

A Sunscreen-based Photocage for Carbonyl Groups

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Abstract: Photoremovable protecting groups (PPG) have been exploited in a large set of chemical and biological applications, due to their ability to provide spatial and temporal control over light-triggered activation. In this work, we explore the concept of a new photocage compound based on the commercial UVA/UVB filter oxybenzone (OB, 2-hydroxy-4-methoxybenzophenone) for photoprotection and controlled release of carbonyl groups. The point here is that oxybenzone not only acts as a mere PPG, but also provides, once released, UV photoprotection to the carbonyl derivative. This design points to a possible therapeutic approach to reduce the severe photoadverse effects of drugs containing a carbonyl chromophore.

Introduction

Photolabile protecting groups (PPGs) are now integral part of the organic chemist toolbox. Their removal, which generally takes place in neutral media and without the addition of any reagent, makes them appealing alternatives to the conventional methods employing basic, acidic, reductive or oxidative conditions. A salient feature relies on the accurate spatial and temporal control of the photodeprotection process that has been exploited in advantageous approaches for the release of chemicals such as acids, bases, oxidants, ions, drugs, pheromones or fragrances.^[1-11] In this context, PPGs have found a wide range of applications in organic chemistry, biochemistry, biology, polymer science, lithography, toiletry, pest-control, etc.^[1-11]

Among the available PPGs, relatively few have found utility for caging carbonyl functional groups.^[6-9] These PPGs are applicable not only in multi-step organic synthesis, where carbonyls often require protection against nucleophiles, oxidative or reductive agents, but also for biological purposes to release bioactive compounds. Early work on carbonyl caging compounds was based on acetals from *o*-nitrophenylethylene glycol.^[12, 13] Later, a series of 1,3-dioxolane and 1,3-dioxane derivatives have been investigated to optimize the photouncaging process.^[8, 14-20]

With this background, our interest was to explore the concept of sunscreen-based photocages for photoprotection and controlled release of carbonyl compounds. This is a new PPG application recently addressed by our group to release a photosensitive drug together with its UV-protector shield, which would make special sense for carbonyl compounds in view of their well-established photoreactivity.^[34, 35] Until now, we have made use of the phenacyl-like structure of the avobenzone diketo

tautomer to cage the carboxylic acid group of non-steroidal anti-inflammatory drugs such as ketoprofen and diclofenac.^[34, 35]

In the present work, the commercial UVA/UVB filter oxybenzone (OB) has been the cornerstone of our new carbonyl photocage design (Figure 1A). Actually, this solar filter plays a dual role acting not only as the photoremovable group but also providing an efficient UV shield effect to protect the carbonyl-derived drug after its photorelease. We have proven the concept studying derivative **1** as a new carbonyl photocage for the photorelease of a water soluble aromatic ketone (4-carboxybenzophenone, CBP) along with OB (Figure 1A).

Results and Discussion

As a first experiment, the UV-Vis absorption spectra of the carbonyl compound, 4-carboxybenzophenone (CBP), and the oxybenzone sunscreen (OB) were recorded in H₂O:MeCN (40:60, v:v) (Figure 1B). The former exhibits a maximum at 257 nm, whereas the latter, as expected for a UVA/UVB filter, shows a broad band with maxima at ca. 287 and 325 nm, which should provide the purported protection to CBP. This was confirmed by HPLC analysis of simulated solar light irradiations (SSL) of CBP alone and in the presence of OB (Figure S1).

Then, the photolabile compound **1** was synthesized in four steps (Scheme 1). First, the carboxylic acid of 4-carboxybenzophenone (CBP) was esterified to compound **3**, then selective reduction of the ketone was achieved by using NaBH₄. The obtained alcohol reacted with oxybenzone (OB) in the presence of triphenylphosphine (PPh₃) and diisopropyl azodicarboxylate (DIAD) through a Mitsunobu reaction to yield the diaryl ether **5**, which finally gave rise to **1** after basic hydrolysis. The UV-Vis absorption spectra of photocage **1** displays a long wavelength band peaking at 310 nm that reaches the UVA region, and making conceivable the photorelease using SSL.

The progress of steady-state photolysis of **1** (2x10⁻⁴ M) in oxygen-free MeCN:H₂O (60:40, v:v) was followed by HPLC. It was observed that both OB and CBP are photoreleased together with other photoproducts (Figure 1C). The peaks corresponding to **1**, OB and CBP were assigned by comparison with standards, and were quantified along the irradiation to obtain the kinetic curves. Moreover, peaks eluting at 2.3 and 3.4 min exhibit the kinetic behavior of an intermediate with an increase of area to a maximum after 60 min followed by a decrease.

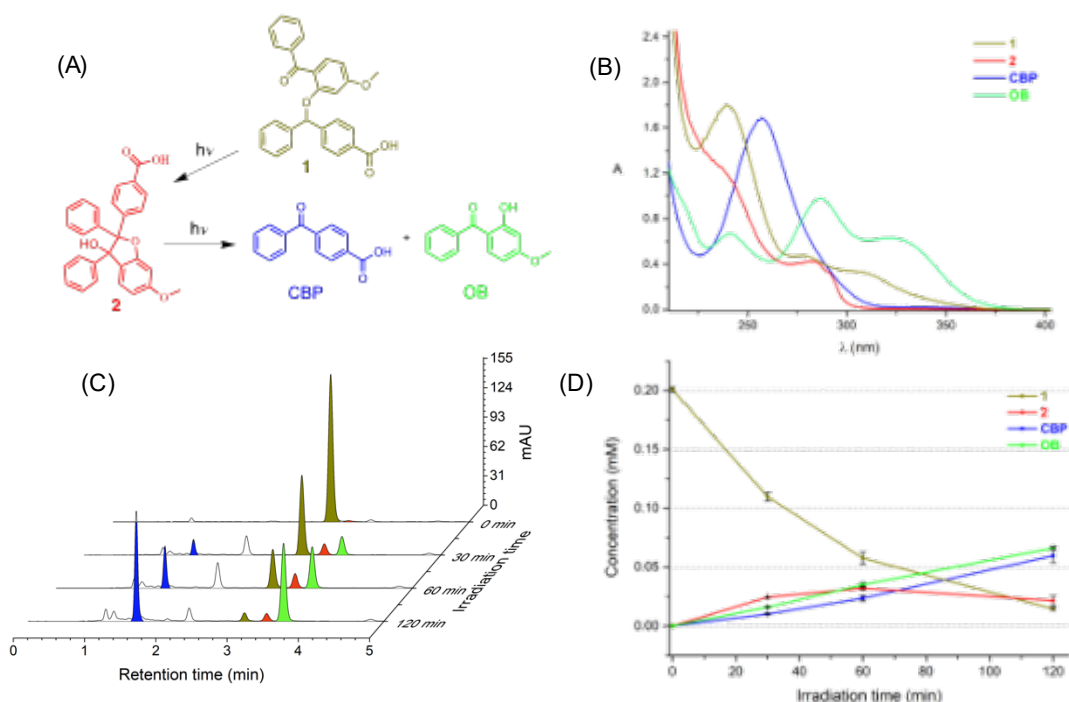
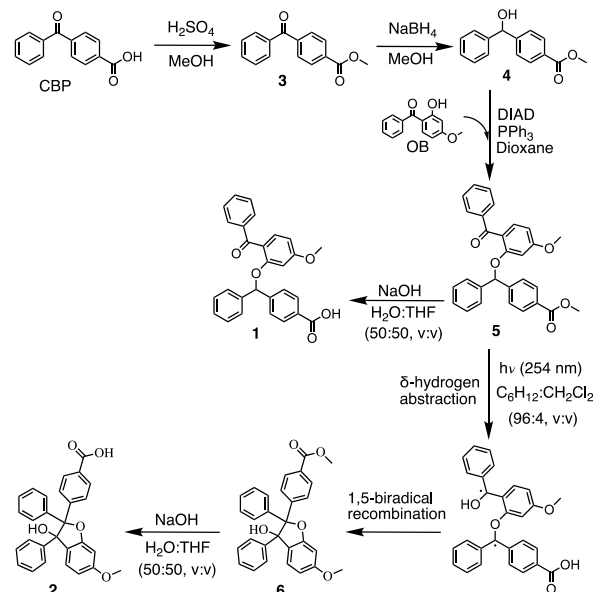


Figure 1. (A) Photorelease of CBP and OB from new carbonyl photocage **1** (B) UV-Vis absorption spectra in oxygen-containing MeCN:H₂O (60:40, v:v) of **1**, **2**, CBP and OB at same concentration (6.6×10^{-5} M), (C) HPLC chromatograms registered at 280 nm for an oxygen-free MeCN:H₂O (60:40, v:v) solution of **1** (2×10^{-4} M), upon irradiation at different times with simulated solar light, and (D) kinetic traces of **1**, **2**, CBP and OB.

These compounds were assigned to the diastereoisomers of cyclic intermediate **2** (see SI). They are obtained from **1** by an intramolecular hydrogen abstraction and a subsequent C-C coupling of the formed biradical (see Scheme 1 for a similar reaction of the methyl ester **5**). Indeed, this intermediate is in turn a clear photocage for CBP, which is then released together with OB.

In order to get a deeper understanding about the photorelease process of OB and CBP from this cyclic intermediate, **2** was synthesized and used for additional steady-state photolysis experiments. In a first stage, an oxygen-containing solution of compound **2** in MeCN:H₂O (60:40, v:v) was irradiated with SSL to confirm the intermediate capacity to photorelease OB and CBP (Figure S3D). Then, to simplify the quantitation process, experiments were performed using a low pressure Hg lamp with a monochromatic output at 254 nm under atmosphere of N₂ or air. Compound **2** (2×10^{-4} M) dissolved in anhydrous MeCN or in MeCN:H₂O (60:40, v:v) was irradiated, and the reaction was followed by UV-Vis absorption spectrophotometry. In all cases, it was observed an absorption increase as a function of irradiation time, and a new band peaking at ca. 325 nm appeared, pointing to OB formation. A similar behavior was observed under the different conditions (Figure S2).

Moreover, to reach a more accurate analysis of the irradiated samples, aliquots were taken at periodic intervals and analyzed by HPLC. The compound **2** was consumed during the irradiation irrespective of the employed conditions, whereas the release of CBP strongly differed depending on the presence of oxygen and/or water. As shown in Figure 2 for an oxygen-containing MeCN:H₂O solution, the peak of compound **2**, eluting at 3.4 min, decreased giving basically rise to the formation of the desired CBP (at 1.5 min), together with OB (at 3.7 min). The yields of the photoproducts determined after 60 min of irradiation are summarized in Table 1. The results were clearly affected by the presence of O₂ or H₂O. In oxygen-containing aqueous acetonitrile,



Scheme 1. Synthesis of compounds **1** and **2**

the yields of CBP and OB were markedly higher and the formation of undesired byproducts was minimized (Figure S3). Remarkably, when oxygen and water were present in the solution, CBP yield reached 51.7%, whereas the yield of OB grew from 7.6% to 21.1%. A quantum yield of ca. 0.16 was determined for the photoreaction by means of an established procedure using as standard the photocyclization of *N*-methyl-diphenylamine to *N*-methylcarbazole in oxygen-containing acetonitrile (see Experimental Section).^[36]

Table 1. Yields of compounds **2**, CBP and OB obtained after 60 min of irradiation under different conditions.

	Conversion (%)	4-CBP (%)	OB (%)
Anhydrous MeCN, N ₂	85.4±0.3	9.1±1.6	7.6±1.2
MeCN/H ₂ O, N ₂	89.1±0.7	6.1±0.3	19.0±0.5
Anhydrous MeCN, Air	82.4±1.8	36.3±1.4	20.6±0.5
MeCN/H ₂ O, Air	87.8±0.7	51.7±1.2	21.1±0.4

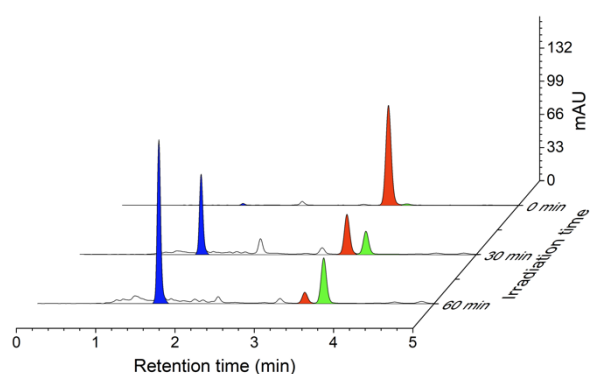


Figure 2. HPLC chromatograms registered at 280 nm for an oxygen-containing MeCN:H₂O (60:40, v:v) solution of **2** (2×10^{-4} M), upon irradiation at different times at 254 nm.

The obtained results are in accordance with the fact that formal incorporation of an oxygen atom to dyad **2** is required to release CBP and OB (Figure 1A).

To experimentally settle whether the oxygen comes from H₂O and if so where it is finally incorporated, photodeprotection was carried out using MeCN:H₂¹⁸O as solvent. In this context, an oxygen-containing solution of **2** in either MeCN/H₂O or MeCN/H₂¹⁸O was exposed to 254 nm light, and the reaction mixture was analyzed by UPLC-HRMS. When H₂O was used, mass spectra of the CBP and OB peaks were coincident with the expected natural isotopic pattern, with *m/z* values of 227.0714 and 229.0864 as [M+H]⁺, respectively. Conversely, for the reaction in H₂¹⁸O a CBP peak at *m/z* 229.0743 increased and its exact mass corresponded to that of ¹⁸O labeled CBP. By contrast, no significant changes were observed for OB (see Figure S4). Thus, comparison of the MS spectra for the CBP peak showed that ratio between the intensity of the ions at *m/z* 229.0743 and 227.0706 was higher in the presence than in the absence of H₂¹⁸O (1/3 vs 1/33, respectively). Moreover, no changes in the isotopic pattern were observed for CBP in H₂¹⁸O solution left in the dark for hours (see Figure S4).

Altogether, these results demonstrate that at least part of the oxygen of CBP arises from water present in the solvent, and supports that in aerobic atmosphere the yield of CBP formation is enhanced in aqueous acetonitrile. Nonetheless, the reaction still takes place under aerobic anhydrous conditions, albeit to a lesser extent, showing that atmospheric oxygen is also capable to trigger

the process. Consequently, the lowest efficiency is observed for oxygen-free anhydrous acetonitrile.

In order to explain the obtained results and to get insights into the mechanistic details of the photoprocess, laser flash photolysis (LFP) experiments were performed at 266 nm. The transient absorption spectrum obtained for N₂-bubbled aqueous solutions of **2** is shown in Figure 3. It exhibits a maximum at 350 nm together with a shapeless band growing until 700 nm characteristic of hydrated electron (e_{aq}⁻), which was quenched under N₂O atmosphere (Figure 3, top). The linear variation of the hydrated electron absorbance at 680 nm as a function of the laser intensity reflected a monophotonic process (Figure 3, bottom). Furthermore, the log-log representation fitted linearly with a slope of 1.2 (Figure S5, top) confirming the one-photon nature of the ionization process, which could thus occur under steady-state photolysis. Consistently, LFP studies carried out using (2,4-dimethoxyphenyl)acetic acid (DMFA) as a model of the dialkoxyaryl group of **2** also gave rise to e_{aq}⁻ (see Figure S5, right). Interestingly, the 4-carboxyaryl moiety can act as a good electron acceptor and thus be reduced during the process either through an intramolecular electron transfer process or through trapping of hydrated electron.

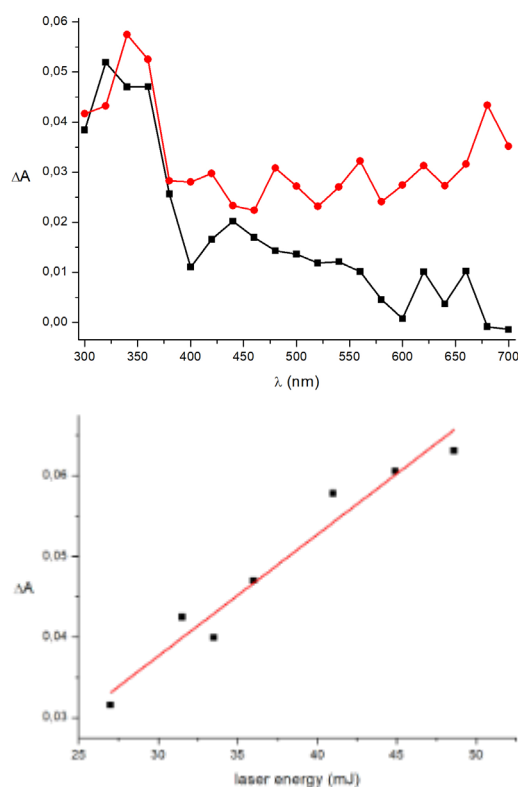
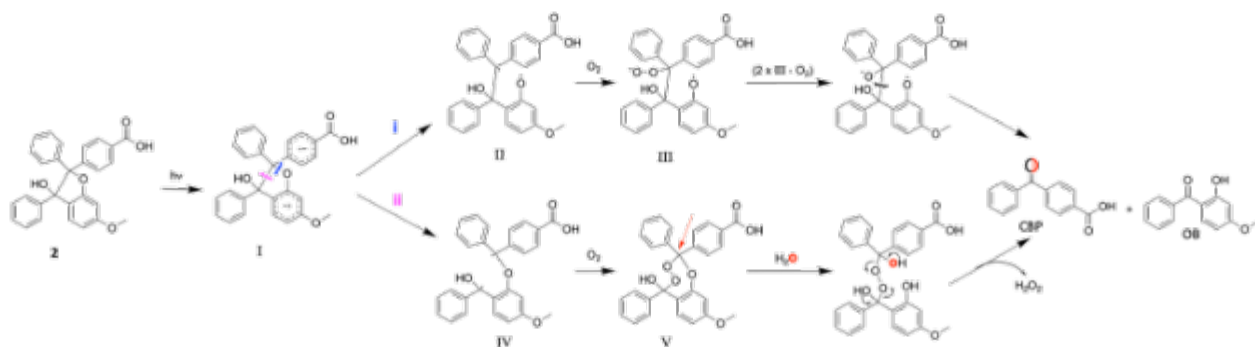


Figure 3. Top: transient absorption spectra of **2** in H₂O under N₂ (red line) or N₂O (black line) 0.04 μs after the 266 nm laser pulse (laser energy: 33 mJ). Bottom: laser energy dependence of the transient absorption intensity at 680 nm of the N₂ solution.



Scheme 2. Photorelease mechanism from photocage 2.

Actually, comparison of the kinetic traces of hydrated electron at 680 nm revealed a faster decay for **2** (Figure S5, $\tau \sim 270$ ns) than for DMFA (Figure S5, $\tau \sim 400$ ns), which is in agreement with electron trapping by the 4-carboxyaryl moiety of **2**.

On the basis of these data, a possible mechanism is outlined in Scheme 2. The photorelease process might be triggered by the photoinduced formation of biradical zwitterion I (Scheme 2). This intermediate can evolve through two different pathways depending on the mesolytic cleavage of the benzylic C-O bond (route *i*) or C-C bond (route *ii*). In the former case, the obtained biradical II is trapped by O₂ leading to III, which after dimerization and subsequent fragmentation yields the desired CBP and OB. The C-C cleavage, route *ii*, gives rise to biradical IV that reacts with O₂ to form the cyclic endoperoxide intermediate V. In the presence of water, it hydrolyzes to yield, after loss of H₂O₂, CBP and OB. In this context, incorporation of ¹⁸O to CBP demonstrates that water attacks at the benzylic position of the carboxyaryl moiety, which is actually the most electrophilic carbon.

Conclusion

In summary, the concept of sunscreen-based photocages for carbonyl compounds has been proven in the present work, using compounds **1** and **2**, which serve as precursors of the target aromatic ketone along with its UV-filter shield. Further work is in progress to optimize the yields of the uncaging processes and to explore the scope of this approach with differently substituted ketones, such as acetophenone derivatives, and aldehydes.

Experimental Section

Synthesis.

Methyl 4-benzoylbenzoate (3). Concentrated sulfuric acid (0.025 mL, 0.44 mmol) was added to a solution of 4-benzoylbenzoic acid (0.5 g, 2.2 mmol) in anhydrous MeOH (15 mL). The solution was stirred at 75 °C for 17 h and then cooled to room temperature. The solvent was removed under reduced pressure. The crude product was redissolved in dichloromethane and washed with saturated sodium bicarbonate. Finally, the organic phase was dried with anhydrous magnesium sulfate, filtered, and the filtrate was concentrated *in vacuo*. The pure product **3** was obtained without further purification. Yield: 0.421 g (77%). ¹H NMR (300 MHz,

CDCl₃): δ (ppm) 8.15 (d, $J = 8.6$ Hz, 2H), 7.82 (m, 4H), 7.68 – 7.57 (m, 1H), 7.55 – 7.42 (m, 2H), 3.97 (s, 3H). HRMS (ESI-TOF) m/z [M+H]⁺ calculated for C₁₅H₁₃O₃: 241.0865; found: 241.0859.

Methyl 4-[hydroxy(phenyl)methyl]benzoate (4). Compound **3** (0.328 g, 1.36 mmol) was dissolved in a mixture of anhydrous methanol (5 mL) and anhydrous dichloromethane (2 mL). The resulting solution was cooled to 0 °C, and then NaBH₄ (0.072 g, 1.9 mmol) was added portionwise during 2 h. Subsequently, the solution was allowed reaching room temperature, and stirred for 3 h. To quench the excess of NaBH₄, the solution was cooled in an ice bath, and then water (5 mL) was added. The resulting mixture was stirred for 30 min. The mixture of solvents were removed under reduced pressure, then the afforded crude was redissolved with dichloromethane (20 mL) and washed with water. Finally, the combined organic extracts were dried with MgSO₄, filtered, and the solvent was removed under reduced pressure. The pure product **4** was obtained without further purification. Yield: 0.282 g (85%). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.91 (d, $J = 8.4$ Hz, 2H), 7.38 (d, $J = 8.1$ Hz, 2H), 7.33 – 7.11 (m, 5H), 5.79 (d, $J = 3.3$ Hz, 1H), 3.81 (s, 3H), 2.40 (d, $J = 3.3$ Hz, 1H). HRMS (ESI-TOF) m/z [M+H]⁺ calculated for C₁₅H₁₅O₃: 243.1021; found: 243.1021.

Methyl 4-[(2-benzoyl-5-methoxyphenoxy)(phenyl)methyl]benzoate (5). To a solution of compound **4** (0.249 g, 1.03 mmol) and triphenylphosphine (PPh₃) (0.324 g, 1.23 mmol) in anhydrous dioxane (5.5 mL) was added oxybenzone (0.353 g, 1.55 mmol) and diisopropyl azodicarboxylate (DIAD) (0.350 mL, 2 mmol). The solution was stirred at room temperature for 4 h. The crude reaction mixture was concentrated under reduced pressure and purified by column chromatography (cyclohexane/ethyl acetate, 4:1; silica gel) to give the pure product **5**. Yield: 0.340 g (73%). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.95 – 7.80 (m, 4H), 7.60 – 7.41 (m, 4H), 7.20 (m, 7H), 6.55 (dd, $J = 8.5, 2.0$ Hz, 1H), 6.48 (d, $J = 2.0$ Hz, 1H), 6.19 (s, 1H), 3.86 (s, 3H), 3.71 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 195.9, 166.5, 163.1, 157.2, 145.9, 140.2, 139.5, 132.3, 132.3, 129.8, 129.5, 129.2, 128.6, 128.1, 127.9, 126.1, 125.9, 122.4, 105.6, 101.4, 81.8, 55.3, 51.9. HRMS (ESI-TOF) m/z [M+H]⁺ calculated for C₂₉H₂₅O₅: 453.1702; found: 453.1713.

4-(3-hydroxy-6-methoxy-2,3-diphenyl-2,3-dihydrobenzofuran-2-yl)benzoic acid (1). Compound **5** (0.191 g, 0.42 mmol) was dissolved in a mixture of 1 M aq. NaOH (2 mL) and THF (2 mL). The resulting solution was stirred for 22 h at room temperature. The mixture was acidified to pH 1 using 1 M aq. HCl, then the resulting mixture was extracted with dichloromethane (3 x 10 mL), dried over anhydrous MgSO₄, and rotary evaporated to afford compound **1** (0.127 g) in a 69% yield. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.88 (d, *J* = 8.1 Hz, 2H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.47 (m, 4H), 7.25 – 6.98 (m, 7H), 6.54 (dd, *J* = 8.7, 1.8 Hz, 1H), 6.41 (d, *J* = 1.8 Hz, 1H), 6.12 (s, 1H), 3.73 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 196.29, 163.29, 157.39, 146.57, 140.29, 139.61, 132.55, 132.51, 130.52, 129.67, 129.27, 128.86, 128.27, 128.09, 126.33, 126.09, 122.68, 105.85, 101.60, 82.15, 55.54. HRMS (ESI-TOF) *m/z* [M+H]⁺ calculated for C₂₈H₂₃O₅: 439.1545; found: 439.1550. Molar absorption coefficients in MeCN:H₂O (60:40, v:v): log ε = 3.9 (280 nm), 3.7 (310 nm).

Methyl 4-(3-hydroxy-6-methoxy-2,3-diphenyl-2,3-dihydrobenzofuran-2-yl)benzoate (6). An oxygen-free solution of compound **5** (0.170 g, 0.376 mmol) in 211 mL cyclohexane and 9 mL dichloromethane was irradiated for 90 min using a Luzchem photoreactor (model LZC-4V) with 8 lamps with a maximum output at 355 nm. Then, the solvent was removed under vacuum. Purification was performed by column chromatography (cyclohexane/ethyl acetate, 6:1; silica gel). Product **6** was obtained by resolution of the diastereoisomeric mixture (0.058 g) in a 34% yield. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.07 – 7.96 (d, *J* = 8.7 Hz, 2H), 7.95 – 7.83 (d, *J* = 8.7 Hz, 2H), 7.15 (m, 5H), 7.08 – 6.90 (m, 5H), 6.82 (m, 2H), 6.48 (dd, *J* = 8.3, 2.2 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 166.9, 162.6, 160.2, 146.0, 140.9, 140.8, 129.2, 129.1, 128.1, 127.8, 127.4, 127.4, 127.3, 127.2, 127.0, 126.5, 125.9, 108.3, 99.5, 96.4, 87.8, 55.8, 52.2. HRMS (ESI-TOF) *m/z* [M-OH]⁺ calculated for C₂₉H₂₃O₄: 435.1596; found: 435.1595. Based on the spectroscopic data, this compound has the two phenyl groups in *cis* arrangement.

4-(3-hydroxy-6-methoxy-2,3-diphenyl-2,3-dihydrobenzofuran-2-yl)benzoic acid (2). Compound **6** (0.057 g, 0.13 mmol) was dissolved in a mixture of 1 M aq. NaOH (0.56 mL) and THF (0.56 mL). The resulting solution was stirred for 22 h at room temperature. The mixture was acidified to pH 1 using 1 M aq. HCl, then the resulting mixture was extracted with dichloromethane (3 x 10 mL), dried over anhydrous MgSO₄, and rotary evaporated to afford compound **2** (0.013 g) in a 23% yield. ¹H NMR (300 MHz, MeOD): δ (ppm) 7.97 (d, *J* = 8.5 Hz, 2H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.21 – 6.88 (m, 10H), 6.84 (d, *J* = 2.2 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.50 (dd, *J* = 8.3, 2.2 Hz, 1H), 3.86 (s, 3H). ¹³C NMR (75 MHz, MeOD): δ (ppm) 162.3, 160.1, 146.4, 141.9, 141.6, 128.1, 127.8, 127.5, 126.8, 126.6, 126.5, 126.1, 125.5, 107.4, 99.1, 95.4, 86.9, 54.6. HRMS (ESI-TOF) *m/z* [M-OH]⁺ calculated for C₂₈H₂₁O₄: 421.1440; found: 421.1439. Molar absorption coefficient in MeCN:H₂O (60:40, v:v): log ε = 3.8 (283 nm).

Instrumentation

UV-Vis. The absorption spectra were registered with a simple beam spectrophotometer (Cary 50) using a quartz cell of 1 cm optical path.

Steady-State Photolysis. All irradiations were carried out at room temperature using 3 mL quartz cuvettes of 1 cm optical path. Photolysis of compound **2** were run using a Luzchem photoreactor (model LZC-4V, 8W) with one low pressure Hg lamp with an output at 254 nm. Irradiation of compound **1** was carried out in a mixture of MeCN:H₂O (60:40, v:v) under oxygen-free conditions using a simulated solar light (SSL) obtained from a Xenon arc lamp solar simulator (Thermo Oriol 91192-1000) equipped with a AM 1.5 filter Global to better match the solar emission spectra, its output was of 86 mW/cm². Solutions of compound **2** (2 x 10⁻⁴ M) were prepared in anhydrous acetonitrile or in MeCN:H₂O (60:40, v:v) under nitrogen or air, and irradiations were run in quartz cells of 1 cm optical path. The oxygen-free and anhydrous solution of **2** was prepared in a dry box. The course of the photoreaction was followed by UV-Vis absorption spectrometry and HPLC.

HPLC. All irradiation mixtures were analyzed by a 1100 Series Agilent HPLC equipped with a diode array detector (DAD), for all chromatograms the detection wavelength was 280 nm. Irradiations were analyzed using a Zorbax Eclipse Plus C18 (4.6 x 100 mm, 3.5 Micron) column, and the chromatographic conditions were an isocratic mixture of water at pH 3 (35%) and acetonitrile (65%) at a flow rate of 1 mL/min. The injection volume was of 10 μL. The areas of the peaks were integrated by using the "OpenLab CDS ChemStation Edition" software supplied by Agilent. The percent yields were determined from calibration curves of pure samples of OB, CBP, **1** and **2**.

The quantum yield of the photoreaction was established using *N*-methylidiphenylamine in MeCN as actinometer ($\phi_{\text{ref}} = 0.45$) irradiating at 254 nm.^[36, 37]

UPLC-HRMS. Exact mass values were determined by using a QToF spectrometer coupled with a liquid chromatography system. The separation was carried out by UPLC on a Zorbax Eclipse Plus C18 column (4.6 x 100 mm, 3.5-micron). The mobile phase was a gradient prepared from 0.1% aqueous formic acid solution (component A) and 0.1% formic acid in acetonitrile (component B). The column was equilibrated with A:B (80:20; v:v) as mobile phase at a flow rate of 0.5 mL min⁻¹. The amount of component A was maintained at this composition for 3 min, then decreased from 80 to 0% in 7 min, kept at 0% for 5 min, restored to the initial composition in 2 min, and finally maintained at this composition for 3 min. The injection volume was of 5 μL. The ESI source was operated in positive ionization mode with the capillary voltage at 3 kV. The temperature of the source and desolvation was set at 80 and 400 °C, respectively. The cone and desolvation gas flows were 20 and 800 L h⁻¹, respectively. All data were collected in centroid mode. Leucine-enkephalin was used as the lock mass generating an [M + H]⁺ ion (*m/z* 556.2771) at a concentration of 250 pg/mL and flow rate of 50 μL/min to ensure accuracy during

the MS analysis. MS/MS spectra of compound **2** were measured for parent ion at m/z 421.14, using a V_{coll} of 30 V.

Laser Flash Photolysis. Laser flash photolysis experiments were performed exciting at 266 nm, using the 4th harmonic of a pulsed Nd:YAG laser (L52137V LOTIS TII) with a pulse duration of 6-8 ns. The full system consists in a pulsed laser, a Xenon lamp (Lo 255 Oriol), a monochromator (Oriol 77200), a photomultiplier (Oriol 70705) and an oscilloscope (TDS-640A Tektronic). The output signal from the oscilloscope was transferred to a personal computer. All experiments were performed in a quartz cell of 1 cm optical path length. Compound **2** was prepared in water such as its 266 nm absorption was of ca. 0.3. Before running the experiment, solutions were flushed with N₂ or N₂O for 15 min. A laser intensity ranging from 27 to 49 mJ per pulse was used.

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