A Controlled Synthesis of Nature-Mimicking Benzofurans and their Corresponding Dimers[1]

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Abstract: Benzofurans functionalized with hydroxy and acetyl functionalities are not only the core structures found in a large number of biologically important natural products, but also the vital precursors for several naturally occurring furanoflavonoids. Numerous synthetic methodologies are available in the literature for the synthesis of functionalized benzofurans but access to benzofurans with adjacent hydroxy and acetyl functionalities shows paucity of references. In this paper we report highly convenient synthesis of nature-mimicking benzofurans and their dimers from easily accessible precursors.

Key words: benzofuran, dihydrobenzofuran, benzofuran dimer, Amberlyst 15, bibenzofuran

Benzofurans, dihydrobenzofurans and their dimers in isolated or rigid conformations are key structural units found in a large number of medicinal plants.[2] They are usually active constituents of plant extracts used in traditional remedies, and play a pivotal role in the natural defence mechanisms of their sources. A few structures representatives of naturally occurring benzofurans[3] are shown in Figure 1. In nature's library of benzofuran derivatives, most features a benzofuran motif functionalized on benzenoid ring with an adjacent hydroxy and acetyl functionality but differ in their point of attachments. For example, euparin possessed a 5-acetyl-6-hydroxybenzofuran skeleton, while ageratone possessed a 6-acetyl-5-hydroxybenzofuran ring system. Similarly, 4(6)-hydroxytremetone possessed 5-acetyl-4(6)-hydroxy-2,3-dihydrobenzofuran architecture, while viscidone possessed 6-acetyl-5-hydroxy-2,3-dihydrobenzofuran ring system. These positional isomeric core structures present real challenges to natural product chemists in assigning the correct structure for an unknown compound. In addition, these benzofurans with an adjacent hydroxy and acetyl functionality are key precursors for the synthesis of several naturally occurring angular and linear furanoflavonoids.[4] Therefore, a synthetic route leading to *ortho*-hydroxybenzofuran methyl ketones with particular attributes would be of general interest.

Numerous synthetic methodologies are available in the literature for the construction of benzofuran ring and due to its wide-ranging applications; several new synthetic approaches have been developed in recent years.[5,6] The most common procedures include palladium-catalyzed coupling of substituted 2-halophenols and the appropriate alkynes, a Dötz benzannulation approach using α,β-

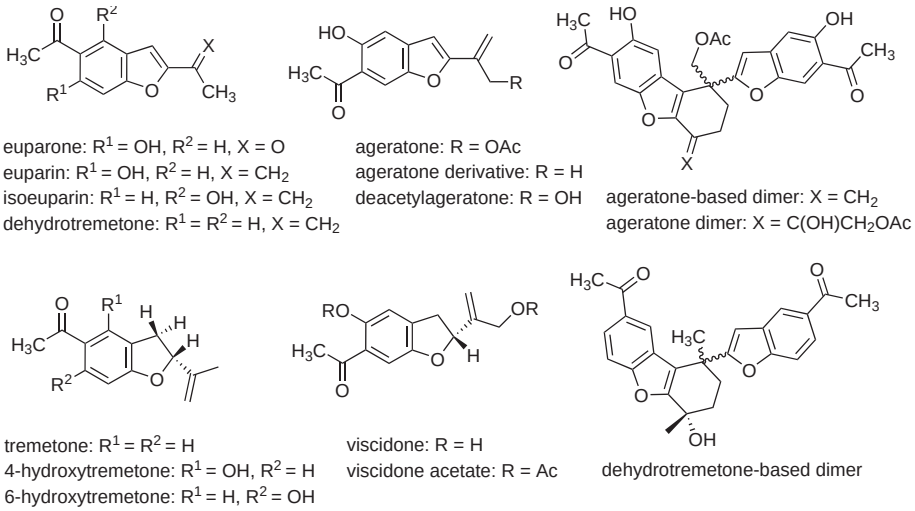

Figure 1 Examples of naturally occurring benzofurans, dihydrobenzofurans and their dimers bearing hydroxy and acetyl functionalities.

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unsaturated chromium carbene complexes and copper-catalyzed intramolecular ring-closure reactions. Unfortunately the extension of these procedures in preparing naturally occurring benzofurans suffers from the limited use of expensive palladium catalysts, the selective preparation of organometal complexes, the protection–deprotection of free hydroxy and acetyl functionality and/or harsh reaction conditions. Recently, Kotschy et al.[7] highlighted the difficulties they encountered in the total synthesis of dehydrotremetone in which Sonogashira coupling failed even under the best conditions known today. Though these natural products (Figure 1) are structurally very simple but only the partial synthesis of some of the natural benzofurans (euparin, tremetone and dehydrotremetone) using functionalized benzofurans as precursors have been reported, and these have involved multiple steps.[8] The wide-ranging applications and limitations of existing protocols prompted us to devise a general synthetic strategy directed towards the preparation of the core benzofurans with an adjacent hydroxy and acetyl functionality.

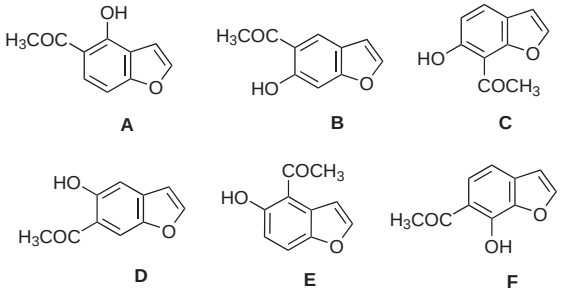
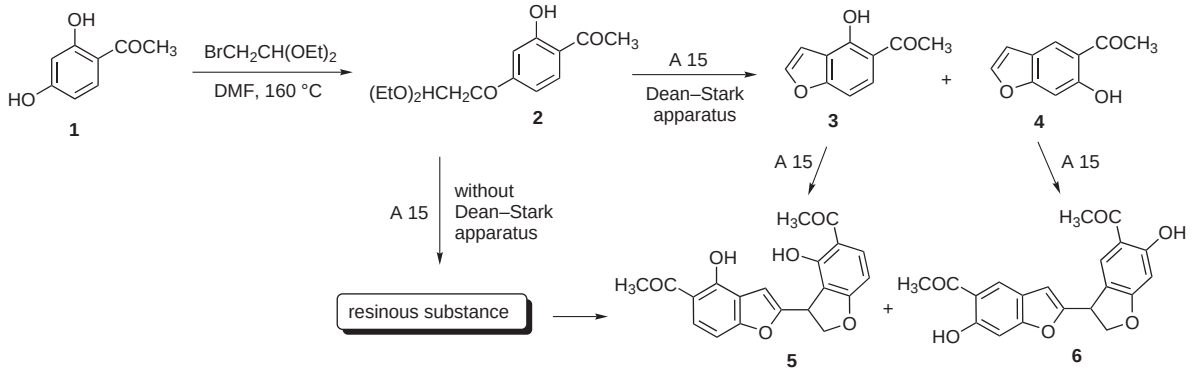


Figure 2 Six possible isomers of hydroxybenzofuran methyl ketone (**A**–**F**).

There are only six isomeric structures possible in *ortho*-hydroxybenzofuran methyl ketones (**A**–**F**) with the consideration that only one hydroxy and one acetyl group is attached adjacent to each other on the benzenoid ring of the benzofuran as shown in Figure 2. Although these benzofurans **A**–**F** are structurally very simple, they have been prepared mainly through manipulation on properly functionalized benzofurans in multiple steps in moderate yields.[9] In this paper we report two-step synthesis of isomeric benzofurans **A**–**E** together with the Amberlyst 15 catalyzed controlled dimerization of these benzofurans to bibenzofurans, which are similar to naturally occurring bis(benzofurans) and apparently formed by a similar mechanism.

Our strategy for the synthesis of 5-acetyl-4-hydroxybenzofuran (**A**) and 5-acetyl-6-hydroxybenzofuran (**B**) include a reaction of resacetophenone (**1**) and bromoacetaldehyde diethyl acetal in the presence of anhydrous potassium carbonate in dry DMF, which afforded 1-[4-(2,2-diethoxyethoxy)-2-hydroxyphenyl]ethanone (**2**) in 90% yield (Scheme 1). Many examples of the cyclization of functionalized phenoxyacetals to corresponding benzofurans are reported[10] in the literature using various Lewis acids ($SnCl_4$, $AlCl_3$, BF_3, $ZnCl_2$) and organic acids (H_2SO_4, TFA, H_3PO_4, PPA, HCOOH, PTSA). Unfortunately, the majority of them leads to low yield of desired benzofuran along with major polymerized resinous material containing mixture of compounds. These cyclizations are extremely dependent on the presence of substituents on the phenyl ring and the conditions employed. During these investigations we found that this ring-closure step can be effectively performed using Amberlyst 15 (A 15, a sulfonic acid cation exchange resin) as a catalyst and polymerization step can be controlled with concomitant removal of azeotropes generated in situ during cyclization. Thus we attempted cyclization of phenoxyacetal **2** in refluxing toluene using Amberlyst 15 as a catalyst with concomitant removal of azeotropes using Dean–Stark apparatus. Interestingly, two major products, 5-acetyl-4-hydroxybenzofuran (**3**) and 5-acetyl-6-hydroxybenzofuran (**4**) were isolated in 38% and 54% yield, respectively (Scheme 1). In the absence of Dean–Stark apparatus, the cyclization of **2** resulted in extensive polymerization, leading to a resinous substance containing a mixture of compounds as a major product, similar to the polymeric compound obtained by various acid-catalyzed cyclizations (Scheme 1).

Such a minor change in the reaction conditions for the cyclization of phenoxyacetals to benzofuran prompted us to identify compounds from the resinous mixture, which have not been reported prior to this study. On repeated column chromatography in combination with preparative



Scheme 1

TLC separation, we isolated two products **5** and **6** from the resinous mixture in low yields. The mass spectrum of compound **6** showed molecular ion peak at *m/z* = 352, which corresponds to two units of benzofuran **3** or **4**. The ^{1}H NMR spectroscopic analysis of **6** revealed two methyl singlets at δ = 2.53 and 2.68 ppm and two hydroxy group singlets at δ = 12.46 and 13.02 ppm, and four aromatic protons singlets at δ = 6.43, 6.99, 7.58 and 7.91 ppm, which confirmed the possibility of a dimer of benzofuran **4**. A multiplet at δ = 4.75–4.80 ppm for two protons and a multiplet at δ = 4.92–4.96 ppm for one proton revealed that one of the furan rings of the dimer is reduced under acidic conditions. These dimers can be of two types such as 2′,3′-dihydro[2,3′]bibenzofuran or 2′,3′-dihydro[3,2′]-bibenzofuran depending upon substituents on the benzofuran ring. A literature search on dimerization of benzofuran revealed that a natural benzofuran kellinone has been reported to form a dimer under acidic conditions.[11] The presence of a peak at δ = 6.46 ppm for CH-3 in ^{1}H NMR spectrum of **6** and absence of a peak at around δ = 7.56 ppm for CH-2 proton allowed us to propose a structure as 5,5′-diacetyl-6,6′-dihydroxy-2′,3′-dihydro[2,3′]bibenzofuran. Finally, the structure of **6** was confirmed by a single crystal X-ray analysis.[12] The conformation of **6** along with the atomic numbering scheme is shown in Figure 3. Similarly, other isolated product **5** was assigned as 5,5′-diacetyl-4,4′-dihydroxy-2′,3′-dihydro-[2,3′]bibenzofuran. The formation of bibenzofuran from phenoxyacetal revealed that as soon as the benzofuran is formed through cyclization, it got converted into bibenzofuran by self-dimerization in aqueous acidic medium. These bibenzofurans are similar to natural dimers of ageratone or dehydrotremetone as shown in Figure 1.

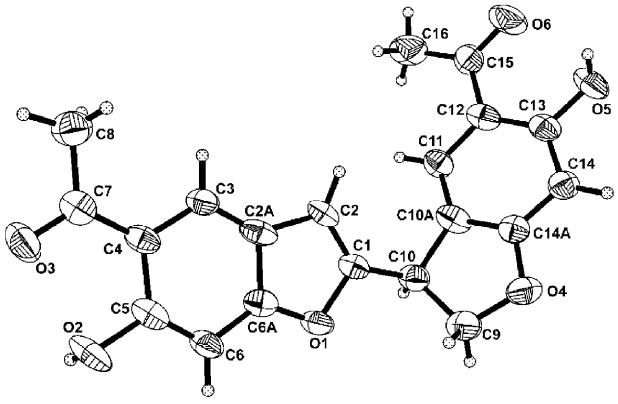
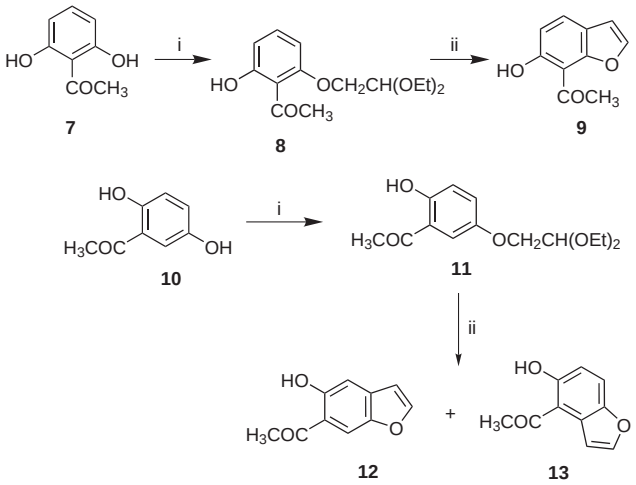


Figure 3 ORTEP view of compound **6** with arbitrary numbering.

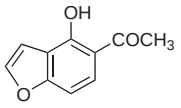
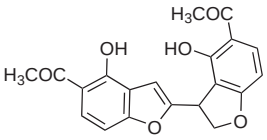
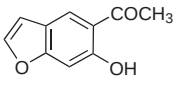
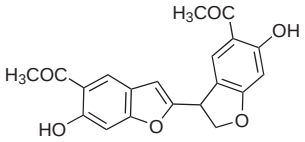
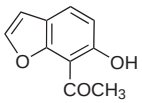
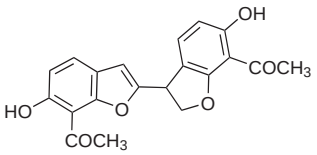
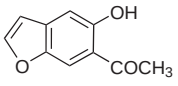
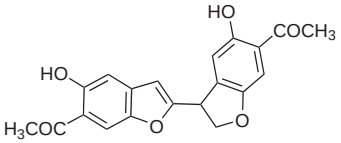
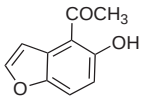
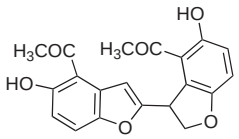
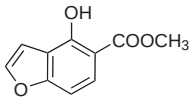
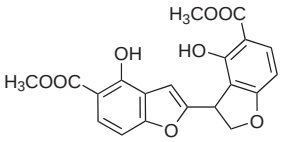
With the demonstration of the utility of this route, we set out to prepare a series of substituted benzofurans (**C**–**F**) and their dimeric bibenzofurans in a controlled manner. These benzofurans (**C**–**F**) with adjacent hydroxy and acetyl groups have been prepared either from functionalized benzofurans[9a,b] or coumarins[9c] in multisteps. Our approach for preparing these useful benzofurans followed a two-step procedure as demonstrated for the compounds **3** and **4**. The compound 6-hydroxy-7-acetylbenzofuran (**9** or **C**) was prepared in 85% yield by the reaction of 2,6-dihydroxyacetophenone **7** and bromoacetaldehyde diethyl acetal to form a phenoxyacetal **8**, followed by Amberlyst 15 catalyzed cyclization under simultaneous removal of water using Dean–Stark assembly (Scheme 2). Similarly, 6-acetyl-5-hydroxybenzofuran (**12** or **D**) and 4-acetyl-5-hydroxybenzofuran (**13** or **E**) were synthesized in good yields from commercially available 2,5-dihydroxyacetophenone (**10**) through a phenoxyacetal intermediate **11** as shown in Scheme 2.



Scheme 2 *Reagents and conditions*: i) $BrCH_2CH(OEt)_2$, DMF, 140 °C; ii) A 15, toluene, reflux.

Apart from naturally occurring benzofurans, natural dimers have also been isolated from *Ageratum houstonianum*,[3g] *Ophryosporus charua*[3h] and *Encelia canescens*[3i] in minor quantities. The biosynthetic route of such dimers have been proposed through a Diels–Alder-type reaction between two units of ageratone or dehydrotremetone, followed by allylic hydroxylation or hydroperoxidation of the initial adducts.[3h] An alternative biosynthetic approach for natural dimeric chromenes and mixed dimers has been proposed through acid-catalyzed addition of 6-hydroxytremetone to acetyl chromene followed by isomerization.[3i] The formation of similar type of benzofuran dimers (**5** and **6**) from acid-catalyzed cyclization of phenoxyacetals supports the mechanism proposed by Bohlmann et al.[3i] for the formation of mixed dimers. Recently five-membered heteroaryl-based atropisomeric ligands have been developed for asymmetric synthesis.[13] Therefore, we became interested to prepare dimers of these benzofurans (**3**, **4**, **9**, **12**–**14**) in the presence of Amberlyst 15 separately. The precursor **14** was prepared by the reaction of diazocyclohexane-1,3-dione with vinyl acetates in presence of rhodium acetate followed by dehydration, esterification and aromatization.[4h] Compound **3** on refluxing in toluene with Amberlyst 15 selectively afforded 2′,3′-dihydro[2,3′]bibenzofuran (**5**) in 89% yield along with some unreacted benzofuran **3**. Similarly another set of compounds (**4**, **9**, **12**–**14**, Table 1) was treated

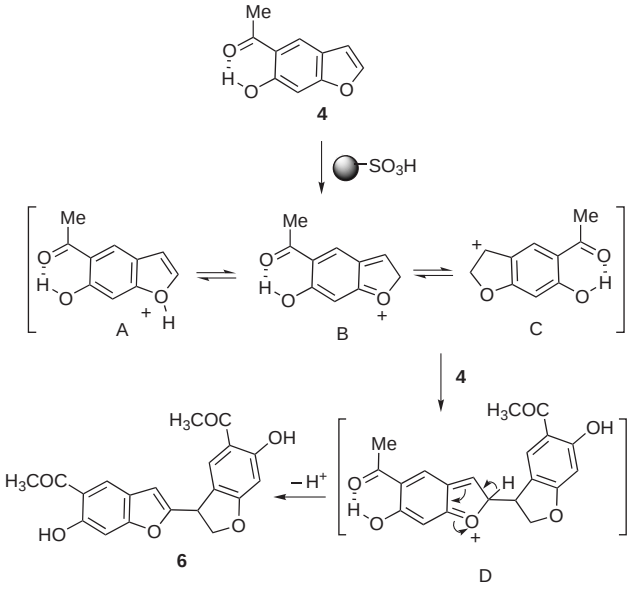
Table 1 Amberlyst 15 Catalyzed Dimerization of *ortho*-Hydroxybenzofuran Methyl Ketones

Reactant	Product	Yield (%)
 **3**	 **5**	89
 **4**	 **6**	81
 **9**	 **15**	92
 **12**	 **16**	75
 **13**	 **17**	83
 **14**	 **18**	86

under the same reaction conditions to afford bibenzofurans (**6**, **15**–**18**) in good yields. All the synthesized compounds were characterized by spectroscopic analyses.[14,15]

With these observations, we propose a possible mechanism for the formation of bibenzofuran from *ortho*-hydroxybenzofuran methyl ketone in the presence of Amberlyst 15 catalyst (Scheme 3). The mechanism for the dimerization, using Amberlyst 15 might involve protonation of benzofuran **4** to form a carbonium ion intermediate C followed by attack of the other molecule of **4** at the β-position of the intermediate C to form an intermediate bibenzofuran D. This intermediate on deprotonation affords 2′,3′-dihydro-[2,3′]bibenzofuran (**6**) as shown in Scheme 3.

In summary, we have demonstrated a highly convenient two-step general synthesis of nature-mimicking benzofuran derivatives bearing hydroxy and acetyl groups at adjacent positions, which were difficult to prepare through known methodologies. We have also demonstrated an Amberlyst 15 catalyzed, controlled dimerization of these benzofurans to 2′,3′-dihydro[2,3′]bibenzofurans, which are similar to the natural dimers. In particular, the synthesis of *ortho*-hydroxybenzofuran methyl ketone requires concomitant removal of an azeotropic mixture during the cyclization of phenoxyacetals; however, bibenzofurans can directly be prepared without removal of azeotropic contents. The ease of controlled cyclization and selective dimerization in the presence of the catalyst Amberlyst 15 and its reusability over several uses opens a new avenue in the exploration of the chemical and biological potential of these interesting molecules.



Scheme 3 A possible mechanism for dimerization of 5-acetyl-6-hydroxybenzofuran.

Acknowledgment

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(12) Crystal data of **6**: $C_{20}H_{16}O_6$, M = 352.33, triclinic, space group P-1, a = 8.186 (1), b = 9.265 (2), c = 12.134 (3) Å, α = 95.27 (1)°, β = 100.54 (1)°, γ = 112.47 (2)°, V = 822.7 (3) Å^3, T = 293 K, Z = 2, μ (MoK$_\alpha$) = 0.11 mm^{-1}, $R1$ = 0.1302 for 993 I > 4σ(I) and 0.2971 for all 2838 data. CCDC (No. 604409) contains the supplementary crystallographic data. These data can be obtained free of charge from www.ccdc.cam.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK; fax: +44(1223)336033; email: deposit@ccdc.cam.ac.uk]. Programs: XSCANS [Siemens Analytical X-ray Instrument Inc.: Madison, Wisconsin, USA 1996], SHELXTL-NT [Bruker AXS Inc.: Madison, Wisconsin, USA 1997].

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(14) **Synthesis of *ortho*-Hydroxybenzofuran Methyl Ketones (3,4,9,12,13) – General Procedure.**

The phenoxyacetal (**2**, **8**, **11**; 20 g, 0.075 mol) was refluxed in dry toluene (30 mL) with Amberlyst 15 (2.5 g) at 120 °C for 6–8 h with concomitant removal of the azeotrope using a Dean–Stark apparatus. The resulting reaction mixture was filtered and the resin was washed with an excess of toluene. The filtrate thus obtained was concentrated to dryness and two pure compounds were isolated by silica gel column chromatography using EtOAc–hexane (1:10) as eluent.

Compound **3**: white solid; mp 92–93 °C (Lit.[4h] 92–93 °C). MS (FAB): *m/z* = 177 [M$^+$ + 1]. IR (KBr): 1640 (CO), 3421 (OH) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.66 (s, 3 H, CH_3), 7.00 (d, J = 2.2 Hz, 1 H, H-3), 7.04 (d, 1 H, J = 8.8 Hz, H-7), 7.57 (d, 1 H, J = 2.2 Hz, H-2), 7.66 (d, 1 H, J = 8.8 Hz, H-6), 13.28 (s, 1 H, OH).

Compound **4**: white solid; mp 101–102 °C (Lit.[9a] 96 °C). MS (FAB): *m/z* = 177 [M$^+$ + 1]. IR (KBr): 1638 (CO), 3426 (OH) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.70 (s, 3 H, CH_3), 6.72 (d, 1 H, J = 2.2 Hz, H-3), 7.04 (s, 1 H, H-7), 7.56 (d, 1 H, J = 2.2 Hz, H-2), 8.00 (s, 1 H, H-4), 12.40 (s, 1 H, OH).

Compound **9**: white solid; mp 111–112 °C (Lit.[9c] 110 °C). MS (FAB): *m/z* = 177 [M$^+$ + 1]. IR (KBr): 1638 (CO), 3432 (OH) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.90 (s, 3 H, CH_3), 6.76 (d, J = 2.2 Hz, 1 H, H-3), 6.90 (d, 1 H, J = 8.6 Hz, H-5), 7.62 (d, 1 H, J = 2.2 Hz, H-2), 7.66 (d, 1 H, J = 8.6 Hz, H-4), 12.85 (s, 1 H, OH).

Compound **12**: white solid; mp 120–121 °C. MS (FAB): *m/z* = 177 [M$^+$ + 1]. IR (KBr): 1629 (CO), 3447 (OH) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.60 (s, 3 H, CH_3), 6.86 (s, 1 H, ArH), 6.91 (d, J = 2.2 Hz, 1 H, H-3), 7.02 (s, 1 H, ArH), 7.19 (d, 1 H, J = 2.2 Hz, H-2), 11.81 (s, 1 H, OH).

Compound **13**: white solid; mp 98–99 °C (Lit.[9a] 103–104 °C). MS (FAB): *m/z* = 177 [M$^+$ + 1]. IR (KBr): 1628 (CO), 3443 (OH) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.80 (s, 3 H, CH_3), 6.94 (d, 1 H, J = 9.0 Hz, CH), 6.98 (d, 1 H, J = 2.2 Hz, H-3), 7.64 (d, 1 H, J = 9.0 Hz, ArH), 7.76 (d, 1 H, J = 2.2 Hz, H-2), 13.02 (s, 1 H, OH).

Compound **14**: white solid; mp 104–105 °C (Lit.[4h] 105 °C). MS (FAB): *m/z* = 193 [M$^+$ + 1]. IR (KBr): 1678 (CO), 3502

(OH) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.97 (s, 3 H, OCH_3), 6.98 (d, *J* = 2.2 Hz, 1 H, H-3), 7.03 (d, 1 H, *J* = 8.8 Hz, H-7), 7.57 (d, 1 H, *J* = 2.2 Hz, H-2), 7.78 (d, 1 H, *J* = 8.8 Hz, H-6), 13.18 (s, 1 H, OH).

(15) **Synthesis of 2′,3′-Dihydro[2,3′]bibenzofurans (5, 6 and 15–18) – General Procedure.**

The *ortho*-hydroxybenzofuran methyl ketone (10 mmol) was refluxed in toluene (35 mL) with Amberlyst 15 (0.22 g) at 120 °C for 6–10 h. The resulting reaction mixture was filtered and the resin was washed with an excess of toluene. The filtrate thus obtained was concentrated to dryness and a pure compound was isolated by silica gel column chromatography using 7% EtOAc in hexane (1:10) as eluent.

Compound **5**: yellow solid; mp 149–150 °C. MS (FAB): *m/z* = 353 [M^+ + 1]. IR (KBr): 1638 (CO), 3433 (OH) cm^{-1}. ^1H NMR (200 MHz $CDCl_3$): δ = 2.57 (s, 3 H, CH_3), 2.64 (s, 3 H, CH_3), 4.81–4.88 (m, 1 H, CH), 4.89–4.94 (m, 2 H, CH_2), 6.48 (d, 1 H, *J* = 8.6 Hz, ArH), 6.68 (s, 1 H, CH), 6.96 (d, 1 H, *J* = 8.8 Hz, ArH), 7.60 (d, 1 H, *J* = 8.8 Hz, ArH), 7.70 (d, 1 H, *J* = 8.6 Hz, ArH), 12.83 (s, 1 H, OH), 13.15 (s, 1 H, OH).

Compound **6**: yellow solid; mp 189–190 °C. MS (FAB): *m/z* = 353 [M^+ + 1]. IR (KBr): 1641 (CO), 3427 (OH) cm^{-1}. ^1H NMR (200 MHz $CDCl_3$): δ = 2.53 (s, 3 H, CH_3), 2.68 (s, 3 H, CH_3), 4.75–4.80 (m, 2 H, CH_2), 4.92–4.96 (m, 1 H, CH), 6.43 (s, 1 H, ArH), 6.46 (s, 1 H, CH), 6.99 (s, 1 H, ArH), 7.58 (s, 1 H, ArH), 7.91 (s, 1 H, ArH), 12.46 (s, 1 H, OH), 13.02 (s, 1 H, OH).

Compound **15**: yellow solid; mp 110–111 °C. MS (FAB): *m/z* = 353 [M^+ + 1]. IR (KBr): 1637 (CO), 3449 (OH) cm^{-1}. ^1H NMR (200 MHz $CDCl_3$): δ = 2.69 (s, 3 H, CH_3), 2.82 (s, 3 H, CH_3), 4.80–4.88 (m, 2 H, CH_2), 4.97–5.02 (m, 1 H, CH), 6.44 (s, 1 H, CH), 6.52 (d, 1 H, *J* = 8.4 Hz, ArH), 6.88 (d, 1 H, *J* = 8.6 Hz, ArH), 7.30 (d, 1 H, *J* = 8.4 Hz, ArH), 7.56 (d, 1 H, *J* = 8.6 Hz, ArH), 12.74 (s, 1 H, OH), 12.81 (s, 1 H, OH). ^{13}C NMR (200 MHz $CDCl_3$): δ = 31.6 (CH_3), 32.0 (CH_3), 41.1 (CH), 77.2 (CH_2), 103.5 (=CH), 107.3, 107.5, 110.3, 114.5, 117.2, 120.5, 128.5, 131.9, 154.2, 156.5, 161.8, 161.9, 164.0, 202.3, 203.5.

Compound **16**: yellow solid; mp 192–193 °C. MS (FAB): *m/z* = 353 [M^+ + 1]. IR (KBr): 1648 (CO), 3422 (OH) cm^{-1}. ^1H NMR (200 MHz $CDCl_3$): δ = 2.53 (s, 3 H, CH_3), 2.68 (s, 3 H, CH_3), 4.75–4.80 (m, 2 H, CH_2), 4.82–4.99 (m, 1 H, CH), 6.43 (s, 1 H, ArH), 6.46 (s, 1 H, CH), 6.99 (s, 1 H, ArH), 7.58 (s, 1 H, ArH), 7.91 (s, 1 H, ArH), 12.47 (s, 1 H, OH), 13.03 (s, 1 H, OH).

Compound **17**: yellow semi-solid. MS (FAB): *m/z* = 353 [M^+ + 1]. IR (KBr): 1645 (CO), 3437 (OH) cm^{-1}. ^1H NMR (200 MHz $CDCl_3$): δ = 2.50 (s, 3 H, CH_3), 2.57 (s, 3 H, CH_3), 4.73–4.88 (m, 3 H, CH and CH_2), 6.41 (d, 1 H, *J* = 8.6 Hz, ArH), 6.61 (s, 1 H, CH), 6.95 (d, 1 H, *J* = 8.6 Hz, ArH), 7.50–7.66 (m, 2 H, ArH), 12.76 (s, 1 H, OH), 13.08 (s, 1 H, OH).

Compound **18**: yellow solid; mp 184–185 °C. MS (FAB): *m/z* = 385 [M^+ + 1]. IR (KBr): 1678 (CO), 3426 (OH) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.91 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 4.78–4.95 (m, 3 H, CH and CH_2), 6.65 (s, 1 H, CH), 6.47 (d, 1 H, *J* = 8.6 Hz, ArH), 6.96 (d, 1 H, *J* = 8.8 Hz, ArH), 7.72 (d, 1 H, *J* = 8.8 Hz, ArH), 7.81 (d, 1 H, *J* = 8.6 Hz, ArH), 12.42 (s, 1 H, OH), 13.01 (s, 1 H, OH).