Stereoselective *O*-glycosylation reactions employing diphenylphosphinate and propane-1,3-diyl phosphate as anomeric leaving groups

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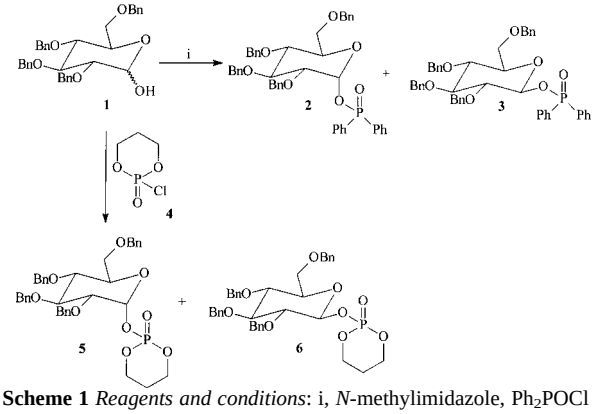
Glycosidation of tetra-*O*-benzyl-D-glucose using diphenylphosphinate as the leaving group afforded β-*O*-linked glycosides as the major products, whilst the use of propane-1,3-diyl phosphate as the leaving group resulted in the exclusive formation of β-*O*-linked glycoside.

The essential role that glycoconjugates play in a large number of molecular processes is now well recognised. The impact of these complex molecules in biological processes such as neuronal development, fertilisation, proliferation of cells and the organisation into specific tissues is truly remarkable.[1] Furthermore in tumours there are changes in the carbohydrate structures found at the cell surface and these appear to be intimately involved with metastasis.[2] Carbohydrates are also important in inducing protective antibody response which is responsible for the protection of the organism during infection.[3] As a direct consequence of these properties there has been a resurgence of interest in the chemistry of carbohydrates by both chemists and biologists and thus an enormous amount of methodology has been developed for *O*-glycosylation.[4] In particular there have been a number of reports regarding glycosyl donors that have a phosphorus atom in the leaving group at the anomeric centre. Interest in this has arisen due to the fact that phosphorus compounds can be readily modified by several other atoms allowing the preparation of a range of leaving groups. The coupling reactions of glycosyl diphenyl phosphates, glycosyl diphenylphosphinimidates and glycosyl phosphoramidates have received much attention;[5] in all of these reports 1,2-*trans*-β-linked glycosides are formed with a stereoselectivity of *ca.* 3 : 1 in favour of the β-isomer. The employment of *S*-glycosyl phosphorodimidothioates has also been reported and affords 1,2-*cis*-glycosidic linkages,[6] and the use of dimethylphosphinothioate as glycosyl donors has also been investigated.[7]

In order to extend the scope of this methodology we decided to investigate the possibility of using the diphenylphosphinyl group for coupling of sugars with peptides/amino acids. Our attraction to this approach was derived from the fact that its use had been elegantly demonstrated for the coupling and *N*-protection of amino acids.[8] One of the major considerations in adopting this approach was the principle that one should be able to utilise the same coupling reagent for the synthesis of oligosaccharides and peptides, although in the former case we are forming a glycosidic bond rather than an amide bond; however the leaving group is the same in both reactions. In addition the employment of the diphenylphosphinate and propane-1,3-diyl phosphate groups[9] should result in the preparation of *O*-glycosides with improved stability, enabling ready isolation and storage of these compounds. Additionally we chose to study propane-1,3-diyl phosphate as the leaving group as this would provide a comparison of the effect of pK_a on leaving group ability. Furthermore the introduction of the cyclic phosphate group would allow us to assess the influence of steric requirements at the anomeric centre.

We chose to investigate the coupling at the anomeric centre of tetra-*O*-benzyl-D-glucopyranose. Our attraction to this was multi-faceted, with the major consideration being that there would be no participation by the C-2 substituent in the coupling reaction; furthermore, these processes had received scant attention in the literature and in addition we would have a flexible method that would allow the synthesis of *O*-glycopyranosides.

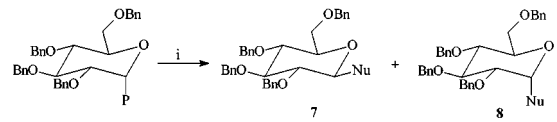


Scheme 1 *Reagents and conditions*: i, *N*-methylimidazole, Ph_2POCl

Treatment of tetra-*O*-benzyl-D-glucopyranose **1** with diphenylphosphinyl chloride and *N*-methylimidazole resulted in the formation of the phosphinates **2**‡ and **3** (ratio 10 : 1) in 95% yield (Scheme 1), which could be separated by column chromatography. However for ease we conducted all of our reactions with this anomeric mixture, which could be stored at −20 °C for 3–4 months without decomposition.[10] Similar treatment of **1** with the cyclic phosphoryl chloride **4** resulted in formation of the phosphates **5**‡ and **6**, which were inseparable by chromatography, in 65% yield, (ratio *ca.* 10 : 1).

We thus proceeded to study the reactions of the phosphinates **2** and **3** and also of the cyclic phosphates **5** and **6** with a range of nucleophiles (Scheme 2, Table 1). In the case of the reaction of n-butanol with pure **2** there was little difference in the stereochemical outcome of the reaction to that found using the anomeric mixture. In general the chemical yield was excellent, however the observed stereoselectivity in these cases was poor, being in the order of 3 : 1 in favour of the desired β-isomer. The stereochemistry of products was established by ^{1}H and ^{13}C NMR analysis. The ^{13}C NMR spectra were particularly useful as the β-isomers **7** had chemical shifts above δ 100 whilst the α-isomers **8** had a resonance at *ca.* δ 96,[11] allowing assignment of the newly formed stereocentre.

In the case where we employed propane-1,3-diyl phosphate as the leaving group the stereoselectivity was improved, with the β-isomer being the major compound in the case of oxygen nucleophiles. To our surprise the use of serine- and thereonine-derived nucleophiles resulted in the formation of **8** as the major isomer; this may be as a result of a hydrogen bonding interaction with the N–H, resulting in delivery from the α-face of the

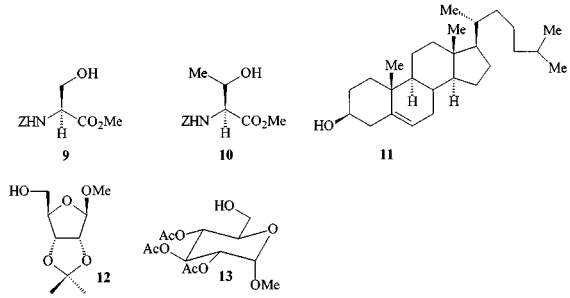


Scheme 2 *Reagents and conditions*: i, nucleophile (1 equiv.), TMSOTf (1 equiv.), −78 °C, 25 min

Table 1 Results of reaction of **2**, **3**, **5** and **6** with nucleophiles

Phosphinate/ phosphate	Nucleophile	Yield (%)[a]	Ratio **7** : **8**
2	Bu^{n}OH	89	2 : 1
2 and **3**	Bu^{n}OH	90	2 : 1
2 and **3**	MeOH	94	4 : 1
2 and **3**	Pr^{i}OH	93	3.5 : 1
2 and **3**	**9**	88	2.5 : 1
2 and **3**	**10**	94	1 : 2
2 and **3**	**11**	85	2 : 1
2 and **3**	**12**	92	2 : 1
2 and **3**	**13**	84	3 : 1
5 and **6**	Bu^{n}OH	99	7 only
5 and **6**	MeOH	96	7 : 3
5 and **6**	Pr^{i}OH	98	7 : 3
5 and **6**	**9**	91	1 : 2
5 and **6**	**10**	83	1 : 2
5 and **6**	**11**	88	4 : 1
5 and **6**	**12**	68	7 only
5 and **6**	**13**	72	7 only

[a] All yields are for isolated products.



glucose. We were gratified to observe that we had attained our goal of excellent selectivity in the formation of **7** in the cases where we employed sugar-derived nucleophiles. This is particularly encouraing as we have a 2-*O*-benzyl protecting group which is non-participating in glycosylation reactions and would be expected to result in the formation of the α-glycosides. As a result of these findings one could, in principle, use *O*-benzyl protected sugars as starting materials and by changing the activating group of the glycosyl donor either desired stereoisomer can be obtained, thus alleviating the need for differentially protected starting sugars.

We have thus established that tetra-*O*-benzyl-D-glucopyranose can be converted into *O*-linked glycosides with high stereoselectivity in the cases where we employed propane-1,3-diyl phosphate as the leaving group, adding to the methodology available for the synthesis of complex carbohydrates.

We thank Professor R. Ramage (Edinburgh University) for helpful discussions and encouragement. We also thank the EPSRC for access to the mass spectrometry service at the University of Wales, Swansea (Director, Dr J. A. Ballantine).

Notes and References

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‡ All compounds gave satisfactory spectral and microanalytical data. *Selected data* for **2**:[10] $[\alpha]_D$ +83.3 (*c* 4.3, $CHCl_3$); δ_H(400 MHz, $CDCl_3$) 3.62–3.77 (4H, m), 3.86–4.07 (2H, m), 4.36 (1H, d, *J* 11.87), 4.47 (1H, d, *J* 10.50), 4.51 (1H, d, *J* 11.87), 4.60 (1H, d, *J* 11.22), 4.73 (1H, d, *J* 11.22), 4.80 (1H, d, *J* 10.56), 4.85 (1H, d, *J* 10.56), 4.96 (1H, d, *J* 11.21), 5.99 (1H, dd, *J* 3.3, 11.9), 7.10–7.84 (m, 30H); δ_C(100.40 MHz, $CDCl_3$) 68.08 (C-6), 72.10, 73.21, 74.64, 76.67, 79.14 (C-4), 79.20 (C-2), 81.13 (C-3), 84.28 (C-5), 92.79 (C-1), 127.41–128.24 (Ar-C), 130.31–132.40 (Ar-C), 137.57–138.40 (Ar-C); δ_P(161.70 MHz, $CDCl_3$) 32.50. For **5**: mp 101–103 °C; $[\alpha]_D$ +65.7 (*c* 1.4, $CHCl_3$); δ_H(270 MHz, $CDCl_3$) 1.55–1.63 (1H, m, J_{PH} 15.2), 2.14–2.28 (1H, m, J_{PH} 15.2), 3.61–3.78 (4H, m), 3.89–3.99 (2H, m), 4.15–4.41 (4H, m), 4.44 (1H, d, *J* 11.87), 4.52 (1H, d, *J* 11.87), 4.56 (1H, d, *J* 11.87), 4.63 (1H, d, *J* 11.21), 4.71 (1H, d, *J* 11.87), 4.80 (1H, d, *J* 10.56), 4.84 (1H, d, *J* 11.22), 4.94 (1H, d, *J* 11.22), 5.85 (1H, dd, *J* 10.56, 3.30), 7.13–7.37 (20H, m); δ_C(67.8 MHz, $CDCl_3$) 25.84 (1C, d, *J* 7.01), 68.14, 68.65 (d, *J* 7.01), 68.86 (d, *J* 7.01), 75.51, 76.94, 79.03, 94.78, 127.60–128.09 (Ar-C), 137.50–138.47 (Ar-C); δ_P(109.25 MHz, $CDCl_3$) −10.99; *m/z* (EI) 660.6 (M^+) (Found: C, 67.4; H, 6.3; P, 4.7. $C_{37}H_{41}O_9P$ requires C, 67.3; H, 6.3; P, 4.7%). For **6**: (selected features) δ_H(270 MHz, $CDCl_3$) 5.24 (1H, app t, *J* 13.19, 7.26); δ_C(67.8 MHz, $CDCl_3$) 98.44; δ_P(109.25 MHz, $CDCl_3$) −10.60. For **7** (Nu = OBu): mp 69–71 °C; $[\alpha]_D$ +16.5 (*c* 1.3, $CHCl_3$); δ_H(270 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.26), 1.35–1.71 (4H, m), 3.41–3.50 (2H, m), 3.52–3.69 (4H, m), 3.73 (1H, dd, *J* 10.55, 1.98), 3.97 (1H, dt, *J* 12.53, 5.93), 4.39 (1H, d, *J* 7.91, H-1), 4.51 (1H, d, *J* 11.21), 4.55 (1H, d, *J* 11.87), 4.61 (1H, d, *J* 12.54), 4.71 (1H, d, *J* 10.55), 4.76 (1H, d, *J* 11.21), 4.80 (1H, d, *J* 10.56), 4.91 (1H, d, *J* 10.55), 4.93 (1H, d, *J* 10.56), 7.10–7.37 (20H, m); δ_C(67.8 MHz, $CDCl_3$) 13.85, 19.29, 31.82, 67.88, 69.02, 69.78, 73.45, 74.85, 74.98, 75.66, 77.96, 82.29, 84.72, 103.60 (C-1), 127.58–128.37 (Ar-C), 138.23, 138.32, 138.61, 138.74 (Found M^+, 596.3138. $C_{38}H_{44}O_6$ requires 596.3138). For **7** (Nu = **13**):[12] $[\alpha]_D$ +65.5 (*c* 3.3, $CHCl_3$); δ_H(270 MHz, $CDCl_3$) 1.99 (3H, s), 2.02 (3H, s), 2.08 (3H, s), 3.29 (3H, s), 3.41–3.55 (3H, m), 3.64–3.80 (2H, m), 3.84–3.97 (4H, m), 4.38 (1H, d, *J* 8.57), 4.46 (1H, d, *J* 11.87), 4.49 (1H, d, *J* 11.87), 4.56 (1H, d, *J* 11.87), 4.58 (1H, d, *J* 10.55), 4.64 (1H, d, *J* 11.21), 4.74 (1H, d, *J* 11.22), 4.81–4.85 (3H, m), 4.89 (1H, d, *J* 10.55), 4.91 (1H, d, *J* 11.21), 5.36 (1H, app t, *J* 4.62), 7.03–7.27 (20H, m); δ_C(67.8 MHz, $CDCl_3$) 20.68, 20.70, 29.59, 66.83, 68.43, 69.51, 70.24, 70.82, 73.15, 74.67, 74.82, 75.12, 75.47, 80.21, 81.27, 82.49, 84.71, 96.61 (C-1′), 102.93 (C-1), 127.52–128.51 (Ar-C), 137.72, 138.06, 138.34, 138.50, 170.10, 170.29, 170.40.

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Received in Liverpool, UK, 6th July 1998; 8/05206I