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# Copper(I)-Catalyzed Intramolecular O-Arylation for the Synthesis of 2,3,4,9-Tetrahydro-1*H*-xanthen-1-ones with Low Loads of CuCl

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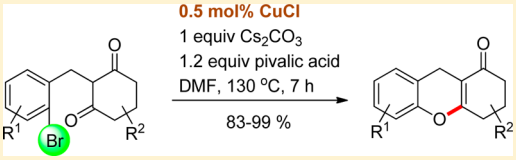
Supporting Information

**ABSTRACT:** As little as 0.5 mol % CuCl is sufficient to catalyze the intramolecular O-arylation of easily accessible 2-(2-bromobenzyl)cyclohexane-1,3-diones to provide the corresponding 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones with yields ranging from 83% to 99%.




## INTRODUCTION

Over the past decade, Cu(I)-catalyzed coupling reactions between aryl halides and different nucleophiles have experienced a renaissance and resulted in the development of more efficient processes for the formation of C−C as well as C−N, C−O, and C−S bonds.[1,2] The combination of such arylations with other transformations to domino processes is particularly valuable because it offers new opportunities for the synthesis of heterocyclic frameworks.[3] Due to their interesting biological activities, xanthenes and xanthenones have attracted much attention from different fields including natural product chemistry, synthetic organic chemistry, and medicinal chemistry.[4]

Apart from the fully unsaturated xanthenes and xanthenones, partially saturated compounds such as the tetrahedroxanthenones have attracted a great deal of interest, as many compounds with this structure element exhibit remarkable biological activities. Typical examples of biologically active tetrahydroxanthenones of natural origin include (a) the antibacterial, antifungal, and algicidal blennolides A and B, which have been isolated from the endophytic fungus *Blennoria* sp.,[5] (b) the monomers of the antitumor agents secalonic acids B and D, respectively,[6] (c) α- and β-diversonolic esters, which have been isolated from *Pencillium diversum*,[7] (d) globosuxanthone B from *Chaetomium globosum*,[8] and (e) the antibacterial 3,4-dihydroglobosuxanthone A from several endophytic fungi (Figure 1).[9] This is the reason why the synthesis of tetrahydroxanthenones is of considerable interest to medicinal chemistry.

Over the years, several synthetic methods have been developed for the preparation of the 2,3,4,4a-tetrahydro-1*H*-xanthen-1-one skeleton (Figure 2, A).[4a,10] One of the most prominent methods is the domino oxa-Michael addition/aldol reaction between a salicylic aldehyde and a cyclohexenone.[10d−f,h] This transformation allows the preparation of enantiomerically pure 2,3,4,4a-tetrahydroxanthen-1-ones[10e,f] and has been applied to the total syntheses of blennolide C[11a] and diversinol.[11b]

In contrast, only a few methods are available for the efficient synthesis of 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones (Figure 2, B). They include several one-pot protocols such as the condensation of 2-hydroxybenzyl alcohol with 1,3-cyclohexanedione in HMPA at 185 °C,[12e] the reaction between β-functionalized enamines and 2-hydroxybenzyl alcohols at higher temperatures,[12d] the domino reaction between salicylic aldehyde and 1,3-cyclohexanedione catalyzed by *p*-TSA[12c] or promoted by $Me_3SiI$,[12a] and the reaction of in situ-generated *o*-quinone methides with 3-dimethylamino-2-cyclohexen-1-ones in DMF at higher temperatures.[12b]

Recently, we have discovered that the Cu(I)-catalyzed domino reaction between 2-bromobenzyl bromides **1** and β-ketoesters **2** can be used for the efficient and selective synthesis of 4*H*-chromenes **4** with yields ranging from 65% to 88%.[3b] It was assumed that the domino reaction is based on an intermolecular C-benzylation of a 2-bromobenzyl bromide **1** with a β-ketoester **2** and subsequent intramolecular O-arylation of **3** (Scheme 1).

It is remarkable that upon reaction of 2-bromobenzyl bromides **1** with acyclic β-ketoesters **2** there was no product resulting from a domino intermolecular O-benzylation/intramolecular C-arylation. There was only one exception, namely, the reaction between 2-bromobenzyl bromide (**1a**) and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**5**) (Scheme 2). Here, the formation of 45% of the expected cyclized product **6** was accompanied by 19% of benzyl ether **7**, which originates from an intermolecular O-benzylation.

## RESULTS AND DISCUSSION

On the basis of our previous results, we decided to develop a domino reaction to 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones and related skeletons based on the intermolecular C-benzylation of a 2-halobenzyl halide with a cyclic 1,3-diketone and subsequent intramolecular O-arylation. The results of our study are disclosed in this contribution.

The starting point was the Cu(I)-catalyzed reaction between 1 equiv of 2-bromobenzyl bromide (**1a**) and 2 equiv of 1,3-cyclohexanedione (**8a**). When **1a** and **8a** were reacted in the presence of 1 mol % CuCl as the catalyst, 4 equiv of $Cs_2CO_3$ as the base, and 1.2 equiv of pivalic acid, 18% of the xanthenone **9a** as well as 29% of the O-benzylated product **10a** were

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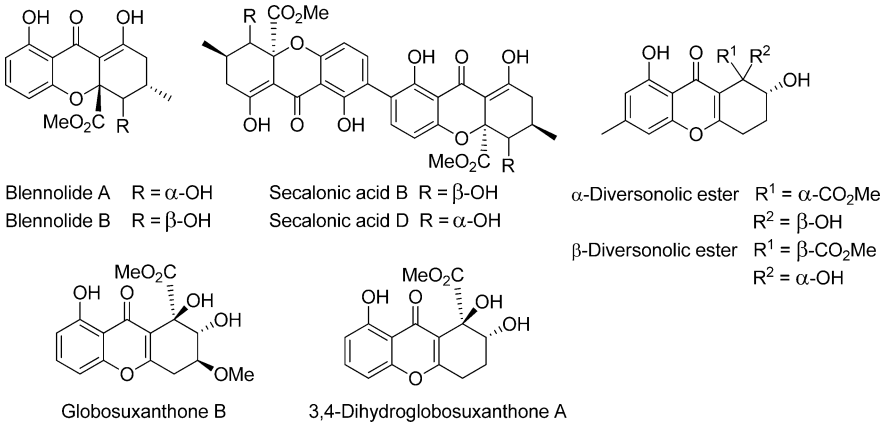



**Figure 1.** Selected biologically active natural products with a tetrahydroxanthenone core.

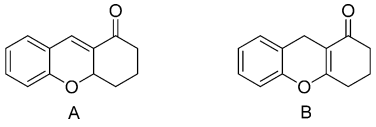


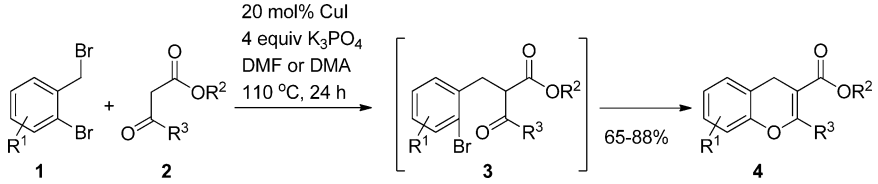

**Figure 2.** The structures of the 2,3,4,4a-tetrahydro-1*H*-xanthen-1-one (**A**) and the 2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**B**) skeleton.

isolated (Scheme 3). By optimizing the reaction conditions with respect to Cu(I) source, base, additive, solvent, and reaction conditions, we were able to increase the combined yield of **9a** and **10a** to 71% and the portion of the desired xanthenone to 35% (Table 1, entry 1). It was not possible, however, to suppress the formation of the O-benzylated product. Similar results were observed in the reactions between 2-bromobenzyl bromide (**1a**) and the substituted 1,3-cyclohexanediones **8b**,**c**,**e** (Table 1, entries 2–4).

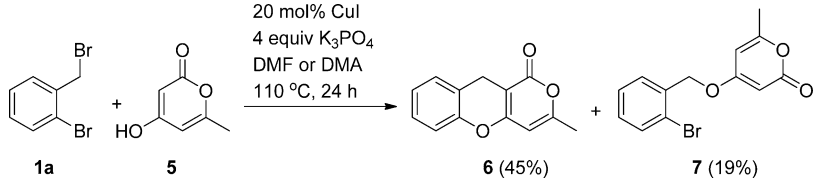
In addition, the one-pot approach to 2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9a**) was also tried using 2-chlorobenzyl bromide (**1b**) and 2-iodobenzyl bromide (**1c**) as substrates. When 2-chlorobenzyl bromide (**1b**) and 1,3-cyclohexanedione (**8a**) were reacted with 20 mol % CuI, 4 equiv of $Cs_2CO_3$ in DMF at 130 °C for 10 min, 35% of the O-benzylated product (**10b**) and 26% of the C-benzylated intermediate (**11b**) could be isolated. The cyclized product **9a** could not be observed. With 2-iodobenzyl bromide (**1c**) as the 2-halobenzyl halide, 19% of the xanthenone **9a**, 41% of the O-benzylated product **10c**, and 5% of the C-benzylated intermediate **11c** were formed. Obviously, the nature of the 2-halobenzyl bromide has only little influence on the extent to which O-benzylation takes place (Scheme 4).

To solve this problem, which is due to the competition between C- and O-benzylation, we were looking for methods that allow for the exclusive formation of C-benzylated products upon reaction between a 2-halobenzyl halide and a 1,3-dicarbonyl.

**Scheme 1. Domino Reaction between 2-Bromobenzyl Bromides 1 and *β*-Ketoesters 2 for the Synthesis of 4*H*-Chromenes**




**Scheme 2. Cu(I)-Catalyzed Reaction of 2-Bromobenzyl Bromide (1a) with Pyrone 5**




**Scheme 3. Initial Experiment for the Cu(I)-Catalyzed Synthesis of 2,3,4,9-Tetrahydro-1*H*-xanthen-1-ones from 2-Bromobenzyl Halides and Cyclic 1,3-Diketones**

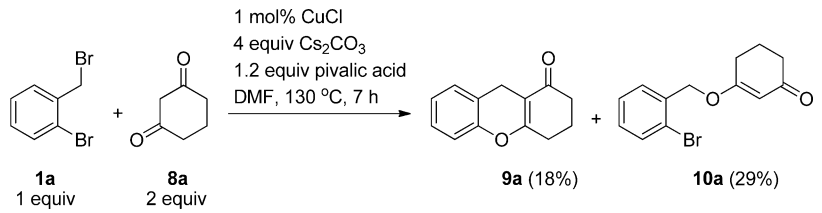




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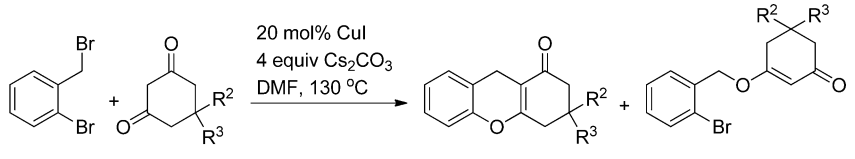
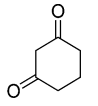
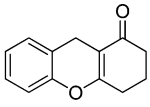
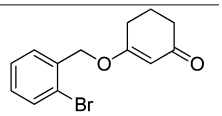
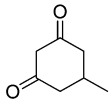
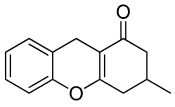
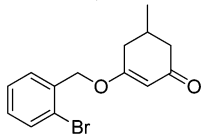
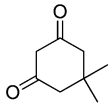
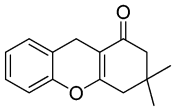
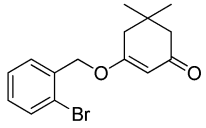
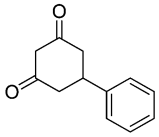
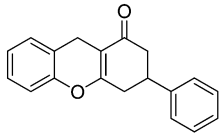
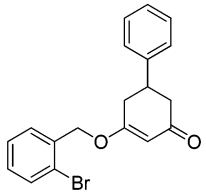
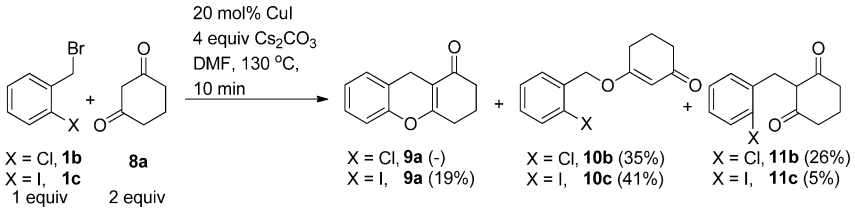
**Table 1. Cu(I)-Catalyzed One-Pot Approach to 2,3,4,9-Tetrahydro-1*H*-xanthen-1-ones in the Absence of Any Ligand**




| entry | 1,3-dione | time (min) | yield **9** (%) | yield **10** (%) |
|---|---|---|---|---|
| 1 |  **8a** | 10 |  **9a**, 35% |  **10a**, 36% |
| 2 |  **8b** | 60 |  **9b**, 37% |  **10d**, 36% |
| 3 |  **8c** | 10 |  **9c**, 35% |  **10e**, 36% |
| 4 |  **8e** | 60 |  **9e**, 38% |  **10g**, 30% |

**Scheme 4. Cu(I)-Catalyzed One-Pot Approach to 2,3,4,9-Tetrahydro-1*H*-xanthen-1-ones Using 2-Halobenzyl Bromides 1b and 1c as Substrates**




After several methods were explored,[13] the protocol of Marsden et al. was finally employed.[13a] It was found that the reaction between 1 equiv of 1,3-cyclohexanedione (**8a**) and 1.5 equiv of 2-bromobenzyl bromide (**1a**) in the presence of 1 equiv of 1 M aq NaOH at 100 °C exclusively gave 2-(2-bromobenzyl)-cyclohexane-1,3-dione (**11a**) in 71% yield (Table 2, entry 1). However, we did not succeed in combining the reaction conditions of the successful C-benzylation (**1a** + **8a** → **11a**) with the reaction conditions of the Cu(I)-catalyzed intramolecular Ullmann reaction to a new domino process. This is why we decided to perform the synthesis of xanthenones **9** in two discrete steps. The substrates required for the intramolecular Ullmann reaction, i.e., the benzylated cyclic 1,3-diketones **11b**–**o**, were prepared according to the synthesis of **11a** with yields ranging from 45% to 83% (Table 2, entries 2–15).[14]

Initial experiments regarding the Cu(I)-catalyzed intramolecular O-arylation of **11a** were performed under the conditions that had proven successful for the reactions between **1a** and **8a**,**c**, i.e., 20 mol % CuI, 4 equiv of $Cs_2CO_3$, DMF, 130 °C, 10 min (Table 1). The results were disappointing because the cyclization product **9a** was obtained in only 25% yield (Scheme 5).

In accordance with earlier experience from our own as well as from other groups,[15] further experiments demonstrated that the yields of xanthenone **9a** could be significantly improved when the reactions were performed in the presence of an acidic additive such as acetic acid, propionic acid, pivalic acid, or isovaleric acid. At the same time, the amount of CuI could be reduced to 1 mol % and the amount of $Cs_2CO_3$ could be reduced to 2 equiv. It turned out that isovaleric acid and pivalic acid were markedly superior to propionic acid and acetic acid (Table 3, entries 1–4). Despite our finding that the best yield was obtained with 0.5 equiv of isovaleric acid, all further optimizations were performed with pivalic acid as the additive because isovaleric acid is malodorous. Further experiments


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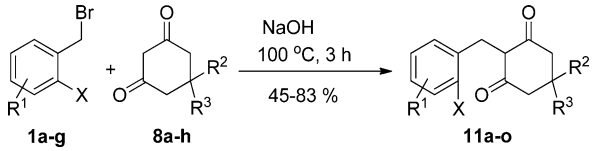
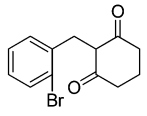
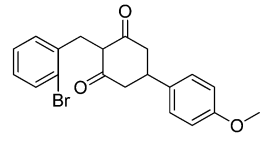
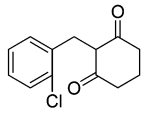
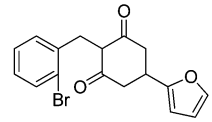
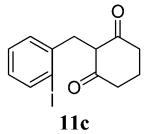
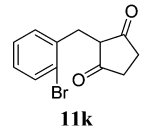
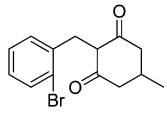
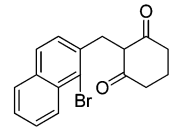
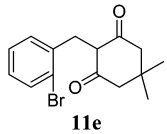
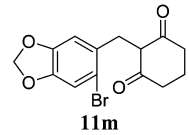
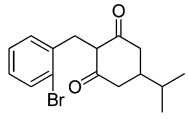
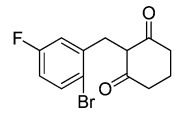
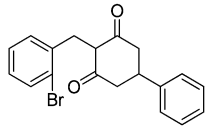
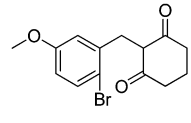
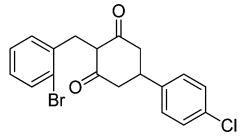
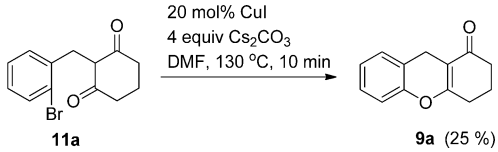
**Table 2. Benzylation of Cyclic 1,3-Diones 8a–h with 2-Halobenzyl Bromides and Related Compounds 1a–g**




| entry | product | yield (%) | entry | product | yield (%) |
|---|---|---|---|---|---|
| 1 |  **11a** | 71 | 9 |  **11i** | 80 |
| 2 |  **11b** | 51 | 10 |  **11j** | 75 |
| 3 |  **11c** | 60 | 11 |  **11k** | 45 |
| 4 |  **11d** | 75 | 12 |  **11l** | 60 |
| 5 |  **11e** | 68 | 13 |  **11m** | 61 |
| 6 |  **11f** | 83 | 14 |  **11n** | 67 |
| 7 |  **11g** | 56 | 15 |  **11o** | 50 |
| 8 |  **11h** | 82 | | | |

**Scheme 5. Initial Experiment for the Cu(I)-Catalyzed Intramolecular O-Arylation of 11a**




revealed that the amount of pivalic acid had a strong impact on the outcome of the reaction (Table 3, entries 6–10). Increasing the amount of pivalic acid resulted in higher yields of **9a**. The product **9a** could be isolated with 95% yield when the intramolecular O-arylation of **11a** was run with 1.2 equiv of pivalic acid as the additive (Table 3, entry 10). In the absence of any additive, the yield dropped to 58% (Table 3, entry 5).

Additional experiments devoted to the influence of the copper source as well as the amount of the Cu(I)-catalyst clearly demonstrated that the conversion of **11a** to **9a** could be catalyzed not only by CuI but also by CuCl, CuBr, CuCN, and CuOTf. With all catalysts the yields exceeded 90% (Table 4, entries 1–5). All further reactions were carried out with CuCl as the copper source because this is one of the cheapest Cu(I)


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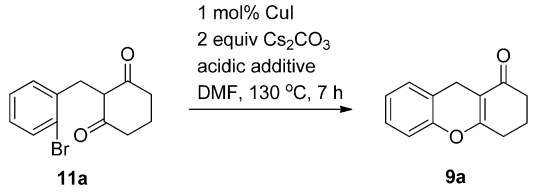
**Table 3. Influence of Acidic Additives on the Cu(I)-Catalyzed Intramolecular O-Arylation of 11a[a]**

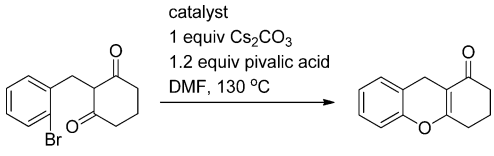



11a 9a

| entry | acidic additive | additive (equiv) | yield 9a (%) |
|---|---|---|---|
| 1 | pivalic acid | 0.5 | 77 |
| 2 | acetic acid | 0.5 | 48 |
| 3 | propionic acid | 0.5 | 63 |
| 4 | isovaleric acid | 0.5 | 83 |
| 5 | pivalic acid | 0 | 58 |
| 6 | pivalic acid | 0.2 | 61 |
| 7 | pivalic acid | 0.3 | 63 |
| 8 | pivalic acid | 0.8 | 77 |
| 9 | pivalic acid | 1.0 | 78 |
| 10 | pivalic acid | 1.2 | 95 |

[a]The reactions were performed in a sealed tube with 0.5 mmol **11a** in 2 mL DMF.

**Table 4. Influence of the Copper Source and the Amount of CuCl on the Intramolecular O-Arylation of 11a[a]**




11a 9a

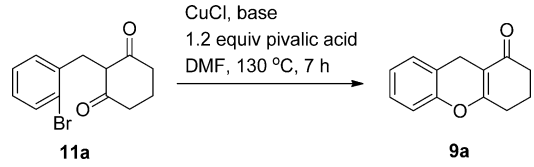
| entry | catalyst | mol % catalyst | time (h) | yield (%) |
|---|---|---|---|---|
| 1 | CuI | 1 | 7 | 98 |
| 2 | CuBr | 1 | 7 | 93 |
| 3 | CuCl | 1 | 7 | 96 |
| 4 | CuCN | 1 | 7 | 96 |
| 5 | CuOTf | 1 | 7 | 98 |
| 6 | CuCl | 0.5 | 7 | 95 |
| 7 | CuCl | 0.1 | 7 | 51 |
| 8 | CuCl | 0.1 | 22 | 89 |
| 9 | – | – | 7 | – |

[a]The reactions were performed in a sealed tube with 0.5 mmol of **11a** in 2 mL of DMF.

salts available. Furthermore, it was found that the cyclization of **11a** to **9a** tolerates a reduction of the catalyst load from 1 to 0.5 mol % CuCl without loss of yield. A further decrease of the catalyst load to 0.1 mol % was also possible, but the reaction time had to be extended to 22 h to achieve high yields (Table 4, entries 7, 8). In recent years, a number of protocols have been developed for copper-catalyzed reactions with low loads of the copper source and *N*,*N*′-dimethylethylenediamine (DMEDA), 2,2,6,6-tetramethyl-3,5-heptanedione (TMHD), L-proline, and 4,7-dimethoxy-1,10-phenanthroline as the ligands.[2c,16] A prominent example comes from Bolm, who has established that as little as 0.001 mol % CuO is sufficient to catalyze the intermolecular O-arylation of aryl iodides. When the transformation of **11a** to **9a** was performed under Bolm's conditions, i.e., 0.001 mol % CuO, 2 equiv of $Cs_2CO_3$, 20 mol % TMHD in DMF at 135 °C for 24 h, the desired cyclization product **9a** was isolated in 45% yield. When the amount of CuO was increased to 0.1 mol %, the yield amounted to 60%. A control experiment underlines the importance of the Cu(I) salt on the outcome of the O-arylation. In the absence of any copper source no product formation could be observed (Table 4, entry 9). Noteworthy, all experiments described in Table 4 were conducted in the presence of no more than 1 equiv of $Cs_2CO_3$ as the base.

Another set of experiments was used to test the influence of different bases. $Cs_2CO_3$ could be replaced with both $K_2CO_3$ and $K_3PO_4$, but the yields dropped to 75% and 47%, respectively (Table 5, entries 2, 3). NaOEt and DABCO were not suitable (Table 5, entries 4, 5). Finally, we briefly examined the

**Table 5. Influence of the Base and the Amount of $Cs_2CO_3$ on the Intramolecular O-Arylation of 11a[a]**




11a 9a

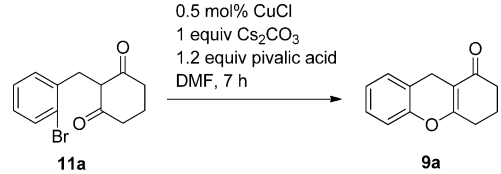
| entry | CuCl (mol %) | base | base (equiv) | yield (%) |
|---|---|---|---|---|
| 1 | 0.5 | $Cs_2CO_3$ | 1.0 | 95 |
| 2 | 0.5 | $K_2CO_3$ | 1.0 | 75 |
| 3 | 0.5 | $K_3PO_4$ | 1.0 | 47 |
| 4 | 0.5 | NaOEt | 1.0 | 2 |
| 5 | 0.5 | DABCO | 1.0 | traces |
| 6 | 1 | $Cs_2CO_3$ | 1.0 | 95 |
| 7 | 1 | $Cs_2CO_3$ | 1.5 | 91 |
| 8 | 1 | $Cs_2CO_3$ | 2.0 | 99 |

[a]The reactions were performed in a sealed tube with 0.5 mmol **11a** in 2 mL of DMF.

influence of the amount of $Cs_2CO_3$. Varying its amount in the range of between 1 and 2 equiv had only little impact on the yield of **9a** (Table 5, entries 6–8).

Finally, it was demonstrated that lowering the reaction temperature from 130 °C to 100 °C resulted in a significantly decreased yield of **9a** (Table 6, entry 2). At 50 °C no product

**Table 6. Influence of the Reaction Temperature[a]**




11a 9a

| entry | *T* (°C) | yield (%) |
|---|---|---|
| 1 | 130 | 95 |
| 2 | 100 | 61 |
| 3 | 50 | 0 |

[a]The reactions were performed in a sealed tube with 0.5 mmol of **11a** in 2 mL of DMF.

was formed (Table 6, entry 3). In summary, the highest yield of **9a** was obtained when the cyclization of **11a** was run with 0.5 mol % CuCl, 1.2 equiv of pivalic acid, and 1 equiv of $Cs_2CO_3$ in DMF at 130 °C for 7 h in a sealed vial (Table 4, entry 6). When 2-(2-chlorobenzyl)-1,3-cyclohexanedione (**11b**) was reacted under optimized reaction conditions, only 13% of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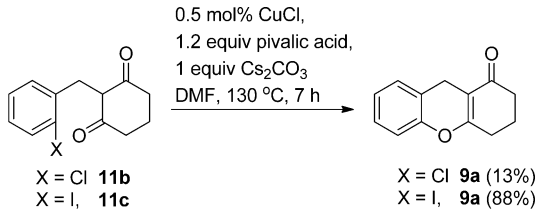
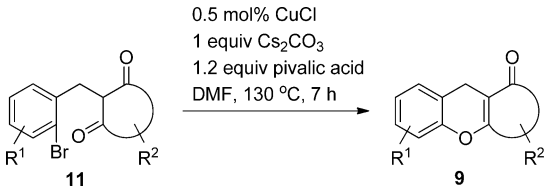
the xanthenone **9a** could be isolated (Scheme 6). In addition, 68% of the substrate was reisolated. With the iodo-substituted substrate **11c**, 88% of the xanthenone **9a** and only 5% of the starting material were observed. From these results it is clear that the bromo-substituted substrate **11a** is the most suitable one.

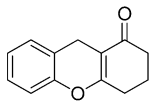
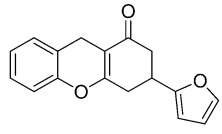
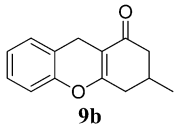
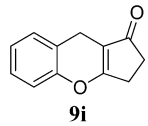
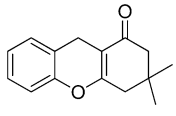
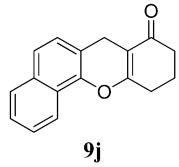
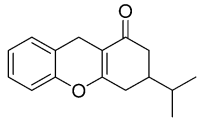
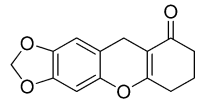
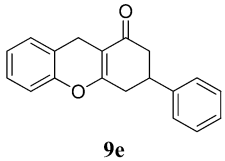
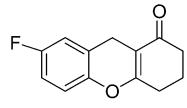
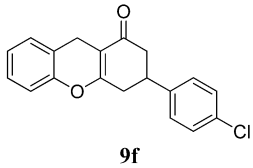
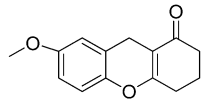
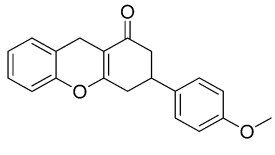
**Scheme 6. CuCl-Catalyzed Intramolecular O-Arylation of Substituted 2-(2-Halobenzyl)-1,3-dicarbonyls 11b,c**




With the optimized protocol in hand, we studied the substrate scope of the Cu(I)-catalyzed intramolecular O-arylation of 2-(2-bromoaryl)-1,3-dicarbonyls. It was found that, in addition to **11a**, several substituted 2-(2-bromobenzyl)-1,3-cyclohexanediones **11d−j** derived from different 5-monosubstituted and 5,5-disubstituted 1,3-cyclohexanediones could be reacted to yield the corresponding xanthenones **9b−h** with yields ranging from 87% to 99% as the sole products (Table 7, entries 2−8). It was also possible to use 2-(2-bromobenzyl)-1,3-cyclopentanedione (**11k**) as the substrate (Table 7, entry 9). Finally, it was

**Table 7. CuCl-Catalyzed Intramolecular O-Arylation of Substituted 2-(2-Bromobenzyl)-1,3-dicarbonyls 11a,d−m**




| entry | product | yield (%) | entry | product | yield (%) |
|---|---|---|---|---|---|
| 1 |  **9a** | 95 | 8 |  **9h** | 87 |
| 2 |  **9b** | 92 | 9 |  **9i** | 54 |
| 3 |  **9c** | 98 | 10 |  **9j** | 83 |
| 4 |  **9d** | 99 | 11 |  **9k** | 85 |
| 5 |  **9e** | 91 | 12 |  **9l** | 87 |
| 6 |  **9f** | 93 | 13 |  **9m** | 88 |
| 7 |  **9g** | 95 | | | |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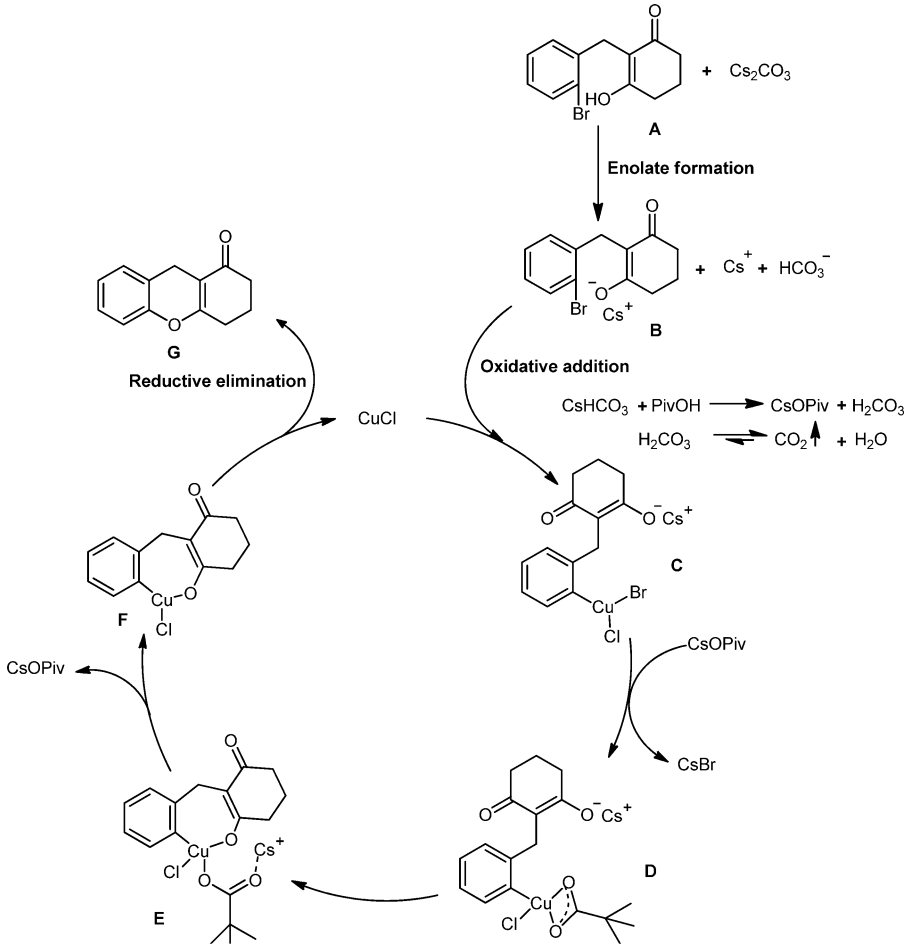
**Scheme 7. Plausible Catalytic Cycle for the CuCl-Catalyzed Intramolecular O-Arylation of Substituted 2-(2-Halobenzyl)-1,3-dicarbonyls in the Presence of Pivalic Acid**




demonstrated that several substituted 2-(2-bromoaryl)-1,3-cyclohexanediones **11l–o** derived from different aryl bromides are tolerated as substrates (Table 7, entries 10–13). These results suggest that the newly developed method offers a broad range of potential applications for the synthesis of 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones and related O-heterocycles. As far as we are aware, there is only a single example for the intramolecular O-arylation of a 2-(2-halobenzyl)-1,3-dicarbonyl in the literature. Fang and Li reported that **11a** can be cyclized to **9a** in 89% yield using 10 mol % CuI as the copper source, 2 equiv of $Cs_2CO_3$ as the base, and 20 mol % DMEDA as the ligand.[17] Our studies clearly established that several 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones can be obtained in a highly selective and efficient manner by intramolecular O-arylation of 2-(2-bromobenzyl)-1,3-dicarbonyls using as little as 0.5 mol % CuCl catalyst and only 1 equiv of $Cs_2CO_3$. Therefore, the method presented here is a valuable supplement to other methods for the synthesis of 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones.

Although a mechanistic investigation of the CuCl-catalyzed intramolecular O-arylation of substituted 2-(2-halobenzyl)-1,3-dicarbonyls has not been performed, a tentative proposal is presented in Scheme 7. It is assumed that the mechanism starts with the reaction of **A** with $Cs_2CO_3$ to give the corresponding cesium enolate **B** and $CsHCO_3$. Then the oxidative addition of the Cu(I) species into the aryl bromide bond of **B** takes place with formation of **C**. This is followed by a bromide/pivalate exchange to produce the chelated Cu complex **D**. The required cesium pivalate is generated from pivalic acid and $CsHCO_3$ which stems from the reaction of enol **A** with $Cs_2CO_3$. Intramolecular attack of the cesium enolate on the chelated Cu center furnishes intermediate **E** which deliberates cesium pivalate to give **F**. It is assumed that chelation of Cu with the pivalate stabilizes **D**, thereby facilitating the coupling reaction. Finally, **F** undergoes reductive elimination with formation of the 2,3,4,9-tetrahydro-1*H*-xanthen-1-one **G** (≙ **9a**) and regeneration of CuCl. It is noteworthy that Pd complexes similar to **D** and **E** have been proposed recently.[18] The proposal is in accordance with our finding that the reaction cannot be run efficiently when the combination of 1 equiv of $Cs_2CO_3$ and 1.2 equiv of pivalic acid is replaced by 1 or 1.2 equiv of cesium pivalate. When the reaction of **11a** was run with 1 equiv of cesium pivalate in the presence of 0.5 mol % CuCl in DMF at 130 °C for 7 h, the yield of **9a** amounted only to 52%. The same outcome was observed with 1.2 equiv of cesium pivalate. The reason is that with 1 or 1.2 equiv of cesium pivalate the concentration of cesium ions is not sufficient for the simultaneous formation of the cesium enolate **B** and the formation of the cesium pivalate required for the chelation of **C**. With 2 or 2.5 equiv of cesium pivalate, the yield of **9a** could be increased to 88% and 95%, respectively. The proposed mechanism is also corroborated by the observation that $CO_2$ is formed during the reaction. It is assumed that $CO_2$ is generated from the reaction between $CsHCO_3$ and pivalic acid to give cesium pivalate and $H_2CO_3$, which in turn decomposes to $CO_2$ and $H_2O$.


dx.doi.org/10.1021/jo3018318 | *J. Org. Chem.* 2012, 77, 10194–10210

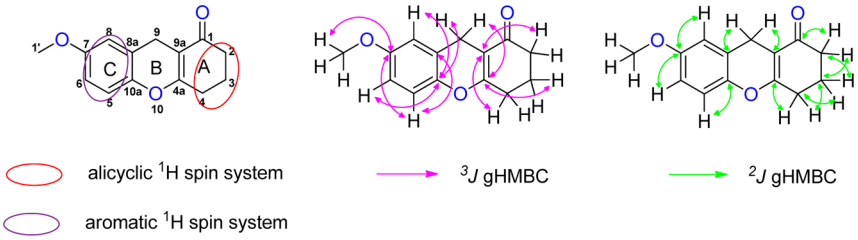



**Figure 3.** $^1$H spin systems and important HMBC correlations (H↔C) for **9m**.

The structures of all compounds were unambiguously elucidated by mass spectrometry and NMR spectroscopy. Structure elucidation of all compounds and full assignment of the $^1$H and $^{13}$C chemical shifts were achieved by evaluating their gCOSY, gHSQC, and gHMBC spectra. For example, compound **9m** contains four $^1$H spin systems, one consisting of the protons attached to carbons C-2, C-3, and C-4 of ring A. The second spin system contains the two protons attached to C-9 of ring B, the third spin system contains the three protons of the $OCH_3$ group, and the fourth comprises the aromatic protons 5-H, 6-H, 8-H attached to the aromatic ring C. The sequence of the protons of the ring A and C spin systems was determined by analysis of the gCOSY spectrum. To confirm the proposed structure, we used gHMBC to fix the positions of the six quaternary carbons C-1, C-4a, C-7, C-8a, C-9a, and C-10a. Carbon C-9a showed strong $^3J$-HMBC correlations to protons 2-H and 4-H, C-8a to proton 5-H, C-10a to protons 6-H, 8-H, and 9-H, C-7 to protons 1′-H and 5-H, and C-4a to 3-H and 9-H. These findings established that the two rings A and C are linked by the four carbons C-4a, C-9a, C-8a, and C-10a as shown in Figure 3.

## CONCLUSIONS

A simple to execute and efficient method for the synthesis of substituted 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones from easily accessible *o*-bromobenzyl bromides and cyclic 1,3-dicarbonyls as starting materials has been developed. 2,3,4,9-Tetrahydro-1*H*-xanthen-1-ones can be synthesized in a one-pot reaction between 2-bromobenzyl bromides and 1,3-cyclohexanediones via Cu(I)-catalyzed domino intermolecular C-benzylation/intramolecular O-arylation. The competing O-benzylation in the initial step, which could not be suppressed under the conditions of the Cu(I)-catalyzed domino reaction, gave rise to the formation of benzyl ethers as side products. The synthesis of the 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones in two steps has proven to be a valuable alternative to the domino process, as no side product formation occurred. The required C-benzylated 1,3-diones could be obtained selectively by reacting 2-bromobenzyl bromides with 1,3-diones under basic conditions with yields ranging from 45% to 83%. Subsequently, the 2-(2-bromobenzyl)-cyclohexane-1,3-diones were cyclized to the corresponding 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones by Cu(I)-catalyzed intramolecular O-arylation in 83% to 99% yield. Best results were obtained when the cyclizations were performed with 0.5 mol % CuCl as the catalyst, 1.2 equiv of pivalic acid as an additive, and 1 equiv of $Cs_2CO_3$ as the base.

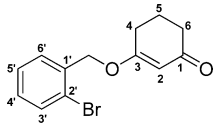
## EXPERIMENTAL SECTION

**General Remarks.** All commercially available reagents were used without further purification. Glassware was dried for 4 h at 140 °C in an oven. Solvents used in reactions were distilled over appropriate drying agents prior to use. Solvents used for extraction and purification were distilled prior to use. Reaction temperatures are reported as bath temperature. Thin-layer chromatography (TLC) was performed on TLC silica gel 60 F254. Compounds were visualized with UV light ($\lambda$ = 254 nm) and/or by immersion in an ethanolic vanillin solution or by immersion in a $KMnO_4$ solution followed by heating. Products were purified by flash chromatography on silica gel, 0.04−0.063 mm. Melting points were obtained on a melting point apparatus with open capillary tubes and are uncorrected. IR spectra were measured on a FT-IR-spectrometer. UV/vis spectra were recorded with a spectrophotometer. $^1$H ($^{13}$C) NMR spectra were recorded at 300 (75) MHz using $CDCl_3$, $CD_3OD$, and DMSO-$d_6$ as the solvent. The $^1$H and $^{13}$C chemical shifts were referenced to residual solvent signals at $\delta$ H/C 7.26/77.00 ($CDCl_3$), 3.31/49.10 ($CD_3OD$), and 2.50/39.50 (DMSO-$d_6$) relative to TMS as internal standard. HSQC-, HMBC-, and COSY-spectra were recorded on an NMR spectrometer at 300 MHz. 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), quin (quintet), m (multiplet), and br (broad). 1D and 2D homonuclear NMR spectra were measured with standard pulse sequences. Low-resolution electron impact mass spectra (MS) and exact mass electron impact mass spectra (HRMS) were obtained at 70 eV using a double focusing sector field mass spectrometer. Intensities are reported as percentages relative to the base peak ($I$ = 100%).

**General Procedure I for the CuI-Catalyzed Domino Reaction between 2-Halobenzyl Bromides 1a−c and 1,3-Cyclohexanediones 8a-c,e.** A dry 10 mL vial was equipped with a magnetic stir bar, charged with 2-halobenzyl bromide **1** (1 mmol), 1,3-cyclohexanedione **8** (2 mmol), CuI (38 mg, 20 mol %), and $Cs_2CO_3$ (1.303 g, 4 mmol), and sealed. The sealed tube was evacuated and backfilled with argon two times. Then, freshly distilled DMF (2 mL) was added, and the reaction mixture was stirred at 130 °C for the time given in Table 1. After cooling to room temperature, the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The crude product was subjected to flash column chromatography over silica gel to yield the products.

*Reaction between **1a** and **8a**.* According to general procedure I, 2-bromobenzyl bromide (**1a**) (250 mg, 1.0 mmol), 1,3-cyclohexanedione (**8a**) (224 mg, 2.0 mmol), CuI (38 mg, 20 mol %), and $Cs_2CO_3$ (1.303 g, 4.0 mmol) were reacted in a sealed tube under argon at 130 °C for 10 min. Column chromatography over silica gel (petroleum ether/EtOAc = 8:2) afforded 2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9a**) as a white solid in 35% yield (70 mg, 0.35 mmol) and 3-[(2-bromophenyl)methoxy]-2-cyclohexen-1-one (**10a**) as a colorless liquid in 36% yield (100 mg, 0.36 mmol).

*3-[(2-Bromophenyl)methoxy]-2-cyclohexen-1-one (**10a**).* $R_f$ = 0.10 (petroleum ether/EtOAc = 8:2); IR (ATR) $\nu$ 1651 (s) (C=O), 1600, 1361, 1219, 1176, 1133, 1028, 822, 750 cm$^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 243 (4.30) nm; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.03 (quin, $^3J$ (5-H, 6-H) = 6.6 Hz, $^3J$ (4-H, 5-H) = 6.3 Hz, 2H, 5-H), 2.38 (t-like, $^3J$ (5-H, 6-H) = 6.9 Hz, 2H, 6-H), 2.51 (t-like, $^3J$ (4-H, 5-H) = 6.3 Hz, 2H, 4-H), 4.97 (s, 2H, $CH_2$), 5.50 (s, 1H, 2-H), 7.24





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(ddd, $^3J$ (4′-H, 5′-H) = 6.6 Hz, $^3J$ (3′-H, 4′-H) = 6.0 Hz, $^4J$ (4′-H, 6′-H) = 1.5 Hz, 1H, 4′-H), 7.34 (ddd, $^3J$ (4′-H, 5′-H) = 7.2 Hz, $^3J$ (5′-H, 6′-H) = 7.5 Hz, 1H, 5′-H), 7.42 (dd, $^3J$ (5′-H, 6′-H) = 7.5 Hz, 1H, 6′-H), 7.59 (dd, $^3J$ (3′-H, 4′-H) = 7.8 Hz, 1H, 3′-H); $^{13}$C NMR (75 MHz, $CDCl_3$ ) $\delta$ 21.2 (C-5), 28.9 (C-4), 36.7 (C-6), 69.8 ($CH_2$), 103.6 (C-2), 122.9 (C-2′), 127.6 (C-5′), 129.2 (C-6′), 129.9 (C-4′), 132.9 (C-3′), 134.4 (C-1′), 177.1 (C-3), 199.6 (C-1); MS (EI, 70 eV) $m/z$ (%) 280 (8) $[M]^+$, 201 (10) $[280 - Br]^+$, 171 (100), 90 (20), 28 (6); HRMS (EI, $M^+$) calcd for $C_{13}H_{13}BrO_2$ (280.0099), found 280.0094.

*Reaction between **1b** and **8a**.* According to general procedure I, 2-chlorobenzyl bromide (**1b**) (206 mg, 1.0 mmol), 1,3-cyclohexanedione (**8a**) (224 mg, 2.0 mmol), CuI (38 mg, 20 mol %) and $Cs_2CO_3$ (1.303 g, 4.0 mmol) were reacted in a sealed tube under argon at 130 °C for 10 min. Column chromatography over silica gel (petroleum ether/EtOAc = 8:2) afforded 3-[(2-chlorophenyl)methoxy]-2-cyclohexen-1-one (**10b**) as a colorless liquid in 35% yield (84 mg, 0.35 mmol) and 2-[(2-chlorophenyl)methyl]-3-hydroxy-2-cyclohexen-1-one (**11b**) as white solid in 26% yield (62 mg, 0.26 mmol).

*3-[(2-Chlorophenyl)methoxy]-2-cyclohexen-1-one (**10b**).* $R_f$ = 0.11 (petroleum ether/EtOAc = 8:2); IR (ATR) $\nu$ 1645 (s) (C═O), 1595, 1364, 1223, 1178, 1134, 1057, 846, 756 $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 217 (3.98), 243 (4.27) nm; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.00 (quin, $^3J$ (5-H, 6-H) = 6.6 Hz, $^3J$ (4-H, 5-H) = 6.3 Hz, 2H, 5-H), 2.36 (t-like, $^3J$ (5-H, 6-H) = 7.2 Hz, 2H, 6-H), 2.48 (t-like, $^3J$ (4-H, 5-H) = 6.3 Hz, 2H, 4-H), 4.98 (s, 2H, $CH_2$), 5.49 (s, 1H, 2-H), 7.28 (overlapped, 2H, 4′-H and 5′-H), 7.35−7.43 (m, 2H, 3′-H and 6′-H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 21.1 (C-5), 28.8 (C-4), 36.6 (C-6), 67.5 ($CH_2$), 103.5 (C-2), 126.9 (C-5′), 129.1 (C-6′), 129.5 (C-4′), 129.6 (C-3′), 132.7 (C-2′), 133.1 (C-1′), 177.2 (C-3), 199.6 (C-1); MS (EI, 70 eV) $m/z$ (%) 236 (10) $[M]^+$, 201 (3) $[236-Cl]^+$, 125 (100), 28 (96); HRMS (EI, $M^+$) calcd for $C_{13}H_{13}ClO_2$ (236.0604), found 236.0606.

*Reaction between **1c** and **8a**.* According to general procedure I, 2-iodobenzyl bromide (**1c**) (297 mg, 1.0 mmol), 1,3-cyclohexanedione (**8a**) (224 mg, 2.0 mmol), CuI (38 mg, 20 mol %), and $Cs_2CO_3$ (1.303 g, 4.0 mmol) were reacted in a sealed tube under argon at 130 °C for 10 min. Column chromatography over silica gel (petroleum ether/EtOAc = 8:2) afforded 2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9a**) as a white solid in 19% yield (38 mg, 0.19 mmol), 3-[(2-iodophenyl)-methoxy]-2-cyclohexen-1-one (**10c**) as a white solid in 41% yield (134 mg, 0.41 mmol) and 2-[(2-iodophenyl)methyl]-3-hydroxy-2-cyclohexen-1-one (**11c**) as white solid in 5% yield (17 mg, 0.05 mmol).

*3-[(2-Iodophenyl)methoxy]-2-cyclohexen-1-one (**10c**).* mp 106−107 °C; $R_f$ = 0.09 (petroleum ether/EtOAc = 8:2); IR (ATR) $\nu$ 1641 (s) (C═O), 1600, 1348, 1223, 1180, 1140, 1011, 818, 748 $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 233 (4.28) nm; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.03 (quin, $^3J$ (5-H, 6-H) = 6.6 Hz, $^3J$ (4-H, 5-H) = 6.3 Hz, 2H, 5-H), 2.39 (t-like, $^3J$ (5-H, 6-H) = 7.2 Hz, 2H, 6-H), 2.51 (t, $^3J$ (4-H, 5-H) = 6.3 Hz, 2H, 4-H), 4.89 (s, 2H, $CH_2$), 5.51 (s, 1H, 2-H), 7.02−7.08 (m, 1H, 4′-H), 7.37−7.41 (m, 2H, 5′-H and 6′-H), 7.87 (d, $^3J$ (3′-H, 4′-H) = 7.5 Hz, 1H, 3′-H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 21.2 (C-5), 28.8 (C-4), 36.7 (C-6), 74.1 ($CH_2$), 97.8 (C-2′), 103.7 (C-2), 128.4 (C-5′), 128.9 (C-6′), 130.1 (C-4′), 137.3 (C-1′), 139.5 (C-3′), 177.2 (C-3), 199.7 (C-1); MS (EI, 70 eV) $m/z$ (%) 328 (94) $[M]^+$, 268 (24), 217 (100), 201 (92), 171 (16), 28 (96); HRMS (EI, $M^+$) calcd for $C_{13}H_{13}IO_2$ (327.9960), found 327.9948.

*Reaction between **1a** and **8b**.* According to general procedure I, 2-bromobenzyl bromide (**1a**) (250 mg, 1.0 mmol), 5-methyl-1,3-cyclohexanedione (**8b**) (252 mg, 2.0 mmol), CuI (38 mg, 20 mol %), and $Cs_2CO_3$ (1.303 g, 4.0 mmol) were reacted in a sealed tube under argon at 130 °C for 60 min. Column chromatography over silica gel (petroleum ether/EtOAc = 8:2) afforded 3-methyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9b**) as a white solid in 37% yield (80 mg, 0.37 mmol) and 3-[(2-bromophenyl)methoxy]-5-methyl-2-cyclohexen-1-one (**10d**) as a white solid in 36% yield (105 mg, 0.36 mmol).

*3-[(2-Bromophenyl)methoxy]-5-methyl-2-cyclohexen-1-one (**10d**).* mp 42−46 °C; $R_f$ = 0.32 (petroleum ether/EtOAc = 8:2); IR (ATR) $\nu$ 1648 (s) (C═O), 1599, 1363, 1214, 1196, 1136, 1031, 988, 770, 666 $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 243 (4.30) nm; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.10 (d, $^3J$ ($CH_3$, 5-H) = 6.3 Hz, 3H, $CH_3$), 2.03−2.12 (m, 1H, 6-Hb), 2.25 (dd, $^3J$ (4-Hb, 5-H) = 12.0 Hz, 2H, 4-Hb and 5-H), 2.42−2.55 (m, 2H, 4-Ha and 6-Ha), 4.96 (s, 2H, $CH_2$), 5.48 (s, 1H, 2-H), 7.22 (ddd, $^3J$ (4′-H, 5′-H) = 6.3 Hz, $^3J$ (3′-H, 4′-H) = 7.5 Hz, $^4J$ (4′-H, 6′-H) = 1.2 Hz, 1H, 4′-H), 7.34 (ddd, $^3J$ (4′-H, 5′-H) = 7.2 Hz, $^3J$ (5′-H, 6′-H) = 7.5 Hz, 1H, 5′-H), 7.42 (dd, $^3J$ (5′-H, 6′-H) = 7.5 Hz, 1H, 6′-H), 7.59 (dd, $^3J$ (3′-H, 4′-H) = 7.8 Hz, 1H, 3′-H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 20.9 ($CH_3$), 28.8 (C-5), 37.0 (C-4), 45.1 (C-6), 69.8 ($CH_2$), 103.2 (C-2), 122.9 (C-2′), 127.6 (C-5′), 129.2 (C-6′), 129.9 (C-4′), 132.9 (C-3′), 134.4 (C-1′), 176.5 (C-3), 199.6 (C-1); MS (EI, 70 eV) $m/z$ (%) 294 (8) $[M]^+$, 215 (9) $[294 - Br]^+$, 170 (100), 90 (34), 44 (24), 28 (80); Anal. Calcd for $C_{14}H_{15}BrO_2$ (295.17): C, 56.97; H, 5.12. found: C, 56.93; H, 5.10.

*Reaction between **1a** and **8c**.* According to general procedure I, 2-bromobenzyl bromide (**1a**) (250 mg, 1.0 mmol), 5,5-dimethyl-1,3-cyclohexanedione (**8c**) (280 mg, 2.0 mmol), CuI (38 mg, 20 mol %), and $Cs_2CO_3$ (1.303 g, 4.0 mmol) were reacted in a sealed tube under argon at 130 °C for 10 min. Column chromatography over silica gel (petroleum ether/EtOAc = 8:2) afforded 3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9c**) as a white solid in 35% yield (80 mg, 0.35 mmol) and 3-[(2-bromophenyl)methoxy]-5,5-dimethyl-2-cyclohexen-1-one (**10e**) as a pale yellow liquid in 36% yield (111 mg, 0.36 mmol).

*3-[(2-Bromophenyl)methoxy]-5,5-dimethyl-2-cyclohexen-1-one (**10e**).* $R_f$ = 0.36 (petroleum ether/EtOAc = 8:2); IR (ATR) $\nu$ 1653 (s) (C═O), 1604, 1356, 1220, 1203, 1143, 1022, 820, 750 $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 245 (4.28) nm; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.09 (s, 6H, 2 × $CH_3$), 2.23 (s, 2H, 6-H), 2.37 (s, 2H, 4-H), 4.96 (s, 2H, $CH_2$), 5.48 (s, 1H, 2-H), 7.20 (ddd, $^3J$ (4′-H, 5′-H) = 6.3 Hz, $^3J$ (3′-H, 4′-H) = 6.3 Hz, $^4J$ (4′-H, 6′-H) = 1.5 Hz, 1H, 4′-H), 7.33 (ddd, $^3J$ (4′-H, 5′-H) = 7.5 Hz, $^3J$ (5′-H, 6′-H) = 6.9 Hz, 1H, 5′-H), 7.41 (dd, $^3J$ (5′-H, 6′-H) = 6.3 Hz, $^4J$ (4′-H, 6′-H) = 1.2 Hz, 1H, 6′-H), 7.57 (dd, $^3J$ (3′-H, 4′-H) = 7.5 Hz, 1H, 3′-H); $^{13}$C NMR (75 MHz, $CDCl_3$ ) $\delta$ 2 × 28.2 (2 × $CH_3$), 32.5 (C-5), 42.7 (C-4), 50.7 (C-6), 69.8 ($CH_2$), 102.4 (C-2), 122.8 (C-2′), 127.5 (C-5′), 129.0 (C-6′), 129.8 (C-4′), 132.8 (C-3′), 134.4 (C-1′), 175.4 (C-3), 199.3 (C-1); MS (EI, 70 eV) $m/z$ (%) 308 (16) $[M]^+$, 229 (9) $[308 - Br]^+$, 169 (100), 90 (30), 69 (7), 28 (8); HRMS (EI, $M^+$) calcd for $C_{15}H_{17}BrO_2$ (308.0412), found 308.0433.

*Reaction between **1a** and **8e**.* According to general procedure I, 2-bromobenzyl bromide (**1a**) (250 mg, 1.0 mmol), 5-phenyl-1,3-cyclohexanedione (**8e**) (376 mg, 2.0 mmol), CuI (38 mg, 20 mol %), and $Cs_2CO_3$ (1.303 g, 4.0 mmol) were reacted in a sealed tube under argon


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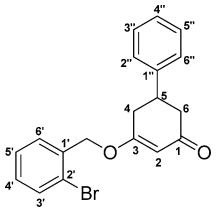
at 130 °C for 60 min. Column chromatography over silica gel (petroleum ether/EtOAc = 8:2) afforded 3-phenyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9e**) as a white solid in 38% yield (105 mg, 0.38 mmol) and 3-[(2-bromophenyl)methoxy]-5-phenyl-2-cyclohexen-1-one (**10g**) as a pale yellow liquid in 30% yield (107 mg, 0.30 mmol).

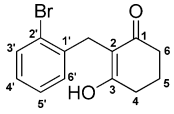
*3-[(2-Bromophenyl)methoxy]-5-phenyl-2-cyclohexen-1-one (**10g**).* $R_f$ = 0.23 (petroleum ether/EtOAc = 8:2); IR (ATR) $\nu$ 1651




(s) (C═O), 1600, 1347, 1215, 1189, 1028, 820, 751, 698 $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 245 (4.28) nm; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.60 (dd, $^2J$ (6-Ha, 6-Hb) = 16.2 Hz, $^3J$ (5-H, 6-Ha) = 12.0 Hz, 1H, 6-Ha), 2.69 (dd, $^2J$ (6-Ha, 6-Hb) = 16.0 Hz, $^3J$ (5-H, 6-Hb) = 4.5 Hz, 1H, 6-Hb), 2.70−2.85 (m, 2H, 4-H), 3.45−3.48 (m, 1H, 5-H), 5.01 (s, 2H, $CH_2$), 5.59 (s, 1H, 2-H), 7.23 (ddd, $^3J$ (4′-H, 5′-H) = 7.5 Hz, $^3J$ (3′-H, 4′-H) = 7.5 Hz, $^4J$ (4′-H, 6′-H) = 1.8 Hz, 1H, 4′-H), 7.29−7.31 (m, 3H, 2″-H, 6″-H and 4″-H), 7.34 (overlapped, 3H, 3″-H, 5″-H and 5′-H), 7.42 (dd, $^3J$ (5′-H, 6′-H) = 7.7 Hz, $^4J$ (4′-H, 6′-H) = 1.7 Hz, 1H, 6′-H), 7.60 (dd, $^3J$ (3′-H, 4′-H) = 8.0 Hz, $^4J$ (3′-H, 5′-H) = 1.2 Hz, 1H, 3′-H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 36.4 (C-4), 39.3 (C-5), 43.9 (C-6), 70.1 ($CH_2$), 103.5 (C-2), 122.9 (C-2′), 126.7 (C-2″ and C-6″), 127.1 (C-4″), 127.6 (C-5′), 128.8 (C-3″ and C-5″), 129.2 (C-6′), 129.9 (C-4′), 132.9 (C-3′), 134.3 (C-1′), 142.5 (C-1″), 176.1 (C-3), 198.6 (C-1); MS (EI, 70 eV) *m*/*z* (%) 356 (9) $[M]^+$, 277 (9) $[356 - Br]^+$, 217 (8), 169 (100), 131 (10), 90 (24), 69 (8), 28 (57); HRMS (EI, $M^+$) calcd for $C_{19}H_{17}BrO_2$ (356.0412), found 356.0386.

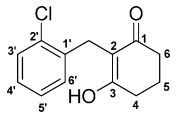
**General Procedure II for the Synthesis of Starting Materials 11.**[13a] The 1,3-cyclohexanedione **8** (10 mmol) was dissolved in aqueous NaOH (1 M, 10 mL) at 0 °C. The 2-halobenzyl bromide **1** (15 mmol) was added to the resulting solution. The mixture was heated at 100 °C for 3 h and then allowed to cool to room temperature. The solid formed was filtered and washed successively with petroleum ether (5 mL), cold water (5 mL), and cold diethyl ether (3 mL) until a pale beige solid was obtained. The crude product was recrystallized from dichloromethane/methanol (1:1) to afford the corresponding 2-[(2-haloaryl)methyl]-3-hydroxy-2-cyclic-1-one **11**.

**Synthesis and Characterization of Starting Materials 11.** *2-[(2-Bromophenyl)methyl]-3-hydroxy-2-cyclohexen-1-one (**11a**).*[13b]



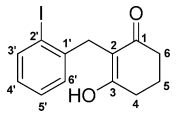

According to general procedure II, 1,3-cyclohexanedione (**8a**) (1.12 g, 10 mmol) was dissolved in aqueous NaOH (400 mg, 1 M, 10 mL) at 0 °C. 2-Bromobenzyl bromide (**1a**) (3.75 g, 15 mmol) was added, and the mixture was heated at 100 °C for 3 h. The crude product was recrystallized from dichloromethane/methanol (1:1) to afford 2-[(2-bromophenyl)methyl]-3-hydroxy-2-cyclohexen-1-one (**11a**) as a white solid in 71% yield (2.0 g, 7.1 mmol): mp 190−191 °C (dichloromethane/methanol) (lit.[13b] mp 189−191 °C); $R_f$ = 0.12 (petroleum ether/EtOAc = 6:4); IR (ATR) $\nu$ 2558 (w) (O−H), 1635 (conjugated C═O), 1557, 1359, 1271, 1187, 1067, 1013, 918, 742, 658 (C−Br) $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 251 (4.16) nm; $^1H$ NMR (300 MHz, $CD_3OD$) $\delta$ 2.04 (quin-like, $^3J$ (5-H, 6-H) = 6.3 Hz, $^3J$ (4-H, 5-H) = 6.3 Hz, 2H, 5-H), 2.51 (t-like, $^3J$ (5-H, 6-H) = 6.3 Hz, $^3J$ (4-H, 5-H) = 6.6 Hz, 4H, 4-H and 6-H), 3.64 (s, 2H, $CH_2$), 6.98 (overlapped, 2H, 4′-H and 6′-H), 7.16 (ddd, $^3J$ (5′-H, 6′-H) = 7.5 Hz, $^3J$ (4′-H, 5′-H) = 7.5 Hz, 1H, 5′-H), 7.50 (dd, $^3J$ (3′-H, 4′-H) = 8.1 Hz, 1H, 3′-H); $^{13}C$ NMR (75 MHz, $CD_3OD$) $\delta$ 22.1 (C-5), 29.2 ($CH_2$), 2 × 33.9 (C-4 and C-6), 114.2 (C-2), 125.9 (C-2′), 2 × 128.2 (C-4′ and C-5′), 129.5 (C-6′), 133.4 (C-3′), 141.1 (C-1′).

*2-[(2-Chlorophenyl)methyl]-3-hydroxy-2-cyclohexen-1-one (**11b**).* According to general procedure II, 1,3-cyclohexanedione (**8a**)



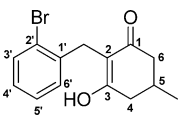

(1.12 g, 10 mmol) was dissolved in aqueous NaOH (400 mg, 1 M, 10 mL) at 0 °C. 2-Chlorobenzyl bromide (**1b**) (3.08 g, 15 mmol) was added, and the mixture was heated at 100 °C for 3 h. The crude product was recrystallized from dichloromethane/methanol (1:1) to afford 2-[(2-chlorophenyl)methyl]-3-hydroxy-2-cyclohexen-1-one (**11b**) as a white solid in 51% yield (1.2 g, 5.1 mmol): mp 191−193 °C (dichloromethane/methanol); $R_f$ = 0.14 (petroleum ether/EtOAc = 6:4); IR (ATR) $\nu$ 2395 (w) (O−H), 1638 (conjugated C═O), 1557, 1383, 1357, 1270, 1187, 1038, 1014, 920, 745, 692 (C−Br) $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 252 (4.02) nm; $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.93 (quin, $^3J$ (5-H, 6-H) = 6.3 Hz, $^3J$ (4-H, 5-H) = 6.3 Hz, 2H, 5-H), 2.42 (overlapped, 4H, 4-H and 6-H), 3.53 (s, 2H, $CH_2$), 6.96 (dd, $^3J$ (5′-H, 6′-H) = 7.2 Hz, $^4J$ (4′-H, 6′-H) = 2.1 Hz, 1H, 6′-H), 7.12−7.20 (m, 2H, 4′-H and 5′-H), 7.37 (dd, $^3J$ (3′-H, 4′-H) = 6.9 Hz, $^4J$ (3′-H, 5′-H) = 1.5 Hz, 1H, 3′-H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta$ 20.6 (C-5), 24.9 ($CH_2$), 2 × 32.7 (C-4 and C-6), 111.3 (C-2), 126.8 (C-5′), 127.0 (C-4′), 128.5 (C-6′), 128.6 (C-3′-H), 133.1 (C-1′), 138.1 (C-2′); MS (EI, 70 eV) *m*/*z* (%) 236 (2) $[M]^+$, 201 (60) $[236-Cl]^+$, 145 (14), 28 (100); HRMS (EI, $M^+$) calcd for $C_{13}H_{13}ClO_2$ (236.0604), found 236.0604.

*2-[(2-Iodophenyl)methyl]-3-hydroxy-2-cyclohexen-1-one (**11c**).*[13d] According to general procedure II, 1,3-cyclohexanedione




(**8a**) (560 mg, 5 mmol) was dissolved in aqueous NaOH (200 mg, 1 M, 5 mL) at 0 °C. 2-Iodobenzyl bromide (**1c**) (2.23 g, 7.5 mmol) was added, and the mixture was heated at 100 °C for 3 h. The crude product was recrystallized from dichloromethane/methanol (1:1) to afford 2-[(2-iodophenyl)methyl]-3-hydroxy-2-cyclohexen-1-one (**11c**) as a white solid in 60% yield (980 mg, 3.0 mmol): mp 161−162 °C (dichloromethane/methanol) (lit.[13d] mp 154−155 °C); $R_f$ = 0.17 (petroleum ether/EtOAc = 6:4); $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.93 (quin, $^3J$ (5-H, 6-H) = 6.3 Hz, $^3J$ (4-H, 5-H) = 6.3 Hz, 2H, 5-H), 2.42 (t-like, $^3J$ (5-H, 6-H) = 6.0 Hz, $^3J$ (4-H, 5-H) = 6.3 Hz, 4H, 4-H and 6-H), 3.40 (s, 2H, $CH_2$), 6.88 (overlapped, 2H, 4′-H and 6′-H), 7.23 (ddd, $^3J$ (5′-H, 6′-H) = 7.5 Hz, $^3J$ (4′-H, 5′-H) = 7.5 Hz, 1H, 5′-H), 7.81 (dd, $^3J$ (3′-H, 4′-H) = 7.8 Hz, $^4J$ (3′-H, 5′-H) = 0.9 Hz, 1H, 3′-H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta$ 20.6 (C-5), 32.5 ($CH_2$), 2 × 33.3 (C-4 and C-6), 101.7 (C-2′), 112.0 (C-2), 127.3 (C-5′), 127.5 (C-4′), 128.0 (C-6′), 138.5 (C-3′), 142.5 (C-1′).

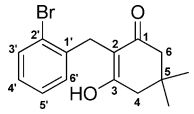
*2-[(2-Bromophenyl)methyl]-3-hydroxy-5-methyl-2-cyclohexen-1-one (**11d**).* According to general procedure II, 5-methyl-1,3-cyclo-




hexanedione (**8b**) (1.26 g, 10 mmol) was dissolved in aqueous NaOH (400 mg, 1 M, 10 mL) at 0 °C. 2-Bromobenzyl bromide (**1a**) (3.75 g, 15 mmol) was added, and the mixture was heated at 100 °C for 3 h. The crude product was recrystallized from dichloromethane/methanol (1:1) to afford 2-[(2-bromophenyl)methyl]-3-hydroxy-5-methyl-2-cyclohexen-1-one (**11d**) as a white solid in 75% yield (2.2 g, 7.5 mmol): mp 205−207 °C (dichloromethane/methanol); $R_f$ = 0.24

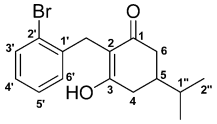
(petroleum ether/EtOAc = 6:4); IR (ATR) $\nu$ 2359 (w) (O−H), 1637 (conjugated C═O), 1556, 1314, 1247, 1215, 1145, 1044, 1021, 751, 678 (C−Br) $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 252 (4.14) nm; $^1H$ NMR (300 MHz, $CD_3OD$) $\delta$ 1.12 (d, $^3J$ ($CH_3$, 5-H) = 5.7 Hz, 3H, $CH_3$), 2.25−2.32 (m, 3H, 4-Hb, 5-Hb and 6-H), 2.52 (br dd, $^2J$ (4-Ha, 4-Hb) = 12.3 Hz, $^2J$ (6-Ha, 6-Hb) = 12.3 Hz, 2H, 4-Ha and 6-Ha), 3.63 (s, 2H, $CH_2$), 6.95 (dd, $^3J$ (5′-H, 6′-H) = 7.5 Hz, 1H, 6′-H), 7.01 (ddd, $^3J$ (4′-H, 5′-H) = 7.5 Hz, $^3J$ (3′-H, 4′-H) = 7.5 Hz, 1H, 4′-H), 7.16 (ddd, $^3J$ (4′-H, 5′-H) = 7.5 Hz, $^3J$ (5′-H, 6′-H) = 6.9 Hz, 1H, 5′-H), 7.50 (dd, $^3J$ (3′-H, 4′-H) = 7.8 Hz, 1H, 3′-H); $^{13}C$ NMR (75 MHz, $CD_3$ OD) $\delta$ 21.3 ($CH_3$), 29.2 ($CH_2$), 30.0 (C-5), 2 × 42.1 (C-6 and C-4), 113.7 (C-2), 125.9 (C-2′), 2 × 128.2 (C-4′ and C-5′), 129.7 (C-6′), 133.4 (C-3′), 141.1 (C-1′); Anal. Calcd for $C_{14}H_{15}BrO_2$ (295.17): C, 56.97; H, 5.12. found: C, 56.77; H, 5.13.

*2-[(2-Bromophenyl)methyl]-3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one (**11e**).* According to general procedure II, 5,5-dimethyl-1,3-



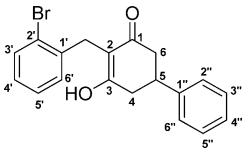
cyclohexanedione (**8c**) (1.40 g, 10 mmol) was dissolved in aqueous NaOH (400 mg, 1 M, 10 mL) at 0 °C. 2-Bromobenzyl bromide (**1a**) (3.75 g, 15 mmol) was added, and the mixture was heated at 100 °C for 3 h. The crude product was recrystallized from dichloromethane/methanol (1:1) to afford 2-[(2-bromophenyl)methyl]-3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one (**11e**) as a white solid in 68% yield (2.1 g, 6.8 mmol): mp 188−189 °C (dichloromethane/methanol); $R_f$ = 0.33 (petroleum ether/EtOAc = 6:4); IR (ATR) $\nu$ 2969 (w) (O−H), 1643 (conjugated C═O), 1562, 1370, 1249, 1022, 848, 752, 650 (C−Br) $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 253 (4.06) nm; $^1H$ NMR (300 MHz, $CD_3OD$) $\delta$ 1.13 (s, 6H, 2 × $CH_3$), 2.39 (s, 4H, 4-H and 6-H), 3.65 (s, 2H, $CH_2$), 7.01 (overlapped, 2H, 4′-H and 6′-H), 7.16 (ddd, $^3J$ (4′-H, 5′-H) = 7.5 Hz, $^3J$ (5′-H, 6′-H) = 7.2 Hz, 1H, 5′-H), 7.50 (dd, $^3J$ (3′-H, 4′-H) = 8.1 Hz, 1H, 3′-H); $^{13}C$ NMR (75 MHz, $CD_3$ OD) $\delta$ 2 × 28.8 (2 × $CH_3$), 29.1 ($CH_2$), 33.1 (C-5), 2 × 47.7 (C-6 and C-4), 113.1 (C-2), 125.8 (C-2′), 128.2 (C-5′), 128.3 (C-4′), 129.9 (C-6′), 133.4 (C-3′), 141.2 (C-1′); Anal. Calcd for $C_{15}H_{17}BrO_2$ (309.20): C, 58.27; H, 5.54. found: C, 58.24; H, 5.56.

*2-[(2-Bromophenyl)methyl]-3-hydroxy-5-isopropyl-2-cyclohexen-1-one (**11f**).* According to general procedure II, 5-isopropyl-1,3-



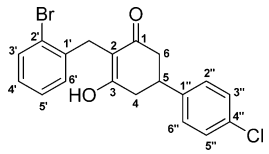
cyclohexanedione (**8d**) (771 mg, 5 mmol) was dissolved in aqueous NaOH (200 mg, 1 M, 5 mL) at 0 °C. 2-Bromobenzyl bromide (**1a**) (1.88 g, 7.5 mmol) was added, and the mixture was heated at 100 °C for 3 h. The crude product was recrystallized from dichloromethane/methanol (1:1) to afford 2-[(2-bromophenyl)methyl]-3-hydroxy-5-isopropyl-2-cyclohexen-1-one (**11f**) as a white solid in 83% yield (1.35 g, 4.18 mmol): mp 188−189 °C (dichloromethane/methanol); $R_f$ = 0.41 (petroleum ether/EtOAc = 6:4); IR (ATR) $\nu$ 2532 (w) (O−H), 1620 (conjugated C═O), 1558, 1303, 1245, 1208, 1148, 1038, 750, 654 (C−Br) $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 269 (3.44) nm; $^1H$ NMR (300 MHz, $CD_3OD$) $\delta$ 0.99 (d, $^3J$ (1″-H, 2″-H) = 6.6 Hz, 6H, 2 × $CH_3$), 1.60−1.67 (m, 1H, 1″-H), 1.93−1.97 (m, 1H, 5-H), 2.32 (ddd, $^2J$ (4-Ha, 4-Hb) = 12.0 Hz, $^2J$ (6-Ha, 6-Hb) = 12.0 Hz, $^3J$ (4-Hb, 5-H) = 4.8 Hz, $^3J$ (5-H, 6-Hb) = 4.8 Hz, 2H, 4-Hb and 6-Hb), 2.51 (dd, $^2J$ (4-Ha, 4-Hb) = 12.3 Hz, $^2J$ (6-Ha, 6-Hb) = 12.3 Hz, $^3J$ (4-Ha, 5-H) = 4.8 Hz, $^3J$ (5-H, 6-Ha) = 4.8 Hz, 2H, 4-Ha and 6-Ha), 3.63 (s, 2H, $CH_2$), 6.94 (dd, $^3J$ (5′-H, 6′-H) = 7.2 Hz, 1H, 6′-H), 7.01 (ddd, $^3J$ (3′-H, 4′-H) = 7.5 Hz, $^3J$ (4′-H, 5′-H) = 7.5 Hz, 1H, 4′-H), 7.16 (ddd, $^3J$ (4′-H, 5′-H) = 7.5 Hz, $^3J$ (5′-H, 6′-H) = 6.9 Hz, 1H, 5′-H), 7.50 (dd, $^3J$ (3′-H, 4′-H) = 8.1 Hz, 1H, 3′-H); $^{13}C$ NMR (75 MHz, $CD_3$ OD) $\delta$ 2 × 20.1 (2 × $CH_3$), 29.2 ($CH_2$), 33.2 (C-1″), 2 × 38.0 (C-6 and C-4), 41.3 (C-5), 113.7 (C-2), 125.9 (C-2′), 2 × 128.2 (C-4′ and C-5′), 129.7 (C-6′), 133.4 (C-3′), 141.0 (C-1′); Anal. Calcd for $C_{16}H_{19}BrO_2$ (323.22): C, 59.45; H, 5.92. found: C, 59.26; H, 5.91.

*2-[(2-Bromophenyl)methyl]-3-hydroxy-5-phenyl-2-cyclohexen-1-one (**11g**).* According to general procedure II, 5-phenyl-1,3-cyclo-



hexanedione (**8e**) (1.88 g, 10 mmol) was dissolved in aqueous NaOH (400 mg, 1 M, 10 mL) at 0 °C. 2-Bromobenzyl bromide (**1a**) (3.75 g, 15 mmol) was added, and the mixture was heated at 100 °C for 3 h. The crude product was recrystallized from dichloromethane/methanol (1:1) to afford 2-[(2-bromophenyl)methyl]-3-hydroxy-5-phenyl-2-cyclohexen-1-one (**11g**) as a white solid in 56% yield (2.0 g, 5.6 mmol): mp 228−229 °C (dichloromethane/methanol); $R_f$ = 0.36 (petroleum ether/EtOAc = 6:4); IR (ATR) $\nu$ 2554 (w) (O−H), 1634 (conjugated C═O), 1558, 1331, 1245, 1211, 1041, 912, 748, 701, 656 (C−Br) $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 253 (4.11) nm; $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 2.56 (br dd, $^2J$ (4-Ha, 4-Hb) = 15.6 Hz, $^2J$ (6-Ha, 6-Hb) = 15.6 Hz, 2H, 4-Hb and 6-Hb), 2.80 (ddd, $^3J$ (4-Ha, 5-H) = 11.7 Hz, $^3J$ (5-H, 6-Ha) = 11.7 Hz, $^2J$ (4-Ha, 4-Hb) = 16.2 Hz, $^2J$ (6-Ha, 6-Hb) = 16.2 Hz, 2H, 4-Ha and 6-Ha), 3.41−3.49 (m, 1H, 5-H), 3.54 (br s, 2H, $CH_2$), 6.98 (dd, $^3J$ (5′-H, 6′-H) = 7.5 Hz, 1H, 6′-H), 7.09 (ddd, $^3J$ (3′-H, 4′-H) = 7.5 Hz, $^3J$ (4′-H, 5′-H) = 7.5 Hz, 1H, 4′-H), 7.23 (overlapped, 2H, 4″-H and 5′-H), 7.32−7.40 (m, 4H, 2″-H, 3″-H, 5″-H, and 6″-H), 7.56 (dd, $^3J$ (3′-H, 4′-H) = 8.1 Hz, 1H, 3′-H), 10.91 (bs, 1H, 3-H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta$ 27.9 ($CH_2$), 38.2 (C-5), 2 × 38.7 (C-4 and C-6), 111.2 (C-2), 124.3 (C-2′), 126.6 (C-4″), 2 × 126.9 (C-2″ and C-6″), 127.3 (C-5′), 127.4 (C-4′), 2 × 128.5 (C-3″ and C-5″), 128.6 (C-6′), 131.9 (C-3′), 139.4 (C-1′), 143.6 (C-1″); Anal. Calcd for $C_{19}H_{17}BrO_2$ (357.24): C, 63.88; H, 4.80. found: C, 63.59; H, 4.81.

*2-[(2-Bromophenyl)methyl]-5-(4-chlorophenyl)-3-hydroxy-2-cyclohexen-1-one (**11h**).* According to general procedure II, 5-(4-



chlorophenyl)-1,3-cyclohexanedione (**8f**) (2.23 g, 10 mmol) was dissolved in aqueous NaOH (400 mg, 1 M, 10 mL) at 0 °C. 2-Bromobenzyl bromide (**1a**) (3.75 g, 15 mmol) was added, and the mixture was heated at 100 °C for 3 h. The crude product was recrystallized from dichloromethane/methanol (1:1) to afford 2-[(2-bromophenyl)methyl]-5-(4-chlorophenyl)-3-hydroxy-2-cyclohexen-1-one (**11h**) as a white solid in 82% yield (3.2 g, 8.2 mmol): mp 241−242 °C (dichloromethane/methanol); $R_f$ = 0.30 (petroleum ether/EtOAc = 6:4); IR (ATR) $\nu$ 2516 (w) (O−H), 1620 (conjugated C═O), 1556, 1318, 1246, 1212, 1041, 821, 751, 673 (C−Br) $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 253 (4.00) nm; $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 2.58 (br dd, $^3J$ (4-Hb, 5-H) = 3.5 Hz, $^3J$ (5-H, 6-Hb) = 3.5 Hz, $^2J$ (4-Ha, 4-Hb) = 16.2 Hz, $^2J$ (6-Ha, 6-Hb) = 16.2 Hz, 2H, 4-Hb and 6-Hb), 2.79 (ddd, $^3J$ (4-Ha, 5-H) = 12.0 Hz, $^3J$ (5-H, 6-Ha) = 12.0 Hz, $^2J$ (4-Ha, 4-Hb) = 16.0 Hz, $^2J$ (6-Ha, 6-Hb) = 16.0 Hz, 2H, 4-Ha and 6-Ha), 3.42−3.51 (m, 1H, 5-H), 3.54 (br s, 2H, $CH_2$), 6.97 (dd, $^3J$ (5′-H, 6′-H) = 7.6 Hz, $^4J$ (4′-H, 6′-H) = 1.6 Hz, 1H, 6′-H), 7.09 (ddd, $^3J$ (3′-H, 4′-H) = 7.6 Hz, $^3J$ (4′-H, 5′-H) = 7.6 Hz, $^4J$ (4′-H, 6′-H) = 1.7 Hz, 1H, 4′-H), 7.22 (ddd, $^3J$ (4′-H, 5′-H) = 7.5 Hz, $^3J$ (5′-H, 6′-H) = 7.5 Hz, $^4J$ (3′-H, 5′-H) = 1.4 Hz, 1H, 5′-H), 7.36−7.45 (m, 4H, 2″-H, 6″-H, 3″-H, and 5″-H), 7.56 (dd, $^3J$ (3′-H, 4′-H) = 7.8 Hz, $^4J$ (3′-H, 5′-H) = 1.3 Hz, 1H, 3′-H), 10.92 (br s, 1H, 3-H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta$ 27.9 ($CH_2$), 37.6 (C-5), 2 × 38.1 (C-6 and C-4), 111.2 (C-2), 124.3 (C-2′), 127.3 (C-5′), 127.4 (C-4′), 2 × 128.4 (C-2″ and C-6″), 128.6 (C-6′), 2 × 128.9 (C-3″ and C-5″), 131.2 (C-4″), 131.9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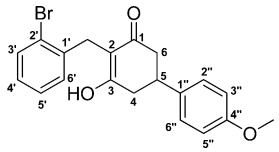
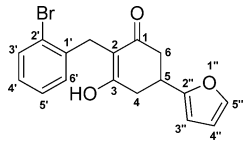
(C-3′), 139.4 (C-1′), 142.6 (C-1″); Anal. Calcd for $C_{19}H_{16}BrClO_2$ (391.69): C, 58.26; H, 4.12. found: C, 58.30; H, 4.14.

*2-[(2-Bromophenyl)methyl]-3-hydroxy-5-(4-methoxyphenyl)-2-cyclohexen-1-one (**11i**).* According to general procedure II, 5-(4-



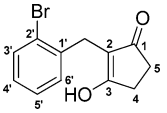
methoxyphenyl)-1,3-cyclohexanedione (**8g**) (2.18 g, 10 mmol) was dissolved in aqueous NaOH (400 mg, 1 M, 10 mL) at 0 °C. 2-Bromobenzyl bromide (**1a**) (3.75 g, 15 mmol) was added, and the mixture was heated at 100 °C for 3 h. The crude product was recrystallized from dichloromethane/methanol (1:1) to afford 2-[(2-bromophenyl)methyl]-3-hydroxy-5-(4-methoxyphenyl)-2-cyclohexen-1-one (**11i**) as a white solid in 80% yield (3.1 g, 8.0 mmol): mp 218−219 °C (dichloromethane/methanol); $R_f$ = 0.31 (petroleum ether/EtOAc = 6:4); IR (ATR) $\nu$ 2551 (w) (O−H), 1630 (conjugated C═O), 1558, 1513, 1326, 1245, 1212, 1040, 829, 757, 656 (C−Br) $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 252 (4.16) nm; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 2.53 (br dd, $^3J$ (4-Hb, 5-H) = 7.5 Hz, $^3J$ (5-H, 6-Hb) = 7.5 Hz, $^2J$ (4-Ha, 4-Hb) = 16.5 Hz, $^2J$ (6-Ha, 6-Hb) = 16.5 Hz, 2H, 4-Hb and 6-Hb), 2.75 (ddd, $^3J$ (4-Ha, 5-H) = 11.7 Hz, $^3J$ (5-H, 6-Ha) = 11.7 Hz, $^2J$ (4-Ha, 4-Hb) = 15.9 Hz, $^2J$ (6-Ha, 6-Hb) = 15.9 Hz, 2H, 4-Ha and 6-Ha), 3.33−3.42 (m, 1H, 5-H), 3.53 (br s, 2H, $CH_2$), 3.73 (br s, 3H, OMe), 6.90 (br dd, $^3J$ (2″-H, 3″-H) = 8.7 Hz, $^3J$ (5″-H, 6″-H) = 8.7 Hz, 2H, 3″-H and 5″-H), 6.96 (dd, $^3J$ (5′-H, 6′-H) = 7.5 Hz, 1H, 6′-H), 7.09 (ddd, $^3J$ (3′-H, 4′-H) = 6.3 Hz, $^3J$ (4′-H, 5′-H) = 7.5 Hz, $^4J$ (4′-H, 6′-H) = 1.2 Hz, 1H, 4′-H), 7.22 (ddd, $^3J$ (4′-H, 5′-H) = 7.5 Hz, $^3J$ (5′-H, 6′-H) = 7.5 Hz, 1H, 5′-H), 7.30 (br dd, $^3J$ (2″-H, 3″-H) = 8.7 Hz, $^3J$ (5″-H, 6″-H) = 8.7 Hz, 2H, 2″-H and 6″-H), 7.56 (dd, $^3J$ (3′-H, 4′-H) = 7.5 Hz, 1H, 3′-H), 10.85 (br s, 1H, 3-H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 27.9 ($CH_2$), 37.5 (C-5), 2 × 38.0 (C-6 and C-4), 55.0 (−OCH $_3$), 111.1 (C-2), 2 × 113.8 (C-3″ and C-5″), 124.3 (C-2′), 127.35 (C-5′), 127.40 (C-4′), 2 × 127.9 (C-2″ and C-6″), 128.6 (C-6′), 131.9 (C-3′), 135.5 (C-1″), 139.4 (C-1′), 157.9 (C-4″); Anal. Calcd for $C_{20}H_{19}BrO_3$ (387.27): C, 62.03; H, 4.95. found: C, 61.81; H, 4.95.

*2-[(2-Bromophenyl)methyl]-5-(furan-2-yl)-3-hydroxy-2-cyclohexen-1-one (**11j**).* According to general procedure II, 5-(furan-2-yl)-1,3-



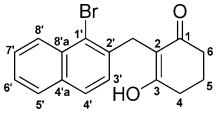
cyclohexanedione (**8h**) (891 mg, 5 mmol) was dissolved in aqueous NaOH (200 mg, 1 M, 5 mL) at 0 °C. 2-Bromobenzyl bromide (**1a**) (1.88 g, 7.5 mmol) was added, and the mixture was heated at 100 °C for 3 h. The crude product was recrystallized from dichloromethane/methanol (1:1) to afford 2-[(2-bromophenyl)methyl]-5-(furan-2-yl)-3-hydroxy-2-cyclohexen-1-one (**11j**) as a white solid in 75% yield (1.3 g, 3.75 mmol): mp 231−232 °C (dichloromethane/methanol); $R_f$ = 0.34 (petroleum ether/EtOAc = 6:4); IR (ATR) $\nu$ 2550 (w) (O−H), 1640 (conjugated C═O), 1559, 1361, 1316, 1251, 1215, 1042, 755, 730, 663 (C−Br) $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 253 (4.12) nm; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 2.62−2.88 (m, 4H, 4-H and 6-H), 3.49 (br s, 2H, $CH_2$), 3.52−3.58 (m, 1H, 5-H), 6.17 (d, $^3J$ (3″-H, 4″-H) = 3.3 Hz, 1H, 3″-H), 6.41 (ddd, $^3J$ (3″-H, 4″-H) = 3.0 Hz, $^3J$ (4″-H, 5″-H) = 1.8 Hz, 1H, 4″-H), 6.81 (dd, $^3J$ (5′-H, 6′-H) = 7.5 Hz, 1H, 6′-H), 7.06 (ddd, $^4J$ (4′-H, 6′-H) = 1.2 Hz, $^3J$ (4′-H, 5′-H) = 6.3 Hz, $^3J$ (3′-H, 4′-H) = 7.5 Hz, 1H, 4′-H), 7.16 (ddd, $^3J$ (4′-H, 5′-H) = 6.3 Hz, $^3J$ (5′-H, 6′-H) = 7.5 Hz, 1H, 5′-H), 7.54 (dd, $^3J$ (3′-H, 4′-H) = 7.8 Hz, 1H, 3′-H), 7.59 (br s, 1H, 5″-H), 10.92 (br s, 1H, 3-H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 27.8 ($CH_2$), 31.5 (C-5), 2 × 38.7 (C-4 and C-6), 104.9 (C-3″), 110.3 (C-4″), 111.3 (C-2), 124.2 (C-2′), 127.3 (C-5′), 127.4 (C-4′), 128.5 (C-6′), 131.9 (C-3′), 139.3 (C-1′), 141.7 (C-5″), 156.4 (C-2″); Anal. Calcd for $C_{17}H_{15}BrO_3$ (347.20): C, 58.81; H, 4.35. found: C, 58.62; H, 4.38.

*2-[(2-Bromophenyl)methyl]-3-hydroxy-2-cyclopenten-1-one (**11k**).* According to general procedure II, 1,3-cyclopentanedione (**8i**)



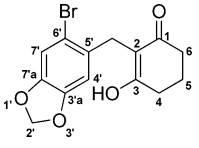
(981 mg, 10 mmol) was dissolved in aqueous NaOH (400 mg, 1 M, 10 mL) at 0 °C. 2-Bromobenzyl bromide (**1a**) (3.75 g, 15 mmol) was added, and the mixture was heated at 100 °C for 3 h. The crude product was recrystallized from dichloromethane/methanol (1:1) to afford 2-[(2-bromophenyl)methyl]-3-hydroxy-2-cyclopenten-1-one (**11k**) as a green solid in 45% yield (1.2 g, 4.5 mmol): mp 172−173 °C (dichloromethane/methanol); $R_f$ = 0.06 (petroleum ether/EtOAc = 6:4); IR (ATR) $\nu$ 2351 (w) (O−H), 1557, 1350, 1258, 1172, 1029, 769, 740, 652 (C−Br) $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 239 (4.18) nm; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 2.58 (s, 4H, 4-H and 5-H), 3.52 (s, 2H, CH $_2$), 7.05 (overlapped, 2H, 4′-H and 6′-H), 7.20 (ddd, $^3J$ (4′-H, 5′-H) = 8.1 Hz, $^3J$ (5′-H, 6′-H) = 6.9 Hz, 1H, 5′-H), 7.52 (dd, $^3J$ (3′-H, 4′-H) = 7.8 Hz, 1H, 3′-H); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 28.4 ($CH_2$), 2 × 31.5 (C-4 and C-5), 115.8 (C-2), 125.6 (C-2′), 128.4 (C-5′), 128.7 (C-4′), 130.6 (C-6′), 133.6 (C-3′), 139.8 (C-1′); Anal. Calcd for $C_{12}H_{11}BrO_2$ (267.12): C, 53.96; H, 4.15. found: C, 53.83; H, 4.20.

*2-[(1-Bromonaphthalen-2-yl)methyl]-3-hydroxy-2-cyclohexen-1-one (**11l**).* According to general procedure II, 1,3-cyclohexanedione



(**8a**) (560 mg, 5 mmol) was dissolved in aqueous NaOH (200 mg, 1 M, 5 mL) at 0 °C. 1-Bromo-2-(bromomethyl)naphthalene (**1d**) (2.25 g, 7.5 mmol) was added, and the mixture was heated at 100 °C for 3 h. The crude product was recrystallized from dichloromethane/methanol (1:1) to afford 2-[(1-bromonaphthalen-2-yl)methyl-3-hydroxy-2-cyclohexen-1-one (**11l**) as a white solid in 60% yield (1.0 g, 3.0 mmol): mp 226−227 °C (dichloromethane/methanol); $R_f$ = 0.06 (petroleum ether/EtOAc = 6:4); IR (ATR) $\nu$ 2579 (w) (O−H), 1637 (conjugated C═O), 1558, 1356, 1271, 1184, 1011, 809, 734, 670 (C−Br) $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 276 (3.74), 287 (3.76) nm; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.95 (quin-like, $^3J$ (5-H, 6-H) = 6.3 Hz, $^3J$ (4-H, 5-H) = 6.3 Hz, 2H, 5-H), 2.44 (t-like, $^3J$ (4-H, 5-H) = 5.7 Hz, $^3J$ (5-H, 6-H) = 5.7 Hz, 4H, 4-H and 6-H), 3.77 (s, 2H, $CH_2$), 7.13 (dd, $^3J$ (3′-H, 4′-H) = 8.4 Hz, 1H, 3′-H), 7.53 (ddd, $^3J$ (5′-H, 6′-H) = 7.2 Hz, $^3J$ (6′-H, 7′-H) = 7.5 Hz, 1H, 6′-H), 7.64 (ddd, $^3J$ (6′-H, 7′-H) = 7.2 Hz, $^3J$ (7′-H, 8′-H) = 7.5 Hz, 1H, 7′-H), 7.80 (dd, $^3J$ (3′-H, 4′-H) = 8.4 Hz, 1H, 4′-H), 7.90 (dd, $^3J$ (5′-H, 6′-H) = 8.1 Hz, 1H, 5′-H), 8.21 (dd, $^3J$ (7′-H, 8′-H) = 8.4 Hz, 1H, 8′-H), 10.81 (br s, 1H, 3-H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 20.5 (C-5), 29.0 (CH $_2$), 2 × 38.7 (C-4 and C-6), 112.0 (C-2), 122.9 (C-1′), 125.8 (C-6′), 126.1 (C-8′), 126.5 (C-3′), 127.2 (C-4′), 127.6 (C-7′), 128.1 (C-5′), 131.6 (C-8′a), 132.7 (C-4′a), 138.5 (C-2′); MS (EI, 70 eV) $m/z$ (%) 332 (8) $[M]^+$, 251 (100) $[332 - Br]^+$, 195 (7), 152 (5), 126 (6); HRMS (EI, $M^+$) calcd for $C_{17}H_{15}BrO_2$ (330.0255), found 330.0256.

*2-[(6-Bromo-1,3-benzodioxol-5-yl)methyl]-3-hydroxy-2-cyclohexen-1-one (**11m**).* According to general procedure II, 1.3-cyclohexanedione



(**8a**) (560 mg, 5 mmol) was dissolved in aqueous NaOH (200 mg, 1 M, 5 mL) at 0 °C. 5-Bromo-6-(bromomethyl)benzo[*d*][1,3]dioxole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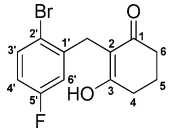
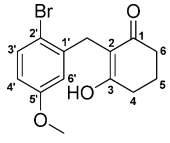
(**1e**) (2.21 g, 7.5 mmol) was added, and the mixture was heated at 100 °C for 3 h. The crude product was recrystallized from dichloromethane/methanol (1:1) to afford 2-[(6-bromo-1,3-benzodioxol-5-yl)methyl]-3-hydroxy-2-cyclohexen-1-one (**11m**) as a white solid in 61% yield (1.0 g, 3.08 mmol): mp 191−192 °C (dichloromethane/methanol); $R_f$ = 0.10 (petroleum ether/EtOAc = 6:4); IR (ATR) $\nu$ 2550 (w) (O−H), 1630 (conjugated C═O), 1557, 1499, 1475, 1341, 1224, 1177, 1039, 1008, 935, 867 $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 203 (4.55), 248 (4.20), 294 (3.62) nm; $^1H$ NMR (300 MHz, $CD_3OD$) $\delta$ 2.03 (quin, $^3J$ (5-H, 6-H) = 6.3 Hz, $^3J$ (4-H, 5-H) = 6.3 Hz, 2H, 5-H), 2.50 (t-like, $^3J$ (4-H, 5-H) = 6.6 Hz, $^3J$ (5-H, 6-H) = 6.6 Hz, 4H, 4-H and 6-H), 3.53 (s, 1H, $CH_2$), 5.89 (s, 2H, 2′-H), 6.46 (s, 1H, 4′-H), 6.97 (s, 1H, 7′-H); $^{13}C$ NMR (75 MHz, $CD_3OD$) $\delta$ 22.1 (C-5), 29.0 ($CH_2$), 2 × 33.9 (C-4 and C-6), 102.9 (C-2′), 109.5 (C-4′), 113.2 (C-7′), 114.6 (C-2), 115.5 (C-6′), 134.5 (C-5′), 147.8 (C-7′a), 148.8 (C-3′a); Anal. Calcd for $C_{14}H_{13}BrO_4$ (325.15): C, 51.71; H, 4.03. found: C, 51.61; H, 4.09.

*2-[(2-Bromo-5-fluorophenyl)methyl]-3-hydroxy-2-cyclohexen-1-one (**11n**).* According to general procedure II, 1,3-cyclohexanedione



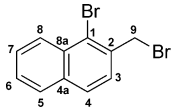

(**8a**) (224 mg, 2 mmol) was dissolved in aqueous NaOH (80 mg, 1 M, 2 mL) at 0 °C. 1-Bromo-4-fluorobenzylbromide (**1f**) (804 mg, 3 mmol) was added, and the mixture was heated at 100 °C for 3 h. The crude product was recrystallized from dichloromethane/methanol (1:1) to afford 2-[(2-bromo-5-fluorophenyl)methyl]-3-hydroxy-2-cyclohexen-1-one (**11n**) as a white solid in 67% yield (400 mg, 1.34 mmol): mp 199−200 °C (dichloromethane/methanol); $R_f$ = 0.14 (petroleum ether/EtOAc = 6:4); IR (ATR) $\nu$ 3126 (w) (O−H), 1590, 1372, 1257, 1187, 1006, 800, 749, 692 (C−Br) $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 251 (4.13) nm; $^1H$ NMR (300 MHz, $CD_3OD$) $\delta$ 2.05 (quin, $^3J$ (4-H, 5-H) = 6.6 Hz, $^3J$ (5-H, 6-H) = 6.6 Hz, 2H, 5-H), 2.52 (t, $^3J$ (5-H, 6-H) = 6.5 Hz, $^3J$ (4-H, 5-H) = 6.5 Hz, 4H, 6-H and 4-H), 3.62 (s, 2H, $CH_2$), 6.68 (br d, $^4J$ (4′-H, 6′-H) = 3.0 Hz, $^3J$ (5′-H, 6′-F) = 10.1 Hz, 1H, 6′-H), 6.80 (br ddd, $^3J$ (3′-H, 4′-H) = 8.2 Hz, $^3J$ (4′-H, 5′-F) = 8.2 Hz, 1H, 4′-H), 7.51 (dd, $^3J$ (3′-H, 4′-H) = 8.8 Hz, $^4J$ (3′-H, 5′-F) = 5.6 Hz, 1H, 3′-H); $^{13}C$ NMR (75 MHz, $CD_3OD$) $\delta$ 22.1 (C-5), 29.4 ($CH_2$), 2 × 33.9 (C-4 and C-6), 113.7 (C-2), 115.1 (d, $^2J$ (C−F) = 23.0 Hz, C-4′), 116.5 (d, $^2J$ (C−F) = 23.7 Hz, C-6′), 119.9 (d, $^4J$ (C−F) = 3.0 Hz, C-2′), 134.6 (d, $^3J$ (C−F) = 8.2 Hz, C-3′), 143.9 (d, $^3J$ (C−F) = 7.2 Hz, C-1′), 163.7 (d, $^1J$ (C−F) = 243.5 Hz, C-5′), 2 × 189.5 (C-1 and C-3); Anal. Calcd for $C_{13}H_{12}BrFO_2$(299.14): C, 52.20; H, 4.04. found: C, 52.01; H, 4.10.

*2-[(2-Bromo-5-methoxyphenyl)methyl]-3-hydroxy-2-cyclohexen-1-one (**11o**).* According to general procedure II, 1,3-cyclohexanedione



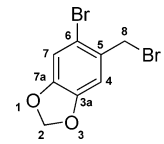

(**8a**) (560 mg, 5 mmol) was dissolved in aqueous NaOH (200 mg, 1 M, 5 mL) at 0 °C. 1-Bromo-4-methoxybenzyl bromide (**1g**) (2.1 g, 7.5 mmol) was added, and the mixture was heated at 100 °C for 3 h. The crude product was recrystallized from dichloromethane/methanol (1:1) to afford 2-[(2-bromo-5-methoxyphenyl)methyl]-3-hydroxy-2-cyclohexen-1-one (**11o**) as a white solid in 50% yield (774 mg, 2.5 mmol): mp 149−150 °C (dichloromethane/methanol); $R_f$ = 0.09 (petroleum ether/EtOAc = 6:4); IR (ATR) $\nu$ 2550 (w) (O−H), 1675 (conjugated C═O), 1569, 1364, 1273, 1186, 1008, 804, 763, 680 (C−Br) $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 233 (4.15), 250 (4.15) nm; $^1H$ NMR (300 MHz, $CD_3OD$) $\delta$ 2.05 (quin, $^3J$ (4-H, 5-H) = 6.6 Hz, $^3J$ (5-H, 6-H) = 6.6 Hz, 2H, 5-H), 2.51 (t-like, $^3J$ (4-H, 5-H) = 6.6 Hz, $^3J$ (5-H, 6-H) = 6.6 Hz, 4H, 4-H and 6-H), 3.59 (s, 2H, $CH_2$), 3.70 (s, 3H, OMe), 6.51 (dd, $^4J$ (4′-H, 6′-H) = 3.0 Hz, 1H, 6′-H), 6.62 (dd, $^3J$ (3′-H, 4′-H) = 5.7 Hz, $^4J$ (4′-H, 6′-H) = 3.0 Hz, 1H, 4′-H), 7.38 (dd, $^3J$ (3′-H, 4′-H) = 8.7 Hz, 1H, 3′-H); $^{13}C$ NMR (75 MHz, $CD_3OD$) $\delta$ 22.1 (C-5), 29.2 ($CH_2$), 2 × 33.9 (C-4 and C-6), 55.8 (OMe), 113.2 (C-4′), 114.2 (C-2), 116.0 (C-6′), 116.3 (C-2′), 133.8 (C-3′), 142.1 (C-1′), 160.5 (C-5′); Anal. Calcd for $C_{14}H_{15}BrO_3$(311.17): C, 54.04; H, 4.86. found: C, 53.77; H, 4.83.

*1-Bromo-2-(bromomethyl)naphthalene (**1d**).*[19] In a round-bottomed flask, 1-bromo-2-methylnaphthalene (3.69 g, 16.7 mmol)




was dissolved in $CCl_4$ (100 mL), followed by *N*-bromosuccinimide (2.97 g, 16.7 mmol) and benzoyl peroxide (3 mg). The reaction mixture was refluxed for 3 h, cooled to room temperature, and washed with saturated $NaHCO_3$ (50 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Recrystallization from cyclohexane afforded 1-bromo-2-(bromomethyl)naphthalene (**1d**) as a colorless solid in 72% yield (3.6 g, 12.0 mmol): mp 103−104 °C (lit.[19] mp 103−105 °C); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 4.87 (s, 2H, 9-H), 7.51−7.62 (m, 3H, 3-H, 6-H and 7-H), 7.78−7.83 (m, 2H; 4-H and 5-H), 8.34 (br d, $^3J$ (7-H, 8-H) = 8.7 Hz, 1H, 8-H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 34.7 (C-9), 124.9 (C-1), 127.2 (C-8), 127.6 (C-7), 127.7 (C-3), 127.8 (C-6), 128.1 (C-4), 128.3 (C-5), 132.5 (C-2), 134.1 (C-8a), 134.9 (C-4a).

*5-Bromo-6-bromomethylbenzo[1,3]dioxole (**1e**).*[20] A round-bottomed flask was charged with piperonyl alcohol (15.0 g, 98.7 mmol) and

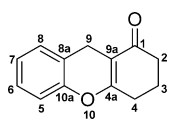



acetic acid (30 mL). After cooling to 0 °C, a mixture of bromine (2.0 mL, 116.4 mmol) and acetic acid (15 mL) was added slowly. The reaction mixture was stirred at room temperature for 10 h. The precipitate was filtered, washed with distilled water, and dried in vacuo to afford the crude product. Recrystallization from methanol delivered 5-bromo-6-bromomethylbenzo[1,3]dioxole (**1e**) as a white solid in 86% yield (25 g, 85 mmol): mp 92−93 °C (methanol) (lit.[20] mp 91.5−92.5 °C); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 4.55 (s, 2H, 8-H), 5.99 (s, 2H, 2-H), 6.91 (s, 1H, 4-H), 7.01 (s, 1H, 7-H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 34.1 (C-8), 102.1 (C-2), 110.5 (C-4), 113.1 (C-7), 115.6 (C-5), 129.9 (C-6), 147.6 (C-7a), 148.7 (C-3a).

**General Procedure III for the CuCl-Catalyzed Domino Reaction.** A dry 10 mL vial was equipped with a magnetic stir bar, charged with the 2-[(2-haloaryl)methyl]-3-hydroxy-2-cyclic-1-one derivative **11** (1 mmol), CuCl (0.495 mg, 0.005 mmol), $Cs_2CO_3$ (326 mg, 1 mmol), and pivalic acid (123 mg, 1.2 mmol), and sealed. The sealed tube was evacuated and backfilled with argon two times. Then, freshly distilled DMF (2 mL) was added, and the reaction mixture was stirred at 130 °C for 7 h. After cooling to room temperature, the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The crude product was purified by flash column chromatography over silica gel to afford the product.

## SYNTHESIS AND CHARACTERIZATION OF XANTHENONES AND RELATED COMPOUNDS

**2,3,4,9-Tetrahydro-1*H*-xanthen-1-one (9a).**[12d,e] *Synthesis of **9a** using **11a** as Substrate. Method A.* According to general





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procedure III, **11a** (281 mg, 1.0 mmol), CuCl (0.495 mg, 0.5 mol %), $Cs_2CO_3$ (326 mg, 1.0 mmol), and pivalic acid (123 mg, 1.2 mmol) were reacted in a sealed tube under argon at 130 °C for 7 h. Column chromatography over silica gel (petroleum ether/EtOAc = 8:2) afforded 2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9a**) as a white solid in 95% yield (190 mg, 0.95 mmol).

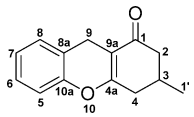
*Method B.* **11a** (281 mg, 1.0 mmol), CuCl (0.495 mg, 0.5 mol %), and cesium pivalate (585 mg, 2.5 mmol) were reacted in a sealed tube under argon at 130 °C for 7 h. Column chromatography over silica gel (petroleum ether/EtOAc = 8:2) afforded 2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9a**) as a white solid in 94% yield (188 mg, 0.94 mmol).

*Synthesis of **9a** Using **11b** as Substrate.* According to general procedure III, **11b** (237 mg, 1.0 mmol), CuCl (0.495 mg, 0.5 mol %), $Cs_2CO_3$ (326 mg, 1.0 mmol), and pivalic acid (123 mg, 1.2 mmol) were reacted in a sealed tube under argon at 130 °C for 7 h. Column chromatography over silica gel (petroleum ether/EtOAc = 8:2) afforded 2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9a**) as a white solid in 13% yield (25 mg, 0.13 mmol) and 2-[(2′-chlorophenyl)methyl]-3-hydroxy-2-cyclohexen-1-one (**11b**) as white solid in 68% (161 mg, 0.68 mmol) was reisolated.

*Synthesis of **9a** Using **11c** as Substrate.* According to general procedure III, **11c** (328 mg, 1.0 mmol), CuCl (0.495 mg, 0.5 mol %), $Cs_2CO_3$ (326 mg, 1.0 mmol), and pivalic acid (123 mg, 1.2 mmol) were reacted in a sealed tube under argon at 130 °C for 7 h. Column chromatography over silica gel (petroleum ether/EtOAc = 8:2) afforded 2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9a**) as a white solid in 88% yield (175 mg, 0.88 mmol) and 2-[(2′-iodophenyl)methyl]-3-hydroxy-2-cyclohexen-1-one (**11c**) as white solid in 5% (16 mg, 0.05 mmol) was reisolated.

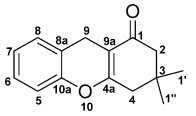
mp 92–93 °C (lit.[12e] mp 90.5–91.5 °C); $R_f$ = 0.49 (petroleum ether/EtOAc = 1:1); IR (ATR) $\nu$ 1637 (s) (C═O), 1582, 1454, 1387, 1233, 1183, 1132, 993, 759 $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 282 (3.91) nm; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.05 (tt, $^3J$ (2-H, 3-H) = 6.6 Hz, $^3J$ (3-H, 4-H) = 6.6 Hz, 2H, 3-H), 2.46 (t-like, $^3J$ (2-H, 3-H) = 6.6 Hz, 2H, 2-H), 2.55–2.59 (m, 2H, 4-H), 3.52 (s, 2H, 9-H), 6.95 (d-like, $^3J$ (5-H, 6-H) = 7.8 Hz, 1H, 5-H), 7.05 (ddd, $^4J$ (5-H, 7-H) = 1.3 Hz, $^3J$ (6-H, 7-H) = 6.6 Hz, $^3J$ (7-H, 8-H) = 7.5 Hz, 1H, 7-H), 7.15 (partially overlapped, 2H, 6-H and 8-H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 20.6 (C-3), 21.1 (C-9), 27.7 (C-4), 36.6 (C-2), 110.0 (C-9a), 116.3 (C-5), 120.8 (C-8a), 124.5 (C-7), 127.5 (C-6), 129.6 (C-8), 149.7 (C-10a), 166.8 (C-4a), 198.0 (C-1); MS (EI, 70 eV) *m*/*z* (%) 200 (100) $[M]^+$, 172 (12) $[200 - C_2H_4]^+$, 144 (54) $[172 - CO]^+$, 115 (20), 28 (20).

*3-Methyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**9b**).* According to general procedure III, **11d** (295 mg, 1.0 mmol), CuCl (0.495 mg,



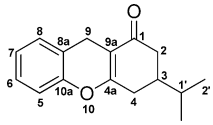
0.5 mol %), $Cs_2CO_3$ (326 mg, 1.0 mmol), and pivalic acid (123 mg, 1.2 mmol) were reacted in a sealed tube under argon at 130 °C for 7 h. Column chromatography over silica gel (petroleum ether/EtOAc = 8:2) afforded 3-methyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9b**) as a white solid in 92% yield (197 mg, 0.92 mmol): mp 97–98 °C; $R_f$ = 0.54 (petroleum ether/EtOAc = 1:1); IR (ATR) $\nu$ 1637 (vs) (C═O), 1581, 1393, 1235, 1133, 1013, 758, 658 $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 294 (3.32) nm; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.12 (d, $^3J$ (1′-H, 3-H) = 6.0 Hz, 3H, 1′-H), 2.09–2.19 (m, 1H, 2-Hb), 2.24–2.34 (m, 2H, 3-H and 4-Hb), 2.50–2.59 (m, 2H, 2-Ha and 4-Ha), 3.49 (d, $^2J$ (9-Ha, 9-Hb) = 19.8 Hz, 1H, 9-Hb), 3.51 (d, $^2J$ (9-Ha, 9-Hb) = 19.8 Hz, 1H, 9-Ha), 6.95 (d-like, $^3J$ (5-H, 6-H) = 7.8 Hz, 1H, 5-H), 7.04 (ddd, $^4J$ (5-H, 7-H) = 1.8 Hz, $^3J$ (6-H, 7-H) = 5.7 Hz, $^3J$ (7-H, 8-H) = 6.3 Hz, 1H, 7-H), 7.15 (partially overlapped, 2H, 6-H and 8-H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 21.0 (C-1′), 21.1 (C-9), 28.3 (C-3), 35.7 (C-4), 45.0 (C-2), 109.5 (C-9a), 116.4 (C-5), 120.8 (C-8a), 124.5 (C-7), 127.5 (C-6), 129.7 (C-8), 149.8 (C-10a), 166.2 (C-4a), 198.0 (C-1); MS (EI, 70 eV) *m*/*z* (%) 214 (100) $[M]^+$, 199 (18) $[214 - CH_3]^+$, 172 (28) $[199 - C_2H_3]^+$, 144 (76) $[172 - CO]^+$, 115 (35), 28 (16); HRMS (EI, $M^+$) calcd for $C_{14}H_{14}O_2$ (214.0994), found 214.0984.

*3,3-Dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**9c**).*[12c,e] According to general procedure III, **11e** (309 mg, 1.0 mmol), CuCl



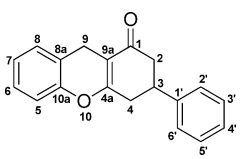
(0.495 mg, 0.5 mol %), $Cs_2CO_3$ (326 mg, 1.0 mmol), and pivalic acid (123 mg, 1.2 mmol) were reacted in a sealed tube under argon at 130 °C for 7 h. Column chromatography over silica gel (petroleum ether/EtOAc = 9:1) afforded 3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9c**) as a white solid in 98% yield (224 mg, 0.98 mmol): mp 95–96 °C (lit.[12e] mp 96–97.5 °C); $R_f$ = 0.84 (petroleum ether/EtOAc = 1:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.12 (s, 6H, 2 × $CH_3$), 2.33 (s, 2H, 2-H), 2.43 (s, 2H, 4-H), 3.52 (s, 2H, 9-H), 6.95 (dd, $^3J$ (5-H, 6-H) = 7.8 Hz, 1H, 5-H), 7.06 (ddd, $^3J$ (6-H, 7-H) = 6.6 Hz, $^3J$ (7-H, 8-H) = 7.5 Hz, 1H, 7-H), 7.16 (ddd, $^3J$ (5-H, 6-H) = 6.3 Hz, $^3J$ (6-H, 7-H) = 7.2 Hz, $^3J$ (7-H, 8-H) = 7.2 Hz, 2H, 6-H and 8-H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 21.0 (C-9), 2 × 28.4 (2 × $CH_3$), 32.1 (C-3), 41.5 (C-4), 50.6 (C-2), 108.7 (C-9a), 116.4 (C-5), 120.8 (C-8a), 124.6 (C-7), 127.6 (C-6), 129.7 (C-8), 149.9 (C-10a), 165.1 (C-4a), 197.9 (C-1); MS (EI, 70 eV) *m*/*z* (%) 228 (100) $[M]^+$, 213 (31) $[228 - CH_3]^+$, 185 (20) $[213 - C_2H_4]^+$, 171 (16) $[185 - CH_2]^+$, 144 (29), 115 (15), 28 (14).

*3-Isopropyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**9d**).* According to general procedure III, **11f** (323 mg, 1.0 mmol), CuCl (0.495 mg,



0.5 mol %), $Cs_2CO_3$ (326 mg, 1.0 mmol), and pivalic acid (123 mg, 1.2 mmol) were reacted in a sealed tube under argon at 130 °C for 7 h. Column chromatography over silica gel (petroleum ether/EtOAc = 9:1) afforded 3-isopropyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9d**) as a white solid in 99% yield (240 mg, 0.99 mmol): mp 74–75 °C; $R_f$ = 0.62 (petroleum ether/EtOAc = 1:1); IR (ATR) $\nu$ 1642 (vs) (C═O), 1491, 1387, 1226, 1196, 1153, 1137, 761, 661 $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 290 (3.69) nm; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.96 (dd, $^3J$ (1′-H, CH $_3$) = 4.2 Hz, $^4J$ (2′-H, 3-H) = 2.7 Hz, $^4J$ (CH $_3$, $CH_3$) = 2.4 Hz, 6H, 2 × $CH_3$), 1.59–1.69 (m, 1H, 1′-H), 1.91–1.99 (m, 1H, 3-H), 2.11–2.21 (m, 1H, 2-Hb), 2.31–2.40 (m, 1H, 4-Hb), 2.51–2.61 (m, 2H, 2-Ha and 4-Ha), 3.45 (d, $^2J$ (9-Ha, 9-Hb) = 19.8 Hz, 1H, 9-Hb), 3.54 (d, $^2J$ (9-Ha, 9-Hb) = 19.8 Hz, 1H, 9-Ha), 6.95 (d-like, $^3J$ (5-H, 6-H) = 8.1 Hz, 1H, 5-H), 7.05 (ddd, $^3J$ (6-H, 7-H) = 6.3 Hz, $^3J$ (7-H, 8-H) = 7.5 Hz, $^4J$ (5-H, 7-H) = 2.1 Hz, 1H, 7-H), 7.15 (partially overlapped, 2H, 6-H and 8-H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 19.5 ($CH_3$), 19.6 ($CH_3$), 21.2 (C-9), 31.6 (C-4), 32.0 (C-1′), 39.5 (C-3), 40.8 (C-2), 109.5 (C-9a), 116.4 (C-5), 120.8 (C-8a), 124.6 (C-7), 127.6 (C-6), 129.7 (C-8), 149.9 (C-10a), 166.8 (C-4a), 198.4 (C-1); MS (EI, 70 eV) *m*/*z* (%) 242 (100) $[M]^+$, 199 (28) $[242 - C_3H_{7}]^+$, 173 (10), 144 (17), 115 (10); HRMS (EI, $M^+$) calcd for $C_{16}H_{18}O_2$ (242.1306), found 242.1307.

*3-Phenyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**9e**).* According to general procedure III, **11g** (357 mg, 1.0 mmol), CuCl (0.495 mg,



0.5 mol %), $Cs_2CO_3$ (326 mg, 1.0 mmol), and pivalic acid (123 mg, 1.2 mmol) were reacted in a sealed tube under argon at 130 °C for 7 h. Column chromatography over silica gel (petroleum ether/EtOAc = 9:1) afforded 3-phenyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9e**) as a white solid in 91% yield (251 mg, 0.91 mmol): mp 108–109 °C;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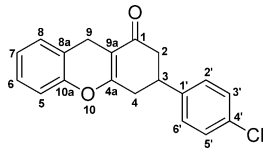
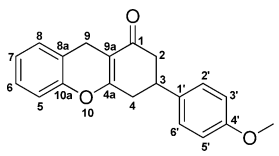
$R_f$ = 0.68 (petroleum ether/EtOAc = 1:1); IR (ATR) $\nu$ 1639 (vs) (C═O), 1456, 1392, 1227, 1128, 877, 756, 699 $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 295 (3.35) nm; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.68 (dd, $^3J$ (2-Hb, 3-H) = 12.2 Hz, $^2J$ (2-Ha, 2-Hb) = 16.0 Hz, 1H, 2-Hb), 2.79 (dd, $^3J$ (2-Ha, 3-H) = 4.8 Hz, $^2J$ (2-Ha, 2-Hb) = 16.0 Hz, 1H, 2-Ha), 2.79−2.85 (m, 2H, 4-H), 3.39−3.52 (m, 1H, 3-H), 3.53 (d, $^2J$ (9-Ha, 9-Hb) = 20.0 Hz, 1H, 9-Hb), 3.61 (d, $^2J$ (9-Ha, 9-Hb) = 20.0 Hz, 1H, 9-Ha), 6.95−7.00 (m, 1H, 5-H), 7.08 (ddd, $^3J$ (6-H, 7-H) = 7.2 Hz, $^3J$ (7-H, 8-H) = 6.6 Hz, 1H, 7-H), 7.16−7.21 (m, 2H, 6-H and 8-H), 7.25−7.32 (overlapped, 3H, 2′-H, 4′-H, and 6′-H), 7.34−7.42 (m, 2H, 3′-H and 5′-H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 21.2 (C-9), 35.2 (C-4), 38.7 (C-3), 43.7 (C-2), 109.8 (C-9a), 116.5 (C-5), 120.7 (C-8a), 124.7 (C-7), 2 × 126.7 (C-2′ and C-6′), 127.1 (C-4′), 127.6 (C-6), 2 × 128.8 (C-3′ and C-5′), 129.7 (C-8), 142.5 (C-1′), 149.8 (C-10a), 165.9 (C-4a), 197.1 (C-1); MS (EI, 70 eV) $m/z$ (%) 276 (100) $[M]^+$, 185 (46) $[276 - C_7H_7]^+$, 158 (18), 144 (30), 115 (16), 28 (5); HRMS (EI, $M^+$) calcd for $C_{19}H_{16}O_2$ (276.1150), found 276.1165.

*3-(4′-Chlorophenyl)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**9f**).* According to general procedure III, **11h** (392 mg, 1.0 mmol), CuCl



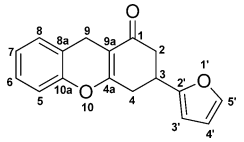
(0.495 mg, 0.5 mol %), $Cs_2CO_3$ (326 mg, 1.0 mmol), and pivalic acid (123 mg, 1.2 mmol) were reacted in a sealed tube under argon at 130 °C for 7 h. Column chromatography over silica gel (petroleum ether/EtOAc = 9:1) afforded 3-(4′-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9f**) as a brown solid in 93% yield (288 mg, 0.93 mmol): mp 130−132 °C; $R_f$ = 0.61 (petroleum ether/EtOAc = 1:1); IR (ATR) $\nu$ 1639 (s) (C═O), 1489, 1391, 1223, 1127, 1013, 820, 760 $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) = 292 (3.67) nm; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.63 (dd, $^3J$ (2-Hb, 3-H) = 12.3 Hz, $^2J$ (2-Ha, 2-Hb) = 16.0 Hz, 1H, 2-Hb), 2.74 (dd, $^3J$ (2-Ha, 3-H) = 4.6 Hz, $^2J$ (2-Ha, 2-Hb) = 16.0 Hz, 1H, 2-Ha), 2.74−2.79 (m, 2H, 4-H), 3.37−3.48 (m, 1H, 3-H), 3.51 (d, $^2J$ (9-Ha, 9-Hb) = 19.8 Hz, 1H, 9-Hb), 3.60 (d, $^2J$ (9-Ha, 9-Hb) = 19.8 Hz, 1H, 9-Ha), 6.94−6.99 (m, 1H, 5-H), 7.08 (ddd, $^4J$ (5-H, 7-H) = 0.9 Hz, $^3J$ (6-H, 7-H) = 7.2 Hz, $^3J$ (7-H, 8-H) = 6.6 Hz, 1H, 7-H), 7.15−7.19 (overlapped, 2H, 6-H and 8-H), 7.15−7.22 (m, 2H, 2′-H and 6′-H), 7.30−7.36 (m, 2H, 3′-H and 5′-H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 21.2 (C-9), 35.1 (C-4), 38.1 (C-3), 43.6 (C-2), 109.9 (C-9a), 116.5 (C-5), 120.6 (C-8a), 124.8 (C-7), 127.7 (C-6), 2 × 128.0 (C-2′ and C-6′), 2 × 128.9 (C-3′ and C-5′), 129.7 (C-8), 132.8 (C-4′), 140.9 (C-1′), 149.7 (C-10a), 165.6 (C-4a), 196.6 (C-1); MS (EI, 70 eV) $m/z$ (%) 310 (100) $[M]^+$, 185 (61) $[310 - C_7H_6Cl]^+$, 158 (29), 144 (45), 115 (24), 32 (19), 28 (78); HRMS (EI, $M^+$) calcd for $C_{19}H_{15}ClO_2$ (310.0761), found 310.0767.

*3-(4′-Methoxyphenyl)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**9g**).* According to general procedure III, **11i** (387 mg, 1.0 mmol),



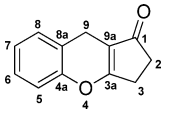
CuCl (0.495 mg, 0.5 mol %), $Cs_2CO_3$ (326 mg, 1.0 mmol), and pivalic acid (123 mg, 1.2 mmol) were reacted in a sealed tube under argon at 130 °C for 7 h. Column chromatography over silica gel (petroleum ether/EtOAc = 8:2) afforded 3-(4′-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9g**) as a white solid in 95% yield (292 mg, 0.95 mmol): mp 179−181 °C; $R_f$ = 0.56 (petroleum ether/EtOAc = 1:1); IR (ATR) $\nu$ 1637 (s) (C═O), 1513, 1391, 1249, 1229, 1030, 826, 757 $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 291 (3.63) nm; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.62 (dd, $^3J$ (2-Hb, 3-H) = 12.5 Hz, $^2J$ (2-Ha, 2-Hb) = 16.4 Hz, 1H, 2-Hb), 2.75 (dd, $^3J$ (2-Ha, 3-H) = 4.4 Hz, $^2J$ (2-Ha, 2-Hb) = 16.4 Hz, 1H, 2-Ha), 2.72−2.79 (m, 2H, 4-H), 3.33−3.46 (m, 1H, 3-H), 3.51 (d, $^2J$ (9-Ha, 9-Hb) = 19.6 Hz, 1H, 9-Hb), 3.60 (d, $^2J$ (9-Ha, 9-Hb) = 19.6 Hz, 1H, 9-Ha), 3.81 (s, 3H, -$OCH_3$), 6.89−6.92 (m, 2H, 3′-H and 5′-H), 6.95−6.98 (m, 1H, 5-H), 7.07 (ddd, $^4J$ (5-H, 7-H) = 1.4 Hz, $^3J$ (6-H, 7-H) = 7.0 Hz, $^3J$ (7-H, 8-H) = 7.9 Hz, 1H, 7-H), 7.15−7.18 (overlapped, 2H, 6-H and 8-H), 7.15−7.21 (m, 2H, 2′-H and 6′-H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 21.2 (C-9), 35.5 (C-4), 38.0 (C-3), 44.0 (C-2), 55.3 (−$OCH_3$), 109.8 (C-9a), 2 × 114.1 (C-3′ and C-5′), 116.5 (C-5), 120.7 (C-8a), 124.7 (C-7), 3 × 127.6 (C-6, C-2′ and C-6′), 129.7 (C-8), 134.6 (C-1′), 149.8 (C-10a), 158.6 (C-4′), 165.9 (C-4a), 197.2 (C-1); MS (EI, 70 eV) $m/z$ (%) 306 (100) $[M]^+$, 185 (36) $[306 - C_8H_9O]^+$, 172 (13), 144 (41), 115 (12), 28 (23); HRMS (EI, $M^+$) calcd for $C_{20}H_{18}O_3$ (306.1256), found 306.1265.

*3-(Furan-2′-yl)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**9h**).* According to general procedure III, **11j** (347 mg, 1.0 mmol), CuCl



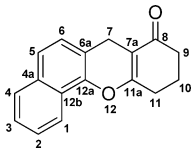
(0.495 mg, 0.5 mol %), $Cs_2CO_3$ (326 mg, 1.0 mmol), and pivalic acid (123 mg, 1.2 mmol) were reacted in a sealed tube under argon at 130 °C for 7 h. Column chromatography over silica gel (petroleum ether/EtOAc = 9:1) afforded 3-(furan-2′-yl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9h**) as a white solid in 87% yield (231 mg, 0.87 mmol): mp 113−114 °C; $R_f$ = 0.63 (petroleum ether/EtOAc = 1:1); IR (ATR) $\nu$ 1637 (s) (C═O), 1490, 1394, 1233, 1176, 1127, 990, 759 $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 292 (3.64) nm; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.65 (dd, $^3J$ (2-Hb, 3-H) = 11.1 Hz, $^2J$ (2-Ha, 2-Hb) = 16.4 Hz, 1H, 2-Hb), 2.83 (overlapping, 1H, 2-Ha), 2.77−2.95 (m, 2H, 4-H), 3.49 (d, $^2J$ (9-Ha, 9-Hb) = 20.0 Hz, 1H, 9-Hb), 3.46−3.60 (m, 1H, 3-H), 3.58 (d, $^2J$ (9-Ha, 9-Hb) = 20.0 Hz, 1H, 9-Ha), 6.10 (dt, $^3J$ (3′-H, 4′-H) = 3.2 Hz, $^4J$ (3′-H, 5′-H) = 0.8 Hz, 1H, 3′-H), 6.31 (dd, $^3J$ (3′-H, 4′-H) = 3.2 Hz, $^3J$ (4′-H, 5′-H) = 1.8 Hz, 1H, 4′-H), 6.97 (dd, $^3J$ (5-H, 6-H) = 7.8 Hz,1H, 5-H), 7.04−7.09 (m, 1H, 7-H), 7.14−7.19 (m, 2H, 6-H and 8-H), 7.36 (dd, $^3J$ (4′-H, 5′-H) = 1.8 Hz, $^4J$ (3′-H, 5′-H) = 0.7 Hz, 1H, 5′-H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 21.1 (C-9), 32.2 (C-3), 32.4 (C-4), 40.9 (C-2), 104.8 (C-3′), 109.9 (C-9a), 110.1 (C-4′), 116.4 (C-5), 120.6 (C-8a), 124.7 (C-7), 127.6 (C-6), 129.7 (C-8), 141.7 (C-5′), 149.7 (C-10a), 155.7 (C-2′), 165.1 (C-4a), 196.2 (C-1); MS (EI, 70 eV) $m/z$ (%) 266 (100) $[M]^+$, 185 (24) $[266 - C_5H_5O]^+$, 158 (11), 144 (47), 115 (29), 28 (8); HRMS (EI, $M^+$) calcd for $C_{17}H_{14}O_3$ (266.0943), found 266.0944.

*2,3-Dihydrocyclopenta[b]chromen-1(9H)-one (**9i**).*[12c,e] According to general procedure III, **11k** (267 mg, 1.0 mmol), CuCl (0.495 mg,



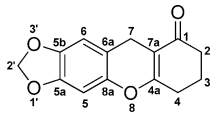
0.5 mol %), $Cs_2CO_3$ (326 mg, 1.0 mmol), and pivalic acid (123 mg, 1.2 mmol) were reacted in a sealed tube under atmosphere at 130 °C for 7 h. Column chromatography over silica gel (petroleum ether/EtOAc = 7:3) afforded 2,3-dihydrocyclopenta[*b*]chromen-1(9*H*)-one (**9i**) as a white solid in 54% yield (100 mg, 0.54 mmol): mp 195−196 °C (lit.[12e] mp 195−197 °C); $R_f$ = 0.34 (petroleum ether/EtOAc = 1:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.51−2.54 (m, 2H, 2-H), 2.70−2.73 (m, 2H, 3-H), 3.50 (s, 2H, 9-H), 7.04 (dd, $^3J$ (5-H, 6-H) = 8.1 Hz, 1H, 5-H), 7.09 (ddd, $^3J$ (6-H, 7-H) = 6.6 Hz, $^3J$ (7-H, 8-H) = 8.1 Hz, 1H, 7-H), 7.16−7.22 (m, 2H, 6-H and 8-H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 20.8 (C-9), 25.8 (C-3), 33.3 (C-2), 114.2 (C-9a), 117.2 (C-5), 119.6 (C-8a), 125.1 (C-7), 128.0 (C-6), 130.4 (C-8), 150.8 (C-4a), 179.2 (C-3a), 203.4 (C-1); MS (EI, 70 eV) $m/z$ (%) 186 (84) $[M]^+$, 158 (24) $[186 - C_2H_4]^+$, 128 (13), 44 (54), 28 (100).

*10,11-Dihydro-7H-benzo[c]xanthen-8(9H)-one (**9j**).* According to general procedure III, **11l** (331 mg, 1.0 mmol), CuCl (0.495 mg, 0.5 mol %), $Cs_2CO_3$ (326 mg, 1.0 mmol), and pivalic acid (123 mg,



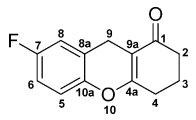
1.2 mmol) were reacted in a sealed tube under argon at 130 °C for 7 h. Column chromatography over silica gel (petroleum ether/EtOAc = 8:2) afforded 10,11-dihydro-7*H*-benzo[*c*]xanthen-8-(9*H*)-one (**9j**) as a white solid in 83% yield (207 mg, 0.83 mmol): mp 160−161 °C; $R_f$ = 0.49 (petroleum ether/EtOAc = 1:1); IR (ATR) $\nu$ 1645 (s) (C═O), 1599, 1379, 1216, 1179, 1129, 1016, 807, 777, 744 $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 223 (4.69), 227 (4.69), 232 (4.64), 264 (3.67), 312 (3.82) nm; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.11 (tt, $^3J$ (9-H, 10-H) = 6.3 Hz, $^3J$ (10-H, 11-H) = 6.6 Hz, 2H, 10-H), 2.50 (t-like, $^3J$ (9-H, 10-H) = 6.3 Hz, 2H, 9-H), 2.66−2.70 (m, 2H, 11-H), 3.65 (br s, 2H, 7-H), 7.19 (d-like, $^3J$ (5-H, 6-H) = 8.4 Hz, 1H, 6-H), 7.45−7.55 (overlapped, 3H, 2-H, 3-H and 5-H), 7.78 (dd, $^3J$ (3-H, 4-H) = 7.2 Hz, $^4J$ (2-H, 4-H) = 1.5 Hz, 1H, 4-H), 8.15 (d, $^3J$ (1-H, 2-H) = 7.8 Hz, 1H, 1-H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 20.6 (C-10), 21.7 (C-7), 27.6 (C-11), 36.7 (C-9), 110.2 (C-7a), 115.5 (C-12b), 120.7 (C-1), 123.6 (C-6a), 124.0 (C-2), 126.0 (C-3), 126.2 (C-5), 126.9 (C-6), 127.6 (C-4), 133.2 (C-4a), 144.2 (C-12a), 166.6 (C-11a), 198.1 (C-8); MS (EI, 70 eV) *m*/*z* (%) 250 (100) $[M]^+$, 233 (7), 194 (22), 165 (16); HRMS (EI, $M^+$) calcd for $C_{17}H_{14}O_2$ (250.0994), found 250.1014.

*2,3-Dihydro-4H-[1,3]dioxolo[4,5-b]xanthen-1(7H)-one (**9k**).* According to general procedure III, **11m** (325 mg, 1.0 mmol), CuCl



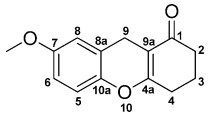
(0.495 mg, 0.5 mol %), $Cs_2CO_3$ (326 mg, 1.0 mmol), and pivalic acid (123 mg, 1.2 mmol) were reacted in a sealed tube under argon at 130 °C for 7 h. Column chromatography over silica gel (petroleum ether/EtOAc = 8:2) afforded 2,3-dihydro-4*H*-[1,3]dioxolo[4,5-*b*]xanthen-1(7*H*)-one (**9k**) as a buff colored solid in 85% yield (208 mg, 0.85 mmol): mp 162−164 °C; $R_f$ = 0.42 (petroleum ether/EtOAc = 1:1); IR (ATR) $\nu$ 1645 (s) (C═O), 1502, 1385, 1215, 1179, 1136, 1027, 999, 926, 853, 764 $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 306 (3.82) nm; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.06 (tt, $^3J$ (2-H, 3-H) = 6.3 Hz, $^3J$ (3-H, 4-H) = 6.6 Hz, 2H, 3-H), 2.45 (t-like, $^3J$ (2-H, 3-H) = 6.9 Hz, 2H, 2-H), 2.50−2.54 (m, 2H, 4-H), 3.41 (s, 2H, 7-H), 5.92 (s, 2H, 2′-H), 6.49 (s, 1H, 5-H), 6.56 (s, 1H, 6-H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 20.6 (C-3), 21.5 (C-7), 27.6 (C-4), 36.7 (C-2), 98.3 (C-5), 101.3 (C-2′), 108.0 (C-6), 109.4 (C-7a), 112.7 (C-6a), 144.0 (C-8a), 144.4 (C-5b), 146.6 (C-5a), 166.6 (C-4a), 198.0 (C-1); MS (EI, 70 eV) *m*/*z* (%) 243 (100) $[M]^+$, 227 (8) $[243 - O]^+$, 201 (5), 188 (25), 28 (7); HRMS (EI, $M^+$) calcd for $C_{14}H_{12}O_4$ (244.0736), found 244.0742.

*7-Fluoro-2,3,4,9-tetrahydro-1H-xanthen-1-one (**9l**).* According to general procedure III, **11n** (299 mg, 1.0 mmol), CuCl (0.495 mg,



0.5 mol %), $Cs_2CO_3$ (326 mg, 1.0 mmol), and pivalic acid (123 mg, 1.2 mmol) were reacted in a sealed tube under argon at 130 °C for 7 h. Column chromatography over silica gel (petroleum ether/EtOAc = 8:2) afforded 7-fluoro-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9l**) as a white solid in 87% yield (189 mg, 0.87 mmol): mp 165−166 °C; $R_f$ = 0.47 (petroleum ether/EtOAc = 1:1); IR (ATR) $\nu$ 1640 (s) (C═O), 1494, 1384, 1220, 1193, 1129, 999, 863, 826, 798 $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 277 (3.93) nm; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.05 (tt, $^3J$ (3-H, 4-H) = 6.3 Hz, $^3J$ (2-H, 3-H) = 6.6 Hz, 2H, 3-H), 2.45 (t-like, $^3J$ (2-H, 3-H) = 6.9 Hz, 2H, 2-H), 2.53−2.57 (m, 2H, 4-H), 3.48 (s, 2H, 9-H), 6.81−6.90 (overlapped, 2H, 6-H and 8-H), 6.92 (dd, $^4J$ (5-H, 7-F) = 5.0 Hz, $^3J$ (5-H, 6-H) = 8.7 Hz, 1H, 5-H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 20.5 (C-3), 21.5 (C-9), 27.6 (C-4), 36.6 (C-2), 109.0 (C-9a), 114.3 (d, $^2J$ (C−F) = 23.7 Hz, C-6), 115.6 (d, $^2J$ (C−F) = 23.0 Hz, C-8), 117.6 (d, $^3J$ (C−F) = 8.7 Hz, C-5), 122.5 (d, $^3J$ (C−F) = 8.1 Hz, C-8a), 145.8 (d, $^4J$ (C−F) = 2.5 Hz, C-10a), 159.1 (d, $^1J$ (C−F) = 243.0 Hz, C-7), 166.7 (C-4a), 197.8 (C-1); MS (EI, 70 eV) *m*/*z* (%) 218 (100) $[M]^+$, 190 (19) $[218 - C_2H_4]^+$, 162 (46) $[190 - CO]^+$, 133 (26), 28 (9); HRMS (EI, $M^+$) calcd for $C_{13}H_{11}FO_2$ (218.0743), found 218.0742.

*7-Methoxy-2,3,4,9-tetrahydro-1H-xanthen-1-one (**9m**).* According to general procedure III, **11o** (311 mg, 1.0 mmol), CuCl (0.495 mg,



0.5 mol %), $Cs_2CO_3$ (326 mg, 1.0 mmol), and pivalic acid (123 mg, 1.2 mmol) were reacted in a sealed tube under argon at 130 °C for 7 h. Column chromatography over silica gel (petroleum ether/EtOAc = 8:2) afforded 7-methoxy-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**9m**) as a white solid in 88% yield (203 mg, 0.88 mmol): mp 113−115 °C; $R_f$ = 0.42 (petroleum ether/EtOAc = 1:1); IR (ATR) $\nu$ 1636 (s) (C═O), 1495, 1386, 1219, 1181, 1130, 1034, 997, 868, 813 $cm^{-1}$; UV ($CH_3CN$) $\lambda_{max}$ (log $\varepsilon$) 285 (4.08) nm; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.04 (tt, $^3J$ (3-H, 4-H) = 6.3 Hz, $^3J$ (2-H, 3-H) = 6.6 Hz, 2H, 3-H), 2.44 (t-like, $^3J$ (2-H, 3-H) = 6.9 Hz, 2H, 2-H), 2.51−2.56 (m, 2H, 4-H), 3.47 (s, 2H, 9-H), 3.76 (s, 3H, -$OCH_3$), 6.64 (br d, $^4J$ (6-H, 8-H) = 2.7 Hz, 1H, 8-H), 6.69 (overlapped, 1H, 6-H), 6.88 (dd, $^3J$ (5-H, 6-H) = 8.7 Hz, 1H, 5-H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 20.6 (C-3), 21.6 (C-9), 27.7 (C-4), 36.6 (C-2), 55.5 (−$OCH_3$), 109.1 (C-9a), 113.3 (C-6), 113.7 (C-8), 117.2 (C-5), 121.6 (C-8a), 143.8 (C-10a), 156.2 (C-7), 166.9 (C-4a), 198.0 (C-1); MS (EI, 70 eV) *m*/*z* (%) 230 (100) $[M]^+$, 202 (8) $[230 - C_2H_4]^+$, 174 (30) $[202 - CO]^+$, 159 (10) $[174 - CH_3]^+$, 28 (7); HRMS (EI, $M^+$) calcd for $C_{14}H_{14}O_3$ (230.0943), found 230.0927.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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