JOC The Journal of Organic Chemistry

Article

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

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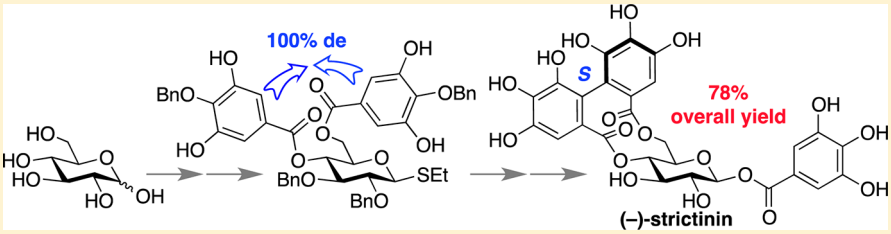
Supporting Information



ABSTRACT: This paper describes a total synthesis of (−)-strictinin, an ellagitannin that is 1-*O*-galloyl-4,6-*O*-(*S*)-hexahydroxydiphenoyl (HHDP)-*β*-D-glucose. In the study, total efficiency of the synthesis was improved to produce a 78% overall yield in 13 steps from D-glucose. In the synthesis, formation of the 4,6-(*S*)-HHDP bridge including the 11-membered bislactone ring was a key step, in which intramolecular aryl−aryl coupling was adopted. The coupling was oxidatively induced by $CuCl_2$−*n*-$BuNH_2$ 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.

INTRODUCTION

(−)-Strictinin (**1**), 1-*O*-galloyl-4,6-*O*-(*S*)-hexahydroxydiphenoyl (HHDP)-*β*-D-glucopyranose (Figure 1), is an ellagitannin

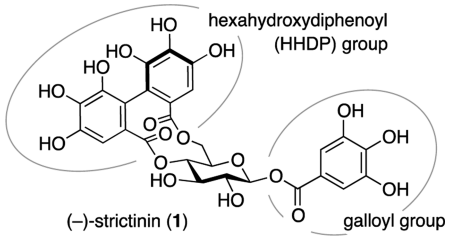


Figure 1. Structure of (−)-strictinin (**1**).

that was first isolated from the leaves of *Casuarina stricta* (Casuarinaceae) and whose structure was characterized by Okuda et al.[1,2] Since then, many plant species have been revealed to produce **1**.[3] In addition, **1** is a compound that has frequently appeared in tea sciences.[4] Because of its relatively good availability compared to that of general natural ellagitannins, the biological activities of **1** have been extensively examined and found to be significant in pharmaceutical utilization, including antiallergic and immunostimulating activities.[5−12]

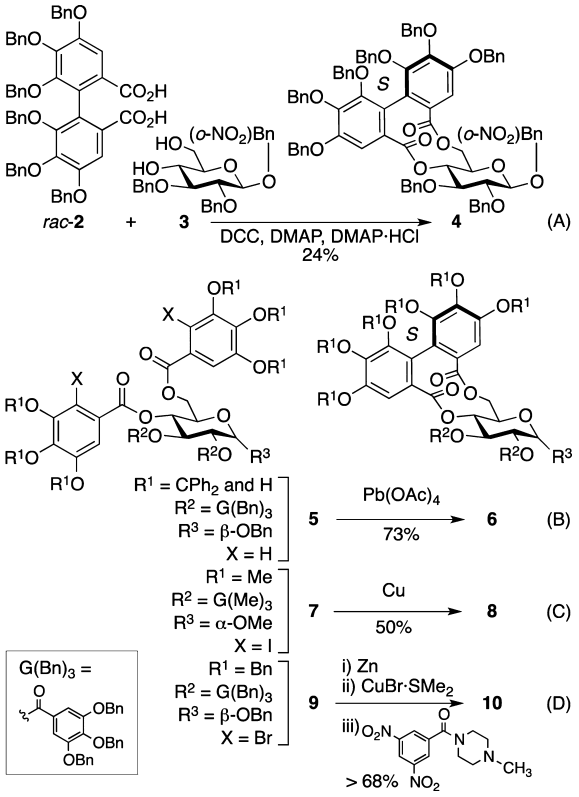
Despite the investigations of its biological activities and attempts to isolate **1**, the synthesis of **1** has only been reported by Khanbabaee et al.[13] They achieved the total synthesis of **1** through double esterification (Scheme 1, eq A). The 4,6-(*S*)-HHDP compound **4** is obtained as a single 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**.[14] 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.[15] However, the preparation of (*S*)-**2** requires extra synthetic steps.[16] Improvements in the 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.[17]

For the formation of the 4,6-HHDP bridge, intramolecular coupling of the galloyl groups on the 4- and 6-oxygens of glucose has been the other strategy. The coupling was first employed by Feldman et al. (Scheme 1, eq B) in the synthesis of tellimagrandin I,[18] 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** (Scheme 1, eq C).[19] Most recently, Spring et al. applied their original method of aryl−aryl coupling to 4,6-HHDP formation (Scheme 1, eq D).[20] This 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.[21] 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

Received: February 9, 2013
Published: April 8, 2013

dx.doi.org/10.1021/jo4003135 | J. Org. Chem. 2013, 78, 4319−4328

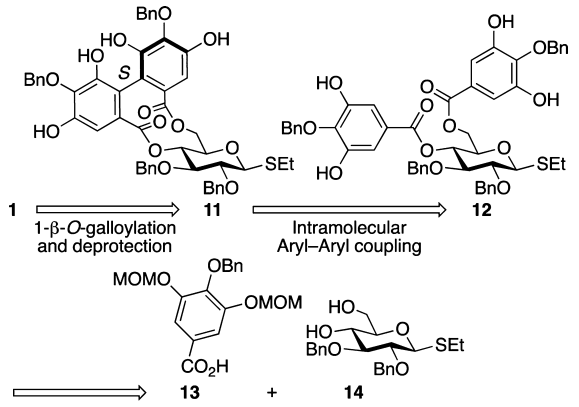
Scheme 1. Previous Formation of the 4,6-HHDP Bridge



additional steps required for the preinstallation of bromine. In the study, we described the total synthesis of **1** where we emphasized the overall efficiency and the optimized formation of the 4,6-(*S*)-HHDP bridge.

The retrosynthetic analysis of **1** is outlined in Scheme 2. We envisioned a *β*-selective esterification would install the required

Scheme 2. Retrosynthetic Analysis of 1

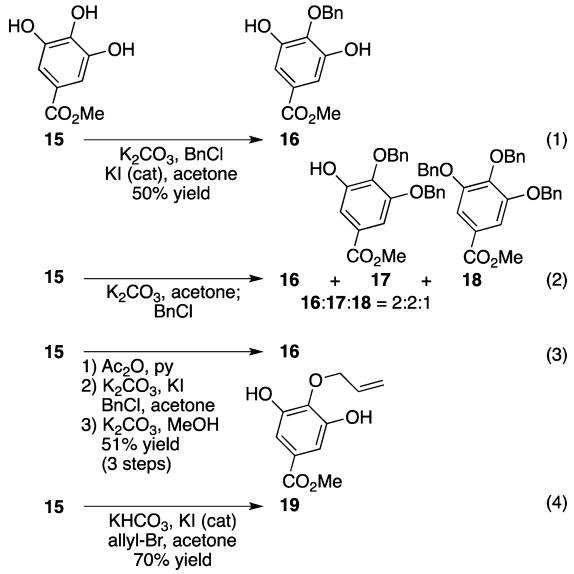


anomeric galloyl group at the final stage of the synthesis. To construct the 4,6-HHDP group of **11**, the bridge would be constructed by $CuCl_2$–*n*-$BuNH_2$ mediated aryl–aryl bond formation.[16,22,23] The digallate **12** would be installed by simple esterification of known carboxylic acid **13**[24,25] and diol **14**.[26] In the synthesis, we focused on high overall yield and stable reproducibility. For this purpose, in the first half of this report we describe improved methods of synthesizing the starting materials **13** and **14**, although they are known compounds. In the latter half, a new synthetic method for **1**, starting from **13** and **14**, is described.

RESULTS AND DISCUSSION

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).[24] Later, Pearson and

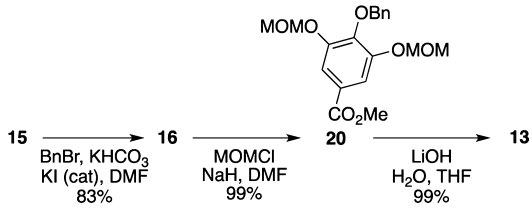
Scheme 3. Previous 4-*O*-Selective Benzylation and Allylation of 15



Bruhn reported the difficulty of reproducibility in this method, along with inherent low regioselectivity in benzylation of **15** (Scheme 3, eq 2).[25] They therefore developed the three-step sequence (Scheme 3, 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** (Scheme 3, eq 4) by changing the base from K_2CO_3 to $KHCO_3$ and by the addition of KI as a catalyst.[27]

On the basis of the above information, we improved the regioselective benzylation of **15** (Scheme 4). Thus, treatment of

Scheme 4. Preparation of 13



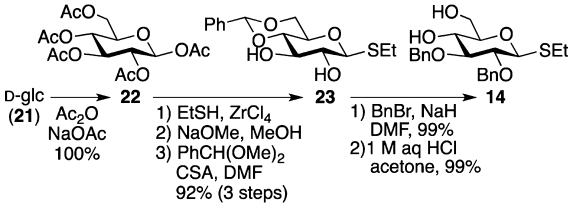
15 with BnBr and $KHCO_3$ in the presence of catalytic KI in DMF produced **16** as the major product along with **17** and **18** as the minor products. A chromatographic separation provided pure **16** in 83% yield. Purification by washing the powdered mixture of **16**, **17**, and **18** with toluene was also possible because of the higher solubility of the byproducts **17** and **18** in toluene than that of **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**

dx.doi.org/10.1021/jo4003135 | J. Org. Chem. 2013, 78, 4319–4328

from D-glucose (**21**) have been found in the literature.[26,28−30] However, the reported yields are less satisfactory in several steps; therefore we optimized each reaction condition to improve efficiency (Scheme 5).

Scheme 5. Synthesis of 14



Reported by Wolfrom and Juliano, per-acetylation of **21** is known to prepare the β-pentaacetylglucose in moderate yield (73%). We found an optimized condition that significantly improved the yield by slow addition of powdered **21** in gently refluxed Ac_2O and NaOAc.

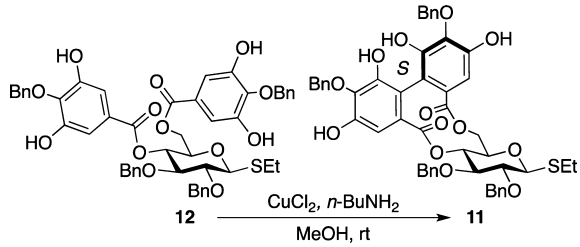
The three-step transformation of **22** to **23** includes (1) Lewis acid mediated β-selective ethylthio glucosidation,[31−39] (2) deacetylation,[32] and (3) regioselective benzylidene formation.[40] We improved the efficiency based on Little's method for the first step.[33] We found the cause of the reported moderate yield (74%) to be decomposition of desired ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside that 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 a blackish color.[41] Accordingly, the next deacetylation soon after the workup of the first step made the decomposition insignificant. The purity of the deacetylated product was excellent, allowing 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 carrying 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 the method developed by Crich and Bowers[26] with the slight modification of 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.

Total Synthesis of 1. 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[42] (Scheme 6). This digalloylation 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.

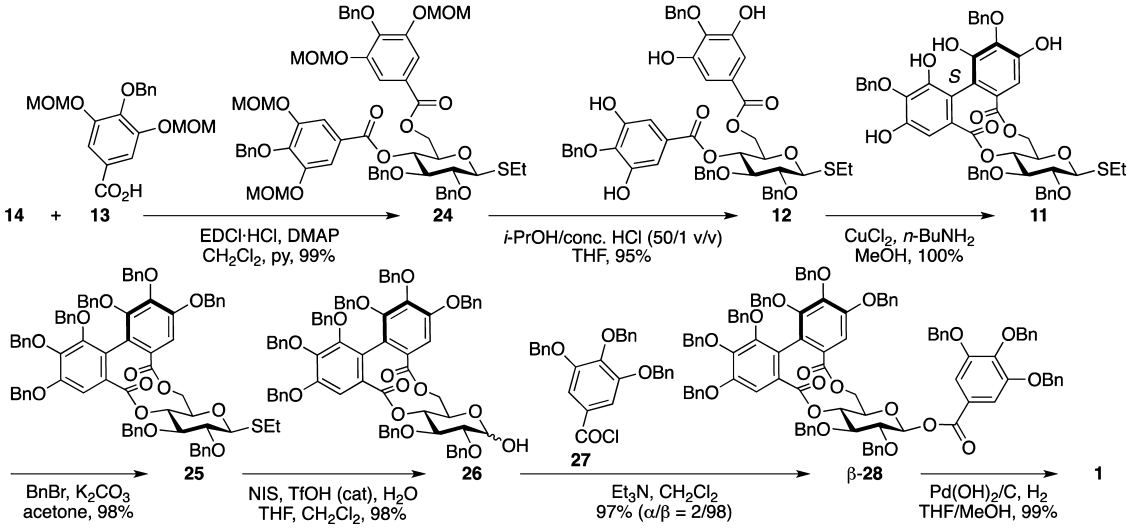
For the transformation of **12** to **11**, we began by using our previously reported method for $CuCl_2$−*n*-$BuNH_2$ catalyzed aryl−aryl coupling reaction (Table 1, entry 1). The coupling

Table 1. Optimizations of Intramolecular Aryl−Aryl Coupling of 12



entry	$CuCl_2$ (equiv)	*n*-$BuNH_2$ (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

Scheme 6. Synthesis of 1



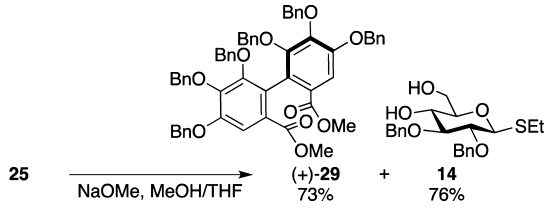
dx.doi.org/10.1021/jo4003135 | J. Org. Chem. 2013, 78, 4319−4328

reaction using 5 equiv of $CuCl_2$ and 20 equiv of *n*-$BuNH_2$ provided 11-membered bislactone **11** in 34% yield, although these reaction conditions were previously used to construct the 12-membered 1,6- and 3,6-HHDP bridge.[22,23] Similar diminished productivity due to ring contraction has been observed in the construction of 10-membered HHDP-bislactone rings.[16] The low yield was due to solvolytic degradation of galloyl and HHDP esters induced by *n*-$BuNH_2$. Accordingly, we reduced the quantity of the reagents, keeping the 1/4 ratio of $CuCl_2$ to *n*-$BuNH_2$ (Table 1, entry 2), which enhanced the yield to 70%. However, a further quantitative decrease of the concentrations of the reagents (Table 1, entry 3) prolonged the reaction time, which resulted in a decreased yield. The 1/4 ratio of $CuCl_2$ to amine has been reported by Brussee et al. to be the optimized reaction condition for intermolecular coupling of 2-naphthol.[43]

We then changed the ratio of $CuCl_2$ to *n*-$BuNH_2$. 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 an excessive amount of *n*-$BuNH_2$ 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 ratios of $CuCl_2$ to *n*-$BuNH_2$, the reaction conditions that afforded **11** in 99% and 100% yield in 30 and 15 min, respectively (Table 1, entries 5 and 6). The quick completion of the coupling reaction before the solvolysis became conspicuous was the key 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^3 chirality of the pyranose was completely transferred to the axial chirality of the HHDP group.

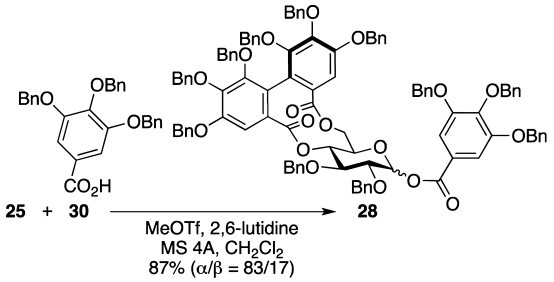
The axial chirality of **11** was confirmed by the liberation of the HHDP group, introducing it to a known compound. Thus, after benzylation of the phenolic hydroxy groups of **11** providing **25** (Scheme 6), the HHDP part was released by solvolysis to produce dimethyl diester **29** (Scheme 7). The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

Scheme 7. Solvolysis of 25



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.[45,46] Thus, treatment of thioglucoside **25** with MeOTf in the presence of **30** and MS 4A provided **28** in an α-selective manner (α/β = 83/17). The α-preference of the glycosyl esterification was similar to the stereoselectivities in glycosylation using a 2-*O*-benzylated glycosyl donor.[47] Accordingly, we investigated the

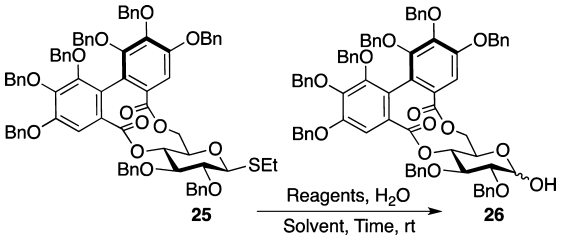
Scheme 8. Glycosyl Esterification of 25



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[48] was poor in

Table 2. Hydrolysis of the Anomeric Ethylthio Group of 25



entry	reagents	solvent	time (h)	yield (%)
1	NBS	THF	0.25–4	18–70[a]
2	MeOTf	THF	2	65
3	$Sn(OTf)_2$, PhIO	THF	2	0
4	$Yb(OTf)_3$, PhIO	THF	2	0[a]
5	NIS	THF	9.5	57[a]
6	NISac	MeCN	0.08	65 (55)[a]
7	NIS H_2SO_4, silica	CH_2Cl_2, THF	36	ND[b]
8	NIS, cat. TfOH	CH_2Cl_2, THF	0.5	98

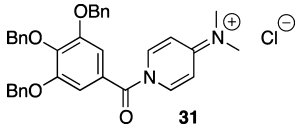
[a]Reaction temperature was 0 °C. [b]Not determined. Reaction temperature was 0 °C to rt.

reproducibility (Table 2, 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[49] provided **26** in moderate yield (Table 2, entry 2) along with an inseparable byproduct, the structure of which was unidentified. The use of PhIO in combination with Lewis acids[50] produced no desired product (Table 2, entries 3 and 4). The employment of NIS resulted in moderate yield (Table 2, entry 5). Darko's reaction using *N*-iodosaccharin (NISac) proceeded rapidly, but the yield of **26** was moderate (Table 2, entry 6).[51] Mukhopadhyay's protocol using NIS and H_2SO_4 immobilized on silica produced **26** along with many byproducts (Table 2, entry 7).[52] After these attempts, we found that application of van Boom's method[53] using NIS and a catalytic amount of TfOH was quite effective; **26** was formed in 98% yield (Table 2, 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 TfOH to a solution of **25** resulted in a low yield. According to the armed–disarmed theory, as stated by Mydock and Demchenko,[54] thioglucoside **25** is classified as a disarmed glycosyl donor from which the generation of an oxocarbenium intermediate is

dx.doi.org/10.1021/jo4003135 | J. Org. Chem. 2013, 78, 4319–4328

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.[55] 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_3N to afford β-**28** stereoselectively in 97% yield (α/β = 2/98).[57,58] Both the addition of a catalytic amount of DMAP to the reaction mixture and the adoption of Steglich's condensation[59] resulted in low anomeric stereoselectivity, to provide **28** as an α/β = 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.[60] Acylation using acid chlorides in the presence of Et_3N has actualized this property by Bols and Hansen.[57] In the presence of DMAP, the higher reactivity of galloylpyridinium ion intermediate **31** would allow the acylation of the axial hydroxy group (α-OH in this case) to decrease the stereoselectivity.



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Finally, the hydrogenolytic cleavage of the 11 benzyl groups of β-**28** provided **1** in 99% yield (Scheme 6), and its physical and spectral data (optical rotation, ^{1}H NMR, IR, HRMS) were identical to those of natural strictinin.[2] For the final purification, successive chromatography on ODS (Cosmosil 75C18-OPN) and then on TOYOPEARL HW-40C[61] was effective in affording **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-β-D-glucopyranoside (four 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 $MgSO_4$ 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 is represented as "the general drying procedure" in the following experimental methods.

The ^{1}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 follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. The ^{13}C NMR data are reported as the chemical shift with the hydrogen multiplicity obtained from the DEPT spectra. The multiplicities are abbreviated as follows: s, C; d, CH; t, CH_2; and q, CH_3. When the number for carbon was greater 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 for Obtaining the Best Yield.* To a solution of methyl gallate (**15**) (2.00 g, 10.9 mmol) in DMF (100 mL) were added $KHCO_3$ (2.17 g, 21.7 mmol), KI (10.8 mg, 65.2 μmol), and BnBr (1.86 g, 10.9 mmol) at rt under an 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_2O (30 mL) to the residue, the aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with saturated aq NH_4Cl, H_2O, 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, which was charged on the top of a column with 70 g of SiO_2 (dry loading method), that adsorbed the products was brown. 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.[24,25]

(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 $KHCO_3$ (50.0 g, 499 mmol), KI (300 mg, 1.81 mmol), and BnBr (50.0 g, 292 mmol) at rt under a N_2 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 $NaHCO_3$, H_2O, and brine. After the general drying procedure, a white solid was obtained containing **15** (1.4%), **16** (78.3%), **17** (18.9%), and **18** (1.4%). The ratio was determined by ^{1}H NMR spectra. The mixture was successively washed with (1) saturated aq $NaHCO_3$ 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** does. 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 an Ar atmosphere, and the mixture was stirred for 1 h at rt. The reaction was quenched by addition of saturated aq NH_4Cl until the pH of the mixture became ∼6. After concentration of the mixture to remove most of the DMF, H_2O (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_4Cl, H_2O, and brine. After the general drying procedure, the mixture was purified by column chromatography (350 g of SiO_2, *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^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $[M + Na]^+$ calcd for $C_{19}H_{22}O_7Na$ 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 $LiOH·H_2O$ (6.93 g, 165 mmol) in H_2O (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 the THF and MeOH. H_2O (20 mL) was added to the resulting mixture. 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 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.[23]

Penta-*O*-acetyl-β-D-glucopyranose (22). To a gently refluxed Ac_2O (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

dx.doi.org/10.1021/jo4003135 | J. Org. Chem. 2013, 78, 4319−4328

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_2O 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 been adequately characterized (mp and optical rotation of **22** have been reported),[28] we describe the data: mp 130−135 °C, lit.[28] 133.5−134 °C; $[\alpha]_D^{25}$ +3.9 (*c* 1.00, $CHCl_3$), lit.[13] $[\alpha]_D^{22}$ +2 (*c* 0.9, $CHCl_3$); IR (neat) 3029, 2969, 2951, 2907 1755, 1740, 1381, 1372, 1233, 1224, 1046, 914, 704, 642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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* $[M + Na]^+$ calcd for $C_{16}H_{22}O_{11}Na$ 413.1057, found 413.1060.

Ethyl 4,6-*O*-Benzylidene-1-thio-β-D-glucopyranoside (23). To a solution of pentaacetate **22** (3.00 g, 7.69 mmol) in CH_2Cl_2 (80 mL) were added ethanethiol (573 mg, 9.22 mmol) and $ZrCl_4$ (2.15 g, 9.22 mmol). The mixture was stirred for 2 h at 0 °C under an Ar atmosphere. The reaction was quenched by addition of ice/water (50 mL). The aqueous mixture was extracted with CH_2Cl_2. The combined organic layer was successively washed with 1 M aq HCl, saturated aq $NaHCO_3$, H_2O, 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 $PhCH(OMe)_2$ (1.40 g, 9.23 mmol) and CSA (536 mg, 2.31 mmol) at rt. The reaction was carried out using a rotary evaporator under reduced pressure (∼15 mmHg) removing methanol for 2 h at rt; stirring of the 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 $NaHCO_3$ until a white powder precipitated. It was cooled to 0 °C and filtered using a Hirsch funnel. The crude product was purified by recrystallization (EtOAc/*n*-hexane) to afford **23** (2.21 g, 92% for three steps) as a white powder. ^1H NMR data for 2,3-diol **23** were identical to the literature data.[40]

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 an Ar atmosphere. The mixture was stirred for 2 h at 0 °C. To the reaction mixture was added saturated aq NH_4Cl 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_4Cl, H_2O, and brine. After the general drying procedure, the resulting residue was purified by successive column chromatography (30 g of SiO_2, *n*-hexane/EtOAc = 6/1 to 2/1, followed by 30 g of SiO_2, *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, ^1H NMR data of which were identical to the literature data.[62]

Ethyl 2,3-Di-*O*-benzyl-1-thio-β-D-glucopyranoside (14). *(i) Hydrolysis 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 ∼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 aq $NaHCO_3$, H_2O, and brine. After the general drying procedure, the resulting residue was purified by column chromatography (2 g of SiO_2, *n*-hexane/EtOAc = 9/1 to 2/1) to afford 4,6-diol **14** (40.6 mg, 99% yield) as a straw-colored amorphous solid, ^1H NMR data of which were identical to the literature data.[29]

(ii) Hydrolysis Using Aqueous Acetic Acid. A solution of ethyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (808 mg, 1.70 mmol) in aq AcOH (AcOH, 40 mL; H_2O, 10 mL) was refluxed for 30 min and then cooled to rt. Toluene (50 mL) was added to the mixture, and the solution was concentrated to remove AcOH and H_2O azeotropically. This procedure was repeated five times. The resulting residue was purified by column chromatography (20 g of SiO_2, *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-D-glucopyranoside (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_2Cl_2 (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 an Ar atmosphere. The reaction was quenched by addition of 1 M aq HCl until the pH of the mixture became ∼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_2, *n*-hexane/EtOAc = 4/1 to 2/1) to afford 4,6-digallate **24** (2.33 g, 99% yield) as a colorless amorphous solid: $[\alpha]_D^{25}$ −14.6 (*c* 1.56, $CHCl_3$); 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^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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* = 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9 (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 (nine 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* $[M + Na]^+$ calcd for $C_{58}H_{64}O_{17}SNa$ 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 of 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 eluant used 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 the mixture had cooled to rt, the reaction was quenched by addition of saturated aq $NaHCO_3$ until the pH of the mixture became ∼7. After concentration of the mixture to remove most of the *i*-PrOH, the aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with saturated aq $NaHCO_3$, H_2O, and brine. After the general drying procedure, the resulting residue was purified by column chromatography (60 g of SiO_2, *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, $CHCl_3$); 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^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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* = 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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* $[M + Na]^+$ calcd for $C_{50}H_{48}O_{13}SNa$ 911.2713, found 911.2670.

dx.doi.org/10.1021/jo4003135 | J. Org. Chem. 2013, 78, 4319−4328

Table 1: Ethyl 4,6-(a*S*)-[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 $CuCl_2$ (15.1 mg, 112 μmol) and *n*-$BuNH_2$ (32.9 mg, 450 μmol) in MeOH (1 mL) was stirred for 30 min at rt to prepare a blue solution of $CuCl_2$–*n*-$BuNH_2$ complex under an Ar atmosphere. Then a solution of digallate **12** (20.0 mg, 22.5 μmol) in MeOH (1 mL) was added to the solution of $CuCl_2$–*n*-$BuNH_2$ complex. The mixture was stirred for 4 h at rt. The reaction mixture was diluted with Et_2O (3 mL), and 5 M aq HCl (5 mL) and Et_2O (3 mL) were added. After extraction of the aqueous mixture with Et_2O, the combined organic layer was successively washed with 3 M aq HCl, H_2O, saturated aq $NaHCO_3$, H_2O, and brine. After the general drying procedure, the resulting residue was purified by column chromatography (3 g of SiO_2, *n*-hexane/EtOAc = 6/1 to 2/1) to afford **11** (6.8 mg, 34% yield).

Entry 2. A solution of $CuCl_2$ (9.1 mg, 68 μmol) and *n*-$BuNH_2$ (19.8 mg, 270 μmol) 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 μmol) in MeOH (1.2 mL). The mixture was stirred for 13 h at rt. The subsequent procedures were the same as those in Entry 1 and afforded **11** (13.9 mg, 70% yield).

Entry 3. A solution of $CuCl_2$ (7.6 mg, 56 μmol) and *n*-$BuNH_2$ (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 the same as those in Entry 1 and afforded **11** (16.2 mg, 65% yield).

Entry 4. A solution of $CuCl_2$ (30.3 mg, 225 μmol) and *n*-$BuNH_2$ (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 μmol) in MeOH (3 mL). The mixture was stirred for 2.5 h at rt. The reaction mixture was diluted with Et_2O (5 mL), and 5 M aq HCl (10 mL) and Et_2O (5 mL) were added. After extraction of the aqueous mixture with Et_2O, the combined organic layer was successively washed with 3 M aq HCl, H_2O, saturated aq $NaHCO_3$, H_2O, and brine. After the general drying procedure, the resulting residue was purified by column chromatography (8 g of SiO_2, *n*-hexane/EtOAc = 6/1 to 2/1) to afford **11** (88.4 mg, 89% yield).

Entry 5. A solution of $CuCl_2$ (30.3 mg, 225 μmol) and *n*-$BuNH_2$ (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 μmol) in MeOH (3 mL). The mixture was stirred for 30 min at rt. The subsequent procedures were the same as those in Entry 4 and afforded **11** (98.3 mg, 99% yield) as a yellow syrup.

Entry 6. A solution of $CuCl_2$ (30.3 mg, 225 μmol) and *n*-$BuNH_2$ (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 the same as those in Entry 4 and afforded **11** (99.7 mg, 100% yield): $[\alpha]_D^{24}$ −28.1 (*c* 1.60, $CHCl_3$); 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^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 (eight peaks 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* $[M + Na]^+$ calcd for $C_{50}H_{46}O_{13}SNa$ 909.2557, found 909.2516.

Ethyl 4,6-(a*S*)-[4,4′,5,5′,6,6′-Hexakisbenzyloxy-1,1′-biphenyl-2,2′-dicarboxylate]-2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside (25). A mixture of tetraol **11** (98.3 mg, 111 μmol), K_2CO_3 (122 mg, 885 μmol), and BnBr (151 mg, 885 μmol) in acetone (2.5 mL) was stirred for 13 h at rt under an Ar atmosphere. The mixture was then filtered through a cotton–Celite pad to remove excess K_2CO_3. Saturated aq NH_4Cl (10 mL) was added to the filtrate. The aqueous mixture was extracted with Et_2O. 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_2, *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, $CHCl_3$); 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^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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* $[M + Na]^+$ calcd for $C_{78}H_{70}O_{13}SNa$ 1269.4435, found 1269.4393.

Table 2: 4,6-(a*S*)-[4,4′,5,5′,6,6′-Hexakisbenzyloxy-1,1′-biphenyl-2,2′-dicarboxylate]-2,3-di-*O*-benzyl-D-glucopyranose (26). *Entry 1.* To a solution of thioglucoside **25** (25.2 mg, 20.2 μmol) in THF (1.1 mL) and H_2O (300 μL) was added NBS (9.0 mg, 51 μmol) at 0 °C. The mixture was stirred for 10 min at 0 °C. To the mixture was added 10% aq $Na_2S_2O_3$. 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 resulting residue was purified by column chromatography (1.5 g of SiO_2, *n*-hexane/EtOAc = 4/1 to 0/1) to afford **26** (12.0 mg, 49% yield). This procedure was repeated six times using **25** and NBS (12.5 and 4.5 mg, 25.2 and 9.0 mg, 64.2 and 23 mg, 100 and 29 mg, 115 and 41 mg, and 898 and 892 mg, respectively) to provide **26** in 40, 49, 68, 18, 70, and 22% yield, respectively.

Entry 2. To a solution of **25** (20 mg, 16 μmol) in THF (300 μL) were added MeOTf (26 mg, 160 μmol) and H_2O (10 mg, 560 μmol) at rt. The mixture was stirred for 2 h at rt. To the mixture was added Et_3N (100 μL). The mixture was diluted with Et_2O (10 mL) and washed with brine. After the general drying procedure, the resulting residue was purified by column chromatography (2 g of SiO_2, *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 μmol) in THF (300 μL) were added $Sn(OTf)_2$ (6.7 mg, 160 μmol), PhIO (4.6 mg, 20 μmol), and H_2O (10 mg, 560 μmol) at rt. The mixture was stirred for 2 h at rt. To the mixture was added saturated aq $NaHCO_3$. 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 **26** was not produced.

Entry 4. To a solution of **25** (20 mg, 16 μmol) in THF (300 μL) were added $Yb(OTf)_3$ (9.9 mg, 160 μmol), PhIO (4.6 mg, 20 μmol), and H_2O (10 mg, 560 μmol) at 0 °C. The mixture was stirred for 2 h at 0 °C. To the mixture was added saturated aq $NaHCO_3$. 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 **26** was not produced.

Entry 5. To a solution of **25** (100 mg, 80 μmol) in a mixture of THF (1.2 mL) and H_2O (200 μL) was added NIS (45.1 mg, 20 μmol) at 0 °C. The mixture was stirred for 1.5 h at 0 °C. To the mixture was added additional NIS (90 mg, 40 μmol). The mixture was stirred for an additional 8 h. To the mixture was added a 10% aq $Na_2S_2O_3$ solution. 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 resulting residue was purified by column chromatography (10 g of SiO_2, *n*-hexane/EtOAc = 6/1 to 2/1) to afford **26** (54.7 mg, 57% yield).

dx.doi.org/10.1021/jo4003135 | J. Org. Chem. 2013, 78, 4319–4328

Entry 6. (1) To a solution of **25** (20 mg, 16 μmol) in a mixture of MeCN and H_2O (10/1 v/v, 0.5 mL) was added NISac[51] (9.9 mg, 32 μmol) at rt. The mixture was stirred for 5 min. To the mixture was added 10% aq $Na_2S_2O_3$. The aqueous mixture was extracted with Et_2O, and the combined organic layer was successively washed with H_2O and brine. After the general drying procedure, the resulting residue was purified by column chromatography (2.0 g of SiO_2, *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_2O (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 $Na_2S_2O_3$. The subsequent procedures were the same as those described above and afforded **26** (10.7 mg, 55% yield).

Entry 7. To a solution of **25** (20 mg, 16 μmol) in a mixture of CH_2Cl_2 and H_2O (10/1 v/v, 300 μL) were added H_2SO_4–silica[52] (5 mg) and NIS (4.3 mg, 19 μmol) at 0 °C. The mixture was stirred for 15 min at rt. Production of a trace amount **26** was detected by a mass spectrum and TLC analysis. To the reaction mixture were added THF (100 μL) and H_2O (50 μL) 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_2O (1.0 mL) in CH_2Cl_2 (10 mL) was added a solution of NIS (225 mg, 1.00 mmol) and TfOH (10.2 mg, 67.8 μmol) in THF/CH_2Cl_2 (40/1 v/v, 10 mL). The mixture was stirred for 30 min at rt. To the reaction mixture was added 10% aq $Na_2S_2O_3$ until the mixture became colorless. The aqueous mixture was extracted with Et_2O. The combined organic layer was successively washed with H_2O and brine. After the general drying procedure, the resulting residue was purified by column chromatography (15 g of SiO_2, *n*-hexane/EtOAc = 1/0 to 1/1) to afford **26** (246 mg, 98% yield, α/β = 49/51) as a colorless syrup whose NMR data were identical to the literature data:[14] $[\alpha]_D^{25}$ −42.5 (*c* 1.24, $CHCl_3$), lit.[14] $[\alpha]_D^{20}$ −48 (*c* 0.9, $CHCl_3$); HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{76}H_{66}O_{14}Na$ 1225.4350, found 1225.4290.

4,6-(a*S*)-[4,4′,5,5′,6,6′-Hexakisbenzyloxy-1,1′-biphenyl-2,2′-dicarboxylate]-2,3-di-*O*-benzyl-1-[3,4,5-trisbenzyloxybenzoyl]-D-glucopyranose (28). To a solution of hemiacetal **26** (246 mg, 204 μmol) in CH_2Cl_2 (5 mL) was added triethylamine (1 mL). The mixture was stirred for 5 min at rt under an Ar atmosphere. This mixture was added to a solution of **27** (376 mg, 819 μmol) in CH_2Cl_2 (15 mL) at rt. The mixture was stirred for 17 h at rt under an Ar atmosphere. The reaction was quenched by addition of 3 M aq HCl until the pH of the mixture became ∼7. The aqueous mixture was extracted with CH_2Cl_2. The combined organic layer was successively washed with H_2O 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 three times after the general drying procedure. Then the filtrate was concentrated. The obtained syrup was purified by column chromatography (30 g of SiO_2, *n*-hexane/EtOAc = 1/0 to 3/1) to afford **28** (324 mg, 97% yield, α/β = 2/98) as a yellow syrup. The anomeric ratio was determined by HPLC (column, YMC-Pack R&D SIL, D-SIL-5-A, 250 × 20 mm, S-5 μm, 120A; eluant, *n*-hexane/EtOAc = 6/1).

Data for α-**28**: $[\alpha]_D^{24}$ −24.0 (*c* 0.15, $CHCl_3$); 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^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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]$^+$ calcd for $C_{104}H_{88}O_{18}Na$ 1648.5902, found 1648.5962.

Data for β-**28**: $[\alpha]_D^{25}$ −36.5 (*c* 0.23, $CHCl_3$); 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^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, 9.8 Hz, 1H), 3.80 (dd, *J* = 8.3, 9.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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), 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]$^+$ calcd for $C_{104}H_{88}O_{18}Na$ 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 $Pd(OH)_2$ on carbon (20 wt %, 26.4 mg, 188 μmol). The mixture was stirred for 3 h at rt under a H_2 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. ^{1}H NMR data for **1** were identical to the literature data (see Supporting Information):[2] $[\alpha]_D^{24}$ −2.94 (*c* 0.16, MeOH), lit.[2] $[\alpha]_D$ −3.1 (*c* 0.4, MeOH); ^{13}C NMR (100 MHz, acetone-d_6) 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]$^-$ calcd for $C_{27}H_{21}O_{18}$ 633.0728, found 633.0685.

Dimethyl (a*S*)-4,4′,5,5′,6,6′-Hexakisbenzyloxybiphenyl-6,6′-dicarboxylate (a*S*-29). To a solution of **25** (50.0 mg, 40.1 μmol) 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 and 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 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_2, *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 colorless oils. ^{1}H NMR data and optical rotation for **29** were identical to the literature data.[44]

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_2Cl_2 (4 mL) were added MeOTf (26.3 mg, 160 μmol) and MS 4A (30.0 mg) at rt under an Ar atmosphere. The mixture was stirred for 1 h. Then, to the mixture was added additional 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 became ∼6. 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 resulting residue was purified by column chromatography (15.0 g of SiO_2, *n*-hexane/EtOAc = 7/1 to 0/1) to afford **28** (56.4 mg, 87% yield, α/β = 83/17) as a colorless syrup. The anomeric ratio was determined on the basis of integration of the anomeric proton peak of the ^{1}H NMR spectrum.

dx.doi.org/10.1021/jo4003135 | *J. Org. Chem.* 2013, 78, 4319–4328

■ ASSOCIATED CONTENT

Supporting Information

Comparison of ^{1}H NMR spectra of synthetic and natural strictinin, the full description of general methods, and ^{1}H and ^{13}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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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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

■ REFERENCES

(1) Okuda, T.; Yoshida, T.; Ashida, M.; Yazaki, K. *Chem. Pharm. Bull.* **1982**, *30*, 766−769.

(2) Okuda, T.; Yoshida, T.; Ashida, M.; Yazaki, K. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1765−1772.

(3) (a) Balanophoraceae: Jiang, Z.-H.; Hirose, Y.; Iwata, H.; Sakamoto, S.; Tanaka, T.; Kouno, I. *Chem. Pharm. Bull.* **2001**, *49*, 887−892. (b) Betulaceae: (i) Jin, Z.-X.; Ito, H.; Yoshida, T. *Phytochemistry* **1998**, *48*, 333−338. (ii) Lee, M. W.; Tanaka, T.; Nonaka, G.; Nishioka, I. *Phytochemistry* **1992**, *31*, 2835−2839. (iii) Ishimatsu, M.; Tanaka, T.; Nonaka, G.; Nishioka, I. *Phytochemistry* **1989**, *28*, 3179−3184. (c) Casuarinaceae: (i) Okuda, T.; Yoshida, T.; Ashida, M.; Yazaki, K. *Chem. Pharm. Bull.* **1982**, *30*, 766−769. (ii) Okuda, T.; Yoshida, T.; Ashida, M.; Yazaki, K. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1765−1772. (d) Coriariaceae: Hatano, T.; Hattori, S.; Okuda, T. *Chem. Pharm. Bull.* **1986**, *34*, 4533−4539. (e) Elaeagnaceae: (i) Ito, H.; Miki, K.; Yoshida, T. *Chem. Pharm. Bull.* **1999**, *47*, 536−542. (ii) Yoshida, T.; Tanaka, K.; Chen, X. M.; Okuda, T. *Phytochemistry* **1991**, *30*, 663−666. (iii) Yoshida, T.; Namba, O.; Kurokawa, K.; Amakura, Y.; Liu, Y.-Z.; Okuda, T. *Chem. Pharm. Bull.* **1994**, *42*, 2005−2010. (f) Fagaceae: Feng, H.; Nonaka, G.; Nishioka, I. *Phytochemistry* **1988**, *27*, 1185−1189. (g) Geraniaceae: Latte, K. P.; Kolodziej, H. *Phytochemistry* **2000**, *54*, 701−708. (h) Juglandaceae: Tanaka, T.; Kouno, I. *J. Nat. Prod.* **1996**, *59*, 997−999. (i) Melastomataceae: (i) Yoshida, T.; Ito, H.; Hipolito, I. J. *Phytochemistry* **2005**, *66*, 1972−1983. (ii) Ling, S.-K.; Tanaka, T.; Kouno, I. *J. Nat. Prod.* **2002**, *65*, 131−135. (iii) Yoshida, T.; Nakata, F.; Hosotani, K.; Nitta, A.; Okuda, T. *Phytochemistry* **1992**, *31*, 2829−2833. (iv) Yoshida, T.; Haba, K.; Nakata, F.; Okano, Y.; Shingu, T.; Okuda, T. *Chem. Pharm. Bull.* **1992**, *40*, 66−71. (j) Myrtaceae: (i) El-shenawy, S. M.; Marzouk, M. S.; El Dib, R. A.; Abo Elyazed, H. E.; Shaffie, N. M.; Moharram, F. A. *Rev. Latinoam. Quim.* **2008**, *36*, 103−120. (ii) Yoshimura, M.; Ito, H.; Miyashita, K.; Hatano, T.; Taniguchi, S.; Amakura, Y.; Yoshida, T. *Phytochemistry* **2008**, *69*, 3062−3069. (iii) Shimoda, H.; Tanaka, J.; Kikuchi, M.; Fukuda, T.; Ito, H.; Hatano, T.; Yoshida, T. *J. Agric. Food Chem.* **2008**, *56*, 4444−4449. (iv) Fukuda, T.; Ito, H.; Yoshida, T. *Phytochemistry* **2003**, *63*, 795−801. (v) Tanaka, T.; Orii, Y.; Nonaka, G.; Nishioka, I. *Chem. Pharm. Bull.* **1993**, *41*, 1232−1237. (vi) Maruyama, Y.; Matsuda, H.; Matsuda, R.; Kubo, M.; Hatano, T.; Okuda, T. *Shoyakugaku Zasshi* **1985**, *39*, 261−269. (k) Punicaceae: Tanaka, T.; Nonaka, G.; Nishioka, I. *Phytochemistry* **1985**, *24*, 2075−2078. (l) Rosaceae: (i) Ochir, S.; Park, B. J.; Nishizawa, M.; Kanazawa, T.; Funaki, M.; Yamagishi, T. *J. Nat. Med.* **2010**, *64*, 383−387. (ii) Ito, H.; Nishitani, E.; Hatano, T.; Nakanishi, T.; Inada, A.; Murata, H.; Inatomi, Y.; Matsuura, N.; Ono, K.; Lang, F. A.; Murata, J.; Yoshida, T. *Nat. Med. (Tokyo, Jpn.)* **2001**, *55*, 218. (iii) Lin, J.-H.; Huang, Y.-F. *Chin. Pharm. J. (Taipei, Taiwan)* **1996**, *48*, 231−244. (iv) Hatano, T.; Ogawa, N.; Yasuhara, T.; Okuda, T. *Chem. Pharm. Bull.* **1990**, *38*, 3308−3313. (m) Stachyuraceae: (i) Hatano, T.; Yazaki, K.; Okonogi, A.; Okuda, T. *Chem. Pharm. Bull.* **1991**, *39*, 1689−1693. (ii) Part i of ref 3c. (iii) Part ii of ref 3c. (n) Theaceae: Yagi, K.; Goto, K.; Nanjo, F. *Chem. Pharm. Bull.* **2009**, *57*, 1284−1288.

(4) (a) Ku, K. M.; Choi, J. N.; Kim, J.; Kim, J. K.; Yoo, L. G.; Lee, S. J.; Hong, Y.-S.; Lee, C. H. *J. Agric. Food Chem.* **2010**, *58*, 418−426. (b) Li, H.; Tanaka, T.; Zhang, Y.-J.; Yang, C.-R.; Kouno, I. *Chem. Pharm. Bull.* **2007**, *55*, 1325−1331. (c) Dou, J.; Lee, V. S. Y.; Tzen, J. T. C.; Lee, M.-R. *J. Agric. Food Chem.* **2007**, *55*, 7462−7468. (d) Nakai, M.; Fukui, Y.; Asami, S.; Toyoda-Ono, Y.; Iwashita, T.; Shibata, H.; Mitsunaga, T.; Hashimoto, F.; Kiso, Y. *J. Agric. Food Chem.* **2005**, *53*, 4593−4598. (e) Niino, H.; Sakane, I.; Okanoya, K.; Kuribayashi, S.; Kinugasa, H. *J. Agric. Food Chem.* **2005**, *53*, 3995−3999. (f) Maeda-Yamamoto, M.; Nagai, H.; Asai, K.; Moriwaki, S.; Horie, H.; Kohata, K.; Tachibana, H.; Miyase, T.; Sano, M. *Food Sci. Technol. Res.* **2004**, *10*, 186−190. (g) Hashimoto, F.; Nonaka, G.; Nishioka, I. *Chem. Pharm. Bull.* **1992**, *40*, 1383−1389.

(5) Antiallergic: Tachibana, H.; Kubo, T.; Miyase, T.; Tanino, S.; Yoshimoto, M.; Sano, M.; Yamamoto-Maeda, M.; Yamada, K. *Biochem. Biophys. Res. Commun.* **2001**, *280*, 53−60.

(6) Antiviral: Saha, R. K.; Takahashi, T.; Kurebayashi, Y.; Fukushima, K.; Minami, A.; Kinbara, N.; Ichitani, M.; Sagesaka, Y. M.; Suzuki, T. *Antiviral Res.* **2010**, *88*, 10−18.

(7) Anti-HIV: Yoshida, T.; Ito, H.; Hatano, T.; Kurata, M.; Nakanishi, T.; Inada, A.; Murata, H.; Inatomi, Y.; Matsuura, N.; Ono, K.; Nakane, H.; Noda, M.; Lang, F. A.; Murata, J. *Chem. Pharm. Bull.* **1996**, *44*, 1436−1439.

(8) Antiinflammatory: Lee, C.-J.; Chen, L.-G.; Liang, W.-L.; Wang, C.-C. *Food Chem.* **2009**, *118*, 315−322.

(9) Antioxidant: Zhou, B.; Yang, Li.; Liu, Z.-L. *Chem. Phys. Lipids* **2004**, *131*, 15−25.

(10) Enhancement of other activities: Gondoin, A.; Grussu, D.; Stewart, D.; McDougall, G. J. *Food Res. Int.* **2010**, *43*, 1537−1544.

(11) Inhibition of enzymes: Toshima, A.; Matsui, T.; Noguchi, M.; Qiu, J.; Tamaya, K.; Miyata, Y.; Tanaka, T.; Tanaka, K. *J. Sci. Food Agric.* **2010**, *90*, 1545−1550.

(12) Immunostimulating activity: Monobe, M.; Ema, K.; Kato, F.; Maeda-Yamamoto, M. *J. Agric. Food Chem.* **2008**, *56*, 1423−1427.

(13) Khanbabaee, K.; Schulz, C.; Lötzerich, K. *Tetrahedron Lett.* **1997**, *38*, 1367−1368.

(14) Khanbabaee, K.; Lötzerich, K. *Eur. J. Org. Chem.* **1999**, 3079−3083.

(15) Yamaguchi, S.; Ashikaga, Y.; Nishii, K.; Yamada, H. *Org. Lett.* **2012**, *14*, 5928−5931.

(16) Asakura, N.; Fujimoto, S.; Michihata, N.; Nishii, K.; Imagawa, H.; Yamada, H. *J. Org. Chem.* **2011**, *76*, 9711−9719.

(17) Pouységu, L.; Deffieux, D.; Malik, G.; Natangelo, A.; Quideau, S. *Nat. Prod. Rep.* **2011**, *28*, 853−874.

(18) Feldman, K. S.; Ensel, S. M.; Minard, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 1742−1745.

(19) Dai, D.; Martin, O. R. *J. Org. Chem.* **1998**, *63*, 7628−7633.

(20) Zheng, S.; Laraia, L.; O'Connor, C. J.; Sorrell, D.; Tan, Y. S.; Xu, Z.; Venkitaraman, A. R.; Wu, W.; Spring, D. R. *Org. Biomol. Chem.* **2012**, *10*, 2590−2593.

(21) Su, X.; Thomas, G. L.; Galloway, W. R. J. D.; Surry, D. S.; Spandl, R. J.; Spring, D. R. *Synthesis* **2009**, 3880−3896.

(22) Kasai, Y.; Michihata, N.; Nishimura, H.; Hirokane, T.; Yamada, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 8026−8029.

(23) Yamada, H.; Nagao, K.; Dokei, K.; Kasai, Y.; Michihata, N. *J. Am. Chem. Soc.* **2008**, *130*, 7566−7567.

(24) ElSohly, H. N.; Ma, G. E.; Turner, C. E.; ElSohly, M. A. *J. Nat. Prod.* **1984**, *47*, 445−452.

(25) Pearson, A. J.; Bruhn, P. R. *J. Org. Chem.* **1991**, *56*, 7092−7097.

(26) Crich, D.; Bowers, A. A. *J. Org. Chem.* **2006**, *71*, 3452−3463.
(27) Freeman, A. W.; Chrisstoffels, L. A. J.; Fréchet, J. M. J. *J. Org. Chem.* **2000**, *65*, 7612−7617.
(28) Wolfrom, M. L.; Juliano, B. O. *J. Am. Chem. Soc.* **1960**, *82*, 1673−1677.
(29) Garegg, P. J.; Kvarnström, I.; Niklasson, A.; Niklasson, G.; Svensson, S. C. T. *J. Carbohydr. Chem.* **1993**, *12*, 933−953.
(30) *Methods in Carbohydrate Chemistry. Vol. 2: Reactions of Carbohydrates*; Whistler, R. L., Wolfrom, M. L., Eds.; Academic Press: New York, 1963.
(31) Lemieux, R. U. *Can. J. Chem.* **1951**, *29*, 1079−1091.
(32) Vic, G.; Hastings, J. J.; Howarth, O. W.; Crout, D. H. G. *Tetrahedron: Asymmetry* **1996**, *7*, 709−720.
(33) Contour, M.-O.; Defaye, J.; Little, M.; Wong, E. *Carbohydr. Res.* **1989**, *193*, 283−287.
(34) Das, S. K.; Roy, J.; Reddy, K. A.; Abbineni, C. *Cabohydr. Res.* **2003**, *338*, 2237−2240.
(35) Weng, S.-S.; Lin, Y.-D.; Chen, C.-T. *Org. Lett.* **2006**, *8*, 5633−5636.
(36) Sanhueza, C. A.; Dorta, R. L.; Vázquea, J. T. *Tetrahedron: Asymmetry* **2008**, *19*, 258−264.
(37) Jamoisa, F.; Gofficc, F. L.; Yvina, J. C.; Plusquellecb, D.; Ferriéres, V. *Open Glycosci.* **2008**, *1*, 19−24.
(38) Wang, H.; Su, F.; Zhou, L.; Chen, X.; Le, P. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2796−2800.
(39) Weng, S.-S. *Tetrahedron Lett.* **2009**, *50*, 6414−6417.
(40) Verduyn, R.; Douwes, M.; van der Klein, P. A. M.; Mösinger, E. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1993**, *49*, 7301−7316.
(41) After being recrystallized from a mixture of Et_2O and *n*-hexane, the derived colorless ethylthioglucoside survived intact at −20 °C for a year.
(42) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed.* **1978**, *17*, 569−583.
(43) Brussee, J.; Groenendijk, J. L. G.; te Koppele, J. M.; Jansen, A. C. A. *Tetrahedron* **1985**, *41*, 3313−3319.
(44) Kashiwada, T.; Huang, L.; Ballas, L. M.; Jiang, J. B.; Janzen, W. P.; Lee, K.-H. *J. Med. Chem.* **1994**, *37*, 195−200.
(45) Garegg, P. J. *Acc. Chem. Res.* **1992**, *25*, 575−580.
(46) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734−753.
(47) Fukase, K.; Hasuoka, A.; Kinoshita, I.; Aoki, Y.; Kusumoto, S. *Tetrahedron* **1995**, *51*, 4923−4932.
(48) Motawia, M. S.; Marcussen, J.; Moeller, B. L. *J. Carbohydr. Chem.* **1995**, *14*, 1279−1294.
(49) Lönn, H. *Carbohydr. Res.* **1985**, *139*, 105−113.
(50) Fukase, K.; Kinoshita, I.; Kanoh, T.; Nakai, Y.; Hasuoka, A.; Kusumoto, S. *Tetrahedron* **1996**, *52*, 3897−3904.
(51) Darko, D. *Synlett* **2000**, *4*, 544−546.
(52) Dasgupta, S.; Roy, B.; Mukhopadhyay, B. *Carbohydr. Res.* **2006**, *341*, 2708−2713.
(53) Duynstee, H. I.; de Koning, M. C.; Ovaa, H.; van der Marel, G. A.; van Boom, J. H. *Eur. J. Org. Chem.* **1999**, 2623−2632.
(54) Mydock, L. K.; Demchenko, A. V. *Org. Lett.* **2008**, *10*, 2103−2106.
(55) Jensen, H. H.; Nordstrøm, L. U.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205−9213.
(56) Ren, Y.; Himmeldirk, K.; Chen, X. *J. Med. Chem.* **2006**, *49*, 2829−2837.
(57) Bols, M.; Hansen, H. C. *Acta Chem. Scand.* **1993**, *47*, 818−822.
(58) Binkely, R. C.; Ziepfel, J. C.; Himmeldirk, K. B. *Carbohydr. Res.* **2009**, *344*, 237−239.
(59) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed.* **1978**, *17*, 522−524.
(60) Boons, G.-J., Ed. In *Carbohydrate Chemistry*; Blackie Academic and Professional, Thomson Science: London, 1998; pp 21−25 and 108−110.
(61) Yoshida, T.; Tanaka, K.; Chen, X.-M.; Okuda, T. *Phytochemistry* **1989**, *28*, 2451−2454.
(62) van Seteijin, A. M. P.; Kamerling, J. P.; Viegenthart, F. G. *Carbohydr. Res.* **1992**, *225*, 229−245.