Stereoselective Synthesis of New Halogen-containing D-Homoestrone Derivatives

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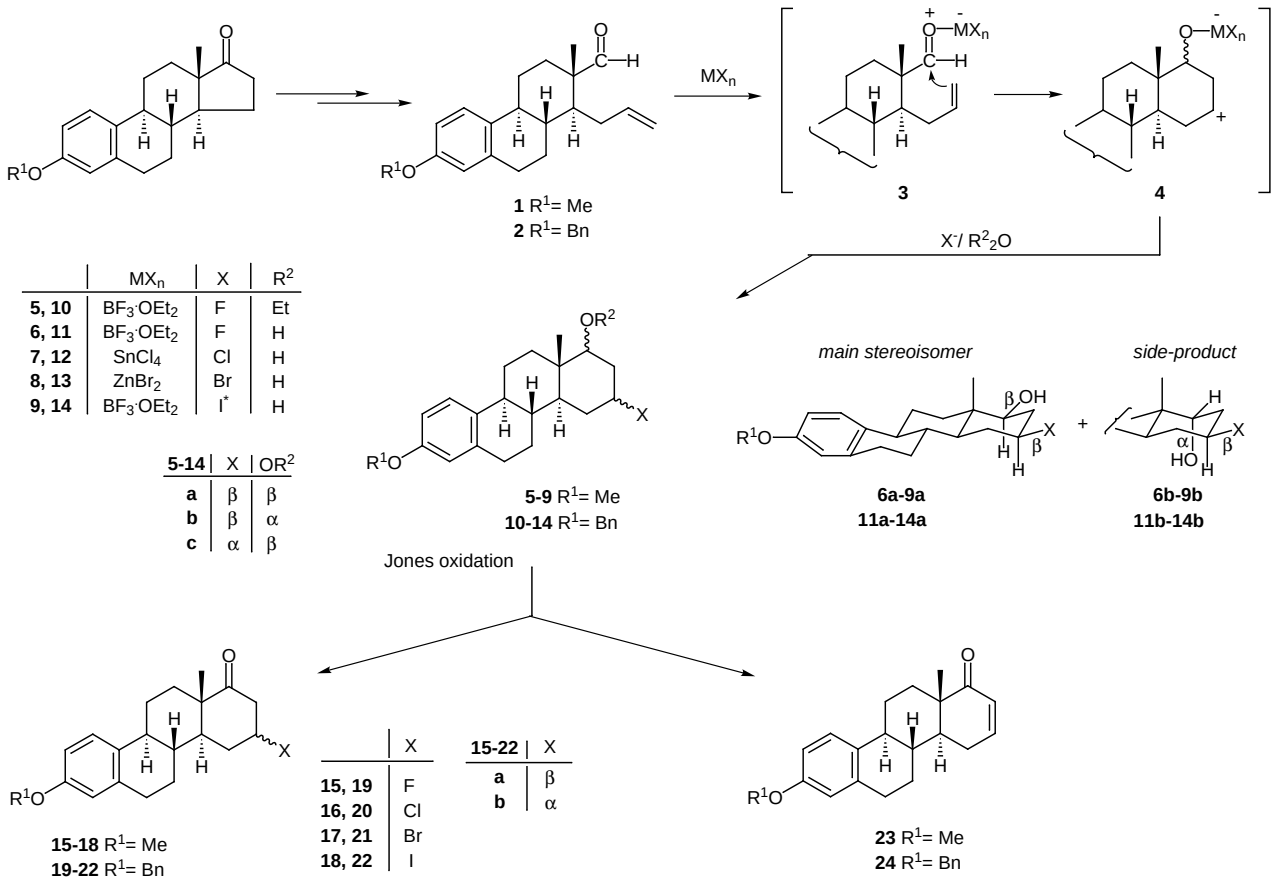
Received 12 November 2001

Abstract: The Lewis acid-induced cyclization of the 3-methyl and 3-benzyl ethers of an unsaturated secoestrone aldehyde furnished D-homosteroids containing 16β-oriented halogens on the sterane skeleton.

Key words: Lewis acids, intramolecular Prins reaction, fluorination, stereoselective synthesis, D-homosteroids

The cyclization of olefinic aldehydes by an internal Prins mechanism is a well-known procedure for the formation of five-[1], six-[2] and seven-membered[3] rings. The presence of Lewis acids presumably results in a predominantly stepwise ionic pathway via a β-hydroxy-carbocation affording homoallylic alcohols or/and γ-halohydrins depending on the reaction conditions,[4] though mainly reactions catalyzed by $BF_3{\cdot}OEt_2$ and chlorine-containing acids leading to unsaturated compounds have been studied. However the cationic process leading to 1,3-halohydrins often competes with the '*ene*' reaction, and can even become the exclusive pathway. We recently reported that halogenated D-homoestrone derivatives can readily be obtained by Lewis acid-catalyzed cyclization of arylimines



	MX_n	X	R^2
5, 10	$BF_3{\cdot}OEt_2$	F	Et
6, 11	$BF_3{\cdot}OEt_2$	F	H
7, 12	$SnCl_4$	Cl	H
8, 13	$ZnBr_2$	Br	H
9, 14	$BF_3{\cdot}OEt_2$	I*	H

5-14	X	OR^2
a	β	β
b	β	α
c	α	β

	X
15, 19	F
16, 20	Cl
17, 21	Br
18, 22	I

15-22	X
a	β
b	α

* The iodine is from the NaI applied

Scheme

Synlett 2002, No. 3, 04 03 2002. Article Identifier:
1437-2096,E;2002,0,03,0419,0422,ftx,en;G32801ST.pdf.

ISSN 0936-5214

derived from the normal secoestrone aldehyde (**1**) and substituted anilines.[5] All of these reactions exhibited high chemo- and stereoselectivity, and homoallylic alcohols were not produced.

We now describe the ring closure of aldehydes **1** and **2** (Scheme), derived from the 3-methyl and 3-benzyl ethers of estrone,[6] which furnished halo-D-homoestrone derivatives in good yields. Treatment of the aldehyde (**1** or **2**) with 1.1 equivalents 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 led chemoselectively to the corresponding halohydrins.[7–9] Furthermore, all these transformations proceeded in a highly stereoselective manner, with the 16β-halo-17aβ-hydroxy-D-homosteroids (**6a**–**9a, 11a**–**14a**) as main products, and the 16β-halo-17aα-hydroxy isomers (**6b**–**9b, 11b**–**14b**) as minor products (Table, entries 1–8). The favored formation of the 16β,17aβ diastereomers can be explained by addition of the alkene moiety to the intermediate oxonium ion *anti* to the angular methyl group in **3,** which allows the hydroxy group to take up the β position. However, the stereoselective addition of the nucleophile to the cation **4** takes place *syn* to the angular methyl group. This is not surprising since the halo atom probably prefers an equatorial orientation. When $BF_3{\cdot}OEt_2$ in CH_2Cl_2 was used to prepare fluoro derivatives, one more (**6c** or **11c**) of the four possible isomers was detected (entries 1 and 5). The addition of fluorine in either the 16α or the 16β position can be explained by its small atomic size, comparable to that of hydrogen, though particularly 16β-fluorination occurred. The 17a-ethyl ethers (**5a,b**, **10a,b**), produced by transetherification of the 17a-hydroxy group with the applied $BF_3{\cdot}OEt_2$, were also obtained and isolated, but in overall amounts of less than 5% (entries 1 and 5).

The structures of the products were determined by NMR spectroscopy; the stereochemistry at C-16 and C-17a in ring D of the D-homosteroids (**6a**–**9a, 11a**–**14a)** 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 **6b**–**9b** and **11b**–**14b**), and from the 16-H multiplet at around δ = 3.9-5.0, which corresponds to two diaxial and two axial-equatorial couplings.

The stereoisomerism of the 17a-hydroxy group was also proved by oxidation. The enantiopure main products and the mixtures of the 17a isomers with *Jones* reagent (8 N) in acetone[10] resulted in 16β-halo-17a-ketones (**15a**–**22a**) as main products. By the elimination of hydrogen halides, 16,17-unsaturated oxo compounds[11] (**23**, **24**) were also obtained (Scheme). The halo-ketone and the enone were found to be produced in a ratio of nearly 2:1 in each reaction (entries 9–16). Oxidation of the 16-fluoro-17a-hydroxy isomers after separation of the 17a-ethers by

Table Ring Closure of Aldehydes

Entry	Substrate(s)	Reagent (equiv)	Overall yield [%]	Products	Ratio[a]
1	**1**	$BF_3{\cdot}OEt_2$ (1.1)	90	**5a**+**5b** **6a**+**6b**+**6c**	5[b] 65:12:8
2	**1**	$SnCl_4$ (1.1)	83	**7a**+**7b**	73:10
3	**1**	$ZnBr_2$ (1.1)	84	**8a**+**8b**	69:15
4	**1**	$BF_3{\cdot}OEt_2$ (0.17), NaI (5)	80	**9a**+**9b**	72:8
5	**2**	$BF_3{\cdot}OEt_2$ (1.1)	90	**10a**+**10b** **11a**+**11b**+**11c**	3[b] 71:9:7
6	**2**	$SnCl_4$ (1.1)	80	**12a**+**12b**	75:5
7	**2**	$ZnBr_2$ (1.1)	85	**13a**+**13b**	78:7
8	**2**	$BF_3{\cdot}OEt_2$ (0.17), NaI (5)	71	**14a**+**14b**	65:6
9	**6a**+**6b**+**6c**	Jones	91	**15a**+**15b**+**23**	59:7:25
10	**7a**+**7b**	*Jones*	97	**16a**+**23**	62:35
11	**8a**+**8b**	*Jones*	94	**17a**+**23**	63:31
12	**9a**+**9b**	*Jones*	90	**18a**+**23**	62:28
13	**11a**+**11b**+**11c**	*Jones*	95	**19a**+**19b**+**24**	61:9:25
14	**12a**+**12b**	*Jones*	95	**20a**+**24**	65:30
15	**13a**+**13b**	*Jones*	93	**21a**+**24**	60:33
16	**14a**+**14b**	*Jones*	91	**22a**+**24**	59:32

[a] Determined after purification by column chromatography.
[b] **5a**, **5b** and **10a**, **10b** were not separated in pure form.

column chromatography also gave the corresponding 16α-fluoro-17a-ketone in small quantities (entries 9 and 13). The ^{1}H NMR spectra of **15**–**22** reveal that the C-17a-H signal has disappeared as compared to the spectra of the corresponding 17a-hydroxy compounds, while the 17-H double doublet (J = 10.0 Hz, J = 2.0 Hz) at around δ = 5.9 and the C-16 multiplet at around δ = 6.9 can be identified in the spectra of the conjugated derivatives **23** and **24**.

In conclusion, this is a simple and efficient synthesis of halogenated D-homoestrone derivatives involving the use of different Lewis acids and intramolecular cationic cyclization. In addition to its simplicity and the mild reaction conditions, the method provides products with high selectivity, which makes it a very useful process for the substitution of various halogens onto the sterane skeleton.

Acknowledgement

We thank the Hungarian Scientific Research Fund (OTKA T032265) and the Hungarian Ministry of Education (FKFP 0110/2000) for financial support of this work.

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(7) **Spectroscopic Data of 16β-Fluoro-D-homoestra-1,3,5(10)-triene-3,17aβ-diol-3-methyl ether(6a)**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (s, 3 H, 18-H_3), 2.84 (m, 2 H, 6-H_2), 3.27 (m, 1 H, 17aα-H), 3.78 (s, 3 H, 3-OMe), 4.54 (dm, 1 H, J = 48.5 Hz, 16α-H), 6.63 (d, 1 H, $J_{4\text{-}2}$ = 2.7 Hz, 4-H), 6.72 (dd, 1 H, $J_{2\text{-}1}$ = 8.6 Hz, $J_{2\text{-}4}$ = 2.7 Hz, 2-H) and 7.21 (d, 1 H, $J_{1\text{-}2}$ = 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).

(8) **Typical Procedure for the Synthesis of 16β-Chloro-D-homoestra-1,3,5(10)-triene-3,17a-diol-3-methyl Ether Isomers (7a and 7b):** 298 mg (1.00 mmol) of **1** was dissolved in 5 mL of ice-cold CH_2Cl_2 and 0.13 mL (278 mg, 1.1 mmol) of anhydrous $SnCl_4$ in 2 mL of CH_2Cl_2 was added dropwise during stirring of the mixture under an argon atmosphere for 2 h. The solution was then diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were dried over Na_2SO_4. Evaporation in vacuo and purification by column chromatography (silica gel, CH_2Cl_2) afforded 244 mg (73%) of **7a** and 34 mg (10%) of **7b** as white solids. **7a**: 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, 3 H, 18-H_3), 2.85 (m, 2 H, 6-H_2), 3.28 (m, 1 H, 17aα-H), 3.78 (s, 3 H, 3-OMe), 3.90 (m, 1 H, 16α-H), 6.63 (d, 1 H, $J_{4\text{-}2}$ = 2.7 Hz, 4-H), 6.72 (dd, 1 H, $J_{2\text{-}1}$ = 8.6 Hz, $J_{2\text{-}4}$ = 2.7 Hz, 2-H) and 7.21 (d, 1 H, $J_{1\text{-}2}$ = 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 *m/z* (relative intensity): 336(37), 334 (M^+, 100), 173(13) and 147(7). **7b**: mp 92–94 ºC; R_f 0.31 (EtOAc–CH_2Cl_2 = 2: 98); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (s, 3 H, 18-H_3), 2.84 (m, 2 H, 6-H_2), 3.54 (bs, 1 H, 17aβ-H), 3.78 (s, 3 H, 3-OMe), 4.29 (m, 1 H, 16α-H), 6.63 (d, 1 H, $J_{4\text{-}2}$ = 2.7 Hz, 4-H), 6.72 (dd, 1 H, $J_{2\text{-}1}$ = 8.6 Hz, $J_{2\text{-}4}$ = 2.7 Hz, 2-H) and 7.21 (d, 1 H, $J_{1\text{-}2}$ = 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 *m/z* (relative intensity): 336(27), 334 (M^+, 100), 173(10) and 147(5). – $C_{20}H_{27}ClO_2$. The compounds give correct elemental analyses.

(9) **Typical Procedure for the Synthesis of 16β-Bromo-D-homoestra-1,3,5(10)-triene-3,17a-diol-3-benzyl Ether Isomers (13a and 13b):** A mixture of 375 mg (1 mmol) of secoestrone-3-benzyl ether **2** and 478 mg (1.00 mmol) of anhydrous $ZnBr_2$ in 5 mL of CH_2Cl_2 was heated for 2 h and then stirred overnight at r.t. The suspension was diluted with water (10 mL) and neutralized with $NaHCO_3$, the aqueous phase was extracted with CH_2CH_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 (silica gel, CH_2Cl_2) to give 355 mg (78%) of **13a** as a white solid and 31 mg (7%) of **13b** as a yellow oil. **13a**: mp 103–105 °C; R_f 0.24 (CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (s, 3 H, 18-H_3), 2.84 (m, 2 H, 6-H_2), 3.27 (m, 1 H, 17aα-H), 4.00 (m, 1 H, 16α-H), 5.02 (s, 2 H, 3-benzyl-CH_2), 6.71 (d, 1 H, $J_{4\text{-}2}$ = 2.6 Hz, 4-H), 6.79 (dd, 1 H, $J_{2\text{-}1}$ = 8.6 Hz, $J_{2\text{-}4}$ = 2.6 Hz, 2-H), 7.19 (d, 1 H, $J_{1\text{-}2}$ = 8.6 Hz, 1-H), 7.32 (m, 1 H, 4'-H), 7.38 (m, 2 H, 3'-H and 5'-H) and 7.43 (m, 2 H, 2'-H and 6'-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.9 (C-18), 25.9, 26.5, 29.9, 35.4, 36.8, 38.2 (C-16), 38.3 (C-13), 41.5, 43.5 and 47.4 (C-8 and C-9), 48.1 (C-14), 69.9 (3-benzyl-CH_2), 78.4 (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'), 132.6 (C-10), 137.2 (C-1'), 137.6 (C-5) and 156.8 (C-3). **13b**: R_f 0.37 (CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (s, 3 H, 18-H_3), 2.83 (m, 2 H, 6-H_2), 3.47 (bs, 1 H, 17aβ-H), 4.42 (m, 1 H, 16α-H), 5.02 (s, 2 H, 3-benzyl-CH_2), 6.71 (d, 1 H, $J_{4\text{-}2}$ = 2.7 Hz, 4-H), 6.78 (dd, 1 H, $J_{2\text{-}1}$ = 8.7 Hz, $J_{2\text{-}4}$ = 2.7 Hz, 2-H), 7.19 (d, 1 H, $J_{1\text{-}2}$ = 8.7 Hz, 1-H), 7.31 (m, 1

H, 4'-H), 7.37 (m, 2 H, 3'-H and 5'-H) and 7.42 (m, 2 H, 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, 36.0, 37.3 (C-13), 39.0 (C-16), 40.5, 42.8 and 43.0 (C-8 and C-9), 48.7 (C-14), 69.9 (3-benzyl-CH_2), 76.8 (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 *m/z* (relative intensity): 456(12), 454 (M^+, 13) and 91(100). − $C_{26}H_{31}O_2Br$. The compounds give correct elemental analyses.

(10) **Typical Procedure for the Oxidation of 16β-Chloro-D-homoestra-1,3,5(10)-triene-3,17a-diol-3-methyl Ether Isomers.** 0.35 mL of *Jones* reagent (8 N) was added dropwise to 335 mg (1.00 mmol) of pure **7a** or a mixture of **7a** and **7b** in 4 mL of ice-cold acetone, and the solution was stirred until complete conversion (TLC) was achieved (1 h). 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, and the crude product was purified by column chromatography (silica gel, PE–CH_2Cl_2 = 20:80) to afford 206 mg (62%) of **16a** and 104 mg (35%) of **23** as white solids. **16a**: mp 130–132 °C; R_f 0.53 (PE–CH_2Cl_2 = 20:80); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.15 (s, 3 H, 18-H_3), 2.86 (m, 2 H, 6-H_2), 3.76 (s, 3 H, 3-OMe), 4.00 (m, 1 H, 16α-H), 6.62 (d, 1 H, J_{4-2} = 2.7 Hz, 4-H), 6.71 (dd, 1 H, J_{2-1} = 8.6 Hz, J_{2-4} = 2.7 Hz, 2-H) and 7.19 (d, 1 H, J_{1-2} = 8.6 Hz, 1-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.8 (C-18), 25.6, 26.6, 29.8, 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). − $C_{20}H_{25}ClO_2$. **23**: mp: 159–161 °C, R_f 0.31 (PE–CH_2Cl_2 = 20:80); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.05 (s, 3 H, 18-H_3), 2.87 (m, 2 H, 6-H_2), 3.77 (s, 3 H, 3-OMe), 5.95 (m, 1 H, 16-H), 6.63 (d, 1 H, J_{4-2} = 2.7 Hz, 4-H), 6.72 (dd, 1 H, J_{2-1} = 8.6 Hz, J_{2-4} = 2.7 Hz, 2-H), 6.88 (m, 1 H, 17-H) and 7.22 (d, 1 H, J_{1-2} = 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). − $C_{20}H_{24}O_2$. The compounds give correct elemental analyses.

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