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AN EXTREMELY MILD AND GENERAL METHOD FOR THE STEREOCONTROLLED CONSTRUCTION OF 1,2-*CIS*-GLYCOSIDIC LINKAGES *VIA S*-GLYCOPYRANOSYL PHOSPHORODIAMIDIMIDOTHIOATES

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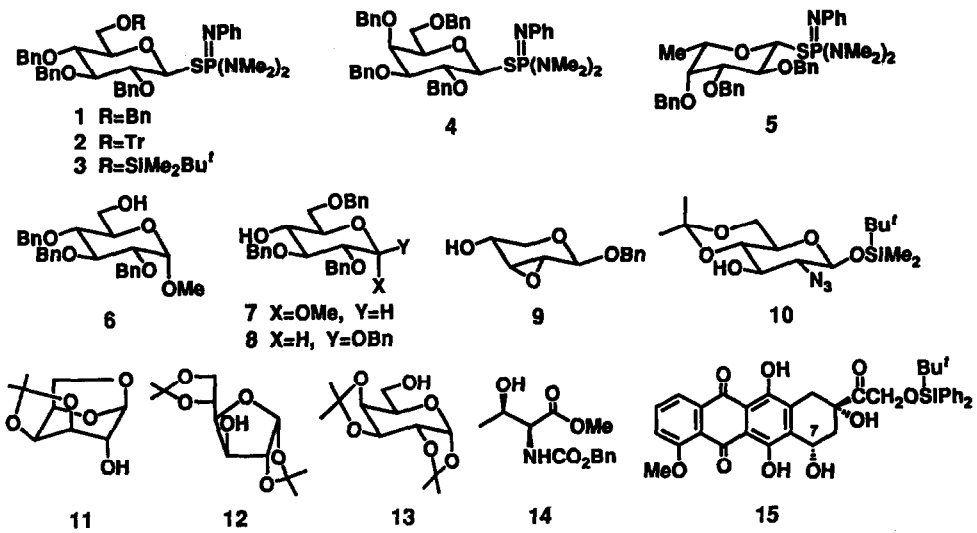
Summary: A highly stereocontrolled construction of 1,2-*cis*-glycosidic linkages under extremely mild reaction conditions has been developed by using *S*-glycopyranosyl *N,N,N',N'*-tetramethyl-*N''*-phenylphosphorodiamidimidothioates with a non-participating *O*-2-benzyl group as glycosyl donors in the presence of 2,6-lutidinium *p*-toluenesulfonate and tetrabutylammonium iodide.

The growing significance of glycosides and oligosaccharides as constituents of biologically important compounds such as saponins, cardenolides, antibiotics, glycolipids, and glycoproteins has sparked considerable interest in expeditious methods for the stereocontrolled construction of the glycosidic linkages. Despite the recent advances[1,2] in this field, however, there still exists a continuing demand for appreciable developments in terms of mildness, efficacy, generality, and stereocontrol.

Considering that the leaving group of glycosyl donors is one of the most fundamental parameters responsible for the selectivity and yield of glycosidation reactions, our efforts centered on the development of new glycosyl donors. We were intrigued by the feasibility of using the phosphorus-containing leaving groups,[3] on the prospect that a number of variations of substituents on the phosphorus atom could make "tailor-made glycosyl donors" readily available. We recently developed efficient methods for the stereocontrolled construction of 1,2-*trans*-glycosidic linkages by the device of shelf-stable glycosyl donors incorporating diphenyl phosphate[4] or *P,P*-diphenyl-*N*-(*p*-toluenesulfonyl)phosphinimidate[5] as leaving groups. Herein, we wish to report on an extremely mild and general procedure for the stereocontrolled construction of 1,2-*cis*-glycosidic linkages exploiting *S*-glycopyranosyl *N,N,N',N'*-tetramethyl-*N''*-phenylphosphorodiamidimidothioates with a non-participating *O*-2-benzyl group as glycosyl donors.

Construction of 1,2-*cis*-glycosidic linkages in a stereocontrolled manner has been the focus of much recent attention.[6] We envisaged that this challenging problem could be solved by judicious choice of substituents on the phosphorus atom in the leaving groups and promoters in favor of S_N2-like mechanism, thus focusing on the readily available 1,2-*trans*-related 1-thio-glycopyranose bearing a non-participating benzyl group on *O*-2 as the source of the glycosyl donors. After considerable experimentation, it was found that coupling of *S*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-*N,N,N',N'*-tetramethyl-*N''*-phenylphosphorodiamidimidothioate **1**[7] (1.1 equiv.) with suitably protected glycosides **6**,**7**,**9**, and**10** (1.0 equiv.) in toluene in the presence of 2,6-lutidinium *p*-toluenesulfonate (LPTS)[9] (1.15 equiv.) and pulverized molecular sieves 4A at 23 °C proceeded under kinetic control to lead to the preponderant formation of 1,2-*cis*-linked disaccharides (entries 1, 4, 7, 9, and 11 in Table 1). The combination of LPTS as a promoter[10] and toluene

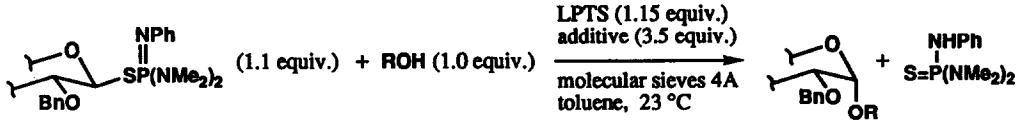


as a solvent proved to be the superior choice for allowing considerable levels of 1,2-*cis*-selectivity as well as extremely mild reaction conditions, with which the acid-labile groups such as epoxy, acetal, or *O*-tert-butyldimethylsilyl groups are completely comparable.

Although the 1,2-*cis*-glycosidation reactions developed here involved several features,[11] the stereoselectivity was not necessarily satisfactory in view of the requisite levels for current synthetic carbohydrate chemistry. In an effort to enhance the degrees of the stereoselectivity, we reasoned that if this method could be coupled with Lemieux's glycosidation method[6a] *via* halide ion catalyzed process, the new version would constitute an extremely mild procedure for the highly stereocontrolled construction of 1,2-*cis*-glycosidic linkages. However, the glycosidation of **1** with **6** or **7** in the presence of tetrabutylammonium bromide, the most widely used additive,[6c,j,k] took much longer reaction times than the original method, though 1,2-*cis*-selectivity of up to 96% was attained (entries 2 and 5). In stark contrast, we were pleased to find that this goal could be readily achieved by the use of tetrabutylammonium iodide as an additive. As seen from Table 1, the new version required almost the same reaction times as the original procedure, but afforded even higher levels of 1,2-*cis*-selectivity (entries 3, 6, 8, 10, and 12).[14] It should be noted that this is the first successful use of tetrabutylammonium iodide as an additive. Apart from α-D-glucosylation, the method was advantageously extended to α-D-galactosylation and α-L-fucosylation (entries 18-22), in which toluene-CH_2Cl_2 (1:1) proved to be the solvent of choice. Furthermore, the mildness and generality of this method was demonstrated by a range of variations possible in glycosyl donors and acceptors.

In conclusion, the present method based on *S*-glycopyranosyl phosphorodiamidimidothioates constitutes an exceptionally mild procedure for the highly stereocontrolled construction of 1,2-*cis*-glycosidic linkages, and thus represent a promising addition to the existing methods. Further extension of this method to the construction of carbohydrate-containing natural products and analogues of medicinal importance are currently in progress in these laboratories.

Table1. 1,2-*cis*-Glycosidation reaction of *S*-glycopyranosyl phosphorodiamidimidothioates 1-5



entry	donor	acceptor	additive	time, h	yield,[a] %	α : β [b]	δ ^{13}C [c,d]	$[\alpha]_D^{23}$/°(c, $CHCl_3$)[c]	ref.
1	1	6	—	16	85	80:20	97.3	+58.2 (1.12)	6b
2	1	6	Bu_4NBr	48	82	94:6			
3	1	6	Bu_4NI	16	83	91:9			
4	1	7	—	55	71	86:14	96.6	+46.2 (1.20)	6b
5	1	7	Bu_4NBr	96	72	96:4			
6	1	7	Bu_4NI	55	72	93:7			
7	1	9	—	55	72	87:13	95.5	+50.0 (0.97)	
8	1	9	Bu_4NI	55	76	91:9			
9	1	10	—	55	75	86:14	96.3	+24.7 (0.83)	
10	1	10	Bu_4NI	55	77	93:7			
11	1	11	—	55	72	87:13	96.9	+29.9 (1.31)	6e
12	1	11	Bu_4NI	55	73	92:8			
13	1	12	Bu_4NI	55	73	94:6	98.0	+44.9 (1.15)	6b
14	1	14	Bu_4NI	55	80	93:7	98.0	+32.9 (1.12)	6i
15	1	15[e]	Bu_4NI	55	79	>99:1	94.8	+284.7 (0.55)	
16	2	11	Bu_4NI	55	74	>99:1	96.3	+18.4 (1.12)	
17	3	11	Bu_4NI	55	72	94:6	96.3	+28.0 (1.02)	
18[f]	4	8	Bu_4NI	55	70	93:7	97.5	+18.2 (1.50)	6k
19[f]	4	11	Bu_4NI	55	71	92:8	98.3	+15.3 (0.38)	
20[f]	4	13	Bu_4NI	10	73	91:9	97.6	+3.2 (1.32)	6g
21[f]	5	8	Bu_4NI	55	72	93:7	97.7	-38.1 (1.12)	6k
22[f]	5	12	Bu_4NI	55	70	94:6	96.8	-95.3 (0.73)	6a

[a] Isolated total yield. [b] Determined by HPLC and ^{13}C NMR(100 MHz, $CDCl_3$) analysis. [c] Values for the 1,2-*cis*-linked glycosides or disaccharides purified by flash chromatography on silica gel. [d] Chemical shifts for the anomeric centers newly formed. [e] C-7 hydroxy group was glucosylated. [f] Performed in toluene-CH_2Cl_2 (1:1).

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7. The 1,2-*trans*-related *S*-glycopyranosyl phosphorodiamidimidothioates **1-5** were prepared from the corresponding 2,3,4,6-tetra-*O*- or 2,3,4-tri-*O*-protected glycopyranoses in 56-63% overall yields by the following sequence: (1) MsCl, 2,6-lutidine, CH_2Cl_2, 23 °C, 10 h; (2) KSC(=S)OEt, benzene-EtOH (2:1), 23 °C, 8 h; (3) NaOMe, MeOH, 40 °C, 1 h; (4) *n*-BuLi (1.1 equiv.), THF, -78 °C, 0.5 h; $PhN{=}P(NMe_2)_2Cl$[8] (1.1 equiv.), HMPA, 23 °C, 3 h . These donors can be stored without decomposition in the freezer (at -20 °C) for several months
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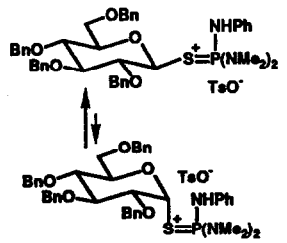
10. The corresponding 2,4,6-collidinium salt (CPTS) was almost equally effective, but the use of the pyridinium salt (PPTS) met with less success.

protonation of the nitrogen atom with LPTS, which are in equilibrium *via* glycopyranosyl tosylate[12] in favor of the β- salt due to the reverse anomeric effect,[13] followed by the back side attack with acceptor alcohols on these intermediates. In less polar toluene, the nucleophilic displacement by cyclohexylmethanol is competitive with the anomeric equilibration of the salts, and thus much higher 1,2-*cis*-selectivity is obtained from **1** than from **1'**. On the other hand, the attack of cyclohexanol is slow compared to the equilibration, **1** exhibiting slightly higher selectivity than **1'**. In more polar dichloromethane, since the equilibrium is reached prior to the attack by alcohols, the almost unchanged ratios are attained regardless of the anomeric configuration of the donors and alcohols.

entry	donor	ROH	solvent	time, h	yield, %	α : β
1	**1**	*c*-$C_6H_{11}CH_2OH$	toluene	10	83	82 : 18
2	**1'**	*c*-$C_6H_{11}CH_2OH$	toluene	10	84	60 : 40
3	**1**	*c*-$C_6H_{11}OH$	toluene	15	85	88 : 12
4	**1'**	*c*-$C_6H_{11}OH$	toluene	15	83	78 : 22
5	**1**	*c*-$C_6H_{11}CH_2OH$	CH_2Cl_2	10	78	77 : 23
6	**1'**	*c*-$C_6H_{11}CH_2OH$	CH_2Cl_2	10	79	76 : 24
7	**1**	*c*-$C_6H_{11}OH$	CH_2Cl_2	15	77	79 : 21
8	**1'**	*c*-$C_6H_{11}OH$	CH_2Cl_2	15	76	80 : 20



12. Glycosidation of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl tosylate with cyclohexylmethanol or cyclohexanol in toluene was found to result in the α:β ratio of 52:48 and 54:46, respectively.
13. A. J. Kirby, "*The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*," Springer-Verlag, New York, 1983, pp. 15-17.
14. The glycosidation is thought to proceed *via* the glycopyranosyl iodide generated *in situ*. For the limited use of glycopyranosyl iodide derivatives as glycosyl donors, see: F. K. Kronzer and C. Schuerch, *Carbohydr. Res.*, **34**, 71 (1974).

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