Monophosphorylation of 1,4:3,6-dianhydro-D-mannitol

G. I. Kurochkina, N. O. Soboleva, M. K. Grachev, L. K. Vasyanina, and E. E. Nifant´ev*

Department of Chemistry, Moscow Pedagogical State University,
3 Nesvizhskii per., 119021 Moscow, Russian Federation.
Fax: +7 (095) 246 7766. E-mail: chemdept@mtu-net.ru

Efficient procedures were developed for the synthesis of monophosphorylated derivatives of 1,4:3,6-dianhydro-D-mannitol. The latter are of interest as compounds bearing different phosphorus-containing fragments on a three-dimensional matrix having an inner chiral cavity.

Key words: 1,4:3,6-dianhydro-D-mannitol, phosphorylation, chiral cavity.

1,4:3,6-Dianhydro-D-mannitol (**1**) is a chiral diol containing closely-spaced hydroxy groups in *endo* orientations with respect to the inner cavity. This product was used for solving various chemical problems, including those, which require the involvement of trivalent phosphorus reagents. For example, phosphorylation of compound **1** with phosphoramides afforded valuable bidentate ligands for enantioselective catalysis[1—4] or complex chiral molecular cavities.[5]

It is essential that all studies revealed the tendency of dianhydromannitol to phosphorylation at both hydroxy groups giving rise to either bisphosphorylation products[4] or cyclophosphorylation products.[4,6] The latter situation was observed when a deficient amount of phosphorylating reagents was used.[4]

In the design of new bidentate P^{III}-containing ligands for homogeneous catalysis, the trend today is to prepare compounds whose molecules contain structurally different (rather than identical) complex-forming groups (see, for example, the recent studies in this field[7]). In some cases, this leads to unexpected nonadditive changes in the activity and selectivity of catalysts based on such compounds.[2] Interestingly, the second P^{III}-coordinating center in catalysts constructed with the use of a diol matrix can be either absent[3,8] or replaced by a P^{V}-containing residue, for example, by the phosphine oxide group.[9] In the latter case, a combination of hard and soft phosphorus-containing fragments in the bidentate ligand can also facilitate its adaptation to the coordinating metal.

The aim of the present study was to develop a procedure for monophosphorylation of 1,4:3,6-dianhydro-D-mannitol (**1**) by trivalent phosphorus derivatives. Earlier, it has been hypothesized[4] that hydrogen bonds play a great role in the starting dianhydromannitol system. According to this assumption, efficient intramolecular hydrogen bonds are present in diol **1** under consideration, these bonds being responsible for a decrease in the nucleophilicity of the hydroxy groups. The primary event of monophosphorylation causes the cleavage of hydrogen bonds. As a result, the second (free) hydroxy group freed from hydrogen bonds becomes more active and is more readily subjected to phosphorylation than the hydroxy groups of the starting diol.

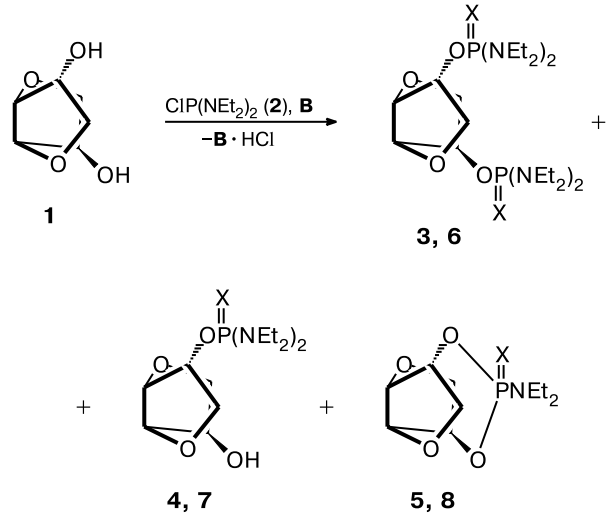
Hence, one would expect that the cleavage of hydrogen bonds in starting diol **1** (for example, under the action of amines) will make it possible to perform directed phosphorylation. This gave impetus to our study of phosphorylation of diol **1** with a series of phosphorochloridates in the presence of tertiary amines of different nature. First, we examined tetraethylphosphorodiamidic acid chloride ($ClP(NEt_2)_2$, **2**), which was used in phosphorylation as solutions in different solvents. In preliminary experiments, we found that a tenfold molar excess of the amine was an amount of choice. All experiments were carried out under standard conditions involving phosphorylation itself and stabilization of the primary product as a stable thiophosphoryl compound (see the Experimental section). The course of the reaction was monitored by ^{31}P NMR spectroscopy from the appearance of signals of the corresponding trivalent phosphorus compounds **3—5**, the disappearance of a signal of the starting phosphorodiamidic acid chloride **2**, and (after the quantitative addition of sulfur) the appearance of signals of the corresponding phosphorothionate derivatives **6—8** (Scheme 1).

In studies of the reactions in DMF in the presence of amines of different nature, it was found that the highest yield of derivative **7** was attained with the use of triethylamine (Table 1). It should be noted that the use of less basic amines and sterically hindered diisopropylethylamine instead of triethylamine led to the formation of bis- and cyclophosphorylated derivatives **6** and **8** as the major reaction products. The reaction involving pyridine as an acceptor of hydrogen chloride (see the Experimental section) gave the product in only 75% yield. The reaction, which was performed in the absence of bases under conditions of removal of hydrogen chloride with a slow

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 4, pp. 957—960, April, 2003.

1066-5285/03/5204-1009 $25.00

Scheme 1



3—5: X is a lone electron pair
6—8: X = S

B = NEt_3, NBu^n_3, $PhCH_2NMe_2$, Py, $EtNPr^i_2$, $PhNMe_2$

stream of argon, afforded cyclophosphorothionate **8** in a yield of at most 45%, bisphosphorothionate **6** in ~11% yield, and a mixture of products with unknown structures. The use of *N*,*N*-dimethylbenzylamine and much less basic *N*,*N*-dimethylaniline gave virtually the same results, the target compound **7** being virtually absent, which is, apparently, associated with the lower solvating ability of these amines. An excess of amine influences the completeness of the transformation of phosphorodiamidic acid chloride **2**. Thus, the reaction with a tenfold molar excess of pyridine proceeded most slowly. Triethylamine proved to be the most efficient amine in this reaction. The reaction with triethylamine was completed by 93% and 95% during 30 min and 1 h, respectively, the percentage ratio of products **6—8** changing with time (Table 2). Because of this, further experiments aimed at searching for an optimum solvent were carried out in the presence of triethylamine (Table 3). It was found that the reactions in dioxane and *o*-xylene afforded monophosphorylated derivative **7** as the major product. Interestingly, the reaction with the use of pyridine as the solvent and acceptor of hydrogen chloride afforded predominantly cyclophosphorylated product **8** as well as a mixture of bis- (**6**) and monophosphorylated (**7**) derivatives in approximately equal amounts. By contrast, the addition of triethylamine to pyridine, as expected, led to a substantial increase in the percentage of monophosphorylated derivative **7**.

Unlike the earlier experiments[4] on bisphosphorylated derivative **3**, the formation of cyclic phosphite **5** was not accompanied by the formation of hexaethylphosphorous triamide ($P(NEt_2)_3$) as a product of intramolecular dephosphorylation of bisphosphite **3**. Therefore, the reaction under the conditions used gave rise to cyclic phosphite **5** through the intramolecular replacement in monophosphorylated derivative **4** rather than through intramolecular dephosphorylation.[4]

Table 1. Influence of the nature of amine **B** on the ratio between products **6—8** in the reaction mixture* (24 h, 20 °C)

B	*C*** (%)	Content of products **6—8** (%)		
		6	**7**	**8**
NEt_3	100	18	60	22
NBu^n_3	93	32	5	63
$PhCH_2NMe_2$	93	57	—	43
Py	74	36	2	62
$EtNPr^i_2$	89	59	8	33
$PhNMe_2$	95	53	—	47
—	92	11	—	45

* The compositions of the reaction mixtures were analyzed by ^{31}P NMR spectroscopy with the use of the following chemical shifts of trivalent (**2—5**) and pentavalent (**6—8**) phosphorus derivatives (δ): 153 (**2**); 137 (**3**);[5] 137 (**4**); 148 (**5**);[5,6] 76 (**6**); 79 (**7**); and 68 (**8**).
** The conversion.

Table 2. Changes in the ratio between products **6—8** in the reaction mixture (24 h, 20 °C, DMF, **B** = NEt_3) with time

Time/h	*C** (%)	Content of products **6—8** (%)		
		6	**7**	**8**
0.5	93	17	64	19
1	95	24	58	18
24	100	18	60	22

* Conversion.

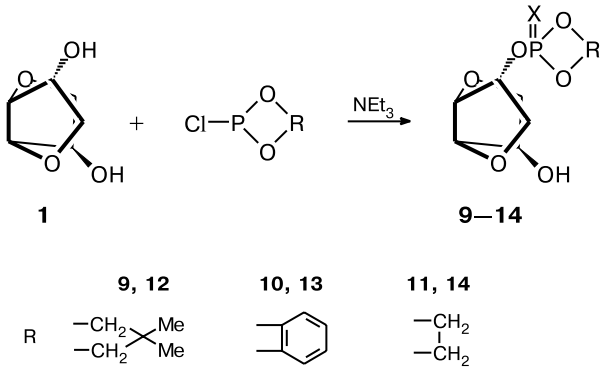
Table 3. Influence of the nature of the solvent on the ratio between products **6—8** in the reaction mixture (24 h, 20 °C) in the presence of a tenfold excess of NEt_3 (**B**)

Solvent	*C** (%)	Content of products **6—8** (%)		
		6	**7**	**8**
DMF	100	18	60	22
$CHCl_3$	100	64	8	28
MeCN	100	26	52	22
Dioxane	100	6	89	5
Py (without NEt_3)	70	20	20	80
Py	100	33	55	12
THF	97	22	70	8
o-Xylene	100	6	94	—
C_6H_6	100	21	79	—

* Conversion.

The procedures developed in the present study for the synthesis of monophosphorylated derivatives of type **4** were used for the preparation of compounds **9—11**. After the addition of sulfur, the latter were isolated as individual monophosphorylated derivatives **12—14** (Scheme 2).

Scheme 2



9—11: X is a lone electron pair
12—14: X = S

The new efficient procedures for the preparation of monophosphorylated 1,4:3,6-dianhydro-D-mannitol derivatives open up new opportunities for original studies of this promising compound.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker WP-250 instrument at 250 MHz with Me_4Si as the internal standard. The ^{31}P—{^{1}H} NMR spectra were measured on a Bruker WP-80 spectrometer at 32.4 MHz with 85% H_3PO_4 as the external standard. All syntheses were carried out under dry argon with the use of anhydrous solvents. The TLC analysis was performed on Silufol UV-366 plates using the following systems: C_6H_6—dioxane, 3 : 1 (*A*); C_6H_6—dioxane, 1 : 3 (*B*); $CHCl_3$—EtOH, 1 : 1 (*C*); $CHCl_3$—Me_2CO, 3 : 1 (*D*).

1,4:3,6-Dianhydro-D-mannitol (**1**)[10] and phosphorylating reagents[11] were prepared according to procedures described earlier.

Phosphorylation of diol 1 with diamidochlorophosphite 2 (general procedure). Diamidochlorophosphite **2** (0.122 g, 0.58 mmol) was added with stirring to a solution of diol **1** (0.0852 g, 0.58 mmol) and amine **B** (5.8 mmol) (see Table 1) in a solvent (2 mL) (see Table 3) at 20 °C. The reaction mixture was kept at 20 °C for 18 h, finely dispersed sulfur (0.019 g, 0.58 mmol) was added, and the reaction mixture was stirred at 20 °C for 4 h. The composition of the reaction mixture was analyzed by ^{31}P NMR spectroscopy (see Tables 1 and 3).

1,4:3,6-Dianhydro-2-*O*-bis(diethylamido)thiophosphoryl-D-mannitol (7) was prepared according to the general procedure with the use of NEt_3 as the acceptor of HCl in dioxane. The reaction mixture was filtered to remove the precipitate of $Et_3N \cdot HCl$ that formed and an excess of sulfur. The solvent was distilled off *in vacuo* and the product was isolated by reprecipitation from a solution in benzene (2 mL) with hexane (1 mL). The yield was 0.17 g (83%), R_f 0.80 (*A*). Found (%): C, 47.72; H, 8.33; P, 8.75. $C_{14}H_{29}N_2O_4PS$. Calculated (%): C, 47.71; H, 8.29; P, 8.79. ^{31}P NMR (DMF), δ: 79.4. ^{1}H NMR ($CDCl_3$), δ: 1.07 (t, 12 H, $NCH_2C\underline{H}_3$, ^3J = 6.9 Hz); 2.76—2.94 (m, 1 H, OH); 2.94—3.22 (m, 8 H, $NC\underline{H}_2CH_3$); 3.54 and 3.65 (both dd, 1 H each, H(1)$_a$, H(6)$_a$, ^2J = 9.1 Hz, ^3J = 6.9 Hz); 3.93 and 4.02 (both dd, 1 H each, H(1)$_b$, H(6)$_b$, ^2J = 8.8 Hz, ^3J = 6.9 Hz); 4.21—4.31 (m, 1 H, H(2)); 4.43 (pseudotriplet, 1 H, H(3), ^3J = 4.9 Hz); 4.52 (pseudotriplet, 1 H, H(4), ^3J = 4.9 Hz); 4.79—4.99 (m, 1 H, H(5)).

2-*O*-(5,5-Dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)-1,4:3,6-dianhydro-D-mannitol (12). 2-Chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane (0.576 g, 3.45 mmol) was added with stirring to a solution of diol **1** (0.505 g, 3.45 mmol) in dioxane (8 mL) and NEt_3 (3.49 g, 0.0345 mol) at 20 °C. The reaction mixture was kept at 20 °C for 20 h and filtered to remove the precipitate of $Et_3N \cdot HCl$ that formed. Then finely dispersed sulfur (0.11 g, 3.45 mmol) was added and the reaction mixture was kept at 20 °C for 20 h. An excess of sulfur was filtered off and the solvent was removed. The product was isolated by reprecipitation from benzene (5 mL) with hexane (3 mL). The yield was 0.81 g (76%), R_f 0.50 (*B*). Found (%): C, 42.61; H, 6.19; P, 9.96. $C_{11}H_{19}O_6PS$. Calculated (%): C, 42.58; H, 6.17; P, 9.98. ^{31}P NMR (dioxane), δ: 59.9. ^{1}H NMR ($CDCl_3$), δ: 0.91 and 1.26 (both s, 3 H each, MeC_{eq}, MeC_{ax}); 3.81—3.98 (m, 4 H, CH_{eq}, H(1)$_a$, H(6)$_a$); 4.14 (dd, 2 H, H(1)$_b$, H(6)$_b$, ^2J = 9.3 Hz, ^3J = 6.3 Hz); 4.24 and 4.34 (both dd, 1 H each, CH_{ax}, ^2J = 10.7 Hz); 4.63 (dd, 2 H, H(3), H(4), ^3J = 3.7 and 1.2 Hz); 4.95—5.07 (m, 2 H, H(2), H(5)).

2-*O*-(2-Thioxobenzo-1,3,2-dioxaphospholan-2-yl)-1,4:3,6-dianhydro-D-mannitol (13). 2-Chlorobenzo-1,3,2-dioxaphospholane (0.569 g, 3.26 mmol) was added with stirring to a solution of diol **1** (0.477 g, 3.26 mmol) in DMF (10 mL) and NEt_3 (3.29 g, 0.0326 mol) at 0 °C. The reaction mixture was kept at 20 °C for 20 h and filtered to remove the precipitate of $Et_3N \cdot HCl$. Then finely dispersed sulfur (0.104 g, 3.26 mmol) was added and the reaction mixture was kept at 20 °C for 20 h. An excess of sulfur was filtered off and the solvent was evaporated. The product was isolated by reprecipitation from benzene (5 mL) with hexane (3 mL), isolated, and dried *in vacuo*. Product **13** was obtained as a vitreous solid compound in a yield of 0.90 g (87%), m.p. 62 °C, R_f 0.80 (*C*). Found (%): C, 45.60; H, 4.18; P, 9.75. $C_{12}H_{13}O_6PS$. Calculated (%): C, 45.57; H, 4.14; P, 9.79. ^{31}P NMR (DMF), δ: 63.5. ^{1}H NMR ($CDCl_3$), δ: 3.89—4.31 (m, 4 H, H(1)$_a$, H(6)$_a$, H(1)$_b$, H(6)$_b$); 4.77 (dd, 2 H, H(3), H(4), ^3J = 4.2 and 3.7 Hz); 4.94—5.20 (m, 2 H, H(2), H(5)); 6.83—7.16 (m, 4 H, Ar).

2-*O*-(2-Thioxo-1,3,2-dioxaphospholan-2-yl)-1,4:3,6-dianhydro-D-mannitol (14). 2-Chloro-1,3,2-dioxaphospholane (0.427 g, 3.38 mmol) was added with stirring to a solution of diol **1** (0.494 g, 3.38 mmol) in DMF (10 mL) and NEt_3 (3.42 g, 0.0338 mol) at 0 °C. The reaction mixture was kept at 20 °C for 20 h and filtered to remove the precipitate of $Et_3N \cdot HCl$. Then finely dispersed sulfur (0.108 g, 3.38 mmol) was added and the reaction mixture was kept at 20 °C for 20 h. An excess of sulfur was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in acetone (15 mL), undissolved sulfur was filtered off, and the filtrate was concentrated *in vacuo*. The viscous oily compound was triturated in a mortar with a small amount of water to give a white powder, which was filtered off and dried *in vacuo*. The yield was 0.32 g (35%), m.p. 197—198 °C

(with decomp.), R_f 0.60 (*D*). Found (%): C, 35.87; H, 4.93; P, 11.51. $C_8H_{13}O_6PS$. Calculated (%): C, 35.82; H, 4.89; P, 11.55. ^{31}P NMR (DMF), δ: 81.0. ^{1}H NMR ($CDCl_3$), δ: 3.98 (m, 2 H, $H(1)_a$, $H(6)_a$, ^2J = 9.3 Hz, ^3J = 6.6 Hz); 4.09 (dd, 2 H, $H(1)_b$, $H(6)_b$, ^2J = 9.3 Hz, ^3J = 6.6 Hz); 4.34—4.44 (m, 4 H, CH_{eq}, CH_{ax}); 4.75 (dd, 2 H, H(3), H(4), ^3J = 3.8 and 1.6 Hz); 5.18—5.30 (m, 2 H, H(2), H(5)).

This study was financially supported by the Russian Foundation for Basic Research (Project No. 02-03-32694).

References

1. M. T. Reetz and T. Neugebauer, *Angew. Chem., Int. Ed.*, 1999, **38**, 179.
2. D. G. Blackmond, T. Rosner, T. Neugebauer, and M. T. Reetz, *Angew. Chem., Int. Ed.*, 1999, **38**, 2196.
3. M. T. Reetz and G. Mehler, *Angew. Chem., Int. Ed.*, 2000, **39**, 3889.
4. M. K. Grachev, K. L. Anfilov, A. R. Bekker, and E. E. Nifant´ev, *Zh. Obshch. Khim.*, 1995, **65**, 1946 [*Russ. J. Gen. Chem.*, 1995, **65** (Engl. Transl.)].
5. G. I. Kurochkina, M. K. Grachev, L. K. Vasyanina, A. E. Piskaev, and E. E. Nifant´ev, *Dokl. Akad. Nauk,* 2000, **371**, 189 [*Dokl. Chem.*, 2000 (Engl. Transl.)].
6. E. E. Nifant´ev, O. M. Plotnikova, N. G. Ruchkina, L. K. Vasyanina, and A. R. Bekker, *Zh. Obshch. Khim.*, 1992, **62**, 2456 [*Russ. J. Gen. Chem.*, 1992, **62** (Engl. Transl.)].
7. (a) M. T. Reetz and M. Pasto, *Tetrahedron Lett.*, 2000, **41**, 3315; (b) G. Francio, F. Faraone, and W. Leitner, *Angew. Chem., Int. Ed.*, 2000, **39**, 1428; (c) R. Noyori and T. Ohkuma, *Angew. Chem., Int. Ed.*, 2001, **40**, 40; (d) D. Selent, D. Hess, K.-D. Wiese, D. Röttger, C. Kunze, and A. Börner, *Angew. Chem., Int. Ed.*, 2001, **40**, 1696; (e) K. Nozaki, T. Matsuo, F. Shibahara, and T. Hiyama, *Adv. Synth. Catal.*, 2001, **343**, 61; (f) K. W. Kottsieper, U. Kühner, and O. Stelzer, *Tetrahedron Asymmetry*, 2001, **12**, 1159.
8. D. Selent, K.-D. Wiese, D. Röttger, and A. Börner, *Angew. Chem., Int. Ed.*, 2000, **39**, 1639.
9. V. V. Grushin, *J. Am. Chem. Soc.*, 1999, **121**, 5831.
10. J. Bakos, B. Heil, and L. Marko, *J. Organomet. Chem.*, 1983, **253**, 249.
11. E. E. Nifant´ev and A. I. Zavalishina, *Khimiya elementoorganicheskikh soedinenii* [*Chemistry of Organometallic Compounds*], MGPI, Moscow, 1980, 91 pp. (in Russian).

Received July 18, 2002;
in revised form November 1, 2002