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A Photo-Favorskii Ring Contraction Reaction: The Effect of Ring Size

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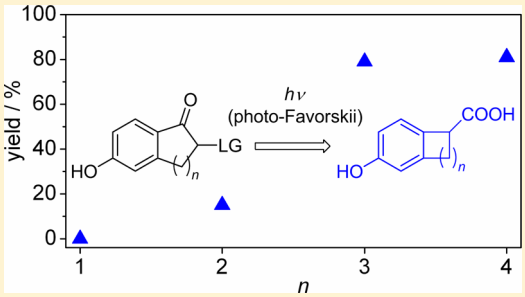
Supporting Information

ABSTRACT: The effect of ring size on the photo-Favorskii induced ring-contraction reaction of the hydroxybenzocycloalkanonyl acetate and mesylate esters (**7a−d**, **8a−c**) has provided new insight into the mechanism of the rearrangement. By monotonically decreasing the ring size in these cyclic derivatives, the increasing ring strain imposed on the formation of the elusive bicyclic spirocyclopropanone **20** results in a divergence away from rearrangement and toward solvolysis. Cycloalkanones of seven or eight carbons undergo a highly efficient photo-Favorskii rearrangement with ring contraction paralleling the photochemistry of *p*-hydroxyphenacyl esters. In contrast, the five-carbon ring does not rearrange but is diverted to the photosolvolysis channel avoiding the increased strain energy that would accompany the formation of the spirobicyclic ketone, the "Favorskii intermediate **20**". The six-carbon analogue demonstrates the bifurcation in reaction channels, yielding a solvent-sensitive mixture of both. Employing a combination of time-resolved absorption measurements, quantum yield determinations, isotopic labeling, and solvent variation studies coupled with theoretical treatment, a more comprehensive mechanistic description of the rearrangement has emerged.

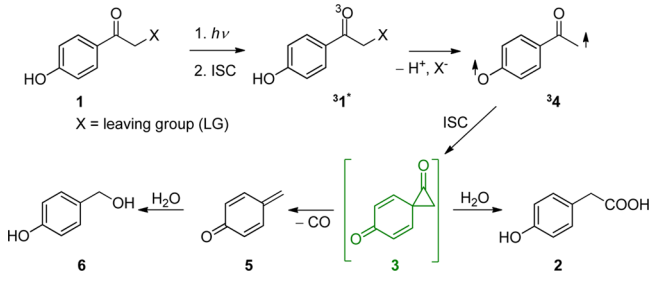


INTRODUCTION

Photochemical rearrangements have been the testing ground for many of the most important advances in development of a mechanism-based understanding in organic photochemistry beginning with the dienone rearrangements of α-santonin to lumisantonin by Zimmerman in the early 1960s.[1,2] Zimmerman developed a four-step paradigm during his studies on the mechanism of the reactions of 4,4-disubstituted cyclohexa-2,4-dien-1-one as a model for α-santonin which has also provided a simplified model for proposing mechanisms in photochemistry using a classic "electron pushing" approach.[3−5] The four-step paradigm consisted of (1) excitation (defining the reactive excited state), (2) bond alteration (in that excited state), (3) demotion (relaxation to the ground state energy surface), and (4) further bond alteration (through ground state, classical processes) to the final photoproducts. This paradigm has served the field of organic photochemistry very well for over half a century and has been useful in predicting the photochemical reactivity of complex organic molecules including the more intricate subtleties of stereochemistry, solvent, substituent, and steric effects that influence the product distributions in a photochemical reaction like that of α-santonin.[2,6−13]

In our investigations of the photochemistry of the *p*-hydroxyphenacyl chromophore, one of the newer photoremovable protecting groups, we have turned our attention to the mechanism and versatility of the reaction. Irradiation of *p*-hydroxyphenacyl esters (**1**, pHP X; X = carboxylate) releases the leaving group X while the chromophore undergoes an unusual rearrangement that has been described as a photo-Favorskii rearrangement.[14] The products, *p*-hydroxyphenylacetic acid (**2**, 95%) and *p*-hydroxybenzyl alcohol (**6**, <5%), are the signatures of this rearrangement (Scheme 1).[15−18] The reaction is highly efficient and the photochemical yields are quantitative. pHP has therefore developed into a useful protecting group for the photorelease of bioactivators such as amino acids, oligopeptides, nucleotides, and thiol derivatives in

Scheme 1. Photolysis of the pHP Chromophore



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fields such as neurobiology, enzyme catalysis, and biochemistry.[19−22]

Whereas interest has centered on the photorelease reactions of pHP and its applications, little work has been reported on the full range of reactivity of this chromophore when embedded in larger molecular frameworks.[23] Unlike its namesake, the classic ground-state Favorskii rearrangement that has received extensive investigation,[24−30] the range of possibilities and the theoretical treatments of the photo-Favorskii rearrangement[14] have not been adequately addressed. The current understanding of the photo-Favorskii mechanism also continues to be the subject of considerable debate.[31−37]

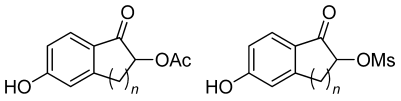
The reaction mechanism begins with excitation to the pHP triplet that releases the leaving group via an adiabatic, water-assisted pathway to the triplet biradical ^{3}**4** that collapses to a ground-state spirodione **3**, the Favorskii intermediate.[38,39] The spirodione **3**, which has eluded detection, either is hydrolyzed to *p*-hydroxyphenylacetic acid (**2**) or decarbonylates to *p*-quinone methide (**5**) that adds water to form the minor product *p*-hydroxybenzyl alcohol (**6**).

Just as in the history of its ground-state counterpart, the mechanism of the photo-Favorskii rearrangement is the subject of considerable conjecture on the details of the rearrangement process, especially those surrounding the intermediacy of the cyclopropanone **3**. Investigations of cyclic ketones impose ring strain on the reaction course and are intended to test the ease of formation, the stability, and the relative reactivity of the putative spirodione **3**. Thus ring strain effects might help define the partitioning of **3** among pathways available to the intermediates using our spectroscopic and product study techniques reported earlier[40] and the theoretical advances on the basic chromophore made available recently by the examination of the photophysics of *p*-hydroxyacetophenone.[31]

In extending the reach of the photo-Favorskii reaction and seeking more information on the mechanistic limits of the rearrangement, a monotonic series of hydroxybenzocycloalkanones (**7a−d**, **8a−c**) have been synthesized and their photochemistry examined (Chart 1). The ring sizes of the parent cyclic ketones were chosen for this study to test the limits of ring strain[41,42] on both the known and hypothetical intermediates (^{3}**1**, **3**, **4**, and **5**) proposed for the photo-Favorskii transformation. Precedence for ring-size effects on the ground-state Favorskii rearrangement have been reported[43−45] that may serve as models to compare and contrast with results found of the hydroxybenzocycloalkanones **7**.

Here we report the synthesis, photophysical properties, and photochemistry in water/acetonitrile solutions of a monotonic series of ring-expanded acetates **7a−d** (n = 1−4) and mesylates **8a−c** (n = 1−3) (Chart 1). The mechanistic conclusions are supported by the results from studies of the solvent effects, isotope exchange reactions, quenching effects and laser flash photolysis (LFP) experiments, and by quantum-chemical calculations.

Chart 1. Hydroxybenzocycloalkanone Derivatives



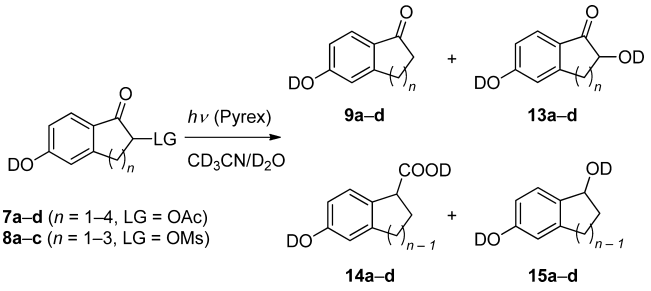
7a-d (n = 1–4) **8a-c** (n = 1–3)

RESULTS

Synthesis of *p*-Hydroxybenzocycloalkanones Derivatives. The acetates **7a−d** (n = 1−4) were synthesized by direct α-acetoxylation of the benzyloxybenzocycloalkanones **10** to yield **11**[46] followed by removal of the benzyl protection. Bromination of **9a−c** (n = 1−3)[47] and subsequent silver-promoted sulfoxydebromination[23] of **12** gave rise to the mesylates **8a−c** (n = 1−3; Scheme 2); see also the Supporting Information for the synthesis of **9c,d** (Scheme S1, Supporting Information).

Photochemistry of Acetates and Mesylates. Each ester (Scheme 3) was irradiated at 313 nm in acetonitrile/water mixtures (~7 × 10^{-2} M) through a Pyrex filter (>300 nm). The progress of the reaction was monitored by ^{1}H NMR and GC until 95% of the ketone was consumed (see Tables 1 and 2). In most cases, four different photoproducts, reduction (**9**), hydrolysis (**13**), and rearrangement to ring contracted acid **14** and benzyl alcohol **15**, were observed. The rearrangement products **14** and **15** were not observed among the photo-

Scheme 3. Products from Photolysis of 7a−d and 8a−c



Scheme 2. Synthesis of 7a−d and 8a−c

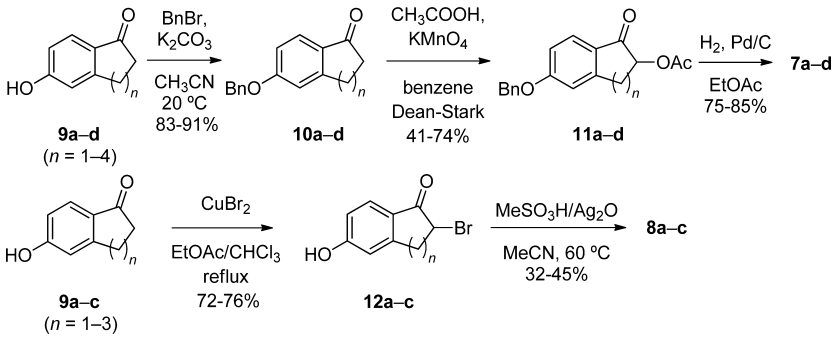


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Table 1. Photoproduct Distribution from Irradiation of 7a–d in D_2O/CD_3CN (70:30, v/v)

compd[a]	% yield of 9[b]	% yield of 13[b]	% yield of 14[c]	% yield of 15[c]
7a	6	86	*d*	*d*
7b	7	57	13	8
7c	5	4	59	20
7d	5	6	73	8

[a]Nondegassed solutions (~7×10^{-2} M) were irradiated in an NMR tube at $\lambda > 280$ nm (Pyrex) to >95% conversion. Average yields are shown. The confidence intervals at the 95% confidence level for all chemical yields determinations are below 3%. [b]Determined by GC. [c]Determined by ^{1}H NMR. [d]Not formed.

Table 2. Photoproduct Distribution as a Function of the Ratio of D_2O/CD_3CN

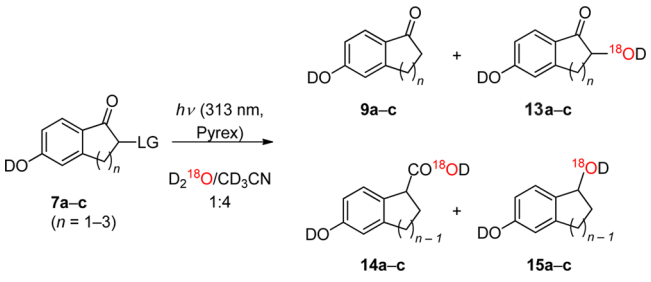
compd[a]	D_2O/CD_3CN (v/v)	% yield of 9b[b]	% yield of 13b[b]	% yield of 14b[c]	% yield of 15b[c]
7b	5:95	17	28	16	13
	10:90	14	29	17	14
	20:80	11	41	18	12
	30:70	11	47	17	12
	70:30	7	57	13	8
8b	70:30	5	56	16	8

[a]Nondegassed solutions (~7×10^{-2} M) were irradiated in an NMR tube at $\lambda > 300$ nm (Pyrex) to >95% conversion. Average yields are shown. The confidence intervals at the 95% confidence level for all chemical yields determinations are below 3%. [b]Determined by GC. [c]Determined by ^{1}H NMR.

products when $n = 1$ but were most prominent for $n = 3$ and 4. The structures of the photoproducts were established by comparison of the ^{1}H and ^{13}C NMR and HPLC/HRMS data with independently synthesized derivatives (Supporting Information) or comparison with literature values. The chemical yields from irradiations of all four acetates **7a–d** in D_2O/CD_3CN (70:30, v/v) mixture are shown in Table 1. The photoproduct distribution for **7b** and **8b** as a function of the concentration of H_2O in CH_3CN is summarized in Table 2; complete photoproduct yields for all seven ketone irradiations are shown in Tables S1–S4 (Supporting Information).

^{18}O Exchange Experiments. Irradiation of **7a–c** (~7×10^{-2} M) in $D_2{}^{18}O/CD_3CN$ (20:80, v/v) was performed in an NMR tube under the same conditions as those described above. Incorporation of ^{18}O into the three products **13**, **14**, and **15** was determined by comparison of the observed exact mass with theoretical values (Scheme 4). ^{18}O was not incorporated into the starting esters **7** or the reduction products **9**. The location of the ^{18}O in the hydrolysis product **13** and the two Favorskii

Scheme 4. ^{18}O Isotope Distribution in Photoproducts from Photolysis in $D_2{}^{18}O/CD_3CN$ Mixture



rearrangement products **14** and **15** (shown in Scheme 4) was determined by comparison of the fragmentation patterns for the labeled and unlabeled derivatives (Supporting Information).

Quantum Yields Measurements. The quantum yields for disappearance of **7a–d** and **8a–c** were obtained in degassed D_2O/CD_3CN (30:70, v/v) by irradiation at $\lambda = 313$ nm (Table 3). The reaction conversion was monitored by ^{1}H NMR.

Table 3. Quantum Yields for the Disappearance of 7 and 8.[a]

ester	Φ^b
7a	0.38
7b	0.24
7c	0.26
7d	0.34
8a	0.70
8b	0.64
8c	0.63

[a]Degassed solutions (~4×10^{-3} M) were irradiated in D_2O/CD_3CN (30:70, v/v) at $\lambda = 313$ (±5) nm. The conversion was less than 10%. The confidence intervals at the 95% confidence level for all quantum yields determinations are below 0.05. [b]Valerophenone was used as an actinometer ($\Phi = 0.30$ in benzene).[48]

Quenching Experiment. To confirm the triplet multiplicity of the excited state responsible for the formation of photoproducts, D_2O/CD_3CN (30:70, v/v) solutions of the acetates of **7a** or **7b** (5.5×10^{-2} M) were irradiated at $\lambda = 366$ (±5) nm in the presence of naphthalene (1.6×10^{-1} M) as a triplet quencher ($E_T = 60.5$ kcal mol^{-1};[49] naphthalene does not absorb at this wavelength). The reaction progress was monitored by NMR. Less than 5% conversion was observed after 7 days of irradiation, while the reaction was completed within several hours in the absence of a quencher. Dissolved oxygen had no significant effect on the photoreaction efficiency.

Irradiation in the Presence of DCl. A solution of **7b** in D_2O/CD_3CN (30:70, v/v) mixture containing a small amount of DCl was irradiated through a Pyrex filter until the conversion reached ~95%. The yield of **13b** and the sum of yields of **14b** and **15b** remained nearly unchanged compared to the irradiation in the absence of DCl (see Table S2, Supporting Information). However, the ratio **14b** to **15b** increased, favoring **14b**. The added acid had no effect on samples kept in the dark.

Reaction of 12b under Favorskii Rearrangement Conditions. Treatment of 2-bromo-6-hydroxynaphthalen-1(2*H*)-one (**12b**) under Favorskii rearrangement conditions using anhydrous $ZnCl_2$ in refluxing MeOH[44,45] gave 2-methoxy-6-hydroxynaphthalen-1(2*H*)-one **16** and the reduced ketone **9b** in a ratio of 3:1. Neither of the Favorskii rearrangement products **14b** or **15b** were detected (Scheme 5). However, similar treatment of pHP Br gave a good yield of the rearranged methyl *p*-hydroxyphenyl acetate (**19**)[50] and solvolysis product **18**[51] in a 2:3 ratio, but none of the reduction product.

Quantum Chemical Calculations. The isodesmic reaction shown in Scheme 6 is proposed such that the strain imposed on the spirodione structures **20** by the presence of two small rings could be compared to that in **20c**, where the homologous *p*-hydroxyphenyl ketones are assumed to be strain-free. This approach has the advantage that errors which result from neglecting a part of the electron correlation cancel. The same approach connected with the levels of theory used (vide infra)

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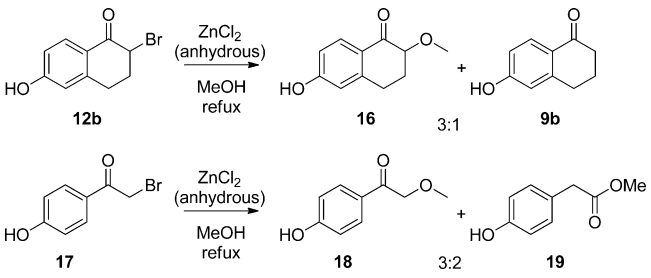
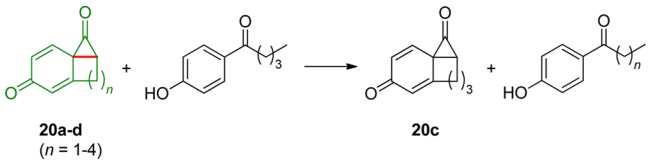
Scheme 5. Ground-State Favorskii Conditions for Reactions of 12b and 17



Scheme 6. Isodesmic Reaction for Estimating the Relative Ring Strains in 20a–d



20a-d (*n* = 1-4) **20c**

has proven to give satisfactory results.[52,53] The enthalpy change calculated according to Scheme 6 is summarized in Table 4. In the case of **20a**, optimizations at the RB3LYP or RMP2 levels of theory with the 6-31G+(d) or 6-311+G(d,p) basis sets resulted, however, in a spontaneous cleavage of the spiro bond (highlighted in red, Scheme 6) and the formation of an open planar structure resembling that of the corresponding triplet biradical. The ring strain in **20a** was, therefore, estimated from geometry possessing the spiro bond constrained to 1.698 Å, the bond length obtained from RB3LYP/6-31+G(d) optimization of a related system, the bicyclo[2.1.0]pentan-5-one.[54]

Table 4. Ring Strain for 20a,b,d Relative to 20c Calculated According to Scheme 6

compd	ΔH^a (M06-2X, kcal mol^{-1}, 0 K)	ΔH^a (MP2, kcal mol^{-1}, 0 K)
20a	−25.2[b]	−25.7[b]
20b	−2.1	−1.9
20c	0.0[c]	0.0[c]
20d	−1.3	−1.2

[a]Calculated with the 6-311+G(2df,2p) basis set on B3LYP/6-31+G(d) geometries. The ZPVE was scaled by 0.9857.[55] [b]An estimate based on spirodione **20a** with spiro bond length constrained to 1.69752 Å (see text). [c]Equals zero by definition (Scheme 6).

An alternative pathway that has been proposed by Phillips[56] suggested that the formation of the rearranged acid **2** occurs adiabatically in the triplet manifold. We used the UB3LYP/6-31+G(d) level of theory with polarizable continuum model (PCM, acetonitrile) to account for the collective properties of the surrounding solvent to model the triplet PES. We attempted to find the local minimum, which would correspond to the spirodione **3** but no such minimum could be found. However, we localized a transition state **21** resembling the structure of the spirodione, which connects the energy minimum of the triplet biradical ^{3}**4** and its rearranged product **22** (Scheme 7), which upon ISC and subsequent trapping by water might yield the final acid **2**. The barrier for this process calculated at M06−2X/6-311+G(2df,2p) level of theory in PCM at 0 K is 52.6 kcal mol^{-1}.

Nanosecond Laser Flash Photolysis (LFP). Nanosecond LFP (λ_{exc} = 266 nm) of a water/acetonitrile (30:70, v/v) solution of **7b** was performed using the conditions employed for *p*-hydroxyacetophenone reported by Heger, Wirz, and co-workers to confirm the decay pathways accompanying the *p*-hydroxyphenacyl PPGs.[31] Excitation of an aerated solution of **7b** produced the transient absorption spectra of two species with maxima at 410 and 358 nm within the first 30 ns (Figure 1, top, black) after the laser flash, which we attribute to the conjugate base of triplet ^{3}**7b**, the triplet anion ^{3}**23b** (Scheme 8), and its tautomeric form, the triplet quinoid enol ^{3}**24b**, respectively.[31] The anion ^{3}**23** decays to ^{3}**24** (Figure 1, top, red), which then decays to the ground-state conjugate base of **7b** with an absorption maximum at 332 nm as seen from the end spectrum (>5 μs). Excitation of a solution of **7b** with addition of a drop of perchloric acid leads exclusively to the formation of triplet quinone ^{3}**24b** (Figure 1, bottom), which again subsequently decays to the ground state conjugate base of

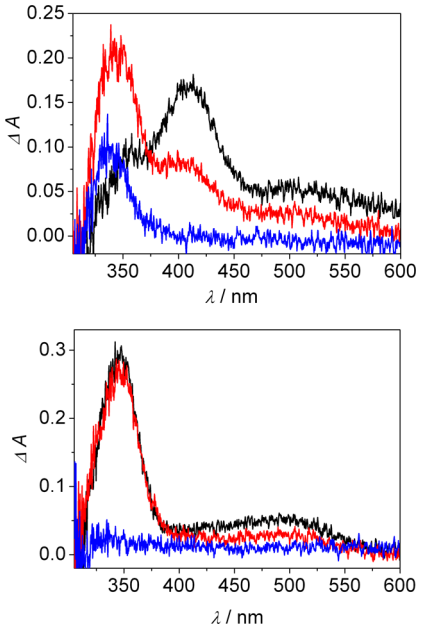
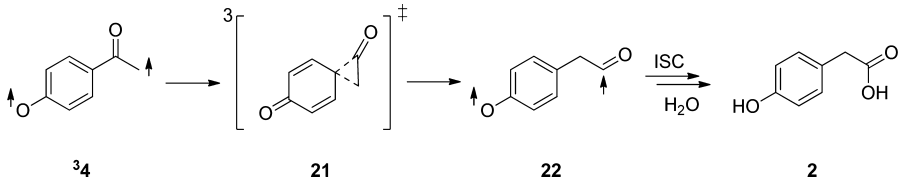


Figure 1. Transient absorption spectra of **7b** in an water/acetonitrile (30:70, v/v) mixture without (top) and with (bottom) a drop of perchloric acid recorded 30 ns (black), 100 ns (red), and 5 μs (blue) after a 266 nm laser flash.

Scheme 7. Reaction of the Triplet Biradical ^{3}4



^{3}**4** **21** **22** **2**

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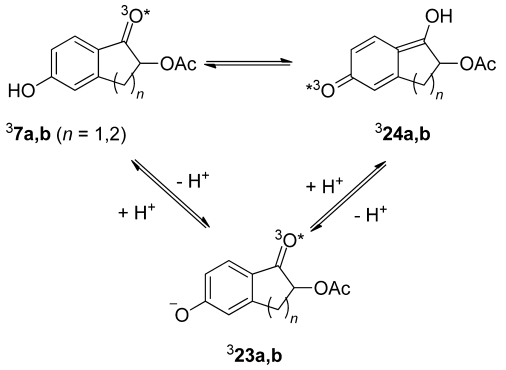
Scheme 8. Observed Transients in the LFP Experiments



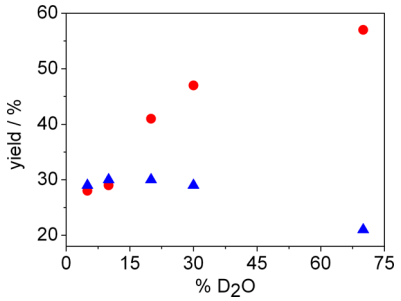


Figure 2. Chemical yield dependence of the photoproducts (red circles: **13b**; blue triangles: the sum of **14b** and **15b**) formation from **7b** on increasing concentrations of D_2O in CD_3CN.

7b. The same behavior as that of **7b** was observed upon excitation of **9b** and **7a** in water/acetonitrile solutions (Figures S27−29 and Table S5, Supporting Information). Similar spectra upon laser excitation in water/acetonitrile solutions were recorded throughout the whole series of the hydroxybenzocycloalkanones (**7**−**9**).

DISCUSSION

Our results establish that tethering the acetyl group of pHP to the phenol ring does not prevent rearrangement for rings of seven or eight carbons. In fact, photolysis of **7c,d** and mesylate **8c** in aqueous acetonitrile formed the Favorskii products **14c,d** and the accompanying benzyl alcohols **15c,d** along with minor amounts of an unrearranged reduction product **9c,d** and solvolysis α-hydroxy ketone **13c,d**.

The minor reduction products **9a**−**d** (5−7%, Table 1) had previously been reported for photolyses performed in reducing solvents (THF, MeOH, or *i*-PrOH) and when reducing additives are present.[57−60] The yields for all four platforms are not dependent on ring size, the leaving group, or solvent variations within the range of our investigations and therefore are not being considered further.

In a similar manner, the relative yields of α-hydroxy ketones **13c,d** are nearly constant (4−9%) with changes in H_2O concentration (Tables S3 and S4, Supporting Information) as are the total yields of the rearrangement products **14c,d** + **15c,d**. (The two "Favorskii" products will be treated as their sum for remainder of this discussion.) Thus, the C7 and C8 ring platforms behave as anticipated using photo-Favorskii rearrangement conditions.

A significant change from the C7 and C8 reactions occurs with the photoproduct distribution from **7b**, **8b** (the 6-hydroxydihydronaphthalen-1(2*H*)-one acetate and mesylate) as evidenced by the increase in α-hydroxy ketone **13b** accompanied by decrease in the Favorskii products (**14b** + **15b**) (Table 1). This shift in the product distribution is reflected in the photolysis of the mesylate ester **8b** in 70/30 D_2O/CD_3CN which resulted in essentially the same product distribution. Thus, the two esters of widely different leaving group nucleofugacity generated only minor variation in the product concentrations. On the other hand, the α-hydroxy-ketone solvolysis product did increase significantly for both esters with an increase in the solvent water content (Table 2 and Figure 2).

Because the source of the α-hydroxy ketone had not been pursued in past studies,[32,61] we felt that it was imperative that we explore its origin. In question is whether the α-C−OAc bond or the O−$COCH_3$ acetate ester bond was broken by photolysis. To differentiate between the two pathways, **7b** along with **7c**, the larger C7 ring, and **7a**, the smaller C5 ring acetate esters, were irradiated in ^{18}O-enriched D_2O. In each case, the solvolysis product had incorporated an isotopically labeled ^{18}O (HRMS) at the α-hydroxy group (Scheme 4) establishing that all three of these esters suffered heterolytic cleavage with the departure of the intact leaving group paralleling the initial photo-Favorskii rearrangement step. The ^{18}O content for all three α-hydroxy products (**13a**−**c**) was constant (75% ^{18}O) and reflected the solvent ^{18}O content. Furthermore, the extent of ^{18}O incorporation in both of the rearrangement products **14** and **15** matched the results of the α-hydroxy products, supporting the conclusion that the solvent, here H_2O, serves as the trapping agent for the penultimate reactive precursors that form the three final products **14**, **15**, and **13** . Since no ^{18}O incorporation was found for the starting ester nor in the reduction product, any ground state prephotolysis or photo-induced ketone or leaving group exchange processes had not occurred.

The C5 esters **7a** and **8a** gave only the α-hydroxy ketone **13a** and the reduction product upon photolysis. No rearrangement products are detected from either the acetate or the mesylate (Table 1 and Table S1, Supporting Information). Neither the solvent water content nor the change in leaving group significantly changed the ratio of these two products, the ratio being less sensitive to solvent variation than found for **7b** and **8b**. For **7a** and **8a**, photosolvolysis is, by far, the major pathway.

The quantum efficiencies for disappearance for all seven reactions were dependent on the nature of the leaving group but were apparently independent of ring size (Table 3). The acetate quantum efficiencies were ~0.30 ± 0.08, typical of many pHP acetate esters (e.g., pHP OAc Φ_{-OAc} = 0.4) whereas the mesylate esters were narrowly clustered around 0.66 ± 0.04, nearly twice that of the acetates but somewhat less than the mesylates in the pHP series (pHP MsO, Φ_{-MsO} = 0.93).[19,61] The trend for the product ratios and the constancy of the quantum efficiencies for the acetates are clearly demonstrated for this series of hydroxybenzocycloalkanones in Figure 3 and Table 5, respectively.

The same dramatic departure from a Favorskii reaction favoring rearrangement to other pathways was found with 6-membered ring ground-state reactions for the two examples shown in Scheme 9. No rearrangement products were formed from either the α-bromo or α-diiodo cyclohexanones, whereas larger ring sizes successfully rearranged to the carboxylic esters under Favorskii conditions.[43−45] There is a resistance to rearrangement in the ground state which may be imposed on

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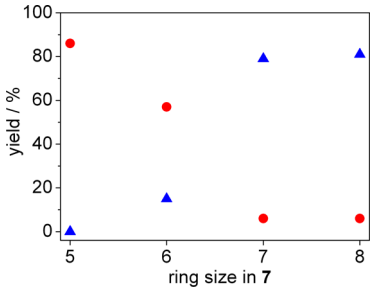


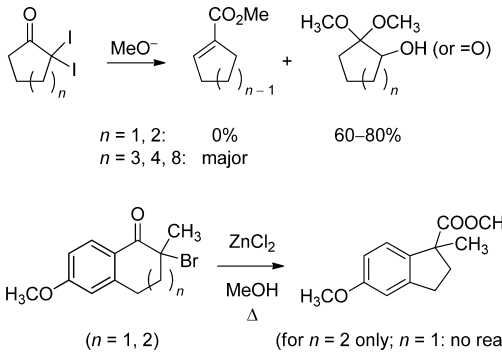
Figure 3. Dependence of photoproducts chemical yields (red circles: **13**; blue triangles: the sum (**14** + **15**) on the ring size of **7a–d** irradiated in water/acetonitrile (70:30, v/v).

Table 5. Effect of Ring Size on Change in the Distribution of the Major Products from 7a–d

ring size	n	$\Phi^{a,b}$	ΔH^c (MP2)	% of **13**	% of (**14** + **15**)
no ring (pHP)	0	0.40[32]	N/A[d]	<5[32,62]	>95
8 (**7d**)	4	0.34	−1.2	7	81
7 (**7c**)	3	0.26	0.0[e]	4	79
6 (**7b**)	2	0.24	−1.9	57	21
5 (**7a**)	1	0.38	−25.7[f]	86	0

[a]The confidence intervals at the 95% confidence level are shown. [b]Valerophenone was used as an actinometer (Φ = 0.30 in benzene).[48] [c]Strain Energy (kcal mol^{-1}, 0 K) calculated with the 6-311+G(2df,2p) basis set on B3LYP/6-31+G(d) geometries. The ZPVE was scaled by 0.9857.[55] [d]Not available by the computational protocol used here (see Scheme 6). [e]Equals zero by definition (see Scheme 6). [f]An estimate based on spirodione **20a** with spiro bond length constrained to 1.69752 Å (see text).

Scheme 9. Favorskii Ring-Contraction Reactions for a Series of Medium-Sized Rings[43−45]



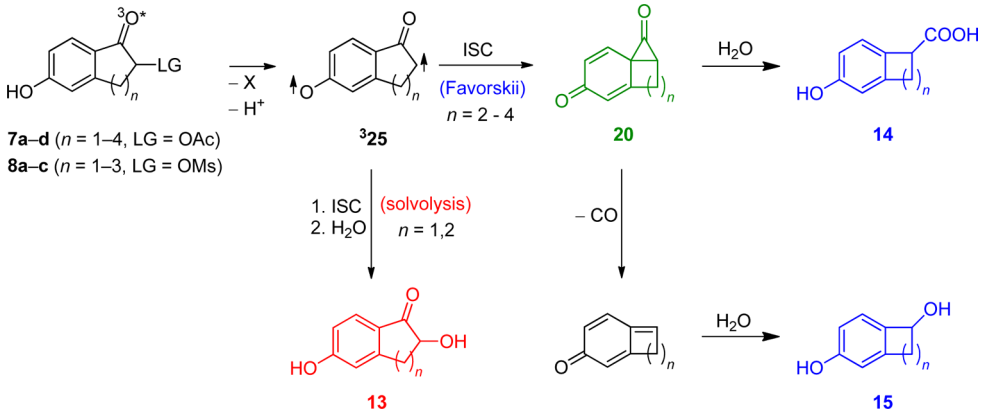
the transition state to the spiroketone by ring strain. As a result, the other divergent pathways such as solvolysis become more competitive when the rearrangement pathway involves the strained bicyclo[3.1.0]hexane intermediate (vide infra).

The current study brings clarity to the photochemistry of the *p*-hydroxyphenacyl protecting group. The results provided here reveal the factors that influence the partitioning of the pHP triplet excited state between product formation and return to ground-state reactant but also provide a triplet-state inventory for these processes.

The triplet states of ^{3}**7a–d**, which are quantitatively generated upon excitation, initially partition among three pathways, a minor reduction pathway and two major channels; a proton transfer channel that generates the triplet conjugate base ^{3}**23** and its quinoid tautomer ^{3}**24** and a heterolytic departure of the leaving group. The former process is the excited-state proton transfer (ESPT) channel[31,32] that has been well documented including the recent report on the parent chromophore, *p*-hydroxyacetophenone[31] and confirmed here for the cycloalkanones **9a–d**. The governing factor for the partition between these two channels is the nature of the leaving group X; the better the leaving group, the more dominant the heterolysis pathway. This has been quantitatively formalized for other pHP derivatives through a linear free energy Bronsted relationship between the rate constants for release and the pK_a of the leaving group.[19,22] In the current study, the two leaving groups fall in the intermediate and high reactivity positions on the pK_a coordinate.

These two channels operate independently as demonstrated by the effects of pH on the photochemistry. Throughout the pH range of 4–7, heterolytic reaction is insensitive to the conditions as has been shown by the constancy of the quantum yields in this pH range by detailed examination of many pHP derivatives.[32,40] In contrast, the ratio of ESPT triplet products varies greatly between conjugate base formation (at higher pH) and the quinoid tautomer (at low pH, Figure 1). Traditionally, the ESPT pathways are understood to be nonproductive channels because the intermediates eventually return to the reactants.[31] When in competition with other product forming reactions, these are considered "energy wasting" processes.[40] This was shown to be the case for the two series examined here, where the nonproductive ESPT process accounted for the difference between quantum yields for product formation and unity. Thus, the ESPT processes account for the remainder of the total energy inventory of the triplet state.

Scheme 10. Effect of Ring Size on Two Diverging Heterolysis Channels in the Photo-Favorskii Rearrangement



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The heterolytic channel is responsible for the formation of the triplet biradical ^{3}**25** (^{3}**4** in the case of pHP; Scheme 10). The triplet biradical ^{3}**25** cannot lead to the Favorskii product formation adiabatically as suggested by Phillips and coworkers[56] (Scheme 7) because of considerable energy demands of the rearrangement.[59] The Favorskii product most likely forms after isc relaxation of triplet biradical ^{3}**25** (^{3}**4**) to the ground-state surface forming the spiroketone **20** (**3**). The observation that the methyl ester of **2** is readily formed by the ground-state, Lewis-acid catalyzed rearrangement of pHP Br (**17**, Scheme 5) argues against the Phillips mechanism. The controlling factor in the partitioning between the Favorskii rearrangement and solvolysis channels is the ease of formation of the singlet-ground-state spirodienedione **20** and **3**. With the seven- and eight-membered rings and the noncyclic pHP analogues, the rearrangement channel is available and dominates the photo initiated reaction, while the five- and six-membered rings falter. The alternative pathway open to the latter two ring systems is solvolysis which accounts for the decrease in the efficiencies of the photorearrangement channel. Consequently, the total quantum yields remain essentially constant within the series in keeping with the triplet state inventory.

The source or origin of the governing factor, ring size, is the rising cost in energy of the bridge closure to form the cyclopropanones **20a–d** which translates into increased ring strain (ΔH, Table 5). As the length of the ring tether decreases below a critical level, the formation of **20** becomes strongly disfavored (**7a,b** and **8a,b**) and an alternative hydrolysis channel dominates for them (Scheme 10). The bifurcation into two parallel pathways occurs as the triplet biradical ^{3}**25** intersystem crosses to the ground state before spiroketone **20** is formed. This suggests that another short-lived intermediate connecting ^{3}**25** and **20** might intervene in the photorearrangement. Additional work is in progress that will explore the factors influencing the partitioning of the two pathways and that tests the tenets of the mechanism proposed here (Scheme 10) including its relationship with the Lewis acid catalyzed rearrangement (Scheme 5).

CONCLUSION

We have shown that, through design testing, a monotonic decrease in tether ring size discourages the formation of the Favorskii spirocyclopropanone intermendiate **20**, diverting the Favorskii rearrangement channel toward solvolysis to unrearranged α-hydroxy ketone products. Conversely, the large ring hydroxybenzocycloalkanones (**7c,d** and **8c**) and *p*-hydroxyphenacyl analogues (**1**) overwhelmingly follow the now well-known photo-Favorskii rearrangement pathway in aqueous media. When the strain energy of the intermediate spiroketone reaches levels that are resistant to closure, the pathway diverts toward solvolysis.

EXPERIMENTAL SECTION

Materials and Methods. NMR spectra were recorded on a 300 MHz spectrometer calibrated to the residual peak of the (major) *d*-solvent. Gas chromatography was performed on a chromatograph equipped with a 15 m (5% diphenyldimethylsiloxane) column with FID detector. Mass spectra were recorded on a GC-coupled (30-m DB-XLB column) mass spectrometer in a positive mode with EI. HRMS data were obtained on a UPLC/MS-TOF apparatus equipped with an ESI interface and a C-18 (1.7 μm, 2.1 × 50 mm) column, using ammonium carbonate in methanol (0.005 M) as a mobile phase. UV spectra were obtained with matched 1.0-cm quartz cells. All column chromatography purification procedures were performed with silica gel. The reagents and solvents of the highest purity available were used as purchased, or they were purified/dried when necessary. All glassware was flame-dried prior to use when water- and/or air-sensitive compounds were used. Compounds **9a,b** and **26a,b** (see Scheme S1 in the Supporting Information) are commercially available; synthesis and characterization of compounds **10a**,[23] **10b**,[63] **27a**,[64] **27b**,[65] **28a**,[66] **28b**,[67] **29a**,[67] **29b**,[68] **30c**,[69] **9c**,[70] **14b**,[71] **14c**[70] have been previously described. Synthetic protocols and analytical data for all new compounds are provided below. Compounds **13d** and **14d** could neither be synthesized nor isolated. Their formation has been confirmed by HPLC/HRMS analysis.

General Procedure for the Synthesis of 10a–d. This procedure has been adapted from our previous work.[23] Potassium carbonate (1.9 g, 13.7 mmol) was added to a solution of **9** (6.1 mmol) and benzyl bromide (0.83 mL, 6.7 mmol) in acetonitrile (35 mL), and the mixture was stirred overnight at 20 °C. The reaction mixture was concentrated under reduced pressure and diluted with water, and the organic material was extracted with ethyl acetate (2 × 20 mL). The organic layers were washed with water (2 × 20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. The title product was purified by column chromatography (ethyl acetate/hexane, 3:7).

*2-(Benzyloxy)-6,7,8,9-tetrahydrobenzo[7]annulen-5-one (**10c**).* Prepared from **9c**. Yield: 1.25 g (83%). Tan solid. Mp: 140.1–141.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.78–1.83 (m, 2H), 1.85–1.90 (m, 2H), 2.72 (t, 2H, J = 5.9 Hz), 2.9 (t, 2H, J = 6.1 Hz), 5.10 (s, 2H), 6.79 (d, 1H, J = 2.1 Hz), 6.88 (dd, 1H, J = 8.6, 2.3 Hz), 7.32–7.43 (m, 5H), 7.78 (d, 1H, J = 8.62 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 20.7, 25.0, 32.8, 40.7, 70.0, 112.5, 115.8, 127.4, 128.1, 128.6, 131.2, 131.8, 136.4, 144.1, 161.8, 204.1. MS (EI, 70 eV): m/z 266, 175, 147, 105, 91, 65, 39. HRMS (APCI$^+$): calcd for $C_{18}H_{19}O_2^+$ (M + H$^+$) 267.1379, found 267.1388. This compound has also been characterized previously.[72]

*2-(Benzyloxy)-7,8,9,10-tetrahydrobenzo[8]annulen-5(6H)-one (**10d**).* Prepared from **9d**. Yield: 1.22 g (83%). Tan solid. Mp: 151.7–152.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.42–1.50 (m, 2H), 1.76–1.90 (m, 4H), 3.0 (t, 2H, J = 7.1 Hz), 3.13 (t, 2H, J = 6.7 Hz), 5.10 (s, 2H), 6.78 (d, 1H, J = 2.6 Hz), 6.89 (dd, 1H, J = 8.8, 2.6 Hz), 7.33–7.44 (m, 5H), 7.95 (d, 1H, J = 8.8 Hz).^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 23.4, 24.5, 27.7, 35.4, 42.9, 70.0, 112.3, 117.5, 127.5, 128.1, 128.6, 131.5, 132.7, 136.4, 143.1, 161.9, 203.19. MS (EI, 70 eV): m/z 280, 237, 195, 165, 105, 91, 65, 39. HRMS (APCI$^+$): calcd for $C_{19}H_{21}O_2^+$ (M + H$^+$) 281.1536, found 281.1546.

General Procedure for the Synthesis of 11a–d. This procedure has been adapted from Demir and Findik.[46] $KMnO_4$ (300 mg, 3 mmol) in a benzene–acetic acid (10:1, 50 mL) mixture was stirred under reflux (a Dean–Stark apparatus) until the purple color of $KMnO_4$ turned brown (~30 min). Compound **10** (1 mmol) was then added to the solution, and reflux was continued. After the starting material was consumed (TLC), the reaction mixture was cooled, diluted with diethyl ether, and neutralized with saturated aq $NaHCO_3$ (20 mL). The resulting organic phase was washed with water (3 × 20 mL) and brine (25 mL) and dried with $MgSO_4$. The solvents were removed under reduced pressure, and the crude mixture of products was purified by column chromatography (ethyl acetate/hexane, 3:7) to give the title compound.

*5-(Benzyloxy)-2,3-dihydro-1-oxo-1H-inden-2-yl Acetate (**11a**).* Prepared from **10a**. Yield: 210 mg (72%). Yellow solid. Mp: 123.3–124.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.17 (s, 3H), 2.97 (dd, 1H, J = 17.0, 4.4 Hz), 3.60 (dd, 1H, J = 17.1, 7.8 Hz), 5.1 (s, 2H), 5.40 (dd, 1H, J = 7.8, 4.6 Hz), 6.93 (d, 1H, J = 1.7 Hz), 7.02 (dd, 1H, J = 8.5, 2.1 Hz), 7.35–7.42 (m, 5H), 7.74 (d, 1H, J = 8.5 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 21.2, 34.1, 70.8, 74.4, 111.2, 117.1, 126.8, 127.85, 128.3, 128.8, 129.1, 136.2, 153.8, 165.7, 170.9, 198.9. MS (EI, 70 eV): m/z 296, 236, 135, 107, 91, 65, 43. HRMS (APCI$^+$): calcd for $C_{18}H_{17}O_4^+$ (M + H$^+$) 297.1121, found 297.1118.

*6-(Benzyloxy)-1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl Acetate (**11b**).* Prepared from **10b**. Yield: 230 mg (74%). Yellow solid. Mp:

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112.2−113.1 °C. ^{1}H NMR (300 MHz, DMSO): δ (ppm) 2.17 (s, 3H), 2.24−2.38 (m, 2H), 3.02 (td, 1H, *J* = 4.3 Hz, 7.9 Hz), 3.10−3.22 (m, 1H), 5.12 (s, 2H), 5.51 (dd, 1H, *J* = 12.9, 5.2 Hz), 6.78 (d, 1H, *J* = 1.9 Hz), 6.93 (dd, 1H, *J* = 8.7, 2.3 Hz), 7.34−7.46 (m, 5H), 8.01 (d, 1H, *J* = 8.74 Hz). ^{13}C NMR (75.5 MHz, DMSO): δ (ppm) 20.4, 27.2, 28.5, 69.4, 73.9, 113.4, 114.2, 124.4, 127.6, 127.9, 128.3, 129.0, 136.2, 146.3, 162.5, 169.2, 191.1. MS (EI, 70 eV): *m*/*z* 310, 268, 250, 177, 149, 91, 64, 43. HRMS (APCI$^+$): calcd for $C_{19}H_{19}O_4^+$ (M + H$^+$) 311.1277, found 311.1287.

*2-(Benzyloxy)-6,7,8,9-tetrahydro-5-oxo-5H-benzo[7]annulen-6-yl Acetate (**11c**).* Prepared from **10c**. Yield: 190 mg (59%). Yellow solid. Mp: 106.1−107.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.73−1.81 (m, 1H), 1.93−2.03 (m, 1H), 2.12−2.22 (m, 5H), 2.89−3.09 (m, 2H), 5.10 (s, 2H), 5.47 (dd, 1H, *J* = 10.9, 5.4 Hz), 6.81 (d, 1H, *J* = 2.3 Hz), 6.90 (dd, 1H, *J* = 8.7, 2.4 Hz), 7.33−7.41 (m, 5H), 7.84 (d, 1H, *J* = 8.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 20.7, 23.1, 28.2, 34.1, 70.0, 77.1, 112.7, 116.2, 127.4, 128.2, 128.6, 129.2, 132.0, 136.2, 144.8, 161.8, 170.2, 197.0. MS (EI, 70 eV): *m*/*z* 324, 282, 264, 236, 173, 91, 65, 43. HRMS (APCI$^+$): calcd for $C_{20}H_{21}O_4^+$ (M + H$^+$) 325.1434, found 325.1436.

*2-(Benzyloxy)-5,6,7,8,9,10-hexahydro-5-oxobenzo[8]annulen-6-yl Acetate (**11d**).* Prepared from **10d**. Yield: 130 mg (41%). Yellow solid. Mp: 117.2−118.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.34−1.48 (m, 1H), 1.58−1.67 (m, 1H), 1.71%1.86 (m, 2H), 1.96−2.05 (m, 2H), 2.17 (s, 3H), 2.84−2.93 (m, 1H), 3.21−3.31 (m, 1H), 5.1 (s, 2H), 5.96 (dd, 1H, *J* = 9.9, 7.8 Hz), 6.78 (d, 1H, *J* = 2.5 Hz, 1H), 6.91 (dd, 1H, *J* = 8.8, 2.5 Hz, 1H), 7.33−7.43 (m, 5H), 8.02 (d, 1H, *J* = 8.8 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 20.7, 20.9, 27.5, 30.2, 35.5, 70.0, 77.2, 112.5, 117.7, 127.4, 128.2, 128.6, 131.0, 131.8, 136.2, 142.0, 162.4, 170.3, 197.0. MS (EI, 70 eV): *m*/*z* 338, 296, 251, 160, 91, 65, 43. HRMS (APCI$^+$): calcd for $C_{21}H_{23}O_4^+$ (M + H$^+$) 339.1590, found 339.1600.

General Procedure for the Synthesis of 7a−d. This procedure has been adapted from Givens and co-workers.[40] Pd/C (10%, 50 mg) was added to a solution of **11** (1.5 mmol) in ethyl acetate (25 mL), and the mixture was stirred under hydrogen atmosphere at 20 °C until the starting material was consumed (TLC). The mixture was filtered through a pad of Celite, and the solvent was evaporated under reduced pressure. The title compound was purified using column chromatography (ethyl acetate/hexane, 2:3).

*2,3-Dihydro-5-hydroxy-1-oxo-1H-inden-2-yl Acetate (**7a**).* Prepared from **11a**. Yield: 260 mg (85%). White solid. Mp: 124.1−125.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.17 (s, 3H), 2.97 (dd, 1H, *J* = 17.1, 4.5 Hz), 3.59 (dd, 1H, *J* = 17.1, 7.8 Hz), 5.42 (dd, 1H, = 7.8, 4.6 Hz), 6.63 (s, 1H), 6.86−6.90 (m, 2H), 7.72 (d, 1H, *J* = 8.3 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 20.7, 35.5, 74.1, 112.3, 116.8, 126.9, 127.5, 153.8, 163.1, 170.7, 199.0. MS (EI, 70 eV): *m*/*z* 206, 163, 146, 135, 107, 77, 43. UV−vis: ε_{313} (CH_3CN/H_2O, 30:70, v/v) = 5711 dm^3 mol^{-1} cm^{-1}; ε_{313} (CH_3CN) = 1172 dm^3 mol^{-1} cm^{-1}. HRMS (APCI$^+$): calcd for $C_{11}H_{11}O_4^+$ (M + H$^+$) 207.0651, found 207.0657.

*1,2,3,4-Tetrahydro-6-hydroxy-1-oxonaphthalen-2-yl Acetate (**7b**).* Prepared from **11b**. Yield: 280 mg (85%). White solid. Mp: 119.1−120.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.21 (s, 3H), 2.26−2.36 (m, 2H), 3.0 (dt, 1H, *J* = 7.2, 3.6 Hz), 3.08−3.19 (m, 1H), 5.51 (dd, 1H, *J* = 12.9, 5.3 Hz), 5.66 (s, 1H), 6.71 (d, 1H, *J* = 1.9 Hz), 6.78 (dd, 1H, *J* = 8.5, 2.4 Hz), 7.97 (d, 1H, *J* = 8.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3/CD_3CN$): δ (ppm) 20.7, 27.8, 29.0, 74.2, 114.1, 116.2, 124.3, 130.2, 145.8, 161.6, 170.1, 191.6. MS (EI, 70 eV): *m*/*z* 220, 202, 177, 160, 149, 121, 91, 77, 43. UV−vis: ε_{313} (CH_3CN/H_2O, 30:70, v/v) = 2665 dm^3 mol^{-1} cm^{-1}; ε_{313} (CH_3CN) = 380 dm^3 mol^{-1} cm^{-1}. HRMS (APCI$^+$): calcd for $C_{12}H_{13}O_4^+$ (M + H$^+$) 221.0808, found 221.0809.

*6,7,8,9-Tetrahydro-2-hydroxy-5-oxo-5H-benzo[7]annulen-6-yl Acetate (**7c**).* Prepared from **11c**. Yield: 280 mg (81%). White solid. Mp: 123.9−125.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.66−1.79 (m, 1H), 1.92−2.02 (m, 1H), 2.17−2.26 (m, 5H, $-CH_3$, $-CH_2$), 2.84−3.03 (m, 2H), 5.48 (dd, 1H, *J* = 11.0, 5.5 Hz), 6.54 (s, 1H), 6.6 (d, 1H, *J* = 2.3 Hz), 6.69 (dd, 1H, *J* = 8.3, 1.9 Hz), 7.74 (d, 1H, *J* = 8.5 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 20.8, 23.0, 28.1, 33.8, 77.3, 113.9, 116.6, 128.4, 132.2, 145.5, 159.7, 170.9, 197.1. MS (EI, 70 eV): *m*/*z* 234, 216, 192, 174, 163, 145, 135, 91, 77, 43. UV−vis: ε_{313} (CH_3CN/H_2O, 30:70, v/v) = 2275 dm^3 mol^{-1} cm^{-1}; ε_{313} (CH_3CN) = 465 dm^3 mol^{-1} cm^{-1}. HRMS (APCI$^+$): calcd for $C_{13}H_{15}O_4^+$ (M + H$^+$) 235.0965, found 235.0968.

*5,6,7,8,9,10-Hexahydro-2-hydroxy-5-oxobenzo[8]annulen-6-yl Acetate (**7d**).* Prepared from **11d**. Yield: 280 mg (75%). White solid. Mp: 129.0−130.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.37 (m, 1H), 1.68 (m, 2H), 1.81 (m, 2H), 2.01 (m, 1H), 2.18 (s, 3H), 2.80 (m, 1H), 3.20 (dt, 1H, *J* = 14.7, 5.7 Hz), 5.98 (t, 1H), 6.43 (s, 1H), 6.54 (d, 1H, *J* = 1.4 Hz), 6.68 (dd, 1H, *J* = 8.6, 1.9 Hz), 7.93 (d, 1H, *J* = 8.7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 20.86, 20.89, 27.3, 30.2, 35.5, 77.5, 113.8, 118.0, 130.5, 132.1, 142.5, 160.1, 171.0, 196.8. MS (EI, 70 eV): *m*/*z* 248, 206, 177, 159, 147, 107, 77, 43. UV−vis: ε_{313} (CH_3CN/H_2O, 30:70, v/v) = 2795 dm^3 mol^{-1} cm^{-1}; ε_{313} (CH_3CN) = 424 dm^3 mol^{-1} cm^{-1}. HRMS (APCI$^+$): calcd for $C_{14}H_{17}O_4^+$ (M + H$^+$) 249.1121, found 249.1125.

General Procedure for the Synthesis of 12a−c. This procedure has been adapted from our previous work.[23] A solution of **9** (6.2 mmol) and copper(II) bromide (3 g, 13.6 mmol) in ethyl acetate/$CHCl_3$ (50 mL, 1:1, v/v) was refluxed overnight. The mixture was cooled to 20 °C, filtered through a pad of silica, concentrated under reduced pressure, and purified by column chromatography (ethyl acetate/hexane, 3:7) to give the title compound.

*2-Bromo-2,3-dihydro-5-hydroxyinden-1-one (**12a**).* Prepared from **9a**. Yield: 1.10 g (76%). Yellow solid. Mp: 173.8−174.8 °C. ^{1}H NMR (300 MHz, DMSO): δ (ppm) 3.22 (dd, 1H, *J* = 18.3, 2.8 Hz), 3.78 (dd, 1H, *J* = 18.3, 7.3 Hz), 4.92 (dd, 1H, *J* = 7.4, 2.9 Hz), 6.84−6.86 (m, 1H), 6.88 (d, 1H, *J* = 2.1 Hz), 7.59 (d, 1H, *J* = 8.2 Hz), 10.79 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO): δ (ppm) 37.1, 46.0, 111.7, 116.6, 124.5, 126.2, 154.5, 164.8, 196.8. MS (EI, 70 eV): *m*/*z* 226, 147, 119, 91, 77, 63. HRMS (APCI$^+$): calcd for $C_9H_8BrO_2^+$ (M + H$^+$) 226.9702, found 226.9708.

*2-Bromo-3,4-dihydro-6-hydroxynaphthalen-1(2H)-one (**12b**).* Prepared from **9b**. Yield: 1.10 g (83%). Yellow solid. Mp: 152.1−153.5 °C. ^{1}H NMR (300 MHz, DMSO): δ (ppm) 2.25−2.35 (m, 1H), 2.46−2.56 (m, 1H), 2.87 (td, 1H, *J* = 16.9, 4.79 Hz), 2.98−3.07 (m, 1H), 4.92 (dd, 1H, *J* = 5.6, 3.6 Hz), 6.69 (d, 1H, *J* = 2.3 Hz), 6.78 (dd, 1H, *J* = 8.6, 2.4 Hz), 7.81 (d, 1H, *J* = 8.6 Hz), 10.52 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO): δ (ppm) 25.9, 31.7, 52.2, 114.1, 114.9, 121.5, 130.3, 145.9, 162.6, 188.4. MS (EI, 70 eV): *m*/*z* 240, 185, 161, 134, 106, 77, 51. HRMS (APCI$^+$): calcd for $C_{10}H_{10}BrO_2^+$ (M + H$^+$) 240.9858, found 240.9858.

*6-Bromo-6,7,8,9-tetrahydro-2-hydroxybenzo[7]annulen-5-one (**12c**).* This compound was not purified. A crude reaction mixture was used in the subsequent synthetic step.

General Procedure for the Synthesis of 8a−c. This procedure has been adapted from our previous work.[23] A solution of **12** (2.7 mmol), silver(I) oxide (900 mg, 4.0 mmol), and methanesulfonic acid (0.35 mL, 5.4 mmol) in acetonitrile (30 mL) was stirred overnight at 60 °C. The reaction mixture was cooled to 20 °C and filtered through a pad of Celite, and the solvent was removed under reduced pressure. The crude product mixture was purified by flash chromatography (ethyl acetate/hexane, 1:1).

*2,3-Dihydro-5-hydroxy-1-oxo-1H-inden-2-yl Methanesulfonate (**8a**).* Prepared from **12a**. Yield: 300 mg (45%). White solid. Mp: 204.1−205.3 °C. ^{1}H NMR (300 MHz, CD_3CN): δ (ppm) 3.14 (dd, 1H, *J* = 17.3, 4.5 Hz), 3.22 (s, 3H), 3.63 (dd, 1H, *J* = 17.2, 8.0 Hz), 5.30 (dd, 1H, *J* = 8.0, 4.5 Hz), 6.89 (d, 1H, *J* = 2.1 Hz), 6.91 (m, 1H), 7.62 (d, 1H, *J* = 9.1 Hz), 7.97 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 34.1, 39.3, 80.2, 113.0, 117.7, 127.0, 127.3, 154.7, 165.4, 197.2. MS (EI, 70 eV): *m*/*z* 242, 226, 163, 146, 135, 107, 91, 77, 65. UV−vis: ε_{313} (CH_3CN/H_2O, 30:70, v/v) = 11,777 dm^3 mol^{-1} cm^{-1}; ε_{313} (CH_3CN) = 3460 dm^3 mol^{-1} cm^{-1}. HRMS (APCI$^+$): calcd for $C_{10}H_{11}O_5S^+$ (M + H$^+$) 243.0321, found 243.0318.

*1,2,3,4-Tetrahydro-6-hydroxy-1-oxonaphthalen-2-yl Methanesulfonate (**8b**).* Prepared from **12b**. Yield: 290 mg (42%). White solid. Mp: 172.5−173.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.31 (m, 1H), 2.48 (m, 1H), 3.06 (m, 2H), 3.19 (s, 3H), 5.28 (dd, 1H, *J* = 12.6, 5.1 Hz), 6.72 (d, 1H, J = 1.6 Hz), 6.80 (dd, 1H, *J* = 8.6, 2.0

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Hz), 7.27 (s, 1H), 7.89 (d, 1H, J = 8.6 Hz). ^{13}C NMR (75.5 MHz, CD_3CN/DMSO): δ (ppm): 27.9, 31.2, 39.0, 81.6, 115.1, 115.9, 124.1, 130.9, 147.3, 164.1, 190.9. MS (EI, 70 eV): m/z 256, 240, 160, 149, 134, 121, 107, 91, 77, 65. UV−vis: ε_{313} (CH_3CN/H_2O, 30:70, v/v) = 3840 dm^3 mol^{-1} cm^{-1}; ε_{313} (CH_3CN) = 1257 dm^3 mol^{-1} cm^{-1}. HRMS (APCI$^+$): calcd for $C_{11}H_{13}O_5S^+$ (M + H$^+$) 257.0478, found 257.0478.

*6,7,8,9-Tetrahydro-2-hydroxy-5-oxo-5H-benzo[7]annulen-6-yl Methanesulfonate (**8c**).* Prepared from **12c** (reaction mixture). Yield: 220 mg (32%). White solid. Mp: 148.6−149.5 °C. ^{1}H NMR (300 MHz, DMSO) δ (ppm) 1.53−1.60 (m, 1H), 1.82−1.89 (m, 1H), 2.10 (m, 1H), 2.20−2.27 (m, 1H), 2.84 (dd, 1H, J = 15.6, 4.7 Hz), 3.09 (t, 1H, J = 13.13 Hz), 3.23 (s, 3H), 5.46 (dd, 1H, J = 10.4, 5.6 Hz), 6.6 (d, 1H, J = 1.6 Hz), 6.74 (dd, 1H, J = 8.5, 2.0 Hz), 7.65 (d, 1H, J = 8.4 Hz), 10.28 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 22.1, 28.7, 32.4, 37.9, 82.4, 113.6, 116.3, 126.4, 131.5, 145.6, 161.3, 194.8. (EI, 70 eV): m/z 270, 191, 163, 145, 127, 107, 91, 77, 65. UV−vis: ε_{313} (CH_3CN/H_2O, 30:70, v/v) = 2703 dm^3 mol^{-1} cm^{-1}; ε_{313} (CH_3CN) = 989 dm^3 mol^{-1} cm^{-1}. HRMS (APCI$^+$): calcd for $C_{12}H_{15}O_5S^+$ (M + H$^+$) 271.0634, found 271.0638.

Synthesis of 7,8,9,10-Tetrahydro-2-methoxybenzo[8]-annulen-5(6*H*)-one (30d). This procedure has been adapted from Ho and Yang.[73] $MeSO_3H$ (53 mL, 0.82 mol) was stirred with **29b** (11.3 mmol) at 20 °C. P_2O_5 (7.7 g, 54.0 mmol) was then added portionwise to the reaction mixture which was stirred for 24 h at 20 °C. The mixture was poured into water (50 mL) and extracted by ethyl acetate (3 × 20 mL). The organic layer was washed with water (3 × 25 mL), aq K_2CO_3 (2 × 20 mL), and brine (25 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure and the title compound was obtained after purification by column chromatography (ethyl acetate/hexane, 1:4). Yield: 760 mg (33%). White solid. Mp: 137.7−139.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.40−1.48 (m, 2H), 1.75−1.89 (m, 4H), 2.99 (t, 2H, J = 7.1 Hz), 3.12 (t, 2H, J = 6.8 Hz), 3.83 (s, 3H), 6.67 (d, 1H, J = 2.5 Hz), 6.80 (dd, 1H, J = 8.7, 2.6 Hz), 7.95 (d, 1H, J = 8.7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 23.2, 24.5, 27.7, 35.4, 42.8, 55.2, 111.5, 116.6, 131.5, 132.5, 143.1, 162.7, 203.0. MS (EI, 70 eV): m/z 204, 189, 177, 161, 148, 120, 91, 77, 63. HRMS (APCI$^+$): calcd for $C_{13}H_{17}O_2^+$ (M + H$^+$) 205.1223, found 205.1229.

Synthesis of 7,8,9,10-Tetrahydro-2-hydroxybenzo[8]-annulen-5(6*H*)-one (9d). This procedure has been adapted from Itoh and co-workers.[74] A mixture of **30d** (600 mg, 2.0 mmol) and $AlCl_3$ (1.3 g, 9.8 mmol) in benzene (50 mL) was refluxed for 3 h. After cooling, the reaction mixture was poured into aq HCl (10%, 30 mL), and the organic species were extracted with ethyl acetate (2 × 30 mL), washed with water (2 × 20 mL), and brine (20 mL), and dried with $MgSO_4$. The solvent was removed under reduced pressure and the title compound was obtained after purification by column chromatography (ethyl acetate/hexane, 3:7). Yield 300 mg (78%).White solid. Mp: 143.1−144.5 °C. ^{1}H NMR (300 MHz, DMSO): δ (ppm) 1.3 (m, 2H), 1.7 (m, 4H), 2.91 (t, 2H, J = 7.1 Hz), 3.07 (t, 2H, J = 6.7 Hz), 6.62 (d, 1H, J = 2.2 Hz), 6.70 (dd, 1H, J = 8.5, 2.2 Hz), 7.75 (d, 1H, J = 8.5 Hz), 10.07 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 22.5, 23.9, 27.1, 34.3, 41.9, 113.3, 117.6, 130.5, 130.9, 143.1, 161.2, 201.0. MS (EI, 70 eV): m/z 190, 161, 147, 134, 106, 91, 77, 65. HRMS (APCI$^+$): calcd for $C_{12}H_{15}O_2^+$ (M + H$^+$) 191.1066, found 191.1068.

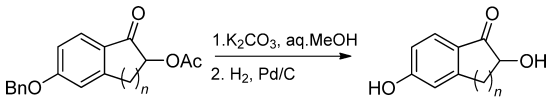
General Procedure for the Synthesis of the Photoproducts as the Analytical Standards. Synthesis of 13b,c. The title compounds were prepared in two steps from the acetates **11** (Scheme 11) according to the known procedures.[40,75] A mixture of **11** (0.65 mmol) and K_2CO_3 (106 mg, 0.77 mmol) in aq methanol (50%, 30 mL) was stirred at 0 °C for 3 h. Water (50 mL) was then added to the reaction mixture, and the organic material was extracted with ethyl acetate (2 × 20 mL). The organic layers were washed with brine (2 × 20 mL), dried with $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give crude reaction mixture which was redissolved in ethyl acetate (25 mL). To the resulting solution Pd/C (10%, 10 mg) was added, and the mixture was stirred under a hydrogen atmosphere (H_2 balloon) at 20 °C until the starting material was consumed (TLC). The mixture was then filtered through a pad of Celite, and the solvent was evaporated under reduced pressure. The title compound **7** (X = OH) was purified by column chromatography (ethyl acetate/hexane, 3:7).

*3,4-Dihydro-2,6-dihydroxynaphthalen-1(2H)-one (**13b**).* Prepared from **11b**. Yield: 70 mg (60%). White solid. Mp: 140.1−141.7 °C. ^{1}H NMR (300 MHz, DMSO): δ (ppm) 1.85 (dq, 1H, J = 12.2, 4.4 Hz), 2.20 (m, 1H), 2.87 (td, 1H, J = 16.7, 3.6 Hz), 2.97 (m, 1H), 4.18 (dd, 1H, J = 12.2, 4.8 Hz), 5.19 (s, 1H), 6.63 (d, 1H, J = 2.1 Hz), 6.73 (dd, 1H, J = 8.5, 1.9 Hz), 7.76 (d, 1H, J = 8.6 Hz), 10.38 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 27.2, 31.8, 72.4, 114.0, 114.4, 123.1, 129.2, 146.6, 162.2, 196.9. MS (EI, 70 eV): m/z 178, 160, 134, 106, 91, 77, 65. HRMS (APCI$^+$): calcd for $C_{10}H_9O_3^-$ (M − H$^+$) 177.0557, found 177.0556.

*6,7,8,9-Tetrahydro-2,6-dihydroxybenzo[7]annulen-5-one (**13c**).* Prepared from **11c**. Yield: 68 mg (56%). White solid. Mp: 127.2−128.5 °C. ^{1}H NMR (300 MHz, CD_3CN): δ (ppm) 1.49−1.57 (m, 1H), 1.60−1.68 (m, 1H), 2.06−2.10 (m, 1H), 2.17−2.22 (m, 1H), 2.81−2.85 (m, 1H), 2.97−3.02 (m, 1H), 3.93 (d, 1H, J = 3.3 Hz), 4.46−4.50 (m, 1H), 6.71 (d, 1H, J = 2.2 Hz), 6.78 (dd, 1H, J = 8.5, 1.6 Hz), 7.54 (s, 1H), 7.87 (d, 1H, J = 8.5 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 23.6, 31.8, 34.6, 75.8, 114.6, 117.5, 128.1, 133.0, 147.8, 162.0, 203.2. MS (EI, 70 eV): m/z 192, 163, 145, 135, 91, 77, 63, 39. HRMS (APCI$^+$): calcd for $C_{11}H_{13}O_3^+$ (M + H$^+$) 193.0859, 193.0857.

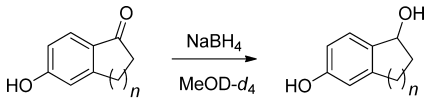
Synthesis of 15b−d. $NaBH_4$ (5 mg, 0.12 mM) was added to a methanol-d_4 solution of **9** (0.06 mM) in an NMR tube under argon atmosphere at 0 °C (Scheme 12). The reaction was analyzed by NMR and used for spiking and HRMS analyses.

Scheme 11. Synthesis of 13b,c



11b,c (*n* = 2,3) **13b,c**

Scheme 12. Synthesis of 15b−d



9a-c (*n* = 1–3) **15b-d**

*2,3-Dihydro-1H-indene-1,5-diol (**15b**).* ^{1}H NMR (300 MHz, CD_3CN): δ (ppm) 1.87−1.93 (m, 1H), 2.35−2.39 (m, 1H), 2.66−2.72 (m, 1H), 2.93−2.99 (m, 1H), 5.08 (t, 1H), 6.67 (s, 2H), 7.17 (d, 1H, J = 7.8 Hz). HRMS (APCI$^-$): calcd for $C_9H_9O_2^-$ (M − H$^+$) 149.0608, found 149.0607.

*1,2,3,4-Tetrahydronaphthalene-1,6-diol (**15c**).* ^{1}H NMR (300 MHz, CD_3CN): δ (ppm) 1.67−1.71 (m, 1H), 1.84−1.95 (m, 3H), 2.58−2.64 (m, 1H), 2.68−2.74 (m, 1H), 4.64 (t, 1H, J = 4.7 Hz), 6.52 (s, 1H), 6.63 (d, 1H, J = 7.2 Hz), 7.19 (d, 1H, J = 8.4 Hz). ^{13}C NMR (75.5 MHz, MeOD): δ (ppm) 19.9, 30.5, 33.7, 68.4, 114.7, 116.0, 131.2, 139.4, 158.1, 170.6. HRMS (APCI$^-$): calcd for $C_{10}H_{11}O_2^-$ (M − H$^+$) 163.0764, found 163.0766.

*6,7,8,9-Tetrahydro-5H-benzo[7]annulene-2,5-diol (**15d**).* ^{1}H NMR (300 MHz, CD_3CN): δ (ppm) 1.44−1.50 (m, 1H), 1.68−1.77 (m,3H), 2.00−2.06 (m, 1H), 2.58−2.63 (m, 1H), 2.832.87 (m, 1H), 4.76−4.77 (m, 1H), 6.53−6.57 (m, 2H), 7.18 (d, 1H, J = 8.2 Hz). ^{13}C NMR (75.5 MHz, MeOD): δ (ppm) 28.7, 29.2, 36.8, 38.0, 74.6, 113.0, 117.6, 127.7, 136.7, 143.5, 157.3. HRMS (APCI$^+$): calcd for $C_{11}H_{13}O_2^-$ (M − H$^+$) 177.0921, found 177.0918.

Irradiation in NMR Tubes (General Procedure). A solution of a phenacyl derivative **7a−d**, **8a−c** (5−8 mg) in D_2O/CD_3CN, (0.45−0.5 mL) was irradiated using 40 W medium-pressure mercury lamp with DMF (in a capillary tube) as an internal standard. Progress of the

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reaction was monitored at regular time intervals by ^{1}H NMR. Identification of the photoproducts was based on spiking with authentic samples and/or using HPLC/MS. After >95% of the starting material was consumed, the reaction mixture was diluted and analyzed by GC (with hexadecane, $c = 10^{-3}$ M, as an internal standard).

Preparative Irradiation. A solution of a phenacyl derivative (**7a,c**; 20−25 mg) in D_2O/CD_3CN, (0.7−0.9 mL) was irradiated using 40 W medium-pressure mercury lamp until the starting material disappeared (^{1}H NMR). The solvents were removed under reduced pressure, and major photoproducts were isolated using column chromatography (ethyl acetate/hexane, 1:1).

*2,3-Dihydro-2,5-dihydroxyinden-1-one (**13a**).* Prepared from **7a** in 82% yield. Yellow solid. Mp: 156.1−157.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.72 (dd, 1H, J = 16.8, 4.5 Hz), 3.37 (dd, 1H, J = 16.8, 7.7 Hz), 4.29 (dd, 1H, J = 7.6, 4.7 Hz), 5.16 (d, 1H), 6.81 (m, 2H), 7.49 (d, 1H, J = 8.9 Hz), 10.22 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 35.4, 72.6, 111.9, 116.0, 125.4, 126.0, 153.8, 164.1, 203.5. MS (EI, 70 eV): m/z 164, 147, 135, 121, 107, 91, 77, 57. HRMS (MS ES$^+$): calcd for $C_9H_9O_3^+$ (M + H$^+$) 165.0546, found 165.0552.

*1,2,3,4-Tetrahydro-6-methoxynaphthalene-1-carboxylic Acid (**14c**).* Prepared from **7c** in 54% yield. White solid. ^{1}H NMR (300 MHz, D_2O): δ (ppm) 1.67−1.71 (m, 1H), 1.85−1.92 (m, 1H), 2.02−2.08 (m, 2H), 2.67−2.78 (m, 2H), 3.62 (t, 1H, J = 5.9 Hz), 6.67−6.72 (m, 2H), 7.03 (d, 1H, J = 8.0 Hz). ^{13}C NMR (75.5 MHz, CD_3CN/D_2O): δ (ppm) 21.6, 28.6, 29.8, 48.7, 113.9, 115.8, 129.3, 131.4, 139.9, 154.3, 185.6. HRMS (MS ES$^+$): calcd for $C_{11}H_{11}O_3^-$ (M − H$^+$): 191.0714, found 191.0716.

Irradiation of 7b in the Presence of an Acid. Two solutions of **7b** (5−8 mg) in D_2O/CD_3CN (30:70, v/v) with a drop of DCl were placed in two NMR tubes. One was kept at ambient temperature for 24 h as a blank sample to monitor the stability of **7b** in the dark. The other was irradiated using a 40 W medium-pressure mercury lamp through a Pyrex filter until the conversion reached ∼95% (^{1}H NMR) with DMF (in a capillary tube) as an internal standard.

$ZnCl_2$ Reaction with 12b. This procedure has been adapted from Maiti and co-workers.[45] Anhydrous $ZnCl_2$ (176 mg, 1.3 mM) is added at room temperature under an atmosphere of nitrogen to methanol (4 mL). The resulting stirred solution was heated at 115 °C and a solution of **12b** (30 mg, 0.13 mM) in methanol (1 mL). The mixture was kept under nitrogen and stirred at 115 °C until the complete conversion of the starting material (TLC). The mixture was then cooled to room temperature, poured into water (5 mL), and extracted with a mixture of diethyl ether/dichloromethane (3 × 5 mL). The combined organic extract was washed with water (2 × 5 mL) and dried with Na_2SO_4. Solvent was evaporated under reduced pressure, and the reaction mixture was submitted for HPLC (UPLC/MS-TOF) analysis (chromatograms are in the Supporting Information, Figures S14 and S15).

Likewise, *p*-hydroxyphenacyl bromide was reacted with $ZnCl_2$ in the same manner. Anhydrous $ZnCl_2$ (634 mg, 4.6 mM) in methanol (4 mL) was heated at 115 °C, and a solution of **17** (100 mg, 0.46 mM) in methanol (1 mL) was added. At complete conversion, the mixture was worked up as above and extracted with dichloromethane (3 × 15 mL), the combined organic extract was washed with water (2 × 15 mL) and dried ($MgSO_4$), and the solvent was evaporated. The products were isolated by column chromatography, and the individual products, **18** and **19**, were determined by comparison of the ^{1}H NMR, MS, GC, and GC/MS properties with authentic samples or the literature values for **18**.[51] A significant amount of Cl/Br exchange occurred as shown by GC/MS. Neither 2-hydroxy-1-(4-hydroxyphenyl)ethanone nor 4-hydroxyacetophenone was shown to be present by GC/MS coinjection of authentic samples.

Isotope Labeling Experiments with $D_2{}^{18}O$. A phenacyl derivative (**7a−c**, 5−8 mg) was dissolved in two NMR tubes in CD_3CN (0.45−0.5 mL). D_2O (0.1 mL) was added to the first one; the same amount of $D_2{}^{18}O$ was placed to the other. Both solutions were irradiated with a 40 W medium-pressure mercury lamp through a Pyrex filter until the starting material was observable by ^{1}H NMR. Both reaction mixtures were subsequently analyzed by HRMS (UPLC/MS-TOF). The products were identified by comparison with the authentic samples and their exact masses.

Quantum Yield Measurements. Quantum yields were obtained on an optical bench consisting of high-pressure 350 or 450 W UV lamps, a 1/8 m monochromator with 200 to 1600 nm grating, set to 313 ± 5 nm. The light intensity was monitored by a Si photodiode detector (UV enhanced) with a multifunction optical power meter. Degassed solutions of **7a−d**, **8a−c** ($c \approx 4 \times 10^{-3}$ M) in D_2O/CD_3CN were irradiated. The reaction conversion was kept below 10% (NMR) to avoid interference of the photoproducts. DMF (in a capillary tube) was used as internal standard. Valerophenone[48] was used as an actinometer.

Quenching Experiments. Two independently prepared solutions of **7a,b** (∼55 mM) in D_2O/CD_3CN with naphthalene (∼160 mM) as a triplet quencher[49] in one of the solutions were degassed and irradiated at 366 nm. The reaction progress was monitored by NMR.

Laser Flash Photolysis Studies. The nanosecond laser flash photolysis (LFP) setup was operated in a right angle arrangement of the pump and probe beams. Laser pulses of ≤700 ps duration at 266 nm (30−80 mJ) were obtained from a Nd:YAG laser and were dispersed over a 4-cm optical path of the quartz cell by a cylindrical concave lens. The absorbance of the sample solution was adjusted to 0.3−0.5 in a 1-cm cuvette at the wavelength of excitation. A pulsed 75-W xenon lamp was used as the source of probe white light. Kinetic (a photomultiplier) and spectrographic (an ICCD camera) detection of the transient absorption was available. Measurements were done at ambient temperature (22 ± 2 °C). The samples were degassed by repeating freeze−thaw cycles under reduced pressure (5 Pa).

Quantum Chemical Calculations. Quantum chemical calculations using density functional theory or MP2 method were performed with the Gaussian 09 package (revision A.02)[76] of programs. Geometries were fully optimized at the RB3LYP/6-31+G(d) level of theory in the case of closed shell species. Unrestricted versions of functionals were employed in calculations of the triplet states. For all stationary points, the harmonic vibrational frequencies were computed to obtain the ZPVE correction which was scaled by 0.9857.[55] Single point energies at the B3LYP geometries were computed with the M06-2X functional or with the MP2 method using the 6-311+G(2df,2p) basis set. This approach has proven to perform satisfactorily well in computations of thermodynamic properties of both closed- and open-shell species.[77] The resulting enthalpies are given at 0 K (E + scaled ZPVE).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthetic and photochemical procedures; laser flash photolysis and computational data; ^{1}H, ^{13}C NMR, absorption, and HRMS spectra of the 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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DEDICATION

This article is dedicated to the memory of Professor Howard E. Zimmerman, University of Wisconsin, Madison (July 5, 1926−February 11, 2012).

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