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Chemoenzymatic synthesis of rhodiooctanoside isolated from Chinese medicines, rhodiolae radix

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Abstract—Direct β-glucosidation between 1,8-octanediol **5** and D-glucose **6** using the immobilized β-glucosidase (EC 3.2.1.21) from almonds with the synthetic prepolymer ENTP-4000 gave mono-β-glucoside **3** in 58% yield, which was converted into *n*-octyl β-D-glucopyranoside **2** by means of a chemoenzymatic method. The coupling of *n*-octyl β-D-glucopyranoside congener **15** and 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl bromide **17**, followed by deprotection afforded the synthetic rhodiooctanoside **1**, which was identical with natural **1** with respect to the spectral data and specific rotation.

1. Introduction

The Chinese natural medicine 'Si Lie Hong Jing Tian' prepared from the roots of *Rhodiola* (R.) *quadrifida* (Pall.) Fisch. et Mey., has been prescribed for hemostatic, antibechic, and tonic purposes in Chinese traditional preparations and used as an endermic liniment for burns and contusions. Rhodiooctanoside **1** was isolated as one of the chemical constituents of *R. quadrifida* by Yoshikawa et al.[1a,b] and found to show potent histamine release inhibitory activity.[1c] The structure of **1** was determined to be octyl α-L-arabinopyranosyl(1 → 6)-β-D-glucopyranoside by spectroscopic analysis and chemical degradation studies.[1a,b] Meanwhile, *n*-octyl β-D-glucopyranoside **2** was isolated from the methanolic extract of the roots of *Rhodiola sachalinensis*,[2] which is a nonionic detergent that is effective for protein solubilization studies.[3] For the enzymatic synthesis of β-D-glucopyranoside congeners, direct β-glycosidation between 1,6-hexanediol and D-glucose using β-glucosidase (EC 3.2.1.21) from almonds by Vic and Crout[4] shows promise, but the substrate used and the reaction conditions are limited. On the other hand, enzymatic synthesis of ω-hydroxyalkyl and *n*-alkyl β-galactopyranosides by the transglycosylation reaction using β-galactosidase is also reported.[5] Herein, we report the total synthesis of rhodiooctanoside **1** based on the selective β-glycosidation between the nonprotected D-glucose **6** and primary alcohols, such as 1-octanol **4** and 1,8-octanediol **5**, catalyzed by the immobilized β-glucosidase (EC 3.2.1.21) from almonds. Retrosynthetically, the synthesis of **1** can be achieved by the coupling reaction of the protected *n*-octyl β-D-glucopyranoside congener and the protected α-L-arabinopyranoside congener. The former can be derived from the β-glucosides **2** and/or **3**, which could be obtained by selective β-glucosidation between D-glucose **6** and 1-octanol **4** and/or 1,8-octanediol **5**, respectively (Scheme 1).

2. Enzymatic β-glycosidation

We have reported previously that the reaction of *p*-nitrophenyl β-D-glucopyranoside **7** and 1-octanol **4** and/or 1,8-octanediol **5** in the presence of commercially available β-glucosidase (EC 3.2.1.21) from almonds affords the β-D-glucopyranosides **2** (2% yield) and/or **3** (25% yield), respectively, via a kinetically controlled procedure. 1,8-Octanediol **5** was found to be better as an acceptor than 1-octanol **4**.[6] On the other hand, there are two approaches for optimizing the product yield from a given glucosidase in enzymatic glucoside synthesis, that is the use of either a high donor or high acceptor concentration.[7] High concentration of both is usually impractical due to solubility limitations. High donor

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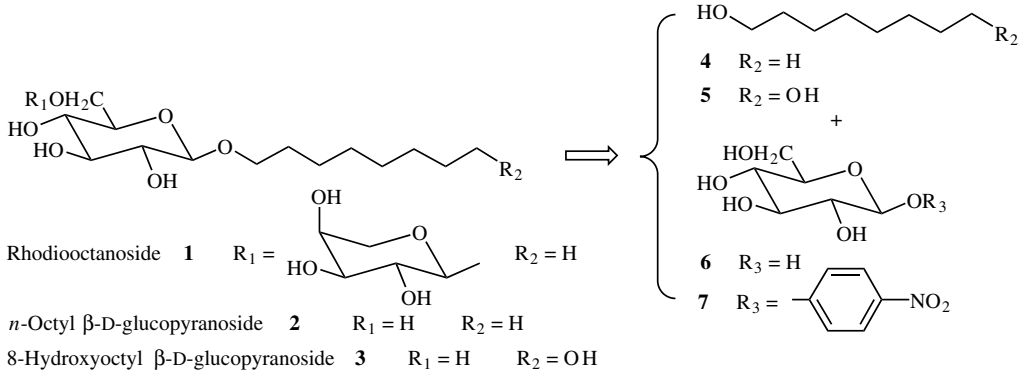
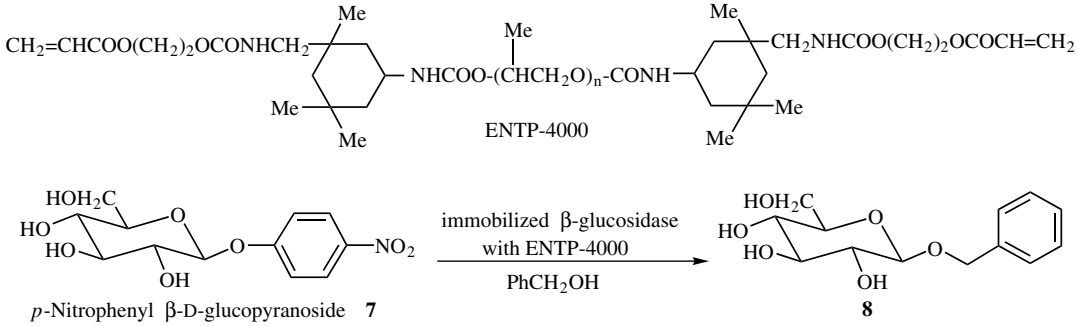


Scheme 1.

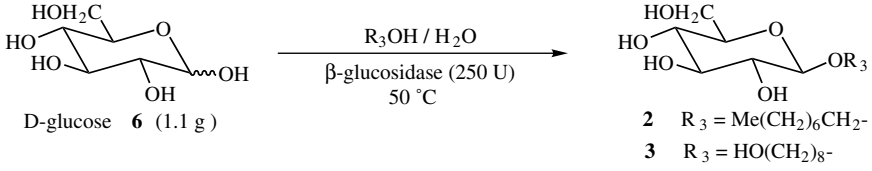


Scheme 2.

concentration is only practical if the donor is inexpensive such as D-glucose. High acceptor concentration is practical if the acceptor is inexpensive or can be recovered from the reaction mixture. Meanwhile, we also reported that the immobilized enzyme, prepared with β-glucosidase and synthetic prepolymer ENTP-4000,[8] catalyzed the β-glucosidation between **7** and benzyl alcohol to give benzyl β-D-glucopyranoside **8** in moderate yield (14.5%) in a phosphate buffer (Scheme 2).[9]

From the above-mentioned background, direct β-glucosidation between D-glucose **6** and 1-octanol **4** and/or 1,8-octanediol **5** using native β-glucosidase as well as the immobilized enzyme was carried out under the reverse hydrolysis procedure (a thermodynamic controlled procedure) with the results shown in Table 1. Immobilization of β-D-glucosidase from almonds on a photo-cross-linkable resin prepolymer (ENTP-4000) was carried out by the reported procedure.[9]

Table 1



Entry	R_3OH (g)	β-Glucosidase	Time	Product **2** or **3**, yield (%)
1	$Me(CH_2)_7OH$ **4** (14.9)	Native	4	**2** (5.0)
2	$Me(CH_2)_7OH$ **4** (14.9)	A	4	**2** (4.9)
3[a]	$Me(CH_2)_7OH$ **4** (14.9)	Recovered A	4	**2** (8.2)
4[b]	$HO(CH_2)_8OH$ **5** (3.6)	A	7	**3** (19.4)
5[c]	$HO(CH_2)_8OH$ **5** (3.6)	Recovered A	7	**3** (16.4)
6	$HO(CH_2)_8OH$ **5** (18.0)	Native	6	**3** (31.2)
7	$HO(CH_2)_8OH$ **5** (18.0)	A	6	**3** (58.0)
8[d]	$HO(CH_2)_8OH$ **5** (18.0)	Recovered A	6	**3** (43.0)

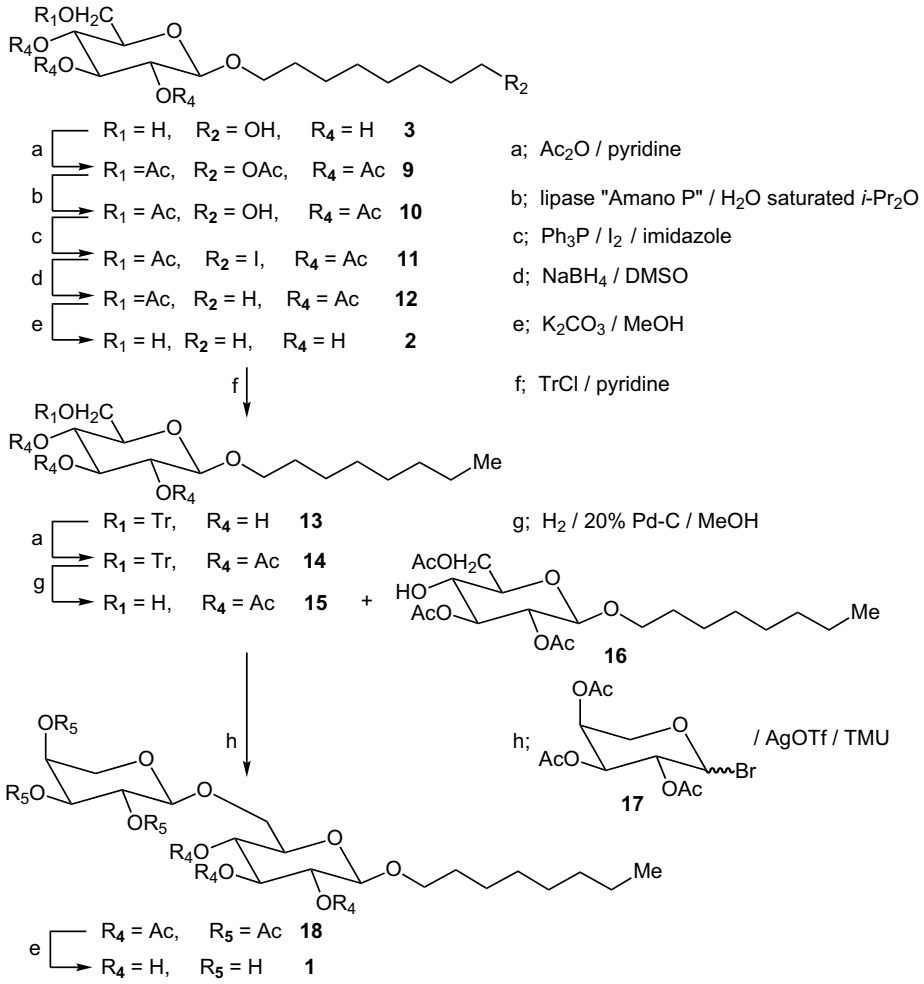
A: immobilized β-glucosidase with ENTP-4000.
[a] The same immobilized enzyme in entry 2 was employed again after filtration.
[b] *tert*-BuOH (27 mL) was employed as additional solvent.
[c] The same immobilized enzyme in entry 4 was employed again after filtration.
[d] The same immobilized enzyme in entry 7 was employed again after filtration.

By applying the reported procedure,[4] when a large amount of 1-octanol **4** (18.7 equiv) was used as an acceptor for D-glucose **6** in the presence of β-glucosidase or the immobilized β-glucosidase, a low yield of *n*-octyl β-D-glucopyranoside **2** (entry 1; 5.0% yield, entry 2; 4.9% yield) was obtained. When the same β-glucosidation was carried out using the recovered immobilized enzyme, the yield of **2** was somewhat better than with the use of native enzyme (entry 3). When 4.0 equiv of 1,8-octandiol **5** was subjected to β-glucosidation using the immobilized β-glucosidase and the recovered immobilized enzyme in a co-solvent system [^{t}BuOH/H_2O = 9:1 (v/v)],[8] moderate yields (entry 4; 19.4% yield, entry 5: 16.4% yield) of 8-hydroxyoctyl β-D-glucopyranoside **3** were obtained. When a large amount of 1,8-octanediol **5** (20.2 equiv) was employed for β-glucosidation using the native enzyme and the immobilized enzyme, the yield of **3** was considerably improved (entry 6; 31.2% yield, entry 7; 58.0% yield). The recovered enzyme was also found to be effective (entry 8; 43.0% yield).

3. Synthesis of rodiooctanoside 1

The conversion of **3** into the desired β-glucoside **2** was carried out by means of a chemoenzymatic method. Acetylation of **3** gave quantitatively pentaacetate **9**, which was treated with lipase Amano P from *Pseudomonas* sp. to provide mono-alcohol **10** in 80% yield along with the starting material **9**. In this enzymatic hydrolysis, the terminal acetyl group on the side chain was selectively hydrolyzed while other acetyl groups on the sugar part were left intact. Treatment of **10** with iodine (I_2) in the presence of triphenylphosphine (Ph_3P) gave quantitatively the corresponding iodide **11**, which was subjected to reduction with $NaBH_4$ to give tetraacetate **12** in 92% yield. Finally, treatment of **12** with K_2CO_3 in MeOH provided the desired β-glucoside **2** in 89% yield. Consequently, the overall yield (38% yield) of **2** from D-glucose **6** via six steps is considerably improved upon in comparison to that (5.0–8.2% yield) by direct β-glucosidation of 1-octanol **4** (Scheme 3).

Tritylation of **2** gave trityl ether **13** (50% yield) along with starting material **2** (50% recovery). Acetylation of **13** afforded quantitatively acetate **14**, which was subjected to hydrogenolysis in the presence of 20% Pd–C to provide a mixture (92% yield) of the desired **15** and **16** (**15**:**16** = 3:1). Reaction of this mixture and 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl bromide **17**[10] in the presence of silver triflate (AgOTf) and tetramethylurea (TMU) gave coupled product **18** in 50% yield. Finally,



Scheme 3.

treatment of **18** with K_2CO_3 in MeOH provided quantitatively the synthetic rhodiooctanoside **1**. The spectral data (^1H and ^{13}C NMR) and specific rotation {$[\alpha]_D = -28.8$ (MeOH)} of synthetic **1** were identical with those {^1H and ^{13}C NMR and $[\alpha]_D = -29.2$ (MeOH)} of natural product **1**.

4. Conclusion

In conclusion, direct β-glucosidation between 1,8-octanediol **5** and D-glucose **6** using the immobilized β-glucosidase from almonds with the synthetic prepolymer ENTP-4000 gave mono-β-glucoside **3** in 58% yield, which was converted into the *n*-octyl β-D-glucopyranoside **2** by means of a chemoenzymatic method. The coupling of *n*-octyl β-D-glucopyranoside congener **15** and 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl bromide **17**, followed by deprotection afforded the synthetic rhodiooctanoside **1**, which was consistent with natural **1** with respect to the spectral data and specific rotation.

5. Experimental

^1H and ^{13}C NMR spectra were recorded on a JEOL EX 400 spectrometer (Tokyo, Japan). Spectral data were taken with 5–10% (w/v) solution in $CDCl_3$ with Me_4Si as an internal reference. Melting points were determined on a Yanaco MP-3S micro melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. The FAB mass spectra were obtained with a JEOL JMS-AX 500 (matrix; glycerol) spectrometer. IR spectra were recorded on a JASCO FT/IR-300 spectrometer. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

5.1. Immobilization of β-D-glucosidase using prepolymer

β-D-Glucosidase (EC 3.2.1.21) from almonds was purchased from Sigma Chemical Co (G-0395, 2.5–3.6 U/mg). Immobilization of β-D-glucosidase from almonds on photocross-linkable resin prepolymer (ENTP-4000) was carried out by the following procedure. One gram of ENTP-4000 was mixed with 10 mg of a photosensitizer, benzoin ethyl ether, and 110 mg of β-D-glucosidase from almonds (3.4 units/mg). The mixture was layered on a sheet of transparent polyester film (thickness, ca. 0.5 mm). The layer was covered with the transparent thin film and then illuminated with chemical lamps (wavelength range, 300–400 nm) for 3 min. The gel film thus obtained was cut into small pieces ($0.5 \times 5 \times 5$ mm) and used for the bioconversion reaction.

5.2. Enzymatic transglycosylation

5.2.1. Synthesis of *n*-octyl β-D-glucopyranoside 2

5.2.1.1. A mixture of D-glucose **6** (1.1 g, 6.1 mmol), 1-octanol (14.9 g, 114.3 mmol), H_2O (2 mL), and β-glucosidase 100 mg (250 unit) was incubated for 4 d at 50 °C. The reaction mixture was directly chromatographed on silica gel (35 g) to give 1-octanol (12.0 g, 80% recovery) from $CHCl_3$ eluent and β-glucoside **2** (89.2 mg, 5.0% yield) as colorless crystals from $CHCl_3$/MeOH = 10:1 eluent. **2**: $[\alpha]_D^{27} = -39.8$ (*c* 0.58, H_2O); IR (KBr): 3412, 2928, 1078, 1036 cm^{-1}, ^1H NMR (MeOH-d_4): δ 4.24 (1H, d, $J = 7.7$ Hz), 3.92–3.84 (2H, m), 3.66 (1H, dd, $J = 5.2$, 12.0 Hz), 3.59–3.50 (1H, m), 3.37–3.23 (3H, m), 3.17 (1H, dd, $J = 7.7$, 9.2 Hz), 1.65–1.58 (2H, m), 1.36–1.30 (10H, m), 0.90 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (MeOH-d_4): δ 104.4 (d), 78.1 (d), 77.9 (d), 75.1 (d), 71.7 (d), 70.9 (t), 62.8 (t), 33.0 (t), 30.8 (t), 30.6 (t), 30.4 (t), 27.1 (t), 23.7 (t), 14.4 (q); FAB MS *m*/*z*: 293 $(M+1)^+$; Anal. Calcd for $C_{14}H_{28}O_6$: C, 57.51; H, 9.65. Found: C, 57.37; H, 9.71.

5.2.1.2. A mixture of D-glucose **6** (1.1 g, 6.1 mmol), 1-octanol (14.9 g, 114.3 mmol), H_2O (2 mL), and the mentioned immobilized β-glucosidase was incubated for 4 d at 50 °C. The reaction mixture was filtered off and the filtrate directly chromatographed on silica gel (35 g) to give 1-octanol (12.5 g, 84% recovery) from $CHCl_3$ eluent and β-glucoside **2** (86.6 mg, 4.9% yield) as colorless crystals from $CHCl_3$/MeOH = 10:1 eluent.

5.2.1.3. A mixture of D-glucose **6** (1.1 g, 6.1 mmol), 1-octanol (14.9 g, 114.3 mmol), H_2O (2 mL), and the recovered immobilized β-glucosidase was incubated for 4 d at 50 °C. The reaction mixture was filtered off and the filtrate directly chromatographed on silica gel (35 g) to give 1-octanol (12.1 g, 81% recovery) from $CHCl_3$ eluent and β-glucoside **2** (144.4 mg, 8.2% yield) as colorless crystals from $CHCl_3$/MeOH = 10:1 eluent.

5.2.2. Synthesis of 8-hydroxyoctyl β-D-glucopyranoside 3

5.2.2.1. A mixture of D-glucose **6** (1.1 g, 6.1 mmol), 1,8-octanediol (3.6 g, 24.4 mmol), *t*-BuOH (27 mL), H_2O (3 mL), and the mentioned immobilized β-glucosidase was incubated for 7 d at 50 °C. The reaction mixture was filtered off and the filtrate directly chromatographed on silica gel (150 g) to give 1,8-octanediol (3.2 g, 90% recovery) from $CHCl_3$/MeOH = 20:1 eluent and β-glucoside **3** (365.2 mg, 19.4% yield) as colorless crystals from $CHCl_3$/MeOH = 9:1 eluent. **3**: mp 126–128 °C; $[\alpha]_D^{29} = -28.4$ (*c* 0.43, MeOH); IR (KBr): 3419, 3236, 2925, 1371, 1030 cm^{-1}, ^1H NMR (D_2O+acetone): δ 4.30 (1H, d, $J = 8.0$ Hz), 3.80–3.75 (2H, m), 3.60–3.50 (2H, m), 3.45 (2H, t, $J = 6.6$ Hz), 3.34 (1H, t, $J = 9.0$ Hz), 3.31–3.28 (1H, m), 3.23 (1H, t, $J = 9.4$ Hz), 3.11 (1H, t, $J = 8.6$ Hz), 1.51–1.37 (4H, m), 1.24–1.14 (8H, m); ^{13}C NMR (D_2O+acetone): δ 103.0 (d), 76.7 (d), 76.7 (d), 74.0 (d), 71.5 (d), 70.5 (t), 62.7 (t), 61.6 (t), 32.1 (t), 29.6 (t), 29.3 (t), 29.3 (t), 25.8 (t), 25.8 (t); FAB MS *m*/*z*: 309 $(M+1)^+$; Anal. Calcd for $C_{14}H_{28}O_7$: C, 54.53; H, 9.15. Found: C, 54.34; H, 9.24.

5.2.2.2. A mixture of D-glucose **6** (1.1 g, 6.1 mmol), 1,8-octanediol (3.6 g, 24.4 mmol), *tert*-BuOH (27 mL), H_2O (3 mL), and the recovered immobilized β-glucosidase was incubated for 7 d at 50 °C. The reaction mix-

ture was filtered off and the filtrate directly chromatographed on silica gel (150 g) to give 1,8-octanediol (3.1 g, 86% recovery) from $CHCl_3$/MeOH = 20:1 eluent and β-glucoside **3** (280.6 mg, 16.4% yield) as colorless crystals from $CHCl_3$/MeOH = 9:1 eluent.

5.2.2.3. A mixture of D-glucose **6** (1.1 g, 6.1 mmol), 1,8-octanediol (18 g, 123.1 mmol), H_2O (2 mL), and β-glucosidase 100 mg (250 unit) was incubated for 7 d at 50 °C. The reaction mixture was directly chromatographed on silica gel (35 g) to give 1,8-octanediol (17.2 g, 95% recovery) from $CHCl_3$/MeOH = 20:1 eluent and β-glucoside **3** (587.0 mg, 31.2% yield) as colorless crystals from $CHCl_3$/MeOH = 9:1 eluent.

5.2.2.4. A mixture of D-glucose **6** (1.1 g, 6.1 mmol), 1,8-octanediol (18 g, 123.1 mmol), H_2O (2 mL), and the mentioned immobilized β-glucosidase was incubated for 6 d at 50 °C. The reaction mixture was filtered off and the filtrate directly chromatographed on silica gel (35 g) to give 1,8-octanediol (17.1 g, 95% recovery) from $CHCl_3$/MeOH = 20:1 eluent and β-glucoside **3** (1.09 g, 58.0% yield) as colorless crystals from $CHCl_3$/MeOH = 10:1 eluent.

5.2.2.5. A mixture of D-glucose **6** (1.1 g, 6.1 mmol), 1,8-octanediol (18 g, 123.1 mmol), H_2O (2 mL), and the recovered immobilized β-glucosidase was incubated for 6 d at 50 °C. The reaction mixture was filtered off and the filtrate directly chromatographed on silica gel (35 g) to give 1,8-octanediol (17.0 g, 94% recovery) from $CHCl_3$/MeOH = 20:1 eluent and β-glucoside **3** (808 mg, 43.0% yield) as colorless crystals from $CHCl_3$/MeOH = 10:1 eluent.

5.3. Conversion of 3 into *n*-octyl β-D-glucopyranoside 2

5.3.1. A mixture of **3** (300 mg, 0.97 mmol), Ac_2O (795 mg, 7.8 mmol), 4-dimethylaminopyridine (DMAP; 10 mg, 0.08 mmol) in pyridine (1 mL, 12.4 mmol) was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with 10% aqueous HCl, 7% aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel [15 g, *n*-hexane/AcOEt (2:1)] to afford **9** (504 mg, quantitative yield) as a colorless syrup. **9**: $[\alpha]_D^{22} = -17.4$ (*c* 0.61, $CHCl_3$); IR (KBr): 1752 cm^{-1}, ^1H NMR ($CDCl_3$): δ 5.20 (1H, t, $J = 9.6$ Hz), 5.08 (1H, t, $J = 9.6$ Hz), 4.98 (1H, t, $J = 8.8$ Hz), 4.49 (1H, d, $J = 8$ Hz), 4.27 (1H, dd, $J = 4.8$, 12.4 Hz), 4.14 (1H, dd, $J = 2.4$, 12.4 Hz), 4.05 (2H, t, $J = 6.8$ Hz), 3.87 (1H, dt, $J = 6.4$, 9.6 Hz), 3.69 (1H, ddd, $J = 2.4$, 4.8, 9.6 Hz), 3.47 (1H, dt, $J = 6.8$, 9.6 Hz), 2.08 (3H, s), 2.04 (3H, s), 2.04 (3H, s), 2.02 (3H, s), 2.01 (3H, s), 1.63–1.54 (4H, m), 1.35–1.25 (8H, m); ^{13}C NMR ($CDCl_3$): δ 171.2 (s), 170.7 (s), 170.3 (s), 169.4 (s), 169.3 (s), 100.8 (d), 77.3 (d), 72.9 (d), 71.8 (d), 71.4 (d), 70.2 (t), 68.5 (d), 64.6 (t), 62.0 (t), 29.4 (t), 29.2 (t), 29.2 (t), 28.6 (t), 25.8 (t), 25.7 (t), 21.0 (q), 20.7 (q), 20.7 (q), 20.6 (q), 20.6 (q); FAB MS *m/z*: 541 $(M+Na)^+$, 519 $(M+H)^+$.

5.3.2. A suspension of **9** (100 mg, 0.193 mmol), lipase Amano P (100 mg) in H_2O saturated *i*-Pr_2O (17 mL) was incubated for 22 h at 33 °C. The reaction mixture was filtered with the aid of Celite and the filtrate then evaporated to give a residue. This was chromatographed on silica gel (15 g) to afford **9** (20 mg, 20% recovery) from *n*-hexane/AcOEt (2:1) eluent and **10** (74 mg, 80% yield) as a colorless syrup from *n*-hexane/AcOEt (1:1) eluent. **10**: $[\alpha]_D^{25} = -20.6$ (*c* 0.67, $CHCl_3$); IR (KBr): 3564, 1752 cm^{-1}, ^1H NMR ($CDCl_3$): δ 5.20 (1H, t, $J = 9.6$ Hz), 5.08 (1H, t, $J = 9.6$ Hz), 4.98 (1H, dd, $J = 8.3$, 9.3 Hz), 4.49 (1H, d, $J = 8.3$ Hz), 4.26 (1H, dd, $J = 4.9$, 11.5 Hz), 4.14 (1H, dd, $J = 5.4$, 11.5 Hz), 3.87 (1H, dt, $J = 6.4$, 9.6 Hz), 3.71–3.67 (1H, m), 3.63 (2H, t, $J = 6.4$ Hz), 3.47 (1H, dt, $J = 6.8$, 9.3 Hz), 2.09 (3H, s), 2.04 (3H, s), 2.03 (3H, s), 2.01 (3H, s), 1.59–1.52 (4H, m), 1.46–1.28 (8H, m); ^{13}C NMR ($CDCl_3$): δ 170.7 (s), 170.4 (s), 169.4 (s), 169.3 (s), 100.8 (d), 72.9 (d), 71.7 (d), 71.4 (d), 70.2 (t), 68.5 (d), 62.9 (t), 62.0 (t), 32.7 (t), 29.3 (t), 29.3 (t), 29.2 (t), 25.7 (t), 25.6 (t), 20.7 (q), 20.6 (q), 20.6 (q), 20.6 (q); FAB MS *m/z*: 515 $(M+K)^+$. Anal. Calcd for $C_{22}H_{36}O_{11}$: C, 55.45; H, 7.62. Found: C, 55.06; H, 7.77.

5.3.3. A mixture of **10** (148 mg, 0.31 mmol), Ph_3P (173 mg, 0.66 mmol), imidazole (45 mg, 0.66 mmol), and I_2 (151 mg, 0.59 mmol) in THF (2.5 mL) was stirred for 30 min at room temperature. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to give a residue. This was chromatographed on silica gel [10 g, *n*-hexane/AcOEt (3:1)] to afford **11** (182 mg, quantitative yield) as a colorless oil. **11**: $[\alpha]_D^{26} = -16.0$ (*c* 0.35, $CHCl_3$); IR (KBr): 1751 cm^{-1}, ^1H NMR ($CDCl_3$): δ 5.20 (1H, t, $J = 9.6$ Hz), 5.08 (1H, t, $J = 10.0$ Hz), 4.98 (1H, t, $J = 8.0$ Hz), 4.49 (1H, d, $J = 8.0$ Hz), 4.27 (1H, dd, $J = 4.4$, 12.0 Hz), 4.16–4.12 (1H, m), 3.87 (1H, dt, $J = 6.0$, 9.6 Hz), 3.71–3.67 (1H, m), 3.48 (1H, dt, $J = 6.4$, 9.6 Hz), 3.18 (2H, t, $J = 8.0$ Hz), 2.09 (3H, s), 2.04 (3H, s), 2.03 (3H, s), 2.01 (3H, s), 1.85–1.53 (6H, m), 1.44–1.24 (6H, m); FAB MS *m/z*: 625 $(M+K)^+$.

5.3.4. A mixture of **11** (921 mg, 1.57 mmol) and $NaBH_4$ (120 mg, 3.16 mmol) in DMSO (15 mL) was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to give a residue. This was chromatographed on silica gel [15 g, *n*-hexane/AcOEt (1:1)] to afford **12** (670 mg, 92 yield) as a colorless needle. **12**: mp 58–60 °C; $[\alpha]_D^{27} = -20.2$ (*c* 0.59, $CHCl_3$); IR (KBr): 1755 cm^{-1}, ^1H NMR ($CDCl_3$): 5.20 (1H, t, $J = 9.3$ Hz), 5.08 (1H, t, $J = 9.8$ Hz), 4.98 (1H, dd, $J = 7.8$, 9.3 Hz), 4.49 (1H, d, $J = 7.8$ Hz), 4.26 (1H, dd, $J = 4.9$, 12.2 Hz), 4.14 (1H, dd, $J = 2.0$, 12.2 Hz), 3.87 (1H, dt, $J = 6.3$, 9.3 Hz), 3.69 (1H, ddd, $J = 2.4$, 4.4, 9.8 Hz), 3.47 (1H, dt, $J = 6.8$, 9.8 Hz), 2.08 (3H, s), 2.04 (3H, s), 2.02 (3H, s), 2.00 (3H, s), 1.63–1.49 (4H, m), 1.34–1.22 (8H, m), 0.88 (3H, t, $J = 6.4$ Hz); ^{13}C NMR ($CDCl_3$): δ 170.7 (s), 170.3 (s), 169.4 (s), 169.3 (s), 100.9 (d), 72.9 (d), 71.8 (d), 71.4 (d), 70.3 (t), 68.5 (d),

62.1 (t), 31.8 (t), 29.4 (t), 29.3 (t), 29.3 (t), 25.8 (t), 22.6 (t), 20.7 (q), 20.6 (q), 20.6 (q), 20.6 (d), 14.1 (q); FAB MS m/z: 499 $(M+K)^+$.

5.3.5. A mixture of **12** (1.41 g, 3.07 mmol) and K_2CO_3 (412 mg, 3.0 mmol) in MeOH (20 mL) was stirred for 25 min at room temperature. The reaction mixture was evaporated to give a residue, which was chromatographed on silica gel [15 g, $CHCl_3$/MeOH (9:1)] to afford **2** (796 mg, 89 yield) as a colorless amorphas. ^1H and ^{13}C NMR spectra of the present **2** were identical with those of enzymatic β-glucoside **2**.

5.4. Conversion of 2 into *n*-octyl β-D-glucopyranoside congener 15

5.4.1. A mixture of **2** (642 mg, 2.2 mmol) and TrCl (667 mg, 2.4 mmol) in pyridine (1 mL, 12.4 mmol) was stirred for 24 h at room temperature. The reaction mixture was diluted with toluene (100 mL) and evaporated under reduced pressure to give a residue, which was chromatographed on silica gel (15 g) to afford **13** (588 mg, 50% yield) as a colorless syrup from $CHCl_3$/MeOH (50:1) eluent and starting material **2** (321 mg, 50% recovery) from $CHCl_3$/MeOH (10:1) eluent. **13**: $[\alpha]_D^{27} = -45.2$ (c 0.63, $CHCl_3$); IR (KBr): 3396 cm^{-1}, ^1H NMR ($CDCl_3$): δ 7.45 (6H, d, $J = 6.8$ Hz), 7.30–7.19 (9H, m), 4.25 (1H, d, $J = 9.2$ Hz), 3.88 (1H, dt, $J = 7.2$, 9.2 Hz), 3.56–3.33 (7H, m), 1.67–1.60 (2H, m), 1.35–1.22 (10H, m), 0.86 (3H, t, $J = 6.8$ Hz); ^{13}C NMR ($CDCl_3$): δ 143.7 (s, Ph-4°), 128.7 (d, Ph-3°), 127.9 (d, Ph-3°), 127.1 (d, Ph-3°), 102.5 (d), 87.0 (s), 76.3 (d), 74.2 (d), 73.6 (d), 71.9 (d), 70.1 (t), 64.3 (t), 31.8 (t), 29.7 (t), 29.4 (t), 29.2 (t), 26.0 (t), 22.6 (t),14.1 (q); FAB MS m/z: 557 $(M+Na)^+$.

5.4.2. A mixture of **13** (700 mg, 1.31 mmol), Ac_2O (669 mg, 6.55 mmol), 4-dimethylaminopyridine (DMAP; 10 mg, 0.08 mmol) in pyridine (2 mL, 25.3 mmol) was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was again diluted with toluene and the whole evaporated to give a residue. This was chromatographed on silica gel [20 g, *n*-hexane/AcOEt (7:1)] to afford **14** (865 mg, quantitative yield) as a colorless syrup. **14**: $[\alpha]_D^{27} = +21.8$ (c 0.51, $CHCl_3$); IR (KBr): 1757 cm^{-1}, ^1H NMR ($CDCl_3$): δ 7.45 (6H, d, $J =$ 7.3 Hz), 7.40–7.20 (9H, m), 5.17–5.12 (2H, m), 5.07–5.02 (1H, m), 4.50 (1H, d, $J = 7.8$ Hz), 3.93 (1H, dt, $J = 6.3$, 9.3 Hz), 3.59–3.53 (2H, m), 3.24 (1H, dd, $J = 2.0$, 10.6 Hz), 3.10 (1H, dd, $J = 4.9$, 10.6 Hz), 2.05 (3H, s), 1.99 (3H, s), 1.72 (3H, s), 1.68–1.58 (4H, m), 1.35–1.24 (8H, m), 0.87 (3H, t, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$): δ 170.5 (s), 169.4 (s), 169.0 (s), 143.6 (s, Ph-4°), 128.7 (d, Ph-3°), 127.8 (d, Ph-3°), 127.0 (d, Ph-3°), 100.8 (d), 86.6 (s), 73.3 (d), 73.2 (d), 71.6 (d), 69.8 (t), 68.9 (d), 62.1 (t), 31.8 (t), 29.5 (t), 29.3 (t), 29.3 (t), 26.0 (t), 22.6 (t), 20.7 (q), 20.7 (q), 20.4 (q), 14.1 (q); FAB MS m/z: 699 $(M+K)^+$. Anal. Calcd for $C_{39}H_{48}O_9+H_2O$: C, 69.00; H, 7.42. Found: C, 69.21; H, 7.17.

5.4.3. A mixture of **14** (650 mg, 0.98 mmol) and 20% Pd–C (148 mg) in MeOH (20 mL) was subjected to catalytic hydrogenolysis at ambient temperature and the reaction mixture filtered with the aid of Celite to give the filtrate. Evaporation of the filtrate gave a residue, which was chromatographed on silica gel [10 g, *n*-hexane/AcOEt (2:1)] to give a mixture **15**:**16** (3:1; 381 mg, 92% yield) as a colorless syrup. **15** and **16**: $[\alpha]_D^{27} = -32.5$ (c 0.63, $CHCl_3$); IR (KBr): 3429, 1753 cm^{-1}, FAB MS m/z: 457 $(M+K)^+$. Anal. Calcd for $C_{20}H_{34}O_9$: C, 57.40; H, 8.19. Found: C, 57.09; H, 8.24. **15**: ^1H NMR ($CDCl_3$): δ 5.25 (1H, t, $J = 9.6$ Hz), 5.03 (1H, t, $J = 9.6$ Hz), 4.96 (1H, dd, $J = 8.0$, 9.6 Hz), 4.52 (1H, d, $J = 8.0$ Hz), 3.90–3.85 (1H, m), 3.77–3.72 (1H, m), 3.64–3.45 (3H, m), 2.05 (3H, s), 2.04 (3H, s), 2.01 (3H, s), 1.58–1.54 (2H, m), 1.32–1.22 (10H, m), 0.88 (3H, t, $J = 6.4$ Hz); ^{13}C NMR ($CDCl_3$): δ 170.3 (s), 170.0 (s), 169.3 (s), 100.8 (d), 73.4 (d), 72.7 (d), 71.5 (d), 70.2 (t), 68.8 (d), 61.3 (t), 31.7 (t), 29.4 (t), 29.2 (t), 29.2 (t), 25.8 (t), 22.6 (t), 20.8 (q), 20.6 (q), 20.6 (q), 14.0 (q).

5.5. Rhodiooctanoside 1

5.5.1. To a solution of the above-mentioned mixture **15** and **16** (290 mg, 0.69 mmol), 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl bromide **17** (347 mg, 1.02 mmol) and tetramethyl urea (TMU, 249 mg, 2.15 mmol) in CH_2Cl_2 (5 mL) was added AgOTf (366 mg, 1.42 mmol) at 0 °C under argon atmosphere. The whole was covered with aluminum foil and stirred for 30 min at room temperature. The reaction mixture was cooled at 0 °C and quenched with AcOEt (15 mL) and 7% aqueous $NaHCO_3$ solution (20 mL). The reaction mixture was extracted with AcOEt and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (20 g) to afford tetraacetate **12** (73 mg, 22% yield) from *n*-hexane/AcOEt (4:1) eluent, **16** (41 mg, 14% recovery), and **18** (233 mg, 50% yield) as a colorless amorphas from *n*-hexane/AcOEt (3:1) eluent in elution order. **18**: mp 122–123 °C; $[\alpha]_D^{27} = -8.5$ (c 0.63, $CHCl_3$); IR (KBr): 1746, 1057 cm^{-1}, ^1H NMR (MeOH-d_4): δ 5.25–5.19 (2H, m), 5.09–5.07 (2H, m), 4.98 (1H, t, $J = 9.6$ Hz), 4.88–4.84 (1H, m), 4.62 (1H, d, $J = 8.0$ Hz), 4.58–4.56 (1H, m), 4.01–3.84 (3H, m), 3.80–3.71 (2H, m), 3.60 (1H, dd, $J = 4.8$, 10.8 Hz), 3.54–3.48 (1H, m), 2.12 (3H, s), 2.08 (3H, s), 2.02 (3H, s), 2.01 (3H, s), 2.00 (3H, s), 1.96 (3H, s), 1.57–1.53 (2H, m), 1.35–1.27 (10H, m), 0.90 (3H, t, $J = 6.8$ Hz); ^{13}C NMR ($CDCl_3$): δ 171.9 (s), 171.7 (s), 171.6 (s), 171.4 (s), 171.2 (s), 171.1 (s), 101.9 (d), 101.7 (d), 74.6 (d), 74.0 (d), 73.0 (d), 71.7 (d), 70.9 (t), 70.5 (d), 70.3 (d), 69.3 (d), 68.4 (t), 64.1 (t), 33.0 (t), 30.6 (t), 30.5 (t), 30.5 (t), 27.1 (t), 23.7 (t), 20.9 (q), 20.8 (q), 20.7 (q), 20.6 (q), 20.6 (q), 20.6 (q), 14.5 (q); FAB MS m/z: 715 $(M+K)^+$. Anal. Calcd for $C_{31}H_{48}O_{16}$: C, 55.02; H, 7.15. Found: C, 55.02; H, 7.20.

5.5.2. A mixture of **18** (100 mg, 0.148 mmol) and K_2CO_3 (20.4 mg, 0.15 mmol) in MeOH (5 mL) was stirred for 15 min at room temperature. The reaction mixture was evaporated to give a residue, which was chromatographed on silica gel [6 g, $CHCl_3$/MeOH (5:1–1:1)] to afford **1** (62 mg, quantitative yield) as a colorless amorphas. **1**: $[\alpha]_D^{24} = -28.8$ (*c* 0.42, MeOH); IR (KBr): 3404, 1055 cm^{-1}, ^1H NMR (MeOH-d_4): δ 4.31 (1H, d, $J = 6.7$ Hz), 4.24 (1H, d, $J = 7.6$ Hz), 4.08 (1H, dd, $J = 1.8$, 11.3 Hz), 3.88–3.81 (3H, m), 3.73 (1H, dd, $J = 5.5$, 11.3 Hz), 3.59 (1H, dd, $J = 7.0$, 8.5 Hz), 3.54–3.50 (3H, m), 3.44–3.41 (1H, m), 3.34–3.29 (2H, m), 3.19–3.16 (1H, m), 1.63–1.58 (2H, m), 1.48–1.25 (10H, m), 0.89 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (MeOH-d_4): δ 105.1, 104.3, 77.9, 76.7, 75.0, 74.1, 72.3, 71.5, 71.0, 69.4, 69.4, 66.7, 33.0, 30.8, 30.5, 30.4, 27.1, 23.7, 14.4; High (FAB) MS (matrix; *m*-nitrobenzylalcohol) *m*/*z*: 447.2195 $(M+Na)^+$, Calcd for $C_{19}H_{36}O_{10}$+Na, 447.2206.

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