SYNTHESIS OF FLUORINATED STEROIDS USING A NOVEL FLUORINATING REAGENT TETRABUTYLAMMONIUM DIFLUORODIMETHYLPHENYLSILICATE (TAMPS)

Pavel HERRMANN[a1], Jaroslav KVÍČALA[b], Vladimír POUZAR[a2] and Hana CHODOUNSKÁ[a3,*]

[a] *Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, v.v.i., Flemingovo nám. 2, 166 10 Prague 6, Czech Republic; e-mail: [1] phermann@centrum.cz, [2] pouzar@uochb.cas.cz, [3] hchod@uochb.cas.cz*

[b] *Department of Organic Chemistry, Institute of Chemical Technology, Prague, Technická 5, 166 28 Prague 6, Czech Republic; e-mail: jaroslav.kvicala@vscht.cz*

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Dedicated to Professor Oldřich Paleta on the occasion of his 70th birthday.

Steroidal 3-fluoroderivatives were prepared from corresponding tosylates using tetrabutylammonium difluorodimethylphenylsilicate as fluorinating agent. The reaction was tested on all four possible C-3 and C-5 stereoisomers of cholestane and 17-oxoandrostane skeletons. In this reaction only one isomer was always formed with opposite configuration at C-3 to starting tosylate. The reaction is accompanied by elimination which affords a mixture of corresponding olefines.

Keywords: Steroidal fluoroderivatives; Stereoselective fluorination; NMR spectroscopy; S_N2 reaction.

In the course of previous research on neurosteroids, a fluorine atom was found to effectively substitute a hydroxy function without harming the biological activity[1,2]. This substitution may lead to improved pharmacological characteristics, such as an enhanced metabolic stability, which seemed promising. Besides the 3α-hydroxyl group, neurosteroids and their metabolites or precursors posses another oxygen (carbonyl or hydroxyl) functional group in position 17 of androstane and 20 of pregnane derivatives. The question of regioselectivity and chemoselectivity of fluorinating agents had to be considered.

The aim of our work was to compare the fluorinating ability of a nucleophilic fluorinating agent[3], tetrabutylammonium difluorodimethylphenyl-

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silicate (TAMPS; Chart 1), in fluorination of selected secondary steroidal tosylates with methods published in literature (cf. Results and Discussion).

Procedures published earlier utilise different fluorinating reagents to convert a hydroxyl group or a convenient intermediate, such as tosylate or mesylate, into a fluorine atom. Tosylates and mesylates react directly with a fluorine anion or with fluorosilicate reagents. Both the reactions mentioned proceed in the S_N2 mechanism with elimination as a side reaction. Thus the reaction affords a mixture of desired fluoro derivatives and olefines in varying ratio. Chiral molecules make it possible to yield two stereoisomeric fluoro derivatives, thus stereolectivity of the reaction is important. Information about toxicity, stability and availability of the reagent is also a important factor in its choice.

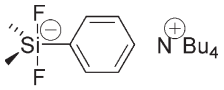


CHART 1

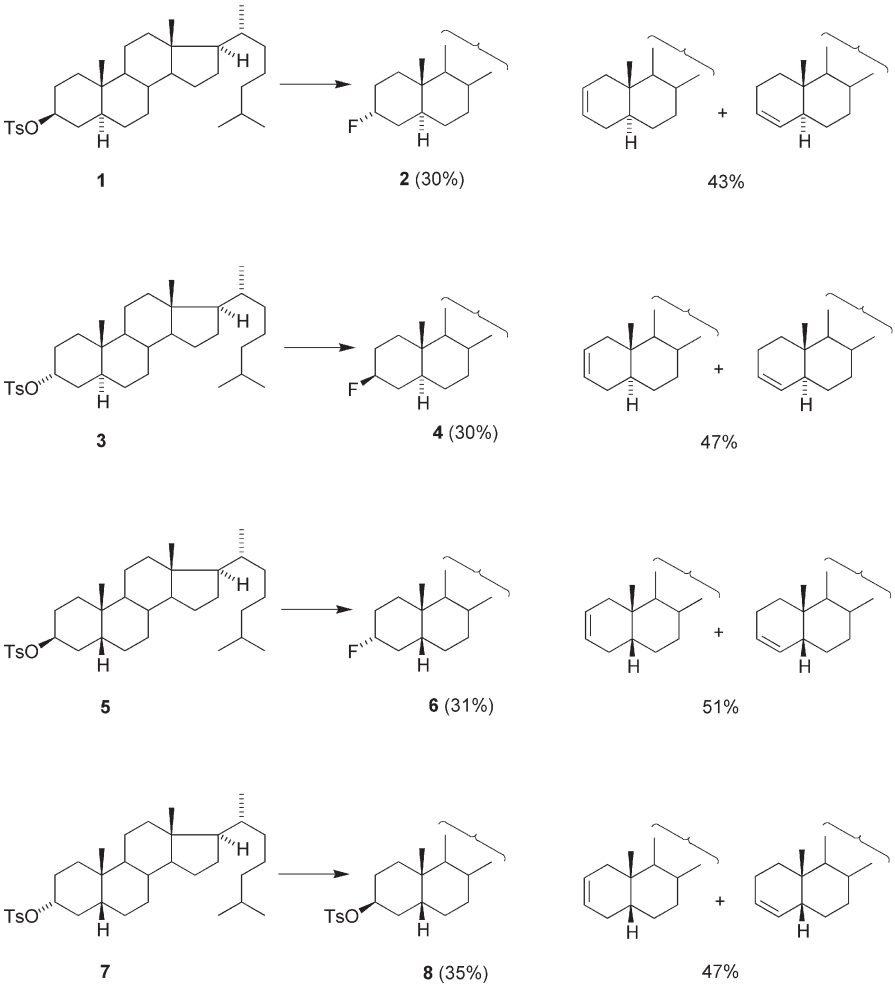
Intermediate tosylates and mesylates were prepared by the reaction of the hydroxyl substrates with sulfonyl chlorides. Because the majority of studies published were done with the tosylates, we used them as well for easier comparison of our findings with data published earlier.

RESULTS AND DISCUSSION

Tosylates used in this paper were prepared according published procedures[4–7]. The reagent TAMPS itself has been developed and successfully tested on aliphatic substrates by Kvíčala and co-workers[3].

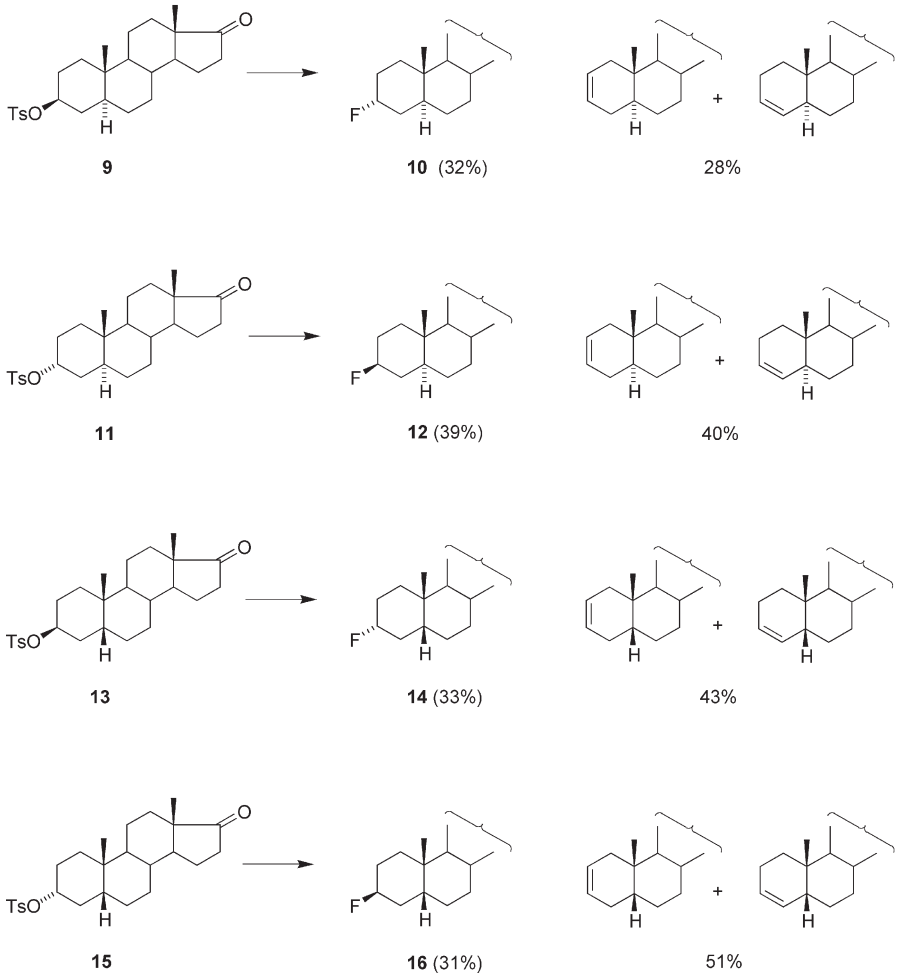
Fluorosteroids (Schemes 1–4) were obtained from the corresponding tosylates after 4–20 h of reflux in acetonitrile under an argon atmosphere, using two equivalents of TAMPS. Our results indicate that the fluorination in position 3 proceeds stereoselectively with inversion of configuration and furnishes pure fluoro derivates (30–39%), accompanied by mixture of corresponding 2-ene and 3-ene olefines (38–51%). Attempts to introduce fluorine into position 17 by this method lead to elimination only. The reagent applied to 7β-tosylate **19** afforded the 7α-fluoro derivative **20**, too, though in a lower yield (21%) and the mixture of olefines (43%). Structures of fluoro derivatives obtained were confirmed by the ^1H and ^{19}F NMR, mass spectra, and combustion analysis. Physical constants (m.p., specific rotation) of known compounds were compared with published data.

The configuration of the fluorine atom was confirmed by the ^{1}H and ^{19}F NMR spectra. The signal of the hydrogen atom in the position 3 has a characteristic chemical shift and shape. Above all, this signal is spliced by a strong geminal interaction ($^{2}J_{H,F} \approx 50$ Hz), as well as by other interactions with protons in the molecule. Really only ^{3}J splitting by vicinal protons in the positions 2 and 3 is observable. Resulting shape of the signal is dou-



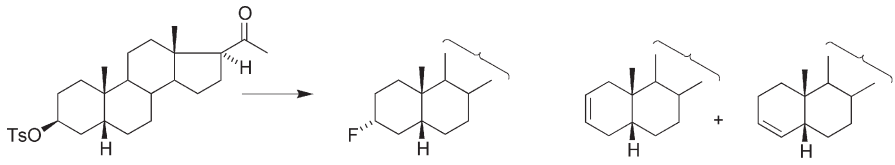
SCHEME 1
Reaction of cholestan-3-yl tosylates with TAMPS

blet of multiplets, whereas that multiplets width matches to the axial ($W \approx 32$ Hz) or equatorial ($W \approx 12$ Hz) orientation. Chemical shifts of axial and equatorial protons are very different, ca. 4.50 and 4.85, respectively. Thus in the ^{1}H NMR spectra it is possible to notice occurrence of the other isomer.



SCHEME 2
Reaction of androstan-3-yl tosylates with TAMPS

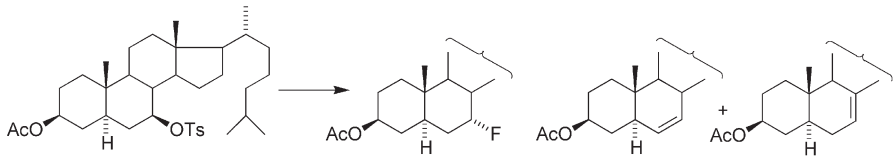
Also the ^{19}F NMR spectra have the characteristic shape and chemical shift of the signal of fluorine atom in the position 3. Geminal interaction $^{2}J_{H,F}$ (ca. 50 Hz) and interaction with the other protons in the molecule take effect. Really only ^{3}J interactions with protons in the adjacent positions 2 and 4 are important and its size depends on their relative orientation. In the case of an axial fluorine atom two interactions with the axial protons are observed, their size is comparable with the geminal interaction constant, it means about 50 Hz, and considerably low order interactions with equatorial protons. Combination of all mentioned effects result in the complex multiplet ($W \approx 165$ MHz).



17 **18** (34%) 48%

SCHEME 3

Isomers with equatorial orientation of fluorine have dihedral angles between C–F and C–H bonds on the neighbouring carbon atoms of roughly the same size, so the $^{3}J_{H,F}$ is approximately equal size and markedly lower than the geminal $^{2}J_{H,F}$. Thus signal of 3-H are two narrow multiplets in the distance equal to $^{2}J_{H,F}$, which is 50 Hz. Chemical shifts of axial fluorine atoms (ca. 178 ppm) and equatorial ones (ca. 164 ppm) are also different. Thus in the ^{19}F NMR spectra it is possible to notice the presence of the other isomer, too.



19 **20** (21%) 46%

SCHEME 4

The comparison of presented fluorinating reagent TAMPS with methods published earlier is limited by the fact that papers discussed below do not contain results of fluorinating reaction for all four possible stereoisomers in the positions 3 and 5 on equal conditions.

The most important methods described in literature are following. Replacement with fluoride ion on anion exchange resin in refluxing toluene was studied[8]. Mesylates on 5α-cholestane skeleton gave corresponding epimeric 3-fluoro derivatives **2** and **4**, their yields were 32 and 20%, respectively, side products was 2-ene derivative (31 and 41%). 3β-Tosylate **1** under identical reaction conditions gave lower yield (21%) of 3α-fluoro derivative **2** and olefin (49%). 3-Fluoro derivatives **10** and **12** were formed in the 5α-androstane series under the same conditions. The yields are 41 and 26%, respectively. The other product is olefin (57 and 37%, respectively). Reaction with the tetrabutylammonium fluoride (TBAF); 3β,5α-tosylate **9** gave 67% of 3α-fluoro derivative **10** and 30% of olefin[9].

Tetrabutylammonium bifluoride in the mixture with methanesulfonyl fluoride[9] reacts directly with 3β-hydroxy-5α-androstan-17-one to yield 82% of a 3α-fluoro derivative **10** and 12% of olefin. The yield of this reaction is higher compared with diethylaminosulfur trioxide (DAST); isolated yields: 47% of the 3α-fluoro derivative **10** and 12% of olefin.

Reaction with tetrabutylphosphonium hydrogen bifluoride[9]; 3β,5α-tosylate **9** afforded 77% of 3α-fluoro derivative **10** and 15% of olefin, corresponding mesylate gave 80% of fluoro derivative **10** and 16% of olefin.

During the reaction with DAST, hydroxy derivatives react directly with inversion of configuration at corresponding reaction centres[10]. 5α-Cholestan-3β-ol afforded 43% of 3α-fluoro derivative **2** and 32% of olefin, no 3β-fluoro derivative was recorded.

Phenyltetraphosphorane[11] reacts directly with hydroxy derivatives as well. 5α-Cholestan-3β-ol afforded 39% of 3α-fluoro derivative **2** and 38% of olefin. Epimeric 3α-hydroxy derivative gave 20% of 3β-fluoro derivative **4** and 76% of olefin. This reagent can not be used in the glass device.

To sum up, the yields of the reactions steroid tosylates with TAMPS are similar to the yields of published earlier. In this reaction only one isomer is always formed and its configuration opposite to the starting tosylate. Unfortunately this S_N2 nucleophilic substitution is accompanied by elimination, which affords a mixture of 2-ene and 3-ene olefins with the significant prevalence of the first isomer.

Some of the above discussed reactions afford higher yields, but exhaustive comparison with our results could not be done because of published reactions were not done with all fours stereoisomers under the same conditions. On contrary, in this work, the possibility of the preparation of 3-fluoro derivatives in all four conceivable combinations of configurations in the positions 3 and 5 of steroid skeleton was examined. The advantage of the TAMPS reagent is in its stereospecifity, furthermore this reaction does

not require any special equipment, the reagent is safe and not moisture sensitive.

EXPERIMENTAL

Melting points were determined on a Koefler melting point microapparatus Boetius (Germany) and are uncorrected. Analytical samples were dried over phosphorus pentoxide at 50 °C/100 Pa. Proton NMR spectra were measured on spectrometer Varian UNITY-200 (at 200 MHz) in $CDCl_3$ with tetramethylsilane as internal reference. ^{19}F NMR spectra were measured on a Bruker Avance II-500 spectrometer (at 470.3 MHz) in $CDCl_3$. Hexafluorobenzene (δ –163.0) was used as external standard. Chemical shifts are given in ppm (δ-scale), coupling constants *J* and widths of multiplets *W* in Hz. Unless otherwise stated, the data were interpreted as the first-order spectra. Mass spectra were measured on spectrometer ZAB-EQ (VG Analytical), EI (70 eV). Thin-layer chromatography (TLC) was performed on silica gel (ICN Biochemicals). Preparative TLC (PLC) was carried out on 200 × 200 mm plates coated with a 0.7 mm thick layer of the same material. For column chromatography, 60–120 μm silica gel was used (Merck). Whenever aqueous solutions of hydrochloric acid were used, concentration was 5% (v/v). Solvents were evaporated on a rotatory evaporator in vacuo (0.25 kPa, bath temperature 40 °C).

Preparation of Fluoro Derivatives. General Method

To the solution of tosylate in the minimum amount of absolute acetonitrile was added, through a septum, a solution of TAMPS in acetonitrile. The reaction mixture was refluxed in an argon atmosphere for 4–20 h. The reaction course was monitored by TLC. After completion the mixture was cooled to room temperature and poured into the water (200 ml). Products were extracted to the ether (100 ml, 3 times). Collected extracts were washed with saturated solution of sodium chloride (250 ml) and dried using anhydrous sodium sulfate, and the solvents evaporated. The residue was chromatographed on four preparative silica gel plates.

3α-Fluoro-5α-cholestane (**2**)

Mixture of tosylate[4] **1** (150 mg, 0.28 mmol), acetonitrile (20 ml) and 0.59 M TAMPS in acetonitrile (0.95 ml, 0.56 mmol) was refluxed for 16 h. PLC: light petroleum–ether (95:5); yield 32 mg (30%) of crystalline product **2**; m.p. 100–101 °C (lit.[8] gives 103–104 °C). ^1H NMR: 0.65 (3 H, s, H-18); 0.78 (3 H, s, H-19); 0.87 (6 H, d, J = 6.1, H-26 and H-27); 0.90 (3 H, d, J = 6.1, H-21); 4.81 (1 H, dm, $J_{F,H-3}$ = 49, H-3). ^{19}F NMR: –176.96 (1 F, m, $J_{F,H-3\beta} \approx J_{F,H-2\beta} \approx J_{F,H-4b} \approx 48$, $J_{F,H-2\alpha} \approx J_{F,H-4\alpha} \approx 12$, F-3α). EI MS, *m/z* (rel. int.): 390 (46, M), 375 (13, M – CH_3), 250 (12), 235 (94), 221 (17), 167 (33), 149 (21), 135 (12), 123 (22), 107 (28), 95 (46), 81 (53), 69 (70), 55 (84), 43 (100). For $C_{27}H_{47}F$ (390.7) calculated: 83.01% C, 12.13% H, 4.86% F; found: 82.79% C, 12.37% H, 4.68% F. In addition to the above, a mixture of olefins (45 mg, 43%) and starting material **1** (14 mg, 9%) were obtained.

3β-Fluoro-5α-cholestane (**4**)

Mixture of tosylate[4] **3** (200 mg, 0.37 mmol), acetonitrile (30 ml) and 0.59 M TAMPS in acetonitrile (1.25 ml, 0.74 mmol) was refluxed for 5.5 h. PLC: light petroleum; yield 43 mg

(30%) of crystalline product **4**; m.p. 75–77 °C (lit.[8] gives m.p. 78–80 °C). ^{1}H NMR: 0.66 (3 H, s, H-18); 0.83 (3 H, s, H-19); 0.87 (6 H, d, J = 6.1, H-26 and H-27); 0.91 (3 H, d, J = 6.1, H-21); 4.48 (1 H, dm, $J_{F,H-3}$ = 50, H-3). ^{19}F NMR: –163.67 (1 F, dm, $J_{F,H-3\alpha}$ = 50, F-3). EI MS, *m/z* (rel. int.): 390 (60, M), 375 (16, M – CH_3), 250 (15), 235 (100), 221 (13), 167 (12), 149 (16), 135 (10), 123 (15), 107 (25), 95 (35), 81 (40), 69 (26), 55 (49), 43 (57). For $C_{27}H_{47}F$ (390.7) calculated: 83.01% C, 12.13% H, 4.86% F; found: 82.73% C, 12.29% H, 5.02% F. In addition to the above, a mixture of olefins (49 mg, 47%) was obtained.

3α-Fluoro-5β-cholestane (**6**)

Mixture of tosylate[5] **5** (150 mg, 0.28 mmol), acetonitrile (20 ml) and 0.59 M TAMPS in acetonitrile (1.0 ml, 0.59 mmol) was refluxed for 6 h. PLC: light petroleum; yield 33 mg (31%) of oily product **6**. ^{1}H NMR: 0.65 (3 H, s, H-18); 0.86 (6 H, d, J = 6.1, H-26 and H-27); 0.90 (3 H, d, J = 6.1, H-21); 0.96 (3 H, s, H-19); 4.87 (1 H, dm, $J_{F,H}$ = 50, $\Sigma J_{H,H}$ = 32, H-3). ^{19}F NMR: –163.22 (1 F, dm, $J_{F,H-3\beta}$ = 50, F-3). EI MS, *m/z* (rel. int.): 390 (82, M), 375 (28, M – CH_3), 250 (10), 235 (100), 221 (13), 167 (15), 149 (22), 135 (13), 123 (18), 107 (34), 95 (50), 81 (55), 69 (38), 55 (75), 43 (94). For $C_{27}H_{47}F$ (390.7) calculated: 83.01% C, 12.13% H, 4.86% F; found: 82.96% C, 12.02% H, 4.77% F. In addition to the above, a mixture of olefins (53 mg, 51%) was obtained.

3β-Fluoro-5β-cholestane (**8**)

Mixture of tosylate[5] **7** (150 mg, 0.28 mmol), acetonitrile (20 ml) and 0.59 M TAMPS in acetonitrile (1.0 ml, 0.59 mmol) was refluxed for 6 h. PLC: light petroleum; yield 38 mg (35%) of oily product **8**. ^{1}H NMR: 0.64 (3 H, s, H-18); 0.84 (3 H, s, H-19); 0.87 (6 H, d, J = 6.1, H-26 and H-27); 0.91 (3 H, d, J = 6.1, H-21); 4.51 (1 H, dm, $J_{F,H-3}$ = 50, H-3). ^{19}F NMR: –178.18 (1 F, m, $J_{F,H-3\beta} \approx J_{F,H-2\beta} \approx J_{F,H-4\beta} \approx 48$, $J_{F,H-2\alpha} \approx J_{F,H-4\alpha} \approx 12$, F-3). EI MS, *m/z* (rel. int.): 390 (55, M), 375 (15, M – CH_3), 250 (12), 235 (100), 221 (16), 167 (20), 149 (18), 135 (13), 123 (17), 107 (31), 95 (50), 81 (52), 69 (39), 55 (70), 43 (91). For $C_{27}H_{47}F$ (390.7) calculated: 83.01% C, 12.13% H, 4.86% F; found: 82.79% C, 11.96% H, 5.06% F. In addition to the above, a mixture of olefins (49 mg, 47%) was obtained.

3α-Fluoro-5α-androstan-17-one (**10**)

Mixture of tosylate[4] **9** (160 mg, 0.36 mmol), acetonitrile (20 ml) and 0.59 M TAMPS in acetonitrile (1.2 ml, 0.72 mmol) was refluxed for 11 h. PLC: light petroleum–acetone; yield 34 mg (32%) of crystalline product **10**; m.p. 112–116 °C (lit.[12] gives m.p. 114–115 °C). ^{1}H NMR: 0.81 (3 H, s, H-18); 0.86 (3 H, s, H-19); 4.83 (1 H, dm, $J_{F,H}$ = 50, H-3). ^{19}F NMR: –177.24 (1 F, m, $J_{F,H-3\beta} \approx J_{F,H-2\beta} \approx J_{F,H-4\beta} \approx 48$, $J_{F,H-2\alpha} \approx J_{F,H-4\alpha} \approx 12$, F-3). EI MS, *m/z* (rel. int.): 292 (80, M), 277 (15, M – CH_3), 248 (36), 235 (17), 221 (30), 167 (15), 149 (16), 121 (15), 108 (40), 91 (50), 79 (65), 67 (80), 55 (78), 41 (100). For $C_{19}H_{29}FO$ (292.4) calculated: 78.04% C, 10.00% H, 6.50% F; found: 77.85% C, 10.13% H, 6.58% F. In addition to the above, a mixture of olefins (27 mg, 28%) and starting material **9** (27 mg, 18%) were obtained.

3β-Fluoro-5α-androstan-17-one (**12**)

Mixture of tosylate[4] **11** (150 mg, 0.34 mmol), acetonitrile (15 ml) and 0.59 M TAMPS in acetonitrile (1.15 ml, 0.67 mmol) was refluxed for 4 h. PLC: light petroleum–acetone (9:1);

yield 38 mg (39%) of crystalline product **12**; m.p. 135–138 °C (lit.[12] gives m.p. 132–135 °C). ^{1}H NMR: 0.86 (6 H, s, H-18 and H-19); 4.48 (1 H, dm, $J_{F,H}$ = 50, $\Sigma J_{H,H}$ = 32, H-3). ^{19}F NMR: –163.99 (1 F, dm, $J_{F,H\text{-}3\alpha}$ = 49.6, F-3). EI MS, *m/z* (rel. int.): 292 (100, M), 277 (13, M – CH_3), 248 (37), 235 (15), 221 (20), 167 (12), 149 (11), 121 (23), 108 (60), 91 (46), 79 (52), 67 (65), 55 (45), 41 (54). For $C_{19}H_{29}FO$ (292.4) calculated: 78.04% C, 10.00% H, 6.50% F; found: 77.89% C, 10.17% H, 6.34% F. In addition to the above, a mixture of olefins (39 mg, 40%) was obtained.

3α-Fluoro-5β-androstan-17-one (**14**)

Mixture of tosylate[6] **13** (200 mg, 0.46 mmol), acetonitrile (30 ml) and 0.59 M TAMPS in acetonitrile (1.6 ml, 0.92 mmol) was refluxed for 4 h. PLC: light petroleum–acetone (95:5); yield 40 mg (33%) of crystalline product **14**; m.p. 123–125 °C. ^{1}H NMR: 0.85 (3 H, s, H-18); 0.95 (3 H, s, H-19); 4.52 (1 H, dm, $J_{F,H}$ = 50, $\Sigma J_{H,H}$ = 32, H-3). ^{19}F NMR: –163.47 (1 F, dm, $J_{F,H\text{-}3}$ = 49.3, F-3). EI MS, *m/z* (rel. int.): 292 (45, M), 277 (10, M – CH_3), 248 (22), 235 (11), 221 (12), 167 (10), 149 (100), 121 (15), 108 (23), 91 (35), 79 (33), 67 (52), 55 (70), 41 (96). For $C_{19}H_{29}FO$ (292.4) calculated: 78.04% C, 10.00% H, 6.50% F; found: 77.75% C, 10.11% H, 6.37% F. In addition to the above, a mixture of olefins (54 mg, 43%) was obtained.

3β-Fluoro-5β-androstan-17-one (**16**)

Mixture of tosylate[6] **15** (170 mg, 0.38 mmol), acetonitrile (20 ml) and 0.76 M TAMPS in acetonitrile (1.3 ml, 0.92 mmol) was refluxed for 5 h. PLC: light petroleum–acetone (95:5); yield 35 mg (31%) of crystalline product **16**; m.p. 123–126 °C (lit.[10] gives m.p. 131 °C). ^{1}H NMR: 0.86 (3 H, s, H-18); 0.99 (3 H, s, H-19); 4.88 (1 H, dm, $J_{F,H}$ = 50, H-3). ^{19}F NMR: –178.45 (1 F, m, $J_{F,H\text{-}3\alpha} \approx J_{F,H\text{-}2\alpha} \approx J_{F,H\text{-}4\alpha} \approx 48$, $J_{F,H\text{-}2\beta} \approx J_{F,H\text{-}4\beta} \approx 12$, F-3). EI MS, *m/z* (rel. int.): 292 (95, M), 277 (10, M – CH_3), 248 (37), 235 (15), 221 (18), 167 (10), 149 (30), 121 (23), 108 (52), 91 (46), 79 (55), 67 (76), 55 (72), 41 (100). For $C_{19}H_{29}FO$ (292.4) calculated: 78.04% C, 10.00% H, 6.50% F; found: 77.81% C, 10.21% H, 6.29% F. In addition to the above, a mixture of olefins (49 mg, 51%) was obtained.

3α-Fluoro-5β-pregnan-20-one (**18**)

Mixture of tosylate[6] **17** (150 mg, 0.32 mmol), acetonitrile (20 ml) and 0.76 M TAMPS in acetonitrile (1.1 ml, 0.64 mmol) was refluxed for 6 h. PLC: light petroleum–acetone (9:1); yield 35 mg (34%) of crystalline product **18**; m.p. 104–106 °C (lit.[2] gives 107–108 °C). ^{1}H NMR: 0.60 (3 H, s, H-18); 0.93 (3 H, s, H-19); 2.12 (3 H, s, H-21); 2.54 (1 H, dd, $J_1 = J_2$ = 9, H-17); 4.53 (1 H, dm, $J_{F,H}$ = 50, H-3). ^{19}F NMR: –163.30 (1 F, dm, $J_{F,H\text{-}3\beta}$ = 50, F-3). EI MS, *m/z* (rel. int.): 320 (52, M), 302 (48), 250 (13), 235 (70), 149 (20), 121 (35), 107 (37), 95 (46), 84 (90), 67 (42), 55 (35), 43 (100). For $C_{21}H_{33}FO$ (320.5) calculated: 78.70% C, 10.38% H, 5.93% F; found: 78.81% C, 10.25% H, 5.82% F. In addition to the above, a mixture of olefins (46 mg, 48%) was obtained.

7α-Fluoro-5α-cholestan-3β-yl Acetate (**20**)

Mixture of tosylate[7] **19** (150 mg, 0.25 mmol), acetonitrile (20 ml) and 0.76 M TAMPS in acetonitrile (0.9 ml, 0.53 mmol) was refluxed for 16 h. PLC: light petroleum–acetone (9:1); yield 24 mg (21%) of crystalline product **20**; m.p. 110–113 °C. ^{1}H NMR: 0.64 (3 H, s, H-18);

0.82 (3 H, s, H-19); 0.87 (6 H, d, J = 6.1, H-26 and H-27); 0.91 (3 H, d, J = 6.1, H-21); 2.02 (3 H, s, OAc); 4.63 (1 H, dm, $J_{F,H}$ = 50, H-7); 4.75 (1 H, m, W = 32, H-3). ^{19}F NMR: –176.53 (1 F, m, $J_{F,H\text{-}7\beta} \approx J_{F,H\text{-}6\beta} \approx J_{F,H\text{-}8\beta} \approx 48$, $J_{F,H\text{-}6\alpha} \approx 12$, F-3α). EI MS, *m/z* (rel. int.): 448 (90, M), 428 (35), 388 (50), 368 (30), 294 (20), 248 (30), 234 (55), 149 (50), 121 (22), 107 (55), 95 (60), 81 (80), 69 (80), 55 (43), 43 (100). For $C_{29}H_{49}FO_2$ (448.7): 77.63% C, 11.01% H, 4.23% F; found: 77.49% C, 10.96% H, 4.14% F. In addition to the above, a mixture of 6(7) and 7(8) olefins (46 mg, 43%) and starting material **19** (18 mg, 12%) were obtained.

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