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Laccase-Catalyzed Domino Reactions between Hydroquinones and Cyclic 1,3-Dicarbonyls for the Regioselective Synthesis of Substituted *p*-Benzoquinones

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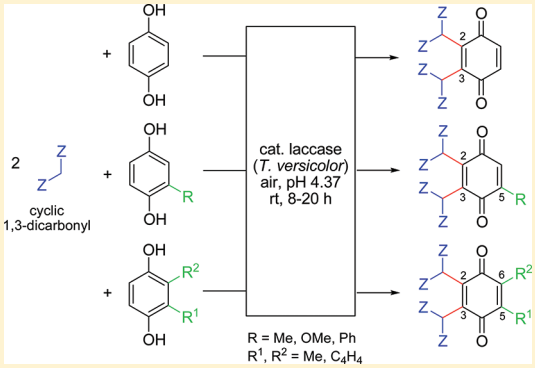
Supporting Information

ABSTRACT: Highly substituted *p*-benzoquinones were obtained in yields ranging from 39% to 98% by laccase-catalyzed domino reactions between hydroquinones and cyclic 1,3-dicarbonyls using aerial oxygen as the oxidant. In almost all reactions bis-adducts with two adjacent 1,3-dicarbonyl substituents on the quinone moiety were formed selectively. The transformations can be regarded as domino oxidation/1,4-addition/oxidation/1,4-addition/oxidation processes. With unsubstituted hydroquinone as the substrate 2,3-disubstituted *p*-benzoquinones were isolated. Bis-adducts were also formed exclusively upon reaction with monosubstituted hydroquinones. In almost all cases the 2,3,5-trisubstituted *p*-benzoquinones were obtained. When 2,3-disubstituted hydroquinones were employed as starting materials the 2,3,5,6-tetrasubstituted *p*-benzoquinones were isolated. The unambiguous structure elucidation of all products has been achieved by NMR spectroscopic methods including spin pattern analysis of the long-range coupled C=O carbons and ^{13}C satellites analysis in ^{1}H NMR spectra.



INTRODUCTION

Today, enzyme-catalyzed transformations occupy a prominent position in organic synthesis as they allow a multitude of transformations to be performed in a selective and efficient manner.[1] Currently, the development of enzyme-catalyzed oxidations is a topic of growing interest to many chemists.[2] Enzymatic oxidative transformations are highly attractive as they can supplement and expand the repertoire of standard methods used for oxidations, replace toxic oxidants, and avoid the formation of toxic byproducts. Furthermore, most enzymatic oxidations can be performed under mild reaction conditions, and very often they do not require organic solvents.[2b] There are several groups of enzymes, including dehydrogenases, oxidases, oxygenases, and peroxidases, that are capable of catalyzing oxidations. Oxidases catalyze the oxidation of a substrate with simultaneous reduction of O_2 to either hydrogen peroxide or to water without incorporation of oxygen into the oxidation product.[3] Among the most interesting oxidases are laccases.[4] Laccases (benzenediol: O_2 oxidoreductase E.C. 1.10.3.2.) mainly occur in fungi but also in plants, insects, and bacteria. They can easily be isolated, and some of them are commercially available. Laccases belong to the blue-copper oxidases and are able to catalyze the oxidation of a substrate with simultaneous reduction of O_2 to give H_2O.[4c] They can be used in aqueous buffer solutions, in biphasic water/organic solvent systems,[5a−d] mixtures of organic solvents and water,[5e] as well as ionic liquid/water systems.[6] Also, they can be immobilized using different techniques such as binding to a carrier,[7a−g] inclusion/entrapment or encapsulation in polymer,[7h−j] and cross-linking.[7k−m] Laccases are capable of oxidizing a variety of compounds.[8] With redox mediators the redox potential of laccases can be extended, allowing for the oxidation of substrates with higher redox potentials.[9] The substrates for laccase-catalyzed oxidations include phenolic compounds;[5a,10] aromatic methyl groups;[11] benzylic, allylic, and aliphatic alcohols;[12] ethers;[13] and benzyl amines and hydroxylamines.[14] The attractiveness of enzyme-catalyzed transformations can be considerably increased when combining them with one or more chemical transformations to new domino processes.[15] In this respect, laccase-catalyzed oxidations are very promising since combinations with a number of chemical transformations such as 1,4-additions and Diels−Alder reactions have already been successful. Examples of laccase-catalyzed domino processes include the synthesis of phenoxazinones by reaction of two *o*-aminophenols[16] and the preparation of 2,3-diaminophenazine by reaction of two molecules of *o*-phenylenediamine.[17] When the laccase-catalyzed oxidation of *o*-phenylenediamine was performed in the presence of aromatic aldehydes, the selective formation of 2-aryl-1*H*-benzimidazoles occurred.[17] As was demonstrated, the laccase-catalyzed oxidation of catechols to *o*-benzoquinone can also be combined with intermolecular Diels−Alder reactions[18] or 1,4-additions of several nucleophiles.[19,20] Using 1,3-dicarbonyls as nucleophiles, several heterocycles are accessible in highly selective and efficient one-pot reactions, including 1*H*-pyrano[4,3-*b*]benzofuran-1-ones,[20g]

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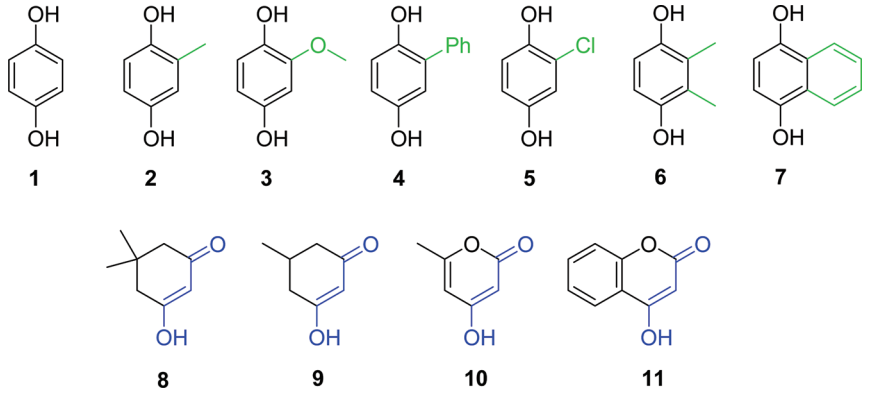

Figure 1. Hydroquinones **1**−**7** and 1,3-dicarbonyls **8**−**11** for the laccase-catalyzed domino reactions.

3,4-dihydro-dibenzofuran-1(2*H*)-ones,[20e] benzofuro[3,2-*c*]-pyridin-1(2*H*)-ones,[20b] benzofuro[3,2-*c*]quinolin-6(5*H*)-ones,[20b] 5-thiocoumestans,[20b] and polycyclic dispiropyrimidinones.[20b]

The objective of the present study was to find out whether the laccase-catalyzed oxidation of hydroquinones to *p*-benzoquinones and the 1,4-addition of 1,3-dicarbonyls to *p*-benzoquinones can be linked to provide a new reaction sequence for the functionalization of hydroquinones. This approach appeared quite promising because it is well-known that *p*-benzoquinones can be reacted with numerous *N*-,[21,22] *O*-,[21,23] *S*-,[21,22a,24] and *C*-nucleophiles,[21,25,26] though not necessarily selectively. With respect to the results presented here the available studies on transformations of *p*-benzoquinones and related compounds with 1,3-dicarbonyls are most interesting. Makosza et al. have reported on the reaction of 2-chloromalonates with 1,4-naphthoquinones to yield 2-substituted naphthoquinones,[26a] and Xu et al. have observed that the reaction of a 1,3-dicarbonyl with 2,3-dichloronaphthoquinone under basic conditions proceeds with formation of a naphtho[2,3-*b*]furan-4,9-dione as the result of a domino 1,4-addition/elimination process.[26b] An efficient procedure for the synthesis of 2,3-dihydronaphtho-[1,2-*b*]furans and related compounds has been developed by De Kimpe et al.[26c] The Yb(OTf)$_3$-catalyzed reaction starts with the conjugate addition of a *β*-ketoester to an activated naphthoquinone followed by intramolecular hemiacetal formation. A similar reaction was found by Chan et al., who reported on the Cu(OTf)$_2$-catalyzed cyclocondensation of 1,4-benzoquinones with several 1,3-diketones to give a variety of substituted 3-acyl-benzofurans.[26d] Direct reaction between hydroquinones and nucleophiles is also feasible when the *in situ* oxidation of the hydroquinone to the corresponding quinone can be performed in the presence of the corresponding nucleophile. A number of reagents, including potassium ferricyanide,[27a] copper(II) sulfate,[27b] Fenton's reagent,[27c] copper(II) acetate, silver(I) oxide,[28b] and sodium iodate,[27a,28b] have been used for the *in situ* generation of *p*-benzoquinone.

Furthermore, it has been demonstrated that the laccase-catalyzed oxidation of hydroquinones to *p*-benzoquinones can be combined with the 1,4-addition of *N*-,[28] *O*-,[29] and *S*-nucleophiles.[30] An interesting example comes from Bhalerao et al., who showed that the preparation of 1,2,4-triazolo-(4,3-b)(4,1,2)benzothiadiazine-8-ones can be achieved by reacting 4-amino-3-mercapto-1,2,4-triazoles with *p*-benzoquinone generated *in situ* by laccase-catalyzed oxidation of hydroquinone.[30a] The oxidation of hydroquinones can also be accomplished electrochemically. Nematollahi et al. have linked the electrochemical oxidation of hydroquinones to the corresponding *p*-benzoquinones with the 1,4-addition of *β*-diketones.[31] In most cases the initially formed 1,4-adducts were transformed into the corresponding benzofuran derivatives under reaction conditions. However, the combination of the laccase-catalyzed oxidation of hydroquinones and related compounds with the 1,4-addition of 1,3-dicarbonyls to the resulting *p*-quinoid systems has not yet been studied.

RESULTS AND DISCUSSION

Here we report on laccase-catalyzed reactions of hydroquinones with cyclic 1,3-dicarbonyls using aerial oxygen as the oxidant. A number of differently substituted hydroquinones, namely, the unsubstituted hydroquinone (**1**), the monosubstituted compounds methylhydroquinone (**2**), methoxyhydroquinone (**3**), phenylhydroquinone (**4**), and chlorohydroquinone (**5**), as well as the disubstituted compounds 2,3-dimethylhydroquinone (**6**) and 1,4-dihydroxynaphthalene (**7**), were chosen as substrates (Figure 1). They were reacted with the following cyclic 1,3-dicarbonyls: 5,5-dimethyl-1,3-cyclohexanedione (**8**), 5-methyl-1,3-cyclohexanedione (**9**), 4-hydroxy-6-methyl-2*H*-pyran-2-one (**10**), and 4-hydroxycoumarin (**11**).

All reactions were performed in acetate buffer (pH 4.37, 0.2 M) at room temperature employing 180 U (15 U/mg, 12 mg, 2.25 U/mL) of a commercially available laccase from *Trametes versicolor*[32] as the catalyst and air as the oxidant. The hydroquinone and the 1,3-dicarbonyl were used in a 1:2 ratio. We started with reacting hydroquinone (**1**) and 5,5-dimethyl-1,3-cyclohexanedione (**8**), which gave the 2,3-disubstituted *p*-benzoquinone **12** in 66% yield (Table 1). Apart from this bis-adduct no other product was isolated. When the reaction of **1** and **8** was run at 50 °C, the yield of **12** decreased to 40%. When the *Trametes versicolor* laccase was replaced by an *Agaricus bisporus* laccase (250 U, 5 U/mg, 50 mg, 3.13 U/mL) (phosphate buffer, 0.2 M, pH 6.00, rt, 20 h) **12** was obtained in only 20% yield after recrystallization. When the reaction of 1 equiv **1** and 2 equiv **8** was conducted in the absence of any laccase, not even a trace of the product **12** was formed. The reaction of hydroquinone (**1**) with 4-hydroxycoumarin (**11**) follows much the same course as the transformation of **1** with **8**. Here, the bis-adduct **13** was isolated in almost quantitative yield (98%) (Table 1). The structures of products **12** and **13** were unambiguously elucidated by NMR spectroscopic methods (see below).

It is assumed that the reaction sequence starts with the laccase-catalyzed oxidation of hydroquinone (**1**) to *p*-benzoquinone (**14**) and is then followed by 1,4-addition of the 1,3-dicarbonyl (**8**, **11**) to **14** (Scheme 1). Subsequent

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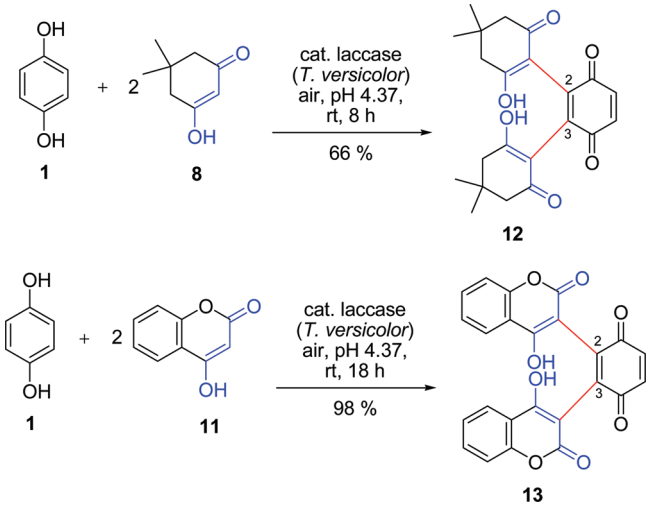
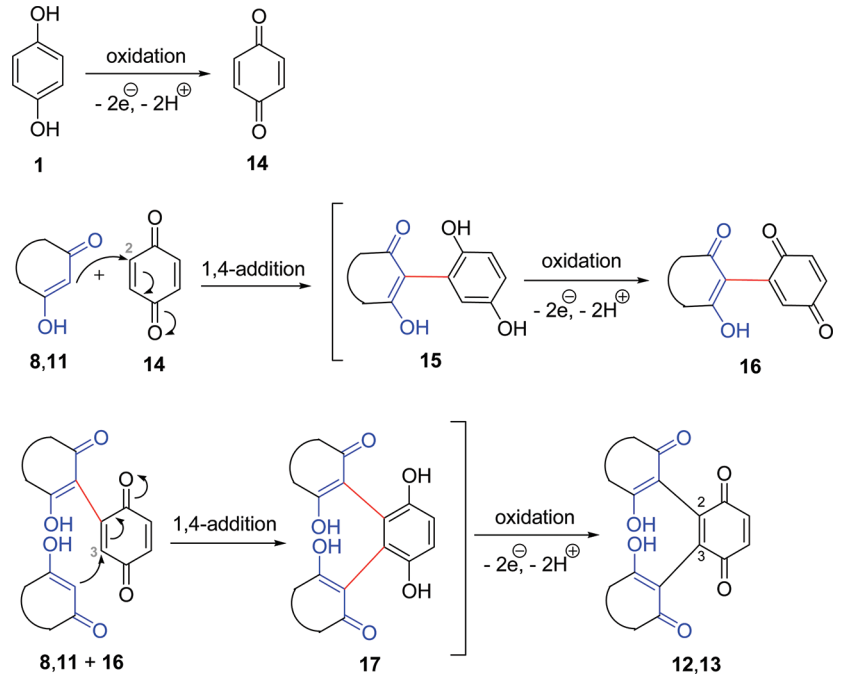
Table 1. Laccase-Catalyzed Domino Reactions of Hydroquinone (1) with 5,5-Dimethyl-1,3-cyclohexanedione (8) and 4-Hydroxycoumarin (11) for the Synthesis of 12 and 13



entry	*p*-hydroquinone	1,3-dicarbonyl	time (h)	product	yield (%)
1	**1**	**8**	8	**12**	66
2	**1**	**11**	18	**13**	98

Scheme 1. Possible Reaction Mechanism for the Reaction of Hydroquinone (1) with 1,3-Dicarbonyls 8, 11



oxidation of the resulting 2-substituted hydroquinone **15** delivers the benzoquinone **16**, which is attacked by a second molecule **8** or **11** to give **17**. The final step is an oxidation resulting in the formation of the 2,3-disubstituted *p*-benzoquinone **12**, **13**.

Notably, none of the two possible benzofuran derivatives **18** or **19** is formed (Figure 2). Instead, the exclusive formation of the noncyclized bis-adducts **12** and **13** takes place. This fact is all the more astonishing given that in most other reactions between 1,3-dicarbonyls and unsubstituted *p*-benzoquinones that have been reported products with a benzofuran skeleton are formed.[26d,31b] It is also remarkable that the reactions proceed with excellent regioselectivity: the 2,3-disubstituted

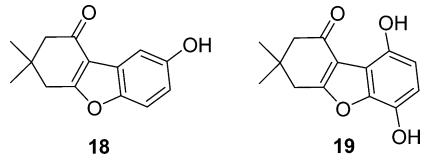


Figure 2. Benzofuran derivatives **18**, **19** as possible products of the reaction between **1** and **8**.

bis-adducts **I** are the only products, while none of the 2,5- and the 2,6-disubstituted products **II** and **III** are formed (Figure 3). The exclusive formation of the 2,3-disubstituted products **I** can be attributed to the fact that the 3-position of the

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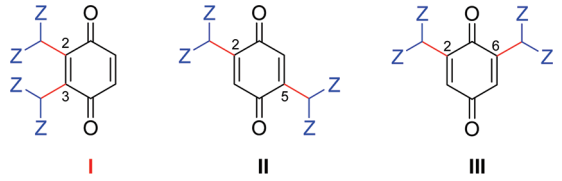


Figure 3. Possible regioisomeric products from the reaction of hydroquinone (**1**) with 1,3-dicarbonyls.

monosubstituted quinone **16** is more electron-deficient than positions 5 and 6.

As already mentioned, the bis-adducts **12** and **13** formed exclusively when the reactions of the 1,3-dicarbonyls **8**, **11** with the hydroquinone **1** were conducted in a 2:1 ratio. When the ratio of **8** and **1** was changed to 1:1, again the bis-adduct **12** was formed exclusively. However, the yield of **12** decreased from 66% to 29%.

With respect to products and product distributions, the results published so far on 1,4-additions of nucleophiles to hydroquinone/*p*-benzoquinone differ greatly.[21−31] In a number of examples, such as the reactions of *p*-benzoquinone with aniline or thiophenol, the monosubstituted *p*-benzoquinones were isolated exclusively and in very good yields.[22a,b,24a] On the other hand, there are also reactions between hydroquinone or *p*-benzoquinone, which have been reported to result in the formation of mixtures of the monoadduct and the bis-adduct. A typical example is the reaction between *p*-benzoquinone and imidazoles (1:1) leading to the formation of mixtures of the monosubstituted, the 2,3-disubstituted, and the 2,5-disubstituted product.[22d] Similar findings are known from the transformations between *p*-benzoquinone and pyrazoles.[22e] With respect to the domino processes presented here the reaction between *p*-benzoquinone electrochemically generated from hydroquinone and 2 equiv of a cyclic 1,3-dicarbonyl (3-hydroxy-1*H*-phenalen-1-one) are particular noteworthy. Under the specific reaction conditions the formation of a 2,5-disubstituted bis-adduct took place, which however could not be isolated but underwent cyclization to the corresponding benzofuran derivative.[31b] The reaction conditions seem to make a big difference: we never observed the formation of benzofuran-type products under the conditions of the laccase-catalyzed reaction.

The results of the reactions of monosubstituted hydroquinones with 1,3-dicarbonyls are summarized in Table 2. Methylhydroquinone (**2**), methoxyhydroquinone (**3**), phenylhydroquinone (**4**), and chlorohydroquinone (**5**) were chosen as monosubstituted hydroquinones and reacted with 5,5-dimethyl-1,3-cyclohexanedione (**8**), 5-methyl-1,3-cyclohexanedione (**9**), 4-hydroxy-6-methyl-2*H*-pyran-2-one (**10**), and 4-hydroxycoumarin (**11**) as the cyclic 1,3-dicarbonyls. When methylhydroquinone (**2**) was treated with 5,5-dimethyl-1,3-cyclohexandione (**8**) the 2,3,5-trisubstituted quinone **20** was formed exclusively in 75% yield (Table 2, entry 1). Obviously, the reaction proceeds with high regioselectivity, as only one out of the three possible regioisomeric bis-adducts **IV**, **V**, and **VI** is formed (Figure 4). This is in accordance to the results

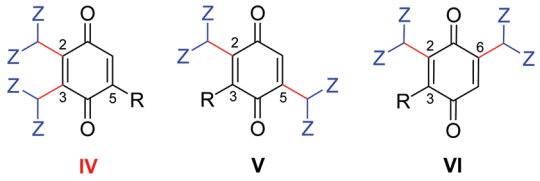
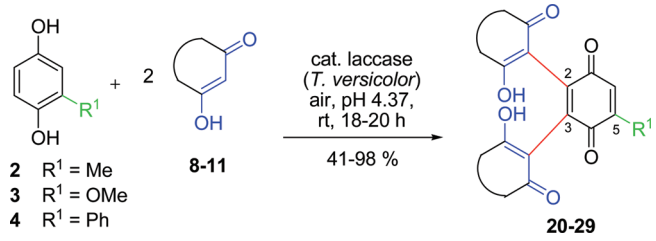


Figure 4. Possible regioisomeric products from the reaction of monosubstituted hydroquinones **2**−**4** with 1,3-dicarbonyls.

obtained with the unsubstituted hydroquinone (**8**). Again, only the regioisomer with both 1,3-dicarbonyl groups occupying positions next to each other is formed.

The reactions of methylhydroquinone (**2**) with 5-methyl-1,3-cyclohexanedione (**9**), 4-hydroxy-6-methyl-2*H*-pyran-2-one (**10**) and 4-hydroxycoumarin (**11**) also proceeded with exclusive formation of the corresponding 2,3,5-trisubstituted bis-adducts **21**-**23** (Table 2, entries 2−4). Similar results were obtained when methoxyhydroquinone (**3**) and phenylhydroquinone (**4**) were reacted with the 1,3-dicarbonyls **8**, **9**, and **11** (Table 2, entries 5−10). In all cases the selective formation of bis-adducts of type **IV**

Table 2. Laccase-Catalyzed Domino Reactions of Monosubstituted Hydroquinones 2−4 with 1,3-Dicarbonyls 8−11 for the Synthesis of 20−29



2 R^1 = Me
3 R^1 = OMe
4 R^1 = Ph

8-11

20-29

entry	*p*-hydroquinone	1,3-dicarbonyl	time (h)	product	yield (%)
1	**2**	**8**	19	**20**	75
2	**2**	**9**	19	**21**	83
3	**2**	**10**	19	**22**	41
4	**2**	**11**	20	**23**	98
5	**3**	**8**	18	**24**	55
6	**3**	**9**	19	**25**	73
7	**3**	**11**	19	**26**	44
8	**4**	**8**	19	**27**	90
9	**4**	**9**	19	**28**	63
10	**4**	**11**	20	**29**	85

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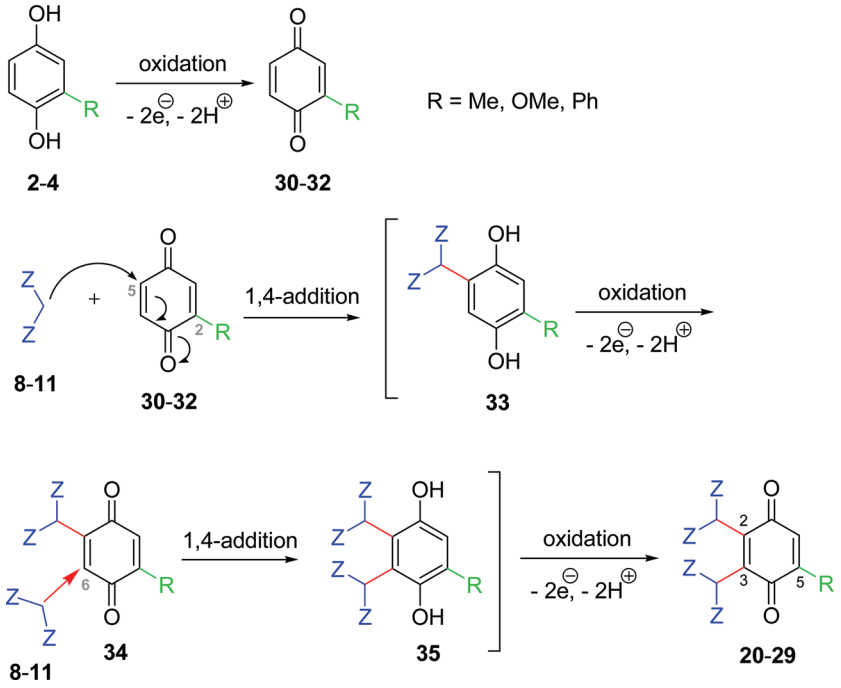
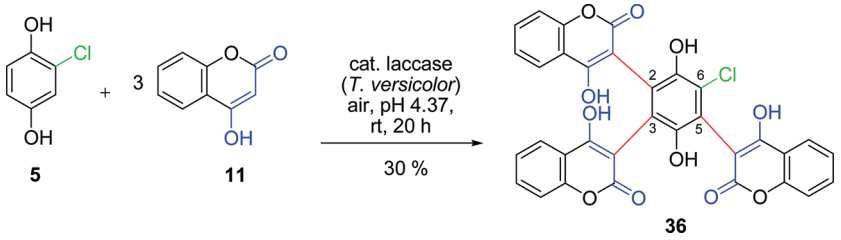
Scheme 2. Possible Reaction Mechanism for the Reaction of Monosubstituted Hydroquinones 2−4 with 1,3-Dicarbonyls 8−11



Scheme 3. Laccase-Catalyzed Domino Reaction of Chlorohydroquinone (5) with 4-Hydroxycoumarin (11) for the Synthesis of 36



took place with yields ranging from 41% to 98%. The structures of the products **20−29** were unambiguously determined by NMR spectroscopic methods (see below). Control reactions were conducted with each of the hydroquinones **2−4** (1 equiv) and **8** (2 equiv) without the laccase under standard conditions. In no case could the formation of an addition product be detected. We assume that the initial attack of the nucleophilic 1,3-dicarbonyls **8−11** takes place on C-5 of the monosubstituted quinones **30−32** (Scheme 2). The reason for its regioselectivity is that C-5 is the most electrophilic carbon atom suitable for a 1,4-addition. Subsequently, the resulting hydroquinone **33** undergoes oxidation to the corresponding 1,4-benzoquinone **34**. Next, the second 1,4-addition of a 1,3-dicarbonyl takes places with the attack occurring at C-6, which is the most electrophilic site of **34** suitable for 1,4-addition. The final oxidation delivers the 2,3,5-trisubstituted bis-adducts **20−29**.

Several studies on reactions of monosubstituted hydroquinones/quinones with nucleophiles have been published investigating, among other things, the influence of the first substituent on the course of the reaction. Furukawa et al., for example, observed that the reactions of methylquinone (2 equiv) with anilines (1 equiv) deliver mixtures of 2,5- and 2,6-disubstituted products in a 2:1 ratio.[22f] Similar results have been obtained by Lalk et al. when they studied the reactions of monosubstituted hydroquinones with *p*-aminobenzoic acid derivatives.[28a,c] From the work of Wilgus et al. who investigated reactions with 1-phenyl-5-mercaptotetrazole as the nucleophile we may conclude that the 1,4-additions of mercaptans to monosubstituted *p*-benzoquinones also proceed with low regioselectivity.[24b] The 1,4-additions of monosubstituted *p*-benzoquinones with indoles are remarkable exceptions since the 2,5-disubstituted *p*-benzoquinones are the only products being isolated.[25b,f,g] Only little is known of transformations with 1,3-dicarbonyls. It has been reported that in the reaction between electrochemically generated formyl-*p*-benzoquinone and 3-hydroxy-1*H*-phenalen-1-one starts with the formation of a 2,5-disubstituted bis-adduct, which then undergoes cyclization to the corresponding benzofuran derivative.[31b] Reactions between methylquinone and malononitrile that have been run under the conditions of a electrochemical oxidation proceed with the exclusive formation of benzofurans, too.[31c] Considering the results that have been reported on 1,4-additions of different nucleophiles to monosubstituted *p*-benzoquinones, our findings are quite notable for the selective formation of type **IV** bis-adducts.

The outcome of the reaction between 1 equiv of chlorohydroquinone (**5**) and 2 equiv of 4-hydroxycoumarin (**11**) came as a surprise (Scheme 3). Instead of the expected 1:2 adduct of type **IV** the formation of the 1:3 adduct **36** was detected. Another surprise was the exclusive formation of a

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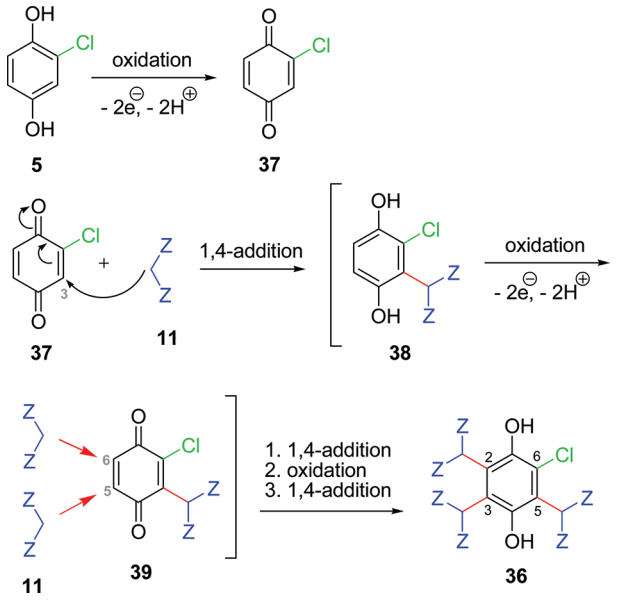
substituted hydroquinone instead of the corresponding *p*-benzoquinone. The 1:3 adduct **36** was also formed exclusively when the substrates **5** and **11** were reacted in 1:3 ratio. In this case **36** could be isolated with 30% yield. In the absence of laccase no reaction between chlorohydroquinone (**5**) and 4-hydroxycoumarin (**11**) was observed. Concerning the mechanism we assume that in the first step the addition of a 1,3-dicarbonyl occurs at C-3 of **37**, which is the most electron-deficient position available for a 1,4-addition (Scheme 4). In the

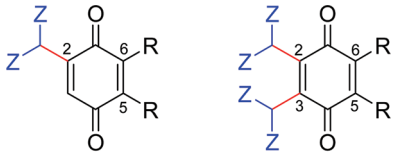
Scheme 4. Possible Reaction Mechanism for the Reaction of Chlorohydroquinone (5) with a 1,3-Dicarbonyl (11)



course of the domino process two more 1,3-dicarbonyls **11** undergo 1,4-additions to the remaining positions C-5 and C-6 of **39**.

A number of studies concerning the 1,4-addition of nucleophiles to hydroquinones/quinones carrying electron-withdrawing substituents has been reported. When the laccase-catalyzed reaction of equimolar amounts of 2-chlorohydroquinone (**5**) and *p*-aminobenzoic acid was performed, the amination took place at both C-3 and C-5, and the corresponding two monoaminated quinones were formed in yields of 38% and 15%, respectively.[28c] With hydroquinones carrying a carbonyl substituent at C-2, the laccase-catalyzed amination with *p*-aminobenzoic acid preferentially takes place at C-3.[28c] When the hydroquinone carries a carboxyl substituent at C-2, the laccase-catalyzed reaction with equimolar amounts of a *p*-aminobenzoic acid derivative occurs with double amination.[28a] Apart from the 3,6-diaminated quinone a small amount of a 3-monoaminated quinone formed. An excess of the amine can be used to suppress the formation of the monoaminated quinone. In the light of the results reported on the addition of nucleophiles to hydroquinones/quinones carrying electron-withdrawing substituents, the formation of a 1:3 adduct like **36** is quite unusual.

Finally, the reactions of 2,3-disubstituted hydroquinones were studied. When 2,3-dimethylhydroquinone (**6**) and 1,4-dihydroxynaphthalene (**7**) were reacted with the 1,3-dicarbonyls **8**–**11** the exclusive formation of bis-adducts of type **VIII** (Figure 5) with yields ranging from 39% to 92% was observed (Table 3). In no case could type **VII** monoadducts be



VII **VIII**

Figure 5. Possible products from the reaction of disubstituted hydroquinones **6**, **7** with 1,3-dicarbonyls.

isolated, meaning that the structure of the products from disubstituted hydroquinones resembles that of the products obtained from the reactions with unsubstituted and monosubstituted hydroquinones. Control reactions in the absence of laccase were conducted between **6** and **8** as well as **7** and **8**. While no product was formed when **6** and **8** were reacted, the reaction between **7** and **8** yielded product **44**. Obviously, air oxidation of 1,4-dihydroxynaphthalene (**7**) to 1,4-naphthoquinone also occurs in the absence of laccase. This is corroborated by the finding that the yields of the 1:2 adduct **44** are comparable under both reaction conditions. Although **40**–**47** display mirror image symmetry, most of the compounds produced a double set of NMR signals. This is probably due to the occurrence of rotamers (for details see Structure Elucidation by NMR).

Certainly the addition of a number of nucleophiles to 2,3-disubstituted hydroquinone/quinones and 1,4-naphthochinone, respectively, has been reported, but results vary a lot. For example, in the reactions between naphthoquinones and indoles, monoadducts are formed selectively,[25f,g] while the reactions of naphthoquinone with imidazole and benzimidazole, respectively, yield bis-adducts.[22d] In connection with the results presented here it is worth mentioning that the laccase-catalyzed reaction of 2,3-dimethylhydroquinone (**6**) with L-phenylalanine has been reported to deliver the monoadduct[28d] and that the electrochemical oxidation of 2,3-dimethylhydroquinone in the presence of 1,3-dicarbonyl compounds has been found to give monoadducts, which partly cyclize to give benzofurans.[31a]

Structure Elucidation by NMR. The preliminary analysis of the NMR and the mass spectra revealed that the laccase-catalyzed reactions between *p*-hydroquinones and 1,3-dicarbonyls exclusively produce bis-adducts made up of 1 equiv of the *p*-benzoquinone and 2 equiv of the 1,3-dicarbonyl (Tables 1–3), except for the tris-adduct **36**, which was obtained from reaction of chlorohydroquinone (**5**) with **11**. The reactions of differently substituted hydroquinones with 1,3-dicarbonyls lead to the formation of different types of regioisomeric bis-adducts. In the reactions of 2,3-disubstituted hydroquinones **6**, **7** only bis-adducts of type **VIII** (**40**–**47**) can be formed (Figure 6), and therefore the structure elucidation proved to be unproblematic. Although the reactions of the monosubstituted hydroquinones can give rise to three types of regioisomers, only the 2,3,5-trisubstituted products of type **IV** were formed (Figure 6). The structural assignment of the products **20**–**29** was straightforward. The HMBC NMR spectra of **20**–**29** show a strong $^{3}J_{H,C}$ correlation between the olefinic proton and the respective carbon of the R′-substituent of the quinone, confirming the general substitution pattern of the products. Also in the reactions of the unsubstituted hydroquinone (**1**) three regioisomeric bis-adducts, namely, the 2,3-, the 2,5-, and the 2,6-disubstituted products, can be formed (Figure 3). The proof of structure for the selectively formed

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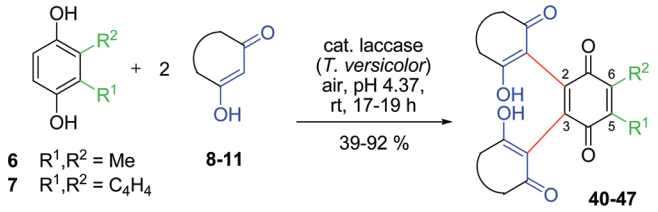
Table 3. Laccase-Catalyzed Domino Reactions of Disubstituted Hydroquinones 6, 7 with 1,3-Dicarbonyls 8−11 for the Synthesis of 40−47



entry	*p*-hydroquinone	1,3-dicarbonyl	time (h)	product	yield (%)
1	**6**	**8**	19	**40**	82
2	**6**	**9**	19	**41**	83
3	**6**	**10**	19	**42**	44
4	**6**	**11**	19	**43**	92
5	**7**	**8**	18	**44**	72
6	**7**	**9**	17	**45**	70
7	**7**	**10**	17	**46**	39
8	**7**	**11**	18	**47**	80

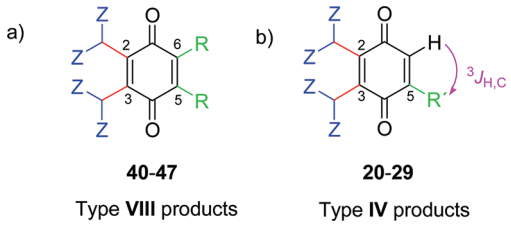


Figure 6. Possible product structures from the reaction of (a) 2,3-disubstituted hydroquinones and (b) monosubstituted hydroquinones.

products **12** and **13** by standard NMR methods turned out to be difficult as the three possible regioisomeric structures **I**−**III** are symmetrical.

The structure elucidation of most of the bis-adducts was also impeded by some additional difficulties. First of all, the ^{13}C NMR spectra of products **12**, **20**, **21**, **24**, **25**, **27**, **28**, **40**, **41**, **44** and **45** do not exhibit all of the expected signals. In particular, signals for the C═O carbons of the 1,3-dicarbonyl substituents are missing. This is probably due to oxo-enol tautomerism and complicated the signal assignment considerably. The chemical shifts of the missing C═O carbons could not even be determined indirectly in the HMBC spectra because the adjacent methylene groups appear as broad humps displaying no HMBC correlation at all. Moreover, the ^{13}C NMR spectra of the symmetrical (**12**, **13**, **40**−**47**) as well as the nonsymmetrical (**20**−**29**) reaction products exhibit a second set of NMR signals that can be attributed to the presence of at least two conformers/rotamers in solution at room temperature.

In order to establish an NMR-based assignment procedure, three model compounds, namely, 2,6-dimethylquinone (**48**), 2,5-dimethylquinone (**49**), and 2,3-dimethylquinone (**50**), were selected for comparing (a) the evaluation of the splitting pattern of the ^{13}C satellites in the ^{1}H NMR spectra of the different isomers and (b) the spin pattern analysis of the long-range coupled C═O carbons in each molecule. Different ^{13}C NMR spectra including the proton broadband decoupled ^{13}C NMR spectra, the fully ^{1}H coupled ^{13}C NMR spectra, and the methyl group protons selectively decoupled ^{13}C NMR spectra of the model compounds **48**−**50** were measured in acetone-d_6 at 75 and at 125 MHz. The latter method was applied in the case of the model compound to have conditions similar to all investigated compounds, which usually possess only a quaternary carbon at that position. The possibility of a 2,6-isomer could easily be ruled out, because in contrast to 2,5-dimethylquinone (**49**) and 2,3-dimethylquinone (**50**), in the proton broadband decoupled ^{13}C NMR spectrum of 2,6-dimethylquinone (**48**) two different signals for the C═O carbons could be observed. The proton broadband decoupled ^{13}C NMR spectra of 2,5-dimethylquinone (**49**) and 2,3-dimethylquinone (**50**) as well as the spectra of the products **12** and **13** display only one signal for the chemically equivalent C═O groups of the quinone substructure. Further arguments for the exclusion of the 2,6-isomer are the appearance of a triplet pattern ($^{3}J_{H,C}$ = 9.9 Hz) for one C═O resonance and the appearance of a broad singlet for the other C═O resonance in the ^{1}H coupled ^{13}C NMR spectrum (Me groups selectively decoupled). The triplet pattern can be explained by the $^{3}J_{H,C}$ coupling between one C═O group and the magnetically equivalent olefinic protons with a coupling constant of 9.9 Hz, and the broad singlet can be attributed to a $^{2}J_{H,C}$ coupling with a small coupling constant between the latter and the other C═O group (Figure 7).

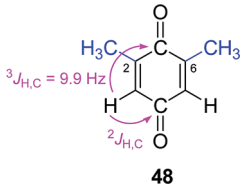


Figure 7. Observed H,C couplings in the ^{1}H coupled ^{13}C NMR spectrum (Me groups selectively decoupled) of 2,6-dimethylquinone (**48**).

The ^{1}H coupled ^{13}C NMR spectra of the other two isomers, the 2,5-dimethylquinone (**49**) and the 2,3-dimethylquinone (**50**), (with selectively decoupled methyl groups) displayed a doublet-like signal for the C═O carbon in 2,5-dimethylquinone (**49**) and a quintet-like signal for 2,3-dimethylquinone (**50**) (Figures 8 and 9; see also Figures A and B in Supporting Information, lower parts of spectra). Replacement of one

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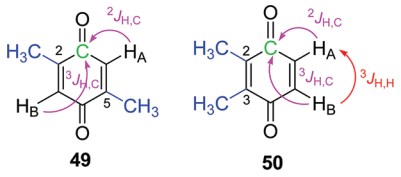


Figure 8. C═O multiplets in the ^{1}H coupled ^{13}C NMR spectra of 2,5-dimethylquinone (**49**) and 2,3-dimethylquinone (**50**) (Me groups selectively decoupled).

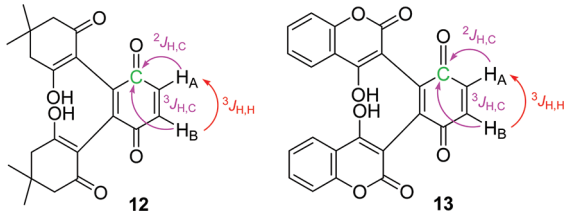


Figure 9. C═O multiplets in the ^{1}H coupled ^{13}C NMR spectra of compound **12** and **13**.

^{12}C═O by ^{13}C═O (approximately 1% natural abundance) abolishes the symmetry in both compounds resulting in an ABX spin system, where the chemical shift difference between the protons A and B corresponds to the difference between the two bond and three bond isotope shifts from the ^{13}C═O.[33] In order to extract the $^{2}J_{H,C}$ and $^{3}J_{H,C}$ coupling constants of the ^{13}C═O multiplets, the NUMMRIT approach[34] implemented in SpinWorks[35] was applied for the analysis of the ^{13}C NMR spectra of the respective isotopomers (Figures 8 and 9; see also Figures A and B in Supporting Information, upper parts of spectra).

Computational analysis of the ^{1}H coupled ^{13}C NMR spectra of compounds **12** and **13** reveals coupling constants of $J_{HA,HB} \approx 10$ Hz, $J_{HA,CO} \approx 0.2$ Hz, and $J_{HB,CO} \approx 11$ Hz for the ABX system indicating a 2,3-substitution pattern similar to the results obtained for 2,3-dimethylquinone (**50**)[36] (Table 4). As a proof of concept the NMR spectra of maleic acid (**51**), maleic acid dimethylester (**52**), and maleic anhydride (**53**) were included as additional reference compounds (see Figure C in Supporting Information), because these compounds exhibit the same substructure as 2,3-dimethylquinone (**50**) and compounds **12** and **13**.

The $J_{H,C}$ coupling constants of the ^{13}C═O multiplets from the ^{1}H coupled ^{13}C NMR spectra of the reference compounds maleic acid (**51**), maleic acid dimethyl ester (**52**) and maleic anhydride (**53**), and the products **12** and **13** obtained by iteration are also summarized in Table 4.

A fast and rapid method to confirm the 2,3-substitution pattern is based on the multiplet pattern analysis of the outer ^{13}C satellite signals of the olefinic protons in the ^{1}H NMR spectra of the compounds in question. In the case of a compound with a 2,3-substitution pattern [**12**, **13**, 2,3-dimethylquinone (**50**), and the maleic acid derivatives **51**–**53**], a doublet with a typical vicinal $^{3}J_{H,H}$ of 10 Hz was observed, whereas only small long-range coupling constants were detected in the case of 2,6-disubstituted compounds [e.g., 2,6-dimethylquinone (**48**), $^{4}J_{H,H} = 0.4$ Hz] or 2,5-disubstituted compounds [e.g., 2,5-dimetylquinone (**49**), $^{5}J_{H,H} = 0.1$ Hz] (Figures 10 and 11; see also Figures D–F in Supporting Information). Summarizing all of these observations, the structures of **12** and **13** are unambiguously assigned as the 2,3-isomer.

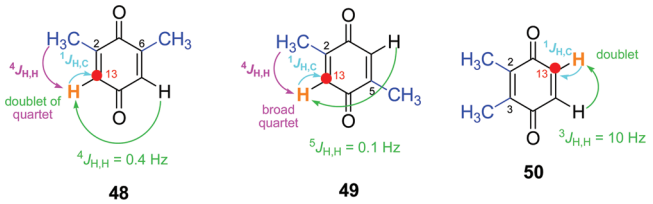


Figure 10. Splitting of the outer ^{13}C satellite signals of the olefinic protons in the ^{1}H NMR spectrum of 2,6-dimethylquinone (**48**), 2,5-dimethylquinone (**49**), and 2,3-dimethylquinone (**50**).

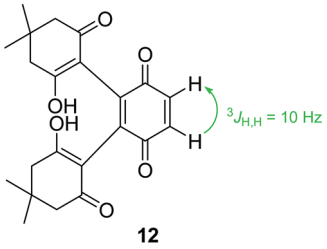
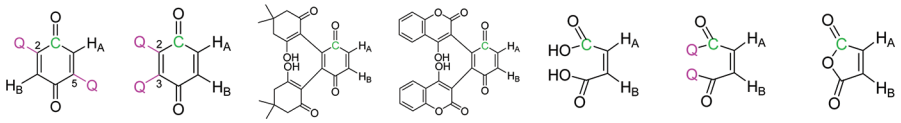


Figure 11. Splitting of the outer ^{13}C satellite signals of the olefinic protons in the ^{1}H NMR spectrum of compound **12**.

In order to address the occurrence of a second set of carbon resonances in the ^{13}C NMR spectra of the analytes, high temperature measurements in different NMR solvents were performed. As an example, the vinylic proton of the 1,3-dicarbonyl moiety of **42** gives rise to two singlets in the ^{1}H NMR spectra recorded in DMSO-d_6 (ratio of the two singlets ~1:1) and acetone-d_6 (ratio of the two singlets ~2:1). This suggests an equilibrium mixture of at least two conformers/rotamers in solution at room temperature. Therefore, compound **42** was heated stepwise from 25 to 120 °C, and ^{1}H NMR spectra were measured in DMSO-d_6 at defined intervals. At the coalescence point of ~120 °C both singlets coalesce into a single signal. This demonstrates that the molecules in question form equilibrium

Table 4. Coupling Constants for ABX Spin System by SpinWorks Analysis



coupling constants [Hz]	2,5-dimethylquinone (**49**)	2,3-dimethylquinone (**50**)	**12**	**13**	maleic acid (**51**)	maleic acid dimethyl ester (**52**)	maleic anhydride (**53**)
HA, HB	0.1	9.9	9.9	10.4	12.0	11.9	5.7
HA, CO	0.2	0.1	0.3	0.2	2.4	2.6	7.7
HB, CO	9.8	11.1	11.1	11.4	13.0	13.3	14.6

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mixtures of isomers at room temperature (Figure G in Supporting Information).

CONCLUSIONS

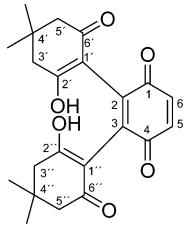
The laccase-catalyzed transformations between differently substituted hydroquinones and 1,3-dicarbonyls offer a new and highly selective access to quinones with two adjacent 1,3-dicarbonyl substituents. The new method makes use of aerial oxygen as the oxidant and proceeds under mild reaction conditions. It can be interpreted as a domino oxidation/1,4-addition/oxidation/1,4-addition/oxidation process. The substitution pattern of the resulting quinones strongly depends on the structure of the hydroquinones employed as substrates. With the unsubstituted hydroquinone as starting material the 2,3-disubstituted *p*-benzoquinones were formed exclusively with yields ranging from 66% to 98%. Also with monosubstituted hydroquinones such as 2-methylhydroquinone, 2-methoxyhydroquinone, and 2-phenylhydroquinone as the substrates only the bis-adducts with two adjacent 1,3-dicarbonyl substituents were formed. The 2,3,5-trisubstituted *p*-benzoquinones were obtained with yields ranging from 41% to 98%. The only exception is the reaction of 2-chlorohydroquinone with 4-hydroxycoumarin, which delivers the 2,3,5,6-tetrasubstituted hydroquinone as the sole product. When 2,3-disubstituted hydroquinones were employed as substrates the 2,3,5,6-tetrasubstituted bis-adducts were the only products. They were isolated in yields ranging from 39% to 92%. The selective transformation of hydroquinones into quinones presented here is a new example for a highly selective laccase-catalyzed oxidative domino process. Another remarkable feature is that the products of the laccase-catalyzed reactions between hydroquinones and 1,3-dicarbonyls differ from the products obtained under electrochemical conditions. In this respect, the present study emphasizes the growing importance of laccases as catalysts in organic transformations in a particular manner.

EXPERIMENTAL SECTION

General Experimental Section. Chemicals, solvents, and the laccase from *Trametes versicolor* are commercially available. Melting points are uncorrected. Analytical thin layer chromatography was performed on precoated silica gel F_{245} aluminum plates with visualization under UV light and by staining using vanillin reagent. IR spectra were recorded using an ATR instrument. Mass spectra and high resolution mass spectra were recorded using the ESI method. NMR spectra were recorded on a 300 or 500 MHz instrument. The ^{1}H and ^{13}C chemical shifts were referenced to residual solvent signal at $\delta_{H/C}$ 2.52/40.23 ppm (DMSO-d_6) or 2.05/29.8 ppm (acetone-d_6) relative to TMS. All 1D NMR (^{1}H,^{13}C) and 2D NMR (COSY, HSQC, HMBC) measurements were performed using standard pulse sequences. LSPD: ^{13}C NMR modified for selective long-range proton decoupling during acquisition with low power decoupling corresponding to $\gamma B_2 \approx 30$ Hz. * means ambiguous assignment of NMR Data.

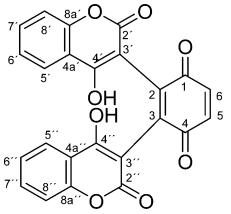
General Procedure for the Laccase-Catalyzed Domino Reaction. A solution of hydroquinone (1 mmol) and 1,3-dicarbonyl (2 mmol) in 0.2 M acetate buffer (80 mL) (pH 4.37) was placed in a 250 mL Erlenmeyer flask. Laccase from *Trametes versicolor* (12 mg) (15 U/mg)[32] was added, and the mixture was vigorously stirred in air at room temperature overnight (17–20 h). The reaction mixture was saturated with solid NaCl and filtered with suction using a Büchner funnel. The filter cake obtained was washed with aq NaCl (15%, 20 mL) and H_2O (5 mL). When no solid product was formed, the reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude products obtained exhibit a purity of at least 90% (NMR). Analytically pure products were obtained by recrystallization.

*2,3-Bis(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)cyclohexa-2,5-diene-1,4-dione (**12**).*



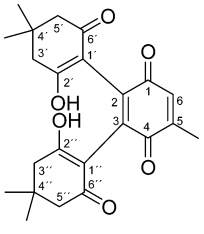
Reaction of **1** (110 mg, 1 mmol) and **8** (280 mg, 2 mmol) according to the general procedure for 8 h gave **12** as an orange solid in 66% yield (253 mg, 0.7 mmol): mp 199–202 °C (CH_2Cl_2); R_f = 0.36 (MeOH/CH_2Cl_2 = 1:9); IR (ATR)$\tilde{\nu}$ 2870, 2550, 1651, 1566 1388, 1343, 1309, 1255, 1154, 1031, 838 cm^{-1}; UV (MeOH) λ_{max} (log ε) 243 nm (4.62); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.98 (s, 6H, CH_3), 1.05 (s, 6H, CH_3), 2.00–2.23 (m, 8H, CH_2), 6.84 ppm (s, 2H, 5-H and 6-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.4 (CH_3), 29.1 (CH_3), 32.2 (C-4′ and C-4″), 47.4 (CH_2), 110.0 (C-1′ and C-1″), 137.4 (C-5 and C-6), 142.9 (C-2 and C-3), 186.2 ppm (C-1 and C-4); MS (ESI) *m*/*z* (%) 769.3 (100) [2M + H]$^+$, 523.2 (16), 385.2 (37) [M + H]$^+$; HRMS calcd for $C_{22}H_{24}O_6$ (384.1573), found 384.1570.

*2,3-Bis(4-hydroxy-2-oxo-2H-chromen-3-yl)cyclohexa-2,5-diene-1,4-dione (**13**).*



Reaction of **1** (110 mg, 1 mmol) and **11** (324 mg, 2 mmol) according to the general procedure for 18 h gave **13** as an orange solid in 98% yield (419 mg, 1 mmol): mp >340 °C (CH_2Cl_2); R_f 0.07 (MeOH/CH_2Cl_2 = 1:9); IR (ATR) $\tilde{\nu}$ 2972, 1663, 1599, 1553, 1515, 1298, 1216, 1103, 825, 754 cm^{-1}; UV (MeOH) λ_{max} (log ε) 213 (4.59), 304 nm (4.13); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.05 (s, 2H, 5-H and 6-H), 7.27 (t, *J* = 8.1 Hz, 4H, arom), 7.55 (dt, *J* = 7.5 Hz, 1.5 Hz, 2H, 7′-H and 7″-H), 7.86 ppm (dd, *J* = 8.1 Hz, 1.5 Hz, 2H, 5′-H and 5″-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 98.5 (C-3′ and C-3″), 116.6 (arom), 119.9 (C-4a′ and C-4a″), 124.1 (arom), 125.2 (C-5′ and C-5″), 132.6 (C-7′ and C-7″), 137.9 (C-5 and C-6), 143.0 (C-2 and C-3), 153.6 (C-8a′ and C-8a″), 161.9 (C-2′ and C-2″), 169.0 (C-4′ and C-4″), 186.5 ppm (C-1 and C-4); MS (ESI) *m*/*z* (%) 451.0 (100) [M + Na]$^+$, 301.1 (20), 284.1 (19), 139.0 (62); HRMS calcd for $C_{24}H_{12}O_8$ (428.0532), found 428.0524.

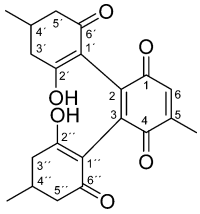
*2,3-Bis(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-5-methylcyclohexa-2,5-diene-1,4-dione (**20**).*



dx.doi.org/10.1021/jo202082v | *J. Org. Chem.* 2012, 77, 445–459

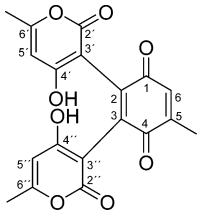
Reaction of **2** (124 mg, 1 mmol) and **8** (280 mg, 2 mmol) according to the general procedure for 19 h gave **20** as a yellow solid in 75% yield (293 mg, 0.7 mmol): mp 218−219 °C (CH_2Cl_2); R_f 0.31 (MeOH/CH_2Cl_2 = 1:9); IR (ATR) $\tilde{\nu}$ 2959, 2555, 1652, 1567, 1386, 1342, 1309, 1256, 1149, 1028, 883, 793, 708 cm^{-1}; UV (MeOH) λ_{max} (log ε) 253 nm (4.50); ^1H NMR (300 MHz, DMSO-d_6) δ 0.98 (s, 6H, CH_3), 1.06 (s, 6H, CH_3), 1.99 (s, 3H, CH_3 on C-5), 2.06−2.28 (m, 8H, CH_2), 6.71 ppm (s, 1H, 6-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.4 (CH_3 on C-5), 27.6, 27.7, 28.2, 28.4 (CH_3), 31.4, 31.5 (C-4′ and C-4″), 47.0 (CH_2), 109.3, 109.6 (C-1′ and C-1″), 133.2 (C-6), 142.0 (C-2 and C-3), 145.1 (C-5), 185.4, 185.5 ppm (C-1 and C-4); MS (ESI) *m*/*z* (%) 421.2 (100) $[M + Na]^+$, 399.2 (61) $[M + H]^+$; HRMS calcd for $C_{23}H_{26}O_6$ (398.1729), found 398.1726.

*2,3-Bis(2-hydroxy-4-methyl-6-oxocyclohex-1-enyl)-5-methylcyclohexa-2,5-diene-1,4-dione (**21**).*



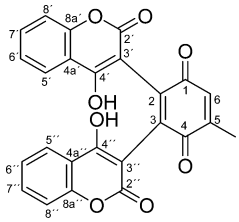
Reaction of **2** (124 mg, 1 mmol) and **9** (252 mg, 2 mmol) according to the general procedure for 19 h gave **21** as an orange solid in 83% yield (306 mg, 0.8 mmol): mp 198−199 °C (CH_2Cl_2); R_f 0.29 (MeOH/CH_2Cl_2 = 1:9); IR (ATR) $\tilde{\nu}$ 2879, 2569, 1652, 1570, 1397, 1327, 1254, 1024 cm^{-1}; UV (MeOH) λ_{max} (log ε) 255 nm (4.52); ^1H NMR (300 MHz, DMSO-d_6) δ 0.98 (d, 3H, CH_3), 1.02 (d, 3H, CH_3), 1.98 (s, 3H, CH_3 on C-5), 2.04−2.43 (m, 10H, CH_2, CH), 6.70 ppm (s, 1H, 6-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 16.2 (CH_3 on C-5), 20.8, 21.2 (CH_3 on C-4′ and C-4″), 27.8, 28.0, 28.6, 28.7 (CH, CH_2), 110.9 (C-1′ and C-1″), 133.9 (C-6), 142.6, 142.7, 142.8, 142.9 (C-2 and C-3), 145.8, 145.9 (C-5), 186.0, 186.2 ppm (C-1 and C-4); MS (ESI) *m*/*z* (%) 393.1 (100) $[M + Na]^+$, 371.2 (14) $[M + H]^+$; HRMS calcd for $C_{21}H_{22}O_6$ (370.1416), found 370.1411.

*2,3-Bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-5-methylcyclohexa-2,5-diene-1,4-dione (**22**).*



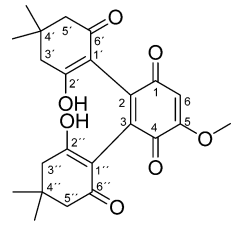
Reaction of **2** (124 mg, 1 mmol) and **10** (252 mg, 2 mmol) according to the general procedure for 19 h gave **22** as a yellow solid in 17% yield after recrystallization (63 mg, 0.2 mmol): mp 236−238 °C (CH_2Cl_2); R_f 0.1 (MeOH/CH_2Cl_2 = 1:9); IR (ATR) $\tilde{\nu}$ 3082, 2681, 1652, 1579, 1447, 1415, 1354, 1258, 1225, 1170, 1087, 994, 806 cm^{-1}; UV (MeOH) λ_{max} (log ε) 202 (4.53), 262 (4.20), 287 nm (4.17); ^1H NMR (300 MHz, DMSO-d_6) δ 2.04 (s, 3H, CH_3 on C-5), 2.17 (s, 6H, CH_3), 5.96, 5.98 (s, 2H, 5′-H and 5″-H), 6.84 ppm (s, 1H, 6-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 16.2 (CH_3 on C-5), 20.1 (CH_3), 96.7, 96.8, 96.9, 97.0 (C-3′ and C-3″), 100.6, 100.7 (C-5′ and C-5″), 134.0 (C-6), 140.8, 140.9 (C-2 and C-3), 146.4 (C-5), 161.7, 161.8, 162.3, 162.9, 163.0, 163.03 (C-4′, C-4″, C-6′ and C-6″), 167.05, 167.1, 167.3, 167.4 (C-2′ and C-2″), 185.4, 185.6, 185.7 ppm (C-1 and C-4); MS (ESI) *m*/*z* (%) 393.1 (100) $[M + Na]^+$, 371.1 (15) $[M + H]^+$; HRMS calcd for $C_{19}H_{14}O_8$ (370.0689), found 370.0685.

*2,3-Bis(4-hydroxy-2-oxo-2H-chromen-3-yl)-5-methylcyclohexa-2,5-diene-1,4-dione (**23**).*



Reaction of **2** (124 mg, 1 mmol) and **11** (324 mg, 2 mmol) according to the general procedure for 20 h gave **23** as an orange solid in 98% yield (432 mg, 1 mmol): mp 277−278 °C (MeOH); R_f 0.08 (MeOH/CH_2Cl_2 = 1:9) IR (ATR) $\tilde{\nu}$ 3076, 1657, 1599, 1556, 1259, 1241, 1215, 1162, 1096, 783, 765 cm^{-1}; UV (MeOH) λ_{max} (log ε) 205 (4.31), 264 nm (3.89); ^1H NMR (300 MHz, DMSO-d_6) δ 2.11 (s, 3H, CH_3 on C-5), 6.95 (bs, 1H, 6-H), 7.29 (d, *J* = 8.4 Hz, 2H, 8′-H and 8″-H), 7.36 (t, *J* = 7.5 Hz, 2H, 6′-H and 6″-H), 7.64 (t, *J* = 7.7 Hz, 2H, 7′-H and 7″-H), 7.88 ppm (d, *J* = 7.8 Hz, 2H, 5′-H and 5″-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 16.4 (CH_3), 98.3, 98.6 (C-3′ and C-3″), 116.6 (C-8′ and C-8″), 116.9 (C-4a′ and C-4a″), 124.6 (C-5′ and C-5″), 124.9 (C-6′ and C-6″), 133.7 (C-7′ and C-7″), 133.8 (C-6), 141.2, 141.5 (C-2 and C-3), 146.5 (C-5), 153.2 (C-8a′ and C-8a″), 160.6 (C-2′ and C-2″), 163.46, 163.5 (C-4′ and C-4″), 185.2, 185.5 ppm (C-1 and C-4); MS (ESI) *m*/*z* (%) 465.1 (100) $[M + Na]^+$; HRMS calcd for $C_{25}H_{14}O_8$ (442.0689), found 442.0683.

*2,3-Bis(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-5-methoxycyclohexa-2,5-diene-1,4-dione (**24**).*



Reaction of **3** (140 mg, 1 mmol) and **8** (280 mg, 2 mmol) according to the general procedure for 18 h gave **24** as a yellow solid in 55% yield (229 mg, 0.6 mmol): mp 237−240 °C (CH_2Cl_2); R_f 0.23 (MeOH/CH_2Cl_2 = 1:9); IR (ATR) $\tilde{\nu}$ 2958, 2571, 1674, 1639, 1598, 1565, 1386, 1336, 1310, 1258, 1216, 1153, 1030, 1001, 845, 734 cm^{-1}; UV (MeOH) λ_{max} (log ε) 202 (4.17), 256 nm (4.46); ^1H NMR (300 MHz, DMSO-d_6) δ 0.97 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.05−2.29 (m, 8H, CH_2), 3.80 (s, 3H, OCH_3), 6.07 ppm (s, 1H, 6-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.4, 29.3 (CH_3), 32.25, 32.3 (C-4′ and C-4″), 47.3 (CH_2), 57.0 (OCH_3), 108.3 (C-6), 109.9, 110.3 (C-1′ and C-1″), 140.8 (C-2), 143.4 (C-3), 159.4 (C-5), 180.8 (C-1), 186.1 ppm (C-4); MS (ESI) *m*/*z* (%) 437.2 (38) $[M + Na]^+$, 415.2 (100) $[M + H]^+$; HRMS calcd for $C_{23}H_{26}O_7$ (414.1679), found 414.1675.

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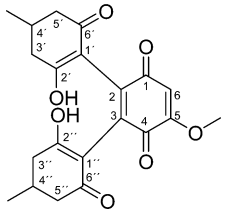
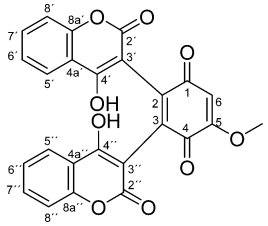
*2,3-Bis(2-hydroxy-4-methyl-6-oxocyclohex-1-enyl)-5-methoxycyclohexa-2,5-diene-1,4-dione (**25**).*



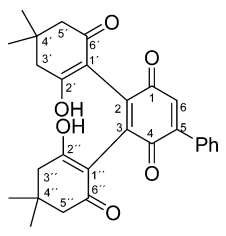
Reaction of **3** (140 mg, 1 mmol) and **9** (232 mg, 2 mmol) according to the general procedure for 19 h gave **25** as an orange solid in 73% yield (282 mg, 0.7 mmol): mp 198−199 °C (CH_2Cl_2); R_f 0.20 (MeOH/CH_2Cl_2 = 1:9); IR (ATR) $\tilde{\nu}$ 2959, 1676, 1643, 1590, 1332, 1254, 1221, 1144, 1026, 987, 841 cm^{-1}; UV (MeOH) λ_{max} (log ε) 242 nm (4.62); ^1H NMR (300 MHz, DMSO-d_6) δ 0.95 (d, J = 6.6 Hz, 3H, CH_3), 0.98 (d, J = 6.6 Hz, 3H, CH_3), 1.89−2.49 (m, 10H, CH, CH_2), 3.77 (s, 3H, OCH_3), 6.03 ppm(s, 1H, 6-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.8, 21.2, 21.3, 21.8 (CH_3), 27.8, 28.0, 28.6, 28.7 (CH_2), 41.7 (C-4′ and C-4″), 56.8 (OCH_3), 108.2 (C-6), 110.6 (C-1′ and C-1″), 140.6, 140.8, 140.9 (C-2), 143.2, 143.3, 143.4, 143.5 (C-3), 159.2, 159.24 (C-5), 180.5, 180.54 (C-1), 185.87, 185.9, 186.0 ppm (C-4); MS (ESI) m/z (%) 409.1 (100) $[M + Na]^+$, 387.1 (32), 231.0 (15); HRMS calcd for $C_{21}H_{22}O_7$ (386.1366), found 386.1358.

*2,3-Bis(4-hydroxy-2-oxo-2H-chromen-3-yl)-5-methoxycyclohexa-2,5-diene-1,4-dione (**26**).*



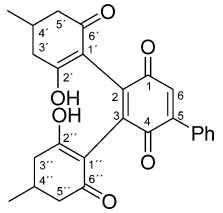
Reaction of **3** (140 mg, 1 mmol) and **11** (324 mg, 2 mmol) according to the general procedure for 19 h gave **26** as a brown solid in 44% yield (202 mg, 0.4 mmol): mp 281−284 °C (CH_2Cl_2); R_f 0.06 (MeOH/CH_2Cl_2 = 1:9); IR (ATR) $\tilde{\nu}$ 3357, 1678, 1645, 1600, 1556, 1513, 1456, 1425, 1232, 1203, 1171, 1106, 1006, 760 cm^{-1}; UV (MeOH) λ_{max} (log ε) 208 (4.57), 272 nm (4.21); ^1H NMR (300 MHz, DMSO-d_6) δ 3.87 (s, 3H, OCH_3), 6.29 (s, 1H, 6-H), 7.26 (m, 4H, 8′-H, 6′-H, 8″-H and 6″-H), 7.54 (t, J = 7.8 Hz, 2H, 7′-H and 7″-H), 7.86 ppm (d, J = 7.8 Hz, 2H, 5′-H and 5″-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 57.2 (OCH_3), 98.1, 99.0 (C-3′ and C-3″), 108.9 (C-6), 116.6 (C8′ and C-8″), 119.8, 120.0 (C-4a′ and C-4a″), 124.10, 124.14 (C-6′ and C-6″), 125.17, 125.25 (C-5′ and C-5″), 132.6 (C-7′ and C-7″), 141.1 (C-2), 143.1 (C-3), 153.59, 153.62 (C-8a′ and C-8a″), 159.5 (C-5), 161.8, 161.9 (C-2′ and C-2″), 168.5, 169.3 (C-4′ and C-4″), 181.2 (C-1), 186.1 ppm (C-4); MS (EI, 70 eV) m/z (%) 458.1 (100) $[M]^+$, 373.0 (33), 310.0 (23); HRMS calcd for $C_{25}H_{14}O_9$ (458.0638), found 458.0638.

*2,3-Bis(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-5-phenylcyclohexa-2,5-diene-1,4-dione (**27**).*



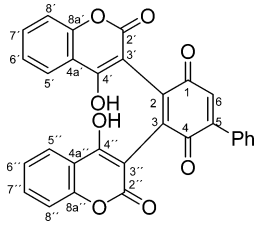
Reaction of **4** (186 mg, 1 mmol) and **8** (280 mg, 2 mmol) according to the general procedure for 19 h gave **27** as a yellow solid in 90% yield (414 mg, 0.9 mmol): mp 157−159 °C (CH_2Cl_2); R_f 0.44 (MeOH/CH_2Cl_2 = 1:9) IR (ATR) $\tilde{\nu}$ 3187, 2960, 1657, 1597, 1399, 1368, 1337, 1275, 1241, 1210, 1117, 732, 712, 695 cm^{-1}; UV (MeOH) λ_{max} (log ε) 243 nm (4.59); ^1H NMR (300 MHz, DMSO-d_6) δ 1.00 (s, 6H, CH_3), 1.07 (s, 6H, CH_3), 2.10−2.40 (m, 8H, CH_2), 6.93 (s, 1H, 6-H), 7.45−7.53 ppm (m, 5H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.3, 28.4, 29.1, 29.2 (CH_3), 32.2, 32.25 (C-4′ and C-4″), 47.5 (CH_2), 110.0, 110.6 (C-1′ and C-1″), 129.0, 129.9, 130.2 (Ph), 133.1 (C-6), 134.3 (Ph C to C-5), 142.3 (C-3), 143.4, 146.3 (C-2 and C-5), 185.5 (C-4), 186.0 ppm (C-1); MS (ESI) m/z (%) 483.2 (96) $[M + Na]^+$, 461.2 (100) $[M + H]^+$; HRMS calcd for $C_{28}H_{28}O_6$ (460.1886), found 460.1882.

*2,3-Bis(2-hydroxy-4-methyl-6-oxocyclohex-1-enyl)-5-phenylcyclohexa-2,5-diene-1,4-dione (**28**).*



Reaction of **4** (186 mg, 1 mmol) and **9** (252 mg, 2 mmol) according to the general procedure for 19 h gave **28** as a green solid in 63% yield (271 mg, 0.6 mmol): mp 189−191 °C (TBME); R_f 0.39 (MeOH/CH_2Cl_2 = 1:9); IR (ATR) $\tilde{\nu}$ 2959, 2660, 2342, 1646, 1584, 1360, 1257, 1225, 1031 cm^{-1}; UV (MeOH) λ_{max} (log ε) 242 nm (4.60); ^1H NMR (300 MHz, DMSO-d_6) δ 1.00 (d, 3H, CH_3), 1.03 (d, 3H, CH_3), 1.90−2.50 (m, 10H, CH, CH_2), 6.92 (s, 1H, 6-H), 7.46−7.50 ppm (m, 5H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.5*, 20.6* (CH_3), 27.2*, 28.0* (CH_2), 128.2, 129.2, 129.4 (Ph), 132.4 (C-6), 133.6 (Ph C to C-5), 141.8* (C-3), 142.7* (C-2), 145.5 (C-5), 184.6*, 185.15* ppm (C-1 and C-4); MS (ESI) m/z (%) 455.2 (100) $[M + Na]^+$, 433.2 (11) $[M + H]^+$; HRMS calcd for $C_{26}H_{24}O_6$ (432.1573), found 432.1567.

*2,3-Bis(4-hydroxy-2-oxo-2H-chromen-3-yl)-5-phenylcyclohexa-2,5-diene-1,4-dione (**29**).*

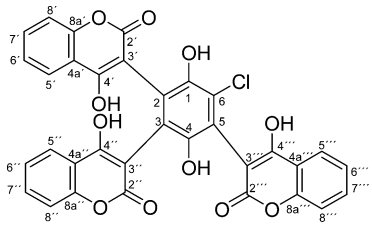


Reaction of **4** (186 mg, 1 mmol) and **11** (324 mg, 2 mmol) according to the general procedure for 20 h gave **29** as a yellow solid in 85% yield (429 mg, 0.9 mmol): mp 290−292 °C (MeOH); R_f 0.17 (MeOH/CH_2Cl_2 = 1:9); IR (ATR) $\tilde{\nu}$ 3050, 1669, 1654, 1600, 1563, 1499, 1272, 1203, 1168, 1101, 898, 771, 753, 703, 687, 671 cm^{-1}; UV (MeOH) λ_{max} (log ε) 202 (4.36), 281 nm (3.77); ^1H NMR (300 MHz, DMSO-d_6) δ 7.19 (s, 1H, 6-H), 7.30 (dd, J = 1.8 Hz, 5.1 Hz, 2H, 8′-H and 8″-H), 7.37 (t, J = 4.8 Hz, 2H, 6′-H and 6″-H), 7.51−7.53, 7.62−7.66 (m, 5H, Ph), 7.65* (t?, 2H, 7′-H and 7″-H), 7.92 ppm (dt?, 2H, 5′-H and 5″-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 98.1, 98.7 (C-3′ and C-3″), 116.6 (C-4a′ and C-4a″), 116.9 (C-8′ and

dx.doi.org/10.1021/jo202082v | J. Org. Chem. 2012, 77, 445−459

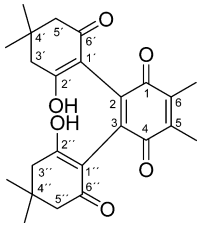
C-8″), 124.7 (C-5′ and C-5″), 125.0 (C-6′ and C-6″), 129.06, 129.14, 130.0, 130.1, 130.4 (Ph), 133.1 (C-6), 133.8 (C-7′ and C-7″), 134.2 (Ph C to C-5), 141.3 (C-3), 141.8 (C-2), 146.7 (C-5), 153.2 (C-8a′ and C-8a″), 160.7 (C-2′ and C-2″), 163.7 (C-4′ and C-4″), 184.3, 185.1 ppm (C-1 and C-4); (MS (ESI) m/z (%) 527.1 (100) $[M + Na]^+$; HRMS calcd for $C_{30}H_{16}O_8$ (504.0845), found 504.0839.

*2,3,5-Tris(4-hydroxy-2-oxo-2H-chromen-3-yl)-6-chloro-1,4-dihydroxybenzene (**36**).*



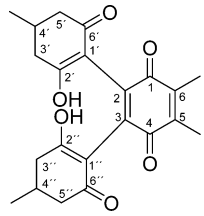
A solution of chlorohydroquinone (**5**) (144 mg, 1 mmol) and 4-hydroxycoumarin (**11**) (486 mg, 3 mmol) in 0.2 M acetate buffer (80 mL) (pH 4.37) was placed in a 250 mL flask. Laccase from *Trametes versicolor* (12 mg) (15 U/mg)[32] was added, and the mixture was vigorously stirred under air at room temperature for 20 h. The reaction mixture was saturated with NaCl and filtered with suction on a Büchner funnel. The filter cake was washed with aq NaCl (15%, 20 mL) and H_2O (5 mL). An analytically pure sample of **36** was obtained by recrystallization from MeOH (187 mg, 30%, white solid): mp 317−318 °C; R_f 0.06 (MeOH/CH_2Cl_2 = 1:9); IR (ATR) $\tilde{\nu}$ 3225, 1682, 1651, 1612, 1570, 1547, 1497, 1426, 1260, 1219, 1192, 1165, 1147, 1107, 1059, 753 cm^{-1}; UV (MeOH) λ_{max} (log ε) 216 (4.77), 284 (4.38), 310 nm (4.46); ^1H NMR (500 MHz, DMSO-d_6) δ 7.21 (s, 1H, 8′-H or 8″-H), 7.23 (s, 1H, 8′-H or 8″-H), 7.31 (t, J = 7.5 Hz, 1H, 6′-H or 6″-H), 7.33 (t, J = 8.0 Hz, 1H, 6′-H or 6″-H), 7.40 (t, J = 7.5 Hz, 1H, 6‴-H), 7.43 (d, J = 8.0 Hz, 1H, 8‴-H), 7.56 (dt, J = 8.0 Hz, J = 1.5 Hz, 1H, 7′-H or 7″-H), 7.57 (dt, J = 8.0 Hz, J = 1.5 Hz, 1H, 7′-H or 7″-H), 7.69 (dt, J = 7.5 Hz, J = 1.5 Hz, 1H, 7‴-H), 7.82 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H, 5′-H or 5″-H), 7.927 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H, 5′-H or 5″-H), 7.934 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H, 5‴-H), 8.37 (s, 1H, OH on C-4‴), 8.62 (bs, 1H, OH on C-1 or C-4), 10.20 (s, 1H, OH on C-4′ or C-4″), 10.95 (s, 1H, OH on C-4′ or C-4″), 12.0 ppm (bs, 1H, OH on C-1 or C-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ 99.8 (C-3‴), 100.1, 100.5 (C-3′ and C-3″), 115.9, 116.0, 116.1, 116.2 (C-8′, C-8″, C-8‴, C-4a′, C-4a″ and C-4a‴), 116.8, 118.8, 119.4 (C-2, C-3 and C-5), 123.5, 123.6, 123.67, 123.72, 123.75, 123.9, 124.0 (C-5′, C-5″, C-5‴, C-6′, C-6″, C-6‴ and C-6), 132.1 (C-7′ and C-7″), 132.5 (C-7‴), 146.0, 148.5 (C-1 and C-4), 152.5, 152.6 (C-8a′ and C-8a″), 152.9 (C-8a‴), 160.7, 161.0, 161.3, 161.6, 161.7, 162.5 ppm (C-2′, C-2″, C-2‴, C-4′, C-4″ and C-4‴); MS (ESI) m/z (%) 647.1 (100) $[M + Na]^+$, 625.1 (31) $[M + H]^+$; HRMS calcd for $C_{33}H_{17}O_{11}Cl$ (624.0459), found 624.0455.

*2,3-Bis(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-5,6-dimethylcyclo-hexa-2,5-diene-1,4-dione (**40**).*



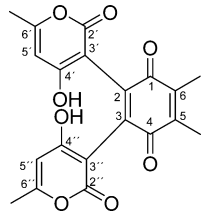
Reaction of **6** (138 mg, 1 mmol) and **8** (280 mg, 2 mmol) according to the general procedure for 19 h gave **40** as a yellow solid in 82% yield (339 mg, 0.8 mmol): mp 200−205 °C (CH_2Cl_2); R_f 0.44 (MeOH/CH_2Cl_2 = 1:9); IR (ATR) $\tilde{\nu}$ 3532, 2960, 1632, 1616, 1591, 1391, 1352, 1326, 1278, 1220, 1148, 1066, 1031, 833, 735 cm^{-1}; UV (MeOH) λ_{max} (log ε) 254 nm (4.43); ^1H NMR (300 MHz, DMSO-d_6) δ 0.98 (s, 6H, CH_3), 1.06 (s, 6H, CH_3), 1.97 (s, 6H, CH_3 on C-5 and C-6), 2.10 (m, 4H, CH_2), 2.22 ppm (m, 4H, CH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.9 (CH_3 on C-5 and C-6), 28.4, 29.1 (CH_3 on C-4′ and C-4″), 32.2 (C-4′ and C-4″), 47.5 (C-5′ and C-5″), 110.4 (C-1′ and C-1″), 140.7 (C-5 and C-6), 142.3 (C-2 and C-3), 185.6 ppm (C-1 and C-4); MS (ESI) m/z (%) 825.4 (100) $[2M + H]^+$, 413.2 (51) $[M + H]^+$; HRMS calcd for $C_{24}H_{28}O_6$ (412.1886), found 412.1880.

*2,3-Bis(2-hydroxy-4-methyl-6-oxocyclohex-1-enyl)-5,6-dimethylcyclo-hexa-2,5-diene-1,4-dione (**41**).*



Reaction of **6** (138 mg, 1 mmol) and **9** (252 mg, 2 mmol) according to the general procedure for 19 h gave **41** as a yellow solid in 83% yield (318 mg, 0.8 mmol): mp 220−222 °C (TBME); R_f 0.36 (MeOH/CH_2Cl_2 = 1:9); IR (ATR) $\tilde{\nu}$ 2934, 1650, 1589, 1282, 1251, 1158, 1140, 1021, 827, 734, 711 cm^{-1}; UV (MeOH) λ_{max} (log ε) 209 nm (4.16); ^1H NMR (300 MHz, DMSO-d_6) δ 0.98 (d, J = 6.3 Hz, 3H, CH_3), 1.02 (d, J = 6.3 Hz, 3H, CH_3), 1.96 (s, 6H, CH_3 on C-5 and C-6), 2.00−2.51 ppm (m, 10H, CH, CH_2,); ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.9 (CH_3 on C-5 and C-6), 20.8, 21.1, 21.2 (CH_3), 27.8, 28.0, 28.6, 28.7 (CH_2), 110.9, 111.0, 111.2, 111.3 (C-1′ and C-1″), 140.6, 140.63 (C-5 and C-6), 142.2, 142.3, 142.4, 142.5 (C-2 and C-3), 185.5 ppm (C-1 and C-4); (MS (ESI) m/z (%) 822.2 (22), 769.3 (100) $[2M + H]^+$, 385.2 (50), 367.2 (10), $[M + H]^+$; Anal. calcd for $C_{22}H_{24}O_6$ (384.42): C, 68.74; H, 6.29; found C, 68.49; H, 6.34.

*2,3-Bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-5,6-dimethylcyclohexa-2,5-diene-1,4-dione (**42**).*



Reaction of **6** (138 mg, 1 mmol) and **10** (252 mg, 2 mmol) according to the general procedure for 19 h gave **42** as an orange solid in 44% yield (168 mg, 0.4 mmol): mp 238−240 °C (CH_2Cl_2); R_f 0.15 (MeOH/CH_2Cl_2 = 1:9); IR (ATR) $\tilde{\nu}$ 2927, 1645, 1556, 1417, 1367, 1279, 1211, 1171, 1067, 997, 848, 751, 724 cm^{-1}; UV (MeOH) λ_{max} (log ε) 241 nm (4.65); ^1H NMR (300 MHz, DMSO-d_6) δ 2.00 (s, 3H, CH_3 on C-5 or C-6), 2.02 (s, 3H, CH_3 on C-5 or C-6), 2.13 (s, 3H, CH_3) 2.16 (s, 3H, CH_3), 5.87, 5.93 ppm (5′-H and 5″-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.1 (CH_3 on C-5 and C-6), 20.0, 20.1 (CH_3), 97.2, 97.23 (C-3′ and C-3″), 101.0, 102.8 (C-5′ and C-5″), 140.6, 141.2, 141.3, 141.5 (C-2, C-3, C-5 and C-6), 162.0, 162.6, 162.7, 162.8 (C-4′, C-6′, C-4″ and C-6″), 167.2, 170.1 (C-2′ and C-2″), 185.2, 185.6 ppm (C-1 and C-4); MS (ESI) m/z (%) 407.1 (100) $[M + Na]^+$, 385.1 (12) $[M + H]^+$; HRMS calcd for $C_{20}H_{16}O_8$ (384.0845), found 384.0843.

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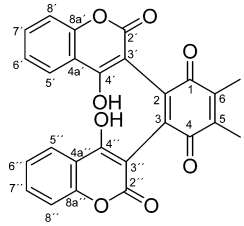
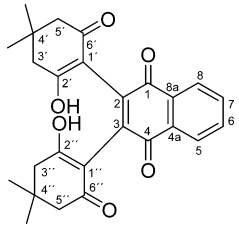
*2,3-Bis(4-hydroxy-2-oxo-2H-chromen-3-yl)-5,6-dimethylcyclohexa-2,5-diene-1,4-dione (**43**).*



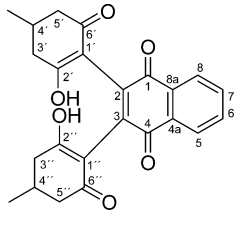
Reaction of **6** (138 mg, 1 mmol) and **11** (324 mg, 2 mmol) according to the general procedure for 19 h gave **43** as a yellow solid in 92% yield (420 mg, 0.9 mmol): mp 307−310 °C (MeOH); R_f 0.20 (MeOH/CH_2Cl_2 = 1:9); IR (ATR) $\tilde{\nu}$ 3076, 1650, 1598, 1555, 1499, 1285, 1295, 1236, 1170, 1117, 1107, 1050, 771, 723 cm^{-1}; UV (MeOH) λ_{max} (log ε) 206 (4.65), 268 nm (4.24); ^1H NMR (300 MHz, DMSO-d_6) δ 2.10 (s, 6H, CH_3), 7.29 (d, J = 8.1 Hz, 2H, 8′-H and 8″-H), 7.36 (t, J = 7.5 Hz, 2H, 6′-H and 6″-H), 7.64 (dt, J = 7.5 Hz, 1.2 Hz, 2H, 7′-H and 7″-H), 7.88 ppm (dd, J = 8.1 Hz, 1.2 Hz, 2H, 5′-H and 5″-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.2 (CH_3), 98.7 (C-3′ and C-3″), 116.5 (C-8′ and C-8″), 116.9 (C-4a′ and C-4a″), 124.6 (C-5′ and C-5″), 124.9 (C-6′ and C-6″), 133.6 (C-7′ and C-7″), 140.9, 141.0 (C-2, C-3, C-5 and C-6), 153.2 (C-8a′ and C-8a″), 160.6 (C-2′ and C-2″), 163.3 (C-4′ and C-4″), 184.8 ppm (C-1 and C-4) MS (ESI) m/z (%) 501.0 (18), 479.0 (100) $[M + Na]^+$, 457.0 (19) $[M + H]^+$; HRMS calcd for $C_{26}H_{16}O_8$ (456.0845), found 456.0837.

*2,3-Bis(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)naphthalene-1,4-dione (**44**).*



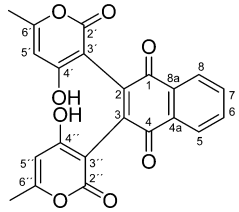
Reaction of **7** (160 mg, 1 mmol) and **8** (280 mg, 2 mmol) according to the general procedure for 18 h gave **44** as a brown solid in 72% yield (313 mg, 0.7 mmol): mp 240−242 °C (CH_2Cl_2); R_f 0.44 (MeOH/CH_2Cl_2 = 1:9); IR (ATR) $\tilde{\nu}$ 2956, 1667, 1608, 1574, 1327, 1279, 1234, 1145, 1028, 1013, 717 cm^{-1}; UV (MeOH) λ_{max} (log ε) 252 nm (4.55); ^1H NMR (300 MHz, DMSO-d_6) δ 1.01 (s, 6H, CH_3), 1.10 (s, 6H, CH_3), 2.04−2.32 (m, 8H, CH_2), 7.86 (m, 2H, arom), 7.99 ppm (m, 2H, arom); ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.6 (CH_3), 28.9 (CH_3), 32.3 (C-4′ and C-4″), 47.5 (CH_2), 110.5 (C-1′ and C-1″), 126.5 (C-5 and C-8), 133.0 (C-4a and C-8a), 134.2 (C-6 and C-7), 145.4 (C-2 and C-3), 183.4 (C-1 and C-4); MS (ESI) m/z (%) 869.4 (100) $[2M + H]^+$, 591.2 (16), 435.2 (40) $[M + H]^+$, 417.2 (13); HRMS calcd for $C_{26}H_{26}O_6$ (434.1729), found 434.1721.

*2,3-Bis(2-hydroxy-4-methyl-6-oxocyclohex-1-enyl)naphthalene-1,4-dione (**45**).*



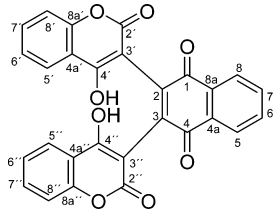
Reaction of **7** (160 mg, 1 mmol) and **9** (252 mg, 2 mmol) according to the general procedure for 17 h gave **45** as a brown solid in 70% yield (283 mg, 0.7 mmol): mp 237−239 °C (CH_2Cl_2); R_f 0.39 (MeOH/CH_2Cl_2 = 1:9); IR (ATR) $\tilde{\nu}$ 2931, 1664, 1615, 1584, 1375, 1315, 1280, 1252, 1008, 710 cm^{-1}; UV (MeOH) λ_{max} (log ε) 252 nm, (4.58); ^1H NMR (300 MHz, DMSO-d_6) δ 1.00 (d, J = 6.3 Hz, 3H, CH_3), 1.04 (d, J = 6.3 Hz, 3H, CH_3), 1.88−2.52 (m, 10H, CH, CH_2), 7.85 (m, 2H, arom), 7.99 ppm (m, 2H, arom) ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.9, 21.2 (CH_3), 27.9, 28.1, 28.6, 28.7 (CH_2), 111.0, 111.1, 111.3, 111.5 (C-1′ and C-1″), 126.5 (C-5 and C-8), 133.0 (C-4a and C-8a), 134.2 (C-6 and C-7), 145.1, 145.2, 145.3, 145.4 (C-2 and C-3), 183.2 ppm (C-1 and C-4); MS (ESI) m/z (%) 429.1 (100) $[M + Na]^+$, 407.2 (37) $[M + H]^+$, 389.1 (19); HRMS calcd for $C_{24}H_{22}O_6$ (406.1416), found 406.1412.

*2,3-Bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)naphthalene-1,4-dione (**46**).*



Reaction of **7** (160 mg, 1 mmol) and **10** (252 mg, 2 mmol) according to the general procedure for 17 h gave **46** as a yellow solid in 39% yield (158 mg, 0.4 mmol): mp 295−298 °C, dec (acetone); R_f 0.18 (MeOH/CH_2Cl_2 = 1:9); IR (ATR) $\tilde{\nu}$ 2858 2641, 1661, 1612, 1578, 1557, 1444, 1413, 1383, 1353, 1284, 1230, 795, 718 cm^{-1}; UV (MeOH) λ_{max} (log ε) 240 nm (4.65); ^1H NMR (300 MHz, DMSO-d_6) δ 2.19 (s, 6H, CH_3), 6.00 (s, 2H, 5′-H and 5″-H), 7.91 (m, 2H, arom), 8.06 ppm (m, 2H, arom); ^{13}C NMR (75 MHz, DMSO-d_6) δ 97.1, 97.2 (C-3′ and C-3″), 100.9, 101.0 (C-5′ and C-5″), 126.8 (C-5 and C-8), 132.6, 132.7 (C-4a and C-8a), 134.8 (C-6 and C-7), 143.2, 143.4 (C-2 and C-3), 161.9, 162.3 (C-4′ and C-4″), 162.9, 163.0 (C-6′ and C-6″), 167.2, 167.7 (C-2′ and C-2″), 182.8, 182.9 ppm (C-1 and C-4); MS (ESI) m/z (%) 1219.2 (28) $[3M + H]^+$, 866.1 (11), 813.2 (100) $[2M + H]^+$, 407.2 (22) $[M + H]^+$; HRMS calcd for $C_{22}H_{14}O_8$ (406.0689), found 406.0684.

*2,3-Bis(4-hydroxy-2-oxo-2H-chromen-3-yl)naphthalene-1,4-dione (**47**).*



Reaction of **7** (160 mg, 1 mmol) and **11** (324 mg, 2 mmol) according to the general procedure for 18 h gave **47** as an orange solid in 80% yield (381 mg, 0.8 mmol): mp 308−310 °C (MeOH); R_f 0.18 (MeOH/CH_2Cl_2 = 1:9); IR (ATR) $\tilde{\nu}$ 3072, 1676, 1652, 1603, 1566, 1499, 1363, 1283, 762, 718 cm^{-1}; UV (MeOH) λ_{max} (log ε) 203 (4.64), 270 nm (4.13); ^1H NMR (300 MHz, DMSO-d_6) δ 7.31 (d, J = 8.4 Hz, 2H, 8′-H and 8″-H), 7.38 (t, J = 7.5 Hz, 2H, 6′-H and 6″-H), 7.66 (dt, J = 7.9 Hz, 1.5 Hz, 2H, 7′-H and 7″-H), 7.91 (dd, J = 7.9 Hz, 1.5 Hz, 2H, 5′-H and 5″-H), 7.97 (m, 2H, 6-H and 7-H), 8.15 ppm

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(m, 2H, 5-H and 8-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 98.7 (C-3′ and C-3″), 116.5 (C-8′ and C-8″), 116.9 (C-4a′ and C-4a″), 124.6 (C-5′ and C-5″), 125.0 (C-6′ and C-6″), 126.9 (C-5 and C-8), 132.9 (C-4a and C-8a), 133.7 (C-7′ and C-7″), 134.6 (C-6 and C-7), 143.4 (C-2 and C-3), 153.2 (C-8a′ and C-8a″), 160.6 (C-2′ and C-2″), 163.4 (C-4′ and C-4″), 182.7 ppm (C-1 and C-4); MS (ESI) m/z (%) 501.1 (100) $[M + Na]^+$, 479.1 (9) $[M + H]^+$; HRMS calcd for $C_{28}H_{14}O_8$ (478.0689), found 478.0682.

■ ASSOCIATED CONTENT

Supporting Information

Full characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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