Fluorination with Xenon Difluoride. 37. Room-Temperature Rearrangement of Aryl-Substituted Ketones to Difluoro-Substituted Ethers

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Introduction

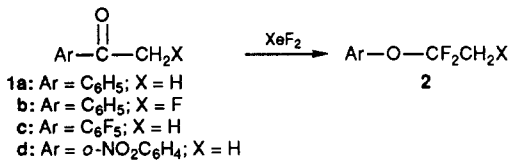
Introduction of fluorine into organic molecules is important and attractive from various points of view, but reagents discovered up to now usually require special laboratory equipment, with a vacuum line and low temperatures often necessary.[1,2] Xenon difluoride is a stable compound, which readily reacts with various organic molecules at room temperature.[3]

Information about the reactivity of xenon difluoride with ketones is very sparse. We have already demonstrated that xenon difluoride reacted with some enol acetates and diketones, the course of the reaction depending on the catalyst used,[4,5] while Tsushima with co-workers[6] and Filler[7] also showed that xenon difluoride converted silyl enol ethers to α-fluoro ketones. Patrick and co-workers[8,9] have reported the conversion of carboxylic acids with xenon difluoride to decarboxylated fluoro derivatives. We have already found that fluorination of 1,3-indandione with xenon difluoride strongly depended on the catalyst used, and a rearranged product has also been observed.[5] We now report our investigations on the reactions of xenon difluoride with various aryl-substituted ketones.

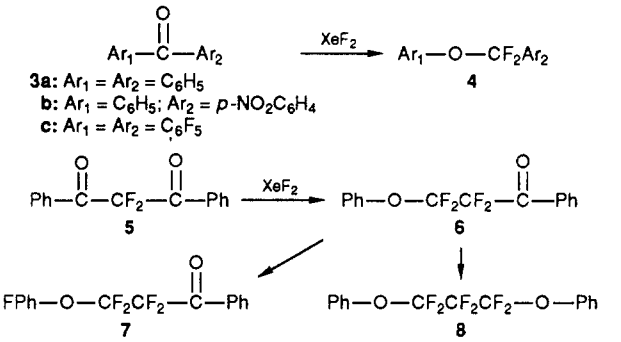
Results and Discussion

In a typical experiment, either 1 or 2 mmol of ketone was dissolved in 2 mL of methylene chloride, 1 mmol of xenon difluoride was added, and a catalytic amount of hydrogen fluoride was introduced into the reaction mixture at room temperature. After 24 h, 20 mL of methylene chloride was added, and after the usual workup, the crude reaction mixture was analyzed by ^1H and ^{19}F NMR and GLC. Under these conditions, skeletal rearrangement occurs, as well as fluorination. Acetophenone gave 23% of 1,1-difluoroethyl phenyl ether (**2a**), and **1b** afforded 52% of 1,1,2-trifluoroethyl phenyl ether (**2b**) (Scheme I).

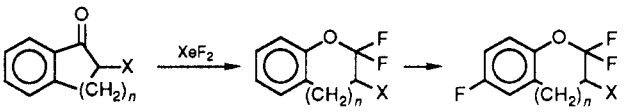
Scheme I



Scheme II



Scheme III



With electron-withdrawing phenyl groups (**1c** and **1d**), high yields of rearranged ether products were obtained only after saturation of the reaction mixture with hydrogen fluoride. Addition of HF also increased the yields of **2a** and **2b**, but fluorination of the phenoxy ring became the dominant process.

We also studied the reactions with diaryl ketones (**3**, Scheme II). Benzophenone (**3a**) was converted in the presence of a catalytic amount of hydrogen fluoride to α,α-difluorobenzyl phenyl ether (**4a**) isolated in 21% yield. Phenyl ring migration as the preferential process in the rearrangement was observed in the fluorination of 4-nitrophenyl phenyl ketone (**3b**), where 20% of α,α-difluoro-4-nitrobenzyl phenyl ether was isolated (by preparative TLC). Perfluorobenzophenone (**3c**) was also very stable in the presence of higher amounts of hydrogen fluoride (saturation of the methylene chloride solution), and only 5% of rearranged perfluoro benzyl phenyl ether (**4c**) was isolated after 90-h reaction at room temperature. The structures of the products **4** were determined on the basis of their NMR spectra, while in their mass spectra the basic peak became the signal corresponding to the $ArCF_2^+$ structure, while the abundance corresponding to the molecular peak diminished from 40% for **4a** to 3% in the case of **4c**. 2,2-Difluoro-1,3-diphenylpropane-1,3-dione (**5**) in the presence of trace amounts of hydrogen fluoride as a catalyst gave only 4% of 1,1,2,2-tetrafluoro-3-oxo-3-phenylpropyl phenyl ether (**6**). The conversion of ketone **5** was increased up to 40%, when an HF–pyridine mixture (70% hydrogen fluoride) was used as solvent. The crude reaction mixture was analyzed by ^{19}F NMR, and the formation of three products in the ratio 6.9:2.7:1 was established.

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Table I. The Effect of Ketone Structure on Rearrangement and Additional Fluorination of the Aromatic Nucleus[a]

	product distribution[b]		
ketone	starting ketone, %	rearranged product, %	aromatic ring fluorination, %
9b	35	43 (**10b**)	22 (**11b**)
5	63	24 + 3.5 (**6** + **8**)	9.5 (**7**)
1d	77	23 (**2d**)	–
3c	100	–	–

[a] Molar ratio of ketone:XeF_2, 1:1; solvent, HF–pyridine mixture (70%); reaction time, 2 h; reaction temperature, 23 °C. [b] Determined by ^1H and ^{19}F NMR spectroscopy.

Further, we studied the conversions of various cycloalkanones (**9**, Scheme III) to rearranged cyclic ethers,[10] which occurred at room temperature in the presence of a catalytic amount of hydrogen fluoride. Rearranged ethers were isolated by preparative TLC in 16–18% yields. Increasing the amount of hydrogen fluoride resulted in a higher conversion of the starting ketone, but rearranged difluoro cyclic ethers were further fluorinated on the aromatic ring.

Fluorination of 2-fluoro-1-indanone (**9b**) in the presence of catalytic amounts of hydrogen fluoride resulted in a reaction mixture containing only 18% of 2,2,3-trifluoro-3,4-dihydro-2*H*-1-benzopyran (**10b**), while higher conversion was achieved in HF–pyridine mixture as a solvent, but besides the trifluoro product **10b**, 2,2,3,6-tetrafluoro-3,4-dihydro-2*H*-1-benzopyran (**11b**) was also formed. An increased amount of xenon difluoride (2 mmol) resulted in complete conversion of starting ketone **9b**, while the crude reaction mixture contained 80% of **11b**. 2-Chloro-1-indanone (**9c**) was converted in 25% yield to rearranged benzopyran derivative **10c** in the presence of a catalytic amount of hydrogen fluoride, while conversion of the starting ketone up to 45% occurred in HF–pyridine solvent, with **10c** being accompanied by **11c**. The structures of the products were determined on the basis of spectroscopic data; in ^{19}F NMR spectra the equivalency of the geminal difluorides, observed in **10a**, **10d**, and **10e**, was lost, and two signals appeared at −79.2 and −87.8 ppm (**10b**), and at −74.5 and −83.2 ppm for **10c**. The fluorine signal corresponding to aromatic fluorination (**11b**, **11c**) appeared at −119 ppm (in both cases) as a ddd signal with all three coupling constants being 6.5 Hz.

In order to obtain information on the effect of the ketone structure on the course of rearrangement, we carried out the reactions in a hydrogen fluoride–pyridine mixture as solvent for 2 h at room temperature, with a ketone to xenon difluoride molar ratio of 1:1. Product distributions in the crude reaction mixtures obtained after 2 h were analyzed by ^{19}F and ^1H NMR spectra and are presented in Table I. From the ketones chosen, 2-fluoro-1-indanone (**9b**) appeared to be the most reactive; however, the amount of product formed by aromatic ring fluorination was also the highest. Under these conditions, 2,2-difluoro-1,3-diphenylpropane-1,3-dione (**5**) gave 37% of products, 2-nitroacetophenone (**1d**) 23% of product without further fluorination, while decafluorobenzophenone (**3c**) was unreactive. In the reactions of aromatic ketones containing electron-donating groups (i.e., 4,4′-dimethoxybenzophenone) with xenon difluoride, aromatic ring fluorination became the main process.

It is known that the catalyst plays an important role in fluorinations with xenon difluoride, and for this reason we studied the influence of other catalysts on the course of fluorination reactions with ketones. Reaction of xenon difluoride with benzophenone in the presence of boron trifluoride gave a crude reaction mixture containing only trace amounts of rearranged product, while the main process occurring was ring fluorination. BF_3-catalyzed reaction with decafluorobenzophenone resulted in products arising from fluorine addition to the perfluoro aromatic ring, similar to that already observed.[10] On the other hand, reaction with 1-indanone did not proceed if boron trifluoride, bonded to polystyrene-4-vinylpyridine, was used as a catalyst, while the similar reaction performed in methanol solution resulted in 30% conversion to 2-fluoro-1-indanone.

Experimental Section

IR spectra were recorded with a Perkin-Elmer 727 B spectrometer and ^1H and ^{19}F NMR spectra with a Varian EM-360 instrument, using Me_4Si or CCl_3F as internal reference. Mass spectra and high-resolution measurements were taken on a CEC-21-110 spectrometer. Gas–liquid partition chromatography was carried out on Varian Aerograph Models 2700 and 3700, and TLC on Merck PSC-Fertigplatten silica gel F-254.

Fluorination of Ketones with Xenon Difluoride. Procedure A. First, 1 or 2 mmol of ketone were dissolved in 2 mL of methylene chloride, and at room temperature 1 mmol of xenon difluoride was added and a catalytic amount of hydrogen fluoride was introduced. After 24 h the reaction mixture was diluted with 20 mL of methylene chloride, washed with aqueous $NaHCO_3$ (15 mL) and water and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo, the crude reaction mixture was analyzed by ^1H, ^{19}F NMR, and GLC, and the pure products were isolated by preparative TLC or GLC.

Procedure B. One millimole of ketone was dissolved in 2 mL of methylene chloride, 1 mmol of xenon difluoride was added, and under stirring hydrogen fluoride was introduced until saturation. After 24–90 h the reaction mixture was diluted with 20 mL of methylene chloride, followed by the above mentioned workup procedure.

Procedure C. One millimole of ketone was dissolved in hydrogen fluoride–pyridine mixture (70%), under stirring 1 mmol of xenon difluoride was added, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with 20 mL of methylene chloride, washed twice with water, aqueous $NaHCO_3$, and water again, and dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo.

Yields of isolated fluorosubstituted products are calculated on the basis of xenon difluoride, and in most cases high amounts of the starting ketone were recovered.

Fluorination of Acetophenone (1a). Procedure A: 2 mmol of ketone; the crude reaction mixture was separated by preparative TLC (SiO_2, petroleum ether–methylene chloride, 3:1), 1.3 mmol of **1a** was recovered, and 36 mg (23%) of **1,1-difluoroethyl phenyl ether (2a)** was isolated as an oily product; NMR ($CDCl_3$) δ_F −64.8 (q, $^3J_{FH}$ = 13 Hz), δ_H 1.87 (t, $^3J_{FH}$ = 13 Hz, 3 H), δ_H 7.1 (br s, 5 H); mass spectrum calcd for $C_8H_8OF_2$ m/z 158.0543, found m/z 158.0540; m/z 159 (M^+ + 1, 3), 158 (M^+, 41), 95 (10), 94 (100), 77 (21), 66 (11), 65 (32), 61 (10), 51 (10), 43 (19).

Fluorination of Fluoromethyl Phenyl Ketone (1b). Procedure A: 1 mmol of ketone; the crude reaction mixture was separated by preparative TLC (SiO_2, petroleum ether–methylene chloride, 3:1), 0.24 mmol of **1b** was recovered, and 92 mg (52%) of **1,1,2-trifluoroethyl phenyl ether (2b)** was isolated as an oily product; NMR ($CDCl_3$) δ_F −80.8 (dt, $^3J_{FF}$ = 16 Hz, $^3J_{FH}$ = 8 Hz, 2 F), δ_F −243.3 (tt, $^2J_{FH}$ = 46 Hz, $^3J_{FF}$ = 16 Hz, 1 F), δ_H 4.57 (dt, $^2J_{FH}$ = 46 Hz, $^3J_{FH}$ = 8 Hz, 2 H), δ_H 7.17 (m, 5 H); mass spectrum calcd for $C_8H_7F_3O$ m/z 176.0449, found m/z 176.0450; m/z 177 (M^+ + 1, 4), 176 (M^+, 41), 143 (7), 95 (11), 94 (100), 84 (13), 83 (12), 77 (31), 65 (15), 39 (13).

Fluorination of Methyl Pentafluorophenyl Ketone (1c). Procedure B: 70 h; 142.8 mg (58%) of **1,1-difluoroethyl pen-**

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tafluorophenyl ether (2c) was isolated by preparative GLC (DEGS 12%, Chromosorb W/AW 80/100, T = 50 °C) as a liquid product, $bp_{101.3kPa}$ 140 °C; NMR ($CDCl_3$) δ_F −67.2 (tq, $^3J_{FH}$ = 13.5 Hz, J_{FF} = 11.5 Hz, 2 F), δ_F −153 (m, 2 F), δ_F −159 (t, J = 21.5 Hz, 1 F), δ_F −164.2 (m, 2 F), δ_H 2.03 (t, $^3J_{FH}$ = 13.5 Hz); mass spectrum calcd for $C_8H_3F_7O$ m/z 248.0072, found m/z 248.0072; m/z 249 (M^+ + 1, 2), 248 (M^+, 21), 233 (24), 229 (6), 184 (100), 167 (18), 155 (10), 136 (14), 117 (14), 65 (43).

Fluorination of Methyl 2-Nitrophenyl Ketone (1d). Procedure B: 24 h; 170 mg (84%) of **1,1-difluoroethyl 2-nitrophenyl ether (2d)** was isolated by preparative TLC (SiO_2, petroleum ether–methylene chloride, 2:1) as an oily product; NMR ($CDCl_3$) δ_F −65.3 (q, $^3J_{FH}$ = 13.5 Hz), δ_H 2 (t, $^3J_{FH}$ = 13.5 Hz, 3 H), δ_H 7.5 (m, 3 H), δ_H 7.95 (m, 1 H); mass spectrum calcd for $C_8H_7NO_3F_2$ m/z 203.0394, found m/z 203.0400; m/z 204 (M^+ + 1, 2), 203 (M^+, 26), 139 (100), 122 (11), 109 (11), 93 (10), 81 (12), 65 (67), 64 (13), 63 (15).

Fluorination of Benzophenone (3a). Procedure A: 1 mmol of ketone; the crude reaction mixture was separated by preparative TLC (SiO_2, n-hexane–methylene chloride, 1:1), 0.62 mmol of **3a** was recovered, and 46 mg (21%) of **α,α-difluorobenzyl phenyl ether (4a)** was isolated as an oily product; NMR ($CDCl_3$) δ_F −65.7 (br s), δ_H 7.4 (m); mass spectrum calcd for $C_{13}H_{10}F_2O$ m/z 220.0699, found m/z 220.0700; m/z 221 (M^+ + 1, 5), 220 (M^+, 40), 128 (17), 127 (100), 77 (26).

Fluorination of 4-Nitrophenyl Phenyl Ketone (3b). Procedure A: 1 mmol of ketone; the crude reaction mixture was separated by preparative TLC (SiO_2, methylene chloride–petroleum ether, 2:1), 0.67 mmol of **3b** was recovered, and 26.5 mg (20%) of **α,α-difluoro-4-nitrobenzyl phenyl ether (4b)** was isolated as a crystalline product, mp 43–46 °C; NMR ($CDCl_3$) δ_F −66 (s), δ_H 7.2 (br s, 5 H), δ_H 7.85 (d, $^3J_{HH}$ = 9 Hz, 2 H), δ_H 8.3 ppm (d, $^3J_{HH}$ = 9 Hz, 2 H); mass spectrum calcd for $C_{13}H_9F_2NO_3$ m/z 265.0550, found m/z 265.0550; m/z 266 (M^+ + 1, 5), 265 (M^+, 32), 172 (100), 142 (18), 127 (10), 126 (59), 125 (22), 114 (53), 77 (21), 76 (12), 75 (19), 65 (28), 63 (10), 51 (17), 50 (15), 39 (28).

Fluorination of Decafluorobenzophenone (3c). Procedure B: 90 h; the crude reaction mixture was separated by preparative TLC (SiO_2, petroleum ether–methylene chloride, 3:1), 0.67 mmol of **3c** was recovered, and 20 mg (5%) of **perfluorobenzyl phenyl ether (4c)** was isolated as an oily product; NMR ($CDCl_3$) δ_F −63.2 (m, 2 F), δ_F −139.2 (m, 2 F), δ_F −148 (m, 1 F), δ_F −151.3 (m, 2 F), δ_F −156.2 (t, $^3J_{FF}$ = 21.5 Hz, 1 F), δ_F −160.5 (m, 2 F), δ_F −162.2 (m, 2 F); mass spectrum calcd for $C_{13}F_{12}O$ m/z 399.9757, found m/z 399.9760; m/z 400 (M^+, 3), 381 (4), 218 (9), 217 (100), 167 (9), 155 (9), 117 (16).

Fluorination of 2,2-Difluoro-1,3-diphenylpropane-1,3-dione (5). Procedure C: the crude reaction mixture was separated by preparative TLC (SiO_2, petroleum ether–methylene chloride, 3:1), followed by preparative GLC (DEGS 12%, Chromosorb W/AW 80/100, T = 170 °C), 0.52 mmol of **5** was recovered; 41 mg (14%) of 1,1,2,2-tetrafluoro-3-oxo-3-phenylpropyl phenyl ether (**6**), 15.8 mg (5%) of 1,1,2,2-tetrafluoro-3-oxo-3-phenylpropyl fluorophenyl ether (**7**), and 10 mg (3%) of 1,1,2,2,3,3-hexafluoro-1,3-diphenoxypropane (**8**) were isolated.

1,1,2,2-Tetrafluoro-3-oxo-3-phenylpropyl phenyl ether (6): oily product; NMR ($CDCl_3$) δ_F −83.7 (t, $^3J_{FF}$ = 4.5 Hz, 2 F), δ_F −115 (t, $^3J_{FF}$ = 4.5 Hz, 2 F), δ_H 7.05 (m, 5 H), δ_H 7.4 (m, 3 H), δ_H 8.0 (m, 2 H); mass spectrum calcd for $C_{15}H_{10}F_4O_2$ m/z 298.0616, found m/z 298.0610; m/z 298 (M^+, 5), 105 (100), 77 (40), 51 (13).

1,1,2,2-Tetrafluoro-3-oxo-3-phenylpropyl fluorophenyl ether (7): oily product; NMR ($CDCl_3$) δ_F −84.2 (t, $^3J_{FF}$ = 4.5 Hz, 2 F), δ_F −115.3 (m, 3 F), δ_H 7.2 (m, 5 H), δ_H 7.6 (m, 3 H), δ_H 8.2 (m, 2 H); mass spectrum calcd for $C_{15}H_9F_5O_2$ m/z 316.0523, found m/z 316.0530; m/z 316 (M^+, 6), 106 (10), 105 (100), 95 (10), 77 (41), 51 (20).

1,1,2,2,3,3-Hexafluoro-1,3-diphenoxypropane (8): oily product; NMR ($CDCl_3$) δ_F −83.7 (t, $^3J_{FF}$ = 3 Hz, 4 F), δ_F −129.2 (pentet, $^3J_{FF}$ = 3 Hz, 2 F), δ_H 7.3 (br s); mass spectrum calcd for $C_{15}H_{10}F_6O_2$ m/z 335.9880, found m/z 335.9880; m/z 337 (M^+ + 1, 14), 336 (M^+, 82), 143 (7), 77 (100), 65 (14), 51 (11).

Fluorination of 1-Indanone (9a). Procedure A: 2 mmol of ketone; the crude reaction mixture was separated by preparative TLC (SiO_2, petroleum ether–methylene chloride, 3:1), 1.45 mmol of **9a** was recovered, and 31 mg (18%) of **2,2-difluoro-3,4-dihydro-2*H*-1-benzopyran (10a)** was isolated as an oily product; NMR ($CDCl_3$) δ_F −70.2 (t, $^3J_{FH}$ = 9 Hz), δ_H 2.32 (tt, $^3J_{FH}$ = 9 Hz, $^3J_{HH}$ = 7 Hz, 2 H), δ_H 3.0 (t, $^3J_{HH}$ = 7 Hz, 2 H), δ_H 7.3 (m, 4 H); mass spectrum calcd for $C_9H_8F_2O$ m/z 170.0543, found m/z 170.0540; m/z 171 (M^+ + 1, 10), 170 (M^+, 100), 169 (14), 151 (12), 149 (26), 106 (30), 86 (11), 84 (18), 78 (58), 77 (17), 51 (20), 39 (16).

Fluorination of 2-Fluoro-1-indanone (9b). Procedure C: the crude reaction mixture was separated by preparative GLC (DEGS 12%, Chromosorb W/AW 80/100, T = 110 °C and 170 °C), 0.25 mmol of **9b** was recovered, and 48.8 mg (24%) of 2,2,3-trifluoro-3,4-dihydro-2*H*-1-benzopyran (**10b**) and 32.8 mg (16%) of 2,2,3,6-tetrafluoro-3,4-dihydro-2H-1-benzopyran (**11b**) were isolated.

2,2,3-Trifluoro-3,4-dihydro-2*H*-1-benzopyran (10b): oily product; NMR ($CDCl_3$) δ_F −79.2 (dddd, $^2J_{FF}$ = 160 Hz, $^3J_{FF}$ = 9.5 Hz, $^3J_{FH}$ = 5 Hz, $^4J_{FH}$ = 2.5 Hz, 1 F), δ_F −87.7 (dddd, $^2J_{FF}$ = 160 Hz, $^3J_{FF}$ = 18 Hz, $^3J_{FH}$ = 5 Hz, $^4J_{FH}$ = 2.5 Hz, 1 F), δ_F −197.8 (m, 1 F), δ_H 3.2 (dm, $^3J_{FH}$ = 25 Hz, 2 H), δ_H 4.95 (ddt, $^2J_{FH}$ = 48 Hz, $^3J_{FH}$ = 5 Hz, $^3J_{HH}$ = 5 Hz, 1 H), δ_H 6.98 (m, 4 H); mass spectrum calcd for $C_9H_7F_3O$ m/z 188.0344, found m/z 188.0345; m/z 189 (M^+ + 1, 10), 188 (M^+, 100), 149 (6), 106 (13), 78 (29).

2,2,3,6-Tetrafluoro-3,4-dihydro-2*H*-1-benzopyran (11b): crystalline product, mp 59–60 °C; NMR ($CDCl_3$) δ_F −78.8 (dddd, $^2J_{FF}$ = 160 Hz, $^3J_{FF}$ = 9.5 Hz, $^3J_{FH}$ = 4.5 Hz, $^4J_{FH}$ = 3 Hz, 1 F), δ_F −87.9 (dddd, $^2J_{FF}$ = 160 Hz, $^3J_{FF}$ = 17 Hz, $^3J_{FH}$ = 4.5 Hz, $^4J_{FH}$ = 3 Hz, 1 F), δ_F −119 (ddd, $^3J_{FH}$ = $^3J_{FH}$ = $^4J_{FH}$ = 6.5 Hz, 1 F), δ_F −197.5 (m, 1 F), δ_H 3.2 (dm, $^3J_{FH}$ = 25 Hz, 2 H), δ_H 4.98 (ddt, $^2J_{FH}$ = 48 Hz, $^3J_{FH}$ = $^3J_{HH}$ = 4.5 Hz, 1 H), δ_H 6.85 (m, 3 H); mass spectrum calcd for $C_9H_6F_4O$ m/z 206.0354, found m/z 206.0355; m/z 207 (M^+ + 1, 9), 206 (M^+, 100), 167 (7), 124 (34), 96 (51).

Fluorination of 2-Chloro-1-indanone (9c). Procedure C: the crude reaction mixture was separated by preparative GLC (DEGS 12%, Chromosorb W/AW 80/100, T = 110 °C and 170 °C), 0.35 mmol of **9c** was recovered, and 20.4 mg (10%) of 2,2-difluoro-3-chloro-3,4-dihydro-2*H*-1-benzopyran (**10c**) and 30.5 mg (14%) of 2,2,6-trifluoro-3-chloro-3,4-dihydro-2*H*-1-benzopyran (**11c**) were isolated.

2,2-Difluoro-3-chloro-3,4-dihydro-2*H*-1-benzopyran (10c): oily product; NMR ($CDCl_3$) δ_F −74.5 (dd, $^2J_{FF}$ = 153 Hz, $^4J_{FH}$ = 4 Hz, 1 F), δ_F −83.2 (ddd, $^2J_{FF}$ = 153 Hz, $^3J_{FH}$ = 7 Hz, $^4J_{FH}$ = 4 Hz, 1 F), δ_H 3.3 (m, 2 H), δ_H 4.4 (dt, $^3J_{FH}$ = $^3J_{HH}$ = 7 Hz, 1 H), δ_H 7.0 (m, 4 H); mass spectrum calcd for $C_9H_7ClF_2O$ m/z 204.0153, found m/z 204.0150; m/z 207 (M^+ + 3, 3), 206 (M^+ + 2, 33), 205 (M^+ + 1, 10), 204 (M^+, 100), 169 (33), 149 (29), 119 (43), 106 (19), 103 (28), 101 (14), 91 (37), 78 (48), 77 (17), 75 (13), 63 (15), 51 (22), 50 (12), 39 (10).

2,2,6-Trifluoro-3-chloro-3,4-dihydro-2*H*-1-benzopyran (11c): oily product; NMR ($CDCl_3$) δ_F −73.8 (dd, $^2J_{FF}$ = 153 Hz, $^4J_{FH}$ = 4 Hz, 1 F), δ_F −82.8 (ddd, $^2J_{FF}$ = 153 Hz, $^3J_{FH}$ = 7 Hz, $^4J_{FH}$ = 4 Hz, 1 F), δ_F −119 (ddd, $^3J_{FH}$ = $^3J_{FH}$ = $^4J_{FH}$ = 6.5 Hz, 1 F), δ_H 3.3 (m, 2 H), δ_H 4.4 (dt, $^3J_{FH}$ = $^3J_{HH}$ = 7 Hz, 1 H), δ_H 6.9 (m, 3 H); mass spectrum calcd for $C_9H_6ClF_3O$ m/z 222.0059, found m/z 222.0060; m/z 225 (M^+ + 3, 3), 224 (M^+ + 2, 32), 223 (M^+ + 1, 9), 222 (M^+, 100), 167 (20), 157 (26), 137 (47), 127 (12), 124 (20), 119 (11), 111 (28), 109 (39), 101 (12), 99 (12), 96 (35), 75 (33), 74 (11), 51 (12), 50 (17).

Fluorination of 1-Tetralone (9d). Procedure A: 2 mmol of ketone; the crude reaction mixture was separated by preparative TLC (SiO_2, petroleum ether–methylene chloride, 3:1), 1.46 mmol of **9d** was recovered, and 33.7 mg (18%) of **2,2-difluoro-2,3,4,5-tetrahydro-2*H*-1-benzoxepin (10d)** was isolated as oily product; NMR ($CDCl_3$) δ_F −66.17 (t, $^3J_{FH}$ = 9.5 Hz), δ_H 2.0 (m, 4 H), δ_H 2.8 (m, 2 H), δ_H 7.1 (br s, 4 H); mass spectrum calcd for $C_{10}H_{10}F_2O$ m/z 184.0700, found m/z 184.0700; m/z 185 (M^+ + 1, 3), 184 (M^+, 29), 107 (100), 91 (11), 77 (13).

Fluorination of 1-Benzosuberone (9e). Procedure A: 2 mmol of ketone; the crude reaction mixture was separated by preparative TLC (SiO_2, petroleum ether–methylene chloride, 3:1), 1.48 mmol of **9e** was recovered, and 32 mg (16%) of **2,2-difluoro-3,4,5,6-tetrahydro-2*H*-1-benzoxocin (10e)** was isolated as oily product; NMR ($CDCl_3$) δ_F −68.3 (br s), δ_H 1.8 (m, 6 H), δ_H 2.82 (m, 2 H), δ_H 7.22 (br s, 4 H); mass spectrum calcd for $C_{11}H_{12}F_2O$ m/z 198.0856, found m/z 198.0850; m/z 199 (M^+ + 1, 9), 198 (M^+, 74), 178 (16), 158 (14), 133 (12), 131 (10), 121 (25), 108 (37), 107 (100), 94 (20), 91 (22), 78 (26), 77 (31), 51 (20), 39 (18).

Registry No. **1a**, 98-86-2; **1b**, 450-95-3; **1c**, 652-29-9; **1d**, 577-59-3; **2a**, 124382-13-4; **2b**, 124382-14-5; **2c**, 124382-15-6; **2d**, 124382-16-7; **3a**, 119-61-9; **3b**, 1144-74-7; **3c**, 853-39-4; **4a**, 114467-84-4; **4b**, 114467-81-1; **4c**, 53106-74-4; **5**, 365-00-4; **6**, 124382-17-8; **7**, 124382-18-9; **8**, 124382-19-0; **9a**, 83-33-0; **9b**, 700-76-5; **9c**, 1579-14-2; **9d**, 529-34-0; **9e**, 826-73-3; **10a**, 124382-20-3; **10b**, 124382-21-4; **10c**, 124382-23-6; **10d**, 124382-24-7; **10e**, 124382-25-8; **11b**, 124382-22-5; **11c**, 124382-26-9; XeF_2, 13709-36-9.

Regiocontrolled Reactions of 7-Desacetylforskolin. 2. Synthesis of 6- and 7-Carbamate Derivatives[1,2]

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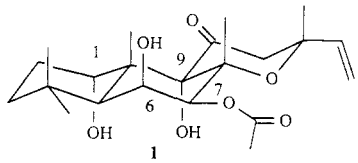
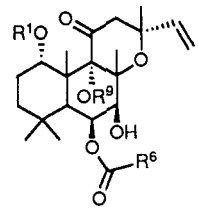
Forskolin (1), a labdane diterpene isolated from the Indian plant *Coleus forskohlii*,[3,4] exhibits unique biological activities attributed to the direct stimulation of adenylate cyclase.[5] The ability of forskolin to enhance c-AMP availability represents a novel therapeutic approach to the treatment of congestive heart failure. Although forskolin displays cardiotonic activity, poor aqueous solubility and insufficient metabolic stability are limitations for clinical applications. As part of a program directed toward the preparation of forskolin-based cardiotonics with improved stability and aqueous solubility, we report regiospecific manipulations which permit the selective preparation of a variety of carbamates and functionalized carbamates at either the 6- or 7-hydroxy positions of forskolin.



1

Recently, we reported[2] selective procedures for acylation at the 1- or 7-positions of the forskolin nucleus. The 1,9-dimethylformamide acetal moiety was introduced for protection of the 1- and 9-hydroxy groups of this system. For the present work, the 1,9-(dimethylformamide acetal) **2** of 7-desacetylforskolin (7-DAF) also served as an ideal starting material (Scheme I). In general, it is known that equatorial alcohols are less hindered than axial alcohols with respect to acylation,[6] and indeed the equatorial 7-hydroxy group of the labdane nucleus was reported[2] to be substantially less hindered and therefore more reactive than the axial 6-hydroxy group. Reaction of **2** with 1,1'-carbonyldiimidazole (CDI) in methylene chloride afforded the acylimidazole intermediate **3**, which upon reaction with pyrrolidine provided 7-desacetyl-7-(1-pyrrolidinocarbonyl)forskolin 1,9-(dimethylformamide acetal) (**4**) in 91% yield with complete regiospecificity. Hydrolysis of **4** in aqueous methanol at 60 °C removed the 1,9-(dimethylformamide acetal) protecting group to give the 7-(1-pyrrolidino) carbamate **5**. This method of carbamate formation offers advantages over the use of isocyanates or carbamoyl chlorides in that the conditions are milder and a wider variety of carbamates may be prepared from **3** using various primary or secondary amines.

Table I



compd	R^1, R^9	R^6	method[a]	yield,[b] %
6a	$N(CH_3)_2$		A B	82 87 (74)[c]
6b	$N(CH_3)_2$	$NHCH_2CH_2OH$	B	80 (68)[c]
6c	$N(CH_3)_2$	$NHNH_2$	A	75
6d	$N(CH_3)_2$	$NH(CH_2)_3N(CH_3)_2$	A	77
8a	H, H		C	50
8b	H, H	$NHCH_2CH_2OH$	C	62

[a] Method A: one-pot reaction from **2**. Method B: reaction from isolated 6,7-carbonate **7**. Method C: $MeOH/H_2O$, 60 °C. [b] Yields are for isolated material of analytical purity. [c] Yields in parentheses are for two steps from **2**.

The reported O to O acylmigration of forskolin esters from the 7- to the 6-position in the presence of alumina[7] or under basic conditions,[2] prompted investigation of the possible rearrangement of the corresponding 7-carbamate derivatives. When a solution of **4** in *tert*-butyl alcohol/THF was treated with an excess of potassium *tert*-butoxide, a rearrangement occurred at 0 °C to provide the 6-(1-pyrrolidino) compound **6a** in 73% yield. Structural assignments of the two isomers were based on the ^1H NMR chemical shifts of the C-6 and C-7 protons.[8]

A direct regiospecific route to the 6-carbamate derivatives **6** and **8** from the 6,7-cyclic carbonate derivative **7** was also developed. The reaction of simple aliphatic and carbohydrate cyclic carbonates with amines has been reported; however, mixtures of carbamates are generally obtained.[9,10] Treatment of acylimidazole intermediate **3** with a hindered nonnucleophilic base such as triethylamine afforded the 6,7-carbonate **7** in 85% yield. Subsequent reaction of **7** with pyrrolidine provided 7-desacetyl-6-(1-pyrrolidinocarbonyl)forskolin 1,9-(dimethylformamide acetal) (**6a**) in 87% yield (method B). In practice, higher yields are achieved by performing the reaction sequence in one step from **2** via the in situ formation of the 6,7-carbonate **7** and treatment with amines to give the protected carbamates **6** (method A). The dimethylformamide protecting group may be removed under the same mild

(1) Dedicated to Prof. Dr. rer. nat. Wolfgang Hilger, Chairman of Hoechst A.G., in honor of his 60th birthday.
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(8) Assignment of the C6 vs C7 protons can be made by the homonuclear off-resonance decoupling of the C5 proton. For **4**, irradiation of the C5 proton at 2.28 ppm caused the broad multiplet at 4.57 ppm (C6) to sharpen to a doublet of doublets. When the C5 proton of **6** (2.40 ppm) is decoupled, the triplet at 5.78 ppm became a sharp doublet.
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