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Fluorination of steroid estrogens with Selectfluor®: Elucidation of regio- and stereoselectivity

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ABSTRACT

Two steroid estrogens, natural estradiol and 8α-estradiol, were fluorinated using Selectfluor® in ionic liquid. Unexpectedly, mostly products of fluorination at position C-10 were isolated instead of corresponding fluorophenols, as it was reported previously. The reaction proceeds stereoselectively, yielding different stereoisomers for different types of the steroid skeleton. Stereoselectivity was proved by 1D/2D NMR experiments and X-ray analysis of obtained products. The obtained compounds are suitable intermediates for synthesis of various classes of estrogens.

1. Introduction

Since steroidal estrogens used in hormonal replacement therapy are proved to be carcinogenic [1], there is an urgent need for corresponding new safe medications. Liehr in his work has shown that carcinogenicity and estrogenicity can be separated [2]; the obvious example is 2-fluoroestradiol **1a** (Fig. 1), an active estrogen that possesses no carcinogenic properties. Unfortunately, this substance is rather hard to synthesize. The known methods include various types of fluorination using decomposition of diazonium salts [3], reactions with acetyl hypofluorite [4], cesium fluorosulfate [5] etc. All of these methods provide yields and regioselectivities only from poor to mediocre and require harsh conditions or highly active instable reagents.

Heravi reported that under treatment by Selectfluor® in ionic liquid estradiol **2a** was converted into 2-fluoroestradiol **1a** with excellent yield [6]. That was the best result of such fluorination so far, although it contradicted with results of some other electrophilic fluorinations using different N–F derivatives [7,8].

In this work we made an attempt to perform this reaction with another substrate, 8α-estradiol **2b**, under the same conditions (Scheme 1); various 2-fluoro-8α-estrogens are known to possess osteo- and cardioprotective properties [9,10] while retaining hormonal activity and can be less vulnerable to metabolic oxidation as compared to natural substrates. Unexpectedly, mostly isolated was the product with fluorination at position C-10, **3b**, along with minute amount of 2- and 4-fluoro-8α-estradiol **1b** and **4b**. Further, we have checked the original method on natural estradiol and got analogous results, that are, in turn, completely different from those reported by Heravi [6]. Structure elucidation and observations on the stereoselectivity of fluorination are reported in this paper. Such compounds can be used in synthesis of antraquinone-estrogen hybrids [11], 3-aminosteroids [12] and 1-hydroxy-4-fluorosteroids [13].

2. Experimental

NMR spectroscopic data were recorded with Bruker DPX-300 and Avance 400 spectrometers (300 and 400 MHz for ^{1}H, 75 and 125 MHz for ^{13}C, respectively) in $CDCl_3$ and DMSO-d_6 and are referenced to the residual solvent proton (δ_H = 7.26 and 2.50 ppm, respectively) and carbon signals (δ_C = 77.00 and 39.52 ppm, respectively). High-resolution mass spectra were recorded with a Bruker Maxis HRMS-ESI-Q-TOF spectrometer (electrospray ionization mode). X-ray diffraction analysis was performed with an Agilent Technologies Xcalibur diffractometer. Melting points were recorded on a Buchi melting point apparatus and are uncorrected. Fine chemicals were purchased from the Sigma-Aldrich Co. LLC. Chromatographic purification was performed using Acros Organics silica gel 60, 35–70 mesh.

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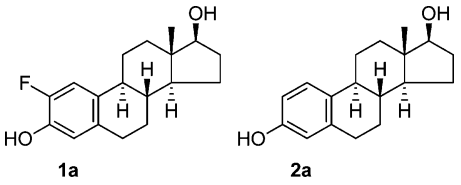


Fig. 1. Structures of 2-fluoroestradiol **1a** and estradiol **2a**.

2.1. General procedure for the reaction of estrogen analogues with Selectfluor®

A suspension of steroid **2a, b** (0.2 mmol) and Selectfluor® (0.21 mmol) in the 1:1 mixture of $bmimBF_4$ (0.2 g) and CH_3OH (0.2 g) was stirred for 1 h at 20 °C. The mixture was then poured in water (50 ml) and extracted with ethyl acetate (3 × 25 ml). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and the solvent was evaporated. Flash chromatography of the residue (petroleum ether/ethyl acetate 4:1) afforded **3a, b** and the mixture of **1a, b**, **4a, b** and starting material **2a, b**.

10β-Fluoroestra-1,4-diene-17β-ol-3-one **3a**. Yield 63%. mp 151–153 °C (lit. mp 152–154 °C [13]).

^{1}H NMR ($CDCl_3$, δ): 0.86 s (3*H*), 0.96–1.56 m (8*H*), 1.60–1.69 m (1*H*), 1.76–1.85 m (1*H*), 1.84–2.04 m (4*H*), 2.04–2.15, 2.40–2.47 m (1*H*), 2.63–2.75 m (1*H*), 3.66 t (1*H*, *J* = 8.5 Hz), 6.04 brs (1*H*), 6.24 d (1*H*, *J* = 10.2 Hz), 7.09 dd (1*H*, *J* = 10.4 Hz, 7.6 Hz).

^{13}C NMR ($CDCl_3$, δ): 10.9, 22.6, 23.5, 30.3, 31.8, 32.6, 35.8, 36.1, 43.1, 49.7, 54.2 d ($J_{C,F}$ = 25.0 Hz), 81.4, 89.2 d ($J_{C,F}$ = 168.0 Hz), 123.6 d ($J_{C,F}$ = 4.4 Hz), 129.4 d ($J_{C,F}$ = 8.1 Hz), 145.1 d ($J_{C,F}$ = 24.2 Hz), 160.3 d ($J_{C,F}$ = 19.1 Hz), 185.1 d ($J_{C,F}$ = 4.4 Hz).

HRMS (ESI–TOF), Calc. for $[M + H]^+$, $[C_{18}H_{24}FO_2]^+$: 291.1755, found 291.1743.

10α-Fluoro-8α-estra-1,4-diene-17β-ol-3-one **3b**. Yield 69%. mp 121–123 °C.

^{1}H NMR (DMSO-d_6): δ 0.69 (s, 3*H*), 0.87–1.69 (m, 9*H*), 1.73–1.95 (m, 2*H*), 2.07–2.34 (m, 2*H*), 2.35–2.45 (m, 2*H*), 3.27–3.46 (m, 1*H*), 4.53 (d, 1*H*, *J* = 4.5 Hz), 6.14 (s, 1*H*), 6.23 (d, 1*H*, *J* = 10.0 Hz), 6.99 (dd, 1*H*, *J* = 10.0 Hz, 6.7 Hz).

^{13}C NMR (DMSO-d_6): δ 13.77, 18.01 ($J_{C,F}$ = 7.1 Hz), 23.01, 25.13, 30.14, 31.51, 35.01, 36.96, 42.63, 47.09, 49.05 ($J_{C,F}$ = 25.5 Hz), 80.69, 90.81 ($J_{C,F}$ = 160.3 Hz), 125.64, 130.25 ($J_{C,F}$ = 8.4 Hz), 147.35 ($J_{C,F}$ = 21.4 Hz), 158.34 ($J_{C,F}$ = 18.6 Hz), 186.02.

HRMS (ESI-TOF), Calc. for $[M + H]^+$, $[C_{18}H_{24}FO_2]^+$: 291.1755, found 291.1751.

2.2. X-ray diffraction studies

Single crystals of **3a** were grown from methanol, single crystals of **3b**—from Et_2O. A suitable crystal was selected and analyzed on a SuperNova, Dual, Cu at zero, Atlas diffractometer. The crystal was kept at 100(2) K during data collection. Using Olex2 [14], the structure was solved with the SHELXS structure solution program using Direct Methods and refined with the SHELXL refinement package using Least Squares minimization [15].

Crystallographic data form compounds have been deposited with the Cambridge Crystallographic Data Center as supplementary material numbers CCDC 1014305 (**3a**) and 1014306 (**3b**).

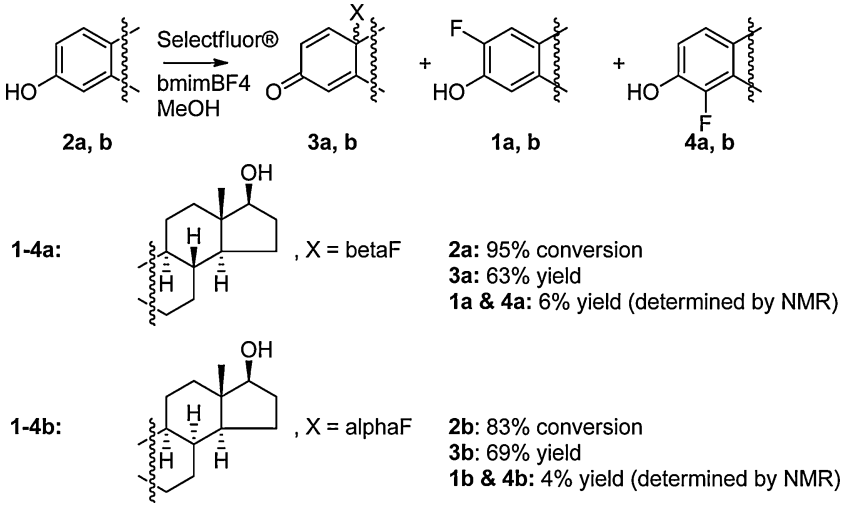
3. Results and discussion

3.1. Synthesis of 10-fluorosteroids

The initial task in this paper was reproduction of previous results [6] with unnatural estrogen analogue, 8α-estradiol **2b**, under the same conditions. However, treatment of this compound with Selectfluor® in 1:1 mixture of ionic liquid ($bmimBF_4$) and methanol for 24 h resulted only in 83% conversion, yielding 10-fluorosteroid **3b** (69%) and an inseparable mixture of 2- and 4-fluoro-8alpha-estradiol **1b** and **4b** (4%, 1:1, determined by NMR) (Scheme 1). Such results were completely unexpected, since the author of original method reported only the products of fluorination at positions 2 and 4 with complete conversion of substrate and corresponding 88%/11% yields, using natural estradiol under the same conditions. We assumed that molecular geometry can affect the regioselectivity of fluorination and conducted a control experiment with natural estradiol as described by Heravi. Nevertheless, our results here were also totally different—incomplete conversion and 10-fluorosteroid **3a** as a main product (Scheme 1).

3.2. Elucidation of fluorination stereoselectivity

The structure of the first analogue **3b** obtained from 8α-estradiol was examined by NMR spectroscopy methods. First, a full signal-atom assignment was performed for ^{1}H and ^{13}C NMR spectra (Table 1). A ^{19}F spectrum was also recorded and displayed



Scheme 1. Fluorination of estradiol **2a** and 8α-estradiol **2b**.

Table 1
Signal-atom assignment for steroid **3b**.

^{1}H assignment		^{13}C assignment	
Atom no	δ(^{1}H), ppm ($^nJ_{H-F}$)	Atom no	δ(^{13}C), ppm ($^nJ_{C-F}$)
1	6.99 (6.5 Hz)	1	146.42 (21.4 Hz)
2	6.23 (1.6 Hz)	2	129.31 (8.4 Hz)
4	6.14 (1.8 Hz)	3	185.12 (4.6 Hz)
6α	2.40	4	124.66 (4.8 Hz)
6β	2.40		
7α	1.81	5	157.42 (18.6 Hz)
7β	1.58		
8α	2.29	6	30.57
9α	2.17 (12.5 Hz)	7	24.19
11α	1.20	8	34.08
11β	1.06		
12α	0.96	9	49.05 (25.5 Hz)
12β	1.60		
14α	1.38	10	90.81 (160.3 Hz)
15α	1.38	11	18.01 (7.1 Hz)
15β	1.38		
16α	1.83	12	36.02
16β	1.26		
17α	3.37	13	41.69
17β-OH	<H_2O>	14	46.15
18	0.69	15	22.07
		16	29.20
		17	79.75
		18	12.82

one double doublet (6.5 and 12.5 Hz) because of scalar interactions with H1 and H9α protons correspondingly. These interactions were established by analysis of multiplet structure of corresponding signals in ^{1}H spectrum as well as cross-peaks in several homo- and heteronuclear correlation spectra (COSY-DQF, J-COSY, HSQC and NOESY) (Fig. 2).

However, the obtained value of vicinal constant $^3J_{F10-H9\alpha}$ = 12.5 Hz cannot serve as unambiguous proof of their mutual *cis*- or *trans*-orientation, and, therefore, cannot be used as a clue for determination of fluorine spatial position.

Therefore, additional NOE experiments were conducted for two types of spatial interactions in the molecule—H–H and H–F.

Firstly, in case of homonuclear experiment, α-orientation was assigned for fluorine atom, based on estimated ratio of distances between protons $r_{H1-H9\alpha}$ = 2.58 Å and $r_{H1-H11\alpha}$ = 2.37 Å. The same conclusion can be made considering results of heteronuclear experiment: integral intensities of H9α, H8α and H6α in ^{1}H spectrum rise upon selective saturation of fluorine signal (Fig. 3).

Thus, the results of homo- and heteronuclear experiments on measuring NOE in this molecule represent independent evidences for α-orientation of fluorine atom at position 10.

Lately, an X-ray crystallographic analysis was performed for both analogues, also confirming the result of NMR studies for 8α-compound **3b** (Table 2) (Fig. 4). Interestingly, the stereoselectivity

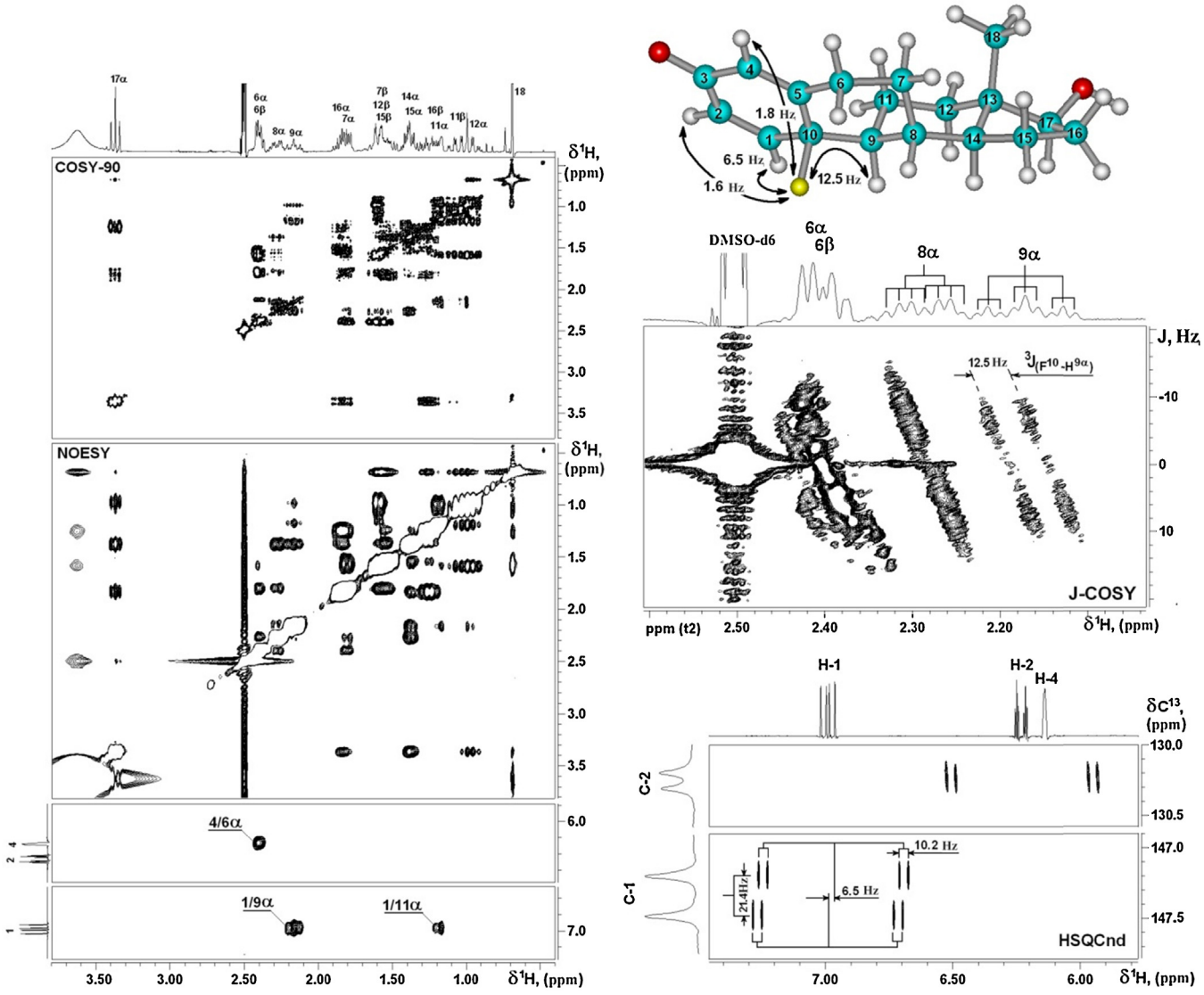


Fig. 2. Fragments of compound's **3b** COSY, NOESY, J-COSY and HSQC spectra used for signal-atom assignment and for determination of scalar constants.

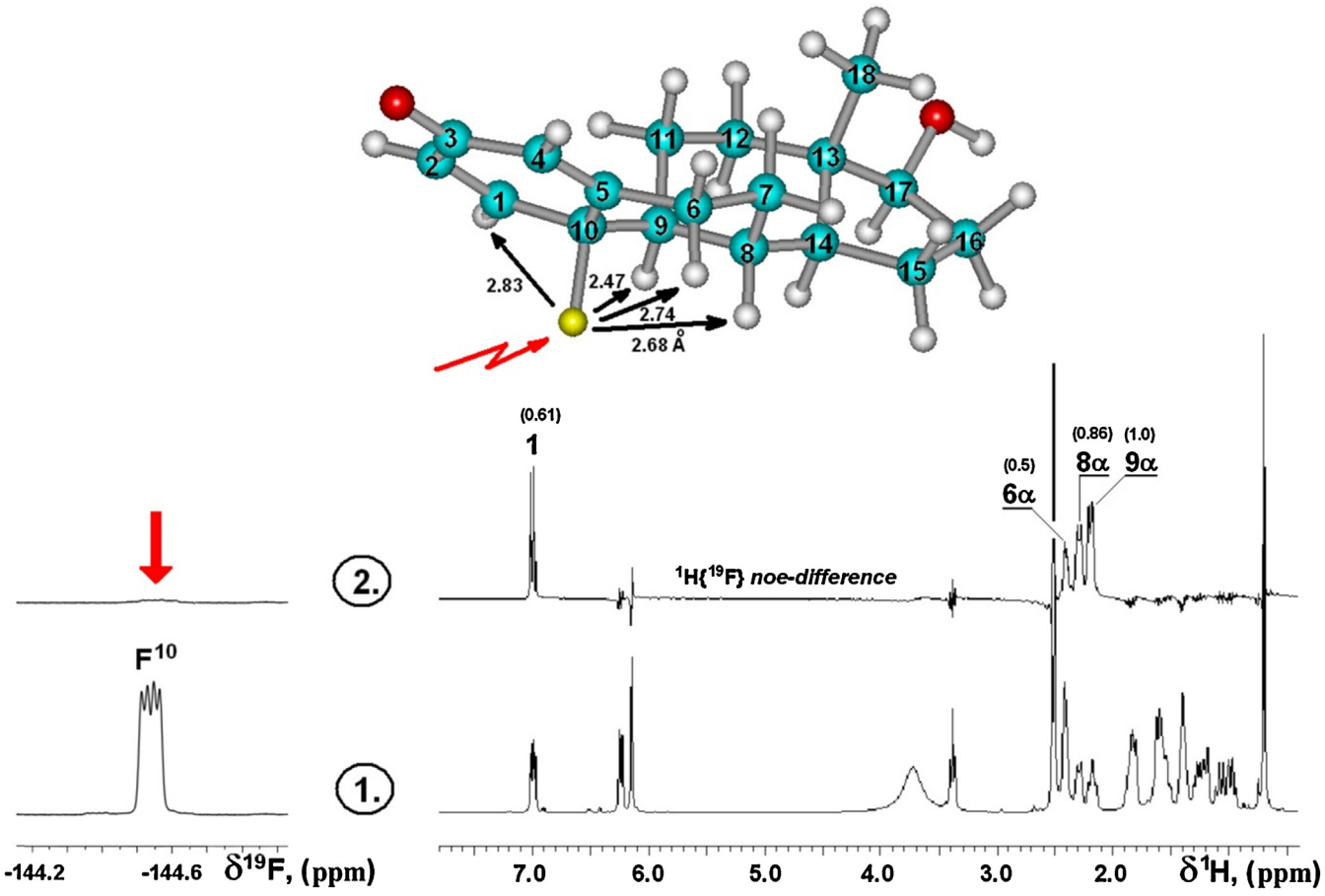


Fig. 3. The results of heteronuclear $^{1}H\{^{19}F\}$ NOE-difference experiment (τ_m = 1.0 s) for compound **3b**.

Table 2
X-ray crystal structure parameters of compounds **3a** and **3b**.

Crystal data and structure refinements		
Compound	**3a**	**3b**
Empirical formula	$C_{18}H_{23}O_2F$	$C_{18}H_{23}O_2F$
Formula weight	290.36	290.36
Temperature (K)	100 (2)	100 (2)
Crystal system	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	*Cc*
a (Å)	6.7680 (2)	15.5496 (2)
b (Å)	12.0219 (3)	15.6885 (3)
c (Å)	18.4639 (6)	24.7217 (4)
α (°)	90.00	90.00
β (°)	90.00	94.2025 (16)
γ (°)	90.00	90.00
Volume (Å^3)	1502.30 (8)	6014.61 (17)
Z	4	16
ρ_{calc} (mg/mm^3)	1.284	1.283
m (mm$^{-1)}$	0.729	0.729
F (000)	624.0	2496.0
Crystal size (mm^3)		0.22 × 0.18 × 0.10
2Θ Range for data collection	8.78 to 145°	7.18 to 144.94°
Index ranges	$-8 \le h \le 8$, $-14 \le k \le 5$, $-18 \le l \le 22$	$-16 \le h \le 19$, $-19 \le k \le 19$, $-30 \le l \le 30$
Reflections collected	7203	34080
Independent reflections	2890[*R*(int) = 0.0300]	9222[*R*(int) = 0.0469]
Data/restraints/parameters	2890/0/192	9222/2/765
Goodness-of-fit on F^2	1.048	1.038
Final R indexes [$I > = 2\sigma$ (*I*)]	R_1 = 0.0331, wR_2 = 0.0811	R_1 = 0.0423, wR_2 = 0.1075
Final *R* indexes [all data]	R_1 = 0.0373, wR_2 = 0.0838	R_1 = 0.0466, wR_2 = 0.1114
Largest diff. peak/hole (e Å^{-3})	0.20/−0.15	0.26/−0.19
Flack parameter	−0.06 (15)	−0.08 (11)

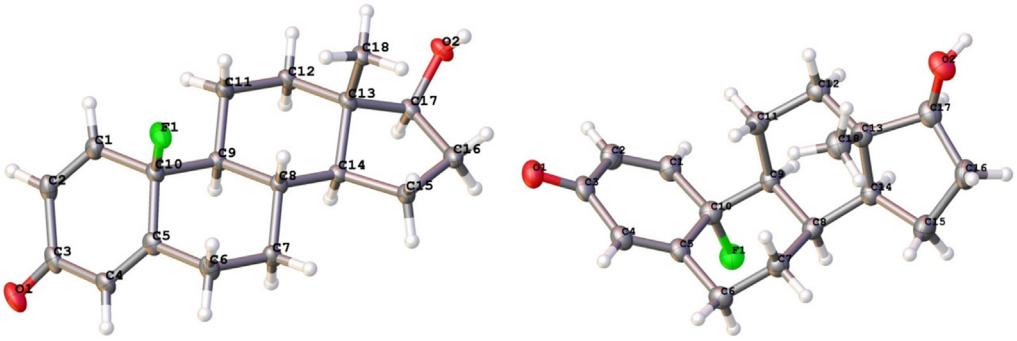


Fig. 4. Molecular structures of **3a** (left) and **3b** (right) (X-Ray data).

of fluorination in case of natural estradiol is reversed and only 10β-fluorosteroid **3a** was obtained. This fact may lead to an assumption that position 10 in 8α-steroids is more hindered for the attack of Selectfluor® from β-face of the molecule. The reversed situation may be surmised for natural steroid estrogens.

Noteworthy, although analogous 10-chlorosteroid readily and irreversibly rearranges into 4-chloroestrone and 2-chloroestrone upon heating in acetonitrile [16], 10β-fluorosteroid **3a** is more stable and remains intact under these conditions.

4. Conclusions

The reaction of estradiol and 8α-estradiol with Selectfluor® in 1:1 mixture of bmimBF_4 and methanol leads to 10-fluorosteroids as main products. The fluorination occurs stereoselectively, yielding 10β-fluorosteroid with natural estradiol as a substrate and 10α-fluorosteroid with 8α-estradiol in good yields. These compounds are suitable intermediates for synthesis of various classes steroids: antraquinone-estrogen hybrids, 3-aminosteroids and 1-hydroxy-4-fluorosteroids.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2014.09.030.

References

[1] The Endogenous Hormones and Breast Cancer Collaborative Group, J. Nat. Cancer Inst. 94 (2002) 606–616.
[2] J.G. Liehr, Mol. Pharmacol. 23 (1983) 278–281.
[3] T. Utne, R.B. Jobson, R.D. Babson, J. Org. Chem. 33 (1968) 2469–2473.
[4] J.S. Ward, C.D. Jones, US4522758, 1985.
[5] L.J. Diorazio, D.A. Widdowson, J.M. Clough, J. Chem. Soc., Perkin Trans. 1 (1992) 421–425.
[6] M.R.P. Heravi, J. Fluorine Chem. 129 (2008) 217–221.
[7] W.T. Pennington, G. Resnati, D.D. DesMarteau, J. Org. Chem. 57 (1992) 1536–1539.
[8] S. Stavber, M. Jereb, M. Zupan, Synlett 1999 (1999) 1375–1378.
[9] V.N. Belov, V.Y. Dudkin, E.A. Urusova, G.L. Starova, S.I. Selivanov, S.V. Nikolaev, N.D. Eshchenko, S.N. Morozkina, A.G. Shavva, Russ. J. Bioorg. Chem. 33 (2007) 293–301.
[10] S.N. Morozkina, A.F. Fidarov, A.G. Shavva, J. Steroid Biochem. Mol. Biol. 126S (2011) e180.
[11] P. Pahari, B. Senapati, D. Mal, Tetrahedron Lett. 48 (2007) 2635–2638.
[12] E. Hecker, M. Hopp, Justus Liebigs Ann. Chem. 692 (1966) 174–179.
[13] J.S. Mills, J. Barrera, E. Olivares, H. García, J. Am. Chem. Soc. 82 (1960) 5882–5889.
[14] O.V. Dolomanov, L.J. Bourhis, R.J. Gildea, J.A.K. Howard, H. Puschmann, J. Appl. Crystallogr. 42 (2009) 339–341.
[15] G.M. Sheldrick, Acta Crystallogr., Sect. A: Found. Crystallogr. 64 (2008) 112–122.
[16] M. Maumy, P. Capdevielle, Tetrahedron 49 (1993) 7455–7462.