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Stereoselective Synthesis of Arabinose-derived Phosphonates

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Abstract: A short, stereoselective synthesis of three new azasugar-derived phosphonates is described. The new compounds are versatile intermediates for the synthesis of glycosyltransferase inhibitors.

There is strong evidence that specific D-arabinosyltransferases play a key role in the biosynthesis of the mycobacterial cell wall.[1,2] As part of a research program aimed at designing inhibitors of these enzymes, we needed to synthesize new types[3] of sugar-derived phosphonates (fig.1) featuring a nitrogen atom as replacement of the ring oxygen in the monosaccharide unit, a strategy which proved to be highly effective in the area of glycosidases,[4] a class of enzymes closely related to glycosyltransferases.[5] In addition, the new compounds contain structural elements expected to confer recognition by the transferases, while preventing the enzymic reaction to proceed. Thus, the 1-phosphate group of the natural substrates is replaced, in our target molecules (**1**,**2** and **3**), by a phosphonate, as a non cleavable isoster.[3,6]

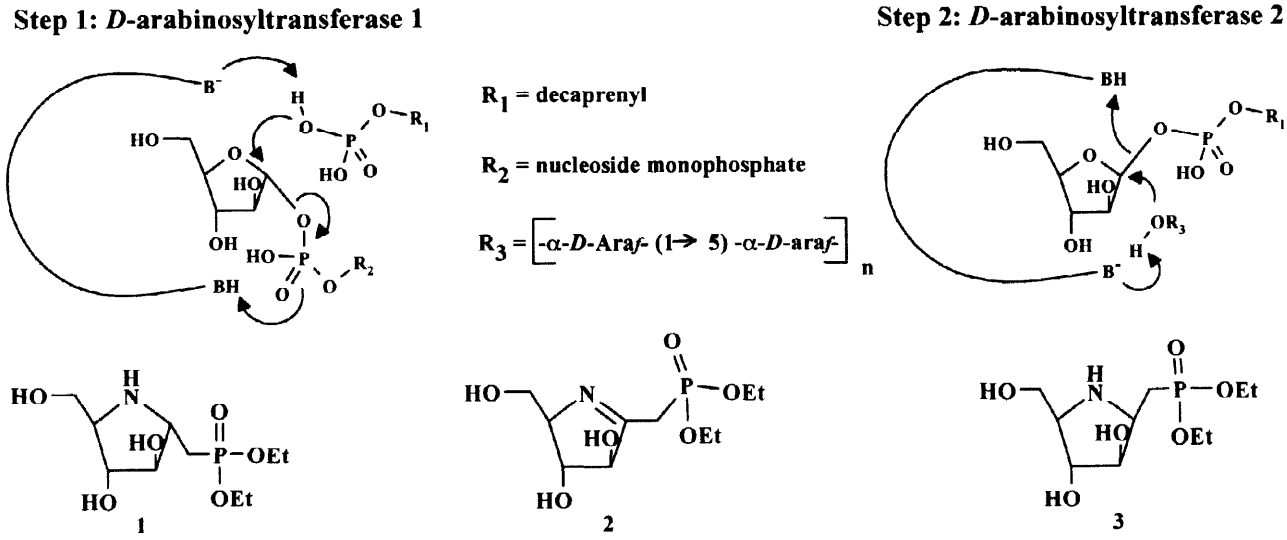

Figure 1: The two proposed ultimate steps of mycobacterial arabinane biosynthesis: proposed transition states for α- and β-(*D*)-arabinofuranosyltransferases and corresponding potential inhibitors.

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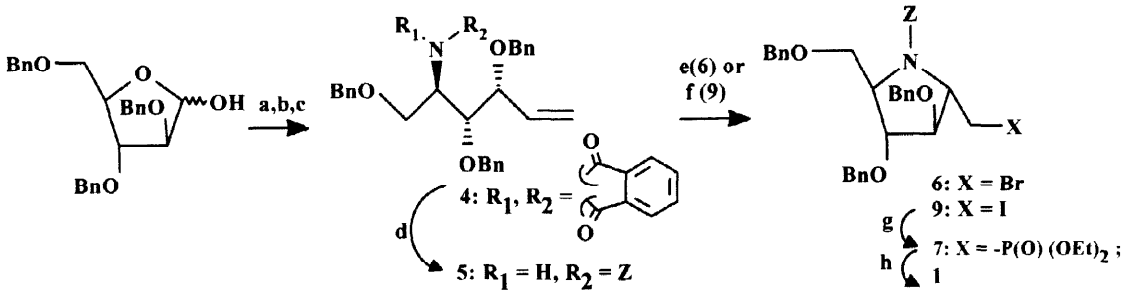
We wanted to design a route in which a readily available common intermediate could be converted in either of our three targets using short synthetic sequences (scheme 1). Our synthesis commenced with Wittig olefination[7] of the commercially available 2,3,5-tri-*O*-benzyl-D-arabinofuranose. Two successive Mitsunobu reactions, first with *p*-nitrobenzoic acid, then with phthalimide, afforded **4**. Hydrazinolysis and protection of the resulting amine afforded the *N*-benzyloxycarbonyl derivative **5**.



(a) *n*-BuLi, $CH_3PPh_3^+Br^-$, THF, 0°C to RT, 85%; (b) *p*-$NO_2PhCOOH$, PPh_3, DEAD, toluene, 0°C to RT, then KOH (2M) in water, reflux, 67%; (c) HNPht, PPh_3, DEAD, toluene, 0°C to RT, 60%; (d) N_2H_4, H_2O/EtOH, reflux then ZCl, aqueous Na_2CO_3, CH_2Cl_2, 0°C, 85%; (e) NBS , HMPA / CH_2Cl_2, 0°C, 50%; (f) NIS, HMPA / CH_2Cl_2, 0°C, 56%; (g) $P(OEt)_3$, reflux, 56%; (h) BCl_3, CH_2Cl_2, -78°C, 90%.

Scheme 1

For the preparation of **1** (scheme 1), a two step sequence involving a NBS-induced ring closure followed by Arbuzov reaction to provide intermediate **7** was envisaged. Based upon literature precedents, the first, ring-forming step, was anticipated to lead predominently to 2,3-*trans*-substituted pyrrolidines.[8,9]

In fact, treatment of **5** with NBS was completely stereoselective, producing the 2-(*S*)-bromomethylpyrrolidine **6** in (50%) yield. Unfortunately, attempts to convert **6** to the desired phosphonate **7**, afforded almost only the cyclic carbamate **8** (fig.2).[9] Eventually, the iodomethylpyrrolidine **9** was prepared from **5**, using NIS as a trigger for the ring closure and allowed to react with triethylphosphite to afford **7** as the major product, in 56% yield, along with carbamate **8** (11%).

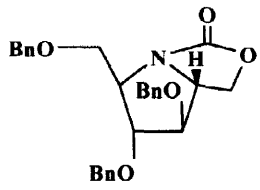


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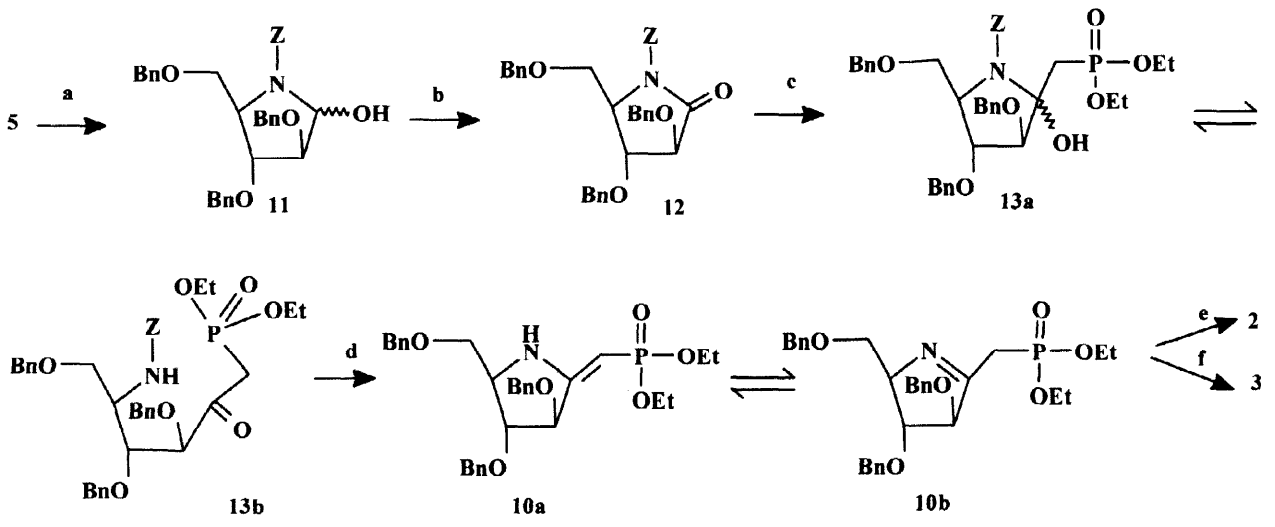
Figure 2

Our second target was the 2-phosphonomethylpyrroline **2**. The only described compound related to **2** is 2-[(diethylphosphono)methyl]-5-methyl-2-pyrroline, whose preparation was not applicable in our case.[10] Our approach is shown in scheme 2: cleavage of the olefinic double bond in **5** ($NaIO_4/OsO_4$) afforded azasugar **11** which was readily converted to the *N*-benzyloxycarbonyllactam **12**. A solution of **12** and $BF_3.Et_2O$ in THF was treated at -78°C with diethoxyphosphonomethyllithium to give the phosphonate **13** as a *ca.* 1 to 1 mixture of closed (**13a**) and opened (**13b**) forms as evidenced by ^{1}H-NMR.[11] Selective hydrogenolysis of the Z group[12] gave the desired **10**. ^{1}H-NMR indicates the presence of the imino and enamino forms in the proportions 1 to 1.[10,13] The conversion **10** → **2** could be carried out very cleanly, using BCl_3,[14] without the imino or phosphonate groups being affected (Scheme 2). Interestingly, in contrast to our previous observations on **10**, the ^{1}H-NMR spectrum of **2** in CD_3OD showed only the signals characteristic of the imino form.



(a) OsO_4 cat, NMO, THF/acetone/H_2O 2/2/1, RT, then $NaIO_4$, RT, 89%; (b) PCC, molecular sieves 4Å, CH_2Cl_2, reflux, 91%; (c) *n*-BuLi, $CH_3P(O)(OEt)_2$, $BF_3.OEt_2$, THF, -78°C, 40%; (d) NH_4OAc, H_2 (P = 1 bar), Pd/C 5%, MeOH RT, 86%; (e) BCl_3, CH_2Cl_2, -78°C, 80%; (f) H_2 (P = 50 bar), Pd/C 10%, MeOH, RT, 80%.

Scheme 2

Inspection of structure **10** suggests that, regardless of the form considered (imine or enamine), reduction of the double bond should result in the preferential formation of the 2(*R*) pyrrolidine **15**. However all our attempts, using metal hydrides[15] invariably led to mixtures of 2(*S*) and 2(*R*) pyrrolidines **14** and **15** (fig.3) in the proportions 3:2. Catalytic hydrogenation was attempted next. In contrast to 2-[(diethylphosphono)methyl]-5-methyl-2-pyrroline,[10] **10** proved to be remarkably resistant to most conditions used.[16] Eventually, using Pd/C 10% as a catalyst and working under pressure (P = 50 bar, 24 h) resulted in clean reduction of the dihydropyrroline **10** and concomitant cleavage of the benzyl ethers to afford **3** in 80% yield, with complete stereoselectivity.

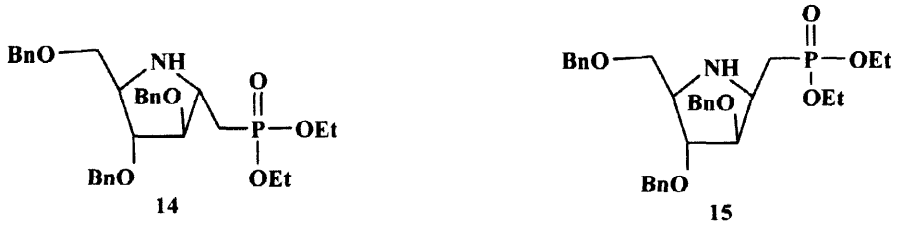


Figure 3

In conclusion, a short synthesis of three new arabinose-derived phosphonates has been accomplished. One of these compounds, the pyrroline derivative **2** is the first example of a new family of unsaturated, phosphonylated azasugars. Compounds **1**, **2** and **3**[17] are versatile intermediates for the synthesis of inhibitors of mycobacterial D-arabinosyltransferases and might themselves exhibit inhibitory activity against glycosyltransferases. Biological evaluation of the new compounds in a variety of glycosyltransferase inhibition assays and further elaboration of the phosphonate moiety are under way. The results of these investigations will be reported in due course.

Acknowledgments:

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11. The ratio **13a** / **13b** was estimated by comparing the intensities of the ^{1}H-NMR signals corresponding to the opened form: δ 5.77 (d, J = 9 Hz, NH) or 2.86 (dd, J = 14 and 22 Hz, -C$\underline{H}_a$H$_b$-P), with those attributed to the closed form at δ 2.45 (m,-CH$_2$-P).
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13. Based on ref. 11, the ratio **10a** / **10b** was estimated by comparing the intensities of the ^{1}H-NMR signals for the two phosphonomethyl (**10b**, imino form) and the phosphonomethylene (**10a**, enamino form) protons: Imino form: δ 3.02 (dd, J = 14 and 20 Hz, -C$\underline{H}_a$H$_b$-P), 3.18 (dd, J = 14 and 20 Hz, -CH$_a\underline{H}_b$-P). Enamino form: d 3.85 (dd, J = 13 and 1 Hz, =C(H)-P), 7.06 (broad s, NH).
14. Kikuchi, Y.; Kurata, H.; Nishiyama, S. and Yamamura, S. *Tetrahedron Lett.* **1997**, *27*, 4795-4798.
15. The following reducing agents were used: LiBH$_4$ / BF$_3$.OEt$_2$, LiBH$_4$ / HBF$_4$, L-Selectride, DIBAH / HBF$_4$, LiAlH$_4$, NaBH$_3$CN / HBF$_4$.
16. Using palladium10% on charcoal (2-propanol, P = 1 bar) no reaction occured at 20°C. In refluxing 2-propanol, only incomplete hydrogenolysis of the benzyl groups and no reduction of the imine / enamine system were observed.
17. All new compounds were purified by chromatography and have satisfactory analytical data (^{1}H-NMR and MS). Data for **1**, **2** and **3** are as followed:

    1: HRMS (FAB), calcd. for C$_{10}$H$_{22}$NO$_6$P: (M$^+$+H) 284.1263, found 284.1257; ^{1}H-NMR (250 MHz, CD$_3$OD) δ 1.33 (6H, two overlapping t, J = 7 Hz, 2 x O-CH$_2$-C$\underline{H}_3$), 1.97 (1H, ddd, J = 15.5, 18.5 and 6.5 Hz, C$\underline{H}_a$H$_b$-P), 2.23 (1H, ddd, J = 15.5, 18.5 and 7 Hz, CH$_a\underline{H}_b$-P), 3.00 (1H, m, H-5), 3.49 (1H, complex, H-2), 3.60 (1H, dd, J = 6 and 11 Hz, C$\underline{H}_a$H$_b$-OH), 3.68 (1H, dd, J = 4.5 and 11 Hz, CH$_a\underline{H}_b$-OH), 3.83 (1H, m, H-4), 3.87 (1H, m, H-3), 4.10 (4H, complex, 2 x O-C$\underline{H}_2$-CH$_3$).

    2: HRMS (FAB), calcd. for C$_{10}$H$_{20}$NO$_6$P: (M$^+$+H) 282.1106, found 282.1106; ^{1}H-NMR (250 MHz, CD$_3$OD) δ 1.33 (6H, two overlapping t, J = 7 Hz, 2 x O-CH$_2$-C$\underline{H}_3$), 2.43 (1H, dd, J = 15 and 24 Hz, C$\underline{H}_a$H$_b$-P), 2.50 (1H, dd, J = 15 and 22.5 Hz, CH$_a\underline{H}_b$-P), 3.52 (1H, broad d, J = 4.5 Hz, H-5), 3.65 (1H, t, d = 9 Hz, H-3), 3.69 (1H, dd, J = 2 and 13 Hz, C$\underline{H}_a$H$_b$-OH), 3.98 (1H, dd, J = 4.5 and 9 Hz, H-4), 4.05 (2H, q, J = 7 Hz, O-C$\underline{H}_2$-CH$_3$), 4.13 (2H, q, J = 7 Hz, O-C$\underline{H}_2$-CH$_3$), 4.22 (1H, dd, J = 4 and 11 Hz, CH$_a\underline{H}_b$-OH).

    3: HRMS (FAB), calcd. for C$_{10}$H$_{22}$NO$_6$P: (M$^+$+H) 284.1263, found 284.1264; ^{1}H-NMR (250 MHz, CD$_3$OD) δ 1.32 (6H,two overlapping t, J = 7.5 Hz, 2 x O-CH$_2$-C$\underline{H}_3$), 1.94 (1H, ddd, J = 15, 16 and 9 Hz, C$\underline{H}_a$H$_b$-P), 2.23 (1H, ddd, J = 15, 19 and 4 Hz, CH$_a\underline{H}_b$-P), 3.01 (1H, td, J = 6.5, 4 and 6 Hz, H-5), 3.21 (1H, complex, H-2), 3.53 (1H, dd, J = 6.5 and 11 Hz, C$\underline{H}_a$H$_b$-OH), 3.64 (1H, t, J = 6 Hz, H-3), 3.66 (1H, dd, J = 4 and 11 Hz, CH$_a\underline{H}_b$-OH), 3.72 (1H, t, J = 6 Hz, H-4), 4.10 and 4.13 (4H,complex, 2 x O-C$\underline{H}_2$-CH$_3$).