

#### Article

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J. Org. Chem., Just Accepted Manuscript • DOI: 10.1021/jo4003135 • Publication Date (Web): 08 Apr 2013 Downloaded from http://pubs.acs.org on April 20, 2013

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#### High Yield Total Synthesis of (-)-Strictinin through Intramolecular Coupling of Gallates

Naoki Michihata, Yuki Kaneko, Yusuke Kasai,<sup>§</sup> Kotaro Tanigawa, Tsukasa Hirokane, Sho Higasa, Hidetoshi Yamada\*

School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda 669-1337, Japan.

hidetosh@kwansei.ac.jp



**ABSTRACT**: This paper describes a total synthesis of (–)-strictinin, an ellagitannin that is 1-*O*-galloyl-4,6-*O*-(*S*)-hexahydroxydiphenoyl (HHDP)- $\beta$ -D-glucose. In the study, total efficiency of the synthesis was improved to obtain 78% overall yield in 13 steps from D-glucose. In the synthesis, formation of the 4,6-(*S*)-HHDP bridge including the eleven-membered bislactone ring was a key step, in which intramolecular aryl–aryl coupling was adopted. The coupling was oxidatively induced by CuCl<sub>2</sub>–*n*-BuNH<sub>2</sub> with perfect control of the axial chirality, and the reaction conditions of this coupling were optimized thoroughly to achieve the quantitative formation of the bridge.

<sup>&</sup>lt;sup>§</sup> Present address: Center for Marine Biotechnology and Biomedicine, Scripps Institution of Oceanography, University of California San Diego, 9500 Gilman Drive, La Jolla, California 92093-0212, USA

#### Introduction

(-)-Strictinin (1), 1-O-galloyl-4,6-O-(S)-hexahydroxydiphenoyl (HHDP)- $\beta$ -D-glucopyranose (Figure 1), is an ellagitannin that was first isolated from the leaves of *Casuarina stricta* 



FIGURE 1. Structure of (–)-strictinin (1)

(Casuarinaceae) and whose structure was characterized by Okuda *et al.*<sup>1,2</sup> Since then, many plant species have been revealed to produce 1.<sup>3</sup> In addition, 1 is a compound that has frequently appeared in tea sciences.<sup>4</sup> Because of its relatively good availability compared to general natural ellagitannins, the biological activities of 1 have been extensively examined and found significant in pharmaceutical utilization including anti-allergic and immunostimulating activities.<sup>5–12</sup>

Despite the investigations to find its biological activities and for where **1** can be isolated from, the synthetic approach of **1** has only been reported by Khanbabaee *et al.*<sup>13</sup> They achieved the total synthesis of **1** through double esterification [Scheme 1, (A)]. The 4,6-(*S*)-HHDP compound **4** is obtained as a single diastereomer via kinetic optical resolution of *rac*-**2**. The yield of this step is 24% because (*R*)-**2** involves intermolecular esterification producing dimers (and perhaps larger oligomers), production of which wastes **3**.<sup>14</sup> This disadvantage was avoided by the adoption of axially chiral HHDP-diacid; thus double esterification with (*S*)-**2** provided the 4,6-HHDP-bridge in the synthesis of the proposed structure of roxbin B.<sup>15</sup> However, the preparation of (*S*)-**2** 

SCHEME 1. Previous formation of the 4,6-HHDP-bridge



requires extra synthetic steps.<sup>16</sup> Improvements in efficiency of the synthesis would increase the availability of not only **1** but also its analogues in pure form, which could help advance research into the intended applications.<sup>17</sup>

For the formation of the 4,6-HHDP-bridge, intramolecular coupling of the galloyl groups on the 4- and 6-oxygens of glucose have been the other strategy. The coupling was first employed by Feldman *et al.* [Scheme 1, (B)] in the synthesis of tellimagrandin I,<sup>18</sup> demonstrating that the axial chirality in **6** could be completely controlled to be *S.* Similar complete diastereoselectivity in the formation of the 4,6-HHDP-bridge was also exhibited by Dai and Martin with Ullmann coupling of **7** (C).<sup>19</sup> Most recently, Spring *et al.* applied their original method of aryl–aryl coupling to the

4,6-HHDP formation (D),<sup>20</sup> that is a three-step synthesis in one pot including halogen–zinc exchange of 2-brominated gallates of **9**, copper salt mediated transmetalation, and oxidation of the resulting organocuprate.<sup>21</sup> However, this coupling requires the 2-brominated gallates as the substrate of the reaction, which slightly decreases the total efficiency of the synthesis due to the additional steps required for the pre-installation of bromine. We here described the total synthesis of **1** where we highlighted on the overall efficiency and the optimized formation of 4,6-(*S*)-HHDP-bridge.

The retrosynthetic analysis of 1 is outlined in Scheme 2. We envisioned a  $\beta$ -selective





esterification would install the required anomeric galloyl group at the final stage of the synthesis. To construct the 4,6-HHDP group of **11**, the bridge would be constructed by  $CuCl_2$ –*n*-BuNH<sub>2</sub> mediated aryl–aryl bond formation.<sup>16,22,23</sup> The digallate **12** would be installed by simple esterification of known carboxylic acid **13**<sup>24,25</sup> and diol **14**.<sup>26</sup> In the synthesis, we focused on high overall yield and stable reproducibility. For this purpose, we improved the methods of synthesizing the starting materials **13** and **14** although they are known compounds, which are

described in the first half of this report. In the latter half, a new synthetic method for 1, starting from 13 and 14, is described.

#### **Results and discussions**

#### Preparation of protected gallic acid 13

The 4-O-selective benzylation of methyl gallate (15) was first reported by ElSohly *et al.* as in Scheme 3 (eq 1).<sup>24</sup> Later, Pearson and Bruhn reported the difficulty of reproducibility in this

#### SCHEME 3. Previous 4-O-selective benzylation and allylation of 15



method, along with inherent low regioselectivity in benzylation of **15** (eq 2).<sup>25</sup> They therefore developed the three-step sequence (eq 3) to improve the efficiency of 4-*O*-benzyl gallate (**16**). On the other hand, Fréchet *et al.* allylated the 4-*O*-position selectively to give **19** (eq 4) by changing the base from  $K_2CO_3$  to KHCO<sub>3</sub> and by the addition of KI as a catalyst.<sup>27</sup>

On the basis of the above information, we improved the regioselective benzylation of **15** (Scheme 4). Thus, treatment of **15** with BnBr and KHCO<sub>3</sub> in the presence of catalytic KI in DMF

**SCHEME 4. Preparation of 13** 



produced **16** as the major product along with **17** and **18** as the minor products. A chromatographic separation provided pure **16** in 83% yield. Purification by washing the powdered mixture of **16**, **17**, and **18** with toluene was also possible because of the higher solubility of the byproducts **17** and **18** into toluene than **16**. Transformation of **16** to carboxylic acid **13** including MOM protection of the phenolic hydroxy groups followed by hydrolysis of the ester proceeded in high yields.

#### High-yield synthesis of ethyl 1-thioglucoside 14

All approaches toward the synthesis of ethyl 1-thioglucoside **14** from D-glucose (**21**) have been found in the literature.<sup>26,28–30</sup> However, the reported yields are less satisfactory in several steps; therefore we optimized each reaction condition to improve efficiency (Scheme 5).

Reported by Wolfrom and Juliano, per-acetylation of **21** is known to prepare the  $\beta$ -pentaacetylglucose in moderate yield (73%). We found an optimized condition by slow addition of powdered **21** into a gently refluxed Ac<sub>2</sub>O and NaOAc improved the yield significantly.

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#### **SCHEME 5. Synthesis of 14**



The three-step transformation of **22** to **23** includes (1) Lewis acid mediated  $\beta$ -selective ethylthio glucosidation,<sup>31–39</sup> (2) deacetylation,<sup>32</sup> and (3) regioselective benzylidene formation.<sup>40</sup> We improved the efficiency on the basis of Little's method for the first step,<sup>33</sup> because we found the cause of the reported moderate yield (74%), that is, decomposition of desired ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio- $\beta$ -D-glucopyranoside was induced by Zr-salts that remained despite the workup procedures. Complete removal of the Zr-salts was difficult to achieve by liquid–liquid extractions between organic and aqueous phases, and besides, the colorless crystal of the desired ethylthioglucoside gradually changed to be blackish.<sup>41</sup> Accordingly, the next deacetylation soon after the workup of the first step made the decomposition insignificant. The purity of the deacetylated product was excellent, and allowed the succeeding benzylidenation to be carried out without purification. For the benzylidenation, the following efforts were effective, using (±)-camphor-10-sulfonic acid (CSA) as the acid catalyst instead of *p*-TsOH as reported, and carried out the reaction under reduced pressure (~15 mmHg) to remove the generated MeOH. By these treatments the yield of the three steps increased to 92% overall.

Transformation from **23** to **14** including benzylation of the 2,3-diol followed by removal of the benzylidene was quantitatively carried out by employing method developed by Crich and Bowers<sup>26</sup> with slight modification using 1 M HCl or aqueous AcOH as the hydrolytic agents for the removal of benzylidene to provide 4,6-diol **14** in 99% and 95% yield, respectively.

The new synthetic steps for total synthesis of 1 commenced with acylation of 4,6-diol 14 with carboxylic acid 13 using a modified Steglich's method<sup>42</sup> (Scheme 6). This digalloylation

#### **SCHEME 6. Synthesis of 1**



successfully gave 4,6-digallate 24 in 99% yield. The four MOM groups of 24 were removed by acidic hydrolysis using a mixture of 2-propanol and concentrated aqueous HCl (50/1 v/v) to afford tetraol 12 in 95% yield. To perform this deprotection in high yield and with reliable reproducibility, the following two points had to be noted: (1) the reaction temperature had to be kept to 50 °C, and (2) the workup had to be started soon after the detection of the removal of all MOM groups.

For the transformation of **12** to **11**, we began by using our previously reported method for  $CuCl_2-n$ -BuNH<sub>2</sub> catalyzed aryl-aryl coupling reaction (Table 1, entry 1). The coupling reaction using 5 equiv of CuCl<sub>2</sub> and 20 equiv of *n*-BuNH<sub>2</sub> provided eleven-membered bislactone **11** in





Entry	CuCl <sub>2</sub> (equiv)	<i>n</i> -BuNH <sub>2</sub> (equiv)	Time (h)	Yield (%)
1	5	20	4	34
2	3	12	13	70
3	2	8	26	65
4	2	12	2.5	89
5	2	20	0.5	99
6	2	30	0.25	100

34% yield, although these reaction conditions were previously used to construct the twelve-membered 1,6- and 3,6-HHDP bridge.<sup>22,23</sup> Similar diminished productivity due to ring contraction has been observed in the construction of ten-membered HHDP-bislactone rings.<sup>16</sup> The low yield was due to solvolytic degradation of galloyl and HHDP esters induced by n-BuNH<sub>2</sub>. Accordingly, we reduced the quantity of the reagents, keeping the 1/4 ratio of CuCl<sub>2</sub> and n-BuNH<sub>2</sub> (entry 2), which enhanced the yield to 70%. However, further quantitative decrease of the reagents (entry 3) prolonged the reaction time, which resulted in decline of the yield. The 1/4 ratio of CuCl<sub>2</sub> and amine has been reported by Brussee *et al.* to be the optimized reaction condition for intermolecular coupling of 2-naphthol.<sup>43</sup>

We then changed the ratio of  $CuCl_2$  and *n*-BuNH<sub>2</sub>. Application of the 1/6 ratio (Table 1, entry 4) shortened the reaction time to 2.5 h; in addition, the yield of **11** was increased to 89%. Monitoring of this reaction indicated that the intramolecular coupling reaction was faster than the

solvolytic cleavage of the ester bonds. These observations suggested that excessive amount of *n*-BuNH<sub>2</sub> might accelerate the rate of the coupling reaction in comparison to the rate of solvolytic degradation. This hypothesis was confirmed by the reaction using 1/10 and 1/15 ratio of the CuCl<sub>2</sub> and *n*-BuNH<sub>2</sub>, the reaction conditions of which afforded **11** in 99% and 100% yield in 30 and 15 min, respectively (entries 5 and 6). The quick completion of the coupling reaction before the solvolysis became conspicuous was the answer to achieving a successful transformation in this case. A noteworthy feature was the excellent diastereoselectivity in the formation of the axially chiral HHDP group; the derived **11** in each entry was obtained as a single diastereomer, indicating that the sp<sup>3</sup> chirality of the pyranose was completely transferred to the axial chirality of the HHDP group.

The axial chirality of **11** was confirmed by the liberation of the HHDP group, introducing it to a known compound. Thus, after benzylation of the phenolic hydroxy groups of **11** providing **25** (Scheme 6), the HHDP part was released by solvolysis to produce dimethyl diester **29** (Scheme 7). The optical rotation of **29** was in agreement with the *S* enantiomer.<sup>44</sup>





For the synthesis of 1-*O*-galloylated **28**, we first attempted direct glycosyl ester formation (Scheme 8) using **25** and carboxylic acid **30** because thioglycosides have commonly been used as glycosyl donors in glycosylation reactions.<sup>45,46</sup> Thus, treatment of thioglucoside **25** with MeOTf





in the presence of **30** and MS 4A provided **28** in an  $\alpha$ -selective manner ( $\alpha/\beta = 83/17$ ). The  $\alpha$ -preference of the glycosyl esterification was similar to the stereoselectivities in glycosylation using a 2-*O*-benzylated glycosyl donor.<sup>47</sup> Accordingly, we investigated the acylation of pyranose **26** (Scheme 6) obtained by hydrolysis of the ethylthio group of **25**.

Despite the seemingly facile transformation, the hydrolysis of the ethylthio group required effort to find the optimal reaction conditions (Table 2). The hydrolysis with NBS<sup>48</sup> was poor in reproducibility (entry 1); the yield of **26** fluctuated in a range of 18–70%. Entries 2–4 present results when general activating procedures of thioglycosides in glycosylations were applied. That is, activation by MeOTf<sup>49</sup> provided **26** in moderate yield (entry 2) along with an inseparable byproduct, the structure of which was unidentified. The use of PhIO in combination with Lewis acids<sup>50</sup> produced no desired product (Entries 3 and 4). The employment of NIS resulted in moderate yield (entry 5). Darko's reaction conditions using *N*-iodosaccharin (NISac) proceeded rapidly, but the yield of **26** was moderate (entry 6).<sup>51</sup> Mukhopadhyay's protocol using NIS and H<sub>2</sub>SO<sub>4</sub> immobilized on silica produced **26** along with many byproducts (entry 7).<sup>52</sup> After these attempts, we found that application of van Boom's method<sup>53</sup> using NIS and a catalytic amount of TfOH was quite effective; **26** was formed in 98% yield (entry 8). To obtain the excellent yield, mixing of NIS and TfOH prior to the reaction with **25** was required. The addition of NIS and

BnO BnO BnO	BnO O O O D O D O D O D D D D D D D D D D D D D	Bn BnO BnO SEt O Solvent,	BnO BnO BnO S, H <sub>2</sub> O Time, rt	OBn BnO OH 26
Entr y	Reagents	Solvent	Time (h)	Yield (%)
1	NBS	THF	0.25–4	18–70 <sup><i>a</i></sup>
2	MeOTf	THF	2	65
3	Sn(OTf) <sub>2</sub> PhIO	THF	2	0
4	Yb(OTf) <sub>3</sub> PhIO	THF	2	0 <sup><i>a</i></sup>
5	NIS	THF	9.5	57 <sup>a</sup>
6	NISac	MeCN	0.08	65 (55) <sup>a</sup>
7	NIS H₂SO₄ silica	CH <sub>2</sub> Cl <sub>2,</sub> THF	36	N.D. <sup><i>b,c</i></sup>
8	NIS cat. TfOH	CH <sub>2</sub> Cl <sub>2</sub> , THF	0.5	98

#### TABLE 2. Hydrolysis of Anomeric Ethylthio Group of 25

<sup>*a*</sup>Reaction temperature was 0 °C. <sup>*b*</sup>N.D. = not determined. <sup>*c*</sup>Reaction temperature was 0 °C to rt.

TfOH into a solution of **25** resulted in a low yield. According to the armed-disarmed theory, as stated by Mydock and Demchenko,<sup>54</sup> thioglucoside **25** is classified as a disarmed glycosyl donor, from which the generation of oxocarbenium intermediate is difficult. In addition, the HHDP-bridge locked the conformation of the  $CH_2O$  group to the *tg*-form, which also deactivates the rate of hydrolysis.<sup>55</sup> These inactivating effects would be the potential reasons for the unexpected hydrolysis-resisting property of **25** at the anomeric position.

In the galloylation at the anomeric position (Scheme 6), acid chloride  $27^{56}$  was employed in the presence of Et<sub>3</sub>N to afford  $\beta$ -28 stereoselectively in 97% yield ( $\alpha/\beta = 2/98$ ).<sup>57,58</sup> Both the addition of a catalytic amount of DMAP to the reaction conditions and adoption of Steglich's

condensation<sup>59</sup> resulted in low anomeric stereoselectivity, to provide **28** as an  $\alpha/\beta = 36/64$  and 45/55 anomeric mixture, respectively. In general, an equatorially oriented anomeric hydroxy group is more reactive than an axially oriented one in acylation.<sup>60</sup> Acylation using acid chlorides in the presence of Et<sub>3</sub>N have actualized this property by Bols and Hansen.<sup>57</sup> In the presence of DMAP, higher reactivity of galloylpyridinium ion intermediate **31** would allow the acylation of the axial hydroxy group ( $\alpha$ -OH in this case) to decrease the stereoselectivity.



Finally, the hydrogenolytic cleavage of the eleven benzyl groups of  $\beta$ -28 provided 1 in 99% yield (Scheme 6), and physical and spectral data (optical rotation, <sup>1</sup>H and <sup>13</sup>C NMR, IR, HRMS) of which were identical to those of natural strictinin.<sup>2</sup> For the final purification, successive chromatography on ODS (Cosmosil 75C<sub>18</sub>-OPN) and then on TOYOPEARL HW-40C<sup>61</sup> was effective to afford 1 as a colorless amorphous solid.

#### Conclusion

We accomplished the total synthesis of (–)-strictinin in 13 steps and in a 78% overall yield from D-glucose. All the synthetic steps were optimized to provide very good yields and stable reproducibility including (1) improvements of the 4-*O*-selective benzylation of methyl gallate and of the synthesis of ethyl 2,3-di-*O*-benzyl-1-thio- $\beta$ -D-glucopyranoside (4 steps from D-glucose, 90% overall yield), (2) completely diastereoselective synthesis of the 4,6-(*S*)-HHDP in quantitative yield, and (3) effective removal of the *disarmed* ethylthio group. This total synthesis demonstrates the possibility of the synthetic supply of strictinin and its analogues.

#### **Experimental section**

**General methods.** Anhydrous MgSO<sub>4</sub> was used to dry organic layers after extraction, and it was removed by filtration through a cotton pad. The filtrate was concentrated and subjected to further purification protocols if necessary. This sequence was represented as "the general drying procedure" in the following experimental methods.

The <sup>1</sup>H NMR data are indicated by chemical shifts, with the multiplicity, the coupling constants, and the integration in parentheses, in this order. The multiplicities are abbreviated as s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, and br: broad. The <sup>13</sup>C NMR data are reported as the chemical shift with the hydrogen multiplicity obtained from the DEPT spectra. The multiplicities are abbreviated as s: C, d: CH, t: CH<sub>2</sub>, and q: CH<sub>3</sub>. When the number for carbon was more than one, the number was added in parentheses.

For a full description of general methods, see Supporting Information.

Methyl 4-*O*-benzylgallate (16), (i) A procedure obtained the best yield. To a solution of methyl gallate (15) (2.00 g, 10.9 mmol) in DMF (100 mL) were added KHCO<sub>3</sub> (2.17 g, 21.7 mmol), KI (10.8 mg, 65.2  $\mu$ mol) and BnBr (1.86 g, 10.9 mmol) at rt under Ar atmosphere. After being stirred for 24 h at rt, the mixture was filtered through a cotton-Celite pad. The filtrate was concentrated to remove DMF. After addition of H<sub>2</sub>O (30 mL) to the residue, the aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with saturated aq NH<sub>4</sub>Cl, H<sub>2</sub>O, and brine. After the general drying procedure, the resulting residue was dissolved in EtOAc (50 mL). To the resulting solution was added silica gel (20 g). The mixture was then concentrated to adsorb the products onto silica gel. The resulting silica gel adsorbed the

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products was brown, which was charged on the top of a column with 70 g of SiO<sub>2</sub> (dry loading method). Elution with *n*-hexane/EtOAc (7/1 to 1/1) produced purified **16** (2.47 g, 83% yield) as a white powder, whose NMR data were identical to the literature data.<sup>24,25</sup> (ii) A procedure for **50** g-scale synthesis. To a solution of methyl gallate (**15**) (53.3 g, 289 mmol) in DMF (700 mL) were added KHCO<sub>3</sub> (50.0 g, 499 mmol), KI (300 mg, 1.81 mmol), and BnBr (50.0 g, 292 mmol) at rt under N<sub>2</sub> atmosphere. After being stirred for 15 h at rt, the mixture was filtered through a cotton-Celite pad. The filtrate was concentrated to remove DMF. To the resulting residue was added 1 M aq HCl (100 mL). The aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with saturated aq NaHCO<sub>3</sub>, H<sub>2</sub>O, and brine. After the general drying procedure, white solid was obtained containing **15** (1.4%), **16** (78.3%), **17** (18.9%), and **18** (1.4%). The ratio was determined by <sup>1</sup>H NMR spectra. The mixture was successively washed with (1) saturated aq NaHCO<sub>3</sub> to remove **15**, (2) *n*-hexane to remove BnBr, and (3) cold toluene to remove **17** and **18** because these two compounds dissolve into toluene more than **16**. Compound **16** (54.6 g, 69% yield) was afforded as a white powder.

**Methyl 4-O-benzyl-3,5-di-O-methoxymethylgallate (20).** To a solution of diol **16** (9.20 g, 33.5 mmol) in DMF (340 mL) were added 60% NaH in mineral oil (4.03 g, 101 mmol) and chloromethyl methyl ether (8.10 g, 101 mmol) at 0 °C under Ar atmosphere, and the mixture was stirred for 1 h at rt. The reaction was quenched by addition of saturated aq NH<sub>4</sub>Cl until the pH of the mixture became ~6. After concentration of the mixture to remove most of DMF, H<sub>2</sub>O (50 mL) was added to the resulting mixture. The aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with saturated aq NH<sub>4</sub>Cl, H<sub>2</sub>O, and brine. After the general drying procedure, the mixture was purified by column chromatography (350 g of SiO<sub>2</sub>, *n*-hexane/EtOAc = 5/1 to 1/1) to afford **20** (12.0 g, 99% yield) as a yellow syrup: IR (neat) 3090, 3066, 3033, 2953, 2907, 1721, 1593, 1499, 1435, 1395 1329, 1304, 1221, 1200, 1156, 1109,

1084, 1048, 1011, 978, 924, 878, 855, 825, 762, 735, 698 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ 7.52 (s, 2H), 7.47–7.43 (m, 2H), 7.34–7.28 (m, 3H), 5.19 (s, 4H), 5.13 (s, 2H), 3.88 (s, 3H), 3.49 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  166.6 (s), 151.1 (s, 2C), 143.1 (s), 137.4 (s), 128.5 (d, 2C), 128.4 (d, 2C), 128.3 (d), 125.8 (s), 112.1 (d, 2C), 95.6 (t, 2C), 75.3 (t), 56.5 (q, 2C), 52.4 (q); HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> Calcd for C<sub>19</sub>H<sub>22</sub>O<sub>7</sub>Na 385.1263, Found 385.1254.

4-*O*-benzyl-3,5-di-*O*-methoxymethylgallic acid (13). To a solution of methyl ester 20 (12.0 g, 33.0 mmol) in THF (110 mL) and MeOH (220 mL) was added LiOH·H<sub>2</sub>O (6.93 g, 165 mmol) in H<sub>2</sub>O (80 mL) at rt. The mixture was heated to reflux for 2 h. The reaction was quenched by addition of 1 M aq HCl until the pH of the mixture became ~1. The aqueous mixture was concentrated to remove most of THF and MeOH. H<sub>2</sub>O (20 mL) was added to the resulting mixture. The aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with H<sub>2</sub>O and brine. After the general drying procedure, the crude product was purified by recrystallization (EtOAc/*n*-hexane) to afford **13** (11.4 g, 99% yield) as a white powder, whose NMR data were identical to the literature data.<sup>23</sup>

**Penta-***O***-acetyl-β-D-glucopyranose (22).** To a gently refluxed Ac<sub>2</sub>O (28.4 g, 278 mmol) containing NaOAc (1.14 g, 13.9 mmol) was slowly added powdered D-glucose (21) (5.00 g, 27.8 mmol) over a period of 15 min. After the mixture was heated to reflux for 5 min, the mixture was cooled to rt. The reaction was then quenched by addition of ice under sonication. During this treatment, 22 was precipitated. The precipitation (white powder) was filtered and washed with H<sub>2</sub>O until the odor of the acetic acid disappeared. The crude product was purified by recrystallization (EtOH) to afford pentaacetate 22 (10.81 g, 100% yield) as a white powder. Because **22** has not adequately characterized (mp and optical rotation of **22** has been reported),<sup>28</sup> we describe the data: mp 130–135 °C, lit.<sup>28</sup> 133.5–134 °C; [α]<sub>D</sub><sup>25</sup> +3.9 (*c* 1.00, CHCl<sub>3</sub>), lit.<sup>13</sup>

 $[\alpha]_D^{22}$  +2 (*c* 0.9, CHCl<sub>3</sub>); IR (neat) 3029, 2969, 2951, 2907 1755, 1740, 1381, 1372, 1233, 1224, 1046, 914, 704, 642 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.71 (d, *J* = 8.2 Hz, 1H), 5.24 (dd, *J* = 9.8, 9.4 Hz, 1H), 5.16–5.10 (m, 2H), 4.29 (dd, *J* = 12.6, 4.6 Hz, 1H), 4.11 (dd, *J* = 12.6, 2.3 Hz, 1H), 3.84 (ddd, *J* = 9.8, 4.6, 2.3 Hz, 1H), 2.11 (s, 3H), 2.09 (s, 3H), 2.03 (s, 6H), 2.01 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  170.7 (s), 170.2 (s), 169.5 (s), 169.4 (s) 169.1 (s), 91.8 (d), 72.9 (d), 72.8 (d), 70.3 (d), 67.9 (d), 61.6 (t), 20.9 (q), 20.8 (q), 20.7 (q, 3C); HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>22</sub>O<sub>11</sub>Na 413.1057, Found 413.1060.

Ethyl 4,6-*O*-benzylidene-1-thio- $\beta$ -D-glucopyranoside (23). To a solution of pentaacetate 22 (3.00 g, 7.69 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (80 mL) were added ethanethiol (573 mg, 9.22 mmol) and ZrCl<sub>4</sub> (2.15 g, 9.22 mmol). The mixture was stirred for 2 h at 0 °C under Ar atmosphere. The reaction was quenched by addition of ice water (50 mL). The aqueous mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layer was successively washed with 1 M aq HCl, saturated aq NaHCO<sub>3</sub>, H<sub>2</sub>O, and brine. After the general drying procedure, the crude product was obtained as a white powder.

A mixture of the crude product and NaOMe (125 mg, 2.31 mmol) in MeOH (80 mL) was stirred for 1 h at rt. To the mixture was added protic ion-exchanger resin, IR-120 PLUS (H), until the pH of the mixture became ~7. Then it was filtered through a cotton pad. The filtrate was concentrated.

To a solution of the resulting residue in DMF (80 mL) were added PhCH(OMe)<sub>2</sub> (1.40 g, 9.23 mmol) and CSA (536 mg, 2.31 mmol) at rt. The reaction was carried out using rotary evaporator under reduced pressure (~15 mmHg) removing methanol for 2 h at rt; stirring of reaction mixture was performed by rotation of the flask. Then the reaction mixture was concentrated to remove most DMF at 80 °C. To the mixture was added saturated aq NaHCO<sub>3</sub> until a white powder

precipitated. It was cooled to 0 °C, and filtered by Hirsch funnel. The crude product was purified by recrystallization (EtOAc/*n*-hexane) to afford **23** (2.21 g, 92% for 3 steps) as a white powder. <sup>1</sup>H NMR data for 2,3-diol **23** was identical to the literature data.<sup>40</sup>

Ethyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside. To a solution of 2,3-diol 23 (1.00 g, 3.20 mmol) and 60% NaH in mineral oil (513 mg, 12.8 mmol) in DMF (30 mL) was added BnBr (2.19 g, 12.8 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 2 h at 0 °C. To the reaction mixture was added saturated aq NH<sub>4</sub>Cl until the pH of the mixture became ~7. The aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with saturated aq NH<sub>4</sub>Cl, H<sub>2</sub>O, and brine. After the general drying procedure, the resulting residue was purified by successive column chromatography (30 g of SiO<sub>2</sub>, *n*-hexane/EtOAc = 6/1 to 2/1, followed by 30 g of SiO<sub>2</sub>, *n*-hexane/EtOAc = 10/1 to 2/1) to afford ethyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (1.55 g, 99%) as a white powder, <sup>1</sup>H NMR data of which was identical to the literature data.<sup>62</sup>

Ethyl 2,3-di-O-benzyl-1-thio-B-D-glucopyranoside (14): Hydrolysis by using aq HCl. To a solution of ethyl 2,3-di-O-benzyl-4,6-O-benzylidene-1-thio-β-D-glucopyranoside (50.0 mg, 105 µmol) in acetone (4 mL) was added 1 M aq HCl (0.1 mL). The mixture was refluxed for 1 h. The reaction was quenched by addition of 1 M aq NaOH until the pH of the mixture became  $\sim$ 7. The mixture was concentrated to remove acetone. The resulting aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with saturated ag NaHCO<sub>3</sub>,  $H_{2O}$ , and brine. After the general drying procedure, the resulting residue was purified by column chromatography (2 g of SiO<sub>2</sub>, *n*-hexane/EtOAc = 9/1 to 2/1) to afford 4,6-diol 14 (40.6 mg, 99%) yield) as a straw color amorphous solid, <sup>1</sup>H NMR data of which was identical to the literature data.<sup>29</sup> **Hvdrolvsis** by using aqueous acetic acid. solution of ethyl А

2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio- $\beta$ -D-glucopyranoside (808 mg, 1.70 mmol) in aq AcOH (AcOH: 40 mL, H<sub>2</sub>O: 10 mL) was refluxed for 30 min, then cooled to rt. Toluene (50 mL) was added to the mixture, and the solution was concentrated to remove AcOH and H<sub>2</sub>O azeotropically. This procedure was repeated five times. The resulting residue was purified by column chromatography (20 g of SiO<sub>2</sub>, *n*-hexane/EtOAc = 2/1 to 0/1) to afford 4,6-diol **14** (628 mg, 95% yield).

Ethyl 2,3-di-O-benzyl-4,6-O-bis(4-O-benzyl-3,5-di-O-methoxymethylgalloyl)-1-thio-β-Dglucopyranoside (24). To a solution of 4,6-diol 14 (891 mg, 2.30 mmol) and carboxylic acid 13 (1.73 g, 4.95 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) and pyridine (5 mL) were added EDCI·HCl (1.27 g, 6.60 mmol) and DMAP (134 mg, 1.10 mmol). The mixture was stirred for 14.5 h at rt under Ar atmosphere. The reaction was quenched by addition of 1 M aq HCl until pH of the mixture became  $\sim 1$ . The aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with  $H_2O$  and brine. After the general drying procedure, the mixture was purified by column chromatography (30 g of SiO<sub>2</sub>, *n*-hexane/EtOAc = 4/1 to 2/1) to afford 4.6-digallate 24 (2.33 g, 99% yield) as a colorless amorphous solid:  $\left[\alpha\right]_{D}^{25}$  -14.6 (c 1.56, CHCl<sub>3</sub>): IR (neat) 3095, 3065, 3030, 2950, 2923, 2851, 1723, 1592, 1497, 1433, 1393, 1327, 1302, 1217, 1194, 1156, 1109, 1048, 924, 865, 800, 756, 735, 698 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.50–7.28 (m, 19H), 7.13–7.08 (m, 5H), 5.27 (dd, J = 9.3, 9.8 Hz, 1H), 5.21–5.12 (m, 12H), 4.92 (d, J = 10.3 Hz, 1H), 4.79 (d, J = 11.0 Hz, 1H), 4.74 (d, J = 10.3 Hz, 1H), 4.66 (d, J = 10.3 11.2 Hz, 1H), 4.58 (d, J = 9.7 Hz, 1H), 4.54 (dd, J = 12.2, 2.5 Hz, 1H), 4.27 (dd, J = 12.2, 7.3 Hz, 1H), 3.90 (ddd, J = 9.8, 7.3, 2.5 Hz, 1H), 3.83 (dd, J = 8.9, 9.3 Hz, 1H), 3.56 (dd, J = 9.7, 8.9 Hz, 1H), 3.47 (s, 6H), 3.45 (s, 6H), 2.82–2.66 (m, 2H), 1.28 (t, J = 7.4 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) & 165.7 (s), 164.9 (s), 151.1 (s, 2C), 151.0 (s, 2C), 143.4 (s), 143.3 (s), 138.0 (s), 137.9 (s), 137.4 (s), 137.4 (s), 128.6–127.8 (9 peaks were observed overlapping many doublets, 20C), 125.4 (s), 124.9 (s), 112.4 (d, 4C), 95.6 (t, 4C), 85.2 (d), 83.7 (d), 81.6 (d), 76.2 (d), 75.8 (t), 75.6 (t), 75.4 (t), 75.4 (t), 71.6 (d), 64.2 (t), 56.6 (q, 2C), 56.5 (q, 2C), 25.2 (t), 15.3 (q); HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> Calcd for C<sub>58</sub>H<sub>64</sub>O<sub>17</sub>SNa 1087.3762, Found 1087.3709.
Ethyl 2,3-di-O-benzyl-4,6-O-bis(4-O-benzylgalloyl)-1-thio-β-D-glucopyranoside (12). To

a solution tetrakis(methoxymethyl ether) 24 (2.60 g, 2.44 mmol) in THF (6 mL) was added a mixture of *i*-PrOH and concd aq HCl (50/1 v/v, 18 mL). The mixture was stirred for 13 h at 50 °C. The eluent to check the reaction by TLC was  $CHCl_3/MeOH/formic$  acid (10/1/0.01), which improved the resolution performance of the spots. After cooling to rt, the reaction was quenched by addition of saturated aq NaHCO<sub>3</sub> until the pH of the mixture became  $\sim$ 7. After concentration of the mixture to remove most of *i*-PrOH, the aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with saturated aq NaHCO<sub>3</sub>, H<sub>2</sub>O, and brine. After the general drying procedure, the resulting residue was purified by column chromatography (60 g of SiO<sub>2</sub>, *n*-hexane/EtOAc = 6/1 to 0/1) to afford tetraol 12 (2.08 g, 95% yield) as a colorless amorphous solid: mp 58–60 °C;  $[\alpha]_D^{26}$  +20.5 (c 1.30, CHCl<sub>3</sub>); IR (neat) 3393, 3112, 3090, 3065, 3033, 2963, 2932, 2882, 1717, 1707, 1601, 1522, 1455, 1356, 1267, 1217, 1183, 1092, 1057, 1030, 1005, 914, 872, 853, 754, 698 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.40–7.29 (m, 15H), 7.18 (br s, 2H), 7.11–7.09 (m, 7H), 5.87 (br s, 4H), 5.36 (dd, J = 9.6, 9.6 Hz, 1H), 5.15–5.08 (m, 4H), 4.93 (d, J = 10.2 Hz, 1H), 4.76 (d, J = 11.1 Hz, 1H), 4.76 (d, J = 10.2 Hz, 1H) 4.62 (d, {J = 10.2 Hz, 1H) 4.62 (d, {J = 10.2 Hz, 1H) 4.62 (d, {J = 10.2 Hz 11.1 Hz, 1H), 4.58 (d, J = 9.5 Hz, 1H), 4.45–4.44 (m, 2H), 3.82–3.76 (m, 2H), 3.60 (dd, J = 9.5, 9.2 Hz, 1H), 2.85–2.70 (m, 2H), 1.33 (t, J = 7.4 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  166.6 (s), 165.8 (s), 149.2 (s, 2C), 149.2 (s, 2C), 138.1 (s), 138.0 (s), 137.8 (s), 137.7 (s), 136.9 (s), 136.9 (s), 129.0-127.8 (11 peaks were observed overlapping many doublets, 20C), 125.0 (s),

124.5 (s), 110.1 (d, 2C), 110.0 (d, 2C), 85.6 (d), 83.5 (d), 81.6 (d), 75.9 (t), 75.6 (d), 75.5 (t), 75.4 (t), 71.4 (d), 63.6 (t), 58.7 (t), 25.3 (t), 15.3 (q); HRMS (ESI-TOF) m/z: [M + Na]<sup>+</sup> Calcd for C<sub>50</sub>H<sub>48</sub>O<sub>13</sub>SNa 911.2713, Found 911.2670.

### Table 1: Ethyl 4,6-(aS)-[4,4',6,6'-tetrahydroxy-5,5'-bisbenzyloxy-1,1'-biphenyl-2,2'dicarboxylate]-2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside (11).

Entry 1. A solution of CuCl<sub>2</sub> (15.1 mg, 112 µmol) and *n*-BuNH<sub>2</sub> (32.9 mg, 450 µmol) in MeOH (1 mL) was stirred for 30 min at rt to prepare a blue solution of CuCl<sub>2</sub>–*n*-BuNH<sub>2</sub> complex under Ar atmosphere. Then a solution of digallate 12 (20.0 mg, 22.5 µmol) in MeOH (1 mL) was added to the solution of CuCl<sub>2</sub>–*n*-BuNH<sub>2</sub> complex. The mixture was stirred for 4 h at rt. The reaction mixture was diluted with Et<sub>2</sub>O (3 mL) and added 5 M aq HCl (5 mL) and Et<sub>2</sub>O (3 mL). After extraction of the aqueous mixture with Et<sub>2</sub>O, the combined organic layer was successively washed with 3 M aq HCl, H<sub>2</sub>O, saturated aq NaHCO<sub>3</sub>, H<sub>2</sub>O, and brine. After the general drying procedure, the resulting residue was purified by column chromatography (3 g of SiO<sub>2</sub>, *n*-hexane/EtOAc = 6/1 to 2/1) to afford 11 (6.8 mg, 34% yield).

Entry 2. A solution of CuCl<sub>2</sub> (9.1 mg, 68  $\mu$ mol) and *n*-BuNH<sub>2</sub> (19.8 mg, 270  $\mu$ mol) in MeOH (0.8 mL) was stirred for 30 min at rt. To this was added a solution of 12 (20.0 mg, 22.5  $\mu$ mol) in MeOH (1.2 mL). The mixture was stirred for 13 h at rt. The subsequent procedures were same with those in Entry 1 to afford 11 (13.9 mg, 70% yield).

Entry 3. A solution of  $CuCl_2$  (7.6 mg, 56 µmol) and *n*-BuNH<sub>2</sub> (16.4 mg, 225 µmol) in MeOH (0.7 mL) was stirred for 30 min at rt. To this was added a solution of 12 (25.0 mg, 28.1 µmol) in MeOH (0.7 mL). The mixture was stirred for 26 h at rt. The subsequent procedures were same with those in entry 1 to afford 11 (16.2 mg, 65% yield).

Entry 4. A solution of CuCl<sub>2</sub> (30.3 mg, 225 µmol) and *n*-BuNH<sub>2</sub> (98.7 mg, 1.35 mmol) in

MeOH (1 mL) was stirred for 1 h at rt. To this was added a solution of digallate **12** (100.0 mg, 112  $\mu$ mol) in MeOH (3 mL). The mixture was stirred for 2.5 h at rt. The reaction mixture was diluted with Et<sub>2</sub>O (5 mL) and added 5 M aq HCl (10 mL) and Et<sub>2</sub>O (5 mL). After extraction of the aqueous mixture with Et<sub>2</sub>O, the combined organic layer was successively washed with 3 M aq HCl, H<sub>2</sub>O, saturated aq NaHCO<sub>3</sub>, H<sub>2</sub>O, and brine. After the general drying procedure, the resulting residue was purified by column chromatography (8 g of SiO<sub>2</sub>, *n*-hexane/EtOAc = 6/1 to 2/1) to afford **11** (88.4 mg, 89% yield).

Entry 5. A solution of CuCl<sub>2</sub> (30.3 mg, 225  $\mu$ mol) and *n*-BuNH<sub>2</sub> (165 mg, 2.25 mmol) in MeOH (1 mL) was stirred for 1 h at rt. To this was added a solution of digallate 12 (100 mg, 112  $\mu$ mol) in MeOH (3 mL). The mixture was stirred for 30 min at rt. The subsequent procedures were same with those in entry 4 to afford 11 (98.3 mg, 99% yield) as a yellow syrup.

Entry 6. A solution of CuCl<sub>2</sub> (30.3 mg, 225 µmol) and *n*-BuNH<sub>2</sub> (247 mg, 3.38 mmol) in MeOH (1 mL) was stirred for 1.25 h at rt. To this was added a solution of digallate **12** (100 mg, 112 µmol) in MeOH (3 mL). The mixture was stirred for 15 min at rt. The subsequent procedures were same with those in entry 4 to afford **11** (99.7 mg, 100% yield):  $[\alpha]_D^{24}$  –28.1 (*c* 1.60, CHCl<sub>3</sub>); IR (neat) 3510, 3424, 3111, 3088, 3065, 3033, 3009, 2961, 2928, 2874, 1743, 1609, 1586, 1499, 1455, 1364, 1181, 1132, 1061, 1044, 974, 916, 845, 814, 752, 698 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.41–7.27 (m, 16H), 7.25–7.14 (m, 4H), 6.67 (s, 1H), 6.47 (s, 1H), 5.90 (br s, 2H), 5.80 (br s, 1H), 5.71 (br s, 1H), 5.18–5.11 (m, 5H), 5.07 (dd, *J* = 9.9, 9.8 Hz, 1H), 4.87 (d, *J* = 10.3 Hz, 1H), 4.78–4.67 (m, 3H), 4.46 (d, *J* = 9.7 Hz, 1H), 3.96 (br d, *J* = 13.0 Hz, 1H), 3.76–3.69 (m, 2H), 3.50 (dd, *J* = 9.7, 9.0 Hz, 1H), 2.83–2.68 (m, 2H), 1.32 (t, *J* = 7.4 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  168.0 (s), 167.2 (s), 149.2 (s), 149.2 (s), 147.4 (s), 147.4 (s), 138.0 (s), 137.9 (s), 136.7 (s, 2C), 136.3 (s), 135.8 (s), 130.6 (s), 129.7 (s), 129.0–128.0 (8 peaks

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were observed overlapping many doublets, 20C), 114.9 (s), 113.3 (s), 108.8 (d), 107.8 (d), 85.9 (d), 83.6 (d), 81.7 (d), 75.9 (t), 75.9 (d), 75.8 (t), 75.6 (t), 75.2 (t), 72.1 (d), 64.0 (t), 25.1 (t), 15.2 (q); HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> Calcd for C<sub>50</sub>H<sub>46</sub>O<sub>13</sub>SNa 909.2557, Found 909.2516.

### Ethvl 4,6-(aS)-[4,4',5,5',6,6'-hexakisbenzyloxy-1,1'-biphenyl-2,2'-dicaboxylate]-2,3-di-**O-benzyl-1-thio-\beta-D-glucopyranoside (25).** A mixture of tetraol 11 (98.3 mg, 111 $\mu$ mol), K<sub>2</sub>CO<sub>3</sub> (122 mg, 885 µmol), and BnBr (151 mg, 885 µmol) in acetone (2.5 mL) was stirred for 13 h at rt under Ar atmosphere. The mixture was then filtered through a cotton-Celite pad to remove excess K<sub>2</sub>CO<sub>3</sub>. Saturated aq NH<sub>4</sub>Cl (10 mL) was added to the filtrate. The aqueous mixture was extracted with Et<sub>2</sub>O. The combined organic layer was successively washed with saturated aq $NH_4Cl$ , $H_2O$ , and brine. After the general drying procedure, the resulting mixture was purified by column chromatography (3 g of SiO<sub>2</sub>, *n*-hexane/EtOAc = 6/1 to 3/1) to afford 25 (137 mg, 98% yield) as a yellow syrup: $[\alpha]_D^{23}$ -37.5 (*c* 1.00, CHCl<sub>3</sub>); IR (neat) 3088, 3063, 3032, 3009, 2928, 2874, 1746, 1593, 1497, 1482, 1455, 1431, 1368, 1333, 1271, 1188, 1145, 1096, 1050, 1045, 1025, 1010, 911, 843, 739, 696 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.49–7.25 (m, 26H), 7.24–7.18 (m, 4H), 7.16–7.09 (m, 6H), 7.03–6.98 (m, 4H), 6.92 (s, 1H), 6.64 (s, 1H), 5.22-4.70 (m, 10H), 4.94-4.70 (m, 8H), 4.50 (d, J = 9.8 Hz, 1H), 3.99 (br d, J = 13.1 Hz, 1H), 3.79-3.73 (m, 2H), 3.56 (dd, J = 9.8, 8.5 Hz, 1H), 2.86-2.71 (m, 2H), 1.34 (t, J = 7.4 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 168.0 (s), 167.0 (s), 152.7 (s), 152.6 (s), 152.5 (s), 152.4 (s), 145.0 (s), 144.6 (s), 138.2 (s, 2C), 138.2 (s, 2C), 137.9 (s, 2C), 137.7 (s), 137.6 (s), 136.7 (s), 136.6 (s), 129.1–127.5 (14 peaks were observed overlapping many doublets, 40C), 124.5 (s), 123.7 (s), 108.1 (d), 108.1 (d), 85.9 (d), 83.7 (d), 82.0 (d), 76.2 (d), 76.0 (t), 75.7 (t), 75.7 (t), 75.2 (t, 2C), 75.2 (t), 72.1 (d), 71.5 (t), 71.4 (t), 63.9 (t), 25.2 (t), 15.2 (q); HRMS (ESI-TOF) m/z: [M + Na]<sup>+</sup> Calcd for C<sub>78</sub>H<sub>70</sub>O<sub>13</sub>SNa 1269.4435, Found 1269.4393.

# Table 2: 4,6-(aS)-[4,4',5,5',6,6'-hexakisbenzyloxy-1,1'-biphenyl-2,2'-dicaboxylate]-2,3-di-O-benzyl-D-gluco-pyranose (26).

Entry 1. To a solution of thioglucoside 25 (25.2 mg, 20.2  $\mu$ mol) in THF (1.1 mL) and H<sub>2</sub>O (300  $\mu$ L) was added NBS (9.0 mg, 51  $\mu$ mol) at 0 °C. The mixture was stirred for 10 min at 0 °C. To the mixture was added 10% aq Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. The aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with H<sub>2</sub>O and brine. After the general drying procedure, the resulting residue was purified by column chromatography (1.5 g of SiO<sub>2</sub>, *n*-hexane/EtOAc = 4/1 to 0/1) to afford 26 (12.0 mg, 49% yield). This procedure was repeated 6 times using 25 and NBS (12.5 mg and 4.5 mg, 25.2 mg and 9.0 mg, 64.2 mg and 23 mg, 100 mg and 29 mg, 115 mg and 41 mg, and 898 mg and 892 mg) to provide 26 in 40, 49, 68, 18, 70, and 22% yield, respectively.

Entry 2. To a solution of 25 (20 mg, 16  $\mu$ mol) in THF (300  $\mu$ L) were added MeOTf (26 mg, 160  $\mu$ mol) and H<sub>2</sub>O (10 mg, 560  $\mu$ mol) at rt. The mixture was stirred for 2 h at rt. To the mixture was added Et<sub>3</sub>N (100  $\mu$ L). The mixture was diluted with Et<sub>2</sub>O (10 mL) and washed with brine. After the general drying procedure, the resulting residue was purified by column chromatography (2 g of SiO<sub>2</sub>, *n*-hexane/EtOAc = 6/1 to 0/1) to afford 26 (12.5 mg, 65% yield).

Entry 3. To a solution of 25 (20 mg, 16  $\mu$ mol) in THF (300  $\mu$ L) were added Sn(OTf)<sub>2</sub> (6.7 mg, 160  $\mu$ mol), PhIO (4.6 mg, 20  $\mu$ mol), and H<sub>2</sub>O (10 mg, 560  $\mu$ mol) at rt. The mixture was stirred for 2 h at rt. To the mixture was added saturated aq NaHCO<sub>3</sub>. The aqueous mixture was extracted with Et<sub>2</sub>O. The combined organic layer was successively washed with brine. A mass spectrum and TLC analysis of this extract indicated that none of 26 was produced.

Entry 4. To a solution of 25 (20 mg, 16  $\mu$ mol) in THF (300  $\mu$ L) were added Yb(OTf)<sub>3</sub> (9.9 mg, 160  $\mu$ mol), PhIO (4.6 mg, 20  $\mu$ mol), and H<sub>2</sub>O (10 mg, 560  $\mu$ mol) at 0 °C. The mixture was

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stirred for 2 h at 0 °C. To the mixture was added saturated aq NaHCO<sub>3</sub>. The aqueous mixture was extracted with  $Et_2O$ . The combined organic layer was successively washed with brine. A mass spectrum and TLC analysis of this extract indicated that none of **26** was produced.

Entry 5. To a solution of 25 (100 mg, 80  $\mu$ mol) in a mixture of THF (1.2 ml) and H<sub>2</sub>O (200  $\mu$ L) was added NIS (45.1 mg, 20  $\mu$ mol) at 0 °C. The mixture was stirred for 1.5 h at 0 °C. To the mixture was added further NIS (90 mg, 40  $\mu$ mol). The mixture was stirred for additional 8 h. To the mixture was added 10% aq Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution. The aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with H<sub>2</sub>O and brine. After the general drying procedure, the resulting residue was purified by column chromatography (10 g of SiO<sub>2</sub>, *n*-hexane/EtOAc = 6/1 to 2/1) to afford **26** (54.7 mg, 57% yield).

Entry 6. (1) To a solution of 25 (20 mg, 16  $\mu$ mol) in a mixture of MeCN and H<sub>2</sub>O (10/1 v/v, 0.5 mL) was added NISac<sup>51</sup> (9.9 mg, 32  $\mu$ mol) at rt. The mixture was stirred for 5 min. To the mixture was added 10% aq Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. The aqueous mixture was extracted with Et<sub>2</sub>O, and the combined organic layer was successively washed with H<sub>2</sub>O and brine. After the general drying procedure, the resulting residue was purified by column chromatography (2.0 g of SiO<sub>2</sub>, *n*-hexane/EtOAc = 6/1 to 1/1) to afford 26 (12.5 mg, 65% yield). (2) To a solution of 25 (20 mg, 16 µmol) in a mixture of MeCN and H<sub>2</sub>O (10/1 v/v, 0.5 mL) was added NISac (9.9 mg, 32 µmol) at 0 °C. The mixture was stirred for 2 h at 0 °C. To the mixture was added 10% aq Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. The subsequent procedures were same with the above to afford 26 (10.7 mg, 55% yield).

Entry 7. To a solution of 25 (20 mg, 16  $\mu$ mol) in a mixture of CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O (10/1 v/v, 300  $\mu$ L) were added H<sub>2</sub>SO<sub>4</sub>-silica<sup>52</sup> (5 mg) and NIS (4.3 mg, 19  $\mu$ mol) at 0 °C. The mixture was stirred for 15 min at rt, Production of trace 26 was detected by a mass spectrum and TLC analysis. To the reaction mixture were added THF (100  $\mu$ L) and H<sub>2</sub>O (50  $\mu$ L) at 0 °C. The mixture was

stirred for 36 h at rt. Although **26** was detected, the reaction was not concluded. In addition, many byproducts appeared during the reaction.

Entry 8. To a stirred mixture of thioglucoside 25 (259 mg, 208 μmol) and H<sub>2</sub>O (1.0 mL) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added a solution of NIS (225 mg, 1.00 mmol) and TfOH (10.2 mg, 67.8 μmol) in THF/CH<sub>2</sub>Cl<sub>2</sub> (40/1 v/v, 10 mL). The mixture was stirred for 30 min at rt. To the reaction mixture was added 10% of aq Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> until the mixture became colorless. The aqueous mixture was extracted with Et<sub>2</sub>O. The combined organic layer was successively washed with H<sub>2</sub>O and brine. After the general drying procedure, the resulting residue was purified by column chromatography (15 g of SiO<sub>2</sub>, *n*-hexane/EtOAc = 1/0 to 1/1) to afford **26** (246 mg, 98% yield,  $\alpha/\beta = 49/51$ ) as a colorless syrup, whose NMR data were identical to the literature data:<sup>14</sup> [ $\alpha$ ]<sub>D</sub><sup>25</sup> -42.5 (*c* 1.24, CHCl<sub>3</sub>), lit.<sup>14</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup> –48 (*c* 0.9, CHCl<sub>3</sub>); HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> Calcd for C<sub>76</sub>H<sub>66</sub>O<sub>14</sub>Na 1225.4350, Found 1225.4290.

4,6-(aS)-[4,4',5,5',6,6'-hexakisbenzyloxy-1,1'-biphenyl-2,2'-dicaboxylate]-2,3-di-*O*-benzy l-1-[3,4,5-trisbenzyloxybenzoyl]-D-glucopyranose (28). To a solution of hemiacetal 26 (246 mg, 204  $\mu$ mol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added triethylamine (1 mL). The mixture was stirred for 5 min at rt under Ar atmosphere. This mixture was added to a solution of 27 (376 mg, 819  $\mu$ mol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) at rt. The mixture was stirred for 17 h at rt under Ar atmosphere. The reaction was quenched by addition of 3 M aq HCl until pH of the mixture became ~7. The aqueous mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layer was successively washed with H<sub>2</sub>O and brine. Besides syrupy 28, 3,4,6-tri-*O*-benzylgallic acid and the corresponding acid anhydride were produced as byproducts. These byproducts were easily crystallized. Therefore, addition of cold EtOAc dissolved the desired 28 mainly, and filtration of the mixture removed the byproducts. This procedure was repeated 3 times after the general drying procedure. Then the

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filtrate was concentrated. The obtained syrup was purified by column chromatography (30 g of SiO<sub>2</sub>, *n*-hexane/EtOAc = 1/0 to 3/1) to afford **28** (324 mg, 97% yield,  $\alpha/\beta = 2/98$ ) as a yellow syrup. The anomeric ratio was determined by the HPLC (column: YMC-Pack R&D SIL, D-SIL-5-A, 250 × 20 mm, S-5 µm, 120A; eluent: *n*-hexane/EtOAc = 6/1).

Data for α-**28**:  $[\alpha]_D^{24}$  –24.0 (*c* 0.15, CHCl<sub>3</sub>); IR (neat) 3108, 3088, 3063, 3031, 3007, 2955, 2923, 2872, 2851, 1748, 1732, 1592, 1497, 1482, 1455, 1431, 1416, 1369, 1329, 1260, 1229, 1211, 1188, 1150, 1100, 1078, 1028, 1003, 961, 911, 858, 843, 804, 739, 696 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.47–7.27 (m, 43H), 7.24–6.97 (m, 14H), 6.92 (s, 1H), 6.79 (s, 1H), 6.40 (d, J = 3.8 Hz, 1H), 5.22–4.69 (m, 24H), 4.06–3.96 (m, 2H), 3.88 (dd, J = 3.8, 9.3 Hz, 1H), 3.77 (br d, J = 13.0 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 167.9 (s), 167.0 (s), 164.4 (s), 152.8 (s), 152.8 (s), 152.7 (s), 152.7 (s, 2C), 152.5 (s), 145.2 (s), 144.7 (s), 143.3 (s), 138.5 (s), 138.3 (s), 137.9 (s), 137.8 (s), 137.6 (s), 137.5 (s, 3C), 136.9 (s, 2C), 136.7 (s), 136.6 (s, 2C), 129.1–127.5 (19 peaks were observed overlapping many doublets, 55C), 124.9 (s), 124.4 (s), 123.8 (s), 110.1 (d, 2C), 108.2 (d), 108.1 (d), 90.9 (d), 79.4 (d), 78.5 (d), 75.8 (t), 75.8 (t), 75.4 (t), 75.3 (t, 2C), 74.6 (t), 73.7 (t), 71.7 (t), 71.6 (t), 71.6 (d), 71.5 (t, 2C), 70.2 (d), 63.5 (t); HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> Calcd for C<sub>104</sub>H<sub>88</sub>O<sub>18</sub>Na 1648.5902, Found 1648.5962.

Data for  $\beta$ -**28**:  $[\alpha]_D^{25}$  –36.5 (*c* 0.23, CHCl<sub>3</sub>); IR (neat) 3090, 3065, 3033, 3007, 2923, 2872, 2853, 2361, 2342, 1746, 1736, 1592, 1499, 1455, 1429, 1370, 1335, 1188, 1144, 1098, 1057, 1028, 976, 910, 844, 825, 815, 739, 696 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.46–7.26 (m, 38H), 7.25–7.17 (m, 7H), 7.15–7.08 (m, 8H), 6.90 (s, 1H), 6.67 (s, 1H), 5.90 (d, *J* = 8.3 Hz, 1H), 5.20 (dd, *J* = 9.8, 9.7 Hz, 1H), 5.17–5.03 (m, 15H), 5.00 (d, *J* = 10.7, 1H), 4.90 (d, *J* = 10.8, 2H), 4.84 (d, *J* = 11.0 Hz, 1H), 4.82 (d, *J* = 11.7 Hz, 1H), 4.77 (d, *J* = 10.7 Hz, 1H), 4.71 (d, *J* = 11.7 Hz, 1H), 4.65 (d, *J* = 11.1 Hz, 1H), 4.55 (d, *J* = 11.1 Hz, 1H), 4.03–3.95 (m, 2H), 3.85 (dd, *J* = 9.4, 10.5 Hz) = 0.50 Hz = 0.50

9.8 Hz, 1H), 3.80 (dd, J = 8.3, 9.4 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  167.9 (s), 167.0 (s), 164.5 (s), 152.8 (s, 2C), 152.8 (s), 152.7 (s), 152.6 (s), 152.5 (s), 145.2 (s), 144.6 (s), 143.3 (s), 138.2 (s), 138.1 (s, 2C), 137.9 (s), 137.8 (s), 137.7 (s), 137.6 (s), 137.5 (s), 136.7 (s, 2C), 136.7 (s, 2C), 136.7 (s, 2C), 136.7 (s), 129.1–127.5 (19 peaks were observed overlapping many doublets, 55C), 124.6 (s), 123.9 (s), 123.7 (s), 109.7 (d, 2C), 108.3 (d), 108.0 (d), 94.8 (d), 81.7 (d), 81.4 (d), 75.7 (t), 75.4 (t), 75.3 (t, 2C), 75.2 (t), 75.2 (t), 75.0 (t), 72.3 (d), 71.9 (d), 71.6 (t), 71.4 (t, 3C), 63.6 (t); HRMS (ESI-TOF) m/z: [M + Na]<sup>+</sup> Calcd for C<sub>104</sub>H<sub>88</sub>O<sub>18</sub>Na 1648.5902, Found 1648.5828.

(-)-Strictinin (1). To a solution of undecabenzyl ether β-28 (61.2 mg, 34.6 µmol) in THF (1 mL) and MeOH (1 mL) was added Pd(OH)<sub>2</sub> on carbon (20 wt. %, 26.4 mg, 188 µmol). The mixture was stirred for 3 h at rt under H<sub>2</sub> atmosphere. The mixture was filtered through a cotton-Celite pad to remove Pd. The concentrated filtrate was purified by reverse phase column chromatography and gel permeation chromatography (2 g of Cosmosil 140C18-PREP, acetone only, followed by 2 g of TOYOPEARL HW-40C, MeOH only) to afford (-)-strictinin (1) (23.6 mg, 99% yield) as a white amorphous solid. <sup>1</sup>H NMR data for **1** were identical to the literature data (see SI):<sup>2</sup> [ $\alpha$ ]<sub>D</sub><sup>24</sup> –2.94 (*c* 0.16, MeOH), lit.<sup>2</sup> [ $\alpha$ ]<sub>D</sub> –3.1 (*c* 0.4, MeOH); <sup>13</sup>C NMR (100 MHz, acetone-*d*<sub>6</sub>) δ 168.5 (s), 168.3 (s), 165.5 (s), 146.1 (s, 2C), 145.0 (s, 2C), 144.8 (s), 144.7 (s), 139.4 (s), 136.5 (s), 136.2 (s), 127.0 (s), 126.6 (s), 120.9 (s), 116.3 (s), 116.0 (s), 110.4 (d, 2C), 108.2 (d), 107.9 (d), 96.0 (d), 75.6 (d), 74.6 (d), 73.3 (d), 72.8 (d), 63.7 (t); HRMS (ESI-TOF) *m/z*; [M – H]<sup>-</sup> Calcd for C<sub>27</sub>H<sub>21</sub>O<sub>18</sub> 633.0728, Found 633.0685.

**Dimethyl (aS)-4,4',5,5',6,6'-hexakisbenzyloxybiphenyl-6,6'-dicarboxylate (aS-29).** To a solution of **25** (50.0 mg, 40.1  $\mu$ mol) in MeOH (2 mL) and THF (1 mL) was added NaOMe (5.4 mg, 0.10 mmol). The mixture was stirred at rt for 1 h, at 55 °C for 3 h, refluxed for 17 h, and cooled to rt. To the mixture was added protic ion-exchanger resin, IR-120 PLUS (H) until the pH

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of the mixture became ~7. The mixture was filtered through a cotton pad. The filtrate was concentrated and purified by column chromatography (5.0 g of SiO<sub>2</sub>, *n*-hexane/EtOAc = 7/1 to 1/3) to afford (a*S*)-**29** (26.4 mg, 73% yield) and **14** (12.4 mg, 76% yield) both as a colorless oil. <sup>1</sup>H NMR data and optical rotation for **29** were identical to the literature data.<sup>44</sup>

**Direct glycosyl ester formation of 25 with 30.** To a solution of **25** (50.0 mg, 40.1 µmol) and carboxylic acid **30** (52.9 mg, 120 µmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) were added MeOTf (26.3 mg, 160 µmol) and MS 4A (30.0 mg) at rt under Ar atmosphere. The mixture was stirred for 1 h. Then, to the mixture were added further MeOTf (26.3 mg, 160 µmol). The mixture was stirred for 7.5 h. To the mixture was added 2,6-lutidine (1 mL). The mixture was refluxed for 9.5 h and cooled to rt. To the mixture was added 1 M aq HCl until the pH of it became ~6. The aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with H<sub>2</sub>O and brine. After the general drying procedure, the resulting residue was purified by column chromatography (15.0 g of SiO<sub>2</sub>, *n*-hexane/EtOAc = 7/1 to 0/1) to afford **28** (56.4 mg, 87% yield,  $\alpha/\beta = 83/17$ ) as a colorless syrup. The anomeric ratio was determined on the basis of integration of anomeric proton peak of the <sup>1</sup>H NMR spectrum.

Acknowledgment. We thank Osaka Synthetic Chemical Laboratories, Inc. for provision of EDCI. JSPS KAKENHI (Grant Number 22550047) and SUBOR grant partly supported this work.

Supporting Information. Comparison of <sup>1</sup>H NMR spectra of synthetic and natural strictinin, the full description of General methods, and <sup>1</sup>H and <sup>13</sup>C NMR spectra for 1, 11–14, 16, 20, 22–26, 28, and 29. This material is available free of charge via the Internet at http://pubs.acs.org.

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