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Synthesis of novel halogen-containing D-homoestrone and 13α-D-homoestrone derivatives by Lewis acid-induced intramolecular Prins reaction

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Dedicated to Professor Lutz F. Tietze on the occasion of his 60th birthday

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Abstract—A simple synthetic route has been developed for the synthesis of 16-halo-D-homosteroids in both the normal and 13-epiestrone series by the Lewis acid-catalyzed cyclization of an unsaturated secoestrone aldehyde and its 13α isomer. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Halogen-containing estrogens are of great importance in the diagnosis[1] and chemotherapy[2] of estrogen receptor-positive human breast tumors. Introduction of halogens into steroidal hormones usually does not affect, but it may enhance the receptor affinity, while at the same time it reduces the tumorigenicity.[3] Additionally, these drugs are often associated with increased potency in consequence of the suppression of undesired metabolic reactions and the reduced binding to serum proteins.[4] Consequently, efforts have been directed toward the synthesis of such analogs of estrogens that are hormonally inactive or at least have a favorable ratio of tumor inhibitory to hormonal activity. Besides the substitution of the strongly electronegative halogens onto the sterane skeleton, other structural modifications, such as D-ring expansion[5] or/and 13-epimerization might alter the receptor site affinity appropriately and result in a reduction of the estrogenic activity of the sex hormone analogs.

Herein we report a stereoselective synthesis of some halogenated D-homoestrone and 13α-D-homoestrone derivatives by means of internal Lewis acid-induced Prins reactions of an unsaturated secoestrone aldehyde and its 13-epimer. The acid-catalyzed cycloaddition of olefinic aldehydes via an intramolecular Prins mechanism generally proceeds by a stepwise ionic pathway. First a β-hydroxy-carbocation is formed by addition of the alkene moiety to the formyl carbon; this is followed by the entry of a nucleophile to give a substituted cycloadduct or result in homoallyl alcohols by elimination. The ratio of the two products is determined mainly by the reaction conditions.[6]

During preliminary experiments, we have synthesized the 3-methyl and 3-benzyl ethers of the secoestrone aldehyde **1a**[8a] and **1b**[8b] via a multistep pathway from estrone 3-methyl and benzyl ether in the normal series. After epimerization of estrone 3-methyl ether, the similar fragmentation was carried out in the 13α series to produce **6**.[†]

We recently reported the Lewis acid-catalyzed aza-Prins cycloaddition of olefinic arylimines **3**, derived from **1a** and substituted anilines **2**, to give 16β-halo-D-homoestrone derivatives **4** (Scheme 1).[7] All of these reactions exhibited high chemo- and stereoselectivity, and homoallylic amines were not produced by elimination. Our aim was next to investigate whether the cyclization of the secoaldehyde **1** and its 13-epimer **6** follows the above stereo- and chemoselectivity.[9] The unsaturated aldehydes **1** and **6** were expected to undergo Prins reactions on treatment with a Lewis acid, via the corresponding oxonium ions **5** and **7**.

2. Results and discussion

The 3-methyl or 3-benzyl ether of aldehyde **1a** or **1b** was

Keywords: cycloadditions; D-homosteroids; halogenation; ring expansion; stereoselectivity.

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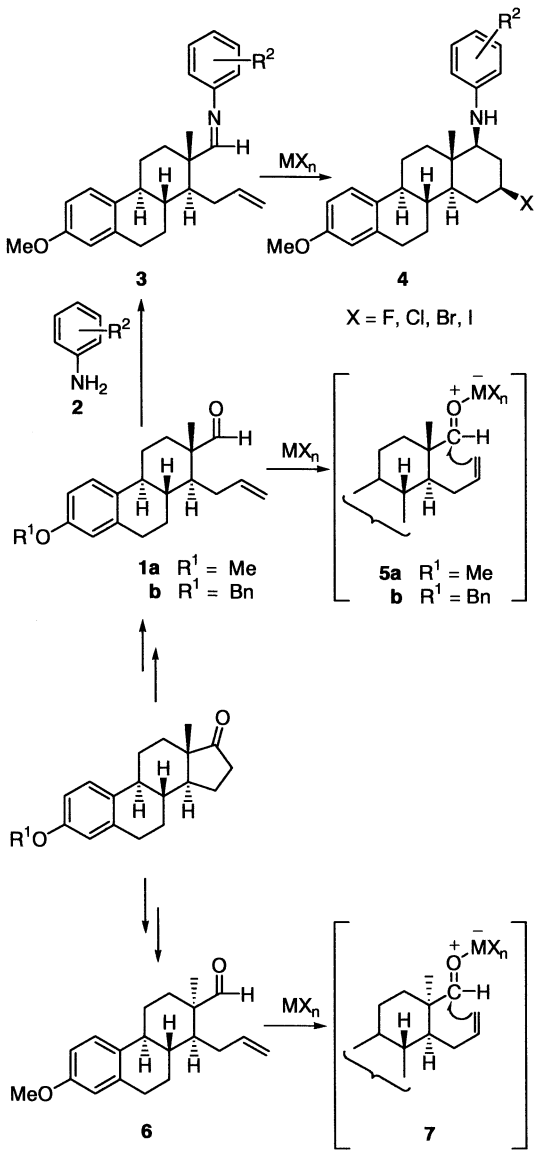
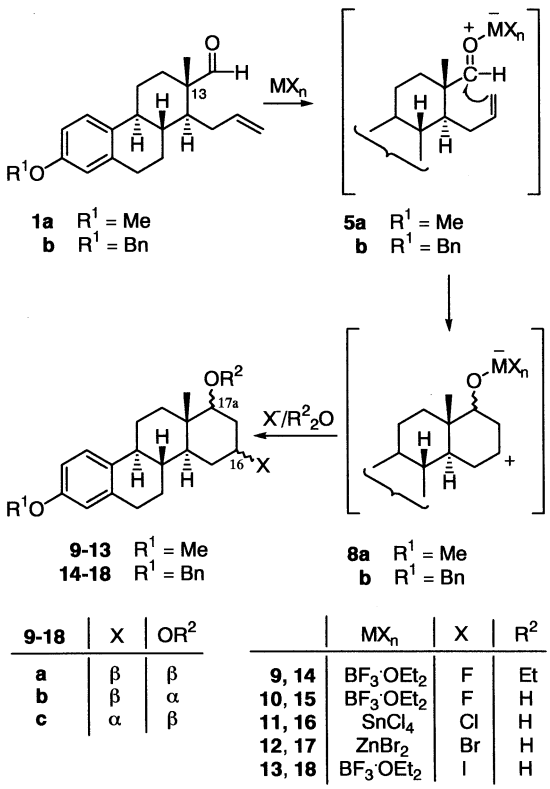


Scheme 1. Synthesis of 17aβ-arylamino-16β-halo-D-homosteroids by internal aza-Prins cyclization via the olefinic arylimines **3**, and the proposed formation of oxonium salts **5** and **7** from the normal and 13-epiestrone derivatives **1** and **6**; MX_n=Lewis acid.



9-18	X	OR^2
a	β	β
b	β	α
c	α	β

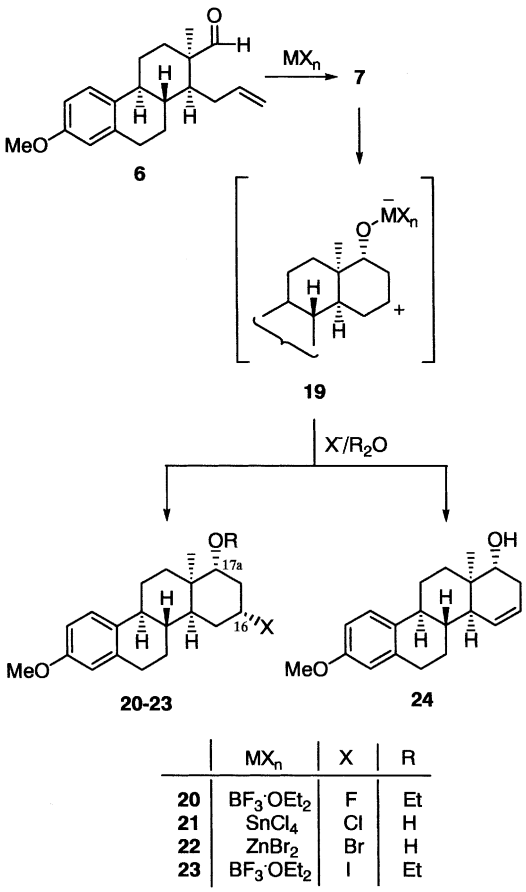
	MX_n	X	R^2
9, 14	$BF_3{\cdot}OEt_2$	F	Et
10, 15	$BF_3{\cdot}OEt_2$	F	H
11, 16	$SnCl_4$	Cl	H
12, 17	$ZnBr_2$	Br	H
13, 18	$BF_3{\cdot}OEt_2$	I	H

Scheme 2. Synthesis of 16-halogenated D-homosteroid analogs **9**–**18** from the estrone derivatives **1a** and **1b**.

treated with 1.1 equiv. of $BF_3{\cdot}OEt_2$, $SnCl_4$ or $ZnBr_2$ or a 5-fold excess of anhydrous NaI in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 to give the corresponding halohydrins chemoselectively; the formation of homoallylic alcohols was not observed. Furthermore, all transformations proceeded in a highly stereoselective manner; only two of the four possible isomers were isolated: the 16β-halo-17aβ-hydroxy-D-homosteroids (**10a**–**13a** and **15a**–**18a**) as main products and the 16β-halo-17aα-hydroxy isomers (**10b**–**13b** and **15b**–**18b**) as minor products (Scheme 2). The reason for the application of the 3-benzyl ether fragment **1b** is that the benzyloxy group can easily be removed by catalytic hydrogenation to give the potentially more active 3-hydroxy derivative. We believe that the compounds are obtained in a two-step mechanism from the initially formed oxonium ion **5** via the secondary carbocation **8** as an intermediate. The cation **8** could be further transformed by the addition of a halide as a nucleophile. The favored formation of the 16β,17aβ diastereomers can be explained by addition of the alkene moiety to the oxonium ion *anti* to the angular methyl group in **5**, while the subsequent addition of the nucleophile to the cation **8** takes place *syn* to the angular methyl group.

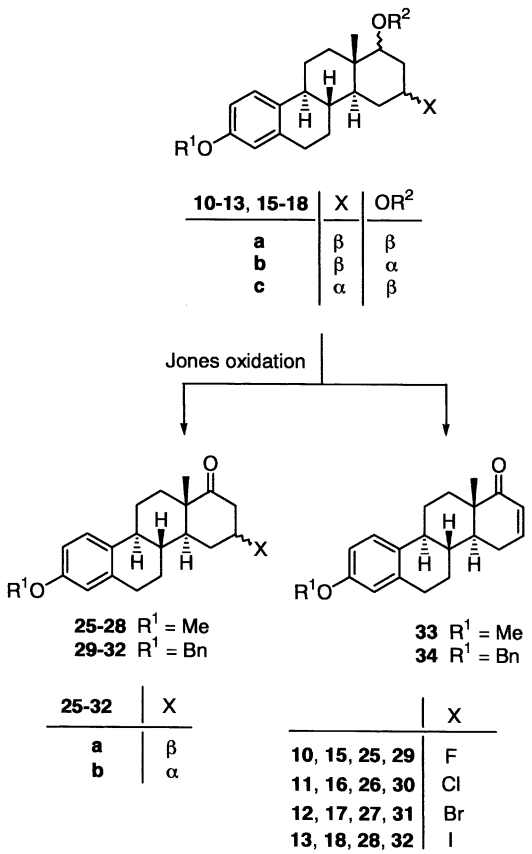
Accordingly, the 17a-hydroxy group and the 16-halogen, both take up the β position, to result in a *cis* product. The entry of the halogen from this direction is not surprising since it probably prefers an equatorial orientation. One additional isomer (**10c** or **15c**) was isolated by using $BF_3{\cdot}OEt_2$ in CH_2Cl_2 to obtain fluoro derivatives. The smaller size of the fluorine atom, comparable to that of hydrogen, could explain the entry from the 16α or 16β position, although in this case the 16β-fluorinated product predominates. During the fluorination, the 17a-ethyl ethers **9a**,**b** and **14a**,**b** were also produced by transetherification of the 17a-hydroxy group with the applied $BF_3{\cdot}OEt_2$, but in overall amounts of less than 5%. Interestingly, this transetherification proved to be predominant when the same $BF_3{\cdot}OEt_2$-initiated cyclization was carried out with the 13α-secoaldehyde **6** (Scheme 3).

The reaction of **6** with 1.1 equiv. of $BF_3{\cdot}OEt_2$ in ice-cold CH_2Cl_2 afforded a single 16-fluorinated-17-ethoxy isomer **20**, while only **23** was obtained when a 5-fold excess of anhydrous NaI in dichloromethane containing 1.1 equiv. of $BF_3{\cdot}OEt_2$ was reacted under reflux. In the latter case, in contrast with the ring closure of the normal secoaldehyde **1**, the stoichiometric amount was needed to accomplish the transformation, instead of a catalytic amount of $BF_3{\cdot}OEt_2$. In spite of the fact that both the propenyl side chain and the formyl group have β orientation in **6**, the rates of reaction in the 13α series and the reactivity of **6** during all cyclizations



	MX_n	X	R
20	$BF_3{\cdot}OEt_2$	F	Et
21	$SnCl_4$	Cl	H
22	$ZnBr_2$	Br	H
23	$BF_3{\cdot}OEt_2$	I	Et

Scheme 3. Synthesis of 16-halogenated D-homosteroid analogs **20**–**24** in the 13α series.



Scheme 4. Oxidation of 16-halo-D-homoestrone derivatives.

were reduced in comparison with those for the normal aldehyde **1**. On treatment of **6** with $ZnBr_2$, two different types of product were produced: the corresponding 16-bromo-17-hydroxy derivative **22** and a homoallylic alcohol **24**, in a nearly 1:1 ratio. In spite of the similar reaction conditions, this was the only case when the formation of the homoallylic alcohol was detected. While the $SnCl_4$-induced cyclization of the normal aldehyde furnished two types of compound (**11a** and **11b** or **16a** and **16b**), the same reaction in the 13-*epi* series resulted stereospecifically in only one product (**21**).

All the experimental results demonstrated that the Prins reaction exhibited high stereoselectivity, which was definitely more expressed in the 13-*epi* series (Table 1). The structural identification of all products was carried out by NMR spectroscopy; the stereochemistry at C-16 and C-17a in ring D of the normal D-homosteroids (**10a**–**13a**, **15a**–**18a**) follows from the 17aα-H doublet-like multiplet at around δ=3.2 (there is a broad singlet at around δ=3.5 for 17aβ-H in **10b**–**13b** and **15b**–**18b**), and from the 16-H multiplet at around δ=3.9–5.0, which corresponds to two diaxial and two axial–equatorial couplings.

The spatial orientation of the 17a-hydroxy function was also

Table 1. Products of the cyclizations of **1** and **6** in the presence of different Lewis acids

Entry	Substrate	Lewis acid (equiv.)	Overall yield (%)	Products	Ratio[a]
1	**1a**	$BF_3{\cdot}OEt_2$ (1.1)	90	**9a**+**9b**	5[b]
				10a+**10b**+**10c**	65:12:8
2	**1a**	$SnCl_4$ (1.1)	83	**11a**+**11b**	73:10
3	**1a**	$ZnBr_2$ (1.1)	84	**12a**+**12b**	69:15
4	**1a**	$BF_3{\cdot}OEt_2$ (0.17), NaI (5)	80	**13a**+**13b**	72:8
5	**1b**	$BF_3{\cdot}OEt_2$ (1.1)	90	**14a**+**14b**	3[b]
				15a+**15b**+**15c**	71:9:7
6	**1b**	$SnCl_4$ (1.1)	80	**16a**+**16b**	75:5
7	**1b**	$ZnBr_2$ (1.1)	85	**17a**+**17b**	78:7
8	**1b**	$BF_3{\cdot}OEt_2$ (0.17), NaI (5)	71	**18a**+**18b**	65:6
9	**6**	$BF_3{\cdot}OEt_2$ (1.1)	75	**20**	75
10	**6**	$SnCl_4$ (1.1)	93	**21**	93
11	**6**	$ZnBr_2$ (1.1)	90	**22**+**24**	45:45
12	**6**	$BF_3{\cdot}OEt_2$ (1.1), NaI (5)	78	**23**	78

[a] Determined after purification by column chromatography.
[b] **9a**,**b** and **14a**,**b** were not separated in pure form.

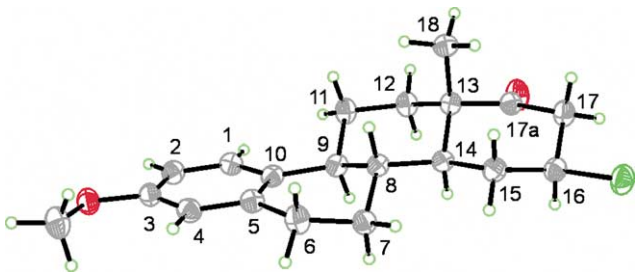


Figure 1. X-ray crystal structure of **26a** with partial atom numbering.

Table 2. Products of oxidation with the Jones reagent

Substrate(s)	Overall yield (%)	Products	Ratio[a]
10a+10b+10c	91	**25a+25b+33**	59:7:25
10a	87	**25a+33**	55:32
11a+11b	97	**26a+33**	62:35
11a	96	**26a+33**	60:36
12a+12b	94	**27a+33**	63:31
12a	92	**27a+33**	60:32
13a+13b	90	**28a+33**	62:28
13a	88	**28a+33**	58:30
15a+15b+15c	95	**29a+29b+34**	61:9:25
15a	94	**29a+34**	62:32
16a+16b	95	**30a+34**	65:30
16a	94	**30a+34**	64:30
17a+17b	93	**31a+34**	60:33
17a	94	**31a+34**	59:35
18a+18b	91	**32a+34**	59:32
18a	90	**32a+34**	57:33

[a] Determined after purification by column chromatography.

indicated by oxidation of the enantiopure main products (**10a–13a** and **15a–18a**) and the mixtures of the 17a-hydroxy isomers (**10a+b–13a+b** and **15a+b–18a+b**) with the Jones reagent (8N) in acetone (Scheme 4). The oxidations resulted in the 16β-halo-17a-ketones **25–28** (Fig. 1)‡ and **29–32** as main products, and 16,17-unsaturated oxo compounds **33**[10] and **34** as minor products, in a ratio of nearly 2:1 in each reaction (Table 2). After removal of the 17a-ethyl ethers **9a,b** and **14a,b** (see Scheme 2) by column chromatography, the oxidation of the 16-fluoro-17a-hydroxy isomers **10a–c** and **15a–c** afforded one more product, the 16α-fluoro-17a-ketone (**25b** or **29b**), but only in small quantities.

The ^{1}H NMR spectra of **25–32** demonstrate the disappearance of the C-17a-H signal as compared to the spectra of the corresponding 17a-hydroxy starting materials, while the 17-H double doublet (J=10.0, 2.0 Hz) at around δ=6.9 can be identified in the spectra of **33** and **34**.

Determination of the exact structures of the 13α-D-homosteroids **20–23** was more difficult. While the natural steroids exhibit a relatively rigid molecular framework, the conformation of rings C and D in 13α-estrones may be flexible.[11] The ^{1}H NMR, ^{13}C NMR and NOESY spectra permitted the conclusion that the 17a substituents and the

‡ Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 182901 (for **26a**) and CCDC 182902 (for **10d**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

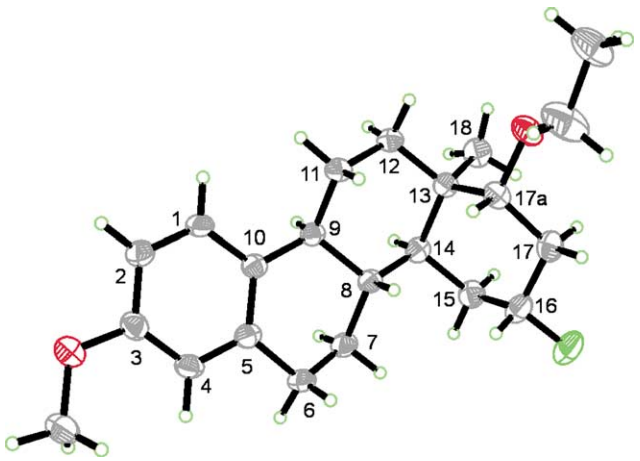


Figure 2. X-ray crystal structure of **20** with partial atom numbering.

16-halo function are on the same face of the molecule. Additionally, the characteristic signals of 17a-H and 16-H displayed very similar shapes to those for the normal derivatives **9–18**: the doublet-like multiplet appears at around δ=3.5 for the 17a-ethoxy compounds **20** and **23**, and at around δ=3.9 for the 17a-hydroxy derivatives **21** and **22**, with the 16-H multiplet at around δ=4.0–4.6. The X-ray crystal structure analysis of **20** confirmed the *cis* anellation of rings C and D, with both in the chair conformation, and the β,β-orientation of the protons on C-16 and C-17a (Fig. 2).‡

3. Conclusions

In summary, we have developed an efficient synthetic route for 16-halogenated D-homoestrone derivatives via the Lewis acid-catalyzed cationic Prins reaction in both the normal and 13α series. The formation of different halogen containing, and particularly fluorinated steroid derivatives usually needs complex, multistep methods,[12] or the substitution takes place on the original sterane skeleton.[13] Here we have described the preparation of well-defined 16-halogenated compounds by the formation of a six-membered ring D and concurrent halogenation. Besides its simplicity and mild reaction conditions, the cyclizations display high chemo- and stereoselectivity.

4. Experimental

Melting points were determined on a Kofler block and are uncorrected. Specific rotation was measured in $CHCl_3$ (c=1) at 20°C with Polamat-A and Perkin–Elmer 241 polarimeters. Mass spectra were obtained on a Varian MAT 311A spectrometer. ^{1}H NMR spectra were obtained in $CDCl_3$ solution at 200 MHz (Varian VXR 200), at 300 MHz (Bruker AMX 300) or at 500 MHz (Varian VXR 500), and the ^{13}C NMR spectra at 50, 75 or 125 MHz on the same instruments. Chemical shifts are reported relative to TMS; J values are given in Hz. ^{13}C NMR spectra are ^{1}H-decoupled. For determination of the multiplicities, the APT pulse sequence was used. Elemental analysis was carried out in the analytical laboratory of the University of Szeged. All solvents were distilled prior to use. The

reactions were monitored by TLC on Kieselgel-G (Merck Si 254 F) layers (0.25 mm thick). The spots were detected by spraying with 5% phosphomolybdic acid in 50% aqueous phosphoric acid. The R_f values were determined for the spots observed by illumination at 254 and 365 nm.

4.1. General procedure for the synthesis of 16-halo-D-homosteroids

298 mg (1.00 mmol) of 13β- or 13α-secoestrone 3-methyl ether (**1a** or **6**) or 375 mg (1.00 mmol) of 13β-secoestrone 3-benzyl ether (**1b**) was dissolved in 5 mL of CH_2Cl_2 and, under defined circumstances, 48% $BF_3{\cdot}OEt_2$ (1.1 mmol) or some other Lewis acid ($SnCl_4$ or $ZnBr_2$; 1.1 mmol) was added dropwise during stirring of the mixture under an argon atmosphere. The reaction was carried out until complete conversion (TLC) was achieved. The solution was then diluted with water (10 mL) and neutralized with $NaHCO_3$, the aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and the combined organic phases were washed with brine and dried over Na_2SO_4. After evaporation in vacuo, the crude product was purified by column chromatography.

4.2. Cyclization of 1a, 1b or 6 in the presence of $BF_3{\cdot}OEt_2$

According to the general procedure, compound **1a** or **6** (298 mg, 1.00 mmol) or **1b** (375 mg, 1.00 mmol) and $BF_3{\cdot}OEt_2$ (48% solution in Et_2O, 0.32 mL, 1.1 mmol) were allowed to react in ice-cold CH_2Cl_2 for 4 h.

4.2.1. D-Homosteroid 10a. The crude product derived from the cyclization of **1a** was purified by column chromatography (silica gel, CH_2Cl_2) to give 207 mg (65%) of **10a** as a colorless oil. R_f 0.25 (EtOAc/$CHCl_3$ 2:98); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 3H, 18-H_3), 1.14–2.50 (overlapping multiplets, 13H), 2.84 (m, 2H, 6-H_2), 3.27 (m, 1H, 17aα-H), 3.78 (s, 3H, 3-OMe), 4.54 (dm, 1H, J=48.5 Hz, 16α-H), 6.63 (d, 1H, J=2.7 Hz, 4-H), 6.72 (dd, 1H, J=8.6, 2.7 Hz, 2-H) and 7.21 (d, 1H, J=8.6 Hz, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9 (C-18), 25.9 (C-11), 26.6 (C-7), 30.0 (C-6), 30.1 (J=17.9 Hz, C-15), 34.9 (J=21.0 Hz, C-17), 36.7 (C-12), 38.8 (C-13), 41.7 (C-8), 43.8 (C-9), 43.9 (J=10.6 Hz, C-14), 55.2 (3-OMe), 74.6 (J=11.0 Hz, C-17a), 90.0 (J=164.1 Hz, C-16), 111.6 (C-2), 113.4 (C-4), 126.2 (C-1), 132.4 (C-10), 137.7 (C-5) and 157.5 (C-3); Anal. calcd for $C_{20}H_{27}FO_2$ (318.44): C, 75.44; H, 8.55; found: C, 75.58; H, 8.37.

4.2.2. D-Homosteroid 10b. The crude product derived from the cyclization of **1a** was purified by column chromatography (silica gel, CH_2Cl_2) to give 38 mg (12%) of **10b** as a colorless oil. R_f 0.32 (EtOAc/$CHCl_3$ 2:98); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H, 18-H_3), 1.16–2.48 (overlapping multiplets, 13H), 2.84 (m, 2H, 6-H_2), 3.65 (m, 1H, 17aβ-H), 3.78 (s, 3H, 3-OMe), 4.89 (dm, 1H, J=48.5 Hz, 16α-H), 6.63 (d, 1H, J=2.7 Hz, 4-H), 6.72 (dd, 1H, J=8.6, 2.7 Hz, 2-H) and 7.21 (d, 1H, J=8.6 Hz, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3 (C-18), 25.9 (C-11), 26.6 (C-7), 30.0 (C-6), 30.6 (J=17.2 Hz, C-15), 35.3 (J=18.3 Hz, C-17), 36.7 (C-12), 38.8 (C-13), 39.0 (C-8), 39.5 (J=9.9 Hz, C-14), 43.1 (C-9), 55.2 (3-OMe), 76.5 (J=13.3 Hz, C-17a), 90.0 (J=168.1 Hz, C-16), 111.7 (C-2), 113.3 (C-4), 126.2 (C-1), 132.5 (C-10), 137.9 (C-5) and 157.5 (C-3); Anal. calcd for $C_{20}H_{27}FO_2$ (318.44): C, 75.44; H, 8.55; found: C, 75.53; H, 8.45.

4.2.3. D-Homosteroid 10c. Purification of the crude product by column chromatography (silica gel, CH_2Cl_2) afforded 25 mg (8%) of **10c** as a colorless oil. R_f 0.34 (EtOAc/$CHCl_3$ 2:98); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 3H, 18-H_3), 1.21–2.40 (overlapping multiplets, 13H), 2.84 (m, 2H, 6-H_2), 3.24 (m, 1H, 17aα-H), 3.76 (s, 3H, 3-OMe), 4.99 (dm, 1H, J=48.5 Hz, 16β-H), 6.63 (d, 1H, J=2.7 Hz, 4-H), 6.72 (dd, 1H, J=8.6, 2.7 Hz, 2-H) and 7.21 (d, 1H, J=8.6 Hz, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.6 (C-18), 25.9 (C-11), 26.6 (C-7), 30.0 (C-6), 30.2 (J=18.0 Hz, C-15), 35.3 (J=21.0 Hz, C-17), 36.7 (C-12), 38.3 (C-8), 38. 8 (C-13), 41.7 (C-9), 43.8 (J=10.6 Hz, C-14), 55.2 (3-OMe), 74.6 (J=11.0 Hz, C-17a), 89.3 (J=172.3 Hz, C-16), 111.7 (C-2), 113.4 (C-4), 126.2 (C-1), 132.4 (C-10), 137.6 (C-5) and 157.5 (C-3); Anal. calcd for $C_{20}H_{27}FO_2$ (318.44): C, 75.44; H, 8.55; found: C, 75.38; H, 8.58.

4.2.4. D-Homosteroid 20. The crude product derived from the cyclization of **6** was purified by column chromatography (silica gel, *tert*-butyl methyl ether/light petroleum 15:85) to give 260 mg (75%) of **20** as colorless crystals. Mp 88–90°C; R_f 0.60 (CH_2Cl_2); $[\alpha]_D^{25}$=+16.2 (c=1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 3H, 18-H_3), 1.15 (t, 3H, J=7.0 Hz, CH_3CH_2), 1.24–2.45 (overlapping multiplets, 13H), 2.83 (m, 2H, 6-H_2), 3.32 (q, 1H, J=7.0 Hz, one of CH_3CH_2), 3.60 (q, 1H, J=7.0 Hz, one of CH_3CH_2), 3.51 (m, 1H, 17aβ-H), 3.76 (s, 3H, 3-OMe), 4.60 (dm, 1H, J=49.0 Hz, 16β-H), 6.62 (d, 1H, J=2.7 Hz, 4-H), 6.71 (dd, 1H, J=8.6, 2.7 Hz, 2-H) and 7.19 (d, 1H, J=8.6 Hz, 1-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.6 (CH_3CH_2), 22.8 (C-18), 26.4, 26.9, 28.5 (d, J=17.0 Hz, C-15), 30.1, 34.1 (d, J=16.8 Hz, C-17), 34.7, 37.3 (C-13), 38.1, 43.3, 47.1 (d, J=12.1 Hz, C-14), 55.2 (3-OMe), 65.2 (O-CH_2), 73.9 (d, J=13.5 Hz, C-17a), 88.1 (d, J=170.4 Hz, C-16), 111.7 (C-2), 113.3 (C-4), 126.3 (C-1), 132.5 (C-10), 137.7 (C-5) and 157.6 (C-3); EI-MS (70 eV) m/z (%): 346 (100) [M^+], 326 (10), 227 (26), 173 (12) and 147 (19); Anal. calcd for $C_{22}H_{31}FO_2$ (346.49): C, 76.26; H, 9.02; found: C, 76.08; H, 9.14. Crystal data, M=346.47; orthorhombic; $P2_12_12_1$; a=8.0450(16) Å, b=11.514(2) Å, c=20.595(4) Å, V=1907.7(7) Å^3; Z=4; μ(Mo Kα)=0.082 mm^{-1}; F_{000}=752; D_C=1.206 g/cm^3; crystal dimensions: 0.30×0.30×0.20 mm^3. A total of 30,670 reflections were collected using φ and ϖ scans to a maximum 2θ value of 58.40°, and 2863 reflections with no intensity cutoff were used in the structure determination. Final R and wR values were 0.043 and 0.116, respectively. The maximum and minimum peaks in the difference map were 0.264 and −0.214 e$^-$/Å^3, respectively.

4.2.5. D-Homosteroid 15a. The crude product derived from the cyclization of **1b** was purified by column chromatography (silica gel, CH_2Cl_2) to give 280 mg (71%) of **15a** as a colorless oil. R_f 0.22 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (s, 3H, 18-H_3), 1.22–2.41 (overlapping multiplets, 13H), 2.84 (m, 2H, 6-H_2), 3.27 (m, 1H, 17aα-H), 4.55 (dm, 1H, J=48.5 Hz, 16α-H), 5.02 (s, 2H, 3-benzyl-CH_2), 6.70 (d, 1H, J=2.6 Hz, 4-H), 6.77 (dd, 1H, J=8.7, 2.6 Hz, 2-H), 7.21 (d, 1H, J=8.7 Hz, 1-H), 7.30 (t-like m,

1H, 4′-H), 7.37 (m, 2H, 3′-H and 5′-H) and 7.42 (m, 2H, 2′-H and 6′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9 (C-18), 25.9 (C-11), 26.6 (C-7), 30.0 (C-6), 30.1 (J=17.6 Hz, C-15), 34.9 (J=20.9 Hz, C-17), 36.7 (C-12), 38.7 (C-13), 41.6 (C-8), 43.8 (C-9), 43.8 (J=10.6 Hz, C-14), 69.9 (3-benzyl-CH_2), 74.5 (J=10.8 Hz, C-17a), 90.0 (J=164.0 Hz, C-16), 112.4 (C-2), 114.5 (C-4), 126.3 (C-1), 127.4 (2C, C-2′ and C-6′), 127.8 (C-4′), 128.5 (2C, C-3′ and C-5′), 132.7 (C-10), 137.3 (C-1′), 137.7 (C-5) and 156.9 (C-3); Anal. calcd for $C_{26}H_{31}FO_2$ (394.53): C, 79.15; H, 7.92; found: C, 79.32; H 8.04.

4.2.6. D-Homosteroid 15b. Purification of the crude product by column chromatography (silica gel, CH_2Cl_2) afforded 36 mg (9%) of **15b** as a colorless oil. R_f 0.32 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 3H, 18-H_3), 1.23–2.41 (overlapping multiplets, 13H), 2.84 (m, 2H, 6-H_2), 3.66 (m, 1H, 17aβ-H), 4.89 (dm, 1H, J=48.5 Hz, 16α-H), 5.02 (s, 2H, 3-benzyl-CH_2), 6.64 (d, 1H, J=2.7 Hz, 4-H), 6.74 (dd, 1H, J=8.6, 2.7 Hz, 2-H), 7.21 (d, 1H, J=8.6 Hz, 1-H), 7.30 (t-like m, 1H, 4′-H), 7.37 (m, 2H, 3′-H and 5′-H) and 7.42 (m, 2H, 2′-H and 6′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3 (C-18), 25.9 (C-11), 26.6 (C-7), 30.0 (C-6), 30.6 (J=17.2 Hz, C-15), 35.3 (J=18.2 Hz, C-17), 36.7 (C-12), 38.8 (C-13), 39.0 (C-8), 39.5 (J=9.8 Hz, C-14), 43.1 (C-9), 69.9 (3-benzyl-CH_2), 76.5 (J=13.3 Hz, C-17a), 90.0 (J=168.1 Hz, C-16), 111.7 (C-2), 113.3 (C-4), 126.2 (C-1), 127.4 (2C, C-2′ and C-6′), 127.8 (C-4′), 128.5 (2C, C-3′ and C-5′), 132.5 (C-10), 137.2 (C-1′), 137.9 (C-5) and 157.5 (C-3); Anal. calcd for $C_{26}H_{31}FO_2$ (394.53): C, 79.15; H, 7.92; found: C, 79.30; H, 7.85.

4.2.7. D-Homosteroid 15c. The crude product derived from the cyclization of **1b** was purified by column chromatography (silica gel, CH_2Cl_2) to give 27 mg (7%) of **15c** as a colorless oil. R_f 0.42 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 3H, 18-H_3), 1.18–2.43 (overlapping multiplets, 13H), 2.84 (m, 2H, 6-H_2), 3.24 (m, 1H, 17aα-H), 4.99 (dm, 1H, J=48.5 Hz, 16β-H), 5.02 (s, 2H, 3-benzyl-CH_2), 6.63 (d, 1H, J=2.7 Hz, 4-H), 6.72 (dd, 1H, J=8.6, 2.7 Hz, 2-H), 7.21 (d, 1H, J=8.6 Hz, 1-H), 7.30 (t-like m, 1H, 4′-H), 7.37 (m, 2H, 3′-H and 5′-H) and 7.42 (m, 2H, 2′-H and 6′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.6 (C-18), 25.9 (C-11), 26.6 (C-7), 30.0 (C-6), 30.2 (J=18.0 Hz, C-15), 35.3 (J=21.0 Hz, C-17), 36.7 (C-12), 38.3 (C-8), 38. 8 (C-13), 41.7 (C-9), 43.7 (J=10.6 Hz, C-14), 69.9 (3-benzyl-CH_2), 74.6 (J=11.0 Hz, C-17a), 89.3 (J=172.3 Hz, C-16), 111.5 (C-2), 113.4 (C-4), 126.2 (C-1), 127.4 (2C, C-2′ and C-6′), 127.8 (C-4′), 128.5 (2C, C-3′ and C-5′), 132.4 (C-10), 137.2 (C-1′), 137.6 (C-5) and 157.5 (C-3); Anal. calcd for $C_{26}H_{31}FO_2$ (394.53): C, 79.15; H, 7.92; found: C, 79.07; H, 7.85.

4.3. Cyclization of 1a, 1b or 6 in the presence of $SnCl_4$

According to the general procedure, compound **1a** or **6** (298 mg, 1.00 mmol) or **1b** (375 mg, 1.00 mmol) and $SnCl_4$ (278 mg, 0.13 mL, 1.1 mmol) were reacted in ice-cold CH_2Cl_2 for 2 h.

4.3.1. D-Homosteroid 11a. The crude product derived from the cyclization of **1a** was purified by column chromatography (silica gel, CH_2Cl_2) to give 244 mg (73%) of **11a** as a white solid. Mp 90–92°C; R_f 0.27 (EtOAc/CH_2Cl_2 2:98); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 3H, 18-H_3), 1.20–2.38 (overlapping multiplets, 13H), 2.85 (m, 2H, 6-H_2), 3.28 (m, 1H, 17aα-H), 3.78 (s, 3H, 3-OMe), 3.90 (m, 1H, 16α-H), 6.63 (d, 1H, J=2.7 Hz, 4-H), 6.72 (dd, 1H, J=8.6, 2.7 Hz, 2-H) and 7.21 (d, 1H, J=8.6 Hz, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9 (C-18), 25.9, 26.6, 30.0, 34.5, 36.8, 37.5 (C-13), 38.3 (C-8), 40.5, 43.5 (C-9), 47.0 (C-14), 55.2 (3-OMe), 56.3 (C-16), 77.9 (C-17a), 111.7 (C-2), 113.4 (C-4), 126.3 (C-1), 132.4 (C-10), 137.7 (C-5) and 157.6 (C-3); EI-MS (70 eV) m/z (%): 336 (37), 334 (100) [M^+], 173 (13) and 147 (7); Anal. calcd for $C_{20}H_{27}ClO_2$ (334.89): C, 71.73; H, 8.13; found: C, 71.65; H, 8.18.

4.3.2. D-Homosteroid 11b. Purification of the crude product by column chromatography (silica gel, CH_2Cl_2) afforded 34 mg (10%) of **11b** as a white solid. Mp 92–94°C; R_f 0.31 (EtOAc/CH_2Cl_2 2:98); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (s, 3H, 18-H_3), 1.25–2.63 (overlapping multiplets, 13H), 2.84 (m, 2H, 6-H_2), 3.54 (bs, 1H, 17aβ-H), 3.78 (s, 3H, 3-OMe), 4.29 (m, 1H, 16α-H), 6.63 (d, 1H, J=2.7 Hz, 4-H), 6.72 (dd, 1H, J=8.6, 2.7 Hz, 2-H) and 7.21 (d, 1H, J=8.6 Hz, 1-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2 (C-18), 26.1, 26.2, 30.0, 34.1, 35.1, 37.4 (C-13), 39.0 (C-8), 39.5, 41.7 and 43.1 (C-9 and C-14), 55.2 (3-OMe), 56.6 (C-16), 76.5 (C-17a), 111.7 (C-2), 113.4 (C-4), 126.2 (C-1), 132.5 (C-10), 137.8 (C-5) and 157.5 (C-3); EI-MS (70 eV) m/z (%): 336 (27), 334 (100) [M^+], 173 (10) and 147 (5); Anal. calcd for $C_{20}H_{27}ClO_2$ (334.89): C, 71.73; H, 8.13; found: C, 71.60; H, 8.27.

4.3.3. D-Homosteroid 21. The crude product derived from the cyclization of **6** was purified by column chromatography (silica gel, *tert*-butyl methyl ether/light petroleum 20:80) to give 312 mg (93%) of **21** as white crystals. Mp 144–146°C; R_f 0.14 (CH_2Cl_2); $[\alpha]_D^{25}$=+63.0 (c=1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 3H, 18-H_3), 1.17–2.46 (overlapping multiplets, 13H), 2.81 (m, 2H, 6-H_2), 3.76 (s, 3H, 3-OMe), 3.95 (overlapping multiplets, 2H, 16β-H and 17aβ-H), 6.61 (d, 1H, J=2.6 Hz, 4-H), 6.70 (dd, 1H, J=8.6, 2.6 Hz, 2-H) and 7.17 (d, 1H, J=8.6 Hz, 1-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8 (C-18), 25.9, 26.9, 30.0, 33.0, 34.9, 37.2 (C-13), 37.5, 41.6, 43.1, 48.8, 53.9, 55.2 (3-OMe), 67.6 (C-17a), 111.8 (C-2), 113.4 (C-4), 126.3 (C-1), 132.4 (C-10), 137.7 (C-5) and 157.7 (C-3); EI-MS (70 eV) m/z (%): 336 (32), 334 (100) [M^+], 173 (14), 147 (10) and 59 (8); Anal. calcd for $C_{20}H_{27}ClO_2$ (334.89): C, 71.73; H, 8.13; found: C, 71.83; H, 8.05.

4.3.4. D-Homosteroid 16a. The crude product derived from the cyclization of **1b** was purified by column chromatography (silica gel, CH_2Cl_2) to give 308 mg (75%) of **16a** as white crystals. Mp 99–101°C; R_f 0.34 (EtOAc/$CHCl_3$ 2:98); $[\alpha]_D^{25}$=+50.2 (c=1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (s, 3H, 18-H_3), 1.18–2.45 (overlapping multiplets, 13H), 2.83 (m, 2H, 6-H_2), 3.27 (m, 1H, 17aα-H), 3.87 (m, 1H, 16α-H), 5.03 (s, 2H, 3-benzyl-CH_2), 6.71 (d, 1H, J=2.6 Hz, 4-H), 6.78 (dd, 1H, J=8.7, 2.6 Hz, 2-H), 7.20 (d, 1H, J=8.7 Hz, 1-H), 7.30 (t-like m, 1H, 4′-H), 7.37 (m, 2H, 3′-H and 5′-H) and 7.42 (m, 2H, 2′-H and 6′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9 (C-18), 25.9, 26.6, 29.0, 34.5, 36.8, 37.5 (C-13), 38.3 (C-8), 40.5, 43.5 (C-9), 46.9 (C-14), 56.3 (C-16), 69.9 (3-benzyl-CH_2), 77.9 (C-17a), 112.5

(C-2), 114.5 (C-4), 126.3 (C-1), 127.4 (2C, C-2′ and C-6′), 127.9 (C-4′), 128.5 (2C, C-3′ and C-5′), 132.7 (C-10), 137.3 (C-1′), 137.7 (C-5) and 156.9 (C-3); EI-MS (70 eV) *m/z* (%): 410 (74) [M^+] and 91 (100); Anal. calcd for $C_{26}H_{31}ClO_2$ (410.99): C, 75.99; H, 7.60; found: C, 75.80; H, 7.53.

4.3.5. D-Homosteroid 16b. Purification of the crude product by column chromatography (silica gel, CH_2Cl_2) afforded 20 mg (5%) of **16b** as a colorless oil. R_f 0.46 (EtOAc/$CHCl_3$ 2:98); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (s, 3H, 18-H_3), 1.19–2.45 (overlapping multiplets, 13H), 2.84 (m, 2H, 6-H_2), 3.54 (bs, 1H, 17aβ-H), 4.27 (m, 1H, 16α-H), 5.03 (s, 2H, 3-benzyl-CH_2), 6.65 (d, 1H, J=2.7 Hz, 4-H), 6.75 (dd, 1H, J=8.6, 2.7 Hz, 2-H), 7.21 (d, 1H, J=8.6 Hz, 1-H), 7.30 (t-like m, 1H, 4′-H), 7.37 (m, 2H, 3′-H and 5′-H) and 7.42 (m, 2H, 2′-H and 6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2 (C-18), 26.1, 26.2, 30.0, 34.1, 35.1, 37.4 (C-13), 39.0 (C-8), 40.5, 41.7 and 43.1 (C-9 and C-14), 56.6 (C-16), 69.8 (3-benzyl-CH_2), 76.5 (C-17a), 112.4 (C-2), 114.5 (C-4), 126.3 (C-1), 127.4 (2C, C-2′ and C-6′), 127.9 (C-4′), 128.5 (2C, C-3′ and C-5′), 132.5 (C-10), 137.3 (C-1′), 137.8 (C-5) and 157.5 (C-3); Anal. calcd for $C_{26}H_{31}ClO_2$ (410.99): C, 75.99; H, 7.60; found: C, 75.83; H, 7.54.

4.4. Cyclization of 1a, 1b or 6 in the presence of $ZnBr_2$

According to the general procedure, compound **1a** or **6** (298 mg, 1.00 mmol) or **1b** (375 mg, 1.00 mmol) and anhydrous $ZnBr_2$ (250 mg, 1.1 mmol) were reacted in CH_2Cl_2 under reflux for 144 h.

4.4.1. D-Homosteroid 12a. The crude product derived from the cyclization of **1a** was purified by column chromatography (silica gel, CH_2Cl_2) to give 262 mg (69%) of **12a** as white crystals. Mp 97–100°C; R_f 0.27 (EtOAc/$CHCl_3$ 2:98); $[\alpha]_D^{25}$=+55.3 (c=1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 3H, 18-H_3), 1.25–2.36 (overlapping multiplets, 13H), 2.85 (m, 2H, 6-H_2), 3.27 (m, 1H, 17aα-H), 3.77 (s, 3H, 3-OMe), 4.00 (m, 1H, 16α-H), 6.62 (d, 1H, J=2.4 Hz, 4-H), 6.70 (dd, 1H, J=8.6, 2.4 Hz, 2-H) and 7.20 (d, 1H, J=8.6 Hz, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9 (C-18), 25.9, 26.6, 30.0, 35.4, 36.8, 38.2, 38.3 (C-8), 41.5, 43.5 (C-9), 47.3 and 48.2 (C-14 and C-16), 55.2 (3-OMe), 78.4 (C-17a), 111.7 (C-2), 113.4 (C-4), 126.2 (C-1), 132.3 (C-10), 137.6 (C-5) and 157.6 (C-3); EI-MS (70 eV) *m/z* (%): 380 (98), 378 (100) [M^+], 298 (22), 173 (36), 147 (24) and 83 (24); Anal. calcd for $C_{20}H_{27}BrO_2$ (379.34): C, 63.33; H, 7.17; found: C, 63.43; H, 7.25.

4.4.2. D-Homosteroid 12b. Purification of the crude product by column chromatography (silica gel, CH_2Cl_2) afforded 57 mg (15%) of **12b** as a colorless oil. R_f 0.63 (EtOAc/$CHCl_3$ 2:98); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 3H, 18-H_3), 1.20–2.32 (overlapping multiplets, 13H), 2.83 (m, 2H, 6-H_2), 3.47 (bs, 1H, 17aβ-H), 3.77 (s, 3H, 3-OMe), 4.42 (m, 1H, 16α-H), 6.62 (d, 1H, J=2.7 Hz, 4-H), 6.71 (dd, 1H, J=8.6, 2.7 Hz, 2-H) and 7.20 (d, 1H, J=8.6 Hz, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2 (C-18), 26.0, 26.2, 30.0, 34.2, 36.1, 37.3 (C-13), 39.0 (C-8), 40.6, 42.8 and 43.1 (C-9 and C-14), 48.7 (C-16), 55.2 (3-OMe), 82.2 (C-17a), 111.6 (C-2), 113.4 (C-4), 126.2 (C-1), 132.5 (C-10), 137.8 (C-5) and 157.5 (C-3); Anal. calcd for $C_{20}H_{27}BrO_2$ (379.34): C, 63.33; H, 7.17; found: C, 63.41; H, 7.25.

4.4.3. D-Homosteroid 22. The crude product derived from the cyclization of **6** was purified by column chromatography (silica gel, CH_2Cl_2) to give 171 mg (45%) of **22** as white crystals. Mp 145–147°C; R_f 0.16 (CH_2Cl_2); $[\alpha]_D^{25}$=+104.2 (c=1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 3H, 18-H_3), 1.17–2.41 (overlapping multiplets, 13H), 2.81 (m, 2H, 6-H_2), 3.76 (s, 3H, 3-OMe), 3.90 (m, 1H, 17aβ-H), 4.07 (m, 1H, 16β-H), 6.61 (d, 1H, J=2.6 Hz, 4-H), 6.70 (dd, 1H, J=8.6, 2.6 Hz, 2-H) and 7.17 (d, 1H, J=8.6 Hz, 1-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7 (C-18), 25.8, 26.8, 29.9, 33.8, 34.9, 37.2 (C-13), 37.3, 42.5, 42.9, 45.2, 49.7, 55.2 (3-OMe), 68.0 (C-17a), 111.7 (C-2), 113.3 (C-4), 126.2 (C-1), 132.3 (C-10), 137.6 (C-5), and 157.6 (C-3); EI-MS (70 eV) *m/z* (%): 380 (100), 378 (98) [M^+], 298 (4), 213 (7), 199 (6), 173 (17) and 147 (16); Anal. calcd for $C_{20}H_{27}BrO_2$ (379.34): C, 63.33; H, 7.17; found: C, 63.21; H, 6.95.

4.4.4. D-Homosteroid 24. The crude product derived from the cyclization of **6** was purified by column chromatography (silica gel, CH_2Cl_2) to give 134 mg (45%) of **24** as white crystals. Mp 137–139°C; R_f 0.12 (CH_2Cl_2); $[\alpha]_D^{25}$=−90.5 (c=1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (s, 3H, 18-H_3), 1.25–2.29 (overlapping multiplets, 11H), 2.81 (m, 2H, 6-H_2), 3.77 (s, 3H, 3-OMe), 4.13 (m, 1H, 17aβ-H), 5.56 (m, 1H, 16-H), 5.88 (m, 1H, 15-H), 6.59 (d, 1H, J=2.6 Hz, 4-H), 6.70 (dd, 1H, J=8.6, 2.6 Hz, 2-H) and 7.18 (d, 1H, J=8.6 Hz, 1-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9 (C-18), 25.9, 27.2, 30.1, 32.9, 34.4, 36.6 (C-13), 43.1, 44.1, 50.2, 55.2 (3-OMe), 66.2 (C-17a), 111.6 (C-2), 113.5 (C-4), 124.5 and 129.6 (C-15 and C-16), 126.4 (C-1), 132.5 (C-10), 137.9 (C-5) and 157.5 (C-3); Anal. calcd for $C_{20}H_{26}O_2$ (298.43): C, 80.50; H, 8.78; found: C, 80.42; H, 8.85.

4.4.5. D-Homosteroid 17a. Purification of the crude product by column chromatography (silica gel, CH_2Cl_2) afforded 355 mg (78%) of **17a** as white crystals. Mp 103–105°C; R_f 0.24 ($CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (s, 3H, 18-H_3), 1.20–2.40 (overlapping multiplets, 13H), 2.82 (m, 2H, 6-H_2), 3.23 (m, 1H, 17aα-H), 3.99 (m, 1H, 16α-H), 5.02 (s, 2H, 3-benzyl-CH_2), 6.71 (d, 1H, J=2.5 Hz, 4-H), 6.78 (dd, 1H, J=8.5, 2.5 Hz, 2-H), 7.20 (d, 1H, J=8.5 Hz, 1-H), 7.31 (t-like m, 1H, 4′-H), 7.38 (m, 2H, 3′-H and 5′-H) and 7.42 (m, 2H, 2′-H and 6′-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.8 (C-18), 25.9, 26.5, 29.9, 35.4, 36.8, 38.2 (C-16), 38.3 (C-13), 41.5, 43.5 (C-9), 47.4 and 48.1 (C-8 and C-14), 69.9 (3-benzyl-CH_2), 78.4 (C-17a), 112.5 (C-2), 114.4 (C-4), 126.2 (C-1), 127.4 (2C, C-2′ and C-6′), 127.8 (C-4′), 128.5 (2C, C-3′ and C-5′), 132.6 (C-10), 137.2 (C-1′), 137.6 (C-5) and 156.8 (C-3); Anal. calcd for $C_{26}H_{31}BrO_2$ (455.44): C, 68.57; H, 6.86; found: C, 68.63; H, 6.95.

4.4.6. D-Homosteroid 17b. The crude product derived from the cyclization of **1b** was purified by column chromatography (silica gel, CH_2Cl_2) to give 32 mg (7%) of **17b** as a colorless oil. R_f 0.37 ($CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (s, 3H, 18-H_3), 1.21–2.42 (overlapping multiplets, 13H), 2.83 (m, 2H, 6-H_2), 3.49 (bs, 1H, 17aβ-H), 4.42 (m, 1H, 16α-H), 5.03 (s, 2H, 3-benzyl-CH_2), 6.74 (d, 1H, J=2.5 Hz, 4-H), 6.78 (dd, 1H, J=8.5, 2.5 Hz, 2-H), 7.20 (d, 1H, J=8.5 Hz, 1-H), 7.31 (t-like m, 1H, 4′-H), 7.37 (m, 2H, 3′-H

and 5′-H) and 7.42 (m, 2H, 2′-H and 6′-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.2 (C-18), 26.0, 26.2, 30.0, 34.2, 36.1, 37.3 (C-13), 38.9 (C-16), 40.5, 42.8 and 43.1 and 48.7 (C-8, C-9 and C-14), 69.9 (3-benzyl-CH_2), 76.7 (C-17a), 112.5 (C-2), 114.5 (C-4), 126.2 (C-1), 127.4 (2C, C-2′ and C-6′), 127.8 (C-4′), 128.5 (2C, C-3′ and C-5′), 132.8 (C-10), 137.3 (C-1′), 137.8 (C-5) and 156.8 (C-3); EI-MS (70 eV) *m/z* (%): 456 (10), 454 (12) [M^+] and 91 (100); Anal. calcd for $C_{26}H_{31}BrO_2$ (455.44): C, 68.57; H, 6.86; found: C, 68.45; H, 6.92.

4.5. Treatment of 1a, 1b or 6 with NaI in the presence of $BF_3{\cdot}OEt_2$

According to the general procedure, compound **1a** or **6** (298 mg, 1.00 mmol) or **1b** (375 mg, 1.00 mmol) and anhydrous NaI (749 mg, 5 mmol) were reacted together, and 48% $BF_3{\cdot}OEt_2$ (0.05 mL, 0.17 mmol **1a** and **1b** or 0.15 mL, 1.1 mmol for **6**) in ice-cold CH_2Cl_2 was added, and the mixture was then stirred at rt for 2 h.

4.5.1. D-Homosteroid 13a. The crude product derived from the cyclization of **1a** was purified by column chromatography (silica gel, CH_2Cl_2) to give 307 mg (72%) of **13a** as white crystals. Mp 88–90°C; R_f 0.32 (EtOAc/$CHCl_3$ 2:98); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H, 18-H_3), 1.25–2.45 (overlapping multiplets, 13H), 2.83 (m, 2H, 6-H_2), 3.26 (m, 1H, 17aα-H), 3.77 (s, 3H, 3-OMe), 4.10 (m, 1H, 16α-H), 6.62 (d, 1H, *J*=2.9 Hz, 4-H), 6.71 (dd, 1H, *J*=8.7, 2.9 Hz, 2-H) and 7.19 (d, 1H, *J*=8.7 Hz, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0 (C-18), 23.5 (C-16), 25.9, 26.6, 30.0, 36.9, 37.6, 38.2 (C-8), 38.5 (C-13), 43.4 (C-9), 43.7, 49.9 (C-14), 55.2 (3-OMe), 79.0 (C-17a), 111.7 (C-2), 113.4 (C-4), 126.2 (C-1), 132.4 (C-10), 137.6 (C-5) and 157.6 (C-3); EI-MS (70 eV) *m/z* (%): 426 (100) [M^+], 299 (19), 298 (37), 281 (36), 173 (38) and 147 (43); Anal. calcd for $C_{20}H_{27}IO_2$ (426.34): C, 56.35; H, 6.38; found: C, 56.47; H, 6.22.

4.5.2. D-Homosteroid 13b. The crude product derived from the cyclization of **1a** was purified by column chromatography (silica gel, CH_2Cl_2) to give 34 mg (8%) of **13b** as a yellowish oil. R_f 0.43 (EtOAc/$CHCl_3$ 2:98); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (s, 3H, 18-H_3), 1.12–2.52 (overlapping multiplets, 13H), 2.83 (m, 2H, 6-H_2), 3.33 (bs, 1H, 17aβ-H), 3.77 (s, 3H, 3-OMe), 4.55 (m, 1H, 16α-H), 6.62 (d, 1H, *J*=2.7 Hz, 4-H), 6.71 (dd, 1H, *J*=8.6, 2.7 Hz, 2-H) and 7.19 (d, 1H, *J*=8.6 Hz, 1-H); Anal. calcd for $C_{20}H_{27}IO_2$ (426.34): C, 56.35; H, 6.38; found: C, 56.43; H, 6.52.

4.5.3. D-Homosteroid 23. Purification of the crude product by column chromatography (silica gel, CH_2Cl_2/light petroleum 50:50) afforded 355 mg (78%) of **23** as colorless crystals. Mp 82–84°C; R_f 0.80 (CH_2Cl_2); $[\alpha]_D^{25}$=+23.8 (*c*=1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 3H, 18-H_3), 1.13 (t, 3H, *J*=7.0 Hz, CH_3CH_2), 1.19–2.47 (overlapping multiplets, 13H), 2.84 (m, 2H, 6-H_2), 3.30 (q, 1H, *J*=7.0 Hz, one of CH_3CH_2), 3.58 (q, 1H, *J*=7.0 Hz, one of CH_3CH_2), 3.49 (m, 1H, 17aβ-H), 3.77 (s, 3H, 3-OMe), 4.19 (m, 1H, 16β-H), 6.63 (d, 1H, *J*=2.7 Hz, 4-H), 6.71 (dd, 1H, *J*=8.6, 2.7 Hz, 2-H), 7.20 (d, 1H, *J*=8.6 Hz, 1-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.6 (Et-CH_3), 22.4 and 22.8 (C-18 and C-16), 26.4, 26.9, 30.1, 35.2, 36.2, 37.0, 37.3 (C-13), 41.5, 42.9, 50.9, 55.2 (3-OMe), 65.3 (O-CH_2), 76.0 (C-17a), 111.8 (C-2), 113.4 (C-4), 126.3 (C-1), 132.6 (C-10), 137.7 (C-5) and 157.6 (C-3); EI-MS (70 eV) *m/z* (%): 454 (100) [M^+], 327 (19), 281 (54), 227 (15), 173 (34) and 147 (51); Anal. calcd for $C_{22}H_{31}IO_2$ (454.40): C, 58.15; H, 6.88; found: C, 58.41; H, 6.95.

4.5.4. D-Homosteroid 18a. The crude product derived from the cyclization of **1b** was purified by column chromatography (silica gel, EtOAc/$CHCl_3$ 5:95) to give 327 mg (65%) of **18a** as white crystals. Mp 134–136°C; R_f 0.30 (EtOAc/$CHCl_3$ 2:98); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 3H, 18-H_3), 1.12–2.50 (overlapping multiplets, 13H), 2.82 (m, 2H, 6-H_2), 3.23 (m, 1H, 17aα-H), 4.08 (m, 1H, 16α-H), 5.02 (s, 2H, 3-benzyl-CH_2), 6.70 (d, 1H, *J*=2.7 Hz, 4-H), 6.77 (dd, 1H, *J*=8.7, 2.7 Hz, 2-H), 7.19 (d, 1H, *J*=8.5 Hz, 1-H), 7.30 (t-like m, 1H, 4′-H), 7.37 (m, 2H, 3′-H and 5′-H) and 7.42 (m, 2H, 2′-H and 6′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9 (C-18), 23.5 (C-16), 25.9, 26.6, 29.9, 36.9, 37.5, 38.1 (C-8), 43.5 (C-9), 43.7, 49.9 (C-14), 69.9 (3-benzyl-CH_2), 78.9 (C-17a), 112.5 (C-2), 114.4 (C-4), 126.3 (C-1), 127.4 (2C, C-2′ and C-6′), 127.9 (C-4′), 128.5 (2C, C-3′ and C-5′), 132.6 (C-10), 137.3 (C-1′), 137.7 (C-5) and 156.8 (C-3); EI-MS (70 eV) *m/z* (%): 502 (100) [M^+], 376 (6), 374 (11), 92 (8) and 91 (100); Anal. calcd for $C_{26}H_{31}IO_2$ (502.44): C, 62.15; H, 6.22; found: C, 62.03; H, 6.34.

4.5.5. D-Homosteroid 18b. The crude product derived from the cyclization of **1b** was purified by column chromatography (silica gel, CH_2Cl_2) to give 30 mg (6%) of **18b** as a yellowish oil. R_f 0.42 (EtOAc/$CHCl_3$ 2:98); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (s, 3H, 18-H_3), 1.23–2.48 (overlapping multipletts, 13H), 2.83 (m, 2H, 6-H_2), 3.33 (bs, 1H, 17aβ-H), 4.52 (m, 1H, 16α-H), 5.02 (s, 2H, 3-benzyl-CH_2), 6.65 (d, 1H, *J*=2.7 Hz, 4-H), 6.74 (dd, 1H, *J*=8.6, 2.7 Hz, 2-H), 7.19 (d, 1H, *J*=8.6 Hz, 1-H), 7.30 (t-like m, 1H, 4′-H), 7.37 (m, 2H, 3′-H and 5′-H) and 7.42 (m, 2H, 2′-H and 6′-H); Anal. calcd for $C_{26}H_{31}IO_2$ (502.44): C, 62.15; H, 6.22; found: C, 62,28; H, 6.31.

4.6. Typical procedure for the oxidation of 16-halo-17a-hydroxy-D-homosteroids

A certain amount of Jones reagent (8 N) was added dropwise to 1.00 mmol of pure 16β-halo-17aβ-hydroxy-D-homosteroid (**10a**–**13a** or **15a**–**18a**) or a mixture of the corresponding 17a isomers (**10**–**13** or **15**–**18**) in 10 mL of acetone, and the solution was stirred until complete conversion (TLC) was achieved. The solution was next poured into ice-water and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with water, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography.

4.7. Oxidation of 3-methoxy-16-fluoro-17a-hydroxy-D-homosteroids

According to the typical procedure, 318 mg (1.00 mmol) of **10a** or a mixture of **10a**, **10b** and **10c** and 0.3 mL of Jones reagent were reacted to give 174 mg (55%) of **25a** and 95 mg (32%) of **33** in the former case, and 187 mg (59%) of **25a**, 22 mg (7%) of **25b** and 74 mg (25%) of **33** in the latter case.

4.7.1. D-Homosteroid 25a. The crude product was purified by column chromatography (silica gel, light petroleum/CH_2Cl_2 20:80) to give **25a** as a colorless oil. R_f 0.42 (light petroleum/CH_2Cl_2 20:80); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (s, 3H, 18-H_3), 1.24–2.43 (overlapping multiplets, 13H), 2.87 (m, 2H, 6-H_2), 3.78 (s, 3H, 3-OMe), 4.68 (dm, 1H, J=49.2 Hz, 16α-H), 6.71 (d, 1H, J=2.5 Hz, 4-H), 6.79 (dd, 1H, J=8.6, 2.5 Hz, 2-H) and 7.20 (d, 1H, J=8.6 Hz, 1-H); Anal. calcd for $C_{20}H_{25}FO_2$ (316.42): C, 75.92; H, 7.96; found: C, 76.05; H, 7.88.

4.7.2. D-Homosteroid 25b. The crude product was purified by column chromatography (silica gel, light petroleum/CH_2Cl_2 20:80) to give **25b** as a colorless oil. R_f 0.53 (light petroleum/CH_2Cl_2 20:80); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (s, 3H, 18-H_3), 1.20–2.43 (overlapping multiplets, 13H), 2.87 (m, 2H, 6-H_2), 3.78 (s, 3H, 3-OMe), 4.97 (dm, 1H, J=48.6 Hz, 16β-H), 6.70 (d, 1H, J=2.6 Hz, 4-H), 6.78 (dd, 1H, J=8.6, 2.6 Hz, 2-H) and 7.20 (d, 1H, J=8.6 Hz, 1-H); Anal. calcd for $C_{20}H_{25}FO_2$ (316.42): C, 75.92; H, 7.96; found: C, 75.81; H, 8.05.

4.7.3. D-Homosteroid 33. The crude product was purified by column chromatography (silica gel, light petroleum/CH_2Cl_2 20:80) to give **25b** as colorless crystals. Mp 159–161°C; R_f 0.31 (light petroleum/CH_2Cl_2 20:80); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 3H, 18-H_3), 1.26–2.56 (overlapping multiplets, 11H), 2.87 (m, 2H, 6-H_2), 3.77 (s, 3H, 3-OMe), 5.95 (m, 1H, 17-H), 6.63 (d, 1H, J=2.7 Hz, 4-H), 6.72 (dd, 1H, J=8.6, 2.7 Hz, 2-H), 6.88 (m, 1H, 16-H) and 7.22 (d, 1H, J=8.6 Hz, 1-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.6 (C-18), 25.9 (2C), 27.2, 29.9, 32.3, 39.3 (C-8), 42.6 (C-9), 44.6 (C-13), 45.5 (C-14), 55.2 (3-OMe), 111.7 (C-2), 113.6 (C-4), 126.3 and 127.8 (C-1 and C-17), 132.2 (C-10), 137.4 (C-5), 147.3 (C-16), 157.7 (C-3) and 205.3 (C-17a); EI-MS (70 eV) m/z (%): 296 (100) [M^+]; Anal. calcd for $C_{20}H_{24}O_2$ (296.41): C, 81.04; H, 8.16; found: C, 81.17; H, 8.32.

4.8. Oxidation of 3-methoxy-16-chloro-17a-hydroxy-D-homosteroids

According to the typical procedure, 335 mg (1.00 mmol) of **11a** or a mixture of **11a** and **11b** and 0.4 mL of Jones reagent were reacted to give 200 mg (60%) of **26a** and 107 mg (36%) of **33** in the former case, and 206 mg (62%) of **26a** and 104 mg (35%) of **33** in the latter case.

4.8.1. D-Homosteroid 26a. Purification of the crude product by column chromatography (silica gel, light petroleum/CH_2Cl_2 20:80) afforded **26a** as colorless crystals. Mp 130–132°C; R_f 0.53 (light petroleum/CH_2Cl_2 20:80); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (s, 3H, 18-H_3), 1.29–2.47 (overlapping multiplets, 11H), 2.81 (m, 1H), 2.86 (m, 2H, 6-H_2), 2.98 (m, 1H), 3.76 (s, 3H, 3-OMe), 4.00 (m, 1H, 16α-H), 6.62 (d, 1H, J=2.7 Hz, 4-H), 6.71 (dd, 1H, J=8.6, 2.7 Hz, 2-H) and 7.19 (d, 1H, J=8.6 Hz, 1-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8 (C-18), 25.6, 26.6, 29.8, 34.3, 32.2, 38.4 (C-8), 43.1 (C-9), 46.6 (C-14), 47.2 (C-13), 47.6 (C-17), 55.2 (C-16), 55.8 (3-OMe), 111.8 (C-2), 113.5 (C-4), 126.3 (C-1), 132.0 (C-10), 137.3 (C-5), 157.7 (C-3) and 210.7 (C-17a); EI-MS (70 eV) m/z (%): 334 (22), 332 (100) [M^+], 212 (12) and 173 (14); Anal. calcd for $C_{20}H_{25}ClO_2$ (332.87): C, 72.17; H, 7.57; found: C, 72.08; H, 7.62. Crystal data, M=332.85; orthorhombic; $P2_12_12_1$; a=5.9432(12) Å, b=8.3380(17) Å, c=34.370(7) Å, V=1703.2(6) Å^3; Z=4; μ(Mo Kα)=0.232 mm^{-1}; F_{000}=712; D_C=1.298 g/cm^3; crystal dimensions: 1×1×1 mm^3. A total of 10,782 reflections were collected using ω scans to a maximum 2θ value of 50°, and 2940 reflections with no intensity cutoff were used in the structure determination. Final R and wR values were 0.036 and 0.099, respectively. The maximum and minimum peaks in the difference map were 0.170 and −0.183 e$^-$/Å^3, respectively.

4.9. Oxidation of 3-methoxy-16-bromo-17a-hydroxy-D-homosteroids

According to the typical procedure, 379 mg (1.00 mmol) of **12a** or a mixture of **12a** and **12b** and 0.4 mL of Jones reagent were reacted to give 226 mg (60%) of **27a** and 95 mg (32%) of **33** in the former case, and 238 mg (63%) of **27a** and 92 mg (31%) of **33** in the latter case.

4.9.1. D-Homosteroid 27a. The crude product was purified by column chromatography (silica gel, light petroleum/CH_2Cl_2 20:80) to give **27a** as colorless crystals. Mp 100–102°C; R_f 0.49 (light petroleum/CH_2Cl_2 20:80); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (s, 3H, 18-H_3), 1.26–2.58 (overlapping multiplets, 11H), 2.88 (m, 2H, 6-H_2), 2.91 (m, 1H), 3.15 (m, 1H), 3.77 (s, 3H, 3-OMe), 4.10 (m, 1H, 16α-H), 6.63 (d, 1H, J=2.5 Hz, 4-H), 6.72 (dd, 1H, J=8.6, 2.5 Hz, 2-H) and 7.19 (d, 1H, J=8.6 Hz, 1-H); Anal. calcd for $C_{20}H_{25}BrO_2$ (377.33): C, 63.66; H, 6.68; found: C, 63.78; H, 6.91.

4.10. Oxidation of 3-methoxy-16-iodo-17a-hydroxy-D-homosteroids

According to the typical procedure, 426 mg (1.00 mmol) of **13a** or a mixture of **13a** and **13b** and 0.5 mL of Jones reagent were reacted to give 246 mg (58%) of **28a** and 89 mg (30%) of **33** in the former case, and 263 mg (62%) of **28a** and 83 mg (28%) of **33** in the latter case.

4.10.1. D-Homosteroid 28a. The crude product was purified by column chromatography (silica gel, light petroleum/CH_2Cl_2 20:80) to give **28a** as a colorless oil. R_f 0.57 (light petroleum/CH_2Cl_2 20:80); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (s, 3H, 18-H_3), 1.33–2.65 (overlapping multiplets, 11H), 2.87 (m, 2H, 6-H_2), 2.98 (m, 1H), 3.27 (m, 1H), 3.77 (s, 3H, 3-OMe), 4.17 (m, 1H, 16α-H), 6.63 (d, 1H, J=2.7 Hz, 4-H), 6.72 (dd, 1H, J=8.6, 2.7 Hz, 2-H) and 7.19 (d, 1H, J=8.6 Hz, 1-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8 (C-18), 20.5 (C-16), 25.6, 26.6, 28.7, 31.9, 36.4, 37.8 (C-9), 42.6 (C-14), 46.6, 47.6 (C-17), 50.3 (C-13), 55.2 (3-OMe), 111.6 (C-2), 113.4 (C-4), 126.3 (C-1), 131.9 (C-10), 137.3 (C-5), 157.7 (C-3) and 210.4 (C-17a); Anal. calcd for $C_{20}H_{25}IO_2$ (424.33): C, 56.61; H, 5.94; found: C, 56.84; H, 6.03.

4.11. Oxidation of 3-benzyloxy-16-fluoro-17a-hydroxy-D-homosteroids

According to the typical procedure, 395 mg (1.00 mmol) of **15a** or a mixture of **15a**, **15b** and **15c** and 0.4 mL of Jones

reagent were reacted to give 243 mg (62%) of **29a** and 119 mg (32%) of **34** in the former case, and 239 mg (61%) of **29a**, 35 mg (9%) of **29b** and 93 mg (25%) of **34** in the latter case.

4.11.1. D-Homosteroid 29a. Purification of the crude product by column chromatography (silica gel, light petroleum/CH_2Cl_2 20:80) afforded **29a** as a colorless oil. R_f 0.46 (light petroleum/CH_2Cl_2 20:80); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (s, 3H, 18-H_3), 1.21–2.83 (overlapping multiplets, 13H), 2.87 (m, 2H, 6-H_2), 4.68 (dm, 1H, J=49.2 Hz, 16α-H), 5.02 (s, 2H, 3-benzyl-CH_2), 6.70 (d, 1H, J=2.6 Hz, 4-H), 6.77 (dd, 1H, J=8.7, 2.6 Hz, 2-H), 7.21 (d, 1H, J=8.7 Hz, 1-H), 7.30 (t-like m, 1H, 4′-H), 7.37 (m, 2H, 3′-H and 5′-H) and 7.42 (m, 2H, 2′-H and 6′-H); Anal. calcd for $C_{26}H_{29}FO_2$ (392.52): C, 79.56; H, 7.45; found: C, 79.65; H, 7.53.

4.11.2. D-Homosteroid 29b. The crude product was purified by column chromatography (silica gel, light petroleum/CH_2Cl_2 20:80) to give **29b** as a colorless oil. R_f 0.55 (light petroleum/CH_2Cl_2 20:80); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (s, 3H, 18-H_3), 1.23–2.80 (overlapping multiplets, 13H), 2.87 (m, 2H, 6-H_2), 4.97 (dm, 1H, J=48.6 Hz, 16β-H), 5.02 (s, 2H, 3-benzyl-CH_2), 6.70 (d, 1H, J=2.6 Hz, 4-H), 6.78 (dd, 1H, J=8.6, 2.6 Hz, 2-H), 7.20 (d, 1H, J=8.6 Hz, 1-H), 7.30 (t-like m, 1H, 4′-H), 7.37 (m, 2H, 3′-H and 5′-H) and 7.42 (m, 2H, 2′-H and 6′-H); Anal. calcd for $C_{26}H_{29}FO_2$ (392.52): C, 79.56; H, 7.45; found: C, 79.74; H, 7.55.

4.11.3. D-Homosteroid 34. The crude product was purified by column chromatography (silica gel, light petroleum/CH_2Cl_2 20:80) to give **34** as colorless crystals. Mp 121–123°C; R_f 0.42 (light petroleum/CH_2Cl_2 20:80); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 3H, 18-H_3), 1.28–2.54 (overlapping multiplets, 11H), 2.85 (m, 2H, 6-H_2), 5.01 (s, 2H, 3-benzyl-CH_2), 5.94 (m, 1H, 17-H), 6.70 (d, 1H, J=2.7 Hz, 4-H), 6.78 (dd, 1H, J=8.6, 2.7 Hz, 2-H), 6.86 (m, 1H, 16-H), 7.21 (d, 1H, J=8.6 Hz, 1-H), 7.30 (t-like m, 1H, 4′-H), 7.37 (m, 2H, 3′-H and 5′-H) and 7.42 (m, 2H, 2′-H and 6′-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.6 (C-18), 25.9 (2C), 27.2, 29.9, 32.3, 39.2 (C-8), 42.6 (C-9), 44.6 (C-13), 45.5 (C-14), 69.9 (3-benzyl-CH_2), 112.5 (C-2), 114.6 (C-4), 126.4 (C-1), 127.3 (2C, C-2′ and C-6′), 127.8 (2C, C-17 and C-4′), 128.5 (2C, C-3′ and C-5′), 132.4 (C-10), 137.3 (C-1′), 137.5 (C-5), 147.3 (C-16), 156.9 (C-3) and 205.2 (C-17a); EI-MS (70 eV) m/z (%): 372 (65) [M^+] and 91 (100); Anal. calcd for $C_{26}H_{28}O_2$ (372.51): C, 83.83; H, 7.58; found: C, 83.95; H, 7.41.

4.12. Oxidation of 3-benzyloxy-16-chloro-17a-hydroxy-D-homosteroids

According to the typical procedure, 411 mg (1.00 mmol) of **16a** or a mixture of **16a** and **16b** and 0.4 mL of Jones reagent were reacted to give 262 mg (64%) of **30a** and 112 mg (30%) of **34** in the former case, and 266 mg (65%) of **30a** and 112 mg (30%) of **34** in the latter case.

4.12.1. D-Homosteroid 30a. Purification of the crude product by column chromatography (silica gel, light petroleum/CH_2Cl_2 20:80) afforded **30a** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (s, 3H, 18-H_3), 1.24–2.45 (overlapping multiplets, 11H), 2.79 (m, 1H), 2.87 (m, 2H, 6-H_2), 2.94 (m, 1H), 3.89 (m, 1H, 16α-H), 5.02 (s, 2H, 3-benzyl-CH_2), 6.71 (d, 1H, J=2.6 Hz, 4-H), 6.77 (dd, 1H, J=8.7, 2.6 Hz, 2-H), 7.21 (d, 1H, J=8.7 Hz, 1-H), 7.30 (t-like m, 1H, 4′-H), 7.37 (m, 2H, 3′-H and 5′-H), 7.42 (m, 2H, 2′-H and 6′-H); Anal. calcd for $C_{26}H_{29}ClO_2$ (408.97): C, 76.36; H, 7.15; found: C, 76.45; H, 7.08.

4.13. Oxidation of 3-benzyloxy-16-bromo-17a-hydroxy-D-homosteroids

According to the typical procedure, 455 mg (1.00 mmol) of **17a** or a mixture of **17a** and **17b** and 0.5 mL of Jones reagent were reacted to give 268 mg (59%) of **31a** and 130 mg (35%) of **34** in the former case, and 272 mg (60%) of **31a** and 123 mg (33%) of **34** in the latter case.

4.13.1. D-Homosteroid 31a. Purification of the crude product by column chromatography (silica gel, light petroleum/CH_2Cl_2 20:80) afforded **31a** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (s, 3H, 18-H_3), 1.26–2.50 (overlapping multiplets, 11H), 2.86 (m, 2H, 6-H_2), 2.90 (m, 1H), 3.20 (m, 1H), 4.05 (m, 1H, 16α-H), 5.02 (s, 2H, 3-benzyl-CH_2), 6.71 (d, 1H, J=2.6 Hz, 4-H), 6.77 (dd, 1H, J=8.7, 2.6 Hz, 2-H), 7.21 (d, 1H, J=8.7 Hz, 1-H), 7.30 (t-like m, 1H, 4′-H), 7.37 (m, 2H, 3′-H and 5′-H) and 7.42 (m, 2H, 2′-H and 6′-H); Anal. calcd for $C_{26}H_{29}BrO_2$ (453.42): C, 68.87; H, 6.45; found: C, 68.92; H, 6.53.

4.14. Oxidation of 3-benzyloxy-16-iodo-17a-hydroxy-D-homosteroids

According to the typical procedure, 502 mg (1.00 mmol) of **18a** or a mixture of **18a** and **18b** and 0.5 mL of Jones reagent were reacted to give 285 mg (57%) of **32a** and 123 mg (33%) of **34** in the former case, and 295 mg (59%) of **32a** and 119 mg (32%) of **34** in the latter case.

4.14.1. D-Homosteroid 32a. The crude product was purified by column chromatography (silica gel, light petroleum/CH_2Cl_2 20:80) to give **32a** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (s, 3H, 18-H_3), 1.30–2.60 (overlapping multiplets, 11H), 2.87 (m, 2H, 6-H_2), 3.20 (m, 2H), 4.09 (m, 1H, 16α-H), 5.02 (s, 2H, 3-benzyl-CH_2), 6.71 (d, 1H, J=2.6 Hz, 4-H), 6.77 (dd, 1H, J=8.7, 2.6 Hz, 2-H), 7.21 (d, 1H, J=8.7 Hz, 1-H), 7.30 (t-like m, 1H, 4′-H), 7.37 (m, 2H, 3′-H and 5′-H) and 7.42 (m, 2H, 2′-H and 6′-H); Anal. calcd for $C_{26}H_{29}IO_2$ (500.42): C, 62.41; H, 5.84; found: C, 62.55; H, 5.98.

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