(methoxycarbonyl)-4-[*N*-benzyl-*N*-[2-(benzylamino)-ethyl]amino]-5(*E*)-[[1,2-bis(methoxycarbonyl)vinyl]thio]-7,7-dimethyl-7*H*-benzo[*b*]thiopyran (10a*E*) was obtained as a red semisolid material (0.018 g, 37% yield): ^{1}H NMR spectral data are given in Table II; MS (CI-CH_4) 704 (M^+, 57), 434 (100), 295 (75), 145 (72), 91 (60); high-resolution MS (M^+) found 704.2222, calcd for $C_{37}H_{40}N_2O_8S_2$ 704.2226; UV (EtOH) 446 (2100), 340s (5500), 268 (12800), 242 (14000), 204 (35000). When a similar reaction was performed with a solution of 8a*Z* (0.045 g) and concd HCl (5.4 μL) in acetonitrile (300 mL), 10a*Z* was obtained, also as an amorphous red material that could be induced to crystallize (mp 100–102 °C, 0.037 g, 82% yield): MS (CI-CH_4) 704 (M^+, 30), 466 (38), 450 (43), 434 (100), 253 (38); high-resolution MS (M^+) found 704.2239, calcd for $C_{37}H_{40}N_2O_8S_2$ 704.2226; UV (EtOH) 450 (1050), 267 (10200), 245 (11200), 205 (28000).

As discussed previously, a mixture of 10b*E* and 10b*Z* was obtained in the chromatographic workup after the reaction of 5b with DMAD. The yield was as high as 22% in some experiments. These compounds may have been formed in silica-catalyzed ring opening of the spiro compounds 8b*E* and 8b*Z*. Repeated chromatography gave no complete separation, but the NMR spectral data of the individual compounds could be extracted from spectra of the mixtures (Table II): MS (CI-NH_3) 553 (M + 1, 100); high-resolution MS (M^+) found 552.1610, calcd for $C_{25}H_{32}N_2O_8S_2$ 552.1600.

Hydrolysis of 8a*E* and 8a*Z*. In a typical experiment, a solution of 8a*E* (0.070 g) and concd HCl (0.8 μL) in 96% aqueous methanol (100 mL) was left for 52 h at ambient temperature. After evaporation and chromatographic workup as in the previous text, two isomeric compounds $C_{21}H_{22}O_9S_2$ were isolated in quantities of 0.013 and 0.018 g. The NMR spectral data conform with structures 13*E* and 14*E*. Besides, a quantity of 10a*E* was obtained (0.023 g). The hydroxylic proton resonance of 14*E* has not been located, possibly because of exchange with acidic impurities, but the framework of this compound follows from the ^{1}H and ^{13}C NMR spectra and from the observation that a dry sample of 14*E* after standing for some months had been transformed to 13*E*. A similar experiment with 8a*Z* over 48 h gave 13*Z* (25% yield) and 14*Z* (60% yield) together with 10a*Z* (15% yield). **2,3-Bis(methoxycarbonyl)-5(*E*)-[[1,2-bis(methoxycarbonyl)-vinyl]thio]-7,7-dimethyl-7,8-dihydrobenzo[*b*]thiopyran-4-one (13*E*)**: ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 6 H), 2.54 (s, 2 H), 3.72 (s, 3 H), 3.78 (s, 3 H), 3.95 (s, 6 H), 6.03 (s, 1 H), 6.25 (s, 1 H); MS (CI-NH_3) 500 (M^+ + 18, 100), 483 (M^+ + 1, 78), 341 (15), 52 (18); high-resolution MS (M^+) found 482.0701, calcd for $C_{21}H_{22}O_9S_2$ 482.0705. The enol analogue 14*E*: ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 6 H), 3.71 (s, 3 H), 3.79 (s, 3 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 5.43 (d, 1 H, J = 1.8 Hz), 6.23 (d, 1 H, J = 1.8 Hz), 5.95 (s, 1 H); MS (CI-NH_3) 500 (M^+ + 18, 100), 483 (M^+ + 1, 45), 391 (100), 342 (58), 194 (59), 178 (92); high-resolution MS (M^+) found 482.0687, calcd for $C_{21}H_{22}O_9S_2$ 482.0705. 13*Z*: ^{1}H NMR ($CDCl_3$) δ 1.02 (s, 6 H), 2.50 (s, 2 H), 3.74 (s, 6 H), 3.86 (s, 6 H), 5.79 (s, 1 H), 6.57 (s, 1 H); MS (16 eV) 482 (M^+, 100), 92 (68), 56 (59). The 4-hydroxy analogue 14*Z*: ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 6 H), 3.78 (s, 3 H), 3.79 (s, 6 H), 3.85 (s, 3 H), 5.39 (d, 1 H, J = 1.8 Hz), 6.00 (d, 1 H, J = 1.8 Hz), 6.43 (s, 1 H); MS (16 eV) 482 (M^+, 15), 433 (100), 275 (68), 262 (33). In one experiment with 8a*Z* in ethanol over 36 h a 25% yield of the ethoxy derivative 15*Z* was also isolated: ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 6 H), 1.26 (t, 3 H), 3.77 (s, 3 H), 3.79 (s, 6 H), 3.84 (s, 3 H), 3.88 (q, 2 H), 5.38 (d, 1 H, J = 1.9 Hz), 5.99 (d, 1 H, J = 1.9 Hz), 6.43 (s, 1 H); MS (16 eV) 510 (M^+, 30), 495 (100), 339 (15), 335 (22), 101 (23). All compounds 13–15 were obtained as noncrystalline materials. The elemental analyses (C, H, N, S) were accurate to within ± 0.4%.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of 8b*E*, 8b*Z*, 15*Z*, and 28. ^{1}H NMR spectra of 13*Z* and 14*Z*. Tables of ^{13}C NMR chemical shifts for 8a*E*, 8a*Z*, 8b*E*, and 8b*Z* (Table Ib), for 10a*E*, 10a*Z*, 10b*E*, 10b*Z*, and 12b*Z* (Table IIb), and for 19 and 28 (Table V). 2D INADEQUATE spectra of 23 in the ranges δ 117–169 (Figure 3) and 119–127 (Figure 4). Detailed description of INADEQUATE experiments. Tables of fractional atomic positional coordinates and equivalent isotropic displacement coefficients for non-hydrogen atoms (Table III), of physical properties and parameters for data collection and refinement (Table IV), of bond lengths (Table VII), of bond angles (Table VIII), of anisotropic displacement coefficients (Table IX), and of H atom coordinates (Table X). Superpositon of the crystal structures of 8a*E* (- - -) and 8a*Z* (—) (Figure 1a), stereo pictures of 8a*E* (Figure 1b) and 8a*Z* (Figure 1c), and a picture of 8a*Z* with numbers (Figure 1e) (47 pages). Ordering information is given on any current masthead page.

N-Fluorobis[(trifluoromethyl)sulfonyl]imide: An Efficient Reagent for the α-Fluorination of Functionalized Carbonyl Compounds

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The *N*-fluorobis[(trifluoromethyl)sulfonyl]imide (1) has been used in the electrophilic fluorination of the lithium enolate of esters, amides, and ketones. The corresponding α-fluorocarbonyl compounds have been obtained in good yields. The α-fluorination of β-diesters, β-diamides, β-keto esters, and β-diketones has been performed either on the neutral compounds or on the metal enolates. In this way some geminal azafluoro, chlorofluoro, fluorooxy compounds have been prepared in nearly quantitative yields. Also some α-keto esters and acids have been selectively monofluorinated in the β-position by simple treatment of the neutral compound with 1.

Introduction

A fluorine atom is frequently used to replace a hydrogen atom (isosteric substitution) or a hydroxyl group (isopolar substitution) in an organic molecule. This is due to the fact that such a replacement imparts specific and often useful properties to the compound with respect to those of the parent, unfluorinated product. Selectively fluorinated substances are finding increasing applications in analytical,[2] biological,[3] and medicinal chemistry.[4] Re-

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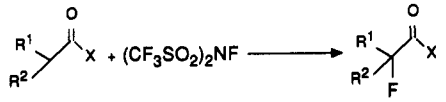
Scheme I



2 a-k 1 3 a-k

Starting Material	R^1	R^2	X	Isolated Yields (%)
2a	H	H	$OCH_2C_6H_5$	76
2b	H	C_2H_5	OC_2H_5	63 [8b]
2c	H	C_6H_5	OC_2H_5	71 [8c]
2d	CH_3	C_6H_5	OC_2H_5	83
2e	C_2H_5	C_6H_5	OC_2H_5	70
2f	H	C_6H_5	$N(i\text{-}C_3H_7)_2$	87
2g	CH_3	C_6H_5	$N(i\text{-}C_3H_7)_2$	85
2h	C_2H_5	C_6H_5	$N(i\text{-}C_3H_7)_2$	70
2i	H	H	C_6H_5	86 [8c]
2k	C_6H_5	C_6H_5	CH_3	81

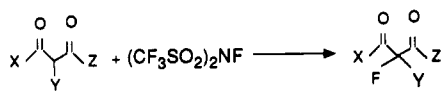
cently, they have become of interest also for the chemistry of polymers[5] and materials.[6]

The synthesis of strategically fluorinated compounds is therefore an important focus of current research, but it remains a difficult task. The introduction of (diethylamino)sulfur trifluoride (DAST) and of the related tris(dialkylamino)sulfonium difluorotrimethylsilicate (TASF)[7] represented major breakthroughs in nucleophilic fluorination, but there is still a demand for a safe, mild, and efficient reagent for electrophilic fluorination.

Most of the agents that are a source of electrophilic fluorine are in fact highly aggressive and sometimes explosive, toxic, unstable, and hygroscopic.[8] Furthermore, they have a limited shelf-life, if any. Recently, some compounds containing the NF functionality[9] have been developed as alternatives for these potentially hazardous reagents. Previous studies from this laboratory have shown how the *N*-fluorobis[(trifluoromethyl)sulfonyl]imide (1) can be synthesized in very high yields by treating the corresponding imide with fluorine.[10] This *N*-fluoro compound 1 was shown to be effective in replacing hydrogen with fluorine in a variety of aromatic compounds and to be excellent for the fluorination of selected carbanions.

Here we report how 1 can be used for the efficient α-monofluorination of several carbonyl substrates having quite different functional groups.

Scheme II



4 a-e 1 5 a-e

Starting Material	X	Z	Y	Isolated Yields (%)
4a	CH_3	OC_2H_5	Cl	95
4b	CH_3	OC_2H_5	$OCOCH_3$	85
4c	CH_3	CH_3	Cl	95
4d	OC_2H_5	OC_2H_5	NO_2	90
4e	$-NCH_2N-$ (CH_3, CH_3)		H	95 (Y=F in 5e)

Results and Discussion

Fluorination of Monocarbonyl Compounds. The lithium enolate of esters, amides, and ketones **2a–i** (generated by standard procedure using lithium diisopropylamide in tetrahydrofuran (THF)) were selectively monofluorinated when treated with the *N*-fluoroimide 1. The fluorination site can carry alkyl and/or aryl residues and can be a methyl group (benzyl acetate (**2a**), acetophenone (**2i**)), a methylene group (ethyl butyrate (**2b**), ethyl phenylacetate (**2c**), *N,N*-diisopropyl-2-phenylacetamide (**2f**)), or a methine group (ethyl 2-phenylpropionate (**2d**), ethyl 2-phenylbutyrate (**2e**), and corresponding *N,N*-diisopropylamides **2g,h**) carbon. ^{19}F NMR spectra of product mixtures showed that the formation of α,α-difluorocarbonyl derivatives never occurred. No hydrolysis of the ester or amide groups was also observed[8b] and α-fluorocarbonyl products **3a–i** were thus obtained in medium to high yields. The reactions are summarized in Scheme I.

Presently, the α-fluorination of esters, amides, and ketones has been performed in most cases by treating a preformed derivative of the carbonyl substrate (e.g. enol acetates,[8g,9e] enol silyl ethers,[8b,c] enamines,[9b,d] enol ethers,[9f] ...) with the fluorinating reagent. When the direct fluo-

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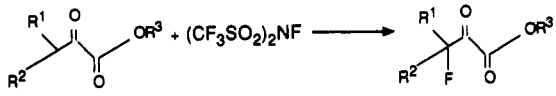
Scheme III



6a-c 1 7a-c

Starting Material	R^1	R^2	R^3	Isolated Yields (%)
6a	CH_3	CH_3	C_2H_5	95 [13]
6b	CH_3	C_2H_5	H	95
6c	H	CH_3	H	95

rination of metal enolates was attempted,[9i] rather low yields have been obtained. On the contrary, our quick, one-step procedure allows the direct fluorination of the carbonyl compound as it works on the metal enolate formed in situ. The tedious preparation of a suitable enolic derivative of the substrate can thus be avoided.

The fluorination reaction of 1,1-diphenylacetone (**2k**) is particularly noteworthy. For this substrate it was not necessary to form the lithium enolate before the treatment with **1** as the fluorination proceeded smoothly on the neutral compound, apparently as a consequence of the easy enolization of this ketone.[11] The high effectiveness of the *N*-fluoroimide **1** in reactions involving the enolic form of a carbonyl substrate is thus evident.

Fluorination of Dicarbonyl Compounds. The monofluorination of the sodium salt of diethyl 2-methylmalonate has already been reported.[10] Following a similar procedure, diethyl 2-nitromalonate (**4d**) has been fluorinated in high yields by treating its lithium salt with the *N*-fluoroimide **1** in THF solution. The direct fluorination of the neutral compound proceeded very slowly (2% yield after 10 days). Differently, β-keto esters and β-diketones, whose enolization is easier than that of β-diesters, did not require the preliminary metallation. Ethyl 2-chloroacetoacetate (**4a**), its 2-acetoxy analogue (**4b**), and 3-chloro-2,4-pentanedione (**4c**) have been fluorinated in quantitative yields by simple treatment with **1** in chloroform solution. The reaction however can be performed in several other solvents. Hydrocarbons (*n*-hexane, *n*-pentane), halogenated compounds (dichloromethane, carbon tetrachloride, 1,1,2,2-tetrachloroethane, Freon-11), ethers (diethyl ether, THF), and polar products (acetonitrile, benzonitrile) were equally effective solvents in the fluorination of **4a**. In all cases the products **5** have been obtained in quantitative yield after approximately 1 h as summarized in Scheme II. Interestingly, 1,3-dimethylbarbituric acid (**4e**) was fluorinated in chloroform solution without preliminary formation of the salt. By employing 2 equiv of **1** the difluoro derivative **5e** was exclusively formed in very high yield.

No metalation has been required for the β-fluorination of α-keto acids and esters **6** (Scheme III). Ethyl 3-methyl-2-oxobutyrate (**6a**) and 3-methyl-2-oxopentanoic acid (**6b**) gave the corresponding β-fluoro derivatives **7a,b** in quantitative yields. 3-Fluoro-2-oxobutyric acid (**7c**) was exclusively formed by treating 2-oxobutyric acid (**6c**) with an equimolar amount of the fluorinating agent **1**. ^{19}F NMR of the crude reaction mixture did not show the presence of 3,3-difluoro-2-oxobutyric acid. Thus the selective monofluorination of a substrate that could undergo a difluorination process was realized.

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Reactions on α-dicarbonyl compounds are quite slow at room temperature and at the beginning they are accelerated by the presence of trace amounts of strong acids (H_2SO_4), probably as the enolization process is thus favored. In this respect, however, the reaction can be considered "autocatalytic": the byproduct of fluorination is the bis[(trifluoromethyl)sulfonyl]imide, which is known to be a super acid.[12] This procedure secures an easy access to the β-fluoro-α-keto acid moiety, which is very useful from a synthetic point of view, but difficult to prepare.[13] The *N*-fluoroimide **1** works on substrates on which the use of molecular fluorine failed.[14]

Conclusions

Although the *N*-fluoroimide **1** requires the use of elemental fluorine for its preparation, this perceived disadvantage by some is more than offset by its versatility and effectiveness as an electrophilic fluorinating reagent of several carbonyl substrates. The lithium enolates of esters, amides, and ketones affords the α-fluorination products in yields generally higher than those reported in the literature for related reactions. The direct fluorination of neutral compounds can be performed when their enolization is reasonably easy (e.g. α- and β-dicarbonyl products). This allowed the high-yield fluorination of α-chloro-β-dicarbonyl substrates, which would hardly survive a metalation step. The fluorinated carbon can carry hydrogen, alkyl, aryl, chlorine, fluorine, nitrogen, and oxygen residues.

The *N*-fluoroimide appears to be much more reactive than some other *N*-fluoro reagents, which, for instance, fluorinate only the salt of β-keto esters.[9d,g] At the same time it is a very mild agent as 3-chloro-3-fluoro-2,4-pentanedione (**5c**) was prepared in quantitative yield and also the very labile ethyl 2-acetoxy-2-fluoroacetoacetate (**5b**) was synthesized in high yield.

Another very useful property of **1** is its stability. It can be stored for years at room temperature, in Teflon vessels, and in the air without any decomposition. Reactions highly sensitive to the presence of impurities, such as the fluorination of the lithium enolates of esters, can be performed with complete success by using either fresh or aged reagent. Nearly the same reaction rates have been observed in the fluorination of ethyl 2-chloroacetoacetate (**4a**) when solvents having very different polarity (e.g. *n*-hexane and acetonitrile) have been employed. This fact leads us to think that although the *N*-fluoroamide **1** behaves as a source of positive fluorine ($F^{\delta+}$), a one-electron-transfer mechanism is operating. The electron-rich enolic form of **4a** may transfer one electron to the electron-deficient *N*-fluoroimide, followed by the homolytic fission of the NF bond of **1**, and the coupling of the fluorine radical with the radical cation of the substrate, and the final loss of a proton would lead to the fluorination product **5a**. A similar mechanism can obviously be extended to the fluorination of other α- and β-dicarbonyl compounds and to the metal enolates of monocarbonyl substrates.[15]

The employment of the *N*-fluoroimide **1** for the selective fluorination of several, differently functionalized organic compounds thus appears to be possible. The scope of the process is now being exploited in the synthesis of several pharmacologically active products.

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Experimental Section

Materials and Methods. All reactions were performed in standard glass apparatus. Lithium enolates were generated under a positive pressure of dry and oxygen-free N_2 in flasks equipped with rubber septa for the introduction of reagents via syringe. THF was freshly distilled from $LiAlH_4$ under N_2, and diisopropylamine was freshly distilled from CaH_2. In other cases commercially available, reagent-grade solvents were employed without purification. Flash column chromatography on silica gel was performed as described in the original paper.[16] Purity of all compounds was established by ^1H and ^{19}F NMR and additionally by ^{13}C NMR and mp, where appropriate. ^{19}F and ^1H NMR were recorded on an IBM NR200AF instrument and ^{13}C NMR on a Bruker AC300. $CDCl_3$ was used as a lock solvent and $CFCl_3$ and tetramethylsilane as internal references unless otherwise stated. The J values for the triplets and quartets from the ethoxy groups were determined to be ~7 Hz.

Fluorination of Monocarbonyl Compounds 2. General Procedure. A solution of the carbonyl compounds **2** (2.0 mmol) in THF (2.0 mL) was added with magnetic stirring and at −80 °C to a solution of LDA (prepared from diisopropylamine (2.2 mmol) and *n*-butyllithium (0.88 mL of a 2.5 M solution in hexanes, Aldrich) in the same solvent (2.0 mL). After 10 min at −80 °C the cooling bath was removed, and the solvent and diisopropylamine were removed under vacuum (2 mmHg) at 10–20 °C. The oily residue was diluted with THF (3.0 mL), the temperature was lowered at −80 °C, and a solution of the *N*-fluoroimide **1** (2.4 mmol) in the same solvent (1.0 mL) was added dropwise. After stirring for 10 min, a saturated aqueous solution of NH_4Cl was added (10 mL) all at once, and the mixture was diluted with water (5.0 mL) and extracted with ethyl acetate (3 × 15 mL). The collected organic phases were dried (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was flash chromatographed to give pure products **3**.

Benzyl fluoroacetate (3a) was prepared starting from benzyl acetate (**2a**); isolated yield 76%; eluting system for flash-chromatography *n*-hexane/diisopropyl ether, 9:1; ^1H NMR δ 4.83 (2 H, d, J = 47.1 Hz), 5.21 (2 H, s), 7.35 (5 H, br s); ^{19}F NMR δ −221.1 (t, J = 47.9 Hz); IR (film) 3028, 2946, 1761 (C=O) cm^{-1}; MS (EI) m/e 168 (M^+), 91, 77. **Ethyl 2-fluorobutanoate (3b)** was prepared starting from ethyl butyrate (**2b**); isolated yield 63%; eluting system for flash chromatography *n*-pentane/ethyl ether, 98:2, ^1H NMR δ 1.03 (3 H, t), 1.31 (3 H, t), 1.6–2.1 (2 H, m), 4.26 (2 H, q), 4.86 (1 H, ddd, J = 49.1, 6.7, 4.8 Hz, CHF); ^{19}F NMR δ −194.1 (dt, J = 49.5, 24.8 Hz) (^{19}F NMR δ −194.1, J = 49.1, 24.4, ref 8b); IR (film) 2972, 1747 (C=O) cm^{-1}; MS (CI) m/e 135 ($M^+ + 1$), 107. **Ethyl 2-fluoro-2-phenylacetate (3c)** was prepared starting from ethyl phenylacetate (**2c**); yield 71%; eluting system for flash chromatography *n*-hexane/ethyl ether, 9:1; ^1H NMR δ 1.24 (3 H, t), 4.23 (2 H, m), 5.77 (1 H, d, J = 47.8 Hz), 7.40 (5 H, br s); ^{19}F NMR δ −180.4 (d, J = 48.0 Hz) (^{19}F NMR δ −180.1, J = 48 Hz, ref 8c). **Ethyl 2-fluoro-2-phenylpropanoate (3d)** was prepared starting from ethyl 2-phenylpropionate (**2d**); isolated yield 83%; eluting system for flash chromatography *n*-hexane/diisopropyl ether, 98:2; ^1H NMR δ 1.22 (3 H, t), 1.91 (3 H, d, J = 22.0 Hz, CH_3CF), 4.19 (2 H, q), 7.2–7.6 (5 H, m); ^{19}F NMR δ −151.9 (q, J = 22.0 Hz); IR (film) 3056, 2980, 1740 (C=O), 1269, 1127 cm^{-1}; MS (EI) m/e 196 (M^+), 123, 103. **Ethyl 2-fluoro-2-phenylbutanoate (3e)** was prepared starting from ethyl 2-phenylbutyrate (**2e**); isolated yield 70%; eluting system for flash chromatography *n*-hexane/ethyl ether, 95:5; ^1H NMR δ 0.96 (3 H, t), 1.25 (3 H, t), 2.1–2.5 (2 H, m), 4.21 (2 H, q), 7.2–7.6 (5 H, m); ^{19}F NMR δ −167.7 (dd, J = 21.0, 27.0 Hz); IR (film) 3057, 2974, 1751 (C=O), 1251, 1133 cm^{-1}; MS (EI) m/e 210 (M^+), 122, 117, 109. ***N*,*N*-Diisopropyl-2-fluoro-2-phenylacetamide (3f)** was prepared starting from *N*,*N*-diisopropyl-2-phenylacetamide (**2f**); mp 86–88 °C; yield 87%; eluting system for flash chromatography *n*-pentane/ethyl acetate, 8:2; mp 86–88 °C; ^1H NMR δ 0.79 (3 H, d), 1.00 (3 H, d), 1.43 (3 H, d), 1.47 (3 H, d), 3.34 (1 H, septet), 3.83 (1 H, septet), 5.95 (1 H, d, J = 49.8 Hz), 7.3–7.5 (5 H, m); ^{19}F NMR δ −171.3 (d, J = 49.8 Hz); IR (Nujol) 1643 (C=O), 1456, 1031 cm^{-1}; MS (EI) m/e 237 (M^+), 222, 194, 160, 128, 109. ***N*,*N*-Diisopropyl-2-fluoro-2-phenylpropanamide (3g)** was prepared starting from *N*,*N*-diisopropyl-2-phenylpropionamide (**2g**); yield 85%; eluting system for flash chromatography *n*-hexane/ethyl ether, 8:2, mp 65–67 °C; ^1H NMR δ 0.50 (3 H, d), 1.08 (3 H, d), 1.44 (6 H, d), 1.76 (3 H, d, J = 23.9 Hz), 3.31 (1 H, septet), 4.07 (1 H, septet), 7.2–7.6 (5 H, m); ^{19}F NMR δ −151.3 (q, J = 23.7 Hz); IR (Nujol) 1644 (C=O), 1449, 1036 cm^{-1}; MS (EI) m/e 251 (M^+), 236, 231, 128, 123, 86. ***N*,*N*-Diisopropyl-2-fluoro-2-phenylbutyramide (3h)** was prepared starting from *N*,*N*-diisopropyl-2-phenylbutyramide (**2h**); isolated yield 70%; eluting system for flash chromatography *n*-hexane/diisopropyl ether, 85:15; mp 72–74 °C; ^1H NMR δ 0.49 (3 H, d), 1.09 (3 H, d), 1.41 (3 H, d), 1.43 (3 H, d), 2.00 (1 H, m), 2.35 (1 H, m), 3.30 (1 H, septet), 4.14 (1 H, septet), 7.2–7.6 (5 H, m); ^{19}F NMR δ −164.7 (t, J = 24.3 Hz); IR (Nujol) 1627 (C=O), 1445, 1038 cm^{-1}; MS (CI) m/e 266 ($M^+ + 1$), 246, 137, 128. **2-Fluoroacetophenone (3i)**: when the general procedure described above was employed for the fluorination of acetophenone (**2i**), 2-fluoroacetophenone (**3i**) was obtained in 11% yield. The main reaction product was 4-fluoro-3-hydroxy-1,3-diphenyl-1-butanone (**3j**): yield 82%; ^1H NMR δ 3.63 and 3.86 (2 H, AB system, CH_2CO), 4.34 and 4.62 (2 H, ddd, $J_{H,F}$ = 48 Hz, CH_2F), 5.05 (1 H, br s, OH); ^{19}F NMR δ −220.7 (t, J = 48.0 Hz); mass spectrum (CI), m/e 259 ($M^+ + 1$), 239, 225. However, when the THF solution of the lithium enolate of acetophenone (**2i**) (2.0 mmol) was added at −80 °C to a cooled solution of the *N*-fluoroimide **1** (6.0 mmol) the yield of 2-fluoroacetophenone (**3i**) was 86%: mp 26 °C; eluting system for flash chromatography: *n*-pentane/ethyl ether 9:1; ^1H NMR δ 5.52 (2 H, d, J = 47.0 Hz), 7.2–8.0 (5 H, m); ^{19}F NMR δ −231.5 (t, J = 46.2 Hz) (^{19}F NMR δ −231.9, J = 47 Hz, ref 8c); MS (EI) m/e 138 (M^+), 105, 77.

1-Fluoro-1,1-diphenylacetone (3k) was synthesized by direct treatment of 1,1-diphenylacetone (**2k**, 2.5 mmol) with the *N*-fluoroimide **1** (2.8 mmol) in $CHCl_3$ (4.0 mL) at 22 °C for 6.0 h: yield 81%; eluting system for flash chromatography *n*-pentane/ethyl ether, 96:4; ^1H NMR δ 2.42 (3 H, d, J = 5.8 Hz), 7.37 (10 H, br s); ^{19}F NMR δ −143.6 (q, J = 5.8 Hz); mass spectrum (CI), m/e 228 (M^+), 209, 185, 151.

Diethyl 2-Fluoro-2-nitromalonate (5d). A solution of LiH (5.2 mmol) and **4d** (4.0 mmol) was refluxed in THF (3.0 mL) for 6.0 h. The reaction mixture was cooled at 0 °C, and a solution of the *N*-fluoroimide **1** (6.0 mmol) in THF (3.0 mL) was added dropwise. The system was stirred at 22 °C for 30 min, saturated aqueous $NaHCO_3$ was added (6.0 mL), and the aqueous phase was extracted with ethyl ether (3 × 20 mL). The collected organic phases were dried (Na_2SO_4), the solvent was evaporated under reduced pressure, and the residue was flash chromatographed (*n*-hexane/ethyl acetate, 85:15) to give diethyl 2-fluoro-2-nitromalonate (**5d**) in 90% yield and in pure form: ^1H NMR δ 1.38 (3 H, t), 4.45 (2 H, q); ^{19}F NMR δ −127.26; ^{13}C NMR δ 13.70 (CH_3), 65.20 (CH_2O), 106.39 (d, $J_{C,F}$ = 261.5 Hz), 158.04 (d, $J_{C,F}$ = 26.2 Hz, CO); IR (film) 2983, 1766 (CO), 1349, 1073; mass spectrum (CI), m/e 224 ($M^+ + 1$), 178.

Fluorination of Dicarbonyl Compounds. General Procedure. A solution of the *N*-fluoroimide **1** (2.2 mmol) in ethanol-free $CHCl_3$ (2.0 mL) was added dropwise at 22 °C to a solution of the dicarbonyl substrate **4** or **6** (2.0 mmol) in the same solvent (2.0 mL). After the mixture was stirred for the time reported below for single compounds, the solvent was removed under reduced pressure and the residue was purified with flash chromatography on silica gel. **Ethyl 2-chloro-2-fluoroacetoacetate (5a)** was prepared starting from ethyl 2-chloroacetoacetate (**4a**); reaction time 1 h; eluting system for flash chromatography *n*-hexane/methylene chloride, 1:1; yield 95%; ^1H NMR δ 1.37 (3 H, t), 2.49 (3 H, d, J = 2.5 Hz), 4.41 (2 H, q); ^{19}F NMR δ −123.7 (d, J = 2.5 Hz); ^{13}C NMR δ 13.52 (CH_3), 23.69 (CH_3), 65.20 (CH_2O), 100.59 (d, $J_{C,F}$ = 263.5 Hz, CF), 163.52 (d, $J_{C,F}$ = 27.6 Hz, COO), 195.25 (d, $J_{C,F}$ = 27.8 Hz, CO); IR (film) 2980, 1761 (CO), 1366 cm^{-1}; MS (CI) m/e 183 and 185 ($M^+ + 1$), 155 and 157. Quantitative yields of **5a** were obtained and reaction times of 45–60 min were needed when **4a** was reacted with the *N*-fluoroimide **1** using as a solvent: *n*-hexane, *n*-pentane, CH_2Cl_2, CCl_4, 1,1,2,2-tetrachloroethane, Freon-11, acetonitrile, benzonitrile. **Ethyl 2-acetoxy-2-fluoroacetoacetate (5b)** was prepared starting from **4b**; reaction time 8 h; eluting system for flash chromatography: *n*-hexane/ethyl ether, 4:6; yield 85%; ^1H NMR

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δ 1.36 (3 H, t), 2.23 (3 H, s), 2.44 (3 H, d, J = 2.6 Hz), 4.35 (2 H, q); ^{19}F NMR δ −122.8 (d, J = 2.5 Hz); ^{13}C NMR δ 13.83 (CH_3), 20.36 (CH_3), 25.00 (CH_3), 64.40 (CH_2O), 102.14 (d, $J_{C,F}$ = 251.8 Hz, CF), 163.19 (d, $J_{C,F}$ = 30.2, COO), 168.86 (s, COO), 197.68 (d, $J_{C,F}$ = 30.7 Hz, CO). **3-Chloro-3-fluoro-2,4-pentanedione (5c)** was prepared starting from **4c**; reaction time 2 h; eluting system for flash chromatography n-hexane/CH_2Cl_2, 85:15; yield 95%, ^{1}H NMR δ 2.48 (d, J = 2.7 Hz); ^{19}F NMR δ −126.2 (septet, J = 2.7 Hz); ^{13}C NMR δ 24.95 (CH_3), 102.84 (d, $J_{C,F}$ = 269.6 Hz, CF), 197.48 (d, $J_{C,F}$ = 27.0 Hz, CO); IR (film) 2925, 1738 (CO) cm^{-1}; MS (CI) m/e 153 and 155 (M^+ + 1). **1,3-Dimethyl-5,5-difluorobarbituric acid (5e)** was prepared starting from 1,3-dimethylbarbituric acid (**4e**) and 2.2 equiv of 1; acetonitrile was used as reaction solvent; reaction time 6 h; eluting system for flash chromatography n-hexane/ethyl acetate 7:3; yield 95%; mp 125–127 °C; ^{1}H NMR δ 3.40 (s); ^{1}H NMR (CD_3CN) δ 3.26 (t, J = 0.5 Hz); ^{19}F NMR δ −108.7; ^{13}C NMR (CD_3CN) δ 29.64 (CH_3), 99.61 (t, $J_{C,F}$ = 245.5 Hz, CF_2), 150.35 (NCON), 160.97 (t, $J_{C,F}$ = 27.8 Hz, $COCF_2$); IR (Nujol) 1687 (CO), 1448, 1304 cm^{-1}; MS (EI) m/e 192 (M^+), 176, 135, 107, 78.

Ethyl 3-fluoro-3-methyl-2-oxobutanoate (7a) was prepared starting from **6a**; reaction time 27 h; eluting system for flash chromatography n-hexane/ethyl ether, 6:4; yield 95%; ^{1}H NMR δ 1.39 (3 H, t), 1.64 (6 H, d, J = 21.6 Hz), 4.41 (2 H, q); ^{19}F NMR δ −151.4 (septet, J = 21.3 Hz) (^{19}F NMR δ −152.0 (septet, J = 21.3 Hz, ref 13)); ^{13}C NMR δ 13.87 (CH_3), 24.14 (d, $J_{C,F}$ = 24.1 Hz, CH_3), 64.00 (CH_2O), 97.85 (d, $J_{C,F}$ = 177.9 Hz, CF), 164.08 (COO), 196.82 (d, $J_{C,F}$ = 35.3 Hz, CO), MS (CI) m/e 163 (M^+ + 1), 143. **3-Fluoro-3-methyl-2-oxopentanoic acid (7b)** was prepared starting from **6b**; $CHCl_3$ saturated with H_2SO_4 was used as reaction solvent; reaction time 24 h; eluting system for flash chromatography CH_2Cl_2/ethyl acetate/acetic acid, 50:50:0.5; yield 95%; ^{1}H NMR δ 0.98 (3 H, d, J = 21.8 Hz), 1.9–2.2 (2 H, m); ^{19}F NMR δ −160.1 (sextet, J = 21.5 Hz); ^{13}C NMR δ 7.05 (CH_3), 21.86 (d, $J_{C,F}$ = 23.2 Hz, CH_3), 30.39 (d, $J_{C,F}$ = 22.5 Hz, CH_2), 99.95 (d, $J_{C,F}$ = 182.0 Hz, CF), 163.5 (COOH), 195.5 (d, $J_{C,F}$ = 32.9 Hz, CO); IR (film) 3300–2500 (COOH), 1748, 1193 cm^{-1}; MS (EI) m/e 148 (M^+), 128, 121, 75. **3-Fluoro-2-oxobutanoic acid (7c)** was prepared starting from **6c**; reaction time 18 h; eluting system for flash chromatography CH_2Cl_2/ethyl acetate/acetic acid, 50:50:0.5; yield 95%; ^{1}H NMR (D_2O) δ 1.36 (3 H, dd, J = 6.3, 25.5 Hz, CH_3), 4.86 (1 H, dq, J = 6.3, 46.7 Hz, CHF); ^{19}F NMR (D_2O) δ −186.2 (dq, J = 25.6, 47.6 Hz); ^{13}C NMR (D_2O) δ 12.74 (d, $J_{C,F}$ = 21.6 Hz, CH_3), 90.97 (d, $J_{C,F}$ = 172.7 Hz, CF), 92.90 (d, $J_{C,F}$ = 23.4 Hz, OCO of the hydrated ketone), 171.92 (COOH).

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Supplementary Material Available: ^{1}H NMR spectra of all new compounds (15 pages). Ordering information is given on any current masthead page.

Synthesis of Synvinolin: Extremely High Conversion Alkylation of an Ester Enolate

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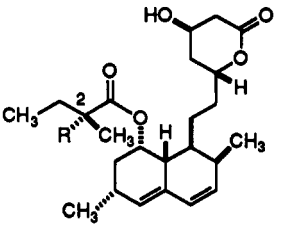
A efficient process for the commercial preparation of the therapeutically important cholesterol lowering drug synvinolin (2: simvastatin, ZOCOR) from mevinolin (1: lovastatin, MEVACOR) is reported. The synthesis relies upon deactivation of the δ-lactone carbonyl toward enolization via conversion to the bis[(*tert*-butyldimethylsilyl)oxy] butylamide 7. An extremely high conversion (99.7%) ester enolate alkylation of 7 affords 8 and 9. Subsequent desilylation and intramolecularly assisted basic amide hydrolysis in the presence of the dimethylbutyrate ester moiety yields 12, which is lactonized to 2. The overall yield from 1 to 2 is 86%.

Introduction

The naturally occurring fungal metabolite mevinolin (1: lovastatin, MEVACOR)[1,2] and the more active semisynthetic derivative[3] synvinolin (2: simvastatin, ZOCOR)[3b] are pharmacologically useful compounds for the lowering of serum cholesterol levels.[4] Although several methods



1 R = H Mevinolin (Lovastatin, MEVACOR®)

2 R = CH_3 Synvinolin (Simvastatin, ZOCOR®)

are available for conversion of 1 to 2, all are complicated by the inability to remove even trace amounts of 1 from

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