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ScienceDirect
Bioorganic & Medicinal Chemistry 16 (2008) 5331–5344
Bioorganic & Medicinal Chemistry

Active core structure of terfestatin A, a new specific inhibitor of auxin signaling

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Received 17 January 2008; revised 26 February 2008; accepted 27 February 2008
Available online 4 March 2008

Abstract—The auxins, plant hormones, regulate many aspects of the growth and development of plants. Terfestatin A (TrfA), a novel auxin signaling inhibitor, was identified in a screen of *Streptomyces* sp. F40 extracts for inhibition of the expression of an auxin-inducible gene. However, the mode of action of TrfA has not been elucidated. To identify the active core structure, 25 derivatives of TrfA were synthesized and their inhibitory activities against auxin-inducible gene expression were evaluated. The structure–activity relationships revealed the essential active core structure of TrfA, 3-butoxy-4-methylbiphenyl-2,6-diol, which will lead to the design of biotin-tagged active TrfA.

1. Introduction

The plant hormones regulate the growth and development of plants. These hormones, such as the auxins, gibberellin, cytokinin, abscisic acid, and ethylene, are low molecular weight organic compounds, as distinct from the proteinaceous hormones found in mammals. Indole-3-acetic acid (IAA: **2**), an auxin, plays a crucial role in many aspects of plant development including cell division, elongation, and differentiation. At the whole plant level, auxins regulate tropisms, apical dominance and root development, and ultimately control the architecture of adult plants.[1]

Recent molecular biological and genetic studies of auxin signaling have revealed that three major families of genes (*Aux*/*IAA*s, *GH3*s and *SUAR*s) are induced in response to auxins.[2] Of the three families, it has been demonstrated that the *AUX*/*IAA* family plays a critical role in auxin signaling. *AUX*/*IAA*s encode a nuclear localized transcriptional repressor capable of heterodimerization with auxin-responsive factors (ARFs) families of transcription regulators. This heterodimerization represses the expression of primary auxin-responsive genes by interrupting the interaction of ARF with auxin-responsive promoters.[3] It has been demonstrated that ubiquitin–proteasome-dependent proteolysis of AUX/IAA repressor is crucial for primary auxin-responsive gene expression and various subsequent developmental processes, including lateral root growth, hypocotyl elongation, gravitropism, and photomorphogenesis.[1] *TIR1* encodes an F-box protein that interacts with the Skp1 and Cdc53 (cullin) proteins to form ubiquitin ligase complexes called SCFs. SCF^{TIR1} complex is involved in the proteolytic pathway that leads to auxin-dependent degradation of AUX/IAA repressors.[4] Auxins promote the interaction between AUX/IAAs and TIR1 protein and enhance the ubiquitination of AUX/IAA proteins and the subsequent degradation rate of repressor, ultimately enhancing auxin-responsive gene expression.[4–6] Recent reports have demonstrated that TIR1 is one of the six auxin receptors (TIR1 and AFBs 1-5)[7] and that auxins enhance the interaction between TIR1 and AUX/IAA repressor.[8,9]

In the course of screening for specific inhibitors of auxin signaling, we have found a novel and specific inhibitor of auxin signaling, designated terfestatin A (TrfA (**1**), Fig. 1A).[10,11] TrfA was identified in a screen of *Streptomyces* sp. F40 extracts for inhibition of the expression of

Keywords: Auxin; Structure–activity relationships; Terfestatin A; Terphenyl; TIR1.
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doi:10.1016/j.bmc.2008.02.085

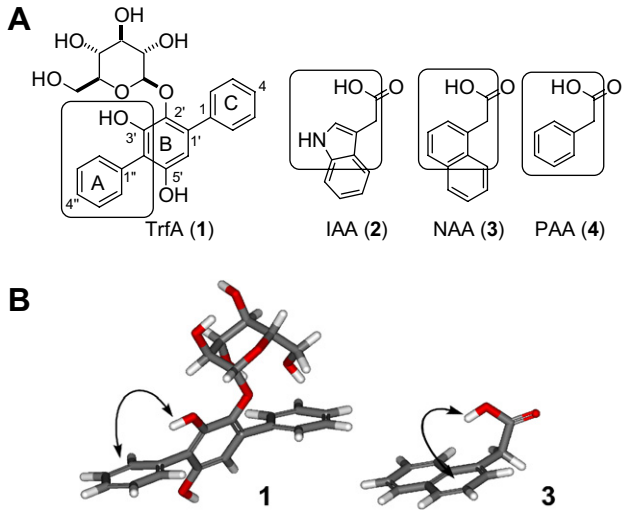


Figure 1. Structures of terfestatin A (**1**) and auxins (**2**–**4**) and the stable confomations of **1** and NAA.

an auxin-responsive GUS reporter construct.[10] TrfA specifically blocks auxin-responsive gene expression and physiological auxin responses in roots.[11] Conformational analysis of the TrfA structure revealed structural similarities between the auxins and TrfA (Fig. 1A and B). The positions of the aromatic ring and the carboxyl group in auxins such as indole-3-acetic acid (IAA: **2**) and 1-naphthaleneacetic acid (NAA: **3**) closely match the positions of the aromatic A ring and the phenolic hydroxyl group in TrfA (Fig. 1B). In addition, phenylacetic acid (**4**) also was known to display weak auxin activity. Therefore, we expected that TrfA mimics auxin and acts as an auxin antagonist. However, biological investigation of TrfA demonstrated that TrfA does not bind to TIR1, leaving two possible explanations of TrfA action.[11] One is that TrfA selectively interacts with other auxin receptors such as AFBs 1–5. The second is that TrfA does not act on AFB receptors, but acts on the signaling components regulating auxin-dependent AUX/IAA proteolysis. The identification of the target protein of TrfA would provide direct evidence for the inhibitory mechanism of action of TrfA. Biotin-tagged TrfA is the critical probe that would allow us to identify the target protein by affinity chromatography.

To design biotin-tagged TrfA, we investigated the structure–activity relationships of TrfA by examining the characteristics of its derivatives. Here, we propose an active core structure of TrfA based on its structure–activity relationships and report the design of biologically active biotin-tagged TrfA.

2. Results and discussion

2.1. The structure–activity relationships of the phenolic hydroxyl group and the glucoside moiety in TrfA

To assess the role of hydroxyl groups in the inhibitory activity, TrfA derivatives (**1a**–**c** and **9**) were synthesized (Fig. 2). The synthesis of **9** is summarized in Scheme 1.

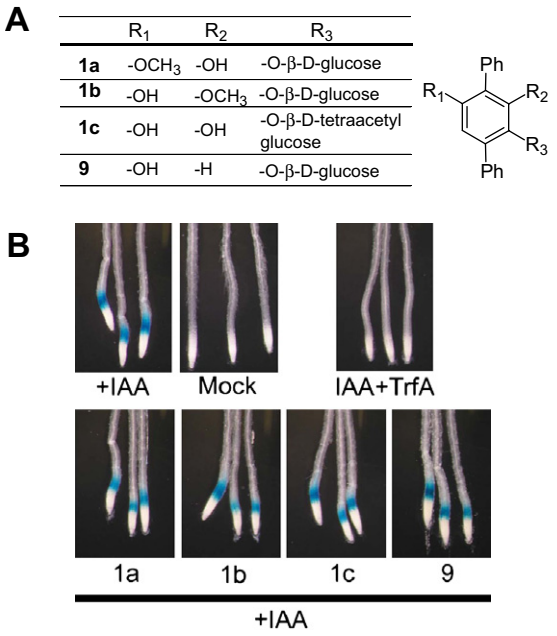
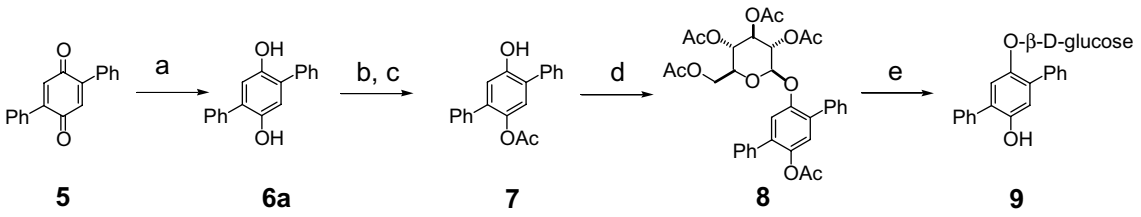


Figure 2. (A) Structures of the derivatives **1a**–**c** and **9**. (B) Effects of derivatives on the auxin-induced gene expression. Arabidopsis *BA3::GUS* transgenic reporter line was treated with 50 μM solutions of the derivatives in the presence of 1 μM IAA for 5 h. IAA-induced GUS expression was visualized by histochemical staining using X-Gluc for 3–4 h. The photos of the root tips were taken on three representatives.

2,5-Diphenylbenzoquinone (**5**) was reduced by sodium borohydrate to yield phenol (**6a**). Selective alkaline hydrolysis of the diacetate (**6b**) gave a monoacetate (**7**). This monoacetate was glycosylated by treatment with acetobromo-α-glucose and cesium bicarbonate, followed by alkaline hydrolysis to yield the dehydroxylated TrfA derivative (**9**). Monomethylated derivatives (**1a** and **1b**) were synthesized according to essentially the same procedure described previously.[10] The biological activities of the derivatives were evaluated by their inhibitory activities against auxin-induced reporter gene expression using Arabidopsis *BA3::GUS* transgenic plants.[12] The *BA3::GUS* line carries the GUS reporter gene under the control of an auxin-responsive promoter, and it rapidly expresses GUS enzyme in response to auxin.[12] The inhibition of auxin-induced GUS enzymatic activity was visualized by histochemical staining using X-Gluc as a chromogenic substrate or was fluorometrically quantified using 4-methyl umbelliferyl-β-D-glucuronide as a fluorogenic substrate.

Loss of the hydroxyl group in the $\mathbf{R}_2$ position of TrfA (derivative **9**) completely abolished the inhibitory effect on *BA3::GUS* expression (Fig. 2). Methylation of the hydroxyl groups at $\mathbf{R}_1$ or $\mathbf{R}_2$ (**1a**: $\mathbf{R}_1 = OCH_3$, **1b**: $\mathbf{R}_2 = OCH_3$) also caused complete inactivation (Fig. 2). These results suggest that both hydroxyl groups are essential to retain the activity of TrfA, and contributes to binding TrfA to the target protein.

TrfA has a β-glucoside moiety, and aglycon itself did not show inhibitory activity (data not shown). In addition,



Scheme 1. Reagents and conditions: (a) $NaBH_4$, MeOH, rt, 1 h, 70%; (b) Ac_2O, DMAP, CH_2Cl_2, 0 °C, 1 h, 93%; (c) KOH, MeOH, −18 °C, 1 h, 81%; (d) Cs_2CO_3, acetobromo-α-D-glucose, CH_3CN, rt, 24 h, 79%; (e) KOH, MeOH, rt, 1 h, 90%.

TrfA derivatives having tetraacetylglucoside (**1c**) were also found to be inactive (Fig. 2A). This suggests the glycoside residue is essential for inhibitory activity. To further elucidate the role of the glucoside moiety of TrfA, we substituted an alkyl ether chain in place of the glucoside moiety (Fig. 3A). The alkyl ether derivatives (**12a–k**) were synthesized by reaction of the intermediate (**10**) with the corresponding alkyl bromide, TBAI, and sodium hydride, followed by the deprotection of the benzyl groups (Fig. 3A and B). The inhibitory activities of **12a–k** are shown in Figure 3B. The ethyl ether and propyl ether derivatives (**12a** and **12b**) displayed weak inhibitory activities toward *BA3::GUS* expression. The butyl ether derivative (**12c**) retained inhibitory activity. The introduction of 4-chlorobutyl ether (**12f**), and methoxylmethyl ether groups (**12g**) produced the same inhibitory activity as the butyl ether derivative (**12c**). On the other hand, the pentyl ether derivative (**12d**) was less active. The introduction of isopropyl ether (**12h**), isobutyl ether (**12i**), cyclopropylmethyl ether (**12j**), hexyl ether (**12e**) and cyclohexylmethyl ether (**12k**) completely abolished the activity. From these results, we conclude the glucoside moiety is not essential for the binding to the target protein, but the size and length of the carbon chain are crucial to the inhibitory activity. Therefore, the glucoside moiety in TrfA acts as an anchor to hold TrfA at the binding site of the target protein. As a result of investigating the structure–activity relationships for the sugar moiety, we found that the introduction of a biotin-tagged linkage into the sugar moiety would abolish the activity.

2.2. The structure–activity relationships of the phenyl A ring in TrfA

We next synthesized A ring-substituted TrfA derivatives to investigate the role of the phenyl A ring in the activity (Scheme 2). Suzuki coupling was used as the key step to introduce the various substituents into phenyl A ring of TrfA. 2,5-Dihydroxybenzaldehyde (**13**) was protected with benzyl groups to afford dibenzylaldehyde (**14**). Monobenzylether (**15**) was obtained by selective deprotection using magnesium bromide.[13] Compound **15**

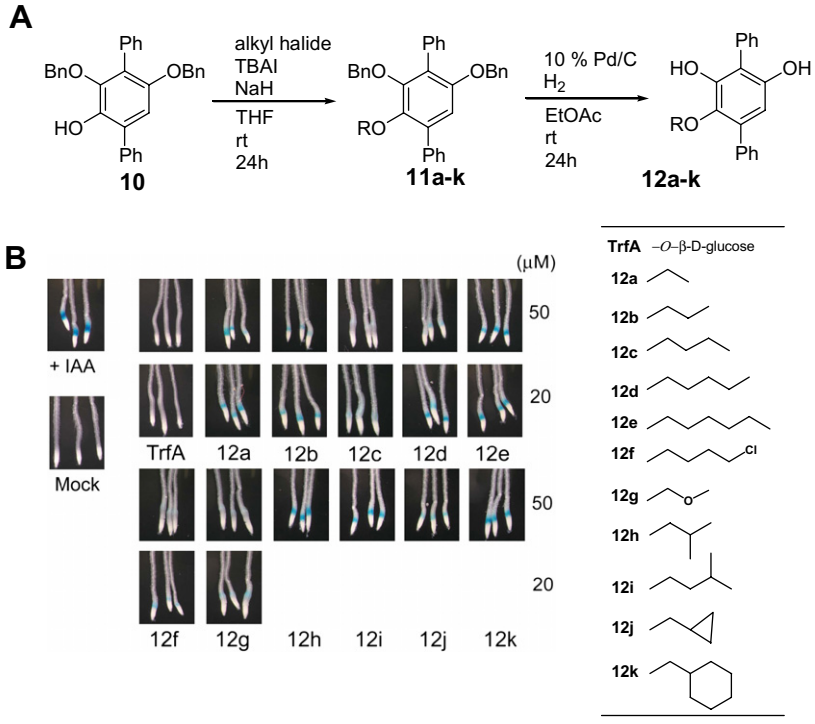
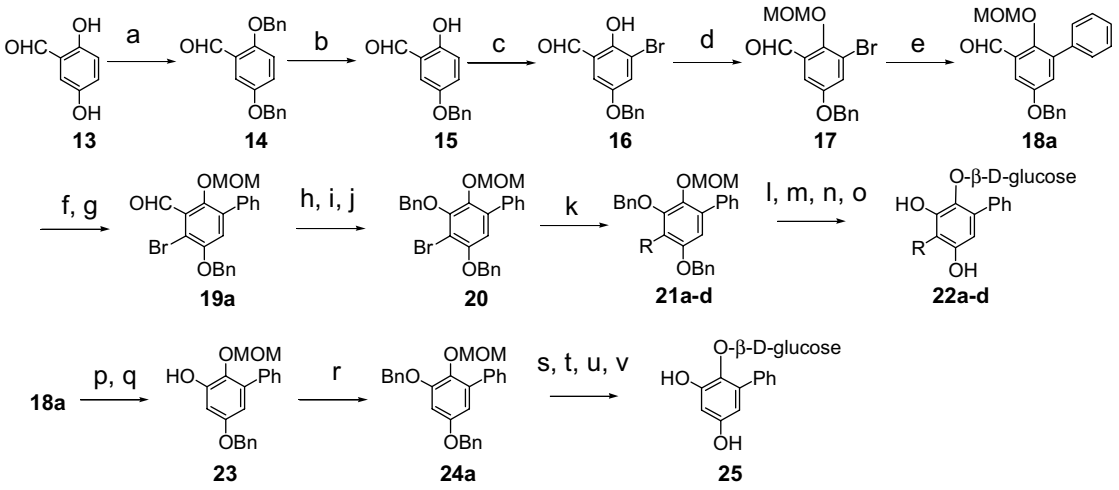


Figure 3. (A) Synthetic scheme for the 2′-alkyl ether derivatives (**12a–k**). (B) Effects of **12a–k** on the auxin-induced gene expression. Arabidopsis *BA3::GUS* transgenic reporter line was treated with 20 or 50 μM solutions of the derivatives in the presence of 1 μM IAA for 5 h. The photos of the root tips were taken on three representatives.



Scheme 2. Reagents and conditions: (a) BnBr, K_2CO_3, CH_3CN, reflux, 4 h; (b) MgBr, benzene/Et_2O = 7:1, reflux, 8 h; (c) Br_2, AcONa, AcOH, rt, 3 h; (d) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, 6 h; (e) $PhB(OH)_2$, $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME/EtOH = 5:1, reflux, 3 h; (f) Br_2, AcONa, AcOH, 50 °C, 4 h; (g) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, 6 h; (h) *m*-CPBA, CH_2Cl_2, 0 °C–rt, 24 h; (i) KOH, MeOH, rt, 1 h; (j) BnBr, K_2CO_3, reflux, 2 h; (k) R-$B(OH)_2$, $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME/EtOH = 5:1, reflux, 3 h; (l) AcCl, MeOH, 0 °C–rt, 2 h; (m) Cs_2CO_3, acetobromo-α-D-glucose, CH_3CN, rt, 24 h; (n) 10% Pd/C, H_2, EtOAc, rt, 12 h; (o) KOH, MeOH, rt, 1 h; (p) *m*-CPBA, CH_2Cl_2, 0 °C–rt, 8 h; (q) same as I; (r) BnBr, K_2CO_3, reflux, 1 h; (s) AcCl, MeOH, 0 °C–rt, 2 h; (t) same as m, CH_3CN, rt, 24 h; (u) same as n; (v) same as o.

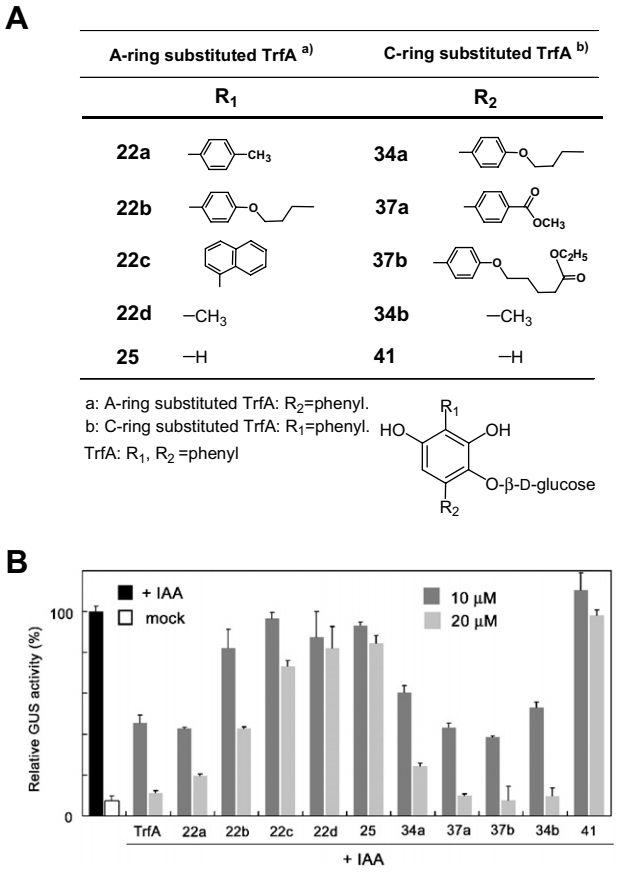


Figure 4. (A) Structures of the A-ring-substituted derivatives and the B-ring-substituted derivatives. (B) Effects of the derivatives on the auxin-induced gene expression. Arabidopsis *BA3::GUS* transgenic reporter line was treated with 10 and 20 μM solutions of the derivatives in the presence of 1 μM IAA for 5 h. IAA-induced GUS expression was determined fluorometrically by the fluorogenic substrate, 4-methyl umbelliferyl β-D-glucuronide. Values are means ± SD of three-independent experiments.

was treated with bromine to yield **16**.[14] The hydroxyl group in **16** was protected by the MOM group and then coupled with various phenyl boronic acids by Suzuki coupling to yield biphenyl (**18a**). In this coupling, the reaction did not proceed unless the hydroxyl group of **16** was protected. Therefore, biphenyl **18a** was brominated and then protected by an MOM group. The aldehyde group in **19a** was converted to a hydroxyl group by Baeyer–Villiger oxidation, followed by alkaline hydrolysis. The corresponding boronic acids (Fig. 4A) were coupled with the key intermediate (**20**) by Suzuki coupling after protection with benzyl groups. The MOM group in **21a–d** was deprotected, and then the glycoside was introduced by treatment with acetobromoglucose and cesium bicarbonate. The deprotection of the benzyl and acetyl groups yielded the A-ring-substituted TrfA derivatives (**22a–d**). The biphenyl derivative of TrfA (**25**) was synthesized from the intermediate (**18a**) as shown in Scheme 2. The synthetic schemes for the A-ring-substituted TrfA derivatives (Fig. 4A) are summarized in Scheme 2.

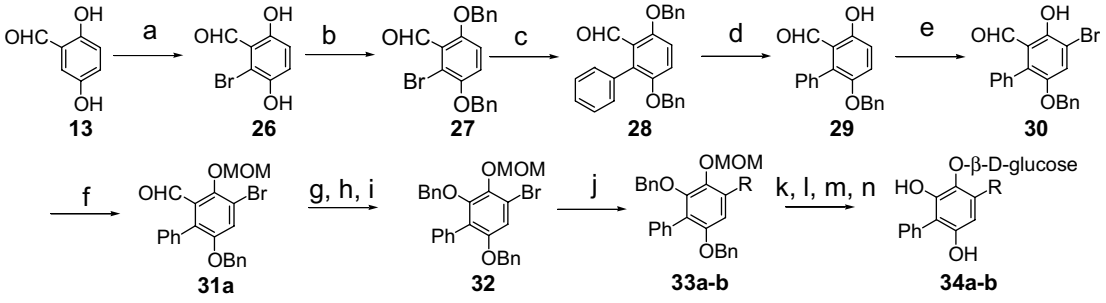
Derivatives **22d** and **25**, which lack the aromatic A-ring, were found to have lost the ability to inhibit *BA3::GUS* expression (Fig. 4A and B). This suggests that the aromatic A-ring of TrfA is important for this activity. The introduction of a methyl group at the *p*-position of the A-ring (**22a**) did not affect the activity, whereas the introduction of a butylether group (**22b**) caused considerable reduction of the activity (Fig. 4A and B). Conformational analysis implied that TrfA mimics auxin (Fig. 1B). NAA (**3**) is a synthetic auxin. Derivative **22c**, which has a naphthalene ring as an A-ring, was designed to mimic the NAA molecule (Figs. 1A and B). However, the inhibitory activity of **22c** was dramatically decreased. This suggests that the large naphthalene A-ring could not fit into the binding pocket of target protein. Alternatively, ^1H and ^{13}C NMR spectra of

22c showed two sets of signals from two rotational isomers due to restricted rotation of the naphthalene ring in **22c**, whereas there is free rotation between the phenyl ring and the hydroxyl group in TrfA. Therefore, derivative **22c** would not be able to adopt the conformation required between the A-ring and the hydroxyl group to enable binding to the target protein. These results indicate it would be impossible to introduce the biotin-tagged linker at the phenyl A-ring without loss of the original activity of TrfA.

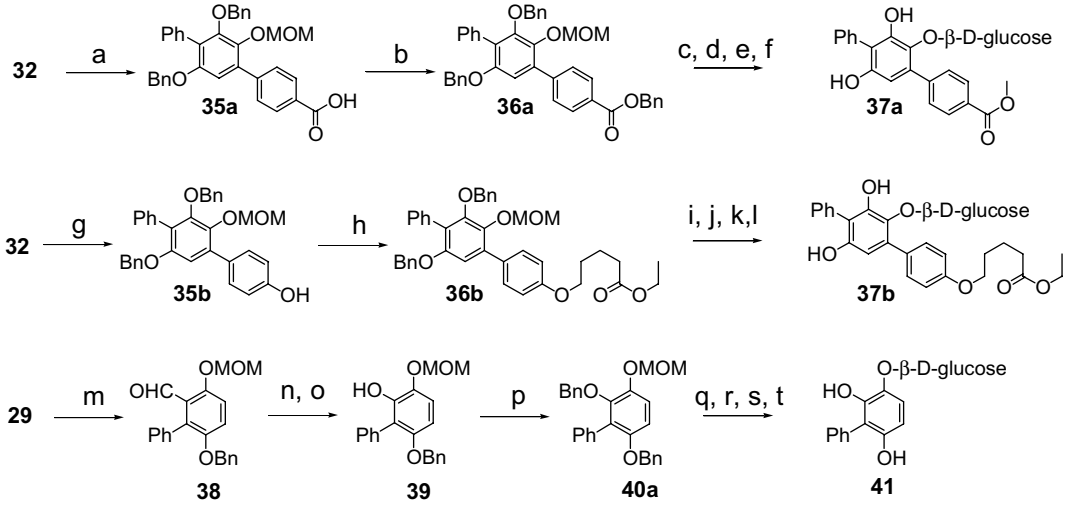
2.3. The structure activity–relationships of the phenyl C-ring in TrfA

To address the role of the C-ring of TrfA in the inhibitory activity, C-ring-substituted TrfA derivatives were synthesized (Schemes 3 and 4). 2,5-Dihydroxybenzaldehyde (**13**) was brominated[15] and then protected with benzyl groups to afford aldehyde (**27**). This aldehyde was coupled with phenyl boronic acid by Suzuki coupling to give a biphenyl (**28**). The selective deprotection of the benzyl group, followed by bromination, yielded biphenyl aldehyde (**30**). Aldehyde (**30**) was protected by the MOM group, and then converted to the key intermediate (**32**) by Baeyer–Villiger oxidation and alkaline hydrolysis, followed by protection with a benzyl group. Suzuki coupling of **32** with the corresponding boronic acids (Fig. 4A) gave terphenyls (**33a–b** and **35a–b**). The deprotection and glycosylation of terphenyls (**33a–b** and **36a–b**) were performed via essentially the same procedures described above to yield C-ring-substituted TrfA derivatives (**34a–b** and **37a–b**). Biphenyl TrfA derivative (**41**) was synthesized from intermediate (**29**) by the same procedures as used for **34a** (Scheme 4).

Biphenyl derivative **41**, which lacks a phenyl C-ring, was completely inactive (Fig. 4A and B). On the other hand, biphenyl **34b** with a methyl group instead of a phenyl C-ring exhibited inhibitory activity to the same extent as TrfA. These results suggest that the aromatic C-ring is not essential for activity but the C1 chain (methyl group), at least, is required for activity. It is possible that the methyl group in **34b** might contribute to hold **34b** in the binding site of the target protein. Derivative **34a** (4-



Scheme 3. Reagents and conditions: (a) Br_2, $CHCl_3$, rt, 3 h; (b) BnBr, K_2CO_3, reflux, 4 h; (c) $PhB(OH)_2$, $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME/EtOH = 5:1, reflux, 2 h; (d) MgBr, benzene/Et_2O = 7:1, reflux, 4 h; (e) Br_2, AcONa, AcOH, rt, 3 h; (f) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, 6 h; (g) *m*-CPBA, CH_2Cl_2, 0 °C–rt, 24 h; (h) KOH, MeOH, rt, 1 h; (i) BnBr, K_2CO_3, CH_3CN, reflux, 1 h; (j) R-$B(OH)_2$, $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME/EtOH = 5:1, reflux, 3 h; (k) AcCl, MeOH, 0 °C–rt, 2 h; (l) Cs_2CO_3, acetobromo-α-D-glucose, CH_3CN, rt, 24 h; (m) 10% Pd/C, H_2, EtOAc, rt, 12 h; (n) KOH, MeOH, rt, 1 h.



Scheme 4. Reagents and conditions: (a) 4-carboxy-$PhB(OH)_2$, $Pd(PPh_3)_4$ 2 M NaOH aq, DME/EtOH = 5:1, reflux, 3 h; (b) BnBr, K_2CO_3, CH_3CN, reflux, 1 h; (c) TFA, CH_2Cl_2, rt, 2 h; (d) Cs_2CO_3, acetobromo-α-D-glucose, CH_3CN, rt, 24 h; (e) 10% Pd/C, H_2, EtOAc, rt, 9 h; (f) AcCl, MeOH, 0 °C–rt, 2 h; (g) 4-hydroxy-$PhB(OH)_2$, $Pd(PPh_3)_4$ 2 M NaOH aq, DME/EtOH = 5:1, reflux, 2 h; (h) 5-bromo-valerate, K_2CO_3, CH_3CN, reflux, 6 h; (i) TFA, CH_2Cl_2, rt, 1 h; (j) same as d; (k) 10% Pd/C, H_2, EtOAc, rt, 6 h; (l) KOH, MeOH, rt, 1 h; (m) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, 3 h; (n) *m*-CPBA, CH_2Cl_2, 0 °C–rt, 8 h; (o) same as l; (p) BnBr, K_2CO_3, reflux, 2 h; (q) AcCl, MeOH, 0 °C–rt, 1 h; (r) same as d; (s) same as k; (t) same as l.

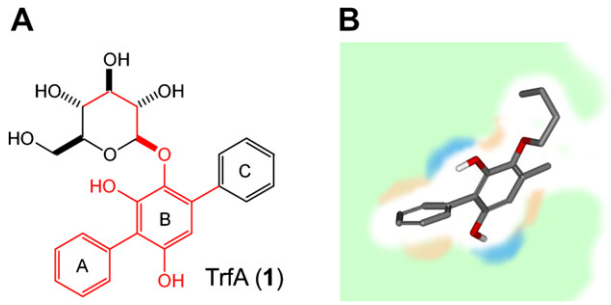


Figure 5. (A) Active core structure of terfestatin A (**1**). (B) Proposed binding model of active core structure of **1** to the target protein.

butoxyphenyl as a C-ring) had almost the same activity as TrfA, in contrast to **22b** (4-butoxyphenyl as an A-ring). Consistent with the model, the C-ring would be located outside of the binding site in the target protein (Fig. 1B). To design an active biotin-tagged TrfA affinity probe for the identification of target proteins, derivatives **37a** and **37b** would be useful intermediates to link to a biotin-tagged probe. As expected, derivatives **37a** and **37b** showed potent activity similar to that of TrfA. Therefore, the introduction of a biotin linker would be possible at the *o*-position on the phenyl C-ring without loss of activity.

3. Conclusions

The binding model of TrfA was proposed based on the structure–activity study of TrfA. To find active core structure, 25 derivatives of TrfA were synthesized and evaluated with regard to inhibitory activity against auxin-responsive gene expression. We identified the essential active core structure of TrfA as 3-butoxy-4-methylbiphenyl-2,6-diol (Fig. 5A). The results of structure–activity relationships propose the binding model of essential active core structure to the target protein as shown in our model (Fig. 5B). In our proposed model, A- and B-rings of TrfA are recognized in binding pocket of target protein. On the other hand, C-ring would not be recognized by target protein and the sugar moiety is not essential for the binding of TrfA. In addition, we demonstrated that **37a** and **37b**, key intermediates for biotin-tagged TrfA, maintain the original activity of TrfA. In a future study, these results will enable us to design biotin-tagged TrfA or solid support-linked TrfA for affinity chromatography of the target protein.

4. Experimental

4.1. Biological assay

4.1.1. Hormone induction. Arabidopsis transgenic *BA3::GUS* line was used in this assay.[12] The seedlings (n = 10–15) were grown vertically for 5 days in continuous light. They were transferred to a 12-well micro-titer plate containing 1 mL of a germination medium (GM, 0.5× Murashige and Skoog salts (Gibco BRL, Gaithersburg, MD), 1% sucrose, 1× B5 vitamins, and 0.2 g/L 2-(4-morpholino)-ethane sulfonic acid (MES), pH 5.8) containing the indicated hormone and/or chemicals and then incubated for the indicated time to induce each responsive gene.

4.1.2. Histochemical and quantitative measurements of GUS reporter activity. For GUS histochemical analysis, the *BA3::GUS* seedlings were washed with a GUS-staining buffer (100 mM sodium phosphate, pH 7.0, 10 mM EDTA, 0.5 mM $K_4Fe(CN)_6$, 0.5 mM $K_3Fe(CN)_6$, and 0.1% Triton X-100) and transferred to GUS-staining buffer containing 1 mM 5-bromo-4-chloro-3-indolyl β-D-glucuronide (X-Gluc), the substrate for histochemical staining. They were then incubated at 37 °C until sufficient staining developed (3–4 h). For quantitative measurement, the excised roots after reporter gene induction (n = 15–20) were homogenized in an extraction buffer as previously described.[12] After centrifugation to remove cell debris, GUS activity was measured using 1 mM 4-methyl umbelliferyl β-D-glucuronide as a fluorogenic substrate at 37 °C. The protein concentration was determined by Bradford protein assay (Bio-Rad Japan, Japan). The experiments were repeated at least three times with three replications.

4.2. General experimental conditions

All melting points were measured on a melting-point apparatus (Gallenkamp, UK) and are uncorrected. Optical rotations were measured with a SEPT-200 polarimeter (Horiba, Japan). IR spectra on a model 1720 spectrometer (Horiba). ^1H and ^{13}C NMR spectra were recorded on a JEOL lambda 500 NMR spectrometer (JEOL, Japan) or Bruker ARX 400 NMR spectrometer (Bruker, Germany). Chemical shifts are shown as δ values from TMS as the internal reference. Peak multiplicities are quoted in Hz. ^{13}C NMR data of compounds are listed in Supplemental data. Mass spectra were measured on a JMS-700 spectrometer (JEOL, Japan). Column chromatography was carried out on columns of silica gel 60 (230–400 mesh, Merck, Japan) and ODS gel (ODS DM1020T, Fuji Silysia Chemical, Japan).

4.3. Modification of phenolic hydroxyl in TrfA (1a, 1b, and 9)

4.3.1. 2′,3′-Dihydroxy-5′-methoxy-*p*-terphenyl 2′-β-D-glucoside (1a). The synthetic procedure of **1a** was essentially same as described in Yamazoe et al.[10] The synthetic procedures, yields, physico-chemical and spectroscopic data of **1a** were described in Supporting information.

4.3.2. 2′,5′-Dihydroxy-3′-methoxy-*p*-terphenyl 2′-β-D-glucoside (1b). The synthetic procedure of **1b** was essentially same as described in Yamazoe et al.[10] The synthetic procedures, yields, physico-chemical and spectroscopic data of **1b** were described in Supporting information.

4.3.3. 2′,5′-Dihydroxy-*p*-terphenyl (6a). To a suspension of **5** (200 mg, 0.77 mmol) in MeOH (5.0 mL) was added sodium borohydride (116 mg, 3.1 mmol), the mixture

was stirred for 1 h at room temperature. The resulting solution was added into water (100 mL), and then extracted with EtOAc (3× 100 mL). The organic layer was washed with saturated NH_4Cl solution and brine. After drying over Na_2SO_4, the layer was concentrated in vacuo. The residue was purified by a silica gel column chromatography with hexane/EtOAc (7:3) to give **6a** (141 mg, yield 70%) as a white powder; ^{1}H NMR (400 MHz, acetone-d_6/CD_3OD = 1:1): δ 7.64–7.61 (m, 4H), 7.41–7.37 (m, 4H), 7.30–7.26 (m, 2H), 6.90 (s, 2H); HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{18}H_{14}O_2$: 262.0994. Found: 262.0973.

4.3.4. 2′-Acetoxy-5′-hydroxy-*p*-terphenyl (7). To a solution of **6a** (100 mg, 0.38 mmol) in CH_2Cl_2 (5.0 mL) were added acetic anhydride (84 μL, 0.76 mmol) and 4-dimethylaminopyridine (93 mg, 0.76 mmol). The mixture was stirred for 1 h at room temperature. The resulting solution was added into water (50 mL) and extracted with EtOAc (3× 50 mL). The organic layer was washed successively with saturated Na_2CO_3 solution, saturated NH_4Cl solution, and brine. After drying over Na_2SO_4, the solvent was removed in vacuo. The residue was purified by a silica gel column chromatography with hexane/EtOAc (4:1) to give the intermediate, 2′,5′-diacetoxy-*p*-terphenyl **6b** (123 mg, yield 93%) as a yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.45 (m, 4H), 7.43–7.39 (m, 4H), 7.37–7.23 (m, 2H), 7.20 (s, 2H), 2.08 (s, 6H); HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{22}H_{18}O_4$: 346.1205. Found: 346.1211.

To a suspension of **6b** (100 mg, 0.29 mmol) in MeOH (5.0 mL) was added potassium hydroxide (18 mg, 0.32 mmol) at −18 °C and, the mixture was stirred for 30 min at −18 °C. The resulting solution was added to 1 N HCl (50 mL), and extracted with EtOAc (3× 50 mL). The organic layer was washed with saturated Na_2CO_3 solution and saturated NH_4Cl solution. After drying over Na_2SO_4, the solvent was removed in vacuo. The residue was purified by a silica gel column chromatography with hexane/EtOAc (3:1) to give **7** (72 mg, yield 81%) as a white powder: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.50 (m, 4H), 7.47–7.33 (m, 6H), 6.91 (s, 2H), 5.26 (s, 1H, OH), 2.08 (s, 3H); Anal. Calcd for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30. Found: C, 79.11; H, 5.41; HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{20}H_{16}O_3$: 304.1099. Found: 304.1073.

4.3.5. 2′,5′-Dihydroxy-*p*-terphenyl 2′-β-D-glucoside (9). The glycosylation of **7** was performed by essentially the same procedure as previously described.[10] Cesium carbonate (107 mg, 0.32 mmol: 2 equiv) and acetobromo-α-D-glucose (200 mg, 0.48 mmol: 3 equiv) were added to a solution of **7** (50 mg, 0.16 mmol) in CH_3CN (5.0 mL). The mixture was stirred for 24 h at room temperature. The resulting solution was added into water (100 mL) and extracted with EtOAc (3× 100 mL). The organic layer was washed with saturated NH_4Cl solution and brine. The solvent was removed in vacuo after drying over Na_2SO_4. The residue was purified by a silica gel column chromatography with hexane/EtOAc (3:2) and ODS column chromatography with MeOH/H_2O (9:1) to give 5′-acetoxy-2′-hydroxy-*p*-terphenyl 2′-β-D-tetraacetylglucoside **8** (82 mg, yield 79%) as a white powder: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, 2H, J = 7.5 Hz), 7.46–7.42 (m, 3H), 7.41–7.32 (m, 5H), 7.28 (s, 1H), 7.13, (s, 1H), 5.19–5.15 (m, 2H), 5.10–5.06 (m, 1H), 5.02–5.00 (m, 1H), 4.15 (d, 1H, *J* = 4.3 Hz), 3.85 (quint, 1H, *J* = 4.8 Hz), 2.11 (s, 3H), 2.02 (s, 3H), 1.96 (s, 3H), 1.74 (s, 3H), 1.53 (s, 3H); Anal. Calcd for $C_{34}H_{34}O_{12}$: C, 64.35; H, 5.40. Found: C, 64.18; H, 5.63; HR-FABMS: *m/z* $[M+Na]^+$; Calcd for $C_{34}H_{34}O_{12}Na$: 657.1948. Found: 657.1929.

Compound **8** (50 mg, 79 μmol) was hydrolyzed by MeOH solution of KOH (31 mg, 0.55 mmol, in 5 mL MeOH) for 1 h at room temperature. The resulting solution was added to 1 N HCl, (25 mL) and extracted with EtOAc (3× 25 mL). The organic layer was washed with saturated NH_4Cl solution and brine. The solvent was removed in vacuo after drying over Na_2SO_4. The residue was purified by a silica gel column chromatography with $CHCl_3$/MeOH (4:1) to give **9** (30 mg, yield 90%) as a pale yellow powder: mp 103–104 °C; $[\alpha]_D^{25}$ +47.2° (*c* 0.1, MeOH); IR (KBr): ν_{max} 3379, 2923, 2853, 1600, 1483, 1404, 1262, 1190, 1072, 828, 701 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ 7.65–7.62 (m, 4H), 7.41–7.37 (m, 4H), 7.31–7.28 (m, 2H), 7.26 (s, 1H), 6.88 (s, 1H), 4.92 (d, 1H, *J* = 7.24 Hz), 3.84 (d, 1H, *J* = 11.6 Hz), 3.66 (dd, 1 H, *J* = 12.0, 5.0 Hz), 3.43–3.30 (m, 3H); HR-FABMS: *m/z* $[M+Na]^+$; Calcd for $C_{24}H_{24}O_7Na$: 447.1420. Found: 447.1415.

4.4. General method for the synthesis of 2′-alkyl ether derivatives (12a–k)

3′,5′-Dibenzyloxy-2′-hydroxy-*p*-terphenyl (**10**) was prepared as previously described.[13] To a solution of **10** (50 mg, 0.11 mmol) in THF (5.0 mL) were added alkyl halide (0.22 mmol), *tert*-butyl ammonium iodide (81 mg, 0.22 mmol) and sodium hydride (5 mg, 0.22 mmol), and then stirred for 24 h at room temperature. The resulting solution was added to water (50 mL) and extracted with EtOAc (3× 50 mL). The organic layer was washed with saturated NH_4Cl solution and brine and then dried over Na_2SO_4. After removal of solvent in vacuo, the residue was purified by a silica gel column chromatography to give **11a**–**k**. Compounds **11a**–**k** in EtOAc (4.0 mL) were hydrogenolyzed by H_2 (1 atm) and catalytic amounts of 10% Pd/C at room temperature for 24 h to yield compounds **12a**–**k**, respectively. The yields, physico-chemical and spectroscopic data of compounds **12a**–**k** were described in Supporting information.

4.5. Synthesis of A-ring-substituted derivatives (22a–d and 25)

4.5.1. 2,5-Dibenzyloxybenzaldehyde (14). To a suspension of **13** (3.00 g, 21.7 mmol) in CH_3CN (130 mL), benzyl bromide (6.40 mL, 54.4 mmol) and potassium carbonate (7.50 g, 54.4 mmol) were added. The mixture was refluxed for 4 h. After cooling at room temperature, the resulting solution was added to water (500 mL), and extracted with EtOAc (3× 500 mL). The organic layer was washed with saturated NH_4Cl solution and brine,

and then dried over Na_2SO_4. After concentration of the EtOAc layer in vacuo, the residue was purified by a silica gel column chromatography with hexane/EtOAc (9:1) to give **14** (6.01 g, yield 87%) as a pale yellow crystal: mp 88–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.05 (s, 1H), 7.44–7.16 (m, 10H), 7.17 (dd, 1H, J = 9.1, 3.3 Hz), 6.97 (d, 1H, J = 9.1 Hz), 5.12 (s, 2H), 5.02 (s, 2H); Anal. Calcd for $C_{21}H_{18}O_3$: C, 79.22; H, 5.70. Found: C, 79.12; H, 5.56; HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{21}H_{18}O_3$: 318.1252. Found: 318.1262.

4.5.2. 5-Benzyloxy-2-hydroxybenzaldehyde (15). Selective removal of 2-benzyl group of **14** was performed as previously described.[13] To a suspension of **14** (6.00 g, 18.9 mmol) in benzene/diethyl ether (7:1, 130 mL) was added magnesium bromide (4.17 g, 22.64 mmol), the mixture was refluxed for 8 h. After cooling at room temperature, to the resulting solution was added 1 N HCl, and extracted with EtOAc. The organic layer was washed with saturated Na_2CO_3 solution and brine. The solvent was removed in vacuo after drying over Na_2SO_4. The residue was purified by a silica gel column chromatography with hexane/EtOAc (9:1) to give **16** (3.62 g, yield 84%) as a yellow powder: mp 85–87 °C; IR (KBr): ν 3105, 2930, 2852, 1664, 1618, 1589, 1485, 1387, 1271, 1158, 1019 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.67 (s, 1H), 9.80 (s, 1H), 7.43–7.37 (m, 4H), 7.35–7.32 (m, 1H), 7.21 (dd, 1H, J = 9.2, 3.1 Hz), 7.05 (d, 1H, J = 3.1 Hz), 6.92 (d, 1H, J = 9.1 Hz), 5.04 (s, 1H); HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{14}H_{12}O_3$: 228.0786. Found: 228.0775.

4.5.3. 5-Benzyloxy-3-bromo-2-hydroxybenzaldehyde (16). To a solution of **15** (3.50 g, 15.4 mmol) in acetic acid (100 mL) were added sodium acetate (1.89 g, 23.0 mmol) and bromine (0.60 mL, 23.0 mmol), the mixture was stirred for 3 h at room temperature. 5% $Na_2S_2O_3$ solution (300 mL) was added to the reaction solution and then extracted with EtOAc (3× 300 mL). The organic layer was washed with 5% $Na_2S_2O_3$ solution, saturated Na_2CO_3 solution, and brine. The organic layer was dried over Na_2SO_4 and then concentrated in vacuo. The residue was purified by a silica gel column chromatography with hexane/EtOAc (4:1) to give **15** (4.35 g, yield 93%) as a yellow powder: mp 92–93 °C; IR (KBr): ν 3087, 3060, 2898, 2864, 1649, 1613, 1450, 1269, 1132, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.15 (s, 1H), 9.77 (s, 1H), 7.49 (d, 1H, J = 2.7 Hz), 7.41–7.38 (m, 4H), 7.37–7.34 (m, 1H), 7.08 (d, 1H, J = 3.1Hz), 5.05 (s, 1H); Anal. Calcd for $C_{14}H_{11}O_3Br$: C, 54.75; H, 3.61. Found: C, 54.88; H, 3.79; HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{14}H_{11}O_3{}^{79}Br$ and $C_{14}H_{11}O_3{}^{81}Br$: 305.9892 and 307.9873. Found: 305.9889 and 307.9842.

4.5.4. 5-Benzyloxy-3-bromo-2-methoxymethoxybenzaldehyde (17). To a solution of **16** (4.30 g, 14.1 mmol) in CH_2Cl_2 (100 mL) were added chloromethyl methyl ether (1.58 mL, 21.2 mmol) and *N*-ethyl diisopropylamine (4.85 mL, 28.2 mmol), the mixture was stirred for 6 h at room temperature. The resulting solution was washed with saturated NH_4Cl solution and extracted with CH_2Cl_2 (3× 300 mL). The organic layer was dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by a silica gel column chromatography with $CHCl_3$ to give **17** (4.78 g, yield 97%) as a pale yellow powder: mp 61–63 °C; IR (KBr): ν 3068, 2990, 2942, 1689, 1592, 1453, 1380, 1309, 1226, 1158, 1023 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.27 (s, 1H), 7.47 (d, 1H, J = 3.1 Hz), 7.41–7.33 (m, 6H), 5.12 (s, 1H), 5.04 (s, 1H), 3.59 (s, 3H); HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{16}H_{15}O_4{}^{79}Br$ and $C_{16}H_{15}O_4{}^{81}Br$: 350.0154 and 352.0135. Found: 350.0163 and 352.0144.

4.5.5. 5-Benzyloxy-2-methoxymethoxy-biphenyl-3-carbaldehyde (18a). To a solution of **17** (4.70 g, 13.4 mmol) in DME/EtOH (5:1, 75 mL) were added phenyl boronic acid (3.28 g, 26.9 mmol), tetrakis (triphenylphosphine)-palladium (0) (776 mg, 0.67 mmol) and 2 M Na_2CO_3 solution (30 mL), the mixture was refluxed for 3 h. After cooling at room temperature, the reaction solution was filtered on the ceilte, and added to 1N HCl (300 mL), and then extracted with EtOAc (3× 300 mL). The organic layer was washed with saturated Na_2CO_3 solution and brine. The organic layer was dried over $Na_2SO_4$and concentratedin vacuo. The residue was purified by a silica gel column chromatography with $CHCl_3$ to give **18a** (4.53 g, yield 97%) as a pale yellow powder: mp 56–58 °C; IR (KBr): ν 2947, 2876, 1681, 1596, 1496, 1376, 1326, 1221, 1023 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.41 (s, 1H), 7.49 (d, 2H, J = 7.0 Hz), 7.40-7.37 (m, 5H), 7.35–7.31 (m, 3H), 7.29–7.26 (m, 1H), 7.23 (d, 1H, J = 5.4 Hz); Anal. Calcd for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.86; H, 5.98; HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{22}H_{20}O_4$: 348.1362. Found: 348.1379.

4.5.6. 5-Benzyloxy-4-bromo-2-methoxymethoxy-biphenyl-3-carbaldehyde (19a). To a solution of **18a** (4.50 g, 12.9 mmol) in acetic acid (100 mL) were added sodium acetate (1.59 g, 19.4 mmol) and bromine (0.50 mL, 19.4 mmol), the mixture was stirred for 6 h at 50 °C. The solution was added to 5% $Na_2S_2O_3$ solution (300 mL), and then extracted with EtOAc (3× 300 mL). The organic layer was washed with saturated Na_2CO_3 solution and brine. The EtOAc layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by a silica gel column chromatography with hexane/EtOAc (4:1) to give a 5-benzyloxy-4-bromo-2-hydroxy-biphenyl-3-carbaldehyde (**18b**: 3.46 g, yield 70%) as a yellow powder: mp 99–100 °C; IR (KBr): ν 3437, 2920, 2854, 1630, 1586, 1496, 1403, 1341, 1287, 1123, 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.20 (s, 1H), 10.44 (s, 1H), 7.50–7.30 (m, 10H), 7.24 (s, 1H), 5.11 (s, 2H); HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{20}H_{15}O_3{}^{79}Br$ and $C_{20}H_{15}O_3{}^{81}Br$: 382.0205 and 384.0187. Found: 382.0189 and 384.0196.

Thereafter, to a solution of **18b** (3.40 g, 8.90 mmol) in CH_2Cl_2 (100 mL), chloromethyl methyl ether (1.0 mL, 13.4 mmol) and *N*-ethyl diisopropylamine (3.1 mL, 17.8 mmol) were added. The mixture was stirred for 6 h at room temperature. The resulting solution was added to saturated NH_4Cl solution (250 mL), and extracted with EtOAc (300 mL). The organic layer was washed with brine and concentrated in vacuo after drying over Na_2SO_4. The residue was purified by a silica gel column chromatography with $CHCl_3$ to give **19a** (3.56 g,

yield 94%) as a yellow oil: IR (KBr): ν 2935, 2890, 1701, 1576, 1496, 1375, 1239, 1157, 1123, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.42 (s, 1H), 7.49–7.46 (m, 4H), 7.44–7.35 (m, 6H), 7.13 (s, 1H), 5.18 (s, 2H), 4.65 (s, 2H), 3.05 (s, 3H); HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{22}H_{19}O_4{}^{79}Br$ and $C_{22}H_{19}O_4{}^{81}Br$: 426.0467 and 428.0449. Found: 426.0464 and 428.0462.

4.5.7. 3,5-Dibenzyloxy-4-bromo-2-methoxymethoxybiphenyl (20). 3-Chloroperoxybenzoic acid (4.25 g, 24.7 mmol) was added to a solution of **19a** (3.50 g, 8.22 mmol) in CH_2Cl_2 (100 mL) under ice cooling. The reaction mixture was kept in ice bath for 1 h and then stirred for 24 h at room temperature. The resulting solution was added to 5% $Na_2S_2O_3$ solution (300 mL) and extracted with EtOAc (3× 300 mL). The organic layer was successively washed with saturated Na_2CO_3 solution, saturated NH_4Cl solution, and brine. After drying over Na_2SO_4, solvent was removed in vacuo. The residue was suspended in methanolic KOH solution (920 mg, 16.4 mmol in 75 mL of MeOH). The suspension was stirred for 1 h at room temperature. The resulting solution was added to 1 N HCl (300 mL) and extracted with EtOAc (3× 300 mL). The EtOAc layer was washed with saturated Na_2CO_3 solution and brine. The solvent was removed in vacuo and dried over Na_2SO_4. The residue was purified by a silica gel column chromatography with hexane/EtOAc (4:1) to give 5-benzyloxy-3-hydroxy-4-bromo-2-methoxymethoxy-biphenyl (**19b**: 2.05 g, two steps yield 64%) as a yellow powder: mp 68–70 °C; IR (KBr): ν 3336, 2943, 1593, 1572, 1500, 1452, 1398, 1275, 1145, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, 2H, J = 7.0 Hz), 7.44–7.29 (m, 8H), 6.50 (s, 1H), 5.11 (s, 2H), 4.72 (s, 2H), 3.34 (s, 3H); HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{21}H_{19}O_4{}^{79}Br$ and $C_{21}H_{19}O_4{}^{81}Br$: 414.0467 and 416.0449. Found: 414.0480 and 416.0450.

To a solution of **19b** (2.00 g, 4.83 mmol) in CH_3CN (40 mL) were added benzyl bromide (0.69 mL, 5.80 mmol) and potassium carbonate (0.80 g, 5.80 mmol), the mixture was refluxed for 2 h. After cooling at room temperature, the reaction mixture was added to water (200 mL) and then extracted with EtOAc (3× 300 mL). The organic layer was washed with saturated NH_4Cl solution and dried over Na_2SO_4. After evaporation in vacuo, the residue was purified by a silica gel column chromatography with hexane/EtOAc (9:1) to give **20** (2.31 g, yield 95%) as a pale yellow crystal: mp 108–109 °C; IR (KBr): ν 2940, 1573, 1496, 1415, 1367, 1250, 1157, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.63–7.27 (m, 15H), 6.76 (s, 1H), 5.13 (s, 2H), 5.13 (s, 2H), 4.83 (s, 2H), 2.92 (s, 3H); Anal. Calcd for $C_{28}H_{25}O_4Br$: C, 66.54; H, 4.99. Found: C, 66.31; H, 4.68; HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{28}H_{25}O_4{}^{79}Br$ and $C_{28}H_{25}O_4{}^{81}Br$: 504.0926 and 506.0920. Found: 504.0938 and 506.0915.

4.5.8. 3′,5′-Dibenzyloxy-4″-methyl-2′-methoxymethoxy-*p*-terphenyl (21a). To a solution of **20** (61 mg, 0.12 mmol) in DME/EtOH (5:1, 4.0 mL) were added *p*-tolyl boronic acid (32 mg, 0.24 mmol), tetrakis (triphenylphosphine)-palladium(0) (7 mg, 6 μmol: 0.05 equiv) and 2 M Na_2CO_3 solution (1.5 mL), the mixture was refluxed for 3 h. After cooling at room temperature, the resulting solution was filtered on Celite and added to 1 N HCl (25 mL), and extracted with EtOAc (3× 25 mL). The organic layer was washed with saturated Na_2CO_3 solution and brine. After drying over Na_2SO_4, the solvent was removed in vacuo. The residue was purified by a silica gel column chromatography with hexane/EtOAc (5:1) to give **21a** (47 mg, yield 76%) as a pale yellow powder; ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, 2H, J = 7.9 Hz), 7.44–7.20 (m, 14H), 7.02–7.00 (m, 2H), 6.80 (s, 1H), 4.99 (s, 2H), 4.73 (s, 2H), 4.73 (s, 2H), 2.92 (s, 3H), 2.42 (s, 3H); HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{35}H_{32}O_4$: 516.2301. Found: 516.2287.

4.5.9. 2′,3′,5′-Trihydroxy-4″-methyl-*p*-terphenyl 2′-β-D-glucoside (22a). Acetyl chloride (9.0 μL, 0.13 mmol) was added dropwise to a suspension of **21a** (44 mg, 85 μmol), in MeOH (3.0 mL) under ice cooling, and the mixture was stirred for 2 h at room temperature. The resulting solution was poured into water, and extracted with EtOAc (3× 25 mL). The organic layer was washed with saturated Na_2CO_3 solution and brine, and then dried over Na_2SO_4. After removal of solvent in vacuo, the residue was purified by a silica gel column chromatography with hexane/EtOAc (4:1) to give the intermediate 3′,5′-dibenzyloxy-2′-hydroxy-4″-methyl-*p*-terphenyl (**21e**: 40 mg, yield 99%) a pale yellow powder; ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, 2H, J = 7.7 Hz), 7.52 (d, 2H, J = 8.0 Hz), 7.42 (t, 2H, J = 7.8 Hz), 7.35–7.22 (m, 11H), 7.11–7.09 (m, 2H), 6.84 (s, 1H), 5.75 (s, 1H, OH), 4.94 (s, 2H), 4.43 (s, 2H), 2.44 (s, 3 H); HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{33}H_{28}O_3$: 472.2038. Found: 472.2044.

Thereafter, to a solution of **21e** (38 mg, 81 μmol) in CH_3CN (4.0 mL) were added acetobromo-α-D-glucose (99 mg, 0.24 mmol: 3 equiv) and cesium carbonate (52 mg, 0.16 mmol: 2 equiv), and the mixture was stirred for 24 h at room temperature. The resulting solution was added to water (20 mL), and extracted with EtOAc (3× 20 mL). The organic layer was washed with saturated NH_4Cl solution and brine. The solvent was removed in vacuo after drying over Na_2SO_4. The residue was purified by a silica column chromatography with hexane/EtOAc (3:2) and ODS column chromatography with MeOH/H_2O (9:1) to give 3′,5′-dibenzyloxy-2-hydroxy-4″-methyl-*p*-terphenyl 2′-β-D-tetraacetylglucoside (**21f**: 46 mg, yield 70%) as a pale yellow powder; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, 2H, J = 7.0 Hz), 7.41 (t, 2H, J = 7.6 Hz), 7.37–7.19 (m, 13H), 6.99–6.96 (m, 2H), 6.77 (s, 1H), 5.14 (d, 1H, J = 7.2 Hz), 5.05–4.97 (m, 5H), 4.85 (d, 1H, J = 10.7 Hz), 4.58 (d, 1H, J = 10.7 Hz), 3.96 (dd, 1H, J = 12.3, 3.5 Hz), 3.73 (dd, 1H, J = 12.3, 2.3 Hz), 3.40–3.36 (m, 1H), 2.42 (s, 3H), 1.95 (s, 6 H), 1.93 (s, 3H), 1.84 (s, 3H); HR-FABMS: *m/z* $[M+Na]^+$; Calcd for $C_{47}H_{46}O_{12}Na$: 825.2887. Found: 825.2883.

Intermediate **21f** (40 mg, 50 μmol) was hydrogenolyzed by H_2 (1 atm) and catalytic amounts of 10% Pd/C (2 mg) in EtOAc (3 mL) for 12 h at room temperature. The reaction mixture was filtered on Celite, and the fil-

trate was concentrated in vacuo. The residue without further purification was hydrolyzed by methanolic KOH solution (17 mg, 0.3 mmol: 6 equiv in 3 mL of MeOH) at room temperature for 1 h to give **22a** (18 mg, two steps yield 80%) as a pale yellow crystal: mp 145–147 °C; ^{1}H NMR (400 MHz, CD_3OD): δ 7.53 (d, 2H, J = 7.3 Hz), 7.38 (t, 2H, J = 7.3 Hz), 7.32–7.29 (m, 3H), 7.20 (d, 2H, J = 8.0 Hz), 6.38 (s, 1H), 4.28 (d, 1H, J = 7.8 Hz), 3.48 (dd, 1H, J = 11.8, 2.7 Hz), 3.40 (dd, 1H, J = 11.5, 4.9 Hz), 3.36–3.33 (m, 2H), 3.25–3.18 (m, 1H); HR-FABMS: m/z $[M+Na]^+$; Calcd for $C_{25}H_{26}O_8Na$: 477.1525. Found: 477.1513.

4.5.10. A-ring TrfA derivatives (22b–d) and the corresponding intermediates (21b–d). The synthetic procedure of **21b–d** and **22b–d** were essentially same as **21a** and **22d**, respectively. The procedures, yields, physico-chemical and spectroscopic data of c **21b–d** and **22b–d** were described in Supporting information.

4.5.11. 5-Benzyloxy-3-hydroxy-2-methoxymethoxybiphenyl (23). The same procedure described at **20** (**19a–b**) was employed with **18a** (350 mg, 1.00 mmol). With Baeyer–Villiger oxidation and alkaline hydrolysis of **18a**, the title compound **23** (306 mg, two steps yield 90%) was obtained as a yellow crystal; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, 2H, J = 7.0 Hz), 7.44–7.38 (m, 5H), 7.36–7.34 (m, 1H), 7.33–7.29 (m, 2H), 7.07 (s, 1H), 6.64 (d, 1H, J = 3.0Hz), 6.51 (d, 1H, J = 3.0 Hz), 5.02 (s, 2H), 4.68 (s, 2H), 3.42 (s, 3H); Anal. Calcd for $C_{21}H_{20}O_4$: C, 74.98; H, 5.99. Found: C, 75.13; H, 6.12; HR-EIMS: m/z $[M]^+$; Calcd for $C_{21}H_{20}O_4$: 336.1362. Found: 336.1372.

4.5.12. 3,5-Dibenzyloxy-2-methoxymethoxy-biphenyl (24a). The same procedure described at **20** (**19b–20**) was employed with **23** (250 mg, 0.74 mmol). With the introduction of benzyl group into **23**, the title compound **24a** (312 mg, yield 99%) was obtained as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, 2H, J = 7.2 Hz), 7.44–7.35 (m, 10H), 7.33–7.30 (m, 3H), 6.65 (d, 1H, J = 2.8 Hz), 6.57 (d, 1H, J = 2.8 Hz), 5.09 (s, 2H), 5.01 (s, 2H), 4.81 (s, 2H), 2.92 (s, 3H); HR-EIMS: m/z $[M]^+$; Calcd for $C_{28}H_{26}O_4$: 426.1831. Found: 426.1831.

4.5.13. 2,3,5-Trihydroxy-biphenyl 2-β-D-glucoside (25). The same procedure described at **22a** (**21a–e**) was employed with **24a** (200 mg, 0.47 mmol). With removal of methoxymethyl group in **24a**, the intermediate 3,5-dibenzyloxy-2-hydroxy-biphenyl (**24b**: 172 mg, yield 96%) was obtained as a pale yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, 2H, J = 7.5 Hz), 7.42–7.29 (m, 13H), 6.63 (d, 1H, J = 2.8 Hz), 6.60 (d, 1H, J = 2.8 Hz), 5.56 (s, 1H), 5.06 (s, 2H), 4.98 (s, 2H); HR-EIMS: m/z $[M]^+$; Calcd for $C_{26}H_{22}O_3$: 382.1569. Found: 382.1564.

Thereafter, the same procedure described at **22a** (**21e–f**) was employed with **24b** (100 mg, 0.26 mmol). With the glycosylation of **24b**, the intermediate 3,5-dibenzyloxy-2-hydroxy-biphenyl 2-β-D-tetracetylglucoside (**24c**: 114 mg, yield 61%) was obtained as a pale yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, 4H, J = 7.4 Hz), 7.43–7.30 (m, 11H), 6.64 (d, 1H, J = 2.7 Hz), 6.55 (d, 1H, J = 2.7 Hz), 5.13–4.94 (m, 7H), 3.86 (dd, 1H, J = 12.2, 4.0 Hz), 3.70 (dd, 1H, J = 12.1, 2.1 Hz), 3.36–3.32 (m, 1H), 1.95 (s, 6H), 1.95 (s, 3H), 1.73 (s, 3H); Anal. Calcd for $C_{40}H_{40}O_{12}$: C, 67.41; H, 5.66. Found: C, 67.31; H, 5.52; HR-FABMS: m/z $[M+Na]^+$; Calcd for $C_{40}H_{40}O_{12}Na$, 735.2417. Found, 735.2390.

Thereafter, the same procedure described at **22a** (**21f–22a**) was employed with **24c** (80 mg, 112 μmol). With the hydrogenolysis and alkaline hydrolysis of **24c**, the title compound **25** (32 mg, two steps yield 80%) was obtained as a pale yellow powder: mp 70–71 °C; ^{1}H NMR (400 MHz, CD_3OD): δ 7.48 (d, 2H, J = 7.6 Hz), 7.36 (t, 2H, J = 7.4 Hz), 7.29 (t, 1H, J = 7.5 Hz), 6.35 (d, 1H, J = 2.7 Hz), 6.24 (d, 1H, J = 2.7 Hz), 4.29 (d, 1H, J = 7.7 Hz), 3.50 (d, 1H, J = 14.6 Hz), 3.42 (dd, 1H, J = 11.8, 4.9 Hz), 3.34 (bs, 1H), 3.26–3.19 (m, 2H), 3.02–2.96 (m, 1H); HR-FABMS: m/z $[M+Na]^+$; Calcd for $C_{18}H_{20}O_8Na$, 387.1056. Found, 387.1061.

4.6. Synthesis of C-ring-substituted derivatives (34a and 34b)

4.6.1. 2-Bromo-3,6-dihydroxybenzaldehyde (26). To a suspension of 2,5-dihydroxybenzaldehyde (**13**: 3.00 g, 21.7 mmol) in $CHCl_3$ (150 mL) were added sodium acetate (2.67 g, 32.6 mmol) and bromine (0.84 mL, 32.6 mmol), the mixture was stirred for 3 h at room temperature. The resulting solution was added to 10% $Na_2S_2O_3$ solution (150 mL), and extracted with $CHCl_3$ (2× 100 mL). The organic layer was washed with saturated Na_2CO_3 solution and saturated NH_4Cl solution. The solvent was removed in vacuo after drying over Na_2SO_4. The residue was purified by a silica gel column chromatography with hexane/EtOAc (7:3) to give **26** (3.76 g, yield 80%) as a yellow needle crystal: mp 88–89 °C; IR (KBr): ν 3266, 2907, 2829, 1632, 1609, 1573, 1459, 1288, 1240, 1171 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.64 (s, 1H), 10.27 (s, 1H), 7.24 (d, 1H, J = 9.1 Hz), 6.91 (d, 1H, J = 9.1 Hz), 5.46 (s, 1H); Anal. Calcd for $C_7H_5O_3$ Br: C, 38.74; H, 2.32. Found: C, 38.89; H, 2.31; HR-EIMS: m/z $[M]^+$; Calcd for $C_7H_5O_3{}^{79}Br$ and $C_7H_5O_3{}^{81}Br$: 215.9422 and 217.9401. Found: 215.9423 and 217.9422.

4.6.2. 3,6-Dibenzyloxy-2-bromobenzaldehyde (27). The same procedure described at **15** was employed with **26** (3.70 g, 17.1 mmol). The title compound **27** (4.88 g, yield 72%:) was obtained as a yellow needle crystal: mp 79–80 °C; IR (KBr): ν 3029, 2900, 2869, 1682, 1563, 1496, 1376, 1265, 1159, 1011 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.44 (s, 1H), 7.43–7.32 (m, 10H), 7.00 (d, 1H, J = 9.1 Hz), 6.88 (d, 1H, J = 9.1 Hz), 5.07 (s, 4H); HR-EIMS: m/z $[M]^+$; Calcd for $C_{21}H_{17}O_3{}^{79}Br$ and $C_{21}H_{17}O_3{}^{81}Br$: 396.0361 and 398.0341. Found: 396.0373 and 398.0339.

4.6.3. 3,6-Dibenzyloxy-biphenyl-2-carbaldehyde (28). The same procedure described at **18a** was employed with **27** (4.80 g, 12.1 mmol). The title compound **28** (4.39 g, yield 92%:) was obtained as a yellow oil: IR (KBr): ν 3030, 2933, 2866, 1695, 1584, 1497, 1378, 1260, 1186, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.05 (s,

1H), 7.47–7.35 (m, 7H), 7.32–7.28 (m, 3H), 7.29–7.22 (m, 2H), 7.11–7.08 (m, 3H), 6.95 (d, 1H, $J = 9.1$ Hz), 5.14 (s, 2H), 4.89 (s, 2H); HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{27}H_{22}O_3$: 394.1569. Found: 394.1567.

4.6.4. 6-Benzyloxy-3-hydroxy-biphenyl-2-carbaldehyde (29). The same procedure described at **15** was employed with **28** (4.30 g, 10.9 mmol). The title compound **29** (2.91 g, yield 88%) was obtained as a yellow needle crystal: mp 62–64 °C; IR (KBr): *v* 3100, 2878, 1650, 1579, 1460, 1384, 1281, 1171, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.51 (s, 1H), 9.63 (s, 1H), 7.44–7.42 (m, 3H), 7.33–7.31 (m, 2H), 7.26–7.22 (m, 4H), 7.08–7.06 (m, 2H), 6.92 (d, 1H, $J = 9.1$ Hz), 4.85 (s, 2H); Anal. Calcd for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30. Found: C, 78.88; H, 5.23; HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{20}H_{16}O_3$: 304.1099. Found: 304.1089.

4.6.5. 6-Benzyloxy-4-bromo-3-hydroxy-biphenyl-2-carbaldehyde (30). The same procedure described at **16** was employed with **29** (2.80 g, 9.21 mmol). The title compound **30** (3.30 g, yield 94%:) was obtained as a yellow needle crystal: mp 123–124 °C; IR (KBr): *v* 3422, 3028, 2942, 2894, 1643, 1566, 1438, 1395, 1270, 1133, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 12.06 (s, 1H), 9.59 (s, 1H), 7.53 (s, 1H), 7.46–7.44 (m, 3H), 7.32–7.30 (m, 2H), 7.26–7.24 (m, 3H), 7.09–7.07 (m, 2H), 4.88 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 153.7, 148.4, 136.1, 135.8, 132.0, 130.9, 128.4, 128.4, 128.1, 127.9, 127.8, 127.0, 119.0, 109.8, 72.5; HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{20}H_{15}O_3{}^{79}Br$ and $C_{20}H_{15}O_3{}^{81}Br$: 382.0205 and 384.0184. Found: 382.0222 and 382.0209.

4.6.6. 6-Benzyloxy-4-bromo-3-methoxymethoxy-biphenyl-2-carbaldehyde (31a). The same procedure described at **17** was employed with **30** (3.20 g, 8.38 mmol). The title compound (3.56 g, yield 94%) was obtained as a yellow oil: IR (KBr): *v* 3031, 2928, 2830, 1699, 1650, 1563, 1497, 1453, 1372, 1253, 1129, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.76 (s, 1H), 7.43–7.40 (m, 4H), 7.29–7.25 (m, 5H), 7.14–7.12 (m, 2H), 5.14 (s, 2H), 4.98 (s, 2H), 3.62 (s, 3H); HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{22}H_{19}O_4{}^{79}Br$ and $C_{22}H_{19}O_4{}^{81}Br$: 426.0467 and 428.0446. Found: 426.0485 and 428.0439.

4.6.7. 2,6-Dibenzyloxy-4-bromo-3-methoxymethoxy-biphenyl (32). The same procedure described at **20** (**19a**–**b**) was employed with **31a** (3.40 g, 7.98 mmol). With Baeyer–Villiger oxidation and alkaline hydrolyses of **31a**, the intermediate 6-benzyloxy-4-bromo-2-hydroxy-3-methoxymethoxy-biphenyl (**31b**: 2.84 g, two steps yield 86%) was obtained as a pale yellow powder: mp 168–169 °C; IR (KBr): *v* 3298, 3032, 2940, 2830, 1605, 1573, 1476, 1395, 1277, 1155, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, 4H, $J = 4.3$ Hz), 7.37–7.31 (m, 1H), 7.27–7.22 (m, 3H), 7.16 (d, 2H, $J = 7.3$ Hz), 7.04 (s, 1H), 6.76 (s, 1H), 5.07 (s, 2H), 4.93 (s, 2H), 3.57 (s, 3H); HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{21}H_{19}O_4{}^{79}Br$ and $C_{21}H_{19}O_4{}^{81}Br$: 414.0467 and 416.0446. Found: 414.0438 and 416.0421.

Thereafter, the same procedure described at **20** (**19b**–**20**) was employed with **31b** (2.80 g, 6.76 mmol). With protection by benzyl group of **31b**, the title compound **32** (2.86 g, yield 84%) was obtained as a pale yellow oil: IR (KBr): *v* 3031, 2935, 1578, 1497, 1365, 1310, 1251, 1234, 1159, 1124, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.30 (m, 5H), 7.24–7.13 (m, 8H), 7.01 (s, 1H), 6.92–6.90 (m, 2H), 5.17 (s, 2H), 4.88 (s, 2H), 4.61 (s, 2H), 3.61 (s, 3H); Anal. Calcd for $C_{28}H_{25}O_4Br$: C, 66.54; H, 4.99. Found: C, 66.23; H, 4.63; HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{28}H_{25}O_4{}^{79}Br$ and $C_{28}H_{25}O_4{}^{81}Br$: 504.0936 and 506.0915. Found: 504.0946 and 506.0927.

4.6.8. 3′,5′-Dibenzyloxy-4-butoxy-2′-methoxymethoxy-*p*-terphenyl (33a). Compound **32** (78 mg, 0.16 mmol) was coupled with 4-buthoxyphenyl boronic acid (60 mg, 0.31 mmol) by the same procedure described at **21a** to give **33a** (69 mg, yield 78%) as a pale yellow powder; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, 2H, $J = 8.7$ Hz), 7.47 (d, 2H, $J = 7.3$ Hz), 7.41 (t, 2H, $J = 7.0$ Hz), 7.37–7.34 (m, 1H), 7.29–7.18 (m, 8H), 6.99–6.96 (m, 8H), 6.80 (s, 1H), 4.99 (s, 2H), 4.91 (s, 2H), 4.74 (s, 2H), 4.01 (t, 2H, $J = 6.5$ Hz), 3.01 (s, 3H), 1.80 (quint, 2H, $J = 6.5$ Hz), 1.52 (sext, 2H, $J = 7.4$ Hz), 1.00 (t, 3H, $J = 7.3$ Hz); HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{38}H_{38}O_5$, 574.2719. Found: 574.2733.

4.6.9. 2′,3′,5′-Trihydroxy-4-butoxy-*p*-terphenyl 2′-β-D-glucoside (34a). The same procedure described at **22a** (**21a**–**e**) was employed with **33a** (67 mg, 0.12 mmol). With deprotection of methoxymethyl group of **33a**, the intermediate, 3′,5′-dibenzyloxy-4-butoxy-2′-hydroxy-*p*-terphenyl (**33c**: 61 mg, yield 98%) was obtained as a yellow powder; ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, 2H, $J = 7.2$ Hz), 7.54 (d, 2H, $J = 8.6$ Hz), 7.45 (t, 2H, $J = 7.7$ Hz), 7.28–7.24 (m, 6H), 7.20 (d, 2H, $J = 7.3$ Hz), 7.08–7.06 (m, 2H), 6.97 (d, 2H, $J = 8.7$ Hz), 6.84 (s, 1H), 5.74 (s, 1H, OH), 4.93 (s, 2H), 4.42 (s, 2H), 4.01 (t, 2H, $J = 6.5$ Hz), 1.79 (quint, 2H, $J = 6.6$ Hz), 1.51 (sext, 2H, $J = 7.6$ Hz), 0.99 (t, 2H, $J = 7.4$ Hz); HR-EIMS: *m/z* $[M]^+$; Calcd for $C_{36}H_{34}O_4$, 530.2457. Found, 530.2460.

Thereafter, the same procedure described at **22a** (**21e**–**f**) was employed with **33c**, (60 mg, 0.11 mmol). With glycosylation of **33c**, the intermediate, 3′,5′-dibenzyloxy-4-butoxy-*p*-terphenyl-2′-yl-β-D-glucose 2,3,4,6-tetraacetate (**33d**: 80 mg, yield 82%) as a pale yellow powder; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46–7.32 (m, 7H), 7.30–7.19 (m, 8H), 6.96–6.93 (m, 4H), 6.77 (s, 1H), 5.16 (d, 1H, $J = 7.6$ Hz), 5.08–5.02 (m, 3H), 4.99 (d, 2H, $J = 5.1$ Hz), 4.86 (d, 1H, $J = 10.7$ Hz), 4.57 (d, 1H, $J = 10.7$ Hz), 4.04 (t, 2H, $J = 7.4$ Hz), 3.99 (dd, 1H, $J = 12.6$, 3.9 Hz), 3.79 (dd, 1H, $J = 12.6$, 2.4 Hz), 3.44–3.40 (m, 1H), 1.96 (s, 3H), 1.96 (s, 3H), 1.94 (s, 3H), 1.86 (s, 3H), 1.83 (quint, 2H, $J = 6.3$ Hz), 1.54 (sext, 2H, $J = 7.6$ Hz), 1.02 (t, 3H, $J = 7.3$ Hz); HR-FABMS: *m/z* $[M+Na]^+$; Calcd for $C_{50}H_{52}O_{13}Na$, 883.3306. Found, 883.3279. Thereafter, the tetraacetate **33d** (30 mg, 41 μmol) was hydrogenolyzed (H_2 [1 atm] and 10% Pd/C) and hydrolyzed (KOH in MeOH) by a similar procedure described at **22a** (**21f**–**22a**) to yield the title compound **34a** (18.6 mg, two steps yield 62%) as a pale yellow powder: mp 188–189 °C; ^1H NMR (400 MHz, CD_3OD): δ 7.46 (d, 2H, $J = 8.6$ Hz), 7.43 (d, 2H, $J = 8.3$ Hz), 7.36 (t, 2H, $J = 7.5$ Hz), 7.21 (t,

1H, J = 7.1 Hz), 6.92 (d, 2H, J = 8.5 Hz), 6.39 (s, 1H), 4.29 (d, 1H, J = 7.8 Hz), 3.99 (t, 2H, J = 6.3 Hz), 3.53 (d, 1H, J = 11.8 Hz), 3.45 (dd, 1H, J = 11.5, 4.8 Hz), 3.39–3.34 (m, 1H), 3.27–3.20 (m, 2H), 3.01–2.99 (m, 1H), 1.76 (quint, 2H, J = 7.2 Hz), 1.51 (sext, 2H, J = 7.5 Hz), 0.99 (t, 3H, J = 7.4 Hz); HR-FABMS: m/z $[M+Na]^+$; Calcd for $C_{28}H_{32}O_9Na$, 535.1944. Found, 535.1920.

4.6.10. 3,5-Dibenzyloxy-2-methoxymethoxy-4-methylbiphenyl (33b) and 2,3,5-trihydroxy-4-methylbiphenyl 2-β-D-glucoside (34b). The synthetic procedure of **33b** and **34b** was essentially same as **33a** and **34a**, respectively. The procedures, yields, physico-chemical and spectroscopic data of **33b** and **34b** were described in Supporting information.

4.7. Synthesis of B-ring-substituted derivatives (37a, 37b and 41)

4.7.1. 3′,5′-Dibenzyloxy-2′-methoxymethoxy-*p*-terphenyl-4-carboxylic acid (35a). Compound **32** (438 mg, 0.869 mmol) was coupled with 4-carboxyphenyl boronic acid (286 mg, 1.74 mmol) by the same procedure described at **21a** to give **35a** (409 mg, yield 86%) as a yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, 2H, J = 8.3 Hz), 7.72 (d, 2H, J = 8.3 Hz), 7.48–7.40 (m, 5H), 7.29–7.19 (m, 8H), 7.00–6.98 (m, 2H), 6.83 (s, 1H), 5.01 (s, 2H), 4.95 (s, 2H), 4.74 (s, 2H), 2.96 (s, 3H); HR-FABMS: m/z $[M+Na]^+$; Calcd for $C_{35}H_{30}O_6Na$, 569.1940. Found, 569.1918.

4.7.2. 3′,5′-Dibenzyloxy-2′-methoxymethoxy-*p*-terphenyl-4-carboxylic acid benzyl ester (36a). To a solution of **35a** (100 mg, 0.183 mmol) in CH_3CN (6.0 mL) were added benzyl bromide (33 μL, 0.27 mmol) and potassium carbonate (38 mg, 0.275 mmol), and the mixture was refluxed for 1 h. After cooling at room temperature, the resulting solution was added to water (50 mL), and extracted with EtOAc (3× 50 mL). The organic layer was washed with saturated NH_4Cl solution and brine. The solvent was removed in vacuo and dried over Na_2SO_4. The residue was purified by a silica gel column chromatography with hexnane/EtOAc (7:1) to give **36a** (106 mg, yield 91%) as a yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, 2 H, J = 8.4Hz), 7.66 (d, 2H, J = 8.4 Hz), 7.47–7.43 (m, 4H), 7.42–7.31 (m, 6H), 7.29–7.18 (m, 8H), 6.99–6.96 (m, 2H), 6.79 (s, 1H), 5.39 (s, 2H), 4.99 (s, 2H), 4.92 (s, 2H), 4.73 (s, 2H), 2.93 (s, 3H); HR-FABMS: m/z $[M+Na]^+$; Calcd for $C_{42}H_{36}O_6Na$, 659.2410. Found, 659.2430.

4.7.3. 3′,5′-Dibenzyloxy-2′-hydroxy-4-methoxycarbonyl-*p*-terphenyl 2′-β-D-glucoside (37a). A solution of **36a** (100 mg, 0.157 mmol) in trifluoroacetic acid (3.0 mL) was stirred for 1 h at room temperature. The resulting solution was added to saturated Na_2CO_3 solution (100 mL) and extracted with EtOAc (3× 100 mL). The organic layer was washed with saturated NH_4Cl solution and brine. The solvent was removed in vacuo after drying over Na_2SO_4. The residue was purified by a silica gel column chromatography with hexane/EtOAc (3:2) to give intermediate, 3′,5′-dibenzyloxy-2′-hydroxy-4-benzyloxycarbonyl-*p*-terphenyl **36c** (81 mg, yield 90%) as a yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, 2H, J = 8.4 Hz), 7.68 (d, 2H, J = 8.3 Hz), 7.61 (d, 2H, J = 7.7 Hz), 7.45 (q, 2H, J = 6.8 Hz), 7.41–7.32 (m, 4H), 7.30–7.24 (m, 5H), 7.23–7.19 (m, 3H), 7.08–7.05 (m, 2H), 6.85 (s, 1H), 5.84 (s, 1H, OH), 5.38 (s, 2H), 4.94 (s, 2H), 4.41 (s, 2H); HR-FABMS: m/z $[M+H]^+$; Calcd for $C_{40}H_{33}O_5$, 593.2328. Found, 593.2350.

Thereafter, to a solution of phenol **36c** (75 mg, 0.13 mmol) was added acetobromo-α-D-glucose (162 mg, 0.395 mmol) and cesium carbonate (86 mg, 0.26 mmol). The mixture was stirred for 24 h at room temperature. The resulting solution was added to water (50 mL) and extracted with EtOAc (3× 50 mL). The organic layer was washed with saturated NH_4Cl solution and brine, dried over Na_2SO_4, The solvent was removed in vacuo after drying over Na_2SO_4. The residue was purified by a silica gel column chromatography with hexane/EtOAc (3:2) to give 3′,5′-dibenzyloxy-2′-hydroxy-4-benzyloxycarbonyl-*p*-terphenyl 2′-β-D-tetraacetylglucoside (**36d**: 102 mg, yield 84%) as a pale yellow powder. This tetraacetate **36d** was hydrogenolyzed (H_2 [1 atm] and 10% Pd/C) by a similar procedure described at **22a** (**21f**–**22a**) to yield 2′,3′,5′-trihydroxy-*p*-terphenyl 4-carboxylic acid 2′-β-D-tetraacetylglucoside (**36e**) as a yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$:CD_3OD = 1:1): δ 8.08 (d, 2H, J = 8.3 Hz), 7.57 (d, 2H, J = 8.3 Hz), 7.49–7.43 (m, 4H), 7.37–7.33 (m, 1H), 6.45 (s, 1H), 5.13 (dt, 1H, J = 7.2, 2.6 Hz), 5.04 (dd, 2H, J = 7.1, 2.6 Hz), 4.65 (d, 1H, J = 7.9 Hz), 4.13 (dd, 1H, J = 12.3, 5.2 Hz), 3.97 (dd, 1H, J = 12.3, 2.4 Hz), 3.65-3.61 (m, 1H), 1.99 (s, 3H), 1.97 (s, 3H), 1.93 (s, 3H), 1.83 (s, 3H); HR-FABMS: m/z $[M+Na]^+$; Calcd for $C_{33}H_{32}O_{14}Na$, 675.1690. Found, 675.1675.

Tetraacetate **36e** was transesterified in anhydrous methanolic HCl solution (a drop of acetyl chloride into 2 mL of anhydrous MeOH) at room temperature for 2 h. The reaction mixture was added into saturated NH_4Cl solution (25 mL) and extracted with EtOAc (3× 25 mL). The solvent was removed in vacuo and then purified by a silica gel column chromatography with $CHCl_3$/MeOH (4:1) to give **37a** as a pale yellow powder (20 mg, three steps yield 65%): mp 177–178 °C; ^{1}H NMR (400 MHz, CD_3OD): δ 8.04 (d, 2H, J = 8.3 Hz), 7.66 (d, 2H, J = 8.3 Hz), 7.43 (d, 2H, J = 7.6 Hz), 7.38 (t, 2H, J = 7.4 Hz), 7.30–7.25 (m, 1H), 6.42 (s, 1H), 4.29 (d, 1H, J = 7.9 Hz), 3.92 (s, 3H), 3.46 (dd, 1H, J = 11.7, 2.9 Hz), 3.41 (dd, 1H, J = 11.7, 4.6 Hz), 3.23 (t, 1H, J = 8.5 Hz), 3.23 (m, 2H, J = 9.1 Hz), 3.02 (m, 1H); HR-FABMS: m/z $[M+Na]^+$; Calcd for $C_{26}H_{26}O_{10}Na$, 521.1424. Found, 521.1450.

4.7.4. 3′,5′-Dibenzyloxy-2′-methoxymethoxy-*p*-terphenyl-4-ol (35b). The same procedure described at **21a** was employed with **32** (254 mg, 0.501 mmol), 4-hydroxyphenyl boronic acid (139 mg, 1.01 mmol). The title compound **35b** (230 mg, yield 88%) was obtained as a yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49–7.16 (m, 7H), 7.25–7.15 (m, 8H), 6.98–6.96 (m, 2H), 6.84 (d, 2H, J = 8.5 Hz), 6.78 (s, 1H), 4.93 (s, 2H), 4.93 (s, 2H), 4.73 (s, 2H), 3.04 (s, 3H); HR-EIMS: m/z $[M]^+$; Calcd for $C_{34}H_{30}O_5$: 518.2093. Found: 518.2090.

4.7.5. 3′,5′-Dibenzyloxy-2′-methoxymethoxy-*p*-terphenyl-4-yloxy-pentanoic acid ethyl ester (36b). To a solution of **35b** (150 mg, 0.19 mmol) in CH_3CN (8.0 mL) was added ethyl 5-bromo-valerate (60 μL, 0.38 mmol) and potassium carbonate (52 mg, 0.38 mmol), and the mixture was refluxed for 4 h. After cooling at room temperature, the resulting solution was added to water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl solution and brine. After drying over Na_2SO_4, the solvent was removed in vacuo. The residue was purified by a silica gel column chromatography with hexane/EtOAc (7:3) to give **36b** (178 mg, yield 95%) as a pale yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, 2H, J = 8.6 Hz), 7.47 (d, 2H, J = 8.6 Hz), 7.41 (t, 2H, J = 6.9 Hz), 7.38–7.34 (m, 1H), 7.30–7.18 (m, 8H), 6.99–6.97 (m, 2H), 6.96 (d, 2H, J = 8.6 Hz), 6.80 (s, 1H), 4.99 (s, 2H), 4.91 (s, 2H), 4.74 (s, 2H), 4.15 (q, 2H, J = 7.1 Hz), 4.03–4.01 (m, 2H), 3.02 (s, 3H), 2.42–2.39 (m, 2H), 1.87–1.85 (m, 4H), 1.27 (t, 3H, J = 7.1 Hz); HR-FABMS: m/z $[M+Na]^+$; Calcd for $C_{41}H_{42}O_7Na$, 669.2828. Found, 669.2826.

4.7.6. 2′,3′,5′-Trihydroxy-*p*-terphenyl-4-yloxy-pentanoic acid ethyl ester 2′-β-D-glucoside (37b). The same procedure described at **37a** (**36a**–**c**) was employed with **36b** (151 mg, 234 μmol). The intermediate, 5′-dibenzyloxy-2′hydroxy-*p*-terphenyl-4-yloxy-pentanoic acid ethyl ester (**36f**: 113 mg, yield 80%) was obtained as a yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, 2H, J = 7.2 Hz), 7.54 (d, 2H, J = 8.7 Hz), 7.47 (t, 2H, J = 7.7 Hz), 7.40–7.36 (m, 1H), 7.28–7.23 (m, 6H), 7.20 (d, 2H, J = 7.9 Hz), 7.08–7.05 (m, 2H), 6.96 (d, 2H, J = 8.8 Hz), 6.84 (s, 1H), 5.77 (s, 1H, OH), 4.93 (s, 2H), 4.42 (s, 2H), 4.14 (q, 2H, J = 7.1 Hz), 4.03–4.00 (m, 2H), 2.41–2.38 (m, 2H), 1.86–1.83 (m, 4H), 1.26 (t, 3H, J = 7.1 Hz); HR-FABMS: m/z $[M+Na]^+$; Calcd for $C_{39}H_{38}O_6Na$, 625.2566. Found, 625.2557.

Thereafter, phenol **36f** (111 mg, 184 μmol) was glycosylated by the same procedure at **37a** (**36c**–**d**) to give 3′,5′-dihydroxy-*p*-terphenyl-4-yloxy-pentanoic acid ethyl ester-2′-*O*-β-D-tetraacetyl glucoside (**36g**: 148 mg, yield 86%) as a pale yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.34 (m, 7H), 7.30–7.18 (m, 8H), 6.96–6.94 (m, 2H), 6.93 (d, 2H, J = 8.7 Hz), 5.17 (d, 1H, J = 7.2 Hz), 5.08–5.05 (m, 3H), 5.00 (d, 2H, J = 5.1 Hz), 4.85 (d, 1H, J = 10.6 Hz), 4.57 (d, 1H, J = 10.6 Hz), 4.16 (q, 2H, J = 7.1 Hz), 4.05 (br s, 2H), 3.98 (dd, 1H, J = 12.3, 3.8 Hz), 3.78 (dd, 1H, J = 12.3, 2.3 Hz), 3.44–3.40 (m, 1H), 2.44–2.41 (m, 2H), 1.96 (s, 6H), 1.93 (s, 3H), 1.89–1.88 (m, 4H), 1.87 (s, 3H), 1.28 (t, 3H, J = 7.3 Hz); HR-FABMS: m/z $[M+Na]^+$; Calcd for $C_{53}H_{56}O_{15}Na$, 955.3517. Found, 955.3516.

Compound **36 g** (148 mg, 155 μmol) was hydrogenolyzed (H_2 (1 atm) and 10% Pd/C) and hydrolyzed (KOH in MeOH) at 0 °C by the same procedure described at **22a** (**21f**–**22a**) to yield the title compound **37b** (20 mg, two steps yield 22%) as a yellow powder: mp 98.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, 2H, J = 8.7 Hz), 7.42 (d, 2H, J = 6.9 Hz), 7.37 (t, 2H, J = 7.5 Hz), 7.27 (t, 1H, J = 7.2 Hz), 6.94 (d, 2H, J = 8.6 Hz), 6.37 (s, 1H), 4.29 (d, 1H, J = 7.9 Hz), 4.13 (q, 2H, J = 7.1 Hz), 4.03 (br. s, 2H), 3.53 (dd, 1H, J = 11.8, 2.6 Hz), 3.45 (dd, 1H, J = 11.8, 5.0 Hz), 3.37–3.35 (m, 1H), 3.28–3.20 (m, 2H), 3.03–2.99 (m, 1H), 2.45–2.40 (m, 2H), 1.83–1.81 (m, 4H), 1.26 (t, 3H, J = 7.1 Hz); HR-FABMS: m/z $[M+Na]^+$; Calcd for $C_{31}H_{36}O_{11}Na$, 607.2155. Found, 607.2162.

4.7.7. 6-Benzyloxy-3-methoxymethoxy-biphenyl-2-carbaldehyde (38). Compound **29** (300 mg, 0.987 mmol) was protected by methoxymethyl group as described at **17** to give the title compound **38** (316 mg, yield 92%) as a yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (s, 1H), 7.45–7.39 (m, 3H), 7.31–7.24 (m, 5H), 7.19–7.11 (m, 4H), 5.23 (s, 2H), 4.94 (s, 2H), 3.53 (s, 3H); HR-EIMS: m/z $[M]^+$; Calcd for $C_{22}H_{20}O_4$: 348.1362. Found: 348.1370.

4.7.8. 6-Benzyloxy-2-hydroxy-3-methoxymethoxy-biphenyl (39). The same procedure was employed at **20** (**19a**–**b**) with **38** (302 mg, 0.868 mmol). With Baeyer–Villiger oxidation and alkaline hydrolyses of **38**, the title compound **39** (262 mg, two steps yield 90%) was obtained as a yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49–7.42 (m, 4H), 7.37–7.33 (m, 1H), 7.29–7.18 (m, 5H), 7.01 (d, 1H, J = 8.8 Hz), 6.49 (d, 1H, J = 8.8 Hz), 5.98 (s, 1H, OH), 5.16 (s, 2H), 4.94 (s, 2H), 3.53 (s, 3H); HR-EIMS: m/z $[M]^+$; Calcd for $C_{21}H_{20}O_4$: 336.1362. Found: 336.1366.

4.7.9. 2,6-Dibenzyloxy-3-methoxymethoxy-biphenyl (40a). The same procedure was employed at **20** (**19b**–**20**) with **39** (252 mg, 0.751 mmol). With protection by benzyl group of **39**, the title compound **40a** (259 mg, yield 80%), was obtained as a yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.33 (m, 5H), 7.30–7.17 (m, 8H), 7.09 (d, 1H, J = 9.1Hz), 7.00–6.97 (m, 2H), 6.73 (d, 1H, J = 9.1 Hz), 5.16 (s, 2H), 4.94 (s, 2H), 4.67 (s, 2H), 3.53 (s, 3H); HR-EIMS: m/z $[M]^+$; Calcd for $C_{28}H_{26}O_4$: 426.1831. Found: 426.1832.

4.7.10. 2,6-Dibenzyloxy-biphenyl-3-ol 3-β-D-glucoside (41). The same procedure was employed at **22a** (**21a**–**e**) with **40a** (200 mg, 0.469 mmol). With the removal of methoxymethyl group of **40a**, the intermediate, 2,6-dibenzyloxy-3-hydroxy-biphenyl **40b** (158 mg, yield 88%) was obtained as a pale yellow powder: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, 2H, J = 7.6 Hz), 7.46 (t, 2H, J = 7.3 Hz), 7.39 (t, 1H, J = 7.2 Hz), 7.30–7.22 (m, 6H), 7.18 (br d, 2H, J = 6.8 Hz), 7.07–7.05 (m, 2H), 6.87 (d, 1H, J = 8.9 Hz), 6.74 (d, 1H, J = 8.9 Hz), 5.42 (s, 1H, OH), 4.90 (s, 2H), 4.37 (s, 2H); HR-EIMS: m/z $[M]^+$; Calcd for $C_{26}H_{22}O_3$: 382.1569. Found: 382.1549.

Thereafter, same procedure described at **22a** (**21e**–**f**) was employed with **40b** (100 mg, 0.261 mmol). With the glycosylation of **21h**, the intermediate 2,6-dibenzyloxy-biphenyl-3-yl-β-D-glucose 2,3,4,6-tetraacetate (**40c**: 151 mg, yield 81%) was obtained as a white powder: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.35 (m, 5H), 7.30–7.21 (m, 4H), 7.18–7.14 (m, 4H), 7.09 (d, 1H, J = 9.1 Hz), 6.90–6.87 (m, 2H), 6.67 (d, 1H, J = 9.1 Hz), 5.36–5.18 (m, 4H), 5.07 (d, 1H, J = 7.7 Hz), 4.99–4.92 (m, 2H), 4.75 (d, 1H, J = 10.5 Hz), 4.52 (d, 1H,

J = 10.5 Hz), 4.31 (dd, 1H, J = 12.3, 5.1 Hz), 4.16 (dd, 1H, J = 12.3, 2.3 Hz), 3.85–3.80 (m, 1H), 2.06 (s, 3H), 2.04 (s, 6H), 2.01 (s, 3H), 1.80 (s, 3H); HR-FABMS: m/z $[M+Na]^+$; Calcd for $C_{40}H_{40}O_{12}Na$, 735.2417. Found, 735.2426.

Thereafter, the same procedure described at **22a** (**21f**–**22a**) was employed with **40c** (100 mg, 140 μmol). With the hydrogenolysis and alkaline hydrolysis of **40c**, the title compound **41** (33 mg, two steps yield 60%) was obtained as a pale yellow powder: mp 118–119 °C; ^1H NMR (400 MHz, CD_3OD): δ 7.36–7.13 (m, 4H), 7.29–7.23 (m, 1H), 7.06 (d, 1H, J = 8.8 Hz), 6.34 (d, 1H, J = 8.8 Hz), 4.60 (d, 1H, J = 7.3 Hz), 3.89 (d, 1H, J = 12.2 Hz), 3.72 (dd, 1H, J = 12.2, 4.9 Hz), 3.47–3.34 (m, 4H); HR-FABMS: m/z $[M+Na]^+$; Calcd for $C_{18}H_{20}O_8Na$, 387.1056. Found, 387.1037.

Acknowledgments

This work was supported by JSPS Grant-in Aid for scientific research to KH (18510197).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2008.02.085.

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