A Short Synthesis of 2-Deoxy-2-fluoro-*ribo*-D-pentopyranose

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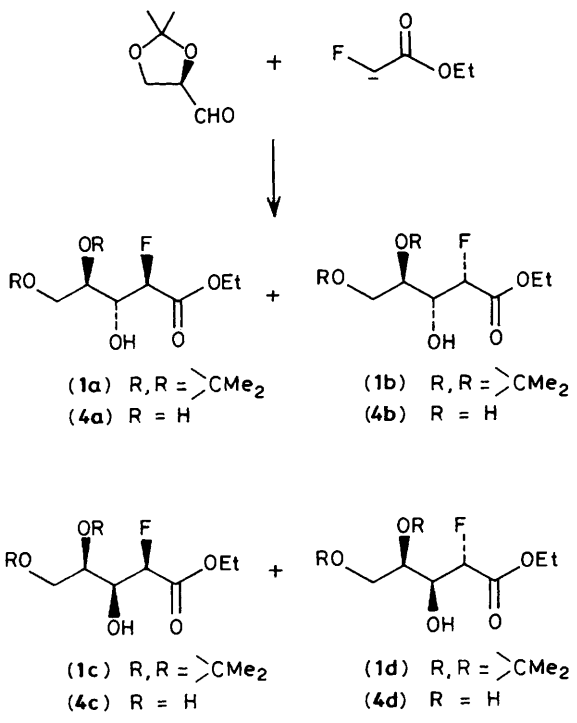
A short synthesis of 2-deoxy-2-fluoro-*ribo*-D-pentopyranose from the diastereofacially selective reaction between glyceraldehyde acetonide and the lithium enolate of ethyl fluroacetate is described.

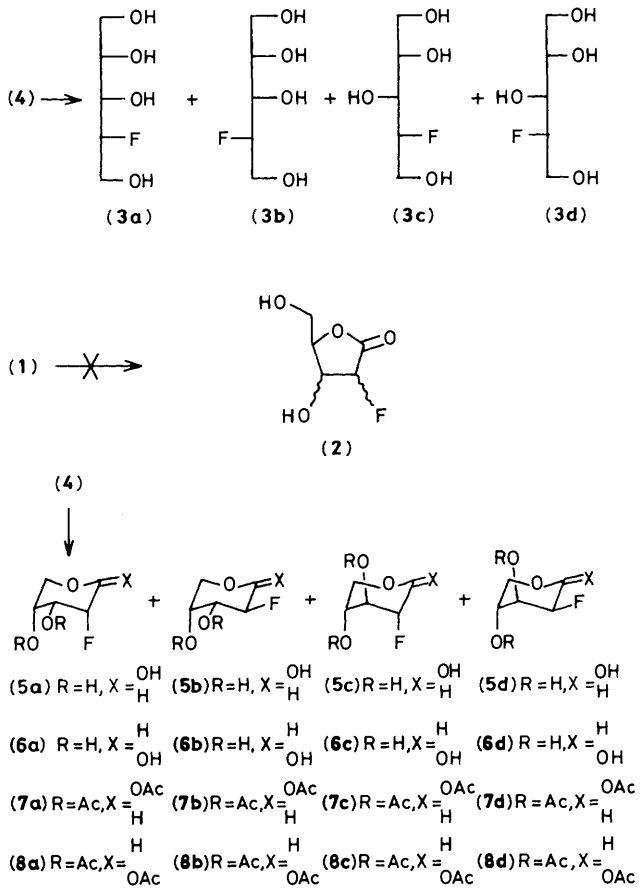
2-Deoxy-2-fluorocarbohydrates have found considerable utility in anti-viral drugs, such as 2-fluoro-5′-iodo-arabinosylcytosine, FIAC, and 2-fluoro-5′-methylarabinosyl-uracil, FMAU.[1] 2-Deoxy-2-fluoropentoses have been prepared by several different procedures: however all these procedures require several steps for the protection and functionalization of the substrate sugar[2] prior to fluorination. Even with recent advances in direct fluorination[3] and in the fluorination of anions,[4] contemporary fluorination methods[5] still have several significant drawbacks, requiring the use of reagents which are expensive or difficult to prepare.

The synthesis of 2-deoxy-2-fluoropentoses by the addition



of the lithium enolate of ethyl fluoroacetate to glyceraldehyde acetonide followed by deprotection of the glycol and reduction of the ester is extremely efficient. The successful total syntheses of a number of carbohydrates have employed glyceraldehyde acetonide[6] as a convenient electrophilic stereogenic three-carbon fragment.[7] Prior to our recent investigations,[8] the utility of the lithium enolate of ethyl fluoroacetate in synthesis had not been realized.[9] If reactions of this fluorinated enolate proceed with diastereofacial selectivity[10] reacting according to Felkin's rule, the carbohydrate products will be selectively formed in either the *arabino* or *ribo* configuration. No previous studies of the diastereofacial selectivity of fluorinated enolates have been reported, although the non-selective preparation of fluoroalditols has been described.[11] Use of the commercially available ethyl ester of fluoroacetic acid also facilitates further synthetic transformations such as reduction of the ester to the sugar aldehyde.

In our preliminary studies, addition of *R*-glyceraldehyde acetonide to a solution of the lithium enolate of ethyl fluoroacetate, prepared by the addition of ethyl fluoroacetate† to lithium hexamethyldisilazide in tetrahydrofuran (THF) solution, resulted in an 83% yield of an apparent 1.2 : 1 mixture of compounds as determined by n.m.r. spectroscopy.‡ The crude product was purified by chromatography on silica gel eluting with dichloromethane–acetone. Treatment of (**1**) with 2 M HCl overnight at room temperature or 90% aqueous trifluroacetic acid at 0 °C for 7 h[7e] failed to yield lactones (**2**). Instead a mixture of the deprotected glycols (**4**) was isolated in 98—92% yield. Without further purification, this mixture was treated with an excess of di-isobutylaluminum hydride (DiBAL) in THF solution and underwent a ready reduction to alditols (**3**). Reduction with a



stoicheiometric amount of DiBAL in THF yielded on hydrolysis a 74% mixture of carbohydrates (**5**) and (**6**). Peracylation with acetic anhydride in triethylamine in the presence of 4,4-dimethylaminopyridine to form (**7**) and (**8**)‡ eased the chromatographic separation of the mixture by silica gel chromatography with methylene chloride–acetone.

The relative proportions of the product carbohydrates were determined by gas chromatography.§ The major product constituted 63% of the mixture. Determination of the configuration of the major product was possible by n.m.r. spectroscopy. The ^{19}F n.m.r. spectrum corroborated the gas chromatographic analysis. Four sets of fluorine resonances were observed with the most intense resonances at δ −202.4 and −203.5 p.p.m., relative to CCl_3F, assigned to (**7a**) and (**8a**), the β- and α-*ribo* configurations. The ^1H and ^{13}C n.m.r. spectral properties of crystalline (**7a**) isolated by chromatography confirmed the structure of the major product as β-2-deoxy-2-fluoro-1,3,4-triacetoxy-*ribo*-D-pentopyranose. Spectral data (9.39 T) in $CDCl_3$ solution in p.p.m. from Me_4Si: ^{13}C n.m.r. δ 90.75 (dd, $J_{C,F}$ 30.53 Hz, C-1), 84.71 (d, $J_{C,F}$ 189.21 Hz, C-2), 65.96 (d, $J_{C,F}$ 18.32 Hz, C-3), 66.14 (C-4), 62.77 (C-5), 169.7 (C=O), 20.71 (CH_3); ^1H n.m.r. δ 6.23 ($J_{H\text{-}1,H\text{-}2}$ 3.2, $J_{H\text{-}1,F}$ 6.5 Hz, H-1), 5.4 ($J_{H\text{-}2,H\text{-}3}$ 3.2, $J_{H\text{-}3,F}$ 25.2 Hz, H-3), 5.19 (m, H-4), 4.56 ($J_{H\text{-}2,F}$ 48 Hz, H-2), 4.03 ($J_{H\text{-}4,H\text{-}5}$ 3.2, $J_{H\text{-}5,H\text{-}5'}$ 12.9 Hz, H-5), 3.93 ($J_{H\text{-}5',H\text{-}4}$ 4.8 Hz, H-5'), 2.16 (s, CH_3), 2.14 (s, CH_3), and 2.13 (s, CH_3).

Our failure to detect significant formation of the *xylo* [(**7c**), (**8c**)] or *lyxo* [(**7d**), (**8d**)] isomers reflects the diastereofacial selectivity of the lithium enolate of ethyl fluoroacetate.

† Ethyl fluoroacetate is extremely poisonous, causing convulsions and ventricular fibrillation. It was only handled using syringe techniques in an efficient fume hood.

‡ Satisfactory elemental analyses were obtained.

§ 50 m × 0.25 mm OV-101 at 70—200 °C at 5 °C per minute.

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