PREPARATION OF INTERMEDIATES FOR FLUORINATED LIGNANS BY CONJUGATED AND TANDEM ADDITIONS ON 3-FLUOROFURAN-2(5*H*)-ONE

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Dedicated to Professor Otakar Červinka on the occasion of his 75th birthday.

Two syntheses of 3-fluorofuran-2(5*H*)-one (**1**) based on Wittig–Horner reaction of ethyl (diethoxyphosphoryl)fluoroacetate (**15**) with 2-oxoethyl acetate (**16**) or on transformation of D-erythronolactone (**10**) are given. 3-Fluorofuran-2(5*H*)-one (**1**) and ethyl 2-fluorobut-2-enoate (**2**) undergo conjugate addition with soft nucleophiles based on arenecarboxaldehyde dithioacetals **7** to form 2-fluorolactones **3** and 2-fluoroalkanoates **4**. Intermediate enolates can be trapped in the sense of tandem addition with arenecarboxaldehydes **8** or (arylmethyl)bromides **9** to form intermediates **5** and **6** for fluorolignans. Although the conjugate addition proceeds with low stereoselectivity yielding mixture of both diastereoisomers, the electrophile in tandem addition attacks the intermediary fluoroenolate exclusively *anti* to its bulky β-substituent in good accord with non-fluorinated furan-2(5*H*)-ones.

Key words: Conjugate additions; Tandem additions; 2-Fluorobut-2-enoate; 2-Fluorobut-2-en-4-olide; Butenolides; Lignans; Lactones; Dithioacetals; Fluorinated compounds.

The butanolide or butenolide ring system is frequently present in biologically active compounds. Podophyllotoxin and some its derivatives possess antineoplastic or antiviral activity[1] and hence became the challenge for synthetic chemists. Tandem addition of umpoled arenecarboxaldehydes on furan-2(5*H*)-one[2] or its chiral 5-substituted derivatives[3] and trapping of intermediated enolates with aromatic electrophiles belongs to most frequent and straightforward procedures leading to lignan intermediates.

Little is known about conjugate addition on 2-fluoroalkenoates with the exception of 2-fluoroprop-2-enoates[4], as well as about the chemistry of enolates of 2-fluoroalkanoates[5] with the exception of 2-fluoroacetates[6]. From the results, two main drawbacks of α-fluoroenolates in comparison with non-fluorinated ones can be recognized, *viz.* lower stability of α-fluoroenolates resulting in decomposition and increased hardness of the fluorinated α-carbon with enhanced tendency to *O*-alkylation of the enolate. Except for our preliminary report[7], no tandem addition on fluorinated alkenoates have been reported.

Introduction of fluorine into biologically active molecules often results in distinctive modification of their biological properties[8]. The traditional approach to preparation of fluorinated compounds relies on nucleophilic or electrophilic fluorination[9]. On the other hand, the role of easily accessible *fluorinated building blocks* forming a family, which could be called *fluorine pool* in analogy to *chiral pool* for chiral compounds, is still more acknowledged[10].

Various substituted fluorofuranones have been synthesized and either used as intermediates or directly studied for biological activity[11]. We recently reported[7] the preparation of a new fluorinated building block, 3-fluorofuran-2(5*H*)-one (**1**) and some of its reactions including pilot experiments with conjugate and tandem addition. As products of these reactions are important intermediates for fluorinated lignans, we wish to report here the synthesis of fluorolactone **1** and results of extended study of its behaviour in conjugate and tandem additions in full detail. For comparison, we also studied the above reaction with an open-chain fluoroalkenoate, ethyl 2-fluorobut-2-enoate (**2**).

Recently, preparation of fluorinated podophyllotoxin by direct electrophilic fluorination has been published[12] with the aim to prevent racemization at the C3 carbon of the furanone ring accompanied by loss of biological activity. This work underlines the importance of fluorinated lignans.

EXPERIMENTAL

General Comments

Temperature data are uncorrected. ^{1}H NMR 1D and 2D spectra were recorded with a Varian Gemini 300 HC spectrometer at 300.1 MHz using TMS as internal standard, ^{13}C NMR spectra were recorded with a Bruker AM 400 spectrometer at 100.6 MHz using TMS as internal standard, and ^{19}F NMR spectra were recorded with a Bruker WP-80 SY spectrometer at 76.5 MHz

using $CFCl_3$ as internal standard with upfield values designed negative. FTIR spectra were recorded with a Nicolet 740 instrument in KBr.

All manipulations and reactions including organometallic reagents were performed with exclusion of moisture and atmospheric oxygen in oven-dried apparatuses. 2-*O*-Tosyl-D-erythrono-1,4-lactone (**11**) was prepared from easily available D-erythrono-1,4-lactone (**10**) according to ref.[13]. 2-Deoxy-2-fluoro-L-threono-1,4-lactone (**13**, (3*S*,4*R*)-3-fluoro-4-hydroxy-3,4-dihydrofuran-2(3*H*)-one) was formed by fluorination of 2,3-anhydro-D-erythronolactone (**12**, (1*R*,5*R*)-3,6-dioxabicyclo[3.1.0]hexan-2-one)[14]. Ethyl fluoroiodoacetate (**14**) was prepared from ethyl chlorofluoroacetate[15] by the Finkelstein reaction[16]. 2-Oxoethyl acetate (**16**) was synthesized[17] from 1-ethoxyethylene diacetate[18]. Ethyl 2-fluorobut-2-enoate (**2**, *E*/*Z* ratio 89 : 11) was prepared by the Wittig–Horner reaction according to ref.[19]. A series of substituted [bis(phenylsulfanyl)methyl]benzenes **7a**–**7d**, *viz*. [bis(phenylsulfanyl)methyl]benzene (**7a**), 1-[bis(phenylsulfanyl)methyl]-4-methoxybenzene (**7b**), 4-[bis(phenylsulfanyl)methyl]-1,2-dimethoxybenzene (**7c**), and 5-[bis(phenylsulfanyl)methyl]-1,3-benzodioxole (**7d**), was prepared from corresponding commercially available aldehydes **8a**–**8d** by reaction with benzenethiol under $AlCl_3$ catalysis according to ref.[3a]. 5-(Bromomethyl)-1,2,3-trimethoxybenzene (**9b**) was prepared from 3,4,5-trimethoxybenzaldehyde (**8e**) by $NaBH_4$ reduction followed by bromination[3a].

2,3-Anhydro-D-erythronolactone (**12**)

A 250 ml flask equipped with a magnetic stirbar, reflux condenser and drying adapter (anhydrous $CaCl_2$) was charged with dried KF (11.62 g, 200 mmol), tosylated lactone **11** (13.61 g, 50.0 mmol), and MeCN (120 ml). The mixture was refluxed while stirring for 4 h, cooled, MeCN was added (150 ml) and solids removed by chromatography over a short column (SiO_2). Evaporation of solvents followed by distillation afforded epoxylactone **12** as viscous oil (3.39 g, 67.8%, b.p. 62–65 °C/250 Pa, ref.[14] 79 °C/100 Pa).

Ethyl (Diethoxyphosphoryl)fluoroacetate (**15**)

A flask equipped with a magnetic stirbar, reflux condenser and vacuum source was charged with fluoroiodoacetate **14** (6.39 g, 27.5 mmol) and triethyl phosphite (5.5 g, 33 mmol). Vacuum was set to 4 kPa and the reaction mixture was heated to reflux for 19 h while stirred. Fluorophosphonoacetate **15** (4.94 g, 74.2%, b.p. 104–107 °C/7 Pa, ref.[20] 107–109 °C/40 Pa) was obtained by distillation of the reaction mixture.

Ethyl 4-Acetoxy-2-fluorobut-2-enoate (**17**)

A 1 000 ml flask equipped with magnetic stirbar, septum and external cooling bath was charged with fluorophosphonoacetate **15** (43.39 g, 179.2 mmol) and THF (360 ml). The mixture was cooled to –80 °C while stirred and BuLi solution (2.5 M in hexanes, 80 ml, 200 mmol) was dropwise syringed to it, followed after 15 min by addition of 2-oxoethyl acetate **16** (17.32 g, 169.8 mmol). The resulting mixture was stirred for 2 h at –80 °C and heated to room temperature. THF was removed on a vacuum rotary evaporator and diethyl ether (200 ml) followed by water (200 ml) was added to the crude reaction product. The water layer was removed and extracted with diethyl ether (3 × 300 ml), organic phases were collected, dried with anhydrous $MgSO_4$, the drying agent was filtered off and diethyl ether was removed on a vacuum rotary evaporator to afford crude fluoroester **17** (30.7 g, 95.0%), which

was directly used in the next step. Distillation of a representative sample of the crude product (1.00 g, 5.26 mmol) afforded pure product **17** as colourless liquid (659 mg, 62.6%, b.p. 50–51 °C/130 Pa, *E/Z* ratio 90 : 10). ^{1}H NMR (300.1 MHz, $CDCl_3$): (*E*)-isomer 1.36 t, 3 H, $^3J_{H,H}$ = 7.1 (CH_3CH_2); 2.06 s, 3 H, (CH_3CO); 4.30 q, 2 H, $^3J_{H,H}$ = 7.1 (CH_3CH_2); 5.04 dd, 2 H, $^3J_{H,H}$ = 6.5, $^4J_{H,F}$ = 3.2 (CH_2CH=); 5.96 dt, 1 H, $^3J_{H,H}$ = 6.5, $^3J_{H,F}$ = 18.6 (CH=CF); (*Z*)-isomer 1.36 t, 3 H, $^3J_{H,H}$ = 7.1 (CH_3CH_2); 2.06 s, 3 H, (CH_3CO); 4.30 q, 2 H, $^3J_{H,H}$ = 7.1 (CH_3CH_2); 4.80 dd, 2 H, $^3J_{H,H}$ = 6.7, $^4J_{H,F}$ = 2.6 (CH_2CH=); 6.21 dt, 1 H, $^3J_{H,H}$ = 6.8, $^3J_{H,F}$ = 31.9 (CH=CF). ^{13}C NMR (100.6 MHz,$CDCl_3$): (*E*)-isomer 13.9 s (CH_3CH_2); 20.4 s (CH_3CO); 58.9 d, $^3J_{C,F}$ = 8 (CH_2CH=); 62.0 s (CH_3CH_2); 118.2 d, $^2J_{C,F}$ = 21 (CH=CF); 147.9 d, $^1J_{C,F}$ = 260 (CH=CF); 160.3 d, $^2J_{C,F}$ = 35, (CF=CO); 170.4 s (CH_3CO); (*Z*)-isomer signals are too weak for assignment. ^{19}F NMR (76.5 MHz, $CDCl_3$): (*E*)-isomer –119.8 dt, 1 F, $^3J_{H,F}$ = 19, $^4J_{H,F}$ = 3 (=CF); (*Z*)-isomer –124.5 dt, 1 F, $^3J_{H,F}$ = 31, $^4J_{H,F}$ = 3 (=CF). IR ($CHCl_3$): 1 740 s, 1 875 w, 3 026 w. For $C_8H_{11}FO_4$ (190.2) calculated: 50.5% C, 5.8% H, 10.0% F; found: 49.5% C, 6.0% H, 9.6% F.

3-Fluorofuran-2(5*H*)-one (**1**)

Method A. A 10 ml flask equipped with Hückmann adapter and a source of vacuum was charged with P_2O_5 (4.25 g, 1.50 mmol) and fluorolactone **13** (898 mg, 7.48 mmol). Vacuum was set to 2 kPa and the mixture was heated to 200 °C for 4 h while distilling the product off continunously. Washing the Hückmann adapter with $CHCl_3$ and removing solvent *in vacuo* yielded pure furanone **1** (238 mg, 31.0%).

Method B. A 1 000 ml flask equipped with magnetic stirbar was charged with crude fluoroester **17** (29.63 g, 155.9 mmol), dioxane (250 ml), and aqueous NaOH solution (10%, 250 ml). The resulting two-phase system was stirred overnight at room temperature The resulting homogeneous solution was extracted with CH_2Cl_2 (2 × 200 ml) to remove organic admixtures (mainly various acetals from preparation of oxoester **16**) and then acidified with HCl (1 : 1) to pH 1. The two-phase system formed was continuously extracted with $CHCl_3$ for 12 h. The organic phase was dried with anhydrous $MgSO_4$, the drying agent was filtered off and solvents were removed on a rotary vacuum evaporator. Final vacuum distillation afforded product **1** as colourless liquid (8.61 g, 56.0%, b.p. 98–99 °C/2 kPa). ^{1}H NMR (300.1 MHz, $CDCl_3$): 4.90 dd, 2 H, $^3J_{H,H}$ = 1.8, $^4J_{H,F}$ = 5.9 (CH_2CH=); 6.90 q, 1 H, $^3J_{H,H}$ = $^3J_{H,F}$ = 2.0 (CH_2CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): 66.8 d, $^3J_{C,F}$ = 8 (CH_2); 123.2 d, $^2J_{C,F}$ = 8 (CH=); 148.9 d, $^1J_{C,F}$ = 277 (=CF); 165.6 d, $^2J_{C,F}$ = 32 (CO). ^{19}F NMR (76.5 MHz, $CDCl_3$): –142.2 dt, 1 F, $^3J_{H,F}$ = 2, $^4J_{H,F}$ = 6 (=CF). IR ($CHCl_3$): 1 682 m, 1 785 s, 3 025 w, 3 116 w. For $C_4H_3FO_2$ (102.1) calculated: 47.1% C, 3.0% H, 18.6% F; found: 46.9% C, 3.4% H, 18.3% F.

Conjugate Additions. General Procedure

A flask equipped with magnetic stirbar, rubber septum and cooling bath was charged with arenecarboxaldehyde dithioacetal **7** and THF, cooled to –80 °C, and a small excess of BuLi (105%, given concentration in hexanes) was added dropwise to it. After 1 h, an equivalent of unsaturated fluorolactone **1** or fluoroester **2** was added dropwise and the resulting mixture was stirred for 3 h at –80 °C. The reaction was stopped by quenching with HCl (10% solution in THF) at –80 °C. The reaction mixture was allowed to reach room temperature and solvents were removed on a rotary vacuum evaporator. The product was isolated by repeated column chromatography.

3-Fluoro-4-[phenylbis(phenylsulfanyl)methyl]-4,5-dihydrofuran-2(3H)-one (**3a**). Reaction of dithioacetal **7a** (685 mg, 2.22 mmol), BuLi solution (1.40 ml, 1.89 mol l^{-1}, 2.50 mmol), and fluorolactone **1** (202 mg, 1.98 mmol) in THF (6 ml) afforded after purification by column chromatography (SiO_2, 20 × 3 cm, gradient elution first with petroleum ether–CH_2Cl_2 4 : 1, then with CH_2Cl_2) fluorolactone **3a** (white crystals, 352 mg, 41.4%, m.p. 46–52 °C) as a mixture of diastereoisomers ((3*R**,4*R**)/(3*R**,4*S**) = 57 : 43). ^{1}H NMR (300.1 MHz, $CDCl_3$): (3*R**,4*R**)-**3a** 3.50 ddt, 1 H, $^3J_{H,H}$ = 8.2, $^3J_{H,H}$ = 6.6 (t), $^3J_{H,F}$ = 25.8 (C**H**-CHF); 4.41 dd, 1 H, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 7.1 (OC$\mathbf{H}_a$$H_b$-CH); 4.58 t, 1 H, $^2J_{H,H}$ = $^3J_{H,H}$ = 9.3 (OC$H_a$$\mathbf{H}_b$-CH); 5.31 dd, 1 H, $^3J_{H,H}$ = 6.1, $^2J_{H,F}$ = 49.5 (CHF); 7.23–7.35 m, 13 H (Ar-H); 7.68 d, 2 H, $^3J_{H,H}$ = 8.2 (Ar-H); (3*R**,4*S**)-**3a** 3.20 ddt, 1 H, $^3J_{H,H}$ = 7.1 (t), $^3J_{H,H}$ = 6.6, $^3J_{H,F}$ = 20.3 (C**H**-CHF); 4.54 dd, 1 H, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 7.1 (OC$\mathbf{H}_a$$H_b$-CH); 4.90 dd, 1 H, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 6.6 (OC$H_a$$\mathbf{H}_b$-CH); 5.17 dd, 1 H, $^3J_{H,H}$ = 7.2, $^2J_{H,F}$ = 50.6 (CHF); 7.10–7.80 m, 15 H (Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): (3*R**,4*R**)-**3a** 50.3 d, $^3J_{C,F}$ = 19 (CH-CHF); 67.8 d, $^4J_{C,F}$ = 5 (OCH_2-CH); 69.3 s ($C(SPh)_2$); 88.4 d, $^1J_{C,F}$ = 190 (CHF); 128.8–136.8 all s, 18 C (C_{Ar}); 171.1 d, $^2J_{C,F}$ = 16 (CO); (3*R**,4*S**)-**3a** 48.3 d, $^3J_{C,F}$ = 17 (CH-CHF); 68.5 s (OCH_2-CH); 69.8 s ($C(SPh)_2$); 86.7 d, $^1J_{C,F}$ = 199 (CHF); 128.8–136.8 all s, 18 C (C_{Ar}); 171.3 d, $^2J_{C,F}$ = 16 (CO). ^{19}F NMR (76.5 MHz, $CDCl_3$): (3*R**,4*R**)-**3a** –187.1 dd, 1 F, $^2J_{H,F}$ = 50, $^3J_{H,F}$ = 26 (CHF); (3*R**,4*S**)-**3a** –202.4 dd, 1 F, $^2J_{H,F}$ = 51, $^3J_{H,F}$ = 21 (CHF). IR ($CHCl_3$): 1 026 m, 1 219 s, 1 440 m, 1 478 w, 1 799 s, 3 025 w. For $C_{23}H_{19}FO_2S_2$ (410.5) calculated: 67.3% C, 4.6% H; found: 65.5% C, 4.78% H.

3-Fluoro-4-[(4-methoxyphenyl)bis(phenylsulfanyl)methyl]-4,5-dihydrofuran-2(3H)-one (**3b**). Reaction of dithioacetal **7b** (708 mg, 2.09 mmol), BuLi solution (1.32 ml, 1.89 mol l^{-1}, 2.25 mmol), and fluorolactone **1** (205 mg, 2.01 mmol) in THF (6 ml) afforded after purification by repeated column chromatography (first SiO_2, 30 × 3 cm, eluent petroleum ether–CH_2Cl_2 1 : 1, then SiO_2, 15 × 3 cm, eluent CH_2Cl_2) fluorolactone **3b** (white crystals, 462 mg, 52.4%) as a mixture of diastereoisomers ((3*R**,4*R**)/(3*R**,4*S**) 44 : 56). ^{1}H NMR (300.1 MHz, $CDCl_3$): (3*R**,4*R**)-**3b** 3.44 ddt, 1 H, $^3J_{H,H}$ = 8.2, $^3J_{H,H}$ = 6.6 (t), $^3J_{H,F}$ = 25.8 (C**H**-CHF); 3.82 s, 3 H (CH_3O); 4.29 dd, 1 H, $^2J_{H,H}$ = 10.0, $^3J_{H,H}$ = 7.2 (OC$\mathbf{H}_a$$H_b$-CH); 4.55 dd, 1 H, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 8.8 (OC$H_a$$\mathbf{H}_b$-CH); 5.27 dd, 1 H, $^3J_{H,H}$ = 6.1, $^2J_{H,F}$ = 50.0 (CHF); 6.85 d, 2 H, $^3J_{H,H}$ = 8.8 (Ar-H); 7.23–7.35 m, 10 H (Ar-H); 7.60 d, 2 H, $^3J_{H,H}$ = 8.2 (Ar-H); (3*R**,4*S**)-**3b** 3.11 dq, 1 H, $^3J_{H,H}$ = 7.1 (q), $^3J_{H,F}$ = 22.9 (C**H**-CHF); 3.81 s, 3 H (CH_3O); 4.53 dd, 1 H, $^2J_{H,H}$ = 9.3, $^3J_{H,H}$ = 7.1 (OC$\mathbf{H}_a$$H_b$-CH); 4.85 dd, 1 H, $^2J_{H,H}$ = 9.3, $^3J_{H,H}$ = 6.6 (OC$H_a$$\mathbf{H}_b$-CH); 5.14 dd, 1 H, $^3J_{H,H}$ = 6.6, $^2J_{H,F}$ = 50.6 (CHF); 6.83 d, 2 H, $^3J_{H,H}$ = 9.3 (Ar-H); 7.08–7.38 m, 10 H (Ar-H); 7.52 d, 2 H, $^3J_{H,H}$ = 8.9 (Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): (3*R**,4*R**)-**3b** 50.3 d, $^2J_{C,F}$ = 19 (CH-CHF); 55.9 s (OCH_3); 67.8 d, $^3J_{C,F}$ = 8 (OCH_2-CH); 67.6 s ($C(SPh)_2$); 88.2 d, $^1J_{C,F}$ = 190 (CHF); 114.5 s, 2 C (C_{Ar}); 129.4–135.9 all s, 15 C (C_{Ar}); 160.2 s (C_{Ar}-OCH_3); 171.3 d, $^2J_{C,F}$ = 22 (CO); (3*R**,4*S**)-**3b** – this diastereoisomer was not sufficiently separated from the former one to enable unequivocal assignment. ^{19}F NMR (76.5 MHz, $CDCl_3$): (3*R**,4*R**)-**3b** –187.5 dd, 1 F, $^2J_{H,F}$ = 50, $^3J_{H,F}$ = 26 (CHF); (3*R**,4*S**)-**3b** –202.9 dd, 1 F, $^2J_{H,F}$ = 51, $^3J_{H,F}$ = 22 (CHF). IR ($CHCl_3$): 1 027 m, 1 091 w, 1 257 s, 1 440 w, 1 509 m, 1 793 s, 3 012 w. Microanalysis was not accomplished due to low stability of the product.

4-[(3,4-Dimethoxyphenyl)bis(phenylsulfanyl)methyl]-3-fluoro-4,5-dihydrofuran-2(3H)-one (**3c**). Reaction of dithioacetal **7c** (733 mg, 1.99 mmol), BuLi solution (0.90 ml, 2.19 mol l^{-1}, 1.99 mmol), and fluorolactone **1** (204 mg, 2.00 mmol) in THF (6 ml) afforded after purification by repeated column chromatography (first SiO_2, 30 × 3 cm, eluent petroleum ether–CH_2Cl_2 1 : 1, then SiO_2, 15 × 3 cm, eluent CH_2Cl_2) fluorolactone **3c** (white crystals, 538 mg, 57.2%, m.p. 48–51 °C) as a mixture of diastereoisomers ((3*R**,4*R**)/(3*R**,4*S**) 63 : 37). ^{1}H NMR (300.1 MHz, $CDCl_3$): (3*R**,4*R**)-**3c** 3.44 ddt, 1 H, $^3J_{H,H}$ = 8.8, $^3J_{H,H}$ = 6.6 (t), $^3J_{H,F}$ = 25.8 (C**H**-CHF);

3.77 s, 3 H (CH_3O); 3.89 s, 3 H (CH_3O); 4.48 dd, 1 H, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 7.1 (OC**H**$_a$H$_b$-CH); 4.58 dd, 1 H, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 8.8 (OCH$_a$**H**$_b$-CH); 5.30 dd, 1 H, $^3J_{H,H}$ = 6.1, $^2J_{H,F}$ = 49.5 (CHF); 6.77 d, 2 H, $^3J_{H,H}$ = 8.8 (Ar-H); 7.22–7.35 m, 11 H (Ar-H); (3*R**,4*S**)-**3c** 3.10 ddt, 1 H, $^3J_{H,H}$ = 7.1 (t), $^3J_{H,H}$ = 6.6, $^3J_{H,F}$ = 21.4 (C**H**-CHF); 3.79 s, 3 H (CH_3O); 3.89 s, 3 H (CH_3O); 4.50 dd, 1 H, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 7.1 (OC**H**$_a$H$_b$-CH); 4.85 dd, 1 H, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 6.6 (OCH$_a$**H**$_b$-CH); 5.16 dd, 1 H, $^3J_{H,H}$ = 6.6, $^2J_{H,F}$ = 50.5 (CHF); 6.74–7.52 m, 13 H (Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): (3*R**,4*R**)-**3c** 50.3 d, $^2J_{C,F}$ = 18 (CH-CHF); 56.6 s, 2 C (OCH_3); 67.9 d, $^3J_{C,F}$ = 5 (OCH_2-CH); 69.3 d, $^3J_{C,F}$ = 14 ($C(SPh)_2$); 88.4 d, $^1J_{C,F}$ = 190 (CHF); 111.0–121.7 all s, 3C (C_{Ar}); 129.7–131.3 all s, 13 C (C_{Ar}); 149.4 s (C_{Ar}-OCH_3); 149.8 s (C_{Ar}-OCH_3); 171.3 d, $^2J_{C,F}$ = 22 (CO); (3*R**,4*S**)-**3c** – this diastereoisomer was not sufficiently separated from the former one to enable unequivocal assignment. ^{19}F NMR (76.5 MHz, $CDCl_3$): (3*R**,4*R**)-**3c** –186.8 dd, 1 F, $^2J_{H,F}$ = 50, $^3J_{H,F}$ = 26 (CHF); (3*R**,4*S**)-**3c** –202.3 dd, 1 F, $^2J_{H,F}$ = 51, $^3J_{H,F}$ = 22 (CHF). IR ($CHCl_3$): 1 025 s, 1 145 m, 1 259 s, 1 515 s, 1 797 s, 3 027 w. For $C_{25}H_{23}FO_4S_2$ (470.6) calculated: 63.8% C, 4.9% H; found: 63.9% C, 5.1% H.

4-[(1,3-Benzodioxol-5-yl)bis(phenylsulfanyl)methyl]-3-fluoro-4,5-dihydrofuran-2(3H)-one (**3d**). Reaction of dithioacetal **7d** (702 mg, 1.99 mmol), BuLi solution (0.90 ml, 2.19 mol l^{-1}, 1.99 mmol), and fluorolactone **1** (207 mg, 2.03 mmol) in THF (6 ml) afforded after purification by repeated column chromatography (first SiO_2, 15 × 3 cm, eluent $CHCl_3$, then SiO_2, 15 × 3 cm, eluent petroleum ether–CH_2Cl_2 1 : 1) fluorolactone **3d** (white crystals, 127 mg, 13.8%, m.p. 95–106 °C) as a mixture of diastereoisomers ((3*R**,4*R**)/(3*R**,4*S**) 72 : 28). ^{1}H NMR (300.1 MHz, $CDCl_3$): (3*R**,4*R**)-**3d** 3.39 ddt, 1 H, $^3J_{H,H}$ = 8.2, $^3J_{H,H}$ = 6.8 (t), $^3J_{H,F}$ = 25.8 (C**H**-CHF); 4.40 dd, 1 H, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 7.1 (OC**H**$_a$H$_b$-CH); 4.54 dd, 1 H, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 8.8 (OCH$_a$**H**$_b$-CH); 5.28 dd, 1 H, $^3J_{H,H}$ = 6.0, $^2J_{H,F}$ = 50.0 (CHF); 6.02 s, 2 H (OCH_2O); 6.71 d, 1 H, $^3J_{H,H}$ = 8.2 (Ar-H); 7.03 d, 1 H, $^3J_{H,H}$ = 8.2 (Ar-H); 7.38 s, 1 H (Ar-H); 7.24–7.37 m, 10 H (Ar-H); (3*R**,4*S**)-**3d** 3.09 dq, 1 H, $^3J_{H,H}$ = 6.6 (q), $^3J_{H,F}$ = 20.3 (C**H**-CHF); 4.48 dd, 1 H, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 7.1 (OC**H**$_a$H$_b$-CH); 4.87 dd, 1 H, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 6.0 (OCH$_a$**H**$_b$-CH); 5.15 dd, 1 H, $^3J_{H,H}$ = 6.6, $^2J_{H,F}$ = 50.5 (CHF); 5.97 s, 2 H (OCH_2O); 6.67 d, 1 H, $^3J_{H,H}$ = 8.2 (Ar-H); 7.08 d, 1 H, $^3J_{H,H}$ = 8.2 (Ar-H); 7.17–7.39 m, 11 H (Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): (3*R**,4*R**)-**3d** 50.5 d, $^2J_{C,F}$ = 19 (CH-CHF); 67.7 d, $^3J_{C,F}$ = 5 (OCH_2-CH); 70.2 s ($C(SPh)_2$); 88.3 d, $^1J_{C,F}$ = 190 (CHF); 102.4 s (OCH_2O); 108.4 s (C_{Ar}); 110.8 s (C_{Ar}); 123.3 s (C_{Ar}); 129.7–136.0 all s, 13 C (C_{Ar}); 148.5 s (C_{Ar}-OCH_2); 149.0 s (C_{Ar}-OCH_2); (3*R**,4*S**)-**3d** – this diastereoisomer was not sufficiently separated from the former one to enable unequivocal assignment. ^{19}F NMR (76.5 MHz, $CDCl_3$): (3*R**,4*R**)-**3d** –187.2 dd, 1 F, $^2J_{H,F}$ = 50, $^3J_{H,F}$ = 26 (CHF); (3*R**,4*S**)-**3d** –202.6 dd, 1 F, $^2J_{H,F}$ = 50, $^3J_{H,F}$ = 20 (CHF). IR ($CHCl_3$): 1 041 s, 1 103 w, 1 240 s, 1 431 m, 1 466 s, 1 505 s, 1 795 s, 3 028 w. For $C_{24}H_{19}FO_4S_2$ (454.5) calculated: 63.4% C, 4.2% H; found: 62.9% C, 4.5% H.

Ethyl 3-[(3,4-dimethoxyphenyl)bis(phenylsulfanyl)methyl]-2-fluorobutanoate (**4**). Reaction of dithioacetal **7c** (770 mg, 2.09 mmol), BuLi solution (1.32 ml, 1.89 mol l^{-1}, 2.25 mmol), and fluoroester **2** (261 mg, 1.98 mmol) in THF (6 ml) afforded after purification by repeated column chromatography (first SiO_2, 20 × 3 cm, eluent CH_2Cl_2, then SiO_2, 15 × 3 cm, eluent petroleum ether–EtOAc 3 : 2) fluoroester **4** (white crystals, 787 mg, 79.6%) as a mixture of diastereoisomers ((2*R**,3*R**)/(2*R**,3*S**) 69 : 31). ^{1}H NMR (300.1 MHz, $CDCl_3$): (2*R**,3*R**)-**4** 1.16 d, 3 H, $^3J_{H,H}$ = 7.1 (C**H**$_3$CH); 1.26 t, $^3J_{H,H}$ = 7.1 (C**H**$_3$CH$_2$O); 2.80 dq, 1 H, $^3J_{H,H}$ = 7.1, $^3J_{H,F}$ = 30.0 (C**H**-CHF); 3.77 s, 3 H (OCH_3); 3.87 s, 3 H (OCH_3); 4.12 q, 2 H, $^3J_{H,H}$ = 7.2 (OC**H**$_2$CH$_3$); 5.95 d, 1 H, $^2J_{H,F}$ = 49.5 (CHF); 6.78–7.42 m, 13 H (Ar-H); (2*R**,3*S**)-**4** 1.15 d, 3 H, $^3J_{H,H}$ = 7.1 (C**H**$_3$CH); 1.18 t, $^3J_{H,H}$ = 7.1 (C**H**$_3$CH$_2$O); 2.88 d of quintet, 1 H, $^3J_{H,H}$ = 6.5, $^3J_{H,F}$ = 21.0 (C**H**-CHF); 3.77 s, 3 H (OCH_3); 3.88 s, 3 H (OCH_3); 4.09 q, 2 H, $^3J_{H,H}$ = 7.2 (OC**H**$_2$CH$_3$); 5.13 dd,

1 H, $^3J_{H,H}$ = 6.0, $^2J_{H,F}$ = 47.8 (CHF). ^{13}C NMR spectra were not recorded due to low stability of the product. ^{19}F NMR (76.5 MHz, $CDCl_3$): (2*R**,3*R**)-**4** –200.5 dd, 1 F, $^2J_{H,F}$ = 49, $^3J_{H,F}$ = 29 (CHF); (2*R**,3*S**)-**4** –177.4 dd, 1 F, $^2J_{H,F}$ = 48, $^3J_{H,F}$ = 21 (CHF). IR ($CHCl_3$): 1 026 s, 1 140 m, 1 261 s, 1 440 m, 1 465 m, 1 511 s, 1 583 s, 1 728 s, 3 026 w. Microanalysis was not accomplished due to low stability of the product.

Tandem Additions. General Procedure

A flask equipped with a magnetic stirbar, rubber septum and cooling bath was charged with arenecarboxaldehyde dithioacetal **7**, THF, cooled to –80 °C and a small excess of BuLi (105%, given concentration in hexanes) was added dropwise. After 1 h, one equivalent of unsaturated fluorolactone **1** was added dropwise and the resulting mixture was stirred at –80 °C for 3 h. The solution of fluoroenolate thus formed was transferred with a cooled (solid CO_2) Teflon capillary into a stirred arenecarboxaldehyde **8** or (arylmethyl)bromide **9** (*ca* 0.8 equivalent with respect to fluorocompound) cooled to –80 °C. The resulting mixture was stirred at –80 °C for 0.5 h and at –30 °C for 2 h. The reaction was stopped by quenching with HCl (10% solution in THF) at –80 °C. The reaction mixture was allowed to reach room temperature and solvents were removed by rotary vacuum evaporator. The product was isolated by repeated column chromatography. Attempts to perform analogous tandem additions with fluoroester **2** were only marginally successful due to low stability of the products[21].

3-Fluoro-3-[hydroxy(3,4,5-trimethoxyphenyl)methyl]-4-[phenylbis(phenylsulfanyl)methyl]-4,5-dihydrofuran-2(3H)-one (**5a**). The reaction of dithioacetal **7a** (682 mg, 2.21 mmol), BuLi solution (1.40 ml, 1.89 mol l^{-1}, 2.50 mmol), and fluorolactone **1** (206 mg, 2.02 mmol) in THF (6 ml) with 3,4,5-trimethoxybenzaldehyde (**8e**, 295 mg, 1.51 mmol) in THF (2 ml) afforded after purification by column chromatography (SiO_2, 20 × 3 cm, gradient elution first with CH_2Cl_2, then with EtOAc) fluorolactone **5a** (white crystals, 787 mg, 64.3%, m.p. 76–86 °C) as a mixture of two diastereoisomers (*syn*-(1′*R**,3*R**,4*S**)/*anti*-(1′*R**,3*S**,4*R**) 19 : 81). ^{1}H NMR (300.1 MHz, $CDCl_3$): *syn*-(1′*R**,3*R**,4*S**)-**5a** – this diastereoisomer was not sufficiently separated from the latter one to enable unequivocal assignment; *anti*-(1′*R**,3*S**,4*R**)-**5a** 3.09 d, 1 H, $^3J_{H,H}$ = 4.4 (OH); 3.34 d, 1 H, $^3J_{H,H}$ = 7.7 (CH_2-C**H**-CF); 3.70 s, 6 H (CH_3O); 3.82 s, 3 H (CH_3O); 4.40 dd, 1 H, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 7.7 (OC**H**$_a$H$_b$-CH); 5.08 dd, 1 H, $^3J_{H,H}$ = 3.9, $^3J_{H,F}$ = 8.8 (C**H**-OH); 5.24 d, 1 H, $^2J_{H,H}$ = 9.9 (OCH$_a$**H**$_b$-CH); 6.47 s, 2 H (Ar-H); 6.92–7.99 m, 15 H (Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): *syn*-(1′*R**,3*R**,4*S**)-**5a** – this diastereoisomer was not sufficiently separated from the latter one to enable unequivocal assignment; *anti*-(1′*R**,3*S**,4*R**)-**5a** 46.3 d, $^2J_{C,F}$ = 16 (CH_2-CH-CF); 57.0 s, 2 C, (CH_3O); 61.6 s, 1 C, (CH_3O); 69.0 s (OCH_2-CH); 70.2 s (C(SPh)$_2$); 75.9 d, $^2J_{C,F}$ = 11 (CF-CH-OH); 95.8 d, $^1J_{C,F}$ = 209 (CF); 103.7–106.7 all s, 7 C (C_{Ar}); 127.8–138.5 all s, 14 C (C_{Ar}); 154.0 s, 2 C (C_{Ar}-OCH_3); 154.2 s (C_{Ar}-OCH_3). ^{19}F NMR (76.5 MHz, $CDCl_3$): *syn*-(1′*R**,3*R**,4*S**)-**5a** –165.6 d, 1 F, $^3J_{H,F}$ = 10 (CF); *anti*-(1′*R**,3*S**,4*R**)-**5a** –168.4 d, 1 F, $^3J_{H,F}$ = 9 (CF). IR ($CHCl_3$): 1 131 s, 1 230 m, 1 333 w, 1 422 w, 1 464 m, 1 507 w, 1 599 w, 1 766 m, 3 022 w. For $C_{33}H_{31}FO_6S_2$ (606.7) calculated: 65.4% C, 5.1% H; found: 64.9% C, 5.4% H.

4-[(3,4-Dimethoxyphenyl)bis(phenylsulfanyl)methyl]-3-fluoro-3-[hydroxy(3,4,5-trimethoxyphenyl)-methyl]-4,5-dihydrofuran-2(3H)-one (**5b**). The reaction of dithioacetal **7c** (772 mg, 2.10 mmol), BuLi solution (1.30 ml, 1.89 mol l^{-1}, 2.30 mmol), and fluorolactone **1** (202 mg, 1.98 mmol) in THF (6 ml) with 3,4,5-trimethoxybenzaldehyde (**8e**, 310 mg, 1.58 mmol) in THF (2 ml) afforded after purification by column chromatography (first SiO_2, 30 × 3 cm, eluent CH_2Cl_2,

then SiO_2, 20 × 3 cm, eluent CH_2Cl_2–EtOAc 6 : 1) fluorolactone **5b** (white crystals, 765 mg, 58.0%, m.p. 77–90 °C) as a mixture of two diastereoisomers (*syn*-(1′*R**,3*R**,4*S**)/*anti*-(1′*R**,3*S**,4*R**) 27 : 73). ^{1}H NMR (300.1 MHz, $CDCl_3$): *syn*-(1′*R**,3*R**,4*S**)-**5b** 3.10 dd, 1 H, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 7.8 (OC**H**$_a$H$_b$-CH); 3.48 d, 1 H, $^3J_{H,H}$ = 6.6 (CH_2-C**H**-CF); 3.63–3.88 m, 15 H (CH_3O); 4.95 d, 1 H, $^3J_{H,F}$ = 9.9 (C**H**-OH); 5.05 d, 1 H, $^2J_{H,H}$ = 9.9 (OCH$_a$**H**$_b$-CH); 6.40–7.99 m, 15 H (Ar-H); *anti*-(1′*R**,3*S**,4*R**)-**5b** 3.23 d, 1 H, $^3J_{H,H}$ = 7.8 (CH_2-C**H**-CF); 3.63–3.88 m, 15 H (CH_3O); 4.32 dd, 1 H, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 8.7 (OC**H**$_a$H$_b$-CH); 5.05 d, 1 H, $^3J_{H,F}$ = 8.8 (C**H**-OH); 5.18 d, 1 H, $^2J_{H,H}$ = 9.3 (OCH$_a$**H**$_b$-CH); 6.40–7.99 m, 15 H (Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): *syn*-(1′*R**,3*R**,4*S**)-**5b** – this diastereoisomer was not sufficiently separated from the latter one to enable unequivocal assignment; *anti*-(1′*R**,3*S**,4*R**)-**5b** 46.8 d, $^2J_{C,F}$ = 18 (CH_2-CH-CF); 56.4 s, 1 C (CH_3O); 56.6 s, 1 C (CH_3O); 56.9 s, 2 C (CH_3O); 57.0 s, 1 C (CH_3O); 61.7 d, $^2J_{C,F}$ = 15 (CF-CH-OH); 69.6 s (OCH_2-CH); 70.7 s (C(SPh)$_2$); 95.8 d, $^1J_{C,F}$ = 206 (CF); 104.2–113.9 all s, 5 C (C_{Ar}); 129.2–138.2 all s, 14 C (C_{Ar}); 148.9–154.0 all s, 5 C (C_{Ar}-OCH_3). ^{19}F NMR (76.5 MHz, $CDCl_3$): *syn*-(1′*R**,3*R**,4*S**)-**5b** –165.1 d, 1 F, $^3J_{H,F}$ = 10 (CF); *anti*-(1′*R**,3*S**,4*R**)-**5b** –168.0 d, 1 F, $^3J_{H,F}$ = 9 (CF). IR and elemental analyses were not accomplished due to low stability of the product.

4-[(1,3-Benzodioxol-5-yl)bis(phenylsulfanyl)methyl]-3-fluoro-3-(hydroxyphenylmethyl)-4,5-dihydrofuran-2(3H)-one (**5c**). The reaction of dithioacetal **7d** (703 mg, 2.00 mmol), BuLi solution (0.90 ml, 2.19 mol l^{-1}, 2.00 mmol), and fluorolactone **1** (210 mg, 2.06 mmol) in THF (6 ml) with benzaldehyde (**8a**, 190 mg, 1.79 mmol) in THF (2 ml) afforded after purification by column chromatography (first SiO_2, 15 × 3 cm, eluent EtOAc, then SiO_2, 30 × 3 cm, eluent petroleum ether–EtOAc 7 : 3) fluorolactone **5c** (white crystals, 589 mg, 51.1%, m.p. 190–194 °C) as a mixture of diastereoisomers (*syn*-(1′*R**,3*R**,4*S**)/*anti*-(1′*R**,3*S**,4*R**) 38 : 62). ^{1}H NMR (300.1 MHz, $CDCl_3$): *syn*-(1′*R**,3*R**,4*S**)-**5c** 2.86 dd, 1 H, $^2J_{H,H}$ = 8.6, $^3J_{H,H}$ = 6.9 (OC**H**$_a$H$_b$-CH); 3.14 bs, 1 H (OH); 3.43 d, 1 H, $^3J_{H,H}$ = 5.1 (CH_2-C**H**-CF); 4.83 d, 1 H, $^2J_{H,H}$ = 10.3 (OCH$_a$**H**$_b$-CH); 5.09 d, 1 H, $^3J_{H,F}$ = 10.3 (C**H**-OH); 5.95 s, 2 H (OCH_2O); 6.56–7.70 m, 18 H (Ar-H); *anti*-(1′*R**,3*S**,4*R**)-**5c** 2.61 s, 1 H (OH); 3.16 d, 1 H, $^3J_{H,H}$ = 8.2 (CH_2-C**H**-CF); 4.04 dd, 1 H, $^2J_{H,H}$ = 9.3, $^3J_{H,H}$ = 8.2 (OC**H**$_a$H$_b$-CH); 5.06 d, 1 H, $^2J_{H,H}$ = 11.0 (OCH$_a$**H**$_b$-CH); 5.10 d, 1 H, $^3J_{H,F}$ = 10.4 (C**H**-OH); 5.94 s, 2 H (OCH_2); 6.19 d, 1 H, $^3J_{H,H}$ = 8.2 (Ar-H); 6.25 d, 1 H, $^3J_{H,H}$ = 8.2 (Ar-H); 6.75–7.67 m, 16 H (Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): *syn*-(1′*R**,3*R**,4*S**)-**5c** – this diastereoisomer was not sufficiently separated from the latter one to enable unequivocal assignment; *anti*-(1′*R**,3*S**,4*R**)-**5c** 46.2 d, $^2J_{C,F}$ = 16 (CH_2-CH-CF); 69.6 s (OCH_2-CH); 72.0 s (C(SPh)$_2$); 74.3 d, $^2J_{C,F}$ = 25 (CF-CH-OH); 96.0 d, $^1J_{C,F}$ = 209 (CF); 101.1 s (OCH_2O); 106.4 s, 1 C (C_{Ar}); 109.7 s, 1 C (C_{Ar}); 125.3–139.6 all s, 19 C (C_{Ar}); 146.3 s, 1 C (C_{Ar}-OCH_2); 146.5 s, 1 C (C_{Ar}-OCH_2); 170.7 d, $^2J_{C,F}$ = 24 (CO). ^{19}F NMR (76.5 MHz, $CDCl_3$): *syn*-(1′*R**,3*R**,4*S**)-**5c** –165.7 dd, 1 F, $^3J_{H,F}$ = 10, $^3J_{H,F}$ = 2 (CF); *anti*-(1′*R**,3*S**,4*R**)-**5c** –169.1 dd, 1 F, $^3J_{H,F}$ = 9, $^3J_{H,F}$ = 1 (CF). IR ($CHCl_3$): 1 042 m, 1 142 w, 1 239 s, 1 408 m, 1 487 s, 1 505 m, 1 786 s, 3 022 w. For $C_{31}H_{25}FO_5S_2$ (560.7) calculated: 66.4% C, 4.5% H; found: 65.3% C, 4.8% H.

4-[(1,3-Benzodioxol-5-yl)bis(phenylsulfanyl)methyl]-3-fluoro-3-[hydroxy(3,4,5-trimethoxyphenyl)-methyl)-4,5-dihydrofuran-2(3H)-one (**5d**). Reaction of dithioacetal **7d** (706 mg, 2.01 mmol), BuLi solution (0.90 ml, 2.19 mol l^{-1}, 2.00 mmol), and fluorolactone **1** (206 mg, 2.02 mmol) in THF (6 ml) with 3,4,5-trimethoxybenzaldehyde (**8e**, 296 mg, 1.51 mmol) in THF (2 ml) afforded after purification by column chromatography (first SiO_2, 15 × 3 cm, eluent petroleum ether–EtOAc 6 : 4, then SiO_2, 30 × 3 cm, eluent $CHCl_3$–EtOAc 9 : 1) fluorolactone **5d** (white crystals, 767 mg, 58.4%, m.p. 188–195 °C) as a mixture of two diastereoisomers (*syn*-(1′*R**,3*R**,4*S**)/*anti*-(1′*R**,3*S**,4*R**) 45 : 55). ^{1}H NMR (300.1 MHz, $CDCl_3$): *syn*-(1′*R**,3*R**,4*S**)-**5d**

3.00 bs, 1 H (OH); 3.12 dd, 1 H, $^2J_{H,H}$ = 9.8, $^3J_{H,H}$ = 7.5 (OC**H**$_a$H$_b$-CH); 3.41 d, 1 H, $^3J_{H,H}$ = 7.5 (CH_2-C**H**-CF); 3.81 s, 3 H (CH_3O); 3.86 s, 6 H (CH_3O); 4.95 d, 1 H, $^2J_{H,H}$ = 10.4 (OCH$_a$**H**$_b$-CH); 5.06 d, 1 H, $^3J_{H,F}$ = 10.4 (C**H**-OH); 5.98 s, 2 H (OCH_2O); 6.51–7.76 m, 15 H (Ar-H); *anti*-(1′*R**,3*S**,4*R**)-**5d** 2.80 s, 1 H (OH); 3.22 d, 1 H, $^3J_{H,H}$ = 7.5 (CH_2-C**H**-CF); 3.72 s, 6 H (CH_3O); 3.84 s, 3 H (CH_3O); 4.29 dd, 1 H, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 7.7 (OC**H**$_a$H$_b$-CH); 5.07 d, 1 H, $^3J_{H,F}$ = 8.3 (C**H**-OH); 5.12 d, 1 H, $^2J_{H,H}$ = 9.9 (OCH$_a$**H**$_b$-CH); 5.93 s, 2 H (OCH_2); 6.17 d, 1 H, $^3J_{H,H}$ = 8.7 (Ar-H); 6.29 d, 1 H $^3J_{H,H}$ = 8.7 (Ar-H); 6.46 s, 2 H (Ar-H); 6.76 d, 2 H, $^3J_{H,H}$ = 7.5 (Ar-H); 7.02 s, 1 H (Ar-H); 7.12–7.42 m, 6 H (Ar-H); 7.71 d, 1 H, $^3J_{H,H}$ = 7.7. ^{13}C NMR (100.6 MHz, $CDCl_3$): *syn*-(1′*R**,3*R**,4*S**)-**5d** 47.6 d, $^2J_{C,F}$ = 16 (CH_2-CH-CF); 57.2 s, 2 C (CH_3O); 60.2 s, 1 C (CH_3O); 61.2 s (OCH_2-CH); 76.3 d, $^3J_{C,F}$ = 3 ($C(SPh)_2$); 76.3 d, $^2J_{C,F}$ = 31 (CF-CH-OH); 96.9 d, $^1J_{C,F}$ = 206 (CF); 102.8 s (OCH_2O); 106.1 s, 1 C (C_{Ar}); 106.3 s, 2 C (C_{Ar}); 111.4 s, 1 C (C_{Ar}); 123.5–140.3 all s, 15 C (C_{Ar}); 148.4 s, 1 C (C_{Ar}-OCH_2); 148.6 s, 1 C (C_{Ar}-OCH_2); 155.0 s, 3 C (C_{Ar}-OCH_3); 175.1 d, $^2J_{C,F}$ = 23 (CO); *anti*-(1′*R**,3*S**,4*R**)-**5d** – this diastereoisomer was not sufficiently separated from the former one to enable unequivocal assignment. ^{19}F NMR (76.5 MHz, $CDCl_3$): *syn*-(1′*R**,3*R**,4*S**)-**5d** –165.6 dd, 1 F, $^3J_{H,F}$ = 10, $^3J_{H,F}$ = 2 (CF); *anti*-(1′*R**,3*S**,4*R**)-**5d** –168.5 d, 1 F, $^3J_{H,F}$ = 9, $^3J_{H,F}$ = 1 (CF). IR ($CHCl_3$): 1 026 m, 1 138 m, 1 240 s, 1 465 s, 1 509 s, 1 594 s, 1 728 m, 1 786 m, 3 012 m. Microanalysis was not accomplished due to low stability of the product.

4-[(3,4-Dimethoxyphenyl)bis(phenylsulfanyl)methyl]-3-fluoro-3-(phenylmethyl)-4,5-dihydrofuran-2(3H)-one (**6a**). The reaction of dithioacetal **7c** (768 mg, 2.09 mmol), BuLi solution (1.32 ml, 1.89 mol l^{-1}, 2.25 mmol), and fluorolactone **1** (204 mg, 2.00 mmol) in THF (6 ml) with benzyl bromide (**9a**, 269 mg, 1.57 mmol) in THF (2 ml) afforded after purification by column chromatography (SiO_2, 30 × 3 cm, gradient elution first with petroleum ether–CH_2Cl_2 1 : 1, then with CH_2Cl_2) single diastereoisomer of fluorolactone (3*R**,4*R**)-**6a** (white crystals, 448 mg, 40.0%, m.p. 148–153 °C). ^{1}H NMR (300.1 MHz, $CDCl_3$): 3.19 dd, 1 H, $^2J_{H,H}$ = 13.5, $^3J_{H,F}$ = 20.2 (Ar-C**H**$_a$H$_b$-CF); 3.24 m, 2 H (CH_2-C**H**-CF + Ar-CH$_a$**H**$_b$-CF); 3.60 dd, 1 H, $^2J_{H,H}$ = 10.4, $^3J_{H,H}$ = 7.7 (OC**H**$_a$H$_b$-CH); 3.80 s, 3 H (CH_3O); 3.86 s, 3 H (CH_3O); 4.96 dd, 1 H, $^2J_{H,H}$ = 10.4, $^4J_{H,F}$ = 2.2 (OCH$_a$**H**$_b$-CH); 6.50–7.64 m, 18 H (Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 41.9 d, $^2J_{C,F}$ = 25 (Ar-CH_2-CF); 47.2 d, $^2J_{C,F}$ = 21 (CH_2-CH-CF); 56.2 s, 1 C (CH_3O); 56.8 s, 1 C (CH_3O); 67.0 s (OCH_2-CH); 95.3 d, $^1J_{C,F}$ = 211 (CF); the rest of carbon signals could not be unequivocally assigned due to partial decomposition of the mixture. ^{19}F NMR (76.5 MHz, $CDCl_3$): –161.3 ddd, 1 F, $^3J_{H,F}$ = 23, $^3J_{H,F}$ = 15, $^4J_{H,F}$ = 2 (CF). IR ($CHCl_3$): 1 026 m, 1 146 m, 1 258 s, 1 485 m, 1 514 s, 1 603 w, 1 791 s, 3 026 m. Microanalysis was not accomplished due to low stability of the product.

4-[(3,4-Dimethoxyphenyl)bis(phenylsulfanyl)methyl]-3-fluoro-3-[(3,4,5-trimethoxyphenyl)methyl]-4,5-dihydrofuran-2(3H)-one (**6b**). Reaction of dithioacetal **7c** (776 mg, 2.11 mmol), BuLi solution (1.32 ml, 1.89 mol l^{-1}, 2.25 mmol), and fluorolactone **1** (202 mg, 1.98 mmol) in THF (6 ml) with 5-(bromomethyl)-1,2,3-trimethoxybenzene (**9b**, 408 mg, 1.56 mmol) in THF (2 ml) afforded after purification by column chromatography (SiO_2, 40 × 3 cm, gradient elution first with petroleum ether–CH_2Cl_2 1 : 2, then with CH_2Cl_2) single diastereoisomer of fluorolactone (3*R**,4*R**)-**6b** (white crystals, 736 mg, 57.2%, m.p. 117–125 °C). ^{1}H NMR (300.1 MHz, $CDCl_3$): 2.99 dd, 1 H, $^2J_{H,H}$ = 13.7, $^3J_{H,F}$ = 24.2 (Ar-C**H**$_a$H$_b$-CF); 3.18 t, 1 H, $^2J_{H,H}$ = $^3J_{H,F}$ = 13.8 (Ar-CH$_a$**H**$_b$-CF); 3.18 m, 1 H (CH_2-C**H**-CF); 3.74 s, 6 H (CH_3O); 3.82 s, 9 H (CH_3O); 3.93 ddd, 1 H, $^2J_{H,H}$ = 10.4, $^3J_{H,H}$ = 7.2, $^4J_{H,F}$ = 4.2 (OC**H**$_a$H$_b$-CH); 5.07 d, 1 H, $^2J_{H,H}$ = 9.9 (OCH$_a$**H**$_b$-CH); 6.26 s, 2 H, (Ar-H); 6.44 d, 1 H, $^3J_{H,H}$ = 8.8 (Ar-H); 6.80 d, 1 H, $^3J_{H,H}$ = 8.8 (Ar-H); 6.80–7.64 m, 11 H (Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 43.7 d, $^2J_{C,F}$ = 26 (Ar-CH_2-CF); 48.7 d, $^2J_{C,F}$ = 17 (CH_2-CH-CF); 56.5 s, 1 C (CH_3O); 56.6 s, 1 C (CH_3O); 56.9 s,

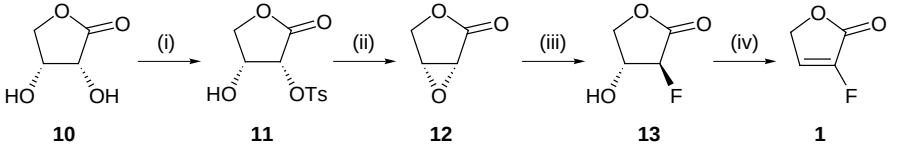
2 C (CH_3O); 61.6 s, 1 C (CH_3O); 68.2 s (OCH_2-CH); 69.5 s ($C(SPh)_2$); 94.9 d, $^1J_{C,F}$ = 209 (CF); 107.9 s, 2 C (C_{Ar}); 109.8 s, 1 C (C_{Ar}); 114.2 s, 1 C (C_{Ar}); 121.3 s, 1 C (C_{Ar}); 128.4–138.5 all s, 14 C (C_{Ar}); 148.9 s, 1 C (C_{Ar}-OCH_3); 149.2 s, 1 C (C_{Ar}-OCH_3); 154.0 s, 3 C (C_{Ar}-OCH_3); 174.2 d, $^2J_{C,F}$ = 25 (CO). ^{19}F NMR (76.5 MHz, $CDCl_3$): –162.0 ddd, 1 F, $^3J_{H,F}$ = 29, $^3J_{H,F}$ = 14, $^4J_{H,F}$ = 5 (CF). IR ($CHCl_3$): 1 026 m, 1 132 s, 1 257 s, 1 405 m, 1 513 s, 1 592 m, 1 791 m, 3 025 m. For $C_{35}H_{35}FO_7S_2$ (650.8) calculated: 64.8% C, 5.1% H; found: 64.4% C, 5.9% H.

RESULTS AND DISCUSSION

Preparation of 3-Fluorofuran-2(5H)-one (**1**)

From retrosynthetic analysis, two approaches leading to fluorolactone **1** were formulated, *viz.* transformation of appropriately substituted non-fluorinated butanolides or butenolides and the formation of (*E*)-2-fluoroalkenoate from a pair of two-carbon fragments followed by ring closure.

The first approach uses fluorobutanolide **11**, previously made from 2-bromo-2-deoxy-D-threonolactone[14], as the key intermediate. We prepared fluorolactone **11** from easily accessible[13] D-erythronolactone **10** (Scheme 1).



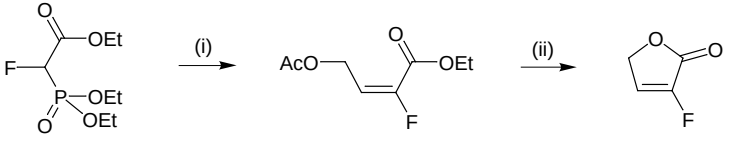
10 **11** **12** **13** **1**

(i) TsCl, pyridine, -25 °C, 72 h, 73%; (ii) KF, acetone, reflux, 12 h, 68%; (iii) $Et_3N.3HF$, 70 °C, 72 h, 41%; (iv) P_2O_5, 200 °C, 2 h, 31%

SCHEME 1

Noteworthy is the good yield of epoxide **12** formed by overall intramolecular *syn* substitution of tosylate **11** although in an analogous open-chain tosylate, the attack of the internal nucleophile is exclusively *anti* (ref.[22]). The probable intermediate of the reaction was fluorolactone **13**. The same product in a lower yield was obtained when sodium carbonate was used instead of potassium fluoride. As nucleophilic substitution of tosylate by carbonate ion has been observed[23], we assume again that two consecutive substitutions with double inversion on the C-2 carbon occurred. The main drawback of the synthesis as depicted in Scheme 1 is the moderate yields of the two last steps, *viz.* opening of the epoxide ring by fluoride ion and dehydration of fluorolactone **13** to fluorobutenolide **1**. We therefore turned our attention to the other approach.

Numerous ways can be used for the preparation of 2-fluorobut-2-enoates, but most of them are either non-stereoselective[24] or lead to *Z*-configuration of the double bond[25]. The only method for constructing (*E*)-2-fluoroalk-2-enoates employs the Wittig–Horner reaction of fluorophoshonoacetate **15** with an appropriate aldehyde[11] and we therefore followed this route. The published synthesis of fluoroester **15** starts from relatively expensive bromotrifluoroethene[11]. Instead, we used cheap chlorotrifluoroethene, which required one more reaction step, *viz.* transformation of ethyl chlorofluoroacetate[15] to ethyl fluoroiodoacetate **14** by the Finkelstein reaction[16]. We were not able to prepare the second key intermediate, 2-oxoethyl acetate (**16**), in the pure state by described procedure[17]. However, the reaction of **16** of low purity with phosphonoacetate **15** afforded 4-substituted fluorobutenoate **17** with the desired (*E*)-configuration, which, after alkaline hydrolysis of both ester groups, afforded, after acidification and continuous extraction, the target fluorolactone **1** in an acceptable yield (Scheme 2). Acid-base manipulation enabled to remove successively both organic and inorganic admixtures leaving pure product **1**.



15 **17** **1**

(i) 1. BuLi; 2. $AcOCH_2CHO$ (**16**), THF, -80 °C, 2 h, 95%; (ii) 1. NaOH, dioxane, H_2O, 20 °C, 12 h; 2. HCl, H_2O, 20 °C, 12 h, 56%

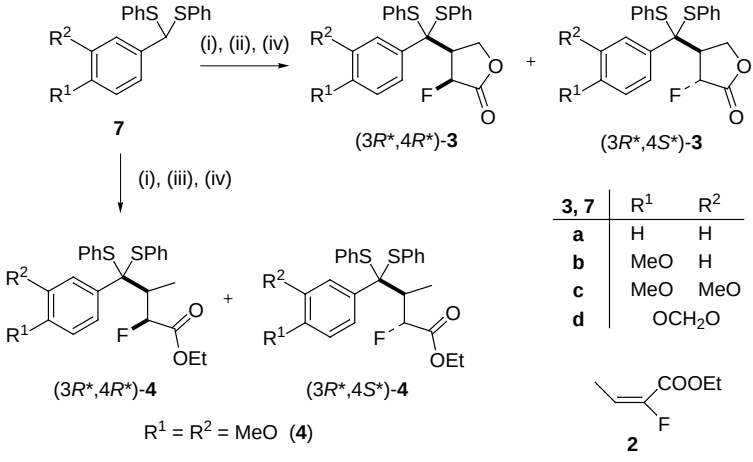
SCHEME 2

Conjugate Additions

Soft carbon nucleophiles such as the lithium salts of dithioacetals **7a**–**7d** attack fluorofuranone **1**, or fluoroester **2** by conjugate addition at C-3 as the softer electrophilic centre (Scheme 3).

Compounds **3** and **4** were obtained by quenching the enolates with hydrochloric acid in poor to moderate yields. Products **3** and **4** suffer from low stability and therefore, in some cases, we were not to able to perform complete analysis before decomposition. Extensive decomposition is probably the source of low yield of **3d**, too. The ratios of individual diastereoisomers were estimated from NMR spectra of crude reaction mixtures and are listed together with yields in Table I.

Hydrogen-fluorine vicinal coupling constants $^3J_{H,F}$ in diastereoisomers **3** formed mostly to a greater extent (designed 3*R**,4*R**) have a value of 26 Hz compared with 20 Hz in the mostly minor diastereoisomers (designed 3*R**,4*S**). From molecular mechanics calculations[26], compounds **3** with a bulky substituent on C-3 in pseudoequatorial position seem to prefer envelope conformation and the dihedral angle F–C–C–H *ca* 40° and *ca* 170° for the *trans* and *cis* isomers, respectively (see Fig. 1). As the coupling constant



(i) BuLi, THF, -80 °C, 1 h; (ii) **1**, -80 °C, 3 h; (iii) **2**, -80 °C, 3 h; (iv) HCl, THF, -80 °C

SCHEME 3

TABLE I
Conjugate additions of dithioacetal **7** based anions on fluoroesters **1** and **2**

Dithioacetal	Fluoroester	Product	R^1	R^2	Yield %	Product diastereoisomer ratio, %	
						(*R**,*R**)	(*R**,*S**)
7a	**1**	**3a**	H	H	41.4	57	43
7b	**1**	**3b**	MeO	H	52.4	44	56
7c	**1**	**3c**	MeO	MeO	57.2	63	37
7d	**1**	**3d**	OCH_2O		13.8	72	28
7c	**2**	**4**	MeO	MeO	79.6	69	31

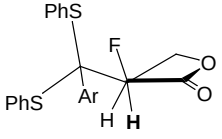
should be larger for *anti* compared with *gauche* conformation[27], major diastereoisomers are most probably the *cis* isomers (which corresponds to 3*R**,4*R**), formed preferentially due to steric hindrance by the bulky substitutent at C-3. A similar relationship can be observed for hydrogen-hydrogen vicinal coupling constant $^3J_{H,H}$. We assume that diastereoisomers of open-chain fluoroester **4** behave similarly.

Tandem Additions

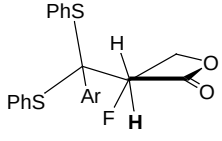
We succeeded in performing tandem additions on fluorofuranone **1** using lithium salts of dithioacetals **7** as nucleophiles and arenecarboxaldehydes **8** or arylmethyl bromides **9** as electrophiles. The results including the ratios of diastereoisomers formed are listed in Table II. Analogous product formed from fluoroester **2** proved to be highly unstable and hence only brief ^{19}F NMR spectra could be recorded before decomposition[21].

To obtain acceptable yields, optimized reaction conditions had to be maintained, *viz.* formation of carbanion by the action of butyllithium, inverse addition of the preformed fluorinated enolate to the electrophile at low temperature, and setting the temperature for the second step of tandem addition to –30 °C (Scheme 4).

The products **5** contain three asymmetric centres, but only two diastereoisomers, *syn* and *anti* were isolated. This indicates that the arenecarboxaldehyde attack proceeds exclusively *anti* to the bulky β-substituent of fluoroenolate in accord with known tandem additions on non-fluorinated butenolides[2,3] and in line with protonation, in which the effect is not so marked as expected with a less bulky electrophile. Moreover, hydrogen-fluorine vicinal coupling constant $^3J_{H,F}$ fell below an observable limit (≈2 Hz) which implies the *trans* configuration according to published[28] data

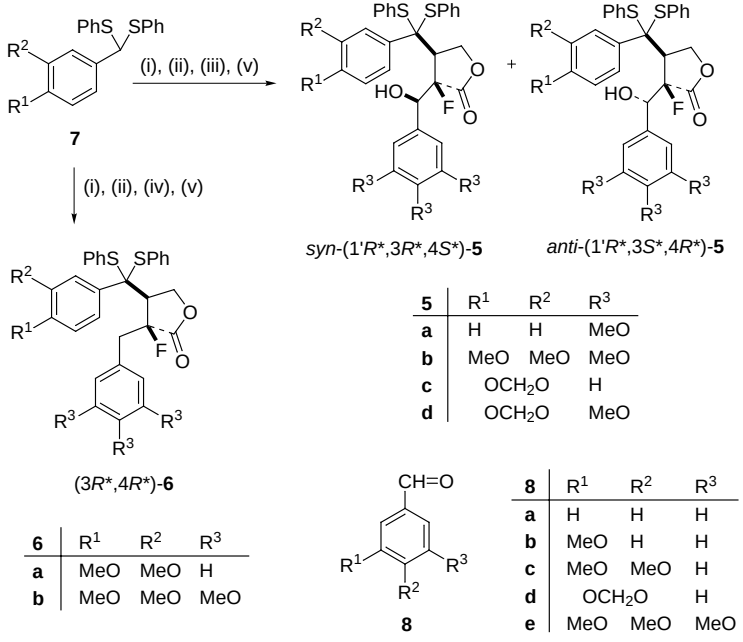


(3*R**,4*R**)-**3**
$^3J_{HF}$ ~ 26 Hz
$^3J_{HH}$ ~ 6 Hz



(3*R**,4*S**)-**3**
$^3J_{HF}$ ~ 20 Hz
$^3J_{HH}$ ~ 7 Hz

FIG. 1
Most stable conformers of both diastereoisomers of fluorolactone **3**



5	R^1	R^2	R^3
a	H	H	MeO
b	MeO	MeO	MeO
c	OCH_2O		H
d	OCH_2O		MeO

6	R^1	R^2	R^3
a	MeO	MeO	H
b	MeO	MeO	MeO

8	R^1	R^2	R^3
a	H	H	H
b	MeO	H	H
c	MeO	MeO	H
d	OCH_2O		H
e	MeO	MeO	MeO

(i) BuLi, THF, -80 °C, 1 h; (ii) **1**, -80 °C, 3 h; (iii) inverse addition, PhCHO (**8a**) or 3,4,5-$(MeO)_3$PhCHO (**8e**), -80 °C, 0.5 h, then -30 °C, 2 h; (iv) inverse addition, $PhCH_2Br$ (**9a**) or 3,4,5-$(MeO)_3PhCH_2Br$ (**9b**), -80 °C, 0.5 h, then -30°C, 2 h; (v) HCl, THF, -80 °C

SCHEME 4

TABLE II

Tandem additions of dithioacetal **7** based anions on fluorolactone **1**

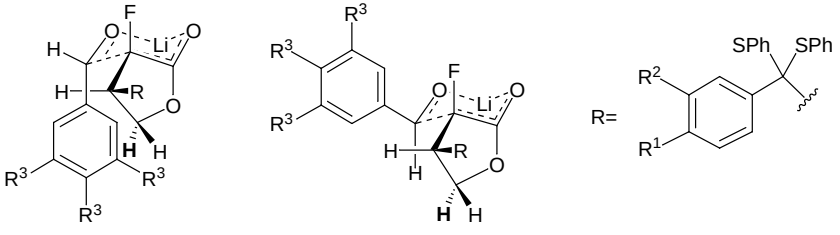
Dithio-acetal	Fluoro-ester	Electrophile	Product	R^1	R^2	R^3	Yield %	Relative diastereo-isomer ratio, %	
								syn	*anti*
7a	**1**	**8e**	**5a**	H	H	MeO	64.3	19	81
7c	**1**	**8e**	**5b**	MeO	MeO	MeO	58.0	27	73
7d	**1**	**8a**	**5c**	OCH_2O		H	51.1	38	62
7d	**1**	**8e**	**5d**	OCH_2O		MeO	58.4	45	55
7c	**1**	**9a**	**6a**	MeO	MeO	H	40.0	–	
7c	**1**	**9b**	**6b**	MeO	MeO	MeO	57.2	–	

on substituted fluorobutanolides. Relative configurations were estimated on the basis of generally accepted Zimmerman–Traxler model of transition state for aldol reaction[29], which should prefer formation of *anti* diastereoisomers **5** (see Fig. 2).

Another indirect support for the relative configurations of tandem addition products comes from ^{1}H NMR spectra. In the *syn* adducts **5**, the NMR shift of one proton of the CH_2O group of the furanone ring has a surprisingly low value (2.8–3.2 ppm, confirmed by 2D COSY NMR experiments) relative to the same proton shift of the *anti* diastereoisomers **5** (4.0–4.4 ppm) and also relative to the other proton of the CH_2O group (4.8–5.1 ppm). Provided that hydrogen bond in compounds **5** is formed between the hydroxyl group and the carbonyl oxygen or fluorine, products **5** tend to adopt conformation similar to the transition state (Fig. 2). For assumed *syn* diastereoisomers, this results in placing one of the hydrogens of the furanone ring (boldfaced in Fig. 2) above the aromatic ring. This hydrogen is then observed at a higher local magnetic field with a corresponding upfield shift of its signal.

Similarly to aldol products **5**, trapping of intermediate fluoroenolate by arylmethyl bromides **9** in tandem additions resulted in the formation of single diastereoisomer as a result of exclusive *anti* attack.

Compounds **3**–**6** are important synthetic intermediates for the synthesis of fluorinated lignans, and underline the importance of fluorofuranone **1** as a readily available starting material. In contrast to direct electrophilic fluorination of podophyllotoxin[12], synthetic approach allows for preparation of unnatural analogues of podophyllotoxin lignans. The main drawback of the tandem addition approach is limited stability of the products.



syn-(1'*R**,3*R**,4*S**)-**5** *anti*-(1'*R**,3*S**,4*R**)-**5**

FIG. 2
Zimmerman–Traxler models of transition states of the second step of tandem addition of dithioacetal **7** based anion on fluorolactone **1** with arenecarboxaldehyde **8**

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