New Fluorobutenolide Templates for Synthesis

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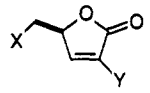
Strategies for the synthesis of organic substances have been greatly expanded through retrosynthetic analytical procedures.[1,2] Such procedures feature a broad range of useful synthetic intermediates known as synthons[3] and chirons.[4] The chemistry of chirons, enantiomerically pure functional intermediates, has been extensively developed in the work of Hanessian and co-workers.[4,5] (*R*)-and-(*S*)-4-(hydroxymethyl)-2-buten-4-olides (**1a**) have been particularly examined as chiral templates for the synthesis of a wide range of chiral and biologically interesting substances related to antibiotics and carbohydrates.



1a (X=OH, Y=H)
1b (X=OH, Y=F)
6 (X=COOH, Y=F)

Fluorinated chiral molecules have received considerable attention because of their applications in biomedicinal, analytical, and polymer sciences.[6] Our interests in the synthesis of selectively fluorinated materials have led to the developement of two fluorinated templates related to (*S*)-**1a**. The chiral template, 2-fluoro-4-(hydroxymethyl)-2-buten-4-olide (*S*)-(−)-**1b** and the racemic template, 4-(carboxymethyl)-2-fluoro-2-buten-4-olide (**6**) have been synthesized in anticipation that they will serve as general templates for the synthesis of a wide variety of useful fluorinated materials. The syntheses of **1b** and **6** are the subject of this report.

The synthesis of (*S*)-(−)-**1b** was accomplished as outlined in Scheme 1. Several Wittig procedures were tried for the preparation of (*E*)-**2** and (*Z*)-**2** and are summarized in Table 1. The fluorophosphonate method of Etemad-Moghadam and Seyden-Penne[7] with D-glyceraldehyde acetonide[8] proved very successful for the exclusive preparation of the (*E*)-**2** isomer in 51% yield. However, when the fluorophosphonate procedure was used with D-glyceraldehyde acetonide generated *in situ* according to Burton and Thenappen, an (*E*)-**2**:(*Z*)-**2** mixture was obtained in 44% yield with a 10/1 (*E*)-**2**:(*Z*)-**2** ratio.[9] The (fluorocarbethoxymethylene)tri-*n*-butylphosphorane reagent developed by Burton, Gurusamy, and Cox showed no isomer selectivity and furnished equal amounts of (*E*)-**2** and (*Z*)-**2** in 52% yield.[10]

The lactone, (*S*)-(−)-**1b**, was formed when either pure (*E*)-**2** or mixtures of (*E*)-**2** and (*Z*)-**2** were treated with *p*-toluenesulfonic acid in a methanol solution at room temperature. Pure (*E*)-**2** furnished pure (*S*)-(−)-**1b** in 76% yield without need for derivatization or chromatographic separation. When (*E*)-**2**:(*Z*)-**2** mixtures were cyclized, (*S*)-(−)-**1b** had to be converted to the 5-silyl derivative (*S*)-**1c** for chromatographic separation from the uncyclized alkene (*Z*)-**3**. Lactone (*S*)-**1c** was converted to the 1-hydroxy lactone (*S*)-**4** on reaction with DIBAL. The 2,3 double bond was not reduced under these conditions.

Alternatively, a simple route to the analogous 4-(carboxymethyl)-2-fluoro-2-buten-4-olide (**6**) was discovered through the sulfuric acid mediated cyclization of 2-fluoro-2(*E*),4(*Z*)-muconic acid. The muconic acid was generated *in situ* from the corresponding methyl ester (**5**) which was obtained by the oxidation of commercially available 3-fluorocatechol. The oxidation process is based on a method described by Pieken and Kozarich for the oxidation of 4-fluorocatechol[11] (Scheme 2). NMR data for ester **5** was consistant with the 2(*E*),4(*Z*) configuration. During the preparation of **5**, another stereoisomer was obtained, 2(*E*),4(*E*), but optimal conditions for the preparation of this isomer were not determined.

The ester **5** was converted to 2-fluoromuconic acid by basic hydrolysis followed by treatment with concentrated sulfuric acid. The acid treatment also served to effect cyclization to **6** in 42% yield from **5**. NMR examination of the crude reaction mixtures did not reveal the presence of isomer **7**. Presumably, the 2-fluorine of 2-fluoromuconic acid directs the major portion of protonation to the 4,5 bond which then leads to **6**. In contrast, reaction of 3-fluoromuconic acid with sulfuric acid results in protonation of the fluorine-containing 2,3 bond.[11]

In summary, the synthetic development of both chiral (*S*)-(−)-**1b** and racemic **6** permits opportunities for new synthetic strategies based on these materials as templates. The use of **1b** as a chiron for fluorocarbohydrate synthesis is currently in progress.

Experimental Section

General. All solvents were dried prior to use. NMR spectra were recorded on a JOEL FX-90Q at 90 MHz for proton and 84.25 MHz for fluorine. Proton spectra are referenced with tetramethylsilane (δ 0.0), and fluorine spectra are referenced with trifluoroacetic acid (δ 0.0). Mass spectra were obtained from Washington University, St. Louis, MO, Department of Psychiatry, School of Medicine.

Ethyl (*S*)-2-Fluoro-4,5-dihydroxy-4,5-isopropylidene-2-pentenoate Isomers ((*E*)-2,(*Z*)-2) (Procedure A). The following procedure was adapted from Etemad-Moghadam and Seyden-Penne.[7] A flame-dried 100-mL round-bottom flask was charged with a solution of triethyl 2-fluorophosphoethanoate (4.56 g, 19 mmol) in 20 mL of dried tetrahydrofuran. The solution was cooled under nitrogen to −78 °C, and 12.5 mL of 1.6 M *n*-butyllithium (in hexanes) was injected by syringe. After 20 min, D-glyceraldehyde acetonide[8] (2.45 g, 19 mmol) in 5 mL of tetrahydrofuran was injected at −78 °C, and the mixture was stirred for 1 h. The mixture was allowed to warm to room

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Scheme 1

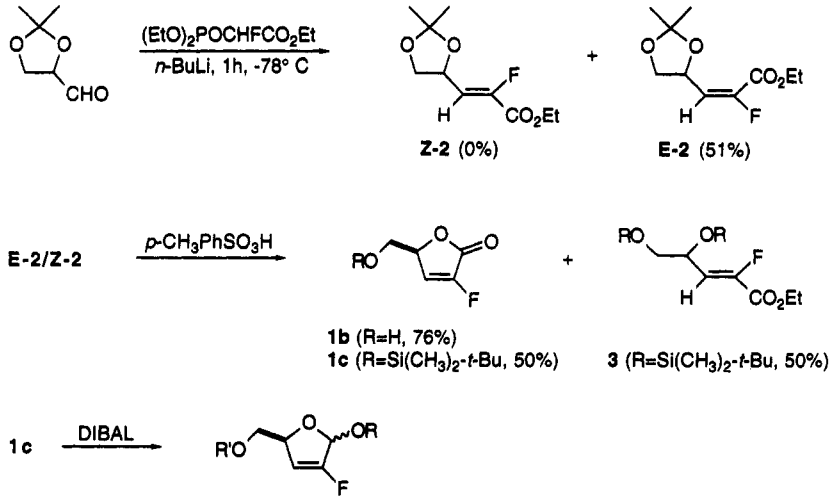
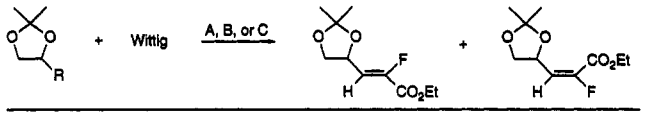
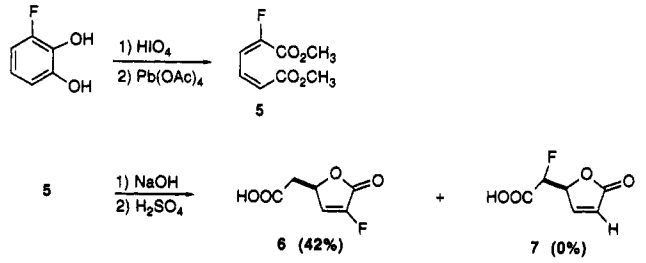


Table 1. Wittig Reaction Procedures for (*Z*)-2 and (*E*)-2



Wittig	(*Z*)-2 (% yield)	(*E*)-2 (% yield)
A. R = CHO (1) *n*-Bu_3P, $BrCHFCO_2Et$, 2d, rt (2) *n*-BuLi (3) reflux, 22 h	26	26
B. R = CHO $(EtO)_2POCHFCO_2Et$, *n*-BuLi, THF, −78 °C, 1 h	0	51
C. R = CO_2CH_3 (1) DIBAL, −78 °C, THF, 30 min (2) $EtO_2POCHFCO_2Et$, *n*-BuLi, THF, −78 °C, 1 h	4	40

Scheme 2



temperature over a 6-h period, and 80 mL of 6 M hydrochloric acid was added.

The organic layer was separated, extracted with ether (2 × 50 mL), and washed with a saturated sodium chloride solution (2 × 25 mL) followed by water (25 mL). The solution was dried ($MgSO_4$), concentrated on a rotary evaporator, and purified by column chromatography (silica gel, 500 × 30 mm) with a methylene chloride/hexane (9:1) solution to give 2.10 g (51%) of (*S*)-(+)-(*E*)-**2**. The product was homogeneous on TLC and showed no ^{19}F NMR evidence for the presence of the (*Z*)-**2** isomer. ^1H NMR ($CDCl_3$, TMS) δ 1.33 (CH_3, m, 6H), 4.1 (CH, CH_2, m, 3H), 5.80, 5.88, 6.01, 6.10 (vinyl, dd, J_{HF} = 19.11 Hz, J_{34} = 7.69 Hz; ^{19}F NMR ($CDCl_3$, TFA) δ −43.25 (d, *J* = 19.52 Hz); $[\alpha]_D^{23}$ +3.27 (1, $CHCl_3$). Isomer (*Z*)-**2** was observed in mixtures from other Wittig products and showed δ −49.63 (*J* = 32 Hz).

Procedure B. The following procedure was adapted from the work of Burton and Thenappen in which the aldehyde was prepared *in situ* by reduction of the ester with DIBAL.[9]

The lithium salt of triethyl 2-fluorophosphoethanoate was prepared on a 19 mmol scale as described in procedure A. In a separate flask methyl (*R*)-(+)-2,2-dimethyldioxolane-4-carboxylate (2.40 g, 15 mmol) in 15 mL of dry THF was stirred and cooled to −78 °C, and DIBAL (15 mmol, 15 mL of 1.0 M solution in dichloromethane) were added by syringe. After 30 min, the lithium salt solution was added to the aldehyde mixture. The mixture was stirred at −78 °C for 1 h and allowed to warm to room temperature over 5 h. The reaction was quenched with water, extracted with methylene chloride (2 × 50 mL), and dried ($MgSO_4$) to give 44% of crude **2** ^{19}F NMR analysis a (*E*)-**2**:(*Z*)-**2** ratio of 9:1. This material could be used for cyclization to the lactone without interference from the (*Z*)-**2** isomer.

Procedure C. The following procedure is adapted from the work of Burton, Gurusamy, and Cox[10] who used the tri-*n*-butylphosphorane Wittig reagent. (Fluorocarbethoxymethylene)tri-*n*-butylphosphorane was prepared and used *in situ*. Ethyl bromofluoroacetate[12] (3.70 g, 20 mmol) was added to a cooled benzene solution of tri-*n*-butylphosphine (4.06 g, 20 mmol). The mixture was stirred at room temperature for 2 days under nitrogen. It was treated with *n*-butyllithium–hexane (10 mL, 1.6 M) and 20 mL of dry ether, stirred at room temperature for 4 h, and followed by a dropwise addition of D-glyceraldehyde acetonide (15 mmol) in benzene (10 mL). The mixture was heated at reflux under nitrogen for 18–22 h, allowed to cool, and washed with water (3 × 30 mL), and the organic phase was dried (Na_2SO_4). After solvent evaporation and chromatography over silica gel (500 × 30 mm) with methylene chloride/hexane (9:1), 2.25 g (52%) of a 1:1 (*E*)-**2**:(*Z*)-**2** mixture by ^{19}F NMR analysis was obtained.

(*S*)-(−)-2-Fluoro-4-(hydroxymethyl)-2-buten-4-olide (1b). A solution of **2** (1.03 g, 4.6 mmol) in 5 mL of methanol was treated with 200 mg of *p*-toluenesulfonic acid and stirred at room temperature for 2 h. Sodium carbonate (0.65 g) was added, and the mixture was stirred for 30 min. Ethyl ether (15 mL) was added, and the crude product was filtered. The solid residue was washed with ether (3 × 20 mL), and the combined ether extracts were evaporated to give pure **1b** as a clear white oil, 0.47 g (76%): ^1H NMR ($CDCl_3$) δ 3.88 (CH_2, m), 5.09 (CH, m), 6.76 (vinyl H, t, *J* = 1.46 Hz); ^{19}F NMR δ −63.48 (d, *J* = 5.10 Hz); $[\alpha]_D^{28}$ -28.5 (1, $CHCl_3$). The optical purity of **1b** was not determined, but the synthetic method used would not likely affect the chiral center. Anal. Calcd for $C_5H_5FO_3$: C, 45.45; H, 3.79; F, 14.39. Found: C, 45.35; H, 3.70; F, 14.21.

Compound **1b** was converted to the 5-*tert*-butyldimethylsilyl derivative as follows. A solution of *tert*-butyldimethylsilyl chloride (1.7 g, 10 mmol), sodium iodide (100 mg), 4-(dimethylamino)pyridine (100 mg), and **1b** (0.98 g, 4.5 mmol) was prepared in 5 mL of methylene chloride. A mixture containing imidazole (0.79 g) dissolved in 5 mL of methlyene chloride was added, and the reaction mixture was stirred for 24 h at room temperature. After the reaction was washed with water (3 × 15 mL) and dried

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(Na_2SO_4), the methylene chloride was removed, and the product was purified by column chromatography (silica gel, 450 × 10 mm) using a methylene chloride/hexane (19:1) solution. **(*S*)-2-Fluoro-4-[(*tert*-butyldimethlysiloxy)methyl]-2-buten-4-olide (1c)** was obtained as a white solid: mp 43–45 °C (550 mg, 50%); ^{1}H NMR ($CDCl_3$) δ 0.04 (di-CH_3, s), 0.86 (*t*-Bu, s), 3.86 (CH_2, m), 5.00 (CH, m), 6.71 (vinyl, t, J = 1.79 Hz); ^{19}F NMR δ −65.80 (J_{HF} = 5.12 Hz); ^{13}C NMR δ −5.50 (di-CH_3), 18.16 (CH_3 of *t*-Bu), 25.75 (C of *t*-Bu), 63.29 (CH_2, d, J_{CF} = 2.45 Hz), 77.32 (C4, d, J_{CF} = 6.10), 123.51 (C3, d, J_{CF} = 7 Hz), 143.45, 152.61 (C2, d, J_{CF} = 257.3 Hz), 166.7 (C1, d, J_{CF} = 31 Hz); mass spectrum (CI, CH_4), 247 (M + 1), calcd mol wt 246.

Cyclization of (*E*)-**2** and (*Z*)-**2** mixtures produced **1b** and ethyl (*Z*)-2-fluoro-4,5-dihydroxy-2-pentenoate (**3**), which were purified by conversion to the silyl derivative as described above. Separation was accomplished by column chromatography (silica gel, 450 × 10 mm) with methylene chloride/hexane (5.5:1). After (*E*)-**2** was obtained as an early fraction, **ethyl (*S*)-2-fluoro-4,5-bis[(*tert*-butyldimethylsiloxy)methyl]-2(*Z*)-pentenoate (3)** eluted as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.04 (di-CH_3, s), 0.88 (*t*-Bu, s), 1.33 (CH_3 of ethyl, t, J = 7 Hz), 3.58 ($CH_2OSi(CH_3)_2$-*t*-Bu, m), 4.29 (CH_2 of ethyl, q, J = 7 Hz), 4.68 ($CH_2OSi(CH_3)_2$-*t*-Bu, m) 5.86 and 6.24 (vinylic, dd, J_{HH} = 9 Hz, J_{HF} = 32 Hz); ^{19}F NMR δ −50.77 (d of m, J_{HF} = 34 Hz); mass spectrum mol wt calcd 434, found 434.

1-Hydroxy-2-fluoro-4-[(*tert*-butyldimethylsiloxy)methyl]-2-buten-4-olide (4a). Lactone **1c** (500 mg, 2 mmol) and 5 mL of methylene chloride were placed in a dry 50-mL round-bottom flask under nitrogen atmosphere. The contents were cooled to −78 °C, and 2.2 mL of 1.6 M DIBAL in methylene chloride was added. The mixture was stirred for 1 h. The cold mixture was treated with dilute nitric acid, washed with water, and dried (Na_2SO_4). Evaporation of the solvent gave anomers of **4a** as a clean oil (0.42 g, 83%): IR (neat) 3200 cm^{-1} (OH); ^{1}H NMR ($CDCl_3$) δ 0.05 (di-CH_3, s), 0.79 (*t*-Bu, m), 3.24 (CH, d, J = 1.32 Hz), 3.90 (CH_2, m), 5.20 (CH, m), 6.73 (vinyl-H, t, J = 1.79 Hz); ^{19}F NMR δ −63.97 (d, J_{HF} = 5.50 Hz); ^{13}C NMR δ −5.67 (di-CH_3, s), 17.33 (CH_3 of *t*-Bu), 25.48 (C of *t*-Bu), 64.80 (C5, d, J = 5.90 Hz), 69.25 (C1, s), 77.96 (C4, d, J = 7.32 Hz), 123.81 (C3, d, J = 6.11 Hz), 143.45, 152.61 (C2, d, J = 257.3 Hz); mass spectrum (CI, CH_4) 249 (M + 1), calcd mol wt 248.

Dimethyl 2-Fluoro-2(*E*),4(*Z*)-muconate (5). To a solution of 3-fluorocatechol (1.02 g, 8.0 mmol) in 30 mL of methylene chloride was added a solution of $NaIO_4$ (2.0 g, 9.3 mmol) in 20 mL of deionized water and 5–10 mg of tetra-*n*-butylammonium bromide. The resulting reddish-brown mixture was allowed to stir for 10 min at room temperature and then poured into a 250-mL separatory funnel. The organic layer was quickly filtered through a cone of Na_2SO_4 and collected into a 250-mL round-bottom flask covered with aluminum foil. The solvent was evaporated, leaving 3-fluoro-1,2-benzoquinone as a brick red solid.

A solution of the 3-fluoro-1,2-benzoquinone in 75 mL of benzene/methanol (1:1) was cooled to 0 °C. Solid lead tetraacetate (4.3 g, 9.7 mmol) was added, and the mixture was stirred in the dark at 0 °C for 1 h. After evaporation, the mixture was extracted with hexane (3 × 30 mL), and the combined extracts were dried ($MgSO_4$) and evaporated to give **5** as pale yellow to white crystals in 15–25% yields: mp 45–47 °C; ^{1}H NMR ($CDCl_3$) δ 3.78 (s, CH_3), 3.90 (s, CH_3), 5.97 (dd, 1H, H5, $J_{4,5}$ = 11.5 Hz), 7.62 (m, 1H, H4, $J_{3,4}$ = 11.5 Hz, $J_{4,5}$ = 11.5 Hz), 7.86 (m, 1H, H3, $J_{H3,F}$ = 19.3 Hz, $J_{3,4}$ = 11.5); ^{19}F NMR ($CDCl_3$) δ −36.14 (d, $J_{H3,F}$ = 19.3 Hz).

On occasion, the dimethyl 2-fluoro-2(*E*),4(*E*)-muconate isomer was formed, but the causes for the stereochemical divergence are unknown. The 2(*E*),4(*E*) isomer was obtained as a pale yellow oil: ^{1}H NMR δ 3.79 (s, CH_3), 3.89 (s, CH_3), 6.12 (d, H5, $J_{4,5}$ = 15.0 Hz), 6.50 (m, H3, $J_{3,4}$ = 12.0 Hz, $J_{3,F}$ = 18.0 Hz), 8.13 (dd, H4, $J_{3,4}$ = 12.0 Hz, $J_{4,5}$ = 15.0 Hz); ^{19}F NMR ($CDCl_3$) δ −36.14 (d, J = 18.0 Hz). Anal. Calcd for $C_8H_9FO_4$: C, 51.06; H, 4.79; F, 10.11. Found: C, 50.95; H, 4.80.

2-Fluoro-4-carboxymethyl-2-buten-4-olide (6). Dimethyl 2(*E*),4(*E*)-2-fluoromuconate (**5**, 100 mg, 0.53 mmol) was treated with one pellet of sodium hydroxide dissolved is 5 mL of water. The mixture was stirred at room temperature for 30 min and extracted with 20 mL of ether. The aqueous phase was evaporated to dryness to give the diacid salt which was cyclized. The diacid salt was mixed with 5 mL of concentrated sulfuric acid, and the mixture was stirred for 8 h at 85–90 °C. The brown mixture was treated with ice (5–10 g) and extracted with ether. The ether layer was dried and evaporated to give **6** as a slightly yellow oil (36 mg, 42%). Purification was accomplished by HPLC (C18, 10%) with $CH_3OH/H_2O/H_3PO_4$ (90:9.9:0.1) at a flow rate of 1 mL/min: ^{1}H NMR (acetone-d_6) δ 2.87 (dd, 2H, CH_2), 5.42 (m, 1H, CH), 7.15 (dd, 1H, vinylic); ^{19}F NMR δ −63.4 (dd, J_{HF} = 3 Hz). Anal. Calcd for $C_6H_5FO_4$: C, 45.00; H, 3.13; F, 11.88. Found: C 45.21; H, 3.01; F, 11.99.

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