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Synthesis of 8-aryl-3,5,7,3',4'-*penta*-*O*-methylcyanidins from the corresponding quercetin derivatives by reduction with $LiAlH_4$

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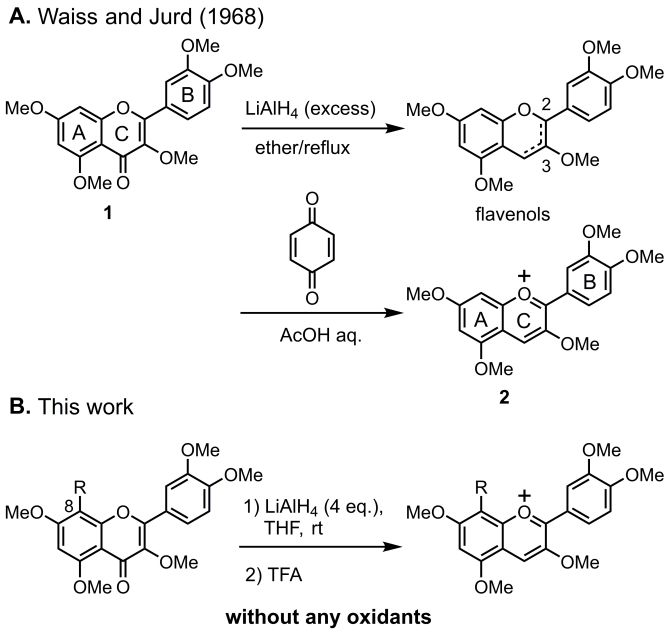
ABSTRACT

Synthesis of 8-aryl-3,5,7,3',4'-*penta*-*O*-methylcyanidins from the corresponding quercetin derivatives by reduction with $LiAlH_4$ is reported. Regioselective iodination at the 8-position of *penta*-*O*-methylquercetin followed by a Suzuki-Miyaura reaction gave the 8-arylated quercetin derivatives. By the reduction of 8-arylated quercetins using 4 equiv. of $LiAlH_4$ at room temperature for 30 min, the corresponding anthocyanidins were obtained with a good yield.

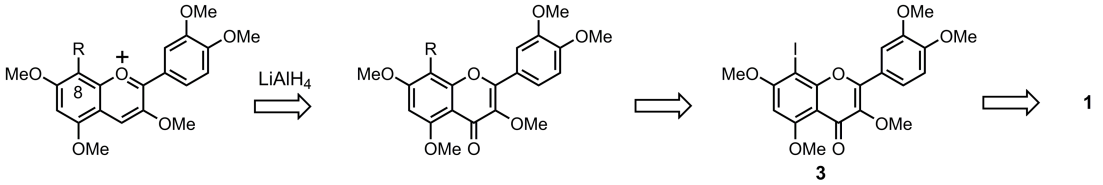
Anthocyanidins, which are polyphenol pigments responsible for the colors of flowers, leaves, and fruits,[1] have attracted attention as functional food colorants[2] with various pharmacological properties.[3] Recently, their material utility in applications such as sensitizers for dye-sensitized solar cells (DSSCs)[4] and molecular switching system[5] have also been explored. We have been studying the mechanisms of flower coloration[1b,c] and the usage of anthocyanins for DSSCs. To advance these studies, the synthesis of anthocyanins and anthocyanidins are essential. In DSSC research, we focused especially on the introduction of an aryl group at the 8-position of the A-ring to elevate the HOMO level of the dye to match the conducting band of TiO_2. However, until now, the efficient synthesis of 8-substituted anthocyanidin has not been reported. Here, we report an efficient synthetic route of 8-arylanthocyanidins from flavonols.

From the other point of view, structural transformation of anthocyanin from flavonols is also one of important subjects for study. In 1910's it was already reported that the reduction of flavonol gives anthocyanidin.[6] This transformation reaction has been paid much attention to both chemical and biological community due to developing the synthetic method as well as understanding of anthocyanin biosynthetic pathway.[7] Because the reduction of flavonols may give flav-2-en-3,4-diol, which has the same oxidation level as with anthocyanindin and this compound is proposed to be an intermediate in biosynthetic pathway of anthocyanin.[8,9] However, the involvement of the flav-2-en-3,4-diol in biosynthetic pathway is not clear even today.[8]

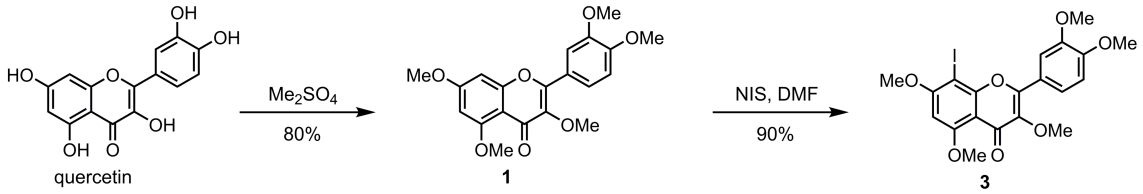
Concerning with reduction reaction Zn or Mg was used as a reagent at the early of 20th century. In 1950, the usage of $LiAlH_4$ was reported by Mirza and Robinson.[10] Afterward, Waiss and Jurd reported the transformation from *penta*-*O*-methylquercetin (**1**) to *penta*-*O*-methylcyanidin (**2**) by a two-step reaction using $LiAlH_4$ reduction followed by quinone oxidation (Scheme 1, A).[11] Recently, Sundeep et al. reported that the reduction of *penta*-*O*-benzylquercetin by $LiAlH_4$ afforded *penta*-*O*-benzylflavenols.[12] From these experimental results, it has been believed that the $LiAlH_4$ reduction of *per*-*O*-alkylflavonol gives



Scheme 1. Synthesis of anthocyanidin by $LiAlH_4$.

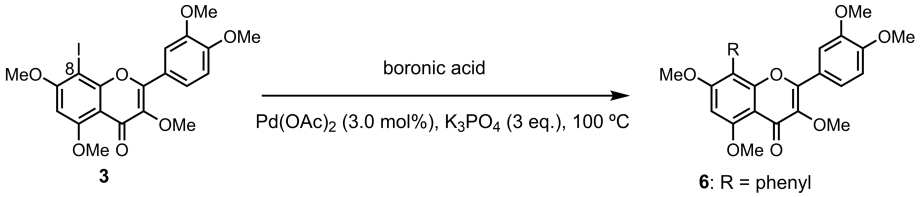


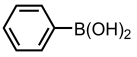
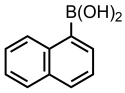
Scheme 2. Retrosynthetic strategy to 8-aryl-3,5,7,3',4'-*penta*-*O*-methyl-cyanidin.



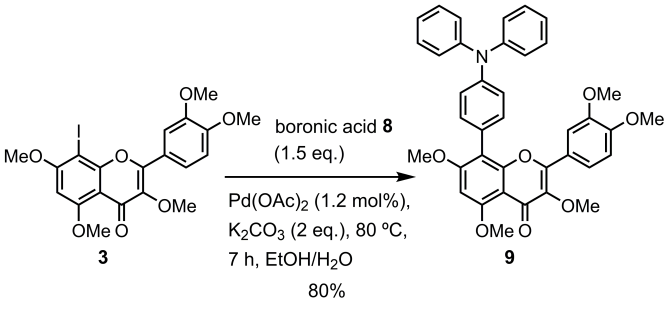
Scheme 3. Synthesis of 8-iodo-3,5,7,3',4'-*penta*-*O*-methylquercetin (**3**).

Table 1. Suzuki-Miyaura coupling of 8-iodo-3,5,7,3',4'-*penta*-*O*-methylquercetin (**3**) with boronic acid **4** and **5**



Entry	Boronic acid	Product	PPh_3 (mol%)	Solvent	Time (h)	Yield (%)[a]
1	 **4**	**6**	3	CPME	12	61
2	**4**	**6**	0	CPME	6	79
3	**4**	**6**	0	toluene	7	90
4	 **5**	**7**	3	CPME	18	69
5	**5**	**7**	0	CPME	24	36
6	**5**	**7**	0	toluene	10	57
7	**5**	**7**	3	toluene	10	66

2 equiv. of boronic acid was used in all reactions.
[a] Isolated yield.



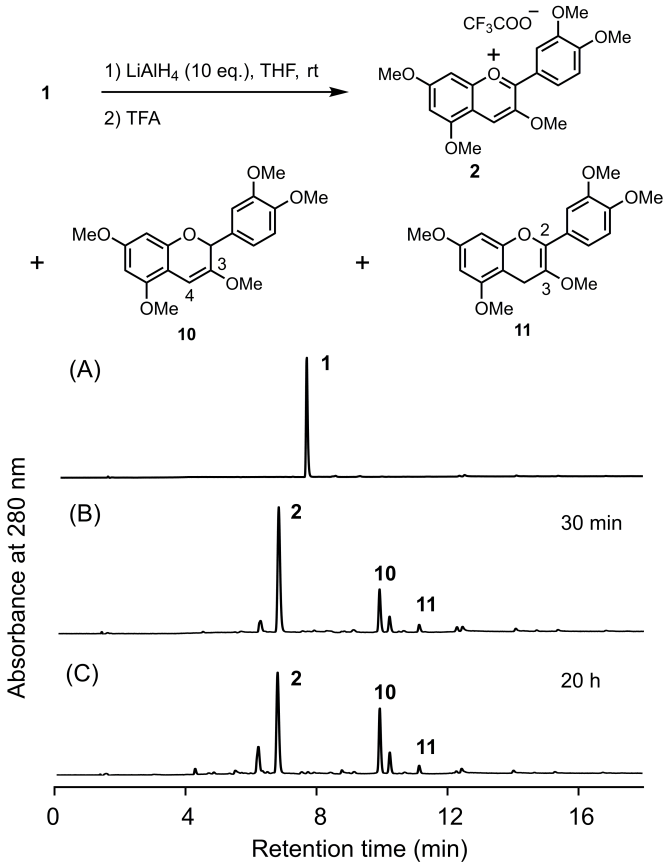
Scheme 4. Synthesis of 3,5,7,3',4'-*penta*-*O*-methyl-8-[4-(diphenylamino)-phenyl]quercetin (**9**)

per-*O*-alkylflavenol, and to obtain anthocyanidins, further oxidation should be necessary.[11,13] In contrast to previous reports, we found that when the amount of $LiAlH_4$ and reaction temperature were controlled, *penta*-*O*-methylquercetin (**1**) directly gave *penta*-*O*-methylcyanidin (**2**) in a good yield (Scheme 1, B). It is note that this new findings afforded not only a concise synthetic pathway without an oxidation step but also a clue of the understanding of biotransformation reaction to anthocyanidin. Using this synthetic method, we synthesized various 8-aryl-3,5,7,3',4'-*penta*-*O*-methyl-cyanidins.

Our retrosynthesis is shown in Scheme 2. 8-aryl-3,5,7,3',4'-*penta*-*O*-methylcyanidins was obtained by $LiAlH_4$ reduction of the corresponding 8-arylated quercetin derivatives. The introduction of the 8-aryl group could be realized by a Suzuki-Miyaura

reaction of 8-iodo-*penta*-*O*-methylquercetin (**3**) with various boronic acids. **3** was prepared by regioselective iodination of *penta*-*O*-methylquercetin (**1**).

We have already established the preparation of *penta*-*O*-methylquercetin (**1**);[14] therefore, our synthesis was commenced with regioselective iodination of **1**. Since the C-atom at the 8-position of **1** has the highest electron density, the treatment of **1** with NIS (*N*-iodosuccinimide) in DMF gave the 8-iodinated compound **3** as a sole regioisomer in 90% yield (Scheme 3).[15] Then, a Suzuki-Miyaura coupling reaction of **3** with boronic acids (**4** and **5**) was carried out in the presence of $Pd(OAc)_2$ and K_3PO_4 at 100 °C (Table 1). Since a phosphine ligand was usually added,[16] we tried the standard condition with phenylboronic acid (**4**) in the presence of PPh_3 in CPME (cyclopentyl methyl ether) for 12 h and obtained the desired 8-phenylflavonol (**6**) in 61% yield (Table 1, entry 1). Unexpectedly, without PPh_3, the yield increased to as high as 79% (Table 1, entry 2).[17] As a further optimization, the use of toluene gave **6** in 90% yield (Table 1, entry 3). Based on these results, the reaction of 1-naphthylboronic acid (**5**) without PPh_3 in toluene was examined. However, the yield of **7** was moderate (57%). Therefore, we resurveyed the combinations of ligand and solvent and found that with PPh_3 in CPME the yield was the highest (69%) (Table entries 4-7). The coupling reaction of **3** with 4-(diphenylamino)phenylboronic acid (**8**) was examined according to Liu's ligand-free condition (Scheme 4).[18] The reaction of **3** with **8** in the presence of $Pd(OAc)_2$ and K_2CO_3 in $EtOH/H_2O$ at 80 °C under Ar gave the desired coupling product **9** in 80% yield.

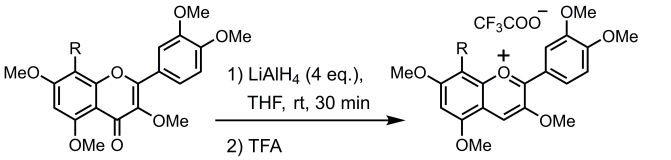


(A) The starting material **1**. (B) The reaction mixture for 30 min. (C) The reaction mixture for 20 h.

Figure 1. HPLC chromatogram of the reduction of **1** with LAH.

Since the requisite *penta*-*O*-methylquercetins (**1**, **6**, **7**, and **9**) were in hand, we examined the transformation reaction to methylcyanidins (Table 2). At first, 3,5,7,3',4'-*penta*-*O*-methylquercetin (**1**) was reduced by 1 equiv. of $LiAlH_4$ in THF at room temperature. Previous reports claimed that the reduction of **1** by $LiAlH_4$ should afford mixtures of flavenols (flav-2-enol **10** and flav-3-enol **11**), which could be oxidized easily to 3,5,7,3',4'-*penta*-*O*-methylcyanidin (**2**) by quinone oxidants (Scheme 1, A).[9,11] However, in our experiment, 1 equiv. of $LiAlH_4$ gave 3,5,7,3',4'- *penta*-*O*-methylcyanidin (**2**) as a major product.

Table 2. Synthesis of 8-aryl-3,5,7,3',4'-*penta*-*O*-methylcyanidins (**2**, **12**-**14**) from the corresponding flavonols (**1**, **6**, **7**, **9**) by using $LiAlH_4$



1: R = H
6: R = phenyl
7: R = 1-naphthyl
9: R = 4-(diphenylamino)phenyl

2: R = H
12: R = phenyl
13: R = 1-naphthyl
14: R = 4-(diphenylamino)phenyl

Entry	Flavonol	Product	Yield (%)[a]
1	**1**	**2**	70
2	**6**	**12**	41
3	**7**	**13**	57
4	**9**	**14**	66

[a] Isolated yield.

With further examination, we could detect the generation of flav-3-enol **10** and flav-2-enol **11** when a large excess of $LiAlH_4$ (10 equiv.) was used (Figure 1).[19] In this reaction for 30 min, **1** was disappeared and **2**, **10**, and **11** was generated. When the reaction time was 20 h, **2** was deceased and both **10** and **11** was increased. Thus, the generation of flavenols might be due to the over-reduction of **2**.[12,20] Thus, we concluded that **2** could be obtained by $LiAlH_4$ reduction at room temperature when the amount of the reagent was controlled. Finally, we established the reaction condition as 4 equiv. of $LiAlH_4$ in THF at room temperature to obtain **2** in 70% yield.[21] Using this direct transformation protocol, $LiAlH_4$ reduction of 8-aryl-3,5,7,3',4'-*penta*-*O*-methylquercetins (**6**, **7**, and **9**) afforded the corresponding 8-aryl-3,5,7,3',4'-*penta*-*O*-methylcyanidins (**12**, **13**, and **14**) in 41, 57, and 66% yield, respectively (Table, 2).

In conclusion, we developed a synthetic route for 8-aryl-3,5,7,3',4'-*penta*-*O*-methylcyanidins from the corresponding quercetin derivatives through $LiAlH_4$ reduction. Our re-visiting experiments revealed that the reduction of *penta*-*O*-methylcyanidins from the corresponding quercetin derivatives by 4 equiv. of $LiAlH_4$ at room temperature transformed directly to *penta*-*O*-methylcyanidins.

Acknowledgments

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21. Reduction of **1** with $LiAlH_4$: To a solution of 3,5,7,3',4'-*penta-O*-methylquercetin (**1**) (50 mg, 0.13 mmol) in anhydrous THF (2.5 mL) was added $LiAlH_4$ (0.52 mL, 0.52 mmol, 1.0 M solution in THF) slowly at room temperature. After stirring for 30 min at room temperature, the reaction mixture was added distilled water (2.5 mL) and 15% TFA aq. (2.5 mL) at 0 ºC. After THF was removed under reduced pressure, the residue was added with 0.5% TFA aq. (15 mL). After the crude products were extracted with CH_2Cl_2 (15 mL x 3), the combined organic phases were dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure and the residue was purified by flash silica gel chromatography (33% AcOEt/Hexane with 0.5% TFA → AcOEt with 0.5% TFA → 1% MeOH/AcOEt with 0.5% TFA → 3% MeOH/AcOEt with 0.5% TFA) to give **2** (44 mg, 70%) as a dark red solid.

Supplementary Material

Supplementary data including the detailed experimental procedures and spectral data related to this article can be found at the journal's homepage.