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# Combination of enzyme- and Lewis acid-catalyzed reactions: a new method for the synthesis of 6,7-dihydrobenzofuran-4(5*H*)-ones starting from 2,5-dimethylfuran and 1,3-cyclohexanediones†

Chimène Asta,[a] Dietmar Schmidt,[a] Jürgen Conrad,[a] Wolfgang Frey[b] and Uwe Beifuss*[a]

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The Lewis acid-catalyzed domino 1,2-addition/1,4-addition/elimination between (*Z*)-3-hexene-2,5-dione and 1,3-dicarbonyls delivers 3-methyl-6,7-dihydrobenzofuran-4(5*H*)-ones exclusively with yields up to 82%. The combination of this new process with the laccase-catalyzed formation of (*Z*)-3-hexene-2,5-dione by oxidative cleavage of 2,5-dimethylfuran allows for the synthesis of 6,7-dihydrobenzofuran-4-(5*H*)-ones starting directly from 2,5-dimethylfuran.

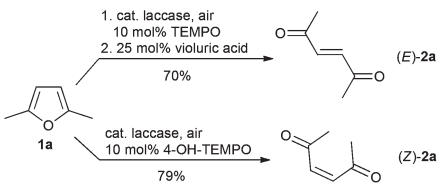


## Introduction

One-pot multistep reactions are a powerful tool in organic synthesis.[1] They contribute to the further development of sustainable synthetic methods because the required workup and purification steps, the use of solvents and the production of waste can be reduced to a minimum.[2] The combination of different chemical transformations in one-pot reactions has been known for a very long time and, accordingly, a multitude of examples exist in the literature. Classic examples of this type are the Hantzsch dihydropyridine synthesis, the Strecker reaction, the Biginelli reaction and the Ugi reaction.[1] There also exist a great number of examples of the combination of enzymatic transformations.[3] On the other hand, the number of chemoenzymatic one-pot multistep reactions is only modest.[3,4] However, interest in the combination of enzyme-catalyzed and chemically catalyzed transformations has greatly increased over the last few years. Apart from dynamic kinetic resolutions, combining a lipase-catalyzed resolution and a metal-catalyzed racemization,[5,6] the focus is on the combination of oxidoreductases with organocatalysts[7] and metal-based catalysts.[8] As part of a synthetic program devoted to the development of combinations of enzyme-catalyzed oxidations with chemical reactions we have developed a number of processes implementing the laccase-catalyzed generation of quinoid systems in chemoenzymatic processes.[9]

Furans and annulated furans are heterocyclic skeletons which occur in numerous natural products and exhibit extraordinary biological activities.[10] The 6,7-dihydrobenzofuran-4-(5*H*)-one skeleton and derivatives thereof are not only present in a number of natural products,[11] but also play a role as intermediates in the synthesis of biologically active compounds.[12] Despite considerable efforts towards their synthesis, there still is a strong demand for more efficient synthetic approaches.[13]

2,5-Dimethylfuran (**1a**) is a platform chemical which can be obtained from renewable raw materials and is considered as a serious candidate to become a substitute for fossil fuels.[14,15] The downstream chemistry of 2,5-dimethylfuran (**1a**), however, remains largely unexplored.[16] Recently, we have reported that the laccase-catalyzed ring opening of 2,5-dimethylfuran (**1a**) using air as an oxidant stereoselectively yields (*Z*)- or (*E*)-3-hexene-2,5-dione (**2a**) depending on the mediator employed (Scheme 1).[17] The combination of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and violuric acid gives (*E*)-3-hexene-2,5-dione (*E*)-(**2a**), while in the presence of 4-hydroxy-TEMPO,




**Scheme 1** Laccase-catalyzed ring opening of 2,5-dimethylfuran (**1a**).

[a]*Bioorganische Chemie, Institut für Chemie, Universität Hohenheim, Garbenstraße 30, D-70599 Stuttgart, Germany. E-mail: ubeifuss@uni-hohenheim.de; Fax: (+49)711-459-22951*

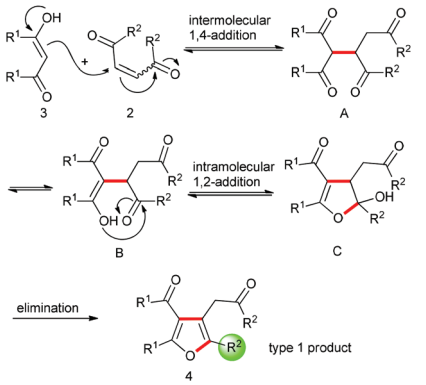
[b]*Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany*

†Electronic supplementary information (ESI) available: $^{1}H$ and $^{13}C$ NMR spectra for compounds **5a–h**. CCDC 926712 (**5b**) 926713 (**5d**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob40926k

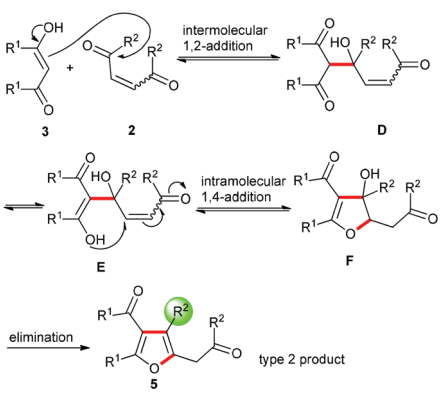
(*Z*)-3-hexene-2,5-dione (*Z*)-(**2a**) is obtained in 79% yield. The selective formation of the less stable (*Z*)-3-hexene-2,5-dione (*Z*)-(**2a**) with 4-hydroxy-TEMPO as the mediator is highly significant, as the number of methods for the synthesis of (*Z*)-2-ene-1,4-diones (*Z*)-**2** is rather limited.[18] The (*Z*)-selective ring cleavage could be extended to a variety of symmetrical and unsymmetrical 2,5-dialkylfurans **1**.[17] With the new method for the preparation of (*Z*)-2-ene-1,4-diones in mind, it was attractive to combine it with suitable chemical transformations.

Considering the reaction between 2-ene-1,4-diones **2** and 1,3-dicarbonyls **3** it was assumed that either a domino intermolecular 1,4-addition/intramolecular 1,2-addition/elimination (*via* **A**, **B** and **C**) with formation of furans **4** (type 1 product) (Scheme 2) or a domino intermolecular 1,2-addition/intramolecular 1,4-addition/elimination (*via* **D**, **E** and **F**) with formation of furans **5** (type 2 product) (Scheme 3) could occur.

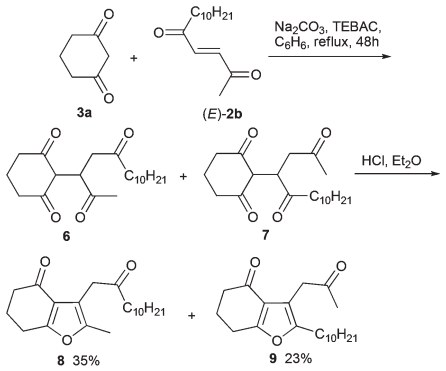
So far, there has been only a single report from Scettri *et al.*, who studied a few reactions of (*E*)-2-ene-1,4-diones **2** with 1,3-dicarbonyls **3** (Scheme 4).[19] They found that the two-step procedure between (*E*)-pentadec-3-ene-2,5-dione (*E*)-(**2b**) and 1,3-cyclohexanedione (**3a**) using triethylbenzyl ammonium chloride (TEBAC) delivered a mixture of the 2-methyl-substituted 6,7-dihydrobenzofuran-4(5*H*)-one **8** and the 2-decyl-substituted 6,7-dihydrobenzofuran-4(5*H*)-one **9** (type 1 products). It is supposed that the transformation starts with an intermolecular 1,4-addition under basic conditions, which is followed by an intramolecular 1,2-addition and elimination under acidic conditions.




**Scheme 2** Formation of type 1 products by domino intermolecular 1,4-addition/intramolecular 1,2-addition/elimination.




**Scheme 3** Formation of type 2 products by domino intermolecular 1,2-addition/intramolecular 1,4-addition/elimination.

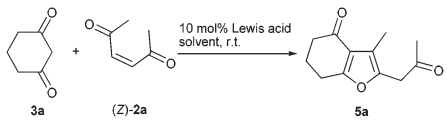



**Scheme 4** Reaction of (*E*)-2-ene-1,4-dione (*E*)-(**2b**) with 1,3-cyclohexanedione (**3a**) according to Scettri *et al.*[19]

## Results and discussion

The reaction between (*Z*)-3-hexene-2,5-dione (*Z*)-(**2a**) and 1,3-cyclohexanedione (**3a**) was chosen as a model reaction. 1 equiv. (*Z*)-**2a** and 3 equiv. 1,3-cyclohexanedione (**3a**) were reacted in the presence of 10 mol% of different Lewis acids[20] in $CH_2Cl_2$ at r.t. (Table 1, entries 1–12). With 10 mol%

**Table 1** Regioselective synthesis of **5a** by reaction of **3a** with (*Z*)-**2a** in the presence of different Lewis acids[a]




| Entry | Lewis acid | Solvent | *t* (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $InBr_3$ | $CH_2Cl_2$ | 24 | 73 |
| 2 | $ZnBr_2$ | $CH_2Cl_2$ | 24 | 71 |
| 3 | $MgBr_2$ | $CH_2Cl_2$ | 24 | 29[c] |
| 4 | $Mg(ClO_4)_2$ | $CH_2Cl_2$ | 48 | 65 |
| 5 | $LiClO_4$ | $CH_2Cl_2$ | 24 | 66 |
| 6 | $FeCl_3$ | $CH_2Cl_2$ | 24 | 41[c] |
| 7 | $BF_3{\cdot}OEt_2$ | $CH_2Cl_2$ | 24 | 10[c] |
| 8 | $TiCl_4$ | $CH_2Cl_2$ | 24 | 9[c] |
| 9 | $Yb(OTf)_3$ | $CH_2Cl_2$ | 48 | 67 |
| 10 | $Sc(OTf)_3$ | $CH_2Cl_2$ | 48 | 68 |
| 11 | $Gd(OTf)_3$ | $CH_2Cl_2$ | 48 | 74 |
| 12 | $Cu(OTf)_2$ | $CH_2Cl_2$ | 48 | 56 |
| 13 | $Gd(OTf)_3$ | $H_2O$ | 48 | 24 |
| 14 | $Gd(OTf)_3$ | 0.01 M acetate buffer (pH 4.5) | 48 | 49 |
| 15 | $Gd(OTf)_3$ | $CH_3CN$ | 6 | 13[c] |
| 16 | $Gd(OTf)_3$ | THF | 24 | 34[c] |
| 17 | $Gd(OTf)_3$ | EtOH | 42 | Traces |

[a] 1 mmol (*Z*)-**2a** was reacted with 3 mmol **3a**. [b] Yields refer to isolated yields. [c] Along with (*E*)-**2a** as major product.

$Gd(OTf)_3$ as the catalyst, 3-methyl-2-(2-oxopropyl)-6,7-dihydrobenzofuran-4(5*H*)-one (**5a**) was isolated in 74% yield (Table 1, entry 11). It is interesting to note that the type 2 product **5a** was formed exclusively. Not even a trace of the corresponding regioisomer **4a** could be isolated. This result implies that the transformation proceeds as a domino intermolecular 1,2-addition/intramolecular 1,4-addition/elimination. Similar results, *i.e.* the exclusive formation of **5a**, were obtained with 10 mol% $InBr_3$, $ZnBr_2$, $Mg(ClO_4)_2$, $LiClO_4$, $Yb(OTf)_3$, $Sc(OTf)_3$ and $Cu(OTf)_2$ (Table 1). But with all these Lewis acids the yields of **5a** were slightly lower than with $Gd(OTf)_3$. The transformation could also be catalyzed with $MgBr_2$, $FeCl_3$, $BF_3{\cdot}OEt_2$ and $TiCl_4$. However, with these catalysts the yields of **5a** did not exceed 41% (Table 1, entries 3 and 6–8) and the formation of **5a** was accompanied by the isomerization of (*Z*)-**2a** to (*E*)-**2a**. In addition to $CH_2Cl_2$, the $Gd(OTf)_3$-catalyzed transformation was also run in a number of other solvents, including $H_2O$, 0.01 M acetate buffer pH 4.5, $CH_3CN$, THF and EtOH. However, the yields of **5a** were considerably lower than in $CH_2Cl_2$ (Table 1, entries 13–17).

To study the scope of the new transformation, (*Z*)-3-hexene-2,5-dione (*Z*)-(**2a**) was reacted with different 1,3-dicarbonyls **3** (Fig. 1) in the presence of 10 mol% $Gd(OTf)_3$. The transformations with the substituted 1,3-cyclohexanediones **3b–f** delivered the 6,7-dihydrobenzofuran-4(5*H*)-ones **5b–f** with yields ranging between 51 and 82% (Scheme 5). The new domino 1,2-addition/1,4-addition/elimination is not restricted to 1,3-cyclohexanediones as substrates. This is substantiated by the reaction of (*Z*)-**2a** with 2,4-pentanedione (**3g**) which affords the tetrasubstituted furan **5g** in 60% yield.

It is noteworthy to mention the outcome of a control experiment with (*E*)-3-hexene-2,5-dione (*E*)-(**2a**). When (*E*)-**2a** was reacted with **3a** in the presence of 10 mol% $Gd(OTf)_3$ in $CH_2Cl_2$ at r.t. for 48 h, only 9% of 3-methyl-2-(2-oxopropyl)-6,7-dihydrobenzofuran-4(5*H*)-one (**5a**) along with 52% of the substrate (*E*)-3-hexene-2,5-dione (*E*)-(**2a**) were isolated (Scheme 6). This clearly demonstrates the influence of the double bond geometry of the enedione on the outcome of the domino reaction.

The successful development of the new domino process for the synthesis of 6,7-dihydrobenzofuran-4(5*H*)-ones starting from (*Z*)-**2a** and 1,3-dicarbonyls **3** prompted us to consider whether it is possible to combine it with the laccase-catalyzed generation of (*Z*)-3-hexene-2,5-dione (*Z*)-(**2a**). This would allow

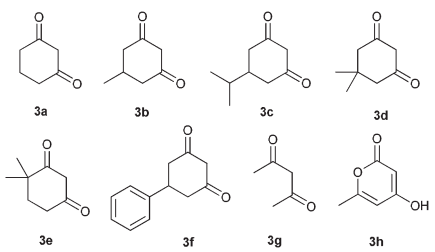
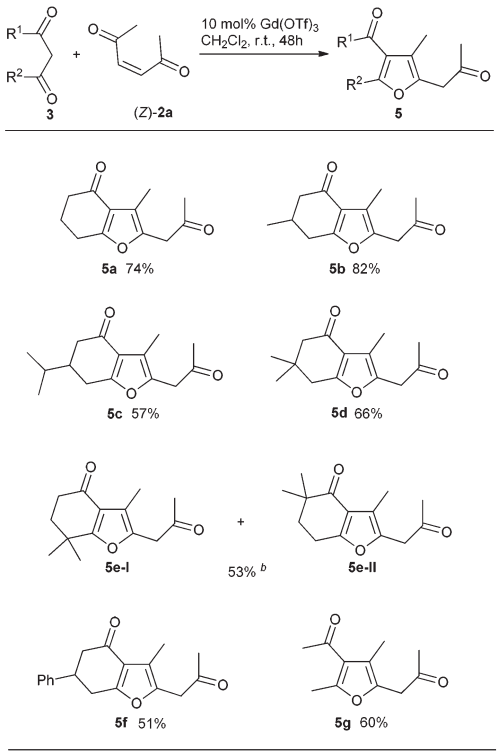
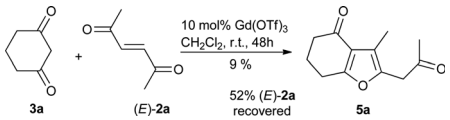



**Fig. 1** 1,3-Dicarbonyls **3** for the $Gd(OTf)_3$-catalyzed reaction with (*Z*)-3-hexene-2,5-dione (*Z*)-**2a**.




[a] 1 mmol of (*Z*)-**2a** was reacted with 3 mmol of **3**.
[b] **5e** was obtained as a 61:39-mixture of regioisomers.
[c] Yields refer to isolated yields after column chromatography.

**Scheme 5** $Gd(OTf)_3$-catalyzed reaction of (*Z*)-3-hexene-2,5-dione (*Z*)-**2a** with 1,3-dicarbonyls **3**.[a,c]

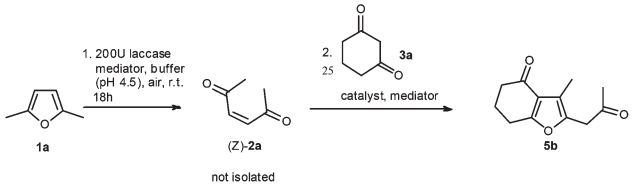



**Scheme 6** $Gd(OTf)_3$-catalyzed reaction of (*E*)-3-hexene-2,5-dione (*E*)-(**2a**) with **3a**.

for the preparation of 6,7-dihydrobenzofuran-4(5*H*)-ones and related compounds starting from 2,5-dimethylfuran (**1**) and 1,3-dicarbonyls **3** in a single synthetic step. Initial experiments revealed that the reaction did not proceed as expected when 1 equiv. 2,5-dimethylfuran (**1a**) and 3 equiv. 1,3-cyclohexanedione (**3a**) were reacted in the presence of 200 U laccase (*Trametes versicolor*), 10 mol% TEMPO and 10 mol% $Gd(OTf)_3$ in acetate buffer (0.1 M) at r.t. for 72 h. Under these conditions only traces of **5a** were formed. However, when 1 equiv. 2,5-dimethylfuran (**1a**) and 1 equiv. 1,3-cyclohexanedione (**3a**) were reacted under the conditions of the oxidative cleavage of **1a** (200 U laccase, 10 mol% 4-hydroxy-TEMPO, air) in acetate buffer at r.t. for 18 h, *i.e.* without any additional Lewis acid, the yield of **5a** amounted to 4% (Table 2, entry 1); using 3 equiv. 1,3-cyclohexanedione (**3a**) the yield was 15% (Table 2, entry 2). Despite the low yields, these experiments proved that the one-pot synthesis of **5a** is possible even in the absence of any Lewis acid. The yield of **5a** could be increased when the

**Table 2** Synthesis of **5a** in one-pot starting from **1a** and **3a**[a]




| Entry | Mediator | (mol%) | Catalyst | (mol%) | $T$ (°C) | $t$ (h) | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | 4-Hydroxy-TEMPO | 10 | — | — | r.t. | 48 | 4[b] |
| 2 | 4-Hydroxy-TEMPO | 10 | — | — | r.t. | 48 | 15 |
| 3 | 4-Hydroxy-TEMPO | 10 | $Yb(OTf)_3$ | 10 | r.t. | 48 | 24[c] |
| 4 | 4-Hydroxy-TEMPO | 10 | $Yb(OTf)_3$ | 10 | r.t. | 48 | 19[c,d] |
| 5 | 4-Hydroxy-TEMPO | 10 | $Yb(OTf)_3$ | 10 | 70 | 6 | 23 |
| 6 | 4-Hydroxy-TEMPO | 10 | $Yb(OTf)_3$ | 10 | 70 | 6 | 19 |
| 7 | 4-Hydroxy-TEMPO | 10 | $Yb(OTf)_3$ | 10 | r.t. | 48 | 32 |
| 8 | 4-Hydroxy-TEMPO | 25 | $Yb(OTf)_3$ | 10 | r.t. | 48 | 39 |
| 9 | 4-Hydroxy-TEMPO | 25 | $Sc(OTf)_3$ | 10 | r.t. | 48 | 42 |
| 10 | 4-Hydroxy-TEMPO | 25 | $Gd(OTf)_3$ | 10 | r.t. | 48 | 40 |
| 11 | 4-Hydroxy-TEMPO | 25 | $Cu(OTf)_2$ | 10 | r.t. | 48 | 25 |
| 12 | 4-Hydroxy-TEMPO | 25 | DMAP | 10 | r.t. | 48 | 22 |
| 13 | 4-Hydroxy-TEMPO | 25 | Pyridine | 10 | rt | 48 | 24 |
| 14 | 4-Acetamido-TEMPO | 25 | $Gd(OTf)_3$ | 10 | r.t. | 48 | 52 |
| 15 | TEMPO | 25 | $Gd(OTf)_3$ | 10 | r.t. | 48 | 51 |
| 16 | 4-Acetamido-TEMPO | 25 | $Gd(OTf)_3$ | 20 | r.t. | 48 | 55 |
| 17 | TEMPO | 25 | $Gd(OTf)_3$ | 20 | r.t. | 48 | 50 |
| 18 | 4-Acetamido-TEMPO | 25 | $Gd(OTf)_3$ | 20 | 50 | 12 | 39 |
| 19 | TEMPO | 25 | $Gd(OTf)_3$ | 20 | 50 | 12 | 45 |
| 20 | 4-Acetamido-TEMPO | 25 | $Gd(OTf)_3$ | 20 | r.t. | 48 | 54[e] |

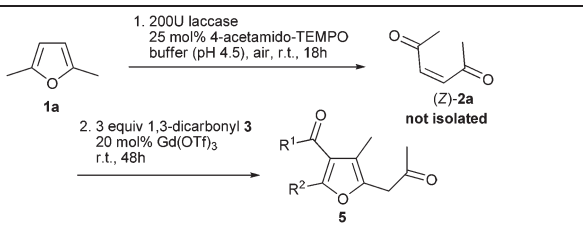
[a] 1 mmol of **1a** was reacted with 3 equiv. of **3a**. [b] 1 equiv. of **3a** was reacted. [c] 0.1 mmol of DL-alanine was used. [d] 0.2 mmol of NaOH were used. [e] 20 mol% of sodium dodecyl sulfate (SDS) were used.

Lewis acid was added after completion of the oxidative cleavage of **1a**, *i.e.* after 18 h. With 10 mol% of $Yb(OTf)_3$ the yield could be raised to 32% (Table 2, entry 7). An increase of the reaction temperature had no positive impact on the outcome, but when the amount of 4-hydroxy-TEMPO was raised to 25 mol% the product could be isolated in 39% yield (Table 2, entry 8). Similar results were observed with $Sc(OTf)_3$ and $Gd(OTf)_3$; with these Lewis acids **5a** was formed in 42 and 40%, resp. (Table 2, entries 9, 10). With $Cu(OTf)_2$, however, the yield of **5a** did not exceed 25% (Table 2, entry 11). Then, the influence of different amounts (10 and 20 mol%) of $Gd(OTf)_3$ on the outcome was studied (Table 2, entries 14–17). These experiments were performed with $Gd(OTf)_3$ since this Lewis acid is cheaper than $Yb(OTf)_3$ and $Sc(OTf)_3$. With 10 mol% $Gd(OTf)_3$ in the presence of 25 mol% 4-acetamido-TEMPO or TEMPO the yield of **5a** could be increased to 52 and 51%, resp. (Table 2, entries 14, 15). Using 20 mol% $Gd(OTf)_3$, the yields of **5a** amounted to 55 and 50% (Table 2, entries 16, 17).

Finally, it was established that raising the reaction temperature of the second step to 50 °C did not pay off (Table 2, entries 18, 19).

After optimizing the reaction conditions, the scope of the one-pot synthesis of the 6,7-dihydrobenzofuran-4(5*H*)-ones **5** with respect to the 1,3-dicarbonyls was studied (Table 3). For this purpose, the reaction of **1a** was performed with the substituted 1,3-cyclohexanediones **3b–e**. In all cases, the one-pot approach delivered the corresponding 6,7-dihydrobenzofuran-4(5*H*)-ones **5a–e** exclusively. The yields were in the range between 26 and 55%. The reaction could also be performed with **3h** as the 1,3-dicarbonyl (Table 3, entry 6 and Fig. 2). It should be noted that the synthesis of 6,7-dihydrobenzofuran-4(5*H*)-ones in one pot by the combination of an enzyme-catalyzed with a Lewis acid-catalyzed reaction has been achieved. However, it was obvious that the yields of **5** required substantial improvement.

**Table 3** Substrate scope of the one-pot synthesis of 6,7-dihydrobenzofuran-4-(5*H*)-ones **5**




| Entry | Product | Yield (%) |
|---|---|---|
| 1 | **5a** | 55 |
| 2 | **5b** | 40 |
| 3 | **5c** | 29 |
| 4 | **5d** | 26 |
| 5 | **5e–I + 5e–II** | 27 |
| 6 | **5h** | 25 |

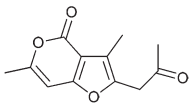


**Fig. 2** Structure of **5h**.

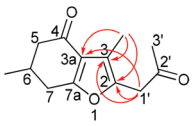


**Fig. 3** Important HSQMBC correlations of **5b**.

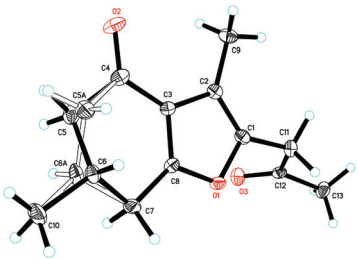


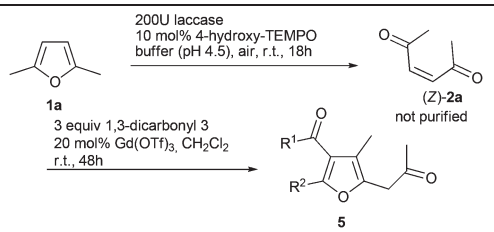
**Fig. 4** Structure of 3,6-dimethyl-2-(2-oxopropyl)-6,7-dihydrobenzofuran-4(5*H*)-one (**5b**), derived from X-ray crystal structure analysis.

Considering the finding that the Lewis acid-catalyzed synthesis of 6,7-dihydrobenzofuran-4(5*H*)-ones **5** from (*Z*)-3-hexene-2,5-dione (*Z*)-(**2a**) and 1,3-dicarbonyls **3** could be run best in $CH_2Cl_2$ as the solvent, we speculated that the low yields of the one-pot approach could be attributed to the aqueous medium employed. We were wondering whether the yields could be improved by a solvent change after the oxidative cleavage of **1a**. Accordingly, a new protocol was developed. After completion of the laccase-catalyzed oxidative cleavage of **1a** under the best conditions shown in Scheme 1,[17] the reaction product was extracted with $CH_2Cl_2$. After drying and concentrating, the resulting solution of (*Z*)-**2a** in $CH_2Cl_2$ was mixed with 3 equiv. 1,3-cyclohexanedione (**3a**) and 20 mol% $Gd(OTf)_3$ and the resulting reaction mixture was stirred for 48 h at r.t. Using this experimental procedure, 3-methyl-2-(2-oxopropyl)-6,7-dihydrobenzofuran-4(5*H*)-one (**5a**) was isolated in 60% yield (Table 4). After the successful demonstration of the value of this approach, the reactions of **1a** with **3b–g** were also conducted under the new conditions. Gratifyingly, the yields of the corresponding furans **5b–g** were in the range between 45 and 60%. This constitutes a significant improvement over the one-pot protocol.

The structures of all compounds were confirmed using MS and NMR methods. The full assignment of all $^1H$ and $^{13}C$ chemical shifts was achieved by evaluating their COSY, HSQC and HMBC spectra. The $^1H$ NMR spectra of 3,6-dimethyl-2-(2-oxopropyl)-6,7-dihydrobenzofuran-4(5*H*)-one (**5b**) shows one singlet at $\delta$ = 3.62 ppm corresponding to the methylene protons of C-1′ and two singlets at $\delta$ = 2.14 and $\delta$ = 2.16 ppm representing the protons of the methyl groups 3-Me and at C-3′. Moreover, the $^{13}C$ NMR spectra confirm the presence of the methylene signal at $\delta$ = 40.8 ppm (C-1′) and the C=O signals at $\delta$ = 195.1 ppm (C-4) and $\delta$ = 203.7 ppm (C-2′), respectively. Additionally, the HSQMBC pulse sequence was used for the unambiguous determination of the $^1H$–$^{13}C$ long range coupling constants. Concerning **5b**, the most important HSQMBC correlations to the aromatic carbons are depicted in Fig. 3. The large coupling constant $^2J$(H,C) = 7 Hz between 1′-H ($\delta$ = 3.62 ppm) and C-2 ($\delta$ = 144.3 ppm) and the smaller ones $^3J$(H,C) = 3 Hz between 1′-H and C-3 ($\delta$ = 116.0 ppm) as well as $^4J$(H,C) = 5.1 Hz between 1′-H and C-3a ($\delta$ = 120.7 ppm) confirm the methylene group to be attached to C-2. Further, 3-Me shows three important correlations, namely to C-2 [$^3J$(H,C) = 5.5 Hz], to C-3 [$^2J$(H,C) = 7 Hz] and to C-3a [$^3J$(H,C) = 2.9 Hz]. Consequently, 3-Me is proved to be attached to C-3.

Unequivocal evidence for the structures of **5b** and **5d** was provided by X-ray crystal structure analysis. For this purpose, crystals of **5b** and **5d** were studied by X-ray crystal structure analysis. The structure of **5b** is depicted in Fig. 4 and reveals that the methyl group is attached to C-3 and not to C-2.

**Table 4** Substrate scope of the synthesis of 6,7-dihydrobenzofuran-4(5*H*)-ones **5** from **1a** and **3** without purification of (*Z*)-**2a**




| Entry | Product | Yield (%) |
|---|---|---|
| 1 | **5a** | 60 |
| 2 | **5b** | 53 |
| 3 | **5c** | 45 |
| 4 | **5d** | 54 |
| 5 | **5e–I + 5e–II** | 53 |
| 6 | **5f** | 53 |
| 7 | **5g** | 56 |

## Conclusions

In summary, the Lewis acid-catalyzed domino 1,2-addition/1,4-addition/elimination between (*Z*)-3-hexene-2,5-dione and 1,3-dicarbonyls delivers 3-methyl-6,7-dihydrobenzofuran-4(5*H*)-ones exclusively with yields up to 82%. The combination of this new Lewis acid-catalyzed process with the laccase-catalyzed oxidative cleavage of 2,5-dimethylfuran to (*Z*)-3-hexene-2,5-dione allows for the synthesis of 6,7-dihydrobenzofuran-4(5*H*)-ones without isolation/purification of the intermediate (*Z*)-3-hexene-2,5-dione.

## Experimental section

### General remarks

All chemicals and the laccase (*Trametes versicolor*) were purchased from commercial suppliers and were used without further purification unless otherwise indicated. Solvents used for extraction and purification were distilled prior to use. The pH of the buffer was adjusted using a pH 330/SET-1 pH-meter. Analytical thin layer chromatography (TLC) was performed on aluminum-backed plates coated with silica gel with F254 indicator (Merck). Compounds were visualized using UV light (254 nm) or with vanillin/$H_2SO_4$ as a solution in ethanol. Flash chromatography was carried out using silica gel 60 M, 230–400 mesh (Macherey & Nagel). Melting points were determined using a Büchi melting point apparatus B-545 with open capillary tubes and are uncorrected. UV/Vis spectra were recorded using a Varian Cary 50. IR spectra were measured using a Perkin-Elmer Spectrum One FT-IR spectrum. $^1$H ($^{13}$C) NMR spectra were recorded at 300 (75) MHz using a Varian $^{Unity}$Inova spectrometer with $CDCl_3$ ($\delta$ = 7.26 ppm in $^1$H NMR spectra and $\delta$ = 77.0 ppm in $^{13}$C NMR spectra) as internal standards. Coupling constants $J$ [Hz] were directly taken from the spectra and are not averaged. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), sep (septet) and m (multiplet). HSQC-, HMBC- and COSY-spectra were recorded using a Varian $^{Unity}$Inova at 300 MHz. Electron impact low resolution mass spectra (EI) and electron impact high resolution mass spectra (HRMS) were recorded at 70 eV using a Finnigan MAT 95 instrument. The intensities are reported as percentages relative to the base peak ($I$ = 100%).

**General procedure A for the Gd(OTf)$_3$-catalyzed synthesis of 6,7-dihydrobenzofuran-4(5*H*)-ones 5a–g starting from (*Z*)-3-hexene-2,5-dione (*Z*)-(2a) and 1,3-dicarbonyls 3a–g.** A 50 mL round-bottomed flask equipped with a magnetic stir bar was charged with (*Z*)-3-hexene-2,5-dione (*Z*)-(**2a**) (112 mg, 1 mmol), a 1,3-dicarbonyl **3** (3 mmol), Gd(OTf)$_3$ (60 mg, 0.1 mmol) and $CH_2Cl_2$ (10 mL). The mixture was stirred for 48 h at r.t. After concentration the reaction mixture *in vacuo*, the crude product was purified by flash chromatography on $SiO_2$ (petroleum ether–EtOAc = 1 : 1) to afford the 6,7-dihydrobenzofuran-4(5*H*)-one **5**.

**General procedure B for the one-pot synthesis of 5a–e,h in aqueous medium starting from 2,5-dimethylfuran (1a) and 1,3-dicarbonyls 3a–e,h.** A 250 mL round-bottomed flask equipped with a magnetic stir bar was charged with 2,5-dimethylfuran (**1a**) (96 mg, 1 mmol), *n*-octane (1 mL), 0.01 M acetate buffer pH 4.5 (10 mL), 4-acetamido-TEMPO (53 mg, 0.25 mmol) and 200 U laccase (*Trametes versicolor*) and sealed with a septum. The mixture was stirred for 18 h at r.t. Then, the 1,3-dicarbonyl **3** (3 mmol) and Gd(OTf)$_3$ (120 mg, 0.2 mmol) were added and the mixture was stirred at r.t. for 48 h. The reaction mixture was saturated with NaCl (1 g) and extracted with $CH_2Cl_2$ (4 × 25 mL). The combined organic phases were dried over $Na_2SO_4$. After removal of the solvents *in vacuo*, the crude product was purified by flash chromatography on $SiO_2$ (petroleum ether–EtOAc = 1 : 1) to afford the 6,7-dihydrobenzofuran-4(5*H*)-one **5**.

**General procedure C for the synthesis of 5a–g starting from 2,5-dimethylfuran (1a) and 1,3-dicarbonyls 3a–g without purification of (*Z*)-2a.** A 250 mL round-bottomed flask equipped with a magnetic stir bar was charged with 2,5-dimethylfuran (**1a**) (96 mg, 1 mmol), *n*-octane (1 mL), 0.01 M acetate buffer pH 4.5 (10 mL), 4-hydroxy-TEMPO (17 mg, 0.1 mmol) and 200 U laccase (*Trametes versicolor*) and sealed with a septum. The mixture was stirred for 18 h at r.t., then saturated with NaCl (1 g) and extracted with $CH_2Cl_2$ (4 × 25 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated *in vacuo* to a volume of *ca.* 10 mL. Then, the 1,3-dicarbonyl **3** (3 mmol) and Gd(OTf)$_3$ (120 mg, 0.2 mmol) were added. After stirring at r.t. for 48 h and concentration the reaction mixture *in vacuo*, the crude product was purified by flash chromatography on $SiO_2$ (petroleum ether–EtOAc = 1 : 1) to afford the 6,7-dihydrobenzofuran-4(5*H*)-one **5**.

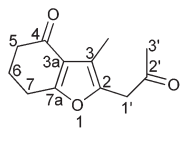
**Determination of laccase activity.**[21] A 0.1 M solution of ABTS (0.3 mL) in 0.01 M acetate buffer (pH = 4.5) was diluted with 0.01 M acetate buffer (2.6 mL, pH = 4.5) and treated with a solution of laccase in the same buffer (0.1 mL). The change in absorption was followed using UV/Vis spectroscopy ($\lambda$ = 414 nm). One unit was defined as the amount of laccase (*Trametes versicolor*, Fluka) that converts 1 mmol of ABTS per minute at pH = 4.5 at r.t.

**Synthesis and analytical data for 5a–5h**

*3-Methyl-2-(2-oxopropyl)-6,7-dihydrobenzofuran-4(5*H*)-one (**5a**).* According to the general procedure A, a solution of (*Z*)-3-hexene-2,5-dione (*Z*)-(**2a**) (112 mg, 1 mmol) and 1,3-cyclohexanedione (**3a**) (336 mg, 3 mmol) in $CH_2Cl_2$ was reacted in the presence of Gd(OTf)$_3$ (60 mg, 0.1 mmol) for 48 h. Purification afforded **5a** (152 mg, 0.74 mmol, 74%).

According to the general procedure B, 1,3-cyclohexanedione (**3a**) (336 mg, 3 mmol) and Gd(OTf)$_3$ (120 mg, 0.2 mmol) were added to the reaction mixture of the laccase-catalyzed ring opening of 2,5-dimethylfuran (**1a**) (96 mg, 1 mmol) in acetate buffer and the mixture was reacted for 48 h. Purification afforded **5a** (113 mg, 0.55 mmol, 55%).

According to the general procedure C, the crude product solution in $CH_2Cl_2$ resulting from the laccase-catalyzed ring opening of 2,5-dimethylfuran (**1a**) was subjected to 1,3-cyclohexanedione (**3a**) (336 mg, 3 mmol) and Gd(OTf)$_3$ (120 mg, 0.2 mmol). The reaction mixture was stirred for 48 h. Purification furnished **5a** (124 mg, 0.6 mmol, 60%).



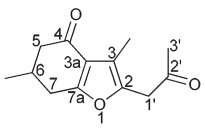

Yellow oil; $R_f$ = 0.53 (PE–EtOAc = 2 : 1); IR (ATR): $\tilde{\nu}$ = 2951 (w; $CH_2$, $CH_3$), 1717 (m; C=O, carbonyl), 1666 (s; C=O, enone), 1579 (m; C=C), 1357 cm$^{-1}$; UV/Vis ($CH_3CN$): $\lambda_{max}$ (log $\varepsilon$) = 210 (4.18), 265 nm (3.61); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.12 (2 H, m, 6-H), 2.14 (3 H, s, 3-Me), 2.16 (3 H, s, 3′-H), 2.44 (2 H, t,

$^3J$ (5-H, 6-H) = 6.3 Hz, 5-H), 2.80 (2 H, t, $^3J$ (7-H, 6-H) = 6.3 Hz, 7-H), 3.61 (2 H, s, 1′-H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 8.9 (3-Me), 22.5 (C-6), 23.4 (C-5), 29.2 (C-3′), 38.1 (C-7), 40.7 (C-1′), 116.0 (C-3), 121.0 (C-3a), 144.0 (C-2), 166.2 (C-7a), 195.4 (C-4), 203.6 (C-2′); MS (EI, 70 eV): *m*/*z* (%) = 206 (20) $[M]^+$, 163 (100) $[M - CH_3CO]^+$, 43 (48); HRMS (EI, $M^+$) calculated for $C_{12}H_{14}O_3$: 206.0943; found: 206.0936.

*3,6-Dimethyl-2-(2-oxopropyl)-6,7-dihydrobenzofuran-4(5*H*)-one (**5b**).* According to the general procedure A, a solution of (*Z*)-3-hexene-2,5-dione (*Z*)-(**2a**) (112 mg, 1 mmol) and 5-methyl-1,3-cyclohexanedione (**3b**) (378 mg, 3 mmol) in $CH_2Cl_2$ was reacted in the presence of $Gd(OTf)_3$ (60 mg, 0.1 mmol) for 48 h. Purification afforded **5b** (180 mg, 0.82 mmol, 82%).

According to the general procedure B, 5-methyl-1,3-cyclohexanedione (**3b**) (378 mg, 3 mmol) and $Gd(OTf)_3$ (120 mg, 0.2 mmol) were added to the reaction mixture of the laccase-catalyzed ring opening of 2,5-dimethylfuran (**1a**) (96 mg, 1 mmol) in acetate buffer and the mixture was reacted for 48 h. Purification afforded **5b** (88 mg, 0.4 mmol, 40%).

According to the general procedure C, the crude product solution in $CH_2Cl_2$ resulting from the laccase-catalyzed ring opening of 2,5-dimethylfuran (**1a**) was subjected to 5-methyl-1,3-cyclohexanedione (**3b**) (378 mg, 3 mmol) and $Gd(OTf)_3$ (120 mg, 0.2 mmol). The reaction mixture was stirred for 48 h. Purification furnished **5b** (117 mg, 0.53 mmol, 53%).

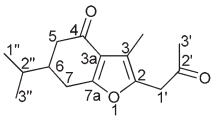



Yellowish solid; mp 106–108 °C; $R_f$ = 0.62 (PE–EtOAc = 2 : 1); IR (ATR): $\tilde{\nu}$ = 2961, 2927 (w; $CH_2$, $CH_3$), 1709 (m; C═O, carbonyl), 1666 (s; C═O, enone), 1583 $cm^{-1}$ (m; C═C); UV/Vis ($CH_3CN$): $\lambda_{max}$ (log $\varepsilon$) = 207 (4.18), 268 nm (3.61); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.15 (3 H, d, $^3J$ (1″-H, 6-H) = 6.2 Hz, 1″-H), 2.14 (3 H, s, 3-Me), 2.16 (3 H, s, 3′-H), 2.21 (1 H, dd, $^3J$ (5-$H_{ax}$, 6-H) = 11.2 Hz, $^2J$ (5-$H_{ax}$, 5-$H_{eq}$) = 15 Hz, 5-$H_{ax}$), 2.34–2.45 (1 H, m, 6-H), 2.48 (1 H, dd, $^3J$ (7-$H_{ax}$, 6-H) = 10.5 Hz, $^2J$ (7-$H_{ax}$, 7-$H_{eq}$) = 17 Hz, 7-$H_{ax}$), 2.49 (1 H, dd, $^3J$ (5-$H_{eq}$, 6-H) = 3 Hz, $^2J$ (5-$H_{eq}$, 5-$H_{ax}$) = 15.8 Hz, 5-$H_{eq}$), 2.88 (1 H, dd, $^3J$ (7-$H_{eq}$, 6-H) = 4.5 Hz, $^2J$ (7-$H_{eq}$, 7-$H_{ax}$) = 16.4 Hz, 7-$H_{eq}$), 3.62 (2 H, s, 1′-H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 8.9 (3-Me), 21.1 (6-Me), 29.2 (C-3′), 30.7 (C-6), 31.6 (C-7), 40.8 (C-1′), 46.7 (C-5), 116.0 (C-3), 120.7 (C-3a), 144.3 (C-2), 165.9 (C-7a), 195.1 (C-4), 203.7 (C-2′); MS (EI, 70 eV): *m*/*z* (%) = 220 (4) $[M]^+$, 177 (82) $[M - CH_3CO]^+$, 135 (10); HRMS (EI, $M^+$) calculated for $C_{13}H_{16}O_3$: 220.1099; found: 220.1102. Crystals suitable for X-ray diffraction analysis were grown from EtOAc and cyclohexane.

*6-Isopropyl-3-methyl-2-(2-oxopropyl)-6,7-dihydrobenzofuran-4-(5*H*)-one (**5c**).* According to the general procedure A, a solution of (*Z*)-3-hexene-2,5-dione (*Z*)-(**2a**) (112 mg, 1 mmol) and 5-isopropyl-1,3-cyclohexanedione (**3c**) (462 mg, 3 mmol) in $CH_2Cl_2$ was reacted in the presence of $Gd(OTf)_3$ (60 mg, 0.1 mmol) for 48 h. Purification afforded **5c** (141 mg, 0.57 mmol, 57%).

According to the general procedure B, 5-isopropyl-1,3-cyclohexanedione (**3c**) (462 mg, 3 mmol) and $Gd(OTf)_3$ (120 mg, 0.2 mmol) were added to the reaction mixture of the laccase-catalyzed ring opening of 2,5-dimethylfuran (**1a**) (96 mg, 1 mmol) in acetate buffer and the mixture was reacted for 48 h. Purification afforded **5c** (72 mg, 0.29 mmol, 29%).

According to the general procedure C, the crude product solution in $CH_2Cl_2$ resulting from the laccase-catalyzed ring opening of 2,5-dimethylfuran (**1a**) was subjected to 5-isopropyl-1,3-cyclohexanedione (**3c**) (462 mg, 3 mmol) and $Gd(OTf)_3$ (120 mg, 0.2 mmol). The reaction mixture was stirred for 48 h. Purification furnished **5c** (112 mg, 0.45 mmol, 45%).




Yellow oil; $R_f$ = 0.65 (PE–EtOAc = 2 : 1); IR (ATR): $\tilde{\nu}$ = 2959 (w; $CH_2$, $CH_3$), 1765 (w), 1717 (m; C═O, carbonyl.), 1670 (s; C═O, enone), 1582 (m; C═C), 1370 $cm^{-1}$; UV/Vis ($CH_3CN$): $\lambda_{max}$ (log $\varepsilon$) = 209 (4.23), 268 nm (3.42) $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.95 (3 H, d, $^3J$(1″-H, 2″-H) = 1.5 Hz, 1″-H), 0.98 (3 H, d, $^3J$ (3″-H, 2″-H) = 1.5 Hz, 3″-H), 1.65–1.76 (2.14 (1 H, m, 6-H), 1.98–2.11 (1 H, m, 2″-H), 2.14 (3 H, s, 3-Me), 2.16 (3 H, s, 3′-H), 2.24 (1 H, dd, $^3J$ (5-$H_b$, 6-H) = 12.5 Hz, $^2J$ (5-$H_b$, 5-$H_a$) = 15.7 Hz, 5-$H_b$), 2.52 (1 H, dd, $^3J$ (5-$H_a$, 6-H) = 0.9 Hz, $^2J$ (5-$H_a$, 5-$H_b$) = 15.8 Hz, 5-$H_a$), 2.54 (1 H, dd, $^3J$ (7-$H_b$, 6-H) = 11.2 Hz, $^2J$ (7-$H_b$, 7-$H_a$) = 16.9 Hz, 7-$H_b$), 2.85 (1 H, dd, $^3J$ (7-$H_a$, 6-H) = 5 Hz, $^2J$ (7-$H_a$, 7-$H_b$) = 17 Hz, 7-$H_a$), 3.62 (2 H, s, 1′-H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 8.9 (3-Me), 19.46 (C-1″), 19.68 (C-3″), 27.07 (C-3′), 29.2 (C-2″), 31.6 (C-7), 31.88 (C-6), 40.8 (C-1′), 42.04 (C-5), 115.9 (C-3), 120.8 (C-3a), 144.3 (C-2), 166.6 (C-7a), 195.1 (C-4), 203.7 (C-2′); MS (EI, 70 eV): *m*/*z* (%) 248 (92) $[M]^+$, 206 (82) $[M - CH_3COH]^+$, 135 (97); HRMS (EI, $M^+$) calculated for $C_{15}H_{20}O_3$: 248.1412; found: 248.1384.

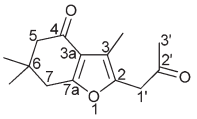
*3,6,6-Trimethyl-2-(2-oxopropyl)-6,7-dihydrobenzofuran-4(5*H*)-one (**5d**).* According to the general procedure A, a solution of (*Z*)-3-hexene-2,5-dione (*Z*)-(**2a**) (112 mg, 1 mmol) and 5,5-dimethyl-1,3-cyclohexanedione (**3d**) (420 mg, 3 mmol) in $CH_2Cl_2$ was reacted in the presence of $Gd(OTf)_3$ (60 mg, 0.1 mmol) for 48 h. Purification afforded **5d** (154 mg, 0.66 mmol, 66%).

According to the general procedure B, 5,5-dimethyl-1,3-cyclohexanedione (**3d**) (420 mg, 3 mmol) and $Gd(OTf)_3$ (120 mg, 0.2 mmol) were added to the reaction mixture of the laccase-catalyzed ring opening of 2,5-dimethylfuran (**1a**) (96 mg, 1 mmol) in acetate buffer and the mixture was reacted for 48 h. Purification afforded **5d** (61 mg, 0.26 mmol, 26%).

According to the general procedure C, the crude product solution in $CH_2Cl_2$ resulting from the laccase-catalyzed ring opening of 2,5-dimethylfuran (**1a**) was subjected to 5,5-dimethyl-1,3-cyclohexanedione (**3d**) (420 mg, 3 mmol) and

$Gd(OTf)_3$ (120 mg, 0.2 mmol). The reaction mixture was stirred for 48 h. Purification furnished **5d** (126 mg, 0.54 mmol, 54%).

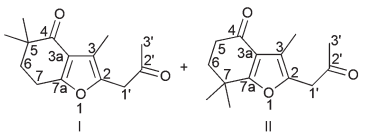


Yellowish solid; mp 74–76 °C; $R_f$ = 0.64 (PE–EtOAc = 2 : 1); IR (ATR): $\tilde{\nu}$ = 2959 (w; $CH_2$, $CH_3$), 1765 (w), 1714 (m; C═O, carbonyl), 1667 (s; C═O, enone), 1594 (m), 1372 $cm^{-1}$ (m); UV/Vis ($CH_3CN$): $\lambda_{max}$ (log $\varepsilon$) = 209 (4.20), 258 nm (4.08); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.11 (6 H, s, 6-Me), 2.14 (3 H, s, 3-Me), 2.16 (3 H, s, 3′-H), 2.32 (2 H, s, 5-H), 2.67 (2 H, s, 7-H), 3.62 (2 H, s, 1′-H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 8.9 (3-Me), 28.6 (6-Me), 29.2 (C-3′), 35.0 (C-6), 37.4 C-7), 40.9 (C-1′), 52.5 (C-5), 115.9 (C-3), 119.9 (C-3a), 144.4 (C-2), 165.4 (C-7a), 194.8 (C-4), 203.7 (C-2′); MS (EI, 70 eV): *m*/*z* (%) = 234 (68) $[M]^+$, 191 (100) $[M - CH_3CO]^+$, 135 (100); HRMS (EI, $M^+$) calculated for $C_{14}H_{18}O_3$: 234.1256; found: 234.1249. Crystals suitable for X-ray diffraction analysis were grown from EtOAc and cyclohexane.

*3,5,5-Trimethyl-2-(2-oxopropyl)-6,7-dihydrobenzofuran-4(5H)-one (**5e–I**) and 3,7,7-trimethyl-2-(2-oxopropyl)-6,7-dihydrobenzofuran-4(5H)-one (**5e–II**).* According to the general procedure A, a solution of (*Z*)-3-hexene-2,5-dione (*Z*)-(**2a**) (112 mg, 1 mmol) and 4,4-dimethyl-1,3-cyclohexanedione (**3e**) (420 mg, 3 mmol) in $CH_2Cl_2$ was reacted in the presence of $Gd(OTf)_3$ (60 mg, 0.1 mmol) for 48 h. Purification afforded a mixture of regioisomers **5e–I** and **5e–II** (124 mg, 0.53 mmol, 53%).

According to the general procedure B, 4,4-dimethyl-1,3-cyclohexanedione (**3e**) (420 mg, 3 mmol) and $Gd(OTf)_3$ (120 mg, 0.2 mmol) were added to the reaction mixture of the laccase-catalyzed ring opening of 2,5-dimethylfuran (**1a**) (96 mg, 1 mmol) in acetate buffer and the mixture was reacted for 48 h. Purification afforded a mixture of regioisomers **5e–I** and **5e–II** (63 mg, 0.27 mmol, 27%).

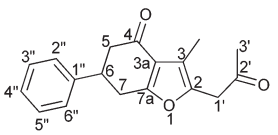
According to the general procedure C, the crude product solution in $CH_2Cl_2$ resulting from the laccase-catalyzed ring opening of 2,5-dimethylfuran (**1a**) was subjected to 4,4-dimethyl-1,3-cyclohexanedione (**3e**) (420 mg, 3 mmol) and $Gd(OTf)_3$ (120 mg, 0.2 mmol). The reaction mixture was stirred for 48 h. Purification furnished a mixture of regioisomers **5e–I** and **5e–II** (124 mg, 0.53 mmol, 53%).



Yellow oil; $R_f$ = 0.67 (PE–EtOAc = 2 : 1); IR (ATR): $\tilde{\nu}$ = 2965, 2930 (w; $CH_2$, $CH_3$), 1719 (m; C═O, carbonyl), 1668 (s; C═O, enone), 1585 (m; C═C), 1357 $cm^{-1}$; UV/Vis ($CH_3CN$): $\lambda_{max}$ (log $\varepsilon$) = 207 (4.00), 266 nm (3.50); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.15 (6 H, s, 2 × 5-Me) (**I**), 1.32 (6 H, s, 2 × 7-Me) (**II**), 1.94 (2 H, t, $^3J$ (6H, 7-H) = 6.4 Hz, 6-H) (**I**), 1.95 (2 H, m, part. ov.,6-H) (**II**), 2.114 (3 H, s, 3-Me) (**II**), 2.119 (3 H, s, 3-Me) (**I**), 2.13 (3 H, s, 3′-H), 2.16 (3 H, s, 3′-H), 2.45–2.48 (2 H, m, 5-H) (**II**), 2.79–2.84 (2 H, m, 7-H) (**I**), 3.62 (4 H, s, 2 × 1′-H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 8.86 (3-Me) (**II**), 8.93 (3-Me) (**I**), 20.9 (C-7) (**I**), 24.1 (5-Me) (**I**), 25.9 (7-Me) (**II**), 29.1 (C-3′) (**II**), 29.2 (C-3′) (**I**), 32.7 (C-7) (**II**), 35.9 (C-5) (**II**), 36.4 (C-6) (**I**), 37.8 (C-6) (**II**), 40.9 (2 × C-1′), 42.1 (C-5) (**I**), 115.9 (C-3) (**II**), 116.6 (C-3) (**I**), 118.8 (C-3a) (**II**), 119.2 (C-3a) (**I**), 144.0 (C-2), 144.3 (C-2), 164.4 (C-7a) (**I**), 172.0 (C-7a) (**II**), 195.4 (C-4) (**II**), 200.7 (C-4) (**I**), 203.7 (2 × C-2′); MS (EI, 70 eV): *m*/*z* (%) 234 (28) $[M]^+$, 191 (100) $[M - CH_3CO]^+$, 28 (82); HRMS (EI, $M^+$) calculated for $C_{14}H_{18}O_3$: 234.1256; found: 234.1249.

*3-Methyl-6-phenyl-2-(2-oxopropyl)-6,7-dihydrobenzofuran-4(5H)-one (**5f**).* According to the general procedure A, a solution of (*Z*)-3-hexene-2,5-dione (*Z*)-(**2a**) (112 mg, 1 mmol) and 5-phenyl-1,3-cyclohexanedione (**3f**) (564 mg, 3 mmol) in $CH_2Cl_2$ was reacted in the presence of $Gd(OTf)_3$ (60 mg, 0.1 mmol) for 48 h. Purification afforded **5f** (144 mg, 0.51 mmol, 51%).

According to the general procedure C, the crude product solution in $CH_2Cl_2$ resulting from the laccase-catalyzed ring opening of 2,5-dimethylfuran (**1a**) was subjected to 5-phenyl-1,3-cyclohexanedione (**3f**) (564 mg, 3 mmol) and $Gd(OTf)_3$ (120 mg, 0.2 mmol). The reaction mixture was stirred for 48 h. Purification furnished **5f** (150 mg, 0.53 mmol, 53%).

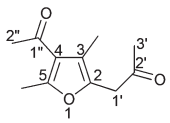


Yellow oil; $R_f$ = 0.67 (PE–EtOAc = 2 : 1); IR (ATR): $\tilde{\nu}$ = 2929 (w; $CH_2$, $CH_3$), 1766 (w), 1732 (s; C═O, carbonyl), 1671(s; C═O, enone), 1580 (m; C═C), 1372 (m), 1239 (s), 1043 $cm^{-1}$ (s); UV/Vis ($CH_3CN$): $\lambda_{max}$ (log $\varepsilon$) = 209 (4.38), 268 nm (3.5); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 2.18 (3 H, s, 3-Me), 2.20 (3 H, s, 3′-H), 2.68–2.81 (2 H, m, spectra higher order, 5-H), 3.00 (1 H, dd, $^2J$ (7-$H_a$, 7-$H_b$) = 17.2 Hz, $^3J$ (7-$H_a$, 6-H) = 10.9 Hz, 7-$H_a$), 3.10 (1 H, dd, $^2J$ (7-$H_b$, 7-$H_a$) = 17.1 Hz, $^3J$ (7-$H_b$, 6-H) = 5.2 Hz, 7-$H_b$), 3.44–3.56 (1 H, m, 6-H), 3.66 (2 H, s, 1′-H), 7.26–7.31 (2 H, m, 2″-H, 6″-H), 7.33–7.40 (3 H, m, 3″-H, 4″-H, 5″-H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 9 (3-Me), 29.3 (C-3′), 31.3 (C-7), 40.8 (C-6), 41.2 (C-1′), 45.5 (C-5), 116.1 (C-3), 121.0 (C-3a), 126.7 (C-2″, C-6″), 127.2 (C-4″), 128.8 (C-3″, C-5″), 142.5 (C-1″), 144.7 (C-2), 165.4 (C-7a), 194.0 (C-4), 203.5 (C-2′); MS (EI, 70 eV): *m*/*z* (%) = 282 (32) $[M]^+$, 239 (100) $[M - CH_3CO]^+$, 135 (93); HRMS (EI, $M^+$) calculated for $C_{18}H_{18}O_3$: 282.1256; found: 220.1237.

*1-(4-Acetyl-3,5-dimethylfuran-2-yl)propan-2-one (**5g**).* According to the general procedure A, a solution of (*Z*)-3-hexene-2,5-dione (*Z*)-(**2a**) (112 mg, 1 mmol) and acetylacetone (**3g**) (300 mg, 3 mmol) in $CH_2Cl_2$ was reacted in the presence of Gd $(OTf)_3$ (60 mg, 0.1 mmol) for 48 h. Purification afforded **5g** (116 mg, 0.6 mmol, 60%).

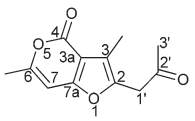
According to the general procedure C, the crude product solution in $CH_2Cl_2$ resulting from the laccase-catalyzed ring opening of 2,5-dimethylfuran (**1a**) was subjected to

acetylacetone (**3g**) (300 mg, 3 mmol) and $Gd(OTf)_3$ (120 mg, 0.2 mmol). The reaction mixture was stirred for 48 h. Purification furnished **5g** (109 mg, 0.56 mmol, 56%).




Yellow oil; $R_f$ = 0.53 (PE–EtOAc = 2 : 1); IR (ATR): $\tilde{\nu}$ = 2973, 2931 (w; $CH_2$, $CH_3$), 1711 (m; C═O, carbonyl), 1655 (s; C═O, enone), 1559 (m; C═C), 1354 $cm^{-1}$ (m); UV/Vis ($CH_3CN$): $\lambda_{max}$ (log $\varepsilon$) = 207 (4.2), 273 nm (3.7); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 2.10 (3 H, s, 3-Me), 2.15 (3 H, s, 3′-H), 2.41 (3 H, s, 2″-H), 2.52 (3 H, s, 5-Me), 3.60 (2 H, s, 1′-H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 10.6 (3-Me), 15.2 (5-Me), 29.1 (C-3′), 30.8 (C-2″), 40.9 (C-1′), 117.5 (C-3), 123.2 (C-4), 142.6 (C-2), 157.6 (C-5), 194.7 (C-1″), 203.9 (C-2′); MS (EI, 70 eV): *m*/*z* (%) 194 (7) $[M]^+$, 151 (31) $[M - CH_3CO]^+$, 43 (100), 28 (86); HRMS (EI, $M^+$) calculated for $C_{11}H_{14}O_3$: 194.0943; found: 194.0927.

*3,6-Dimethyl-2-(2-oxopropyl)-4*H*-furo[3,2c]pyran-4-one* (***5h***). According to the general procedure B, 4-hydroxy-6-methyl-2-pyron (**3h**) (378 mg, 3 mmol) and $Gd(OTf)_3$ (120 mg, 0.2 mmol) were added to the reaction mixture of the laccase-catalyzed ring opening of 2,5-dimethylfuran (**1a**) (96 mg, 1 mmol) in acetate buffer and the mixture was reacted for 48 h. Purification afforded **5h** (56 mg, 0.25 mmol, 25%).




Yellow oil; $R_f$ = 0.52 (PE–EtOAc = 2 : 1); IR (ATR): $\tilde{\nu}$ = 2926 (w; $CH_2$, $CH_3$), 1712 (s; C═O), 1616 (m), 1575 (m; C═C), 1358 (m), 1158 (m), 947 $cm^{-1}$ (m); UV/Vis ($CH_3CN$): $\lambda_{max}$ (log $\varepsilon$) = 248 (3.9), 298 nm (3.3); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 2.19 (3 H, s, 3′-H), 2.23 (3 H, s, 3-Me), 2.30 (3 H, s, 1″-H), 3.7 (2 H, s, 1′-H), 6.3 (1 H, s, 7-H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 8.5 (3-Me), 20.2 (C-1″), 29.3 (C-3′), 41.0 (C-1′), 52.5 (C-5), 115.9 (C-3), 95.7 (C-7), 109.2 (C-3a), 116.1 (C-3), 145.3 (C-2), 159.5.4 (C-6), 160.2 (C-7a), 161.0 (C-4), 202.8 (C-2′); MS (EI, 70 eV): *m*/*z* (%) 220 (86) $[M]^+$, 177 (100) $[M - CH_3CO]^+$, 137 (77); HRMS (EI, $M^+$) calculated for $C_{12}H_{12}O_4$: 220.0892; found: 220.0722.

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