SYNTHESIS OF SOME NOVEL 16-AZAESTRONES AND 17-AZA-D-HOMOESTRONES. THE X-RAY CRYSTAL STRUCTURE OF 3-METHOXY-16-AZA-14β-1,3,5-(10)-ESTRATRIEN-15-ONE

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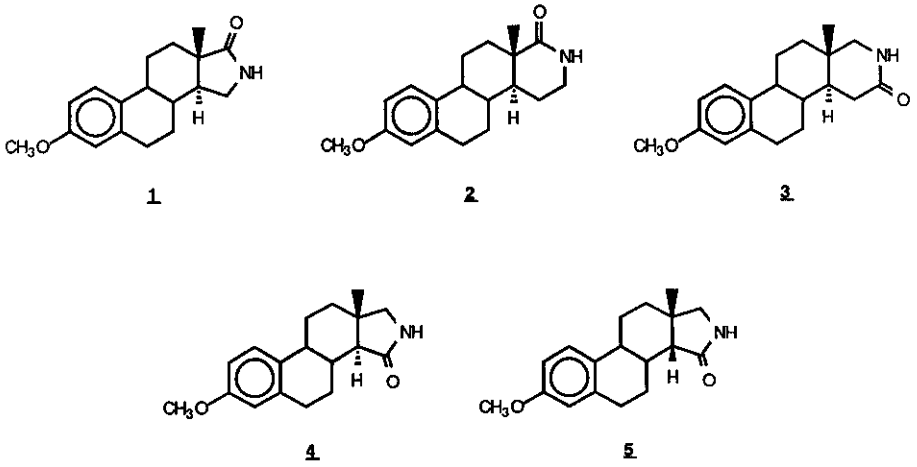
Abstract - The efficient syntheses of several new 16-azaestrones and 17-aza-D-homoestrones from estrone methyl ether are reported. These include 3-methoxy-17-aza-D-homo-1,3,5(10)-estratrien-17a-one (2), 3-methoxy-17-aza-D-homo-1,3,5(10)-estratrien-16-one (3) and the 14α and 14β epimers of 3-methoxy-16-aza-1,3,5(10)-estratrien-15-one (4 and 5, respectively). Novel carbinol amide derivatives 27a, 27b and 28 of the 16-azaestrone system were also prepared. The configuration at C-14 of azaestrones 4 and 5 was suggested on the basis of thermodynamic arguments, supported by evidence derived from ^{1}H-nmr spectra, and confirmed by an X-ray crystal structure of the 14β-isomer.

Dedicated to Professor Sir Derek H.R. Barton on the occasion of his seventieth birthday.

The replacement of one or more carbon atoms of a steroid molecule with nitrogen or other heteroatoms often results in useful alterations to its biological properties. For instance, various azasteroids are reported to possess antibacterial[1], antifungal[2], hypocholesterolemic[3] and neuromuscular blocking activity[4], and are known to inhibit the enzyme 5α-reductase in the conversion of testosterone to dihydrotestosterone.[5] Consequently, there has been considerable interest in the synthesis of aza- and other heterocyclic steroids, and many such compounds have been prepared.[6] For the past few years, we have been interested in the chemistry of heterocyclic azasteroids where the nitrogen atom is part of a reactive functional group such as an N-acyl imine[7], carbinol amide[7b], or N-chlorolactam[8] moiety. These compounds can be obtained by oxidation or chlorination of the corresponding lactams, and are expected to bind covalently to their receptor proteins, or to enzymes which transform them. This type of behaviour would in turn be potentially useful in affinity-labeling studies of steroid receptors, in enzyme inhibition, and in the chemotherapy of breast and prostate cancer.[9] In connection with this work, we required a convenient source of D-ring azaestrone lactams 1-5. Despite the plethora of azasteroids reported to date, there is a paucity of known synthetic routes to the desired 16-aza- and 17-aza-D-homoestrones, and

of compounds 1-5, only lactam 1 has been previously reported.[10] We now describe efficient syntheses of the novel azaestrones 2-5 from estrone methyl ether, as well as a study of the stereochemistry at C-14 of the isomers 4 and 5.

Chart 1



RESULTS AND DISCUSSION

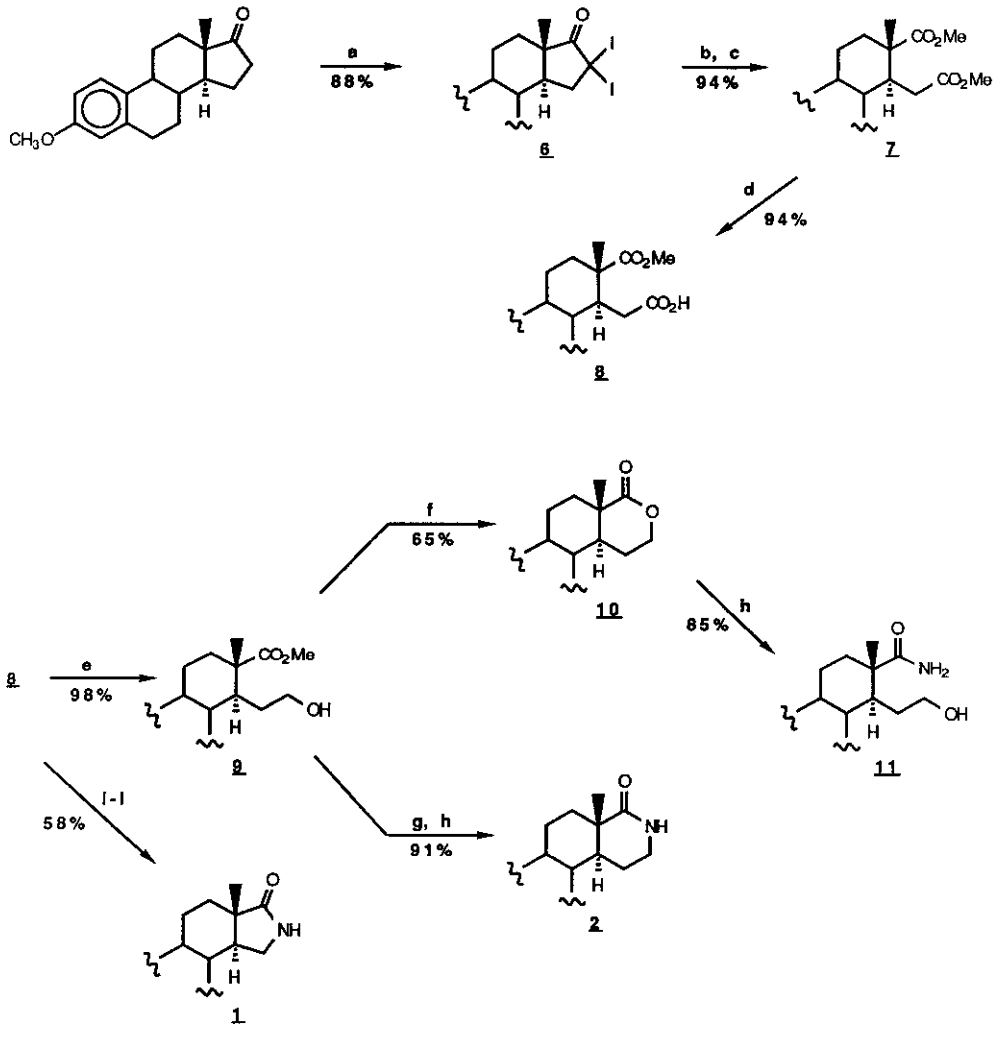
Two approaches to D-homoazasteroids from 17-keto precursors are readily apparent. First, Beckmann rearrangements of the corresponding oximes are known to afford ring-expanded δ-lactams, but occur regioselectively to afford chiefly the 17a-aza isomers.[11,12] The second approach, which is more suitable for the preparation of D-homoazasteroids 2 and 3, proceeds via the cyclization of a suitably functionalized D-seco intermediate with a nitrogen nucleophile. The synthesis of normal-sized D-ring azasteroids requires that an appropriate cyclization step be preceded by the degradation of one carbon atom from the original precursor. This was achieved by a Curtius rearrangement[10a] or by ozonolysis of a D-homo enol lactone intermediate[10b] in two previous syntheses of the 16-aza derivative 1.

Synthesis of 17-Aza-D-Homoestrones 2 and 3

The synthesis of the D-homoazasteroid 2 was achieved via the route shown in Scheme 1. Estrone methyl ether was converted to the half ester 8 by a variation of the method of Heer and Miescher.[13,14] Reduction of the carboxylic acid moiety of 8 with borane-tetrahydrofuran (THF) complex produced the hydroxy ester 9. Spontaneous cyclization of 9 to the known[10b] lactone 10 occurred upon standing for several days, or more rapidly upon treatment with sodium hydride. Lactone 10 underwent ring-opening with ammonia to provide the hydroxy amide 11, which comprises a

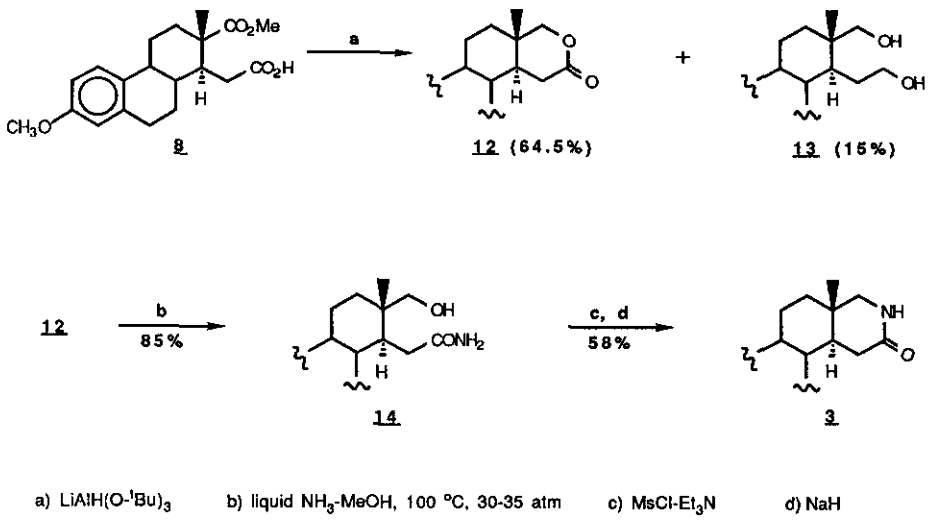
potential precursor of lactam 2. However, a more efficient route to the latter compound was devised, wherein hydroxy ester 9 was tosylated and the crude product was reacted with liquid ammonia in methanol at 100°C in a pressure reactor to afford the desired δ-lactam 2 in 91% yield. The γ-lactam 1 was also obtained from 8 by a variation of the Curtius rearrangement approach reported by Kierstead et al.[10a]

Scheme 1



The key intermediate half ester 8 also served as a convenient source of the D-homoazasteroid 3 (Scheme 2). Reduction of 8 with lithium tri-t-butoxyaluminum hydride produced lactone 12 in 64.5% yield, along with the diol 13 (15%). An attempt to recycle the unwanted diol by Jones oxidation to 12 was only partly successfully as the two hydroxyl groups proved of comparable reactivity and resulted in a 1:1 mixture of the isomeric lactones 10 and 12. Ring-opening of 12 with liquid ammonia in methanol at 100°C afforded the hydroxy amide 14, which was smoothly mesylated in the presence of triethylamine and cyclized upon treatment with sodium hydride to provide lactam 3 in 58% yield.

Scheme 2



a) $LiAlH(O\text{-}^tBu)_3$ b) liquid NH_3-MeOH, 100 °C, 30-35 atm c) MsCl-Et_3N d) NaH

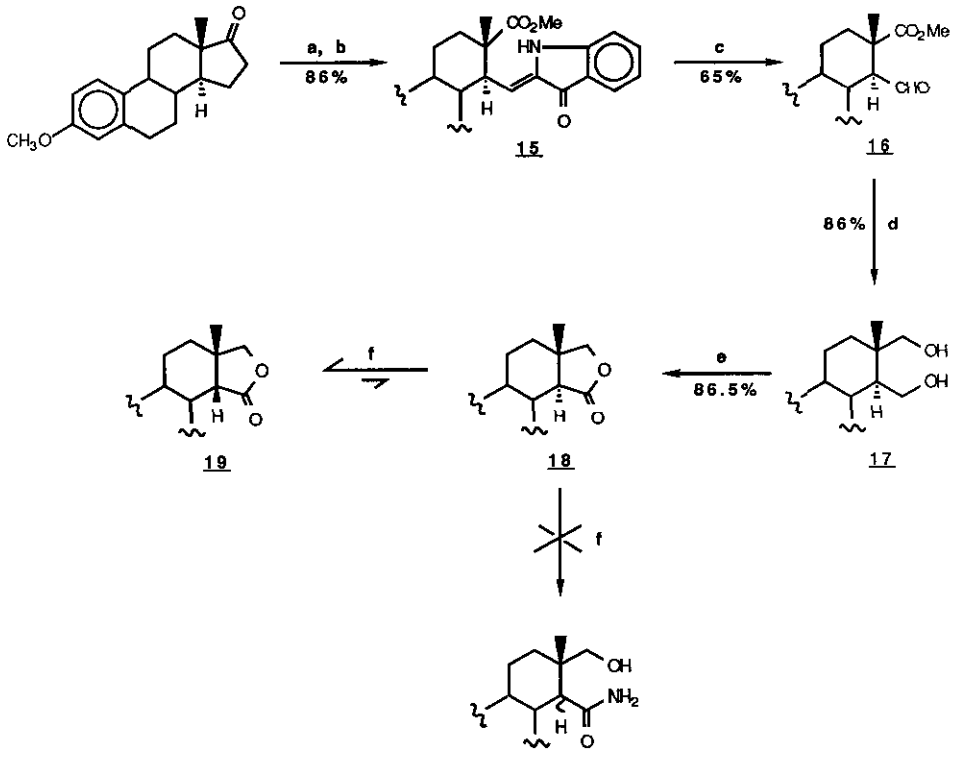
Synthesis of 16-Azaestrones 4 and 5

A similar approach to that shown in Scheme 2 was attempted for the synthesis of the normal D-ring lactam isomers 4 and 5, via aminolysis of 18, the γ-lactone homologue of δ-lactone 12. Ring-opening and degradation of C-16 in estrone methyl ether was performed as indicated in Scheme 3 via the indoxyl 15.[15] In contrast to the androstane series, oxidative cleavage of 15 to aldehyde 16 or the corresponding carboxylic acid with chromium trioxide[16,17] or ozone[17] gave unsatisfactory results, but oxidation with sodium periodate and osmium tetroxide[18] afforded aldehyde 16 in 65% yield. The aldehyde was reduced to the corresponding diol 17 with lithium aluminum hydride, and subjected to Jones oxidation to produce the 16-oxa lactone 18 in a highly selective manner, unlike the homologous diol 13, which had furnished a 1:1 mixture of isomeric lactones under similar con-

ditions. Unfortunately, all attempts to open lactone 18 with ammonium hydroxide, liquid ammonia in methanol at 100°, or sodium amide in liquid ammonia failed, in contrast to the efficient amminolysis of the corresponding δ-lactone 12 (or its isomer 10). A possible explanation for the lack of reactivity of 18 is that it undergoes epimerization to the thermodynamically favoured[10b,19] 14β-isomer 19 faster than ring-opening. Since the normally accessible α-face of the trans-isomer 18 is considerably more congested in the cis-isomer 19, nucleophilic attack and formation of the tetrahedral intermediate required for ring-opening is suppressed. The recovery of epimerized lactone 19 from these reactions is consistent with this explanation.

A second approach to lactams 4 and 5 is summarized in Scheme 4. Aldehyde 16 was subjected to Jones oxidation and the resulting crude carboxylic acid was amidated via its acyl chloride to afford amide 20. Selective reduction of the ester group was effected with lithium tri-t-butoxyaluminum hydride to give alcohol 21 in poor yield, accompanied by imide 22. An attempt to cyclize

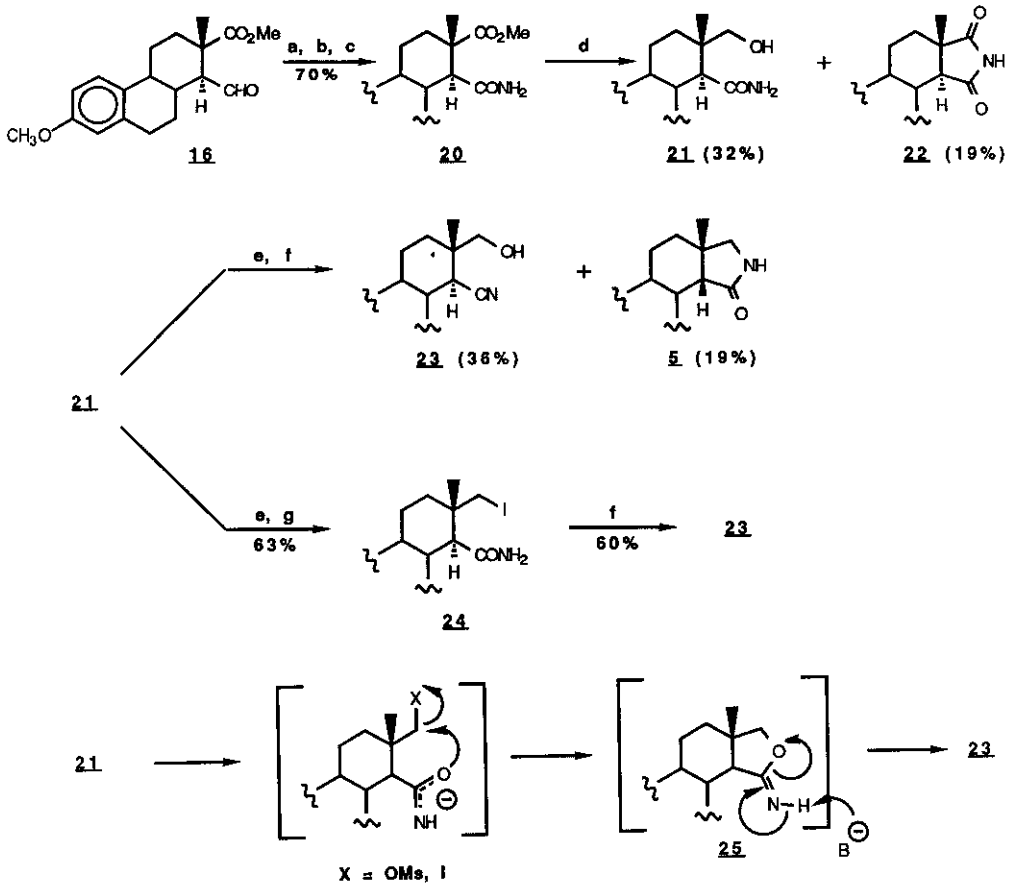
Scheme 3



a) o-nitrobenzaldehyde, KOH b) CH_2N_2 c) OsO_4-$NaIO_4$ d) $LiAlH_4$ e) Jones oxidation f) $NaNH_2$-liquid NH_3

21 by mesylation and treatment with base, by analogy to the conversion of 14 to lactam 3, resulted in the formation of the nitrile 23 in 36% yield and the desired lactam 5[20] in only 19% yield. This was rationalized by assuming that the initial mesylate can be attacked by either the N or O atom of the ambident amide anion to afford the desired products 4 and 5, or the intermediate 25, respectively. Fragmentation of the latter, as illustrated in Scheme 4, accounts for the formation of the unwanted nitrile 23. Somewhat surprisingly, prior conversion of the mesylate to the iodide (a softer leaving group) 24 resulted in an even greater proclivity for O-attack[21] and an enhanced yield of nitrile 23. In view of the poor yield in both the reduction of 20 to 21 and the cyclization of 21 to 4 or 5, this approach was abandoned.

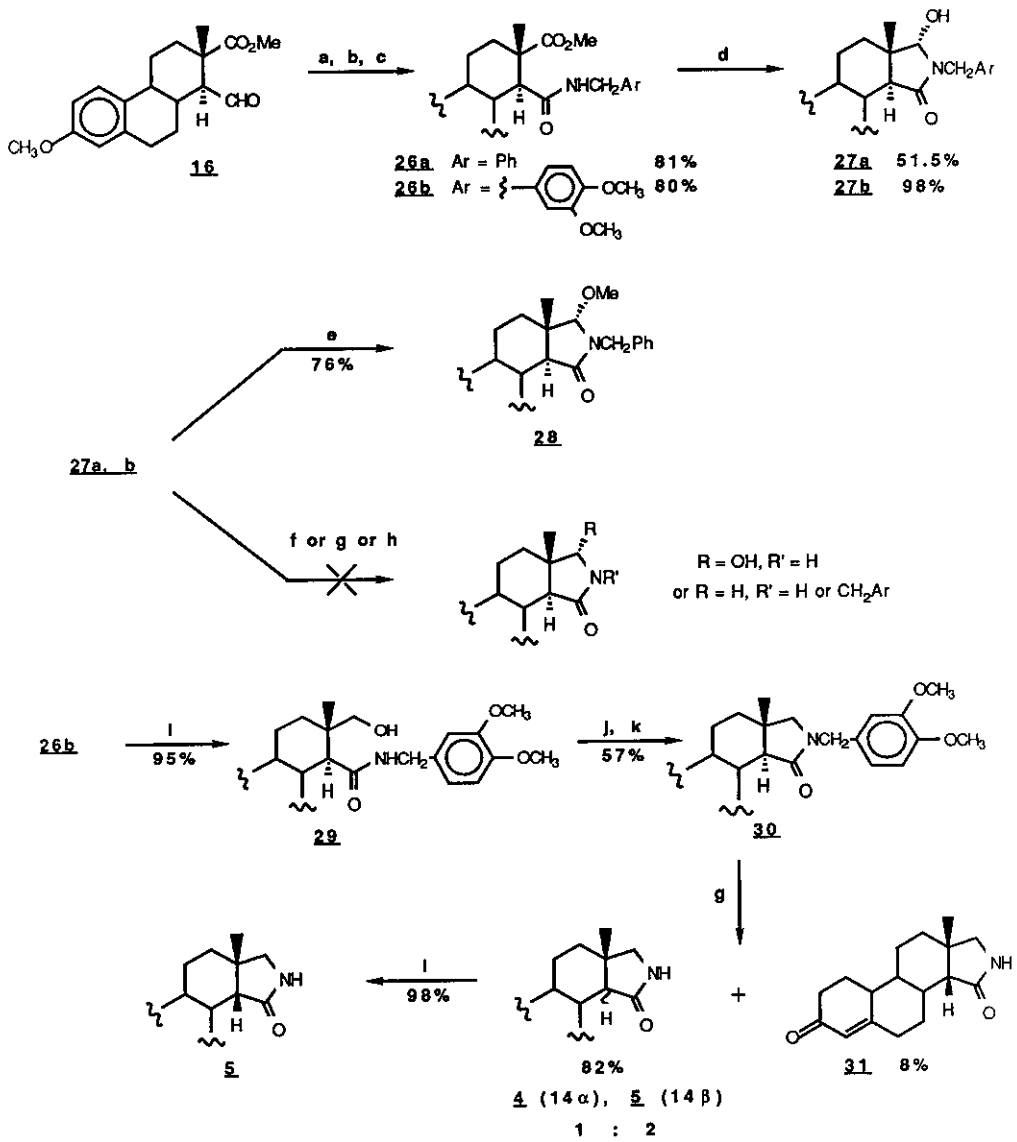
Scheme 4



a) Jones oxidation b) ClCOCOCl c) NH_4OH d) $LiAlH(O\text{-}^tBu)_3$ e) MsCl-Et_3N f) NaH g) NaI

In order to avoid the undesired formation of nitrile 23, cyclization attempts were made with protected, secondary amides 26a and 26b (Scheme 5). These compounds were obtained in the same manner as the primary amide 20, except that benzylamine and veratrylamine were employed instead of ammon-

Scheme 5



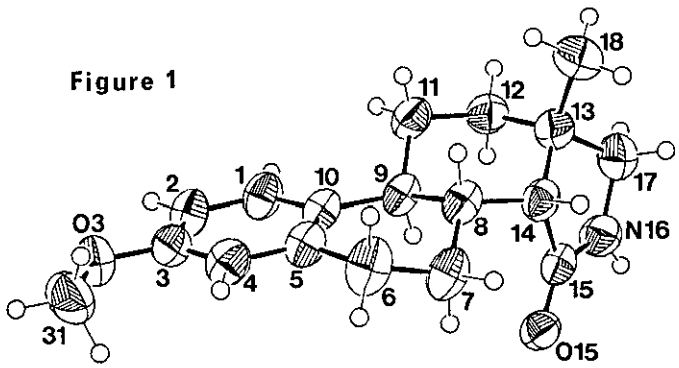
a) Jones oxidation b) ClCOCOCl c) $ArCH_2NH_2$ d) $LiAlH(O\text{-}^tBu)_3$ e) TsOH-MeOH f) H_2-Pd g) Na-liquid NH_3
h) $NaBH_3CN$ i) $LiBH_4$ j) MsCl-Et_3N k) NaH l) KO-^{t}Bu

ium hydroxide. The reduction of 26a and 26b with lithium tri-t-butoxyaluminum hydride, however, did not produce the expected hydroxy amide analogous to 21 in Scheme 4. Instead, partial reductive amidation occurred to afford the cyclic carbinol amides 27a and 27b. The product 27a underwent facile acid-catalyzed exchange of the hydroxyl group with methanol to produce the methyl ether 28.[22] This confirms the carbinol amide structure of 27a and supports our premise that steroidal carbinol amides should react with appropriate nucleophiles in biological systems.[7b] The carbinol amides are therefore of interest in their own right, but unfortunately, the deprotection of 27a and 27b by hydrogenolysis of the N-benzyl linkage could not be accomplished using either catalytic hydrogenation or sodium in liquid ammonia.[23] Similarly, the reduction of the carbinol amide moiety of 27a and 27b to the corresponding N-benzyllactams with sodium cyanoborohydride[24] failed. Finally, 26b was reduced to the hydroxy amide 29 with lithium borohydride, and 29 was cyclized to the N-veratryllactam 30 via the corresponding mesylate. Careful deprotection of 30 with sodium in liquid ammonia then afforded a 1:2 mixture of the isomeric[25] γ-lactams 4 and 5, accompanied by a small amount of the Birch reduction product 31. When the mixture of 4 and 5 was treated with potassium t-butoxide in t-butanol, isomerization of 4 to 5 was virtually quantitative. Evidently the cis-fused 14β-isomer 5 is thermodynamically more stable (as is the case in the corresponding lactones 18 and 19[10b]) and is the exclusive product of equilibration.

Stereochemical Assignment of Azasteroids 4 and 5

The configurations of azasteroids 4 and 5 were tentatively assigned as 14α and 14β, respectively, on the basis of the expected greater thermodynamic stability of the C/D cis-isomer 5. The configurations of lactones 18 (14α) and 19 (14β) were previously assigned by Baran[10b] on similar thermodynamic arguments. Furthermore, the chemical shift of the angular methyl group C-18 is 0.10 ppm farther downfield in the C/D cis lactone 19 (δ 1.20) than in the trans isomer 18 (δ 1.10). This trend is also evident in lactams 4 (δ 1.09) and 5 (δ 1.19), as well as in other, carbocyclic 14α, 14β steroid isomers.[26] Finally, the above structural assignments were unequivocally confirmed by an X-ray crystal structure of the 14β-isomer, 5, shown in Figure 1.

Figure 1



EXPERIMENTAL SECTION

Melting points were determined on an A.H. Thomas hot-stage apparatus and are uncorrected. Ir spectra were recorded on a Nicolet 5DX spectrometer, using KBr disks for solid samples and thin films for oils unless otherwise indicated. ^{1}H- and ^{13}C-Nmr spectra were obtained at 200 MHz with a Varian XL200 or a Bruker AC-E 200 spectrometer, with $CDCl_3$ as the solvent and either $CHCl_3$ or tetramethylsilane as the internal standard. Mass spectra were recorded on a Kratos MS80 or a VG 7070 spectrometer. Optical rotations were measured on a Rudolph Autopol III polarimeter in $CHCl_3$ solution unless otherwise noted. Elemental analyses were performed by Dr. W.S. Lin (University of Calgary). Preparative TLC was carried out on Analtech 20×20 cm glass plates coated with 1 mm of silica-gel GF, and flash chromatography was performed with silica-gel (60-200 mesh). Estrone was purchased from the Aldrich Co. or the Sigma Co. and was converted to estrone methyl ether by a literature method[27]. Jones reagent was prepared as described previously.[28] All other reagents were purchased from commercial sources and purified by standard methods as necessary.

Colourless single crystals of 5 were grown by slow evaporation of a methanol solution. A crystal of dimensions 0.11 × 0.28 × 0.42 mm was used for data collection with an Enraf Nonius CAD-4F automated diffractometer, Ni-filtered CuK_α radiation (λ = 1.54178Å), and omega/2θ scans. The crystal system is monoclinic, space group $P2_1$, a = 10.2973(7), b = 5.9939(3), c = 13.5978(6)Å, β = 110.244(5)°, V = 787.43(8)Å^3, Z = 2, density (calc) = 1.204 g cm^{-3} and μ = 6.24 cm^{-1}. Two quadrants of data were collected to a maximum theta of 75°; of the 4068 reflections measured, the 3912 replicative data were averaged to obtain 1779 unique reflections of which 1701 had $I > 2.0\ \sigma(I)$. The structure was solved by direct methods. All H atoms were identified in difference Fourier syntheses. The final cycles of least squares varied the positions of all atoms, the anisotropic thermal parameters of the non-H atoms, the isotropic thermal parameters of the H atoms, and the isotropic extinction parameter (final value $1.85(5)\times10^{-5}$). The refinement converged with a maximum shift/error of 0.01, R = 0.044, and R_w = 0.041 for the 1701 observed reflections. The programs used were those of the XTAL 2.2 system.[29] The drawing of the molecule was made with the program ORTEP II.[30] Tables of coordinates, thermal parameters, bond distances and bond angles are available, on request, from the authors.

16-Hydroxy-3-methoxy-16,17-seco-1,3,5(10)-estratrien-17-oic acid methyl ester (9)

The half ester 8 (3.98 g, 11.5 mmol) was prepared by the partial saponification[14] of the diester 7.[31] It was dissolved in 40 ml of dry THF and borane-THF complex (14.0 ml of 1.0 M solution in

THF, 14 mmol) was added dropwise. The reaction mixture was stirred for 30 min under nitrogen and was then quenched with 40 ml of H_2O. After concentration under reduced pressure, the hydroxy ester was extracted with several portions of ether and the combined organic extracts were washed with H_2O and aqueous NaCl, dried ($MgSO_4$), and evaporated in vacuo. The crude product was separated by flash chromatography (elution with 40% ethyl acetate-hexane) to afford 3.75 g (98%) of 9 as a homogeneous (TLC) oil: Ir 3430, 1726, 1254, 1238 cm^{-1}. The hydroxy ester 9 slowly cyclized to the corresponding lactone 10 on standing for several days.

3-Methoxy-17-oxa-D-homo-1,3,5(10)-estratrien-17a-one (10)

The hydroxy ester 9 (346 mg, 1.00 mmol) was dissolved in 10 ml of dry THF and treated with sodium hydride (53 mg of a 50% dispersion in mineral oil, 1.1 mmol). The reaction mixture was stirred for 1 h under nitrogen and the solution was filtered through Celite and the solvent evaporated in vacuo. The crude product crystallized from acetone-hexane to afford 194.5 mg (65%) of lactone 10; mp 165-167°C; $[\alpha]_D$ +84° (c. 2.54), (lit.[10b] mp 167-168°C; $[\alpha]_D$ +86.5°).

3-Methoxy-17-aza-D-homo-1,3,5(10)-estratrien-17a-one (2)

The hydroxy ester 9 (3.75 g, 11.3 mmol) was stirred overnight at room temperature with p-toluenesulfonyl chloride (4.38 g, 23.0 mmol) in 40 ml of pyridine. The solution was poured into 400 ml of ice-cold 4% aqueous $NaHCO_3$ and left overnight at 0°C. The aqueous layer was separated and the oily residue was taken up in ether. The organic solution was washed with concentrated aqueous $CuSO_4$, H_2O, and aqueous NaCl, dried ($MgSO_4$), and evaporated under reduced pressure to afford 4.68 g (98%) of the crude tosylate. This was dissolved in 20 ml of methanol and transferred to a precooled stainless steel Parr high pressure reaction vessel, maintained at -78°C. After the addition of 50 ml of liquid ammonia, the reactor was sealed and heated for 16 h at 100°C. The reactor was again cooled to -78°C, the valve of the reactor was opened, and ammonia was allowed to evaporate by slowly warming to room temperature. The remaining solvent was evaporated in vacuo and the crude residue was purified by flash chromatography (elution with 40% acetone - chloroform) to afford 3.08 g (91%) of lactam 2; mp 210-212°C (sealed capillary); $[\alpha]_D$ +127° (c. 0.725); Ir 3180, 1649, 1498, 1037 cm^{-1}; ^1H-Nmr δ 7.24 (d, J = 9 Hz, 1 H), 6.8-6.64 (m, 2 H), 5.58 (br s, exchanged in D_2O, 1 H), 3.78 (s, 3 H), 3.38 (m, 2 H), 2.89 (m, 2 H), 2.4-1.3 (complex, 11 H), 1.20 (s, 3 H); mass spectrum, m/z (relative intensity) 299 (M^+, 100), 199 (57). Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.34; H, 8.59; N, 4.44.

3-Methoxy-17-oxa-D-homo-1,3,5(10)-estratrien-16-one (12)

The half ester 8 (7.12 g, 20.55 mmol) and lithium tri-tert-butoxyaluminum hydride (16.7 g, 65.8 mmol) were refluxed in 100 ml of dry THF for 2 days. The solution was cooled to room temperature and the reaction was quenched and treated with 100 ml of 10% aqueous HCl. The solution was extracted with three portions of chloroform and the organic extracts were combined, washed with 5%

aqueous Na_2CO_3, H_2O, and aqueous NaCl, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was separated by flash chromatography (elution with 40% ethyl acetate-hexane) to afford 3.98 (64.5%) of the desired lactone 12, which was recrystallized from ethyl acetate-hexane, mp 173-176°C (lit.[32] mp 189°C, dec.). The identity and purity of the sample was confirmed by its ir and ^{1}H-nmr spectra, and by its elemental analysis. Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.61; H, 8.27.

Further elution afforded 913 mg (15%) of 3-methoxy-16,17-seco-1,3,5(10)-estratriene-16,17-diol 13, which was recrystallized from acetone: mp 144-145°C (lit.[10b] mp 147°C).

17-Hydroxy-3-methoxy-16,17-seco-1,3,5(10)-estratrien-16-carboxamide (14)

The lactone 12 (3.98 g, 13.25 mmol) was treated with 40 ml of methanol and 70 ml of liquid ammonia in a high pressure reaction vessel at 100°C for 16h, as described in the preparation of lactam 2. After removal of the solvent, the crude product was recrystallized from methanol-H_2O to afford 3.59 g (85%) of the hydroxy amide 14; mp 182-184°C; $[\alpha]_D$ +63° (c. 0.45, MeOH); Ir 3452, 3275, 3191, 1646, 1617, 1502, 1051 cm^{-1}; ^{1}H-Nmr δ 7.23 (d, J = 9 Hz, 1 H), 6.75-6.63 (m, 2 H), 5.86 (br s, exchanged D_2O, 1 H), 5.46 (br s, exchanged D_2O, 1 H), 3.78 (s, 3 H), 3.62-3.52 (complex, collapsed to d, J = 12 Hz, upon exchange, 2 H, OH and H-17), 3.24-3.18 (m collapsed to d, J = 12 Hz, upon exchange, 1 H, H-17), 2.91-2.86 (m, 2 H), 2.45-1.25 (complex, 11 H), 0.70 (s, 3H); mass spectrum, m/z (relative intensity) 317 (M^+, <1), 300 (100), 186 (81). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 72.13; H, 8.73; N, 4.52.

3-Methoxy-17-aza-D-homo-1,3,5(10)-estratrien-16-one (3)

Methanesulfonyl chloride (0.92 ml, 11.9 mmol) was added dropwise to a solution of the hydroxy amide 14 (2.52 g, 7.93 mmol) and triethylamine (1.67 ml, 11.9 mmol) in 300 ml of dry THF. The reaction mixture was stirred at room temperature under nitrogen for 2 h. The solution was concentrated in vacuo and 200 ml of ethyl acetate were added. The organic solution was washed twice with aqueous NaCl, dried ($MgSO_4$), and evaporated under reduced pressure. The mesylate was dissolved in 25 ml of DMF, NaH (1.90 g of a 50% dispersion in mineral oil, 39.65 mmol) was added, and the reaction mixture was stirred for 3 h. The reaction was quenched with H_2O and the solution was acidified with 10% aqueous HCl to pH <1. The resulting precipitate was extracted with dichloromethane and the combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The crude product was separated by flash chromatography (elution with 50% acetone-chloroform) to afford 1.38 g (58%) of the lactam 3, which was recrystallized from chloroform-acetone: mp 280-282°C; $[\alpha]_D$ +29° (c. 2.29); Ir 3191, 1656, 1612, 1491, 1259 cm^{-1}; ^{1}H-Nmr δ 7.21 (d, J = 9 Hz, 1 H), 6.76-6.64 (m, 2 H), 6.12 (br s, exchanged D_2O, 1 H), 3.78 (s, 3 H), 3.09 (d, J = 12 Hz, 1 H), 2.97 (dd, J = 4, 12 Hz, collapsed to d, J = 12 Hz upon exchange, 1 H), 2.89-2.83 (m, 2 H), 2.65 (dd, J = 6, 18 Hz, 1 H), 2.38-1.24 (complex, 10 H), 1.01 (s, 3 H); mass spectrum, m/z (relative intensity) 299 (M^+,

100). Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.48; H, 8.45; N, 4.57.

3-Methoxy-15-oxo-D-nor-15,17-seco-1,3,5(10)-estratrien-17-oic acid methyl ester (16)

The indoxylidene 15 was prepared as reported previously.[15] It (8.00 g, 18.5 mmol) was dissolved in 200 ml of dioxane, followed by the addition of 40 ml of H_2O, OsO_4 (47 mg, 0.19 mmol), and powdered sodium m-periodate (31.8 g, 148 mmol). The reaction mixture was refluxed for 24 h, cooled to room temperature, and diluted with 400 ml of H_2O. The resulting precipitate was extracted three times with 150 ml of ether and the combined organic extracts were washed ten times with 150 ml of H_2O, followed by aqueous NaCl, dried ($MgSO_4$), and evaporated in vacuo. The crude product was purified by flash chromatography (elution with 20% ethyl acetate-hexane) to give 3.83 g (65%) of the aldehyde 16, which was recrystallized from methanol: mp 96.5-97.5°C; $[\alpha]_D$ +96° (c 0.87); Ir 2727, 1736, 1718, 1609, 1499, 1238, 1116, 1034 cm^{-1}; ^{1}H-Nmr δ 9.82 (d, J = 3 Hz, 1 H), 7.21 (d, J = 9 Hz, 1 H), 6.76-6.64 (m, 2 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 2.87-2.80 (complex, 3 H), 2.45-2.33 (complex, 2 H), 2.05-1.45 (complex, 6 H), 1.28 (s, 3 H); mass spectrum, m/z (relative intensity) 316 (M^+, 75), 187 (100), 159 (98). Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.40; H, 7.77.

3-Methoxy-D-nor-15,17-seco-1,3,5(10)-estratriene-15,17-diol (17)

The aldehyde 16 (1.50 g, 4.75 mmol) in 10 ml of dry THF was added dropwise to a suspension of lithium aluminum hydride (540 mg, 14.2 mmol) in 20 ml of dry THF. The reaction mixture was stirred for 1 h at room temperature under nitrogen. The reaction was quenched and treated with H_2O and 20% NaOH. The solution was filtered through Celite and the filtrate was evaporated in vacuo. The oily residue was separated by flash chromatography (elution with 40% acetone-chloroform) to afford 1.18 g (86%) of the diol 17. The product was recrystallized from acetone and methanol-H_2O, mp 142-144°C; $[\alpha]_D$ +34° (c. 2.37) (lit.[10b] mp 147°C; $[\alpha]_D$ +17°).

3-Methoxy-16-oxa-14α-1,3,5(10)-estratrien-15-one (18)

The diol 17 (1.14 g, 3.93 mmol) was dissolved in 50 ml of acetone and cooled to 0°C. Jones reagent (ca. 1.6 ml) was added dropwise until a faint colour of the reagent persisted over a period of 5 min. After an additional 10 min at 0°C the reaction mixture was poured into ice-water and the resulting precipitate was extracted with several portions of ether. The combined ether extracts were washed with 4% aqueous $NaHCO_3$, H_2O and aqueous NaCl, dried ($MgSO_4$), and evaporated in vacuo. The product was recrystallized from methanol to afford 973 mg (86.5%) of the desired lactone 18: mp 144-146°C; $[\alpha]_D$ +25° (c. 1.805); (lit.[10b] mp 148-149°C; $[\alpha]_D$ +25.5°).

Attempted ring-opening of lactone 18

Lactone 18 (177 mg, 0.62 mmol) in 10 ml of dry THF, was added to 50 ml of liquid ammonia containing a trace of sodium amide in a high pressure reaction vessel at -78°C. The vessel was sealed and stirred overnight at room temperature. After removal of volatile material, the residue con-

sisted of nearly pure 3-methoxy-16-oxa-14β-1,3,5(10)-estratrien-15-one (19); which was recrystallized from methanol, mp 159-160°C; $[\alpha]_D$ +191° (c. 2.6); (lit.[10b] mp 161°C; $[\alpha]_D$ +200°).

3-Methoxy-15-carbamoyl-D-nor-15,17-seco-1,3,5(10)-estratrien-17-oic acid methyl ester (20)

The aldehyde 16 (5.54 g, 17.5 mmol) in 100 ml of acetone was stirred with 7 ml of Jones reagent at 0°C for 1 h. The solution was poured into 500 ml of ice-water and the resulting precipitate was extracted with several portions of ether. The combined organic extracts were washed with H_2O and aqueous NaCl, dried ($MgSO_4$), and evaporated in vacuo. Oxalyl chloride (5.5 ml, 63 mmol) was added to the resulting acid and the reaction mixture was stirred for 3 h at room temperature under nitrogen. Excess oxalyl chloride was then removed under reduced pressure, two separate portions of hexane were added to the residue, and the solvent was again removed in vacuo after each one. The acid chloride was dissolved in 20 ml of dry THF and added dropwise to 100 ml of an ice-cold solution of concentrated aqueous NH_4OH. The resulting precipitate was extracted with several portions of ether and the combined ether extracts were washed with H_2O and aqueous NaCl, dried ($MgSO_4$), and evaporated in vacuo. The crude product was separated by flash chromatography (elution with 40% acetone-chloroform) to give 4.06 g (70%) of amide 20 as a solid; Ir 3450, 3360, 3191, 1720, 1670, 1610, 1501, 1238 cm^{-1}; ^{1}H-Nmr δ 7.19 (d, J = 8 Hz, 1 H), 6.75-6.63 (m, 2 H), 5.85 (br s, exchanged D_2O, 1 H), 5.30 (br s, exchanged D_2O, 1 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 2.76 (d, J = 11 Hz) superimposed on 2.98-1.26 (complex, s at 1.31, total 14 H); mass spectrum, m/z (relative intensity) 331 (M^+, 4), 286 (24), 43 (100).

17-Hydroxy-3-methoxy-D-nor-15,17-seco-1,3,5(10)-estratriene-15-carboxamide (21) and 3-Methoxy-16-aza-1,3,5(10)-estratriene-15,17-dione (22)

The amide 20 (4.06 g, 12.3 mmol) and lithium tri-tert-butoxyaluminum hydride (13.10 g, 51.5 mmol) were refluxed in 100 ml of dry THF under nitrogen for 8 h. The reaction was quenched and treated with 150 ml of 10% aqueous HCl. The organic layer was separated, concentrated in vacuo and taken up in dichloromethane. This was washed with 10% aqueous HCl, H_2O, dried ($MgSO_4$), and evaporated in vacuo. The crude product was separated by flash chromatography to afford two products. Elution with 40% ethyl acetate-hexane provided 687 mg (19%) of imide 22, which was recrystallized from acetone-hexane: mp 220-223°C; $[\alpha]_D$ -18° (c. 1.085); Ir 3275, 1770, 1732, 1609, 1577, 1498, 1313, 1253, 1239, 1073, 1034 cm^{-1}; ^{1}H-Nmr δ 7.47 (br s, exchanged D_2O, 1 H), 7.19 (d, J = 8 Hz, 1 H), 6.77-6.66 (m, 2 H), 3.79 (s, 3 H), 2.96-2.82 (complex, 3 H), 2.52 (d, J = 11 Hz) superimposed on 2.56-1.54 (complex, total 8 H), 1.31 (s, 3 H); mass spectrum, m/z (relative intensity) 299 (M^+, 100), 160 (95). Anal. Calcd. for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.24; H, 7.14; N, 4.51.

Elution with 40% acetone-chloroform afforded 1.19 g (32%) of the desired product 21, which was recrystallized from acetone: mp 200-202°C; $[\alpha]_D$ +34° (c. 1.475, MeOH); Ir 3501, 3367, 3276,

1670, 1237 cm^{-1}; ^{1}H-Nmr δ 7.22 (d, J = 9 Hz, 1 H), 6.76-6.63 (m, 2 H), 5.98 (br s, exchanged D_2O, 1 H), 5.48 (br s, exchanged D_2O, 1 H), 3.78 (s, 3 H), 3.54 (d, J = 11 Hz, 1 H), 3.34 (d, J = 11 Hz, 1 H), 2.96-2.83 (complex, 2 H), 2.41 (d, J = 11.5 Hz) superimposed on 2.44-1.26 (complex, total 10 H), 0.93 (s, 3 H); mass spectrum, m/z (relative intensity) 303 (M^+, 2), 286 (70). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.08; H, 8.35; N, 4.73.

Attempted cyclization of hydroxy amide 21

Methanesulfonyl chloride (0.20 ml, 2.56 mmol) was added dropwise to a solution of the hydroxy amide 21 (390 mg, 1.28 mmol) and triethylamine (0.36 ml; 2.56 mmol) in 20 ml of dry THF at 0°C under nitrogen. The solution was stirred for 1 h, 80 ml of ethyl acetate were added, and the reaction mixture was washed with aqueous NaCl, dried ($MgSO_4$), and evaporated in vacuo. The residue was dissolved in 20 ml of DMF and NaH (1.22 g of a 50% dispersion in mineral oil, 25.6 mmol) was added. The mixture was stirred overnight at room temperature under nitrogen, and was then quenched, diluted with H_2O and acidified with 10% aqueous HCl to a pH <1. The resulting precipitate was extracted with several portions of ethyl acetate and the combined organic extracts were washed with H_2O and aqueous NaCl, dried ($MgSO_4$), and evaporated in vacuo. The residue was separated by flash chromatography (elution with 10% acetone-chloroform) to afford two products. The less polar component afforded 129 mg (36%) of 17-hydroxy-3-methoxy-D-nor-15,17-seco-1,3,5(10)-estratriene-15-nitrile (23), as a solid; Ir 3450, 2236, 1611, 1501, 1258, 1042 cm^{-1}; ^{1}H-Nmr δ 7.21 (d, J = 9 Hz, 1 H), 6.77-6.65 (m, 2 H), 3.79 (s, 3 H), 3.69 (d, J = 11 Hz, 1 H), 3.44 (d, J = 11 Hz, 1 H), 2.96-2.82 (m, 2 H), 2.72 (d, J = 11.5 Hz, 1 H), 2.38-1.26 (complex, 9 H), 1.04 (s, 3 H); mass spectrum, m/z (relative intensity) 285 (M^+, 100), 199 (53); exact mass calcd for $C_{18}H_{23}NO_2$: 285.1729, found: 285.1722. The more polar component gave 71 mg (19%) of the desired product, 3-methoxy-16-aza-14β-1,3,5(10)-estratrien-15-one (5), which was recrystallized from ethyl acetate: mp 187-189°C; $[\alpha]_D$ +194° (c. 0.2); Ir 3241, 1697, 1610, 1502, 1272, 1037 cm^{-1}; ^{1}H-Nmr δ 7.19 (d, J = 9 Hz, 1 H), 6.74-6.63 (m, 2 H), 5.59 (br s, exchanged D_2O, 1 H), 3.78 (s, 3 H), 3.11 (d, J = 9 Hz, 1 H), 2.94-2.54 (complex, total 5 H), 2.29-1.28 (complex, 7 H), 1.19 (s, 3 H); mass spectrum, m/z (relative intensity) 285 (M^+, 64), 187 (38), 98 (100). Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.78; H, 8.34; N, 4.64. The iodide 24 was prepared by treating the mesylate of 21 with excess NaI in refluxing acetone. Attempted cyclization of iodide 24 with NaH in DMF, as in the case of the mesylate described above, resulted in the formation of 60% of the nitrile 23, identical to the previous sample.

N-Benzyl-15-carbamoyl-3-methoxy-D-nor-15,17-seco-1,3,5(10)-estratrien-17-oic acid methyl ester (26a)

The aldehyde 16 (1.68 g, 5.31 mmol) was converted to the acid chloride as in the preparation of

amide 20. The acid chloride was taken up in 5 ml of dichloromethane and added dropwise to an ice-cold solution of benzylamine (2.90 ml, 26.55 mmol) and triethylamine (2.50 ml, 17.7 mmol) in 20 mL of dichloromethane. The reaction mixture was stirred for 15 min and the resulting precipitate was filtered. The filtrate was evaporated in vacuo and the residue was separated by flash chromatography (elution with 20% ethyl acetate-hexane) to give 1.815 g (81%) of the title compound 26a as a solid: Ir 3288, 1725, 1644, 1500, 1251, 1158 cm^{-1}; ^{1}H-Nmr δ 7.36-7.16 (complex, 6 H), 6.76-6.64 (m, 2 H), 6.16 (br t, J = 5 Hz, 1 H), 4.56 (dd, J = 15, 7 Hz, 1 H), 4.25 (dd, J = 15, 5 Hz, 1 H), 3.78 (s, 3 H), 3.53 (s, 3 H), 2.98-2.83 (m, 2 H), 2.68 (d, J = 11 Hz, 1 H), 2.37-2.26 (m, 2 H), 1.99-1.29 (complex, s at 1.29, total 9 H); mass spectrum, m/z (relative intensity) 421 (M^+, 44), 389 (22), 361 (5), 177 (64), 91 (100); exact mass calcd for $C_{26}H_{31}NO_4$: 421.2253; found: 421.2249.

N-Benzyl-17-hydroxy-3-methoxy-16-aza-1,3,5(10)-estratrien-15-one (27a)

Lithium tri-tert-butoxyaluminum hydride (1.34 g, 5.28 mmol) and the amide 26a (1.01 g, 2.40 mmol) were refluxed for 1 h in 50 ml of dry THF. The reaction was cooled to 0°C, quenched and treated with 10% aqueous HCl to dissolve the precipitated salts. The organic layer was separated, concentrated in vacuo, diluted with chloroform, washed with H_2O and aqueous NaCl, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was recrystallized from chloroform-acetone to afford 483 mg (51.5%) of carbinol amide 27a: mp 220-223°C; $[\alpha]_D$ +57° (c. 0.575); Ir 3276, 1660, 1607, 1501, 1241 cm^{-1}; ^{1}H-Nmr δ 7.32 (s, 5 H), 7.18 (d, J = 9 Hz, 1 H), 6.75-6.66 (m, 2 H), 4.75 (d, J = 15 Hz, 1 H), 4.69 (d, J = 9 Hz, collapsed to s upon D_2O exchange, 1 H), 4.24 (d, J = 15 Hz, 1 H), 3.79 (s, 3 H), 3.07-2.88 (complex, 3 H), 2.07 (d, J = 9 Hz, exchanged D_2O) superimposed on 2.38-1.50 (complex, total 9 H), 0.95 (s, 3 H); mass spectrum, m/z (relative intensity) 391 (M^+, 24), 228 (19), 91 (100).

N-Benzyl-3,17-dimethoxy-16-aza-1,3,5(10)-estratrien-15-one (28)

The carbinol amide 27a (97.8 mg, 0.25 mmol) and p-toluenesulfonic acid (2.4 mg) were refluxed for 2 h in 10 ml of methanol. The solvent was evaporated in vacuo and the crude product was purified by flash chromatography (elution with 40% ethyl acetate-hexane) to afford 77.0 mg (76%) of the methyl ether 28 as a solid white foam: Ir 1702, 1499, 1257, 1085, 1075 cm^{-1}; ^{1}H-Nmr δ 7.38-7.29 (m, 5H), 7.20 (d, J = 9 Hz, 1 H), 6.75-6.67 (m, 2 H), 4.95 (d, J = 15 Hz, 1 H), 4.07 (d, J = 15 Hz, 1 H), 4.00 (s, 1 H), 3.79 (s, 3 H), 3.40 (s, 3 H), 3.08-2.90 (complex, 3 H), 2.38 (d, J = 11 Hz) superimposed on 2.42-1.27 (complex, total 8 H), 0.82 (s, 3 H); mass spectrum, m/z (relative intensity) 405 (M^+, 39), 228 (30), 91 (100); exact mass calcd for $C_{26}H_{31}NO_3$: 405.2304; found: 405.2279.

N-(3,4-Dimethoxybenzyl)-15-carbamoyl-3-methoxy-D-nor-15,17-seco-1,3,5(10)-estratrien-17-oic acid methyl ester (26b)

The aldehyde 16 (4.95 g, 15.6 mmol) was converted to the acid chloride as in the preparation of amide 20. The acid chloride was taken up in a small amount of dichloromethane and added dropwise to an ice-cold solution of 3,4-dimethoxybenzylamine (7.00 ml, 46.9 mmol) and triethylamine (6.60 ml, 46.9 mmol) in 100 mL of dichloromethane. The mixture was stirred at 0°C for 30 min, concentrated in vacuo, and the residue was taken up in ethyl acetate. The solution was washed with H_2O and aqueous NaCl and evaporated in vacuo. The crude product was purified by flash chromatography (elution with 40% ethyl acetate-hexane) to afford 6.05 g (80%) of 26b. The product was recrystallized from ethyl acetate-hexane: mp 129-131°C; $[\alpha]_D$ +65° (c. 1.94); Ir 3318, 1728, 1654, 1516, 1261, 1235, 1028 cm^{-1}; ^{1}H-Nmr δ 7.18 (d, J = 9 Hz, 1 H), 6.83-6.63 (complex, 5 H), 6.13 (br t, J = 6 Hz, 1 H), 4.51 (dd, J = 14, 7 Hz, 1 H), 4.17 (dd, J = 14, 5 Hz, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.78 (s, 3H), 3.50 (s, 3 H), 3.1-2.7 (m, 2 H), 2.65 (d, J = 11 Hz, 1 H), 2.47-2.26 (complex, 2 H), 2.04-1.30 (complex, s at 1.30, total 9 H); mass spectrum, m/z (relative intensity) 481 (M^+, 53), 449 (52), 421 (6), 151 (100). Anal. Calcd for $C_{28}H_{35}NO_6$: C, 69.83; H, 7.33; N, 2.91. Found: C, 69.60; H, 7.33; N, 2.87.

N-(3,4-Dimethoxybenzyl)-17-hydroxy-3-methoxy-16-aza-1,3,5(10)-estratrien-15-one (27b)

The procedure for the preparation of carbinol amide 27a was followed to afford the title compound 27b in 98% yield. The product was recrystallized from acetone-hexane: mp 174-176°C; $[\alpha]_D$ +58° (c. 1.035); Ir 3275, 1653, 1605, 1515, 1257, 1234, 1025 cm^{-1}; ^{1}H-Nmr δ 7.17 (d, J = 9 Hz, 1 H), 6.89-6.65 (complex, 5 H), 4.68 (d, J = 9 Hz, collapsed to s upon D_2O exchange, 1 H), 4.66 (d, J = 15 Hz, 1 H), 4.18 (d, J = 15 Hz, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.78 (s, 3 H), 3.07-2.89 (complex, 3 H), 2.19 (d, J = 9 Hz, exchanged D_2O) superimposed on 2.37-2.17 (complex, total 3 H), 1.98-1.51 (complex, 6 H), 0.94 (s, 3 H); mass spectrum, m/z (relative intensity) 451 (M^+, 54), 433 (37), 282 (31), 151 (72), 43 (100). Anal. Calcd for $C_{27}H_{33}NO_5$: C, 71.82; H, 7.37; N, 3.10. Found: C, 71.73; H, 7.44; N, 2.81.

N-(3,4-Dimethoxybenzyl)-17-hydroxy-3-methoxy-D-nor-15,17-seco-1,3,5(10)-estratriene-15-carboxamide (29)

The ester 26b (2.58 g, 5.36 mmol) in 10 ml of dry THF, was slowly added to a refluxing solution of lithium borohydride (351 mg, 16.1 mmol) in 30 ml of dry THF. After 1 h the reaction was quenched and treated with 10% aqueous HCl, diluted with ethyl acetate, washed with H_2O and aqueous NaCl, dried ($MgSO_4$), and evaporated to afford 2.305 g (95%) of hydroxy amide 29. The product was recrystallized from ethyl acetate: mp 160-161°C; $[\alpha]_D$ +59° (c. 1.11); Ir 3409, 3270, 1652, 1609, 1516, 1239, 1026 cm^{-1}; ^{1}H-Nmr δ 7.19 (d, J = 9 Hz, 1 H), 6.88-6.61 (complex, 5 H), 6.3 (br s, 1 H), 4.41 (d, J = 6 Hz, 2 H), 3.87 (s, 6 H), 3.77 (s, 3 H), 3.38 (d, J = 11 Hz, 1 H), 3.27 (d, J =

11 Hz, 1 H), 2.93-2.75 (complex, 2 H), 2.33 (d, J = 11 Hz) superimposed on 2.35-1.38 (complex, 10 H), 0.90 (s, 3 H); mass spectrum, m/z (relative intensity) 453 (M^+, 41), 435 (29), 151 (87), 43 (100). Anal. Calcd for $C_{27}H_{35}NO_5$: C, 71.50; H, 7.78; N, 3.09. Found: C, 71.63; H, 7.68; N, 3.23.

N-(3,4-Dimethoxybenzyl)-3-methoxy-16-aza-1,3,5(10)-estratrien-15-one (30)

The cyclization of hydroxy amide 29 (5.2 g, 11.5 mmol) to lactam 30 was effected by the same method as described for the preparation of lactam 3. The crude product was separated by flash chromatography (elution with 50% ethyl acetate-hexane) to afford 2.87 g (57%) of the title compound 30. The product was recrystallized from acetone-hexane: mp 141-143°C; $[\alpha]_D$ -32° (c. 1.66); Ir 1678, 1605, 1501, 1460, 1412, 1239, 1029 cm^{-1}; ^{1}H-Nmr δ 7.17 (d, J = 8 Hz, 1 H), 6.81-6.65 (complex, 5 H), 4.51 (d, J = 14 Hz, 1 H), 4.22 (d, J = 14 Hz, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.78 (s, 3 H), 3.05-2.81 (complex, 5 H), 1.95 (d, J = 11 Hz) superimposed on 2.4-1.4 (complex, total 8 H), 0.92 (s, 3 H); mass spectrum, m/z (relative intensity) 435 (M^+, 20), 322 (15), 151 (46), 43 (100). Anal. Calcd for $C_{27}H_{33}NO_4$: C, 74.45; H, 7.64; N, 3.22. Found: C, 74.25; H, 7.84; N, 3.22.

Deprotection of lactam 30

Lactam 30 (1.19 g, 2.74 mmol) in 10 ml of dry THF was slowly added to a refluxing solution of sodium (632 mg, 27.5 mmol) in 75 ml of liquid ammonia. After 20 min the reaction was quenched with solid ammonium chloride until the dark blue colour disappeared. The ammonia was allowed to evaporate overnight and the residue was taken up in ethyl acetate. The solution was washed with H_2O and aqueous NaCl, dried ($MgSO_4$), and evaporated in vacuo. The crude product was separated by flash chromatography (elution with 20% acetone-chloroform) to afford in increasing order of polarity: a) 146 mg of 3-methoxy-16-aza-14α-1,3,5(10)-estratrien-15-one (4), which was recrystallized from acetone: mp 210-213°C; $[\alpha]_D$ +12° (c. 0.715); Ir 3205, 1691, 1499, 1277, 1255, 1039 cm^{-1}; ^{1}H-Nmr δ 7.19 (d, J = 8 Hz, 1 H), 6.75-6.65 (m, 2 H), 5.82 (br s, exchanged, 1 H), 3.79 (s, 3 H), 3.14-2.89 (complex, 5 H), 2.39-2.27 (complex, 2 H), 1.91 (d, J = 11 Hz) superimposed on 1.94-1.41 (complex, total 6 H), 1.09 (s, 3 H); mass spectrum, m/z (relative intensity) 285 (M^+, 100), 270 (18), 98 (64). Anal. calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.38; H, 8.02; N, 4.80. b) 420 mg of an unseparated mixture of the two C-14 isomers 4 and 5. c) 76 mg of lactam 5, identical to an authentic sample prepared from hydroxy amide 21. Total yield of 4 and 5: 82%, in a ratio of ca. 1:2 as determined by ^{1}H-NMR analysis of the original crude mixture. d) 56.5 mg (8%) of 16-aza-14β-4-estrene-3,15-dione (31), which was recrystallized from acetone: mp 234-237°C; $[\alpha]_D$ +148° (c. 0.655); Ir 3206, 3093, 1693, 1672 cm^{-1}; ^{1}H-Nmr δ 5.84 (s, 1 H), 5.62 (br s, exchanged D_2O, 1 H), 3.08 (d, J = 9 Hz, 1 H), 2.87 (dd, J = 9, 2 Hz, collapsed to d, J = 9 Hz upon D_2O exchange, 1 H), 2.71-1.08 (complex, s at 1.20, total 19 H); ^{13}C-Nmr δ 199.7 (C-3), 177.4 (C-15), 166.1 (C-5), 124.5 (C-4), 21.7 (C-18); mass spectrum, m/z (relative intensity), 273 (M^+, 66), 98 (100). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C,

74.45; H, 8.31; N, 5.00.

Isomerization of lactam 4 to lactam 5

A 1:2 mixture of lactams 4 and 5 (200 mg, 0.70 mmol) and potassium tert-butoxide (200 mg; 1.78 mmol) was refluxed under nitrogen for 30 min in 20 ml of tert-butanol. The reaction was quenched with 10% HCl and the resulting precipitate of KCl was filtered and the filtrate evaporated in vacuo. The residue was taken up in ethyl acetate and washed with H_2O and NaCl solution, dried ($MgSO_4$), and evaporated in vacuo to afford 195 mg (98%) of pure 5, which was identical to the previous sample.

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20. The configuration of this lactam was established as 14β by comparison with authentic samples of both the 14α- and 14β-isomers. Epimerization of C-14 occurred during and not before the formation of 5, as compounds 20-23 all exhibit J = 11.1 to 11.5 Hz for the coupling between H-8 and H-14, typical of the 14α-configurations.

21. Since the N atom is a softer nucleophile than the O atom, a softer leaving group might be expected to enhance reaction through N. Clearly other factors override these considerations in the present case. For an excellent discussion of the properties of ambident nucleophiles, see I. Fleming, in "Frontier Orbitals and Organic Chemical Reactions", J. Wiley, Chichester, 1976, Chapter 3.2.

22. This presumably occurs via an electrophilic acyliminium intermediate. The OH and OMe functions at C-17, in 27a,b and 28 are tentatively shown with the α-configuration on the basis of stability considerations.

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25. Epimerization at C-14 occurred during, and not before, the deprotection step as compounds 26a,b, and 28-30 all display J = 11.2-11.4 Hz for the coupling constant between H-8 and H-14, indicative of the 14α-configuration.

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