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Cerium ammonium nitrate-mediated the oxidative dimerization of *p*-alkenylphenols: a new synthesis of substituted (±)-*trans*-dihydrobenzofurans

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ABSTRACT

A new method for the preparation of substituted dihydrobenzofurans is described. The *p*-alkenylphenols, mediated by cerium ammonium nitrate (CAN), undergo the oxidative dimerization to generate substituted dihydrobenzofurans including (±)-conocarpan, (±)-licarin A, (±)-acuminatin, as well as their related substituted dihydrobenzofurans.

1. Introduction

Due to the diverse biological activities, 2,3-dihydrobenzo-furan derivatives have become an attractive category for researchers and received considerable results in the passing decades.[1] The major biological activities reported include the treatment of traumatic and ischemic central nervous system injury,[2a] the effectiveness in treating of arteriosclerosis, hepatopathy, and cerebrovascular disease,[2b] the antitubercular activity,[2c] and the potent trypanocidal and antileishmanial activities,[2d] as well as others. Major synthetic methods, which were reported include the oxidative cycloaddition of a 2-cyclohexenone or *R*-tetralone and an alkene with dried $Mn(OAc)_3$,[3] the reactions of 2-hydroxyaryl β-unsaturated ketones with dimethylsulfonium carbonylmethylides,[4] the reaction of *o*-nitrotoluenes and aromatic aldehydes in the presence of TBAF,[5] the reaction of phenols with 2-aryl-2,2-dialkylacetaldehydes in the presence of an acid catalyst,[6] the ring-opening of arylsubstituted epoxides, and then by cyclodehydration,[7] via a diastereoselective palladium-catalyzed oxyarylation reaction of *o*-aminophenols and phenylpropenes in one pot,[8] from *N*-thiophosphinyl imines and sulfur ylides,[9] the K_2CO_3-catalyzed domino reactions of salicylic aldehyde derivatives and 2-halo-1,3-dicarbonyl compounds,[10] as well as the dimerization of *p*-alkenylphenol or their esters by Ag_2O,[11] $K_3Fe(CN)_6$,[12] and iodobenzene diacetate.[13] Furthermore, the oxidative dimerization of isoeugenol or relative compounds to yield dihydrobenzofurans by means of enzyme biocatalysts including by horseradish peroxidase and H_2O_2 at citrate phosphate buffer pH 3 in methanol,[14] by anionic potato peroxidase,[15] by crude onion peroxidase,[16] as well as others also have been reported. However, despite numerous methods have been disclosed, drawbacks, such as reaction time, yield of product, reaction conditions, synthetic steps, reagents with environmental concerning, and structures of biocatalyst remain to be addressed. Therefore, it prompts us to develop a new, CAN-mediated, concise, and efficient method for the diastero-selective preparation of 2,3-substituted dihydrobenzofurans, i.e., (±)-conocarpan (**2a**),[17] (±)-licarin A (**2b**),[18] (±)-acuminatin (**2c**),[19] as well as their relative congeners by the oxidative dimerization of *p*-alkenylphenols (**1**) (Scheme 1).

2. Results and discussion

'In order to conquer the common disadvantage of low yield in radical dimerization and achieve an optimum reaction conditions, the reaction of isoeugenol (**1b**) with CAN under various conditions for yielding (±)-licarin A (**2b**) was carefully studied. The results were provided in Table 1.

As shown in Table 1, the amount of CAN, reaction time, and solvents have significant effects on the yield of (±)-licarin A (**2b**). For example, 1.5 equiv of CAN that was used could produce **2b** in the highest yield (81%) (entry 5) but 0.5 equiv (33%) (entry 1) or 2.0 equiv (55%) (entry 6) of CAN that was used could reduce the yield of **2b**.

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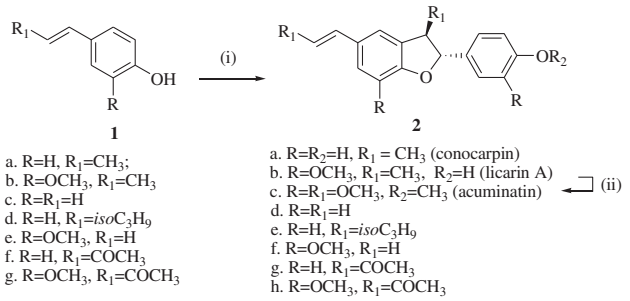
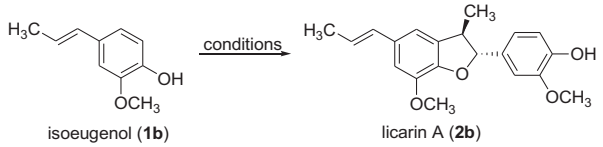


Reagents and condition: i. CAN, THF, 0°C, 0.5 hr, 81-85%; ii. CH_3I, K_2CO_3, acetone, reflux, 5 hr, 94%

Scheme 1. CAN-mediated the oxidative coupling of *p*-alkenylphenols for the synthesis of (±)-*trans*-2,3-substituted dihydrobenzofurans and their congeners.

Table 1
Reaction of isoeugenol (**1b**) with CAN to yield (±)-licarin A (**2b**) under various conditions at 0 °C

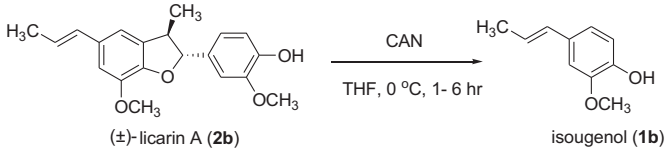


isoeugenol (**1b**) licarin A (**2b**)

Entry	CAN (equiv)	Time (h)	Solvent	Yield (%)
1	0.5	2	THF	33[b]
2	1.0	2	THF	46[b]
3	1.5	2	THF	60
4	1.5	0.5	THF	73
5	1.5	0.5[a]	THF	81
6	2.0	0.5	THF	55
7	1.5	0.5	CH_2Cl_2	0[b]
8	1.5	0.5	DMSO	59
9	1.5	0.5	1,4-Dioxane	51

[a] CAN in THF was added dropwise.
[b] Accompanied with the recovery of starting material.

Thus, from the above experimental results, 1.5 equiv of CAN is the appropriate amount for producing **2b** in good yield. Furthermore, the addition of CAN to isoeugenol (**1b**) in THF by drops increases the yield of (±)-licarin A (**2b**) to 81% (entry 5). Comparing to reaction solvents, the yield of **2b** in THF is in a range of 81–73% (entries 5 and 6), in DMSO is in 59% (entry 8), in 1,4-dioxane is 51% (entry 9), and in CH_2Cl_2 is 0% (entry 7) were observed'. Furthermore, this radical dimerization is sensitive to reaction time. While prolonged the reaction time, the lower % yield of product **2b** was observed (entries 3 and 4). Due to this given result, the oxidative dimerization reaction of isoeugenol (**1b**) to yield (±)-licarin A (**2b**) that depends on not only the concentration of CAN but also reaction time is understood. To clarify and to explain this phenomenon, the same reaction condition (described in Table 1, entry 4) was applied to treat pure (±)-licarin A (**2b**) with CAN to see what would be happened. Surprisingly, the % of conversion of **2b** to **1b** was discovered while examining the reaction from 1 to 6 h by 1 h interval (Scheme 2).



(±)-licarin A (**2b**) isougenol (**1b**)

Scheme 2. The % of conversion of **2b** to **1b** by CAN that is examined from 1 h to 6 h.

The result of conversion of **2b** to **1b** by treating with CAN was provided in Table 2.

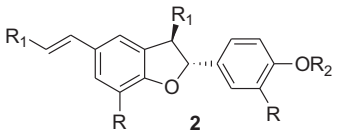
From the results obtained in Table 2, the longer reaction time (from 1–6 h), the more conversion of **2b** to **1b** (from 11% to 52%) observed (entries 1–6). But when the reaction time is over 24 h, neither **1b** nor **2b** can be isolated due to yielding unidentified high polarity products (the reaction mixture can be developed by TLC: silica gel, ethyl acetate or MeOH). Therefore, the reaction time for dimerization of isoeugenol by CAN should be controlled cautiously. For increasing the diversity, a series of dihydrobenzofurans (**2a**–**h**) are synthesized by basing on the resulting optimum condition (CAN 1.5 equiv slowly dropped into *p*-alkenylphenol (**1a**–**g**) in solvent THF, at 0 °C). Furthermore, treatment of (±)-licarin A (**2b**) with methyl iodide in the presence of K_2CO_3 to yield (±)-acuminatin (**2c**) was also reported. The yields (%) of **2a**–**h** obtained were provided in Table 3.

Table 2
The result of % of conversion of **2b** to **1b** by CAN from 1 h to 6 h

Entry	Time (h)	Yield (%)[a] (**1b**)	Recovery (%)[a] (**2b**)
1	1	11	82
2	2	19	71
3	3	27	62
4	4	43	46
5	5	49	40
6	6	52	33
7	>24	0	0

[a] Isolated yield from silica gel column chromatography (*n*-hexane/ethyl acetate=1:1).

Table 3
The yields (%) of dihydrobenzofurans (**2a**–**h**) from *p*-alkenylphenols mediated by CAN

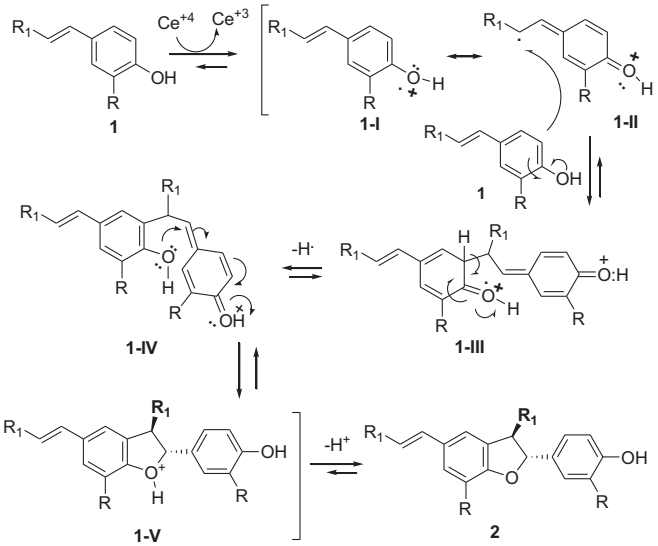


a. R=R2=H, R1 = CH3 (conocarpin); b. R=OCH3, R1=CH3, R2=H (licarin A)
c. R=R1=OCH3, R2=CH3 (acuminatin); d. R=R1=R2=H
e. R=R2=H, R1=isoC3H9; f. R=OCH3, R1=R2=H
g. R=R2=H, R1=COCH3; h. R=OCH3, R1=COCH3, R2=H

Compound	Yield (%)	Compound	Yield (%)
2a	85	**2e**	84
2b	81	**2f**	86
2c	94	**2g**	88
2d	82	**2h**	89

The structural elucidation of dihydrobenzofurans (**2a**–**h**) that synthesized was determined by spectral data, such as ^{1}H NMR, ^{13}C NMR, EI-MS, and HRMS, which all matched the proposed structures. For example, the ^{1}H NMR (400 MHz, $CDCl_3$) of (±)-licarin A, **2b** shown one doublet signal with three protons at δ 1.38 (J=6.8 Hz) indicated the presence of methyl group (C*H*$_3$CH=CH); one double doublet signal with three protons at δ 1.87 (J=6.8, 1.6 Hz) indicated the presence of methyl group at C3–CH_3, one doublet quartet signal with one proton at δ 3.45 (J=9.6, 6.8 Hz) indicated the presence of H-3, two singlet signals each with three protons at δ 3.88 and 3.89 indicated the presence of two methoxy groups, one doublet signal with one proton at δ 5.10 (d, J=9.6 Hz) indicated the presence of H-2. Due to the coupling constant J=9.6 Hz between H-2 and H-3, the stereochemistry of C2–C3 of **2b** could be deduced as *trans*-form.[18] Other signals, such as at δ 5.63 (s, 1H, ArOH), 6.11 (dq, J=15.6, 6.8 Hz, 1H, ArCH=C*H*CH$_3$), 6.36 (dq, J=15.6, 1.6 Hz, 1H, ArC*H*=CHCH$_3$), 6.77 (s, 1H, ArH), 6.79 (s, 1H, ArH), 6.88 (d, J=8.4 Hz, 1H, ArH), 6.91 (d, J=8.4 Hz, 1H, ArH), and 6.97 (s, 1H, ArH) are consistent with the data required for (±)-licarin A and also matched with the pattern of previously reported data.[18b] In addition, the spectral data of **2b** including ^{13}C NMR, EI-MS, and HRMS all fit in the structure with (±)-licarin A.

Furthermore, the reaction mechanism of CAN-mediated the oxidative dimerization of *p*-alkenylphenols for the synthesis of *trans*-2,3-substituted or the related dihydrobenzo-furans could be rationally proposed and illustrated as follows (Scheme 3).



Scheme 3. The proposed mechanism for the formation of *trans*-2,3-substituted or 2-substituted dihydrobenzofurans from *p*-alkenylphenols mediated by CAN.

Initially, mediated by CAN, one lone pair electron on oxygen of *p*-alkenylphenol (**1**) is lost to give a radical cation transient **1-I**, which has stabilized by transient **1-II** with resonance. Then, the radical cation transient **1-II** is coupled with *p*-alkenylphenol (**1**) to generate the transient **1-III**. Subsequently, by restoring the aromatic ring, a protonated 4-methylenecyclohexa-2,5-dienone-like cation, the transient **1-IV** which R^1 and the neighboring group are far apart, is generated. After undergoing the intramolecular conjugated addition, the protonated transient **1-V** was spontaneously generated in *trans*-configuration. Finally, the product *trans*-2,3-substituted or 2-substituted dihydrobenzo-furan (**2**) is yielded after deprotonation.

3. Conclusion

In this study, a new and an efficient method for the preparation of (±)-*trans*-dihydrobenzofurans and related dihydrobenzo-furans from *p*-alkenylphenols mediated by CAN, is established. We also figure out that the high concentration of CAN and long reaction time is a disadvantage for this oxidative dimerization.

4. Experimental

4.1. General

Melting points (Yanaco micro melting-point apparatus) were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Gemini-200 or Varian Unity plus 400 Spectrometer. Chemical shifts were measured in parts per million with respect to TMS. Elemental analyses were recorded on a Heraeus CHN–O Rapid analyzer. Mass spectra were recorded on a Chem./hp/middle spectrometer connected to a Hewlett Packard series II model gas–liquid chromatography. HRMS spectra were performed on a JEOL JMS SX/SX 102A instrument. Silica gel (230–400 mesh) for column chromatography and precoated silica gel plates (60 F_{254}) for TLC was purchased from E. Merck Co. UV light (254 nm) was used to detect spots on TLC plates after development.

*4.1.1. General procedure for the preparation of p-vinylphenols (**1a**, **1c**, **1d**, and **1e**).* A mixture of alkyl triphenylphosphonium bromide (15 mmol) in THF (20 mL) was treated with potassium *tert*-butoxide (2.81 g, 25 mmol). After stirring for 10 min at room temperature, a solution of *p*-hydroxybenzaldehydes (10 mmol) in THF (10 mL) was added in drops to the above suspension, and the resulting mixture was stirred at room temperature for 4 h, which was monitored by TLC. The resulting solution was quenched with saturated NH_4Cl solution (50 mL), and concentrated in vacuo to remove THF. The concentrated mixture was extracted with CH_2Cl_2 (5×20 mL). The organic layers were washed with brine (20 mL) and dried over $MgSO_4$ were filtered, evaporated, and the residue was purified by column chromatography (ethyl acetate/*n*-hexane=1:15) to give pure **1a**, **1c**, **1d**, and **1e**.

*4.1.1.1. ((E)-4-Propenyl)phenol (**1a**).*[20] Compound **1a** (1.11 g, 83%) was obtained as colorless liquid, R_f=0.46 (ethyl acetate/*n*-hexane=1:5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.82 (d, J=7.2 Hz, 3H, ArCH=CHCH_3), 5.66 (dq, J=18.0, 7.2 Hz, 1H, ArCH=C*H*CH$_3$), 6.30 (d, J=18.0 Hz, 1H, ArC*H*=CHCH$_3$), 6.79 (d, J=8.8 Hz, 2H, ArH), 7.05 (s, 1H, ArOH), 7.14 (d, J=8.8, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 115.0, 123.5, 125.1, 127.0, 129.0, 130.1, 130.4, 153.6; EI-MS (70 eV) m/z (rel intensity, %) 134 (M^+, 99), 133 (100), 107 (22), 105 (58), 91 (23), 79 (29), 77 (27); HRMS calcd for $C_9H_{10}O$: 134.0732. Found: 134.0730.

*4.1.1.2. Isoeugenol (**1b**).* Compound (**1b**) was purchased from Alfa Aesar, a Johnson Matthey Co.

*4.1.1.3. 4-Vinylphenol (**1c**).*[21] Compound **1c** (0.98 g, 82%) was obtained as colorless liquid, R_f=0.49 (ethyl acetate/*n*-hexane=1:5); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.10 (dd, J=11.0, 0.8 Hz, 1H, ArCH=CH_aH$_b$), 5.58 (dd, J=17.6, 1.0 Hz, 1H, ArCH=CH$_a$H$_b$), 6.62 (s, 1H, ArOH), 6.67 (dd, J=17.6, 11.0 Hz, 1H, ArC*H*=CH$_a$H$_b$), 6.79 (d, J=8.6 Hz, 2H, ArH), 7.27 (d, J=8.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 111.4, 115.4, 127.5, 130.3, 136.1, 155.4; EI-MS (70 eV) m/z (rel intensity, %) 120 (M^+,100), 119 (12), 108 (4), 107 (4), 92 (9), 91 (36), 65 (4); HRMS calcd for C_8H_8O: 120.0575. Found: 120.0575.

*4.1.1.4. 4-((E)-3-Methylbut-1-enyl)phenol (**1d**).*[22] Compound **1d** (1.29 g, 80%) was obtained as colorless liquid, R_f=0.47 (ethyl acetate/*n*-hexane=1:5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (d, J=6.4 Hz, 6H, ArCH=CHCH*Me*$_2$), 2.88 (m, 1H, ArCH=CHC*H*Me$_2$), 5.06 (s, 1H, ArOH), 5.38 (dd, J=18.0, 10.4 Hz, 1H, ArCH=C*H*CHMe$_2$), 6.21 (d, J=18.0 Hz, 1H, ArC*H*=CHCHMe$_2$), 6.79 (d, J=8.8 Hz, 2H, ArH), 7.15 (d, J=8.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.2, 27.1, 115.0, 125.7, 130.0, 130.6, 139.1, 154.1; EI-MS (70 eV) m/z (rel intensity, %) 162 (M^+, 38), 147 (100), 132 (9), 119 (22), 107 (18), 89 (37), 77 (9); HRMS calcd for $C_{11}H_{10}O$: 162.1045. Found: 162.1046.

*4.1.1.5. 2-Methoxy-4-vinylphenol (**1e**).*[21] Compound **1e** (1.23 g, 82%) was obtained as colorless liquid, R_f=0.49 (ethylacetate/*n*-hexane=1:5); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.91 (s, 3H, ArOCH$_3$), 5.10 (dd, J=10.6, 0.8 Hz, 1H, ArCH=CH_aH$_b$), 5.60 (dd, J=17.6, 0.8 Hz, 1H, ArCH=CH$_a$H$_b$), 5.65 (s, 1H, OH), 6.64 (dd, J=17.6, 10.8 Hz, 1H, ArC*H*=CH$_a$H$_b$), 6.92 (m, 3H, ArH), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.9, 108.0, 111.4, 114.3, 120.0, 130.3, 136.6, 145.6, 146.6; EI-MS (70 eV) m/z (rel intensity, %) 150 (M^+, 100), 137 (8), 135 (54), 107 (33), 80 (19), 78 (10), 77 (25); HRMS calcd for $C_9H_{10}O_2$: 150.0681. Found: 150.0680.

*4.1.2. General procedure for the preparation of compounds (**1f**,**g**).* To a stirred solution of *p*-hydroxybenzaldehydes (10 mmol) in anhydrous acetone (15 mL) was added 10% NaOH solution (25 mL), and the mixture was stirred for 3 h at room temperature. Acidification using 10% HCl until the color change of Congo red paper from red to blue. The resulting mixture was extracted with dichloromethane (30 mL×3). The organic layers were washed with brine (20 mL) and

dried over $MgSO_4$ were filtered, evaporated, and the residue was purified by column chromatography (ethyl acetate/*n*-hexane=1:10) to give pure **1f**–**g**.

*4.1.2.1. (E)-4-(4-Hydroxyphenyl)but-3-en-2-one (**1f**).*[23] Compound **1f** (1.39 g, 86%) was obtained as colorless crystals, mp 109 °C, R_f=0.47 (ethyl acetate/*n*-hexane=1:2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.42 (s, 3H, $COCH_3$), 6.63 (d, *J*=16.2 Hz, 1H, ArCH=C*H*COCH$_3$), 6.95 (d, *J*=8.8 Hz, 2H, ArH), 7.46 (d, *J*=8.8 Hz, 2H, ArH), 7.55 (d, *J*=16.2 Hz, 1H, ArC*H*=CHCOCH$_3$), 8.32 (s, 1H, ArOH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.1, 116.2, 124.0, 126.1, 130.5, 145.2, 159.3, 175.7; EI-MS (70 eV) *m*/*z* (rel intensity, %) 162 (M^+, 33), 161 (55), 147 (100), 146 (32), 119 (70), 91 (83), 65 (25); HRMS calcd for $C_{10}H_{10}O_2$: 162.0681. Found: 162.0680.

*4.1.2.2. (E)-4-(4-Hydroxy-3-methoxyphenyl)but-3-en-2-one (**1g**).*[24] Compound **1g** (1.63 g, 85%) was obtained as yellow crystals, mp 127–128 °C, R_f=0.49 (ethyl acetate/*n*-hexane=1:2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.37 (s, 3H, $COCH_3$), 3.92 (s, 3H, $ArOCH_3$), 6.24 (s, 1H, ArOH), 6.59 (d, *J*=16.2 Hz, ArCH=C*H*COCH$_3$), 6.94 (d, *J*=8.0 Hz, 1H, ArH), 7.08 (d, *J*=8.0 Hz, 1 ArH), 7.11 (s, 1H, ArH), 7.46 (d, 1H, *J*=16.2 Hz, ArC*H*=CHCOCH$_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.2, 55.9, 109.3, 114.8, 123.4, 124.8, 126.8, 143.8, 146.9, 148.3, 179.5; EI-MS (70 eV) *m*/*z* (rel intensity, %) 192 (M^+, 61), 191 (42), 177 (54), 175 (32), 145 (100), 117 (47), 89 (31); HRMS calcd for $C_{11}H_{12}O_2$: 192.0786. Found: 192.0788.

*4.1.3. General procedure for the preparation of natural occurring (±)-dihydrobenzofurans (**2a**,**b**).* A solution of **1a**,**b** (2 mmol) in THF (50 mL) was added dropwise with ceric ammonium nitrate (1.64 g, 3 mmol)/THF (50 mL) under the protection of dried nitrogen at 0 °C for 1.5 h. Then, quenched with brine (20 mL), and concentrated in vacuo to remove THF, and extracted with CH_2Cl_2 (40 mL×3). The organic layer was combined, dried over $MgSO_4$, and filtered in sequence. The filtrate was concentrated in vacuo to remove solvent. The resulting residue was purified by silica gel column chromatography (ethyl acetate/*n*-hexane=1:6) to give **2a**,**b**, respectively.

*4.1.3.1. 2-(4-Hydroxyphenyl)-3-methyl-5-((E)-propenyl)-2,3-dihydrobenzofuran [(±)-conocarpan, **2a**].* Compound **2a** (0.45 g, 85%) was obtained as colorless crystals, mp 119–120 °C (lit.[17] mp 120–123 °C); R_f=0.45 (ethyl acetate/*n*-hexane=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (d, *J*=6.8 Hz, 3H, C_3–C*H*$_3$), 1.90 (d, *J*=8.4 Hz, 3H, ArCH=CHC*H*$_3$), 3.41 (dq, *J*=8.8, 6.8 Hz, 1H, H-3), 5.10 (d, *J*=8.8 Hz, 1H, H-2), 5.38 (s, 1H, ArOH), 5.69 (d, *J*=18.4 Hz, 1H, ArC*H*=CHCH$_3$), 6.37 (dq, *J*=18.4, 8.4 Hz, 1H, ArCH=C*H*CH$_3$), 6.78 (d, *J*=8.0 Hz, 1H, ArH), 6.83 (dd, *J*=8.0, 2.0 Hz, 1H, ArH), 7.13 (d, *J*=8.4 Hz, 2H, ArH), 7.27 (d, *J*=8.4 Hz, 2H, ArH), 7.29 (d, *J*=2.0 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7, 17.8, 45.2, 92.6, 109.0, 115.5, 120.8, 124.1, 124.8, 127.8, 126.3, 129.0, 129.6, 130.7, 155.7, 157.7; EI-MS (70 eV) *m*/*z* (rel intensity, %) 266 (M^+, 100), 252 (9), 251 (47), 224 (12), 223 (22), 131 (12), 121 (20); HRMS calcd for $C_{18}H_{18}O_2$: 266.1310. Found: 266.1310.

*4.1.3.2. 2-(4-Hydroxy-3-methoxyphenyl)-3-methyl-5-((1E)-propenyl)-2,3-dihydrobenzofuran [(±)-licarin A, **2b**].*[13,18] Compound **2b** (0.53 g, 81%) was obtained as colorless crystals, mp 133–134 °C (lit. mp 132–133 °C); R_f=0.45 (ethyl acetate/*n*-hexane=1:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (d, *J*=6.8 Hz, 3H, C_3–C*H*$_3$), 1.87 (dd, *J*=6.8, 1.6 Hz, 3H, ArCH=CHC*H*$_3$), 3.45 (dq, *J*=9.6, 6.8 Hz, 1H, H-3), 3.88 (s, 3H, $ArOCH_3$), 3.89 (s, 3H, $ArOCH_3$), 5.10 (d, *J*=9.6 Hz, 1H, H-2), 5.63 (s, 1H, ArOH), 6.11 (dq, *J*=15.6, 6.8 Hz, 1H, ArCH=C*H*CH$_3$), 6.36 (dd, *J*=15.6, 1.6 Hz, 1H, ArC*H*=CHCH$_3$), 6.77 (s, 1H, ArH), 6.79 (s, 1H, ArH), 6.88 (d, *J*=8.4 Hz, 1H, ArH), 6.91 (d, *J*=8.4 Hz, 1H, ArH), 6.97 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.6, 18.4, 45.6, 55.9, 56.0, 93.8, 108.9, 109.2, 113.3, 114.1, 120.0, 123.5, 130.9, 132.1, 132.2, 133.3, 144.1, 145.8, 146.6, 146.7; EI-MS (70 eV) *m*/*z* (rel intensity, %) 326 (M^+, 100), 311 (25), 309 (7), 284 (11), 283 (11), 279 (6), 151 (6); HRMS calcd for $C_{20}H_{22}O_4$: 326.1518. Found: 326.1521.

*4.1.3.3. Preparation of 2-(3,4-dimethoxyphenyl)-7-methoxy-3-methyl-5-((E)-propenyl)-2,3-dihydrobenzofuran [(±)-acuminatin (**2c**)].*[19] (±)-Licarin A (**2b**) (0.65 g, 2 mmol) dissolved in acetone (30 mL) was added K_2CO_3 (0.41 g, 3 mmol), and respectively added methyl iodide (0.34 mL, 2.4 mmol). The reaction mixture was heated to reflux for 5 h (monitoring by TLC). After the end of reaction, the mixture was filtered from Celite 545 to remove solid, and the giving filtrate was concentrated in vacuo to remove the solvent to give crude product. After purification by silica gel column chromatography (ethyl acetate/*n*-hexane=1:10) afforded (±)-acuminatin (**2c**). Compound **2c** (0.64 g, 94%) was obtained as pale yellow crystals, mp 120–121 °C; R_f=0.47 (ethyl acetate/*n*-hexane=1:5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (d, *J*=6.8 Hz, 3H, C_3–C*H*$_3$), 1.87 (dd, *J*=6.4, 1.6 Hz, 3H, ArCH=CHC*H*$_3$), 3.46 (dq, *J*=9.6, 6.8 Hz, 1H, H-3), 3.87 (s, 3H, $ArOCH_3$), 3.88 (s, 3H, $ArOCH_3$), 3.90 (s, 3H, $ArOCH_3$), 5.12 (d, *J*=9.6 Hz, 1H, H-2), 6.11 (dq, *J*=15.6, 6.4 Hz, 1H, ArCH=C*H*CH$_3$), 6.36 (dq, *J*=15.6, 1.6 Hz, 1H, ArC*H*=CHCH$_3$), 6.78 (d, *J*=8.0 Hz, 1H, ArH), 6.83 (s, 1H, ArH), 6.85 (s, 1H, ArH), 6.96 (dd, *J*=8.0, 2.0 Hz, 1H, ArH), 6.98 (d, *J*=2.0 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.6, 18.4, 45.6, 55.9, 93.7, 109.3, 109.5, 110.8, 113.3, 119.2, 123.5, 130.9, 132.2, 132.7, 132.2, 133.3, 144.2, 146.6, 149.1; EI-MS (70 eV) *m*/*z* (rel intensity, %) 340 (M^+, 100), 325 (33), 309 (12), 297 (11), 165 (20), 164 (11), 151 (12); HRMS calcd for $C_{21}H_{24}O_4$: 340.1675. Found: 340.1677.

*4.1.3.4. 2-(4-Hydroxyphenyl)-5-vinyl-2,3-dihydrobenzo-furan (**2d**).*[25] Compound **2d** (0.39 g, 82%) was obtained as colorless liquid, R_f=0.46 (ethyl acetate/*n*-hexane=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.19 (dd, *J*=15.8, 8.4 Hz, 1H, H_a-3), 3.57 (dd, *J*=15.8, 9.2 Hz, 1H, H_b-3), 4.98 (s, 1H, ArOH), 5.09 (dd, *J*=10.6, 1.2 Hz, 1H, ArCH=CH_aH_b), 5.58 (dd, *J*=17.6, 1.2 Hz, 1H, ArCH=CH_aH_b), 5.70 (dd, *J*=9.2, 8.4 Hz, 1H, H-2), 6.66 (dd, *J*=17.6, 10.6 Hz, 1H, ArC*H*=CH_aH_b), 6.80 (s, 1H, ArH), 6.82 (d, *J*=8.4 Hz, 2H, ArH), 7.20 (d, *J*=8.4 Hz, 2H, ArH), 7.23 (d, *J*=7.6 Hz, 1H, ArH), 7.28 (d, *J*=7.6 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.8, 83.6, 107.9, 110.0, 114.6, 121.4, 125.8, 126.4, 126.8, 129.5, 131.0, 135.6, 156.5, 158.5; EI-MS (70 eV) *m*/*z* (rel intensity, %) 238 (M^+, 100), 237 (15), 223 (8), 221 (11), 209 (7), 165 (7), 115 (6); HRMS calcd for $C_{16}H_{14}O_2$: 238.0994. Found: 238.0992.

*4.1.3.5. 2-(4-Hydroxyphenyl)-3-isopropyl-5(3-methylbut-1-(E)-enyl)-2,3-dihydrobenzofuran (**2e**).* Compound **2e** (0.54 g, 84%) was obtained as colorless liquid, R_f=0.43 (ethyl acetate/*n*-hexane=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (d, *J*=6.8 Hz, 6H, ArCHCHCH*Me*$_2$), 1.04 (dd, *J*=6.8 Hz, 6H, ArCH=CHCH*Me*$_2$), 2.88 (m, 1H, CHCHC*H*Me$_2$), 4.26 (dd, *J*=9.2, 6.8 Hz, 1H, H-3), 4.86 (m, 1H, ArCH=CHC*H*Me$_2$), 4.92 (s, 1H, ArOH), 5.40 (d, *J*=9.2 Hz, 1H, H-2), 6.78 (d, *J*=15.4 Hz, 1H, ArC*H*=CHCHMe$_2$), 6.80 (d, *J*=15.4, 1.2 Hz, 1H, ArCH=C*H*CHMe$_2$), 6.84 (s, 1H, ArH), 7.12 (d, *J*=8.8 Hz, 1H, ArH), 7.16 (d, *J*=8.8 Hz, 1H, ArH), 7.29 (d, *J*=8.4 Hz, 2H, ArH), 7.31 (d, *J*=8.4 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.0, 17.8, 20.1, 23.2, 27.1, 29.7, 74.2, 86.4, 115.1, 115.4, 115.9, 116.0, 125.8, 128.4, 128.6, 129.7, 129.8, 139.0, 155.2, 158.4; EI-MS (70 eV) *m*/*z* (rel intensity, %) 322 (M^+, 14), 218 (68), 217 (25), 162 (98), 161 (94), 148 (23), 147 (100); HRMS calcd for $C_{22}H_{26}O_2$: 322.1933. Found: 322.1932.

*4.1.3.6. 2-(3-Methoxy-4-hydroxyphenyl)-7-methoxy-5-vinyl-2,3-dihydrobenzofuran (**2f**).*[26] Compound **5c** (0.51 g, 86%) was obtained as colorless liquid, R_f=0.45 (ethyl acetate/*n*-hexane=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.25 (dd, *J*=15.6, 8.8 Hz, 1H, H_a-3), 3.57 (dd, *J*=15.6, 9.2 Hz, 1H, H_b-3), 3.87 (s, 3H, $ArOCH_3$), 3.90 (s, 3H, $ArOCH_3$), 5.14 (dd, *J*=9.2, 8.8 Hz, 1H, H-2), 5.60 (dd, *J*=17.6, 0.8 Hz, 1H, ArCH=CH_aH_b), 5.66 (s, 1H, ArOH), 5.73 (dd, *J*=10.8, 0.8 Hz, 1H, ArCH=CH_aH_b), 6.65 (dd, *J*=17.6, 10.8 Hz, 1H, ArC*H*=CH_aH_b), 6.85 (s, 1H,

ArH), 6.88 (d, J=8.0 Hz, 1H, ArH), 6.90 (d, J=8.0 Hz, 1H, ArH), 6.91 (s, 1H, ArH), 6.95 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.5, 55.9, 56.0, 85.6, 108.7, 109.5, 111.4, 114.2, 115.1, 119.5, 128.0, 131.6, 133.1, 136.7, 144.2, 145.6, 146.6, 147.8; EI-MS (70 eV) m/z (rel intensity, %) 298 (M^+, 100), 251 (6), 233 (9), 223 (9), 204 (8); HRMS calcd for $C_{18}H_{18}O_4$: 298.1205. Found: 298.1204.

*4.1.3.7. 3-Acetyl-2-(4-hydroxyphenyl)-5-[(1E)-3-oxo-1-butenyl]-2,3-dihydrobenzofuran (**2g**).* Compound **2g** (0.57 g, 88%) was obtained as colorless liquid, R_f=0.42 (ethyl acetate/n-hexane=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H, $COCH_3$), 2.38 (s, 3H, $COCH_3$), 4.32 (d, J=8.8 Hz, 1H, H-3), 6.03 (d, J=8.8 Hz, 1H, H-2), 6.60 (d, J=15.6 Hz, 1H, ArCH=C*H*$COCH_3$), 6.84 (d, J=8.4 Hz, 2H, ArH), 6.90 (d, J=8.8 Hz, 1H, ArH), 6.93 (s, 1H, ArH), 7.29 (s, 1H, ArOH), 7.16 (d, J=8.8 Hz, 1H, ArH), 7.45 (d, J=8.4 Hz, 2H, ArH), 7.51 (d, J=15.6 Hz, 1H, ArC*H*=CH$COCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.3, 28.5, 63.3, 85.9, 110.7, 115.7, 115.8, 124.7, 127.2, 127.6, 130.3, 131.2, 132.9, 143.8, 156.7, 161.7, 199.2, 204.0; EI-MS (70 eV) m/z (rel intensity, %) 323 (M^+, 8), 322 (34), 281 (18), 280 (100), 265 (12), 237 (10), 219 (12); HRMS calcd for $C_{20}H_{19}O_4$: 323.1283. Found: 323.1282.

*4.1.3.8. 3-Acetyl-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-5-[(1E)-3-oxo-1-butenyl]-2,3-dihydrobenzofuran (**2h**).* Compound **2h** (0.68 g, 89%) was obtained as colorless liquid, R_f=0.40 (ethyl acetate/n-hexane=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.32 (s, 3H, $COCH_3$), 2.37 (s, 3H, $COCH_3$), 3.86 (s, 3H, $ArOCH_3$), 3.93 (s, 3H, $ArOCH_3$), 4.40 (d, J=8.8 Hz, 1H, H-3), 6.08 (d, J=8.8 Hz, 1H, H-2), 6.61 (d, J=16.0 Hz, 1H, ArCH=C*H*$COCH_3$), 6.86 (d, J=8.4 Hz, 1H, ArH), 7.00 (d, J=2.0 Hz, 1H, ArH), 7.08 (s, 1H, ArOH), 7.15 (dd, J=8.4, 2.0 Hz, 1H, ArH), 7.17 (d, J=2.0 Hz, 1H, ArH), 7.38 (d, J=2.0 Hz, 1H, ArH), 7.43 (d, J=16.0 Hz, 1H, ArC*H*=CH–$COCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.7, 27.3, 55.5, 56.1, 63.7, 86.8, 108.6, 111.0, 112.1, 113.7, 114.6, 117.8, 119.1, 122.6, 125.2, 126.0, 126.2, 127.3, 143.0, 143.2, 194.7, 198.3; EI-MS (70 eV) m/z (rel intensity, %) 382 (M^+, 28), 313 (21), 311 (100), 293 (22), 279 (30), 293 (22), 237 (18), 138 (22), 137 (69); HRMS calcd for $C_{22}H_{22}O_6$: 382.1416. Found: 382.1414.

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