

# Total Synthesis of Amentoflavone

Hae-II Park<sup>1</sup>, Chuan-Ling Si<sup>2\*</sup> and Jianjun Chen<sup>3,4\*</sup><sup>1</sup>College of Pharmacy, Kangwon National University, Chuncheon, Korea<sup>2</sup>Tianjin Key Laboratory of Pulp and Paper, College of Materials Science and Chemical Engineering, Tianjin University of Science and Technology, Tianjin, P R China<sup>3</sup>Department of Pharmaceutical Sciences, South College, Knoxville, TN, USA<sup>4</sup>Department of Pharmaceutical Sciences, College of Pharmacy, Chicago State University, Chicago, IL, USA

## Abstract

An efficient total synthesis of amentoflavone, a valuable natural product, utilizing Suzuki coupling with pinacolatoboronflavone derivatives and iodoflavone was reported for the first time in this work. The method can be applied to the synthesis of various other C-C biflavonoids and biphenyls, therefore the current work could serve as an excellent solution to the availability of many bioactive natural biflavonoids.

**Keywords:** Total synthesis; Amentoflavone; Flavone; Biflavone; Suzuki coupling

**Abbreviations:** DMSO: Dimethyl Sulfoxide; DMF: Dimethylformamide; NMR: Nuclear Magnetic Resonance; TLC: Thin Layer Chromatography; LCMS: Liquid Chromatography Mass Spectrometry

## Introduction

Amentoflavone, a biflavonoid, is ubiquitously found in plants such as *Calophyllum inophyllum* [1], *Eucommia ulmoides*, *Selaginella doederleinii* [2], *Paulownia tomentosa* var. *tomentosa*, *Ginkgo biloba* [3,4], *Juglans sigillata*, *Hypericum perforatum* [4,5]. A wide variety of bioactivities such as anti-viral, anti-inflammatory, anti-tumor, anti-depressant, anti-oxidant, anti-microbial, analgesic, antiplasmodial, leishmanicidal, lowering blood lipid and hepatoprotective activities have been reported for amentoflavone and its derivatives [1-3,5-9]. Due to the limited natural abundance, the massive production of amentoflavone is not possible from natural resources. Therefore, total synthesis of amentoflavone would be significant as it will be able to solve the availability issue of amentoflavone. Although the synthesis of amentoflavone through Suzuki-reaction was reported [10,11] two decades ago, which was to link the flavonyl-8-boronic acid with the 3'-iodoflavone to produce amentoflavone, no synthetic effort has been made ever since to explore an alternative scheme such that the flavonyl-3'-boronic acid ester can be linked to the 8-iodoflavone through Suzuki coupling. It would be highly beneficial to the scientific community if this alternative scheme is successful, as this will provide a similar but different route for the synthesis of amentoflavone and other similar biflavonoids, because the preparation of flavonylboronic acid, the key intermediate for the synthesis of biflavonoids, from the corresponding halogenated flavone is sometimes problematic due to steric hindrance or unfavorable electronic effects from neighboring substituting groups in the aromatic ring. Therefore, the goal of this work is to provide an alternative synthetic scheme for the production of amentoflavone and other similar biflavonoids utilizing the coupling of flavonyl-3'-boronic acid ester and 8-iodoflavone, instead of the reported method which was based on the coupling of two different intermediates, the flavonyl-8-boronic acid and the 3'-iodoflavone [10]. Here we describe an efficient synthetic pathway to generate amentoflavone.

## Experimental

All reagents were purchased from Sigma-Aldrich Chemical Co., Fisher Scientific (Pittsburgh, PA), Alfa Aesar (Ward Hill, MA), and AK Scientific (Mountain View, CA) and were used without further purification. The solvents for moisture sensitive reactions were freshly distilled, and the reactions were carried out under an argon

atmosphere. DMF were dried by Barium oxide overnight before refluxed and distilled under reduced pressure. CHCl<sub>3</sub> and CH<sub>3</sub>CN were refluxed and distilled from calcium hydride prior to use. Routine thin layer chromatography (TLC) was carried out on aluminum-backed Uniplates (Analtech, Newark, DE). Column chromatography was performed on Merck 230-400 mesh silica gel. <sup>1</sup>H-NMR spectra were recorded on a JEOL ECS instrument (400 MHz) spectrometer. <sup>13</sup>C-NMR spectra were recorded on a JEOL ECS instrument (100 MHz) spectrometer. Chemical shifts are reported in ppm downfield relative to tetramethylsilane as an internal standard. Mass spectra were collected on a Shimadzu LCMS 2020 mass spectrometer. All melting points were measured with Fisher-Johns melting point apparatus and are uncorrected. Glassware for reactions requiring anhydrous conditions was dried by flame prior to use.

### 3'-Iodo-4-methoxybenzaldehyde (2)

*p*-Anisaldehyde (1 eqv) was dissolved in glacial acetic acid, iodine monochloride/ICl (1 eqv) solution (1 M in CH<sub>2</sub>Cl<sub>2</sub>) was dropped to the reaction mixture heated to 60°C and stirred for 10 h, then saturated Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> (aqueous) was dropped to the reaction mixture until the solution was clear, evaporated to remove CH<sub>2</sub>Cl<sub>2</sub> and standed in ice-bath for 30 min during this period a white precipitate formed, filtered and got white solid, crystallized from MeOH resulted in the desired product. Yield: 55%. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 9.78 (s, 1H), 8.28 (t, J=1.4 Hz, 1.2 Hz, 2.4 Hz, 1H), 7.80 (d, J=7.6 Hz, 1H), 6.89 (d, J=8.2 Hz, 1H), 3.94 (s, 3H). MS (ESI) calculated for C<sub>8</sub>H<sub>7</sub>IO<sub>2</sub>, 262.0; found, 263.0 [M+H]<sup>+</sup>.

### 4,4',6'-trimethoxy-3-iodo-2'-hydroxychalcone (3)

Following the method as described in synthesis of 4,4',6'-trimethoxy-3'-iodo-2'-hydroxy-chalcone (9). Yield: 90%. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 12.12 (s, 1H), 7.80 (s, 1H), 7.71 (d, J=9.0 Hz, 2H), 7.45 (d, J=7.8 Hz, 1H), 6.88 (d, J=7.8 Hz, 1H), 6.05 (s, 1H), 5.90 (s, 1H), 3.88 (s,

\*Corresponding authors: Jianjun Chen, Department of Pharmaceutical Sciences, College of Pharmacy, Chicago State University, Chicago, IL, 60628, USA, Tel: 773-821-2659; E-mail: [jchen21@csu.edu](mailto:jchen21@csu.edu)

Chuan-ling Si, Tianjin Key Laboratory of Pulp and Paper, Tianjin University of Science and Technology, Tianjin 300457, P R China, E-mail: [sichli@tust.edu.cn](mailto:sichli@tust.edu.cn)

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3H), 3.81 (s, 3H), 3.80 (s, 3H). MS (ESI) calculated for  $C_{18}H_{17}IO_5$ , 440.0; found, 440.9 [M+H]<sup>+</sup>.

#### 4',5,7-Trimethoxy-3'-iodoflavone (4)

Following the method as described in preparing 4',5,7-trimethoxy-8-iodoflavone (10) above. Yield: 98%. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 8.05 (d, J=2.0 Hz, 1H), 7.72 (dd, J=2.2 Hz, 2.0 Hz, 1H), 6.96 (d, J=8.4 Hz, 1H), 6.65 (s, 1H), 6.55 (d, J=2.8 Hz, 1H), 6.35 (d, J=2.0 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.88 (s, 3H). MS (ESI) calculated for  $C_{18}H_{15}IO_5$ , 438.0; found, 439.0 [M+H]<sup>+</sup>.

#### 4',5,7-trimethoxy-3'-pinacolatoboronflavone (5)

An oven-dried round-bottomed flask equipped with magnetic stir bar and a rubber septum was allowed to cool to room temperature in a desiccator, the flask was charged with PdCl<sub>2</sub>(dppf) (5% eqv), Bis (pinacolato) diboron (1.3 eqv), 4',5,7-trimethoxy-3'-iodoflavone (4) (1.0 eqv), and potassium acetate (4 eqv), then distilled DMF was added to the flask through a syringe, the mixture was degassed by nitrogen gas for 5 min, followed by raising the temperature to 80°C, refluxed for overnight, monitored by TLC with solvent system of chloroform-methanol (100:3). The mixture was cooled to room temperature, celite filtered, and hydrochloric acid (10%) was added to destroy DMF, then extracted by ethyl acetate. The organic layer was washed by brine and water, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude material was purified by column (CHCl<sub>3</sub>-MeOH (100:1) to afford the target compound. Yield: 50%. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 8.20 (d, J=2.8 Hz, 1H), 7.81 (d, J=2.0 Hz, 1H), 7.10 (d, J=9.0 Hz, 1H), 6.65 (s, 1H), 6.52 (d, J=2.8 Hz, 1H), 6.40 (d, J=2.4 Hz, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 3.86 (s, 3H), 1.32 (s, 12H). MS (ESI) calculated for  $C_{24}H_{27}BO_7$ , 438.2; found, 439.1 [M+H]<sup>+</sup>.

#### 2-Hydroxy-4,6-dimethoxy-acetophenone (7)

2,4,6-Trihydroxyacetophenone (1 eqv) was dissolved in anhydrous acetone with stirring and potassium carbonate (3 eqv) was added in portions to give a yellow solution, resulting solution was stirred for 5 min, then dimethylsulfate (2 eqv) was added, heated to 60°C, stirred and refluxed for 8 h, monitored by TLC with solvent system of hexane-acetone (5:1), the solution was cooled to room temperature, filtered and concentrated in vacuum to get yellow solid, the solid was washed with water and crystallized from methanol to yield the as 2-hydroxy-4,6-dimethoxyacetophenone. Yield: 98%. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 6.03 (d, J=2.0 Hz, 1H), 5.88 (d, J=2.8 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 2.62 (s, 3H). MS (ESI) calculated for  $C_{10}H_{12}O_4$ , 196.1; found, 197.0 [M+H]<sup>+</sup>.

#### 2-Hydroxy-3-iodo-4,6-dimethoxy-acetophenone (8)

2-Hydroxy-4,6-dimethoxyacetophenone (1 eqv) was dissolved in glacial acetic acid, iodine (1 eqv) solution in CHCl<sub>3</sub> was added to the reaction mixture in ice-bath, HNO<sub>3</sub> (70%, w/w) was dropped in (1 drop/1 mmol), stirred in ice-bath for 3 h, monitored by TLC with solvent system of hexane-acetone (4:1, w/w). Saturated Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> (aqueous) was dropped to the reaction mixture until the color did not change any more, extracted with dichloromethane and washed with water for 3 times respectively. Organic layer was separated and dried over magnesium sulfate, concentrated *in vacuo* to yield brown solid. Yield: 93%. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 5.99 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.61 (s, 3H). MS (ESI) calculated for  $C_{10}H_{11}IO_4$ , 322.0; found, 323.0 [M+H]<sup>+</sup>.

#### 4,4',6'-Trimethoxy-3'-iodo-2'-hydroxy-chalcone (9)

2-Hydroxy-3-iodo-4,6-dimethoxy-acetophenone (1 eqv) was

dissolved in MeOH stirred for 5~10 min until the solid dissolved completely, KOH (2 eqv) was added and stirred until the solution became solid and 4-methoxybenzaldehyde (1 eqv) was added to the reaction mixture, stirred for 20 h, 3% hydrochloric acid was added to the solution follow by c-HCl until the solution was acidic (PH 6.5~7.0), some yellow solid formed and filtered, washed with water, recrystallized from MeOH to afford the title compound as yellow solid. Yield: 90%. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 12.39 (s, 1H), 7.78 (d, J=4.6 Hz, 2H), 7.56 (d, J=8.6 Hz, 2H), 6.01 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.80 (s, 3H). MS (ESI) calculated for  $C_{18}H_{17}IO_5$ , 440.0; found, 441.0 [M+H]<sup>+</sup>.

#### 4',5,7-trimethoxy-8-iodoflavone (10)

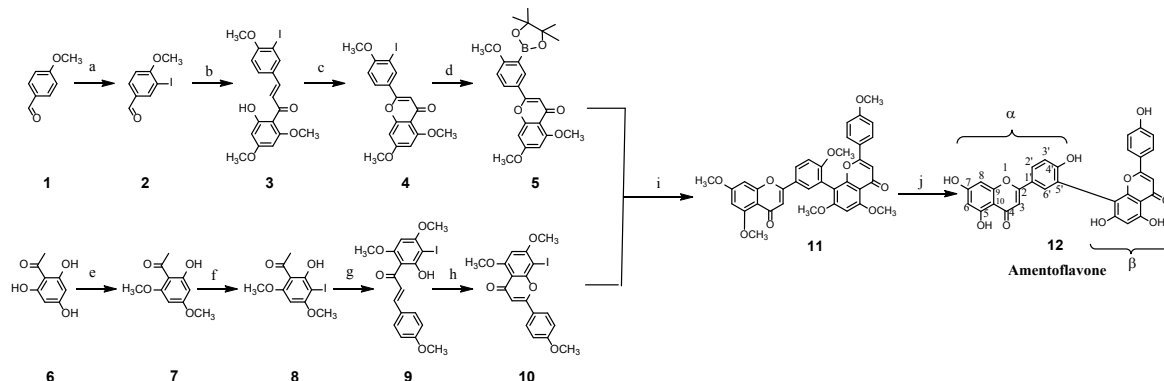
4,4',6'-Trimethoxy-3'-iodo-2'-hydroxychalcone (1 eqv) was dissolved in DMSO and iodine (0.3 eqv) was added to the resulted solution and heated with stirring to 100°C overnight, cooled the reaction to room temperature. Saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (aqueous) was added to the solution until the color no longer changed, filtered and the solid was crystallized from MeOH to afford the title compound. Yield: 95%. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.96 (d, J=8.8 Hz, 2H), 7.04 (d, J=9.0 Hz, 2H), 6.70 (s, 1H), 6.48 (s, 1H), 4.06 (s, 3H), 4.01 (s, 3H), 3.89 (s, 3H). MS (ESI) calculated for  $C_{18}H_{15}IO_5$ , 438.0; found, 438.8 [M+H]<sup>+</sup>.

#### 4',5,7,4''',5'',7''-Hexamethoxy-amentoflavone (11)

An oven-dried round-bottomed flask equipped with magnetic stir bar and a rubber septum was allowed to cool to room temperature in a desiccator, the flask was charged with tetrakis (triphenylphosphine) palladium (5% eqv), 4',5,7-trimethoxy-3'-pinacolatoboron flavone (1.2 eqv), 4',5,7-trimethoxy-8-iodoflavone (1.0 eqv), and NaOH (4 eqv), then distilled DMF-water (9:1) was added to the flask by syringe, the mixture was degassed by nitrogen gas for 10 min, followed by raising the temperature to 80°C, refluxed for overnight. The mixture was cooled to room temperature, celite filtered, and hydrochloric acid (10%) was added to destroy DMF, then extracted by ethyl acetate, the organic layer was washed by brine and water, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated *in vacuo*, the crude material was purified by crystallization in MeOH or separated by column (CHCl<sub>3</sub>-MeOH (100:1) to afford the target compound. Yield: 51%. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ 7.89 (d, J=8.0 Hz, 1H), 7.83 (d, J=2.4 Hz, 1H), 7.39 (d, J=8.0 Hz, 2H), 7.12 (d, J=8.8 Hz, 1H), 6.74 (d, J=8.0 Hz, 2H), 6.71 (s, 1H), 6.68 (s, 1H), 6.49 (s, 1H), 6.43 (s, 1H), 6.34 (s, 1H), 4.08 (s, 3H), 4.03 (s, 3H), 3.99 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H), 3.90 (s, 3H). MS (ESI) calculated for  $C_{36}H_{30}O_{10}$ , 622.2; found, 623.1 [M+H]<sup>+</sup>.

#### Amentoflavone (12)

4',5,7,4''',5'',7''-Hexamethoxy-amentoflavone (1 eqv) was dissolved in CHCl<sub>3</sub> and BBr<sub>3</sub> (6 eqv, 1 M solution in CH<sub>2</sub>Cl<sub>2</sub>) was added to the solution and refluxed at 65°C for 10 h. Reaction was monitored by TLC in CHCl<sub>3</sub>-MeOH (20:1). The reaction mixture was cooled to RT followed by adding MeOH to destroy BBr<sub>3</sub>, concentrated *in vacuo*. The crude solid was washed with saturated NaHCO<sub>3</sub> (aqueous), filtered and washed by MeOH to afford the final product as a yellow solid. Yield: 86%. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ 7.99 (d, J=7.8 Hz, 1H), 7.87 (d, J=2.4 Hz, 1H), 7.40 (d, J=8.6 Hz, 2H), 7.19 (d, J=8.4 Hz, 1H), 6.82 (d, J=9.0 Hz, 2H), 6.76 (s, 1H), 6.70 (s, 1H), 6.58 (s, 1H), 6.53 (s, 1H), 6.39 (s, 1H). <sup>13</sup>C-NMR (100 MHz, DMSO-d<sub>6</sub>): δ 180.0, 179.7, 163.2, 162.1, 159.6, 159.1, 158.3, 157.5, 156.1, 155.6, 155.4, 151.8, 130.1, 126.8, 126.6, 123.9, 119.3, 119.0, 114.6, 114.0, 103.1, 102.7, 102.3, 101.1, 91.3, 91.2. Mp: 254~255°C (lit. 254~256°C) [4]. MS (ESI) calculated for  $C_{36}H_{18}O_{10}$ , 538.1; found, 561.0 [M+Na]<sup>+</sup>.



**Scheme 1:** Synthesis of Amentoflavone. Reagents and conditions: a. ICl, CH<sub>3</sub>COOH, 60°C; b. KOH, 2-hydroxy-4,6-dimethoxyacetophenone, MeOH, 0°C; c. I<sub>2</sub>, DMSO, 100°C; d. Bis(pinacolato)diboron, PdCl<sub>2</sub>(dppf), HAc, DMF, 80°C; e. K<sub>2</sub>CO<sub>3</sub>, (CH<sub>3</sub>)<sub>2</sub>SO<sub>4</sub>; f. c-HNO<sub>3</sub>, HAc, CHCl<sub>3</sub>, I<sub>2</sub>, 0°C; g. KOH, *p*-anisaldehyde (compound 1), MeOH, 0°C; h. I<sub>2</sub>, DMSO, 100°C; i. Pd(PPh<sub>3</sub>)<sub>4</sub>, NaOH, DMF: H<sub>2</sub>O (9:1), 80°C; j. BBr<sub>3</sub>, CHCl<sub>3</sub>, 65°C.

## Results

The synthesis of amentoflavone is outlined in Scheme 1 by coupling flavones 5 and 10 which were prepared under reported conditions [12-15]. Briefly, *p*-anisaldehyde (1) was iodinated at the 3-position to afford compound 2. Compound 2 was condensed with 2-hydroxy-4,6-dimethoxyacetophenone to produce the chalcone compound 3. Compound 3 underwent a ring cyclization reaction in the presence of iodine to form the flavone compound 4. The iodine moiety in compound 4 was converted to the pinacol functionality to yield 4',5,7-trimethoxy-3'-pinacolatoboronflavone (5). While the other part, 4',5,7-trimethoxy-8-iodoflavone (10), was synthesized from the starting reagent of 2,4,6-trihydroxyacetophenone (6). Briefly, compound 6 was first methylated at the 2 and 4 position to give the 2-hydroxy-4,6-dimethoxyacetophenone (7). Compound 7 was iodinated at the 3-position to produce compound 8 which was condensed with *p*-anisaldehyde to generate chalcone 9. Compound 9 undertook a ring closure reaction to afford flavone compound 10. A Suzuki reaction was applied by coupling compound 5 and compound 10 to yield the biflavone compound 11. Finally compound 11 was subject to demethylation in the presence of BBr<sub>3</sub> to achieve the final compound-amentoflavone (12).

## Discussion and Conclusion

We have developed an efficient total synthesis of amentoflavone, a valuable natural product, utilizing Suzuki coupling with flavonyl-3'-boronic ester and 8-iodoflavone. This method is similar to but different from the reported procedure [10,11] that coupled the flavonyl-8-boronic acid and 3'-iodoflavone to form amentoflavone. Mass, NMR and melting point confirmed compound 12 is amentoflavone, as compared with data in literatures [4]. The overall yield is about 17% which is highly efficient. The new method provides an alternative method for the synthesis of amentoflavone which can be applied to the generation of other natural and biologically active biflavonoids and biphenyls for which the extensive preclinical development is often hampered by the limited availability of these compounds from natural resources. Therefore, the current work could serve as an excellent solution to the availability of many bioactive biflavonoids.

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