

# An efficient solid-phase synthesis of substituted benzofuran using selenium-bound resin

Yin jun Zhang and Yu guang Wang\*

**A very efficient solid-phase synthesis of substituted benzofuran using polymer-supported selenium resin is described. The advantages of the new method are good yields, high purity, straightforward operations, broad range and high diversity of products, lack of odor, and good stability of the resins. The easy work-up procedure makes the method suitable for building parallel libraries. Copyright © 2012 John Wiley & Sons, Ltd.**

**Keywords:** polymer-supported selenium resin; selenium-induced cyclization; benzofuran; solid-phase synthesis; oxidative cleavage

## Introduction

Solid-phase combinatorial chemistry has been successfully applied in the preparation of many chemical compound libraries, and over the past few years a large variety of solid-phase reactions have been developed.<sup>[1]</sup> Benzofurans are of great interest because of their applications in pharmacology and their wide distribution in nature.<sup>[2]</sup> They constitute an important class of naturally occurring oxygen heterocycles known for their various biological activities such as their antioxidative, peroxisome proliferator activated receptor (PPAR) agonists, antifungal phytoalexins, antiviral, antimicrobial, antineoplastic, and anti-inflammatory properties.<sup>[3]</sup> As a result, a number of routes leading to differently substituted benzofurans have been described in the literature.<sup>[4]</sup> However, to the best of our knowledge, this methodology has not been employed for solid-phase organic synthesis (SPOS) using selenium resin. Since the first organoselenium resin<sup>[5]</sup> used in SPOS with the combined advantages of decreased volatility and simplification of product workup was reported in 1976, several research groups,<sup>[6]</sup> including ours,<sup>[7]</sup> have developed selenium-based approaches for SPOS. Herein, we report an investigation on the preparation of substituted benzofuran via selenium-bound resin. We planned to perform the selenium electrophilic cyclization reaction<sup>[8]</sup> of polystyrene-supported selenenyl bromide **1**, to afford polystyrene-supported 2-selenylmethyl-2,3-dihydro-benzofuran **3**, and then to afford a small library of substituted benzofurans **5** (Scheme 1) through oxidative cleavage.

## Results and Discussion

Our initial experiments began by studying the selenium electrophilic cyclization reaction of polystyrene-supported selenenyl bromide **1** and substituted *o*-allyl phenol **2**. Polystyrene-supported selenenyl bromide<sup>[9]</sup> (resin **1**) (Br: 1.25 mmol g<sup>-1</sup>) was smoothly reacted with substituted *o*-allyl phenol in the presence of dichloromethane at room temperature to afford the corresponding polystyrene-supported 2-selenylmethyl-2,3-dihydrobenzofuran **3**. During the reaction, it was obvious that the dark resin **1** converted to yellow resin **3**. Unfortunately, in the next oxidative cleavage reaction in the presence of H<sub>2</sub>O<sub>2</sub>, we did not obtain the expected

target product **5**, despite the use of different oxidants (e.g. mCPBA (3-chloroperoxybenzoic acid), NaIO<sub>4</sub>) (Scheme 2).

In order to solve these problems, we decided to study the oxidation cleavage reaction of the corresponding small molecule.<sup>[10]</sup>

7-Methyl-2-phenylselenylmethyl-2,3-dihydrobenzofuran **6** was oxidized by 30% hydrogen peroxide to afford selenium sulfoxide **7** easily. After several exploratory experiments, we found that the benzofuran **5f** could be obtained by heating the selenium sulfoxide **7** in toluene in the presence of a small amount of 1,8-diazabicyclo [5,4,0]undec-7-ene (DBU) (Scheme 3).

Referring to the above oxidation cleavage conditions of small molecules, we had an oxidative elimination reaction of resin **3b**, and 2,5-dimethylbenzofuran **5b** was successfully obtained. The follow-up optimization of the oxidative elimination reaction conditions gave better reaction conditions, which were H<sub>2</sub>O<sub>2</sub> as oxidant and DBU as base at a temperature of 80°C (Table 1, Entry 5).

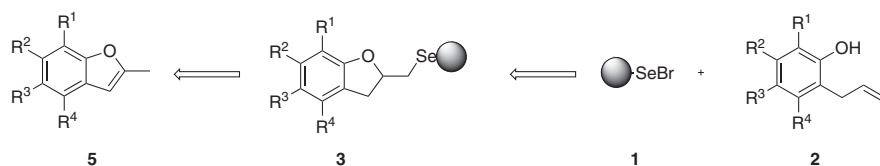
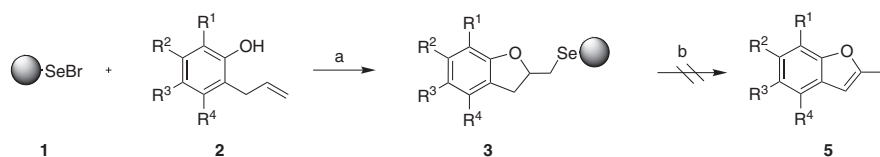
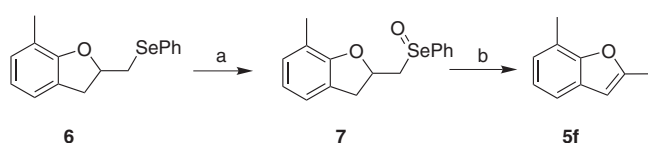
To test the scope of this SPOS protocol, the polystyrene-supported selenium-induced cyclization reactions of a series of substituted *o*-allyl phenol **2** and oxidative elimination reaction of resin **3b** were studied under the above conditions. Finally, benzofurans **5** were obtained in good yields and purities; R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> can be H, halogen, alkyl or ester group respectively. All the products were characterized by spectroscopic measurements. The results are summarized in Table 2. High-performance liquid chromatography (HPLC) analysis showed that the purities of the products were above 88% in most cases.

## Conclusions

In summary, we have developed an efficient method for the synthesis of substituted benzofuran using polymer-supported selenium resin. The 2-methylbenzofuran derivatives were synthesized in three steps, providing 66–84% overall yields and excellent purity. The currently described procedure represents a convenient

\* Correspondence to: Yu guang Wang, College of Biological and Environmental Engineering, Zhejiang University of Technology, Hangzhou, Zhejiang, 310014, P. R. of China. E-mail: yuguangw@zjut.edu.cn

College of Biological and Environmental Engineering, Zhejiang University of Technology, Hangzhou, Zhejiang, 310014, People's Republic of China

**Scheme 1.** Retrosynthetic route of the multi-substituted 2-methyl benzofuran.**Scheme 2.** Reagents and conditions: (a) 1.5 equiv.  $N(Et)_3$ ,  $CH_2Cl_2$ , r.t., 2.0 h; (b) 10.0 equiv.  $H_2O_2$ , THF, r.t., 20.0 h.**Scheme 3.** Reagents and conditions: (a) 10.0 equiv.  $H_2O_2$ , THF, r.t., 3.0 h; (b) 0.2 equiv. DBU, toluene,  $80^\circ C$ , 3.0 h.

synthetic route for benzofuran compounds with several advantages over the other methods, which are good yield, high purity, straightforward operation, broad range and high diversity of the products, lack of odor, mild reaction conditions and good stability of the resins. In particular, the procedure is suitable for application to the automated synthesis of diverse benzofuran-based compounds.

## Experimental

### General Information

Melting points are uncorrected. Starting materials were obtained from commercial suppliers and used without further purification.  $CH_2Cl_2$  was distilled from  $CaH_2$  immediately prior to use, and THF was distilled from sodium/benzophenone immediately prior to use. Polystyrene (H 1000, 100–200 mesh, cross-linked with 1% divinylbenzene) was purchased from commercial sources.  $^1H$  NMR (400 MHz) and  $^{13}C$  NMR (100 MHz) spectra were recorded on a Bruker Avance (400 MHz) spectrometer, using  $CDCl_3$  as the solvent and tetramethylsilane (TMS) as internal standard. Mass spectra (electron impact (EI), 70 eV) were recorded on a Agilent 5975C mass spectrometer. Infrared spectra were recorded on a Bruker Tensor27 spectrometer.

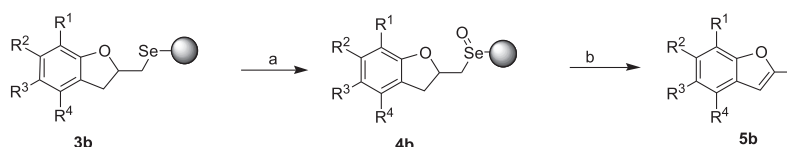
**Table 1.** Optimization of solid-phase conditions of oxidative eliminate of **3b**

| Entry | Oxidant  | Base, temp. ( $^\circ C$ ) | Yield of <b>5a</b> (%) <sup>a</sup> | Purity (%) <sup>b</sup> |
|-------|----------|----------------------------|-------------------------------------|-------------------------|
| 1     | $H_2O_2$ | Pyridine, 60               | 22                                  | >70                     |
| 2     | $H_2O_2$ | Pyridine, 80               | 34                                  | >75                     |
| 3     | $H_2O_2$ | Pyridine, 90               | 34                                  | >75                     |
| 4     | $H_2O_2$ | DBU, 60                    | 81                                  | >85                     |
| 5     | $H_2O_2$ | DBU, 80                    | 90                                  | >88                     |
| 6     | $H_2O_2$ | DBU, 90                    | 89                                  | >88                     |
| 7     | $H_2O_2$ | $Na_2CO_3$ , 60            | 24                                  | >70                     |
| 8     | $H_2O_2$ | $Na_2CO_3$ , 80            | 36                                  | >75                     |
| 9     | $H_2O_2$ | $Na_2CO_3$ , 90            | 36                                  | >75                     |
| 10    | MCPBA    | Pyridine, 80               | 39                                  | >65                     |
| 11    | MCPBA    | DBU, 80                    | 81                                  | >80                     |
| 12    | MCPBA    | $Na_2CO_3$ , 80            | 35                                  | >60                     |
| 13    | $NaIO_4$ | Pyridine, 80               | 33                                  | >75                     |
| 14    | $NaIO_4$ | DBU, 80                    | 79                                  | >80                     |
| 15    | $NaIO_4$ | $Na_2CO_3$ , 80            | 31                                  | >75                     |

<sup>A</sup>Amount based on the loading of selenium bromide resin (Br, 1.25 mmol  $g^{-1}$ ).

<sup>a</sup> Yields of the crude products based on the loading of selenium bromide resin (Br, 1.25 mmol  $g^{-1}$ ).

<sup>b</sup> Determined by HPLC analysis.

**Table 2.** Solid-phase synthesis of benzofurans **5**Reagents and conditions: (a) 20.0 equiv.  $\text{H}_2\text{O}_2$ , r.t., THF, 6 h; (b) 0.5 equiv. DBU,  $80^\circ\text{C}$ , toluene, 8 h.

| <b>5</b>  | $R^1$ | $R^2$           | $R^3$ | $R^4$ | Yield % <sup>a</sup> | Purity (%) <sup>b</sup> |
|-----------|-------|-----------------|-------|-------|----------------------|-------------------------|
| <b>5a</b> | H     | H               | H     | H     | 82                   | 92                      |
| <b>5b</b> | H     | H               | Me    | H     | 80                   | 92                      |
| <b>5c</b> | H     | H               | F     | H     | 79                   | 90                      |
| <b>5d</b> | H     | H               | Cl    | H     | 79                   | 91                      |
| <b>5e</b> | H     | H               | I     | H     | 76                   | 89                      |
| <b>5f</b> | Me    | H               | H     | H     | 84                   | 93                      |
| <b>5g</b> | H     | Me              | H     | H     | 83                   | 94                      |
| <b>5h</b> | H     | Cl              | H     | H     | 82                   | 92                      |
| <b>5i</b> | H     | Ph              | H     | H     | 81                   | 90                      |
| <b>5j</b> | H     | H               | OH    | H     | 80                   | 90                      |
| <b>5k</b> | H     | H               | H     | OH    | 80                   | 91                      |
| <b>5l</b> | COOMe | H               | H     | H     | 81                   | 92                      |
| <b>5m</b> | H     | CH <sub>3</sub> | H     | OH    | 80                   | 88                      |
| <b>5n</b> | Me    | OH              | H     | H     | 81                   | 90                      |
| <b>5o</b> | Cl    | H               | Cl    | H     | 82                   | 90                      |
| <b>5p</b> | —     | —               | —     | —     | 66                   | 85                      |
| <b>5q</b> | —     | —               | —     | —     | 72                   | 88                      |
| <b>5r</b> | —     | —               | —     | —     | 77                   | 89                      |
| <b>5s</b> | —     | —               | —     | —     | 78                   | 90                      |

<sup>a</sup>Yields of the crude products based on the loading of selenium bromide resin (Br,  $1.25 \text{ mmol g}^{-1}$ ).<sup>b</sup>Determined by HPLC analysis.

High-resolution mass spectrometry (HRMS) was performed on a Waters GCT premier instrument. HPLC was performed on an Waters e2695 (2996 photodiode array detector) high-performance liquid chromatograph. The samples were further purified by thin-layer chromatography TLC for  $^{13}\text{C}$  NMR and microanalyses.

#### Typical Procedure for the Preparation of Polystyrene-Supported 2-Selenylmethyl-2,3-dihydrobenzofuran **3**

To a suspension of the swollen polystyrene-supported selenenyl bromide resin **1** (0.8 g,  $1.25 \text{ mmol Br g}^{-1}$ ) in  $\text{CH}_2\text{Cl}_2$  (10 ml), substituted *o*-allyl phenol **2** (3.0 mmol) was added. After stirring for 10 min at room temperature, triethylamine (1.5 mmol) was added and the mixture was stirred for 4.0 h. The resin was collected on a filter and washed successively with  $\text{H}_2\text{O}$  ( $20 \text{ ml} \times 2$ ), THF ( $10 \text{ ml} \times 2$ ), ethanol ( $10 \text{ ml} \times 2$ ), THF– $\text{H}_2\text{O}$  (2:1) ( $10 \text{ ml} \times 2$ ) THF ( $10 \text{ ml} \times 2$ ), and then dried under vacuum overnight to afford resin **3**.

#### Typical Procedure for the Preparation of Substituted 2-Methylbenzofuran **5** (Products **5a–s**)

30%  $\text{H}_2\text{O}_2$  (2.0 ml) was added to a suspension of the swollen prepared resin **3** in THF (15 ml). After stirring for 5.0 h at room temperature, the resin **4** was collected by filtration, washed with  $\text{H}_2\text{O}$  ( $20 \text{ ml} \times 2$ ), THF ( $10 \text{ ml} \times 2$ ), THF– $\text{H}_2\text{O}$  (2:1) ( $10 \text{ ml} \times 2$ ), THF ( $10 \text{ ml} \times 2$ ),  $\text{CH}_2\text{Cl}_2$  ( $10 \text{ ml} \times 2$ ), and toluene ( $10 \text{ ml} \times 2$ ).

The washed resin **4** was suspended in toluene (15 ml), DBU (0.5 mmol) was added, and the mixture was stirred for 8.0 h at  $80^\circ\text{C}$ . The mixture was filtered, and the resin was washed with  $\text{CH}_2\text{Cl}_2$  ( $15 \text{ ml} \times 2$ ). The filtrate was washed with 0.25M HCl ( $30 \text{ ml} \times 2$ ), saturated sodium bicarbonate solution ( $35 \text{ ml} \times 2$ ), dried with anhydrous magnesium sulfate, and evaporated to dryness under vacuum to obtain the crude products **5a–s**. Further purification was via flash chromatography with *n*-hexane–EtOAc (6:1 v/v) as the eluent for microanalyses.

**2-Methylbenzofuran (5a)**

Colorless oil.  $^1\text{H}$  NMR spectral data were consistent with data reported in the literature;<sup>[11]</sup>  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  155.5 ( $\text{O}=\text{C}$ ), 154.8 (2-C), 129.0 ( $\text{Ar}=\text{C}$ ), 123.2 ( $\text{Ar}=\text{C}$ ), 122.5 ( $\text{Ar}=\text{C}$ ), 120.1 ( $\text{Ar}=\text{C}$ ), 110.7 ( $\text{Ar}=\text{C}$ ), 102.7 (3-C), 14.3 ( $=\text{CH}_3$ ); MS (EI)  $m/z$  132 ( $\text{M}^+$ ); IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) 3132, 2981, 1610, 1466, 1252, 1198, 1148, 849, 795; HRMS (EI):  $m/z$  calcd for  $\text{C}_9\text{H}_8\text{O}$ : 132.0575, found: 132.0578.

**2,5-Dimethylbenzofuran (5b)**

Colorless oil.  $^1\text{H}$  NMR spectral data were consistent with data reported in the literature;<sup>[11]</sup>  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  155.5 ( $\text{O}=\text{C}$ ), 153.1 (2-C), 131.7 ( $\text{Ar}=\text{C}$ ), 129.3 ( $\text{Ar}=\text{C}$ ), 124.2 ( $\text{Ar}=\text{C}$ ), 120.0 ( $\text{Ar}=\text{C}$ ), 110.1 ( $\text{Ar}=\text{C}$ ), 102.3 (3-C), 21.3 (5- $\text{CH}_3$ ), 14.1 (2- $\text{CH}_3$ ); MS (EI)  $m/z$  146 ( $\text{M}^+$ ); IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) 3421, 2921, 1607, 1474, 1443, 1259, 1200, 1156, 943, 929, 797, 742; HRMS (EI):  $m/z$  calcd for  $\text{C}_{10}\text{H}_{10}\text{O}$ : 146.0732, found: 146.0735.

**5-Fluoro-2-methylbenzofuran (5c)**

Colorless oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.33–6.90 (m, 3H, Ar), 6.34 (s, H, 3-H), 2.45 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  159.6 ( $J=235.5\text{Hz}$ ,  $\text{F}=\text{C}$ ), 157.9 ( $\text{O}=\text{C}$ ), 151.4 ( $\text{Ar}=\text{C}$ ), 130.5 ( $J=10.8\text{Hz}$ ,  $\text{Ar}=\text{C}$ ), 111.5 ( $J=10.4\text{Hz}$ ,  $\text{Ar}=\text{C}$ ), 110.9 ( $J=26.3\text{Hz}$ ,  $\text{Ar}=\text{C}$ ), 106.2 ( $J=24.6\text{Hz}$ ,  $\text{Ar}=\text{C}$ ), 103.4 ( $J=3.2\text{Hz}$ ,  $\text{Ar}=\text{C}$ ), 14.5 ( $=\text{CH}_3$ ); MS (EI)  $m/z$  150 ( $\text{M}^+$ ); IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) 3442, 2924, 1611, 1470, 1186, 1164, 938, 854, 766, 736. HRMS (EI):  $m/z$  calcd for  $\text{C}_9\text{H}_7\text{FO}$ : 150.0481, found: 150.0480.

**5-Chloro-2-methylbenzofuran (5d)**

Colorless oil.  $^1\text{H}$  NMR spectral data were consistent with data reported in the literature;<sup>[11]</sup>  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  157.0 ( $\text{O}=\text{C}$ ), 153.1 (2-C), 130.5 ( $\text{Ar}=\text{C}$ ), 127.9 ( $\text{Ar}=\text{C}$ ), 123.1 ( $\text{Ar}=\text{C}$ ), 119.7 ( $\text{Ar}=\text{C}$ ), 114.5 ( $\text{Ar}=\text{C}$ ), 102.3 (3-C), 14.0 ( $=\text{CH}_3$ ); MS (EI)  $m/z$  166 ( $\text{M}^+$ ); IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) 3420, 2922, 1601, 1445, 1181, 1064, 942, 906, 865, 793, 694. HRMS (EI):  $m/z$  calcd for  $\text{C}_9\text{H}_7\text{ClO}$ : 166.0185, found: 166.0188.

**5-Iodo-2-methylbenzofuran (5e)**

Low-melting-point solid.  $^1\text{H}$  NMR spectral data was consistent with data reported in the literature;<sup>[12]</sup> MS (EI)  $m/z$  258 ( $\text{M}^+$ ); IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2922, 1613, 1601, 1440, 1180, 1062, 952, 909, 698. HRMS (EI):  $m/z$  calcd for  $\text{C}_9\text{H}_7\text{IO}$ : 257.9542, found: 257.9540.

**2,7-Dimethylbenzofuran (5f)**

Colorless oil.  $^1\text{H}$  NMR spectral data were consistent with data reported in the literature;<sup>[11]</sup>  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  155.0 ( $\text{O}=\text{C}$ ), 153.8 (2-C), 128.6 ( $\text{Ar}=\text{C}$ ), 124.0 ( $\text{Ar}=\text{C}$ ), 122.4 ( $\text{Ar}=\text{C}$ ), 120.8 ( $\text{Ar}=\text{C}$ ), 117.5 ( $\text{Ar}=\text{C}$ ), 102.8 (3-C), 15.0 (7- $\text{CH}_3$ ), 14.1 (2- $\text{CH}_3$ ); MS (EI)  $m/z$  146 ( $\text{M}^+$ ); IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3055, 2921, 1610, 1487, 1258, 1190, 938, 799, 744, 617. HRMS (EI):  $m/z$  calcd for  $\text{C}_{10}\text{H}_{10}\text{O}$ : 146.0732, found: 146.0729.

**2,6-Dimethylbenzofuran (5g)**

Colorless oil.  $^1\text{H}$  NMR spectral data were consistent with data reported in the literature;<sup>[11]</sup>  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  155.2 ( $\text{O}=\text{C}$ ), 154.7 (2-C), 134.1 ( $\text{Ar}=\text{C}$ ), 126.7 ( $\text{Ar}=\text{C}$ ), 123.7 ( $\text{Ar}=\text{C}$ ), 119.6 ( $\text{Ar}=\text{C}$ ), 111.0 ( $\text{Ar}=\text{C}$ ), 102.3 (3-C), 21.7 (6- $\text{CH}_3$ ), 14.1 (2- $\text{CH}_3$ ); MS (EI)  $m/z$  146 ( $\text{M}^+$ ); IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3035, 2926, 1609, 1485, 1288, 1268, 1110, 952, 814, 602. HRMS:  $m/z$  calcd for  $\text{C}_{10}\text{H}_{10}\text{O}$ : 146.0732, found: 146.0733.

**6-Chloro-2-methylbenzofuran (5h)**

Colorless oil.  $^1\text{H}$  NMR spectral data were consistent with data reported in the literature;<sup>[11]</sup> MS (EI)  $m/z$  166 ( $\text{M}^+$ ).

**2-Methyl-6-phenylbenzofuran (5i)**

Colorless oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.64–7.62 (m, 3H, Ar), 7.50 (d,  $J=8.0\text{Hz}$ , 1H, Ar), 7.47–7.43 (m, 3H, Ar), 7.36–7.33 (m, 1H, Ar), 6.39 (s, 1H, 3-H), 2.47 (s, 3H,  $=\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  156.1 ( $\text{O}=\text{C}$ ), 155.4 (2-C), 141.6 ( $\text{Ar}=\text{C}$ ), 136.9 ( $\text{Ar}=\text{C}$ ), 128.9 ( $\text{Ar}=\text{C}$ ), 128.5 ( $\text{Ar}=\text{C}$ ), 127.9 ( $\text{Ar}=\text{C}$ ), 126.9 ( $\text{Ar}=\text{C}$ ), 122.0 ( $\text{Ar}=\text{C}$ ), 120.1 ( $\text{Ar}=\text{C}$ ), 109.2 ( $\text{Ar}=\text{C}$ ), 102.5 (3-C), 14.2 ( $=\text{CH}_3$ ); MS (EI)  $m/z$  208 ( $\text{M}^+$ ); IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3033, 2922, 1601, 1475, 1421, 1278, 1288, 1090, 950, 821, 696. HRMS (EI):  $m/z$  calcd for  $\text{C}_{15}\text{H}_{12}\text{O}$ : 208.0888, found: 208.0890.

**2-Methylbenzofuran-5-ol (5j)**

$^1\text{H}$  NMR spectral data were consistent with data reported in the literature;<sup>[13]</sup> MS (EI)  $m/z$  148 ( $\text{M}^+$ ).

**2-Methylbenzofuran-4-ol (5k)**

Colorless oil.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectral data were consistent with data reported in the literature<sup>[14]</sup>; MS (EI)  $m/z$  148 ( $\text{M}^+$ ); IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3340, 2919, 1603, 1463, 1221, 1024, 950, 866, 780. HRMS (EI):  $m/z$  calcd for  $\text{C}_9\text{H}_8\text{O}_2$ : 148.0524, found: 148.0522.

**2-Methylbenzofuran-7-carboxylic acid methyl ester (5l)**

Colorless oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.84 (d,  $J=8.0\text{Hz}$ , 1H, Ar), 7.64 (d,  $J=8.0\text{Hz}$ , 1H, Ar), 7.39 (s, 1H, 3-Ar), 7.22 (t,  $J=8.0\text{Hz}$ , 1H, Ar), 3.98 (s, 3H,  $\text{O}=\text{CH}_3$ ), 2.53 (s, 3H,  $=\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  165.5 ( $\text{O}=\text{C}$ ), 156.8 ( $\text{O}=\text{C}$ ), 153.5 (2-C), 131.0 ( $\text{Ar}=\text{C}$ ), 125.6 ( $\text{Ar}=\text{C}$ ), 124.9 ( $\text{Ar}=\text{C}$ ), 122.2 ( $\text{Ar}=\text{C}$ ), 114.4 ( $\text{Ar}=\text{C}$ ), 102.4 (3-C), 52.1 ( $\text{O}=\text{CH}_3$ ), 14.1 (2- $\text{CH}_3$ ); MS (EI)  $m/z$  190 ( $\text{M}^+$ ); IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3406, 2928, 1730, 1588, 1319, 1049, 978, 819, 735. HRMS (EI):  $m/z$  calcd for  $\text{C}_{11}\text{H}_{10}\text{O}_3$ : 190.0630, found: 190.0630.

**2,6-Dimethylbenzofuran-4-ol (5m)**

Solid (m.p. 85–87°C).  $^1\text{H}$  NMR spectral data were consistent with data reported in the literature;<sup>[14]</sup>  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  156.8 ( $\text{O}=\text{C}$ ), 153.5 (2-C), 147.8 ( $\text{Ar}=\text{C}$ ), 134.2 ( $\text{Ar}=\text{C}$ ), 115.6 ( $\text{Ar}=\text{C}$ ), 109.2 ( $\text{Ar}=\text{C}$ ), 104.3 ( $\text{Ar}=\text{C}$ ), 99.0 ( $\text{Ar}=\text{C}$ ), 21.6 (6- $\text{CH}_3$ ), 14.1 (2- $\text{CH}_3$ ); MS (EI)  $m/z$  162 ( $\text{M}^+$ ); IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3320, 2917, 1592, 1435, 1310, 1054, 962, 900, 819, 696. HRMS (EI):  $m/z$  calcd for  $\text{C}_{10}\text{H}_{10}\text{O}_2$ : 162.0681, found: 162.0681.

**2,7-Dimethylbenzofuran-6-ol (5n)**

Colorless oil.  $^1\text{H}$  NMR spectral data were consistent with data reported in the literature;<sup>[15]</sup>  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  154.5 ( $\text{Ar}=\text{C}$ ), 154.3 ( $\text{Ar}=\text{C}$ ), 150.2 ( $\text{Ar}=\text{C}$ ), 122.2 ( $\text{Ar}=\text{C}$ ), 116.8 ( $\text{Ar}=\text{C}$ ), 110.9 ( $\text{Ar}=\text{C}$ ), 107.0 ( $\text{Ar}=\text{C}$ ), 102.4 (3-C), 14.0 (2- $\text{CH}_3$ ), 8.2 (7- $\text{CH}_3$ ); MS (EI)  $m/z$  162 ( $\text{M}^+$ ); IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3409, 3279, 2920, 1607, 1425, 1270, 1151, 1074, 932, 815. HRMS:  $m/z$  calcd for  $\text{C}_{10}\text{H}_{10}\text{O}_2$ : 162.0681, found: 162.0682.

**5,7-Dichloro-2-methylbenzofuran (5o)**

White solid (m.p. 74–76°C).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.32(1)–7.31(6) (d,  $J=2.0\text{Hz}$ , 1H, Ar), 7.29–7.20 (d,  $J=1.6\text{Hz}$ , 1H, Ar), 6.35 (s, 1H, 3-H), 2.41 (s, 3H,  $=\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  158.0 ( $\text{Ar}=\text{C}$ ), 149.1 ( $\text{Ar}=\text{C}$ ), 131.4 ( $\text{Ar}=\text{C}$ ), 128.1 ( $\text{Ar}=\text{C}$ ), 123.2 ( $\text{Ar}=\text{C}$ ), 118.4 ( $\text{Ar}=\text{C}$ ), 116.5 ( $\text{Ar}=\text{C}$ ), 103.0 (3-C), 14.0 ( $=\text{CH}_3$ ); MS (EI)  $m/z$  200 ( $\text{M}^+$ ); IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3420, 3078, 1605, 1438, 1410, 1259, 1171, 1077, 929, 866, 840, 775; HRMS (EI):  $m/z$  calcd for  $\text{C}_9\text{H}_6\text{Cl}_2\text{O}$ : 199.9796, found: 199.9798.

**2-Methyl-5,6-methylenedioxybenzofuran (5p)**

Low-melting-point solid.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectral data were consistent with data reported in the literature;<sup>[15]</sup> MS (EI)  $m/z$  176

(M<sup>+</sup>); IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3318, 2959, 1605, 1466, 1319, 1271, 1157, 1049, 948, 810. HRMS (EI):  $m/z$  calcd for C<sub>10</sub>H<sub>8</sub>O<sub>3</sub>: 176.0473, found: 176.0474.

#### 2-Methylnaphtho[1,2-b]furan (5q)

Low-melting-point solid. <sup>1</sup>H NMR spectral data were consistent with data reported in the literature;<sup>[16]</sup> <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  155.3 (Ar=C), 149.4 (Ar=C), 128.5 (Ar=C), 127.9 (Ar=C), 126.9 (Ar=C), 125.6 (Ar=C), 125.1 (Ar=C), 123.0 (Ar=C), 121.9 (Ar=C), 120.0 (Ar=C), 116.4 (Ar=C), 103.1 (3-C), 14.1 (=CH<sub>3</sub>); MS (EI)  $m/z$  182 (M<sup>+</sup>); IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3062, 2921, 1633, 1580, 1359, 1182, 1139, 993, 938, 906, 797, 756, 693; HRMS (EI):  $m/z$  calcd for C<sub>13</sub>H<sub>10</sub>O: 182.0732, found: 182.0733.

#### 2-Methylnaphtho[2,1-b]furan (5r)

Solid (m.p. 56–58 °C). <sup>1</sup>H NMR spectral data were consistent with data reported in the literature;<sup>[16]</sup> <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  154.2 (Ar=C), 152.1 (Ar=C), 130.3 (Ar=C), 128.8 (Ar=C), 127.6 (Ar=C), 125.8 (Ar=C), 125.1 (Ar=C), 124.2 (Ar=C), 123.9 (Ar=C), 123.5 (Ar=C), 112.1 (Ar=C), 101.9 (3-C), 14.3 (=CH<sub>3</sub>); MS (EI)  $m/z$  182 (M<sup>+</sup>); IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3063, 2929, 1628, 1588, 1383, 1186, 1135, 1005, 940, 902, 794, 696. HRMS (EI):  $m/z$  calcd for C<sub>13</sub>H<sub>10</sub>O: 182.0732, found: 182.0729.

#### 2-Methyl-naphtho[2,3-b]furan (5s)

Solid (m.p. 72–74 °C). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.95–7.92 (m, 3H, Ar), 7.83 (s, 1H, Ar), 7.46–7.42 (m, 2H, Ar), 6.50 (m, 1H, 3-H), 2.53 (s, 3H, =CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  158.1 (Ar=C), 153.9 (Ar=C), 130.7 (Ar=C), 130.4 (Ar=C), 127.8 (Ar=C), 127.7 (Ar=C), 124.3 (Ar=C), 123.7 (Ar=C), 117.4 (Ar=C), 105.9 (Ar=C), 102.1 (3-C), 14.3 (=CH<sub>3</sub>); MS (EI)  $m/z$  182 (M<sup>+</sup>); IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3065, 2927, 1625, 1584, 1447, 1132, 1026, 942; HRMS (EI):  $m/z$  calcd for C<sub>13</sub>H<sub>10</sub>O: 182.0732, found: 182.0733.

## Acknowledgements

We are grateful for the financial support of Zhejiang Province Natural Science Foundation of China (project no. Y4090410) and Science and Technology Department of Zhejiang Province Foundation of China (project no. 2010C32022).

## References

- [1] a) G. N. Guillermo, G. M. Rosario, F. C. Asia, M. G. R. Jose, F. M. Antonio, *Comb. Sci.* **2011**, *13*, 458; b) V. Barbora, K. Viktor, S. Miroslav, H. Jan, *Comb. Sci.* **2011**, *13*, 496; c) M. Kimihito, O. Chieko, Y. Mayumi, H. Kenichi, K. Miwa, F. Yoshiyasu, H. Hideaki, *J. Comb. Chem.* **2010**, *12*, 311; d) R. E. Dolle, B. Le Bourdonnec, A. J. Goodman, G. A. Morales, J. M. Salvino, W. Zhang, *J. Comb. Chem.* **2007**, *9*, 855; e) R. E. Dolle, B. Le Bourdonnec, G. A. Morales, K. J. Moriarty, J. M. Salvino, *J. Comb. Chem.* **2006**, *8*, 597; f) R. E. Dolle, *J. Comb. Chem.* **2005**, *7*, 739; g) R. E. Dolle, K. H. Nelson, *J. Comb. Chem.* **1999**, *1*, 235.
- [2] a) Y. X. Tan, Y. Yang, T. Zhang, R. Y. Chen, D. Q. Yu, *Fitoterapia* **2010**, *81*, 742; b) C. Wiese, E. G. Maestrup, D. Schepmann, J. M. Vela, J. Holenz, H. Buschmann, B. Wuensch, *J. Pharm. Pharmacol.* **2009**, *6*, 631; c) D. T. Connor, W. A. Cetenko, M. D. Mullican, R. J. Sorenson, P. C. Unangst, R. J. Weikert, R. L. Adolphson, A. Kennedy, D. O. Thueson, *J. Med. Chem.* **1992**, *35*, 958.
- [3] a) H. Lu, G. T. Liu, *Planta Med.* **1992**, *58*, 311; b) C. Frederic, M. Paul, G. Rene, C. Pascale, A. B. Valerie, B. Jean, R. Pierre, D. H. Caignard, D. Catherine, *Lett. Org. Chem.* **2006**, *3*, 103; c) G. A. Kraus, I. Kim, *Org. Lett.* **2003**, *5*, 1191; d) E. Navarro, S. J. Alonso, J. Trujillo, E. Jorge, C. Pérez, *J. Nat. Prod.* **2001**, *64*, 134; e) Z. F. Hu, L. L. Chen, J. Qi, Y. H. Wang, H. Zhang, B. Y. Yu, *Fitoterapia* **2011**, *82*, 190; f) M. Sun, C. Zhao, G. A. Gfesser, C. Thiffault, T. R. Miller, K. Marsh, J. Wetter, M. Curtis, R. Faghih, T. A. Esbenshade, A. A. Hancock, M. Cowart, *J. Med. Chem.* **2005**, *48*, 6482; g) X. Z. Jiang, W. L. Liu, W. Zhang, F. Q. Jiang, Z. Gao, H. Zhang, L. Fu, *Eur. J. Med. Chem.* **2011**, *46*, 3526.
- [4] a) Y. K. Liu, J. Q. Qian, S. J. Lou, Z. Y. Xu, *J. Org. Chem.* **2010**, *75*, 6300; b) B. Gabriele, R. Mancuso, E. Lupinacci, G. Salerno, L. Veltri, *Tetrahedron* **2010**, *66*, 6156; c) K. Kokubo, K. Harada, E. Mochizuki, T. Oshima, *Tetrahedron Lett.* **2010**, *51*, 955; d) V. Fiandanese, D. Bottalico, G. Marchese, A. Punzi, M. R. Quarta, M. Fittipaldi, *Synthesis* **2009**, *22*, 3853; e) K. C. Majumdar, B. Chattopadhyay, S. Chakravorty, *Synthesis* **2009**, *4*, 674.
- [5] R. Michels, M. Kato, W. Heitz, *Makromol. Chem.* **1976**, *177*, 2311.
- [6] a) F. Zaragoza, *Angew. Chem. Int. Ed.* **2000**, *39*, 2077; b) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G. Q. Cao, S. Barluenga, H. J. Mitchell, *J. Am. Chem. Soc.* **2000**, *122*, 9939; c) K. Fujita, S. Hashimoto, A. Oishi, Y. Taguchi, *Tetrahedron Lett.* **2003**, *44*, 3793; d) R. J. Cohen, D. L. Fox, R. N. Salvatore, *J. Org. Chem.* **2004**, *69*, 4265.
- [7] a) X. Huang, W. M. Xu, *Org. Lett.* **2003**, *5*, 4649; b) W. M. Xu, E. Tang, X. Huang, *Synthesis* **2004**, *13*, 2094; c) Y. G. Wang, W. M. Xu, X. Huang, *J. Comb. Chem.* **2007**, *9*, 513; d) J. Cao, X. Huang, *J. Comb. Chem.* **2010**, *12*, 1; e) J. F. Xu, X. Huang, *J. Comb. Chem.* **2009**, *11*, 938; f) X. Huang, J. Cao, J. Q. Huang, *J. Comb. Chem.* **2009**, *11*, 515; g) X. Huang, J. F. Xu, *J. Comb. Chem.* **2009**, *11*, 350; h) J. Cao, X. Huang, *J. Comb. Chem.* **2008**, *10*, 526.
- [8] K. C. Nicolaou, J. A. Pfefferkorn, G. Q. Cao, *Angew. Chem. Int. Ed.* **2000**, *39*, 734.
- [9] K. C. Nicolaou, J. Pastor, S. Barluenga, N. Winssinger, *Chem. Commun.* **1998**, *18*, 1947.
- [10] M. Tiecco, L. Testaferri, M. Tingoli, F. Marini, *J. Org. Chem.* **1993**, *58*, 1349.
- [11] A. Alemagna, C. Baldoli, P. Buttero, E. Licandro, S. Maiorana, *Synthesis* **1987**, *2*, 192.
- [12] K. Orito, T. Hatakeyama, M. Takeo, H. Sugimoto, M. Tokuda, *Synthesis* **1997**, *1*, 23.
- [13] Y. D. Shen, Y. X. Tian, X. Z. Bu, L. Q. Gu, *Eur. J. Med. Chem.* **2009**, *44*, 3915.
- [14] M. J. Mphahlele, T. B. Moekwa, *Org. Biomol. Chem.* **2005**, *3*, 2469.
- [15] S. W. Youn, J. I. Eom, *Org. Lett.* **2005**, *7*, 3355.
- [16] Y. L. Chow, X. M. Zhou, T. J. Gaitan, Z. Z. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 3813.