The First Total Synthesis of 4,4′-Biisofraxidin†

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The 4,4′-biisofraxidin, isolated from *balsamina L.* was synthesized for the first time in the total yield of 7% by 11 steps, in which the key step was the cyclization and Ni(0)-catalyzed coupling reaction.

Keywords total synthesis, 4, 4′-biisofraxidin, cyclization, nickel(0), coupling reaction

Introduction

4,4′-Biisofraxidin (**1**), a new biscoumarin,[1] was isolated by Wanchai De-Eknamkul and his co-workers from the root cultures of impatiens *balsamina L.* (*Balsaminaceae*), which has long been used in Thailand as a traditional folk medicine. The leaves of *Balsaminaceae* are usually used for the treatment of abscensses, nail ingrowth and dermatophytosis. In continuation of our interest in synthesis of natural compounds by using the modified Ni(0)-catalyzed Ullmann coupling reaction,[2,3] we selected the symmetric compound 4,4′-biisofraxidin (**1**) as the target molecule (Fig. 1).

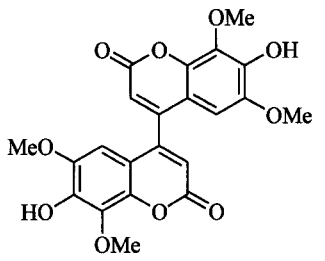

Fig. 1 Structure of 4,4′-biisofraxidin (**1**).

Results and discussion

In our previous paper, we have reported a Ni(0)-catalyzed modified Ullmann-type coupling reaction which is suitable for the highly sterically-hindered benzyl iodide.[2,3] Based on this method, we designed a concise route for the total synthesis of 4,4′-biisofraxidin (**1**) as shown in Scheme 1.

Bromination of 2, 4-dihydroxy-benzaldehyde (**2**) with bromine[4] or Bu_4NBr_3[5] afforded compound 3,5-dibromo-2,4-dihydroxy-benzaldehyde (**3**) in yield of 74% or 78%, respectively. As shown in Table 1, methoxylation of **3** with NaOMe gave compound **4** in various yields depending on the reaction conditions.[4] The best yield was obtained when DMF-MeOH was used as the solvent in the presence of 0.1 equiv. of CuCl. Benzoylation of the compound **4** gave the compound **5** in 73% yield. The ketone **7** was obtained after addition reaction of compound **5** with MeMgCl and oxidation of compound **6** by PCC,[6] and debenzoylation of **7** selectively gave the compound **8**.[7]

As the cyclization[8] of compound **8** with sodium and $CO(OEt)_2$ under reflux failed, the free hydroxyl in compound **8** was protected with $ClCO_2Me$ to give compound **9** in 80% yield and then cyclization under the basic condition to provide compound **10** in 79% yield. According to the coupling reaction condition, attempts to prepare the bromated precursor or iodinated one failed. Therefore, the free hydroxyl group was transformed into tosylate and subjected to coupling reaction.[2,3] The expected compound **12** was isolated in 60% yield. Under acidic condition,

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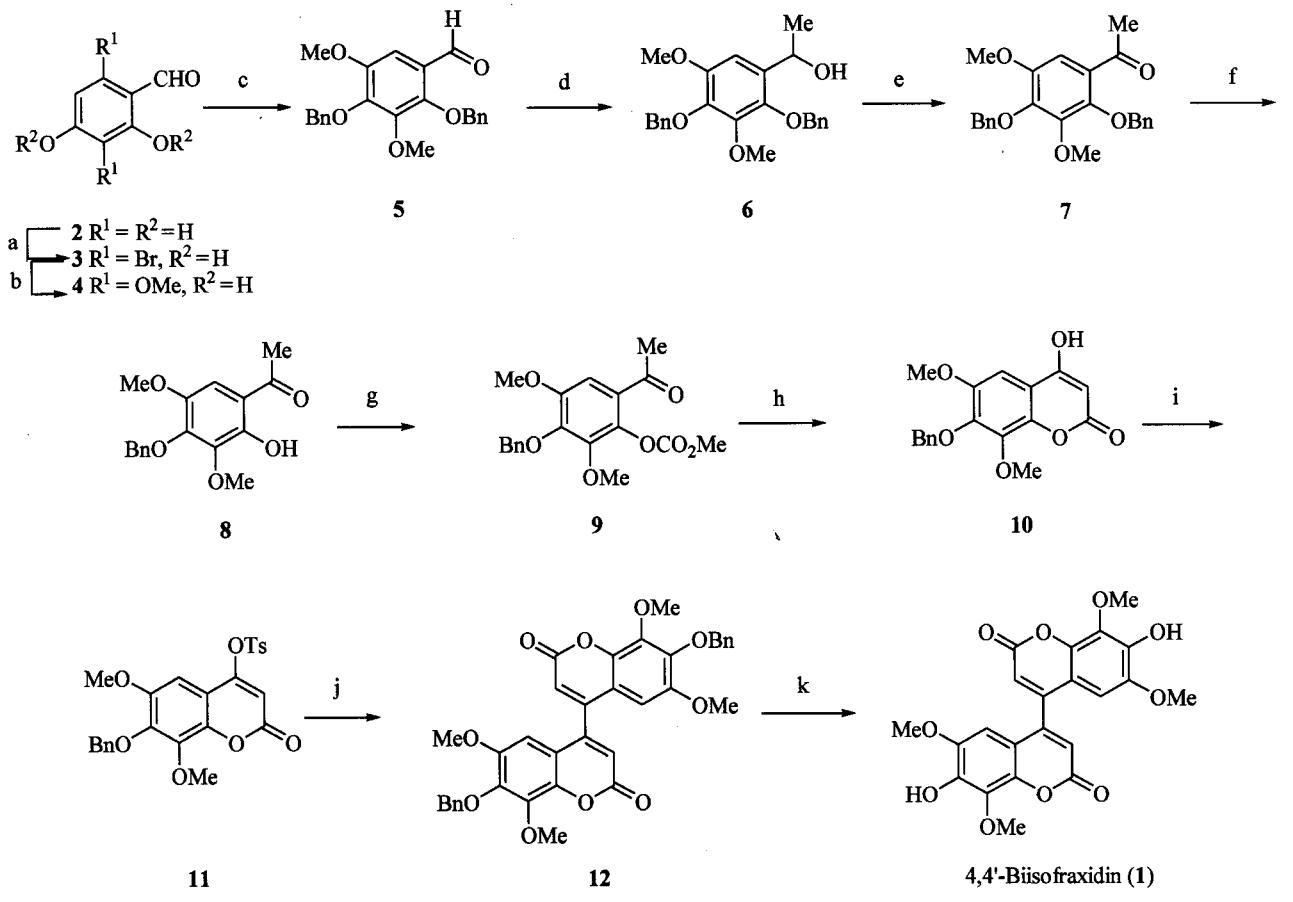
Scheme 1



Reagents and conditions: (a) Br_2/AcOH, r.t. or Bu_4NBr_3/EtOH, r.t.; (b) NaOMe, CuCl/DMF, reflux; (c) BnBr/pyridine, r.t.; (d) MeMgCl/THF, −78 ℃; (e) PCC/CH_2Cl_2, r.t.; (f) HCl-AcOH (1∶5), r.t.; (g) $ClCO_2Me$/pyridine, r.t.; (h) *t*-BuOK/*t*-BuOH, reflux; (i) TsCl/pyridine, r.t.; (j) $NiCl_2(PPh_3)_2$, PPh_3, NaH/toluene, 90 ℃; (k) HCl-AcOH, r.t..

Table 1 Various situation of methoxylation of compound **3** [a]

Entry	Catalyst (Equiv.)	Reagent	Solvent	Yield of **4** (%)
1	CuI (0.1)	NaOMe	DME	0
2	CuI (1.6)	NaOMe	DME-MeOH	13
3	CuI (1.0)	NaOMe	DME	42
4	CuCl (0.1)	NaOMe	DMF	85
5	CuCl (0.1)	NaOMe	DMF-MeOH	100

[a] All these reactions were performed under reflux temperature.

debenzolation of coupling product gave directly the target molecule 4, 4′-biisofraxidin (**1**). The structure of the synthetic sample was characterized by its spectra as compared with that reported in the literature.[1]

In summary, the natural product 4, 4′-biisofraxidin (**1**) was successfully synthesized for the first time through 11 steps in 7% overall yield.

Experimental

General methods

The solvents are used directly without further purification unless noticed. $NiCl_2(PPh_3)_2$ was prepared accord-

ing to the reported procedure.[9] PPh_3 was recrystallized in 95% EtOH. Zinc dust was activated by 2% HCl, water, absolute EtOH and diethyl ether, respectively, and then dried under vacuum at r.t. for 3 h. TsCl was recrystallized in *n*-hexane. PCC was prepared according to the known procedure.[6] The ^1H NMR spectra were recorded in $CDCl_3$ at 300 MHz. Mass spectra were recorded by EI method. IR spectra were recorded on a Digibal FT-IR spectrometer. Elemental analysis was performed on a Heraeus Rapid-CHNO instrument. Purification of reaction products was carried out by flash chromatography using the 300—400 mesh silica gel.

3,5-*Dibromo*-2,4-*dihydroxy-benzaldehyde* (**3**)[4]

A 250-mL three-necked flask was dried, flashed with argon, charged with 2, 4-dihydroxy-benzaldehyde (**2**, 1.38 g, 10 mmol) and 100 mL of CH_2Cl_2-MeOH (1:1). After the solid was dissolved while stirring, a 70 mL solution of Bu_4NBr_3 (10 g, 21 mmol) in CH_2Cl_2-MeOH (1:1) was added dropwise at 0 ℃ over 40 min. After addition the reaction mixture was stirred at r.t. for 6 h. Then the solvent was removed from evaporator, the residue was diluted with water, and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, and dried over Na_2SO_4 (anhydrous). Further purification by flash chromatography (CH_2Cl_2 : ethyl acetate = 4:1) afforded compound **3** (2.3 g, 7.8 mmol, 78%). ^1H NMR (300 MHz, $CDCl_3$) δ: 11.99 (s, 1H, CHO), 9.69 (s, 1H, ArH), 7.71 (s, 1H, OH), 6.64 (s, 1H, OH); MS (EI) *m/z* (%): 298 (M^+ + 2, 34), 297 (M^+ + 1, 54), 296 (M^+, 79), 295 (M^+ − 1, 100), 294 (M^+ − 2, 60), 293 (M^+ − 3, 52), 251 (10.02), 250 (9.90).

2,4-*Dihydroxy*-3,5-*dimethoxy-benzaldehyde* (**4**)[4]

A 50-mL over-dried flask was flashed with argon, charged with sodium (1.12 g, 48.7 mmol). 15 mL of methanol was added gently while stirring. After the sodium was completely dissolved, methanol was removed under vacuum. Then 6 mL of dry DMF and anhydrous CuCl (56 mg, 0.57 mmol) were added. And the dry DMF (12 mL) solution of 3,5-dibromo-2,4-dihydroxy-benzaldehyde (**3**, 1.488 g, 5.02 mmol) was added dropwise over 10 min at r.t.. After stirring for 4 h, DMF was removed under vacuum and the residue was diluted with water, neutralized at 0 ℃ with 5% HCl (aq.), stirred for 1 h at r.t., and extracted with $CHCl_3$ (3 × 100 mL). The organic solution was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified on a silica gel column (CH_2Cl_2) to yield a yellow oil (1.0 g, 100%). ^1H NMR (300 MHz, $CDCl_3$) δ: 9.68 (s, 1H, CHO), 6.73 (s, 1H, ArH), 3.98 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 2.95 (s, 1H, OH), 2.87 (s, 1H, OH); MS (EI) *m/z* (%): 198 (M^+, 100), 152 (23.18), 127 (23.35), 99 (21.26), 55 (39.41), 53 (31.54), 43 (43.19), 41 (30.38).

2,4-*Bisbenzyloxy*-3,5-*dimethoxy-benzaldehyde* (**5**)

A 50-mL over-dried flask was charged with compound **4** (400 mg, 2 mmol), 20 mL of dry acetone and K_2CO_3 (1.118 g, 8.1 mmol). After the mixture was stirred at r.t. for 30 min, benzylbromide (0.7 mL, 5.7 mmol) was added dropwise. The mixture was refluxed for 2.5 h, then filtered, washed with acetone. The filtrate was evaporated. Further purification by column chromatography (hexane/ethyl acetate = 9:1) gave the product **5** (73%). ^1H NMR (300 MHz, $CDCl_3$) δ: 10.08 (s, 1H, CHO), 7.49—7.34 (m, 10H, Ar × 2), 7.07 (s, 1H, ArH), 5.23 (s, 2H, CH_2), 5.13 (s, 2H, CH_2), 3.93 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3); FT-IR (KBr) ν: 3033, 2941, 2870, 1681, 1591, 1498 cm^{-1}; MS (EI) *m/z* (%): 378 (M^+, 7.52), 287 (18.50), 259 (6.58), 198 (3.76), 181 (13.26), 92 (7.98), 91 (100), 65 (7.30). Anal. calcd for $C_{23}H_{22}O_5$: C 73.00, H 5.86; found C 72.82, H 5.89.

1-(2,4-*Bisbenzyloxy*-3,5-*dimethoxy-phenyl*)-*ethanol* (**6**)

A 100-mL over-dried three-necked flask was flashed with argon. The compound **5** (1.978 g, 5.1 mmol) and 30 mL of dry THF were added. 7.5 mL of CH_3MgCl (3.0 mol/L in THF) was added dropwise via a syringe at − 78 ℃. The mixture was stirred for 2 h at 78 ℃, then it was allowed to raise to room temperature and stirred for an additional 1 h. Then the mixture was quenched with saturated NH_4Cl (aq.), extracted with ethyl acetate (3 × 100 mL), and dried over $MgSO_4$ (anhydrous). The product **6** was obtained after purification on a silica gel column by flash chromatography techniques (hexane/ethyl acetate = 4:1) (1.867 g, 90%). ^1H NMR (300 MHz, $CDCl_3$)

δ: 7.54—7.36 (m, 10H, Ar × 2), 6.71 (s, 1H, ArH), 5.10 (s, 2H, CH_2), 5.04 (s, 2H, CH_2), 5.02 (m, 1H, CH), 3.92 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 1.40 (d, J = 6.45 Hz, 3H, CH_3), 1.65 (s, 1H, OH); FT-IR (KBr) ν: 3551, 3030, 2976, 2867, 2932, 2840, 1593, 1498, 1483 cm^{-1}; MS (EI) *m/z* (%): 394 (M^+, 2.17), 303 (9.36), 286 (2.90), 183 (2.93), 155 (3.06), 92 (7.98), 91 (100), 65 (6.38), 43 (4.89). Anal. calcd for $C_{24}H_{26}O_5$: C 73.08, H 6.64; found C 73.22, H 6.62.

1-(2,4-*Bisbenzyloxy*-3,5-*dimethoxy-phenyl*)-*ethanone* (**7**)

A 250-mL flask was charged with the compound **6** (5.281 g, 13.3 mmol), 150 mL of CH_2Cl_2 and PCC (4.591 g, 21.4 mmol). The mixture was stirred at r.t. for 2 h. After 50 mL of diethyl ether was added, the mixture was stirred for an additional 30 min, then filtered and washed by CH_2Cl_2. The filtrate was concentrated and the residue was purified on a silica gel column (hexane/ethyl acetate = 4 : 1) and gave the product **7** (4.69 g, 90%). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.51—7.34 (m, 10H, Ar × 2), 7.03 (s, 1H, ArH), 5.17 (s, 2H, CH_2), 5.04 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 2.55 (s, 3H, CH_3); FT-IR (KBr) ν: 3033, 2939, 2840, 1673, 1590, 1498, 1482 cm^{-1}; MS (EI) *m/z* (%): 392 (M^+, 1.87), 350 (8.43), 301 (28.44), 259 (12.19), 181 (8.85), 92 (8.29), 91 (100), 65 (11.73), 43 (5.43). Anal. calcd for $C_{24}H_{24}O_5$: C 73.45, H 6.16; found C 73.27, H 6.24.

1-(4-*Benzyloxy*-2-*hydroxy*-3,5-*dimethoxy-phenyl*)-*ethanone* (**8**)

A 100-mL flask was charged with compound **7** (1.4 g, 3.6 mmol), 20 mL of glacial acetic acid and 60 mL of 1:5 (V : V) mixture of concentrated hydrochloric acid and glacial acetic acid. The mixture was stirred at 25 ℃ for 50 min, diluted with water and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with water (3 × 10 mL), brine, and dried over anhydrous $MgSO_4$. Further purification on a silica gel column (hexane/ethyl acetate = 10:1) gave the product **8** (857 mg, 77%). ^1H NMR (300 MHz, $CDCl_3$) δ: 12.39 (s, 1H, OH), 7.50—7.34 (m, 5H, Ar), 6.93 (s, 1H, ArH), 5.22 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 2.59 (s, 3H, $COCH_3$); FT-IR (KBr) ν: 3010, 1673, 1627, 1487, 1580 cm^{-1}; MS (EI) *m/z* (%): 302 (M^+, 12.24), 260 (26.54), 183 (6.35), 92 (8.27), 91 (100), 69 (5.69), 65 (7.16), 46 (7.18). Anal. calcd for $C_{17}H_{18}O_5$: C 67.54, H 6.00; found C 67.59, H 6.07.

Carbonic acid 6-*acetyl*-3-*benzyloxy*-2,4-*dimethoxy-phenyl ester methyl ester* (**9**)

A 100-mL three-necked flask was framed and flashed with argon, charged with compound **8** (783 mg, 2.59 mmol) and 30 mL of dry pyridine. 5 mL of $ClCO_2CH_3$ was added dropwise at r.t.. After stirring for 24 h, pyridine was removed under vacuum. The residue was purified on a silica gel column (hexane/ethyl acetate = 8 : 1) and gave **9** (770 mg, 2.14 mmol). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.48—7.32 (m, 5H, Ar), 7.14 (s, 1H, ArH), 5.13 (s, 2H, CH_2), 3.96 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.88 (s, 3H, CO_2CH_3), 2.55 (s, 3H, $COCH_3$); FT-IR (KBr) ν: 3035, 1756, 1682, 1576, 1491, 1457 cm^{-1}; MS (EI) *m/z* (%): 360 (M^+, 0.50), 318 (8.40), 284 (5.22), 269 (5.60), 219 (4.74), 91 (100), 69 (9.24), 65 (5.76), 43 (6.41). Anal. calcd for $C_{19}H_{20}O_7$: C 63.33, H 5.59; found C 63.40, H 5.94.

7-*Benzyloxy*-4-*hydroxy*-6,8-*dimethoxy-chromen*-2-*one* (**10**)

A 50-mL three-necked flask was framed and flashed with argon. The compound **9** (770 mg, 2.14 mmol), 30 mL of dry *t*-BuOH and *t*-BuOK (2.223 g, 19.8 mmol) were added. The mixture was refluxed while stirring for 6 h. After addition of 30 mL of cooled water, the mixture was acidified with 5% hydrochloric acid with vigorous stirring, then extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with brine, and dried over Na_2SO_4. Further purification by column chromatography (hexane/ethyl acetate = 4 : 1) gave the product **10** (555 mg, 79%). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.49—7.31 (m, 5H, Ar), 7.08 (s, 1H, PhH), 5.54 (s, 1H, OH), 5.11 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.36 (s, 1H, CH); FT-IR (KBr) ν: 3034, 2941, 1651, 1591, 1544, 1298, 1257 cm^{-1}; MS (EI) *m/z* (%): 328 (M^+,

1.40), 302 (9.61), 260 (17.86), 219 (5.91), 183 (4.65), 91 (100), 69 (13.71), 65 (7.76), 43 (10.28). Anal. calcd for $C_{18}H_{16}O_6$: C 65.85, H 4.91; found C 65.66, H 4.98.

4,4'-Biisofraxidin (**1**)[1]

A 50-mL three-necked flask was framed and flashed with argon. The compound **10** (377 mg, 1.15 mmol), 12 mL of dry pyridine and TsCl (424 mg, 2.22 mmol) were added. The mixture was stirred for 24 h at r.t.. $NaHCO_3$ (aq.) was added, and the mixture was extracted with ethyl acetate (4 × 20 mL). The combined organic layers were washed with water (2 × 10 mL), brine, and dried over Na_2SO_4. Further purification by column chromatography (hexane/ethyl acetate = 8 : 1) gave the product 7-benzyloxy-4-(*p*-methylphenylsulfonyl)-6,8-dimethoxy-chromen-2-one (**11**, 300 mg, 54%). A 25-mL flask was framed and flashed with argon, charged with the compound **11** (270 mg, 0.56 mmol), $NiCl_2(PPh_3)_2$ (204 mg, 0.31 mmol), PPh_3 (163 mg, 0.62 mmol), zinc dust (121 mg, 1.86 mmol), NaH (71 mg, 3.0 mmol) and 10 mL of dry toluene. The mixture was stirred at 90 ℃ for 8 h, then cooled down to r.t., quenched with 2% hydrochloric acid and diluted by CH_2Cl_2. The mixture was stirred vigorously at r.t. overnight. The organic layer was separated and the water layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. Further purification by column chromatography (hexane/ethyl acetate = 4 : 1) gave the coupling product **12** (209 mg, 60%). The compound **12** (17 mg, 0.027 mmol), 1 mL of concentrated hydrochloric acid and 4 mL of glacial acetic acid were added into a 10-mL flask. The mixture was stirred at room temperature for 30 min. 5 mL of $NaHCO_3$ (aq.) was added and the mixture was extracted with ethyl acetate (3 × 5 mL), dried over anhydrous Na_2SO_4. Further purification by column chromatography (hexane/ethyl acetate = 4 : 1) gave the product **1** (10 mg, 81%). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.35 (s, 2H, PhH), 6.31 (s, 2H, CH), 6.23 (s, 2H, OH), 4.15 (s, 6H, OCH_3), 3.75 (s, 6H, OCH_3); FT-IR (KBr) ν: 3346, 1711, 1603, 1563, 1504, 1466, 1218, 1096 cm^{-1}; MS (EI) *m/z* (%): 443 ($M^+ + 1$, 21.67), 442 (M^+, 85.15), 414 (16.08), 400 (22.94), 399 (100), 397 (13.24), 381 (12.92), 355 (15.45). HRMS calcd for $C_{22}H_{18}O_{10}$ 442.0900, found 442.0909.

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