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TETRAHEDRON: *ASYMMETRY*

Synthesis of a difluorinated carbasugar from D-ribose via intramolecular nitrone cycloaddition reaction

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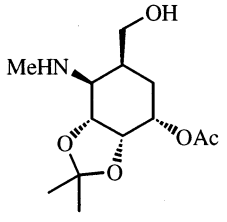
Abstract

Difluorinated carbasugar **3** has been synthesised from D-ribose via an intramolecular nitrone cycloaddition reaction with an overall yield of 22%.

Carbasugars are cyclic monosaccharide analogues in which the ring oxygen atom is substituted by a methylene group.[1,2] Because of their close structural resemblance, some carbasugars may be accepted in biological systems in place of the real furanose or pyranose sugars. There has been considerable interest in recent years in the synthesis of carbasugars as carbohydrate mimics, particularly as glycosidase inhibitors.[3] One of the main synthetic strategies used for the construction of carbasugars is the transformation of carbohydrates to carbocycles.[4] Among the methods available for the transformation is the intramolecular nitrone cycloaddition (INC) reaction which has been used particularly for the synthesis of amino carbasugars.[5] By employing such a method, we had previously synthesised compounds **1** and **2**, as key intermediates for the synthesis of shikimic acid.[5e] To further our work in this area, we decided to replace the methylene group in these amino carbasugars with a difluoromethylene group, reasoning that these fluorinated compounds would have modified biological activities due to the electronic and stereoelectronic effects associated with the fluorines.[6] In this communication, we report the synthesis of difluorinated carbasugar **3** from D-ribose.



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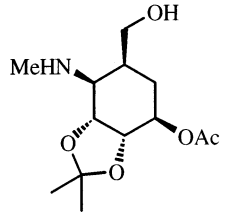

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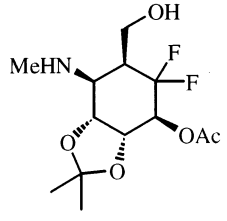

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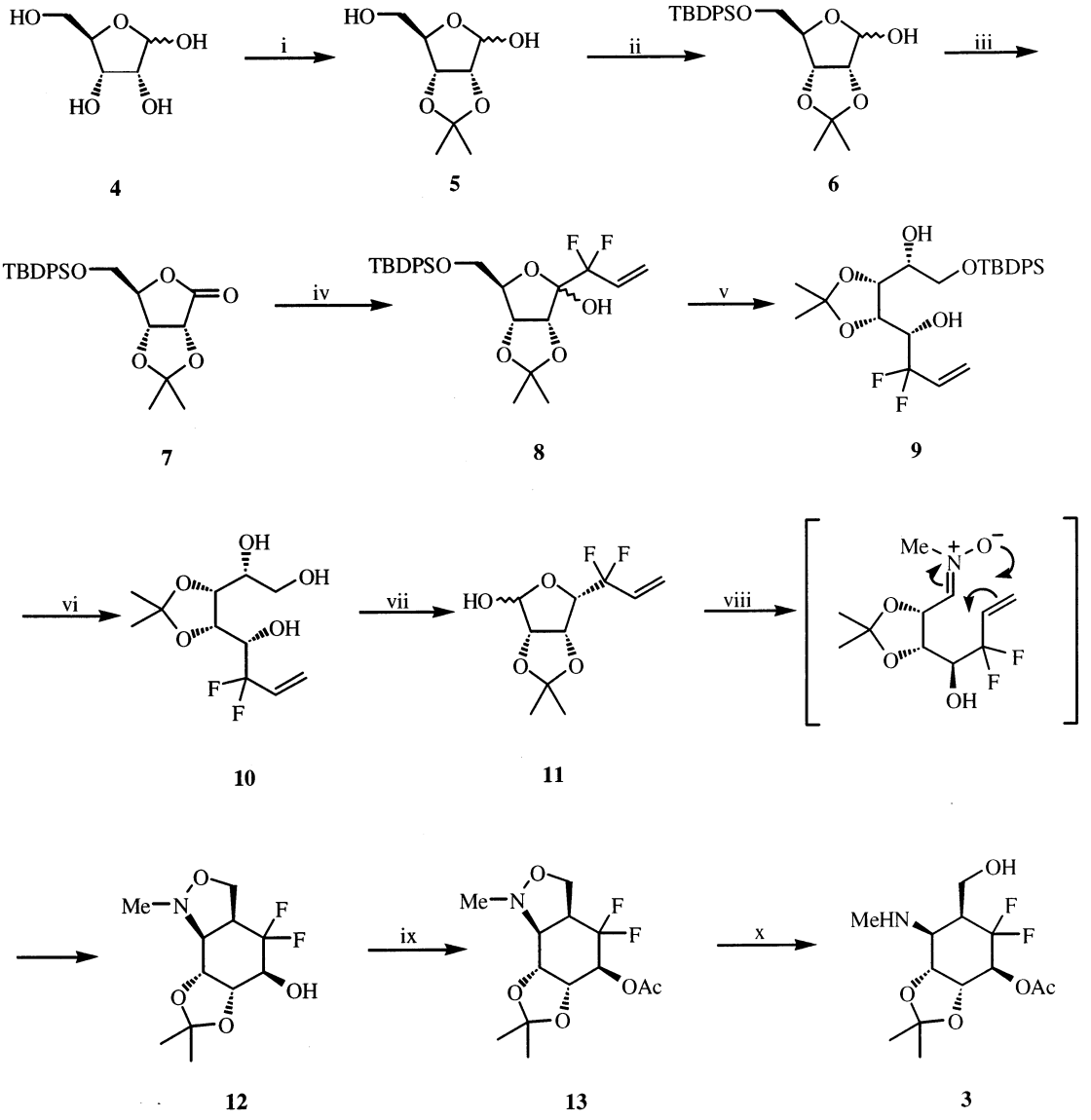
The synthesis of carbasugar **3** is outlined in Scheme 1. Isopropylidenation of D-ribose with acetone and a small amount of concentrated hydrochloric acid as catalyst gave cleanly the acetonide **5**[7] (90%). Selective protection of the primary hydroxy group in **5** as the corresponding *tert*-butyldiphenylsilyl ether **6**, followed by oxidation with potassium permanganate then led to the lactone **7** in 73% of yield, mp 97–99°C, $[\alpha]_D$ −17.3 (*c* 1.04 in $CHCl_3$) (lit.,[8] mp 68°C). For the next step, the lactol **8**[9] was obtained in 82% yield based on recovered starting material by adding *n*-BuLi to a solution of lactone **7** and 3-bromo-3,3-difluoropropene at −100°C.[10] We



Scheme 1. *Reagents and conditions:* i, acetone, aq. HCl (37%, cat.), rt, 4 h (90%); ii, TBDPSCl, Et_3N, DMAP (cat.), CH_2Cl_2, rt, 3 h (98%); iii, $KMnO_4$, acetone, 60°C, 2 h (74%); iv, 3,3-difluoro-3-bromopropene, *n*-BuLi, THF–ether–pentane (5:1:1), −100°C, 2.5 h (82%); v, $NaBH_4$, MeOH, reflux, 5 h (66%); vi, *n*-Bu_4NF, THF, rt, 6 h (84%); vii, $NaIO_4$, H_2O, rt, 1 h (95%); viii, MeNHOH·HCl, pyridine, rt, 12 h (85%); ix, Ac_2O, DMAP (cat.), pyridine, rt, 12 h (100%); x, $Pd(OH)_2$–C (20%), H_2 (5 atm), EtOH, rt, 19 h (92%)

have found that it was necessary to carry out the reaction at such a low temperature in order to minimise the formation of byproduct resulting from the addition of *n*-BuLi to the lactone **7**. The sodium borohydride reduction of lactol **8** in methanol at room temperature was sluggish, but proceeded well when being refluxed to give the diol **9** (66%) with the desired *syn*- (*threo*-) stereochemical relationship between the new stereogenic centre and its adjacent stereogenic carbon. The formation of the *syn*- (*threo*-) isomer is consistent with the reduction of the hemiacetal proceeding via a Felkin–Anh transition state.[5e] Deprotection of **8** with tetra-*n*-butylammonium fluoride in THF afforded the triol **10** (84%), which was then cleaved by sodium periodate in water to provide the lactol **11** (95%), existing almost exclusively as the α anomer, $[\alpha]_D$ +18.4 (*c* 1.14 in $CHCl_3$). Treatment of lactol **11** with an excess of *N*-methylhydroxylamine hydrochloride in pyridine at room temperature led to the formation of the isoxazolidine **12** as the only product in 85% yield, mp 65–66°C, $[\alpha]_D$ −53.9 (*c* 0.75 in $CHCl_3$). Furthermore, in our previous work with compounds **1** and **2**, their corresponding nitrones were isolated under such reaction conditions and were subsequently heated in refluxing toluene to effect the intramolecular nitrone cycloaddition.[5e] However, in the case of difluorinated lactol **11**, the formation of nitrone and its cyclisation occurred concomitantly to afford directly the isoxazolidine **12** in a single step. That the cycloaddition occurred from the least hindered face was predicted on the basis of our earlier findings in the case of **1** and **2**. The stereochemistry at the newly formed two stereogenic centres of the isoxazolidine and also that of the stereogenic centre created by the sodium borohydride reduction in **12** were confirmed by X-ray crystallography (Fig. 1).[11] Acetylation of isoxazolidine **12** afforded quantitatively the acetate **13**, mp 75.5–77°C, $[\alpha]_D$ −39.6 (*c* 1.24 in $CHCl_3$), which was hydrogenated in ethanol in the presence of Pearlman's catalyst (20% palladium hydroxide on carbon)[12] to cleave the N–O bond in the isoxazolidine ring. The resulting amino carbasugar **3** was obtained in 92% yield, mp 90–91.5°C, $[\alpha]_D$ −72.9 (*c* 1.68 in $CHCl_3$).

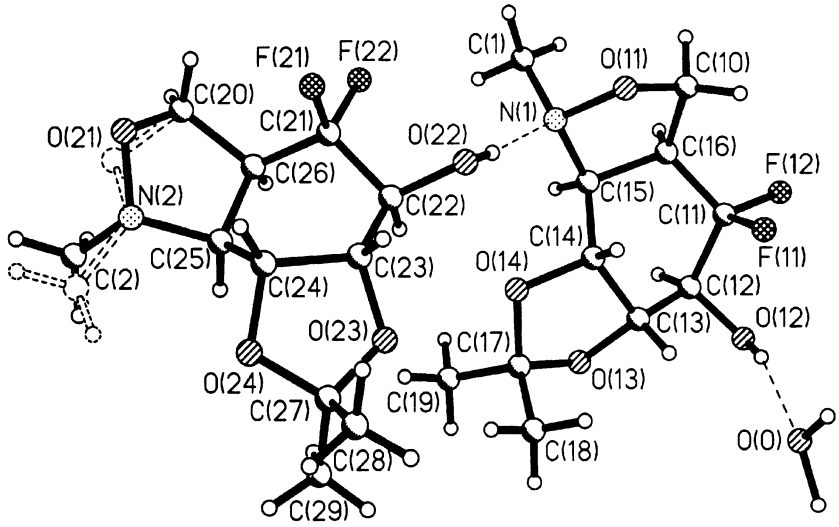


Figure 1. Asymmetric unit in the crystal of isoxazolidine **12**, comprising two molecules of **12** (one disordered) and one H_2O, linked by hydrogen bonds. The absolute configuration was inferred from that of D-ribose.

Compounds **1**–**3** have been screened as herbicides. Unfortunately, these compounds did not show any significant activity in the tests. Our current efforts are directed towards preparations of other difluorinated carbasugars and also the further functionalisation of **3** into other useful synthetic targets.

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9. All new compounds reported were fully characterised (IR, ^{1}H and ^{13}C NMR, HRMS and/or elemental analyses). Selected data: Compound **3**: ν_{max}(KBr)/cm^{-1} 3457, 3305, 2994, 2983, 2915, 2871, 1756 (C=O), 1382, 1224, 1091, 1068, 1024; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, s, Me), 1.52 (3H, s, Me), 2.18 (3H, s, COMe), 2.42–2.55 (1H, m, C*H*CH$_2$OH), 2.55 (3H, s, NMe), 3.00 (2H, br s, NH, OH), 3.27–3.31 (1H, m, C*H*NMe), 3.94 (1H, dd, *J* 11.9 and 3.9 Hz, C*H*HOH), 4.12 (1H, dd, *J* 11.9 and 6.3 Hz, CH*H*OH), 4.28 (1H, dd, *J* 6.9 and 5.5 Hz, C*H*ORCHOAc), 4.37 (1H, apparent t, *J* 5.1 Hz, C*H*ORCHN), 5.29 (1H, ddd, J_{FH} 21.3 and 4.1 Hz, J_{HH} 6.9 Hz, C*H*OAc); δ_C (100.6 MHz, $CDCl_3$) 20.67 (COMe), 26.08 (Me), 27.79 (Me), 35.15 (NMe), 41.81 (t, J_{FC} 19.83 Hz, *C*HCH$_2$OH), 59.00 (dd, J_{FC} 4.32 and 4.19 Hz, CH$_2$OH), 59.67 (d, CHN), 71.55 (dd, J_{FC} 22.94 and 20.37 Hz, *C*HOAc), 74.35 (*C*HORCHN), 75.86 (d, J_{FC} 4.88 Hz, *C*HORCHOAc), 110.25 (*C*Me$_2$), 121.02 (dd, J_{FC} 253.1 and 248.6 Hz, CF$_2$), 169.57 (C=O); δ_F (376.5 MHz, $CDCl_3$) −117.82 (ddd, J_{FF} 256.9 Hz, J_{FH} 26.1 and 21.8 Hz), −106.85 (dt, J_{FF} 256.9 Hz, J_{FH} 2.8 Hz) [*m*/*z* HRMS (CI, NH_3). Found: MH$^+$ 310.1466, $C_{13}H_{22}F_2NO_5$ requires 310.1466] (Found: C,

50.61; H, 6.95; N, 4.49. $C_{13}H_{21}F_2NO_5$ requires C, 50.48; H, 6.84; N, 4.53%). Compound **13**: δ_H (270 MHz, $CDCl_3$) 1.35 (3H, s, Me), 1.51 (3H, s, Me), 2.20 (3H, s, COMe), 2.73 (3H, s, NMe), 3.18–3.37 (2H, m, C*H*CH_2ON, CHN), 4.10–4.24 (3H, m, CH_2ON, C*H*ORCHN), 4.39 (1H, dd, *J* 7.3 and 6.6 Hz, C*H*ORCHOAc), 5.31 (1H, dd, J_{FH} 27.1 Hz, J_{HH} 7.3 Hz, C*H*OAc); δ_C (67.8 MHz, $CDCl_3$) 20.56 (COMe), 25.00 (Me), 27.42 (Me), 43.60 (NMe), 47.46 (t, J_{FC} 22.84 Hz, *C*HCH_2ON), 63.10 (d, J_{FC} 7.27 Hz, CH_2ON), 69.33 (m, CHN), 71.76 (t, J_{FC} 19.73 Hz, *C*HOAc), 74.44 (*C*HORCN), 75.54 [apparent dd, J_{FC} 6.2 (or 5.2) and 3.1 (or 2.1) Hz, *C*HORCHOAc], 110.17 (*C*Me_2), 119.71 (dd, J_{FC} 251.3 and 249.2 Hz, CF_2), 169.64 (C=O); δ_F (282.4 MHz, $CDCl_3$) −119.58 (dt, J_{FF} 254.7 Hz, J_{FH} 25.4 Hz), −106.31 (dd, J_{FF} 245.7 Hz, J_{FH} 8.5 Hz) (Found: C, 50.78; H, 6.20; N, 4.51. $C_{13}H_{19}F_2NO_5$ requires C, 50.81; H, 6.23; N, 4.56%).

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11. Crystal data: $C_{11}H_{17}F_2NO_4 \cdot 1/2H_2O$ (confirmed by microanalysis; found: C, 48.08; H, 6.65; N, 5.06; requires C, 48.17; H, 6.61; N, 5.11%), orthorhombic space group $P2_12_12_1$ (no. 19), at $T=150$ K, $a=9.404(1)$, $b=9.545(1)$, $c=28.578(2)$ Å, $V=2565.2(4)$ Å^3, $Z=8$, 11 748 reflections (4436 unique), $R=0.041$ on 3880 data with $I \geq 2\sigma(I)$. Cambridge Crystallographic Data Centre deposition no. CCDC-149683.
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