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New synthetic route to (*S*)-(–)-equol through allylic substitution

Yuji Takashima, Yuichi Kobayashi *

Department of Biomolecular Engineering, Tokyo Institute of Technology, Box B52, Nagatsuta-cho 4259, Midori-ku, Yokohama 226-8501, Japan

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ABSTRACT

Allylic substitution of allylic picolinate **5** with a copper reagent derived from *p*-MeOC$_6$H$_4$MgBr (**6**) and CuBr·Me$_2$S produced the anti S$_N$2′ product **7** with high regioselectivity and efficient chirality transfer. Oxidative cleavage of the olefinic function to the alcohol followed by bromination afforded bromide **16**, which upon demethylation and intramolecular ether ring formation furnished (*S*)-(−)-equol (**3**).

Daidzein (**1**), one of the major isoflavonoids found in soy,[1,2] has attracted interest as a dietary phytoestrogen (Fig. 1).[3] After ingestion, **1** is transformed to dihydrodaidzein, tetrahydrodaidzein (**2**), equol (**3**), and *O*-demethyl-angolensin (**4**) by intestinal bacteria such as gut microflora.[4] Among these derivatives, equol (**3**) is most effective in stimulating an estrogenic response.[5] Natural equol has the *S* chirality and binds to estrogen receptor β (ERβ) 13 times more strongly than the *R* isomer.[6] Interestingly, the (*R*)-isomer is moderately ERα selective. In contrast to the activity of daidzein as dietary phytoestrogen; however, **3** was recently reported to induce breast cancer cell proliferation at 100 nM levels,[7] evoking controversy regarding equol's health benefit to human. The role of equol would be clarified by biological studies using equol and its analogs.

Previously, equol has been obtained by the bacterial metabolism of daidzein,[8] by enantiomer separation of racemate using chiral HPLC,[6] and by organic synthesis[9] through the Evans asymmetric alkylation.[10] However, the former two methods are less attractive in regard to the production scale and uncertainty for efficiency in obtaining derivatives. On the other hand, the alkylation is potentially flexible. However, the synthesis reported suffers from the moderate yields in several steps, which led us to investigate a different synthetic approach to equol.

Recently, we reported an allylic substitution reaction of allylic picolinates with aryl nucleophiles derived simply from ArMgBr and CuBr·Me$_2$S that proceeds with sufficient levels of reactivity

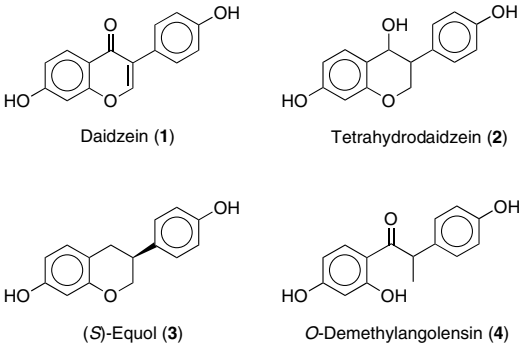
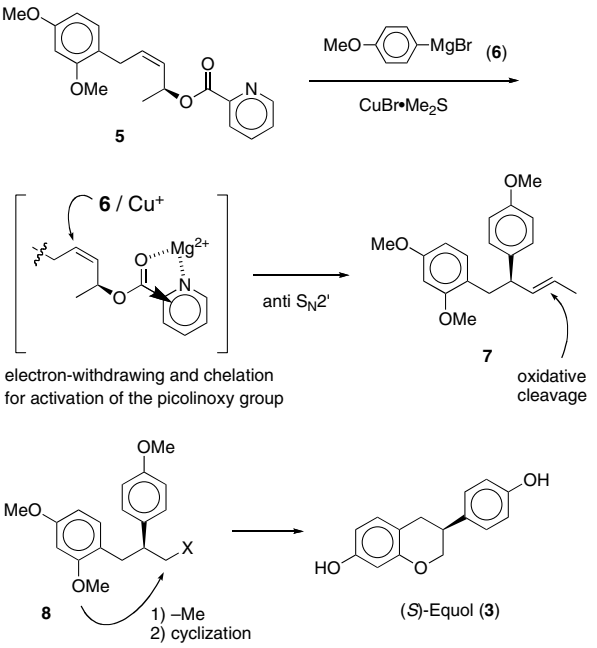


Figure 1. Daidzein and its metabolites.



Scheme 1. Synthesis route to (*S*)-equol (**3**).

* Corresponding author. Tel./fax: +81 45 924 5789.
E-mail address: ykobayas@bio.titech.ac.jp (Y. Kobayashi).

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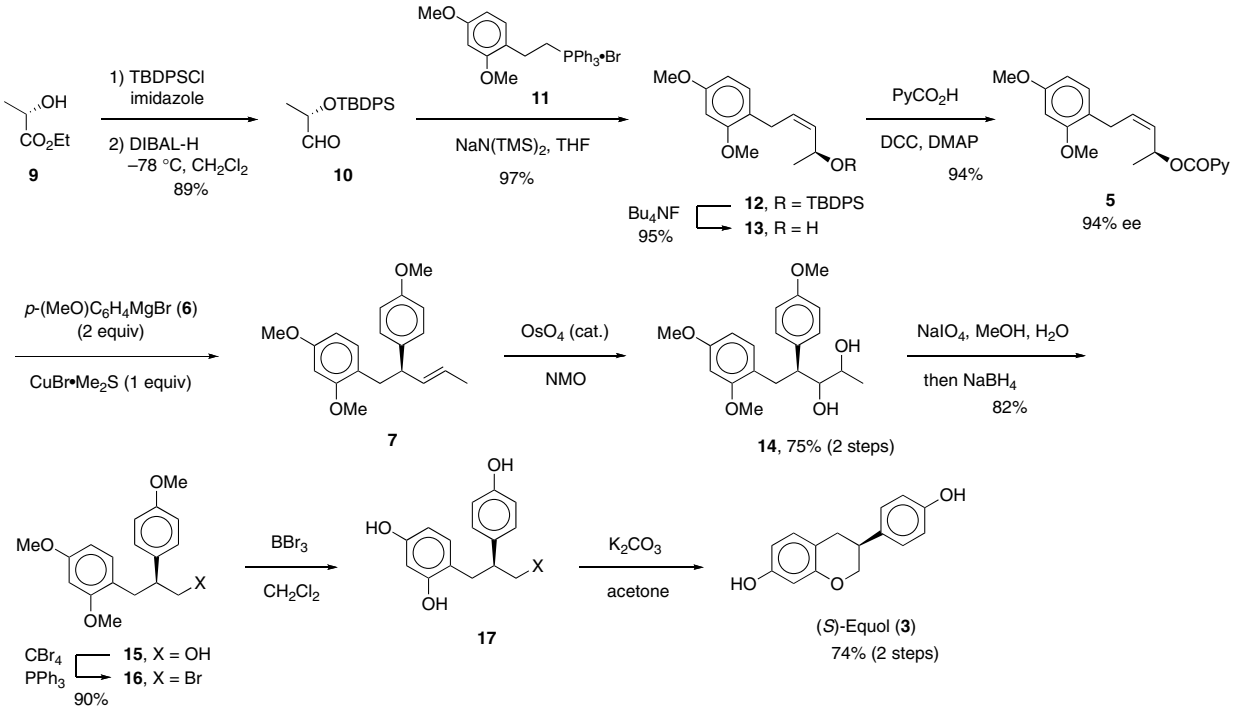
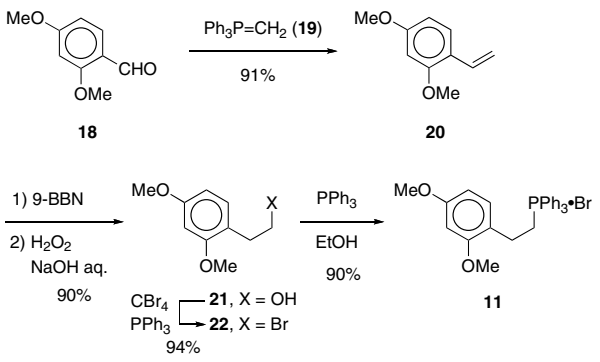


Scheme 2. Synthesis of (*S*)-equol (**3**).

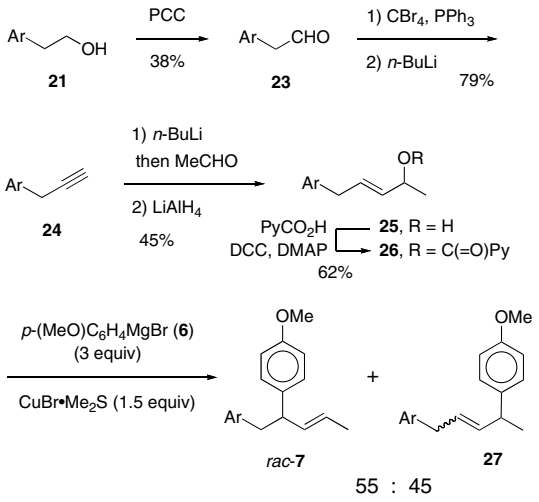
and anti S_N2' selectivity.[11] The synthetic advantage of the reaction system is the efficient and selective delivery of aryl anions into the allylic system, whereas the previous allylation with aryl anions usually afforded a mixture of regioisomers. The electron-withdrawing nature of the 2-pyridyl group and the coordination of the carbonyl oxygen and the pyridyl nitrogen to $MgBr_2$ are responsible for the success. With this allylic substitution in mind, we designed an entirely new synthesis of (*S*)-equol (**3**) as outlined in Scheme 1, in which anti S_N2' reaction of **5** with a copper reagent derived from *p*-$MeOC_6H_4MgBr$ (**6**) and $CuBr{\cdot}Me_2S$ would furnish olefin **7** that possesses the requisite chirality and the framework of **3**. Herein, we present our preliminary results in this regard.

The key compound **5** was synthesized from natural ethyl L-(−)-lactate (**9**), which was converted to aldehyde **10** by the literature procedure[12] in good yield (Scheme 2). The Wittig salt **11** of aldehyde **10** was synthesized by a sequence delineated in Scheme 3. Reaction of aldehyde **18** with anion **19** derived from $[PPh_3CH_3]^+Br^-$ and *n*-BuLi afforded olefin **20**, which was converted to the phosphonium salt **11** by hydroboration with 9-BBN, bromination of the resulting alcohol, and subsequent reaction with PPh_3 in EtOH.[13] Wittig reaction of aldehyde **10** and the anion derived from **11** and $NaN(TMS)_2$ gave *cis*-olefin **12** stereoselectively, which was converted to the picolinate ester **5** by desilylation followed by esterification with $PyCO_2H$ using DCC and DMAP. The enantiomeric excess of **5** was determined as 94% by chiral HPLC (Chiralcel AD-H, hexane/*i*-PrOH = 95/5, 1.0 mL/min, t_R (min) = 24.6 (*S*), 34.4 (*R*)), while the cis/trans ratio was 12 ~ 14:1 by ^1H NMR spectroscopy. An authentic sample of the *trans*-isomer **26** was synthesized from alcohol **21** as summarized in Scheme 4.

According to the procedure reported,[11] the key transformation of **5** with the copper reagent (2 equiv) derived from **6** and $CuBr{\cdot}Me_2S$ in a 2:1 ratio was carried out at −50 °C for 1 h to afford product **7** with a small quantity of byproduct(s) derived from the reagent (Scheme 2). A similar reaction was also conducted with the *trans*-isomer **26** to afford a mixture of *rac*-**7** and the regioisomer **27** in a 55:45 ratio by ^1H NMR spectros-



Scheme 3. Preparation of the Wittig salt **11**.



Scheme 4. Preparation and substitution reaction of the *trans*-olefin **26**. Ar = 2,4-$(MeO)_2C_6H_3$–.

copy[14] (Scheme 4), thus confirming that **7** derived from **5** and **6** was free of the regioisomer **27**. On the other hand, the absolute configuration and the chirality transfer was determined at a later stage of the synthesis because of unsuccessful purification at the mixture of **7** and the by-product(s).

The mixture of **7** and the by-product(s) was submitted to the conventional dihydroxylation to give the diol **14** as a diastereomeric mixture, which was isolated by chromatography in 75% yield from **5**. Oxidative cleavage of the diol followed by reduction of the aldehyde intermediate in one flask afforded alcohol **15** in 82% yield. The enantiomeric excess of **15** was 91% by chiral HPLC, and thus chirality transfer for the allylic substitution was calculated to be 97% or more.[15]

An attempted demethylation and bromination of the primary hydroxy group with BBr_3[16] gave unidentified product(s). After several unsuccessful trials, it was found that bromination of **15** followed by demethylation of the methoxy bromide **16** with BBr_3 successfully afforded the bromophenol **17**, which without purification was converted to equol (**3**) by exposure to K_2CO_3 in acetone in 74% yield from **16**. Equol thus synthesized had 91% ee by chiral HPLC.[17] However, the specific rotation ($[\alpha]_D^{25}$ −13 (*c* 0.21, EtOH)) was inconsistent with those reported for equol of 100% and >99% ee ($[\alpha]_D^{24}$ −23.0 (*c* not given, EtOH);[8] $[\alpha]_D^{24}$ −23.5 (*c* not given, EtOH),[9], respectively).[18] Its ^1H and ^{13}C NMR spectra and mp were consistent with those reported[8,9] and the structure was also supported by the ^{13}C APT signals.[17]

In summary, we established a new method to synthesize (*S*)-equol (**3**) from L-lactate **9** in 31.6% total yield over 11 steps (24.6% from **18** over 13 steps), which is higher than the method reported.[9] Since the allylic substitution (**5** + **6**/CuBr) is applicable to various picolinates and ArMgBr, compounds with similar structures to equol would be readily accessible. Furthermore, the D-isomer is commercially available at a reasonable cost, and thus (*R*)-enantiomers of equol and similar compounds are also accessible.[19]

Acknowledgment

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14. Chemical shifts of CH_3 δ 1.61 ppm for the former and 1.31 ppm for the latter.
15. There still remains a possibility of a few percentage racemization at the aldehyde stage.
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17. HPLC analysis (Chiralcel AD-H, hexane/*i*-PrOH = 90/10, 1.0 mL/min, t_R (min) = 38.7 for *R*-isomer, 49.4 for **1**); mp 190–191 °C (lit.[8] 190.8 °C; lit.[9] 192–193 °C); $[\alpha]_D^{25}$ −13 (*c* 0.21, EtOH); IR (Nujol) 3358, 1615, 1598, 1151, 1024, 829 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.70–2.90 (m, 2H), 2.95–3.07 (m, 1H), 3.89 (t, *J* = 10.5 Hz, 1H), 4.10–4.18 (dm, *J* = 8 Hz, 1H), 6.19 (d, *J* = 2.5 Hz, 1H), 6.28 (dd, *J* = 8, 2.5 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 2H), 9.16 (s, 1H), 9.28 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 31.3 (+), 37.2 (−), 70.2 (+), 102.5 (−), 108.0 (−), 112.6 (+), 115.2 (−), 128.3 (−), 130.1 (−), 131.6 (+), 154.5 (+), 156.1 (+), 156.5 (+).
18. Since sufficient chemical purity of our equol was confirmed by ^1H NMR and TLC analyses and by measurement of mp, presently we have no adequate reason for the difference.
19. Synthesis of racemic equol was reported: Gharpure, S. J.; Sathiyanarayanan, A. M.; Jonnalagadda, P. *Tetrahedron Lett.* **2008**, *49*, 2974–2978.