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DIRECT AND STEREOSELECTIVE CONSTRUCTION OF β-MANNOSIDIC LINKAGES CAPITALIZING ON 4,6-*O*-BENZYLIDENE-PROTECTED D-MANNOPYRANOSYL DIETHYL PHOSPHITE†

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Abstract – A direct and practical method for the stereoselective construction of β-mannosidic linkages has been developed by using 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranosyl diethyl phosphite as a glycosyl donor and trimethylsilyl triflate as a promoter.

The development of new methods for stereocontrolled glycosidation reaction is one of the most fundamental challenges in the synthesis of various glycoconjugates as well as oligosaccharides.[1] Among the 1,2-*cis*- and 1,2-*trans*-glycopyranoside bonds involving α- or β-linkage, the construction of the 1,2-*cis*-β-mannosidic linkage in the core region of asparagine-linked glycoprotein oligosaccharides is the most difficult to realize, because the anomeric effect as well as the steric repulsion between a non-participating group disposed axially at C-2 and an incoming alcohol favors the formation of the 1,2-*trans*-α-mannosidic linkage.[2] Departing from the seminal work of Paulsen and Lockhoff on the direct construction of this linkage *via* S_N2-type displacement under the influence of insoluble silver silicate,[3] a number of indirect methods involving the epimerization at C-2 of accessible β-glucosides,[4] the hexo-2-ulosyl bromide approach,[5] the reductive cleavage of mannosyl anomeric orthoesters,[6] the intramolecular aglycon delivery using temporary mixed acetal or silyl ether connectors,[7,8] and the intramolecular mannosylation *via* prearranged glycosides,[9] have been developed. Although these methods provide reliable access to pure β-mannosides, it is clear that a direct β-mannosylation method would constitute an ideal procedure in terms of efficiency and practicality.[10–12] In this regard, the direct protocol developed by Crich and Sun is a notable recent landmark in this field, in which the activation of 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-protected mannopyranosyl sulfoxide or thioglycoside at –78 ˚C in dichloromethane with triflic anhydride or benzenesulfenyl triflate, respectively, is followed by the

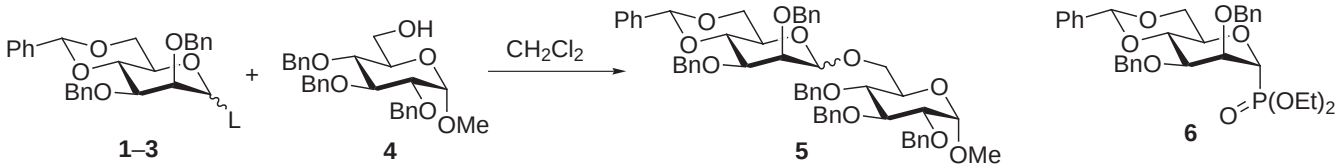
† Dedicated to Professor Yuichi Kanaoka on the occasion of his 75th birthday.

addition of acceptor alcohols to provide β-mannosides in high yields and with excellent levels of selectivity.[13] They claimed that the success of the two methods hinges critically on the presence of the 4,6-*O*-benzylidene group, where the β-mannosyl triflate as a common intermediate generated *in situ* from the donors reacts predominantly *via* an S_N2-like displacement.[13,14] More recently, the effectiveness of the same intermediate was recognized by Weingart and Schmidt[15] with the corresponding trichloroacetimidate and by Kim and coworkers[16] with the 2-(hydroxycarbonyl)benzyl 4,6-*O*-benzylidenemannoside, although the precise mechanism for the preferential formation of β-mannosides remains to be elucidated.[17]

We have recently developed glycosyl donors carrying a variety of phosphorus-containing leaving groups, the glycosidations of which constitute mild and efficient methods for the highly stereocontrolled construction of 1,2-*trans*-α- and 1,2-*cis*-β-glycosidic linkages with or without a participating group at C2.[18] As a logical extension of our studies, we addressed the direct construction of β-mannosidic linkages in the 4,6-*O*-benzylidene-protected system.

At the outset of this work, we explored the glycosidation of 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranosyl diethyl phosphite (**1**) (α:β=97:3)[19,20] with *O*-6-unprotected glycoside (**4**) as a highly

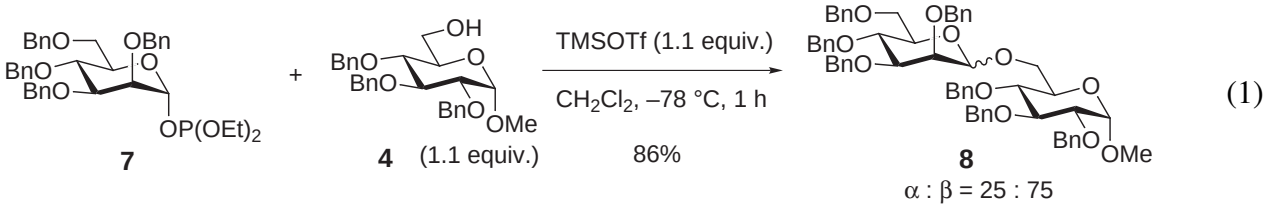
Table 1. Glycosidation of 4,6-*O*-Benzylidene Acetal-Protected Mannopyranosyl Donors with **4**[a]



entry	mannopyranosyl donor[b]		promoter	temp.	time	mannoside (**5**)	
		L		°C	h	yield, %[c]	α:β[d]
1	**1**	$OP(OEt)_2$	TMSOTf	–45	0.5	83	10:90
2[e]	**1**	$OP(OEt)_2$	TfOH	–65	6	79	9:91
3	**2**	$OP(O)(OPh)_2$	TMSOTf[f]	–30	1	54	10:90
4	**3**	$OP(O)(NMe_2)_2$	TMSOTf[g]	–30	2	55	12:88
5[h]	**1**	$OP(OEt)_2$	TMSOTf	–45	0.5	65[i]	8:92
6[h]	**1**	$OP(OEt)_2$	TMSOTf	–78	2	55[i]	5:95
7[j]	**1**	$OP(OEt)_2$	TMSOTf	–45	0.5	79	10:90
8	**1**	$OP(OEt)_2$	TMSOTf	–23	0.25	74	11:89
9	**1**	$OP(OEt)_2$	TMSOTf	0	0.25	75	12:88

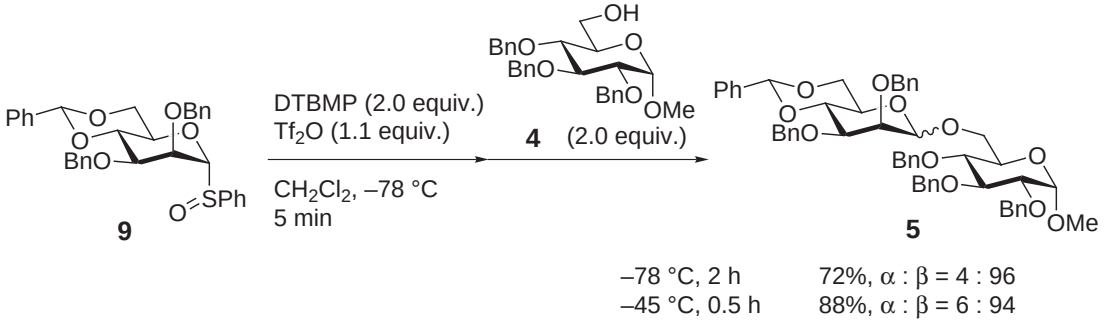
[a] Donor/acceptor/promoter molar ratio=1.0/1.1/1.1. [b] The anomeric ratio of the donors: **1**, 97:3; **2**, 100:0; **3**, 100:0. [c] Isolated yield based on the donor used. [d] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6 φ 250 mm; eluent, 17% ethyl acetate in hexane; flow rate, 1.0 mL/min; t_R α-mannoside, 21.1 min; t_R β-mannoside, 24.4 min). [e] In the presence of pulverized molecular sieves 4A. [f] The reaction was performed with 1.5 equiv. of TMSOTf. [g] The reaction was performed with 2.0 equiv. of TMSOTf. [h] After a solution of **1** and TMSOTf in CH_2Cl_2 was stirred at –45 °C for 0.5 h, alcohol (**4**) was added at the indicated temperature. [i] Phosphonate (**6**) was obtained as a by-product in *ca.* 15–20% yield. [j] Donor (**1**) was added to a solution of acceptor (**4**) and TMSOTf in CH_2Cl_2 at –45 °C.

reactive alcohol in the presence of trimethylsilyl triflate (TMSOTf).[23] After some experimentation, the coupling in dichloromethane at –45 ˚C was found to proceed to completion within 30 min to give the corresponding mannoside (**5**) in 83% yield with an α:β ratio of 10:90 (Table 1, entry 1), where –45 ˚C was the temperature limit for smooth coupling. As expected from Crich's work,[13] it was ascertained that the presence of the 4,6-*O*-benzylidene group was crucial for the high β-selectivity because a modest α:β ratio of 25:75 was observed with 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl diethyl phosphite (**7**)[19] (eq. 1). The use of triflic acid as a promoter made it possible to conduct the reaction at –65 ˚C;



(1)

however, little variation in β-selectivity was observed (entry 2). We next examined the TMSOTf-promoted glycosidation of the corresponding diphenyl phosphate (**2**)[19] and tetramethylphosphorodiamidate (**3**)[19] with **4** in dichloromethane. Both couplings were found to proceed at –30 ˚C, a higher temperature than that required for **1**, providing mannoside (**5**) in moderate yields with virtually the same β-selectivities as that with **1** (entries 3 and 4).[24] Although these mannosyl donors (**1**–**3**) can serve as precursors for the *in situ* generation of the β-mannosyl triflate, it is clear that the phosphite method is the method of choice for this glycosidation in terms of reaction rate and product yield. However, it was found that the observed β-selectivity (α:β=10:90) did not agree with the selectivity (α:β ratio with **4** was 4:96 at –78 ˚C and 6:94 at –45 ˚C) obtained by us using the corresponding sulfoxide (**9**) (eq. 2).[13] At this point, we speculated that the difference in



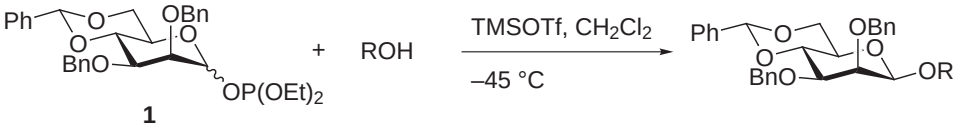
(2)

stereoselectivity between the phosphite method and the sulfoxide method might be attributed to the mode of addition of the reactants. Whereas Crich's optimal protocol consists of the prior activation of **9** with triflic anhydride before the addition of an acceptor alcohol, our procedure involves the dropwise addition of TMSOTf to a mixture of **1** and **4** in dichloromethane. Thus, we focused on the possibility of improving the β-selectivity by changing the mixing sequence. Pretreatment of donor (**1**) with TMSOTf in dichloromethane at –45 °C for 30 min followed by the addition of alcohol (**4**) was found to increase the α:β ratio to 8:92 (entry 5). This protocol enabled further enhancement of the β-selectivity by lowering the temperature during addition to –78 ˚C (entry 6). It is worthy of note that the observed

selectivity (α:β=5:95) is comparable to that obtained by the sulfoxide method. However, the permuted order of addition provided much lower yields of mannoside (**5**) due to the inevitable formation (*ca.* 15–20%) of phosphonate (**6**).[25] On the other hand, no difference in stereoselectivity was observed under "inverse conditions" originally developed by Schmidt,[26,27] where **1** was added to a mixture of **4** and TMSOTf at –45 °C (entry 7). These results, together with the finding of the little effect of reaction temperature (entry 1 *vs* 8 and 9), strongly suggest that the problem of the phosphite method is that the mannosyl donor (**1**) cannot be cleanly converted into the β-mannosyl triflate by treatment with TMSOTf before the addition of an acceptor alcohol. This also means that Crich's optimal protocol is crucial not only for the preferential formation of β-mannosides using Kahne's sulfoxide glycosidation method[28] but also for general use whenever an efficient *in situ* generation of the β-mannosyl triflate from 4,6-*O*-benzylidene-protected mannosyl donors is possible.[16]

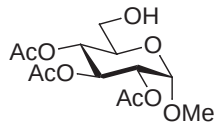
Then, we explored the mannosylation of a range of acceptor alcohols with **1**. The examples highlighted in Table 2 deserve some comments. In all cases, TMSOTf-mediated glycosidations in dichloromethane at –45 °C were found to offer a facile and high-yielding entry to β-mannosides, in which the α:β ratios ranged from 24:76 to 11:89. In accord with the mechanistic hypothesis, β-selectivity increased with an increase in the reactivity of the acceptor alcohol. As already mentioned by Crich, the mannosylation of

Table 2. Glycosidation of 4,6-*O*-Benzylidene-Protected Mannopyranosyl Diethyl Phosphite (**1**)[a]



1

entry	acceptor	time min	product	
			yield, %[b]	α:β[c]
1	**10**	30	85	11:89
2	**11**	60	84	11:89
3	**12**	30	89	24:76
4	**13**	60	72	17:83
5	**14**	30	77	15:85[d]
6	**15**	30	85	14:86[e]
7	**16**	30	89	11:89
8	**17**	30	89	16:84
9	**18**	15	87	15:85
10	**19**	30	86	17:83



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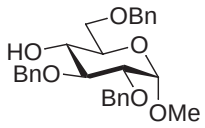

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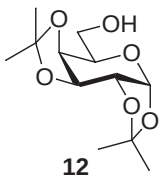

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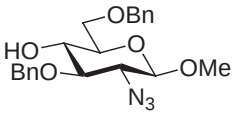

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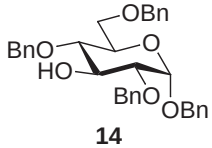

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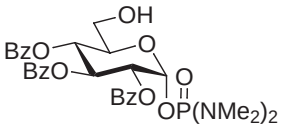

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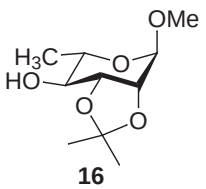

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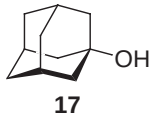

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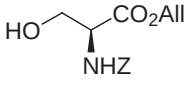

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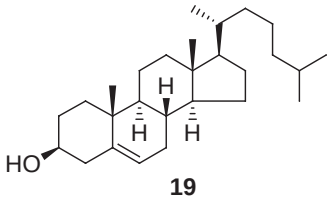

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[a] Donor/acceptor/promoter molar ratio = 1.0/1.1/1.1. [b] Isolated yield based on the donor used. [c] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6 × 250 mm; eluent, 5~17% ethyl acetate in hexane or 5~20% THF in hexane; flow rate, 1.0 mL/min). [d] Determined by 500 MHz ^{1}H NMR. [e] Determined by 125 MHz ^{13}C NMR.

1,2:3,4-di-*O*-isopropylidenegalactose (**12**), a notoriously unreactive primary alcohol, exhibited much lower selectivity than that of the exceedingly sterically hindered *O*-4-unprotected glycoside (**11**) (entry 2 *vs* 3), although the reason remains to be known. It should be noted that the glycosidation of *O*-4-unprotected glucosamine derivative (**13**) led to the predominant formation of β-mannoside,[29] which constitutes a building block of the *N*-linked glycoproteins (entry 4). It is also noteworthy that chemoselective glycosidation was realized by using *O*-6-unprotected glucosyl tetramethylphosphorodiamidate (**15**) as a disarmed acceptor because **15** was unaffected by such conditions when kept at temperatures below –5 ˚C (entry 6).[30]

In summary, we have developed a method for the direct construction of β-mannosidic linkages capitalizing on 2,3-di-*O*-benzyl-4,6-*O*-benzylidene mannopyranosyl diethyl phosphite, in which a new aspect of the glycosyl phosphite method has been demonstrated. Although the β-selectivities achieved here are inferior to those reported by Crich with the sulfoxide or thioglycoside method, the present method has the following advantages in terms of practicality: (i) high product yield can be achieved with approximately equimolar proportions of glycosyl donors and acceptors; (ii) the reaction is very clean, allowing very easy isolation of the product, in contrast to the sulfoxide method that produces several by-products derived from the sulfinate moiety; and (iii) TMSOTf is a stable and inexpensive reagent compared to benzenesulfenyl triflate required for the thioglycoside method which must be prepared *in situ* by reacting benzenesulfenyl chloride with silver triflate.[31]

ACKNOWLEDGMENTS

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min at this temperature, the mixture was quenched with triethylamine (0.1 mL). The mixture was poured into a two-layer mixture of AcOEt (5 mL) and saturated aqueous $NaHCO_3$ (5 mL), and the whole mixture was extracted with AcOEt (15 mL). The organic extract was successively washed with saturated aqueous $NaHCO_3$ (2×5 mL) and brine (2×5 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* were followed by column chromatography (silica gel 5 g, 4:1 *n*-hexane/AcOEt) to provide mannoside (**5**) (74 mg, 83%, α:β = 10:90) as a white solid.

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