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Fluorine-Containing Butanolides and Butenolides. Vinylic Fluorine Displacement in 4,4-Dialkyl-2,3-difluoro-2-buten-4-olides and a Novel Rearrangement Induced by Organolithium Addition to a Carbonyl Group

Oldřich Paleta,[a,*] Andrew Pelter,[b] Josef Kebrle,[a] Zdeněk Duda[a] and Jan Hajduch[a]

[a]*Department of Organic Chemistry, Institute of Chemical Technology, Technická 5, 166 28 Prague 6, Czech Republic*
[b]*Department of Chemistry, University of Wales Swansea, Singleton Park, Swansea SA2 8PP, United Kingdom*

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Abstract—2,3-Difluoro-4,4-dimethyl-2-buten-4-olide (**1**) and spirocyclic 2,3-difluoro-4,4-(pentane-1,5-diyl)-2-buten-4-olide (**2**) were modified by vinylic displacement of fluorine with some O- and C-nucleophiles. Sodium and lithium alkoxides, substituted phenoxides and protected glucose alkoxides reacted by 1,4-addition followed by the expulsion of fluoride ion to give 3-substituted derivatives (**4–24**). Softer Grignard reagents in the form of a copper (I) bromide-dimethyl sulfide complex reacted in the same way as O-nucleophiles to afford 3-alkyl- or 3-aryl derivatives (**25–26**). Harder organolithium reagents attacked the carbonyl group to give unstable hydroxy compounds that rearranged spontaneously to furan(2*H*)-3-ones (**27**–**29**) in a novel oxygen rearrangement reaction.

Introduction

The 2-buten-4-olide ring is a component of several classes of bioactive natural compounds. Well-known examples are isoprenoids,[1] piperolides[2,3,4] and fadyenolides[2,5] (with sedative properties), cardolides (e.g digitoxin), carotenoids[6] and retinoids[6] (e.g. pteridinin causing planctonic 'red tide'). There are many other natural bioactive 2-buten-4-olides, e.g. with antitumor activity,[7] cytotoxic properties[8] to human tumor cells, intestinal carcinogenicity inhibition[9] and also with HIV-1 protease-inhibitor activity.[10] Butenolides isolated from the group of *Annonaceae* plants[11] have exhibited a significant activity against lymphocytic leukemia system, and cytotoxic butenolides from *Melodorum fruticosum*[12] showed activities against several tumor lines. New bioactive properties can also be created by the synthesis of analogues of natural butenolides, as in the case of some retinoids that were proved to have antitumor[13] and antitumor-promoter activity.[14] Numerous butenolide derivatives are claimed in patent literature as drugs, pharmaceuticals and biocides. 2-Buten-4-olides with halogen substituents (chlorine, bromine) attached to the double bond[15] have been developed as cytostatics.[15] However some of them, occurring in chlorinated drinking water, appeared to be mutagenic.[16]

Our research on fluorine-containing butenolides has been stimulated by the above mentioned biological activities together with the fact that fluoro substituents (such as F, CF_3, OCF_3 etc.) are powerful modifiers of chemical and biological properties of organic compounds[17,18] as documented by hundreds of pharmaceuticals and biocides. A combination of a fluorine substituent with a 2-buten-4-olide ring could thus afford compounds with new and interesting bioactivity. Some fluorinated analogs of tetronic and L-ascorbic acids have recently been prepared[19] for biochemical studies and 2-fluoro-4-hydroxy-3-styryl-2-buten-4-olide exhibited phospholipase inhibitory effect.[20]

Vinylic displacement of a halogen offers the possibility of modifying the starting structure of a butenolide with retention of the double bond. As previously reported,[15,21,22] several 2,3-dihalogeno-2-buten-4-olides underwent halogen displacement with some nucleophiles, but ring opening as a consequence of a series of consecutive reactions has also been observed.[22] Displacement of vinylic fluorine and other halogens by a nucleophilic reagent has become a general synthetic method in aliphatic and alicyclic organofluorine chemistry.[23–26] Halogen atoms have been substituted in 3-halogeno-2-alkenoates[23,26] or in perfluoroolefins,[27] while in the case of 2,3,3-trifluoroacrylate addition of alkanols took place.[28] In reaction with secondary amines, vinylic fluorine displacement followed by subsequent addition of a secondary molecule has been reported.[28,29] No such reactions have been applied, to our knowledge, to fluorine containing

Keywords: vinylic fluorine displacement; butanolides; butenolides; organolithium addition rearrangement; hard and soft nucleophiles.
* Corresponding author. E-mail: paletao@vscht.cz

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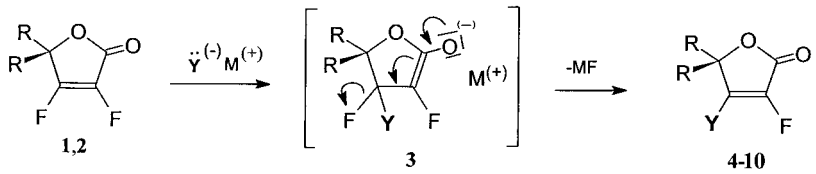


Scheme 1. (1) R=CH_3; (2) R–R=–$(CH_2)_5$–; M=Li, Na, MgBr.CuBr.Me_2S; R=CH_3; Y=CH_3O (4), C_2H_5O (5), C_3H_7O (6), $(CH_3)_2CHO$ (7), C_4H_9O (8), $(CH_3)_3CO$ (9), R–R=–$(CH_2)_5$–, Y=CH_3O (10).

2-buten-4-olides. In our preliminary communication,[30] we reported a method for the preparation of a variety of α-fluorinated butenolides by vinylic displacement of fluorine and also a novel rearrangement of the fluorinated 2-hydroxy-2,5-dihydrofuran ring. Here we discuss all our results including the mechanism of the rearrangement.

Results and discussion

Reactions of oxyanions

All reactions with sodium and lithium alkoxides carried out took place as in Scheme 1. The oxyanions attacked the β-carbon in difluorobutenolides **1** or **2** with complete regioselectivity to give products (**4**–**10**) of vinylic displacement of fluorine (Scheme 1). The mechanism can be formulated (Scheme 1) as a 1,4-addition followed by the expulsion of fluoride ion from the intermediate metal enolate **3**, which appeared to be unable to abstract proton from the superfluous methanol present in the mixture. The β-carbon of α,β-unsaturated carbonyl compounds has been usually considered as a softer electrophilic center[31] than the carbon of a carbonyl group. However, the presence of a fluorine atom at the α-carbon can substantially change its hardness and enable the attack of alkoxide ions that are generally classified as hard nucleophiles.[31] Oxyanions of various hydroxy compounds reacted analogously (Figs. 1 and 2), to give **11**–**24**.

This result is in contrast with the reactivity of similar structures, e.g. 2-fluoro-2-buten-4-olide reacted at the carbonyl group with ring opening,[32] or methyl 2,3-difluoro-3-[4-(2,2-dimethyl-1,3-dioxolanyl)]-2-propenoate[33] that added a second methanol molecule, or methyl 2,3,3-trifluoroacrylate that reacted with the addition of methanol.[28] Non-fluorinated 2-buten-4-olides added methanol,[34] while the reaction with methanolic hydroxide[35] led mainly to ring opening.

We carried out the reactions of the butenolide **2** first with sodium methoxide in various conditions (Table 1) including excess methanol to optimise reaction yields and isolation procedure. The best yields were obtained by the 'dry procedure' based on a short-column separation of salts. The reactions of branched alkoxides were slower than that of primary alkoxides.

Sodium monoalkoxides of protected polyhydroxy compounds and sugars reacted in a similar way to simple alkoxides (products **11**–**13**, Fig. 1). Nucleophilic displacement of vinylic fluorine, to our knowledge, has not previously been carried out with such oxyanions. The

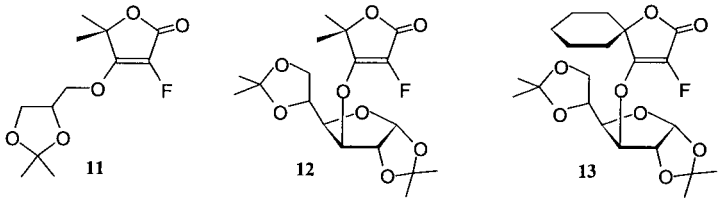
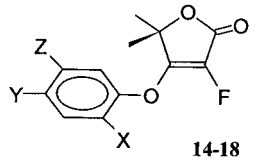
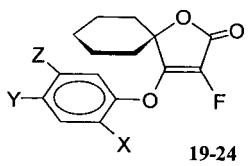


Figure 1.



14, X = Y = Z = H
15, X = Z = H, Y = Cl
16, X = Y = Cl, Z = H
17, X = F, Y = H, Z = CH_3
18, X = Z = H, Y = SCF_3



19, X = Cl, Y = Z = H
20, X = Z = H, Y = Cl
21, X = Z = H, Y = NO_2
22, X = F, Y = H, Z = CH_3
23, X = Z = H, Y = OCF_3
24, X = Z = H, Y = SCF_3

Figure 2.

Table 1. Optimisation of yields in the reactions of some sodium alkoxides

Entry	Butenolide	Alkanol	Base	Solvent	Temperature	Procedure[a]	Yield	Product
1	**1**	MeOH	Na	MeOH	55	A	29[b]	**4**
2	**1**	MeOH	NaH	DME	55	B	39[b]	**4**
3	**1**	MeOH	Na	MeOH	rt	C	72[b]	**4**
4	**1**	MeOH	Na	MeOH	reflux	D	79[b]	**4**
5	**1**	MeOH	NaH	DME	−50 to rt	E	86[b]	**4**
6	**1**	Bu^{t}OH	Na	Bu^{t}OH	reflux	A	0[c]	**9**
7	**1**	Bu^{t}OH	NaH	DME	−40 to rt	C	53[b]	**9**
8	**2**	MeOH	Na	MeOH	reflux	A	35[b]	**10**
9	**2**	MeOH	Na	MeOH	reflux	D	83[b]	**10**
10	**2**	MeOH	BuLi	MeOH	−70 to rt		85[b]	**10**

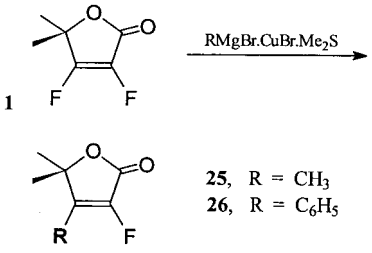
[a] For details, see Experimental.
[b] Complete conversion of the starting material **1** or **2** as checked by ^{19}F NMR.
[c] No conversion of the starting material **1** was detected.

reaction took place even with sterically hindered 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose.

Sodium phenoxides reacted with **1** and **2** by vinylic fluorine displacement as shown in Fig. 2 according to Scheme 1 and moderate to good yields of phenoxide products **14**–**24** were obtained. New fluorinated butenolide derivatives **14**–**24** could display some biocide properties as is known for similar non-fluorinated butenolides.[36]

Reactions of soft carbanions

The reagents used were methyl- or phenylmagnesium bromide modified with copper(I) bromide-dimethyl sulfide. Their reactions with **1** gave exclusively β-substituted butenolides **25**, **26** (equation 1) according to Scheme 1. Products of the attack on the carbonyl group were not observed. The reaction thus gives the possibility of modifying **1** and **2** at position 3 with various alkyl and aryl substituents using complexed Grignard reagents.



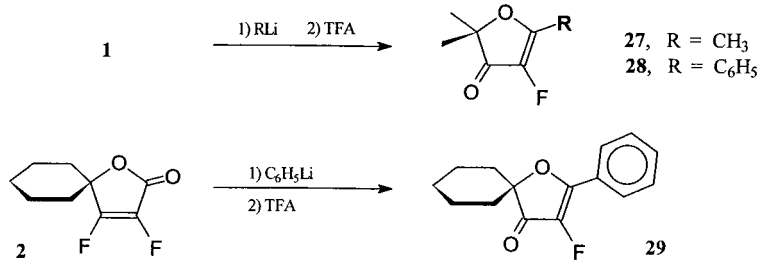
(1)

Reactions of hard carbanions and a novel rearrangement

Methyllithium and phenyllithium surprisingly[1] afforded compounds **27** and **28** as the end products in reactions with **1** (Scheme 2). Compounds **27** and **28** were isomeric with the products **25** and **26**, but did not contain the 2-buten-4-olide ring as shown by the absence of bands at ca. 1775–1780 cm^{-1} in their IR spectra. Instead, each contained a ketone group (δ_C ca. 195–198 ppm; ν_{max} 1706–1723 cm^{-1}). The pattern of the signals in the ^{13}C NMR were similar for the pair **27** and **28** and differed considerably from the pair **25** and **26** (Table 2). Attempts to use the INADEQUATE NMR technique to define the connectivity of the chain of four carbon atoms foundered on the long relaxation times and the spread of the signals.

With respect to the formulae of **27** and **28** it appeared that the carbonyl group was attacked by organolithium reagents, which behaved in this reaction as hard C-nucleophiles. This regioselectivity can be caused by the ablity of the lithium ion in RLi to coordinate with the carbonyl oxygen.[37] By the addition of organolithiums, the skeleton of compounds **27** and **28** was formed (intermediates **30** and **33**, Scheme 3). X-Ray analysis of compound **28** confirmed[30] its structure and the close overall similarity of **27** and **28** allowed the assignment of structure **27** (Scheme 2). Similarly spirocyclic **2** was observed to give **29** (Scheme 2) and thus, the reaction has not been influenced by the rigid spirocyclic annelation at C4.

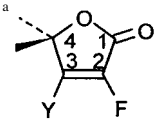
To gather further insight into the mechanistic pathway leading from **30** to the end-intermediate **36** we tried to identify some intermediates (Scheme 3). The reaction mixture from the reaction of **1** with phenyllithium was quenched with trifluoroacetic acid followed by rapid neutralisation with sodium bicarbonate and the resulting crude product was rapidly purified and at once examined by ^{1}H and ^{13}C NMR spectroscopy. It was shown to be a mixture of three

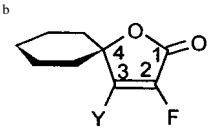


Scheme 2.

Table 2. Some spectral data of the starting compounds **1** and **2** and products **4–29**

Compound Y	X	δ_F	δ_C C-1	X C-2	X C-3	X C-4	ν_{max} (C=O s, C=C s)
1[a]	F	128.1 s 165.6 s	162.0 d[c]	126.4 d $^1J_{CF}$=299	160.2 d $^1J_{CF}$=273	78.0 d[c]	1802, 1757
2[b]	F	127.4 s 166.4 s	162.9 d[c]	127.1 d $^1J_{CF}$=290	159.9 d $^1J_{CF}$=269	80.5	1801, 1749
4[a]	MeO	178.8 s	164.4 d J_{CF}=26.8	125.2 d J_{CF}=257	158.9 d J_{CF}=6.14	78.7 d J_{CF}=4.6	1773, 1706
5[a]	EtO	178.1 s	164.8 d J_{CF}=26.6	124.7 d $^1J_{CF}$=256.5	158.2 d J_{CF}=5.63	78.9 d J_{CF}=5.4	1775, 1703
6[a]	PrO	177.8 s	164.6 d J_{CF}=26.7	124.7 d $^1J_{CF}$=266	158.2 d J_{CF}=6.1	78.7 d J_{CF}=5.4	1775, 1703
7[a]	Pr^{i}O	177.0 s	164.6 d[c]	123.9 d $^1J_{CF}$=256	157.4	78.8 d J_{CF}=5	1775, 1700
8[a]	BuO	177.8 s	164.6 d J_{CF}=26.1	124.8 d $^1J_{CF}$=256	158.3 d J_{CF}=5.5	78.9 d J_{CF}=5.8	1775, 1703
9[a]	Bu^{t}O	166.5 s	165.5 d[c]	122.6 d $^1J_{CF}$=255	154.8	79.5 d J_{CF}=6.1	1773, 1693
10[b]	MeO	178.7 q J_{HF}=3.5	165.4 d J_{CF}=26.2	126.3 d $^1J_{CF}$=257.5	159.9 d J_{CF}=6.5	80.7 d J_{CF}=3.9	1774, 1705
11[a]	DMDOMO[d]	176.0 s	163.0 d[c]	125.1 d $^1J_{CF}$=258	157.8 d J_{CF}=6.1	78.8 d J_{CF}=4.6	–
12[a]	DIPGF[e]	173.6 s	163.0 d[c]	125.3 d $^1J_{CF}$=260	156.1 d J_{CF}=6.1	78.8 d J_{CF}=4.5	1780, 1712
13[b]	(DIPGF)	173.6 s	164.8 d J_{CF}=26.6	126.4 d $^1J_{CF}$=260	157.1 d J_{CF}=6.1	80.7 d J_{CF}=3.5	1778, 1708
14[a]	PhO	165.6 s	164.0 d J_{CF}=26	125.5 d $^1J_{CF}$=265	156 d J_{CF}=5.5	79.0 d J_{CF}=3.4	–
15[a]	4Cl-C_6H_4O	164.8 s	163.6 d J_{CF}=25.8	125.6 d $^1J_{CF}$=265	155.6 d J_{CF}=4.7	79.0 d J_{CF}=3.0	1781, 1714
16[a]	2,4Cl_2-C_6H_3O	165.5 s	164.1 d J_{CF}=25.8	124.6 d $^1J_{CF}$=264.1	149.0 d J_{CF}=158.6	79.8 s	1762, 1711
17[a]	2F-5Me-C_6H_3O	170.2 s 137.0 dd J_{CF}=5.2; 3.5	164.2 d J_{CF}=25.7	124.8 d $^1J_{CF}$=302.3	156.9 d J_{CF}=51.1	79.7 d J_{CF}=2.9	1781, 1716
18[a]	4CF_3S-C_6H_4O	162.3 s 43.4 s	163.9 d J_{CF}=26.3	128.5 d $^1J_{CF}$=265.1	155.6 d J_{CF}=67.6	79.8	1782, 1714
19[b]	2Cl-C_6H_4O	170.2 s	164.6 d J_{CF}=25.7	128 d $^1J_{CF}$=264	157.5 d J_{CF}=7.5	81.6 d J_{CF}=3.1	1778, 1713
20[b]	4Cl-C_6H_4O	164.4 s	very weak	126.8 d $^1J_{CF}$=266.4	156.7	81.0	1775, 1711
21[b]	4NO_2-C_6H_4O	161.2 s	very weak	126.9 d $^1J_{CF}$=269.4	157.7	80.3	1779, 1714
22[b]	2F-5Me-C_6H_3O	170.2 s	165 d J_{CF}=25.2	127 d $^1J_{CF}$=255	157.5	81.1	1779, 1720
23[b]	4CF_3O-C_6H_4O	164.3 s 58.8 s	164.6 d J_{CF}=15.8	121.1 d $^1J_{CF}$=257.7	156.6 d J_{CF}=5.6	81.1	1778, 1712
24[b]	4CF_3S-C_6H_4O	162.3 s 43.5 s	164.6 d J_{CF}=29.3	127.3 d $^1J_{CF}$=267.8	156.5	81.2	1779, 1713
25[a]	Me	153.7 s	163.9 d[c]	143.1 d $^1J_{CF}$=271.6	142.3	83.1 d J_{CF}=7.0	1778, 1744
26[a]	Ph	145.2 s	163.6 d[c]	125.3 d $^1J_{CF}$=279.4	142.1	83.5 d J_{CF}=5.9	1776, 1670
27[d]	Me	187.7 s	176.0 d	144.1 d $^1J_{CF}$=259	197.9	88.6 d[c]	1723, 1642
28[f]	Ph	180.4 s	166.7 d J_{CF}=13.6	140.9 d $^1J_{CF}$=263.2	195.3	86.5 d J_{CF}=6.4	1706, 1626
29[g]	Ph	180.5 s	167.3 d J_{CF}=13.6	142.3 d $^1J_{CF}$=263.9	195.9 d J_{CF}=10.3	88.8 d J_{CF}=6.9	1705, 1625

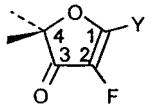
[a] 

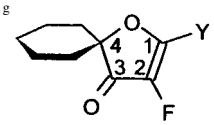
[b] 

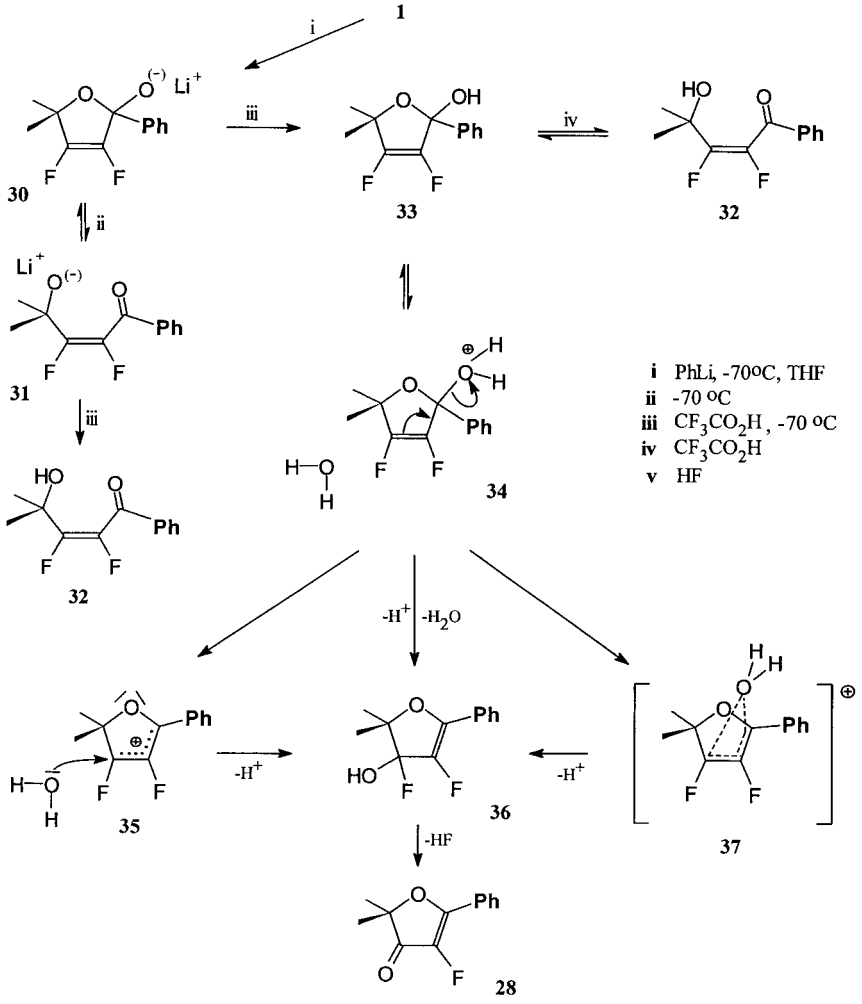
[c] Coupling constant not determined.

[d] (2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy.

[e] O-(1,2:5,6-diisopropylidene-α-D-glucofuranosyl).

[f] 

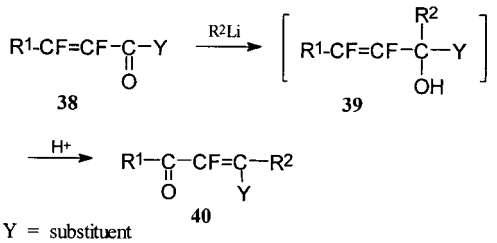
[g] 



Scheme 3.

compounds almost certainly **32**, **33** and **28**. After standing for 12 h in the NMR tube the spectra corresponded to **28** only and the solution was strongly acidic; no other NMR signals were detected.

The structure of the primary addition product **33** is an allylic alcohol with a fluorinated double bond. It is known from the literature[27,38–41] that such aliphatic compounds are unstable and rearrange, especially in the presence of mineral acid, by a mechanism similar to the rearrangement of substituted allylic alcohols **39**,[27,38–41] as in equation 2.



(2)

Y = substituent

No such reaction has been reported on the dihydrofuran skeleton. With the facts mentioned above the mechanism of the transformation of the starting **1** to **27** or **28** can be formulated in Scheme 3. Hemiacetal salt **30** formed in the reaction of **1** with RLi is very probably in equilibrium with the ring opened lithium alkoxide **31**. From the lithium salts, free hydroxy compounds **32** and **33** are liberated by quenching the reaction mixture with trifluoroacetic acid. The disappearing NMR signals mentioned above are in accord with these unstable intermediates. Protonated hemiacetal **34** is an unstable intermediate that rearranges to **36**. The transfer of water species on the allylic system can be intermolecular (**35**) or intramolecular (**37**) and leads α-fluoro hydroxy compound **36**. This immediately eliminates hydrogen fluoride to give the end 3(2*H*)-furanone **28**. The liberated HF acts as the catalyst and the rearrangement is thus autocatalysed. We have tried to monitor the rearrangement by ^{19}F NMR under different conditions (mineral acid concentration, solvent and concentration) to obtain a time dependence concentration of intermediates **32**, **33** but so far without success. The study of the scope and limitations of the rearrangement is being continued.

Conclusions

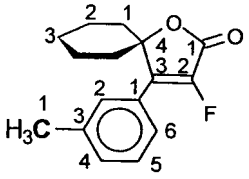
A general method for the nucleophilic vinylic substitution of 3-F in 4,4-dialkyl-2,3-difluoro-2-buten-4-olides with a variety of oxyanions and with soft carbanionic reagents has been developed. Organolithiums behaved as hard

nucleophiles reacting at the carbonyl group to give unstable hydroxy compounds that undergo a novel rearrangement to give 2,2,5-trisubstituted 4-fluoro-3(2*H*)-furanones. The rearrangement is not influenced by rigid 4,4-spirocyclic annelation in the starting butenolide.

Experimental

Instrumentation

The temperature data were not corrected. GC analyses were performed on a Chrom 5 instrument (Laboratorní přístroje, Prague, 1984; FID, 380×0.3 cm packed column, silicone elastomer E-301 on Chromaton N-AW-DMCS (Lachema, Brno), nitrogen, i.e. GCa) and on a PU 4400 instrument (Philips Analytical, Cambridge, 1990; capillary column 500×0.02 cm, methyl silicon film-layer 25 μm, i.e. GCb). NMR spectra were recorded on a Bruker 400 AM (FT, ^{19}F at 376 MHz), Bruker AC 400 (Forchheim,1993; FT, ^{19}F at 376 MHz), and Bruker WP 80 SY (FT, ^{19}F at 75.4 MHz) instruments: tetramethylsilane (^{1}H and ^{13}C) and $CFCl_3$ (^{19}F) as the internal standards, chemical shifts in ppm (*s* singlet, *d* doublet, *t* triplet, *q* quartet, *quin* quintet, *sex* sextet, *hep* heptet, *m* multiplet), coupling constants *J* in Hz, solvents used were $CDCl_3$ and DMSO-d_6 as bought. For assignment of signals in NMR spectra, the individual atoms in structures are indicated according to the example:



The bold C-atom is indicated in the butenolide structure as C-3-3-1 (i.e. butenolide ring - aromatic ring - side chain). Hydrogen atoms are indicated according to the corresponding carbon atoms, i.e. H-atom in the CH_3 group is indicated as H-3-3-1.

Mass spectra (EI, CI) were scanned on a GC-Mass Spectrometer tandem VG/12-253 Masslab Quadrupole Spectrometer (VG, Manchester, 1986). High-resolution molecular ion was scanned on a VG Analytical Model YAB-E High Resolution Reverse Geometry Double Foccusing Instrument (VG, Manchester, 1986). Infra-red spectra were recorded on a Perkin-Elmer 1700X FT-IR spectrometer (Beaconsfield, 1988; absorption bands intensity: *s* strong, *m* medium, *w* weak). Molecular formulae were determined by high resolution mass spectrometry on a sample which was pure by tlc, hplc and NMR or by microanalysis. Analytical TLC was performed on silica gel (Merck) mounted on aluminium cards with fluorescent indicator (254 nm) and on pre-coated glass-backed plates and visualised by UV light or cerium^{IV} nitrate.

Chemicals and reagents

Column chromatography was carried out using Merck Kieselgel (63–100 μm). Methanol, ethanol, propanol, 2-propanol, 1-butanol, *tert*-butylalcohol, petroleum ether (bp 40–60°C), dichloromethane, diethyl ether, dimethoxyethane (DME) and *N,N*-dimethylformamide were purified and dried in a standard manner.[42] Tetrahydrofuran was distilled in a still from sodium-benzophenone ketyl. The following chemicals and reagents were purchased as follows: CFC-113 (1,1,2-trichloro-1,2,2-trifluoroethane) from Spolek pro chemickou a hutní vúrobu (Ústí n.L., CR), potassium fluoride (Fluka); sodium hydride (in mineral oil), cuprous bromide, dimethylsulfane, phenylmagnesium bromide (diethyl ether), butyllithium (2.5 M in hexane), methyllithium (diethyl ether), and phenyllithium (2 M in benzene/ether 75/25), trifluoroacetic acid (all from Aldrich or Sigma-Aldrich); phenol and 4-chlorophenol (Fluka), the other phenols and thiophenols (Baeyer AG) were used without further purification.

Dry potassium fluoride was prepared as follows: Anhydrous KF was heated in an iron bowl with a Meker gas burner for 1 h, then rapidly ground to powder, which was further dried in the reaction flask under vacuum (oil pump) at 160°C for 2 h. Cu(I)Br-dimethyl sulfide complex was prepared according to the described procedure[43] and 2,3-difluoro-4,4-dimethyl-2-buten-4-olide (**1**) were prepared in better yields (62–69%) than previously reported.[44] The preparation of 2,3-difluoro-4,4-(pentane-1,5-diyl)-2-buten-4-olide (**2**) will be published in another paper.[45]

Experimental Procedures

2,3-Difluoro-4,4-dimethyl-2-buten-4-olide (1). Improved procedure:[44] Powdered potassium fluoride (16.4 g, 0.282 mol) was dried under vacuum (oil pump) in a 50 ml flask for 1 h; the flask was then pressure-equalised with argon, fitted with a Claisen condenser and a trap that was connected to atmosphere through a hydraulic seal (conc. sulfuric acid). The flask was then heated to 190–195°C and 2,3,3-trifluoro-4,4-dimethylbutan-4-olide was added dropwise to KF through the neck of the condenser. The liquid distillate (bp 103–105°C/130 mm Hg), product **1** (4.32 g, 94.8%; purity 95%, GCa), was used for reactions. δ_H 1.62(6H, d, J_{FH}=1.0, H-5). δ_C, 23.9(CH_3).

2-Fluoro-3-methoxy-4,4-dimethyl-2-buten-4-olide (4). Reactions were carried out in a double-necked 5 ml flask equipped with a Dimroth reflux condenser with $CaCl_2$ drying tube, magnetic follower and septum cap.

Procedure A. Sodium cuts (0.42 g, 18.3 mmol) were put into a flask with methanol (1.5 ml). A solution of butenolide **1** (0.27 g, 1.82 mmol) in methanol (1.5 ml) was then added at rt and the flask was heated at 55°C for 30 min. The mixture was cooled to rt and then diluted with CFC-113 (15 ml), extracted with water, which, in turn, was twice extracted with diethyl ether. The combined organic extracts were evaporated to give **4** (85 mg, 29%) as a white solid, mp 76–86°C that was recrystallised from hexane (mp 82–86°C).

Procedure B. Sodium hydride (0.112 g, 4.67 mmol) was put into a flask with DME (3 ml). Butenolide **1** (0.165 g, 1.11 mmol) was then added and the flask was heated at 55°C for 70 min. The mixture was then diluted with water (5 ml), acidified (pH ca.1) and extracted with diethyl ether (3×5 ml). The combined extracts were dried over

magnesium sulfate and solvent removed in vacuo to give crude **4**. Purification by chromatography (20 g of silica gel, diethyl ether) gave butenolide **4** (70.3 mg, 39%) as white crystals (mp 85–87°C).

Procedure C. According to procedure *A*, a mixture of methanol (1.5 ml) to which were subsequently added sodium cuts (31 mg, 1.35 mmol) and a solution of **1** (0.20 g, 1.35 mmol) in methanol (1.5 ml) was stirred at rt for 12.5 h and then evaporated to dryness. The solid obtained was extracted with diethyl ether, filtered, centrifuged and the solvent was removed to give pure **4** (0.155 g, 72%) (mp 84–87°C).

Procedure D. According to procedure *A*, a mixture of methanol (1.5 ml) to which were subsequently added sodium cuts (31 mg, 1.35 mmol) and a solution of **1** (0.20 g, 1.35 mmol) in methanol (1.5 ml) was refluxed for 1.5 h and then treated as in *C*. The solid crude product was extracted with dichloromethane and purified by short-column chromatography (silica gel 5 g, dichloromethane) to give pure **4** (0.171 g, 79%), mp 86–87°C.

Procedure E. A solution of methanol (42 mg, 1.31 mmol) in DME (1 ml) was added to sodium hydride (31 mg, 1.29 mmol and decanted with petroleum ether). After the reaction was finished (0.5–1 h), the flask was cooled to −60°C and **1** was added dropwise with a syringe through a septum. The mixture was stirred for 2 h at −60°C, then allowed to warm to rt and DME was distilled off. The residue was diluted with dichloromethane and subjected to short-column chromatography (5 g of silica gel, dichloromethane) that gave **4** (0.178 g, 87%) (purity check by TLC, 254 nm detection). δ_H, 1.48(6H, s, $2CH_3$), 4.18(3H, d, J_{FH}=3.4, CH_3O). δ_C 24.4(CH_3), 60.1(d, J_{CF}=3.8, CH_3O). m/z (intensity), 160(25)M^+, 145(100), 129(12), 117(25), 103(55), 87(15), 43(40). HRMS found 160.0536, $C_7H_9FO_3$ requires $[M]^+$, 160.05357. ν_{max} (cm^{-1}), 1773, 1747, 1706, 1636.

3-Ethoxy-2-fluoro-4,4-dimethyl-2-buten-4-olide (5). Procedure A (as for **4**); **1** (0.40 g, 2.70 mmol); yield (oil), 0.25 g (53%), purity 95% (GCb). δ_H, 1.43(3H, t, J_{HH}=7.1, H-3-2), 1.48(6H, d, J_{FH}=0.83, H-4-1), 4.48(2H, dq, J_{FH}=2.45, J_{HH}=7.1, H-3-1). δ_C, 14.9(C-3-2), 24.5(C-4-1), 69.0(d, J_{CF}=3.2, C-3-1). m/z (intensity), 176(3), 175(34), 174(35)M^+, 159(16), 146(20), 141(8), 131(58), 103(66), 69(35), 43(100), 42(13), 39(13). HRMS found 174.0692, $C_8H_{11}FO_3$ requires $[M]^+$, 174.06922.

2-Fluoro-4,4-dimethyl-3-propoxy-2-buten-4-olide (6). Procedure D (as for **4**); **1** (0.285 g, 1.92 mmol); yield (oil) 0.301 g (83%), purity 99% (GCb). δ_H: 1.02(3H, t, J_{HH}=7.5, HC-3-3), 1.49(6H, s, H-4-1), 1.81(2H, sex, J_{HH}=6.9, H-3-2), 4.37(2H, dt, J_{HH}=6.5, J_{FH}=2.6, H-3-1). δ_C, 9.8(C-3-3), 22.6(d, J_{CF}=2.0, C-3-2), 24.5(d, J_{CF}=1.3, C-4-1), 74.5(d, J_{CF}=3.4, C-3-1). ν_{max} (cm^{-1}), 1775, 1747, 1703, 1632. m/z (intensity), 188(10)M^+, 146(35), 131(20), 103(10), 87(8), 69(13), 43(100). HRMS found 188.0849, $C_9H_{13}FO_3$ requires $[M]^+$, 188.08487.

2-Fluoro-3-isopropoxy-4,4-dimethyl-2-buten-4-olide (7). Procedure A (as for **4**); **1** (1.095 g, 7.39 mmol); yield (oil) after trap-to-trap distillation at 14 mm Hg 0.516 g (37%), purity 96% (GCa). δ_H, 1.40(6H, dd, J_{FH}=1.0, J_{HH}=6.6, H-3-2), 1.47(6H, d, J_{FH}=1.0, H-4-1), 4.89(1H, dhep, J_{FH}=2.4, J_{HH}=6.6, H-3-1). δ_C, 22.1(C-3-2), 24.4(C-4-1), 76.4(d, J_{CF}=4.1, C-3-1). ν_{max} (cm^{-1}): 1775, 1746, 1700, 1627. m/z (intensity), 189(3), 188(4)M^+, 174(14), 146(17), 131(8), 129(9), 128(7), 103(10), 87(10), 72(7), 69(32), 59(23), 43(100), 41(27). HRMS found 188.0849, $C_9H_{11}FO_3$ requires $[M]^+$, 188.08487.

3-Butoxy-2-fluoro-4,4-dimethyl-2-buten-4-olide (8). Procedure A (as for **4**); **1** (0.389 g, 2.64 mmol); yield (oil) after trap-to-trap distillation at 12 mm Hg 0.17 g (32%), purity 95% (GCb). δ_H, 0.98(3H, t, J_{HH}=7.4, H-3-4), 1.4-1.5(2H, m, H-3-3), 1.48(6H, d, J_{FH}=0.9, H-4-1), 1.73–1.8(2H, m, H-3-2), 4.42(2H, dt, J_{FH}=2.6, J_{HH}=6.6, H-3-1). δ_C, 13.5(C-3-4), 18.6(C-3-3), 24.5(C-4-1), 31.2(C-3-2), 72.9(2H, d, J_{CF}=4.3, C-3-1). m/z (intensity), 203(3)M^+, 148(13), 146(12), 87(7), 69(13), 59(10), 58(70, 58(100), 56(18), 43(19), 41(37). HRMS found 203.1083, $C_{10}H_{15}FO_3$ requires $[M]^+$, 203.10835.

2-Fluoro-3-*tert*-butoxy-4,4-dimethyl-2-buten-4-olide (9). Procedure E (as for **4**); **1** (0.276 g, 1.86 mmol), yield (oil), 0.202 g (54%), mp 84–89°C. δ_H, 1.45(6H, d, J_{FH}=0.9, H-4-1), 1.50(9H, d, J_{FH}=0.9, H-3-2). δ_C, 24.5(C-3-2), 28.1(d, J_{CF}=6.0, C-4-1), 83.7(C-3-1). m/z (intensity), 203(2)M^+, 147(7), 129(9), 87(5), 57(100), 43(9), 41(18). HRMS found 203.1083, $C_{10}H_{15}FO_3$ requires $[M]^+$, 203.10835.

2-Fluoro-3-methoxy-(1,5-pentane-1,5-diyl)-2-buten-4-olide (10). A solution of butyllithium (0.5 ml) was added dropwise through a septum cap to dry methanol (1.5 ml) at −70°C while stirring for 15 min. A solution of **2** (0.184 g, 0.987 mmol) in methanol (0.5 ml) was then added dropwise and the mixture was then allowed to warm to rt. The mixture was then quenched with trifluoroacetic acid and neutralised with a solution of Na_2CO_3. The residue was then treated as in Procedure E; yield of **10**, 0.166 g (85%), mp 130–132°C. δ_H, 1.57–1.81 (5×2H, m, H-4-1- H-4-5), 4.16(3H, d, J_{FH}= 3.5, H-3-1). δ_C, 21.9(C-4-3), 24.8(C-4-2,4), 33.7 (C-4-1,5), 60.6(d, J_{CF}=3.8, C-3-1). Anal. calcd. for $C_{10}H_{13}FO_3$ C, 59.99; H, 6.54. Found C, 59.88; H, 6.47.

3-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy]-2-fluoro-4,4-dimethyl-2-buten-4-olide (11). Procedure B (as for **4**; rt); **1** (0.5 g, 3.38 mmol); yield (oil) by trap-to-trap distillation at 12 mm Hg, 0.263 g (30%), purity 94% (GCa). δ_H: 1.38(3H, d, J_{FH}=0.6, H-4-1), 1.44(3H, d, J_{FH}=0.4, H-4-1), 1.51(6H, s, H-3-1-2-1), 3.81-3.88(1H, m, H-3-1), 4.12–4.19(1H, m, H-3-1),), 4.40–4.48(3H, m, H-3-1-4,5). δ_C, 0 24.4(C-4-1), 25.1, 26.6, 65.5(C-3-1-5), 72.6(d, J_{CF}=3.7, C-3-1), 73.0(C-3-1-4), 110.2(C-3-1-2). m/z (intensity), 189(8), 147(12), 146(13), 131(9), 129(15), 113(12), 103(10), 87(11), 69(38), 60(9), 59(26), 43(100), 42(15), 41(28), 39(17). Anal. calcd. for $C_{12}H_{17}FO_5$ C, 55.38; H, 6.58. Found C, 55.64; H, 6.78.

3-*O*-(1,2:5,6-diisopropylidene-α-D-glucofuranosyl)-2-fluoro-4,4-dimethyl-2-buten-4-olide (12). Procedure B (as for **4**; rt); **1** (1.53 g, 5.88 mmol), the crude **12** was sublimed (1.167 g) and a part of sublimate (0.71 g) was purified by chromatography (50 g of silica gel, toluene/ethanol, 20/1) to

give 0.384 g (60.8%) of **22**, mp 172–175°C. δ_H: 1.31(3H, s), 1.35(3H, s), 1.42(3H, s), 1.49(3H, s), 1.52(3H, s), 1.54(3H, s), 4.0(1H, dd, J_{HH}=8.7, J_{HH}=5.2), 4.13–4.25(3H, m), 4.68(1H, dd, J_{HH}=7.5, J_{HH}=2.8), 5.12(1H, t, J_{HH}=1.7), 5.95(1H, d, J_{HH}=3.6). δ_C: 24.5(C-3-5), 25.1, 26.2, 26.7, 26.8, 67.7(C-3-6), 72.0, 80.4, 82.7, 84.0(d, J_{CF}=3.7, C-3-3), 105.1(C-3-1), 109.7, 112.9. m/z (intensity), 390(2), 389(7), 388(7), 373(17), 315(8), 129(10), 127(12), 113(12), 102(8), 101(100), 99(7), 86(19), 85(10), 84(30), 83(11), 81(12), 73(18), 72(12), 71(11), 69(18), 59(27), 55(20), 43(78), 42(7), 41(12). HRMS found 388.1533, $C_{18}H_{25}FO_8$ requires $[M]^+$, 388.15335.

3-*O*-(1,2:5,6-diisopropylidene-α-D-glucofuranosyl)-2-fluoro-4,4-(1,5-pentanediyl)-2-buten-4-olide (13). Procedure B (as for **4**; rt); **2** (207 mg, 1.10 mmol), 1,2:5,6-diisopropylidene-α-D-glucofuranose (337 mg, 1.30 mmol). The crude product was purified by chromatography (10 g of silica gel, toluene/ethanol 20/1) to give white solid **13**, (346 mg, 73%), mp 153–158°C. δ_H: 1.21–1.76(10H, m), 1.32(3H, s), 1.34(3H, s), 1.42(3H, s), 1.54(3H, s), 4.0(1H, dd, J_{HH}=8.5, J_{HH}=5.4), 4.13–4.25 (3H, m), 4.66(1H, dd, J_{HH}=7.2, J_{HH}=3) 5.12(1H, t, J_{HH}=1.9), 5.94(1H, d, J_{HH}=3.7). δ_C: 21.9(C-4-3), 24.7(C-4-2), 25.8, 26.8, 27.3, 27.4, 33.7(C-4-1), 33.9(C-4-5), 68.3(C-3-6), 72.6(C-3-5), 81.0(C-3-4), 83.3(C-3-2), 84.5(d, J_{CF}=4.3, C-3-3), 105.7(C-3-1), 110.3, 113.5. Anal. calcd. for $C_{21}H_{29}FO_8$ C, 58.87; H, 6.84. Found C, 58.75; H, 6.43.

2-Fluoro-4,4-dimethyl-3-phenoxy-2-buten-4-olide (14). Procedure B (as for **4**); phenol (128 mg, 1.36 mmol), **1** (200 mg, 1.35 mmol); the crude product was twice purified by chromatography (5 and 40 g of silica gel, dichloromethane) to give 55 mg (83%) of **14** as white crystals, mp 97–101.5°C. δ_H: 1.66(6H, d, J_{FH}=0.8, H-4-1), 7.14–7.18(2H, m, H-3-3), 7.25–7.30(1H, m, H-3-4), 7.39–7.44(2H, m, H-3-2). δ_C: 24.6(C-4-1), 118.8(C-3-3), 126.4 (d, J_{CF}=2.8, C-3-4), 129.9 (d, J_{CF}=4.9, C-3-2), 153.9 (C-3-1). Anal. calcd. for $C_{12}H_{11}FO_3$ C, 64.86; H, 4.99. Found C, 64.59; H, 5.23.

3-(4-Chlorophenoxy)-2-fluoro-4,4-dimethyl-2-buten-4-olide (15). Procedure E (as for **4**); 4-chlorophenol (291 mg, 2.26 mmol), **1** (335 mg, 2.26 mmol); the crude product was twice purified by chromatography (35 and 30 g of silica gel, dichloromethane) to give 202 mg (35%) of **15** as white crystals, mp 93–97°C. δ_H: 1.65 (6H, d, J_{FH}=0.8, H-4-1), 7.10–7.13 (2H, m, H-3-3), 7.36-7.39 (2H, m, H-3-2). δ_C: 24.6(C-4-1), 120.2(C-3-3), 129.9 (d, J_{CF}=1.4, C-3-2), 131.7 (C-3-4), 152.3(C-3-1). m/z (intensity): 258(40), 257(56), 256(100), 243(16), 241(52), 201(18), 199(60), 139(17), 130(14), 129(65), 128(28), 111(16), 99(8), 87(9), 73(10), 63(13), 50(10), 43(48), 39(11). HRMS found 256.0303, $C_{12}H_{10}ClFO_3$ requires $[M]^+$, 256.03025.

3-(2,4-Dichlorophenoxy)-2-fluoro-4,4-dimethyl-2-buten-4-olide (16). Procedure E (as for **4**; tetrahydrofuran, rt 15 h); 2,4-dichlorophenol (190 mg, 1.20 mmol), sodium hydride 60% (50 mg, 1.25 mmol), THF (8 ml), butenolide **1** (150 mg, 1.01 mmol); silica gel 10 g, yield 120 mg (42%), mp 92–95°C (white crystals). ^{1}H NMR: δ_H: 1.69(6H, s, H-4-1), 6.93 (1H, d, J_{HH}=10, arom.), 7.20 (1H, dd, J_{HH}=10, J_{HH}=1.1, arom), 7.22(1H, s, arom.). ^{13}C NMR: δ_C: 25.2(C-4-1), 117.9(C-3-5), 117.9(C-3-5), 122.8(C-3-3), 127.3(C-3-4), 131.2(C-3-6), 133.5(C-3-2). Anal. calcd. for $C_{12}H_9Cl_2FO_3$ C, 49.51; H, 3.12; F, 6.53. Found C, 49.46; H, 3.08; F, 6.45.

2-Fluoro-3-(2-fluoro-5-methylphenoxy)-4,4-dimethyl-2-buten-4-olide (17). Procedure E (as for **4**); 2-fluoro-5-methylphenol (200 mg, 1.53 mmol), sodium hydride (33.5 mg, 1.52 mmol), **2** (200 mg, 1.35 mmol); crude product chromatography (see **19**; dichloromethane), yield of **17**, 230 mg (71 %), mp 84–86°C. δ_H: 1.64(6H, m, J_{HF}=0.8, H-4-1), 2.348(3H, s, H-3-4-1), 7.05–7.14(3H, m, J_{FH}=9.8, J_{FH}=3.8, J_{HF}=3.3, arom.). δ_C: 21.3(C-3-5-1), 25.2(C-4-1), 117.2(d, J_{CF}=18.3, C-3-3), 122.6(C-3-5), 128.8(d, J_{CF}=6.3, C-3-6), 135.6(d, J_{CF}=4.1, C-3-1), 141.5(d, J_{CF}=12.6, C-3-4), 150.6(d, J_{CF}=247, C-3-2). Anal. calcd. for $C_{13}H_{12}F_2O_3$ (254.2) C, 61.38; H, 4.72; F, 14.95. Found C, 61.24; H, 4.72; F, 15.16.

2-Fluoro-4,4-dimethyl-3-[(4–trifluoromethylthio)phenoxy]-2-buten-4-olide (18). Procedure E (as for **4**; tetrahydrofuran 8 ml, rt 16 h); (4-trifluoromethylthio)phenol (200 mg, 1.12 mmol), sodium hydride 60% (50 mg, 1.25 mmol), **1** (150 mg, 1.01 mmol); silica gel (see **19**; dichloromethane/petroleum ether 1/1), yield of **18**, 138 mg (43%), mp 80–82°C. δ_H: 1.69(6H, s, H-4-1), 7.22(1H, dd, J_{HH}=8.8, J_{HH}=2.2, arom), 7.73(1H, d, J_{HH}=8.8, arom.). δ_C: 25.3(C-4-1), 117.3(C-3-1), 120.4(C-3-2), 125(q, J_{CF}=377.3, C-3-4-1), 127.9(C-3-4), 138.9(C-3-3). Anal. calcd. for $C_{13}H_{10}F_4O_2S$ C, 48.45; H, 3.11; F, 23.59. Found C, 48.23; H, 3.20; F, 23.82.

3-(2-Chlorophenoxy)-2-fluoro-4,4-(1,5-pentanediyl)-2-buten-4-olide (19). Procedure E (as for **4**; tetrahydrofuran, −50°C, rt 3 h); 2-chlorophenol (153 mg, 1.19 mmol), **2** (208 mg, 1.11 mmol), sodium hydride (32 mg, 1.45 mmol). Chromatography (silica gel 10 g, dichloromethane) of the crude product gave **19**, 102 mg (31 %), mp 86–88°C. δ_H: 1.22–2.14(10H, m), 7.11–7.36(2H, m), 7.47(2H, dt, J_{HH}=7.7, J_{HH}=2.0). δ_C: 23(C-4-3), 25.5(C-4-2), 34.6(C-4-1), 123.4(arom.), 126.9(C-3-2), 129.9(arom.), 130.5(arom.), 132.4 (arom.), 151.7(C-3-1). Anal. calcd. for $C_{15}H_{14}FClO_3$ C, 60.72; H, 4.76. Found C, 60.22; H, 4.94.

3-(4-Chlorophenoxy)-2-fluoro-4,4-(1,5-pentanediyl)-2-buten-4-olide (20). Procedure E (as for **4**; tetrahydrofuran, rt 5 h); 4-chlorophenol (164 mg, 1.28 mmol), **2** (201 mg, 1.07 mmol); chromatography of the crude product (see **19**), gave **20**, 187 mg (59.3%) as white crystals, mp 110–113°C. δ_H: 1.72–2.05(10H, m), 7.09(2H, dd, J_{HH}=8.9, J_{FH}=1.6), 7.37(2H, d, J_{HH}=8.9). δ_C: 22.1(C-4-3), 24.8(C-4-2), 33.9(C-4-1), 120.8(d, J_{CF}=1.6, C-3-2), 130.6(C-3-3), 132.3(C-3-4), 153.3(C-3-3). Anal. calcd. for $C_{15}H_{14}FClO_3$ C, 60.72; H, 4.76. Found C, 60.94; H, 4.99.

2-Fluoro-3-(4-nitrophenoxy)-4,4-(1,5-pentanediyl)-2-buten-4-olide (21). Procedure E (as for **4**; tetrahydrofuran, reflux 5 h); 4-nitrophenol (164 mg, 1.19 mmol), **2** (200 mg, 1.06 mmol). Chromatography (see **19**) of the crude product gave **21**, 110 mg (33.7%), mp 127–129°C. δ_H: 1.78–2.02(10H, m), 7.28(2H, dd, J_{HH}=9.1, J_{FH}=1.7), 8.32(2H, d, J_{HH}=9.4). δ_C: 21.1(C-4-3), 23.8(C-4-2), 32.9(C-4-1), 118.7(d, J_{CF}=2.2, C-3-2), 125.6(C-3-3), 145.5(C-3-1).

Anal. calcd. for $C_{15}H_{14}NFO_5$ C, 58.63; H, 4.59; N, 4.56. Found C, 58.79; H, 4.75; N, 4.55.

2-Fluoro-3-(2-fluoro-5-methylphenoxy)-4,4-(1,5-pentanediyl)-2-buten-4-olide (22). Procedure E (as for **19**); 2-fluoro-5-methylphenol (164 mg, 1.28 mmol), sodium hydride (33.5 mg, 1.52 mmol), **2** (207 mg, 1.1 mmol). Chromatography (see **19**; dichloromethane/petroleum ether 5:1) of the crude product gave **22**, 118 mg (40 %), mp 75–77°C. δ_H: 1.18–2.08(10H, m, H-4-1 to 4-5), 2.34(3H, s, H-3-4-1), 6.98-7.11(2H, m, arom.), 7.26(1H, s, arom). δ_C: 21.3(C-3-5), 21.9(C-4-3), 24.8(C-4-2), 33.8(C-4-1), 117.4(d, J_{CF}=17.7, C-3-3), 122.6(C-3-6), 128.8(d, J_{CF}=6.3, C-3-4), 135.6(d, J_{CF}=4, C-3-5), 141.8(d, J_{CF}=13.1, C-3-1), 152.8(d, J_{CF}=248, C-3-2). Anal. calcd. for $C_{16}H_{16}F_2O_3$ C, 65.30; H, 5.48. Found C, 65.19; H, 5.61.

2-Fluoro-4,4-(1,5-pentanediyl)-3-[(4–trifluoromethoxy)-phenoxy]-2-buten-4-olide (23). Procedure E (as for **19**); tetrahydrofuran, −50°C, rt 3 h); 4-(trifluoromethoxy)phenol (200 mg, 1.12 mmol), **2** (200 mg, 1.06 mmol). Chromatography (see **19**) of the crude product gave **23**, 125 mg (36.8 %), mp 79–81°C. δ_H: 0.82–2.08(10H, m), 7.13–7.32(2H, dm, J_{HH}=3.5). δ_C: 22.1(C-4-3), 24.9(C-4-2), 34(C-4-1), 120.8(C-3-2), 123.2(C-3-3), 127(q, J_{CF}=267, C-3-4-1), 147.5(C-3-4), 152.8(C-3-1). Anal. calcd. for $C_{16}H_{14}F_4O_4$ C, 55.49; H, 4.07. Found C, 55.13; H, 4.35.

2-Fluoro-4,4-(1,5-pentanediyl)-3-[(4–trifluoromethylthio)-phenoxy]-2-buten-4-olide (24). Procedure E (as for **22**); 4-(trifluoromethylthio)phenol (253 mg, 1.3 mmol), **2** (204 mg, 1.1 mmol). Chromatography (see **19**; dichloromethane/petroleum ether 9/1) of the crude product gave **24**, 151 mg (34.8 %), mp 112–114°C. δ_H: 1.22–2.06(10H, m), 7.2(2H, dd, J_{HH}=8.7, J_{FH}=1.6), 7.7(2H, d, J_{HH}=8.6). δ_C: 21.8(C-4-3), 24.6(C-4-2), 33.7 (C-4-1), 120.2(C-3-2), 122.6(C-3-4), 130.0(q, J_{CF}=309, C-3-4-1), 138.9(C-3-3), 156.1(C-3-1). Anal. calcd. for $C_{16}H_{14}F_4O_3S$ C, 53.04; H, 3.90. Found C, 53.00; H, 4.04.

2-Fluoro-3,4,4-trimethyl-2-buten-4-olide (25). Dimethyl sulfide (0.4 ml) and THF (2.5 ml) were added to CuBr.Me_2S (328 mg, 1.6 mmol) in a flask (with magnetic stirring bar) in a dry-ice bath (−30°C). Methylmagnesium bromide solution (diethyl ether, 1 ml, 3.17 M, 3.17 mmol) was added to the flask and then, at −10°C, a solution of **1** (238 mg, 1.61 mmol) in THF (5 ml) was added and the mixture was stirred for 12 h at rt. The mixture was then quenched with trifluoroacetic acid, the acidic solution was neutralised with solid sodium carbonate and after filtration evaporated to dryness. Repeated short-column chromatography of the crude product (twice on silica gel 5 g, dichloromethane) gave **25**, 128 mg (55%) of purity 97% (GCb). δ_H: 1.49(6H, d, J_{FH}=0.8, H-4-1), 1.97(3H, d, J_{FH}=2.3, H-3-1). δ_C: 8.3(C-3-1), 24.7(d, J_{CF}=2.2, C-4-1). m/z (intensity): 144(20) M^+,129(100), 101(57), 87(8), 57(10), 43(55). HRMS found 144.0587, $C_7H_9FO_2$ requires $[M]^+$, 144.05867.

2-Fluoro-4,4-dimethyl-3-phenyl-2-buten-4-olide (26). Same procedure as for **25**. Quantities were dimethyl sulfide (0.4 ml) and THF (4 ml), CuBr.Me_2S (316 mg, 1.54 mmol), phenylmagnesium bromide solution (THF, 5 ml, 0.615 M, 3.075 mmol), **1** (150 mg, 1.01 mmol) in THF (8 ml). Purification was carried out by chromatography (silica gel 30 g, dichloromethane) to give **26**, yield 160 mg (77%), mp 120–123°C. δ_H: 1.73(6H, d, J_{FH}=1.0, H-5), 7.45–7.54(3H, m), 7.59–7.64(2H, m). δ_C: 26.5(C-4-1), 127.4(d, J_{CF}=4.9, C-3-1), 128.3(d, J_{CF}=6.0), 129.3, 130.5. HRMS found 206.0743, $C_{12}H_{11}FO_2$ requires $[M]^+$, 206.07431.

4-Fluoro-2,2,5-trimethyl-3(2*H*)-furanone (27). A solution of methyllithium (diethyl ether, 1.43 M, 5 ml, 7.150 mmol) was added to a stirred mixture of THF (10 ml) and butenolide **1** (1.056 g, 7.130 mmol) at −70°C and the mixture was stirred for 2 h, then further stirred for 4 h at −35 to −40°C. The reaction was quenched with trifluoroacetic acid and neutralised by sodium carbonate at rt and evaporated. The concentrate was twice purified by short-column chromatography (see **25**), followed by trap-to-trap distillation of the crude product (0.7 g) to give 0.495 (48%) of oily colourless **27**. Refluxing **27** with THF (5 ml), water (2 ml) and 1M-HCl for 3 h caused no change (NMR, GC). δ_H: 1.41(6H, d, J_{FH}=0.9, H-2-1), 2.27(3H, d, J_{FH}=2.4, H-5-1). δ_C: 13.3(d, J_{CF}=2.8, C-5-1), 23.0(C-2-1). m/z (intensity): 144(40)M^+, 143(40), 129(17), 183(13), 86(14), 76(22), 69(5), 58(35), 53(10), 43(100), 39(25). HRMS found 144.0587, $C_7H_9FO_2$ requires $[M]^+$, 144.05866.

4-Fluoro-2,2-dimethyl-5-phenyl-3(2*H*)-furanone (28). Same procedure used as for **27**; phenyllithium (diethyl ether, 1.97 M, 2.8 ml, 5.52 mmol), THF (10 ml), **1** (816 mg, 5.510 mmol). The mixture was allowed to warm to rt for 2 h and then additionally stirred for 2 h at rt and after quenching and neutralisation purified on a short column. Solvents were rapidly removed rapidly in vacuo at 30°C. The residue consisted of a mixture of **28** and intermediate **33**; in 12 h the **33** which disappeared from the mixture in 12 h (followed by GCb, checked by NMR) during which the mixture became strongly acidic. After short-column chromatography, the product was finally chromatographed (silica gel 60 g, dichloromethane) to yield 0.952 g (84%) of pure **28** as an oil, which crystallised in 5 d (mp 35–38°C). δ_H: 1.52(6H, d, J_{FH}=0.5, H-2-1), 7.54(3H, m), 7.97(2H, m). δ_C: 23.3(C-2-1), 127.2(C-5-1), 127.3(d, J_{CF}=5.8), 128.9, 132.7. m/z (intensity), 206(95)M^+, 191(8), 129(10), 120(100), 105(20), 99(2), 94(8), 84(11), 77(11), 49(50), 39(11). HRMS found 206.0743, $C_{12}H_{11}FO_2$ requires $[M]^+$, 206.07431.

4-Fluoro-2,2-dimethyl-2,2-(1,5-pentanediyl)-5-phenyl-3(2*H*)-furanone (29). Same procedure used as for **28**; phenyllithium (diethyl ether, 1.97 M, 0.65 ml, 1.3 mmol), THF (2.5 ml), **2** (204 mg, 1.08 mmol). Short-column chromatography of the crude product showed after 2 d only signals assigned to **29** (^{19}F NMR) and final chromatography (silicagel 15 g, dichloromethane) gave solid **29**, 136 mg (51%) of pure. δ_H: 1.32–1.87(10H, m), 7.3–7.6(3H, m), 7.98(2H dd, J_{FH}=1.2, J_{HH}=8.0). δ_C: 22.1(C-2-3), 24.9(C-2-2), 32.6(C-2-1), 127.9(d, J_{CF}=6.5, C-5-2), 128.1(d, J_{CF}=7.1, C-5-1), 129.5, 133.3. Anal. calcd. for $C_{15}H_{15}FO_2$ C, 73.15; H, 6.14. Found C, 72.85; H, 6.06.

Attempt to trap intermediates 32 and 33 in the formation of 28. Same procedure used as for **28**; phenyllithium (diethyl ether, 1.97 M, 1.4 ml, 2.76 mmol), THF (10 ml),

butenolide **1** (408 mg, 2.76 mmol). After quenching, neutralisation, short-column purification and removal of solvent, the mixture was immediately analysed by NMR which showed the presence of 3 compounds, **32** and **33** together with **28**; GCb confirmed the mixture of 3 compounds. The signals of **32** and **33** decreased with time, while the NMR signals of **28** increased. The time dependence of signal intensity was irreproducible. ^{1}H NMR: δ_H: 1.52(s, **28**), ca. 1.6(qs, **32**, **33**), 4.8(OH, bs, **32**), 5.8(OH, br s, **33**). δ_F (signals of intermediates): −114.1(s, **32**), −143.1(s, **32**), −159.2(qd, **33**) −162.9(qd, **33**). δ_C (signals of intermediates): 135(d, J_{CF}=ca. 280), 142(qd, J_{CF}=ca. 280), 163(qd, J_{CF}=284), 189.3(d, J_{CF}=34, C=O, **32**).

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