Monatshefte für Chemie 137, 83–103 (2006)
DOI 10.1007/s00706-005-0406-8

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Azasteroids. Reaction of Chiral *N,N*-Maleoyl Amino Acids with 1-(1-Trimethylsiloxyvinyl)-3,4-dihydronaphthalene

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Received April 11, 2005; accepted (revised) May 11, 2005
Published online January 5, 2006

Summary. The cycloaddition between *N,N*-maleoyl amino acid esters and 1-(1-trimethylsiloxyvinyl)-3,4-dihydronaphthalene gave 11-(trimethylsiloxy) derivatives of 16-azaestra-1,3,5(10)-trienes. These were transformed by desilylation into the parent 11-oxo-derivatives, which reacted with hydroxylamines to 11-hydroxyimino derivatives. The stereochemistry of the products was elucidated using different NMR methods, HPLC, CD, X-ray structure analysis, and calculations. It was found that mixtures of diastereoisomers were obtained from these cycloadditions. Reactions using chiral maleoyl amino acid derivatves did not change this result. The chiral center did not provoke stereoselectivity, probably caused by the flexibility of the chiral side chain. A directing influence of the side chain was found only in reactions with derivatives of phenylalanine. This might be explained as an interaction between the aromatic system and the carbonyl groups of the imide moiety. This interaction kept the aromatic ring in its position in the final product, and was found in the X-ray crystallographic analysis, and agreed with results of calculations.

Keywords. Azasteroids; 2-Trialkylsiloxy-1,3-diene; Maleimides, chiral; *Diels-Alder* reaction; Crystallographic structure analysis.

Introduction

Natural steroids with 8β, 9α, 13β, and 14α configuration, halogenated and partially modified derivatives, and azaderivatives like the 5α-reductase inhibitor finasteride or the C-11 phenyl substituted antigestagene mifepristone are used as highly potent drugs [1, 2]. These derivatives are characterized either by unusual substituents, like mifepristone, or by an azasteroid structure like finasteride. There are

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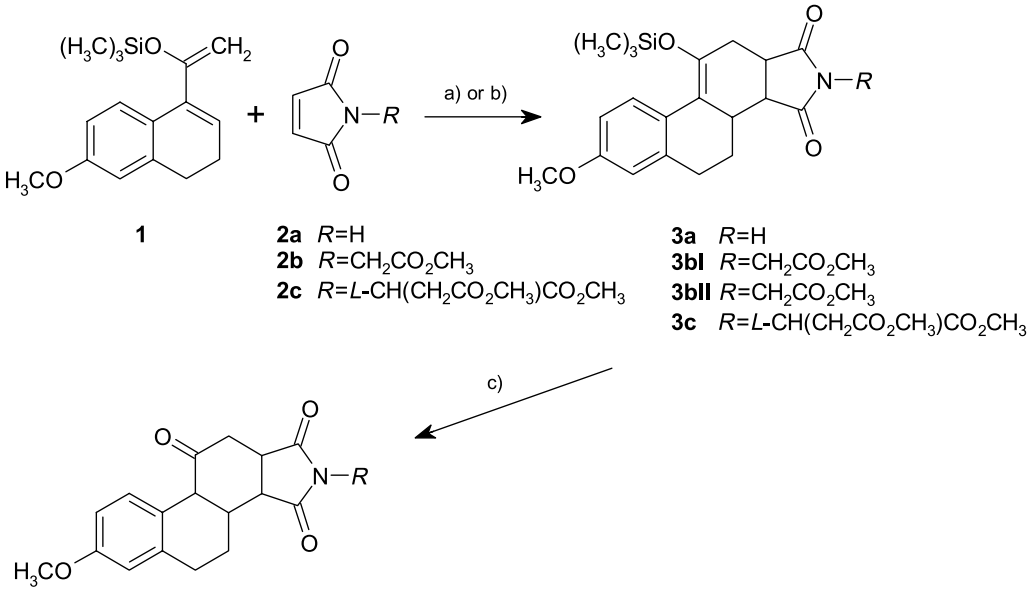
many syntheses described for azasteroids containing the nitrogen atom either in ring A or in ring B of the steroid skeleton [3]. In preceding papers we have described a synthesis route to azasteroids by *Diels-Alder* reactions between 1-(1-siloxyvinyl)olefines and dienophiles like maleimides, citraconimide, and triazolidinones [4], and reactions between cyclopentadiene and maleimides [5]. Here we report about our experiments to use chiral *N*-substituted maleimides bearing the chiral center in the substituent [5] as chiral inductors in *Diels-Alder* reactions with 1-(1-siloxyvinyl)-3,4-dihydronaphthalene derivatives.

Results and Discussion

The synthesis of the siloxydiene **1** was done following a literature procedure, and it is reported that the reaction between **1** and maleimide (**2a**) or alkyl/aryl substituted maleimides in toluene yielded 3-methoxy-11-(trialkylsiloxy)-18-nor-16-azaestra-1,3,5(10),9(11)-tetraene-15,17-dione derivatives [6]. We tried to use this synthesis for the reaction between **1** and substituted maleimides, mainly chiral *N*,*N*-maleoyl amino acid derivatives [5], to study if the chiral center in the dienophiles could induce an enantioselective cycloaddition. To find the optimum conditions the reactions were performed in CH_2Cl_2, *THF*, benzene, toluene, or without any solvent at different temperatures (20, 40, 60, 80, 100°C), and with reaction times of 4–16 h.

Performing the reaction without any solvent was in many examples the best way. From the reaction between **1** and the maleoyl glycinate **2b** at 60°C for 6 h, we isolated after addition of a mixture from *n*-hexane and Et_2O two fractions: **I**, mp



Scheme 1

142–143°C (**3bI**), and **II**, mp 120–125°C (**3bII**), and from the residue a small amount of **4bII**. From the reaction between **1** and the maleoyl *L*-asparaginate **2c** we obtained one crystalline product **3c** (26%), mp 132.5–134°C, and $[\alpha]_D^{20} = -38.0^\circ\,\mathrm{cm}^{-2}\,\mathrm{g}^{-1}$ ($c = 2$, CH_2Cl_2) (Scheme 1).

Reactions between **1** and the maleoyl amino acid derivatives **5a**–**5i**, **7a**–**7c**, and **10** done under these conditions yielded highly viscous residues, which we could not transform into pure crystalline materials. Neither crystallization nor CC with silica-gel or Al_2O_3 were successful, and TLC and HPLC experiments (Et_2O/*n*-hexane 1/1) showed mixtures of at least four products.

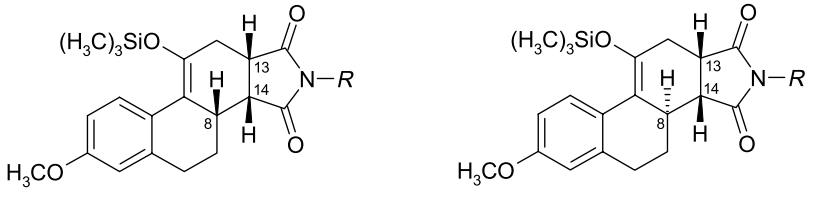
Looking for more appropriate conditions we tried reactions catalyzed by *Lewis* acids. Using $EtAlCl_2$, $ZnCl_2 \times Et_2O$, or $TiCl_4$ at low temperatures failed completely. From most experiments we isolated after hydrolytic work-up only 1-acetyl-3,4-dihydronaphthalene (from **1**). Finally, we tried a reaction catalyzed by $LiClO_4$ [7] using 3 equivalents $LiClO_4$ in reactions between **1** and **2b**, and **2c** in CH_2Cl_2, and indeed, after work-up we obtained **3bI**/**3bII** (52%), and **3c** (33%). The obtained products **3bI** and **3bII** were identical with those from the 'dry' reaction (mp, HPLC, spectroscopy, $[\alpha]_D^{20}$), and in HPLC experiments with the crude mixture of **3bI** and **3bII** a ratio 87:13 was found. In the not purified mixture of **3bI** and **3bII** obtained from a 'dry' reaction, 60°C, 3 h, the ratio was 66:34.

Unfortunately, the analogous reaction between **1** and the *L*-phenylalanine derivative **5e** gave a highly viscous material, which could not be purified.

The IR spectra of **3a**, **3bI**, **3bII**, and **3c** were characterized by the carbonyl bands of the imide moiety at *ca.* 1770 and 1700 cm^{-1}, whereas the carbonyl bands of the ester functions were found at 1750–1760 cm^{-1}. The asymmetrically substituted double bond at C-9(11) caused intensive bands at 1605–1630 cm^{-1}.

Considering that the cycloaddition had occured as an *endo* addition we had to discuss at least 2 possible configurations, each racemic: Structure I *syn-cis* (8β, 13β, 14β), and structure II *anti-cis* (8α, 13β, 14β) (Scheme 2)[†]. In compounds with a chiral *R* at position 16, diastereoisomers had to be considered.

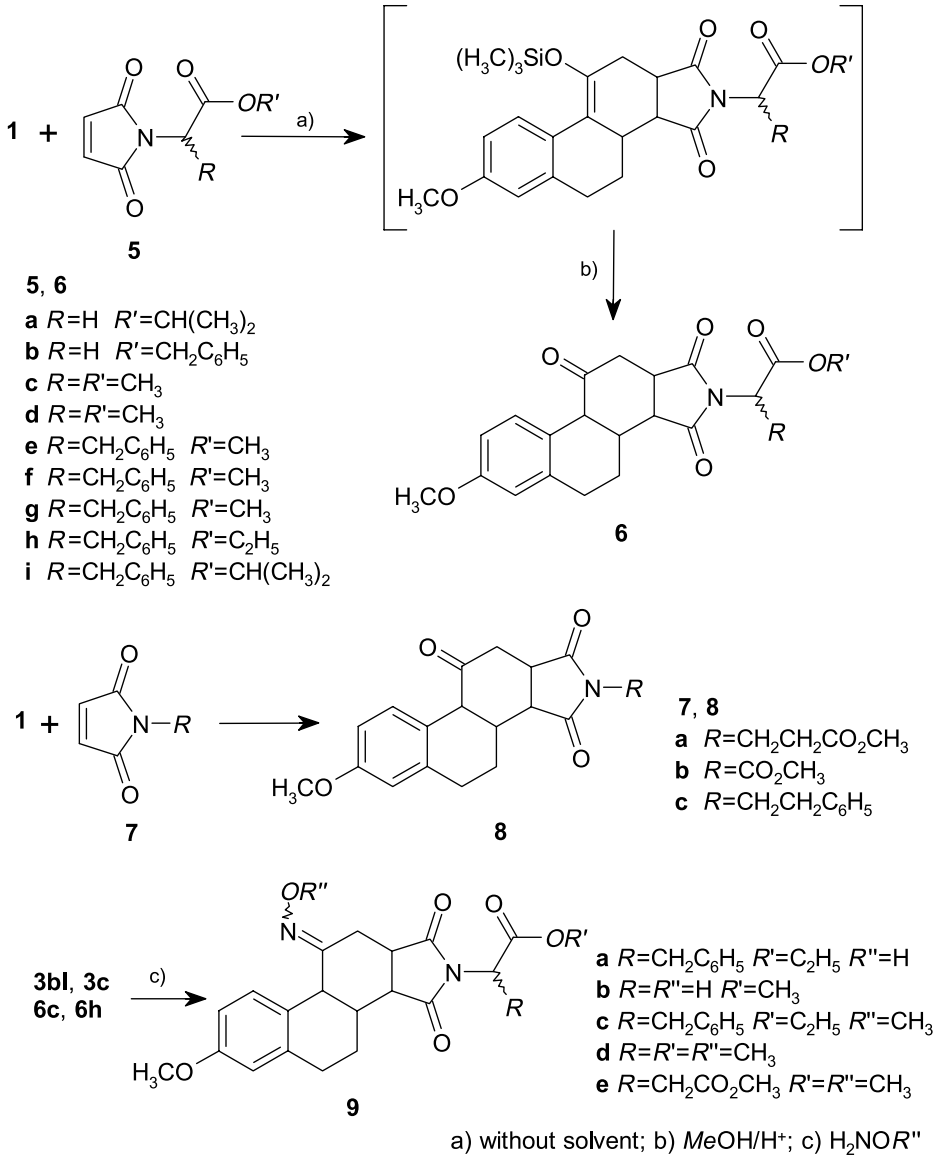
The ^{1}H NMR spectra showed the characteristic resonance signals of the protons of the functional groups, trimethylsilyl, methoxy, ester, *etc*. As each functional group gave only one clear signal we excluded mixtures of diastereoisomers. The



Scheme 2

[†] So far reactions yielded racemic compounds; thus, we use in this paper the α/β nomenclature as common in steroid chemistry; the R/S nomenclature is used only when the absolute configuration is known

spectra of **3bI** and **3bII** differed in two aspects: In the spectra of **3bII** the signal of 14-H at $\delta = 2.73$ ppm (dd) was shifted highfield compared with that of **3bI** found at $\delta = 3.18$ ppm (dd). The coupling constant $J_{13\text{-H}/14\text{-H}}$ was ≈9 Hz in both spectra, but $J_{8\text{-H}/14\text{-H}}$ was found to be 10.5 Hz in the spectra of **3bII**, and 5.7 Hz in the spectra of **3bI**. Interpreting these values following the modified *Karplus* rules [8] we estimated a torsion angle $\phi_{8\text{-H}/14\text{-H}} \approx 48°$ in **3bI**, while the value in **3bII** was $\phi \approx 154°$. Therefore we postulate for **3bI** the structure **I** and for **3bII** structure **II**. More difficult to interprete were the spectra of **3c**. Most protons showed 2 signals, and ^{13}C NMR spectra confirmed a mixture of diastereoisomers, but we were unable to separate the isomers. HPLC experiments showed for **3a**, **3bI**, and **3bII** each one peak using a RP-18 phase, and two peaks on a (*S*,*S*)-Whelk-O1 phase (chiral).



Scheme 3

Although the spectroscopic data of **3c** looked like from a mixture of diastereoisomers we found with RP-18 and Chiracel OJ-R phase only one peak ($k' = 4.18$ resp. $k' = 3.38$).

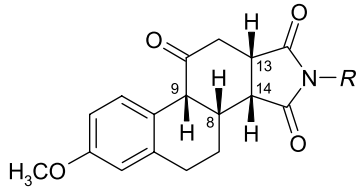
The desilylation of **3a**, **3bI**, and **3bII** was successful using *Me*OH and HCl [9] yielding **4a**, mp 205–210°C [6], **4bI**, mp 160–165°C, and **4bII**, mp 160–168°C. The reaction of **3c** in boiling *Me*OH with conc. HCl gave **4c** (44%).

As from the reaction between **1** and the maleoyl amino acid derivatives **5a**–**5i** no defined trimethylsiloxy derivatives were obtained, the viscous residues of these reactions were treated with *Me*OH and HCl, whereby the crystalline products **6a** (23%), **6b** (15%), **6c** (10%), **6d** (6%), **6e** (40%), **6f** (39%), and **6g** (31%) were obtained. Using similar conditions made the products **6h**–**8c** available (Scheme 3). In some reactions the desilylation occurred at room temperature, in some when warmed or refluxed, in some other reactions no acid was necessary, and **8b** and **8c** were obtained using *Ac*OH (see Exp.).

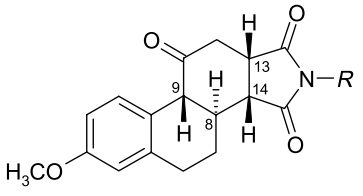
The IR spectra of all 11-oxo derivatives showed two intensive carbonyl bands at 1770–1780 and 1700–1710 cm^{-1}, representing the C=O groups of the imide part and the 11-oxo group. The C=O bands of the ester moiety were found at 1730–1750 cm^{-1}, and the intensive bands between 1585 and 1610 cm^{-1} represented the imide groups.

By cleavage of the siloxy group forming the 11-oxo derivatives a new chiral center was formed at C-9. Considering that the stereochemical properties at C-8, C-13, and C-14 were not influenced (changed) by the cleavage reaction at C-11 we had to discuss four stereoisomers (Scheme 4): Structure **III** *cis-syn-cis* (8β, 9β, 13β, 14β), structure **IV** *trans-anti-cis* (8α, 9β, 13β, 14β), structure **V** *trans-syn-cis* (8β, 9α, 13β, 14β), and structure **VI** *cis-anti-cis* (8α, 9α, 13β, 14β).

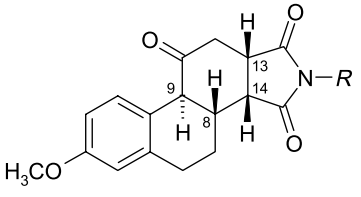
^{1}H NMR data of **4a** (R=H) were congruent with the reported data [6]. The spectra of **4bI** (R=$CH_2CO_2CH_3$) showed signals of the protons 1-H, 4-H, and 2-H at $\delta = 7.24$ (d), 6.61 (dd), and 6.77 (d) ppm. Two singlets were found from the protons of the methoxy group at C-3 and from the ester group, at $\delta = 3.79$ and



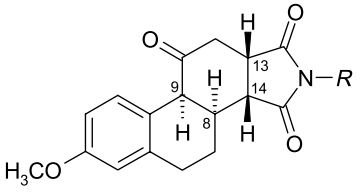
Structure III (*cis-syn-cis*)



Structure IV (*trans-anti-cis*)



Structure V (*trans-syn-cis*)



Structure VI (*cis-anti-cis*)

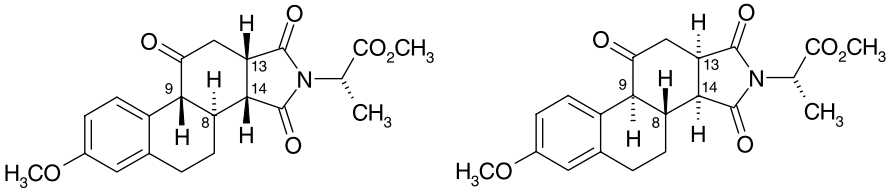
Scheme 4

3.77 ppm. The spectra of the other 11-oxo derivatives showed the analogous signals in the same range. Differences were found concerning the substituent at position 16 and the protons at C-7, C-8, C-9, C-12, C-13, and C-14.

The data show nearly analogous shift values for **4bI–6d** with an aliphatic substituent in position 16, and for compounds **6e–6i** with a phenyl ring part of the substituent at position 16 exhibiting that the aromatic system in the side chain influenced the shift values of the steroidal skeleton. A significant difference was noticed between the values of **4bI** with 8β-configuration, and its 8α isomer **4bII**. From the cross signals $^3J_{8,9}$, $^4J_{1,9}$, $^5J_{2,9}$, $^5J_{4,9}$ found in the ^{1}H,^{1}H-COSY spectrum of **4bI** the doublet of 9-H was located at $\delta = 3.44$ ppm, $^3J_{8,9} = 8.4$ Hz, and using the *Karplus-Garbisch* relation the torsion angle was estimated as $\phi \sim 36^\circ$ indicating a *cis* orientation, that means **III** with 8β-H and 9β-H. The spectra of **4bII** contained two separated double doublets of 12-H at $\delta = 2.77$ and 2.98 ppm with $J_{gem} = 17.3$ Hz, and $^3J_{12,13} = 7.3$ and 11.0 Hz, and one doublet of a doublet at $\delta = 3.10$ ppm for 14-H. The coupling $^3J_{13,14} = 9.0$ Hz indicated the *cis* orientation, 13β-H, 14β-H, and from the coupling $^3J_{8,14} = 11.4$ Hz resulted a torsion angle $\phi \sim 160^\circ$ indicating a *trans* orientation. As we could not resolve the multiplets of 9-H and 13-H we optimized and calculated the structure of **4bII** (PM3, HYPERCHEM [10]), and compared the experimental spectrum with the spectrum of the optimized structure [11]. This gave for 9-H $\delta = 3.44$ ppm, for 13-H $\delta = 3.47$ ppm, and the coupling constants $^3J_{12,13} = 7.4$ and 10.9 Hz, $^3J_{13,14} = 9.0$ Hz, and $^3J_{8,9} = 12.8$ Hz. The last value indicated a *trans* orientation, and thereby 8α-H and 9β-H (**IV**) for **4bII**.

The data of the analogous isopropyl ester **6a** and the benzyl ester **6b** were similar to those of the methyl ester **4bII**. Therefore, these compounds should have the same relative stereochemistry, 8α, 9β, 13β, and 14β (structure **IV**). In contrast, the spectra of **4c**, prepared from maleoyl L-asparaginate, showed for most protons of the steroidal skeleton and for the protons of the substituent at position 16 two sets of signals. One 12-H was registered as 2 double doublets ($\Delta\delta = 4.7$ Hz) with $^2J_{12,12} = 17.4$ Hz, and $^3J_{12,13} = 7.1$ and 7.6 Hz, confirmed by an ^{1}H,^{1}H-COSY spectrum. Even 14-H showed 2 double doublets at $\delta = 3.04$–3.12 ppm, with $^3J_{13,14} = 9.1$ Hz, $^3J_{8,14} = 2.0$ Hz ($\Delta\delta = 11.4$ Hz), $^3J_{13,14} = 9.1$ Hz, and $^3J_{8,14} = 11.4$ Hz with $\Delta\delta = 2.0$ Hz. One set agreed with the *syn-cis* (8β, 13β, 14β) conformation, the other one with the *anti-cis* (8α, 13β, 14β) conformation. From the ^{1}H,^{1}H-COSY spectra 2 double doublets of 8-H were found with $^3J_{7,8} = 2.6$ Hz, and $^3J_{7,8}$ and $^3J_{8,14} \sim 11.9$ Hz. These values would fit to the *anti-cis* isomer. From the cross signal of 8-H and 9-H 2 doublets for 9-H at $\delta = 3.43$ and 3.44 ppm, $^3J_{8,9} = 11.5$, 12.8 Hz were found, and from the *Karplus-Garbisch* relation a torsion angle $\phi \sim 160^\circ$ or 173° resulted, both speaking for the *trans* orientation of 8-H und 9-H supporting the structure **IV** of **4c**. Therefore, the observed two sets of signals might be explained by two diastereoisomers formed by two enantiomeric steroidal skeletons with the (*S*)-configuration in the side chain at position 16.

There is no difference between the ^{1}H NMR spectra of the isomeric 2-substituted propionates **6c** obtained from maleoyl L-alaninate and **6d** from maleoyl D-alaninate. A partial definitive correlation of the signals was possible using the data of the ^{1}H,^{1}H-COSY spectra. For 1-H, 9-H, 12-H, 13-H, and 14-H, each two signals with $\Delta\delta = 5$–8 Hz were registered. Furthermore, the signals of the α-H and of the methyl



Proposed diastereoisomers of **6c** deduced from NMR data

Scheme 5

group of the side chain showed two sets of signals $\Delta\delta \sim 1$ Hz. The signals of 14-H (dd) with $^3J_{13,14} = 9.0$ Hz and $^3J_{8,14} = 4.7$ Hz ($\Delta\delta = 11.4$ Hz), or with $^3J_{13,14} = 9.0$ Hz and $^3J_{8,14} = 11.4$ Hz ($\Delta\delta = 4.7$ Hz) might be explained as in the spectra of **4c**. The first group with $^3J_{8,14} = 4.7$ Hz looked like the *syn-cis* form (8β, 13β, 14β), the second group with $^3J_{8,14} = 11.4$ Hz like the *anti-cis* orientation (8α, 13β, 14β). We could not detect the coupling between 8-H and 14-H in the multiplet of 8-H. In the ^{1}H,^{1}H-COSY spectrum of **6c** we found long-range couplings of 1-H, 2-H, and 4-H with 9-H. From this fact, and from the cross signal of 8-H with 9-H the *trans* orientation of 8-H and 9-H (8α, 9β, structure **IV**) was deduced. Furthermore, as the ^{13}C NMR spectra of **6c** showed double signals for the C-atoms 1, 7, 8, 10, 11, 13, and 17, we propose for **6c** a mixture of 2 diastereoisomers with (*S*)-configuration in the side chain as shown in Scheme 5.

As the spectral data of **6d** were similar, we propose for **6d** the analogous structure with (*R*)-configuration in the side chain. The ^{1}H NMR data of the 3 isomeric compounds **6e**–**6g** obtained from reactions with the isomers of maleoyl phenylalaninate, *L*-, *D*,*L*-, and *D*- (Table 1), showed no significant differences. Between $\delta = 6.61$ ppm and $\delta = 7.28$ ppm the signals of 1-H, 2-H, and 4-H, and the signals of the phenyl ring were recorded. α- and β-protons of the substituent at position 16 caused an ABX-system at $\delta = 5.10$, 3.48, and 3.51 ppm with $^2J_{AB} = 14.1$ Hz, $^3J_{AX} = 12.3$ Hz, and $^3J_{BX} = 4.7$ Hz. Protons of 3-O*Me* and ester O*Me* were found at $\delta = 3.78$ and 3.81 ppm. Using ^{1}H,^{1}H-COSY and ^{13}C,^{1}H-COSY

Table 1. Selected ^{1}H NMR data of **6e**, and torsion angles ϕ (a *Karplus*, b *Karplus-Garbisch*)

	δ/ppm	J/Hz	ϕ/°, a	ϕ/°, b
8-H	1.31 (dd)	$^3J_{8,9} = 12.2$	150–180	169.5
		$^3J_{8,14} = 11.3$	145–180	159.0
9-H	3.28 (dd)	$^3J_{8,9} = 12.2$	150–180	165.9
12-H	2.78 (dd)	$^2J_{12,12} = 17.0$	10–45/135–160	37.7/142.2
		$^3J_{12,13} = 8.1$		
12-H	2.46 (dd)	$^2J_{12,12} = 17.0$	0–40/135–175	31.9/147.9
		$^3J_{12,13} = 9.3$		
13-H	3.22 (dd)	$^3J_{12,13} = 17.2$, 9.3	0–40/135–175	31.9/147.9
		$^3J_{12,13} = 8.1$	10–45/135–160	37.7/142.2
		$^3J_{13,14} = 8.8$, 8.8	0–38/135–165	34.4/145.4
14-H	2.85 (dd)	$^3J_{13,14} = 8.8$	0–38/135–165	34.4/145.4, 159.0
		$^3J_{8,14} = 11.3$	145–189	

data the signals of protons of the steroidal skeleton were determined. The relevant data obtained for **6e** are collected in Table 1.

Using the *Karplus* and the *Karplus-Garbisch* rules we calculated from the relevant coupling constants $^3J_{8,9}$ and $^3J_{8,14}$ the torsion angles $\phi \sim 150–180°$ and 145–180°, 165.9° and 159.0° resp. Considering the cycloaddition was a *cis* addition, from $^3J_{13,14} = 8.8$ Hz followed torsion angles of 0–38°, 34.4° resp., and from this results a *trans-anti-cis* orientation of 8-H, 9-H, 13-H, and 14-H (structure **IV**). This conclusion was partially supported by N*O*E experiments. Irradiation at $\delta = 1.31$ ppm (8-H) caused weak positive effects on the signals of 9-H, 12-H, and 14-H, irradiation at $\delta = 3.28$ ppm (9-H) resulted in weak positive effects on the signals of 8-H, 12-H, and a strong effect on 14-H, irradiation at $\delta = 3.22$ ppm (13-H) gave strong effects on the signals of 12-H and 14-H, and finally irradiation at $\delta = 2.85$ ppm (14-H) caused strong effects on the signals of 9-H and 13-H. Spectral data of the ethyl ester **6h** and the isopropyl ester **6i**, both obtained from reactions with the parent *L-Phe* derivative were congruent to those of **6e**, and therefore we postulate analogous structures.

The ^{1}H NMR spectra of **8a** obtained from the *N*,*N*-maleoyl *β-Ala* derivative **7a**, **8b** from the maleoyl carbamate **7b** (alternative from **4a** and methyl chloroformiate), and **8c** from *N*-(2-phenylethyl)maleimide (**7c**) and **1**, showed the signals of the substituent at position 16, and similar patterns for the steroidal part as all other derivatives. The signals of 13-H and 14-H supported the *cis* addition, but as an exact resolution of the signals of 8-H and 9-H was not possible, we described the relative configuration as 8ξ, 9ξ, 13β, and 14β.

All 11-oxo derivatives were proved by HPLC experiments using mixtures from *Me*CN and H_2O as the mobile phase and RP-18 (achiral) and Chiracel OJ-R or (*S*,*S*)-Whelk-O1 (chiral) columns. As expected, **4a**, **4bI**, **4bII**, **6a**, **6b**, **8a**, **8b**, and **8c** having no chiral center in the substituent at position 16, gave one peak on the achiral RP-18 phase, but showed as racemates two peaks on the chiral (*S*,*S*)-Whelk-O1 or Chiralcel OJ-R phase. The result of **4c** seemed to be not clear, only one peak was found on both phases. The HPLC data of **6c** and **6d** supported the interpretation of their NMR data. The isolated compounds existed as two isomers, which caused one peak on the RP-18 phase. On Chiracel OJ-R each compound caused two peaks (ratio 1:1) with identical λ values.

Surprising observations were made when the compounds **6e**, **6f**, and **6g**, obtained from reactions with the isomers of *N*,*N*-maleoyl phenylalaninate, were examined by HPLC. **6e** and **6g**, derivatives of *L-Phe* and *D-Phe*, showed each only one peak on the RP-18 and on the Chiracel OJ-R phase. The derivative of *D,L-Phe*, **6f**, gave 2 peaks on the RP-18 phase (ratio 1:1), and 4 peaks on the Chiracel OJ-R phase. This indicated that **6f** was isolated as a mixture of two racemic diastereoisomers, a result congruent with the results from NMR spectroscopy. On the other hand, from the reaction between **1** and *N*,*N*-maleoyl-*L-Phe*-O*Me* (**5e**) we isolated the pure enantiomer **6e**, and from the reaction between **1** and *N*,*N*-maleoyl-*D-Phe*-O*Me* (**5g**) we isolated the pure enantiomer **6g**.

As the isolated yields from these reactions were not higher than 40%, we proved the reaction between **1** and the *L-Phe* derivative by following the reaction course at 50°C over 6 h by analyzing probes on RP-18 phase at the beginning and then after 1, 2, 4, and 6 h. After 1 h the turn-over was 52%, and after 6 h 66%, and

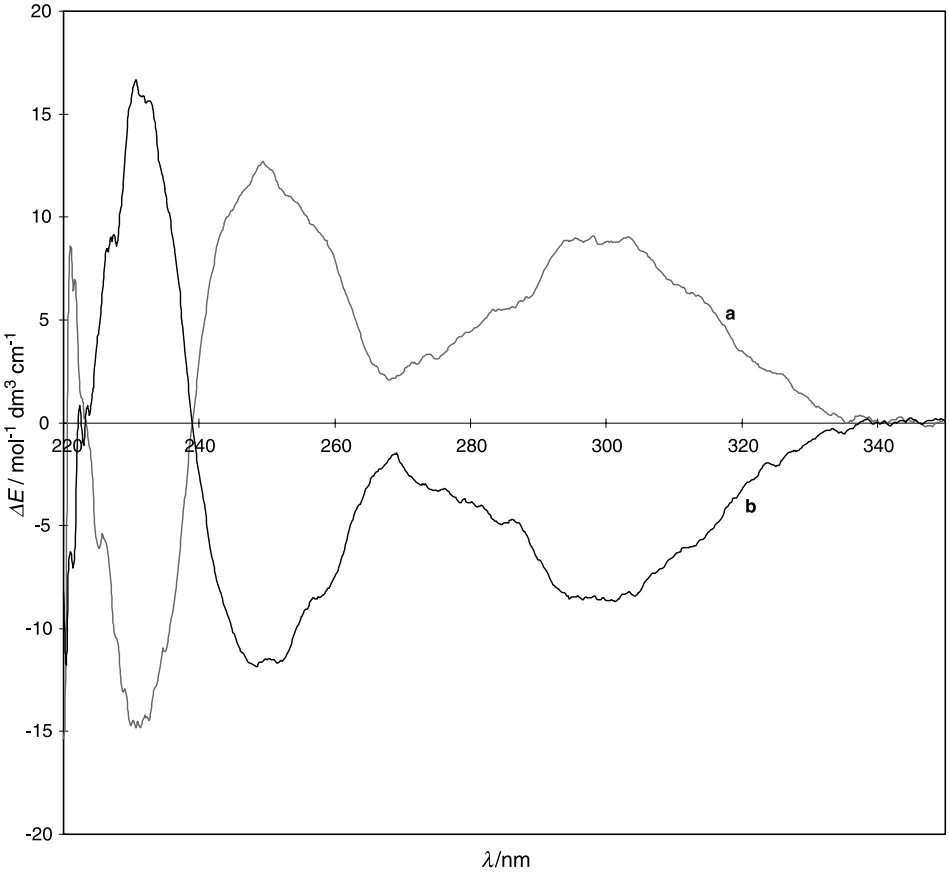


Fig. 1. CD spectra of **6e** (a) and **6g** (b) in CH_2Cl_2

we detected after 1 h two compounds, ratio 1:5.8, and after 6 h ratio 1:5.5. The major compound was the silylenol ether of the isolated **6e** (*anti-cis*), and the minor compound was the *syn-cis* isomer. When similar experiments were done with hydrolytic work-up we detected 2 products, the 11-oxo derivatives **6e** and **6g**, and we found, that the *anti-cis* adduct was much faster hydrolyzed than the *syn-cis* adduct. These results demonstrated that the reaction between **1** and **5e** was stereoselective.

For proving the enantiomeric character of **6e** and **6g** we recorded the CD spectra in CH_2Cl_2 (Fig. 1). The spectrum of **6e** showed *Cotton* effects for $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ at $\lambda = 298$ nm (+9), 249 nm (+13), 230 nm (−14.8), and 221 nm (+8.5). As the spectrum of **6g** was the mirror image, **6e** and **6g** should be enantiomers [12].

Structures of **6e** and **6g** were calculated using HYPERCHEM. We report here the data and results for **6g**. Optimization with MM+ resulted in a minimum energy $\Delta\delta E_{pot}$ for the chair-boat (ring B, ring C) and the chair-chair conformation, in which the phenyl ring of the side chain is located over ring D. A similar conformation was favored when we used a PM3 calculation. The X-ray crystallographic analysis of **6g** gave a very similar result (Fig. 2), and the analysis of **6e** established the enantiomers.

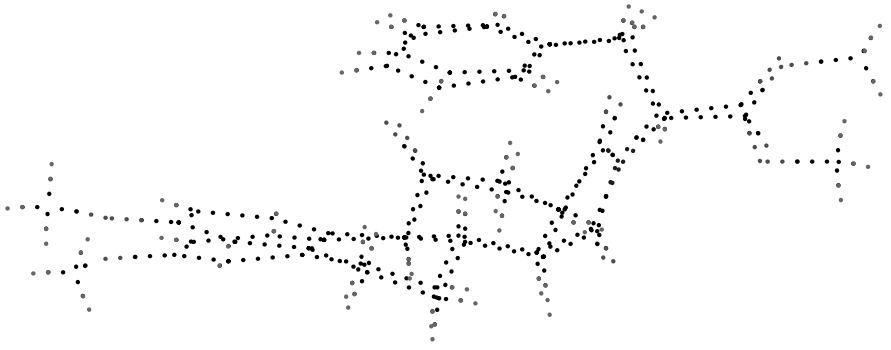


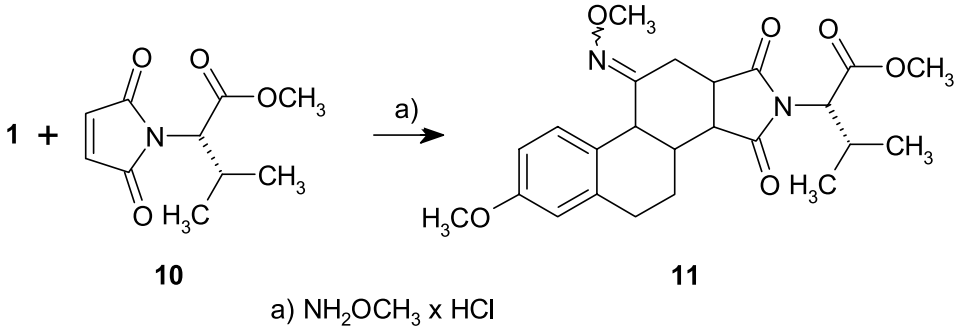
Fig. 2. Superposition of the X-ray analysis structure of **6g** with the calculated, MM+ optimized, conformation of **6g**

Comparing the calculated conformation of **6g** with the phenyl ring of the side-chain at position 16 above the steroidal skeleton resulted for MM+ a RMS gradient of 0.3, and for PM3 a RMS gradient of 0.6. The superposition of the MM+ optimized conformation with the structure of the X-ray analysis is given in Fig. 2. Only small differences are visible concerning the orientation of the ester group and of the methoxy group. The benzyl group is fixed above the steroidal skeleton in both structures.

Compounds **3bI**, **3c**, **6c**, and **6h** were transformed by standard procedures into the 11-hydroxyimino or the 11-methoxyimino derivatives **9a**–**9e** with satisfactory yields up to 90% (Scheme 3).

Compound **11** (Scheme 6) was obtained as a crystalline product from the crude reaction mixture of the reaction between **1** and *N*,*N*-maleoyl-*L*-*Val*-O*Me* (**10**), without isolation of the 11-oxo derivative from this reaction.

The IR spectra of **9a**–**11** showed the expected 3 carbonyl bands around 1775 and 1710 cm^{-1} from the CO groups in positions 15 and 17, and the CO bands of the ester groups around 1730 cm^{-1}. Compounds **9a** and **9b** were formed as E/Z mixtures (~1:1), which could be seen from HPLC experiments and from the two signals of the hydroxyl proton or the methoxy group in their ^1H NMR spectra. Compounds **9c**-**11** gave in all HPLC experiments only one peak, either their isomers were not separated, or each existed only as one stereoisomer. Detailed studies of the NMR



Scheme 6

spectra showed that the stereochemistry (*trans-anti-cis*) of the steroidal skeleton was not changed by the transformation of the 11-oxo derivatives into the oximes.

Summarizing our experiments we observed that the cycloaddition between **1** and maleimides bearing a chiral substituent at the nitrogen did not occur stereoselectively. This might be caused by the flexibility of the chiral side chain. A mixture of diastereoisomers was formed in all reactions as in reactions with maleimides bearing an achiral side chain. The ratio of diastereoisomers was influenced by the substituents at the chiral center, the α-position of the parent amino acid. If this substituent was a small aliphatic group like methyl, the ratio was about 1:1. If the substituent was a benzyl group from phenylalanine, the ratio rose to 6:1, and we isolated after workup the major isomer. The effect of the phenyl (benzyl) group in the side chain might be explained as an interaction between the aromatic system and the carbonyl groups of the imide moiety during the cycloaddition. This interaction kept the phenyl ring in its position in the final product, and was found in the X-ray crystallographic analysis of **6g** (Fig. 2) and **6e**.

Experimental Part

Mp: Mikroheiztisch PHMX 80/2778. IR spectra (KBr): Perkin-Elmer IR 1310. ^{1}H NMR spectra: Bruker DPX 200 (200 MHz), Bruker DPX 300 (300 MHz), ^{13}C NMR spectra: Bruker DPX 300 (75.43 MHz). Internal standard *TMS*, $\delta_{TMS} = 0.00$ ppm. ^{1}H/^{13}C values from 300/75.43 MHz spectra in $CDCl_3$, if not otherwise noted. Optical rotation: Polartronic D. Elementary analyses: Institute of Pharmacy (Perkin-Elmer Elemental Analyzer 2400 CHN), or Institute of Chemistry, University of Greifswald. All compounds gave satisfactory elemental analyses. Dimethoxyethane (*DME*) and tetrahydrofuran (*THF*) were stored with KOH, then refluxed with Na and benzophenone, and distilled prior to use. Other solvents were dried/purified according to literature procedures. *LDA* (lithium diisopropylamide) was freshly prepared by mixing equimolar amounts of (*i-Pr*)$_2$NH and *Bu*Li (*n*-butyl lithium, 15% in *n*-hexane) in *THF* at −78°C. HPLC: System LaChrom, series 7000 Merck Hitachi. Columns: LiChrospher 250-4, RP-18, 5 µm; (*S,S*)-Whelk-O1, 250-4, 5 µm; Chiraspher, 250-4, 5 µm, Chirobiotic T. Molecular modeling: Hyperchem® 4.0, Hypercube, Inc.; Hyperchem™ 6.0 (Demo version), Hypercube, Inc.

Abbreviations: CC=column chromatography (silica gel 60, Merck 7734, 0.040–0.063 mm); *AcOEt* = ethyl acetate; *tlc* = thin layer chromatography (pre-coated plates, silica gel 60 F_{254}, Merck 5554); *al* = aliphatic; *ar* = aromatic.

6-Methoxy-1-(1-trimethylsiloxyvinyl)-3,4-dihydronaphthaline (**1**) [6], and *N,N*-maleoyl amino acid derivatives [5] were prepared according to literature.

(8β,13β,14β)-3-Methoxy-11-(trimethylsiloxy)-18-nor-16-azaestra-1,3,5(10),9(11)-tetraene-15,17-dione (**3a**, $C_{20}H_{25}NO_4Si$) [6]

Compound **1** (6 g, 23.2 mmol) and **2a** (2.23 mg, 23 mmol) in 60 cm^3 toluene were refluxed for 3 h. Yield 7.95 g (98%); colorless crystals; mp 196–201°C (dec, acetone); IR: $\bar{\nu} = 3167$ (NH), 3066 (C=CH, *ar* CH), 2958, 2837 (*al* CH), 1776, 1702 (CO), 1629, 1606 (C=CH) cm^{-1}; ^{1}H NMR (200 MHz): $\delta = 0.12$ (s, Si*Me*$_3$), 1.98–2.11 (m, 7-H), 2.23 (dddd, $^2J_{7,7} = 12.3$ Hz, $^3J_{7,8} = 12.3$ Hz, $^3J_{6,7} = 12.3$ Hz, $^3J_{6,7} = 3.4$ Hz, 7-H), 2.46–2.74 (m, 2 6-H, 8-H, 12-H), 2.80 (dd, $^2J_{12,12} = 15.4$ Hz, $^3J_{12,13} = 1.6$ Hz, 12-H), 3.12 (dd, $^3J_{8,14} = 5.6$ Hz, $^3J_{13,14} = 8.9$ Hz, 14-H), 3.24 (ddd, $^3J_{12,13} = 6.8$ Hz, $^3J_{12,13} = 1.6$ Hz, $^3J_{13,14} = 9.0$ Hz, 13-H), 3.78 (s, O*Me*), 6.61 (d, $^5J_{2,4} = 2.5$ Hz, 4-H), 6.66 (dd, $^3J_{1,2} = 8.6$ Hz, $^5J_{2,4} = 2.8$ Hz, 2-H), 7.85 (d, $^3J_{1,2} = 8.5$ Hz, 4-H), 7.93 (s, H–N) ppm; HPLC: $k' = 4.86$, $t_0 = 2.22$ min (RP-18, *Me*CN/H_2O 6/4); $k_1' = 2.07$, $k_2' = 2.34$, $t_0 = 2.16$ min ((*S,S*)-Whelk-O1 *n*-hexane/*AcOEt* 8/2).

*Reaction of **1** with Methyl N,N-Maleoylglycinate*

Method a: A mixture from **1** (1.8 g, 5.7 mmol) and *N,N*-maleoyl-*Gly*-O*Me* (**2b**, 0.96 g, 5.7 mmol) was heated for 4 h to 80°C. After cooling to room temperature, and dropwise addition of 50 cm^3 *n*-hexane/Et_2O (1/1) first **3bI** (830 mg, 33%), and then a mixture from **3bI** and **3bII** (825 mg, 33%) were obtained as colorless precipitates. Pure **3bII** was isolated after fractionizing crystallization from *Me*OH. Keeping the mother liquor for 1 h at room temperature, gave additional **4bII** (80 mg, 4%).

Method b: $LiClO_4$ (1.33 g, 12.5 mmol) was added with stirring to a suspension of **2b** (423 mg, 2.5 mmol) in 20 cm^3 CH_2Cl_2, and after 20 min **1** (0.8 g, 2.5 mmol) in 10 cm^3 CH_2Cl_2 was dropwise added, stirring was continued for 3 h at room temperature, then the mixture was diluted with 20 cm^3 of a saturated solution of NaCl, and extracted with 100 cm^3 *Ac*O*Et*. The organic layer was separated, dried (Na_2SO_4), and evaporated *in vacuo*. After addition of a few cm^3 of Et_2O, the precipitate was separated. Yield 572 mg (52%) of a mixture of **3bI** and **3bII**.

Methyl 2-[(8β,13β,14β)-3-Methoxy-11-(trimethylsiloxy)-18-nor-15,17-dioxo-16-azaestra-1,3,5(10),9(11)-tetraen-16-yl]acetate (**3bI**, $C_{23}H_{29}NO_6Si$)

Yield 1.23 g (49%); colorless crystals; mp 142–143°C; IR: $\bar{\nu} = 3012$ (*ar* CH), 2951, 2940, 2873, 2838 (*al* CH), 1759, 1704 (CO), 1623, 1605 (C=C) cm^{-1}; ^1H NMR: $\delta = 0.12$ (s, SiMe_3), 2.08 (dddd, $^2J_{7,7} = 12.7$ Hz, $^3J_{6,7} = 5.8$ Hz, $^3J_{6,7} = 3.6$ Hz, $^3J_{7,8} = 3.4$ Hz, 7-H), 2.24 (dddd, $^2J_{7,7} = 12.6$ Hz, $^3J_{6,7} = 12.6$ Hz, $^3J_{6,7} = 3.2$ Hz, $^3J_{7,8} = 12.6$ Hz, 7′-H), 2.49–2.57 (m, 8-H), 2.55 (ddd, $^2J_{12,12} = 15.4$ Hz, $^3J_{12,13} = 6.8$ Hz, $J = 1.7$ Hz, 12-H), 2.66–2.74 (m, 6-H, 6′-H), 2.83 (dd, $^2J_{12,12} = 15.4$ Hz, $^3J_{12,13} = 1.7$ Hz, 12′-H), 3.18 (dd, $^3J_{13,14} = 8.9$ Hz, $^3J_{8,14} = 5.7$ Hz, 14-H), 3.28 (ddd, $^3J_{13,14} = 8.9$ Hz, $^3J_{12,13} = 6.9$ Hz, $^3J_{12,13} = 1.7$ Hz, 13-H), 3.63 (s, O*Me*), 3.77 (s, O*Me*), 4.16 (s, NCH_2), 6.61 (d, $^4J_{2,4} = 2.8$ Hz, 4-H), 6.65 (ddd, $^3J_{1,2} = 8.6$ Hz, $^4J_{2,4} = 2.8$ Hz, $J = 0.4$ Hz, 2-H), 7.84 (d, $^3J_{1,2} = 8.6$ Hz, 1-H) ppm; ^{13}C NMR: $\delta = 0.62$ (SiMe_3), 25.23 (C-7), 31.07, 31.13 (C-6, CH_2), 37.99 (C-13), 39.54 (C-12), 41.28 (C-8), 43.54 (C-14), 52.53 (O*Me*), 55.08 (O*Me*), 111.17 (C-2), 112.54 (C-4), 113.08 (C-10), 125.46 (C-11), 129.93 (C-1), 139.72 (C-5), 143.68 (C-9), 157.17 (C-3), 166.87 (CO), 176.68 (C-15), 178.33 (C-17) ppm; HPLC: $k' = 3.53$, $t_0 = 1.76$ min (RP-18, *Me*CN/H_2O 7/3); $k' = 2.97$, $t_0 = 2.09$ min (Chiralcel OJ-R, *Me*CN/H_2O 1/1); $k_1' = 1.32$, $k_2' = 1.74$, $t_0 = 1.98$ min ((*S*,*S*)-Whelk-O1, *n*-hexane/*Et*OH 1/1).

Methyl 2-[(8α,13β,14β)-3-Methoxy-11-(trimethylsiloxy)-18-nor-15,17-dioxo-16-azaestra-1,3,5(10),9(11)tetraen-16-yl]acetate (**3bII**, $C_{23}H_{29}NO_6Si$)

Yield 425 mg (17%); colorless crystals; mp 120–125°C (*Me*OH); ^1H NMR: $\delta = 0.14$ (s, SiMe_3), 1.70 (m, 7-H), 2.42 (dd, $^2J_{12,12} = 15.2$ Hz, $^3J_{12,13} = 11.5$ Hz, 12-H), 2.48–2.71 (m, 6-H, 6′-H, 7′-H, 8-H), 2.73 (dd, $^3J_{8,14} = 10.5$ Hz, $^3J_{13,14} = 9.5$ Hz, 14-H), 2.74 (dd, $^2J_{12,12} = 15.2$ Hz, $^3J_{12,13} = 7.2$ Hz, 12′-H), 3.20 (ddd, $^3J_{12,13} = 11.4$ Hz, $^3J_{12,13} = 7.2$ Hz, $^3J_{13,14} = 9.4$ Hz, 13-H), 3.78 (s, O*Me*), 3.80 (s, O*Me*), 4.28 (s, NCH_2), 6.65 (d, $^4J_{2,4} = 2.7$ Hz, 4-H), 6.72 (dd, $^3J_{1,2} = 8.7$ Hz, $^4J_{2,4} = 2.8$ Hz, 2-H), 7.98 (d, $^3J_{1,2} = 8.7$ Hz, 1-H) ppm; ^{13}C NMR: $\delta = 0.61$ (s, SiMe_3), 27.89 (C-7), 30.04, 31.51 (C-6, CH_2), 37.65 (C-13), 39.12 (C-12), 41.29 (C-8), 45.86 (C-14), 52.72 (O*Me*), 55.13 (O*Me*), 111.38 (C-2), 112.58 (C-4), 114.53 (C-10), 125.40 (C-11), 130.02 (C-1), 139.83 (C-5), 145.02 (C-9), 157.20 (C-3), 167.26 (CO), 177.57 (C-15), 177.76 (C-17) ppm; HPLC: $k' = 5.42$, $t_0 = 1.76$ min (RP-18, *Me*CN/H_2O 7/3); $k' = 4.28$, 4.67, $t_0 = 1.77$ min (Chiralcel OJ-R, *Me*CN/H_2O 1/1).

Dimethyl (S)-2-[(8ξ,13β,14β)-3-Methoxy-11-(trimethylsiloxy)-18-nor-15,17-dioxo-16-azaestra-1,3,5(10),9(11)tetraen-16-yl]succinate (**3c**, $C_{26}H_{33}NO_8Si$)

Method a: A mixture from **1** (1.5 g, 4.7 mmol) and *N,N*-maleoyl-*L-Asp*(O*Me*)$_2$ (**2c**, 1.13 g, 4.7 mmol) was heated to 70°C for 22 h. After cooling to room temperature, the mixture was diluted with Et_2O, and the precipitate was separated. Yield 618 mg (26%).

Method b: From $LiClO_4$ and **2c** (603 mg, 2.5 mmol) as described for **3bI**/**3bII**. Yield 425 mg (33%); colorless needles; mp 132.5–134°C (*Me*OH); $[\alpha]_D^{20} = -38.0°\ cm^{-2}\ g^{-1}$ ($c = 2$, CH_2Cl_2); IR: $\bar{\nu} = 2955$, 2836 (*al* CH), 1773, 1751, 1704 (CO), 1623, 1606 (C=C) cm^{-1}; ^1H NMR: $\delta = 0.14$

(s, Si*Me*$_3$), 1.70–1.74 (m, 7-H), 2.36, 2.40 (2dd, $^2J_{12,12} = 15.3$ Hz, $^3J_{12,13} = 6.7$ Hz, 12-H), 2.33–2.74 (m, 6-H, 6′-H, 7′-H, 8-H, 14-H), 2.69, 2.72 (2dd, $^2J_{12,12} = 15.3$ Hz, $^3J_{12,13} = 1.8$ Hz, 12′-H), 3.07, 3.08 (2AMX, $^2J_{AM} = 16.6$ Hz, $^3J_{AX} = 9.3$ Hz, β-H$_{Asp}$), 3.14, 3.18 (2ddd, $^3J_{12,13} = 1.8$ Hz, $^3J_{12,13} = 7.2$ Hz, $^3J_{13,14} = 9.5$ Hz, 13-H), 3.27 (AMX, $^2J_{AM} = 16.6$ Hz, $^3J_{MX} = 5.7$ Hz, β'-H$_{Asp}$), 3.69, 3.69 (2s, 2 O*Me*), 3.76 (s, O*Me*), 3.80 (s, O*Me*), 5.21 (AMX, $^3J_{AX} = 9.3$ Hz, $^3J_{MX} = 5.6$ Hz, α-H), 6.65 (d, $^4J_{2,4} = 2.8$ Hz, 4-H), 6.72 (dd, $^3J_{1,2} = 8.8$ Hz, $^4J_{2,4} = 2.8$ Hz, 2-H), 7.97 (d, $^3J_{1,2} = 8.8$ Hz, 1-H) ppm; ^{13}C NMR: $\delta = 0.59$ (Si*Me*$_3$), 27.76, 27.85 (C-7), 29.91 (C-6), 31.26, 31.36 (CH$_2$), 32.78, 32.82 (C-12), 37.46, 37.48 (C-13), 40.95, 41.06 (C-8), 45.41, 45.54 (C-14), 48.50 (C-α), 52.05 (O*Me*), 53.12 (O*Me*), 55.08 (O*Me*), 111.33 (C-2), 112.53 (C-4), 114.41 (C-10), 125.37 (C-11), 129.98 (C-1), 139.78 (C-5), 144.86, 144.91 (C-9), 157.18 (C-3), 168.08 (CO), 177.29, 177.42, 177.43, 177.50 (C-15, C-17) ppm; HPLC: $k' = 4.18$, $t_0 = 1.76$ min (RP-18, *Me*CN/H$_2$O 7/3); $k' = 3.38$, $t_0 = 1.81$ min (Chiralcel OJ-R, *Me*CN/H$_2$O 1/1).

(8β,9β,13β,14β)-3-Methoxy-18-nor-16-azaestra-1,3,5(10)-triene-11,15,17-trione (**4a**, $C_{17}H_{17}NO_4$) [6]

Compound **3a** (0.9 g, 2.4 mmol) and 1.5 cm^3 conc. HCl in 30 cm^3 *Me*OH were refluxed for 30 min. After cooling, the precipitate was separated. Yield 580 mg (91%); colorless crystals; mp 205–210°C (*Me*OH); IR: $\bar{\nu} = 3167$ (NH), 3054 (*ar* CH), 2929 (*al* CH), 1774, 1705 (CO), 1612, 1580, 1503 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 0.88$ (m, 7-H), 1.44–1.54 (m, 7′-H), 1.98–2.04 (m, 6-H), 2.82–2.92 (m, 6-H, 8-H, 12-H, 12′-H), 3.43–3.50 (m, 9-H, 13-H, 14-H), 3.77 (s, O*Me*), 6.62 (d, $^4J_{2,4} = 2.5$ Hz, 4-H), 6.77 (dd, $^3J_{1,2} = 8.5$ Hz, $^4J_{2,4} = 2.5$ Hz, 2-H), 7.22 (d, $^3J_{2,4} = 8.7$ Hz, 1-H), 7.80 (s, H–N) ppm; HPLC: $k' = 0.2$, $t_0 = 1.85$ min (RP-18, *Me*CN/H$_2$O 1/1); $k_1' = 11.86$, $k_2' = 16.57$, $t_0 = 2.59$ min ((*S*,*S*)-Whelk-O1, *n*-hexane/*i-Pr*OH/*Me*CN 7/2.5/0.5).

Methyl 2-[(8β,9β,13β,14β)-3-Methoxy-18-nor-11,15,17-trioxo-16-azaestra-1,3,5(10)-trien-16-yl]acetate (**4bI**, $C_{20}H_{21}NO_6$)

Some (*ca.* 5) drops of conc. HCl were added to **3bI** (726 mg, 1.64 mmol) dissolved in 30 cm^3 boiling *Me*OH, the mixture was refluxed for 1–2 min, and slowly cooled to room temperature. Yield 205 mg (34%); colorless needles; mp 160–165°C (*Me*OH); IR: $\bar{\nu} = 3008$ (*ar* CH), 2960, 2934, 2857, 2839 (*al* CH), 1778, 1750, 1707 (CO), 1606 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 1.36$–1.57 (m, 7-H), 2.03–2.09 (m, 7′-H), 2.83–2.94 (m, 6-H, 6′-H, 8-H, 12-H, 12′-H), 3.37–3.53 (m, 9-H, 13-H, 14-H), 3.77 (s, O*Me*), 3.79 (s, O*Me*), 4.32 (s, NCH$_2$), 6.61 (d, $^4J_{2,4} = 2.5$ Hz, 4-H), 6.77 (dd, $^3J_{1,2} = 8.5$ Hz, $^4J_{2,4} = 2.7$ Hz, 2-H), 7.24 (d, $^3J_{2,4} = 8.8$ Hz, 1-H) ppm; HPLC: $k' = 0.79$, $t_0 = 1.76$ min (RP-18, *Me*CN/H$_2$O 7/3); $k_1' = 2.08$, $k_2' = 2.49$, $t_0 = 1.75$ min (Chiralcel OJ-R, *Me*CN/H$_2$O 4/6).

Methyl 2-[(8α,9β,13β,14β)-3-Methoxy-18-nor-11,15,17-trioxo-16-azaestra-1,3,5(10)-trien-16-yl]acetate (**4bII**, $C_{20}H_{21}NO_6$)

Obtained as a by-product from the synthesis of **3bII**. Yield 80 mg (4%); colorless crystals; mp 160–168°C (*Me*OH); IR: $\bar{\nu} = 3035$ (*ar* CH), 2993, 2950, 2916, 2848 (*al* CH), 1782, 1748, 1709.5 (CO), 1608, 1584 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 1.58$–1.74 (m, 7-H), 2.21 (dddd, $^2J_{8,14} = 11.7$ Hz, $^3J_{7,8} = 11.7$ Hz, $^3J_{7,8} = 2.3$ Hz, $^3J_{8,9} = 11.7$ Hz, 8-H), 2.77 (dd, $^2J_{12,12} = 17.3$ Hz, $^3J_{12,13} = 11.1$ Hz, 12-H), 2.79–2.90 (m, 6-H, 6′-H, 7′-H), 2.98 (dd, $^2J_{12,12} = 17.3$ Hz, $^3J_{12,13} = 7.3$ Hz, 12′-H), 3.10 (dd, $^3J_{13,14} = 9.0$ Hz, $^3J_{8,14} = 11.4$ Hz, 14-H), 3.47 (ddd, $^3J_{12,13} = 7.4$ Hz, $^3J_{12,13} = 10.9$ Hz, $^3J_{13,14} = 9.0$ Hz, 13-H), 3.44 (d, $^3J_{8,9} = 12.8$ Hz, 9-H), 3.77 (s, O*Me*), 3.78 (s, O*Me*), 4.29 (s, NCH$_2$), 6.63 (d, $^4J_{2,4} = 2.7$ Hz, 4-H), 6.78 (dd, $^3J_{1,2} = 8.7$ Hz, $^4J_{2,4} = 2.7$ Hz, 2-H), 7.37 (d, $^3J_{1,2} = 8.8$ Hz, 1-H) ppm; ^{13}C NMR: $\delta = 28.08$ (C-7), 29.53 (C-6), 37.95 (CH$_2$), 38.02, 38.07 (C-13, C-8), 39.31 (C-12), 45.48 (C-14), 52.24 (C-9), 52.82 (O*Me*), 55.18 (O*Me*), 111.89 (C-2), 113.60 (C-4), 121.43 (C-10), 131.47 (C-1), 138.44 (C-5), 158.34 (C-3), 166.96 (CO), 176.44 (C-15), 176.52 (C-17), 204.66 (C-11) ppm; HPLC: $k' = 0.82$, $t_0 = 1.76$ min (RP-18, *Me*CN/H$_2$O 7/3); $k_1' = 1.04$, $k_2' = 1.15$, $t_0 = 2.09$ min (Chiralcel OJ-R, *Me*CN/H$_2$O 1/1).

Dimethyl (S)-3-[(8α,9β,13β,14β)-3-Methoxy-18-nor-11,15,17-trioxo-16-azaestra-1,3,5(10)-tetraen-16-yl]succinate (**4c**, $C_{23}H_{25}NO_8$)

From **3c** (250 mg, 0.48 mmol), as described for **4bI**. Yield 95 mg (44%); colorless crystals; mp 145–148°C (*Ac*O*Et*); $[\alpha]_D^{20} = -46.4°\ cm^{-2}\ g^{-1}$ ($c = 1$, CH_2Cl_2); IR: $\bar{\nu} = 2954$ (*al* CH), 1778, 1741, 1711 (CO), 1610 (C=C) cm^{-1}; ^1H NMR: $\delta = 1.66$ (m, 7-H), 2.12–2.26 (2dddd, $^3J_{7,8} = 2.6$ Hz, $^3J_{7,8} = 11.9$ Hz, $^3J_{8,9} = 11.9$ Hz, $^3J_{8,14} = 11.9$ Hz, 8-H), 2.74 (dd, $^2J_{12,12} = 17.4$ Hz, $^3J_{12,13} = 11.4$ Hz, 12-H), 2.79–2.88 (m, 6-H, 6′-H, 7′-H), 2.94, 2.96 (2dd, $^2J_{12,12} = 17.4$ Hz, $^3J_{12,13} = 7.1$, 7.6 Hz, 12′-H), 3.08, 3.09 (2dd, $^3J_{13,14} = 9.1$ Hz, $^3J_{8,14} = 11.4$ Hz, 14-H), 3.14, 3.14 (2AMX, $^2J_{AM} = 16.6$ Hz, $^3J_{AX} = 9.7$ Hz, β-H_{Asp}), 3.24, 3.24 (2AMX, $^2J_{AM} = 16.6$ Hz, $^3J_{MX} = 5.5$ Hz, β'-H_{Asp}), 3.39–3.51 (m, 13-H), 3.43, 3.44 (2d, $^3J_{8,9} = 11.5$, 12.8 Hz, 9-H), 3.66, 3.67 (2s, O*Me*), 3.76 (s, O*Me*), 3.78 (s, O*Me*), 5.18 (AMX, $^3J_{AX} = 9.7$ Hz, $^3J_{MX} = 5.5$ Hz, α-H_{Asp}), 6.64 (d, $^4J_{2,4} = 2.4$ Hz, 4-H), 6.78, 6.79 (dd, $^3J_{1,2} = 8.6$ Hz, $^4J_{2,4} = 2.6$ Hz, 2-H), 7.35, 7.38 (2d, $^3J_{1,2} = 8.6$ Hz, 1-H) ppm; HPLC: $k' = 1.44$, $t_0 = 1.76$ min (RP-18, *Me*CN/H_2O 7/3); $k_1' = 1.12$, $k_2' = 1.29$, $t_0 = 1.87$ min (Chiralcel OJ-R, *Me*CN/H_2O 1/1).

Isopropyl 2-[(8α,9β,13β,14β)-3-Methoxy-18-nor-11,15,17-trioxo-16-azaestra-1,3,5(10)-trien-16-yl]acetate (**6a**, $C_{22}H_{25}NO_6$)

From **1** (1.36 g, 4.3 mmol) and *N,N*-maleoyl-*Gly*-O*iPr* (**5a**) (0.84 g, 4.3 mmol) for 6 h at 50°C, as described for **3bI** (*a*). After cooling to room temperature, the mixture was diluted with 100 cm^3 acetone/Et_2O (1/10). Yield 398 mg (23%); colorless crystals; mp 170–172°C (*Ac*O*Et*); IR: $\bar{\nu} = 2984$, 2950, 2840 (*al* CH), 1781, 1737, 1707 (CO), 1608, 1584 (C=C) cm^{-1}; ^1H NMR: $\delta = 1.25$ (d, $^3J = 6.3$ Hz, 2 *Me*), 1.67 (m, 7-H), 2.14–2.26 (m, 8-H), 2.72-2.87 (m, 6-H, 6′-H, 7′-H, 12-H), 2.98 (dd, $^2J_{12,12} = 17.6$ Hz, $^3J_{12,13} = 7.3$ Hz, 12′-H), 3.10 (dd, $^3J_{8,9} = 11.2$ Hz, $^3J_{13,14} = 9.1$ Hz, 14-H), 3.46 (ddd, $^3J_{12,13} = 7.3$ Hz, $^3J_{12,13} = 10.9$ Hz, $^3J_{13,14} = 8.8$ Hz, 13-H), 3.43 (d, $^3J_{8,9} = 12.3$ Hz, 9-H), 3.78 (s, O*Me*), 4.24 (s, NCH_2), 5.04 (spt, $^3J = 6.3$ Hz, CH), 6.64 (d, $^4J_{2,4} = 2.6$ Hz, 4-H), 6.78 (dd, $^3J_{1,2} = 8.5$ Hz, $^4J_{2,4} = 2.6$ Hz, 2-H), 7.37 (d, $^3J_{1,2} = 8.5$ Hz, 1-H) ppm; HPLC: $k' = 5.05$, $t_0 = 1.89$ min (RP-18, *Me*CN/H_2O 1/1); $k_1' = 1.77$, $k_2' = 2.09$, $t_0 = 1.80$ min (Chiralcel OJ-R, *Me*CN/H_2O 1/1).

Benzyl 2-[(8α,9β,13β,14β)-3-Methoxy-18-nor-11,15,17-trioxo-16-azaestra-1,3,5(10)-trien-16-yl]acetate (**6b**, $C_{26}H_{25}NO_6$)

From **1** (1.89 g, 5.9 mmol) and *N,N*-maleoyl-*Gly*-O*Bn* (**5b**) (1.46 g, 5.9 mmol) for 6 h at 50°C, as described for **3bI** (*a*). After hydrolysis with 0.5 *N* HCl the organic layer was diluted with *Ac*O*Et*, washed with a saturated solution of $NaHCO_3$, dried ($MgSO_4$), and evaporated. 20 cm^3 *Me*OH were added, and after 12–24 h the precipitate was collected. Yield 320 mg (15%); mp 153–156°C (dec, *Me*OH); IR: $\bar{\nu} = 3066$, 3035 (*ar* CH), 2994, 2950, 2915, 2839 (*al* CH), 1780, 1741, 1708 (CO), 1608, 1584 (C=C), 749, 696 (*ar* C=C) cm^{-1}; ^1H NMR: $\delta = 1.56$–1.71 (m, 7-H), 2.12 (dddd, $^3J_{7,8} = 2.1$ Hz, $^3J_{7,8} = 11.7$ Hz, $^3J_{8,9} = 11.7$ Hz, $^3J_{8,14} = 11.7$ Hz, 8-H), 2.68 (dd, $^2J_{12,12} = 17.3$ Hz, $^3J_{12,13} = 11.2$ Hz, 12-H), 2.75–2.82 (m, 6-H, 6′-H, 7′-H), 2.94 (dd, $^2J_{12,12} = 17.3$ Hz, $^3J_{12,13} = 7.3$ Hz, 12′-H), 3.08 (dd, $^3J_{13,14} = 9.1$ Hz, $^3J_{8,14} = 11.3$ Hz, 14-H), 3.41 (d, $^3J_{8,9} = 12.3$ Hz, 9-H), 3.44 (ddd, $^3J_{12,13} = 7.6$ Hz, $^3J_{12,13} = 10.8$ Hz, $^3J_{13,14} = 8.8$ Hz, 13-H), 3.78 (s, O*Me*), 4.33 (s, NCH_2), 5.16 (s, OCH_2), 6.63 (d, $^4J_{2,4} = 2.6$ Hz, 4-H), 6.78 (dd, $^3J_{1,2} = 8.8$ Hz, $^4J_{2,4} = 2.6$ Hz, 2-H), 7.27–7.33 (m, 5 *ar* H), 7.36 (d, $^3J_{1,2} = 8.8$ Hz, 1-H) ppm; HPLC: $k' = 10.70$, $t_0 = 2.20$ min (RP-18, *Me*CN/H_2O 1/1); $k_1' = 15.47$, $k_2' = 17.00$, $t_0 = 1.81$ min (Chiralcel OJ-R, *Me*CN/H_2O 4/6).

Methyl (S)-2-[(8ξ,9ξ,13β,14β)-3-Methoxy-18-nor-11,15,17-trioxo-16-azaestra-1,3,5(10)-trien-16-yl]propionate (**6c**, $C_{21}H_{23}NO_6$)

N,N-Maleoyl-L-*Ala*-O*Me* (**5c**, 1.35 g, 7.4 mmol) in 10 cm^3 toluene was dropwise added with stirring to a solution of **1** (2.3 g, 7.4 mmol) in 10 cm^3 toluene. Stirring was continued for 6 h at 60°C, then the solvent was evaporated, and the residue was purified by CC (*n*-hexane/Et_2O 1/1), elution with CH_2Cl_2. Yield 270 mg (10%); colorless crystals; mp 152–159°C (*Me*OH); $[\alpha]_D^{20} = -36.0°\ cm^{-2}\ g^{-1}$ ($c = 1$, CH_2Cl_2); IR: $\bar{\nu} = 3000$ (*ar* CH), 2952, 2930, 2867 (*al* CH), 1774, 1735, 1707 (CO), 1610 (C=C) cm^{-1}; ^1H NMR: $\delta = 1.59$–1.74 (m, 7-H), 1.62, 1.62 (2d, $^3J = 7.3$ Hz, Me_{Ala}), 2.16 (m, 8-H),

2.71 (dd, $^2J_{12,12} = 17.4$ Hz, $^3J_{12,13} = 11.4$ Hz, 12-H), 2.74–2.88 (m, 6-H, 6′-H, 7′-H), 2.95, 2.98 (2dd, $^2J_{12,12} = 17.4$ Hz, $^3J_{12,13} = 1.5$ Hz, 12′-H), 3.04, 3.08 and 3.06, 3.07 (2dd, $^3J_{8,14} = 11.4$ Hz, $^3J_{13,14} = 9.0$ Hz, 14-H), 3.39–3.50 (m, 9-H, 13-H), 3.74 (s, O*Me*), 3.78 (s, O*Me*), 4.83 (2q, $^3J = 7.3$ Hz, Hz, α-H_{Ala}), 6.64 (d, $^4J_{2,4} = 2.7$ Hz, 4-H), 6.79 (dd, $^3J_{1,2} = 8.7$ Hz, $^4J_{2,4} = 2.8$ Hz, 2-H), 7.35, 7.37 (d, $^3J_{1,2} = 8.7$ Hz, 1-H) ppm; ^{13}C NMR: $\delta = 14.25$ (*Me*$_{Ala}$), 28.12, 28.23 (C-7), 29.57 (C-6), 37.84, 37.95 (C-13), 37.98 (C-12), 38.24, 38.32 (C-8), 45.37 (C-14), 48.16 (C-9), 52.28 (C-α_{Ala}), 52.91 (O*Me*), 55.21 (O*Me*), 111.93 (C-2), 113.64 (C-4), 121.42, 121.47 (C-10), 131.50, 131.54 (C-1), 138.45 (C-5), 158.38 (C-3), 169.39 (CO_{Ala}), 176.35, 176.46, 176.49 (C-15, C-17), 204.74, 204.81 (C-11) ppm; HPLC: $k' = 3.10$, $t_0 = 1.98$ min (RP-18, *Me*CN/H_2O 1/1); $k_1' = 1.96$, $k_2' = 2.34$, $t_0 = 1.83$ min (Chiralcel OJ-R, *Me*CN/H_2O 45/55).

Methyl (R)-2-[(8ξ,9ξ,13β,14β)-3-Methoxy-18-nor-11,15,17-trioxo-16-azaestra-1,3,5(10)- trien-16-yl]propionate (**6d**, $C_{21}H_{23}NO_6$)

From *N*,*N*-maleoyl-*D-Ala*-O*Me* (**5d**, 1.35 g, 7.4 mmol) as described for **6c**. Yield 165 mg (6%); colorless crystals; mp 154–159°C (*Me*OH); $[\alpha]_D^{20} = +32.7$ cm^{-2} g^{-1} ($c = 1$, CH_2Cl_2); IR: $\bar{\nu} = 3000$ (*ar* CH), 2952, 2930, 2868 (*al* CH), 1774, 1735, 1707 (CO), 1611 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 1.58$–1.73 (m, 7-H), 1.62, 1.62 (2d, $^3J = 7.3$ Hz, *Me*$_{Ala}$), 2.16 (m, 8-H), 2.71 (dd, $^2J_{12,12} = 17.4$ Hz, $^3J_{12,13} = 11.3$ Hz, 12-H), 2.79–2.82 (m, 6-H, 6′-H, 7′-H), 2.96, 2.96 (2dd, $^2J_{12,12} = 17.2$ Hz, $^3J_{12,13} = 1.3$ Hz, 12′-H), 3.04, 3.08 and 3.05, 3.07 (2dd, $^3J_{8,14} = 11.4$ Hz, $^3J_{13,14} = 9.0$ Hz, 14-H), 3.39–3.47 (m, 9-H, 13-H), 3.74 (s, O*Me*), 3.78 (s, O*Me*), 4.85 (2q, $^3J = 7.4$ Hz, α-H_{Ala}), 6.64 (d, $^4J_{2,4} = 2.6$ Hz, 4-H), 6.78 (dd, $^3J_{1,2} = 8.6$ Hz, $^4J_{2,4} = 2.5$ Hz, 2-H), 7.34, 7.36 (d, $^3J_{1,2} = 8.7$ Hz, 1-H) ppm; HPLC: $k' = 3.90$, $t_0 = 1.75$ min (RP-18, *Me*CN/H_2O 1/1); $k_1' = 3.65$, $k_2' = 4.23$, $t_0 = 1.75$ min (Chiralcel OJ-R, *Me*CN/H_2O 4/6).

Methyl (S)-2-[(8S,9R,13S,14R)-3-Methoxy-18-nor-11,15,17-trioxo-16-azaestra-1,3,5(10)-trien-16-yl]-3-phenylpropionate (**6e**, $C_{27}H_{27}NO_6$)

A mixture from *N*,*N*-maleoyl-*L-Phe*-O*Me* (**5e**) (1.54 g, 5.9 mmol) and **1** (1.9 g, 5.9 mmol) was warmed without any solvent for 6 h to 60°C. After cooling to room temperature, 50 cm^3 *Me*OH were added with stirring, later the precipitate was separated. Yield 1.1 g (40%); colorless needles; mp 202–207°C (*Me*OH); $[\alpha]_D^{20} = -134.6°$ cm^{-2} g^{-1} ($c = 1$, CH_2Cl_2); IR: $\bar{\nu} = 3029$, 3007 (*ar* CH), 2950, 2934, 2914, 2894 (*al* CH), 2856 (O*Me*), 1775, 1740, 1705 (CO), 1610, 1506 (C=C), 755, 706 (*ar* C=C) cm^{-1}; ^{1}H NMR: $\delta = 1.31$ (dddd, $^3J_{8a,14a} = 11.8$ Hz, $^3J_{7a,8a} = 11.8$ Hz, $^3J_{7e,8a} = 2.6$ Hz, $^3J_{8a,9a} = 11.8$ Hz, 8-H_a), 1.49 (dddd, $^2J_{7,7} = 12.2$ Hz, $^3J_{6a,7a} = 12.2$ Hz, $^3J_{6e,7a} = 5.1$ Hz, $^3J_{7a,8a} = 12.2$ Hz, 7-H_a), 2.46 (dd, $^2J_{12,12} = 17.0$ Hz, $^3J_{12,13} = 9.3$ Hz, 12-H), 2.43–2.50 (m, $J = 2.5$ Hz, $J = 5.0$ Hz, 7-H_e), 2.59 (ddd, $^2J_{6,6} = 16.7$ Hz, $^3J_{6a,7a} = 12.3$ Hz, $^3J_{6a,7e} = 5.0$ Hz, 6-H_a), 2.69 (ddd, $^2J_{6,6} = 16.7$ Hz, $^3J_{6e,7a} = 4.9$ Hz, $^3J_{6e,7e} = 2.5$ Hz, 6-H_e), 2.78 (dd, $^2J_{12,12} = 17.0$ Hz, $^3J_{12,13} = 8.1$ Hz, 12′-H), 2.85 (dd, $^3J_{13,14a} = 8.8$ Hz, $^3J_{8a,14a} = 11.3$ Hz, 14-H_a), 3.22 (ddd, $^3J_{13,14a} = 8.8$ Hz, $^3J_{12,13} = 9.3$ Hz, $^3J_{12,13} = 8.1$ Hz, 13-H), 3.28 (d, $^3J_{8a,9a} = 12.2$ Hz, 9-H_a), 3.78 (s, O*Me*), 3.81 (s, O*Me*), 3.48 (ABX, $^2J_{AB} = 14.1$ Hz, $^3J_{AX} = 12.3$ Hz, β-H), 3.51 (A<u>B</u>X, $^2J_{AB} = 14.1$ Hz, $^3J_{BX} = 4.7$ Hz, β'-H), 5.10 (ABX, $^3J_{AX} = 12.3$ Hz, $^3J_{BX} = 4.7$ Hz, α-H), 6.61 (d, $^4J_{2,4} = 2.7$ Hz, 4-H), 6.76 (dd, $^3J_{1,2} = 8.7$ Hz, $^4J_{2,4} = 2.7$ Hz, 2-H), 7.10–7.28 (m, 5 *ar* H, 1-H) ppm; ^{13}C NMR: $\delta = 27.57$ (C-7), 29.27 (C-6), 33.67 ($CH_{2(Phe)}$), 37.60 (C-12), 37.93 (C-13), 38.68 (C-8), 45.36 (C-14), 52.31 (C-9), 52.76 (C-α), 53.00 (O*Me*), 55.20 (O*Me*), 111.86 (C-2), 113.58 (C-4), 121.54 (C-10), 127.26 (C-4′), 128.63 (C-3′, C-5′), 129.11 (C-2′, C-6′), 131.34 (C-1), 136.07 (C-1′), 138.35 (C-5), 158.33 (C-3), 168.53 (CO_{Phe}), 176.06 (C-15), 176.54 (C-17), 204.98 (C-11) ppm; HPLC: $k' = 7.99$, $t_0 = 1.89$ min (RP-18, *Me*CN/H_2O 1/1); $k' = 8.34$, $t_0 = 1.85$ min (Chiralcel OJ-R, *Me*CN/H_2O 45/55); $k' = 4.20$, $t_0 = 1.96$ min ((*S*,*S*)-Whelk-O1, *n*-hexane/*Et*OH 1/1).

Methyl (S)-2-[(8S,9R,13S,14R)-3-Methoxy-18-nor-11,15,17-trioxo-16-azaestra-1,3,5(10)-trien-16-yl]-3-phenylpropionate and Methyl (R)-2-[(8R,9S,13R,14S)-3-Methoxy-18-nor-11,15,17-trioxo-16-azaestra-1,3,5(10)-trien-16-yl]-3-phenylpropionate (**6f**, $C_{27}H_{27}NO_6$)

From **1** (1 g, 3.7 mmol) and *N*,*N*-maleoyl-*L*,*D-Phe*-O*Me* (**5f**, 1 g, 3.7 mmol) as described for **6e**. Yield 0.67 g (39%); colorless crystals; mp 178–184°C (*Me*OH); $[\alpha]_D^{20} = 0°$ cm^{-2} g^{-1} ($c = 1$, CH_2Cl_2);

IR: $\bar{\nu} = 3003$ (*ar* CH), 2950 (*al* CH), 2861 (O*Me*), 1775, 1741, 1706 (CO), 1609, 1506 (C=C), 755, 747, 703 (*ar* C=C) cm^{-1}; ^1H NMR: $\delta = 1.30$ (dddd, $^3J_{8a,14a} = 11.8$ Hz, $^3J_{7a,8a} = 11.8$ Hz, $^3J_{7e,8a} = 2.5$ Hz, $^3J_{8a,9a} = 11.8$ Hz, 8-H_a), 1.49 (dddd, $^2J_{7,7} = 12.1$ Hz, $^3J_{6a,7a} = 12.1$ Hz, $^3J_{6e,7a} = 5.1$ Hz, $^3J_{7a,8a} = 12.1$ Hz, 7-H_a), 2.46 (dd, $^2J_{12,12} = 17.0$ Hz, $^3J_{12,13e} = 9.3$ Hz, 12-H), 2.42–2.50 (m, $J = 2.5$ Hz, $J = 5.0$ Hz, 7-H_e), 2.53–2.73 (m, 6-H_a, 6-H_e), 2.77 (dd, $^2J_{12,12} = 16.9$ Hz, $^3J_{12,13} = 8.1$ Hz, 12′-H), 2.85 (dd, $^3J_{13,14a} = 8.9$ Hz, $^3J_{8a,14a} = 11.3$ Hz, 14-H_a), 3.22 (ddd, $^3J_{13,14a} = 9.0$ Hz, $^3J_{12,13} = 9.3$ Hz, $^3J_{12,13} = 8.1$ Hz, 13-H), 3.28 (d, $^3J_{8a,9a} = 12.3$ Hz, 9-H_a), 3.80 (s, O*Me*), 3.81 (s, O*Me*), 3.47 (ABX, $^2J_{AB} = 14.1$ Hz, $^3J_{AX} = 12.3$ Hz, β-H), 3.51 (A<u>B</u>X, $^2J_{AB} = 14.1$ Hz, $^3J_{BX} = 4.7$ Hz, β'-H), 5.09 (ABX, $^3J_{AX} = 12.3$ Hz, $^3J_{BX} = 4.7$ Hz, α-H), 6.61 (d, $^4J_{2,4} = 2.6$ Hz, 4-H), 6.76 (dd, $^3J_{1,2} = 8.7$ Hz, $^4J_{2,4} = 2.7$ Hz, 2-H), 7.09–7.28 (m, 5 *ar* H, 1-H) ppm; ^{13}C NMR: $\delta = 27.55$ (C-7), 29.26 (C-6), 33.65 ($CH_{2(Phe)}$), 37.58 (C-12), 37.90 (C-13), 38.65 (C-8), 45.35 (C-14), 52.30 (C-9), 52.74 (C-α), 53.01 (O*Me*), 55.20 (O*Me*), 111.84 (C-2), 113.55 (C-4), 121.48 (C-10), 127.26 (C-4_{Phe}), 128.62 (C-3_{Phe}, C-5_{Phe}), 129.09 (C-2_{Phe}, C-6_{Phe}), 131.34 (C-1), 136.04 (C-1_{Phe}), 138.34 (C-5), 158.32 (C-3), 168.51 (CO_{Phe}), 176.04 (C-15), 176.53 (C-17), 204.97 (C-11) ppm; HPLC: $k' = 7.99$, $t_0 = 1.89$ min (RP-18, *Me*CN/H_2O 1/1); $k' = 7.88$, 8.35, $t_0 = 1.85$ min (Chiralcel OJ-R *Me*CN/ H_2O 45:55).

Methyl (R)-2-[(8R,9S,13R,14S)-3-Methoxy-18-nor-11,15,17-trioxo-16-azaestra-1,3,5(10)-trien-16-yl]-3-phenylpropionate (**6g**, $C_{27}H_{27}NO_6$)

From **1** (1 g, 3.7 mmol) and *N,N*-maleoyl-D-*Phe*-O*Me* (**5g**, 1 g, 3.7 mmol), as described for **6e**. Yield 0.53 g (31%); colorless needles; mp 202–206°C (*Me*OH); $[\alpha]_D^{20} = +132.0°\,cm^{-2}\,g^{-1}$ ($c = 1$, CH_2Cl_2); IR: $\bar{\nu} = 3029$, 3008 (*ar* CH), 2951, 2934, 2914, 2895 (*al* CH), 2856 (O*Me*), 1775, 1740, 1706 (CO), 1611, 1506 (C=C), 755, 706 (*ar* C=C) cm^{-1}; ^1H NMR: $\delta = 1.31$ (dddd, $^3J_{8a,14a} = 11.8$ Hz, $^3J_{7a,8a} = 11.8$ Hz, $^3J_{8a,9a} = 11.8$ Hz, $^3J_{7e,8a} = 2.5$ Hz, 8-H_a), 1.49 (dddd, $^2J_{7,7} = 12.2$ Hz, $^3J_{6a,7a} = 12.2$ Hz, $^3J_{6e,7a} = 5.2$ Hz, $^3J_{7a,8a} = 12.2$ Hz, 7-H_a), 2.46 (dd, $^2J_{12,12} = 17.0$ Hz, $^3J_{12,13} = 9.3$ Hz, 12-H), 2.43–2.50 (m, $J = 2.5$ Hz, $J = 5.0$ Hz, 7-H_e), 2.59 (ddd, $^2J_{6,6} = 16.7$ Hz, $^3J_{6a,7a} = 12.2$ Hz, $^3J_{6a,7e} = 5.2$ Hz, 6-H_a), 2.69 (ddd, $^2J_{6,6} = 16.7$ Hz, $^3J_{6e,7a} = 4.9$ Hz, $^3J_{6e,7e} = 2.5$ Hz, 6-H_e), 2.78 (dd, $^2J_{12,12} = 17.0$ Hz, $^2J_{12,13} = 8.1$ Hz, 12′-H), 2.85 (dd, $^3J_{13,14a} = 8.8$ Hz, $^3J_{8a,14a} = 11.3$ Hz, 14-H_a), 3.22 (ddd, $^3J_{13,14a} = 8.9$ Hz, $^3J_{12,13e} = 9.3$ Hz, $^3J_{12,13} = 8.1$ Hz, 13-H), 3.28 (d, $^3J_{8a,9a} = 12.1$ Hz, 9-H_a), 3.48 (ABX, $^2J_{AB} = 14.1$ Hz, $^3J_{AX} = 12.3$ Hz, β-H), 3.51 (ABX, $^2J_{AB} = 14.1$ Hz, $^3J_{BX} = 4.7$ Hz, β'-H), 3.78 (s, O*Me*), 3.81 (s, O*Me*), 5.10 (ABX, $^3J_{AX} = 12.3$ Hz, $^3J_{BX} = 4.7$ Hz, α-H), 6.61 (d, $^4J_{2,4} = 2.7$ Hz, 4-H), 6.76 (dd, $^3J_{1,2} = 8.7$ Hz, $^4J_{2,4} = 2.8$ Hz, 2-H), 7.10–7.29 (m, 5 *ar* H, 1-H) ppm; ^{13}C NMR: $\delta = 27.56$ (C-7), 29.26 (C-6), 33.65 ($CH_{2(Phe)}$), 37.59 (C-12), 37.90 (C-13), 38.65 (C-8), 45.35 (C-14), 52.31 (C-9), 52.74 (C-α), 53.02 (O*Me*), 55.20 (O*Me*), 111.85 (C-2), 113.56 (C-4), 121.50 (C-10), 127.27 (C-4_{Phe}), 128.63 (C-3_{Phe}, C-5_{Phe}), 129.10 (C-2_{Phe}, C-6_{Phe}), 131.35 (C-1), 136.05 (C-1_{Phe}), 138.35 (C-5), 158.30 (C-3), 168.52 (CO_{Phe}), 176.06 (C-15), 176.54 (C-17), 204.98 (C-11) ppm; HPLC: $k' = 8.01$, $t_0 = 1.89$ min (RP-18, *Me*CN/H_2O 1/1); $k' = 7.88$, $t_0 = 1.85$ min (Chiralcel OJ-R, *Me*CN/H_2O 45/55).

X-Ray Crystallographic Analysis of ***6g***

A clear prism crystal of $C_{27}H_{27}NO_6$ of 0.35×0.15×0.15 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC5R diffractometer with graphite monochromated Cu–Kα radiation and a rotating anode generator. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 24 carefully centered reflections in the range $42.71 < 2\theta < 59.04°$ corresponded to a primitive monoclinic cell with $a = 8.668(5)$ Å, $b = 9.098(8)$ Å, $\beta = 96.37(3)°$, $c = 14.710(4)$ Å, and $V = 1153(1)$ Å^3. For $Z = 2$ and FW = 461.51, the calculated density is 1.33 g/cm^3. Based on the systematic absences of: 0k0: $k \neq 2n$ packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be $P2_1$ (#4). The data were collected at 23 ± 1°C using the ω-2θ scan technique to a maximum 2θ value of 120.1°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.30° with a take-off angle of 6.0°. Scans of $(1.26 + 0.30 \tan\theta)°$ were made at a speed of 8.0°/min (in omega). The weak reflections

($I < 10.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm, the crystal to detector distance was 400 mm, and the detector aperture was $9.0 \times 13.0\,mm^2$ (horizontal × vertical). Of the 1980 reflections which were collected, 1844 were unique ($R_{int} = 0.047$). The intensities of three representative reflection were measured after every 150 reflections. No decay correction was applied. The linear absorption coefficient, μ, for Cu–Kα radiation is $7.7\,cm^{-1}$. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.97 to 1.00. The data were corrected for *Lorentz* and polarization effects.

The structure was solved by direct methods [13] and expanded using *Fourier* techniques [14]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 1586 observed reflections ($I > 3.00\sigma(I)$) and 307 variable parameters and converged (largest parameter shift was 0.06 times its *esd*) with unweighted and weighted agreement factors. The standard deviation of an observation of unit weight was 2.18. The weighting scheme was based on counting statistics and included a factor ($p = 0.012$) to downweight the intense reflections. Plots of $\sum w(|Fo| - |Fc|)^2$ *versus* $|Fo|$, reflection order in data collection, sin (θ/λ), and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference *Fourier* map corresponded to 0.16 and $-0.20\ e^-/Å^3$. Neutral atom scattering factors were taken from Ref. [15]. Anomalous dispersion effects were included in F_{calc} [16]; the values for $\Delta f'$ and $\Delta f''$ were those of Ref. [17]. The values for the mass attenuation coefficients were those of Ref. [18]. All calculations were performed using the teXsan [19] software package of Molecular Structure Corporation. Compound **6e** was also measured, and proved to be enantiomeric to **6g**. The results of the X-ray analysis were deposited at the CDC, deposition number ##.

Ethyl (S)-2-[(8S,9R,13S,14R)-3-Methoxy-18-nor-11,15,17-trioxo-16-azaestra-1,3,5(10)-trien-16-yl]-3-phenylpropionate (**6h**, $C_{28}H_{29}NO_6$)

From **1** (2.3 g, 7.4 mmol) and *N,N*-maleoyl-L-*Phe*-O*Et* (**5h**) (2.0 g, 7.4 mmol), as described for **6e**. Yield 1.38 g (40%); colorless crystals; mp 182–186°C (dec, *Et*OH); $[\alpha]_D^{20} = -130.0°\ cm^{-2}\ g^{-1}$ ($c = 5$, CH_2Cl_2); IR: $\bar{\nu} = 3005$ (*ar* CH), 2949, 2931, 2891, 2836 (*al* CH), 1776, 1739, 1705 (CO), 1610 (C=C), 1268, 1256 (C–O–C), 754, 705 (*ar* C=C) cm^{-1}; ^{1}H NMR (200 MHz): $\delta = 1.40$ (t, $^3J = 7.1$ Hz, *Me*), 1.31–1.68 (m, 7-H, 8-H), 2.57 (dd, $^2J_{12,12} = 16.9$ Hz, $^3J_{12,13} = 9.3$ Hz, 12-H), 2.51–2.64 (m, 7′-H), 2.69–2.83 (m, 6-H, 6′-H), 2.89 (dd, $^2J_{12,12} = 16.9$ Hz, $^3J_{12,13} = 8.1$ Hz, 12′-H), 2.95 (dd, $^3J_{13,14} = 9.0$ Hz, $^3J_{8,14} = 10.7$ Hz, 14-H), 3.32 (ddd, $^3J_{13,14} = 8.9$ Hz, $^3J_{12,13} = 9.3$ Hz, $^3J_{12,13} = 8.1$ Hz, 13-H), 3.39 (d, $^3J_{8,9} = 11.9$ Hz, 9-H_a), 3.49–3.61 (ABX, β-H, β'-H), 3.88 (s, O*Me*), 4.37 (q, $^3J = 7.1$ Hz, OCH_2), 5.18 (ABX, α-H), 6.71 (d, $^4J_{2,4} = 2.4$ Hz, 4-H), 6.86 (dd, $^3J_{1,2} = 8.6$ Hz, $^4J_{2,4} = 2.5$ Hz, 2-H), 7.20–7.39 (m, 5 *ar* H, 1-H) ppm; HPLC: $k' = 8.59$, $t_0 = 1.98$ min (RP-18, *Me*CN/H_2O 1/1); $k' = 4.77$, $t_0 = 1.8$ min (Chiralcel OJ-R, *Me*CN/H_2O 1/1).

Isopropyl (S)-2-[(8S,9R,13S,14R)-3-Methoxy-18-nor-11,15,17-trioxo-16-azaestra-1,3,5(10)-trien-16-yl]-3-phenylpropionate (**6i**, $C_{29}H_{31}NO_6$)

From **1** (1.2 g, 4.5 mmol) and *N,N*-maleoyl-L-*Phe*-O*iPr* (**5i**) (1.3 g, 4.5 mmol) as described for **6e**. Yield 270 mg (12%); mp 160–164°C (*i-Pr*OH); $[\alpha]_D^{20} = -137°\ cm^{-2}\ g^{-1}$ ($c = 1$, CH_2Cl_2); IR: $\bar{\nu} = 3061$, 3027 (*ar* CH), 2986, 2954, 2931, 2890, 2859, 2837 (*al* CH), 1779, 1727, 1709 (CO), 1610 (C=C) cm^{-1}; ^{1}H NMR (200 MHz): $\delta = 1.24$–1.55 (m, 7-H, 8-H), 1.26 (d, $^3J = 6.2$ Hz, *Me*), 1.29 (d, $^3J = 6.2$ Hz, *Me*), 2.42–2.55 (m, 7′-H), 2.48 (dd, $^2J_{12,12} = 17.0$ Hz, $^3J_{12,13} = 9.4$ Hz, 12-H), 2.59–2.66 (m, 6-H, 6′-H), 2.75 (dd, $^2J_{12,12} = 17.0$ Hz, $^3J_{12,13} = 8.9$ Hz, 12′-H), 2.85 (dd, $^3J_{13,14} = 8.9$ Hz, $^3J_{8a,14a} = 11.3$ Hz, 14-H), 3.20 (ddd, $^3J_{13,14} = 8.9$ Hz, $^3J_{12,13} = 9.4$ Hz, $^3J_{12,13} = 8.9$ Hz, 13-H), 3.29 (d, $^3J_{8,9} = 11.7$ Hz, 9-H), 3.44–3.54 (ABX, β-H, β'-H), 3.78 (s, O*Me*), 5.07 (ABX, α-H), 5.09 (spt, $^3J = 6.1$ Hz, CH), 6.61 (d, $^4J_{2,4} = 2.5$ Hz, 4-H), 6.76 (dd, $^3J_{1,2} = 8.5$ Hz, $^4J_{2,4} = 2.7$ Hz, 2-H), 7.09–7.78 (m, 5 *ar* H, 1-H) ppm; ^{13}C NMR: $\delta = 21.73$, 21.79 (2 *Me*), 27.63 (C-7), 29.32 (C-6), 33.72 ($CH_{2(Phe)}$), 37.68 (C-12), 37.95 (C-13),

38.71 (C-8), 45.33 (C-14), 52.34 (C-9), 53.10 (C-α), 55.15 (O*Me*), 70.00 (CH), 111.88 (C-2), 113.60 (C-4), 121.60 (C-10), 127.18 (C-4_{Phe}), 128.61 (C-3_{Phe}, C-5_{Phe}), 129.14 (C-2_{Phe}, C-6_{Phe}), 131.40 (C-1), 136.35 (C-1_{Phe}), 138.37 (C-5), 158.37 (C-3), 167.50 (CO_{Phe}), 176.14 (C-15), 176.53 (C-17), 205.00 (C-11) ppm; HPLC: $k' = 16.98$, $t_0 = 1.98$ min (RP-18, *Me*CN/H_2O 1/1); $k' = 12.63$, $t_0 = 1.85$ min (Chiralcel OJ-R, *Me*CN/H_2O 45/55).

Methyl 3-[(8ξ,9ξ,13β,14β)-3-Methoxy-18-nor-11,15,17-trioxo-16-azaestra-1,3,5(10)-trien-16-yl]propionate (**8a**, $C_{21}H_{23}NO_6$)

A mixture from *N,N*-maleoyl-β-*Ala*-O*Me* (**7a**, 1.24 g, 6.74 mmol) and **1** (2.16 g, 6.74 mmol) was heated to 70°C for 22 h. After cooling to room temperature the mixture was dissolved in *Et*$_2$O/*PE* 1/1. After cooling to 0°C for 2–4 d the precipitate was collected. Yield 545 mg (21%); colorless crystals; mp 169–173°C (*Me*OH/*Ac*O*Et*); IR: $\bar{\nu} = 3007$ (*ar* CH), 2944, 2834 (*al* CH), 1772, 1725, 1701 (CO), 1611, 1576 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 1.39$, 1.82–1.88 (2m, 7-H, 8-H), 2.68 (t, $^3J = 7.1$ Hz, 2 α-H), 2.79–2.92 (m, 6-H, 6′-H, 7′-H, 12-H, 12′-H), 3.33–3.43 (m, 9-H, 13-H, 14-H), 3.69 (s, O*Me*), 3.77 (s, O*Me*), 3.87 (dt, $^3J = 7.1$ Hz, $J = 1$ Hz, 2 β-H), 6.60 (d, $^4J_{2,4} = 2.6$ Hz, 4-H), 6.76 (dd, $^3J_{1,2} = 8.5$ Hz, $^4J_{2,4} = 2.7$ Hz, 2-H), 7.21 (d, $^3J_{1,2} = 8.6$ Hz, 1-H) ppm; HPLC: $k' = 2.26$, $t_0 = 1.75$ min (RP-18, *Me*CN/H_2O 1/1); $k_1' = 4.91$, $k_2' = 5.22$, $t_0 = 1.77$ min (Chiralcel OJ-R, *Me*CN/H_2O 3/7).

Methyl [(8ξ,9ξ,13β,14β)-3-Methoxy-18-nor-11,15,17-trioxo-16-azaestra-1,3,5(10)-trien-16-yl]formiate (**8b**, $C_{19}H_{19}NO_6$)

Method a: At 0°C, methyl chloroformiate (47 mm^3, 0.62 mmol) was dropwise added to a solution of **4a** (186 mg, 0.62 mmol) and *N*-methylmorpholine (62.5 mg, 0.62 mmol) in *Ac*O*Et* (20 cm^3). After stirring for 4 h at 0°C, the precipitate was separated, washed with *Ac*O*Et*, and the combined *Ac*O*Et* was evaporated *in vacuo*. A few cm^3 of *Me*OH were added to the residue, and after some h the precipitate was collected.

Method b: A mixture from **1** (1.5 g, 5.3 mmol) and *N*-(methoxycarbonyl)maleimide (**7b**, 0.83 g, 5.3 mmol) in 10 cm^3 toluene was stirred for 5 h at 50°C. Then the solvent was evaporated, the residue was dissolved in a few cm^3 of *Me*OH, 3 drops of conc. HCl were added, and after addition (with stirring) of 50 cm^3 *Et*$_2$O the precipitate was collected. Yield (a) 63 mg (28%); (b) 0.91 g (48%); colorless crystals; mp 153–155.5°C (*Ac*O*Et*); IR: $\bar{\nu} = 2931$, 2844 (*al* CH), 1812, 1769, 1716 (CO), 1610 (C=C) cm^{-1}; ^{1}H NMR (200 MHz): $\delta = 1.33$–1.55 (m, 7-H), 1.90–1.96 (m, 7′-H), 2.79–3.08 (m, 6-H, 6′-H, 8-H, 12-H, 12′-H), 3.48–3.50 (m, 9-H, 13-H, 14-H), 3.77 (s, O*Me*), 4.03 (s, O*Me*), 6.61 (d, $^4J_{2,4} = 2.4$ Hz, 4-H), 6.70 (dd, $^4J_{2,4} = 2.6$ Hz, $^3J_{1,2} = 8.5$ Hz, 2-H), 7.16 (d, $^3J_{1,2} = 8.4$ Hz, 1-H) ppm; ^{13}C NMR: $\delta = 22.60$ (C-7), 28.88 (C-6), 34.65 (C-12), 36.97 (C-13), 38.27 (C-8), 43.43 (C-14), 50.79 (C-9), 55.17 (O*Me*), 77.23 (O*Me*), 112.43 (C-2), 113.42 (C-4), 123.24 (C-10), 131.94 (C-1), 136.17 (C-5), 148.62 (CO), 159.14 (C-3), 172.73 (C-15), 174.10 (C-17), 205.12 (C-11) ppm; HPLC: $k' = 1.60$, $t_0 = 1.98$ min (RP-18, *Me*CN/H_2O 1/1); $k_1' = 5.13$, $k_2' = 10.64$, $t_0 = 1.98$ min ((*S,S*)-Whelk O1, *n*-hexane/*Et*OH 1/1 + 2% *Me*CN).

(8ξ,9ξ,13β,14β)-3-Methoxy-16-(2-phenylethyl)-18-nor-16-azaestra-1,3,5(10)-trien-11,15,17-trione (**8c**, $C_{25}H_{25}NO_4$)

A mixture of *N*-(2-phenylethyl)maleimide (**7c**, 1 g, 5 mmol) and **1** (1.6 g, 5 mmol) was heated for 2 h to 60°C. After cooling to room temperature, a mixture of *Ac*O*Et* and *Et*$_2$O (100 cm^3, 1/10) was added with stirring, and then the precipitate was collected. Yield 270 mg (13%); colorless crystals; mp 153–156°C (*Ac*O*Et*); IR: $\bar{\nu} = 3064$, 3028.2 (*ar* CH), 2937, 2866, 2840 (*al* CH), 1766, 1691 (CO), 1612 (C=C), 702 (*ar* C=C) cm^{-1}; ^{1}H NMR: $\delta = 1.28$–1.80 (m, 7-H, 7′-H), 2.67–3.39 (m, 6-H, 6′-H, 8-H, 12-H, 12′-H, CH_2), 3.65–3.87 (m, 9-H, 13-H, 14-H, CH_2), 3.76–3.77 (3s, O*Me*), 6.61 (d, $^4J_{2,4} = 2.6$ Hz, 4-H), 6.75 (dd, $^4J_{2,4} = 2.6$ Hz, $^3J_{1,2} = 8.7$ Hz, 2-H), 7.19–7.37 (m, 5 *ar* H), 7.39 (d, $^3J_{1,2} = 8.7$ Hz, 1-H) ppm; HPLC: $k_1' = 4.66$, $k_2' = 5.66$, $k_3' = 8.13$, $t_0 = 1.75$ min (RP-18, *Me*CN/H_2O 1/1); $k_1' = 3.73$, $k_2' = 8.35$, $k_3' = 9.27$, $k_4' = 11.51$, $k_5' = 13.15$, $t_0 = 1.75$ min (Chiralcel OJ-R *Me*CN/H_2O 4:6).

Ethyl (S)-2-[(E/Z,8S,9R,13S,14R)-11-Hydroxyimino-3-methoxy-18-nor-15,17-dioxo-16-azaestra-1,3,5(10)-trien-16-yl]-3-phenylpropionate (**9a**, $C_{28}H_{30}N_2O_6$)

A solution of *Ac*ONa (0.9 g, 11 mmol) and $H_2NOH \cdot HCl$ (0.8 g, 11 mmol) in 30 cm^3 H_2O was added to a solution of **6h** (476 mg, 1 mmol) in 20 cm^3 *THF* with stirring, and *Me*OH was added until a clear solution was formed. The mixture was stirred for 16 h, H_2O was added, and the precipitate was collected. Yield 440 mg (90%); colorless crystals; mp 178–182°C (*Me*OH); $[\alpha]_D^{20} = -176.7°\ cm^{-2}\ g^{-1}$ ($c = 0.5$, *Me*CN); IR: $\bar{\nu} = 3464$ (OH), 3005 (*ar* CH), 2949, 2891, 2836 (*al* CH), 1776, 1729, 1705 (CO), 1610, 1584 (C=C), 754, 705 (*ar* C=C) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 200 MHz): $\delta = 0.95$–1.41 (m, 7-H, 8-H), 1.17 (t, $^3J = 7.1$ Hz, *Me*), 2.09–3.63 (m, 6-H, 6′-H, 7′-H, 9-H, 12-H, 12′-H, 13-H, 14-H), 3.70 (s, O*Me*), 4.15 (m, CH_2), 5.01–5.08 (m, α-H_{Phe}), 6.61–6.73 (m, 2-H, 4-H), 7.11–7.21 (m, 5 *ar* H, 1-H), 10.69 (s, H–O) ppm; HPLC: $k' = 1.93$, 2.67, $t_0 = 1.76$ min (RP-18, *Me*CN/H_2O 7/3); $k_1' = 3.57$, $k_2' = 4.90$, $t_0 = 2.09$ min (Chiralcel OJ-R, *Me*CN/H_2O 1/1).

*Methyl *2-[(E/Z,8β,9β,13β,14β)-11-Hydroxyimino-3-methoxy-18-nor-15,17-dioxo-16-azaestra-1,3,5(10)-trien-16-yl]acetate* (**9b**, $C_{20}H_{22}N_2O_6$)

From **3bI** (222 mg, 0.5 mmol) as described for **9a**. Yield 138 mg (71%); colorless crystals; mp 203–206°C (*Me*OH); IR: $\bar{\nu} = 3254$ (OH), 2998, 2955, 2899, 2837 (*al* CH), 1779, 1751, 1712 (CO), 1610, 1585 (C=C) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.21$ (m, 7-H), 1.71–1.75 (m, 7′-H), 2.46–2.57 (m, 8-H), 2.62–2.90 (m, 6-H, 6′-H, 12-H, 12′-H), 3.26–3.46 (m, 13-H), 3.54 (dd, $^3J_{8,14} = 7.1$ Hz, $^3J_{13,14} = 9.3$ Hz, 14-H), 3.66 (d, $^3J_{8,9} = 3.6$ Hz, 9-H), 3.68, 3.69 (2s, 2 O*Me*), 4.18, 4.24 (AB, each $^2J_{AB} = 17.3$ Hz, 2 α-H_{Gly}), 6.60 (d, $^5J_{2,4} = 2.5$ Hz, 4-H), 6.65 (dd, $^3J_{1,2} = 8.4$ Hz, 2-H), 7.00, 7.24 (2d, each $^3J_{1,2} = 8.4$ Hz, 2 1-H), 10.67, 10.80 (2s, H–O) ppm; HPLC: $k_1' = 1.57$, $k_2' = 1.77$, $t_0 = 1.75$ min (RP-18, *Me*CN/H_2O 1/1); $k_1' = 3.11$, $k_2' = 6.34$, $k_3' = 6.64$, $t_0 = 1.77$ min (Chiralcel OJ-R, *Me*CN/H_2O 3/7).

Ethyl (S)-2-[(8S,9R,13S,14R)-3-Methoxy-11-methoxyimino-18-nor-15,17-dioxo-16-azaestra-1,3,5(10)-trien-16-yl]-3-phenylpropionate (**9c**, $C_{29}H_{32}N_2O_6$)

A mixture from 0.86 g *Ac*ONa and 2.05 cm^3 of a solution of H_2N–O*Me* · HCl (25% in 10% HCl) in 30 cm^3 H_2O was dropwise added with stirring to a solution of **6h** (476 mg, 1 mmol) in 30 cm^3 *THF*. *Me*OH was added until a homogeneous mixture was formed, which was stirred for 12 h. Then 150 cm^3 H_2O were added, and the precipitate was collected. Yield 404 mg (80%); colorless crystals; mp 153–156°C (*Ac*O*Et*); $[\alpha]_D^{20} = -175.0°\ cm^{-2}\ g^{-1}$ ($c = 1$, CH_2Cl_2); IR: $\bar{\nu} = 2998$, 2978, 2927 (*al* CH), 1775, 1730, 1709 (CO), 1608, 1583 (C=C), 701 (*ar* C=C) cm^{-1}; ^{1}H NMR: $\delta = 1.16$ (dddd, $^3J_{7,8} = 3.1$ Hz, $^3J_{7,8} = 11.7$ Hz, $^3J_{8,9} = 11.7$ Hz, $^3J_{8,14} = 11.7$ Hz, 8-H), 1.27 (t, $^3J = 7.2$ Hz, *Me*), 1.46 (dddd, $^3J_{6,7} = 6.6$ Hz, $^2J_{7,7} = 11.7$ Hz, $^3J_{6,7} = 11.7$ Hz, $^3J_{7,8} = 11.7$ Hz, 7-H), 2.28–2.35 (m, 7′-H), 2.45 (dd, $^2J_{12,12} = 15.7$ Hz, $^3J_{12,13} = 9.1$ Hz, 12-H), 2.61 (dd, $^3J_{13,14} = 8.6$ Hz, $^3J_{8,14} = 11.6$ Hz, 14-H), 2.68–2.74 (m, 6-H, 6′-H), 2.95 (ddd, $^3J_{13,14} = 8.6$ Hz, $^3J_{12,13} = 8.6$ Hz, $^3J_{12,13} = 8.6$ Hz, 13-H), 3.10 (dd, $^2J_{12,12} = 15.6$ Hz, $^3J_{12,13} = 8.0$ Hz, 12′-H), 3.24 (d, $^3J_{8,9} = 11.7$ Hz, 9-H), 3.39–3.51 (ABX, β-H, β'-H), 3.78 (s, NO*Me*), 3.87 (s, O*Me*), 4.10–4.33 (m, CH_2), 5.01 (ABX, α-H), 6.61 (d, $^4J_{2,4} = 2.6$ Hz, 4-H), 6.70 (dd, $^3J_{1,2} = 8.5$ Hz, $^4J_{2,4} = 2.6$ Hz, 2-H), 7.05–7.18 (m, 5 *ar* H), 7.35 (d, $^3J_{1,2} = 8.5$ Hz, 1-H) ppm; HPLC: $k' = 4.73$, $t_0 = 1.76$ min (RP-18, *Me*CN/H_2O 7/3); $k' = 13.00$, $t_0 = 1.89$ min (Chiralcel OJ-R, *Me*CN/H_2O 45/55).

Methyl (S)-2-[(8α,9β,13β,14β)-3-Methoxy-11-methoxyimino-18-nor-15,17-dioxo-16-azaestra-1,3,5(10)-trien-16-yl]propionate (**9d**, $C_{22}H_{26}N_2O_6$)

From **6c** (280 mg, 0.73 mmol) as described for **9c**. Yield 71 mg (23%); colorless crystals; mp 182–185°C (*Ac*O*Et*); $[\alpha]_D^{20} = +98.9°\ cm^{-2}\ g^{-1}$ ($c = 0.9$, CH_2Cl_2); IR: $\bar{\nu} = 2996$, 2945, 2852, 2815 (*al* CH), 1776, 1754, 1706 (CO), 1612 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 1.58$ (d, $^3J = 7.3$ Hz, Me_{Ala}), 1.61 (dddd, $^3J_{6,7} = 6.1$ Hz, $^2J_{7,7} = 11.7$ Hz, $^3J_{6,7} = 11.7$ Hz, $^3J_{7,8} = 11.7$ Hz, 7-H), 1.94 (dddd, $^3J_{7,8} = 3.0$ Hz, $^3J_{7,8} = 11.7$ Hz, $^3J_{8,9} = 11.7$ Hz, $^3J_{8,14} = 11.7$ Hz, 8-H), 2.53 (ddd, $^2J_{12,12} = 16.6$ Hz, $^3J_{12,13} = 10.6$ Hz, $J = 0.8$ Hz, 12-H), 2.62–2.82 (m, 6-H, 6′-H, 7-H), 2.86 (dd, $^3J_{8,14} = 11.4$ Hz, $^3J_{13,14} = 8.8$ Hz, 14-H),

3.16 (ddd, $^3J_{12,13} = 7.5$ Hz, $^3J_{12,13} = 10.7$ Hz, $^3J_{13,14} = 8.8$ Hz, 13-H), 3.34 (dd, $^2J_{12,12} = 16.7$ Hz, $^3J_{12,13} = 7.4$ Hz, 12′-H), 3.43 (d, $^3J_{8,9} = 11.8$ Hz, 9-H), 3.73 (s, O*Me*), 3.78 (s, O*Me*), 3.85 (s, NO*Me*), 4.80 (q, $^3J = 7.3$ Hz, α-H), 6.63 (d, $^4J_{2,4} = 2.7$ Hz, 4-H), 6.73 (dd, $^3J_{1,2} = 8.7$ Hz, $^4J_{2,4} = 2.8$ Hz, 2-H), 7.43 (d, $^3J_{1,2} = 8.7$ Hz, 1-H) ppm; HPLC: $k' = 2.31$, $t_0 = 1.76$ min (RP-18 *Me*CN/H_2O 7/3); $k' = 6.16$, $t_0 = 1.80$ min (Chiralcel OJ-R, *Me*CN/H_2O 4/6).

Dimethyl (S)-2-[(8α,9β,13β,14β)-3-Methoxy-11-methoxyimino-18-nor-15,17-dioxo-16-azaestra-1,3,5(10)-trien-16-yl]succinate (**9e**, $C_{24}H_{28}N_2O_8$)

From **3c** (270 mg, 0.52 mmol) as described for **9c**. Yield 41 mg (17%); colorless crystals; mp 190–193°C (*Ac*O*Et*); $[\alpha]_D^{20} = +35.6°$ cm^{-2} g^{-1} ($c = 0.7$, CH_2Cl_2); IR: $\bar{\nu} = 3005$ (*ar* CH), 2952, 2903, 2854, 2830 (*al* CH), 1779, 1743, 1711 (CO), 1612, 1575 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 1.61$ (dddd, $^3J_{6,7} = 6.0$ Hz, $^2J_{7,7} = 11.6$ Hz, $^3J_{6,7} = 11.6$ Hz, $^3J_{7,8} = 11.6$ Hz, 7-H), 1.97 (dddd, $^3J_{7,8} = 2.9$ Hz, $^3J_{7,8} = 11.6$ Hz, $^3J_{8,9} = 11.6$ Hz, $^3J_{8,14} = 11.6$ Hz, 8-H), 2.54 (dd, $^2J_{12,12} = 16.6$ Hz, $^3J_{12,13} = 10.6$ Hz, 12-H), 2.66–2.89 (m, 6-H, 6′-H, 7′-H), 2.88 (dd, $^3J_{8,14} = 11.4$ Hz, $^3J_{13,14} = 9.1$ Hz, 14-H), 3.07 (AMX, $^2J_{AM} = 16.6$ Hz, $^3J_{AX} = 9.5$ Hz, β-H), 3.13–3.22 (m, 13-H), 3.24 (AMX, $^2J_{AM} = 16.6$ Hz, $^3J_{MX} = 5.6$ Hz, β'-H), 3.34 (dd, $^2J_{12,12} = 16.6$ Hz, $^3J_{12,13} = 7.4$ Hz, 12′-H), 3.43 (d, $^3J_{8,9} = 11.7$ Hz, 9-H), 3.67, 3.74, 3.78 (3s, 3 O*Me*), 3.85 (s, NO*Me*), 5.18 (AMX, $^3J_{AX} = 9.5$ Hz, $^3J_{MX} = 5.6$ Hz, α-H), 6.63 (d, $^4J_{2,4} = 2.6$ Hz, 4-H), 6.73 (dd, $^3J_{1,2} = 8.6$ Hz, $^4J_{2,4} = 2.6$ Hz, 2-H), 7.44 (d, $^3J_{1,2} = 8.6$ Hz, 1-H) ppm; ^{13}C NMR: $\delta = 23.15$, 23.50 (CH_2), 27.77, 27.99 (C-7), 29.70 (C-6), 32.66, 32.71 (C-12), 38.03, 38.38 (C-13), 39.16, 39.44 (C-8), 44.52, 44.68 (C-14), 45.46, 45.54 (C-9), 48.57 (C-α), 52.11 (O*Me*), 53.18 (O*Me*), 55.13 (O*Me*), 61.74 (NO*Me*), 111.48 (C-2), 113.36, 113.41 (C-4), 124.32, 124.47 (C-10), 131.31, 131.55 (C-1), 138.34, 138.40 (C-5), 155.00 (C-11), 158.00 (C-3), 167.97, 170.27 (CO), 176.64, 176.71, 176.85, 177.07 (C-15, C-17) ppm; HPLC: $k' = 2.13$, $t_0 = 1.76$ min (RP-18, *Me*CN/H_2O 7/3); $k' = 5.85$, $t_0 = 1.80$ min (Chiralcel OJ-R, *Me*CN/H_2O 4/6).

Methyl (S)-2-[(8α,9β,13β,14β)-3-Methoxy-11-methoxyimino-18-nor-15,17-dioxo-16-azaestra-1,3,5(10)-trien-16-yl]-3-methylbutyrate (**11**, $C_{24}H_{30}N_2O_6$)

A mixture from **1** (2 g, 4.6 mmol) and *N*,*N*-maleoyl-L-*Val*-O*Me* (**10**, 1.36 g, 4.6 mmol) was heated to 70°C for 22 h. Then 10 cm^3 *THF* were added, and a solution of *Ac*ONa (3.95 g) and 9.3 cm^3 H_2N–O*Me* · HCl (25% in 10% HCl) in 130 cm^3 H_2O was added. Stirring was continued for 12 h, and after addition of H_2O the precipitate was collected. Yield 1.37 g (37%); colorless crystals; mp 209–214°C (*Ac*O*Et*); $[\alpha]_D^{20} = +77.8°$ cm^{-2} g^{-1} ($c = 2$, CH_2Cl_2); IR: $\bar{\nu} = 2993$, 2962, 2940, 2900, 2853, 2830 (*al* CH), 1777, 1752, 1705 (CO), 1613 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 0.83$, 1.12 (2d, $^3J = 8.7$ Hz, 2 *Me*), 1.63 (dddd, $^3J_{6,7} = 6.4$ Hz, $^2J_{7,7} = 11.8$ Hz, $^3J_{6,7} = 11.8$ Hz, $^3J_{7,8} = 11.8$ Hz, 7-H), 1.93 (dddd, $^3J_{7,8} = 3.0$ Hz, $^3J_{7,8} = 11.7$ Hz, $^3J_{8,9} = 11.7$ Hz, $^3J_{8,14} = 11.7$ Hz, 8-H), 2.51 (ddd, $^2J_{12,12} = 16.6$ Hz, $^3J_{12,13} = 10.7$ Hz, $J = 0.8$ Hz, 12-H), 2.59–2.85 (m, 6-H, 6′-H, 7-H, β-H), 2.87 (dd, $^3J_{8,14} = 11.4$ Hz, $^3J_{13,14} = 8.9$ Hz, 14-H), 3.19 (ddd, $^3J_{12,13} = 7.5$ Hz, $^3J_{12,13} = 10.6$ Hz, $^3J_{13,14} = 8.8$ Hz, 13-H), 3.35 (dd, $^2J_{12,12} = 16.6$ Hz, $^3J_{12,13} = 7.5$ Hz, 12′-H), 3.44 (d, $^3J_{8,9} = 11.7$ Hz, 9-H), 3.70 (s, O*Me*), 3.78 (s, O*Me*), 3.85 (s, NO*Me*), 4.39 (d, $^3J = 8.5$ Hz, α-H), 6.63 (d, $^4J_{2,4} = 2.7$ Hz, 4-H), 6.73 (dd, $^3J_{1,2} = 8.7$ Hz, $^4J_{2,4} = 2.8$ Hz, 2-H), 7.44 (dd, $^3J_{1,2} = 8.7$ Hz, $J = 0.4$ Hz, 1-H) ppm; HPLC: $k' = 2.99$, $t_0 = 1.81$ min (RP-18, *Me*CN/H_2O 7/3); $k' = 4.74$, $t_0 = 1.81$ min (Chiralcel OJ-R, *Me*CN/H_2O 1/1).

Acknowledgements

We thank Degussa AG, for generous support with chemicals, E. Merck KGaG, Darmstadt, for continuous support with chromatography materials and biological tests, the "Fonds der Chemischen Industrie" for financial support, Dr. *M. Kindermann*, Chemistry Dept., University of Greifswald, for the COSY experiments, and PD Dr. *T. Jira*, PMC Greifswald, for the CD spectra.

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