A Facile and Quantitative Preparation of Activated Cyclic Sugar Derivatives Using $HgBr_2$ and 2,4,6-Collidine

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A combination of mercury(II) bromide ($HgBr_2$) and 2,4,6-collidine was found to promote the formation of activated cyclic sugar derivatives such as 1,2-orthoesters and an oxazoline derivative in quantitative yields at room temperature. A slightly hindered skew like conformation of the lactose orthoester derivative was revealed by ^1H NMR analysis. It was also suggested that the reaction of a lactose 1,2-orthoester with trimethylsilyl azide proceeded smoothly to give β-lactosyl azide stereoselectively which is a useful intermediate for constructing glycopeptides and neoglycoconjugates.

Reactive intermediates of aldoses are required in the chemical syntheses of a variety of *O*-, *N*-, *S*-, and *C*-glycosides. 1,2-Orthoesters of aldoses have been useful not only for syntheses of simple 1,2-*trans*-glycoside[1—3] but for temporary protection of 1,2-dihydroxyl groups.[4] These orthoesters have been prepared in moderate yields from acetohalo sugars using promoters such as Et_4NBr–2,4,6-collidine,[5] *N*,*N*-dimethylformamide dialkylacetals–silver triflate,[6] silver triflate–2,4,6-collidine,[7] trialkylstannyl methoxide–Et_4NBr,[8] and silver nitrate–2,4,6-collidine,[9] the procedures employed sometimes cause difficulties in handling, purification processes and require expensive reagents. Therefore, a simpler and more efficient procedure might be expected to achieve easier-handling, higher-yields, versatility, and lower costs of the reactions. In this paper we introduce a convenient and versatile method for the preparation of reactive cyclic aldoses such as orthoesters and oxazoline derivatives from acetohalo sugar using an economical and efficient catalyzing system of $HgBr_2$ and 2,4-collidine.

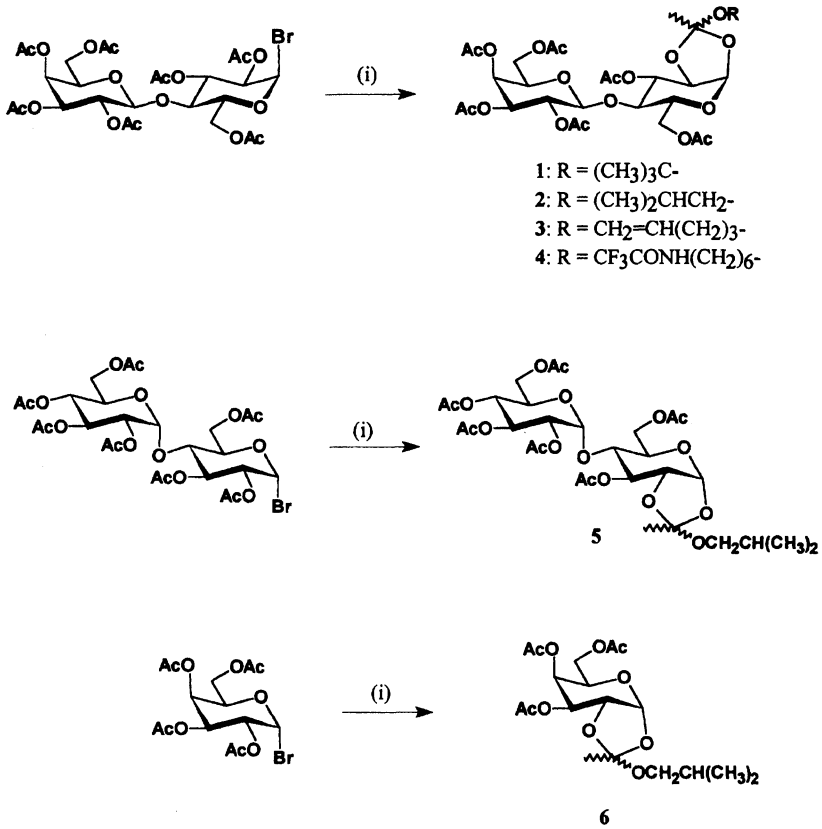
Results and Discussion

Synthesis of 1,2-Orthoesters. Orthoesters and oxazoline derivatives have been known as major by-product or intermediates of glycosidation reactions from acetohalo sugars and other highly labile compounds.[10] These activated cyclic aldoses are, however, effective and economical reagents for production of simple glycosides for the preparation of neoglycoconjugates.[11]

In the course of our synthetic studies on neoglycoconjugates, we have previously reported the preparation of a number of *N*-protected 6-aminohexyl glycosides by the reaction of acetohalo sugars with alcohols using mercury(II) cyanide [$Hg(CN)_2$] as catalyst.[12,13] As is observed in common Königs–Knorr type glycosidation reactions, we had also observed copious formation of 1,2-orthoesters. It is generally accepted that acetoxonium cation is presumably formed initially, and the alcoholic oxygen atom either attacks the anomeric carbon under slightly acidic condition or the methyl linked carbon of the acetoxonium cation under weakly basic conditions such as pyridine[4] and 2,4,6-collidine.[5] Therefore, when the alcoholic oxygen attacks the carbon in the presence of a mild base, 1,2-orthoester can be formed as the main product.

Our interest, therefore, was directed toward a simple combination of mercury(II) salts and weak bases to achieve high yield formation of orthoesters. A combination of $HgBr_2$ and 2,4,6-collidine turned out to be the most convenient reagent for the preparation of orthoesters and oxazolines as shown in Scheme 1. It required only an equivalent amount of $HgBr_2$ and an excess of 2,4,6-collidine to promote efficient formation of a variety of orthoesters. Table 1 shows versatility of this procedure for the almost quantitative preparation of lactose, maltose, and galactose 1,2-orthoesters.

Synthesis of an Oxazoline Derivative by $HgBr_2$–2,4,6-Collidine. It was also observed that 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[14] was effectively converted to the oxazoline derivative under the same condition employed for the preparation of orthoesters. The mechanism for this reaction can be understood as follows: First, bromide ion from $HgBr_2$ induces in situ anomerization of glycosyl chloride (perhaps forming a β-bromide), and then cyclization proceeds smoothly to afford an oxazoline derivative (Scheme 2). Although similar methods based on the same mechanism have been used for the preparation of oxazoline derivatives,[15,16] the present method



Scheme 1. Reagents and conditions. (i) R-OH, powdered MS 4 Å, $HgBr_2$, and 2,4,6-collidine in 1 : 1 : 1 (v/v/v) of benzene–nitoromethane–chloroform at ambient temperature.

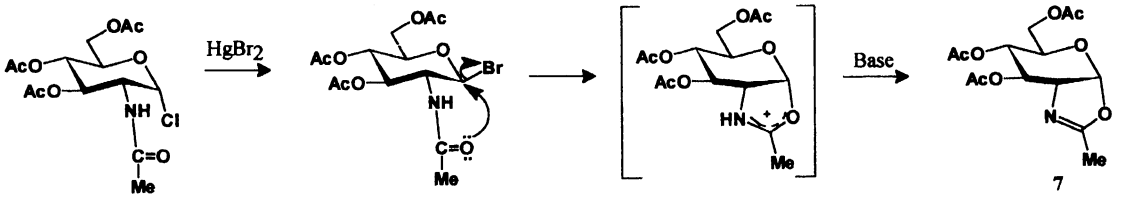
Table 1. Orthoester Formation from Acetobromo Sugars with Alcohols

Products	Acetobromo sugar[a] molar amount	$HgBr_2$ molar amount	Collidine molar amount	Yields %
1	1.5	1.0	3	ca. 30[b]
1	1.5	1.0	30	ca. 30[b]
2	1.5	1.0	3	99
2	1.5	1.0	10	q.y.
2	1.5	1.0	30	q.y.
3	1.5	1.0	30	q.y.
4	1.5	1.0	3	q.y.
4	1.5	1.5	3	q.y.
4	1.1	1.0	3	93
5	1.7[c]	1.0	3	q.y.
6	1.5	1.0	3	99

a) Molar ratio against alcohols used. b) By TLC. c) The bromide was not pure by TLC.

is more practical and is higher yields.

Conformation of a 1,2-Orthoester of a Disaccharide. Conformation of 1,2-orthoesters derived from monosaccharides was discussed in detail by Lemieux et al.[5] They have concluded that general monosaccharide orthoesters have slightly distorted pyranose ring and cyclic orthoester formation seems to have no significant effect on the conformation of the pyranose ring itself. Since there is little information on the conformation of disaccharidic 1,2-orthoesters, we analyzed the conformation of C-4 substituted orthoester derivatives compared with those of monosaccharide orthoester. ^1H NMR data of the 1,2-orthoesters prepared in this work are listed in Tables 2 and 3. Although it is evident in view of the magnitudes of coupling constants that disaccharide 1,2-orthoesters show distorted pyranose ring similar to some of well known monosaccharide 1,2-orthoesters, specific long-range coupling between H-2 and H-4 were also observed in the cases for lactose and maltose 1,2-orthoesters. From the vicinal coupling-constants in addition to the long-range coupling data between H-2 and H-4 of compound **2**,



Scheme 2. A proposed mechanism of the formation of oxazoline derivative **7**.

Table 2. ^{1}H NMR Data for Synthesized Compounds[a)]

Hydr. atm.	Chemical shifts (δ) and multiplicity				
	2	**3**	**4**	**5**	**6**
H-1	5.65, d	5.65, d	5.65, d	5.71, d	5.81, d
H-2	4.31, ddd	4.31, ddd	4.29, ddd	4.34, ddd	4.31, dd
H-3	5.54, dd	5.54, dd	5.52, dd	5.05, dd	5.06, dd
H-4	3.65, d	3.65, dd	3.66, d	3.64, d	5.43, dd
H-5	3.87, ddd	3.86, ddd,	3.85, ddd	3.90, ddd	4.3[b)]
H-6a	4.1[b)]	4.1[b)]	4.1[b)]	4.21, dd	4.17, dd
H-6b	4.25, dd	4.25, dd	4.26, dd	4.31, dd	4.12, dd
H-1′	4.63, d	4.62, d	4.61, d	5.53, d	
H-2′	5.19, dd	5.19, dd	5.19, dd	4.87, dd	
H-3′	5.01, dd	5.01, dd	5.00, dd	5.06, t	
H-4′	5.38, dd	5.38, dd	5.38, dd	5.41, t	
H-5′	3.95, dt	3.95, dt	3.94, dt	4.04, ddd	
H-6′a	4.1[b)]	4.1[b)]	4.1[b)]	4.08, dd	
H-6′b	4.1[b)]	4.1[b)]	4.1[b)]	4.25, dd	

a) ^{1}H NMR data were measured in $CDCl_3$ with tetramethylsilane as an internal standard at 20 °C. b) Overlapped and could not be determined.

Table 3. ^{1}H–^{1}H Coupling Constants for Synthesized Compounds[a)]

Coupled protons	J-values (Hz)				
	2	**3**	**4**	**5**	**6**
$J_{1,2}$	5.1	5.1	5.1	5.3	4.8
$J_{2,3}$	2.7	2.7	2.6	2.8	6.8
$J_{2,4}$	0.9	1.1	1.0	1.3	ND
$J_{3,4}$	1.5	1.3	1.3	0.6	3.4
$J_{4,5}$	9.6	9.7	9.6	8.8	2.5
$J_{5,6a}$	5.4	5.4	5.4	5.8	6.6
$J_{5,6b}$	2.3	2.3	2.2	2.2	6.6
$J_{6a,6b}$	12.0	12.0	12.1	12.2	11.4
$J_{1',2'}$	7.9	7.9	7.9	4.0	
$J_{2',3'}$	10.4	10.4	10.4	10.3	
$J_{3',4'}$	3.5	3.5	3.5	9.5	
$J_{4',5'}$	0.9	1.0	1.0	10.1	
$J_{5',6'a}$	6.6	6.6	6.8	2.2	
$J_{5',6'b}$	6.6	6.6	6.8	4.4	
$J_{6'a,6'b}$	b	b	b	12.7	

a) Condition was described in Table 2. b) Overlapped and could not be determined.

all proton dihedral angles were estimated by employing the modified Karplus equation[17)] and a proposed conformation is shown as an inset of Fig. 1. In comparison with the monosaccharide 1,2-orthoester which exhibits a slightly distorted pyranose ring, disaccharide 1,2-orthoesters seem to have further hindered skew-like conformation. This data suggests that the bulky substituents at C-4 position of the reducing glucose residue greatly influence the conformation of the orthoester-bearing sugar moiety as indicated in the case for oxazoline derivatives.[18,19)]

Synthesis of Lactosyl Azide from an Lactose 1,2-Orthoester. As a novel example of the availability of disaccharide orthoesters, we found a facile procedure for the preparation of β-lactosyl azide from lactose 1,2-(*i*-butyl orthoacetate). The reaction of lactose orthoester (**2**) with trimethylsilyl azide (TMS-N_3) proceeded in the presence of the catalytic amount of tin(IV) chloride ($SnCl_4$) as a promoter and gave the expected β-lactosyl azide **8** in 86% yield (Scheme 3). It is to be noted that this reaction is regarded as an excellent and widely applicable method for the preparation of glycosyl azides, because the conventional ways using acetohalo sugars and silver azide included some difficulties such as dangerous handling and lower yields.[20)] This compound will be a valuable intermediate for constructing glycopeptides and related neoglycoconjugates.

In conclusion, we found an efficient method for the preparation of aldose 1,2-orthoester and oxazoline derivatives using an inexpensive $HgBr_2$–2,4,6-collidine system.

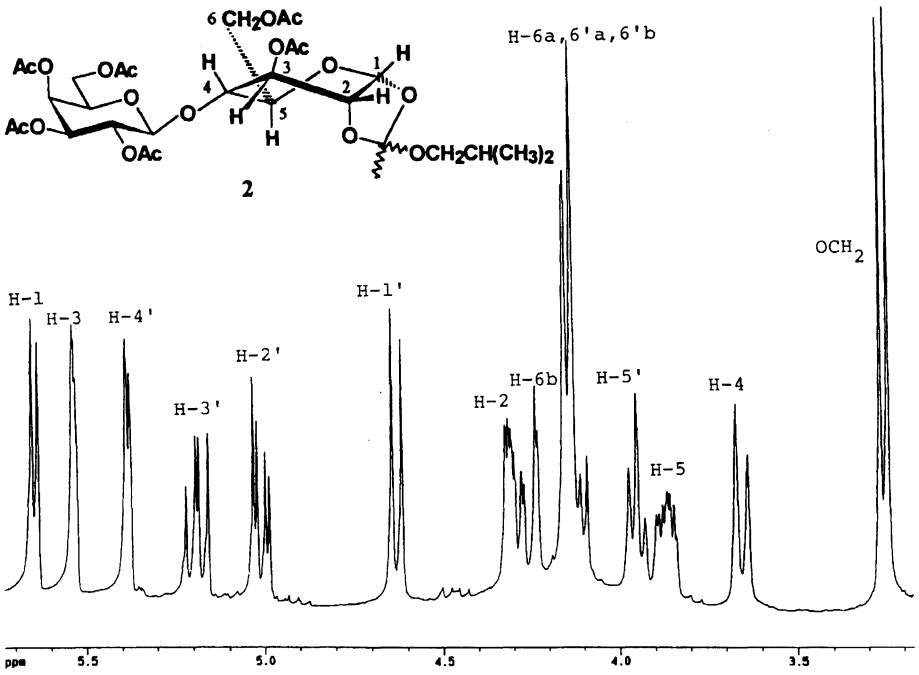
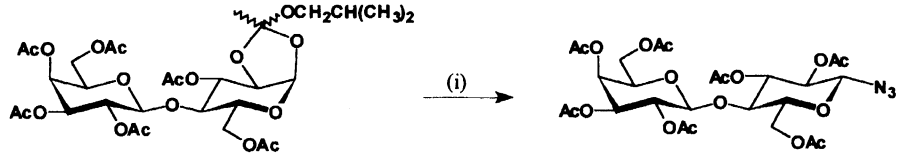


Fig. 1. ^{1}H NMR spectrum of compound **2**.



Scheme 3. Reagents and conditions. (i) TMS-N_3 and $SnCl_4$, in 1,2-dichloroethane at ambient temperature.

Experimental

Materials and Methods. Unless otherwise stated, all commercially available solvents and reagents were used without further purification. Benzene, chloroform ($CHCl_3$), 1,2-dichloroethane, nitoromethane, methanol (MeOH) were stored over molecular sieves 3 Å (MS 3 Å) before use. Powdered molecular sieves 4 Å (MS 4 Å) was dried over in vacuo at ca. 100 °C for overnight immediately before use. ^{1}H NMR spectra were recorded at 300 MHz with a Bruker AMX-300 spectrometer in chloroform-*d* using tetramethylsilane (TMS) as internal standard. Ring-proton assignments in NMR were made by first-order analysis of the spectra, and were supported by homonuclear decoupling experiments. Reactions were monitored by thin-layer chromatography (TLC) on a precoated plate of silica gel 60 F_{254} (layer thickness, 0.25 mm; E. Merck, Darmmstadt, Germany). The solvent systems used were (A) 2 : 1, (B) 1 : 1 (C) 1 : 2 (v/v) toluene–ethyl acetate, and (D) 65 : 25 : 4 (v/v/v) chloroform–methanol–water. For detection of the sugar components, TLC sheets were sprayed with (a) a solution of 85 : 10 : 5 (v/v/v) methanol–concd sulfuric acid–*p*-anisaldehyde, and heated for a few minutes (for carbohydrate) or with (b) an aqueous solution of 5 wt% potassium permanganate and heated similarly (for detection of double bond). Column chromatography was performed on silica gel (Silica Gel 60; 0.015—0.040 mm, E. Merck) or Sephadex LH-20 (Pharmacia Fine Chemicals). All evaporations were performed at below 45 °C under diminished pressure.

3,6-Di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-glucopyranose 1,2-[6-(Trifluoroacetamido)-1-hexyl orthoacetate] (4). A mixture of powdered MS 4 Å (5 g), mercury(II) bromide ($HgBr_2$) (1.91 g, 5.2 mmol), 2,4,6-collidine (2.0 mL, 15 mmol), and 6-(trifluoroacetamido)-1-hexanol (1.07 g, 5.0 mmol) in 1 : 1 (v/v) of benzene–nitromethane (20 mL) was stirred for 20 min at room temperature. A solution of 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-D-glucopyranosyl bromide[21] (5.25 g, 7.5 mmol) in 10 mL of dry chloroform was added dropwisely to the mixture. The reaction mixture was continuously stirred for 22 h at room temperature. The mixture was filtered and the filtrate was evaporated. The residue was diluted with chloroform, and the chloroform solution was successively washed with 0.5 M aq sulfuric acid (1 M=1 mol dm^{-3}), saturated sodium hydrogencarbonate, and 1.5 M sodium chloride, then dried over anhydrous sodium sulfate, filtered, and evaporated. The syrupy residue was purified by passing through Sephadex LH-20 column (5 cm×200 cm) with 95% ethanol as eluent. The fractions containing the title compound (by TLC and phenol–sulfuric acid assay) was combined and concentrated. The syrup was subsequently chromatographed on silica gel

eluting first 3:1 then 1:1 (v/v) of toluene–ethyl acetate. The yield of **4** was 4.25 g (q.y.) as a clear syrup: R_F 0.47 (solvent C), ^{1}H NMR ($CDCl_3$) δ=1.37 (m, 4H, $2CH_2$), 1.58 (m, 4H, $2CH_2$), 1.72 (s, 3H, CH_3), 1.98, 2.04, 2.07, 2.12, 2.13, 2.17 (each s, 18H, $6COCH_3$), 3.36 (dd, 2H, J=6.8 Hz, $NHCH_2$), 3.48 (t, 2H, J=6.4 Hz, OCH_2), 6.64 (brs, 1H, NH), and the data of the ring protons are given in Tables 2 and 3.

3,6-Di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-glucopyranose 1,2-(*i*-Butyl orthoacetate) (2). 2,3,6-Tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-D-glucopyranosyl bromide (1.05 g, 1.50 mmol) was allowed to react with *i*-butyl alcohol (92.3 mL, 1.0 mmol) in the same manner as described above for the preparation of **4**. The compound **2** had R_F 0.49 (solvent B), ^{1}H NMR ($CDCl_3$) δ=0.90 (d, 6H, J=6.7 Hz, $2CH_3$), 1.72 (s, 3H, CH_3), 1.78 (m, 1H, CH), 1.98, 2.04, 2.07, 2.12, 2.13, 2.17 (each s, 18H, $6COCH_3$), 3.26 (d, 2H, J=6.6 Hz, OCH_2), and the data of the ring protons are given in Tables 2 and 3.

3,6-Di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-glucopyranose 1,2-(4-Pentenyl orthoacetate) (3). A title compound was prepared from 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-D-glucopyranosyl bromide (1.05 g, 1.50 mmol) with 4-pentenyl alcohol (0.104 mL, 1.0 mmol) using the same condition as described for **4**. The compound **3** had R_F 0.50 (solvent B), 0.66 (solvent C), ^{1}H NMR ($CDCl_3$) δ=1.72 (s, 3H, CH_3), 1.81 (m, 2H, OCH_2CH_2), 1.98, 2.04, 2.07, 2.12, 2.12, 2.17 (each s, 18H, $6COCH_3$), 2.15 (m, 2H, CH_2CH=), 3.49 (t, 2H, J=6.5 Hz, OCH_2), 5.00 (m, 2H, CH=CH_2), 5.80 (m, 1H, CH=CH_2), and the data of the ring protons are given in Tables 2 and 3.

3,6-Di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-α-D-glucopyranose 1,2-(*i*-Butyl orthoacetate) (5). The title compound was prepared from crude 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-D-glucopyranosyl bromide[21] (2.01 g, 2.87 mmol) with *i*-butyl alcohol (0.156 mL, 1.69 mmol) using the same condition as described for **4**. The compound **5** had R_F 0.52 (solvent B), ^{1}H NMR ($CDCl_3$) δ=0.90 (dd, 6H, J=6.7 Hz, $2CH_3$), 1.73 (s, 3H, CH_3), 1.80 (m, 1H, OCH_2CH), 2.03, 2.04, 2.09, 2.10, 2.11, 2.13 (each s, 18H, $6COCH_3$), 3.23 (m, 2H, OCH_2), and the data of the ring protons are given in Tables 2 and 3.

3,4,6-Tri-*O*-acetyl-α-D-galactopyranose 1,2-(*i*-Butyl orthoacetate) (6). A title compound was prepared from 2,3,4,6-tetra-*O*-acetyl-D-galactopyranosyl bromide[21] (0.62 g, 1.5 mmol) with *i*-butyl alcohol (92.3 mL, 1.0 mmol) by the same manner for the preparation of **4**. The compound **6** had R_F 0.60 (solvent A), ^{1}H NMR ($CDCl_3$) δ=0.90 (dd, 6H, J=6.7 Hz, $2CH_3$), 1.59 (s, 3H, CH_3), 1.82 (m, 1H, OCH_2CH), 2.07, 2.07, 2.12 (each s, 9H, $3COCH_3$), 3.27 (dd, 2H, J=6.7 and <1 Hz, OCH_2), and the data of the ring protons are given in Tables 2 and 3.

2-Methyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-*d*]-2-oxazoline (7).[18] A mixture of powdered MS 4 Å (1 g), $HgBr_2$ (1.02 g, 2.84 mmol), and 2,4,6-collidine (1.09 mL, 8.20 mmol) in 1:1 (v/v) of benzene–nitromethane (4 mL) was stirred for 40 min at room temperature. To this solution was slowly added a solution of crude 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[14] (1.00 g, 2.73 mmol) in 2 mL of dry chloroform, then the mixture was continuously stirred for 3 h at 50 °C. The reaction mixture was evaporated in vacuo, diluted with chloroform, and filtered. The filtrate was washed with saturated sodium hydrogencarbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residual syrup was subjected to chromatography on a column of silica gel with 100:200:1 (v/v/v) of toluene–ethyl acetate–triethylamine as the eluent to give pure oxazoline derivative **7** (0.76 g, 84.4%); R_F 0.60 (solvent A), ^{1}H NMR ($CDCl_3$) δ=2.09, 2.16, 2.12 (each s, 9H, $3COCH_3$), 2.10 (s, 3H, CH_3–oxazoline), 3.61 (dt, 1H, $J_{5,6}$=4.5 Hz, H-5), 4.14 (m, 1H, H-2), 4.18 (d, 2H, H-6a and -6b), 4.93 (dt, 1H, $J_{2,4}\approx$1 Hz, $J_{4,5}$=9.3 Hz, H-4), 5.27 (t, 1H, $J_{3,4}$=2.4 Hz, H-3), and 5.98 (d, 1H, $J_{1,2}$=7.4 Hz, H-1) [lit, ^{1}H NMR ($CDCl_3$) δ=2.09 (d, 3H, CH_3–oxazoline), 3.61 (dt, 1H, $J_{5,6}$=4.0 Hz, H-5), 4.14 (m, 1H, $J_{2,3}$=2.6 Hz, H-2), 4.18 (d, 2H, H-6a and -6b), 4.94 (dq, 1H, $J_{2,4}$=1.5 Hz, $J_{4,5}$=9.2 Hz, H-4), 5.27 (dd, 1H, $J_{3,4}$=2.2 Hz, H-3), and 5.97 (d, 1H, $J_{1,2}$=7.3 Hz, H-1)].[18]

2,3,6-Tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranosyl Azide (8).[22] A solution of an orthoester **2** (0.67 g, 0.97 mmol) in dry 1,2-dichloroethane (6 mL) was treated with trimethylsilyl azide (TMS-N_3) (428 μL, 2.90 mmol) and 1.0 M tin(IV) chloride in dichloromethane (97 μL, 97 μmol) as a promoter for 11 h at room temperature. The reaction mixture was poured into a cold saturated sodium hydrogencarbonate solution, extracted by chloroform, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resulting syrup was purified with a column of silica gel using 2:1 (v/v) of toluene–ethyl acetate as eluent, to give clear syrup of **8** (0.55 g, 85.9%); R_F 0.54 (solvent C), ν_{max} 2121 (N_3), 1755 (C=O), 1370, 1220, 1062 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.96—2.15 (each s, 21H, $7COCH_3$), 3.70 (ddd, 1H, $J_{5,6a}$= 5.0 Hz and $J_{5,6b}$=2.0 Hz, H-5), 3.82 (t, 1H, $J_{4,5}$=9.9 Hz, H-4), 3.88 (t, 1H, $J_{5',6'a}$=7.1 Hz $J_{5',6'b}$=6.6 Hz, H-5′), 4.08 (dd, 1H, $J_{6'a,6'b}$=11.1 Hz, H-6′a), 4.12 (dd, 1H, H-6a), 4.13 (dd, 1H, H-6′b), 4.49 (d, 1H, $J_{1',2'}$=7.8 Hz, H-1′), 4.51 (dd, 1H, $J_{6a,6b}$=12.1 Hz, H-6b), 4.63 (d, 1H, $J_{1,2}$=8.8 Hz, H-1), 4.86 (dd, 1H, $J_{2,3}$=9.5 Hz H-2), 4.96 (dd, 1H, $J_{3',4'}$=3.4 Hz, H-3′), 5.10 (dd, 1H, $J_{2',3'}$=10.4 Hz, H-2′), 5.21 (t, 1H, $J_{3,4}$=9.0 Hz, H-3), 5.35 (dd, 1H, $J_{4',5'}$=1.0 Hz, H-4′) [lit, ^{1}H NMR ($CDCl_3$) δ=3.75 ($J_{5,6b}$=1.5 Hz, H-5), 3.78 (H-6′a), 3.86 ($J_{4,5}\approx$9 Hz, H-4), 3.98 (H-5′), 4.15 (H-6′b), 4.58 ($J_{1',2'}$=7.5 Hz, H-1′), 4.52 (H-6b), 4.72 ($J_{1,2}$=8.5 Hz, H-1), 4.85 ($J_{2,3}\approx$9 Hz H-2), ca. 5.0 ($J_{3',4'}\approx$3 Hz, H-3′), 5.07 (H-2′), 5.22 ($J_{3,4}\approx$9 Hz, H-3), 5.34 ($J_{4',5'}\approx$0.5 Hz, H-4′].[22]

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