

## 4-, 5-, 6-, and 7-Hydroxybenzofuran: a unified strategy for a two-step synthesis of versatile benzofuranic building blocks

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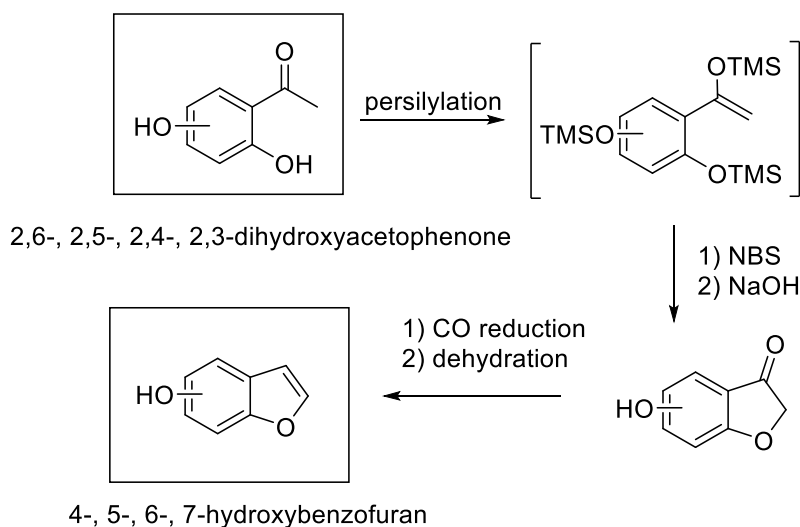
Received 05-13-2022

Accepted Manuscript 06-20-2022

Published on line 06-28-2022

### Abstract

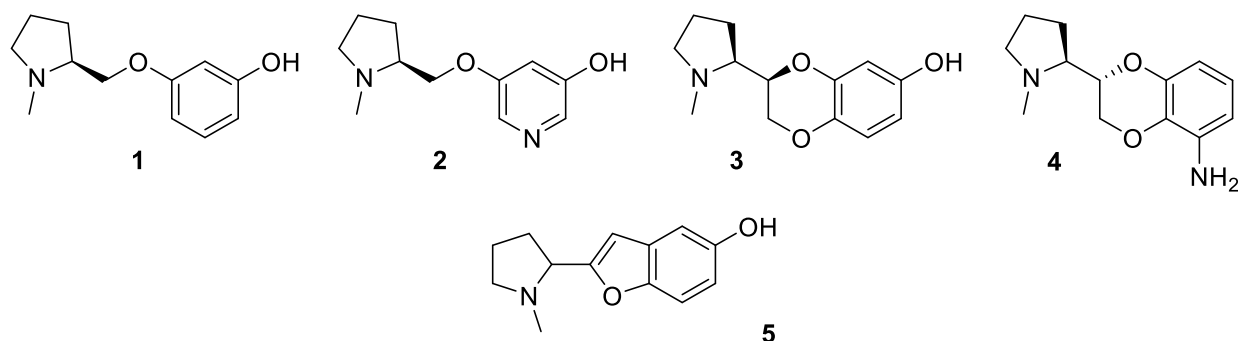
Over several decades, many different strategies have been reported to prepare 4-, 5-, 6-, and 7-hydroxybenzofuran (HBF), which are very important synthetic intermediates. Interested in addition of their 2-lithiated *O*-protected derivatives to transient 1-pyrroline as a straightforward way to nicotinoids, we have developed a unique two-step procedure to obtain 4-, 5-, 6-, and 7-HBF from 2,6-, 2,5-, 2,4- and 2,3-dihydroxyacetophenone, respectively, by conversion into 4-, 5-, 6- and 7-hydroxybenzofuranone and successive reduction of these latter with lithium borohydride. On the basis of the overall yields, the number of steps and the availability of the starting materials, such a synthetic strategy can be advantageously compared with the literature methods, here briefly reviewed, developed to synthesize the four HBFs.



**Keywords:** Hydroxybenzofuran, dihydroxyacetophenone, hydroxybenzofuranone, lithium borohydride

## Introduction

Benzofuran and benzodioxane are among the most frequently occurring scaffolds in natural and synthetic bioactive compounds.<sup>1,2</sup> We had experience with their versatility, bioisosteric interchangeability and combination in developing selective ligands of different receptors and enzymes, but particularly of the  $\alpha 4\beta 2$  nicotinic acetylcholine receptor.<sup>3-6</sup> The selective affinity and activity at this neuronal receptor subtype and its stoichiometric isoforms are strictly related to the structure of the ligand's aromatic portion, which mainly interacts with the minus side of the receptor binding site, and to its decoration with hydrophilic substituents, such as OH and NH<sub>2</sub>.<sup>6-9</sup> Examples of this are the  $\alpha 4\beta 2$  nicotinic acetylcholine receptor agonists **1-5** shown in Figure 1.<sup>6,8,10,11</sup>

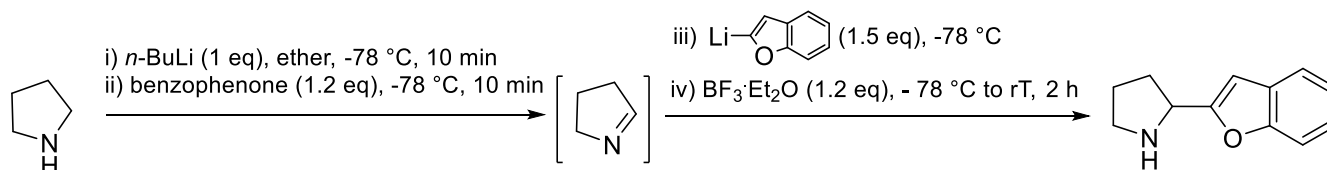
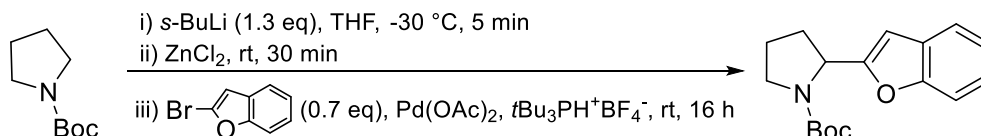


**Figure 1.** Examples of prolinol aryl ethers and pyrrolidinyl benzodioxanes acting as  $\alpha 4\beta 2$  nicotinic acetylcholine receptor agonists.

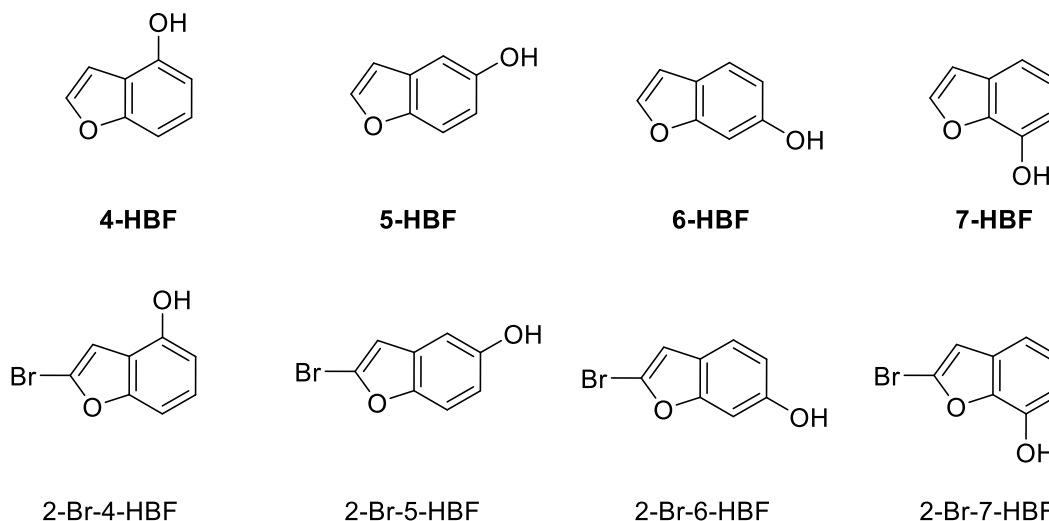
Fulfilled SAR investigation of these hits requires, among others, characterization of a number of their regioisomers. In the case of the pyrrolidinyl benzofuran **5**, this would mean availability of its 4-, 6- and 7-hydroxy isomers. The recently published addition of 2-benzofuranyllithium to the cyclic imine generated in situ from *N*-lithiated pyrrolidine<sup>12</sup> suggests a straightforward way to these positional isomers and to series of regioisomers with other substituents in alternative to Negishi coupling, which would instead require pyrrolidine *N*-Boc protection, on one side, and bromine substituent at benzofuran C(2) on the other<sup>13</sup> (Figure 2).

Feasibility and advantages of such an approach are obviously conditioned by the ready accessibility of the four hydroxybenzofurans (HBFs), namely 4-hydroxy-, 5-hydroxy-, 6-hydroxy-, and 7-hydroxy benzofuran (**4-**, **5-**, **6-**, and **7-HBF** respectively) and, consequently, of their properly *O*-protected derivatives, compared to that of the corresponding 2-bromo analogues (Figure 3). To our knowledge, the literature reports only the preparation of 2-bromo-6-HBF from 2,4-dihydroxybenzaldehyde, CBr<sub>4</sub> and PPh<sub>3</sub>,<sup>14</sup> and, in our experience, the procedure can be reproduced for 2-bromo-5-HBF from 2,5-dihydroxybenzaldehyde,<sup>6</sup> but it is very problematic for 2-bromo-7-HBF from 2,3-dihydroxybenzaldehyde due to low yield. On the other hand, high-cost 2,6-dihydroxybenzaldehyde discourages any attempt to convert it into 2-bromo-4-HBF.

## Addition of 2-benzofuranylithium to transient 1-pyrroline

Lithiation-Transmetalation-Negishi coupling of *N*-Boc pyrrolidine

**Figure 2.** Comparison between the reported addition of 2-benzofuranylithium to transient 1-pyrroline (ref. 12) and the potential application of the protocol of lithiation-transmetalation-Negishi coupling of *N*-Boc pyrrolidine (ref.13) to 2-bromobenzofuran.



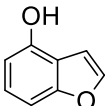
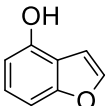
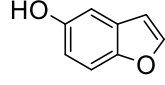
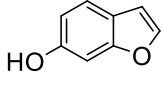
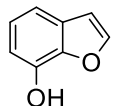
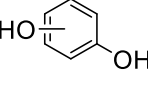
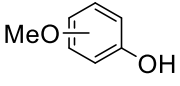
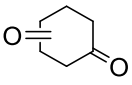
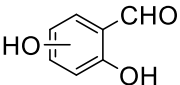
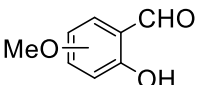
**Figure 3.** The four regioisomeric hydroxybenzofurans and their 2-bromo analogues. The literature reports only the preparation of 2-Br-5-HBF and 2-Br-6-HBF from 2,5- and 2,4-dihydroxybenzaldehyde respectively (refs. 14 and 6).

Many methods have been developed to synthesize the four positional isomers of benzofuran hydroxylated at the benzene ring. Almost all of them use a properly mono- or disubstituted phenol as a starting material and their key step is the cyclization to give the benzo-condensed five-membered heterocycle. The reverse strategy, namely the formation of the furo-condensed six-membered cycle, is rare. An example is the Diels-Alder reaction of 2-nitrofurane with Danishefsky's diene to give **5-HBF**.<sup>15</sup>

The literature syntheses based on the formation of the five-membered heterocycle are classified in Table 1 according to the two starting synthons, that are a six-membered cyclic compound and a functionalized 1-3 carbons unit. The starting cyclic compound can be a diphenol, a methoxyphenol, 1,4-benzoquinone, hydroquinone or cyclohexanedione, in which a two-carbon unit must be inserted to obtain the oxygenated heterocycle,<sup>16-24</sup> or, alternatively, a hydroxy- or methoxy-substituted salicylaldehyde, which needs the

insertion of only one carbon instead.<sup>25-28</sup> Almost all the syntheses require at least three steps. The overall yields are all lower than 55%, except that of **6-HBF** from 4-methoxysalicylaldehyde (73%), which is claimed in a paper dedicated to the improvement of **6-HBF** synthesis.<sup>27</sup> The simpler two-step procedures, reported for **4-HBF** and **7-HBF**, are not significantly ameliorative in spite of one less step.<sup>25,28</sup> The least accessible HBF seems to be **7-HBF** and the most critical reactions are generally aromatization and decarboxylation.

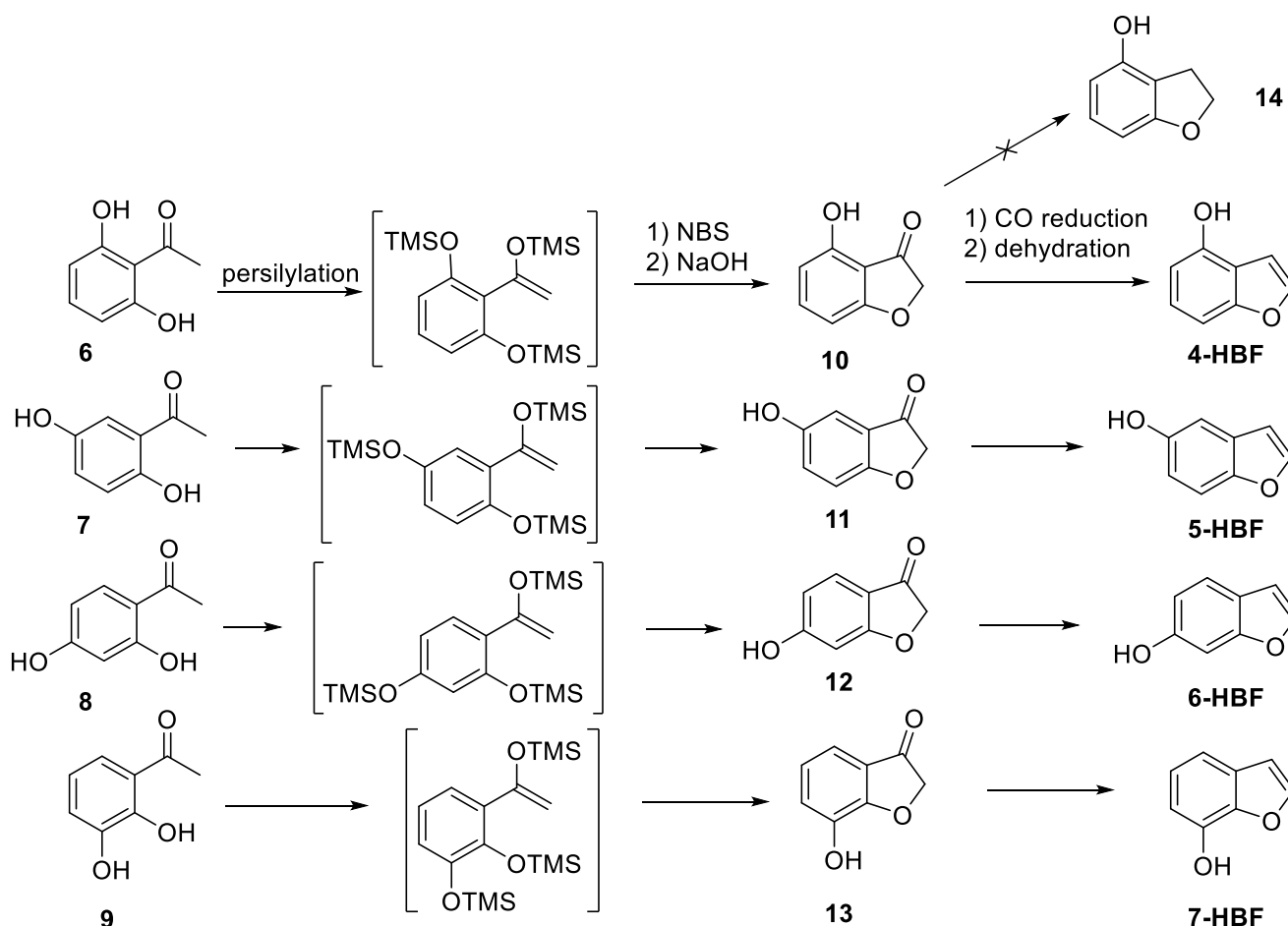
**Table 1.** Synthetic strategies reported in the literature for the synthesis of HBFs: synthons, number of steps and yields

Starting cyclic compound	Products			
	4-HBF	5-HBF	6-HBF	7-HBF
				
		1,4-benzoquinone CH <sub>3</sub> CHO, 3 steps; 54%*; ref.16	resorcinol ClCH <sub>2</sub> CN, 3 steps; 51%; ref. 17,18	
		4-methoxyphenol BrCH <sub>2</sub> CH(OEt) <sub>2</sub> 3-4 steps; 10-35%** ref. 19-21	3-methoxyphenol BrCH <sub>2</sub> CH(OEt) <sub>2</sub> 3 steps; 10% ref. 20, 22	2-methoxyphenol BrCH <sub>2</sub> CH(OEt) <sub>2</sub> 3 steps; 10% ref. 20
	1,3-cyclohexanedione BrCH <sub>2</sub> COCOOH or BrCH <sub>2</sub> CH(OEt) <sub>2</sub> 3 steps; ~50% ref. 23,24			
	6-hydroxysalicylaldehyde BrCH <sub>2</sub> COOEt, 2 steps; 44%; ref. 25		4-hydroxysalicylaldehyde CH <sub>3</sub> NO <sub>2</sub> , 3 steps; 57%; ref. 26	
			4-methoxysalicylaldehyde ClCH <sub>2</sub> COOH; 3 steps; 73%; ref. 27	3-methoxysalicylaldehyde ClCH <sub>2</sub> COOEt; 2 steps; 20%; ref. 28

\*Overall yield reported for the last two steps of the synthesis of 3-methyl-5-HBF starting from propionaldehyde. \*\*The synthesis was also accomplished starting from 4-benzyloxyphenol, obtained from hydroquinone, by four steps and 35% yield (ref. 21).

## Results and Discussion

In search of a more efficient method applicable to the synthesis of all four HBFs, our attention was drawn to a one-pot conversion of 2,6-dihydroxyacetophenone (**6**) into 4-hydroxybenzofuran-3-one (**10**), claimed as highly efficient (>90% yield), by persilylation in THF, followed by treatment with *N*-bromosuccinimide and then with NaOH (Scheme 1).<sup>29,30</sup> Such a transformation, abandoned by the authors because of the unsuccessful successive reduction to desired 4-hydroxydihydrobenzofuran (**14**) (Scheme 1), could be also applied to the three regioisomers of 2,6-dihydroxyacetophenone bearing only one of the two hydroxyls *ortho* positioned, namely **7**, **8**, and **9**, so obtaining all the four positional isomers of hydroxybenzofuran-3-one (**10-13**) and, after carbonyl reduction and dehydration, the desired four HBFs. The planned strategy is shown in Scheme 1.



**Scheme 1.** Planned syntheses of the four regioisomeric hydroxybenzofurans from four positional isomers of dihydroxyacetophenone.

Uncertainties were connected to the one-pot obtainment of the intermediate 5-, 6- and 7-hydroxybenzofuranones (**11-13**) from the starting dihydroxyacetophenones **7-9** according to the new procedure, but above all to the efficiency of the subsequent reduction of the hydroxybenzofuranones to the corresponding HBFs.

With regard to the first step, the experimental details of the one-pot conversion of **6** into **10** are reported only in patents<sup>31-34</sup> and with yields much lower (~ 50%) than those mentioned above (>90%). Under less

severe conditions of temperature (0 °C instead of – 78 °C) and in shorter time than those reported in patents, we transformed **6** into **10** with 97% yield after chromatographic purification, thus confirming the high efficiency of the literature undetailed experimental procedures.<sup>29,30,35</sup> Analogous results (86% yield) were obtained applying the same procedure to convert **8** into **12**. It is to be noted that the conversion of unprotected **8** into the corresponding  $\alpha$ -bromoacetophenone and the subsequent cyclization to **12** have been reported in 21% overall yield.<sup>36</sup> Otherwise, the one-pot conversion of the dihydroxyacetophenones bearing the hydroxyls reciprocally *para* and *ortho* positioned, namely **7** and **9**, to **11** and **13**, respectively, was not so efficient likely because accompanied by oxidation reactions. The dihydroxyacetophenone **7** was persilylated, brominated and desilylated and the crude  $\alpha$ -bromoacetophenone was cyclized by treatment with sodium methoxide in methanol under nitrogen to give **11**, which was isolated as a crude by aqueous HCl/ethyl acetate extraction but not purified by chromatography. The dihydroxyacetophenone **9** was converted into the corresponding  $\alpha$ -bromoacetophenone and, without isolation, cyclized to **13** by adding NaOH to the reaction mixture and then extracted, after acidification with HCl, into ethyl acetate and used as a crude in the successive reductive dehydration.

In the literature, this second step has been investigated only for **10** and **12**. The authors, who reported the conversion of **6** into **10**, observed that **10** is converted to a mixture of **4-HBF** and of the undehydrated intermediate 2,3-dihydrobenzo[*b*]furan-3,4-diol by NaBH<sub>4</sub>.<sup>29</sup> Difficulties in univocal reductive dehydration to **6-HBF** without overreduction to 2,3-dihydrobenzo[*b*]furan-6-ol were reported for **12** by other researchers.<sup>18</sup> These screened a variety of reagents in THF, such as LiAlH<sub>4</sub>, DIBAL, BH<sub>3</sub>·THF, Red-Al, NaBH<sub>4</sub> and LiBH<sub>4</sub>, concluding that LiBH<sub>4</sub> followed by HCl/H<sub>2</sub>O quench was the best option giving minimum overreduction by-product and the highest yield of **6-HBF** (68%). We decided to use these conditions to reduce the four hydroxybenzofuranones. Pure **10** and **12** were converted into **4-HBF** and **6-HBF** with 76% and 60% yield respectively. Therefore, the overall yields from dihydroxyacetophenones **6** and **8** to the corresponding HBFs were 74% and 52% respectively. Crude **11** and **13** were reduced to **5-HBF** and **7-HBF** with final yields, calculated on the starting acetophenones **7** and **9**, of 61% and 45% respectively.

## Conclusions

In summary, a two-step procedure has been developed to obtain the four regioisomeric benzofurans hydroxylated at benzene ring from the four regioisomeric dihydroxyacetophenones bearing one of the two hydroxyls *ortho* positioned. The unitary approach is based on the conversion of dihydroxyacetophenones into hydroxybenzofuranones followed by the reduction to hydroxybenzofurans. Such a strategy was allowed by the successful application to all four substrates of the procedure reported for the one-pot conversion of 2,6-dihydroxyacetophenone to 4-hydroxybenzofuran-3-one and then, as the second step, of the reported reduction of 6-hydroxybenzofuran-3-one to **6-HBF** with LiBH<sub>4</sub>. Given the availability of the four starting ketones, the only two steps and the overall yields, the four procedures can be advantageously compared with the literature methods, here briefly reviewed, developed to prepare these important synthetic intermediates.

## Experimental Section

**General.** All chemicals and solvents were used as received from commercial sources or prepared as described in the literature. Flash chromatography purifications were performed using Biotage® Isolera® flash purification

system using KP-Sil 32-63  $\mu\text{m}$  60 Å cartridges and Merck Silica Gel 60 (0.040-0.063  $\mu\text{m}$ ). TLC analyses were performed using 0.25mm silica gel plates on aluminium foil, containing a fluorescent indicator (Macherey-Nagel Alugram® SilG/UV 254). The spots were visualized under UV light ( $\lambda$  254nm). The staining of TLC plates was performed with potassium permanganate; *R<sub>f</sub>* values are given for guidance.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at 300 and 75 MHz using Varian Mercury 300 spectrometer. Chemical shifts are reported in ppm relative to residual solvent ( $\text{CHCl}_3$  and MeOH) as internal standard. HRMS spectra were acquired by using the orbitrap analyzer of a LTQ Orbitrap XL instrument. Sample was introduced by flow injection directly into the APCI interface (Finnigan IonMax). Sample flow ( $10 \mu\text{L min}^{-1}$ ) was mixed with  $300 \mu\text{L min}^{-1}$  of water containing 0.1% HCOOH and nebulized by using 50 units of nitrogen (20 units of sheath gas, 30 units of auxiliary gas) at 400 °C. Ionization was achieved by 5  $\mu\text{A}$  of corona discharge. Resolution was set at 100000 (FWHM at 400 *m/z*) and scan range was 100-500 *m/z*. Melting points were determined by Büchi Melting Point B-540 apparatus.

**General procedure for the synthesis of compounds 10, 11, 12, and 13.** LiHMDS (21.7 mL of 1 M solution in THF) was added dropwise to a stirred solution of proper dihydroxyacetophenone (1000 mg, 6.57 mmol) in anhydrous THF (10 mL) at 0 °C under  $\text{N}_2$ . TMSCl (2.8 mL, 21.7 mmol) was then added dropwise. The resulting solution was stirred at 0 °C for 15 min. NBS (1.29 g, 7.23 mmol) was added and the resulting mixture was stirred at rt for 3 hours. For preparation of **10**, **12** and **13**, 1 M NaOH (20 mL) was added and the reaction mixture was stirred at rt for 15 min. 1 M HCl (30 mL) was added and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to give the crude product, which was purified by chromatography on silica gel (**10** and **12**) or directly used in the successive reduction step (**13**). In the case of **11**, isolated as a crude and, analogously to **13**, directly submitted to the successive reduction, a different procedure was followed after the 3 hours reaction with NBS.

**4-Hydroxybenzofuran-3(2H)-one (10).** Obtained from 2,6-dihydroxyacetophenone as a pale-yellow solid in 97% yield after flash column chromatography on silica gel (petroleum ether/EtOAc, 8:2); mp 116 – 118 °C; *R<sub>f</sub>* (cyclohexane/EtOAc 8:2) 0.4;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.75 (bs, 1H, exchange with  $\text{D}_2\text{O}$ ), 7.49 (t, *J* 8.2 Hz, 1H), 6.60 (dd, *J* 8.2, 4.4 Hz, 1H), 6.49 (d, *J* 8.2 Hz, 1H), 4.65 (s, 2H);<sup>37</sup>  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  200.91, 172.94, 156.28, 140.49, 109.30, 107.98, 104.11, 74.48. HRMS (APCI) Molecular formula:  $\text{C}_8\text{H}_6\text{O}_3$ ; Experimental signal of  $[\text{M}+\text{H}]^+$  species: 151.03871; Experimental error: -1.7 ppm.

**6-hydroxybenzofuran-3(2H)-one (12).** Obtained from 2,4-dihydroxyacetophenone as a yellow solid in 86% yield after flash column chromatography on silica gel (petroleum ether/EtOAc, 8:2); mp 235 – 237 °C (lit.<sup>38</sup>: 243 – 246 °C); *R<sub>f</sub>* (cyclohexane/EtOAc 7:3) 0.29;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.48 (d, *J* 8.5 Hz, 1H), 6.57 (dd, *J* 8.5, 2.0 Hz, 1H), 6.46 (d, *J* 2.0 Hz, 1H), 4.63 (s, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  198.65, 176.88, 167.55, 124.82, 112.82, 111.73, 97.92, 75.24.<sup>39</sup>

**7-hydroxybenzofuran-3(2H)-one (13).** Obtained from 2,3-dihydroxyacetophenone as a crude product and used in the successive reaction without purification; *R<sub>f</sub>* (cyclohexane/EtOAc 7:3) 0.21.

**5-hydroxybenzofuran-3(2H)-one (11).** LiHMDS (21.7 mL of 1 M solution in THF) was added dropwise to a stirred solution of 2,5-dihydroxyacetophenone (1000 mg, 6.57 mmol) in anhydrous THF (10 mL) at 0 °C under  $\text{N}_2$ . TMSCl (2.8 mL, 21.7 mmol) was then added dropwise. The resulting solution was stirred at 0 °C for 15 min. NBS (1.29 g, 7.23 mmol) was added and the resulting mixture was stirred at rt for 3 hours. 1 M HCl (30 mL) was added, and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure. The crude was dissolved in MeOH (15 mL) and MeONa (391 mg, 7.23 mmol) was added under  $\text{N}_2$ . The reaction mixture was stirred at rt for 1 hour. Then, 1 M HCl (30 mL) was added, and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic

layers were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to give the crude product, which was used in the successive reaction without purification; *Rf* (cyclohexane/EtOAc 8:2) 0.23.

**General procedure for the synthesis of compounds 4-HBF, 5-HBF, 6-HBF, and 7-HBF.**  $\text{LiBH}_4$  was added to a solution of hydroxybenzofuran-3(2H)-one in anhydrous THF (20 mL) at 0 °C. For purified **10** and **12** (1000 mg, 6.66 mmol), 3.7 mL of 2 M solution of  $\text{LiBH}_4$  were used, while crude **11** and **13**, respectively resulting from the previous reaction on 1000 mg of 2,5- and 2,3-dihydroxyacetophenone, were treated with 7.3 mL of 2 M solution of  $\text{LiBH}_4$  in THF. The resulting solution was stirred at 0 °C for 15 min and at rt for 16 h. Then, ice water (10 mL) was slowly added, followed by HCl 1 M (10 mL). The resulting mixture was extracted with EtOAc (3 × 15 mL) and the combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure to give the crude product, which was purified by flash chromatography on silica gel eluting with 8:2 petroleum ether/EtOAc.

**4-Hydroxybenzofuran (4-HBF).** Obtained from **10** as a white solid in 76% yield using 7.4 mmol of  $\text{LiBH}_4$  (3.7 mL of 2 M solution in THF) after flash column chromatography on silica gel (petroleum ether/EtOAc, 8:2); mp 55.1 – 56.3 °C (lit. <sup>40</sup>: 56 – 58 °C); *Rf* (cyclohexane/EtOAc 8:2) 0.33; <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.55 (d, *J* 2.3 Hz, 1H), 7.15 – 7.12 (m, 2H), 6.85 (d, *J* 2.3 Hz, 1H), 6.63 (dd, *J* 6.2, 2.3 Hz, 1H), 5.12 (bs, 1H, exchange with  $\text{D}_2\text{O}$ ); <sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  156.83, 149.30, 143.68, 125.01, 116.68, 107.70, 104.49, 103.19. <sup>41</sup> Molecular formula:  $\text{C}_8\text{H}_6\text{O}_2$ ; Experimental signal of  $[\text{M}+\text{H}]^+$  species: 135.04388; Experimental error: -1.3 ppm.

**5-Hydroxybenzofuran (5-HBF).** Obtained from crude **11** as a pink solid in 61% yield (overall yield calculated on 1000 mg of starting 2,5-dihydroxyacetophenone) using 14.6 mmol of  $\text{LiBH}_4$  (7.3 mL of 2 M solution in THF) after flash column chromatography on silica gel (petroleum ether/EtOAc, 8:2); mp 56.2 – 57.1 °C (lit. <sup>42</sup>: 58 – 59 °C); *Rf* (cyclohexane/EtOAc 8:2) 0.30; <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.59 (d, *J* 2.0 Hz, 1H), 7.36 (d, *J* 8.8 Hz, 1H), 7.03 (d, *J* 2.6 Hz, 1H), 6.83 (dd, *J* 8.8, 2.6 Hz, 1H), 6.66 (d, *J* 2.0 Hz, 1H), 4.93 (bs, 1H, exchange with  $\text{D}_2\text{O}$ ); <sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  151.33, 150.06, 145.99, 128.29, 112.96, 111.79, 106.46, 106.17. <sup>42</sup>

**6-Hydroxybenzofuran (6-HBF).** Obtained as a white solid from **12** in 65% yield using 7.4 mmol of  $\text{LiBH}_4$  (3.7 mL of 2 M solution in THF) after flash column chromatography on silica gel (petroleum ether/EtOAc, 8:2); mp 53.5 – 54.1 °C (lit. <sup>42</sup> 54 – 55 °C); *Rf* (cyclohexane/EtOAc 8:2) 0.44; <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.53 (dd, *J* 4.4, 2.3 Hz, 1H), 7.42 (d, *J* 8.4 Hz, 1H), 6.99 (d, *J* 2.0 Hz, 1H), 6.79 (dd, *J* 8.4, 2.3 Hz, 1H), 6.69 (d, *J* 2.0 Hz, 1H), 4.90 (s, 1H, exchange with  $\text{D}_2\text{O}$ ); <sup>43</sup> <sup>13</sup>C NMR (75 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  155.14, 143.43, 120.68, 119.86, 111.63, 108.72, 105.85, 97.20. HRMS (APCI) Molecular formula:  $\text{C}_8\text{H}_6\text{O}_2$ ; Experimental signal of  $[\text{M}+\text{H}]^+$  species: 135.04390; Experimental error: -1.2 ppm.

**7-Hydroxybenzofuran (7-HBF).** Obtained from crude **13** as a light yellow oil in 45% yield (overall yield calculated on 1000 mg of starting 2,3-dihydroxyacetophenone) using 14.6 mmol of  $\text{LiBH}_4$  (7.3 mL of 2 M solution in THF) after flash column chromatography on silica gel (petroleum ether/EtOAc, 8:2); *Rf* (cyclohexane/EtOAc 8:2) 0.36; <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.61 (d, *J* 2.3 Hz, 1H), 7.20 – 7.07 (m, 2H), 6.84 (dd, *J* 7.6, 1.2 Hz, 1H), 6.78 (d, *J* 2.0 Hz, 1H), 5.33 (bs, 1H, exchange with  $\text{D}_2\text{O}$ ); <sup>44</sup> <sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  144.84, 143.31, 140.99, 129.05, 123.72, 113.40, 110.40, 107.27. <sup>45</sup>

## Acknowledgements

We gratefully acknowledge financial support from Università degli Studi of Milano. We are grateful to prof. Luca Regazzoni for HRMS analyses.



## Supplementary Material

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of compounds **10,12**, **4-HBF**, **5-HBF**, **6-HBF**, and **7-HBF**.

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