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Cyclic phosphonomethylphosphinates: a new type of phosphorus-containing sugars

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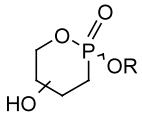
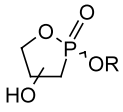
Abstract—The first synthesis of *arabino*-configured cyclic phosphonomethylphosphinates is described. The key step is the condensation of the triethylester of *H*-phosphinylphosphonate **10** on an hydroxyaldehyde **11** derived from a D-arabinal derivative followed by a cyclization induced under acetylation conditions.

Sugar analogs like **I** and **II** (see below), in which the anomeric carbon atom is replaced by phosphorus (glycophostones) have received continuous attention.[1] These compounds may mimic the transition state involved in glycosidase-catalyzed hydrolytic reactions and have been suggested as possible inhibitors of these enzymes. Similarly, cyclic phosphonomethylphosphinates of type **III** or **IV** can be viewed as stable transition state analogs of reactions involving sugar-1-phosphates (e.g. glycosyltransferases, purine phosphorylases, …etc.). Despite their potentially interesting biological properties, structures like **III** and **IV** are, to the best of our knowledge, unprecedented in the literature.



I



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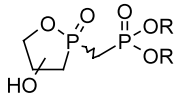
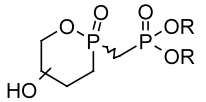


III



IV

In this work, we describe the synthesis of the first type **III**, D-arabinose-derived, cyclic phosphonomethylphosphinate. This compound was designed as possible transition state inhibitor of mycobacterial arabinosyltransferases known to play a crucial role in the biosynthesis of the arabinan part of the mycobacterial cell wall. Inhibition of arabinosyltransferases may constitute a new approach to the treatment of mycobacterial diseases.[2]

Our first, apparently straightforward approach to this class of compounds (shown in Fig. 1), involves the Abramov coupling of a phosphite with protected D-erythrose and the cyclization of the resulting α-hydroxy phosphinate to the corresponding phostone, followed by activation and coupling with a methyl phosphonate. In such an approach, stereoselectivity problems were anticipated. There are only a few examples of type **II** phostones preparation[1f–h] which renders the stereoselectivity of the Abramov reaction (to give either *ribo*- or *arabino*-derivatives) difficult to predict. Another issue was the unknown stereochemical outcome of the unprecedented subsequent coupling with a methylphosphonate.

As can be seen in Scheme 1, the synthesis worked well up to the transient cyclic phosphochloridate **6**. Thus, starting from thymidine, the di-*O*-*t*-butyldimethylsilylarabinal **2** was obtained in 60% overall yield.[3] Oxidative opening of this arabinal yielded the aldehyde **3** which was converted to the mixture of hydroxyphosphonates **4** by treatment with trimethylphosphite in acetic acid. Finally, base-induced cyclization to the phostonic methyl ester **5** (a mixture of four isomers) followed by treatment with hot oxalylchloride as previously described[4] led to the phosphochloridate **6**. Unfortunately, although the formation of **6** could be ascertained by clean conversion back to phostonic

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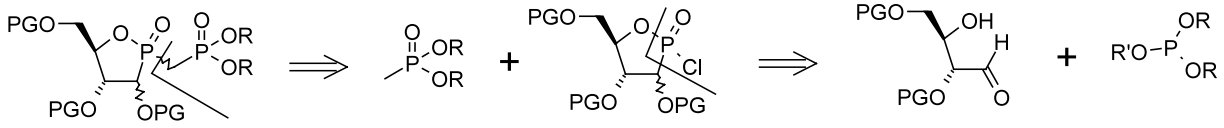
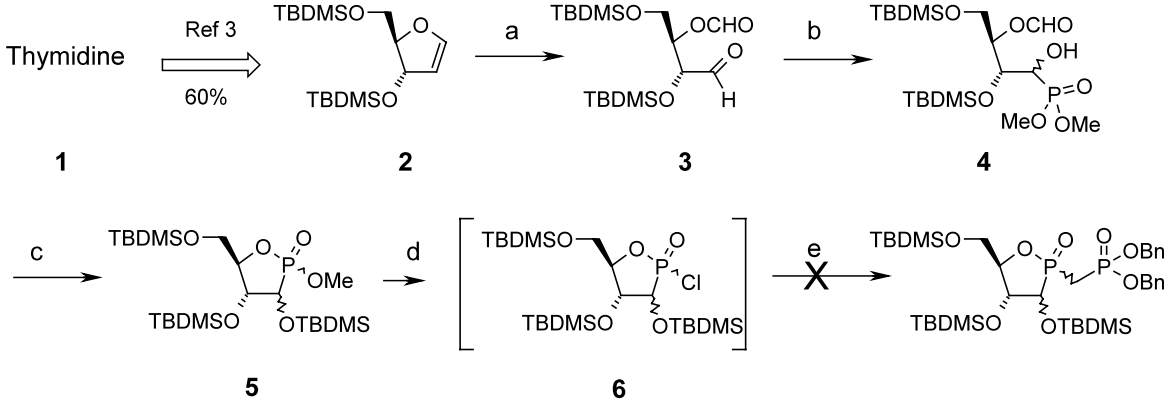


Figure 1. Initial retrosynthetic approach to type **III** phosphonymethylphostones.



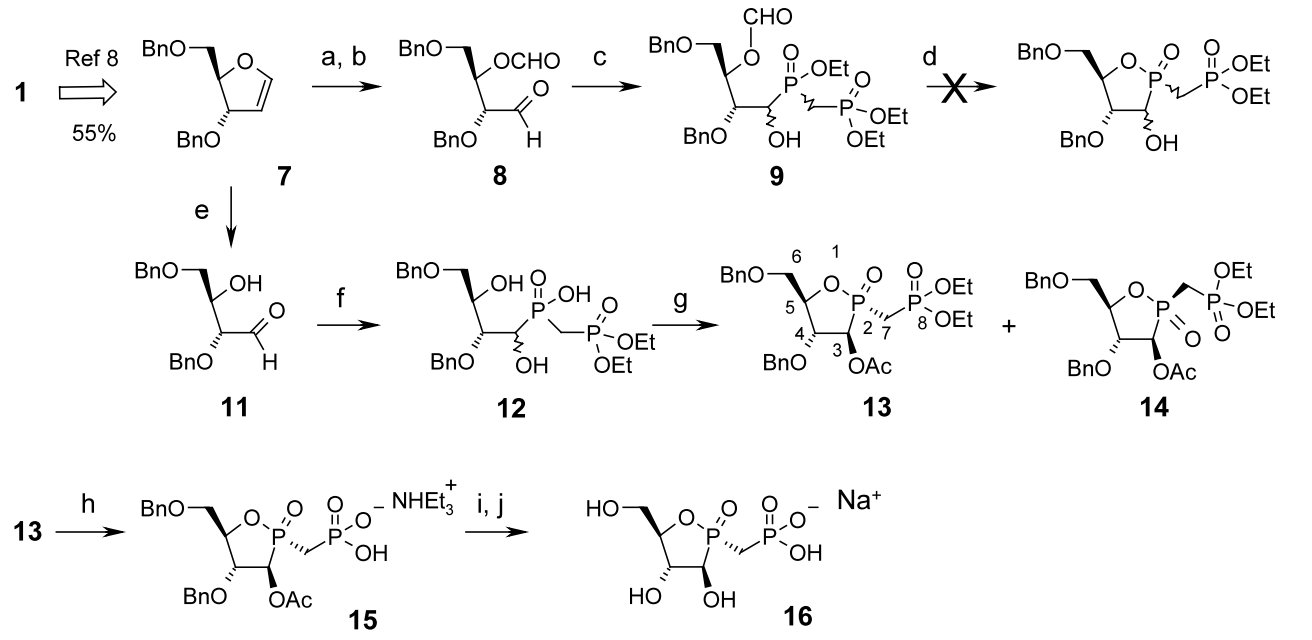
Scheme 1. *Reagents and conditions*: (a) OsO_4, NMO, 6 h, rt, then $NaIO_4$, 1 h, rt; (b) $P(OCH_3)_3$, AcOH, 1.5 h, rt, 68% for a and b; (c) CH_3ONa, THF, 1.5 h, 0°C, then TBDMSCl, DMF, 48 h, 45°C, 72%; (d) $(COCl)_2$, 12 h, 65°C; (e) $CH_3P(O)(OBn)_2$, *n*-BuLi, THF, −78°C to rt.

esters (e.g. benzyl), every effort to couple **6** with the anion derived from methyldibenzylphosphonate failed.[5]

Faced with the failure of our initial synthetic plans, we turned to an alternative strategy based upon our recently described method for preparing phosphonomethylphosphinates from aldehydes.[6] This approach, which is depicted in Scheme 2, would allow the entire phosphonomethylphosphino moiety to be introduced prior to cyclization, avoiding the preceding problems.

The 3-formyloxyaldehyde **8** was prepared by oxidative cleavage of the di-*O*-benzylarabinal **7**[7] (obtained from 2′,3′-di-*O*-benzylthymidine).[8] Although quite unstable, aldehyde **8** could be obtained with a purity of over 95%, as evidenced by ^1H and ^{13}C NMR, by fast filtration over a short pad of silicagel, using CH_2Cl_2 as eluent. Coupling of **8** with the *H*-phosphinylphosphonate **10** proceeded smoothly to afford the phosphinylphosphonate **9** in 60% yield. Unfortunately, unlike simple phosphonates, **9** proved to be reluctant to base-induced formate removal/cyclization, giving rise only to complex mixtures of undefined polar compounds as shown by TLC and ^{31}P NMR. Using the deformylated aldehyde **11**[9] led to an intriguing result. Instead of the expected phostone, we observed the exclusive formation of the acyclic phosphinic acid **12**. One can reasonably assume the following sequence of events: (1) coupling of the *H*-phosphinylphosphonate **10** with **11**, (2) transient formation of a phostone by intramolecular attack of the free 5-hydroxyl group (see Scheme 2 for numbering), (3) hydrolysis of the phostone by traces of water present in the potassium carbonate used as a base or in the solvent. Although the foreseen cyclization did not occur, the unexpected formation of **12** proved to be beneficial by rendering possible the selective activation of the free phosphinic acid. Our initial attempts to activate P–OH by treatment with DCC, mesylchloride, or pivaloylchloride, as occasionally reported in the literature,[10] met with little success. In contrast, treatment by acetic anhydride in pyridine, which proved to be very efficient in our group for the synthesis of other carbohydrate-derived phostones,[11] led, after much experimentation, to phostones **13** and **14**, obtained in satisfactory (42%) yield.[12]

The structure of the protected phostones **13** and **14** and, in particular the *arabino* configuration and the configuration of the anomeric phosphorus was determined by careful NMR studies[13] and comparison with literature data when available. In $^{31}P\{^1H\}$ NMR, the ring phosphorus in **13** and **14** appears as a doublet at 45 and 54 ppm, respectively, relative to H_3PO_4 in agreement with other previously described five-membered ring phostone derivatives.[1f,h,11] In ^1H NMR, complete attribution of the protons was deduced from the COSY spectra of **13** and **14**. In the case of **13**, the absence of coupling beween H-3 and P, observed in ^1H NMR spectroscopy and the small coupling observed for **14** ($J_{H\text{-}3,P}=1.9$ Hz) are indicative of an *arabino* configuration. These values have been previously observed in the case of 3,6-dideoxy-*arabino*-phostones as opposed to the *ribo* analogs ($J_{H\text{-}3,P} \geq 4$ Hz).[1g] The *arabino* configuration of **13** and **14** as well as their configuration at P-2 were further established using NOESY experiments.[14] Inspection of the ^1H NMR spectra of **13** and **14** confirmed the configuration of the ring phosphorus: in **14**, H-3 is deshielded by 0.2 ppm compared to the same proton in **13** in agreement with its *cis* relationship with the oxygen atom in the neighbouring P=O.[1g,i]



Scheme 2. *Reagents and conditions*: (a) OsO_4, NMO, 12 h, rt, then SiO_2 chromatography, 77%; (b) $NaIO_4$, 3 h, rt, then filtration over SiO_2 (eluent CH_2Cl_2), 50%; (c) $(H)(OEt)P(O)CH_2P(O)(OEt)_2$ = **10**, K_2CO_3, 12 h, THF, rt, 60%; (d) CH_3ONa cat. THF, 1.5 h, 0°C; (e) OsO_4, NMO, 12 h, rt, then $NaIO_4$, 4 h, rt, 75%; (f) **10**, K_2CO_3, 12 h, THF, rt, 55%; (g) Ac_2O, 1 h, rt, then pyridine, 12 h, 42%; (h) TMSBr (20 equiv.), CH_2Cl_2, rt, 24 h, then Et_3N, 65%; (i) BCl_3 (15 equiv.), CH_2Cl_2; 12 h, –40°C (j) NaOH (0.1N), 2 min, rt, then HCl (0.1N) down to pH 6, 90% for i and j.

Phostone **13** could be deprotected as follows: treatment with TMSBr and quenching with Et_3N afforded the unstable mono triethylammonium salt **15**.[15] Using the same conditions, **14** led to a complex, untractable mixture. Sequential boron trichloride treatment (to remove the benzyl-protecting groups) and brief treatment with diluted sodium hydroxide (to remove the remaining acetate) afforded the free phosphonylphostone **16** in over 90% purity as evidenced by ^1H and ^{31}P NMR.[13,15]

Acknowledgements

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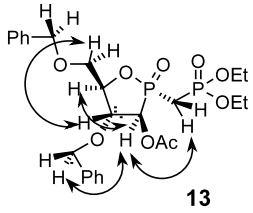
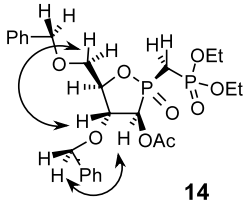
References

1. See for instance for phostones of type **I**: (a) Darrow, J. W.; Drueckhammer, D. G. *J. Org. Chem.* **1994**, *59*, 2976–2985; (b) Harvey, T. C.; Simiand, C.; Weiler, L.; Withers, S. G. *J. Org. Chem.* **1997**, *62*, 6722–6725; (c) Hannessian, S.; Rogel, O. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2441–2446; (d) Hannessian, S.; Rogel, O. *J. Org. Chem.* **2000**, *65*, 2667–2674; (e) Stoianova, D. S.; Hanson, P. R. *Org. Lett.* **2001**, *3*, 3285–3288; for phostones of type **II**: (f) Wroblewski, A. E. *Carbohydr. Res.* **1984**, *125*, C1–C4; (g) Wroblewski, A. E *Z. Naturforsch.* **1986**, *41b*, 791–792; (h) Wroblewski, A. E. *Liebigs Ann. Chem.* **1986**, 1448–1455; (i) Wroblewski, A. E. *Tetrahedron* **1983**, *39*, 1809–1816.
2. See for instance: Lee, R. E.; Brennan, P. J.; Besra, G. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 951–954 and references cited therein.
3. Cameron, M.; Cush, S.; Hammer, R. *J. Org. Chem.* **1997**, *62*, 9065–9069.
4. See for instance: Jacobsen, N. E.; Bartlett, P. A. *J. Am. Chem. Soc.* **1983**, *105*, 1613–1619.
5. Coupling was also attempted directly on the phostonic methylester **5**, without success.
6. Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **2001**, *42*, 8451–8453.
7. Benzyl protecting groups were chosen in order to avoid migration problems which can be encountered with silyl protecting groups. Better results were obtained when the oxidative cleavage was performed using the isolated diols resulting from the osmylation step.
8. Marcotte, S.; Baudoin, G.; Pannecoucke, X.; Feasson, C.; Quirion, J.-C. *Synthesis* **2001**, 929–933.
9. The stability of the formyl group toward aqueous metaperiodate is limited. See: Takahashi, Y.; Ueda, C.; Tsuchiya, T.; Kobayashi, Y. *Carbohydr. Res.* **1993**, *249*, 57–76. We took advantage of this observation for the preparation of **11**. At the oxidative cleavage step, **11** (contaminated with about 15% of starting material) was obtained by simply maintaining the reaction mixture at room temperature for a few hours. The freshly prepared, crude aldehyde, was used as such for the next coupling step.
10. See for instance: (a) Gilham, P. T.; Khorana, H. G. *J. Am. Chem. Soc.* **1958**, *80*, 6212–6222; (b) Sigurdssoon, S.; Stomberg, R. J. *Chem. Soc., Perkin Trans. 2* **2002**, 1682–1688.
11. Bosco, M.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **2003**, *44*, 2347–2349.

12. The best results were obtained by adding acetic anhydride directly to the reaction mixture containing **12**, removal of the solvents and treatment of the crude residue with acetic anhydride/pyridine. The very sensitive phostones could be purified, although with much decomposition. Rapid filtration on a small column of SiO_2 or even neutral Al_2O_3 resulted in a total decomposition of the phostones but two successive chromatographies on 0.2 mm thick silicagel plates, afforded **13** and **14** in 15 and 5% yield, respectively. After the first chromatography, only a mixture of **13** and **14**, in a respective 3/2 ratio, could be obtained in 42% yield.
13. *Selected analytical data*: **13**: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ 1.26 (3H, t, $J=7.2$ Hz, -OCH$_2$CH_3), 1.29 (3H, t, $J=7.2$ Hz, -OCH$_2$CH$_3$), 2.15 (3H, s, -C(O)-CH_3), 2.72 (1H, ddd, $J=16$, 20.8, 22.8 Hz, H-7), 3.14 (1H, dt, $J=16$, 18.4 Hz, H-7), 3.62 (1H, dd, $J=5.2$, 11.6 Hz, H-6), 3.72 (1H, dd, $J=2.4$, 11.6 Hz, H-6), 4.14 (4H, m, -OCH_2CH$_3$), 4.46 (1H, t, $J=8$ Hz, H-4), 4.51 (1H, m, H-5), 4.52 (1H, ABq, $J=11.6$ Hz, -OCH_2Ph), 4.58 (1H, ABq, $J=11.6$ Hz, -OCH_2Ph), 4.60 (1H, ABq, $J=12$ Hz, -OCH_2Ph), 4.72 (1H, ABq, $J=12$ Hz, -OCH_2Ph), 5.35 (1H, d, $J=8$ Hz, H-3), 7.2–7.4 (10H, m, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$, 300 K) δ 16.26 (OCH$_2$CH_3), 16.32 (OCH$_2$CH_3), 20.24 (OC(O)CH_3), 28.10 (dd, $J=87$, 135 Hz, C-7), 62.54 (d, $J=6.5$ Hz, OCH$_2$CH$_3$), 62.76 (d, $J=6.5$ Hz, OCH$_2$CH$_3$), 68.92 (d, $J=4$Hz, C-6), 72.97 (CH$_2$Ph), 73.45 (CH$_2$Ph), 75.92 (d, $J=94.6$ Hz, C-3), 77.02 (d, $J=17$Hz, C-4), 79.92 (d, $J=3.5$ Hz, C-5), 127.7–128.4 (aromatic carbons), 137.23 (aromatic quaternary carbon), 137.79 (aromatic quaternary carbon), 171.22 (d, $J=2.5$ Hz, OC(O)CH$_3$). ^{31}P NMR (161.9 MHz, $CDCl_3$, 300 K) δ 17.48 (d, $J=9.6$ Hz, P-8), 45.59 (d, $J=9.6$Hz, P-2). HRMS calcd for $C_{25}H_{39}O_9P_2$ (M+H$^+$) 541.1756, found 541.1766. **14**: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ 1.35 (6H, t, $J=7.1$ Hz, -OCH$_2$CH_3), 2.17 (3H, s, -C(O)CH_3), 2.67 (2H, m, H-7), 3.58 (1H, dd, $J=4.9$, 11.3 Hz, H-6), 3.71 (1H, dd, $J=4$, 8.2 Hz, H-4), 4.30 (1H, dt, $J=4$, 8 Hz, H-4), 4.38 (1H, m, H-5), 4.39 (1H, ABq, $J=11.2$ Hz, -OCH_2Ph), 4.51 (1H, ABq, $J=12.2$ Hz, -OCH_2Ph), 4.59 (1H, ABq, $J=12.2$ Hz, -OCH_2Ph), 4.63 (1H, ABq, $J=11.2$ Hz, -OCH_2Ph), 5.65 (1H, dd, $J=1.9$, 4 Hz, H-3), 7.2–7.4 (10H, m, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$, 300 K) δ 16.28 (OCH$_2$CH_3), 16.34 (OCH$_2$CH_3), 20.67 (OC(O)CH_3), 26.01 (dd, $J=86.9$, 136 Hz, C-7), 63.03 (d, $J=4.8$ Hz, OCH$_2$CH$_3$), 63.09 (d, $J=6$ Hz, OCH$_2$CH$_3$), 66.77 (d, $J=103.5$ Hz, C-3), 68.98 (d, $J=3$Hz, C-6), 72.97 (CH$_2$Ph), 73.61 (CH$_2$Ph), 75.51 (d, $J=17.3$ Hz, C-4), 82.17 (C-5), 127.8–128.6 (aromatic carbons), 136.54 (aromatic quaternary carbon), 137.60 (aromatic quaternary carbon), 169.06 (OC(O)CH$_3$). ^{31}P NMR (161.9 MHz, $CDCl_3$, 300 K) δ 16.99 (d, $J=6$ Hz, P-8), 53.95 (d, $J=6$ Hz, P-2). HRMS calcd for $C_{25}H_{39}O_9P_2$ (M+H$^+$) 541.1756, found 541.1725. **15**: ^{1}H NMR (400 MHz, CD_3OD, 300 K) δ 1.20 (9H, t, $J=7$ Hz, HN$^+$(CH$_2$CH_3)$_3$), 2.02 (3H, s, -C(O)-CH_3), 2.57 (1H, ddd, $J=16$, 19.9, 22.6 Hz, H-7), 2.92 (1H, broad q, $J=16$ Hz), 3.09 (6H, q, $J=7$ Hz, HN$^+$(CH_2CH$_3$)$_3$), 3.55 (1H, broad d, $J=11.5$ Hz, H-6), 3.68 (1H, broad d, $J=11.5$ Hz, H-6), 4.38 (1H, ABq, $J=11.8$ Hz, -OCH_2Ph), 4.40 (2H, m, H-4 and H-5), 4.47 (1H, ABq, $J=11.8$ Hz, -OCH_2Ph), 4.53 (1H, ABq, $J=11.8$ Hz, -OCH_2Ph), 4.62 (1H, ABq, $J=11.8$ Hz, -OCH_2Ph), 5.27 (1H, broad d, $J=8$ Hz, H-3). ^{31}P NMR (161.9 MHz, CD_3OD, 300 K) δ 11.96 (d, $J=9.8$ Hz, P-8), 49.82 (d, $J=9.8$ Hz, P-2) **16**: ^{1}H NMR (400 MHz, D_2O, 300 K) δ 2.06 (1H, broad q, $J=16$ Hz, H-7), 2.15 (1H, broad q, $J=16$ Hz, H-7), 3.65 (1H, dd, $J=6.5$, 11.8 Hz, H-6), 3.79 (1H, broad dt, $J=2.8$, 6.5 Hz, H-5), 3.83 (1H, broad dd, $J=2.8$, 11.8 Hz, H-6), 3.88–4.00 (2H, m, H-3, H-4). ^{13}C NMR (100.6 MHz, D_2O, 300 K) δ 63.44 (C-6), 70.25 (d, $J=107.3$ Hz, C-3), 70.79 (C-4 or C-5), 71.28 (d, $J=8.4$ Hz, C-4 or C-5). ^{31}P NMR (161.9 MHz, D_2O, 300 K) δ 14.60 (P-8), 38.40 (P-2).
14. The results from the NOESY experiments are shown below:



13



14

15. The free phosphonylphostone **16** appears to be more stable than its partially protected precursor **15**. The structure of **16** is tentatively attributed. Five-membered ring phostones are base-sensitive (see Ref. 11) and, although we used the mildest possible conditions for acetate removal, we cannot absolutely exclude that a *furano-*/*pyrano-* isomerization took place. However, the relatively high chemical shift of the ring phosphorus P-2 (38.40 ppm relative to H_3PO_4) compared to the expected value for an acyclic phosphinic acid (ca. 28 ppm for **12**) as well as for a six-membered ring phostone derivative (below 25 ppm, see: Refs. 1a–e) favors the proposed structure. As further evidences, the preference for the formation of five- over six-membered ring *arabino* phostones from acyclic precursors has been already stated (Ref. 1g) and in the case of a pyranose derivative, at least one of the H-6 is expected to be strongly coupled to P-2 (Ref. 1b).