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Stereoselective glycosylation using the long-range effect of a [2-(4-phenylbenzyl)oxycarbonyl]benzoyl group

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Abstract—Highly α-selective glucosylation was effected by virtue of the solvent effect of cyclopentyl methyl ether and the long-range assistance of bulky 6-*O*-protective groups. Higher α-selectivity was obtained by the use of this solvent in comparison to conventional diethyl ether. α-Selectivity was further improved with the influence of 6-*O*-substituents, such as TBDPS and phthaloyl groups, the latter being mono esterified with a bulky alcohol.

1. Introduction

Stereoselective glycosylation has been an important issue for efficient synthesis of oligosaccharides.[1–3] In particular, selective formation of 1,2-*cis*-glycosides is generally a difficult issue, since no assisting effect such as participation of a neighboring group is available.[3] In the present study, we investigated a new practical method for stereoselective 1,2-*cis*-α-D-glucosylation by using bulky protecting groups for long-range stereocontrol. Among those tested a new phthaloyl ester proved to be quite promising.

Previously, we have reported an efficient method for glycosylation using thioglycoside donors and hypervalent iodine reagents prepared from PhIO and Lewis acids as promoters.[4–7] α-Glucosides were preferentially obtained by virtue of the solvent effect of diethyl ether and the α-directing effect of perchlorates, which have been widely employed for selective α-glycosylations.[4–9] We have also observed that long-range participation[5–7,10] as well as steric demands[6,7] of 6-*O*-protective groups in glycosyl donors increased the α-selectivity of the reaction (Fig. 1).[3] Herein, we further develop this approach and have succeeded in securing higher α-selective

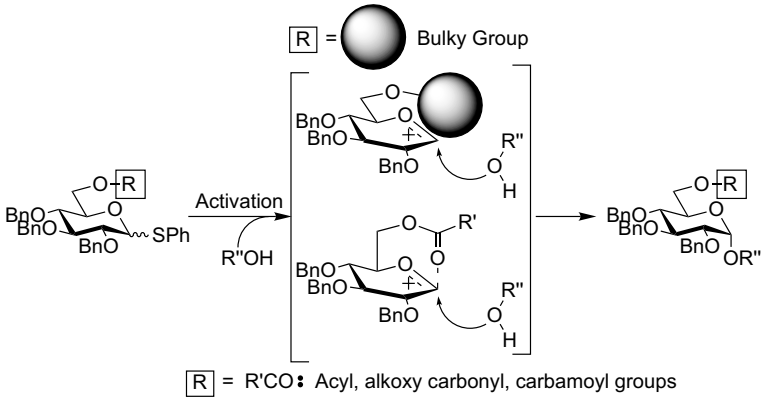

Figure 1. α-Selective glucosylation by using the effects of 6-*O*-substituents.

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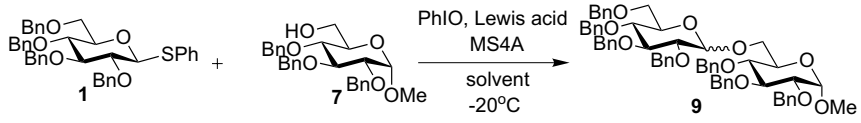


Scheme 1.

glycosylation by the combined use of the favorable solvent effect of cyclopentyl methyl ether and the steric effect of bulky [2-(4-phenylbenzyl)oxycarbonyl]benzoyl groups at the 6-position of glycosyl donors. This procedure enables us to avoid the use of perchlorates many of which are explosive and can cause serious problems in laboratories.

2. Results and discussion

The solvent effect of cyclopentyl methyl ether (CPME), a new solvent recently becoming available, was first examined. 1,4-Dioxane was shown to be a more efficient participating solvent than diethyl ether probably owing to its structure, where the oxygen lone pair of the former is more accessible for the participation.[11] Since dioxane is hygroscopic and thus not favorable for such reactions where strictly anhydrous conditions are required, we checked other less hygroscopic ethers and found that *tert*-butyl methyl ether gave better α-selectivity than diethyl ether.[12] *t*-Butyl methyl ether is, however, not stable enough to strong acids often employed for glycosylation reactions. These results led us to examine a new solvent, CPME. In view of its high stability against oxidation and high boiling point (106 °C), the use of this solvent was expected to improve the safety of experimental procedures and to be a good choice provided that a sufficient α-orienting effect is exerted by this solvent. In order to check the solvent effect, 2,3,4,6-tetrabenzylated thioglycoside **1** was employed as a standard donor, free methyl glycoside **8** with a free 6-OH group as an acceptor, and $Sn(OTf)_2$ as a Lewis acid. Glycosylation reactions were carried out using 1.3 equiv of PhIO, 0.6 equiv of Lewis acid, and 1.2 equiv of the donor **1** against the acceptor **8** under Ar atmosphere in the presence of molecular sieves 4 Å at −20 °C to give disaccharide **9** (Scheme 1). As seen in Table 1 (entries 1 and 2), higher α-selectivity was obtained using CPME than in the corresponding reaction in diethyl ether.

Table 1. Reaction conditions and products of α-selective glycosylation

Entry	Lewis acid	Solvent	Temp. (°C)	Time	Yield (%)	α:β
1	$Sn(OTf)_2$	Et_2O	−20	<5 min	82	72:28
2	$Sn(OTf)_2$	CPME	−20	<5 min	80	78:22
3	TMSOTf	CPME	−20	1 h	89	84:16
4	TBSOTf	CPME	−20	5.5 h	80	79:21
5	TESOTf	CPME	−20	2 h	82	66:34

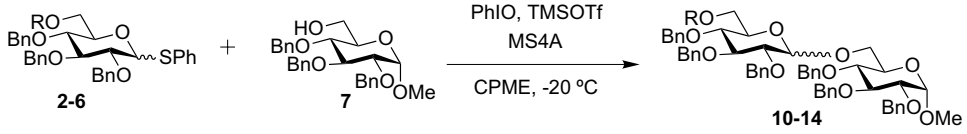
Table 2. Effect of 6-*O*-substituents for α-selectivity

Entry	Donor	Acceptor	Time	Product	Yield (%)	α:β
1	**2**	**7**	6 h	10	53	100:0
2	**3**	**7**	5 h	11	85	90:10
3	**4**	**7**	45 min	12	79	97:3
4	**5**	**7**	1.5 h	13	53	100:0
5	**6**	**7**	45 min	14	83	100:0
6[a]	**6**	**8**	6 h	15	75	100:0

Glycosylation reactions were carried out by use of a donor (1.2 equiv), PhIO (1.3 equiv), and TMSOTf (0.6 equiv) against an acceptor under Ar atmosphere in the presence of molecular sieves 4 Å at −20 °C in CPME.
[a] Reaction conditions, see text.

The influence of Lewis acid catalysts was next examined. In our previous papers, we showed that Lewis acid such as $SnCl_2$–$AgClO_4$, $SnCl_4$–$AgClO_4$, $SbCl_3$–$AgClO_4$, $TMSClO_4$, $Mg(ClO_4)_2$ gave satisfactory α-selectivities in glycosylation.[5–7] As mentioned above, however, perchlorates are explosive and their use should be avoided. In the present study, various triflates were examined in place of perchlorates. Though TMSOTf gave the highest α-selectivity and chemical yield among those tested (Table 1, entries 2–5), stereoselectivity was greatly depressed from those obtained with perchlorates and practically acceptable values were never obtained.

To improve the α-selectivity of triflate-promoted glycosylation, the effect of 6-*O*-protective groups was examined with thioglucosyl donors having various substituents at the 6-*O*-position (Scheme 2). As summarized in Table 2, the reaction with 6-*O*-*tert*-butyldiphenylsilylated donor **2** proceeded slowly but gave the desired **10** with perfect α-selectivity (Table 2, entry 1). The yield of the product was, however, moderate, since a considerable amount of byproducts were formed. Hence, phthaloyl half-esters were designed as new functional groups for enhancing anomeric stereocontrol (Fig. 2). The idea was based on our previous work on successful stereoselective glycosylation using a 'molecular clamp' method, where a bridge tethering acceptor and donor components together controls their spatial



Scheme 2.

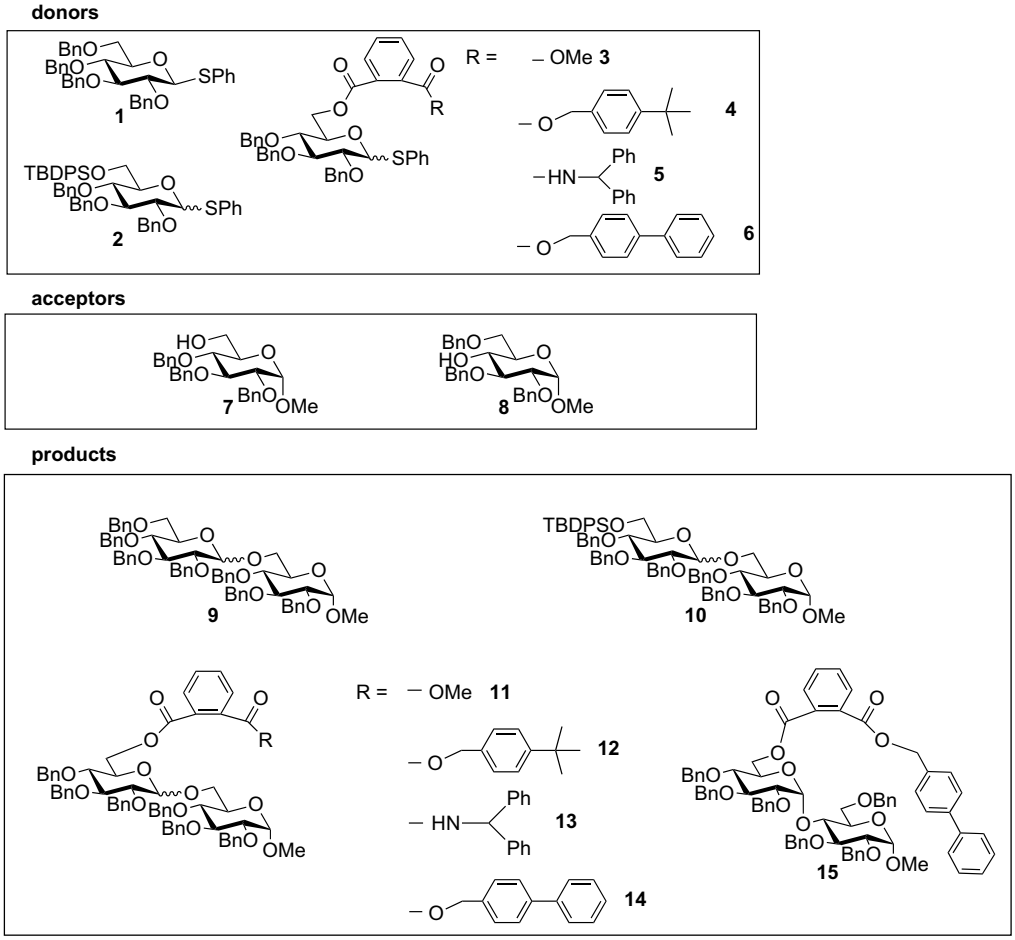


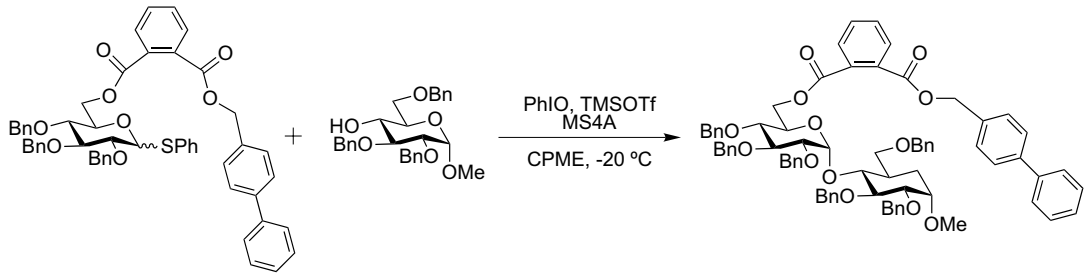
Figure 2. Structure of glycosyl donors, acceptors, and products.

arrangement, kinetically accelerates the glycosylation, and allows a stereoselective reaction. Intramolecular glycosylation between the donor and acceptor tethered with a phthaloyl bridge at their 6-positions proceeded smoothly to give the desired α(1→4) glycoside with high stereoselectivity.[13,14] A dipole repulsion between two carbonyl groups in the phthaloyl moiety may have controlled the direction of the two ester parts. This led us to an idea that a phthaloyl half-ester part may cover the upper face of the donor moiety to inhibit the attack of an acceptor from the β-face of the former.

The effect of a phthaloyl half-ester was examined by using methyl ester **3** as a glycosyl donor. The yield was very much improved from the value with TBDMS donor **2** but the α-selectivity remained as low as 9:1 (Table 2, entry 2). Even so, the latter value indicates a slight but positive α-directing influence of the 6-*O*-phthaloyl function as compared to the conventional benzyl function. In fact, the α-selectivity was greatly improved when more bulky 4-*tert*-butylbenzyl ester **4** was used as a donor (Table 2, entry 3). Absolute α-selectivity was obtained by using benzhydrylamide **5** as a donor but the yield again dropped to an unsatisfactory, moderate level (Table 2, entry 4). In the case of the biphenylmethyl ester **6**, the glycosylation proceeded smoothly to give the desired α-glycoside **14** in a high yield with absolute α-selectivity (Table 2, entry 5).

The glucosylation of an acceptor **8** possessing a more hindered 4-hydroxyl group proceeded more slowly and hydrolysis of the donor **6** was observed during the reaction. When the reaction was accelerated by the use of 2.3 equiv of PhIO, 1.0 equiv of TMSOTf, and 2.0 equiv of donor **6** against acceptor **8**, the desired α(1→4) glycoside **15** was obtained in a satisfactory yield again with perfect α-selectivity (Table 2, entry 6, Scheme 3).

Molecular modeling of the oxocarbenium ion intermediate of this reaction was carried out in order to explain the high α-orienting effect of the 6-*O*-[2-(4-phenylbenzyl)oxycarbonyl]benzoyl group. A simplified structure of the oxocarbenium ion intermediate was used for the calculation: the benzyl ethers were changed to methyl ethers and the biphenylmethyl group was changed to a benzyl group. The lowest energy conformation was explored by using MacroModel (v7.1) Mixed MCMM/LowMode Search using OPLS-AA force field and then the geometry of energy minimum was optimized with DFT calculation using B3LYP, 6–31G** (Jaguar v 4.1) (Fig. 3, **A**). In the lowest energy conformation **A**, the phthaloyl half-ester part efficiently shields the upper face of the pyranose ring and hence favor the attack of the glycosyl acceptor from the opposite side to lead to the preferential formation of α-glycosides. The conformation **B** that can afford β-glycoside was 6.3 kJ less stable than **A** and hence considered to be a minor one.



Scheme 3.

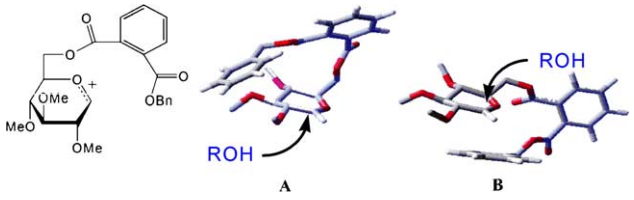


Figure 3. The lowest energy conformation of oxocarbenium intermediate (A) and the conformation that shields α-face (B).

3. Conclusion

In summary, a new practical and operationally simple procedure has been developed for highly α-selective glucosylation by using a phthaloyl group mono-esterified with bulky biphenylmethanol and the solvent effect of CPME. The phthaloyl half-ester and its structural analogues may be useful as an auxiliary group for other diastereoselective reactions as well.

4. Experimental section

^{1}H NMR spectra were measured with JEOL JMN-GSX 400 or JEOL EX 270 spectrometers. The chemical shifts in $CDCl_3$ are given in δ values from tetramethylsilane as an internal standard. Mass spectra were obtained on Applied Biosystem Marinar™ Biospectrometry Workstation. Elemental analysis was performed by the staff of the department. Silica-gel column chromatography was carried out using Kieselgel 60 (Merck, 0.040–0.063 mm) at medium pressure (2–4 kg/cm^2). Precoated Kieselgel 60 F254 (Merck, 0.5 mm) was used for preparative thin layer chromatography. Anhydrous cyclopentyl methyl ether was distilled from sodium. Anhydrous Et_2O was purchased from Kanto Chemicals, Tokyo. Molecular sieves 4 Å was activated by heating at 250 °C in vacuo for 3 h. The reactions were quenched by addition of saturated aqueous $NaHCO_3$ and extracted with EtOAc and then the organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo, unless otherwise noted.

4.1. Phenyl 2,3,4-tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-1-thio-β-D-glucopyranoside 2

To a solution of phenyl 2,3,4-tri-*O*-benzyl-1-thio-D-glucopyranoside[13] (200.0 mg, 368.5 μmol) and imidazole (30.1 mg, 442.2 μmol) in CH_2Cl_2 (3 mL) was added TBDPSCl (121.6 mg, 114.7 μL, 442.2 μmol) at 0 °C under Ar atmosphere and the reaction mixture was stirred at room temperature overnight. The reaction was then worked up as usual. The residue was purified by silica-gel flash column chromatography (toluene/EtOAc = 15:1) to give **2** as a colorless syrup (272 mg, 95%). ESI-MS (positive) m/z = 803.3 [(M+Na)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.77 (d, J = 6.84 Hz, 2H), 7.70 (d, J = 6.84 Hz, 2H), 7.60 (d, J = 5.62 Hz, 1H), 7.60 (d, J = 7.32 Hz, 1H), 7.41–7.15 (m, 24H, aromatic), 4.90–4.84 (m, 4H, –CH_2Ph × 2), 4.75–4.67 (m, 2H, –CH_2Ph), 4.71 (d, $J_{1,2}$ = 9.28 Hz, 1H, H-1), 3.96 (dd, $J_{3,4}$ = 7.57 Hz, $J_{3,2}$ = 8.71 Hz, 1H, H-3), 3.93 (dd, $J_{5,6}$ = 3.66 Hz, $J_{5,4}$ = 5.75 Hz, 1H, H-5), 3.79 (dd, $J_{6a,6b}$ = 17.58 Hz, $J_{6a,5}$ = 9.28 Hz, 1H, H-6a), 3.72 (dd, $J_{6b,6a}$ = 17.58 Hz, $J_{6b,5}$ = 9.28 Hz, 1H, H-6b), 3.55 (dd, $J_{2,3}$ = 8.79 Hz, $J_{2,1}$ = 9.28 Hz, 1H, H-2), 3.40 (d, $J_{4,3}$ = 7.57 Hz, 1H, H-4). Found: C, 75.10; H, 6.68; S, 4.04. Calcd for $C_{49}H_{52}O_5SSi$: C, 75.35; H, 6.71; S, 4.11.

4.2. Phenyl 2,3,4-tri-*O*-benzyl-6-*O*-[2-(methoxycarbonyl)benzoyl]-1-thio-α-D-glucopyranoside 3

To a solution of phenyl 2,3,4-tri-*O*-benzyl-6-*O*-(2-carbonylbenzoyl)-1-thio-α-D-glucopyranoside[13] (30.0 mg, 43.0 μmol) in MeOH (1 mL) was added $TMSCHN_2$ (30 μL, 60.0 μmol) at room temperature and the reaction mixture was stirred for 30 min. The reaction was quenched by addition of AcOH and concentrated in vacuo. The residue was purified by silica-gel flash column chromatography (toluene/EtOAc = 10:1) to give **3** as a colorless syrup (22.7 mg, 75%). ESI-MS (positive) m/z = 727.2 [(M+Na)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.76–7.10 (m, 24H, aromatic), 5.59 (d, $J_{1,2}$ = 5.13 Hz, 1H, H-1), 5.03–4.61 (m, 6H, –CH_2Ph × 3), 4.55–4.44 (m, 3H, H-5, H-6a, H-6b), 3.95 (dd, $J_{3,4}$ = $J_{3,2}$ = 9.52 Hz, 1H, H-3), 3.88 (dd, $J_{2,3}$ = 9.52 Hz, $J_{2,1}$ = 5.13 Hz, 1H, H-2), 3.78 (s, 3H, –OCH_3), 3.57 (dd, $J_{4,5}$ = 9.03 Hz, $J_{4,3}$ = 9.52 Hz, 1H, H-4). Found: C, 71.48; H, 5.73; S, 4.46. Calcd for $C_{33}H_{34}O_5S$: C, 71.57; H, 5.72; S, 4.55.

4.3. Phenyl 2,3,4-tri-*O*-benzyl-6-*O*-[[2-(4-*tert*-butylbenzyl)oxycarbonyl]benzoyl]-1-thio-α-D-glucopyranoside 4

To a solution of phenyl 2,3,4-tri-*O*-benzyl-6-*O*-(2-carbonylbenzoyl)-1-thio-α-D-glucopyranoside[13] (50.0 mg, 72.4 μmol) in CH_2Cl_2 (1 mL) were added 4-*tert*-butylbenzyl alcohol (14.2 mg, 15.3 μL, 86.8 μmol), DIC

(11.8 mg, 14.7 μL, 94.1 μmol) and DMAP (cat.) at room temperature under Ar atmosphere and the reaction mixture was stirred overnight. The reaction was quenched by addition of AcOH and MeOH. Insoluble materials were filtered through Celite® and the filtrate was concentrated in vacuo. The residue was purified by silica-gel preparative thin layer chromatography (toluene/EtOAc = 5:1) to give **4** as a colorless syrup (59.6 mg, 98%). ESI-MS (positive) m/z = 859.3 [(M+Na)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.70–6.99(m, 28H, aromatic), 5.52 (d, $J_{1,2}$ = 5.13 Hz, 1H, H-1), 5.18 and 5.11 (each d, J_{gem} = 12.21 Hz, 2H, –CH_2Ph), 4.93 and 4.77 (each d, J_{gem} = 12.45 Hz, 2H, –CH_2Ph), 4.81 and 4.54 (each d, J_{gem} = 10.74 Hz, 2H, –CH_2Ph), 4.67 and 4.59 (each d, J_{gem} = 11.72 Hz, 2H, –CH_2Ph), 4.43–4.32 (m, 3H, H-5, H-6a, H-6b), 3.87 (dd, $J_{3,4}$ = $J_{3,2}$ = 9.52 Hz, 1H, H-3), 3.81 (dd, $J_{2,3}$ = 9.52 Hz, $J_{2,3}$ = 5.13 Hz, 1H, H-2), 3.48 (dd, $J_{4,5}$ = 8.52 Hz, $J_{4,3}$ = 9.52 Hz, 1H, H-4), 1.20 (s, 9H, –C(CH_3)$_3$). Found: C, 73.33; H, 6.23; S, 3.60. Calcd for $C_{52}H_{52}O_8S\cdot0.8H_2O$: C, 73.35; H, 6.16; S, 3.77.

4.4. Phenyl 2,3,4-tri-*O*-benzyl-6-*O*-[2-(diphenylmethylaminocarbonyl)benzoyl]-1-thio-α-D-glucopyranoside 5

To a solution of phenyl 2,3,4-tri-*O*-benzyl-6-*O*-(2-carbonylbenzoyl)-1-thio-α-D-glucopyranoside[13] (50.0 mg, 72.4 μmol) in CH_2Cl_2 (1 mL) were added Ph_2CHNH_2 (15.9 mg, 15 μL, 86.8 μmol), DIC (11.8 mg, 14.7 μL, 94.1 μmol) and DMAP (cat.) at room temperature under Ar atmosphere and the reaction mixture was stirred overnight. The reaction was quenched by addition of AcOH and MeOH. Insoluble materials were filtered through Celite® and the filtrate was concentrated in vacuo. The residue was purified by silica-gel preparative thin layer chromatography (toluene/EtOAc = 10:1) to give **8** as a colorless syrup (55.2 mg, 89%). ESI-MS (positive) m/z = 878.3 [(M+Na)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.84 (d, $J_{NH,CH}$ = 7.81 Hz, 1H, —CON*H*—), 7.73–7.01 (m, 32H, aromatic), 6.45–6.40 (m, 2H, aromatic), 6.28 (d, $J_{CH,NH}$ = 7.81 Hz, 1H, –C*H*Ph$_2$), 5.28 (d, $J_{1,2}$ = 5.13 Hz, 1H, H-1), 5.01 and 4.82 (each d, J_{gem} = 10.74 Hz, 2H, –CH_2Ph), 4.91 and 4.63 (each d, J_{gem} = 10.99 Hz, 2H, –CH_2Ph), 4.75 and 4.64 (each d, J_{gem} = 11.48 Hz, 2H, –CH_2Ph), 4.57 (dd, $J_{6a,6b}$ = 11.72 Hz, $J_{6a,5}$ = 2.20 Hz, 1H, H-6a), 4.45 (dd, $J_{5,6b}$ = 5.62 Hz, $J_{5,4}$ = 9.52 Hz, 1H, H-5), 4.37 (dd, $J_{6b,6a}$ = 11.72 Hz, $J_{6b,5}$ = 5.62 Hz, 1H, H-6b), 3.95 (t, $J_{3,4}$ = $J_{3,2}$ = 9.52 Hz, 1H, H-3), 3.29 (dd, $J_{2,3}$ = 9.52 Hz, $J_{2,1}$ = 5.13 Hz, 1H, H-2), 3.55 (t, $J_{4,5}$ = $J_{4,3}$ = 9.52 Hz, 1H, H-4). Found: C, 74.76; H, 5.70; N, 1.73; S, 3.76. Calcd for $C_{54}H_{49}NO_7S\cdot0.7H_2O$: C, 74.73; H, 5.69; N, 1.61; S, 3.69.

4.5. Phenyl 2,3,4-tri-*O*-benzyl-6-*O*-[[2-(4-phenylbenzyl)oxycarbonyl]benzoyl]-1-thio-α-D-glucopyranoside 6

To a solution of phenyl 2,3,4-tri-*O*-benzyl-6-*O*-(2-carbonylbenzoyl)-1-thio-α-D-glucopyranoside[13] (50.0 mg, 72.4 μmol) in CH_2Cl_2 (1 mL) were added 4-biphenylmethanol (16.0 mg, 86.8 μmol), DIC (11.8 mg, 14.7 μL, 94.1 μmol) and DMAP (cat.) at room temperature under Ar atmosphere and the reaction mixture was stirred overnight. The reaction was quenched by addition of AcOH and MeOH. Insoluble materials were filtered through Celite® and the filtrate was concentrated in vacuo. The residue was purified by silica-gel preparative thin layer chromatography (toluene/EtOAc = 5:1) to give **10** as a colorless syrup (59.9 mg, 97%). ESI-MS (positive) m/z = 879.3 [(M+Na)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for α-anomer 7.75–7.63 (m, 28H, aromatic), 5.58 (d, J1,2 = 5.13 Hz, 1H, H-1), 5.32 and 5.25 (each d, J_{gem} = 12.45 Hz, 2H, –CH_2Ph), 4.99 and 4.78 (each d, J_{gem} = 10.74 Hz, 2H, –CH_2Ph), 4.88 and 4.61 (each d, J_{gem} = 10.74 Hz, 2H, –CH_2Ph), 4.73 and 4.64 (each d, J_{gem} = 11.72 Hz, 2H, –CH_2Ph), 4.50–4.43 (m, 3H, H-5, H-6a, H-6b), 3.81 (dd, $J_{3,4}$ = 9.02 Hz, $J_{3,2}$ = 9.77 Hz, 1H, H-3), 3.87 (dd, $J_{2,3}$ = 9.77 Hz, $J_{2,1}$ = 5.13 Hz, 1H, H-2), 3.54 (t, $J_{4,5}$ = $J_{4,3}$ = 9.03 Hz, 1H, H-4). Found: C, 74.95; H, 5.60; S, 3.74. Calcd for $C_{54}H_{48}O_8S\cdot0.5H_2O$: C, 74.89; H, 5.59; S, 3.71.

4.6. Methyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 9

To a mixture of phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **1** (81.7 mg, 129 μmol), methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **7** (50 mg, 108 μmol), PhIO (30.8 mg, 140 μmol) and molecular sieves 4 Å in CPME (1 mL) was added Lewis acid (64.6 μmol) at −20 °C under Ar atmosphere. The reaction was then worked up as usual. The residue was purified by silica-gel preparative thin layer chromatography (toluene/EtOAc = 5:1) to give **9** as a colorless syrup. ESI-MS (positive) m/z = 1009.5 [(M+Na)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) α-anomer 7.25–7.03 (m, 35H, aromatic), 4.90 (d, $J_{1',2'}$ = 3.66 Hz, 1H, H-1′), 4.89–4.32 (m, 14H, –CH_2Ph × 7), 4.47 (d, $J_{1,2}$ = 3.42 Hz, 1H, H-1), 3.90 (t, $J_{3',4'}$ = $J_{3',2'}$ = 9.28 Hz, 1H, H-3′), 3.88 (t, $J_{3,4}$ = $J_{3,2}$ = 9.28 Hz, 1H, H-3), 3.76–3.48 (m, 8H, H-4, H-5, H-6a, H-6b, H-4′, H-5′, H-6a′, H-6b′), 3.46 (dd, $J_{2',3'}$ = 9.28 Hz, $J_{2',1'}$ = 3.66 Hz, 1H, H-2′), 3.36 (dd, $J_{2,3}$ = 9.28 Hz, $J_{2,3}$ = 3.42 Hz, 1H, H-2), 3.27 (s, 3H, –OCH_3); β-anomer 3.24 (s, 3H, –OCH_3). Found: C, 74.86; H, 6.73. Calcd for $C_{62}H_{66}O_{11}\cdot0.5H_2O$: C, 74.81; H, 6.68.

4.7. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-D-glucopyranosyl-α-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 10

To a mixture of **2** (34.1 mg, 43.7 μmol), **7** (16.9 mg, 36.4 μmol), PhIO (10.4 mg, 47.3 μmol) and molecular sieves 4 Å in CPME (0.5 mL) was added TMSOTf (4.8 mg, 4.0 μL, 21.8 μmol) at −20 °C under Ar atmosphere. After the reaction mixture was stirred for 6 h, the reaction was worked up as usual. The residue was purified by silica-gel preparative thin layer chromatography (toluene/EtOAc = 10:1) to give **10** as a colorless syrup (19.4 mg, 53%, α:β = 100:0). ESI-MS (positive) m/z = 1157.4 [(M+Na)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.61 (dd, J = 1.47, 8.06 Hz, 2H), 7.57 (dd, J = 1.47, 8.06 Hz, 2H), 7.51–7.05 (m, 36H, aromatic), 4.93 (d, J = 3.42 Hz, 1H, H-1′), 4.90–4.46 (m, 12H, –CH_2Ph × 6), 3.92 (dd, $J_{3',4'}$ = 6.10 Hz, $J_{3',2'}$ = 9.52 Hz,

1H, H-3′), 3.88 (dd, $J_{3,4}$ = 6.10 Hz, $J_{3,2}$ = 9.52 Hz, 1H, H-3), 3.74–3.69 (m, 4H, H-6a′, H6b′, H-6a, H-6b), 3.67 (d, $J_{5,6}$ = 3.66 Hz, 1H, H-5), 3.63 (d, $J_{5',6'}$ = 5.37 Hz, 1H, H-5′), 3.59 (d, $J_{4,3}$ = 6.10 Hz, 1H, H-3), 3.55 (d, $J_{4',3'}$ = 6.10 Hz, 1H, H-4′), 3.46 (dd, $J_{2',3'}$ = 9.52 Hz, $J_{2',1'}$ = 3.42 Hz, 1H, H-2′), 3.33 (dd, $J_{2,3}$ = 9.52 Hz, $J_{2,1}$ = 3.42 Hz, 1H, H-2), 3.28 (s, 3H, –OCH_3), 0.95 (s, 9H, –C(CH_3)$_3$). Found: C, 74.21; H, 6.89. Calcd for $C_{71}H_{78}O_{11}Si_1{\cdot}0.8H_2O$: C, 74.22; H, 6.84.

4.8. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-[2-(methoxycarbonyl)benzoyl]-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 11

To a mixture of **3** (20.0 mg, 28.4 μmol), **7** (11.0 mg, 23.6 μmol), PhIO (6.8 mg, 30.7 μmol) and molecular sieves 4 Å in CPME (0.5 mL) was added TMSOTf (3.1 mg, 2.6 μL, 14.2 μmol) at −20 °C under Ar atmosphere. After the reaction mixture was stirred for 5 h, the reaction was worked up as usual. The residue was purified by silica-gel preparative thin layer chromatography (toluene/EtOAc = 10:1) to give **11** as a colorless syrup (7 mg, 85%, α:β = 90:10). ESI-MS (positive) *m*/*z* = 1081.4 [(M+Na)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for α-anomer 7.60–7.08 (m, 34H, aromatic), 4.89 (d, $J_{1',2'}$ = 4.88 Hz, 1H, H-1′), 4.87–4.50 (m, 12H, –CH_2Ph × 6), 4.47 (d, $J_{1,2}$ = 3.42 Hz, 1H, H-1), 4.42–4.33 (m, 3H, H-5′, H-6a′, H-6b′), 3.94–3.87 (m, 3H, H-3, H-3′, H-4′), 3.73 (s, 3H, –OCH_3), 3.79–3.51 (m, 4H, H-4, H-5, H-6a, H-6b), 3.43 (dd, $J_{2',3'}$ = 9.52 Hz, $J_{2',1'}$ = 3.42 Hz, 1H, H-2′), 3.32 (dd, $J_{2,3}$ = 9.52 Hz, $J_{2,1}$ = 3.42 Hz, 1H, H-2), 3.27 (s, 3H, –OCH_3). β-anomer 3.24 (s, 3H, –OCH_3).

4.9. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-[[2-(4-*tert*-butylbenzyl)oxycarbonyl]benzoyl]-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 12

To a mixture of **4** (216 mg, 258 μmol), **7** (100 mg, 215 μmol), PhIO (61.6 mg, 280 μmol) and molecular sieves 4 Å in CPME (2 mL) was added TMSOTf (28.7 mg, 23.3 μL, 129 μmol) at −20 °C under Ar atmosphere. After the reaction mixture was stirred for 45 min, the reaction was worked up as usual. The residue was purified by silica-gel flash chromatography (toluene/EtOAc = 5:1) to give **12** as a colorless syrup (203 mg, 79%, α:β = 97:3). ESI-MS (positive) *m*/*z* = 1214.4 [(M+Na)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) α anomer 7.70–7.13 (m, 38H, aromatic), 5.27 and 5.21 (each d, J_{gem} = 11.96 Hz, 2H, –CH_2Ph), 4.96 (d, $J_{1',2'}$=3.17 Hz, 1H, H-1′), 4.92 and 4.81 (each d, J_{gem} = 10.25 Hz, 2H, –CH_2Ph), 4.92 and 4.78 (each d, J_{gem} = 10.50 Hz, 2H, –CH_2Ph), 4.87 and 4.66 (each d, J_{gem} = 11.96 Hz, 2H, –CH_2Ph), 4.87 and 4.60 (each d, J_{gem} = 11.23 Hz, 2H, –CH_2Ph), 4.67 and 4.55 (each d, J_{gem} = 11.96 Hz, 2H, –CH_2Ph), 4.65 (d, J_{gem} = 11.21 Hz, 2H, –CH_2Ph × 2), 4.53 (d, $J_{1,2}$ = 3.42 Hz, 1H, H-1), 4.46–4.36 (m, 2H, H-6a′, H-6b′), 4.39 (dd, $J_{5',6a'}$ = 11.78 Hz, $J_{5',4'}$ = 9.28 Hz, 1H, H-5′), 4.02–3.94 (m, 3H, H-3, H-3′, H-4′), 3.82–3.69 (m, 3H, H-5, H-6a, H-6b), 3.61 (t, $J_{4,5}$ = $J_{4,3}$ = 9.28 Hz, 1H, H-4), 3.53 (dd, $J_{2',3'}$ = 6.59 Hz, $J_{2',1'}$ = 3.42 Hz, 1H, H-2′), 3.29 (dd, $J_{2,3}$ = 9.52 Hz, $J_{2,1}$ = 3.42 Hz, 1H, H-2), 3.34 (s, 3H, –OCH_3), 1.29 (s, 9H, –C(CH_3)$_3$). β-anomer 3.31 (s, 3H, –OCH_3). Found: C, 72.93; H, 6.64. Calcd for $C_{74}H_{78}O_{14}{\cdot}1.5H_2O$: C, 72.94; H, 6.46.

4.10. Methyl 2,3,4-*O*-tri-benzyl-6-*O*-[2-(diphenylmethylaminocarbonyl)benzoyl]-D-glucopyranosyl-α-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 13

To a suspension of **5** (30.0 mg, 35.0 μmol), **7** (13.6 mg, 29.2 μmol), PhIO (8.3 mg, 38.0 μmol) and molecular sieves 4 Å in CPME (0.3 mL) was added TMSOTf (3.9 mg, 3.2 μL, 17.5 μmol) at −20 °C under Ar atmosphere. After the reaction mixture was stirred for 1.5 h, the reaction was worked up as usual. The residue was purified by silica-gel preparative thin layer chromatography (toluene/EtOAc = 5:1) to give **13** as a colorless syrup (7.8 mg, 53%, α:β = 100:0). ESI-MS (positive) *m*/*z* = 1232.6 [(M+Na)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.82 (d, $J_{NH,CH}$ = 7.57 Hz, 1H, –CON*H*–), 7.78–7.12 (m, 42H, aromatic), 6.46–6.44 (m, 2H, aromatic), 6.41 (d, $J_{CH,NH}$ = 7.57 Hz, 1H, –C*H*Ph$_2$), 4.97 and 4.75 (each d, J_{gem} = 11.23 Hz, 2H, –CH_2Ph), 4.94 (d, $J_{1',2'}$ = 3.66 Hz, 1H, H-1′), 4.90 and 4.62 (each d, J_{gem} = 10.99 Hz, 2H, –CH_2Ph), 4.84 and 4.58 (each d, J_{gem} = 10.99 Hz, 2H, –CH_2Ph), 4.76 and 4.71 (each d, J_{gem} = 11.72 Hz, 2H, –CH_2Ph), 4.68 and 4.43 (each d, J_{gem} = 12.21 Hz, 2H, –CH_2Ph), 4.65 and 4.47 (each d, J_{gem} = 11.96 Hz, 2H, –CH_2Ph), 4.54 (d, $J_{1,2}$ = 3.66 Hz, 1H, H-1), 4.52–4.40 (m, 3H, H-5′, H-6a′, H-6b′), 4.03–3.90 (m, 3H, H-3, H-3′, H-4′), 3.81–3.75 (m, 2H, H-5, H-6a), 3.71–3.56 (m, 2H, H-4, H-6b), 3.52 (dd, $J_{2',3'}$ = 9.52 Hz, $J_{2',1'}$ = 3.66 Hz, 1H, H-2′), 3.40 (dd, $J_{2,3}$ = 9.52 Hz, $J_{2,1}$ = 3.66 Hz, 1H, H-2), 3.34 (s, 3H, –OCH_3). Found: C, 72.41; H, 6.26; N, 1.12. Calcd for $C_{76}H_{75}NO_{13}{\cdot}2.8H_2O$: C, 72.45; H, 6.00; N, 1.11.

4.11. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-[[2-(4-phenylbenzyl)oxycarbonyl]benzoyl]-D-glucopyranosyl-α-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 14

To a suspension of **6** (221 mg, 258 μmol), **7** (100 mg, 215 μmol), PhIO (61.6 mg, 280 μmol) and molecular sieves 4 Å in CPME (2 mL) was added TMSOTf (28.7 mg, 23.3 μL, 129 μmol) at −20 °C under Ar atmosphere. After the reaction mixture was stirred for 45 min, the reaction was worked up as usual. The residue was purified by silica-gel flash chromatography (toluene/EtOAc = 5:1) to give **14** as a colorless syrup (216 mg, 83%, α:β = 100:0). $[\alpha]_D^{25}$ = +0.3 (*c* 1.37, $CHCl_3$); ESI-MS (positive) *m*/*z* = 1232.4 [(M+Na)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.72–7.15 (m, 43H, aromatic), 5.33 and 5.28 (each d, J_{gem} = 12.45 Hz, 2H, –CH_2Ph), 4.95 (d, $J_{1',2'}$ = 3.42 Hz, 1H, H-1′), 4.94 and 4.79 (each d, J_{gem} = 10.74 Hz, 2H, –CH_2Ph), 4.94 and 4.77 (each d, J_{gem} = 10.74 Hz, 2H, –CH_2Ph), 4.89 and 4.65 (each d, J_{gem} = 11.96 Hz, 2H, –CH_2Ph), 4.84 and 4.57 (each d, J_{gem} = 10.50 Hz, 2H, –CH_2Ph), 4.67 and 4.53 (each d, J_{gem} = 12.21 Hz, 2H, –CH_2Ph), 4.64 (d, J_{gem} = 11.96 Hz, 2H, –CH_2Ph × 2), 4.53 (d, $J_{1,2}$ = 3.66 Hz, 1H, H-1), 4.46–4.41 (m, 2H, H-6a′, H-6b′), 4.39 (dd, $J_{5',6a'}$ = 11.96 Hz, $J_{5',4'}$ = 9.76 Hz,

1H, H-5′), 4.01–3.94 (m, 3H, H-3, H-3′, H-4′), 3.81–3.69 (m, 3H, H-5, H-6a, H-6b), 3.60 (t, $J_{4,5} = J_{4,3} = 9.28$ Hz, 1H, H-4), 3.52 (dd, $J_{2',3'} = 9.03$ Hz, $J_{2',1'} = 3.42$ Hz, 1H, H-2′), 3.38 (dd, $J_{2,3} = 9.52$ Hz, $J_{2,1} = 3.66$ Hz, 1H, H-2), 3.33 (s, 3H, –OCH_3). Found: C, 73.61; H, 6.12. Calcd for $C_{76}H_{74}O_{14}\cdot 1.6H_2O$: C, 73.66; H, 6.18.

4.12. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-[[2-(4-phenylbenzyl)oxycarbonyl]benzoyl]-D-glucopyranosyl-α-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside 15

To a suspension of **6** (369 mg, 431 μmol), methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **8** (100 mg, 215 μmol), PhIO (109 mg, 495 μmol) and molecular sieves 4 Å in CPME (2 mL) was added TMSOTf (47.9 mg, 38.9 μL, 215 μmol) at −20 °C under Ar atmosphere. After the reaction mixture was stirred for 6 h, the reaction was worked up as usual. The residue was purified by silica-gel flash chromatography (toluene/EtOAc = 13:1) to give **6** as a colorless syrup (150 mg, 75%, α:β = 100:0). $[\alpha]_D^{25} = +0.5$ (*c* 1.81 $CHCl_3$); ESI-MS (positive) *m/z* = 1233.5 [$(M+Na)^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.71–7.11 (m, 43H, aromatic), 5.55 (d, $J_{1',2'} = 3.66$ Hz, 1H, H-1′), 5.26 and 5.22 (each d, $J_{gem} = 12.21$ Hz, 2H, –CH_2Ph), 4.95 and 4.77 (each d, $J_{gem} = 11.72$ Hz, 2H, –CH_2Ph) 4.84 and 4.71 (each d, $J_{gem} = 10.74$ Hz, 2H, –CH_2Ph), 4.80 and 4.54 (each d, $J_{gem} = 10.99$ Hz, 2H, –CH_2Ph), 4.63 and 4.51 (each d, $J_{gem} = 11.96$ Hz, 2H, –CH_2Ph), 4.56 (d, $J_{gem} = 11.96$ Hz, 4H, –CH_2Ph × 2), 4.55 (d, $J_{1,2} = 3.66$ Hz, 1H, H-1), 4.44 and 4.38 (each d, $J_{gem} = 11.96$ Hz, 2H, –CH_2Ph), 4.29 (d, $J_{6a',5'} = J_{6b',5'} = 2.93$ Hz, 2H, H-6a′, H-6b′), 4.02 (t, $J_{3,4} = J_{3,2} = 9.28$ Hz, 1H, H-3), 3.95 (t, $J_{4,5} = J_{4,3} = 9.28$ Hz, 1H, H-4), 3.90 (t, $J_{3',4'} = J_{3',2'} = 9.28$ Hz, 1H, H-3′), 3.89 (td, $J_{5',6a'} = J_{5',6b'} = 2.93$ Hz, $J_{5',4'} = 9.28$ Hz, 1H, H-5′), 3.79–3.73 (m, 3H, H-5, H-6a, H-6b), 3.52 (dd, $J_{2,3} = 9.28$ Hz, $J_{2,1} = 3.66$ Hz, 1H, H-2), 3.45 (t, $J_{4',5'} = J_{4',3'} = 9.28$ Hz, 1H, H-4′), 3.37 (dd, $J_{2',3'} = 9.28$ Hz, $J_{2',1'} = 3.66$ Hz, 1H, H-2′), 3.33 (s, 3H, –OCH_3). Found: C, 74.60; H, 6.16. Calcd for $C_{76}H_{74}O_{14}\cdot 0.7H_2O$: C, 74.60; H, 6.10.

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