AN EFFICIENT CONSTRUCTION OF 1,2-*TRANS*-β-GLYCOSIDIC LINKAGES *VIA* BENZYL-PROTECTED GLYCOPYRANOSYL *P,P*-DIPHENYL-*N*-(*p*-TOLUENESULFONYL)-PHOSPHINIMIDATES

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An efficient 1,2-*trans*-glycosidation reaction without neighbouring group participation has been developed using benzyl-protected *P,P*-diphenyl-*N*-(*p*-toluenesulfonyl)phosphinimidates as glycosyl donors in the presence of trimethylsilyl triflate or boron trifluoride etherate.

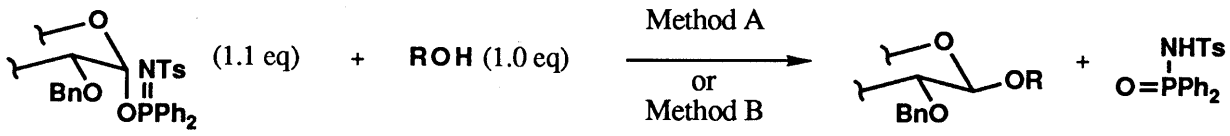
KEYWORDS glycosidation; 1,2-*trans*-glycosidic linkage; phosphinimidate; steroidal glycoside

Due to the increasingly recognized biological significance of saccharide residues of carbohydrate-containing biomolecules, the development of expeditious methods for the stereocontrolled construction of the glycosidic linkages is becoming of paramount importance in synthetic organic chemistry.[1,2] Our interest in this area has led to the design of the leaving groups of glycosyl donors allowing excellent shelf-lives, as well as their activation without resorting to precious, explosive, or toxic heavy-metal salts as promoters. In an effort to capitalize on the phosphorus-containing leaving groups, we recently developed rapid and efficient methods for the stereocontrolled construction of 1,2-*trans*-β-glycosidic linkages by the devise of shelf-stable benzyl- or benzoyl-protected glycopyranosyl diphenyl phosphates[3] or benzoyl-protected *P,P*-diphenyl-*N*-(*p*-toluenesulfonyl)phosphinimidates[4] as glycosyl donors, in which the respective promoter of choice was trimethylsilyl triflate (TMSOTf) or $BF_3 \cdot OEt_2$. As an extension of the phosphinimidate method, we now turned our attention to the glycosidation using benzyl-protected glycopyranosyl *P,P*-diphenyl-*N*-(*p*-toluenesulfonyl)phosphinimidates as glycosyl donors, some features of which are described herein.

Benzyl-protected glycopyranosyl phosphinimidates (**1** and **2**) were readily prepared by condensation of the 1-*O*-lithium salts of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose and -α-D-galactopyranose with *P,P*-diphenyl-*N*-(*p*-toluenesulfonyl)phosphinimidic chloride[5] (THF, -78 °C, 0.5 h). These donors could be stored in the freezer (at -20 °C) for at least several weeks without detectable deterioration.

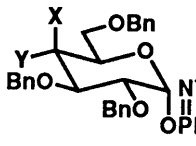
Initial attempts at the glycosidation reactions were performed with suitably protected glycoside alcohols as acceptors. After surveying a variety of conditions, coupling of the phosphinimidates (**1** and **2**) (1.1 eq) with alcohols (**3**-**8**) (1.0 eq) in propionitrile in the presence of TMSOTf (1.2 eq) at -55 °C was found to proceed smoothly to give the 1,2-*trans*-β-linked disaccharides in high yields and with high levels of stereoselectivity (method A, entries 1-6 in Table I). The combined use of TMSOTf as promoter and propionitrile as solvent proved to be the best choice for allowing considerable levels of 1,2-*trans*-selectivity. It should be noted that the alcohols bearing the acid-labile epoxy or acetal groups are safely glycosylated (entries 3, 4, and 6). From the result that the glycosidation of a 33:67 mixture[6] of **1** and its β-anomer under the above conditions gave essentially the same yields and stereoselectivities as that of **1**, the glycosidation reaction apparently proceeds through the thermodynamically more stable α-D-glycopyranosyl triflate followed by the backside attack of alcohols on this intermediate.

Table I. 1,2-*trans*-Glycosidation of Benzyl-Protected Glycopyranosyl *P*,*P*-Diphenyl-*N*-(*p*-toluenesulfonyl)-phosphinimidates (**1** and **2**)

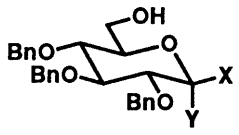


Entry	Donor	Acceptor	Method [a]	Time (h)	Yield (%)[b]	α:β [c]	$\delta^{13}C$ [d]
1	**1**	**3**	A	0.3	88	4:96	103.8(97.3)
2	**1**	**5**	A	0.5	84	12:88	102.4(96.6)
3	**1**	**6**	A	0.5	82	8:92	103.7(95.5)
4	**1**	**7**	A	0.5	79	13:87	103.2(96.9)
5	**2**	**4**	A	0.3	84	9:91	104.3(98.0)
6	**2**	**8**	A	0.3	82	8:92	104.7(97.6)
7	**1**	**9**	B	6	74	10:90	102.0(94.7)
8	**1**	**10**	B	6	72	13:87	102.3(94.7)[e]
9	**1**	**11**	B	6	72	7:93	101.0(94.8)
10	**1**	**12**	B	8	70	12:88	101.9(94.8)
11	**2**	**11**	B	6	73	11:89	101.1(95.4)

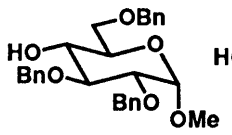
a) Method A: TMSOTf (1.0 M in CH_2Cl_2, 0.12 mmol) was added to a solution of donor (0.11 mmol) and acceptor (0.1 mmol) in propionitrile (2 ml) at -70 °C, and the reaction was performed at -55 °C under argon atmosphere. Method B: $BF_3{\cdot}OEt_2$ (1.0 M in CH_2Cl_2, 0.11 mmol) was added to a mixture of donor (0.11 mmol), acceptor (0.1 mmol), and pulverized 4Å molecular sieves (50 mg) in CH_2Cl_2 (2.5 ml) at -23 °C, and the reaction was carried out at this temperature in a sealed tube. After the reaction was complete, the product was isolated by extractive workup and subsequent chromatography on silica gel. b) Isolated total yield based on the acceptor used. c) Determined by HPLC analysis. d) Chemical shifts (δ ppm) in ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) for the anomeric centers newly formed. Values in parentheses correspond to those of 1,2-*cis*-linked glycosides and disaccharides. e) Ref. 9.



1 X=H, Y=OBn
2 X=OBn, Y=H



3 X=H, Y=OMe
4 X=OBn, Y=H



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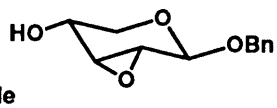

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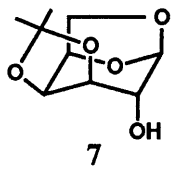

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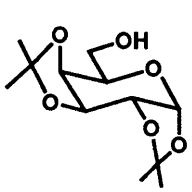

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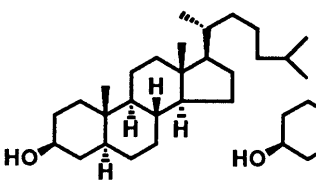

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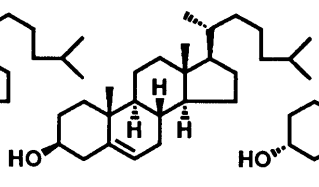

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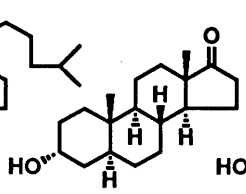

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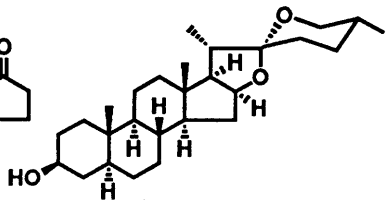

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On these positive notes, we then directed our efforts to the extension of this protocol to the construction of steroidal glycosides, with which the phosphate method[3] without neighbouring group participation proved to be less than satisfactory.[7] While the foregoing procedure (method A) also met with less success,[8] it was found that condensation of the phosphinimidates (**1** and **2**) (1.1 eq) with steroidal alcohols (**9**-**12**) (1.0 eq) in dichloromethane in the presence of $BF_3 \cdot OEt_2$ (1.1 eq) and pulverized 4Å molecular sieves at -23 °C led to the preponderant formation of 1,2-*trans*-β-linked steroidal glycosides in good yields (method B, entries 7-11 in Table I).[10] In view of the lack of versatile methods for 1,2-*trans*-glycosidation of steroidal glycosides without the anchimeric assistance by the *O*-2-acyl group,[11] our procedure should be of great promise.

In summary, the effectiveness of the benzyl-protected glycopyranosyl phosphinimidates as glycosyl donors has been demonstrated by proper choice of promoters and solvents. More complex application of the glycosidation method are currently under investigation.

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