EXPEDIENT STEREOSPECIFIC SYNTHESIS OF β-MANNOSIDES FROM A GLUCOSE-DERIVED 1,2-ORTHOESTER

Eisuke Kaji* and Yugo Hosokawa

School of Pharmaceutical Sciences, Kitasato University, Shirokane 5 - 9 - 1, Minato-ku, Tokyo 108-8641, Japan

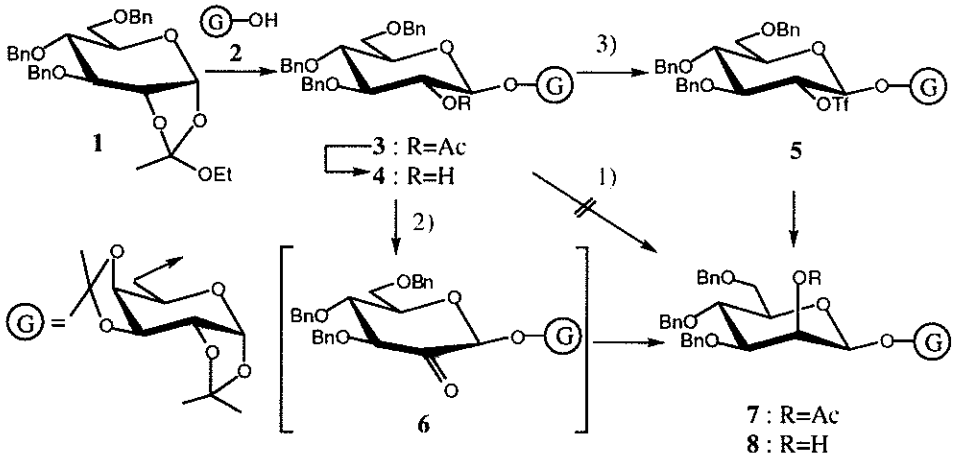
Abstract – A new, stereospecific synthesis of β-mannosides from glucose-derived 1,2-orthoester has been developed using a simple four-step procedure. For the synthesis of β-D-Man-(1→6)-D-Gal, a 6-OH free galactose derivative was glycosylated with the orthoester to yield β-D-Glc-(1→6)-D-Gal; the Glc unit of which was epimerized into the β-mannoside in good yield.

β-Mannosides are of particular importance due to their biological function as the core constituent sugar unit of *N*-linked glycoproteins,[1] bacterial capsular polysaccharides,[2] phosphomannans,[3] and lipopolysaccharides.[4] An efficient method of synthesizing β-mannosides is needed to achieve a sufficient quantity of the oligosaccharides, which can then be used as indispensable probes for immunological and pharmacological studies.[5]

However, for glycoside synthesis a highly stereoselective synthesis of β-mannosides still remains to be established, since they have to be arranged without the use of both the anomeric effect and the neighboring group participation of 2-acyloxy group.[6] Some of these requirements for acquisition of β-mannosidic linkage have been achieved through the use of direct glycosidation of mannosyl donors, either *via* S_N2 type displacement of the anomeric leaving group,[7] intramolecular aglycon derivery method,[8] or through other means.[9] On the other hand, indirect methods have also been utilized, wherein a variety of building blocks, such as 2-ulosyl bromides[10,11] and glucosyl halides[12] possessing selectively protected 2-OH group are available from glucose or galactose as mannosyl precursors. However, every method described to date has had some disadvantages in terms of stereoselectivity or practicality.

We report here an expedient route to β-mannosides which has both stereospecificity as well as practically useful capacities employing a glucose 1,2-orthoester derivative. This method is based on the hypothesis that glycosidation of the orthoester would yield a significant level of β-glucosides, which are in turn readily epimerized to β-mannosides by several of the methods as depicted in the Scheme.

An indirect β-mannosyl donor, namely 3,4,6-tri-*O*-benzyl-α-D-glucopyranose 1,2-ethylorthoacetate (**1**)[10] was readily prepared in 69% yield in two steps from acetobromoglucose.[13] The β-specific glycosidation of **1** was substantiated with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2**) as a glycosyl acceptor. Various coupling conditions were evaluated (c.f. Table 1), and Entry 7 promoted by camphorsulfonic acid (CSA) employing a 0.06 molar equivalent to **2** in dichloroethane under reflux yielded the best result.



1) Mitsunobu inversion ; 2) oxidation - reduction : 3) *via* O-Tf inversion

In none of the tested conditions was α(1→6)-isomer observed in the reaction mixture. The only byproduct isolated in this manner was determined to be low yield ethyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-gluco-pyranoside (**9**). The disaccharide (**3**) was subjected to de-*O*-acetylation under Zémplen conditions (catalytic NaOMe in MeOH) to yield 2'-OH free disaccharide (**4**) in 67% yield. The resulting compound (**4**) was determined to be a versatile precursor of β-mannoside by means of the following methods; 1) Mitsunobu inversion, 2) oxidation-reduction, and 3) S_N2 type inversion through 2'-*O*-triflate derivative of **4**.

Table 1. Coupling Reactions of the Donor (**1**) with the Acceptor (**2**)[a]

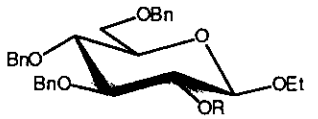
Entry	**1** (mol eq.)	**2** (mol eq.)	Promoter[b]	(mol eq.)	Time (h)	Bath Temp. (℃)	Yield (%) of **3**
1	1.5	1.0	TfOH	(0.03)	2	95	7.2
2	2.0	1.0	TfOMe	(0.06)	2	95	—
3	1.5	1.0	*p*-TsOH	(0.03)	4	95	21.4
4	1.0	1.5	*p*-TsOH	(0.02)	4	95	20.4
5	1.5	1.0	CSA	(0.03)	4	95	30.9
6	1.5	1.0	CSA	(0.03)	4	115	45.5
7	1.5	1.0	CSA	(0.06)	2	115	53.9
8[c]	1.5	1.0	CSA	(0.06)	2	115	36.2
9	1.5	1.0	CSA	(0.12)	2	115	45.2

a) The reactions were carried out in 1,2-dichloromethane in the presence of tetraethylammonium perchlorate of 1.0 molar equiv. unless otherwise noted. b) Abbreviations: TfOH = Trifluoromethanesulfonic acid; TfOMe = Methyl trifluoromethanesulfonate; *p*-TsOH = *p*-Toluenesulfonic acid; CSA = Camphorsulfonic acid. c) Tetraethylammonium perchlorate was not used.

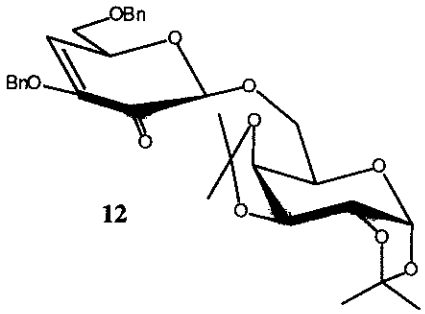
A variety of Mitsunobu conditions was applied to **4** in such a way that various combinations of the reagents, including phosphines, aliphatic and aromatic acids, and alkyl azodicarboxylates were employed.[14] However, the result was almost complete recovery of the starting materials. Since the Mitsunobu reaction is inherently hindered by steric hindrance, we decided to test ethyl glycoside (**10**), derived from **9**, under similar conditions. Compound (**10**) did not yield the mannoside, but the corresponding glucoside (**11**) in

only a 3% yield. At this stage, we concluded that Mitsunobu inversion cannot be applied in such a case.

Next, an oxidation-reduction approach was examined for **4**. Although this reaction has been reported by Danishefsky *et al.*,[10] to give **7** in 60% yield, their access to **4** was completely different from that of the present study. First, we followed the above method, but only a 48% yield of **7** was attained. In order to improve the yield of **7**, we tried to isolate the intermediary 2-uloside (**6**) by oxidation of **4** with DMSO-Ac_2O/pyridine. Unexpectedly, the main product, isolable in 59%, was characterized to be 3,4-unsaturated 2-uloside (**12**). As compound (**6**) readily generates **12**, it seemed inadvisable to apply an oxidation-reduction method in this case.



9: R = Ac
10: R = H
11: R = $COC_6H_4OMe(p)$



12

^{13}C-NMR: 117.05 (C-4'), 184.40(C-2')

UV: λmax^{MeOH} = 200 nm (log ε = 4.24)
λmax^{MeOH} = 258 nm (log ε = 3.82)

Lastly, we attempted the third method, namely 2-*O*-triflate inversion, wherein the compound (**4**) was triflated with triflic anhydride in pyridine - CH_2Cl_2 to yield 2-*O*-triflate (**5**) in 77% yield. Some of the reaction conditions are summarized in note.[15] Finally, 2-OTf inversion was subjected with either cesium acetate / 18-crown-6 or tetrabutylammonium acetate to produce the desired mannoside (**7**) in 50% and 68% yield, respectively (c.f. Table 2). Accordingly, the latter conditions are recommended for the preparative purpose.

In summary, the easy accessibility of **1** (69% yield in only 2 steps from acetobromoglucose), and simple and efficient manipulations for large-scale adaptable glycosidation and 2-OTf inversion render the glucose 1,2-orthoester (**1**) a versatile indirect β-D-mannosyl donor, with which β-D-Man-(1 → 6)-D-Gal disaccharide can be stereospecifically synthesized in a reasonable yield. Various extentions of this method are under progress.

Table 2. S_N2 Displacement of *O*-Triflate with Acetate Nucleophiles

Entry	**5** (mol eq)	Nucleophile (mol eq.)	18-Crown-6 (mol eq.)	Bath Temp.(℃)	Yield (%) of **7**
1	1.0	CsOAc (3.0)	(3.0)	r t	0
2	1.0	CsOAc (3.0)	(3.0)	60	50.2
3	1.0	CsOAc (3.0)	(3.0)	130	—
4	1.0	Bu_4NOAc (3.0)	—	60	68.0

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13. We attempted to prepare a cyanoethylidene and phenylthioethylidene analog other than ethoxyethylidene derivative (**1**), but the trials failed because of the instability of the *O*-benzylation reaction.
14. The following reagents were employed for the Mitsunobu reaction: triphenylphosphine and tributylphosphine as phosphines; formic acid, chloroacetic acid, *p*-nitrobenzoic acid, and *p*-methoxybenzoic acid as carboxylic acids, diethyl azodicarboxylate and *N,N,N',N'* -tetramethyl azodicarboxylate as azo compounds.
15. *O*-Triflate (**5**) was obtained in the following manner: A mixture of **4** (69.2 mg, 0.1 mmol), triflic anhydride (50 μL, 0.3 mmol), and pyridine (0.30 mL, 3.7 mmol) in dry dichloromethane (1 mL) was stirred at room temperature for 3 h. Aqueous workup and short column chromatography readily yielded **5** (63.5 mg, 77.1%) as a colorless syrup. MS (FAB) m/z: 847 $[M+Na]^+$; ^{13}C-NMR (75 MHz in $CDCl_3$) δ: 96.29 (C-1), 99.44 (C-1'), 118.40 ($\underline{C}F_3$).

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