New Synthetic Methods and Reagents for Complex Carbohydrates. IX. Aryl D-Glucopyranosides and 1-Aryl-1-deoxy-D-glucopyranoses from 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl Dimethylphosphinothioate

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Synopsis. The reactions of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl dimethylphosphinothioate and phenolic compounds gave the corresponding aryl α-D-glucopyranosides predominantly in good yields, even when the trimethylsiloxy derivatives of benzene, which are known to afford 1-aryl-1-deoxy-D-glucopyranoses by the conventional methods, were used as acceptors. On the other hands, 1-ary-1-deoxy-β-D-glucopyranose was obtained in good yield when 1,3,5-trimethoxybenzene was used as an acceptor.

Aryl glycosides and glycosylphenols are widely found in natural products.[1] Much attention has been paid to the unique structures of these glycosides, and the syntheses of these compounds have become an active area of research. The glycosidation of phenols using the classical method[2] gave aryl glycosides in only low yields. Although several new aryl glycosidation using glycosyl fluoride,[3,4] glycosyl sulfoxide,[5] etc.[6] have been reported, the yields were not necessarily high in spite of the use of excesses of substrates and activators. Several Friedel–Crafts-type *C*-glycosylation reactions[7] and *O*→*C* glycoside rearrangements[8] have been also reported. These reactions were done in good yields, but excesses of nucleophiles or strong Lewis acids were required.

We have already reported a series of glycosidations by the glycosyl dimethylphosphinothioates.[9] The glycosyl dimethylphosphinothioates are very stable, and easily reacted with alcohols (1 equiv) under the mild conditions using silver perchlorate (1 equiv) as an activator in benzene at room temperature. In this paper, we describe the reactivities of 2,3,4,6-tetra-*O*-benzyl-α-D-glycopyranosyl dimethylphosphinothioate and phenolic compounds.

Results and Discussion

First, we examined the reaction of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl dimethylphosphinothioate (**1**)[9a,9e] and phenol (1 equiv) using silver perchlorate ($AgClO_4$) (1 equiv) as an activator in the presence of molecular sieves (MS) 4A in benzene. Phenyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**2**) was obtained in 75% yield with an anomer ratio of $\alpha/\beta=58/42$ (Fig. 1).

Similarly, the reaction of **1** using 4-methoxyphenol or 1-naphthol as acceptors gave the corresponding aryl α-D-glucopyranosides predominantly in 79% and 65% yields, respectively. However, the glucosidation of **1** and 2,6-dimethylphenol gave the corresponding glucopyranoside in only 37% yield. This poor yield was considered to be due to the hindered hydroxyl function of 2,6-dimethylphenol.

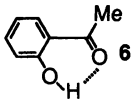
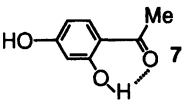
By the way, the glucosidation of **1** and 2′-hydroxyacetophenone (**6**) having the phenolic hydroxyl group hydrogen-bonded to carbonyl group using $AgClO_4$ failed to happen. It is well-known that the phenolic hydroxyl groups with intramolecular hydrogen bonds have less reactivity for the glycosidation.[4] For this reason, the glucosidation of **1** and 2′,4′-dihydroxyacetophenone (**7**) (1 equiv) using $AgClO_4$ (1 equiv) gave 4-acetyl-3-hydroxyphenyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**8**) in 68% yield with an anomer ratio of $\alpha/\beta=65/35$ regioselectively without forming 2-acetyl-5-hydroxyphenyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside.

During these reactions, glycosylphenols by the *O*→*C* glycoside rearrangement[8] could not be detected. These results are given in Table 1.

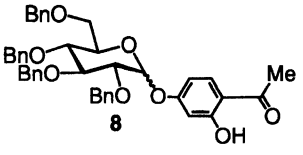
Secondly, we tried the Fredel–Crafts type reaction of **1** and alkoxy aromatic compounds. The reaction of **1** and 1,3,5-trimethoxybenzene (2 equiv) using $AgClO_4$ (1 equiv) as an activator in the presence of MS 4A gave the corresponding 2-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1,3,5-trimethoxybenzene (**9**) in 69% yield stereoselectively.

Similarly, we examined the reaction of **1** and alkoxy

Table 1. The Reactions of **1** and Several Phenols

Entry	Phenols	Product	Yield/%	α/β Ratio[a]
1	Phenol	**2**	75	58/42
2	4-Methoxyphenol	**3**	79	65/35
3	1-Naphthol	**4**	65	73/27
4	2,6-Dimethylphenol	**5**	37	50/50
5	 **6**		—	
6	 **7**	8[b]	68	65/35

a) The ratios were determined by the isolated yields.
b) The structure of **8** was below.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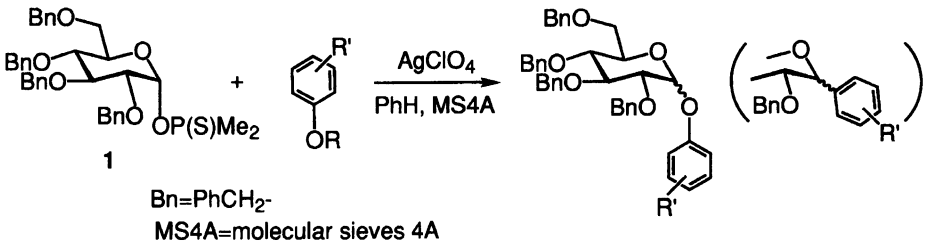
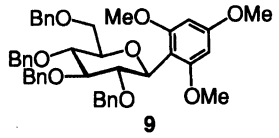
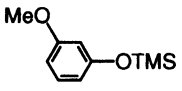
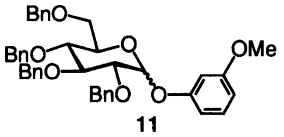
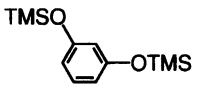
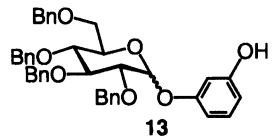
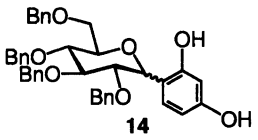


Fig. 1. Glucosidation of **1** and several aromatic compounds using $AgClO_4$.

Table 2. The Reaction of **1** and Alkoxy Aromatic Compounds

Entry	Aryl compounds	Product	Yield/%	α/β Ratio
1	1,3,5-Trimethoxybenzene	 **9**	69 (47)[a]	β
2	1,3-Dimethoxybenzene	No Reaction		
3	 **10**	 **11**	74	67/33[b]
4	 **12**	 **13**	44[c]	65/35[b]

a) The yield using 1 equiv amount of 1,3,5-trimethoxybenzene. b) Determined by the measurement of ^{1}H NMR. c) Compound **14** was obtained in 16% yield.


14

aromatic compounds (1 equiv) such as 1,3-dimethoxybenzene, 1-methoxy-3-(trimethylsiloxy)benzene (**10**), and 1,3-bis(trimethylsiloxy)benzene (**12**) using $AgClO_4$ (1 equiv). These derivatives were used as acceptors for *C*-glycosylation reaction by several conventional methods.[10] The reaction of **1** and 1,3-dimethoxybenzene could not proceed, however, the glucosidation using **10** as an acceptor gave 3-methoxyphenyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**14**) in 74% yield with an anomer ratio α/β=67/33. When compound **12** was used as an acceptor under similar reaction conditions, 4-hydroxyphenyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**13**) and 4-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-1,3-benzenediol (**14**) were obtained in 44 and 16% yields, respectively. These results are given in Table 2.

As mentioned above, the reactions of **1** using 1 equiv portions of phenolic compounds and $AgClO_4$ gave the glucosides. Even when the trimethylsiloxy derivatives of benzene, which are known to afford 1-aryl-1-deoxy-D-glucopyranose by the conventional methods, were used as acceptors, the glucosides could be obtained predominantly. It was found that the reactivity of *C*-nucleophiles for **1** was lower than those of *O*-nucleophiles.

Experimental

The melting points were measured with a Laboratory Devices MEL-TEMP apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL FX-90A and EX-400 spectrometers with tetramethylsilane used as an internal standard in $CDCl_3$. The optical rotations were recorded on a JASCO DIP-360 digital polarimeter using a 0.1 dm cell.[11]

General Glucosidation Procedure. To a benzene solution (2 ml) of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl dimethylphosphinothioate (**1**) (0.2 mmol) and phenols (0.2 mmol) {or dialkoxybenzene (0.2 mmol) or 1,3,5-trimethoxybenzene (0.4 mmol)} was added silver perchlorate (0.2 mmol) in the presence of molecular sieves 4A (ca. 100 mg);

the mixture was stirred overnight in a dark place. A 5% sodium sulfide solution and ethyl acetate was added to the reaction mixture. The insoluble materials were filtered off, and the filtrate was extracted with ethyl acetate. The organic layer was washed with a 5% sodium sulfide solution and a saturated NaCl solution, and then dried over anhydrous sodium sulfate. The extracts were filtered, and concentrated in vacuo to afford the crude glucoside. The residue was purified by thin-layer chromatography on silica gel. The yields and the anomer ratios are given in Tables 1 and 2.

Phenyl 2,3,4,6-Tetra-*O*-benzyl-α- and β-D-glucopyranoside (2): The anomers were separated by thin-layer chromatography (diisopropyl ether/hexane=1/2). α Anomer: $[\alpha]_D^{24}$ +74.1° (*c* 1.89, $CHCl_3$); ^{13}C NMR δ=95.6 (C-1) (lit,[6b] $[\alpha]_D^{20}$ +82° (*c* 2.0, $CHCl_3$); ^{13}C NMR δ=95.4 (C-1)). β Anomer: $[\alpha]_D^{24}$ −5.9° (*c* 1.2, $CHCl_3$); ^{13}C NMR δ=101.8 (C-1) (lit,[6b] $[\alpha]_D^{20}$ −9° (*c* 1.0, $CHCl_3$); ^{13}C NMR δ=101.6 (C-1)).

4-Methoxyphenyl 2,3,4,6-Tetra-*O*-benzyl-α- and β-D-glucopyranoside (3): The anomers were separated by thin-layer chromatography ($CHCl_3$/hexane=3/2). α Anomer: $[\alpha]_D^{24}$ +87.1° (*c* 2.48, $CHCl_3$); ^{13}C NMR δ=96.5 (C-1) (lit,[6b] $[\alpha]_D^{20}$ +92° (*c* 1.0, $CHCl_3$); ^{13}C NMR δ=96.3 (C-1)). β Anomer: $[\alpha]_D^{24}$ +14.1° (*c* 1.56, $CHCl_3$); ^{13}C NMR δ=102.9 (C-1) (lit,[6a] $[\alpha]_D^{20}$ −2.4° (*c* ca. 0.5, $CHCl_3$); ^{13}C NMR δ=102.6 (C-1)).

1-Naphthyl 2,3,4,6-Tetra-*O*-benzyl-α- and β-D-glucopyranoside (4): The anomers were separated by thin-layer chromatography ($CHCl_3$/hexane=3/2). α Anomer: $[\alpha]_D^{24}$ +86.4° (*c* 2.32, $CHCl_3$); ^{13}C NMR δ=96.4 (C-1) (lit,[6b] $[\alpha]_D^{20}$ +72° (*c* 1.0, $CHCl_3$); ^{13}C NMR δ=96.3 (C-1)). β Anomer: $[\alpha]_D^{24}$ −25.8° (*c* 0.775, $CHCl_3$); ^{13}C NMR δ=101.6 (C-1) (lit,[6a] $[\alpha]_D^{20}$ −54.9° (*c* ca. 0.5, $CHCl_3$); ^{13}C NMR δ=101.3 (C-1)).

2,6-Dimethylphenyl 2,3,4,6-Tetra-*O*-benzyl-α- and β-D-glucopyranoside (5): The anomers were separated by thin-layer chromatography ($CHCl_3$/hexane=3/2). α Anomer: $[\alpha]_D^{24}$ +48.2° (*c* 1.14, $CHCl_3$); ^{13}C NMR δ=99.6 (C-1) (lit,[6b] $[\alpha]_D^{20}$ +46° (*c* 0.8, $CHCl_3$); ^{13}C NMR δ=99.5 (C-1)). β Anomer: $[\alpha]_D^{24}$ +39.7° (*c* 1.29, $CHCl_3$); ^{13}C NMR δ=104.2 (C-1) (lit,[6b] $[\alpha]_D^{20}$ +25° (*c* 1.0, $CHCl_3$); ^{13}C NMR δ=104.1 (C-1)).

4-Acetyl-3-hydroxyphenyl 2,3,4,6-Tetra-*O*-benzyl-α- and β-D-glucopyranoside (8): Found (α,β-mixture): C, 74.72; H, 6.49%. Calcd for $C_{42}H_{42}O_8$: C, 74.76; H, 6.72%. The anomers were separated by thin-layer chromatography ($CHCl_3$/hexane=1/1). α Anomer: $[\alpha]_D^{24}$ +128° (*c* 1.13, $CHCl_3$); mp 110—111 °C; ^1H NMR δ=12.61 (1H, OH), 5.43 (1H, d, *J*=3.4 Hz, H-1), 2.57 (3H, s, CH_3); ^{13}C NMR δ=202.8 (C=O), 95.0 (C-1, J_{CH}=171.0 Hz), 26.3 (CH_3). β Anomer: $[\alpha]_D^{24}$ +6.8° (*c* 0.59, $CHCl_3$); ^1H NMR δ=12.63 (1H, OH), 5.07 (1H, d, *J*=7.3 Hz, H-1), 2.57 (3H, s, CH_3); ^{13}C NMR δ=202.9 (C=O), 100.4 (C-1, J_{CH}=161.8 Hz), 26.4 (CH_3).

2-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-1,3,5-trimethoxybenzene (9): $[\alpha]_D^{24}$ +5.7° (*c* 1.4, $CHCl_3$); ^1H NMR δ=3.81 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.70 (3H, s, OCH_3); ^{13}C NMR δ=56.1 (OCH_3), 55.8 (OCH_3), 55.3 (OCH_3) (lit,[10a] $[\alpha]_D^{20}$ +5.4° (*c* 1.0, $CHCl_3$)).

3-Methoxyphenyl 2,3,4,6-Tetra-*O*-benzyl-α- and β-D-glucopyranoside (11): ^1H NMR δ=5.48 (d, *J*=3.9 Hz, H-1α), 5.00 (d, *J*=7.3 Hz, H-1β), 3.75 ($OCH_3\alpha$), 3.72 ($OCH_3\beta$); ^{13}C NMR δ=101.6 (C-1β, J_{CH}=161.7 Hz), 95.3 (C-1α, J_{CH}=171.0 Hz) (lit,[6b] ^{13}C NMR δ=95.4 (C-1α)).

3-Hydroxyphenyl 2,3,4,6-Tetra-*O*-benzyl-α- and β-D-glucopyranoside (13): ^1H NMR δ=5.41 (d, *J*=3.3 Hz, H-1α), 4.96 (d, *J*=6.8 Hz, H-1β); ^{13}C NMR δ=101.6 (C-1β, J_{CH}=163.6 Hz), 95.4 (C-1α, J_{CH}=171.0 Hz). Found (α,β-mixture): C, 73.25; H, 6.26%. Calcd for $C_{40}H_{40}O_7 \cdot H_2O$: C, 73.83, H, 6.51%. Compound **14**: ^{13}C NMR δ=73.5 (C-1α), 74.5 (C-1β) (lit,[10f] ^{13}C NMR δ=73.8 (C-1α), 74.8 (C-1β)).

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11) Several optical rotations did not agree with those of the literature. We assumed these differences could be caused by the following reasons; 1) the data were measured by the individual apparatus and cell length; 2) the elemental analyses in the literature did not agree; 3) a few data in the literature was not given an accurate concentration value.