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Synthesis of haginin E, equol, daidzein, and formononetin from resorcinol via an isoflavene intermediate

Sie-Rong Li [a,b], Po-Yuan Chen [a], Liang-Yeu Chen [a,b], Yi-Fang Lo [a], Ian-Lih Tsai [b], Eng-Chi Wang [a,*]

[a] Faculty of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung City 807, Taiwan
[b] Graduate Institute of Pharmaceutical Sciences, Kaohsiung Medical University, Kaohsiung City 807, Taiwan

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ABSTRACT

New syntheses of haginin E, equol, daidzein and formononetin are described in this Letter. Through a sequence of a Wittig reaction, O-alkylation, and another Wittig reaction, 4-benzyloxysalicylaldehyde, which was prepared from resorcinol in two steps, was converted into the desired diene in one pot. Subsequently, the prepared diene was subjected to ring-closing metathesis using Grubbs' catalyst (II) to construct the desired isoflavene intermediate. Using the prepared isoflavene, certain isoflavonoids such as haginin E, equol, daidzein, formononetin and other related compounds were derived smoothly and in good overall yields.

The skeletons of haginin E (**1**), equol (**2**), daidzein (**3**) and formononetin (**4**) (Fig. 1) all belong to the isoflavonoid family. Because of their phytoestrogenic properties and diverse biological activities, isoflavonoids have attracted the attention of both natural product chemists and synthetic chemists.[1]

Haginin E (**1**) was first isolated from the stems of *Lespedeza homoloba*, and was initially found to have antioxidative activity against lipid peroxidation in the rat brain homogenate test.[2] In more recent reports, **1** has been disclosed to efficiently induce apoptosis in epithelial ovarian carcinoma cells, but has little effect on normal tissues.[3] Moreover, it has been shown that **1** can inhibit proliferation in various human cancer cells in vitro and in vivo.[4] **1** has become an important compound, has been registered and named phenoxodiol, and is in phase 3 clinical trials for the treatment of ovarian cancer.[5] Nevertheless, the total synthesis of **1** (phenoxodiol) has received no attention, except for semi-syntheses from daidzein (**3**) or formononetin (**4**).[6] On the other hand, equol (**2**)[7] is known to have a high binding affinity to estrogen receptors, and causes direct inhibition of the growth of estrogen-dependent breast cancer.[8] In addition, other bioactivities, including anti-prostate cancer[9] and cardiovascular disease therapy,[10] have also been reported in recent studies. However, to date, only a few synthetic methods for racemic equol have been reported, including the hydrogenation of natural **3** or **4**,[11] and production via a Diels–Alder reaction between *o*-quinone methides and aryl substituted enol ethers.[12] Furthermore, the racemic equol can be easily separated into (*R*-) and (*S*-) form by chiral column that has been studied.[11d] Other related chiral synthetic methods, including preparation via intramolecular Buchwald etherification to generate the chroman ring as the key intermediate,[13] and synthesis from ethyl L-(−)-lactate via sequential reactions,[14] have been directed at (*S*)-equol. In addition, daidzein (**3**)[15] and formononetin (**4**),[16] which belong to the soy isoflavones, have also attracted attention due to their diverse biological activities, such as estrogenic,[17] anti-breast cancer,[18] hormone replacement theraputic[19] and cancer chemoprevention activities.[20] Most of the synthetic strategies towards **3** and **4** include acid-induced cyclization,[21] Suzuki–Miyaura cross-coupling,[22] and other methods.[23]

In spite of the fact that several methods for the synthesis of haginin E (**1**), equol (**2**), daidzein (**3**), and formononetin (**4**) have been reported, some disadvantages still exist, including tedious reaction

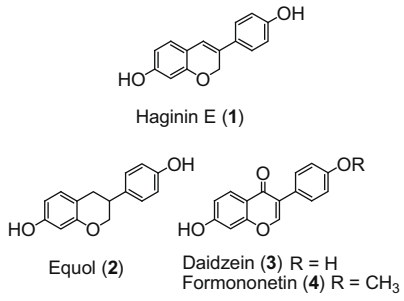

Figure 1. Structure of isoflavene haginin E; isoflavan equol; and isoflavones daidzein, formononetin.

* Corresponding author. Tel.: +886 7 3121101; fax: +886 7 3125339.
E-mail address: enchwa@kmu.edu.tw (E.-C. Wang).

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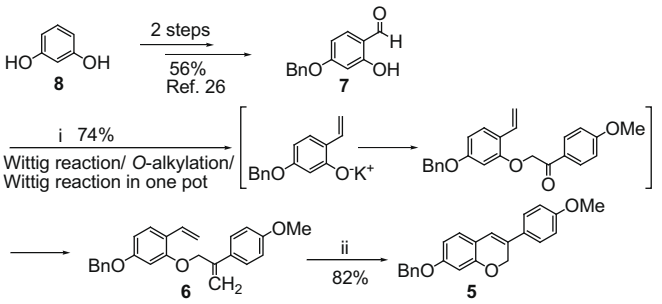
conditions, low yields, and multistep sequences. In addition, the lack of diversity for preparing these compounds is also a shortcoming. Therefore, developing a synthetic strategy that is efficient, having a low number of steps, and providing diverse access to these bioactive compounds is an important goal. Herein, we disclose a new, concise, and efficient approach to the title compounds.

Since the discovery of Grubbs' catalyst for RCM, it has become a powerful tool in many areas of synthetic chemistry.[24] Even though some strategies for 2*H*-chromenes have been reported,[25] the synthesis of isoflavene **5** as a common intermediate for the title compounds has not been disclosed. In a retro-synthetic sense (Scheme 1), compounds **1**–**4** could be derived from isoflavene **5** by several discrete reactions. Compound **5**, which belongs to the isoflavene family, could be accessed by the reaction of diene **6** under RCM conditions. The diene **6** could be prepared from the aldehyde **7** in one pot, without isolation of the intermediates, and compound **7** could be prepared from resorcinol (**8**) in two steps according to known procedures.[26]

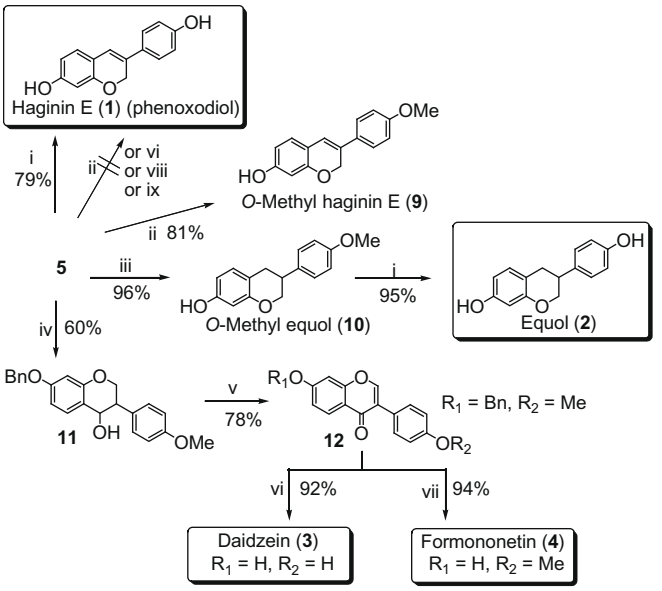
As shown in Scheme 2, 4-benzyloxysalicylic aldehyde (**7**), prepared from resorcinol (**8**) in two steps in 56% yield,[26] was reacted with methylene(triphenyl)phosphorane (MTPP), which was generated from methyltriphenylphosphine bromide (MTPPB) and potassium *tert*-butoxide at 0 °C in situ. Without work-up, the reaction mixture was continually treated with 2-bromo-4′-methoxyacetophenone to undergo O-alkylation in refluxing THF for 1 h, which was monitored by TLC. Subsequently, the prepared intermediate, which was not isolated, was further reacted with MTPP to undergo another Wittig reaction to afford the desired diene **6** in a one pot yield of 74%. The diene **6** was then subjected to RCM using Grubbs (II) catalyst to furnish the isoflavene **5** in 82% yield.

The synthesis of haginin E, equol, daidzein and formononetin from isoflavene intermediate **5** is depicted in Scheme 3. When isoflavene **5** was treated with TBAI/BCl_3,[27] haginin E (phenoxodiol) (**1**) was obtained in 79% yield. In contrast, when isoflavene **5** was treated with BCl_3, selective debenzylation took place to afford *O*-methyl haginin E (**9**) as a sole product in 81% yield. Other O-demethylation conditions such as $AlCl_3$/EtSH, $AlCl_3/CH_2Cl_2$ and $AlCl_3$/nitrobenzene/reflux gave messy products. Treatment of isoflavene **5** with $Pd(OH)_2$/C and cyclohexene (Pearlman's reagent) in refluxing ethanol promoted O-debenzylation and reduction of the chromene ring in one step, yielding *O*-methylequol **10** in 96% yield. Finally, *O*-methylequol **10** was smoothly demethylated with TBAI/BCl_3[27] to furnish equol (**2**) in 95% yield. Using the general procedure of hydroboration–oxidation, isoflavene **5** was converted into chroman-4-ol **11** in a yield of 60%. Chroman-4-ol **11** was treated with DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) in refluxing 1,4-dioxane to undergo oxidation-dehydrogenation to give isoflavone **12** in 78% yield. After the deprotection of isoflavone **12** with $AlCl_3$/EtSH,[28] daidzein (**3**) was produced in 92% yield. Moreover, isoflavone **12** was selectively debenzylated with Pearlman's reagent to give formononetin (**4**) in 94% yield.

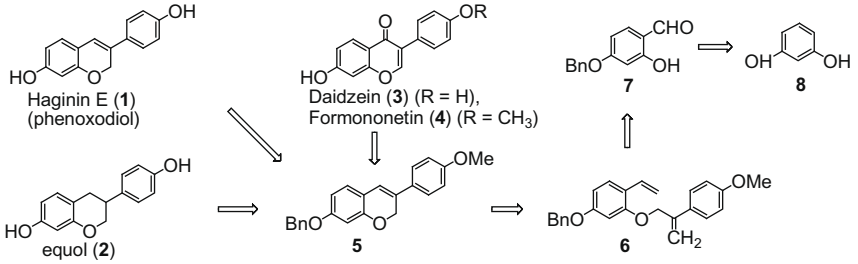
All compounds (**1**–**6**, **9**–**12**) that we have synthesized were fully characterized and gave satisfactory spectral data,[29] including IR, ^1H NMR, ^{13}C NMR, EI-MS and HRMS or elemental analysis. In conclusion, we herein provide a new and efficient strategy to avoid the production of needless waste and without the requirement of lengthy purification processes for the preparation of diene **6**, the precursor of isoflavene **5**. Furthermore, we have established a new, practical route for the synthesis of bioactive isoflavonoids, including haginin E (phenoxodiol) (**1**), equol (**2**), daidzein (**3**), formononetin (**4**) and other related compounds from the common isoflavene intermediate **5**, which was obtained from economic and commercially available resorcinol (**8**).



Scheme 2. Synthesis of isoflavene intermeditate **5**. Reagents and conditions: (i) (a). MTPPB, *t*-BuOK, THF, 0 °C 2 h; (b). 2-bromo-4′-methoxyacetophenone, reflux, 1 h; c. MTPPB, *t*-BuOK, THF, 0 °C, 1 h. (ii) Grubbs 2nd, CH_2Cl_2, 40 °C, 8 h.



Scheme 3. Synthesis of haginin E (phenoxodiol) (**1**), equol (**2**), daidzein (**3**) and formononetin (**4**) from isoflavene intermeditate **5**. Reagents and conditions: (i) BCl_3, *n*-Bu_4NI, CH_2Cl_2, −78 °C to 0 °C, 2 h; (ii) BCl_3, CH_2Cl_2, 0 °C, 10 min. (iii) $Pd(OH)_2$, EtOH, cyclohexene, reflux, 2 h; (iv) BH_3–SMe_2, THF, 0 °C, 4 h, then H_2O, 10% NaOH, 37% H_2O_2, 30 min; (v) DDQ, 1,4-dioxane, reflux, 8 h; (vi) $AlCl_3$, EtSH, CH_2Cl_2, 0 °C, 30 min.; (vii) $Pd(OH)_2$, EtOH, cyclohexene, reflux, 1 h; (viii) $AlCl_3$, CH_2Cl_2, 0 °C, 1 h; (ix) $AlCl_3$, nitrobenzene, reflux, 1 h.



Scheme 1. Retrosynthesis of haginin E (**1**), equol (**2**), daidzein (**3**) and formononetin (**4**).

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.159.

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29. All analytical data and experimental procedures are given as Supplementary data.