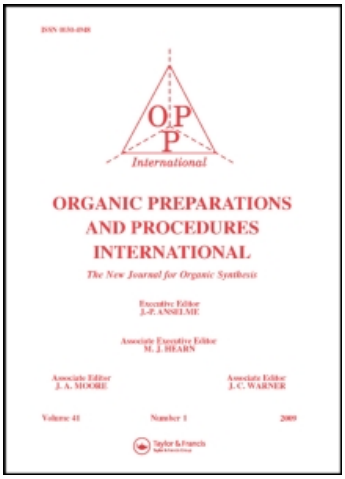


Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A SIMPLE PROCEDURE FOR THE PREPARATION OF 2-PHOSPHORYLATED FURANOSES

Clemens Lamberth[ab]
[a] Department of Organic Chemistry and Biochemistry, Technical University, Darmstadt, Darmstadt, Germany [b] Chemical Research, Sandoz Agro Ltd., Basel, Switzerland

To cite this Article Lamberth, Clemens(1994) 'A SIMPLE PROCEDURE FOR THE PREPARATION OF 2-PHOSPHORYLATED FURANOSES', Organic Preparations and Procedures International, 26: 5, 595 — 598
To link to this Article: DOI: 10.1080/00304949409458066
URL: http://dx.doi.org/10.1080/00304949409458066

2. Z. Paryzek, *ibid.*, 1222 (**1979**); Z. Paryzek and R. Wydra, *Steroids*, **38**, 141 (1981).

3. J. F. Cavalla and J. F. McGhie, *J. Chem. Soc.*, 744 (**1951**).

4. L. H. Briggs, J. P. Bartley and P. S. Rutledge, *J. Chem. Soc. Perkin Trans. 1*, 581 (**1972**).

5. E. V. Lassak, J. T. Pinhey and J. J. H. Simes, *Australian J. Chem.*, **26**, 1051 (1973).

6. C. W. Shoppee, J. C. Coll and R. E. Lack, *J. Chem. Soc. (C)*, 1581 (**1968**).

7. Z. Paryzek and R. Wydra, *Monatsh. Chem.*, **111**, 1427 (1980); J. Martynow and Z. Paryzek, Unpublished results.

8. M. Yamashita, M. Noara, T. Murae, T. Tsuyuki and T. Takahashi, *Bull. Chem. Soc. Jpn*, **60**, 1383 (1987); L. H. Briggs, J. P. Bartley and P. S. Rutledge, *J. Chem. Soc. Perkin Trans. 1*, 806 (**1973**).

****

A SIMPLE PROCEDURE FOR THE PREPARATION OF 2-PHOSPHORYLATED FURANOSES

Submitted by (*03/22/94*)

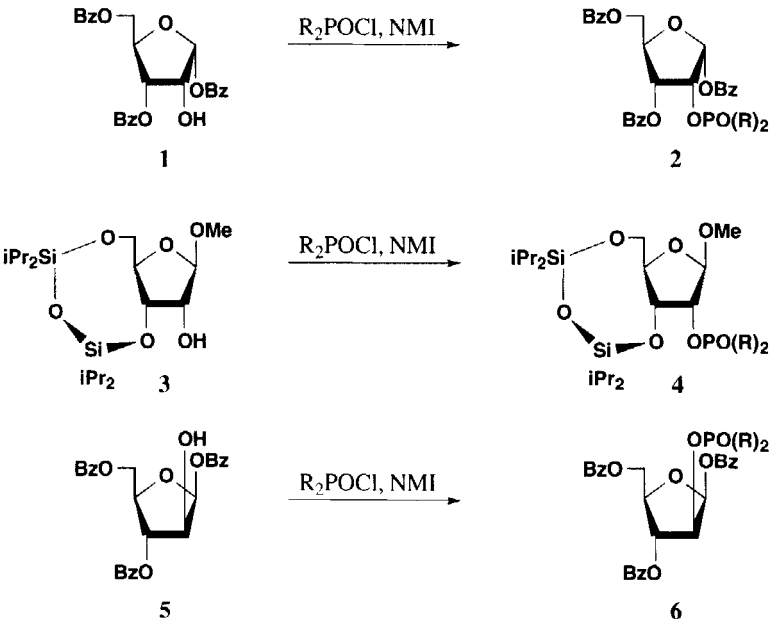
Clemens Lamberth†

Department of Organic Chemistry and Biochemistry
Technical University Darmstadt
D-64287 Darmstadt, GERMANY

Furanoic carbohydrates which bear a phosphate group in the 2-position play particularly important roles in certain metabolic key processes. For example, 2-phosphorylated ribonucleosides belong to the most potent inhibitors of ribonuclease T_1[1] and dihydrofolate reductase.[2] Usually the synthesis of sugar phosphates employs neutral phosphotriesters as intermediates, which allow purification and further transformations in organic solvents as well as specific deprotection to the free phosphate.[3] Diphenyl phosphorochloridate and other diorganophosphoryl chlorides have been the subject of manifold applications in the introduction of the phosphoryl group. Unfortunately, the reaction of sterically hindered hydroxy functions as in the 2-position of furanoses with phosphorochloridates, is known to be difficult and low-yielding.[4,5] Therefore a general and efficient approach to 2-phosphorylated and phosphinylated riboses and arabinoses was sought.

Herein we report that the transformation of a partially protected furanose with a phosphorochloridate and 1-methylimidazole (NMI) leads to the corresponding sugar-2-phosphate in high yields. Compared to 5-chloro-1-methylimidazole,[5] which is also known as an active phosphorylating

catalyst, 1-methylimidazole[6] is much cheaper and more easily separable from the product. Because it is possible to remove the employed benzoyl[7] and tetraisopropyldisiloxanylidene[8] protecting groups without affecting the phosphate, an easy access to free 2-phosphorylated sugars is found.



a) R = OPh; b) R = OiPr; c) R = OEt; d) R = OCH_2CCl_3; e) R = NMe_2; f) R = Ph

TABLE 1. Yields, Physical Constants and Elemental Analyses of Phosphorylated and Phosphinylated Riboses and Arabinoses

Cmpd	Yield (%)	Time (hrs)	mp (°C)	Elemental Analyses (Found) C		H	
2a	89	16	86	65.72	(65.87)	4.49	(4.47)
2b	60	16	90-92	61.33	(61.47)	5.64	(5.69)
2c	89	8	91	60.19	(60.22)	5.23	(5.21)
2d	74	8	52	44.75	(44.51)	3.13	(3.19)
2e	93	62	oil	60.40	(60.63)	5.57	(5.61)
2f	92	16	oil	68.88	(68.54)	4.72	(4.57)
4a	45	16	oil	56.41	(56.67)	7.42	(7.49)
6a	77	16	132	65.72	(65.69)	4.49	(4.41)

TABLE 2. ^{1}H NMR and ^{31}P NMR Data of Phosphorylated and Phosphinylated Riboses and Arabinoses

Cmpd	^{1}H NMR (δ)	^{31}P NMR (δ) λ
2a	4.58 (dd, J = 3.0, 12.5 Hz, 1H, H-5), 4.67 (dd, J = 3.0, 12.5 Hz, 1H, H-5'), 4.75 (dt, J = 2.0, 3.0 Hz, 1H, H-4), 5.36 (ddd, J = 4.2, 6.2 Hz, 1H, H-2), 5.66 (dd, J = 2.0, 6.2 Hz, 1H, H-3), 6.75 (d, J = 4.2 Hz, 1H, H-1), 7.05 - 8.11 (m, 25H, ArH)	- 12.39 (d, 1P, J_{P-H} = 8.9)
2b	1.18 (d, J = 6.0 Hz, 6H, iPrH), 1.20 (d, J = 6.0 Hz, 6H, iPrH), 4.55 - 4.67 (m, 4H, H-5, H-5', iPrH), 4.78 (dt, J = 2.0 Hz, 1H, H-4), 5.12 (ddd, J = 4.4, 6.5 Hz, 1H, H-2), 5.74 (dd, J = 2.0, 6.5 Hz, 1H, H-3), 6.79 (d, J = 4.4 Hz, 1H, H-1), 7.31 - 8.20 (m, 15H, ArH)	- 2.90 (q, 1P, J_{P-H} = 7.4)
2c	1.17 (t, J = 7.8 Hz, 6H, EtH), 3.98 - 4.09 (m, 4H, EtH), 4.61 (dd, J = 3.8, 12.5 Hz, 1H, H-5), 4.68 (dd, J = 3.8, 12.5 Hz, 1H, H-5'), 4.79 (dt, J = 2.0, 3.8 Hz, 1H, H-4), 5.17 (ddd, J = 4.4, 6.5 Hz, 1H, H-2), 5.75 (dd, J = 2.0, 6.5 Hz, 1H, H-3), 6.80 (d, J = 4.4 Hz, 1H, H-1), 7.30 - 8.25 (m, 15H, ArH)	- 1.32 (sep., 1P, J_{P-H} = 8.1)
2d	4.56 (d, J = 6.5 Hz, 4H, CH_2CCl_3), 4.65 (dd, J = 3.2, 11.8 Hz, 2H, H-5, H-5'), 4.84 - 4.86 (m, 1H, H-4), 5.30 (ddd, J = 4.2, 6.5 Hz, 1H, H-2), 5.79 (dd, J = 2.1, 6.5 Hz, 1H, H-3), 6.86 (d, J = 4.2 Hz, 1H, H-1), 7.34 - 8.15 (m, 15H, ArH)	- 5.01 (sep., 1P, J_{P-H} = 6.4)
2e	2.59, 2.63, 2.68, 2.72 (4s, 12H, MeH), 4.54 - 4.74 (m, 3H, H-4, H-5, H-5'), 5.66 - 5.69 (m, 2H, H-2, H-3), 5.93 (d, J = 5.5 Hz, 1H, H-1), 7.35 - 8.11 (m, 15H, ArH)	+ 20.15 (m, 1P, J_{P-H} = 9.7)
2f	4.56 (dd, J = 3.6, 12.1 Hz, 1H, H-5), 4.64 (dd, J = 3.0, 12.1Hz, 1H, H-5'), 4.80 (q, J = 2.0, 3.0, 3.6 Hz, 1H, H-4), 5.19 (ddd, J = 4.2, 6.4 Hz, 1H, H-2), 5.67 (dd, J = 2.0, 6.4 Hz, 1H, H-3), 6.69 (d, J = 4.2 Hz, 1H, H-1), 7.29 - 8.18 (m, 25H, ArH)	+ 34.53 (d, 1P, J_{P-H} = 9.1)
4a	0.85 - 1.09 (m, 28H, iPrH), 3.27 (s, 3H, MeH), 3.91 (dd, J = 6.8, 12.5 Hz, 1H, H-5), 3.98 - 4.05 (m, 2H, H-4, H-5'), 4.59 (dd, J = 4.2 Hz, 1H, H-3), 4.75 (s, 1H, H-1), 4.86 (dd, J = 4.2 Hz, 1H, H-2), 7.11 - 7.33 (m, 10H, ArH)	- 12.18 (d, 1P, J_{P-H} = 7.3)
6a	4.45 - 4.57 (m, 2H, H-4, H-5), 4.75 (dd, J = 3.5, 11.8 Hz, 1H, H-5'), 5.55 (ddd, J = 4.7, 7.8 Hz, 1H, H-2), 5.96 (dd, J = 6.2, 7.8 Hz, 1H, H-3), 6.64 (d, J = 4.7 Hz, 1H, H-1), 6.96 - 8.00 (m, 25H, ArH)	- 12.26 (d, 1P, J_{P-H} = 8.0)

EXPERIMENTAL SECTION

Melting points were determined using a Buchi SMP-20 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WM-300 spectrometer at 300 MHz, using $CDCl_3$ as solvent and TMS as an internal standard. ^{31}P NMR spectra were obtained on a Bruker WM-300 spectrometer at 121.5 MHz, using $CDCl_3$ as solvent and phosphoric acid (85%) as an external standard. Chemical shifts are reported in ppm downfield from the standard (δ = 0.00 ppm). Column chromatography was

performed on E.Merck silica gel 60 (40 - 63 μm), using diethyl ether-pentane mixtures as eluent. The starting materials **1**, **3** and **5** were obtained according to literature procedures.[9-11]

Typical Procedure.- 1,3,5-Tri-O-benzoyl-α-D-ribofuranose (**1**; 5.0 g, 11 mmol) was placed in a two-necked flask with septum, gas inlet and magnetic stirring bar. After being purged with argon, the compound was dissolved in dry dichloromethane (100 mL) and the flask was cooled in an ice-water bath. Diphenyl phosphorochloridate (4.5 g, 17 mmol) and 1-methylimidazole (1.5 g, 18mmol) were added dropwise within 15 min. Stirring was continued for 16 hrs with gradual warming to room temperature. The solvent was then distilled off and the oily residue redissolved in dichloromethane and evaporated a second time to remove traces of 1-methylimidazole. A solution of the residue in dichloromethane (200 mL) was washed successively with ice-water (100 mL), saturated aqueous sodium hydrogen carbonate solution (2 x 100 mL) and water (100 mL). The organic layer was dried over magnesium sulfate and the solvent removed *in vacuo*. The oily residue was purified by crystallization from diethyl ether-pentane or by flash chromatography (elution with 1:1 diethyl ether-pentane) to give 1,3,5-tri-O-benzoyl-2-O-(diphenylphosphoryl)-α-D-ribofuranose (**2a**;[12] 6.7 g, 89 %).

REFERENCES

† Current address: Sandoz Agro Ltd., Chemical Research, CH-4002 Basel, Switzerland.

1. J. Granzin, R. Puras-Lutzke, O. Landt, H.-P. Grunert, U. Heinemann, W. Saenger and U. Hahn, *J. Mol. Biol.*, **225**, 533 (1992).
2. S. R. Stone, A. Mark and J. F. Morrison, *Biochemistry*, **23**, 4340 (1984).
3. L. A. Slotin, *Synthesis*, 737 (**1977**).
4. F. Wold and C.E. Ballou, *J. Am. Chem. Soc.*, **81**, 2368 (1959).
5. J. H. van Boom, J.F.M. de Rooy and C.B. Reese, *J. Chem. Soc. Perkin Trans. I*, 2513 (**1973**).
6. C. Broka, T. Hozumi, R. Arentzen and K. Hakura, *Nucl. Acids Res.*, **8**, 5461 (1980).
7. R. M. de Lederkremer, V. B. Nahmad and O. Varela, *J. Org. Chem.*, **59**, 690 (1994).
8. W. T. Markiewicz, *J. Chem. Res. Synop.*, 24 (**1979**).
9. P. R. Brodfuehrer, C. Sapino and H. G. Howell, *J. Org. Chem.*, **50**, 2597 (1985).
10. J. P. Schaumberg, G. C. Hokanson, J. C. French, E. Smal and D. C. Baker, *ibid.*, **50**, 1651 (1985).
11. R. K. Ness and H. G. Fletcher, *J. Am. Chem. Soc.*, **80**, 2007 (1958).
12. A. Koch, C. Lamberth, F. Wetterich and B. Giese, *J. Org. Chem.*, **58**, 1083 (1993).