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Expeditious synthesis of 2,3-dihydro-2-alkoxy-3-methylenebenzofurans from *N*-benzofuran-3-ylmethyl *N*,*N*,*N*-trialkylammonium bromides: a new approach to access the natural product, 2-hydroxy-3-methylene-6-methyl-2, 3-dihydrobenzofuran

Yuanxiang Wang, Ao Zhang *

Synthetic Organic & Medicinal Chemistry Laboratory (SOMCL), Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences, Shanghai 201203, China

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ABSTRACT

A highly efficient strategy was developed to construct a natural product-based library of 2-alkoxy-3-methylene-2,3-dihydrobenzofurans from *N*-benzofuran-3-ylmethyl *N*,*N*,*N*-trialkylammonium bromides.

1. Introduction

Benzofurans belong to one of the most studied structural units in both the synthetic and medicinal chemistry community.[1] They are widely embedded in many biologically interesting natural products and synthetic analogues.[1,2] Among this large family, benzofuranols represent a fairly small family featured with the furan-2,3 double bond shifting from inside to outside of the furan fragment and with a C2-hemiacetal function.[3] This series of compounds were barely studied due to the limited source and very few available synthetic protocols. The prototypic member of this unique class is compound **1**, a naturally occurring benzofuranol. This compound was first isolated from the roots of the Heleium hybrid in 1969 and reported to have a strong nematicidal activity in vitro.[3a] This compound has become a challenging synthetic target and till now only three syntheses have been reported (Fig. 1). The first synthesis was reported by Bohlmann and co-workers[3a] who in 1969 used 6-methylbenzofuran-3(2*H*)-one (**5**) as the key intermediate followed by a C2-alkylation, MeMgI-nucleophilic attack at the carbonyl moiety in **4** and H_2O-elimination of **3**. In 1977, Divakar et al.[4] reported another synthesis starting from 4,7-dimethyl-2*H*-chromen-2-one (**8**) which was first pyrrolyzed to yield 2-(prop-1-en-2-yl)phenyl acetate (**7**), followed by SeO_2-oxidization and saponification. The last synthesis was reported in 1997 by Snieckus and co-workers[5] who first developed an anionic homologous Fries rearrangement strategy to construct the key intermediate **11** and then converted it to 3-(methoxymethylene)-6-methylbenzofuran-2(3*H*)-one (**10**) followed by sequential reduction and base-induced retro-Michael reaction. The former two synthetic methods suffered from very low yields and harsh reaction conditions, and the third synthesis, although claiming to provide an improvement over the previous methods, provided the target compound (**1**) in only 42–56% yield from intermediate **11**. Therefore, a more practical method allowing for an expeditious access to benzofuranol (**1**) is still needed.

We recently initiated an approach to synthesize a large library of 3-alkoxymethyl benzofurans (**I**, Fig. 2) by reacting bromide **12**[6] with a line of sodium alkoxides for our high-throughput screening (HTS) program. Although the exact mechanism of this substitution reaction was not investigated, we envisioned that it may proceed by formation of an active species A, which is then converted to product **I** through a S_N1 or S_N2 nucleophilic substitution pathway (Fig. 2).[7] Alternatively, a conjugated species B might also be formed during this transformation, and could likely provide compound **II** with the furan-2,3 double bond shifting to the outside of the ring system. Since the formation of aromatic product **I** through species A is preferred in most cases, the production of compound **II** through species B would be largely dependent on the leaving ability of the X

* Corresponding author. Tel./fax: +86 21 50806035.
E-mail address: aozhang@mail.shcnc.ac.cn (A. Zhang).

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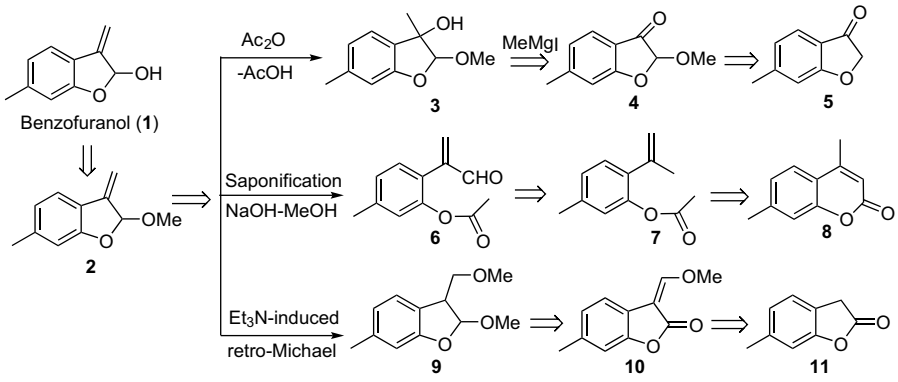


Figure 1.

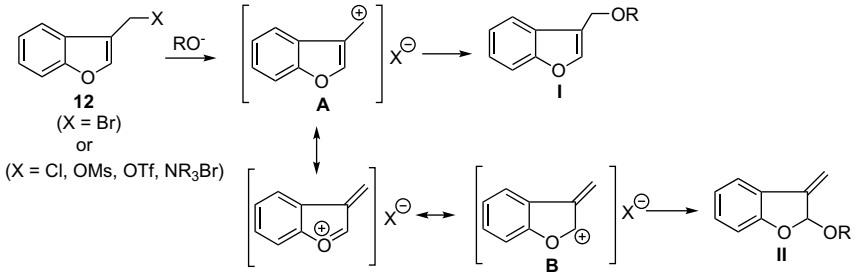


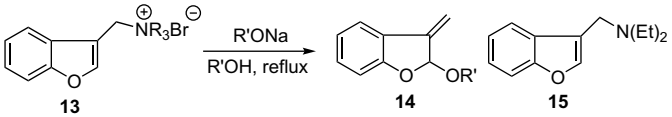
Figure 2.

group in **12**. We envisioned that if the leaving ability of X group in **12** was slowed down, there might be a chance to form product **II** that contains a similar structural scaffold as in the natural product **1**. To identify an appropriate X group, we prepared a small series of benzofurans **12** with various X group, including –Br, –Cl, –OAc, –OMs, –OTf and $-NEt_3Br$, and explored their reactions with sodium alkoxides. To our surprise, we found that compound **II** can be obtained dominantly over **I** by using *N*-benzofuran-3-ylmethyl *N*,*N*,*N*-triethylammonium bromide salt (**13a**) as the substrate, whereas other substrates only gave the directly substituted product **I**. Although the exact mechanism is not clear, we believe that the slowest leaving ability of $-NEt_3Br$ among the substituents (–Br, –Cl, –OAc, –OMs, –OTf and $-NEt_3Br$) we explored plays a critical role. Herein we wish to present our investigation on this transformation, improved synthesis of the natural product **1** and the construction of a library of its analogs in details.

2. Results and discussion

The ammonium bromide salts **13a** and **13b** were prepared by reacting benzofuran-3-ylmethyl bromide **12**[6] with an excess of Et_3N or Me_3N (in EtOH) in quantitative yields.[8,9] The salts were highly moisture-sensitive and had to be stored in a vacuum. To achieve complete transformation, a large amount of sodium or potassium alkoxides prepared in situ[10] or obtained from a commercially available source was used. As summarized in Table 1, most commonly-used sodium alkoxides participated in this reaction very well, and the expected 2-alkyloxy-3-methylene-2,3-dihydrobenzofurans **14a-f** were obtained in moderate to good yields. In all cases, the directly substituted products (**I**) were not observed. It was of note that using steric alkoxides or alkoxides with a slightly longer chain, *N*,*N*-diethylaminomethyl benzofuran **15**[9] was obtained as a by-product, especially in the case of *t*-BuOK (entry 6), where **15** was obtained as the major product in 83% yield. The production of compound **15** can be rationalized by a β-H Hoffmann elimination[11] from substrate **13a**. To block this path, *N*-benzofuran-3-ylmethyl *N*,*N*,*N*-trimethyl ammonium bromide **13b** lacking a β-H was employed. As expected, all alkoxides participated efficiently, and the expected products **14f–j** (Table 1, entries 7–11) were isolated in high yields, no by-product **15** was observed.

Table 1
Reaction of ammonium bromides **13** with various sodium alkoxides[a]



Entry	Substrate	R′	Temp	Time (min)	Product	Yield[b] (%)
1	**13a**	Me[c]	70	120	**14a**	64
2	**13a**	Et[c]	80	120	**14b**	70
3	**13a**	*n*-Pr	100	120	**14c**	46 (trace[e])
4	**13a**	*n*-Bu	120	120	**14d**	74 (10[e])
5	**13a**	*i*-Pr	85	30	**14e**	64 (28[e])
6	**13a**	*t*-Bu[d]	85	120	**14f**	8 (83[e])
7	**13b**	*t*-Bu[d]	85	60	**14f**	68
8	**13b**	*i*-Bu	100	30	**14g**	88
9	**13b**	*i*-Pentyl	120	30	**14h**	85
10	**13b**	*n*-Hexyl	120	30	**14i**	90
11	**13b**	$C_2H_5(Me)CH$	100	30	**14j**	88

[a] Unless specified, sodium alkoxides were prepared in situ.
[b] Isolated yield.
[c] Commercially available 20 equiv was used.
[d] *t*-BuOK (20 equiv) was used.
[e] Yield for compound **15**.

To further examine the efficacy of this reaction and to expand our collection of the unique class of compounds, a series of sodium alkoxides prepared from sodium metal and several high boiling

alcohols including diols (Table 2, entries 1–4, 8) and mono end-capped diols (entries 5–7, 9, 10) was employed. As demonstrated in Table 2, all these alkoxides reacted with ammonium salt **13a** much quicker than the alkoxides listed in Table 1. All these reactions were completed in less than 30 min providing the corresponding benzofuranols **14k–t** in high yields. The mono-end capped diols (entries 5–9) reacted more efficiently than non-protected diols, with complete reaction in 10 min (entries 1–4). No directly substituted, or Hoffmann elimination products were observed.

Table 2
Reaction of ammonium bromide **13a** with various sodium alkoxides[a]

13a **14**

Entry	R′–	Time (min)[c]	Product	Yield[b] (%)
1	$HO(CH_2)_2$–	30	**14k**	82
2	$HO(CH_2)_3$–	30	**14l**	82
3	$HO(CH_2)_4$–	30	**14m**	72
4	$HO(CH_2)_5$–	30	**14n**	71
5	$MeOCH_2CH_2$–	10	**14o**	85
6	$EtOCH_2CH_2$–	10	**14p**	86
7	*i*-$PrOCH_2CH_2$–	10	**14q**	88
8	$HO(CH_2)_2O(CH_2)_2$–	10	**14r**	88
9	$MeO(CH_2)_2O(CH_2)_2$–	5	**14s**	79
10	$EtO(CH_2)_2O(CH_2)_2$–	5	**14t**	75

[a] Sodium alkoxides (in alcohol, 20% v/v) were prepared in situ.
[b] Isolated yield.
[c] Reaction completion time determined by TLC.

Encouraged by the results obtained above, we decided to complete the synthesis of the natural product **1**. Similarly, salt **16** was prepared from 6-methylbenzofuran-3-ylmethyl bromide[12] and Me_3N in EtOH in quantitative yield (Scheme 1). Treating salt **16** with excess MeONa (20 equiv) in MeOH under reflux provided 2-methoxy-6-methyl-3-methylene-2,3-dihydrobenzofuran (**17**) in 83% yield. Following a literature procedure,[3a,4,5] precursor **17** was hydrolyzed to yield the target compound **1** in 85% yield. Compared to the methods reported, our protocol was more efficient and afforded benzofuranol **1** in three steps with 70% overall yield from a more commonly used intermediate, 6-methylbenzofuran-3-ylmethyl bromide.

3. Conclusions

We have developed an efficient strategy to construct a library of 2-alkoxy-3-methylene-2,3-dihydrobenzofurans by using benzofuran-3-ylmethyl *N*,*N*,*N*-trialkylammonium bromide salts as the substrate. Thus, treating these salts with various sodium/potassium alkoxides which were readily prepared in situ from sodium metal and simple alcohols, diols or mono-end capped diols afforded the corresponding 2-alkoxy-3-methylene-2,3-dihydrobenzofurans in high yield. This convenient approach was applied to prepare the natural product **1**, which was obtained in three steps with 70% overall yield from a common intermediate, 6-methylbenzofuran-3-ylmethyl bromide.

4. Experimental

4.1. General procedure[8,9] for the preparation of ammonium salts 13a, 13b and 16

Et_3N (10 mL) or Me_3N (in EtOH, 10 mL, 33%) was added to a solution of 3-bromomethylbenzofuran[6,12] (15 mmol) in THF–$CHCl_3$ (20 mL, vol/vol: 3:1). The mixture was stirred at rt overnight. After removal of the solvents, a yellow residue was obtained which was then washed with petroleum ether to afford an off-white solid in quantitative yield. *For salt* ***13a***. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (s, 1H), 7.83 (d, J=6.6 Hz, 1H), 7.44 (d, J=8.7 Hz, 1H), 7.28 (m, 2H), 5.15 (s, 2H), 3.51 (q, J=7.2 Hz, 6H), 1.48 (t, J=7.2 Hz, 9H). *For* ***13b***. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (s, 1H), 8.04 (d, J=6.9 Hz, 1H), 7.46 (d, J=8.9 Hz, 1H), 7.27 (m, 2H), 5.33 (s, 2H), 3.44 (s, 9H). *For salt* ***16***. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (s, 1H), 7.88 (d, J=9.0 Hz, 1H), 7.29 (s, 1H), 7.10 (d, J=8.4 Hz, 1H), 5.32 (s, 2H), 3.45 (s, 9H), 2.43 (s, 3H).

4.2. General procedure for the preparation of 2-alkoxy-2,3-dihydro-3-methylenebenzofurans 14a–t

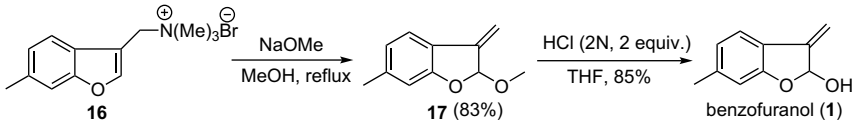
To a solution of sodium alcoholate (20 equiv, obtained commercially or prepared in situ from sodium metal with alcohol) in the corresponding alcohol (25 mL), was added quickly salt **13a** or **13b** (1 equiv). The mixture was heated at reflux or 120 °C (for high boiling alcohols) for the time indicated in Tables 1 and 2. The reaction was cooled, quenched with water, and extracted with Et_2O (3×40 mL). The combined ether phase was washed with brine, dried over anhyd Na_2SO_4, and evaporated. The crude product was purified with column chromatograph (petroleum ether/CH_2Cl_2=20:1) to give 2,3-dihydro-2-alkoxy-3-methylenebenzofurans **14a–t**.

*4.2.1. 2-Methoxy-2,3-dihydro-3-methylenebenzofuran (**14a**)*[4]

Yellow oil; MS (EI) 162 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (d, J=7.5 Hz, 1H), 7.22 (d, J=8 Hz, 1H), 6.89 (m, 2H), 5.98 (t, J=2.1 Hz, 1H), 5.70 (d, J=2.1 Hz, 1H), 5.33 (d, J=1.5 Hz, 1H), 3.52 (s, 3H).

*4.2.2. 2-Ethoxy-2,3-dihydro-3-methylenebenzofuran (**14b**)*[4]

Yellow oil; MS (EI) 176 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (d, J=7.5 Hz, 1H), 7.21 (t, J=7.8 Hz, 1H), 6.88 (m, 2H), 6.03 (t, J=2.0 Hz, 1H), 5.68 (d, J=2.1 Hz, 1H), 5.33 (d, J=1.8 Hz, 1H), 3.92 (dq, J=9.6, 7.2 Hz, 1H), 3.71 (dq, J=9.6, 7.2 Hz, 1H), 1.29 (t, J=7.0 Hz, 3H).



16 **17** (83%) benzofuranol (**1**)

Scheme 1.

*4.2.3. 2-n-Propoxy-2,3-dihydro-3-methylenebenzofuran (**14c**)*

Colorless oil; MS (EI) 190 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (d, J=7.5 Hz, 1H), 7.22 (t, J=7.8 Hz, 1H), 6.88 (m, 2H), 6.04 (t, J=2.0 Hz, 1H), 5.66 (d, J=2.1 Hz, 1H), 5.32 (d, J=2.1 Hz, 1H), 3.81 (dt, J=9.3, 6.6 Hz, 1H), 3.59 (dt, J=9.3, 6.9 Hz, 1H), 1.68 (m, 2H), 0.96 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.9, 143.5, 130.6, 124.2, 121.0, 120.9, 110.4, 106.7, 106.5, 69.5, 22.9, 10.5. HRMS (EI) calcd for $C_{12}H_{14}O_2$ (M^+) 190.0994, found 190.0997.

*4.2.4. 2-n-Butoxy-2,3-dihydro-3-methylenebenzofuran (**14d**)*

Colorless oil; MS (EI) 204 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (d, J=8.7 Hz, 1H), 7.22 (t, J=8.4 Hz, 1H), 6.85 (m, 2H), 6.03 (t, J=1.8 Hz, 1H), 5.68 (d, J=2.1 Hz, 1H), 5.32 (d, J=1.8 Hz, 1H), 3.86 (dt,

J=9.3, 6.6 Hz, 1H), 3.64 (dt, *J*=9.3, 6.6 Hz, 1H), 1.63 (m, 2H), 1.42 (m, 2H), 0.93 (t, *J*=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.9, 143.5, 130.6, 124.2, 121.0, 120.9, 110.3, 106.6, 106.5, 67.5, 31.6, 19.1, 13.7; HRMS (EI) calcd for $C_{13}H_{16}O_2$ (M^+) 204.1150, found 204.1148.

*4.2.5. 2-Isopropoxy-2,3-dihydro-3-methylenebenzofuran (**14e**)*

Colorless oil; MS (EI) 190 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (d, *J*=7.5 Hz, 1H), 7.21 (t, *J*=7.8 Hz, 1H), 6.87 (m, 2H), 6.08 (t, *J*=2.0 Hz, 1H), 5.65 (d, *J*=2.1 Hz, 1H), 5.28 (d, *J*=1.8 Hz, 1H), 4.14 (m, 1H), 1.31 (d, *J*=6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.8, 144.1, 130.6, 124.2, 121.0, 120.8, 110.4, 106.4, 105.4, 71.6, 23.6, 22.2; HRMS (EI) calcd for $C_{12}H_{14}O_2$ (M^+) 190.0994, found 190.0995.

*4.2.6. 2-t-Butoxy-2,3-dihydro-3-methylenebenzofuran (**14f**)*

Colorless oil; MS (EI) 204 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (d, *J*=7.5 Hz, 1H), 7.20 (t, *J*=7.8 Hz, 1H), 6.85 (m, 2H), 6.20 (t, *J*=2.0 Hz, 1H), 5.65 (d, *J*=2.1 Hz, 1H), 5.28 (d, *J*=1.8 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.9, 145.2, 130.5, 124.0, 121.0, 120.6, 110.4, 105.8, 101.9, 28.8; HRMS (EI) calcd for $C_{13}H_{16}O_2$ (M^+) 204.1150, found 204.1141.

*4.2.7. 2-i-Butoxy-2,3-dihydro-3-methylenebenzofuran (**14g**)*

Colorless oil; MS (EI) 204 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41 (d, *J*=7.5 Hz, 1H), 7.23 (t, *J*=7.6 Hz, 1H), 6.91 (m, 2H), 6.05 (t, *J*=1.8 Hz, 1H), 5.69 (d, *J*=2.1 Hz, 1H), 5.34 (d, *J*=1.5 Hz, 1H), 3.65 (m, 1H), 3.39 (m, 1H), 1.96 (m, 1H), 0.96 (d, *J*=6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.8, 143.4, 130.6, 124.2, 121.0, 120.8, 110.3, 106.6 (two), 74.3, 28.4, 19.3, 19.2; HRMS (EI) calcd for $C_{13}H_{16}O_2$ (M^+) 204.1150, found 204.1155.

*4.2.8. 2-i-Pentoxy-2,3-dihydro-3-methylenebenzofuran (**14h**)*

Colorless oil; MS (EI) 218 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (d, *J*=7.8 Hz, 1H), 7.22 (t, *J*=7.8 Hz, 1H), 6.88 (m, 2H), 6.03 (s, 1H), 5.68 (s, 1H), 5.32 (s, 1H), 3.88 (m, 1H), 3.66 (m, 1H), 1.75 (m, 1H), 1.55 (m, 2H), 0.92 (d, *J*=7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.9, 143.4, 130.6, 124.2, 121.0, 120.9, 110.3, 106.7, 106.4, 66.2, 38.3, 24.8, 22.5; HRMS (EI) calcd for $C_{14}H_{18}O_2$ (M^+) 218.1307, found 218.1307.

*4.2.9. 2-n-Hexoxy-2,3-dihydro-3-methylenebenzofuran (**14i**)*

Colorless oil; MS (EI) 232 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (d, *J*=7.8 Hz, 1H), 7.22 (t, *J*=7.8 Hz, 1H), 6.90 (m, 2H), 6.04 (t, *J*=2.1 Hz, 1H), 5.68 (d, *J*=2.4 Hz, 1H), 5.33 (d, *J*=1.8 Hz, 1H), 3.88 (m, 1H), 3.66 (m, 1H), 1.66 (m, 2H), 1.34 (m, 6H), 0.91 (t, *J*=3.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.9, 143.4, 130.6, 124.2, 121.0, 120.8, 110.3, 106.6, 106.4, 67.9, 31.5, 26.5, 25.6, 22.5, 13.9; HRMS (EI) calcd for $C_{15}H_{20}O_2$ (M^+) 232.1463, found 232.1464.

*4.2.10. 2-(2′-Methylpropoxy)-2,3-dihydro-3-methylene-benzofuran (**14j**)*

Colorless oil; MS (EI) 204 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (d, *J*=7.2 Hz, 1H), 7.22 (t, *J*=7.5 Hz, 1H), 6.88 (m, 2H), 6.07 (s, 1H), 5.66 (d, *J*=1.8 Hz, 1H), 5.30 (d, *J*=10.2 Hz, 1H), 3.90 (m, 1H), 1.67 (m, 1H), 1.53 (m, 1H), 1.32 (d, *J*=6.6 Hz, 1.6H), 1.28 (d, *J*=6.3 Hz, 1.4H), 1.01 (t, *J*=7.5 Hz, 1.6H), 0.93 (t, *J*=7.5 Hz, 1.4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.9, 160.8, 144.2, 144.1, 130.5, 124.2, 124.1, 121.0, 120.7, 110.4, 106.6, 106.4, 106.3, 105.1, 78.0, 76.3, 29.9, 29.4, 21.2, 19.5, 9.8; HRMS (EI) calcd for $C_{13}H_{16}O_2$ (M^+) 204.1150, found 204.1156.

*4.2.11. 2-(2′-Hydroxyethoxy)-2,3-dihydro-3-methylene-benzofuran (**14k**)*

Colorless oil; MS (EI) 192 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (d, *J*=7.2 Hz, 1H), 7.23 (t, *J*=7.8 Hz, 1H), 6.90 (m, 2H), 6.07 (t, *J*=1.8 Hz, 1H), 5.70 (d, *J*=2.1 Hz, 1H), 5.36 (d, *J*=1.8 Hz, 1H), 3.92 (m, 1H), 3.82 (m, 3H), 2.34 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.4, 142.8, 130.6, 123.9, 121.1, 120.9, 110.3, 107.1, 106.3, 69.1, 61.5; HRMS (EI) calcd for $C_{11}H_{12}O_3$ (M^+) 192.0786, found 192.0783.

*4.2.12. 2-(3′-Hydroxypropoxy)-2,3-dihydro-3-methylene benzofuran (**14l**)*

Colorless oil; MS (EI) 206 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (d, *J*=7.2 Hz, 1H), 7.21 (t, *J*=7.8 Hz, 1H), 6.90 (m, 2H), 6.03 (t, *J*=1.8 Hz, 1H), 5.68 (d, *J*=1.8 Hz, 1H), 5.36 (d, *J*=1.5 Hz, 1H), 3.97 (dt, *J*=9.6, 6.0 Hz, 1H), 3.79 (m, 3H), 2.22 (s, 1H), 1.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.6, 143.1, 130.6, 124.0, 121.0, 120.9, 110.2, 106.8, 106.2, 65.3, 60.1, 32.0; HRMS (EI) calcd for $C_{12}H_{14}O_3$ (M^+) 206.0943, found 206.0946.

*4.2.13. 2-(4′-Hydroxybutoxy)-2,3-dihydro-3-methylene-benzofuran (**14m**)*

Colorless oil; MS (EI) 220 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (d, *J*=8.4 Hz, 1H), 7.21 (t, *J*=7.6 Hz, 1H), 6.88 (m, 2H), 6.02 (t, *J*=3.0 Hz, 1H), 5.68 (d, *J*=2.1 Hz, 1H), 5.32 (d, *J*=1.8 Hz, 1H), 3.88 (dt, *J*=9.6, 6.0 Hz, 1H), 3.66 (m, 3H), 1.89 (s, 1H), 1.69 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.7, 143.1, 130.6, 124.0, 120.9, 110.2, 106.8, 106.2, 67.5, 62.1, 29.3, 25.9; HRMS (EI) calcd for $C_{13}H_{16}O_3$ (M^+) 220.1099, found 220.1098.

*4.2.14. 2-(5′-Hydroxypentoxy)-2,3-dihydro-3-methylene-benzofuran (**14n**)*

Colorless oil; MS (EI) 234 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (d, *J*=7.5 Hz, 1H), 7.21 (t, *J*=7.6 Hz, 1H), 6.88 (m, 2H), 6.02 (t, *J*=1.6 Hz, 1H), 5.68 (d, *J*=2.1 Hz, 1H), 5.32 (d, *J*=1.8 Hz, 1H), 3.85 (dt, *J*=9.6, 6.0 Hz, 1H), 3.64 (m, 3H), 1.68 (m, 2H), 1.59 (m, 2H), 1.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.8, 143.3, 130.6, 124.1, 121.0, 120.9, 110.3, 106.8, 106.3, 67.6, 62.6, 32.2, 29.2, 22.1; HRMS (EI) calcd for $C_{14}H_{18}O_3$ (M^+) 234.1256, found 234.1249.

*4.2.15. 2-(2′-Meoxyethoxy)-2,3-dihydro-3-methylene benzofuran (**14o**)*

Yellow oil; MS (EI) 206 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (d, *J*=7.5 Hz, 1H), 7.21 (t, *J*=7.8 Hz, 1H), 6.88 (m, 2H), 6.10 (t, *J*=1.8 Hz, 1H), 5.69 (d, *J*=2.1 Hz, 1H), 5.38 (d, *J*=1.8 Hz, 1H), 3.92 (dt, *J*=9.6, 6.0 Hz, 1H), 3.76 (dt, *J*=9.6, 6.0 Hz, 1H), 3.60 (t, *J*=4.8 Hz, 2H), 3.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.7, 142.8, 130.5, 124.1, 120.9 (two), 110.2, 107.1, 106.2, 71.4, 65.9, 58.9; HRMS (EI) calcd for $C_{12}H_{14}O_3$ (M^+) 206.0943, found 206.0936.

*4.2.16. 2-(2′-Ethoxyethoxy)-2,3-dihydro-3-methylene-benzofuran (**14p**)*

Brown oil; MS (EI) 220 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (d, *J*=7.5 Hz, 1H), 7.20 (t, *J*=7.8 Hz, 1H), 6.87 (m, 2H), 6.11 (t, *J*=1.8 Hz, 1H), 5.69 (d, *J*=2.1 Hz, 1H), 5.37 (d, *J*=1.5 Hz, 1H), 3.92 (dt, *J*=9.6, 6.0 Hz, 1H), 3.78 (dt, *J*=9.6, 6.0 Hz, 1H), 3.64 (t, *J*=5.1 Hz, 2H), 3.53 (q, *J*=7.0 Hz, 2H), 1.21 (t, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.7, 142.9, 130.5, 124.1, 120.9, 110.2, 107.1, 106.2, 69.4, 66.5, 66.2, 15.0; HRMS (EI) calcd for $C_{13}H_{16}O_3$ (M^+) 220.1099, found 220.1095.

*4.2.17. 2-(2′-Isopropoxyethoxy)-2,3-dihydro-3-methylene benzofuran (**14q**)*

Yellow oil; MS (EI) 234 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (d, *J*=7.5 Hz, 1H), 7.20 (t, *J*=7.8 Hz, 1H), 6.88 (m, 2H), 6.12 (t, *J*=2.0 Hz, 1H), 5.68 (d, *J*=2.4 Hz, 1H), 5.37 (d, *J*=1.8 Hz, 1H), 3.91 (m, 1H), 3.80 (m, 1H), 3.64 (m, 3H), 1.17 (d, *J*=7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.7, 143.0, 130.5, 124.1, 120.9, 110.2, 107.0, 106.4, 71.8, 67.0, 66.7, 22.0, 21.8; HRMS (EI) calcd for $C_{14}H_{18}O_3$ (M^+) 234.1256, found 234.1251.

*4.2.18. 2-(2-(2-Hydroxyethoxy)ethoxy)-3-methylene-2,3-dihydrobenzofuran (**14r**)*

Yellow oil; MS (EI) 236 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (d, *J*=7.8 Hz, 1H), 7.19 (t, *J*=7.8 Hz, 1H), 6.87 (m, 2H), 6.07 (s, 1H), 5.68 (s, 1H), 5.34 (s, 1H), 3.92 (m, 1H), 3.78 (m, 1H), 3.69 (m, 4H),

3.57 (m, 2H), 2.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.6, 142.8, 130.6, 124.0, 121.0, 120.9, 110.3, 107.1, 106.2, 72.3, 70.0, 66.4, 61.5; HRMS (EI) calcd for $C_{13}H_{16}O_4$ (M^+) 236.1049, found 236.1052.

*4.2.19. 2-(2-(2-Methoxyethoxy)ethoxy)-3-methylene-2,3-dihydrobenzofuran (**14s**)*

Colorless oil; MS (EI) 250 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (d, J=7.2 Hz, 1H), 7.20 (t, J=7.6 Hz, 1H), 6.87 (m, 2H), 6.09 (s, 1H), 5.67 (d, J=2.1 Hz, 1H), 5.36 (d, J=1.5 Hz, 1H), 3.94 (m, 1H), 3.80 (m, 1H), 3.70 (t, J=4.2 Hz, 2H), 3.65 (t, J=4.8 Hz, 2H), 3.54 (t, J=3.9 Hz, 2H), 3.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.7, 142.9, 130.6, 124.1, 120.9 (two), 110.3, 107.1, 106.3, 71.8, 70.4, 70.2, 66.3, 58.9; HRMS (EI) calcd for $C_{14}H_{18}O_4$ (M^+) 250.1205, found 250.1206.

*4.2.20. 2-(2-(2-Ethoxyethoxy)ethoxy)-3-methylene-2,3-dihydrobenzofuran (**14t**)*

Colorless oil; MS (EI) 264 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (d, J=7.8 Hz, 1H), 7.20 (t, J=7.8 Hz, 1H), 6.87 (m, 2H), 6.09 (t, J=1.8 Hz, 1H), 5.67 (d, J=2.1 Hz, 1H), 5.36 (d, J=1.5 Hz, 1H), 3.92 (dt, J=9.6, 6.0 Hz, 1H), 3.82 (dt, J=9.6, 6.0 Hz, 1H), 3.71 (t, J=4.8 Hz, 2H), 3.65 (t, J=4.5 Hz, 2H), 3.57 (t, J=4.5 Hz, 2H), 3.51 (q, J=7.2 Hz, 2H), 1.19 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.7, 143.0, 130.5, 124.1, 120.9 (two), 110.3, 107.1, 106.3, 70.6, 70.2, 69.7, 66.5, 66.3, 15.0; HRMS (EI) calcd for $C_{15}H_{20}O_4$ (M^+) 264.1362, found 264.1362.

4.3. *N*-((Benzofuran-3-yl)methyl)-*N*-ethylethanamine (15)[9]

Yellow oil; MS (EI) 203 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (d, J=7.5 Hz, 1H), 7.53 (s, 1H), 7.47 (d, J=7.8 Hz, 1H), 7.26 (m, 2H), 3.71 (s, 2H), 2.56 (q, J=7.1 Hz, 4H), 1.08 (t, J=7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.4, 142.7, 128.2, 124.0, 122.2, 120.5, 118.2, 111.2, 46.8, 46.6, 11.9; HRMS (EI) calcd for $C_{13}H_{17}NO$ (M^+) 203.1310, found 203.1318.

4.4. 2-Methoxy-6-methyl-3-methylene-2,3-dihydrobenzofuran 17[3a,4,5]

To a solution of CH_3ONa (50%, 760 mg, 7 mmol) in MeOH (10 mL), was added quaternary ammonium salt **16** (100 mg, 0.35 mmol). The mixture was heated at 70 °C for 2 h. The solvent was evaporated, and the residue was taken up in cold water. The mixture was extracted with ether, washed with brine, and evaporated. The residue was purified by silica gel column chromatograph (petroleum ether/CH_2Cl_2=5:1) to afford the title compound **17** as a colorless oil (51 mg, 83%).

MS (EI) 176 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, J=7.5 Hz, 1H), 6.74 (d, J=7.8 Hz, 1H), 6.71 (s, 1H), 5.97 (t, J=1.8 Hz, 1H), 5.62 (d, J=1.8 Hz, 1H), 5.27 (d, J=0.9 Hz, 1H), 3.51 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.1, 142.9, 141.3, 121.9, 121.5, 120.6, 110.8, 107.2, 105.6, 54.2, 21.8; HRMS (EI) calcd for $C_{11}H_{12}O_2$ (M^+) 176.0837, found 176.0837.

4.5. 6-Methyl-3-methylene-2,3-dihydrobenzofuran-2-ol (1)[3a,4,5]

This compound was prepared from **17** by using a literature procedure[3a,4,5] in 85% yield. As stated in the literature, this compound is not stable, and co-existed with a small amount (~20%) of its hemiacetal-opened aldehyde based on the ^{1}H NMR spectra. MS (EI) 162 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.68 (s, 1*H*), 7.26 (d, J=4.5 Hz, 1H+1*H*), 7.07 (s, 1*H*), 6.74 (d, J=7.5 Hz, 1H+1*H*), 6.67 (s, 1H+1*H*), 6.39 (s, 1*H*), 6.17 (s, 1H+1*H*), 5.57 (s, 1H), 5.31 (s, 1H), 3.54 (s, 1H), 2.32 (s, 3H+3*H*).

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra of all the new compounds and the natural product **1**. This material is available free of charge via the Internet. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.06.049.

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