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FULL PAPER

Total Synthesis of Mallotusinin

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Abstract: We describe the total synthesis of mallotusinin that bears a tetrahydroxydibenzofuranoyl (THDBF) bridge between the 2-oxygen and 4-oxygen of glucose on corilagin with a 3,6-*O*-(*R*)-hexahydroxydiphenoyl (HHDP) bridge. The key features of the total synthesis are: (1) improvements of our previously reported method to synthesize corilagin; (2) an establishment of forming the THDBF skeleton via an unusual intramolecular S_NAr reaction of an HHDP analog, and (3) the application of two-step bislactonization strategy for an HHDP bridge construction into the 2,4-*O*-THDBF bridge construction. Oxidative phenol coupling of 1,2,4-orthoacetyl-3,6-di-(4-*O*-benzylgalloyl)-α-D-glucopyranose and the orthoester cleavage of the coupling product without the pyranose–furanose ring transformation are key reactions for the improvement synthesis of corilagin, which enabled the adequate supplement of a corilagin precursor for developing the mallotusinin synthesis. These established methods are expected to development of the synthesis of other ellagitannins with a bridge between the two oxygens of corilagin.

Introduction

Mallotusinin (**1**) is one of the monomeric ellagitannins, usually comprising D-glucose, galloyl group(s), and one or more axial chiral hexahydroxydiphenoyl (HHDP) groups (Figure 1). The Nishioka and Nonaka group isolated **1** in 1989, along with 18 other ellagitannins from the bark of *Mallotus japonicus*.[1] The remarkable structural features of **1** include the pyranose ring of D-glucose exhibiting a flipped chair conformation and further component, a tetrahydroxydibenzofuranoyl (THDBF) group bridging between the 2-oxygen and 4-oxygen (2-O and 4-O) of the glucose. Ellagitannins with a 3,6-*O*-(*R*)-HHDP bridge, as corilagin (**2**),[2] possess such pyranose conformation owing to the lock by the bridge. The 3,6-*O*-(*R*)-HHDP bridged ellagitannins often contain an additional bridge between the 2-O and 4-O of the glucose via esterification,[3] and mallotusinin (**1**) is a representative ellagitannin. These ellagitannins exhibit a variety of biological activities,[4] e.g., **1** shows antioxidant activity and antiproliferative activity against MCF-7 breast cancer cell lines,[5] which are expected to lead to the development of medicinal chemistry. However, no published reports of these synthesis exist; thus, their total syntheses are one of the most important challenges of ellagitannin chemistry.

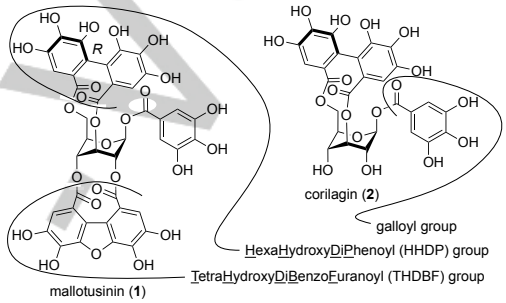

Figure 1. Structures of mallotusinin (**1**) and corilagin (**2**).

The task for the synthesis of mallotusinin (**1**) is the formation of the 2,4-*O*-THDBF bridge. The bridge construction appears difficult because no examples of constructing a bridge other than an HHDP bridge on D-glucose have been reported to date. Because the bridge is formed by the two ester bonds, double esterification or two-step bislactonization strategy for constructing an HHDP bridge has the potential for constructing the THDBF bridge.[6] The double esterification strategy is used to form two ester bonds of HHDP bridged compound **3** in one-pot using chiral or racemic HHDP-derived dicarboxylic acid **4** or the corresponding diacyl halide and diol **5** with a glucose moiety (Scheme 1a). The 4,6-*O*-(*S*)-HHDP bridge has often been constructed by this method using (*S*)-**4**.[7–9] The use of racemic **4** proceeds via kinetic resolution to provide only the (*S*)-HHDP bridged compound.[10] This strategy has also been applied into synthesizing 2,3-*O*-(*R*)-HHDP- and 2,3-*O*-(*S*)-HHDP-bridged glucoses.[8, 9c, 11–13] The reaction using racemic **4** provides both diastereomers, the ratio of which varies under reaction conditions.[13] On the other contrary, the two-step bislactonization strategy entails mono-acylation of diol **5** with HHDP-derived acid anhydride **6**, followed by intramolecular lactonization of produced seco acid **7** (Scheme 1b). This method enabled to form 1,2-*O*-(*S*)-,[9d] 1,2-*O*-(*R*)-,[9a, 9c] 4,6-*O*-(*S*)-,[9c] and 4,6-*O*-(*R*)-HHDP bridges,[14] the construction of which was difficult via double esterification strategy. We expected that either of the two strategies would allow the formation of the 2,4-*O*-THDBF bridge of **1**. Therefore, the fragments requisite for the synthesis of **1** are 2,4-diol **8**, where the phenolic hydroxy groups of corilagin (**2**) are protected, and dicarboxylic acid **9** with a THDBF moiety (Scheme 1c). Although the synthesis of **9** has not been reported, use of methodology for

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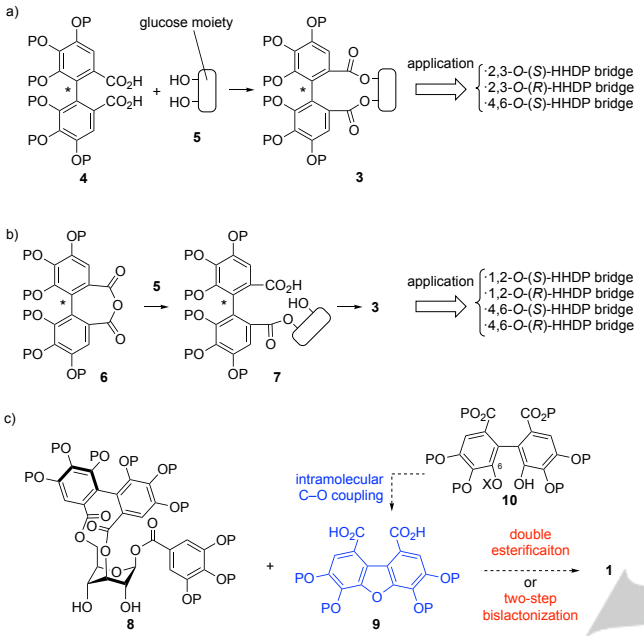
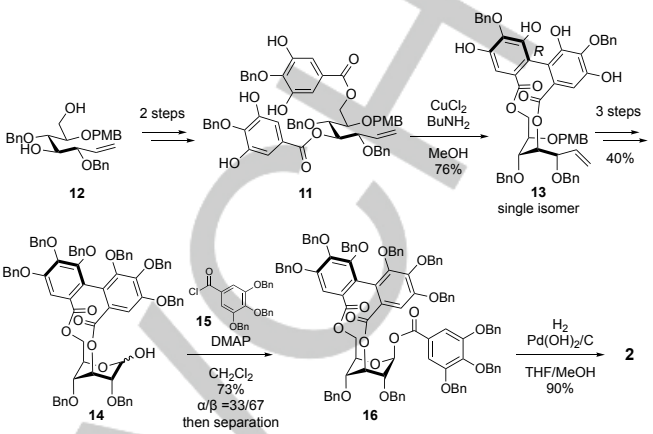
constructing a dibenzofuran skeleton[15] will allow the synthesis. The selection of HHDP-derived compound **10**, where the function at the 6-position is replaced into a triflate group or its analog, will be suitable as the precursor of **10** because **10** can be prepared through derivatization of a carboxyl-group protected compound of **4**. Thus, we plan to use palladium catalyzed intramolecular C–O coupling of **10** for synthesizing **9**.[16]



Scheme 1. (a) Double esterification strategy. (b) Two-step bislactonization strategy. (c) Synthetic strategy of the 2,4-O-THDBF bridge of **1**. P = protecting group. X = trifluoromethanesulfonyl (Tf) or its analog.

We have previously reported the total synthesis of corilagin (**2**) (Scheme 2).[17] The 3,6-*O*-(*R*)-HHDP bridge of **2** was constructed via $CuCl_2$/$BuNH_2$ mediated oxidative phenol coupling of acyclic tetra-ol **11**, which was prepared from glucose-derived compound **12**[18] in two steps, providing **13** as a single isomer. After reconstruction of the pyranose ring in three steps, treatment of **14** with tri-*O*-benzylgalloyl chloride **15** and 4-dimethylaminopyridine (DMAP) gave an anomeric mixture of galloyl ester **16**, β-isomer being the major isomer. Following separation of diastereomeric-mixture, β-**16** was subjected to hydrogenolysis, which produced corilagin (**2**).

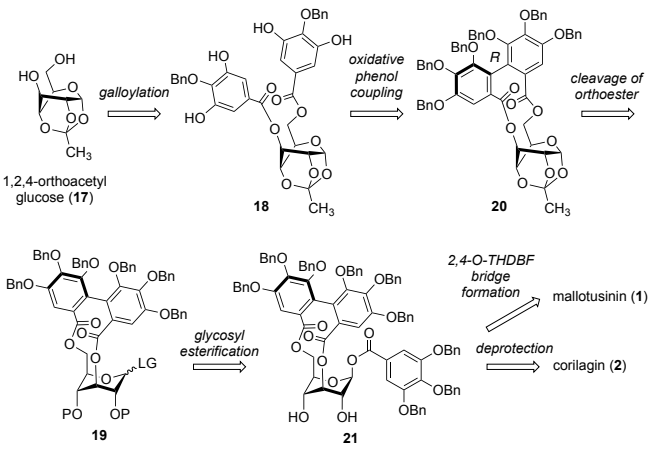
This method is inapplicable to the synthesis of mallotusinin (**1**) due to inefficient transformation into **2** and the benzyl (Bn) protections of the 2-O and 4-O of **16**. The established route requires the pyranose ring opening-closing sequence for constructing the 3,6-*O*-(*R*)-HHDP bridge, resulting in an increase in the total steps for **2** and decrease in the overall yield. Fair yield and stereoselectivity for anomeric galloylation of **14** also increases the inefficiency of the synthesis. Our goal is to achieve the total synthesis of **1**; thus, supplying adequate amount of **2** and its precursor is essential. Further, the two Bn groups on the glucose of **16** disadvantage the development. Because the phenolic hydroxy groups of the HHDP and galloyl group are also benzylated, selective cleavage of the two protections is required for the synthesis of **1**. However, owing to less reactivity, removal of the two Bn groups without affecting other Bn groups is impossible. Here we report improvements in the synthesis of **2**, and the first total synthesis of **1** via the construction of the 2,4-*O*-THDBF bridge on **2**. An unique reaction encountered in forming the THDBF moiety is also described.



Scheme 2. Previously established route for synthesizing corilagin (**2**). Ph = phenyl, Bn = benzyl, PMB = *p*-methoxybenzyl, Bu = butyl, Me =methyl, DMAP = 4-dimethylaminopyridine, THF = tetrahydrofuran.

Results and Discussion

Considering the abovementioned methods, we designed a new synthetic route of **2** as shown in Scheme 3. The most important task for the efficient synthesis of **2** was to establish a method for constructing a 3,6-*O*-(*R*)-HHDP bridge on the glucose moiety. Recently, we succeeded in construction of 3,6-*O*-(*R*)-HHDP bridge via oxidative phenol coupling of penta-(4-benzylgalloyl)-β-glucose; however, the adoption is unreasonable due to low yields.[9a] Flipping the pyranose ring from the inherent equatorial-rich conformation to an axial-rich conformation is unfavorable due to 1,3-diaxial repulsion, causing the difficulty in formation of the 3,6-*O*-(*R*)-HHDP bridge on D-glucose. We expected that the use of 1,2,4-orthoacetylglucose (**17**),[19] where the 3-O and 6-O are locked in an axial conformation by the ortho ester bridge, would result in a solution. The two galloyl moieties of the digalloylated compound **18** are proximal; thus, we expect progress toward oxidative phenol coupling. Stereoselective



Scheme 3. Synthetic strategy of mallotusinin (**1**) and corilagin (**2**).

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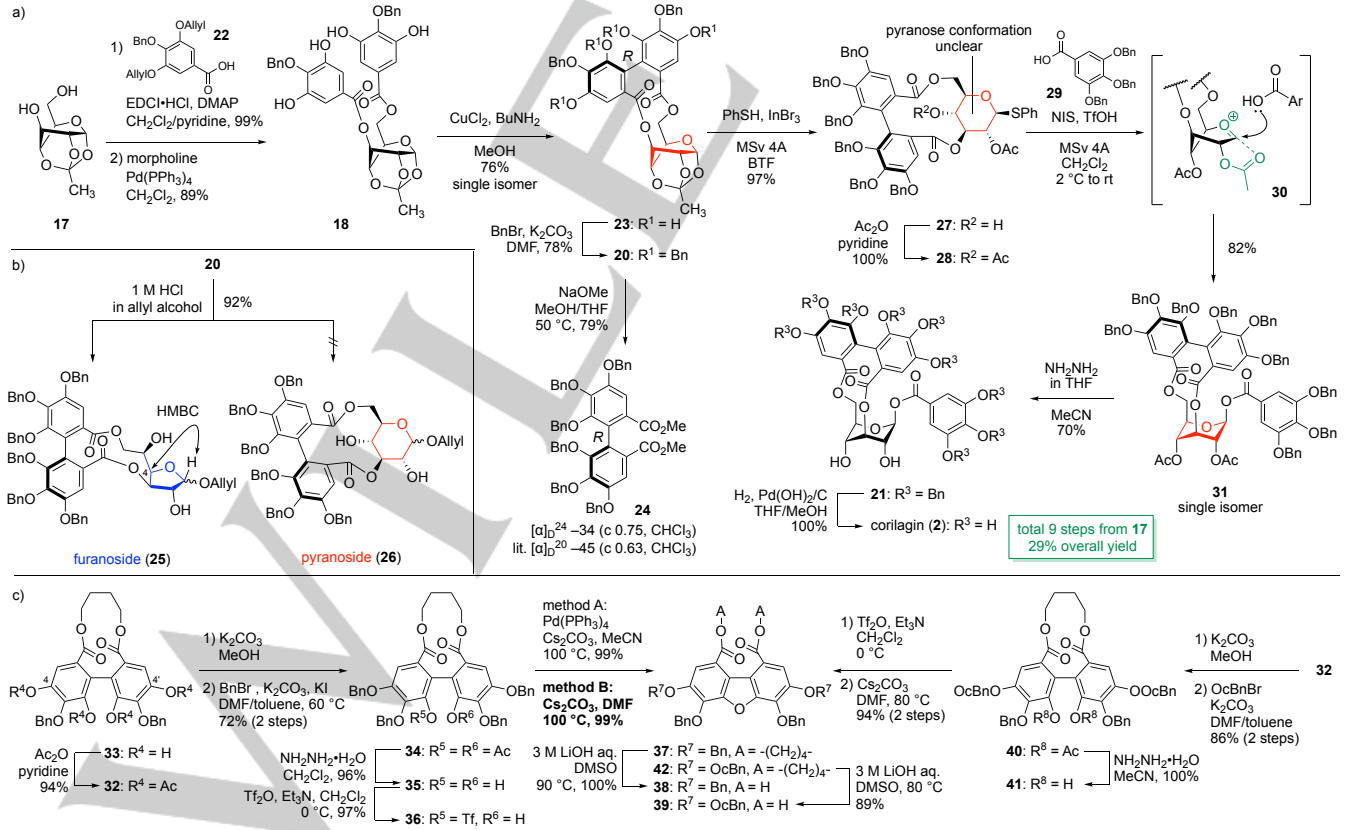
incorporation of a galloyl group at the anomeric position is attainable via glycosyl esterification[20] of **19** derived from the (*R*)-HHDP bridged compound **20** through the orthoester cleavage. The use of the acyl group is suitable for the two hydroxy group protection of **19** because the neighboring group participation of the 2-O acyl group drives β-selective glycosylation.[21] Finally, chemoselective removal of the two acyl groups could provide 2,4-diol **21** of a precursor of mallotusinin (**1**).

Based on the synthesis strategy, we first constructed the 3,6-*O*-(*R*)-HHDP bridge (Scheme 4a). The coupling precursor **18** was prepared via condensation of the two hydroxy group of 1,2,4-orthoacetylglucose (**17**) with 3,5-di-*O*-allyl-4-*O*-benzylgallic acid **22**[9d] using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl) and DMAP, followed by removal of the four allyl groups. As expected, $CuCl_2$/$BuNH_2$ mediated intramolecular oxidative phenol coupling[17] of **18** proceeded smoothly to give the 3,6-*O*-(*R*)-HHDP bridged compound **23** in 76% yield as a single isomer. The axial chirality was ensured by comparing the optical rotation value of the derived methyl ester **24** with that of reported (*R*)-**24**.[22] Benzylation of the four phenolic hydroxy groups of **23** provided **20**, which was then subjected to methanolysis to deliver **24**. The optical rotation value was approximate to the literature value, showing that the axial chirality produced by the oxidative phenol coupling of **18** was (*R*).

Cleavage of the orthoester moiety on benzylated compound **20** required detailed examination. Treatment of **20** with 1 M HCl allyl alcohol solution provided only furanoside **25** without the production of pyranoside **26** (Scheme 4b). The HMBC spectrum detected correlation between the anomeric proton and the carbon at 4-position, which identified the furanose structure. This result mirrors our previous findings for acid hydrolysis of 1,2,4-*O*-orthoacetyl-3,6-*O*-(*o*-xylylene)glucose,[19b] and suggests that furanoside **25** is more thermodynamically stable than pyranoside **26**. Transformation of the pyranose ring into the furanose ring arises through intramolecular attack by releasing the hydroxy group at 4-position on a generated oxocarbenium ion.[23] The following two successful methods for obtaining 3,6-*O*-(*o*-xylylene)glucopyranoside were attempted next: thioglycosylation using thiophenol and trimethylsilyl triflate[23] and thermal glycosylation using *p*-methoxyphenol.[19b] Although **20** decomposed in the former method, the latter method provided the desired product, but resulted in unacceptable yields with low reproducibility. These modified reaction conditions were also examined, but the results were unsatisfactory [See Supporting Information (SI)-S-1]. In contrast, recently reported reaction conditions for cleaving the orthoester of 1,2,4-*O*-orthoacetyl-3,6-*O*-(1,1'-(ethane-1,2-diyl)dibenzene-2,2'-bis(methylene)glucose caused the desired conversion smoothly.[19a] Thus, treatment of **20** in benzotrifluoride containing molecular sieves 4A with thiophenol and indium bromide induced anomeric phenylthiolation along with the cleavage of the orthoester to furnish pyranoside **27** in high yield in a highly stereoselective manner (Scheme 4a). The β-configuration of the anomeric proton was assumed by the fact that $^3J_{HH}$ value of anomeric proton of **27** was 6.9 Hz, which was 2.1 Hz higher than that of **20**. Because the pyranose conformation of **27** was not determined, the pyranose ring was purposely illustrated as a plane structure. Establishment of this conversion allowed us to supply adequate amounts of **27** to enable the development to the synthesis of **1**.



Scheme 4. (a) The second-generation synthetic route of corilagin (**2**). (b) The result of acid hydrolysis of orthoester **20**. (c) Synthesis of dicarboxylic acid **38** and **39** possessing a THDBF moiety. EDCI·HCl =1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, DMF = *N*,*N*-dimethylformamide, Msv = molecular sieves, BTF = benzotrifluoride, Ac = acetyl, NIS = *N*-iodosuccinimide, Et = ethyl, DMSO = dimethyl sulfoxide, OcBn =*p*-octylbenzyl.

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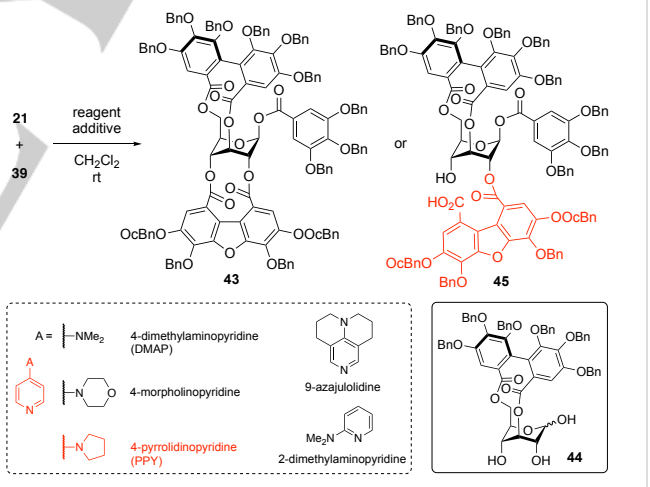
Transforming β-thioglycoside **27** into corilagin (**2**) was achieved in four steps (Scheme 4a). After acetylation of the remaining hydroxy group of **27**, the resulting compound **28** was subjected to glycosyl esterification with tri-*O*-benzylgallic acid (**29**) using *N*-iodosuccinimide and triflic acid.[24] The reaction proceeded in high β-selectivity via the formation of oxocarbenium ion **30**, where the 2-O acetyl group probably involves the neighboring group participation, to provide galloyl ester **31** in 82% yield as a single isomer. The multiplicity of the proton signals in the pyranose ring of **31** were broad singlet or doublet with 1.7 Hz of the spin coupling constant, showing that the pyranose conformation of **31** was a flipped chair form.[17] Subsequently, chemoselective removal of two Ac groups at 2-O and 4-O of **31** in the presence of the galloyl and HHDP ester was examined. Several experiments showed that treatment of **31** in acetonitrile with a solution of hydrazine in tetrahydrofuran (THF) gave the best outcome, resulting in diol **21** in 70% yield (See SI-S-2). Removal of all Bn groups of **21** via hydrogenolysis completed the total synthesis of corilagin (**2**). The overall yield from 1,2,4-orthoacetylglucose (**17**) was 29%, completed in nine steps.

Toward synthesis of mallotusinin (**1**), we next turned our attention to the preparation of the THDBF unit of **1** using the strategy as shown in Scheme 1c (Scheme 4c). Methanolysis of the tetra-acetylated compound of **32** derived from tetra-ol **33**[17] removed the two Ac groups at the 4- and 4'-position selectively.[9b] After Bn protection of the resulting two hydroxy groups, hydrazinolysis of the two Ac group of **34** provided diol **35**. Mono-triflation of **35** provided the desired precursor **36** for constructing the THDBF moiety. Aimed intramolecular C–O coupling of **36** proceeded smoothly via treatment of **36** with catalytic tetrakistriphenylphosphine palladium (0) and cesium carbonate in *N*,*N*-dimethylformamide (DMF) at 100 °C to provide **37** in 99% yield (method A). Unexpectedly, **37** was also obtained in the same yield under the basic conditions without the palladium catalyst (method B). This interesting reaction is discussed further below. Hydrolysis of obtained **37** in dimethyl sulfoxide at 100 °C provided the desired dicarboxylic acid **38**.

The insolubility of **38** meant that changing the protecting groups on the dibenzofuran skeleton was necessary. Hard solubility in dichloromethane made conducting the esterification reaction required for next step in the synthesis difficult. The insolubility would be attributed to intermolecular robust π-stacking interactions among the Bn groups and the THDBF moiety of **38**. We hypothesized that the attachment of alkyl groups to the benzene ring of the Bn groups would decrease the interactions by steric hindrance of the alkyl groups, resulting in an improvement in the solubility of the corresponding dicarboxylic acid in organic solvents. Hence, we designed **39** where the 4-O- and 4'-O- Bn groups of **38** were replaced by the *p*-octylbenzyl (OcBn) group.[25] The synthesis of **39** followed that of **38** except for a step to protect the 4- and 4'-oxygens of **33**. Thus, OcBnBr[26] rather than BnBr was used in the second step to transform **32** into **34**, providing **40**. The 4-step conversion of **40** into **39** proceeded similarly to that of **34** into **38**. The dicarboxylic acid **39** easily dissolved in dichloromethane, allowing us to proceed with the next reaction to construct the 2,4-*O*-THDBF bridge.

The results of the double esterification reaction of diol **21** with dicarboxylic acid **39** are summarized in Table 1. We first treated the two reactants with EDCI·HCl in the presence of DMAP.[9] Although desired bislactone **43** was obtained, the isolated yield was only 4% yield (entry 1). The TLC monitoring in the reaction suggested degradation of diol **21**. Nucleophilic attack by DMAP on the galloyl ester appeared to induce the decomposition because the *m*/*z* ion peak of **44**, which lost the galloyl moiety of **21**, was detected in the MS analysis of the reaction. To suppress the side reaction, other additives were then used. Although 2-dimethylaminopyridine[27] and 9-azajulolidine[28] did not produce **43** (entries 2–3), 4-morpholinopyridine[29] increased the yield to 15% (entry 4). In contrast, the reaction with 4-pyrrolidinopyridine (PPY)[30] produced seco acid **45** in 73% yield (entry 5). The structure was confirmed by using NMR analysis because the proton signal of the 2-O of **45** was observed in a 1.35 ppm lower field than that of **21** detected at 4.19 ppm. A compound esterified between the 4-O of **21** and **39** was not detected. This result suggested that PPY should be used as the optimized additive in subsequent experiments. To obtain **43** in an acceptable yield, other condensation reagents were screened. Although the use of *N*,*N*'-dicyclohexylcarbodiimide (DCC)[31] gave a similar result for entry 5 (entry 6), the Shina reagent (6-methyl-2-nitro benzoic acid anhydride; MNBA)[32] supplied bislactone **43**; however, the isolated yield remained at 23% (entry 7). We also examined the use of a condensation reagent under absence of PPY, such as pentafluoroanilinium trifluoromethane sulfonate,[33] 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride,[34] 1-methyl-2-fluoropyridinium tosylate,[35] and 1-[bis(dimethyl-amino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium

Table 1. Esterification of diol **21** with dicarboxylic acid **39**.



entry	reagent	additive	product (%)[a]
1	EDCI·HCl	DMAP	**43** (4%)
2	EDCI·HCl	2-(dimethylamino)pyridine	not detected
3	EDCI·HCl	9-azajulolidine	not detected
4	EDCI·HCl	4-morpholinopyridine	**43** (15%)
5	**EDCI·HCl**	**4-pyrrolidinopyridine (PPY)**	**45 (73%)**
6	DCC	PPY	**45** (72%)
7	MNBA	PPY	**45** (23%)

[a]Isolated yield. DCC = *N*,*N*'-dicyclohexylcarbodiimide, MNBA = 6-methyl-2-nitro benzoic acid anhydride.

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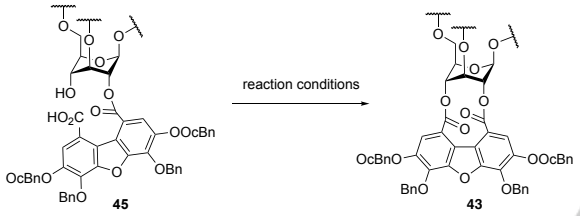
3-oxide hexafluorophosphate;[36] however, all reactions did not give the desired product (See SI-S-3). Therefore, we shifted to using two-step bislactonization strategy for constructing the 2,4-*O*-THDBF bridge efficiently.

The intramolecular lactonization of **45** proceeded under the Yamaguchi and Shina reaction conditions (Table 2). Treatment of **45** with 2,4,6-trichlorobenzoyl chloride (TCBCl)[37] and PPY in toluene at 70 °C provided **43** in 36% yield (entry 1). The yield of **43** increased by replacing toluene into acetonitrile (entry 2), indicating that selection of the solvent is crucial for the reaction. Although the use of DMF caused **45** to be decomposed (entry 3), the reaction in THF under reflux gave the best outcome to give **43** in 69% yield (entry 4). The treatment with MNBA in the presence of PPY also supplied **45** (entry 5), but the isolated yield was in 48% yield. We also attempted the intramolecular lactonization of an acyl chloride, prepared from **45** and oxalyl chloride; however, no production of **43** occurred (entry 6).

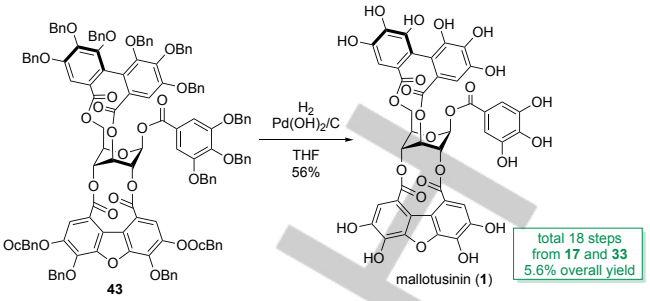
Table 2. Optimization of the intramolecular lactonization of **45**.



entry	reaction conditions	product (%)[a]
1	TCBCl, PPY, toluene, 70 °C	36
2	TCBCl, PPY, MeCN, 70 °C	56
3	TCBCl, PPY, DMF, 70 °C	decomposed
4	**TCBCl, PPY, THF, reflux**	**69**
5	MNBA, PPY, CH_2Cl_2, rt	48
6	1) oxayl chloride, DMF, toluene, 70 °C 2) triethylamine, CH_2Cl_2, rt	decomposed

[a]Isolated yield. TCBCl = 2,4,6-trichlorobenzoyl chloride.

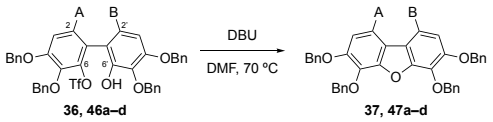
Scheme 5 shows the final step for the synthesis of mallotusinin (**1**). Obtained bislactone **43** was subjected to hydrogenolysis to remove all Bn and OcBn groups, which produced **1** in 56% yield. The ^{1}H NMR and ^{13}C NMR spectra of synthetic **1** were similar, but not identical, to those of natural **1** (See SI-S-4). The reason for this disagreement is probably differences in the aggregation state of **1** caused by the phenolic hydroxyl groups. Pleasingly, the respective signals of synthesized **1** and natural**1** coalesced in the ^{1}H and ^{13}C NMR spectra of the mixture. (See SI-S-5) Therefore, we concluded that the structures of synthesized **1** and natural **1** were the same. The overall yields of **1** from 1,2,4-orthoacetylglucose (**17**) and the known compound **33** was 5.6%, completed in 18 steps.

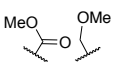


Scheme 5. Total synthesis of mallotusinin (**1**).

The unusual reaction of **36** to construct the dibenzofuran skeleton **37** (Table 3, entry 1) led us to examine this reaction further. We found that this reaction proceeded via the intramolecular aromatic nucleophilic substitution (S_NAr) reaction. However, the S_NAr reaction appeared disfavored because of the presence of two benzyl ethers of the electrophilic benzene ring of **36**. Additionally, the inductive effect of the ester substituted into the benzene ring was inefficient because the ester is in a *meta*-position relative to the triflate group. To identify the key factors for the reaction, we synthesized analogs **46a–d**, with partly changed substituents at the 2- and 2'-positions (See SI-S-6), and treated these compounds with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF at 70 °C (Table 3). To exclude metal-cation effects of a base in the reaction, DBU was selected as the base. We also

Table 3. Trial to form a dibenzofuran skeleton by using alcohol **46a–d**.



entry	reactant	A B	time	product
1[a]	**36**		20 h	**37** (99%[c])
2[b]	**36**		1 h	**37** (86%[c])
3	**46a**		8 h	**47a** (52%[c])
4	**46b**		6 h	**47b** = **47a** (47%[c])
5	**46c**		21 h	**47c** (not detected)
6	**46d**		4 h	**47d** (not detected)

[a]Cesium carbonate was used as the base, and the reaction was performed at 100 °C. [b]The reaction was performed at 100 °C. [c]Isolated yield. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

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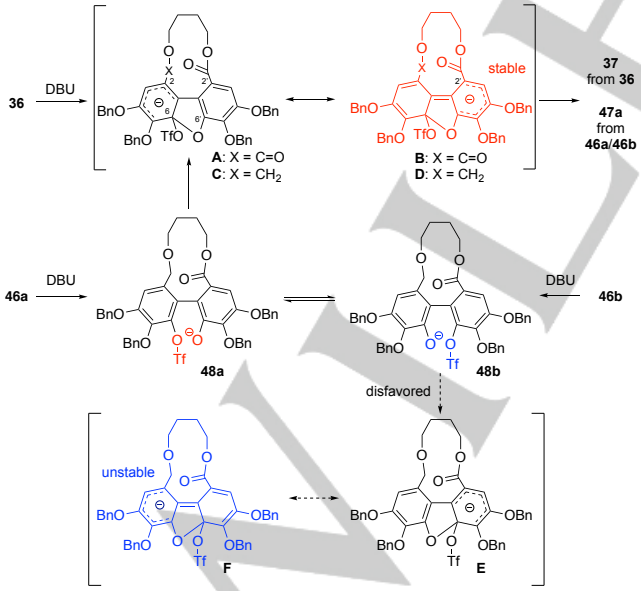
treated **36** with DBU to confirm the production of **37** in 86% yield (entry 2). The reaction of **46a** and **46b**, reducing one ester moiety of **36** to ether, provided desired compound **47a** in 52% yield and 47% yield, respectively (entries 3 and 4). Cyclic diether compound **46c** did not provide the desired compound, indicating that one carbonyl moiety at the 2 or 2' position was essential for the S_NAr reaction (entry 5). Notably, no reaction proceeded when using mono-ester **46d** (entry 6), which showed that the butane tether was crucial for inducing the S_NAr reaction of **36**. The tether restricts the rotation of the aryl-aryl bond, allowing the biphenyl structure to form a configuration, where the location between the hydroxy group of **36** and the carbon at 6-position was proximal. Furthermore, the generated complex **A** via the intramolecular attack by the oxygen on the carbon can form another complex **B** through a mesomeric effect of the ester at the 2'-postion (Scheme 6). This stabilizing effect contributed to allow the production of the Meisenheimer complex in *situ*, inducing the intramolecular S_NAr reaction. Because the reaction of mono-ester **46a** also proceeded, the formation of the Meisenheimer complex **C** prepared from phenolate anion **48a** would be favored because it enables the formation of the more stable complex **D**. In contrast, the generation of Meisenheimer complex **E** from **48b** is disfavored because another considerable complex **F** is instable due to lack of ester at the 2-position; nevertheless, the reaction of **46b** occurred. The reason will be isomerization of the phenolate anion **48b** into **48a** via intramolecular migration of the Tf group in *situ* (Scheme 6). An intramolecular S_NAr reaction to form a dibenzofuran skeleton has been developed;[38] but, no examples using electron-rich compounds such as **36** and **46a** exist. The Ullmann coupling is an alternative method in the construction; however, the reaction often requires harsh conditions.[39] Our established reaction conditions proceed at 70–100 °C, indicating that this reaction will be used in a new synthetic method to create dibenzofuran compounds from biphenyl compounds.



Scheme 6. Proposed mechanism of production of **37**/**47a** from **36**/**46a**/**46b**.

Conclusion

We succeeded in the total synthesis of mallotusinin (**1**) by improving our previously established synthetic route of corilagin (**2**). The key steps in the second-generation synthesis of **2** involved (1) construction of the 3,6-*O*-(*R*)-HHDP bridge via oxidative phenol coupling without opening the pyranose ring and (2) efficient cleavage of the orthoester of **20** without the pyranose–furanose ring transformation. The highly β-selective glycosyl esterification of **28** also facilitated the supply diol **21** as the precursor of **1** and **2**. The THDBF unit **39** requisite for synthesis of **1** was prepared from the mono-triflate compound of the HHDP derivative **41** using the unique intramolecular S_NAr reaction. We also accomplished the construction method of the 2,4-*O*-THDBF bridge of **1** via two-step bislactonization entailing mono-acylation of **21** with **39** using EDCI·HCl and PPY, followed by intramolecular lactonization of obtained seco acid **45** under optimized Yamaguchi lactonization conditions. The established method is applicable to the synthesis of other ellagitannins with a bridge between 2-O and 4-O of corilagin (**2**). Furthermore, provision of these ellagitannins will advance the development of medicinal chemistry.

Experimental Section

General information: All commercially available reagents were used as received. All moisture and air sensitive reactions were carried out in glassware equipped with rubber septa (or a septum) under the positive pressure of argon or nitrogen after degassing using sonic wave. When necessary, the glassware was dried under reduced pressure by heating with a heat-gun and solvents were distilled prior to use. The substrates were azeotropically dried if needed by evaporation of their acetonitrile or toluene solution several times to remove trace water that may be contained to the substrates. Molecular sieves (Msv) were dried under reduced pressure by heating with a heat-gun before use. The reaction mixture was magnetically stirred. Concentration was performed under reduced pressure. The reactions were monitored by TLC and mass spectra (MS). Anhydrous $MgSO_4$ or Na_2SO_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 was represented as "the general drying procedure" in the following experimental methods. TLC was performed on Merck pre-coated silica gel 60 F-254 plates or Merck RP-19 F-254 plates. Spots were visualized by exposure to UV light, or by immersion into a solution of 2% anisaldehyde, 5% H_2SO_4 in ethanol or a solution of 10% phosphomolybdic acid in ethanol, followed by heating at ca. 200 °C. Column chromatography was performed on Merck silica gel 60 (63–200 or 40–63 μm) and Kanto Chemical silica gel 60 N (Spherical, neutral, 40–50 or 63–210 μm), for ordinary phase or Nacalai Tesque Cosmosil 140C18-PREP for reverse phase. The other carrier materials were noted in each case. Gel permeation chromatography (GPC) measurement was performed on a Japan Analytical Industrial Co., Ltd. (JAI) LC-9260IINEXT equipped with a JAI RI-700NEXT refractive index detector and JAI JAIGEL-1H-40 and JAI JAIGEL-2H-40 columns using chloroform ($CHCl_3$) as an eluent (14 mL/min). The melting points were determined using a Yanagimoto micro-melting point apparatus and uncorrected. Optical rotations were determined using a JASCO DIP-370 polarimeter with a 100 mm cell with transmitting the sodium D-line. IR spectra were recorded on JASCO FT/IR-4200, or Shimazu IRAffinity-1S, and the major absorbance bands are all reported in wavenumbers (cm^{-1}). HRMS were recorded on a JEOL JMS-T100LC spectrometer at School of Science and Technology, Kwansei Gakuin University, a JEOL JMS-SX102A at Global Facility Center, Hokkaido University, and JEOL JMS-700 and Waters SYNAPT G2-Si HDMS mass spectrometers at Tokushima Bunri University. The data are reported in units of mass to charge. NMR spectra were recorded on JNM-ECX-500, and ECA-500 instruments at 400, and 500 MHz for ^1H and 101, 126 MHz for ^{13}C, respectively, with either TMS or residual proton of

deuterated solvent as internal reference in the indicated solvent in each parenthesis. The ^{1}H NMR spectroscopic data are indicated by a chemical shift (δ), with the multiplicity, the coupling constants, the integration, and the assignments in parentheses in this order. The multiplicities are abbreviated as s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, and br: broad. The ^{13}C NMR spectroscopic data are reported as the chemical shift (δ), with the hydrogen multiplicity obtained from the DEPT spectra and the assignments in parentheses. The multiplicities are abbreviated as s: C, d: CH, t: CH_2, and q: CH_3. When the number of the carbon was more than one, the number was added in the parentheses.

Synthesis of 3,6-di-*O*-(3,5-di-*O*-allyl-4-*O*-benzyl)galloyl-1,2,4-*O*-ortho-acetyl-α-D-glucopyranose (49): To a stirred solution of **17** (362 mg, 1.77 mmol) in CH_2Cl_2 (21 mL) and pyridine (14 mL) were added EDCI·HCl (1.09 g, 5.69 mmol), DMAP (382 mg, 3.12 mmol), and **22**[9d] (1.71 g, 5.02 mmol) at rt. After stirring for 9 h at rt, to the mixture was added H_2O (100 mL). The mixture was extracted with CH_2Cl_2 (40 mL × 3). The combined organic layer was successively washed with H_2O (100 mL) and brine (100 mL). After the general drying procedure, the residue was purified by column chromatography (30 g of SiO_2, hexane/EtOAc = 7/3) to give **49** (1.49 g, 1.76 mmol, 99% yield) as a white amorphous solid. $[\alpha]_D^{25}$ –6.6 (c 1.55, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) δ 7.48–7.44 (m, 4H, Bn), 7.34–7.27 (m, 6H, Bn), 7,25 (s, 2H, galloyl), 7.25 (s, 2H, galloyl), 6.03 (ddt, *J* = 17.2, 10.3, 5.2 Hz, 2H, allyl), 6.02 (ddt, *J* = 17.2, 10.3, 5.2 Hz, 2H, allyl), 5.83 (br d, *J* = 4.6 Hz, 1H, H-1), 5.43 (dd, *J* = 4.6, 1.7 Hz, 1H, H-3), 5.41 (ddt, *J* = 17.2, 1.7, 1.2 Hz, 2H, allyl), 5.40 (ddt, *J* = 17.2, 1.7, 1.2 Hz, 2H, allyl), 5.28 (ddt, *J* = 10.3, 1.7, 1.2 Hz, 2H, allyl), 5.26 (ddt, *J* = 10.3, 1.7, 1.2 Hz, 2H, allyl), 5.13 (s, 2H, Bn), 5.12 (s, 2H, Bn), 4.82 (dd, *J* = 6.9, 6.3 Hz, 1H, H-5), 4.67–4.61 (m, 2H, H-2, H-6), 4.60 (ddd, *J* = 5.2, 1.7, 1.2 Hz, 4H, allyl), 4.58 (ddd, *J* = 5.2, 1.7, 1.2 Hz, 4H, allyl), 4.47 (dd, *J* = 11.2, 6.9 Hz, 1H, H-6), 4.42 (dd, *J* = 4.6, 1.7 Hz, 1H, H-4), 1.69 (s, 3H, orthoester). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 165.7 (s, galloyl), 165.2 (s, galloyl), 152.7 (s, 2C, galloyl), 152.6 (s, 2C, galloyl), 142.8 (s, galloyl), 142.5 (s, galloyl), 137.5 (s, 2C, Bn), 133.1 (d, 2C, allyl), 133.0 (d, 2C, allyl), 128.6 (d, 2C, Bn), 128.6 (d, 2C, Bn), 128.3 (d, 4C, Bn), 128.2 (d, 2C, Bn), 124.5 (s, galloyl), 123.7 (s, galloyl), 119.6 (s, orthoester), 118.0 (t, 2C, allyl), 117.9 (t, 2C, allyl), 109.1 (d, 2C, galloyl), 109.0 (d, 2C, galloyl), 97.7 (d, C-1), 75.3 (d, C-5), 75,1 (t, Bn), 75.1 (t, Bn), 72.4 (d, C-2), 71.1 (d, C-4), 70.2 (t, 2C, allyl), 70.1 (t, 2C, allyl), 65.5 (d, C-3), 64.5 (t, C-6), 20.3 (q, orthoester). IR (ATR) 3087, 3017, 2923, 2872, 1717, 1422, 1332, 1200, 1130, 757 cm^{-1}. HRMS (MALDI) *m/z* $[M + Na]^+$ calcd for $C_{48}H_{48}O_{14}Na$ 871.2936, found 871.2919.

Synthesis of coupling precursor 18: To a stirred solution of **49** (14.5 g, 17.1 mmol) in CH_2Cl_2 (170 mL) were added morpholine (7.44 g, 85.4 mmol) and $Pd(PPh_3)_4$ (370 mg, 0.320 mmol) at rt. After stirring for 10 h at rt, to the mixture was added H_2O (100 mL). The mixture was extracted with CH_2Cl_2 (200 mL × 4). The combined organic layer was successively washed with H_2O (100 mL) and brine (100 mL). After the general drying procedure, the residue was purified by column chromatography (90 g of SiO_2, hexane/EtOAc = 2/1) to give **18** (10.5 g, 15.2 mmol, 89% yield) as a yellow amorphous solid. $[\alpha]_D^{24}$ –1.2 (c 0.49, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.39–7.32 (m, 10H, Bn), 7,29 (s, 2H, galloyl), 7.18 (s, 2H, galloyl), 6.43 (br s, 2H, OH), 5.83 (d, *J* = 4.6 Hz, 1H, H-1), 5.81 (br s, 2H, OH), 5.43 (dd, *J* = 4.6, 1.7 Hz, 1H, H-3), 5.18 (s, 2H, Bn), 5.17 (dd, *J* = 11.5, 9.2 Hz, 1H, H-6), 5.12 (s, 2H, Bn), 4.91 (dd, *J* = 9.2, 4.6 Hz, 1 H, H-5), 4.59 (ddd, *J* = 4.6, 2.3, 1.7 Hz, 1H, H-2), 4.31 (dd, *J* = 4.6, 2.3 Hz, 1H, H-4), 4.21 (dd, *J* = 11.5, 4.6 Hz, 1H, H-6), 1.69 (s, 3H, orthoester). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 166.9 (s, galloyl), 164.9 (s, galloyl), 149.4 (s, 2C, galloyl), 149.2 (s, 2C, galloyl), 138.2 (s, galloyl), 138.1 (s, galloyl), 136.8 (s, Bn), 136.4 (s, Bn), 129.3 (d, Bn), 129.2 (d, Bn), 129.0 (d, 3C, Bn), 128.8 (d, 2C, Bn), 128.8 (d, 2C, Bn), 125.2 (s, galloyl), 124.2 (s, galloyl), 119.7 (s, orthoester), 110.3 (d, 2C, galloyl), 110.2 (d, 2C, galloyl), 97.8 (d, C-1), 75.9 (t, Bn), 75.4 (t, Bn), 75.1 (d, C-5), 72.3 (d, C-2), 70.8 (d, C-4), 64.9 (d, C-3), 64.8 (t, C-6), 20.3 (q, orthoester). IR (ATR) 3064, 3014, 2966, 2916, 2870, 1716, 1597, 1521, 1454, 1406, 1300, 1269, 1213, 1198, 800, 748, 696 cm^{-1}. HRMS (ESI) *m/z* $[M - H]^-$ calcd for $C_{36}H_{32}O_{14}$ 687.1714, found 687.1714.

Synthesis of 3,6-*O*-(*R*)-HHDP bridged compound 23: To a stirred solution of $CuCl_2$ (314 mg, 2.33 mmol) in MeOH (20 mL) was added $BuNH_2$ (703 mg, 9.61 mmol) at rt. After stirring for 1 h at rt, to the mixture was added a solution of **18** (540 mg, 0.784 mmol) in MeOH (60 mL) via cannula. After stirring for 1.5 h at rt, Et_2O (150 mL), H_2O (50 mL), and saturated NH_4Cl aq. (50 mL) were added to the reaction mixture. The aqueous mixture was extracted with Et_2O (100 mL) and EtOAc (100 mL × 2). The combined organic layer was successively washed with saturated NH_4Cl aq. (100 mL), H_2O (50 mL), and brine (50 mL). After the general drying procedure, the residue was purified by column chromatography (10 g of SiO_2, hexane/EtOAc = 3/1) to give **23** (410 mg, 0.597 mmol, 76% yield) as a yellow amorphous solid. $[\alpha]_D^{23}$ +21 (c 0.81, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.40–7.36 (m, 10H, Bn), 6.89 (s, 1H, HHDP), 6.66 (s, 1H, HHDP), 5.89 (s, 1H, OH), 5.81 (d, *J* = 4.6 Hz, 1H, H-1), 5.73 (s, 1H, OH), 5.52 (s, 1H, OH), 5.27 (s, 1H, OH), 5.24 (dd, *J* = 4.1, 2.3 Hz, 1H, H-3), 5.19–5.12 (m, 4H, Bn), 4.88 (dd, *J* = 8.5, 3.2 Hz, 1H, H-5), 4.69 (dd, *J* = 12.4, 8.5 Hz, 1H, H-6), 4.55 (dd, *J* = 4.1, 3.9 Hz, 1H, H-4), 4.54 (ddd, *J* = 4.6, 3.9, 2.3 Hz, 1H, H-2), 3.96 (dd, *J* = 12.4, 3.2 Hz, 1H, H-6), 1.66 (s, 3H, orthoester). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ 167.8 (s, HHDP), 166.1 (s, HHDP), 149.3 (s, HHDP), 149.2 (s, HHDP), 147.7 (s, HHDP), 147.6 (s, HHDP), 136.5 (s, HHDP or Bn), 136.4 (s, HHDP or Bn), 136.2 (s, HHDP or Bn), 135.5 (s, HHDP or Bn), 129.3 (s, HHDP), 129.1 (d, 2C, Bn), 129.0 (d, 2C, Bn), 128.9 (d, 2C, Bn), 128.8 (d, 4C, Bn), 128.4 (s, HHDP), 119.7 (s, orthoester), 113.8 (s, HHDP), 111.9 (s, HHDP), 109.1 (d, HHDP), 109.0 (d, HHDP), 97.2 (d, C-1), 75.7 (t, Bn), 75.5 (t, Bn), 73.5 (d, C-5), 72.8 (d, C-2), 69.4 (d, C-4), 65.2 (t, C-6), 64.3 (d, C-3), 20.3 (q, orthoester). IR (ZnSe thin film) 3424, 3033, 1736, 1586, 1499, 1453, 1368, 1235, 1136, 1051, 758, 700 cm^{-1}. HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{36}H_{30}O_{14}Na$, 709.1533, found 709.1509.

Synthesis of benzylated compound 20: To a stirred solution of **23** (732 mg, 1.07 mmol) in DMF (11 mL) were added K_2CO_3 (1.55 g, 11.2 mmol) and BnBr (1.87 g, 10.9 mmol) at rt. After stirring for 10 h at rt, to the mixture was added H_2O (20 mL). The reaction mixture was extracted with EtOAc (40 mL × 3). The combined organic layer was successively washed with H_2O (40 mL) and brine (40 mL). After the general drying procedure, the residue was purified by column chromatography (30 g of SiO_2, hexane/EtOAc = 3/1 to 2/1) to give **20** (877 mg, 0.837 mmol, 78% yield) as a yellow amorphous solid. $[\alpha]_D^{24}$ +34 (c 0.68, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) δ 7.47–7.27 (m, 16H, Bn), 7.25–7.21 (m, 4H, Bn), 7.16–7.08 (m, 7H, Bn, HHDP), 7.02 (s, 1H, HHDP), 6.95–6.90 (m, 4H, Bn), 5.84 (d, *J* = 4.8 Hz, 1H, H-1), 5.27 (dd, *J* = 4.6, 1.8 Hz, 1H, H-3), 5.22 (d, *J* = 11.7 Hz, 1H, Bn), 5.16 (d, *J* = 11.5 Hz, 1H, Bn), 5.14 (d, *J* = 11.7 Hz, 1H, Bn), 5.12 (d, *J* = 11.5 Hz, 1H, Bn), 5.02 (d, *J* = 11.0 Hz, 1H, Bn), 5.00 (d, *J* = 10.4 Hz, 1H, Bn), 4.95 (d, *J* = 11.0 Hz, 1H, Bn), 4.94 (d, *J* = 11.5 Hz, 1H, Bn), 4.92 (d, *J* = 10.4 Hz, 1H, Bn), 4.90 (d, *J* = 11.0 Hz, 1H, Bn), 4.86 (dd, *J* = 8.2, 2.8 Hz, 1H, H-5), 4.85 (d, *J* = 11.0 Hz, 1H, Bn), 4.80 (dd, *J* = 12.4, 8.2 Hz, 1H, H-6), 4.66 (d, *J* = 11.0 Hz, 1H, Bn), 4.57 (ddd, *J* = 4.8, 2.1, 1.8 Hz, 1H, H-2), 4.53 (dd, *J* = 4.6, 2.1 Hz, 1H, H-4), 3.92 (dd, *J* = 12.4, 2.8 Hz, 1H, H-6), 1.67 (s, 3H, orthoester). ^{13}C NMR (126 MHz, $CDCl_3$, 22 °C) δ 167.6 (s, HHDP), 165.8 (s, HHDP), 152.4 (s, HHDP), 152.3 (s, HHDP), 152.1 (s, HHDP), 152.1 (s, HHDP), 145.4 (s, HHDP), 144.6 (s, HHDP), 137.9 (s, Bn), 137.5 (s, Bn), 137.4 (s, Bn), 137.1 (s, Bn), 136.5 (s, Bn), 136.4 (s, Bn), 128.6–127.4 (overlapping 30 doublets and 1 singlet: 14 peaks were observed, 31C, Bn, HHDP), 127.3 (s, HHDP), 124.8 (s, HHDP), 123.4 (s, HHDP), 119.6 (s, orthoester), 109.8 (d, HHDP), 109.0 (d, HHDP), 97.1 (d, C-1), 75.4 (t, 2C, Bn), 74.9 (t, Bn), 74.7 (t, Bn), 73.5 (d, C-5), 72.7 (d, C-2), 71.5 (t, Bn), 71.2 (t, Bn), 69.3 (d, C-4), 64.7 (t, C-6), 64.2 (d, C-3), 20.2 (q, orthoester). IR (ATR) 3088, 3064, 3030, 3016, 2951, 2880, 1738, 1591, 1497, 1454, 1433, 1409, 1366, 1215, 1190, 1094, 1055, 746, 696 cm^{-1}. HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{64}H_{54}O_{14}Na$ 1069.3411, found 1069.3411.

Synthesis of diester 24: To a stirred solution of **20** (35.0 mg, 33.4 μmol) in MeOH (3.0 mL) and THF (1.5 mL) was added NaOMe (18.1 mg, 16.7 μmol) at rt. After stirring for 19 h at 50 °C, to the mixture was added amberlite IR-120. The reaction mixture was filtered through a cotton pad, and concentrated. The residue was purified by silica gel chromatography (13 g of SiO_2, hexane/EtOAc = 5/1, then EtOAc/MeOH = 1/1) to give **24** (24.0 mg, 26.5 μmol, 79% yield) as yellow syrup. The NMR spectral data was identical to the literature data.[22a] The optical rotation was $[\alpha]_D^{24}$ −34 (c 0.75, $CHCl_3$), the sign of which was agreed with the literature data {$[\alpha]_D^{25}$ –45 (c 1.00, $CHCl_3$)},[22b] showing that the axial chirality of **24** was *R*.

Synthesis of β-thioglycoside 27: To a stirred suspension of **20** (876 mg, 0.836 mmol) in BTF (16.8 mL) and Msv 4A (2.50 g) was added PhSH (109 mg, 0.989 mmol) at rt. After stirring for 30 min at rt, $InBr_3$ (88.9 mg, 0.251 mmol) was added to the mixture. After stirring for 9 h at rt, the mixture was filtered through a Celite pad to remove Msv 4A. 1 M NaOH aq. (30 mL) was added to the filtrate, then the mixture was extracted with EtOAc (50 mL × 3). The combined organic layer was successively washed with 1 M NaOH aq. (50 mL), H_2O (50 mL), and brine (50 mL). After the general drying procedure, the residue was purified by column chromatography (15 g of SiO_2, hexane/EtOAc = 5/1 to 3/1) to give **27** (942 mg, 0.813 mmol, 97% yield) as a yellow amorphous solid. $[\alpha]_D^{24}$ +7.6 (c 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) δ 7.52–7.49 (m, 4H, Bn), 7.46–7.30 (m, 15H, Bn), 7.27–7.22 (m, 6H, Bn), 7.16 (s, 1H, HHDP), 7.13–7.07 (m, 6H, Bn), 7.04 (s, 1H, HHDP), 6.94–6.90 (m, 4H, Bn), 5.42 (d, *J* = 6.9 Hz, 1H, H-1), 5.28 (ddd, *J* = 6.9, 1.7, 1.0 Hz, 1H, H-2), 5.21 (d, *J* = 11.5 Hz, 1H, Bn), 5.16 (d, *J* = 11.5 Hz, 1H, Bn), 5.11 (d, *J* = 11.5 Hz, 1H, Bn), 5.10 (d, *J* = 11.5 Hz, 1H, Bn), 5.02 (d, *J* = 10.9 Hz, 1H, Bn), 5.01 (d, *J* = 10.9 Hz, 1H, Bn), 4.98 (d, *J* = 10.9 Hz, 1H, Bn), 4.97 (d, *J* = 10.9 Hz, 1H, Bn), 4.95

(d, *J* = 10.9 Hz, 1H, Bn), 4.90 (d, *J* = 10.9 Hz, 1H, Bn), 4.84 (dd, *J* = 3.4, 1.7 Hz, 1H, H-3), 4.82 (d, *J* = 10.9 Hz, 1H, Bn), 4.71 (d, *J* = 10.9 Hz, 1H, Bn), 4.61–4.53 (m, 3H, H-5, H-6, H-6), 4.51 (ddd, *J* = 6.9, 3.4, 1.0 Hz, 1H, H-4), 2.56 (d, *J* = 6.9 Hz, 1H, 4-OH), 2.13 (s, 3H, Ac). ^{13}C NMR (126 MHz, $CDCl_3$, 23 °C) δ 169.5 (s, Ac), 167.2 (s, HHDP), 166.1 (s, HHDP), 152.6 (s, HHDP), 152.5 (s, HHDP), 152.5 (s, HHDP), 152.1 (s, HHDP), 145.4 (s, HHDP), 145.0 (s, HHDP), 137.9 (s, Bn), 137.7 (s, Bn), 137.6 (s, Bn), 137.4 (s, Bn), 136.6 (s, 2C, Bn), 133.4 (s, SPh), 132.2 (d, 2C, SPh), 129.2 (d, 2C, SPh), 128.8–127.6 (overlapping 31 doublets and 1 singlet: 16 peaks were observed, 32C, SPh, Bn, HHDP), 127.4 (s, HHDP), 124.8 (s, HHDP), 124.0 (s, HHDP), 110.1 (d, HHDP), 109.0 (d, HHDP), 81.9 (d, C-1), 77.6 (d, C-5), 75.5 (t, 2C, Bn), 74.9 (t, Bn), 74.9 (t, Bn), 72.8 (d, C-3), 71.6 (d, C-2), 71.5 (t, Bn), 71.3 (t, Bn), 64.4 (t, C-6), 62.6 (d, C-4), 21.1 (q, Ac). IR (ATR) 3618–3322, 3088, 3063, 3030, 2945, 2878, 1738, 1589, 1454, 1365, 1215, 1188, 1093, 908, 746, 694 cm^{-1}. HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{70}H_{60}O_{14}SNa$ 1179.3601, found 1179.3599.

Synthesis of acetylated compound 28: To a stirred solution of **27** (136 mg, 0.118 mmol) in pyridine (0.8 mL) was added Ac_2O (0.4 mL) at rt. After stirring for 4 h at rt, to the mixture was added 1 M hydrochloric acid (15 mL). The mixture was extracted with EtOAc (20 mL × 3). The combined organic layer was successively washed with 1 M hydrochloric acid (20 mL), H_2O (20 mL), and brine (20 mL). After the general drying procedure, the residue was purified by column chromatography (10 g of SiO_2, hexane/EtOAc =7/3) to give **28** (141 mg, 0.118 mmol, 100% yield) as a yellow amorphous solid. $[\alpha]_D^{24}$ +8.1 (*c* 0.84, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 24 °C) δ 7.52 (d, *J* = 7.5 Hz, 4H, Bn), 7.48–7.31 (m, 16H, Bn), 7.29–7.20 (m, 5H, Bn), 7.15 (s, 1H, HHDP), 7.14 (s, 1H, HHDP), 7.12–7.08 (m, 6H, Bn), 6.92–6.90 (m, 4H, Bn), 5.51 (d, *J* = 3.4 Hz, 1H, H-4), 5.23 (d, *J* = 9.2 Hz, 1H, H-2), 5.21 (d, *J* = 10.9 Hz, 1H, Bn), 5.17 (d, *J* = 11.5 Hz, 1H, Bn), 5.11 (d, *J* = 11.5 Hz, 1H, Bn), 5.09 (d, *J* = 10.9 Hz, 1H, Bn), 5.06 (d, *J* = 9.2 Hz, 1H, H-1), 5.01 (d, *J* = 10.9 Hz, 2H, Bn), 4.97 (d, *J* = 10.9 Hz, 1H, Bn), 4.97 (d, *J* = 3.4 Hz, 1H, H-3), 4.96 (d, *J* = 10.9 Hz, 1H, Bn), 4.92 (d, *J* = 10.9 Hz, 1H, Bn), 4.90 (d, *J* = 10.9 Hz, 1H, Bn), 4.80 (d, *J* = 10.9 Hz, 1H, Bn), 4.72 (dd, *J* = 10.9, 5.2 Hz, 1H, H-6), 4.69 (d, *J* = 10.9 Hz, 1H, Bn), 4.40 (ddd, *J* = 5.2, 4.6 Hz, 1H, H-5), 4.36 (dd, *J* = 10.9, 4.6 Hz, 1H, H-6), 2.14 (s, 3H, Ac), 2.10 (s, 3H, Ac). ^{13}C NMR (126 MHz, $CDCl_3$, 24 °C) δ 169.4 (s, Ac), 169.3 (s, Ac), 167.4 (s, HHDP), 165.3 (s, HHDP), 152.5 (s, HHDP), 152.4 (s, HHDP), 152.2 (s, HHDP), 152.0 (s, HHDP), 145.4 (s, HHDP), 145.0 (s, HHDP), 137.9 (s, Bn), 137.6 (s, Bn), 137.6 (s, Bn), 137.3 (s, Bn), 136.6 (s, Bn), 136.5 (s, Bn), 132.6 (s, SPh), 132.4 (d, 2C, SPh), 129.1 (d, 2C, SPh), 128.7–127.3 (overlapping 30 doublets and 2 singlets: 18 peaks were observed, 32C, Bn, HHDP), 124.6 (s, HHDP), 123.6 (s, HHDP), 110.2 (d, HHDP), 109.7 (d, HHDP), 81.9 (d, C-1), 77.4 (d, C-5), 75.5 (t, Bn), 75.4 (t, Bn), 74.9 (t, Bn), 74.8 (t, Bn), 71.6 (t, Bn), 71.2 (t, Bn), 71.0 (d, C-2), 70.8 (d, C-3), 65.2 (t, C-6), 64.7 (d, C-4), 20.9 (q, 2C, Ac). IR (ATR) 3064, 3030, 3016, 2943, 2878, 1742, 1589, 1454, 1368, 1215, 1096, 1028, 746, 694, 667 cm^{-1}. HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{72}H_{62}O_{15}SNa$ 1221.3707, found 1221.3711.

Synthesis of galloyl ester 31: To a stirred suspension of **28** (601 mg, 0.501 mmol) in CH_2Cl_2 (25.0 mL) and Msv 4A (1.0 g) was added 3,4,5-tris(benzyloxy)benzoic acid (**29**) (338 mg, 0.768 mmol) at 2 ºC. After stirring for 30 min at 2 ºC, NIS (228 mg, 1.01 mmol) and TfOH (102 mg, 0.680 mmol) were added to the mixture. After stirring for additional 40 min at rt, to the mixture was added 10% $Na_2S_2O_3$ aq. (100 mL). The reaction mixture was extracted with CH_2Cl_2 (100 mL × 3). The combined organic layer was successively washed with H_2O (100 mL) and brine (100 mL). After the general drying procedure, the mixture was dissolved in EtOAc, then the solution was filtered through a SiO_2 on cotton pad. After the filtrate was evaporated, the residue was purified by GPC (1.4 MPa, 3 cycles, 50 min for 1 cycle) to give **31** (627 mg, 0.410 mmol, 82% yield) as a yellow amorphous solid. $[\alpha]_D^{20}$ –27 (*c* 1.20, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) δ 7.48 (d, *J* = 7.5 Hz, 2H, Bn), 7.42–7.33 (m, 13H, Bn, galloyl), 7.29–7.15 (m, 21H, Bn), 7.11–7.06 (m, 8H, Bn, HHDP), 6.97 (br dd, *J* = 6.9, 2.3 Hz, 2H, Bn), 6.92 (s, 1H, HHDP), 6.78 (d, *J* = 6.9 Hz, 2H, Bn), 6.49 (br s, 1H, H-1), 5.65 (br d, *J* = 1.7 Hz, 1H, H-4), 5.29 (br s, 1H, H-2), 5.20 (d, *J* = 11.5 Hz, 1H, Bn), 5.16 (dd, *J* = 10.9, 10.3 Hz, 1H, H-6), 5.12 (d, *J* = 11.5 Hz, 1H, Bn), 4.98 (d, *J* = 10.9 Hz, 1H, Bn), 5.02 (d, *J* = 1.7 Hz, 1H, H-3), 5.00 (d, *J* = 11.5 Hz, 2H, Bn), 4.96–4.90 (m, 5H, Bn), 4.84 (d, *J* = 11.5 Hz, 1H, Bn), 4.79 (d, *J* = 11.5 Hz, 1H, Bn), 4.77–4.72 (m, 3H, Bn, H-5), 4.46 (dd, *J* = 10.9, 5.7 Hz, 1H, H-6), 4.45 (d, *J* = 10.9 Hz, 1H, Bn), 4.40 (d, *J* = 10.9 Hz, 1H, Bn), 4.36 (d, *J* = 10.9 Hz, 1H, Bn), 2.20 (s, 3H, Ac), 2.16 (s, 3H, Ac). ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C) δ 169.3 (s, 2C, Ac), 167.5 (s, HHDP), 165.3 (s, HHDP), 164.6 (s, galloyl), 153.0 (s, 3C, galloyl, HHDP), 152.5 (s, 2C, HHDP), 152.3 (s, HHDP), 145.4 (s, HHDP), 144.8 (s, HHDP), 143.6 (s, galloyl), 138.0 (s, Bn), 137.9 (s, Bn), 137.7 (s, 2C, Bn), 137.5 (s, Bn), 136.7 (s, 2C, Bn), 136.7 (s, Bn), 136.2 (s, Bn), 128.7–127.4 (overlapping 45 doublets and 1 singlet : 17 peaks were observed, 46C, Bn, HHDP), 126.9 (s, HHDP), 125.4 (s, HHDP), 123.6 (s, HHDP), 123.5 (s, galloyl), 109.4 (d, HHDP), 109.0 (d, 2C, galloyl), 108.1 (d, HHDP), 92.8 (d, C-1), 75.5 (t, Bn), 75.2 (t, Bn), 75.1 (t, 2C, Bn), 74.4 (t, Bn), 72.3 (d, C-5), 71.4 (t, Bn), 71.3 (t, 2C, Bn), 71.0 (t, Bn), 67.2 (d, C-2), 66.4 (d, C-3), 63.8 (t, C-6), 62.1 (d, C-4), 21.1 (q, Ac), 21.0 (q, Ac). IR (ATR) 3063, 3030, 2933, 2876, 1745, 1589, 1498, 1454, 1335, 1215, 1093, 1057, 910, 842, 750, 696. HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{94}H_{80}O_{20}Na$ 1551.5152, found 1551.5141.

Synthesis of diol 21: To a stirred solution of **31** (627 mg, 0.410 mmol) in MeCN (4.1 mL) was added 1.0 M of hydrazine in THF (1.6 mL, 1.6 mmol) at rt. After stirring for 14 h at rt, to the mixture was added 1 M hydrochloric acid (20 mL). The mixture was extracted with EtOAc (80 mL × 3). The combined organic layer was successively washed with 1 M hydrochloric acid (30 mL), H_2O (30 mL), and brine (30 mL). After the general drying procedure, the residue was purified by column chromatography (10 g of SiO_2, hexane/EtOAc =7/2 to 3/1) to give **21** (414 mg, 0.286 mmol, 70% yield) as a yellow amorphous solid. $[\alpha]_D^{22}$ –26 (*c* 0.75, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) δ 7.45 (d, *J* = 6.9 Hz, 2H, Bn), 7.41–7.32 (m, 12H, Bn, galloyl), 7.27–7.04 (m, 29H, Bn), 6.97 (dd, *J* = 7.6, 1.7 Hz, 2H, Bn), 6.94 (s, 1H, HHDP), 6.74 (s, 1H, HHDP), 6.74 (dd, *J* = 7.2, 1.7 Hz, 2H, Bn), 6.53 (s, 1H, H-1), 5.19 (dd, *J* = 11.5, 11.2 Hz, 1H, H-6), 5.17 (d, *J* = 11.5 Hz, 1H, Bn), 5.09 (d, *J* = 11.5 Hz, 1H, Bn), 5.03 (d, *J* = 11.5 Hz, 1H, Bn), 4.98 (br s, 1H, H-3), 4.97 (d, *J* = 10.9 Hz, 2H, Bn), 4.96 (d, *J* = 10.9 Hz, 1H, Bn), 4.95 (d, *J* = 11.5 Hz, 1H, Bn), 4.93 (d, *J* = 10.9 Hz, 1H, Bn), 4.89 (d, *J* = 11.5 Hz, 1H, Bn), 4.87 (d, *J* = 10.9 Hz, 3H, Bn), 4.74 (d, *J* = 11.5 Hz, 1H, Bn), 4.73 (d, *J* = 10.9 Hz, 1H, Bn), 4.72–4.68 (m, 2H, H-4, 2-OH), 4.48 (d, *J* = 11.5 Hz, 1H, Bn), 4.42 (dd, *J* = 11.2, 8.0 Hz, 1H, H-6), 4.36 (d, *J* = 10.9 Hz, 1H, Bn), 4.36 (dd, *J* = 11.5, 8.0 Hz, 1H, H-5), 4.35 (d, *J* = 10.9 Hz, 1H, Bn), 4.19 (br d, *J* = 6.9 Hz, 1H, H-2), 4.73 (d, *J* = 11.5 Hz, 1H, Bn), 3.68 (br d, *J* = 7.5 Hz, 1H, 4-OH). ^{13}C NMR (126 MHz, $CDCl_3$, 23 °C) δ 167.7 (s, HHDP), 165.9 (s, HHDP), 165.2 (s, galloyl), 153.1 (s, 2C, galloyl), 152.9 (s, HHDP), 152.5 (s, HHDP), 152.4 (s, HHDP), 152.3 (s, HHDP), 145.4 (s, HHDP), 144.5 (s, HHDP), 143.5 (s, galloyl), 137.9 (s, Bn), 137.9 (s, Bn), 137.7 (s, Bn), 137.6 (s, Bn), 137.5 (s, Bn), 136.7 (s, 2C, Bn), 136.5 (s, Bn), 136.1 (s, Bn), 129.1 (s, HHDP), 128.7–127.2 (overlapping 45 doublets: 17 peaks were observed, 45C, Bn), 126.8 (s, HHDP), 125.4 (s, HHDP), 123.7 (s, galloyl), 123.4 (s, HHDP), 109.4 (d, HHDP), 108.8 (d, 2C, galloyl), 107.5 (d, HHDP), 96.5 (d, C-1), 75.7 (t, Bn), 75.2 (t, Bn), 75.1 (t, 2C, Bn), 74.5 (d, C-5), 74.4 (t, Bn), 71.4 (t, Bn), 71.2 (t, 2C, Bn), 70.5 (t, Bn), 68.3 (d, C-3), 67.0 (d, C-2), 64.0 (t, C-6), 61.3 (d, C-4). IR (ATR) 3600–3000, 3032, 2943, 2932, 1738, 1709, 1589, 1499, 1454, 1213, 1192, 1097, 1022, 734, 696 cm^{-1}. HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{90}H_{76}O_{18}Na$ 1467.4929, found 1467.4926.

Synthesis of corilagin (2): A mixture of **21** (106 mg, 73.4 μmol) and $Pd(OH)_2$/C (20 wt. %, 58.9 mg, 39.0 μmol) in THF (2.0 mL) and methanol (2.0 mL) was stirred under H_2 atmosphere at rt. After stirring for 15 h at rt, the mixture was filtered through a cotton-Celite pad to remove the catalyst. After the filtrate was concentrated, the residue was purified by column chromatography (5 g of Sephadex G-25, $CHCl_3$/MeOH = 6/1) to give **2** (46.4 mg, 73.1 μmol, 100% yield). The ^{1}H and ^{13}C NMR spectral data were in agreement with that of our previously synthesized **2**.[17] Please see SI-S-7 for details. ^{1}H NMR (400 MHz, acetone-d_6, 24 °C) δ 8.02–7.41 (br s, 9H, OH), 7.14 (s, 2H, galloyl), 6.86 (s, 1H, HHDP), 6.70 (s, 1H, HHDP), 6.38 (s, 1H, H-1), 5.14 (br s, 2H, OH), 4.96 (dd, *J* = 11.0, 10.8 Hz, 1H, H-6), 4.84 (br s, 1H, H-3), 4.53 (br dd, *J* = 10.8, 8.9 Hz, 1H, H-5), 4.47 (br s, 1H, H-4), 4.11 (dd, *J* = 11.0, 8.9 Hz, 1H, H-6), 4.10 (br s, 1H, H-2). ^{13}C NMR (101 MHz, acetone-d_6, 24 °C) δ 168.5 (s, HHDP), 167.2 (s, HHDP), 165.1 (s, galloyl), 145.9 (s, 2C, galloyl), 145.4 (s, HHDP), 145.0 (s, HHDP), 144.9 (s, HHDP), 144.8 (s, HHDP), 139.2 (s, galloyl), 137.1 (s, HHDP), 136.6 (s, HHDP), 125.8 (s, HHDP), 125.5 (s, HHDP), 120.8 (s, galloyl), 116.4 (s, HHDP), 115.9 (s, HHDP), 110.9 (d, 2C, galloyl), 110.0 (d, HHDP), 108.1 (d, HHDP), 94.1 (d, C-1), 75.6 (d, C-5), 70.5 (d, C-3), 68.9 (d, C-2), 64.3 (t, C-6), 62.2 (d, C-4). HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{22}O_{18}Na$ 657.0701, found 657.0704.

Synthesis of tetra-acetylated compound 32: To a stirred solution of **33**[17] (600 mg, 1.08 mmol) in pyridine (10 mL) was added Ac_2O (4 mL). After stirring for 15 min at rt, 1 M hydrochloric acid (20 mL) was added to the mixture. The aqueous mixture was extracted with EtOAc (20 mL × 3). The combined organic layer was successively washed with 1 M hydrochloric acid (10 mL), H_2O (10 mL), and brine (10 mL). After the general drying procedure, the residue was purified by column chromatography (28 g of SiO_2, hexane/EtOAc = 10/1 to 0/1) to give **32** (752 mg, 1.02 mmol, 94% yield) as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C) δ 7.43 (s, 2H, HHDP), 7.42–7.30 (m, 10H, Bn), 5.11 (d, *J* = 11.5 Hz, 2H, Bn), 4.98 (d, *J* = 11.5 Hz, 2H, Bn), 4.46–4.37 (m, 2H, butane linker), 4.23–4.13 (m, 2H, butane linker), 2.19 (s, 6H, Ac), 1.99–1.91 (m, 2H, butane linker), 1.90 (s, 6H, Ac), 1.80–1.72 (m, 2H, butane linker). ^{13}C NMR (101 MHz, $CDCl_3$, 24 °C) δ 168.3 (s, 2C, Ac), 167.6 (s, 2C, Ac), 165.8 (s, 2C, HHDP), 146.0 (s, 2C, HHDP), 143.7 (s, 2C, HHDP), 143.4 (s, 2C, HHDP), 136.9 (s, 2C, Bn), 129.0 (s, 2C, HHDP), 128.6 (d, 4C, Bn), 128.3

(d, 2C, Bn), 127.7 (d, 4C, Bn), 126.7 (s, 2C, HHDP), 121.5 (d, 2C, HHDP), 75.6 (t, 2C, Bn), 65.7 (t, 2C, butane linker), 25.9 (t, 2C, butane linker), 20.8 (q, 2C, Ac), 20.2 (q, 2C, Ac). IR (ATR) 3065, 3032, 2982, 2954, 2911, 1775, 1737, 1606, 1569, 1410, 1371, 1286, 1241, 1184, 1049, 1013, 974, 859, 786, 700 cm^{-1}.HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{40}H_{36}O_{14}Na$ 763.2003, found 763.1982.

Synthesis of diacetate 34: A mixture of K_2CO_3 (305 mg, 2.21 mmol) and **32** (711 mg, 0.961 mmol) in MeOH (10 mL) was stirred for 30 min at rt. After 1 M hydrochloric acid (20 mL) was added to the stirred mixture, the aqueous mixture was extracted with EtOAc (30 mL × 3). The combined organic layer was successively washed with 1 M hydrochloric acid (30 mL), H_2O (30 mL), and brine (30 mL). After the general drying procedure, the residue was purified by column chromatography (23 g of SiO_2, hexane/EtOAc = 5/1 to 1/1) to give diol. To a stirred solution of the obtained product in a mixture of DMF and toluene (v/v = 5/1, 10 mL) were added K_2CO_3 (389 mg, 2.35 mmol), KI (10.0 mg, 60.2 μmol), and BnBr (402 mg, 2.35 mmol) at rt. The mixture was stirred at 60 °C for 3 h. After cooling to rt, to the mixture was added 1 M hydrochloric acid (10 mL). The aqueous mixture was extracted with EtOAc (40 mL × 2). The combined organic layer was successively washed with 1 M hydrochloric acid (40 mL), H_2O (40 mL), and brine (40 mL). After the general drying procedure, the residue was purified by recrystallization from EtOAc/hexane to give **34** (576 mg, 0.689 mmol, 72% yield in 2 steps) as a white solid. mp 205.1–206.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) δ 7.49–7.27 (m, 20H, Bn), 7.23 (s, 2H, HHDP), 5.20 (d, *J* = 11.1 Hz, 4H, Bn), 5.13 (d, *J* = 11.1 Hz, 2H, Bn), 5.03 (d, *J* = 11.1 Hz, 2H, Bn), 4.50–4.42 (m, 2H, butane linker), 4.16–4.09 (m, 2H, butane linker), 2.03–1.95 (m, 2H, butane linker), 1.89 (s, 6H, Ac), 1.83–1.76 (m, 2H, butane linker). ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C) δ 168.0 (s, 2C, Ac), 166.9 (s, 2C, HHDP), 151.8 (s, 2C, HHDP), 143.4 (s, 2C, HHDP), 142.8 (s, 2C, HHDP), 137.5 (s, 2C, Bn), 136.3 (s, 2C, Bn), 129.1 (s, 2C, HHDP), 128.8 (d, 4C, Bn), 128.5 (d, 4C, Bn), 128.4 (d, 2C, Bn), 128.3 (d, 4C, Bn), 128.1 (d, 2C, Bn), 127.9 (d, 4C, Bn), 121.8 (s, 2C, HHDP), 111.5 (d, 2C, HHDP), 74.8 (t, 2C, Bn), 71.3 (t, 2C, Bn), 65.6 (t, 2C, butane linker), 26.1 (t, 2C, butane linker), 20.5 (q, 2C, Ac). IR (ATR) 3065, 3032, 2937, 2873, 1734, 1605, 1577, 1455, 1417, 1357, 1196, 1139, 1084, 1069, 914, 820, 793 cm^{-1}. HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{50}H_{44}O_{12}Na$ 859.2730, found 859.2760.

Synthesis of diol 35: To a stirred mixture of **34** (550 mg, 0.657 mmol) in CH_2Cl_2 (6.5 mL) was added $N_2H_4{\cdot}H_2O$ (132 mg, 2.63 mmol). After stirring for 20 min at rt, the mixture was concentrated under reduced pressure. The residue was diluted with EtOAc (40 mL), and the organic solution was successively washed with H_2O (20 mL) and brine (20 mL). After the general drying procedure, the residue was purified by recrystallization from acetone/hexane to give **35** (477 mg, 0.634 mmol, 96% yield) as a white solid. mp 87.2–88.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) δ 7.48–7.28 (m, 20H, Bn), 6.91 (s, 2H, HHDP), 5.8 (s, 2H, OH), 5.2 (d, *J* = 11.0 Hz, 4H, Bn), 5.12 (d, *J* = 11.0 Hz, 2H, Bn), 5.12 (d, *J* = 11.0 Hz, 2H, Bn), 4.41–4.48 (m, 2H, butane linker), 4.15–4.08 (m, 2H, butane linker), 2.04–1.93 (m, 2H, butane linker), 1.88–1.76 (m, 2H, butane linker). ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C) δ 167.8 (s, 2C, HHDP), 150.7 (s, 2C, HHDP), 148.3 (s, 2C, HHDP), 137.1 (s, 2C, Bn), 136.9 (s, 2C, HHDP), 136.6 (s, 2C, HHDP), 129.3 (s, 2C, HHDP), 128.8 (d, 4C, Bn), 128.7 (d, 4C, Bn), 128.6 (d, 4C, Bn), 128.5 (d, 2C, Bn), 128.3 (d, 2C, Bn), 127.8 (d, 4C, Bn), 115.4 (s, 2C, HHDP), 105.5 (d, 2C, HHDP), 75.6 (t, 2C, Bn), 71.0 (t, 2C, Bn), 65.4 (t, 2C, butane linker), 26.2 (t, 2C, butane linker). IR (ATR) 3509, 3065, 3032, 2945, 2871, 1733, 1716, 1603, 1577, 1454, 1334, 1217, 1196, 1087, 911, 739, 695 cm^{-1}. HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{46}H_{40}O_{10}Na$ 775.2519, found 775.2506.

Synthesis of triflate 36: To a stirred solution of **35** (1.29 g, 1.71 mmol) in CH_2Cl_2 (120 mL) were added Et_3N (223 mg, 2.20 mmol) and Tf_2O (621 mg, 2.20 mmol) at 0 °C. After stirring for 20 min at 0 °C, to the mixture was added 1 M hydrochloric acid (100 mL). The aqueous mixture was extracted with EtOAc (150 mL × 3). The combined organic layer was successively washed with H_2O (100 mL) and brine (100 mL). After the general drying procedure, the residue was purified by recrystallization from acetone/hexane to give **36** (1.47 g, 1.66 mmol, 97% yield) as a white solid. mp 100.3–101.5 °C: ^{1}H NMR (400 MHz, $CDCl_3$, 26 °C) δ 7.52–7.27 (m, 21H, Bn, HHDP), 7.01 (s, 1H, HHDP), 5.88 (s, 1H, OH), 5.33–5.06 (m, 8H, Bn), 4.50–4.40 (m, 2H, butane linker), 4.20–4.11 (m, 2H, butane linker), 2.03–1.95 (m, 2H, butane linker), 1.84–1.76 (m, 2H, butane linker). ^{13}C NMR* (101 MHz, $CDCl_3$, 24 °C) δ 166.8 (s, 2C, HHDP), 151.7 (s, HHDP), 150.9 (s, HHDP), 150.7 (s, HHDP), 148.1 (s, HHDP), 142.4 (s, HHDP), 142.1 (s, 2C, Bn), 137.3 (s, Bn), 137.0 (s, Bn), 136.3 (s, 1H, HHDP), 135.8 (s, 1H, HHDP), 129.3 (s, HHDP), 129.3–127.8 (overlapping 20 doublets: 14 peaks were observed, Bn), 122.3 (s, HHDP), 113.3 (s, HHDP), 112.7 (d, HHDP), 106.2 (d, HHDP), 75.9 (t, Bn), 75.4 (t, Bn), 71.6 (t, Bn), 71.1 (t, Bn), 65.9 (t, butane linker), 65.5 (t, butane linker), 25.9 (t, 2C, butane linker). IR (ATR) 3522, 3066, 3033, 2942, 2867, 1735, 1605, 1578, 1454, 1334, 1197, 1084, 914, 792, 734 cm^{-1}. HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{47}H_{39}F_3O_{12}SNa$ 907.2012, found 907.2002. *The CF_3 signal was not detected.

Synthesis of dibenzofuran 37: Method A: To a stirred suspension of **36** (20.0 mg, 22.6 μmol) and Cs_2CO_3 (14.7 mg, 45.1 μmol) in MeCN (1 mL) was added $Pd(PPh_3)_4$ (0.2 mg, 0.2 μmol) at rt. After stirring for 8 h at 100 °C, the reaction mixture was then diluted with Et_2O (5 mL) and filtered through a cotton-Celite pad to remove Pd catalyst and Cs salt. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (2 g of SiO_2, hexane/EtOAc = 4/1) to give **37** (20.0 mg, 22.4 μmol, 99%) as a white solid. Method B: A mixture of **36** (20.0 mg, 22.6 μmol) and Cs_2CO_3 (14.7 mg, 45.1 μmol) in DMF (1 mL) was stirred for 20 h at 100 °C. The reaction mixture was diluted with Et_2O (5 mL) and filtered through a cotton-Celite pad to remove Cs salt. After H_2O (5 mL) was added to the filtrate, the aqueous mixture was extracted with EtOAc (10 mL × 3). The combined organic layer was successively washed with H_2O (10 mL × 2) and brine (10 mL). The general drying procedure afforded **37** (20.0 mg, 22.4 μmol, 99% yield) as a white solid. mp 121–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.51–7.45 (m, 8H, Bn), 7.44 (s, 2H, THDBF), 7.42–7.28 (m, 12H, Bn), 5.39 (s, 4H, Bn), 5.21 (s, 4H, Bn), 4.48 (m, 4H, butane linker), 2.08 (m, 4H, butane linker). ^{13}C NMR (101 MHz, $CDCl_3$, 22 °C) δ 168.3 (s, 2C, THDBF), 150.4 (s, 2C, THDBF), 150.1 (s, 2C, THDBF), 137.2 (s, 2C, THDBF), 136.6 (s, 2C, Bn), 136.5 (s, 2C, Bn), 128.8 (d, 4C, Bn), 128.6 (d, 4C, Bn), 128.4 (d, 4C, Bn), 128.4 (d, 2C, Bn), 128.3 (d, 2C, Bn), 127.8 (d, 4C, Bn), 122.1 (s, 2C, THDBF), 117.4 (s, 2C, THDBF), 112.9 (d, 2C, THDBF), 75.5 (t, 2C, Bn), 72.3 (t, 2C, Bn), 65.6 (t, 2C, butane linker), 26.9 (t, 2C, butane linker). IR (ATR) 3088, 3066, 3029, 2966, 2928, 1779, 1735, 1707, 1635, 1541, 1455, 1320, 1285, 1093, 1028, 983, 778 cm^{-1}. HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{46}H_{38}O_9Na$ 757.2414, found 757.2404.

Synthesis of dicarboxylic acid 38: To a solution of **37** (11.3 mg, 15.4 μmol) in DMSO (0.75 mL) was added 3 M LiOH aq. (0.25 mL) at rt. After stirred at 90 °C for 19 h, the mixture was cooled to rt, and 1 M hydrochloric acid (5 mL) was added to the mixture. The aqueous mixture was extracted with EtOAc (10 mL × 3). The combined organic layer was successively washed with H_2O (10 mL × 4) and brine (10 mL). After the general drying procedure, the residue was purified by trituration with acetone to give **38** (10.4 mg, 15.4 μmol, 100% yield) as a white solid. mp 275.0–275.5 °C. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C) δ 12.9 (br s, 2H, CO_2H), 7.52–7.46 (m, 8H, Bn), 7.45–7.40 (m, 6H, Bn, THDBF), 7.38–7.30 (m, 8H, Bn), 5.37 (s, 4H, Bn), 5.30 (s, 4H, Bn). ^{13}C NMR (126 MHz, DMSO-d_6, 26 °C) δ 168.5 (s, 2C, THDBF), 150.0 (s, 2C, THDBF), 149.8 (s, 2C, THDBF), 137.5 (s, 2C, Bn), 137.3 (s, 2C, Bn), 135.4 (s, 2C, THDBF), 129.0 (d, 4C, Bn), 128.9 (d, 4C, Bn), 128.8 (d, 2C, Bn), 128.7 (d, 4C, Bn), 128.6 (d, 2C, Bn), 128.2 (d, 4C, Bn), 124.1 (s, 2C, THDBF), 117.4 (s, 2C, THDBF), 112.5 (d, 2C, THDBF), 75.2 (t, 2C, Bn), 71.6 (t, 2C, Bn). IR (ATR) 3504, 3065, 3031, 2942, 1733, 1603, 1417, 1333, 1197, 1084, 981, 735, 696 cm^{-1}. HRMS (unanalyzable due to impossibility of ionization).

Synthesis of OcBn-protected compound 40: To a stirred solution of **32** (1.07 g, 1.44 mmol) in MeOH (16.0 mL) was added K_2CO_3 (790 mg, 5.72 mmol) at rt. After stirring for 20 min at rt, to the mixture was added 1 M hydrochloric acid (15 mL). The mixture was extracted with EtOAc (40 mL × 3). The combined organic layer was successively washed with H_2O (40 mL) and brine (40 mL). The general drying procedure gave diol. To a stirred solution of the crude product in DMF (25.0 mL) and toluene (3.0 mL) were added K_2CO_3 (597 mg, 4.34 mmol) and OcBnBr[26] (1.22 g, 4.31 mmol) at rt. After stirring for 2 h at rt, to the mixture was added 1 M hydrochloric acid (50 mL). The reaction mixture was extracted with EtOAc (50 mL × 3). The combined organic layer was successively washed with H_2O (50 mL) and brine (50 mL). After the general drying procedure, the residue was purified by column chromatography (10 g of SiO_2, hexane/EtOAc = 6/1) to give **40** (1.32 g, 1.24 mmol, 86% yield in 2 steps) as a yellow amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$, 24 °C) δ 7.37 (d, *J* = 8.0 Hz, 4H, OcBn), 7.32 (dd, *J* = 7.7, 2.3 Hz, 4H, Bn), 7.33–7.25 (m, 6H, Bn), 7.23 (s, 2H, HHDP), 7.20 (d, *J* = 8.0 Hz, 4H, OcBn), 5.21 (d, *J* = 10.9 Hz, 2H, Bn), 5.15 (d, *J* = 11.5 Hz, 2H, OcBn), 5.09 (d, *J* = 11.5 Hz, 2H, OcBn), 5.03 (d, *J* = 10.9 Hz, 2H, Bn), 4.45 (br dd, *J* = 11.5, 7.5 Hz, 2H, butane linker), 4.11 (br dd, *J* = 11.5, 5.2 Hz, 2H, butane linker), 2.62 (t, *J* = 7.5 Hz, 4H, OcBn), 1.96 (m, 2H, butane linker), 1.89 (s, 6H, Ac), 1.79 (m, 2H, butane linker), 1.66 (quintet, *J* = 7.5 Hz, 4H, OcBn), 1.38–1.24 (m, 20H, OcBn), 0.88 (t, *J* = 6.8 Hz, 6H, OcBn). ^{13}C NMR (126 MHz, $CDCl_3$, 24 °C) δ 167.9 (s, 2C, Ac), 166.8 (s, 2C, HHDP), 151.7 (s, 2C, HHDP), 143.3 (s, 2C, OcBn), 143.2 (s, 2C, HHDP), 142.7 (s, 2C, HHDP), 137.5 (s, 2C, Bn), 133.4 (s, 2C, OcBn), 129.0 (s, 2C, HHDP), 128.7 (d, 4C, OcBn), 128.3 (d, 6C, Bn), 128.3 (d, 4C, Bn), 128.0 (d, 4C, OcBn), 121.6 (s, 2C, HHDP), 111.4 (d, 2C, HHDP), 74.7 (t, 2C, Bn), 71.2 (t, 2C, OcBn), 65.5 (t, 2C, butane linker), 35.8 (t, 2C, OcBn), 32.0 (t, 2C, OcBn), 31.6 (t, 2C, OcBn), 29.6 (t, 2C, OcBn), 29.4 (t, 2C, OcBn), 29.3 (t, 2C, OcBn), 26.0 (t, 2C, butane linker), 22.7 (t, 2C, OcBn), 20.4 (q, 2C, Ac), 14.2 (q, 2C, OcBn). IR

(ATR) 3032, 3030, 2953, 2924, 2855, 1773, 1734, 1601, 1487, 1454, 1412, 1366, 1323, 1192, 1082, 858, 810, 750 cm^{-1}. HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{66}H_{76}O_{12}Na$ 1083.5234, found 1083.5230.

Synthesis of diol 41: To a stirred solution of **40** (1.65 g, 1.55 mmol) in MeCN (31.0 mL) was added $N_2H_4{\cdot}H_2O$ (340 mg, 6.79 mmol) at rt. After stirring for 30 min at rt, to the mixture was added 1 M hydrochloric acid (60 mL). The mixture was extracted with EtOAc (100 mL × 3). The combined organic layer was successively washed with 1 M hydrochloric acid (60 mL), H_2O (60 mL), and brine (60 mL). After the general drying procedure, the residue was purified by column chromatography (20 g of SiO_2, hexane/EtOAc = 3/1) to give **41** (1.52 g, 1.55 mmol 100% yield) as a white amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$, 24 °C) δ 7.35 (d, *J* = 8.0 Hz, 4H, OcBn), 7.33 (dd, *J* = 6.0, 2.9 Hz, 4H, Bn), 7.30–7.26 (m, 6H, Bn), 7.19 (d, *J* = 8.0 Hz, 4H, OcBn), 6.90 (s, 2H, HHDP), 5.87 (br s, 2H, OH), 5.17 (d, *J* = 11.5 Hz, 2H, Bn), 5.11 (d, *J* = 10.9 Hz, 2H, OcBn), 5.09 (d, *J* = 11.5 Hz, 2H, Bn), 5.04 (d, *J* = 10.9 Hz, 2H, OcBn), 4.43 (br dd, *J* = 9.7, 9.5 Hz, 2H, butane linker), 4.08 (br dd, *J* = 9.7, 4.0 Hz, 2H, butane linker), 2.62 (t, *J* = 7.7 Hz, 4H, OcBn), 1.94 (m, 2H, butane linker), 1.78 (m, 2H, butane linker), 1.61 (quintet, *J* = 7.7 Hz, 4H, OcBn), 1.38–1.22 (m, 20 H, OcBn), 0.87 (t, *J* = 7.5 Hz, 6H, OcBn). ^{13}C NMR (126 MHz, $CDCl_3$, 24 °C) δ 167.7 (s, 2C, HHDP), 150.7 (s, 2C, HHDP), 148.2 (s, 2C, HHDP), 143.0 (s, 2C, OcBn), 137.2 (s, 2C, Bn), 136.9 (s, 2C, HHDP), 133.7 (s, 2C, OcBn), 129.2 (s, 2C, HHDP), 128.6 (d, 4C, OcBn), 128.6 (d, 4C, Bn), 128.5 (d, 4C, Bn), 128.3 (d, 2C, Bn), 127.8 (d, 4C, OcBn), 115.3 (s, 2C, HHDP), 105.5 (d, 2C, HHDP), 75.4 (t, 2C, Bn), 70.9 (t, 2C, OcBn), 65.3 (t, 2C, butane linker), 35.8 (t, 2C, OcBn), 31.9 (t, 2C, OcBn), 31.6 (t, 2C, OcBn), 29.5 (t, 2C, OcBn), 29.4 (t, 2C, OcBn), 29.3 (t, 2C, OcBn), 26.1 (t, 2C, butane linker), 22.7 (t, 2C, OcBn), 14.2 (q, 2C, OcBn). IR (ATR) 3680–3040, 3061, 3013, 2926, 2855, 1726, 1717, 1603, 1578, 1497, 1335, 1234, 1142, 1096, 997, 752, 696 cm^{-1}. HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{62}H_{72}O_{10}Na$ 999.5023, found 999.5020.

Synthesis of dibenzofuran 42: To a stirred solution of **41** (1.19 g, 1.21 mmol) in CH_2Cl_2 (25.0 mL) were added Et_3N (146 mg, 1.44 mmol) and Tf_2O (361 mg, 1.28 mmol) at 0 ºC. After stirring for 15 min at 0 ºC, to the mixture was added H_2O (50 mL). The mixture was extracted with CH_2Cl_2 (60 mL × 3). The combined organic layer was successively washed with H_2O (60 mL) and brine (60 mL). The general drying procedure gave mono-triflate. To a solution of the crude product in DMF (40.5 mL) were added Cs_2CO_3 (808 mg, 2.48 mmol) at 80 ºC. After stirring for 7 h at 80 ºC, to the mixture was added 1 M hydrochloric acid (40 mL). The mixture was extracted with EtOAc (60 mL × 3). The combined organic layer was successively washed with 1 M hydrochloric acid (60 mL), H_2O (60 mL), and brine (60 mL). After the general drying procedure, the residue was purified by column chromatography (35 g of SiO_2, hexane/EtOAc = 4/1) to give **42** (1.09 g, 1.14 mmol, 94% yield in 2 steps) as a yellow syrup. ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) δ 7.49 (dd, *J* = 6.9, 2.9 Hz, 4H, Bn), 7.47 (s, 2H, THDBF), 7.39 (d, *J* = 8.0 Hz, 4H, OcBn), 7.34–7.31 (m, 6H, Bn), 7.23 (d, *J* = 8.0 Hz, 4H, OcBn), 5.41 (s, 4H, Bn), 5.20 (s, 4H, OcBn), 4.51 (br s, 4H, butane linker), 2.65 (t, *J* = 7.7 Hz, 4H, OcBn), 2.10 (br s, 4H, butane linker), 1.67 (quintet, *J* = 7.7 Hz, 4H, OcBn), 1.35–1.30 (m, 20H, OcBn), 0.91 (t, *J* = 6.9 Hz, 6H, OcBn). ^{13}C NMR (126 MHz, $CDCl_3$, 23 °C) δ 168.3 (s, 2C, THDBF), 150.4 (s, 2C, THDBF), 150.1 (s, 2C, THDBF), 143.2 (s, 2C, OcBn), 137.2 (s, 2C, Bn), 136.6 (s, 2C, THDBF), 133.8 (s, 2C, OcBn), 128.8 (d, 4C, OcBn), 128.5 (d, 4C, Bn), 128.4 (d, 4C, Bn), 128.3 (d, 2C, Bn), 127.9 (d, 4C, OcBn), 122.0 (s, 2C, THDBF), 117.4 (s, 2C, THDBF), 113.0 (d, 2C, THDBF), 75.5 (t, 2C, Bn), 72.3 (t, 2C, OcBn), 65.5 (t, 2C, butane linker), 35.9 (t, 2C, OcBn), 32.0 (t, 2C, OcBn), 31.6 (t, 2C, OcBn), 29.6 (t, 2C, OcBn), 29.5 (t, 2C, OcBn), 29.4 (t, 2C, OcBn), 26.9 (t, 2C, butane linker), 22.8 (t, 2C, OcBn), 14.2 (q, 2C, OcBn). IR (ATR) 3062, 3030, 2924, 2853, 1824, 1717, 1627, 1590, 1516, 1454, 1378, 1317, 1209, 1093, 997, 815, 732, 696 cm^{-1}. HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{62}H_{70}O_9Na$ 981.4918, found 981.4918.

Synthesis of dicarboxylic acid 39: To a stirred solution of **42** (267 mg, 0.278 mmol) in DMSO (28 mL) was added 3 M LiOH aq. (1.0 mL) at 80 ºC. After stirring for 2 d at 80 ºC, to the mixture was further added 3 M LiOH aq. (1.0 mL) at 80 ºC. After stirring for 2 d at 80 ºC, to the mixture was added 1 M hydrochloric acid (100 mL). The mixture was extracted with EtOAc (100 mL × 3). The combined organic layer was successively washed with 1 M hydrochloric acid (50 mL), and then diluted with hexane (100 mL). The organic layer was successively washed with H_2O (50 × 4 mL) and brine (50 mL). After the general drying procedure, the residue was purified by trituration with MeOH to give **39** (224 mg, 0.247 mmol, 89% yield) as a white solid. mp 249.0–250.9 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) δ 7.49 (dd, *J* = 6.6, 4.0 Hz, 4H, Bn), 7.46 (s, 2H, THDBF), 7.36 (d, *J* = 8.0 Hz, 4H, OcBn), 7.33–7.30 (m, 6H, Bn), 7.20 (d, *J* = 8.0 Hz, 4H, OcBn), 5.42 (s, 4H, Bn), 5.16 (s, 4H, OcBn), 2.62 (t, *J* = 7.5 Hz, 4H, OcBn), 1.62 (quintet, *J* = 7.5 Hz, 4H, OcBn), 1.38–1.23 (m, 20H, OcBn), 0.87 (t, *J* = 7.5 Hz, 6H, OcBn). ^{13}C NMR (126 MHz, $CDCl_3$, 23 °C) δ 175.2 (s, 2C, CO_2H), 150.4 (s, 2C, THDBF), 150.3 (s, 2C, THDBF), 143.3 (s, 2C, OcBn), 137.4 (s, 2C, THDBF), 137.2 (s, 2C, Bn), 133.6 (s, 2C, OcBn), 128.8 (d, 4C, OcBn), 128.6 (d, 4C, Bn), 128.4 (d, 6C, Bn), 127.9 (d, 4C, OcBn), 121.0 (s, 2C, THDBF), 117.7 (d, 2C, THDBF), 112.4 (s, 2C, THDBF), 75.5 (t, 2C, Bn), 72.5 (t, 2C, OcBn), 35.9 (t, 2C, OcBn), 32.0 (t, 2C, OcBn), 31.6 (t, 2C, OcBn), 29.6 (t, 2C, OcBn), 29.5 (t, 2C, OcBn), 29.4 (t, 2C, OcBn), 22.8 (t, 2C, OcBn), 14.3 (q, 2C, OcBn). IR (ATR) 3300–2800, 3063, 3030, 2954, 2853, 2629, 1701, 1626, 1597, 1454, 1261, 1179, 1111, 864, 814, 696 cm^{-1}. HRMS (FAB) *m*/*z* [M]$^+$ calcd for $C_{58}H_{64}O_9$ 904.4550, found 904.4559.

Synthesis of seco acid 45 (Table 1, entry 5): To a stirred solution of **21** (64.5 mg, 44.6 μmol) and **39** (56.5 mg, 62.4 μmol) in CH_2Cl_2 (4.5 mL) were added EDCI·HCl (26.2 mg, 137 μmol) and PPY (8.2 mg, 55 μmol) at rt. After stirring for 45 min at rt, to the mixture was added 1 M hydrochloric acid (7 mL). The separated organic layer was successively washed with H_2O (20 mL) and brine (20 mL). After the general drying procedure, the residue was purified by column chromatography (10 g of SiO_2, hexane/EtOAc = 4/1 to 2/1) to give **45** (75.8 mg, 32.5 μmol, 73% yield) as a yellow syrup. $[\alpha]_D^{22}$ –17 (*c* 0.76, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 24 °C) δ 7.52 (s, 1H, THDBF), 7.49–7.35 (m, 19H, Bn, OcBn, THDBF, galloyl), 7.35–7.02 (m, 44H, Bn, OcBn, H-1), 7.01 (d, *J* = 7.5 Hz, 2H, Bn), 7.00 (s, 1H, HHDP), 6.93 (s, 1H, HHDP), 6.77 (d, *J* = 6.9 Hz, 2H, Bn), 5.54 (s, 1H, H-2), 5.42 (s, 2H, Bn), 5.42 (s, 2H, Bn), 5.31 (s, 1H, H-3), 5.28 (dd, *J* = 10.9, 8.0 Hz, 1H, H-6), 5.22–5.12 (m, 6H, OcBn, Bn), 5.07 (d, *J* = 11.5 Hz, 1H, Bn), 5.03–4.88 (m, 10H, Bn), 4.82 (dd, *J* = 10.9, 10.0 Hz, 1H, H-5), 4.75 (d, *J* = 10.9 Hz, 2H, Bn), 4.69 (s, 1H, H-4), 4.48 (dd, *J* = 10.0, 8.0 Hz, 1H, H-6), 4.39 (d, *J* = 10.9 Hz, 1H, Bn), 4.33 (br d, *J* = 10.9 Hz, 1H, Bn), 4.32 (br d, *J* = 10.9 Hz, 1H, Bn), 2.61 (br t, *J* = 7.5 Hz, 2H, OcBn), 2.58 (br t, *J* = 7.5 Hz, 2H, OcBn), 1.63–1.56 (m, 4H, OcBn), 1.38–1.26 (m, 20H, OcBn), 0.87 (t, *J* = 7.5 Hz, 3H, OcBn), 0.86 (t, *J* = 7.5 Hz, 3H, OcBn). ^{13}C NMR (126 MHz, $CDCl_3$, 24 °C) δ 169.3 (s, CO_2H), 167.5 (s, HHDP), 166.0 (s, HHDP), 166.0 (s, THDBF), 165.5 (s, galloyl), 153.2 (s, 2C, galloyl), 152.9 (s, HHDP), 152.6 (s, 2C, HHDP), 152.4 (s, HHDP), 150.6 (s, THDBF), 150.6 (s, THDBF), 150.2 (s, THDBF), 150.1 (s, THDBF), 145.4 (s, HHDP), 144.7 (s, HHDP), 144.1 (s, galloyl), 143.3 (s, OcBn), 143.3 (s, OcBn), 137.9 (s, 2C, Bn), 137.6 (s, Bn), 137.6 (s, 2C, Bn), 137.2 (s, THDBF), 137.2 (s, Bn), 137.1 (s, THDBF), 137.1 (s, Bn), 136.7 (s, 2C, Bn), 136.5 (s, Bn), 136.2 (s, Bn), 133.7 (s, OcBn), 133.6 (s, OcBn), 128.9–127.3 (overlapping 63 doublets and 1 singlet: 22 peaks were observed, 64C, Bn, OcBn, HHDP), 127.0 (s, HHDP), 125.3 (s, HHDP), 123.7 (s, galloyl), 123.2 (s, HHDP), 121.1 (s, THDBF), 120.3 (s, THDBF), 118.0 (s, THDBF), 117.7 (s, THDBF), 112.6 (d, THDBF), 112.3 (d, THDBF), 109.3 (d, 3C, galloyl, HHDP), 107.9 (d, HHDP), 93.2 (d, C-1), 75.7 (t, Bn), 75.5 (t, Bn), 75.5 (t, Bn), 75.2 (t, Bn), 75.2 (t, Bn), 75.1 (t, Bn), 74.8 (d, C-5), 74.4 (t, Bn), 72.4 (t, 2C, OcBn), 71.5 (t, 2C, Bn), 71.4 (t, Bn), 71.1 (t, Bn), 67.9 (d, C-3), 67.6 (d, C-2), 64.0 (t, C-6), 60.5 (d, C-4), 35.9 (t, 2C, OcBn), 32.0 (t, 2C, OcBn), 31.6 (t, OcBn), 31.6 (t, OcBn), 29.6 (t, 2C, OcBn), 29.5 (t, OcBn), 29.5 (t, OcBn), 29.4 (t, 2C, OcBn), 22.8 (t, 2C, OcBn), 14.2 (q, 2C, OcBn). IR (ATR) 3600–3050, 3032, 2924, 2854, 1737, 1589, 1498, 1454, 1369, 1190, 1096, 1015, 732, 694 cm^{-1}. HRMS (unanalyzable due to instability under ionization conditions).

Synthesis of 2,4-*O*-THDBF bridged compound 43 (Table 2, entry 4): To a stirred solution of **45** (37.3 mg, 16.0 μmol) in THF (0.76 mL) was added TCBCl (7.8 mg, 32 μmol). After stirring for 1 h at reflux, to the mixture was added PPY (ca. 4.7 mg, ca. 32 μmol) at reflux. After stirring for 14 min at reflux, to the mixture was add 1 M hydrochloric acid (5 mL). The mixture was extracted with EtOAc (20 mL × 3). The combined organic layer was successively washed with H_2O (20 mL) and brine (20 mL). After the general drying procedure, the residue was purified by column chromatography (10 g of SiO_2, hexane/EtOAc = 9/1 to 5/1) to give **43** (25.6 mg, 11.1 μmol, 69% yield) as a yellow syrup. $[\alpha]_D^{24}$ +14 (*c* 0.26, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.54 (s, 1H, THDBF), 7.51–7.06 (m, 62 H, Bn, OcBn, galloyl, THDBF), 7.03 (s, 1H, HHDP), 7.01–6.98 (m, 2H, Bn), 6.97 (s, 1H, HHDP), 6.82 (br s, 1H, H-3), 6.78 (d, *J* = 7.5 Hz, 2H, Bn), 6.49 (s, 1H, H-1), 5.56 (br s, 2H, H-2, H-4), 5.41 (s, 2H, Bn), 5.35 (s, 2H, Bn), 5.23–5.12 (m, 6H, Bn, OcBn), 5.05 (dd, *J* = 10.9, 9.9 Hz, 1H, H-6), 5.04 (d, *J* = 10.9 Hz, 1H, Bn), 5.00–4.92 (m, 7H, Bn, H-5), 4.89 (d, *J* = 10.9 Hz, 1H, Bn), 4.88 (d, *J* = 11.5 Hz, 2H, Bn), 4.76 (d, *J* = 10.9 Hz, 1H, Bn), 4.74 (d, *J* = 10.9 Hz, 1H, Bn), 4.73 (d, *J* = 10.9 Hz, 1H, Bn), 4.67 (dd, *J* = 10.9, 8.0 Hz, 1H, H-6), 4.45 (d, *J* = 10.9 Hz, 1H, Bn), 4.36 (d, *J* = 10.9 Hz, 1H, Bn), 4.29 (d, *J* = 10.9 Hz, 1H, Bn), 2.66–2.60 (m, 4H, OcBn), 1.67–1.60 (m, 4H, OcBn), 1.38–1.26 (m, 20H, OcBn), 0.91–0.87 (m, 6H, OcBn). ^{13}C NMR (126 MHz, $CDCl_3$, 24 °C) δ 168.6 (s, THDBF), 167.8 (s, HHDP), 166.7 (s, THDBF), 165.3 (s, HHDP), 164.6 (s, galloyl), 153.1 (s, 2C, galloyl), 153.0 (s, HHDP), 152.7 (s, HHDP), 152.6 (s, HHDP), 152.5 (s, HHDP), 150.7 (s, THDBF), 150.5 (s, THDBF), 150.5 (s, THDBF), 150.3 (s, THDBF), 145.7 (s, HHDP), 144.9 (s, HHDP), 143.7 (s, galloyl), 143.4 (s, OcBn), 143.4 (s, OcBn), 138.0 (s, Bn), 137.9 (s, Bn), 137.7 (s, Bn), 137.7 (s, Bn), 137.5 (s, THDBF), 137.2 (s, Bn), 137.1 (s, Bn), 137.1 (s, Bn), 136.7

(s, Bn), 136.7 (s, 2C, Bn), 136.2 (s, Bn), 135.9 (s, THDBF), 133.5 (s, OcBn), 133.5 (s, OcBn), 128.9–127.4 (overlapping 63 doublets and 1 singlets: 11 peaks were observed, 64C, Bn, OcBn, HHDP), 126.5 (s, HHDP), 125.6 (s, HHDP), 123.5 (s, THDBF), 123.4 (s, HHDP), 122.9 (s, galloyl), 118.9 (s, THDBF), 116.4 (s, THDBF), 115.7 (s, THDBF), 114.8 (d, THDBF), 109.8 (d, HHDP), 109.5 (d, THDBF), 108.9 (d, 2C, galloyl), 108.0 (d, HHDP), 93.3 (d, C-1), 75.7 (t, Bn), 75.6 (t, Bn), 75.6 (t, Bn), 75.3 (t, Bn), 75.3 (t, Bn), 75.1 (t, Bn), 74.5 (t, Bn), 73.5 (d, C-5), 72.5 (t, Bn), 72.3 (t, Bn), 71.6 (t, Bn), 71.3 (t, 2C, Bn), 71.0 (t, Bn), 70.4 (d, C-2), 67.0 (d, C-4), 64.3 (t, C-6), 61.5 (d, C-3), 35.9 (t, 2C, OcBn), 32.1 (t, 2C, OcBn), 31.7 (t, OcBn), 31.6 (t, OcBn), 29.6 (t, 2C, OcBn), 29.5 (t, 2C, OcBn), 29.4 (t, 2C, OcBn), 22.8 (t, 2C, OcBn), 14.3 (q, 2C, OcBn). IR (ATR) 3063, 3032, 2924, 2855, 1744, 1711, 1589, 1499, 1369, 1209, 1182, 1094, 1013, 959, 906, 729, 694 cm^{-1}. HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{148}H_{136}O_{25}Na$ 2336.9302, found 2336.9280.

Synthesis of mallotusinin (1): A mixture of **43** (9.0 mg, 3.9 μmol) and $Pd(OH)_2/C$ (20 wt. %, 13.6 mg, 19.4 μmol) in THF (0.8 mL) was stirred under H_2 atmosphere at rt. After stirring for 1.5 h at rt, the mixture was filtered through a Celite pad to remove the catalyst and carbon. After the filtrate was concentrated, the residue was purified by column chromatography (3 g of Sephadex G-25, MeOH/water = 3/2) to give **1** (2.0 mg, 2.2 μmol, 56% yield) as a brown amorphous solid. $[\alpha]_D^{24}$ –15 (*c* 0.21, $CHCl_3$). ^1H NMR (500 MHz, acetone-d_6, 24 °C) δ 7.35 (s, 1H, THDBF), 7.13 (s, 2H, galloyl), 7.10 (s, 1H, THDBF), 7.09 (s, 1H, HHDP), 6.69 (s, 1 H, HHDP), 6.69 (br d, *J* = 4.0 Hz, 1H, H-3), 6.32 (d, *J* = 3.4 Hz, 1H, H-1), 5.43 (ddd, *J* = 3.4, 1.7, 1.2 Hz, 1H, H-2), 5.33 (br d, *J* = 4.0 Hz, 1H, H-4), 4.86 (br dd, *J* = 8.0, 6.3 Hz, 1H, H-5), 4.66 (br dd, *J* = 12.0, 8.0 Hz, 1H, H-6), 4.34 (dd, *J* = 12.0, 6.3 Hz, 1H, H-6). ^{13}C NMR (126 MHz, acetone-d_6, 24 °C) δ 169.2 (s, THDBF), 168.5 (s, HHDP), 167.2 (s, THDBF), 166.5 (s, HHDP), 165.0 (s, galloyl), 147.2 (s, THDBF or HHDP), 147.0 (s, THDBF or HHDP), 146.1 (s, 2C, galloyl), 145.4 (s, THDBF or HHDP), 145.4 (HHDP), 145.2 (s, THDBF or HHDP), 145.0 (s, HHDP or THDBF), 145.0 (s, HHDP or THDBF), 144.6 (s, THDBF), 139.8 (s, 2C, galloyl), 137.6 (s, HHDP), 136.5 (s, HHDP), 136.0 (s, THDBF), 133.3 (s, THDBF), 125.5 (s, HHDP), 125.0 (s, HHDP), 120.4 (s, galloyl or THDBF), 120.2 (s, galloyl or THDBF), 116.5 (s, THDBF), 116.5 (s, HHDP), 116.1 (d, THDBF), 115.8 (s, THDBF), 115.4 (d, THDBF), 115.2 (s, HHDP), 111.1 (s, THDBF), 110.5 (d, 2C, galloyl), 110.0 (d, HHDP), 108.4 (d, HHDP), 92.1 (d, C-1), 75.8 (d, C-5), 74.1 (d, C-2), 68.6 (d, C-4), 64.8 (t, C-6), 63.4 (d, C-3). IR (ATR) 3545–2965, 2881, 1733, 1716, 1699, 1616, 1541, 1362, 1219, 1036, 772 cm^{-1}. HRMS (ESI) *m/z* $[M – H]^–$ calcd for $C_{41}H_{25}O_{25}$ 917.0685, found 917.0681.

Synthesis of dibenzofuran 47a (Table 3, entry 3): To a stirred solution of **46a** (11.6 mg, 13.3 μmol) in DMF (0.5 mL) was added DBU (4.5 mg, 30 μmol) at 70 ºC. After stirring for 8 h at 70 ºC, to the mixture was added 1 M hydrochloric acid (1 mL). The mixture was extracted with EtOAc (10 mL × 4). The combined organic layer was successively washed with 1 M hydrochloric acid (1 mL), H_2O (30 mL), and brine (30 mL). After the general drying procedure, the residue was purified by column chromatography (3 g of SiO_2, hexane/EtOAc = 6/1 to 5/1) to give **47a** (5.0 mg, 6.9 μmol, 52% yield) as a yellow syrup. ^1H NMR (500 MHz, $CDCl_3$, 22 °C) δ 7.52–7.49 (m, 4H, Bn), 7.47–7.43 (m, 4H, Bn), 7.41–7.28 (m, 12H, Bn), 7.17 (s, 1H, dibenzofuran), 6.83 (s, 1H, dibenzofuran), 5.36 (s, 2H, Bn), 5.29 (s, 2H, Bn), 5.19 (s, 2H, Bn), 5.19 (s, 2H, Bn), 4.65–4.62 (m, 4H, benzylic, butane linker), 3.69–3.65 (m, 2H, butane linker), 2.00–1.94 (m, 2H, butane linker), 1.87–1.82 (m, 2H, butane linker). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 168.9 (s, ester), 151.4 (s, dibenzofuran), 150.5 (s, dibenzofuran), 150.1 (s, dibenzofuran), 149.4 (s, dibenzofuran), 137.6 (s, Bn), 137.4 (s, Bn), 137.1 (s, Bn), 136.9 (s, Bn), 135.8 (s, dibenzofuran), 133.6 (s, dibenzofuran), 128.7–127.6 (d, overlapping 20 doublets and 1 singlet: 7 peaks were observed, 21C, Bn, dibenzofuran), 124.0 (s, dibenzofuran), 118.2 (s, dibenzofuran), 117.2 (s, dibenzofuran), 112.6 (d, dibenzofuran), 110.6 (d, dibenzofuran), 75.7 (t, Bn), 75.5 (t, Bn), 74.3 (t, benzylic), 72.4 (t, Bn), 72.4 (t, Bn), 71.8 (t, butane linker), 63.3 (t, butane linker), 28.7 (t, butane linker), 25.2 (t, butane linker). IR (ATR) 3017, 2926, 2855, 1713, 1605, 1514, 1454, 1416, 1215, 1099, 748, 696, 667 cm^{-1}. HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{46}H_{40}ONa$ 743.2621, found 743.2610.

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Keywords: mallotusinin • corilagin • intramolecular S_NAr reaction• two-step bislactonization • total synthesis

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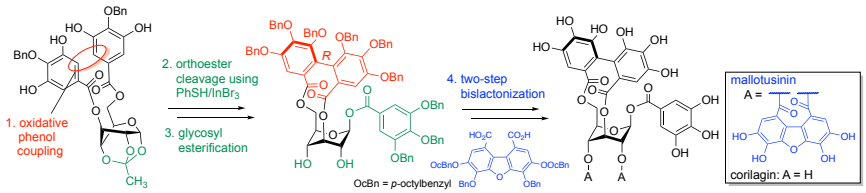

We describe the total synthesis of mallotusinin via the second-generation synthesis of corilagin. The key steps are as follows: (1) oxidative phenol coupling of 1,2,4-orthoacetyl-3,6-di-(4-*O*-benzylgalloyl)-α-D-glucopyranose; (2) orthoester cleavage along with thioglycosylation followed by β-selective glycosyl esterification; (3) two-step bislactonization to construct a 2,4-*O*-tetrahydroxydibenzofuranoyl bridge on corilagin.