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A Stereocontrolled Construction of 2-Deoxy-β-glycosidic Linkages *via* 1,2-*trans*-β-Glycosidation of 2-Deoxy-2-[(*p*-methoxyphenyl)thio]glycopyranosyl *N,N,N',N'*-Tetramethylphosphoroamidates

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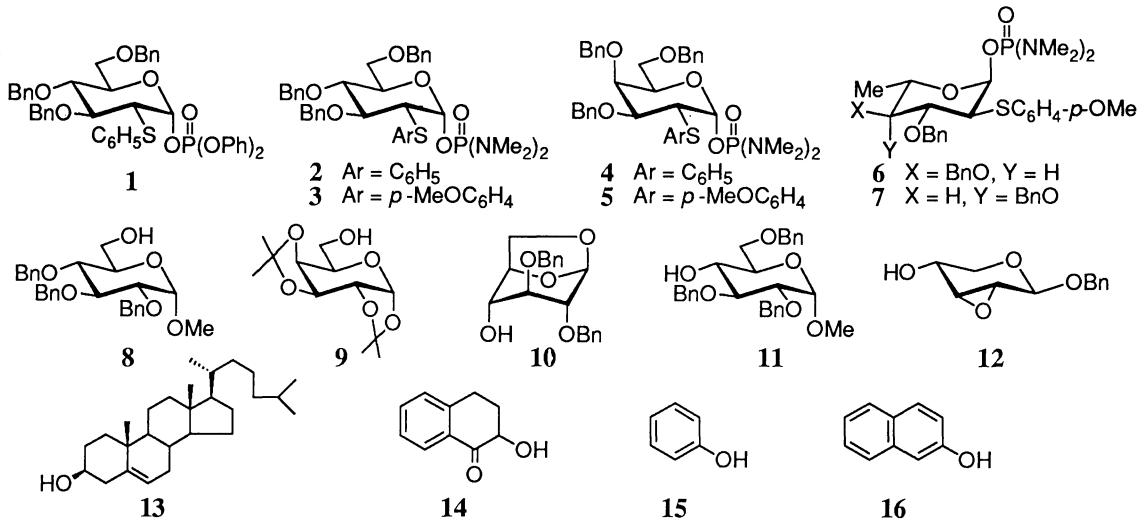
A stereocontrolled synthesis of 2-deoxy-β-glycosides has been achieved by developing a salient 1,2-*trans*-glycosidation method with 2-deoxy-2-[(*p*-methoxyphenyl) thio]glycopyranosyl *N,N,N',N'*-tetramethylphosphoroamidates as glycosyl donors followed by a reductive removal of the *p*-methoxyphenylthio group with Raney nickel. The *p*-methoxyphenylthio group equatorially disposed at C-2 has proven to be an excellent stereodirecting auxiliary.

The increasingly recognized importance of 2-deoxy sugars as integral constituents of numerous natural products of biological significance, inter alia, antitumor antibiotics including aureolic acid, orthosomycin, anthracycline, and calicheamicin/esperamicin families, has spurred development of expeditious methods for the stereocontrolled construction of α or β-linked 2-deoxyglycosides.[1-5] With regard to the stereocontrolled formation of the 2-deoxy-α-glycosidic linkages,[1,2] electrophile-mediated addition of the acceptor alcohols to the double bond of glycals followed by a reductive removal of the substituents at C-2 constitutes a general and convenient method.[1] Despite the great deal of work, however, the construction of the 2-deoxy-β-glycosidic linkages still remains a formidable problem in terms of efficacy, generality, and stereocontrol. As part of a program to develop new glycosidation methods capitalizing on the phosphorus-containing leaving groups,[6] we now wish to report a highly stereocontrolled construction of the 2-deoxy-β-glycosidic linkages in the 2-deoxy series of D-gluco-, D-galacto-, L-rhamno-, and L-fucopyranosides, in which a key feature of the glycosidation is the combination of shelf-stable glycosyl donors incorporating *N,N,N',N'*-tetramethylphosphoroamidate as a leaving group and the *p*-methoxyphenylthio group equatorially disposed at C-2 as a stereodirecting auxiliary.

Among several approaches to 2-deoxy-β-glycosides,[3,4] the most dominant methods involve 1,2-trans-glycosidation with neighboring group participation by equatorially installed 2-substituents such as bromo, phenylthio, or phenylseleno groups followed by a reductive removal of such groups.[3] Considering the ready access to benzyl-protected 2-deoxy-2-(phenylthio)glycopyranose[3c] coupled with the facile incorporation of diphenyl phosphate as a leaving group,[6a] we first examined the glycosidation of 3,4,6-tri-*O*-benzyl-2-deoxy-2-phenylthio-α-D-glucopyranosyl diphenyl phosphate (**1**) with cyclohexanol. Although the coupling in dichloromethane in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (1.3 equiv.) at -78 °C proceeded to completion within 10 min to afford the corresponding 1,2-*trans*-β-glucoside with the α:β ratio of 3:97 and in 91% yield, poor shelf-stability of the phosphate precluded further development. To overcome this problem, we planned to change the leaving group from the diphenyl phosphate to the recently introduced *N,N,N',N'*-tetramethylphosphoroamidate.[7] As might be expected, the 2-deoxy-2-phenylthio-α-D-glucopyranosyl

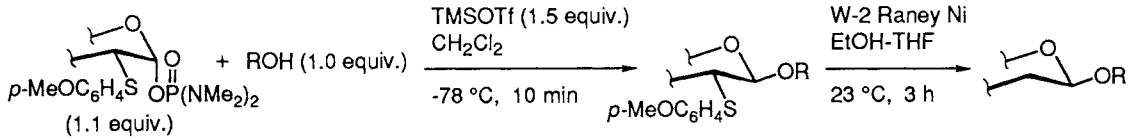


phosphoroamidate **2** was found not only to be quite stable and easily handled but also to give the similar results under the above glycosidation conditions. On this positive result, our model studies were then directed to the construction of 2-deoxy-β-D-galactosidic linkage. However, the glycosidation of the 2-deoxy-2-phenylthio-α-D-galactopyranosyl phosphoroamidate **4** with cyclohexanol under the foregoing conditions resulted in less satisfactory stereoselectivity (α:β=13:87). At this point, we reasoned that by switching the phenylthio group to the more powerfully participating *p*-methoxyphenylthio group, much higher levels of β-selectivity could be achieved. Indeed, we found that glycosidation of the 2-deoxy-2-(*p*-methoxyphenyl)thio-α-D-galactopyranosyl phosphoroamidate **5**[8] with cyclohexanol gave the α:β ratio of 8:92, and virtually complete stereocontrol (α:β=<1:>99) was attained with the 2-deoxy-2-(*p*-methoxyphenyl)thio-α-D-glucopyranosyl phosphoroamidate **3**.

Armed with these results, we then applied this method to the construction of the 2-deoxy-β-glycosidic linkages from a range of 2-deoxy sugars and acceptor alcohols with different reactivities. Some representative results are summarized in Table 1. Among a variety of Lewis acids screened, TMSOTf was found to be the best choice for allowing extremely rapid and high-yielding glycosidation at -78 °C, under the conditions of which the acid-sensitive alcohols were safely glycosylated. It should be noted that the glycosidations of **3** and **6** with phenolic and acyloin aglycons found in the aureolic acid antibiotics as well as the more common sugar alcohols led to the virtually exclusive formation of the corresponding 1,2-*trans*-β-linked glycosides or disaccharides, whereas the stereoselectivities of those of **5** and **7** bearing axial substituents at C-4 were found to be satisfactory only with the alcohols but not with phenols.[10] It is also worthy of note that the superiority of the present glycosidation to Schmidt's trichloroacetimidate procedure[3c] is manifested through glycosylation of the acceptor alcohol **10** (α:β ratio: <1:>99 vs. 1:3). Exposure of the glycosides or disaccharides on W-2 Raney nickel[11] in ethanol at 23 °C led to conversion to the 2-deoxy-β-glycosides or 2'-deoxy-β-disaccharides with high anomeric purities, in which the reductive removal of the *p*-methoxyphenylthio group in the glycoside of 2-naphthol (**16**) could be carried out in only low yield due to the formation of 3,4,6-tri-*O*-benzyl-D-glucal as a by-product.

A typical procedure is illustrated as follows (Table 1, entry 3): TMSOTf (1.0 M in dichloromethane, 0.23 ml) was added to a stirred solution of the donor **3** (114 mg, 0.162 mmol) and the acceptor **10** (50 mg, 0.146 mmol) in dichloromethane (2 ml) at -78 °C under an argon atmosphere. After 10 min of stirring at this temperature, the mixture was quenched with triethylamine (0.2 ml). The whole mixture was partitioned between ethyl acetate (30 ml) and satd. $NaHCO_3$ solution (5 ml), and the separated organic layer was washed with brine,

Table 1. Synthesis of 2-deoxy-β-glycopyranosides *via* glycosidation of 2-deoxy-2-[(*p*-methoxyphenyl)thio]-glycopyranosyl *N, N, N', N'*-tetramethylphosphoroamidates[a)]



			Glycoside			2-Deoxy-β-glycoside		
Entry	Donor	Acceptor	Yield/%	α : β[b)]	$[\alpha]_D^{23}$/°(*c*, $CHCl_3$)[c)]	Yield/%	δ ^{13}C[d)]	$[\alpha]_D^{23}$/°(*c*, $CHCl_3$)
1	**3**	**8**	95	<1 : >99	+0.2 (1.90)	76	100.0	+21.4 (1.21)
2	**3**	**9**	93	<1 : >99	-62.2 (1.84)	72	100.4	-53.1 (1.91)
3	**3**	**10**	95	<1 : >99	-68.0 (1.64)	74	98.7	-36.2 (1.46)
4	**3**	**11**	94	<1 : >99	-32.4 (2.01)	72	99.9	+15.2 (1.61)
5	**3**	**12**	96	<1 : >99	-10.9 (1.70)	75	99.0	-17.0 (1.32)
6	**3**	**13**	64	<1 : >99	-5.7 (1.82)	68	98.0	-30.5 (1.66)
7	**3**	**14**	97	<1 : >99	—[e)]	62	97.4, 99.7	—[e)]
8	**3**	**16**	90	3 : 97	+12.3 (1.95)	42	97.9	-49.4 (1.32)
9	**5**	**8**	84	9 : 91	+7.3 (1.34)	69	100.8	+7.4 (1.40)
10	**5**	**11**	81	11 : 89	-9.0 (1.70)	62	100.5	-3.0 (1.83)
11	**5**	**13**	65	8 : 92	-7.0 (1.78)	70	98.4	-42.1 (1.12)
12	**6**	**11**	85	<1 : >99	+62.4 (1.55)	64	100.4	+14.3 (1.00)
13	**6**	**14**	97	2 : 98	—[e)]	60	97.2, 99.4	—[e)]
14	**6**	**15**	87	3 : 97[f)]	—	61	97.3	—
15	**7**	**9**	90	11:89	-37.8 (1.83)	72	101.1	-22.0 (1.54)

a) The reaction was carried out according to the typical experimental procedure, unless otherwise stated. b) The ratio was determined by HPLC and 400 MHz ^1H NMR. c) Values for the β-glycosides or disaccharides purified by flash chromatography (silica gel) or recrystallization. d) Chemical shifts (δ ppm) in ^{13}C NMR (100 MHz, $CDCl_3$) for the anomeric centers newly formed. e) Due to the epimeric mixture at C-2' in the acyloin moiety, optical rotation was not taken. f) An anomeric mixture was not separated.

and then dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product, which was purified by chromatography (silica gel, 5:2 hexane-ethyl acetate) to give the corresponding 1,2-*trans*-β-linked disaccharide (125 mg, 95%) as a pale yellow caramel. To a stirred solution of the disaccharide (80 mg, 0.089 mmol) in THF (1 ml) was added W-2 Raney nickel (4 ml of sediment in ethanol) in three portions over 2 h at room temperature. After 1 h, the mixture was diluted with THF (10 ml), and the catalyst was filtered off. Concentration of the filtrate *in vacuo* followed by chromatography (silica gel, 3:1 hexane-ethyl acetate) afforded the target 2'-deoxy-β-disaccharide (50 mg, 74%) as a colorless caramel.

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8) The glycosyl donors used here were prepared from the corresponding glycopyranoses obtained by addition of *p*-methoxyphenylsulfenyl chloride[9] to the benzyl-protected glycals followed by hydrolysis according to the method of Schmidt[3c] (*n*-BuLi (1.05 equiv.), THF, -78 °C, 20 min; $O=P(NMe_2)_2Cl$ (1.01 equiv.), HMPA, -40 °C, 2 h, ca. 80%).

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10) Glycosidation of **5** with **15** and **16** gave the aryl galactopyranosides with the α:β ratio of 73:27 and 72:28, respectively. Coupling of **7** with **15** led to the predominant formation of the phenyl α-fucopyranoside (α:β=90:10).

11) W-2 Raney nickel used in the case of the glycosides of the phenolic and acyloin aglycons was prepared according to the well-established protocol.[12] In the other cases, however, the catalyst modified by shortening the digestion time to 1.5 h at 100 °C was used.

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