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The Synthesis of 3-Amino-2,3-dideoxy-2-fluoro-xyloses from a 3-Fluoroazetidinone.

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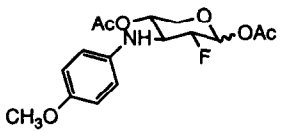
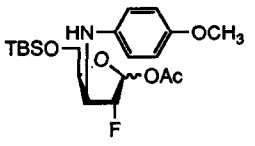
Abstract: Optically active 4-(3',3'-dimethyl-2',4'-dioxol-1-yl)-3-fluoro-2-azetidinone, prepared by the ketene-imine cycloaddition method, is a convenient building block for asymmetric synthesis. This β-lactam has been transformed into 1-*O*-acetyl-5-*O*-(*tert*-butyldimethylsilyl)2,3-dideoxy-2-fluoro-3-(4-methoxyphenyl)amino-D-*xylo*-pentafuranose and the gentosamine analog, 1,4-di-*O*-acetyl-2,3-dideoxy-2-fluoro-3-)4-methoxyphenyl)amino D-*xylo*-pentapyranose.

The continuing need for new antibiotics and anti-neoplastic agents has sparked interest in the synthesis of derivatives of the 3-amino sugar constituents of these materials. β-Lactams have been useful precursors for 3-amino sugar syntheses. In a classic example, the β-lactam prepared by cycloaddition of chlorosulfonyl isocyanate to (*E*)-1,3-pentadiene was converted to L-*N*-benzoyldaunosamine.[1] The successful employment of the ketene-imine [2+2] cycloaddition to form a β-lactam intermediate which has been employed in the three step synthesis of an analog of gentosamine,[2] suggested to us the utility of this strategy for the preparation of optically active fluorinated analogs of gentosamine. Previously β-lactam intermediates had been used to prepared difluorinated daunosamine analogs in a related manner.[3]

Although there are many reports of the synthesis of 3-amino-3-deoxy-D-*xylo*-furanoses[4] and pyranoses,[5-9] none report the preparation of fluorinated analogues of gentosamine or 2-fluoro-3-amino-D-xylofuranose, **1** and **2**. Preparation of such novel compounds is facilitated by the availability of an an optically pure 3-fluoroazetidinone **3**.[10]



1



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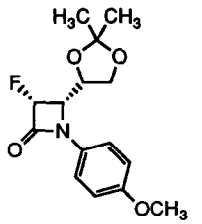


3

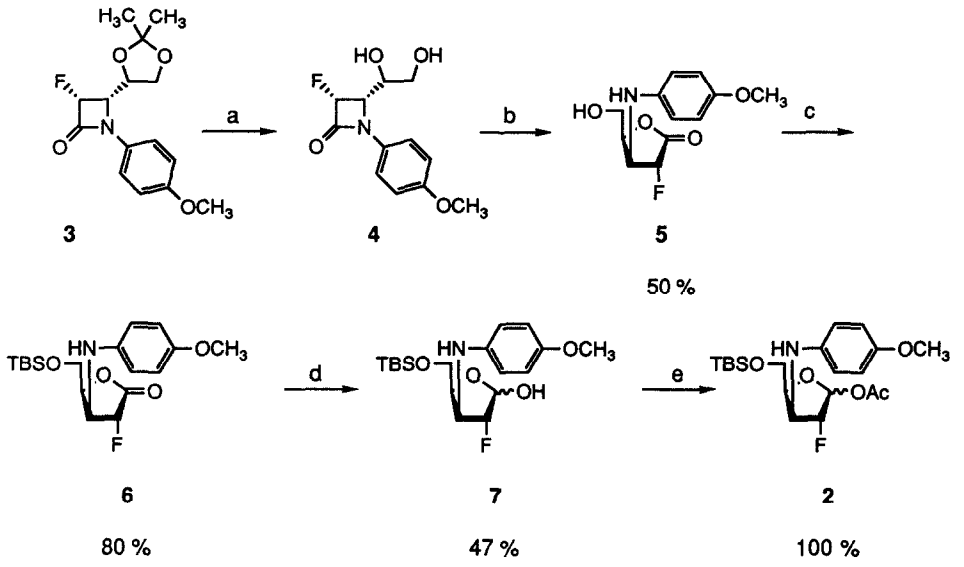
Fluoroketene-Imine Cycloaddition

To a dichloromethane solution of the *p*-anisidine imine of (D)-glyceraldehyde acetonide and 2.02 equivalents of triethylamine (Et3N) was added dropwise a dichloromethane solution of 1.28 equivalents of fluoroacetyl chloride. A single diastereoisomer, (^{19}F NMR: δ -202.27 ppm, d, $J_{H,F}$ = 55 Hz) of the 3-fluoroazetidinone **3** was isolated in 68 % yield.[11] The absolute stereochemistry at C-3, C-4 and C-5 was confirmed by single crystal X-ray diffraction studies.[10b]

Preparation of the 3-Amino-2,3-dideoxy-2-fluoro-D-*xylo*-furanose

Hydrolysis of the acetonide **3** with 90% (v/v) trifluoroacetic acid at room temperature yielded the 5,6-diol **4** with the lactam ring intact; heating overnight was required for conversion to **5**. The hydroxy group at C-5 was protected[12] with 1.25 equivalents of *tert*-butyldimethylchlorosilane and 2.5 equivalents of imidazole in *N,N*-dimethylformamide (DMF). Desilylation of the desired ether takes place on chromatography with silica gel or Florisil when ethyl acetate is used as eluent. Nonetheless analytically pure material could be isolated with little accompanying desilylation by using 1:9 ethyl acetate:hexane for elution. More efficient isolation of material, sufficiently pure for further transformation, was possibleby evaporation of DMF from crude silyloxy ether *in vacuo* .

Lactone **6** was reduced to the lactol **7** with 1.24 equivalents of diisobutylaluminumhydride (DIBAL-H) in ether at -78 °C.[13] After stirring for 2.5 h, chromatography of the product yielded the β-anomer and α-anomer in a 3:1 ratio.[14] The 48 % yield is apparently a result of difficulty of the separation of the lactols from partially desilylated material.



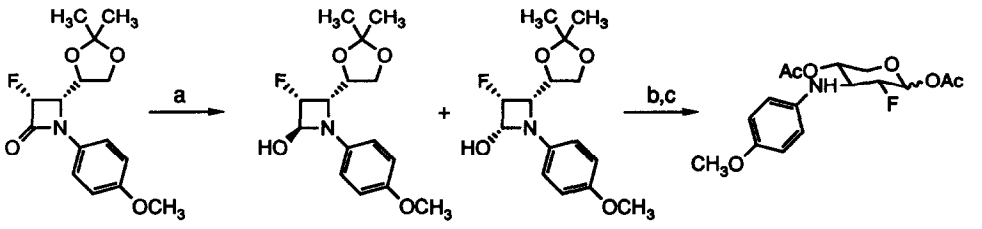
(a) 90 % TFA (aq), RT, (b) 90 % TFA (aq), heat, (c) TBSCl, imidazole, DMF, RT, overnight, (d) DIBAL-H, Et_2O, -75 °C, 2.5 h, (e) AcCl, Et_3N, CH_2Cl_2, RT, 30 min.

The acetylation of the anomeric hydroxyl of **7** in dichloromethane is quantitative using 1.1 equivalents of acetyl chloride in the presence of 2.2 equivalents of triethylamine. The anomeric ratio for the 1-*O*-acetyl-3-amino-2,3-dideoxy-2-fluoro-D-xylofuranoses **2** is unchanged at 1:3.[14] The attempted acetylation of **7** using 1.1 equivalents of acetic anhydride in the presence of 2.2 equivalents of pyridine resulted in lower yields of product.

Preparation of the 3-Amino-2,3-dideoxy-2-fluoro-D-*xylo*-pyranose Derivative

The 2-fluoro-2-deoxy-gentosamine derivative **1** can be prepared by either the trifluoroacetic acid hydrolysis of the β-lactam **3** followed by DIBAL-H reduction of the 5-hydroxy-1,4-lactone[2] or in the preferred

manner, DIBAL-H reduction of the β-lactam **3** followed by acid hydrolysis of the aminal.[3] Treatment of **3** with DIBAL-H at -78 °C for 2.5 h, was followed by quneching of the reaction mixture with 1 equivalent of methanol. The reduction of the β-lactam yielded **8** and **9** in 79 % yield in a 2.6 : 1 ratio. Hydrolysis of the lactols, **8** and **9**, at room temperature in 90 % TFA followed by acetylation in the usual manner yielded the 3-amino-1,4-diacetoxy-2,3-dideoxy-2-fluoro-D-xylopyranoses **1** in 63 % yield.[15]



3 **8** **9** **1**

57 % 22 % 63 %

(a) DIBAL-H, THF, -78 °C, 2.5 h, (b) 90 % TFA (aq), RT, overnight, (c) Ac_2O, pyridine, RT, 24 h.

Conclusion

From one asymmetric center present in the *p*-anisyl imine of 2,3-*O*-isopropylidene-D-glyceraldehyde the two additional asymmetric centers of the *xylo*-pentose can be established by the fluoroketene-imine cycloaddition method. This method will be applied in the future to the preparation of other important 3-aminosugars such as the 2-fluoro-L-daunosamine derivative, by employing a 3-fluoroazetidinone derived from cycloaddition of fluoroketene and an imine based on D-threonine.[16]

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11. A CH_2Cl_2 (15 mL) solution of 5.2 mL (0.059 mol) of fluoroacetyl chloride was added dropwise to a CH_2Cl_2 (100 mL) solution of *p*-anisidine imine of (D)-glyceraldehyde acetonide (10.8 g, 0.046 mol) and triethylamine (12.9 mL, 0.093 mol) under argon atmosphere below 35 °C. After stirring overnight at room temperature, the dark brown reaction mixture was washed with aqueous sodium bicarbonate, brine and water. The organic phase was dried over magnesium sulfate and concentrated. Recrystallization of the crude from absolute ethanol yielded 9.2 g (68 %) of white needles. M.P. = 154-156 °C; $[\alpha]_D^{25}$ +77.9° (c 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.8-7.7 (m, 4H, aromatic), 5.52 (dd, $J_{H3,F}$ = 54 Hz, $J_{H3,H4}$ = 6 Hz, 1H, C<u>H</u>F), 4.41 (ddd, $J_{H4,H4'}$ = 8Hz, $J_{H4',H5'}$ = 2 Hz, 1H, C<u>H</u>CH$_2$O), 4.38 (ddd, $J_{H4,H4'}$ = 8Hz, $J_{H4',H5'}$ = 2 Hz, 1H, C<u>H</u>CH$_2$O), 4.28 (dd, $J_{H4',H5'}$ = 2 Hz, $J_{H5',H5',gem}$ = 9 Hz, 1H, CHCH-<u>H</u>), 4.26 (dd, $J_{H4',H5'}$ = 2 Hz, $J_{H5',H5',gem}$ = 9 Hz, 1H, CHCH-<u>H</u>), 3.82 (dd, $J_{H3,H4}$ = 6 Hz, $J_{H4,H4'}$ = 8 Hz, 1H, C<u>H</u>N), 3.79 (dd, $J_{H3,H4}$ = 6 Hz, $J_{H4,H4'}$ = 8 Hz, 1H, C<u>H</u>N), 3.77 (s, 3H, OC<u>H</u>$_3$), 1.54 (s, 3H, CC<u>H</u>$_3$), 1.36 (s, 3H, CC<u>H</u>$_3$). ^{13}C NMR ($CDCl_3$): δ 160.33 (d, $J_{C2,F}$ = 24 Hz, <u>C</u>=O), 157.01 , 149.94 , 130.47 , 119.70, 114.09, 110.34 (<u>C</u>(CH$_3$)$_2$), 90.35 (d, $J_{C3,F}$ = 223 Hz, <u>C</u>HF), 88.88 (<u>C</u>H$_2$O), 66.61 (d, $J_{C4',F}$ = 4 Hz, <u>C</u>HO), 62.03 (d, $J_{C4,F}$ = 21 Hz, <u>C</u>HN), 55.39 (O<u>C</u>H$_3$), 26.62 (C<u>C</u>H$_3$), 24.87 (C<u>C</u>H$_3$). Calcd. for $C_{15}H_{14}FNO_4$: C, 60.87; H, 6.06; N, 4.71. Found: C, 61.01; H, 6.14; N, 4.74.

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14. For **2**: $[\alpha]_D^{31}$ -7.2° (c 0.3, $CHCl_3$). IR (neat): 3388 (w), 2926 (s), 2854 (m),1751 (m), 1514(s), 1464 (m), 1375 (w), 1235 (m), 1104 (m), 1015 (m), 838 (m), 781 (m) cm^{-1} ^1H NMR ($CDCl_3$): δ 6.73 (m, 4H, aromatic), 6.37 (d, $J_{H1,H2}$ = 4 Hz, 1H, C<u>H</u>OAc, α-anomer), 6.28 (dd, $J_{H1,F}$ = 14 Hz, $J_{H1,H2}$ = 2 Hz, 1H, C<u>H</u>OAc, β-anomer), 5.07 (dd, $J_{H2,F}$ = 56 Hz, $J_{H1,H2}$ = 17 Hz, 1H, C<u>H</u>F, α-anomer), 5.03 (ddd, $J_{H1,H2}$ = 2 Hz, $J_{H2,H3}$ = 3 Hz, $J_{H2,F}$ = 54 Hz, 1H, C<u>H</u>F, β-anomer), 4.60 (d, $J_{H3,NH}$ = 8 Hz 1H, N<u>H</u>), 4.53 (ddd, $J_{H3,H4}$ = 6 Hz, $J_{H4,H5}$ = 4 Hz, $J_{H4,H5'}$ = 2 Hz, 1H, C<u>H</u>O), 4.21-4.36 (m, 1H, C<u>H</u>N), 4.01 (dd, $J_{H4,H5}$ = 5 Hz, 1H, OC<u>H</u>$_2$ (α-anomer)), 3.99 (d, $J_{H4,H5}$ = 4 Hz, $J_{H5,H5',gem}$ = 11 Hz, 1H, TBSOCH-<u>H</u>), 3.88 (dd, $J_{H4,H5}$ = 2 Hz, $J_{H5,H5',gem}$ = 11 Hz, 1H, TBDMSiOCH-<u>H</u>), 3.78 (s, 3H, OC<u>H</u>$_3$), 2.19 (s, 3H, C(O)C<u>H</u>$_3$, α-anomer), 2.10 (s, 3H, C(O)C<u>H</u>$_3$, β-anomer), 0.97 (s, 9H, C(C<u>H</u>$_3$)$_3$, β-anomer), 0.96 (s, 9H, C(C<u>H</u>$_3$)$_3$, α-anomer), 0.13 (s, 6H, SiC<u>H</u>$_3$, β-anomer),0.12 (s, 6H, SiC<u>H</u>$_3$, α-anomer). ^{19}F NMR ($CDCl_3$): δ -190.81 (ddd, $J_{H2,F}$ = 54 Hz, $J_{H1,F}$ = $J_{H3,F}$ = 14 Hz, β-anomer), -202.25 (dd, $J_{H2,F}$ = 56 Hz, $J_{H3,F}$= 17 Hz, α-anomer). Calcd. for $C_{20}H_{32}FNO_5Si$: C, 58.09; H, 7.80; N, 3.39. Found: C, 58.33; H, 7.83; N, 3.16.

15. For **1**: $[\alpha]_D^{30}$ +40.4° (c 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 6.7 (m, 4H, aromatic), 6.34 (d, $J_{H1,H2}$ = 3 Hz, 1H, C<u>H</u>OAc), 5.98 (dd, $J_{H1,F}$ = 7 Hz, $J_{H1,H2}$ = 4 Hz, 1H, C<u>H</u>OAc), 4.95 (m, 1H, C<u>H</u>O), 4.45 (ddd, $J_{H2,F}$ = 47 Hz, $J_{H1,H2}$ = 4 Hz, $J_{H2,H3}$ = 11 Hz, 1H, C<u>H</u>F), 4.35 (ddd, $J_{H2,F}$ = 48 Hz, $J_{H1,H3}$ = $J_{H1,H2}$ = 5 Hz, 1H, C<u>H</u>F), 4.12 (m, 1H, N<u>H</u>), 4,08 (m, 1H, N<u>H</u>), 3.8 (m, 1H, C<u>H</u>N), 3.75 (s, 3H, OC<u>H</u>$_3$), 3.68 (d, $J_{H4,H5}$ = 6 Hz, 1H, C<u>H</u>$_2$O), 3.64 (d, $J_{H4,H5}$ = 7 Hz, 1H, C<u>H</u>$_2$O), 2.23 (s, 3H, C(O)C<u>H</u>$_3$), 2.19 (s, 3H, C(O)C<u>H</u>$_3$), 2.01 (s, 3H, C(O)C<u>H</u>$_3$), 1.90 (s, 3H, C(O)C<u>H</u>$_3$). ^{19}F NMR ($CDCl_3$): δ -192.94 (dd, $J_{H2,F}$ = 40 Hz, $J_{H,F}$ = 9 Hz), -199.79 (dd, $J_{H2,F}$ = 44 Hz, $J_{H,F}$ = 9 Hz). Calcd. for $C_{16}H_{20}FNO_6$: C, 56.30; H, 5.91; N, 4.10. Found: C, 56.04; H, 6.07; N, 3.88.

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