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Completely Regioselective Synthesis of 5- and 6- Amino and Fluoro-hexofuranoses via cyclic sulphates.

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Abstract: The nucleophilic opening of new and previously described 5,6- and 3,5-glucohexofuranose cyclic sulphates is a regioselective and efficient way to prepare 6- and 5-azido(amino)- and 6- and 5-fluoro-aldofuranose derivatives (D-gluco and L-ido configurations). © 1998 Published by Elsevier Science Ltd. All rights reserved.

The cyclic sulphates of *vic*-diols are compounds which have been known for a long time, but until recently, they have not been widely used in organic synthesis, probably due to the lack of a good method for their preparation. Ten years ago, the catalytic oxidation of cyclic sulphites using ruthenium trichloride with sodium periodate was reported[1] as a very general method for the synthesis of cyclic sulphates. Since then, the scope of the method has been studied, and the interest for the synthetic applications of these compounds has grown continuously. Most of the synthetic uses of the cyclic sulphates described until now are based on nucleophilic displacement reactions. These sulphates are synthetic equivalents of epoxides and cyclic sulphites, with the advantages of a greater reactivity and versatility than cyclic sulphites and, in many cases, than oxiranes.[2] In spite of this interest, the applications in carbohydrate chemistry are limited,[2-7] especially in the case of fluoroderivatives, about which we have found data on the preparation only of 4-fluoro-D-xylulose[8] derivatives and 2-deoxy-2-fluoro-D-glucose.[9]

The introduction of an azido function into a sugar molecule is an interesting target because azidosugars play important roles in the synthesis of oligosaccharides,[10] in the treatment of infectious diseases[11] and because they can easily be reduced to amino sugars. Recently, 5- and 6-aminosugars are being applied to the preparation of azasugars[12] and to the stereocontrolled syntheses of *C*-nucleosides.[13] The introduction of an amino function into the position 5 of aldohexofuranoses is a non-trivial problem as the described methods, based on the reduction of 5-oxime derivatives[14] or on the inversion of the configuration of C-5 derivatives,[15] have a high number of steps, substitution competes with elimination, and/or mixtures of diastereomers, which are difficult to resolve, are formed. These difficulties are especially important in the case of minor configurations, such as L-*ido*.

At the same time the carbohydrate fluoro derivatives exhibit interesting antileukaemia[16] and anti-retroviral[17] activities. These biological properties are probably due to a modification of the protein-carbohydrate interactions. Substitution of a hydroxyl group by a fluorine atom can provide insight into whether the hydroxyl group removed was involved in critical hydrogen-bond interactions with the protein-binding site. The fluorine atom can act as hydrogen bond acceptor but not as hydrogen bond donor, and in this way can inform about the

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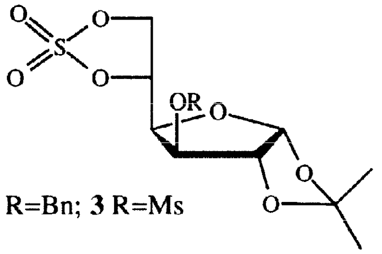
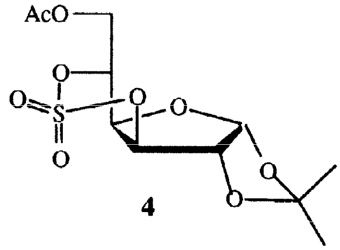
role of the removed hydroxyl group. Consequently the synthesis of fluorosugars is a major challenge in carbohydrate chemistry. The described methods to introduce a fluorine atom in the position 6 of glycopyranoses[18,19] and glycofuranoses[19] have low-medium yields, especially in the second case, where the data are very scarce. Some attempts[20] to introduce a fluorine atom in the position 5 of hexofuranoses (only 6-deoxy derivatives) have been carried out, but elimination overwhelmingly predominated on substitution.

We now communicate a new way to prepare 5- and 6- azido, amino, and fluoro sugars starting from previously described[3] (**1**, **2**) and new (**3**, **4**) glucofuranose 5,6- and 3,5-cyclic sulphates which were prepared from suitably protected glucofuranose derivatives. Compounds **3** and **4**[21] were easily prepared in practically quantitative yields through the corresponding cyclic sulphites, which were obtained as diastereomeric mixtures and directly oxidised with $NaIO_4$-$RuCl_3 \cdot 3H_2O$ following the method described by Sharpless.[1]



1 R=Ac; **2** R=Bn; **3** R=Ms



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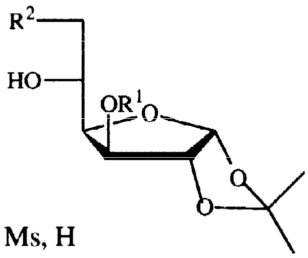
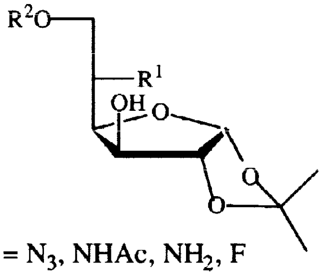


5 R^1= Ac, Bn, Ms, H
R^2= N_3, NH_2, F



6 R^1= N_3, NHAc, NH_2, F
R^2= Ac, H

The nucleophilic ring opening of the cyclic sulphates **1-3** with sodium azide in DMF at 50 °C gave, after elimination of the solvent and treatment with a catalytic amount of 1:10 H_2SO_4:H_2O in THF, the corresponding 6-azido-6-deoxy-glucofuranose derivative (**5**, R^1 = Ac, Bn, Ms; R^2 =N_3) in quantitative yield. As expected, the nucleophilic attack took place on the less hindered primary position in a completely regioselective manner. In the case of **3** no displacement of the mesyloxy group on C-3 was observed either during the described conditions for the opening of the sulphate ring, or on treatment with sodium azide at 105 °C in DMF. Catalytic (10% Pd/C) hydrogenation (r.t, 1 atm of pressure for 50 min) of the 6-deoxy-6-azidoglucofuranose derivatives yielded quantitatively the corresponding 6-amino glucose derivative (**5**, R^1 =Ac, Bn, Ms; R^2 = NH_2). In the case of the 3-*O*-benzyl compound, debenzylation took place when a reaction time of 12 h was used, obtaining the 3-*O*-unprotected 6-amino-1,2-*O*-isopropylidene-6-deoxy-α-D-glucofuranose (**5**, R^1 = H, R^2 = NH_2).

The nucleophilic opening of the non-vicinal cyclic sulphate **4** with sodium azide, using the same experimental conditions and work-up described above, produced quantitatively, and with 100% of regioselectivity, the 5-azido-5-deoxy-L-ido derivative (**6**, R^1 = N_3, R^2 =Ac). When this compound was reduced, simultaneous O-N transacetylation took place, and the 5-acetamido-5-deoxy derivative (**6**, R^1 = NHAc, R^2 = H) was isolated. The 5-amino-1,2-*O*-isopropylidene-5-deoxy-β-L-idofuranose (**6**, R^1 = NH_2, R^2 = H) could be prepared by deacetylation (90%) of the 6-*O*-acetyl azide (**6**, R^1 = N_3, R^2 =Ac) and after reduction (quantitative).

The 6-fluoro-6-deoxy glucofuranoses (**5**, R^1 = Ac, Bn, Ms; R^2 = F) were prepared by opening of the sulphate ring of **1-3** using tetraethylammonium fluoride dihydrate as nucleophile in acetone at r.t (2 h). The yields were 85-90% and the reaction was completely regioselective. The yields became virtually quantitative when anhydrous tetrabutylammonium fluoride was used as fluorinating reagent.

To introduce a fluorine atom in the position 5 of a glucofuranose derivative, we have started from the cyclic sulphate **4**. The reaction has been carried out with several nucleophiles and conditions (see table I) and, although the elimination, with formation of the 4,5 unsaturated derivative, competed with the substitution to obtain the 5-fluorocompound (entries a, b), the amount of the latter was significant. The best yield of the fluoroderivative **6** (R^1 = F, R^2 = H) was using tris(dimethylamino)sulphur (trimethylsilyl)difluoride (TAS-F) as nucleophile and the conditions of entry c, in this case there was practically no formation of elimination product.

Table 1

Fluorination reactions on compound **4**.

Entry	Nucleophile/**4** ratio	Conditions	Elimination: Substitution
a	Bu_4NF 4:1	DMF 65 °C 15 min	3:1
b	Bu_4NF 4:1	DMF 0°C 40 h	3:1.8
c	TAS-F 3:1	CH_2Cl_2 -10°C 24h, and after 35°C 72h	1:100

The azido-, amino-, and fluorosugars[22] **5** and **6** were stable compounds, whose analytical and spectroscopic data[23] (IR, ^{1}H-, and ^{13}C-NMR) confirmed the structure. Thus, the IR spectra of the azido derivatives showed a band at ≈ 2104 cm^{-1} for the azido group, and the chemical shift for the resonance of C-6 was ≈ 54.0 ppm for the 6-azido compounds, ≈ 45.0 ppm for the 6-amino compounds, and ≈ 84.5 ppm for the 6-fluoro derivatives. The $^1J_{C-F}$ coupling constants for **5** (R_2 = F) and **6** (R_1 = F) were ≈ 170 Hz.

In conclusion, we describe a new and efficient method to introduce the azido (amino) and fluoro functions into the positions 5 and 6 of glucofuranose derivatives. As the 1,2-O-isopropylidene group is easy to remove[24], the method can give access to pyranoid and furanoid D-gluco and L-ido derivatives. The reactions are experimentally easy and the overall yields are better than in other described methods.[14,15,18,19]

The scope and limitations of this method are currently under study in our laboratory.

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21. Selected data for **4**: $[\alpha]_D^{24}$+38° (*c* 1.0, dichloromethane); mp 116-118°C dec; IR ν_{max} 1753, 1398, 1254, 1204, 1094, 1042, 866 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$) δ 6.06 (d, 1 H, $J_{1,2}$=3.7, H-1), 5.19 (d, 1 H, $J_{3,4}$=2.5, H-3), 5.00 (t d, 1 H, $J_{4,5}$=2.5, $J_{5,6a}$= $J_{5,6b}$=6.4, H-5), 4.79 (d, 1 H, H-2), 4.57 (m, 1 H, H-6a), 4.54 (m, 1 H, H-6b), 4.35 (t, 1 H, H-4), 2.13(s, 3 H, COCH_3), 1.53, 1.36 (each s, each 3 H, C(CH_3)$_2$); ^{13}C-NMR (125.7 MHz; CDCl$_3$) δ 169.9 (CO), 113.2 (*C*(CH$_3$)$_2$), 104.8 (C-1), 85.1 (C-3), 82.9 (C-5), 82.5 (C-2), 71.7 (C-4), 61.5 (C-6), 26.5, 26.0 (C(*C*H$_3$)$_2$), 20.4 (CO*C*H$_3$); FABMS *m/z* 347 (95, [M+Na]$^+$). Compound **4** gave satisfactory microanalysis (C,H,N,S).
22. All are new compounds except 6-azido-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose which was previously described. [Saeki, H.; Ohki, E. *Chem. Pharm. Bull.* **1968**, *16*, 2471].
23. As examples the structural data of the following compounds are given:

    5-azido-5-deoxy-1,2-O-isopropylidene-β-L-idofuranose had$[\alpha]_D^{24}$-57° (*c* 1.0, dichloromethane); mp 72-74°C; IR ν_{max} 3443, 2104, 1740, 1373, 1260, 1082, 1020 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$) δ 5.98 (d, 1 H, $J_{1,2}$=3.7, H-1), 4.53 (d, 1 H, H-2), 4.32 (dd, 1 H, $J_{6a,6b}$=11.7, H-6a), 4.22 (m, 1 H, H-3), 4.14 (dd, 1 H, H-6b), 4.13 (dd, 1 H, $J_{3,4}$=2.5, H-4), 3.94 (t d, 1 H, $J_{4,5}$=7.6, $J_{5,6a}$=3.4, $J_{5,6b}$=7.6, H-5), 2.66 (d, 1 H, OH), 2.13(s, 3 H, COCH_3), 1.50, 1.32 (each s, each 3 H, C(CH_3)$_2$); ^{13}C-NMR (125.7 MHz; CDCl$_3$) δ 170.9 (CO), 112.0 (*C*(CH$_3$)$_2$), 104.5 (C-1), 85.2 (C-2), 79.6 (C-4), 75.2 (C-3), 63.8 (C-6), 59.8 (C-5), 26.7, 26.1 (C(*C*H$_3$)$_2$), 20.6 (CO*C*H$_3$); FABMS *m/z* 310 (100, [M+Na]$^+$).

    5- deoxy -5-fluoro-1,2-O-isopropylidene-β-L-idofuranose had $[\alpha]_D^{24}$-10° (*c* 0.8, dichloromethane); IR ν_{max} 3455, 2965, 1742, 1377, 1260, 1084, 1020 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$) δ 5.94 (d, 1 H, $J_{1,2}$=3.7, H-1), 4.90 (dtd, 1 H, $J_{4,5}$=6.3, $J_{5,6a}$=2.6, $J_{5,6b}$=6.3, $J_{5,F}$=49.4, H-5), 4.46 (m, 1 H, H-2), 4.37 (ddd, 1 H, $J_{6a,F}$=27.0, $J_{6a,6b}$= 12.7, H-6a), 4.29 (ddd, 1 H, $J_{6b,F}$=23.6, H-6b), 4.22 (ddd, 1 H, $J_{3,4}$=2.9, $J_{4,F}$=17.1, H-4), 4.21 (m, 1 H, H-3), 2.06(s, 3 H, COCH_3), 1.43, 1.26 (each s, each 3 H, C(CH_3)$_2$); ^{13}C-NMR (125.7 MHz; CDCl$_3$) δ 170.9 (CO), 112.1 (*C*(CH$_3$)$_2$), 104.8 (C-1), 90.5 (d, $^1J_{5,F}$=176, C-5), 85.3 (C-2), 78.6 (d, $^2J_{4,F}$=17.6, C-4), 75.5 (d, $^3J_{3,F}$=5.7, C-3), 63.6 (d, $^2J_{6,F}$=22.6, C-6), 26.7, 26.2 (C(*C*H$_3$)$_2$), 20.6 (CO*C*H$_3$); FABMS *m/z* 265 (85, [M+1]$^+$).
24. See for example Wolfrom, M.L.; Thomas, G.H.S. *Methods Carbohydr. Chem.* **1963**, *II*, 32-34 and see also reference 13.