Pergamon

Tetrahedron Vol. 50, No. 22, pp. 6523-6536, 1994

0040-4020/94 $7.00+0.00

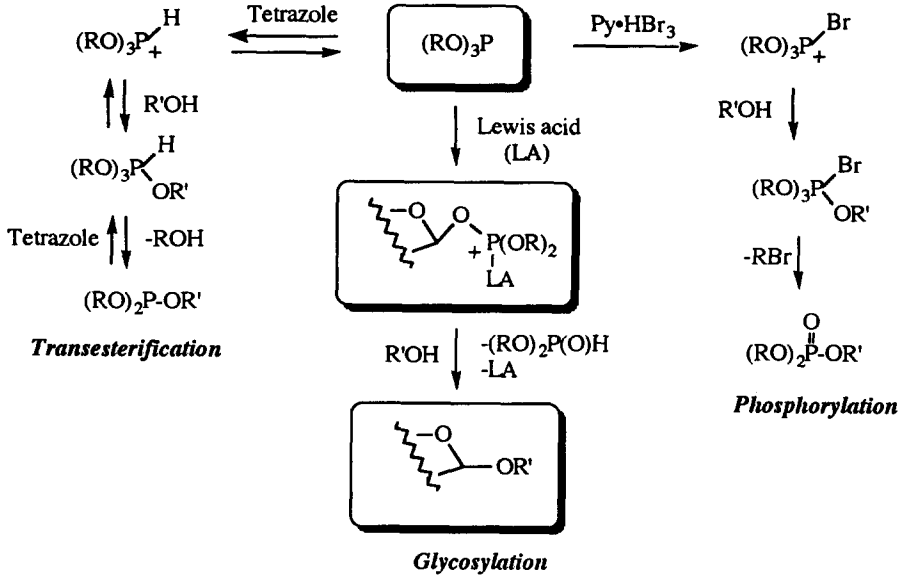
0040-4020(94)E0253-P

GLYCOSYLATION USING GLYCOSYL PHOSPHITE AS A GLYCOSYL DONOR

Yutaka Watanabe,* Chikara Nakamoto, Takashi Yamamoto, and Shoichiro Ozaki
Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790, Japan

Abstract: Glycosylation using glycosyl phosphites as glycosyl donors in the presence of a Lewis acid such as $ZnCl_2$ or $ZnCl_2$-$AgClO_4$ has afforded the glycosides including sialoglycosides in good yields.

A phosphite forms the phosphonium salt by the interaction with a Lewis acid owing to its Lewis basic character. We have utilized this property in transesterification of a trialkyl phosphite in the presence of 1*H*-tetrazole.[1] A readily oxidizable property of the phosphite was also utilized for the phosphorylation via phosphonium salt which was *in situ* formed by the action of pyridinium hydrobromide perbromide.[2] When a glycosyl phosphite is transformed to the phosphonium salt, the resulting phosphoniooxy group acts as a strong leaving group in the nucleophilic substitution at the anomeric carbon center. Based on the consideration, we have investigated an efficient glycosylation method and planed to synthesize glycosyl phosphatidyl inositols (GPI).[3]

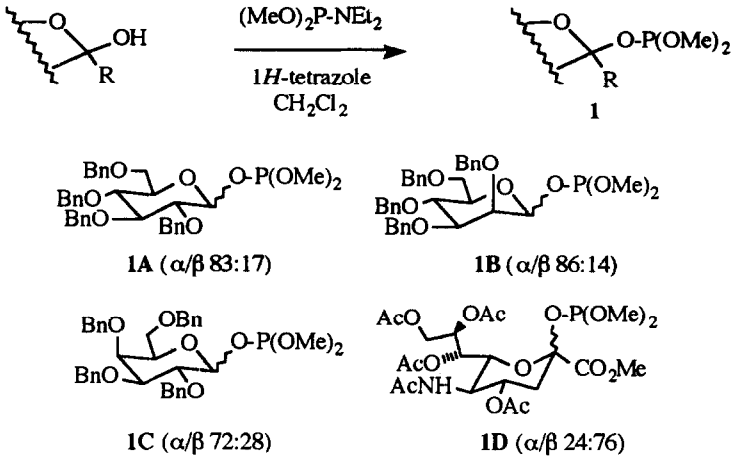


In recent years, a number of methodologies for glycosylation have appeared, which involve various types of glycosyl donors and their combination with activators.[4] However, glycosyl phosphite as a glycosyl donor has not appeared until 1992 while P(V) derivatives have been actively investigated.[5] Thus, Schmidt[6] and Wong[7] groups have revealed at the same period that sialyl diethyl or dibenzyl phosphite is a very useful reagent for sialoglycoside synthesis where trimethylsilyl trifluoromethanesulfonate (TMSOTf) was employed to activate the phosphite. We

also communicated the identical glycosylation method using glucosyl, mannosyl, and galactosyl dimethyl phosphites and activators such as $ZnCl_2$ and $ZnCl_2$-$AgClO_4$ independently later.[8] Here we report our results in full detail and compare the efficiency of activators.

Results and Discussion

Synthesis of phosphites. According to the phosphoramidite approach,[9] 1-hydroxyl sugars such as 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose, -D-mannopyranose, and -D-galactopyranose were transformed smoothly and quantitatively to the corresponding phosphites **1** by the reaction with 1.3 molar equivalent each of dimethyl *N,N*-diethylphosphoramidite or other amidites and 1*H*-tetrazole in CH_2Cl_2 at room temperature while 1.7 to 2.3 molar equivalents of the reagents were required to obtain sterically hindered sialyl dimethyl phosphite **1D** in around 93% yield. Both groups of Schmidt[6] and Wong[7] reported to yield diethyl and dibenzyl 2-sialyl phosphite only with β-configuration respectively when the phosphitylation was conducted in THF in place of CH_2Cl_2. Phosphitylation has been generally carried out by using excess of tetrazole as Wong et al. used 2 fold excess of tetrazole toward phosphoramdites in the reaction mentioned above. However, we point out that such an excess amount of tetrazole is not necessary and rather might cause a side reaction. In fact, we observed the reaction of 1-glucosyl phosphite **1A** with tetrazole resulting in the formation of *N*-(glucosyl)tetrazole.

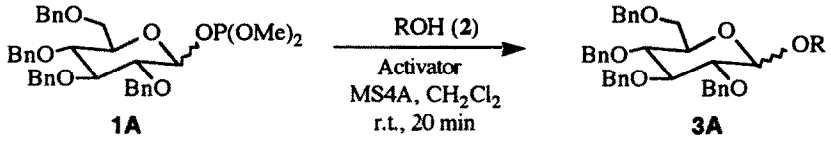


Scheme 1. Synthesis of glycosyl phosphites

The resultant α/β anomeric mixture, the ratio of which was determined by ^1H- and ^{31}P NMR was used after a general work-up procedure without purification while the phosphites are purified on silica gel using an eluting solution containing 2-3% of triethylamine if necessary. These phosphites can be stored in a desiccator under an inert atmosphere.

Glycosylation using glycosyl phosphites. A Lewis acid to promote the reaction of glycosyl phosphite with an alcohol was first explored by the use of glucopyranosyl dimethyl phosphite **1A**. As shown in Table 1, various Lewis acids were effective in the case of 3-phenylpropanol (**2a**) and cyclohexanol (**2b**). Glycosylation of 4-*O*-unprotected methyl glucopyranoside **2g** was effected by using $ZnCl_2$-$AgClO_4$. These results suggested that

$ZnCl_2$ or $ZnCl_2$-$AgClO_4$ was the choice of promoter. In particular, the latter mixed reagent had a strong ability to promote the reaction, while the anomeric ratio was about 1:1 in cases of simple alcohols. However, the quantity of α-glycosides derived from alcohols with low reactivity such as **2g** (run 23 and 24 in Table 1) and inositol derivative **2h** (run 7 in Table 7) increased. Use of the phosphite in excess gave generally better results than that of excess of alcohol (compare entries 7 and 8, and 17 and 18 in Table 1). Changing the ratio of $ZnCl_2$ to $AgClO_4$ from 1 : 1 to 1 : 2, the reaction rate increased and 20 mol% of $ZnCl_2$ 40 mol% of $AgClO_4$ was sufficient as shown in Table 2. When using $ZnCl_2$ alone in the reaction of the unreactive **2g** with **1A** caused the formation of a fairly amount of the 1-chloro derivative from the glycosyl donor as a by-product, addition of $AgClO_4$ suppressed its formation completely. Therefore, $AgClO_4$ plays important roles in acceleration of the reaction and extrusion of the chloride ion in the reaction medium. The mixed reagent, $ZnCl_2$-$AgClO_4$ has not been used so far as an activator in the glycosylation. The combined reagent (92% yield of **3Aa**, run 11 in Table 1) gave much better results than combination with AgOTf (60%).



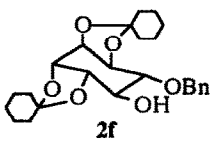
1A **3A**

Table 1. Screening of an activator in the glycosylation

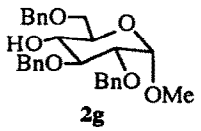
Run	ROH (equiv)	Activator (equiv)	Product	Yield %	α/β Ratio	Run	ROH (equiv)	Activator (equiv)	Product	Yield %	α/β Ratio
1	**2a** (1.0)	NIS-TfOH (1.0-0.1)	**3Aa**	86	55/45	14	**2a** (1.0)	$BiCl_3$-$AgClO_4$ (1.0-2.0)	**3Aa**	93	53/47
2	**2a** (1.1)	$CuCl_2$ (1.1)	**3Aa**	80	58/42	15	**2b** (1.1)	MeOTf (1.1)[b]	**3Ab**	87	50/50
3	**2a** (1.1)	$Cu(OTf)_2$ (1.1)	**3Aa**	89	66/34	16	**2b** (1.0)	NIS-TfOH[c] (1.0-0.1)	**3Ab**	85	57/43
4	**2a** (1.0)	$SbCl_3$ (1.0)	**3Aa**	83	40/60						
5	**2a** (1.1)	MeOTf (4.4)[a]	**3Aa**	87	43/57	17	**2b** (0.75)	$ZnCl_2$ (1.1)	**3Ab**	100	22/78
6	**2a** (2.2)	I_2 (2.2)[a]	**3Aa**	92	81/19	18	**2b** (1.0)	$ZnCl_2$ (1.0)	**3Ab**	82	22/78
7	**2a** (0.75)	$ZnCl_2$ (1.1)	**3Aa**	100	25/75	19	**2b** (1.2)	$BiCl_3$ (1.0)	**3Ab**	76	24/76
8	**2a** (1.0)	$ZnCl_2$ (1.0)	**3Aa**	88	20/80	20	**2b** (2.2)	I_2 (2.2)[a]	**3Ab**	91	81/19
9	**2a** (1.0)	$ZnBr_2$ (1.0)	**3Aa**	80	32/68	21	**2g** (1.1)	NIS-TfOH (1.0-0.1)	**3Ag**	28	60/40
10	**2a** (1.0)	ZnI_2 (1.0)	**3Aa**	71	30/70						
11	**2a** (1.0)	$ZnCl_2$-$AgClO_4$ (1.0-2.0)	**3Aa**	92	52/48	22	**2g** (0.75)	$ZnCl_2$ (1.2)[d]	**3Ag**	43	45/55
12	**2a** (1.0)	$BiCl_3$ (1.0)	**3Aa**	84	20/80	23	**2g** (0.75)	$ZnCl_2$-$AgClO_4$[e] (1.1-2.2)	**3Ag**	81	68/32
13	**2a** (1.0)	$BiBr_3$ (1.0)	**3Aa**	67	17/83	24	**2g** (0.5)	$ZnCl_2$-$AgClO_4$[f] (1.1-2.2)	**3Ag**	100	66/34

[a] Ethyldiisopropylamine (slightly excess in molar quantity based on the alcohol) added. [b] K_2CO_3 (quantity like in the footnote a) added. [c] Conducted at 1 °C. [d] For 13 h reacted. [e] For 3 h reacted. [f] For 1 h reacted.

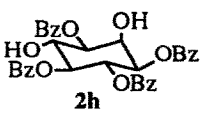
2a: $Ph(CH_2)_3OH$
2b: Cyclohexanol
2c: *t*-Butanol
2d: 3β-Cholestanol
2e: Cholesterol



2f



2g



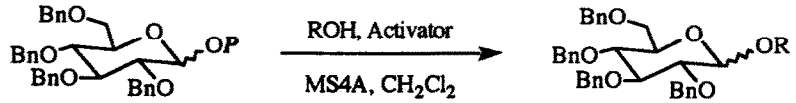
2h

2i: (+)-Menthol

Table 2. Examination of molar ratio of $ZnCl_2$ and $AgClO_4$[a]

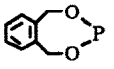
Run	ROH	equiv and ratio[b] of $ZnCl_2$ & $AgClO_4$	Time	Yield %	Ratio α/β
1	**2d**	1.1 & 2.2 (1 : 2)	20 min	95	42/58
2	**2d**	1.1 & 0.5 (2 : 1)	20 min	98	44/56
3	**2d**	0.2 & 0.1 (2 : 1)	18 h	99	43/57
4	**2d**	0.2 & 0.2 (1 : 1)	12 h	100	42/58
5	**2d**	0.2 & 0.4 (1 : 2)	1.5 h	100	43/57
6	**2g**	0.2 & 0.4 (1 : 2)	3.0 h	86	66/34

[a] An alcohol (0.75 equiv) was treated with the phosphite **1A** (1.0 equiv) in the presence of the catalyst and MS 4A at room temperature. [b] Shown in parentheses.



1 **3A**

Table 3. Comparison of substituents on the phosphorus moiety

Run	*P*	ROH (equiv)	Activator (equiv)	Time h	Yield %	Ratio α/β
1	$(EtO)_2P$	**2a** (0.75)	$ZnCl_2$ (1.1)	1/3	100	35/65
2	$(EtO)_2P$	**2g** (0.75)	$ZnCl_2$-$AgClO_4$ (1.1-2.2)	4	88	69/31
3	$(MeO)_2P$	**2g** (0.75)	$ZnCl_2$-$AgClO_4$ (1.1-2.2)	3	81	68/32
4		**2d** (0.8)	$ZnCl_2$-$AgClO_4$ (0.5-1.0)	2	86	32/68
5	Ph_2P	**2d** (1.0)	$ZnCl_2$ (1.1)	10	77	15/85

The effect of substituent in the phosphorus moiety was examined and the ethoxy and *o*-xylylenedioxy groups as well as the methoxy were found to give similar results as shown in Table 3. Diphenylphosphinite derivative which was prepared by using diphenylphosphinous chloride in place of the amidite in the presence of ethyldiisopropylamine gave also similar results, but the glycosyl donor was so unstable that its handling was difficult.

In order to know factors affecting the anomeric ratio in the glycosylation, effects of solvent and temperature were examined by using the model reaction of glucopyranosyl phosphite **1A** with some alcohols in the presence of *N*-iodosuccinimide (NIS)-trifluoromethanesulfonic acid (TfOH)[10] and zinc catalysts. The results (Table 4) showed that as observed generally,[11] ethyl ether gave α-anomer and acetonitrile β-one at room temperature predominantly. But interestingly, the reaction in the ether at lower temperatures increased the kinetic product, β-anomer, which in turn, predominated at around -70 °C (Table 5). This tendency was also observed in CH_2Cl_2.[12] Suzuki et al. reported similar temperature effect.[12]

Table 4. Solvent effect[a]

Run	Solvent	ROH (equiv)	Activator (equiv)	Yield %	Ratio α/β
1	CH_2Cl_2	**2a** (0.75)	$ZnCl_2$ (1.1)	100	25/75
2	CH_2Cl_2	**2c** (0.75)	$ZnCl_2$ (1.1)	99	31/69
3	Et_2O	**2c** (0.75)	$ZnCl_2$-$AgClO_4$ (1.1-2.2)	100	75/25
4	CH_2Cl_2	**2d** (0.75)	$ZnCl_2$ (1.1)	86	22/78
5	Et_2O	**2d** (0.75)	$ZnCl_2$-$AgClO_4$ (1.0-2.0)	94	84/16
6	CH_2Cl_2	**2a** (1.0)	NIS-TfOH (1.0-0.1)	86	55/45
7	Et_2O	**2a** (1.0)	NIS-TfOH (1.0-0.1)	75	76/24
8	PhMe	**2a** (1.0)	NIS-TfOH (1.0-0.1)	91	66/34
9	CH_3CN	**2a** (1.0)	NIS-TfOH (1.0-0.1)	64	25/75

[a] The reaction with the phosphite **1A** (1.0 equiv) was conducted in the presence of MS 4A at room temperature for 20 min.

Table 5. Temperature effect on the anomeric ratio[a]

Run	Solvent	Temp.	Time	Yield %	Ratio α/β
1	CH_2Cl_2	r.t.	20 min	86	55/45
2	CH_2Cl_2	3 °C	2.5 h	82	50/50
3	CH_2Cl_2	-21 °C	15 min	89	31/69
4	CH_2Cl_2	-45 °C	20 min	85	20/80
5	CH_2Cl_2	-68 °C	20 min	82	13/87
6	Et_2O	r.t.	20 min	75	76/24
7	Et_2O	1 °C	20 min	83	70/30
8	Et_2O	-21 °C	15 min	79	55/45
9	Et_2O	-43 °C	20 min	88	52/48
10	Et_2O	-72 °C	20 min	89	27/73

[a] The reaction of **1A** (1.0 equiv) with **2a** (1.0 equiv) in the presence of NIS-TfOH (1.0-0.1 equiv) and MS 4A was utilized for the purpose.

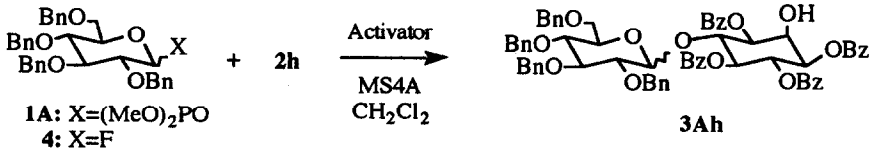
Keeping these results in mind, various glycosides were prepared by the use of benzyl-protected mannopyranosyl **1B** and galactopyranosyl phosphites **1C** as well as **1A**. The results are collected in Table 6 which includes some data appeared already in other tables. Glycosyl donors employed here were all benzyl protected derivatives. When dimethyl 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl phosphite as an example of an acyl-protected glycosyl donor was reacted with 3-phenylpropanol **1a** in the presence of $ZnCl_2$-$AgClO_4$, the glycoside (30% yield) was accompanied by 41% of 3-phenylethyl acetate. On the other hand, 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-mannopyranosyl phosphite acted as an effective glycosyl donor in the presence of $ZnCl_2$-$AgClO_4$ and NIS-TfOH. These results will be reported elsewhere in due course.

Table 6. Synthesis of various glycosides by the phosphite methodology[a]

Run	1	2 (equiv.)	Activator (equiv)	Product	Yield %	Ratio α/β
1	**1A**	**2c** (0.75)	$ZnCl_2$ (1.1)	**3Ac**	99	31/69
2	**1A**	**2d** (0.75)	$ZnCl_2$ (1.1)	**3Ad**	86	22/78
3	**1A**	**2d** (0.75)	$ZnCl_2$-$AgClO_4$ (1.1-2.2)	**3Ad**	95	42/58
4	**1A**	**2e** (0.75)	$ZnCl_2$ (1.1)	**3Ae**	89	25/75
5	**1A**	**2f** (0.5)	$ZnCl_2$ (1.1)	**3Af**	89	37/63
6	**1A**	**2g** (0.5)	$ZnCl_2$-$AgClO_4$ (1.1-2.2)	**3Ag**	100	66/34
7	**1A**	**2g** (0.75)	$ZnCl_2$-$AgClO_4$ (0.2-0.4)	**3Ag**	86	66/34
8	**1B**	**2a** (1.2)	$ZnCl_2$ (1.2)	**3Ba**	83	51/49
9	**1B**	**2b** (1.2)	$ZnCl_2$ (1.2)	**3Bb**	83	40/60
10	**1B**	**2g** (0.75)	$ZnCl_2$-$AgClO_4$ (1.2-2.4)	**3Bg**	76	α only
11	**1C**	**2a** (1.2)	$ZnCl_2$ (1.1)	**3Ca**	70	26/74
12	**1C**	**2b** (1.2)	$ZnCl_2$ (1.1)	**3Cb**	77	18/82

[a] Reaction conditions: MS 4A, CH_2Cl_2, r.t., 20 min.

In connection with determining the absolute configuration of 4-α-D-glucopyranosyl-*myo*-inositol, glycosylation of 1,3,5,6-tetra-*O*-benzoyl-*myo*-inositol was necessary.[13] For this purpose, 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl fluoride **4**, bromide, and imidate as well as phosphite **1A** as glycosyl donors were examined and in particular, combination of the phosphite derivative **1A** with $ZnCl_2$-$AgClO_4$ or NIS-TfOH and fluoride **4**[14] with trifluoromethanesulfonic anhydride (Tf_2O)[15] was found to be equally effective (Table 7).



1A: X=$(MeO)_2PO$
4: X=F

3Ah

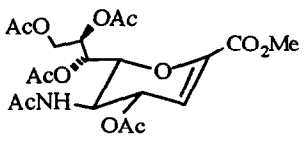
Table 7. Glycosylation of 1,3,4,6-tetra-*O*-benzoyl-*myo*-inositol 2h

Run	Glycosyl donor	Equiv of **2h**	Activator (equiv)	Conditions	Yield, % α	β
1	**4**	0.5	Tf_2O (0.5)	r.t., 18 h[a]	76	11
2	**4**	2.0	Cp_2ZrCl_2-$AgClO_4$ (5.0-5.0)	-20 °C, 0.5 h	55	4
3	**4**	2.0	Cp_2HfCl_2-$AgClO_4$ (1.0-2.0)	-60 °C, 1.5 h	30	10
4	**4**	0.85	$SnCl_2$-$AgClO_4$ (1.0-1.0)	-20 °C, 1 h then r.t., 4 h	48	14
5	**1A**	1.1	MeOTf (1.1)	r.t., overnight	60	2
6	**1A**	0.5	NIS-TfOH (1.0-0.1)	r.t., 20 min	76	14
7	**1A**	0.75	$ZnCl_2$-$AgClO_4$ (1.1-2.2)	r.t., 43 h	75	24

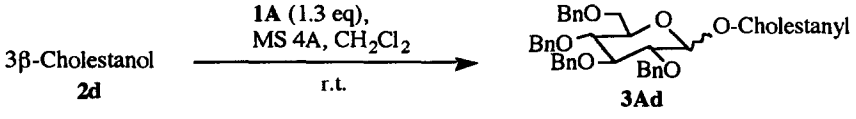
[a] Et_2O in place of CH_2Cl_2.

As mentioned already, at the stage of almost completion of the present investigation, Schmidt[6] and Wong[7] groups reported the similar glycosylation for an efficient synthesis of sialoglycoside where TMSOTf was employed

as a promoter and diethyl[6] and dibenzyl[7] esters used as phosphites, respectively. We compared then their Lewis acid with our $ZnCl_2$-$AgClO_4$ and NIS-TfOH in the phosphite-based glycosylation. According to their reported procedures in which excess of the alcohol component was used, the corresponding glycosides were obtained in slightly lower yields than our procedure using excess of the phosphite as shown already in the cases using glycosyl phosphites. The reaction of **1A** with 3β-cholestanol (**2d**) in the presence of the silyl catalyst in CH_2Cl_2 proceeded faster than that using the zinc catalyst to afford the glycoside **3Ad** in yield and anomeric ratio comparable to those in the latter case. Sialylation of alcohols using dimethyl phosphite **1D** as the glycosyl donor in the presence of the silyl and zinc catalyst proceeded smoothly in both cases (Table 8). Glycosylation of 3β-cholestanol and (+)-menthol in acetonitrile gave α-anomers predominantly while in dichloromethane β-anomers predominated. In the case of 3-phenylpropanol in the presence of TMSOTf or NIS-TfOH α-sialoside was the major product in both solvents. Employment of $ZnCl_2$-$AgClO_4$ in acetonitrile generally gave poor results presumably because depression of the catalytic activity of the zinc catalyst resulting from coordination of the solvent to the Zn^{2+}. Formation of the 2,3-dehydro derivative **5**[16] has been a serious problem in the sialylation. In the phosphite-based glycosylation, such an undesirable product was suppressed by adding a catalyst at -42 °C and then conducting the reaction at the temperature shown in Table 8 while initiation of

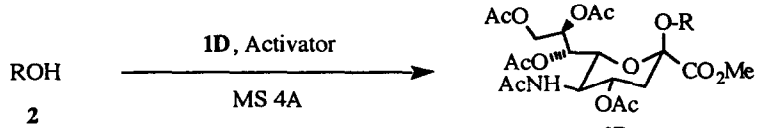


5



3Ad

TMSOTf (0.1 eq), 20 min: 89% (α/β 50/50)
$ZnCl_2$ (0.2 eq)/$AgClO_4$ (0.4 eq), 1.5 h: 100% (α/β 43/57)



3D

Table 8. Comparison of promoters in the reaction of 1D with 2.

Run	ROH	Equiv of 1D	Activator (equiv)[a]	Solvent	Temp.[b]	Time	Product	Yield %	Ratio α/β
1	**2a**	0.9	TMSOTf (0.1)	CH_2Cl_2	-23 °C	30 min	**3Da**	66	61/39
2	**2a**	0.9	TMSOTf (0.1)	CH_3CN	-23 °C	30 min	**3Da**	69	74/26
3	**2a**	1.3	NIS-TfOH (1.0-0.1)	CH_3CN	r.t.	1.5 h	**3Da**	61	66/34
4	**2d**	0.9	TMSOTf (0.1)	CH_2Cl_2	r.t.	1.5 h	**3Dd**	78	23/77
5	**2d**	1.3	$ZnCl_2$-$AgClO_4$ (0.2-0.4)	CH_2Cl_2	r.t.	5.0 h	**3Dd**	85	14/86
6	**2i**	0.9	TMSOTf (0.1)	CH_2Cl_2	-42 °C	40 min	**3Di**	68	20/80
7	**2i**	1.3	$ZnCl_2$-$AgClO_4$ (0.2-0.4)	CH_2Cl_2	r.t.	5.0 h	**3Di**	83	16/84

[a] Based on **1D**. [b] The catalyst was added at -42 °C and then the mixture was stirred at the temperature shown in each experiment.

the reaction at a higher temperature yielded a some extent of **5**. It should be noted that, when sialylation of 3β-cholestanol using TMSOTf was carried out several times variable amounts of the*O*-silylated cholestanol were isolated and yields of the sialoglycoside sometimes were reduced. The relationship between reaction conditions and silyl ether formation is now unclear.

In conclusion, the phosphite is quite useful as a glycosyl donor and the present glycosylation using $ZnCl_2$, $ZnCl_2$-$AgClO_4$, or NIS-TfOH is promising. The rather weak Lewis acid, $ZnCl_2$ realizes a mild glycosylation. The following facts also prove usefulness of the phosphite-based glycosylation. Schmidt[6] and Wong[7] have showed that sialylation using sialyl phosphites affords the sialosides in good yields which are higher than or comparable to that from other known methods. Furthermore, Corey and Wu very recently reported that, while a variety of known glycosylation methodologies and also the phosphite procedure using TMSOTf as a catalyst reported by Schmidt and Wong's groups failed, the present combination of 1-glycosyl phosphite, **1A** and the $ZnCl_2$-$AgClO_4$ catalyst was successfully utilized in the synthesis of paeoniflorin to accomplish glycosylation of sterically hindered alcohol.[17]

Experimental

All the melting points were uncorrected. NMR spectra (^1H, ^{13}C, and ^{31}P) were recorded on a JEOL JNM-GSX270 (270 MHz for ^1H). When $CDCl_3$ was used in NMR, TMS (δ=0.0) was used for proton spectra and the signal of the solvent (δ=77.0) for carbon spectra as references. In the case of ^{31}P NMR, 85% H_3PO_4 (δ=0.0) was used as an external standard and positive chemical shifts are downfield from it. ^{13}C and ^{31}P NMRs were all taken under ^1H-decoupled conditions. IR spectra were recorded on a Hitachi EPI-G3. Elemental analyses were performed on a Perkin-Elmer 240C. Flash chromatography was utilized for column chromatography by using Wako Pure Chemical Industries, silica gel, Wakogel C-300. Anhydrous reaction atmosphere was achieved by nitrogen gas. Anhydrous solvents used here were prepared in a usual manner. Extracts obtained after work-up were dried over $MgSO_4$ or Na_2SO_4. The anomeric ratio of glycosylation products **3A, 3B, and 3C** were determined by ^1H NMR (^{13}C NMR was utilized in some cases.) and HPLC analyses: System 1=Super Micro Bead Silica Gel™ (Fuji-Davison Chemical Ltd.), AcOEt-C_6H_{14} 1:5; System 2=Super Micro Bead Silica Gel™, AcOEt-C_6H_{14} 1:10; System 3=Wakosil™ (Wako Pure Chemical Industries Ltd.), CH_3CN-H_2O 9:1. The ratio of sialoglycosides **3D** were determined by integral ratio of equatorial H_3 in the ^1H NMR spectrum.[7b]

Dimethyl *N,N*-diethylphosphoramidite.[18] To a solution of MeOH (17.1 ml, 421 mmol) and triethylamine (80 ml, 574 mmol) in ethyl ether (150 ml) cooled by a Dry-Ice-acetone bath was added dropwise below 0 °C an ethyl ether (80 ml) solution of *N,N*-diethylphosphoramidous dichloride[19] (33.3 g, 191 mmol) and the mixture was stirred overnight. After addition of aq. 5% $NaHCO_3$ solution and ethyl ether, the organic phase was washed with aq. 5% $NaHCO_3$ (twice) and brine, dried, filtered. The residue was subjected to distillation under reduced pressure to give the amidite (20 g, 63% yield). bp 65-66 °C/40 mmHg; ^1H NMR ($CDCl_3$) δ=1.07 (6 H, t, *J*=7.02 Hz), 3.07 (4 H, dq, *J*=9.46 and 7.02 Hz), 3.41 (6 H, d, *J*=12.51 Hz); ^{31}P NMR ($CDCl_3$) δ=150.64. *Anal.* Calc. for $C_6H_{16}NO_2P$: C, 43.63; H, 9.76; N, 8.48%. Found: C, 44.02; H, 9.75; N, 8.38%.

Synthesis of glycosyl phosphites.

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl dimethyl phosphite (1A). A mixture of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (31.3 mg, 58 μmol), 1*H*-tetrazole (6.1 mg, 87 μmol), and dimethyl *N,N*-diethylphosphoramidite (12.4 μl, 75 μmol) in CH_2Cl_2 (1 ml) was stirred at room temperature for 1 h and ethyl ether and H_2O were added. The organic layer was washed with H_2O and brine, dried (Na_2SO_4), and concentrated to afford chromatographically pure phosphite (36.6 mg, 100% yield) which was employed for glycosylation without further purification. ^1H NMR (for α-anomer, $CDCl_3$) δ=3.53 (3 H, d, *J*=10.68 Hz), 3.55 (3 H, d, *J*=10.07 Hz), 3.47-3.78 (5 H, complex), 3.99 (1 H, *J*=9.5 Hz), 4.70 (2 H, s), 4.46 and 4.60 (2 H, ABq, *J*=12.0 Hz), 4.48 and 4.96 (2 H, ABq, *J*=11.0 Hz), 4.81 and 4.84 (2 H, ABq, *J*=10.7 Hz), 5.54 (1 H, dd, *J*=8.2 and 3.4 Hz), and 7.10-7.46 (20 H, complex); ^{31}P NMR ($CDCl_3$) δ=141.13 (α) and 142.18 (β). Integral ratio (α/β) of these peaks was 83 : 17.

In a similar manner, other glycosyl phosphites were prepared quantitatively and used without purification.

2,3,4,6-Tetra-*O*-benzyl-D-mannopyranosyl dimethyl phosphite (1B). ^1H NMR (for α-anomer, $CDCl_3$) δ=3.40 (3 H, d, *J*=10.5 Hz), 3.44 (3 H, d, *J*=10.5 Hz), 3.40-4.10 (6 H, complex), 4.47-5.00 (8 H, complex), 5.53 (1 H, dd, *J*=7.9 and 1.8 Hz), and 7.12-7.56 (20 H, complex); ^{31}P NMR ($CDCl_3$) δ=140.98 (α) and 141.20 (β); α/β 86 : 14.

2,3,4,6-Tetra-*O*-benzyl-D-galactopyranosyl dimethyl phosphite (1C). ^1H NMR (for α-anomer, $CDCl_3$) δ=3.40-3.66 (9 H, complex), 3.96 (1 H, dd, *J*=10.1 and 2.6 Hz), 4.10 (1 H, dd, *J*=10.1 and 3.4 Hz), 4.17 (1 H, t, *J*=6.4 Hz), 4.39-4.99 (8 H, complex), 5.60 (1 H, dd, *J*=8.6 and 3.4 Hz), and 7.22-7.24 (20 H, complex); ^{31}P NMR ($CDCl_3$) δ=141.41 (α) and 141.66 (β); α/β 72 : 28.

Methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2-(dimethyl phosphityl)-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonate (1D): The procedure was essentially similar to that for glucopyranosyl phosphite **1A** except for the reaction time (1.5 h) and quantities of the amidite and 1*H*-tetrazole (1.5 to 2.3 molar equivalent each). ^1H NMR ($CDCl_3$) δ=1.89 (3 H, s, Ac for β), 2.03 (6 H, s, Ac for β), 2.08 (3 H, s, Ac for β), 2.14 (3 H, s, Ac for β), 2.04 (6 H, s, Ac for α), 2.07 (3 H, s, Ac for α), 2.12 (3 H, s, Ac for α), 2.13 (3 H, s, Ac for α), 1.89-2.14 (1 H x 2, complex, H_3-ax), 2.48 (1 H, dd, *J*=13.1 and 4.9 Hz, H_3-eq for β), 2.71 (1 H, dd, *J*=13.1 and 4.9 Hz, H_3-eq for α), 3.57 (3 H, d, *J*=10.0 Hz, $POCH_3$ for β), 3.59 (3 H, d, *J*=10.7 Hz, $POCH_3$ for β), 3.52 (3 H, d, *J*=10.4 Hz, $POCH_3$ for α), 3.55 (3 H, d, *J*=9.3 Hz, $POCH_3$ for α), 3.83 (3 H x 2, s x 2, CO_2CH_3), 4.17-4.21 (2 H x 2, complex, H_5 and H_9), 4.28 (1 H, dd, *J*=10.4 and 2.1 Hz, H_6 for β), 4.38 (1 H, dd, *J*=10.4 and 2.1 Hz, H_6 for α), 4.63 (1 H x 2, dd, *J*=12.5 and 2.4 Hz, $H_{9'}$), 5.16 (1 H x 2, m, H_8), 5.30 (1 H x 2, m, H_4), 5.42 (1 H x 2, dd, *J*=3.7 and 2.1 Hz, H_7), and 5.46 (1 H x 2, d, *J*=10.1 Hz, NH); ^{31}P NMR ($CDCl_3$) δ=137.15 (α) and 138.85 (β); α/β 20 : 80.

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl diethyl phosphite. ^1H NMR (for α-anomer, $CDCl_3$) δ=1.23 (6 H, t, *J*=7.7 Hz), 3.58-4.04 (10 H, complex), 4.46 and 4.60 (2 H, ABq, *J*=12.2 Hz), 4.48 and 4.84 (2 H, ABq, *J*=10.7 Hz), 4.81 and 4.95 (2 H, ABq, *J*=11.0 Hz), 4.70 (2 H, s), 5.57 (1 H, dd, *J*=8.5 and 3.4 Hz), and 7.20-7.44 (20 H, complex); ^{31}P NMR ($CDCl_3$) δ=140.38 (α) and 141.03 (β); α/β 77 :23.

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl *o*-xylylene phosphite was used without any characterization except for TLC analysis [R_f (ethyl acetate-hexane 1:2) 0.81].

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl diphenylphosphinite. A mixture of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (49 mg, 91 μmol), ethyldiisopropylamine (17.4 μl, 100 μmol), and diphenylphosphinous chloride (18.4 μl, 100 μmol) in CH_2Cl_2 (1.5 ml) was stirred at room temperature for 1 h and

ethyl ether and H_2O were added. The organic layer was washed with H_2O and brine, dried, and concentrated. The residue was subjected to column chromatography on silica gel (ethyl acetate/hexane, 1:15 involving 1% triethylamine) to afford the phosphinite (26.2 mg, 40% yield). ^1H NMR (for α-anomer, $CDCl_3$) δ=3.54 (1 H, ddd, *J*=9.2, 7.0, and 2.8 Hz), 3.61-3.73 (4 H, complex), 3.61-3.73 (1 H, m), 3.76 (1 H, ddd, *J*=11.0, 7.6, and 3.4 Hz), 4.02 (1 H, t, *J*=9.2 Hz), 4.43-4.99 (8 H, complex), 5.19 (1 H, d, *J*=8.2 Hz), 6.06 (1 H, d, *J*=4.0 Hz), and 6.94-7.60 (30 H, complex); ^{31}P NMR ($CDCl_3$) δ=118.22 and 118.24. The anomeric ratio was obtained by the integration of anomeric protons; α/β 1:1.

Glycosylation procedure

Representative glycosylation procedure: Synthesis of 3-phenylpropyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside. To a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl dimethyl phosphite (43.7 mg, 69 μmol) and 3-phenylpropanol (9.3 μl, 69 μmol) in CH_2Cl_2 (1 ml) with powdered molecular sieves 4A (60 mg) was added $ZnCl_2$ (9.4 mg, 69 μmol) and $AgClO_4$ (28.6 mg, 140 μmol), and the mixture was stirred at room temperature for 20 min. After addition of H_2O, the mixture was filtered through a pad of Celite and washed with AcOEt. The filtrate was washed with aq $NaHCO_3$ and brine, dried, and concentrated. The residue was chromatographed on silica gel (AcOEt-C_6H_{14} 1:2) to give the corresponding glucoside **3Aa** (41.7 mg, 92% yield, α/β 52:48). The anomeric ratio of **3Aa** was analyzed by HPLC (Fuji Davison Chemical Ltd., Super Micro Bead Silica Gel, AcOEt-C_6H_{14} 1:5, 0.5 ml/min).

In the cases of sialoglycoside synthesis, the activators were added exceptionally at -42 °C to prevent the formation of the 2,3-dehydro derivative **5**.

3Aa ^1H NMR ($CDCl_3$) δ=1.98 (2 H, hex, *J*=8.2 Hz), 2.71 (2 H, m), 3.46 (2 H, t, *J*=8.2 Hz), 3.40-3.76 (5 H, complex), 3.98 (1 H, dt, *J*=9.38 and 6.58 Hz), 4.39 (1 H, *J*=7.6 Hz, H_1 for β), 4.53 and 4.60 (2 H for β, ABq, *J*=12.2 Hz), 4.52 and 4.78 (2 H for β, ABq, *J*=10.7 Hz), 4.74 and 4.92 (2 H for β, ABq, *J*=11.0 Hz), 4.81 and 4.98 (2 H for β, ABq, *J*=11.0 Hz), 7.10-7.26 (25 H, complex). *Anal.* Calc. for $C_{43}H_{46}O_6$: C, 78.39; H, 7.04%. Found: C, 78.68; H, 7.03%. System 1 was used for HPLC analysis.

3Ab ^1H NMR ($CDCl_3$) δ=1.15-2.10 (10 H, m), 3.60 (1 H, dd, *J*=9.5 and 4.0 Hz, H_2 for α), 3.59 (1 H, m), 3.68 (1 H, t, *J*=9.5 Hz, H_4 for α), 3.66 (1 H, m, H_6 for α), 3.78 (1 H, dd, *J*=10.4 and 3.7 Hz, H_{6a} for α), 3.93 (1 H, m, H_5 for α), 4.05 (1 H, t, *J*=9.5 Hz, H_3 for α), 4.50 and 4.66 (2 H, ABq, *J*=12.0 Hz, $PhCH_2$ for α), 4.52 and 4.87 (2 H, ABq, *J*=10.7 Hz, $PhCH_2$ for α), 4.69 and 4.79 (2 H, ABq, *J*=12.0 Hz, $PhCH_2$ for α), 4.85 and 5.04 (2 H, ABq, *J*=12.0 Hz, $PhCH_2$ for α), 5.00 (1 H, d, *J*=4.0 Hz, H_1 for α), 7.13-7.44 (20 H, complex). *Anal.* Calc. for $C_{40}H_{46}O_6$: C, 77.14; H, 7.44%. Found: C, 76.89; H, 7.52%. System 1 for HPLC.

3Ac ^1H NMR ($CDCl_3$) δ=1.26 (9 H, s, *t*-Bu for α), 1.32 (9 H, s, *t*-Bu for β), 3.41 (1 H, dd, *J*=9.5 and 7.9 Hz, H_2 for β), 3.43 (1 H, m, H_5 for β), 3.51 (1 H, dd, *J*=9.5 and 3.7 Hz, H_2 for α), 3.52 (1 H, t, *J*=9.5 Hz, H_3 for β), 3.58-3.68 (4 H, complex), 3.69 (1 H, dd, *J*=10.4 and 2.4 Hz, H_6 for α), 3.74 (1 H, dd, *J*=10.4 and 4.3 Hz, H_{6a} for α), 3.96 (1 H, ddd, *J*=9.5, 4.3, and 2.4 Hz, H_5 for α), 3.99 (1 H, t, *J*=9.5 Hz, H_3 for α), 4.56 (1 H, d, *J*=7.9 Hz, H_1 for β), 5.12 (1 H, d, *J*=3.7 Hz, H_1 for α), 4.40-4.84 (8 H, complex), 7.18-7.35 (20 H, complex). *Anal.* Calc. for $C_{38}H_{44}O_6$: C, 76.48; H, 7.43%. Found: C, 76.19; H, 7.43%. System 2 for HPLC.

3Ad ^{1}H NMR (for β anomer, $CDCl_3$) δ=0.56-2.05 (46 H, cholestanyl protons), 3.46 (1 H, t, *J*=8.9 Hz, H_3), 3.46 (1 H, m, H_5), 3.56 (1 H, t, *J*=8.9 Hz, H_4), 3.64 (1 H, dd, *J*=8.9 and 5.2 Hz, H_2), 3.66 (1 H, dd, *J*=10.7 and 6.4 Hz, H_6), 3.65 (1 H, m), 3.77 (1 H, m), 4.60 (1 H, d, *J*=5.2 Hz, H_1), 4.52-5.01 (8 H, complex), 7.11-7.40 (20 H, complex). *Anal.* Calc. for $C_{61}H_{82}O_6$: C, 80.40; H, 9.07%. Found: C, 80.41; H, 9.09%. System 2 for HPLC.

3Ae ^{1}H NMR (for β anomer, $CDCl_3$) δ=0.65-2.50 (42 H, cholesteryl protons), 3.45 (1 H, t, *J*=8.2 Hz, H3), 3.56 (1 H, t, *J*=8.2 Hz, H_4), 3.45 (1 H, m, H_5), 3.61 (1 H, m, cholesteryl H_3), 3.64 (1 H, dd, *J*=8.2 and 6.7 Hz, H_2), 3.65 (1 H, dd, *J*=8.9 and 4.9 Hz, H_6), 3.74 (1 H, m, H_{6a}), 4.59 (1 H, d, *J*=6.7 Hz, H_1), 4.49-5.01 (8 H, complex), 5.29 (1 H, m, cholesteryl H_6 for α), 5.36 (1 H, m, cholesteryl H_6 for β), 7.12-7.40 (20 H, complex). *Anal.* Calc. for $C_{61}H_{80}O_6$: C, 80.57; H, 8.87%. Found: C, 80.17; H, 8.94%. System 1 for HPLC.

3Af ^{1}H NMR ($CDCl_3$) δ=1.23-1.76 (20 H, complex), 3.35-3.68 (6 H, complex), 3.59 (1 H, m), 3.84 (1 H, dd, *J*=12.0 and 7.4 Hz), 3.90 (1 H, dd, *J*=12.0 and 7.4 Hz), 3.99 (1 H, t, *J*=9.8 Hz), 4.17-5.03 (15 H, complex), 5.59 (1 H, d, *J*=3.7 Hz, H_1 for α), 7.01-7.38 (25 H, complex). *Anal.* Calc. for $C_{59}H_{68}O_{11}$: C, 74.35; H, 7.19%. Found: C, 74.24; H, 7.29%. System 3 for HPLC.

3Ag ^{1}H NMR ($CDCl_3$) δ=3.36 (3 H, s, OMe for β), 3.37 (3 H, s, OMe for α), 3.30-3.52 (1 H x 2, complex), 3.43-3.52 (1 H x 2, complex), 3.52-3.75 (5 H x 2, complex), 3.78-3.87 (2 H x 2, complex), 3.89 (1 H, t, *J*=9.1 Hz, $H_{3'}$ for α), 3.93 (1 H, t, *J*=9.1 Hz, $H_{3'}$ for β), 4.02 (1 H, t, *J*=9.1 Hz, H_3 for α), 4.07 (1 H, t, *J*=9.1 Hz, H_3 for β), 4.24-5.12 (15 H, complex), 5.67 (1 H, d, *J*=3.7 Hz, H_1 for α), 7.07-7.42 (35 H, complex). *Anal.* Calc. for $C_{62}H_{66}O_{11}$: C, 75.43; H, 6.74%. Found: C, 75.08; H, 6.75%. System 3 for HPLC.

3Ba ^{1}H NMR ($CDCl_3$) δ=1.80 (2 H, m), 2.60 (2 H, m), 3.35 (1 H, m, H_5), 3.63-3.80 (5 H, complex), 3.90 (1 H, dd, *J*=9.3 and 2.9 Hz, H_{6a}), 3.95 (1 H, t, *J*=9.3 Hz, H_3), 4.38 (1 H, s, H_1 for β),4.50 and 4.87 (2 H, ABq, *J*=10.8 Hz, $PhCH_2$), 4.53 and 4.63 (2 H, ABq, *J*=12.2 Hz, $PhCH_2$), 4.64 (2 H, s, $PhCH_2$), 4.70 and 4.76 (2 H, ABq, *J*=11.4 Hz, $PhCH_2$), 4.87 (1 H, d, *J*=1.9 Hz, H_1 for α), 7.09-7.40 (25 H, complex). *Anal.* Calc. for $C_{43}H_{46}O_6$: C, 78.39; H, 7.04%. Found: C, 78.04; H, 7.18%. System 2 for HPLC.

3Bb ^{1}H NMR ($CDCl_3$) δ=1.12-2.04 (10 H, m), 3.43 (1 H, m, H_5), 3.49 (1 H, dd, *J*=9.2 and 3.1 Hz, H_6 for β), 3.57 (1H, m, $H_{1'}$), 3.67-3.88 (4 H, complex), 3.92 (1 H, dd, *J*=8.9 and 4.9 Hz, H_6 for α), 3.98 (1 H, t, *J*=8.9 Hz, H_4 for α), 4.60 (1 H, d, *J*=1.8 Hz, H_1 for β), 4.99 (1 H, d, *J*=1.8 Hz, H_1 for α), 4.39-5.04 (8 H, complex), 7.13-7.51 (20 H, complex); ^{13}C NMR ($CDCl_3$, partial) δ=95.68 (C_1 for α), 99.49 (C_1 for β).[12] *Anal.* Calc. for $C_{40}H_{46}O_6$: C, 77.14; H, 7.44%. Found: C, 77.24; H, 7.52%. System 3 for HPLC.

3Bg ^{1}H NMR ($CDCl_3$) δ=3.39 (3 H, s), 3.53 (1 H, dd, *J*=9.5 and 3.7 Hz), 3.54-3.80 (9 H, complex), 3.85 (1 H, dd, *J*=9.2 and 3.1 Hz), 3.97 (1 H, t, *J*=9.5 Hz), 4.20 and 4.30 (2 H, ABq, *J*=12.2 Hz), 4.40-4.70 (10 H, complex), 5.08 and 4.84 (2 H, ABq, *J*=11.9 Hz), 4.61 (1 H, d, *J*=3.7 Hz), 5.29 (1 H, d, *J*=2.1 Hz), 7.10-7.37 (35 H, complex); ^{13}C NMR ($CDCl_3$, partial) δ=97.70 ($C_{1'}$ for α-glucosyl), 100.50 (C_1 for α-mannosyl). *Anal.* Calc. for $C_{62}H_{66}O_{11}$: C, 75.43; H, 6.74%. Found: C, 75.17; H, 6.78%. System 2 and 3 for HPLC.

3Ca ^{1}H NMR ($CDCl_3$) δ=2.00 (2 H, m), 2.73 (2 H, m), 3.45-3.74 (5 H, complex), 3.87 (1 H, dd, *J*=9.6 and 7.9 Hz), 3.91 (1 H, t, *J*=3.1 Hz), 4.00 (1 H, ddd, *J*=9.2, 6.1, and 3.1 Hz), 4.38 (1 H, d, *J*=7.9 Hz), 4.43 and 4.48 (2 H, ABq, *J*=11.6 Hz), 4.65 and 4.97 (2 H, ABq, *J*=11.6 Hz), 4.73 and 4.78 (2 H, ABq, *J*=11.9 Hz), 4.82 and 4.90 (2 H, ABq, *J*=11.0 Hz), 7.14-7.42 (25 H, complex). *Anal.* Calc. for $C_{43}H_{46}O_6$: C,

78.39; H, 7.04%. Found: C, 78.25; H, 7.14%. The anomeric ratio was determined by HPLC anaysis (System 2) and the integral ratio of anomeric protons (δ=4.23, *J*=7.32 Hz for β anomer; δ=4.85, *J*=2.75 Hz for α anomer) in the ^{1}H NMR spectrum of the hydrogenolytic debenzylation product.

3Cb ^{1}H NMR ($CDCl_3$) δ=1.18-2.06 (10 H, complex), 3.53 (1 H, dd, *J*=9.8 and 3.1 Hz), 3.54-3.61 (2 H, complex), 3.70 (1 H, m), 3.82 (1 H, dd, *J*=9.8 and 7.6 Hz), 3.89 (1 H, m), 4.07 (1 H, m), 4.48 (1 H, d, *J*=7.6 Hz), 4.42 and 4.48 (2 H, ABq, *J*=11.9 Hz), 4.64 and 4.95 (2 H, ABq, *J*=11.9 Hz), 4.78 and 4.91 (2 H, ABq, *J*=11.9 Hz), 4.77 and 4.99 (2 H, ABq, *J*=11.0 Hz), 7.22-7.45 (20 H, complex); ^{13}C NMR ($CDCl_3$, partial) δ=95.45 (C_1 for α), 102.12 (C_1 for β). *Anal.* Calc. for $C_{40}H_{46}O_6$: C, 77.14; H, 7.44%. Found: C, 76.87; H, 7.58%. System 2 for HPLC.

3Da ^{1}H-NMR ($CDCl_3$) δ=1.8-2.17 (3 H x 2, complex, H_{3ax} and $H_{2'}$ for α and β), 1.89, 2.04, 2.05, 2.14, and 2.15 (3 H x 5, sx5, Ac for α), 1.88, 2.02, 2.03, 2.06, and 2.14 (3 H x 5, sx5, Ac for β), 2.47 (1 H, dd, J=12.82 and 4.88 Hz, H_{3eq} for β), 2.61 (1 H, dd, *J*=12.81 and 4.57 Hz, H_{3eq} for α), 2.62-2.78 (2 H x 2, complex, CH_2Ph for α and β) 3.22 (1 H, dt, *J*=9.46 and 6.40 Hz, $H_{1'}$ for α), 3.37 (1 H, dt, *J*=9.50 and 6.40 Hz, $H_{1'}$ for β) 3.53 (1 H, dt, *J*=9.50 and 6.40 Hz, $H_{1'}$ for β), 3.75 (3 H, s, OCH_3 for α), 3.77 (3 H, s, OCH_3 for β), 3.70-3.88 (2 H, complex, $H_{1'}$ for α), 4.03-4.15 (2 H for α and 3 H for β, complex), 4.30 (1 H, dd, *J*=12.51 and 2.44 Hz, H_9 for α), 4.78-4.90 (2 H, complex, H_4 for α and H_9 for β), 5.17 (1 H, m, H_4 for β), 5.28-5.40 (3 H x 2, complex, $H_{7,8}$ and NH for α and β), 7.15-7.33 (5 H x 2, complex, aromatic H for α and β). *Anal.* Calc. for $C_{29}H_{39}O_{13}N$: C, 57.14; H, 6.45; N, 2.30%. Found: C, 56.79; H, 6.46; N, 2.46%.

3Dd ^{1}H NMR ($CDCl_3$) δ=0.58-2.17 (47 H, complex, steroidal protons and H_{3ax}), 1.87, 2.02, 2.06, 2.08, 2.13 (3 H x 5, s x 5), 2.49 (1 H, dd, *J*=13.1 and 4.9 Hz, H_{3eq} for β), 2.56 (1 H, dd, *J*=13.1 and 4.9 Hz, H_{3eq} for α), 3.68 (1 H, m), 3.78 (3 H, s, CH_3O for β), 3.81 (3 H, s, CH_3O for α), 4.05-4.19 (2 H, complex), 4.15 (1 H, dd, *J*=12.5 and 8.2 Hz), 4.80 (1 H, m, H_4 for α), 4.95 (1 H, dd, *J*=12.5 and 2.1 Hz), 5.11 (1 H, m), 5.27 (1 H, m, H_4 for β), 5.38-5.50 (2 H, complex). *Anal.* Calc. for $C_{47}H_{75}NO_{13}$: C, 65.48; H, 8.77; N, 1.62%. Found: C, 65.56; H, 9.00; N, 1.67%.

3Dl ^{1}H NMR ($CDCl_3$) δ=0.70 (3 H for β, d, *J*=6.7 Hz), 0.81(3 H for α, d, *J*=7.0 Hz), 0.85 (3 H for α, d, *J*=6.4 Hz), 0.90 (3 H x 2 for α and β, d, *J*=6.7 Hz x 2), 0.92 (3 H for β, d, *J*=6.4 Hz), 0.79-1.65 (16 H for α and β, complex), 1.90, 2.03, 2.04, 2.11, and 2.16 (3 H x 5 for α, s x 5), 1.86, 2.01, 2.04, 2.07, and 2.14 (3 H x 5 for β, s x 5), 1.8-2.1 (2 H for α and β, complex), 2.50 (1 H, dd, *J*=12.8 and 4.6 Hz, H_{3eq} for β), 2.60 (1 H, dd, *J*=12.8 and 4.6 Hz, H_{3eq} for α), 3.25 (1 H for β, dt, *J*=10.4 and 4.3 Hz), 3.81 (6 H for α and β, s), 4.11 (1 H for β, t, *J*=10.4 Hz), 4.19 (1 H for β, dd, *J*=10.4 and 2.4 Hz), 4.23 (1 H for β, dd, J=12.5 and 9.2 Hz), 4.0-4.3 (6 H for α and β, complex), 4.83 (1 H for α, m), 4.97 (1 H for β, dd, *J*=12.5 and 2.1 Hz), 5.17 (1 H for β, br), 5.24 (1 H for β, m), 5.41 (1 H for β, m), 5.22-5.52 (5 H, complex, H_4, H_7, H_8, and NH for α and NH for β). *Anal.* Calc. for $C_{30}H_{47}NO_{13}$: C, 57.22; H, 7.43; N, 2.50%. Found: C, 57.32; H, 7.52; N, 2.22%.

Acknowledgment: This work was financially supported by CIBA-GEIGI Foundation (Japan) for the Promotion of Science (Y.W.).

References and Notes

1. Watanabe, Y.; Maehara, S.; Ozaki, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1879-80.
2. Watanabe, Y.; Komoda, Y.; Ozaki, S. *Tetrahedron Lett.* **1992**, *33*, 1313-16. Watanabe, Y.; Inada, E.; Jinno, M.; Ozaki, S. *ibid.* **1993**, *34*, 497-500.
3. Murakata, C.; Ogawa, T. *Tetrahedron Lett.* **1991**, *32*, 671-674. Murakata, C.; Ogawa, T. *Carbohydr. Res.* **1992**, *235*, 95-114. Udodong, U. E.; Madsen, R.; Roberts, C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1993**, *115*, 7886-7887.
4. For the latest review, see: Toshima K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503-31.
5. Michalska, M.; Borowiecka, J. *J. Carbohydr. Chem.* **1983**, *2*, 99-103. Inazu, T.; Hosokawa, H.; Satoh, Y. *Chem. Lett.* **1985**, 297-300. Bielawska H.; Michalska, M. *J. Carbohydr. Chem.* **1986**, *5*, 445-458. Inazu, T.; Yamanoi, T. *Chem. Lett.* **1989**, 69-72. Hashimoto, S.; Honda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1989**, 685-687. Yamanoi, T.; Inazu, T. *Chem. Lett.* **1990**, 849-852. Hashimoto, S.; Honda, T.; Ikegami, S. *Heterocycles* **1990**, *30*, 775-778. Hashimoto, S.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1990**, *31*, 4769-4772. Bielawska, H.; Michalska, M. *J. Carbohydr. Chem.* **1991**, *10*, 107-112. Hashimoto, S.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1991**, *32*, 1653-1654. Hashimoto, S.; Yanagiya, Y.; Honda, T.; Harada, H.; Ikegami, S. *ibid.* **1992**, *33*, 3523-3526. Laupichler, L.; Sajus, H.; Thiem, J. *Synthesis* **1992**, 1133-1136. Yamanoi, T.; Nakamura, K.; Takeyama, H.; Yanagihara, K.; Inazu, T. *Chem. Lett.* **1993**, 343-346. Yamanoi, T.; Nakamura, K.; Sada, S.; Goto, M.; Furusawa, Y.; Takano, M.; Fujioka, A.; Yanagihara, K.; Satoh, Y.; Hosokawa, H.; Inazu, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2617-2622.
6. Martin, T.J.; Schmidt, R.R. *Tetrahedron Lett.* **1992**, *33*, 6123-6126.
7. (a) Kondo, H.; Ichikawa, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **1992**, *114*, 8748-8750. (b) Sim, M. M.; Kondo, H.; Wong, C.-H. *ibid.* **1993**, *115*, 2260-2267.
8. Watanabe, Y.; Nakamoto, C.; Ozaki, S. *Synlett* **1993**, 115-116.
9. Beaucage. S. L.; Iyer, R. P. *Tetrahedron* **1992**, *48*, 2223-2311. Beaucage. S. L.; Iyer, R. P. *ibid.* **1993**, *49*, 1925-1963. Beaucage. S. L.; Iyer, R. P. *ibid.* **1993**, *49*, 6123-6194. Beaucage. S. L.; Iyer, R. P. *ibid.* **1993**, *49*, 10441-10488.
10. Mootoo, D. R.; Konradsson, P.; Fraser-Ried, B. *J. Am. Chem. Soc.* **1989**, *111*, 8540-8542.
11. Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1379-1382. Ratcliffe, A.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 747-750. Schmidt, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694-696. Vankar, Y. D.; Vankar, P. S.; Behrendt, M.; Schmidt, R. R. *Tetrahedron* **1991**, *47*, 9985-9992. Sinaÿ, P. *Pure Appl. Chem.* **1991**, *63*, 519-528. Wessel, H. P.; Englert, G.; Stangier, P. *Helv. Chim. Acta* **1991**, *74*, 682-696.
12. Suzuki, K.; Maeta, H.; Suzuki, T.; Matsumoto, T. *Tetrahedron Lett.* **1989**, *30*, 6879-6862.
13. Watanabe, Y.; Nakamoto, C.; Ozaki, S.; Sato, M.; Koizumi, K. *J. Carbohydr. Chem.* **1993**, *12*, 685-692.
14. Mukaiyama, T.; Hashimoto, Y.; Shoda, S. *Chem. Lett.* **1983**, 935-938.
15. Wessel, H. P. *Tetrahedron Lett.* **1990**, *31*, 6863-6866. Wessel, H. P.; Ruiz, N.; *J. Carbohydr. Chem.* **1991**, *10*, 901-910. Dobarro-Rodriguez, A.; Trumtel, M.; Wessel, H. P. *J. Carbohydr. Chem.* **1992**, *11*, 255-263.
16. Okamoto, K.; Kondo, T.; Goto, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 631-636.
17. Corey, E. J.; Wu, Y.-J. *J. Am. Chem. Soc.* **1993**, *115*, 8871-8872.

18. Slightly different procedures for the synthesis of the similar type of amidites are available in the following literatures: Uhlmann, E.; Engels, J. *Tetrahedron Lett.* **1986**, *27*, 1023-1026. Pederson, R. L.; Esker, J.; Wong, C.-H. *Tetrahedron*, **1991**, *47*, 2643-2648. Fukase, K.; Kamikawa, T.; Iwai, Y.; Shiba, T.; Rietschel, E. T.; Kusumoto, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3267-3273.
19. Issleib, K.; Seidel. W. *Chem. Ber.* **1959**, *92*, 2681-2694.

(*Received in Japan* 7 *February* 1994; *accepted* 22 *March* 1994)