A Concise Synthesis of Natural Benzofuran Neolignans and Analogues

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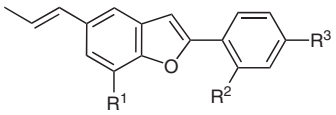
Received 23 March 2010; revised 2 April 2010

Abstract: The first total synthesis of four naturally occurring benzofuran neolignans and two analogues was achieved in four steps in 44–51% overall yield. Key steps involved a two-step construction of benzofuran nucleus and a Suzuki coupling. This synthesis has been proven straightforward and efficient, and more related analogues can be prepared for structure-activity relationship explorations.

Key words: benzofuran, neolignan, McMurry reaction, Suzuki coupling

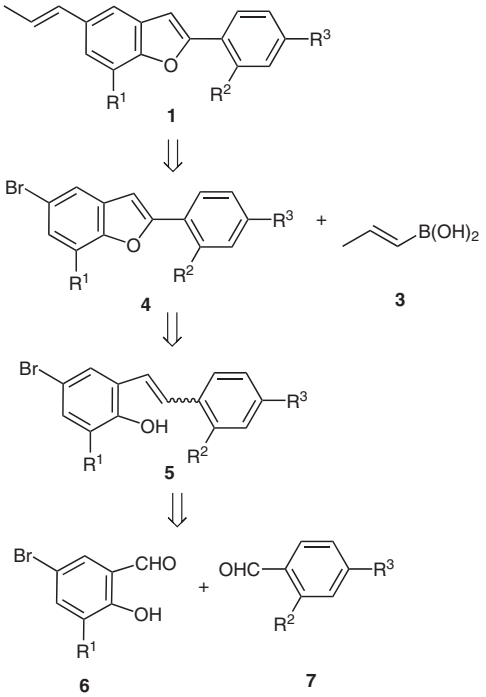
Lignans and neolignans are richly present in nature and exhibit a broad range of biological activities.[1] Benzofuran lignans and neolignans are characteristic members of this family. Various benzofuran neolignans such as ailanthoidol,[2] XH-14,[3] obovaten,[4] egonol,[5] and homoegonol[6] have been isolated and attracted wide attention for their significant pharmacological potentials. Benzofuran neolignans **1a–d** (Figure 1) were isolated from Krameria species.[7] Among them, compound **1a** exhibited valuable antifungal activity[8] and potential for use as antioxidants and radical scavengers.[9] Although preparation for neolignans such as ailanthoidol,[10] XH-14,[11] obovaten,[1] and egonol[12] have been reported, total synthesis of neolignans **1a–d** has not been documented. To this end we continued our efforts to develop a reliable and efficient synthetic route to these benzofuran neolignans and analogues, and thus to explore the corresponding biological activities.



	R^1	R^2	R^3
1a	H	OH	OH
1b	OMe	OH	OH
1c	H	H	OH
1d	OMe	H	OH

Figure 1 Naturally occurring benzofuran neolignans **1**

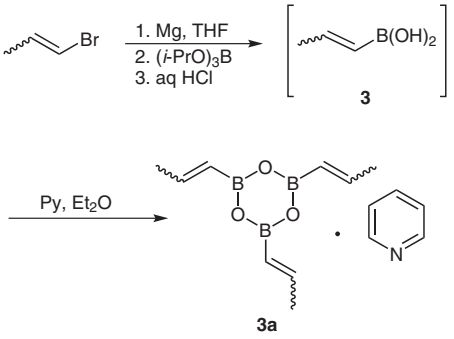
As outlined in Scheme 1, our retrosynthetic analysis of these neolignans **1a–d** envisaged a convergent Suzuki coupling between (*E*)-prop-1-enylboronic acid (**3**) and 5-bromobenzofurans **4**. The key intermediate 5-bromobenzofuran **4** could be obtained via oxidative cyclization from the corresponding *o*-vinylphenol **5**, which can be formed through a selective McMurry cross-coupling of readily available 5-bromosalicylaldehyde or 5-bromo-3-methoxysalicylaldehyde with an aromatic aldehyde **7**. This efficient route should allow for the synthesis of gram quantities of the neolignans to facilitate the preparation of their analogues as well as corresponding biological activity evaluation.



Scheme 1 Retrosynthetic analysis of neolignans **1**

In Scheme 2, the boronic acid **3** required for Suzuki couplings was prepared and then converted into 2,4,6-tri(1-propenyl)cyclotriboroxane–pyridine complex **3a** according to the reported procedure.[13] The ratio of pyridine to cyclotriboroxane in the complex **3a** was about 1:1.3 as confirmed by its ^{1}H NMR spectrum. Following Suzuki coupling of **4** with **3a**, compounds **2** (Scheme 3) were obtained as a mixture of *E*/*Z*-isomers based on their ^{1}H NMR and ^{13}C NMR spectra. Debenzylation of **2** with $TiCl_4$ gave the final products **1** as single *E*-isomers in high yields. This indicated that a mixture of *trans*- and *cis*-1-bromoprop-1-ene can be used instead of more expensive (*E*)-1-bromoprop-1-ene.

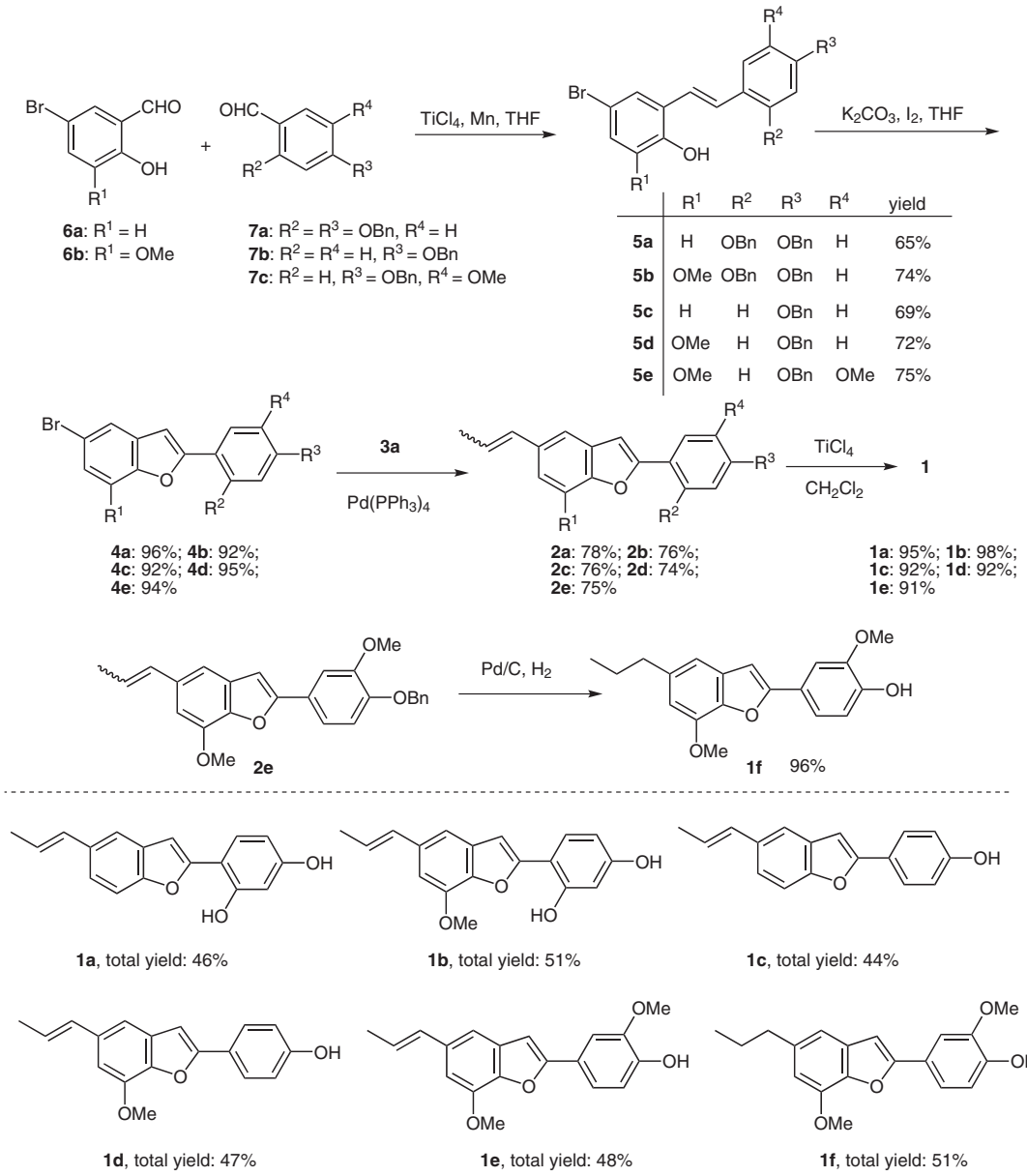
SYNTHESIS 2010, No. 15, pp 2547–2552
Advanced online publication: 17.06.2010
DOI: 10.1055/s-0029-1218826; Art ID: Z07510SS



Scheme 2 Synthesis of 2,4,6-tri[(*E*/*Z*)-1-propenyl]cyclotriboroxane-pyridine complex **3a**

As shown in Scheme 3, the key intermediate bromobenzofurans **4a–e** were prepared through a two-step protocol with 62–71% overall yield: first, *o*-vinylphenols **5a–e** were prepared via the selective McMurry cross-couplings[14] using readily available 5-bromosalicylaldehyde (**6a**) or 5-bromo-3-methoxysalicylaldehyde (**6b**) with aromatic aldehydes **7a–c** in 65–75% isolated yields, and oxidative cyclization of **5a–e** using I_2/K_2CO_3[15] furnished benzofurans in high yields (>90%). The natural products neolignans **1a–d** were obtained in 44–51% overall yield by incorporating the 1-propenyl building block into the bromobenzofurans **4a–e** via a sequential reaction of Suzuki couplings using **3a**, and debenzylation of **2a–e**.

It should be noted that our synthetic strategy can be readily applied to the synthesis of neolignan analogues. For instance, (*E*)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-5-(prop-1-enyl)benzofuran (**1e**) was also facilely prepared in a similar manner (Scheme 3). Another analogue, 2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-5-propylbenzofuran (**1f**), which was once synthesized by Scammells[16] in



Scheme 3 Total synthesis of natural neolignans **1a–d** and two analogues **1e**,**f**

24% overall yield and evaluated as adenosine antagonist, was synthesized in a total yield of 51% starting from **6a** and **7c**.

In summary, we have achieved an efficient total synthesis of naturally occurring neolignans **1a–d** and two analogues **1e**,**f** from readily available aldehydes in four steps in an overall yield of 44–51%. This has featured a very effective approach to construct the neolignan skeleton employing a two-step synthesis of bromobenzofuran and a sequential Suzuki coupling. Because the reagents are readily available and the operations are straightforward, our synthesis proves to be more convenient and effective with higher yields compared with previously reported methods.

All glassware was oven-dried (120 °C) and cooled under a stream of argon gas. The reagents and solvents used for the pinacol-type couplings were freshly distilled or dehydrated before use. All other starting materials were obtained from commercial suppliers and were used without further purification. Petroleum ether (PE) used refers to the fraction boiling in the range 60–90 °C. Analytical TLC was conducted using QDHY GF254 plates. Column chromatography was performed using QDYD silica gel (200–300 mesh). Melting points were recorded on a TECH X-4 microscopic instrument and are uncorrected. IR spectra were obtained using a Vaatar 360 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, using a Bruker Avance 400 spectrometer and TMS as the internal standard. Mass spectra were recorded on a Traces MS spectrometer. Elemental analyses were obtained using an Elementar Vario EL instrument.

2-(2,4-Dibenzyloxystyryl)-4-bromophenol (5a); Typical Procedure

Under argon, a four-necked flask equipped with a magnetic stirrer was charged with Mn powder (1.4 g, 24 mmol) and THF (80 mL). The mixture was cooled to –5 to 0 °C, and $TiCl_4$ (1.3 mL, 12 mmol) was added by a syringe slowly by keeping the temperature under 0 °C. The suspension was warmed to r.t. and stirred for 0.5 h, then heated at reflux for 2.5 h. The mixture was again cooled to –5 to 0 °C, and a solution of 5-bromosalicylaldehyde (**6a**; 0.48 g, 2.4 mmol) and 2,4-dibenzyloxybenzaldehyde (**7a**; 0. 89 g, 2.8 mmol) in THF (30 mL) was added slowly. After the addition, the reaction mixture was heated at reflux until the carbonyl compounds were consumed (monitored by TLC). The reaction was quenched with 10% aq $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude material was purified by flash chromatography over silica gel (PE–EtOAc, 5:1) to give the title product **5a** as a white solid; mp 133–134 °C.

IR (KBr): 3341, 1608, 1505, 1180 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 2.4 Hz, 1 H), 7.32–7.50 (m, 12 H), 7.19 (d, *J* = 2.4 Hz, 1 H), 7.15–7.17 (m, 1 H), 6.68 (d, *J* = 7.3 Hz, 1 H), 6.59–6.62 (m, 2 H), 5.11 (s, 2 H), 5.06 (s, 2 H), 4.86 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 157.4, 151.9, 136.8, 136.7, 130.5, 129.5, 128.69, 128.65, 128.2 128.1, 128.07, 127.8, 127.5, 127.3, 126.8, 120.0, 119.8, 117.5, 113.3, 106.6, 101.0, 70.6, 70.2.

MS (EI): *m*/*z* (%) = 486 (15, [^{81}Br, M$^+$]), 395 (15), 181 (20), 91 (100).

Anal. Calcd for $C_{28}H_{23}BrO_3$: C, 69.00; H, 4.76. Found: C, 68.98; H, 4.86.

2-(2,4-Dibenzyloxystyryl)-4-bromo-6-methoxyphenol (5b)

White solid; mp 114–115 °C.

IR (KBr): 3410, 1599, 1505, 1426, 1279 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 9.3 Hz, 1 H), 7.47–7.48 (m, 1 H), 7.44–7.45 (m, 2 H), 7.29–7.42 (m, 10 H), 6.84 (m, 1 H), 6.59–6.61 (m, 2 H), 5.78 (s, 1 H), 5.12 (s, 2 H), 5.05 (s, 2 H), 3.89 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 157.2, 147.2, 142.2, 136.9, 136.8, 128.61, 128.59, 127.9, 127.5, 127.2, 126.3, 125.0, 121.1, 120.3, 119.9, 112.1, 111.6, 106.6, 100.96, 70.5, 70.2, 56.3.

MS (EI): *m*/*z* (%) = 517 (23, [^{81}Br, M$^+$]), 425 (23), 346 (20), 91 (100).

Anal. Calcd for $C_{29}H_{25}BrO_4$: C, 67.32; H, 4.87. Found: C, 67.58; H, 5.14.

2-(4-Benzyloxystyryl)-4-bromophenol (5c)

White solid; mp 150–152 °C.

IR (KBr): 3444, 1606, 1511, 1247 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 2.4 Hz, 1 H), 7.25–7.40 (m, 7 H), 7.13 (dd, *J* = 2.4, 8.5 Hz, 1 H), 7.00 (dd, *J* = 6.4, 3.6 Hz, 2 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 6.61 (d, *J* = 8.5 Hz, 1 H), 5.02 (s, 2 H), 4.86 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 151.8, 136.8, 131.7, 130.9, 130.7, 130.1, 129.4, 128.6, 128.1, 128.0, 127.5, 127.2, 119.4, 117.5, 115.1, 113.4.

MS (EI): *m*/*z* (%) = 382 (85, [^{81}Br, M$^+$]), 291 (85), 181 (100), 151 (90).

Anal. Calcd for $C_{21}H_{17}BrO_2$: C, 66.16; H, 4.49. Found: C, 66.38; H 4.78.

2-(4-Benzyloxystyryl)-4-bromo-6-methoxyphenol (5d)

White solid; mp 123–125 °C.

IR (KBr): 3504, 1600, 1510, 1477, 1242 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.5 Hz, 2 H), 7.51 (d, *J* = 7.5 Hz, 2 H), 7.24–7.43 (m, 6 H), 7.06 (d, *J* = 9.0 Hz, 2 H), 6.99 (d, *J* = 1.5 Hz, 1 H), 5.17 (s, 2 H), 3.91 (s, 3 H), 3.00 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 148.5, 143.2, 137.4, 130.6 129.4, 128.4, 127.83, 127.78, 127.6, 126.0, 120.4, 119.7, 115.1, 112.8, 110.8, 69.6, 55.9.

MS (EI): *m*/*z* (%) = 410 (40, [^{81}Br, M$^+$]), 319 (65), 197 (80), 91 (100).

Anal. Calcd for $C_{22}H_{19}BrO_3$: C, 64.25; H, 4.66. Found: C, 64.53; H, 4.94.

2-(4-Benzyloxy-3-methoxystyryl)-4-bromo-6-methoxyphenol (5e)

White solid; mp 138–139 °C.

IR (KBr): 3419, 1595, 1513, 1462, 1266 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 7.2 Hz, 2 H), 7.35–7.39 (m, 2 H), 7.30–7.32 (m, 2 H), 7.17–7.21 (m, 1 H), 7.04–7.10 (m, 2 H), 6.99–7.01 (m, 1 H), 6.85–6.87 (m, 2 H), 5.85 (s, 1 H), 5.18 (s, 2 H), 3.95 (s, 3 H), 3.90 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.8, 148.2, 147.3, 142.3, 137.1, 131.0, 130.2, 128.6, 127.8, 127.2, 125.4, 121.1, 120.0, 119.8, 113.96, 112.3, 111.7, 109.5, 71.0, 56.4, 56.0.

MS (EI): *m*/*z* (%) = 440 (20, [^{81}Br, M$^+$]), 349 (100), 241 (25), 96 (100).

Anal. Calcd for $C_{23}H_{21}BrO_4$: C, 62.60; H, 4.80. Found: C, 62.38; H, 4.52.

2-(2,4-Dibenzyloxyphenyl)-5-bromobenzofuran (4a); Typical Procedure

To a solution of *o*-vinylphenol **5a** (4.86 g, 10 mmol) in THF (100 mL) was added anhyd K_2CO_3 (7.7 g, 55.5 mmol) and the mixture was stirred for 10 min. I_2 (14.1 g, 55.5 mmol) was added, and the mixture was stirred at r.t. until **5a** was consumed. The mixture was poured into sat. aq $NaHCO_3$ (150 mL) and treated with sat. aq $NaHSO_3$ (50 mL) to remove the unreacted I_2. The mixture was extracted with EtOAc (3 × 50 mL), the combined organic layers were dried (Na_2SO_4) and concentrated. The crude material was purified by flash chromatography over silica gel (PE–EtOAc, 5:1) to give the title product **4a** as a white solid; mp 151–153 °C.

IR (KBr): 1609, 1499, 1445, 1297 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 9.3 Hz, 1 H), 7.60 (s, 1 H), 7.98 (d, *J* = 9.3 Hz, 1 H), 7.60 (d, *J* = 1.5 Hz, 1 H), 7.50 (d, *J* = 1.6 Hz, 1 H), 7.27–7.48 (m, 10 H), 7.09 (s, 1 H), 6.71 (dd, *J* = 2.1, 7 Hz, 1 H), 5.20 (s, 2 H), 5.11 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 156.98, 153.7, 152.4, 136.5, 136.2, 128.8, 128.7, 128.3, 128.2, 127.7, 127.6, 126.3, 123.3, 115.5, 112.7, 111.98, 106.3, 103.9, 100.8, 70.7, 70.3.

MS (EI): *m*/*z* (%) = 484 (45, [^{81}Br, M^+]), 393 (15), 181 (35), 91 (100).

Anal. Calcd for $C_{28}H_{21}BrO_3$: C, 69.29; H, 4.36. Found: C, 69.05; H, 4.10.

2-(2,4-Dibenzyloxyphenyl)-5-bromo-7-methoxybenzofuran (4b)

White solid; mp 123–125 °C.

IR (KBr): 1607, 1505, 1473, 1288 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.95 (dd, *J* = 1.3, 7.7 Hz, 1 H), 7.27–7.42 (m, 10 H), 7.15 (d, *J* = 1.7 Hz, 1 H), 6.99 (s, 2 H), 6.78 (d, *J* = 1.7 Hz, 1 H), 6.60–6.63 (m, 1 H), 5.11 (s, 2 H), 5.01 (s, 2 H), 3.94 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 156.9, 153.6, 145.3, 141.8, 136.6, 136.3, 132.9, 128.7, 128.6, 128.3, 128.4, 128.3, 128.1, 127.7, 127.6, 115.9, 115.4, 112.6, 109.8, 106.3, 104.1, 100.7, 70.7, 70.3, 56.4.

MS (EI): *m*/*z* (%) = 514 (25) [^{81}Br, M^+], 425 (20), 344 (20), 91 (100).

Anal. Calcd for $C_{29}H_{23}BrO_4$: C, 67.58; H, 4.50. Found: C, 67.50; H, 4.78.

2-(4-Benzyloxyphenyl)-5-bromobenzofuran (4c)

White solid; mp 197–199 °C.

IR (KBr): 1607, 1579, 1504, 1441, 1247 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.6 Hz, 2 H), 7.69 (s, 1 H), 7.37–7.49 (m, 7 H), 7.07–7.09 (d, *J* = 9.0 Hz, 2 H), 6.85 (s, 1 H), 5.16 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.5, 157.3, 153.5, 136.6, 131.5, 128.7, 128.2, 127.5, 127.5, 126.63, 126.56, 123.2, 123.0, 115.9, 115.3, 99.1, 70.1.

MS (EI): *m*/*z* (%) = 380 (40, [^{81}Br, M^+]), 287 (35), 179 (45), 91 (100).

Anal. Calcd for $C_{21}H_{15}BrO_2$: C, 66.51; H, 3.99. Found: C, 66.27; H, 3.98.

2-(4-Benzyloxyphenyl)-5-bromo-7-methoxybenzofuran (4d)

White solid; mp 146–148 °C.

IR (KBr): 1612, 1506, 1471, 1250 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 9.0 Hz, 2 H), 7.36–7.49 (m, 5 H), 7.31 (d, *J* = 14.5 Hz, 1 H), 7.07 (d, *J* = 10 Hz, 2 H), 6.91 (d, *J* = 1.5 Hz, 1 H), 6.83 (s, 1 H), 5.15 (s, 2 H), 4.05 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.5, 157.2, 145.5, 142.8, 136.6, 132.4, 128.7, 128.1, 127.5, 126.7, 122.9, 115.9, 115.7, 115.2, 112.8, 109.8, 99.4, 70.1, 56.4.

MS (EI): *m*/*z* (%) = 408 (50, [^{81}Br, M^+]), 318 (45), 240 (100).

Anal. Calcd for $C_{22}H_{17}BrO_3$: C, 64.56; H, 4.19. Found: C, 64.50; H, 3.83.

2-(4-Benzyloxy-3-methoxyphenyl)-5-bromo-7-methoxybenzofuran (4e)

White solid; mp 154–155.6 °C.

IR (KBr): 1613, 1513, 1476, 1208 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.47 (m, 7 H), 7.30 (d, *J* = 1.7 Hz, 2 H), 6.93–6.95 (m, 1 H), 6.90 (d, *J* = 1.7 Hz, 1 H), 6.82 (s, 1 H), 5.22 (s, 2 H), 4.03 (s, 3 H), 4.00 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2, 149.8, 149.0, 145.4, 142.8, 136.8, 132.3, 128.6, 128.0, 127.3, 123.3, 118.2, 115.9, 115.7, 113.9, 109.8, 108.7, 99.8, 71.0, 56.3, 56.2.

MS (EI): *m*/*z* (%) = 438 (15, [^{81}Br, M^+]), 346 (60), 240 (45), 91 (100).

Anal. Calcd for $C_{23}H_{19}BrO_2$: C, 62.88; H, 4.36. Found: C, 63.10; H, 4.59.

2,4,6-Tri[(*E*/*Z*)-1-propenyl]cyclotriboroxane-Pyridine Complex 3a[13]

Triisopropyl borate (18.5 mL, 89.2 mmol) was added to THF (75 mL) in a flame-dried, four-necked flask kept under argon. The flask was cooled to -78 °C in a dry ice/acetone bath, and prop-1-enylmagnesium bromide (freshly prepared and titrated according to the standard procedure,[17] 1.0 M in THF, 50 mL, 50 mmol) was added dropwise over about 30 min to the borate solution. After the addition of the Grignard reagent, the reaction was allowed to stir for 1 h at –78 °C. The reaction was quenched by adding 30% aq HCl (30 mL). After stirring for 30 min, the solution was warmed to r.t. and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to about 25 mL. Pyridine (10 mL) was added to the solution and the resulting mixture was stirred at r.t. for 5 h. The solvents were evaporated to give a pale yellow oil. Distillation under reduced pressure (85–90 °C/0.1 Torr) gave the product as an oil, which solidified when stored in a refrigerator; yield: 3.3 g (70%).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.75 (d, *J* = 5.6 Hz, 2 H), 7.95 (t, *J* = 7.6 Hz, 1 H), 7.54–7.55 (m, 2 H), 6.41–6.62 (m, 4 H), 5.50 (d, *J* = 17.3 Hz, 2 H), 5.39 (d, *J* = 13.6 Hz, 2 H), 1.77–1.99 (m, 12 H).

MS (EI): *m*/*z* (%) = 204 (3, [M^+]), 162 (8), 79 (100).

(*E*/*Z*)-2-(2,4-Dibenzyloxyphenyl)-5-(propenyl)benzofuran (2a); Typical Procedure

Bromobenzofuran **4a** (6.1g, 12.5 mmol) was dissolved in DME (100 mL), and $Pd(PPh_3)_4$ (0.125 g, 0.625 mmol) was added. The mixture was stirred at r.t. under N_2 for 20 min. Anhyd K_2CO_3 (1.7 g, 12.5 mmol), H_2O (20 mL), and **3a** (3.5 g, 12.5 mmol) were added, and the mixture was heated under reflux under N_2 for 30 h. The mixture was cooled to r.t. and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude material was purified by flash chromatography over silica gel (PE–EtOAc, 5:1) to give the title product **2a** as a white solid; mp 163–165 °C.

IR (KBr): 1602, 1494, 1453, 1377 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.91–7.93 (m, 1 H), 7.43 (d, *J* = 7.2 Hz, 2 H), 7.26–7.44 (m, 10 H), 7.05–7.19 (m, 2 H), 6.63–

6.65 (m, 2 H), 6.38–6.46 (m, 1 H), 5.64–6.14 (m, 1 H), 5.14 (s, 2 H), 5.03 (s, 2 H), 1.84–1.86 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 155.8, 151.7, 151.5, 135.7, 135.5, 131.2, 130.3, 129.2, 128.9, 127.71, 127.65, 127.2, 127.1, 127.0, 126.67, 126.63, 126.55, 119.8, 116.9, 112.3, 109.4, 109.1, 105.3, 103.6, 99.9, 69.6, 69.3, 17.43, 13.6.

MS (EI): *m*/*z* (%) = 446 (10, [M$^+$]), 355 (7), 91 (100).

Anal. Calcd for $C_{31}H_{26}O_3$: C, 83.38; H, 5.87. Found: C, 83.20; H, 6.13.

(*E*/*Z*)-2-(2,4-Dibenzyloxyphenyl)-7-methoxy-5-(propenyl)benzofuran (2b)
White solid; mp 120–122 °C.

IR (KBr): 1611, 1506, 1463, 1287, 1186 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (dd, *J* = 9.6, 5.6 Hz, 1 H), 7.35–7.51 (m, 10 H), 7.13 (d, *J* = 12.4 Hz, 1 H), 7.04 (dd, *J* = 2.8, 1.0 Hz, 1 H), 6.69–6.80 (m, 3 H), 6.43–6.52 (m, 1 H), 5.74–6.21 (m, 1 H), 5.21 (s, 2 H), 5.10 (s, 2 H), 4.05 (s, 3 H), 1.89–2.06 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8, 144.8, 144.4, 142.3, 141.7, 136.7, 136.5, 133.8, 133.1, 131.8, 131.6, 131.5, 130.4, 128.7, 128.6, 128.3, 128.2, 128.15, 128.10, 127.7, 127.6, 127.57, 125.6, 124.2, 113.6, 113.2, 107.9, 106.3, 104.9, 104.89, 104.4, 100.8, 100.79, 70.6, 70.3, 56.2, 56.15, 18.37, 14.65.

MS (EI): *m*/*z* (%) = 476 (15, [M$^+$]), 386 (20), 91 (100).

Anal. Calcd for $C_{31}H_{26}O_3$: C, 83.38; H, 5.87. Found: C, 83.20; H. 5.59.

(*E*/*Z*)-2-(4-Benzyloxyphenyl)-5-(propenyl)benzofuran (2c)
White solid; mp 195–197 °C.

IR (KBr): 1611, 1505, 1253, 1026 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.80 (m, 2 H), 7.34–7.47 (m, 8 H), 7.05 (dd, *J* = 9.2, 2.8 Hz, 2 H), 6.86 (d, *J* = 11 Hz, 1 H), 6.17–6.55 (m, 1 H), 5.73–5.85 (m, 1 H), 5.13 (s, 2 H), 1.89–1.95 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 156.4, 154.0, 136.7, 132.5, 131.1, 129.7, 128.6, 128.1, 127.48, 127.45, 126.4, 125.1, 124.4, 122.0, 117.7, 115.2, 110.8, 99.8, 70.1, 18.5.

MS (EI): *m*/*z* (%) = 340 (50, [M$^+$]), 249 (75), 91 (100).

Anal. Calcd for $C_{24}H_{20}O_2$: C, 84.68; H, 5.92. Found: C, 84.39; H, 5.63.

(*E*/*Z*)-2-(4-Benzyloxyphenyl)-7-methoxy-5-(propenyl)benzofuran (2d)
White solid; mp 158–160 °C.

IR (KBr): 1608, 1505, 1383, 1248 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.8 Hz, 2 H), 7.25–7.39 (m, 5 H), 6.95–7.02 (m, 3 H), 6.74–6.78 (m, 1 H), 6.65 (s, 1 H), 6.37–6.45 (m, 1 H), 5.67–6.21 (m, 1 H), 5.04 (s, 2 H), 3.97 (s, 3 H), 1.82–1.89 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 155.5, 144.0, 143.6, 141.8, 135.8, 133.1, 132.4, 130.4, 130.3, 130.0, 129.3, 127.6, 127.0, 126.5, 125.5, 124.9, 123.5, 122.5, 114.2, 112.3, 109.7, 107.0, 103.5, 99.2, 69.1, 55.19, 55.15.

MS (EI): *m*/*z* (%) = 370 (55, [M$^+$]), 279 (100), 165 (30), 91 (80).

Anal. Calcd for $C_{25}H_{22}O_3$: C, 81.06; H, 5.99. Found: C, 81.29; H, 5.72.

(*E*/*Z*)-2-(4-Benzyloxy-3-methoxyphenyl)-7-methoxy-5-(propenyl)benzofuran (2e)
White solid; mp 104–105.4 °C.

IR (KBr): 1609, 1513, 1275 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.47 (m, 7 H), 7.09–7.17 (m, 1 H), 6.94 (d, *J* = 8.3 Hz, 1 H), 6.72–6.89 (m, 2 H), 6.51 (dd, *J* = 11.5, 1.3 Hz, 1 H), 5.76–5.81 (m, 1 H), 5.21 (s, 2 H), 4.04 (s, 3 H), 3.99 (s, 3 H), 1.94–1.96 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4, 149.8, 148.7, 144.5, 142.7, 136.9, 133.4, 132.3, 130.9, 130.2, 128.6, 128.0, 127.9, 127.3, 126.0, 123.9, 118.2, 118.0, 115.9, 115.7, 114.0, 113.3, 113.1, 109.9, 108.7, 107.8, 100.6, 99.8, 71.0, 56.2, 56.1, 14.7.

MS (EI): *m*/*z* (%) = 400 (20, [M$^+$]), 369 (100), 225 (40).

Anal. Calcd for $C_{26}H_{24}O_4$: C, 77.98; H, 6.04. Found: C, 78.16; H, 6.28.

(*E*)-2-(2,4-Dihydroxyphenyl)-5-(propenyl)benzofuran (1a); Typical Procedure
To a solution of **2a** (4.5 g, 10 mmol) in CH_2Cl_2 (250 mL) was added $TiCl_4$ (2.4 mL, 22.0 mmol) dropwise by a syringe at r.t. The mixture was stirred until completion of the reaction (monitored by TLC). The mixture was quenched by slowly adding distilled H_2O (25 mL) and treated with activated carbon. After filtration of the resulting mixture and concentration, the residue was subjected to flash chromatography over silica gel (PE–EtOAc, 3:1) to give the title product **1a** as a white solid; mp 179–181 °C (Lit.[7a] mp 181–184 °C).

IR (KBr): 3435, 2924, 2854, 1622, 1453 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.93 (m, 1 H), 7.42 (d, *J* = 7.2 Hz, 2 H), 7.05–7.19 (m, 2 H), 6.62–6.64 (m, 2 H), 6.45 (d, *J* = 17.1 Hz, 1 H), 6.07–6.14 (m, 1 H), 4.64 (s, 2 H), 4.19 (s, 1 H), 1.84 (d, *J* = 6.2 Hz, 3 H).

(*E*)-2-(2,4-Dihydroxyphenyl)-7-methoxy-5-(propenyl)benzofuran (1b)
White solid; mp 169–171 °C (Lit.[7a] mp 172–174 °C).

IR (KBr): 3390, 2927, 1621, 1453 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–8.07 (m, 1 H), 7.04–7.15 (m, 2 H), 6.69–6.80 (m, 3 H), 6.49 (d, *J* = 16.2 Hz, 1 H), 6.14–6.23 (m, 1 H), 4.75 (s, 1 H), 4.45 (s, 1 H), 4.05 (s, 3 H), 1.91 (d, *J* = 5.4 Hz, 3 H).

(*E*)-2-(4-Hydroxyphenyl)-5-(propenyl)benzofuran (1c)
White solid; mp 196–198 °C (Lit.[7a] mp 208–211 °C).

IR (KBr): 3298, 1604, 1508, 1456 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77–7.80 (m, 2 H), 7.49–7.50 (m, 1 H), 7.04–7.06 (m, 2 H), 6.84–6.87 (m, 3 H), 6.49 (d, *J* = 17.3 Hz, 1 H), 6.18–6.24 (m, 1 H), 4.86 (s, 1 H), 1.90 (d, *J* = 5.2 Hz, 3 H).

(*E*)-2-(4-Hydroxyphenyl)-7-methoxy-5-(propenyl)benzofuran (1d)
White solid; mp 176–178 °C (Lit.[7a] mp 177–179 °C).

IR (KBr): 3338, 1667, 1458, 1377 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.75 (m, 2 H), 6.96–7.02 (m, 3 H), 6.74–6.78 (m, 1 H), 6.65 (s, 1 H), 6.44 (d, *J* = 16.1 Hz, 1 H), 6.10–6.15 (m, 1 H), 4.65 (s, 1 H), 3.97 (s, 3 H), 1.86 (d, *J* = 5.4 Hz, 3 H).

(*E*)-2-(4-Hydroxy-3-methoxyphenyl)-7-methoxy-5-(propenyl)benzofuran (1e)[18]
White solid; mp 198–199.5 °C.

IR (KBr): 3419, 2931, 1605, 1583, 1477, 1437, 1142 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 7.2 Hz, 2 H), 7.09–7.16 (m, 1 H), 6.72–6.97 (m, 3 H), 6.49–6.52 (d, *J* = 16.8 Hz, 1 H), 5.98–6.10 (m, 1 H), 5.79 (s, 1 H), 4.05 (s, 3 H), 3.96 (s, 3 H), 1.95 (d, *J* = 5.5 Hz, 3 H).

2-(4-Hydroxy-3-methoxyphenyl)-7-methoxy-5-propylbenzofuran (1f)

Compound **2e** (0.6 g, 1.5 mmol) was dissolved in MeOH (15 mL). Pd/C (10%, 0.13 g) was added and the reaction mixture was stirred under 1 atm of H_2 at r.t. After **2e** was consumed (monitored by TLC), the mixture was filtered and evaporated to dryness. The crude material was purified by flash chromatography over silica gel (PE–EtOAc, 3:1) to give the product as a white solid (0.45 g, 96%); mp 105–107 °C; (Lit.[16] mp 106–107 °C).

IR (KBr): 3191, 1607, 1461, 1377, 1298, 1151 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.19 (s, 1 H), 6.45–6.77 (m, 5 H), 5.47 (s, 1 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 2.40 (t, *J* = 7.4 Hz, 2 H), 1.46–1.56 (m, 2 H), 0.85 (t, *J* = 7.3 Hz, 3 H).

Acknowledgment

We gratefully acknowledge the National Nature Science Foundation of China (Grant 20672014) for financial support and Dr. Yao Ma for revising this manuscript.

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