PERCHLORIC ACID IN 1,4-DIOXANE AND PERFLUOROOCTANESULFONIC 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*-acetylglycosides. Either the α- or β-anomer of the disaccharide, methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,5-tri-*O*-benzyl-D-ribofuranosyl)-α-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.[1] Surprisingly, however, rather few have been reported for the Brønsted acid-catalyzed glycosylation since the classical Fisher method had been reported.[2] In connection with the mechanistic study of our lanthanoid(III) trifluoromethanesulfonate-catalyzed glycosylations,[3,4] we re-examined the effectiveness of triflic acid (TfOH) as a protonic acid-catalyst[5] for the glycosyltion of 1-*O*-methoxyacetylglucopyranoside[3] 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[6] (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.[7]

The glycosylations of acetyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**1**) and acetyl 2,3,5-tri-*O*-benzyl-β-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.[8] The formation of β-glycosides generally dominated in acetonitrile[9] while α-glycosides were dominant in ether[10] as previously reported. The glycosylation in acetonitrile proceeded rapidly and

Table 1. Glycosylation in MeCN[a]

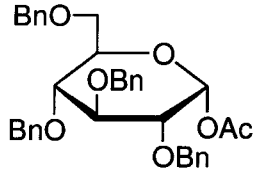
Run	Donor	Acceptor	Catalyst	Time/h	Product	
					Yield/%	α / β
1	**1**	1-octanol	A	0.5	98	30 : 70
2		1-octanol	B	3	97	14 : 86
3		**3**	A[b]	7	84	13 : 87
4		**4**	B[c]	0.5	94	32 : 68
5		cholesterol	A	1	95	18 : 82
6		6-bromo-2-naphthol	A	12	91	80 : 20[d]
7		PhSH	B	0.5	99	55 : 45
8		1-octanol	B	0.5	98	7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

[a] 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. [b] 0.3 eq. [c] 0.01 eq. [d] By the comparison with the authentic β-anomer derived from the commercial β-glycoside.

Table 2. Glycosylation in Et_2O[a]

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

[a] 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. [b] At room temperature. [c] 1.0 eq. [d] ω-Hydroxy-α,α-dithiophenylacetal was obtained as a major by-product.



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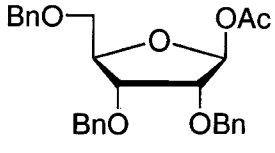

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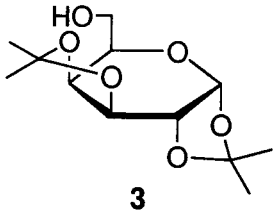

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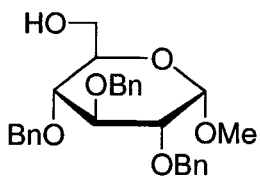

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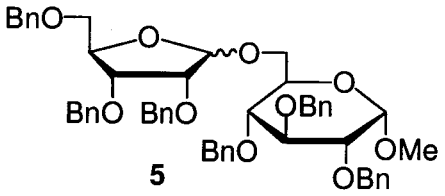
the stereochemistries of the products were not affected by the α/β ratios of the starting glycosyl donors. Especially noteworthy is the completely stereoselective formation of disaccharide (**5**) in either the α- (Run 8 in Table 2) or β-forms (Run 11 in Table 1) simply by choosing the solvent.[11] It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



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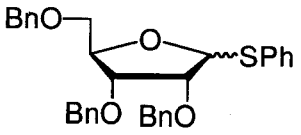

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Table 3. Epimerization Test of **5** and **6**[a]

Run	Disaccharide	Additive	α / β ratio[b]
1	**5**-α	none	66 : 34
2	**5**-α	**2** (0.05 eq)	85 : 15
3	**5**-α	**4** (0.2 eq)	98 : 2
4	**5**-β	none	β only
5	**6**-α	none	α only
6	**6**-β	none	β only

[a] Conditions: 5 mol% $HClO_4$, Et_2O, reflux, 2 h. [b] Determined by ^{1}H-NMR.
α-Anomer: δ 5.14 (d, 1H, *J*=2.3 Hz); β-anomer: δ 5.06 (d, 1H, *J*=0.99 Hz) for **5**.
α-Anomer: δ 5.76 (d, 1H, *J*=5.4 Hz); β-anomer: δ 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-α-D-ribofuranosyl)-D-glucopyranoside (5)[13]

5-α: To a mixture of **2** (462 mg, 1 mmol) and **4** (464 mg, 1.2 mmol) in dry ether (5 mL) was added a $HClO_4$ solution in 1,4-dioxane (0.1 mol dm^{-3}, 0.5 mL, 5 mol%). After stirring for 2 h under reflux, the reaction mixture was treated with triethylamine (11 μL, 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**-α. Selected ^{1}H NMR (400 MHz, $CDCl_3$) δ 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_3); FABMASS m/z (rel. intensity) 889 (M+Na, 60), 181 (100), 153 (10).

5-β: This compound was prepared by using 10 mol% of PfOH (CH_3CN, rt, 0.5 h) in 95% yield. Selected ^1H NMR (400 MHz, $CDCl_3$) δ 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_3); FABMASS m/z (rel. intensity) 889 (M+Na, 38), 181 (100), 153 (33).

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