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Unified syntheses of gramniphenols F and G, cicerfuran, morunigrol C and its derivative

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ABSTRACT

The first syntheses of natural benzofurans, gramniphenols F and G, morunigrol C and its 3′,5′-di-*O*-methyl analogue along with the synthesis of cicerfuran are achieved by a unified synthetic sequence using 7-hydroxycoumarin, 5-bromoresorcinol, 2,4-dihydroxybenzaldehyde, and sesamol as building blocks. Ramirez *gem*-dibromoolefination, Miyaura borylation, Suzuki coupling have been successfully exploited in the synthesis. Additionally, their *anti*-inflammatory effects were also investigated in lipopolysaccharide (LPS)-induced RAW-264.7 macrophages. The compounds exhibited significant inhibition of iNOS mediated nitric oxide (NO) production with no cytotoxicity at 10 μM concentration and IC_{50} values are found in the range from 9.1 to 25.2 μM.

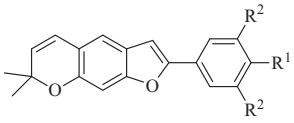
Introduction

Benzofuran core is a prominent structural unit in a variety of bioactive natural products as well as synthetic materials. In particular, 2-substituted benzofurans are acknowledged as important scaffolds for drug development.[1] Numerous natural and non-natural 2-substituted benzofurans have been investigated as antioxidant, antifungal, *anti*-inflammatory, antimicrobial, PPAR-δ agonists, anti-HIV, anti-tumor, and anti-platelet agents.[1,2] Some benzofurans showed pesticide and insecticidal activity.[3] Recently, ^{18}F and ^{99m}Tc labeled benzofurans were applied in positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging, respectively, for β-amyloid plaques in Alzheimer's disease.[4] In supramolecular chemistry, extended molecular frameworks of benzofurans are useful as bowl-shaped hosts.[5] Some benzofuran derivatives were explored in organic semiconductors including organic field effect transistors (OFETs), phosphorescent organic light-emitting diodes (PhOLEDs), and organic photovoltaic cells (OPVCs).[6] Their wide range of pharmacological and physical properties have triggered extensive and enduring efforts toward the synthesis of these important heterocyclic compounds.

Gramniphenols F (**1**) and G (**2**) (Fig. 1) have recently been isolated from *Arundina gramnifolia* and they displayed anti-tobacco mosaic virus activity.[7] Morunigrol C (**3**) (Fig. 1) was isolated from the bark of *Morus nigra*.[8] Compound **4** is a synthetic analogue of **3**. Cicerfuran (**5**) (Fig. 1) was isolated from *Cicer bijugum* and displayed potent antifungal activity.[9] Few groups reported the synthesis of cicerfuran (**5**).[10]

Results and discussion

Continuing our interest[11] in the synthesis of natural bioactive compounds and their derivatives, we have realized that

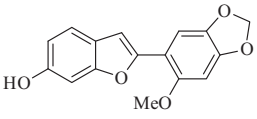


R^1 = OH, R^2 = H; **Gramniphenol F (1)**

R^1 = OMe, R^2 = H; **Gramniphenol G (2)**

R^1 = H, R^2 = OH; **Morunigrol C (3)**

R^1 = H, R^2 = OMe; **3',5'-Di-*O*-methylmorunigrol C (4)**



Cicerfuran (5)

Figure 1. Structures of natural (**1**–**3** and **5**) and synthetic (**4**) benzofurans.

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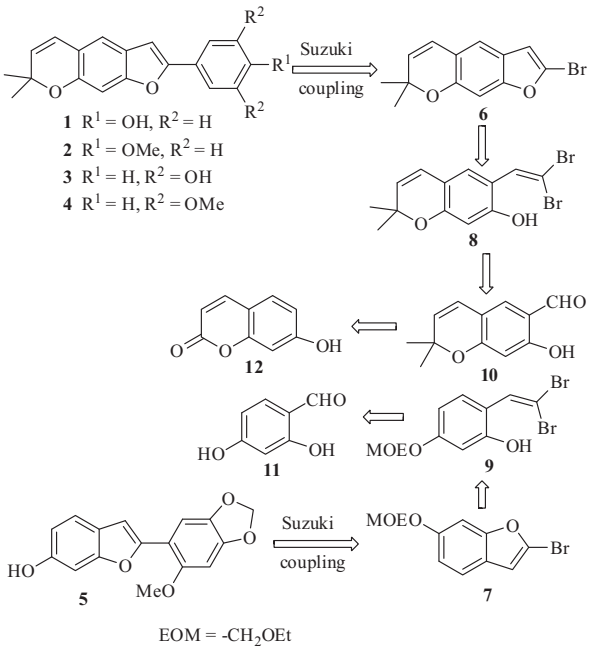
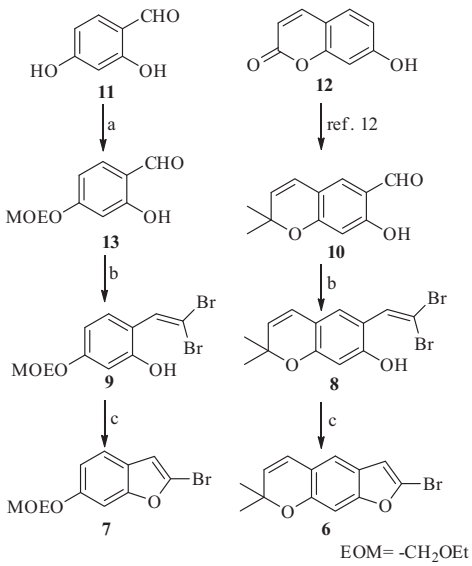


Scheme 1. Retrosynthetic analysis of benzofurans **1**–**5**.

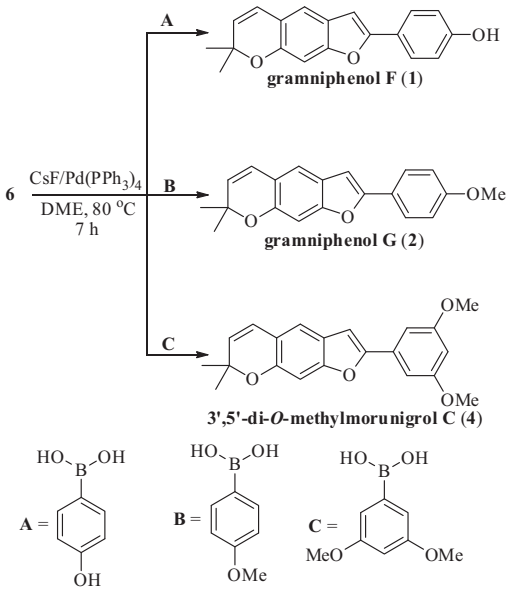
benzofurans **1**–**5** can be accessed by a common synthetic route involving Ramirez *gem*-dibromoolefination and Suzuki coupling as key steps (Scheme 1).

Accordingly, we commenced the synthesis with the protection of compound **11** (Scheme 2). Treatment of **11** with chloromethyl ethyl ether (EOM-Cl) using K_2CO_3/tetrabutylammonium iodide (TBAI) system provided compound **13** in 79% yield. Construction of benzofurans **1**–**4** began from chromene aldehyde **10**, which was available from 7-hydroxycoumarin **12** in four pots and 56% yield.[12]

Next, compounds **10** and **13** were subjected to Ramirez *gem*-dibromoolefination[13] using triethylamine (Et_3N) as a scavenger to yield **8** and **9** in moderate yields, respectively. Intramolecular cross-coupling of *gem*-dibromoolefins **8** and **9** using anhyd



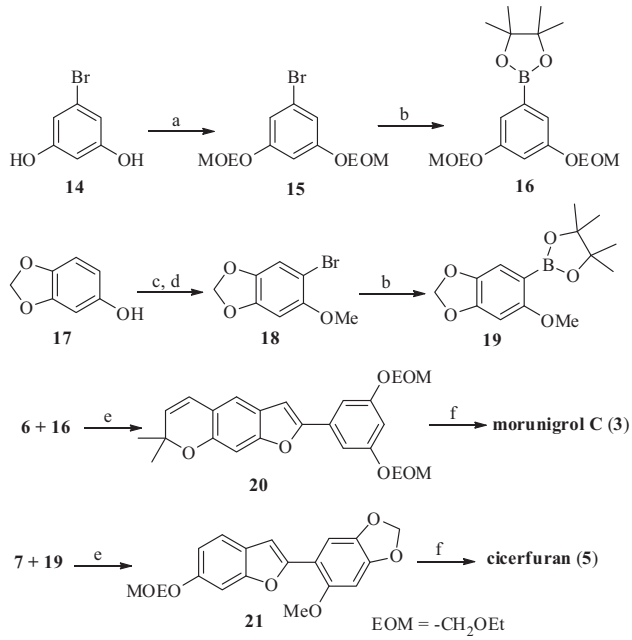
Scheme 2. Synthesis of 2-bromobenzofurans **6** and **7**. Reagents and conditions: (a) chloromethyl ethyl ether, K_2CO_3, TBAI, acetone, rt, overnight, 79%. (b) carbon tetrabromide/triphenylphosphine, Et_3N, CH_2Cl_2, 0 °C–30 min then rt–2 h, 57% (**8**), 58% (**9**). (c) Anhyd K_3PO_4/CuI, THF, sealed tube, 80 °C, 6 h, 80% (**6**), 87% (**7**).



Scheme 3. Synthesis of benzofurans **1**, **2,** and **4**.

K_3PO_4/CuI produced 2-bromobenzofurans **6** and **7** in high yields, respectively.[14]

Compound **6** was subjected to Suzuki coupling[15] with commercially available 4-hydroxyphenylboronic acid, 4-methoxyphenylboronic acid, and 3,5-dimethoxyphenylboronic acid using cesium fluoride (CsF) as a base and dimethoxyethane (DME) as a solvent medium to furnish the desired benzofurans **1**, **2,** and **4** in 90%, 84%, and 89% yields, respectively (Scheme 3). All of the products were obtained as white solids (see the Supplementary material). Demethylation of compound **4** to achieve compound **3** using BCl_3 as well as BBr_3 was not successful.



Scheme 4. Synthesis of morunigrol C (**3**) and cicerfuran (**5**). Reagents and conditions: (a) chloromethyl ethyl ether, K_2CO_3, TBAI, acetone, rt, 20 h, 76%. (b) Bis(pinacolato)diboron, anhyd KOAc, $PdCl_2(dppf)\cdot CH_2Cl_2$, 1,4-dioxane, 80 °C, overnight. 69% (**16**), 66% (**19**). (c) 1.5 M tetraethylammonium hydroxide, dimethyl sulfate, 0 °C–rt, 1 h, 100%. (d) Bromine (Br_2), THF, 0 °C, 5–10 min, 95%. (e) Aq 2.0 M K_2CO_3, $Pd(PPh_3)_4$, THF, 80 °C, 48 h, sealed tube, 85%. (**20**), 89% (**21**). (f) Dowex® 50WX8, MeOH, 35 °C, 24 h, 97% (**3**), 18 h, 98% (**5**).

Table 1
Anti-inflammatory activities and proliferation effects of benzofurans **1–5**

Compound	No production (% inhibition)[a,b]		Proliferation		IC_{50} (μM)
	1 μmol/L	10 μmol/L	1 μmol/L	10 μmol/L	
Medium	0.13 ± 0.87 (99.87)	0.13 ± 0.87 (99.87)	100 ± 1.25	100 ± 1.25	
1	93.46 ± 8.36 (6.54)	76.04 ± 2.01 (23.96)*	93.03 ± 1.12	96.12 ± 2.98	16.0
2	90.43 ± 3.06 (9.57)	84.34 ± 7.12 (15.66)	96.46 ± 2.46	93.93 ± 5.61	25.2
3	88.47 ± 6.34 (11.53)	67.75 ± 8.68 (32.25)*	97.47 ± 3.37	95.58 ± 3.23	12.9
4	100.00 ± 1.73 (0.0)	60.89 ± 8.70 (39.11)**	92.63 ± 4.45	93.98 ± 3.11	9.1
5	93.77 ± 11.20 (6.23)	57.50 ± 11.20 (42.5)**	96.44 ± 4.21	93.92 ± 3.56	10.6
L-NMMA	79.10 ± 4.10 (20.9)	7.60 ± 4.00 (92.4)**	98.64 ± 2.92	97.61 ± 5.63	2.69

[a] The results are reported as mean value ± SEM for $n = 3$. Statistical significance is based on the difference when compared with LPS-treated groups (*P <0.01, **P <0.001).
[b] Inhibition is based on LPS as shown in parenthesis.

For the synthesis of morunigrol C (**3**) and cicerfuran (**5**), the other coupling partners, that is, boronic esters were prepared from 5-bromoresorcinol (**14**) and sesamol (**17**), respectively (Scheme 4).

Treatment of **14** with chloromethyl ethyl ether (EOM-Cl) followed by Miyaura borylation[16] using catalytic [1,1′-bis (diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane ($PdCl_2(dppf)\cdot CH_2Cl_2$) afforded boronic ester **16**. Methylation of **17** followed by bromination[17] and subsequent Miyaura borylation provided the boronic ester **19** in 66% yield. Next, Suzuki coupling of 2-bromobenzofurans **6** and **7** with the corresponding boronic esters **16** and **19** using aq. 2.0 M K_2CO_3/Pd $(PPh_3)_4$ accomplished compounds **20** and **21** in 85% and 89% yields, respectively. Finally, deprotection of the EOM-ether group of **20** and **21** with Dowex® 50WX8 resin led to the natural products **3** and **5** in 97% and 98% yields, respectively. All the products **1–5** were settled from their spectral (^1H, ^{13}C NMR and MS) data.

anti-Inflammatory activity

Inflammation is a protective attempt of host to eradicate injurious stimuli and initiate healing.[18] In this process, activated inflammatory cells (neutrophils, eosinophils, mononuclear phagocytes and macrophages) secrete increased amounts of nitric oxide (NO), prostaglandins (PGs) and cytokines, such as interleukin (IL)-1ß, IL-6, and tumor necrosis factor (TNF). Among these, one of the most prominent is NO which is a small, lipophilic and transient free-radical species generated from L-arginine by three types of nitric oxide synthase (NOS) enzymes *viz.* endothelial (eNOS) and neuronal (nNOS) (both expressed constitutively) and inducible (iNOS). Excess NO production causes inflammation, asthma, diabetes, cancer, stroke, and neurodegenerative disorders.[19] Therefore, control of the excess NO production may exert *anti*-inflammatory effects.

Inhibition of iNOS mediated NO production in LPS-stimulated RAW 264.7 cells by benzofurans **1–5** was determined using N^G-monomethyl-L-arginine acetate (L-NMMA)[20] as a positive control following the similar procedure to our previous method.[21] Briefly, RAW 264.7 murine macrophages obtained from Korean Cell Bank (Seoul, Korea) were cultured in Dulbecco's modified Eagle's medium (DMEM), supplemented with 10% fetal bovine serum (FBS), 100 U/mL penicillin and 100 μg/mL streptomycin (obtained from Hyclone, Logan, UT, USA) at 37 °C in 5% CO_2. The effects of the various compounds on cell viability were tested using the CellTiter 96® AQueous One Solution (Promega, Madison, MI, USA) assay of cell proliferation. This assay was used to determine the number of viable cells remaining after the culturing process was complete. RAW264.7 cells were plated at a density of 2×10^4 cells in a 96-well flat-bottom plate, and each compound was added to each plate at indicated concentrations. After a 24 h incubation period, the number of viable cells were counted according to the manufacturer's instructions. The amount of nitrite produced by mouse macrophages was indicated by the amount that was measured in RAW264.7 cell culture supernatant. RAW264.7 cells were plated at a density of 5×10^4 cells in a 96-well cell culture plate with 200 μL of culture medium and incubated for 12 h. They were then treated with indicated concentrations of the benzofurans **1–5** plus LPS (500 ng/mL) and incubated for another 18 h. The amount of nitrite was measured using the Griess reagent system (Promega, Madison, MI, USA) according to the manufacturer's instructions.

The inhibitory activities of **1–5** on iNOS mediated NO production in LPS-stimulated RAW 264.7 cells were evaluated and the results are shown in Table 1. The compounds exhibited up to 42% inhibition of iNOS mediated nitric oxide (NO) production with no cytotoxicity at 10 μM concentration. IC_{50} (μM) values of these compounds **1–5** were evaluated using Prism 4.0 software (GraphPad Software, San Diego, CA, USA) and the values were 16.0, 25.2, 12.9, 9.1 and 10.6.

In summary, we have applied a unified strategy for the first syntheses of natural benzofurans gramniphenols F and G, morunigrol C and its 3′,5′-di-*O*-methyl derivative along with the synthesis of cicerfuran using commercially feasible 7-hydroxycoumarin, 2,4-dihydroxybenzaldehyde, 5-bromoresorcinol and sesamol as building blocks. Ramirez *gem*-dibromoolefination, Miyaura borylation, Suzuki coupling have been successfully exploited in the synthesis. In addition, their *anti*-inflammatory effects were also investigated in lipopolysaccharide (LPS)-induced RAW-264.7 macrophages. The compounds exhibited significant inhibition of iNOS mediated nitric oxide (NO) production with no cytotoxicity at 10 μM concentration and IC_{50} values are found in the range from 9.1 to 25.2 μM.

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Supplementary data

Supplementary data (experimental procedures and characterization data and copies of ^1H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.02.006.

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