Directed phosphorylation of 2-*C*-hydroxymethyl-2,3:5,6-di-*O*-isopropylidene-D-mannofuranose

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Directed α- or β-phosphorylation of 2-*C*-hydroxymethyl-2,3:5,6-di-*O*-isopropylidene-D-mannofuranose is possible, this depends on the nature of the phosphorylating agent.

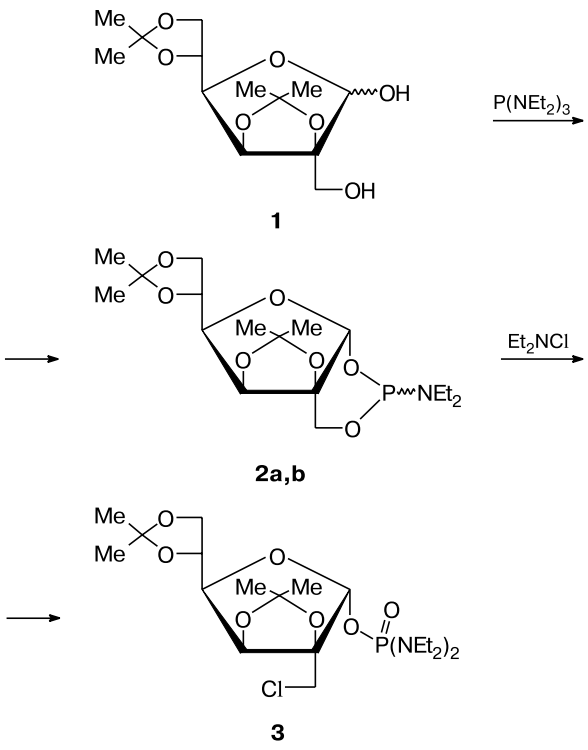
Key words: branched-chain sugars, anomeric center, phosphorylation, glycosyl phosphites, stereoselectivity.

Phosphorylation of carbohydrates containing an unprotected glycosidic center with phosphorus(III) reagents, for example, amides of phosphorous acid[1,2] or the corresponding mixed anhydrides[3] has been proposed for the syntheses of glycosyl phosphite derivatives. High reactivity, accessibility, and experimental convenience are advantages of these reagents. It is also substantial that glycosyl phosphites can easily be further transformed into the corresponding P^V analogs. In most cases, this approach gives a mixture of anomers, whose ratio depends on the nature of a carbohydrate. Stereoselective syntheses of α- and β-glycosyl phosphites, as well as α- and β-glycosyl phosphates, usually faces considerable difficulties. Therefore, a search for new methods of solving this problem seems urgent.

In the present work, we continue our studies[4] on α- and β-phosphorylation of the glycosidic center of 2-*C*-hydroxymethyl-2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**1**). A characteristic feature of monosaccharide **1** [5] is the presence of a hydroxymethyl group vicinal to the glycosidic center. This group is phosphorylated first being sterically most accessible, which can favor subsequent stereoselective α- or β-phosphorylation of the glycosidic center.

We have previously shown[4] that the reaction of compound **1** with hexaethylphosphorous triamide affords a mixture of cyclophosphites **2a,b** with a dioxaphosphorinane ring containing only the α-form of this monosaccharide and differing in the configuration of the P atom. Treatment of a mixture of cyclophosphites **2a,b** with *N*-chlorodiethylamine[6] at ~20 °C results in opening of the dioxaphosphorinane ring and formation of α-glycosyl phosphorodiamidate **3** isolated by chromatography in ~100% yield (Scheme 1).

Scheme 1



1 **2a,b** **3**

The structure of compound **3** was confirmed by ^{31}P, ^{1}H, and ^{13}C spectroscopy. The ^{31}P NMR spectrum exhibits a singlet at δ 4.5, and in the ^{1}H NMR spectrum the signal for H(1) is a doublet due to the coupling with the P atom ($^{3}J_{H(1),P}$ = 3.3 Hz). The ^{13}C NMR spectrum also contains the signals for the C(1) and C(2) atoms as doublets ($^{2}J_{C(1),P}$ = 4.2 Hz and $^{3}J_{C(2),P}$ = 3.9 Hz).

The aforementioned fact, *viz.*, the ability of the primary alcohol group at C(2´) to undergo faster phosphorylation, was also used for the synthesis of the β-anomeric phosphorylation product. Therefore, we assumed that the

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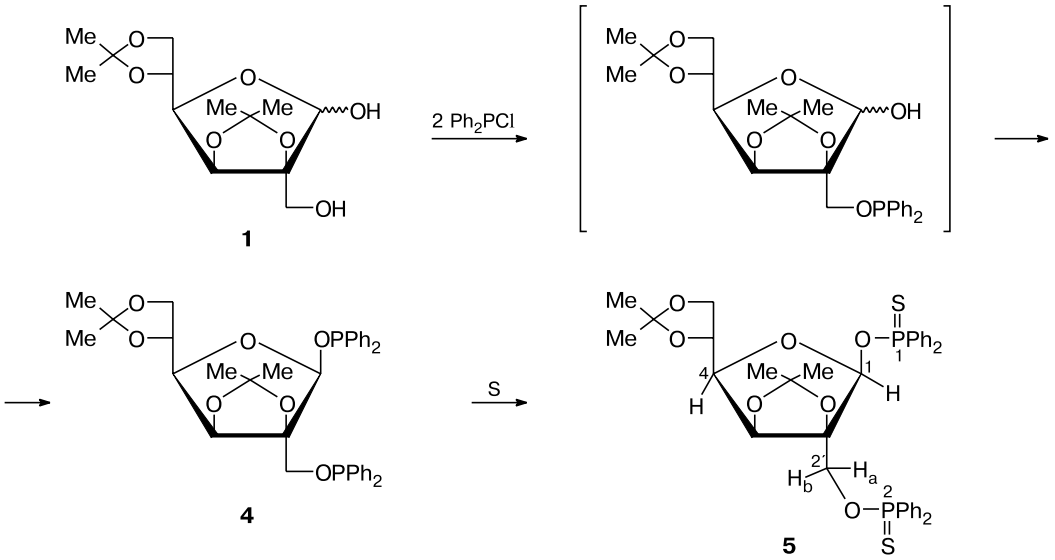
Scheme 2



introduction of a bulky group into position 2′ in the first step will impede the approach of a phosphorylating agent to the α-anomeric hydroxyl in the final step. Hence, the β-anomer should preferably be phosphorylated. We chose accessible diphenylchlorophosphine as the required bulky phosphorylating agent (Scheme 2).

Compound **4** is formed in 85% yield. Its ^{31}P NMR spectrum contains two signals as singlets in the region characteristic of phosphinites (δ 117.9 and 113.6). Since product **4** is rather labile and is decomposed during chromatographic purification, this was subjected to sulfurization and characterized as the respective bis(thionophosphinate) **5**. Sulfurization occurs readily at ~20 °C. Product **5** was isolated in the individual state by column chromatography, and its structure was confirmed by ^{31}P, ^{1}H, and ^{13}C NMR spectroscopy. The ^{31}P NMR spectrum exhibits two signals as singlets in the region characteristic of thionophosphinates (δ 84.9 and 82.1). Couplings of the C(1) and C(2) atoms with P(1) ($^{2}J_{C(1),P(1)}$ = 6.1 Hz, $^{3}J_{C(2),P(1)}$ = 8.9 Hz) and of the C(2) and C(2′) atoms with P(2) ($^{2}J_{C(2'),P(2)}$ = 4.6 Hz, $^{3}J_{C(2),P(2)}$ = 9.5 Hz) were observed in the ^{13}C NMR spectrum.

^{1}H NMR spectroscopy with the use of NOE was employed to confirm the configuration of the anomeric center of product **5**. The NOESY spectrum of this compound exhibits nontrivial cross-peaks H(1)/H(2′a), H(1)/H(2′b), and H(1)/H(4), indicating the spatial proximity of the corresponding protons. This is possible only in the case of the β-configuration of the product.

It is noteworthy that a mixture of α- and β-isomers in a ratio of 1 : 1 is formed when a less bulky phosphorylating agent, *viz.*, 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane,[7] is used for the phosphorylation of compound **1** under similar conditions. The ^{31}P NMR spectrum of this mixture contains signals at δ 112.2, 121.9, and 119.7 in a ratio of 1 : 1 : 2, respectively. The signal at δ 119.7 can be assigned to P(2) at the C(2′) atom, because its environment is the same for both anomers. The ^{31}P NMR spectrum of the mixture obtained after sulfurization also exhibits three signals (δ 61.5, 59.0, and 58.8) in a ratio of 2 : 1 : 1, respectively. As in the previous case, the signal with the doubled intensity at δ 61.5 can be attributed to P(2) at the C(2′) atom. We could not separate these anomers because of their similar chromatographic mobilities.

Thus, we found that the presence of the 2-*C*-hydroxymethyl group in the carbohydrate structure allows its stereoselective α- or β-phosphorylation of the anomeric center depending on the nature of the phosphorylating agent used.

Experimental

All experiments with phosphorus(III) compounds were carried out under dry nitrogen in thoroughly dried solvents. ^{1}H, ^{13}C, and ^{31}P spectra were recorded on an Avance 300 Bruker instrument (300.13, 75.47, and 121.46 MHz, respectively) for $CDCl_3$ solutions at 30 °C using Me_4Si as an internal standard. In NOESY experiment, the time of mixing was 600 ms. For recording ^{31}P NMR spectra, 75% H_3PO_4 was used as a standard. Optical rotation was determined on a DIP-360 polarimeter. Silufol UV-254 plates were used for TLC. Column chromatography was carried out on silica gel L 100/160 μm using the following eluents: benzene—dioxane, 3 : 1 (*A*) and light petroleum—dioxane, 3 : 1 (*B*).

2-*C*-Hydroxymethyl-2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose *R*- and *S*-1,2′-(*N*,*N*-diethyl)cyclophosphor-

amidites) (2a,b). A mixture of monosaccharide **1** (0.5 g, 1.7 mmol) and $P(NEt_2)_3$ (0.7 mL, 2.6 mmol) was placed in a distillation apparatus and heated for 1 h at 100 °C. The course of the reaction was monitored by the amount of diethylamine that distilled off. After the completion of the reaction, the excess of the phosphorylating agent was distilled *in vacuo*, and the remaining syrup was introduced into the subsequent reaction without additional purification. The yield of the product was 0.6 g (90%), R_f 0.65, 0.80 (*A*); δ_P 134 and 128 in a ratio of 45 : 55.

2-*C*-Chloromethyl-2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose *N*,*N*,*N*′,*N*′-tetraethylphosphoramidate (3). A solution of *N*-chlorodiethylamine (0.2 g, 2 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of a mixture of isomeric cyclophosphites **2a,b** (0.78 g, 2 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was left for 24 h at ~20 °C, then the solvent was distilled off *in vacuo*, and the residue was dissolved in benzene and chromatographed on a column with silica gel (eluent *A*). The yield was 0.94 g (98%), syrupy liquid, R_f 0.6 (*A*), $[\alpha]_D^{20}$ −12.5 (*c* 0.03, $CHCl_3$). Found (%): C, 52.06; H, 8.04; P, 6.41. $C_{21}H_{40}ClN_2O_7P$. Calculated (%): C, 52.03; H, 8.26; P, 6.39. ^{1}H NMR, δ: 0.92 (t, 12 H, 4 $\underline{Me}CH_2$, J = 7.2 Hz); 1.09, 1.24, 1.26, 1.36 (all s, 3 H each, 2 Me_2C); 2.90 (m, 8 H, 4 $MeC\underline{H}_2$); 3.96 (dd, 1 H, H(6a), $J_{H(6a),H(6b)}$ = 9.9 Hz, $J_{H(6a),H(5)}$ = 4.9 Hz); 3.98 (dd, 1 H, H(6b), $J_{H(6a),H(6b)}$ = 9.9 Hz, $J_{H(6b),H(5)}$ = 7.2 Hz); 4.17 (ddd, 1 H, H(5), $J_{H(6b),H(5)}$ = 7.2 Hz, $J_{H(6a),H(5)}$ = 4.9 Hz, $J_{H(5),H(4)}$ = 7.8 Hz); 4.38 (d, 1 H, H(3), $J_{H(3),H(4)}$ = 2.8 Hz); 4.47 (dd, 1 H, H(4), $J_{H(4),H(5)}$ = 7.8 Hz, $J_{H(4),H(3)}$ = 2.8 Hz); 4.63 (s, 2 H, CH_2Cl); 5.76 (d, H(1), $J_{H(1),P}$ = 3.3 Hz). ^{13}C NMR, δ: 14.34 (s, 4 $\underline{Me}CH_2$); 25.33, 25.72, 26.76, 27.02 (all s, 2 $\underline{Me}_2C$); 40.41, 40.51 (both s, 4 $MeC\underline{H}_2$); 64.41 (s, C(2′)); 66.87 (s, C(6)); 72.80 (s, C(5)); 83.38 (s, C(3)); 83.72 (s, C(4)); 88.64 (d, C(2), $J_{C(2),P}$ = 3.9 Hz); 106.29 (d, C(1), $J_{C(1),P}$ = 4.17 Hz); 109.28, 114.15 (both s, 2 $Me_2\underline{C}$). ^{31}P NMR: δ 4.57.

2-*C*-Hydroxymethyl-2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranose 1,2′-bis(diphenylthionophosphinate) (5). A solution of monosaccharide **1** (0.5 g, 1.7 mmol) and Et_3N (0.48 mL) in dioxane (10 mL) under dry nitrogen was added dropwise with vigorous stirring to a solution of Ph_2PCl (0.76 g, 3.4 mmol) in dioxane (5 mL) at ~20 °C. The reaction mixture was stirred for 3 h, a precipitate of $Et_3N \cdot HCl$ was filtered off, and the solvent was removed *in vacuo*. The residue was dissolved in benzene (5 mL), sulfur (0.16 g, 5 mmol) was added, and the resulting mixture was left for 24 h at ~20 °C. During the reaction, sulfur dissolves. The solvent was removed *in vacuo*, and the residue was chromatographed on a column with silica gel (eluent *B*). The yield was 0.92 g (74%), syrupy liquid, R_f 0.4 (*B*), $[\alpha]_D^{20}$ −9.2 (*c* 0.03, $CHCl_3$). Found (%): C, 61.28; H, 5.81; P, 8.14. $C_{37}H_{40}O_7P_2S_2$. Calculated (%): C, 61.50; H, 5.54; P, 8.59. ^{1}H NMR, δ: 1.26, 1.27, 1.31, 1.38 (all s, 3 H each, 2 Me_2C); 2.85 (dd, 1 H, H(6a), $J_{H(6a),H(6b)}$ = 8.9 Hz, $J_{H(6a),H(5)}$ = 6.1 Hz); 3.69 (dd, 1 H, H(6b), $J_{H(6a),H(6b)}$ = 8.9 Hz, $J_{H(6b),H(5)}$ = 4.0 Hz); 3.76 (dd, 1 H, H(4), $J_{H(4),H(5)}$ = 8.9 Hz, $J_{H(4),H(3)}$ = 3.1 Hz); 4.18 (ddd, 1 H, H(5), $J_{H(5),H(4)}$ = 8.9 Hz, $J_{H(5),H(6a)}$ = 6.1 Hz, $J_{H(5),H(6b)}$ = 4.0 Hz); 4.34 (dd, 1 H, H(2′a), $J_{H(2'a),H(2'b)}$ = 11.0 Hz, $J_{H(2'a),P(2)}$ = 6.1 Hz); 4.49 (dd, 1 H, H(2′b), $J_{H(2'a),H(2'b)}$ = 11.0 Hz, $J_{H(2'b),P(2)}$ = 8.5 Hz); 4.75 (d, 1 H, H(3), $J_{H(3),H(4)}$ = 3.1 Hz); 6.23 (d, 1 H, H(1), $J_{H(1),P(1)}$ = 8.9 Hz); 7.42—7.93 (m, 20 H, 4 Ph). ^{13}C NMR, δ: 24.93, 26.88, 27.25, 27.30 (all s, 4 Me); 63.54 (d, C(2′), $J_{C(2'),P(2)}$ = 4.6 Hz); 66.14 (s, C(6)); 71.90 (s, C(5)); 81.75 (s, C(3)); 82.30 (s, C(4)); 94.36 (dd, C(2), $J_{C(2),P(1)}$ = 8.9 Hz, $J_{C(2),P(2)}$ = 9.5 Hz); 103.18 (d, C(1), $J_{C(1),P(1)}$ = 6.1 Hz); 114.68, 109.21 (both s, 2 $Me_2\underline{C}$); 128.06—135.43 (4 Ph). ^{31}P: δ 84.9 and 82.1.

***R*- and *S*-1,2′-Bis-*O*-(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)-2-*C*-hydroxymethyl-2,3:5,6-di-*O*-isopropylidene-D-mannofuranose.** A solution of monosaccharide **1** (0.5 g, 1.7 mmol) and Et_3N (0.35 g, 0.48 mL) in dioxane (5 mL) was added dropwise with stirring and cooling to a solution of 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane (0.58 g, 0.47 mL, 3.4 mmol) in dioxane (5 mL). The mixture was stirred for 2 h at ~20 °C under argon and filtered, and the filtrate was concentrated. The residue was dissolved in benzene (5 mL), sulfur (0.16 g, 5 mmol) was added, and the resulting mixture was left for 24 h at ~20 °C. During the reaction, sulfur dissolves. The solvent was evaporated *in vacuo*, and the residue was dissolved in benzene and chromatographed on a column with silica gel (eluent *A*). The yield was 0.71 g (67%), syrupy liquid, R_f 0.8 (*B*).

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