## Natural Product Synthesis

Total Synthesis of (+)-Davidiin**

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Nature occasionally presents us with unusual chemical structures. Although thermodynamic effects regulate the conformation of D-glucopyranose to a $^4C_1$ form with more substituents in an equatorial than in an axial position (equatorial-rich form), nature allows the existence of a $^1C_4$ or a twist-boat conformation with more substituents in an axial than in an equatorial position (axial-rich) of glucose through the introduction of a bridge. This peculiar structure sporadically appears in ellagitannins, a structurally and biologically diverse class of hydrolysable tannins.[1] Ellagitannins with $^1C_4$ and twist-boat conformers are designated as axial-rich ellagitannins in this communication; (+)-davidiin (1) is a typical example.
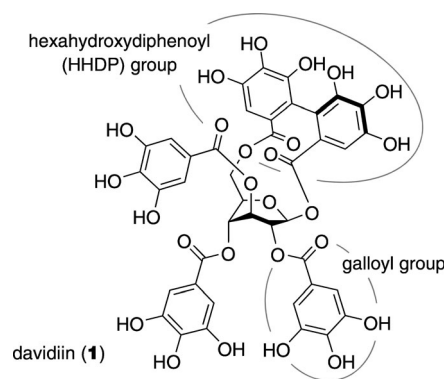

davidiin (1)

(+)-Davidiin (1) was isolated from *Davidia involucrata* (Dove tree) by Haslam and co-workers.[2,3] Subsequently, Okuda and co-workers isolated 1 from *Acer saccharum* (Sugar Maple).[4] The compound inhibits the binding of a ligand to a μ-opioid receptor.[5] Structurally, 1 has an (*S*)-hexahydroxydiphenoyl (HHDP)[6] group, which forms an intramolecular bridge between the 1-β- and the 6-oxygen atoms of D-glucopyranose. The existence of the bridge keeps the glucose ring in the thermodynamically unfavorable

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conformation. Based on ^{1}H NMR data, Haslam and co-workers established that the conformation of the glucopyranose ring is of a skew-boat type.[2,3] The axial chirality of the HHDP group was predicted to be *S* by circular dichroism.[2]

A synthetic approach to axial-rich ellagitannins still remains undeveloped. The only previously synthesized axial-rich ellagitannin is corilagin (5; Scheme 1),[7] although total syntheses of more than a dozen other ellagitannins have been achieved to supply natural ellagitannins and systematically designed analogues in pure form.[8–10] Herein, we describe the total synthesis of compound 1. In this synthesis, a conformational lock of the glucose to an axial-rich form, induced by steric repulsion between adjacent bulky silyloxy groups, played a pivotal role in 1) the β-selective formation of the glycosyl ester at the anomeric position, 2) the formation of the 1,6-HHDP bridge, and 3) the complete control of axial chirality in the formation of the HHDP group.

A challenging problem had to be solved before a successful synthetic route toward 1 could be developed. The formation of the 1,6-HHDP bridge with simultaneous conformational inversion of the pyranose ring into the thermodynamically unfavorable axial-rich form was impossible. This problem became evident during an attempt to carry out the intramolecular aryl–aryl coupling of 2 [Eq. (1)], that is, the desired product 3 was not produced by treatment of 2 with
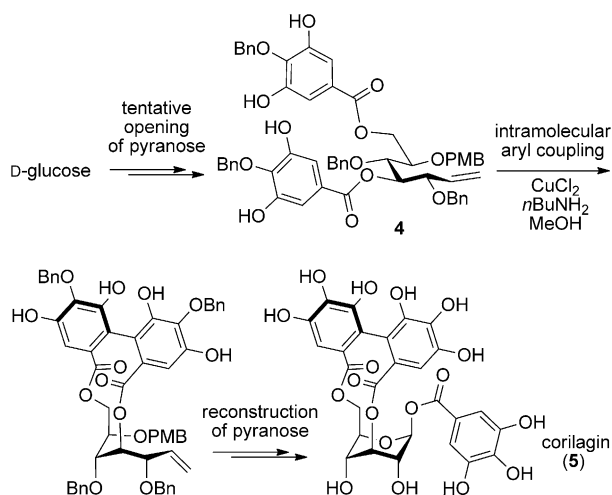

$$ (1) $$
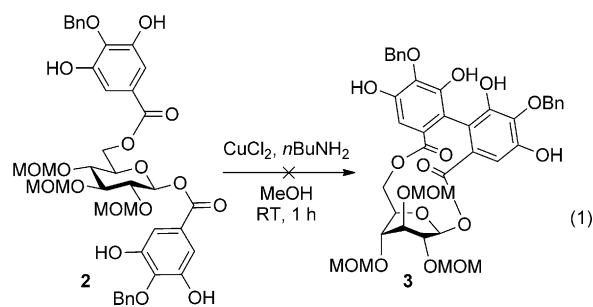
$CuCl_2/nBuNH_2$, a reagent combination that effectively coupled 4-O-benzylated gallates intramolecularly.[7,11] We encountered a similar problem in the synthesis of 5,[12] and overcame it by using a temporary-ring-opening strategy (Scheme 1),[7] in which the flexible conformation of digallate 4 allowed the two galloyl groups to get in close proximity to each other, and thus their intramolecular coupling. After the formation of the 3,6-HHDP bridge, reconstruction of the pyranose ring furnished the HHDP-bridged glucopyranose moiety of 5. However, we were not able to apply this concept to the formation of the 1,6-HHDP structure of 1, because one of the "arms" of the bridge is in the anomeric position. Accordingly, to allow the two galloyl groups to get in close

Scheme 1. Synthetic route toward **5**.

proximity to each other, the conformation of the glucopyranose should be locked into an axial-rich form.

The strategy for the total synthesis of **1** is outlined in Scheme 2. The retrosynthetic analysis started with the disconnection of the three galloyl groups of **1**, which would be acylated in the final stage of the synthesis. To form the 1,6-HHDP group of **6**, the aryl–aryl bond was disconnected. Because this disconnection removed the foundation of the axial-rich conformation, we applied the conformational-lock strategy on the basis of steric repulsion of the adjacent bulky silyl groups to overcome the problem,[13] as in tri-TIPS ether **7**. This strategy has recently been applied to obtain anomeric stereoselectivity in glycosylation reactions.[14–16] The aryl–aryl coupling was expected to occur with CuCl$_2$/nBuNH$_2$ as the oxidizing agent.[7] For digallate **7**, the gallate at the anomeric position was disconnected because the axially-oriented bulky silyloxy group would have hindered the approach of protected gallic acid **8** on the α face, thus allowing the β-selective
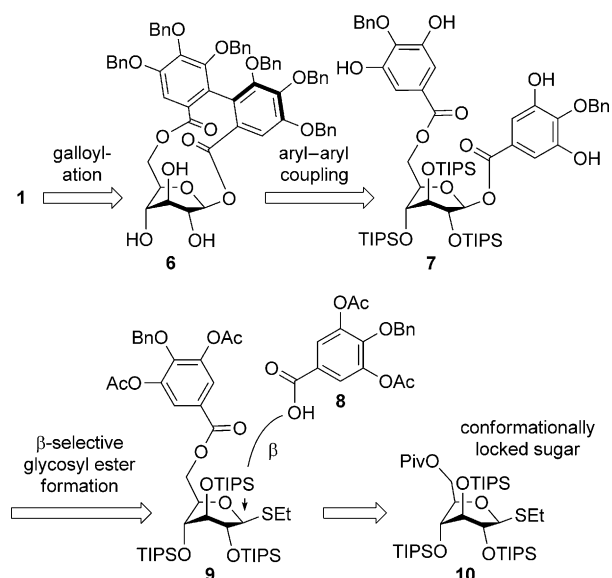
formation of the glycosyl ester with tri-TIPS ether **9**.[15,16] This "glycosyl donor" **9** would be derived from known, conformationally locked compound **10**.[15]

The synthesis commenced with the reductive removal of the pivaloyl ester of **10** with iBu$_2$AlH (Scheme 3). The acylation of the resulting alcohol **11** with acid chloride **12** furnished the "glycosyl donor" **9**. Treatment of **9** with MeOTf and 4 Å molecular sieves in the presence of carboxylic acid **8** as the nucleophile provided β-**13** in 83% yield as a single diastereomer. The stereochemistry at the anomeric center of β-**13** was confirmed by ^{1}H NMR analysis after desilylation to return the pyranose ring to the $^4C_1$ conformation, followed by acetylation of the resulting triols.
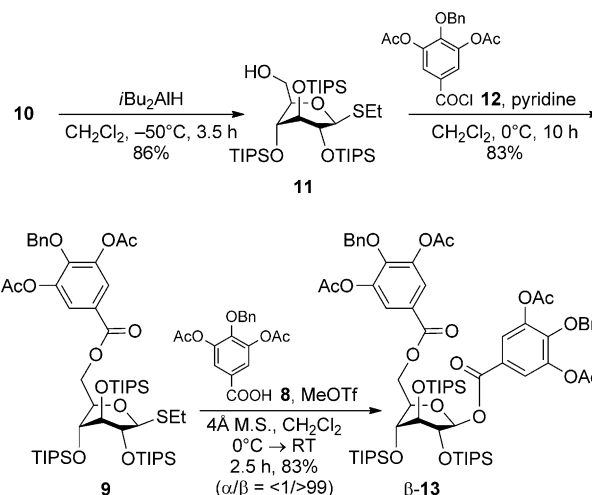

Scheme 3. Stereoselective synthesis of β-**13**.

The excellent β selectivity of the glycosyl ester formation is noteworthy. Although β-selective galloylation is possible when the glucopyranose is in an equatorial-rich conformation,[17] realization of β selectivity has been difficult with axial-rich glucopyranose, with the anomeric hydroxy group of the carbohydrate moiety as the nucleophile and protected gallate as the electrophile.[7,12] The solution to this problem was the inversion of the electrophilic/nucleophilic roles to achieve β selectivity with the axial-rich conformer.

The coupling precursor **7** was obtained quantitatively by aminolysis of the acetyl groups of β-**13** (Scheme 4) through the application of Nomura's reaction conditions,[18] employing hydrazine monohydrate. The galloyl esters remained intact. In the ^{1}H NMR spectra, the $^3J_{H-H}$ coupling constants between the protons on the pyranose ring of **7** were H1–H2: 2.6 Hz, H2–H3: 0 Hz, H3–H4: 0 Hz, H4–H5: 2.3 Hz. These small coupling constants showed that **7** maintained an axial-rich form, thus indicating the robustness of the conformational lock, because the adjacent silyloxy groups on the pyranose kept the ring in the axial-rich conformation, even when two protected gallates were in the 1- and 6-positions.

The 1,6-HHDP moiety embedded in the 12-membered bislactone ring could be formed by intramolecular coupling of 4-O-benzylated gallates of **7** with CuCl$_2$/nBuNH$_2$ as oxidizing agent in MeOH to afford **14** in 75% yield (Scheme 4), thus

Scheme 2. Retrosynthetic analysis of davidiin (**1**).
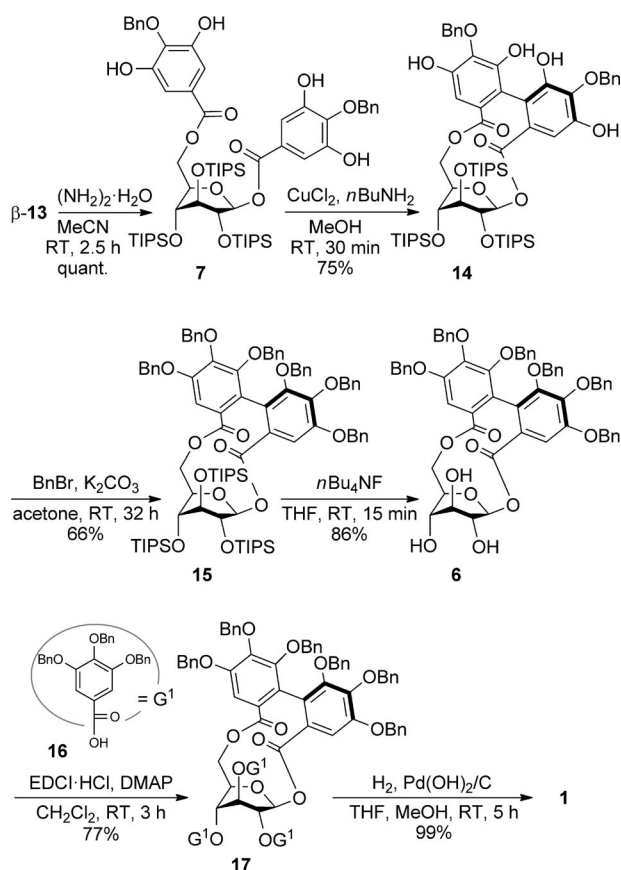
Scheme 4. Synthesis of **1**.

demonstrating the wide applicability of the synthetic method to obtain the HHDP group. Coupling product **14** was obtained as a single diastereomer, thus indicating that the sp³ central chirality of the pyranose was completely transferred to the axial chirality of the HHDP group.

Natural ellagitannins have been assumed to arise from penta-*O*-galloyl-β-D-glucopyranose through oxidative coupling of gallates to form HHDP groups.[19] The axial chirality of the HHDP groups is believed to originate from diastereoselective coupling induced by conformational constraints within polysubstituted glucopyranose substrates (Schmidt–Haslam hypothesis).[8,20] Previous synthetic investigations showed the validity of the hypothesis in the chemical formation of HHDP groups.[7–10] The predominant atropselectivity of the 1,6-HHDP group observed in the synthesis of **14** also supports the hypothesis, although it is unclear how nature controls the conformation of the glucose part.

The following four steps transformed compound **14** to natural product **1**. Benzylation of the phenolic hydroxy groups of **14** provided the hexa-*O*-benzyl ether **15**. The (*S*)-axial chirality was confirmed at this stage by solvolytic removal of the HHDP group followed by comparison of the optical rotation with reported data.[21] Removal of the TIPS groups in **15** furnished 2,3,4-triol **6**, in which the conformation of the pyranose ring remained almost unchanged, according to the ¹H NMR analysis. Acylation of the 2,3,4-triol with tri-*O*-benzylgallic acid (**16**) under the conditions of a modified Steglich's method[22] afforded perbenzylated davidiin **17**.

Finally, hydrogenolytic removal of the fifteen benzyl groups gave davidiin (**1**). Compounds **15**, **6**, **17**, and **1** were all single diastereomers, thus indicating that the axial chirality remained intact during the conversion. The spectroscopic data of synthetically obtained **1** were identical to those of the naturally occurring **1**.[3,4]

In summary, we have accomplished the first total synthesis of (+)-davidiin (**1**). The synthesis was concise, proceeded in nine steps and gave the product in 19% overall yield from known carbohydrate **10**. In this work, a conformational lock to the axial-rich form enabled 1) the β-stereoselective formation of the glycosyl ester, 2) the formation of the 1,6-HHDP bridge, and 3) the complete control of the axial chirality of the HHDP group. In addition, this synthesis expands the scope of conformationally locked carbohydrates, applications of which have to date focused on glycosylation chemistry. This work also constitutes the first total synthesis of a 1,6-HHDP-bridged ellagitannin. Because of the many known similar naturally occurring ellagitannins, the conformational-lock strategy could become a general method to axial-rich natural ellagitannins and artificial analogues.

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[6] Alphabetical list of abbreviations used in this manuscript; Ac = acetyl; Bn = benzyl; Bu = butyl; DMAP = 4-(dimethylamino)-pyridine; EDCI = *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbo-diimide; Et = ethyl; HHDP = hexahydroxydiphenoyl; Me = methyl; MOM = methoxymethyl; M.S. = molecular sieves; NMR = nuclear magnetic resonance; Piv = pivaloyl; PMB = *p*-methoxybenzyl; RT = room temperature; Tf = trifluoromethanesulfonyl; TIPS = triisopropylsilyl.

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