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A 2,4-*O*-[(*Z*)-2-butenylene]-bridged glucopyranose: efficient construction of the bicyclic skeleton and its axial-rich twist-boat conformation

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ABSTRACT

Synthesis and conformational analyses of 1-*O*-acetyl-3,6-di-*O*-benzyl-2,4-*O*-[(*Z*)-2-butenylene]-β-D-glucopyranose are described. The construction of the trioxabicyclo[6.3.1]dodecane skeleton of the compound was initiated from a ring-opened glucose, followed by the successive cyclization of first the nine-membered ring and then the six-membered ring. The pyranose of the compound was in $^{3}S_{1}$, an axial-rich twist-boat conformation. This result demonstrated an alternative method for the restriction of the pyranose into the axial-rich twist-boat conformation in contrast to the procedures that use bulky silyl protecting groups.

1. Introduction

Conformation of a pyranose is generally in a chair form that has more equatorial substituents. Exceptions to this generality have sporadically occurred during synthetic studies to prove that the pyranose can stably attain an axial-rich conformer.[1] Intentional ring flips have also been investigated to control diastereoselectivity and reactivity in glycosidations and carbohydrate-related syntheses.[2] Recently, we have demonstrated the significance of twist-boat forms (e.g., **1**, Fig. 1)[3] in contrast to the initial concept of axial-rich conformation assuming the chair form.[4] As in **1**, steric hindrance due to bulky trialkylsilyl protecting groups has typically restricted the pyranose rings in the axial-rich sugars that have been used in glycosidations. Shoehorning the silyl groups into a tight space introduces these restrictions, and thus, vigorous reaction conditions are usually required.[5] Additionally, owing to the tensioned structure, a part of the silyl group easily migrates to another hydroxy group.[3b] To apply such conformational restriction without these disadvantages due to the silyl groups, further studies would be needed to look for alternative method for regulation of a pyranose into the axial-rich conformation, hopefully as a twist-boat structure.

Construction of a bridged structure would be a simple solution for the restriction of pyranoses.[6] In the common bridged sugars, 1,6-anhydro-β-D-glucopyranose (**2**) and 1,2,4-*O*-ethylidyne-α-

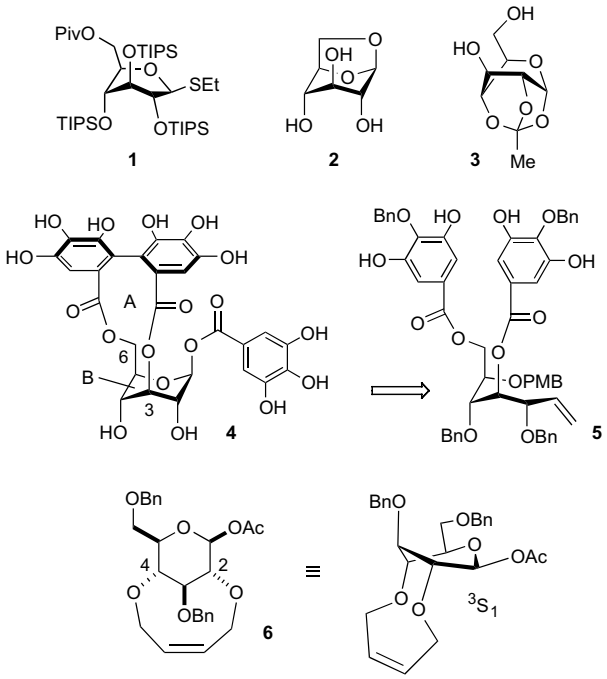

Figure 1.

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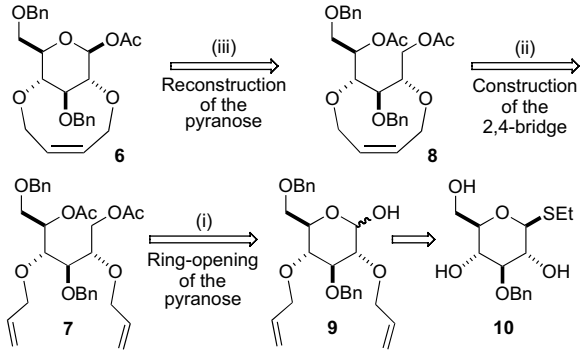
D-glucopyranose (**3**), the anomeric positions participate as one ends of the bridge, and thus, they have not been commonly used as glycosyl donors in glycosidation reactions. Therefore, new designs are needed for stable axial-rich twist-boat conformers with a removable bridge between discontiguous hydroxy groups at sites other than the anomeric position. The structure of corilagin (**4**),[7] a natural ellagitannin, is one of the solution to meet the requirements, because its pyranose ring is in a twist-boat or $^1C_4$ conformation.[8] Toward synthesis of the 3,6-*O*-bridged structure, we know that (1) the direct formation of the bridge involving ring flip of the pyranose into the contra-thermodynamic conformation is difficult, and (2) the stepwise construction of the two rings (A then B) was effective when starting from the acyclic synthetic intermediate (**5**).[9] We report herein that this synthetic strategy was successfully applied to a 2,4-*O*-bridged structure, ultimately affording the derivative of glucose **6**, a stable twisted-boat conformer (Fig. 1) possessing a removable (*Z*)-2-butenylene bridge.[10]

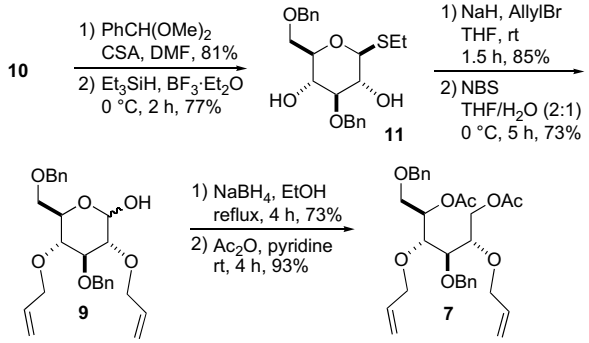
2. Results and discussion

The following steps achieved the bicyclic structure of **6**, that is, (i) ring opening of the pyranose, (ii) construction of the 2,4-bridge, and (iii) reconstruction of the pyranose (Scheme 1). The skeleton of **6** is a trioxabicyclo[6.3.1]dodecane, and the 2,4-*O*-(*Z*)-2-butenylene bridge secures the pyranose ring in the axial-rich conformation. We designed an acyclic **7** as the precursor of the stepwise cyclizations whose allyl groups were first cyclized to prepare the nine-membered ring providing **8**, followed by regioselective oxidation of the anomeric position to reconstruct the pyranose ring. The key intermediate **7** was prepared by the ring opening of the protected glucose **9**, which was easily introduced from the known ethylthioglucoside **10**. In this study, we reduced the anomeric aldehyde to open the pyranose ring because we planned to apply ring closing metathesis (RCM)[11] of two allyl groups in a later step of the synthesis. Although olefination of the carbonyl group has been the traditional procedure to open the pyranose ring, we avoided this method due to potential conflicts with the allyl groups in the RCM step.



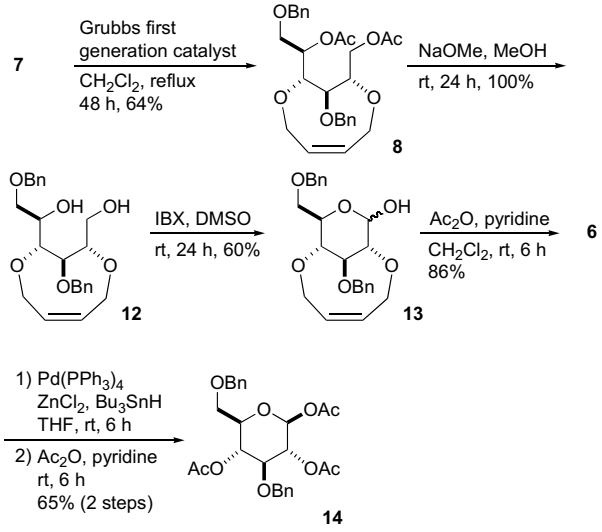
Scheme 1. Retrosynthetic analysis of **6**.

According to the retrosynthetic analysis (Scheme 1), the RCM-precursor **7** was initiated by treatment of ethylthio 3-*O*-benzyl-β-D-glucopyranoside (**10**)[12] with benzaldehyde dimethyl acetal and camphorsulfonic acid (CSA) in DMF, which gave the corresponding 4,6-*O*-benzylidene compound in 81% yield (Scheme 2). The benzylidene group of this intermediate was then regioselectively cleaved by triethylsilane and boron trifluoride etherate to give **11** in 77% yield.[13] Then, the double allylation of the 2- and 4-hydroxy groups was undertaken, followed by the hydrolysis of the ethylthio group to afford **9** in 61% yield (two steps). The hydrolysis was achieved using NBS as the activator despite the presence of the two allyl groups that could also react with the reagent. The reaction of the ethylthio group was faster, and thereby afforded **9** without influencing the double bonds. Pyranose **9** was then reduced by $NaBH_4$ in refluxing ethanol giving the corresponding glucitol in 73% yield, and subsequent acetylation of the diol provided **7**.



Scheme 2. Synthesis of ring-opened precursor **7** for RCM.

The successive intramolecular RCM and reconstruction of the pyranose ring converted diacetate **7** to **6** (Scheme 3). Thus, treatment of **7** with 20 mol% of Grubbs first generation catalyst in refluxing dichloromethane prepared the nine-membered ring to give the desired product **8** in 64% yield as the single *Z*-geometric isomer together with 32% of recovered **7**. Traces of cross-metathesis product were detected by ESIMS but were not collected. Technically, the catalyst was added in four portions during the reaction time at 12 h intervals to increase the yield. Treatment of **7** with the Grubbs second generation catalyst produced more cross-metathesis product. No RCM reaction occurred with the corresponding diol, thus the protection of the hydroxy groups was indispensable. Methanolysis of the RCM product **8** removed the two acetyl groups providing diol **12**. The regioselective oxidation at the primary alcohol of **12** using 2-iodoxybenzoic acid (IBX) reconstructed the pyranose ring to afford hemiacetal **13** in 62% yield as an inseparable anomeric mixture. The conformational analysis of the anomeric mixture **13** was difficult because its ^1H NMR was complex. Fortunately, acetylation of **13** provided a single diastereomer **6** in 84% yield, whose further structural determination was possible including its anomeric stereochemistry. The (*Z*)-2-butenylene bridge of **6** was smoothly removed according to the Bistri and Sollogoub's method[10] to give the monocyclic **14**.



Scheme 3. Synthesis of **6**.

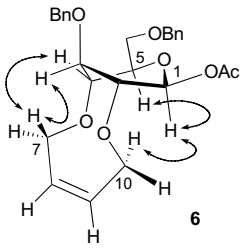


Figure 2. NOE correlations performed for the conformational determination.

Table 1
$^3J_{HH}$ between the protons on the pyranose ring of **6** and the calculated dihedral angles

Position	$^3J_{HH}$ (Hz)	Calcd angle (°)
H-1–H-2	6.2	149
H-2–H-3	0.0	~90
H-3–H-4	3.0	58
H-4–H-5	1.3	~90

Complete assignment of the NMR peaks, NOESY experiments, and analyses of the vicinal proton couplings illustrated the conformation of **6**. The assignment of ^{1}H and ^{13}C NMR peaks was performed using H–H COSY, HMQC, and HMBC spectra in benzene-d_6.[14] The NOESY spectra exhibited diastereotopic assignments of the allylic protons at the 7- and 10-position (Fig. 2). The correlations between H-1 and H-10α, between H-3 and H-7β, and between H-4 and H-7β indicated the conformation of the (*Z*)-2-butenylene moiety. Additionally, the correlations between H-1 and H-5 revealed that both of these protons were axially oriented, and thus, the C-1–O–C-5 part of the pyranose was not flipped from the thermodynamically stable form of glucopyranose possessing equatorial acetoxy and benzyloxymethyl groups on C-1 and C-5, respectively. Analyses of the coupling constants attributed to the vicinal protons on the pyranose rings ($^3J_{HH}$) in the ^{1}H NMR spectra determined the $^3S_1$ conformations of the pyranose ring. Table 1 presents the coupling constants observed in **6** in benzene-d_6 as well as the dihedral angles of the adjacent C–H bonds calculated by the modified Karplus equation.[15] Although the solution of the Karplus equation has two values for a given coupling constant, the cyclic structure limits the possible dihedral angles. Therefore, only the most plausible set of the dihedral angles are listed in the Table. The models prepared according to these dihedral angles indicated that the pyranose ring is in a twist-boat conformation ($^3S_1$) with three axial (C-2, C-3, and C-4 positions) and two equatorial substituents (C-1 and C-5 positions) as in the conformationally represented **6** (Fig. 2).

3. Conclusion

A 2,4-*O*-(*Z*)-2-butenylene bridged glucose derivative **6** was synthesized via stepwise cyclizations of acyclic **7**. This achievement enhanced the efficacy of the synthetic strategy toward the bridged bicyclic system restricting the pyranose into an axial-rich conformation. The revealed $^3S_1$ conformation of **6** showed that the 2,4-*O*-bridge provides a new method to restrict the conformation of the pyranose into the twist boat.

4. Experimental

4.1. General procedure

All moisture and air sensitive reactions were performed under a positive pressure of nitrogen. Anhydrous $MgSO_4$ was used to dry organic layers after extraction, and it was removed by filtration through a cotton pad. The filtrate was evaporated and subjected to further purification protocols if necessary.

The melting points are uncorrected. Specific optical rotations were determined with a 100 mm cell at 589 nm. The major absorbance bands in IR spectra are all reported in wavenumbers (cm^{-1}). High resolution mass spectra were obtained by electrospray ionization (ESI) and are reported in units of mass to charge.

^{1}H NMR data are indicated by a chemical shift with the multiplicity, the coupling constants, the integration, and the assignment in parentheses in this order. The multiplicities are abbreviated as s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, and br: broad. ^{13}C NMR data are reported as the chemical shift with the hydrogen multiplicity obtained from the DEPT spectra in parentheses. The multiplicities are abbreviated as s: C, d: CH, t: CH_2, and q: CH_3.

4.2. Ethylthio 3,6-di-*O*-benzyl-β-D-glucopyranoside (11)

A solution of **10** (3.48 g, 11.1 mmol), benzaldehyde dimethyl acetal (3.04 g, 20.0 mmol), and camphorsulfonic acid (400 mg, 1.69 mmol) in DMF (30 mL) was heated to 100 °C for 1 h. Then the reaction proceeded under a reduced pressure at ~15 mmHg for additional 2 h to remove methanol. After cooling to room temperature, aqueous $NaHCO_3$ was added to the solution and it was extracted with CH_2Cl_2. The combined organic layer was washed with brine. The concentrated extract was purified by column chromatography (silica gel 100 g, hexane/ethyl acetate=8:1 to 3:1) to give ethylthio 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (3.59 g, 81%) as a white crystal, whose NMR data were identical to the literature data.[13] To a solution of ethylthio 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (1.73 g, 4.30 mmol) and triethylsilane (5.00 g, 43.0 mmol) in dry CH_2Cl_2 (50 mL), $BF_3\cdot Et_2O$ (916 mg, 6.45 mmol) was added at 0 °C. The solution was stirred at 0 °C for 2 h and quenched with aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was washed with brine. The concentrated extract was purified by column chromatography (silica gel 50 g, hexane/ethyl acetate=8:1 to 4:1) to give **11** (1.33 g, 77%) as a colorless syrup. $[\alpha]_D^{25}$ −52.0 (*c* 0.92, $CHCl_3$); IR (thin film) ν_{max} (cm^{-1}): 3445, 3063, 3030, 2870, 1607, 1497, 1454, 1362, 1265, 1209, 1123, 1071, 1028, 739, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32–7.18 (m, 10H, Ph), 4.89 (d, *J*=11.7 Hz, 1H, Bn), 4.75 (d, *J*=11.7 Hz, 1H, Bn), 4.52 (d, *J*=12.1 Hz, 1H, Bn), 4.48 (d, *J*=12.1 Hz, 1H, Bn), 4.26 (d, *J*=9.6 Hz, 1H, H-1), 3.68 (dd, *J*=10.4, 4.1 Hz, 1H, H-6a), 3.65 (dd, *J*=10.4, 5.0 Hz, 1H, H-6b), 3.56 (dd, *J*=9.6, 8.7 Hz, 1H, H-4), 3.46–3.40 (m, 2H, H-2 and H-5), 3.34 (dd, *J*=8.7, 8.5 Hz, 1H, H-3), 2.66 (br, 2H, SCH_2CH_3), 2.40 (br, 2H, OH), 1.23 (t, *J*=7.4 Hz, 3H, SCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.5 (s), 137.8 (s), 128.6 (d), 128.4 (d), 128.0 (d), 127.9 (d), 127.7 (d), 127.7 (d), 86.2 (d), 85.1 (d), 78.3 (d), 74.7 (t), 73.6 (t), 72.7 (d), 71.4 (d), 70.4 (t), 24.4 (t), 15.4 (q); ESIHRMS (*m*/*z*) [M+Na^+] calcd for $C_{22}H_{28}O_5S$ 427.1555, found 427.1551.

4.3. 2,4-Di-*O*-allyl-3,6-di-*O*-benzyl-D-glucopyranose (9)

NaH (60% in oil, 0.77 g, 19 mmol) was added to a solution of **11** (1.30 g, 3.22 mmol) in dry THF (30 mL) at room temperature. After stirring for 30 min, allyl bromide (1.54 g 12.8 mmol) was added. The mixture was stirred for 1.5 h at room temperature and the reaction was quenched by slow addition of cold methanol. The solvent and excessive allyl bromide were removed under vacuum, and then saturated aqueous NH_4Cl was added. The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine. The concentrated extract was purified by column chromatography (silica gel 40 g, hexane/ethyl acetate=20:1 to 10:1) to give ethylthio 2,4-di-*O*-allyl-3,6-di-*O*-benzyl-β-

D-glucopyranoside (1.32 g, 85%) as colorless oil. To a solution of ethylthio 2,4-di-*O*-allyl-3,6-di-*O*-benzyl-β-D-glucopyranoside (936 mg, 1.93 mmol) in THF/H_2O (2:1, 30 mL) at 0 °C, solid NBS (1.00 g, 5.62 mmol) was added in small portions (ca. 10 mg every 2 min interval). This procedure took 5 h. Then, solid $Na_2S_2O_3$ was added and THF was removed under vacuum. The mixture was extracted with ethyl acetate and washed with brine. The concentrated extract was purified by column chromatography (silica gel 30 g, hexane/ethyl acetate=9:1 to 3:1) to give **9** (4:1 anomeric mixture, 625 mg, 73%) as white crystals. Mp 89.5–91.0 °C; $[\alpha]_D^{24}$ +50.6 (*c* 0.47, $CHCl_3$); IR (thin film) ν_{max} (cm^{-1}): 3385, 3029, 2920, 2855, 1725, 1645, 1539, 1454, 1360, 1269, 1090, 916, 745, 698; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 91.3 (d, C-1 of major isomer), 97.3 (d, C-1 of minor isomer); ESIHRMS (*m*/*z*) [M+Na^+] calcd for $C_{26}H_{34}O_6$ 463.2097, found 463.2094.

4.4. 1,5-Di-*O*-acetyl-2,4-di-*O*-allyl-3,6-di-*O*-benzyl-D-glucitol (7)

$NaBH_4$ (300 mg, 7.89 mmol) was added to a solution of **9** (869 mg, 1.98 mmol) in ethanol (100 mL), and the mixture was heated to reflux for 4 h. After cooling, ethanol was removed under vacuum. Water was then added to the residue and the mixture was extracted with ethyl acetate. The combined organic layer was washed with brine. The concentrated extract was purified by column chromatography (silica gel 15 g, hexane/ethyl acetate=2:1) to give 2,4-di-*O*-allyl-3,6-di-*O*-benzyl-D-glucitol (639 mg, 73%) as colorless syrup. A mixture of 2,4-di-*O*-allyl-3,6-di-*O*-benzyl-D-glucitol (148 mg, 0.335 mmol), acetic anhydride (1 mL), and pyridine (2 mL) was stirred for 4 h at room temperature. Then methanol (2 mL) was added and the solution was stirred for additional 20 min. The excessive reagents were removed under vacuum. Then 1 M HCl was added and the solution was extracted with ethyl acetate. The combined organic layer was successively washed with H_2O and brine. The concentrated extract was purified by column chromatography (silica gel 5 g, hexane/ethyl acetate=3:1) to give **7** (164 mg, 93%) as a colorless syrup. $[\alpha]_D^{25}$ +4.0 (*c* 1.11, $CHCl_3$); IR (thin film) ν_{max} (cm^{-1}): 3030, 2917, 2868, 1740, 1647, 1496, 1454, 1372, 1238, 1098, 739, 700; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.33–7.26 (m, 10H, Ph), 5.89 (dddd, *J*=17.2, 6.0, 6.0, 2.8 Hz, 1H, OCH_2CH=CH_2), 5.87 (dddd, *J*=17.2, 5.6, 5.6, 2.0 Hz, 1H, OCH_2CH=CH_2), 5.27–5.19 (m, 3H, OCH_2CH=CH_2 and H-5), 5.17–5.11 (m, 2H, OCH_2CH=CH_2), 4.65 (s, 2H, Bn), 4.52 (d, *J*=12.0 Hz, 1H, Bn), 4.47 (d, *J*=12.0 Hz, 1H, Bn), 4.30 (dd, *J*=12.0, 4.0 Hz, 1H, H-1a), 4.19 (dd, *J*=12.0, 6.4 Hz, 1H, H-1b), 4.16–4.05 (m, 4H, OCH_2CH=CH_2), 3.85 (dd, *J*=5.2, 4.8 Hz, 1H, H3), 3.83 (dd, *J*=11.0, 3.6 Hz, 1H, H6a), 3.78 (ddd, *J*=6.4, 5.2, 4.0 Hz, 1H, H2), 3.69 (dd, *J*=11.0, 6.0 Hz, 1H, H6b), 3.68 (dd, *J*=4.8, 4.8 Hz, 1H, H4), 2.04 (s, 3H, Ac), 2.00 (s, 3H, Ac); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.7 (s), 170.1 (s),138.0 (s), 137.9 (s), 134.7 (d), 128.4 (d), 128.3 (d), 128.3 (d), 127.7 (d), 127.6 (d), 117.4 (t), 116.9 (t), 78.2 (d), 78.2 (d), 76.7 (d), 74.6 (t), 73.4 (t), 73.2 (d), 73.1 (t), 72.2 (t), 68.2 (t), 64.1 (t), 21.1 (q), 20.9 (q); ESIHRMS (*m*/*z*) [M+Na^+] calcd for $C_{30}H_{38}O_8$ 549.2464, found 549.2448.

4.5. 1,5-Di-*O*-acetyl-3,6-di-*O*-benzyl-2,4-*O*-(*Z*-2-buten-1,4-yl)-D-glucitol (8)

To a solution of **7** (250 mg, 0.475 mmol) in dried dichloromethane (400 mL) was added Grubbs first generation catalyst (20 mg, 0.024 mmol), and then the solution was heated to reflux for 12 h. Then the catalyst was further added (60 mg, 0.072 mmol) in three portions every 12 h. The total reaction time was 48 h. The solution was concentrated to 10 mL and subjected to column chromatography (silica gel 25 g, hexane/ethyl acetate=5:1 to 2:1) to afford unreacted **7** (79 mg, 32%) and **8** (152 mg, 64%) as a colorless syrup. $[\alpha]_D^{25}$ −26.3 (*c* 0.29, $CHCl_3$); IR (thin film) ν_{max} (cm^{-1}): 3025, 2919, 2849, 1740, 1454, 1372, 1235, 1103, 1047, 741, 700; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.28–7.19 (m, 10H, Ph), 5.63–5.61 (m, 2H, CH_2CH=$CH$$CH_2$), 5.06 (dt, *J*=9.5, 2.8 Hz, 1H, H-5), 4.96 (dd, *J*=13.4, 5.0 Hz, 1H, C*Ha*HCH=$CHCH_2$), 4.72 (dd, *J*=14.8, 3.6 Hz, 1H, CH_2CH=CHC*Ha*H), 4.57 (d, *J*=11.2 Hz, 1H, Bn), 4.50 (d, *J*=11.2 Hz, 1H, Bn), 4.48 (d, *J*=12.0 Hz, 1H, Bn), 4.42 (d, *J*=12.0 Hz, 1H, Bn), 4.19 (dd, *J*=11.2, 7.7 Hz, 1H, H-1a), 4.04 (dd, *J*=11.2, 5.6 Hz, 1H, H-1b), 4.04–3.95 (m, 2H, CH*Hb*CH=CHCH*Hb*), 3.69 (d, *J*=2.8 Hz, 2H, H-6), 3.68 (ddd, *J*=7.7, 5.6, 1.2 Hz, 1H, H-2), 3.63 (dd, *J*=9.5, 1.2 Hz, 1H, H-4), 3.53 (dd, *J*=1.2, 1.2 Hz, 1H, H-3), 1.97 (s, 3H, Ac), 1.94 (s, 3H, Ac); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.7 (s), 169.9 (s), 137.9 (s), 137.8 (s), 131.3 (d), 128.7 (d), 128.4 (d), 128.3 (d), 128.1 (d), 127.8 (d), 127.7 (d), 78.9 (d), 76.7 (d), 75.4 (d), 74.0 (t), 73.3 (t), 72.8 (d), 69.7 (t), 68.1 (t), 66.6 (t), 65.9 (t), 21.1 (q), 20.9 (q); ESIHRMS (*m*/*z*) [M+Na^+] calcd for $C_{28}H_{34}O_8$ 521.2151, found 521.2129.

4.6. 3,6-Di-*O*-benzyl-2,4-*O*-(*Z*-2-buten-1,4-yl)-D-glucitol (12)

Sodium methoxide (8.0 mg, 0.15 mmol) was added to the solution of **8** (152 mg, 0.305 mmol) in MeOH (10 mL), and the solution was stirred for 24 h at ambient temperature. The mixture was neutralized with Amberlite IR-120 (H^+), filtered through a cotton pad, and concentrated to give **12** as a colorless syrup (126 mg, 100%). $[\alpha]_D^{24}$ −16.6 (*c* 0.96, $CHCl_3$); IR (thin film) ν_{max} (cm^{-1}): 3445, 3029, 2920, 1651, 1454, 1356, 1101, 739, 698; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.31–7.18 (m, 10H, Ph), 5.64–5.59 (m, 2H, CH_2CH=$CH$$CH_2$), 5.00 (dd, *J*=13.6, 5.6 Hz, 1H, C*Ha*HCH=$CHCH_2$), 4.72 (dd, *J*=16.0, 2.8 Hz, 1H, CH_2CH=CHC*Ha*H), 4.65 (d, *J*=11.6 Hz, 1H, Bn), 4.59 (d, *J*=11.6 Hz, 1H, Bn), 4.50 (d, *J*=11.6 Hz, 1H, Bn), 4.46 (d, *J*=11.6 Hz, 1H, Bn), 3.99 (dd, *J*=13.6, 4.4 Hz, 1H, CH*Hb*CH=$CHCH_2$), 3.89 (dd, *J*=16.0, 2.4 Hz, 1H, CH_2CH=CHCH*Hb*), 3.85 (br s, 1H, H-2), 3.83 (ddd, *J*=8.8, 4.6, 2.8 Hz, 1H, H-5), 3.73 (dd, *J*=11.0, 8.8 Hz, 1H, H-6a), 3.64 (dd, *J*=9.6, 2.8 Hz, 1H, H-4), 3.56–3.53 (m, 2H, H-1), 3.44 (dd, *J*=11.0, 4.6 Hz, 1H, H-6b), 3.24 (dd, *J*=9.4, 1.0 Hz, 1H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.5 (s), 137.7 (s), 131.6 (d), 128.5 (d), 128.5 (d), 128.3 (d), 128.0 (d), 127.9 (d), 127.9 (d), 127.6 (d), 82.4 (d), 79.4 (d), 75.6 (d), 74.1 (t), 73.4 (t), 71.1 (t), 70.3 (d), 69.6 (t), 66.5 (t), 65.0 (t); ESIHRMS (*m*/*z*) [M+Na^+] calcd for $C_{24}H_{30}O_6$ 437.1940, found 437.1938.

4.7. 3,6-Di-*O*-benzyl-2,4-*O*-(*Z*-2-buten-1,4-yl)-D-glucopyranse (13)

A solution of **12** (26 mg, 0.063 mmol) and IBX (52 mg, 0.19 mmol) in DMSO (2 mL) was stirred at ambient temperature for 24 h. After the addition of water, the mixture was filtered through a cotton–Celite pad and the residue was washed with ethyl acetate. The filtrate was extracted with ethyl acetate and the combined organic layer was washed with brine. The concentrated extract was purified by column chromatography (silica gel 6 g, hexane/ethyl acetate=5:1 to 2:1) to afford **13** (15.6 mg, 60%) as a colorless syrup, together with recovered **12** (7 mg, 27%). IR (thin film) ν_{max} (cm^{-1}): 3447, 3029, 2920, 2861, 1732, 1454, 1096, 739, 698; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.29–7.17 (m, 10H, Ph), 5.78–5.46 (m, 2H), 5.27–5.05 (m, 1H), 4.87–4.71 (m, 1H), 4.60–4.32 (m, 6H), 4.26–4.11 (m, 1H), 3.81–3.56 (m, 5H), 3.47–3.44 (m, 1H), 2.91 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.3 (s), 137.6 (s), 131.8 (d), 131.6 (d), 128.9 (d), 128.4 (d), 128.3 (d), 127.9 (d), 127.7 (d), 127.5 (d), 88.7 (d), 78.1 (d), 75.5 (d), 74.6 (d), 73.5 (t), 73.4 (t), 72.2 (t), 71.6 (t), 70.7 (d), 70.2 (t); ESIHRMS (*m*/*z*) [M+Na^+] calcd for $C_{24}H_{28}O_6$ 435.1784, found 435.1782.

4.8. 1-*O*-Acetyl-3,6-di-*O*-benzyl-2,4-*O*-(*Z*-2-buten-1,4-yl)-β-D-glucopyranose (6)

A mixture of **13** (14 mg, 0.034 mmol), acetic anhydride (0.1 mL), and pyridine (0.2 mL) in CH_2Cl_2 (2 mL) was stirred for 6 h at room temperature. Then the solvent and excessive reagents were removed under vacuum, and the resulting residue was purified by column chromatography (silica gel 6 g, hexane/ethyl acetate=6:1 to 3:1) to afford **6** (13.2 mg, 86%) as a colorless syrup. $[\alpha]_D^{24}$ −16.2 (*c* 0.27, $CHCl_3$); IR (thin film) ν_{max} (cm^{-1}): 3029, 2920, 2853, 1753, 1454, 1370, 1219, 1105, 739, 698; ^1H NMR (400 MHz, C_6D_6) δ: 7.23–7.04 (m, 10H), 6.82 (d, *J*=6.2 Hz, 1H), 5.49–5.43 (m, 1H), 5.14 (dd, *J*=13.5, 9.4 Hz, 1H), 5.08 (ddd, *J*=11.7, 4.1, 3.2 Hz, 1H), 4.68 (d, *J*=3.0 Hz, 1H), 4.57 (br dd, *J*=8.2, 6.0 Hz, 1H), 4.40 (br d, *J*=6.2 Hz, 1H), 4.40–4.33 (m, 1H), 4.38 (d, *J*=11.9 Hz, 1H), 4.35 (d, *J*=11.9 Hz, 1H), 4.26 (d, *J*=11.9 Hz, 1H), 4.23 (d, *J*=11.9 Hz, 1H), 3.86 (dd, *J*=9.6, 8.2 Hz, 1H), 3.80 (ddd, *J*=3.0, 1.3, 1.3 Hz, 1H), 3.75 (dd, *J*=9.6, 6.0 Hz, 1H), 3.64 (dd, *J*=13.5, 6.6 Hz, 1H), 3.31 (ddd, *J*=18.1, 4.1, 1.2 Hz, 1H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ: 169.3 (s), 138.9 (s), 138.4 (s), 133.3 (d), 128.6 (d), 128.5 (d), 128.5 (d), 127.9 (d), 127.8 (d), 127.8 (d), 127.6 (d), 90.9 (d), 79.6 (d), 78.8 (d), 78.5 (d), 75.5 (d), 73.3 (t), 71.6 (t), 71.2 (t), 70.2 (t), 61.6 (t), 20.6 (q); ESIHRMS (*m*/*z*) [M+Na^+] calcd for $C_{26}H_{30}O_7$ 477.1889, found 477.1884.

4.9. 1,2,4-Tri-*O*-acetyl-3,6-di-*O*-benzyl-β-D-glucopyranose (14)

To a stirred mixture of **6** (2.6 mg, 5.7 μmol), $Pd(PPh_3)_4$ (3.3 mg, 2.9 μmol), and $ZnCl_2$ (11.7 mg, 86 μmol) in THF (0.2 mL) was added Bu_3SnH (25 mg, 86 μmol). The mixture was stirred for 6 h at rt. THF was evaporated from the mixture, and the resulting residue was purified by column chromatography (silica gel 1 g, hexane/ethyl acetate=8:1 to 2:1) to afford 1-*O*-acetyl-3,6-di-*O*-benzyl-D-glucopyranose, which molecular weight was confirmed by ESILRMS (*m*/*z*) [M+Na^+] calcd for $C_{22}H_{26}O_7$ 425.2, found 425.2. The compound was then diluted with pyridine (0.1 mL) and Ac_2O (0.1 mL) was added to the mixture. It was stirred for 6 h at rt and then evaporated. The resulting residue was purified by column chromatography (silica gel 1 g, hexane/AcOEt=5:1 to 4:1) to afford **14** (1.8 mg, 65%). IR (thin film) ν_{max} (cm^{-1}): 3090, 3063, 3033, 2919, 2874, 1755, 1367, 1221, 1063, 1035, 909, 741, 700; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.22 (m, 10H), 5.65 (d, *J*=8.0 Hz, 1H, H-1), 5.17 (dd, *J*=9.6, 9.4 Hz, 1H, H-4), 5.16 (dd, *J*=9.4, 8.0 Hz, 1H, H-2), 4.60 (s, 2H, Bn), 4.51 (d, *J*=11.9 Hz, 1H, Bn), 4.48 (d, *J*=11.9 Hz, 1H, Bn), 3.74 (dd, *J*=9.4, 9.4 Hz, 1H, H-3), 3.70 (ddd, *J*=9.6, 5.0, 3.4 Hz, 1H, H-5), 3.57 (dd, *J*=10.8, 3.4 Hz, 1H, H-6), 3.52 (dd, *J*=10.8, 5.0 Hz, 1H, H-6), 2.09 (s, 3H), 1.97 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ: 169.6 (s), 169.5 (s), 169.3 (s), 137.9 (s), 137.8 (s), 128.6 (d, 2C), 128.5 (d, 2C), 128.2 (d, 2C), 128.0 (d), 128.0 (d, 2C), 127.9 (d), 92.3 (d), 80.2 (d), 74.4 (d), 74.1 (t), 73.8 (t), 71.8 (d), 70.3 (d), 70.0 (t), 20.1 (q), 20.9 (q), 20.9 (q); ESIHRMS (*m*/*z*) [M+Na^+] calcd for $C_{26}H_{30}O_9$ 509.1788, found 509.1778.

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Supplementary data

Detailed General procedure and Table for full assignment of ^1H and ^{13}C NMR of **6**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.01.019.

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