An Efficient Total Synthesis of Mulberrofuran B and L

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An efficient approach has been developed for the synthesis of mulberrofuran B and L from 2,4-dihydroxybenzaldehyde and 5-bromoresorcinol. The key steps of the synthesis are neutral Al_2O_3-mediated regioselective geranylation, Ramirez *gem*-dibromoolefination, and the Suzuki coupling.

Keywords: 2,4-Dihydroxybenzaldehyde, Regioselective geranylation, Miyaura borylation, Ramirez *gem*-dibromoolefination, Suzuki coupling, Mulberrofuran

Introduction

Heterocyclic structures have significant roles in the biological activities of pharmaceuticals. Benzofurans and their derivatives in particular are important scaffolds for drug development.[1]

Several natural and non-natural 2-substituted benzofurans have been investigated as antifungal,[2] antioxidant,[3] anti-inflammatory,[4] antimicrobial,[5] peroxisome proliferator-activated receptor (PPAR-δ) agonists,[6] anti-HIV, antitumor and antiplatelet agents.[7] Some benzofurans showed pesticidal and insecticidal activity.[8] In supramolecular chemistry, extended molecular frameworks of benzofurans can be used as bowl-shaped hosts.[9] Recently, ^{18}F and ^{99m}Tc-labeled benzofuran derivatives were tested by positron emission tomography (PET) and single-photon emission computed tomography (SPECT) imaging, respectively, for β-amyloid plaques in Alzheimer's disease.[10] Their wide range of biological and pharmacological properties has triggered extensive and enduring efforts toward the syntheses of these important heterocyclic compounds.

Mulberrofuran B and L (Figure 1), 2-arylbenzofuran derivatives isolated from the root bark of the cultivated mulberry tree (Japanese name "Rosô" a cultivated variety of *Morus lhou* (ser.) koidz.) displayed moderate cytotoxic activity.[11] Previously, Mann *et al.* developed a method for the synthesis of mulberrofuran B that utilizes chromium and toxic tin reagents.[12]

In continuation of our work[13] on the synthesis of bioactive natural products and their derivatives, herein we wish to describe a straightforward synthesis of mulberrofuran B and L utilizing Al_2O_3-mediated regioselective geranylation, Ramirez *gem*-dibromoolefination, and the Suzuki coupling as the key steps.

Results and Discussion

Retrosynthetic approach for mulberrofuran B and L synthesis is depicted in Scheme 1. We envisaged that the target molecules could be achieved from intermediates **3**, **4**, and **5** by Suzuki coupling reaction, in which **3** and **4** could easily be prepared by means of regioselective geranylation of 2,4-dihydroxybenzaldehyde followed by Ramirez *gem*-dibromoolefination and intramolecular cyclization sequence. Intermediate **5** could be obtained from 5-bromoresorcinol by Miyaura borylation.

Accordingly, we commenced the synthesis from 2,4-dihydroxybenzaldehyde (**9**). As shown in Scheme 2, neutral alumina (Al_2O_3)-mediated regioselective geranylation of **9** with 1-bromo-3-methyl-2-butene gave the geranylated aldehyde **10**.[14] Treatment of about half portion of **10** with MeI and the remaining portion with chloromethyl ethyl ether in acetone in the presence of K_2CO_3 afforded **6** and **7** in high yields, respectively. 5-Bromoresorcinol (**8**) was protected as its ethoxy methylene ether **11** in 79% yield using chloromethyl ethyl ether in the presence of *N*,*N*-diisopropylethylamine (DIEA). Miyaura borylation[15] of compound **11** using bis(pinacolato)diboron, KOAc, and catalytic amount of $PdCl_2$(dppf) afforded **5** in 95% yield, which is a common key intermediate for the synthesis of mulberrofuran B and L.

Next, compounds **6** and **7** were subjected to Ramirez *gem*-dibromolefination.[16] Preformation of the active PPh_3CBr_2 ylide from PPh_3 and CBr_4 in CH_2Cl_2 at 0 °C, followed by slow addition of NEt_3 and aldehyde **6**, provided the *gem*-dibromoolefin **12** while with the aldehyde **7**, the corresponding *gem*-dibromoolefin **13** was obtained. A mild and ligand-free copper-catalyzed cross-coupling of compounds **12** and **13** ensued 2-bromobenzofurans **3** and **4** and the yields were 89 and 85%, respectively.[17] Compounds **3** and **4** were then subjected to Suzuki coupling[18] reaction with compound **5** using K_2CO_3 (2.0M aq. solution) as base and catalytic $Pd(PPh_3)_4$ in THF to furnish 2-aryl benzofurans **14** and **15**, respectively. Finally, deprotection of 2-aryl benzofurans **14** and **15** using Dowex resin in MeOH at room temperature gave the target molecules, mulberrofuran B (**1**) and L (**2**) in 67 and 77%, respectively.

In conclusion, we have developed an efficient approach for the synthesis of mulberrofuran B (**1**) and L (**2**). Neutral Al_2O_3-mediated regioselective geranylation, Ramirez *gem*-dibromoolefination, and the Suzuki coupling are the key

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transformations of the present method. Application of the present method for the synthesis of other prenyl (geranyl)-substituted natural 2-aryl benzofurans is in progress and will be disclosed in due course.

Experimental

All chemicals were purchased from Sigma-Aldrich (Munich, Germany) and Alfa Aesar Chemicals (Lancashire, UK) and were used without further purification unless noted otherwise. ^{1}H-NMR spectra were recorded at Varian Mercury-300 MHz FT-NMR (Varian, Palo Alto, CA, USA) and 75 MHz for ^{13}C, with the chemical shift (δ) reported in parts per million (ppm) relative to TMS and the coupling constants (*J*) quoted in Hertz. $CDCl_3$ was used as a solvent and an internal standard. Mass spectra were recorded using a JMS-700 (JEOL) spectrometer (JEOL Ltd, Tokyo, Japan). Melting points were measured on a MEL-TEMP II apparatus (Laboratory Devices, Inc Holliston MA, USA) and were uncorrected. Thin-layer chromatography (TLC) was performed on DC-Plastikfolien 60, F_{254} (layer thickness 0.2 mm; Merck, Darmstadt, Germany) plastic-backed *silica* gel plates and visualized by UV light (254 nm) or staining with *p*-anisaldehyde.

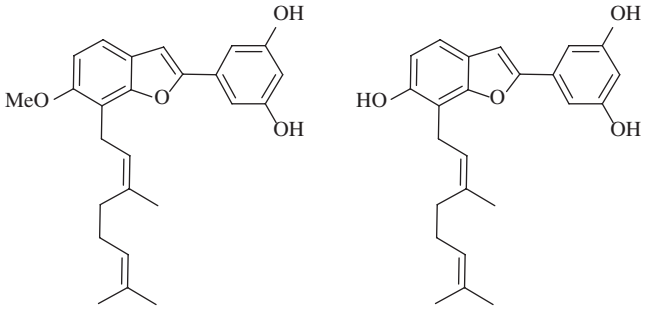
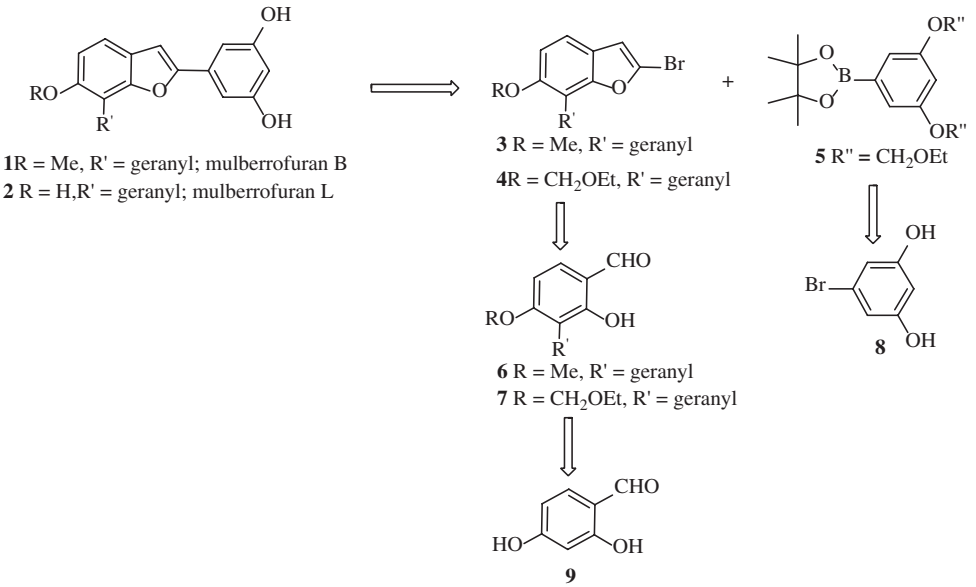


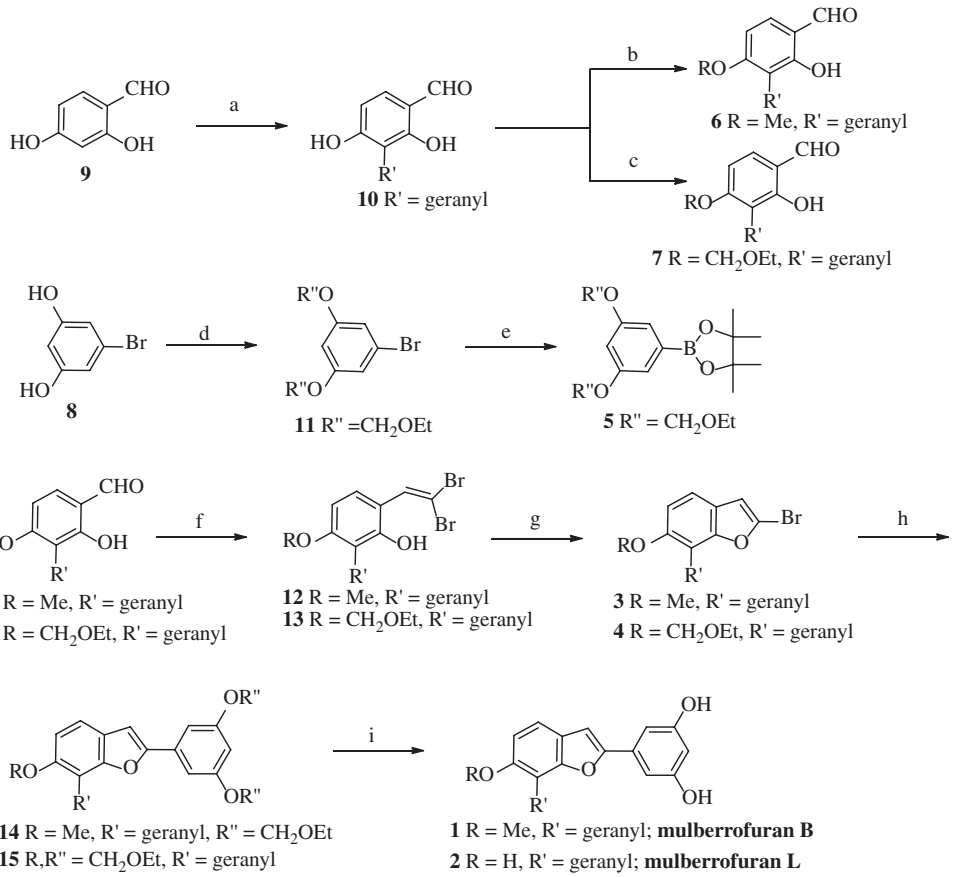
Figure 1. Structures of mulberrofuran B (**1**) and L (**2**).

3-(3,7-Dimethylocta-2,6-dien-1-yl)-2,4-dihydroxybenzaldehyde (10). To a stirred suspension of 2,4-dihydroxybenzaldehyde, **9** (0.2 g, 1.45 mmol) and neutral Al_2O_3 (10.0 g) in diethyl ether (100 mL) was added 1-bromo-3-methyl-2-butene under nitrogen atmosphere and the suspension was stirred for 3 days at room temperature. Al_2O_3 was filtered off, washed with ether (50 mL), and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/hexane = 1/5) to yield the product **10** (0.138 g, 35%) as white solid. R_f = 0.32 (EtOAc/hexane = 1/3); mp 119–121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.75 (1H, s), 9.65 (1H, s), 7.29 (1H, d, *J* = 8.7 Hz), 6.46 (1H, d, *J* = 8.7 Hz), 6.35 (1H, s), 5.25 (1H, t, *J* = 6.9 Hz), 5.03 (1H, t, *J* = 6.5 Hz), 3.45 (2H, d, *J* = 6.9 Hz), 2.08 (4H, br s), 1.81 (3H, s), 1.66 (3H, m), 1.58 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 162.5, 161.5, 139.9, 133.4, 132.1, 123.5, 120.5, 115.0, 113.5, 109.0, 39.7, 26.4, 25.8, 21.4, 17.8, 16.4.

3-(3,7-Dimethylocta-2,6-dien-1-yl)-2-hydroxy-4-methoxybenzaldehyde (6). To a stirred suspension of **10** (0.465 g, 1.69 mmol) and K_2CO_3 (0.281 g, 2.03 mmol) in acetone (15 mL) were added methyl iodide (0.13 mL, 2.03 mmol) under nitrogen atmosphere at room temperature. The suspension was stirred for 8 h at room temperature. Reaction mixture was filtered through celite pad, washed with acetone (30 mL), and the filtrate was concentrated *in vacuo*. EtOAc (30 mL) and H_2O (20 mL) were added to the residue and two layers separated. The aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layer was washed with brine (2 × 40 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/hexane = 1/6) to yield the product **6** (0.459 g, 94%) as a colorless liquid. R_f = 0.52 (EtOAc/hexane = 1/5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.40 (1H, s), 9.69 (1H, s),



Scheme 1. Retrosynthetic analysis for the synthesis of mulberrofuran B and L.



Scheme 2. Reagents and conditions: (a) geranyl bromide, neutral Al_2O_3, ether, room temperature (rt), 72 h, 35%; (b) MeI, K_2CO_3, acetone, rt, 8 h, 94%; (c) chloromethyl ethyl ether, K_2CO_3, TBAI, acetone, rt, overnight, 72%; (d) chloromethyl ethyl ether, *N*,*N*-diisopropylethylamine, CH_2Cl_2, rt, 6 h, 79%; (e) bis(pinacolato)diboron, KOAc, $PdCl_2$(dppf), 1,4-dioxane, 80 °C, 11 h, 95%; (f) CBr_4, PPh_3, NEt_3, CH_2Cl_2, 0 °C, 30 min, then rt, 1 h, 45%; (**12**), 46% (**13**); (g) K_3PO_4, CuI, THF, 80 °C, 11 h, 89% (**3**), 85% (**4**); (h) **5**, K_2CO_3 (2.0 M aq. Solution), $Pd(PPh_3)_4$, THF, 80 °C, 48 h, 50% (**14**), 60% (**15**); (i) Dowex resin, MeOH, rt, 3 days, 67% (**1**), 77% (**2**).

7.35 (1H, d, *J* = 8.7 Hz), 6.54 (1H, d, *J* = 8.7 Hz), 5.17 (1H, t, *J* = 7.2 Hz), 5.04 (1H, t, *J* = 6.5 Hz), 3.90 (3H, s), 3.34 (2H, d, *J* = 7.2 Hz), 2.03–1.98 (4H, m), 1.77 (3H, s), 1.63 (3H, s), 1.56 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 163.9, 160.6, 135.4, 133.5, 131.1, 124.2, 121.3, 117.1, 115.5, 103.0, 55.9, 39.8, 26.7, 25.7, 21.4, 17.7, 16.2.

3-(3,7-Dimethylocta-2,6-dien-1-yl)-4-(ethoxymethoxy)-2-hydroxybenzaldehyde (7). To a stirred suspension of **10** (0.5 g, 1.82 mmol) and K_2CO_3 (0.655 g, 4.74 mmol) in acetone (20 mL) were added chloromethyl ethyl ether (0.21 mL, 2.19 mmol) and tetrabutylammonium iodide (TBAI) (0.034 g, 0.09 mmol) under nitrogen atmosphere at room temperature. The suspension was stirred for overnight at room temperature. Reaction mixture was filtered through celite pad, washed with acetone (40 mL), and the filtrate was concentrated *in vacuo*. EtOAc (30 mL) and H_2O (20 mL) were added to the residue and two layers separated. The aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layer was washed with brine (2 × 40 mL), dried over anhydrous Na_2SO_4, and was concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/hexane = 1/8) to yield the product **7** (0.436 g, 72%) as a colorless liquid. R_f = 0.42 (EtOAc/hexane = 1/5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.44 (1H, s), 9.69 (1H, s), 7.32 (1H, d, *J* = 8.7 Hz), 6.76 (1H, d, *J* = 8.7 Hz), 5.31 (2H, s), 5.18 (1H, t, *J* = 7.2 Hz), 5.04 (1H, t, *J* = 6.5 Hz), 3.71 (2H, q, *J* = 6.9 Hz), 3.36 (6H, s), 2.20–1.88 (4H, m), 1.78 (3H, s), 1.63 (3H, s), 1.56 (3H, s), 1.21 (2H, t, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7, 161.6, 160.9, 135.4, 133.1, 131.2, 124.2, 121.3, 117.8, 115.8, 105.8, 92.6, 64.7, 39.8, 26.7, 25.8, 21.6, 17.7, 16.2, 15.2.

1-Bromo-3,5-bis(ethoxymethoxy)benzene (11). To a stirred solution of 5-bromoresocinol, **8** (0.809 g, 4.28 mmol) in CH_2Cl_2 (15 mL) was added DIEA (2.98 mL, 17.12 mmol) under nitrogen atmosphere at room temperature. After stirring for 15 min, chloromethyl ethyl ether (0.21 mL, 2.19 mmol) was added dropwise and the mixture was stirred for 6 h at room temperature. After completion of the reaction, H_2O (10 mL) was added and two layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layer was washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/hexane = 1/6) to yield the product **11** (1.03 g, 79%) as a colorless liquid. R_f = 0.7 (EtOAc/hexane = 1/5); ^{1}H NMR (300 MHz, $CDCl_3$) δ

7.08 (2H, d, J = 2.4 Hz), 6.82 (1H, t, J = 2.4 Hz), 5.21 (4H, s), 3.72 (4H, q, J = 6.9 Hz), 1.32 (12H, s), 1.22 (6H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 115.3, 108.2, 93.1, 83.8, 64.3, 24.9, 15.2.

2-(3,5-Bis(ethoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5). To a 15 mL sealed tube equipped with a magnetic stir bar were added compound **11** (0.1 g, 0.33 mmol), bis(pinacolato)diboron (0.125 g, 0.49 mmol), KOAc (0.096 g, 0.98 mmol), and 1,4-dioxane (2 mL), and the mixture was degassed for 3 min. $PdCl_2$(dppf) (0.026 g, 0.04 mmol) was added to the mixture and degassed for another 3 min. The reaction was then stirred at 80 °C for 11 h. Solvent was removed under reduced pressure and the crude was purified by column chromatography (EtOAc/hexane = 1/7) to yield the product **5** (0.109 g, 95%) as a colorless liquid. R_f = 0.65 (EtOAc/hexane = 1/5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (2H, d, J = 2.4 Hz), 6.82 (1H, t, J = 2.4 Hz), 5.21 (4H, s), 3.72 (4H, q, J = 6.9 Hz), 1.32 (12H, s) 1.22 (6H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 115.3, 108.2, 93.1, 83.8, 64.3, 24.9, 15.2.

6-(2,2-Dibromovinyl)-2-(3,7-dimethylocta-2,6-dien-1-yl)-3-methoxyphenol (12). To a stirred solution of PPh_3 (2.281 g, 8.7 mmol) in CH_2Cl_2 (8.7 mL) at 0 °C was added a solution of CBr_4 (1.443 g, 4.35 mmol) in CH_2Cl_2 (4.5 mL). After 10 min, NEt_3 (1.21 mL, 8.7 mmol) was added dropwise and stirred for an additional 5 min, after which a solution of compound **6** (0.417 g, 1.45 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise over 10 min. The internal temperature was maintained below 10 °C, over the addition of all reagents. The vessel was stirred for an additional 30 min at 0 °C, after which it was allowed to warm to room temperature and stirred for an additional 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution. The phases were then separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layer was washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4 and was concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/hexane = 1/5) to yield the product **12** (0.289 g, 45%) as a pale orange color liquid. R_f = 0.59 (EtOAc/hexane = 1/5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (1H, d, J = 8.7 Hz), 7.53 (1H, s), 6.49 (1H, d, J = 8.7 Hz), 5.70 (1H, s), 5.20 (1H, t, J = 7.2 Hz), 5.03 (1H, t, J = 6.5 Hz), 3.81 (3H, s), 3.43 (2H, d, J = 7.2 Hz), 2.17–2.04 (4H, m), 1.81 (3H, s), 1.69 (3H, s), 1.60 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7 153.3, 139.5, 132.2, 132.1, 126.9, 123.5, 121.2, 116.4, 114.4, 102.5, 88.2, 55.7, 39.7, 26.3, 25.8, 22.4, 17.8, 16.2.

6-(2,2-Dibromovinyl)-2-(3,7-dimethylocta-2,6-dien-1-yl)-3-(ethoxymethoxy)phenol (13). Following the procedure used for compound **12** preparation, where compound **7** (222 mg, 0.67 mmol) was used instead of **6**. The crude was purified by column chromatography (EtOAc/hexane = 1/5) to yield the product **12** (0.15 g, 46%) as a pale orange color liquid. R_f = 0.55 (EtOAc/hexane = 1/5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, s), 7.50 (1H, d, J = 8.7 Hz), 6.70 (1H, d, J = 8.7 Hz), 5.67 (1H, s), 5.23 (2H, s), 5.21 (1H, t, J = 7.2 Hz), 5.03 (1H, t, J = 6.5 Hz), 3.72 (2H, q, J = 6.9 Hz), 3.45 (2H, d, J = 7.2 Hz), 2.17–1.99 (4H, m), 1.82 (3H, s), 1.68 (3H, s), 1.60 (3H, s), 1.23 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 153.2, 139.5, 132.2, 132.1, 126.9, 123.4, 121.2, 117.1, 115.5, 106.1, 93.4, 88.7, 64.5, 39.7, 26.3, 25.8, 22.7, 17.8, 16.2, 15.2.

2-Bromo-7-(3,7-dimethylocta-2,6-dien-1-yl)-6-methoxybenzofuran (3). To a 15 mL sealed tube equipped with a magnetic stir bar were added the *gem*-dibromoolefin **12** (0.222 g, 0.50 mmol), CuI (0.004 g, 0.02 mmol), and K_3PO_4 (0.212 g, 1.00 mmol). The tube was flushed with nitrogen for 3 min, after which THF (2.5 mL) was added at room temperature. The mixture was then stirred at 80 °C for 11 h, after which it was allowed to cool to room temperature. The contents were filtered over a pad of celite and washed with copious amounts of Et_2O. The filtrate was concentrated under reduced pressure. The crude was purified by column chromatography (EtOAc/hexane = 1/8) to yield the product **3** (0.161 g, 89%) as a colorless liquid. R_f = 0.59 (EtOAc/hexane = 1/10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (1H, d, J = 7.8 Hz), 6.83 (1H, d, J = 7.8 Hz), 6.60 (1H, s), 5.29 (1H, t, J = 7.5 Hz), 5.04 (1H, t, J = 6.9 Hz), 3.86 (3H, s), 3.56 (2H, d, J = 6.9 Hz), 2.09–1.92 (4H, m), 1.81 (3H, s), 1.62 (3H, s), 1.56 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 154.6, 135.6, 131.2, 126.4, 124.2, 122.3, 121.4, 116.8, 113.8, 108.1, 108.0, 56.7, 39.8, 26.7, 25.7, 22.7, 17.7, 16.2.

2-Bromo-7-(3,7-dimethylocta-2,6-dien-1-yl)-6-(ethoxymethoxy)benzofuran (4). Following the procedure used for compound **3** preparation, where compound **13** (0.19 g, 0.39 mmol) was used instead of **12**. The crude was purified by column chromatography (EtOAc/hexane = 1/8) to yield the product **4** (0.135 g, 85%) as a colorless liquid. R_f = 0.65 (EtOAc/hexane = 1/10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (1H, d, J = 8.7 Hz), 7.04 (1H, d, J = 8.7 Hz), 6.61 (1H, s), 5.28 (1H, t, J = 7.2 Hz), 5.23 (2H, s), 5.03 (1H, t, J = 6.5 Hz), 3.74 (2H, q, J = 6.9 Hz), 3.57 (2H, d, J = 7.2 Hz), 2.10–1.92 (4H, m), 1.82 (3H, s), 1.61 (3H, s), 1.55 (3H, s), 1.23 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 152.3, 135.6, 131.2, 126.6, 124.1, 123.0, 121.4, 116.9, 114.9, 111.8, 108.1, 94.2, 64.3, 39.8, 26.7, 25.7, 23.0, 17.7, 16.2, 15.2.

2-(3,5-Bis(ethoxymethoxy)phenyl)-7-(3,7-dimethylocta-2,6-dien-1-yl)-6-methoxybenzofuran (14). To a 15 mL sealed tube equipped with a magnetic stir bar were added compound **3** (0.033 g, 0.09 mmol), compound **5** (0.044 g, 0.12 mmol), 2.0 M K_2CO_3 aqueous solution (0.13 mL), and THF (1 mL), and the mixture was degassed for 3 min. $Pd(PPh_3)_4$ (0.01 g, 0.01 mmol) was added and degassed for another 3 min. The reaction mixture was then stirred at 80 °C for 48 h. Solvent was removed under reduced pressure. The crude was purified by column chromatography (EtOAc/hexane = 1/8) to yield the product **14** (0.023 g, 50%) as a colorless liquid. R_f = 0.51 (EtOAc/hexane = 1/5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (1H, d, J = 9.0 Hz), 7.16 (2H, d, J = 2.4 Hz), 6.92 (1H, s), 6.85 (1H, d, J = 9.0 Hz), 6.72 (1H, t, J = 2.4 Hz), 5.40 (1H, t, J = 7.2 Hz), 5.28 (4H, s), 5.07 (1H, t,

J = 6.3 Hz), 3.92 (3H, s), 3.79 (4H, q, J = 6.9 Hz), 3.68 (2H, d, J = 7.2 Hz), 2.12–1.97 (4H, m), 1.93 (3H, s), 1.62 (3H, s), 1.56 (3H, s), 1.28 (6H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 155.0, 154.6, 154.1, 135.2, 132.6, 131.1, 124.3, 122.7, 121.8, 117.7, 113.8, 108.0, 106.0, 104.5, 101.9, 93.2, 64.4, 56.7, 39.8, 26.8, 25.7, 22.9, 17.7, 16.3, 15.2.

2-(3,5-Bis(ethoxymethoxy)phenyl)-7-(3,7-dimethylocta-2,6-dien-1-yl)-6-(ethoxymethoxy)benzofuran (15). Following the procedure used for compound **14** preparation, where compound **4** (0.03 g, 0.07 mmol) was used instead of **3**. The crude was purified by column chromatography (EtOAc/hexane = 1/8) to yield the product **15** (0.024 g, 60%) as a colorless liquid. R_f = 0.57 (EtOAc/hexane = 1/5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (1H, d, J = 8.4 Hz), 7.15 (2H, d, J = 2.4 Hz), 7.05 (1H, d, J = 8.4 Hz), 6.92 (1H, s), 6.71 (1H, t, J = 2.4 Hz), 5.37 (1H, t, J = 7.2 Hz), 5.26 (2H, s), 5.25 (4H, s), 5.03 (1H, t, J = 6.5 Hz), 3.75 (4H, q, J = 7.2 Hz), 3.74 (2H, q, J = 7.2 Hz), 3.66 (2H, d, J = 7.2 Hz), 2.09–1.93 (4H, m), 1.89 (3H, s), 1.59 (3H, s), 1.52 (3H, s), 1.25 (9H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 154.8, 154.0, 152.6, 135.3, 132.5, 131.2, 124.2, 123.4, 121.7, 117.9, 114.8, 111.6, 106.0, 104.6, 102.0, 94.3, 93.2, 64.4, 39.8, 26.7, 25.7, 23.1, 17.7, 16.4, 15.2.

5-(7-(3,7-Dimethylocta-2,6-dien-1-yl)-6-methoxybenzofuran-2-yl)benzene-1,3-diol; mulberrofuran B (1). To a stirred solution of compound **14** (0.014 g, 0.03 mmol) in MeOH (2 mL) was added Dowex resin (40 mg) under nitrogen atmosphere and the mixture was stirred at room temperature for 3 days. The resin was filtered, washed with EtOAc (10 mL), and the filtrate was concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/hexane = 1/3) to yield the product **1** (0.007 g, 67%) as a white solid. R_f = 0.15 (EtOAc/hexane = 1/5); mp 65–67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (1H, d, J = 8.4 Hz), 6.89 (1H, s), 6.88 (2H, d, J = 2.4 Hz), 6.86 (1H, d, J = 8.4 Hz), 6.31 (1H, t, J = 2.4 Hz), 5.38 (1H, t, J = 6.9 Hz), 5.04 (1H, t, J = 6.3 Hz), 3.89 (3H, s), 3.64 (2H, d, J = 6.9 Hz), 2.09–1.93 (4H, m), 1.88 (3H, s), 1.60 (3H, s), 1.54 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 155.0, 154.2, 154.1, 135.3, 133.0, 131.3, 124.2, 122.6, 121.8, 117.8, 113.7, 108.0, 104.1, 102.5, 102.0, 56.8, 39.8, 26.7, 25.7, 23.1, 17.8, 12.4; EI-MS *m/z* 392 (M^+, base), 269, 207, 165, 123. HRMS (EI) calcd. for $C_{25}H_{28}O_4$ M^+ 392.1988, found 392.1987.

5-(7-(3,7-Dimethylocta-2,6-dien-1-yl)-6-methoxybenzofuran-2-yl)benzene-1,3-diol (mulberrofuran L) (2). Following the procedure used for compound **1** preparation, where compound **15** (0.02 g, 0.04 mmol) was used instead of **14**. The crude was purified by column chromatography (EtOAc/hexane = 1/5) to yield the product **2** (0.01 g, 77%) as a white solid. R_f = 0.12 (EtOAc/hexane = 1/5); mp 148–151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (1H, d, J = 8.4 Hz), 6.87 (2H, d, J = 2.4 Hz), 6.84 (1H, s), 6.76 (1H, d, J = 8.4 Hz), 6.32 (1H, t, J = 2.4 Hz), 5.40 (4H, br s), 5.04 (1H, t, J = 6.3 Hz), 3.71 (2H, d, J = 7.2 Hz), 2.17–2.02 (4H, m), 1.87 (3H, s), 1.66 (3H, s), 1.57 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 154.0, 153.8, 152.4, 139.1, 133.0, 132.0, 123.6, 122.1, 120.8, 118.6, 112.9, 110.2, 104.1, 102.6, 102.3, 39.7, 26.5, 25.8, 23.2, 17.8, 16.4; EI-MS *m/z* 378 (M^+, base), 293, 254, 207, 123. HRMS (EI) calcd. for $C_{24}H_{26}O_4$ M^+ 378.1831, found 378.1831.

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