acidic in $Me_2SO$. Although these notions do not give quantitative acidity values, they may be of some use to the organic chemist.

## V. Conclusion

In summary, a new algorithm for $pK_a$ prediction has been implemented in the computer synthesis program CAMEO. Key organizing principles have been developed to account for substituent effects on acidity. The algorithm is general and capable of predicting $pK_a$'s for a vast number of organic compounds with an average error of 1.5 $pK_a$ units.

**Acknowledgment.** This work was supported by a grant from the National Science Foundation. We are also grateful to Professor Frederick G. Bordwell and his coworkers for helpful comments and for providing the experimental database that made this study possible.

**Registry No.** $Me_2SO$, 67-68-5.

# Selective Fluorination of Steroids Using Elemental Fluorine

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Elemental fluorine, when diluted with nitrogen, replaces tertiary deactivated hydrogens via the extremely rare electrophilic substitution on a saturated $sp^3$ carbon. This work describes such substitutions on steroids including the cases of the less common 3α-ol and 5β series. Depending on the location of the deactivating oxygenated functions in the steroid one can direct the substitution on any of the tertiary 5, 9, 14, 17, or 25 positions. A full retention of configuration is observed, in accordance with the proposed substitution mechanism. One of the major differences between the 3α- and the 3β-sterols is the fact that in the latter series we have never witnessed fluorination at the 5 position, while in the 3α-ol derivatives the formation of the 5C–F bond is quite common. A second difference between the 5α- and the 5β-steroids concerns the fluorination of the electronically favorable 9 position. In the 5β series the A/B cis arrangement sterically prevents the approach to this position so the 9C–H bond remains untouched. Some leads are also presented as to the question whether or not this reaction can be carried out efficiently at higher than the usual −75 °C. CNDO calculations, coupled with the MM1 program, offer good criteria as to which single tertiary site of the few present will be substituted by the fluorine atom.

It is quite likely that no other single chemical group of compounds has captured the chemist's attention so intensely as the steroids. Despite this, however, only extremely few works have been devoted to the study of activating sites on the four-ring skeleton, when these are remote from any conventional functional group such as a double bond, a carbonyl, or a heteroatom. Among these works one should mention the outstanding Breslow's "remote control" functionalization[1] and Mazur's radical chlorination[2] and silica supported ozone oxidation.[3] Most of these examples, and a few other attempts, are of a radical nature and have certain limitations. To perform reactions on deactivated sites in an ionic mode, a simple and yet unique reagent has been lacking.

In the past, one of us participated in the only published work showing that elemental fluorine can substitute a deactivated tertiary hydrogen in some common steroids.[4] We describe now the unusual reaction of $F_2$ with some less common 5β- and 3α-sterols which may help clarify the role of electronic as against stereochemical factors, concentrations, temperature, and solvent influences on the reaction course.[5] This approach can also be of biological importance since many selectively fluorinated compounds, especially among steroids, have potential biological activity either in pharmacology.[6] or in radiodiagnostic studies using $^{18}F$ derivatives with positron emitting tomography (PETT).[7]

As a part of our program in studying the unique substitution reaction at saturated centers, we have conducted research also on substrates other than steroids, showing that the mechanism of this substitution is of an ionic nature.[8] The reactive species is the electrophilic part of the $F_2$ dipole, which attacks the electrons of the corresponding C–H bond leading to a substitution with a full retention of the configuration.[8] The medium in which the reaction is performed is of crucial role. If a nonpolar solvent such as $CFCl_3$ is used, no encouragement for the $F_2$ polarization exists and the main course of the reaction is found to be an indiscriminate radical one. The same is true with hydrogen containing nonpolar solvents such as hexane or pentane. When, however, $CHCl_3$ is used as a cosolvent with $CFCl_3$[9] it serves as a radical scavenger and probably more important, it increases the medium polarity and acts

(1) Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170.
(2) Cohen, Z.; Mazur, Y. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 281.
(3) Cohen, Z.; Mazur, Y. *J. Org. Chem.* **1979**, *44*, 2318.
(4) Alker, D.; Barton, D. H. R.; Hesse, R. H.; James, J. L.; Markwell, R. E.; Pechet, M. M.; Rozen, S.; Takeshita, T.; Toh, H. T. *Nouv. J. Chim.* **1980**, *4*, 239.
(5) For a preliminary communication on the fluorination of bile acids, see: Rozen, S.; Ben-Shushan, G. *Tetrahedron Lett.* **1984**, *25*, 1947.
(6) Filler, R.; Kobayashi, Y., Ed. *Biomedicinal Aspects of Fluorine Chemistry*; Elsevier Biomedical Press: Amsterdam, 1982.
(7) See for example: Dagani, R. *Chem. Eng. News* **1981**, *59(13)*, 30.
(8) See, for example: (a) Rozen, S.; Gal, C. *J. Fluorine Chem.* **1985**, *27*, 143. (b) Gal, C.; Rozen, S. *Tetrahedron Lett.* **1984**, *25*, 449. (c) Gal, C.; Rozen, S. *Tetrahedron Lett.* **1985**, *26*, 2793. (d) Rozen, S.; Gal, C.; Faust, Y. *J. Am. Chem. Soc.* **1980**, *102*, 6860.
(9) The $CHCl_3$ which usually serves as a cosolvent with $CFCl_3$ can be replaced with other polar solvents which have somewhat acidic hydrogen such as $CH_3NO_2$ or AcOH, with little change in the reaction outcome.

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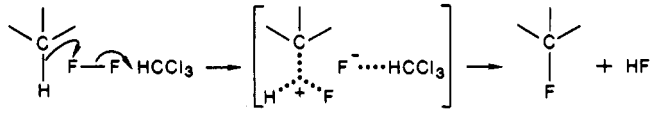
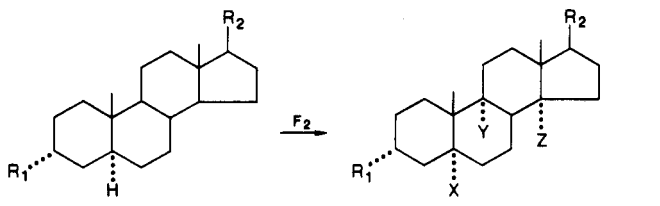
as an acceptor, through hydrogen bonding, for the $F^-$ which starts to form in the transition state.



In order for such a substitution to be successful, the fluorine molecule should also be attracted to a hydrogen with relatively high ionic character, which at the same time enjoys the highest p orbital contribution to its bond with a carbon.[10] Usually therefore tertiary carbon–hydrogen bonds would be the most suitable for such an attack by $F_2$. Obviously the existence of any electron-withdrawing group such as an oxygen atom will affect the electron density of the nearby C–H bonds mainly by diminishing their p character. This fact has two opposing effects on the selectivity of the fluorination reaction. By deactivating some of the nearby tertiary hydrogens toward electrophilic substitution the number of the potential sites for fluorination is reduced. On the other hand, one has to remember that although radical pathways are highly suppressed, they are not completely eliminated, mainly because of the weakness of the F–F bond. Since the presence of electron-withdrawing groups slows down any electrophilic reactions, greater opportunity for the undiscriminating radical fluorinations exist, resulting in more fluorinated tars.

When no functional groups are present in the steroidal skeleton, as in the case of 5α-androstane (1), the C–H bonds with the highest p character are at the 9, 14, and 5 positions.[11] When 1 was reacted with nitrogen diluted



1: $R_1 = R_2 = H$
4: $R_1$ = OAc; $R_2 = H$
7: $R_1 = H$; $R_2$ = OAc
10: $R_1$ = OAc; $R_2$ = COMe ···OH
12: $R_1$ = OAc; $R_2 = O$=

2: $R_1 = R_2 = X = Z = H$; $Y = F$
3: $R_1 = R_2 = X = Y = H$; $Z = F$
5: $R_1$ = OAc; $R_2 = X = Z = H$; $Y = F$
6: $R_1$ = OAc; $R_2 = X = Y = H$; $Z = F$
8: $R_1 = X = Z = H$; $R_2$ = OAc; $Y = F$
9: $R_1 = Y = Z = H$; $R_2$ = OAc; $X = F$
11: $R_1$ = OAc; $R_2$ = COMe ···OH; $X = Z = H$; $Y = F$
13: $R_1$ = OAc; $R_2 = O$=; $X = Z = H$; $Y = F$
14: $R_1$ = OAc; $R_2 = O$=; $Y = Z = H$; $X = F$

fluorine at −75 °C, a fast reaction took place. Two main fractions were isolated after chromatography. The main one proved to be 9α-fluoroandrostane (2), 20% yield, while the second was found to be the 14α-fluoro derivative (3) formed in 15% yield. It is likely that the low yields result from the fact that 1 does not benefit from any electron-withdrawing group which can deactivate some of the additional tertiary C–H bonds.

The selectivity was indeed improved when an electron-withdrawing group was introduced as in the case of 5α-androstan-3α-ol acetate (4). With less suitable hydrogens now available for substitution, we were able to isolate the 9α-fluoro-5α-androstan-3α-ol acetate (5) in 35% yield along with 30% yield of the 14α-fluoro derivative (6). Changing the site of the electron-withdrawing group as in 5α-androstan-17β-ol acetate (7) results in deactivation of the 14C–H bond, thus allowing the formation of the 9α-fluoro (8) and 5α-fluoro (9) derivatives in 30% yield each.

The 5α-fluoro derivatives are characterized by signals at −160 to −165 ppm in the $^{19}F$ NMR spectrum, by a paramagnetic shift of 0.15 ppm of the 19-Me group in $^1H$ NMR, and by $^{13}C$ NMR spectroscopy.[12-14] The fluorination at the 5 position was also confirmed by X-ray crystallography.

Placing electronegative groups at each end of the molecule further improves the selectivity. MO calculations for 20-oxo-5α-pregnane-3α,17α-diol 3-acetate (10) show that the 9C–H bond possesses the highest electron density among all the tertiary C–H bonds in 10. When this compound was reacted with elemental fluorine only substitution of the 9α-hydrogen with the fluorine atom did indeed take place producing the 9α-fluoro-20-oxo-5α-pregnane-3α,17α-diol 3-acetate (11) in 60% yield. It seems, however, that this uncommon electrophilic substitution is highly sensitive even to small differences in the electron density at various parts of the molecule.[8] When the process of substitution of a particular hydrogen becomes difficult, other sites will start to play a more important role. Thus replacing the hydroxyl at position 17 by the stronger electron withdrawing carbonyl group as in the case of 17-oxo-5α-androstan-3α-ol acetate (12) resulted in a stronger deactivation of the 9 position. This reduced the rate of fluorination at this site and 9α-fluoro-17-oxo-5α-androstan-3α-ol acetate (13) was obtained in only 40% yield; it also accounts for the formation of the accompanying 5α-fluoro-17-oxoandrostan-3α-ol acetate 14, isolated in 30% yield. Substitution at the 5 position (as in 14) constitutes one of the major differences between the 3β- and 3α-sterols. While in the former series we have never witnessed fluorination at that site,[4] in the less common 3α derivatives we find the fluorine atom at position 5 quite frequently. It is very likely that the carbonyl of the axial acetate group, along with the external chloroform molecule which is a necessary cosolvent, helps to polarize the fluorine molecule while it nears the 5 position. It also may stabilize the transition state through mutual attractions between the electron pairs of the oxygen and the fluorine. Such positive interactions between two very electronegative atoms do exist and are well documented.[15] In the 3β-sterols the acetate group will act only as an electron-withdrawing force and thereby completely deactivate the tertiary hydrogen at the 5 position toward any electrophilic substitution.

The $^{13}C$ NMR spectrum fully supports the structure of 14. The C-5, α to the fluorine atom, experiences a paramagnetic shift of 55 ppm ($^1J_{CF}$ = 180 Hz). The β-carbons

(10) Wiberg, K. B. *Tetrahedron* **1968**, *24*, 1083. Wiberg, K. B. *Sigma Molecular Orbital Theory*, Singaloglu, O., Ed.; Yale University Press: New Haven and London, 1970; p 179.

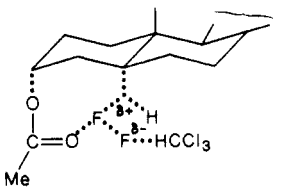
(11) The geometry of all the steroid molecules described in this work has been determined using Allinger's MM1 calculations. Then the ratio of the squares of the bond indices $B^2_{C(p)-H}/B^2_{C(s)-H}$ was calculated by using the CNDO/2 program. This ratio can be indicative of the relative p orbital contribution to any C–H bond in the molecule (see also ref 10). While we have isolated molecules with fluorine at 5, 9, 14, 17, and 25, we have never seen a fluorination at the 8- or 20C–H bond. The CNDO/2 calculations indicate that the electron density in these bonds is lower than most of the other tertiary ones, but what is probably more important is the great sterical hindrance at the 8β position, originating from the unbrella-like 18 and 19 methyl groups and from the flexible side chain on the 20 position.

(12) The structures of all fluorinated steroidal products were confirmed by $^1H$ and $^{19}F$ spectroscopy,[4] by comparing the optical rotation and relevant $\Delta M_D$'s,[13] and by studying their $^{13}C$ NMR spectra.[14] It is of interest to note that in all 9α-fluoro steroids studied so far, the fluorine atom resonates at −179.5 to −180.0 ppm while the range for all 14α-fluoro derivatives is −163.5 to −164.5 ppm.

(13) Barton, D. H. R.; Hesse, R. H.; Markwell, R. E.; Pechet, M. M.; Rozen, S. *J. Am. Chem. Soc.* **1976**, *98*, 3036 and ref 9 therein.

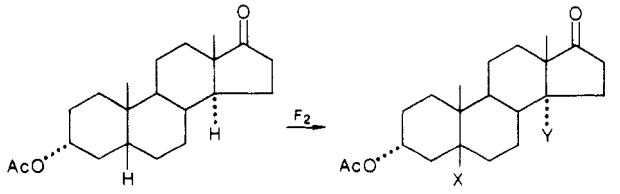
(14) Rozen, S.; Ben-Shushan, G. *Magn. Reson. Chem.* **1985**, *23*, 116.

(15) Philips, L.; Wray, V. *J. Chem. Soc., Chem. Commun.* **1973**, *90*. Zefirov, N. S.; Samoshin, V. V.; Sabotin, O. A.; Baranenkov, V. I.; Wolfe, S. *Tetrahedron* **1978**, *34*, 2953.



at positions 4, 6, and 10 are also shifted to a lower field by 1 to 3.5 ppm ($^2J_{CF}$ = 20–26 Hz). The γ-carbons, however, which are very sensitive to the stereochemical environment,[14] are divided into two groups. The gauche carbons C3, C7, and C9 undergo diamagnetic shifts of 2 to 7 ppm, while the γ anti 19-carbon is shifted to lower field by 4.5 ppm.

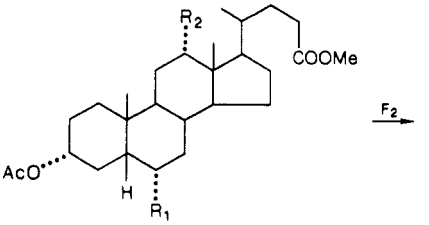
In addition to the already mentioned electronic ones, sterical considerations also play an important role in the fluorination of that large group of 5β-steroids which have never been directly fluorinated before[5] and of which the bile acids are important members. The compound 17-oxo-5β-androstan-3α-ol acetate (**15**) presents a typical case. After the usual treatment with nitrogen-diluted fluorine at −75 °C, two main fractions were isolated and characterized. The first one proved to be 17-oxo-5β-fluoroandrostan-3α-ol acetate (**16**), 35% yield, while the second was identified as the 14α-fluoro isomer **17**, in 25% yield. Two main differences between this case and the corresponding 5α derivative **12** can be noticed immediately. The first is the absolute absence of any 9 fluorination, despite the fact that this C–H bond is apparently most suitable for electrophilic reactions since it possess the highest p orbital contribution when compared to the rest of the tertiary C–H bonds. This phenomenon is consistent in all the A/B cis steroids which we have examined. It seems that the ring A, which in the 5β series is perpendicular to the steroidal plane, completely blocks the mutual approach of the pair of molecules, $F_2$ and $CHCl_3$, to the 9αC–H bond. As a result, the second difference between **12** and **15** emerges, and in the latter case we find the fluorine atom on either one of the two tertiary positions at 14 or 5. It should be noted that the fluorination of **15** is slower than that of **12**, since both the 5 and 14 sites are closer to an electron-withdrawing group than is the 9 one. We thus see, again, that when favorable conditions for electrophilic substitution of a certain hydrogen do exist, the fluorination will proceed easily, and only when these conditions are worsened, the somewhat less suitable hydrogens will start to react. Considering the alleged reactivity of elemental fluorine, such stereo- and regiospecificity is quite remarkable.



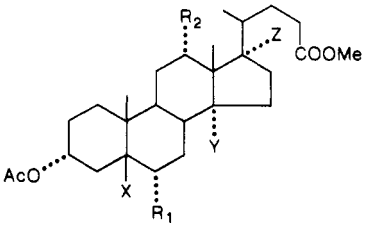
**15** **16**: Y = H; X = F
**17**: X = H; Y = F

Compound **16**, the first example of fluorination at the 5β position, offers no exception to the rigorous stereospecificity of the electrophilic front-side fluorination. The cis A/B ring arrangement was preserved after the fluorination as evidenced by the $[\alpha]_D$ +90° [16] and also by the $^1H$ NMR spectrum, which shows a substantial paramagnetic shift of 0.3 ppm for the axial 3β proton due to the 1,3 interactions with the axial fluorine at position 5 and a paramagnetic shift of 0.02 ppm for the 19-Me group (d, $J$ = 0.9 Hz). The $^{19}F$ NMR spectrum shows a narrow multiplet at −151 ppm ($W_{h/2}$ = 40 Hz) in agreement with one ax–ax and three eq–ax and eq–eq interactions. The chemical shift and the width of the signal are in good accordance with the data for the *cis*-decalin system.[17] Another proof for the 5β configuration of the fluorine is derived from the $^{13}C$ NMR which shows a downfield shift of all three β carbons C-4, C-6, and C-10 by 2.2 ppm ($^2J_{CF}$ = 20 Hz), 0.5 ppm ($^2J_{CF}$ = 14 Hz), and 4.9 ppm ($^2J_{CF}$ = 18 Hz), respectively, a diamagnetic shift of all three γ gauche carbons (C-3, 3.4 ppm; C-19, 6.5 ppm ($^3J_{CF}$ = 6 Hz), and C-1, 2.1 ppm), and again a paramagnetic shift of the γ carbons in anti configuration to the F atom, C-9, 3.5 ppm ($^3J_{CF}$ = 6 Hz) and C-7, 4.2 ppm.[14]

In the case of 3α-hydroxy-5β-cholanic acid 3-acetate, methyl ester (**18**), which lacks the electron-withdrawing carbonyl from the 17 position, the 14α-C–H bond becomes less deactivated and thus more susceptible toward electrophilic fluorination. Thus 14α-fluoro-3α-hydroxy-5β-cholanic acid 3-acetate, methyl ester (**19**) is formed in 35% yield. As with cholesterol and cholestanol derivatives,[4] we have in addition isolated and identified an about 10% yield of the 17α-fluoro derivative **20**, characterized, among other things, by its $^{19}F$ NMR spectrum showing a typical quartet at −171 ppm ($J$ = 31 Hz). Here again we notice the same trend as before, namely, other tertiary sites become more susceptible to the electrophilic fluorination, as they become relatively less deactivated.



**18**: $R_1 = R_2 = H$
**21**: $R_1$ = OAc; $R_2$ = H
**24**: $R_1$ = H; $R_2$ = OAc



**19**: $R_1 = R_2 = X = Z = H$; Y = F
**20**: $R_1 = R_2 = X = Y = H$; Z = F
**22**: $R_1$ = OAc; $R_2 = X = Z = H$; Y = F
**23**: $R_1$ = OAc; $R_2 = X = Y = H$; Z = F
**25**: $R_1 = Y = Z = H$; $R_2$ = OAc; X = F
**26**: $R_1 = X = Z = H$; $R_2$ = OAc; Y = F
**27**: $R_1 = X = Y = H$; $R_2$ = OAc; Z = F

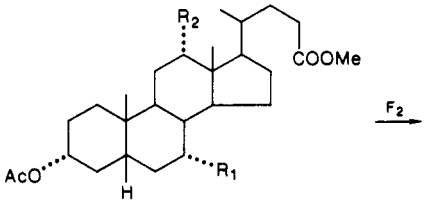
The presence of another electron-withdrawing group as in 3α,6α-dihydroxy-5β-cholanic acid 3,6-diacetate, methyl ester (**21**), increases the deactivation of the 14 position and hence makes the 17C–H bond a relatively better candidate for substitution. Thus the two main compounds isolated were 3α,6α-dihydroxy-14α-fluoro-5β-cholanic acid 3,6-diacetate, methyl ester (**22**) in 25% yield and the 17α-fluoro derivative **23** in 15% yield. When the oxygenated functions are more evenly distributed on the steroidal skeleton, as in 3α,12α-dihydroxy-5β-cholanic acid 3,12-diacetate, methyl ester (**24**), all tertiary C–H bonds are more or less

(16) The optical rotation of the starting 5β-steroid is $[\alpha]_D$ +102° and that of the 5α-fluoro derivative **14** is $[\alpha]_D$ +57°.

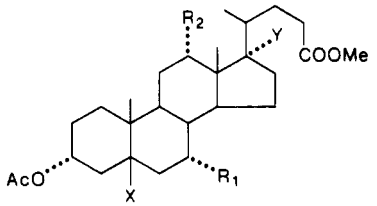
(17) *Unpublished* results as yet. See however also ref 8b.

equally deactivated as also indicated by CNDO/2 calculations. The reaction is slowed down and eventually all of the three 5β-fluoro, 14α-fluoro, and 17α-fluoro derivatives, **25**, **26**, and **27**, respectively, were obtained, but in only 10% yield each.

Replacing the acetate group of **24** with the much stronger electron-withdrawing carbonyl moiety, as in 3α-hydroxy-12-oxo-5β-cholanic acid 3-acetate, methyl ester (**28**) completely deactivates both the 14 and the 17 positions and makes the whole process of electrophilic substitution more difficult. It is thus quite understandable that only the 5β-fluoro-3α-hydroxy-12-oxocholanic acid 3-acetate, methyl ester (**29**) was obtained and then again only in 20% yield. When yet another acetate is present as in the 3α,7α,12α-trihydroxy-5β-cholanic acid 3,7,12-triacetate, methyl ester (**30**), the fluorination is slowed down by at least a factor of 4 compared to the previous reactions.[18] Still, since the 17 position is the only available tertiary carbon which is not deactivated by two acetate groups, as are the 5 and the 14 sites, we were eventually able to isolate, although in low 25% yield, 17α-fluoro-3α,7α,12α-trihydroxy-5β-cholanic acid 3,7,12-triacetate, methyl ester (**31**).




**28**: $R_1 = H$; $R_2 = O=$
**30**: $R_1 = R_2 = OAc$
**32**: $R_1 = OAc$; $R_2 = O=$

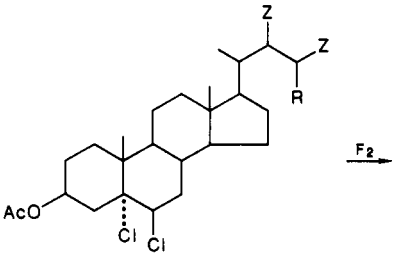



**29**: $R_1 = Y = H$; $R_2 = O=$; $X = F$
**31**: $R_1 = R_2 = OAc$; $X = H$; $Y = F$

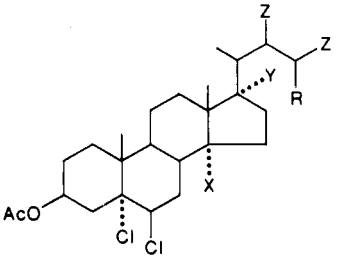
It is not surprising, then, that replacing one of the acetate groups in the already strongly deactivated **30** with a carbonyl, as in 3α,7α-dihydroxy-12-oxo-5β-cholanic acid 3,7-diacetate, methyl ester (**32**), causes a complete deactivation. Even a prolonged treatment with a higher than usual $F_2$ concentration leaves this compound untouched.

Similar to oxygen, in its hydroxyl or carbonyl form, which has a strong deactivating efect, other electronegative elements such as chlorine also exhibit such an influence on the nearby tertiary carbon–hydrogen bonds. The effect has to be taken into consideration mainly when the steroidal molecule has a double bond which has to be protected. Since bromination or epoxidation cannot be efficiently used for this purpose,[19] it is very convenient to add chlorine to the olefinic bond, react the compound with $F_2$, and then remove the two vicinal chlorine atoms with Zn. Thus when 5α,6β-dichlorocholestan-3β-ol acetate (**33**) is fluorinated, the electronegative chlorine atoms deactivate the nearby 9 and 14 positions so only the most remote tertiary hydrogen still within the steroidal skeleton is substituted, to produce 5α,6β-dichloro-17α-fluorocholestan-3β-ol acetate (**34**) in 50% yield along with an additional 20% yield of the 17α,25-difluoro derivative (**35**).

5α,6β-Dichloro-3β-hydroxycholanic acid 3-acetate, methyl ester (**36**) has a shorter side chain. Consequently the 14 position starts to react as well, although quite reluctantly. This explains the 25% yield of 5α,6β-dichloro-17α-fluoro-3β-hydroxycholanic acid acetate, methyl ester (**37**) accompanied by the 14α-fluoro isomer (**38**) obtained in 10% yield. The 9, 17, 24, and 25 tertiary positions are all entirely deactivated in 5α,6β,22,23-tetrachloro-24-ethyl-3β-hydroxycholestane 3-acetate (protected stigmasterol acetate **39**). Thus only a substitution reaction on the 14 position is allowed and **40** is formed in 50% yield.




**33**: $R = CH_2CHMe_2$; $Z = H$
**36**: $R = COOMe$; $Z = H$
**39**: $R = CH(Et)CHMe_2$; $Z = Cl$




**34**: $R = CH_2CHMe_2$; $X = Z = H$; $Y = F$
**35**: $R = CH_2CFMe_2$; $X = Z = H$; $Y = F$
**37**: $R = COOMe$; $X = Z = H$; $Y = F$
**38**: $R = COOMe$; $Y = Z = H$; $X = F$
**40**: $R = CH(Et)CHMe_2$; $Y = H$; $Z = Cl$; $X = F$

The fluorination reaction is exothermic, since two very strong bonds, C–F and H–F, are eventually formed. Because of this we have carried out these reactions at low temperature with efficient vibromixing, in order to dissipate the generated local heat which can encourage fluorine radical formation. The question remains if keeping the temperature low is the only way to encourage ionic reactions and depress radical ones. It seems that the answer is negative. In a few cases we have performed the fluorination reaction at much higher temperatures using a mixture of $CFCl_3/CH_3COOH$, with or without $CHCl_3$ as an additional cosolvent. The added acetic acid increases the polarity of the solvent, thus encouraging the ionic pathway. It is possible that solvatation also takes place, so there are more ways to dissipate energy through vibrational and rotational excitation of the many bonds of the acetic acid. This energy would otherwise be used for homolytic cleavage of the F–F bond. Thus, when similar concentrations of $F_2$ in nitrogen were passed at similar rates through solutions of **4**, **7**, **12**, **33**, and **39** in AcOH containing solvent at 0 °C, we obtained exactly the same product distribution, but with yields reduced by 30% to 50%. Another surprising similarity is connected with the rates of the reactions. In a few cases the reactions performed at 0 °C were a bit faster than those carried out at

(18) By the term "slowing down the reaction" we mean that one has to increase the $F_2$ amount passed through the reaction mixture in order to consume a certain amount of the starting material. This is practically the only indicative criteria, because nitrogen-diluted fluorine is almost insoluble in the solvents we are working with and, hence, the reaction rate is fully dependent on the concentration of fluorine in the nitrogen and on its flow rate.

(19) (a) Gal, C.; Ben-Shushan, G.; Rozen, S. *Tetrahedron Lett.* **1980**, *21*, 5067. (b) Rozen, S.; Brand, M. *J. Org. Chem.* **1981**, *46*, 733.

−75 °C, in others the rates were about the same, and in still others the reactions were even somewhat slower. This behavior, however, is in full accordance with the notion that the reaction takes place mainly between the substrate and the dissolved fluorine, as little of this as there may be, and not the fluorine in the gas phase which bubbles through the solution and sometimes escapes unreacted. The solubility and thus the concentration of the fluorine in the reaction solvent is of course higher at low temperatures, offseting the usual trend of a slower reaction at a lower temperature.

These experiments indicate that it is possible even at relatively high temperatures to control the homolytical cleavage of the elemental fluorine, at least to a certain degree. These results also raise hope that in the future more suitable conditions will be found for the selective monofluorination and thus make these reactions more appealing for industrial large scale use.

In conclusion, when the conditions are favorable, the stereo- and regiospecific reaction described here proceeds in yields up to 60%, yields which can be considered as excellent taking into consideration the unique nature of this substitution of remote and deactivated hydrogens. We have found in this work also some limiting factors which play an important role in electrophilic fluorination. Fortunately enough, these effects are quite limited, so that the majority of steroidal molecules can still be efficiently activated at sites which practically no other reagent can attack.

## Experimental Section

$^1$H NMR spectra were recorded with Bruker WH-90 and Bruker WH-360 spectrometers at 90- and 360-MHz, respectively, with $CDCl_3$ as a solvent and $Me_4Si$ as an internal standard. The $^{19}$F spectra were measured at 84.67 and 338.8 MHz, respectively, and are reported in parts per million upfield from $CFCl_3$, which also served as internal standard. The proton broad band decoupled $^{13}$C NMR spectra were recorded on Bruker WH-90 and WH-300 spectrometers at 22.63 and 75.46 MHz, respectively. $CDCl_3$ served as a solvent and $Me_4Si$ as internal standard. Optical rotations were determined in $CHCl_3$ (c 1.0) with a Perkin-Elmer 141 polarimeter. Mass spectra were measured with a Du Pont 21-491B spectrometer. IR spectra were recorded as neat films, in $CHCl_3$ solution or in KBr pellets, on a Perkin-Elmer 177 spectrophotometer.

**General Fluorination Procedure.** A description of the set-up and the procedure for working with elemental fluorine has previously been described.[20] Although mentioned in previous works, it is worth stressing again that $F_2$ should be treated with care since it is a strong oxidizer. The work should be conducted in an efficient hood or in a well-ventilated area. If elementary precautions are taken, work with fluorine is relatively simple. In the past we have had no bad experiences working with this element. The reactions were usually carried out on scales of 1–2 mmol. Unless otherwise stated, the reactions were monitored by TLC and NMR and usually stopped when the conversion reached about 90%. The fluorine concentration was 4–6% in $N_2$. This mixture was passed as a slow stream through a vigorously stirred solution of the substrate containing NaF as a hydrogen fluoride scavenger. The term "worked up as usual" means stopping the reaction by pouring it into 500 mL of water, washing the organic layer with $NaHCO_3$ solution followed by water until neutral, drying the organic layer over $MgSO_4$, and finally evaporating the solvent. The crude product was usually purified by vacuum flash chromatrography using Silica gel 60-H (Merck) and if needed also by HPLC (Waters) on Merck's LiChrosorb Si-100. If the crude reaction mixture is not immediately purified, it is advisable to add a drop or two of pyridine or hexamethyldisilazane to capture the small amount of HF which may be formed with time. Without these bases the HF will autocatalyze additional elimination of HF and the compounds will eventually decompose.

The $^{13}$C NMR spectra of the fluorinated compounds and their analyses have already been published by us[14] and will not be reported again here.

**Fluorination of 5α-Androstane (1).** A 0.42-g sample of **1** was treated with 2% $F_2$ in $N_2$ and after the completion of the reaction, it was worked up as usual and flashed chromatographed with petroleum ether, followed by final purification by HPLC using cyclohexane as eluent. The less polar compound was the 9α-fluoro isomer **2**: yield 20%; mp 72 °C (MeOH); $[\alpha]_D$ −6.7°; $^1$H NMR δ 0.887 (Me-19, 3 H, s), 0.698 (Me-18, 3 H, s); $^{19}$F NMR −180.3 (m, $W_{h/2}$ = 80 Hz); MS, *m/e* 260 ($M^+$), 240 [$(M - HF)^+$], 225 [$(M - HF - Me)^+$]. The second fraction proved to be the 14α-fluoro derivative **3**: yield 15%; mp 53 °C (MeOH); $[\alpha]_D$ −1.75°; $^1$H NMR δ 0.946 (Me-19, 3 H, s), 0.698 (Me-18, 3 H, s); $^{19}$F NMR −166.3 (m, $W_{h/2}$ = 75 Hz); MS, *m/e* 260 ($M^+$), 240 [$(M - HF)^+$], 225 [$(M - HF - Me)^+$].

**Fluorination of 5α-Androstan-3α-ol Acetate (4).** A 0.45-g sample of **4** was fluorinated with 5% $F_2$ in $N_2$. After the usual workup, the crude was chromatographed by HPLC using 10% EtOAc in cyclohexane as eluent. The first fraction proved to be the 14α-fluoro derivative **6**: yield 30%; mp 141 °C (MeOH); $^1$H NMR δ 0.821 (Me-18, 3 H, s), 0.801 (Me-19, 3 H, s), 2.032 (Ac, 3 H, s), 5.02 (H-C3, 1 H, m); $^{19}$F NMR −166 (m). The more polar fraction was identified as the 9α-fluoro isomer **5**: 35% yield; mp 120 °C (MeOH); $^1$H NMR δ 0.661 (Me-18, 3 H, s), 0.929 (Me-19, 3 H, s), 2.034 (Ac, 3 H, s), 5.020 (H-C3, 1 H, m); $^{19}$F NMR −180 (m). Anal. Calcd for $C_{21}H_{33}FO_2$: C, 75.00; H, 9.82. Found: C, 75.17; H, 9.85.

**Fluorination of 5α-Androstan-17β-ol Acetate (7).** A 0.55-g sample of **7** was fluorinated with 5% $F_2$ and then worked up as usual. Two fluoro derivatives, **8** and **9**, were obtained in 30% yield each, but we were not able to fully separate them from each other although the mixture was free from any other contaminations: $^{19}$F NMR −180.0 (F-C9, m), −165.5 (F-C5, m). Anal. Calcd for $C_{21}H_{33}FO_2$: C, 75.00; H, 9.82. Found: C, 74.72; H, 9.84.

**Fluorination of 20-oxo-5α-pregnane-3α,17α-diol 3-acetate (10)** was performed on 0.39 g as described above, and after the usual workup and HPLC using 25% EtOAC in cyclohexane as eluent the 9α-fluoro derivative **11** was obtained in 60% yield: mp 190 °C (MeOH); $^1$H NMR δ 0.697 (Me-18, 3 H, s), 0.909 (Me-19, 3 H, s), 2.048 (Ac, 3 H, s), 2.26 (Ac, 3 H, s), 4.98 (H-C3, 1 H, m); $^{19}$F NMR −180 (m).

**Fluorination of 17-oxo-5α-androstan-3α-ol acetate (12)** was executed with 5% $F_2$ on 0.46 g of steroid. the crude reaction mixture was chromatographed by HPLC using 25% EtOAc in cyclohexane. The less polar fraction proved to be the 9α-fluoro derivative **13**: 40% yield; mp 128 °C ($Et_2O$); $[\alpha]_D$ +69°; $^1$H NMR δ 0.869 (Me-18, 3 H, s), 0.929 (Me-19, 3 H, s), 2.052 (Ac, 3 H, s), 4.94 (H-C3, 1 H, m); $^{19}$F NMR −180.0 (m). Anal. Calcd for $C_{21}H_{31}FO_3$: C, 72.00; H, 8.86. Found: C, 71.73; H, 8.78. The more polar compound isolated was the 5α-fluoro isomer **14**: 30% yield; mp 174 °C ($Et_2O$); $[\alpha]_D$ +57°; $^1$H NMR δ 0.876 (Me-18, 3 H, s), 0.978 (Me-19, 3 H, s), 2.042 (Ac, 3 H, s), 5.01 (H-C3, 1 H, m); $^{19}$F NMR −161.0 (m). Anal. Calcd for $C_{21}H_{31}FO_3$: C, 72.00; H, 8.86. Found: C, 71.75; H, 8.83.

**Fluorination of 17-oxo-5β-androstan-3α-ol acetate (15)** with 5% $F_2$ was carried out as described above. The crude reaction mixture was chromatographed by HPLC using 25% EtOAc in cyclohexane. The first compound eluted was the 14α-fluoro derivative **17**: 25% yield; mp 96 °C (MeOH); $[\alpha]_D$ +94°; $^1$H NMR δ 0.959 (Me-18, 3 H, s), 0.994 (Me-19, 3 H, s), 2.025 (Ac, 3 H, s), 4.72 (H-C3, 1 H, m); $^{19}$F NMR −164.0 (m). Anal. Calcd for $C_{21}H_{31}FO_3$: C, 72.00; H, 8.86. Found: C, 71.82; H, 8.67. The more polar 5β-fluoro isomer **16** was obtained in 35% yield: mp 120 °C (MeOH); $[\alpha]_D$ +90°; $^1$H NMR δ 0.864 (Me-18, 3 H, s), 0.980 (Me-19, 3 H, d, *J* = 0.9 Hz), 2.018 (Ac, 3 H, s), 5.08 (H-C3, 1 H, m); $^{19}$F NMR −151.0 (m). Anal. Calcd for $C_{21}H_{31}FO_3$: C, 72.00; H, 8.86. Found: C, 71.84; H, 8.61.

**Fluorination of 3α-hydroxy-5β-cholanic acid 3-acetate, methyl ester (18)** was performed with 5% $F_2$ as described previously. Two compounds were isolated and purified after HPLC using 10% EtOAc in cyclohexane. The less polar, minor component, proved to be the 17α-fluoro derivative **20**, obtained in 10% yield: mp 158 °C (MeOH); $[\alpha]_D$ +34.2°; $^1$H NMR δ 0.721

(20) See for example: Rozen, S.; Lerman, O. *J. Org. Chem.* **1980**, *45*, 672. Lerman, O.; Rozen, S. *Ibid.* **1980**, *45*, 4122. Reference 19b.

(Me-18, 3 H, s), 0.929 (Me-19, 3 H, s), 2.025 (Ac, 3 H, s), 3.671 (MeOOC, 3 H, s) 4.73 (H-C3, 1 H, m); $^{19}$F NMR −171.0 (q, $J$ = 31 Hz). Anal. Calcd for $C_{27}H_{43}FO_4$: C, 72.16; H, 9.57. Found: C, 72.10; H, 9.42. The more polar fraction was identified as the 14$\alpha$-fluoro isomer **19**, obtained in 35% yield: mp 133 °C (MeOH); $[\alpha]_D$ +39.3°; $^1$H NMR $\delta$ 0.779 (Me-18, 3 H, s), 0.929 (Me-19, 3 H, s), 2.021 (Ac, 3 H, s), 3.671 (MeOOC, 3 H, s), 4.73 (H-C3, 1 H, m); $^{19}$F NMR −164.0 (m). Anal. Calcd for $C_{27}H_{43}FO_4$: C, 72.16; H, 9.57. Found: C, 71.91; H, 9.37.

**Fluorination of 3$\alpha$,6$\alpha$-dihydroxy-5$\beta$-cholanic acid 3,6-diacetate, methyl ester (21)** was carried out as described above. Two compounds were isolated by HPLC using 20% EtOAc in cyclohexane. The less polar compound was the 17$\alpha$-fluoro derivative **23** obtained in 15% yield: mp 124 °C (MeOH); $[\alpha]_D$ +14.6°; $^1$H NMR $\delta$ 0.724 (Me-18, 3 H, s), 0.978 (Me-19, 3 H, s), 2.018 (Ac, 3 H, s), 2.014 (Ac, 3 H, s), 3.671 (MeOOC, 3 H, s), 4.73 (H-C3, 1 H, m), 5.10 (H-C6, 1 H, m); $^{19}$F NMR −171.0 (q, $J$ = 31 Hz). Anal. Calcd for $C_{29}H_{45}FO_6$: C, 68.50; H, 8.86. Found: C, 67.84; H, 8.78. The more polar fraction was the 14$\alpha$-fluoro derivative **22**, obtained in 25% yield: mp 108 °C (MeOH); $[\alpha]_D$ +22.3°; $^1$H NMR $\delta$ 0.779 (Me-18, 3 H, s), 0.975 (Me-19, 3 H, s), 2.021 (Ac, 3 H, s), 2.041 (Ac, 3 H, s), 3.671 (MeOOC, 3 H, s), 4.73 (H-C3, 1 H, m), 5.10 (H-C6, 1 H, m); $^{19}$F NMR −164.0 (m). Anal. Calcd for $C_{29}H_{45}FO_6$: C, 68.50; H, 8.86. Found: C, 68.33; H, 8.70.

**Fluorination of 3$\alpha$,12$\alpha$-dihydroxy-5$\beta$-cholanic acid 3,12-diacetate, methyl ester (24)** was carried out with 7% $F_2$, and after the usual workup, the crude was chromatographed by HPLC using 25% EtOAc in cyclohexane. The 17$\alpha$-fluoro derivative **27** could be obtained in a pure form in 10% yield: mp 140 °C (MeOH); $[\alpha]_D$ +101.3°; $^1$H NMR $\delta$ 0.763 (Me-18, 3 H, s), 0.910 (Me-19, 3 H, s), 2.031 (Ac, 3 H, s), 2.083 (Ac, 3 H, s), 3.668 (MeOOC, 3 H, s), 4.70 (H-C3, 1 H, m), 5.40 (H-C12, 1 H, m); $^{19}$F NMR −168.0 (q, $J$ = 31 Hz). The second fraction proved to be a mixture of **25** and **26** in 10% yield each, which we were unable to separate: $^{19}$F NMR −151 (F-C5, m), 163.5 (F-C14, m).

**Fluorination of 3$\alpha$-hydroxy-12-oxo-5$\beta$-cholanic acid acetate, methyl ester (28)** using 7% $F_2$ was carried out as described above. After the usual workup and HPLC chromatography using 30% EtOAc in cyclohexane, only the 5$\beta$-fluoro derivative **29** was obtained in 20% yield: mp 150 °C (MeOH); $[\alpha]_D$ +88°; $^1$H NMR $\delta$ 1.034 (Me-18, Me-19, 6 H, s), 2.015 (Ac, 3 H, s), 3.668 (MeOOC, 3 H, s) 4.95 (H-C3, 1 H, m); $^{19}$F NMR −151.0 (m).

**Fluorination of 3$\alpha$,7$\alpha$,12$\alpha$-trihydroxy-5$\beta$-cholanic acid 3,7,12-triacetate, methyl ester (30)** was performed with 7% $F_2$ and took much longer then usual. The crude reaction mixture was worked up as usual and then chromatographed by HPLC using 30% EtOAc in cyclohexane. The 17$\alpha$-fluoro derivative **31** was obtained in 25%: mp 103 °C (MeOH); $^1$H NMR $\delta$ 0.769 (Me-18, 3 H, s), 0.929 (Me-19, 3 H, s), 2.041 (Ac, 3 H, s), 2.08 (Ac, 3 H, s), 2.132 (Ac, 3 H, s), 3.658 (MeOOC, 3 H, s), 4.60 (H-$C_3$, 1 H, m), 4.99 (H-C7, 1 H, m), 5.40 (H-$C_{12}$, 1 H, m); $^{19}$F NMR −168.0 (q, $J$ = 31 Hz).

**Fluorination of 5$\alpha$,6$\beta$-dichlorocholestan-3$\beta$-ol acetate (33)** was carried out as described above. Two compounds were separated by HPLC and proved to be the 17$\alpha$-fluoro derivative **34** obtained in 50% yield and the 17$\alpha$,25-difluoro derivative **35**, in 20% yield. **34** and **35** were hydrolyzed and dechlorinated with Zn, producing the corresponding fluoro cholesterols **34a** and **35a** which have already been described.[4]

**Fluorination of 5$\alpha$,6$\beta$-dichloro-3$\beta$-hydroxycholanic acid 3-acetate, methyl ester (36)** was carried on 0.5 g using 5% $F_2$. After the usual workup and HPLC chromatography two compound were isolated. The less polar one was the 17$\alpha$-fluoro derivative **37** obtained in 25% yield: mp 165 °C (MeOH); $[\alpha]_D$ −45.3°; $^1$H NMR $\delta$ 0.776 (Me-18, 3 H, s), 1.379 (Me-19, 3 H, s), 2.041 (Ac, 3 H, s), 3.671 (MeOOC, 3 H, s), 4.36 (H-C6, 1 H, m), 5.35 (H-C3, 1 H, m); $^{19}$F NMR −171.0 (q, $J$ = 31 Hz). Anal. Calcd for $C_{27}H_{41}Cl_2FO_4$: C, 62.55; H, 7.91. Found: C, 62.38; H, 8.07. The second compound isolated in 10% yield was the 14$\alpha$-fluoro isomer: mp 162 °C (MeOH); $[\alpha]_D$ −32.1°; $^1$H NMR $\delta$ 0.835 (Me-18, 3 H, s), 1.376 (Me-19, 3 H, s), 2.041 (Ac, 3 H, s), 3.668 (MeOOC, 3 H, s), 4.41 (H-C6, 1 H, m), 5.29 (H-C3, 1 H, m); $^{19}$F NMR −164.0 (m). Anal. Calcd for $C_{27}H_{41}Cl_2FO_4$: C, 62.55; H, 7.91. Found: C, 62.42; H, 7.82.

**Fluorination of 5$\alpha$,6$\beta$,22,23-tetrachloro-24-ethyl-3$\beta$-hydroxycholestane 3-acetate (39)** was carried out as usual. The reaction mixture was then worked up and chromatographed by HPLC using 5% EtOAc in cyclohexane. A single monofluoro derivative was obtained in 50% and was identified as the 14$\alpha$-fluoro derivative **40**: $^1$H NMR $\delta$ 1.379 (Me-18, 3 H, s), 1.428 (Me-19, 3 H, s), 2.041 (Ac, 3 H, s), 4.20 (H-C22, H-C23, 2 H, m), 4.41 (H-C6, 1 H, m), 5.35 (H-C3, 1 H, m); $^{19}$F NMR −163.5 (m). Anal. Calcd for $C_{32}H_{51}Cl_4FO_2$: C, 60.59; H, 7.98. Found: C, 61.02; H, 8.21.

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