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Chemical synthesis and tyrosinase-inhibitory activity of isotachioside and its related glycosides

Takashi Matsumoto[a], Takuya Nakajima[a], Takehiro Iwadate[b], Ken-ichi Nihei[a,b,*]

[a] Department of Applied Biological Chemistry, School of Agriculture, Utsunomiya University, Tochigi, 321-0943, Japan
[b] Department of Applied Life Science, United Graduate School of Agricultural Science, Tokyo University of Agriculture and Technology, Tokyo, 183-8509, Japan

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Dedicated to the memory of Professor Toshikatsu Okuno (1940–2017)

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ABSTRACT

Isotachioside (**1**) and its related natural product **2** are isolated from *Isotachis japonica* and *Protea neriifolia*, respectively, and are categorized as analogs of arbutin (**3**), a tyrosinase inhibitor for practical use. Both of the natural products and several derivatives such as glucoside **4**, xyloside **5**, cellobioside **6**, and maltoside **7** were synthesized via Schmidt glycosylation as a key step, and their tyrosinase inhibitory activity was evaluated. The half maximal inhibitory concentration (IC_{50}) of **1**–**3** could not be determined even when the concentration was increased to 1000 μM. Contrastingly, glycosides **4**–**7**, missing methyl and benzoyl groups, acted as tyrosinase inhibitors with IC_{50}s of 417 μM, 852 μM, 623 μM, and 657 μM, respectively. Among these novel inhibitors, derivative **4** was the most potent, indicating that the structural combination of resorcinol and glucose was significant for inducing the inhibitory effect.

1. Introduction

Hyperpigmentation of mammalian skin is responsible for the excess deposition of melanin [1,2]. Melanin biosynthesis results from the enzymatic action of tyrosinase (EC,1.14.18.1), a copper-containing oxidoreductase, which catalyzes two successive reactions including the *o*-hydroxylation of tyrosine and the *o*-quinone formation of DOPA [3,4]. Thus, the inhibition of tyrosinase can lead to the regulation of abnormal melanogenesis caused by several types of stress such as sunlight-induced irritation and scratching [5]. In addition, enzymatic oxidation is a key step in food browning and insectile development [6–8], because various monophenols and *o*-diphenols in plants and insects are recognized as substrates of the tyrosinase family [9–13]. Therefore, tyrosinase inhibitors are promising substances for the development of novel antiaging, food antibrowning, antifungal, and insecticidal agents [14,15].

Isotachioside (2-methoxy-4-hydroxyphenyl-*β*-D-glucoside; **1**) and 2,4-dihydroxyphenyl-(6′-*O*-benzoyl)-*O*-*β*-D-glucoside (**2**) were first isolated from *Isotachis japonica* (Hepaticae) and *Protea neriifolia* (Proteaceae), respectively (Fig. 1) [16,17]. Both structures possess a high similarity to arbutin (**3**), which has previously been used as a whitening agent in cosmetics [18,19]. The essential whitening mechanism of the glycoside **3** is considered to be the inhibition of the oxidation by tyrosinase and, in particular, the water-soluble property can expand its applications. However, evaluation of the inhibitory activity of tyrosinase as well as the total synthesis of the natural arbutin analogs **1** and **2** has not been achieved to date. Therefore, in this study, we conducted the concise chemical synthesis of **1**, **2**, and **4**–**7** to develop a novel water-soluble tyrosinase inhibitor and evaluated their tyrosinase-inhibitory activity.

2. Results and discussion

2.1. Chemical synthesis of the natural glucoside 1

The starting material, 2,4-dihydroxybenzaldehyde, was transformed into phenol **8** through benzyl etherification and Baeyer–Villiger oxidation (Scheme 1) [20,21]. A glucose donor, **9**, was synthesized in several steps including peracetylation of glucose, removal of the 1-acetyl moiety, and imino esterification [22,23]. In the presence of a catalytic amount of boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$), **8** was glycosylated with **9** under low-temperature conditions to obtain the glucoside **10** in an excellent yield (94%). In contrast, glucoside **10** was obtained in only a moderate yield (55%) by using a phase transfer catalyst under basic condition in a previous work [17]. Trimethylsilyl trifluoromethanesulfonate could be useful as a Lewis acid because the glycosylation proceeded to yield **10** with 82% [24].

Diphenol **11** was obtained from **10** with 94% yield by catalytic hydrogenolysis at room temperature (rt). The selective protection of the phenolic hydroxyl at the C-4 of **11** was achieved by the treatment of

* Corresponding author. Department of Applied Biological Chemistry, School of Agriculture, Utsunomiya University, Tochigi, 321-0943, Japan.
E-mail address: nihei98@cc.utsunomiya-u.ac.jp (K.-i. Nihei).

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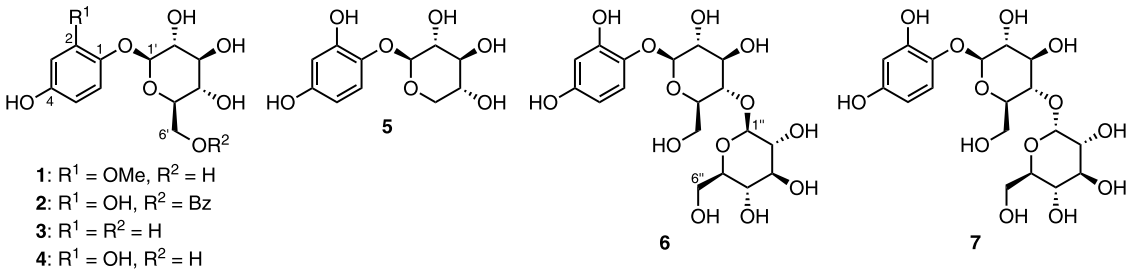
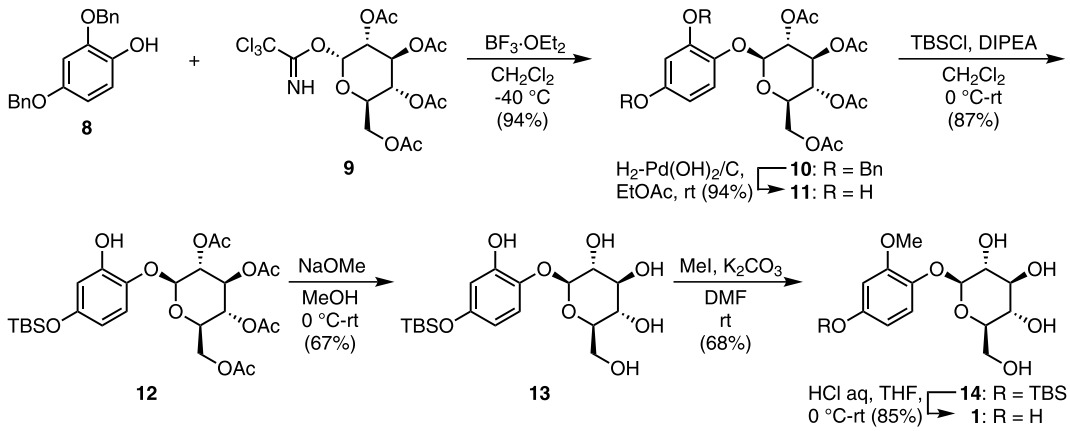


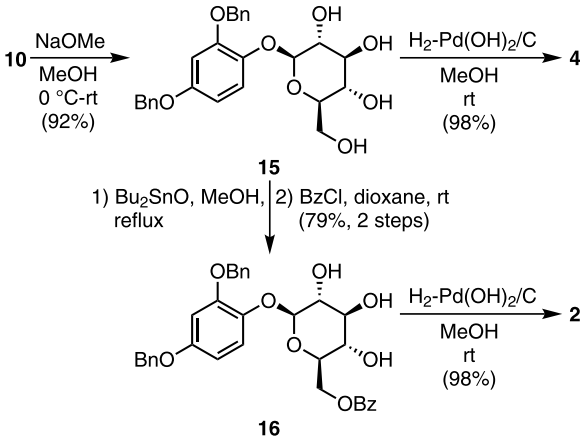
Fig. 1. Structure of **1**–**7**.



Scheme 1. Synthesis of **1**.

tert-butyldimethylchlorosilane (TBSCl) and *N*,*N*-diisopropylethylamine (DIPEA) in CH_2Cl_2 (87% yield). When the solvent was replaced by *N*,*N*-dimethylformamide (DMF), the excess production of a disilyl derivative could not be avoided. In addition, the silylation did not proceed smoothly when using imidazole as a base.

The methylation at the 2-OH of silyl ether **12** failed with the use of MeI and several bases such as K_2CO_3, DBU, or DIPEA. One reason for this failure arose from the steric hindrance of the peracetylated glucoside. Thus, all the acetyl groups of **12** were removed by transesterification (67% yield). When polyol **13** was treated with MeI and K_2CO_3, the ether **14** was synthesized with 68% yield. Finally, the removal of the TBS group under acidic conditions yielded the natural glucoside **1** with 85%. The obtained spectral data were consistent with those that were previously reported [16,25–27]. The total yield of **1** from **8** was 30% over six steps.



Scheme 2. Synthesis of **2** and **4**.

2.2. Chemical synthesis of natural glucoside 2

Transesterification of **10** using NaOMe yielded the polyol **15** with 92% (Scheme 2). The monoester **16** could not be prepared by the direct benzoylation of **15** with benzoyl chloride (BzCl), when pyridine, 4-dimethylaminopyridine, or trimethylamine were used as bases and when the reaction temperatures were controlled within −40 °C to 80 °C. The hydroxyl group at C-6 in **3** was selectively benzoylated with benzoic acid by using bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride as a coupling reagent [17]. Although this method was applied, **16** could not be isolated by the chromatographic purification using a silica gel column.

Dibutyltin oxide (Bu_2SnO) forms a nucleophilic O–Sn linkage, which has been used as an effective additive for the regioselective monoacylation of several polyols [28]. In particular, methyl β-D-glucopyranoside can be transformed into the 6-benzoyl derivative with over 80% yield through the preparation of the stannylidene complex followed by treatment with BzCl [29]. As a result of the application of this procedure, **16** was synthesized from **15** with 79% yield. Finally, the hydrogenolysis of **16** resulted in the natural glucoside **2** with an excellent yield (98%). The spectral data obtained was in accordance with those that had been reported previously [17]. The total yield of **2** from **8** was 67% over five steps.

2.3. Tyrosinase-inhibitory activity of 1 and 2

The inhibitory activity of the natural glucosides **1** and **2** was evaluated by using a commercially available tyrosinase. Unfortunately, the half maximal inhibitory concentrations (IC_{50}s) could not be identified, even when the concentration of both synthetic compounds was increased up to 1000 μM (Table 1). It has been reported previously that the standard substance **3** can act as a weak tyrosinase inhibitor (IC_{50} = 8.4 mM) [30]. This low efficacy is partially due to **3** having a monophenolic structure that acts as alternative substrate [10,12,13]. However, several resorcinol glycosides represented potent tyrosinase-inhibitory activity without oxidation of the substrate [31].