Rhododendrol glycosides as stereospecific tyrosinase inhibitors

Takehiro Iwadate ^a, Ken-ichi Nihei ^{a,b,*}

^a Department of Applied Life Science, United Graduate School of Agricultural Science,
Tokyo University of Agriculture and Technology, Tokyo 183-8509, Japan

^b Department of Applied Biological Chemistry, Faculty of Agriculture, Utsunomiya
University, Tochigi 321-0943, Japan

*Corresponding author. Tel.: +81 28 649 5412; fax: +81 28 649 5401.

E-mail address: nihei98@cc.utsunomiya-u.ac.jp (K. Nihei).

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Abstract

Rhododendrol derivatives **3–12** have been synthesized in six steps, including aldol condensation and/or trichloroacetimidate glycosylation as the key reactions. Each derivative showed effective inhibition of tyrosinase-catalyzed oxidation processes. In particular, a series of synthetic derivatives having an *R*-stereogenic center at C-2 proved to be more potent than their respective epimers. In addition, the glycosylation on the phenylbutanoid scaffold increased the difference in activity between the isomers. This suggests that the sugar moiety plays an important role in eliciting their potent inhibitory activity.

1. Introduction

Tyrosinase (EC.1.14.8.1), known as polyphenol oxidase, is an oxidoreductase that is distributed widely in nature. It catalyzes two consecutive oxidations, i.e., the *o*-hydroxylation of monophenols and the oxidation of *o*-diphenols.¹ The generated *o*-quinones can spontaneously polymerize to form various biopigments and biopolymers such as melanin. The control of tyrosinase activity is therefore considerably important in medicinal and cosmetic fields because the excessive production of melanin causes hyperpigmentation.²⁻⁵ Tyrosinase is also responsible for the molting process of insects,⁶ the infection of plant pathogenic fungi,⁷ and the degradation of bioactive food polyphenols.⁸ Therefore, the development of novel and effective tyrosinase inhibitors has long been pursued.^{9,10}

Figure 1. Structure of 1-12, 20, and 21.

Naturally occurring polyphenols such as flavonoids¹¹ and chalcones¹² often possess tyrosinase inhibitory activity. Their efficacy stems partly from a monophenolic structure that acts as a substrate analog for tyrosinase. Epirhododendrin (**1**) isolated from *Acer nikoense*¹³ and rhododendrin (**2**) from *Rhododendron chrysanthum*,¹⁴ which are classified as monophenol glycosides, are potential candidates for developing novel and water soluble tyrosinase inhibitors (Fig. 1). However, such monophenols are highly susceptible to enzymatic oxidation by tyrosinase as alternative substrates.¹⁵⁻¹⁷ Conversely, several polyphenols containing the resorcinol motif are known as potent

tyrosinase inhibitors that are not susceptible to oxidation.¹⁸⁻²² Thus, it was envisaged that the transformation of the monophenol structures of **1** and **2** into the corresponding resorcinols might lead to novel, effective, and hydrophilic tyrosinase inhibitors.²³ Herein, we describe concise syntheses of rhododendrols **3–12** as well as an evaluation of their tyrosinase inhibitory activities.

2. Results and discussion

2.1. Synthesis and tyrosinase inhibitory activities of **3** and **4**

Benzaldehyde derivative **13**,²⁴ which was prepared from commercially available 2,4-dihydroxybenzaldehyde, was converted to enone **14** through aldol condensation²⁵ with acetone in 94% yield (Scheme 1). By catalytic hydrogenation using palladium-activated carbon ethylenediamine complex [Pd(en)/C]²⁶ in toluene under cooling conditions (10 °C), selective reduction of **14** was achieved to produce **15** in 80% yield. When THF, EtOAc, or 1,4-dioxane was used as the solvent in this step, the reaction yield decreased to approximately 40%. Ketone **15** was transformed into alcohol **16** by hydride reduction in excellent yield (98%). Conversely, one-step synthesis of **16** from **14** was accomplished in low yield (36%) by using NaBH₄ in the presence of CoCl₂.²⁷

Scheme 1. Synthesis of the aglycone part. Reagents and conditions: (a) acetone, NaOH, H₂O, EtOH, 0 °C to rt, 94%; (b) H₂-Pd(en)/C, PhMe, 10 °C, 80%; (c) NaBH₄, EtOH, Et₂O, 0 °C to rt, 98%; (d) H₂-Pd(OH)₂/C, EtOAc, rt, 100%.

Koenigs–Knorr reaction²⁸ was initially applied in the glycosylation step between **16** and 2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranosyl bromide. However, the reaction proceeded sluggishly, and the isolated yield of glucoside **18** was only 12%. Using imidate **17**²⁹ as a glycosyl donor and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as a Lewis acid, a complex mixture was detected on a TLC plate. Remarkably, **18** was obtained in 50% yield (Scheme 2) when trimethylsilyl trifluoromethanesulfonate (TMSOTf) was used instead of $\text{BF}_3 \cdot \text{Et}_2\text{O}$. Resorcinol **19** was furnished in 82% yield from **18** by hydrogenolysis using Pearlman's catalyst.³⁰ Finally, the treatment of **19** with NaOMe produced glucosides **3** and **4** as an epimeric mixture in 89% yield. The yield of **3** and **4** was 27% over the six steps from **13**.

Scheme 2. Synthesis of glucosides **3** and **4**, and xylosides **7** and **8**.
 Reagents and conditions: (a) **16**, TMSOTf, CH_2Cl_2 , -40°C , 50%; (b) H_2 -Pd(OH)₂/C, EtOAc, rt, 82%; (c) NaOMe, MeOH, 0°C to rt, then, Amberlite IR-120H, 89%; (d) **16**, TMSOTf, CH_2Cl_2 , -40°C , 48%; (e) H_2 -Pd(OH)₂/C, EtOAc, rt, 65%; (f) NaOMe, MeOH, 0°C to rt, then, Amberlite IR-120H, 99%.

The separation of **3** and **4** was achieved by preparative HPLC employing conventional ODS columns.³¹ The stereochemistries of the aglycone parts of **3** and **4** were determined as *S* and *R*, respectively, by comparison with previously reported ^1H and ^{13}C NMR data for **1** and **2**.³² The evaluation of the tyrosinase inhibitory activities of

3 and **4** revealed that they showed more potent activity than that of kojic acid (**20**), a commercially used tyrosinase inhibitor (Table 1), although their efficacies were lower than that of 4-hexylresorcinol (**21**).³³ IC₅₀ of the mixture of **1** and **2** could not be estimated within 100 μ M.²³ Accordingly, tyrosinase inhibitory activity was significantly improved by the introduction of a hydroxy group at C-2'. In particular, the activity of **4** containing the *R*-stereogenic center at C-2 was two-fold higher than that of **3**.

Table 1
Tyrosinase inhibitory activities of **3–12**, **20**, and **21**

Compounds tested	IC ₅₀ (μ M) ^a	Compounds tested	IC ₅₀ (μ M) ^a
3	4.72 $\pm$ 0.58	4	2.30 $\pm$ 0.15
5	2.17 $\pm$ 0.20	6	1.78 $\pm$ 0.10
7	4.56 $\pm$ 0.48	8	1.72 $\pm$ 0.17
9	3.83 $\pm$ 0.45	10	1.51 $\pm$ 0.10
11	4.13 $\pm$ 0.69	12	1.98 $\pm$ 0.17
20	9.15 $\pm$ 0.71	21	0.56 $\pm$ 0.02

^a The IC₅₀ values represent means $\pm$ SE of three different experiments.

The difference in activities between the epimers suggested that the rhododendrol glucosides are tyrosinase inhibitors that recognize the stereochemical environment in the enzyme structure. However, the role of the sugar moiety was still unclear. Hence, the enantiomeric pair of the aglycone was synthesized and evaluated for its inhibitory effect on oxidations catalyzed by tyrosinase.

2.2. Synthesis and tyrosinase inhibitory activities of **5** and **6**

An enantiomeric mixture of **5** and **6** was prepared in 100% yield from **16** by hydrogenolysis using Pd(OH)₂ on carbon (Scheme 1). Unfortunately, **5** and **6** could not be separated. However, the enantiomeric pair of **16** was isolated by chiral HPLC employing a Chiralcel OD-H column under normal-phase conditions.³⁴ The

enantiopurities of these compounds were confirmed by a modified Mosher's method.³⁵

After hydrogenation over a Pd catalyst, **5** and **6** were furnished in 100% yield.

The evaluation of tyrosinase inhibitory activities showed **5** and **6** to be more effective than glucosides **3** and **4** (Table 1). In particular, the efficacy of **6** as the *R*-enantiomer was five-fold stronger than that of **20**. However, the difference between the activities of the enantiomeric pair of **5** and **6** was imperceptible. This result suggested that the modification with a sugar moiety was likely to enhance the stereochemical recognition for inhibition. Moreover, potent water soluble tyrosinase inhibitors have been developed by xylosylation, cellobiosylation, and maltosylation on the polyphenolic core.²² Thus, several further rhododendrols with a hydrophilic sugar moiety were synthesized by a similar synthetic route as used for **3** and **4**.

2.3. Synthesis and tyrosinase inhibitory activities of **7–12**

Racemic aglycone **16** and xylose donor **22** were coupled using TMSOTf under cooling conditions (−40 °C) to furnish xyloside **23** in 48% yield (Scheme 2). Resorcinol **22** was obtained in moderate yield (65%) by hydrogenolysis of **23** in the presence of Pd(OH)₂ on carbon. Finally, **24** was converted to an epimeric mixture of xylosides **7** and **8** in excellent yield (99%). The yield of **7** and **8** was 23% over the six steps from **13**.

By using imidate **25** and two equivalents of **16**, the glycosylation proceeded to produce **26** in 20% yield (Scheme 3). When only one equivalent of **16** was used in this step, an acetylated derivative of **16** was detected as a major product.²³ The β facial attack of acceptor **16** was probably blocked because the oxocarbenium intermediate generated from **25** was sterically hindered.³⁶ Although several alternative modifications, such as a change of Lewis acid and the application of Koenigs–Knorr conditions were

explored, the glycosylation could not be further optimized. The obtained cellobioside **26** was transformed into resorcinol **27** by hydrogenolysis in high yield (99%). The transesterification of **27** using NaOMe followed by neutralization produced a mixture of cellobiosides **9** and **10** in 86% yield.

Scheme 3. Synthesis of cellobiosides **9** and **10**, and maltosides **11** and **12**. Reagents and conditions: (a) **16** (2 equiv.), TMSOTf, CH₂Cl₂, -40 °C, 20%; (b) H₂-Pd(OH)₂/C, EtOAc, rt, 99%; (c) NaOMe, MeOH, 0 °C to rt, then, Amberlite IR-120H, 86%; (d) **16** (2 equiv.), TMSOTf, CH₂Cl₂, -40 °C, 13%; (e) H₂-Pd(OH)₂/C, EtOAc, rt, 84%; (f) NaOMe, MeOH, 0 °C to rt, then, Amberlite IR-120H, 65%.

Glycosylation between aglycone **16** and maltose donor **28** was accomplished under similar conditions as used to synthesize **26**, although the isolated yield of **29** was low (13%). Maltoside **29** was transformed into resorcinol **30** by hydrogenolysis in 84% yield. Finally, treatment with NaOMe furnished **11** and **12** in 65% yield.

The synthetic derivatives **7–12** were isolated by RP-HPLC, and their stereochemistries were determined by comparison with the spectral data of **3** and **4**. The evaluation of the inhibitory activities of **7–12** using tyrosinase (Table 1) revealed that the derivatives having an *R*-stereogenic center at C-2 were more potent inhibitors than their epimers. This tendency remained unchanged when the sugar moiety was replaced by various saccharides such as xylose, cellobiose, and maltose. Although the difference of the sugar part was slightly influenced on the activity, cellobioside **10** bearing a

relatively bulky sugar moiety might be the most active inhibitor among all the synthetic compounds.

Although some chiral substrates of tyrosinase have shown high affinity in binding to its active site,³⁷ stereospecific inhibitors have rarely been developed against this enzymatic oxidation.^{38,39} The hydrophilic interaction between inhibitor and tyrosinase has not been thoroughly investigated in contrast to the extensive studies on the hydrophobic effect of the inhibitors.⁴⁰⁻⁴² The direction of the sugar moiety on the phenylbutanoid clearly influenced the tyrosinase inhibitory activity, suggesting that their hydrophilic property should be key to understanding the stereochemical recognition. In addition, the sugar moiety of the tyrosinase inhibitor plays an important role in improving the solubility in water, which may lead to lower cytotoxicity.^{4,43} Thus, the compounds synthesized in this study may represent unique candidates for developing highly effective and safe tyrosinase inhibitors.

3. Conclusion

On the basis of the structures of rhododendrin and epirhododendrin, novel tyrosinase inhibitors have been designed and synthesized through a short pathway. Stereospecific and effective hydrophilic inhibitors have thereby been developed. In particular, cellobioside **10** has proved to be a potent inhibitor about six-fold more effective than **20**. Further biological studies of rhododendrol derivatives obtained by chemical approaches are currently underway in our laboratory.

4. Experimental

4. 1. General

NMR spectra were recorded in CD₃OD or CDCl₃, or CD₃COCD₃ on a JEOL EX-400 spectrometer (¹H at 400 MHz and ¹³C at 100 MHz). Chemical shifts were recorded as ppm relative to the solvent signal for CD₃OD (3.30 ppm for ¹H NMR, 49.0 ppm for ¹³C NMR), CDCl₃ (7.24 ppm for ¹H NMR, 77.0 ppm for ¹³C NMR), or CD₃COCD₃ (2.05 ppm for ¹H NMR, 29.8 ppm for ¹³C NMR). HRMS spectra were measured on an AB SCIEX TripleTOF 5600 or a JEOL AccuTOF mass spectrometer fitted with an electrospray ion source in positive or negative ionization mode. IR spectra were measured with a PerkinElmer Paragon 1000 PC or Frontier FT-IR spectrometer. Optical rotations were recorded on a Jasco P-1020 polarimeter. Preparative RP-HPLC was performed on a Hitachi LaChrome Elite instrument.³¹ Preparative chiral-HPLC was performed on a Hitachi L-6300 instrument equipped with a Chiralcel OD-H column (4.6 mm × 250 mm). A flow rate of 1.0 mL/min and a detection wavelength of 254 nm were used for both separations.

4. 2. 4-(2',4'-Dibenzyloxyphenyl)-but-3-ene-2-one (**14**)

Aqueous NaOH solution (1.25 M, 5.8 mL, 7.25 mmol) was added dropwise to a stirred suspension of **13** (1.89 g, 5.94 mmol) in acetone (5.8 mL, 77.2 mmol) and EtOH (40 mL) at 0 °C. After being stirred for 2 h at 0 °C, the resultant solution was stirred for 1 h at room temperature. The reaction mixture was adjusted to pH 4 with 1 M aqueous HCl solution at 0 °C and diluted with H₂O (100 mL). The resultant mixture was extracted with EtOAc (200 mL). The organic layer was washed with 1% aqueous HCl solution (50 mL × 3) and brine (50 mL × 2). The combined aqueous layers were extracted with EtOAc (30 mL) and the combined organic layers were dried over Na₂SO₄. Filtration and concentration followed by recrystallization from EtOAc in hexane gave the titled

compound **14** (1.99 g, 94%) as a yellow-green needle, mp 119 °C. IR (film) ν_{max} 1654, 1602, 1276, 1248 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, J = 16.4 Hz, 1H, H-4), 7.49 (d, J = 8.4 Hz, 1H, H-6'), 7.40–7.33 (m, 10H, Bn), 6.67 (d, J = 16.4 Hz, 1H, H-3), 6.00–6.58 (m, 2H, H-3'', H-5''), 5.10 (s, 2H, Bn), 5.04 (s, 2H, Bn), 2.30 (s, 3H, H-1). ^{13}C NMR (100 MHz, CDCl_3) δ 199.1 (C-2), 162.0 (C-2'), 158.8 (C-4'), 138.6 (C-4), 136.33 (Bn), 136.28 (Bn), 129.8 (C-6'), 128.7 (Bn), 128.23 (Bn), 128.15 (Bn), 127.5 (Bn), 127.2 (Bn), 125.7 (C-3), 117.0 (C-1'), 106.9 (C-5'), 100.7 (C-3'), 70.5 (Bn), 70.2 (Bn), 27.1 (C-1). ESIHRMS m/z 359.1654 $[\text{M}+\text{H}]^+$ (calcd for $\text{C}_{24}\text{H}_{23}\text{O}_3$, 359.1647).

4. 3. 4-(2',4'-Dibenzyloxyphenyl)-but-2-one (**15**)

To a solution of **14** (24 mg, 68.6 μmol) in toluene (1 mL) was added 10% Pd(en)/C (2.5 mg). The reaction mixture was stirred for 1 h at 0 °C under a balloon of H_2 and filtered through a pad of Celite. The filtrate was concentrated and the residue was purified by silica gel chromatography (10–15% EtOAc in hexane) to give the title compound **15** (20 mg, 80%) as a white solid. By recrystallization from EtOAc in hexane, an analytical sample was obtained as a colorless plate, mp 62 °C. IR (film) ν_{max} 1714, 1614, 1166 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.42–7.29 (m, 10H, Bn), 7.04 (d, J = 8.2 Hz, 1H, H-6'), 6.58 (d, J = 2.4 Hz, 1H, H-3'), 6.49 (dd, J = 8.2, 2.4 Hz, 1H, H-5'), 5.03 (s, 2H, Bn), 5.00 (s, 2H, Bn), 2.86 (dd, J = 8.0, 7.2 Hz, 2H, H-4), 2.69 (dd, J = 8.0, 7.2 Hz, 2H, H-3), 2.06 (s, 3H, H-1). ^{13}C NMR (100 MHz, CDCl_3) δ 208.9 (C-2), 158.5 (C-2'), 157.3 (C-4'), 137.02 (Bn), 136.99 (Bn), 130.3 (C-6'), 128.58 (Bn), 128.56 (Bn), 128.55 (Bn), 128.0 (Bn), 127.9 (Bn), 127.5 (Bn), 127.1 (Bn), 122.2 (C-1'), 105.3 (C-5'), 100.6 (C-3'), 70.2 (Bn), 69.9 (Bn), 43.9 (C-4), 29.9 (C-3), 24.5 (C-1). ESIHRMS m/z 361.1806 $[\text{M}+\text{H}]^+$ (calcd for $\text{C}_{24}\text{H}_{25}\text{O}_3$, 361.1804).

4. 4. 4-(2',4'-Dibenzyloxyphenyl)-but-2-ol (**16**)

NaBH₄ (1.88 g, 13.6 mmol) was added slowly to a 50% EtOH/Et₂O solution (140 mL) of **15** (4.49 g, 12.4 mmol) at 0 °C. After being stirred for 30 min at room temperature, saturated aqueous NH₄Cl solution (70 mL) was poured into the reaction mixture at 0 °C. The resultant solution was extracted with EtOAc (200 mL). The organic layer was washed with saturated aqueous NH₄Cl solution (50 mL × 3) and brine (50 mL × 2). The combined aqueous layers were extracted with EtOAc (30 mL) and the combined organic layers were dried over Na₂SO₄. Filtration and concentration followed by crystallization from EtOAc in hexane gave the titled compound **16** (4.41 g, 98%) as a white solid. IR (film) $\nu_{\max}$ 3386, 1612, 1506, 1167 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.42–7.30 (m, 10H, Bn), 7.05 (d, *J* = 8.2 Hz, 1H, H-6'), 6.60 (d, *J* = 2.4 Hz, 1H, H-3'), 6.52 (d, *J* = 8.2, 2.4 Hz, 1H, H-5'), 5.03 (s, 1H, Bn), 5.02 (s, 1H, Bn), 5.01 (s, 2H, Bn), 3.71 (m, 1H, H-2), 2.73 (dt, *J* = 13.8, 6.2 Hz, 1H, H-4), 2.65 (ddd, *J* = 13.8, 7.8, 6.0 Hz, 1H, H-4), 1.72–1.66 (m, 2H, H-3), 1.15 (d, *J* = 6.2 Hz, 1H, H-1). ¹³C NMR (100 MHz, CDCl₃) δ 158.3 (C-2'), 157.3 (C-4'), 137.03 (Bn), 136.84 (Bn), 130.3 (C-6'), 128.61 (Bn), 128.57 (Bn), 127.98 (Bn), 127.96 (Bn), 127.5 (Bn), 127.3 (Bn), 123.2 (C-1'), 105.7 (C-5'), 100.6 (C-3'), 70.19 (Bn), 70.18 (Bn), 67.0 (C-2), 39.9 (C-4), 25.6 (C-3), 23.2 (C-1). ESIHRMS *m/z* 385.1778 [M+Na]⁺ (calcd for C₂₄H₂₆NaO₃, 385.1780).

By a chiral-HPLC with 10% *i*-PrOH in hexane as the eluting solvent at room temperature, (*R*)-**16** and (*S*)-**16** were separated. (*R*)-**16**: *t_R* = 8.1 min, [α]_D²⁵ -4.6 (c 0.15, CHCl₃). (*S*)-**16**: *t_R* = 9.9 min, [α]_D²⁷ +7.1 (c 0.19, CHCl₃). The configuration was determined by modified Mosher's method.³⁵

4. 5. (*S*)-4-(2',4'-Dihydroxyphenyl)-but-2-ol (**5**)

To a solution of (*S*)-**16** (4.7 mg, 13.0 μ mol) in EtOAc (1 mL) was added 5% Pd(OH)₂ on carbon (0.2 mg). The reaction mixture was stirred for 12 h under a balloon of H₂ at room temperature and filtered through a pad of Celite. The filtrate was concentrated and the residue was purified by silica gel chromatography (70–100% EtOAc in hexane) to give the title compound **5** (2.4 mg, 100%) as a white solid. For biological evaluation, **5** was further purified by solid phase extraction with Sep-Pak Plus C-18 cartridge (0–40% MeCN in H₂O) followed by preparative RP-HPLC (20% MeCN in H₂O, t_R = 4.6 min). $[\alpha]_D^{26}$ +18.3 (c 0.43, MeOH). IR (film) $\nu_{\max}$ 3394, 1458 cm⁻¹. ¹H NMR (400 MHz, CD₃COCD₃) δ 8.21 (s, 1H, OH), 8.01 (s, 1H, OH), 6.85 (d, J = 8.1 Hz, 1H, H-6'), 6.33 (d, J = 2.5 Hz, 1H, H-3'), 6.24 (dd, J = 8.1, 2.5 Hz, 1H, H-5'), 3.69 (d, J = 6.0 Hz, 1H, H-2), 3.40 (s, 1H, OH), 2.57 (dd, J = Hz, 2H, H-4), 1.62 (m, 2H, H-3), 1.12 (d, J = 6.2 Hz, 3H, H-1). ¹³C NMR (100 MHz, CD₃COCD₃) δ 157.2 (C-2'), 156.7 (C-4'), 131.2 (C-6'), 120.2 (C-1'), 107.4 (C-5'), 103.5 (C-3'), 67.1 (C-2), 40.6 (C-4), 26.3 (C-3), 23.8 (C-1). ESIHRMS m/z 181.0865 [M–H][–] (calcd for C₁₀H₁₃O₃, 181.0865).

4. 6. (*R*)-4-(2',4'-Dihydroxyphenyl)-but-2-ol (**6**)

The similar treatment of (*R*)-**16** (4.6 mg, 12.7 μ mol) as that described above gave the titled compound **6** (2.3 mg, 100%). $[\alpha]_D^{26}$ –18.3 (c 0.43, MeOH). The ¹H and ¹³C NMR, ESIHRMS, and IR data were in complete agreement with those of **5**.

4. 7.

2-(2'',3'',4'',6''-Tetra-*O*-acetyl- β -D-glucopyranosyl)-4-(2',4'-dibenzyloxyphenyl)-butane (**18**)

A TMSOTf solution (0.6 mL, 79 mM in CH₂Cl₂, 23.7 μmol) was slowly added to a stirred solution of **16** (43 mg, 118 μmol) and 2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranosyl trichloroacetimidate (**17**) (116 mg, 237 μmol) in CH₂Cl₂ (1 mL) at –40 °C. After being stirred for 30 min at –40 °C, the reaction was quenched with TEA (20 μL) and the resultant solution was allowed to warm to room temperature. Saturated aqueous NH₄Cl solution (20 mL) was poured into the solution and the resultant mixture was extracted with EtOAc (50 mL). The organic layer was washed with saturated aqueous NaHCO₃ solution (20 mL $\times$ 3) and brine (20 mL $\times$ 2). The combined aqueous layers were extracted with EtOAc (50 mL) and the combined organic layers were dried over Na₂SO₄. Filtration and concentration followed by silica gel chromatography (20–30% EtOAc in hexane) gave an approximately 1:1 diastereomeric mixture of the title compound **18** (41 mg, 50%) as a colorless oil. IR (film) ν_{max} 1755, 1377, 1221, 1038 cm^{–1}. ¹H NMR (400 MHz, CDCl₃) δ 7.41–7.28 (m, 10H, Bn), 7.06 (d, J = 8.2 Hz, 0.5H, H-6'), 6.99 (d, J = 8.2 Hz, 0.5H, H-6''), 6.57 (d, J = 2.4 Hz, 0.5H, H-3'), 6.56 (d, J = 2.4 Hz, 0.5H, H-3''), 6.49 (dd, J = 8.2, 2.4 Hz, 0.5H, H-5'), 6.46 (dd, J = 8.2, 2.4 Hz, 0.5H, H-5''), 5.17 (t, J = 9.5 Hz, 0.5H, H-3'''), 5.16 (t, J = 9.5 Hz, 0.5H, H-3'''), 5.08–4.93 (m, 2H, H-4'', H-2''), 5.017 (s, 1H, Bn), 5.005 (s, 1H, Bn), 5.000 (s, 1H, Bn), 4.991 (s, 1H, Bn), 4.49 (d, J = 8.0 Hz, 1H, H-1''), 4.20 (dd, J = 12.2, 5.0 Hz, 1H, H-6''), 4.11–4.05 (m, 1H, H-6''), 3.77–3.54 (m, 2H, H-5'', H-2), 2.74–2.48 (m, 2H, H-4), 2.04–1.94 (m, 12H, Ac), 1.88–1.62 (m, 2H, H-3), 1.22 (d, J = 6.2 Hz, 1.5H, H-1), 1.08 (d, J = 6.2 Hz, 1.5H, H-1). ¹³C NMR (100 MHz, CDCl₃) δ 170.8 (Ac), 170.7 (Ac), 170.40 (Ac), 170.39 (Ac), 169.445 (Ac), 169.435 (Ac), 169.3 (Ac), 158.4 (C-2'), 158.2 (C-2''), 157.39 (C-4'), 157.37 (C-4''), 137.3 (Bn), 137.1 (Bn), 137.0 (Bn), 130.4 (C-6'), 130.0 (C-6''), 128.59 (Bn), 128.57 (Bn), 128.5 (Bn), 128.0 (Bn), 127.93 (Bn), 127.89 (Bn), 127.8 (Bn),

127.55 (Bn), 127.54 (Bn), 127.13 (Bn), 127.06 (Bn), 123.4 (C-1'), 123.1 (C-1'), 105.3 (C-5'), 105.1 (C-5'), 101.0 (C-1''), 100.7 (C-3'), 100.6 (C-3'), 99.3 (C-1''), 78.0 (C-2), 75.8 (C-2), 73.0 (C-3''), 71.60 (C-5''), 71.59 (C-5''), 71.57 (C-2''), 71.5 (C-2''), 70.2 (Bn), 70.1 (Bn), 69.9 (Bn), 69.8 (Bn), 68.7 (C-4''), 68.6 (C-4''), 62.2 (C-6''), 36.91 (C-4), 36.88 (C-4), 25.7 (C-3), 25.6 (C-3), 21.7 (C-1), 20.7 (Ac), 20.64 (Ac), 20.63 (Ac), 20.6 (Ac), 19.8 (C-1). ESIHRMS m/z 731.2466 $[M+K]^+$ (calcd for $C_{38}H_{44}KO_{12}$, 731.2470).

4. 8.

2-(2'',3'',4'',6''-Tetra-*O*-acetyl- β -D-glucopyranosyl)-4-(2',4'-dihydroxyphenyl)-butane
(**19**)

To a solution of **18** (62 mg, 90.1 μ mol) in EtOAc (5 mL) was added 10% Pd(OH)₂ on carbon (6 mg). The reaction mixture was stirred for 12 h under a balloon of H₂ at room temperature and filtered through a pad of Celite. The filtrate was concentrated, and the residue was purified by silica gel chromatography (60–70% EtOAc in hexane) to give the title compound **19** (38 mg, 82%) as a colorless oil. IR (film) $\nu_{\max}$ 3418, 1753, 1227, 1039 cm^{-1} . ¹H NMR (400 MHz, CDCl₃) δ 6.88 (d, J = 8.2 Hz, 0.5H, H-6'), 6.86 (d, J = 8.2 Hz, 0.5H, H-6'), 6.33 (d, J = 2.4 Hz, 1H, H-3'), 6.30 (dd, J = 8.2, 2.4 Hz, 1H, H-5'), 5.20 (t, J = 9.5 Hz, 0.5H, H-3''), 5.19 (t, J = 9.5 Hz, 0.5H, H-3''), 5.11–4.95 (m, 2H, H-4'', H-2''), 4.58 (d, J = 8.0 Hz, 0.5H, H-1''), 4.54 (d, J = 8.0 Hz, 0.5H, H-1''), 4.23–4.08 (m, 2H, H-6''), 3.83–3.63 (m, 2H, H-5'', H-2), 2.57–2.41 (m, 2H, H-4), 2.07–1.98 (m, 12H, Ac), 1.76–1.59 (m, 2H, H-3), 1.23 (d, J = 6.3 Hz, 1.5H, H-1), 1.10 (d, J = 6.3 Hz, 1.5H, H-1). ¹³C NMR (100 MHz, CDCl₃) δ 171.5 (Ac), 171.1 (Ac), 170.7 (Ac), 170.5 (Ac), 170.0 (Ac), 169.7 (Ac), 169.6 (Ac), 155.19 (C-4'), 155.17 (C-4'), 154.8 (C-2'), 154.7 (C-2'), 130.6 (C-6'), 130.5 (C-6'), 119.80 (C-1'), 119.79 (C-1'), 107.4

(C-5'), 107.3 (C-5'), 103.3 (C-3'), 102.9 (C-3'), 100.8 (C-1''), 99.2 (C-1''), 78.1 (C-2), 75.5 (C-2), 73.0 (C-3''), 72.8 (C-3''), 71.7 (C-2''), 71.6 (C-2''), 71.50 (C-5''), 71.49 (C-5''), 68.6 (C-4''), 68.5 (C-4''), 62.1 (C-6''), 62.0 (C-6''), 37.1 (C-4), 37.0 (C-4), 25.0 (C-3), 24.3 (C-3), 21.6 (C-1), 20.7 (Ac), 20.62 (Ac), 20.61 (Ac), 20.59 (Ac), 20.57 (Ac), 19.9 (C-1). ESIHRMS m/z 535.1792 $[M+Na]^+$ (calcd for $C_{24}H_{32}NaO_{12}$, 535.1792).

4. 9. (*S*)-2- β -D-Glucopyranosyl-4-(2',4'-dihydroxyphenyl)-butane (**3**) and (*R*)-2- β -D-glucopyranosyl-4-(2',4'-dihydroxyphenyl)-butane (**4**)

NaOMe (150 μ L, 5.2 M in MeOH, 399 μ mol) was slowly added to a solution of **19** (34 mg, 66.5 μ mol) in MeOH (1 mL) at 0 °C and the resultant solution was stirred for 1 h at 0 °C. After being stirred for 1 h at room temperature, the solution was neutralized with Amberlite IR-120H at 0 °C. Filtration and concentration followed by solid phase extraction with Sep-Pak Plus C-18 cartridge (0–40% MeCN in H_2O) gave the mixture of **3** and **4** (20 mg, 89%) as a colorless oil. By preparative RP-HPLC (12% MeCN in H_2O), **3** (t_R = 9.6 min) and **4** (t_R = 8.7 min) were separated.

Glucoside **3**: $[\alpha]_D^{26}$ –21.8 (c 0.43, MeOH); IR (film) ν_{max} 3508, 1622, 1074 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ 6.88 (d, J = 8.2 Hz, 1H, H-6'), 6.25 (d, J = 2.4 Hz, 1H, H-3'), 6.20 (dd, J = 8.2, 2.4 Hz, 1H, H-5'), 4.34 (d, J = 7.8 Hz, 1H, H-1''), 3.83 (dd, J = 11.9, 2.3 Hz, 1H, H-6''), 3.83–3.78 (m, 1H, H-2), 3.65 (dd, J = 11.9, 5.4 Hz, 1H, H-6''), 3.36–3.15 (m, 4H, H-3'', H-4'', H-5'', H-2''), 2.64–2.51 (m, 2H, H-4), 1.88–1.63 (m, 2H, H-3), 1.26 (d, J = 6.2 Hz, 3H, H-1); ^{13}C NMR (100 MHz, CD_3OD) δ 157.3 (C-4'), 156.9 (C-2'), 131.5 (C-6'), 121.0 (C-1'), 107.4 (C-5'), 104.0 (C-3), 103.5 (C-1''), 78.1 (C-3''), 77.8 (C-5''), 77.4 (C-2), 75.4 (C-2''), 71.6 (C-4''), 62.7 (C-6''), 38.3 (C-4), 26.4 (C-3), 22.1 (C-1); ESIMS m/z 343.14 $[M-H]^-$.

Glucoside **4**: $[\alpha]_{\text{D}}^{27} -36.6$ (c 0.23, MeOH); IR (film) ν_{max} 3424, 1622, 1074 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ 6.89 (d, $J = 8.1$ Hz, 1H, H-6'), 6.24 (d, $J = 2.4$ Hz, 1H, H-3'), 6.19 (dd, $J = 8.1, 2.4$ Hz, 1H, H-5'), 4.33 (d, $J = 7.8$ Hz, 1H, H-1''), 3.92–3.87 (m, 1H, H-2), 3.86 (dd, $J = 11.9, 2.4$ Hz, 1H, H-6''), 3.69 (dd, $J = 11.8, 5.4$ Hz, 1H, H-6''), 3.37–3.15 (m, 4H, H-3'', H-4'', H-5'', H-2''), 2.65–2.48 (m, 2H, H-4), 1.88–1.63 (m, 2H, H-3), 1.20 (d, $J = 6.2$ Hz, 3H, H-1); ^{13}C NMR (100 MHz, CD_3OD) δ 157.3 (C-4'), 156.9 (C-2'), 131.5 (C-6'), 122.0 (C-1'), 107.4 (C-5'), 103.5 (C-3'), 102.2 (C-1''), 78.1 (C-3''), 77.8 (C-5''), 75.7 (C-2), 75.1 (C-2''), 71.7 (C-4''), 62.8 (C-6''), 38.8 (C-4), 26.5 (C-3), 20.0 (C-1); ESIHRMS m/z 343.1388 $[\text{M}-\text{H}]^-$ (calcd for $\text{C}_{16}\text{H}_{23}\text{O}_8$, 343.1393).

4. 10. 2-(2'',3'',4''-Tri-*O*-acetyl- β -D-xylopyranosyl)-4-(2',4'-dibenzyloxyphenyl)-butane (**23**)

TMSOTf (5 μL , 28 μmol) was slowly added to a stirred solution of **16** (53 mg, 146 μmol) and 2,3,4-tri-*O*-acetyl- α -D-xylopyranosyl trichloroacetimidate (**22**) (246 mg, 587 μmol) in CH_2Cl_2 (1.5 mL) at -40°C . After being stirred for 30 min at -40°C , the reaction was quenched with TEA (10 μL) and the resultant solution was allowed to warm to room temperature. Concentration followed by silica gel chromatography (20% EtOAc in hexane) gave an approximately 1:1 diastreomeric mixture of the title compound **23** (43 mg, 48%) as a colorless oil. IR (film) ν_{max} 1728, 1331, 1215, 1073 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.41–7.28 (m, 10H, Bn), 7.05 (d, $J = 8.2$ Hz, 0.5H, H-6'), 7.00 (d, $J = 8.2$ Hz, 0.5H, H-6'), 6.57 (d, $J = 2.4$ Hz, 0.5H, H-3'), 6.56 (d, $J = 2.4$ Hz, 0.5H, H-3'), 6.51–6.46 (dd, $J = 8.2, 2.4$ Hz, 1H, H-5'), 5.14 (t, $J = 9.1$ Hz, 0.5H, H-3''), 5.13 (t, $J = 8.5$ Hz, 0.5H, H-3''), 5.03 (s, 1H, Bn), 5.02 (s, 1H, Bn), 5.00 (s, 1H, Bn), 4.99 (s, 1H, Bn), 4.95–4.85 (m, 2H, H-4'', H-2''), 4.51 (d, $J = 6.8$ Hz, 0.5H, H-1''),

4.46 (d, $J = 7.3$ Hz, 0.5H, H-1"), 4.09–4.04 (m, 1H, H-5"), 3.79–3.64 (m, 1H, H-2), 3.28 (dd, $J = 11.8, 8.6$ Hz, 1H, H-5"), 3.23 (dd, $J = 11.7, 9.5$ Hz, 1H, H-5"), 2.76–2.48 (m, 2H, H-4), 2.08–2.01 (m, 9H, Ac), 1.87–1.66 (m, 2H, H-3), 1.20 (d, $J = 6.2$ Hz, 1.5H, H-1), 1.08 (d, $J = 6.1$ Hz, 1.5H, H-1). ^{13}C NMR (100 MHz, CDCl_3) δ 170.3 (Ac), 170.2 (Ac), 169.9 (Ac), 169.8 (Ac), 169.4 (Ac), 158.3 (C-2'), 158.2 (C-2'), 157.3 (C-4'), 137.2 (Bn), 137.07 (Bn), 137.05 (Bn), 137.0 (Bn), 130.2 (C-6'), 129.9 (C-6'), 128.57 (Bn), 128.55 (Bn), 128.5 (Bn), 128.0 (Bn), 127.9 (Bn), 127.8 (Bn), 127.7 (Bn), 127.54 (Bn), 127.53 (Bn), 127.1 (Bn), 127.0 (Bn), 123.4 (C-1'), 123.1 (C-1'), 105.2 (C-5'), 105.1 (C-5'), 100.9 (C-1"), 100.6 (C-3'), 100.5 (C-3'), 98.7 (C-1"), 77.2 (C-2), 74.8 (C-2), 72.0 (C-3"), 71.43 (C-3"), 71.39 (C-4"), 71.0 (C-4"), 70.13 (Bn), 70.11 (Bn), 69.8 (Bn), 69.7 (Bn), 69.1 (C-2"), 68.9 (C-2"), 62.1 (C-5"), 61.8 (C-5"), 37.1 (C-4), 36.8 (C-4), 25.8 (C-3), 25.7 (C-3), 21.6 (C-1), 20.8 (Ac), 20.72 (Ac), 20.70 (Ac), 20.66 (Ac), 19.5 (C-1). ESIHRMS m/z 643.2513 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{35}\text{H}_{40}\text{NaO}_{10}$, 643.2519).

4. 11. 2-(2'',3'',4''-Tri-*O*-acetyl- β -D-xylopyranosyl)-4-(2',4'-dihydroxyphenyl)-butane
(**24**)

To a solution of **23** (19 mg, 30.4 μmol) in EtOAc (1 mL) was added 10% $\text{Pd}(\text{OH})_2$ on carbon (2 mg). The reaction mixture was stirred for 2 h under a balloon of H_2 at room temperature and filtered through a pad of Celite. The filtrate was concentrated and the residue was purified by silica gel chromatography (60–70% EtOAc in hexane) to give the title compound **24** (9 mg, 65%) as a colorless oil. IR (film) ν_{max} 3418, 1741, 1369, 1217, 1037 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 6.91–6.86 (m, 1H, H-6'), 6.35–6.30 (m, 1H, H-3'), 5.89 (d, $J = 5.6$ Hz, 1H, H-5'), 5.20–5.14 (m, 1H, H-3''), 5.00–4.90 (m, 2H, H-4'', H-2''), 4.58 (d, $J = 7.0$ Hz, 0.5H, H-1''), 4.43 (d, $J = 7.2$ Hz,

0.5H, H-1"), 4.16–4.08 (m, 1H, H-5"), 3.79–3.69 (m, 1H, H-2), 3.28 (m, 0.5H, H-5"), 3.23 (m, 0.5H, H-5"), 2.62–2.43 (m, 2H, H-4), 2.10–2.02 (m, 9H, Ac), 1.73–1.68 (m, 2H, H-3), 1.23 (d, $J = 6.1$ Hz, 1.5H, H-1), 1.11 (d, $J = 5.6$ Hz, 1.5H, H-1). ^{13}C NMR (100 MHz, CDCl_3) δ 170.33 (Ac), 170.27 (Ac), 169.9 (Ac), 169.84 (Ac), 169.82 (Ac), 169.5 (Ac), 155.1 (C-2'), 155.03 (C-2'), 154.95 (C-4'), 154.6 (C-4'), 130.8 (C-6'), 130.5 (C-6'), 119.9 (C-1'), 119.8 (C-1'), 107.51 (C-5'), 107.50 (C-5'), 103.3 (C-3'), 103.1 (C-3'), 100.5 (C-1"), 99.4 (C-1"), 77.2 (C-2), 75.2 (C-2), 71.7 (C-3"), 71.6 (C-3"), 71.4 (C-4"), 71.2 (C-4"), 68.9 (C-2"), 68.8 (C-2"), 62.3 (C-5"), 62.0 (C-5"), 37.5 (C-4), 37.1 (C-4), 24.9 (C-3), 24.0 (C-3), 21.5 (C-1), 20.8 (Ac), 20.74 (Ac), 20.72 (Ac), 20.70 (Ac), 20.68 (Ac), 19.7 (C-1). ESIHRMS m/z 463.1573 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{21}\text{H}_{28}\text{NaO}_{10}$, 463.1580).

4. 12. (*S*)-2- β -D-Xylopyranosyl-4-(2',4'-dihydroxyphenyl)-butane (**7**)

(*R*)-2- β -D-xylopyranosyl-4-(2',4'-dihydroxyphenyl)-butane (**8**)

NaOMe (185 μL , 5.2 M in MeOH, 942 μmol) was slowly added to a stirred solution of **24** (69 mg, 157 μmol) in MeOH (2 mL) at 0 °C and the resultant solution was stirred for 1 h at 0 °C. After being stirred for 1h at room temperature, the solution was neutralized with Amberlite IR-120H at 0 °C. Filtration and concentration followed by solid phase extraction with Sep-Pak Plus C-18 cartridge (0–40% MeCN in H_2O) gave the mixture of **7** and **8** (48 mg, 99%) as a colorless oil. By preparative RP-HPLC (10% MeCN in H_2O), **7** ($t_R = 9.9$ min) and **8** ($t_R = 7.7$ min) were separated.

Xyloside **7**: $[\alpha]_D^{26} -4.2$ (c 0.05, MeOH); IR (film) ν_{max} 3418, 1622, 1048 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ 6.87 (d, $J = 8.2$ Hz, 1H, H-6'), 6.26 (d, $J = 2.4$ Hz, 1H, H-3'), 6.21 (dd, $J = 8.2, 2.4$ Hz, 1H, H-5'), 4.28 (d, $J = 7.6$ Hz, 1H, H-1"), 3.83 (dd, $J = 11.4, 5.3$ Hz, 1H, H-5"), 3.73 (sext, $J = 6.2$ Hz, 1H, H-2), 3.65 (ddd, $J = 10.3, 8.9, 5.3$

Hz, 1H, H-5''), 3.32–3.28 (m, 1H, H-3''), 3.16 (dd, $J = 9.4, 7.6$ Hz, 1H, H-2''), 3.15 (dd, $J = 11.4, 10.3$ Hz, 1H, H-5''), 2.63–2.51 (m, 2H, H-4), 1.88–1.62 (m, 2H, H-3), 1.23 (d, $J = 6.2$ Hz, 3H, H-1); ^{13}C NMR (100 MHz, CD_3OD) δ 157.3 (C-4'), 156.9 (C-2'), 131.5 (C-6'), 121.0 (C-1'), 107.4 (C-5'), 104.8 (C-1''), 103.5 (C-3'), 77.9 (C-3''), 77.7 (C-2), 75.2 (C-2''), 71.2 (C-4''), 66.8 (C-5''), 38.6 (C-4), 26.4 (C-3), 22.1 (C-1); ESIHRMS m/z 313.1270 $[\text{M}-\text{H}]^-$ (calcd for $\text{C}_{15}\text{H}_{21}\text{O}_7$, 313.1287).

Xyloside **8**: $[\alpha]_{\text{D}}^{26} -9.3$ (c 0.70, MeOH); IR (film) ν_{max} 3468, 1684, 1094, 824 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ 6.89 (d, $J = 8.2$ Hz, 1H, H-6'), 6.25 (d, $J = 2.4$ Hz, 1H, H-3'), 6.19 (dd, $J = 8.1, 2.4$ Hz, 1H, H-5'), 4.27 (d, $J = 7.6$ Hz, 1H, H-1''), 3.85 (dd, $J = 11.4, 5.3$ Hz, 1H, H-5''), 3.81 (m, 1H, H-2), 3.49 (ddd, $J = 10.2, 8.9, 5.3$ Hz, 1H, H-4''), 3.33–3.28 (m, 1H, H-3''), 3.18 (m, 1H, H-5''), 3.16 (dd, 1H, H-2''), 2.60–2.48 (m, 2H, H-4), 1.83–1.62 (m, 2H, H-3), 1.19 (d, $J = 6.2$ Hz, 3H, H-1); ^{13}C NMR (100 MHz, CD_3OD) δ 157.2 (C-4'), 156.9 (C-2'), 131.4 (C-6'), 121.1 (C-1'), 107.3 (C-5'), 103.5 (C-3'), 103.0 (C-1''), 77.9 (C-3''), 75.9 (C-2), 74.9 (C-2''), 71.3 (C-4''), 66.9 (C-5''), 38.8 (C-4), 26.6 (C-3), 20.0 (C-1); ESIMS m/z 313.14 $[\text{M}-\text{H}]^-$.

4. 13.

2-(2'',2''',3'',3''',4''',6'',6'''-Hepta-*O*-acetyl- β -D-cellobiosyl)-4-(2',4'-dibenzyloxyphenyl)-butane (**26**)

TMSOTf (2 μL , 11 μmol) was slowly added to a stirred solution of **16** (100 mg, 275 μmol) and 2,2',3,3',4',6,6'-hepta-*O*-acetyl- α -D-cellobiosyl trichloroacetimidate (**25**) (108 mg, 138 μmol) in CH_2Cl_2 (1.5 mL) at -40°C . After being stirred for 30 min at -40°C , the resultant solution was quenched with TEA (10 μL) and allowed to warm to room temperature. Concentration followed by silica gel chromatography (40% EtOAc

in hexane) gave an approximately 1:1 diastereomeric mixture of the title compound **26** (28 mg, 20%) as a colorless oil. IR (film) $\nu_{\max}$ 1745, 1367, 1219, 1035 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.41–7.30 (m, 10H, Bn), 7.04 (d, $J = 8.2$ Hz, 0.5H, H-6'), 6.98 (d, $J = 8.2$ Hz, 0.5H, H-6'), 6.57 (d, $J = 2.2$ Hz, 0.5H, H-3'), 6.55 (d, $J = 2.2$ Hz, 0.5H, H-3'), 6.49 (dd, $J = 8.2, 2.2$ Hz, 0.5H, H-5'), 6.46 (dd, $J = 8.2, 2.2$ Hz, 0.5H, H-5'), 5.16–5.10 (m, 2H, H-3'', H-3'''), 5.04 (m, 1H, H-4''), 5.01–4.99 (s, 4H, Bn), 4.93–4.84 (m, 2H, H-2'', H-2'''), 4.48–4.42 (m, 3H, H-1'', H-1''', H-6''), 4.35 (dd, $J = 12.4, 4.4$ Hz, 1H, H-6''), 4.06–4.00 (m, 2H, H-6'''), 3.75–3.62 (m, 3H, H-4''', H-5'', H-2), 3.51–3.45 (m, 1H, H-5'''), 2.72–2.46 (m, 2H, H-4), 2.07–1.93 (m, 21H, Ac), 1.83–1.64 (m, 2H, H-3), 1.18 (d, $J = 6.1$ Hz, 1.5H, H-1), 1.07 (d, $J = 6.1$ Hz, 1.5H, H-1). ^{13}C NMR (100 MHz, CDCl_3) δ 170.5 (Ac), 170.4 (Ac), 170.3 (Ac), 170.2 (Ac), 176.90 (Ac), 176.88 (Ac), 169.5 (Ac), 169.3 (Ac), 169.1 (Ac), 158.3 (C-2'), 158.2 (C-2'), 157.33 (C-4'), 137.2 (Bn), 137.08 (Bn), 137.07 (Bn), 137.0 (Bn), 130.4 (C-6'), 130.0 (C-6'), 128.58 (Bn), 128.55 (Bn), 128.5 (Bn), 127.97 (Bn), 127.93 (Bn), 127.89 (Bn), 127.8 (d, Bn), 127.55 (d, Bn), 127.53 (d, Bn), 127.1 (d, Bn), 127.0 (d, Bn), 123.4 (C-1'), 123.1 (C-1'), 105.2 (C-5'), 105.1 (C-5'), 101.0 (C-1''), 99.2 (C-1''), 100.8 (C-1'''), 100.6 (C-3'), 100.5 (C-3'), 78.0 (C-2), 76.7 (C-4''), 75.8 (C-2), 72.9 (C-3'', C-3'''), 72.7 (C-3'', C-3'''), 72.4 (C-5'', C-5'''), 71.9 (C-5'', C-5'''), 71.81 (C-2''), 71.80 (C-2''), 71.6 (C-2'''), 70.2 (Bn), 70.1 (Bn), 69.8 (Bn), 69.7 (Bn), 67.8 (C-4''), 62.0 (C-6'''), 61.9 (C-6''), 61.9 (C-6'''), 61.6 (C-6''), 36.9 (C-4), 25.8 (C-3), 25.7 (C-3), 21.7 (C-1), 20.8 (Ac), 20.7 (Ac), 20.65 (Ac), 20.63 (Ac), 20.56 (Ac), 20.55 (Ac), 20.5 (Ac), 19.8 (C-1). ESIHRMS m/z 1003.3579 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{50}\text{H}_{60}\text{NaO}_{20}$, 1003.3576).

4. 14.

2-(2'',2''',3'',3''',4''',6'',6'''-Hepta-*O*-acetyl- β -D-cellobiosyl)-4-(2',4'-dihydroxyphenyl)-butane (**27**)

To a solution of **26** (49 mg, 50.3 μ mol) in EtOAc (2 mL) was added 10% Pd(OH)₂ on carbon (5 mg). The reaction mixture was stirred for 4 h under a balloon of H₂ at room temperature and filtered through a pad of Celite. The filtrate was concentrated and the residue was purified by silica gel chromatography (70% EtOAc in hexane) to give the title compound **27** (40 mg, 99%) as a colorless oil. IR (film) ν_{max} 3434, 1748, 1373, 1228, 1039 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 6.89 (d, J = 8.1 Hz, 0.5H, H-6'), 6.87 (d, J = 8.1 Hz, 0.5H, H-6'), 6.34–6.30 (m, 2H, H-3', H-5'), 5.19–5.11 (m, 2H, H-3'', H-3'''), 5.04 (t, J = 9.4 Hz, 1H, H-4''), 4.93–4.84 (m, 2H, H-2'', H-2'''), 4.57 (dd, J = 12.0, 2.0 Hz, 0.5H, H-6''), 4.47 (dd, J = 12.0, 2.0 Hz, 0.5H, H-6''), 4.53–4.47 (m, 2H, H-1'', H-1'''), 4.345 (dd, J = 12.4, 2.2 Hz, 0.5H, H-6'''), 4.351 (dd, J = 12.5, 2.1 Hz, 0.5H, H-6'''), 4.10–4.01 (m, 2H, H-6'', H-6'''), 3.79 (t, J = 9.4 Hz, 1H, H-4'''), 3.74–3.68 (m, 1H, H-2), 3.64 (ddd, J = 9.4, 4.3, 2.2 Hz, 1H, H-5''), 3.57–3.51 (m, 1H, H-5'''), 2.58–2.44 (m, 2H, H-4), 2.08–1.97 (m, 21H, Ac), 1.78–1.60 (m, 2H, H-3), 1.21 (d, J = 6.2 Hz, 1.5H, H-1), 1.10 (d, J = 6.1 Hz, 1.5H, H-1). ¹³C NMR (100 MHz, CDCl₃) δ 171.0 (Ac), 170.63 (Ac), 170.61 (Ac), 170.5 (Ac), 170.31 (Ac), 170.26 (Ac), 170.2 (Ac), 170.00 (Ac), 179.97 (Ac), 169.7 (Ac), 169.40 (Ac), 169.38 (Ac), 169.2 (Ac), 155.3 (C-2'), 155.1 (C-2'), 154.9 (C-4'), 154.7 (C-4'), 130.6 (C-6'), 130.4 (C-6'), 119.9 (C-1'), 119.8 (C-1'), 107.5 (C-5'), 107.4 (C-5'), 103.5 (C-3'), 103.0 (C-3'), 100.7 (C-1''), 99.1 (C-1''), 77.6 (C-2), 76.6 (C-4''), 76.3 (C-4''), 75.6 (C-2), 72.9 (C-3''), 72.9 (C-3''), 72.8 (C-3'''), 72.6 (C-5''), 72.4 (C-5'''), 72.0 (C-5'''), 71.9 (C-5''), 71.9 (C-2''), 71.65 (C-2''), 71.63 (C-2'''), 67.8 (C-4''), 68.7 (C-4''), 61.9 (C-6''), 61.5 (C-6'''), 37.1 (C-4), 24.9 (C-3), 24.1 (C-3),

21.6 (C-1), 20.8 (Ac), 20.7 (Ac), 20.65 (Ac), 20.59 (Ac), 20.55 (Ac), 20.53 (Ac), 20.0 (C-1). ESIHRMS m/z 801.2808 $[M+H]^+$ (calcd for $C_{36}H_{49}O_{20}$, 801.2817).

4. 15. (*S*)-2- β -D-Cellobiosyl-4-(2',4'-dihydroxyphenyl)-butane (**9**) and (*R*)-2- β -D-cellobiosyl-4-(2',4'-dihydroxyphenyl)-butane (**10**)

NaOMe (71 μ L, 5.2 M in MeOH, 371 μ mol) was slowly added to a stirred solution of **27** (20 mg, 24.7 μ mol) in MeOH (1 mL) at 0 °C and the resultant solution was stirred for 1 h at 0 °C. After being stirred for 1h at room temperature, the solution was neutralized with Amberlite IR-120H at 0 °C. Filtration and concentration followed by solid phase extraction with Sep-Pak Plus C-18 cartridge (0–40% MeCN in H_2O) gave a mixture of **9** and **10** (11 mg, 86%) as a colorless oil. By preparative RP-HPLC (10% MeCN in H_2O), **9** (t_R = 14.2 min) and **10** (t_R = 13.2 min) were separated.

Cellobioside **9**: $[\alpha]_D^{26}$ –15.4 (c 0.27, MeOH); IR (film) ν_{max} 3418, 1639, 1024 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ 6.88 (d, J = 8.2 Hz, 1H, H-6'), 6.24 (d, J = 2.4 Hz, 1H, H-3'), 6.20 (dd, J = 8.2, 2.4 Hz, 1H, H-5'), 4.41 (d, J = 7.8 Hz, 1H, H-1''), 4.37 (d, J = 7.8 Hz, 1H, H-1'''), 3.87 (dd, J = 11.8, 1.7 Hz, 1H, H-6''), 3.88–3.84 (m, 2H, H-6'', H-6'''), 3.79 (sext, J = 6.2 Hz, 1H, H-2), 3.65 (dd, J = 11.8, 5.4 Hz, 1H, H-6'''), 3.56 (t, J = 9.1 Hz, 1H, H-3''), 3.50 (t, J = 8.8 Hz, 1H, H-3'''), 3.38–3.31 (m, 4H, H-4'', H-4''', H-5'', H-5'''), 3.25–3.19 (m, 2H, H-2'', H-2'''), 2.64–2.52 (m, 2H, H-4), 1.88–1.62 (m, 2H, H-3), 1.26 (d, J = 6.2 Hz, 3H, H-1); ^{13}C NMR (100 MHz, CD_3OD) δ 157.4 (C-4'), 156.9 (C-2'), 131.5 (C-6'), 121.0 (C-1'), 107.4 (C-5'), 104.6 (C-3'), 103.8 (C-1''), 103.5 (C-1'''), 80.7 (C-4''), 78.1 (C-5'''), 77.9 (C-5''), 77.5 (C-2), 76.5 (C-3'''), 76.3 (C-3''), 75.1 (C-2'''), 74.9 (C-2''), 71.4 (C-4'''), 62.4 (C-6'''), 61.9 (C-6''), 38.2 (C-4), 26.4 (C-3), 22.1 (C-1); ESIMS m/z 505.19 $[M-H]^-$.

Cellobioside **10**: $[\alpha]_D^{25}$ -34.3 (c 0.26, MeOH); IR (film) $\nu_{\max}$ 3383, 2952, 1621, 1066, 1026 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ 6.89 (d, $J = 8.2$ Hz, 1H, H-6'), 6.24 (d, $J = 2.4$ Hz, 1H, H-3'), 6.19 (dd, $J = 8.1, 2.4$ Hz, 1H, H-5'), 4.42 (d, $J = 7.8$ Hz, 1H, H-1''), 4.36 (d, $J = 7.8$ Hz, 1H, H-1'''), 3.88–3.85 (m, 4H, H-2, H-6'', H-6'''), 3.65 (dd, $J = 11.8, 5.4$ Hz, 1H, H-6'''), 3.59 (dd, $J = 9.0, 9.1$ Hz, 1H, H-3''), 3.51 (t, $J = 8.9$ Hz, 1H, H-3'''), 3.39–3.31 (m, 4H, H-4'', H-4''', H-5'', H-5'''), 3.27–3.19 (m, 2H, H-2'', H-2'''), 2.65–2.49 (m, 2H, H-4), 1.88–1.64 (m, 2H, H-3), 1.20 (d, $J = 6.2$ Hz, 3H, H-1); ^{13}C NMR (100 MHz, CD_3OD) δ 157.3 (C-4'), 156.9 (C-2'), 131.5 (C-6'), 121.1 (C-1'), 107.3 (C-5'), 104.5 (C-1'''), 104.6 (C-3'), 102.2 (C-1''), 80.9 (C-4''), 78.1 (C-5'''), 77.9 (C-5''), 76.5 (C-3'''), 76.4 (C-3''), 75.8 (C-2), 75.0 (C-2''), 74.8 (C-2'''), 71.4 (C-4'''), 62.4 (C-6'''), 62.0 (C-6''), 38.7 (C-4), 26.5 (C-3), 20.0 (C-1); ESIHRMS m/z 505.1921 $[\text{M}-\text{H}]^-$ (calcd for $\text{C}_{22}\text{H}_{33}\text{O}_{13}$, 505.1921).

4. 16.

2-(2'',2''',3'',3''',4''',6'',6'''-Hepta-*O*-acetyl- β -D-maltosyl)-4-(2',4'-dibenzyloxyphenyl)-butane (**29**)

TMSOTf (20 μL , 111 μmol) was slowly added to a stirred solution of **16** (0.98 mg, 2.70 mmol) and 2,2',3,3',4',6,6'-hepta-*O*-acetyl- α -D-maltosyl trichloroacetimidate (**28**) (1.77 mg, 2.27 μmol) in CH_2Cl_2 (20 mL) at -40°C . After being stirred for 30 min at -40°C , the reaction was quenched with TEA (20 μL) and the resultant solution was allowed to warm to room temperature. Concentration followed by silica gel chromatography (40% EtOAc in hexane) gave an approximately 1:1 diastereomeric mixture of the title compound **29** (178 mg, 13%) as a colorless oil. IR (film) $\nu_{\max}$ 1744, 1367, 1215, 1027, 752 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.41–7.29 (m, 10H, Bn),

7.05 (d, $J = 8.2$ Hz, 0.5H, H-6'), 6.99 (d, $J = 8.2$ Hz, 0.5H, H-6'), 6.57 (d, $J = 2.4$ Hz, 0.5H, H-3'), 6.56 (d, $J = 2.4$ Hz, 0.5H, H-3'), 6.49 (dd, $J = 8.2, 2.2$ Hz, 0.5H, H-5'), 6.47 (dd, $J = 8.2, 2.2$ Hz, 0.5H, H-5'), 5.40 (d, $J = 2.8$ Hz, 0.5H, H-1'''), 5.39 (d, $J = 2.8$ Hz, 0.5H, H-1'''), 5.36 (dd, $J = 10.4, 9.6$ Hz, 0.5H, H-3'''), 5.35 (dd, $J = 10.4, 9.6$ Hz, 0.5H, H-3'''), 5.22 (t, $J = 9.3$ Hz, 1H, H-3''), 5.05–5.00 (m, 5H, H-4'', Bn), 4.86–4.76 (m, 2H, H-2'', H-2'''), 4.517 (d, $J = 8.0$ Hz, 0.5H, H-1''), 4.515 (d, $J = 8.0$ Hz, 0.5H, H-1''), 4.41 (dd, $J = 12.0, 2.7$ Hz, 0.5H, H-6''), 4.40 (dd, $J = 12.0, 2.7$ Hz, 0.5H, H-6''), 4.23 (dd, $J = 12.4, 4.1$ Hz, 1H, H-6'', H-6'''), 4.18 (dd, $J = 12.4, 4.1$ Hz, 1H, H-6'', H-6'''), 4.01 (ddd, $J = 12.4, 4.1, 2.2$ Hz, 1H, H-5'''), 3.96–3.92 (m, 2H, H-4''', H-6''), 3.77–3.63 (m, 1H, H-2), 3.57–3.52 (m, 1H, H-5''), 2.73–2.46 (m, 2H, H-4), 2.10–1.92 (m, 21H, Ac), 1.84–1.66 (m, 2H, H-3), 1.20 (d, $J = 6.2$ Hz, 1.5H, H-1), 1.07 (d, $J = 6.2$ Hz, 1.5H, H-1). ^{13}C NMR (100 MHz, CDCl_3) δ 170.56 (Ac), 170.55 (Ac), 170.54 (Ac), 170.52 (Ac), 170.45 (Ac), 170.3 (Ac), 170.0 (Ac), 169.6 (Ac), 169.4 (Ac), 158.3 (C-2'), 158.2 (C-2'), 157.4 (C-4'), 157.3 (C-4'), 137.2 (Bn), 137.09 (Bn), 137.07 (Bn), 137.0 (Bn), 130.4 (C-6'), 129.9 (C-6'), 128.59 (Bn), 128.58 (Bn), 128.55 (Bn), 128.5 (Bn), 128.0 (Bn), 127.92 (Bn), 127.8 (Bn), 127.89 (Bn), 127.55 (Bn), 127.53 (Bn), 127.1 (Bn), 127.0 (Bn), 123.3 (C-1'), 123.1 (C-1'), 105.2 (C-5'), 105.1 (C-5'), 100.55 (C-1''), 100.6 (C-3'), 100.52 (C-3'), 98.7 (C-1''), 95.4 (C-1'''), 78.0 (C-2), 75.8 (C-2), 75.63 (C-3''), 75.60 (C-3''), 72.8 (C-4''), 72.44 (C-2''), 72.40 (C-2''), 71.8 (C-5''), 70.2 (Bn), 70.1 (Bn), 70.0 (C-2'''), 69.8 (Bn), 69.7 (Bn), 69.3 (C-3'''), 68.44 (C-5'''), 68.42 (C-5'''), 68.0 (C-4'''), 63.0 (C-6'''), 62.9 (C-6'''), 61.52 (C-6''), 61.48 (C-6''), 36.92 (C-4), 36.87 (C-4), 25.8 (C-3), 25.7 (C-3), 21.7 (C-1), 20.92 (Ac), 20.91 (Ac), 20.8 (Ac), 20.70 (Ac), 20.66 (Ac), 20.61 (Ac), 20.59 (Ac), 20.56 (Ac), 19.8 (C-1). ESIHRMS m/z 998.4022 $[\text{M}+\text{NH}_4]^+$ (calcd for $\text{C}_{50}\text{H}_{64}\text{NO}_{20}$, 998.4022).

4. 17. 2-(2'',2''',3'',3''',4''',6'',6'''-Hepta-*O*-acetyl- β -D-maltosyl)-4-(2',4'-dihydroxyphenyl)-butane (**30**)

To a solution of **29** (271 mg, 277 μ mol) in EtOAc (5 mL) was added 10% Pd(OH)₂ on carbon (27 mg). The reaction mixture was stirred for 2 h under a balloon of H₂ at room temperature and filtered through a pad of Celite. The filtrate was concentrated, and the residue was purified by silica gel chromatography (70% EtOAc in hexane) to give the title compound **30** (186 mg, 84%) as a colorless oil. IR (film) ν_{max} 3436, 1747, 1369, 1224, 1037 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 6.88 (d, J = 8.0 Hz, 0.5H, H-6'), 6.87 (d, J = 8.0 Hz, 0.5H, H-6'), 6.33–6.30 (m, 2H, H-3', H-5'), 5.41, 5.39 (d, J = 3.9 Hz, 1H, H-1'''), 5.35 (t, J = 10 Hz, 1H, H-3'''), 5.27–5.22 (m, 1H, H-3''), 5.04 (t, J = 9.8 Hz, 0.5H, H-4'''), 5.03 (t, J = 9.8 Hz, 0.5H, H-4''), 4.85–4.78 (m, 2H, H-2'', H-2'''), 4.61 (d, J = 8.0 Hz, 0.5H, H-1''), 4.57 (d, J = 8.0 Hz, 0.5H, H-1'), 4.57–4.43 (m, 1H, H-6''), 4.26–3.93 (m, 5H, H-6''', H-4''', H-6'', H-5'''), 3.77–3.70 (m, 1H, H-5''), 3.64–3.62 (m, 1H, H-2), 2.60–2.43 (m, 2H, H-4), 2.10–1.90 (m, 21H, Ac), 1.86–1.60 (m, 2H, H-3), 1.23 (d, J = 6.2 Hz, 1.5H, H-1), 1.11 (d, J = 6.0 Hz, 1.5H, H-1). ¹³C NMR (100 MHz, CDCl₃) δ 171.2 (Ac), 170.8 (Ac), 170.71 (Ac), 170.68 (Ac), 170.6 (Ac), 170.5 (Ac), 170.4 (Ac), 170.2 (Ac), 170.0 (Ac), 169.7 (Ac), 169.5 (Ac), 155.2 (C-2'), 155.1 (C-2'), 154.9 (C-4'), 154.7 (C-4'), 130.6 (C-6'), 130.4 (C-6'), 119.9 (C-1'), 119.8 (C-1'), 107.5 (C-5'), 107.4 (C-5'), 103.4 (C-3'), 103.0 (C-3'), 100.3 (C-1''), 98.8 (C-1''), 95.5 (C-1'''), 95.4 (C-1'''), 77.8 (C-2), 75.6 (C-3''), 75.3 (C-2), 72.9 (C-4''), 72.5 (C-4''), 72.4 (C-2''), 72.3 (C-2''), 72.2 (C-5''), 72.0 (C-5''), 70.0 (C-2'''), 69.4 (C-3'''), 69.3 (C-3'''), 68.4 (C-5'''), 68.0 (C-4'''), 62.9 (C-6'''), 62.6 (C-6'''), 61.5 (C-6''), 37.0 (C-4), 25.0 (C-3), 24.2 (C-3), 21.7 (C-1), 20.94 (Ac), 20.92 (Ac), 20.8 (Ac), 20.70 (Ac), 20.69 (Ac), 20.6 (Ac), 20.57

(Ac), 20.56 (Ac), 20.5 (Ac), 20.0 (C-1). ESIHRMS m/z 823.2638 $[M+Na]^+$ (calcd for $C_{36}H_{48}NaO_{20}$, 823.2637).

4. 18. (*S*)-2- β -D-Maltosyl-4-(2',4'-dihydroxyphenyl)-butane (**11**) and (*R*)-2- β -D-maltosyl-4-(2',4'-dihydroxyphenyl)-butane (**12**)

NaOMe (0.63 mL, 5.2 M in MeOH, 3.25 mmol) was slowly added to a stirred solution of **30** (173 mg, 217 μ mol) in MeOH (5 mL) at 0 °C and the resultant solution was stirred for 1 h at 0 °C. After being stirred for 1h at room temperature, the resultant solution was neutralized with Amberlite IR-120H at 0 °C. Filtration and concentration followed by solid phase extraction with Sep-Pak Plus C-18 cartridge (0–40% MeCN in H_2O) gave a mixture of **11** and **12** (71.3 mg, 65%) as a colorless oil. By preparative RP-HPLC (10% MeCN in H_2O), **11** (t_R = 14.7 min) and **12** (t_R = 13.5 min) were separated.

Maltoside **11**: $[\alpha]_D^{25} +18.9$ (c 0.13, MeOH); IR (film) ν_{max} 3733, 2841, 1028 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ 6.87 (d, J = 8.2 Hz, 1H, H-6'), 6.25 (d, J = 2.4 Hz, 1H, H-3'), 6.20 (dd, J = 8.2, 2.4 Hz, 1H, H-5'), 5.15 (d, J = 3.8 Hz, 1H, H-1'''), 4.35 (d, J = 7.8 Hz, 1H, H-1''), 3.86–3.77 (m, 4H, H-6'', H-6''', H-2), 3.69–3.51 (m, 5H, H-5''', H-6'', H-3'', H-3''', H-4'''), 3.43 (dd, J = 9.7, 3.8 Hz, 1H, H-2'''), 3.36–3.20 (m, 4H, H-5'', H-4'', H-2'', H-2'''), 2.63–2.51 (m, 2H, H-4), 1.88–1.63 (m, 2H, H-3), 1.26 (d, J = 6.2 Hz, 3H, H-1); ^{13}C NMR (100 MHz, CD_3OD) δ 157.4 (C-4'), 156.9 (C-2'), 131.5 (C-6'), 121.0 (C-1'), 107.4 (C-5'), 103.9 (C-1''), 103.5 (C-3'), 102.9 (C-1'''), 81.3 (C-4''), 77.9 (C-3''), 77.5 (C-2), 76.5 (C-3'''), 75.1 (C-5''), 75.0 (C-5'''), 74.8 (C-2''), 74.2 (C-2'''), 71.5 (C-4''), 62.8 (C-6'''), 62.2 (C-6''), 38.2 (C-4), 26.4 (C-3), 22.1 (C-1); ESIHRMS m/z 505.1917 $[M-H]^-$ (calcd for $C_{22}H_{33}O_{13}$, 505.1921).

Maltoside **12**: $[\alpha]_D^{25} +23.1$ (c 0.14, MeOH); IR (film) $\nu_{\max}$ 3411, 2342, 1028 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ 6.89 (d, $J = 8.2$ Hz, 1H, H-6'), 6.24 (d, $J = 2.4$ Hz, 1H, H-3'), 6.19 (dd, $J = 8.1, 2.4$ Hz, 1H, H-5'), 5.14 (d, $J = 3.8$ Hz, 1H, H-1'''), 4.40 (d, $J = 7.8$ Hz, 1H, H-1''), 3.90–3.81 (m, 4H, H-6'', H-6''', H-2), 3.71–3.54 (m, 5H, H-5'', H-6'', H-3'', H-3''', H-4'''), 3.51 (dd, $J = 9.7, 3.8$ Hz, 1H, H-2'''), 3.36–3.20 (m, 4H, H-5'', H-4'', H-2'', H-2'''), 2.65–2.48 (m, 2H, H-4), 1.89–1.63 (m, 2H, H-3), 1.20 (d, $J = 6.2$ Hz, 3H, H-1); ^{13}C NMR (100 MHz, CD_3OD) δ 157.3 (C-4'), 156.9 (C-2'), 131.5 (C-6'), 121.1 (C-1'), 107.3 (C-5'), 103.5 (C-3'), 102.9 (C-1''), 102.2 (C-1'''), 81.4 (C-4''), 77.9 (C-3''), 76.5 (C-3'''), 75.8 (C-2), 75.1 (C-5''), 74.8 (C-5'''), 74.7 (C-2''), 74.2 (C-2'''), 71.5 (C-4'''), 62.7 (C-6'''), 62.2 (C-6''), 38.7 (C-4), 26.5 (C-3), 20.0 (C-1); ESIHRMS m/z 505.1913 $[\text{M}-\text{H}]^-$ (calcd for $\text{C}_{22}\text{H}_{33}\text{O}_{13}$, 505.1921).

4. 19. Tyrosinase inhibitory assay

Tyrosinase (E.C.1.14.18.1) purchased from Sigma–Aldrich. All inhibitors were first dissolved in DMSO and used for the experiment by appropriate dilution with DMSO. First, 0.3 mL of a 5.0 mM of L-DOPA aqueous solution was mixed with 0.6 mL of 0.25 M sodium phosphate buffer (pH 6.8) and 1.9 mL of water, incubated at 30 °C for 5 min. Then, 0.1 mL of the DMSO solution of the inhibitor and 0.1 mL of enzyme solution (4.8 units/mL) were added, in this order, to the mixture. This solution was immediately monitored for the formation of dopachrome by measuring the linear increase in optical density at 475 nm. The reaction was carried out under a constant temperature of 30 °C. Absorption measurements were recorded using a Jasco V-630 spectrophotometer. The experimental data were analyzed by using Sigma Plot 9.0 to estimate IC_{50} values.

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Figure and Scheme captions

Figure 1. Structure of **1-12**, **20**, and **21**.

Scheme 1. Synthesis of the aglycone part. Reagents and conditions: (a) acetone, NaOH, H₂O, EtOH, 0 °C to rt, 94%; (b) H₂-Pd(en)/C, PhMe, 10 °C, 80%; (c) NaBH₄, EtOH, Et₂O, 0 °C to rt, 98%; (d) H₂-Pd(OH)₂/C, EtOAc, rt, 100%.

Scheme 2. Synthesis of glucosides **3** and **4**, and xylosides **7** and **8**. Reagents and conditions: (a) **16**, TMSOTf, CH₂Cl₂, -40 °C, 50%; (b) H₂-Pd(OH)₂/C, EtOAc, rt, 82%; (c) NaOMe, MeOH, 0 °C to rt, then, Amberlite IR-120H, 89%; (d) **16**, TMSOTf, CH₂Cl₂, -40 °C, 48%; (e) H₂-Pd(OH)₂/C, EtOAc, rt, 65%; (f) NaOMe, MeOH, 0 °C to rt, then, Amberlite IR-120H, 99%.

Scheme 3. Synthesis of cellobiosides **9** and **10**, and maltosides **11** and **12**. Reagents and conditions: (a) **16** (2 equiv.), TMSOTf, CH₂Cl₂, -40 °C, 20%; (b) H₂-Pd(OH)₂/C, EtOAc, rt, 99%; (c) NaOMe, MeOH, 0 °C to rt, then, Amberlite IR-120H, 86%; (d) **16** (2 equiv.), TMSOTf, CH₂Cl₂, -40 °C, 13%; (e) H₂-Pd(OH)₂/C, EtOAc, rt, 84%; (f) NaOMe, MeOH, 0 °C to rt, then, Amberlite IR-120H, 65%.