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Synthesis of intermediate derivatives from Schweinfurthin G using chiral ionic liquid

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Abstract. Schweinfurthins possess a wide diversity of important biological and pharmacological activities. To date, more than fifty schweinfurthins and their analogues have been prepared for the investigation of structure-function relationships. Schweinfurthin G, one of the most representative of schweinfurthins containing the hexahydroxanthene moiety, was found to strongly inhibit the growth of cancer cell lines when evaluated on the U87 cell line (EC_{50} of 0.04 µM), and on the KB cell line (IC_{50} of 0.06 µM). Ionic liquids have been regarded as "solvents of the future" and applied in various fields. They have been utilized most widely in modern organic synthesis as an environmentally friendly alternative to conventional organic solvents and catalysts due to their flexible, nonvolatile, noncorrosive, low viscous properties and they still maintain similar and sometimes enhanced chemical selectivity and reactivity of organic reactions. In this paper, we present the synthesis of intermediate compounds **2** and **3**, which are the key compounds for synthesizing the derivatives of schweinfurthin G using chiral ionic liquid. These compounds are the key blocks to further synthesize schweinfurthin G derivatives for biological activity tests.

Keywords: schweinfurthin G derivatives, stilbene, Dess-Martin periodinane oxidation, selenium dioxide oxidation, ionic liquid.

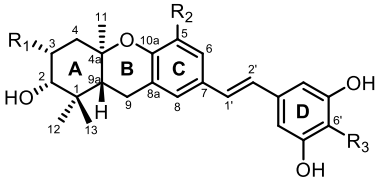
Classification number: 1.1.2., 2.10.2

1. INTRODUCTION

Schweinfurthins (Figure 1) are naturally occurring compounds that possess a 1,2-diphenylethylene skeleton and display a promising and potent differential cytotoxicity against a number of cancer cell lines [1 - 3]. Due to their potential anticancer properties and interesting biological and pharmaceutical properties, their semi-synthesis and total synthesis have received considerable attention from researchers. More than fifty schweinfurthins and their analogues

have been prepared for the investigation of structure-function relationships so far [4 - 8]. It was important to note that the hexahydroxanthene tricyclic core and a stilbene in the *trans* orientation of schweinfurthins are essential for their biological activities [9, 10]. Through comparisons of the cytotoxicity of schweinfurthin analogues with different chemical modifications, it was found that the para-position of the D-ring is a site amenable to modifications without significant loss in biological activity.

Schweinfurthin G is one of the most representative of schweinfurthins containing the hexahydroxanthene moiety, which were originally detected and isolated from *Macaranga alnifolia* [2]. Schweinfurthin G was found to strongly inhibit the growth of cancer cell lines when evaluated on the U87 cell line (EC_{50} of 0.04 µM), and on the KB cell line (IC_{50} of 0.06 µM) [4, 11]. However, only a few papers are available about its total synthesis as well as its derivatives [12]. Our group has been interested in the design, synthesis, and biological evaluation of a series of new schweinfurthin G derivatives that improve their cytotoxicity and increase their stability. Ionic liquids (ILs) have been regarded as "solvents of the future" and applied in various fields such as electrochemistry, nanotechnology, analytical chemistry, and extraction processes, especially in modern organic synthesis [13]. They have been utilized most widely in modern organic synthesis as an environmentally friendly alternative to conventional organic solvents and catalysts due to their flexible, nonvolatile, noncorrosive, low viscous properties and they still maintain similar and sometimes enhanced chemical selectivity and reactivity of organic reactions [14, 15]. In this paper, we present the synthesis of intermediate compounds **2** and **3** using chiral ionic liquid under microwave activation. These compounds are the key compounds for synthesizing the derivatives of schweinfurthin G (scheme 2).



Schweinfurthin A: R_1 = OH, R_2 = OH, R_3 = Geranyl
Schweinfurthin B: R_1 = OH, R_2 = OCH_3, R_3 = Geranyl
Schweinfurthin E: R_1 = OH, R_2 = OCH_3, R_3 = Prenyl
Schweinfurthin F: R_1 = H, R_2 = OCH_3, R_3 = Prenyl
Schweinfurthin G: R_1 = H, R_2 = OH, R_3 = Prenyl
Vedelianin : R_1 = OH, R_2 = OH, R_3 = Prenyl

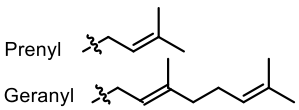


Figure 1. Structures of schweinfurthin G and other schweinfurthins isolated from plants.

2. MATERIALS AND METHODS

2.1. General experimental procedures

Melting points were recorded on a Boetius instrument. ^1H and ^{13}C-NMR spectra were recorded on Bruker 500 and 600 MHz spectrometers as indicated with either the $CDCl_3$ (δ_H 7.24 ppm, δ_C 77.0 ppm) or CD_3OD (δ_H 3.30 ppm, δ_C 49.0 ppm) signal as internal standard. *J* values are expressed in Hz. Flash column chromatography (CC) was performed using silica-gel (Kieselgel 60, 230 - 400 mesh, Merck). For thin layer chromatography (TLC), pre-coated silica-gel 60 F_{254} (0.25 mm, Merck) plates were used. All chemicals were purchased from Merck and Sigma-Aldrich and used without any further purification. Unless otherwise specified, all

reactions were carried out in oven-dried glassware in a nitrogen atmosphere using freshly distilled dry solvents under anhydrous conditions.

2.2. Detailed experiments

2.2.1. General procedure for the synthesis of ((5-((E)-2-((2R,4aR,9aR)-2,5-bis((tert-butyldimetylsilyl)oxy)-1,1,4a-trimetyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-7-yl)vinyl)-2-(3-metylbut-2-en-1-yl)-1,3-phenylene)bis(oxy))bis(tert-butyldimetylsilan) (1)

Added to a rounded bottom flask was schweinfurthin G (100 mg, 0.215 mmol, 1 eq), followed by anhydrous DMF (3 mL), imidazole (146.4 mg, 2.15 mmol, 10 eq), and DMAP (2.62 mg, 0.0215 mmol, 0.1 eq) under a nitrogen atmosphere. Then, TBSCl (325 mg, 2.15 mmol, 10 eq) was slowly added to the reaction mixture at 0 °C. The reaction mixture was then warmed up to room temperature and stirred for 15 hours. When the reaction was completed, water was added to the reaction mixture, and the reaction was extracted with ethyl acetate (3 times x 20 mL). The ethyl acetate phases were combined and dried over sodium sulfate, and the solvent was evaporated under reduced pressure to obtain a crude residue. The crude residue was purified on a silica gel chromatographic column with a gradient *n*-hexane/ethyl acetate mixture, yielding compound **1** as a pale-yellow solid (160 mg, 81 %).

Compound **1**: Pale-yellow solid, ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H (ppm): 0.06 (3H, s, CH_3-Si, TBS); 0.07 (3H, s, CH_3-Si, TBS); 0.17 (3H, s, CH_3-Si, TBS); 0.18 (3H, s, CH_3-Si, TBS); 0.25 (12H, s, 4 x CH_3-Si, TBS); 0.84 (3H, s, CH_3, H-11); 0.90 (9H, s, CH_3 x 3, TBS); 1.01 (27H, s, CH_3 x 9, TBS); 1.02 (3H, s, CH_3, H-12); 1.22 (3H, s, CH_3, H-13); 1.54 - 1.61 (2H, m, H-3); 1.62 (1H, m, H-9a); 1.64 (3H, s, CH_3, H-4″); 1.69 (3H, s, CH_3, H-5″); 1.75 (1H, m, H_a-4); 1.99 (1H, dt, J = 3.0, 13.0 Hz, H_b-4); 2.69 (2H, m, CH_2, H-9); 3.27 (2H, d, J = 6.0 Hz, CH_2, H-1″); 3.37 (1H, dd, J = 4.0, 11.5 Hz, H-2); 5.14 (1H, t, J =7.0 Hz, H-2″); 6.55 (2H, s, H-4′ + H-8′); 6.73 (1H, d, J =16.0 Hz, H-2′); 6.77 (1H, d, J =16.0 Hz, H-1′); 6.81 (1H, d, J =2.0 Hz, H-6); 6.86 (1H, d, J =2.0 Hz, H-8). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C (ppm): -4.9 (CH_3, TBS); -4.3 (CH_3, TBS); -4.2 (CH_3, TBS); -4.1 (CH_3, TBS); -4.0 (CH_3, TBS); -3.9 (CH_3, TBS); 14.8 (C-12); 18.0 (C_q, TBS); 18.1 (C_q, TBS); 18.4 (C_q, TBS); 18.5 (C_q, TBS); 20.1 (C-5″); 23.4 (C-9); 23.5 (C-3); 25.5 (C-11); 25.8 (CH_3, TBS); 25.8 (CH_3, TBS); 25.9 (C-12); 27.9 (C-13); 28.7 (C-1″) ; 37.9 (C-4); 39.0 (C-1); 47.1 (C-9a); 77.2 (C-4a); 78.6 (C-2); 109.9 (CH, C-4′+C-8′); 116.7 (C-6); 120.9 (C-8); 123.1 (C-6″); 123.2 (C-7); 124.0 (C-8a); 126.4 (C-2′); 127.9 (C-1′); 128.9 (C-3″); 130.4 (C-2″); 135.9 (C-3′); 144.5 (C-5); 144.6 (C-10a); 154.7 (C-5′ + C-7′).

2.2.2. General procedure for the synthesis of (E)-4-(4-((E)-2-((4aR,9aR)-2,5-bis((tert-butyldimetylsilyl)oxy)-1,1,4a-trimetyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-7-yl)vinyl)-2,6-bis((tert-butyldimetylsilyl)oxy)phenyl)-2-metylbut-2-en-1-ol (2)

Added to a rounded 25 mL flask was compound **1** (150 mg, 0.163 mmol, 1 eq), followed by a mixture of CH_2Cl_2 and MeOH (CH_2Cl_2 :MeOH (4:1)). Then, SeO_2 (18.1 mg, 0.163 mmol, 1 eq) and *t*-BuOOH (70 % in water) (21 mg, 0.163 mmol, 1 eq) were added to the above solution at 0 °C, respectively. The reaction mixture was raised to room temperature and stirred at room temperature. After 48 hours, the reaction was stopped when no significant change in compound **1** was observed on the TLC plate. Water was added to the reaction, and the resulting mixture was extracted with ethyl acetate (3 times × 30 mL). The ethyl acetate layers were combined and dried over sodium sulfate, and the solvent was evaporated under reduced pressure to obtain a crude residue. The crude residue was purified on a silica gel chromatographic column (*n*-

hexane/ethyl acetate gradient) to afford compound **2** (yellow solid, 31.5 mg, 24 % yield), compound **3** (yellow solid, 43.3 mg, 33 % yield), and recover starting material **1** (37.5 mg, 25 %).

Compound **2**: Yellow solid, ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H (ppm): 0.06 (3H, s, CH_3-Si, TBS); 0.08 (3H, s, CH_3-Si, TBS); 0.17 (3H, s, CH_3-Si, TBS); 0.19 (3H, s, CH_3-Si, TBS); 0.26 (12H, s, 4 x CH_3-Si, TBS); 0.84 (3H, s, CH_3, H-11); 0.91 (9H, s, CH_3 x 3, TBS); 1.01 (27H, s, CH_3 x 9, TBS); 1.02 (3H, s, CH_3, H-12); 1.22 (3H, s, CH_3, H-13); 1.54 - 1.61 (2H, m, H-3); 1.62 (m, 1H, H-9a); 1.72 (1H, m, H_b-4); 1.77 (3H, s, H-4″); 2.00 (1H, dt, *J* = 3.0, 12.5 Hz, H_b-4); 2.69 (2H, m, H-9); 3.34 (2H, d, *J* = 6.5 Hz, H-1″); 3.37 (1H, dd, *J* =4.0, 11.5 Hz, H-2); 3.96 (2H, s, H-5″); 5.45 (1H, t, *J* =7.0 Hz, H-2″); 6.56 (2H, s, H-4′ + H-8′); 6.71 (1H, d, *J* =16.0 Hz, H-2′); 6.74 (1H, d, *J* =16.0 Hz, H-1′); 6.81 (1H, d, *J* =2.0 Hz, H-6); 6.87 (1H, d, *J* =2.0 Hz, H-8). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C (ppm): -4.9 (CH_3, TBS); -4.3 (CH_3, TBS); -4.2 (CH_3, TBS); -4.1 (CH_3, TBS); -4.0 (CH_3, TBS); -3.9 (CH_3, TBS); 14.1 (C-12); 14.8 (C-4″); 18.1 (C_q, TBS); 18.4 (C_q, TBS); 18.5 (C_q, TBS); 18.5 (C_q, TBS); 20.1 (C-5″); 23.1 (C-9); 23.5 (C-3); 25.8 (C-11); 25.9 (CH_3, TBS); 25.9 (CH_3, TBS); 27.9 (C-13); 28.7 (C-1″) ; 37.9 (C-4); 39.0 (C-1); 47.1 (C-9a); 69.3 (C-5″); 77.2 (C-4a); 78.6 (C-2); 109.9 (CH, C-4′+C-8′); 116.7 (C-6); 121.0 (C-8); 122.1 (C-6″); 123.2 (C-7); 126.2 (C-2″); 126.3 (C-2′); 128.1 (C-1′); 128.9 (C-3″); 134.1 (C-8a); 136.3 (C-3′); 144.6 (C-5); 144.7 (C-10a); 154.8 (C-5′ + C-7′).

Compound **3**: Yellow solid, ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H (ppm): 0.07 (3H, s, CH_3-Si, TBS); 0.08 (3H, s, CH_3-Si, TBS); 0.17 (3H, s, CH_3-Si, TBS); 0.19 (3H, s, CH_3-Si, TBS); 0.27 (12H, s, 4 x CH_3-Si, TBS); 0.85 (3H, s, CH_3, H-11); 0.91 (9H, s, CH_3 x 3, TBS); 0.99 (18H, s, CH_3 x 6, TBS); 1.01 (3H, s, CH_3, H-12); 1.02 (9H, s, CH_3 x 3, TBS); 1.23 (3H, s, CH_3, H-13); 1.61 (1H, m, H-3); 1.62 (m, 1H, H-9a); 1.71 (1H, m, H_a-4); 1.83 (3H, s, CH_3, H-4″); 2.00 (1H, dt, *J* =3.0, 9.5 Hz, H_b-4); 2.69 (2H, m, CH_2, H-9); 3.37 (1H, dd, *J* =4.0, 11.5 Hz, H-2); 3.63 (2H, d, *J* =5.5 Hz, CH_2, H-1″); 6.53 (1H, t, *J* =7.0 Hz, H-2″); 6.58 (2H, s, H-4′ + H-8′); 6.71 (1H, d, *J* =16.0 Hz, H-2′); 6.74 (1H, d, *J* =16.0 Hz, H-1′); 6.81 (1H, d, *J* =2.0 Hz, H-6); 6.86 (1H, d, *J* =2.0 Hz, H-8), 9.34 (1H, s, CHO). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C (ppm): -4.9 (CH_3, TBS); -4.3 (CH_3, TBS); -4.2 (CH_3, TBS); -4.1 (CH_3, TBS); -4.0 (CH_3, TBS); -3.9 (CH_3, TBS); 9.4 (C-4″); 14.8 (C-12); 18.1 (C_q, TBS); 18.3 (C_q, TBS); 18.5 (C_q, TBS); 18.5 (C_q, TBS); 20.1 (C-11); 23.5 (C-9); 24.6 (C-3); 25.8 (CH_3, TBS); 25.9 (CH_3, TBS); 27.9 (C-13); 28.7 (C-1″) ; 37.9 (C-4); 39.0 (C-1); 47.1 (C-9a); 77.2 (C-4a); 78.6 (C-2); 109.7 (CH, C-4′+C-8′); 116.7 (C-6); 119.3 (C-6′); 121.1 (C-6); 123.2 (C-8a); 125.9 (C-8); 128.6 (C-1′); 128.7 (C-2′); 129.5 (C-7); 137.2 (C-3′); 138.7 (C-3″); 144.6 (C-5); 144.9 (C-10a); 154.9 (C-5′ + C-7′); 155.2 (C-2″), 195.3 (C=O).

2.2.4. General procedure for the synthesis of (E)-4-(4-((E)-2-((4aR,9aR)-2,5-bis((tert-butyldimetylsilyl)oxy)-1,1,4a-trimetyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-7-yl)vinyl)-2,6-bis((tert-butyldimetylsilyl)oxy)phenyl)-2-metylbut-2-en-1-ol (2)

$NaBH_4$ (2.3 mg, 0.06 mmol, 1.5 eq) was slowly added to a cooled solution (0 ^{o}C, bath temperature) of compound **3** (30 mg, 0.04 mmol, 1 eq) in anhydrous THF (2 mL) under argon . The resulting mixture was stirred at 0 ^{o}C for 10 minutes, then warmed up to room temperature and stirred for one hour. When the reaction was completed, the mixture was cooled, poured into a mixture of ice and water, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by column chromatography (silica gel, elution by *n*-hexane/ethyl acetate) to afford product **2** as a pale yellow oil (75 % yield).

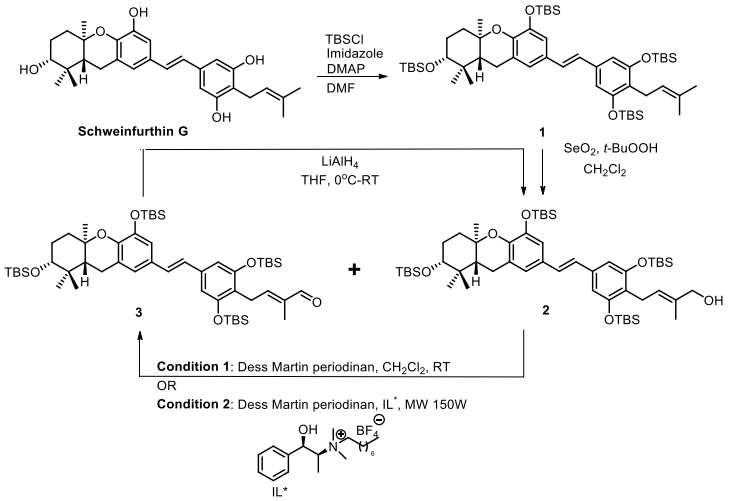
2.2.5. General procedure for the synthesis of (E)-4-(4-((E)-2-((4aR,9aR)-2,5-bis((tert-butyldimetylsilyl)oxy)-1,1,4a-trimetyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-7-yl)vinyl)-2,6-bis((tert-butyldimetylsilyl)oxy)phenyl)-2-metylbut-2-enal (3) without ionic liquid

Added to a rounded-bottom flask were compound **2** (100 mg, 0.124 mmol, 1 eq) and DMP (157.8 mg, 0.372 mmol, 3eq) in anhydrous CH_2Cl_2 (3 mL) at room temperature. The reaction was then stirred at room temperature for 6 hours. After the reaction was completed, the reaction mixture was added with water, extracted with ethyl acetate (3 times × 10 ml). The ethyl acetate phases were dried over anhydrous sodium sulfate and the solution was evaporated under reduced pressure to obtain a crude residue. The crude residue was purified on a silica gel column (*n*-hexane/EtOAc gradient) to yield compound **3** as a yellow powder (75 mg, 75 %).

2.2.6. General procedure for the synthesis of (E)-4-(4-((E)-2-((4aR,9aR)-2,5-bis((tert-butyldimetylsilyl)oxy)-1,1,4a-trimetyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-7-yl)vinyl)-2,6-bis((tert-butyldimetylsilyl)oxy)phenyl)-2-metylbut-2-enal (3) using ionic liquid

Compound **2** (200 mg, 0.248 mmol, 1 eq) and the ionic liquid *N*-octyl-*N*-methylephedrinium tetrafluoroborate (940.5 mg, 2.48 mmol, 10 eq) were placed into the reaction vessel. Then DMP (315.5 mg, 0.744 mmol, 3 eq) was added to the reaction mixture, which was then irradiated with microwaves at 150 W for 15 minutes. After the reaction was completed, the reaction mixture was added with water, extracted with ethyl acetate (3 times × 20 ml). The ethyl acetate phases were dried over anhydrous sodium sulfate, and the solution was evaporated under reduced pressure to obtain a crude residue. The crude residue was purified on a silica gel column (*n*-hexane/EtOAc gradient) to yield compound **3** as a yellow powder (184 mg, 92 %).

3. RESULTS AND DISCUSSION



Scheme 1. Synthesis of alcohol **2** and aldehyde **3**.

Our strategy for the synthesis of schweinfurthin derivatives is based on the extension of the side chain at the D-ring of schweinfurthin G. From this perspective, the synthesis of schweinfurthin G derivatives consists of four main steps: (1) introduction of the hydroxyl protecting group, (2) modification of the isoprenyl group of schweinfurthin G (more correctly, selenium-mediated allylic oxidation of the isoprenyl side chain), (3) employment of the multicomponent reactions to the modified isoprenyl chain, and (4) deprotection of protecting groups to obtain schweinfurthin G derivatives. In this paper, steps 1 and 2 were described in detail (Scheme 1).

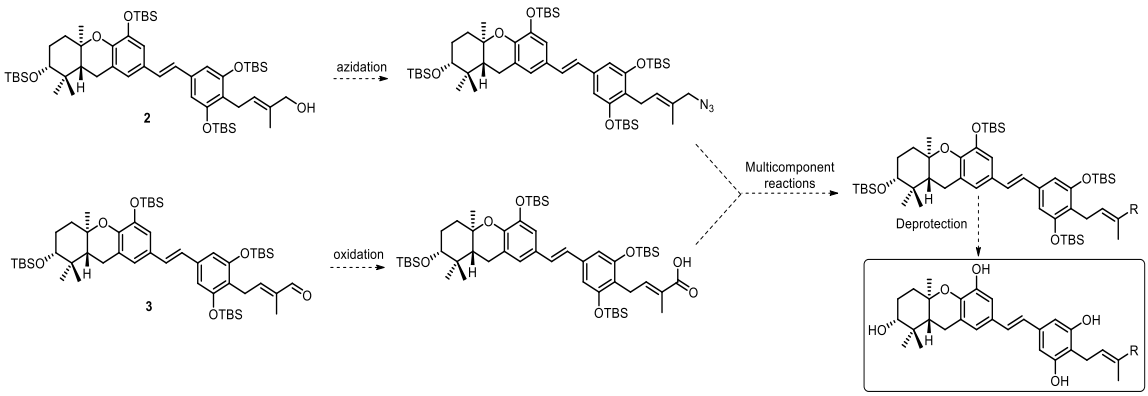
Initial synthetic efforts were focused on the trials of protecting groups for the hydroxyl groups. Silyl ethers are usually used as protecting groups for alcohols in organic synthesis. In our process, the *tert*-butyl(dimethyl)silyl (TBS) group was chosen to be an appropriate protecting group due to its simple installation, its stability under various reaction conditions, and its mild removal at the end of the synthesis process with high selectivity [16]. Thus, schweinfurthin G was treated with dimethyl-*tert*-butylsilyl chloride (10 eq), imidazole (10 eq) and DMAP (0.1 eq) in anhydrous dimethylformamide at room temperature for 15 hours, producing the tetra-silyl ether **1** in 81 % yield.

After the protection of schweinfurthin G was successful with a good yield, the modification of the isoprenyl side chain of **1**, also the key reaction in our strategy, was carried out through the oxidation with *tert*-butyl hydroperoxide/selenium dioxide in dichloromethane and methanol. Changing the proportion of selenium dioxide from the catalytic amount to the stoichiometric amount had little effect on the formation of alcohol **2** and aldehyde **3**. The rate of reaction was faster, compounds **2** and **3** were obtained in 24 % and 33 % yield, respectively, and about 25 % of the starting material **1** remained unreacted. It was interesting to note that in the ^{1}H-NMR spectrum of compound **3**, the chemical shift of the adjacent proton of the aldehyde proton was shifted to downfield due to the conjugated effect with the aldehyde group (δ_H ~ 6.53 ppm, in $CDCl_3$). Upon each purpose, alcohol **2** and aldehyde **3** could be converted to each other. Aldehyde **3** could be easily reduced to alcohol **2** through a $NaBH_4$ reduction in anhydrous THF (75 % yield). Moreover, alcohol **2** could be oxidized to the corresponding aldehyde **3** using hypervalent iodine reagents Dess-Martin-Periodinane (DMP) or iodoxybenzoic acid (IBX). The oxidation reaction was faster and cleaner in ionic liquids as compared to conventional solvents and it was easy to recover the ionic liquid after the reaction. In this paper, *N*-octyl-*N*-metylephedrinium tetrafluoroborate, a chiral ionic liquid possessing a chiral ephedrinium cation, was chosen to use in the oxidation reaction.

Table 1. IBX- and DMP-promoted oxidation of alcohol **2** into aldehyde **3** under various conditions.

Entry	Reagent	Conditions	Yield (%)
1	Dess-Martine Periodinane	CH_2Cl_2, RT, 6 hours	75
2	Dess-Martine Periodinane	IL*, MW 150 W, 15 minutes	92
3	2-Iodoxybenzoic acid	THF, 60 ^oC, 5 hours	70
4	2-Iodoxybenzoic acid	IL*, MW 150 W, 1 hour	85

The Dess-Martin oxidation of alcohol **2** proceeded smoothly upon treatment with Dess-Martine under microwave irradiation, affording the corresponding aldehyde **3** in 92 % yield in 15 minutes, compared with 75 % yield in 6 hours when using the conventional method (in CH_2Cl_2). When IBX was used without ionic liquid, the reaction required higher temperature (60 ^oC) in THF to obtain product **3** in moderate yield (70 %). The yield of the reaction was improved (85 %) when IBX was immobilized in ionic liquids, and the oxidation reaction underwent smoothly under milder conditions (entry 4, Table 1). In all of the oxidation experiments, no over-oxidation of aldehyde **3** to the corresponding carboxylic acid was observed. Thus, the use of a recyclable ionic liquid made this oxidation reaction simple, more convenient, and avoided the use of toxic organic solvents such as THF and CH_2Cl_2.



Scheme 2. Future direction of synthesis of schweinfurthin G derivatives.

4. CONCLUSIONS

In summary, the intermediates alcohol **2** and aldehyde **3** have been successfully synthesized from schweinfurthin G, using chiral ionic liquid. These compounds are the key blocks to further synthesize schweinfurthin G derivatives for biological activity tests (Scheme 2).

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CRediT authorship contribution statement. Pham Van Cuong and Doan Thi Mai Huong contributed to the co design of the study and wrote the manuscript. Nguyen Thuy Linh, Bui Thi Minh Anh, Tran Van Hieu, Phi Thi Dao and Tran Thu Huong performed experiments and analyzed data. All authors contributed to the manuscript revision, and read and approved the submitted version.

Declaration of competing interest. We declare that we have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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