Green Organocatalytic Synthesis of Dihydrobenzofurans by Oxidation–Cyclization of Allylphenols

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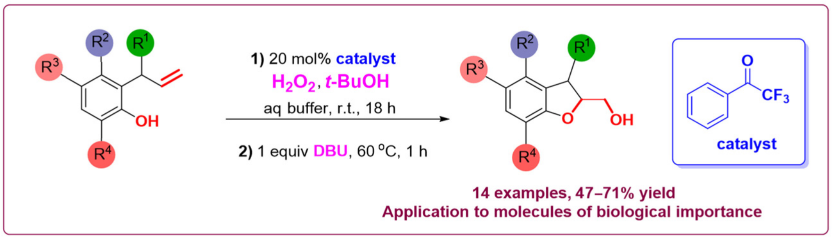

14 examples, 47–71% yield
Application to molecules of biological importance

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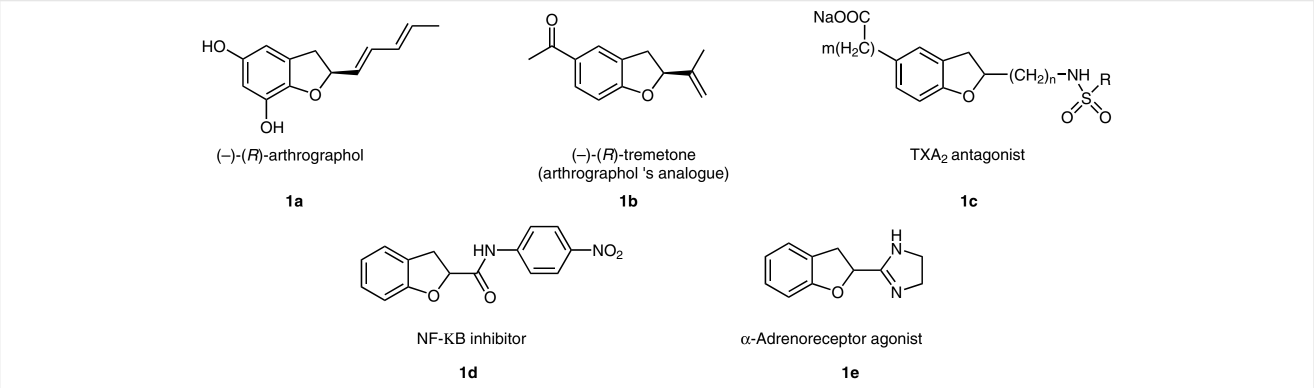
Abstract A green and cheap protocol for the synthesis of dihydrobenzofurans via an organocatalytic oxidation of *o*-allylphenols is presented. The use of 2,2,2-trifluoroacetophenone and H$_2$O$_2$ as the oxidation system, leads to a highly useful synthetic method, where a variety of substituted *o*-allylphenols were cyclized in high yields.

Key words organocatalysis, oxidation, cyclization, dihydrobenzofurans, hydrogen peroxide, green chemistry

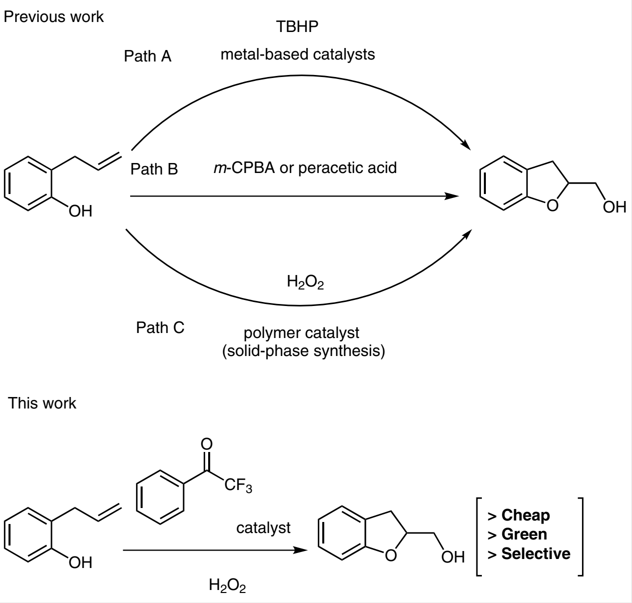
Substituted dihydrobenzofurans constitute an important family in naturally occurring oxygen heterocycles.[1] Numerous metabolites bearing a phenol or polyphenol groups are biochemically useful classes of compounds presenting inhibition against numerous enzymes. (–)-(*R*)-Arthrographol (**1a**) was reported to possess antifungal and chitin synthase inhibitory action[2] (Figure 1) and a plethora of analogues have been reported (Figure 1, e.g., **1b**).[3] Dihydrobenzofurans derivatives have also been synthesized as TXA$_2$ antagonists (Figure 1, **1c**).[4] The potent biological activities of TXA$_2$ may play an important role in many diseases, such as asthma[5] and chronic obstructive arterial disease.[6] Furthermore, dihydrobenzofuran analogues have been developed as anticancer agents (prostate) and inhibitors of NF-κB (Figure 1, **1d**).[7] NF-κB is a protein complex that controls transcription of DNA. Incorrect regulation of NF-κB has been linked to cancer and improper immune development.[8] Additionally, the dihydrobenzofuran ring system was found to possess presynaptic α_1-adrenoreceptor partial agonist properties (Figure 1, **1e**).[9]

As a consequence of their bioactive properties, a variety of pathways has been reported for their synthesis (Scheme 1). Epoxidation of *o*-allylphenols, followed by intramolecular epoxide opening by the phenolic hydroxy moiety is the most common synthetic strategy, utilizing a plethora of oxidants.



(–)-(*R*)-arthrographol **1a**
(–)-(*R*)-tremetone (arthrographol 's analogue) **1b**
TXA$_2$ antagonist **1c**
NF-KB inhibitor **1d**
α-Adrenoreceptor agonist **1e**

Figure 1 Bioactive molecules bearing the dihydrobenzofuran motif

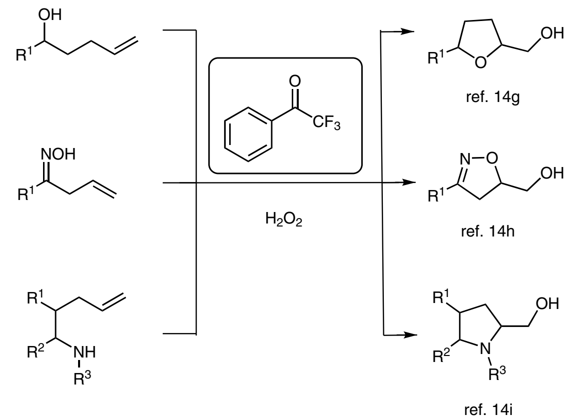


Scheme 1 Synthetic pathways for the synthesis of dihydrobenzofurans

Metal-catalyzed epoxidation of olefins is one of the most prevalent pathways because of its high regio- and stereoselectivity.[10] Catalysts based on Ti[10a] or V[11] have been reported utilizing *tert*-butyl hydroperoxide (TBHP) as the oxidant (Scheme 1, path A). Despite the widespread popularity of these reactions, the toxicity of metals and high levels of inorganic waste make their application harmful for the environment. A very popular metal-free method for the synthesis of dihydrobenzofurans is the oxidation utilizing *m*-chloroperobenzoic acid[3b,7] or peracetic acid (Scheme 1, path B).[12] In these cases, the epoxidation was followed by an intramolecular cyclization, requiring either heating or a base additive. Furthermore, a solid-phase approach for the synthesis of dihydrobenzofurans has been reported performing the epoxidation and cyclization of *o*-allylphenols utilizing a polymer-supported catalyst and H_2O_2 as the oxidant (Scheme 1, path C).[13]

Previously, we were engaged in developing a novel organocatalytic oxidative protocol that could employ hydrogen peroxide as the oxidant.[14] Hydrogen peroxide is a green and environmentally friendly oxidant, since its only byproduct is water. However, its poor oxidation power requires its activation by a catalyst. Normally, this is realized by the use of a metal catalyst, which has been associated with high toxicity and waste production. A few years ago, we identified 2,2,2-trifluoroacetophenone as the appropriate organocatalyst for the hydrogen peroxide activation.

We initially demonstrated its use in the oxidation of silanes to silanols,[14a] tertiary amines and azines to *N*-oxides,[14b] and to the epoxidation of alkenes.[14c] Later on, this oxidative protocols were employed in the oxidation of allylic amines followed by a Meisenheimer rearrangement[14d] and very recently in the oxidation of sulfides[14e] and anilines,[14f] where we studied also the reaction mechanism, excluding the possibility of the involvement of a dioxirane intermediate. More recently, we employed this oxidation protocol in cyclization reactions (Scheme 2). Thus, so far, we have successfully demonstrated the synthesis of tetrahydrofurans,[14g] isoxazolines,[14h] pyrrolidines, and indolines.[14i] In this work, our environmentally friendly protocol provides a new, cheap, and easy synthetic pathway to dihydrobenzofurans utilizing 2,2,2-trifluoroacetophenone as the catalyst and H_2O_2 as the oxidant (Scheme 1, bottom).[14]



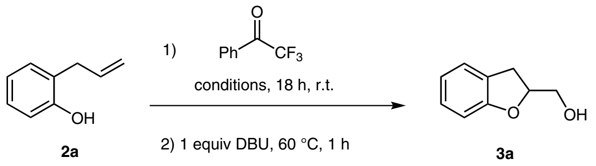
Scheme 2 Oxidation and cyclization protocols utilizing 2,2,2-trifluoroacetophenone and H_2O_2

Our study began by employing the optimum reaction conditions for the epoxidation of *o*-allylphenol (**2a**) (Table 1). Starting with 10 mol% catalyst and 3 equivalents of $MeCN/H_2O_2$, the yield of the desired dihydrobenzofuran **3a** was low (Table 1, entry 1). Increasing the equivalents of the oxidant led to higher reaction yields (entries 2–4). Increasing the catalyst loading to 20 mol% afforded the desired product **3a** in 64% yield (entry 5). A variety of organic solvents was then tested giving the cyclized product **3a** in lower yields (entries 6–9).

Next, we focused on employing the optimum reaction conditions in a variety of substrates (Scheme 3). Starting from 4-substituted *o*-allylphenols with electron-rich and electron-poor substituents, the 2-hydroxy-2,3-dihydrobenzofurans **3a**–**h** were obtained in 47–64% yields (Scheme 3).

In the case of 3-substituted *o*-allylphenol, the yield slightly dropped (Scheme 3, **3i**). Furthermore, 6-substituted *o*-allylphenols were tested, affording the desired products **3j** and **3k** in 58 and 70% yields (Scheme 3). In an attempt to further expand the possibilities of this method, an *o*-allylphenol with substitution in the allyl group was tested, leading to a 53% yield of the product **3l** (Scheme 3). In addition, protected tyrosine **2m** and phenolphthalein-derived **2n** were used successfully. The dihydrobenzofurans **3m** and **3n** were isolated in 50 and 57% yields, proving that our organocatalytic protocol works on more complex substrates.

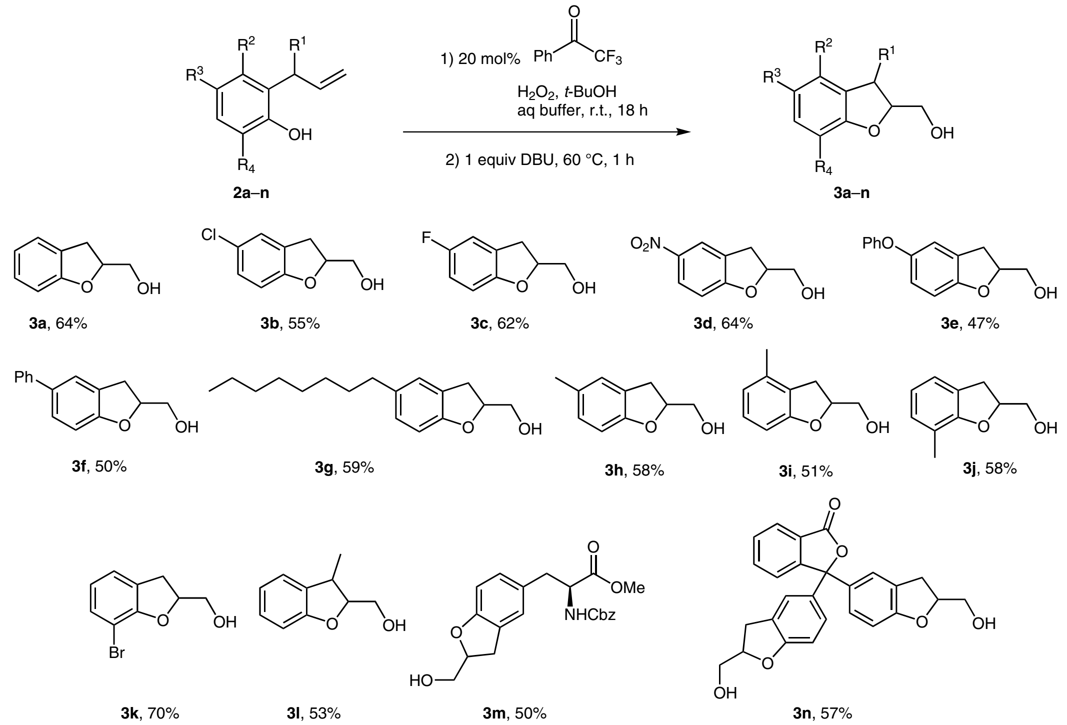
Table 1 Optimization of the Reaction Conditions for the Organocatalytic Synthesis of Dihydrobenzofurans



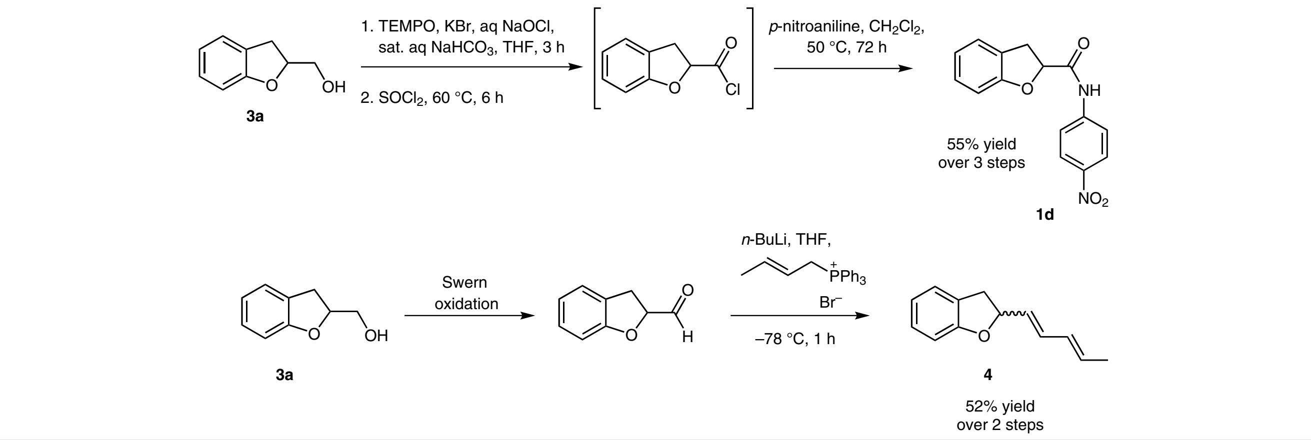
Entry	Catalyst (mol%)	MeCN/H_2O_2 (equiv)	Solvent	Concentration (mmol/mL)	Yield (%)[a]
1	10	3	*t*-BuOH	0.5	12
2	10	10	*t*-BuOH	0.5	27
3	10	16	*t*-BuOH	0.5	30
4	10	16	*t*-BuOH	0.5	51
5	**20**	**16**	***t*-BuOH**	**1.0**	**64**[b]
6	20	16	MeCN	1.0	60
7	20	16	EtOAc	1.0	51
8	20	16	petroleum ether	1.0	22
9	20	16	$CHCl_3$	1.0	29

[a] Yield determined by crude ^{1}H NMR analysis.
[b] Isolated yield.

Finally, starting from dihydrobenzofuran **3a**, we synthesized the anticancer inhibitor of NF-κB **1d** and an arthrographol analogue, compound **4** (Scheme 4). Starting from **3a**, a TEMPO-mediated oxidation led to the corresponding acid, which was treated with thionyl chloride leading to the intermediate acyl chloride. Finally, coupling with *p*-nitroaniline led to NF-κB inhibitor **1d** in 55% yield over three steps without the need for intermediate purification. Similarly, Swern oxidation of **3a** led to the corresponding aldehyde, which was submitted to Wittig olefination leading to



Scheme 3 Substrate scope for the organocatalytic oxidation of *o*-allylphenols



Scheme 4 Synthesis of dihydrobenzofurans exhibiting biological properties

arthrographol analogue **4** as a mixture of isomers in 52% yield over two steps. The desired products were isolated in good yields in both cases.

In conclusion, a green and cheap organocatalytic pathway for the synthesis of dihydrobenzofurans is described. Starting from a variety of substituted *o*-allylphenols, the desired products were obtained in moderate to good yields, utilizing 2,2,2-trifluoroacetophenone as the catalyst and H_2O_2 as the oxidant. This protocol was demonstrated in the synthesis of a potent anticancer agent and an analogue of a natural product.

Chromatographic purification of products was accomplished using forced-flow chromatography on Merck silica gel 60 F_{254} 230–400 mesh. TLC was performed on aluminum backed silica plates (0.2 mm, 60 F_{254}). Visualization of the developed chromatogram was performed by fluorescence quenching using phosphomolybdic acid, anisaldehyde, or $KMnO_4$ stains. Melting points were determined on a Buchi 530 hot stage apparatus and are uncorrected. Mass spectra (ESI) were recorded on a Finnigan Surveyor MSQ LC-MS spectrometer. HRMS spectra were recorded on Thermo Orbitrap Velos spectrometer. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on Varian Mercury (200 MHz, 188 MHz, and 50 MHz, respectively), and are internally referenced to residual solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (standard abbreviations), coupling constant, and assignment. Data for ^{19}F NMR are reported in terms of chemical shift (δ ppm) and are internally referenced to trifluoroacetic acid. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). Mass spectra and conversions of the reactions were recorded on a Shimadzu GCMS-QP2010 Plus Gas Chromatograph Mass Spectrometer utilizing a MEGA column (MEGA-5, film thickness: 0.25 μm, I.D.: 0.25 mm, L: 30 m, T_{max}: 350 °C, column ID # 11475).

The preparation and properties of the starting *o*-allylphenols **2a–n** are provided in the Supporting Information.

Organocatalytic Oxidation of *o*-Allylphenols 2 to Dihydrobenzofurans 3; General Procedure

The respective *o*-allylphenol **2** (0.40 mmol) was placed in a round-bottomed flask followed by consecutive addition of *t*-BuOH (0.4 mL), 2,2,2-trifluoro-1-phenylethanone (7.0 mg, 0.08 mmol), aqueous buffer solution (0.4 mL, 0.6 M K_2CO_3/4 × 10^{-4} M EDTA disodium salt), MeCN (0.64 mL, 6.40 mmol), and 30% aq H_2O_2 (1.38 mL, 6.40 mmol). The reaction mixture was left stirring for 18 h. The crude product was dried (Na_2SO_4) and the solvent was removed in vacuo. The mixture was dissolved in CH_2Cl_2 (1.00 mL) followed by addition of DBU (54.0 mg, 0.40 mmol). The mixture was stirred for 1 h at 60 °C and then purified by flash column chromatography (40–60% EtOAc in PE) to afford the desired product **3**.

(2,3-Dihydrobenzofuran-2-yl)methanol (3a)[13]

Colorless oil; yield: 38.4 mg (64%).

^{1}H NMR ($CDCl_3$): δ = 7.19–7.06 (2 H, m, ArH), 6.89–6.77 (2 H, m, ArH), 4.99–4.83 (1 H, m, CH), 3.85 (1 H, dd, *J* = 12.0, 3.3 Hz, C*H*HOH), 3.73 (1 H, dd, *J* = 12.0, 6.3 Hz, CH*H*OH), 3.25 (1 H, dd, *J* = 15.6, 9.4 Hz, C*H*H), 3.00 (1 H, dd, *J* = 15.6, 7.5 Hz, CH*H*), 2.17 (1 H, br s, OH).

^{13}C NMR ($CDCl_3$): δ = 159.0, 128.0, 126.5, 125.0, 120.6, 109.4, 83.0, 64.8, 31.2.

MS (ESI): *m*/*z* = 149 (100%, $[M – H]^-$).

(5-Chloro-2,3-dihydrobenzofuran-2-yl)methanol (3b)[3b]

Pale yellow oil; yield: 36.1 mg (55%).

^{1}H NMR ($CDCl_3$): δ = 7.05–6.83 (2 H, m, ArH), 6.68 (1 H, d, *J* = 8.4 Hz, ArH), 4.99–4.79 (1 H, m, CH), 3.82 (1 H, dd, *J* = 12.0, 3.4 Hz C*H*HOH), 3.70 (1 H, dd, *J* = 12.0, 6.2 Hz, CH*H*OH), 3.20 (1 H, dd, *J* = 15.4, 9.4 Hz, C*H*H), 2.95 (1 H, dd, *J* = 15.4, 7.4 Hz, CH*H*), 1.66 (1 H, br s, OH).

^{13}C NMR ($CDCl_3$): δ = 157.8, 130.0, 128.5, 127.8, 125.1, 110.3, 83.6, 64.6, 31.1.

MS (ESI): *m*/*z* = 163 (100%, $[M – H]^-$).

(5-Fluoro-2,3-dihydrobenzofuran-2-yl)methanol (3c)

Colorless oil; yield: 41.7 mg (62%).

^{1}H NMR ($CDCl_3$): δ = 6.90–6.64 (3 H, m, ArH), 4.99–4.86 (1 H, m, CH), 3.90–3.65 (2 H, m, CH_2OH), 3.24 (1 H, dd, *J* = 15.7, 9.3 Hz, C*H*H), 3.02 (1 H, dd, *J* = 15.7, 7.6 Hz, CH*H*), 1.97 (1 H, s, OH).

^{13}C NMR ($CDCl_3$): δ = 161.0 (d, *J* = 2.0 Hz), 157.4 (d, *J* = 237.0 Hz), 127.9 (d, *J* = 8.9 Hz), 114.1 (d, *J* = 24.1 Hz), 112.1 (d, *J* = 24.8 Hz), 109.4 (d, *J* = 8.6 Hz), 83.5, 64.7, 31.4 (d, *J* = 1.7 Hz).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –82.4 (s).

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_9H_9FO_2$: 167.0509; found: 167.0500.

(5-Nitro-2,3-dihydrobenzofuran-2-yl)methanol (3d)[15]

Yellow solid; yield: 50.0 mg (64%); mp 58–60 °C.

^{1}H NMR (CD_3OD): δ = 8.08–7.98 (2 H, m, ArH), 6.81 (1 H, d, *J* = 9.6 Hz, ArH), 5.10–4.90 (1 H, m, CH), 3.81 (1 H, dd, *J* = 12.3, 3.5 Hz, C*H*HOH), 3.68 (1 H, dd, *J* = 12.3, 5.2 Hz, CH*H*OH), 3.33 (1 H, dd, *J* = 16.3, 9.5 Hz, C*H*H), 3.11 (1 H, dd, *J* = 16.3, 7.3 Hz, CH*H*).

^{13}C NMR (CD_3OD): δ = 166.7, 141.9, 129.3, 125.4, 121.1, 108.9, 86.1, 63.6, 30.2.

MS (ESI): *m*/*z* = 194 (100%, [M – H]$^-$).

(5-Phenoxy-2,3-dihydrobenzofuran-2-yl)methanol (3e)

Colorless oil; yield: 45.5 mg (47%).

^{1}H NMR ($CDCl_3$): δ = 7.33–7.18 (3 H, m, ArH), 7.07–6.70 (5 H, m, ArH), 5.01–4.88 (1 H, m, CH), 3.88 (1 H, dd, *J* = 12.1, 3.4 Hz, C*H*HOH), 3.76 (1 H, dd, *J* = 12.1, 6.1 Hz, CH*H*OH), 3.22 (1 H, dd, *J* = 15.8, 9.4 Hz, C*H*H), 3.00 (1 H, dd, *J* = 15.8, 7.6 Hz, CH*H*), 1.68 (1 H, br s, OH).

^{13}C NMR ($CDCl_3$): δ = 158.6, 155.3, 150.3, 133.5, 129.5, 122.3, 119.5, 117.4, 117.0, 115.3, 83.5, 64.7, 31.5.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{15}H_{14}O_3$: 241.0865; found: 241.0865.

(5-Phenyl-2,3-dihydrobenzofuran-2-yl)methanol (3f)

Colorless oil; yield: 45.2 mg (50%).

^{1}H NMR ($CDCl_3$): δ = 7.59–7.25 (7 H, m, ArH), 6.89–6.79 (1 H, d, *J* = 8.6 Hz, ArH), 5.03–4.90 (1 H, m, CH), 3.89 (1 H, dd, *J* = 12.1, 3.3 Hz, C*H*HOH), 3.76 (1 H, dd, *J* = 12.1, 6.2 Hz, CH*H*OH), 3.30 (1 H, dd, *J* = 15.6, 9.2 Hz, C*H*H), 3.06 (1 H, dd, *J* = 15.6, 7.2 Hz, CH*H*), 1.66 (1 H, br s, OH).

^{13}C NMR ($CDCl_3$): δ = 158.7, 141.1, 134.2, 133.4, 128.6, 127.1, 126.7, 126.5, 123.8, 109.5, 83.4, 64.8, 31.2.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for ($C_{15}H_{14}O_3$): 225.0921; found: 225.0923.

(5-Octyl-2,3-dihydrobenzofuran-2-yl)methanol (3g)

Yellow oil; yield: 61.8 mg (59%).

^{1}H NMR ($CDCl_3$): δ = 6.98–6.80 (2 H, m, ArH), 6.70–6.66 (1 H, m, ArH), 4.95–4.82 (1 H, m, CH), 3.91–3.64 (2 H, m, CH_2OH), 3.21 (1 H, dd, *J* = 15.5, 9.3 Hz, C*H*H), 2.97 (1 H, dd, *J* = 15.5, 7.5 Hz, CH*H*), 2.55–2.45 (2 H, m, CH_2), 2.00 (1 H, s, OH), 1.64–1.45 (3 H, m, 3 × C*H*H), 1.35–1.10 (9 H, m, 9 × C*H*H), 0.86 (3 H, t, *J* = 6.3 Hz, CH_3).

^{13}C NMR ($CDCl_3$): δ = 157.0, 135.3, 130.5, 127.8, 124.9, 108.9, 83.0, 64.9, 35.4, 32.1, 31.9, 31.3, 29.5, 29.3, 22.7, 14.1.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{17}H_{26}O_2$: 261.1860; found: 261.1858.

(5-Methyl-2,3-dihydrobenzofuran-2-yl)methanol (3h)[16]

Colorless oil; yield: 89.3 mg (58%).

^{1}H NMR ($CDCl_3$): δ = 7.05–6.83 (2 H, m, ArH), 6.75–6.50 (1 H, m, ArH), 4.99–4.79 (1 H, m, CH), 3.90–3.65 (2 H, m, CH_2OH), 3.20 (1 H, dd, *J* = 15.7, 9.4 Hz, C*H*H), 2.95 (1 H, dd, *J* = 15.7, 7.4 Hz, CH*H*), 2.26 (3 H, s, CH_3).

^{13}C NMR ($CDCl_3$): δ = 156.9, 129.9, 128.3, 126.5, 125.6, 108.9, 83.0, 64.9, 31.2, 20.7.

MS (ESI): *m*/*z* = 163 (100%, [M – H]$^-$).

(4-Methyl-2,3-dihydrobenzofuran-2-yl)methanol (3i)[3b]

Colorless oil; yield: 33.5 mg (51%).

^{1}H NMR ($CDCl_3$): δ = 7.04–6.93 (1 H, m, ArH), 6.73–6.59 (2 H, m, ArH), 4.97–4.82 (1 H, m, CH), 3.88–3.66 (2 H, m, CH_2OH), 3.15 (1 H, dd, *J* = 15.8, 8.8 Hz, C*H*H), 2.90 (1 H, dd, *J* = 15.8, 7.6 Hz, CH*H*), 2.22 (3 H, s, CH_3), 1.65 (1 H, br s, OH).

^{13}C NMR ($CDCl_3$): δ = 158.8, 128.0, 127.0, 121.6, 116.2, 106.7, 82.8, 65.0, 30.2, 19.9.

MS (ESI): *m*/*z* = 163 (100%, [M – H]$^-$).

(7-Methyl-2,3-dihydrobenzofuran-2-yl)methanol (3j)[3b]

Colorless oil; yield: 38.0 mg (58%).

^{1}H NMR ($CDCl_3$): δ = 7.01–6.91 (2 H, m, ArH), 6.78–6.71 (1 H, m, ArH), 4.96–4.82 (1 H, m, CH), 3.84 (1 H, dd, *J* = 12.0, 3.5 Hz, C*H*HOH), 3.72 (1 H, dd, *J* = 12.0, 6.2 Hz, CH*H*OH), 3.23 (1 H, dd, *J* = 15.6, 9.5 Hz, C*H*H), 3.00 (1 H, dd, *J* = 15.6, 7.6 Hz, CH*H*), 2.20 (3 H, s, CH_3), 1.66 (1 H, br s, OH).

^{13}C NMR ($CDCl_3$): δ = 157.5, 129.2, 125.7, 122.3, 120.5, 119.7, 82.6, 65.0, 31.5, 15.3.

MS (ESI): *m*/*z* = 163 (100%, [M – H]$^-$).

(7-Bromo-2,3-dihydrobenzofuran-2-yl)methanol (3k)[17]

Pale yellow oil; yield: 63.6 mg (70%).

^{1}H NMR ($CDCl_3$): δ = 7.25 (1 H, d, *J* = 7.7 Hz, ArH), 7.08 (1 H, d, *J* = 7.7 Hz, ArH), 6.72 (1 H, t, *J* = 7.7 Hz, ArH), 5.05–4.92 (1 H, m, CH), 3.92 (1 H, dd, *J* = 12.3, 3.2 Hz, C*H*HOH), 3.75 (1 H, dd, *J* = 12.3, 5.6 Hz, CH*H*OH), 3.33 (1 H, dd, *J* = 15.9, 9.4 Hz, C*H*H), 3.16 (1 H, dd, *J* = 15.9, 7.7 Hz, CH*H*).

^{13}C NMR ($CDCl_3$): δ = 156.5, 131.0, 128.1, 123.9, 122.0, 102.5, 83.6, 64.4, 31.9.

MS (ESI): *m*/*z* = 226 (100%, [M – H]$^-$).

(3-Methyl-2,3-dihydrobenzofuran-2-yl)methanol (3l)[9]

MeCN was used instead of *t*-BuOH; colorless oil; yield: 34.8 mg (53%); 1:1 diastereomeric mixture.

^{1}H NMR ($CDCl_3$): δ = 7.20–7.05 (2 H, m, ArH), 6.91–6.77 (2 H, m, ArH), 4.88–4.78 (0.5 H, m, 0.5 × CH), 4.43–4.34 (0.5 H, m, 0.5 × CH), 3.95–3.70 (2 H, m, CH_2OH), 3.69–3.56 (0.5 H, m, 0.5 × CH), 3.38–3.28 (0.5 H, m, 0.5 × CH), 1.36 (1.5 H, d, *J* = 7.2 Hz, 1.5 × CH_3), 1.25 (1.5 H, d, *J* = 7.2 Hz, 1.5 × CH_3).

^{13}C NMR ($CDCl_3$): δ = 158.7, 158.2, 132.4, 132.0, 128.2, 128.1, 123.9, 123.8, 120.8, 120.7, 109.6, 109.5, 90.9, 85.8, 63.9, 62.0, 37.7, 37.6, 18.9, 14.1.

MS (ESI): *m*/*z* = 163 (100%, [M – H]$^-$).

Methyl (2*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-[2-(hydroxymethyl)-2,3-dihydrobenzofuran-5-yl]propanoate (3m)

MeCN was used instead of *t*-BuOH; yellow oil; yield: 77 mg (50%); $[\alpha]_D^{25}$ +39.4 (*c* 0.5, $CHCl_3$).

^1H NMR ($CDCl_3$): δ = 7.32–7.25 (5 H, m, ArH), 6.88–6.62 (3 H, m, ArH), 5.36 (1 H, br d, *J* = 8.0 Hz, NH), 5.07 (2 H, s, OCH_2), 4.95–4.80 (1 H, m, CH), 4.60–4.50 (1 H, m, CH), 3.85–3.65 (5 H, m, CH_2OH and OCH_3), 3.22–2.87 (4 H, m, 2 × CH_2).

^{13}C NMR ($CDCl_3$): δ = 176.0, 172.2, 158.3, 155.8, 136.0, 128.9, 128.4, 128.1, 128.0, 127.7, 127.0, 125.8, 109.3, 83.2, 67.0, 64.7, 55.0, 52.3, 37.4, 31.1.

HRMS (ESI): *m*/*z* $[M - H]^-$ calcd for $C_{21}H_{23}NO_6$: 384.1453; found: 384.1450.

3,3-Bis[2-(hydroxymethyl)-2,3-dihydrobenzofuran-5-yl]isobenzofuran-1(3*H*)-one (3n)

For the preparation of **3n**, double the amounts of MeCN and 30% aq H_2O_2 (i.e., 12.80 mmol) were used; colorless oil; yield: 97.9 mg (57%).

^1H NMR ($CDCl_3$): δ = 7.90–7.86 (1 H, m, ArH), 7.70–7.41 (4 H, m, ArH), 7.10–6.98 (3 H, m, ArH), 6.65–6.61 (2 H, m, ArH), 4.92–4.78 (2 H, m, 2 × OCH), 3.83–3.64 (4 H, m, 2 × CH_2OH), 3.14 (2 H, dd, *J* = 15.6, 9.2 Hz, 2 × C*H*H), 2.91 (2 H, dd, *J* = 15.6, 7.5 Hz, 2 × CH*H*), 1.58 (2 H, br s, 2 × OH).

^{13}C NMR ($CDCl_3$): δ = 170.0, 159.3, 152.5, 134.1, 133.2, 129.9, 129.1, 128.3, 127.3, 127.1, 125.8, 125.2, 123.9, 108.8, 83.6, 64.5, 30.9.

HRMS (ESI): *m*/*z* $[M - H]^-$ calcd for $C_{26}H_{22}O_6$: 428.1271; found: 428.1270.

N-(4-Nitrophenyl)-2,3-dihydrobenzofuran-2-carboxamide (1d)[7]

A solution of **3a** (0.30 g, 2.00 mmol) in THF and sat. aq $NaHCO_3$ (1:1, 12 mL) was stirred at r.t. and then TEMPO (59.1 mg, 0.38 mmol) and KBr (60.7 mg, 0.51 mmol) were added. A solution of aq NaOCl (2.5% w/v, 2 mL) was introduced in the reaction mixture. The mixture was stirred at r.t. for 3 h and then transferred to a separating funnel and treated with aq 1 N NaOH (25 mL). The aqueous layer was acidified with HCl (37% w/w) to pH 1 and extracted with CH_2Cl_2 (3 × 20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude acid was used in the next step.

The crude acid was added to $SOCl_2$ (2.90 mL, 40.00 mmol) at 60 °C and kept for 6 h. The reaction mixture was then concentrated in vacuo. The mixture was diluted with Et_2O (2 × 5 mL) and concentrated in vacuo again. The crude acid chloride was used in the next step.

To a solution of the crude acid chloride in anhyd CH_2Cl_2 (5 mL) was added a solution of *p*-nitroaniline (1.10 g, 8.00 mmol) in anhyd CH_2Cl_2 (10 mL) and the mixture was stirred at 50 °C for 72 h. The crude mixture was concentrated in vacuo and purified by flash column chromatography (20% EtOAc in PE) to afford the desired product **1d**; white solid; yield: 312.3 mg (55%); mp 109–112 °C.

^1H NMR ($CDCl_3$): δ = 8.67 (1 H, br s, NH), 8.21 (2 H, d, *J* = 9.0 Hz, ArH), 7.77 (2 H, d, *J* = 9.0 Hz, ArH), 7.00–6.93 (2 H, m, ArH), 5.28 (1 H, dd, *J* = 10.6, 6.8 Hz, OCH), 3.70 (1 H, dd, *J* = 16.5, 10.6 Hz, C*H*H), 3.52 (1 H, dd, *J* = 16.5, 6.8 Hz, CH*H*).

^{13}C NMR ($CDCl_3$): δ = 170.4, 157.7, 143.9, 142.5, 128.5, 125.3, 125.0, 124.9, 122.3, 119.4, 109.8, 80.3, 33.8.

MS (ESI): *m*/*z* = 285 (100%, $[M + H]^+$).

Arthrographol Analogue 4

A solution of oxalyl chloride (0.26 g, 2.00 mmol) in anhyd CH_2Cl_2 (10 mL) was cooled to –78 °C under an argon atmosphere and then anhyd DMSO (0.16 g, 2.00 mmol) was added dropwise. After stirring for 20 min at –78 °C, a solution of **3a** (0.30 g, 2.00 mmol) in anhyd CH_2Cl_2 (3 mL) was added to the reaction mixture. The mixture was stirred at –78 °C for 1 h and then treated with Et_3N (0.21 g, 2.00 mmol) at the same temperature. The reaction mixture was allowed to reach r.t., poured into crushed ice, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude aldehyde was used in the next step.

n-BuLi (1.6 M solution of hexane, 2.50 mL, 4.00 mmol) was added to a suspension of crotyl triphenylphosphonium bromide (2.32 g, 4.00 mmol) in anhyd THF (10 mL) at 0 °C to give an orange-red solution. After 10 min, the solution was cooled to –78 °C and a solution of the aldehyde in anhyd THF (2 mL) was added dropwise. The mixture was stirred at –78 °C for 2 h, then warmed to r.t., and quenched with H_2O (5 mL). The solution was transferred to a separating funnel, diluted with H_2O (15 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (10% EtOAc in PE) to afford the desired product **4** as a 1:1 mixture of *cis*/*trans* isomers; colorless oil; yield: 193.4 mg (52%).

^1H NMR ($CDCl_3$): δ = 7.19–7.09 (2 H, m, ArH), 6.89–6.79 (2 H, m, ArH), 6.52–6.03 (2 H, m, 2 × =CH), 5.94–5.49 (2.5 H, m, 2 × =CH and 0.5 × OCH), 5.22 (0.5 H, dd, *J* = 16.5, 8.3 Hz, 0.5 × OCH), 3.47–3.31 (1 H, m, C*H*H), 3.06–2.93 (1 H, m, CH*H*), 1.84 (1.5 H, d, *J* = 6.7 Hz, 1.5 × CH_3), 1.80 (1.5 H, d, *J* = 6.7 Hz, 1.5 × CH_3).

^{13}C NMR ($CDCl_3$): δ = 159.3, 137.2, 137.0, 133.9, 133.5, 132.9, 132.0, 131.3, 130.4, 128.6, 128.5, 128.4, 128.0, 127.2, 126.1, 124.8, 109.4, 109.3, 83.4, 78.7, 36.7, 36.2, 18.4, 18.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{14}O$: 187.1117; found: 187.1115.

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Supporting Information

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