A Rapid and Efficient Synthesis of 1,2-*trans*-β-Linked Glycosides *via* Benzyl- or Benzoyl-protected Glycopyranosyl Phosphates

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A highly stereocontrolled construction of 1,2-*trans*-β-glycosidic linkage with or without neighbouring-group participation has been achieved using benzyl- or benzoyl-protected glycopyranosyl phosphates as glycosyl donors in the presence of trimethylsilyl triflate (TMSOTf).

The growing interest in glycosides and oligosaccharides as constituents of biologically important compounds such as antibiotics, glycolipids, glycoproteins, and immunodeterminants has stimulated development of new methods for the efficient and stereocontrolled construction of the glycosidic linkages.[1] However, there is an enormous effort to devise practical glycosidation procedures using shelf-stable glycosyl donors without resorting to precious, explosive, or toxic heavy-metal salts as promoters. Considering that the leaving group of glycosyl donors is one of the most fundamental parameters responsible for the selectivity and yield of glycosidation, we were intrigued by the feasibility of using glycosyl phosphates as glycosyl donors [equation (1)]. Although glycosyl phosphates are of great significance as intermediates

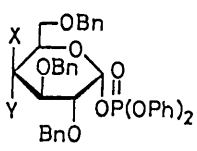
$$\text{Gly–OH} \longrightarrow \text{Gly–O}\overset{\overset{\text{O}}{\|}}{\text{P}}(\text{OR})_2 \xrightarrow{\text{R'OH}} \text{Gly–OR'} \qquad (1)$$

in the biological glycosyl transfer,[2] no attention has been paid to their synthetic utility as glycosyl donors. We now report a rapid and efficient procedure for the stereocontrolled construction of 1,2-*trans*-β-glycosidic linkage *via* benzyl- or benzoyl-protected glycopyranosyl phosphates, which fulfills the above requirements.

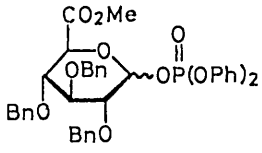
Table 1. Glycosidation of benzyl-protected glycopyranosyl diphenyl phosphates (**1**—**3**).[a]

Entry	Phosphate	Alcohol	% Yield[b] (α : β)[c]	$[\alpha]_D^{22}$/°(*c*, $CHCl_3$)[d]	Ref.
1	(**1**)	(**7**)	84 (3 : 97)	+18.9 (1.2)	4a
2	(**1**)	(**10**)	85 (7 : 93)	+16.9 (1.7)	4b
3	(**1**)	(**12**)	81 (5 : 95)	+6.89 (1.8)	
4	(**1**)	(**13**)	80 (7 : 93)	+57.0 (1.0)	4c
5	(**1**)	(**14**)	80 (7 : 93)	+2.10 (1.2)	
6	(**1**)	(**15**)	78 (10 : 90)	−6.40 (2.0)[e]	4d
7	(**2**)	(**8**)	87 (7 : 93)	−7.20 (1.9)	4e
8	(**2**)	(**11**)	83 (14 : 86)	+1.62 (1.3)	4e
9	(**2**)	(**16**)	88 (8 : 92)	−91.8 (2.3)	4f
10	(**3**)	(**7**)	78 (14 : 86)	+12.8 (1.2)	4g

[a] All reactions were carried out on 0.5 mmol scale. [b] Isolated total yield. [c] Determined by h.p.l.c. [d] Values for the 1,2-*trans*-β-linked disaccharides purified by flash chromatography (silica gel). [e] $[\alpha]_{577}^{22}$ −6.7° (*c* 1.9) [lit.[4d] $[\alpha]_{578}^{20}$ −7.4° (*c* 1.7)].



(**1**) X=H, Y=OBn
(**2**) X=OBn, Y=H



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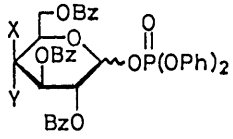
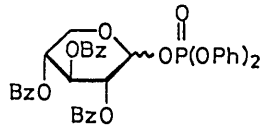


(**4**) X=H, Y=OBz
(**5**) X=OBz, Y=H



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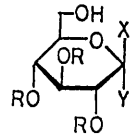
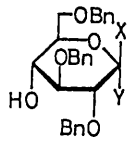
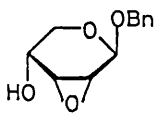


(**7**) R=Bn, X=H, Y=OMe
(**8**) R=Bn, X=OBn, Y=H
(**9**) R=Bz, X=H, Y=OMe



(**10**) X=H, Y=OMe
(**11**) X=OBn, Y=H



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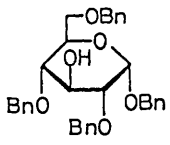

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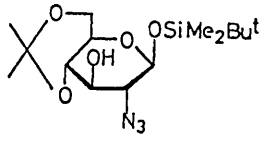

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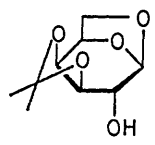

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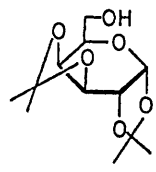
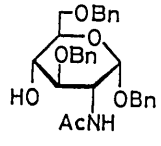


(**16**)



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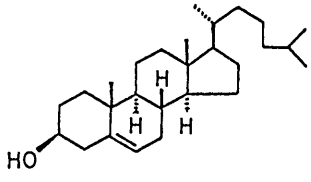

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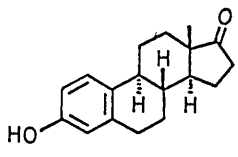

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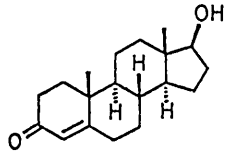

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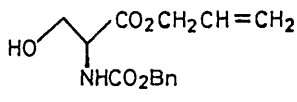

(**21**)

Bn = $PhCH_2$, Bz = PhCO

Firstly, we investigated glycosidation of the glycopyranosyl phosphates with non-participating substituents on C-2. Benzyl-protected glycopyranosyl diphenyl phosphates (**1**—**3**)†‡ with considerable shelf-life were readily prepared by treatment of the corresponding 1-*O*-lithium salts with diphenyl phosphorochloridate according to Shiba's method.[3] Coupling of the phosphates (1.0 equiv.) with a variety of suitably protected glycosides (1.1 equiv.) in propionitrile in the presence of trimethylsilyl triflate (TMSOTf) (1.1 equiv.) at −78 °C was found to proceed to completion within 5 to 10 min, affording the 1,2-*trans*-linked disaccharides with high degrees of stereoselectivity and in high yields. Some representative results are presented in Table 1. Among a variety of Brønsted and Lewis acids tested as promoters, TMSOTf was the only one capable of activating the phosphoryloxy group

† Satisfactory spectroscopic and analytical data were obtained for all new compounds.

‡ The anomeric composition of the phosphates (**1**–**3**) was determined by 400 MHz ^1H n.m.r. spectroscopy [α : β ratio, (**1**), > 99 : 1; (**2**), >99 : 1; (**3**), 84 : 16].

Table 2. Glycosidation of benzoyl-protected glycopyranosyl diphenyl phosphates (**4**—**6**).[a]

Entry	Phosphate	Alcohol	% Yield	N.m.r. data[b] δ^1H[c]	N.m.r. data[b] $\delta^{13}C$[d]	$[\alpha]_D^{22}$/°(c, $CHCl_3$)
1	(**4**)	(**7**)	92	4.82	101.3	+22.1 (2.7)
2	(**4**)	(**9**)	95	4.97	101.8	+47.2 (2.3)
3	(**4**)	(**10**)	83	4.78	101.3	−3.0 (1.7)
4[e]	(**4**)	(**18**)	90	4.93	99.6	+14.1 (0.71)[f]
5	(**4**)	(**19**)	92	5.37	99.6	+78.6 (1.1)
6	(**5**)	(**12**)	79	5.21	101.1	+87.5 (1.2)[g]
7	(**5**)	(**17**)	83	5.08	100.4	+76.1 (1.7)
8	(**5**)	(**20**)	72	4.82	102.5	+123 (1.1)
9	(**6**)	(**21**)	89	5.27	100.3	−23.6 (1.2)

[a] The reactions were carried out at room temperature on 0.5 mmol scale, unless otherwise stated. Products were isolated by column chromatography (silica gel). [b] Chemical shifts for the anomeric centres newly formed. [c] In $CDCl_3$ at 400 MHz. [d] In $CDCl_3$ at 100 MHz. [e] Performed at 0 °C. [f] Ref. 9a. [g] Ref. 9b.

below −25 °C, and proved to be the best choice for allowing extremely rapid glycosidation with high β-selectivity. It should be noted that the acid-labile groups such as epoxy, acetal, or *O*-t-butyldimethylsilyl groups are compatible with the reaction conditions (entries 3, 5, 6, and 9). The glycosidation of 2,3,4,6-tetra-*O*-benzyl-α or β-D-glucopyranosyl dibenzyl phosphate[5] showed that the anomeric configuration of the donors was not crucial to either the stereochemical outcome or final yield of this glycosidation. Hence, the glycosidation reaction is presumed to proceed *via* the thermodynamically more stable α-ion pair consisting of pyranoxoium ion and phosphate anion–TMSOTf complex followed by the backside attack with alcohols on this intermediate.

Armed with these positive results, glycosidation of the glycopyranosyl phosphates with participating substituent on C-2 was next explored. An initial attempt at TMSOTf-promoted glycosidation of 2,3,4,6-tetra-*O*-acetyl-D-glycopyranosyl diphenyl phosphate in both the absence and presence of 2,6-lutidine, 2,4,6-collidine, or 1,1,3,3-tetramethylurea met with failure due to the significant formation of 2-hydroxy α- and β-linked glycosides frequently observed in proton-catalysed glycosidation.[6] In stark contrast, however, condensation of the benzoyl-protected[6c,7] glycopyranosyl diphenyl phosphates (**4**–**6**)§ (1.0 equiv.) with a wide range of alcohols or suitably protected glycosides (1.1 equiv.) in dichloromethane in the presence of TMSOTf (1.1 equiv.) and 1,1,3,3-tetramethylurea (1.1 equiv.) at room temperature for 1 h led exclusively to the formation of 1,2-*trans*-linked glycosides or disaccharides, with no trace of the products debenzoylated on *O*-2 or the orthoesters. Table 2 shows the considerable scope and versatility of this simple method of glycosidation.

In summary, the potential usefulness of the diphenylphosphoryloxy group as the leaving group of glycosyl donors has been demonstrated. The present method has advantages in allowing operational simplicity and practical value as well as a facile entry to 1,2-*trans*-linked glycosides, and thus should be a potent alternative to Schmidt's trichloroacetimidate procedure.[1b,4d]

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§ These substances [α:β ratio, (**4**), 57:43; (**5**), 73:27; (**6**), 67:33] with excellent shelf-life were prepared from the corresponding per-*O*-benzoyl-D-glycopyranoses in 51—56% overall yields by a three-step operation: i, thiophenol (1.1 equiv.), $SnCl_4$ (1.0 equiv.), benzene; ii, *cf.* ref. 8. HgO (2.0 equiv.), $BF_3{\cdot}OEt_2$ (2.0 equiv.), tetrahydrofuran (THF)–H_2O (85:15), 50 °C; iii, *cf.* ref. 3. Bu^nLi (1.05 equiv.), $ClPO(OPh)_2$ (1.1 equiv.), THF, −78 °C.

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