Synthesis of a New Phenol Glycoside, Neohancoside C from *Cynanchum hancockianum*

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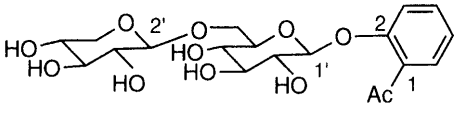
Neohancoside C (1) is a new phenol glycoside isolated from *Cynanchum hancockianum*, which is a Chinese folk medicine having antitumor activity. The synthesis of 1, 2-acetylphenyl β-D-xylopyranosyl-(1→6)-β-D-glucopyranoside, was achieved by phase-transfer-catalyzed glycosidation using glycosyl bromide.

Key words neohancoside C; synthesis; phenol glycoside; *Cynanchum hancockianum*; phase-transfer-catalyzed glycosidation

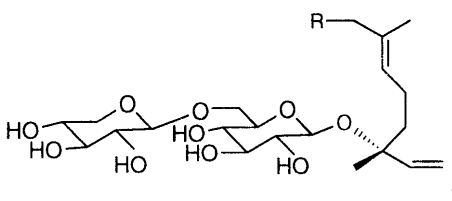
Cynanchum hancockianum (MAXIM) Al. ILJINSKI (Asclepiadaceae), distributed in Inner Mongolia, is a Chinese folk medicine possessing antitumor activity. Our detailed examination of the constituents of this plant has led to the isolation and structure determination of various novel compounds, such as triterpenes (hancockinol, hancolupenol),[1,2] a modified steroid (hancopregnane),[3] a steroid glycoside (hancoside),[4] and four diglycosides, neohancosides A, B, C (**1**), and D.[4,5] The availability of these compounds was insufficient to allow investigation of their bioactivities, and this led us to examine their synthesis. Neohancosides A, B, and C (**1**) are glycosides which have a common disaccharide, β-D-xylopyranosyl-(1→6)-β-D-glucopyranose. We have already reported the total synthesis of neohancosides A and B in the previous papers.[6,7] Recently many phenol glycosides have been isolated from plants, and some of them show a variety of biological activities such as immunological,[8] antihypertensive,[9] antiinflammatory,[10] antibacterial[10] and antitumor activities.[11] Here we report the synthesis and characterization of the phenol glycoside neohancoside C (**1**).

Results and Discussion

The strategy employed to synthesize **1** involves the glycosylation reaction of 2-hydroxyacetophenone with a glucose unit, followed by the selective deprotection of the 6′-*O*-protecting group in the glucose unit, then glycosidation of the resulting monoglycoside with a xylose unit to obtain phenol diglycoside. The key reaction in this synthesis is glycosidation of 2-hydroxyacetophenone. We have already applied Suzuki's method[12] to the synthesis of neohancosides A and B[6,7] using glucosyl fluoride **2**[6,7] as a donor and zirconocene dichloride–$AgClO_4$ as a promoter to glycosylate the linalool moiety with a glucose unit. We also intended initially to use the fluoride **2** to glycosylate 2-hydroxyacetophenone with a glucose unit in the synthesis of neohancoside C. Matsumoto *et al.* have reported[13] the effectiveness of hafnocene dichloride–$AgClO_4$ for coupling reaction between glycosyl fluoride and substituted phenols and found that an electron-withdrawing group such as a 4-acetyl group on the phenols retards the reaction. Yamaguchi *et al.* also reported[14] the successive glycosidation of phenols with acetylated glycosyl fluoride in the presence of $BF_3 \cdot OEt_2$ as a promoter and stated that the glycosidation did not occur when the phenolic hydroxyl group was strongly hydrogen-bonded to a neighboring group such as 2-hydroxyacetophenone or 2-nitrophenol. It seems clear that the electronegativity of the acetyl group and the strong intramolecular hydrogen bonding between the hydroxyl and the carbonyl group of 2-hydroxyacetophenone make it difficult to form a glycosylic linkage between 2-hydroxyacetophenone and the glucose unit. Indeed, our attempts to glycosidate **2** with 2-hydroxyacetophenone using zirconocene dichloride–$AgClO_4$ and **3** with 2-hydroxyacetophenone using AgOTf failed, giving only complex degradation products of the sugar and the coupling reaction did not occurred in both cases. On the other hand, Sidhu *et al.*[15] have reported the phase-transfer-catalyzed synthesis of acetylated aryl β-D-glycosides using glycosyl bromide as a donor in the presence of benzyltriethylammonium bromide (BTEAB) in the mixed solvent of aqueous NaOH–$CHCl_3$, and they successively connected 2-nitrophenol to acetylated glycosyl bromide. Thus, we chose the above method for the key reaction of 2-hydroxyacetophenone and the glucose unit.



Neohancoside C (**1**)



R=H Neohancoside A
R=OH Neohancoside B

Fig. 1

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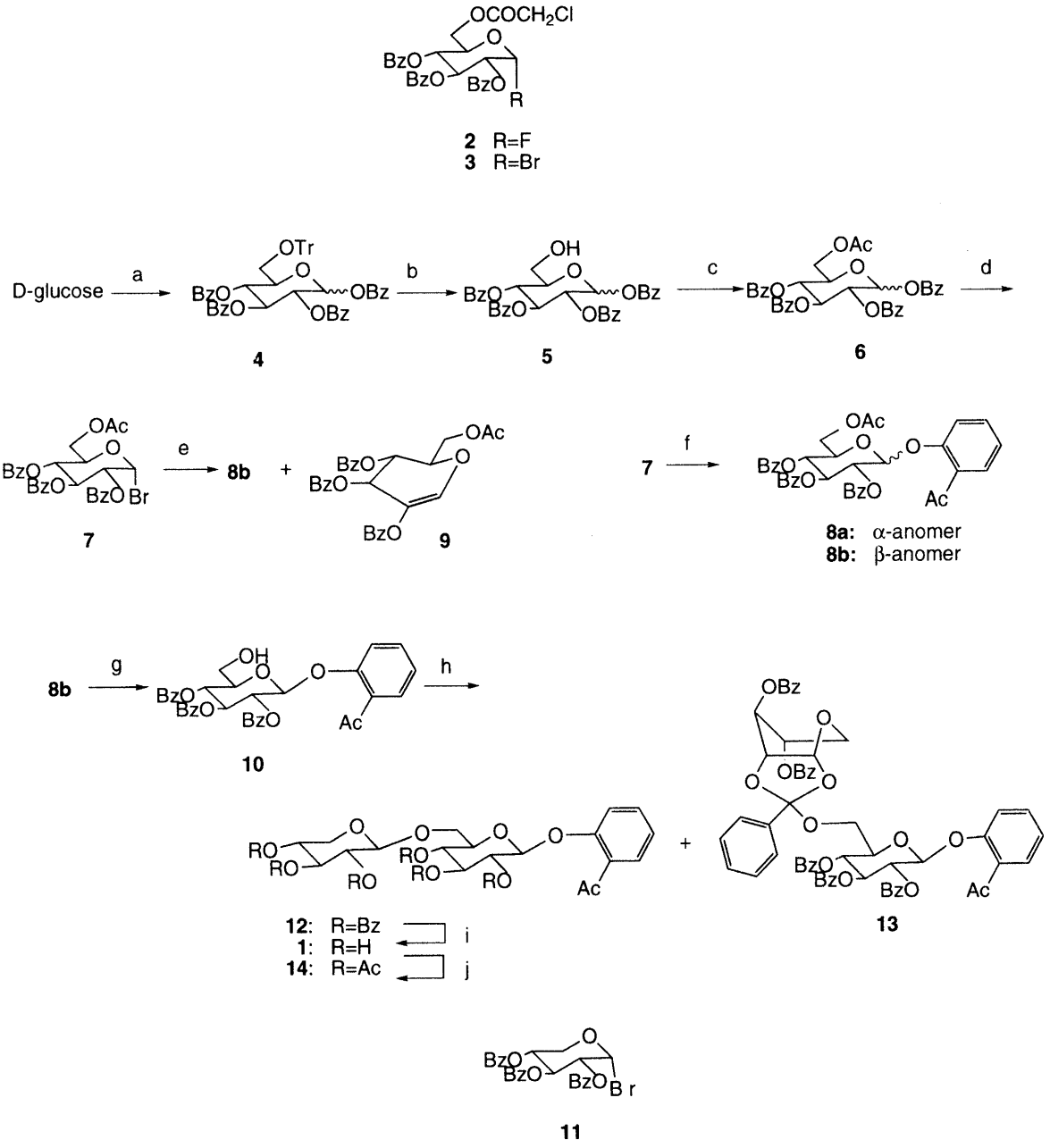

a) 1) trityl chloride, DMAP, triethylamine, DMF, rt, 24h; 2) benzoyl chloride, pyridine, -20 °C, 30 min, rt, 24h, 65% from glucose; b) HBF_4, CH_3CN, rt, 1h, 65%; c) Ac_2O, pyridine, rt; 1h, quant.; d) 30% HBr-AcOH, CH_2Cl_2, rt, 3h, quant.; e) 2-hydroxyacetophenone, BTEAB, 1.25N aq. NaOH, $CHCl_3$, 60 °C, 1.8h, **8b** 38%; f) 2-hydroxyacetophenone, $CdCO_3$, MS-4A, toluene, reflux, 21h, **8a**: 44%, **8b**: 43%; g) 1% HCl-MeOH, rt, 25h, 82%; h) **11**, AgOTf, MS-4A, 2,4,6-collidine, CH_2Cl_2, -40 °C, 1h, **12**: 33%, **13**: 14% ; i) 2.8% NaOMe, MeOH-THF (1:1), rt, 5h, 77%; j) Ac_2O, pyridine, rt, 24h, 84%.

Chart 1

It is important to select an appropriate 6′-*O*-protecting group to accomplish the second glycosylation reaction of phenolglycoside with the xylose unit. We initially tried a chloroacetyl group. The glycosidation of **3** with 2-hydroxyacetophenone in the presence of BTEAB in aqueous NaOH–$CHCl_3$ was carried out, but the chloroacetyl group was easily lost under this alkaline condition. Thus, we chose an acetyl group as the 6-*O*-protective group, since it is more stable to basic conditions and can be differentiated from a benzoyl group by deprotection under mild acidic conditions.

The key compound **7** was prepared from D-glucose as shown in Chart 1. For the synthesis of 1,2,3,4-tetra-*O*-benzoyl α- and β-D-glucopyranose (**5**), we applied the procedure described by Kevac and Glaudemans.[16] Thus, selective tritylation of the primary hydroxyl group of D-glucose with trityl chloride in the presence of dimethylaminopyridine (DMAP) and triethylamine, followed by benzoylation with benzoyl chloride afforded **4** in 65% total yield. Detritylation of **4** by treatment with HBF_4 gave the alcohol **5**. This was acetylated by treatment with Ac_2O and pyridine to give an anomeric mixture **6**, quantitatively.

Compound **6** was converted quantitatively to the bromide **7** by treatment with 30% HBr–AcOH. It is noteworthy that the bromide **7** is stable for many days even at room temperature. Glycosylic reaction of 2-hydroxyacetophenone with the bromide **7** was carried out in the presence of BTEAB in the mixted solvent of aqueous 1.25 N NaOH and $CHCl_3$ to give the desired phenol glycoside **8b** in 38.1% yield accompanied with the β-elimination product[15] **9**. To improve the yield of **8b**, we applied another method for glycosylation using $CdCO_3$ as described in the literature.[17] Although the glycosylation reaction occurred almost quantitatively, the yield of the desired β-anomer (**8b**) was 44% and a similar amount of α-anomer (**8a**) was obtained. Yamaguchi *et al.*[14] reported that phenols with an electron-withdrawing group are more susceptible to isomerization to the α-anomer than phenols with an electron-donating group in the glycosidation reaction. It is presumed that the formation of the α-anomer **8a** results from the electronegativity of the acetyl group. Selective deprotection of the acetyl group of **8b** in the presence of the benzoyl group was carried out by treatment with 1% HCl–MeOH, affording the alcohol **10** in 82% yield. Glycosylation reaction of the alcohol **10** with 2,3,4-tri-*O*-benzoylxylosyl bromide (**11**) in the presence of AgOTf, MS-4A, 2,4,6-collidine at $-40\,^{\circ}C$ afforded the desired phenol diglycoside **12** in 33.2% yield together with its orthoester **13** in 14.1% yield. It has been reported[7,18] that Koenigs–Knorr condensation of a 1,2-*trans*-2-acetyl (benzoyl, pivaloyl)-glycosyl bromide with an alcohol in the presence of 2,4,6-collidine (lutidine, pyridine) leads to the formation of a 1,2-orthoester. Several experiments were carried out to improve the yield of the diglycoside **12** and to suppress the production of the orthoester by variation of the temperature (-20—$20\,^{\circ}C$). The best yield was obtained at $-40\,^{\circ}C$, and raising the temperature caused an increase in the production of the orthoester **13**; at $-20\,^{\circ}C$, the yields of **12** and **13** were 16.2 and 35.9%, respectively. Debenzoylation of **12** by treatment with a methanol solution of NaOMe afforded neohancoside C (**1**) in 77% yield. Acetylation of **1** with Ac_2O and pyridine gave the hexaacetate (**14**) quantitatively. Compound **14** was identified with neohancoside C (**1**) hexaacetate[5] based on a comparison of the ^1H- and ^{13}C-NMR spectra. Thus, we achieved the synthesis of neohancoside C in eight steps in 4.2% total yield and neohancoside C (**1**) was characterized by melting point, optical rotation, ^1H- and ^{13}C-NMR. Examination of bioactivities such as antitumor activity is under way.

Experimental

Melting points were taken on a Yanagimoto hot-stage and are uncorrected. ^1H- and ^{13}C-NMR were recorded on Varian VXR-300 and XL-400 spectrometers. The signals were assigned on the basis of ^1H–^1H correlation spectroscopy (COSY), distortionless enhancement by polarization transfer (DEPT), heteronuclear multiple quantum coherence (HMQC), and heteronuclear multiple bond connectivity (HMBC) experiments. Mass spectra were obtained on a JEOL JMX-DX 300 mass spectrometer (low-resolution mass spectrometry) and a JEOL JMS-AX505 HA mass spectrometer (high-resolution mass spectrometry). Flash column chromatography was performed on Silica gel 60 H (Merck). Thin-layer chromatography (TLC) was done on Silica gel 60 PF_{254} (Merck).

A Mixture of 1,2,3,4-Tetra-*O*-benzoyl-6-*O*-trityl-α- and β-D-glucopyranose (4) DMAP (64.0 mg, 0.52 mmol), triethylamine (2.60 ml, 18.7 mmol), and trityl chloride (3.22 g, 11.6 mmol) were added to a solution of D-glucose (1.88 g, 10.4 mmol) in dimethylformamide (DMF) (15.5 ml), and the mixture was stirred at room temperature for 24 h. Pyridine (31.0 ml, 0.38 mol) was added, then benzoyl chloride (9.70 ml, 84.1 mmol) was added dropwise at $-20\,^{\circ}C$ during 30 min under argon. The mixture was stirred for 24 h, then concentrated *in vacuo*, and the residue was poured into ice water (100 ml) and extracted with $CHCl_3$ (100 ml × 3). The organic layer was washed with 3 N H_2SO_4 (30 ml × 2), saturated aqueous $NaHCO_3$ (30 ml × 2), and water (30 ml), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (*n*-hexane : AcOEt = 5 : 1) to afford the anomeric mixture **4** as colorless crystals (1.01 g, 65% total yield): Compound **4** (30 mg) was purified by preparative TLC (toluene) to give the α-anomer (5.1 mg) and the β-anomer (21.0 mg) as light yellow crystals. α-anomer: mp 94—96 °C. $Rf = 0.74$ (benzene : AcOEt = 10 : 1). $[\alpha]_D^{26}$ +69.06° ($c = 1.37$, $CHCl_3$). ^1H-NMR (300 MHz, $CDCl_3$) δ_H: 3.22 (1H, dd, $J = 2.0$, 11.0 Hz, 6-Ha), 3.44 (1H, dd, $J = 4.0$, 11.0 Hz, 6-Hb), 4.37 (1H, ddd, $J = 2.0$, 4.0, 10.0 Hz, 5-H), 5.72 (1H, dd, $J = 3.5$, 10.0 Hz, 2-H), 5.89 (1H, t, $J = 10.0$ Hz, 4-H), 6.20 (1H, t, $J = 10.0$ Hz, 3-H), 6.93 (1H, d, $J = 3.5$ Hz, 1-H), 6.90—8.20 (35H, benzoyl × 4, trityl). HR-FAB-MS *m/z*: 861.2684 $[M+Na]^+$ Calcd for $C_{53}H_{42}NaO_{10}$: 861.2676. β-anomer: mp 82—84 °C. $Rf = 0.74$ (benzene : AcOEt = 10 : 1). $[\alpha]_D^{26}$ −8.10° ($c = 0.42$, $CHCl_3$). ^1H-NMR (300 MHz, $CDCl_3$) δ_H: 3.24 (1H, dd, $J = 4.0$, 11.0 Hz, 6-Ha), 3.47 (1H, dd, $J = 2.0$, 11.0 Hz, 6-Hb), 4.10 (1H, m, 5-H), 5.84 (1H, t, $J = 10.0$ Hz, 4-H), 5.85 (1H, dd, $J = 7.0$, 10.0 Hz, 2-H), 5.87 (1H, t, $J = 10.0$ Hz, 3-H), 6.25 (1H, d, $J = 7.0$ Hz, 1-H), 7.00—8.10 (35H, benzoyl × 4, trityl). HR-FAB-MS *m/z*: 861.2671 $[M+Na]^+$, Calcd for $C_{53}H_{42}NaO_{10}$: 861.2676.

A Mixture of 1,2,3,4-Tetra-*O*-benzoyl-α- and β-D-glucopyranose (5) A solution of **4** (1.4 g, 3.4 mmol) in acetonitrile (10.0 ml) was treated with HBF_4 (1.0 ml, 23.5 mmol). The mixture was stirred at room temperature for 1 h, then neutralized with triethylamine (2.0 ml, 14.3 mmol) and evaporated *in vacuo*. The residue was purified by flash column chromatography (hexane : AcOEt = 5 : 2) to give **5** as colorless crystals (1.01 g, 65%). HR-FAB-MS *m/z*: 596.1674 $[M+Na]^+$; Calcd for $C_{34}H_{28}NaO_{10}$: 596.1683.

A Mixture of 6-*O*-Acetyl-1,2,3,4-tetra-*O*-benzoyl-α- and β-D-glucopyranose (6) A solution of **5** (0.15 g, 0.25 mmol) and Ac_2O (0.5 ml) in pyridine (1.0 ml) was stirred at room temperature for 1 h. The residue was diluted with water (20 ml) and extracted with $CHCl_3$ (20 ml × 3). The $CHCl_3$ layer was washed with 5% HCl (20 ml × 2), saturated aqueous $NaHCO_3$ (20 ml × 2), and saturated aqueous NaCl (20 ml × 2), dried over Na_2SO_4, then concentrated *in vacuo*. The residue was purified by preparative TLC (hexane : AcOEt = 2 : 1) to give the anomeric mixture **6** as colorless crystals (0.16 g, 99%). $Rf = 0.45$ (hexane : AcOEt = 2 : 1). HR-FAB-MS *m/z*: 661.1677 $[M+Na]^+$; Calcd for $C_{36}H_{30}NaO_{11}$: 661.1686. ^1H-NMR (300 MHz) α-anomer δ_H: 4.22—4.41 (2H, m, 6-H_2), 4.48 (1H, ddd, $J = 10.5$, 4.0, 3.0 Hz, 5-H), 5.65 (1H, dd, $J = 10.5$, 4.0 Hz, 2-H), 5.77 (1H, t, $J = 10.5$ Hz, 4-H), 6.29 (1H, t, $J = 10.5$ Hz, 3-H), 6.83 (1H, d, $J = 4.0$ Hz, 1-H). 7.20—8.0 (20H, m, benzoyl × 4); β-anomer δ_H 4.22—4.41 (2H, m, 6-H_2), 4.27 (1H, m, 5-H), 5.72 (1H, t, $J = 9.5$ Hz, 4-H), 5.83 (1H, dd, $J = 9.5$, 8.0 Hz, 2-H), 6.00 (1H, t, $J = 9.5$ Hz, 3-H), 6.25 (1H, d, $J = 8.0$ Hz, 1-H), 7.20—8.0 (20H, m, benzoyl × 4).

6-*O*-Acetyl-2,3,4-tri-*O*-benzoyl-α-D-glucopyranosyl bromide (7) A solution of **6** (58.0 mg, 0.09 mmol) in CH_2Cl_2 (1 ml) was treated with 30% HBr–AcOH (0.6 ml) at 0 °C. The mixture was stirred at room temperature for 3 h, then neutralized with saturated aqueous $NaHCO_3$ (8 ml), and extracted with $CHCl_3$ (50 ml). The $CHCl_3$ layer was washed with saturated aqueous $NaHCO_3$ (10 ml), and saturated aqueous NaCl (10 ml × 2), dried over Na_2SO_4 and evaporated *in vacuo* to give the crude product **7** quantitatively as colorless crystals (57.0 mg). mp 55—60 °C. $Rf = 0.55$ (hexane : AcOEt = 2 : 1). $[\alpha]_D^{27}$ +101.0° ($c = 0.97$, $CHCl_3$). ^1H-NMR (300 MHz) δ_H: 2.11 (3H, s, 6-Ac). 4.28 (1H, dd, $J = 12.7$, 3.0 Hz, 6-Ha), 4.37 (1H, dd, $J = 12.5$, 4.0 Hz, 6-Hb), 4.59 (1H, ddd, $J = 10.0$, 4.0, 3.0 Hz, 5-H), 5.30 (1H, dd, $J = 10.0$, 4.0 Hz, 2-H), 5.72 (1H, t, $J = 10.0$ Hz, 4-H), 6.22 (1H, t, $J = 10.0$ Hz, 3-H), 6.85 (1H, d, $J = 4.0$ Hz, 1-H), 7.20—8.0 (15H, m, benzoyl × 3). HR-FAB-MS *m/z*: 619.0605 $[M+Na]^+$; Calcd for $C_{29}H_{25}{}^{79}BrNaO_9$: 619.0580, *m/z*: 621.0521 $[M+Na]^+$; Calcd for $C_{29}H_{25}{}^{81}BrNaO_9$: 621.0559.

2-Acetylphenyl 6′-*O*-Acetyl-2′,3′,4′-tri-*O*-benzoyl-α- and β-D-glucopyranoside (8a and 8b) Method 1: A mixture of 2-hydroxyacetophenone (94.1 mg, 0.69 mmol), 1.25 N aqueous NaOH (0.70 ml, 0.88 mmol), and BTEAB (76.7 mg, 0.28 mmol) was added to a solution of **7** (200 mg, 0.34 mmol) in $CHCl_3$ (1.4 ml) and the whole was stirred at 60 °C for

1.8 h. It was then cooled to 0 °C, and partitioned between $CHCl_3$ (80 ml) and H_2O (50 ml). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC (hexane : AcOEt = 2 : 1) to give **8b** as light yellow amorphous crystals (83.5 mg, 38%) and **9** as a light yellow oil (134 mg). **8b**, mp 60—65 °C. Rf = 0.31 (hexane : AcOEt = 2 : 1). $[\alpha]_D^{27}$ +15.61° (c = 1.01, $CHCl_3$). ^{1}H-NMR (300 MHz) δ_H: 2.04 (3H, s, 6′-OAc), 2.52 (3H, s, 2-Ac), 4.21 (1H, ddd, J = 9.5, 5.7, 2.8 Hz, 5′-H), 4.29 (1H, dd, J = 12.0, 2.8 Hz, 6′-Ha), 4.38 (1H, dd, J = 12.0, 5.7 Hz, 6′-Hb), 5.53 (1H, d, J = 7.5 Hz, 1′-H), 5.69 (1H, t, J = 9.5 Hz, 4′-H), 5.88 (1H, dd, J = 9.5, 7.5 Hz, 2′-H), 5.98 (1H, t, J = 9.5 Hz, 3′-H), 7.12 (1H, ddd, J = 8.0, 7.0, 1.0 Hz, 5-H), 7.13 (1H, d, J = 7.0 Hz, 3-H), 7.45 (1H, m, 4-H), 7.66 (1H, dd, J = 8.0, 2.2 Hz, 6-H), 7.24—7.60 (9H, benzoyl), 7.81—7.97 (6H, benzoyl). ^{13}C-NMR (100.6 MHz) δ_C: 20.6 (q, $OCO\underline{C}H_3$), 31.7 (q, $CO\underline{C}H_3$), 62.4 (t, 6′-C), 69.1 (d, 4′-C), 71.5 (d, 2′-C), 72.5 (d, 5′-C), 72.9 (d, 3′-C), 98.8 (d, 1′-C), 115.5 (d, 3-C), 123.3 (d, 5-C), 133.6 (benzoyl-C), 130.3 (d, 6-C), 133.1 (d, 4-C), 155.2 (s, 2-C), 128.3, 128.4, 128.5, 129.7, 129.8, 133.4, 133.5, 133.6 (benzoyl-C), 165.0, 165.1, 165.7, 170.4 (s, 2′,3′,4′-$O\underline{C}OC_6H_5$, 6′-$O\underline{C}OCH_3$), 199.4 (s, 1-$\underline{C}OCH_3$). HR-FAB-MS m/z: 675.1855 $[M+Na]^+$; Calcd for $C_{37}H_{32}NaO_{11}$: 675.1842. **9**, Rf = 0.49 (hexane : AcOEt = 2 : 1). ^{1}H-NMR (300 MHz) δ_H: 4.42 (1H, m, 5-H), 4.67 (2H, m, 6-H_2), 5.73 (1H, dd, J = 4.7, 4.0 Hz, 4-H), 6.08 (1H, d, J = 4.0 Hz, 3-H), 6.93 (1H, s, 1-H), 7.37—7.63 (9H, benzoyl). 7.94—8.13 (6H, benzoyl). HR-FAB-MS m/z: 517.1501 $[M+1]^+$; Calcd for $C_{29}H_{25}O_9$: 517.1499.

Method 2: A solution of 2-hydroxyacetophenone (50 mg, 0.37 mmol) in dry toluene (3.0 ml) containing $CdCO_3$ (254 mg, 1.47 mmol) was refluxed for 4 h with removal of the generated water through MS-4A in a dropping funnel. Then the bromide **7** (438 mg, 0.74 mmol) was added and the mixture was refluxed for a further 21 h. The hot reaction mixture was immediately filtered through a Celite pad, and the solid was washed with hot $CHCl_3$ (10 ml). The filtrate and the washings were combined and evaporated *in vacuo*. The residue was purified by preparative TLC (hexane : AcOEt = 2 : 1) to give **8a** as colorless crystals (106.3 mg, 44%) and **8b** as light yellow amorphous crystals (103 mg, 43%). **8a**, mp 63—65 °C. Rf = 0.42 (hexane : AcOEt = 2 : 1). $[\alpha]_D^{27}$ +16.32° (c = 0.98, $CHCl_3$). ^{1}H-NMR (300 MHz) δ_H: 2.05 (3H, s, 6′-OAc), 2.87 (3H, s, 2-Ac), 4.21—4.42 (3H, m, 5′-H, 6′-H_2), 5.50 (1H, dd, J = 10.0, 3.5 Hz, 2′-H), 5.76 (1H, m, 4′-H), 6.14 (1H, d, J = 3.5 Hz, 1′-H), 6.37 (1H, t, J = 10.0 Hz, 3′-H), 7.12 (1H, ddd, J = 7.5, 7.0, 1.0 Hz, 5-H), 7.26—7.56 (11H, m, benzoyl, 3, 4-H), 7.74 (1H, dd, J = 7.5, 2.0 Hz, 6-H), 7.88—7.98 (6H, m, benzoyl). ^{13}C-NMR (100.6 MHz) δ_C: 20.6 (q, $OCO\underline{C}H_3$), 32.4 (q, $CO\underline{C}H_3$), 61.9 (t, 6′-C), 68.5 (d, 4′-C), 69.0 (d, 5′-C), 70.0 (d, 3′-C), 71.6 (d, 2′-C), 94.9 (d, 1′-C), 114.8 (d, 3-C), 122.9 (d, 5-C), 130.6 (d, 6-C), 133.3 (d, 4-C), 155.0 (s, 2-C), 128.4, 128.5, 128.6, 128.7, 129.7, 129.8, 133.6, 133.7 (benzoyl-C), 165.2, 165.7, 165.8, 170.4 (2′,3′,4′-$O\underline{C}OC_6H_5$, 6′-$O\underline{C}OCH_3$), 199.3 (s, 1-$\underline{C}OCH_3$). HR-FAB-MS m/z: 675.1884 $[M+Na]^+$; Calcd for $C_{37}H_{32}NaO_{11}$: 675.1842. **8b** was identical with **8b** described above (method 1) by comparison of the ^{1}H-NMR spectra.

2-Acetylphenyl 2′,3′,4′-Tri-*O*-benzoyl-β-D-glucopyranoside (10) A solution of **8b** (116 mg, 0.18 mmol) in 1% HCl–MeOH (12.6 ml) was stirred at room temperature for 25 h. The mixture was neutralized with triethylamine and evaporated *in vacuo*. The residue was purified by preparative TLC (hexane : AcOEt = 1 : 1) to give **10** as light yellow crystals (88.1 mg, 82%). mp 68—74 °C; Rf = 0.59 (hexane : AcOEt = 1 : 1). $[\alpha]_D^{27}$ +19.04° (c = 1.04, $CHCl_3$). ^{1}H-NMR (300 MHz) δ_H: 2.55 (3H, s, 1-Ac), 2.60 (1H, br, 6′-OH), 3.79 (1H, dt, J = 13.5, 5.0 Hz, 6′-Ha), 3.87 (1H, ddd, J = 13.5, 10.0, 2.0 Hz, 6′-Hb), 3.95 (1H, ddd, J = 10.0, 5.0, 2.0 Hz, 5′-H), 5.49 (1H, d, J = 7.8 Hz, 1′-H), 5.58 (1H, t, J = 10.0 Hz, 4′-H), 5.87 (1H, dd, J = 10.0, 7.8 Hz, 2′-H), 6.03 (1H, t, J = 10.0 Hz, 3′-H), 7.10 (1H, dd, J = 8.5, 0.9 Hz, 3-H), 7.13 (1H, dt, J = 0.9, 7.8 Hz, 5-H), 7.46 (1H, m, 4-H), 7.62 (1H, dd, J = 7.8, 2.0 Hz, 6-H), 7.20—7.56 (9H, m, benzoyl), 7.80—8.00 (6H, m, benzoyl). HR-FAB-MS m/z: 633.1801 $[M+Na]^+$; Calcd for $C_{35}H_{30}NaO_{10}$: 633.1737.

2-Acetylphenyl 2″,3″,4″-Tri-*O*-benzoyl-β-D-xylopyranosyl-(1→6)-2′,3′,4′-tri-*O*-benzoyl-β-D-glucopyranoside (12) Compound **10** (20.6 mg, 0.03 mmol), AgOTf (16.8 mg, 0.06 mmol) in toluene (0.4 ml) and 2,4,6-collidine (7.6 mg, 0.06 mmol) were added to a mixture of MS-4A (51.6 mg) in CH_2Cl_2 (2 ml) at −40 °C under argon. After stirring for 15 min, the bromide **11** (34.7 mg, 0.07 mmol) was added and the mixture was stirred at −40 °C for 1 h. It was then filtered through a Celite pad and the filtrate was diluted with $CHCl_3$ (50 ml), washed with 10% aqueous $Na_2S_2O_3$ (10 ml) and water (10 ml), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC (benzene : AcOEt = 20 : 1 × 3) to give the diglycoside **12** as colorless crystals (11.8 mg, 33%) and the orthoester **13** as colorless crystals (5 mg, 14%). **12**, mp 90—100 °C. Rf = 0.58 (benzene : AcOEt = 20 : 1 × 3). $[\alpha]_D^{27}$ +23.94° (c = 0.66, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 2.46 (3H, s, 2-Ac), 3.61 (1H, dd, J = 12.0, 7.3 Hz, 5″-Ha), 3.89 (1H, dd, J = 11.5, 7.0 Hz, 6′-Ha), 4.07 (1H, dd, J = 11.5, 2.0 Hz, 6′-Hb), 4.20 (1H, ddd, J = 10.0, 7.0, 2.0 Hz, 5′-H), 4.35 (1H, dd, J = 12.0, 4.2 Hz, 5″-Hb), 4.85 (1H, d, J = 5.5 Hz, 1″-H), 5.25 (1H, dt, J = 4.2, 7.3 Hz, 4″-H), 5.37 (1H, dd, J = 7.3, 5.5 Hz, 2″-H), 5.44 (1H, d, J = 7.5 Hz, 1′-H), 5.53 (1H, t, J = 10.0 Hz, 4′-H), 5.70 (1H, t, J = 7.3 Hz, 3″-H), 5.80 (1H, dd, J = 10.0, 7.5 Hz, 2′-H), 5.94 (1H, t, J = 10.0 Hz, 3′-H), 7.05 (1H, t, J = 7.5 Hz, 5-H), 7.11 (1H, d, J = 8.0 Hz, 3-H), 7.20—7.56 (19H, m, benzoyl, 4-H), 7.59 (1H, dd, J = 7.5, 1.5 Hz, 6-H), 7.75—8.00 (12H, m, benzoyl). HR-FAB-MS m/z: 1077.2958 $[M+Na]^+$; Calcd for $C_{61}H_{50}NaO_{17}$: 1077.2946. **13**, mp 89—100 °C. Rf = 0.66 (benzene : AcOEt = 20 : 1 × 3). $[\alpha]_D^{27}$ +3.48 (c = 0.46, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 2.48 (3H, s, 2-Ac), 3.50 (1H, dd, J = 11.0, 2.5 Hz, 6′-Ha), 3.59 (1H, dd, J = 12.0, 8.5 Hz, 5″-Ha), 3.64 (1H, dd, J = 11.0, 6.0 Hz, 6′-Hb), 4.07 (1H, ddd, J = 9.0, 6.0, 2.5 Hz, 5′-H), 4.09 (1H, dd, J = 12.0, 7.0 Hz, 5″-Hb), 4.54 (1H, ddd, J = 4.7, 3.3, 1.5 Hz, 2″-H), 5.20 (1H, ddd, J = 8.5, 7.0, 2.0 Hz, 4″-H), 5.48 (1H, d, J = 7.0 Hz, 1′-H), 5.62 (1H, t, J = 9.5 Hz, 4′-H), 5.65 (1H, dd, J = 3.3, 2.0 Hz, 3″-H), 5.84 (1H, d, J = 4.7 Hz, 1″-H), 5.85 (1H, dd, J = 9.5, 7.0 Hz, 2′-H), 5.90 (1H, t, J = 9.5 Hz, 3′-H), 6.97 (1H, dd, J = 1.0, 8.0 Hz, 3-H), 7.10—7.64 (23H, m, benzoyl, 4,5,6-H), 7.78—8.10 (10H, m, benzoyl). HR-FAB-MS m/z: 1077.2950 $[M+Na]^+$; Calcd for $C_{61}H_{50}NaO_{17}$: 1077.2946.

2-Acetylphenyl β-D-Xylopyranosyl-(1→6)-β-D-glucopyranoside (1) A solution of **12** (11.8 mg, 0.01 ml) in MeOH–tetrahydrofuran (THF) (2 ml, 1 : 1) was treated with 2.8% NaOMe–MeOH (0.26 ml, 0.14 mmol), and the mixture was stirred at room temperature for 5 h. It was then neutralized with IR-120 (H^+), filtered and evaporated *in vacuo*. The residue was purified by preparative TLC ($CHCl_3$: MeOH = 5 : 1) and recrystallized from benzene to afford **1** as colorless crystals (3.7 mg, 77%). mp 117—118 °C. Rf = 0.20 ($CHCl_3$: MeOH = 5 : 1). $[\alpha]_D^{27}$ +26.51° (c = 0.08, $CHCl_3$). ^{1}H-NMR (400 MHz) δ_H: 2.90 (3H, s, 2-Ac), 3.60 (1H, dd, J = 11.0, 10.0 Hz, 5″-Ha), 4.05 (1H, dd, J = 8.5, 7.0 Hz, 2″-H), 4.12 (1H, dd, t, J = 8.5 Hz, 3″-H), 4.19 (1H, t, J = 9.0 Hz, 4′-H), 4.21 (1H, m, 4″-H), 4.29 (1H, dd, J = 10.0, 9.0 Hz, 3′-H), 4.26 (1H, dt, J = 1.5, 10.0 Hz, 2′-H), 4.31 (1H, dd, J = 11.0, 5.0 Hz, 5″-Hb), 4.31 (1H, m, 5′-H), 4.37 (1H, dd, J = 11.0, 6.0 Hz, 6′-Ha), 4.86 (1H, d, J = 11.0 Hz, 6′-Hb), 5.00 (1H, d, J = 7.0 Hz, 1″-H), 5.58 (1H, d, J = 10.0 Hz, 1′-H), 6.98 (1H, dt, J = 0.8, 7.5 Hz, 5-H), 7.54 (1H, ddd, J = 8.5, 7.5, 1.7 Hz, 4-H), 7.87 (1H, dd, J = 8.5, 0.8 Hz, 3-H), 7.92 (1H, dd, J = 7.5, 1.7 Hz, 6-H). HR-FAB-MS m/z: 453.1389 $[M+Na]^+$; Calcd for $C_{19}H_{26}NaO_{11}$: 453.1373.

2-Acetylphenyl 2″,3″,4″-Tri-*O*-acetyl-β-D-xylopyranosyl-(1→6)-2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranoside (14) A solution of **1** (3 mg, 0.007 mmol) and Ac_2O (0.1 ml) in pyridine (0.2 ml) was stirred at room temperature for 24 h, then concentrated *in vacuo* and the residue was purified by preparative TLC (hexane : AcOEt = 10 : 1) to give **14** as colorless crystals (4 mg, 84.2%): mp 193—194 °C ($CHCl_3$–hexane, lit. 5: 194—195°C). $[\alpha]_D^{27}$ −65.71° (c = 0.35, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra of **14** were superimposable on those of the natural product.[5]

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