2-Fluoro-2-buten-4-olide, a New Fluorinated Synthon. Preparation; 1,2-, 1,4- and Tandem Additions

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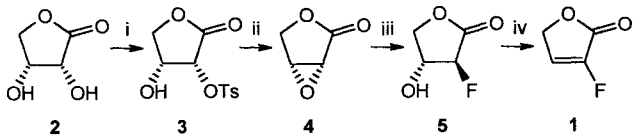
Abstract: 2-Fluoro-2-buten-4-olide (**1**) was prepared either by transformation of D-erythronolactone or by Wittig-Horner reaction of ethyl (diethoxyphosphoryl)fluoroacetate with acetoxyacetaldehyde followed by ring closure. It can be transformed by 1,2-addition of nitrogen or hard carbon nucleophiles to fluorinated hydroxyamides or diols and by 1,4-addition of soft carbon nucleophiles to β-alkylated 2-fluorobutan-4-olides. Tandem addition leads to α,β disubstituted 2-fluorobutan-4-olides which are intermediates for the synthesis of fluorinated lignans.

The butanolide or butenolide ring system is frequently present in biologically active compounds and 2-buten-4-olide and its derivatives have been used for the preparation of lignans including podophyllotoxin analogues by tandem addition.[1] The chemistry of 2-fluoroalkenoates, with the exception of 2-fluoroacrylates, is quite unknown.[2] We therefore turned our attention to 2-fluoro-2-buten-4-olide (**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 **5**, previously made from *D*-2-bromo-2-deoxythreonolide,[3] as the key intermediate. We prepared fluorolactone **5** from easily accessible[4] *D*-erythronolide **2** (Scheme 1).

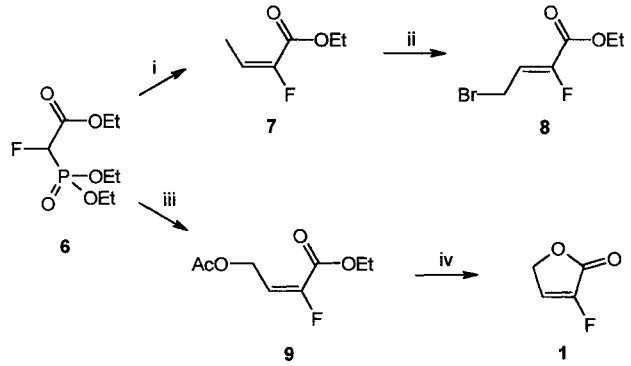


i TsCl, pyridine, -25°C, 72 h, 73%; ii KF, acetone, reflux, 12 h, 66%; iii $NEt_3.3HF$, 70°C, 72 h, 41%; iv P_2O_5, 200°C, 2 h, 31%.

Scheme 1

Noteworthy is the good yield of epoxide **4** formed by overall intramolecular *syn*-substitution of tosylate **3**, although in an analogous open chain tosylate the attack of the internal nucleophile is exclusively *anti*.[5] The probable intermediate of the reaction was fluorolactone **5**. The same product in lower yield was obtained when sodium carbonate was used instead of potassium fluoride. As nucleophilic substitution of tosylate by carbonate ion has been observed,[6] we suppose 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 **5** to fluorobutenolide **1**.[7] We therefore turned our attention to the second approach.

Numerous ways can be used for the preparation of 2-fluoro-2-butenoates, but most of them are either non-stereoselective[8] or lead to a *Z*-orientation of the double bond.[9] The only method for constructing *E*-2-fluoro-2-alkenoates employs the Wittig-Horner reaction of fluorophoshonate **6** with an appropriate aldehyde[10] and we therefore followed this route. Attempts to use acetaldehyde as the corresponding electrophile[10] and then functionalise the γ-position of *E*-fluorobutenoate **7** by bromination with NBS[11] resulted in isomerization to yield *Z*-4-bromofluorobutenoate **8** (Scheme 2). However, reaction of acetoxyacetaldehyde[12] with phosphonate **6** afforded 4-substituted fluorobutenoate **9** with the desired *E*-configuration, which after basic hydrolysis of both ester groups afforded on acidification the target fluorobutenolide **1** in an acceptable yield (Scheme 2).



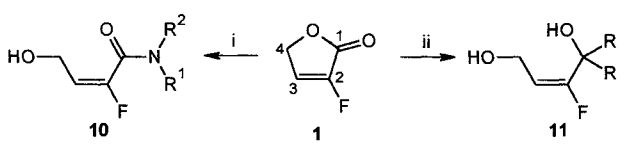
i BuLi then CH_3CHO, THF, -78°C, 1 h, 48%; ii NBS, $CHCl_3$, reflux; iii BuLi then $AcOCH_2CHO$, THF, -78°C, 2 h, 95%; iv NaOH, dioxan, H_2O, 20°C, 12 h then HCl, H_2O, 20°C, 0.1 h, 56%.

Scheme 2

1,2-Additions

Dimethylamine and lithium anilide were treated with **1** and both attacked the harder carbonyl carbon. This was followed by opening the lactone ring to fluorinated unsaturated hydroxyamides **10a** ($R^1 = R^2 = Me$) and **10b** (R^1 = Ph, R^2 = H) (Scheme 3). This is in contrast with 2-fluoroacrylates and 2-buten-4-olide, which are both attacked by nitrogen nucleophiles at C-3.[13]

Hard carbon nucleophiles such as butyllithium or phenyllithium reacted with **1** by a characteristic double 1,2-addition to the carbonyl group to afford a low yield of unsaturated fluorodiols **11a**, **11b** (Scheme 3).

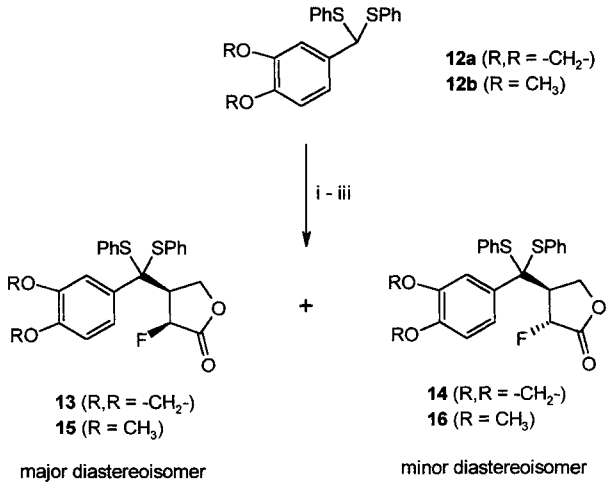


i $R^1 = R^2$ = Me: Me_2NH, THF, 20°C, 2 h, 90% for **10a**; R^1 = Ph, R^2 = H: PhNHLi, THF, -78°C to 20°C, 3 h, 44% for **10b**; ii R = Bu: BuLi, THF, -78°C to 20°C, 3 h, 31% for **11a**; R = Ph: PhLi, THF, -78°C to 20°C, 4 h, 19% for **11b**.

Scheme 3

1,4-Additions

Soft carbon nucleophiles such as the lithium salts of dithioacetals **12a**, **12b** attack **1** by 1,4-addition at C-3 as the softer electrophilic centre (Scheme 4).



i BuLi, THF, -78°C, 1 h; ii **1**, -78°C, 3 h; iii HCl, THF, -78°C to 20°C; R,R = $-CH_2-$: 60%, **13** : **14** = 2:1; R = Me : 58%, **15** : **16** = 3 : 1.

Scheme 4

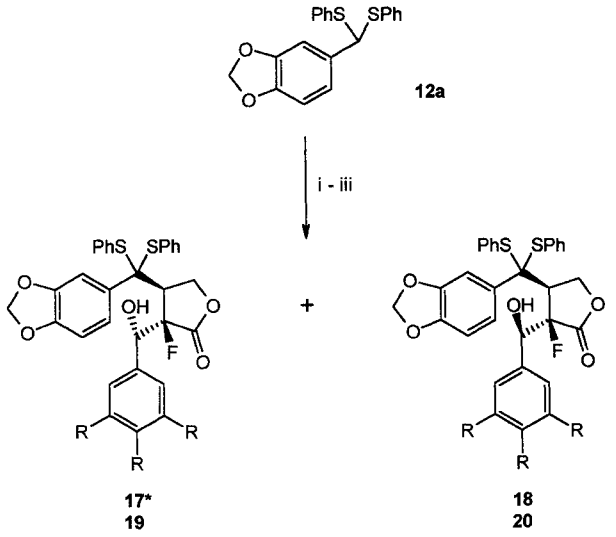
Compounds **13-16** were obtained by quenching the enolates with hydrochloric acid (Scheme 4). Hydrogen-fluorine vicinal coupling constants $^3J_{HF}$ in the major diastereoisomers **13** and **15** have value 26 Hz compared with 20 Hz in the minor diastereoisomers **14** and **16**. From molecular mechanics calculations compounds **13-16** seem to prefer envelope conformation with bulky substituent on C-3 in pseudoequatorial position and the respective dihedral angle F-C-C-H ~40° and ~170° for the *trans* and *cis* isomers. As the interaction constant should be larger for *anti* as compared to *gauche* conformation[14], the major diastereoisomers **13**, **15** are most probably the *cis*-isomers, formed preferentially due to steric hindrance by the bulky substitutent at C-3.

Tandem additions

To our knowledge, no tandem additions on fluorinated alkenoates have been published. Also the information about enolates of 2-fluoroalkanoates is rather scarce[15] with the exception of enolates of fluoroacetates.[16]

We succeeded in performing tandem additions on fluorobutenolide **1** using the lithium salt of dithioacetal **12a** as nucleophile and benzaldehyde, and 3,4,5-trimethoxybenzaldehyde as the electrophiles. For good results, inverse addition of preformed fluorinated enolate to the aldehyde at -40°C proved to be necessary (Scheme 5).

The products contain three asymmetric centres, but only two diastereoisomers **17** and **18** with benzaldehyde and **19** and **20** with 3,4,5-trimethoxybenzaldehyde were isolated indicating that aldehyde attack proceeds exclusively *anti* to the bulky β-substituent of the fluoroenolate in accord with known tandem additions on non-fluorinated butenolides[1], 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 $^3J_{HF}$ fell below observable limit (~ 2 Hz) what implies the *trans* configuration according to published[17] data on substituted fluorobutanolides. When R = H, the ratio of **17**:**18** is 6:4 and when R = OMe, the ratio of **19**:**20** is 7:3. The relative configurations on the carbon bearing the benzylic



i BuLi, THF, -78°C, 1 h; ii **1**, -78°C, 2 h; iii inverse addition to ArCHO, -40°C, 2 h then HCl, THF, -78°C to 20°C; R = H: 51%, R = MeO: 58%.

*The configuration of ArCHOH is arbitrary.

Scheme 5

hydroxyl group have not yet been assigned and will be the subject of further study. Compounds **17** to **20** are important synthetic intermediates for the synthesis of fluorinated lignans, and underline the importance of fluorobutenolide **1** as a readily available starting material.

Acknowledgements

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(7) All yields given are preparative yields. Reaction products were fully characterized by 1D and 2D NMR spectroscopy, IR spectroscopy and by elemental analysis. Spectroscopic data for **1:** ^1H NMR δ 4.90 (dd, 2H, J = 2.0 and 6.0 Hz), δ 6.90 (q, 1H, J = 2,1 Hz); ^{13}C NMR δ 66.8 (d, J = 8 Hz), δ 123.2 (d, J = 8 Hz), δ 148.9 (d. J = 277 Hz), δ 165.6 (d, J = 32 Hz); ^{19}F NMR δ -142 (dt, 1F, J = 3 and 6 Hz).

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