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6-Nitro-2-benzothiazolyl α-Mannoside: A Highly Efficient Mannosyl Donor in Constructing β-Man(1→4)GlcN Linkage and Its Application to the Synthesis of the Pentasaccharide Core of *N*-Glycans

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An efficient and concise synthesis of the β-Man(1→4)GlcN linkage that exists in *N*-linked glycans has been established. Direct β-mannosylations of the 4-OH group of glucosamine derivatives by using 6-nitro-2-benzothiazolyl 3,6-di-*O*-allyl-2,4-di-*O*-benzyl-α-D-mannopyranoside (**3α**) proceed smoothly in the presence of a catalytic amount of $HB(C_6F_5)_4$ in CH_2Cl_2 at −78 °C to afford the desired β-mannosides in high yields. The β-trisaccharide **14β**, a key building block for the synthesis of the pentasaccharide core **20**, is directly prepared from the mannosyl donor **3α** and chitobiose acceptor **10** in high yield. In addition, this mannosylation method has successfully been applied to a wide range of glycosyl acceptors derived from glucosamine in a highly efficient manner. Further, the pentasaccharide core **20** that is commonly present in *N*-linked glycans can also be synthesized readily according to this direct mannosylation strategy.

Development of a new and useful stereoselective glycosylation reaction is one of the most fundamental and important topics in carbohydrate chemistry.[1] β-Mannosides are frequently found in many biologically-relevant oligosaccharides and glycoconjugates, including *N*-linked core pentasaccharide, which are common to all *N*-glycans.[2] Despite the importance, to synthesize β-mannoside is considered one of the most difficult problems in carbohydrate chemistry because of the following reasons: i) α-Mannoside formation is thermodynamically more favored than β-mannoside due to its anomeric effect; ii) the β-axial hydroxy group at the *C*-2 position blocks access to the β-face; and iii) neighboring participation effect can not be utilized in β-mannoside formation. To date, however, some methods[3] have been developed to overcome these problems and effective β-mannoside formation has been materialized; namely, 1) effective epimerization of β-glucoside or galactoside at the *C*-2 position;[4] 2) intramolecular aglycon delivery mannosylation;[5] and 3) direct intermolecular mannosylation. Of the methods reported, a catalytic or stoichiometric direct mannosylation[6–13] turned out to be most effective for convenient construction of the β-mannoside. Reactions using mannosyl donors such as mannosyl phosphinothioate,[6] phosphate,[7] halide,[8] or sulfoxide[9] in combination with suitable activators, and a donor having 1,2-stannylene acetal[10] were then reported. The best results were obtained with donors having an electron-withdrawing protecting group at the *O*-2 position[11] or a cyclic acetal protecting group at *O*-4,6 positions.[12,13] However, each particular case still requires careful review of techniques, protecting groups, promoters, and synthetic strategies. To the best of our knowledge, Crich's direct coupling method[12] is the best way to form the β-Man(1→4)GlcN linkage with the use of 2-azido-2-deoxy glucose[14,15] or the 2-deoxy-2-sulfonamide chitobiose derivative[16] having a reactive 4-hydroxy group, while β-mannosylation of 2-deoxy-2-*N*-phthaloyl (Phth) glucose having a less reactive 4-hydroxy group afforded the desired products in moderate yields.[15]

It was recently disclosed from our laboratory that 6-nitro-2-benzothiazolyl α-mannoside (**1**), a novel glycosyl donor, is reactive enough to construct β-saccharide linkages via the S_N2-type process (Scheme 1).[17a,b,c]

Different from other glycosyl acceptors, however, β-mannosylation of the 4-hydroxy group of the glucosamine derivative resulted in a moderate yield and some modifications were needed in order to improve the β-stereoselectivity. In this paper, we would like to report a general and effective method for the β-mannosylation of the 4-hydroxy group of glucosamine derivatives with the mannosyl donor **3α**, as well as the synthesis of the pentasaccharide core **20** that commonly exists in *N*-glycans.

Results and Discussion

β-Selective Mannosylation of Glucosamine Derivatives Using 6-Nitro-2-benzothiazolyl α-Mannoside. The present study started from preparing 6-nitro-2-benzothiazolyl 3,6-di-*O*-allyl-2,4-di-*O*-benzyl-α-D-mannopyranoside (**3α**) from the precursor **2**[18] according to our previously reported-procedure.[17] The condensation reaction proceeded smoothly by using potassium bis(trimethylsilyl)amide [$KN(SiMe_3)_2$] at room temperature to afford 6-nitro-2-benzothiazolyl α-mannoside (**3α**) in 77% yield as the major product (Scheme 2). 6-Nitro-2-benzothiazolyl β-mannoside (**3β**) was detected by thin-layer chromatography, although it was too labile to isolate in pure form. The

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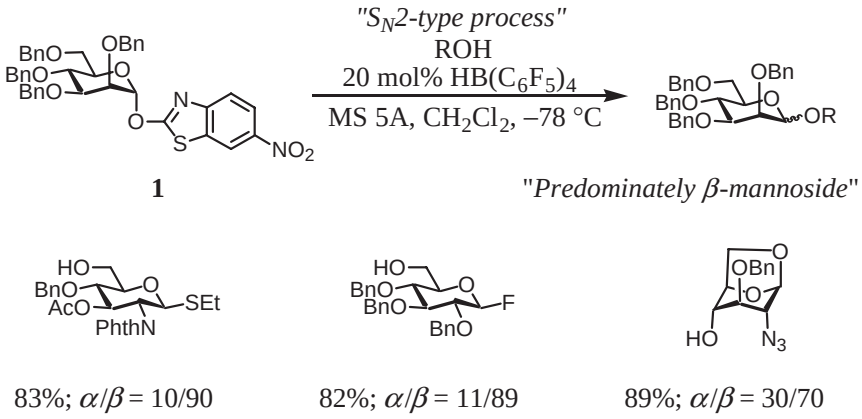
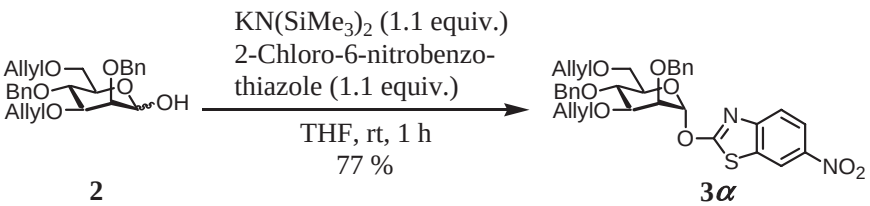
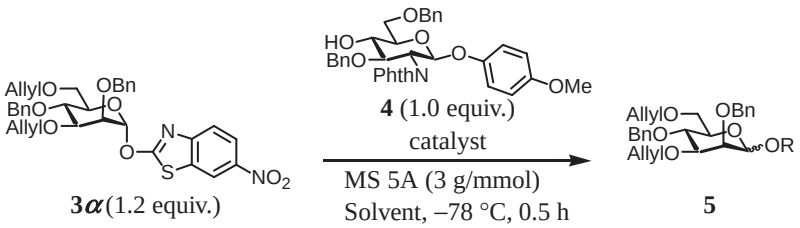


Scheme 1.



Scheme 2.

Table 1. Effects of Catalyst and Solvent



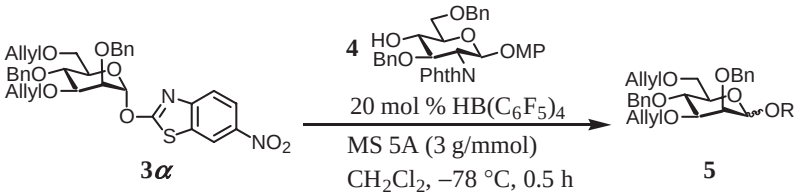
Entry	Catalyst	Solvent	Yield/% (α/β)[a]
1	20 mol % $HB(C_6F_5)_4$	toluene	63 (42/58)
2	20 mol % $HB(C_6F_5)_4$	CH_2Cl_2	77 (33/67)
3	20 mol % $TrB(C_6F_5)_4$	CH_2Cl_2	34 (53/47)
4[b]	20 mol % $TMSB(C_6F_5)_4$	CH_2Cl_2	79 (38/62)
5	20 mol % TfOH	CH_2Cl_2	98 (94/6)
6	20 mol % TfOH	toluene	90 (95/5)
7	20 mol % TMSOTf	CH_2Cl_2	93 (91/9)

a) The α/β ratios were determined by isolations of each stereoisomers. b) Generated from $AgB(C_6F_5)_4$ and TMSCl in toluene–Et_2O (1:1), and the supernatant was used.

mannosyl donor **3α** was easily purified by column chromatography and was stored for several months in a refrigerator under an argon atmosphere. The anomeric configuration of **3α** was determined as α-mannoside by measurement of its NMR spectrum, which showed $^1J_{CH} = 177$ Hz between 1-H and C-1.[19]

At first, we tried to investigate suitable combinations of activator and solvent for the mannosylation of *p*-methoxyphenyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**4**)[20] with **3α** under the previously reported conditions[17a,b,c] (Table 1). As a result, CH_2Cl_2 gave a better outcome of β-selectivities compared to toluene (Entries 1 and 2), which was used in the β-selective mannosylation[17a,b,c] reported previously from our laboratory. The highest β-stereoselectivity was achieved when tetrakis(pentafluorophenyl)boric acid[21] [$HB(C_6F_5)_4$] was employed in CH_2Cl_2 at −78 °C (Entry 2, 77%, $\alpha/\beta = 33/67$), where both catalysts, TfOH and TMSOTf, induced α-selectivities conversely (Entries 5–7). Although TfOH and TMSOTf were useful catalysts in constructing β-mannoside,[17a,b,c] the reason for these reversal selectivities is not yet clear. Here, neither of the mechanisms of the above tetrakis(pentafluorophenyl)borates that achieved high β-stereoselectivities are explained clearly; however, it suggests that a protic acid or Lewis acid having a $^-B(C_6F_5)_4$ anion did play an important role[17,21] in determining β-selectivity (Entries 1–4).

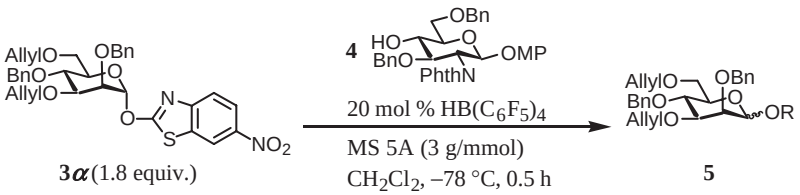
Table 2. Examination of Molecular Ratios between Donor **3α** and Acceptor **4**



Entry	**3α** (equiv)	**4** (equiv)	Yield/% (α/β)[a]
1	1.2	1	77 (33/67)
2	1.4	1	89 (31/69)
3	1.6	1	94 (34/66)
4	1.8	1	95 (33/67)
5	2.0	1	89 (31/69)
6	1	1.2	63 (34/66)
7	1	1.4	61 (30/70)
8	1	1.6	67 (35/65)

a) The α/β ratios were determined by isolations of each stereoisomers.

Table 3. Examination of the Concentration of the Solvent



Entry	Concentration/10^{-2} M	Yield/% (α/β)[a]
1	5	98 (32/68)
2	4	95 (33/67)
3	3	98 (30/70)
4	2.5	90 (33/67)
5[b]	3	89 (37/63)

a) The α/β ratios were determined by isolations of each stereoisomers. b) The reaction was carried out at −94 °C.

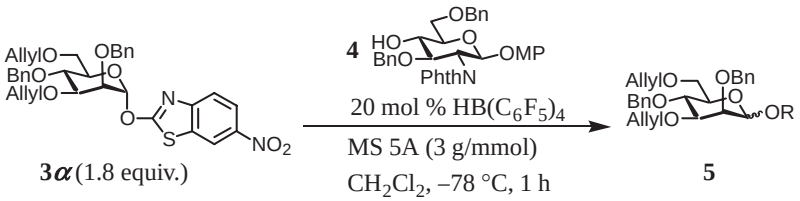
In order to improve the yield of mannoside, the molar ratios between the mannosyl donor **3α** and glycosyl accepter **4** were examined (Table 2). The use of an excess amount of the mannosyl donor **3α** was examined first, but β-selectivities remained approximately the same (Entries 1–5), while the use of an excess amount of the glycosyl acceptor **4** in the present systems gave unsatisfactory results (Entries 6–8).

In order to improve the β-selectivity of the present mannosylation, the reaction should proceed via a S_N2-like process. The concentration of the reaction mixture and the experimental procedure both play important roles in performing the reaction by a S_N2-like process, but not by a S_N1 process. Once the oxocarbenium intermediate was generated from the mannosyl donor **3α** (S_N1 process), the α-mannoside was formed predominantly due to the steric repulsion at the *C*-2 position. The reaction concentrations were further examined in detail (Table 3). Although there are the same β-selectivities irrespective of concentration, the highest β-selectivity was observed when the reaction was carried out in 0.03 M CH_2Cl_2 at −78 °C (Entry 3). Carring out the reaction at a lower temperature (−94 °C) did not improve the β-selectivity, contrary to the expectation (Entry 5).

In the present mannosylation procedure, $HB(C_6F_5)_4$ was finally added to the mixture of the mannosyl donor **3α** and glycosyl acceptors **4** in the presence of MS 5A in CH_2Cl_2 at −78 °C (Method A). In order to improve β-selectivity, the experimental procedure was further screened carefully. That is, the mannosyl donor **3α** was added to the suspension of the glycosyl acceptor, $HB(C_6F_5)_4$, and MS 5A in CH_2Cl_2 at −78 °C in a reverse order (Method B). As shown in Table 4, the dropwise addition of the mannosyl donor **3α** to the mixture (Method B) increased the β-selectivities dramatically in comparison with Method A. Of those procedures, the addition of the mannosyl donor within 30 min was optimal and provided the desired mannoside in 99% ($\alpha/\beta = 18/82$) with high β-selectivity (Entry 4).

Since the conditions of the present procedure had been established, the scope of this mannosylation reaction was studied next. Direct β-mannosylations of several glycosyl acceptors, such as the 2-deoxy-2-*N*-phthaloyl glucose derivatives **4**, **6**,[22] and **10**,[23] 2-azido-2-deoxy glucose derivative **7**,[24] *N*-Troc (Troc: 2,2,2-trichloroethoxycarbonyl) glucosamine derivative **8**, and the 2-acetoamido-2-deoxy glucosamine derivative **9**[25] with the mannosyl donor **3α**, was tried in the presence of cat-

Table 4. Examination of the Addition Time of **3α**



Entry[a)]	Addition time of **3α**/min	Yield/% (α/β)[d)]
1[b),c)]	0	98 (30/70)
2	5	93 (27/73)
3	10	98 (27/73)
4	30	99 (18/82)
5	120	89 (17/83)

a) Method B. b) Method A. c) The reaction time was 0.5 h. d) The α/β ratios were determined by isolations of each stereoisomers.

alytic amounts of $HB(C_6F_5)_4$ and MS 5A in CH_2Cl_2 at $-78\,^{\circ}C$ (Table 5). Then, it was revealed that the present mannosylation method was applicable to several glycosyl acceptors except the 2-acetoamido-2-deoxy glucosamine derivative **9**. The chemoselective mannosylation of the glycosyl acceptor **6** having a fluorine atom on its reducing end gave the disaccharide **11**[26] in 91% ($\alpha/\beta = 26/74$) yield without causing any damage to a fluorine-atom linked at their anomeric position (Entry 2). However, the β-stereoselectivity was lower than the other glycosyl acceptors since the fluorine-atom at an anomeric position reduced the nucleophilicity of the hydroxy group at the *C*-4 position of the glycosyl acceptor **6**. It should be noted that the mannoside **11** obtained from the mannosyl donor **3α** and glycosyl acceptor **6** can be directly utilized for further elongation of the saccharide chain without any protecting group manipulation.[26] Therefore, this mannosylation is used to accomplish chemoselective synthesis of oligo- and poly-saccharide. The 2-azido-2-deoxy glucose derivative **7** gave the best result in the present method to afford the desired mannoside **12** in 95% ($\alpha/\beta = 13/87$) with high selectivity (Entry 3). This tendency was consistent with the results reported by Crich's group.[15] Since the 2-azido group reduced steric hindrance around the hydroxy group at the *C*-4 position and allowed reaction with the mannosyl donor **3α** via a S_N2-like process, the desired high β-selectivity is achieved. High β-selectivity was also observed when the *N*-Troc glucosamine derivative **8** was used (Entry 4), whereas no desired product was obtained in the case of using the 2-acetoamido-2-deoxy glucosamine derivative **9**, because $HB(C_6F_5)_4$ is deactivated by 2-acetoamide's Lewis basicity (Entry 5). Furthermore, it is interesting to note that the chitobiose acceptor **10** gave the desired trisaccharide **14**, which could be used as a key building block for the synthesis of the pentasaccharide core after removal of allyl ether groups.[26] This is the first example of the direct mannosylation of the chitobiose acceptor **10** that proceeded to give the corresponding mannoside **14** in high yield with high β-selectivity. The anomeric configurations of all mannosides were confirmed by $^1J_{CH}$ coupling constant measurements.[19]

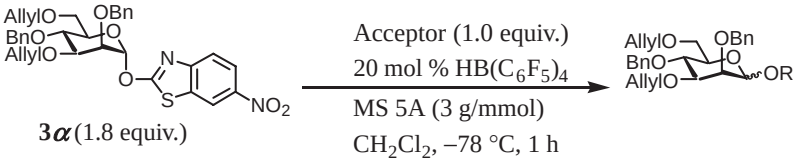
In order to confirm the advantage of using the mannosyl donor **3α** in the direct mannosylation reaction, the corresponding α-mannosyl trichloroacetimidate **15** was prepared for the control experiment. The mannosylation of the glycosyl acceptor **4** with the mannosyl donor **15** was tried under the optimized conditions (Table 6) and afforded the desired mannoside in moderate yield; this was considered inferior to the mannosyl donor **3α**. Therefore, the mannosyl donor **3α** proved to be suitable in constructing the β-Man(1→4)GlcN linkage in a highly convenient manner compared to that of using the α-mannosyl trichloroacetimidate **15**.

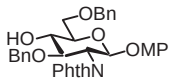
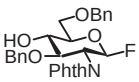
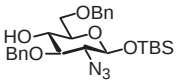
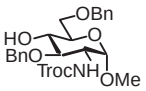
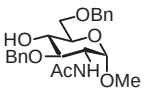
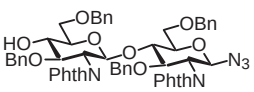
The Synthesis of the Pentasaccharide Core of *N*-Glycans. *N*-Linked glycans are known to play numerous important biological roles in cellular interactions. They are generally divided into three classes: namely, high-mannose, complex, and hybrid types depending on the structures of oligosaccharide chains.[2] All types of *N*-linked glycans contain a common structure of the glycopeptide **16**, including the β-Man(1→4)GlcNAc linkage (Fig. 1). Although many synthetic strategies for the synthesis of the pentasaccharide core or related oligosaccharides have been reported, long linear steps and many protecting group manipulations are required in synthesizing those oligosaccharides.[3,27] In this section, the synthesis of the pentasaccharide core **20** in a highly efficient manner is described.

The trisaccharide **14β**, a key building block of preparing the pentasaccharide core **20**, was easily synthesized from the mannosyl donor **3α** and chitobiose acceptor **10**, as described in the previous section. Then, our attention was focused on how to remove the allyl ether groups of the trisaccharide **14β**. Although deallylation of the trisaccharide **14β** by an iridium-catalyzed process with a two-step procedure had already been reported,[26] palladium(II) dichloride[28] was selected as a catalyst for the preparation of the trisaccharide acceptor **17**[26] in the present experiment. As shown in Scheme 3, the trisaccharide **14β** smoothly reacted with $PdCl_2$ in MeOH to give the diol **17** in 97% yield by a simple operation. No isomerization was observed at the β-mannoside linkage during this deallylation step.

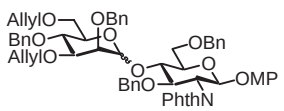
In order to complete the synthesis of the pentasaccharide core **20**, the double mannosylation reaction of the trisaccharide accepter **17** was tried (Table 7). At first, the mannosyl trichloroacetimidate **18**[29] was selected as the mannosyl donor, which has widely been utilized for biantennary oligosaccharide chain synthesis.[30] Double mannosylation of the trisaccharide acceptor **17** with the mannosyl trichloroacetimidate **18** by the use of

Table 5. Mannosylation of Several Glycosyl Acceptor with **3α**



Entry	Acceptor	Mannoside	Yield/% (α/β)[a]
1	 **4**	**5**	99 (18/82)
2[b]	 **6**	**11**	91 (26/74)
3	 **7**	**12**	95 (13/87)
4	 **8**	**13**	83 (18/82)
5	 **9**	—	Not detected
6	 **10**	**14**	95 (20/80)

a) The α/β ratios were determined by isolations of both stereoisomers. b) The reaction time was 0.2 h.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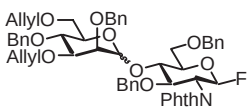
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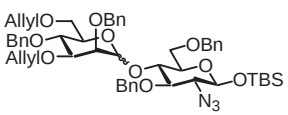
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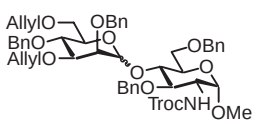
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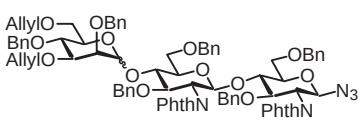
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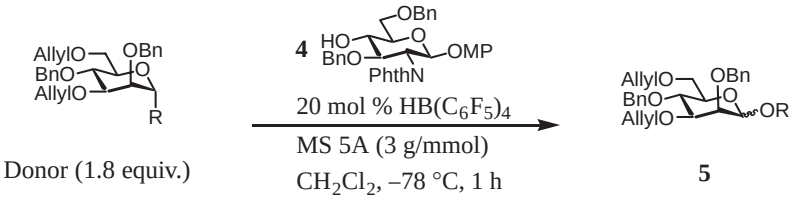
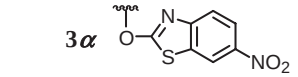
catalytic amounts of TfOH, TMSOTf, or TBSOTf gave a complex mixture (Entries 1, 2, and 3). These results suggested that the double mannosylation reaction should be employed under milder conditions as not to give any damage to acid-labile β-mannoside. Eventually, the installation of the α-mannosyl moiety was cleanly achieved in excellent yield using the mannosyl chloride **19** and AgOTf as an activator (Entry 4).[26]

It is important to note that the pentasaccharide core **20** was readily prepared in three steps with 66% yield from the mannosyl donor **3α** and chitobiose acceptor **10**. The synthetic strategy reported herein presents a useful and more efficient method than those previously reported. The pentasaccharide core **20** was converted to the glycopeptide **16** after several steps, as reported by Ogawa.[26]

Table 6. The Experiment for Comparing Mannosyl Donors **3α** and **15**



Entry	Donor (R)	Yield/% (α/β)[a]
1	**3α** 	99 (18/82)
2	**15**[b] 	56 (21/79)

a) The α/β ratios were determined by isolations of each stereoisomers. b) $\alpha/\beta = 94/6$.

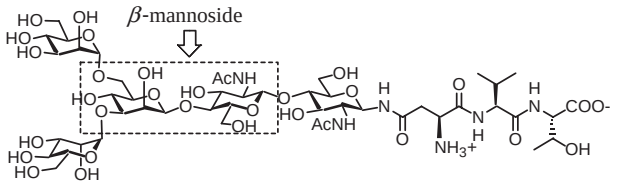


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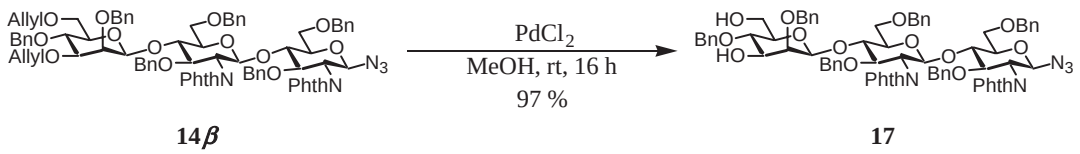
Fig. 1.

Conclusion

A direct β-mannosylation of the 4-hydroxy group of glucosamine derivatives with the mannosyl donor **3α** by using a catalytic amount of $HB(C_6F_5)_4$ in CH_2Cl_2 at $-78\,^{\circ}C$ has been developed. The salient features of this approach are: 1) The mannosyl donor **3α** was easily prepared from the corresponding 1-hydroxy sugar, 2) high β-stereoselectivities and excellent yield in constructing β-mannosides, 3) broad substrate scope, and 4) β-mannosylation reaction proceeds smoothly when the sterically hindered chitobiose acceptor **10** was used. Further, the pentasaccharide core **20** that is commonly present in *N*-linked glycans could be readily synthesized conveniently by our direct mannosylation strategy.

Experimental

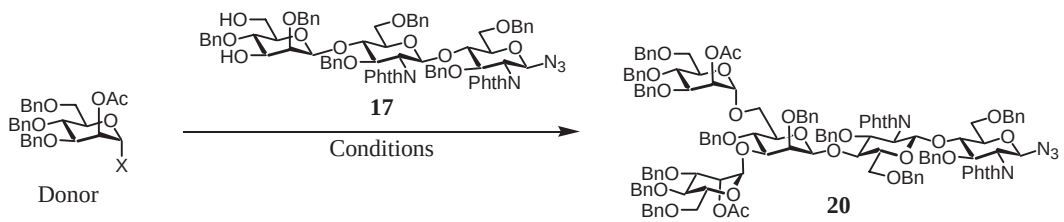
General. All melting points were measured on a Yanaco MP-S3 micro melting point apparatus. Infrared spectra were recorded on a Horiba FT-300 infrared spectrometer or Sens IR Technologies Travel IR. ^{1}H NMR spectra were recorded on a JEOL JNM-EX270 (270 MHz) or JEOL JNM-LA500 (500 MHz) spectrometer; chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. ^{13}C NMR

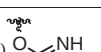


14β **17**

Scheme 3.

Table 7. Synthesis of the Protected Pentasaccharide Core **20**



Entry	Donor	Conditions	Yield/%
1		20 mol % TfOH, CH_2Cl_2, MS 5A, -78 to $-40\,^{\circ}C$	Complex mixture
2	**18**[a]	20 mol % TMSOTf, Et_2O, MS 4A, $-40\,^{\circ}C$	Complex mixture
3		20 mol % TBSOTf, CH_2Cl_2, $-20\,^{\circ}C$	Complex mixture
4	**19** 	AgOTf, CH_2Cl_2, MS 4A, rt	90

a) $\alpha/\beta = 93/7$.

spectra were recorded on a JEOL JNM-EX270L (68 MHz) or JEOL JNM-LA500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million relative to tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$; δ 77.0 ppm). High resolution mass spectra (HRMS) were recorded on a JEOL JMS-SX102A mass spectrometer. Optical rotations were recorded on a Jasco P-1020 polarimeter. Analytical TLC was done on precoated (0.25 mm) silica gel 60 F_{254} plates (E. Merck). Thin-layer chromatography was performed on Wakogel B-5F. Column chromatography was performed on Silica gel 60 (Merck).

All reactions were carried out under an argon atmosphere in dried glassware, unless otherwise noted. All reagents were purchased from Tokyo Kasei Kogyo, Kanto Chemical, or Aldrich, and used without further purification, unless otherwise noted. TfOH was simply distilled and used for glycosylation. $HB(C_6F_5)_4$ was generated according to the published procedures. CH_2Cl_2 was distilled from P_2O_5, then from CaH_2 and was stored over molecular sieves 4A. Toluene was distilled from P_2O_5, and was stored over molecular sieves 4A. Dry THF was purchased from Kanto Chemical. Powdered and pre-dried (at 260 °C/133 Pa, 6 h) molecular sieves 5A (MS 5A) were used in the glycosylation reactions.

6-Nitro-2-benzothiazolyl 3,6-Di-*O*-allyl-2,4-di-*O*-benzyl-D-mannopyranoside (3α). To a solution of 3,6-di-*O*-allyl-2,4-di-*O*-benzyl-D-mannopyranose (**2**) (2.00 g, 4.54 mmol) in THF (45.4 mL) was added potassium bis(trimethylsilyl)amide (0.50 M in toluene, 10.0 mL, 5.00 mmol) at 0 °C. After stirring for 0.5 h at the same temperature, 2-chloro-6-nitrobenzothiazole[17] (1.07 g, 5.00 mmol) was added to the reaction mixture. After additional stirring for 1 h at room temperature, the mixture was quenched by adding sat. aq $NaHCO_3$. The aqueous layer was extracted with EtOAc, washed with brine, and dried over Na_2SO_4. After filtration and evaporation, the residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 10/1 + 1% Et_3N) to afford **3α** (2.17 g, 77%).

3α: Colorless oil; R_f 0.61 (hexane/ethyl acetate, 2/1, v/v); $[\alpha]_D^{23}$ +61.0° (*c* 1.06, $CHCl_3$); IR (neat) 3080, 2866, 1704, 1575, 1520, 1452, 1338, 1253, 1121, 892, 744, 697, 614 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.69 (dd, J = 1.6, 11.0 Hz, 1H), 3.75 (dd, J = 4.5, 11.0 Hz, 1H), 3.85–4.16 (m, 8H), 4.65 (d, J = 10.8 Hz, 1H), 4.86 (s, 2H), 4.95 (d, J = 10.8 Hz, 1H), 5.10–5.36 (m, 4H), 5.80–6.00 (m, 2H), 6.46 (s, 1H, H-1), 7.25–7.50 (m, 10H), 7.77 (d, J = 8.9 Hz, 1H), 8.28 (dd, J = 2.0, 8.9 Hz, 1H), 8.59 (d, J = 2.0 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 68.6, 71.3, 72.4, 72.8, 72.8, 73.9, 74.6, 75.3, 78.6, 99.8 (C-1, J_{C-H} = 177 Hz), 117.0, 117.1, 117.8, 121.3, 122.0, 127.8, 127.9, 128.0, 128.0, 128.4, 132.3, 134.5, 134.6, 137.6, 138.2, 143.9, 153.6, 173.8; HRMS m/z calcd for $C_{33}H_{35}N_2O_8S$ $[M+H]^+$ 619.2114, found 619.2119.

Mannosylation Using $HB(C_6F_5)_4$ as Catalyst (Method A). To a stirred suspension of MS 5A (150 mg), the mannosyl donor **3α** (0.06 mmol), the glycosyl acceptor (0.05 mmol) in CH_2Cl_2 (1.25 mL) was successively added $HB(C_6F_5)_4$ (0.05 M in toluene–Et_2O (1:1), 0.20 mL, 0.01 mmol)[21b] at −78 °C. After completion of the mannosylation reaction was verified by monitoring TLC, the reaction was quenched by adding sat. aq $NaHCO_3$. Then, the mixture was filtered through Celite and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over Na_2SO_4. After filtration and evaporation, the resulting residue was purified by preparative TLC (silica gel) to afford the corresponding disaccharide.

Mannosylation Using $HB(C_6F_5)_4$ as Catalyst (Method B). To a stirred suspension of MS 5A (150 mg) and the glycosyl acceptor (0.05 mmol) in CH_2Cl_2 (0.5 mL) was successively added $HB(C_6F_5)_4$ (0.05 M in toluene–Et_2O (1:1), 0.20 mL, 0.01 mmol)[21b] at −78 °C; 5 min later a solution of the mannosyl donor **3α** (0.09 mmol) in CH_2Cl_2 (1.25 mL) added over 30 min. After the completion of the mannosylation reaction was verified by monitoring TLC, the reaction was quenched by adding sat. aq $NaHCO_3$. Then, the mixture was filtered through Celite and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over Na_2SO_4. After filtration and evaporation, the resulting residue was purified by preparative TLC (silica gel) to afford the corresponding disaccharide.

***p*-Methoxyphenyl 3,6-Di-*O*-benzyl-4-*O*-(3′,6′-di-*O*-allyl-2′,4′-di-*O*-benzyl-D-mannopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside (5).** This compound was synthesized from the mannosyl donor **3α** and glycosyl acceptor **4**.

5α: Colorless oil; R_f 0.54 (toluene/ethyl acetate, 7/1, v/v); $[\alpha]_D^{23}$ +59.9° (*c* 1.04, $CHCl_3$); IR (neat) 3060, 3033, 2869, 1775, 1715, 1503, 1459, 1386, 1217, 1105, 925, 832, 732 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.56–4.17 (m, 18H), 4.24 (d, J = 12.0 Hz, 1H), 4.41 (dd, J = 6.2, 7.8 Hz, 1H), 4.45–4.70 (m, 6H), 4.91 (d, J = 10.9 Hz, 1H), 5.05–5.40 (m, 4H), 5.30 (s, 1H, H-1^2), 5.56 (d, J = 7.9 Hz, 1H, H-1^1), 5.80–6.00 (m, 2H), 6.55–7.05 (m, 9H), 7.20–7.75 (m, 19H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 55.4, 55.5, 69.3, 71.0, 72.2, 72.3, 72.9, 73.2, 74.6, 74.8, 75.0, 75.0, 75.2, 78.7, 79.3, 80.4, 97.3 (C-1^1), 100.4 (C-1^2, J_{C-H} = 169 Hz), 114.2, 116.5, 116.8, 118.5, 118.5, 123.3, 127.12, 127.2, 127.3, 127.4, 127.5, 127.54, 127.6, 128.0, 128.0, 128.1, 128.2, 128.3, 131.4, 133.7, 134.8, 137.6, 138.1, 138.4, 138.5, 150.8, 155.2, 173.8; HRMS m/z calcd for $C_{61}H_{63}NNaO_{13}$ $[M+Na]^+$ 1040.4197, found 1040.4197.

5β:[26a] Colorless oil; R_f 0.40 (toluene/ethyl acetate, 7/1, v/v); $[\alpha]_D^{23}$ +30.1° (*c* 1.03, $CHCl_3$); IR (neat) 3063, 3031, 2866, 1774, 1714, 1605, 1503, 1459, 1387, 1218, 1106, 924, 831, 730 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.26–3.39 (m, 1H), 3.27 (dd, J = 2.8, 9.4 Hz, 1H), 3.60–3.75 (m, 8H), 3.77 (d, J = 2.8 Hz, 1H), 3.83 (dd, J = 9.4, 9.4 Hz, 1H), 3.90–4.00 (m, 4H), 4.09 (dd, J = 8.1, 8.1 Hz, 1H), 4.32 (dd, J = 8.1, 10.6 Hz, 1H), 4.41 (dd, J = 7.9, 10.6 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.51 (d, J = 12.6 Hz, 1H), 4.55 (s, 1H, H-1^2), 4.58 (d, J = 11.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.87 (d, J = 11.0 Hz, 1H), 4.89 (s, 2H), 4.99 (d, J = 12.6 Hz, 1H), 5.00–5.35 (m, 4H), 5.62 (d, J = 7.9 Hz, 1H, H-1^1), 5.70–6.00 (m, 2H), 6.55–6.95 (m, 9H), 7.20–7.90 (m, 19H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 55.5, 55.6, 68.5, 69.3, 70.7, 72.3, 73.5, 74.0, 74.6, 74.6, 74.8, 75.0, 75.0, 75.9, 77.4, 78.9, 82.5, 97.6 (C-1^1), 101.4 (C-1^2, J_{C-H} = 151 Hz), 114.3, 116.4, 116.6, 118.7, 123.2, 126.7, 127.3, 127.6, 127.6, 127.7, 127.8, 127.9, 127.9, 128.01, 128.3, 128.4, 131.5, 133.6, 134.7, 135.0, 137.8, 138.5, 138.8, 138.8, 150.8, 155.3, 173.8.

Methyl 3,6-Di-*O*-benzyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (8). Hydrogen chloride in diethyl ether at room temperature was added to a mixture of methyl 3-*O*-benzyl-4,6-*O*-benzyliden-2-deoxy-2-(2,2,2-trichloroethoxycabonylamino)-α-D-glucopyranoside[31] (100 mg, 0.18 mmol) and sodium cyanohydroborate (115 mg, 1.80 mmol) in tetrahydrofuran (0.90 mL) containing molecular sieves 4A (100 mg), until the evolution gas ceased. After additional stirring for 2.5 h at room temperature, the mixture was diluted with EtOAc and water, filtered, and the solution was extracted with water, and then with sat. aq $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by thin-layer chromatography (hexane/ethyl acetate, 3/2, v/v) to afford **8** (49.8 mg, 50%).

8: Colorless solid, mp 88–90 °C; R_f 0.66 (hexane/ethyl acetate, 1/1, v/v); $[\alpha]_D^{27}$ +50.7° (*c* 1.00, $CHCl_3$); IR (ATR) 3322, 2924, 1705, 1540, 1094, 1041, 815, 732, 695 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.68 (d, $J = 4.9$ Hz, 1H), 3.37 (s, 3H), 3.56 (dd, $J = 8.1$, 10.0 Hz, 1H), 3.65–3.80 (m, 4H), 3.97 (ddd, $J = 3.5$, 10.0, 10.0 Hz, 1H), 4.50–4.90 (m, 7H, including H-1), 5.15 (d, $J =$ 10.0 Hz, 1H), 7.20–7.40 (m, 10H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 54.5, 55.2, 69.9, 70.0, 71.9, 73.6, 74.4, 74.6, 80.1, 95.4, 98.7 (C-1), 127.6, 127.8, 127.8, 128.4, 128.5, 137.7, 138.2, 154.1; HRMS *m/z* calcd for $C_{24}H_{29}Cl_3NO_7$ $[M + H]^+$ 548.1010, found 548.1010.

3,6-Di-*O*-benzyl-4-*O*-(3′,6′-di-*O*-allyl-2′,4′-di-*O*-benzyl-D-mannopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranosyl Fluoride (11).[26a] This compound was synthesized from the mannosyl donor **3α** and glycosyl acceptor **6**.

11α: Colorless oil; R_f 0.47 (toluene/ethyl acetate, 9/1, v/v); $[\alpha]_D^{23}$ +53.7° (*c* 1.04, $CHCl_3$); IR (neat) 3065, 3030, 2869, 1776, 1718, 1459, 1385, 1120, 926, 742 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.50–4.12 (m, 14H), 4.18 (d, $J = 12.2$ Hz, 1H), 4.24–4.40 (m, 2H), 4.53–4.70 (m, 6H), 4.90 (d, $J = 10.9$ Hz, 1H), 5.15–5.30 (m, 4H), 5.28 (s, 1H, H-1^2), 5.70–6.00 (m, 3H, including H-1^1), 6.70–7.00 (m, 5H), 7.10–7.50 (m, 15H), 7.67 (m, 4H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 55.4 (d, $J = 21.8$ Hz), 68.9, 69.3, 71.0, 72.3, 72.4, 72.9, 73.4, 74.7, 74.8, 75.0, 75.0, 75.1, 78.2, 78.2, 79.3, 79.3, 100.5 (C-1^2, $J_{C-H} = 171$ Hz), 104.7 (d, $J = 215.6$ Hz, C-1^1), 116.6, 116.9, 123.4, 127.1, 127.4, 127.5, 127.7, 127.8, 128.0, 128.1, 128.2, 128.3, 131.4, 133.9, 134.8, 134.9, 137.5, 138.6, 167.7; HRMS *m/z* calcd for $C_{54}H_{56}FNNaO_{11}$ $[M + Na]^+$ 936.3735, found 936.3741.

11β: Colorless oil; R_f 0.34 (toluene/ethyl acetate, 9/1, v/v); $[\alpha]_D^{23}$ +32.9° (*c* 1.02, $CHCl_3$); IR (neat) 3030, 2867, 1776, 1718, 1459, 1384, 1082, 926, 729 cm; ^1H NMR (270 MHz, $CDCl_3$) δ 3.25 (dd, $J = 2.8$, 9.6 Hz, 1H), 3.25–3.37 (m, 1H), 3.50–3.75 (m, 7H), 3.82 (dd, $J = 9.6$, 9.6 Hz, 1H), 3.89–4.02 (m, 4H), 4.05–4.16 (m, 1H), 4.18–4.35 (m, 2H), 4.48 (d, $J = 13.0$ Hz, 1H), 4.53 (s, 1H, H-1^2), 4.58 (d, $J = 10.7$ Hz, 1H), 4.67 (d, $J = 12.2$ Hz, 1H), 4.80–4.92 (m, 3H), 4.96 (d, $J = 13.0$ Hz, 1H), 5.00–5.35 (m, 4H), 5.65–6.00 (m, 3H, including H-1^1), 6.70–6.92 (m, 5H), 7.20–7.50 (m, 15H), 7.73 (m, 4H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 55.5 (d, $J = 21.8$ Hz), 68.0, 69.3, 70.7, 72.3, 73.6, 74.0, 74.6, 74.6, 74.8, 75.0, 75.9, 76.3 (d, $J = 9.5$ Hz), 78.2, 82.4, 101.2 (C-1^2, $J_{C-H} =$ 155 Hz), 104.7 (d, $J = 214.4$ Hz, C-1^1), 116.4, 116.6, 123.3, 126.8, 127.4, 127.6, 127.7, 127.7, 127.8, 127.9, 127.9, 128.1, 128.3, 128.5, 131.4, 133.8, 133.8, 134.7, 134.9, 138.5, 138.7, 138.7, 167.6; HRMS *m/z* calcd for $C_{54}H_{56}FNNaO_{11}$ $[M + Na]^+$ 936.3735, found 936.3742.

***t*-Butyldimethylsilyl 2-Azido-3,6-di-*O*-benzyl-4-*O*-(3′,6′-di-*O*-allyl-2′,4′-di-*O*-benzyl-D-mannopyranosyl)-2-deoxy-β-D-glucopyranoside (12).** This compound was synthesized from the mannosyl donor **3α** and glycosyl acceptor **7**.

12α: Colorless oil; R_f 0.40 (hexane/ethyl acetate, 5/1, v/v); $[\alpha]_D^{23}$ +11.7° (*c* 1.15, $CHCl_3$); IR (neat) 3030, 2928, 2860, 2109, 1460, 1359, 1261, 1114, 1069, 998, 924, 842, 783, 740, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.16 (s, 3H), 0.18 (s, 3H), 0.94 (s, 9H), 3.22–3.45 (m, 3H), 3.50–3.82 (m, 8H), 3.85–4.10 (m, 5H), 4.27 (d, $J = 12.2$ Hz, 1H), 4.39 (d, $J = 12.2$ Hz, 1H), 4.48–4.65 (m, 5H, including H-1^1), 4.88 (d, $J = 10.9$ Hz, 1H), 4.98 (d, $J =$ 11.4 Hz, 1H), 5.05–5.35 (m, 5H, including H-1^2), 5.78–5.97 (m, 2H), 7.10–7.40 (m, 20H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −5.3, −4.3, 17.9, 25.6, 68.4, 69.2, 69.3, 70.9, 72.2, 72.3, 72.8, 73.2, 74.4, 74.7, 74.7, 75.0, 75.8, 76.8, 79.3, 82.8, 97.1 (C-1^1), 100.2 (C-1^2, $J_{C-H} = 171$ Hz), 116.4, 116.8, 126.8, 127.2, 127.4, 127.5, 127.6, 128.0, 128.0, 128.2, 128.3, 128.4, 134.8, 135.0, 138.0, 138.4, 138.4, 138.5; HRMS *m/z* calcd for $C_{52}H_{67}N_3NaO_{10}Si$ $[M + Na]^+$ 944.4493, found 944.4493.

12β: Colorless oil; R_f 0.29 (hexane/ethyl acetate, 5/1, v/v); $[\alpha]_D^{23}$ −31.0° (*c* 1.26, $CHCl_3$); IR (neat) 3352, 3065, 3030, 2860, 2360, 2219, 2109, 1460, 1360, 1261, 1067, 925, 843, 784, 739, 699 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.16 (s, 6H), 0.94 (s, 9H), 3.20–3.43 (m, 5H), 3.49 (dd, $J = 5.1$, 10.6 Hz, 1H), 3.55–3.68 (m, 3H), 3.74 (s, 1H), 3.80–4.05 (m, 6H), 4.40–4.63 (m, 5H, including H-1^1, H-1^2), 4.68 (d, $J = 10.9$ Hz, 1H), 4.81 (d, $J =$ 11.4 Hz, 1H), 4.87 (d, $J = 11.4$ Hz, 1H), 5.00–5.33 (m, 5H), 5.68–5.95 (m, 2H), 7.20–7.45 (m, 20H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −5.2, −4.3, 18.0, 25.6, 68.4, 68.7, 69.4, 70.7, 72.3, 73.5, 74.0, 74.7, 74.7, 74.8, 74.8, 75.0, 76.0, 76.7, 81.0, 82.4, 97.1 (C-1^1), 100.9 (C-1^2, $J_{C-H} = 152$ Hz), 127.2, 127.3, 127.5, 127.6, 127.7, 128.0, 128.0, 128.0, 128.3, 128.4, 134.7, 135.0, 137.9, 138.5, 138.8, 138.9; HRMS *m/z* calcd for $C_{52}H_{67}FN_3NaO_{11}Si$ $[M +$ Na]$^+$ 944.4493, found 944.4493.

Methyl 3,6-Di-*O*-benzyl-4-*O*-(3′,6′-di-*O*-allyl-2′,4′-di-*O*-benzyl-D-mannopyranosyl)-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (13). This compound was synthesized from the mannosyl donor **3α** and glycosyl acceptor **8**.

13α: Colorless oil; R_f 0.50 (hexane/ethyl acetate, 2/1, v/v); $[\alpha]_D^{26}$ +55.8° (*c* 1.01, $CHCl_3$); IR (ATR) 2904, 1739, 1512, 1453, 1096, 1045, 1026, 816, 734, 696 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.38 (s, 3H), 3.50–4.10 (m, 16H), 4.26 (d, $J = 12.2$ Hz, 1H), 4.35 (d, $J = 12.2$ Hz, 1H), 4.50–4.75 (m, 8H, including H-1^2), 4.88 (d, $J = 10.9$ Hz, 1H), 5.05–5.31 (m, 6H, including H-1^1), 5.78–5.95 (m, 2H), 7.10–7.40 (m, 20H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 54.7, 55.1, 69.1, 69.4, 80.6, 70.8, 72.2, 72.3, 72.8, 73.2, 74.1, 74.5, 74.8, 75.0, 75.7, 77.5, 79.4, 80.6, 95.3, 98.4 (C-1^1), 100.4 (C-1^2, $J_{C-H} = 175$ Hz), 116.3, 116.7, 127.0, 127.2, 127.3, 127.4, 127.5, 127.6, 127.6, 127.9, 128.0, 128.2, 128.3, 128.4, 134.8, 134.9, 137.7, 138.3, 138.4, 138.6, 153.9; HRMS *m/z* calcd for $C_{50}H_{58}Cl_3NNaO_{12}$ $[M + Na]^+$ 992.2922, found 992.2915.

13β: Colorless oil; R_f 0.40 (hexane/ethyl acetate, 2/1, v/v); $[\alpha]_D^{26}$ +31.1° (*c* 1.03, $CHCl_3$); IR (ATR) 2864, 1738, 1091, 1047, 734, 696 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.10–3.30 (m, 2H), 3.37 (s, 3H), 3.50 (dd, $J = 4.9$, 10.9 Hz, 1H), 3.53–4.10 (m, 13H), 4.45 (dd, $J = 12.0$ Hz, 1H), 4.45 (s, 1H, H-1^2), 4.50–5.35 (m, 15H, including H-1^1), 5.68–5.95 (m, 2H), 7.16–7.50 (m, 20H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 54.6, 55.2, 68.6, 69.4, 70.5, 70.7, 72.3, 73.6, 74.0, 74.6, 74.7, 75.0, 75.0, 76.0, 77.3, 78.1, 82.5, 95.4, 98.5 (C-1), 101.0 (C-1^2, $J_{C-H} = 157$ Hz), 116.1, 116.5, 127.1, 127.3, 127.5, 127.7, 127.7, 127.8, 128.0, 128.0, 128.3, 128.5, 134.8, 135.1, 137.7, 138.6, 138.9, 139.1, 154.1; HRMS *m/z* calcd for $C_{50}H_{58}Cl_3NNaO_{12}$ $[M + Na]^+$ 992.2922, found 992.2915.

3,6-Di-*O*-benzyl-4-*O*-[3′,6′-di-*O*-benzyl-4′-*O*-(3″,6″-di-*O*-allyl-2″,4″-di-*O*-benzyl-D-mannopyranosyl)-2′-deoxy-2′-phthalimido-β-D-glucopyranosyl]-2-deoxy-2-phthalimido-β-D-glucopyranosyl Azido (14).[26] This compound was synthesized from the mannosyl donor **3α** and glycosyl acceptor **10**.

14α: Colorless oil; R_f 0.56 (toluene/ethyl acetate, 5/1, v/v); $[\alpha]_D^{23}$ +24.1° (*c* 1.34, $CHCl_3$); IR (neat) 3475, 3032, 2872, 2359, 2115, 1775, 1715, 1459, 1385, 1119, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.30–3.42 (m, 3H), 3.53 (d, $J = 10.4$ Hz, 1H), 3.60 (dd, $J = 1.8$, 11.0 Hz, 1H), 3.67 (dd, $J = 4.9$, 11.0 Hz, 1H), 3.73 (dd, $J = 4.3$, 11.0 Hz, 1H), 3.78–3.85 (m, 3H), 3.88–3.99 (m, 3H), 4.00–4.10 (m, 4H), 4.13 (dd, $J = 8.5$, 10.4 Hz, 1H), 4.16–4.23 (m, 3H), 4.33 (dd, $J = 8.9$, 11.0 Hz, 1H), 4.45–4.56

(m, 7H), 4.50 (s, 1H, H-1^3), 4.62 (d, J = 11.0 Hz, 1H), 4.63 (d, J = 11.9 Hz, 1H), 4.85 (d, J = 12.8 Hz, 1H), 4.90 (d, J = 11.0 Hz, 1H), 5.08–5.15 (m, 2H), 5.13 (d, J = 8.9 Hz, 1H, H-1^1), 5.20–5.32 (m, 3H), 5.25 (d, J = 8.9 Hz, 1H, H-1^2), 5.80–5.92 (m, 2H), 6.70–6.97 (m, 10H), 7.10–7.87 (m, 28H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.1, 56.3, 67.7, 68.6, 69.3, 71.0, 72.2, 72.4, 72.8, 72.8, 73.0, 74.4, 74.5, 74.8, 75.0, 75.0, 75.2, 76.4, 78.2, 79.5, 80.4, 85.5 (C-1^1), 96.7 (C-1^2), 100.1 (C-1^3, J_{C-H} = 172 Hz), 116.4, 116.7, 123.1, 123.3, 123.7, 126.9, 127.0, 127.2, 127.2, 127.4, 127.4, 127.4, 127.5, 127.5, 127.6, 127.8, 127.9, 128.1, 128.1, 128.1, 128.3, 128.3, 131.5, 133.7, 134.9, 135.0, 137.8, 138.1, 138.2, 138.5, 138.6, 138.7, 167.1, 167.4, 167.8, 168.6; HRMS m/z calcd for $C_{82}H_{81}N_5NaO_{17}$ $[M + Na]^+$ 1430.5525, found 1430.5521.

14β: Colorless oil; R_f 0.35 (toluene/ethyl acetate, 5/1, v/v); $[\alpha]_D^{19}$ +5.6° (c 1.47, $CHCl_3$); IR (neat) 3032, 2869, 2114, 1775, 1715, 1459, 1385, 1256, 1110, 728 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.20–3.33 (m, 3H), 3.35–3.50 (m, 3H), 3.55 (d, J = 10.7 Hz, 1H), 3.56 (d, J = 10.7 Hz, 1H), 3.63 (d, J = 11.0 Hz, 1H), 3.67 (d, J = 11.0 Hz, 1H), 3.76 (s, 1H), 3.82 (dd, J = 9.8, 9.8 Hz, 1H), 3.85–3.93 (m, 4H), 4.00–4.25 (m, 6H), 4.43–4.50 (m, 7H), 4.55 (s, 1H, H-1^3), 4.80–4.95 (m, 4H), 4.98 (d, J = 10.4 Hz, 1H), 5.01 (d, J = 12.8 Hz, 1H), 5.10–5.20 (m, 2H), 5.16 (d, J = 9.5 Hz, 1H, H-1^1), 5.25–5.33 (m, 2H, including H-1^2), 5.68–5.77 (m, 1H), 5.82–5.92 (m, 1H), 6.70–7.90 (m, 38H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.2, 56.6, 67.7, 68.1, 69.4, 70.7, 72.3, 72.3, 72.7, 74.0, 74.5, 74.8, 74.8, 75.0, 75.0, 75.2, 76.0, 76.4, 77.5, 79.1, 82.5, 85.5 (C-1^1), 97.0 (C-1^2), 101.5 (C-1^3, $^1J_{C-H}$ = 156 Hz), 116.2, 116.6, 123.1, 123.3, 123.5, 126.7, 127.0, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.0, 128.1, 128.3, 128.3, 128.5, 131.5, 131.5, 131.8, 133.7, 133.9, 134.8, 135.1, 137.9, 138.2, 138.4, 138.6, 139.0, 139.1, 167.6, 168.4.

3,6-Di-*O*-allyl-2,4-di-*O*-benzyl-D-mannopyranosyl Trichloroacetimidate (15). A solution of 3,6-di-*O*-allyl-2,4-di-*O*-benzyl-D-mannopyranose (**2**) (100 mg, 0.23 mol) in CH_2Cl_2 (1.20 mL) and trichloroacetonitrile (0.03 mL, 0.27 mmol) was treated with DBU (0.04 mL, 0.27 mmol) and stirred for 3.5 h at 0 °C under argon. The reaction mixture was diluted with dichloromethane and extracted subsequently with a sat. aq NH_4Cl solution and water. The organic solution was dried (Na_2SO_4) and concentrated to dryness. The residue was purified by preparative TLC (hexane/ethyl acetate = 3/1, +1% Et_3N) to give **15** (69.7 mg, 52%) as an anomeric mixture (α/β = 94/6).

15α: Colorless oil; R_f 0.57 (hexane/ethyl acetate, 3/1, v/v); $[\alpha]_D^{19}$ +31.9° (c 1.05, $CHCl_3$); IR (ATR) 2910, 2868, 1727, 1671, 1064, 967, 921, 829, 795, 736, 697 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.60–4.20 (m, 10H), 4.64 (d, J = 10.7 Hz, 1H), 4.80 (s, 2H), 4.93 (d, J = 10.7 Hz, 1H), 5.10–5.32 (m, 4H), 5.80–6.00 (m, 2H), 6.38 (d, J = 1.5 Hz, 1H, H-1), 7.20–7.60 (m, 10H), 8.55 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 68.8, 71.1, 72.3, 72.5, 73.2, 74.1, 74.6, 75.3, 79.0, 91.0, 96.2 (C-1, $^1J_{C-H}$ = 177 Hz), 116.8, 117.0, 127.6, 127.7, 127.8, 128.1, 128.2, 128.3, 134.6, 134.8, 137.9, 138.4, 160.3; HRMS m/z calcd for $C_{28}H_{32}Cl_3NNaO_6$ $[M + Na]^+$ 606.1193, found 606.1188.

3,6-Di-*O*-benzyl-4-*O*-[3′,6′-di-*O*-benzyl-4′-*O*-(2″,4″-di-*O*-benzyl-β-D-mannopyranosyl)-2′-deoxy-2′-phthalimido-β-D-glucopyranosyl]-2-deoxy-2-phthalimido-β-D-glucopyranosyl Azido (17).[26] Palladium(II) dichloride (2.8 mg, 0.16 mmol) was added to a mixture of the trisaccharide **14β** (28 mg, 0.02 mmol) in MeOH (1.5 mL) under an argon atmosphere. After completion of the deallylation reaction was verified by monitoring TLC (16 h), the mixture was filtered through Celite and concentrated in vacuo. The residue was purified by thin-layer chromatography (toluene/ethyl acetate = 7/1, v/v) to afford **17** (25.5 mg, 97%).

17: Colorless oil; R_f 0.41 (hexane/ethyl acetate, 1/1, v/v); $[\alpha]_D^{27}$ +6.1° (c 1.05, $CHCl_3$); IR (ATR) 2872, 2114, 1775, 1710, 1384, 1070, 1026, 719, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.29 (d, J = 9.5 Hz, 1H), 3.08–3.14 (m, 1H), 3.24–3.28 (m, 1H), 3.37–3.46 (m, 4H), 3.46–3.60 (m, 3H), 3.60–3.73 (m, 3H), 4.02–4.09 (m, 2H), 4.14–4.30 (m, 4H), 4.40 (d, J = 12.2 Hz, 1H), 4.46 (d, J = 12.2 Hz, 1H), 4.49–4.59 (m, 5H), 4.60 (s, 1H, H-1^3), 4.65 (d, J = 11.6 Hz, 1H), 4.81 (d, J = 11.0 Hz, 1H), 4.88 (d, J = 12.8 Hz, 1H), 4.95 (d, J = 12.2 Hz, 1H), 5.02 (d, J = 11.6 Hz, 1H), 5.17 (d, J = 9.5 Hz, 1H, H-1^1), 5.30 (d, J = 7.9 Hz, 1H, H-1^2), 6.75–7.00 (m, 10H), 7.20–7.40 (m, 20H), 7.50–7.90 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.2, 56.4, 67.7, 67.7, 72.7, 73.3, 74.1, 74.5, 74.6, 74.6, 75.2, 75.3, 75.5, 76.4, 76.5, 76.7, 77.0, 78.3, 78.9, 85.6 (C-1^1), 97.0 (C-1^2), 101.3 (C-1^3, $^1J_{C-H}$ = 152 Hz), 123.1, 123.3, 123.6, 126.9, 127.0, 127.1, 127.3, 127.4, 127.7, 127.8, 127.8, 127.8, 127.9, 128.0, 128.0, 128.2, 128.4, 128.5, 128.5, 131.3, 131.5, 131.6, 133.7, 133.9, 134.1, 138.1, 138.2, 138.2, 138.4, 138.6, 167.5, 168.5.

3,6-Di-*O*-benzyl-4-*O*-{3′,6′-di-*O*-benzyl-4′-*O*-[3″,6″-bis-*O*-(2‴-*O*-acetyl-3‴,4‴,6‴-tri-*O*-benzyl-α-D-mannopyranosyl)-2″,4″-di-*O*-benzyl-β-D-mannopyranosyl]-2′-deoxy-2′-phthalimido-β-D-glucopyranosyl}-2-deoxy-2-phthalimido-β-D-glucopyranosyl Azido (20).[26] The mannosyl donor **19** (154 mg, 0.30 mmol) in CH_2Cl_2 (2.0 mL) was added to a mixture of the trisaccharide acceptor **17** (100 mg, 0.08 mmol) and silver triflate (135 mg, 0.53 mmol) and MS 4A (1.0 g) in CH_2Cl_2 (10.0 mL) at −40 °C under an argon atmosphere. After additional stirring for 17.5 h at room temperature, the mixture was filtered through Celite, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over Na_2SO_4. After filtration and evaporation, the resulting residue was purified by preparative TLC (hexane/ethyl acetate, 120/75, v/v) to afford **20** (154.0 mg, 90%).

20: Colorless form; R_f 0.12 (hexane/ethyl acetate, 2/1, v/v); $[\alpha]_D^{27}$ +21.0° (c 1.03, $CHCl_3$); IR (ATR) 2869, 2115, 1713, 1384, 1233, 1072, 1053, 720, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.80 (s, 3H), 2.09 (s, 3H), 3.15–3.20 (m, 2H), 3.30–3.45 (m, 4H), 3.51 (dd, J = 10.1, 10.1 Hz, 1H), 3.55–4.25 (m, 22H), 4.30–4.70 (m, 17H), 4.61 (d, J = 1.8 Hz, 1H, H-1^3), 4.72–4.90 (m, 5H), 4.86 (s, 1H, H-1^4), 5.05 (d, J = 12.2 Hz, 1H), 5.15 (d, J = 9.5 Hz, 1H, H-1^1), 5.16 (s, 1H, H-1$^{4'}$), 5.23 (d, J = 7.6 Hz, 1H, H-1^2), 5.33 (s, 1H), 5.51 (s, 1H), 6.60–7.80 (m, 68H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.6, 20.9, 66.4, 67.6, 67.6, 68.1, 68.6, 68.6, 68.9, 71.1, 71.1, 71.8, 71.8, 72.3, 72.6, 73.0, 73.2, 73.4, 74.0, 74.1, 74.1, 74.5, 74.5, 74.6, 74.7, 74.9, 74.9, 75.1, 76.4, 76.6, 76.7, 77.6, 77.9, 78.0, 85.4 (C-1^1), 96.9 (C-1^2), 98.2 (C-1$^{4'}$), 99.5 (C-1^4), 101.9 (C-1^3), 123.0, 123.2, 123.4, 126.8, 126.9, 127.2, 127.3, 127.3, 127.4, 127.5, 127.6, 127.6, 127.7, 127.7, 128.0, 128.0, 128.1, 128.1, 128.1, 128.2, 128.3, 128.3, 128.3, 128.5, 131.4, 131.7, 133.5, 133.7, 137.7, 137.8, 137.8, 137.9, 137.9, 138.1, 138.2, 138.3, 138.4, 138.4, 138.5, 138.6, 138.7, 167.3, 168.0, 170.0, 170.0.

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References

1 Reviews on glycosylations: a) H. Paulsen, *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155. b) R. R. Schmidt, *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212. c) H. Kuntz, *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 294. d) P. Sinaÿ, *Pure Appl. Chem.* **1991**,

63, 519. e) K. Suzuki, T. Nagasawa, *J. Synth. Org. Chem., Jpn.* **1992**, *50*, 378. f) K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503. g) B. Ernst, G. W. Hart, P. Sinaÿ, *Carbohydrate in Chemistry and Biology*, WILEY-VCH, Weinheim, **2000**, Part 1.

2 R. A. Dwek, *Chem. Rev.* **1996**, *96*, 683.

3 Recent review on β-mannoside synthesis: a) G. Arsequell, G. Valencia, *Tetrahedron: Asymmetry* **1999**, *10*, 3045. b) J. J. Gridley, H. M. I. Osborn, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1471. c) B. Ernst, G. W. Hart, P. Sinaÿ, *Carbohydrate in Chemistry and Biology*, WILEY-VCH, Weinheim, **2000**, Part 1, p. 320. d) C.-H. Wong, *Carbohydrate-Based Drug Discovery*, WILEY-VCH, Weinheim, **2003**, p. 253.

4 a) G. Ekborg, B. Lindberg, J. Lönngren, *Acta Chem. Scand.* **1972**, *26*, 3287. b) M. Miljkovic, M. Gligorijevic, D. Glisin, *J. Org. Chem.* **1974**, *39*, 3223. c) F. W. Lichtenthaler, E. Kaji, S. Weprek, *J. Org. Chem.* **1985**, *50*, 3505. d) H.-W. Hagedorn, R. Brossmer, *Helv. Chim. Acta* **1986**, *69*, 2127. e) H. Kunz, W. Gunther, *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1086. f) J. Alais, S. David, *Carbohydr. Res.* **1990**, *201*, 69. g) F. W. Lichtenthaler, T. Schneider-Adams, *J. Org. Chem.* **1994**, *59*, 6728. h) I. Matsuo, M. Isomura, R. Walton, K. Ajisaka, *Tetrahedron Lett.* **1996**, *37*, 8795.

5 a) G. Stork, H. S. Suh, G. Kim, *J. Am. Chem. Soc.* **1991**, *113*, 7054. b) F. Barresi, O. Hindsgaul, *Can. J. Chem.* **1994**, *72*, 1447. c) A. Dan, Y. Ito, T. Ogawa, *Tetrahedron Lett.* **1995**, *36*, 7487. d) T. Ziegler, G. Lemanski, A. Rakoczy, *Tetrahedron Lett.* **1995**, *36*, 8973. e) A. Dan, Y. Ito, T. Ogawa, *J. Org. Chem.* **1995**, *60*, 4680. f) G. Stork, J. J. La Clair, *J. Am. Chem. Soc.* **1996**, *118*, 247. g) M. Lergenmüller, T. Nukada, K. Kuramochi, A. Dan, T. Ogawa, Y. Ito, *Eur. J. Org. Chem.* **1999**, 1367. h) I. Matsuo, Y. Ito, *Carbohydr. Res.* **2003**, *338*, 2163.

6 T. Yamanoi, K. Nakamura, H. Takeyama, K. Yanagihara, T. Inazu, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1359.

7 O. J. Plante, E. R. Palmacci, P. H. Seeberger, *Org. Lett.* **2000**, *2*, 3841.

8 a) H. Paulsen, O. Lockhoff, *Chem. Ber.* **1981**, *114*, 3102. b) P. Garegg, P. Ossowski, *Acta Chem. Scand., Ser. B* **1983**, *37*, 249. c) C. A. A. van Boeckel, T. Beetz, *Recl. Trav. Chim. Pays-Bas. Belg.* **1987**, *106*, 596.

9 a) K. Toshima, K. Kasumi, S. Matsumura, *Synlett* **1998**, 643. b) H. Nagai, K. Kawahara, S. Matsumura, K. Toshima, *Tetrahedron Lett.* **2001**, *42*, 4159.

10 G. Hodosi, P. Kovác, *J. Am. Chem. Soc.* **1997**, *119*, 2335.

11 a) L. F. Awad, E. S. El Ashry, C. Schuerch, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1587. b) A. A.-H. Abdel-Rahman, S. Jonke, E. S. El Ashry, R. R. Schmidt, *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2972.

12 a) D. Crich, S. Sun, *J. Org. Chem.* **1996**, *61*, 4506. b) D. Crich, S. Sun, *J. Org. Chem.* **1997**, *62*, 1198. c) D. Crich, S. Sun, *J. Am. Chem. Soc.* **1998**, *120*, 435. d) D. Crich, S. Sun, *Tetrahedron* **1998**, *54*, 8321. e) D. Crich, S. Sun, *Org. Lett.* **2000**, *2*, 4067. f) D. Crich, S. Sun, *J. Am. Chem. Soc.* **2001**, *123*, 9015. g) D. Crich, H. Li, *J. Org. Chem.* **2002**, *67*, 4640. h) D. Crich, M. Smith, *J. Am. Chem. Soc.* **2002**, *124*, 8867. i) D. Crich, *J. Carbohydr. Chem.* **2002**, *21*, 667. j) D. Crich, P. Jayalath, *Org. Lett.* **2005**, *7*, 2277.

13 a) R. Weingart, R. R. Schmidt, *Tetrahedron Lett.* **2000**, *41*, 8753. b) K. S. Kim, J. H. Kim, Y. J. Lee, Y. J. Lee, J. Park, *J. Am. Chem. Soc.* **2001**, *123*, 8477. c) T. Tsuda, S. Sato, S. Nakamura, S. Hashimoto, *Heterocycles* **2003**, *59*, 509. d) J. D. C. Codée, L. H. Hossain, P. H. Seeberger, *Org. Lett.* **2005**, *7*, 3251. e) H. Nagai, K. Sasaki, S. Matsumura, K. Toshima, *Carbohydr. Res.* **2005**, *340*, 337. f) S. Tanaka, M. Takashima, H. Tokimoto, Y. Fujimoto, K. Tanaka, K. Fukase, *Synlett* **2005**, 2325.

14 V. Dudkin, D. Crich, *Tetrahedron Lett.* **2003**, *44*, 1787.

15 D. A. Crich, V. Dudkin, *J. Am. Chem. Soc.* **2001**, *123*, 6819.

16 V. Dudkin, J. S. Miller, S. J. Danishefsky, *Tetrahedron Lett.* **2003**, *44*, 1791.

17 a) T. Hashihayata, H. Mandai, T. Mukaiyama, *Chem. Lett.* **2003**, *32*, 442. b) T. Hashihayata, T. Mukaiyama, *Heterocycles* **2003**, *61*, 51. c) T. Hashihayata, H. Mandai, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 169. d) H. Mandai, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 702.

18 T. Ogawa, T. Kitajima, T. Nukada, *Carbohydr. Res.* **1983**, *123*, C5.

19 K. Bock, C. Pedersen, *J. Chem. Soc., Perkin Trans. 2* **1974**, 293.

20 T. Nakano, Y. Ito, T. Ogawa, *Carbohydr. Res.* **1993**, *243*, 43.

21 a) H. Jona, H. Mandai, T. Mukaiyama, *Chem. Lett.* **2001**, 426. b) H. Jona, H. Mandai, W. Chavasiri, K. Takeuchi, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 291. c) Ref. 13f.

22 O. Kanie, Y. Ito, T. Ogawa, *J. Am. Chem. Soc.* **1994**, *116*, 12073.

23 M. R. Pratt, C. R. Bartizan, *J. Am. Chem. Soc.* **2003**, *125*, 6149.

24 C. Murakata, T. Ogawa, *Carbohydr. Res.* **1992**, *234*, 75.

25 S. S. Rana, J. J. Barlow, K. L. Matta, *Carbohydr. Res.* **1983**, *113*, 257.

26 a) I. Matsuo, Y. Nakahara, Y. Ito, T. Nukada, Y. Nakahara, T. Ogawa, *Bioorg. Med. Chem.* **1995**, *3*, 1455. b) Z.-W. Guo, Y. Nakahara, T. Ogawa, *Tetrahedron Lett.* **1997**, *38*, 4799. c) Z.-W. Guo, Y. Nakahara, Y. Nakahara, T. Ogawa, *Bioorg. Med. Chem.* **1997**, *5*, 1917.

27 a) S. Weiler, R. R. Schmidt, *Tetrahedron Lett.* **1998**, *39*, 2299. b) M. V. Chiesa, R. R. Schmidt, *Eur. J. Org. Chem.* **2000**, 3541.

28 M. Adinolfi, A. Iadonisi, *J. Org. Chem.* **2005**, *70*, 5316.

29 T. G. Mayer, R. R. Schmidt, *Eur. J. Org. Chem.* **1999**, 1153.

30 a) Y. Du, M. Zhang, F. Kong, *Tetrahedron* **2001**, *57*, 1757. b) D. M. Ratner, O. J. Plante, P. H. Seeberger, *Eur. J. Org. Chem.* **2002**, 826. c) X. Schratt, C. Unverzagt, *Tetrahedron Lett.* **2005**, *46*, 691.

31 S. Inamura, K. Fukase, S. Kusumoto, *Tetrahedron Lett.* **2001**, *42*, 7613.