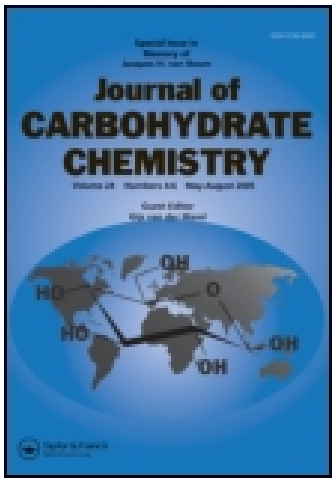

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Synthesis of 3-O-β-D-Glucopyranosyl-(3R)-hydroxybutanolide (Kinsenoside) and 3-O-β-D-Glucopyranosyl-(3S)-hydroxybutanolide (Goodyeroside A)

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Synthesis of 3-*O*-β-D-Glucopyranosyl-(3*R*)-hydroxybutanolide (Kinsenoside) and 3-*O*-β-D-Glucopyranosyl-(3*S*)-hydroxybutanolide (Goodyeroside A)

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The first synthesis of 3-*O*-β-D-glucopyranosyl-(3*R*)-hydroxybutanolide (Kinsenoside) and 3-*O*-β-D-glucopyranosyl-(3*S*)-hydroxybutanolide (Goodyeroside A) is described. The diastereomers of the aglycon in 2-*O*-β-D-gulucopyranosyl-1,2,4-butanetriol derivatives, which were separable precursors of Kinsenoside and Goodyeroside A, were synthesized from optically nonactive 1,2,4-butanetriol and α-D-glucopyranosyl trichloroacetimidate in excellent yields.

Keywords Glycoside, Glycosylation, Lactone, Natural product, Oxidation

INTRODUCTION

Anoectochilus formosanus Hay has been used as a crude drug in Taiwan for lung disease, pleurodynia, abdomenal pain, fever, hypertension, and snake

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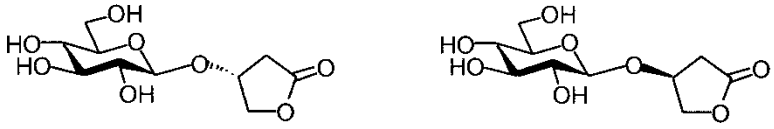
bites.[1,2] In 1993, Ito and coworkers reported the isolation of a simple aliphatic glucoside, which was characterized as 3-*O*-β-D-glucopyranosyl-(3*R*)-hydroxybutanolide **1** (Kinsenoside), from *Anoectochilus koshunensis*.[3] Several bioactive molecules related to Kinsenoside were also found from an undefined *Anoectochilus* species.[4] From a study of the components of *A. formosanus*, butanoic acid glucosides have been of great interest.[5] However, the structure-bioactivity relationship had not been studied because of the difficulty of the cultivation of *A. formosanus* Hay. Goodyeroside A **2**, which is a diastereomer of **1** on the aglycon part, is expected as a substitute of **1**,[6] but there is not sufficient information about its bioactivity to use as a drug. To study the structure-bioactivity relationship, we planned the synthesis of **1** and **2** (Fig. 1). In this communication, we would like to report an efficient large-scale synthesis of **1** and **2** and related analogue synthesis.

RESULTS AND DISCUSSION

The chemical stability of **1** and **2**, which are easily decomposed by the β-elimination of an aglycon moiety to give glucose under the basic conditions, is important in planning the synthetic route. We suggest that the aglycon residue is constructed by oxidation of the hydroxymethyl group after the regio- and stereoselective glycosylation. The synthetic strategy based on the glycosylation of a 1,2,4-butanetriol derivative is shown in Fig. 2.

Many types of 1,2,4-butanetriol derivatives are commercially available. However, optically active forms are very expensive and difficult to use in large-scale synthesis. We tried to use the optically nonactive 1,2,4-butanetriol and to separate the diastereomers after construction of the glycosidic linkage. A partly protected 1,2,4-butanetriol for the glycosylation was synthesized as shown in Sch. 1.

Construction of the β-glucoside was accomplished using the imidate method (Sch. 2).[7] Reaction of 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate **8** with butanetriol **7** in CH_2Cl_2 at room temperature in the presence of Me_3SiOTf (1 equiv.) gave the corresponding β-glucoside 9 as a 1:1 diastereomeric mixture on the aglycon part. Deprotection of the *O*-allyl group of **9** by use of $PdCl_2$[8] gave alcohols **10** (*R*, *S*) as chromatographically



1 (Kinsenoside) **2** (Goodyeroside A)

Figure 1: Structures of Kinsenoside and Goodyeroside A.

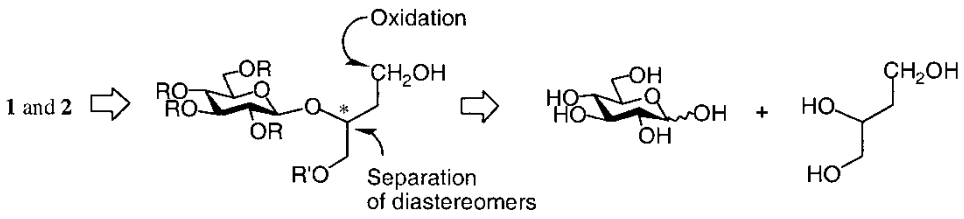
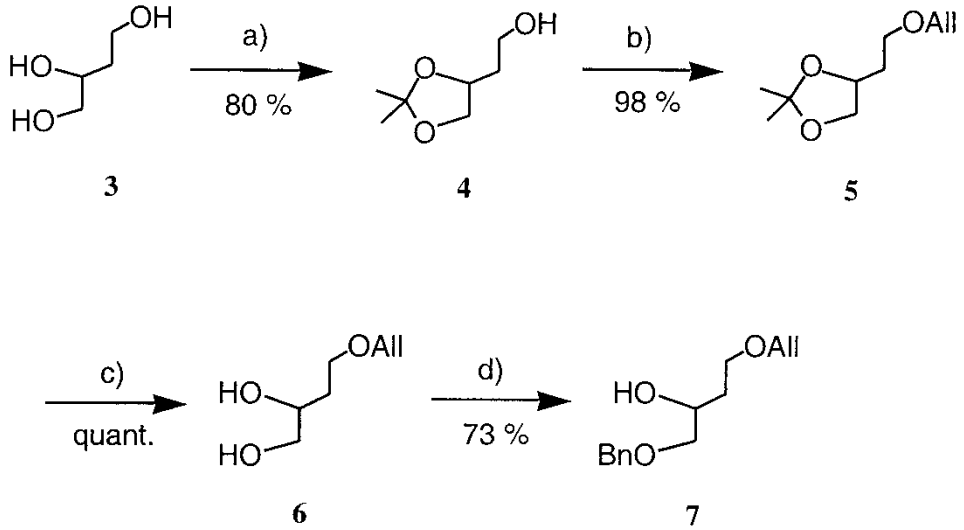
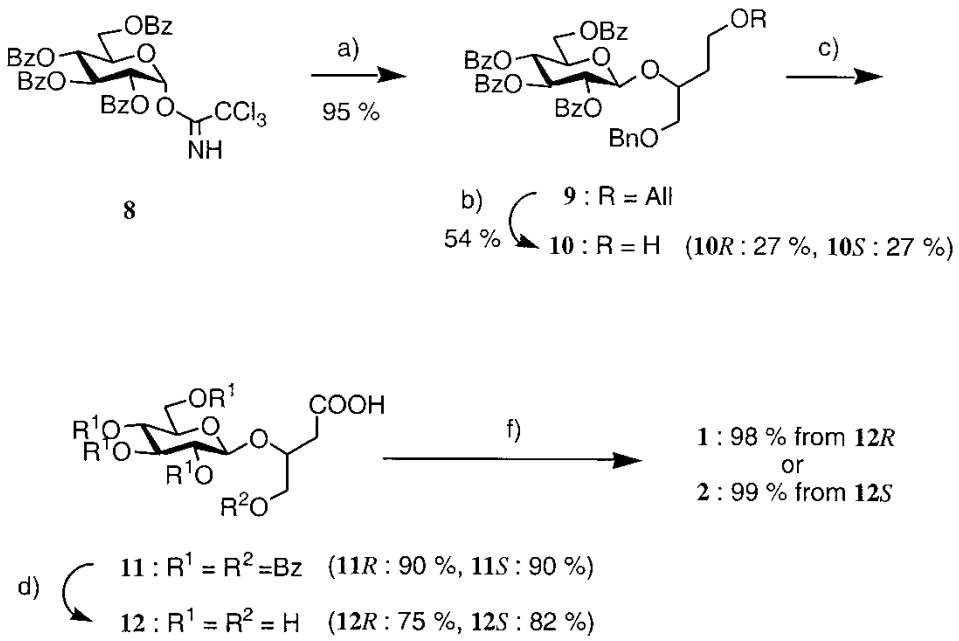


Figure 2: Synthetic plan of **1** and **2**.

separable diastereomers. Compound **10** (*R*, *S*) was individually oxidized to carboxylic acid **11** (*R*, *S*) by the agency of the ruthenium reagent.[9] Under this condition, the benzyl group was also oxidized to the benzoyl group. De-*O*-benzoylation of compound **12** (*R*, *S*) gave Kinsenoside and Goodyeroside A as the acid form, which were converted to Kinsenoside **1** and Goodyeroside A **2** by treatment with acid from ion-exchange resin (DOWEX® 50WX-4) in H_2O. The spectral data of **1** and **2** were in good agreement with the reported data of the natural product.[5,10] The structure of **1** was already confirmed by X-ray analysis of the peracetate.[5] The structure of **2** was newly confirmed by a comparison with the spectral data of perbenzoate **14** derived from **2** (Sch. 3). Treatment of **2** with benzoyl chloride in pyridine gave a perbenzoate derivative **14** in a good yield. This compound was also synthesized from optically active (3*S*)-hydroxybutylolactone **13** and imidate **8**, and the spectral data agreed with those of **14** derived from **2**.



Scheme 1: Synthesis of partly protected 1,2,4-butanetriol derivative: (a) TsOH, acetone; (b) Allyl bromide, NaH, DMF; (c) DOWEX® 50WX-4, MeOH; (d) $(n\text{-Bu})_2SnO$, toluene then BnBr, CsF, DMF.



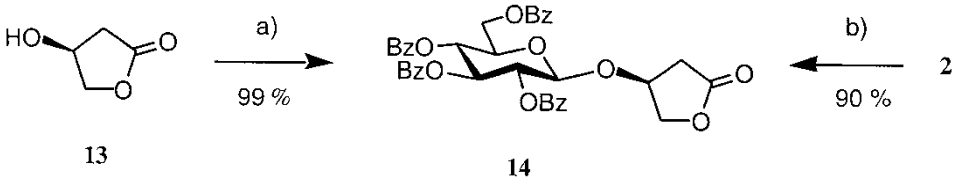
Scheme 2: Synthesis of **1** and **2**: (a) **7**, Me_3SiOTf, Molecular sieves AW-300, CH_2Cl_2, 0°C; (b) $PdCl_2$, AcONa-AcOH buffer (pH = 4.5), 1,4-dioxane; (c) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O; (d) NaOMe, MeOH; (e) DOWEX® 50WX-4, H_2O.

Thus, Kinsenoside **1** and Goodyeroside A **2** were synthesized by the same route with construction of the aglycon residue after the regio- and stereoselective glycosylation. This method is promising for the supply of related analogues of **1** and **2**.

EXPERIMENTAL

General Methods

Optical rotations were measured at 25°C with a HORIBA polarimeter SEPA-300. NMR spectra were measured on a JEOL JNM-ECP 400



Scheme 3: Synthesis of tetra-benzoate **14**: (a) **8**, Me_3SiOTf, Molecular sieves AW-300, CH_2Cl_2, 0°C; (b) BzCl, pyridine.

spectrometer (400 MHz). ^{1}H-NMR were recorded in $CDCl_3$, CD_3OD, or D_2O using Me_4Si (δ 0.00) or DOH (δ 4.81) as the internal standard. ^{13}C-NMR spectra were recorded in $CDCl_3$, CD_3OD, or D_2O using $CDCl_3$ (δ 77.0), CD_3OD (δ 49.0), acetone (δ 30.3), or 1,4-dioxane (δ 67.6) as the internal standard. Coupling constants were measured in Hz. Silica gel column chromatography was performed using Wakogel C-300 (Wako Pure Chemical Industries, Ltd.). Analytical TLC was performed on aluminium plates coated with silica gel 60 F254 (Merck). Molecular sieves were purchased from Aldrich Chemical Company, Inc., and activated at 180°C under vacuum immediately prior to use.

*(±)-1,2-O-Isopropylidene-1,2,4-butanetriol (**4**)*

To an acetone solution (50 mL) of **3** (3.0 g, 28 mmol) were added $CuSO_4$ (13.5 g, 84.9 mmol) and *p*-TsOH (5.4 g, 28.3 mmol). After being stirred for 6 hr at room temperature, the reaction mixture was poured into 1 M NaOH and the insoluble component was filtered. Most of acetone in the filterate was evaporated and the residue was diluted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 1:1 ∼ 0:1) to afford **4** (3.3 g, 80%) as an oil; ^{1}H-NMR ($CDCl_3$) δ 4.26 (qt, 1H, H-2, J = 6.2 Hz), 4.09 (dd, 1H, H-1a, J = 6.2, 7.9 Hz), 3.77 (m, 2H, H-4), 3.59 (dd, 1H, H-1b, J = 7.9, 7.9 Hz), 2.93 (br s, 1H, OH), 1.85–1.79 (m, 2H, H-3), 1.42 and 1.36 (each s, 6H, acetonide); ^{13}C-NMR ($CDCl_3$) δ 108.79, 74.51 (C-2), 69.28 (C-1), 59.89 (C-4), 35.63 (C-3), 26.71, 25.51. Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.36; H, 9.76.

*(±)-1,2-O-Isopropylidene-4-O-allyl-1,2,4-butanetriol (**5**)*

To a DMF (5 mL) solution of **4** (320 mg, 2.20 mmol) was added NaH (128 mg, 4.40 mmol) at 0°C. After being stirred for 30 min, to the mixture was added allyl bromide (AllBr, 0.462 mL, 0.44 mmol) dropwise at a temperature kept below 0°C. After being stirred for 6 hr at rt, the mixture was poured into saturated aqueous NH_4Cl (600 mL) and extracted with EtOAc (100 mL × 3). The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 9:1 ∼ 4:1) to give **5** (4.13 g, 98%) as an oil; ^{1}H-NMR ($CDCl_3$) δ 5.95–5.85 (m, 1H, CH_2-C*H*=CH_2), 5.26 (br d, 1H, CH_2-CH=C*H*$_2$, J = 17.2 Hz), 5.17 (br d, 1H, CH_2-C*H*=C*H*$_2$, J = 10.3 Hz), 4.20 (qt, 1H, H-2, J = 7.0 Hz), 4.06 (br t, 1H, H-1a, J = 7.0 Hz), 3.96 (br d, 2H, C*H*$_2$-CH=CH_2, J = 5.5 Hz), 3.59–3.48 (m, 3H, H-1b, 4a, 4b), 1.93–1.80 (m, 2H, H-3), 1.40 and 1.35 (each s, 6H, acetonide); ^{13}C-NMR ($CDCl_3$) δ 134.62, 116.63, 108.36, 73.71 (C-2), 71.77, 69.51 (C-1), 66.82 (C-4), 33.74 (C-3), 26.80, 25.64. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.58; H, 9.66.

*(±)-4-O-Allyl-1,2,4-butanetriol (**6**)*

To a MeOH (2 mL) solution of **5** (200 mg, 1.07 mmol) were added Dowex® 50WX-4 (*ca*. 50 mg) and H_2O (2 mL). After being stirred for 22 hr at rt, the mixture was filtered and concentrated *in vacuo* to afford **6** (157 mg, quant.) as an oil; ^{1}H-NMR (CD_3OD) δ 5.96–5.86 (m, 1H, CH_2-C*H*=CH_2), 5.26 (br d, 1H, CH_2-CH=C*H*$_2$, J = 17.2 Hz), 5.15 (br d, 1H, CH_2-CH=C*H*$_2$, J = 10.3 Hz), 3.98 (d, 2H, C*H*$_2$-CH=CH_2, J = 5.5 Hz), 3.77–3.71 (m, 1H, H-2), 3.63–3.54 (m, 2H, H-4), 3.49 (dd, 1H, H-1a, J = 4.8, 11.2 Hz), 3.44 (dd, 1H, H-1b, J = 6.2, 11.2 Hz), 1.83–1.75 (m, 1H, H-3a), 1.66–1.57 (m, 1H, H-3b); ^{13}C-NMR ($CDCl_3$) δ 136.13, 117.05, 72.78, 70.61 (C-2), 68.11 (C-4), 67.37 (C-1), 34.42 (C-3). Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.57; H, 9.73.

*(±)-4-O-Allyl-1-O-benzyl-1,2,4-butanetriol (**7**)*

To a toluene (50 mL) solution of **6** (2.35 g, 16.2 mmol) was added (n-Bu)$_2$SnO (4.83 g, 19.4 mol). After being stirred for 3 hr at reflux temperature, the solvent was removed by evaporation. To a DMF (30 mL) solution of the residue were added CsF (5.4 g, 36 mol) and BnBr (2.02 mL, 17.0 mol), and the mixture was stirred for 12 hr at 0°C. The reaction mixture was poured into 1M NaOH (700 mL) and extracted with EtOAc (100 mL × 3). The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (n-hexane: EtOAc = 1:0 ∼ 3:1) to give **7** (2.8 g, 73%) as a syrup; ^{1}H-NMR ($CDCl_3$) δ 7.35–7.30 (m, 5H, phenyl), 5.92–5.83 (m, 1H, CH_2-C*H*=CH_2), 5.25 (d, 1H, CH_2-CH=C*H*$_2$, J = 17.2 Hz), 5.16 (d, 1H, CH_2-CH=C*H*$_2$, J = 11.0 Hz), 4.53 (s, 2H, benzyl), 4.02–3.95 (m, 1H, H-2), 3.95 (d, 2H, C*H*$_2$-CH=CH_2, J = 5.9 Hz), 3.61 (ddd, 1H, H-4a, J = 9.5, 6.2, 6.2 Hz), 3.56 (ddd, 1H, H-4b, J = 9.5, 6.2, 6.2 Hz), 3.47 (dd, 1H, H-1a, J = 4.0, 9.5 Hz), 3.40 (dd, 1H, H-1b, J = 7.0, 9.5 Hz), 3.22 (br s, 1H, OH), 1.77–1.72 (m, 2H, H-3); ^{13}C-NMR ($CDCl_3$) δ 137.89, 134.42, 128.27, 127.61, 126.80, 116.89, 74.18, 73.15, 71.83, 68.89, 67.61, 32.98. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.45; H, 8.29.

*4-O-Allyl-1-O-benzyl-2-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)-1,2,4-butanetriol (**9**)*

The mixture of acceptor **7** (0.78 g, 5.94 mmol), imidate **8** (2.20 g, 2.97 mmol), and molecular sieves 4Å (AW-300, *ca.* 1 g) in CH_2Cl_2 (50 mL) was stirred for 2 hr at room temperature under an argon atmosphere. To this mixture was added Me_3SiOTf (0.66 g, 2.97 mmol) at 0°C. After being stirred for 10 min, the reaction was stopped by addition of Et_3N (3.00 g, 29.7 mmol). The solution was filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (n-hexane:EtOAc = 5:1) to afford ***9R*** and ***9S*** (2.30 g, 95%) as an unseparable mixture (***9R***:***9S*** = 1:1); ^{1}H-NMR ($CDCl_3$)

δ 8.07–7.84 and 7.56–7.19 (m, 25H, phenyl), 5.94 (dd, 0.5H, H-3′, $J = 9.9$, 9.9 Hz), 5.92 (dd, 0.5H, H-3′, $J = 9.9$, 9.9 Hz), 5.87–5.72 (m, 1H, CH_2-C*H*=CH_2), 5.72 (dd, 0.5H, H-4′, $J = 9.9$, 9.9 Hz), 5.67 (dd, 0.5H, H-4′, $J = 9.9$, 9.9 Hz), 5.58 (dd, 0.5H, H-2′, $J = 9.9$, 8.4 Hz), 5.56 (dd, 0.5H, H-2′, $J = 9.9$, 8.4 Hz), 5.21 (d, 0.5H, H-1′, $J = 8.4$ Hz), 5.15–5.08 (m, 2H, CH_2-CH=CH_2), 5.01 (d, 0.5H, H-1′, $J = 8.4$ Hz), 4.65 (dd, 0.5H, H-6′a, $J = 2.9$, 8.8 Hz), 4.62 (dd, 0.5H, H-6′a, $J = 2.9$, 8.8 Hz), 4.52–4.44 (m, 2H, H-6′b and benzyl), 4.30, 4.23 (each d, 1H, benzyl, $J = 12.1$′Hz), 4.17–4.11 (m, 1.5H, H-2 and H-5′), 4.04–3.98 (m, 0.5H, H-2), 3.92–3.81 (m, 2H, C*H*$_2$-CH=CH_2), 3.72–3.26 (m, 4H, H-1 and H-4), 1.92–1.73 (m, 2H, H-3); ^{13}C-NMR ($CDCl_3$) δ 166.09, 166.07, 165.83, 165.21, 165.16, 164.90, 138.28, 138.05, 134.94, 134.77, 133.38–133.10, 129.81–127.33, 116.60, 116.51, 101.78, 100.85, 77.97, 77.24, 76.17, 73.86, 73.23, 73.08, 73.02, 72.73, 72.19, 72.11, 71.94, 71.78, 71.49, 69.81, 66.43, 65.97, 63.21, 63.09, 32.34.

*1-O-Benzyl-2-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)-1,2,4-butanetriol (**10R**, **10S**)*

To a 1,4-dioxane solution (2 mL) of the mixture (**9*R***:**9*S*** = 1:1, 105 mg, 0.129 mmol) were added an acetic acid buffer (pH 4.5, 2 mL) and $PdCl_2$ (46 mg, 0.26 mmol). After being stirred for 24 hr at room temperature, the solution was diluted with CH_2Cl_2 (*ca.* 10 mL), washed with saturated aqueous $NaHCO_3$ (*ca.* 50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 9:1 ∼ 4:6) to afford **10*R*** (27 mg, 27%) and **10*S*** (27 mg, 27%), respectively. Compound **10*R***: $[\alpha]_D + 27.2^\circ$ (*c* 0.47, CH_2Cl_2); mp: 152 ∼ 154°C (crystalized from EtOH and *n*-hexane); Rf = 0.2 (*n*-hexane:EtOAc = 6:4); ^{1}H-NMR ($CDCl_3$) δ 8.03–7.23 (m, 25H, phenyl), 5.89 (dd, 1H, H-3′, $J = 9.9$, 9.7 Hz), 5.65 (dd, 1H, H-4′, $J = 9.5$, 9.7 Hz), 5.52 (dd, 1H, H-2′, $J = 7.9$, 9.7 Hz), 5.03 (d, 1H, H-1′), 4.61 (dd, 1H, H-6′a, $J = 3.3$, 12.1 Hz), 4.46 (dd, 1H, H-6′b, $J = 5.1$, 12.1 Hz), 4.47, 4.43 (each d, 2H, benzyl, $J = 11.7$ Hz), 4.12 (ddd, 1H, H-5′, $J = 3.3$, 5.1, 9.5 Hz), 4.02 (m, 1H, H-3), 3.71 (dd, 1H, H-4a, $J = 4.8$, 10.1 Hz), 3.55 (dd, 1H, H-4b, $J = 5.9$, 10.1 Hz), 3.51 (m, 2H, H-1a, 1b), 1.77 (m, 2H, H-2a, 2b), 1.54 (br s, 1H, OH); ^{13}C-NMR ($CDCl_3$) δ 166.07, 165.78, 165.19, 165.10, 137.96, 133.44, 133.42, 133.22, 133.15, 129.74, 129.72, 128.40, 128.34, 127.61, 101.55 (C-1′), 78.25 (C-3), 73.38 (benzyl), 72.91 (C-3′), 72.67 (C-4), 72.23 (C-2′), 72.20 (C-5′), 69.74 (C-4′), 63.14 (C-6′), 58.72 (C-1), 34.94 (C-2). Anal. Calcd for $C_{45}H_{42}O_{12}$:C, 69.76; H, 5.46. Found: C, 70.03; H, 5.47. Compound **10*S***: $[\alpha]_D + 3.8^\circ$ (*c* 0.49, CH_2Cl_2); Rf = 0.3 (*n*-hexane:EtOAc = 6:4); ^{1}H-NMR ($CDCl_3$) δ 8.13–7.18 (m, 25H, phenyl), 5.96 (dd, 1H, H-3′, $J = 9.5$, 9.9 Hz), 5.69 (dd, 1H, H-4′, $J = 9.9$, 9.5 Hz), 5.54 (dd, 1H, H-2′, $J = 7.7$, 9.9 Hz), 5.24 (d, 1H, H-1′, $J = 7.7$ Hz), 4.89 (dd, 1H, H-6′a, $J = 2.6$, 12.5 Hz), 4.39 (dd, 1H, H-6′b, $J = 5.5$, 12.5 Hz), 4.32, 4.21 (each d, 2H, benzyl, $J = 12.1$ Hz), 4.24–4.15 (m, 2H, H-3, H-5′), 3.86 (m, 1H, H-1b), 3.40 (dd, 1H,

H-4a, $J = 3.3$, 10.3 Hz), 3.35 (dd, 1H, H-4b, $J = 7.3$, 10.3 Hz), 2.84 (br s, 1H, OH), 1.69 (m, 1H, H-2a), 1.56 (m, 1H, H-2b); ^{13}C-NMR ($CDCl_3$) δ 166.31, 166.74, 165.20, 165.11, 137.86, 133.50, 133.30, 133.18, 133.12, 129.82–128.24, 101.08 (C-1′), 75.59 (C-3), 74.20 (C-4), 73.28 (benzyl), 72.81 (C-3′), 72.35 (C-5′), 71.97 (C-2′), 69.46 (C-4′), 62.53 (C-6′), 58.07 (C-1), 33.97 (C-2). Anal. Calcd for $C_{45}H_{42}O_{12}$: C, 69.76; H, 5.46. Found: C, 69.67; H, 5.74.

*4-O-Benzoyl-3-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)-(**3R**)-3,4-dihydroxy-butanoic Acid (**11R**)*

To a solution (CCl_4; 1.2 mL, MeCN; 1.2 mL, and H_2O; 1.8 mL) of **10*R*** (20 mg, 26×10^{-3} mmol) were added $NaIO_4$ (17 mg, 77×10^{-3} mmol) and $RuCl_3$ (1 mg, 4.8×10^{-3} mmol). After being stirred for 18 hr at room temperature, the solution was diluted with CH_2Cl_2 (*ca.* 10 mL), washed with 1M HCl (*ca.* 50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane:EtOAc = 1:1 ∼ 1:2) to afford **11*R*** (19 mg, 90%); $[\alpha]_D + 5.9^\circ$ (*c* 0.41, acetone); mp: 193 ∼ 195°C (crystalized from acetone and *n*-hexane); ^{1}H-NMR ($CDCl_3$) δ 8.00–7.81 and 7.52–7.25 (m, 25H, phenyl), 5.97 (dd, 1H, H-3′, $J = 9.7$, 9.7 Hz), 5.64 (dd, 1H, H-4′, $J = 9.7$, 9.7 Hz), 5.53 (dd, 1H, H-2′, $J = 7.9$, 9.7 Hz), 5.15 (d, 1H, H-1′, $J = 7.9$ Hz), 4.60 (1H, dd, H-4a, $J = 4.8$, 12.1 Hz), 4.59 (dd, 1H, H-6′a, $J = 2.9$, 12.1 Hz), 4.50 (ddd, 1H, H-3, $J = 4.8$, 5.9, 6.2 Hz), 4.43 (1H, dd, H-6′b, $J = 5.5$, 12.1 Hz), 4.35 (dd, 1H, H-4b, $J = 5.9$, 12.1 Hz), 3.22 (ddd, 1H, H-5′, $J = 2.9$, 5.5, 9.7 Hz), 2.60 (d, 2H, H-2, $J = 6.2$ Hz); ^{13}C-NMR ($CDCl_3$) δ 174.62, 166.06, 166.01, 165.83, 165.19, 165.03, 133.43, 133.26, 133.17, 133.14, 133.04, 129.79–128.28, 101.83, 74.98, 72.81, 72.24, 71.85, 69.65, 65.81, 63.02, 37.11. Anal. Calcd for $C_{46}H_{38}O_{14}$:C, 67.33; H, 4.77. Found: C, 67.15; H, 4.74.

*4-O-Benzoyl-3-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)-(**3S**)-3,4-dihydroxy-butanoic Acid (**11S**)*

Compound **11*S*** was obtained from **10*S*** in the same manner as described for **11*R*** (90%); $[\alpha]_D + 13.6^\circ$ (*c* 0.47, acetone); ^{1}H-NMR ($CDCl_3$) δ 8.01–7.71 and 7.55–7.15 (m, 25H, phenyl), 5.88 (dd, H-3′, $J = 9.7$, 9.7 Hz), 5.70 (dd, 1H, H-4′, $J = 9.7$, 9.7 Hz), 5.52 (dd, 1H, H-2′, $J = 8.1$, 9.7 Hz), 5.08 (d, 1H, H-1′, $J = 8.1$ Hz), 4.73 (dd, 1H, H-6′a, $J = 3.7$, 12.1 Hz), 4.59–4.53 (m, 1H, H-3), 4.49 (dd, 1H, H-6′b, $J = 4.0$, 12.1 Hz), 4.28 (d, 2H, H-4, $J = 5.1$ Hz), 4.10 (ddd, 1H, H-5′, $J = 3.4$, 4.0, 9.7 Hz), 2.85 (dd, 1H, H-2a, $J = 7.3$, 16.1 Hz), 2.65 (dd, 1H, H-2b, $J = 5.1$, 16.1 Hz); ^{13}C-NMR ($CDCl_3$) δ 173.13, 166.61, 165.94, 165.74, 165.16, 165.01, 133.46, 133.42, 133.22, 133.08, 133.04, 129.85–128.22, 101.35, 75.33, 72.74, 72.18, 71.72, 69.77, 65.77, 62.90, 37.63. Anal. Calcd for $C_{46}H_{38}O_{14}$: C, 67.33; H, 4.77. Found: C, 67.23; H, 4.85.

*3-O-(β-D-Glucopyranosyl)-(3R)-3,4-dihydroxy-butanoic Acid (**12R**)*

To a NaOMe (2 mg, 4×10^{-2} mmol) in MeOH (0.4 mL) solution (0.1 M) was added **11*R*** (19 mg, 24×10^{-3} mmol). After being stirred for 3 hr, the mixture was diluted with H_2O (10 mL) and washed with CH_2Cl_2 (2 mL). The water layer was neutralized with DOWEX® 50WX-4 and evaporated *in vacuo* to afford **12*R*** (5.0 mg, 75%) as a syrup. Compound **12*R*** was identified by comparison with an authentic sample; ^{1}H-NMR (D_2O) δ 4.59 (d, 1H, H-1′, $J = 7.9$ Hz), 4.24–4.18 (m, 1H, H-3), 3.92 (dd, 1H, H-6′a, $J = 2.2$, 12.4 Hz), 3.75–3.71 (m, 2H, H-4a and H-6′b), 3.62 (dd, 1H, H-4b, $J = 6.2$, 12.1 Hz), 3.52 (dd, 1H, H-3′, $J = 9.2$, 9.9 Hz), 3.51–3.47 (m, 1H, H-5′), 3.40 (dd, 1H, H-4′, $J = 9.9$, 9.9 Hz), 3.29 (dd, 1H, H-2′, $J = 7.9$, 9.2 Hz), 2.51 (dd, 1H, H-2a, $J = 7.0$, 14.7 Hz), 2.44 (dd, 1H, H-2b, $J = 5.9$, 14.7 Hz); ^{13}C-NMR (D_2O) δ 179.44, 101.75, 78.94, 75.94, 75.62, 73.36, 69.70, 63.92, 60.80, 39.67. (lit.)[5] $[\alpha]_D$ −5.8° (*c* 1.2, MeOH); Positive FAB-MS: m/z 283 $[M + H]^+$; ^{1}H-NMR (CD_3OD) δ 4.44 (d, 1H, H-1′, $J = 7.9$ Hz), 4.12 (dddd, 1H, H-3, $J = 7.3$, 5.9, 5.9, 4.3 Hz), 3.85 (dd, 1H, H-6′a, $J = 1.7$, 11.9 Hz), 3.65 (dd, 1H, H-6′ b, $J = 6.1$ Hz), 3.64 (dd, 1H, H-4, $J = 4.3$, 12.5 Hz), 3.59 (dd, 1H, H-4b, $J = 5.9$ Hz), 3.37 (dd, 1H, H-3′, $J = 8.9$, 8.9 Hz), 3.30 (dd, 1H, H-4′, $J = 8.9$ Hz), 3.36 (m, 1H, H-5′), 3.19 (dd, 1H, H-2′), 2.47 (dd, 1H, H-2a, $J = 7.3$, 14.9 Hz), 2.38 (dd, 1H, H-2b, $J = 5.9$ Hz); ^{13}C-NMR (CD_3OD) δ 179.6, 104.1, 80.3, 78.0, 77.9, 75.4, 71.5, 66.0, 62.7, 41.3.

*3-O-(β-D-Glucopyranosyl)-(3S)-3,4-dihydroxy-butanoic Acid (**12S**)*

Compound **12*S*** was obtained from **11*S*** in the same manner as described for **12*R*** (82%); Compound **12*S*** was identified by comparison with an authentic sample; ^{1}H-NMR (D_2O) δ 4.59 (d, 1H, H-1′, $J = 8.3$ Hz), 4.25–4.18 (m, 1H, H-3), 3.89 (d, 1H, H-6′a, $J = 12.1$ Hz), 3.74–3.61 (m, 3H, H-4a, H-4b and H-6′b), 3.50 (dd, 1H, H-3′, $J = 9.0$, 9.4 Hz), 3.45–3.39 (m, 1H, H-5′), 3.37 (dd, 1H, H-4′, $J = 9.2$, 9.4 Hz), 3.29 (dd, 1H, H-2′, $J = 8.3$, 9.0 Hz), 2.54 (dd, 1H, H-2a, $J = 7.3$, 15.0 Hz), 2.42 (dd, 1H, H-2b, $J = 5.9$, 15.0 Hz). (lit.)[10] $[\alpha]_D$ −19.3° (*c* 0.4, H_2O); Positive FAB-MS: m/z 283 $(M + H)^+$, 305 $(M + Na)^+$; Negative FAB-MS: m/z 281 $(M - H)^-$; HR-FAB-MS: m/z 281.0883 $(M - H)^-$ (Calcd for $C_{10}H_{17}O_9$ 281.0872); ^{1}H-NMR (CD_3OD) δ 4.43 (d, 1H, H-1′, $J = 7.9$ Hz), 4.15 (m, 1H, H-3), 3.86 (dd, 1H, H-6′a, $J = 2.0$, 11.9 Hz), 3.66 (dd, 1H, H-6′b, $J = 5.1$ Hz), 3.63 (dd, 1H, H-4a, $J = 4.5$, 12.3 Hz), 3.58 (dd, 1H, H-4b, $J = 5.9$ Hz), 3.35 (dd, 1H, H-3′, $J = 8.9$, 8.9 Hz), 3.34 (m, 1H, H-5′), 3.22 (dd, 1H, H-4′, $J = 8.9$ Hz), 3.18 (dd, 1H, H-2′), 2.57 (dd, 1H, H-2a, $J = 6.9$, 15.5 Hz), 2.48 (dd, 1H, H-2b, $J = 5.6$ Hz); ^{13}C-NMR (CD^3OD) δ 177.2, 104.1, 79.7, 78.0, 78.0, 75.2, 71.6, 65.6, 62.7, 38.9.

*3-O-(β-D-Glucopyranosyl)-(3R)-hydroxy-butylolactone (**1**)*

To a H_2O (0.4 mL) solution of **12*R*** was added DOWEX® 50WX-4 (*ca.* 20 mg). After being stirred for 18 hr, the resin was filtered and the filtrate was

concentrated *in vacuo* to afford **1** (4.6 mg, 98%). Compound **1** was identified by comparison with an authentic sample; $[\alpha]_D + 48.4^\circ$ (*c* 2.0, EtOH); ^{1}H-NMR (D_2O) δ 4.61 (d, 2H, H-4a and H-4b, $J = 2.9$ Hz), 4.56 (d, 1H, H-1′, $J = 7.7$ Hz), 3.92 (dd, 1H, H-6′a, $J = 2.2$, 12.5 Hz), 3.73 (dd, 1H, H-6′b, $J = 5.5$, 12.5 Hz), 3.50 (dd, 1H, H-3′, $J = 9.2$, 9.2 Hz), 3.47 (ddd, 1H, H-5′, $J = 2.2$, 5.5, 9.5 Hz), 3.40 (dd, 1H, H-4′, $J = 9.2$, 9.5 Hz), 3.28 (dd, 1H, H-2′, $J = 7.7$, 9.2 Hz), 3.01 (dd, 1H, H-2a, $J = 6.2$, 18.3 Hz), 2.73 (d, 1H, H-2b, $J = 18.3$ Hz). (lit.) [5] Positive FAB-MS: m/z 265 $(M + H)^+$, 287 $(M + Na)^+$; ^{1}H-NMR (pyridine-d_5) δ 4.90 (d, 1H, H-1′, $J = 7.9$ Hz), 4.87 (m, 1H, H-3), 4.71 (dd, 1H, H-4a, $J = 1.6$, 10.2 Hz), 4.55 (dd, 1H, H-6′a, $J = 2.3$, 11.8 Hz), 4.43 (dd, 1H, H-4b, $J = 4.6$ Hz), 4.35 (dd, 1H, H-6′b, $J = 5.6$ Hz), 4.24 (m, 1H, H-3′), 4.21 (m, 1H, H-4′), 3.95 (m, 1H, H-5′), 2.85 (m, 2H, H-2a and H-2b); ^{13}C-NMR (pyridine-d_5) δ 175.9, 104.1, 78.7, 78.3, 75.2, 74.8, 74.7, 71.4, 62.7, 35.7.

*3-O-(β-D-Glucopyranosyl)-(3S)-hydroxy-butylolactone (**2**)*

Compound **2** was obtained from **12*S*** in the same manner as described for **1** (99%); Compound 2 was identified by comparison with an authentic sample; $[\alpha]_D$ -71.0° (*c* 0.5, H_2O); ^{1}H-NMR (D_2O) δ 4.62 (d, 1H, H-1′, $J = 7.7$ Hz), 4.59 (br s, 2H, H-4a, H-4b), 3.95 (d, 1H, H-6′a, $J = 12.8$ Hz), 3.76 (dd, 1H, H-6′b, $J = 5.5$, 12.8 Hz), 3.54 (dd, 1H, H-3′, $J = 9.2$, 9.2 Hz), 3.50 (m, 1H, H-5′, $J = 5.5$, 9.2 Hz), 3.43 (dd, 1H, H-4′, $J = 9.2$, 9.2 Hz), 3.31 (dd, 1H, H-2′, $J = 7.7$, 9.2 Hz), 3.07 (dd, 1H, H-2a, $J = 6.2$, 18.3 Hz), 2.83 (d, 1H, H-2b, $J = 18.3$ Hz). (lit.)[10] mp: 156 ∼ 157°C (crystalized from EtOH); $[\alpha]_D$ -71.2° (*c* 0.55, H_2O); Positive FAB-MS: m/z 265 $(M + H)^+$, 287 $(M + Na)^+$; HR-FAB-MS: m/z 287.0843 $(M + Na)^+$ (Calcd for $C_{10}H_{16}O_8Na$ 287.0845); ^{1}H-NMR (pyridine-d_5) δ 4.94 (d, 1H, H-1′, $J = 7.9$ Hz), 4.85 (m, 1H, H-3), 4.69 (dd, 1H, H-4a, $J = 1.5$, 10.2 Hz), 4.54 (dd, 1H, H-6′a, $J = 2.3$, 11.7 Hz), 4.41 (dd, 1H, H-4b, $J = 4.7$ Hz), 4.35 (dd, 1H, H-6′b, $J = 5.3$ Hz), 4.22 (dd, 1H, H-3′, $J = 8.9$, 8.9 Hz), 4.19 (dd, 1H, H-4′, $J = 8.9$ Hz), 3.98 (dd, 1H, H-2′), 3.94 (m, 1H, H-5′), 2.88 (dd, 1H, H-2a, $J = 5.2$, 17.8 Hz), 2.84 (dd, 1H, H-2b, $J = 2.5$ Hz); ^{13}C-NMR (pyridine-d_5) δ 176.2, 103.7, 78.7, 78.4, 74.8, 74.7, 74.0, 71.5, 62.8, 36.4.

*3-O-(2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranosyl)-(3S)-3-hydroxy-butylolactone (**14**)*

From 2 To a pyridine solution (0.1 mL) of **2** (3.0 mg, 11×10^{-3} mmol) was added benzoyl chloride (6.6 μL, 57×10^{-3} mmol). After being stirred for 17 hr at room temperature, the reaction was stopped by addition of MeOH (*ca.* 2 mL). The solution was concentrated and the residue was purified by silica gel column chromatography (*n*-hexane:EtOAc = 2:1 ∼ 1:1) to afford **14** (7.0 mg, 90%). *From 13*: The mixture of acceptor **13** (88 mg, 0.86 mmol), imidate **8** (320 mg, 0.432 mmol), and molecular sieves 4Å (AW-300, *ca.* 1 g) in

CH_2Cl_2 (5 mL) was stirred for 1 hr at room temperature under an argon atmosphere. To this mixture was added Me_3SiOTf (96 mg, 0.43 mmol) at 0°C. After being stirred for 30 min, the reaction was stopped by addition of Et_3N (1.03 g, 4.32 mmol). The solution was filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane:EtOAc = 2:1 ∼1:1) to afford **14** (290 mg, 99%) as a powder; $[\alpha]_D$ −2.0° (*c* 0.7, CH_2Cl_2); mp: 215 ∼ 217°C (recrystalized from EtOAc and *n*-hexane); ^{1}H-NMR ($CDCl_3$) δ 8.05–7.81 and 7.58–7.25 (m, 20H, phenyl), 5.91 (dd, 1H, H-3′, $J = 9.5$, 9.5 Hz), 5.67 (dd, 1H, H-4′, $J = 9.5$, 9.5 Hz), 5.52 (dd, 1H, H-2′, $J = 8.1$, 9.5 Hz), 4.97 (d, 1H, H-1′, $J = 8.1$ Hz), 4.69 (dd, 1H, H-6′a, $J = 2.9$, 12.1 Hz), 4.68–4.64 (m, 1H, H-3), 4.49 (dd, 1H, H-6′b, $J = 5.1$, 12.1 Hz), 4.33 (dd, 1H, H-4a, $J = 5.5$, 10.6 Hz), 4.23 (dd, 1H, H-4b, $J = 2.6$, 10.6 Hz), 4.17 (ddd, 1H, H-5, $J = 2.9$, 5.1, 9.5 Hz), 2.77 (dd, 1H, H-2a, $J = 3.3$, 18.3 Hz), 2.71, (dd, 1H, H-2b, $J = 6.2$, 18.3 Hz); ^{13}C-NMR ($CDCl_3$) δ 174.73 (C-1), 165.99, 165.70, 165.11, 164.95, 133.53, 133.43, 133.33, 133.30, 129.79–128.29, 100.29 (C-1′), 74.19 (C-3), 72.87, 72.61, 72.47 (C-3′, 5′, 4), 71.28 (C-2′), 69.32 (C-4′), 62.72 (C-6′), 35.68 (C-2). Anal. Calcd for $C_{38}H_{32}O_{12}$: C, 67.05; H, 4.74. Found: C, 67.29; H, 4.75.

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