May, 1994] © 1994 The Chemical Society of Japan Bull. Chem. Soc. Jpn., **67**, 1359—1366 (1994) 1359

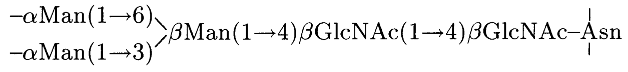
New Synthetic Methods and Reagents for Complex Carbohydrates. VIII. Stereoselective α- and β-Mannopyranoside Formation from Glycosyl Dimethylphosphinothioates with the C-2 Axial Benzyloxyl Group

Takashi Yamanoi, Kazumi Nakamura, Hiroshi Takeyama, Kenji Yanagihara, and Toshiyuki Inazu*
The Noguchi Institute, 1-8-1, Kaga, Itabashi-ku, Tokyo 173

(Received May 26, 1993)

The reactions of mannopyranosyl dimethylphosphinothioates and alcohols using silver perchlorate as an activator in the presence of molecular sieves 4A in benzene at room temperature gave the 1,2-*trans*-α-mannopyranosides in good yields. On the other hand, 1,2-*cis*-β-mannopyranosides could be obtained from the dimethylphosphinothioates by the combined use of iodine and 5 mol% triphenylmethyl perchlorate as an activating system. The syntheses of the derivatives of αMan(1→6)[αMan(1→3)]Man and βMan(1→4)GlcNAc units of glycoproteins by these methods are described.

N-Glycan chains of glycoproteins present on cell surfaces are considered to be responsible for a variety of biological recognition mechanisms and share the following common core structure.[1] (Chart 1)



$$\left.\begin{array}{l}-\alpha\mathrm{Man}(1\to6)\\-\alpha\mathrm{Man}(1\to3)\end{array}\right\rangle\beta\mathrm{Man}(1\to4)\beta\mathrm{GlcNAc}(1\to4)\beta\mathrm{GlcNAc}\text{–}\underset{|}{\overset{|}{\mathrm{A}}}\mathrm{sn}$$

Chart 1.

Highly stereoselective both 1,2-*trans*-α-manno- and 1,2-*cis*-β-mannopyranosylation reactions are necessary to synthesize these carbohydrate chains.

The formation of α-mannopyranosides was expected to be favored in glycosidation even when donors with protective groups of ether type at the C-2 position were used. However, the mannoside synthesis following the intentional conversion of a nonparticipating group at the C-2 position into an acyl group to achieve a high α-selectivity has been reported.[2] Several improved α-mannopyranosylation reactions without using a participating group at the C-2 position have been studied.[3,4]

Compared with the formation of α-mannopyranosides, the formation of β-mannopyranosides is very disadvantageous owing to the stereospecific repulsion of the C-2 axial function and the anomeric effect.[5] The synthesis of the β-mannopyranosidic linkage remains a serious problem in carbohydrate chemistry.

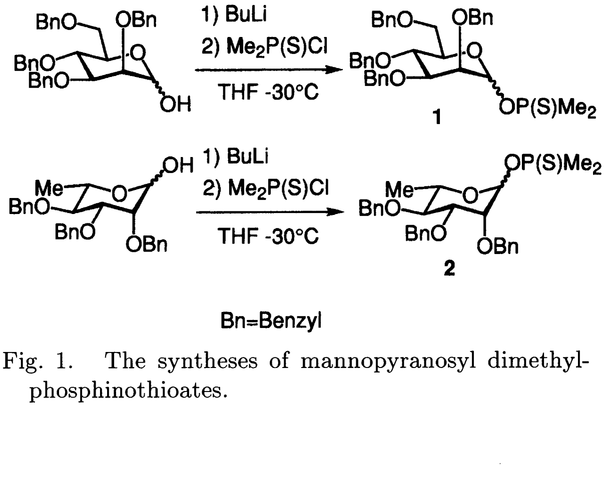
A few approaches for β-mannopyranosides have been reported. The concept of one method is an S_N2 reaction on the anomeric carbon of α-mannopyranosyl bromide using insoluble silver silicate as an activator.[6] Another is stereospecific intramolecular glycosidation using mannopyranosyl donors connected at the C-2 axial hydroxyl function with acceptors by acetal bonds.[7,8]

We have already reported that glycopyranosyl dimethylphosphinothioates with a C-2 nonparticipating equatorial benzyloxyl group gave α-glycopyranosides predominantly in good yields by the reaction of the corresponding alcohols using silver perchlorate ($AgClO_4$) as an activator in the presence of molecular sieves (MS) 4A in benzene at room temperature.[9] Also, the combined use of iodine and a catalytic amount of triphenylmethyl perchlorate ($TrtClO_4$) was effective for this method as an activating system.[10] In this paper, we describe the reaction of glycopyranosyl dimethylphosphinothioates with a C-2 axial benzyloxyl group.

Results and Discussion

2,3,4,6-Tetra-*O*-benzyl-D-mannopyranosyl dimethylphosphinothioate (**1**) was obtained in 75% yield with an anomer ratio of $\alpha/\beta=56/44$ by the reaction of the corresponding 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose[11] and dimethylphosphinothioyl chloride (MptCl)[12] (1.2 equiv) using butyllithium (1.2 equiv) in tetrahydrofuran (THF) at −30 °C. Similarly, 2,3,4-tri-*O*-benzyl-L-rhamnopyranosyl (6-deoxy-L-mannopyranosyl) dimethylphosphinothioate (**2**) was prepared in 89% yield with an anomer ratio of $\alpha/\beta=76/24$ from 2,3,4-tri-*O*-benzyl-L-rhamnopyranose (Fig. 1).[13] These compounds can be stored on the shelf for several months without receiving any care.

The reaction of **1** with some alcohols using $AgClO_4$ (1 equiv) as an activator in benzene at room temperature was attempted as described previously.[9] When 3β-cholestanol (**3**), cyclohexanol (**4**), and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**5**) (1 equiv) were used as acceptors (Fig. 2), the corresponding α-D-mannopyranosides **6**, **7**, and **8** were obtained in 70, 75, and 80% yields, respectively (Table 1). Also, a similar reaction of **2** using **3** and **4** as acceptors gave



Bn=Benzyl

Fig. 1. The syntheses of mannopyranosyl dimethylphosphinothioates.

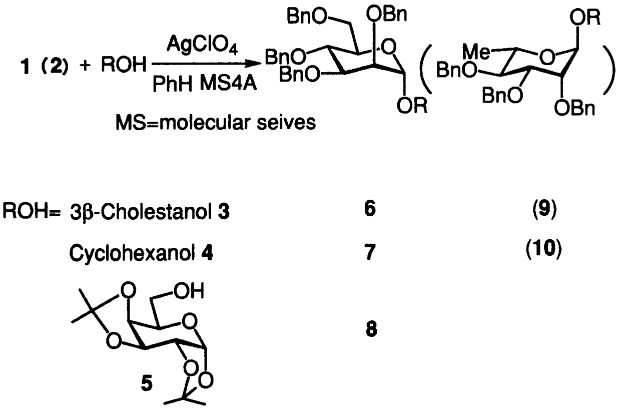


Fig. 2. Glycoside formations from **1** (or **2**) and alcohols using $\mathrm{AgClO_4}$.

Table 1. Mannopyranosylation Reaction Using $\mathrm{AgClO_4}$

Entry	Donor	Alcohol	Yield/%[a]
1	**1**	**3**	70
2	**1**	**4**	75
3	**1**	**5**	80
4	**2**	**3**	90
5	**2**	**4**	80

a) Only α-anomer was detected by ^{13}C NMR spectroscopy in all cases.

3β-cholestanyl 2,3,4-tri-*O*-benzyl-α-L-rhamnopyranoside (**9**) and cyclohexyl 2,3,4-tri-*O*-benzyl-α-L-rhamnopyranoside (**10**) in 90 and 80% yields, respectively. The desired α-mannopyranosides and α-L-rhamnopyranosides were obtained in good yields stereoselectively in all cases. The linkage formed by this glycosidation was confirmed to be α by the signal for anomeric carbon ($J_{\mathrm{C1-H1}}$=ca. 170 Hz) in the ^{13}C NMR spectrum of these glycosides in agreement with the observations of Bock and Pederson.[14] β-Mannopyranosides could not be detected by thin-layer chromatography and ^{13}C NMR. The increased α-selectivity observed in this methods could be attributed to the C-2 axial benzyloxyl group of these dimethylphosphinothioates.[9]

Secondly, we studied the glycosidation by the combined use of iodine (1 equiv) and 10 mol% $\mathrm{TrtClO_4}$ as an activating system as reported previously.[10] The glycosidation of 2,3,4-tri-*O*-benzyl-L-rhamnopyranosyl dimethylphosphinothioate (**2**) and 3β-cholestanol (**3**) gave the corresponding L-rhamnopyranoside **9** in 93% yield with an anomer ratio of α/β=60/40. We were interested in the formation of β-mannopyranoside, indicated by the signal for C-1β of **9** at 99.2 ppm $J_{\mathrm{C1-H1}}$=150.8 Hz) in the ^{13}C NMR spectrum. However, under the reaction conditions using iodine and $\mathrm{TrtClO_4}$ (each 1 equiv) only **9**α was obtained. Based on these findings, we hypothesized that β-mannopyranoside formed in some degree could be converted to thermodynamically stable α-mannopyranoside by a large amount of acidic components.

Our attention was directed to the amount of $\mathrm{TrtClO_4}$. We examined the similar glycosidation of **2** and **3**, changing the amount of $\mathrm{TrtClO_4}$. While only the α-glycoside **9**α was obtained using 50 mol% $\mathrm{TrtClO_4}$, the β-glycoside **9**β was formed predominantly (α/β=40/60) when 5 mol% $\mathrm{TrtClO_4}$ was used. However, **9**α was obtained predominantly by the reactions using a still smaller amount of $\mathrm{TrtClO_4}$ (0.023 equiv or non) (Table 2). From these results, we recognized that the formation of **9**β could not be explained by the anomerization rate alone dependent on the amount of $\mathrm{TrtClO_4}$.

Further, we examined the reactions of **2** and **3** in the presence of iodine (1 equiv) and 5 mol% $\mathrm{TrtClO_4}$ in several kinds of solvents, such as benzene, toluene, fluorobenzene, and dichloromethane. Benzene and fluorobenzene were particuarly effective. Glycosidation intermediates containing solvent molecules have been reported;[15] it was of interest that the molecular sizes of effective solvents were similar.

We examined the reactions of **1** and **2** with several kinds of alcohols, such as **5**, allyl 2,3-di-*O*-benzyl-α-L-rhamnopyranoside (**11**), methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**12**), and allyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**13**) using the iodine–5 mol% $\mathrm{TrtClO_4}$ system in benzene (Fig. 3). The reactions of **1** with **5** and **12** also gave the corresponding *O*-(β-D-mannopyranosyl)-D-glycopyranosides **8** and **17** in 44% (α/β=43/57) and 39% (α/β=24/76) yields, respectively. The reactions of **2** with these acceptors **5**, **11**, and **12** gave the corresponding *O*-(L-rhamnopyranosyl)-glycopyranosides **14**, **15**, and **16** in 81% (α/β=53/47), 46% (α/β=69/31), and 50% (α/β=45/55) yields, respectively (Table 2). However, the rhamnosidation using **13** as an acceptor could not be done. Thus, this dimethylphosphinothioate method using iodine (1 equiv)–5 mol% $\mathrm{TrtClO_4}$ as an activating system was proved to be useful for preparation of β-mannopyranosides, when the reactive alcohols such as primary alcohols were used as acceptors.

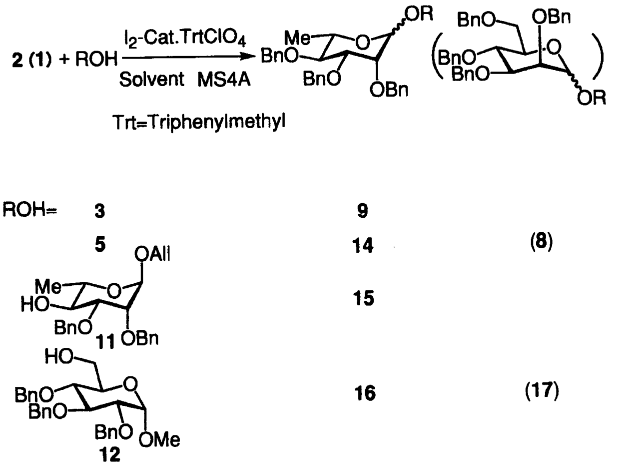


Fig. 3. Glycoside formations from **1** (or **2**) and alcohols using $\mathrm{I_2}$-cat. $\mathrm{TrtClO_4}$.

Table 2. Mannopyranosylation Using I_2 (1 equiv)-cat. $TrtClO_4$ in PhH

Entry	Donor	Alcohol	$TrtClO_4$/equiv	Yield/%	α/β[a)]
1	**2**	**3**	0.5	94	α
2	**2**	**3**	0.1	93	60/40
3	**2**	**3**	0.05	76	40/60
4	**2**	**3**	0.023	84	80/20
5	**2**	**3**	—	79	α
6[b)]	**2**	**3**	0.05	71	α
7[c)]	**2**	**3**	0.05	78	90/10
8[d)]	**2**	**3**	0.05	76	38/62
9	**2**	**5**	0.05	81	53/47[e)]
10	**2**	**11**	0.05	46	69/31[e)]
11	**2**	**12**	0.05	50	45/55[e)]
12	**1**	**5**	0.05	44	43/57[f)]
13	**1**	**12**	0.05	39	24/76[f)]
14	**1**β	**12**	0.05	64	19/81[f)]

a) Determined by HPLC. b) Solvent; CH_2Cl_2. c) Solvent; $PhCH_3$. d) Solvent; PhF. e) Determined by the isolated yield. f) Determined by the measurement of ^1H NMR.

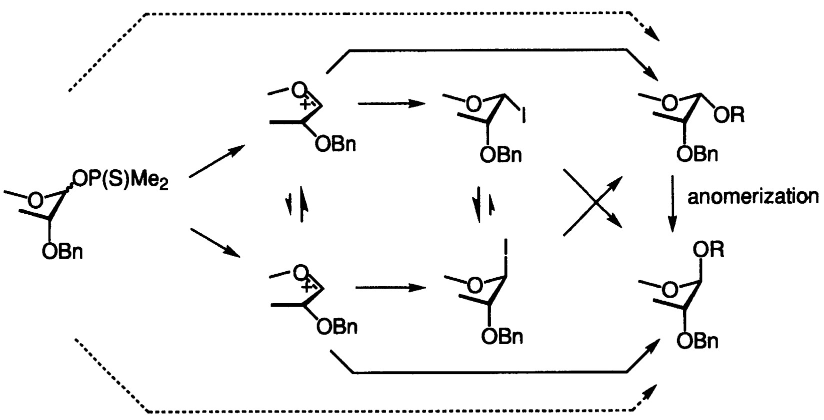


Fig. 4. The estimated mechanism of glycosidation by an S_N1 reaction.

We also recognized the difference of reactivities of these donors. The reactivity of **1** having the 6-benzyloxyl group was lower than those of **2** having a 6-deoxy function. Particularly, a great difference between the α- and β-anomers of **1** was observed. The reaction of the anomer mixture of **1** with **12** gave methyl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-mannopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**17**) in only 39% yield with an anomer ratio of $\alpha/\beta=24/76$. The α-anomer of **1** did not react and was recovered from the reaction mixture quantitatively. The **1**β anomer was obtained from the anomer mixture of **1** by thin-layer chromatography, and this reaction was tried using only the **1**β anomer. The reaction of **1**β with **12** gave **17** in up to 69% yield with an anomer ratio of $\alpha/\beta=19/81$ (Table 2). It was found that the yield could be improved by the reaction using only β-dimethylphosphinothioate.

We considered that this glycosidation could be done mainly by the tight ion-pair mechanism of glycosyl perchlorate and/or the push-pull (S_N2) mechanism, probably via a stable α-glycosyl iodide, which could be prepared from glycosyl perchlorate, as shown in Fig. 4. Accordingly, an adequate amount of $TrtClO_4$ was required to generate α-glycosyl perchlorate or α-glycosyl iodide and also required to prevent the anomerization of β-mannosides to α-mannosides.

On the other hand, 4-*O*-acyl mannosyl donors were known to increase β-selectivity by through-bond interactions.[5)] We have found that glucopyranosyl dimethylphosphinothioate with the C-4 benzoyloxyl group improved the β-selectivity compared with that of a C-4 benzyloxyl group.[16)] We guessed that this effect would be due to the participation of the 4-*O*-acyl group. We then examined the glycosidation using the derivatives of 4-*O*-acyl-2,3-di-*O*-benzyl-L-rhamnopyranosyl dimethylphosphinothioates.

4-*O*-Benzoyl-2,3-di-*O*-benzyl-L-rhamnopyranosyl dimethylphosphinothioate (**18**) was prepared from **11**[17)] as shown in Fig. 5. The deprotection of the allyl group of **11** using $PdCl_2$[18)] gave 2,3-di-*O*-benzyl-L-rhamnopyranose (**19**) in 75% yield. 2,3-Di-*O*-benzyl-L-rhamnopyranosyl dimethylphosphinothioate (**20**) was easily ob-

Table 3. Mannopyranosylation of **18** and Alcohols Using I_2 (1 equiv)–TrtClCO$_4$

Entry	Alcohol	TrtClO$_4$/equiv	Solvent	Yield/%	α/β[a]
1	**3**	1	PhH	66	71/29
2	**3**	0.1	PhH	66	30/70
3	**3**	0.05	PhH	85	18/82
4	**3**	0.015	PhH	48	18/82
5	**3**	0.05	PhCH$_3$	57	20/80
6	**3**	0.05	PhF	69	27/73
7	**3**	0.05	CH_2Cl_2	73	20/80
8	**3**	0.05	$ClCH_2CH_2Cl$	55	27/73
9	**5**	0.05	PhH	61	35/65[b]
10	**12**	0.05	PhH	52	23/77[b]

a) Determined by the measurement of ^{1}H NMR. b) Determined by the isolated yield.

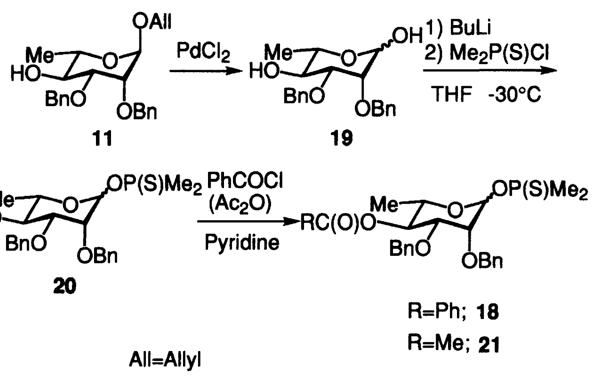


Fig. 5. The syntheses of the 4-*O*-acyl-L-mannopyranosyl dimethylphosphinothioates.

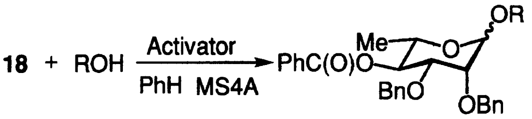


Fig. 6. Glycoside formation from **18** and alcohols using I_2-cat. TrtClO$_4$.

tained in 97% yield with an anomer ratio of $\alpha/\beta=62/38$ from **19** (1 equiv) and MptCl (1 equiv) using butyllithium (1 equiv) in THF at −30 °C, and the benzoylation of **20** using benzoyl chloride in pyridine gave **18** in 73% yield with an anomer ratio of $\alpha/\beta=76/24$. Also, 4-*O*-acetyl-2,3-di-*O*-benzyl-L-mannopyranosyl dimethylphosphinothioate (**21**) was obtained in 80% yield by the reaction of **20** and acetic anhydride in pyridine.

We attempted the reaction of **18** and 3β-cholestanol (**3**) under the conditions of the combined use of iodine (1 equiv) and different amounts of TrtClO$_4$ (5—100 mol%) as activating systems in benzene at room temperature (Fig. 6). We found that the β-selectivity of these reactions also increased in proportion to the decrease in the amount of TrtClO$_4$, and that the yield and β-selectivity of these reactions to form 3β-cholestanyl 4-*O*-benzoyl-2,3-di-*O*-benzyl-L-rhamnopyranoside (**22**) was maximum (85% yield, $\alpha/\beta=18/82$) when 5 mol% TrtClO$_4$ was used (Table 3).

Although the glycosidation with the 4-*O*-benzoyl donor **18** was done in various solvents such as benzene, toluene, fluorobenzene, dichloromethane, and 1,2-dichloroethane, no solvent effect was observed (Table 3). This was different from the reaction of the corresponding 4-*O*-benzyl donor **2**. These findings could indicate that the effect of the 4-*O*-benzoyl group was more important than the solvent effect for the β-selectivity. The reaction of the 4-*O*-acetyl donor **21** with 3β-cholestanol (**3**) (1 equiv) under conditions using iodine (1 equiv)–5 mol% TrtClO$_4$ in benzene gave 3β-cholestanyl 4-*O*-acetyl-2,3-di-*O*-benzyl-L-rhamnopyranoside (**23**) in 64% yield with an anomer ratio of $\alpha/\beta=29/71$. It was found that the benzoyl group was more effective than the acetyl group. The similar glycosidation of **18** with **5** and **12** gave 6-*O*-(4-*O*-benzoyl-2,3-di-*O*-benzyl-rhamnopyranosyl)-1,2:3,4-*O*-isopropylidene-α-D-galactopyranose (**24**) and methyl 6-*O*-(4-*O*-benzoyl-2,3-di-*O*-benzyl-L-rhamnopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**25**) in 61% ($\alpha/\beta=35/65$) and 52% ($\alpha/\beta=23/77$) yields, respectively (Table 3).

The mechanism of the formation of the 1,4-*O*-benzylidene type cation as shown in Fig. 7 would explain the β-selectivity of this reaction. A similar concept based on this 1,4-*O*-benzylidene type cation through the participation of the 4-*O*-acyl group has already been reported.[19]

Further, we demonstrated this method in the syntheses of the derivatives of αMan(1→6)[αMan(1→3)]-Man[20,21] and βMan(1→4)GlcNAc[5,6] which are constituents of the carbohydrate chain in glycoproteins.

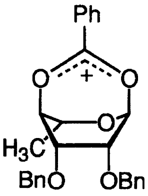


Fig. 7. The formation of the 1,4-*O*-benzylidene type cation.

We planned the dimolar glycosylation of allyl 2,4-di-*O*-benzyl-α-D-mannopyranoside (**26**) with **1** for the synthesis of the derivative of αMan(1→6)[αMan(1→3)]-Man according to the literature (Fig. 8).[2] The reaction of **1** (2 equiv) and **26** using 2 equiv of $AgClO_4$ as an activator gave allyl 3,6-bis-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-2,4-di-*O*-benzyl-α-D-mannopyranoside (**27**) in 78% yield. The signals of the three anomeric carbon atoms of **27** were observed at 100.0 ppm (J_{C1-H1}=172.8 Hz), 98.1 ppm (J_{C1-H1}=174.7 Hz), and 96.4 ppm (J_{C1-H1}=170.9 Hz) by the measurement of ^{13}C NMR spectroscopy of this trisaccharide derivative in accordance with the J_{C1-H1} value for the α-D-glycosyl stereochemistry.[14]

A derivative of the βMan(1→4)GlcNAc[6] unit was synthesized as follows (Fig. 9). 1,6-Anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranose (**28**)[22] was used as an equivalent compound of GlcNAc, because allyl 2-acetamide-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**13**) as an acceptor could not be used as mentioned above. 1,6-Anhydro-2-azido-3-*O*-benzyl-2-deoxy-4-(2,3,4,6-tetra-*O*-benzyl-β-D-mannopyranosyl)-D-glucopyranose (**29**) was obtained in 45% yield with an anomer ratio of α/β=22/78 by the reaction of 2,3,4,6-tetra-*O*-benzyl-β-D-mannopyranosyl dimethylphosphinothioate (**1β**) and **28** (1 equiv) using iodine (1 equiv)–$TrtClO_4$ (0.05 equiv) in the presence of MS 4A in benzene. The signals of the anomeric carbons of **29** were observed at 98.6 ppm ($J_{C1'-H1'}$=154.4 Hz) and 98.1 ppm ($J_{C1'-H1'}$=167.3 Hz) by the measurement of ^{13}C NMR spectroscopy of this compound.

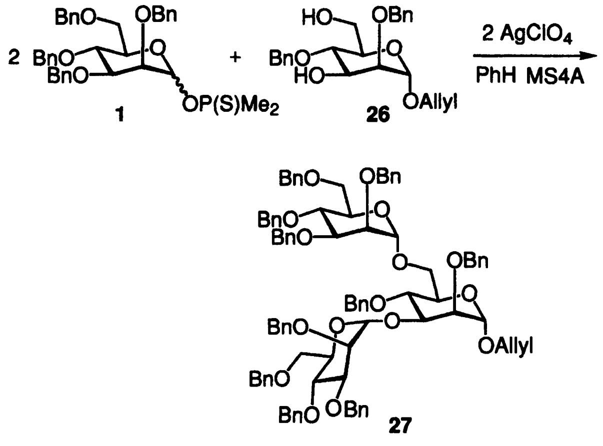


Fig. 8. The synthesis of the derivative of αMan(1→6)-[αMan(1→3)]Man.

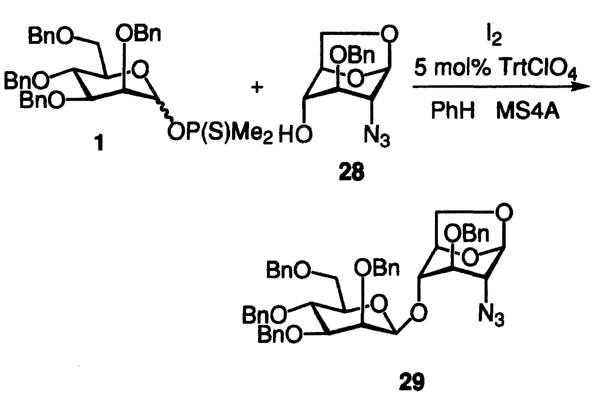


Fig. 9. The synthesis of the derivative of βMan(1→4)-GlcNAc.

Experimental

Melting points were measured with a Laboratory Devices MEL-TEMP apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL FX-90A and EX-400 spectrometers with tetramethylsilane as an internal standard in $CDCl_3$. The spectrum data of ^{1}H and ^{13}C NMR of dimethylphosphinothioates are shown in Table 4. Optical rotations were recorded on a JASCO DIP-360 digital polarimeter.

2,3,4,6-Tetra-*O*-benzyl-D-mannopyranosyl Dimethylphosphinothioate (1): To a solution of 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose[11] (1.0 g, 1.9 mmol) in dry THF (5 ml) at −30 °C was added a 1.5 M (1 M=1 mol dm^{-3}) hexane solution of butyllithium (1.6 ml, 2.4 mmol) under an argon atmosphere. After stirring for 15 min, MptCl[12] (0.31 g, 2.4 mmol) was added to the solution and the mixture was stirred for 1 h at −30 °C, and water and ether were added. The mixture was extracted with ether, and the organic layer was washed with water. After this was dried over sodium sulfate, the ether was evaporated in vacuo to yield the crude oil. The crude product was purified by silica-gel column chromatography to give **1** (0.83 g, 75%) with an anomer ratio of α/β=56/44. Found (α,β-mixture): C, 68.45; H, 6.64%. Calcd for $C_{36}H_{41}O_6PS$: C, 68.34; H, 6.53%. The anomers were separated by thin-layer chromatography (PhH/Et_2O=95/5). α Anomer: $[\alpha]_D^{24}$ +37.7° (*c* 5.55, $CHCl_3$). β Anomer: $[\alpha]_D^{24}$ −24.8° (*c* 4.77, $CHCl_3$).

2,3,4-Tri-*O*-benzyl-L-rhamnopyranosyl Dimethylphosphinothioate (2): Compound **2** (2.2 g, 89%) with an anomer ratio of α/β=76/24 was obtained by a procedure similar to the preparation of **1** using 2,3,4-tri-*O*-benzyl-L-rhamnopyranose[13] (2.0 g, 4.7 mmol), MptCl (0.78 g, 6.1 mmol), and a 1.5 M hexane solution of butyllithium (4.1 ml, 6.1 mmol). Found (α,β-mixture): C, 65.93; H, 6.67%. Calcd for $C_{29}H_{35}O_5PS$: C, 66.14; H, 6.70%.

2,3-Di-*O*-benzyl-L-rhamnopyranose (19): To a solution of allyl 2,3-di-*O*-benzyl-L-rhamnopyranoside (**11**)[17] (5.8 g, 15.1 mmol) in acetic acid (215 ml)–water (6 ml) was added sodium acetate (3.5 g) and palladium chloride (3.4 g, 19.2 mmol), and the mixture was stirred overnight at room temperature. The reaction mixture was filtered off and slowly poured into saturated sodium hydrogencarbonate solution. The solution was extracted with ethyl acetate, and extract was dried over sodium sulfate. After filtration, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (hexane/ethyl acetate=2/1) to give 2,3-di-*O*-benzyl-L-rhamnopyranose (3.9 g, 75%). ^{1}H NMR δ=1.34 (d, *J*=6.3 Hz), 1.32 (d, *J*=6.4 Hz); ^{13}C NMR δ=93.6 (C-1β), 92.9 (C-1α). Found (α,β-mixture): C, 69.09; H, 7.01%. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02%.

2,3-Di-*O*-benzyl-L-rhamnopyranosyl Dimethylphosphinothioate (20): A procedure similar to the preparation of **1** using 2,3-di-*O*-benzyl-L-rhamnopyranose

Table 4. The Data of ^{1}H and ^{13}C NMR Spectrum Dimethylphosphinothioates

Entry	Mannopyranosyl dimethylphosphinothioates	α Anomer		β Anomer	
		H-1/ppm ($J_{1,2}$, J_{HCOP}/Hz)[a)]	C-1/ppm (J_{COP}/Hz)[b)]	H-1/ppm (J_{HCOP}/Hz)[b)]	C-1/ppm (J_{COP}/Hz)[b)]
1	**1**	6.06 (1.6, 12.0)	92.9 (5.5)	5.35 (12.7)	94.6 (5.6)
2	**2**	5.94 (2.0, 12.2)	93.1 (5.5)	5.32 (11.7)	94.5 (5.5)
3	**20**	5.98 (1.7, 12.0)	93.0 (5.5)	5.35 (12.2)	94.5 (7.3)
4	**18**	5.98 (2.0, 12.2)	93.5 (5.5)	5.41 (12.2)	94.4 (7.3)
5	**21**	5.94 (2.0, 11.7)	93.5 (5.6)	5.34 (12.2)	94.4 (7.4)

a) Double-doublet peak was observed. b) Doublet peak was observed.

(**19**) (3.6 g, 10.5 mmol), MptCl (1.4 g, 10.6 mmol), and a 1.62 M hexane solution of butyllithium (6.5 ml, 10.5 mmol) gave **20** (4.5 g, 97%) with an anomer ratio of $\alpha/\beta=62/38$ after purification by column chromatography (hexane/ethyl acetate=8/1). Found (α,β-mixture): C, 60.97; H, 6.80%. Calcd for $C_{22}H_{29}O_5PS$: C, 60.54; H, 6.70%.

2,3-Di-*O*-benzyl-4-*O*-benzyl-L-rhamnopyranosyl Dimethylphosphinothioate (18): To a solution of 2,3-di-*O*-benzyl-L-rhamnopyranosyl dimethylphosphinothioate (**20**) (463 mg, 1.1 mmol) in benzene was added pyridine (0.5 ml, 6.2 mmol) and benzoyl chloride (0.4 ml, 3.5 mmol), and the mixture was stirred overnight. After the addition of a 1 M HCl solution, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with a 1 M HCl solution, and dried over sodium sulfate. The solvent was evaporated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate=6/1) to give **18** (0.42 g, 73%) with an anomer ratio of $\alpha/\beta=65/35$. Found (α,β-mixture): C, 63.80; H, 6.28%. Calcd for $C_{29}H_{33}O_6PS$: C, 64.43; H, 6.15%.

4-*O*-Acetyl-2,3-di-*O*-benzyl-L-rhamnopyranosyl Dimethylphosphinothioate (21): To a pyridine solution (10 ml) of 2,3-di-*O*-benzyl-L-rhamnopyranosyl dimethylphosphinothioate (**20**) (0.91 g, 2.1 mmol) was added acetic anhydride (20 ml). After it was stirred overnight, the reaction mixture was poured into ice-water slowly and extracted with ethyl acetate. After the organic layer was dried over sodium sulfate, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (hexane/ethyl acetate=8/1) to give **21** (0.80 g, 80%) with an anomer ratio of $\alpha/\beta=63/37$. Found (α,β-mixture): C, 60.19; H, 6.59%. Calcd for $C_{24}H_{31}O_6PS$: C, 60.24; H, 6.53%.

General Glycosidation Procedure Using Silver Perchlorate as an Activator: To a solution of dimethylphosphinothioates (0.2 mmol) and alcohol (0.2 mmol) in benzene (2 ml) was added silver perchlorate (0.2 mmol) in the presence of MS 4A (ca. 100 mg), and the mixture was stirred overnight, sheltered from the light. A 5% sodium sulfide solution and ethyl acetate were added to the reaction mixture. Insoluble materials were filtered off, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with a 5% sodium sulfide solution and a saturated NaCl solution and dried over anhydrous sodium sulfate. After filtration, the solvent was concentrated in vacuo to afford the crude glycoside. The residue was purified by thin-layer chromatography on silica gel. The yields are given in Table 1.

General Glycosidation Procedure by the Combined Use of Iodine and 5 mol% TrtClO$_4$ as an Activating System: Into a solution of dimethylphosphinothioates (0.2 mmol), alcohol (0.2 mmol), and TrtClO$_4$ (0.01 mmol) in benzene (1 ml) was dropped a 0.1 M benzene solution of iodine (2 ml, 0.2 mmol) in the presence of MS 4A (ca. 100 mg), and the mixture was stirred overnight. The reaction was quenched by adding a 5% sodium thiosulfate solution. The successive procedure was similar to those described above. The yields are given in Tables 2 and 3.

3*β*-Cholestanyl 2,3,4,6-Tetra-*O*-benzyl-*α*-D-mannopyranoside (6): ^{13}C NMR $\delta=95.9$ (C-1) (lit,[4)] ^{13}C NMR $\delta=95.8$ (C-1)).

Cyclohexyl 2,3,4,6-Tetra-*O*-benzyl-*α*-D-mannopyranoside (7):[23)] ^{13}C NMR $\delta=95.8$ (C-1).

6-*O*-(2,3,4,6-Tetra-*O*-benzyl-D-mannopyranosyl)-1,2:3,4-di-*O*-isopropylidene-*α*-D-galactopyranose (8): ^{1}H NMR $\delta=5.60$ (d, $J=4.8$ Hz, H-1β), 5.52 (d, $J=5.6$ Hz, H-1α), 5.00 (s, H-1$'\alpha$), 4.43 (s, H-1$'\beta$); ^{13}C NMR $\delta=102.3$ (C-1$'\beta$, $J_{\mathrm{C1'-H1'}}=156.3$ Hz), 97.2 (C-1$'\alpha$, $J_{\mathrm{C1'-H1'}}=169.1$ Hz), 96.4 (C-1β), 96.3 (C-1α) (lit,[4)] ^{13}C NMR $\delta=97.3$ (C-1$'\alpha$, $J_{\mathrm{C1'-H1'}}=168.8$ Hz)).

3*β*-Cholestanyl 2,3,4-Tri-*O*-benzyl-L-rhamnopyranoside (9): ^{13}C NMR $\delta=99.2$ (C-1β, $J_{\mathrm{C1-H1}}=150.8$ Hz), 95.6 (C-1α, $J_{\mathrm{C1-H1}}=167.3$ Hz), (lit,[24)] ^{13}C NMR $\delta=95.7$ (C-1α, $J_{\mathrm{C1-H1}}=169$ Hz)).

Cyclohexyl 2,3,4-Tri-*O*-benzyl-*α*-L-rhamnopyranoside (10): ^{1}H NMR $\delta=4.86$ (1H, d, $J=1.5$ Hz, H-1); ^{13}C NMR $\delta=95.7$ (C-1, $J_{\mathrm{C1-H1}}=163.6$ Hz); $[\alpha]_{\mathrm{D}}^{24}-39°$ (*c* 2.6, CHCl$_3$). Found: C, 76.55; H, 7.81%. Calcd for $C_{33}H_{40}O_5$: C, 76.71; H, 7.80%.

6-*O*-(2,3,4-Tri-*O*-benzyl-L-rhamnopyranosyl)-1,2:3,4-di-*O*-isopropylidene-*α*-D-galactopyranose (14): Found (α,β-mixture): C, 68.92; H, 7.16%. Calcd for $C_{39}H_{48}O_{10}$: C, 69.21; H, 7.15%. The anomers were separated by thin-layer chromatography (benzene/ether=95/5). α Anomer: ^{1}H NMR $\delta=5.52$ (1H, d, $J=5.4$ Hz, H-1), 4.89 (1H, d, $J=1.4$ Hz, H-1$'$); ^{13}C NMR $\delta=98.0$ (C-1$'$, $J_{\mathrm{C1'-H1'}}=169.1$ Hz), 96.2 (C-1), 17.9 (C-6$'$); $[\alpha]_{\mathrm{D}}^{24}-52°$ (*c* 3.2, CHCl$_3$) (lit,[25)] $[\alpha]_{\mathrm{D}}^{27}-47°$ (*c* 1.0, CHCl$_3$). β Anomer: ^{1}H NMR $\delta=5.52$ (1H, d, $J=5.4$ Hz, H-1), 4.40 (1H, s, H-

1′); ^{13}C NMR δ=101.7 (C-1′, $J_{C1'-H1'}$=154.4 Hz), 96.2 (C-1); mp 91.5—92.5 °C; $[\alpha]_D^{24}$+8.3° (*c* 0.72, CHCl$_3$).

Allyl 4-*O*-(2,3,4-Tri-*O*-benzyl-L-rhamnopyranosyl)-2,3-di-*O*-benzyl-α-L-rhamnopyranoside (15): Found (α,β-mixture): C, 74.90; H, 7.05%. Calcd for $C_{50}H_{56}O_9$: C, 74.98; H, 7.05%. The anomers were separated by thin-layer chromatography (benzene/ether=4/1). α Anomer: ^{1}H NMR δ=5.27 (1H, d, J=1.5 Hz, H-1), 4.82 (1H, d, J=1.5 Hz, H-1′), 1.32 (3H, d, J=6.4 Hz), 1.31 (3H, d, J=6.4 Hz); ^{13}C NMR δ=99.8 (C-1), 97.0 (C-1′, $J_{C1'-H1'}$=167.3 Hz), 18.3 and 17.8 (C-6 and 6′); $[\alpha]_D^{24}$+17° (*c* 2.2, PhH) (lit,[24] ^{13}C NMR δ=97.0 (C-1′, $J_{C1'-H1'}$=167 Hz). β Anomer: ^{1}H NMR δ=4.79 (1H, d, J=2.4 Hz, H-1), 4.59 (1H, d, J=2.0 Hz, H-1′), 1.27 (3H, d, J=5.9 Hz), 1.22 (3H, d, J=5.9 Hz); ^{13}C NMR δ=101.5 (C-1′, $J_{C1'-H1'}$=156.3 Hz), 97.4 (C-1), 18.3 and 17.9 (C-6 and 6′); $[\alpha]_D^{24}$+82° (*c* 0.88, PhH).

Methyl 6-*O*-(2,3,4-Tri-*O*-benzyl-L-rhamnopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (16): Found (α,β-mixture): C, 75.08; H, 7.02%. Calcd for $C_{55}H_{60}O_{10}$: C, 74.98; H, 6.86%. The anomers were separated by thin-layer chromatography (hexane/ethyl acetate=4/1). α Anomer: ^{1}H NMR δ=3.26 (3H, s, OCH$_3$), 1.30 (3H, d, J=5.9 Hz, H-6′); ^{13}C NMR δ=98.1 (C-1′, $J_{C1'-H1'}$=167.3 Hz), 97.7 (C-1); $[\alpha]_D^{24}$+62° (*c* 1.5, PhH). β Anomer: ^{1}H NMR δ=4.56 (1H, d, J=3.4 Hz, H-1), 4.43 (1H, s, H-1′), 3.35 (3H, s, OCH$_3$), 1.35 (3H, d, J=6.4 Hz, H-6′); ^{13}C NMR δ=101.3 (C-1′, $J_{C1'-H1'}$=152.6 Hz), 98.3 (C-1), $[\alpha]_D^{24}$+86° (*c* 2.5, PhH).

Methyl 6-*O*-(2,3,4,6-Tetra-*O*-benzyl-D-mannopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (17): ^{1}H NMR δ=4.12 (s, H-1′β), 3.33 (s, OCH$_3$β), 3.30 (s, OCH$_3$α); ^{13}C NMR δ=101.4 (C-1′β, $J_{C1'-H1'}$=154.4 Hz), 98.2 (C-1′α, $J_{C1'-H1'}$=171.0 Hz), 97.7 (C-1αβ), 55.0 (OCH$_3$αβ) (lit,[4] ^{13}C NMR δ=98.9 (C-1′α, $J_{C1'-H1'}$=170.2 Hz). Found (α,β-mixture): C, 75.41; H, 6.95%. Calcd for $C_{62}H_{66}O_{11}$: C, 75.43; H, 6.74%.

3β-Cholestanyl 4-*O*-Benzoyl-2,3-di-*O*-benzyl-L-rhamnopyranoside (22): ^{1}H NMR δ=4.96 (d, J=2.0 Hz, H-1α), 4.55 (s, H-1β); ^{13}C NMR δ=99.4 (C-1β, J_{C1-H1}=152.6 Hz), 96.7 (C-1α, J_{C1-H1}=167.3 Hz). Found (α,β-mixture): C, 79.10; H, 9.08%. Calcd for $C_{54}H_{74}O_6$: C, 79.18; H, 9.10%.

3β-Cholestanyl 4-*O*-Acetyl-2,3-di-*O*-benzyl-L-rhamnopyranoside (23): ^{1}H NMR δ=4.91 (d, J=1.5 Hz, H-1α), 4.49 (s, H-1β); ^{13}C NMR δ=99.1 (C-1′β, J_{C1-H1}=152.6 Hz), 96.1 (C-1α, J_{C1-H1}=169.1 Hz). Found (α,β-mixture): C, 77.12; H, 9.38%. Calcd for $C_{49}H_{72}O_6\cdot 1/4\ H_2O$: C, 77.27; H, 9.59%.

6-*O*-(4-*O*-Benzoyl-2,3-di-*O*-benzyl-L-rhamnopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (24): Found (α,β-mixture): C, 67.71; H, 6.78%. Calcd for $C_{39}H_{46}O_{11}$: C, 67.81; H, 6.71%. The anomers were separated by thin-layer chromatography (CH$_2$Cl$_2$). α Anomer: ^{1}H NMR δ=5.54 (1H, d, J=4.9 Hz, H-1), 4.94 (1H, s, H-1′), 1.24 (3H, d, J=6.9 Hz, H-6′); ^{13}C NMR δ=98.3 (C-1′), 96.2 (C-1), 17.6 (C-6′); $[\alpha]_D^{24}$+43° (*c* 2.4, EtOH). β Anomer: ^{1}H NMR δ=5.52 (1H, d, J=5.4 Hz, H-1), 4.48 (1H, s, H-1′), 1.30 (3H, d, J=6.4 Hz, H-6′); ^{13}C NMR δ=101.7 (C-1′, $J_{C1'-H1'}$=154.4 Hz), 96.2 (C-1), 17.6 (C-6′); mp 129.5—130 °C; $[\alpha]_D^{24}-6.1$° (*c* 1.3, EtOH).

Methyl 6-*O*-(4-*O*-Benzoyl-2,3-di-*O*-benzyl-L-rhamnopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (25): Found (α,β-mixture): C, 73.57; H, 6.57%. Calcd for $C_{55}H_{58}O_{11}$: C, 73.81; H, 6.53%. The anomers were separated by thin-layer chromatography (hexane/ethyl acetate=4/1). α Anomer: ^{1}H NMR δ=4.80 (1H, s, H-1′), 4.56 (1H, d, J=3.4 Hz, H-1), 3.28 (3H, s, OCH$_3$), 1.21 (3H, d, J=6.4 Hz, H-6′); ^{13}C NMR δ=98.8 (C-1′), 97.8 (C-1), 55.0 (OCH$_3$), 17.6 (C-6′); $[\alpha]_D^{24}$+18° (*c* 0.91, EtOH). β Anomer: ^{1}H NMR δ=4.62 (1H, d, J=2.9 Hz, H-1), 4.51 (1H, s, H-1′), 3.37 (3H, s, OCH$_3$), 1.27 (3H, d, J=6.3 Hz, H-6′); ^{13}C NMR δ=101.2 (C-1′, $J_{C1'-H1'}$=154.5 Hz), 98.3 (C-1), 55.2 (OCH$_3$), 17.6(C-6′); $[\alpha]_D^{24}$+84° (*c* 3.5, EtOH).

Allyl 3,6-Bis-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-2,4-di-*O*-benzyl-α-D-mannopyranoside (27): To a solution of 2,3,4,6-tetra-*O*-benzyl-D-mannopyranosyl dimethylphosphinothioate (**1**) (278.4 mg, 0.44 mmol) and allyl 2,4-di-*O*-benzyl-α-D-mannopyranoside (**26**)[2] (80.5 mg, 0.2 mmol) in benzene (2 ml) was added silver perchlorate (91.9 mg, 0.44 mmol) in the presence of MS 4A (ca. 100 mg). The following experimental procedure was the same as described above. ^{1}H NMR of three anomeric carbons, δ=5.27 (1H, d, J=1.5 Hz), 5.08 (1H, s), and 4.79 (1H, d, J=1.5 Hz); ^{13}C NMR of three anomeric carbons, δ=100.0 (J_{C-H}=172.8 Hz), 98.1 (J_{C-H}=174.7 Hz), and 96.4 (J_{C-H}=170.9 Hz). $[\alpha]_D^{24}$+35° (*c* 3.3, CHCl$_3$). Found: C, 75.34; H, 6.81%. Calcd for $C_{91}H_{96}O_{16}$: C, 75.60; H, 6.69%.

1,6-Anhydro-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-mannopyranosyl)-β-D-glucopyeanose (29): ^{1}H NMR δ=5.52 (1H, s, H-1), 4.68 (1H, s, H-1′); ^{13}C NMR δ=100.6 (C-1), 98.6 (C-1′, $J_{C1'-H1'}$=154.4 Hz); $[\alpha]_D^{24}-23$° (*c* 1.9, CHCl$_3$). Found: C, 70.28; H, 6.34; N, 4.98%. Calcd for $C_{47}H_{49}N_3O_9$: C, 70.57; H, 6.17; N, 5.25%. Its α anomer was detected by ^{13}C NMR δ=98.1 (C-1′, $J_{C1'-H1'}$=167.3 Hz).

We are deeply indebted to Professor Teruaki Mukaiyama, Science University of Tokyo, for his helpful discussions. A part of this work was supported by a Grant-in-Aid for Science Research No. 03740292 from the Ministry of Education, Science and Culture, and the Special Coodination Funds of the Science and Technology Agency of the Japanese Govermment.

References

1) T. Ogawa and K. Sasajima, *Carbohydr. Res.*, **93**, 231 (1981).

2) T. Ogawa and T. Nukada, *Carbohydr. Res.*, **136**, 135 (1985).

3) P. Fügedi, A. Lipták, P. Nánási, and A. Neszmélyi, *Carbohydr. Res.*, **107**, C5 (1982).

4) K. Suzuki, H. Maeta, T. Suzuki, and T. Matsumoto, *Tetrahedron Lett.*, **30**, 6879 (1989).

5) C. A. A. van Boeckel, T. Beetz, and S. F. van Aelst, *Tetrahedron*, **40**, 4097 (1984).

6) H. Paulsen and R. Lebuhn, *Liebigs Ann. Chem.*, **1983**, 1047.

7) F. Barresi and O. Hindsgaul, *J. Am. Chem. Soc.*, **113**, 9376 (1991).

8) G. Stork and G. Kim, *J. Am. Chem. Soc.*, **114**, 1087 (1992).

9) T. Inazu, H. Hosokawa, and Y. Satoh, *Chem. Lett.*,

1985, 297.

10) T. Inazu and T. Yamanoi, *Chem. Lett.*, **1989**, 69.

11) S. Koto, N. Morishita, Y. Miyata, and S. Zen, *Bull. Chem. Soc. Jpn.*, **49**, 2639 (1976).

12) M. Ueki, T. Inazu, and S. Ikeda, *Bull. Chem. Soc. Jpn.*, **52**, 2424 (1979).

13) J. M. J. Frecht and H. H. Baer, *Carbohydr. Res.*, **42**, 369 (1975).

14) K. Bock, I. Lundt, and C. Pedersen, *Tetrahedron Lett.*, **13**, 1037 (1973).

15) R. R. Schmidt, M. Behrendt, and A. Toepfer, *Synlett*, **1990**, 694, and references cited therein.

16) T. Inazu, K. Nakamura, Y. Furusawa, and T. Yamanoi, "62nd National Meeting of the Chemical Society of Japan," Sapporo, September 1991, Abstr., No. 2E2 11.

17) M. Nishizawa, H. Imagawa, Y. Kan, and H. Yamada, *Tetrahedron Lett.*, **32**, 5551 (1991).

18) T. Ogawa, S. Nakabayashi, and T. Kitajima, *Carbohydr. Res.*, **114**, 225 (1983).

19) Y. Kimura, M. Suzuki, T. Matsumoto, R. Abe, and S. Terashima, *Bull. Chem. Soc. Jpn.*, **59**, 423 (1986).

20) T. Ogawa, K. Katano, and M. Matsui, *Carbohydr. Res.*, **64**, C3 (1978).

21) J. Arnarp and J. Lonngren, *Acta Chem. Scand., Ser. B*, **32**, 696 (1978).

22) H. Paulsen and W. Stenzel, *Chem. Ber.*, **111**, 2348 (1978).

23) S. Kobayashi, K. Koide, and M. Ohno, *Tetrahedron Lett.*, **31**, 2435 (1990).

24) M. Nishizawa, Y. Kan, W. Shimoto, and H. Yamada, *Tetrahedron Lett.*, **31**, 2431 (1990).

25) G. V. Reddy, V. R. Kulkarni, and H. B. Mereyala, *Tetrahedron Lett.*, **30**, 4283 (1989).