Attempt to Synthesize 2,3,5,4′-Tetrahydroxystilbene Derived from 2,3,5,4′-Tetrahydroxystilbene-2-O-β-glucoside (THSG)

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An attempt to synthesize aglycone 1 derived from 2,3,5,4′-tetrahydroxystilbene-2-O-β-glucoside (THSG)
via the Wittig reaction and Mizoroki–Heck reaction is described. In the Wittig protocol, 2,3,5,4′-tetra-
methoxystilbene 2 was obtained. Additionally, a palladium-catalyzed Mizoroki–Heck reaction strategy
yielded 2-aryl-2,3-dihydrobenzofuran 13 instead of derivative 12 in good yield.

Key words Polygonum multiflorum; Mizoroki–Heck reaction; 2-aryl-2,3-dihydrobenzofuran; 2,3,5,4′-
tetrahydroxystilbene-2-O-β-glucoside (THSG)

Dietary polyphenols, such as flavonoids,1) stilbenes2) and
lignans,3) are now recognized for their beneficial uses in
human health care, such as in the treatment and prevention of
cardiovascular diseases. Cancer prevention has also been associated
with consumption of a diet rich in these polyphenols.4,5)

In particular, resveratrol (3,5,4′-trihydroxy-trans stilbene),
a polyphenolic natural product present as a glycoside6) or
methoxide,7) has chemoprevention effects against cardiovas-
cular diseases,8) cancer,9) Alzheimer’s disease and aging10,11) (Fig. 1).

However, the therapeutic potential of resveratrol is limited
because free resveratrol is rapidly absorbed in the upper GI
tract following oral dosing, quickly metabolized to glucuro-
nides and sulfates and quickly cleared from the circulation.12)

2,3,5,4′-Tetrahydroxystilbene-2-O-β-D-glucoside (THSG) is
also a polyphenolic glycoside extracted from the dried root
tuber of Polygonum multiflorum (Fig. 1).

The dried root tuber of Polygonum multiflorum (Radix
Polygoni mutiflori), a traditional herbal drugs in the Chinese
pharmacopeia, has been used as an important health protective
agent and nutritional supplement for thousands of years.13)

Recent pharmacological studies indicated that THSG has
strong antioxidative and free radical scavenging activity.14–16) In addition, THSG is able to reduce hyperlipidemia, prevent
lipid peroxidation, and protect the cardiovascular system.17) It is also effective in the prophylaxis and therapeutic treatment
of Alzheimer’s disease.18)

The usefulness of THSG, however, is limited by its instabil-
ity upon exposure to irradiation and oxygen or at a particular
pH and temperature.19,20) The bioactivities of polyhydroxy stilbene compounds have mainly been attributed to their antioxidative property, which is related to the position of hydroxyl groups.21,22)

In addition, polyhydroxy stilbenes with catechol substitu-
ents dramatically increase antioxidative activity, but the gly-
cosylation of stilbene reduces their activity compared to the
corresponding aglycone.6,21,22)

Therefore, the aglycone 1 (2,3,5,4′-tetrahydroxystilbene)
from THSG is a useful antioxidant and free radical scavenger
and possesses potential therapeutic application to human dis-
ease.

To the best of our knowledge, the aglycone 1 derived from
THSG has rarely been reported on in the literature, and only two reports mention antioxidative activities. Reports indicate that aglycone 1 has very high 1,1-diphenyl-2-picryl-
hydrazyl (DPPH) radical scavenging activity (IC50=0.38 µM)
in vitro, which is nearly a hundred times that of THSG
(IC50=40 µM).23,24)

Our interest in the aglycone 1 stemmed from its high anti-
oxidative activity, therapeutic potential and novel mechanism
of action. However, the systematic investigation of biological
and therapeutic properties of the aglycone 1 is somewhat limited
by its general accessibility. Besides methods of aglycone
1 extraction from plants, efficient methods of aglycone 1 syn-
thesis would be highly desirable.

Fig. 1. Chemical Structure 2,3,5,4′-Tetrahydroxystilbene (1) THSG and Resveratrol

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Results and Discussion

Firstly, we tried to prepare the aglycone 1 via hydrolysis with β-glucosidase according to a previously reported procedure\textsuperscript{23,24} (Chart 1).

However, the desired aglycone 1 was not observed under the conditions. We also tried various other methods and found that glucose was among the reaction products of hydrolysis of THSG with β-glucosidase, indicating the occurrence of deglucosylation. However, the presence of the aglycone 1 could not be confirmed in the obtained/resulting products by HPLC or $^1$H-NMR.

Next, we decided to investigate the synthesis of the aglycone 1 through the Wittig reaction followed by deprotection of (E)-2,3,5,4'-tetramethoxystilbene (2) (Chart 2).

The (E)-2,3,5,4'-tetramethoxystilbene (2) was synthesized in eight steps beginning with Vanillin. The 2,3,5-trimethoxybenzaldehyde (3), which was not available commercially, was synthesized as previously described\textsuperscript{25,26} (Chart 3).

Vanillin is regioselectively brominated at the 5-position to give arylbromide 5 in good yield (90%). Subsequent O-methylation using methyl iodide was followed by Dakin oxidation using $m$-chloroperbenzoic acid in refluxing CH$_2$Cl$_2$ of the resulting product to phenol 7, which underwent nitrile- for -Br exchange on treatment with CuCN in refluxing N,N-dimethylformamide (DMF) in good yield (89%). After conversion of the OH group into methyl ether 9, reduction of the nitrile functional group with diisobutylaluminium hydride followed by mild acidic workup afforded quantitatively the corresponding aldehyde 3.

The 2,3,5,4'-tetramethoxystilbene (2) was prepared by the Wittig reaction. 4-Methoxybenzyltriphenylphosphonium bromide was synthesized from 4-methoxybenzylalcohol by bromination, followed by reaction with triphenylphosphine.\textsuperscript{27}

The phosphonium salt was reacted with the aldehyde 3 in the presence of 15% NaOH as base and $n$Bu$_4$NI to give the desired 2,3,5,4'-tetramethoxystilbene as a mixture of $E$ and $Z$ isomers (Chart 4).

However, chromatographic separation of the $E$ and $Z$ isomers was very difficult in our hands. Fortunately, $Z$ to $E$ isomerization was easily accomplished under iodine catalysis. That is to say, the $E/Z$ mixture of 2,3,5,4'-tetramethoxystilbene was quantitatively converted into the corresponding $E$ stereoisomer by treatment with a catalytic amount of iodine in hexane at reflux.\textsuperscript{28}

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Reagents and conditions: (a) Br$_2$, AcOH, 0°C–r.t., 65% (b) CH$_3$I, K$_2$CO$_3$, r.t., 89% (c) $m$CPBA, CHCl$_3$, reflux, 90% (d) CuCN, reflux, 77% (e) CH$_3$I, K$_2$CO$_3$, r.t., 98% (f) DIBALH, CH$_2$Cl$_2$, 0°C, 78%.

Chart 3. Synthesis of 3
Next, we attempted to convert 2,3,5,4'-tetramethoxystilbene 2 directly into the aglycone 1 by deprotection of methyl ether. Boron tribromide is known to demethylate aromatic methyl ether. Treatment of (E)-2,3,5,4'-tetramethoxystilbene (2) with boron tribromide gave an intractable brown solid that could not be characterized. Furthermore, demethylation of aromatic methyl ether with trimethylsilyl iodide and pyridine in CH₂Cl₂ at −78°C or with sodium isopropyl thiolate in DMF at reflux did not give the aglycone 1. ²⁹

This appeared to confirm the sensitivity of phenolic functional groups such as those in THSG to these reaction conditions. The presence of the second hydroxyl group in the ortho or para position is speculated to be due to its isomerization to o-quinone or p-quinone derivatives. THSG is also thought to be oxidized and hydrolyzed, ultimately, resulting in degradative decomposition, but details of the underlying mechanism remain unknown. ¹⁹ Despite the satisfactory results obtained regarding synthesis of (E)-2,3,5,4'-tetramethoxystilbene (2), the Wittig protocol has general limitations. This method applied to the synthesis of the aglycone 1 requires a preliminary protection of phenolic groups of the starting aromatic compounds and the deprotection of these protective groups under alternative milder conditions.

Because of these difficulties we had to change our synthetic approach as outlined in Chart 5. The key step in the synthesis of the aglycone 1 is to form the stilbene via the Mizoroki–Heck reaction. ²⁹ A palladium-catalyzed Mizoroki–Heck reaction has been also used previously to form resveratrol, glucopyranosides of resveratrol and polymethoxystilbenes. ², ³⁰, ³¹

In our strategy, we used the Mizoroki–Heck reaction of a
suitable bromo derivative 10 with styrene derivative 11 (Chart S). We chose to utilize the acetyl derivative 1 because the Mizoroki–Heck reaction is known to give a better yield. The 2-bromo-6-methoxy-1,4-dihydroquinone (10), was obtained by the Dakin reaction of 5-bromovanillin with m-chloroperbenzoic acid followed by hydrolysis of the ester group. The Mizoroki–Heck reaction was carried out using 5 mol% of Pd(OAc)2 as catalyst, (the concentration of which was calculated based upon 10), Na2CO3 as base, nBu4NI as phase transfer catalyst, and DMF as solvent. However, this coupling reaction did not afford the desired product 12 but instead 2-aryl-2,3-dihydrobenzofuran derivative 13 in good yield (87%).12,33

This reaction appears to proceed as depicted in Chart 6: oxidative addition of the hydroquinone 10 to Pd(0) and subsequent addition of the resulting arylpalladium complex to the carbon–carbon double bond of styrene derivative 11.34

Subsequent intramolecular nucleophilic attack of the phenoxy group (2-hydroxyl group) on the σ-phenoxy group (2-hydroxyl group) on the teleplanic (or phenoxy) oxygen nucleophile is directed towards the 2-aryl-2,3-dihydrobenzofuran (10) resulting in the observed dihydrobenzofuran 14, which is probably accounted for by the coordination of the phenolic (or phenoxy) oxygen to the palladium in the 14.

Conclusion
We are currently exploring the application of the palladium-catalyzed Mizoroki–Heck reaction to the synthesis of 2-aryl-2,3-dihydrobenzofuran derivatives, although we could not afford the aglycone 1 (2,3,5,4′-tetrahydroxystilbene). It is suggested that it is necessary to protect the 2-hydroxyl group for achieve to synthesis of aglycone 1. The results of these studies will be reported in due course.

Conflict of Interest The authors declare no conflict of interest.

References and Notes
32) Typical procedure for the Mizoroki–Heck reaction of 10 and 11: To a stirred solution of 14 (116 mg, 0.53 mmol) in dry DMF (1.5 mL) kept at r.t. under argon were added dry Na2CO3 (169 mg, 1.60 mmol), tetrabutylammonium iodide (233 mg, 0.63 mmol), Pd(OAc)2 (5.9 mg, 0.03 mmol) as catalyst, and DMF as solvent. However, this coupling reaction did not afford the aglycone 1 (2,3,5,4′-tetrahydroxystilbene). It is suggested that it is necessary to protect the 2-hydroxyl group for achieve to synthesis of aglycone 1. The results of these studies will be reported in due course.

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