(trimethylsilyl)-1-pentyn-3-one, 53723-94-7; 5-methyl-1-(trimethylsilyl)-1-hexyn-3-one, 65149-29-3; 1-(trimethylsilyl)-4-hexen-1-yn-3-one, 53723-96-9; 4-chloro-1-(trimethylsilyl)-1-butyn-3-one, 18245-82-4; 2-propanol, 67-63-0.

**Supplementary Material Available:** $^1$H NMR spectra of (*S*)-1-phenyl-2,2,2-trifluoroethanol, (*R*)-1-(2-pyridyl)ethanol, (*R*)-1-(2-furanyl)ethanol, (*R*)-6-methyl-5-hepten-2-ol, (*R*)-5-chloro-2-pentanol, (*R*)-5-norbornen-2-ol, (*R*)-1-(trimethylsilyl)-1-butyn-3-ol, methyl 4-hydroxy-1-(trimethylsilyl)-5-hexynoate, 1-(trimethylsilyl)-1-hexyn-3-one, 4,4-dimethyl-1-(trimethylsilyl)-1-pentyn-3-one, 5-methyl-1-(trimethylsilyl)-1-hexyn-3-one, methyl 4-oxo-6-(trimethylsilyl)-5-pentynoate, 3-oxo-1-(trimethylsilyl)-4-hexen-1-yne, and 4-chloro-1-(trimethylsilyl)-1-butyn-3-one (14 pages). Ordering information is given on any current masthead page.

# Para Fluorination by *N*-Fluorobis[(trifluoromethyl)sulfonyl]imide: Synthesis of 10β-Fluoro-3-oxo-1,4-estradiene Steroids

William T. Pennington, Giuseppe Resnati,[1] and Darryl D. DesMarteau*

*Howard L. Hunter Chemistry Laboratory, Clemson University, Clemson, South Carolina 29629-1905*

*Received July 31, 1991 (Revised Manuscript Received October 28, 1991)*

When 1,3,5(10)-estratrien-3-ols are treated with *N*-fluorobis[(trifluoromethyl)sulfonyl]imide in chloroform solution the ortho and para fluorination products are formed. In contrast, when acetic acid is used as a solvent, fluorination in the para position occurs selectively and 10β-fluoro-3-oxo-1,4-estradiene derivatives are formed in high yields.

The first studies on electrophilic fluorination of estrogen steroids date back to the late fifties and were performed by using perchloryl fluoride.[2,3] Several other reagents providing a "positive fluorine" have been used subsequently to prepare A-ring fluorinated steroids starting from estrogens.[4-10]

Recently, attention has been refocused on this area by the observation that introduction of fluorine in position 2 of 17β-estradiol does not affect the hormonal activity, but reduces its tumorigenicity.[11-13]

As a part of our ongoing study of the synthetic potential of the *N*-fluorobis[(trifluoromethyl)sulfonyl]imide **1**[14] we have investigated the reaction of estrogens **2a–e** with this electrophilic fluorinating agent.

In this paper we describe how under proper reaction conditions a para fluorination occurs selectively and the 10β-fluoro-3-oxo-1,4-estradiene steroids **3a–e** can be obtained in high yields.

## Results and Discussion

**Synthetic Aspects.** When 1,3,5(10)-estratriene-3,17β-diol 17-propionate (**2a**) was treated with the *N*-fluoroimide **1** in chloroform solution a clean reaction occurred at room temperature to give the 2-fluoro-1,3,5(10)-estratriene-3,17β-diol 17-propionate (**3a**), the 4-fluoro isomer **4a**, and the 10β-fluoro-3-oxo-1,4-estradien-17β-ol 17-propionate (**5a**).

**Table I**

| compd | solvent | (3 + 4):5 ratio | 3:4 ratio |
|---|---|---|---|
| **2a** | chloroform | 31:69 | 41:59 |
| | acetonitrile | 38:62 | 46:54 |
| | dioxane | 41:59 | 42:58 |
| | acetic acid | 14:86 | 32:86 |
| **2b** | chloroform | 44:56 | 43:57 |
| | acetic acid | <2:>98 | |
| **2c** | chloroform | 47:53 | 45:55 |
| | acetic acid | <2:>98 | |
| **2d** | chloroform | 32:68 | 40:60 |
| | acetic acid | <2:>98 | |
| **2e** | acetic acid | <2:>98 | |

The para fluorination, i.e., the entrance of the halogen on C-10 to give **5a** through an ipso process, is favored with respect to the ortho fluorination, which gives **3a** and **4a**, and a low selectivity exists between the two ortho positions (see Table I). Furthermore, the reaction forming **5a** is completely stereoselective as fluorine enters exclusively from the β-face of the steroid.[15]

Similar regio- and stereoselectivities were observed when dioxane and acetonitrile were employed as solvents, while the use of acetic acid consistently favored the formation of the para fluorination product **5a**.

When estrone **2b**, 17α-estradiol 17-acetate **2c**, and 3,16α,17β-estratriol 16,17-diacetate **2d** were treated with the *N*-fluoroimide **1** they showed a behavior similar to that of estradiol **2a**. In chloroform solution the monofluoro derivatives **3b–d**, **4b–d**, and **5b–d** were formed for all these substrates and their ratios were similar to those obtained starting from **2a**.

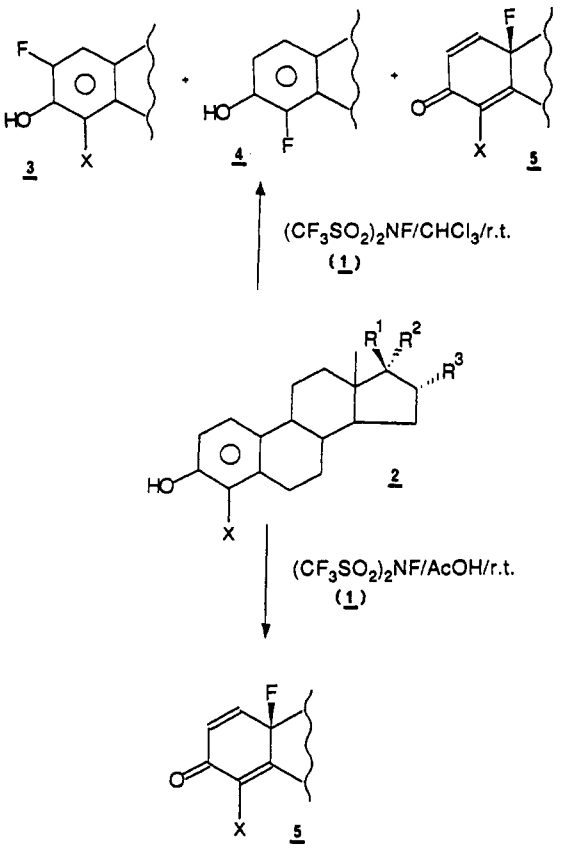
Interestingly, the change of regioselectivity induced by acetic acid was much sharper for these estrogens as **5b–d** were the exclusive products when this solvent was employed.

It was also possible to fluorinate 4-nitroestrone **2e**. Its reaction with the *N*-fluoroimide **1** was slower than that of **2a–d** clearly as a consequence of the presence of the deactivating residue in position four. In acetic acid solu-

(1) Permanent address: Centro Studio Sostanze Organiche Naturali, C.N.R., Piazza Leonardo da Vinci 32, 20133 Milano, Italy.
(2) Mills, J. S. *J. Am. Chem. Soc.* **1959**, *81*, 5515.
(3) Mills, J. S.; Barrera, J.; Olivares, E.; Garcia, H. *J. Am. Chem. Soc.* **1960**, *82*, 5882.
(4) Hecker von E.; Hopp, M. *Liebigs Ann. Chem.* **1966**, *692*, 174.
(5) Barton, D. H. R.; Ganguly, A. K.; Hesse, R. H.; Loo, S. N., Pechet, M. M. *Chem. Commun.* **1968**, 806.
(6) Chavis, C.; Mousseron-Canet, M. *Bull. Soc. Chim. Fr.* **1971**, 632.
(7) Patrick, T. B.; Darling, D. L. *J. Org. Chem.* **1986**, *51*, 3242.
(8) Hebel, D.; Kirk, K. L. *J. Fluorine Chem.* **1990**, *47*, 179.
(9) Bulman Page, P. C.; Hussain, F.; Maggs, J. L.; Morgan, P.; Park, K. B. *Tetrahedron* **1990**, *46*, 1059.
(10) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563.
(11) Liehr, J. G. *Mol. Pharmacol.* **1983**, *23*, 278.
(12) Liehr, J. G.; Stancel, G. M.; Chorich, L. P.; Bousfield, G. R.; Ulebelen, A. A., *Chem. Biol. Interact.* **1986**, *59*, 173.
(13) Li, J. J.; Purdy, R. H., Appelman, E. H.; Klicka, J. K.; Li, S. A. *Mol. Pharmacol.* **1985**, *27*, 559.
(14) (a) Singh, S.; DesMarteau, D. D.; Zuberi, S. S.; Witz, M.; Huang, H. N. *J. Am. Chem. Soc.* **1987**, *109*, 7194. (b) Xu, Z. Q.; DesMarteau, D. D.; Gotoh, Y. *Chem. Commun.* **1991**, 179. (c) Resnati, G.; MesMarteau, D. D. *J. Org. Chem.* **1991**, *56*, 4925. (d) DesMarteau, D. D.; Witz, M. *J. Fluorine Chem.* **1991**, *52*, 7.

(15) The same stereochemical preference was observed in the fluorination of other estrogens with perchloryl fluoride and trifluoromethyl hypofluorite.[3,5,6]

0022-3263/92/1957-1536$03.00/0 




| | $R^1$ | $R^2$ | $R^3$ | X |
|---|---|---|---|---|
| 2a | $OCO\text{-}nC_3H_7$ | H | H | H |
| 2b | O | | H | H |
| 2c | H | $OCO\text{-}CH_3$ | H | H |
| 2d | $OCO\text{-}CH_3$ | H | $OCO\text{-}CH_3$ | H |
| 2e | O | | H | $NO_2$ |

tion the para fluorination product **5e** formed exclusively, and similarly to the other cases it could be isolated in high yield and in pure form.

The usefulness of the *N*-fluoroimide **1** for the synthesis of steroids having a 10β-fluoro-3-oxo-1,4-estradiene functional array starting from estratrienic precursors **2** seems to be quite general as the reaction proceeds invariably in high yields when different functionalities are present on the A or D ring of the starting material.

**Structural Studies.** The structure of the fluorination products **3–5** was drawn mainly from $^1H$, $^{19}F$, and $^{13}C$ NMR spectral properties.

The fluorine spectra of the 2-fluoroestrogens **3a–d** showed a doublet of doublets ($J \approx 9$ and 12 Hz) at lower fields than the doublet of the 4-fluoroisomers **4a–d** ($J \approx 8.7$ Hz). The same coupling constants were found in the signals of the aromatic zone of the proton spectra. These data are consistent with those reported in the literature for some related compounds.[8-10]

A detailed spectroscopic study was performed on 10β-fluoro-3-oxo-1,4-estradien-17β-ol (**5a**) in order to establish unequivocally the 10β position of the fluorine atom. Three protons were present in the low-field part of the $^1H$ NMR spectrum of this compound. The broad singlet at 6.03 ppm, the doublet at 6.23 ppm ($J$ = 10.3 Hz), and the doublet of doublet at 7.07 ppm ($J$ = 10.2 and 7.6 Hz) have been assigned to H-4, H-2, and H-1, respectively. The fluorine spectrum showed a doublet of doublets at −165.7 ppm ($J$ = 28.8 and 7.3 Hz). The smaller coupling constant disappeared on irradiation of H-1 while the larger one disappeared on irradiation of H-9. The exact chemical shift of this proton was determined through carbon–proton heteronuclear correlation experiments. The fluorine atom was thus unequivocally located on C-10. IR and $^{13}C$ data are consistent with the 10-fluoro-3-oxo-1,4-diene functional array. The β-configuration of the halogen was assigned on the basis of the similarity of the Cotton effects of similar products.[3,16] Furthermore, the value of the F-10/H-9 coupling constant is typical for a tertiary axial fluorine coupled with a tertiary axial proton[17] so that the β position of the halogen is supported also by the α position of H-9.

These stereochemical assignments were confirmed through a single-crystal X-ray analysis of 10β-fluoro-1,4-estradiene-3,17-dione (**5b**) (see supplementary material).

The structures of **5c–e** were assigned by analogy with those of **5a,b**.

**Selectivity and Mechanistic Considerations.** When estrogenic steroids **2a–e** were treated with the *N*-fluoroimide **1**, fluorine entered exclusively on position ortho and para to the phenolic oxygen. The same behavior has been observed when phenol, anisole, and cresols were reacted with **1**.[14a] The regioselectivity of the process is thus determined by the strong activating effect of the oxygen. The electrophilic character of the reaction is clearly apparent and is supported by the fact that the fluorination of 4-nitroestrone **2e** is slower than that of the 4-unsubstituted analogue **2b**. The same ortho/para preference has been observed in most of the fluorinations of oxygenated aromatic substrates,[18] xenon difluoride being the unique agent which sometimes gives significant amounts of the meta isomer.[28]

The ortho fluorination derivatives **3** and **4** are the minor reaction products when nonpolar or polar–aprotic solvents are employed, and they are formed in low amount, if any, when acetic acid is used. This is in contrast with the quite marked ortho preference shown when oxygen, or nitrogen, activated aromatics are treated with cesium fluoroxysulfate,[29,30] acetyl hypofluorite,[24,25] and *N*-fluoropyridinium salts.[10] This ortho preference has been attributed either to the addition/elimination of the two fragments of the fluorinating agent across the higher electron density π region of the aryl–oxygen compound[23-25] or to an interaction of the negatively charged part of the fluorinating reagent with the phenolic proton.[7,10,30-32] The hypothesis that such an interaction is more difficult in protic solvents

(16) Mukawa, F.; Dorfman, R. I.; Ringold, H. J. *Steroids* **1963**, *1*, 9.
(17) Jacquesy, J. C.; Jacquesy, R.; Petit, M. *Tetrahedron Lett.* **1970**, 2595.
(18) Fluorine,[19,20] perchloryl fluoride,[21,22] acetyl hypofluorite,[23-25] cesium fluoroxysulfate,[7,26] trifluoromethyl hypofluorite,[27] and *N*-fluoropyridinium salts[10] all give nearly exclusively the ortho and para products.
(19) Misaki, S. *J. Fluorine Chem.* **1981**, *17*, 159.
(20) Misaki, S. *J. Fluorine Chem.* **1982**, *21*, 191.
(21) Taub, D. *Chem. Ind. (London)* **1962**, 558.
(22) Taub, D.; Kuo, C. H.; Wendler, N. L. *J. Org. Chem.* **1963**, *28*, 2752.
(23) Visser, G. W. M.; Bakker, C. N. M.; Halteren, B. W.; Herscheid, J. D. M.; Brinkman, G. A.; Hoekstra, A. *J. Org. Chem.* **1986**, *51*, 1886.
(24) Lerman, O.; Tor, Y.; Hebel, D.; Rozen, S. *J. Org. Chem.* **1984**, *49*, 806.
(25) Lerman, O.; Tor, Y.; Rozen, S. *J. Org. Chem.* **1981**, *46*, 4629.
(26) Stavber, S.; Zupan, M. *Chem. Commun.* **1981**, 148.
(27) Patrick, T. B.; Hayward, E. C. *J. Org. Chem.* **1974**, *39*, 2120.
(28) Anand, S. P.; Quaterman, L. A.; Hyman, H. H.; Migliorese, K. G.; Filler, R. *J. Org. Chem.* **1975**, *40*, 807.
(29) Appelman, E. H.; Basile, L. J.; Hayatsu, R. *Tetrahedron* **1984**, *40*, 189.
(30) Ip, D. P.; Arthur, C. D.; Winans, R. E.; Appelman, E. H. *J. Am. Chem. Soc.* **1981**, *103*, 1964.
(31) Tsushima, T.; Kawada, K.; Tsuji, T.; Misaki, S. *J. Org. Chem.* **1982**, *47*, 1107.
(32) Fifolt, M. J.; Olczak, R. T.; Mundhenke, R. F.; Bieron, J. F. *J. Org. Chem.* **1985**, *50*, 4576.

than in aprotic ones has been used to rationalize the lower ortho preference observed in protic solvents.[23,32]

The results of our experiments reported in Table I and some literature data[33] lead to the generalization that nonionic reagents favor the formation of fluorination products in the para position of para-substituted phenols while ionic ones display ortho selectivity. The easier association of ionic reagents with the phenolic hydroxyl could account for this difference. Being a covalent fluorinating reagent the *N*-fluoroimide **1** has a low tendency to interact with the phenolic oxygen. In protic solvents such an interaction is further disfavored and the para fluorination products form exclusively in most cases.

In general the fluorination could occur by electrophilic substitution,[29,30] radical-cation intermediate,[10,23,28] and addition/elimination process.[24,37] For the *N*-fluoroimide **1** the addition/elimination pathway seems to be disfavored by the fact that this mechanism was shown to be very sensitive to steric hinderance.[24] On the contrary, when both positions ortho to the phenolic oxygen were fluorinated, the more hindered C-4 site was fluorinated preferentially with respect to C-2. Furthermore, when the lithium salt of estrone **2b** was treated with the *N*-fluoroimide **1** in tetrahydrofuran solution (see Experimental Section) the ratio of the products **3b**:**4b**:**5b** was similar to that of the reaction of estrogen in chloroform solution despite the fact the inductive effect should make the ortho positions of lithium phenates even more electron rich than the para one.

Our experimental data do not allow a clear choice between the other two mechanisms for the reaction of the *N*-fluoroimide **1** with electron-rich aromatics. However, the real involment of a positive fluorine (even $F^{\delta+}$) is quite unlikely as a consequence of the high ionization potential of the fluorine atom and the particularly low electron density of the nitrogen atom of **1** (due to the strong electron-withdrawing ability of the two (trifluoromethyl)-sulfonyl residues).[38] On the contrary, the formation of phenoxy radicals in the oxidation of a variety of phenols is well documented. It is of particular interest to remember that on treatment of estrone and estradiol with singlet oxygen the corresponding 10$\beta$-hydroperoxy-3-oxo-1,4-estradiene products are formed[39] and that the radical of 2,4,6-tris(*tert*-butyl)phenol reacts with perfluoropiperidine to give the corresponding *p*-fluoro-*p*-quinoid product.[40]

Consistent with the above, the following may be plausible. Electron-rich substrate **2** transfers one electron to electron-poor *N*-fluoroimide **1**. Phenoxy radical cations of **2** are formed, and they easily lose a proton to give phenoxy radicals which are known to have the highest spin density at the para position.[41] The final transfer of $F^{\bullet}$ to this site by the radical anion of **1** gives the isolated *p*-quinoid products **5**.

## Experimental Section

All reactions were performed in glass apparatus. Commercially available, reagent-grade solvents were employed without purification. Flash column chromatography on silica gel was performed as described in the original paper.[42] Starting estrogens **2** were purchased by Research Plus. In $^{19}F$ (188-MHz), $^{1}H$ (300-MHz), and $^{13}C$ (75-MHz) NMR $CDCl_3$ was used as a lock solvent and $CFCl_3$ and tetramethylsilane were used as internal references. The X-ray analysis of **5b** was performed using a crystal grown by slow evaporation of a dichloromethane/diisopropyl ether solution (see supplementary material).

**Fluorination Reaction of Estrogens 2.** All reactions were performed in a similar manner. A detailed procedure is described below for the fluorination of estradiol propionate **2a**. In all cases $^{1}H$ NMR of crude mixtures showed that reactions were very clean and a complete convertion of **2** into the products **3**–**5** had occurred. Ratios of reaction products reported in Table I were established through $^{19}F$ NMR of the crude reaction mixtures. Compounds **3b–d** and **4b–d** were not isolated in pure form. Their structures were assigned through comparison of $^{1}H$ and $^{19}F$ NMR data with those reported in the literature.[8-10] In other cases, yields, physical, and spectral properties were obtained on pure samples from flash chromatography.

**Fluorination of 3,17$\beta$-Estradiol 17-Propionate 2a. General Procedure.** A solution of the *N*-fluoroimide **1** (311 mg, 1.04 mmol) in ethanol-free chloroform (2.0 mL) was added dropwise at room temperature to a stirred solution of 1,3,5(10)-estratriene-3,17$\beta$-diol 17-propionate (**2a**) (263 mg, 0.80 mmol) in the same solvent (4.0 mL). After stirring for 3 h, a saturated aqueous solution of sodium hydrogen carbonate was added (10 mL), the heterogeneous system was diluted with water (10 mL), and the aqueous layer was extracted with chloroform (3 × 20 mL). The collected organic layers were dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure. $^{1}H$ NMR of the crude reaction mixture showed that no more starting material **2a** was present and that the 2-fluoro-1,3,5(10)-estratriene-3,17$\beta$-diol 17-proprionate (**3a**), the 4-fluoro-1,3,5(10)-estratriene-3,17$\beta$-diol 17-propionate (**4a**), and the 10$\beta$-fluoro-3-oxo-1,4-estradien-17$\beta$-ol 17-propionate (**5a**) were formed cleanly. $^{19}F$ NMR of the same crude mixture revealed that the **3a**:**4a**:**5a** ratio was 12.7:18.3:69.0. Flash chromatography (*n*-hexane/ethyl acetate (7:3)) afforded **3a** and **4a** (70 mg, 25% yield) and **5a** (157 mg, 57% yield). Mixture of **3a** and **4a**: $^{1}H$ NMR $\delta$ 0.83 (s, 3 H, $CH_3$-18), 1.15 (t, 3 H, $CH_3CH_2$), 2.34 (q, 2 H, $CH_2CH_3$), 4.70 (dd, 1 H, H-17), 6.70 (d, 1 H, H-4 for **3a**, $J \approx 9.2$ Hz), 6.79 (t, 1 H, H-2 for **4a**, $J \approx 8.6$ Hz), 6.95 (d, 1 H, H-1 for **4a**, $J \approx 8.6$ Hz), 6.97 (d, 1 H, H-1 for **3a**, $J \approx 12$ Hz); $^{19}F$ NMR $\delta$ −145.3 (dd, F-2 for **3a**, $J \approx 9$, 12 Hz), −146.4 (d, F-4 for **4a**, $J \approx 8.3$ Hz). Anal. Calcd for $C_{21}H_{27}FO_3$: C, 72.80; H, 7.86. Found: C, 73.06; H, 8.04. **5a**: $^{1}H$ NMR $\delta$ 0.89 (s, 3 H, $CH_3$-18), 1.14 (t, 3 H, $CH_3CH_2$), 1.02 and 1.81 (m each, 2 H, H-8 and H-14), 1.19 (m, 1 H, H-9), 2.32 (q, 2 H, $CH_2CH_3$), 4.61 (t, 1 H, H-17), 6.03 (s, 1 H, H-4), 6.22 (d, 1 H, H-3, $J_{H\text{-}2,H\text{-}3} = 10.3$ Hz), 7.09 (dd, 1 H, H-1, $J_{H,F} = 7.6$ Hz); $^{19}F$ NMR $\delta$ −165.8 (dd, F-10, $J_{F,H\text{-}1} = 7.2$ Hz, $J_{F,H\text{-}9} = 29.0$ Hz); $^{13}C$ NMR $\delta$ 9.24 ($CH_3$), 11.91 ($CH_3$-18), 27.72 ($CH_2CH_3$), 35.51 and 49.49 (CH-8 and CH-14), 54.08 (CH-9, $J_{C,F} = 24.5$ Hz), 81.97 (CH-17), 89.11 (C-10, $J_{C,F} = 168.1$ Hz), 123.63 (CH-4, $J_{C,F} = 4.2$ Hz), 129.43 (CH-3, $J_{C,F} = 8.3$ Hz), 145.1 (CH-1, $J_{C,F} = 24.1$ Hz), 174.39 (COO), 184.95 (C-3, $J_{C,F} = 4.07$ Hz), other $CH_2$ at 36.28, 32.58, 31.78, 27.40, 23.67, 22.48; IR (film liquid, KCl), 2935, 1725, 1671 $cm^{-1}$; mass spectrum (EI) *m*/*e* 346 ($M^+$); $[\alpha]^{20}_D$ −17.7° (*c* = 0.90, $CHCl_3$); circular dichroism $[\theta]^{25}_{288}$ +277; $[\theta]^{25}_{367}$ −2.44·10$^3$; $[\theta]^{25}_{382}$ −2.35 × 10$^3$. Anal. Calcd for $C_{21}H_{27}FO_3$: C, 72.80; H, 7.86. Found: C, 72.98; H, 8.01. When acetic acid was used as a reaction solvent, product **5a** was isolated in 76% yield after flash chromatography.

**2-Fluoroestrone 3b and 4-Fluoroestrone 4b.** The fluorination reaction of estrone **2b** in chloroform solution was performed as described above for estradiol propionate **2a**. The ratio of the

(33) Para fluorination products were exclusively formed when estradiol, several structurally similar steroids,[2-4] and an analogue of griseofulvin[21,22] have been treated with perchloryl fluoride. Trifluoromethyl hypofluorite gave para products with some tyrosine derivatives,[34] estrone acetate, and estrone methyl ether,[5,6] but gave the ortho fluorination product with griseofulvin.[35] Ortho fluorination occurred when estradiol was reacted with cesium fluoroxysulfate[7] or *N*-fluoropyridinium salts[8-10] and when a tyrosine-containing peptide was treated with acetyl hypofluorite.[36]

(34) Barton, D. H. R.; Hesse, R. H.; Pechet, M. M.; Toh, H. T. *J. Chem. Soc., Perkin Trans 1* **1974**, 732.

(35) Barton, D. H. R.; Hesse, R. H.; Ogunkoya, L.; Westcott, N. D.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2889.

(36) Hebel, D.; Kirk, K. L.; Cohen, L. A.; Labroo, V. M. *Tetrahedron Lett.* **1990**, *31*, 619.

(37) Patrick, T. B.; Cantrell, G. L.; Chang, C. Y. *J. Am. Chem. Soc.* **1979**, *101*, 7434.

(38) DesMarteau, D. D. et al. To be published.

(39) Lupon, P.; Gomez, J.; Bonet, J. J. *Angew. Chem., Int. Ed. Engl.*, **1983**, *22*, 711.

(40) Polishchuk, V. R.; German, L. S. *Tetrahedron Lett.* **1972**, 5169.

(41) Stone, T. J.; Waters, W. A. *J. Chem. Soc.* **1964**, 213.

(42) Still, W. C.; Kanh, H.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

formed products **3b**, **4b**, and **5b** are reported in Table I.

In another experiment, a suspension of estrone **2b** (405 mg, 1.5 mmol) and lithium hydride (36 mg, 4.5 mmol) in tetrahydrofuran (freshly distilled from $LiAlH_4$, 6.0 mL) was refluxed for 5 h under nitrogen. The reaction was cooled at 0 °C, and a solution of the *N*-fluoroimide **1** (224 mg, 0.75 mmol) in the same solvent (3.0 mL) was added dropwise. The resulting mixture was stirred at room temperature for 1.5 h. $^{19}F$ NMR of this mixture revealed that the ratio (**3b** + **4b**):**5b** was 41:59 and the ratio **3b**:**4b** was 43:57. Mixture of **3b** and **4b**: $^1H$ NMR δ 0.93 (s, 3 H, $CH_3$-18) 6.71 (d, 1 H, H-4 for **3b**, $J_{H\text{-}4,F}$ = 9.2 Hz), 6.81 (t, 1 H, H-2 for **4b**, $J_{H\text{-}1,H\text{-}2} \approx J_{H\text{-}2,F} \approx$ 8.9 Hz), 6.94 (d, 1 H, H-1 for **4b**, $J_{H\text{-}1,F} \approx$ 8.5 Hz), 6.97 (d, 1 H, H-1 for **3b**, $J_{H\text{-}1,F}$ = 11.8 Hz); $^{19}F$ NMR δ −144.7 (dd, F-2 for **3b**, $J_{F,H\text{-}1}$ = 11.9 Hz, $J_{F,H\text{-}4}$ = 9.5 Hz), −145.9 (d, F-4 for **4b**, $J_{F,H\text{-}2}$ = 8.9 Hz).

**10β-Fluoro-1,4-estradiene-3,17-dione (5b)**: flash chromatography *n*-hexane/ethyl acetate (7:3); isolated yield 81%; mp 143–144 °C (lit.[3] mp 143–144 °C); $^1H$ NMR δ 0.97 (s, 3 H, $CH_3$-18), 6.05 (brs, 1 H, H-4), 6.25 (ddd, 1 H, H-2, $J_{H\text{-}1,H\text{-}2}$ = 10.3 Hz, $J$ = 1.2, 1.8 Hz), 7.07 (dd, 1 H, $J_{H,F}$ = 7.7 Hz); $^{19}F$ NMR δ −165.7 (dd, F-10, $J_{F,H\text{-}9}$ = 28.8 Hz, $J_{F,H\text{-}1}$ = 7.5 Hz); $^{13}C$ NMR δ 13.7 ($CH_3$), 54.1 (C-9, $J_{C,F}$ = 24.5 Hz), 89.0 (C-10, $J_{C,F}$ = 168.1 Hz), 123.9 (C-4, $J_{C,F}$ = 4.5 Hz), 129.7 (C-2, $J_{C,F}$ = 8.5 Hz), 144.6 (C-1, $J_{C,F}$ = 23.8 Hz), 184.9 (C-3, $J_{C,F}$ = 4.2 Hz), 219.6 (C-17), other signals at 21.9, 22.2, 31.0, 31.6, 31.8, 35.4, 35.5, 47.7, 50.0; IR (nujol, KCl) 1729, 1665, 1637 $cm^{-1}$; mass spectrum (EI) *m/e* 288.2 ($M^+$); $[\alpha]^{20}_D$ +61.3° (*c* = 1.1, $CHCl_3$). Anal. Calcd for $C_{18}H_{21}FO_2$: C, 74.97; H, 7.34. Found: C, 75.11, H, 7.56.

**2-Fluoro-1,3,5(10)-estratriene-3,17α-diol 17-acetate (3c) and 4-fluoro-1,3,5(10)-estratriene-3,17α-diol 17-acetate (4c)**: $^1H$ NMR δ 0.79 (s, 3 H, $CH_3$-18), 2.10 (s, 3 H, $CH_3CO$), 6.70 (d, 1 H, H-4 for **3c**, $J_{H\text{-}4,F}$ = 8.8 Hz), 6.80 (t, 1 H, H-2 for **4c**, $J_{H\text{-}2,H\text{-}1} \approx J_{H\text{-}2,F} \approx$ 9.0 Hz), 6.95 (d, 1 H, H-1 for **4c**, $J_{H\text{-}1,H\text{-}2} \approx$ 8.5 Hz), 6.98 (d, 1 H, H-1 for **3c**, $J_{H\text{-}1,F} \approx$ 12.0 Hz); $^{19}F$ NMR δ −145.2 (dd, F-2 for **3c**, $J_{F,H\text{-}4} \approx$ 9.0 Hz, $J_{F,H\text{-}1} \approx$ 12 Hz), −146.3 (d, F-4 for **4c**, $J_{F,H\text{-}2} \approx$ 8.7 Hz).

**10β-Fluoro-3-oxo-1,4-estradien-17α-ol 17-acetate (5c)**: flash chromatography *n*-hexane/ethyl acetate (7:3); isolated yield 80%; $^1H$ NMR δ 0.85 (s, 3 H, $CH_3$-18), 2.00 (s, 3 H, $CH_3CO$), 4.83 (d, 1 H, H-17, $J$ = 5.7 Hz), 6.04 (brs, 1 H, H-4), 6.23 (d, 1 H, H-2, $J_{H\text{-}2,H\text{-}1}$ = 10.1 Hz), 7.09 (dd, 1 H, H-1, $J_{H\text{-}2,H\text{-}1}$ = 10.3 Hz, $J_{H\text{-}F}$ = 7.6 Hz); $^{19}F$ NMR δ −166.1 (dd, F-10, $J_{F,H\text{-}1}$ = 7.2 Hz, $J_{F,H\text{-}9} \approx$ 29.0 Hz); $^{13}C$ NMR δ 16.5 ($CH_3$-18), 54.4 (C-9, $J_{C,F}$ = 24.6 Hz), 81.6 (C-17), 89.2 (C-10, $J_{C,F}$ = 168.0 Hz), 123.6 (C-4, $J_{C,F}$ = 4.3 Hz), 129.4 (C-2, $J_{C,F}$ = 8.5 Hz), 145.2 (C-1, $J_{C,F}$ = 23.9 Hz), 170.6 (COO), 185.1 (C-3, $J_{C,F}$ = 4.2 Hz), other signals at 21.2, 22.4, 24.8, 29.9, 31.2, 31.9, 33.4, 35.9, 44.8, 48.7; $[\alpha]^{20}_D$ −22.8 (*c* = 0.6, $CHCl_3$). Anal. Calcd for $C_{20}H_{25}FO_3$: C, 72.26; H, 7.58. Found: C, 72.47; H, 7.88.

**2-Fluoro-1,3,5(10)-estratriene-3,16α,17β-triol 16,17-diacetate (3d) and 4-fluoro-1,3,5(10)-estratriene-3,16α,17β-triol 16,17-diacetate (4d)**: $^1H$ NMR δ 0.86 (s, 3 H, $CH_3$-18), 6.69 (d, 1 H, H-4 for **3d**, $J_{H\text{-}4,F}$ = 9.0 Hz), 6.80 (t, 1 H, H-2 for **4d**, $J_{H\text{-}2,H\text{-}1} = J_{H\text{-}2,F}$ = 8.8 Hz), 6.95 (d, 1 H, H-1 for **4d**, $J_{H\text{-}1,H\text{-}2}$ = 8.8 Hz), 6.98 (d, 1 H, H-1 for **3d**, $J_{H\text{-}1,F}$ = 12 Hz); $^{19}F$ NMR δ −144.7 (dd, F-2 for **3d**, $J_{F,H\text{-}4}$ = 9.0 Hz, $J_{F,H\text{-}1}$ = 12 Hz), −145.9 (d, F-4 for **4d**, $J_{F,H\text{-}2}$ = 8.7 Hz).

**10β-Fluoro-3-oxo-1,4-estradiene-16α,17β-diol 16,17-diacetate (5d)**: flash chromatography *n*-hexane/ethyl acetate (6:4); isolated yield 84%; $^1H$ NMR δ 0.91 (s, 3 H, $CH_3$-18), 2.04, 2.08 (s each, 3 H each, $(CH_3CO)$x2), 4.90 (d, 1 H, H-16, $J_{H\text{-}16,H\text{-}16}$ = 5.7 Hz), 5.15 (ddd, 1 H, H-16, $J_{H\text{-}16,H\text{-}15}$ = 7.7 and 1.9 Hz), 6.04 (s, 1 H, H-4), 6.24 (d, 1 H, H-2, $J_{H\text{-}2,H\text{-}1}$ = 10.3 Hz), 7.05 (dd, 1 H, H-1, $J_{H\text{-}1,H\text{-}2}$ = 10.3 Hz, $J_{H\text{-}1,F}$ = 7.6 Hz); $^{19}F$ NMR δ −165.7 (dd, F-10, $J_{F,H\text{-}9}$ = 28.6 Hz, $J_{F,H\text{-}1}$ = 7.2 Hz); $^{13}C$ NMR δ 12.8 ($CH_3$-18), 53.8 (C-9, $J_{C,F}$ = 24.7 Hz), 77.7 and 85.7 (C-16 and C-17), 89.0 (C-10, $J_{C,F}$ = 168.0 Hz), 123.9 (C-4, $J_{C,F}$ = 4.2 Hz), 129.7 (C-2, $J_{C,F}$ = 8.7 Hz), 144.7 (C-1, $J_{C,F}$ = 23.7 Hz), 159.7 (C-5, $J_{C,F}$ = 18.9), 170.8 and 170.7 (2xCO), 184.9 (C-3, $J_{C,F}$ = 4.6 Hz), other signals at 21.0, 21.1, 22.1, 30.9, 31.6, 32.3, 35.1, 36.1, 43.6, 47.8; IR (film, KCl) 1725, 1686, 1671, 1637 $cm^{-1}$; mass spectrum (EI) *m/e* 390.3 ($M^+$); $[\alpha]^{20}_D$ −79.7° (*c* = 0.6, $CHCl_3$). Anal. Calcd for $C_{22}H_{27}FO_5$: C, 67.67; H, 6.97. Found: C, 67.96; H, 7.18.

**10β-Fluoro-4-nitro-1,4-estradiene-3,17-dione (5e)**: flash chromatography *n*-hexane/ethyl acetate (2:1); isolated yield 85%; $^1H$ NMR δ 0.97 (s, 3 H, $CH_3$-18), 6.38 (d, 1 H, H-2, $J_{H\text{-}1,H\text{-}2}$ = 10.4 Hz), 7.23 (dd, 1 H, H-1, $J_{H\text{-}1,F}$ = 7.7 Hz); $^{19}F$ NMR δ −166.1 (dd, F-10, $J_{F,H\text{-}9}$ = 28.4 Hz); $^{13}C$ NMR δ 13.7 ($CH_3$-18), 54.9 (C-9, $J_{C,F}$ = 24.6 Hz), 89.5 (C-10, $J_{C,F}$ = 175.2 Hz), 127.9 (C-2, $J_{C,F}$ = 8.6 Hz), 144.6 (C-4, $J_{C,F}$ = 6.5 Hz), 145.8 (C-1, $J_{C,F}$ = 24.6 Hz), 150.3 (C-5, $J_{C,F}$ = 22.1 Hz), 173.8 (C-3, $J_{C,F}$ = 3.9 Hz), 219.1 (C-17); IR (film, KCl) 1732, 1680, 1660, 1619 $cm^{-1}$; mass spectrum (EI) *m/e* 333.4 ($M^+$); $[\alpha]^{20}_D$ +102.3 (*c* = 1.5, $CHCl_3$). Anal. Calcd for $C_{18}H_{20}FNO_4$: C, 64.85; H, 6.05. Found: C, 64.99; H, 6.24.

**Acknowledgment.** The partial financial support of this research by the National Science Foundation and the award of a NATO Fellowship (G.R.) are gratefully acknowledged.

**Registry No.** 1, 108388-06-3; **2a**, 18069-79-9; **2b**, 53-16-7; **2c**, 15068-99-2; **2d**, 805-26-5; **2e**, 5976-74-9; **3a**, 138054-57-6; **3b**, 1881-35-2; **3c**, 138054-58-7; **3d**, 138054-59-8; **4a**, 138054-60-1; **4b**, 1881-36-3; **4c**, 138054-61-2; **4d**, 138054-62-3; **5a**, 138054-63-4; **5b**, 794-13-8; **5c**, 138054-64-5; **5d**, 138054-65-6; **5e**, 138054-66-7.

**Supplementary Material Available:** A summary of structural details and tables of atomic coordinates, bond distances and angles, anisotropic thermal parameters, calculated hydrogen atom coordinates, and a thermal ellipsoid plot of molecule two for **5b** (7 pages). Ordering information is given on any current masthead page.