Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2347–2349

TETRAHEDRON LETTERS

Synthesis of sugar-derived phostones by activation of γ-hydroxyphosphonic acids

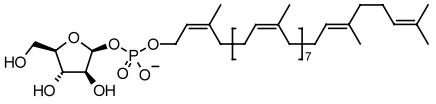
Michaël Bosco, Philippe Bisseret and Jacques Eustache*

Laboratoire de Chimie Organique et Bioorganique associé au CNRS, Université de Haute-Alsace, Ecole Nationale Supérieure de Chimie de Mulhouse 3, rue Alfred Werner, F-68093 Mulhouse Cedex, France

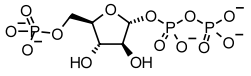
Received 27 November 2002; revised 22 January 2003; accepted 24 January 2003

Abstract—Treatment of carbohydrate-derived γ-hydroxyphosphonic acids under usual acetylation conditions affords the corresponding phostones in good yield. The method could be used for the preparation of free phostones as well as α- and β-phosphonomethylarabinose.

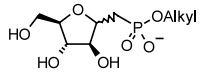
For some time, we have been interested in phosphorus-containing sugar analogs as surrogates of sugar 1-phosphates. The latter compounds are involved in a multitude of biosynthetic pathways. In particular, decaprenylphosphoarabinose **1** is the natural substrate of mycobacterial arabinosyl transferases[1] and 5-phospho-D-arabinosyl pyrophosphate **2** is an intermediate in the biosynthesis of **1**.[2] Both compounds may play a key role in mycobacterial cell-wall assembly and are potential targets for new types of antibiotics.



1



2



3

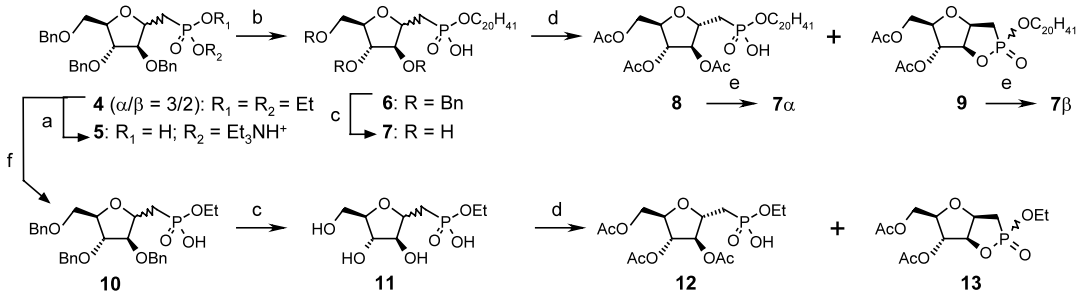
In the course of our studies, we needed to prepare several monoalkyl esters of α- and β-D-arabinofuranosyl-*C*-phosphonate **3**.[3] To this effect (Scheme 1) the phosphonate **4** was prepared as described by Reitz et al. and obtained as a mixture of anomers not separable by chromatography.[4] Selective cleavage of the phosphonyl esters (TMSBr), activation of the resulting phosphonic acid (CCl_3CN) according to Vasella et al.[5] and treatment by eicosanol provided a mixture of protected monophosphonates **6** which was converted to the mixture of free sugar phosphonates **7**. At this point, separation of anomers became necessary and acetylation was performed in the hope that they could be separated at the triacetate level. As shown in Scheme 1, the triacetylated α-phosphonate **8** was indeed formed but, instead of the expected β-D-triacetate, phostones **9** were obtained. Chromatographic separation of **8** and **9** then became obvious and alkaline hydrolysis of both acetate and phostone groups gave phosphonates **7α** and **7β**.

In carbohydrate chemistry, there are several reports of unexpected five-membered phostone formation; for example during hydrogenolysis of γ-benzyloxy-phosphonates (-phosphinates)[6] or while performing an Arbusov reaction on a γ-iodoalcohol.[7,8] We could find only one example related to our work, in which formation of a phostonic acid as a minor side product was observed during acetylation of a modified nucleoside featuring a γ-hydroxyphosphonic acid.[9] In the above examples, phostone (phostonic acid) formation was an unwanted side reaction. In our case, it proved to be an excellent method not only for the preparation of pure α- and β-monoalkylphosphonates, which was our original aim, but also for accessing carbohydrate-derived phostones, a class of compounds with potentially interesting biological activities.

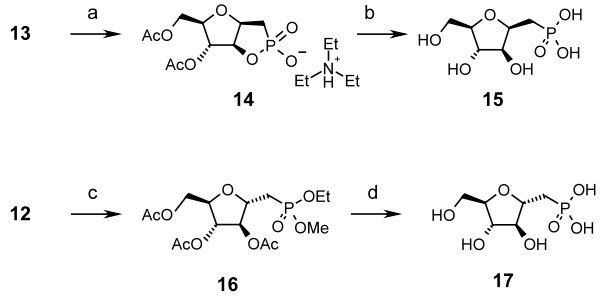
The method could also be used for the preparation of free phostonic acids and free α- and β-arabinofuranosyl-*C*-phosphonic acids. Thus, alkaline treatment of phosphonate **4** provided monoethylphosphonate **10**. Hydrogenolysis of the benzyl protecting groups and acetylation as above again gave a triacetylated α-phosphonate **12** and a mixture of phostones **13**. Final con-

* Corresponding author: Tel.: +33-3-8933-6858; fax: +33-3-8933-6860; e-mail: j.eustache@uha.fr

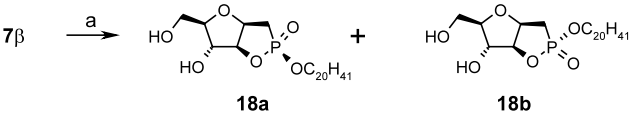
0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00240-5



Scheme 1. *Reagents and conditions*: (a) TMSBr (4 equiv.), CH_2Cl_2, 0°C to rt, 16 h, then NEt_3, quantitative; (b) (i) Cl_3CCN (2 equiv.), pyridine, 15 min (ii) $C_{20}H_{41}OH$, 65°C, 15 h, 83%; (c) H_2 (1 atm), 20% $Pd(OH)_2/C$, $CHCl_3$/MeOH (1/1), 24 h, quantitative; (d) NEt_3, then Ac_2O (20 equiv.), pyridine, 15 h, 51% (**8**) and 31% (**9**) from **7**, 51% (**12**) and 33% (**13**) from **11**; (e) NaOH (0.5 M, 5 equiv.), 2 h, THF, then DOWEX 50W (H^+ form), 90% (**7α**), 85% (**7β**); (f) NaOH (2 M, 9 equiv.), EtOH, 40°C, 3 days, then DOWEX 50W (H^+ form), 97%.



Scheme 2. *Reagents and conditions*: (a) TMSBr (2 equiv.), CH_2Cl_2, 0°C to rt, 15 h, then NEt_3, quantitative; (b) NaOH (1 M, 10 equiv.), EtOH, 50°C, 15 h, then DOWEX 50W (H^+ form), 96%; (c) (i) DOWEX 50W (H^+ form), MeOH, 30 min (ii) CH_2N_2, Et_2O, 79%; (d) (i) TMSBr (4 equiv.), CH_2Cl_2, 0°C to rt, 15 h, (ii) NaOH (0.5 M, 6 equiv.), water, 2 h, then DOWEX 50W (H^+ form), 83%.



Scheme 3. *Reagents and conditions*: (a) Ac_2O (1.2 equiv.), pyridine, 15 h, 22% (**18a**), 26% (**18b**).

version is shown in Scheme 2: selective cleavage of the ethyl group in **13** (TMSBr) and alkaline hydrolysis provided in excellent yield the β-phosphonic acid **15** (Scheme 2). Surprisingly, TMSBr treatment of the α-monoethylphosphonate **12** failed to provide the corresponding phosphonic acid. The problem could be solved by prior conversion to the ethyl methyl phosphonate **16** (CH_2N_2) then TMSBr-induced cleavage followed by saponification of the acetates to afford phosphonic acid **17** in high yield.

The absence of β-triacetate formation during the acetylation of **7**, implied that the mixed phosphonic-acetic anhydride had been formed prior to the acetates and suggested that direct access to non-protected phostonic esters was possible. Thus, the free phosphonate **7β** was treated with acetic anhydride (1.2 equiv.). Analysis of the crude mixture by ^{31}P NMR showed the complete disappearance of signals in the 20 ppm region (characteristic of acyclic phosphonates) while four new signals in the proportion 100/13/10/1 had appeared in the 50 ppm region (characteristic of five-membered phostones). Chromatography allowed the isolation of the two isomeric phostones **18a** (22%) and **18b** (26%) (absolute configuration at the phosphorus atom not determined) as major products thereby confirming preferential formation of a mixed anhydride during the acetylation reaction and showing that the method was indeed applicable for the preparation of free phostones (Scheme 3).[10]

In conclusion, we have developed a simple and efficient method for the formation of carbohydrate phostones which complements the existing ones. Particularly noteworthy is the fact that the method works well with unprotected precursors. In our laboratories, the method was successfully applied to other, more elaborated systems (see companion paper).

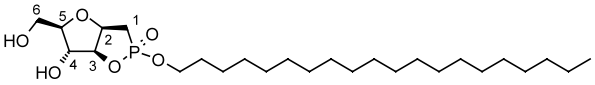
Acknowledgements

We thank Drs. D. Le Nouen and S. Bourg for help with NMR recording and spectra interpretation. This work was done within the frame of a COST program (action D13 New Molecules for Human Health).

References

1. Wolucka, B. A.; McNeil, M. R.; de Hoffmann, E.; Chojnacki, T.; Brennan, P. J. *J. Biol. Chem.* **1994**, *269*, 23328–23335.
2. Scherman, M. S.; Kalbe-Bournonville, L.; Bush, D.; Xin, Y.; Deng, L.; McNeil, M. *J. Biol. Chem.* **1996**, *271*, 29652–29658.
3. While this manuscript was in preparation, the synthesis of analogs of decaprenolphosphoarabinose as inhibitors of arabinosyltransferases was disclosed. See: Centrone, C. A.; Lowary, T. L. *J. Org. Chem.* **2002**, *67*, 8862–8870.

4. Maryanoff, B. E.; Nortey, S. O.; Inners, R. R.; Campbell, S. A.; Reitz, A. B. *Carbohydr. Res.* **1987**, *171*, 259–278.
5. Billault, I.; Vasella, A. *Helv. Chim. Acta* **1999**, *82*, 1137–1149.
6. (a) Yamamoto, H.; Yamamoto, K.; Inokawa, S.; Yamashita, M.; Armour, M.-A.; Nakashima, T. T. *J. Org. Chem.* **1983**, *48*, 435–440; (b) Racha, S.; Vargeese, C.; Vemishetti, P.; El-Subbagh, H. I.; Abushanab, E.; Panzica, R. P. *J. Med. Chem.* **1996**, *39*, 1130–1135.
7. Casero, F.; Cipolla, L.; Lay, L.; Nicotra, F.; Panza, L.; Russo, G. *J. Org. Chem.* **1996**, *61*, 3428–3432.
8. For another example of unexpected phostonic acid formation, see: Morr, M.; Kakoschke, C.; Ernst, L. *Tetrahedron Lett.* **2001**, *42*, 8841–8843.
9. Jones, G. H.; Albrecht, H. P.; Damodaran, N. P.; Moffatt, J. G. *J. Am. Chem. Soc.* **1970**, *92*, 5510–5511.
10. *Selected analytical data*:



18a: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ 4.79 (1H, dt, $J=19$, 4 Hz, H-2), 4.56 (1H, t, $J=4$ Hz, H-3), 4.53 (1H, broad s, H-4), 4.14–4.03 (2H, m, PO(OCH_2CH$_2$)), 3.92–3.87 (2H, m, H-6′+H-5), 3.74 (1H, broad dd, $J=11.6$, 2Hz, H-6), 3.50 (1H, broad d, $J=2$ Hz, C(H-4)O*H*), 2.29 (1H, dd, $J=14.8$, 11.6 Hz, H-1′), 2.09 (1H, td, $J=15.4$, 5.5 Hz, H-1), 1.66 (2H, qn, $J=7$ Hz, PO(OCH$_2$CH_2)), 1.25 (34H, m, aliphatic chain), 0.87 (3H, t, $J=6.5$ Hz, CH$_2$CH_3). ^{13}C NMR (100.69 MHz, $CDCl_3$, 300 K) δ 88.41 (d, $J=8.5$ Hz), 87.69, 78.40, 67.20 (d, $J=7.1$ Hz), 61.88, 32.07, 30.63 (d, $J=5.6$ Hz), 29.86 (11C), 29.80, 29.74, 29.67, 29.50, 29.30, 26.89 (d, $J=122.3$ Hz), 25.62, 22.83, 14.25. ^{31}P NMR (161.9 MHz, $CDCl_3$, 300 K) δ 49.86 ppm, s. HRMS calcd for $C_{26}H_{51}O_6P$ (M+H$^+$) 491.3501, found 491.3490. **18b**: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ 4.80 (1H, dt, $J=4.5$, 31.7 Hz, H-2), 4.68 (1H, t, $J=4.5$ Hz, H-3), 4.45 (1H, d, $J=4.3$ Hz, H-4), 4.12 (2H, q, $J=6.8$ Hz, PO(OCH_2CH$_2$)), 3.89–3.86 (2H, m, H-5+H-6′), 3.71 (1H, m, H-6), 2.24 (1H, dd, $J=16.1$, 10.6 Hz, H-1′), 2.16 (1H, td, $J=15.6$, 5.3 Hz, H-1), 1.68 (2H, qn, $J=6.8$ Hz, PO(OCH$_2$CH_2)), 1.24 (34H, m, aliphatic chain), 0.87 (3H, t, $J=6.6$ Hz, CH$_2$CH_3). ^{13}C NMR (100.69 MHz, $CDCl_3$, 300 K) δ 89.01 (d, $J=9.2$ Hz), 86.93, 78.77, 77.01 (d, $J=6.6$ Hz), 67.81 (d, $J=6.3$ Hz), 61.92, 32.07, 30.62 (d, $J=5.7$ Hz), 29.84 (11C), 29.79, 29.71, 29.64, 29.49, 29.28, 26.26 (d, $J=120.9$ Hz), 25.53, 22.83, 14.24. ^{31}P NMR (161.9 MHz, $CDCl_3$, 300 K) δ 49.82 ppm, s. HRMS calcd for $C_{26}H_{51}O_6P$ (M+H$^+$) 491.3501, found 491.3499.