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Formation of the 1,2,6-orthoester of mannose and its utilization in the glycosylation reaction

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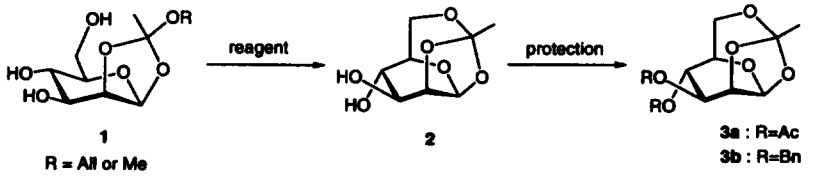
Abstract

The synthesis of mannose 1,2,6-orthoester and its utilization in the glycosylation reaction are described.

Keywords: orthoesters; glycosidation; pyridinium salts; anhydride.

The use of 1,2-*O*-alkyl orthoesters in synthetic carbohydrate chemistry has been well documented; for example, ring opening with various catalysts, differentiating the hydroxyl groups, and the glycosylation reaction.[1–4] As for the glycosylation reaction, it is known that the control of selectivity in glycosylation and ester rearrangement has been the major problem.[1]

In our recent study, protection of the primary alcohol of mannose 1,2-orthoester (**1**)[5,6] using TBDPSCl and imidazole in DMF failed to give the desired 6-*O*-silyl product, instead the 1,2,6-orthoester (**2**) was obtained in good yield. Compound **2** was considered to be formed as a result of the nucleophilic attack by the 6-OH group of **1**. Compound **2**, however, could be a good glycosylation reagent after protection of the remaining hydroxyl groups, because ring opening of the orthoester could be achieved with 2-OH and 6-OH groups being differentiated concurrently (see Schemes 1 and 2).



Scheme 1.

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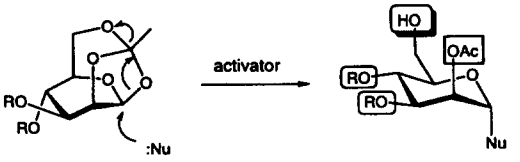


Scheme 2.

Table 1
Formation of mannose 1,2,6-orthoester

entry	Reagent (eq)	Solvent	Additive	R	Time	Yield	
1	TBDPSCl (1.2)	DMF	imidazole	allyl	16 h	**3a**	88%
2	BF_3•OEt_2 (1.2)	pyridine		allyl	24 h	**3a**	56%
3	PPTS (1.2)	pyridine		allyl	12 h	**3b**	78%
4	Py•TfOH (1.2)	pyridine		allyl	8 h	**3a**	89%
5	Py•TfOH (0.2)	pyridine		allyl	72 h	**3a**	72%*
6	Py•HCl (1.2)	pyridine		CH_3	8 h	**3a**	85%
7	imidazole•HCl (1.2 eq)	DMF	imidazole	CH_3	8 h	**3b**	87%

* Triacetate of the starting material was obtained in 12% yield.

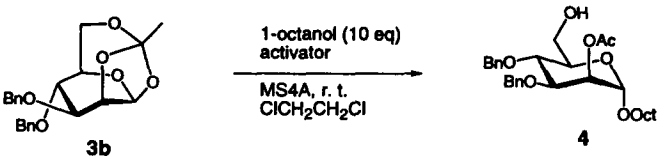
In order to obtain compounds **3**, several conditions were examined (Table 1).[7] It was found that $BF_3 \cdot OEt_2$ and pyridinium or imidazolium salts of protonic acids gave the orthoesters (**3a,b**)[6] in good yields. The best result was obtained when 1.2 equivalents of pyridinium trifluoromethanesulfonate was used [89%, after in situ acetylation of the reaction mixture (entry 3)]. The reaction was shown to be catalytic although it proceeded slowly and the starting material was recovered after 3 days (entry 5). Protection of the 2-OH group of **2** can be carried out without intermediate purification. As shown in entries 2 and 6, the solvent was removed after the reaction and the crude residue was subjected to the benzylation reaction using NaH/BnCl in DMF to give **3b**.

We then utilized the obtained 1,2,6-orthoester in oligosaccharide synthesis. Previous work on the ring opening of 1,2-orthoesters provides access to 1-OH derivatives,[2] 1-halogenated derivatives[3] and glycosides. In addition, Ogawa et al. reported[3,4] that the reaction of mannose *O*-alkyl 1,2-orthoesters in the presence of TMSOTf in dichloroethane gave the corresponding rearranged glycosides. Our 1,2,6-orthoester system may have an advantage in glycosidic bond formation reaction as C-1, O-2, and O-6 are protected in such way that a nucleophilic substitution reaction in a stereo- and regiospecific manner should occur to yield the desired glycoside with O-2 and O-6 already differentiated for further reactions.

Initially, TMSOTf, $BF_3 \cdot OEt_2$ and *p*-TsOH were examined as activators for the reaction of compound **3b** with octanol (10 equiv.) to give the expected mannoside (**4**) (Scheme 3).[8] The glycosylation reactions were shown to be essentially catalytic; however, silylation of the alcohol was observed when TMSOTf was used as an activator, which resulted in a longer reaction time. In the case that *p*-TsOH was used as an activator, formation of a polar material was observed leading to a lower yield compared to the other two conditions. The reaction with $HgBr_2$ resulted in the recovery of staring material even when an excess amount of reagent was used.

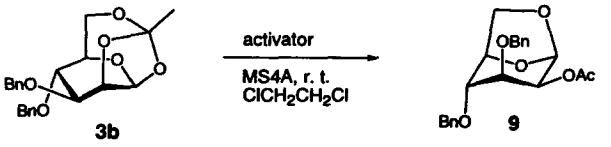
When reactions of **3b** under the same condition without an external nucleophile were examined (Scheme 4), the 1,6-anhydro-mannose derivative was obtained. Although we did not examine the details of the polymerization reactions,[9] the intramolecular reaction must have dominated to form **9**[6] which might undergo further polymerization.[10]

Disaccharide (**6**)[6] was obtained in the same manner using the glucose derivative (**5**) as a nucleophile (Scheme 5). When 1.5 equivalents of **5** were used, reaction of **3b** with the 6-hydroxyl group of the mannose residue of the formed disaccharide **6** took place to yield trisaccharide **8** (14%) in addition to



Activator		Time	Yield
TMSOTf	5.0 eq	1.0 h	75%
BF_3·OEt_2	0.2 eq	1.5 h	81%
p-TsOH	0.2 eq	1.0 h	56%

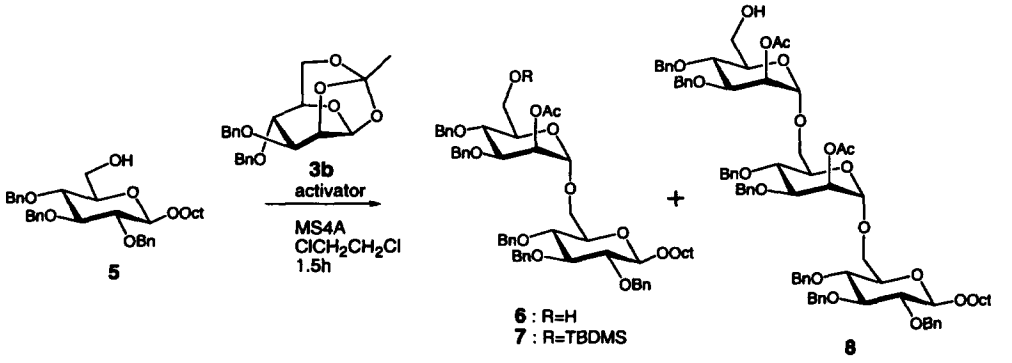
Scheme 3.



Activator		Yield
TMSOTf	0.2 eq	68%
BF_3·OEt_2	0.2 eq	65%

Scheme 4.

the desired **6** (43%). The formation of the trisaccharide was reduced by using an excess amount of the acceptor (**5**). Alternatively, *t*-butyldimethylsilyltrifluoromethanesulfonate (TBDMSOTf) could be used as an activator in order to trap the generated hydroxy group to form the silyl ether **7**. The best result for the formation of disaccharide was when $BF_3 \cdot OEt_2$ was used (75%).



Activator (eq)	5 (eq)[a]	Temp.	Yield 6	7	8
TMSOTf (0.2)	1.5	0 °C	43%	-	14%
TMSOTf (0.5)	3.0	0 °C	60%	-	9%
TMSOTf (0.5)	5.0	0 °C	68%	-	5%
TMSOTf (0.5)	5.0	r. t.	64%	-	5%
TBDMSOTf (1.2)	3.0	r. t.	29%	40%	4%
BF_3·OEt_2 (0.2)	5.0	r. t.[b]	75%	-	trace

[a]Excess amount of acceptor was recovered.
[b]Reaction proceeded very slowly at 0°C.

Scheme 5.

In conclusion, we have found a new family of 1,2,6-orthoesters which were easily obtained from the corresponding 1,2-orthoesters and demonstrated their usefulness as glycosylation reagents.

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References

1. Kochetkov, N. K.; Khorlin, A. J.; Bochkov, A. F. *Tetrahedron* **1967**, *23*, 693–707.
2. Yamazaki, F.; Sato, S.; Nukada, T.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1990**, *201*, 31–50.
3. Ogawa, T.; Sasajima, K. *Carbohydr. Res.* **1978**, *64*, C3–C9.
4. Ogawa, T.; Beppu, K.; Nakabayashi, S. *Carbohydr. Res.* **1981**, *93*, C6–C9.
5. Mazurek, M.; Perlin, A. S. *Can. J. Chem.* **1965**, *43*, 1918–1923.
6. Selected physical data: compound **2**; ^{1}H NMR ($CDCl_3$) δ 5.77 (1H, d, *J*=5.9, H-1), 4.42 (1H, dd, *J*=2.3, 5.9, H-2), 4.04 (1H, d, *J*=13.0, H-6), 4.02 (1H, m, H-5), 3.97 (1H, dd, *J*=1.0, 7.6, H-4), 3.84 (1H, dd, *J*=3.0, 13.0, H-6), 3.63 (1H, dd, *J*=2.3, 7.6, H-3), 1.65 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 123.31 (*ortho*), 100.13 (C-1), 80.54 (C-5), 76.52 (C-2), 71.79 (C-3), 70.37 (C-4), 69.88 (C-6), 23.99 (CH_3). Note: pure compound **2** was obtained by deacetylation of compound **3a** because of difficulty in isolation. Compound **3a**; ^{1}H NMR ($CDCl_3$) δ 5.81 (1H, d, *J*=5.9, H-1), 5.15 (1H, dd, *J*=8.2, H-4), 5.10 (1H, dd, *J*=2.0, 8.2, H-3), 4.54 (1H, dd, *J*=2.0, 5.9, H-2), 4.12 (1H, dd, *J*=3.3, 12.9, H-6), 4.03 (1H, dd, *J*=1.0, 12.9, H-6), 4.01 (1H, dd, *J*=1.0, 3.3, H-5), 2.15, 2.09, 1.68 (3H×3, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 170.80, 170.53 (C=O), 123.43 (*ortho*), 99.17 (C-1), 78.54 (C-5), 73.40 (C-2), 70.82 (C-4), 70.08 (C-3), 68.91 (C-6), 23.63, 21.04, 20.88 (CH_3). Compound **3b**; ^{1}H NMR ($CDCl_3$) δ 7.20–7.10 (10H, m, aromatic), 5.67 (1H, d, *J*=5.6, H-1), 4.44 (1H, dd, *J*=2.3, 5.9, H-2), 4.42 (1H, d, *J*=1.3, 7.6, H-4), 4.05 (1H, dd, *J*=1.3, 3.6, H-5), 4.03 (1H, dd, *J*=11.3, 7.6, H-4), 3.98 (1H, d, *J*=12.9, H-6), 3.65 (1H, dd, *J*=2.3, 7.6, H-3), 3.50 (1H, dd, *J*=3.6, 12.9, H-6), 1.64 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 137.97–127.57 (aromatic), 122.93 (*ortho*), 99.30 (C-1), 79.07 (C-5), 77.11 (C-4), 77.11 (C-3), 73.80 (C-2), 69.71 (C-6), 23.67 (CH_3). Compound **9**; ^{1}H NMR ($CDCl_3$) δ 7.39–7.26 (10H, m, aromatic), 5.44 (1H, s, H-1), 4.83 (1H, dd, *J*=2.0, 5.6, H-2), 4.55 (1H, m, H-5), 4.23 (1H, dd, *J*=1.0, 7.3, H-6), 4.04 (1H, dd, *J*=1.7, 5.6, H-3), 3.45 (1H, bt, *J*=1.7), 2.12 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 170.24 (C=O), 138.37–127.22 (aromatic), 99.35 (C-1), 76.43 (C-4), 74.39 (C-5), 74.20 (C-3), 69.63 (C-2), 64.98 (C-6), 20.86 (CH_3). Compound **6**; ^{1}H NMR ($CDCl_3$) δ 7.30–7.10 (15H, m, aromatic), 5.43 (1H, dd, *J*=1.7, 3.3 Hz, M-2), 4.84 (1H, bs, M-1), 4.36 (1H, d, *J*=7.9, G-1), 3.94 (1H, dd, *J*=3.3, 9.2, M-3), 3.95–3.60 (7H, m, octyl-CH2, M-3, G-3, G-6, M-4, M-5, M-6), 3.50–3.40 (4H, m, G-2, G-4, G-5, octyl-CH_2), 2.13 (3H, s, CH_3), 1.78–1.24 (12H, broad), 0.87 (3H, bt). ^{13}C NMR ($CDCl_3$) δ 170.13 (C=O), 138.40–127.62 (aromatic), 103.52 (G-1), 97.81 (M-1), 84.71 (G-3), 82.21 (G-2), 77.65 (G-4), 77.61 (G-3), 73.87 (G-5, M-4), 71.77 (M-5), 70.12 (octyl-CH), 68.30 (M-2), 66.11 (G-6), 61.89 (M-6), 31.79, 29.69, 29.38, 29.20, 26.15, 22.61 (octyl-CH_2), 21.01 (acetyl-CH_3), 14.05 (octyl-CH_3).
7. Representative procedure: Pyridinium trifluoromethanesulfonate (104.8 mg, 0.457 mmol) was added to a solution of **1** (R=allyl, 100 mg, 0.381 mmol) dissolved in pyr. (3 mL), and the mixture was stirred at room temperature for 8 h. Ac_2O (0.1 mL) was added and the mixture was stirred for 8 h. The reaction mixture was extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated. Purification by column chromatography (hexane:EtOAc=5:1) afforded **3a** (98 mg, 89%).
8. Representative procedure: To a solution of **3b** (25 mg, 0.065 mmol) and 1-octanol (102 μL, 0.65 mmol) in dichloroethane (1 mL), $BF_3 \cdot OEt_2$ (1.6 mL, 0.013 mmol) was added slowly at room temperature. The mixture was stirred for 1.5 h at the same temperature, then extracted with EtOAc. The organic layer was dried ($MgSO_4$), concentrated and purified on a column of silica gel using hexane:EtOAc (3:1) as eluent. Note: 1,6-anhydro compound **9** was not observed probably due to the amount of acceptor used in the reaction (10 equivalents).
9. Polymerization of glucose 1,2,4-orthoester was reported: Nakatsubo, F.; Kamitakahara, H.; Hori, M. *J. Am. Chem. Soc.* **1996**, *118*, 1677–1681.
10. Peat, S. *Adv. Carbohydr. Chem.* **1946**, *2*, 37–77.