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Asymmetric Synthesis of 2-Deoxy-2-fluoro-γ-aldonolactones and their Conversion to 2-Deoxy-2-fluoropentoses

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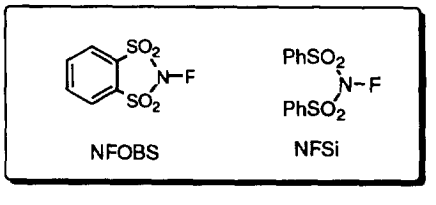
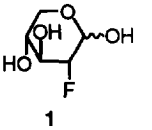
Summary: *2-Fluoro-2-deoxy-γ-xylonic and -lyxonic lactones, **7a** and **7b**, were prepared via the diastereoselective fluorination of the α,β-unsaturated chiral imide **5** followed by dihydroxylation. Lactones **7a** and **7b** were converted to 2-deoxy-2-fluoro-xylo-D-pyranose (**1**) and 2-deoxy-2-fluoro-lyxo-L-pyranose (**2**) by reduction and deprotection.* Copyright © 1996 Elsevier Science Ltd

The development of mild and selective methods for site specific fluorination of organic molecules is of broad interest because of the unique influences this element has on physical, chemical and biochemical properties of organic molecules.[1] Current efforts in this area are focused on the preparation of monofluoro derivatives and enantiomerically pure fluoroorganic compounds for pharmaceutical and agricultural applications.[1-4] Since procedures for the regio and stereocontrolled generation of carbanions and enolates are well established, methodology for their selective fluorination becomes increasingly important. The reagents of choice for the selective fluorination of carbanions and enolates are the easily prepared electrophilic fluorinating reagents *N*-fluoro-*O*-benzenedisulfonimide (**NFOBS**)[5] and *N*-fluorobenzenesulfonimide (**NFSi**)[6] introduced by us and Differding, respectively.



NFOBS NFSi



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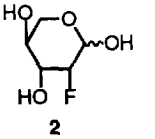


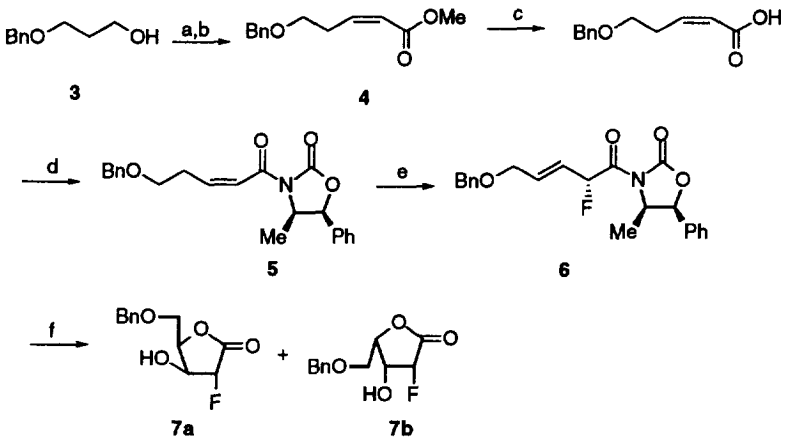
2

The ability of fluorine to function as a hydrogen-bond acceptor, together with the similarities of C-F, C-O bond lengths and size, suggest that replacement of a hydroxyl group by a fluorine atom in bioactive α-hydroxy carbonyl compound could result in useful analogs.[7] Indeed, fluorinated carbohydrates exhibit significant biological activity and are useful probes of biochemical mechanisms.[8] 2-Deoxy-2-fluoropentoses **1** and **2** have been prepared from carbohydrate substrates by several different routes.[9] However, these multistep procedures require protection and/or functionalization of the sugar prior to fluorination. Furthermore, these syntheses necessitate the use of reagents which are either expensive or difficult to prepare and handle. In this letter we describe a new methodology, employing **NFOBS** and **NFSi**, for the asymmetric synthesis of the fluorosugars 2-deoxy-2-fluoro-*xylo*-D-pyranose (**1**) and 2-deoxy-2-fluoro-*lyxo*-L-pyranose (**2**) from a simple

non-carbohydrate precursor. A non-carbohydrate synthesis of 2-deoxy-2-fluoro-*ribo*-D-pentopyranose has been reported by Welch and Eswarakrishnan.[10]

Swern oxidation of commercially available 3-benzyloxy-1-propanol (**3**)[11] gave the corresponding aldehyde which was transformed to the *Z*-α,β-conjugated ester **4** by a Still[12] modification of the Wittig reaction (Scheme 1). After purification by flash chromatography, ester **4** was hydrolyzed with LiOH. The resulting acid was transformed into the pivaloyl anhydride with pivaloyl chloride[13] which, without isolation, was converted to the chiral imide **5** by treatment with the lithium salt of (4*R*,5*S*)-(+)-4-methyl-5-phenyl-2-oxazolidinone.

Scheme 1



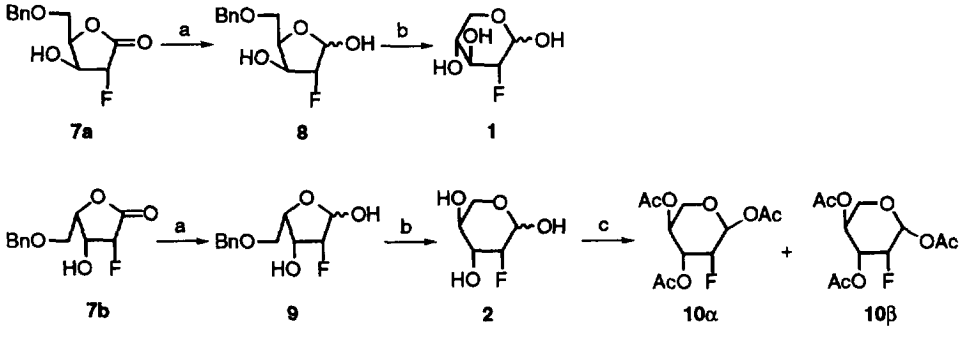
a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 99%; b) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, 18-C-6, **3**, THF, –78 °C, 0.5 h, 94%; c) LiOH, acetone/H_2O, rt, 1 h, 98%; d) i, pivaloyl chloride, Et_3N, THF, –78 °C, 1 h; ii) oxazolidinone, *n*-BuLi, –78 °C, 1 h, 78%; e) i, NaHMDS or LiHMDS, THF, 1 h; ii, **NFOBS** or **NFSi**, –78 °C, 2 h, 76%; f) OsO_4, TMNO, acetone/H_2O (20/1), 94%.

α-Fluorination of the sodium enolate of **5** at –78 °C with **NFOBS** afforded the *E*-α-fluoro imide **6** as the only product in 82% de and 78% yield.[14] The de improved to 88% with the lithium enolate generated using LiHMDS. Significantly, fluorination of the lithium enolate of **5** with **NFSi** gave (2*R*)-**6** as a single diastereoisomer in 76% yield. The improved diastereoselectivity of **NFSi** compared to **NFOBS** is attributed to the greater steric bulk of the former reagent. Dihydroxylation of **6** using a catalytic amount of osmium tetroxide (OsO_4) with trimethylamine N-oxide (TMNO)[15] furnished lactones **7a** and **7b** in 94% yield with a 90% recovery of the Evan's auxiliary. The ratio of the two isomers was 1/2.3 determined by integration of the ^{19}F NMR spectrum of the crude reaction mixture. The overall yield of the two isomers from 3-benzyloxy-1-propanol (**3**) was 50% for the six steps. The low anti selectivity observed in the dihydroxylation of **5** suggests that fluorine is a poor directing group for OsO_4 catalyzed dihydroxylations which is in contrast with the much stronger effect of an allylic hydroxyl group.[16]

Separation of **7a** and **7b** was readily accomplished by flash chromatography (EAOAc/Hex = 1/1) to give **7a** as a glassy oil and **7b** as a white solid. The structures of **7a** and **7b** were first tentatively assigned based on their NMR spectra[8b,17,18] and were confirmed by their transformations to the corresponding known 2-

fluoropentoses **1** and **2** (Scheme 2). This was accomplished by DIBAL reduction of fluorolactone **7a** to the lactal **8** at –78° C in 68% yield. Subsequent removal of the benzyl group by Pd catalyzed hydrogenation completed the synthesis 2-deoxy-2-fluoro-*xylo*-D-pyranose (**1**).[9f,h] The overall yield from **3** was 29%. The same reduction/deprotection sequence afforded 2-deoxy-2-fluoro-*lyxo*-L-pyranose (**2**)[9b,g] in 27% overall yield from **3**. Even though the 2-fluorolyxose **2** is a known compound, spectral data was lacking for comparison and it was further transformed to 1,3,4-tri-*O*-acetyl-2-deoxy-2-fluoro-L-*lyxo*-pyranose (**10α** and **10β**) by acetylation with acetic anhydride in 95% yield as a 2.5/1 mixture of anomers. The reported ^{1}H NMR and ^{13}C NMR spectra of the β-D isomer of **10** matches that of the minor product **10β** which is the enantiomer of the β-D isomer. Consequently, the major product of **10α** is assigned as the α-L anomer.

Scheme 2



a) DIBAL, CH_2Cl_2, –78 °C, 1 h, 68% for **8** and 61% for **9**; b) H_2, Pd/C, MeOH, rt, 2 h, 85% for **1** and 87% for **2**; c) pyridine, Ac_2O, rt, 18 h, 95%.

In summary, the asymmetric synthesis of 2-deoxy-2-fluoro-*xylo*-D-pyranose (**1**) and 2-deoxy-2-fluoro-*lyxo*-L-pyranose (**2**) was accomplished in 27-29% overall yields from a noncarbohydrate precursor. The key step in this synthesis is the highly diastereoselective fluorination of a chiral enolate using the electrophilic fluorinating reagents *N*-fluoro-*O*-benzenedisulfonimide (**NFOBS**) and *N*-fluorobenzenesulfonimide (**NFSi**). Application of this protocol to the asymmetric syntheses of fluoroorganic compounds is in progress.

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18. Some key NMR spectra data (500MHz, $CDCl_3$): **7a**: ^{19}F NMR ($CFCl_3$) δ –198.7 (dd, J = 61.1, 24.4 Hz); ^1H NMR (500 MHz, $CDCl_3$) δ 5.32 (dd, H_2, $J_{H2\text{-}F}$ = 52.8 Hz, $J_{H2\text{-}H3}$ = 7.4 Hz), 4.73 (dt, H_3, $J_{H3\text{-}F}$ = 22.0 Hz, $J_{H3\text{-}H2}$ = 7.7 Hz), 4.64 (dt, H_4, $J_{H4\text{-}H3}$ = 8.1 Hz, $J_{H4\text{-}H5,\ H5'}$ = 1.8 Hz), 4.57 (AB, 2 H (benzylic), J = 11.7), 3.89 (dd, H_5, $J_{H5\text{-}H5'}$ = 11.4 Hz, $J_{H5\text{-}H4}$ = 1.8 Hz), 3.89 (dt, $H_{5'}$, $J_{H5'\text{-}H5}$ = 11.0 Hz, $J_{H5'\text{-}H4}$ = 1.8 Hz, $J_{H5'\text{-}F}$ = 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 169.7 (C1), 95.4 (d, C_2, J = 192.8 Hz), 77.6 (benzylic), 73.9 (C_4), 73.0 (d, C_3, J = 21.7 Hz), 66.8 (C_5). **7b**: ^{19}F NMR ($CDCl_3$) δ –216.8 (d, J = 48.4 Hz); ^1H NMR (500 MHz, $CDCl_3$) δ 5.14 (dd, H_2, $J_{H2\text{-}F}$ = 48.4 Hz, $J_{H2\text{-}H3}$ = 4.4 Hz), 4.55 (AB, 2 H (benzylic) J = 12.0 Hz), 4.60-4.52 (m, 3 H, 2 H (benzylic) and H_3), 4.51-4.48 (m, H_4), 3.88-3.81 (m, H_5, $H_{5'}$), 3.15 (bs, OH); ^{13}C NMR ($CDCl_3$) δ 170.2 (C_1), 86.5 (d, C_2 J = 202.8 Hz), 78.1 (benzylic), 73.8 (C_4), 68.3 (d, C_3, J = 18.8 Hz), 67.5 (C_5).

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