Synthesis of 7,8-Dihydroxy-5-hydroxymethyl-2-phenyl-chroman-4-one; the Aglycon of Actinoflavoside

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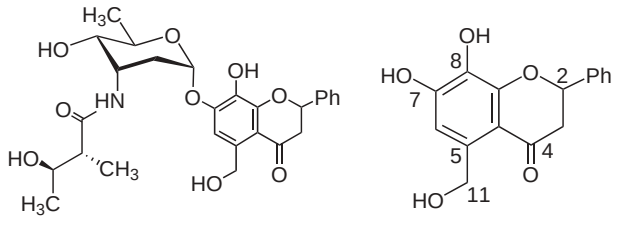
Abstract: The first synthesis of 7,8-dihydroxy-5-hydroxymethyl-2-phenyl-chroman-4-one, the aglycon part of a new-type glucoside, actinoflavoside, was accomplished. The regioselective oxidation of the methyl group at the 5-position in 7,8-dihydroxy-5-methyl-2-phenyl-chroman-4-one derived from 3,4,5-trimethoxytoluene was performed by use of ammonium cerium(VI) nitrate (CAN).

Key words: flavanon, natural product, oxidation, CAN, DDQ

Flavonoid-type glycosides have long been known to exist in ferns or higher plants but they did not exist in lichens, mosses, algae and bacillus.[1] However, a new-type glycoside, 7-{2,3,6-trideoxy-3-[3-(*R*)-hydroxy-2-(*R*)-methylbutanoic acid]amino-α-D-*ribo*-hexopyranosyl}-8-hydroxy-5-hydroxymethyl-2-phenyl-chroman-4-one; actinoflavoside (**1**), was found from a culture fluid of the *Streptmyces* genus ocean bacillus, CNB-689 (Figure 1).[2] The origin and biosynthesis course of **1**, which has a unique structure resembling that of flavonoids of higher plants, are obscure and very interesting. Although the anti-microbial activity of **1** to grampositive fungi was determined, the research did not reach detailed investigation. Recently, we started the total synthesis of **1** in order to examine its chemical nature and physiological activity in detail. The aglycon of **1** is a flavanon including a hydroxymethyl group on the 5-position, but the concise synthetic route has not been known. In this communication, we would like to report the first synthesis of 7,8-dihydroxy-5-hydroxymethyl-2-phenyl-chroman-4-one (**2**),[3] the aglycon of Actinoflavoside (**1**).



1 : Actinoflavoside **2**

Figure 1

At first, we thought that the penta-substituted benzene frame of **2** could be constructed by Friedel–Crafts reaction of methyl 3,4,5-trimethoxybenzoate or 3,4,5-trimethoxybenzyl alcohol. However, acylation of methyl 3,4,5-trimethoxybenzoate with acetyl chloride or acetic anhydride did not proceeded under the substantial conditions. This low reactivity of the benzene part is based on the ester with the electron-withdrawing group. On the other hand, 3,4,5-trimethoxybenzyl alcohol was easily converted to the corresponding dimerization product without the acylated product even under the mild conditions. As a result, we have to try a new strategy as shown in Figure 2. The benzylic hydroxyl group at the 11-position can be constructed by oxidation. In this study, we demonstrated a regio-selective oxidation of the methyl group at the 5-position of 7,8-dihydroxy-5-methyl-2-phenyl-chroman-4-one derivative **3** synthesized from 3,4,5-trimethoxytoluene (**4**).

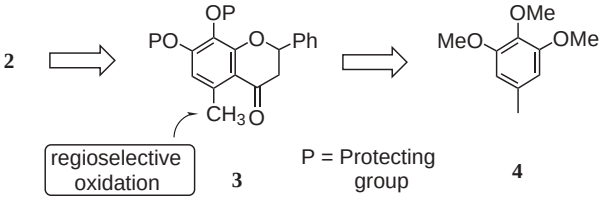


Figure 2

The construction of the penta-substituted benzene frame was achieved by Friedel–Crafts acylation of inexpensive 3,4,5-trimethoxytoluene (**4**) (Scheme 1). In this reaction, a mixture of trimethoxy compound **5** and dimethoxy compound **6** was formed. The 3-phenyl-propenone derivatives **7** or **8** are the products of an aldol-condensation with benzaldehyde. Ring-closing reaction of the corresponding chalcone in the presence of an acid was well known,[4] and we applied it to the synthesis of chromanone derivatives **9** and **10**. Compound **7** was converted into 7,8-dihydroxy-5-methyl-2-phenyl-chroman-4-one (**9**) by de-O-methylation using boron tribromide[5] followed by treatment with an acid form ion-exchange resin (DOWEX® 50WX-4). 7,8-di-O-Protected-5-methyl-2-phenyl-chloman-4-one derivatives **10**–**12** were obtained from **8** or **9**.

To examine the regioselectivity of the oxidation, reactions of 7,8-di-O-protected compounds **10**–**12** and 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ) or diammonium cerium(IV) hexanitrate (CAN), which were general oxidants

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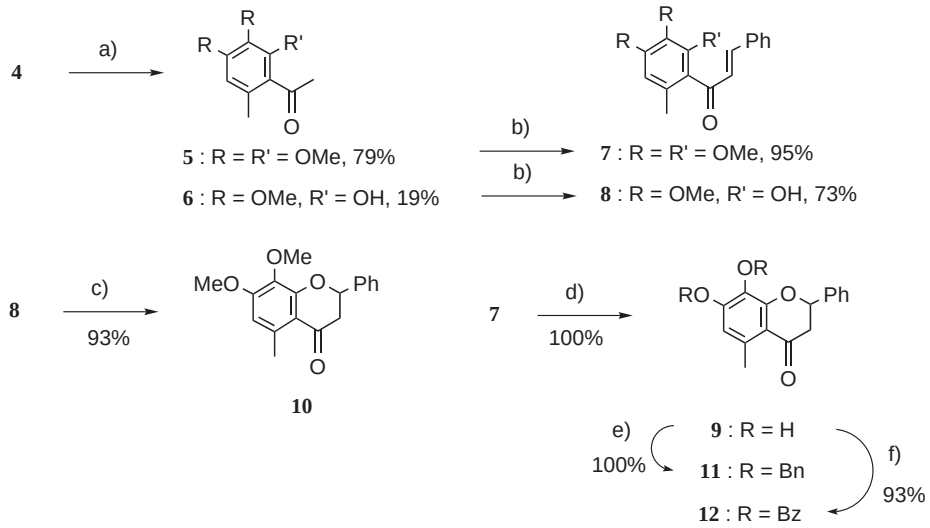


Scheme 1 Synthesis of 2-phenyl-chroman-4-one derivatives. *Reagents and conditions*: a) AcCl, $AlCl_3$, benzene; b) PhCHO, 1 M NaOH, EtOH; c) DOWEX® 50WX-4, MeOH; d) 1. BBr_3, ClC_2H_4Cl 2. DOWEX® 50WX-4, MeOH; e) BnBr, K_2CO_3, acetone; f) BzCl, pyridine, CH_2Cl_2.

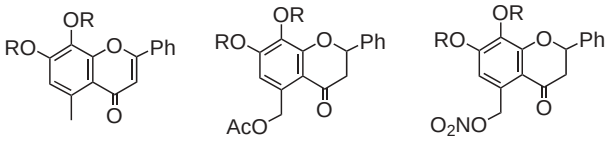
of the methoxybenzyl group, were performed (Table 1 and Figure 3).[6–10]

Interestingly, DDQ promoted rather the 2,3-dehydrogenation than the oxidative hydroxylation at the position-11. The enone derivatives **13**–**15** were the only products of each reaction of 7,8-di-O-protected compounds **10**–**12** and DDQ under reflux conditions in 1,2-dichloroethane containing H_2O (entry 1–3). In this reaction, O-methylated substrate **10** and O-benzylated substrate **11** gave the corresponding enone **13** and **14**, respectively, but yields were lower than that from **12**. This result means the electron-donating substituents at the O-7 or O-8 influence to the oxidation of the substrate. Decrease in probability of the oxidation at the position-11 carried out generation of the enone derivatives. Besides, H_2O molecules were separated in this reaction mixture, and the contact with the corresponding CT-complex seemed to be difficult. It is known that DDQ is an effective reagent in conversion from the flavanon to flavon frame,[11] and the generation of the enone derivatives **13**–**15** in the reactions of compound **10**–**12** is in accord with this assumption. As a result, the compound with a methyl group oxidized at the position-5 was not obtained.

Table 1 Oxidation of 7,8-Dihydroxy-5-methyl-2-phenyl-chroman-4-one Derivatives

Entry	Substrate	Condition[a]	Product (yield, %)
1	10	A	**13** (60)
2	11	A	**14** (14)
3	12	A	**15** (84)
4[b]	10	B	**16** (9), **17** (5)
5	11	B	**18** (54), **19** (14)
6	12	B	No reaction

[a] A: DDQ, ClC_2H_4Cl, H_2O, reflux; B: CAN, HOAc, r.t.
[b] Compound **10** was recovered in 40% yield.



13 : R = Me
14 : R = Bn
15 : R = Bz

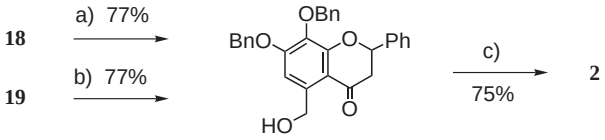
16 : R = Me
18 : R = Bn

17 : R = Me
19 : R = Bn

Figure 3

On the other hand, CAN oxidation of the O-methylated **10** or O-benzylated substrates **11** gave the products with a methyl group oxidized at the position-5 selectively (entry 4 and 5). Generally, CAN is a more powerful oxidant than DDQ, and is capable of forming a cation at the position-11, and the cation was smoothly trapped by an acetoxy or a nitrate anion. In this reaction, an acetoxy or a nitrate anion was provided from the solvent or CAN. Under this condition, O-benzoylated substrate **12** did not react at all and was recovered from the reaction mixture (entry 6). This result is not consistent with the result of DDQ oxidation. In both conditions, generation of a cation at the position-11 or one-electron transfer from the poly-substituted benzene seemed to be blocked by the weak electron-donating effect at the position-7 and 8. Much more studies are needed to discuss the different reactivity in CAN oxidation having an opposite regioselectivity in DDQ oxidation. However, the foregoing finding contributed greatly to the synthesis of **2**.

To an acetic acid solution of O-benzylated substrate **11** was added CAN (4 equiv) and stirred at room temperature. The reaction proceeded smoothly to give a mixture of acetoxy derivative **18** and nitrate derivative **19** which was converted into hydroxymethyl derivative **20**, respectively (Scheme 2).[12] The removal of the O-benzyl group in compound **20** by hydrogenolysis under neutral conditions was efficient to give 7,8-dihydroxy-5-hydroxymethyl-2-phenyl-chroman-4-one (**2**), the aglycon of **1**. The NMR spectrum of **2** completely agreed with that of the natural product described in a previous report.[13]



20

Scheme 2 Synthesis of 7,8-dihydroxy-5-hydroxymethyl-2-phenyl-chroman-4-one. *Reagents and conditions*: a) Et_3N, MeOH; b) $NaNO_2$, 1,4-dioxane, H_2O; c) H_2, Pd-C, EtOH.

Thus, the first synthesis of 7,8-dihydroxy-5-hydroxymethyl-2-phenyl-chroman-4-one (**2**), the aglycon of actinoflavoside (**1**), was accomplished by the regioselective oxidation of a methyl group at the position-5 of 7,8-dibenzyloxy-5-methyl-2-phenyl-chroman-4-one. This route is promising to supply **2** in short steps and to help toward the total synthesis of **1**.

References

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(3) Compound **2** was reported as a recemic form.[2] Actinoflavoside **1** was also isolated as a 1:1 diastereomeric mixture. It is not to be denied completely that isomerization of **1** occurred in the process of isolation.
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(12) To an HOAc solution (100 mL) of 7,8-di-benzyloxy-5-methyl-2-phenyl-chloman-4-one (**11**) (500 mg, 1.11 mmol) was added CAN (2.4 g, 4.44 mmol). The mixture was stirred for 12 h at r.t., then neutralized with 1 M NaOH. A solution was diluted with CH_2Cl_2 and washed with H_2O. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (benzene:acetone = 99:1) to afford 7,8-di-benzyloxy-5-acetoxymethyl-2-phenyl-chloman-4-one (**18**) (303 mg, 54%) and 7,8-di-benzyloxy-5-nitroxymethyl-2-phenyl-chloman-4-one (**19**) (79 mg, 14%), respectively. Compound **18**. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.20–7.48 (m, 15 H, Ph), 6.74 (s, 1 H, H-6), 5.52 (q, 2 H, *J* = 15.4 Hz, H-11), 5.39 (dd, 1 H, *J* = 2.9, 12.8 Hz, H-2), 5.22, 5.05 (each s, 4 H, benzyl), 3.01 (dd, 1 H, *J* = 16.7, 12.8 Hz, H-3a), 2.86 (dd, 1 H, *J* = 16.7, 2.9 Hz, H-3b), 2.11 (s, 3 H, Ac). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 191.8, 170.4, 157.1 (C-9), 156.9 (C-8), 138.7, 137.2, 136.2, 135.6 (C-7), 135.4 (C-10), 128.7, 128.5, 128.2, 128.1, 128.0, 127.2, 125.9, 113.3 (C-5), 106.1 (C-6), 79.2 (C-2), 75.3, 70.9, 64.8 (C-11), 45.5 (C-3), 21.0. Compound **19**. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.20–7.44 (m, 15 H, Ph), 6.72 (s, 1 H, H-6), 5.88 (q, 2 H, *J* = 15.0 Hz, H-11), 5.39 (dd, 1 H, *J* = 3.2, 13.2 Hz, H-2), 5.20, 5.05 (each s, 4 H, benzyl), 3.03 (dd, 1 H, *J* = 16.9, 13.2 Hz, H-3a), 2.88 (dd, 1 H, *J* = 16.9, 3.2 Hz, H-3b). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 192.0, 157.2 (C-9), 157.1 (C-8), 138.4, 137.0, 136.5 (C-7), 135.7, 131.5 (C-10), 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 127.4, 126.0, 113.4 (C-5), 106.7 (C-6), 79.3 (C-2), 75.3, 72.7 (C-11), 71.0, 45.3 (C-3).
(13) Selected spectral data for synthetic aglycon **2**: ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 7.23–7.45 (m, 5 H, Ph), 6.67 (s, 1 H, H-6), 5.50 (dd, 1 H, *J* = 3.1, 12.1 Hz, H-2), 4.69 (q, 2 H, *J* = 15.2 Hz, H-11), 3.08 (dd, 1 H, *J* = 16.7, 12.1 Hz, H-3a), 2.82 (dd, 1 H, *J* = 16.7, 3.1 Hz, H-3b). ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 194.8 (C-4), 153.5 (C-9), 153.2 (C-8), 140.4, 137.8 (C-10), 133.1 (C-7), 129.7, 129.7, 127.5, 112.9 (C-5), 110.0 (C-6), 80.8 (C-2), 64.4 (C-11), 46.1 (C-3).