Oxaphosphoranylation of Methyl α-D-Glucopyranoside with Diethoxytriphenylphosphorane. A Highly Stereoselective Route to Anhydropyranosides

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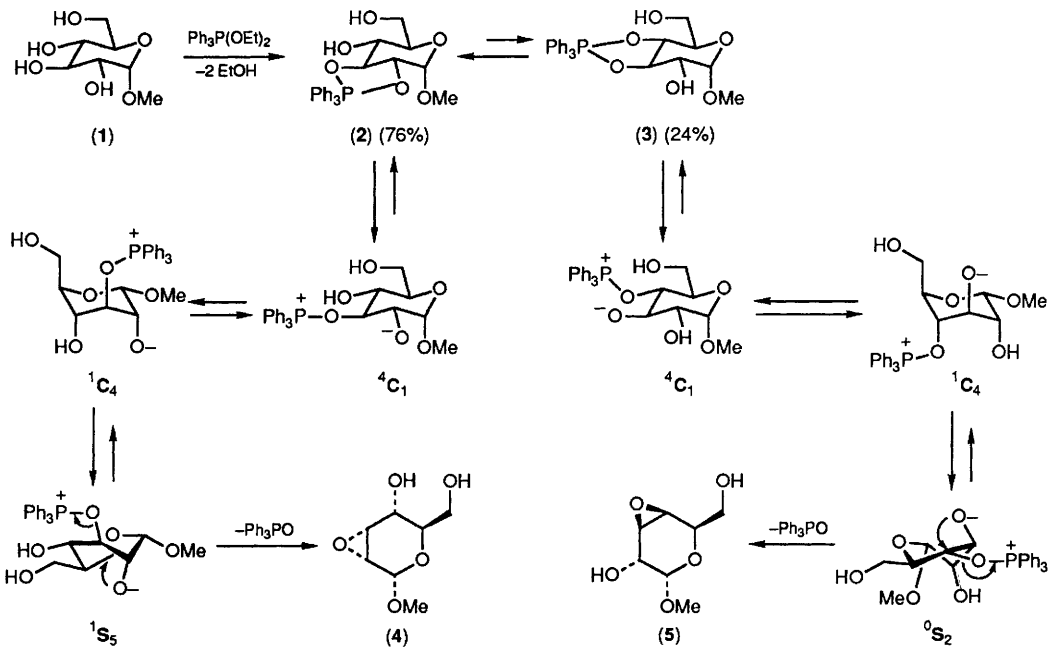
Diethoxytriphenylphosphorane (DTPP) efficiently oxaphosphoranylates methyl α-D-glycopyranoside (**1**) to afford two isomeric 1,3,2λ^5-dioxaphospholanes (**2** and **3**); thermolysis of the mixture of intermediates (**2**) and (**3**) affords methyl 2,3-anhydro-α-D-allopyranoside (**4**) and methyl 3,4-anhydro-α-D-galactopyranoside (**5**); however, in the presence of lithium bromide (LiBr), thermolysis of (**2**) and (**3**) is regiospecific, affording exclusively allopyranoside (**4**).

The synthetic utility of various epoxides having carbohydrate lineage is well established.[1—3] However, synthetic routes to a variety of anhydropyranosides devoid of selective protecting groups, particularly controlled and highly steroselective routes using single step transformations from glucopyranoside (**1**), have not been well documented.[4,5] Herein, we address this issue with disclosure of the 'DTPP-promoted'[6,7] bisoxaphosphoranylation of (**1**) and the ensuing highly efficient, stereoselective formation of anhydropyranosides.

The oxaphosphoranylation of glucopyranoside (**1**) with diethoxytriphenylphosphorane (DTPP)[8] affords two intermediate 1,3,2λ^5-dioxaphospholanes (**2**) (^{31}P NMR δ −36.1



Scheme 1. Mechanistic rationale for bisoxaphosphoranylation and cyclodehydration of methyl α-D-glucopyranoside with DTPP.

p.p.m., referenced to external 85% phosphoric acid)†‡ and (**3**) (δ −37.7 p.p.m.),†‡ where (**2**) is *kinetically* favoured over (**3**) in a ratio of 5:1. Their facile thermal equilibration (*ca.* 25 °C) as shown by ^{31}P NMR in *N,N*-dimethylformamide (DMF) solvent enhances the population of (**3**) although (**2**) still predominates [*i.e.*, (**3**)⇌(**2**); K_{eq} 3.1; ΔG° −0.66 kcal mol^{-1}].

A *ca.* 1:1 mixture of two epoxides (^{13}C NMR), methyl 2,3-anhydro-α-D-allopyranoside (**4**; 45%) and methyl 3,4-anhydro-α-D-galactopyranoside (**5**; 40%), as well as some methyl 3,6-anhydro-α-D-glucopyranoside (**6**; 15%),‡ are formed in DMF or toluene solvent from the thermal decomposition (65—90 °C; 6 h) of the *rapidly* equilibrating 1,3,2λ^5-dioxaphospholanes, (**2**) and (**3**). The structures of anhydropyranosides (**4**)—(**6**) were assigned by 'overlap' comparison of their ^{13}C NMR spectra with those of previously prepared authentic samples.‡

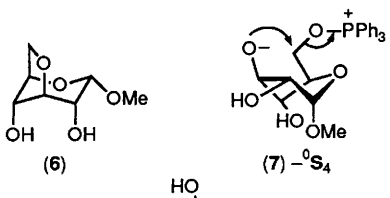
The two betaine intermediates [from dioxaphospholanes (**2**) and (**3**)] adopt either the chair ($^1C_4 \rightarrow {}^4C_1$)[16] or twist-boat ($^1S_5$, $^0S_2$)[16] conformations in order for the C–O$^-$ and –O–$^+$PPh$_3$ groups to assume the requisite 'pre-transition state' antiperiplanar arrangement. From preliminary molecular modelling studies on both chair and twist-boat betaine conformers, we suggest that the twist-boat ($^1S_5$ and $^0S_2$) conformers may also play vital roles as energetically-favoured intermediates (Scheme 1) during this cyclodehydration process. It also seems reasonable that even glucopyranoside (**6**) is formed *via* a transition state possessing the character of betaine (**7**) ($^0S_4$).

Finally, and most notably, when lithium bromide (LiBr)[17] is included in the DMF solution of 1,3,2λ^5-dioxaphospholanes (**2**) and (**3**), a facile decomposition (40 °C) occurs, affording methyl allopyranoside (**4**) as the sole product (>99% by ^{13}C NMR spectroscopy).‡§ Apparently, rapid equilibration of oxaphospholanes (**2**) and (**3**) *via* the intermediate betaines is controlled through Li$^+$ ion co-ordination to the basic anomeric oxygen[18] and relayed to the apical oxygen of the proximal 1,3,2λ^5-dioxaphospholane as depicted in complex (**8**). In this way, the catalytic influence of the Li$^+$ ion is 'site-selective,' thus enhancing the reactivity of 1,3,2λ^5-dioxaphospholane (**2**) [relative to (**3**)]. This specific Li$^+$ ion ligation to both oxygens coupled with the rapid equilibration between (**2**) and (**3**) accounts for the high level of regiospecificy observed in the

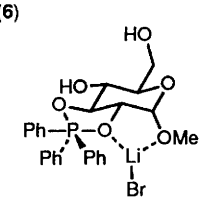
† *Reaction of methyl* α-D-*glucopyranoside* (**1**) *with DTPP.* A solution of DTPP (5.3 ml, 1.6 M in CH_2Cl_2, 8.5 mmol) was admixed with (**1**) (150 mg, 7.7 mmol) which had been previously dried [12 h, 2.5—4.0 mm Hg, *ca.* 70 °C (oil bath)], and the resulting solution was stirred at *ca.* 25 °C for 2 h under reduced pressure (2.5—4.0 mm Hg) to afford two hydrolytically labile 1,3,2λ^5-dioxaphospholanes, (**2**) and (**3**).

‡ *Spectroscopic data* for (**2**): ^{31}P NMR (DMF) δ −36.1 p.p.m., (toluene) δ −37.0 p.p.m.; ^{13}C NMR (DMF) δ 98.5 (d, $^3J_{POCC}$ 11.1 Hz, C-1), 76.1, 75.2, 73.1, 70.1 (d, $^3J_{POCC}$ 13.6 Hz, C-4), 61.8, 55.1, and 125—138 (aromatic carbons). For (**3**): ^{31}P NMR (DMF) δ −37.7 p.p.m., (toluene) δ −39.0 p.p.m.; ^{13}C NMR (DMF) δ 101.9, 76.6, 73.4 (d, $^3J_{POCC}$ 10.1 Hz, C-2)*, 72.8, 72.2 (d, $^3J_{POCC}$ 11.6 Hz, C-5)*, 62.8, 55.4, and 125—138 (aromatic carbons). The * denotes that these resonances may be interchangeable. For (**4**):[9] ^{13}C NMR (DMF) δ 94.6 (C-1), 53.8 (C-2), 54.3 (C-3), 65.4 (C-4), 70.4 (C-5), 61.6 (C-6), and 54.3 (OMe); ^{1}H NMR (D_2O) δ 5.08 (d, $J_{1,2}$ 2.6 Hz, 1-H), ~3.59 (m, 2-H), ~3.72 (m, 3-H), 3.98 (dd, 4-H), ~3.59 (m, 5-H), 3.86 (m, 6-H), ~3.72 (m, 6-H), and 3.47 (s, OMe). For (**5**):[10] ^{13}C NMR (DMF) δ 96.9 (C-1), 65.1 (C-2), 53.7 (C-3), 50.4 (C-4), 66.7 (C-5), 61.7 (C-6), and 54.9 (OMe);[11] ^{1}H NMR (D_2O) δ 4.75 (d, $J_{1,2}$ 2.52 Hz, 1-H), 3.85 (d, 2-H), 3.33 (d, 3-H), 3.45 (d, 4-H), 4.15 (m, 5-H), 3.89 (m, 6-H), and 3.45 (s, OMe).[12] For (**6**):[13,14] ^{13}C NMR (DMF) δ 98.4 (C-1), 71.5 (C-2), 72.0 (C-3), 70.4 (C-4), 75.2 (C-5), 68.5 (C-6), and 56.1 (OMe);[15] ^{1}H NMR ($CDCl_3$) δ 4.92 (d, $J_{1,2}$ 2.6 Hz, 1-H), 3.94 (m, 2-H), ~4.31 (m, 3-H), 4.12 (4-H), ~4.31 (m, 5-H), 3.98 (m, 6-H), 4.16 (6′-H), and 3.63 (s, OMe).

§ α-D-Glucopyranoside (**1**) (1.0 mmol, 0.48 M in 2.1 ml DMF) was transoxaphosphoranylated with DTPP [1.1 mmol, 0.93 M in 1.2 ml tetrahydrofuran (THF)] for 2.5 h under reduced pressure (2.5—4.0 mm Hg). The resulting solution containing dioxaphospholanes (**2**) and (**3**) was added to a DMF solution of LiBr (2.0 mmol) and stirred at 40 °C for 24—36 h to afford methyl allopyranoside (**4**) (>99% by ^{13}C NMR spectroscopy). The DMF solvent was removed (reduced pressure) and chromatographic isolation of (**4**) was accomplished by placing the reaction mixture on silica (30—50 g) and eluting with 80% $CHCl_3$/20% propan-2-ol (500 ml) to afford 80% (**4**).



(6) (7) $-^{0}S_{4}$



(8)

formation of anhydropyranoside (**4**). This latter reaction is remarkable, allowing for the regiospecific cyclodehydration of (**1**) to (**4**) with DTPP/LiBr in a single transformation.

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