Organic Process Research & Development **1997**, *1,* 217–221

Comparison of Commercially Available Reagents for Fluorination of Steroid 3,5-Dienol Acetates

Valérie Reydellet-Casey, Donald J. Knoechel, and Paul M. Herrinton*

Pharmacia & Upjohn, Kalamazoo, Michigan 49001

Abstract:

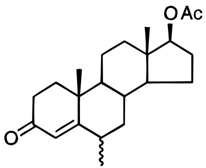
Reactions of steroid 3,5-dienol acetates with electrophilic fluorinating reagents of the *N*-fluoro quaternary salt class were examined for the purpose of selecting a reagent for use in commercial scale synthesis. The neutral *N*-fluorosulfonimides gave high β-fluoro selectivity and moderate yields. In the *N*-fluoropyridinium class, high temperatures or long reaction times required for complete reaction led to low yields. The change in selectivity of fluorination reported at different temperatuers with *N*-fluoropyridinium pyridine heptafluorodiborate (NFPy) was explained by selective dehydrohalogenation of the β-fluoro isomer to the 3-keto 4,6-diene product. With 1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) the elimination was slowed. Additionally, Selectfluor was observed to react with the unactivated double bond in $\Delta^{9(11)}$ steroids to give 11α-fluoro-9β-methyl phenols. Selectfluor was chosen as the optimum reagent, and a process was developed using that reagent. Epimerizations of 6α/β-fluoro steroid mixtures to pure 6α-fluoro steroids were also examined, and conditions for preparation of pure 6α-fluoro steroids were developed.

Introduction

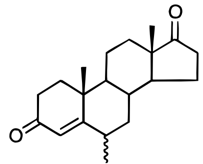
Since the first report of fluorination of the glucocorticoid hormone cortisol in 1954,[1] there has been great interest in fluorinating every position of the steroid nucleus. Introduction of a 6α-fluorine into a glucocorticoid has a large potentiating affect on antiinflammatory activity. Numerous topically active products, including diflorasone diacetate, fluocinolone acetonide, and fluticasone propionate, containing this functionality have been developed and are in clinical use. Incorporation of the 6α-fluorine has been accomplished by opening of 5,6-epoxides with HF,[2] by the addition of mixed halogens (BrF) to $\Delta^{5(6)}$ double bonds,[3] and by reaction of 3,5-dienol acetates with electrophilic fluorinating reagents such as perchloryl fluoride[4] or fluoroxy compounds.[5] Recently several new electrophilic fluorinating reagents of the N−F quaternary salt type have been introduced.[6] These reagents have been used to introduce fluorine at the 6-position of the steroid skeleton by reaction with 3,5-dienol acetates.[7,8] We were interested in replacing perchloryl fluoride in our commercial scale 6α-fluoro steroid preparations with one of these reagents. In this account we describe the examination of several of the N−F type reagents for this purpose.

Results and Discussion

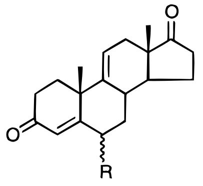
We were interested in preparing 6α-fluorinated steroids **1**−**3**; consequently we studied several commercially available N−F reagents for suitability in large scale operations. We chose to examine *N*-fluorobenzenesulfonimide (NFSI)[9] (**4**), *N*-fluoropyridinium pyridine heptafluorodiborate (NFPy)[9] (**5**), and 1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4 or Selectfluor)[10] (**6**).



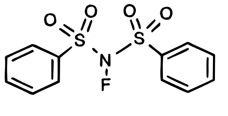
1 R = αF
10 R = βF
11 R = H



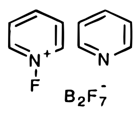
2 R = αF
12 R = βF
13 R = H



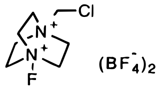
3 R= αF
14 R =βF
15 R = H



4



5



6

---

(1) Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1954**, *76*, 1455.

(2) Bowers, A.; Cuellar Ibanez, L.; Ringold, H. J. *Tetrahedron* **1959**, *7*, 138.

(3) Bowers, A.; Cuellar Ibanez, L.; Denot, E.; Becerra, R. *J. Am. Chem. Soc.* **1960**, *82*, 4001.

(4) (a) Magerlein, B. J.; Pike, J. E.; Jackson, R. W.; Vandenberg, G. E.; Kagan, F. *J. Org. Chem.* **1964**, *29*, 2982. (b) Timko, J. M. DE 3226164, Feb 3, 1983, US Appl. 286306, July 24, 1981. (c) Osawa, Y.; Neeman, M. *J. Org. Chem.* **1967**, *32*, 3055.

(5) Hesse, R. H. *Isr. J. Chem.* **1978**, *17*, 60.

(6) For a review of electrophilic NF fluorinating reagents, see: Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737.

(7) (a) Poss, A. J.; Van Der Puy, D.; Nalewajek, D.; Shia, G. A.; Wagner, W. J.; Frenette, R. L. *J. Org. Chem.* **1991**, *56*, 5962. (b) Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *J. Chem. Soc., Chem. Commun.* **1992**, 595. (c) Lal, G. S. *J. Org. Chem.* **1993**, *58*, 2791.

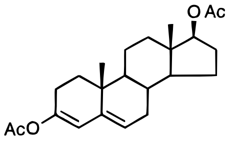
(8) Umetomo, T.; Kawada, K.; Tomita, K. *Tetrahedron Lett.* **1986**, *27*, 4465.

(9) Supplied by Allied Signal Inc., 20 Peabody St., Buffalo, NY.

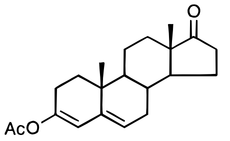
(10) Supplied by Air Products, Allentown, PA.

S1083-6160(96)00045-X CCC: $14.00

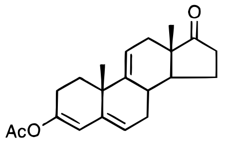
The required 3,5-dienol acetates **7**,[11] **8**,[12] and **9**[4b] have all been prepared previously. We followed a general procedure using acetic anhydride under acidic conditions and isolated all three products as stable crystalline compounds in 85–90% yield. Under these conditions <2% of the 2,4-dienol ester was observed. When isopropenyl acetate was used as the acylating reagent, approximately 10–20% of the undesired 2,4-dienol was formed.



7



8



9

Although fluorination of enol esters has not been reported with *N*-fluorosulfonimides, this class has been used to fluorinate silyl enol ethers with success.[13] In the case of enol acetate **7**, treatment with 1.5 equiv of NFSI at 40 °C in THF for 24 h resulted in complete consumption of the starting enol ester, giving the product as a 5:95 mixture of **1/10** in 55–60% yield. This reaction was unusual in the selectivity for the β-fluoro isomer since the other reagents exhibited essentially no selectivity. The origin of this unusual selectivity is unknown.

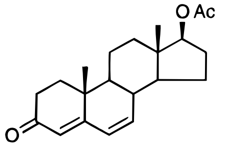
Poss *et al*. reported that upon fluorination of **7** with NFPy at 40 °C a 96% yield of a 1:1 mixture of **1/10** was obtained, while at higher temperature (80 °C) it was reported that a 57% yield of a 4:1 mixture of **1/10** was obtained.[7a] Reaction of **7** with Selectfluor at 0 °C was reported to give a 95% yield of a 1:1.4 mixture of **1/10**.[7b] Similar results were reported for the fluorination of **8** with NFPy[7a] and Selectfluor.[7b]

Our purpose was to selectively prepare the 6α-fluoro steroids; therefore the reported change in selectivity at higher temperature with NFPy was of interest. In an effort to understand these results, fluorination was studied at different temperatures using both NFPy and Selectfluor. Fluorinations of enol acetates **7**–**9** were conducted at 0 and 80 °C in acetonitrile with Selectfluor and at 40 and 80 °C in acetonitrile with NFPy (Table 1). All reactions were carried out for 3 h. At the lower temperature both reagents gave an approximately 1:1 mixture of α/β diastereomers with very little of the desfluoro compound (**11**, **13**, **15**) or other byproducts. Under these conditions Selectfluor gave nearly complete conversion while NFPy gave only 15–20% reaction. At higher temperatures less of the β-fluoro isomers was detected in the products. We observed, however, that another type of product was formed, and the 3-keto 4,6-dienone steroids **16**–**18** were isolated from the reaction mixtures in significant amounts (see Table 1). Additionally, when the lower temperature reactions with NFPy were continued to complete starting material consumption (5 days at 40 °C), the amounts of β-fluoro products decreased, while the amounts of dienones increased.

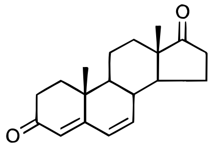
Table 1. **Fluorination of enol acetates with NFPy and Selectfluor**

substrate	temp (°C)	reagent	time (h)	α:β[a]	3-keto 4,6-dienone[a]
7	40	NFPy	120	54:15	24
7	80	NFPy	3	39:46	8
7	0	Selectfluor	3	50:43	0
7	80	Selectfluor	3	50:32	5
8	40	NFPy	120	54:0	41
8	80	NFPy	3	45:5	35
8	0	Selectfluor	3	44:51	0
8	80	Selectfluor	3	73:0	24
9	40	NFPy	120	38:37	24
9	80	NFPy	3	45:34	11
9	0	Selectfluor	3	56:43	0
9	80	Selectfluor	3	45:21	0

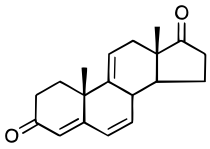
[a] Identification of byproducts and ratios reported in the table were determined by HPLC and NMR and are reported as molar ratios.



16



17



18

Closer examination of these fluorinations revealed that the α- and β-fluoro products were being formed at a 1:1 ratio early in the reaction, but as the reaction progressed the β-fluoro diastereomer disappeared without increasing the amount of α-isomer while the 3-keto 4,6-dienone product increased. This suggested that the β-isomer was selectively undergoing elimination of HF to provide the $\Delta^{6(7)}$ steroid. The β-isomer should be more likely than the α-isomer to undergo this elimination due to the axial orientation of the fluorine. As can be seen from the table, NFPy gave more of the elimination product, presumably due to the presence of pyridine. The long reaction times (5 days) required to get complete conversion with NFPy at 40 °C also led to significant amounts of 3-keto 4,6-dienone byproducts despite reduced temperatures.

With substrate **9**, excess reagent reacted with the isolated 9,11-bond at 80 °C to produce the phenol **19**. This reaction was slower than fluorination of the enol acetate and gave 24% of the 6-fluorophenol after 6 h at 80 °C. The reaction was considerably faster on the desfluoro steroid **15**, giving 72% yield of **20** after 3 h at 80 °C. A similar reaction has been reported on a different substrate using trifluoro(fluorooxy)methane.[14] This reaction did not take place with NFPy, indicating that Selectfluor is the more electrophilic fluorinating reagent.

---

(11) Westphal, U. *Chem. Ber.* **1937**, *70*, 2128.

(12) Pemmarju, N. R.; Edwards, B. E. US Patent 3321495, May 23, 1967.

(13) Differding, E.; Ofner, H. *Synlett* **1991**, 187.

(14) (a) Barton, D. H. R.; Danks, L. J.; Ganguly, A. K.; Hesse, R. H.; Tarzia, G.; Pechet, M. M. *J. Chem. Soc., Chem. Commun.* **1969**, 227. (b) Barton, D. H. R.; Danks, L. J.; Ganguly, A. K.; Hesse, R. H.; Tarzia, G.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1* **1976**, 101.

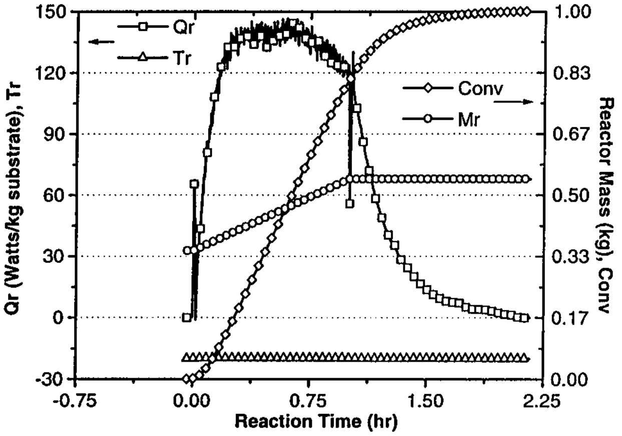
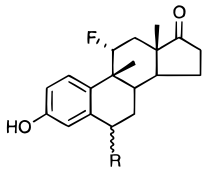


Figure 1. **Selective fluorination using Selectfluor: Qr = heat flow, Tr = reactor temperature, Mr = reactor mass, Conv = heat conversion.**



19 R = F
20 R = H

Selectfluor was chosen as the optimum reagent for fluorination of enol acetate, and we developed its reaction with **9**. From the previous study we knew that at 80 °C reaction of the isolated olefin with excess reagent was a problem, but that at −30 °C this reaction did not proceed at a significant rate. Reactions run at 0 °C were complete in 30 min and gave 65−70% yields of isolated products as mixtures of diastereomers **3** and **14** (1.3:1). Reactions at lower temperatures were studied, and the yield was found to be highest at −25 °C. At <−30 °C the reaction was too slow to be practical (12% complete after 24 h). The stoichiometry of the reaction was studied, and a minimum of 1.1 equiv of Selectfluor was determined to be required for complete conversion of all starting material. The reaction proceeded to about 95% completion at −25 °C but must be warmed to 0−5 °C for 100% conversion using this stoichiometry. By decreasing the reaction temperature and reducing the equivalents of reagent used we were able to increase the yield to 80−85% of isolated product as a 1.3:1 mixture of diastereomers. No change in the diastereoselection was observed at the lower temperature. Some additional solvents were examined for the reaction, but low solubility of Selectfluor in all solvents but DMF limited the useful choices.

The reactions of enol acetates with Selectfluor were quite exothermic, requiring a slow addition of enol acetate to the Selectfluor to maintain the low temperature. In order to estimate the addition rate required for large scale and to understand the process safety, a reaction calorimetry study was done. The reaction calorimetry experiment consisted of a 1 h addition of a homogeneous solution of substrate/acetonitrile at room temperature to Selectfluor in acetonitrile at −20 °C. This was the same mode of addition anticipated in commercial scale preparation. The heat flow profile shown by this reaction was typical of that expected for a semibatch reaction, demonstrating mild heat accumulation (see Figure 1). The total heat liberated corresponded to a heat of reaction of −52 kcal/mol of substrate. The total adiabatic temperature rise for this recipe based on the final mass and heat capacity of the reaction mass was 22 °C. The peak accumulation of heat occurred at the end of the addition and was 19% of the total heat liberated. Adding the sensible heat from the enol acetate solution, a temperature rise of 39 °C could be expected. In the worst case, with no cooling and assuming that the entire addition takes place at once, the reaction mixture could warm from the starting temperature of −25 °C to a high of 4 °C. This scenario is not a threat to process safety, but it could have a negative impact on yield.

The low stereoselectivity of these fluorinations makes them ineffective for direct production of 6α-fluoro steroids. However, if it were possible to convert the 6α/6β mixture to a single diastereomer, use of these reagents could provide an efficient process. Therefore a study of conversion of the **3/14** mixture to >98% **3** was begun. Some basic physical characteristics of **3** and **14** were measured. Under equilibrating conditions in solution (strong acid added) the equatorial isomer **3** was favored in an 83:17 mixture. **3** was less soluble than **14** in many solvents, and crystallization of mixtures led to increased levels of **3** in the crystals and increased **14** in the mother liquors. This situation allows for conversion of a mixture to the desired α-isomer by selective crystallization from an equilibrating solution.

The choice of solvent and acid was critical for success in this process. The diastereomer mixture must have enough solubility to allow rapid equilibration, but the solubility of the desired isomer should be low enough to give a high yield. The mixture of diastereomers had high solubility in methylene chloride, tetrahydrofuran, and acetone, but the high solubility of the desired isomer led to low recoveries of product. The mixture had such low solubility in heptane, methyl *tert*-butyl ether, and toluene that equilibration of the isomers was too slow to be useful. Solvents with moderate solubility including 2-propanol and ethyl acetate showed a preference for solvating the β-fluoro isomer. These solvents were all tested with a variety of acids.

Several acids were surveyed as catalysts. Anhydrous hydrogen chloride gave a rapid equilibration of isomers while, surprisingly, the use of strong acids with nonnucleophilic counterions such as sulfuric, perchloric, or methanesulfonic failed to equilibrate the diastereomers. The amount of hydrogen chloride used had to be minimized because, with larger amounts (>1 equiv) of acid, significant amounts of 6-chloro steroid (up to 8%) were produced. In the case of product **3** the best conditions found for this equilibration were to use ethyl acetate with anhydrous HCl. Stirring a slurry of the **3/14** mixture in ethyl acetate with hydrogen chloride present caused the solution to rapidly equilibrate to the 83/17 mixture. The α-isomer **3** crystallized preferentially from the solution, draining the equilibrium toward **3**. After the slurry had been stirred for 18 h, the crystals had converted from the starting mixture ratio of 57:43 to 97:3, while the solution remained at the equilibrium ratio of 83:17. Filtration of the solids and recrystallization gave a product which was >99% α-isomer in 83% yield.

Conclusions

Selectfluor was selected as the best reagent, and optimized yields for fluorinations were in the 80−85% yield range. Although the stereoselection was low in the fluorination, the mixture of isomers produced by Selectfluor could be equilibrated to the α-isomer by crystallization-driven equilibration. The use of the neutral NFSI reagent gave modest yields and high *β*-fluoro selectivity and was not useful for this application. The NFPy reagent was slow to react with dienol acetates. The apparent increase in α-fluoro selectivity of fluorination reported at different temperatures with NFPy was explained by selective dehydrohalogenation of the *β*-fluoro isomer to the 3-keto 4,6-dienone product. A similar reaction occurred with Selectfluor but to a lesser extent. Additionally, Selectfluor was observed to react with the unactivated double bond in $\Delta^{9(11)}$ steroids to give 11α-fluoro-9*β*-methyl phenols. All side reactions were minimized at lower reaction temperatures and shorter reaction times. Equilibration of mixtures of 6α- and 6*β*-fluoro steroids under acidic conditions may be used to produce pure 6α-fluoro steroids.

Experimental Section

General Methods. Reagents and solvents were reagent grade and used as received unless otherwise noted. NFSI and NFPy were purchase from Allied-Signal, Buffalo, NY, and used as received. Selectfluor was purchased from Air Products and Chemicals Inc., Allentown, PA, and used as received. ^{1}H NMR spectra were obtained at 300 MHz, ^{13}C NMR spectra were measured at 75.4 MHz, and both have been reported in parts per million (ppm) downfield from TMS. ^{19}F NMR spectra were recorded at 282.4 MHz and have been reported in parts per million (ppm) upfield from C_6F_6. Infrared spectra were obtained as mineral oil mulls and are reported in wave numbers (cm^{-1}). Mass spectra were obtained as FAB, electron impact (EI) or chemical ionization (CI) as indicated. Molecular masses have been given in atomic mass units (amu), followed by percent intensity relative to the most abundant ion. Flash chromatography was carried out using Merck 230−400 mesh silica gel from EM reagents. Melting points were determined on a Thomas-Hoover apparatus and have not been corrected. The RC1 experiment was performed following the general procedure for fluorination using Selectfluor and using the SV01 1 L reactor equipped with the Teflon-lined stainless steel lid with a magnetically coupled drive using the Mettler multitiered propeller agitator (at 600 rpm). Teflon diaphragm pumps by Prominent were used in conjunction with the Mettler RD10 dosing controller for reagent additions. The RC1 cool oil reservoir was cooled by an FTS RC-210C-20W two-stage cryostat using Down Corning Syltherm XLT as the cooling loop fluid.

General Procedure for Preparation of Enol Acetates 7,[11] 8,[12] and 9.[4b] Steroid (100 g) was slurried in DMF (80 mL). Ac_2O (180 mL) was added, followed by 48% HBr (5.7 mL), and the reaction temperature was brought up to 55−60 °C. The mixture was stirred at that temperature for 8 h. At that point, the reaction mixture was cooled to 25−30 °C and MeOH (180 mL) was added. The reaction mixture was cooled with an ice/water bath. After solids appeared, the mixture was stirred cold for 30 min before water (360 mL) was added. The slurry was filtered, washed, and triturated three times with water (3 × 250 mL) and once with MeOH (250 mL). The crude enol acetate was dissolved using CH_2Cl_2 (150 mL). The dark solution was distilled at atmospheric pressure until residual volume reached 150 mL. MTBE (250 mL) was added, and distillation was continued until the volume reached 180 mL. MTBE (250 mL) was added again, and distillation was continued until final volume reached 180−200 mL (thick slurry). At that point, the slurry was cooled down with an ice/water bath and stirred cold for 1 h before it was filtered. The cake was rinsed with cold MTBE (150 mL) and dried with 60 °C N_2.

General Fluorination Procedure using *N*-Fluorobenzenesulfonimide (NFSI). Enol acetate (122 mmol) was slurried in THF (250 mL) and warmed up to 35−40 °C until all the steroid was in solution. NFSI (183 mmol, 1.5 equiv) was added and the mixture stirred at 35−40 °C until the reaction was complete. The temperature was brought to 25 °C, and EtOAc (600 mL) and water (550 mL) were added. The phases were separated, and the aqueous phase was extracted with EtOAc (150 mL). The combined organic phases were then washed with sodium bicarbonate (saturated aqueous solution, 300 mL), twice with water (2 × 300 mL), and salt water (300 mL). The resulting pale yellow solution was distilled at reduced pressure to a foam. Ratios of products were determined by HPLC and NMR. Individual products were purified by chromatography over silica gel using 40% ethyl acetate/heptane as eluant.

General Fluorination Procedure Using *N*-Fluoropyridinium Pyridine Heptafluorodiborate (NFPy) or Selectfluor. Enol acetate (122 mmol) was slurried in CH_3CN (250 mL) and warmed to 35−40 °C until all the steroid was in solution. It was then cooled to room temperature. In the meantime, either NPFy (146 mmol, 1.2 equiv) or Selectfluor (146 mmol, 1.2 equiv) was slurried in CH_3CN (500 mL) and the temperature adjusted to the desired reaction temperature. The steroid solution was then added over 10−60 min into the NFPy or Selectfluor slurry maintained at the desired temperature. When the addition was complete, the mixture was stirred for 3 h (5 days for NFPy at 25 °C). The temperature was brought to 25 °C, and EtOAc (600 mL) and water (550 mL) were added. The phases were separated, and the aqueous phase was extracted with EtOAc (150 mL). The combined organic phases were then washed with sodium bicarbonate (saturated aqueous solution, 300 mL), twice with water (2 × 300 mL), and salt water (300 mL). The resulting pale yellow solution was distilled at reduced pressure to a foam. Ratios of products were determined by HPLC and NMR. Individual products were purified by chromatography over silica gel using 40% ethyl acetate/heptane as eluant.

The HPLC procedure was as follows. A sample was prepared by diluting 0.1 mL of reaction mixture with 15 mL of acetonitrile. Injection loop: 10 μL. Column: Alltech Nucleosil, C-18, 5 μm, 15 cm. Flow rate: 1.5 mL/min. Detector: UV dual wavelength at 240 nm for 6-fluoro, 280 nm for 4,6-dienones. Gradient: from 80:20 acetonitrile/water to 100% acetonitrile.

17*β*-Acetoxy-6α-fluoroandrost-4-en-3-one (1):[4c] ^{1}H NMR ($CDCl_3$) δ 6.10 (d, $J = 0.4$ Hz, 1H), 5.10 (dddd, $J = 48$, 12, 6.3, 1.8 Hz, 1H), 2.40 (m, 4H), 2.20 (m, 4H), 1.97 (s, 3H), 1.75 (m, 4H), 1.68 (m, 4H), 1.12 (s, 3H), 1.17 (m, 1H), 0.79

(s, 3H); ^{13}C NMR ($CDCl_3$) δ 198.2, 170.8, 165.4, 119.5, 91.8, 86.6, 52.8, 49.8, 47.5, 39.2, 37.2, 36.1, 35.3, 33.7, 33.1, 31.1, 21.7, 20.8, 20.2, 17.9, 11.7; ^{19}F NMR ($CDCl_3$) δ +22.3 (ddd, J = 48, 9, 5 Hz); mp 174−177 °C.

17β-Acetoxy-6β-fluoroandrost-4-en-3-one (10):[12] ^{1}H NMR ($CDCl_3$) δ 5.82 (d, J = 4.8 Hz, 1H), 5.02 (ddd, J = 49.2, 2.5, 2.5 Hz, 1H), 4.60 (dd, J = 11.0, 10.8 Hz, 1H), 2.48 (m, 4H), 2.20 (m, 4H), 1.97 (s, 3H), 1.77 (m, 4H), 1.68 (m, 4H), 1.24 (s, 3H), 1.13 (m, 1H), 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 199.4, 170.8, 161.4, 128.1, 94.0, 89.0, 53.2, 49.9, 47.6, 38.0, 37.0, 36.8, 35.7, 34.2, 31.2, 29.8, 21.7, 20.8, 20.3, 18.1, 11.7; ^{19}F NMR ($CDCl_3$) δ +5.3 (J = 49, 49, 11 Hz); mp 112−114 °C.

6α-Fluoroandrost-4-ene-3,17-dione (2):[15] ^{1}H NMR ($CDCl_3$) δ 6.04 (s, 1H), 5.08 (dddd, J = 47.8, 12.2, 5.9, 2.0 Hz, 1H), 2.47 (m, 6H), 2.0 (m, 6H), 1.78 (m, 5H), 1.19 (s, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 219.5, 198.5, 165.3, 120.2, 88.0, 53.7, 50.5, 47.5, 39.2, 37.2, 36.3, 35.6, 33.7, 33.1, 31.1, 21.7, 20.2, 18.1, 13.7; ^{19}F NMR ($CDCl_3$) δ +21.6 (ddd, J = 48, 9, 5 Hz); mp 229−231 °C.

6β-Fluoroandrost-4-ene-3,17-dione (12):[15] ^{1}H NMR ($CDCl_3$) δ 5.84 (d, J = 5.4 Hz, 1H), 5.00 (ddd, J = 49.0, 2.7, 2.7 Hz, 1H), 2.49 (m, 6H), 2.03 (m, 6H), 1.78 (m, 4H), 1.33 (s, 3H), 0.98 (m, 1H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 219.5, 199.3, 161.0, 128.7, 93.1, 53.4, 50.9, 47.6, 38.0, 37.0, 36.8, 35.7, 34.2, 31.3, 29.8, 21.7, 20.3, 18.5, 13.8; ^{19}F NMR ($CDCl_3$) δ +3.5 (ddd, J = 49, 49, 12 Hz); mp 136−138 °C.

6α-Fluoroandrosta-4,9(11)-diene-3,17-dione (3):[4b] ^{1}H NMR ($CDCl_3$) δ 6.04 (s, 1H), 5.58 (m, 1H), 5.29 (dddd, J = 48.2, 12.4, 5.4, 1.9 Hz, 1H), 2.51 (m, 6H), 2.08 (m, 6H), 1.60 (m, 3H), 1.34 (s, 3H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 220.0, 198.2, 163.0, 143.0, 120.0, 119.5, 87.7, 47.7, 45.9, 41.5, 37.4, 36.1, 35.1, 34.4, 34.1, 33.4, 26.9, 22.6, 14.0; ^{19}F NMR ($CDCl_3$) δ +21.8 (ddd, J = 47.9, 7.6, 4.2 Hz); mp 248−249 °C.

6β-Fluoroandrosta-4,9(11)-diene-3,17-dione (14):[4b] ^{1}H NMR ($CDCl_3$) δ 5.87 (d, J = 4.8 Hz, 1H), 5.05 (ddd, J = 49.4, 2.81, 2.7 Hz, 1H), 2.72 (m, 1H), 2.50 (m, 6H), 2.11 (m, 4H), 1.62 (m, 3H), 1.46 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 220.3, 199.1, 159.8, 144.0, 128.4, 118.6, 93.6, 91.5, 48.0, 45.9, 40.2, 36.0, 35.2, 34.8, 34.4, 31.0, 27.5, 22.5, 13.9; ^{19}F NMR ($CDCl_3$) δ +6.3 (dddd, J = 47.9, 47.9, 7.6, 4.2 Hz); mp 206−208 °C.

17β-Acetoxyandrosta-4,6-dien-3-one (16):[16] ^{1}H NMR ($CDCl_3$) δ 6.05 (dd, J = 7.3, 7.3 Hz, 2H), 5.62 (s, 1H), 4.57 (dd, J = 12.3, 4.2 Hz, 1H), 2.51 (m, 2H), 1.98 (s, 3H), 1.96 (m, 2H), 1.5−1.1 (m, 9H), 1.05 (s, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 199.7, 171.4, 163.7, 140.3, 128.5, 124.1, 82.4, 50.9, 48.4, 43.7, 37.7, 36.8, 36.4, 34.2, 34.1, 27.8, 23.4, 21.4, 20.5, 16.6, 12.3; mp 143−144 °C.

Androsta-4,6-diene-3,17-dione (17):[17] ^{1}H NMR ($CDCl)_3$ δ 6.10 (dd, J = 7.25 Hz, 2H), 5.6 (s, 1H), 2.4 (m, 4H), 1.7 (m, 11H), 1.20 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 219.3, 199.2, 162.9, 138.3, 128.7, 124.1, 50.7, 48.7, 48.3, 37.0, 36.1, 35.6, 34.0, 33.8, 31.3, 21.4, 20.0, 16.3, 13.7; mp 172−173 °C.

Androsta-4,6,9(11)-triene-3,17-dione (18): ^{1}H NMR ($CDCl_3$) δ 6.15 (s, 2H), 5.58 (s, 1H), 5.49 (m, 1H), 2.4 (m, 6H), 2.1−1.6 (m, 6H), 1.26 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 220.5, 199.4, 164.2, 137.3, 128.0, 124.4, 120.2, 119.8, 46.3, 41.6, 37.4, 36.3, 35.1, 34.4, 34.3, 33.1, 27.2, 22.0, 14.4; MS (EI) 276 (13), 261 (80), 160 (base); IR 3025, 2955, 2860, 1740, 1665, 1580, 1240; UV (EtOH) λ_{max} 284 (19 000). Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.81; H, 7.76. Mp 167−169 °C.

3-Hydroxy-11α-fluoro-9β-methylestra-1,3,5(10)-trien-17-one (19): ^{1}H NMR ($CDCl_3$) δ 7.15 (dd, J = 8.7, 2.4 Hz, 1H), 6.53 (dd, J = 8.7, 2.4 Hz, 1H), 6.48 (m, 1H), 4.68 (ddd, J = 45, 12.6, 3.9 Hz, 1H), 2.66 (m, 2H), 2.10 (m, 1H), 1.98−1.40 (m, 9H), 1.34 (s, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 218.4, 153.9, 137.5, 131.9, 130.3, 115.8, 113.9, 99.4, 48.5, 44.0, 43.0, 38.5, 35.8, 34.7, 28.9, 25.2, 21.9, 19.0, 14.4; ^{19}F NMR ($CDCl_3$) δ +22.6 (d, J = 45 Hz); IR 3375, 2980, 2930, 1730, 1620, 1580, 1500, 1292; MS (EI) 302 (34), 287 (21), 199 (74), 160 (base); UV (EtOH) λ_{max} 285 (1610). Anal. Calcd for $C_{19}H_{23}FO_2$: C, 75.47; H, 7.67; F, 6.28. Found: C, 75.60; H, 7.59; F, 6.32. Mp 238−241 °C.

3-Hydroxy-11α,6α-difluoro-9β-methylestra-1,3,5(10)-trien-17-one (20): ^{1}H NMR ($CDCl_3$) δ 7.53 (dd, J = 8.4, 2.3 Hz, 1H), 6.65 (dd, J = 8.4, 2.7 Hz, 1H), 6.58 (d, J = 2.7 Hz, 1H), 5.30 (dddd, J = 48.2, 12.4, 5.4, 1.9 Hz, 1H), 4.80 (ddd, J = 45.2, 12.7, 3.8 Hz, 1H), 2.6−1.4 (m, 11H), 1.42 (s, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 217.8, 154.0, 137.5, 132.1, 130.6, 119.5, 114.4, 98.2, 87.2, 48.3, 43.8, 43.0, 38.6, 35.6, 34.4, 26.8, 24.8, 22.5, 14.1; ^{19}F NMR ($CDCl_3$) δ +22.6 (d, J = 45 Hz), +21.8 (ddd, J = 47.9, 7.6, 4.2 Hz); IR 3370, 2950, 2930, 1720, 1620, 1580, 1500, 1450, 1290; MS (EI) 320 (4), 302 (49), 199 (68), 160 (base); UV (EtOH) λ_{max} 283 (1800). Anal. Calcd for $C_{19}H_{22}F_2O_2$: C, 71.46; H, 6.63; F, 11.90. Found: C, 71.50; H, 6.61; F, 11.87. Mp 258−261 °C.

Equilibration of Mixture of Compounds 3 and 14 under Acidic Conditions. A mixture of **3** and **14** (50.0 g) was slurried in ethyl acetate (250 mL) at room temperature. The slurry was cooled to 0 °C, and HCl gas was sparged into the slurry until 0.2 g had been added. The resulting purple slurry was then stirred at room temperature for 16−24 h. The slurry was filtered and washed with cold ethyl acetate (50 mL). The solids were dried in a vacuum oven at 35 °C. The resulting crude solids were dissolved in CH_2Cl_2 (100 mL), and ethyl acetate (100 mL) was added. The solution was distilled at atmospheric pressure until the pot temperature reached 62 °C. The resulting mixture was cooled to 0 °C, and the crystals were filtered and washed with cold ethyl acetate (50 mL). The yield was 32.1 g of pure **3**.

Acknowledgment

We would like to acknowledge Mark Mowery for help with NMR analysis and K. P. Shephard for helpful discussions on steroid fluorinations.

Received for review November 5, 1996.⊗

OP960045D

---

(15) Bower, A.; Ringold, H. J. *Tetrahedron* **1958**, *3*, 14.

(16) Schaub, R. E.; Weiss, M. J. *J. Org. Chem.* **1961**, *26*, 3915.

(17) Hanson, J. R.; Siverns, M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1956. Hanson, J. R.; Reese, P. B.; Wadsworth, H. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2941.

⊗ Abstract published in *Advance ACS Abstracts*, February 15, 1997.