Direct α-Fluorination of Ketones Using N−F Reagents

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Abstract: The use of 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (*Accufluor*™ NFTh) as a fluorine atom transfer reagent and methanol as solvent enabled direct regiospecific fluorofunctionalization of the α-carbonyl position in ketones without prior activation of the target molecules. Methoxy or hydroxy substituted derivatives of 1-indanone, 1-tetralone and oxo derivatives of thiophene, benzo[*b*]thiophene, benzofuran and benzopyran were regiospecifically transformed to the corresponding α-fluoro derivatives in high yield, while 2α-fluoro-5α-cholestan-3-one (**28**) and 16α-fluoro-3β-hydroxy-5α-androstan-17-one (**30**) were regio- and stereospecifically obtained starting directly from the corresponding keto steroids.

Key words: fluorination, ketones, *Accufluor*™ NFTh, keto steroids

The versatile application of organofluorine compounds in different branches of industry and medicine[1] is generating a comprehensive interest in and giving a strong impetus to basic and applied research in their related chemistry.[2] Development of new reagents and methods for site-selective introduction of a fluorine atom into organic molecules under mild reaction conditions has for a long time been the main theme of such research. One of the most important breakthroughs in these efforts has been accomplished by the introduction and broad synthetic application of organic molecules incorporating a reactive N–F bond as mild fluorinating reagents.[3] N–F reagents, being easy handling bench top materials usually with optimal stability/reactivity characteristics and attractive costs, have revolutionized the perception of synthesis of fluorinated organic compounds. Fluorination of organic molecules, at least when dealing with site-selective procedures, is no longer the privilege of specialized laboratories with sophisticated equipment and specially trained staff who must comply with severe safety precautions. Manipulation of N–F reagents is an ordinary experimental protocol, convenient for routine work in any organic chemistry laboratory.

One of the most beneficial changes resulting from bonding of a fluorine atom to an organic molecule is often the enhanced bioactivity of such a derivative in comparison to its nonfluorinated analogue.[1,4] On this basis fluorofunctionalization of organic compounds bearing a carbonyl group has been for a long time of special interest,[1] since this reactive functional site is often present in bioactive molecules or in potential building blocks for their synthesis. In our continued interest in this field of fluoroorganic chemistry we now report some results dealing with site-selective fluorination of ketones using N–F reagents.

The carbon atom α to the carbonyl group seems to be the most strategic one for fluorination.[5] As an electron-rich site, this reactive center needs electron-deficient sources of the fluorine moiety. N–F reagents are actually convenient compounds for this purpose as has been demonstrated in regard to the regio as well as the stereoselectivity of fluorofunctionalisation.[2,3,6] As with other electrophilic fluorinating reagents, when using N–F reagents, prior activation of the carbonyl substrate, through enolate anions or enol ethers was reported to be necessary for effective fluorination of the α-carbonyl position, except for sufficiently activated 1,3-dicarbonyl substrates, where direct fluorofunctionalization could be achieved. On the other hand, direct α-fluorination of a comprehensive range of ketones was reported to be effective by using 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (*Accufluor*™ NFTh) as fluorinating reagent,[7] while the regioselectivity of the reaction could be regulated by the solvent.[8] In order to check the related effects of other commercially available and commonly used N–F reagents, we chose 1-tetralone as a model substrate and tried to fluorinate it directly using a representative material from each class of N–F reagents. By keeping the reaction time and temperature constant, the N–F reagent and solvent as variable reaction parameters, the indicative results collected in Table 1 were obtained. In acetonitrile, *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate (FP-B800; **1**) as a representative from the class of *N*-fluoropyridinium salts, readily transformed 1-tetralone to 2-fluoro-1-tetralone in high yield, while in methanol the yield of direct transformation was lower. *N*-fluorobenzenesulfonimide (*Accufluor*™ NFSi; **2**), as a representative of neutral N–F reagents, was found to be ineffective when reaction was carried out in acetonitrile, while the methanol mediated reaction resulted in formation in very high yield of desired product. 1-(Chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoro-borate) (*Selectfluor*™ F-TEDA-BF_4; **3**) and its 1-fluoro-4-hydroxy substituted analogue *Accufluor*™ NFTh **4** are the most representative materials of the *N*-fluoro bicyclic amine salt class of N–F reagents. As evident from the data in Table 1, NFTh seems to be the better reagent for direct conversion of ketones to their α-fluorinated derivatives. Also, methanol is a better reaction medium for this purpose than acetonitrile. The overall conclusion from this

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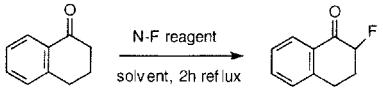
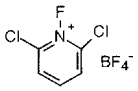
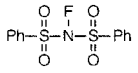
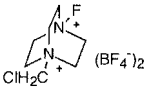
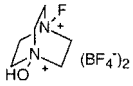
trial experiment is that the NFTh/methanol combination should be the best choice for the direct transformation of a ketone to its α-fluoro substituted derivative.

Table 1 Comparison of the Effect of N–F Reagents for Direct α-Fluorination of Ketones

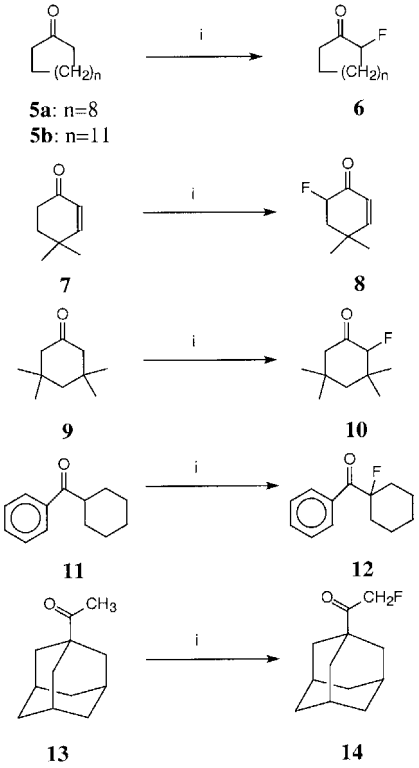


N–F reagent	Solvent	Yield (%)[a]
 FP-B800 **1**	CH_3CN	70
	CH_3OH	40
 Accufluor™ NFSi **2**	CH_3CN	0
	CH_3OH	90
 Selectfluor™ F-TEDA BF_4 **3**	CH_3CN	18
	CH_3OH	73
 Accufluor™ NFTh **4**	CH_3CN	54
	CH_3OH	98

[a] Determined from ^{19}F NMR spectra of crude reaction mixture using octafluoronaphthalene as internal standard.

Encouraged with this insight and previous related experience,[7,8] we tried to apply the method to a comprehensive range of keto functional groups containing organic molecules, specially focusing on those which have been declared as potentially bioactive compounds or have been recognized as valuable synthons for more sophisticated bioactive organic materials. The results of these efforts are collected in the Scheme 1 and Table 2.

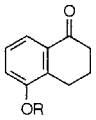
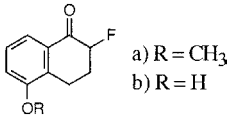
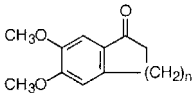
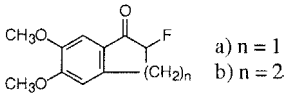
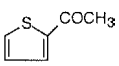
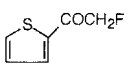
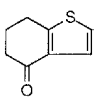
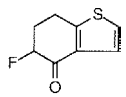
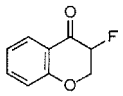
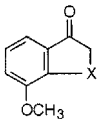
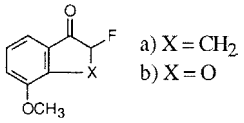
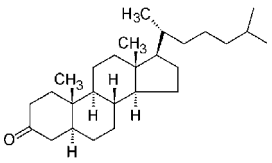
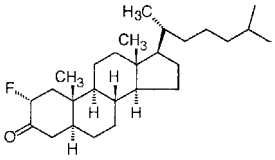
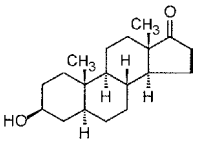
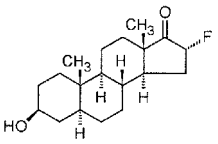
Ketones bearing a saturated carbocyclic ring as the structural element were transformed directly to their α-fluoro functionalized derivatives without any ring opening side reactions being observed. Cyclododecanone (**5a**, Scheme 1) and cyclopentadecanone (**5b**), known as the fragrance material Exaltone,[9] were selectively and almost quantitatively transformed to α-fluoro derivatives **6a**–**b**, as well as 4,4-dimethyl-cyclohex-2-en-1-one (**7**) to 6-fluoro-4,4-dimethyl-cyclohex-2-en-1-one (**8**) and 3,3,5,5-tetramethylcyclohexanone (**9**) to 2-fluoro-3,3,5,5-tetramethylcyclohexanone (**10**). 1-Fluorocyclohexyl phenyl ketone (**12**) and 1-adamantyl fluoromethyl ketone (**14**) were also readily obtained in high yield from the corresponding ketones (**11**) and (**13**) following reaction with NFTh in methanol.



Scheme 1 Direct α-fluorination of carbocyclic ketones. Reagents and conditions: i Ketone (2 mmol), NFTh (2.1 mmol), MeOH (20 mL), reflux 0.5–3 h.

Aromatic ketones possessing a strongly activated aromatic ring could be problematic substrates for the present reaction knowing that behind the position α to the keto group, the aromatic ring is also an electron-rich part of the molecule and thus sensitive to electrophilic reagents. On the other hand, following our previous experience,[8] the regioselectivity of fluorofunctionalization of a variety of such molecules could be regulated. 5-Methoxy-1-tetralone (**15a**, Table 2), known in the literature as valuable starting material for many bioactive molecules and natural products,[10] was thus transformed to (±)-2-fluoro-5-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (**16a**), while its hydroxy analogue **15b**, likewise used as a valuable synthon,[11] or the five membered ring analogue 4-methoxy-1-indanone (**25a**) also gave corresponding α-fluoro derivatives **16b** or **26a** effectively after using the NFTh/methanol reaction protocol. In the same way, 2-fluoro substituted derivatives of 1-indanone (**18a**) or 1-tetralone (**18b**) bearing a dimethoxy functionalized aromatic ring could be readily prepared from starting material **17**. We further checked the reactivity of some target molecules which also include a potentially oxidizable functional group or heteroatom as structural elements behind the keto group. These kinds of molecules could also be problematic target materials for direct fluorofunctionalization since N–F reagents are also known as strong oxidants.[12] We chose two derivatives of thiophene i.e. 2-acetylthiophene (**19**) and 6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one (**21**) as targets and both were directly fluorinated to the corresponding α-fluoro derivatives **20** an **22** in high

Table 2 Direct α-Fluorination of Ketones using *Accufluor*™ NFTh **4** in Methanol[a]

Entry	Ketone	Time	Product	Yield[b] (%)
1	 a) R = CH_3 b) R = H **15**	a) 15 min	 a) R = CH_3 b) R = H **16**	a) 84
2		b) 30 min		b) 77
3	 a) n = 1 b) n = 2 **17**	a) 30 min	 a) n = 1 b) n = 2 **18**	a) 71
4		b) 5 min		b) 78
5	 **19**	5 h	 **20**	71
6	 **21**	1.2 h	 **22**	82
7	 **23**	70 min	 **24**	79
8	 a) X = CH_2 b) X = O **25**	a) 1 h	 a) X = CH_2 b) X = O **26**	a) 89
9		b) 1.5 h		b) 81
10	 **27**	1.5 h	 **28**	78
11	 **29**	1.5 h	 **30**	72

[a] Reaction conditions: ketone (2 mmol), NFTh (2.1 mmol) b. Yields refer to the isolated pure products.

yield, while 2,3-dihydro-4*H*-1-benzopyranone (**23**) was transformed to its 3-fluoro derivative **24** and 7-methoxy-3(2*H*)-benzofuranone (**25b**) to its 2-fluoro derivative **26b**.

Finally, we applied this methodology for direct fluorination of ketones in the case of two keto steroids, namely 5α-cholestan-3-one (**27**) and 3β-hydroxy-5α-androstan-17-one (**29**). Both could be directly fluorinated, using NFTh in methanol. 5α-Cholestan-3-one (**27**) was readily transformed to 2α-fluoro-5α-cholestan-3-one (**28**), showing that one step in a recently reported methodology of fluorination of cholesterol type steroids using 1-fluoropyridinium triflate as reagent and silyl enol ethers of the target keto steroid as starting materials[13] could be avoided. The fluorination of steroid **29** resulted regioselectively in the formation of the 16-fluoro substituted product **30**. The stereochemistry of fluorine atom introduction was assigned on the basis of the coupling constants between the C-16−C-15 protons, the coupling constants between the fluorine atom on the C-16−C-15 protons, and the NOESY spectrum of the product. The proton on C-16 appeared as a dd signal with the characteristic geminal F–H coupling constant of 50.8 Hz and the H–H vicinal coupling constant of 7.3 Hz. By modeling, the structure of the product **30** it can be seen that in its most stable conformer when the C-16 proton occupies an equatorial position, the dihedral angle with the axial H-15 has a value around 20 degrees, while the dihedral angle with the equatorial H-15 is around 90 degrees. Following the Karplus rule, the coupling constants should thus be as actually observed. The signal for the fluorine atom, on the other hand, showed ddd multiplicity with coupling constants of 50.8 Hz, 27.0 Hz, and 26.5 Hz which is also consistent with the model assuming the fluorine atom occupies an axial position.

The stereochemistry on C-16 was also confirmed by the appearance of an interaction on the NOESY spectrum between the C-16 proton and the C-13 methyl group, indicating that they are on the same side of the plane. Hence from all the mentioned arguments and observed spectroscopic data the product **30** was assigned as 16α-fluoro-3β-hydroxy-5α-androstan-17-one. The assigned structure is also reasonable from the mechanistic point of view considering the assumption that the enol tautomer is involved in the fluorination process. In that case the β-face of the steroid **29** is sterically less accessible for the approach of the reagent to the enol tautomer π-bond because of the ring junction β-oriented methyl group.

Considering our actual and some previously reported experience[7,8] 1-fluoro-4-hydroxy-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) (*Accufluor*™ NFTh) seems to be a very convenient reagent for the direct fluorofunctionalization of a broad structural range of ketones. The reaction protocol involving NFTh as the fluorine transfer reagent and methanol as the reaction medium gave the optimal results regarding the regiospecificity of fluorine atom introduction to the α-keto position, even in cases when other potentially active sites were present in the target molecules. The presence of an activated aromatic ring or an oxidizable heteroatom such as sulfur as the structural element did not interfere with regiospecificity of the fluorination, while in addition, regio- and stereoselective fluorofunctionalization of some keto steroids could be achieved following the methodology described.

N-fluoro-2,6-dichloropyridinium tetrafluoroborate (FP-B800; **1**) and 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoro-borate) (*Selectfluor*™ F-TEDA-BF_4; **3**) were purchased from Apollo and used as received. *N*-Fluorobenzenesulfonimide (*Accufluor*™ NFSi; **2**) and 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (*Accufluor*™ NFT H, 50% w/w on alumina; **4**) were received as a gift from Allied Signal and used as obtained. Starting materials in Table 1 were Sigma-Aldrich samples and were used as received. Solvents (ACS grade) were dried prior to use. Petroleum ether with a bp 40–60 °C was used.

Melting points were determined on a Büchi 535 apparatus and are uncorrected. ^{1}H NMR spectra (except for pure products **28** and **30**) were recorded on a Varian EM360 L spectrometer at 60 MHz. Chemical shifts are reported in ppm from TMS as the internal standard. ^{19}F NMR spectra were recorded on a Varian EM360 L spectrometer at 56.4 MHz and chemical shifts are reported in ppm from CCl_3F as the internal standard. Data are reported as follows: chemical shift, multiplicity, coupling constant, integration, and assignment. ^{1}H NMR spectra for compounds **28** and **30** were recorded on a Varian Inova 300 spectrometer at 300 MHz and ^{13}C NMR on the same instrument at 75 MHz. Chemical shifts are reported in ppm from TMS and data for ^{13}C NMR are reported as follows: chemical shift, multiplicity, coupling constant, assignment. NOESY NMR were run with a mixing time of 0.2 s, relaxation delay of 3 s, and 4K data points across F2. IR spectra were recorded on a Perkin-Elmer 1310 spectrometer. Standard KBr pellet procedures were used to obtain IR spectra of solids, while a film of neat material was used to obtain IR spectra of liquid products. Mass spectra were obtained on an Autospec Q instrument under electron impact (EI) conditions at 70 eV. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN analyzer.

Direct Fluorination of Ketones; General Procedure

To a soln of ketone (2 mmol) in MeOH (20 mL), Accufluor™ NFTh (1.35 g, 2.1 mmol, of active compound) was added and the suspension heated under reflux until KI starch paper showed consumption of the fluorinating reagent. The reaction solvent was removed under reduced pressure, the crude reaction mixture dissolved in CH_2Cl_2 (50 mL), insoluble material filtered off, the soln washed with H_2O (50 mL), dried over Na_2SO_4 and the solvent evaporated. The isolated crude reaction mixtures were analyzed by ^{1}H and ^{19}F NMR. The amounts of fluorinated products were determined from the ^{19}F NMR spectra of the crude reaction mixtures using octafluoronaphthalene as an additional standard and yields between 80−95% for α-fluoro carbonyl products were obtained. Since crude α-fluoro carbonyl derivatives were in some cases (**24**, **26**, **28** and **30**) formed partly in dimethylketal form, hydrolysis with 10% aq HCl soln in MeCN was necessary. Pure solid products were obtained by crystallization of crude α-fluoro ketones while liquid products were purified by flash chromatography over SiO_2 followed by distillation under reduced pressure. The spectroscopic data of known compounds **6a**[14] (83% from MeOH, mp 55 °C), **8**[15](84% from pentane; mp 65–66 °C), **10**[16] (84% from pentane; mp 33–34 °C), **14**[17] (75% from pentane−CH_2Cl_2; mp 80 °C), and **28**[13] (78% from pentane−acetone, mp 167–169 °C) were in agreement with reported data. New compounds were fully characterized by NMR, MS, and IR spectroscopy and their purity verified by combustion elemental analysis.

(±)-2-Fluorocyclopentadecanone (6b)

Yield: 82%; white crystals; mp 53.5–55.5 °C (MeOH).

IR (KBr): 2930, 2857, 1721, 1460, 1366, 1063, 1019 cm^{-1}.

^{1}H NMR (60 MHz, $CDCl_3$): δ = 1.3–2.0 [m, 24 H, $(CH_2)_{12}$], 2.3 (t, J_{HH} = 4 Hz, 2 H, CH_2CO), 4.8 (dt, J_{FH} = 51 Hz, J_{HH} = 5 Hz, H2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (d, J_{CF} = 2.0 Hz), 22.3 (d, J_{CF} = 4.5 Hz), 26.1, 26.2, 26.3, 26.4, 26.5, 26.8, 27.3, 27.6, 31.7, 37.4, 42.1, 96.8 (d, J_{CF} = 184.8 Hz, CFH), 208.5 (d, J_{CF} = 16.2 Hz, CO).

^{19}F NMR (56.4 MHz, $CDCl_3$): δ = –191.3 (ddd, J_{FH2} = 51 Hz, J_{FH3a} 20 Hz, J_{FH3e} = 19 Hz, F2).

MS (EI, 70 eV): *m*/*z* (%) = 242 (23) [M^+], 166 (8), 139 (8), 125 (16), 111 (33), 98 (94), 84 (52), 69 (63), 55 (100).

Anal. calcd for $C_{15}H_{27}FO$: C, 74.33; H, 11.23. Found: C, 74.88; H, 11.78.

(1-Fluorocyclohexyl)(phenyl)methanone (12)

Yield: 71%, hygroscopic oily compound.

IR (neat): 1678, 1447, 1258, 1152, 1047, 965 cm^{-1}.

^{1}H NMR (60 MHz, $CDCl_3$): δ = 1.7 [m, 8 H, $(CH_2)_2$], 2.1 (m, 2 H, CH_2), 7.4 (m, 3 H, ArH), 8.1 (m, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1 (d, J_{CF} = 2.1 Hz, CH_2), 24.8 (s, CH_2), 33.2 (d, J_{CF} = 22.6 Hz, CH_2), 100.9 (d, J_{CF} = 188.1 Hz, CF), 128.3 (d, J_{CF} = 1.1 Hz, ArCH), 129.9 (d, J_{CF} = 8.2 Hz, ArCH), 132.9 (s, ArCH), 134.8 (d, J_{CF} = 3.5 Hz, ArC), 201.4 (d J_{CF} = 27.2 Hz, CO).

^{19}F NMR (56.4 M Hz, $CDCl_3$): δ = –164.0 (m).

MS (EI, 70 eV): *m*/*z* (%) = 206 (10) [M^+], 105 (100), 77 (30).

HRMS: *m*/*z* calcd for $C_{13}H_{15}FO$, 206.1110; found, 206.1107.

Anal. calcd for $C_{13}H_{15}FO·1/4H_2O$: C, 74.08; H, 7.41. Found: C, 74.25; H, 7.36.

(±)-2-Fluoro-5-methoxy-3,4-dihydro-1 (2*H*)-naphthalenone (16a)

Yield: 84%, white crystals from pentane−acetone, mp 123.8–125.8 °C.

IR (KBr): 1693, 1598, 1579, 1474, 1443, 1348, 1263, 1119, 1095, 1032, 999, 940, 805, 754 cm^{-1}.

^1H NMR (60 MHz, $CDCl_3$): δ = 1.9–3.6 [m, 4 H, $(CH_2)_2$], 3.9 (s, 3 H, OCH_3), 5.2 (ddd, J_{HF} = 50, 12, 6 Hz, 1 H, H2), 7.2 (d, J_{HH} = 8 Hz, 1 H, H8), 7.4 (dd, J_{HH} = 8, 8 Hz, 1 H, H7), 7.8 (d, J = 8 Hz, 1 H, H6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (d, J_{CF} = 11.7 Hz, C4), 29.2 (d, J_{CF} = 19.5 Hz, C3), 55.7 (s, OCH_3), 91.1 (d, J_{CF} = 191.6 Hz, C2), 114.9 (s, ArCH), 119.1 (s, ArCH), 126.7 (s, ArC), 127.8 (s, ArCH), 131.9 and 132.3 (d, J_{CF} = 2.0 Hz, ArC), 156.7 (s, ArC), 193.7 (d, J_{CF} = 14.9 Hz, CO).

^{19}F NMR (56.4 MHz, $CDCl_3$): δ = –191.5 (md, J_{FH} = 50 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 194 (100) [M^+], 148 (91), 120 (74), 105 (30), 90 (77), 77 (39).

Anal. calcd for $C_{11}H_{11}FO_2$: C, 68.03; H, 5.71. Found: C, 68.49; H, 5.75.

(±)-2-Fluoro-5-hydroxy-3,4-dihydro-1 (2*H*)-naphthalenone (16b)
Yield: 77%; white crystals from $CHCl_3$–CH_3CN; mp198.8–200.7 °C.

IR (KBr): 1670, 1595, 1580,1471, 1330, 1280, 1222, 1110, 1091, 1042, 1007, 967, 912, 852, 811, 796, 708, 753 cm^{-1}.

^1H NMR (300 MHz, CD_3CN): δ = 2.20 (m, 1 H, $H3_a$), 2.50 (m, 1 H, $H3_e$), 2.8 (m, 1 H, $H4_a$), 3.15 (md, J_{HH} = 13.0 Hz, 1 H, $H4_e$), 5.23 (ddd, J_{HF} = 50 Hz, J_{HH} = 12, 6 Hz, 1 H, H2), 7.07 (d, J_{HH} = 7.8 Hz, 1 H, H8), 7.22 (dd, J_{HH} = 8.0, 7.8 Hz, 1 H, H7), 7.43 (s, 1 H, OH), 7.48 (d, J_{HH} = 8 Hz, 1 H, H6).

^{13}C NMR (75 MHz, CD_3CN): δ = 21.8 (d, J_{CF} = 12.8 Hz, C4), 30.1 (d, J_{CF} = 18.7 Hz, C3), 92.4 (d, J_{CF} = 184.8 Hz, C2), 118.4 (s, ArCH), 119.3 (s, ArC), 120.8 (s, ArCH) 128.7 (s, ArCH), 131.4 and 133.8 (d, J_{CF} = 1.6 Hz, ArCH), 155.3 (s, ArC), 194.9 (d, J_{CF} = 14.4 Hz, CO).

^{19}F NMR (56.4 M Hz, CD_3CN): δ = –190.7 (md, J_{FH} = 50 Hz, F2).

MS (EI, 70 eV): *m*/*z* (%) = 180 (80), [M^+], 134 (100), 106 (76), 78 (34).

Anal. calcd for $C_{10}H_9FO_2$: C, 66.66; H, 5.03. Found: C, 66.85; H, 5.16.

(±)-2-Fluoro-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one (18a)
Yield: 71%; white crystals from petroleum ether–acetone; mp 128–130 °C.

IR (KBr): 1707, 1599, 1583, 1497, 1341, 1304, 1265, 1209, 1119, 1050, 1001, 859, 842, 774 cm^{-1}.

^1H NMR (60 MHz, $CDCl_3$): δ = 3.1–3.8 (m, 2 H, H3), 4.0 (s, 3 H, OCH_3), 4.1 (s, 3 H, OCH_3), 5.3 (ddd, J_{HF} = 51 Hz, J_{HH} = 6, 4 Hz, 1 H, H2), 7.0 (s, 1 H, ArH), 7.3 (s, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.2 (d, J_{CF} = 22.0 Hz, C3), 56.1 (s, OCH_3), 56.4 (s, OCH_3), 90.6 (d, J_{CF} = 192.1 Hz, C2), 104.8 (s, ArCH), 107.6 (s, ArCH), 126.7 (d, J_{CF} = 2.1 Hz, ArC), 145.6 (d, J = 6.2 Hz, ArC), 150.1 (s, ArC), 156.9 (s, ArC), 198.4 (d, J_{CF} = 15.3 Hz, CO).

^{19}F NMR (56.4 MHz, $CDCl_3$): δ = –193.2 (ddd, J_{FH} = 51, 21, 9 Hz, F2).

MS (EI, 70 eV): *m*/*z* (%) = 210 (100) [M^+], 195 (31), 167 (18), 139 (24), 91 (43).

Anal. calcd for $C_{11}H_{11}FO_3$: C, 62.85; H, 5.27. Found: C, 63.14; H, 5.40.

(±)-2-Fluoro-6,7-dimethoxy-3,4-dihydro-1-(2*H*)-naphthalenone (18b)
Yield: 78%; white crystals from petroleum ether–acetone; mp 163–164.5 °C.

IR (KBr): 1677, 1600, 1510, 1470, 1453, 1417, 1374, 1338, 1269, 1238, 1224, 1203, 1148, 1073, 1046, 1017, 972, 933, 884, 867, 809, 770 cm^{-1}.

^1H NMR (60 MHz, $CDCl_3$): δ = 2.5 (m, 2 H, H4), 3.1 (m, 2 H, H3), 4.0 (s, 6 H, OCH_3), 5.2 (ddd, J = 49, 12, 6 Hz, 1 H, H2), 6.8 (s, 1 H, ArH), 7.6 (s, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.7 (d, J_{CF} = 12.3 Hz, C4), 30.4 (d, J_{CF} = 19.4 Hz, C3), 56.0 (s, OCH_3), 56.1 (s, OCH_3), 90.9 (d, J_{CF} = 189.6 Hz, C2), 108.5 (d, J_{CF} = 2.0 Hz, ArCH), 110.1 (s, ArCH), 124.2 (s, ArC), 138.2 (d, J = 1.5 Hz, ArC), 148.3 (s, ArC), 154.2 (s, ArC), 192.1 (d, J_{CF} = 14.9 Hz, CO).

^{19}F NMR (56.4 MHz, $CDCl_3$): δ = –191.0 (td, J_{FH} = 49, 9.5 Hz, F2).

MS (EI, 70 eV): *m*/*z* (%) = 224 (88) [M^+], 178 (75), 150 (100), 135 (18), 107 (17), 77 (15).

Anal. calcd for $C_{12}H_{13}FO_3$: C, 64.28; H, 5.84. Found: C, 64.70; H, 6.07.

2-Fluoro-1-(2-thienyl)ethanone (20)
Yield: 71%; white crystals from pentane–acetone; mp 51.3–54.4 °C.

IR (KBr): 1675, 1416, 1255, 1100, 1087, 1053, 922, 857, 775, 750 cm^{-1}.

^1H NMR (60 MHz, $CDCl_3$): δ = 5.4 (d, J_{HF} = 49 Hz, 2 H, CH_2F), 7.3 (dd, J_{HH} = 5, 5 Hz, 1 H, H3), 7.9 (dd, J_{HH} = 5, 2 Hz, 1 H, H4), 8.0 (dd, J_{HH} = 5, 2 Hz, 1 H, H5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 83.8 (d, J_{CF} = 188.1 Hz, CH_2F), 128.5 (d, J_{CF} = 1.5 Hz), 133.2 (d, J_{CF} = 6.2 Hz), 135.0 (d, J_{CF} = 1.0 Hz), 139.9 (d, J_{CF} = 2.5 Hz), 187.2 (d, J_{CF} = 18.0 Hz, CO).

^{19}F NMR (56.4 MHz, $CDCl_3$): δ = –226.7 (t, J_{FH} = 49 Hz, FCH_2).

MS (EI, 70 eV): *m*/*z* (%) = 144 (19) [M^+], 111 (100), 83 (15).

Anal. calcd for C_6H_5FOS: C, 49.99; H, 3.50. Found: C, 49.72; H, 3.49.

(±)-5-Fluoro-6,7-dihydrobenzo[*b*]thiophen-4 (5*H*)-one (22)
Yield: 82%; white crystals from pentane–CH_2Cl_2; mp 52.1–53.3 °C.

IR (KBr): 1680, 1520, 1414, 1356, 1254, 1215, 1120, 1082, 1032, 989, 918, 845, 735, 648 cm^{-1}.

^1H NMR (60 MHz, $CDCl_3$): δ = 2.6 (m, 2 H, H7), 3.2 (m, 2 H, H6), 5.2 (ddd, J_{HF} = 49 Hz, J_{HH} 9.5, 6 Hz, 1 H, H5), 7.2 (d, J_{HH} = 6 Hz, 1 H, H3), 7.5 (d, J_{HH} = 6 Hz, 1 H, H2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.1 (d, J_{CF} = 11.1 Hz, C7), 31.0 (d, J_{CF} = 20.1 Hz, C6), 90.5 (d, J_{CF} = 185.9 Hz, C5), 125.0 (s), 125.1 (s), 136.0 (d, J_{CF} = 1.0 Hz), 155.0 (d, J_{CF} = 1.6 Hz), 187.7 (d, J_{CF} = 16.1 Hz, CO).

^{19}F NMR (56.4 M Hz, $CDCl_3$): δ = –161.2 (td, J_{FH} = 49, 9.4 Hz, F5).

MS (EI, 70 eV): *m*/*z* (%) = 170 (76) [M^+], 124 (100), 96 (89), 70 (25).

Anal. calcd for C_8H_7FOS: C, 56.45; H, 4.15. Found: C, 56.29; H, 4.22.

(±)-3-Fluoro-2,3-dihydro-4*H*-1-benzopyranone (24)
Yield: 79%; white crystals from pentane–acetone; mp 66.5–67.3 °C.

IR (KBr): 1709, 1607, 1575, 1524, 1452, 1283, 1237, 1212, 1146, 1127, 1094, 1036, 1013, 944, 834, 757, 650 cm^{-1}.

^{1}H NMR (60 MHz, $CDCl_3$): δ = 4.6 (m, 2 H, H2), 5.1 (ddd, J_{HF} = 48 Hz, J_{HH} 8, 5 Hz, 1 H, H3), 7.1 (dd, J_{HH} = 8, 8 Hz, 2 H, H6,H7), 7.5 (dd, J_{HH} = 8, 3 Hz, 1 H, H5), 7.9 (dd, J = 8, 3 Hz, 1 H, H8).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 68.7 (d, J_{CF} = 26.2 Hz, C2), 85.6 (d, J_{CF} = 188.0 Hz, C3), 117.9 (s, ArCH), 119.4 (s, ArC) 122.3 (s, ArCH), 127.7 (s, ArCH), 136.8 (s, ArCH), 161.2 (s, ArC), 187.0 (d, J_{CF} = 16.1 Hz, CO).

^{19}F NMR (56.4 MHz, $CDCl_3$): δ = –203.3 (ddd, J_{FH} = 48, 14, 12 Hz, F3).

MS (EI, 70 eV): *m*/*z* (%) = 166 (50) [M^+], 136 (8), 120 (100), 92 (68), 77 (34).

Anal. calcd for $C_9H_7FO_2$: C, 65.06; H, 4.25. Found: C, 65.09; H, 4.26.

(±)-2-Fluoro-4-methoxy-2,3-dihydro-1*H*-inden-1-one (26a)
Yield: 89%; white crystals from petroleum ether–acetone; mp 106.5–108.4 °C.

IR (KBr): 1720, 1592, 1487, 1433, 1267, 1082, 1062, 992, 937, 849, 800, 761 cm^{-1}.

^{1}H NMR (60 MHz, $CDCl_3$): δ = 3.0–3.8 (m, 2 H, H3), 3.9 (s, 3 H, OCH_3), 5.2 (ddd, J_{HF} = 51 Hz, J_{HH} = 7, 5 Hz, 1 H, H2), 7.1–7.5 (m, 3 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.0 (d, J_{CF} = 22.6 Hz, C3), 55.6 (s, OCH_3), 90.5 (d, J_{CF} = 193.2 Hz, C2), 116.0 (s, ArCH), 116.5 (s, ArCH), 129.9 (s, ArCH), 135.1 (d, J_{CF} = 1.1 Hz, C8), 138.7 (d, J = 6.2 Hz, C9), 156.9 (d, J_{CF} = 1.5 Hz, C4), 200.2 (d, J_{CF} = 15.4 Hz, CO).

^{19}F NMR (56.4 MHz, $CDCl_3$): δ = –194.5 (ddd, J_{FH} = 51, 22, 8.5 Hz, F2).

MS (EI, 70 eV): *m*/*z* (%) = 180 (100) [M^+], 165 (50), 145 (39), 137 (36), 109 (43).

Anal. calcd for $C_{10}H_9FO_2$: C, 66.66; H, 5.03. Found: C, 67.09; H, 5.01.

(±)-2-Fluoro-7-methoxy-3-(2*H*)-benzofuranone (26b)
Yield: 81%; yellow crystals from pentane–CH_2Cl_2; mp 61–63 °C.

IR (KBr): 1743, 1601, 1508, 1440, 1321, 1279, 1170, 1100, 1070, 1036, 998, 919, 832, 760 cm^{-1}.

^{1}H NMR (60 MHz, $CDCl_3$): δ = 4.0 (s, 3 H, OCH_3), 5.9 (d, J_{HF} = 59 Hz, 1 H. H2), 7.3 (m, 3 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.5 (s, OCH_3), 103.2 (d, J_{CF} = 238.8 Hz, C2), 116.3 (s, ArCH) 119.5 (s, C8), 120.9 (s, ArCH), 124.4 (s, ArCH), 146.2 (s, C9), 161.1 (s, C7), 193.1 (d, J_{CF} = 14.5 Hz, CO).

^{19}F NMR (56.4 MHz, $CDCl_3$); δ = –140.2 (d, J_{FH} = 59 Hz, F2).

MS (EI, 70 eV): *m*/*z* (%) = 182 (98) [M^+], 164 (22), 153 (35), 133 (36), 104 (52), 91 (14), 76 (100).

Anal. calcd for $C_9H_7FO_3$: C, 59.35; H, 3.87. Found: C, 59.19; H, 4.00.

16α-Fluoro-3β-hydroxy-5α-androstan-17-one (30)
Yield: 72%; white crystals from pentane–acetone; mp 160–162 °C.

IR (KBr): 1742, 1446, 1369, 1299, 1072, 1041, 1003, 918, 869, 847 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.7–2.2 (m, 20H), 0.83 (s, 3 H, CH_3C19), 0.91 (s, 3 H, CH_3C18), 3.58 (m, 1 H, H3), 5.08 (dd, J_{HF} = 50.8 Hz, $J_{H16H15\alpha}$ = 7.3 Hz, 1 H, H16).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.29, 14.06, 20.10, 28.26, 29.79 (d, J_{CF} = 20.4 Hz, C15), 30.60, 31.32, 34.87, 35.66, 36.86, 38.00, 44.76, 47.82, 48.38, 51.46, 54.25, 71.03 (s, C3), 90.17 (d, J_{CF} = 183.45 Hz, C16), 213.49 (d, F_{CF} = 20.4 Hz, CO).

^{19}F NMR (56.4 MHz, $CDCl_3$); δ = –192.7 (ddd, J_{FH16} = 50.8 Hz, J_{FH15} = 27.0, 26.5 Hz, F16).

MS (EI, 70 eV): *m*/*z* (%) = 308 (26) [M^+], 235 (16), 234 (81), 219 (15), 216 (52), 201 (22), 190 (33), 124 (25), 109 (28), 108 (100), 107 (62), 97 (22), 95 (28), 93 (30), 83 (30), 81 (36), 71 (28), 69 (48), 67 (25), 57 (54), 55 (52).

Anal. calcd for $C_{19}H_{29}FO_2$: C, 73.99; H, 9.48. Found: C, 73.66; H, 9.70.

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References

(1) (a) Banks, R. E.; Smart, B. E.; Tatlow, J. C. In *Organofluorine Chemistry. Principles and Commercial Applications*; Plenum Press: New York, **1994**. (b) Hudlicky, M.; Pavlath, A. E. In *Chemistry of Organic Fluorine Compounds II. A Critical Review*; ACS Monograph 187: Washington, **1995**. (c) Hiyama, T. In *Organofluorine Compounds. Chemistry and Applications*; Springer-Verlag: Berlin, **2000**.
(2) Baasner, B.; Hagemann, H.; Tatlow, J. C. In *Methods of Organic Chemistry (Houben-Weyl): Organofluorine Compounds*, Vol. E 10a,10b; Thieme: New York, **1999**.
(3) (a) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737. (b) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431. (c) Furin, G. G.; Fainzilberg, A. A. *Russian Chem. Rev.* **1999**, *68*, 653.
(4) (a) *Organofluorine Compounds in Medicinal Chemistry and Biomedicinal Applications*; Filler, R.; Kobayashi, Y.; Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, **1993**. (b) Resnati, G.; Soloshnok, V. A. In *Fluoroorganic Chemistry: Synthetic Challenges and Biomedicinal Rewards, Tetrahedron Symposia-in-Print No. 58*, 52; Elsievier: Amsterdam, **1996**, 1. (c) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3.
(5) (a) Rozen, S.; Filler, R. *Tetrahedron* **1985**, *41*, 1111; and references therein. (b) Davis, F. A.; Kasu, P. V. N. *Org. Prep. Proced. Int.* **1999**, *31*, 125; and references therein.
(6) (a) Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1988**, *29*, 6087. (b) Davis, F. A.; Han, W.; Murphy, C. K. *J. Org. Chem.* **1995**, *60*, 4730. (c) Davis, F. A.; Zhou, P.; Murphy, C. K.; Sundarababu, G.; Qi, H.; H'an, W.; Przeslawski, R. M.; Chen, B. C.; Carrol, P. J. *J. Org. Chem.* **1998**, *63*, 2273. (d) Liu, Z.; Shibata, N.; Takeuchi, Y. *J. Org. Chem.* **2000**, *65*, 7583. (e) Cahard, D.; Audouard, C.; Plaquevent, J.-C.; Roques, N. *Org. Lett.* **2000**, *2*, 3699. (f) Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001. (g) Enders, D.; Faure, S.; Potthoff, M.; Runsink, J. *Synthesis* **2001**, *15*, 2307.
(7) Stavber, S.; Zupan, M. *Tetrahedron Lett.* **1996**, *37*, 3591.
(8) Stavber, S.; Jereb, M.; Zupan, M. *Chem. Commun.* **2000**, 1323.
(9) Ohloff, G. *In Scent and Fragrances*; Springer-Verlag: Berlin, **1994**.

(10) (a) Meyer, M. D.; Hancock, A. A.; Tietje, K.; Sippy, K. B.; Giardina, W. J.; Kervin, J. F. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2287. (b) Meyer, M. D.; Hancock, A. A.; Tietje, K.; Sippy, K. B.; Prasad, R.; Stout, D. M.; Arendsen, D. L.; Donner, B. G.; Carrol, W. A. *J. Med. Chem.* **1997**, *40*, 1049. (c) Perrone, R.; Berardi, F.; Leopoldo, M.; Tottorella, V.; Fornaretto, M. G.; Caccia, C.; McArthur, R. A. *J. Med. Chem.* **1996**, *39*, 3195. (d) Ragot, J. P.; Steeneck, C.; Alcaraz, M.-L.; Taylor, J. K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1073.

(11) (a) Hamanaka, N.; Takahashi, K.; Nagao, Y.; Torisu, K.; Tokumoto, H.; Kondo, K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1083. (b) Mu, Y. Q.; Gibbs, R. A. *Bioorg. Med. Chem.* **1997**, *5*, 1327.

(12) Gilicinski, A. G.; Pez, G. P.; Syvret, R. G.; Lal, G. S. *J. Fluorine Chem.* **1992**, *59*, 157.

(13) Thomas, M. G.; Suckling, C. J.; Pitt, A. R.; Suckling, K. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3191.

(14) Rozen, S.; Menahem, Y. *J. Fluorine Chem.* **1980**, *16*, 19.

(15) Molines, H.; Wakselman, C. *J. Chem. Soc., Chem. Commun.* **1975**, 232.

(16) Shapiro, B.; Chrysam, M. M. III *J. Org. Chem.* **1973**, *38*, 880.

(17) Leroy, J. *J. Org. Chem.* **1981**, *46*, 206.