New, convenient route for trifluoromethylation of steroidal molecules

Xiang-Shu Fei, Wei-Sheng Tian and Qing-Yun Chen *

Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai, 200032, China

1 PERKIN

A new convenient route for direct trifluoromethylation of steroidal compounds is described. Steroidal alkenyl bromides, derived from steroidal unsaturated ketones, react with $FO_2SCF_2CO_2Me$ in the presence of CuI in DMF to give the corresponding trifluoromethylated steroids in good yields (70–91%).

Introduction

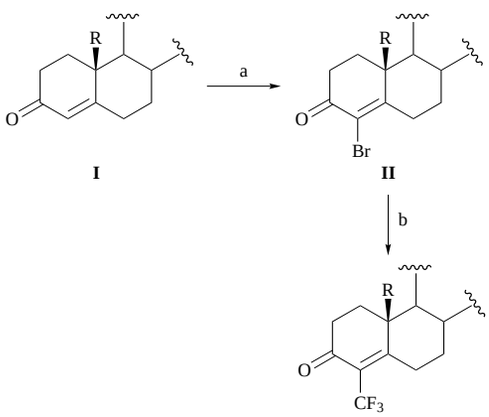
In recent years, the development of new synthetic methods for introducing a trifluoromethyl group into an organic molecule has received much attention because of the unique properties of the trifluoromethylated compounds in materials science and in their biological activities as medicines and agrochemicals.[1] Numerous methods have been employed for the trifluoromethylation of simple organic compounds.[2] With respect to the synthesis of structurally simple natural molecules, using a trifluoromethylated building block followed by several necessary steps seems to be straightforward and convenient.[3] However, for the synthesis of complicated trifluoromethylated natural products, such as steroids, terpenes and alkaloids, the building-block strategy is apparently very difficult if not impossible. Therefore, there is a need for finding some new trifluoromethylation approach which can directly trifluoromethylate these complex natural product molecules. Recently, the trifluoromethylation of hindered steroidal ketones with a modified method (CF_3SiMe_3–Me_4NF)[4] of Ruppert[5,6] has been reported and those fluorinated products showed higher bioactivity than those without this group.[4]

In connection with our previous finding that some inexpensive trifluoromethylating agents, such as $FO_2SCF_2CO_2Me$ (MFSDA),[7] $FO_2SCF_2CF_2OCF_2CO_2Me$[8] and XCF_2CO_2Me (X = Cl, Br, I),[9] can successfully replace halogen in vinyl, allyl, aryl and alkyl halides, we envisaged that our reagents could also be applied to the steroidal molecules. This paper presents our results.

Results and discussion

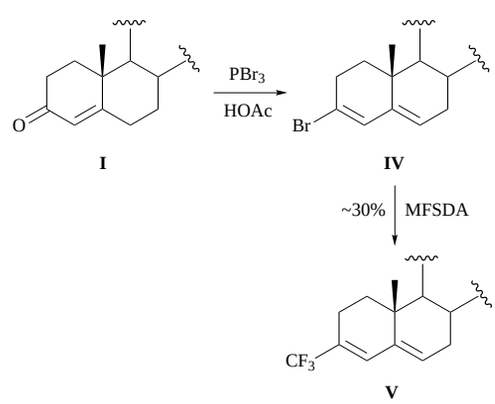
We took some steroidal 4-en-3-ones **I** as the starting materials for C-4 trifluoromethylation. On the basis of the characteristic properties of our trifluoromethylating reagents, a vinyl halide atom (Br or I) must first be introduced on C-4 of steroidal 4-en-3-ones **I**. When the bromination of steroids **I** was attempted with bromine in acetic acid–diethyl ether or with *N*-bromosuccinimide (NBS) in a suitable solvent, it resulted in only allylic bromination with the formation of the corresponding 6-bromo- and 2,6-dibromo-3-oxo-Δ^4-steroids.[9] In the presence of a proton acceptor, *e.g.* 2,4,6-trimethylpyridine (collidine), in the reaction mixture, the allylic bromination was suppressed and the corresponding 4-bromo-3-oxo-Δ^4-steroids **II** were obtained.[10] Thus, in acetic acid, bromination of steroidal 4-en-3-ones **I** in the presence of collidine and diethyl ether led to a monobromo derivative at C-4 **II** in yields of 62–81%. The results are listed in Table 1.

Among our trifluoromethylating reagents, MFSDA was found to be most suitable for steroidal 4-bromo-3-oxo-Δ^4-steroids **II** because of its lower decomposition temperature (~75 °C) compared with other trifluoromethylating agents.[8,9] These 4-bromo-3-oxo-Δ^4-steroids **II** in dimethylformamide (DMF) can be trifluoromethylated on C-4 with MFSDA in the presence of catalytic amounts of CuI to give the corresponding 4-trifluoromethylated products **III** in yields of 70–91% (Scheme 1, Table 1).



Scheme 1 *Reagents and conditions*: **a**, Br_2, HOAc, Et_2O, collidine; **b**, MFSDA, CuI, DMF, 75 °C. R = CH_3, H.

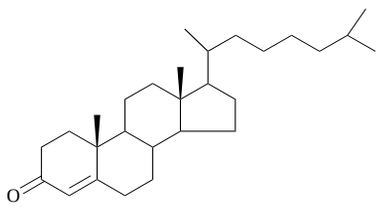
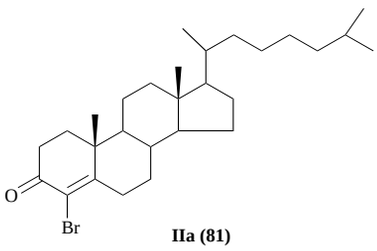
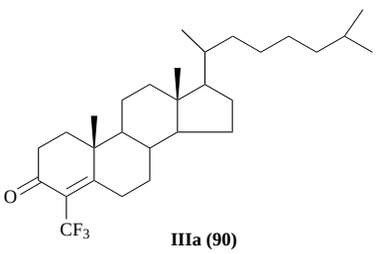
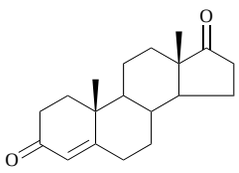
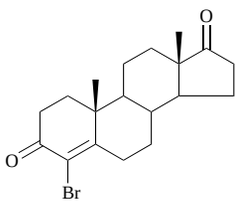
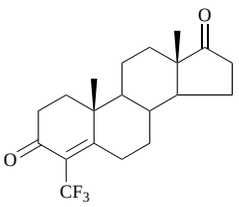
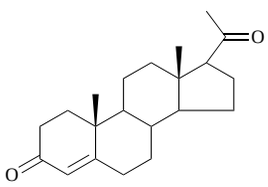
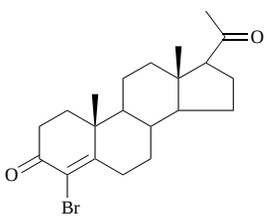
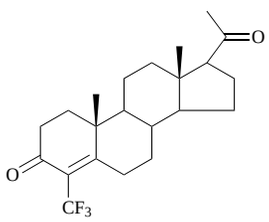
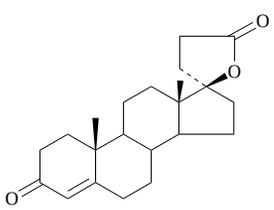
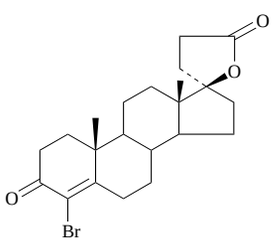
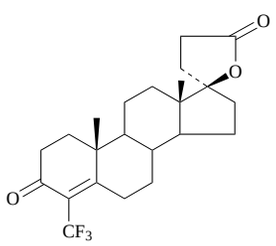
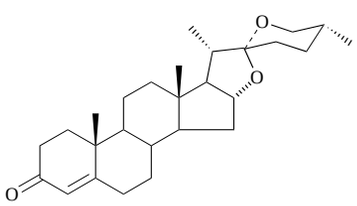
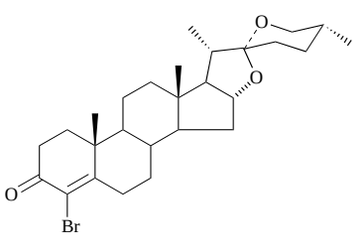
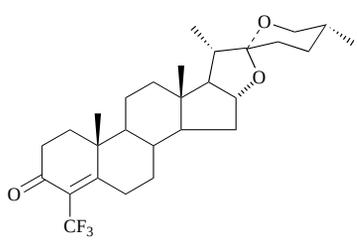
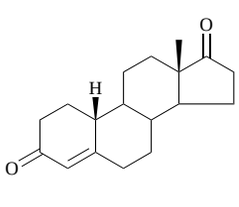
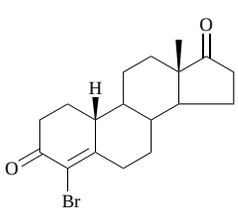
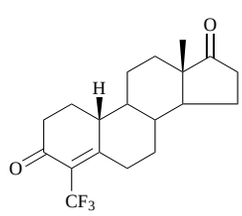
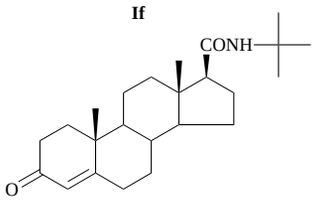
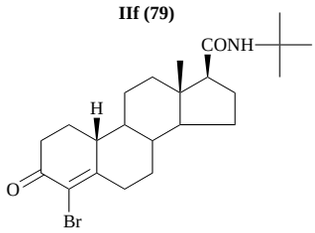
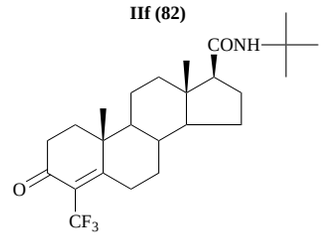
We also prepared several steroidal 3-bromo-$\Delta^{3,5}$-dienes **IV** from steroidal 4-en-3-ones **I**,[12] but the former reacted with MFSDA to afford the corresponding trifluoromethylated products **V** in lower yields (~30%). Prolongation of the reaction time and utilization of a large excess of trifluoromethylating reagent did not improve the yields, but resulted in the occurrence of some side-reactions (Scheme 2).



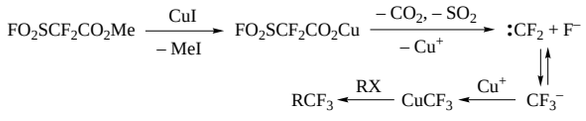
Scheme 2

The mechanism of this trifluoromethylation of unsaturated 4-bromo steroids, like that of simple vinyl bromide, is suggested to proceed as follows: methyl difluoro(fluorosulfonyl)acetate reacts with copper(I) iodide after elimination of SO_2 and CO_2, to yield initially difluorocarbene and fluoride ion, which

Table 1 Products and yields (%)

3-Oxo-Δ^4-steroids **I**	4-Bromo-3-oxo-Δ^4-steroids **II**	4-Trifluoromethyl-3-oxo-Δ^4-steroids **III**
 **Ia**	 **IIa (81)**	 **IIIa (90)**
 **Ib**	 **IIb (80)**	 **IIIb (81)**
 **Ic**	 **IIc (70)**	 **IIIc (74)**
 **Id**	 **IId (62)**	 **IIId (70)**
 **Ie**	 **IIe (73)**	 **IIIe (71)**
 **If**	 **IIf (79)**	 **IIf (82)**
 **Ig**	 **IIg (64)**	 **IIIg (91)**

establish an equilibrium with CF_3^-. In the presence of CuI, the equilibrium is readily shifted to the right to form the nucleophilic species [CF_3CuI^-], which then reacts with the steroidal alkenyl bromide to afford the final product (Scheme 3).[7,13] Compared with compound **IV** containing no electron-withdrawing group, the presence of an electron-withdrawing carbonyl on the C-3 position of species **II** is expected to enhance the trifluoromethylation to give higher yields.[8]



Scheme 3

Experimental

Mps were measured on a Büchi 535 apparatus and are uncorrected. IR spectra were taken on a Shimadzu-440 spectrophotometer. ^{1}H NMR spectra were recorded with a Bruker AM-300 (300 MHz) spectrometer. *J*-Values are given in Hz. ^{19}F NMR were obtained on an EM-360L (60 MHz) spectrometer and chemical shifts were measured in ppm downfield from CF_3CO_2H (TFA) as an external reference and converted to $CFCl_3$ standard by the calculation of $\delta(CFCl_3) = -[77.0 + \delta(TFA)]$. Mass spectra were determined on an HP5989A mass spectrometer. Flash column procedures were conducted on silica gel H (10–40 μm). Dimethylformamide (DMF) was dried over CaH_2 and distilled under vacuum pressure. Light petroleum refers to the fraction distilled at 60–90 °C.

Typical procedure for preparation of compounds II

4-Bromocholest-4-en-3-one IIa. To a solution of cholest-4-en-3-one **Ia** (760 mg, 1.62 mmol) in anhydrous Et_2O (15 ml) and collidine (3 ml) was added bromine (0.8 ml) in acetic acid (10 ml) dropwise. The mixture was stirred in the dark at room temp. for 48 h. After completion of the reaction, collidine hydrobromide was separated. The solution was poured into water (20 ml) and extracted with Et_2O (4 × 25 ml). The combined organic phase was then washed successively with saturated aq. sodium dithionite, 2 M hydrochloric acid, dil. aq. sodium hydrogen carbonate and water, and dried by anhydrous $MgSO_4$. The residue obtained upon evaporation of the solution was chromatographed with light petroleum–AcOEt (50:1 v/v) to give compound **IIa** (745 mg, 90%) as a solid, mp 113.0–113.5 °C; ν_{max}(KBr)/cm^{-1} 2900, 2690, 2595, 1444, 1382, 1280, 1180 and 800; δ_H($CDCl_3$) 0.71 (s, 3 H, 18-H_3), 0.85 (dd, *J* 6.56 and 1.0, 26- and 27-H_3), 0.91 (d, *J* 6.50, 21-H_3), 1.23 (s, 19-H_3) and 3.25 (dt, *J* 14.84 and 3.30, 1 H_2); *m/z* 464 (M^+ + 1, 30.49%), 463 (M^+, 73.43), 462 (M^+ − 1, 53.01), 461 (M^+ − 2, 67.91), 383 (M^+ − Br, 74.40), 381 (63.54), 365 (35.37), 247 (57.63), 227 (37.20), 95 (69.90) and 43 (100).

4-Bromoandrost-4-ene-3,17-dione IIb. 80%, mp 152.5–152.8 °C; ν_{max}(KBr)/cm^{-1} 3000, 2800, 1750, 1690, 1580, 1460, 1390, 1290, 1200, 1060, 1020, 950 and 810; δ_H($CDCl_3$) 0.93 (s, 18-H_3), 1.27 (s, 19-H_3) and 3.35 (ddd, *J* 15.2, 3.20 and 2.95); *m/z* 366 [M(^{82}Br)$^+$, 7.28%], 364 (M^+, 7.64), 285 (M^+ − 1 − Br, 100), 267 (22.84), 243 (14.00), 187 (18.22) and 91 (32.89) (Found: C, 62.47; H, 6.90. Calc. for $C_{19}H_{25}BrO_2$: C, 62.46; H, 6.87%).

4-Bromopregn-4-en-3,20-dione IIc. 70%, mp 162.0–162.5 °C; ν_{max}(KBr)/cm^{-1} 1950, 1850, 1710, 1680, 1580, 1360, 1240, 1200, 950 and 840; δ_H($CDCl_3$) 0.68 (s, 3 H, 18-H_3), 1.24 (s, 19-H_3), 2.13 (s, 21-H_3) and 3.28 (ddd, *J* 15.0, 3.88 and 2.78); *m/z* 394 [M(^{82}Br)$^+$, 1.62%], 392 (M^+, 1.5), 379 [M(^{82}Br)$^+$ − CH_3, 1.1], 377 (M^+ − CH_3, 1.0), 314 [M(^{82}Br)$^+$ − 20.55], 313 (84.60), 295 (60.50), 271 (11.52), 253 (19.86), 147 (39.17), 91 (47.76) and 43 (100).

4-Bromo-3-oxo-17α-pregn-4-ene-21,17-carbolactone IId. 62%, mp 126.0–127.0 °C; ν_{max}(KBr)/cm^{-1} 2920, 1780, 1690, 1580, 1380 and 1180; δ_H($CDCl_3$) 0.99 (s, 18-H_3), 1.26 (s, 19-H_3) and 3.30 (ddd, *J* 15.01, 3.64 and 2.83); *m/z* 422 (M^+ + 1, 5.33%), 421 (M^+, 8.0), 420 (M^+ − 1, 10.6), 403 (4.0), 347 (27.21), 34 (31.49) and 269 (100).

[16β(H),25*R*]-4-Bromospirost-4-en-3-one IIe. 73%, mp 225.0–225.5 °C; ν_{max}(KBr)/cm^{-1} 2900, 1696, 1580, 1456, 1380, 1240, 1180, 1050, 987 and 900; δ_H($CDCl_3$) 0.79 (d, *J* 6.30, 3 H, CH_3), 0.82 (s, 18-H_3), 0.97 (d, *J* 6.79, 3 H, CH_3), 1.25 (s, 19-H_3), 3.22–3.50 (m, 3 H) and 4.11 (dd, *J* 14.86 and 7.58, 1 H); *m/z* 492 [M(^{82}Br)$^+$, 1.0%], 490 (M^+, 1.00), 421 (5.48), 42 (5.85), 378 (19.00), 376 (18.99), 349 (10.67), 347 (10.54), 297 (10.20), 263 (10.81) and 139 (100) (Found: C, 65.67; H, 8.50. Calc. for $C_{27}H_{39}BrO_3$: C, 65.97; H, 8.01%).

4-Bromoestr-4-ene-3,17-dione IIf. 79%, mp 193.4–194.0 °C; ν_{max}(KBr)/cm^{-1} 2800, 1746, 1686 and 1588; δ_H($CDCl_3$) 0.94 (s, 18-H_3) and 3.43 (ddd, *J* 14.93, 3.50 and 2.80); *m/z* 352 (M^+ + 1, 8.28%), 350 (M^+ − 1, 9.26), 295 (11.76), 271 (M^+ − Br, 26.07), 270 (32.62), 213 (11.51), 185 (17.18), 172 (12.33) and 91 (100).

4-Bromo-*N*-(*tert*-butyl)-3-oxoandrost-4-en-17β-carboxamide IIg. 64%, mp 106.0–107.0 °C; ν_{max}(KBr)/cm^{-1} 3400, 2900, 1690, 1680, 1580, 1510, 1450, 1390, 1360, 1260 and 1120; δ_H($CDCl_3$) 0.73 (s, 18-H_3), 1.24 (s, 19-H_3), 1.35 (s, Bu^t) and 5.09 (s, NH); *m/z* 452 [M(^{82}Br)$^+$, 6.03%], 451 [M(^{82}Br)$^+$ − 1, 7.82], 449 (M^+ − 1, 8.91), 434 (M^+ − CH_3, 5.0), 387 (4.5), 370 (55.64), 369 (56.80), 354 (14.39), 313 (14.73), 298 (8.14), 281 (11.50), 269 (11.12), 253 (22.98) and 57 (100) (Found: C, 69.81; H, 8.05; N, 3.00. Calc. for $C_{24}H_{36}BrNO_2$: C, 63.99; H, 8.05; N, 3.11%).

Typical procedure for preparation of compounds III

4-(Trifluoromethyl)cholest-4-en-3-one IIIa. A mixture of bromide **IIa** (100 mg, 0.215 mmol), CuI (50 mg, 0.263 mmol) and MFSDA (0.2 ml) in dry DMF (10 ml) was stirred at 75 °C under nitrogen for 7 h. On completion of the reaction, the mixture was diluted by Et_2O (20 ml) and filtered. The solution was poured into water (20 ml). The mixture was extracted with Et_2O (4 × 20 ml). The combined extracts was washed with water (3 × 5 ml) and dried by anhydrous $MgSO_4$. The residue obtained upon evaporation of the solution was chromatographed with light petroleum–AcOEt (30:1, v/v) to give compound **IIIa** (76 mg, 78%) as a solid, mp 111.0–112.0 °C; ν_{max}(KBr)/cm^{-1} 2980, 2800, 2690, 1600, 1468, 1370, 1346, 1160 and 1124; δ_H($CDCl_3$) 0.71 (s, 3 H, 18-H_3), 0.86 (dd, *J* 6.85 and 1.13, 6 H, 26- and 27-H_3), 0.91 (d, *J* 6.49, 3 H, 21-H_3), 1.25 (s, 19-H_3) and 3.30 (d, br, *J* 14.69, 1 H); ^{19}F NMR (60 MHz; $CDCl_3$) δ −55.3 (s); *m/z* 454 (M^+ + 2, 7.07%), 453 (M^+ + 1, 25.62), 452 (M^+, 17.27), 437 (M^+ − CH_3, 7.667), 383 (M^+ − CF_3, 12.35), 367 (7.14), 339 (8.88), 297 (31.25), 260 (64.29), 247 (34.44), 192 (61.29), 95 (66.47), 69 (47.91) and 43 (100) (Found: C, 74.59; H, 9.97. Calc. for $C_{28}H_{43}F_3O$: C, 74.30; H, 9.57%).

4-(Trifluoromethyl)androst-4-ene-3,17-dione IIIb. 81%, mp 150.0–151.0 °C; ν_{max}(KBr)/cm^{-1} 3000, 1750, 1600, 1350, 1160 and 1120; δ_H($CDCl_3$) 0.93 (s, 3 H, 18-H_3), 1.29 (s, 19-H_3), 3.12 (d, br, *J* 14.82, 1 H). ^{19}F NMR (60 MHz; $CDCl_3$) δ −55.3 (s); *m/z* 355 (M^+ + 1, 7.22%), 354 (M^+, 30.31), 339 (M^+ − CH_3, 7.72), 310 (16.16), 285 (M^+ − CF_3, 25.44), 268 (15.88), 241 (17.87), 192 (100), 107 (78.92) and 69 (17.69) (Found: C, 67.54; H, 7.37. Calc. for $C_{20}H_{25}F_3O_2$: C, 67.78; H, 7.11%).

4-(Trifluoromethyl)pregn-4-ene-3,20-dione IIIc. 74%, mp 124.5–125.5 °C; ν_{max}(KBr)/cm^{-1} 2950, 2800, 1700, 1600, 1460, 1364 and 1120; δ_H($CDCl_3$) 0.68 (s, 3 H, 18-H_3), 1.26 (s, 19-H_3), 2.21 (s, 21-H_3) and 3.05 (d, br, *J* 14.65, 1 H). ^{19}F NMR (60 MHz; $CDCl_3$) δ_H −55.7 (s); *m/z* 382 (M^+, 5.97%), 3.67 (M^+ − Me, 10.78), 364 (4.26), 339 (4.29), 192 (49.85), 190 (59.01), 173 (27.37), 147 (64.39), 133 (37.37) and 43 (100) (Found: C, 69.00; H, 8.11. Element Analysis for $C_{22}H_{29}F_3O_2$ Calc. C, 69.09; H, 7.64%).

3-Oxo-4-(trifluoromethyl)-17α-pregn-4-ene-21,17-carbolactone IIId. 70%, mp 124.0–125.0 °C; ν_{max}(KBr)/cm^{-1} 2900, 1770, 1700, 1638, 1600, 1340, 1180, 1120 cm^{-1}. ($CDCl_3$) 1.00 (s, 18-H_3), 1.28 (s, 19-H_3) and 2.21 (s, 21-H_2); ^{19}F NMR (60 MHz; $CDCl_3$) δ −55.7 (s); *m*/*z* 410 (M^+, 5.10%), 341 ($M^+ - CF_3$, 3.95), 337 (7.90), 310 (6.96), 219 (12.31), 203 (30.74), 149 (15.35), 134 (100) and 55 (64.44) (Found: M^+, 410.2082. Calc. for $C_{22}H_{29}F_3O_2$: 410.2069).

[16β(H),25*R*]-4-(Trifluoromethyl)spirost-4-en-3-one IIIe. 71%, mp 218.0–219.0 °C; ν_{max}(KBr)/cm^{-1} 2900, 1780, 1600, 1456, 1346, 1120, 1056 and 980; δ_H($CDCl_3$) 0.79 (d, *J* 6.18, 3 H, CH_3), 0.83 (s, 3 H, 18-H_3), 0.94 (d, *J* 9.91, CH_3), 1.27 (s, 19-H_3), 2.40–2.48 (m, 2 H), 3.05 (d, br, *J* 14.85, 1 H), 3.35–3.50 (m, 2 H) and 4.42 (dd, *J* 14.72 and 7.48, 1 H); ^{19}F NMR (60 MHz; $CDCl_3$) δ −55.4 (s); *m*/*z* 382 (M^+, 1.2%), 450 (0.86), 421 (4.21), 411 ($M^+ - CF_3$, 6.74), 408 (10.56), 366 (18.95), 351 (6.44), 337 (25.76), 139 (100) and 69 (37.38) (Found: C, 69.47; H, 8.27. Calc. for $C_{28}H_{39}F_3O_3$: C, 69.97; H, 8.18%).

4-(Trifluoromethyl)estr-4-ene-3,17-dione IIIf. 82%, mp 185.6–187.0 °C; ν_{max}/cm^{-1} 2800, 1740, 1690, 1600, 1100 and 1040; δ_H($CDCl_3$) 0.94 (s, 18-H_3) and 3.48 (m); ^{19}F NMR (60 MHz; $CDCl_3$) δ −56.2 (s); *m*/*z* 341 ($M^+ + 1$, 26.76%), 340 (M^+, 79.37), 322 (16.98), 296 (46.73), 281 (30.71), 271 (80.69), 254 (78.03), 227 (32.69), 215 (51.37), 145 (64.81) and 107 (100) (Found: M^+, 340.1638. Calc. for $C_{19}H_{23}F_3O_2$: *M*, 340.1650).

***N*-(*tert*-Butyl)-3-oxo-4-(trifluoromethyl)androst-4-ene-17β-carboxamide IIIg.** 91%, mp 158.0–159.0 °C; ν_{max}(KBr)/cm^{-1} 3499br (NH), 2900, 1680br, 1590, 1510, 1450, 1360, 1260, 1230 and 1120; δ_H($CDCl_3$) 0.74 (s, 18-H_3), 1.26 (s, 19-H_3), 1.35 (s, Bu′) and 5.08 (s, NH); ^{19}F NMR (60 MHz; $CDCl_3$) δ −56.2 (s); *m*/*z* 439 (M^+, 30.73%), 424 ($M^+ - CH_3$, 11.6), 404 (22.75), 384 (11.05), 368 (7.5), 339 (7.95), 248 (19.67), 149 (51.94), 69 (63.88) and 57 (100) (Found: C, 68.22; H, 8.31; N, 2.98. Calc. for $C_{25}H_{36}F_3NO_2$: C, 68.31; H, 8.25; N, 3.19%).

Acknowledgements

We thank Professor W.-Y. Huang for his encouragement and the Chinese National Science Foundation for their financial support of this work.

References

1 J. T. Welch and S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, 1991; J. T. Welch, *Selective Fluorination in Organic and Bioorganic Chemistry*, ACS Symposium Series 456, American Chemical Society, Washington DC, 1991; *Tetrahedron*, 1987, **43**, 3123.
2 M. A. McClinton and D. A. McClinton, *Tetrahedron*, 1992, **48**, 6555.
3 W. S. Tian, Y. R. Luo, Y. Q. Chen and A. J. Yu, *J. Chem. Soc., Chem. Commun.*, 1993, 101 and references therein.
4 Z. Q. Wang and B. F. Ruan, *J. Fluorine Chem.*, 1994, **69**, 1; Z. Q. Wang and S. F. Lu, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 1899.
5 I. Ruppert, K. Schlich and W. Volbach, *Tetrahedron Lett.*, 1984, **25**, 2195.
6 W. Volbach and I. Ruppert, *Tetrahedron Lett.*, 1983, **24**, 5509.
7 Q.-Y. Chen and S.-W. Wu, *J. Chem. Soc., Chem. Commun.*, 1989, 705.
8 Q.-Y. Chen and J.-X. Duan, *J. Chem. Soc., Chem. Commun.*, 1993, 1390.
9 D.-B. Su, J.-X. Duan and Q.-Y. Chen, *Tetrahedron Lett.*, 1991, **32**, 7689; J.-X. Duan, D.-B. Su and Q.-Y. Chen, *J. Fluorine Chem.*, 1993, **61**, 279.
10 C. Djerassi, G. Rosenkranz, J. Romo, St. Kanfmann and J. Pataki, *J. Am. Chem. Soc.*, 1950, **72**, 4534.
11 D. N. Kirk, D. K. Patel and V. Petrow, *J. Chem. Soc.*, 1956, 627.
12 N. H. Baine, F. F. Owings, N. Kline, T. Resnick, L. Ping, M. Fox, R. E. Mewshane, A. M. Tickner and C. J. Kowalski, *J. Org. Chem.*, 1994, **59**, 5987.
13 Q.-Y. Chen and S.-W. Wu, *J. Chem. Soc., Perkin Trans. 1*, 1989, 2385.

Paper 7/06552C
Received 8*th September* 1997
Accepted 19*th December* 1997