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1,2-cis-β-Mannopyranoside Formation by the Dimethylphosphinothioate Method

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1,2-cis-β-Mannopyranosides were obtained predominantly by reactions of mannopyranosyl dimethylphosphinothioate derivatives with several alcohols in the presence of iodine and a catalytic amount of triphenylmethyl perchlorate as the activator in benzene.

In carbohydrate chemistry, a highly stereoselective O-glycosidation is very significant for the synthesis of complex oligosaccharides. In recent years new methods for stereospecific glycosidation have been reported.[1] However the formation of 1,2-cis-β-mannopyranosidic linkage in the carbohydrate chain of N-glycoproteins remains a serious problem owing to its steric repulsion and anomeric effect.[2]

Although several examples of 1,2-cis-β-mannopyranosylation reaction have been reported, such as S_N2 reaction using insoluble silver silicate[3] and intramolecular glycosylation,[4,5] they seem not to be easy to apply to the synthesis of oligosaccharides.

Mannopyranosylation could be assumed as follows. Although 1,2-cis-β-mannopyranosides could be produced even by most reported glycosidation methods, 1,2-cis-β-mannopyranosides would be immediately converted to 1,2-trans-α-mannopyranosides by acidic components from the activators. Certain 1,2-cis-β-mannopyranosides could be obtained without anomerization under

the conditions reducing acid as little as possible.

We previously reported glycosidation using glycosyl dimethylphosphinothioate in the presence of iodine and a catalytic amount of triphenylmethyl perchlorate ($TrtClO_4$) as the activator.[6] Attention was directed to the catalytic amount of $TrtClO_4$ in the glycosidation, and 1,2-cis-β-mannopyranoside synthesis was attempted by this method.

First, we examined reactions of 2,3,4-tri-O-benzyl-6-deoxy-L-mannopyranosyl dimethylphosphinothioate (**1**) and 3β-cholestanol (**2**) with various amounts of $TrtClO_4$.[7] Although only 3β-cholestanyl 1,2-trans-α-mannopyranoside (**3**-α) was obtained using 50 mol% amount of $TrtClO_4$ (entry 1), **3**-β was synthesized predominantly following reduction of $TrtClO_4$ to 5 mol% (entry 3). The time-course of the anomer ratio of the reaction mixture was measured by HPLC, but no anomerization could be detected. Unfortunately **3**-α was predominantly obtained by the reaction using a still smaller amount of $TrtClO_4$ (entries 4 and 5).

Iodine was found essential for this reaction. Iodide anion appeared to be related in some manner to the selectivity (entries 5-11).

Further we examined this reaction using several solvents, such as benzene, toluene, fluorobenzene and dichloromethane. Benzene and fluorobenzene were particularly effective (entries 3 and 8). It was of interest that the molecular size of effective solvents were similar.

Based on the above results, the reaction mechanism except for entries 4 and 5 was considered to be as follows. Mannosyl perchlorate, possibly generated by the reaction of **1** and $TrtClO_4$, immediately reacted with iodide ion to afford α-mannosyl iodide containing solvent molecule. The reaction of alcohol and this intermediate might give the β-mannoside predominantly without anomerization.

Other β-mannosides were obtained using various acceptors. Similarly 2,3,4,6-tetra-O-benzyl-D-mannopyranosyl dimethylphosphinothioate (**4**) gave the corresponding 1,2-cis-β-mannoside predominantly (entry 15).

On the other hand, 4-O-acyl mannosyl donors were known to increase

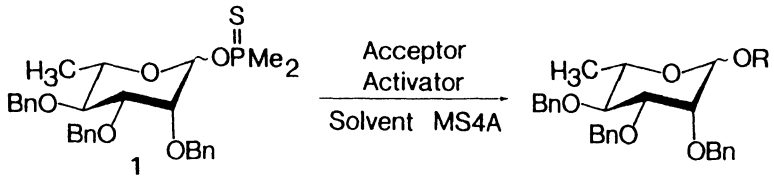

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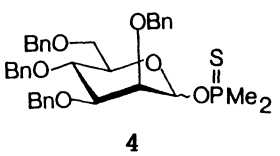
Table 1.[a] Mannopyranosylation reactions using I_2-cat.$TrtClO_4$

Entry	Acceptor	Activator(equiv.)	Solvent	Yield/%	α/β[b]
1	3β-Cholestanol(2)	I_2(1)-$TrtClO_4$(0.5)	PhH	94	α
2	2	I_2(1)-$TrtClO_4$(0.1)	PhH	93	60/40
3	2	I_2(1)-$TrtClO_4$(0.05)	PhH	76	40/60
4	2	I_2(1)-$TrtClO_4$(0.023)	PhH	84	80/20
5	2	I_2(1)	PhH	79	α
6	2	I_2(1)-$TrtClO_4$(0.05)	CH_2Cl_2	71	α
7	2	I_2(1)-$TrtClO_4$(0.05)	$PhCH_3$	78	90/10
8	2	I_2(1)-$TrtClO_4$(0.05)	PhF	76	38/62
9	2	I_2(0.5)-$TrtClO_4$(0.05)	PhH	52	61/39
10	2	I_2(0.25)-$TrtClO_4$(0.05)	PhH	33	53/47
11	2	NaI(1)-I_2(0.25)-$TrtClO_4$(0.05)	PhH	18	37/63
12	6	I_2(1)-$TrtClO_4$(0.05)	PhH	46	69/31
13	7	I_2(1)-$TrtClO_4$(0.05)	PhH	50	45/55
14	8	I_2(1)-$TrtClO_4$(0.05)	PhH	69	50/50
15[c]	2	I_2(1)-$TrtClO_4$(0.05)	PhH	67	30/70
16[d]	2	I_2(1)-$TrtClO_4$(0.05)	PhH	85	18/82
17[d]	6	I_2(1)-$TrtClO_4$(0.05)	PhH	47	43/57
18[d]	7	I_2(1)-$TrtClO_4$(0.05)	PhH	52	23/77
19[d]	8	I_2(1)-$TrtClO_4$(0.05)	PhH	61	35/65

a)Molar ratio ; **1** : acceptor= 1 : 1. b)The anomer ratios were determined by HPLC and ^{1}H NMR. c)Compound **4** was used as a donor. d)Compound **5** was used as a donor.



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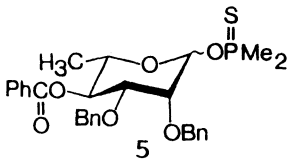

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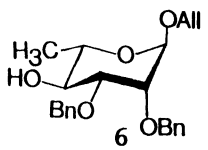

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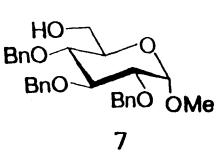

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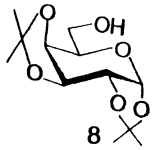

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β-selectivity by through-bond interactions and/or participation of the 4-O-acyl group.[2,8] The reactions of the 4-O-benzoyl derivative **5** with various acceptors were consequently carried out to afford 1,2-cis-β-

mannosides in high selectivity up to α/β=18/82 (entry 16).

More detailed research is presently being conducted.

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