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Regio- and stereoselective anomeric esterification of glucopyranose 1,2-diols and a facile preparation of 2-O-acetylated glucopyranosyl trichloroacetimidates from the corresponding 1,2-diols

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Abstract—A highly regio- and stereoselective anomeric esterification of 3-*O*-allyl (or benzyl, or benzoyl)-4,6-*O*-isopropylidene-α,β-D-glucopyranose with acetyl chloride, or allyl chloroformate, or ethyl chloroformate gave the corresponding 2-OH, 1-β-acetates or -carbonates in excellent yields. The 2-OH, 1-β-acetates were readily converted to the corresponding 2-O-acetylated glucopyranosyl trichloroacetimidates by reaction with trichloroacetonitrile via base promoted acetyl migration, while the 2-OH, 1-β-carbonates were good glycosyl acceptors for the synthesis of (1→2)-linked oligosaccharides.

Keywords: Esterification; Acetyl chloride; Allyl chloroformate; Ethyl chloroformate; Glucopyranose 1,2-diols

1. Introduction

Regioselective introduction of protecting group is of crucial importance in carbohydrate chemistry.[1] Acyl groups, especially acetyl and benzoyl, are generally used as electron-withdrawing protecting groups to block hydroxyls, and also used as good neighboring participating groups at 2-position for anomeric stereocontrol in glycosylation reactions. Although some selective protection approaches such as the use of 1-(benzoyloxy)benzotriazole (BzOBT),[2–5] the dibutyltin oxide mediated selective monoprotection strategy,[6,7] the phase-transfer method,[8] the silver(I) oxide promoted acylation technique,[9] the Cu(II)-mediated acylation procedure,[10] or the selective activation of hydroxyl groups through stannylene compounds,[11] as well as enzyme methods[12] are available, these methodologies are mostly focused on the selective acylation of sugar 2,3- or 4,6-diols. Regioselective protection at the anomeric hydroxyl group is, however, a challenge for chemists.[4,13]

Previously, we have revealed that selective acylation of allyl 4,6-*O*-isopropylidene-α-D-mannopyranoside[14] or allyl 4-*O*-benzoyl-α-L-rhamnopyranoside[15] with acetyl chloride or chloroacetyl chloride in pyridine gave highly selective 3-O-acylation products, and with this method, a series of complex rhamnose and mannose oligosaccharides were synthesized efficiently.[14–18] As an extension to this method, we wish to report herewith the regio- and stereoselective C-1-O-acylation of glucopyranose 1,2-diols and their use in the preparation of glucose trichloroacetimidate donors and oligosaccharides.

The synthesis of 4,6-*O*-isopropylidene-3-*O*-allyl- (**8**), -3-*O*-benzyl- (**9**), and -3-*O*-benzoyl-α,β-D-glucopyranose (**10**) is depicted in Scheme 1. Allylation, or benzylation, or benzoylation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) gave compounds **2**,[19] or **3**, or **4**,[20] respectively. Subsequent hydrolysis was carried out in an aqueous solution of sulfuric acid (4%) under heating at

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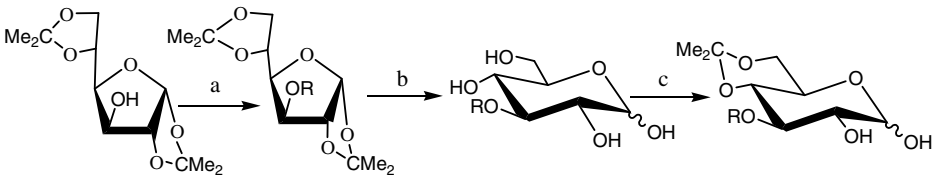


Scheme 1. Reagents and conditions: (a) AllBr, NaH, DMF for **2**; BnBr, NaH, DMF for **3**; BzCl–pyridine for **4**; (b) 4% H_2SO_4, reflux, 3–4 h; (c) TsOH, DMF, 1.05 equiv 2-methoxypropene (overall yield from **1**: 76%, 81%, and 75% for **8**, **9**, and **10**, respectively).

reflux, and the reaction was accompanied by ring expansion.[19] Selective 4,6-O-isopropylidenation of the resultant tetraols **5**–**7** with 2-methoxypropene in DMF in the presence of catalytic amounts of TsOH afforded the target diol compounds. The above three steps were processed in a consecutive manner without chromatographic separation of the intermediates, making a much simplified preparation of **8**–**10**.

The 1,2-diols **8**–**10** were then employed for the selective acylation studies. Benzoylation of **8** with an equivalent amount of benzoyl chloride in pyridine at −15 °C led to a mixture of 1-*O*-Bz, 2-*O*-Bz, and 1,2-di-*O*-Bz products, indicating that the benzoylation was not selective. This phenomenon was also observed in stereoselective benzoylation of D-glucosamine derivatives.[4] When diols **8**–**10** were treated with allyl chloroformate, or ethyl chloroformate, or acetyl chloride in dichloromethane at room temperature in the presence of 4 equiv of pyridine, their C-1 hydroxyl group was selectively blocked, and 1-allyloxyformates **11**, **14**, and **17**, or 1-ethyloxyformates **12**, **15**, and **18**, or 1-acetates **13**, **16**, and **19**, with predominant β anomer were obtained, respectively, after separation by silica gel column chromatography (Table 1, entries 1–9). Low temperature (−15 to −10 °C), slow addition of the dichloromethane diluted acetyl chloride or chloroformates were necessary to ensure the high regioselectivity of the reaction. The regioselectivity was indicated clearly by the ^{1}H NMR spectra of the 1-esters, which exhibited characteristic downfield signals for H-1. Since the proton of the 1-hydroxy group is more acidic than the 2-hydroxy group, the high regioselectivity was not surprising.

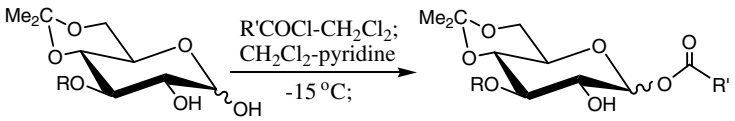
As for the high β anomeric stereoselectivity, it was attributed to the kinetic stereoelectronic effect or 1,3-diaxial repulsion,[21] enabling the C-1-O^- to take the equatorial orientation. Because of the poor solubility of **10** in dichloromethane, more pyridine (10 equiv) was used, and the ratio of α anomer rose considerably (Table 1, entries 7–9). The configuration of the products was readily assigned from their ^{1}H NMR spectra as indicated in Table 1, that is, the α anomers showed small coupling constants ($J_{1,2}$ 3.3–4.0 Hz), while the β anomers showed large coupling constants ($J_{1,2}$ 7.9–8.2 Hz).

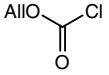
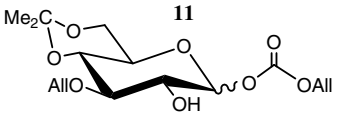
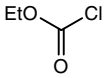
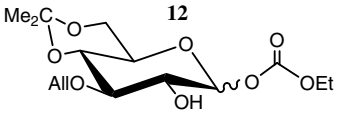
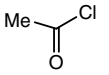
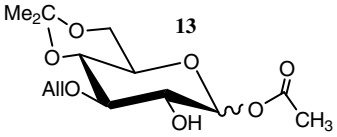
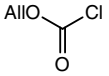
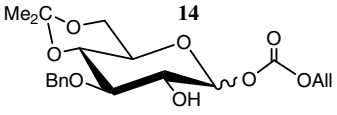
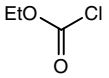
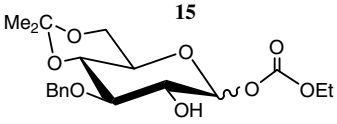
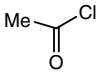
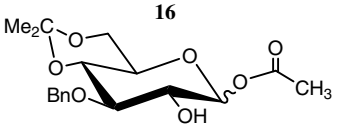
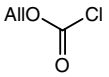
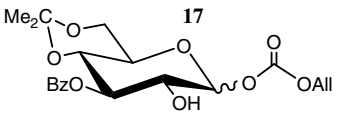
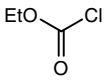
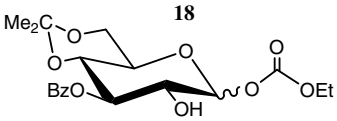
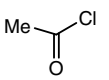
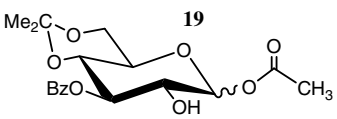
Trichloroacetimidate has widely been used as an excellent leaving group in glycosidic bond formation,[21] and also as a temporary protective group for hydroxyl function.[22–24] In our research, transformation of the 2-OH of the obtained glucosyl acetates and carbonates to the corresponding 2-trichloroacetimidate was studied. It was found that carbonates **14** and **15** were readily converted to the corresponding 2-trichloroacetimidate derivatives by addition of trichloroacetonitrile in the presence of K_2CO_3 and a catalytic amount of DBU, affording **20** and **21** in good yields, and no α/β anomerization was observed (Scheme 2).

However, in the case of acetates **13** and **16**, the reactions gave quite different results. Trichloroacetimidation of **13** and **16** with trichloroacetonitrile under the same conditions gave the corresponding 2-O-acetylated glucopyranosyl trichloroacetimidates **24** (84%) and **25** (79%), respectively. Compounds **24** and **25** showed identical NMR data with those of the authentic samples prepared from **8** and **9** via 1,2-di-O-acetylation, 1-O-deacetylation, and trichloroacetimidation. The facile migration of acyl groups in partially acylated sugars under mildly alkaline conditions is well known and has been the subject of numerous reports in the literature.[25,26] Apparently, migration of the anomeric acetate and anomerization occurred during the process of trichloroacetimidation as outlined in Scheme 3. Similar 1,2-*O*-silyl group migration[27,28] has been noticed by Schmidt and co-workers. Trichloroacetimidates **24** and **25** are very valuable glucopyranosyl donors as they contain orthogonal protective groups, being capable of application in the synthesis of complex branched oligosaccharides. It was also found that transformation of **8** to **24** via **13** (or **9** to **25** via **16**) can be conveniently performed in a one-pot manner, leading to a 70% overall yield for **24** (or 64% for **25**), and thus the preparation of **24** or **25** was greatly simplified.

Our attention turned then toward the formation of (1→2)-linked disaccharides from the obtained glucose 2-OH acetate or 2-OH carbonate acceptors since (1→2)-linked oligosaccharides are abundant in nature.[29–31] It was found that TMSOTf catalyzed condensation of 1-acetate **16** with 2,3,4,6-tetra-*O*-benzoyl-α-D-manno-

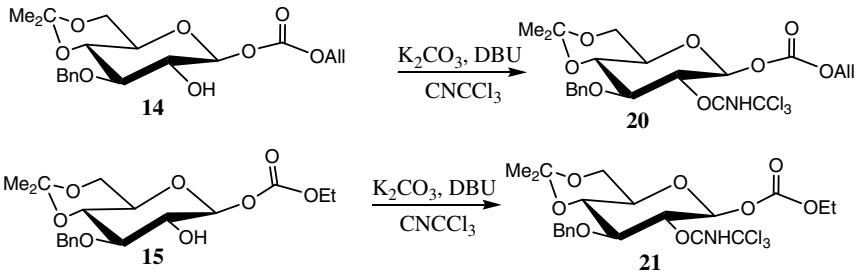
Table 1. Selective esterification reactions of the glucose 1,2-diols



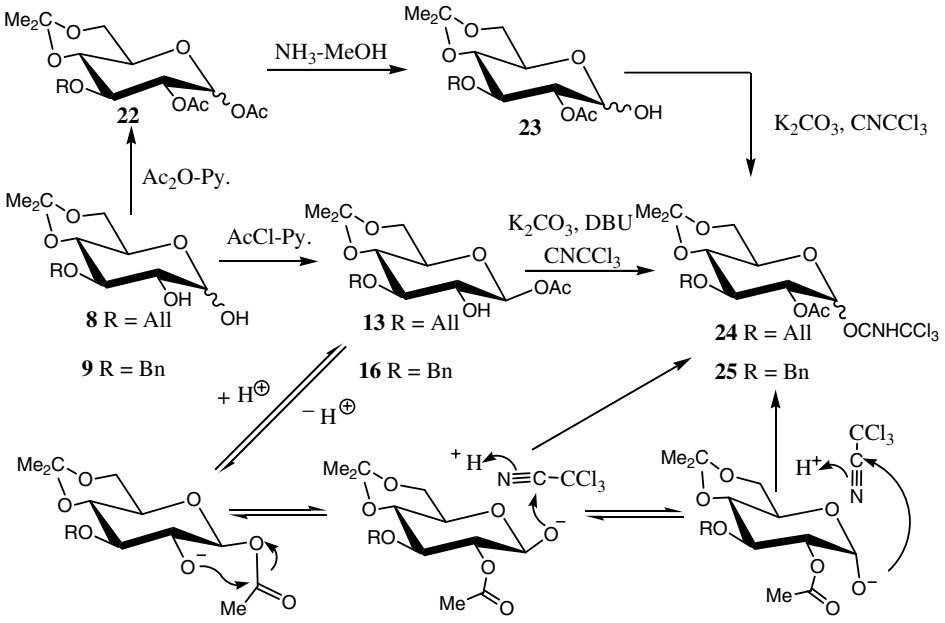
Entry	Reactant number	R′COCl	Product (%)	β:α[a]	Yield (%)	$J_{1,2}$ (Hz)
1	**8**		**11** 	1:0	82	8.2
2	**8**		**12** 	1:0	85	8.5
3	**8**		**13** 	30:1	74	8.0 (β); 3.9 (α)
4	**9**		**14** 	1:0	86	7.9
5	**9**		**15** 	1:0	91	7.9
6	**9**		**16** 	45:1	79	8.8 (β); 3.8 (α)
7	**10**		**17** 	14:1	83	7.9 (β); 3.5 (α)
8	**10**		**18** 	7:1	81	8.0 (β); 3.8 (α)
9	**10**		**19** 	7.3:1	72	8.1 (β); 4.0 (α)

[a] The β:α ratio was estimated from the ^{1}H NMR spectra of the products.

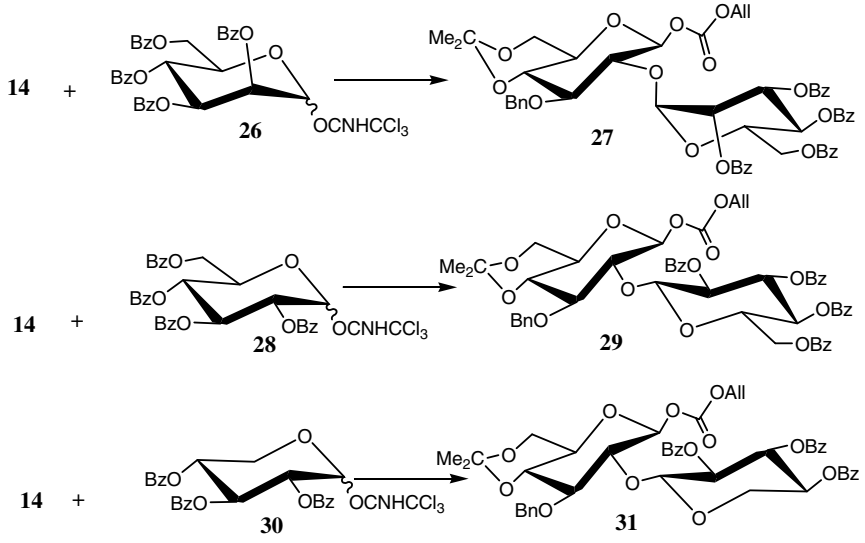
pyranosyl trichloroacetimidate (**26**) was unsuccessful as a complex mixture was obtained. However, coupling reactions of carbonate **14** with trichloroacetimidates **26**, **28**, and **30** in the presence of catalytic TMSOTf under normal conditions[32] produced disaccharides **27** (95%), **29** (88%), and **31** (91%), respectively (Scheme 4). The anomeric center of the sugar residue at the reducing end of the obtained disaccharides kept its β configuration as indicated in the NMR spectra of the disaccharides. Compared to the corresponding acetates,



Scheme 2.



Scheme 3.



Scheme 4. Reagents and conditions: TMSOTf, CH_2Cl_2, −10 °C to rt; 95% for **27**: 88% for **29**, 91% for **31**.

carbonates generally were much more stable presumably because of the resonance effect of the second oxygen.

In conclusion, we have successfully developed a technique for the highly regioselective and stereoselective

esterification of 3-*O*-allyl (or benzyl, or benzoyl)-4,6-*O*-isopropylidene-D-glucopyranose with acetyl chloride, or allyl chloroformate, or ethyl chloroformate to afford the corresponding 2-OH, 1-β-acetates or -carbonates in good yields. With the aid of base promoted acetyl migration, an efficient preparation of the valuable 2-acetate 1-trichloroacetimidate donors from the corresponding glucopyranosyl 1,2-diols via the 1-β-acetate intermediates was achieved. The 2-OH, 1-β-carbonates were proved to be good acceptors in the coupling reactions for the preparation of (1→2)-linked disaccharides.

2. Experimental

2.1. General methods

Optical rotations were determined with a Perkin–Elmer model 241-MC automatic polarimeter for soln in a 1-dm, jacketed cell. NMR spectra were recorded in deuterochloroform soln with a Bruker DPX300 spectrometer, using tetramethylsilane as an internal standard. Elemental analysis was performed on a Yanaco CHN Corder MF-3 automatic elemental analyzer. Thin-layer chromatography (TLC) was performed on Silica Gel HF with detection by charring with 30% (v/v) H_2SO_4 in MeOH or by UV detection. Column chromatography was conducted by elution of a column (8×100 mm, 16×240 mm, 18×300 mm, 35×400 mm) of Silica Gel (200–300 mesh) with EtOAc/petroleum ether (bp 60–90 °C) as the eluent. Analytical LC was performed with a Gilson HPLC consisting of a pump (model 306), stainless steel column packed with Silica Gel (Spherisorb SiO_2, 10×300 mm or 4.6×250 mm), differential refractometer (132-RI Detector), and UV–vis detector (model 118). EtOAc–petroleum ether (bp 60–90 °C) was used as the eluent at a flow rate of 1–4 mL/min. Solutions were concentrated at a temperature <60 °C under diminished pressure.

2.2. General procedure for the preparation of the glucopyranose 1,2-diols 8–10

To a soln of **1** (7.80 g, 30 mmol) in DMF (40 mL) was added 95% NaH (1.13 g, 45 mmol) in small portions at 0 °C. The reaction mixture was stirred for 0.5 h, at the end of which time allyl chloride or benzyl chloride (35 mmol) was added dropwise. (For the synthesis of compound **10**, compound **1** was benzoylated with 1.5 equiv of benzoyl chloride in pyridine, and the work-up procedure was according to the standard method.) After stirring for 2 h at room temperature, TLC (4:1 petroleum ether–EtOAc) indicated that the reaction was complete. The reaction mixture was quenched with MeOH (2 mL), and diluted with CH_2Cl_2 (150 mL), washed with 1 N HCl, water and satd aq $NaHCO_3$. The organic layer was concentrated, and the residue was dissolved in 4% aq H_2SO_4 (200 mL) and then refluxed for 4 h. The resulting soln was cooled down to room temperature and extracted 2 times with EtOAc. The organic phase was discarded and the aq phase was then stirred with $CaCO_3$ (30 g) for 2 h. The reaction mixture was filtered and the residue was repeatedly washed with MeOH. The combined filtrate and washings were evaporated under diminished pressure. The residual syrupy material was treated with a minimum vol of water and filtered in order to remove some insoluble material. The residue was washed with MeOH and the combined filtrate and washings were concentrated to give the 3-O-protected glucopyranose derivatives **5**–**7** as syrups. These syrups were dried under high vacuum for 4 h and then were taken in anhyd DMF (80 mL), $TsOH \cdot H_2O$ (95 mg, 0.5 mmol) and 2-methoxypropene (3.6 mL, 36 mmol) were added successively under N_2 atmosphere. The mixture was stirred at room temperature for 2 h, and TLC (1:1 petroleum ether–EtOAc) indicated that the reaction was complete. $NaHCO_3$ (2.52 g, 30 mmol) was added to the reaction mixture, and the mixture was stirred for an additional 1 h. After filtration, the mixture was concentrated under diminished pressure to give a residue, which was subjected to silica gel column chromatography (2:1 petroleum ether–EtOAc) to give the desired diol compounds.

2.2.1. 3-*O*-Allyl-4,6-*O*-isopropylidene-α,β-D-glucopyranose (8). Yield 5.95 g, overall yield from **1**: 76%, amorphous solid. $[\alpha]_D^{22}$ +33 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 5.95–5.89 (m, 1H, $CH_2{=}CH{-}CH_2O$), 5.26 (d, 1H, *J* 3.1 Hz, H-1, α-anomer), 5.32–5.15 (m, 2H, $CH_2{=}CH{-}CH_2O$), 4.66 (d, 1H, *J* 7.9 Hz, H-1, β-anomer), 4.40–4.33 (m, 2H, $CH_2{=}CH{-}CH_2O$), 3.93–2.88 (m, 6H), 1.49, 1.41 (2s, 6H, Me_2C). Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.09; H, 8.02.

2.2.2. 3-*O*-Benzyl-4,6-*O*-isopropylidene-α,β-D-glucopyranose (9). Yield 7.50 g, overall yield from **1**: 81%, amorphous solid. $[\alpha]_D^{22}$ +30 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.39–7.26 (m, 5H, Ar-*H*), 5.22 (d, 1H, *J* 2.6 Hz, H-1, α-anomer), 4.92–4.69 (m, 2H, CH_2Ph), 4.57 (d, 1H, J_1 6.8 Hz, H-1, β-anomer), 3.92–3.24 (m, 6H), 1.47, 1.42 (2s, 6H, Me_2C, β-anomer), 1.45, 1.41 (2s, 6H, Me_2C, α-anomer). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.76; H, 7.30.

2.2.3. 3-*O*-Benzoyl-4,6-*O*-isopropylidene-α,β-D-glucopyranose (10). Yield 7.30 g, overall yield from **1**: 75%, foamy solid. $[\alpha]_D^{22}$ +26 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.08–7.43 (m, 5H, Bz-*H*), 5.39 (dd, *J* 9.5, 9.7 Hz, H-3, α-anomer), 5.32 (d, 1H, *J* 3.7 Hz, H-1, α-anomer), 5.25 (dd, *J* 9.5, 9.7 Hz, H-3, β-anomer), 4.84 (d, 1H, *J* 7.6 Hz, H-1, β-anomer), 4.05–3.39 (m, 5H), 1.50, 1.43 (2s, 6H, Me_2C, β-anomer), 1.49, 1.42 (2s,

6H, Me_2C, α-anomer). Anal. Calcd for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.03; H, 6.30.

2.3. General procedure for the preparation of compounds 11–19

1,2-Diols (10.0 mmol) were dissolved in dry CH_2Cl_2 (40 mL) containing pyridine (40 mmol for **8** and **9**; 100 mmol for **10**), then under N_2 atmosphere and stirring, a soln of allyl chloroformate, or ethyl chloroformate, or acetyl chloride (11 mmol) in anhyd CH_2Cl_2 (10 mL) was added dropwise within 30 min at −15 to −20 °C. The reaction mixture was slowly warmed to room temperature and stirred for 2 h, at the end of which time TLC (3:1 petroleum ether–EtOAc) indicated that the reaction was complete. The reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with 1 N HCl, satd aq $NaHCO_3$, and the organic layer was dried over Na_2SO_4. The soln was concentrated under diminished pressure, and the residue was purified by column chromatography on a silica gel column (5:1 petroleum ether–EtOAc). Yields and spectral data of **11**–**19** are as follows.

2.3.1. 3-*O*-Allyl-1-*O*-allyloxycarbonyl-4,6-*O*-isopropylidene-β-D-glucopyranose (11). Yield 2.82 g (82%), syrup. $[\alpha]_D^{22}$ +33 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.93–5.78 (m, 2H, $2CH_2$=C*H*–CH_2O), 5.38 (d, 1H, *J* 8.2 Hz, H-1), 5.34–5.09 (m, 4H, $2CH_2$=CH–CH_2O), 4.63–4.56 (m, 2H, CH_2=CH–CH_2O), 4.40–4.10 (m, 2H, CH_2=CH–CH_2O), 3.88 (dd, 1H, *J* 5.2, 10.5 Hz, H-6a), 3.67 (dd, 1H, *J* 10.5, 10.1 Hz, H-6b), 3.61 (dd, 1H, *J* 8.2, 8.8 Hz, H-3), 3.50 (dd, 1H, *J* 8.2, 8.8 Hz, H-2), 3.39 (dd, 1H, *J* 8.8, 8.7 Hz, H-4), 3.37–3.20 (m, 1H, H-5), 3.12 (br s, 1H, O*H*), 1.42, 1.34 (2s, 6H, Me_2C). Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.81; H, 7.02. Found: C, 55.53; H, 6.88.

2.3.2. 3-*O*-Allyl-1-*O*-ethyloxycarbonyl-4,6-*O*-isopropylidene-β-D-glucopyranose (12). Yield 2.82 g (85%), syrup. $[\alpha]_D^{22}$ +52 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.00–5.87 (m, 1H, CH_2=C*H*=CH_2O), 5.45 (d, 1H, *J* 8.5 Hz, H-1), 5.33–5.19 (m, 2H, CH_2=CH–CH_2O), 4.42–4.35 (m, 1H, $1CH_2$=CH–C*H*HO), 4.28–4.17 (m, 3H, $1CH_2$=CH–C*H*HO, CH_3CH_2O), 3.94 (dd, 1H, *J* 5.3, 10.8 Hz, H-6a), 3.75 (dd, 1H, *J* 10.8, 10.8 Hz, H-6b), 3.65 (dd, 1H, *J* 8.8, 9.0 Hz, H-3), 3.50 (dd, 1H, *J* 8.5, 8.8 Hz, H-2), 3.45 (dd, 1H, *J* 9.0, 9.1 Hz, H-4), 3.34–3.35 (m, 1H, H-5), 2.91 (br s, 1H, O*H*), 1.49, 1.41 (2s, 6H, Me_2C), 1.29 (t, 3H, *J* 13.2 Hz, CH_3CH_2O). Anal. Calcd for $C_{15}H_{24}O_8$: C, 54.21; H, 7.28. Found: C, 54.52; H, 7.44.

2.3.3. 1-*O*-Acetyl-3-*O*-allyl-4,6-*O*-isopropylidene-α,β-D-glucopyranose (13). Yield 2.23 g (74%), foamy solid. $[\alpha]_D^{22}$ +49 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.24 (d, 0.03H, *J* 3.90 Hz, H-1, α-anomer), 6.02–5.80 (m, 1H, CH_2=C*H*–CH_2O, α,β-anomer), 5.58 (d, 0.9H, *J* 8.0 Hz, H-1, β-anomer), 5.36–5.11 (m, 2H, CH_2=CH–CH_2O, α,β-anomer), 4.42–4.14 (m, 2H, CH_2=CH–CH_2O, α,β-anomer), 3.92 (dd, 0.9H, *J* 5.5, 10.7 Hz, H-6a, β-anomer), 3.76–3.38 (m, 5H, H-6a, α-anomer; H-2–5, α,β-anomer; H-6b, α,β-anomer), 3.12 (br s, 1H, O*H*), 2.14 (s, 3H, β-CH_3CO), 2.09 (s, 3H, α-CH_3CO), 1.49, 1.41 (2s, 6H, α,β-Me_2C). Anal. Calcd for $C_{14}H_{22}O_7$: C, 55.62; H, 7.33. Found: C, 55.35; H, 7.20.

2.3.4. 1-*O*-Allyloxycarbonyl-3-*O*-benzyl-4,6-*O*-isopropylidene-β-D-glucopyranose (14). Yield 3.38 g (86%), syrup. $[\alpha]_D^{22}$ +41 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40–7.27 (m, 5H, Ar-*H*), 5.98–5.85 (m, 1H, CH_2=C*H*–CH_2O), 5.45 (d, 1H, *J* 7.9 Hz, H-1), 5.40–5.25 (m, 2H, CH_2=CH–CH_2O), 4.90 (d, 1H, *J* 11.6 Hz, C*H*HPh), 4.73 (d, 1H, *J* 11.6 Hz, C*H*HPh), 4.68–4.64 (m, 2H, CH_2=CH–CH_2O), 3.96 (dd, 1H, *J* 5.3, 10.7 Hz, H-6a), 3.79–3.42 (m, 4H, H-2, H-3, H-4, H-6b), 3.44–3.35 (m, 1H, H-5), 2.53 (br s, 1H, O*H*), 1.48, 1.42 (2s, 6H, Me_2C). Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64. Found: C, 60.73; H, 6.78.

2.3.5. 3-*O*-Benzyl-1-*O*-ethyloxycarbonyl-4,6-*O*-isopropylidene-β-D-glucopyranose (15). Yield 3.48 g (91%), syrup. $[\alpha]_D^{22}$ +44 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.25 (m, 5H, Ar-*H*), 5.44 (d, 1H, *J* 7.9 Hz, H-1), 4.93 (d, 1H, *J* 11.7 Hz, C*H*HPh), 4.73 (d, 1H, *J* 11.7 Hz, C*H*HPh), 4.26–4.19 (m, 2H, CH_3CH_2O), 3.94 (dd, 1H, *J* 5.2, 10.6 Hz, H-6a), 3.78–3.50 (m, 4H, H-2, H-3, H-4, H-6b), 3.43–3.35 (m, 1H, H-5), 2.61 (d, 1H, *J* 3.0 Hz, O*H*), 1.47, 1.42 (2s, 6H, Me_2C), 1.31 (t, 3H, *J* 7.2 Hz, CH_3CH_2O). Anal. Calcd for $C_{19}H_{26}O_8$: C, 59.68; H, 6.85. Found: C, 59.66; H, 6.57.

2.3.6. 1-*O*-Acetyl-3-*O*-benzyl-4,6-*O*-isopropylidene-α,β-D-glucopyranose (16). Yield 2.78 g (79%), syrup. $[\alpha]_D^{22}$ +42 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.24 (m, 5H, Ar-*H*, α,β-anomer), 5.35 (d, 0.02H, *J* 3.8 Hz, H-1, α-anomer), 4.84 (d, 0.97H, *J* 8.8 Hz, H-1, β-anomer), 4.85–4.58 (m, 2H, CH_2Ph, α,β-anomer), 4.21 (dd, 0.02H, *J* 5.8, 10.5 Hz, H-6a, α-anomer), 3.95–3.55 (m, 6H, H-2–6, α,β-anomer), 2.05 (s, 2.9H, CH_3CO, β-anomer), 2.03 (s, 0.1H, CH_3CO, α-anomer), 1.49, 1.43 (2s, 6H, Me_2C, α,β-anomer). Anal. Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86. Found: C, 61.30; H, 7.19.

2.3.7. 1-*O*-Allyloxycarbonyl-3-*O*-benzoyl-4,6-*O*-isopropylidene-α,β-D-glucopyranose (17). Yield 3.39 g (83%), foamy solid. For β isomer: $[\alpha]_D^{22}$ +29 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.07–7.44 (m, 5H, Bz-*H*), 6.00–5.87 (m, 1H, CH_2=C*H*–CH_2O), 5.58 (d, 1H, *J* 7.9 Hz, H-1), 5.45–5.29 (m, 2H, CH_2=CH–CH_2O),

5.27 (dd, 1H, *J* 9.3, 9.2 Hz,) 4.70–4.65 (m, 2H, CH_2=CH–CH_2O), 4.03 (dd, 1H, *J* 5.4, 10.8 Hz, H-6a), 3.94–3.77 (m, 3H, H-2, H-4, H-6), 3.59–3.51 (m, 1H, H-5), 3.08 (br s, 1H, O*H*), 1.50, 1.37 (2s, 6H, *Me*$_2$C). Anal. Calcd for $C_{20}H_{24}O_9$: C, 58.82; H, 5.92. Found: C, 59.03; H, 5.77.

2.3.8. 3-*O*-Benzoyl-1-*O*-ethyloxycarbonyl-4,6-*O*-isopropylidene-α,β-D-glucopyranose (18). Yield 3.21 g (81%), foamy solid. For β isomer: $[\alpha]_D^{22}$ +33 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.08–7.44 (m, 5H, Bz-H), 5.58 (d, 1H, *J* 8.0 Hz, H-1), 5.26 (dd, 1H, *J* 9.2, 9.3 Hz, H-3), 4.30–4.23 (m, 2H, CH_3CH_2O), 4.04 (dd, 1H, *J* 5.0, 10.5 Hz, H-6a), 3.92–3.76 (m, 3H, H-2, H-4, H-6b), 3.59–3.50 (m, 1H, H-5), 3.00 (d, 1H, *J* 4.3 Hz, O*H*), 1.49, 1.37 (2s, 6H, *Me*$_2$C), 1.33 (t, 3H, *J* 9.4 Hz, CH_3CH$_2$O). Anal. Calcd for $C_{19}H_{24}O_9$: C, 57.57; H, 6.10. Found: C, 57.84; H, 6.02.

2.3.9. 1-*O*-Acetyl-3-*O*-benzoyl-4,6-*O*-isopropylidene-α,β-D-glucopyranose (19). Yield 2.64 g (72%), foamy solid. $[\alpha]_D^{22}$ +36 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.09–7.43 (m, 5H, Bz-*H*, α,β-anomer), 6.21 (d, 0.11H, *J* 4.0 Hz, H-1, α-anomer), 5.73 (d, 0.88H, *J* 8.1 Hz, H-1, β-anomer), 5.40 (dd, 0.11H, *J* 9.2, 9.3 Hz, H-3, α-anomer), 5.26 (dd, 0.88H, *J* 9.2, 9.3 Hz, H-3, β-anomer), 4.36–3.50 (m, 5H, H-2–6, α,β-anomer), 2.97 (br s, 1H, O*H*), 2.20 (s, 0.33H, CH_3CO, α-anomer), 215 (s, 2.64H, CH_3CO, β-anomer), 1.49, 1.37 (2s, 6H, *Me*$_2$C, α,β-anomer). Anal. Calcd for $C_{18}H_{22}O_8$: C, 59.01; H, 6.05. Found: C, 59.29; H, 6.23.

2.4. General procedure for the preparation of compounds 20, 21, 24, and 25

Compound **14**, or **15**, or **13**, or **16** (5 mmol) and K_2CO_3 (2.0 g) were dried under high vacuum for 4 h and then CH_2Cl_2 (20 mL) was added to the mixture. Then under N_2 atmosphere, CCl_3CN (1.0 mL, 10 mmol) was added, the mixture was stirred for 2 h, at the end of which time DBU (135 μL, 0.9 mmol) was added. The reaction mixture was stirred for 12 h, and TLC (2:1 petroleum ether–EtOAc) indicated that the reaction was complete. After filtration, the mixture was concentrated under diminished pressure to give a residue, purification of the crude product on a silica gel column with 5:1 petroleum ether–EtOAc as the eluent furnished the desired compounds.

2.4.1. 3-*O*-Benzyl-1-*O*-allyloxycarbonyl-4,6-*O*-isopropylidene-2-*O*-trichloroacetimidoyl-β-D-glucopyranose (20). Yield 2.39 g (89%), syrup. $[\alpha]_D^{22}$ +19 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.65 (s, 1H, CN*H*CCl$_3$), 7.31–7.23 (m, 5H, Ar-*H*), 5.94–5.68 (m, 1H, CH_2=C*H*–CH$_2$O), 5.71 (d, 1H, *J* 8.0 Hz, H-1), 5.41 (dd, 1H, *J* 8.0 8.1 Hz, H-2), 5.38–5.23 (m, 2H, CH_2=CH–CH$_2$O), 4.83–4.71 (m, 2H, CH_2Ph), 4.67–4.55 (m, 2H, CH_2=CH–CH_2O), 4.01–3.75 (m, 4H, H-3, H-4, H-6), 3.51-3.43 (m, 1H, H-5), 1.50, 1.43 (2s, 6H, *Me*$_2$C). Anal. Calcd for $C_{22}H_{26}Cl_3NO_8$: C, 49.04; H, 4.86; N, 2.60. Found: C, 49.31; H, 5.02; N, 2.98.

2.4.2. 3-*O*-Benzyl-1-*O*-ethyloxycarbonyl-4,6-*O*-isopropylidene-2-*O*-trichloroacetimidoyl-β-D-glucopyranose (21). Yield 2.45 g (93%), syrup. $[\alpha]_D^{22}$ +27 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.65 (s, 1H, CN*H*CCl$_3$), 7.32–7.24 (m, 5H, Ar-*H*), 5.72 (d, 1H, *J* 8.0, H-1), 5.41 (dd, 1H, *J* 8.0, 8.1 Hz, H-2), 4.83–4.71 (m, 2H, CH_2Ph), 4.21 (q, 2H, *J* 7.1 Hz, OCH_2CH$_3$), 4.01–3.75 (m, 4H, H-3, H-4, H-6), 3.51–3.45 (m, 1H, H-5), 1.49, 1.43 (2s, 6H, *Me*$_2$C), 1.26 (t, 3H, *J* 7.1 Hz, OCH$_2$CH_3). Anal. Calcd for $C_{21}H_{26}Cl_3NO_8$: C, 47.88; H, 4.97; N, 2.66. Found: C, 47.75; H, 4.71; N, 2.29.

2.4.3. 2-*O*-Acetyl-3-*O*-allyl-4,6-*O*-isopropylidene-α,β-D-glucopyranosyl trichloroacetimidate (24). Yield 1.87 g (84%), syrup. $[\alpha]_D^{22}$ +20 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.66 (s, 1H, CN*H*CCl$_3$, β-anomer), 8.60 (s, 1H, CN*H*CCl$_3$, α-anomer), 6.45 (d, 1H, *J* 3.9 Hz, H-1, α-anomer), 5.83 (d, 1H, *J* 8.2 Hz, H-1, β-anomer), 5.93–5.76 (m, 1H, CH_2=C*H*–CH$_2$O, α,β-anomer), 5.29–5.12 (m, 2H, CH_2=CH–CH$_2$O, α,β-anomer), 5.21 (dd, 1H, *J* 8.1, 8.2 Hz, H-2, β-anomer), 4.99 (dd, 1H, *J* 3.9, 8.2 Hz, H-2, α-anomer), 4.31–3.43 (m, 5H, H-3, H-4, H-5, H-6), 2.05 (s, 3H, CH_3CO, α-anomer), 2.04 (s, 3H, CH_3CO, β-anomer), 1.52, 1.43 (2s, 6H, *Me*$_2$C, α-anomer), 1.51, 1.42 (2s, 6H, *Me*$_2$C, β-anomer). Anal. Calcd for $C_{16}H_{22}Cl_3NO_7$: C, 43.02; H, 4. 96; N, 3.14. Found: C, 42.83; H, 4.70; N, 3.30.

2.4.4. 2-*O*-Acetyl-3-*O*-benzyl-4,6-*O*-isopropylidene-α,β-D-glucopyranosyl trichloroacetimidate (25). Yield 1.96 g (79%), syrup. $[\alpha]_D^{22}$ +12 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.65 (s, 1H, CN*H*CCl$_3$, β-anomer), 8.58 (s, 1H, CN*H*CCl$_3$, α-anomer), 7.35–7.24 (m, 5H, Ar-*H*, α,β-anomer), 6.46 (d, 1H, *J* 3.8 Hz, H-1, α-anomer), 5.83 (d, 1H, *J* 7.9 Hz, H-1, β-anomer), 5.24 (dd, 1H, *J* 7.8, 7.9 Hz, H-2, β-anomer), 5.00 (dd, 1H, *J* 3.8, 7.9 Hz, H-2, α-anomer), 4.88–4.64 (m, 2H, CH_2Ph, α,β-anomer), 4.02–3.46 (m, 5H, H-3, H-4, H-5, H-6), 1.97 (s, 3H, CH_3CO, α-anomer), 1.96 (s, 3H, CH_3CO, β-anomer), 1.51, 1.45 (2s, 6H, *Me*$_2$C, α-anomer), 1.50, 1.44 (2s, 6H, *Me*$_2$C, β-anomer). Anal. Calcd for $C_{20}H_{24}Cl_3NO_7$: C, 48.36; H, 4.87; N, 2.82. Found: C, 48.00; H, 4.59; N, 3.05.

2.5. General procedure for the coupling reaction: synthesis of compounds 27, 29, and 31

Compound **12** (120 mg, 0.30 mmol) and sugar trichloroacetimidates **26**, or **28**, or **30** (0.36 mmol) were dried together under high vacuum for 4 h, then dissolved in anhyd CH_2Cl_2 (10 mL). TMSOTf (1.8 μL, 0.010 mmol)

was added at −10 °C under N_2 atmosphere. The reaction mixture was stirred for 2 h, during which time the temperature was gradually warmed to ambient temperature. Then the mixture was neutralized with Et_3N and concentrated to dryness under diminished pressure and the residue was purified by flash chromatography (4:1 petroleum ether–EtOAc). The physical data of the obtained disaccharides **27**, **29**, and **31** are as follows.

2.5.1. 2,3,4,6-Tetra-*O*-benzoyl-α-D-mannopyranosyl-(1→2)-1-*O*-allyloxycarbonyl-3-*O*-benzyl-4,6-*O*-isopropylidene-β-D-glucopyranose (27). Yield 277 mg (95%), foamy solid. $[\alpha]_D^{22}$ +14 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.10–7.17 (m, 25H, 5Ar-*H*), 6.08 (dd, 1H, *J* 10.2 Hz, H-4′), 5.86 (dd, 1H, *J* 3.3, 10.2 Hz, H-3′), 5.95–5.82 (m, 1H, $OCH_2CH{=}CH_2$), 5.67 (d, 1H, *J* 8.0 Hz, H-1), 5.59 (dd, 1H, *J* 1.4, 3.3 Hz, H-2′), 5.41 (d, 1H, *J* 1.4 Hz, H-1′), 5.34–5.17 (m, 2H, $OCH_2CH{=}CH_2$), 5.09–4.76 (m, 2H, CH_2Ph), 4.74–4.46 (m, 3H), 4.30 (dd, 1H, *J* 2.1, 12.5 Hz, H-6′a), 4.04–3.73 (m, 6H), 3.15–3.44 (m, 1H), 1.52, 1.45 (2s, 6H, Me_2C); ^{13}C NMR: δ 166.0, 165.5, 165.4, 165.1, 153.2, 137.9, 133.3, 133.2, 132.8, 131.1, 130.2, 129.8, 129.7, 129.3, 129.2, 129.1, 128.5, 128.4, 128.3, 128.2, 128.0, 119.0, 99.5, 98.0, 96.9, 78.9, 77.2, 75.7, 74.8, 70.3, 69.8, 69.3, 68.9, 67.7, 66.6, 62.0, 29.0, 19.8. Anal. Calcd for $C_{54}H_{52}O_{17}$: C, 66.66; H, 5.39. Found: C, 66.84; H, 5.70.

2.5.2. 2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→2)-1-*O*-allyloxycarbonyl-3-*O*-benzyl-4,6-*O*-isopropylidene-β-D-glucopyranose (29). Yield 257 mg (88%), foamy solid. $[\alpha]_D^{22}$ +8.0 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.02–7.19 (m, 25H, 5Ar-*H*), 5.85 (dd, 1H, *J* 9.8 Hz, H-4′), 5.90–5.77 (m, 1H, $OCH_2CH{=}CH_2$), 5.68 (dd, 1H, *J* 9.8 Hz, H-3′), 5.67 (d, 1H, *J* 8.9 Hz, H-1), 5.55 (dd, 1H, *J* 9.0, 9.8 Hz, H-2′), 5.33–5.19 (m, 2H, $OCH_2CH{=}CH_2$), 522 (d, 1H, *J* 9.0 Hz, H-1′), 4.65–4.32 (m, 6H), 4.08–3.84 (m, 3H), 3.72–3.53 (m, 3H), 3.36–3.21 (m, 1H), 1.38, 1.25 (2s, 6H, Me_2C); ^{13}C NMR: δ 166.1, 165.8, 165.2, 165.1, 153.3, 138.59, 133.3, 133.2, 133.1, 132.9, 131.1, 129.8, 129.7, 129.6, 129.5, 129.1, 128.9, 128.8, 128.3, 128.2, 128.2, 127.6, 127.5, 119.1, 101.1, 99.3, 96.4, 81.4, 79.1, 77.2, 74.5, 73.8, 73.1, 72.1, 72.0, 69.8, 68.9, 67.0, 63.3, 61.9, 28.9, 18.9. Anal. Calcd for $C_{54}H_{52}O_{17}$: C, 66.66; H, 5.39. Found: C, 66.48; H, 5.24.

2.5.3. 2,3,4-Tri-*O*-benzoyl-β-D-xylopyranosyl-(1→2)-1-*O*-allyloxycarbonyl-3-*O*-benzyl-4,6-*O*-isopropylidene-β-D-glucopyranose (31). Yield 229 mg (91%), foamy, solid. $[\alpha]_D^{22}$ +22 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.01–7.13 (m, 20H, 4Ar-*H*), 5.93–5.80 (m, 1H, $OCH_2CH{=}CH_2$), 5.85 (dd, 1H, *J* 5.4 Hz, H-3′), 5.56 (d, 1H, *J* 7.9 Hz, H-1), 5.42 (d, 1H, *J* 4.4 Hz, H-1′), 5.36–5.21 (m, 3H, H-2′, $OCH_2CH{=}CH_2$), 5.18 (m, 1H, H-4′), 4.75–4.41 (m, 5H), 4.00–3.69 (m, 6H), 3.44–3.35 (m, 1H), 1.42, 1.33 (2s, 6H, Me_2C). Anal. Calcd for $C_{46}H_{46}O_{15}$: C, 65.86; H, 5.53. Found: C, 65.59; H, 5.44.

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