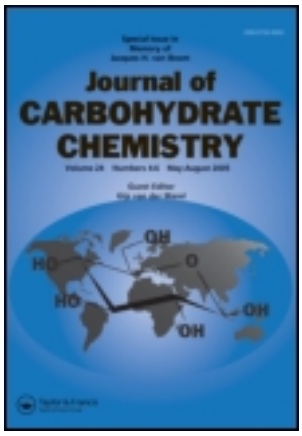

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PRACTICAL β-STEREOSELECTIVE O-GLYCOSYLATION OF PHENOLS WITH PENTA-O-ACETYL-β-D-GLUCOPYRANOSE

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COMMUNICATION

PRACTICAL β-STEREOSELECTIVE *O*-GLYCOSYLATION OF PHENOLS WITH PENTA-*O*-ACETYL-β-D-GLUCOPYRANOSE

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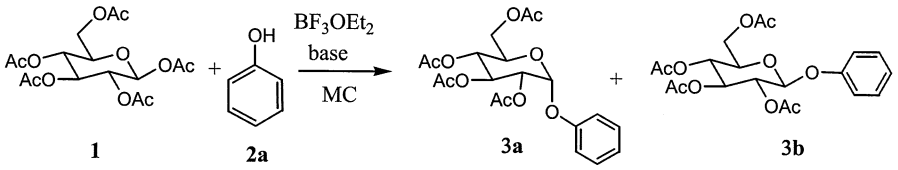
O-Glycosylation of phenol derivatives is an important synthetic method for natural products containing carbohydrate molecules.[1] Although various *O*-glycosylation methods have been studied in order to improve stereoselectivity and yield by changing the leaving groups, catalysts and solvents, previous methods are not always satisfactory in terms of ease and practicality.[1–7] Recently Oyama *et al.* reported the glycosylation of phenols with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl fluoride in the presence of $BF_3 \cdot OEt_2$ and hindered base in order to achieve high β-stereoselectivity.[7,8] However, it is not easy to obtain the starting glycosylating reagent, 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl fluoride.[8]

Compared to other leaving groups, an acetoxy group can be a very convenient anomeric leaving group in glycosylation reactions. For example penta-*O*-acetyl-β-D-glucopyranose can be prepared more easily than other glucosyl donors. We have therefore tried to develop a new β-stereoselective *O*-glucosylation of phenols by using penta-*O*-acetyl-β-D-glucopyranose. The results of our glycosylation experiments of phenol are shown in **Table 1**.

It is well known that the glycosylation of phenols with penta-*O*-acetyl-β-D-glucopyranose gives phenyl β-glucosides as major products, due to the neighbouring group effect of the 2-*O*-acetyl group. A serious drawback of the method is conversion to some extent of the kinetically stable phenyl β-glucoside **3b** into the thermodynamically stable α-anomer **3a** during the glycosylation reaction (entry 1).[9] However, glycosylation of phenol with penta-*O*-acetyl-β-D-glucose in the presence of $BF_3 \cdot Et_2O$ and organic base results in both high yield and high β-

Table 1. Glycosylation of Phenol with Penta-*O*-acetyl-β-D-glucopyranose



1 **2a** **3a** **3b**

	$BF_3{\cdot}OEt_2$ (eq)	base (eq)	rxn time (h)	yield[a] (%)	ratio[b] (**3a/3b**)
1	2.5	0	5.5	72	18/82
2	2.5	TEA (0.1)	3	89	7/93
3	2.5	TEA (0.5)	3	92	2/98
4	2.5	TMG[c] (0.5)	5	89	4/96
5	2.5	2,6-lutidine (0.5)	5.5	91	3/97
6	2.5	DTBMP[d] (0.5)	7	88	3/97
7	2.5	TEA (1)	5	87	3/97
8	1.5	TEA (1)	11	72	1/99
9	1.5	TEA (0.5)	5.5	87	2/98
10	4	TEA (2)	2	80	2/98
11	10	TEA (1)	0.5	92	9/91

a: isolated yield. b: isolated ratio. c: 1,1,3,3-tetramethylguanidine. d: 2,6-di-*tert*-butyl-4-methylpyridine.

stereoselectivity compared to glycosylation without organic base as shown in **Table 1**.

Glycosylation of phenol in the presence of 2.5 equivalents of $BF_3{\cdot}Et_2O$ and 0.5 equivalent of triethylamine to penta-*O*-acetyl-β-D-glucopyranose gave the highest yield and excellent β-stereoselectivity (entry 3). The addtion of more than 0.5 equivalent of triethylamine decreased the reaction rate and the yield, but still gave high β-stereoselectivity (entry 7). It is reported that base can abstract the proton quickly from the adduct intermediate cation[7] of phenol in the glycosylation of phenols with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl fluoride, and prevent isomerization of the β-isomer to the α-anomer.

We have also examined the glycosylation of several substituted phenols with penta-*O*-acetyl-β-D-glucopyranose (**Table 2**). As shown in **Table 2**, the glycosylation of phenols substituted with an electron withdrawing group retarded the reaction rate (**2h**-**2j**). The reaction rate was also affected by the location of substituent, the order of reaction rate being; ortho < meta < para, irrespective of substituent structure.

By taking advantage of this method, we have synthesized arbutin,[10] a widely used natural whitening agent. Deacetylation[11] of phenyl-β-glucoside **4b** with sodium methoxide in methanol affords arbutin as shown in the scheme below.

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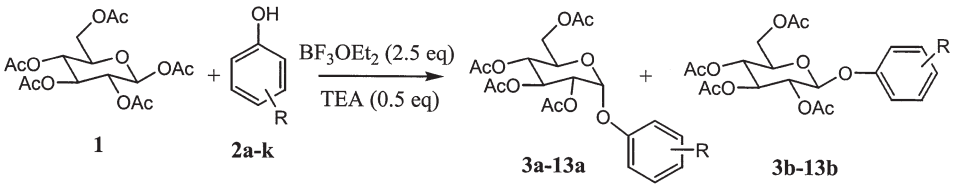
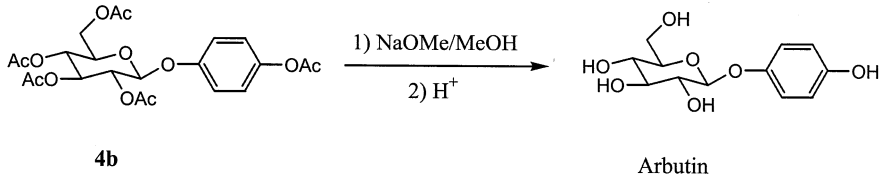
Table 2. Glycosylation of Several Phenols with Penta-*O*-acetyl-β-D-glucopyranose



2	R	rxn time (h)	yield (%)[a]	product ratio (α/β)[b]
a	H	3	92	**3a/3b**=2/98
b	4-CH_3COO	24	92	**4a/4b**=2/98
c	4-Cl	7	91	**5a/5b**=1/99
d	4-MeO	8	90	**6a/6b**=2/98
e	2-Br	27	86	**7a/7b**=1/99
f	3-Br	10	88	**8a/8b**=2/98
g	4-Br	6	91	**9a/9b**=2/98
h	2-NO_2 c	120	75	**10a/10b**=2/98
i	3-NO_2	92	86	**11a/11b**=1/99
j	4-NO_2	41	91	**12a/12b**=2/98
k	3-C_6H_5	3	83	**13a/13b**=2/98

a: The yields were isolated b: The ratios of α/β were determined by gas chromatography.
c: 5 equivalents of $BF_3 \cdot OEt_2$ and 1 equivalent of TEA were used.



4b Arbutin

Scheme.

EXPERIMENTAL

A typical procedure for the glucosylation is as follows: to a mixture of penta-*O*-acetyl-β-D-glucopyranose (10 mmol) and phenol derivative (15 mmol) under a nitrogen atomosphere, was added triethylamine (5 mmol) in methylene chloride (20 mL) and then $BF_3 \cdot OEt_2$ (25 mmol) in methylene chloride (5 mL) over 30 min. The reaction mixture was then kept stirring for the time shown in **Table 2.** Saturated aqueous sodium bicarbonate (20 mL) was added to the reaction mixture, and the reaction mixture was then extracted with ethyl acetate (30 mL × 2). The organic layer was dried over magnesium sulfate and the filtrate was concentrated in a vacuum evaporator. The residue was chromatographed on silica gel to give the phenyl glucoside product.

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