Conformational Design for 13α-Steroids

Bruno Schönecker,*,† Corinna Lange,† Manuela Kötteritzsch,† Wolfgang Günther,†
Jennie Weston,† Ernst Anders,† and Helmar Görls‡

Institut für Organische Chemie und Makromolekulare Chemie der Friedrich-Schiller-Universität Jena, Humboldtstr. 10 and Institut für Anorganische und Analytische Chemie der Friedrich-Schiller-Universität Jena, Lessingstr. 8, D-07743 Jena, Germany

c8scbr@uni-jena.de

Received January 26, 2000

The diastereomeric 16-bromo- and 16-azido-17-alcohols **5**−**8**, **11**, **12**, **16**, and **17** and 17-ketones **3**, **4**, **9**, and **10** of the 13α-estra-1,3,5(10)-triene series were synthesized as precursors for biologically active compounds and chiral ligands for metal complexation. Conformational investigations of these and some other compounds via X-ray analysis and ^{1}H NMR spectroscopy show the existence of compounds with the classical steroid conformation (ring C chair, restricted conformation of ring D) and such with an atypical ring C twist-boat and a flexible ring D conformation. It could be shown that 17*β*-substituents or flattening of the D-ring are responsible for the twist-boat conformation, whereas compounds containing a 17α-substituent or 17-keto group possess the classical conformation. By varying the substituents, compounds with either of these conformations can be intentionally synthesized. MO calculations confirmed the relative stability of the twist-boat conformation.

Introduction

Natural 13*β*-estra-1,3,5(10)-trienes possess a tetracyclic steroidal framework with an aromatic A-ring and *trans*-junctions of the B/C- and C/D-rings (Figure 1). The B-ring has a half-chair or sofa conformation; the C-ring possesses a chair conformation. The pseudorotation of the cyclopentane D-ring is restricted to nearly 1/10 of that of cyclopentane.[1] The resulting relatively rigid steroidal framework has two oxygen functionalities in the 3- and 17-positions separated by well-defined distances that are important for the biological activity of the female sex hormones estradiol and estrone. This rigid framework, typical for natural steroids, is frequently used for stereochemical investigations. In connection with such investigations,[2] we are interested in compounds with an inverted configuration at C13, namely, 13α-estra-1,3,5(10)-trienes which possess a *cis*-junction of the C- and D-rings. These compounds, similar to natural steroids, should exhibit a relatively rigid molecular framework. In contrast to the natural 13*β*-estra-1,3,5(10)-trienes, these derivatives possess a quasi-equatorial 13α-methyl group and a D-ring that is directed to the *β*-side and exhibits a similarly strongly restricted pseudorotation (Figure 1). In this case, a 13α,14*β*-half-chair is the basic conformation. The phase angle Δ, a parameter for the pseudorotation, has a value of +36° for the 13α-envelope and −36° for the 14*β*-envelope conformation, respectively. This corresponds to 1/10 of the complete pseudorotation cycle[1,3] (Figure 2).

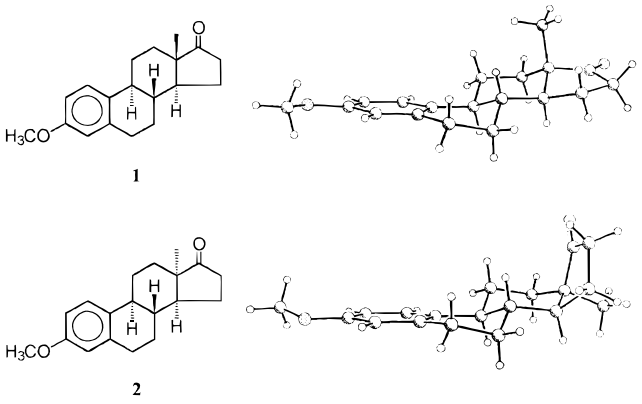


Figure 1. 3-Methoxy-estra-1,3,5(10)-triene-17-one (**1**) and 3-methoxy-13α-estra-1,3,5(10)-triene-17-one (**2**).

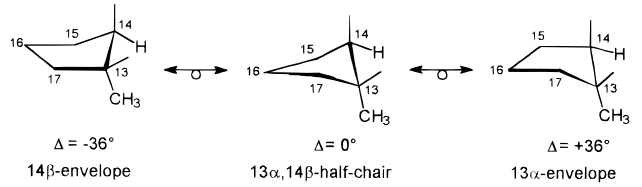


Figure 2. D-ring conformations of 13α-steroids (phase angle Δ = −36° to Δ = +36°).

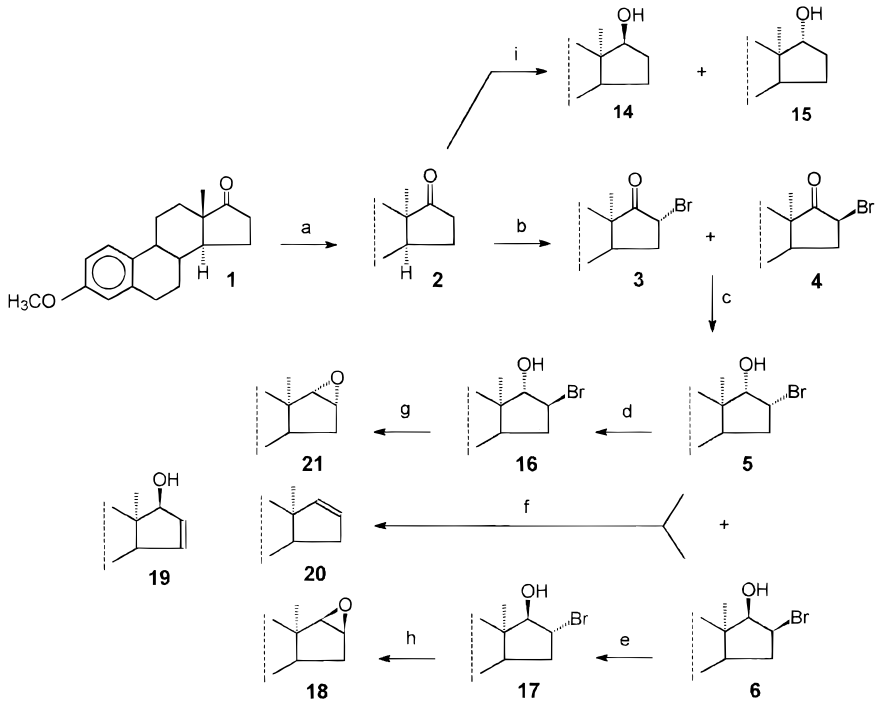
13α-Estrone and some of its derivatives were first obtained by Butenandt and co-workers via a photochemical isomerization at C13 and subsequent reactions.[4] Somewhat later, Nambara and co-workers synthesized and investigated the conformation of a series of new 13α-estra-1,3,5(10)-trienes, which contain substituents at C16.[5] Their ^{1}H NMR investigations seemed to confirm

* Tel: +49 (0)3641-948225. Fax: +49 (0)3641-948292.
† Institut für Organische Chemie und Makromolekulare Chemie.
‡ Institut für Anorganische und Analytische Chemie.

(1) Altona, C.; Geise, H. J.; Romers, C. *Tetrahedron* **1968**, *24*, 13.
(2) (a) Schönecker, B. *Z. Chem.* **1982**, *22*, 186. (b) Krieg, R.; Dubs, M.; Görls, H.; Schönecker, B. *Chem. Ber.* **1996**, *129*, 1497. (c) Dubs, M.; Krieg, R.; Görls, H.; Schönecker, B. *Steroids* **2000**, *65*, 305.
(3) (a) Geise, J.; Altona, C.; Romers, C. *Tetrahedron Lett.* **1967**, 1383. (b) Portheine, J. C.; Romers, C. *Acta Crystallogr.* **1970**, *B26*, 1791.
(4) Butenandt, A.; Wolff, A.; Karlson, P. *Ber. Dtsch. Chem. Ges.* **1941**, *74*, 1308.

10.1021/jo000108x CCC: $19.00
Published on Web 08/15/2000

Scheme 1. Syntheses of 13α-Estra-1,3,5(10)-trienes I: 16,17-Bromohydrins and 16,17-Epoxides[a]



[a] Reagents and conditions: (a) AcOH, 1,2-phenylenediamine, reflux (78%); (b) benzene/MeOH, $CuBr_2$, reflux (93%, **3**/**4** = 2/1); (c) MeOH/THF, $NaBH_4$, 0 °C (58% of **5**, 27% of **6**); (d) DMPU, 70 °C (59%); (e) DMPU, 70 °C, (12.5%); (f) AcOH, Zn, reflux (74%); (g) MeOH, methanolic K_2CO_3, 60 °C (93%); (h) THF, methanolic KOH, 60 °C (91%); (i) MeOH/THF, $NaBH_4$, rt (55% of **14**, 36% of **15**); MeOH/THF, L-Selectride, rt (78% of **14**, 8.4% of **15**).

the presence of the assumed conformation (Figure 1).[5,6] The only evidence in the literature for a flexible twist-boat conformation in the C-ring is the X-ray analysis published in 1975 of a related compound containing a 15-double bond in the D-ring, 3-methoxy-16-(4-bromobenzoyloxy)-13α-estra-1,3,5(10),15-tetraene-17-one.[7]

In this paper, we report on the synthesis of the four diastereomeric 16,17-azido alcohols **7**, **8**, **11**, and **12** and the corresponding two 16,17-azido ketones **9** and **10** of the 13α series, starting from the known 13α-estrone 3-methyl ether (**2**) and the corresponding 16-bromo ketones **3** and **4** and 16,17-bromohydrins **5**, **6**, **16**, and **17**. Subsequent structural investigations (X-ray, NMR, and ab initio calculations) gave the remarkable result that the conformation of 13α-estra-1,3,5(10)-trienes depends strongly upon the substitution pattern of the D-ring and results either in the expected conformation (Figure 1) or in an unusual steroid conformation with a twist-boat C-ring. We compare our findings for the 13α series with the amino alcohols of 13*β* series[8] and their derivatives[2] in view of their capability to bind transition metal ions and to transfer chiral information. The consequences of the availability of such conformationally different steroids for biological applications[9] are discussed.

Results and Discussion

Syntheses. From the known chemical methods for the epimerization of steroidal 17-ketones,[4,10] we chose that from Yaremenko and Khvat, which is a method for reactions of the androstane series using 1,2-phenylenediamine and acetic acid.[11] Starting from estrone 3-methyl ether (**1**), we obtained nearly 80% 13α-estrone 3-methyl ether (**2**) in one step after chromatographic purification (Scheme 1). A one-step bromination of **2** with copper(II) bromide resulted in a 2:1 mixture of the corresponding 16α- and 16*β*-bromo ketones **3** and **4**. Similar results have been reported by Nambara and co-workers for bromination of the enolacetate of **2**.[5a] In addition, reduction of these bromo ketones with lithium aluminum hydride to give the corresponding *cis*-bromohydrins **5** and **6** have been described by this research group.[5a] We reduced the bromo ketones **3** and **4** with sodium borohydride to obtain compounds **5** and **6**. Treatment of the bromohydrins **5** and **6** with lithium azide in HMPTA lead to the new *trans*-azido alcohols **7** and **8** (Scheme 2). Side reactions lead, however, to considerable amounts of the ketone **2** (originating from the *β*,*β*-bromohydrin **6**) and the 17*β*-hydroxy-15-olefin **19**. Very small quantities of 16*β*,17*β*-epoxide **18** were obtained, which originated from **6** by epimerization of the 16*β*-bromo substituent and subse-

(5) (a) Nambara, T.; Kudo, T.; Hosoda, H.; Motojima, K.; Goya, S. *Chem. Pharm. Bull.* **1969**, *17*, 2366. (b) Nambara, T.; Kudo, T. *Chem. Pharm. Bull.* **1972**, *20*, 2156. (c) Goto, J.; Sudo, K.; Nambara, T. *Chem. Pharm. Bull.* **1974**, *22*, 1140.

(6) (a) Nambara, T.; Hosoda, H.; Goya, S. *Chem. Pharm. Bull.* **1968**, *16*, 1266. (b) Nambara, T.; Hosoda, H.; Usui, M. *Chem. Pharm. Bull.* **1969**, *17*, 1687.

(7) Nambara, T.; Kudo, T.; Hosoda, H.; Iitaka, Y.; Kikutani, N. *Chem. Pharm. Bull.* **1975**, *23*, 320.

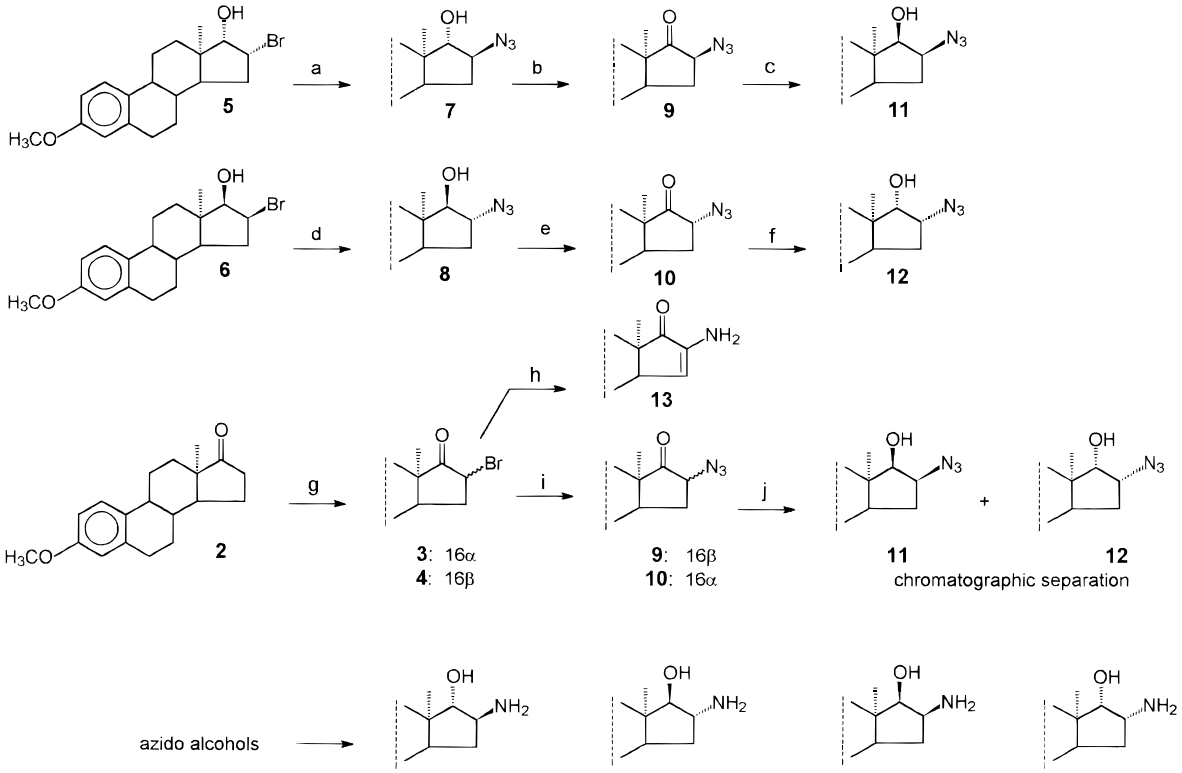
(8) Schönecker, B.; Ponsold, K. *Tetrahedron* **1975**, *31*, 1113.

(9) (a) Schönecker, B.; Wyrwa, R.; Möllmann, U.; Krieg, R.; Dubs, M. Ger. Offen. DE 19633206, 1996 [*Chem. Abstr.* **1998**, *128*, 205039c]. (b) Krieg, R.; Wyrwa, R.; Möllmann, U.; Görls, H.; Schönecker, B. *Steroids* **1998**, *63*, 531.

(10) (a) Wehrli, H.; Schaffner, K. *Helv. Chim. Acta* **1962**, *45*, 385. (b) Boar, R. B.; Jetuah, F. K.; McGhie, J. F.; Robinson, M. S.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2163. (c) Boivin, J.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron Lett.* **1992**, *33*, 7849.

(11) Yaremenko, F. G.; Khvat, A. V. *Mendeleev Commun.* **1994**, 187 [*Chem. Abstr.* **1995**, *122*, 214318w].

Scheme 2. Syntheses of 13α-Estra-1,3,5(10)-trienes II: 16,17-Azido Alcohols[a]



[a] Reagents and conditions: (a) HMPTA, LiN_3, 90 °C (66%); (b) acetone, CrO_3/H_2SO_4, 0 °C (92%); (c) MeOH/THF, $NaBH_4$, 0 °C (69%); (d) HMPTA, LiN_3, 90 °C (48%); (e) acetone, CrO_3/H_2SO_4, 0 °C (78%); (f) MeOH/THF, $NaBH_4$, 0 °C (55%); (g) benzene/MeOH, $CuBr_2$, reflux (93%, **3**/**4** = 2/1); (h) DMF, NaN_3, rt to 50 °C (95%); (i) HMPTA, AcOH, LiN_3, 0 °C (96%, **9**/**10** = 1/1); (j) MeOH/THF, $NaBH_4$, 0 °C (39% of **11**, 24% of **12** related to **3**/**4**).

quent ring closure. In practice, it would be advantageous to avoid a separation of the bromo ketones **3** and **4** and to separate the bromohydrins **5** and **6** by chromatography after the reduction of the bromo ketone mixture. The *cis*-azido alcohols **11** and **12** should be available from stereoselective reduction of the azido ketones **9** and **10**.[8,12] Steroidal azido ketones with vicinal functions are relatively unstable compounds, especially under basic conditions, as a result of their ease of epimerization and nitrogen cleavage.[12] To arrive at a concrete statement about the stability of these azido ketones, we investigated the reaction of the mixture of bromo ketones **3** and **4** with lithium azide in *N*,*N*-dimethylformamide at 50 °C. The product **13** was obtained via a smooth reaction. Compound **13** exists as an enamino ketone (^{1}H NMR investigation) and resulted from the epimeric azido ketones **9** and **10** under cleavage of nitrogen (Scheme 2). Further reactions with the pure α-bromo ketone **3** and lithium azide in HMPTA below room temperature and with differing amounts of acetic acid lead to the quantitative formation of the azido ketones **9** and **10**. This reaction succeeds in a relatively short time at 0 °C. As a result of the easy epimerization, both azido ketones were produced in nearly equal amounts. A similar result was found for the reaction of the bromo ketone mixture **3** and **4** with lithium azide/HMPTA/acetic acid below room temperature. The mixture of the azido ketones **9** and **10** was then reduced with sodium borohydride. After separation with MPLC, the *cis*-azido alcohols with 16*β*,17*β*- and 16α,17α-configurations (**11** and **12**) were obtained. To produce the azido ketones **9** and **10** in pure form, the *trans*-azido alcohols **7** and **8** were oxidized (Jones oxidation).[8,12b] Under these conditions, only small amounts of the epimeric azido ketones could be detected (TLC and ^{1}H NMR spectroscopy). Reduction of the pure azido ketones gave the *cis*-azido alcohols **11** and **12**, whose configuration could be determined in this way. In contrast to the stereospecific reduction of the bromo ketones, reduction of the azido ketones also resulted in small amounts of the corresponding *trans*-azido alcohols **7** and **8**.

For comparative conformational investigations, we needed both of the known 17*β*- and 17α-hydroxy compounds **14** and **15** (Scheme 1), which Nambara and coworkers synthesized by reduction of the ketone **2** with sodium borohydride.[5a] Using tetrahydrofuran/MeOH as the solvent, we obtained, as reported by Nambara's group, an excess of the 17*β*-hydroxy compound **14** (**14**:**15** ≈ 3:2). With L-Selectride as the reductant, the proportion of **14** could be raised significantly (**14**:**15** > 9:1). The equally interesting *trans*-bromohydrins **16** and **17** have not yet been reported in the literature. We therefore investigated, if easy cleavage of the C−Br bond in the *cis*-bromohydrins **5** and **6** by heating in dipolar aprotic solvents[13] would result in a practical synthesis of the desired *trans*-bromohydrins **16** and **17**. The 16*β*,17α-bromohydrin **6** could indeed be obtained by heating the 16α,17α-bromohydrin **5** in DMSO and in HMPTA. TLC control showed that the ketone **2** was also formed. Use of HMPTA has the advantage over DMSO that a significantly smaller portion of **2** was produced. The reaction also proceeds in a similar fashion in DMPU (*N*,*N*′-

(12) (a) Ponsold, K.; Pohle, G. *J. Prakt. Chem.* **1967**, *35*, 142. (b) Schönecker, B.; Ponsold, K. *J. Prakt. Chem.* **1971**, *313*, 817.

(13) Schönecker, B.; Ponsold, K.; Grosse, P. *Z. Chem.* **1974**, *14*, 472.

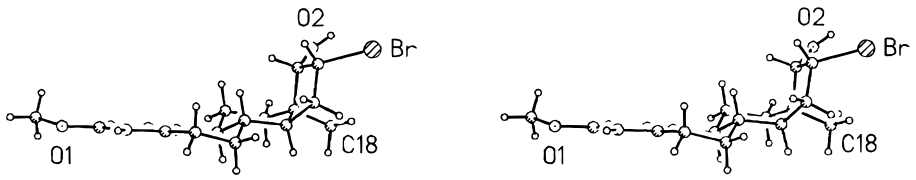


Figure 3. Molecular structure of 16α-bromo-3-methoxy-13α-estra-1,3,5(10)-triene- 17α-ol (**5**) (stereoview).

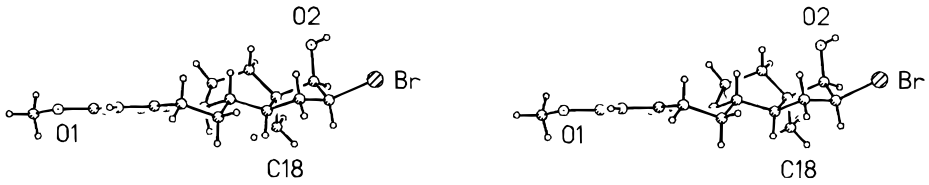


Figure 4. Molecular structure of 16*β*-bromo-3-methoxy-13α-estra-1,3,5(10)-triene- 17*β*-ol (**6**) (stereoview).

dimethyl-propylenurea). Chromatographic separation of the reaction mixture resulted in 60−70% of the *trans*-bromohydrin **16**. The analogous epimerization of the 16*β*,17*β*-bromohydrin **6** to 16α,17*β*-*trans*-bromohydrin **17** succeeded with smaller yields since the elimination reaction to the ketone **2** is preferred, so that only about 12−15% of **17** could be obtained after MPLC. In any case, this epimerization method should be well suited for the synthesis of other new bromo steroids.

We utilized the 16-olefin **20** (Scheme 1), which has also been described by Nambara's group,[5b] for further addition reactions, as well as for the corresponding conformational investigations. For the synthesis of **20** in 74% yield, we reduced the *cis*-bromohydrin mixture with zinc and acetic acid.[5b] Since the epoxidation of **20** with magnesium monoperoxyphthalate does not proceed stereoselectively, we synthesized the equally interesting 16,17-epoxides **18** and **21** from the *trans*-bromohydrins **16** and **17** by ring closure with methanolic potassium carbonate or KOH, respectively.

Conformational Investigations. The solid state conformation of the well-known *cis*-bromohydrins **5** and **6** was investigated by X-ray analysis. For **5** (16α,17α-configuration), the expected conformation (Figure 3) in which the C-ring takes on a chair conformation and the five-membered D-ring a conformation lying between the 13α-envelope and the 13α,14*β*-half-chair form (Δ = 12.5°, see Figure 2) was found. In contrast to **5**, compound **6**, which contains 16*β*- and 17*β*-substituents, exhibits a completely different conformation containing a twist-boat conformation for the C-ring and a 16α-envelope form for the D-ring (Figure 4). Ab initio calculations at the HF/6-31G(d) level of theory confirm that, for both compounds **5** and **6**, the twist-boat conformation is indeed the thermodynamically more stable one. This conformer of **5** is calculated to be 1.7 kcal/mol and that of **6** to be 2.2 kcal/mol more stable than the chair conformer (Table 1).

Figures 3−5 show the molecular structures of **5** and **6** as well as selected torsional angles. The most obvious conformational differences between **5** and **6** are to be found in the C- and D-rings. This is especially evident for the torsion angles over C13−C14 between the neighboring C-atoms in ring C (C12 and C8) and ring D (C17 and C15). These angles are −40.5° and −41.7° in compound **5** and 11.5° and 4.5° in compound **6** (Figure 5). In addition, the torsional angles for the 13α-methyl group (C18) and the 14α-hydrogen with −40° for **5** and 3.4° for **6** show that the methyl group in **6** takes on a quasi-axial

Table 1. Energies, Zero Point Contributions, and Relative Stabilities of Selected Steroids with Twist-Boat C-ring and Chair C-ring Conformations[a]

steroid	conformation	E[b]	ZPE[b]	Δ*E*[b]
5	twist-boat C-ring	−3453.670 604	0.438 480	0.00
	chair C-ring	−3453.668 077	0.438 726	+1.72
6	twist-boat C-ring	−3453.670 673	0.438 406	0.00
	chair C-ring	−3453.667 474	0.438 776	+2.22
14	twist-boat C-ring	−884.354 660	0.448 345	0.00
	chair C-ring	−884.353 033	0.448 557	+1.14

[a] All values were calculated at the HF/6-31G(d) level of theory [b] All energies and zero point energies (ZPE) are given in hartree; the relative energies (Δ*E* values) are in kcal/mol.

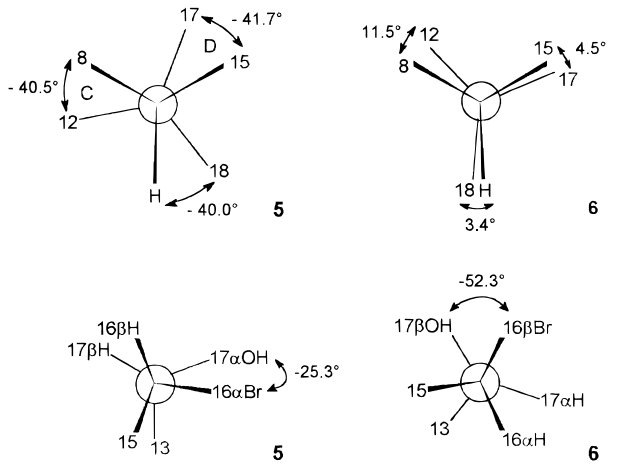


Figure 5. Newman projection of the 16,17-bromohydrins **5** and **6** along the bonds C14−C13 and C16−C17 and torsional angles.

arrangement at the C8−C12-boatlike C-ring with a nearly eclipsed arrangement to the 14α-H. For interactions between the 16- and 17- substituents, the important torsion angles about the C16−C17 bond are for compound **5** −25.3° and for **6** −52.5° (Figure 5). In addition, the drastic conformational changes in the D-ring of **6** is of interest. According to the Dreiding models, the D-ring can, with assistance from the flexible C-ring, in principle accomplish the whole pseudorotation cycle (Δ = +360° and −360°). If one assumes the 13α,14*β*-half-chair to be the basic conformation, then the experimentally observed 16α-envelope form for **6** would have a phase angle Δ = 180° relative to the basic conformation (Figure 2). This suggests that a pseudorotation of a quarter of the entire cycle has already taken place (see Figure 6).

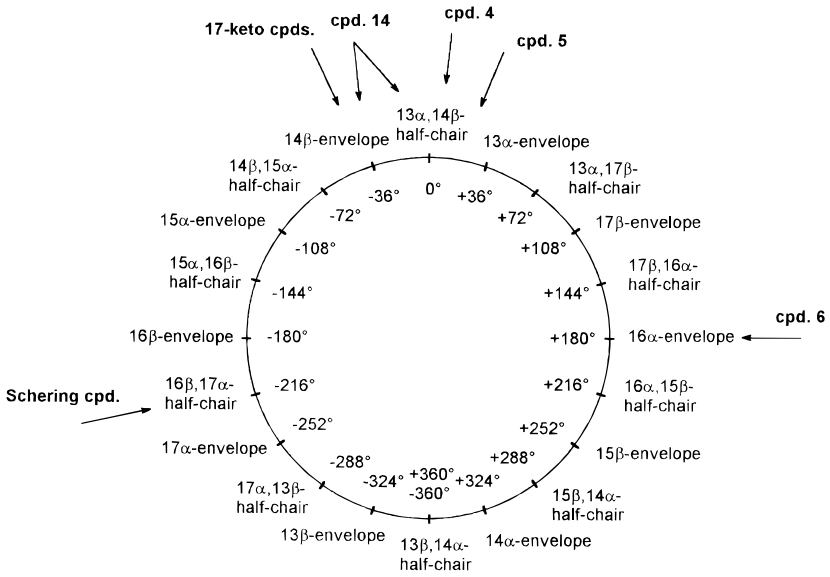


Figure 6. Pseudorotation pathway.

The different conformations of the five-membered ring in 13α-steroids was further investigated via an X-ray analysis of 17*β*-ethinyl-11*β*-(4-fluorphenyl)-17α-hydroxy-13α-methyl-gona-4,9-diene-3-one, which has been described by the Schering group in connection with the investigation of antigestagenic properties of 11*β*,17*β*-disubstituted 19-nor-13α-steroids.[14] A comparison with the data from **6** shows that the Schering compound, probably necessitated through unfavorable steric repulsions of the 17*β*- and 11*β*-substituents in the chair conformation of the C-ring, takes on a C-ring twist-boat conformation that forces the D-ring to assume a 16*β*,17α-half-chair conformation. In addition, molecular mechanics calculations support a twist-boat C-ring conformation for 11*β*-unsubstituted compounds.[15] If one again takes the 13α,14*β*-half-chair conformation of the D-ring as the starting point, pseudorotation in the same direction as for **6** results in an angle for the Schering compound of Δ = 504° (for rotation in the opposite direction Δ = −216°). There lies an absolute value of Δ = 324° (360° meaning inversion of the cyclopentane ring!) between **6** (Δ = 180°) and the Schering compound (Δ = 504°), which demonstrates a large leeway for the conformation of the D-ring in 13α-steroids and further suggests the possibility of realizing preferred conformations of the steroidal framework of 13α-steroids through specific substituent variation. These results indicate that an inverted chiral center at C13 causes a fundamental difference in the framework, which is to be differentiated from the rigid framework of naturally occurring steroids (Figure 1). This offers the unusual possibility of synthesizing compounds having either a normal conformation with a chair C-ring and a conformationally restricted D-ring, (see **5**), as well as compounds displaying a twist-boat C-ring and different D-ring conformations (see **6** and Schering compound).

It would be especially interesting to discover by substituent variation, especially in the D-ring, to what extent a conversion of the C-ring can be accomplished in order to obtain further information about the twist-boat conformation. To consider this question, we reviewed more X-ray data reported for 13α-steroids. For tetrahydroveralkamine hydroiodide (Figure 7) it has been discovered that for the 13α,14α-configuration[16] the molecule possesses a hydrogen atom (18-nor-13α-steroid) instead of a 13-methyl group, a 17*β*-methyl group, a 17α-C-chain with a piperidine ring and a hydroxyl group in 16*β*-position.

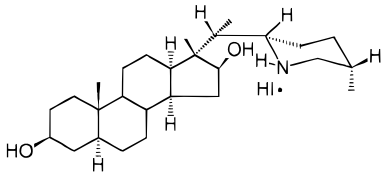


Figure 7. Tetrahydroveralkamine hydroiodide.

Especially noteworthy is the existence of two molecular conformations in the ratio of 2:1. These conformers correspond to a chair form of the C-ring and to a boat conformation of the C-ring, respectively. The existence of a boat conformation is attributed to the lack of unfavorable steric repulsions between 17*β*-methyl group and 8*β*- and 11*β*-hydrogen atoms in this conformation. The fact that a considerable number of molecules with a chair form of the C-ring exist, is explained on the basis of an intramolecular hydrogen bridge between the NH-group of the piperidine ring and the 16*β*-hydroxy group. This causes a deformation of the hydrindane system so that a considerable increase in the distance between the 17*β*-methyl group and the 11*β*-hydrogen atom results. This compound is an example for the conformational flexibility, which can be possible for 13α-steroids. The *N*-acetyl-16-keto compound in which a hydrogen bridge is not possible should, according to ORD measurements, exist in solution purely in the boat form.

Kreiser and co-workers have recently published the X-ray data for 17α-(4-chlorobenzoyloxy)-3-methoxy-13α-gona-1,3,5(10)-triene (also a 18-nor-13α-steroid).[17] This

(14) Herrmann, C.; Hoyer, G.-A.; Neef, G.; Schomburg, D.; Wiechert, R. *Liebigs Ann. Chem.* **1986**, 1317.
(15) Bohl, M.; Schubert, G.; Ponsold, K.; Reck, G.; Höhne, E.; Simon, K. *J. Mol. Graphics* **1989**, *7*, 122.
(16) Höhne, E.; Seidel, I.; Adam, G.; Schreiber, K.; Tomko, J. *Tetrahedron* **1972**, *28*, 4019.
(17) Kuhl, A.; Schollmeyer, D.; Schürmann, M.; Preut, H.; Kreiser, W. *Acta Crystallogr., Sect. C* **1998**, *54*, 521.

compound has, as expected, the C-ring in the chair conformation since the D-ring contains no substituents with β-configuration. The H13−C13−C14−H14 torsion angle (−45.7°) is similar to the corresponding C18−C13−C14−H14 torsion angle for our 16α,17α-bromohydrin **5** (−40°). Detailed results about the molecular structure of 3β-(4-bromobenzoyloxy)-13α-androst-5-en-17-one (13α-steroid with 17-keto group) has been reported by Portheine and Romers.[3b] In this case, the C-ring also displays the chair conformation (no β-substituents in the D-ring, C17 sp^2-hybridized). The torsion angles C17−C13−C14−C15 (−38°) and C12−C13−C14−C8 (−42°) comply with the "equality rule". However, they display a considerable distortion similar to that observed in the α,α-bromohydrin **5** (corresponding torsional angles of −41.7° and −40.5°, see above) and for 17α-(4-chlorobenzoyloxy)-3-methoxy-13α-gona-1,3,5(10)-triene (−40.5° and −45.4°). If a distortion was not present, a torsional angle of about −55° for the C-ring would be expected. This distortion causes the otherwise very short distances between 11β-H and 8β-H and the C17 as well as the 17β-H (in **5**) to be substantially increased. In addition, the D-ring with its sp^2-hybridized C17 shows with $\Delta = -34°$ almost a 14β-envelope conformation. A similar D-ring conformation ($\Delta = -37.1°$) results for a 13α-steroid containing a 17-keto group, a 8(9)-double bond and a 14α-hydroxy group (14α-hydroxy-13α-methyl-1,7,17-trioxo-10β-carbomethoxy-5β-gon-8-ene). As a result of the presence of the double bond, the C-ring takes on a half-chair form.[18]

Our results and the data from the above investigations lead to the hypothesis that 13α-steroids that do not possess 16β- or 17β-substituents generally exhibit the normal steroid conformation containing a C-ring in a chair conformation and a D-ring with a conformation between the 14β- and the 13α-envelope form ($\Delta = -36$ to +36°). 16β- and 17β-substituents can, however, lead to a conversion of the C-ring to a twist-boat in connection with different D-ring conformations. An exception to this is the compound with a 15-double bond, which, despite the absence of 16β- and 17β-substituents, displays a twist-boat conformation of the C-ring. This could be caused by the presence of the 15-double bond[7] in the D-ring of the molecule. This subject will be discussed below in comparison with the 15-enamino ketone **13**.

For the sake of more clearly defining the presented theories, we have carried out X-ray analysis on other compounds of interest. Simultaneous ^{1}H NMR investigations on these compounds have also provided definitive results about the conformations present in solution.

We now discuss the X-ray analyses carried out for the 17-ketone **2**, the 16β-bromo ketone **4** (obtained pure by MPLC-separation of the bromination mixture of **3** and **4**) and for the 17β-hydroxy compound **14** obtained from **2** as the main reduction product. All three compounds exist in the solid state in the normal steroid conformation (Figures 1, 8, and 9).

The D-ring of the 17-ketone **2** has almost an ideal 14β-envelope conformation ($\Delta = -34.9°$) and therefore closely resembles the 13α-androst-5-en-17-one. This can also seen from the torsion angles about the C13−C14 bond, which displays the same flattening of the C-ring as in the 13α-androst-5-en-17-one. This flattening is also observed for compounds **4** and **14**. The 16β-bromo ketone

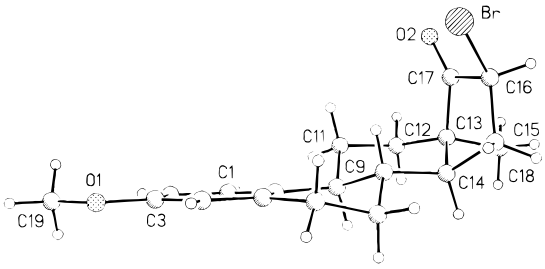


Figure 8. Molecular structure of 16β-bromo-3-methoxy-13α-estra-1,3,5(10)-triene-17-one (**4**).

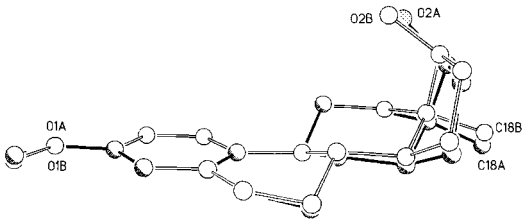


Figure 9. Molecular structure of 3-methoxy-13α-estra-1,3,5-(10)-triene-17β-ol (**14**) (molecule A and B).

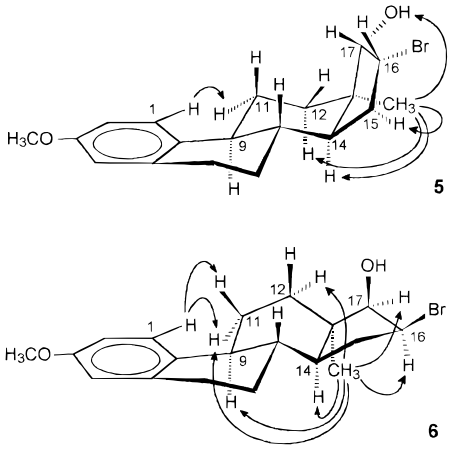


Figure 10. Selected connectivities from 2D-NOESY experiments on the 16,17-bromohydrins **5** and **6**.

4 possesses nearly the 13α,14β-half-chair conformation ($\Delta = 3.7°$). For the 17β-hydroxy compound **14**, two conformations of the D-ring are present in the solid state for which intermolecular hydrogen bridges between the 17β-OH group and 3-methoxy group, have been found. About half of the molecules form two bridges with their 17β-OH group; one to the 3-methoxy group of one molecule and one to the 17β-OH group of another molecule. The remaining half build only one bridge to the 17β-OH group of another molecule. The Δ-values of −36.8° and −2.1° suggest a 14β-envelope and a 13α,14β-half-chair conformation.

Of special interest for the reactivity of this class of compounds, including their biological interactions, is the determination of the conformation in solution. In addition, a comparison to the X-ray data would be meaningful. Simple ball-and-stick model considerations (Figure 10, example bromohydrins **5** and **6**) show that ^{1}H NMR NOESY experiments make discrimination between a C-chair or C-twist-boat conformation possible. In particular, the easily observable signals of the 1-H ($\delta = 7.15$ ppm, respectively. 7.17 ppm, d, 1H, in $CDCl_3$,) and for the 13α-methyl group 18-H ($\delta = 1.13$ ppm, respectively.

(18) Drouin, M.; Ruel, R.; Michel, A. G. *Acta Crystallogr., Sect. C* **1991**, *47*, 1689.

Table 2. Results of 2D-NOESY Experiments on 16,17-Bromohydrines 5 and 6

5		6	
proton (δ/ppm)	cross-peak to proton (δ/ppm)	proton (δ/ppm)	cross-peak to proton (δ/ppm)
1-H (7.17)	11α-H (2.30)	1-H (7.15)	11β-H (1.73)
			11α-H (2.27)
18-H (1.13)	12α-H (1.48)	18-H (1.01)	9α-H (2.28)
	14α-H (1.56)		11α-H (2.27)
	15α-H (2.40)		12α-H (1.45)
	17α-O*H* (2.04)		14α-H (1.34)
			16α-H (4.50)
			17α-H (3.63)

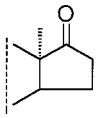
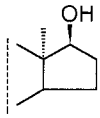
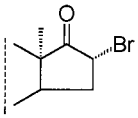
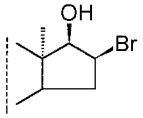
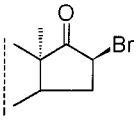
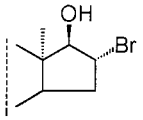
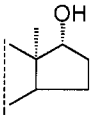
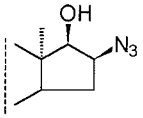
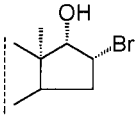
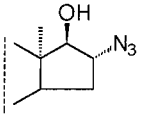
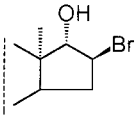
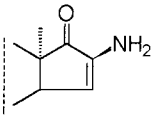
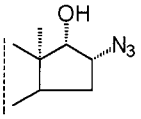
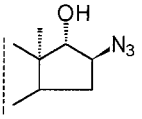
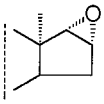
1.01 ppm, s, 3H,) should be suitable as probes. For the classical chair conformation only one cross-peak between the 1H and the 11α-H is to be expected. In the case of the twist-boat conformation, cross-peaks to 11α-H and to 11β-H should be found. For the chair conformation, there should be, in addition to the cross-peaks to the α-protons at the D-ring, another cross-peak between the quasi-equatorial methyl group and the 12α-H. In the twist-boat conformation with a nearly axial arrangement of the methyl group one should observe additional cross-peaks to the 9α- and 11α-protons.

The values for the measured cross-peaks to the bromohydrins **5** and **6** show that the expectations were correct (Table 2). In addition, it can be seen that **5** exists in solution in the classical conformation and **6** in the ring C twist-boat conformation. Characteristic of the latter conformation is the appearance of cross-peaks between 1-H and 11β-H which shows a smaller intensity owing to the greater distance as compared to 11α-H. For the 13α-methyl group (18-H) with twist-boat conformation there appear additional cross-peaks to 11α-H and 9α-H (broad peak due to similar δ-values for 11α-H and 9α-H). The cross-peak of **6** between 18-H and 16α-H displays, moreover, that, similar to the solid state, the D-Ring assumes a conformation approximating the 16α-envelope form.

NMR investigations for the 17-ketone **2** and for the 16β-bromo ketone **4** show also the classical conformation in solution as well as in the solid state. NOESY experiments (cross-peaks 1-H to 11α-H and 11β-H and broad cross-peak 18-H to 9α-H and 11α-H) show that 17β-hydroxy compound **14** exists in solution in the twist-boat conformation. Ab initio calculations on **14** predict, in accordance with the NMR investigations, that the twist-boat conformation is thermodynamically sligthly more stable than the classical one (1.1 kcal/mol at HF/6-31G-(d) level of theory, see Table 1). It is obvious from these findings that the presence of a single 17β-substituent can induce a twist-boat conformation. In addition, 17β-monosubstitution can lead to compounds with flexible conformation (**14**: two C-chair conformations in the solid state, in solution twist-boat conformation). It is suspected that intermolecular hydrogen bridges in the solid state of **14** represent a stabilizing factor for the classical conformation.

For the remaining compounds discussed in the synthesis section, the conformational analyses have been carried out using the NOESY experiments described. The conformations thus determined are summarized in Table 3 for all compounds. All compounds containing a 17α-hydroxy or a 17-keto group display a chair conformation for ring C in solution. It is obvious that a single 16β-substituent (bromo or azide) cannot bring about a conversion to the twist-boat conformation, whereas a 17β-substituent apparently can.

Table 3. Conformations of the Investigated Compounds

C-ring chair		C-ring twist-boat	
2		**14**	
3		**6**	
4		**17**	
15		**11**	
5		**8**	
16		**13**	
12		**20**	
7		**21**	

Another route to producing compounds with a twist-boat conformation is demonstrated by 3-methoxy-16-(4-bromobenzoyloxy)-13α-estra-1,3,5(10),15-tetraene-17-one[7] and 15-enamino ketone **13**. Both compounds are produced from substances containing, in addition to a 17-keto group, a 16-keto or a 16-imino group, which rearranges to the more stable 16-hydroxy-15-ene and 16-amino-15-ene structures during the conversion of C-ring into the twist-boat conformation. In this way, an energetically more favorable conformation of C-ring in conjunction with the flat cyclopentene results. The investigation of the well-known 3-methoxy-13α-estra-1,3,5(10),16-tetraene (**20**) should show if a 16-double bond is adequate to stabilize the twist-boat conformation. Knowledge of the 16,17-epoxides **18** and **21** should show if an incorporation of the strained three-membered ring can actually lead to a twist-boat conformation. Corresponding NMR data confirm that for the olefin **20** and the α-epoxide **21** in solution the twist-boat conformation does exist. Surprisingly, the NMR data for the β-epoxide **18** do not confirm the twist-boat conformation.

This demonstrated second route to the realization of the twist-boat conformation should offer the possibility

Table 4. ^{1}H NMR Data of 13α-Estra-1,3,5(10)-trienes ($CDCl_3$, 250 MHz, δ [ppm])

compd	18-H (s, 3H)	6-H (m, 2H)	16-H	17-H	1-H (d, ^3J = 8.6 Hz, 1H)	other signals[a]
2	1.03	2.81			7.16	
3	1.24	2.81	4.20 (t, ^3J = 9.2 Hz, 1H)		7.15	
4	1.10	2.81	4.55 (dd, ^3J = 9.8, 1.8 Hz, 1H)		7.17	
5	1.13	2.78	4.63 (m,1H)	3.85 (m, 1H)	7.17	
5 + TAI[b]	1.25		4.63 (m,1H)	4.97 (d, ^3J = 7.5 Hz, 1H)		8.46 (s, NH)
6	1.01	2.77	4.50 (m,1H)	3.63 (m, 1H)	7.15	
6 + TAI[b]	1.17		4.50 (m,1H)	5.06 (d, ^3J = 4.2 Hz, 1H)		8.32 (s, NH)
7	0.96	2.80	3.83 (m,1H)	4.01 (m, 1H)	7.19	
7 + TAI[b]	1.06		4.09 (m,1H)	5.34 (d, ^3J = 7.3 Hz, 1H)		8.38 (s, NH)
8	1.14	2.76	3.80 (m,1H)	3.63 (m, 1H)	7.12	
8 + TAI[b]	1.21		4.03 (m,1H)	4.92 (d, ^3J = 5.2 Hz, 1H)		8.30 (s, NH)
9	1.11	2.81	4.11 (dd, ^3J = 9.7, 2.5 Hz, 1H)		7.16	
10	1.09	2.81	3.83 (t, ^3J = 9.7 Hz, 1H)		7.15	
11	0.98	2.80	4.07 (m, 1H)	3.69 (m, 1H)	7.15	
11 + TAI[b]	1.16		3.96 (m, 1H)	5.05 (d, ^3J = 4.5 Hz, 1H)		8.30 (s, NH)
12	0.96	2.79	4.10 (m, 1H)	4.10 (m, 1H)	7.19	
12 + TAI[b]	1.14		4.28 (m, 1H)	5.15 (d, ^3J = 7.5 Hz, 1H)		8.44 (s, NH)
13	1.20	2.77			7.16	6.33 (s, 1H, 15-H)
13 + TAI[b]	1.25					7.83 (s, 1H, 15-H)
						9.49 (s, NH)
						9.90 (s, NH)
14	0.93	2.80		3.80 (m, 1H)	7.17	
14 + TAI[b]	1.06			5.01 (m, 1H)		8.13 (s, NH)
15	0.92	2.78		4.16 (m, 1H)	7.21	
15 + TAI[b]	1.05			5.25 (m, 1H)		8.30 (s, NH)
16	0.93	2.77	4.18 (m, 1H)	4.30 (m, 1H)	7.20	
16 + TAI[b]	1.01		4.34 (m, 1H)	5.68 (d, ^3J = 7.7 Hz, 1H)		8.39 (s, NH)
17	1.22	2.75	4.12 (m, 1H)	3.84 (m, 1H)	7.11	
17 + TAI[b]	1.32		4.25 (m, 1H)	5.24 (d, ^3J = 5.9 Hz, 1H)		8.30 (s, NH)
18	0.94	2.76	3.08 (m, 1H)	3.35 (d, ^3J = 2.4 Hz, 1H)	7.20	
19	0.99	2.76	6.30 (dd, ^3J = 5.8, 2.6 Hz, 1H)	4.13 (br.s, 1H)	7.19	5.87 (m, 1H, 15-H)
19 + TAI[b]	1.08		6.44 (dd, ^3J = 5.8, 2.6 Hz, 1H)	5.35 (d, ^3J = 2.4 Hz, 1H)		5.83 (m, 1H, 15-H)
20	1.01	2.78	5.55 (m, 1H)	5.48 (dd, ^3J = 5.5 Hz, ^4J = 2.1 Hz, 1H)	7.20	
21	1.25	2.66	3.05 (m, 1H)	3.34 (br.s, 1H)	7.20	

[a] Signals with constant values: δ = 3.74−3.76 (s, 3H, CH_3O), 6.54−6.61 (d, ^4J = 2.6−2.8 Hz, 1H, 4-H), 6.68−6.72 (dd, ^3J = 8.6 Hz, ^4J = 2.6−2.8 Hz, 1H, 2-H). [b] Signals after addition of trichloroacetyl isocyanate.

to synthesize compounds with a 17-keto or a 17α-hydroxy function possessing a twist-boat conformation. Since oxygen functions in the 17-position and in the 3-position are essential for receptor mediated biological activities, this route offers, via conformational control (which would vary the distance between the receptor binding sites in 3 and 17), the possibility to investigate the effects of differing geometries of the C- and D-ring on receptor binding activities.

Conclusion

The present investigation of (now) easily obtainable 13α-steroids show that specific synthesis of compounds exhibiting either the classical steroid conformation (C-ring chair, restricted D-ring conformation) or an atypical C-ring twist-boat and flexible D-ring conformation can be accomplished. This degree of freedom in the conformational design of steroids should allow more detailed investigations of the reactivity and interactions of vicinal functions (defined via a variable torsional angle) and should, in addition, lead to a deeper understanding of the binding of metal ions in catalytic reactions. This should true for vicinal amino alcohols and their derivatives. Furthermore, these findings should be applicable in biochemical investigations for demonstrating receptor binding activity of these types of compounds, especially since the discovery of a second estrogen receptor should improve the accuracy of the available biochemical models. On the basis of these and on previous findings, essential knowledge about the energies of the different conformations can be obtained in future from theoretical calculations.

Experimental Section

General Methods. Solvents were purified, dried and distilled according to convential methods. All reactions were carried out using inert conditions. The reactions were monitored by TLC aluminum sheets, silica gel 60 F_{254} (Merck), 0.2 mm, detection by UV (254 nm), and spraying with a solution of concentrated sulfuric acid (80 mL), EtOH (20 mL) and vanillin (20 mg) and heating at 170 °C. For flash chromatography silica gel 60 (Lichroprep Si 60, 40−63 μm, Merck) was used. MPLC was performed on Lichroprep Si 60, 15−25 μm, Merck. Melting points were measured on a Boëtius micromelting point apparatus (corrected values). Mass spectra were determined at 70 eV in the electron impact mode. ^{1}H and ^{13}C NMR spectra were recorded on 250 or 400 MHz spectrometers in $CDCl_3$ (^{1}H NMR 250 or 400 MHz, ^{13}C NMR 62.5 or 100 MHz). Signals were assigned by DEPT, COSY-DQF, TOCSY and NOESY. The relevant ^{1}H NMR data are summarized in Table 4.

Crystal Structure Analysis. The crystallographic data for **2**, **4**, **5**, **6** and **14** are presented in Table 5. The intensity data for all compounds were collected on a Nonius CAD4 diffractometer, using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). Data were corrected for Lorentz and polarization effects and for absorption only for compounds **4**−**6**.[19]

The structures were solved by direct methods (SHELXS[20]) and refined by full-matrix least squares techniques against

(19) *MOLEN*, An Interactive Structure Solution Procedure; Enraf-Nonius: Delft, The Netherlands, 1990.

(20) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467.

Table 5. Crystallographic Data, Structure Solution, and Refinement of 2, 4, 5, 6 and 14

	2	4	5	6	14
crystallized from	methanol	methanol	methanol	methanol	methanol
formula	$C_{19}H_{24}O_2$	$C_{19}H_{23}BrO_2$	$C_{19}H_{25}BrO_2$	$C_{19}H_{25}BrO_2$	$C_{19}H_{26}O_2$
M_r [g mol^{-1}]	284.38	363.28	365.30	365.30	286.40
habit	colorless prism	colorless prism	colorless prism	colorless prism	colorless prism
crystal size [mm^3]	0.40 × 0.38 × 0.36	0.30 × 0.30 × 0.20	0.40 × 0.38 × 0.36	0.40 × 0.38 × 0.36	0.32 × 0.30 × 0.28
crystal system	monoclinic	orthorhombic	monoclinic	orthorhombic	monoclinic
space group	$P2_1$	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$P2_1$
a [Å]	6.989(1)	6.966(1)	6.925(1)	9.362(1)	6.767(1)
b [Å]	7.232(1)	7.914(1)	7.141(1)	11.419(2)	18.818(3)
c [Å]	15.559(3)	30.312(4)	17.085(4)	15.707(1)	12.302(2)
α [deg]	90.0	90.0	90.0	90.0	90.0
β [deg]	99.77(3)	90.0	94.95(1)	90.0	91.79(1)
γ [deg]	90.0	90.0	90.0	90.0	90.0
V [Å^3]	775.0(2)	1671.1(4)	841.7(3)	1679.2(4)	1565.8(4)
Z	2	4	2	4	4
ρ_{calcd} [g cm^{-3}]	1.219	1.444	1.441	1.445	1.215
F(000)	308	752	380	760	624
μ (Mo Kα) [cm^{-1}]	0.77	24.65	24.47	24.53	0.77
T [K]	183	183	183	183	183
scan mode	$\omega-2\theta$ scan	ψ-scan transmin: 0.20 transmax: 0.28	ψ-scan transmin: 0.256 transmax: 0.335	ψ-scan transmin: 0.227 transmax: 0.275	$\omega-2\theta$ scan
θ range [deg]	2.66−27.52	2.66−27.62	2.39−26.28	2.53−27.38	2.73−26.34
no. of measured reflections	3801	2264	2005	2176	7158
no. of independent reflections	1909	2264	1853	2176	6397
no. of observed reflections $F_0 > 4\sigma(F_0)$	1316	1068	1591	1334	4350
R_{int}	0.045		0.024		0.043
no. of parameters/restraints	190/1	199/0	199/1	207/0	587/1
goodness of fit	1.030	1.114	1.080	1.034	1.046
$R1_{obs}/R1_{all}$	0.040/0.086	0.055/0.080	0.041/0.057	0.037/0.057	0.052/0.108
$wR2_{obs}/wR2_{all}$	0.090/0.131	0.114/0.158	0.107/0.117	0.073/0.094	0.112/0.136
Flack parameter	1(2)	0.00(3)	0.01(2)	0.00(2)	0.5(8)
largest difference peak and hole [e Å^{-3}]	0.204/−0.199	0.522/−0.424	1.786/−0.393	0.311/−0.429	0.166/−0.219

Fo^2 (SHELXL-97[21]). For compound **14** and for the hydroxy-group at O2 of **6** the hydrogen atoms were located by difference Fourier synthesis and refined isotropically, the hydrogen atoms of the other structures were included at calculated positions with fixed thermal parameters. All nonhydrogen atoms were refined anisotropically.[21] XP (SIEMENS Analytical X-ray Instruments, Inc.) was used for structure representations.

Computational Details. As a result of the considerable size of the steroids, we restricted our calculations to the HF/6-31G(d) level of theory. Full geometry optimization and harmonic frequency calculations were carried out at this level using the Gaussian 98[22] suite of programs. All zero point energies were scaled by a factor of 0.91.[23] All relative energies reported in this article contain a correction for the zero point energy.

3-Methoxy-13α-estra-1,3,5(10)-triene-17-one (2). A mixture of 3-methoxy-estra-1,3,5(10)-triene-17-one (**1**) (20 g, 70.3 mmol), acetic acid (200 mL) and *o*-phenylendiamine (10.8 g, 100 mmol) was stirred at 130 °C (bath temperature) for 3 h. After cooling the mixture was slowly poured onto ice, and after some time the precipitate was filtered off, washed with water and dried in vacuo. The crude product (19.4 g, mp 110−125 °C) was purified by chromatography on a short column with silica gel and toluene/acetone (20:1) to give **2** as white crystals (15.5 g, 78%, mp 120−130 °C). An analytical sample was obtained by crystallization from MeOH as white crystals: mp 139−141 °C, ref.[10b] mp 130−133 °C; $[\alpha]^{20}_D$ −32 (*c* 0.86, $CHCl_3$), ref.[10b] [α] −27.5 (*c* 0.5, $CHCl_3$). **2** is slightly less polar than **1**.

16α-Bromo- (3) and 16β-bromo-3-methoxy-13α-estra-1,3,5(10)-triene-17-one (4). A mixture of the ketone **2** (9.0 g, 31.6 mmol), benzene (180 mL), MeOH (180 mL) and copper-(II) bromide (14.0 g, 62.7 mmol) was refluxed with stirring for 45 min and after further addition of copper(II) bromide (4.0 g, 17.9 mmol) for further a 45 min. The mixture was filtered after cooling, the residue was washed with benzene and the filtrate was concentrated to a third of the volume. After addition of toluene and a large volume of water the aqueous phase was separated and twice extracted with toluene/ether (1:1). The organic phases were washed twice with aqueous saturated NaCl solution and with water, dried (Na_2SO_4), evaporated and the residue crystallized from MeOH. The crude crystalline product (10.7 g, 93%, **3** and **4**, 2:1) was used for the reduction to the bromo alcohols **5** and **6**. For the substitution reaction to the azido ketones **9** and **10** and to the enamino ketone **13** the crude product was chromatographed using a short silica gel column with toluene/acetone (20:1) and crystallized from MeOH (8.8 g, **3** and **4**, mp 105−111 °C). The pure bromo ketones **3** and **4** were obtained by MPLC using Lichroprep Si 60, 15−25 μm, a column of 200 mm × 35 mm, and ethyl acetate/isohexane 10:90, rate 40 mL min^{-1}. The 16α-bromo ketone **3** is less polar than the 16β-bromo ketone **4**. From 775 mg of the crude product (**3** and **4**) 440 mg of **3** (57%) and 202 mg of **4** (26%) were obtained as white crystals. **16α-Bromo ketone 3:** mp 125−126 °C (MeOH), ref.[5a] mp 122−123 °C (MEOH); $[\alpha]^{20}_D$ −94 (*c* 0.62, $CHCl_3$), ref.[5a] $[\alpha]_D$ −92.1 (*c* 0.12, $CHCl_3$); UV/Vis (MeOH) λ_{max} (ϵ) 212 (9700), 278 (2000), 287 nm (1900 mol^{-1} dm^3 cm^{-1}); IR ($CHCl_3$) ν 1749 cm^{-1} (C=O, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.76 (C18), 28.18 (C7), 28.24

(21) Sheldrick, G. M. *SHELXL-97*, University of Göttingen, Germany, 1993.

(22) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A. Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *GAUSSIAN98, Revision A.5*; Gaussian, Inc.: Pittsburgh, PA, 1998.

(23) Grev, R. S.; Jansen, C. L.; Schaefer, H. F. III. *J. Chem. Phys.* **1991**, *95*, 5128 and references therein.

(C11), 30.15 (C6), 32.59 (C12), 33.54 (C15), 41.13 (C9), 42.14 (C8), 43.20 (C16), 48.33 (C14), 49.95 (C13), 55.20 (H_3CO), 111.88 (C2), 113.55 (C4), 126.91 (C1), 131.27 (C10), 137.68 (C5), 157.60 (C3), 214.67 (C17). HRMS calcd for $C_{19}H_{23}O_2Br$ (M^+): 362.0876. Found: 362.0870. **16*β*-Bromo ketone 4:** mp 150−154 °C (MeOH), ref.[5a] mp 152−154 °C (MeOH); $[\alpha]^{20}_D$ +41 (*c* 0.61, $CHCl_3$), ref.[5a] $[\alpha]_D$ +51.2 (*c* 0.14, $CHCl_3$); UV/Vis (MeOH) λ_{max} (ϵ) 209 (9000), 278 (2000), 286 nm (1900 mol^{-1} dm^3 cm^{-1}); IR ($CHCl_3$) ν 1748 cm^{-1} (C=O, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.57 (C18), 27.71 (C7), 27.72 (C11), 30.31 (C6), 32.09 (C12), 32.49 (C15), 41.36 (C9), 42.40 (C8), 43.16 (C16), 48.67 (C14), 49.78 (C13), 55.20 (H_3CO), 111.90 (C2), 113.50 (C4), 127.09 (C1), 131.52 (C10), 138.05 (C5), 157.50 (C3), 214.14 (C17). HRMS calcd for $C_{19}H_{23}O_2Br$ (M^+): 362.0876. Found: 362.0870.

16α-Bromo-3-methoxy-13α-estra-1,3,5(10)-triene-17α-ol (5) and 16*β*-Bromo-3-methoxy-13α-estra-1,3,5(10)-triene-17*β*-ol (6). To a stirred solution of crude bromo ketones **3** and **4** (6.0 g, 16.5 mmol) in absolute MeOH (100 mL) and absolute THF (100 mL) at 0 °C was added $NaBH_4$ (1.3 g, 34.2 mmol) in small portions. After 30 min acetone (5.0 mL) was added, and the mixture was concentrated in vacuo and slowly poured onto ice and water with stirring. The precipitate was filtered off, washed with water and dried. The crude mixture of the bromo alcohols **5** and **6** (5.6 g, 93%) was chromatographed over silica gel with toluene. The separated compounds were crystallized from MeOH giving 1.60 g of the less polar compound **6** (16*β*Br, 17*β*OH, 27%) and 3.50 g of the more polar compound **5** (16αBr, 17αOH, 58%). **16α,17α-Bromo alcohol 5:** mp 135−137 °C, ref.[5a] mp 128−129 °C; $[\alpha]^{24}_D$ +35 (*c* 0.61, $CHCl_3$), ref.[5a] $[\alpha]^{24}_D$ +32 (*c* 0.25, $CHCl_3$); IR (CCl_4) ν 3557 cm^{-1} (O−H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.23 (C18), 26.30 (C11), 28.64 (C7), 30.16 (C6), 33.32 (C12), 38.09 (C15), 40.11 (C9), 41.08 (C8), 43.26 (C13), 49.32 (C14), 55.20 (H_3CO), 56.75 (C16), 75.02 (C17), 111.91 (C2), 113.35 (C4), 127.19 (C1), 132.51 (C10), 137.73 (C5), 157.42 (C3). HRMS calcd for $C_{19}H_{25}O_2Br$ (M^+): 364.1032. Found: 364.1058. **16*β*,17*β*-Bromo alcohol 6:** mp 125−128 °C, ref.[5a] mp 118−120 °C; $[\alpha]^{23}_D$ +88 (*c* 0.59, $CHCl_3$), ref.[5a] $[\alpha]_D$ +86 (*c* 0.12, $CHCl_3$); IR (CCl_4) ν 3566 cm^{-1} (O−H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.13 (C11), 28.76 (C7), 30.04 (C18), 30.24 (C6), 30.53 (C12), 38.99 (C9), 39.71 (C15), 42.75 (C13), 43.37 (C8), 51.36 (C14), 55.14 (H_3CO), 55.98 (C16), 82.47 (C17), 112.02 (C2), 113.22 (C4), 127.74 (C1), 133.33 (C10), 137.83 (C5), 157.19 (C3). HRMS calcd for $C_{19}H_{25}O_2Br$ (M^+): 364.1032. Found: 364.1035.

16*β*-Azido-3-methoxy-13α-estra-1,3,5(10)-triene-17α-ol (7). To a stirred solution of the bromo alcohol **5** (1.0 g, 2.74 mmol) in HMPTA (8 mL) was added LiN_3 (0.3 g, 6.1 mmol) at 90 °C. After 1 h the reaction mixture was cooled and poured onto ice and aqueous NaCl solution. The white precipitation was filtered off, washed with water and dried. The mixture of **7** (main product) and **2** was crystallized from MeOH to give pure azido alcohol **7** as white crystals (0.59 g, 66%): mp 157−160 °C; $[\alpha]^{20}_D$+65 (*c* 0.94, $CHCl_3$); IR (CCl_4) ν 3638 (O−H, m), 2104 cm^{-1} (N_3, vs). Anal. Calcd for $C_{19}H_{25}O_2N_3$ (327.4): C, 69.70; H, 7.70; N, 12.83. Found: C, 69.81; H, 7.85; N, 12.67.

16α-Azido-3-methoxy-13α-estra-1,3,5(10)-triene-17*β*-ol (8). Bromo alcohol **6** (1.0 g, 2.74 mmol) was reacted with LiN_3 (0.3 g, 6.1 mmol) as described for the synthesis of **7**. The white sticky reaction mixture was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4) and evaporated. The sticky residue was chromatographed on silica gel with toluene giving the following products (from lower to higher polarity): **16*β*,17*β*-Epoxy-3-methoxy-13α-estra-1,3,5(10)-triene (18)** (15 mg, 2%), colorless oil. HRMS calcd for $C_{19}H_{24}O_2$ (M^+): 284.1770. Found: 284.1781. Identical with **18** obtained from bromo alcohol **17** by ring closure (^1H NMR). **3-Methoxy-13α-estra-1,3,5(10)-triene-17-one (2)** (121 mg, 16%), white crystals, identical with **2** obtained from **1** (^1H NMR). **16α-Azido-3-methoxy-13α-estra-1,3,5(10)-triene-17*β*-ol (8)** (430 mg, 48%): mp 69−72 °C (MeOH/acetone); $[\alpha]^{20}_D$ +97 (*c* 0.98, $CHCl_3$); IR (CCl_4) ν 3625 (O−H, m), 2097 cm^{-1} (N_3, vs). Anal. Calcd for $C_{19}H_{25}O_2N_3$ (327.4): C, 69.70; H, 7.70; N, 12.83 Found: C, 70.13; H, 7.91; N, 12.70. **3-Methoxy-13α-estra-1,3,5(10),15-tetraene-17*β*-ol (19)** (102 mg, 13%), colorless oil. HRMS calcd for $C_{19}H_{24}O_2$ (M^+): 284.1770. Found: 284.1772.

16*β*-Azido-3-methoxy-13α-estra-1,3,5(10)-triene-17-one (9). The azido alcohol **7** (435 mg, 1.33 mmol) was dissolved in absolute acetone (25 mL) using ultrasound. The stirred solution was treated at 0 °C dropwise with a solution of Jones reagent (1.3 mL, 8 N CrO_3 solution in concentrated H_2SO_4). After 20 min a small amount of *2*-propanol was added and after a further 10 min H_2O and ice were added. The white precipitate was filtered off and dried (396 mg of **9**, 92%, a small amount of the epimeric azido ketone **10** is detectable by ^1H NMR), mp 135−145 °C. Crystallization from MeOH/acetone give a pure product of **9**: mp 143−145 °C; $[\alpha]^{20}_D$ −247 (*c* 0.97, $CHCl_3$); IR (CCl_4) ν 2105 (N_3, vs), 1750 cm^{-1} (C=O, s). Anal. Calcd for $C_{19}H_{23}O_2N_3$ (325.4): C, 70.13; H, 7.13; N, 12.91. Found: C, 70.36; H, 7.26; N, 12.88.

16α-Azido-3-methoxy-13α-estra-1,3,5(10)-triene-17-one (10). A stirred solution of the azido alcohol **8** (200 mg, 0.61 mmol) in absolute acetone (10 mL) was treated at 0 °C dropwise with a solution of Jones reagent (0.6 mL, 8 N CrO_3 solution in concentrated H_2SO_4). After 20 min a small amount of 2-propanol was added and after further 10 min the solution was poured into ice and water. After extraction with CH_2Cl_2 the organic phase was washed with H_2O and dried (Na_2SO_4). After evaporation the oily product was crystallized with MeOH (154 mg of **10**, 78%). Recrystallization from MeOH gave pure **10** (107 mg): mp 91−95 °C; $[\alpha]^{20}_D$ +83 (*c* 0.89, $CHCl_3$); IR (CCl_4) ν 2098 (vs, N_3), 1749 cm^{-1} (s, C=O). Anal. Calcd for $C_{19}H_{23}O_2N_3$ (325.4): C, 70.13; H, 7.13; N; 12.91. Found: C, 69.93; H, 7.34; N, 12.47.

16*β*-Azido-3-methoxy-13α-estra-1,3,5(10)-triene-17*β*-ol (11). $NaBH_4$ (25 mg, 0.66 mmol) was added to a stirred solution of the azido ketone **9** (100 mg, 0.31 mmol) in absolute MeOH (2 mL) and absolute THF (2 mL) at 0 °C. After 20 min the reaction mixture was poured into ice and water and extracted with CH_2Cl_2. The organic phase was washed with water, dried and evaporated. The oily residue was purified by thin-layer chromatography over silica gel (Merck, 60 F_{254}, 1 mm) with *n*-heptane/ethyl acetate (5:1) giving the *cis*-azido alcohol **11** (70 mg, 69%) and the *trans*-azido alcohol **7** (10 mg, 10%). **11**: white crystals, mp 103−104 °C (MeOH); identical with compound **11** obtained by MPLC (s. below; ^1H NMR). **7**: white needles, identical with **7** obtained from the bromo alcohol **5** (^1H NMR).

16α-Azido-3-methoxy-13α-estra-1,3,5(10)-triene-17α-ol (12). $NaBH_4$ (65 mg, 1.71 mmol) and the azido ketone **10** (150 mg,0.46 mmol) was reacted in absolute MeOH (5 mL) and absolute THF (3.5 mL) as described for the synthesis of **11** giving a 85:15 mixture of the azido alcohols **12** and **8** (^1H NMR analysis) as a colorless oil (130 mg). Chromatographic purification using a short column with silica gel and toluene/acetone (20:1) and following crystallization with *n*-heptane furnished **12** as white crystals (83 mg, 55%, mp 75−78 °C, a small amount of the *trans*-azido alcohol **8** was detected by ^1H NMR analysis). This compound is identical with **12** obtained by MPLC (see below, ^1H NMR).

Synthesis of the Azido Alcohols (11) and (12) from the Bromo Ketones (3) and (4). A purified mixture of the bromo ketones **3** and **4** (1.0 g, 2.75 mmol) was dissolved in HMPTA (16 mL) and acetic acid (1 mL). The solution was cooled to 0 °C and lithium azide (0.5 g, 10.2 mmol) was added to the stirred solution. After 2 h at 0 °C the reaction mixture was poured into ice and water. The precipitate of the azido ketones **9** and **10** was filtered off, washed with water and dried in vacuo ($CaCl_2$). The product (860 mg, 2.64 mmol, 96% related to **3** and **4**, mixture of **9** and **10**, about 1:1, ^1H NMR analysis) was dissolved with stirring in absolute MeOH (15 mL) and absolute THF (15 mL). The solution was cooled to 0 °C and $NaBH_4$ (400 mg, 10.5 mmol) was added in portions with stirring. After 1 h the mixture was poured into ice and water and extracted with CH_2Cl_2. The organic phase was washed with water and dried (Na_2SO_4). Evaporation gave a yellow oil (840 mg), which was purified and separated by MPLC using Lichroprep Si 60, 15−20 μm (Merck Nr. 9336), *n*-hexane/CH_2Cl_2/ethyl acetate (70:25:5), rate 25 mL min^{-1}. Separation of 2 × 420 mg of the yellow

oil with a column of 380 mm × 30 mm furnished the four azido alcohols **11** (16*β*,17*β*; 355 mg, 39% related to the bromo ketone mixture, white needles), **12** (16α,17α; 215 mg, 24%, white plates), **8** (16α,17*β*; 44 mg, 5%, identical by ^{1}H NMR analysis and TLC with the product from the substitution reaction) and **7** (16*β*,17α; 33 mg, 4%, identical by ^{1}H NMR analysis and TLC with the product from the substitution reaction). **11**: mp 103−104 °C (MeOH); $[\alpha]^{20}_D$ +178 (*c* 0.89, $CHCl_3$); IR (CCl_4) *ν* 3625 (O−H, w), 3570 (O−H, m), 2104 cm^{-1} (N_3, vs). Anal. Calcd for $C_{19}H_{25}O_2N_3$ (327.4): C, 69.70; H, 7.70; N, 12.38. Found. C, 69.59; H, 7.77; N, 12.60. **12**: mp 82−84 °C (MeOH); $[\alpha]^{20}_D$ +26 (*c* 0.78, $CHCl_3$); IR (CCl_4) *ν* 3630 (O−H, w), 3574 (O−H, m), 2107 cm^{-1} (N_3, vs). Anal. Calcd for $C_{19}H_{25}O_2N$ (327.4): C, 69.70, H, 7.70; N, 12.38. Found: C, 69.82; H, 7.83; N, 12.58.

16-Amino-3-methoxy-13α-estra-1,3,5(10),15-tetraene-17-one (13). To a stirred solution of a purified mixture of the bromo ketones **3** and **4** (1.0 g, 2.75 mmol) in *N*,*N*-dimethylformamide (10 mL) was added NaN_3 (600 mg, 9.2 mmol) at room temperature. After 2 h at room temperature and 2 h at 50 °C the reaction mixture was cooled and poured into ice and water. The yellow precipitate of **13** was filtered off, washed and dried in vacuo (770 mg of **13**, 95%): mp 128−140 °C; $[\alpha]^{20}_D$ +4 (*c* 0.95, $CHCl_3$); UV (MeOH) λ_{max} (ϵ) 279 nm (7900); IR (CCl_4) *ν* 3488 (ms), 3387 (ms), 1706 (vs), 1650 (s), 1611 (s), 1584 cm^{-1} (ms). HRMS calcd for $C_{19}H_{23}O_2N$ (M^+): 297.1723. Found 297.1732. Anal. Calcd for $C_{19}H_{23}O_2N$ (297.4): C, 76.73; H, 7.79; N, 4.71. Found: C, 75.67; H, 7.76; N, 4.74.

3-Methoxy-13α-estra-1,3,5(10)-triene-17*β*-ol (14) and 3-Methoxy-13α-estra-1,3,5(10)-triene-17α-ol (15). A: Reduction of 2 with $NaBH_4$. To a stirred solution of **2** (2.0 g, 7.0 mmol) in absolute MeOH (60 mL) and absolute THF (50 mL) $NaBH_4$ (600 mg, 15.8 mmol) was added in portions at 0 °C. After stirring for 3 h at room temperature acetone (4 mL) was added. After some minutes ice and water were slowly added to the mixture. The precipitate was filtered off, washed with water and dried in vacuo (1.92 g). The mixture was chromatographed at silica gel with toluene/acetone (100:1). **14**: less polar 17*β*-hydroxy compound (1.10 g, 3.8 mmol, 55%), mp 77−78 °C (MeOH), ref.[5a] mp 77−78 °C (MeOH); $[\alpha]^{20}_D$ +98 (*c* 0.46, $CHCl_3$), ref.[5a] $[\alpha]_D$ +96 (*c* 0.13, $CHCl_3$); IR ($CHCl_3$) *ν* 3625 cm^{-1} (s); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 26.20 (C15), 8.93 (C7), 29.02 (C11), 29.77 (C18), 30.53 (C6), 31.38 (C12), 33.16 (C16), 40.09 (C9), 42.16 (C8), 44.38 (C13), 51.46 (C14), 55.18 (H_3CO), 83.51 (C17), 111.81 (C2), 113.29 (C4), 127.44 (C1), 133.37 (C10), 138.25 (C5), 157.17 (C3). **15**: more polar 17α-hydroxy compound (0.73 g, 2.5 mmol, 36%), mp 140−143 °C (MeOH), ref.[5a] mp 134−136 °C (MeOH); $[\alpha]^{20}_D$ +21 (*c* 0.16, $CHCl_3$), ref.[5a] $[\alpha]_D$ +9.5 (*c* 0.11, $CHCl_3$); IR ($CHCl_3$) *ν* 3625 cm^{-1} (s); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 22.48 (C18), 23.93 (C15), 26.57 (C11), 28.53 (C7), 30.03 (C16), 30.50 (C6), 33.00 (C12), 42.25 (C9), 42.30 (C8), 43.47 (C13), 50.26 (C14), 55.19 (H_3CO), 74.20 (C17), 111.64 (C2), 113.50 (C4), 126.87 (C1), 132.47 (C10), 138.28 (C5), 157.38 (C3).

B: Reduction of (2) with L-Selectride. To a stirred solution of **2** (1.0 g, 3.5 mmol) in absolute THF (30 mL) was added a solution of L-Selectride (10 mL, 1 M, THF) dropwise at 0 °C. After 1.5 h at room temperature MeOH (5 mL) and methanolic KOH (5 mL, 3%) were added. After cooling to 0 °C H_2O_2 (30% aqueous solution) was slowly added. The white precipitate was dissolved by addition of water. After extraction with CH_2Cl_2 the organic phase was washed with aqueous $FeSO_4$ solution and with water, dried and evaporated. The yellow oil (1.0 g) was chromatographed on silica gel with toluene/acetone (100:1). **14**: white crystals, 782 mg (78%), identical with **14** from $NaBH_4$ reduction (^{1}H NMR). **15**: white crystals, 84 mg (8.4%), identical with **15** from $NaBH_4$ reduction (^{1}H NMR).

16*β*-Bromo-3-methoxy-13α-estra-1,3,5(10)-triene-17α-ol (16). A stirred solution of bromo alcohol **5** (1.0 g, 2.74 mmol) in DMPU (15 mL) was heated at 70 °C for 2 h. After cooling, ice and water were added to the solution. The precipitate was filtered off, washed with water and dried in vacuo (white solid, 992 mg). The mixture was chromatographed on silica gel with toluene and toluene/acetone (100:1). **Ketone 2:** 320 mg (32%), white crystals. **Bromo alcohol 16:** 590 mg (59%), white crystals, mp 130−133 °C. Recrystallization from MeOH gives an analytical pure substance: mp 132−135 °C; $[\alpha]^{20}_D$ +27 (*c* 0.74, $CHCl_3$); IR (CCl_4) *ν* 3618 cm^{-1} (O−H, m). Anal. Calcd for $C_{19}H_{25}O_2Br$ (365.3): C, 62.47; H, 6.90; Br, 21.87. Found: C, 62.67; H, 6.75; Br, 21.63.

16α-Bromo-3-methoxy-13α-estra-1,3,5(10)-triene-17*β*-ol (17). A stirred solution of the bromo alcohol **6** (2.0 g, 5.47 mmol) in DMPU (30 mL) was heated at 70 °C for 5 h. After treatment as described for the synthesis of **16** a yellow solid (1.68 g) was obtained, which was purified and separated by MPLC over Lichroprep Si 60, 15−20 *μ*m (Merck 9336), *n*-hexane/CH_2Cl_2/ethyl acetate (70:25:5), rate 60 mL min^{-1}. Separation of 2 × 0.84 g of the yellow solid using a column of 420 mm × 45 mm furnished the following products: starting material **16** (34 mg, 1.7%, white crystals), ketone **2** (1.05 g, 53%, white crystals), and bromo alcohol **17** (250 mg, 12.5%, colorless oil). **17** was crystallized from *n*-heptane giving 180 mg of white crystals: mp 81−85 °C; $[\alpha]^{20}_D$ +87 (*c* 0.84, $CHCl_3$); IR (CCl_4) *ν* 3606 cm^{-1} (O−H, m). HRMS calcd for $C_{19}H_{25}O_2Br$ (M^+): 364.1032. Found: 364.1050. Anal. Calcd for $C_{19}H_{25}O_2$-Br (365.2): C, 62.47; H, 6.90; Br, 21.87. Found: C, 62.52; H, 7.07; Br, 21.83.

16*β*,17*β*-Epoxy-3-methoxy-13α-estra-1,3,5(10)-triene (18). A mixture of bromo alcohol **17** (75 mg, 0.20 mmol), THF (2 mL) and methanolic KOH (3%, 4 mL) was heated with stirring at 60 °C for 30 min. After cooling, ice and water were added. The white precipitate was filtered off, washed with water and dried in vacuo (white powder, 52 mg, 91%); mp 86−89 °C. Crystallization with MeOH gives **18** as white crystals (17 mg): mp 89−93 °C; $[\alpha]^{20}_D$ +13 (*c* 0.82, $CHCl_3$). HRMS calcd for $C_{19}H_{24}O_2$ (M^+): 284.1770. Found: 284.1772.

3-Methoxy-13α-estra-1,3,5(10),16-tetraene (20). A mixture of bromo alcohols **5** and **6** (790 mg, 2.16 mmol), dissolved in acetic acid (15 mL), was treated with Zn powder (1.33 g, 20.3 mmol). The reaction mixture was heated with stirring under reflux for 1 h. After cooling and filtration ice and water were added and the mixture was extracted with CH_2Cl_2 (three times). The organic phases were washed with aqueous $NaHCO_3$ solution (twice) and water, dried and evaporated. The oily residue (562 mg) was chromatographed over silica gel with *n*-heptane and *n*-heptane/ethyl acetate (95:5) giving **20** as a colorless oil (430 mg, 74%), ref.[5b] colorless oil; $[\alpha]^{20}_D$ −7 (*c* 0.36, $CHCl_3$). MS (EI, 70 eV): *m*/*z* 268 (M^+ 100).

16α,17α-Epoxy-3-methoxy-13α-estra-1,3,5(10)-triene (21). To a stirred solution of the bromo alcohol **16** (500 mg, 1.37 mmol) in absolute MeOH (5 mL) was added methanolic K_2CO_3 (10 mL, 5%) at 60 °C. The reaction mixture was stirred at 60 °C for 30 min. After cooling, ice and water were added. The white precipitate of **21** was filtered off, washed with water and dried under vacuo (white crystals, 364 mg, 93%): mp 120−122 °C; $[\alpha]^{20}_D$ +166 (*c* 0.98, $CHCl_3$). Anal. Calcd for $C_{19}H_{24}O_2$ (284.4): C, 80.24; H, 8.50. Found: C, 79.95; H, 8.85.

Acknowledgment. We thank Prof. S. Schwarz (Jenapharm GmbH & Co. KG) and Prof. W. Kreiser (Universität Dortmund) for useful discussion on the synthesis of 13α-steroids. Financial support by the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich 436) is gratefully acknowledged. We would also like to thank the Schering AG and the Jenapharm GmbH & Co. KG for their gift of steroids.

JO000108X