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# TAMING ELEMENTAL FLUORINE:

# INDIRECT USE OF FLUORINE FOR THE SYNTHESIS OF α-FLUOROKETONES[1]

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## SUMMARY

Fluorine and sodium trifluoroacetate react at -75° to produce a variety of fluoroxy-compounds. Although it is possible to direct the reaction towards the formation of $CF_3COOF$ or $CF_3CF_2OF$, mixtures may be used when only the electrophilic fluorine has to be attached to the molecule of interest. Such is the case of the reaction of enol-acetates with the mixture of the fluoroxy reagents. A wide variety of compounds, including steroids and containing various functional groups, were tested. In most cases the desired α-fluoroketones were obtained in good to very good yields. The new fluorine containing compounds are the compounds numbered 2, 9, 11, 13, 15, 16 and 20.

## INTRODUCTION

Although there are numerous works dealing with the synthesis of fluoro-organic substances, the lack of use of the primary source of the fluorine atoms - namely $F_2$- is striking. The main reason of course is the violent nature of this element. We wish to describe here a selective fluorination using, indirectly, elemental fluorine and resulting in α-fluoroketones.

The synthesis of α-fluoroketones has interested chemists for over 20 years. As a matter of fact, the only practical method for achieving this goal was the action of perchloryl fluoride -$FClO_3$ on various enamines. However, the serious limitations of this reagent are well known. It can be used only with very electron rich olefins; enol-acetates for instance hardly react. $FClO_3$ also tends to form chlorinated or oxygenated compounds. What is probably the most important consideration is its by-product - chloric acid or its salts, which have been responsible for several serious explosions.

About 10 years ago Barton, Hesse and Pechet introduced a new and more efficient reagent, fluoroxytrifluoromethane $CF_3OF$. One of the immediate successes of this compound was its ability to react smoothly with certain

olefins, among them a number of enol-acetates[2]. It has been proved that the reaction involves an electrophilic attack of the oxygen bound fluorine on the electron rich carbon of the double bond, thus formally establishing the existence of a fluorine atom with a partially positive charge. However, it should be borne in mind that $CF_3OF$ is a very expensive reagent and of limited availability.

It has been shown that fluorine itself can be used under appropriate conditions as a source of electrophilic fluorine and accomplish surprisingly selective fluorinations[3]. It was natural to try to react fluorine with electron rich olefins such as enol-acetates, but no matter how mild the conditions used the reaction resulted in a very complicated mixture and no α-fluoroketones could be detected.

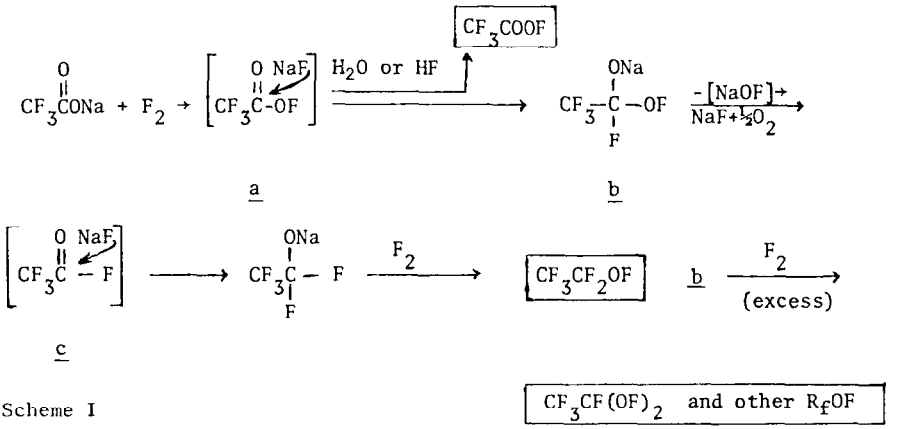
When fluorine is passed through $CFCl_3$ (Freon) a weak oxidizing solution is formed and very quickly a limit is reached above which the oxidizing power does not increase on further passage of fluorine through the solution. It is easy to show that the oxidative power is due to the fluorine itself, soluble in Freon. Adding stilbene, for example, to this solution gives the known [4] 1,2-difluoro-diphenylethane.

$$F_2(\text{solution in Freon}) + PhCH{=}CHPh \rightarrow \underset{F\ \ F}{PhCH\text{-}CHPh}$$

This observation however, is of very limited synthetic use since even at -75°, the upper limit of the solubility of fluorine in Freon is around $4\times10^{-3}$%. We have tried a series of various solvents and found that they are even less suitable for dissolving fluorine, either because the solubility is even lower or because the solvents are not stable to this most reactive element.

In contrast to the above, when fluorine was passed through a suspension of $CF_3COONa$ in Freon, an oxidizing solution was formed and its oxidative power grew constantly with the amount of fluorine passed. During our work, concentrations of up to 20 mmolar with respect to oxidizing agents were reached although this is by no means the upper limit. We found that various fluoroxy compounds are responsible for the oxidative power of this solution (scheme I).

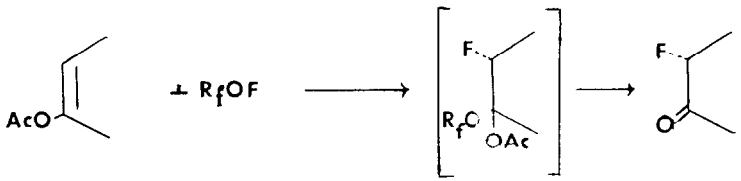
Fluorine reacts with sodium trifluoroacetate and forms a cage pair of molecules a. If water or HF is present, the sodium fluoride in the cage a become solvated and the nucleophilic attack of the $F^-$ is no longer favored. We proved that in such a case the trifluoroacetylhypofluorite $CF_3COOF$ is the main oxidant[5].




Scheme I

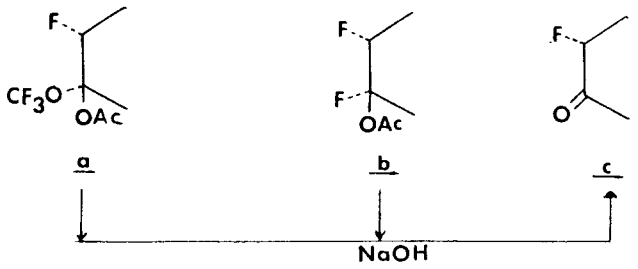
If however, water or any other solvating agents are excluded from the reaction mixture, the fluoride anion in cage a, which is an excellent nucleophile, attacks the positive centre of the nearby carbonyl, thus forming the intermediate b. This species may lose the elements of the extremely unstable salt [NaOF] which then immediately looses oxygen. Again the sodium fluoride thus formed is in a cage pair of molecules, the fluoride anion acts as a nucleophile and eventually the fluoroxypentafluoroethane-$CF_3CF_2OF$ is formed[6]. If an excess of fluorine is used we usually increase the side reactions leading to bis-fluoroxy compounds and other various oxidants which derive their oxidative power from their fluoroxy group-$R_fOF$. It may be worth noting that $F_2$, when passed through a mixture of trifluoroacetic acid and NaF in Freon or through trifluoroacetylfluoride -$CF_3COF$ and NaF, in the same solvent, does not react at all. This fact emphasis the importance of the cages a and c in scheme I.

As it may be seen, all the compounds formed in the reaction of $F_2$ with $CF_3COONa$ have in common the relatively weak oxygen-fluorine bond. The oxygen bound fluorine in all these compounds is attached to excellent leaving groups, such as $CF_3COO^-$ and $R_fO^-$, a feature which makes this fluorine susceptible to nucleophilic attack or in other words turns it into a very good electrophile. Since in the reaction of enol-acetates with $R_fOF$, the ultimate desired product - the α-fluorocarbonyl, does not contain the perfluoroxy group, we thought we would be able to use the whole mixture of the oxidizing products obtained in situ, without any isolation and purification, as a single homogenous reagent. Indeed, when an enol-acetate is added at -75° to such a solution, an instantaneous reaction takes place and usually high yields of the corresponding α-fluoroketones are obtained.




Scheme II

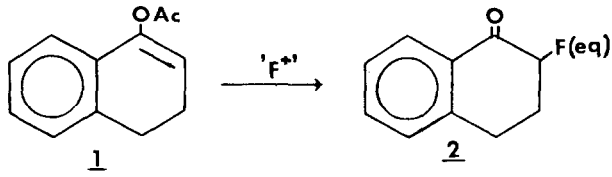
Scheme II was first proposed by Barton and Hesse for the reaction of $CF_3OF$ They, and later we, have shown that the addition reaction of $R_fOF$ to any double bond is mainly in cis mode [5,6,7] So the stereospecifity of the reaction is very good. There is however one important difference between $CF_3OF$ and the mixture of fluoroxy reagents we use. Usually, with $CF_3OF$, three products are formed and may be isolated: the adduct itself a, a difluoro adduct b and the fluoroketone c.



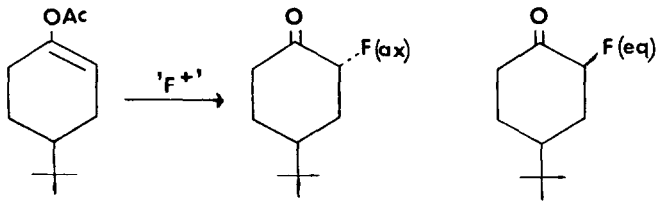

In our case, no compounds of type a or b were found. All $R_fO^-$ groups we are dealing with are better leaving groups than $CF_3O^-$, thus compounds of type a would be much less stable and would be converted to c spontaneously. The difluoro adduct is also missing since all $R_fOF$ compounds are not as good sources for $F^-$ as $CF_3O^-$ ($CF_3O^- \rightarrow CF_2O+F^-$) [2,6].

We shall refer to our oxidizing mixture of reagents as "$F^+$", although of course one should not imagine that we are dealing with the free fluoronium cation, whose energy is much higher than the usual range of energies involved in organic chemistry. Still this notation can be justified. After all we are working with compounds which possess electrophilic fluorine atoms and resemble in several, if not all aspects, other positive species, such as halonium ions. When employing our fluorinating mixture on the enol-acetate of α-tetralone(1) we obtained 2-fluoro-α-tetralone(2) as a single fluorinated product in high yield. The NMR of the hydrogen geminal to fluorine appears at $\delta$=5.1 ppm as a double double doublet with $J_1$=48,

$J_2$=12 and $J_3$=6 Hz. These coupling constants indicate an axial position for the hydrogen or an equatorial one for the fluorine which is also the more stable thermodynamic conformer.



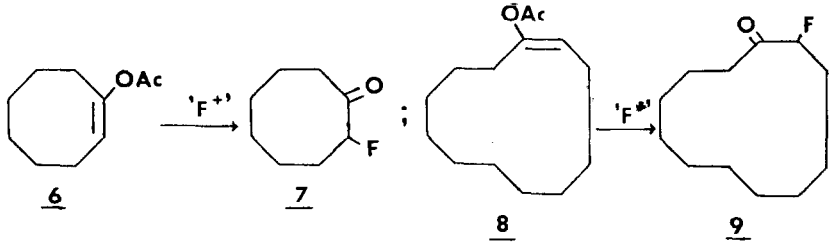

1 2




3 4 5

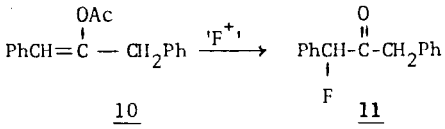
In contrast to 2 two fluorinated compounds were obtained when the enol-acetate of 4-t-butylcyclohexanone(3) was reacted with the fluorinating mixture. The interesting point is that the trans and cis 2-fluoro-4-t-butylcyclohexanone 4 and 5 were obtained in the ratio of 4:3, while other investigators using mainly $FClO_3$ obtained a ratio of 4:5 = 1:7 a ratio which favours the more thermodynamically stable isomer 5[8]. Our results are explained by the cis addition of the $R_fOF$ reagents which takes place from the less hindered α-side of the enol-acetate 3.

Fluorine can be introduced into medium and large rings as efficiently as into the 6 membered ring. Thus 2-fluoro-cyclooctanone(7) and cyclododecanone(9) can easily be synthesized through their corresponding enol-acetates 6 and 8.




6 7 8 9

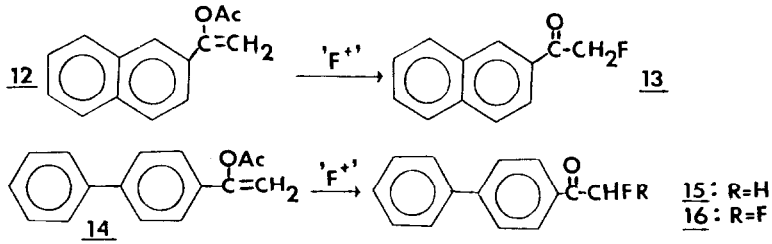
The described reaction is applicable also to straight chain ketones. Dibenzyl ketone was converted to the corresponding enol-acetate 10 and reacted instantaneously with the mixture of the fluoroxy compounds. The 1-fluoro-1,3-diphenyl acetone(11) was obtained in about 50% yield.



10 11

It is worth noting that cyclic α-fluoroketones are stable towards dilute bases, thus permitting the exclusion of potential traces of HF which may cause autocatalytic decomposition. On the other hand, the straight chain α-fluoroketones seem to be unstable to basic media and decompose rapidly. Unless purified without delay they will decompose on storage.

Next, two methyl aryl ketones were investigated. Methyl-2-naphthyl ketone was converted to its enol acetate 12. The main product of the reaction was identified as fluoromethyl-2-naphthyl ketone (13).

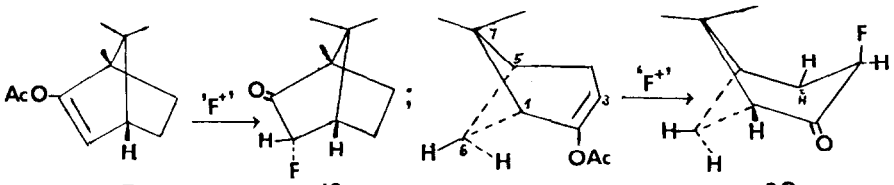


12 13

14 15: R=H 16: R=F

When the enol-acetate of 4-acetyl-biphenyl (14) was fluorinated we obtained two products. The major one was the expected monofluoro ketone 15 (62% yield). The minor product (29% yield) proved to be the gem-difluoromethyl-biphenyl ketone 16. Apart from the correct microanalysis, the NMR ($H^1$ and $F^{19}$) strongly supports the proposed structure of 16. The proton on the difluoromethyl group resonates as a triplet at 6.28 ppm (J=52 Hz) and the two fluorine atoms resonate as a doublet (J=52 Hz) at $\phi^*$ = 122.3 ppm which is a quite typical chemical shift for difluoromethyl ketones. The mass sp. also provides a proof for the proposed structure of 16. Apart from the strong $M^+$ peak at 232, the base peak at m/e = 181 is due to the most favorable cleavage $(M-CHF_2)^+$. Another strong peak is at m/e = 152 for $(C_6H_5-C_6H_4)^+$ proving that the extra fluorine is not attached to either of the aromatic rings[9].We also examined bicyclo compounds and proved that also this type of molecule can readily be fluorinated. We obtained the α-fluorocamphor 18 in a one step reaction from the corresponding enol-acetate 17 in 65% yield. The α-configuration of the fluorine atom is evident from the NMR data. The proton geminal to the fluorine resonates at

4.9 ppm as a double doublet ($J_1$=54; $J_2$=6 Hz) indicating the β-position ($J_2$ would be much smaller for hydrogen at α since the dihedral angle then will be around 90°). Compared to camphor itself one finds almost equal shifts to lower field of all the three methyls in 18 by only 3-4 Hz, indicating that these shifts are caused only by a through-bond (and not through-space) influence - a phenomena that also supports the α-configuration of the fluorine. The very high field in which the fluorine atom itself resonates $\phi^*$ = 202.7 ppm (d, J=54) also indicates an axial fluorine which forms a dihedral angle of 90° with its vicinal proton. The α-configuration is also understandable from the course of the reaction since the fluoroxy reagents have to attack from the less hindered α-side.



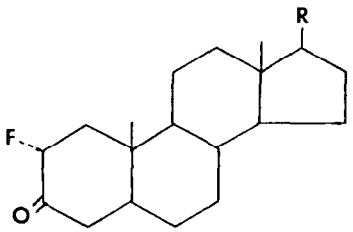

17 18 19 20

Nopinone enol-acetate (19) was synthesized from nopinone and isopropenylacetate. Unlike camphor the more substantial hindrance for approach to the double bond comes from the α-hydrogen at 6 and not from the dimethyl bridge at 7. Consequently the 3β-fluoropopinone (20) was obtained in 80% yield. Again, the configuration (β) can easily be detected from the NMR spectrum. A double doublet for the hydrogen geminal to the fluorine, appears at 4.75 ppm ($J_1$=49; $J_2$=9 Hz). Only in the conformation indicated in 20 can this hydrogen be coupled only by the 4α-H since the dihedral angle between 4β-H and 3H is very close to 90°. Another interesting point arises when observing the chemical shift of the two bridge methyls. While the methyl which is more distant from the carbonyl was not shifted at all, the nearer bridge methyl which in 20 is also close in space to the fluorine atom, is shifted by almost 0.1 ppm to lower field. The FMR spectrum also confirms the β-configuration of the halogen by showing a high coupling constant (24 Hz) between the fluorine and the vicinal hydrogens.

This fluorinating method is also applicable to the steroid chemistry. There are quite a few investigations dealing with α-fluoroketosteroids thus the fluorosteroids here prepared are known, but practically all of them were previously synthethized from their corresponding enamines with $FClO_3$ [10a].

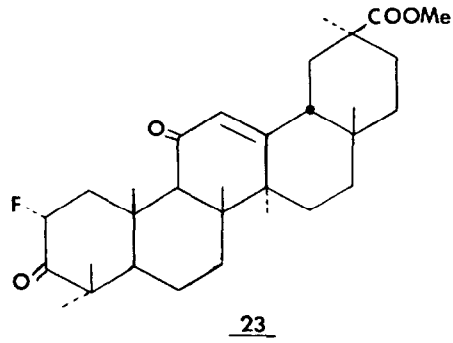
When the much more stable and easy to handle steroidal enolacetates were reacted with the mixture of the fluoroxy compounds we obtained in good to very good yields the corresponding fluoro ketones [10b].

Thus the following 2α-fluoro-3-keto steroids were synthesized.



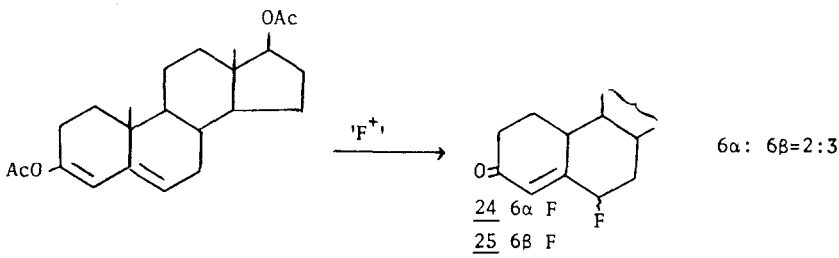

21 R=OAc

22 R=$C_8H_{17}$




23

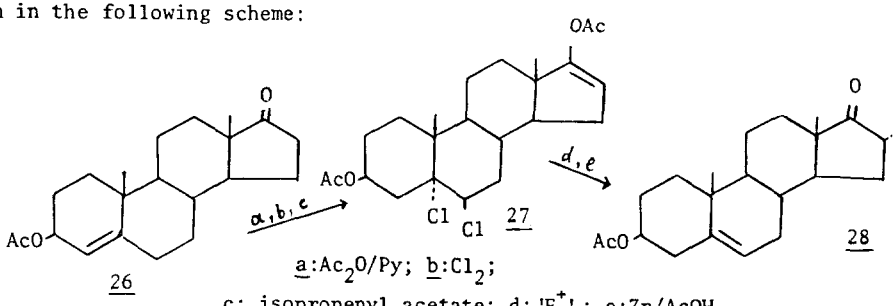
The reaction is also applicable to the synthesis of the important 6-fluorosteroids, as examplified by 6-fluorotestosterone acetate:




24 6α F

25 6β F

Fluorination at the 16 position can be also accomplished effectively as shown in the following scheme:



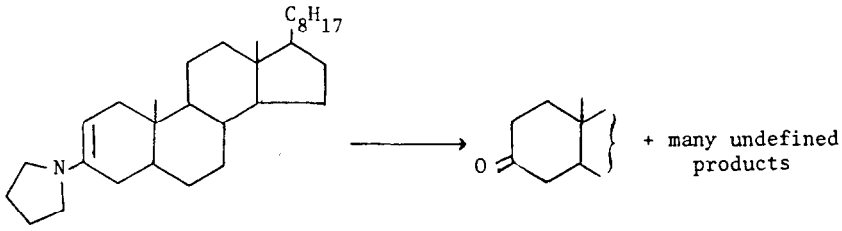

a:$Ac_2O$/Py; b:$Cl_2$;

c: isopropenyl acetate; d: '$F^+$'; e:Zn/AcOH

One can see that a wide variety of functional groups such as ketones, esters, chlorides, enones, unactivated aromatic rings and strained molecules

are not affected by the mild conditions of this reaction so enabling its application to a broad spectrum of substances.

It should be noted however, that when we tried to react enamines, such as 29, we obtained about 50% of the cholestanone itself together with an undefined mixture of many other products. It seems that the electrophilic fluorine has a great tendency to attach itself to the lone pair of the nitrogen, thus destroying the enamine system.




We believe that this new general method for synthesis of α-fluoroketones, which is simple and effective, will replace the old and hazardous synthesis involving $FClO_3$.

## EXPERIMENTAL

### General Remarks

M.ps. were determined with a Buchi capillary apparatus. NMR-$^1$H spectra were measured with a Bruker WH-90 spectrometer at 90 MHz with tetramethysilane as internal standard. $^{19}$F spectra were recorded with a Bruker HFX-10 at 84.67 MHz and were reported in ppm upfield from $CFCl_3$ as internal standard. Mass spectra were measured with a DuPont 21-491B spectrometer. The IR spectra were taken in neat films or in $CHCl_3$ solutions. Silica gel 60 (Merck) 70-230 mesh was used for column chromatography. If necessary further purification was obtained by HPLC with silica gel (Merck) 10μ packing.

Most of the enol-acetates were synthetized from the ketones with isopropenylacetate and are known compounds. Physical data are given only for those enol-acetates which are not found in the literature. Physical data for all the fluorine containing compounds are given and microanalyses also confirm the correct composition for the new compounds.

### Fluorination of Enol-acetates (General Procedure)

About 3% fluorine (Matheson Gas Products), diluted with nitrogen was bubbled through a suspension of $CF_3COONa$ in trichlorofluoromethane (Freon)

at -75°. A good vibronixer was used to ensure efficient mixing. Samples of the solution were treated with an acidic solution of KI and the liberated iodine was titrated with thiosulphate. When the desired quantity of the oxidizing reagents was achieved (usually 2 mole-equivalents), a cold solution of one of the enol-acetates (1-3 mmoles) in a 30 ml $CH_2Cl_2$ was added in one portion. After less than a minute the reaction mixture was poured into dilute thiosulfate solution, the organic layer was separated, washed several times, dried over $MgSO_4$ and evaporated. The crude product was homogenized by chromatography and the fluorine containing fraction(s) were identified.

It may be worth noting that in the IR spectrum the carbonyl absorbtion of the fluorine containing compounds is always shifted from +15 to +30 $cm^{-1}$ in comparison to the unfluorinated ketone.

2-Fluoro-α-tetralone (2) was obtained from 1 in 85% yield, m.p.=38° (from P.E.). IR: 1705$cm^{-1}$ (C=O) NMR: δ=8.2-7.1 (4H,aromatic,m) 5.1 (1H, CHF,ddd, $J_1$=48 $J_2$=12,$J_3$=6Hz), 3.3-2 ppm (4H,benzylic and vicinal to the fluorine,m). Analysis:Found: C,73.02; H,5.29%,M.W.,164 (m.sp.). $C_{10}H_9FO$ requires: C,73.17; H,5.49% M.W.,164.

Trans 2α-fluoro-4-t-butylcyclohexanone (4) and its cis isomer 5 [8]. were obtained in 72% combined yield (4:5 = 4:3). The cis isomer 5 has m.p. of 40°, IR: 1740$cm^{-1}$ (C=O), NMR: δ=4.93 (1H,CHF,ddd,J,=48,$J_2$=11,$J_3$=6Hz), 0.96ppm (9H,t-Bu,s). The hydrate of the trans isomer 4 m.p. 74°, IR: 1730$cm^{-1}$ (C=O), NMR: δ=4.67 (1H,CHF, two narrow m, $J_1$=48Hz, W/2 of each wing 8Hz), 0.91 ppm (9H,t-Bu,s).

2-Fluorocyclooactanone[11](7) was obtained from its enol-acetate in 72%, (oil), IR; 1710$cm^{-1}$ (C=O), NMR: 4.85 ppm (1H,CHF,ddd,$J_1$=48,$J_2$=3,3,$J_3$=6Hz) FMR: 191.8 ppm (quintet,$J_{HF(gem)}$=48; $J_{HF(vic)}$=24Hz).

2-Fluorocyclododecanone (9) from the corresponding enol-acetate in 90% yield, m.p.=54° (from MeOH), IR: 1725$cm^{-1}$ (C=O). NMR: δ=4.86 ppm (1H,CHF, ddd,$J_1$=48,$J_2$=44,$J_3$=7Hz). FMR: $\emptyset^*$=189.9 ppm (sextet,$J_{HF(gem)}$=48,$J_{HF(vic)}$= 18Hz). Analysis: Found: C,71.60; H,10.30%; M.W.,200 (m.sp.)$C_{12}H_{21}FO$ requires: C,72.00; H,10.50%; M.W.,200.

1-Fluoro-1,3-diphenyl-2-propanone (11) 50% yield (based on the enol-acetate), m.p.=53° (P.E.), IR: 1730cm$^{-1}$ (C=O). NMR: δ=7.4-6.8 (10H,aromatic,m), 5.65(1H,CHF,d,J=48Hz),3.71 ppm (2H,benzylic,d,J=3Hz). FMR: $\emptyset^{*}$=183.5 (d,J=48Hz). Analysis: Found: C,78.74; H,5.42%; M.W.,228 (m.sp.). $C_{15}H_{13}FO$ requires: C,78.94; H,5·70%; M.W.,228.

Fluoromethylnaphthyl Ketone(13). This fluoroketone was obtained in 45% yield, m.p.80°. IR: 1705cm$^{-1}$ (C=O) NMR: δ=8.5-7.2 (7H,aromatic, m), 5.73 ppm (2H,$CH_2F$,d,J=48Hz). Analysis: Found: C,76.73; H,4.60%; M.W., 188 (m.sp.) $C_{12}H_9FO$ requires: C,76.59; H,4.79%; M.W.,188.

Enol-acetate of 4-acetylbiphenyl(14)was synthesized from the 4-acetyl-biphenyl with excess isopropenyl acetate and TsOH as catalyst. The reaction mixture was refluxed in an azeotropic apparatus, for 48h, distilling from time to time small amounts of solvent (isopropenyl acetate). The mixture was poured into water, extracted with $CH_2Cl_2$ and worked up in the usual way. Thus 14 was obtained in 80%,m.p.=91°(P.E.).IR: 1765cm$^{-1}$ (C=O). NMR: 7.7-7.1 ppm (9H,aromatic,m),5.42 (1H,Olefinic,d,J=1.5Hz), 4.95(1H,olefinic,d,J=1.5Hz), 2.23 ppm(3H,acetyl,s).

Fluorination of(14) 14 was fluorinated in the usual way. Two compounds were isolated by HPLC. Fluoromethyl-4-biphenyl ketone 15 was isolated in 62% yield, m.p.=131°(P.E)IR: 1700cm$^{-1}$ (C=O). NMR: δ=7.2-8.](9H,aromatic,m), 5.54 ppm.(2H,$CH_2F$,d,J=48Hz). FMR: $\emptyset^{*}$=230.8 ppm (t,J=48Hz). Analysis: Found: C,78.75; H,4.90%; M.W.,214(m.sp.), $C_{14}H_{11}FO$ requires: C,78.50; H,5.14%; M.W.,214.

A second fluorine containing fraction was also isolated and proved to be difluoromethyl-4-biphenyl ketone 16 (29% yield) m.p.=80°(P.E).IR: 1690cm$^{-1}$ (C=O). NMR: δ=7.1-8.4 (9H,aromatic,m). 6.28 ppm (1H,$CHF_2$,t, J=52Hz). FMR: $\emptyset^{*}$=122.3(d,J=52Hz). Analysis: Found: C,72.13; H4.31%,M.W., 232 (m.sp.) $C_{14}H_{10}F_2O$ requires: C,72.41; H,4.31%; M.W.,232.

3α-Fluorocamphor[11](18). The enolacetate of camphor 17 was prepared using BuLi and $Ac_2O$[12]. It was fluorinated and the fluorocamphor was isolated by HPLC, yield 65%,m.p.=180°. IR: 1760cm$^{-1}$ (C=O). NMR: δ=4.9 (1H, CHF,dd,$J_1$=53,$J_2$=6Hz) 1.03,0.97,0.88ppm (3H each, s). FMR: $\emptyset^{*}$=202.7ppm (d,J=53Hz)

3β-Fluoronopinone (20) was obtained in 80% yield as an oil. IR: 1730 $cm^{-1}$ (C=O). NMR: δ=4.75 (1H,CHF,dd,$J_1$=49,$J_2$=9Hz), 1.40 and 0.82ppm (3H each, s). FMR: $\emptyset^*$=165.3ppm (m). Analysis: Found: C,68.89; H,8.09%; M.W., 156 (m.sp.) $C_9H_{13}FO$ requires: C,69.23; H,8.33%; M.W., 156.

5α-androstan-2α-fluoro-3-one-17β-ol acetate[13](21) was prepared from its enolacetate in 50% yield m.p.=196°. IR: 1745 $cm^{-1}$ (C=O). NMR: δ=5.0 (1H,CHF, ddd, $J_1$=48,$J_2$=12, $J_3$=7Hz), 4.57 (1H,H-17α,m),2.02,1.1 and 0.83ppm (for acetyl,Me-19 and Me-18). FMR: $\emptyset^*$=192.5ppm (m)

2α-fluorocholestanone[13](22)- (45% yield) m.p.=172° NMR: δ=4.9 ppm. (1H, CHF,ddd,$J_1$=48,$J_2$=12,$J_3$=7Hz)

2α-fluoro-3-keto methyl glycyrrhetate[14](23) (85% yield) m.p=265°, identical in all respects with an authentic sample.

6α- and 6β- Fluorotestosterone acetate[15](24) and (25): 24 was obtained in 27% based on the enol acetate m.p. 175° and 25 in 43% yield m.p.114°. All spectral data are identical with those published in the literature[15].

5α,6β-Dichloroandrost-16-en-3β,17-diol diacetate (27) A very dilute solution of $Cl_2$ in dry benzene containing 0.3% Pyridine was prepared. A benzene solution containing acetylated 26 was added slowly to the chlorine solution till the yellow colour of the chlorine disappeared. Then more chlorine was added followed by more steroid, repeatedly till no steroid was left. The crude 3β-acetoxy 5α,6β-dichloro-androsta-17-one was then reacted with isopropenyl acetate as described for 14 resulting in 27 - 80% yield ( based on 25) m.p.118°. NMR: δ=5.47 (1H,H-16,d,J=3Hz), 5.32 (1H,H-3α,m), 5.5 (1H, H-6, narrow m), 2.12,2.02 (3H each, 17 and 3β-acet 1s), 1.4 and 0.9ppm (3H each, Me-19 and Me-18).

Androst-5 en-16α-fluoro-17-one-3β-ol acetate[16](28) 27 was fluorinated in the usual way and then dechlorinated by boiling the crude product in EtOH containing Zn dust and a catalytic amount of AcOH. 28 was obtained in 85% yield m.p. 205°. NMR: δ=5.05 (1H,H-16β,J=48Hz.); One wing of the doublet superimposes with the olefinic proton at 5.42ppm and the other with the 3α-proton at 4.67ppm; 2.01 (3H, acetyl), 1.05 and 0.75ppm (3H each, Me 19 and 18 respectively).

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