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Original article

Synthesis and evaluation of bibenzyl glycosides as potent tyrosinase inhibitors

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ABSTRACT

Bibenzyl glycosides **1**–**6** were synthesized from 2,4-dihydoxybenzaldehyde and xylose, glucose, cellobiose or maltose. The key steps in the synthesis were the Wittig reaction and trichloroacetimidate glycosylation. Tests for tyrosinase inhibitory activity showed that all were significantly active, indicating that they are unique hydrophilic tyrosinase inhibitors. Bibenzyl xyloside **2** is a particularly potent inhibitor (IC_{50} = 0.43 μM, 17 times higher than that of kojic acid). These results suggest that the hydrophilic cavity of tyrosinase might accommodate the bulky carbohydrate on the bibenzyl scaffold.

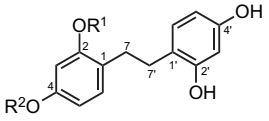
1. Introduction

Tyrosinase, a widely available copper-containing oxidoreductase, catalyzes the oxidation of monophenol and *o*-diphenol to *o*-quinone [1]. In mammals, L-tyrosine serves as a typical monophenol substrate. Numerous phenolics having monophenol and *o*-diphenol structures found in plants and insects are similarly oxidized by tyrosinase [2]. This enzymatic oxidation is the rate-limiting step in several phenomena of colour development and cuticle sclerotization; the remainder of the reaction sequence proceeds spontaneously at physiological conditions [3].

The presence of the oxidation products of L-tyrosine has recently been linked to the demise of neurons in several neurodegenerative disorders such as Parkinson's and Huntington's diseases [4,5]. Thus, the study of tyrosinase inhibition is clearly important for the development of therapeutic agents, and also for that of antioxidants, functional cosmetics and insecticides [6].

An effective tyrosinase inhibitor should optimally be both safe and potent. For maximal safety, a tyrosinase inhibitor should contain a glycoside moiety. For example, the cosmetics industry, which uses tyrosinase inhibitors as whitening agents, has adopted the use of the two glycosides: arbutin, a hydroquinone glycoside, and aloesin, a *C*-glycosylated chromone, primarily because other tyrosinase inhibitors such as linoleic acid, hinokitiol, kojic acid, naturally occurring hydroquinones and catechols are known to cause side effects [7]. On the other hand, 4-substituted resorcinol moiety would be requisite to the potent tyrosinase inhibitor [8,9]. For example, 4-hexylresorcinol is effective for preventing shrimp melanosis and for controlling browning in fresh and dried fruit slices [10,11].

Bibenzyl xyloside **1** was tentatively identified in 1993 in the methanol extract of *Chlorophytum arundinaceum* (liliaceae) [12]. Its structure, shown in Fig. 1, contains both the glycoside and 4-resorcinol moieties. Thus, it shows potential as a key molecule to design novel tyrosinase inhibitors that are safe for use and exhibit potency and hydrophilicity. In this study, we describe the concise



1: R^1 = Xyl, R^2 = H
2: R^1 = H, R^2 = Xyl
3: R^1 = R^2 = Xyl
4: R^1 = H, R^2 = Glc
5: R^1 = H, R^2 = Cel
6: R^1 = H, R^2 = Mal
7: R^1 = R^2 = H

Fig. 1. Structure of bibenzyl derivatives **1**–**7**.

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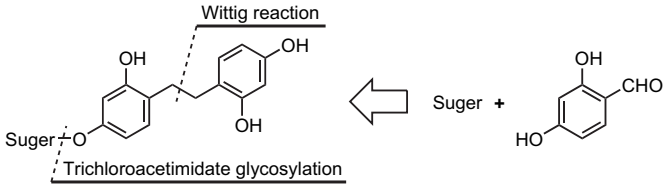


Fig. 2. Synthetic plan for bibenzyl glycosides.

synthesis and tyrosinase inhibitory activity of bibenzyl **1** and its derivatives **2**–**7** [13].

2. Results and discussion

2.1. Synthesis of bibenzyl glycoside *1*

Bibenzyl glycosides were synthesized by the strategic plan shown in Fig. 2. The bibenzyl structure can be assumed to be consisting of two benzaldehydes and a sugar moiety. Leading reactions in the strategic plan were Wittig olefination to form a stilbene scaffold and trichloroacetimidate etherification to introduce a sugar moiety on the phenolic hydroxyl of the bibenzyl. Hence, commercially available 2,4-dihydroxybenzaldehyde and xylose were selected as starting materials.

According to the previous report [14], aldehyde **8**, the left part of the bibenzyl structure, was prepared in two steps from 2,4-dihydroxybenzaldehyde. Reaction of 2,4-dihydroxybenzaldehyde by *O*-benzylation, $NaBH_4$ reduction and chlorination gave chloride **9** [15]. Reaction of chloride **9** with excess triphenylphospine (TPP) furnished phosphonium salt **10** that was transformed to a phosphorus ylide in the presence of lithium hexamethyldisilazide (LiHMDS) as a base (Scheme 1). The ylide was coupled with aldehyde **8** to build the stilbene framework and give stilbene **11** (90%; *cis*:*trans* = 2:1, as determined by ^1H NMR). Selective reduction at the olefinic position of stilbene **11** by H_2–Pd/C-ethylenediamine complex (H_2–Pd(en)/C) furnished bibenzyl **12** (85%) [16]. The removal of the methoxymethyl (MOM) moiety from the structure of bibenzy1 **12** under acidic conditions yielded the corresponding phenol **13** (88%).

Glycosylation of bibenzyl **13** with imidate **14** prepared from D-xylose was quantitatively accomplished using the catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf). Note that the by-product α-glycoside of xyloside **15** was not detected in the chromatographic separation. The use of $BF_3 \cdot Et_2O$ as a Lewis acid decreased reaction yield to approximately 80%. The removal of the benzyl (Bn) protective groups from xyloside **15** by hydrogenolysis with H_2–$Pd(OH)_2$ on carbon, followed by ester exchange on the acetyl moieties by using NaOMe, gave bibenzyl glycoside **1** in excellent yield (94%, two steps). The overall yield of this synthetic scheme from aldehyde **8** was 63% (six steps).

Table 1
Tyrosinase inhibitory activities of bibenzyl derivatives **1**–**7** and kojic acid.

Compounds tested	IC_{50} (μM)
1	1.6 ± 0.43[a]
2	0.43 ± 0.18
3	0.73 ± 0.11
4	0.77 ± 0.04
5	0.68 ± 0.05
6	0.83 ± 0.06
7	0.37 ± 0.06
Kojic acid	7.4 ± 1.4

[a] The IC_{50} values represent means ± SE of three different experiments.

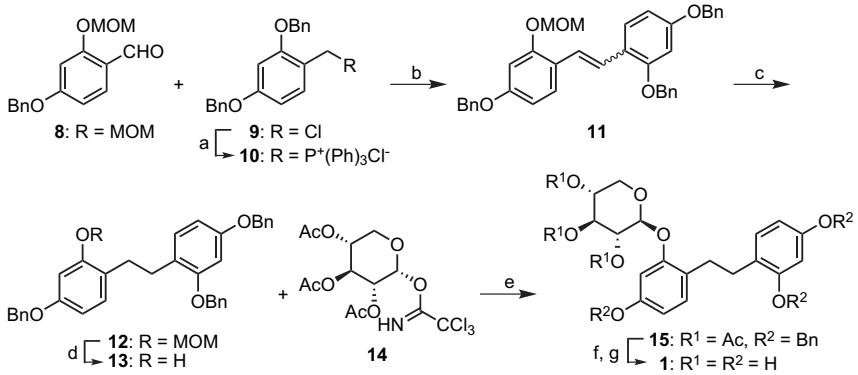
2.2. Tyrosinase inhibitory activity of bibenzyl glycoside *1*

The tyrosinase inhibitory activities of the synthesized bibenzyl glycosides evaluated against L-DOPA oxidation catalyzed by purified tyrosinase, are listed in Table 1. Kojic acid was used as the reference standard. The potent inhibitory activity, IC_{50} = 1.6 μM, was observed for 2-xylosylated bibenzyl **1**, that was 5 times higher than that of kojic acid.

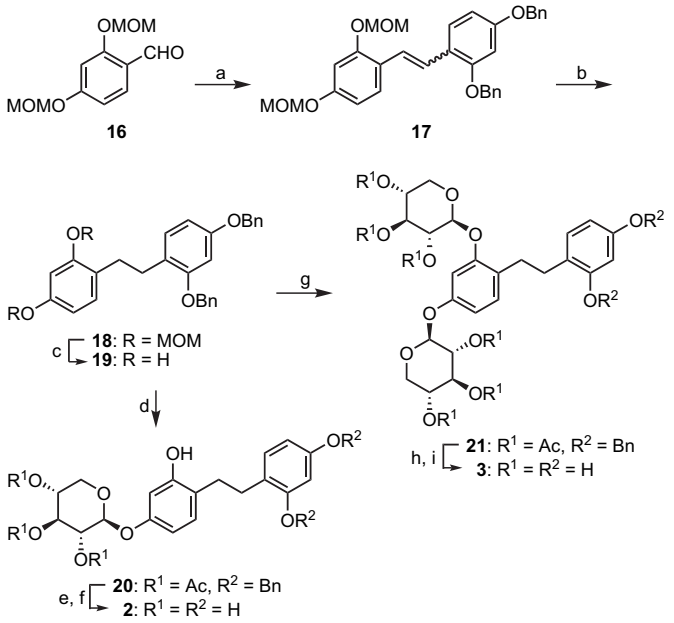
A number of bibenzyls that exhibit various biological activities, such as antifungal, phytotoxic and anti-HIV effects, have been isolated from the extracts of several organisms including liverworts, algae and ferns [17–20]. However, significant tyrosinase inhibitory activity exhibited on the part of a bibenzyl glycoside is a novel observation. This finding prompted us to further investigate derivatives **2**–**7** by a chemical approach.

2.3. Synthesis of bibenzyls *2*–*7*

Bibenzyl glycosides **2** and **3** were synthesized by a procedure similar to that of bibenzyl glycoside **1** (Scheme 2). The reaction of 2,4-dihydroxybenzaldehyde with MOMCl gave benzaldehyde **16**. In the presence of LiHMDS, the Wittig reaction of benzaldehyde **16** with phosphonium salt **10** furnished stilbene **17** (84%; *cis*:*trans* = 3:2, as determined by ^1H NMR). Pd(en)/C-catalyzed hydrogenation at the olefinic position of stilbene **17** gave bibenzyl **18** (72%). The removal of the MOM moieties from bibenzyl **18** under acidic conditions quantitatively yielded diphenol **19**.



Scheme 1. Synthesis of bibenzyl xyloside **1**. Reagents and conditions: (a) TPP, toluene, reflux, 0.5 h, 59%; (b) LiHMDS, THF, 0 °C to rt, 1 h, 90%; (c) H_2–Pd(en)/C, THF, rt, 12 h, 85%; (d) TsOH, THF, MeOH, reflux, 2 h, 88%; (e) TMSOTf, CH_2Cl_2, 0 °C, 5 min, 100%; (f) H_2–$Pd(OH)_2$/C, EtOAc, rt, 12 h; (g) NaOMe, MeOH, 0 °C, 0.5 h, then H^+, 94% (2 steps).

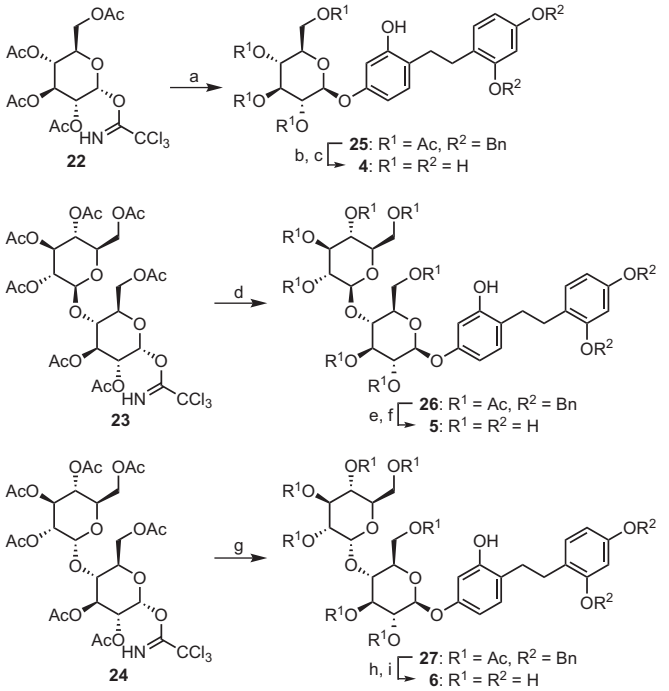


Scheme 2. Syntheses of bibenzyl xylosides **2** and **3**. Reagents and conditions: (a) **10**, LiHMDS, THF, 0 °C to rt, 1 h, 84%; (b) H_2–Pd(en)/C, THF, rt, 12 h, 72%; (c) TsOH, THF, MeOH, reflux, 2 h, 100%; (d) **14**, TMSOTf, CH_2Cl_2, 0 °C, 5 min, 71%; (e) H_2–Pd$(OH)_2$/C, EtOAc, rt, 12 h; (f) NaOMe, MeOH, 0 °C, 0.5 h, then H^+, 85% (2 steps); (g) **14** (excess), TMSOTf, CH_2Cl_2, 0 °C, 5 min, 77%; (h) H_2–Pd$(OH)_2$/C, EtOAc, rt, 12 h; (i) NaOMe, MeOH, 0 °C, 0.5 h, then H^+, 85% (2 steps).

We speculated that the synthesis of bibenzyl glycosides **2** and **3** should be possible by selective glycosylation of diphenol **19**, with chemoselectivity governed by the molar ratio of diphenol **19** to imidate **14**. The reaction of diphenol **19** with 1.5 equivalent of glycosyl donor **14** selectively furnished mono-glycoside **20** (71%). A cross peak between an oxygenated aryl carbon at C-4 and an anomeric proton was observed in the HMBC spectrum, so the glycosylated site on the benzene ring was determined to be as shown in Scheme 2. A mono-glycosylated product at C-2 and diglycoside **21** were not detected by TLC analysis under these conditions, presumably because of steric crowding from alkyl substitution at C-1. The reaction of mono-glycoside **20** by hydrogenolysis at the *O*-benzyl position and the removal of the acetyl group by NaOMe gave the desired bibenzyl glycoside **2** (85%, two steps).

In contrast, the reaction of diphenol **19** with 4.0 equivalent of glycosyl donor **14** gave diglycoside **21** (77%). The successive removal of the benzyl and acetyl groups of diglycoside **21** furnished bibenzyl glycoside **3** (85%, two steps). The overall yields of bibenzyl glycosides **2** and **3** from aldehyde **16** were 37 and 40%, respectively (five steps).

The successful synthesis of mono-glycoside **2** indicated that several bibenzyl derivatives could be obtained by the selective glycosylation of diphenol **19**. The use of imidates **22**–**24**, prepared respectively from D-glucose, D-cellobiose and D-maltose, as glycosyl donors gave glycosides **25**–**27**, respectively by Scheme 3 (74%, 75% and 57%, respectively). Hydrogenolysis followed by the removal of the acetyl groups from the bibenzyls yielded glycosides **4**–**6** (63%, 72% and 56%, respectively). The overall yields of glycosides **4**–**6** from aldehyde **16** were 28%, 33% and 19%, respectively. Symmetric bibenzyl **7** was readily prepared by a method previously reported [21].



Scheme 3. Syntheses of bibenzyl glycosides **4**–**6**. Reagents and conditions: (a) **19**, TMSOTf, CH_2Cl_2, 0 °C, 5 min, 74%; (b) H_2–Pd$(OH)_2$/C, EtOAc, rt, 12 h; (c) NaOMe, MeOH, 0 °C, 0.5 h, then H^+, 63% (2 steps); (d) **19**, TMSOTf, CH_2Cl_2, 0 °C, 5 min, 75%; (e) H_2–Pd$(OH)_2$/C, EtOAc, rt, 12 h; (f) NaOMe, MeOH, 0 °C, 0.5 h, then H^+, 72% (2 steps); (g) **19**, TMSOTf, CH_2Cl_2, 0 °C, 1 h, 57%; (h) H_2–Pd$(OH)_2$/C, EtOAc, rt, 12 h; (i) NaOMe, MeOH, 0 °C, 0.5 h, then H^+, 56% (2 steps).

2.4. Tyrosinase inhibitory activity of bibenzyls 2–7

Xylosylated bibenzyl **2** exhibited a tyrosinase inhibitory activity of IC_{50} = 0.43 μM, 17 times higher than that of kojic acid (Table 1). Aglycone **7** and xyloside **2** exhibited similar inhibitory activities, indicating that glycosylation at the C-4 position of the bibenzyl skeleton has minimal effect on activity. In contrast, C-2-xylosylated bibenzyls **1** and **3** exhibited relatively low inhibitory activities, possibly because the resorcinol moiety could be weakly bound on the active site of tyrosinase for bulky xylosyl substitution at C-2.

Glycosylation at the C-4 position with a large sugar moiety appears to influence inhibitory activity. For example, glucoside **4**, cellobioside **5** and maltoside **6** exhibited relatively low activities (IC_{50} = 0.77, 0.68 and 0.83 μM, respectively). Noted that all the synthesized bibenzyls did not act as substrates, as confirmed by incubated experiments with tyrosinase observed by UV spectrophotometry (data not shown) [22–24]. Although the natural occurrence of xyloside **1** is questionable because of inconsistencies in the ^1H and ^{13}C NMR data for natural **1** and synthetic **1** [12,13], it is appropriate to newly categorize the bibenzyl glycosides as tyrosinase inhibitors that are both potent and hydrophilic.

Hydrophobic substitutions on tyrosinase inhibitors tend to enhance inhibitory activity [25,26]. The isopropyl ester moiety of 4-resorcinol inhibitor was recently reported to interact significantly with the hydrophobic site on tyrosinase [27]. However, hydrophilic interactions between an inhibitor and tyrosinase have not yet been investigated in detail. The high activities of our synthesized bibenzyl glycosides suggest that tyrosinase might possess a hydrophilic cavity that can accommodate a carbohydrate moiety. Taking advantage of this cavity might enable the design of novel tyrosinase inhibitors for practical use.

3. Conclusions

A series of bibenzyl glycosides was synthesized from 2,4-dihydroxybenzaldehyde and D-xylose, D-glucose, D-cellobiose, or

D-maltose via the Wittig reaction and trichloroacetimidate glycosylation. In evaluations of tyrosinase inhibitory activity against L-DOPA oxidation catalyzed by the purified enzyme, all of the synthesized bibenzyl glycosides showed greater activity than the common inhibitor kojic acid, used as a reference standard. Bibenzyl xyloside **2** is particularly potent inhibitor (IC_{50} = 0.43 μM, 17 times higher than that of kojic acid). The high activities of the bulky bibenzyl glycosides suggest that tyrosinase might possess a hydrophilic cavity at its catalytic center. This hydrophilic interaction as well as the known hydrophobic interaction of the compound with the enzyme cavity might be the basis for the development of new and effective tyrosinase inhibitors.

4. Experimental

4.1. Chemistry

4.1.1. General

Optical rotations were recorded by a Horiba SEPA-300. IR spectra were measured with a Horiba FT-720 spectrometer. NMR spectra were recorded with a JEOL EX-400 spectrometer operating at 400 MHz for the ^{1}H NMR spectra and at 100 MHz for the ^{13}C NMR spectra. Chemical shifts were recorded as ppm relative to the TMS signal for $CDCl_3$ or the solvent signal (^{1}H NMR; CH_3OH: 3.30 ppm or pyridine: 8.71 ppm, ^{13}C NMR; CH_3OH: 49.0 ppm or pyridine: 149.2 ppm). HRMS spectra were measured on a JEOL AccuTOF mass spectrometer fitted with an electrospray ion source in positive or negative ionization mode. Preparative HPLC was carried out by using 1.0 mL/min of flow rate with Wakosil-II 5C18 AR Prep as a column and Jasco 880PU as a pump.

4.1.2. 2′,4,4′-Tribenzyloxy-2-methoxymethoxystilbene (*11*)

TPP (2.5 g, 9.5 mmol) and 2,4-di(benzyloxy)benzyl chloride (**9**) [15] (2.0 g, 5.9 mmol) were dissolved in toluene (10 mL) and the resultant solution was refluxed for 0.5 h. The reaction mixture was allowed to cool to room temperature and diluted with hexane (50 mL). Yellowish precipitate was collected by filtration and washed with Et_2O (2 mL) to give compound **10** as a white powder (2.1 g, 59% from **9**), which was used in the next step without further purification.

To a suspension of **10** (0.78 g, 1.3 mmol) in THF (5 mL), 0.84 mL of LiHMDS (1.6 M in THF, 1.3 mmol) was added at 0 °C. The resultant solution was stirred at room temperature for 0.5 h. The solution was then cooled to 0 °C, and a THF (5 mL) solution of 4-benzyloxy-2-methoxymethoxybenzaldehyde (**8**) [14] (0.20 g, 0.73 mmol) was slowly added. After being stirred for 1 h at room temperature, the reaction mixture was poured into Et_2O (60 mL) and washed with saturated aqueous NH_4Cl solution (15 mL × 3) and brine (15 mL × 3). The aqueous layers were extracted with Et_2O (20 mL × 3), and the combined organic layers were dried over Na_2SO_4. Filtration and concentration followed by silica gel chromatography (2.5–5% EtOAc in hexane) gave the title compound **11** (0.37 g; *cis*:*trans* = 2:1, as determined by ^{1}H NMR; 90% from **8**) as colorless oil. IR (film) ν_{max} 3031, 2871, 1604, 1498, 1257, 1026, 735 cm^{-1}. *Cis*-**11**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (15H, m, ArH), 7.13 (2H, d, *J* = 8.3 Hz, ArH), 6.77 (1H, d, *J* = 2.4 Hz, ArH), 6.70 (1H, d, *J* = 12.2 Hz, CH), 6.60 (1H, d, *J* = 12.2 Hz, CH), 6.57 (1H, d, *J* = 2.4 Hz, ArH), 6.43 (1H, dd, *J* = 2.4, 8.3 Hz, ArH), 6.37 (1H, dd, *J* = 2.4, 8.3 Hz, ArH), 5.13 (2H, s, CH_2), 5.05 (2H, s, CH_2), 5.01 (2H, s, CH_2), 4.99 (2H, s, CH_2), 3.45 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0 (C), 158.9 (C), 157.3 (C), 155.9 (C), 137.1 (C), 136.9 (C), 136.8 (C), 130.5 (CH), 130.4 (CH), 128.59 (CH), 128.55 (CH), 128.49 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 127.2 (CH), 124.0 (C), 123.7 (C), 120.6 (CH), 120.1 (CH), 107.4 (CH), 105.8 (CH), 102.5 (CH), 100.7 (CH), 94.9 (CH_2), 70.3 (CH_2), 70.08 (CH_2), 70.05 (CH_2), 56.1 (CH_3). *Trans*-**11**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, d, *J* = 8.8 Hz, ArH), 7.48 (1H, d, *J* = 8.8 Hz, ArH), 7.39 (17H, m, ArH and CH), 6.78 (1H, d, *J* = 2.4 Hz, ArH), 6.63 (1H, dd, *J* = 2.4, 8.8 Hz, ArH), 6.58 (2H, m, ArH), 5.15 (2H, s, CH_2), 5.08 (2H, s, CH_2), 5.05 (4H, s, CH_2), 3.43 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (C), 158.9 (C), 156.9 (C), 155.4 (C), 136.9 (C), 128.60 (CH), 128.55 (CH), 128.02 (CH), 127.97 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.1 (CH), 121.9 (C), 121.7 (C), 121.4 (CH), 121.1 (CH), 108.0 (CH), 106.5 (CH), 102.6 (CH), 100.9 (CH), 94.8 (CH_2), 70.4 (CH_2), 70.2 (CH_2), 70.1 (CH_2), 56.0 (CH_3). ESIHRMS *m*/*z* 581.2282 $[M + Na]^+$ (calcd for $C_{37}H_{34}NaO$, 581.2304).

4.1.3. 2′,4,4′-Tribenzyloxy-2-methoxymethoxybibenzyl (*12*)

A THF (3 mL) solution of **11** (0.11 g, 0.20 mmol) was hydrogenated over 5% Pd(en) on carbon (33 mg) for 12 h under atmospheric pressure [16]. Filtration through Celite 535 and concentration in vacuo followed by silica gel chromatography (2–10% EtOAc in hexane) gave the title compound **12** (95 mg, 85%) as a white solid. IR (film) ν_{max} 3031, 1604, 1498, 1257, 1026, 735 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (15H, m, ArH), 7.01 (1H, d, *J* = 8.8 Hz, ArH), 6.94 (1H, d, *J* = 8.8 Hz, ArH), 6.74 (1H, d, *J* = 2.4 Hz, ArH), 6.59 (1H, d, *J* = 2.4 Hz, ArH), 6.50 (2H, m, ArH), 5.03 (2H, s, CH_2), 5.02 (4H, s, CH_2), 5.01 (2H, s, CH_2), 3.39 (3H, s, CH_3), 2.84 (4H, s, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2 (C), 158.1 (C), 157.4 (C), 155.9 (C), 137.3 (C), 137.2 (C), 130.3 (CH), 130.2 (CH), 128.6 (CH), 128.5 (CH), 127.93 (CH), 127.88 (CH), 127.76 (CH), 127.5 (CH), 127.3 (CH), 124.1(C), 123.8 (C), 106.9 (CH), 105.3 (CH), 102.2 (CH), 100.5 (CH), 94.4 (CH_2), 70.2 (CH_2), 70.1 (CH_2), 69.9 (CH_2), 55.8 (CH_3), 30.7 (CH_2), 30.5 (CH_2). ESIHRMS *m*/*z* 583.2457 $[M + Na]^+$ (calcd for $C_{37}H_{36}NaO_5$, 583.2460).

4.1.4. 2′,4,4′-Tribenzyloxy-2-hydroxybibenzyl (*13*)

$TsOH \cdot H_2O$ (39 mg, 0.21 mmol) was added to a 50% THF/MeOH solution (6 mL) of bibenzyl **12** (95 mg, 0.17 mmol) at room temperature. After refluxed for 2 h, the reaction mixture was poured into EtOAc (60 mL) and washed with H_2O (15 mL × 3) and brine (15 mL × 3). The aqueous layers were extracted with EtOAc (20 mL × 3), and the combined organic layers were dried over Na_2SO_4. Filtration and concentration followed by silica gel chromatography (10–20% EtOAc in hexane) gave the title compound **13** (78 mg, 88%) as a white solid. IR (film) ν_{max} 3400, 3031, 2866, 1612, 1504, 1290, 1026, 735 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (15H, m, ArH), 7.02 (1H, d, *J* = 8.3 Hz, ArH), 6.94 (1H, d, *J* = 8.3 Hz, ArH), 6.61 (1H, d, *J* = 2.4 Hz, ArH), 6.50 (1H, dd, *J* = 2.4, 8.3 Hz, ArH), 6.49 (1H, dd, *J* = 2.4, 8.3 Hz, ArH), 6.47 (1H, bs, OH), 5.11 (2H, s, CH_2), 5.00 (2H, s, CH_2), 4.99 (2H, s, CH_2), 2.76 (4H, m, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5 (C), 157.1 (C), 154.9 (C), 137.1 (C), 137.0 (C), 136.6 (C), 130.4 (CH), 130.3 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.5 (CH), 127.4 (CH), 123.0 (C), 120.1 (C), 106.9 (CH), 105.7 (CH), 102.6 (CH), 100.9 (CH), 70.3 (CH_2), 70.2 (CH_2), 70.0 (CH_2), 31.4 (CH_2), 30.8 (CH_2). ESIHRMS *m*/*z* 515.2224 $[M - H]^-$ (calcd for $C_{35}H_{31}O_4$, 515.2222).

4.1.5. 2-(2″,3″,4″-Tri-O-acetyl-β-D-xylopyranosyl)-2′,4,4′-tribenzyloxybibenzyl (*15*)

To a cold (0 °C) and stirred solution of bibenzyl **13** (29 mg, 56 μmol) and 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl trichloroacetimidate (**14**) (47 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) was added 5 μL of TMSOTf solution (0.11 M in CH_2Cl_2, 0.55 μmol). After being stirred for 5 min at 0 °C, the resultant solution was poured into EtOAc (60 mL) and washed with saturated aqueous $NaHCO_3$ solution (15 mL × 3) and brine (15 mL × 3). The aqueous layers were extracted with EtOAc (20 mL × 3), and the combined organic layers were dried over Na_2SO_4. Filtration and concentration followed by silica gel chromatography (15–25% EtOAc in hexane) gave

the title compound **15** (43 mg, 100% from **13**) as a white solid. $[\alpha]_D^{19}$ −11.8 (*c* 1.27, $CHCl_3$). IR (film) ν_{max} 3031, 1754, 1506, 1220, 1039, 739 m^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (15H, m, ArH), 6.99 (1H, d, J = 8.3 Hz, ArH), 6.86 (1H, d, J = 8.3 Hz, ArH), 6.67 (1H, d, J = 2.0 Hz, ArH), 6.57 (1H, d, J = 2.0 Hz, ArH), 6.52 (1H, dd, J = 2.0, 8.3 Hz, ArH), 6.48 (1H, dd, J = 2.0, 8.3 Hz, ArH), 5.17 (1H, d, J = 6.4 Hz, CH), 5.15 (1H, t, J = 8.4 Hz, CH), 5.01 (8H, m, CH), 4.14 (1H, dd, J = 4.9, 12.2 Hz, CH_2), 3.43 (1H, dd, J = 8.4, 12.2 Hz, CH_2), 2.77 (4H, m, CH_2), 2.06 (3H, s, CH_3), 2.05 (3H, s, CH_3), 1.97 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0 (C), 169.8 (C), 169.3 (C), 158.1 (C), 157.9 (C), 157.3 (C), 155.0 (C), 137.3 (C), 137.1 (C), 130.5 (CH), 130.3 (CH), 128.54 (CH), 128.46 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 127.2 (CH), 124.2 (C), 123.3 (C), 108.1 (CH), 105.2 (CH), 103.0 (CH), 100.4 (CH), 98.2 (CH), 70.6 (CH), 70.14 (CH_2), 70.07 (CH_2), 70.0 (CH), 69.7 (CH_2), 68.3 (CH), 61.6 (CH_2), 30.0 (CH_2), 20.8 (CH_3), 20.6 (CH_3). ESIHRMS *m*/*z* 797.2918 $[M + Na]^+$ (calcd for $C_{46}H_{46}NaO_{11}$, 797.2938).

4.1.6. 2′,4,4′-Trihydroxy-2-(β-D-xylopyranosyl)bibenzyl (*1*)

Bibenzyl **15** (14 mg, 18 μmol) in EtOAc (1 mL) was hydrogenated over 20% $Pd(OH)_2$ on carbon (3 mg) for 12 h. Filtration through Celite 535 and concentration in vacuo followed by silica gel chromatography (EtOAc) gave the phenol as a white solid, which was used in the next step without further purification.

To cold (0 °C) and stirred solution of the phenol in MeOH (5 mL) was added 0.10 mL of NaOMe (5.2 M in MeOH) slowly. After being stirred for 0.5 h at 0 °C, the resultant solution was neutralized with Amberlite IR-120 (H^+). Filtration and concentration followed by solid phase extraction with Sep-Pak Plus C-18 cartridge (0–40% MeCN in H_2O) gave the crude bibenzyl that was further purified by preparative RP-HPLC (20% MeCN in H_2O, t_R = 10.1 min). The title compound **1** (6.5 mg, 94%) was obtained as a colorless solid. $[\alpha]_D^{20}$ −10.6 (*c* 0.09, MeOH). IR (Nujol) ν_{max} 3350, 1603, 1508 cm^{-1}. ^1H NMR (pyridine-d_5, 400 MHz) δ 7.42 (1H, d, J = 2.0 Hz, ArH), 7.33 (1H, d, J = 7.8 Hz, ArH), 7.32 (1H, d, J = 8.0 Hz, ArH), 7.01 (1H, d, J = 2.0 Hz, ArH), 6.90 (1H, dd, J = 2.0, 8.0 Hz, ArH), 6.73 (1H, dd, J = 2.0, 7.8 Hz, ArH), 5.43 (1H, d, J = 7.8 Hz, CH), 4.34 (1H, dd, J = 7.8, 8.3 Hz, CH), 4.28 (1H, dd, J = 4.9, 10.7 Hz, CH_2), 4.26 (1H, m, CH), 4.20 (1H, dd, J = 8.3, 8.8 Hz, CH), 3.66 (1H, m, CH_2), 3.50 (2H, m, CH_2), 3.35 (2H, m, CH_2). ^{13}C NMR (pyridine-d_5, 100 MHz) δ 157.7 (C), 157.6 (C), 157.1 (C), 156.8 (C), 130.9 (CH), 130.3 (CH), 122.6 (C), 120.1 (C), 109.3 (CH), 106.7 (CH), 104.0 (CH), 103.2 (CH), 77.7 (CH), 74.3 (CH), 70.2 (CH), 66.5 (CH_2), 31.2 (CH_2), 31.0 (CH_2). HRESIMS *m*/*z* 377.1240 $[M - H]^-$ (calcd for $C_{19}H_{21}O_8$, 377.1236).

4.1.7. 2′,4′-Dibenzyloxy-2,4-di(methoxymethoxy)stilbene (*17*)

At 0 °C, LiHMDS (1.3 mL, 1.6 M solution in THF, 2.1 mmol) was added to a suspension of **10** (1.3 g, 2.1 mmol) in THF (5 mL). The resultant solution was stirred at room temperature for 0.5 h. The solution was then cooled to 0 °C, and a THF (5 mL) solution of 2,4-di (methoxymethoxy)benzaldehyde (**16**) (0.3 g, 1.3 mmol) was slowly added. After being stirred for 1 h at room temperature, the reaction mixture was poured into EtOAc (100 mL) and washed with saturated aqueous NH_4Cl solution (20 mL × 3) and brine (20 mL × 3). The aqueous layers were extracted with EtOAc (20 mL × 3), and the combined organic layers were dried over Na_2SO_4. Filtration and concentration followed by silica gel chromatography (20–30% EtOAc in hexane) gave the title compound **17** (0.57 g; *cis*:*trans* = 3:2, as determined by ^1H NMR; 84% from **16**) as colorless oil. IR (film) ν_{max} 3031, 2871, 1604, 1498, 1257, 1026, 735 cm^{-1}. *Cis*-**17**; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (10H, m, ArH), 7.13 (1H, d, J = 8.3 Hz, ArH), 7.12 (1H, d, J = 8.3 Hz, ArH), 6.79 (1H, d, J = 2.4 Hz, ArH), 6.71 (1H, d, J = 12.2 Hz, CH), 6.60 (1H, d, J = 12.2 Hz, CH), 6.58 (1H, d, J = 2.4 Hz, ArH), 6.49 (1H, dd, J = 2.4, 8.3 Hz, ArH), 6.37 (1H, dd, J = 2.4, 8.3 Hz, ArH), 5.14 (2H, s, CH_2), 5.13 (2H, s, CH_2), 5.06 (2H, s, CH_2), 4.99 (2H, s, CH_2), 3.47 (3H, s, CH_3), 3.46 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (C), 157.32 (C), 157.28 (C), 155.7 (C), 137.1 (C), 137.0 (C), 130.5 (CH), 130.4 (CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 127.8 (CH), 127.6 (CH), 127.2 (CH), 124.2 (CH), 123.7 (CH), 120.0 (C), 119.8 (C), 109.0 (CH), 105.8 (CH), 103.8 (CH), 100.7 (CH), 94.9 (CH_2), 94.5 (CH_2), 70.3 (CH_2), 70.1 (CH_2), 56.1 (CH_3). *Trans*-**17**; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, d, J = 8.8 Hz, ArH), 7.48 (1H, d, J = 8.8 Hz, ArH), 7.39 (10H, m, ArH), 7.35 (1H, d, J = 16.6 Hz, CH), 7.29 (1H, d, J = 16.6 Hz, CH), 6.80 (1H, d, J = 2.4 Hz, ArH), 6.70 (1H, dd, J = 2.4, 8.8 Hz, ArH), 6.60 (2H, m, ArH), 5.16 (4H, s, CH_2), 5.08 (2H, s, CH_2), 5.06 (2H, s, CH_2), 3.48 (3H, s, CH_3), 3.45 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (C), 157.3 (C), 157.0 (C), 155.3 (C), 137.0 (C), 136.9 (C), 128.61 (CH), 128.55 (CH), 128.0 (CH), 127.9 (CH), 127.5 (CH), 127.4 (CH), 127.10 (CH), 127.05 (CH), 122.32 (CH), 122.26 (C), 121.6 (C), 109.5 (CH), 106.5 (CH), 103.9 (CH), 100.8 (CH), 94.8 (CH_2), 94.5 (CH_2), 70.4 (CH_2), 70.2 (CH_2), 56.13 (CH_3), 56.08 (CH_3). HRESIMS *m*/*z* 532.2003 $[M + Na]^+$ (calcd for $C_{32}H_{32}NaO_6$, 532.2097).

4.1.8. 2′,4′-Dibenzyloxy-2,4-di(methoxymethoxy)bibenzyl (*18*)

A THF (5 mL) solution of **17** (0.20 g, 0.40 mmol) was hydrogenated over 5% Pd(en) on carbon (62 mg) for 12 h [16]. Filtration through Celite 535 and concentration in vacuo followed by silica gel chromatography (15% EtOAc in hexane) gave the title compound **18** (0.15 g, 72%) as a white solid. IR (film) ν_{max} 3031, 1604, 1498, 1257, 1026, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 10H, ArH), 7.03 (1H, d, J = 7.8, Hz, ArH), 6.95 (1H, d, J = 8.3 Hz, ArH), 6.75 (1H, d, J = 2.0 Hz, ArH), 6.58 (2H, m, ArH), 6.50 (1H, dd, J = 1.4, 7.8 Hz, ArH), 5.12 (2H, s, CH_2), 5.04 (2H, s, CH_2), 5.02 (4H, s, CH_2), 3.47 (3H, s, CH_3), 3.40 (3H, s, CH_3), 2.84 (4H, bs, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2 (C), 157.4 (C), 156.4 (C), 155.8 (C), 137.3 (C), 137.1 (C), 130.3 (CH), 130.1 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 127.2 (CH), 125.1 (C), 123.8 (C), 108.6 (CH), 105.3 (CH), 103.4 (CH), 100.5 (CH), 94.7 (CH_2), 94.3 (CH_2), 70.2 (CH_2), 69.9 (CH_2), 56.0 (CH_3), 55.9 (CH_3), 30.6 (CH_2), 30.5 (CH_2). ESIHRMS *m*/*z* 537.2247 $[M + Na]^+$ (calcd for $C_{32}H_{34}NaO_6$, 537.2253).

4.1.9. 2′,4′-Dibenzyloxy-2,4-dihydroxystilbene (*19*)

$TsOH \cdot H_2O$ (0.19 g, 0.38 mmol) was added to a 50% THF/MeOH solution (8 mL) of bibenzyl **18** (0.29 g, 1.5 mmol) at room temperature. After refluxed for 2 h, the reaction mixture was poured into EtOAc (100 mL) and washed with H_2O (20 mL × 3) and brine (20 mL × 3). The aqueous layers were extracted with EtOAc (20 mL × 3), and the combined organic layers were dried over Na_2SO_4. Filtration and concentration followed by silica gel chromatography (30–35% EtOAc in hexane) gave the title compound **19** (0.16 g, 100%) as a white solid. IR (film) ν_{max} 3400, 3031, 2866, 1612, 1504, 1290, 1026, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (10H, m, ArH), 7.03 (1H, d, J = 8.3 Hz, ArH), 6.90 (1H, d, J = 8.3 Hz, ArH), 6.62 (1H, bs, ArH), 6.51 (1H, d, J = 8.3 Hz, ArH), 6.30 (2H, m, ArH), 5.46 (1H, bs, OH), 5.12 (2H, s, CH_2), 5.00 (2H, s, CH_2), 4.73 (1H, bs, OH), 2.75 (4H, m, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5 (C), 157.0 (C), 155.0 (C), 136.9 (C), 136.5 (C), 130.6 (CH), 130.3 (CH), 128.7 (CH), 128.6 (CH), 128.1 (CH), 128.0 (CH), 127.5 (CH), 127.4 (CH), 122.9 (C), 119.9 (C), 107.2 (CH), 105.6 (CH), 103.0 (CH), 100.9 (CH), 70.3 (CH_2), 70.2 (CH_2), 31.4 (CH_2), 30.8 (CH_2). ESIHRMS *m*/*z* 425.1661 $[M - H]^-$ (calcd for $C_{28}H_{25}O_4$, 425.1753).

4.1.10. 4-(2″,3″,4″-Tri-O-acetyl-β-D-xylopyranosyl)-2′,4′-dibenzyloxy-2-hydroxybibenzyl (*20*)

To a cold (0 °C) and stirred solution of bibenzyl **19** (103 mg, 0.24 mmol) and imidate **14** (149 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) was added 21 μL of TMSOTf solution (0.11 M in CH_2Cl_2). After being stirred for 5 min at 0 °C, the resultant solution was poured into EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$ solution (20 mL × 3) and brine (20 mL × 3). The aqueous layers were extracted with EtOAc (20 mL × 3), and the combined organic

layers were dried over Na_2SO_4. Filtration and concentration followed by silica gel chromatography (45% EtOAc in hexane) gave the title compound **20** (117 mg, 71% from **19**) as a white solid. IR (film) ν_{max} 3032, 1753, 1506, 1223, 1039, 737 m^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (10H, m, ArH), 7.04 (1H, d, J = 8.3 Hz, ArH), 6.96 (1H, d, J = 8.8 Hz, ArH), 6.62 (1H, d, J = 2.4 Hz, ArH), 6.51 (1H, dd, J = 2.4, 7.3 Hz, ArH), 6.48 (2H, m, ArH), 5.52 (1H, bs, OH), 5.22 (1H, t, J = 7.8 Hz, CH), 5.15 (1H, dd, J = 6.4, 7.8 Hz, CH), 5.13 (2H, s, CH_2), 5.09 (1H, d, J = 6.4 Hz, CH), 5.01 (2H, s, CH_2), 4.99 (1H, m, CH), 4.20 (1H, dd, J = 4.9, 12.2 Hz, CH_2), 3.49 (1H, dd, J = 7.8, 12.2 Hz, CH_2), 2.76 (4H, s, CH_2), 2.08 (9H, m, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (C), 169.9 (C), 169.5 (C), 158.5 (C), 157.0 (C), 156.1 (C), 154.9 (C), 136.9 (C), 136.5 (C), 130.5 (C), 130.2 (C), 128.7 (CH), 128.6 (CH), 128.1 (CH), 128.0 (CH), 127.5 (CH), 127.4 (CH), 122.8 (C), 122.4 (C), 108.6 (CH), 105.6 (CH), 104.6 (CH), 100.8 (CH), 98.6 (CH), 70.8 (CH), 70.1 (CH_2), 68.5 (CH), 61.8 (CH_2), 31.2 (CH_2), 30.8 (CH_2), 20.7 (CH_3). ESIHRMS m/z 683.2473 $[M - H]^-$ (calcd for $C_{39}H_{39}O_{11}$, 683.2492).

4.1.11. 2,2′,4′-Trihydroxy-4-β-D-xylopyranosylbibenzyl (2)

Bibenzyl **20** (96 mg, 0.12 mmol) in EtOAc (2 mL) was hydrogenated over 20% $Pd(OH)_2$ on carbon (24 mg) for 12 h. Filtration through Celite 535 and concentration in vacuo followed by silica gel chromatography (60–70% EtOAc in hexane) gave the phenol as a white solid, which was used in the next step without further purification.

To cold (0 °C) and stirred solution of the phenol in MeOH (5 mL) was added 110 μL of NaOMe (5.2 M in MeOH) slowly. After being stirred for 0.5 h at 0 °C, the resultant solution was neutralized with Amberlite IR-120 (H^+). Filtration and concentration followed by solid phase extraction with Sep-Pak Plus C-18 cartridge (0–40% MeCN in H_2O) gave the crude bibenzyl that was further purified by preparative RP-HPLC (20% MeCN in H_2O, t_R = 7.5 min). The title compound **2** (40 mg, 85%) was obtained as a colorless solid. $[\alpha]_D^{20}$ −5.6 (*c* 0.17, MeOH). IR (Nujol) ν_{max} 3520, 3350, 1595, 1510 cm^{-1}. ^1H NMR (pyridine-d_5, 400 MHz) δ 7.35 (1H, d, J = 8.3 Hz, ArH), 7.33 (1H, d, J = 8.3 Hz, ArH), 7.22 (1H, d, J = 2.4 Hz, ArH), 7.08 (1H, d, J = 2.4 Hz, ArH), 6.90 (1H, dd, J = 2.4, 8.3 Hz, ArH), 6.80 (1H, dd, J = 2.4, 8.3 Hz, ArH), 5.44 (1H, d, J = 6.8 Hz, CH), 4.31 (1H, m, CH), 4.28 (1H, m, CH_2), 4.26 (1H, m, CH), 4.23 (1H, m, CH), 3.66 (1H, dd, J = 9.3, 10.2 Hz, CH_2), 3.44 (4H, m, CH_2). ^{13}C NMR (pyridine-d_5, 100 MHz) δ 157.7 (C), 157.3 (C), 157.1 (C), 157.0 (C), 130.6 (CH), 130.4 (CH), 123.5 (C), 120.1 (C), 107.2 (CH), 106.6 (CH), 104.4 (CH), 103.3 (CH), 102.8 (CH), 77.8 (CH), 74.2 (CH), 70.3 (CH), 66.6 (CH_2), 30.8 (CH_2), 30.6(CH_2). HRESIMS m/z 377.1234 $[M - H]^-$ (calcd for $C_{19}H_{21}O_8$, 377.1236).

4.1.12. 2,4-Di(2″,3″,4″-tri-O-acetyl-β-D-xylopyranosyl)-2′,4′-dibenzyloxybibenzyl (21)

To a cold (0 °C) and stirred solution of bibenzyl **19** (87 mg, 0.20 mmol) and imidate **14** (387 mg, 9.2 mmol) in CH_2Cl_2 (5 mL) was added 36 μL of TMSOTf solution (0.11 M in CH_2Cl_2). After being stirred for 5 min at 0 °C, the resultant solution was poured into EtOAc (60 mL) and washed with saturated aqueous $NaHCO_3$ solution (15 mL × 3) and brine (15 mL × 3). The aqueous layers were extracted with EtOAc (15 mL × 3), and the combined organic layers were dried over Na_2SO_4. Filtration and concentration followed by silica gel chromatography (40–50% EtOAc in hexane) gave the title compound **21** (149 mg, 77% from **19**) as a white solid. $[\alpha]_D^{19}$ −18.5 (*c* 0.30, $CHCl_3$). IR (film) ν_{max} 1755, 1610, 1506, 1221, 1041, 737 m^{-1}. ^1H NMR (100 MHz, $CDCl_3$) δ 7.38 (10H, m, ArH), 6.99 (1H, d, J = 8.3 Hz, ArH), 6.86 (1H, d, J = 8.3 Hz, ArH), 6.68 (1H, d, J = 2.4 Hz, ArH), 6.57 (1H, d, J = 2.4 Hz, ArH), 6.54 (1H, dd, J = 2.4, 8.3 Hz, ArH), 6.50 (1H, dd, J = 2.4, 8.3 Hz, ArH), 5.15 (6H, m, CH and CH_2), 5.02 (4H, m, CH), 4.99 (2H, m, CH), 4.20 (1H, dd, J = 4.7, 12.1 Hz, CH_2), 4.16 (1H, dd, J = 4.7, 12.1 Hz, CH_2), 3.50 (1H, dd, J = 7.8, 11.7 Hz, CH_2), 3.47 (1H, dd, J = 7.8, 11.7 Hz, CH_2), 2.80 (4H, m, CH_2), 2.04 (18H, m, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0 (C), 169.88 (C), 169.86 (C), 169.8 (C), 169.4 (C), 169.3 (C), 158.2 (C), 157.3 (C), 155.5 (C), 154.8 (C), 137.2 (C), 137.0 (C), 130.6 (CH), 130.2 (CH), 128.53 (CH), 128.48 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 127.3 (CH), 126.5 (C), 123.1 (C), 110.4 (CH), 105.2 (CH), 104.6 (CH), 100.3 (CH), 98.5 (CH), 97.9 (CH), 70.7 (CH), 70.2 (CH_2), 70.1 (CH_2), 69.8 (CH), 69.7 (CH), 69.1 (CH), 68.5 (CH_2), 68.2 (CH_2), 61.8 (CH_2), 61.4 (CH_2), 30.1 (CH_2), 29.9 (CH_2), 20.8 (CH_3). ESIHRMS m/z 965.3307 $[M + Na]^+$ (calcd for $C_{50}H_{54}NaO_{18}$, 965.3208).

4.1.13. 2′,4′-Dihydroxy-2,4-di(β-D-xylopyranosyl)bibenzyl (3)

Bibenzyl **21** (19 mg, 20 μmol) in EtOAc (2 mL) was hydrogenated over 20% $Pd(OH)_2$ on carbon (3 mg) for 12 h. Filtration through Celite 535 and concentration in vacuo followed by silica gel chromatography (70–80% EtOAc in hexane) gave the phenol as a white solid, which was used in the next step without further purification.

To cold (0 °C) and stirred solution of the phenol in MeOH (4 mL) was added 100 μL of NaOMe (5.2 M in MeOH) slowly. After being stirred for 0.5 h at 0 °C, the resultant solution was neutralized with Amberlite IR-120 (H^+). Filtration and concentration followed by solid phase extraction with Sep-Pak Plus C-18 cartridge (0–40% MeCN in H_2O) gave the crude bibenzyl that was further purified by preparative RP-HPLC (15% MeCN in H_2O, t_R = 12.5 min). The title compound **3** (8.7 mg, 85%) was obtained as a colorless solid. $[\alpha]_D^{20}$ −48.0 (*c* 0.05, MeOH). IR (Nujol) ν_{max} 3350, 1508 cm^{-1}. ^1H NMR (pyridine-d_5, 400 MHz) δ 7.49 (1H, bs, ArH), 7.31 (1H, d, J = 8.3 Hz, ArH), 7.28 (1H, d, J = 8.3 Hz, ArH), 7.04 (1H, d, J = 8.3 Hz, ArH), 7.02 (1H, bs, ArH), 6.72 (1H, d, J = 8.3 Hz, ArH), 5.52 (1H, d, J = 5.4 Hz, CH), 5.38 (1H, d, J = 7.3 Hz, CH), 4.28 (8H, m, CH and CH_2), 3.85 (1H, t, J = 9.8 Hz, CH_2), 3.67 (1H, dd, J = 8.8, 11.2 Hz, CH_2), 3.43 (2H, m, CH_2), 3.30 (2H, m, CH_2). ^{13}C NMR (pyridine-d_5, 100 MHz) δ 157.6 (C), 157.2 (C), 156.8 (C), 156.7 (C), 130.8 (CH), 130.1 (CH), 126.0 (C), 119.9 (C), 109.6 (CH), 106.7 (CH), 105.3 (CH), 103.2 (CH), 103.1 (CH), 102.7 (CH), 77.8 (CH), 77.6 (CH), 74.2 (CH), 70.3 (CH), 70.2 (CH), 66.6 (CH_2), 66.5 (CH_2), 30.90 (CH_2), 30.86 (CH_2). HRESIMS m/z 509.1649 $[M - H]^-$ (calcd for $C_{24}H_{29}O_{12}$, 509.1659).

4.1.14. 4-(2″,3″,4″,6″-Tetra-O-acetyl-β-D-glucopyranosyl)-2′,4′-dibenzyloxy-2-hydroxybibenzyl (25)

To a cold (0 °C) and stirred solution of bibenzyl **19** (50 mg, 0.12 mmol) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate (**22**) (140 mg, 0.30 mmol) in CH_2Cl_2 (2 mL) was added 10 μL of TMSOTf solution (0.11 M in CH_2Cl_2). After being stirred for 5 min at 0 °C, the resultant solution was poured into EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$ solution (20 mL × 3) and brine (20 mL × 3). The aqueous layers were extracted with EtOAc (20 mL × 3), and the combined organic layers were dried over Na_2SO_4. Filtration and concentration followed by silica gel chromatography (50–55% EtOAc in hexane) gave the title compound **25** (66 mg, 74% from **19**) as a white solid. $[\alpha]_D^{23}$ −4.48 (*c* 1.46, $CHCl_3$). IR (film) ν_{max} 3033, 1750, 1503, 1220, 1040, 736 m^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (10H, m, ArH), 7.02 (1H, d, J = 7.8 Hz, ArH), 6.95 (1H, d, J = 7.8 Hz, ArH), 6.62 (1H, d, J = 2.4 Hz, ArH), 6.50 (1H, dd, J = 2.4, 7.8 Hz, ArH), 6.47 (1H, d, J = 2.4 Hz, ArH), 6.45 (1H, dd, J = 2.4, 7.8 Hz, ArH), 5.57 (1H, bs, OH), 5.27 (1H, t, J = 8.0 Hz, CH), 5.23 (1H, t, J = 8.0 Hz, CH), 5.13 (1H, m, CH), 5.11 (2H, s, CH_2), 5.00 (2H, s, CH_2), 4.99 (1H, d, J = 6.8 Hz, CH), 4.27 (1H, dd, J = 5.4, 12.2 Hz, CH_2), 4.15 (1H, dd, J = 2.4, 12.2 Hz, CH_2), 3.82 (1H, ddd, J = 2.4, 5.4, 8.0 Hz, CH), 2.75 (4H, m, CH_2), 2.07 (3H, s, CH_3), 2.043 (3H, s, CH_3), 2.037 (3H, s, CH_3), 2.02 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (C), 170.6 (C), 169.73 (C), 169.65 (C), 158.9 (C), 157.3 (C), 156.8 (C), 155.3 (C), 137.2 (C), 136.8 (C), 130.7 (CH), 130.6 (CH), 129.0 (CH), 128.9 (CH), 128.5 (CH), 128.3 (CH), 127.84 (CH), 127.76 (CH), 123.0 (C), 122.8 (C), 109.2 (CH), 106.1 (CH), 105.1 (CH), 101.3 (CH), 99.6 (CH), 73.1 (CH), 72.3 (CH), 71.5 (CH), 70.6 (CH_2), 70.5 (CH_2), 68.7 (CH), 62.3 (CH_2), 31.6 (CH_2), 31.2 (CH_2), 20.9 (CH_3). ESIHRMS m/z 755.2700 $[M - H]^-$ (calcd for $C_{42}H_{43}O_{13}$, 755.2704).

*4.1.15. 4-(β-D-Glucopyranosyl)-2,2′,4′-trihydroxybibenzyl (**4**)*

Bibenzyl **25** (35 mg, 46 μmol) in EtOAc (2 mL) was hydrogenated over 20% $Pd(OH)_2$ on carbon (24 mg) for 12 h. Filtration through Celite 535 and concentration in vacuo followed by silica gel chromatography (60–70% EtOAc in hexane) gave the phenol as a white solid, which was used in the next step without further purification.

To cold (0 °C) and stirred solution of the phenol in MeOH (5 mL) was added 43 μL of NaOMe (5.2 M in MeOH) slowly. After being stirred for 0.5 h at 0 °C, the resultant solution was neutralized with Amberlite IR-120 (H^+). Filtration and concentration followed by solid phase extraction with Sep-Pak Plus C-18 cartridge (0–40% MeCN in H_2O) gave the crude bibenzyl that was further purified by preparative RP-HPLC (20% MeCN in H_2O, t_R = 6.8 min). The title compound **4** (12 mg, 63%) was obtained as a colorless solid. $[\alpha]_D^{21}$ −33.4 (*c* 0.2, MeOH). IR (Nujol) ν_{max} 3522, 3350, 1595, 1510 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz) δ 6.89 (1H, d, *J* = 8.3 Hz, ArH), 6.77 (1H, d, *J* = 8.3 Hz, ArH), 6.56 (1H, d, *J* = 2.4 Hz, ArH), 6.47 (1H, dd, *J* = 2.4, 8.3 Hz, ArH), 6.27 (1H, d, *J* = 2.4 Hz, ArH), 6.16 (1H, dd, *J* = 2.4, 8.3 Hz, ArH), 4.82 (1H, d, *J* = 7.3 Hz, CH), 3.89 (1H, dd, *J* = 2.0, 12.2 Hz, CH_2), 3.70 (1H, dd, *J* = 4.9, 12.2 Hz, CH_2), 3.39 (4H, m, CH), 2.70 (4H, m, CH_2). ^{13}C NMR (CD_3OD, 100 MHz) δ 158.2 (C), 157.3 (C), 157.0 (C), 156.9 (C), 131.44 (CH), 131.39 (CH), 124.3 (C), 121.2 (C), 108.5 (CH), 107.3 (CH), 104.9 (CH), 103.4 (CH), 102.4 (CH), 78.1 (CH), 74.9 (CH), 71.4 (CH), 62.6 (CH_2), 31.4 (CH_2), 31.2 (CH_2). HRESIMS *m*/*z* 431.1376 $[M + Na]^+$ (calcd for $C_{20}H_{24}NaO_9$, 431.1318).

*4.1.16. 4-(2″,2‴,3″,3‴,4″,4‴,6″,6‴-Octa-O-acetyl-β-D-cellobiopyranosyl)-2′,4′-dibenzyloxy-2-hydroxybibenzyl (**26**)*

To a cold (0 °C) and stirred solution of bibenzyl **19** (50 mg, 0.12 mmol) and 2,2′,3,3′,4,4′,6,6′-octa-*O*-acetyl-α-D-cellobiopyranosyl trichloroacetimidate (**23**) (185 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) was added 10 μL of TMSOTf solution (0.11 M in CH_2Cl_2). After being stirred for 5 min at 0 °C, the resultant solution was poured into EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$ solution (20 mL × 3) and brine (20 mL × 3). The aqueous layers were extracted with EtOAc (20 mL × 3), and the combined organic layers were dried over Na_2SO_4. Filtration and concentration followed by silica gel chromatography (70% EtOAc in hexane) gave the title compound **26** (92 mg, 75% from **19**) as a white solid. $[\alpha]_D^{22}$ −14.56 (*c* 1.40, $CHCl_3$). IR (film) ν_{max} 3035, 1750, 1503, 1220, 1040, 734 m^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (10H, m, ArH), 7.01 (1H, d, *J* = 8.3 Hz, ArH), 6.92 (1H, d, *J* = 8.3 Hz, ArH), 6.60 (1H, d, *J* = 2.4 Hz, ArH), 6.48 (1H, dd, *J* = 2.4, 8.3 Hz, ArH), 6.44 (1H, d, *J* = 2.4 Hz, ArH), 6.42 (1H, dd, *J* = 2.4, 8.3 Hz, ArH), 5.64 (1H, bs, OH), 5.22 (1H, t, *J* = 9.3 Hz, CH), 5.11 (3H, m, CH), 5.09 (2H, s, CH_2), 5.05 (1H, t, *J* = 9.8 Hz, CH), 4.99 (2H, s, CH_2), 4.93 (2H, m, CH), 4.49 (2H, m, CH), 4.36 (1H, dd, *J* = 4.4, 12.7 Hz, CH_2), 4.12 (1H, dd, *J* = 5.9, 12.7 Hz, CH_2), 4.04 (1H, dd, *J* = 2.0, 12.7 Hz, CH_2), 3.82 (1H, m, CH), 3.69 (2H, m, CH and CH_2), 2.73 (4H, m, CH_2), 2.02 (21H, m, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (C), 170.4 (C), 170.2 (C), 169.8 (C), 169.6 (C), 169.3 (C), 169.1 (C), 158.5 (C), 157.0 (C), 156.4 (C), 155.0 (C), 136.9 (C), 136.5 (C), 130.4 (CH), 130.2 (CH), 128.7 (CH), 128.6 (CH), 128.1 (CH), 128.0 (CH), 127.5 (CH), 127.4 (CH), 122.7 (C), 122.5 (C), 108.8 (CH), 105.7 (CH), 104.7 (CH), 100.9 (CH), 100.8 (CH), 99.0 (CH), 72.9 (CH), 72.8 (CH), 72.5 (CH), 72.0 (CH), 71.6 (CH), 71.4 (CH), 70.3 (CH_2), 70.2 (CH_2), 67.7 (CH), 61.9 (CH_2), 61.5 (CH_2), 31.2 (CH_2), 30.8 (CH_2), 20.7 (CH_3), 20.6 (CH_3), 20.5 (CH_3). ESIHRMS *m*/*z* 1043.3528 $[M - H]^-$ (calcd for $C_{54}H_{59}O_{21}$, 1043.3549).

*4.1.17. 4-(β-D-Cellobiopyranosyl)-2,2′,4′-trihydroxybibenzyl (**5**)*

Bibenzyl **26** (46 mg, 44 μmol) in EtOAc (2 mL) was hydrogenated over 20% $Pd(OH)_2$ on carbon (24 mg) for 12 h. Filtration through Celite 535 and concentration in vacuo followed by silica gel chromatography (80–85% EtOAc in hexane) gave the phenol as a white solid, which was used in the next step without further purification.

To cold (0 °C) and stirred solution of the phenol in MeOH (5 mL) was added 52 μL of NaOMe (5.2 M in MeOH) slowly. After being stirred for 0.5 h at 0 °C, the resultant solution was neutralized with Amberlite IR-120 (H^+). Filtration and concentration followed by solid phase extraction with Sep-Pak Plus C-18 cartridge (0–40% MeCN in H_2O) gave the crude bibenzyl that was further purified by preparative RP-HPLC (20% MeCN in H_2O, t_R = 6.4 min). The title compound **5** (18 mg, 72%) was obtained as a colorless solid. $[\alpha]_D^{21}$ −66.0 (*c* 0.04, MeOH). IR (Nujol) ν_{max} 3520, 3350, 1595, 1510 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz) δ 6.89 (1H, d, *J* = 8.3 Hz, ArH), 6.77 (1H, d, *J* = 8.3 Hz, ArH), 6.56 (1H, d, *J* = 2.4 Hz, ArH), 6.47 (1H, dd, *J* = 2.4, 8.3 Hz, ArH), 6.27 (1H, d, *J* = 2.4 Hz, ArH), 6.17 (1H, dd, *J* = 2.4, 8.3 Hz, ArH), 4.93 (1H, d, *J* = 7.2 Hz, CH), 4.44 (1H, d, *J* = 7.8 Hz, CH), 3.91 (3H, m, CH and CH_2), 3.66 (2H, m, CH_2), 3.61 (1H, dd, *J* = 8.3, 8.8 Hz, CH), 3.54 (1H, m, CH), 3.48 (1H, dd, *J* = 7.8, 8.3 Hz, CH), 3.32 (3H, m, CH), 3.24 (1H, t, *J* = 8.3 Hz, CH), 2.70 (4H, m, CH_2). ^{13}C NMR (CD_3OD, 100 MHz) δ 158.1 (C), 157.3 (C), 156.93 (C), 156.88 (C), 131.44 (CH), 131.39 (CH), 124.4 (C), 121.2 (C), 108.5 (CH), 107.3 (CH), 104.9 (CH), 104.6 (CH), 103.4 (CH), 102.2 (CH), 80.3 (CH), 78.1 (CH), 77.9 (CH), 76.6 (CH), 76.4 (CH), 74.9 (CH), 74.7 (CH), 71.4 (CH), 62.4 (CH_2), 61.7 (CH_2), 31.3 (CH_2), 31.2 (CH_2). HRESIMS *m*/*z* 569.1876 $[M - H]^-$ (calcd for $C_{26}H_{33}O_{14}$, 569.1870).

*4.1.18. 4-(2″,2‴,3″,3‴,4″,4‴,6″,6‴-octa-O-acetyl-β-D-maltopyranosyl)-2′,4′-dibenzyloxy-2-hydroxybibenzyl (**27**)*

To a cold (0 °C) and stirred solution of bibenzyl **19** (64 mg, 0.15 mmol) and 2,2′,3,3′,4,4′,6,6′-octa-*O*-acetyl-α-D-maltopyranosyl trichloroacetimidate (**24**) (218 mg, 0.28 mmol) in CH_2Cl_2 (2 mL) was added 14 μL of TMSOTf solution (0.11 M in CH_2Cl_2). After being stirred for 1 h at 0 °C, the resultant solution was poured into EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$ solution (20 mL × 3) and brine (20 mL × 3). The aqueous layers were extracted with EtOAc (20 mL × 3), and the combined organic layers were dried over Na_2SO_4. Filtration and concentration followed by silica gel chromatography (60% EtOAc in hexane) gave the title compound **27** (89 mg, 57% from **19**) as a white solid. $[\alpha]_D^{22}$ +42.38 (*c* 0.68, $CHCl_3$). IR (film) ν_{max} 3040, 1735, 1503, 1220, 1040, 735 m^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (10H, m, ArH), 7.04 (1H, d, *J* = 8.3 Hz, ArH), 6.96 (1H, d, *J* = 8.3 Hz, ArH), 6.62 (1H, d, *J* = 2.4 Hz, ArH), 6.51 (1H, dd, *J* = 2.4, 8.3 Hz, ArH), 6.47 (1H, d, *J* = 2.4 Hz, ArH), 6.44 (1H, dd, *J* = 2.4, 8.3 Hz, ArH), 5.69 (1H, bs, OH), 5.43 (1H, d, *J* = 3.9 Hz, CH), 5.37 (1H, t, *J* = 9.8 Hz, CH), 5.31 (1H, t, *J* = 8.8 Hz, CH), 5.12 (2H, s, CH_2), 5.05 (3H, m, CH), 5.01 (2H, s, CH_2), 4.87 (1H, dd, *J* = 3.9, 10.8 Hz, CH_2), 4.47 (1H, dd, *J* = 2.4, 11.7 Hz, CH_2), 4.26 (2H, m, CH and CH_2), 4.07 (2H, m, CH and CH_2), 3.97 (1H, m, CH), 3.84 (1H, m, CH), 2.76 (4H, m, CH_2), 2.06 (21H, m, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 (C), 170.5 (C), 170.2 (C), 170.0 (C), 169.7 (C), 169.5 (C), 158.5 (C), 157.0 (C), 156.2 (C), 155.0 (C), 136.9 (C), 136.5 (C), 130.4 (CH), 130.2 (CH), 128.7 (CH), 128.6 (CH), 128.1 (CH), 128.0 (CH), 127.53 (CH), 127.46 (CH), 122.7 (C), 122.5 (C), 108.8 (CH), 105.7 (CH), 104.8 (CH), 100.9 (CH), 98.6 (CH), 95.6 (CH), 75.3 (CH), 72.7 (CH), 72.2 (CH), 72.0 (CH), 70.3 (CH_2), 70.2 (CH_2), 70.0 (CH), 69.3 (CH), 68.5 (CH), 68.0 (CH), 62.8 (CH_2), 61.6 (CH_2), 31.3 (CH_2), 30.8 (CH_2), 20.9 (CH_3), 20.73 (CH_3), 20.68 (CH_3), 20.62 (CH_3), 20.61 (CH_3), 20.58 (CH_3). ESIHRMS *m*/*z* 1067.3465 $[M + Na]^+$ (calcd for $C_{54}H_{60}NaO_{21}$, 1067.3525).

*4.1.19. 2,2′,4′-Trihydroxy-4-(β-D-maltopyranosyl)bibenzyl (**6**)*

Bibenzyl **27** (49 mg, 46 μmol) in EtOAc (2 mL) was hydrogenated over 20% $Pd(OH)_2$ on carbon (24 mg) for 12 h. Filtration through Celite 535 and concentration in vacuo followed by silica gel chromatography (70–80% EtOAc in hexane) gave the phenol as a white solid, which was used in the next step without further purification.

To cold (0 °C) and stirred solution of the phenol in MeOH (5 mL) was added 28 μL of NaOMe (5.2 M in MeOH) slowly. After being stirred for 0.5 h at 0 °C, the resultant solution was neutralized with Amberlite IR-120 (H^+). Filtration and concentration followed by

solid phase extraction with Sep-Pak Plus C-18 cartridge (0–40% MeCN in H_2O) gave the crude bibenzyl that was further purified by preparative RP-HPLC (17.5% MeCN in H_2O, $t_R = 6.0$ min). The title compound **6** (15 mg, 56%) was obtained as a colorless solid. $[\alpha]_D^{21}$ +21.7 (*c* 0.09, MeOH). IR (Nujol) ν_{max} 3520, 3350, 1600, 1510 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz) δ 6.88 (1H, d, $J = 8.3$ Hz, ArH), 6.76 (1H, d, $J = 8.3$ Hz, ArH), 6.55 (1H, d, $J = 2.4$ Hz, ArH), 6.46 (1H, dd, $J = 2.4$, 8.3 Hz, ArH), 6.26 (1H, d, $J = 2.4$ Hz, ArH), 6.15 (1H, dd, $J = 2.4$, 8.3 Hz, ArH), 5.19 (1H, d, $J = 3.9$ Hz, CH), 4.84 (1H, d, $J = 7.8$ Hz, CH), 3.87 (3H, m, CH and CH_2), 3.66 (5H, m, CH and CH_2), 3.48 (4H, m, CH), 2.69 (4H, m, CH_2). ^{13}C NMR (CD_3OD, 100 MHz) δ 158.1 (C), 157.3 (C), 157.0 (C), 156.9 (C), 131.44 (CH), 131.38 (CH), 124.3 (C), 121.2 (C), 108.4 (CH), 107.2 (CH), 104.9 (CH), 103.4 (CH), 102.9 (CH), 102.3 (CH), 80.9 (CH), 77.8 (CH), 76.7 (CH), 75.1 (CH), 74.8 (CH), 74.5 (CH), 74.4 (CH), 71.5 (CH), 62.8 (CH_2), 62.0 (CH_2), 31.78 (CH_2), 31.68 (CH_2). HRESIMS *m/z* 569.1801 $[M - H]^-$ (calcd for $C_{26}H_{33}O_{14}$, 569.1870).

4.2. Tyrosinase inhibitory assay

Tyrosinase (E.C.1.14.18.1) purchased from Sigma–Aldrich was purified by the procedure as previously reported [28]. The enzyme concentration was adjusted at 1.0 μg/mL by the Bradford method with bovine serum albumin as a standard [29]. 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 10 min. Then, 0.1 mL of the DMSO solution of the inhibitor and 0.1 mL of enzyme solution 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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