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Seven-Step Stereodivergent Total Syntheses of Punicafolin and Macaranganin

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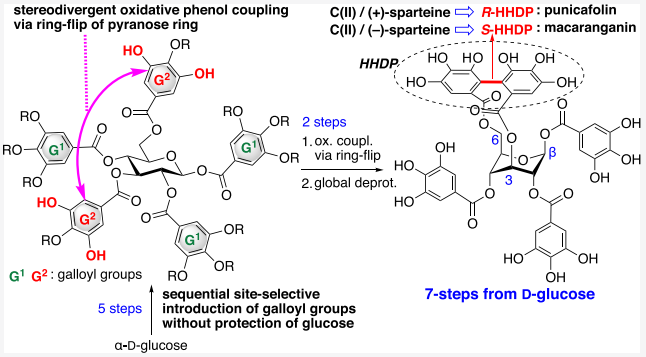
ABSTRACT: The first total syntheses of punicafolin (**1**) and macaranganin (**2**) were achieved in seven steps, respectively, from commercial α-D-glucose. The characteristic features of the synthesis are (1) sequential site-selective introduction of the adequate galloyl groups into unprotected D-glucose by a catalyst-controlled manner and (2) stereodivergent construction of the 3,6-HHDP bridge by oxidative phenol coupling of a common intermediate via a ring-flipping process of the glucose core. Because no protective groups were used for glucose throughout the process, extremely short-step total syntheses of natural glycosides **1** and **2** (MW 938) were performed.



INTRODUCTION

Ellagitannins constitute one of the major classes of hydrolyzable tannins. More than 500 natural products of this ellagitannin family have been structurally characterized, exhibiting a variety of biological activities including antioxidative, anticancer, and antiviral activities.[1] The structures are basically composed of a central sugar core, typically D-glucose, to which are esterified gallic acid (3,4,5-trihydroxybenzoic acid) and hexahydroxydiphenoic (HHDP) acid. Punicafolin (**1**) and macaranganin (**2**) (Scheme 1a) have been isolated from the leaves of *Punica granatum* in 1985 and *Macaranga tanarius* (L.) MUELL. et ARG. in 1990, respectively, by Nishioka and co-workers.[2,3] They are characterized by a 3,6-HHDP group bridged between C(3)−OH and C(6)−OH of the glucose core. Construction of the 3,6-HHDP group has been a synthetic challenge because a less stable axial-rich conformer such as $^1C_4$ conformer of the pyranose ring is required for the formation.[4,5] Natural glycosides **1** and **2** have the same molecular formula and are stereoisomeric to each other concerning the chiral axis of the HHDP group. They show different biological activities depending on the chirality of the 3,6-HHDP groups. Glycoside **1** with an *R*-HHDP group exhibits inhibitory activity of invasion of HT1080 fibrosarcoma cells (IC_{50} = 4.2 μM),[6] while **2** with an *S*-HHDP group acts as a strong inhibitor of prolyl endopeptidase (IC_{50} = 43 nM).[7] Thus, stereodivergent construction of the HHDP groups is an important additional challenge. Here, we report the first total syntheses of **1** and **2** in seven steps, respectively, from D-glucose via sequential site-selective introduction of galloyl groups into unprotected D-glucose without employing any protective groups for hydroxy groups of glucose (Scheme 1a).

Yamada and co-workers reported the first example for the construction of a 3,6-HHDP-bridged glucose skeleton via a ring-opened glucose derivative in 2004.[5c] The strategy was successfully applied to the first total synthesis of a $^1C_4$/*B*-ellagitannin, corilagin, in 2008 (Scheme 1b, route A).[8] Recently, Ikeuchi, Yamada, and co-workers reported an improved synthesis of corilagin via a conformationally fixed intermediate (Scheme 1b, route B).[9] In these precedents, use of a ring-opened pyranose derivative or a conformationally fixed pyranose derivative seemed essential for the construction of the 3,6-HHDP group. For straightforward total synthesis, direct formation of the 3,6-HHDP group from a stable chair $^4C_1$ conformation with all equatorial substituents seems to be more desirable. The potential was demonstrated also by Yamada's group.[10] The regiochemical profile of oxidative phenol coupling of penta-(4-*O*-benzyl)galloylglucose **6** was investigated (Scheme 1c). They carefully isolated the 3,6-HHDP derivative, and the structure was unambiguously clarified to be **7**. Although the formation of **7** was only in a trace amount, this study demonstrated that the direct formation of the 3,6-HHDP glucose derivative with the $^1C_4$ conformation is possible via the ring-flipping process of the glucose derivative with a stable $^4C_1$ conformation.

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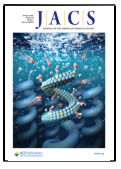

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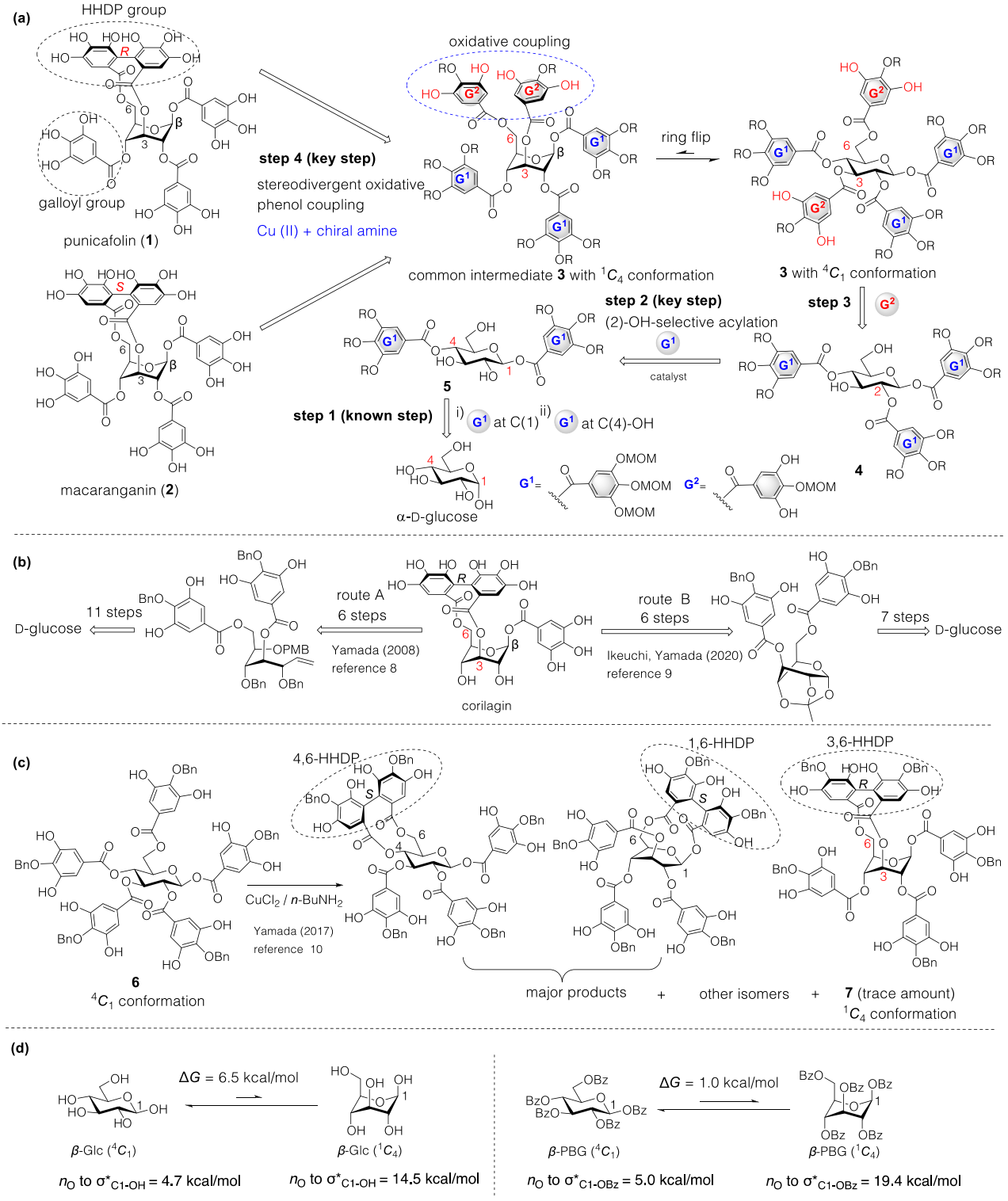
Scheme 1. Structure and Synthetic Strategy for Ellagitannins with a 3,6-HHDP Group[a]



[a](a) This work: Retrosynthetic analysis for total syntheses of punicafolin (**1**) and macaranganin (**2**). (b) Yamada's total synthesis of corilagin. (c) Regiochemical profile of oxidative phenol coupling of penta-(4-*O*-benzyl)galloylglucose derivative **6** reported by Yamada's group. (d) Conformational analysis of glucose (*β*-Glc) and the perbenzoylated derivative (*β*-PBG).

Inspired by Yamada's pioneering studies, we planned a total synthesis of **1** and **2**. The retrosynthetic analysis is shown in Scheme 1a. We envisaged that stereodivergent oxidative phenol coupling between the 3- and 6-galloyl groups of **3** with an unstable $^1C_4$ conformation generated via a ring-flip process from its stable $^4C_1$ conformer is the most straightforward route to **1** and **2** (step 4: key step). Control of the stereochemistry of the oxidative phenol coupling might be achieved by a proper choice of chiral amines in the presence of Cu(II) as the oxidant. The plausibility of the all-axial

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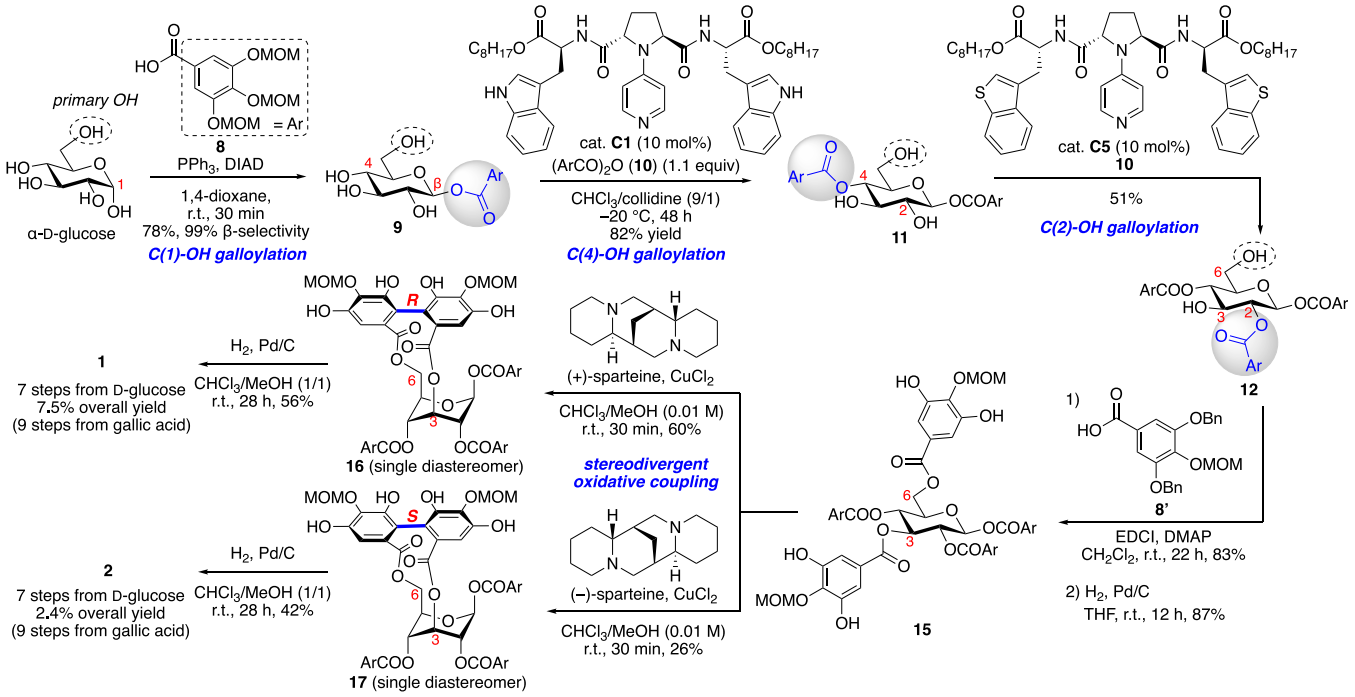
Scheme 2. Total Syntheses of Punicafolin (1) and Macaranganin (2)



conformer of **3** seemed to be of critical importance to realize the construction of the 3,6-HHDP group. The ring-flip process of **3** was estimated by a DFT calculation. Conformational analysis of β-pentabenzoylglucose (β-PBG) as a model of **3** was performed with comparison with that of β-glucose (β-Glc) (Scheme 1d). The optimized geometries of β-PBG and β-Glc were obtained by conformational searches with molecular mechanics (OPLS force field, MCMM) and the subsequent optimization by a DFT calculation at the M06-2X/6-311++G(2d,2p)//M06-2X/6-31G(d) level (For details, see Figures S1 and S27). In both cases, the $^4C_1$ conformer was found to be the most stable and the flipped-chair $^1C_4$ conformer was the most stable among axial-rich conformers. The energy difference between $^4C_1$ and $^1C_4$ conformers of β-Glc was evaluated to be 6.5 kcal/mol, while that of β-PBG was estimated to be only 1.0 kcal/mol. The origin of the relative preference of the all-axial conformer of β-PBG rather than that of β-Glc seemed to be resulting from the stronger orbital interaction between the nonbonding orbital of the ring oxygen with the σ^* orbital of the electron withdrawing C(1)−OBz bond (stronger anomeric effect),[11] which was suggested by natural bond orbital (NBO) analysis (for detailed analysis, see Figure S2). These results suggested that axial-rich conformations of **3** essential for the oxidative phenol coupling could exist to some extent via the ring-flip process of the stable $^4C_1$ conformer (the conformational analysis of β-PBG based on Boltzmann distribution analysis indicates the ratio between β-PBG ($^4C_1$) and β-PBG ($^1C_4$) to be 30:1; for details, see Figure S4).

We then planned site-selective preparation of **3** from D-glucose without employing any protective groups for glucose. Galloyl groups $\mathbf{G^2}$ required for the oxidative phenol coupling were planned to be introduced at C(3)−OH and C(6)−OH. Because the rational precursor for **3** is to be 1,2,4-trigallate **4**, another key step must be site-selective introduction of galloyl group $\mathbf{G^1}$ at C(2)−OH into the known intermediate, 1,4-digallate **5** (step 2). We envisaged that use of our catalyst library for site-selective acylation might be effective for this challenge because chiral pyrrolidinopyridines (PPYs) with various side chains have been shown to promote site-selective acylation of glucose derivatives with intrinsic site-selectivity depending on the side chains for molecular recognition.[12c,d] The strategy for preparation of digallate **5** has already been established by our group[13] via a stereo- and site-selective S_N2-type Mitsunobu glycosylation[14] of gallic acid derivative $\mathbf{G^1}$ with unprotected α-D-glucose as a glycosyl donor followed by catalyst-controlled site-selective introduction of the second galloyl group $\mathbf{G^1}$.[12a−c,13]

RESULTS AND DISCUSSION

Actual synthesis was commenced with α-D-glucose and *O*-MOM-protected gallic acid derivative **8** via a known two-step procedure[13] to give 1,4-digallate **11** in 64% yield from α-D-glucose (Scheme 2). The first key step concerning site-selective introduction of the same galloyl group, **8**, into the C(2)−OH of **11** with three free hydroxy groups was investigated (Scheme 1a, step 2, Table 1). We first examined DMAP-catalyzed acylation of **11** with gallic acid anhydride derivative **10** to assess the inherent reactivity of **11** toward galloylation. Treatment of **11** with **10** in the presence of DMAP (10 mol %) and diisopropylethylamine (DIPEA) in $CHCl_3$ at −20 °C gave the desired 2-*O*-acylate **12** and 3-*O*-acylate **13** in 44 and 36% yield, respectively, with the primary C(6)−OH intact (0% formation of **14**) (entry 1). The relatively higher reactivity of the C(2)−OH and the C(3)−OH toward acylation in the presence of the primary C(6)−OH was also observed in total synthesis of cercidinin A.[15] Furthermore, the lack of the reactivity of the free C(6)−OH in the glucose core in DMAP-catalyzed acylation of a natural cardiac glycoside, lanatoside C, was observed (0% acylation), where the C(6)−OH was suggested to form a strong intramolecular hydrogen bond (2.9 Å for O−H−O distance) by molecular modeling.[12b] We suppose that the intramolecular

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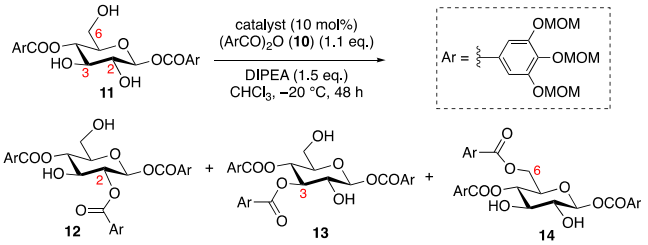
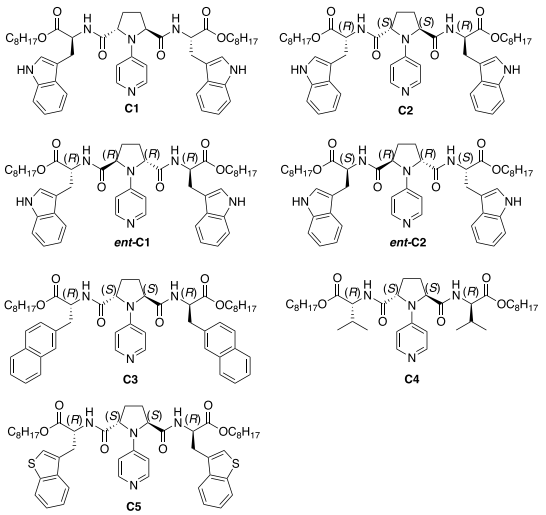
Table 1. Catalyst Screening for the C(2)−OH-Selective Introduction of the Third Galloyl Group into 1,4-Digallate 11



		yield (%)			recovery (%)	site-selectivity (%) for C(2)−OH acylation
entry	catalyst	12	13	14	11	12/(12 + 13 + 14)
1	DMAP	44	36	0	10	55
2	**C1**	32	20	4	24	57
3	**C2**	23	9	1	48	70
4	***ent*-C1**	37	37	3	13	48
5	***ent*-C2**	21	19	3	36	49
6	**C3**	22	5	1	49	79
7	**C4**	13	7	4	37	54
8	**C5**	42	10	4	30	75
9[a]	**C5**	51	13	1	10	78

[a]Acid anhydride **10** (2.2 equiv) and DIPEA (3.0 equiv) were used.



hydrogen bond could be, at least in some part, responsible for the reduced reactivity of the free C(6)−OH.

We then examined a catalyst mini-library including **C1**−**C5**, ***ent*-C1**, and ***ent*-C2**, which were expected to be able to control the site-selectivity of acylation of polyol compounds irrespective of the inherent reactivity of the substrate polyols (Table 1).[16] Catalyst **C1** was first examined because it was shown to be extremely effective for site-selective acylation of D-glucose derivatives.[12c] Treatment of **11** with anhydride **10** in the presence of 10 mol % of **C1** gave the desired 2-*O*-acylate **12** and 3-*O*-acylate **13** in 32 and 20% yield, respectively, with 24% recovery of **11** (57% site-selectivity for C(2)−OH acylation, entry 2). Since the site-selectivity was not improved, its diastereomeric catalysts **C2**, ***ent*-C1**, and ***ent*-C2** were examined (entries 2−4). The highest site-selectivity (70%) was obtained by **C2** with *R*,*S*,*S*,*R* configuration, although the yield was low (23%, entry 2). We then examined catalysts **C3** and **C4** possessing *β*-naphthylalanine- and valine-derived side chains, respectively, with the same *R*,*S*,*S*,*R* configuration as that of **C2** (entries 6 and 7). The yield of the desired C(2)-acylate **12** was low (13−22%) in both cases, while the promising site-selectivity (79%) was observed in the reaction with **C3**. We further examined a newly developed catalyst, **C5** with a 3-benzothiophenyl group instead of the 3-indolyl group of **C2**. Site-selective introduction of the galloly group at C(2)−OH was achieved with **C5** in 42% yield with 75% selectivity (entry 8). Finally, use of 2.2 equiv of anhydride **10** in the presence of **C5** afforded the desired 2-*O*-acylate **12** with moderately acceptable yield and selectivity (entry 9, 51% yield, 78% selectivity). The rationale of the C(2)−OH selectivity in **C5**-catalyzed acylation was totally unclear at this moment.

With the desired 1,2,4-trigallate **12** in hand, 1,2,3,4,6-pentagallate **15** (Scheme 2), the precursor for the key step (step 4 in Scheme 1a: stereodivergent oxidative phenol coupling), was prepared. Condensation of **12** with gallic acid derivative **8′** (protected G^2 in Scheme 1a) followed by hydrogenolysis gave **15** in 72% yield. Construction of the 3,6-HHDP bridge by oxidative phenol coupling of **15** via the presumed ring-flip process of the pyranose core was examined. Treatment of **15** under the standard conditions for oxidative phenol coupling ($CuCl_2$ (3.0 equiv)/*n*-$BuNH_2$ (20 equiv)/$CHCl_3$/MeOH (1/1))[8,17] gave no HHDP-bridged products; instead, decomposition of **15** by solvolysis and/or aminolysis was observed (Table S1, entry 1). We then examined sparteine in place of *n*-$BuNH_2$ according to Quideau's achievement. Recently, Quideau, Deffieux, and co-workers reported (−)-sparteine/Cu(II)-mediated oxidative phenol coupling for the construction of a nonahydroxytriphenoyl (NHTP) group toward total synthesis of a *C*-glucoside ellagitannin, (−)-vescalin.[18] Treatment of **15** with $CuCl_2$ (3.0 equiv) and (+)-sparteine (10 equiv) in $CHCl_3$/MeOH (1/1) at rt for 30 min afforded the desired 3,6-HHDP-bridged product **16** with *R* configuration in 60% yield as a single diastereomer (Scheme 2). Use of smaller amounts (5.0 equiv) of (+)-sparteine resulted in the reduced yield (29%) with complete stereocontrol of the HHDP group formation (Table S1, entry 7). The $^1C_4$ conformation of **16** was suggested by comparison of the chemical shifts and $^3J_{HH}$ of the pyranose moiety in the ^{1}H NMR spectra of **16** with those of **15** (see the Supporting Information). Use of (−)-sparteine for the oxidative phenol coupling of **15** resulted in complete reversal of stereochemistry for the construction of the 3,6-HHDP group. On treatment of **15** with $CuCl_2$ (3.0 equiv) and (−)-sparteine (10 equiv) in $CHCl_3$/MeOH (1/1) at rt for 30 min, the desired product **17** with an (*S*)-3,6-HHDP group was obtained in 26% yield as a single diastereomer. The recovery of **15** was only ∼10% in this transformation. The major reason of the poor material balance seemed to be resulting from solvolysis and aminolysis of **17** and/or the related derivatives. Although the yields are not satisfactory, this is the first successful example of stereodivergent construction of the HHDP groups from a common precursor among the reported syntheses of ellagitannins.[19] Deprotection of the MOM groups of **16** and **17** under the hydrogenation conditions[15,20] afforded **1** and **2** in 56 and 42% yield, respectively (cf. The MOM group remained intact during the transformation of **12** to **15** via hydrogenation conditions in THF. Use of alcoholic solvents is indispensable for the removal of acid-labile groups under hydrogenation conditions.[15,20]). Thus, the first total syntheses of **1** and **2** were achieved in overall seven steps, respectively, from D-glucose (nine steps from gallic acid) without using protective groups for hydroxy groups of glucose. Two

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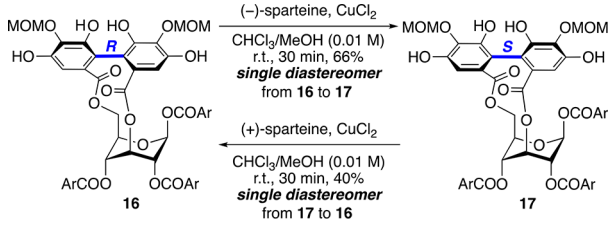
organocatalysts, **C1** and **C5**, played a pivotal role for site-selective introduction of galloyl groups, which could avoid the use of the protective groups.

To get insights into the unprecedented stereodivergent oxidative phenol coupling, we examined whether the stereochemical outcome was determined by a kinetically or thermodynamically controlled manner. The stereochemically pure isomer **16** with an (*R*)-HHDP group was treated under the conditions with (−)-sparteine/Cu(II), which were employed for the conversion from **15** to **17**, to give **17** with an (*S*)-HHDP group as a single diastereomer in 66% yield (Scheme 3). Alternatively, **16** with an (*R*)-HHDP was

Scheme 3. Influence of the Chirality of Sparteine on the Interconversion between Atropisomers 16 and 17



obtained as a single diastereomer in 40% yield on treatment of **17** under the conditions with (+)-sparteine/Cu(II) that were employed for the conversion from **15** to **16**. Thus, generation of axial chirality in the HHDP group was found to be totally governed by thermodynamic control depending on the chiral ligands.[17b,c,21] We then investigated the relative stability of the (*R*)- and (*S*)-3,6-HHDP-bridged glucose core. DFT calculation was performed to assess the most stable structure and the relative stability of punicafolin (**1**) and macaranganin (**2**) (Figure 1). The most stable structure of **1** with an *R*-HHDP group was shown to contain an all-axially substituted glucose core with $^{1}C_{4}$ conformation, while a strained skew boat glucose core with $^{5}S_{1}$ conformation was

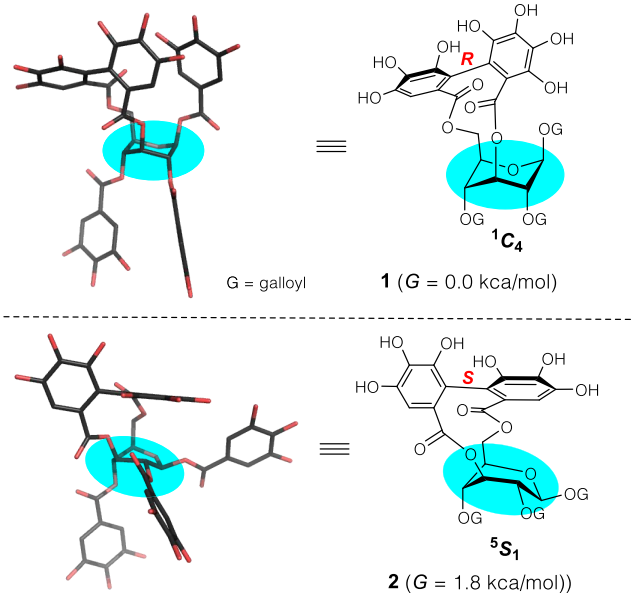


Figure 1. Most stable structures of punicafolin (**1**) and macaranganin (**2**) and the relatve stability calculated by DFT at the M06-2X/6-311++G(2d,2p)//M06-2X/6-31G(d) level in acetone (PCM).

suggested to be the most stable structure of **2**. The former was shown to be more stable than the latter by 1.8 kcal/mol. The preference of the (*R*)-3,6-HHDP bridge with the glucose core was compatible with the observation of exclusive formation of the (*R*)-3,6-HHDP-bridged glucose derivatives during the total synthesis of corilagin and mallotusinin.[8,9] Thermal equilibrium between **16** and **17** was also examined. Treatment of **16** in d_6-DMSO (2 mg/mL) at 130 °C for 30 min gave >99% recovery without any formation of **17**. Partial decomposition was observed on the same treatment of **17** without formation of **16** (data not shown). Thus, thermal equilibrium between **16** and **17** was not observed in the absence of Cu(II).[22,23] Based on all of these results, it was evident that more stable **16** with an (*R*)-HHDP group was converted exclusively to less stable **17** with an (*S*)-HHDP group by treatment with a (−)-sparteine/Cu(II) system under the thermodynamically controlled conditions. We then examined the effects of (−)-sparteine/Cu(II) on the equilibrium process between the (*R*)- and (*S*)-3,6-HHDP groups by DFT calculations using the simplified model (Figure 2). The model was constructed with (*S*)- and

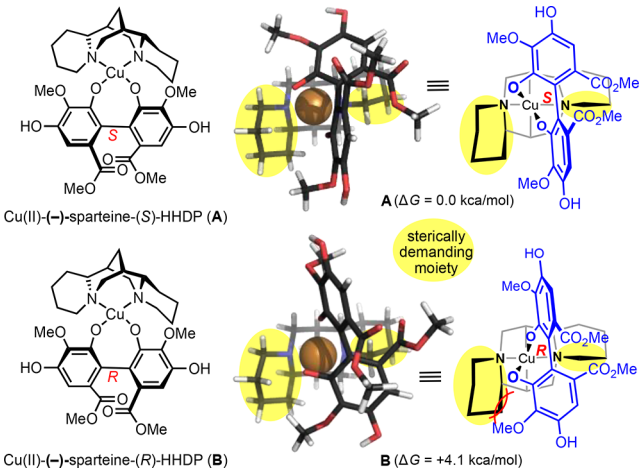


Figure 2. Most stable structures of Cu(II)-(−)-sparteine-(*S*)-HHDP (**A**) and Cu(II)-(−)-sparteine-(*R*)-HHDP (**B**) as models for Cu(II)-**17**-(−)-sparteine and Cu(II)-**16**-(−)-sparteine, respectively, and the relative stability calculated by DFT at the M06/SDD(Cu)/6-311++G(2d,2p)//M06/LanL2DZ(Cu)/6-31G(d,p) level of theory.

(*R*)-HHDP derivatives. The most stable structures of Cu(II)-(−)-sparteine-HHDP (**A**) and Cu(II)-(−)-sparteine-(*R*)-HHDP (**B**) are shown, respectively, in Figure 2. Complex **A** was found to be more stable than **B** by 4.1 kcal/mol due to the lack of unfavorable steric interactions (for the detail, see Figures S3 and S56). Based on these results, matched complexation between **17** and Cu(II)/(−)-sparteine was assumed to be the origin of its higher stability than the mismatched complexation between **16** and Cu(II)/(−)-sparteine.[24]

In conclusion, the first total syntheses of punicafolin (**1**) and macaranganin (**2**) were achieved in seven steps, respectively, from D-glucose, an abundant cheap natural source. The prominent features of the synthesis are sequential site-selective introduction of the adequate galloyl groups into the requisite hydroxy groups of D-glucose and stereodivergent construction of the 3,6-HHDP bridge from a common intermediate via a flipping process of the pyranose ring to the less stable axial-rich conformer. Because no protective groups were used for glucose throughout the process, extremely-short-step total syntheses of

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natural glycosides were achieved. Since structural diversity of ellagitannins stems from regiochemistry of galloyl groups and the HHDP groups, the present strategy based on site-selective introduction of galloyl groups would provide a powerful strategy for total synthesis of a variety of natural and unnatural ellagitannins of biological interests.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c10714.

Experimental details, additional experiment, compound characterization, spectra, and calculation data (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

In memory of the late Professor Hidetoshi Yamada.

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