PERKIN 1 COMMUNICATION

Synthesis of (difluoromethyl)phosphonate azasugars designed as inhibitors for glycosyl transferases

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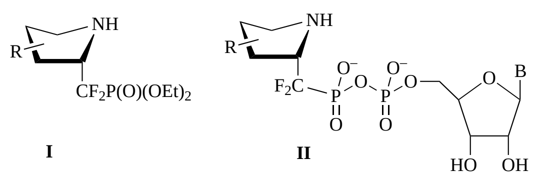
Polyhydroxylated pyrrolidines (azasugars) bearing a (difluoromethylene)phosphonate group at the pseudoanomeric position are prepared by nucleophilic opening of arabino-, ribo- and xylo-furanosylamine with diethyl (lithiodifluoromethyl)phosphonate followed by cyclisation of the amino phosphonate products obtained.

A large variety of polyhydroxylated pyrrolidines resembling sugars in the pyranose and furanose configuration have been used with success as transition-state analogue inhibitors of the corresponding glycosidases.[1] The best results are often obtained with five-membered ring azasugars which closely mimic the flattened shape of the glycosyl cation.[1a,2]

Like glycosidases, glycosyl transferases, which catalyse the transfer of a glycosyl residue from nucleotide diphosphate sugars, are believed to proceed in their catalytic reaction *via* a similar oxocarbenium-like intermediate.[3] These azasugars have also been used as inhibitors of glycosyl transferases.[4] These findings, along with several reports suggesting that (1,1-difluoromethyl)phosphonates are effective phosphate mimics,[5] led us to consider that pyrrolidine azasugars (**I**) bearing a (1,1-difluoromethylene)phosphonate group at C-2 might be valuable derivatives to serve as initial candidates to mimic an important feature of the transition state involved in glycosyl transferase reactions, or to prepare more elaborated models such as stable azasugar nucleotides (**II**).

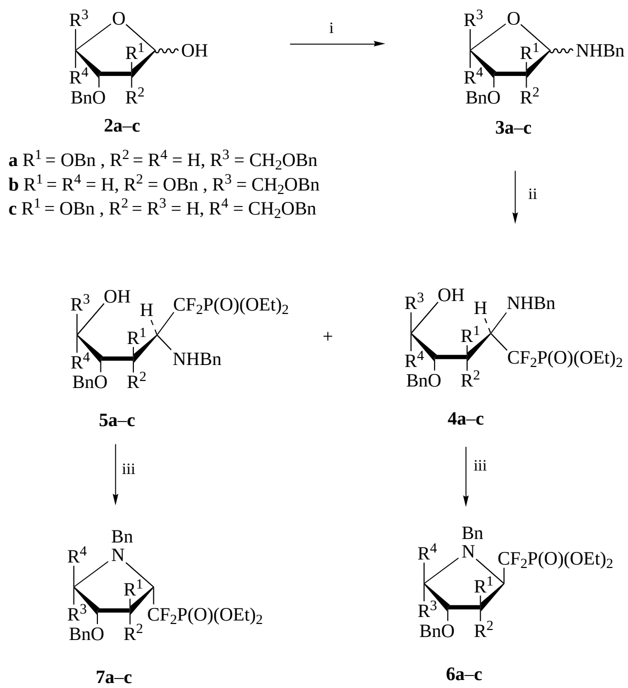


A number of synthetic methods leading to (1,1-difluoroalkyl)phosphonates have been devised;[6] among these, the use of (diethylphosphinoyl)difluoromethyllithium **1** as a (difluoromethylene)phosphonate building-block is often limited because of its relatively weak nucleophilicity and thermal instability.[7] To our knowledge, the reactivity of this lithium salt towards aminosugars derived from aldoses has never been studied.

In this communication we report some preliminary results concerning the condensation of **1** with several furanosylamines derived from protected D-arabinose, D-ribose and L-xylose. As outlined in Scheme 1, the acyclic aminophosphonates obtained this way are useful precursors in building the C-2 branched (difluoromethyl)phosphonate azasugar targets, C-5 epimers of the furanosylamines used.

Commercial 2,3,5-tri-*O*-benzyl-D-arabinose **2a** and the readily prepared 2,3,5-tri-*O*-benzyl-D-ribose[8] **2b** and -L-xylose **2c**[9] were converted in quantitative yields by treatment with benzylamine to the corresponding furanosylamines **3a–c** as anomeric mixtures (α : β ≠ 50 : 50).

Reaction of (diethylphosphinoyl)difluoromethyllithium **1**, prepared in THF by treatment of diethyl (difluoromethyl)phosphonate with LDA at −78 °C according to the method of Obayashi and co-workers,[10] with glycosamines **3a–c** led to the formation of a mixture of the two possible diastereoisomers **4a–c** and **5a–c**. These compounds can be separated by column chromatography on silica gel. As shown in Table 1, similar results, *i.e.* stereochemical outcome of the reaction and combined yields, were obtained in the arabinose, ribose and xylose series. In all cases, the diastereoselection (as determined by ^{19}F NMR spectroscopy) is moderate. The reaction favours the formation of the *threo* product, suggesting that only the stereocentre at C-2 is controlling the addition process as previously observed in the reaction of similar aminofuranosides with Grignard reagents.[11] The configuration at the newly created stereocentre in **4** and **5** was firmly assigned after their conversion to the respective pyrrolidines **6** and **7**. The nuclear Overhauser effect (NOE) on ^{19}F signals observed by saturation of H-3 in the pyrrolidine phosphonates corresponding to the minor compounds **4b** and **5a**,**c** indicated the close proximity of H-3 and the fluorine atoms in the pyrrolidines **6b** and **7a**,**c** (Fig. 1) and confirmed the assigned structures. No NOE was observed for other diastereoisomers.



Scheme 1 *Reagents and conditions:* i; $BnNH_2$, CH_2Cl_2, molecular sieves; ii, $HCF_2P(O)(OEt)_2$, LDA, THF–hexane, −78 °C; iii, MsCl, pyridine

Attempts to improve the yields by changing solvent conditions (THF–HMPA), or by using a large excess (5–10 equiv.) of carbanion **1**, preformed or generated *in situ*, were not success-

Table 1 Diastereoselective addition[a] of **1** to **3a–c**

Entry	Substrate	(α:β)	Products *threo*:*erythro*	Yield[d] (%)
1	**3a**	(40:60)	85:15 (**4a**:**5a**)	52
2	**3b**	(50:50)	75:25 (**5b**:**4b**)	55
3	**3c**	(60:40)	70:30 (**4c**:**5c**)	53
4	**3c**		70:30 (**4c**:**5c**)[b]	44
5	**3c**		70:30 (**4c**:**5c**)[c]	30

[a] Reaction of $LiCF_2P(O)(OEt)_2$ **1** (4.9 equiv.) and aminosugars **3a–c** (1 equiv.). [b] In the presence of $ZnBr_2$ (4.9 equiv.). [c] In the presence of $CeCl_3$ (4.9 equiv.). [d] Isolated yield.

ful, probably due to the great lability of **1**. The cerium method recently described by Lequeux and Percy[12] applied to the xylose derivative **3c** (entry 5, Table 1) did not significantly change our results. For the final cyclisation step, each of the difluorophosphonate derivatives **4a–c** and **5a–c** was esterified with methanesulfonyl chloride to give the corresponding methanesulfonates which underwent smooth nucleophilic displacement with the amino group to form the expected azasugars with inversion of configuration at C-5, in good yields (60–98%). The substantial NOE between H-4 and H-5 in **6a**,**b** and **7a**,**b**, an indication of the *cis* relationship between these protons, confirmed this inversion.

In conclusion, a new class of azasugars with an unprecedented substitution pattern is described. Work is in progress aimed at synthesizing their corresponding nucleotide analogues for an enzymic evaluation as inhibitors of glycosyl transferases.

Experimental

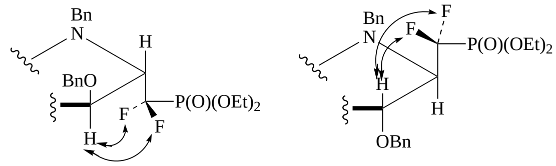
Typical procedure for the conversion of 3 into 4

To a solution of diisopropylamine (0.9 ml, 6.3 mmol) at −78 °C in THF (2 ml) under argon was added *n*-butyllithium (2.5 ml of a 2.5 M solution in hexane, 6.3 mmol). The resulting solution was stirred for 30 min. To this solution of LDA at −78 °C were added dropwise diethyl (1,1-difluoromethyl)phosphonate (1 ml, 5.3 mmol) and, 10 min later, a cold (−78 °C) solution of aminosugar **3a** (0.62 g, 1.2 mmol) in THF (1.5 ml). After 1 h at −78 °C, the reaction was quenched by adding aqueous NH_4Cl (15 ml) and Et_2O (20 ml). The organic layer was further washed with NH_4Cl (3 × 15 ml) and the aqueous phases were extracted once with 20 ml Et_2O. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to give a crude mixture of **4a** and **5a** in a proportion of 85:15 (^{19}F NMR determination). Purification by silica gel flash chromatography (EtOAc–light petroleum, 30:70) gave **4a** (362 mg, 42%) and **5a** (83 mg, 10%) as colourless oils; **4b–c** and **5b–c** were prepared by a similar procedure.

Cyclisation procedure of 4–5 to 6–7

To a solution of **5a** (1.0 g, 1.43 mmol) in pyridine (5 ml) under argon was added methanesulfonyl chloride (220 μl, 1.7 mmol). The resulting solution was stirred overnight at room temperature. Pyridine was evaporated under reduced pressure and the residue was diluted in $CHCl_3$; the solution was washed with water and dried ($MgSO_4$). Evaporation of the solvent and purification of the crude material on a column of silica gel (AcOEt–light petroleum, 30:70) gave **7a** (580 mg, 60%) as a colourless oil.

Selected data: (*J* values are given in Hz and $[a]_D$ values in 10^{-1} deg cm^2 g^{-1}) **6a**: δ_H(C_6D_6, 250 MHz) 7.70–7.05 (20 H, ArH), 5.08 (1 H, dd, *J* 8.4, 8.4, 3-H), 5.00 (1 H of AB, *J* 12.5, CH_2Ph), 4.93 (1 H, dd, *J* 8.4, 6.6, 4-H), 4.75 (1 H of AB, *J* 12.5, CH_2Ph), 4.61 (1 H of AB, *J* 14.7, CH_2Ph), 4.49 (1 H of AB, *J* 12.5, CH_2Ph), 4.44–4.25 (3 H, m, 2-H and 2 H of CH_2Ph), 4.28 (1 H of AB, *J* 12.5, CH_2Ph), 4.19 (1 H of AB, *J* 13.7, CH_2Ph), 4.13–3.98 (4 H, m, CH_2CH$_3$), 3.53 (1 H, d, *J* 6.6, 5-H), 3.52 (1 H, d, *J* 7.9, 6-Ha), 3.28 (1 H, d, *J* 7.9, 6-Hb), 1.09 (3 H, t, *J* 6.3,



7a,c 6b

Fig. 1

CH_3CH$_2$), 1.07 (3 H, t, *J* 6.3, CH_3CH$_2$); δ_C(CDCl$_3$, 62.5 MHz) 139.4–138.3 (4 C, Aryl), 128.2–126.5 (Aryl), 121.9 (dt, $^1J_{C-F}$ 273, $^1J_{C-P}$ 195, CF_2P), 82.5 (4-C), 81.7 (3-C), 73.7, 73.2, 72.7 (3 CH_2Ph), 65.4 (6-C), 65.3 (q, $^2J_{C-F}$ 20, $^2J_{C-P}$ 20, 2-C), 64.1 (m, CH_2CH$_3$), 57.1 (5-C), 54.1 (NCH_2Ph), 16.2 (m, CH$_2$$CH_3$); δ_F(CDCl$_3$, 235.36 MHz, CFCl$_3$) −108.2 (1 F, dd, $^2J_{F-P}$ 107, $^3J_{F-H}$ 10), −108.4 (1 F, dd, $^2J_{F-P}$ 103, $^3J_{F-H}$ 15); δ_P(CDCl$_3$, 101.25 MHz, H$_3$PO$_4$) 7.74 (br t); $[a]_D^{17}$ −34.3 (*c* 3.9 in CHCl$_3$); *m/z* (DCI, NH$_3$) 680 (M$^+$, 69%), 558 (87), 490 (32).

7a: δ_H(C_6D_6, 250 MHz) 7.55–7.05 (20 H, ArH), 4.96 (1 H, dd, *J* 2.9, 2.9, 3-H), 4.75 (1 H of AB, *J* 11.5, CH_2Ph), 4.67 (1 H of AB, *J* 11.5, CH_2Ph), 4.60 (1 H of AB, *J* 11.5, CH_2Ph), 4.40 (1 H of AB, *J* 11.5, CH_2Ph), 4.35 (1 H of AB, *J* 14.5, CH_2Ph), 4.27 (2 H, s, CH_2Ph), 4.20–4.10 (4 H, m, CH_2CH$_3$), 4.16 (1 H, dd, *J* 2.9, 5.5, 4-H), 4.08 (1 H of AB, *J* 14.5, CH_2Ph), 4.03 (1 H, m, 2-H), 3.98 (1 H, dd, *J* 8.8, 6.9, 6-Ha), 3.78 (1 H, ddd, *J* 5.5, 5.4, 6.9, 5-H), 3.68 (1 H, dd, *J* 5.4, 8.8, 6-Hb), 1.05 (6 H, t, *J* 6.3, CH$_2$CH_3); δ_C(CDCl$_3$, 62.5 MHz) 138.0–137.0 (4 C, Aryl), 129.4–127.0 (Aryl), 120.1 (dt, $^1J_{C-F}$ 264, $^1J_{C-P}$ 206, CF_2P), 82.3 (4-C), 81.5 (3-C), 73.1, 71.9, 71.8 (3 C, CH_2Ph), 69.9 (6-C), 69.7 (q, $^2J_{C-F}$ 20, $^2J_{C-P}$ 20, 2-C), 64.4 (4-C), 64.4 (m, CH_2CH$_3$), 58.9 (NCH_2Ph), 16.3 (m, CH$_2$$CH_3$); δ_F(CDCl$_3$, 235.36 MHz, CFCl$_3$) −114.2 (1 F, ddd, $^2J_{F-F}$ 305, $^2J_{F-P}$ 103, $^3J_{F-H}$ 11), −116.3 (1 F, ddd, $^2J_{F-F}$ 305, $^2J_{F-P}$ 107, $^3J_{F-H}$ 19); δ_P(CDCl$_3$, 101.25 MHz, H$_3$PO$_4$) 7.22 (br t); $[a]_D^{20}$ −12.3 (*c* 0.86 in CHCl$_3$); *m/z* (DCI, NH$_3$) 680 (M$^+$, 37%), 558 (23), 171 (100) (Calc. for $C_{38}H_{44}NO_6F_2P$: M$^+$, 679.2874. Found: *M*, 679.2908).

6b: Mp 57–60 °C; δ_H(CDCl$_3$, 250 MHz) 7.31–7.02 (20 H, ArH), 4.62 (1 H of AB, *J* 10.9, CH_2Ph), 4.53 (1 H of AB, *J* 10.9, CH_2Ph), 4.45 (2 H, s, CH_2Ph), 4.31 (1 H, dd, *J* 1.2, 4.9, 3-H), 4.28 (2 H, s, CH_2Ph), 4.16 (1 H of AB, *J* 13.7, CH_2Ph), 4.15–4.02 (5 H, m, CH_2CH$_3$ and 4-H), 3.99 (1 H of AB, *J* 13.7, CH_2Ph), 3.82 (1 H, dd, *J* 6.0, 10.6, 6-Ha), 3.79 (1 H, dd, *J* 3.0, 10.6, 6-Hb), 3.52–3.45 (2 H, m, 2-H and 5-H), 1.20, 1.18 (6 H, 2 t, *J* 6.3, CH$_2$CH_3); δ_C(CDCl$_3$, 62.5 MHz) 140.0–138.0 (4 C, Aryl), 128.4–126.5 (Aryl), 121.0 (dt, $^1J_{C-F}$ 262, $^1J_{C-P}$ 200, CF_2P), 78.7 (4-C), 78.3 (3-C), 73.1, 72.7, 72.3 (3 C, CH_2Ph), 70.5 (q, $^2J_{C-F}$ 20, $^2J_{C-P}$ 20, 2-C), 68.1 (6-C), 64.6 (m, CH_2CH$_3$), 60.6 (5-C), 54.1 (NCH_2Ph), 16.3 (CH$_2$$CH_3$); δ_F(CDCl$_3$, 235.36 MHz, CFCl$_3$) −111.3 (1 F, dd, $^2J_{F-F}$ 309, $^2J_{F-P}$ 103), −115.8 (1 F, ddd, $^2J_{F-F}$ 309, $^2J_{F-P}$ 103, $^3J_{F-H}$ 23); δ_P(CDCl$_3$, 101.25 MHz, H$_3$PO$_4$) 6.83 (br t); $[a]_D^{20}$ +15.1 (*c* 2.3 in CHCl$_3$); *m/z* (DCI, NH$_3$) 680 (M$^+$, 93%), 558 (100), 372 (43) (Calc. for $C_{38}H_{44}NO_6F_2P$: M$^+$, 679.2874. Found: *M*, 679.2849).

7b: δ_H(CDCl$_3$, 250 MHz) 7.30–7.05 (20 H, ArH), 4.71 (1 H of AB, *J* 11.4, CH_2Ph), 4.56 (1 H of AB, *J* 14.9, CH_2Ph), 4.50 (2 H, s, CH_2Ph), 4.29 (2 H, s, CH_2Ph), 4.23–4.02 (5 H, m, CH_2CH$_3$ and 1 H of CH_2Ph), 4.05 (1 H, m, 3-H), 3.85 (1 H of AB, *J* 14.9, CH_2Ph), 3.79 (1 H, dd, *J* 5.5, 9.6, 6-Ha), 3.70 (1 H, dd, *J* 4.1, 7.0, 4-H), 3.68 (1 H, m, 2-H), 3.50 (1 H, dd, *J* 5.9, 9.6, 6-Hb), 3.35 (1 H, ddd, *J* 5.9, 7.0, 5.5, 5-H), 1.25, 1.10 (6 H, 2 t, *J* 6.3, CH$_2$CH_3); δ_C(CDCl$_3$, 62.5 MHz) 138.8–137.8 (Aryl), 129.5–126.9 (Aryl), 121.0 (dt, $^1J_{C-F}$ 268, $^1J_{C-P}$ 197, CF_2P), 79.4 (3-C), 78.9 (4-C), 73.2, 73.0, 72.5 (3 CH_2Ph), 71.5 (6-C), 64.8 (q, 2-C), 64.1 (m, CH_2CH$_3$), 63.7 (5-C), 59.9 (NCH_2Ph), 16.2 (m, CH$_2$$CH_3$); δ_F(CDCl$_3$, 235.36 MHz, CFCl$_3$) −109.2 (1 F, ddd, $^2J_{F-F}$ 305, $^2J_{F-P}$ 103, $^3J_{F-H}$ 16), −112.8 (1 F, ddd, $^2J_{F-F}$ 305, $^2J_{F-P}$ 104, $^3J_{F-H}$ 15); δ_P(CDCl$_3$, 101.25 MHz, H$_3$PO$_4$) 7.3 (br t); $[a]_D^{20}$ +2 (*c* 1.8 in CH$_2$Cl$_2$); *m/z* (DCI, NH$_3$) 680 (M$^+$, 43), 558 (33), 384 (100).

6c: δ_H(C_6D_6, 250 MHz) 7.55–7.05 (20 H, ArH), 4.69 (1 H of AB, *J* 11.7, CH_2Ph), 4.57 (1 H of AB, *J* 11.7, CH_2Ph), 4.52 (1 H of AB, *J* 11.7, CH_2Ph), 4.40 (1 H of AB, *J* 13.7, CH_2Ph), 4.32 (1 H, m, 4-H), 4.30 (1 H of AB, *J* 11.7, CH_2Ph), 4.25 (1 H, m, 3-H), 4.20 (2 H, s, CH_2Ph), 4.23–4.00 (6 H, m, CH_2CH_3, 1 H of CH_2Ph and 2-H), 3.75 (1 H, dd, *J* 7.6, 8.8, 6-Ha), 3.58 (1 H, ddd, *J* 7.6, 6.1, 3.9, 5-H), 3.42 (1 H, dd, *J* 8.8, 6.1, 6-Hb), 1.05, 1.00 (6 H, 2 t, *J* 6.3, CH_2CH_3); δ_C($CDCl_3$, 62.5 MHz) 139.4–137.9 (4 C, Aryl), 129.8–127.3 (Aryl), 121.5 (dt, $^1J_{C-F}$ 269, $^1J_{C-P}$ 209, CF_2P), 83.6 and 83.5 (3-C and 4-C), 72.9, 72.8, 72.0 (3 C of CH_2Ph), 72.7 (6-C), 65.4 (5-C), 64.7 (q, 2-C), 64.4 (m, CH_2CH_3), 60.0 (NCH_2Ph), 16.4 (m, CH_2CH_3); δ_F($CDCl_3$, 235.36 MHz, $CFCl_3$) −110.7 (1 F, ddd, $^2J_{F-F}$ 305, $^2J_{F-P}$ 107, $^3J_{F-H}$ 12), −114.6 (1 F, ddd, $^2J_{F-F}$ 305, $^2J_{F-P}$ 103, $^3J_{F-H}$ 23); δ_P($CDCl_3$, 101.25 MHz, H_3PO_4) 7.35 (br t); $[\alpha]_D^{20}$ −12.9 (*c* 3.1 in $CHCl_3$); *m/z* (DCI, NH_3) 680 (M^+, 94%), 558 (100), 492 (12) (Calc. for $C_{38}H_{44}NO_6F_2P$: M^+, 679.2874. Found: *M*, 679.2858).

7c: δ_H(C_6D_6, 250 MHz) 7.45–7.05 (20 H, ArH), 4.98 (1 H, dd, *J* 1.5, 3.0, 3-H), 4.77 (1 H of AB, *J* 11.6, CH_2Ph), 4.60 (1 H of AB, *J* 11.6, CH_2Ph), 4.51 (1 H of AB, *J* 14.5, CH_2Ph), 4.45 (2 H, s, CH_2Ph), 4.25 (1 H, dd, *J* 1.5, 2.9, 4-H), 4.16 (2 H, s, CH_2Ph), 4.15–4.00 (6 H, m, CH_2CH_3, 1 H of CH_2Ph and 2-H), 3.80 (1 H, ddd, *J* 5.0, 6.1, 3.0, 5-H), 3.59 (1 H, dd, *J* 6.1, 9.8, 6-Ha), 3.54 (1 H, dd, *J* 5.0, 9.8, 6-Hb), 0.98, 0.95 (6 H, 2 t, *J* 6.3, CH_2CH_3); δ_C($CDCl_3$, 62.5 MHz) 139.3–138.2 (4 C, Aryl), 128.2–126.6 (Aryl), 121.5 (dt, $^1J_{C-P}$ 200, CF_2P), 84.6 and 84.1 (3-C and 4-C), 73.1, 71.8, 71.3 (3 C, CH_2Ph), 69.8 (dt, $^2J_{C-F}$ 20, $^2J_{C-P}$ 20, 2-C), 68.0 (6-C), 64.5 (m, CH_2CH_3), 52.6 (NCH_2Ph), 16.3 (m, CH_2CH_3); δ_F($CDCl_3$, 235.36 MHz, $CFCl_3$) −109.8 (1 F, ddd, $^2J_{F-F}$ 313, $^2J_{F-P}$ 103, $^3J_{F-H}$ 7), −112.5 (1 F, ddd, $^2J_{F-F}$ 313, $^2J_{F-P}$ 107, $^3J_{F-H}$ 21); δ_P($CDCl_3$, 101.25 MHz, H_3PO_4) 6.72 (br t); $[\alpha]_D^{20}$ −18.3 (*c* 0.36 in $CHCl_3$); *m/z* (DCI, NH_3) 680 (M^+, 100%), 558 (100), 259 (22) (Calc. for $C_{38}H_{44}NO_6F_2P$: M^+, 679.2874. Found: *M*, 679.2902).

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