.52–2.76 (m, 6α-H, 6β-H, 8β-H), 2.79 (dd, $J = 15.3$, 1.6 Hz, 12α-H), 3.10 (dd, $J = 8.9$, 5.6 Hz, 14β-H), 3.22 (ddd, $J = 8.8$, 7.0, 1.6 Hz, 13β-H), 3.78 (s, O*Me*), 6.61 (d, $J = 2.2$ Hz, 4-H), 6.65 (dd, $J = 8.8$, 2.7 Hz, 2-H), 7.85 (d, $J = 8.4$ Hz, 1-H), 8.25 (bs, H–N) ppm; ^{13}C NMR (*DMSO*-d$_6$): $\delta = 0.48$ (Si*Me*$_3$), 24.64 (C-7), 30.56 (C-6), 30.79 (C-12), 36.97 (C-8), 41.91 (C-13), 43.89 (C-14), 54.78 (O*Me*), 111.03 (C-4), 111.50 (C-9), 112.46 (C-2), 125.45 (C-10), 129.07 (C-1), 139.56 (C-5), 143.56 (C-11), 156.57 (C-3), 179.47 (C-15), 180.74 (C-17) ppm; DEPT 135 (*DMSO*-d$_6$): $\delta = 0.45$ (Si*Me*$_3$), 24.59 (C-7), 30.50 (C-6), 30.74 (C-12), 36.91 (C-8), 41.86 (C-13), 43.85 (C-14), 54.75 (O*Me*), 110.99 (C-4), 112.42 (C-2), 129.02 (C-1) ppm; MS: m/z (%) = 372 (30) [M$^+$+1], 371 (100) [M$^+$], 184 (32), 73 (68), 45 (16).

(8β,13β,14β)-3-Methoxy-11-(trimethylsiloxy)-16-methyl-18-nor-16-azaestra-1,3,5(10),9(11)-tetraene-15,17-dione (**5e**, $C_{21}H_{27}NO_4Si$)

From **4a** (1.45 g, 5.3 mmol) and *N*-methylmaleimide (0.55 g, 5 mmol), 30 cm^3 of toluene, 2.5 h. Yield 1.35 g (70%); colorless crystals; mp 178°C (*n*-hexane/acetone); IR: $\bar{\nu} = 2958$, 2836 (*al* CH), 1770 (CO), 1692, 1630 (=C-OSi), 1607, 1568, 1492, 1378, 1286, 1157, 994, 720, 695 (*ar*) cm^{-1}; ^{1}H NMR: $\delta = 0.09$ (s, Si*Me*$_3$), 2.11 (dddd, $J = 12.6$, 5.8, 3.5, 3.5 Hz, 7β-H), 2.31 (dddd, $J = 12.6$, 12.6, 3.5 Hz, 7α-H), 2.56 (ddd, $J = 15.4$, 7.0, 1.5 Hz, 12β-H), 2.58 (ddd, $J = 14.6$, 12.6, 3.5 Hz, 6β-H), 2.68 (dddd, $J = 12.6$, 5.8, 5.8, 1.5 Hz, 8β-H), 2.73 (ddd, $J = 14.6$, 3.5, 3.5 Hz, 6α-H), 2.85 (dd, $J = 15.4$, 1.6 Hz, 12α-H), 2.93 (s, N*Me*), 3.12 (dd, $J = 8.8$, 5.8 Hz, 14β-H), 3.20 (ddd, $J = 8.8$, 7.0, 1.6 Hz, 13β-H), 3.77 (s, O*Me*), 6.60 (d, $J = 2.5$ Hz, 4-H), 6.41 (dd, $J = 8.8$, 2.5 Hz, 2-H), 7.80 (d, $J = 8.8$ Hz, 1-H) ppm.

(8β,13β,14β)-3-Methoxy-16-phenyl-11-(triisopropylsiloxy)-18-nor-16-azaestra-1,3,5(10),9(11)-tetraene-15,17-dione (**5f**, $C_{32}H_{41}NO_4Si$)

From **4c** (1.8 g, 5 mmol) and *N*-phenylmaleimide (0.9 g, 5.2 mmol), 30 cm^3 of toluene, 8 h. Yield 1.0 g (40%); colorless crystals; mp 205°C (*Me*OH); IR: $\bar{\nu} = 2860$, 2840 (*al* CH), 1770, 1720 (CO), 1610 (=C-OSi), 1570, 1500, 1410, 1050, 880, 710 (*ar*) cm^{-1}; ^{1}H NMR: $\delta = 1.0$ (s, Si(CH*Me*$_2$)$_3$), 2.14 (dddd, $J = 15$, 6, 3.5, 3.5 Hz, 7β-H), 2.38 (dddd, $J = 15$, 15, 15, 3.5 Hz, 7α-H), 2.50 (dd, $J = 15$, 7 Hz, 12β-H), 2.57 (ddd, $J = 15$, 15, 3.5 Hz, 6β-H), 2.71 (m, 8β-H, 6α-H), 2.97 (dd, $J = 15$, 1.5 Hz, 12α-H),

3.21 (dd, $J = 9$, 6 Hz, 14β-H), 3.36 (ddd, $J = 9$, 7, 1.5 Hz, 13β-H), 3.76 (s, O*Me*), 6.59 (d, $J = 3$ Hz, 4-H), 6.64 (dd, $J = 9$, 3 Hz, 2-H), 7.21 (m, 5 *ar* H), 7.78 (d, $J = 9$ Hz, 1-H) ppm; MS: m/z (%) = 531 (92) [M^+], 488 (30), 315 (54), 73 (46), 59 (100).

(8β,13β,14β)-16-Phenyl-11-(trimethylsiloxy)-18-nor-16-azaestra-1,3,5(10),9(11)-tetraene-15,17-dione (**5g**, $C_{25}H_{27}NO_3Si$)
From **4b** (1.22 g, 5 mmol) and *N*-phenylmaleimide (0.9 g, 5 mmol), 30 cm^3 of toluene, 5–8 h. The product was immediately used for the synthesis of **7f**. Yield 0.85 g (40%); colorless crystals; mp 113°C (toluene); IR: $\bar{\nu} = 3100$, 3060, 3040 (*ar* CH), 2960, 2840 (*al* CH), 1780, 1730 (CO), 1630 (=C-OSi), 1600, 1500, 700 (*ar*) cm^{-1}; ^{1}H NMR: $\delta = 0.1$ (s, Si*Me*$_3$), 2.0–3.5 (m, 9 *al* H), 7.0–8.0 (m, 8 *ar* H) ppm.

(8β,13β,14β)-11-(Trimethylsiloxy)-18-nor-16-azaestra-1,3,5(10),9(11)-tetraene-15,17-dione (**5h**, $C_{19}H_{23}NO_3Si$)
From **4b** (0.8 g, 3.3 mmol) and maleimide (0.32 g, 32 mmol), 10 cm^3 of toluene, 3 h. Yield 0.60 g (53%); colorless crystals; mp 220°C (*n*-hexane/acetone); IR: $\bar{\nu} = 3167$ (NH), 3060 (*ar* CH), 2958, 2844 (*al* CH), 1777, 1702 (CO), 1624 (=C-OSi), 1597, 1482, 1440, 1364, 1321, 1265, 1252, 1220, 1189, 1049, 1010, 999, 966, 949, 878, 849, 820 (*ar*) cm^{-1}; ^{1}H NMR (acetone-d_6): $\delta = 0.25$ (s, Si*Me*$_3$), 2.25 (m, 7β-H, 6α-H), 2.70 (m, 6β-H, 7α-H, 8β-H, 12β-H, 14β-H), 3.25 (m, 12α-H, 13β-H), 7.0 (m, 2-H, 3-H, 4-H), 7,87 (m, 1-H) ppm; MS: m/z (%) = 341 (100) [M^+], 326 (6), 229 (12), 185 (10), 184 (56), 75 (30), 73 (92), 45 (16).

(8β,13β,14β)-3-Methoxy-16-phenyl-11-(tert-butyldimethylsiloxy)-18-nor-16-azaestra-1,3,5(10),9(11)-tetraene-15,17-dione (**6a**, $C_{29}H_{35}NO_4Si$)
At −78°C and under N_2, a solution of *Et*$AlCl_2$ (3 cm^3, 5.4 mmol, 1.8% in toluene) was added with stirring to a solution of *N*-phenylmaleimide (0.9 g, 5.2 mmol) in 20 cm^3 CH_2Cl_2, and after stirring for 30 min a solution of **4d** (1.65 g, 5 mmol) in 10 cm^3 CH_2Cl_2 was added. The mixture was stirred for 2 h at −78°C, hydrolyzed with dil. HCl, and extracted with 2 × 100 cm^3 CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), and evaporated *in vacuo*. Yield 1.2 g (49%); light yellow crystals; mp 180°C (*Me*OH/*Ac*O*Et*); IR: $\bar{\nu} = 3010$ (*ar* CH), 2950, 2935, 2860 (*al* CH), 1770, 1705 (CO), 1600, 1570, 1490, 830, 760, 700 (*ar*) cm^{-1}; ^{1}H NMR (80 MHz): $\delta = 0.05$, 0.20 (2s, Si*Me*$_2$), 0.95 (s, C*Me*$_3$), 2.0–3.5 (m, 9 *al* H), 3.8 (s, O*Me*), 6.55–7.95 (m, 8 *ar* H) ppm.

(8β,13β,14β)-3-Methoxy-16-ethyl-11-(tert-butyldimethylsiloxy)-18-nor-16-azaestra-1,3,5(10),9(11)-tetraene-15,17-dione (**6b**, $C_{25}H_{35}NO_4Si$)
From **4d** (1.65 g, 5 mmol) and *N*-ethylmaleimide (0.57 g, 5 mmol), as described for **6a**. Yield 1.4 g (65%); colorless crystals; mp 120°C ($CHCl_3$); IR: $\bar{\nu} = 2960$, 2940, 2860, 2840 (*al* CH), 1770 (CO), 1630 (=C-OSi), 1610, 1490, 1410, 780 (*ar*) cm^{-1}; ^{1}H NMR: $\delta = 0.08$ (s, Si*Me*$_2$), 0.88 (s, C*Me*$_3$), 1.0 (t, $J = 7$ Hz, *Me*), 2.07 (dddd, $J = 15$, 6, 3, 3 Hz, 7β-H), 2.21 (dddd, $J = 15$, 12, 12, 3 Hz, 7α-H), 2.47 (ddd, $J = 15$, 6, 1.5 Hz, 12β-H), 2.51 (ddd, $J = 15$, 12, 3 Hz, 6β-H), 2.59 (dddd, $J = 12$, 6, 6, 1.5 Hz, 8β-H), 2,71 (ddd, $J = 15$, 3, 3 Hz, 6α-H), 2.98 (dd, $J = 15$, 1.5 Hz, 12α-H), 3.10 (dd, $J = 9$, 6 Hz, 14β-H), 3.14 (ddd, $J = 9$, 6, 1.5 Hz, 13β-H), 3.42 (q, $J = 7$ Hz, CH_2), 3.75 (s, O*Me*), 6.57 (m, 2-H, 4-H), 7.71 (dd, $J = 9$, 3 Hz, 1-H) ppm; MS: m/z (%) = 441 (100) [M^+], 384 (56), 259 (60), 73 (64).

(8β,13β,14β)-3-Methoxy-11-(tert-butyldimethylsiloxy)-18-nor-16-azaestra-1,3,5(10),9(11)-tetraene-15,17-dione (**6c**, $C_{23}H_{31}NO_4Si$)
From **4d** (0.86 g, 5.1 mmol) and maleimide (0.25 g, 5 mmol), as described for **6a**. Yield 0.6 g (30%); light yellow liquid; ^{1}H NMR (90 MHz): $\delta = 0.1$ (s, Si*Me*$_2$), 0.9 (s, C*Me*$_3$), 3.3–1.9 (m, 9 *al* H), 3.72 (s, O*Me*), 6.6 (m, 2-H, 4-H), 7.72 (d, $J = 9$ Hz, 1-H), 8.3 (bs, H–N) ppm.

(8β,9β,13β,14β)-3-Methoxy-16-phenyl-18-nor-16-azaestra-1,3,5(10)-triene-11,15,17-trione (**7a**, $C_{23}H_{21}NO_4$)

Compound **5a** (1.0 g, 2.2 mmol) in 30 cm^3 *Me*OH and 1.5 cm^3 of conc. HCl were refluxed for 30 min, the hot solution was filtered, and cooled until crystallization was completed. Yield 0.71 g (85%); colorless crystals; mp 181°C (*Me*OH); IR: $\bar{\nu} = 3060$ (*ar* CH), 2940, 2860, 2840 (*al* CH), 1780, 1740, 1710 (CO), 1610, 1500, 1380, 1280, 1180, 1040, 870 (*ar*) cm^{-1}; ^{1}H NMR (300 MHz): $\delta = 1.55$ (m, 7β-H), 2.06 (m, 7α-H), 2.90 (m, 6α-H, 6β-H, 8β-H, 12β-H, 12α-H), 3.46 (m, 9β-H, 13β-H, 14β-H), 3.76 (s, O*Me*), 6.6 (d, $J = 3$ Hz, 4-H), 6.76 (dd, $J = 9$, 3 Hz, 2-H), 7.22 (d, $J = 9$ Hz, 1-H), 7.3–7.52 (m, 5 *ar* H) ppm; ^{1}H NMR (400 MHz, pyridine-d_5): $\delta = 1.70$ (dddd, $J = 15$, 15, 7.5, 3 Hz, 7β-H), 2.1 (m, 7α-H), 2.8 (m, 6α-H, 6β-H), 3.01 (dddd, $J = 15$, 9, 7.5, 3 Hz, 8β-H), 3.12 (dd, $J = 16$, 6 Hz, 12β-H), 3.30 (ddd, $J = 16$, 16, 6.0 Hz, 12α-H), 3.6 (s, O*Me*), 3.74 (dd, $J = 6$, 3 Hz, 9β-H), 3.90 (dd, $J = 9$, 6 Hz, 14β-H), 4.0 (dd, $J = 16$, 9 Hz, 13β-H), 6.72 (d, $J = 3$ Hz, 4-H), 6.9 (dd, $J = 9$, 3 Hz, 2-H), 7.6–7.3 (m, 5 *ar* H) ppm; ^{13}C NMR (100.61 MHz): $\delta = 22.91$ (C-7), 29.15 (C-8), 35.40 (C-12), 36.67 (C-13), 37.83 (C-14), 42.91 (C-6), 50.78 (C-9), 55.29 (O*Me*), 76.78 (C-11), 112.45 (C-4), 113.59 (C-2), 123.63–128.96 (*ar* C), 129.38 (C-3), 132.09 (C-1), 136.34 (C-5), 158.92 (C-10), 176.22, 177.22, 206.60 (CO) ppm; DEPT 135 (*DMSO*-d_6): $\delta = 22.1$ (CH_2, C-7), 28.6 (CH_2, C-6), 35.4 (CH_2, C-12), 35.8 (C-8), 37.3 (C-9), 42.1 (C-14), 50.0 (C-13), 54.9 (O*Me*), 111.7 (C-2), 112.8 (C-4), 127.0 (C-2′, C-6′), 128.4 (C-4′), 129.0 (C-3′, C-5′), 132.0 (C-1) ppm; MS: m/z (%) = 375 (100) [M^+], 198 (68), 159 (38), 43 (20).

(8β,9β,13β,14β)-16-(4-Bromophenyl)-3-methoxy-18-nor-16-azaestra-1,3,5(10)-triene-11,15,17-trione (**7b**, $C_{23}H_{20}BrNO_4$)

From **5b** (1.9 g, 3.6 mmol) in 50 cm^3 *Me*OH, room temperature, and warming for a few min in a boiling water-bath. Yield 0.7 g (54%); colorless needles; mp 185–192°C (*Ac*O*Et*); IR: $\bar{\nu} = 2936$, 2860 (CH), 1776, 1714 (CO), 1608, 1504, 1491 (*ar*) cm^{-1}; ^{1}H NMR (300 MHz): $\delta = 1.54$ (m, 7α-H), 2.01 (m, 7β-H), 2.91 (m, 6α-H, 6β-H, 8β-H, 12α-H, 12β-H), 3.52 (m, 9β-H, 13β-H, 14β-H), 3.77 (s, O*Me*), 6.62 (d, $J = 2.6$ Hz, 4-H), 6.78 (dd, $J = 8.5$, 2.7 Hz, 2-H), 7.32 (d, $J = 8.8$ Hz, 1-H), 7.16–7.65 (m, 4 *ar* H) ppm.

(8β,9β,13β,14β)-16-Ethyl-3-methoxy-18-nor-16-azaestra-1,3,5(10)-triene-11,15,17-trione (**7c**, $C_{19}H_{21}NO_4$)

From **5c** (1.2 g, 3 mmol) as described for **7a**. Yield 0.89 g (90%); colorless crystals; mp 179°C (*Me*OH); IR: $\bar{\nu} = 3080$, 3000 (*ar* CH), 2960, 2940, 2840 (*al* CH), 1770, 1710, 1690 (CO), 1610, 1505, 1400, 1350, 1110, 820 (*ar*) cm^{-1}; ^{1}H NMR (300 MHz): $\delta = 1.23$ (t, $J = 7$ Hz, *Me*), 1.38 (dddd, $J = 12$, 12, 12, 2.6 Hz, 7α-H), 1.84 (dddd, $J = 12$, 6, 3, 3 Hz, 7β-H), 2.82 (ddd, $J = 12$, 12, 3 Hz, 6β-H), 2.84 (m, 12α-H, 12β-H), 2.86 (m, 6α-H), 2.88 (m, 8β-H), 3.35 (dd, $J = 9$, 6 Hz, 13β-H), 3.35 (dd, $J = 9$, 6 Hz, 14β-H), 3.44 (dd, $J = 4.5$, 1.5 Hz, 9β-H), 3.64 (dq $J = 7$, 1 Hz, CH_2), 3.77 (s, O*Me*), 6.60 (d, $J = 3$ Hz, 4-H), 6.72 (dd, $J = 9$, 3 Hz, 2-H), 7.25 (d, $J = 9$ Hz, 1-H) ppm; ^{13}C NMR (100.61 MHz): $\delta = 13.20$ (*Me*), 22.82 (C-7), 29.16 (C-8), 34.03 (CH_2), 35.48 (C-12), 35.99 (C-13), 37.47 (C-14), 42.58 (C-6), 50.62 (C-9), 55.25 (O*Me*), 112.32 (C-4), 113.48 (C-2), 123.75 (C-2), 132.10 (C-1), 136.39 (C-5), 158.85 (C-10), 177.07, 178.07, 206.83 (CO) ppm; MS: m/z (%) = 328 (25) [$M^+ + 1$], 327 (100) [M^+], 173 (30), 159 (56).

(8β,9β,13β,14β)-3-Methoxy-18-nor-16-azaestra-1,3,5(10)-triene-11,15,17-trione (**7d**, $C_{17}H_{17}NO_4$)

From **5d** (1.0 g, 2.7 mmol), as described for **7a**. Yield 0.74 g (92%); colorless crystals; mp 218°C (*Me*OH); IR: $\bar{\nu} = 3180$ (NH), 3060 (*ar* CH), 2940, 2840, 2790 (*al* CH), 1780, 1720, 1710 (CO), 1610, 1580, 1500, 1360, 840, 820 (*ar*) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$/*DMSO*-d_6): $\delta = 1.33$ (dddd, $J = 15$, 15, 7.5, 3 Hz, 7β-H), 1.76 (m, 7α-H), 2.52 (m, 6β-H), 2.70 (ddd, $J = 15$, 3, 3 Hz, 6α-H), 2.67, 2.76 (2dd, $J = 15$, 6, 1.3 Hz, 12α-H, 12β-H), 2.76 (m, 8β-H), 3.50 (2dd, $J = 9$, 6 Hz, 13β-H, 14β-H),

3.52 (dd, $J = 4.5$, 1.3 Hz, 9β-H), 3.70 (s, O*Me*), 6.60 (dd, $J = 9$, 3 Hz, 4-H), 6.70 (dd, $J = 9$, 3 Hz, 2-H), 7.08 (d, $J = 9$ Hz, 1-H), 11.40 (bs, H–N) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 22.12$ (C-7), 28.55 (C-6), 35.13 (C-8), 35.23 (C-12), 37.70 (C-9), 43.04 (C-14), 49.88 (C-13), 54.80 (O*Me*), 111.50 (C-2), 112.66 (C-4), 125.02 (C-10), 131.98 (C-1), 136.27 (C-5), 157.83 (C-3), 178.92 (C-17), 180.15 (C-15), 207.48 (C-11) ppm; DEPT 135 (*DMSO*-d_6): $\delta = 22.1$ (CH_2, C-7), 28.6 (CH_2, C-6), 35.1 (C-8), 35.2 (CH_2, C-12), 37.7 (C-9), 43.0 (C-14), 49.9 (C-13), 54.8 (O*Me*), 111.5 (C-2), 112.7 (C-4), 132.0 (C-1) ppm; MS: m/z (%) = 300 (20) [M^+], 299 (100), 271 (35), 200 (25), 159 (76), 115 (38).

(8β,9β,13β,14β)-3-Methoxy-16-methyl-18-nor-16-azaestra-1,3,5(10)-triene-11,15,17-dione (**7e**, $C_{18}H_{19}NO_4$)

From **5e** (1.2 g, 3 mmol), as described for **7a**. Yield 0.71 g (75%); colorless crystals; mp 159°C (*Me*OH); IR: $\bar{\nu} = 3060$, 3000 (*ar* CH), 2940, 2840 (*al* CH), 1770, 1720, 1690 (CO), 1610, 1500, 1380, 1270, 820 (*ar*) cm^{-1}; ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta = 1.26$ (m, 7β-H), 1.62 (m, 7α-H), 2.61 (m, 6α-H, 6β-H, 8β-H, 12α-H, 12β-H), 2.85 (s, *Me*), 3.50 (m, 13β-H, 14β-H), 3.58 (dd, $J = 6$, 2 Hz, 9β-H), 3.70 (s, O*Me*), 6.62 (d, $J = 3$ Hz, 4-H), 6.71 (dd, $J = 9$, 3 Hz, 2-H), 7.05 (d, $J = 9$ Hz, 1-H) ppm; MS: m/z (%) = 314 (20) [$M^+ + 1$], 313 (100) [M^+], 285 (30), 159 (90), 115 (58), 91 (25).

(8β,9β,13β,14β)-16-Phenyl-18-nor-16-azaestra-1,3,5(10)-triene-11,15,17-trione (**7f**, $C_{22}H_{19}NO_3$)

From crude **5g** as described for **7a**. Yield 0.40 g (25%); colorless crystals; mp 90°C (*Me*OH); IR: $\bar{\nu} = 3060$, 3020 (*ar* CH), 2940 (*al* CH), 1780, 1720, 1700 (C=O), 1600, 1500, 1380, 1180, 740, 690 (*ar*) cm^{-1}; ^{1}H NMR: $\delta = 1.1$–3.65 (m, 10 *al* H), 7.0–7.65 (m, 9 *ar* H) ppm.

(8β,9β,13β,14β)-18-Nor-16-azaestra-1,3,5(10)-triene-11,15,17-dione (**7g**, $C_{16}H_{15}NO_3$)

From **5h** (0.30 g, 0.9 mmol) in 15 cm^3 *Me*OH, as described for **7a**. Yield 0.12 g (50%); colorless crystals; mp 206°C ($CHCl_3$); IR: $\bar{\nu} = 3276$ (NH), 2945 (*al* CH), 1770, 1722 (CO), 1485, 1437, 1414, 1338, 1294, 1261, 1182, 1035, 1005, 938, 845, 776, 735, 648, 625 (*ar*) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.84$ (ddd, $J = 15$, 6, 4.5 Hz, 7β-H), 2,1 (ddd, $J = 14$, 6, 3 Hz, 6β-H), 2.76–3.0 (m, 4 *al* H), 3.30 (dd, $J = 9$, 5 Hz, 14β-H), 3.44 (m, 9β-H, 12β-H, 13β-H), 7.08 (m, 2-H, 3-H, 4-H), 7.32 (dd, $J = 9$, 3 Hz, 1-H), 11.50 (s, H–N) ppm; MS: m/z (%) = 271 (4) [$M^+ + 2$], 270 (16) [$M^+ + 1$], 269 (100) [M^+], 251 (10), 180 (26), 170 (26), 129 (72), 112 (44), 99 (18), 98 (10), 77 (12), 71 (10), 55 (12), 42 (18).

General Procedure for the Synthesis of Oximes

a. A mixture from $H_2NOH \times HCl$ (0.35 g, 5 mmol) and *Ac*ONa (1.0 g, 10 mmol) was refluxed in 10 cm^3 *Et*OH and then filtered. The ketone (1 mmol) was added to the filtrate, and the reaction mixture was refluxed for 40 min, filtered, and a few cm^3 H_2O were added to the filtrate until it became milky. Cooling to 0–5°C for 24–48 h resulted in a precipitate which was crystallized as noted.

b. An aqueous solution of *Ac*ONa (0.86 g, 10.5 mmol) in 2.5 cm^3 H_2O was added to an aqueous solution of $H_2NOH \times HCl$ (0.73 g, 10.5 mmol) in 2 cm^3 H_2O. The mixture was added with stirring to a solution of the ketone or the trialkylsilyl compound in *THF*, *Me*OH was added until a clear solution was obtained, and stirring was continued at room temperature for 16 h. Then H_2O was added until the precipitate was complete.

(8β,9β,13β,14β)-11-Hydroxyimino-3-methoxy-16-phenyl-18-nor-16-azaestra-1,3,5(10)-triene-15,17-dione (**8a**, $C_{23}H_{22}N_2O_4$)

a. From **7a** (0.38 g, 1.1 mmol). *b*. From **7a** (0.75 g, 2 mmol), 15 cm^3 *THF*. Yield *a*. 0.4 g (50%), *b*. 0.5 g (63%); colorless crystals; mp 222°C (*Me*OH); IR: $\bar{\nu} = 3428$ (OH), 2938 (*al* CH), 1777, 1712 (CO), 1608 (C=N), 1500 (*ar*), 1250 (C–O), 693 (*ar*) cm^{-1}; ^{1}H NMR: $\delta = 1.52$ (m, 7α-H), 1.86 (m, 7β-H), 2.7–2.9 (m, 6α-H, 6β-H, 12β-H), 3.00 (m, 8β-H), 3.35 (m, 12α-H, 14β-H), 3.50 (dd, $J = 8.8$, 6.8 Hz,

13β-H), 3.63 (d, $J = 3.7$ Hz, 9β-H), 3.77 (s, OMe), 6.63 (d, $J = 2.6$ Hz, 4-H), 6.73 (dd, $J = 8.4$, 2.6 Hz, 2-H), 7.06 (d, $J = 8.4$ Hz, 1-H), 7.26–7.5 (m, 5 *ar* H), 7.59 (bs, H–O) ppm.

(8β,9β,13β,14β)-16-(4-Bromophenyl)-11-hydroxyimino-3-methoxy-18-nor-16-azaestra-1,3,5(10)-triene-15,17-dione (**8b**, $C_{23}H_{21}BrN_2O_4$)

b. From **7b** (0.4 g, 0.9 mmol), 10 cm^3 *THF*. Yield 0.3 g (71%); colorless crystals; mp 255–260°C (*Me*OH); IR: $\bar{\nu} = 3244$ (OH), 2990, 2941, 2889, 2832 (CH), 1774, 1706 (CO), 1612, 1503, 1489 (*ar*) cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.42$ (m, 7α-H), 1.67 (m, 7β-H), 2.55 (dddd, $J = 12.6$, 6.2, 3.2, 3.2 Hz, 6α-H), 2.74 (m, 6β-H, 8β-H, 12β-H), 3.13 (dd, $J = 17.6$, 5.1 Hz, 12α-H), 3.50 (dd, $J = 9.3$, 5.6 Hz, 14β-H), 3.58 (dd, $J = 9$, 7 Hz, 13β-H), 3.68 (s, O*Me*), 3.70 (d, $J = 5$ Hz, 9β-H), 6.60 (d, $J = 2.5$ Hz, 4-H), 6.65 (dd, $J = 8.4$, 2.7 Hz, 2-H), 7.00 (d, $J = 8.5$ Hz, 1-H), 7.23–7.73 (m, 4 *ar* H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 19.07$ (C-7), 20.63 (C-6), 27.91 (C-12), 35.30 (C-8), 36.40 (C-9), 41.95 (C-14), 42.66 (C-13), 54.81 (O*Me*), 111.23 (C-2), 112.71 (C-4), 121.19, 127.99, 128.95, 131.22, 131.36, 131.84, 136.06 (*ar* C), 155.56 (C-3), 157.71 (C-11), 176.70 (C-17), 178.00 (C-15) ppm; DEPT 135 (*DMSO*-d_6): $\delta = 19.07$ (CH_2, C-7), 20.63 (CH_2, C-6), 27.91 (CH_2, C-12), 35.30 (C-8), 36.40 (C-9), 41.95 (C-14), 42.66 (C-13), 54.81 (O*Me*), 111.23 (C-2), 112.71 (C-4), 128.95, 131.22, 131.84 (*ar* C) ppm.

(8β,9β,13β,14β)-11-Hydroxyimino-3-methoxy-16-methyl-18-nor-16-azaestra-1,3,5(10)-triene-15,17-dione (**8c**, $C_{18}H_{20}N_2O_4$)

a. From **7e** (0.32 g, 1.1 mmol). Yield 0.09 g (26%); colorless crystals; mp 225°C (*Et*OH); IR: $\bar{\nu} = 3417$ (OH), 2942 (*al* CH), 1777, 1706 (CO), 1610 (C=N), 1501 (*ar*) cm^{-1}; ^{1}H NMR (*DMSO*-d_6/acetone-d_6): $\delta = 1.32$ (m, 7α-H), 1.60 (m, 7β-H), 2.79 (m, 8β-H, 6α-H, 6β-H), 2.81 (s, N*Me*), 2.95 (dd, $J = 15$, 3.4 Hz, 12β-H), 3.35 (m, 12α-H, 13β-H), 3.45 (dd, $J = 9$, 6 Hz, 14β-H), 3.65 (d, $J = 6.8$ Hz, 9β-H), 3.78 (s, O*Me*), 6.60 (d, $J = 2$ Hz, 4-H), 6.65 (dd, $J = 9$, 2 Hz, 2-H), 7.00 (d, $J = 9$ Hz, 1-H) ppm.

(8β,9β,13β,14β)-11-Hydroxyimino-3-methoxy-18-nor-16-azaestra-1,3,5(10)-triene-15,17-dione (**8d**, $C_{17}H_{18}N_2O_4$)

a. From **7d** (0.30 g, 1.0 mmol). *b*. From **7d** (1.3 g, 3.3 mmol), 40 cm^3 *THF*. Yield *a*. 0.25 g (70%), *b*. 0.8 g (77%); colorless crystals; mp 250°C (*Me*OH); IR: $\bar{\nu} = 3400$ (OH), 3265 (NH), 2935 (*al* CH), 1769, 1711 (CO), 1612 (C=N), 1579 (*ar*) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.35$ (m, 7α-H), 1.65 (m, 7β-H), 2.40 (m, 8β-H), 2.74 (m, 6α-H, 6β-H, 12β-H), 2.91 (dd, $J = 18$, 1.5 Hz, 12α-H), 3.35 (m, 13β-H, 14β-H), 3.62 (d, $J = 4.5$ Hz, 9β-H), 3.68 (s, O*Me*), 6.61 (d, $J = 2.5$ Hz, 4-H), 6.64 (dd, $J = 9$, 2.5 Hz, 2-H), 7.0 (d, $J = 9$ Hz, 1-H), 11.15 (s, 16-H) ppm; ^{13}C NMR: $\delta = 19.72$ (C-7), 20.91 (C-12), 28.14 (C-6), 34.88 (C-8), 37.16 (C-13), 42.01 (C-9), 43.83 (C-14), 54.90 (O*Me*), 111.20 (C-4), 112.82 (C-2), 128.25 (C-3), 131.48 (C-1), 136.08 (C-5), 155.95 (C-10), 157.75 (C-11), 179.20, 180.57 (CO) ppm.

General Procedure for the Reaction with BBr_3

A solution of BBr_3 (1 *M* in CH_2Cl_2) was dropwise added at 0°C to a solution of the methoxy compound in CH_2Cl_2, stirring was continued for 3–4 h, then 20 cm^3 CH_2Cl_2 were added, and the mixture was poured onto 30–50 g of crashed ice. After warming to room temperature, the organic layer was separated, and the aqueous layer was extracted with 4×50 cm^3 *Ac*O*Et*. The combined organic layers were washed with H_2O and a satd. aqueous solution of NaCl, dried ($MgSO_4$), and evaporated *in vacuo* (max. 50°C, preferred 20°C).

(8β,9β,13β,14β)-3-Hydroxy-16-phenyl-18-nor-16-azaestra-1,3,5(10)-triene-11,15,17-trione (**9a**, $C_{22}H_{19}NO_4$)

From **7a** (0.4 g, 1.1 mmol) in 30 cm^3 CH_2Cl_2 and 4.5 cm^3 BBr_3. Yield 0.2 g (42%); colorless crystals; mp 217–221°C (*Ac*OH); IR: $\bar{\nu} = 3338$ (OH), 2922 (CH), 1773, 1712 (CO), 1684, 1606, 1499 (*ar*) cm^{-1}.

(8β,9β,13β,14β)-3-Hydroxy-18-nor-16-azaestra-1,3,5(10)-triene-11,15,17-trione (**9b**, $C_{16}H_{15}NO_4$)
From **7d** (0.3 g, 1 mmol) in 30 cm^3 CH_2Cl_2 and 4.0 cm^3 BBr_3. Yield 0.1 g (30%); yellow-brownish crystals; mp 225–236°C (*Ac*O*Et*); IR: $\bar{\nu} = 3188$ (OH), 1750, 1704 (CO), 1614, 1597, 1578 (*ar*) cm^{-1}; HPLC: $k'_1 = 4.75$, $t_0 = 3.09$ (RP-18, *Me*CN/H_2O 37); $k'_{11} = 1.24$, $t_0 = 2.17$ ((S,S)-Whelk-O1, *n*-hexane/2-propanol 7/3); $k'_{11} = 6.99$, $t_0 = 1.83$ (Chiralcel OJ-R, MeCN/H_2O 3/7).

(8β,9β,13β,14β)-16-(4-Bromophenyl)-3-hydroxy-18-nor-16-azaestra-1,3,5(10)-triene-11,15,17-trione (**9c**, $C_{22}H_{18}BrNO_4$)
From **5b** (1.0 g, 2 mmol) and 11 cm^3 BBr_3 in 60 cm^3 CH_2Cl_2. Yield 0.3 g (44%); yellow crystals; mp 295–300°C (*Me*CN); IR: $\bar{\nu} = 3391$ (OH), 2933 (CH), 1763, 1703 (CO), 1611, 1595, 1490 (*ar*) cm^{-1}; HPLC: $k'_1 = 1.53$, $t_0 = 2.09$ (RP-18, *Me*CN/H_2O 7:3); $k'_{11} = 3.57$, $t_0 = 2.17$ ((S,S)-Whelk-O1, *n*-hexane/2-propanol 7/3); $k'_{11} = 14.10$, $t_0 = 2.09$ (Chiralcel OJ-R, *Me*CN/H_2O 1/1).

(RS)-3-Methoxy-16-methyl-11-(trimethylsiloxy)-18-nor-13,14,16-triazaestra-1,3,5(10),9(11)-tetraene-15,17-dione (**10a**, $C_{19}H_{25}N_3O_4Si$)
Compound **4a** (1.45 g, 5.3 mmol) and 4-methyl-1,2,4-triazolin-3,5-dione (0.57 g, 5.5 mmol) in 20 cm^3 *THF* were stirred at −60°C for 1 h. When the reaction was complete (TLC control), the solvent was concentrated *in vacuo*, and the residue was immediately used for the synthesis of **11a**.

(RS)-3-Methoxy-16-phenyl-11-(trimethylsiloxy)-18-nor-13,14,16-triazaestra-1,3,5(10),9(11)-tetraene-15,17-dione (**10b**, $C_{24}H_{27}N_3O_4Si$)
4-Phenyl-1,2,4-triazolin-3,5-dione (0.96 g, 5.5 mmol) and **4a** (1.45 g, 5.3 mmol) in 30 cm^3 *THF* were stirred at −60°C for 2 h. Then the solvent was evaporated *in vacuo*. Yield 1.8 g (75%); colorless crystals; mp 112°C (*Me*OH); IR: $\bar{\nu} = 3010$ (*ar* CH), 2960, 2820 (*al* CH), 1790, 1730 (CO), 1620 (=C-OSi), 1590, 1470 (*ar*), 1270 (C–O) cm^{-1}; ^{1}H NMR (400 MHz): $\delta = 0.10$ (s, Si*Me*$_3$), 1.90 (dddd, $J = 15$, 3, 3, 1.5 Hz, 7β-H), 2.50–3.07 (m, 6α-H, 6β-H, 7α-H), 3.81 (s, O*Me*), 4.00 (dd, $J = 15$, 1.5 Hz, 12β-H), 4.40 (dd, $J = 15$, 1.5 Hz, 12α-H), 4.46 (ddd, $J = 12$, 7.5, 1.5 Hz, 8β-H), 6.64 (d, $J = 3$ Hz, 4-H), 6.75 (dd, $J = 3$, 9 Hz, 2-H), 7.5 (m, 5 *ar* H_{Ph}), 7.90 (d, $J = 9$ Hz, 1-H) ppm.

(8β,9β)-3-Methoxy-16-methyl-18-nor-13,14,16-triazaestra-1,3,5(10)-triene-11,15,17-trione (**11a**, $C_{16}H_{17}N_3O_4$)
4-Methyl-1,2,4-triazolin-3,5-dione (0.57 g, 5.5 mmol) and **4a** (1.45 g, 5.3 mmol) in 20 cm^3 *THF* were stirred for 1–2 h at −60°C. After warming to room temperature, 30 cm^3 *Me*OH and 1.5 cm^3 of conc. HCl were added, and the mixture was refluxed for 10–30 min, the hot solution was filtered, and evaporated *in vacuo*. Yield 0.59 g (80%); colorless crystals; mp 159°C (*Me*OH); IR: $\bar{\nu} = 3005$ (*ar* CH), 2960, 2940, 2840 (*al* CH), 1780, 1720, 1710 (CO), 1620, 1580, 1510, 1470, 1270, 880 (*ar*) cm^{-1}; ^{1}H NMR: $\delta = 1.75$ (dddd, $J = 18$, 12, 12, 3 Hz, 7α-H), 2.20 (m, 7β-H), 2.92 (ddd, $J = 15$, 12, 3 Hz, 6α-H, 6β-H), 3.13 (s, *Me*), 3.80 (s, O*Me*), 3.96 (dd, $J = 6$, 1.5 Hz, 9β-H) 4.21, 4.25 (2d, $J = 15$ Hz, 12β-H, 12α-H), 4.60 (dddd, $J = 12$, 6, 3, 1.5 Hz, 8β-H), 6.67 (d, $J = 3$ Hz, 4-H), 6.79 (dd, $J = 9$, 3 Hz, 2-H), 7.0 (d, $J = 9$ Hz, 1-H) ppm.

(8β,9β)-3-Methoxy-16-phenyl-18-nor-13,14,16-triazaestra-1,3,5(10)-triene-11,15,17-trione (**11b**, $C_{21}H_{19}N_3O_4$)
From **10b** (1.71 g, 3.8 mmol), as described for **7a**. Yield 1.1 g (77%); colorless crystals; mp 163°C (*Me*OH); IR: $\bar{\nu} = 3060$, 3000 (*ar* CH), 2940, 2840 (*al* CH), 1770, 1740, 1720 (CO), 1610, 1500 (*ar*) cm^{-1}; ^{1}H NMR: $\delta = 1.92$ (dddd, $J = 15$, 12, 12, 6 Hz, 7α-H), 2.35 (dddd, $J = 15$, 3, 3, 1.5 Hz, 7β-H), 2.96 (ddd, $J = 15$, 15, 6 Hz, 6α-H, 6β-H), 3.80 (s, O*Me*), 4.07 (dd, $J = 5.5$, 1.5 Hz, 9β-H), 4.35, 4.34 (2d, $J = 15$ Hz, 12β-H, 12α-H), 4.78 (dddd, $J = 12$, 5.5, 3, 1.5 Hz, 8β-H), 6.70 (d, $J = 2$ Hz, 4-H), 6.78 (dd, $J = 9$, 2 Hz, 2-H), 7.0 (d, $J = 9$ Hz, 1-H), 7.50 (m, 5 *ar* H) ppm; MS: m/z (%) = 378 (6) [$M^+ + 1$], 377 (20) [M^+], 160 (100), 93 (18).

(8β,9β)-16-Phenyl-18-nor-13,14,16-triazaestra-1,3,5(10)-triene-11,15,17-trione (**11c**, $C_{20}H_{17}N_3O_3$)
From **4b** (0.50 g, 1.7 mmol) and 4-phenyl-1,2,4-triazolin-3,5-dione (0.3 g, 1.7 mmol), time 1 h, as described for **11a**. Yield 0.35 g (60%); colorless crystals; mp 177°C (*Me*OH); IR: $\bar{\nu} = 2936$ (*al* CH), 1773, 1712 (CO), 1501 (*ar*) cm^{-1}; ^1H NMR: $\delta = 1.70$ (dddd, $J = 15, 15, 15, 3$ Hz, 7α-H), 2.27 (m, 7β-H), 2.9 (m, 6α-H, 6β-H), 3.30 (s, O*Me*), 4.27 (d, $J = 16$ Hz, 12β-H), 4.6 (dd, $J = 6, 1.5$ Hz, 9β-H), 4.64 (d, $J = 16$ Hz, 12α-H), 4.75 (dddd, $J = 15, 7.5, 3, 3$ Hz, 8β-H), 7.15 (m, 4 *ar* H), 7.5 (m, 5 *ar* H) ppm; MS: m/z (%) = 347 (50) [M^+], 191 (15), 190 (20), 130 (100), 129 (80), 115 (40), 91 (25), 77 (10), 51 (5).

(8β,13β,14β)-3-Methoxy-16-phenyl-11-(trimethylsiloxy)-16-azaestra-1,3,5(10),9(11)-tetraene-15,17-dione (**12**, $C_{27}H_{31}NO_4Si$)
From **4a** (450 mg, 1.65 mmol) and α-methyl-*N*-phenylmaleimide (0.28 g, 1.50 mmol) in 20 cm^3 of toluene under N_2, reflux for 1.2 h, as described for **5a**. Yield 0.30 g (40%); colorless crystals; mp 168°C (*Me*OH); IR: $\bar{\nu} = 2959$, 2837 (*al* CH), 1775, 1710 (CO), 1632 (=C-OSi), 1607 (*ar*), 1570, 1492, 1454, 1390, 1362, 1304, 1251, 1214, 1199, 1151, 1135, 1054, 985, 932, 881, 849, 760, 696 (*ar*) cm^{-1}; ^1H NMR: $\delta = 0.04$ (s, Si*Me*$_3$), 1.46 (s, *Me*), 2.02 (dddd, $J = 12.8, 12.8, 12.8, 3.0$ Hz, 7α-H), 2.16 (dddd, $J = 12.8, 6.7, 6.7, 3.6$ Hz, 7β-H), 2.48 (m, 6β-H, 6α-H), 2.62 (dd, $J = 20.9, 1.5$ Hz, 12β-H), 2.68 (ddd, $J = 12.8, 6.7, 3.4$ Hz, 8β-H), 2.86 (d, $J = 3.4$ Hz, 14β-H), 2.90 (dd, $J = 20.9, 2.15$ Hz, 12α-H), 3.76 (s, O*Me*), 6.60 (d, $J = 2$ Hz, 4-H), 6.66 (dd, $J = 9, 2$ Hz, 2-H). 7.06 (m, 2 *ar* H_{Ph}), 7.35 (m, 3 *ar* H_{Ph}), 7.78 (d, $J = 9$ Hz, 1-H) ppm; ^{13}C NMR: $\delta = 0.15$ (Si*Me*$_3$), 22.04 (C-18), 22.68 (C-7), 30.43 (C-6), 30.84 (C-12), 44.99 (C-8), 46.85 (C-14), 49.90 (C-13), 54.69 (O*Me*), 101.88 (C-11), 110.99 (C-9), 111.93 (C-2), 113.26 (C-4), 125.15-129.32 (*ar* C), 131.68 (C-3), 139.49 (C-5), 144.53 (C-10), 156.89 (C-1_{Ph}), 176.99, 179.07 (CO) ppm; MS: m/z (%) = 464 (2) [M^++3], 463 (6) [M^++2], 462 (30) [M^++1], 461 (100) [M^+], 275 (10), 274 (40), 259 (8), 243 812), 75 (10), 73 (50), 45 (6).

1-(1-Methoxyvinyl)-3,4-dihydro-6-methoxynaphthalene (**13**)
See Ref. [9]

(8β,13β,14β)-3,11-Dimethoxy-16-methyl-18-nor-16-azaestra-1,3,5(10),9(11)-tetraene-15,17-dione (**14a**, $C_{19}H_{21}NO_4$)
a. From **13** (1.0 g, 4.5 mmol) and *N*-methylmaleimide (0.45 g, 3.5 mmol) as described for **5a**, 8 h. *b*. **7e** (0.15 g, 0.45 mmol) in 5 cm^3 *Me*OH and 2 cm^3 HC(O*Me*)$_3$ were stirred at room temperature for 12–15 h. Then the solvent was evaporated. Yield *a*. 0.43 g (30%), *b*. 0.14 g (91%); colorless crystals; mp 161°C (*Me*OH/H_2O); IR: $\bar{\nu} = 2936$, 2839 (*al* CH), 1769, 1692 (CO), 1603, 1566 (*ar*), 1266, 1241, 1223 (C–O), 785, 661 (*ar*) cm^{-1}; ^1H NMR: $\delta = 2.10$ (m, 7β-H), 2.25 (m, 7α-H), 2.48 (ddd, $J = 15, 6, 1.5$ Hz, 12β-H), 2.57 (m, 6α-H, 6β-H, 8β-H), 3.09 (dd, $J = 9, 6$ Hz, 14β-H), 3.14 (dd, $J = 15, 1.5$ Hz, 12α-H), 3.21 (ddd, $J = 9, 6, 3$ Hz, 13β-H), 3.60 (s, 11-O*Me*), 3.77 (s, 3-O*Me*), 6.60 (d, $J = 3$ Hz, 4-H), 6.67 (dd, $J = 9, 3$ Hz, 2-H), 7.79 (d, $J = 9$ Hz, 1-H) ppm.

(8β,13β,14β)-3,11-Dimethoxy-16-phenyl-18-nor-16-azaestra-1,3,5(10),9(11)-tetraene-15,17-dione (**14b**, $C_{24}H_{23}NO_4$)
From **13** (1.0 g, 4.5 mmol) and *N*-phenylmaleimide (0.90 g, 5.2 mmol), 6 h, as described for **5a**. Yield 1.5 g (56%); colorless crystals; $R_f = 0.52$ (neutral Al_2O_3, $CHCl_3$); mp 162°C (*Me*OH); IR: $\bar{\nu} = 2933$ (O*Me*), 2840 (*al* CH), 1709 (CO), 1621 (=C–O), 1604 (*ar*), 1305 (C–O), 693 (*ar*) cm^{-1}; ^1H NMR: $\delta = 2.10$ (dddd, $J = 15, 6, 3, 3$ Hz, 7β-H), 2.35 (dddd, $J = 15, 12, 12, 3$ Hz, 7α-H), 2.45 (ddd, $J = 15, 6, 1.5$ Hz, 12β-H), 2.65 (ddd, $J = 15, 12, 3$ Hz, 6β-H), 2.72 (ddd, $J = 12, 6, 1.5$ Hz, 8β-H), 2.78 (ddd, $J = 15, 3, 3$ Hz, 6α-H), 3.20 (dd, $J = 9, 6$ Hz, 14β-H), 3.22 (dd, $J = 15, 1.5$ Hz, 12α-H), 3.40 (ddd, $J = 9, 6, 1.5$ Hz, 13β-H), 3.62 (s, 11-O*Me*), 3.80 (s, 3-O*Me*), 6.55 (d, $J = 3$ Hz, 4-H), 6.70 (dd, $J = 9, 3$ Hz, 2-H), 7.1 (m, 2 *ar* H), 7.4 (m, 3 *ar* H), 7.80 (d, $J = 9$ Hz, 1-H) ppm.

(8β)-3,11-Dimethoxy-16-phenyl-18-nor-13,14,16-triazaestra-1,3,5(10),9(11)-tetraene-15,17-dione (**15**, $C_{22}H_{21}N_3O_4$)

13 (1.0 g, 4.5 mmol) and 4-phenyl-1,2,4-triazolin-3,5-dione (1.05 g, 5.75 mmol) in 30 cm^3 of toluene were stirred at −78°C for 2–5 h. Then 50 cm^3 *Me*OH were added, and the solvent was evaporated *in vacuo*. Yield 950 mg (55%); colorless crystals; mp 142°C (*Me*OH); IR: $\bar{\nu} = 2937$ (*al* CH), 1776, 1712 (CO), 1650 (=C-OSi), 1607, 1497, 767, 692, 647 (*ar*) cm^{-1}; ^1H NMR: $\delta = 1.85$ (m, 7β-H), 3.06 (m, 6α-H, 6β-H, 7α-H), 3.66 (s, 11-O*Me*), 3.81 (s, 3-O*Me*), 4.24 (dd, $J = 15.6$, 1.7 Hz, 12β-H), 4.40 (dd, $J = 15.6$, 1.9 Hz, 12α-H), 4.46 (ddd, $J = 10.2$, 7.3, 2.6 Hz, 8β-H), 6.65 (d, $J = 3$ Hz, 4-H), 6.80 (dd, $J = 9$, 3 Hz, 2-H), 7.5 (m, 5 *ar* H), 7.90 (d, $J = 9$ Hz, 1-H) ppm.

Acknowledgments

We thank Degussa AG for generous support with chemicals, E. Merck KGaG, Darmstadt, for continuous support with chromatography materials and biological testing, the "Fonds der Chemischen Industrie" for financial support, and Dr. *M. Kindermann*, Chemistry Dept. University of Greifswald, for some NMR experiments.

References

[1] Helwig/Otto (2004) Arzneimittel – Handbuch für Ärzte und Apotheker, 10. Aufl. Wiss Verlagsges, Stuttgart
[2] Jones CD, Audia JE, Hirsch LS (1993) J Med Chem **36**: 421; Rasmusson GH, Reyolds GF, Steinberg NG, Patel GF, Liang T, Berman C (1986) J Med Chem **29**: 2298; Rasmusson GH, Brooks JR (1984) J Med Chem **27**: 1690
[3] See Ref. [1], page 22/66; Merck Index 2001, 13th ed, Nr. 6209
[4] Haffner C (1994) Tetrahedron Lett **35**: 1349; Dwivedy I, Singh AK, Singh MM, Ray S (1993) Steroids **58**: 69
[5] Barlaam B, Boivin J, El-Kaim L, Zard SZ (1991) Tetrahedron Lett **32**: 623; Speckamp WN, de Koning H, Pandit UK, Huisman HO (1965) Tetrahedron **21**: 2517; ibid (1966) Tetrahedron Lett 2781; Minuti L, Selvaggi R, Taticchi A (1992) Syn Commm **22**: 1535; Anachenko SN, Torgov IV (1962) Tetrahedron **18**: 1355
[6] Richter F, Otto H-H (1985) Tetrahedron Lett **26**: 4351
[7] Bodtke A, Otto H-H (2004) Pharmazie (accepted)
[8] Goldberg MW, Doebel KJ, Scott WE (1950) US Patent 2.524.787, Chem Abstr **45**: 2508c
[9] Hajos ZG, Doebel KJ, Goldberg MW (1964) J Org Chem **29**: 2527
[10] Winternitz F, Diaz J (1963) Tetrahedron **19**: 1747
[11] Salley jr JJ, Glennon RA (1982) J Het Chem **19**: 545
[12] Paquette LA, Fristad WE, Dime DS, Bailey TR (1980) J Org Chem **45**: 3017
[13] Ireland RE, Thompson WJ, Mandel NS, Mandel GS (1979) J Org Chem **44**: 3583
[14] Richter F (1985) PhD Thesis, University of Freiburg
[15] Sultani A (1994) PhD Thesis, University of Freiburg
[16] Fleming I (1990) Grenzorbitale und Reaktionen organischer Verbindungen. VCH, Weinheim, p 128f
[17] Diels O, Alder K (1928) Liebigs Ann Chem **460**: 98
[18] Merck Index 2001, 13th ed, Nr. 3743, 3738
[19] Mutschler E (2001) Arzneimittelwirkungen, 8th ed. WVG, Stuttgart
[20] Unpublished results
[21] Quin LD, Symmes Jr C (1976) J Org Chem **41**: 238