Catalytic *O*- and *S*-Glycosylation of 1-Hydroxy Sugars

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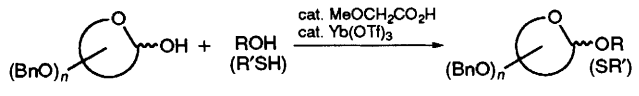
O-Protected 1-hydroxy sugars are effectively cross-coupled with a variety of alcohols and thiols to give the corresponding glycosides by using methoxyacetic acid and ytterbium(III) trifluoromethanesulfonate [$Yb(OTf)_3$] as catalytic promoters.

Although recent intensive studies on the development of new glycosyl donors have yielded a number of useful methods for glycoside synthesis, rather little has been reported for the glycosylation of 1-hydroxy sugars with free alcohols.[1] Our recent finding[2] that some heavy-lanthanide trifluoromethanesulfonates such as $Yb(OTf)_3$[3] can catalyse the glycosylation of 1-*O*-methoxyacetyl sugars[4] prompted us to examine the possibility of the cross-coupling of 1-hydroxy sugars with alcohols in the presence of a catalytic amount of methoxyacetic acid and $Yb(OTf)_3$ (Scheme 1).

When a mixture of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose **1** and octan-1-ol was stirred with methoxyacetic acid and $Yb(OTf)_3$ (30 mol% each) at 53 °C for 8 h in various solvents, the corresponding octyl glucopyranoside was isolated in 97% (1,2-dichloroethane), 89% (toluene), 84% (acetonitrile) and 45% (tetrahydrofuran) yield, respectively. The amount of promoters could be reduced to 10 mol% each without a notable decrease in the yield under similar conditions (96%; 53 °C, 8 h). Although the glycosylation was effected by an even smaller amount of promoters,‡ no reaction took place when either one of the promoters was absent.

In Table 1 are summarized the results of the catalytic glycosylation of **1** and an anomeric mixture of 2,3,5-tri-*O*-benzyl-D-ribofuranoses **2** with various types of glycosyl acceptors. The reactions proceeded smoothly especially when liberated water in the reaction mixture was azeotropically removed by refluxing the solvent through a column of molecular sieves 4 Å (condition B).[5]§ Thus, a variety of



Scheme 1 (Bn = benzyl)

Table 1 Catalytic glycosylation of 1-hydroxy sugars[a]

Entry	1-OH sugar	Acceptor	Conditions[b]	*t*/h	Yield[c] (%)	α:β Ratio[d]
1	**1**	Octan-1-ol	A	20	99	62:38
2	**1**	Octan-1-ol	B	3	99	78:22
3	**1**	**3**	A[e]	36	85	48:52
4	**1**	**4**	B	4	99	75:25
5	**1**	Cyclohexanol	B	3	99	68:32
6	**1**	Cholesterol	B	4	99	67:33
7	**1**	**5**	A[e]	36	81	40:60
8	**1**	**6**	B	5	72	82:18
9	**1**	Thiophenol	B	2	99	63:37
10	**1**	1-Octanethiol	B	3	99	79:21
11	**2**	Octan-1-ol	B	1.5	99	8:92
12	**2**	3β-Cholestanol	B	2	98	4:96
13	**2**	**4**	B	5	92	β only
14	**2**	Thiophenol	B	1.5	96	25:75

[a] The reactions were carried out by use of 1.2 equiv. of the acceptor to the 1-OH sugar in the presence of methoxyacetic acid and $Yb(OTf)_3$ (10 mol% each) unless otherwise stated. [b] A: 1,2-dichloroethane, 53 °C. B: dichloromethane, reflux, molecular sieves 4 Å (see the text). [c] Isolated yield. [d] Determined by ^1H NMR (270 MHz) analysis. [e] Methoxyacetic acid and $Yb(OTf)_3$ (30 mol% each) were used.

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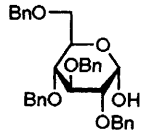
‡ For instance, 1 mol% of promoters gave rise to 40% completion of the glycosylation after 8 h stirring at 53 °C in 1,2-dichloroethane.

§ *Typical procedure* (entry 2): a mixture of **1** (540 mg, 1 mmol), octan-1-ol (189 μl, 1.2 mmol), methoxyacetic acid (7.7 μl, 0.1 mmol) and $Yb(OTf)_3$ (62 mg, 0.1 mmol) in dichloromethane (40 ml) was refluxed for 3 h under argon through a column of activated moelcular sieves 4 Å (*ca.* 28 g).



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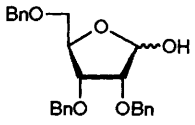

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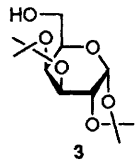

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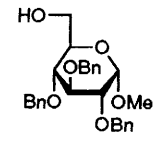

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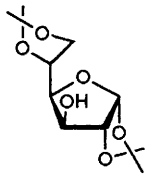

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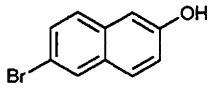

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glycosides including disaccharides, 6-bromo-2-naphthyl glycoside and thioglycosides were prepared in good to excellent yields. The perfect stereoselection observed in the glycosylation of **2** (entry 13) should also be noted.

The mechanism of the present catalytic glycosylation is under investigation.

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References

1 For recent works in this area, see: T. Mukaiyama and S. Suda, *Chem. Lett.*, 1990, 1143; 1991, 431; T. Mukaiyama, K. Matsubara and S. Suda, *Chem. Lett.*, 1991, 981.
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