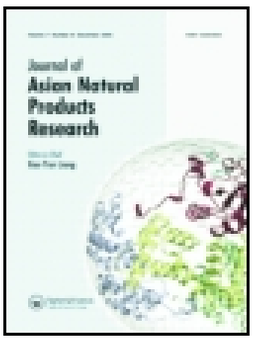

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The synthesis of dendroflorin

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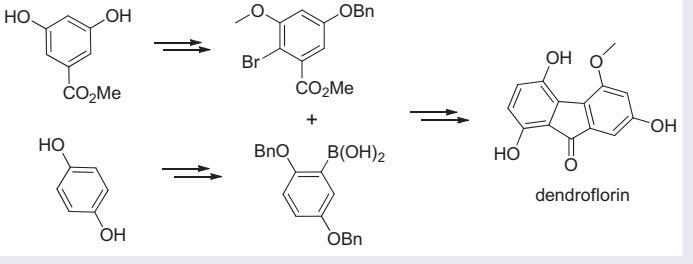
ABSTRACT

The first synthesis of dendroflorin has been achieved in 10 steps with an overall yield of 5.5%. The key step in the synthesis features the biphenyl structure is built through Suzuki–Miyaura reaction. In addition, the *ortho*-localization effect induced by aromatic substituent during the bromination of intermediate **8** is also observed and discussed.



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KEYWORDS
Total synthesis; dendroflorin; Suzuki–Miyaura reaction; localization effect

1. Introduction

Dendroflorin (=1,4,7-trihydroxy-5-methoxy-9*H*-fluoren-9-one, **1**, Figure 1) is a naturally occurring fluorenone isolated from the genus of *Dendrobium* (*D. densiflorum* [1,2], *D. nobile* [3], *D. thyrsiflorum* [4], and *D. brymerianum* [5]) and *Arundina* (*A. gramnifolia* [6]) of the family of Orchidaceae, which exhibited diverse bioactivities such as antisenescence [7], antioxidant [3], anti-tumor [5,8], and immunomodulatory [3]. Two natural fluorenone analogs, dengibsin (**2**) and dengibsinin (**3**), had been synthesized in 1987 in which the diphenyl structure was constructed by Ullman reaction via bromobenzene derivatives [9].

Inspired by the potential bioactivities of natural fluorenones, we sought to develop a synthesis of dendroflorin through Suzuki–Miyaura reaction. The retrosynthetic analysis was shown in Scheme 1, in which the fluorenone structure of dendroflorin was constructed by borophenylic acid **6** and bromobenzoic ester **9** through a Suzuki–Miyaura reaction,

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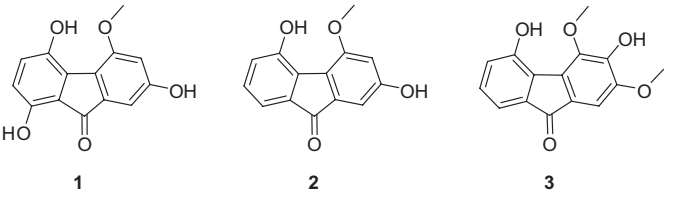
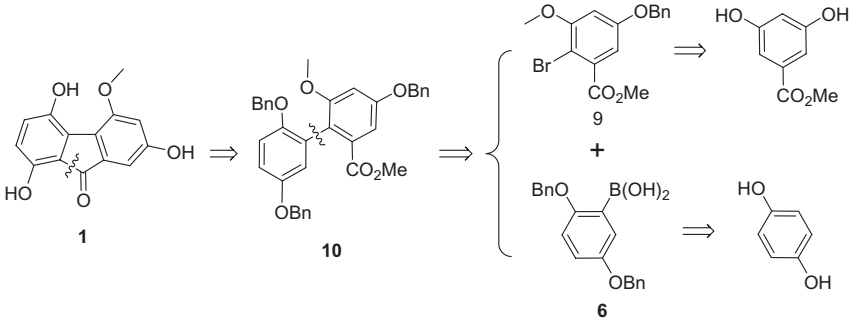
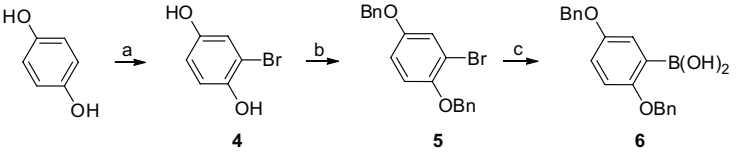


Figure 1. Structures of natural fluorenones.



Scheme 1. Retrosynthetic analysis of **1**.



Reagents and conditions: (a) Br_2, CH_2Cl_2, 0 to 25°C, 4h. 92%; (b) BnBr, K_2CO_3, acetone, reflux, 17h. 89%; (c) (i) n-BuLi, $B(OEt)_3$, THF, -78 to 25°C, 12h; (ii) aq. HCl, pH=3, 25°C, overnight. 81%

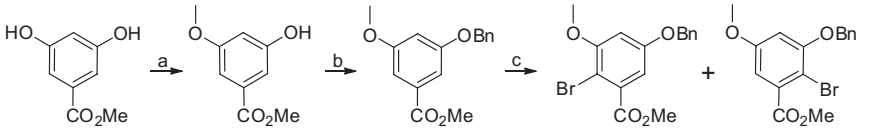
Scheme 2. Synthesis of borophenylic acid **6**.

while the intermediates **6** and **9** were designed from commercially available hydroquinone and methyl 3,5-dihydroxybenzoate, respectively. Herein, we describe the total synthesis of dendroflorin in 10 steps.

2. Results and discussion

The intermediate **6** was synthesized according to routine in Scheme 2. Hydroquinone was treated with liquid bromine to get **4** [10]. After protection as its benzyl ether (BnBr, K_2CO_3, 89%), **5** was dissolved in anhydrous tetrahydrofuran (THF) and cooled down to −78 °C, then n-BuLi and $B(OEt)_3$ were added slowly and separately [11]. Corresponding (2,5-bis(benzyloxy)phenyl)-boronic acid (**6**) was obtained in 66% yield without further purification.

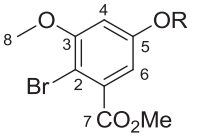
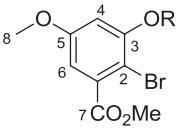
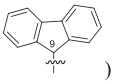
Methyl 3,5-dihydroxybenzoate was methylated, then benzylated to offer methyl 5-(benzyloxy)-3-methoxybenzoate (**8**) (Scheme 3) [12]. To our surprise, the main bromination



Reagents and conditions: (a) Me_2SO_4, K_2CO_3, acetone, reflux, 8h. 53%; (b) BnBr, K_2CO_3, acetone, reflux, 17h. 92%; (c) NBS, CH_3CN, 0 to 25°C

Scheme 3. Synthesis of bromobenzoic ester **9**.

Table 1. Brominated products of **8**, **12**, and **13**.

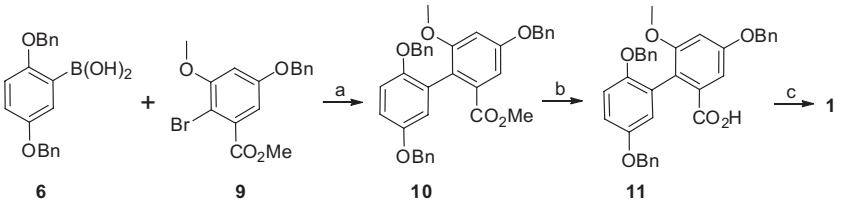
	Products (yield[a])		
Reactant			Ratio
8 (R= )	**9** (33%)	**9b** (51%)	1:1.54
12 (R = )	**12a** (21%)	**12b** (60%)	1:2.86
13 (R = )	**13a** (24%)	**13b** (64%)	1:2.67

[a]Isolated yield.

product was **9b** rather than the target **9** when **8** was brominated by *N*-bromosuccinimide (NBS), even with larger steric hindrance from the benzyloxy orientation (Table 1). A possible reason is that the aromatic substituent (Bn) could form more stable intermedia than methoxyl through dispersing the bromine cation produced by NBS and resulted in preferential bromide. In order to prove the hypothesis, we synthesized **12** and **13** in which the benzyl of **8** was replaced by two stronger conjugated systems, diphenylmethylene or fluorene-9-yl, respectively [13]. The brominated results of **12** and **13** were shown in Table 1, which confirmed the localization effect from the aromatic groups and showed a positive correlation between the intensity of conjugated system and the isomer yield.

Biphenyl core **11** was formed via Suzuki coupling reaction [14] between **6** and **9** followed by hydrolysis of biphenyl ester **10** in H_2O/THF 1:1. Finally, dendroflorin (**1**) was achieved by acylation and intermolecular Friedel–Crafts reaction of **11** and deprotection under the catalysis of $AlCl_3$ at the same time (Scheme 4).

In summary, we have achieved the synthesis of dendroflorin via Suzuki–Miyaura reaction starting from commercially available hydroquinone and methyl-3,5-dihydroxybenzoate. The overall yield of dendroflorin in 10 steps was 5.5%. During the synthesis of **9**, an *ortho*-localization effect by benzyl group through carbocation-π interaction was observed and validated via extending aromatic ring system. Further research for the systematic mechanism is under way in our laboratory.



Reagents and conditions: (a) $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, seal tube, 135°C, 24h. 84%; (b) NaOH, H_2O/THF 1: 1, 90°C,18h. 95%; (c) (i) oxalyl chloride, DMF, CH_2Cl_2, 25°C, 3h; (ii) $AlCl_3$, CH_2Cl_2, 0 to 25°C, 4.5h. 65%.

Scheme 4. Synthesis of dendroflorin (**1**).

3. Experimental

3.1. General experimental procedures

All reactions were performed with dry solvents under anhydrous conditions, unless otherwise noted. Dry THF was distilled over sodium. Acetonitrile (CH_3CN), 1,4-dioxane, trichloromethane ($CHCl_3$), and dichloromethane (CH_2Cl_2) were distilled over calcium hydride. Solvents, starting materials, and reagents used in reactions were obtained commercially from SCRC (Sinopharm Chemical Reagent Co., Ltd, Shanghai, China), J&K Scientific (Chaoyang, Beijing, China), Accela (San Diego, CA, USA), or Adamas (Songjiang, Shanghai, China) and were used without purification, unless otherwise indicated. Silica gel (200–300 mesh, Qingdao Marine Chemical Ltd., Qingdao, China), petroleum ether (PE), acetone, and ethyl acetate (EA) were used for product purification through flash column chromatography. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE III 500 spectrometer (Bruker, Ettlingen, Germany) at 500 (for ^1H) or 125 (for ^{13}C) MHz with TMS as an internal standard. ESI-MS and HRESIMS were obtained on a Bruker Esquire 3000plus (Bruker) and a Waters/Micromass Q-TOF-Ultima mass spectrometers (Waters, Milford, MA, USA), respectively.

3.2. General procedures for the synthetic compounds

3.2.1. Preparation of 2-bromobenzene-1,4-diol (4)

To a 0 °C solution of hydroquinone (10 g, 91 mmol) in $CHCl_3$ (80 ml), bromine (4.68 ml, 91 mmol) was added within 15 min, and the mixture was stirred for 3 h at room temperature. The reaction was concentrated and quenched with 10% $Na_2S_2O_3$ (100 ml). The aqueous phase was extracted with EA (50 ml for 3 times). The organic phase was washed with brine (50 ml) and dried over anhydrous Na_2SO_4, filtered under reduced pressure, and the organic phase concentrated under vacuum. Crude was purified by flash chromatography using PE/acetone (4:1) to yield **4** (15.8 g, 92%) as a light grey solid.

3.2.2. Preparation of 2-bromo-1,4-dibenzyloxy-benzene (5)

Compound **4** (1.89 g, 10 mmol) and K_2CO_3 (2.76 g, 20 mmol) were dissolved in acetone (60 ml), and then benzyl bromide (3.56 g, 30 mmol) was added. The resulting mixture was heated to reflux until TLC showed complete consumption of the hydroquinone (15 h), and the mixture was concentrated *in vacuo*, purified by column chromatography directly using PE/EA (30:1) to give **5** (3.29 g, 89%) as a white solid.

3.2.3. Preparation of (2,5-bis(benzyloxy)phenyl)boronic acid (6)

n-BuLi (1.6 M in hexane, 4.13 ml, 6.6 mmol) was added dropwise to a stirred solution of **5** (2.22 g, 6 mmol) in THF (40 ml) at –78 °C, reamined at the temperature for 1 h, followed by the dropwise addition of triisopropyl borate (4.2 ml, 18 mmol) at –78 °C. This temperature was maintained for 10 min, after which the solution was warmed to room temperature and stirred overnight. The reaction was quenched with a 1 N aqueous HCl solution (50 ml), and the residue was extracted with EA (40 ml for 3 times). The organic layer was separated, washed with brine (50 ml), dried by anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to yield **6** as a white solid (1.63 g, 81% yield) without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 3.2 Hz, 1H), 7.40 (m, 10H), 7.02 (dd, J = 8.9, 3.2 Hz, 1H), 6.90 (d, J = 8.9 Hz, 1H), 6.10 (br s, 2H), 5.08 (s, 2 H), 5.04 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.4, 153.3, 137.3, 137.2, 136.3, 129.1 (2C), 128.7 (2C), 128.0, 127.9 (2C), 127.7 (2C), 127.6, 122.1, 119.7, 112.8, 71.4, 70.7. HRESIMS: m/z 333.1302 $[M - H]^-$ (calcd for $C_{20}H_{18}BO_4$, 333.1298).

3.2.4. Preparation of methyl 3-hydroxy-5-methoxybenzoate (7)

To a solution of methyl 3,5-dihydroxybenzoate (10 g, 59.5 mmol) and K_2CO_3 (16.4 g, 119 mmol) in acetone (80 ml), dimethylsulfate (7.6 g, 59.5 mmol) was added. The reaction mixture was stirred at reflux for 6 h. The residue was filtered and concentrated *in vacuo*. Crude was purified by flash chromatography using PE/EA (4:1) to yield **7** (5.75 g, 53%) as a white solid.

3.2.5. Preparation of methyl 3-(benzyloxy)-5-methoxybenzoate (8)

To a solution of **7** (4.37 g, 24 mmol) and K_2CO_3 (6.6 g, 48 mmol) in acetone (60 ml), BnBr (6.2 g, 50.6 mmol) was added. The reaction mixture was stirred at reflux for 6 h. The residue was filtered and concentrated *in vacuo*. Crude was purified by flash chromatography using PE/EA (10:1) to yield **8** (6.012 g, 92%) as colorless oil.

3.2.6. Preparation of methyl 5-(benzyloxy)-2-bromo-3-methoxybenzoate (9) and methyl 3-(benzyloxy) -2-bromo-5-methoxybenzoate (9b)

To a 0 °C solution of **8** (5.446 g, 20 mmol) in 150 ml CH_3CN, a solution of NBS (3.667 g, 20.6 mmol) in 50 ml CH_3CN was added via addition funnel. The solution was allowed to come to room temperature and stirred for 24 h. The reaction was concentrated and quenched with 10% $Na_2S_2O_3$ (100 ml). The aqueous phase was extracted with EA (50 ml for 3 times). The organic phase was washed with brine (50 ml) and dried over anhydrous Na_2SO_4, filtered under reduced pressure, and the organic phase was concentrated under vacuum. Crude was purified by flash chromatography using PE/EA (15:1) to yield **9** (2.32 g, 33%) and **9b** (3.58 g, 51%) as white solids. **9**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (br d, J = 8.2 Hz, 2H), 7.40 (br t, J = 7.6 Hz, 2H), 7.35 (tt, J = 6.8, 1.9 Hz, 1H), 6.90 (d, J = 2.8 Hz, 1H), 6.66 (d, J = 2.8 Hz, 1H), 5.07 (s, 2H), 3.94 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 158.7, 157.2, 136.0, 134.8, 128.7 (2C), 128.3, 127.6 (2C), 107.1, 103.1, 102.4, 70.6, 56.6, 56.6; NOESY (500 MHz, $CDCl_3$): H-4/H_2-9, H-4/H_3-8, H-6/H_2-9. HRESIMS m/z 349.0084 $[M - H]^-$ (calcd for $C_{16}H_{14}{}^{79}BrO_4$, 349.0081). **9b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (br d, J = 7.5 Hz, 2H), 7.40 (br t, J = 7.6 Hz, 2H), 7.33 (br t, J = 7.4 Hz, 1H), 6.82 (d, J = 2.8 Hz, 1H), 6.62 (d, J = 2.8 Hz, 1H), 5.15 (s, 2H), 3.94 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 159.4, 156.2, 136.0, 134.9, 128.7 (2C), 128.1, 127.0 (2C), 106.7,

104.1, 102.9, 71.2, 55.7, 52.6; NOESY (500 MHz, $CDCl_3$): H-4/H_2-9, H-4/H_3-8, H-6/H_3-8. HRESIMS: *m/z* 349.0087 $[M - H]^-$ (calcd for $C_{16}H_{14}{}^{79}BrO_4$, 349.0081).

3.2.7. Preparation of methyl 2′,4,5′-tris(benzyloxy)-6-methoxy-[1,1′-biphenyl]-2-carboxylate (10)

To a mixture of **6** (1.5 g, 4.5 mmol), **9** (1.053 g, 3 mmol), K_2CO_3 (1,242 g, 9 mmol), and tetrakis-(triphenylphosphine)-palladium (173 mg, 0.15 mmol) in a seal tube, 1,4-dioxane (8 ml) was added. The system was protected with argon gas. The reaction mixture was stirred at 135 °C for 24 h. The reaction was quenched with water (60 ml). The aqueous phase was extracted with diethyl ether (30 ml for 3 times). The organic phase was combined and washed with brine (50 ml) and dried over anhydrous Na_2SO_4, filtered under reduced pressure, and the organic phase was concentrated under vacuum. Crude was purified by flash chromatography using PE/EA (10:1) to yield **10** (1.412 g, 84%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.40 (m, 15H), 7.23 (d, J = 2.7 Hz, 1H), 6.90 (d, J = 2.7 Hz, 1H), 6.86 (d, J = 8.9 Hz, 1H), 6.83 (dd, J = 8.9, 2.7 Hz, 1H), 6.66 (d, J = 2.7 Hz, 1H), 5.08 (s, 2H), 5.06 (s, 2H), 4.99 (s, 2H), 3.93 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3, 158.8, 157.4, 153.7, 149.8, 136.9, 136.8, 136.2, 134.9, 128.9 (2C), 128.8 (2C), 128.7 (2C), 128.5, 128.2, 128.1, 127.8 (2C), 127.6 (2C), 127.3 (2C), 120.2, 115.5, 114.8, 113.3, 107.3, 103.3, 102.5, 72.0, 70.9, 70.7, 56.7, 52.7. HRESIMS: *m/z* 559.2127 $[M - H]^-$ (calcd for $C_{36}H_{31}O_6$, 559.2126).

3.2.8. Preparation of 2′,4,5′-tris(benzyloxy)-6-methoxy-[1,1′-biphenyl]-2-carboxylic acid (11)

To a mixture of **10** (1.4 g, 2.5 mmol) and NaOH (1 g, 25 mmol), water/THF (2:1, 40 ml) was added. The reaction mixture was stirred at 90 °C for 24 h. The reaction was quenched with 1 N aqueous HCl solution and pH value was adjusted to 1. The aqueous phase was extracted with EA (30 ml for 3 times). The organic phase was dried over anhydrous Na_2SO_4, filtered under reduced pressure, and the organic phase was concentrated then under vacuum to yield **11** (1.3 g, 95%) as a white solid without further purification.

3.2.9. Preparation of dendroflorin (1)

To a 0 °C solution of **11** (1.1 g, 2 mmol) in 10 ml CH_2Cl_2, aluminum chloride (1.1 g, 8.2 mmol) was added. The solution was allowed to come to room temperature and stirred for 3 h. The reaction was quenched with crushed ice (20 ml) and 1 N aqueous HCl solution (30 ml). The mixture was extracted with CH_2Cl_2 (30 ml for 3 times). The organic phase was combined and washed with brine (50 ml) and dried over anhydrous Na_2SO_4, filtered under reduced pressure, and the organic phase was concentrated then under vacuum. Crude was purified by flash chromatography using PE/CH_2Cl_2 (2:1) to yield **1** (334 mg, 65%) as red solid. ^1H NMR (500 MHz, $CDCl_3$): δ 8.45 (br s, 1H), 8.39 (s, 1H), 6.89 (d, J = 9.0 Hz, 1H), 6.81 (d, J = 1.7 Hz, 1H), 6.62 (d, J = 9.0 Hz, 1H), 6.58 (d, J = 1.7 Hz, 1H), 4.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 185.3, 157.8, 152.8, 152.5, 144.2, 136.8, 128.6 (2C), 119.3 (2C), 116.6, 105.2, 104.9, 56.8. HRESIMS: *m/z* 257.0457 $[M - H]^-$ (calcd for $C_{14}H_9O_5$, 257.0455).

3.2.10. Preparation of methyl 3-(benzhydryloxy)-5-methoxybenzoate (12)

To a solution of **7** (1.1 g, 6 mmol) and K_2CO_3 (1.66 g, 12 mmol) in anhydrous acetone (20 ml), (bromomethylene)-dibenzene (2.96 g, 12 mmol) was added. The reaction mixture

was stirred at reflux for 12 h. The residue was filtered and concentrated in vacuo. Crude was purified by flash chromatography using PE/EA (10:1) to yield **12** (1.63 g, 78%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (br d, J = 7.7 Hz, 4H), 7.33 (br t, J = 7.3 Hz, 4H), 7.27 (dd, J = 2.3, 1.3 Hz, 1H), 7.26 (br t, J = 7.3 Hz, 2H), 7.13 (dd, J = 2.3, 1.3 Hz, 1H), 6.71 (t, J = 2.0 Hz, 1H), 6.25 (s, 1H), 3.86 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 160.5, 159.0, 140.8 (2C), 131.9, 128.7 (4C), 126.9 (4C), 126.6 (2C), 109.9, 107.6, 107.2, 81.9, 55.5, 52.2. HRESIMS: *m/z* 347.1286 $[M - H]^-$ (calcd for $C_{22}H_{19}O_4$, 347.1289).

3.2.11. Preparation of methyl 5-(benzhydryloxy)-2-bromo-3-methoxybenzoate (12a) & methyl 3-(benzhydryloxy)-2-bromo-5-methoxybenzoate (12b)

To a 0 °C solution of **12** (1.045 g, 3 mmol) in 10 ml CH_3CN, a solution of NBS (550 mg, 3.09 mmol) in 5 ml CH_3CN was added via addition funnel. The solution was allowed to come to room temperature and stirred for 24 h. The mixture was concentrated and quenched with 10% $Na_2S_2O_3$ (30 ml). The aqueous phase was extracted with EA (20 ml for 3 times). The organic phase was washed with brine (50 ml) and dried over anhydrous Na_2SO_4, filtered under reduced pressure, and the organic phase was concentrated under vacuum. Crude was purified by flash chromatography using PE/EA (10:1) to yield **12a** (270 mg, 21%) as a colorless oil and **12b** (769 mg, 60%) as a white solid. **12a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (br d, J = 7.1 Hz, 4H), 7.37 (br t, J = 7.3 Hz, 4H), 7.31 (br t, J = 7.2 Hz, 2H), 6.88 (d, J = 2.7 Hz, 1H), 6.68 (d, J = 2.7 Hz, 1H), 6.23 (s, 1H), 3.89 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.6, 157.4, 156.6, 139.9 (2C), 128.7 (2C), 128.5 (2C), 127.9 (2C), 127.6, 126.9 (2C), 126.5 (2C), 108.7, 103.4, 101.8, 81.9, 56.0, 52.1; NOESY (500 MHz, $CDCl_3$): H-4/H-9, H-4/H_3-8, H-6/H-9. ESI-MS: *m/z* 425/427 $[M - H]^-$, 427/429 $[M + H]^+$. **12b**: ^{1}H NMR (500MHz, $CDCl_3$): δ 7.48 (br d, J = 7.2 Hz, 4H), 7.33 (br t, J = 7.3 Hz, 4H) 7.25 (tt, J = 7.4, 1.9 Hz, 2H), 6.75 (d, J = 2.8 Hz, 1H), 6.52 (d, J = 2.8 Hz, 1H), 6.23 (s, 1H), 3.92 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.2, 159.0, 155.2, 140.5 (2C), 134.7, 128.7 (4C), 127.9 (2C), 126.5 (4C), 106.9, 105.4, 103.3, 82.7, 55.5, 52.6; NOESY (500 MHz, $CDCl_3$): H-4/H-9, H-4/H_3-8, H-6/H_3-8. ESI-MS: *m/z* 425/427 $[M - H]^-$, 427/429 $[M + H]^+$.

3.2.12. Preparation of methyl 3-((9H-fluoren-9-yl)oxy)-5-methoxybenzoate (13)

To a solution of **7** (1.1 g, 6 mmol) and K_2CO_3 (1.66 g, 12 mmol) in anhydrous acetone (20 ml), 9-bromo-9*H*-fluorene (2.94 g, 12 mmol) was added. The reaction mixture was stirred at reflux for 16 h. The residue was filtered and concentrated *in vacuo*. Crude was purified by flash chromatography using PE/EA (10:1) to yield **13** (1.35 g, 65%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (br d, J = 7.6 Hz, 2H), 7.54 (br d, J = 7.5 Hz, 2H), 7.52 (br s, 1H), 7.42 (br t, J = 7.5 Hz, 2H), 7.27 (br t, J = 7.5 Hz, 2H), 7.26 (br s, 1H), 6.77 (t, J = 2.3 Hz, 1H), 6.36 (s, 1H), 3.91 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.8, 160.7, 159.6, 142.5 (2C), 140.6 (2C), 132.1, 129.5 (2C), 127.8 (2C), 125.5 (2C), 120.2 (2C), 109.5, 108.1 (2C), 79.7, 55.6, 52.3. HRESIMS: *m/z* 345.1130 $[M - H]^-$ (calcd for $C_{22}H_{17}O_4$, 345.1132).

3.2.13. Preparation of compounds 13a and 13b

To a 0 °C solution of **13** (1.039 g, 3 mmol) in 10 ml CH_3CN, a solution of NBS (550 mg, 3.09 mmol) in 5 ml CH_3CN was added via addition funnel. The solution was allowed to come to room temperature and stirred for 24 h. The reaction was concentrated and quenched with 10% $Na_2S_2O_3$ (30 ml). The aqueous phase was extracted with EA (20 ml for 3 times). The

organic phase was washed with brine (50 ml) and dried over anhydrous Na_2SO_4, filtered under reduced pressure, and the organic phase was concentrated under vacuum. Crude was purified by flash chromatography using PE/EA (10:1) to yield compound **13a** (306 mg, 24%) as a colorless oil and compound **13b** (817 mg, 64%) as a white solid. **13a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 7.5 Hz, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.28 (t, J = 7.5 Hz, 2H), 7.16 (d, J = 2.8 Hz, 1H), 6.52 (d, J = 2.8 Hz, 1H), 6.32 (s, 1H), 3.92 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.5, 157.5, 156.7, 141.5 (2C), 140.0 (2C), 134.1, 129.1 (2C), 127.5 (2C), 125.0 (2C), 119.8 (2C), 108.9, 104.0, 102.2, 79.4, 56.0, 52.1; NOESY (500 MHz, $CDCl_3$): H-4/H-9, H-4/H_3-8, H-6/H-9. ESI-MS: *m/z* 423/425 $[M - H]^-$, 425/427 $[M + H]^+$. **13b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 2.0 Hz, 2H), 7.59 (d, J = 2.0 Hz, 2H), 7.44 (t, J = 2.0 Hz, 2H), 7.31 (t, J = 2.0 Hz, 2H), 6.84 (d, J = 2.4 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H), 6.33 (s, 1H), 3.95 (s, 3H), 3.59 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.7, 158.5, 155.3, 141.4 (2C), 139.9 (2C), 134.5, 129.1 (2C), 127.4 (2C), 125.1 (2C), 119.7 (2C), 108.1, 105.9, 103.3, 81.1, 55.0, 52.1; NOESY (500 MHz, $CDCl_3$): H-4/H-9, H-4/H_3-8, H-6/H_3-8. ESI-MS: *m/z* 423/425 $[M - H]^-$, 425/427 $[M + H]^+$.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] S.K. Talapatra, S. Bose, A.K. Mallik, and B. Talapatra, *J. Indian Chem. Soc.* **61**, 1010 (1984).
[2] C.Q. Fan, W. Wang, Y.P. Wang, G.W. Qin, and W.M. Zhao, *Phytochemistry* **57**, 1255 (2001).
[3] X. Zhang, J.K. Xu, J. Wang, N.L. Wang, H. Kurihara, S. Kitanaka, and X.S. Yao, *J. Nat. Prod.* **70**, 24 (2007).
[4] Y.Y. Liu, H. Yu, and Y.G. Chen, *Chem. Nat. Compd.* **47**, 275 (2011).
[5] P. Klongkumnuankarn, K. Busaranon, P. Chanvorachote, B. Sritularak, V. Jongbunprasert, and K. Likhitwitayawuid, *Evid Based Compl. Alt.* **2015**, 350410 (2015).
[6] Q.F. Hu, B. Zhou, J.M. Huang, X.M. Gao, L.D. Shu, G.Y. Yang, and C.T. Che, *J. Nat. Prod.* **76**, 292 (2013).
[7] J.H. Jin, Y. Liang, H. Xie, X. Zhang, X.S. Yao, and Z. Wang, *Pharmazie* **63**, 321 (2008).
[8] Y.G. Chen, Y.P. Li, C. Qing, Y.L. Zhang, L.Q. Wang, and Y. Liu, *Food Chem.* **108**, 973 (2008).
[9] M.V. Sargent, *J. Chem. Soc. Perk. Trans.* **1**, 2553 (1987).
[10] P.K. Chhattise, A.V. Ramaswamy, and S.B. Waghmode, *Tetrahedron Lett.* **49**, 189 (2008).
[11] A.C. Benniston, G. Copley, H. Lemmetyinen, and N.V. Tkachenko, *Eur. J. Org. Chem.* **2010**, 2867 (2010).
[12] T.K. Chakraborty and G.V. Reddy, *J. Org. Chem.* **57**, 5462 (1992).
[13] E. Zysman-Colman, K. Arias, and J.S. Siegel, *Can. J. Chem.* **87**, 440 (2009).
[14] N. Miyaura, K. Yamada, and A. Suzuki, *Tetrahedron Lett.* **20**, 3437 (1979).