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A highly convergent and effective synthesis of the phytoalexin elicitor hexasaccharide

Wei Wang, Fanzuo Kong *

Research Center for Eco-Environmental Sciences, Academia Sinica, PO Box 2871, Beijing 100085, People's Republic of China

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Abstract

The peracetylated hexasaccharide 1,2,4-tri-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-6-*O*-(2,3,4-tri-*O*-acetyl-6-*O*-(2,4-di-*O*-acetyl-3,6-di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-glucopyranosyl)-β-D-glucopyranosyl)-α,β-D-glucopyranose **21** was synthesized in a blockwise manner, employing trisaccharide trichloroacetimidate 2,4-di-*O*-acetyl-3,6-di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranosyl trichloroacetimidate **17** as the glycosyl donor, and trisaccharide 4-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-6-*O*-(2,3,4-tri-*O*-acetyl-β-D-glucopyranosyl)-1,2-*O*-(*R*,*S*)ethylidene-α-D-glucopyranose **18** as the acceptor. The donor **17** and acceptor **18** were readily prepared from trisaccharides 3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-6-*O*-(2,3,4-tri-*O*-acetyl-6-*O*-chloroacetyl-β-D-glucopyranosyl)-1,2-*O*-(*R*,*S*)ethylidene-α-D-glucopyranose **10** and 3,6-di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2-*O*-(*R*,*S*)ethylidene-α-D-glucopyranose **11**, respectively, which were obtained from rearrangement of orthoesters 3,4-di-*O*-acetyl-6-*O*-chloroacetyl-α-D-glucopyranose 1,2-(3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2-*O*-(*R*,*S*)ethylidene-α-D-glucopyranosid-6-yl orthoacetate) **8** and 3,4,6-tri-*O*-acetyl-α-D-glucopyranose 1,2-(3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2-*O*-(*R*,*S*)ethylidene-α-D-glucopyranosid-6-yl orthoacetate) **9**, respectively. The orthoesters were prepared from selective coupling of the disaccharide 3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2-*O*-(*R*,*S*)ethylidene-α-D-glucopyranose **4** with 'acetobromoglucose' (tetra-*O*-acetyl-α-D-glucopyranosyl bromide) and 6-*O*-chloroacetylated 'acetobromoglucose', respectively. To confirm the selectivity of the orthoester formation and rearrangement, the disaccharide 4-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2-*O*-(*R*,*S*)ethylidene-α-D-glucopyranose **7** was prepared from **4** by selective tritylation, acetylation and detritylation. The title compound, an elicitor-active D-glucohexaose 3-*O*-(β-D-glucopyranosyl)-6-*O*-(6-*O*-(3,6-di-*O*-(β-D-glucopyranosyl)-β-D-glucopyranosyl)-β-D-glucopyranosyl)-α,β-D-glucopyranose **1**, was finally obtained by Zemplén deacetylation of **21** in quantitative yield.

Keywords: Synthesis; Elicitor-active D-glucohexatose; Orthoester; Rearrangement

1. Introduction

The elicitor-active hexa-β-D-glucopyranosyl-D-glucitol, isolated from the mycelial walls of *Phytophthora megasperma f. sp. glycinea*, induces antibiotic phytoalexin accumulation in soybeans [1]. Biological assays of several oligosaccharides revealed that D-hexaglucoside is the minimum structural element required for high elicitor activity [2]. It should be noted that the β configuration at C-1 of the reducing end sugar is not necessary for elicitor activity [3f], and structural changes at the reducing end of the hexasaccharide only cause small effects on the activity [3k]. This

* Corresponding author. Fax: +86-10-62923563.
E-mail address: fzkong@mail.rcees.ac.cn (F. Kong)

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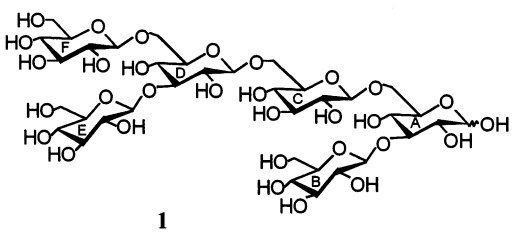
information attracted us to synthesize hexasaccharide **1**, which can be used as a valuable material for biological investigations. The syntheses of the heptasaccharide [3a–e,g,j] and the methyl and allyl glycosides of the hexasaccharide [3f,h,i] have been reported since the discovery of the elicitor. Almost all of the syntheses involved 2- or 3-regioselectivity of the glucopyranoside with tedious separation, and the use of expensive reagents such as alkylsilyl and methoxybenzyl protective groups. In a preliminary communication we reported a new method for the highly convergent and effective synthesis of hexasaccharide **1** [4]. We present here the full account of this synthesis.



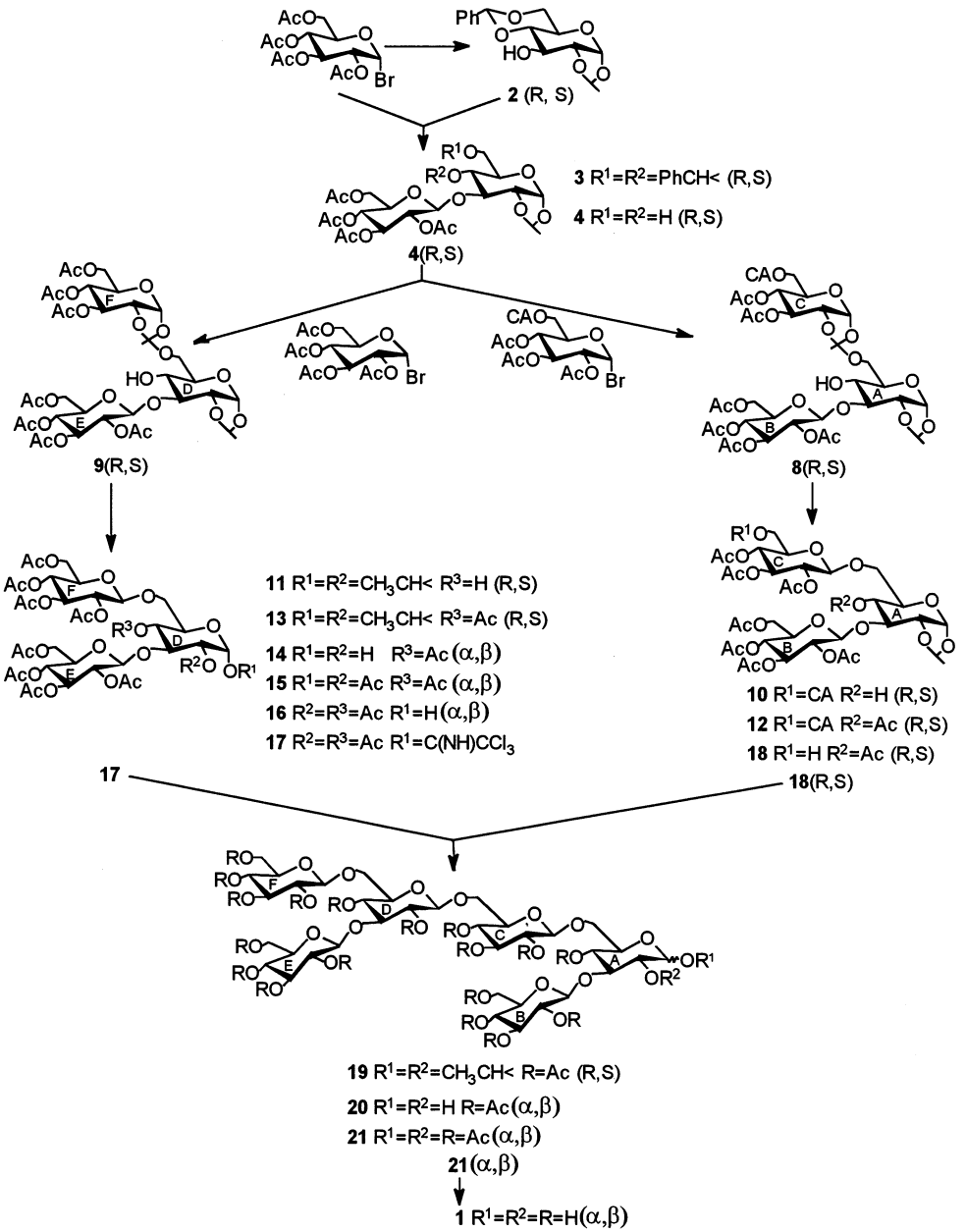
1

2. Results and discussion

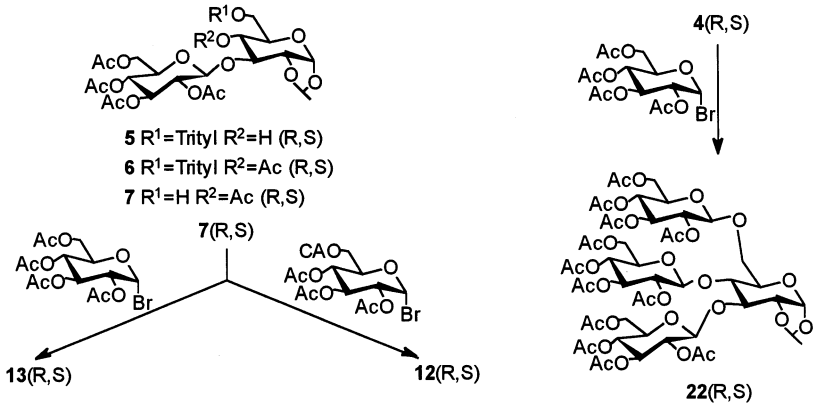
Based on retrosynthetic analysis, two trisaccharide units, ABC and DEF blocks, were built as the coupling acceptor and donor. The two blocks were readily obtained from rearrangement of the corresponding orthoesters, prepared from glycosylation of disaccharide **4** with 'acetobromoglucose' (tetra-*O*-acetyl-α-D-glucopyranosyl bromide) and 6-*O*-chloroacetylated 'acetobromoglucose' [3c], respectively. As shown in Scheme 1, 1,2-*O*-(*R*,*S*)-ethylidene-4,6-*O*-benzylidene-α-D-glucopyranoside (**2**) was used as the key starting material, which was readily prepared from conventional 4,6-*O*-benzylidenation [5,6] of 1,2-*O*-(*R*,*S*)-ethylidene-α-D-glucopyranoside [7]. Coupling [8] of **2** with acetobromoglucose in the presence of AgOTf afforded unique β-(1→3)-linked disaccharide **3** as crystals in high yield (87%). Debenzylidenation [3b] with dichloroacetic acid–water (5:1 v/v) was carried out smoothly, furnishing crystalline diol **4** in a satisfactory yield (90%). An attempt for selective 6-*O*-glycosylation of **4** with 'acetobromoglucose' was not successful; a 4,6-di-*O*-glycosylated tetrasaccharide **22** (see Scheme 2) was the major product even at low temperatures (− 20 to − 40 °C) with a small quantity of the bromide donor (1 equiv). The high reactivity of the 4-OH of **4** was perhaps caused by deformation of the 1,2-*O*-ethylidene-fused pyranose ring. However, we found that the coupling of **4** with acetobromoglucose at room temperature (rt) in the presence of 2,4-lutidine (1.5 equiv), gave orthoester **9** as crystals in quantitative yield. Me_3SiOTf-catalyzed rearrangement [9] of **9** selectively offered the 1,6-linked trisaccharide **11** (76%), and acetylation gave **13**. To confirm the selectivity of the rearrangement, **9** was acetylated first, then isomerized with TMSOTf to produce a compound (74%) identical to **13** [10]. Compounds **9** and **11** were easily identified from their ^1H NMR spectra; the former showed seven acetyl methyl signals at δ 1.99–2.11 and one upfield methyl signal of the orthoester at δ 1.74 (S) or 1.75 (R), and the latter gave all eight methyl signals at the acetyl region (δ 2.00–2.17). Synthesis of the trisaccharide acceptor **18** was accomplished by the same strategy as described for the synthesis of **11** except 6-*O*-chloroacetylated 'acetobromoglucose' was used instead of 'acetobromoglucose'. The orthoester **8** was also crystalline, and its isomerization, acetylation, and dechloroacetylation with thiourea [11] gave the desired trisaccharide acceptor **18** as crystals. Alternative syntheses of **12** and **13** are shown in Scheme 2. Selective tritylation [12] at 6-OH of **4** (giving **5**), followed by acetylation, gave **6** in high yield. Detritylation of **6** with $FeCl_3 \cdot 6H_2O$ at rt furnished the disaccharide acceptor **7** with a free 6-hydroxyl without migration [13]. Coupling of **7** with 'acetobromoglucose' and 6-*O*-chloroacetylated 'acetobromoglucose' afforded two trisaccharides, which yielded ^1H NMR spectra identical to those of **13** and **12**, respectively. This ambiguous and independent path confirmed the regioselectivity in the preparation of orthoesters **8** and **9**. De-ethylidenation [3b] of **13** with 90% CF_3COOH proceeded smoothly to give crystalline 1,2-diol **14**. Acetylation of **14** followed by selective deacetylation at C-1 [14], and treatment [15] with CCl_3CN/DBU furnished the trisaccharide donor **17**.

Coupling [16] of **17** with **18** was promoted with Me_3SiOTf, affording the acetylated hexasaccharide **19**. Zemplén deacetylation afforded the 1,2-ethylidene glucohexaose. De-ethylidenation of **19** followed by acetylation and Zemplén deacetylation [17] furnished the free hexasaccharide **1** as an amorphous solid.

In this synthesis, a new strategy of orthoester formation–rearrangement for the selective glycosylation of primary hydroxyl groups allowed the ready preparation of the related trisaccharide building blocks in large quantities. In addition, the use of acetyl, ethylidene, and benzylidene groups substantially simplified protection and deprotection steps. Furthermore, accessible materials and reagents were used and the reactions were carried out smoothly in high or good yields. Most of the intermediates involved in the synthesis were mixtures consisting of R and S isomers which were well separated and had identical reactivities. This highly convergent and effective synthesis of the title compound is suitable for large-scale preparation.



Scheme 1.



Scheme 2.

3. Experimental

General methods.—Melting points were determined with a 'Mel-Temp' apparatus. Optical rotations were determined with a Perkin–Elmer model 241-MC automatic polarimeter for solutions in a 1-dm, jacketed cell. ^{1}H NMR spectra were recorded with Varian XL-400 and Varian XL-200 spectrometers, for solutions in $CDCl_3$ with Me_4Si as the internal standard. Chemical shifts are expressed in ppm downfield from the internal Me_4Si absorption. R,S isomer assignment was based on previous assignments [18] for 1,2-*O*-ethylidene sugar derivatives. Mass spectra were recorded with a VG PLATFORM mass spectrometer using the ESI technique to introduce the sample. Thin-layer chromatography (TLC) was performed on silica gel HF, detection being affected by charring with 30% (v/v) sulfuric acid in methanol or sometimes 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 (100–200 mesh) using 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 a UV–vis detector (model 118), and 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.

*4,6-*O*-Benzylidene-1,2-*O*-(*R,S*)-ethylidene-α-*D*-glucopyranose* (**2**).—According to the previously reported method [7], a solution of 'acetobromoglucose' (10 g, 24.4 mmol) in anhyd MeCN (70 mL) was added to tetrabutylammonium iodide (5 g, 13.6 mmol) and $NaBH_4$ (2.1 g, 56.8 mmol) at 0 °C. After stirring for 18 h at rt, TLC (2:1 petroleum ether–EtOAc) indicated the reaction was complete. Filtration and concentration of the filtrate gave a residue which was subjected to column chromatography (2:1 petroleum ether–EtOAc) to afford 2,3,4-tri-*O*-acetyl-1,2-*O*-(*R,S*)-ethylidene-α-D-glucopyranose (7.3 g, 22.0 mmol). Zemplén deacetylation of the R,S mixture furnished the unprotected triol (R,S) in quantitative yield. To a solution of the triol (R,S) (4.5 g, 21.7 mmol) in α,α-diethoxytoluene (7.6 g, 42 mmol), was added freshly dried $ZnCl_2$ (2 g). The mixture was stirred vigorously at rt for 4 h. No starting material remained by TLC (2:1 petroleum ether–EtOAc) detection. CH_2Cl_2 (30 mL) was added to dilute the mixture. Filtration and concentration of the filtrate gave a syrup, which was purified by column chromatography (2:1 petroleum ether–EtOAc) to yield the title compound **2** (5.6 g, 88%). Further purification by column chromatography (2:1 petroleum ether–EtOAc) gave the R and S isomers as crystals. For R isomer: mp 91–92 °C; $[\alpha]_D^{20} + 70.5°$ (*c* 1.1, $CHCCl_3$); ^{1}H NMR: δ 7.56–7.32 (m, 5 H, Ph–H), 5.53 (s, 1 H, PhC*H*), 5.46 (d, 1 H, $J_{1,2}$ 4.2 Hz, H-1), 5.15 (q, 1 H, *J* 4.4 Hz, CH_3CH), 4.38 (dd, 1 H, $J_{1,2}$ 4.2 Hz, $J_{2,3}$ 9.2 Hz, H-2), 4.04–3.88 (m, 3 H, H-4, 6), 3.68 (t,

1 H, *J* 9.2 Hz, H-3), 3.60–3.45 (m, 1 H, H-5), 1.48 (d, 3 H, *J* 4.4 Hz, C*H*$_3$CH); For S isomer: mp 112–114 °C; $[\alpha]_D^{20}$ + 74.5° (*c* 1.0, $CHCCl_3$); ^{1}H NMR: δ 5.51 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.45 (q, 1 H, *J* 4.6 Hz, CH_3CH), 4.35 (dd, 1 H, $J_{1,2}$ 4.0 Hz, $J_{2,3}$ 9.8 Hz, H-2), 4.22 (t, 1 H, *J* 6.0 Hz, H-4), 3.96 (dd, 1 H, $J_{2,3}$ 9.8 Hz, $J_{3,4}$ 6.0 Hz, H-3), 3.50 (t, *J* 9.8 Hz, H-5), 1.40 (d, 3 H, *J* 4.6 Hz, C*H*$_3$CH). Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.22; H, 6.16. Found: C, 61.37; H, 6.21.

3-O-*(2,3,4,6-Tetra*-O-*acetyl-β*-D-*glucopyranosyl)-4,6*-O-*benzylidene-1,2*-O-*(*R,S*)-ethylidene*-α-D-*glucopyranose* (**3**).—A solution of 'acetobromoglucose' (6.15 g, 15 mmol), **2** (2.95 g, 10 mmol), and 4Å activated molecular sieves (1.5 g) in anhyd CH_2Cl_2 (40 mL) was stirred under N_2 for 1 h at rt and then cooled to − 5 °C. A solution of silver triflate (3.85 g, 15 mmol) and 2,4-lutidine (1 mL, 8.7 mmol) in 1:1 anhyd CH_2Cl_2–toluene (15 mL) was added dropwise with stirring for 30 min under N_2 (to ensure anhydrous conditions). The mixture was stirred for 4 h; TLC (2:1 petroleum ether–EtOAc) showed the presence of one major product. The reaction was quenched with 4 mL of pyridine and 20 mL of 10% aq $Na_2S_2O_3$, the mixture was filtered through Celite, and the solid was washed with CH_2Cl_2 (40 mL). The filtrate was washed sequentially with N HCl (50 mL), satd aq $NaHCO_3$ (50 mL), and satd aq NaCl (50 mL). The aqueous washings were re-extracted with CH_2Cl_2 (30 mL), the combined organic solutions were dried and concentrated, and the residue was subjected to flash chromatography with 2:1 petroleum ether–EtOAc as the eluent to give **3** (5.4 g, 87%) as a syrup. Further purification by column chromatography (2:1 petroleum ether–EtOAc) gave the R and S isomers as crystals. For R isomer: mp 119–120 °C; $[\alpha]_D^{20}$ − 45.4° (*c* 1.6, $CHCl_3$); ^{1}H NMR: δ 7.31–7.12 (m, 5 H, Ph–H), 5.58 (s, 1 H, PhC*H*), 5.48 (d, 1 H, $J_{1,2}$ 5.1 Hz, H-1), 5.44–4.72 (m, 4 H, H-2′, 3′, 4′, CH_3CH), 4.70 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1′), 4.37 (dd, 1 H, $J_{1,2}$ 5.1 Hz, $J_{2,3}$ 10.0 Hz, H-2), 4.20–3.50 (m, 8 H, H-3, 4, 5, 5′, 6, 6′), 2.09, 2.06, 2.03, 2.01 (4 s, 12 H, 4 C*H*$_3$CO), 1.50 (d, 3 H, *J* 5.1 Hz, C*H*$_3$CH). For S isomer: mp 128–130 °C; $[\alpha]_D^{20}$ + 66.8° (*c* 1.7, $CHCl_3$); ^{1}H NMR: δ 5.50 (d, 1 H, $J_{1,2}$ 4.9 Hz, H-1), 5.45 (q, 1 H, *J* 5.3 Hz, CH_3CH), 4.76 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1′), 1.41 (d, 3 H, *J* 5.3 Hz, C*H*$_3$CH). Anal. Calcd for $C_{29}H_{36}O_{15}$: C, 55.77; H, 5.81. Found: C, 55.71; H, 5.90.

3-O-*(2,3,4,6-Tetra*-O-*acetyl-β*-D-*glucopyranosyl)-1,2*-O-*(*R,S*)-ethylidene*-α-D-*glucopyranose* (**4**).—Compound **3** (5 g, 8 mmol) was dissolved in AcOH (30 mL) and treated with 4:1 $Cl_2CHCOOH$–H_2O (2.5 mL) at rt for 6 h, after which TLC (1:1 petroleum ether–EtOAc) indicated that the reaction was complete. The reaction mixture was diluted with H_2O, extracted with CH_2Cl_2 (3 × 50 mL), and the organic phase was washed with satd aq Na_2CO_3 (3 × 50 mL) and H_2O (2 × 50 mL), dried, and concentrated to yield crude **4** (R,S) (3.9 g, 90%) as crystals. Further purification by column chromatography (1:1 petroleum ether–EtOAc) gave the R and S isomers as crystals. For R isomer: mp 139–140 °C; $[\alpha]_D^{20}$ + 45.0° (*c* 1.3, $CHCl_3$); ^{1}H NMR: δ 5.46 (d, 1 H, $J_{1,2}$ 5.0 Hz, H-1), 5.26 (t, 1 H, *J* 9.5 Hz, H-3), 5.15 (q, 1 H, *J* 4.9 Hz, CH_3CH), 5.03 (t, 2 H, *J* 9.5 Hz, H-2′, 4′), 4.65 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1′), 4.27 (d, 1 H, *J* 12.0 Hz, H-6′$_a$), 4.10 (dd, 1 H, $J_{1,2}$ 5.0 Hz, $J_{2,3}$ 6.4 Hz, H-2), 4.10 (d, 1 H, *J* 12.0 Hz, H-6′$_b$), 3.91–3.59 (m, 6 H, H-3, 4, 5, 5′, 6), 2.10, 2.08, 2.05, 2.02 (4 s, 12 H, 4 C*H*$_3$CO), 1.46 (d, 3 H, *J* 4.9 Hz, C*H*$_3$CH); For S isomer: mp 170–171 °C; $[\alpha]_D^{20}$ + 50.3° (*c* 1.4, $CHCl_3$); ^{1}H NMR: δ 5.50 (d, 1 H, $J_{1,2}$ 4.7 Hz, H-1), 5.42 (q, 1 H, *J* 4.7 Hz, CH_3CH), 4.62 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1′), 1.38 (d, 3 H, *J* 4.7 Hz, C*H*$_3$CH). Anal. Calcd for $C_{22}H_{32}O_{15}$: C, 49.25; H, 6.01. Found: C, 49.11; H, 6.01.

3-O-*(2,3,4,6-Tetra*-O-*acetyl-β*-D-*glucopyranosyl)-1,2*-O-*(*R,S*)-ethylidene-6*-O-*trityl-α*-D-*glucopyranose* (**5**).—According to a reported method [12], to a solution of **4** (3.2 g, 6 mmol) in pyridine (15 mL) was added triphenylmethyl chloride (4.2 g, 2.5 equiv), and the mixture was stirred for 48 h at rt. TLC (2:1 petroleum ether–EtOAc) showed the starting material had disappeared. The reaction mixture was poured into ice-water (50 mL) and allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the organic phase was washed sequentially with 5% aq AcOH (3 × 30 mL), satd aq Na_2CO_3 (30 mL), and H_2O (30 mL).

The solution was dried and concentrated to a syrup, which was subjected to column chromatography (2:1 petroleum ether–EtOAc) to yield **5** (4.4 g, 94%) as an R,S mixture. Further purification by column chromatography (3:1 petroleum ether–EtOAc) gave the R and S isomers as syrups. For R isomer: $[\alpha]_D^{20}$ + 55.4° (*c* 1.7, $CHCl_3$); ^{1}H NMR: δ 7.50–7.19 (m, 15 H, Ph–H), 5.54 (d, 1 H, $J_{1,2}$ 4.2 Hz, H-1), 5.26 (t, 1 H, *J* 9.2 Hz, H-3′), 5.17 (q, 1 H *J* 4.0 Hz, CH_3CH), 5.04 (t, 1 H, *J* 9.2 Hz, H-2′), 5.00 (t, 1 H, *J* 9.6 Hz, H-4′), 4.62 (d, 1 H, $J_{1',2'}$ 8.2 Hz, H-1′), 4.25–4.06 (m, 3 H, H-2, 6′), 3.90–3.26 (m, 6 H, H-3, 4, 5, 5′, 6), 2.08, 2.04, 2.01, 1.92 (s, 12 H, 4 CH_3CO), 1.42 (d, 3 H, *J* 4.0 Hz, CH_3CH); For S isomer: $[\alpha]_D^{20}$ + 61.4° (*c* 1.5, $CHCl_3$); ^{1}H NMR: δ 5.66 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.43 (q, 1 H *J* 4.3 Hz, CH_3CH), 4.62 (d, 1 H, *J* 8.0 Hz, H-1′), 1.37 (d, 3 H, *J* 4.3 Hz, CH_3CH). Anal. Calcd for $C_{41}H_{46}O_{15}$: C, 63.23; H, 5.95. Found: C, 63.51; H, 6.02.

4-O-*Acetyl-3*-O-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-1,2*-O-*(*R,S*)-ethylidene-6*-O-*trityl-α*-D-*glucopyranose* (**6**).—Compound **5** (4 g, 5.1 mmol) was dissolved in pyridine (dry, 5 mL) and the solution was cooled to 0 °C. Ac_2O (3 mL) was added and the solution was stirred at rt for 4 h. The reaction mixture was treated as described for the preparation of **5**. Further purification by column chromatography (3:1 petroleum ether–EtOAc) gave the R and S isomers as syrups. For R isomer: $[\alpha]_D^{20}$ + 58.6° (*c* 1.1, $CHCl_3$); ^{1}H NMR: δ 7.44–7.20 (m, 15 H, Ph–H), 5.64 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-1), 5.29 (dd, 1 H, $J_{3,4}$ 3.0 Hz, $J_{4,5}$ 9.7 Hz, H-4), 5.24 (t, 1 H, *J* 9.1 Hz, H-3′), 5.09 (q, 1 H, *J* 4.8 Hz, CH_3CH), 5.05 (t, 1 H, *J* 9.1 Hz, H-2′), 5.00 (t, 1 H, *J* 9.1 Hz, H-4′), 4.86 (d, 1 H, *J* 7.5 Hz, H-1′), 4.24–3.72 (m, 6 H, H-2, 3, 5, 5′, 6′), 3.30 (dd, 1 H, $J_{5,6a}$ 4.3 Hz, $J_{6a,6b}$ 10.5 Hz, H-6_a), 3.10 (dd, $J_{5,6b}$ 4.3 Hz, $J_{6a,6b}$ 10.5 Hz, H-6_b), 2.04, 2.02, 2.02, 1.96, 1.89 (s, 15 H, 5 CH_3CO), 1.48 (d, *J* 4.8 Hz, CH_3CH); For S isomer: $[\alpha]_D^{20}$ + 71.1° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 5.67 (d, 1 H, $J_{1,2}$ 4.6 Hz, H-1), 5.53 (q, 1 H, *J* 4.9 Hz, CH_3CH), 4.79 (d, 1 H, *J* 7.6 Hz, H-1′), 1.39 (d, *J* 4.9 Hz, CH_3CH). Anal. Calcd for $C_{43}H_{48}O_{16}$: C, 62.92; H, 5.89. Found: C, 63.21; H, 5.78.

4-O-*Acetyl-3*-O-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-1,2*-O-*(*R,S*)-ethylidene-α*-D-*glucopyranose* (**7**).—To a solution of **5** (4 g, 4.9 mmol) in CH_2Cl_2 (50 mL) was added solid $FeCl_3 \cdot 6H_2O$ (2.7 g, 2 equiv). The mixture was stirred at rt for 5 h, at the end of which time the reaction was complete as indicated by TLC (2:1 petroleum ether–EtOAc). Water was added, and the mixture was diluted with CH_2Cl_2. The organic layers were combined, dried, and concentrated to give **7** (2.4 g, 83%) as a syrup. Further purification by column chromatography (2:1 petroleum ether–EtOAc) gave the R and S isomers as crystals. For R isomer: mp 96–98 °C; $[\alpha]_D^{20}$ + 40.1° (*c* 2.0, $CHCl_3$); ^{1}H NMR: δ 5.57 (d, 1 H, $J_{1,2}$ 5.1 Hz, H-1), 5.22 (dd, 1 H, $J_{3,4}$ 2.3 Hz, $J_{4,5}$ 9.1 Hz, H-4), 5.21 (t, 1 H, *J* 9.2 Hz, H-3′), 5.11 (q, 1 H, *J* 5.4 Hz, CH_3CH), 5.08 (t, 1 H, *J* 9.2 Hz, H-2′), 4.98 (t, 1 H, *J* 9.2 Hz, H-4′), 4.83 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1′), 4.24–3.80 (m, 6 H, H-2, 3, 5, 5′, 6′), 3.75 (dd, 1 H, $J_{5,6a}$ 5.1 Hz, $J_{6a,6b}$ 12.4 Hz, H-6_a), 3.62 (dd, 1 H, $J_{5,6b}$ 5.1 Hz, $J_{6a,6b}$ 12.4 Hz, H-6_b), 2.13, 2.10, 2.07, 2.05, 2.03 (s, 15 H, 5 CH_3CO), 1.49 (d, 3 H, *J* 5.4 Hz, CH_3CH); For S isomer: mp 110–112 °C; $[\alpha]_D^{20}$ + 47.4° (*c* 2.1, $CHCl_3$); ^{1}H NMR: δ 5.59 (q, 1 H, *J* 5.2 Hz, CH_3CH), 5.58 (d, 1 H, $J_{1,2}$ 5.1 Hz, H-1), 4.84 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1′), 1.37 (d, 3 H, *J* 5.2 Hz, CH_3CH). Anal. Calcd for $C_{24}H_{34}O_{16}$: C, 49.83; H, 5.92. Found: C, 49.71; H, 5.98.

3,4-Di-O-*acetyl-6*-O-*chloroacetyl-α*-D-*glucopyranose 1,2-(3*-O-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-1,2*-O-*(*R,S*)-ethylidene-α*-D-*glucopyranosid-6-yl orthoacetate)* (**8**).—To a stirred mixture of **4** (1.07 g, 2.0 mmol), 6-*O*-chloroacetylated 'acetobromoglucose' (1.07 g, 2.4 mmol), 2,4-lutidine (270 μL, 2.4 mmol), and 4Å molecular sieves (2 g) in CH_2Cl_2 (dry, 30 mL) was added silver triflate (0.617 g, 2.4 mmol) under a nitrogen atmosphere in a dark room. The reaction was carried out at rt and monitored by TLC (1:1 petroleum ether–EtOAc). After completion of the reaction, the mixture was partitioned between CH_2Cl_2 (40 mL) and H_2O (40 mL) and the organic phase was washed with 10% aq $Na_2S_2O_3$ (20 mL) and aq NaCl (30 mL) and concentrated under reduced pressure. The residual oil was purified by column chromatography with 1:1 petro-

leum ether–EtOAc as the eluent giving the product **8** (R,S) as an amorphous solid in 94% yield (1.7 g); this crude product could be used directly for further rearrangement. Further purification of **8** by HPLC (1:1 petroleum ether–EtOAc) gave the R and S isomers as crystals. For R isomer: mp 74–75 °C; $[\alpha]_D^{20}$ − 3.5° (*c* 1.1, $CHCl_3$); ^{1}H NMR: δ 5.72 (d, 1 H, $J_{1,2}$ 5.8 Hz, H-1_C), 5.57 (q, 1 H, *J* 5.2 Hz, CH_3CH), 5.53 (d, 1 H, $J_{1,2}$ 5.2 Hz, H-1_A), 4.68 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1_B), 4.13 (s, 2 H, CH_2ClCO), 2.13–2.04 (6 s, 18 H, 6 CH_3CO), 1.75 (s, 3 H, CH_3CO_3), 1.48 (d, 3 H, *J* 5.2 Hz, CH_3CH); For S isomer: mp 70–72 °C; $[\alpha]_D^{20}$ + 4.5° (*c* 1.5, $CHCl_3$); ^{1}H NMR: δ 5.73 (d, 1 H, $J_{1,2}$ 5.1 Hz, H-1_C), 5.51 (d, 1 H, $J_{1,2}$ 4.6 Hz, H-1_A), 5.42 (q, 1 H, *J* 4.6 Hz, CH_3CH), 4.66 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1_B), 4.10 (s, 2 H, CH_2ClCO), 1.39 (d, 3 H, *J* 4.6 Hz, CH_3CH). Anal. Calcd for $C_{36}H_{49}O_{24}Cl$: C, 47.98; H, 5.48. Found: C, 47.82; H, 5.44.

3,4,6-Tri-O-*acetyl*-α-D-*glucopyranose 1,2-(3*-O-*(2,3,4,6-tetra*-O-*acetyl*-β-D-*glucopyranosyl)-1,2*-O-*(*R,S*)-ethylidene*-α-D-*glucopyranosid-6-yl orthoacetate)* (**9**).—As described in the preparation of **8**, the coupling of compound **4** (1.0 g, 1.9 mmol) with 'acetobromoglucose' (0.94 g, 2.3 mmol) was carried out in the presence of silver triflate (590 mg, 2.3 mmol) and lutidine (265 μL, 2.3 mmol) to furnish **9** (R,S) (1.58 g, 96%) as an amorphous solid. Further purification by HPLC (1:1 petroleum ether–EtOAc) gave the R and S isomers as crystals. For R isomer: mp 67–68 °C; $[\alpha]_D^{20}$ + 43.7° (*c* 1.3, $CHCl_3$); ^{1}H NMR: δ 5.73 (d, 1 H, $J_{1,2}$ 5.1 Hz, H-1_F), 5.49 (d, 1 H, $J_{1,2}$ 4.9 Hz, H-1_D), 5.40 (q, 1 H, *J* 4.9 Hz, CH_3CH), 4.64 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1_E), 2.11–2.03 (7 s, 21 H, 7 CH_3CO), 1.74 (s, 3 H, CH_3CO_3), 1.36 (d, 3 H, *J* 4.9 Hz, CH_3CH); For S isomer: mp 78–80 °C; $[\alpha]_D^{20}$ + 49.3° (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 5.74 (d, 1 H, $J_{1,2}$ 5.1 Hz, H-1_F), 5.50 (d, 1 H, $J_{1,2}$ 4.7 Hz, H-1_D), 5.41 (q, 1 H, *J* 4.9 Hz, CH_3CH), 4.63 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1_E), 1.35 (d, 3 H, *J* 4.9 Hz, CH_3CH). Anal. Calcd for $C_{36}H_{50}O_{24}$: C, 49.89; H, 5.81. Found: C, 50.08; H, 5.70.

3-O-*(2,3,4,6-Tetra*-O-*acetyl*-β-D-*glucopyranosyl)-6*-O-*(2,3,4-tri*-O-*acetyl-6*-O-*chloroacetyl*-β-D-*glucopyranosyl)-1,2*-O-*(*R,S*)-ethylidene*-α-D-*glucopyranose* (**10**).—To a stirred mixture of **8** (720 mg, 0.80 mmol) and 4Å molecular sieves (0.5 g) in CH_2Cl_2 (dry, 20 mL) was added TMSOTf (14 μL, 0.1 equiv) at 0 °C under a nitrogen atmosphere. The reaction was monitored by TLC (1:1 petroleum ether–EtOAc). After completion of the reaction, triethylamine (15 μL) was added to the mixture and the reaction was allowed to warm to rt. The mixture was filtered and the filtrate was treated with N HCl (20 mL), satd aq Na_2CO_3 (20 mL), and H_2O (20 mL), dried, and concentrated. The residue was subjected to column chromatography with 1:1 petroleum ether–EtOAc as the eluent, giving product **10** (R,S) as a syrup in 72% yield (518 mg). Further purification by HPLC (1:1 petroleum ether–EtOAc) gave the R and S isomers as syrups. For R isomer: $[\alpha]_D^{20}$ − 8.3° (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 5.50 (d, 1 H, $J_{1,2}$ 4.7 Hz, H-1_A), 5.20 (q, 1 H, *J* 4.7 Hz, CH_3CH), 4.80 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1_C), 4.64 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1_B), 4.11 (s, 2 H, CH_2ClCO), 2.07–1.99 (7 s, 21 H, 7 CH_3CO), 1.47 (d, 3 H, *J* 4.7 Hz, CH_3CH); For S isomer: $[\alpha]_D^{20}$ + 3.8° (*c* 0.8, $CHCl_3$); ^{1}H NMR: δ 5.62 (d, 1 H, $J_{1,2}$ 4.4 Hz, H-1_A), 5.50 (q, 1 H, *J* 4.4 Hz, CH_3CH), 4.79 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1_C), 4.55 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1_B), 1.35 (d, 3 H, *J* 4.4 Hz, CH_3CH). Anal. Calcd for $C_{36}H_{49}O_{24}Cl$: C, 47.98; H, 5.48. Found: C, 47.73; H, 5.31.

3,6-Di-O-*(2,3,4,6-tetra*-O-*acetyl*-β-D-*glucopyranosyl)-1,2*-O-*(*R,S*)-ethylidene*-α-D-*glucopyranose* (**11**).—As described for the preparation of **10**, the rearrangement of **9** (780 mg, 0.9 mmol) with TMSOTf (0.1 equiv) in dry CH_2Cl_2 at 0 °C afforded **11** (R,S) in 76% yield (592 mg). Further purification by HPLC (1:1 petroleum ether–EtOAc) gave the R and S isomers as crystals. For R isomer: mp 87–88 °C; $[\alpha]_D^{20}$ − 2.3° (*c* 0.8, $CHCl_3$); ^{1}H NMR: δ 5.56 (d, 1 H, $J_{1,2}$ 5.0 Hz, H-1_D), 5.21 (q, 1 H, *J* 5.2 Hz, CH_3CH), 4.90 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1_F), 4.73 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1_E), 2.15–2.00 (8 s, 24 H, 8 CH_3CO), 1.48 (d, 3 H, *J* 5.2 Hz, CH_3CH); For S isomer: mp 77–78 °C; $[\alpha]_D^{20}$ + 1.7° (*c* 0.4, $CHCl_3$); ^{1}H NMR: δ 5.63 (q, 1 H, *J* 5.5 Hz, CH_3CH), 5.51 (d, 1 H, $J_{1,2}$ 5.1 Hz, H-1_D), 4.85 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1_F), 4.72 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1_E), 1.32 (d, 3 H, *J* 5.5 Hz, CH_3CH). Anal. Calcd for $C_{36}H_{50}O_{24}$: C, 49.89; H, 5.81. Found: C, 49.76; H, 5.92.

4-O-*Acetyl-3*-O-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-6*-O-*(2,3,4-tri*-O-*acetyl-6*-O-*chloroacetyl-β*-D-*glucopyranosyl)-1,2*-O-*(*R,S*)-ethylidene-α*-D-*glucopyranose* (**12**)

Method A. To a stirred solution of **10** (480 mg) in pyridine (1 mL) was added Ac_2O (0.5 mL) dropwise at 0 °C, and the reaction was continued for 2 h. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was washed with N HCl (10 mL), satd aq Na_2CO_3 (10 mL) and H_2O (10 mL), dried, and concentrated. The residue was purified by column chromatography (1:1 petroleum ether–EtOAc) to furnish **12** (R,S) (450 mg, 90%).

Method B. To a mixture of **7** (580 mg, 1.0 mmol), 6-*O*-chloroacetylated 'acetobromoglucose' (504 mg, 1.2 mmol), 2,4-lutidine (80 μL, 0.69 mmol), and 4Å molecular sieves (0.5 g) in CH_2Cl_2 (dry, 20 mL) was added silver triflate (308 mg, 1.2 mmol) under a nitrogen atmosphere in a dark room at −5 °C. The reaction was carried out at −5 °C and monitored by TLC (1:1 petroleum ether–EtOAc). After completion of the reaction, pyridine (3 mL) and 10% aq $Na_2S_2O_3$ (20 mL) were added and to the mixture, the mixture was filtered, and the solid was washed with CH_2Cl_2 (20 mL). The filtrate was treated as for the preparation of **3** to furnish **12** (R,S) in 80% yield (750 mg). Further purification by HPLC (1:1 petroleum ether–EtOAc) gave the R and S isomers as syrups. For R isomer: $[\alpha]_D^{20}$ −11.2° (*c* 0.5, $CHCl_3$); ^{1}H NMR: δ 5.52 (d, 1 H, $J_{1,2}$ 4.8 Hz, H-1_A), 5.30–4.88 (m, 8 H, H-2_B, 2_C, 3_B, 3_C, 4_A, 4_B, 4_C, CH_3CH), 4.80 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1_C), 4.66 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1_B), 4.44–3.56 (m, 11 H, H-2_A, 3_A, 5_A, 5_B, 5_C, 6_A, 6_B, 6_C), 4.11 (s, 2 H, CH_2ClCO), 2.08, 2.07, 2.07, 2.03, 2.02, 2.01, 2.01, 1.99 (8 s, 24 H, 8 CH_3CO), 1.43 (d, 3 H, *J* 4.8 Hz, CH_3CH); For S isomer: $[\alpha]_D^{20}$ + 5.5° (*c* 0.7, $CHCl_3$); ^{1}H NMR: δ 5.61 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-1_A), 5.49 (q, 1 H, *J* 4.4 Hz, CH_3CH), 4.77 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1_C), 4.53 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1_B), 1.35 (d, 3 H, *J* 4.4 Hz, CH_3CH). Anal. Calcd for $C_{38}H_{51}O_{25}Cl$: C, 48.39; H, 5.45. Found: C, 48.16; H, 5.31.

4-O-*Acetyl-3,6-di*-O-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-1,2*-O-*(*R,S*)-ethylidene-α*-D-*glucopyranose* (**13**)

Method A. Acetylation of **11** (480 mg) with Ac_2O/pyridine at rt for 2 h furnished **13** (500 mg) in quantitative yield.

Method B. Under the same conditions as described for the preparation of **12**, the coupling of **7** (580 mg, 1 mmol) and 'acetobromoglucose' (492 mg, 1.2 mmol) furnished **13** (R,S) as an amorphous solid in 85% yield (770 mg). Further purification by HPLC (1:1 petroleum ether–EtOAc) gave the R and S isomers as syrups. For R isomer: $[\alpha]_D^{20}$ −0.9° (*c* 0.5, $CHCl_3$); ^{1}H NMR: δ 5.50 (d, 1 H, $J_{1,2}$ 4.8 Hz, H-1_D), 5.25–5.15 (m, 2 H, H-4_D, CH_3CH), 5.12–4.93 (m, 6 H, H-2_E, 2_F, 3_E, 3_F, 4_E, 4_F), 4.80 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1_F), 4.63 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1_E), 4.28–3.60 (m, 12 H, H-2_D, 3_D, 4_D, 5_D, 5_E, 5_F, 6_D, 6_E, 6_F), 2.08, 2.07, 2.07, 2.06, 2.04, 2.02, 2.02, 2.00, 2.00 (9 s, 27 H, 9 CH_3CO), 1.45 (d, 3 H, *J* 4.8 Hz, CH_3CH); For S isomer: $[\alpha]_D^{20}$ + 27.5° (*c* 0.3, $CHCl_3$); ^{1}H NMR: δ 5.63 (d, 1 H, $J_{1,2}$ 4.4 Hz, H-1_D), 5.50 (q, 1 H, *J* 4.7 Hz, CH_3CH), 4.81 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1_F), 4.54 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1_E), 1.36 (d, 3 H, *J* 4.7 Hz, CH_3CH). Anal. Calcd for $C_{38}H_{52}O_{25}$: C, 50.22; H, 5.77. Found: C, 50.48; H, 5.58.

3,6-Di-O-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-1,2,4-tri*-O-*acetyl-α,β*-D-*glucopyranose* (**15**).—Compound **13** (481 mg, 0.53 mmol) was treated with 90% F_3CCOOH (3 mL) at rt for 1 h, and the solution was concentrated and co-concentrated with toluene. The residue was dissolved in pyridine (5 mL) and treated with Ac_2O (3 mL) for 2 h. After conventional work-up, the residue was subjected to column chromatography (1:1 petroleum ether–EtOAc) to yield the title compound **15** as a syrupy mixture of α and β anomers in a 2:1 ratio (358 mg, 70%); $[\alpha]_D^{20}$ −1.9° (*c* 1.1, $CHCl_3$); ^{1}H NMR: δ 6.21 (d, 2/3 H, $J_{1,2}$ 3.8 Hz, H-$1_{D\alpha}$), 5.59 (d, 1/3 H, $J_{1,2}$ 7.8 Hz, H-$1_{D\beta}$), 5.21–4.80 (m, 7 H, H-2_D, 2_E, 2_F, 3_E, 3_F, 4_E, 4_F), 4.65 (d, 2/3 H, $J_{1,2}$ 8.4 Hz, H-$1_{F\alpha}$), 4.60 (d, 1/3 H, $J_{1,2}$ 8.4 Hz, H-$1_{F\beta}$), 4.56 (d, 1/3 H, $J_{1,2}$ 8.4 Hz, H-$1_{E\beta}$), 4.50 (d, 2/3 H, $J_{1,2}$ 8.4 Hz, H-$1_{E\alpha}$), 4.46–3.40 (m, 11 H, H-3_D, 4_D, 5_D, 5_E, 5_F, 6_D, 6_E, 6_F), 2.19–1.97 (m, 33 H, 11 CH_3CO). Anal. Calcd for $C_{40}H_{54}O_{27}$: C, 49.69; H, 5.63. Found: C, 49.44; H, 5.78.

2,4-Di-O-*acetyl-3,6-di*-O-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-α,β*-D-*glucopyranose* (**16**).—To a stirred solution of **15** (242 mg, 0.25 mmol) in DMF (dry, 1 mL) was added hydrazine acetate (24 mg, 0.26 mmol). Stirring was maintained at rt for 50 min. The mixture was poured into H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Combined extracts were washed with H_2O (3 × 10 mL), dried, and concentrated to give **16** (226 mg, 98%) as a syrupy anomeric mixture (α/β, 1:3) after column chromatography (1:1 petroleum ether–EtOAc); $[\alpha]_D^{20}$ + 3.8° (*c* 1.1, $CHCl_3$); ^{1}H NMR: δ 5.37 (d, 1/4 H, $J_{1,2}$ 3.8 Hz, H-$1_{D\alpha}$), 5.35 (d, 3/4 H, $J_{1,2}$ 3.6 Hz, H-$1_{D\beta}$), 5.22 (t, 1 H, *J* 9.6 Hz, H-4_D), 5.13–4.78 (m, 7 H, H-2_D, 2_E, 2_F, 3_E, 3_F, 4_E, 4_F), 4.67 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1_F), 4.56 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1_E), 4.34–3.58 (m, 10 H, H-3_D, 5_D, 5_E, 5_F, 6_D, 6_E, 6_F), 2.10–1.98 (m, 30 H, 10 CH_3CO). Anal. Calcd for $C_{38}H_{52}O_{26}$: C, 49.35; H, 5.67. Found: C, 49.12; H, 5.78.

2,4-Di-O-*acetyl-3,6-di*-O-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-α*-D-*glucopyranosyl trichloroacetimidate* (**17**).—Trichloroacetonitrile (Cl_3CCN, 69 μL, 3 equiv) and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU, 9 μL, 0.25 equiv) were added to a solution of **16** (203 mg, 0.22 mmol) in anhyd CH_2Cl_2 (10 mL), and the mixture was stirred at 0 °C for 1 h, at the end of which time TLC showed the starting material had disappeared. The solvents were evaporated, and flash chromatography (1:1 EtOAc–petroleum ether) of the residue gave the trisaccharide donor **17** (188 mg, 80%), which was used directly in the glycosylation reaction. ^{1}H NMR ($CDCl_3$): δ 8.50 (bs, 1 H, N*H*), 6.53 (bs, 1 H, H-1_D), 5.30 (t, 1 H, *J* 9.6 Hz, H-4_D), 5.26–4.67 (m, 7 H, H-2_D, 2_E, 2_F, 3_E, 3_F, 4_E, 4_F), 4.69 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1_F), 4.55 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1_E), 4.50–3.48 (m, 10 H, H-3_D, 5_D, 5_E, 5_F, 6_D, 6_E, 6_F), 2.09, 2.09, 2.07, 2.06, 2.06, 2.05, 2.02, 2.01, 2.01, 1.99 (10 s, 30 H, 10 CH_3CO).

4-O-*Acetyl-3*-O-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-6*-O-*(2,3,4-tri*-O-*acetyl-β*-D-*glucopyranosyl)-1,2*-O-*(*R,S*)-ethylidene-α*-D-*glucopyranose* (**18**).—Compound **12** (280 mg, 0.30 mmol) was dissolved in anhyd EtOH (20 mL), and thiourea (40 mg) was added. The mixture was heated at 90 °C for 1 h, at the end of which time TLC showed the starting material had disappeared. The reaction was cooled to rt, and the mixture extracted with CH_2Cl_2 (20 mL). The organic solution was washed with H_2O (20 mL) and concentrated, and the residue was subjected to column chromatography (1:1 petroleum ether–EtOAc) to yield the title compound **18** (193 mg, 74%). Further purification by HPLC (1:1 petroleum ether–EtOAc) gave the R and S isomers as crystals. For R isomer: mp 93–95 °C; $[\alpha]_D^{20}$ − 1.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 5.51 (d, 1 H, $J_{1,2}$ 4.7 Hz, H-1_A), 5.22–4.90 (m, 8 H, H-2_B, 2_C, 3_B, 3_C, 4_A, 4_B, 4_C, CH_3CH), 4.76 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1_C), 4.58 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1_B), 4.21–3.45 (m, 11 H, H-2_A, 3_A, 5_A, 5_B, 5_C, 6_A, 6_B, 6_C), 2.09, 2.07, 2.05, 2.03, 2.00, 1.96, 1.93, 1.91 (8 s, 8 CH_3CO), 1.41 (d, 3 H, *J* 5.1 Hz, CH_3CH); For S isomer: mp 87–90 °C; $[\alpha]_D^{20}$ + 12.6° (*c* 1.4, $CHCl_3$); ^{1}H NMR: δ 5.55 (d, 1 H, $J_{1,2}$ 4.6 Hz, H-1_A), 5.46 (q, 1 H, *J* 4.9 Hz, CH_3CH), 4.72 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1_C), 4.51 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1_B), 1.28 (d, 3 H, *J* 4.9 Hz, CH_3CH). Anal. Calcd for $C_{36}H_{50}O_{24}$: C, 49.89; H, 5.81. Found: C, 49.75; H, 5.81.

4-O-*Acetyl-3*-O-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-6*-O-*(2,3,4-tri*-O-*acetyl-6*-O-*(2,4-di*-O-*acetyl-3,6-di*-O-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-β*-D-*glucopyranosyl)-β*-D-*glucopyranosyl)-1,2*-O-*(*R,S*)-ethylidene-α*-D-*glucopyranose* (**19**).—A mixture of compound **17** (50 mg, 0.047 mmol) and **18** (41 mg, 0.047 mmol) in anhyd CH_2Cl_2 (10 mL) under N_2 was stirred with activated 4Å molecular sieves for 1 h at rt. The mixture was cooled to − 78 °C and TMSOTf (0.8 μL, 0.1 equiv) in anhyd CH_2Cl_2 (1 mL) was added dropwise. The mixture was stirred at − 30 °C for 30 min, at the end of which time TLC (1:1.5 petroleum ether–EtOAc) indicated that the reaction was complete. The reaction mixture was neutralized with Et_3N (0.1 mL), filtered through Celite, and the filtrate was concentrated. The residue was purified by column chromatography with 1:1.5 petroleum ether–EtOAc as the eluent to yield **19** (R,S) as an amorphous solid (56 mg, 68%). Further purification of **19** (R,S) by HPLC with 1:1.5 petroleum ether–EtOAc as the eluent furnished the R and S isomers. For R isomer: mp

97–100 °C, $[\alpha]_D^{20} - 8.6°$ (*c* 0.5, $CHCl_3$); ^1H NMR: δ 5.51 (d, 1 H, $J_{1,2}$ 4.1 Hz, H-1_A), 5.25–4.83 (m, 16 H, H-2_B, 2_C, 2_D, 2_E, 2_F, 3_B, 3_C, 3_E, 3_F, 4_A, 4_B, 4_C, 4_D, 4_E, 4_F, CH_3CH), 4.80, 4.73, 4.62, 4.58, 4.56 (5 d, 5 H, $J_{1,2}$ 8.2 Hz, H-1_B, 1_C, 1_D, 1_E, 1_F), 4.33–3.41 (m, 21 H, H-2_A, 3_A, 3_C, 5_A, 5_B, 5_C, 5_D, 5_E, 5_F, 6_A, 6_B, 6_C, 6_D, 6_E, 6_F), 2.13–1.93 (m, 54 H, 18 CH_3CO), 1.47 (d, 3 H, *J* 4.9 Hz, CH_3CH); For S isomer: mp 102–103 °C; $[\alpha]_D^{20} + 15.9°$ (*c* 0.9, $CHCl_3$); ^1H NMR: δ 5.54 (d, 1 H, $J_{1,2}$ 4.6 Hz, H-1_A), 5.45 (q, 1 H, *J* 4.4 Hz, CH_3CH), 4.74, 4.67, 4.60, 4.55, 4.49 (5 d, 5 H, $J_{1,2}$ 8.2 Hz, H-1_B, 1_C, 1_D, 1_E, 1_F), 1.23 (d, 3 H, *J* 4.4 Hz, CH_3CH). Anal. Calcd for $C_{74}H_{100}O_{49}$: C, 50.11; H, 5.68. Found: C, 50.04; H, 5.76.

*1,2,4-Tri-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-6-*O*-(2,3,4-tri-*O*-acetyl-6-*O*-(2,4-di-*O*-acetyl-3,6-di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-β-*D*-glucopyranosyl)-β-*D*-glucopyranosyl)-α,β-*D*-glucopyranose* (**21**).—As described in the preparation of **15**, compound **19** (42 mg, 0.023 mmol) was treated with 90% F_3CCOOH (1.5 mL) at rt for 1.5 h and the mixture was concentrated and co-concentrated with toluene. The residue was dissolved in pyridine (1 mL) and treated with Ac_2O (0.5 mL) for 2 h. After conventional work-up, the residue was subjected to column chromatography (1:1.5 petroleum ether–EtOAc) to yield the title compound **21** (α/β, 2:1) (30 mg, 72%) as an amorphous solid; mp 108–111 °C; $[\alpha]_D^{20} + 16.0°$ (*c* 0.5, $CHCl_3$); ^1H NMR: δ 6.13 (d, 2/3 H, $J_{1,2}$ 3.1 Hz, H-$1_{A\alpha}$), 5.50 (d, 1/3 H, $J_{1,2}$ 9.3 Hz, H-$1_{A\beta}$), 5.47–5.13 (m, 16 H, H-2_A, 2_B, 2_C, 2_D, 2_E, 2_F, 3_B, 3_C, 3_E, 3_F, 4_A, 4_B, 4_C, 4_D, 4_E, 4_F), 4.85–4.45 (m, 5 H, $J_{1,2}$ 8.3 Hz, H-1_B, 1_C, 1_D, 1_E, 1_F), 4.40–3.35 (m, 20 H, H-3_A, 3_D, 5_A, 5_B, 5_C, 5_D, 5_E, 5_F, 6_A, 6_B, 6_C, 6_D, 6_E, 6_F), 2.04–1.88 (m, 60 H, 20 CH_3CO). Anal. Calcd for $C_{76}H_{102}O_{51}$: C, 49.84; H, 5.61. Found: C, 49.66; H, 5.51.

*3,4,6-Tri-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-1,2-*O*-(*R,S*)-ethylidene-α-*D*-glucopyranose* (**22**).—A solution of acetobromoglucose (410 g, 1.0 mmol), **4** (540 mg, 1.0 mmol), and 4Å activated molecular sieves (1 g) in anhyd CH_2Cl_2 (20 mL) was stirred under N_2 for 1 h at rt and then cooled to −5 °C. A solution of silver triflate (260 mg, 1.0 mmol) and 2,4-lutidine (0.1 mL, 0.87 mmol) in 1:1 anhyd CH_2Cl_2–toluene (5 mL) was added dropwise with stirring, over a 30 min period under N_2. The mixture was stirred for 4 h, at the end of which time TLC (2:1 petroleum ether–EtOAc) showed the presence of one major product and the disappearance of acetobromoglucose. The reaction was quenched with 0.4 mL pyridine and 4 mL 10% aq $Na_2S_2O_3$, the mixture was filtered through Celite, and the filtrate was handled as described for the preparation of **3** to yield the tetrasaccharide **22** (R,S) (361 mg, 30% based on **4**). After purification by column chromatography (1:1 petroleum ether–EtOAc) and by analytical LC (2:1 petroleum ether–EtOAc), the pure R and S isomers were obtained; ^1H NMR (R): δ 5.40 (d, 1 H, *J* 5.1 Hz, H-1), 5.28–4.93 (m, 10 H, H-2′, 2″, 2‴, 3′, 3″, 3‴, 4′, 4″, 4‴, CH_3CH), 4.84, 4.70, 4.68 (3 d, 3 H, *J* 7.9 Hz, H-1′, 1″, 1‴), 4.44–3.70 (m, 15 H, H-2, 3, 4, 5, 5′, 5″, 5‴, 6, 6′, 6″, 6‴), 2.08, 2.07, 2.05, 2.04, 2.04, 2.04, 2.03, 2.03, 2.03, 2.02, 2.01, 2.01 (12 s, 36 H, CH_3CO), 1.46 (d, 3 H, *J* 4.8 Hz, CH_3CH); (S): δ 5.56 (q, 1 H, *J* 4.1 Hz, CH_3CH), 5.44 (d, 1 H, *J* 5.1 Hz, H-1), 4.80, 4.65, 4.64 (3 d, 3 H, *J* 8.2 Hz, H-1′, 1″, 1‴), 1.37 (d, 3 H, *J* 4.1 Hz, CH_3CH).

*3-*O*-(β-*D*-Glucopyranosyl)-6-*O*-(6-*O*-(3,6-di-*O*-(β-*D*-glucopyranosyl)-β-*D*-glucopyranosyl)-β-*D*-glucopyranosyl)-α,β-*D*-glucopyranose* (**1**).—The protected hexasaccharide **21** (19 mg, 0.01 mmol) was suspended in freshly distilled MeOH (5 mL), a solution of sodium methoxide (2 M, 0.1 mL) was added, and the mixture was stirred overnight at rt. TLC showed that the reaction was complete. The resulting solution was de-ionized with Amberlite IR-120 (H^+) anion-exchange resin, filtered, and concentrated. The hexasaccharide **1** was obtained after chromatography on Sephadex G-25 (H_2O solvent) as an amorphous powder (9.5 mg, 96%) after freeze-drying; $[\alpha]_D^{20} - 14.9°$ (*c* 0.1, MeOH); ESMS for $C_{36}H_{62}O_{31}$ (990.86): 989.6 $[M-1]^+$.

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