

**PERCHLORIC ACID IN 1,4-DIOXANE AND PERFLUORO-OCTANESULFONIC ACID AS PRACTICAL CATALYSTS FOR THE STEREOSELECTIVE GLYCOSYLATION OF 1-*O*-ACETYLGLYCOSIDES**

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**Abstract** – A perchloric acid solution in 1,4-dioxane and perfluorooctanesulfonic acid was found to be practical catalysts for the stereoselective glycosylation of 1-*O*-acetylglucosides. Either the  $\alpha$ - or  $\beta$ -anomer of the disaccharide, methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,5-tri-*O*-benzyl-D-ribofuranosyl)- $\alpha$ -D-glucopyranoside, was synthesized with complete stereoselectivities simply by changing the solvent. Epimerization of the kinetic product can effectively be suppressed in ether by the excess use of the polyoxygenated substrates.

1-*O*-Acylglycosides have been widely used as useful glycosyl donors for the glycosylation, and a number of Lewis acids have been invented for their activation.<sup>1</sup> Surprisingly, however, rather few have been reported for the Brønsted acid-catalyzed glycosylation since the classical Fisher method had been reported.<sup>2</sup> In connection with the mechanistic study of our lanthanoid(III) trifluoromethanesulfonate-catalyzed glycosylations,<sup>3,4</sup> we re-examined the effectiveness of triflic acid (TfOH) as a protonic acid-catalyst<sup>5</sup> for the glycosylation of 1-*O*-methoxyacetylglucopyranoside<sup>3</sup> with 1-octanol and found that it completed the reaction within 1 h at room temperature affording the corresponding glycoside in excellent yield. TfOH is, however, not easy to handle; it fumes in air and is highly corrosive. Therefore, from a practical point of view, we selected perfluorooctanesulfonic acid (PFOH, catalyst A) and also a 0.1 M perchloric acid solution in 1,4-dioxane<sup>6</sup> (catalyst B) as an alternative protonic acid catalyst since the former is a stable solid with less hygroscopicity than TfOH and the latter can be stored and conveniently used without loss of its activity, and both are commercially available.<sup>7</sup>

The glycosylations of acetyl 2,3,4,6-tetra-*O*-benzyl- $\alpha$ -D-glucopyranoside (**1**) and acetyl 2,3,5-tri-*O*-benzyl- $\beta$ -D-ribofuranoside (**2**) with various glycosyl acceptors were carried out in the presence of catalyst A or B. As shown in Tables 1 and 2, the primary, secondary and sugar alcohols, phenols, and thiols could be used as effective glycosyl acceptors, and the corresponding *O*- and *S*-glycosides were obtained in excellent yields.<sup>8</sup> The formation of  $\beta$ -glycosides generally dominated in acetonitrile<sup>9</sup> while  $\alpha$ -glycosides were dominant in ether<sup>10</sup> as previously reported. The glycosylation in acetonitrile proceeded rapidly and

Table 1. Glycosylation in MeCN<sup>a</sup>

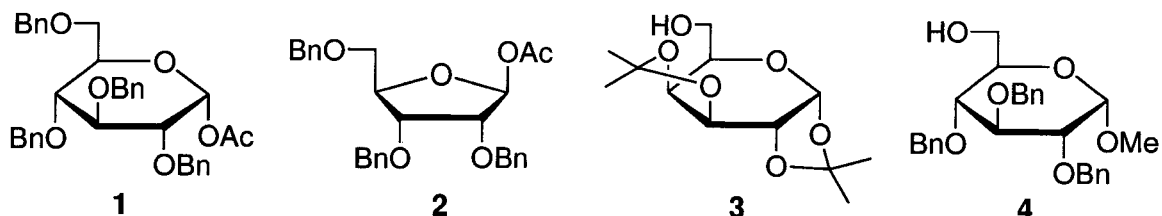
Run	Donor	Acceptor	Catalyst	Time/h	Product	
					Yield/%	$\alpha / \beta$
1	<b>1</b>	1-octanol	A	0.5	98	30 : 70
2		1-octanol	B	3	97	14 : 86
3		<b>3</b>	A <sup>b</sup>	7	84	13 : 87
4		<b>4</b>	B <sup>c</sup>	0.5	94	32 : 68
5		cholesterol	A	1	95	18 : 82
6		6-bromo-2-naphthol	A	12	91	80 : 20 <sup>d</sup>
7		PhSH	B	0.5	99	55 : 45
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8		1-octanol	B	0.5	98	7 : 93
9	<b>2</b>	<b>3</b>	A <sup>b</sup>	0.5	98	$\beta$ only
10		<b>4</b>	A	0.5	95 (5)	$\beta$ only
11		<b>4</b>	B	0.5	95 (5)	$\beta$ only
12		cholesterol	A	0.5	98	6 : 94
13		PhSH	B	0.25	98 (6)	50 : 50

<sup>a</sup> The reactions were carried out at 23°C by using glycosyl donor (1 eq), acceptor (1.2 eq), and the catalyst A (0.1 eq) or B (0.05 eq) unless otherwise noted. <sup>b</sup> 0.3 eq. <sup>c</sup> 0.01 eq. <sup>d</sup> By the comparison with the authentic  $\beta$ -anomer derived from the commercial  $\beta$ -glycoside.

Table 2. Glycosylation in Et<sub>2</sub>O<sup>a</sup>

Run	Donor	Acceptor	Catalyst	Time/h	Product	
					Yield/%	$\alpha / \beta$
1	<b>1</b>	1-octanol	B	11 <sup>b</sup>	89	94 : 6
2		<b>4</b>	A	19 <sup>b</sup>	85	92 : 8
3		<b>4</b>	B	2	91	94 : 6
4		cyclohexanol	B	3.5	95	94 : 6
5		cholesterol	B	2	75	87 : 13
6		PhSH <sup>c</sup>	B	6	34 <sup>d</sup>	75 : 25
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7	<b>2</b>	1-octanol	B	0.5	98	15 : 85
8		<b>4</b>	B	2	90 (5)	$\alpha$ only
9		cholesterol	B	1	94	14 : 86
10		PhSH <sup>c</sup>	B	0.5 <sup>b</sup>	97 (6)	90 : 10

<sup>a</sup> The reactions were carried out at 35°C by using glycosyl donor (1 eq), glycosyl acceptor (1.2 eq), and the catalyst A (0.1 eq) or B (0.05 eq) unless otherwise noted. <sup>b</sup> At room temperature. <sup>c</sup> 1.0 eq. <sup>d</sup>  $\omega$ -Hydroxy- $\alpha, \alpha$ -dithiophenylacetal was obtained as a major by-product.



the stereochemistries of the products were not affected by the  $\alpha/\beta$  ratios of the starting glycosyl donors. Especially noteworthy is the completely stereoselective formation of disaccharide (**5**) in either the  $\alpha$ - (Run 8 in Table 2) or  $\beta$ -forms (Run 11 in Table 1) simply by choosing the solvent.<sup>11</sup> It is interesting to note that the reactions of **2** with 1-octanol or with cholesterol in ether (Runs 7 and 9 in Table 2) predominantly afforded the  $\beta$ -anomers though the related glycosylation with **4** exclusively yielded the  $\alpha$ -anomer (**5- $\alpha$** ). The production of the  $\beta$ -anomers seems to be the result of epimerization of the initially formed  $\alpha$ -anomers. In fact, the  $\alpha$ -rich product ( $\alpha/\beta=61:39$ ) was obtained in 55% yield when the reaction with cholesterol was stopped after 10 min. Furthermore, the epimerization test<sup>12</sup> of **5** and **6** under the conditions similar to the glycosylation revealed that the primary products are kinetic ones, and the epimerization of **5- $\alpha$**  can be suppressed by the excess use of the polyoxygenated substrates (Runs 2 and 3 in Table 3).

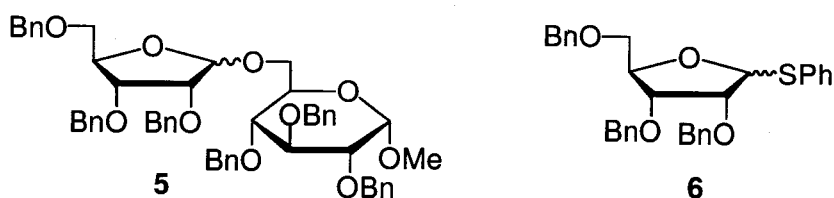


Table 3. Epimerization Test of **5** and **6**<sup>a</sup>

Run	Disaccharide	Additive	$\alpha/\beta$ ratio <sup>b</sup>
1	<b>5-<math>\alpha</math></b>	none	66 : 34
2	<b>5-<math>\alpha</math></b>	<b>2</b> (0.05 eq)	85 : 15
3	<b>5-<math>\alpha</math></b>	<b>4</b> (0.2 eq)	98 : 2
4	<b>5-<math>\beta</math></b>	none	$\beta$ only
5	<b>6-<math>\alpha</math></b>	none	$\alpha$ only
6	<b>6-<math>\beta</math></b>	none	$\beta$ only

<sup>a</sup> Conditions: 5 mol% HClO<sub>4</sub>, Et<sub>2</sub>O, reflux, 2 h. <sup>b</sup> Determined by <sup>1</sup>H-NMR.  $\alpha$ -Anomer:  $\delta$  5.14 (d, 1H,  $J=2.3$  Hz);  $\beta$ -anomer:  $\delta$  5.06 (d, 1H,  $J=0.99$  Hz) for **5**.  $\alpha$ -Anomer:  $\delta$  5.76 (d, 1H,  $J=5.4$  Hz);  $\beta$ -anomer:  $\delta$  5.45 (d, 1H,  $J=2.9$  Hz) for **6**.

In conclusion, a mild and convenient method for the highly stereoselective synthesis of disaccharides has been developed.

## EXPERIMENTAL

### Methyl 2,3,4-Tri-O-benzyl-6-O-(2,3,5-tri-O-benzyl- $\alpha$ -D-ribofuranosyl)-D-glucopyranoside (**5**)<sup>13</sup>

**5- $\alpha$** : To a mixture of **2** (462 mg, 1 mmol) and **4** (464 mg, 1.2 mmol) in dry ether (5 mL) was added a HClO<sub>4</sub> solution in 1,4-dioxane (0.1 mol dm<sup>-3</sup>, 0.5 mL, 5 mol%). After stirring for 2 h under reflux, the reaction mixture was treated with triethylamine (11  $\mu$ L, 0.79 mmol) then passed through a short column of silica gel and eluted with ether. The concentration of the eluate followed by purification using column chromatography on silica gel (hexane/ethyl acetate=5:1) afforded 779 mg (90%) of **5- $\alpha$** . Selected <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.14 (d, 1H,  $J=2.3$  Hz, 1'-H), 4.56 (d, 1H,  $J=3.6$  Hz, 1-H), 3.33 (s, 3H, -OCH<sub>3</sub>); FABMASS  $m/z$  (rel. intensity) 889 (M+Na, 60), 181 (100), 153 (10).

5- $\beta$ : This compound was prepared by using 10 mol% of PfoH (CH<sub>3</sub>CN, rt, 0.5 h) in 95% yield. Selected <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.06 (d, 1H,  $J=0.99$  Hz, 1'-H), 4.58 (d, 1H,  $J=3.6$  Hz, 1-H), 3.29 (s, 3H, -OCH<sub>3</sub>); FABMASS  $m/z$  (rel. intensity) 889 (M+Na, 38), 181 (100), 153 (33).

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