Asymmetric syntheses of daedalin A and quercinol and their tyrosinase inhibitory activity

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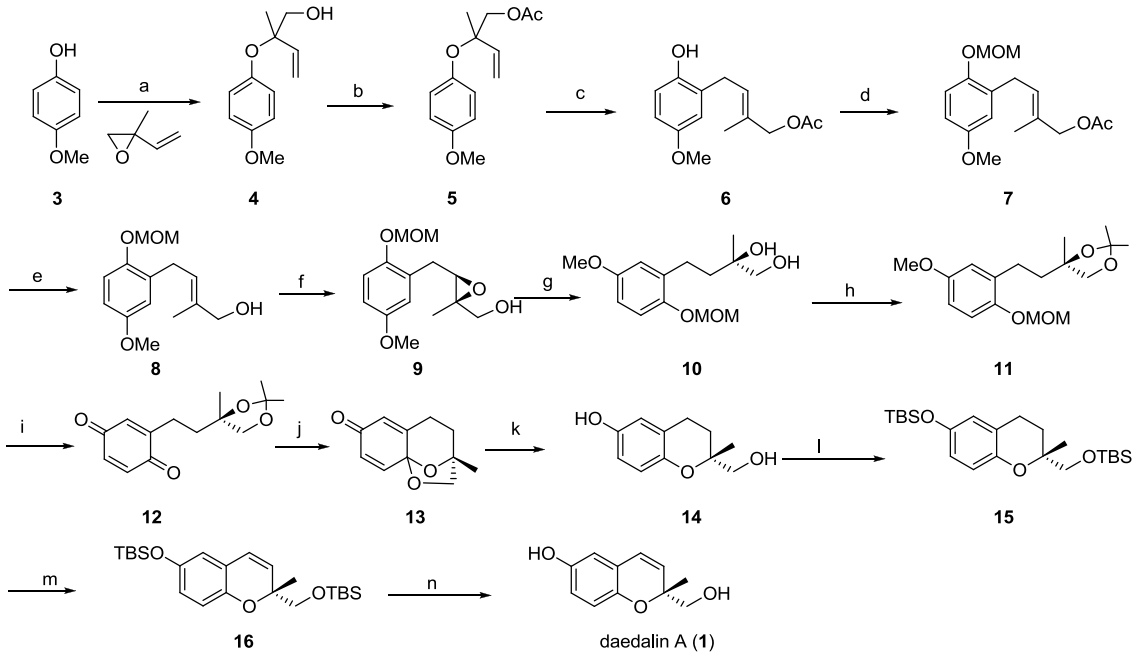
Abstract: Stereoselective syntheses of daedalin A and quercinol, an enantiomer of daedalin A, is described. The tyrosinase inhibitory activities of daedalin A and quercinol were examined. The activity of quercinol was weaker than that of daedalin A at high concentration.

Dermal hyper-pigmentation, caused by the accumulation of melanin, is initiated by oxidation of tyrosine by tyrosinase, a key enzyme of melanin biosynthesis. [1] Tyrosinase inhibitors such as arbutin, kojic acid, ellagic acid, and rucinol have been used as pharmaceutical constituents of cosmetics in order to prevent hyper-pigmentation. In an effort to find new types of tyrosinase inhibitors, we have screened culture broths from mushroom mycelia for tyrosinase inhibitory activity, and found that the mycelial culture of *Daedalia dickinsii* showed significant activity. Based on the spectroscopic data, the bioactive compound was elucidated as (2*R*)-6-hydroxymethyl-2-methyl-*2H*-chromene, named daedalin A (**1**). [2,3] We have synthesized racemic **1** and it showed weaker activity than **1**.[3] Quercinol (**2**), an enantiomer of daedalin A (**1**), was also isolated from the fungus of *Daedalea quercina* by Hertweck and co-workers.[4] They reported that compound **2** showed anti-inflammatory activity.[4] It is very difficult to obtain enough amount of daedalin A (**1**) and quercinol (**2**) for the biological study because the mycelia cultures of *Daedalia dickinsii* and/or *Daedalea quercina* are limited. Thus, syntheses of **1**, **2**, and their analogues are important for the biological study. Especially, synthesis of **2** is required because the tyrosinase inhibitory activity of **2** has not been reported yet. Herein, we wish to describe an asymmetric synthesis of **1** and **2** and their tyrosinase inhibitory activity (Figure 1).

Figure 1. The structure of daedalin A (**1**) and quercinol (**2**).

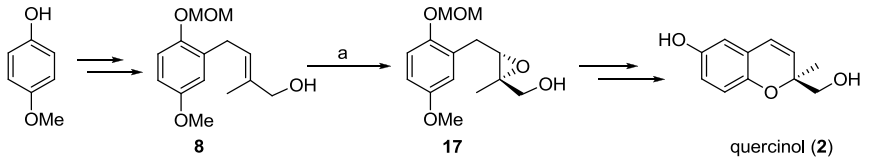
The synthesis of daedalin A (**1**) is described as follows. Compound **4** was synthesized from 4-methoxyphenol and vinyloxirane using Pd-catalyzed *O*-alkylation using Kirschleger's method with modification.[5] In this reaction Kirschleger used 1.5 mol% of $Pd(PPh_3)_4$ at room temperature, however, sometimes the yield of desired product was low. Thus, we used 1 mol% of $Pd(PPh_3)_4$ at 0^oC to give desired product in high yield. Acetylation, Claisen rearrangement followed by Sharpless asymmetric epoxidation gave **9**.[5,6] Reduction with $LiAlH_4$ followed by protecting 1,2-diol with 2,2-dimethoxypropane afforded **11**. Oxidative demethylation of **11** with ceric ammonium nitrate (CAN) afforded **12** only in 21% yield with complex mixture.[7] Probably the product was decomposed under acidic medium. Thus, we used silver (II) dipicolinate $\{Ag(DPAH)_2\}$ in the presence of AcONa as an oxidant to give **12** in 96% yield.[8] This method is useful for oxidizing acid sensitive substrate because oxidation can be proceeded under neutral medium. Transformation from **12** to **14** was achieved using Kirschleger's method.[6] Protection of the hydroxy groups of **14** with TBSCl and imidazole afforded **15**. Treatment of **15** with DDQ afforded **16**.[9] Finally, deprotection of the TBS ether of **16** with TBAF furnished daedalin A (**1**) in good yield. Recrystallization ($CHCl_3$) gave colourless solid whose melting point was 136-138 ^oC. The specific rotation value of synthetic **1** was much higher than that of reported. All the spectral data of synthetic **1** were in good agreement with those of natural **1**. (Scheme 1).[2]



Scheme 1. Synthesis of daedalin A (**1**).

Reagents and conditions: (a) 0.5 mol % of $Pd(PPh_3)_4$, CH_2Cl_2, 0°C (93%); (b) Ac_2O, Et_3N, DMAP, AcOEt (quant.). (c) HCl (gas), CH_2Cl_2 (99%). (d) MOMCl, *i*-Pr_2NEt, CH_2Cl_2 (99%). (e) K_2CO_3, MeOH (quant.). (f) TBHP, Ti(O-*i*Pr)$_4$, L-(+)-DET, CH_2Cl_2 (78%). (g) $LiAlH_4$, diethyl ether, (88%). (h) DMP, *p*-TsOH (quant.). (i) $Ag(DPAH)_2$, AcONa, MeCN-H_2O (96%). (j) 1N HCl, MeOH (90%). (k) Red-Al, THF, -78 °C (92%). (l) TBSCl, imidazole, DMF (quant.). (m) DDQ, benzene (81%). (n) TBAF, THF (95%).

Synthesis of quercinol (**2**) was achieved as the same procedure of daedalin A (**1**) except that D-(–)-DET was used in the Sharpless epoxidation. The melting point and specific rotation values were higher than those reported. All the spectral data of synthetic **2** were in good agreement with those of natural **2** (Scheme 2).[4]



Scheme 2. Synthesis of quercinol (**2**).

Reagent and condition: (a) TBHP, Ti(O-*i*Pr)$_4$, D-(–)-DET, CH_2Cl_2 (89%).

The HPLC analysis of the synthetic **1** and **2** using chiral column showed more than 99% ee, respectively.

The tyrosinase inhibitory activities of **1** and **2** were examined. Interestingly, the tyrosinase inhibitory activity of **2** was weaker than that of **1** at higher concentration (400 μM). This result suggested that the mechanism of action of quercinol (**2**), which has an opposite stereochemistry at C-2 position, might be different from that of daedalin (**1**) in the tyrosinase inhibitory activity (Table 1).[3]

Table 1. Tyrosinase inhibitory activities of **1**, **2** and ±daedalin A.

	Inhibition ± SD (%)[a]			
compound	100 μM	200 μM	400 μM	IC_{50} (μmol/l)
daedalin A (**1**)	28.6 ± 5.0	48.4 ± 1.1	61.6 ± 1.0	208
quercinol (**2**)	30.7 ± 6.7	43.9 ± 1.2	48.1 ± 1.7	490
±daedalin A	23.7 ± 5.7	45.5 ± 3.1	55.6 ± 1.1	289

[a]Each value is expressed as the means ± SD from three tests.

In summary asymmetric syntheses of daedalin A (**1**) and quercinol (**2**) was achieved. The tyrosinase inhibitory activity of **2** was weaker than that of **1** at high concentration. The study of the inhibitory mechanism of **2** is currently underway.

Supplementary data

Supplemental material available: spectroscopic and physical data of **1** and **2**, biological assays. Supplementary data associated with this article can be found, in the online version, at doi:

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