Observation of heavy atom effects in the development of water soluble caged 4-hydroxy-*trans*-2-nonenal†

Paul B. Jones,* Robert G. Brinson,‡ Saurav J. Sarma and Salwa Elkazaz

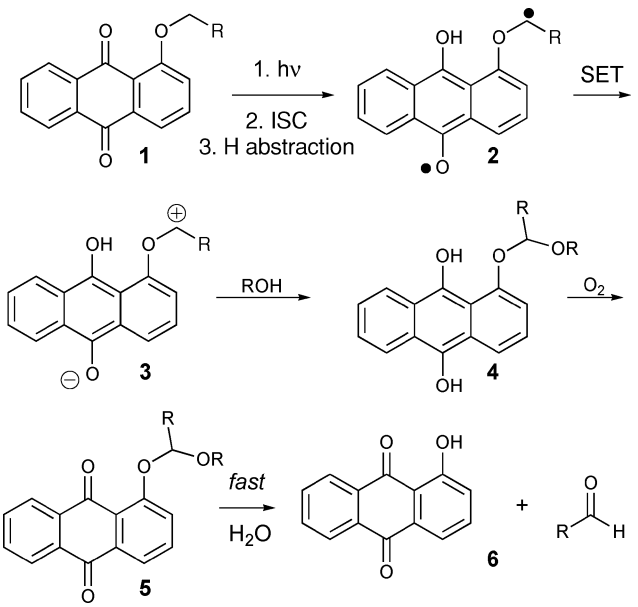
Received 27th June 2008, Accepted 5th August 2008
First published as an Advance Article on the web 19th September 2008
DOI: 10.1039/b810954k

During the course of our study on the photochemistry of 1-alkoxy-9,10-anthraquinones, we have developed a second generation of a caged 4-hydroxy-*trans*-2-nonenal (4-HNE). As we optimized the anthraquinonyl chromophore to achieve water solubility, we studied the photochemistry of various substituents to understand their effect on the photochemistry. We observed a significant heavy atom effect that severely reduced the rate of oxidative cleavage of the alkoxy group. Based on the results of our substituent study, we designed a new caged 4-HNE that is soluble under physiological conditions, and that releases 4-HNE photochemically in high yield.

Introduction

Development of photolabile "caged" molecules, including carbonyl compounds, with biological relevance has received greater attention over the last few years.[1] Ideally a caged molecule is inert, can be delivered in a high temporal and spatial manner, and subsequently can be photolyzed under either aerobic or anaerobic conditions to release the bioactive molecule. Such a design would have application in synthesis, biophysics and photodynamic therapy (PDT), which relies on photosensitization of porphyrins under aerobic conditions for the production of singlet oxygen.[2] Indeed, the requirement of oxygen for PDT limits its use, since many tumors operate until hypoxic conditions.[3] While several of the caging strategies address this limitation, many of them to date require ultraviolet light and/or produce highly toxic by-products.[1] To address these issues, our lab recently developed a strategy for releasing caged bioactive aldehydes, such as acrolein and 4-hydroxy-*trans*-2-nonenal (4-HNE),[4] that is oxygen independent. These caged molecules are based on the 1-alkoxy-9,10-anthraquinonyl chromophore, whose absorption of light tails out to about 450 nm. 4-HNE, a product of both enzymatic and non-enzymatic lipid peroxidation,[5] in particular is known to hinder cell functions severely. At high enough concentrations (>100 ppm), this results in cell death.[6]

A drawback to the photorelease strategy for 4-HNE described above is the lack of solubility of the caged molecule under physiological conditions. Our goal has been to develop a second generation that is water soluble and photochemically releases 4-HNE in high yield. The mechanism of this photo reaction for 1-alkoxy-9,10-anthraquinones has been previously described in detail.[7] Briefly, the photochemical oxidative cleavage of 1-alkoxy-9,10-anthraquinones proceeds *via* an intramolecular δ-hydrogen abstraction (Scheme 1). Excited triplet **1** initially abstracts a δ-hydrogen to produce **2**. This is followed by electron transfer that gives zwitterion **3**. The zwitterion can be trapped by a nucleophile, usually solvent, to produce acetal **4**, which is relatively stable to hydrolysis.[7a] However, upon oxidation of hydroquinone **4** to anthraquinone **5**, hydrolysis occurs readily. The result is a 1-hydroxyanthraquinone **6**, and an aldehyde.



Scheme 1

We report below the results of our study of the effect of substituents on the photochemical oxidative cleavage of 1-alkoxy-9,10-anthraquinones. The observed effects are explained best by the influence of the various reaction factors on the fate of the diradical intermediate **2**. The behavior of diradical intermediates is known to have a significant impact on the outcome of many photochemical reactions.[8,9] The study resulted in the optimization of a water soluble caged 4-HNE that photochemically generated 4-HNE in high yield at various pHs.

Department of Chemistry, Wake Forest University, Winston-Salem, NC, USA. E-mail: jonespb@wfu.edu; Fax: 336-758-4656; Tel: 336-758-3708

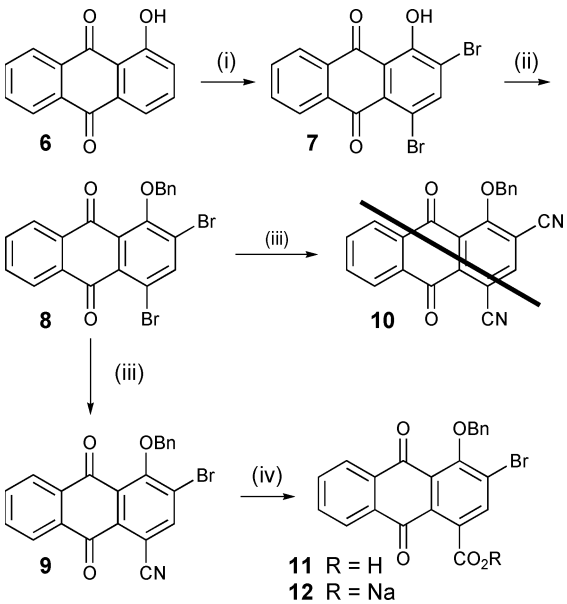
† CCDC reference number 650843. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b810954k

‡ Current address: Center for Advanced Research in Biotechnology, Rockville, MD, USA.

Results and discussion

Synthesis

In order to increase the water solubility of the anthraquinones, we planned to introduce multiple carboxylate substituents to the anthraquinone. Our initial target was the dicarboxylate corresponding to di-nitrile **10**, which we planned to prepare from **8** as shown in Scheme 2. Unfortunately, cyanation of the bromide in the 2-position of **8** could not be accomplished under any of the conditions we attempted. In contrast, cyanation of the bromide in the 4-position proceeded in good yield. The regioselectivity of the reaction was established by crystallography.[10] Hydrolysis of nitrile **9** to give carboxylate **11** went smoothly. The corresponding sodium salt (**12**) was quite soluble in water (>10 mM easily achieved).

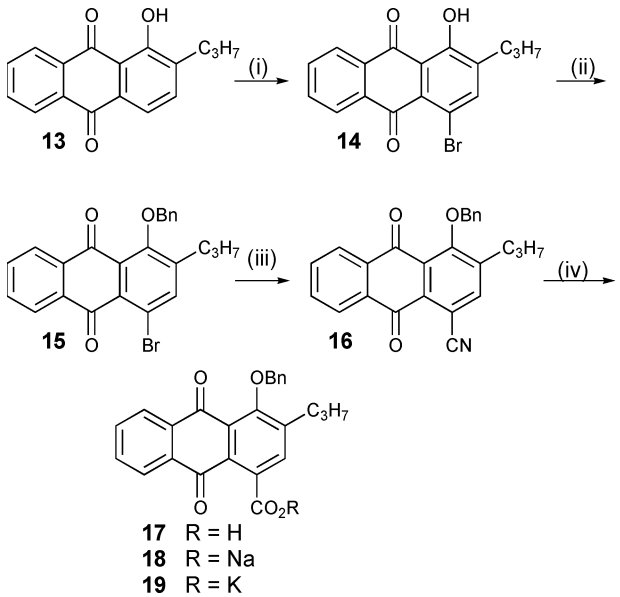


Scheme 2 *Reagents and conditions*: (i) Br_2, NaOAc, AcOH, reflux, 97%; (ii) BnBr, TBAF, DMF, rt, 93%; (iii) CuCN, DMF, 80 °C, 74%; (iv) NaOH, EtOH, reflux, 93%.

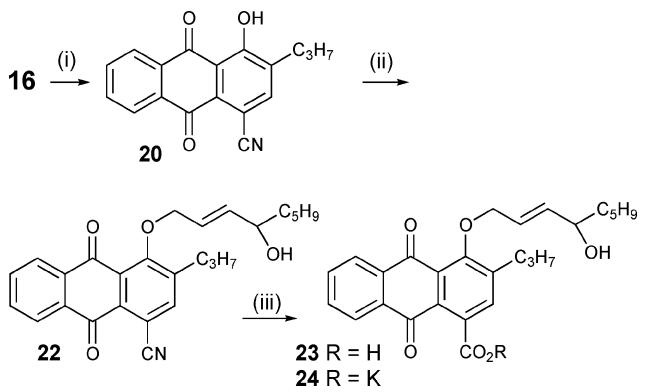
With a water soluble anthraquinone in hand, we proceeded to investigate the photochemistry of **11** and **12**. Photolysis of these two compounds in methanol did, indeed, result in cleavage of the benzyl group. However, this reaction was surprisingly inefficient, and yields were much lower than expected, presumably due to the lack of steric bulk in the 2-position. Previous studies have shown that an alkyl group in this position accelerates the desired photochemical reaction[7b] while minimizing unwanted side reactions.[11]

Thus, we turned to anthraquinones with a 2-propyl group. The propyl group is easily installed in the 2-position by Claisen reaction of 1-allyloxy-9,10-anthraquinone and hydrogenation of the resulting alkene.[4,11] Anthraquinone **13** was brominated in quantitative yield to give **14**, which was alkylated with benzyl bromide to give **15** (Scheme 3). Benzyl ether **15** was cyanated with CuCN to give nitrile **16**, which was hydrolyzed to afford acid **17**.

For synthesis of water soluble caged HNE, the benzyl group of **16** was removed photochemically to give **20** (Scheme 4). The phenol was then alkylated with 1-bromonon-2-en-4-ol (**21**)[4] using TBAF to give nitrile **22**. Finally, **22** was hydrolyzed to give



Scheme 3 *Reagents and conditions*: (i) Br_2, NaOAc, AcOH, 50 °C, 100%; (ii) BnBr, TBAF, DMF, rt, 93%; (iii) CuCN, DMF, 80 °C, 99%; (iv) NaOH (or KOH), EtOH, reflux, 78% (**17**).



Scheme 4 *Reagents and conditions*: (i) hν (366 nm), MeOH–air, 75%; (ii) **21**, TBAF, DMF, rt, 74%; (iii) KOH, EtOH, reflux, 65% (**23**).

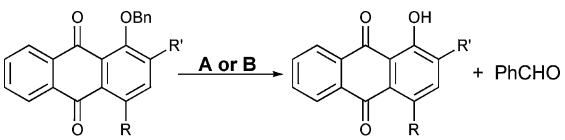
caged 4-HNE **23**, which could be converted to the corresponding potassium salt **24** by treatment with KH in dry THF. This salt was freely soluble in aqueous systems at concentrations lower than 10 mM.

Photochemistry

In order to compare the effects of the substituents, each anthraquinone benzyl ether was photolyzed and the relative rate of disappearance of starting ether determined. Since measurement of product formation is inherently unreliable in this system due to a series of dark reactions subsequent to the primary photochemical step, the rate of disappearance of starting ether was monitored by following the reduction of the distinctive benzyl ^{1}H NMR singlet. Each anthraquinone was photolyzed alongside 2-propyl-1-benzyloxy-9,10-anthraquinone, **25**, which was used as a standard reaction.[7b] The photocleavage reaction of **25** has been studied both by Blankespoor *et al.* and our laboratory and is well understood. Photolyses were performed in triplicate in solvent mixtures of DMSO–methanol or DMSO–water using a 150 W

Hg/Xe lamp in combination with a grating monochromator at a wavelength of 405 nm (±5 nm). All compounds were normalized to the absorbance of a 5 mM solution of **17** at 405 nm. Data was analyzed by ^{1}H NMR relative to the internal standard 2,4,6-trimethylbenzoic acid or its corresponding sodium salt for photolyses in D_2O. The data was plotted as time (min) against $\ln([AQ]_o/[AQ]_t)$, where $[AQ]_o$ is the integral value at $t = 0$ and $[AQ]_t$ is the integral value at time point, t. Linear regression was performed on the data to give a straight line; R^2 values were 0.95 or higher. The slope of the linear regression was used as the relative rate. See the experimental section for complete details of the photolyses.

In general, electron-withdrawing substituents *para* to the benzyloxy group slowed the rate of the photoreaction relative to **25**. This attenuation is modest, with the relative efficiency only approximately halved going from **25** to **16**, **17** or **18** (Table 1, entries 1, 3–5). The relatively high efficiency exhibited by **29** shows that the effect of the *para* electron-withdrawing group is due to a resonance effect, as the photolysis of a molecule with a carboxylate that is not electronically tied to the benzyloxy group, but is sterically closer, actually proceeds more efficiently than in the standard reaction. The increased relative rate of **29** over **25** (1.55 : 1), is presumably due to the slight increase in steric bulk of the 2-substituent in **29** (entry 8).



25 R = H; R' = *n*-C_3H_7 — **13** R = H; R' = *n*-C_3H_7
15 R = Br; R' = *n*-C_3H_7 — **14** R = Br; R' = *n*-C_3H_7
16 R = CN; R' = *n*-C_3H_7 — **20** R = CN; R' = *n*-C_3H_7
17 R = CO_2H; R' = *n*-C_3H_7 — **26** R = CO_2H; R' = *n*-C_3H_7
18 R = CO_2Na; R' = *n*-C_3H_7 — **27** R = CO_2Na; R' = *n*-C_3H_7
11 R = CO_2H; R' = Br — **28** R = CO_2H; R' = Br
29 R = H; R' = CH_2CO_2H — **30** R = H; R' = CH_2CO_2H

Scheme 5 *Reagents and conditions*: (A) hν (405 nm), 4 : 1 CD_3OD–DMSO-*d6*; (B) hν (405 nm), 4 : 1 D_2O–DMSO-*d6*. See Table 1 for relative rates and additional details.

The molecule with a bromide in the *para* position, **15**, reacted with the least efficiency with a relative rate of 0.21 (entry 2). Along with the results of photolysis of **11**, this suggested a heavy atom effect. To test this hypothesis, experiments were run with **25** in the presence of iodoform at concentrations of 0, 28, 55, 110 mM (entries 1, 9–11). Increasing the concentration of iodoform led to a proportional decrease in relative efficiency for the reaction. A control experiment with 110 mM $CDCl_3$ resulted in no decrease in the relative efficiency (entry 12). Clearly, the forward reaction rate is decreased in the presence of heavy atoms.

Photolyses of **18** in 1 : 4 DMSO-*d6*–D_2O with 0, 50, 100, 250 mM LiCl; 100 mM LiI; and 100 mM CsI were carried out to measure the effect of ionic strength on the rate of the photocleavage (entries 6, 13–17). Increasing the ionic strength of the solution led to modest increases in reaction rate that leveled off between 100 and 250 mM. When the added salt included a heavy atom (LiI or CsI), the reaction was slowed. A concentration of 100 mM CsI completely stopped the reaction over the photolysis time examined, which is consistent with our heavy atom observations above.

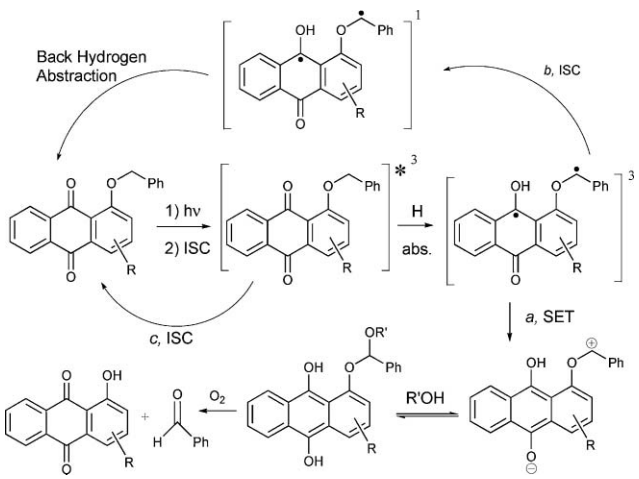
Table 1 Relative rate of the disappearance of the benzyl group. The monochromator used was set at 405 nm (±5 nm)

Entry	Substrate	Solvent[b]	Additive	Relative rate
1	**25**	A	—	1.00
2	**15**	A	—	0.21
3	**16**	A	—	0.50
4	**17**	A	—	0.58
5	**18**	A	—	0.46
6	**18**	B	—	1.02
7	**11**	A	—	<0.05[a]
8	**29**	A	—	1.55
9	**25**	A	28 mM CHI_3	0.56
10	**25**	A	55 mM CHI_3	0.25
11	**25**	A	110 mM CHI_3	0.19
12	**25**	A	110 mM $CHCl_3$	1.02
13	**18**	B	50 mM LiCl	1.08
14	**18**	B	100 mM LiCl	1.47
15	**18**	B	250 mM LiCl	1.47
16	**18**	B	100 mM LiI	0.39
17	**18**	B	100 mM CsI	0

[a] **11** was not irradiated in direct comparison with the other compounds listed, but an estimate of the ratio was made by comparing the rate of **11** and 1-benzyloxy-9,10-anthraquinone (see ref. 11). [b] For solvent conditions, see Scheme 5.

Mechanistic rationale

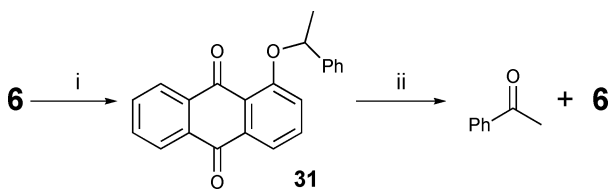
The mechanistic model put forward in Scheme 6 explains the observations in the photolysis of anthraquinones bearing electron-withdrawing groups *para* to the benzyloxy group and the heavy atom effect. The effect of a *para* electron-withdrawing group (entries 3–5) should destabilize the benzylic cation, reducing the rate of the single electron transfer (SET) (Scheme 6, path *a*—the forward, productive path) and, thus, the overall efficiency of the reaction. However, upon photolysis in D_2O, the rate of **18** increased to a rate comparable to the standard reaction (**25** in methanol–DMSO, entry 1). This is presumably due to increased stabilization of the zwitterion by the more polar solvent D_2O (compare entries 1, 5 and 6). Increasing the ionic strength would add additional stabilization to the zwitterion, resulting in slightly increased relative rates compared to the photolysis without salt (entries 6, 13–17). Thus, the more polar environment and increased rate of SET can overcome the inhibiting effect of the conjugated carboxylate.



Scheme 6 Mechanistic proposal for the heavy atom effect.

From further analysis of our data, we hypothesized that the observed effect of heavy atoms increased the rate of intersystem crossing (ISC) from either T1 anthraquinone (path *c*) or by a back hydrogen abstraction from the triplet diradical (path *b*). Anthraquinones undergo ISC with a quantum efficiency of 1.[12] Thus, heavy atoms should not significantly affect the efficiency of reaching the T1 excited state from which the initial hydrogen abstraction occurs. However, back hydrogen abstraction to give starting material requires a second ISC in going from the triplet diradical to the singlet diradical. Return to ground state anthraquinone from the T1 state requires ISC as well. This spin-flip could be facilitated by a heavy atom effect that would accelerate paths *b* and *c* without affecting path *a*. The result would be diminished efficiency in oxidative cleavage of the 1-alkoxy group. Thus, paths *a*, *b* and *c* are partitioned based on the relative rate of ISC and SET, with any increase in ISC or decrease in SET favoring paths *b* and *c*, the reverse reaction, in terms of desired product.

To test these possibilities, both racemic and optically active anthraquinone **31** were prepared by Mitsunobu alkylation using *sec*-phenethyl alcohol, which is commercially available as both the racemate and as an enriched enantiomer (Scheme 7). Compound **31** was prepared without the 2-propyl group to decrease the steric bulk at this position and to reduce the efficiency of pathway *a*, since our goal was to study the possibility of path *b*. Photolysis of optically active **31** allowed testing of racemization. If path *b* operated, recovered **31** following photolysis should have a lower optical activity than the starting material. Thus, **31** with 99.8% ee was photolyzed in a Rayonet reactor using 419 nm lamps in benzene–methanol containing 250 mM CHI_3. At 72% conversion, recovered **31** had an optical purity of 88% ee. This confirms that path *b* does operate in this reaction, although the experiment did not rule out path *c*. It seems likely that both pathways *b* and *c* are responsible for the reduction in rate of oxidative cleavage of the alkoxy group in the presence of heavy atoms.



Scheme 7 *Reagents and conditions*: (i) Ph_3P, DIAD, THF, 1-phenylethanol; (ii) hν, (419 nm), MeOH–PhH–CHI_3.

Caged 4-hydroxynonenal (HNE)

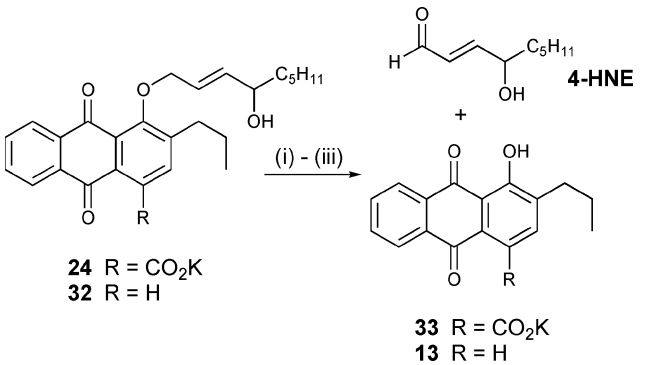
Given our observations above, we determined that the optimum 4-HNE releasing molecule would be soluble in aqueous systems and free of heavy atoms. Despite the deleterious effect of having an electron-withdrawing group attached to the anthraquinone itself, the synthetic difficulty in working with **29** led us to **24** as a suitable water soluble caged 4-HNE candidate. Hence, we studied the photochemistry of **24** in buffered solutions at pH 5.0, 7.0 and 9.0, respectively. We also carried out a comparison of **24** with the previously prepared **32** and **25** using the conditions and procedures described in Scheme 5 and Table 1. The results of this study are shown in Table 2. By dissolving the caged HNE **24** in aqueous solvent, which is not possible with caged HNE **32**, the photorelease of HNE was rendered more efficient by a factor of approximately three (3.96–1.25, Table 2, entries 4 and 2, respectively).

Table 2 Relative rate of the disappearance of caged HNE

Entry	Substrate	Solvent[a]	Relative rate
1	**25**	A	1.00
2	**24**	A	1.25
3	**32**	A	2.10
4	**24**	B	3.96

The monochromator used was set at 405 nm (±5 nm).[a] For solvent conditions, see Scheme 5.

The caged 4-HNE **24** was freely soluble at 10 mM in all buffers studied and the yields of 4-HNE were high in all systems. 4-HNE was obtained in 84%, 87% and 97% yield in pH 5.0, 7.0, and 9.0 buffers, respectively (Scheme 8). Separation of 4-HNE from **33** was accomplished by simple chemical extraction. In addition, **33** can be recycled to make additional caged aldehydes.



Scheme 8 *Reagents and conditions*: (i) hν (419 nm), buffer; (ii) petroleum ether extraction; (iii) 1 N HCl, ether extraction. See text for yields.

Conclusions

Substituent effects were observed on the rate of photocleavage of 1-alkoxy-9,10-anthraquinones with electron-withdrawing groups in conjugation with the quinone slowing the reaction. A significant heavy atom inhibition was also observed. The effect of solvent and ionic strength had a slight accelerating effect on the reaction. These observations are consistent with the efficiency of the reaction being determined by the partitioning of the triplet 1,5-diradical between single-electron transfer (SET) and intersystem crossing (ISC). Factors that favor SET accelerate the reaction while those favoring ISC slow the reaction. Using this data, we designed a water soluble caged 4-HNE that photochemically released 4-HNE in high yield using visible light. Our previous work has shown that the photochemical cleavage proceeds under both aerobic and anaerobic conditions.[4] Hence, this second generation of caged aldehydes represents an important advance in PDT agents that can be photo-activated with visible light and under hypoxic conditions. Initial investigations on the biological viability of these agents are underway. Additionally, synthetic work continues to extend the chromophore of these agents toward longer wavelengths, which will increase their utility in biological systems.

Experimental section

General

Unless otherwise indicated, all reagents and solvents were obtained commercially and used without further purification. Melting points were measured on a Meltemp II apparatus and are uncorrected. Thin-layer chromatography was performed on silica gel (250 μm thickness doped with fluorescein) unless otherwise indicated. The chromatograms were visualized with UV light (254 nm or 365 nm). Column chromatography was performed using silica gel (60 Å) or basic alumina (58 Å). HPLC analyses were carried out using a Shimadzu LC-10AT LC with SPD-10AV UV–Vis detector and a Daicel Chiracel OD-H column with an eluent of 95 : 5 hexane–iPrOH. ^{1}H and ^{13}C NMR spectra were run on a Bruker 300 MHz or 500 MHz NMR spectrometer. All photochemical reactions were carried out in Pyrex glassware. Preparative solutions were stirred by magnetic stirring throughout photolysis. Anaerobic reactions were degassed by three cycles of freeze–pump–thaw; the solutions were not backfilled with Ar. Solutions were photolyzed in borosilicate NMR tubes, unless otherwise indicated, using a monochromator (Oriel) set to 405 nm with a 10 nm bandpass in conjunction with a focused 150 W Hg/Xe lamp. CCDC 650843 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/products/csd/request/, by emailing data request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

1-Benzyloxy-2-propyl-9,10-anthraquinone 25 (Method A). To a yellow-orange solution of **13**[11] (3.76 mmol) in 1 : 1 DMF–THF (38 ml) was added benzyl bromide (15.0 mmol) and TBAF (7.51 mmol). The solution turned a deep purple and was stirred for eight hours. The reaction was considered finished when the reaction mixture had turned back to a yellowish color. The crude mixture was diluted with EtOAc, washed with 1 N HCl, extracted with EtOAc (2 × 100 ml), washed with water (3 × 200 ml), washed with brine (200 ml) and concentrated *via* rotary evaporation. The crude solid was recrystallized from hexanes to give yellow needles (1.0 g, 76%). Mp 98.0–99.5 °C (hexanes); found C, 80.6; H, 5.7. Calcd. for $C_{24}H_{20}O_3$: C, 80.9; H, 5.7%; IR (nujol) 3400–2400, 3032, 2924, 1684, 1674, 1593 cm^{-1}; ε (405 nm) 1325 M^{-1} cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 0.93 (t, $J = 7.4$ Hz, 3H, CH_3), 1.58–1.71 (m, 2H, CH_2), 2.67–2.72 (m, 2H, Ar-CH_2), 5.05 (s, 2H, OCH_2), 7.34–7.47 (m, 3H, Ar-H), 7.60–7.64 (m, 3H, Ar-H), 7.73–7.82 (m, 2H, Ar-H), 8.12 (d, $J = 7.9$ Hz, 1H, Ar-H), 8.25–8.33 (m, 2H, Ar-H); δ_C(125 MHz, $CDCl_3$) 183.2, 182.7, 157.5, 145.5, 137.2, 135.6, 134.9, 134.1, 133.8, 133.4, 132.7, 128.5, 128.3, 128.1, 127.3, 126.6, 125.9, 123.6, 76.2, 32.5, 23.3, 14.0. HRMS (EI): found MNa+ 379.1302, $C_{24}H_{20}O_3Na$+ requires 379.1305.

1-Benzyloxy-4-bromo-2-propyl-9,10-anthraquinone 15. Using Method A, **14** (7.28 g, 21.1 mmol) gave yellow-orange crystals (8.5 g, 93%). Mp 123.0–125.0 °C (hexanes); found C, 66.05; H, 4.3; Br, 18.65. Calcd. for $C_{24}H_{19}BrO_3$: C, 66.2; H, 4.4; Br, 18.4%. IR (nujol) 3030, 2954, 1675, 1593, 1568 cm^{-1}; ε (405 nm) 792 M^{-1} cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 0.93 (t, $J = 7.3$ Hz, 3H, CH_3), 1.56–1.68 (m, 2H, CH_2), 2.61–2.66 (m, 2H, CH_2), 5.04 (s, 2H, OCH_2), 7.36–7.46 (m, 3H, Ar-H), 7.55–7.58 (m, 2H, Ar-H), 7.73–7.79 (m, 2H, Ar-H), 7.85 (s, 1H, Ar-H), 8.18–8.25 (m, 2H, Ar-H); δ_C (75 MHz, $CDCl_3$) 182.5, 182.3, 157.5, 145.9, 142.3, 136.8, 134.1, 133.8, 133.7, 133.6, 130.1, 128.6, 128.5, 128.4, 128.3, 126.8, 126.7, 117.2, 76.9, 32.1, 23.1, 14.0.

1-(4-Hydroxy-2-nonenyloxy)-4-cyano-2-propyl-9,10-anthraquinone 22. Using Method A, **20** and **21**[4] (226 mg, 0.776 mmol) gave a yellow solid (241.9 mg, 74%). Mp 90.0–92.0 °C; found: C, 74.95; H, 6.9; N, 3.1. Calcd. for $C_{27}H_{29}NO_4$: C, 75.15; H, 6.8; N, 3.25%. δ_H (300 MHz, $CDCl_3$, Me_4Si) 0.88–0.92 (m, 3H, CH_3), 1.01 (t, $J = 7.4$ Hz, 3H, CH_3), 1.25–1.55 (m, 8H, 4 CH_2), 1.64–1.75 (m, 2H, CH_2), 2.75–2.80 (m, 2H, CH_2), 4.15–4.24 (m, 1H, CHOH), 4.59 (d, $J = 5.8$ Hz, 2H, OCH_2), 6.22 (dd, $J = 15.6$, 6.0 Hz, =CH), 6.00–6.09 (m, 1H, =CH), 7.79–7.86 (m, 2H, Ar-H), 7.92 (s, 1H, Ar-H), 8.22–8.27 (m, 1H, Ar-H), 8.28–8.32 (m, 1H, Ar-H). δ_C (75 MHz, $CDCl_3$) 181.6, 160.8, 145.7, 141.1, 138.3, 135.6, 134.8, 134.2, 134.0, 132.1, 127.6, 127.2, 126.8, 124.9, 118.0, 106.9, 72.0, 63.7, 37.1, 32.3, 31.7, 25.0, 23.0, 22.6, 14.00, 13.97. HRMS (EI) found MH+ 454.1981; $C_{27}H_{29}O_4H$+ requires 454.1989.

1-Benzyloxy-2,4-dibromo-9,10-anthraquinone 8. Using Method A, **7**[13] (26.2 mmol) and benzyl bromide (104.7 mmol) gave **8** (11.52 g, 93%). Mp 172.0–174.0 °C (CH_3OH); found: C, 53.4; H, 2.6; Br, 33.8. Calcd. for $C_{21}H_{12}Br_2O_3$: C, 53.4; H, 2.6; Br, 33.9%. δ_H (300 MHz, $CDCl_3$, Me_4Si) 5.16 (s, 2H, OCH_2), 7.35–7.47 (m, 3H, Ar-H), 7.69–7.73 (m, 2H, Ar-H), 7.75–7.81 (m, 2H, Ar-H), 8.16–8.23 (m, 2H, Ar-H), 8.30 (s, 1H, Ar-H); δ_C (75 MHz, $CDCl_3$) 181.9, 181.4, 155.7, 144.6, 136.0, 134.13, 134.07, 133.7, 133.4, 131.9, 130.0, 128.9, 128.6, 127.3, 127.0, 126.8, 117.6, 76.1. HRMS (EI) found MNa+ 494.9022; $C_{21}H_{12}Br_2O_3Na$+ requires 494.9025.

2-(1-(Benzyloxy)-9,10-anthraquinonyl)-acetic acid 29. Using Method A, 2-allyl-1-hydroxy-9,10-anthraquinone (1.0 g, 3.79 mmol) and benzyl bromide (15 mmol, 2.56 g) gave 2-allyl-1-benzyloxy-9,10-anthraquinone (**29a**) (584 mg, 1.65 mmol, 44%). Crude alkene **29a** (250 mg, 0.70 mmol) was dissolved in dichloromethane (30 mL) and cooled in a dry ice–acetone bath. Ozone was bubbled through the solution until a persistent blue color was observed. Dimethyl sulfide (10 mL) was added and the cold bath removed. The solution was allowed to stir for 6 h. The solution was concentrated *in vacuo* to give a yellow solid. The solid was dissolved in $CHCl_3$ (5 mL) and precipitated by the addition of hexane (10 mL). The solid was collected by filtration and washed extensively with hexane. The crude aldehyde (**29b**) was carried on without further purification. Crude yield: 222 mg, 0.62 mmol, 89%. Aldehyde **29b** (154 mg, 0.43 mmol) and 2-methyl-2-butene (6 mL) were dissolved in tBuOH (25 mL) and cooled in an ice–water bath. To this solution was added, dropwise, a solution of NaH_2PO_4 (415 mg, 3.06 mmol) and $NaClO_2$ (442 mg, 3.86 mmol) in water (8 mL). The resulting mixture was allowed to warm to ambient temperature and stir overnight (14 h). The reaction mixture was poured into 0.1 M HCl (aq.) (100 mL) and extracted 3 × 50 mL with EtOAc. The combined organic layers were washed with water (1 × 50 mL), brine (1 × 50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow solid. The crude solid was recrystallized from hot hexane–EtOAc to give the desired acid as yellow crystals (80 mg, 0.22 mmol, 50%). δ_H (300 MHz, DMSO-*d6*, Me_4Si) 11.3 (bs, 1H, OH), 8.19 (m, 2H, Ar-H), 8.08 (d, $J = 8.1$ Hz, 1H, Ar-H), 7.72 (m, 2H, Ar-H), 7.62 (d, $J = 8.1$ Hz, 1H, Ar-H), 7.49 (d,

J = 6.6 Hz, 2H, Ar-H), 7.30 (m, 3H, Ar-H), 5.00 (s, 2H, OCH_2), 3.66 (s, 2H, CH_2). δ_C (75 MHz, DMSO-*d6*) 183.1, 182.9, 175.3, 158.1, 137.2, 137.1, 136.6, 135.7, 135.2, 134.6, 134.1, 133.0, 129.10, 129.05, 128.5, 127.8, 127.1, 126.3, 124.1, 60.8, 35.9. HRMS (EI) found MNa+ 395.0884; $C_{23}H_{16}O_5Na$+ requires 395.08990.

1-Benzyloxy-2-bromo-4-cyano-9,10-anthraquinone 9 (Method B). To a suspension of **8** (2.12 mmol) in DMF (21 ml) was added cuprous cyanide (4.24 mmol). The reaction mixture was then heated to 75 °C and stirred for 22 hours. The reaction was considered complete by TLC (1 : 1 EtOAc–hexanes). The crude mixture was diluted with ethyl acetate (250 ml), washed with 1 N HCl (250 ml), water (2 × 250 ml), brine (100 ml), dried with $MgSO_4$, and concentrated *via* rotary evaporation. The crude solid was then preabsorbed onto basic alumina and purified through a basic alumina plug (3 : 1 $CHCl_3$–hexanes to neat $CHCl_3$) to give a yellow solid (571.3 mg, 74%). Mp 238.0–240.0 °C. δ_H (300 MHz, DMSO-*d6*, Me_4Si) 5.12 (s, 2H, OCH_2), 7.35–7.48 (m, 3H, Ar-H), 7.62–7.65 (m, 2H, Ar-H), 7.92–8.00 (m, 2H, Ar-H), 8.16–8.22 (m, 2H, Ar-H), 8.76 (s, 1H, Ar-H). δ_C (75 MHz, DMSO-d6) 180.6, 180.5, 158.4, 143.5, 136.9, 136.1, 135.0, 134.4, 133.7, 131.8, 128.6, 128.39, 128.36, 128.3, 126.8, 126.5, 126.3, 116.6, 107.1, 75.9. HRMS (EI) found MNa+ 439.99065; $C_{22}H_{12}BrNO_3Na$+ requires 439.989273.

1-Benzyloxy-4-cyano-2-propyl-9,10-anthraquinone 16. Using Method B, **15** (2.30 mmol) gave **16** as a pure yellow solid (864.1 mg, 99%). Mp 158.0–160.0 °C (hexanes); found: C, 78.26; H, 4.85; N, 3.62. Calcd for $C_{24}H_{19}BrO_3$: C, 78.72; H, 5.02; N, 3.67%. IR (nujol) 3058, 3032, 2943, 1676, 1592, 1528 cm^{-1}; ε (405 nm) 438 M^{-1} cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_3Si) 0.92 (t, J = 7.3 Hz, 3H, CH_3), 1.54–1.67 (m, 2H, CH_2), 2.64–2.69 (m, 2H, Ar-CH_2), 5.09 (s, 2H, OCH_2), 7.36–7.46 (m, 3H, Ar-H), 7.51–7.54 (m, 2H, Ar-H), 7.82–7.85 (m, 2H, Ar-H), 7.92 (s, 1H, Ar-H), 8.28–8.33 (m, 2H, Ar-H). δ_C (75 MHz, $CDCl_3$) 181.5, 180.8, 160.9, 145.9, 141.1, 136.3, 135.6, 134.7, 134.2, 134.0, 132.0, 128.64, 128.56, 138.4, 127.3, 127.2, 126.8, 118.0, 106.9, 77.4, 32.2, 22.9, 13.9. HRMS (EI) found MNa+ 404.12579; $C_{25}H_{19}NO_3Na$+ requires 404.125712.

1-Benzyloxy-2-bromo-9,10-anthraquinone-4-carboxylic acid 11. (Method C). To a suspension of **9** (2.06 mmol) in 74% EtOH (18 ml) was added a 2.5 M solution of NaOH (8.24 mmol). The reaction mixture, which reddened over the course of the reaction, was refluxed for 35 minutes and was considered complete *via* TLC (1 : 1 EtOAc–hexanes). The reaction mixture was poured into 3% H_2SO_4 (4 ml), forming a yellow precipitate. The crystals were cooled to 0 °C, filtered, and washed with water (2 × 30 ml). The yellow crystals were then dried *in vacuo* (768.7 mg, 93%). Mp 214.0–216.0 °C (CH_3OH). IR (nujol) 3300–2450, 3033, 2924, 1682, 1674, 1594, 1538 cm^{-1}; ε (405 nm) 1380 M^{-1} cm^{-1}; δ_H (300 MHz, DMSO-*d6*, Me_4Si) 5.07 (s, 2H, OCH_2), 7.37–7.48 (m, 3H, Ar-H), 7.66–7.68 (m, 2H, Ar-H), 7.88–7.99 (m, 2H, Ar-H), 8.10–8.21 (m, 2H, Ar-H), 8.21 (s, 1H, Ar-H). δ_C (75 MHz, DMSO-*d6*) 181.7, 180.9, 168.6, 155.4, 136.4, 136.3, 134.8, 134.2, 133.9, 133.3, 132.0, 131.3, 128.5, 128.3, 128.2, 127.6, 126.9, 126.7, 126.2, 75.1. HRMS (EI) found MH+ 436.99912; $C_{22}H_{13}BrO_5H$+ requires 437.001912.

1-Benzyloxy-2-propyl-9,10-anthraquinone-4-carboxylic acid 17. Using Method C, **16** (0.865 mmol) gave **17** as a yellow solid (268.6 mg, 78%). Mp 153.0–156.0 °C (CH_3OH). The sodium or potassium salt (**18** or **19**, respectively) was obtained by treating **17** in THF with 1 equiv. of the corresponding metal hydride, stirring and concentrating. Found C, 74.60; H, 4.89. Anal. calcd. for $C_{22}H_{20}O_5$: C, 74.99; H, 5.03%. IR (nujol) 3500–2400, 3034, 2922, 1695, 1592 cm^{-1}; ε (405 nm) 870 M^{-1} cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 0.95 (t, J = 7.3 Hz, 3H, CH_3), 1.59–1.72 (m, 2H, CH_2), 2.68–2.73 (m, 2H, Ar-CH_2), 5.06 (s, 2H, OCH_2), 7.36–7.48 (m, 3H, Ar-H), 7.57–7.61 (m, 2H, Ar-H), 7.71 (s, 1H, Ar-H), 7.76–7.85 (m, 2H, Ar-H), 8.24–8.32 (m, 2H, Ar-H). δ_C (75 MHz, $CDCl_3$) 182.7, 182.2, 173.5, 158.9, 145.8, 136.8, 134.6, 134.4, 134.2, 133.8, 132.4, 131.4, 130.0, 128.6, 128.4, 127.4, 127.0, 126.2, 76.8, 32.4, 23.1, 14.1. HRMS (EI) found MH+ 401.13822; $C_{25}H_{20}O_5H$+ requires 401.138351.

1-(4-Hydroxy-2-nonenyl)oxy-2-propyl-9,10-anthraquinone-4-carboxylic acid (water soluble, caged 4-HNE) 23. Using Method C, **22** (358 mg, 0.834 mmol) gave a yellow powder (244.8 mg, 65%). Mp 163.0–170.0 °C dec (CH_3OH). IR (nujol) 3420–2550, 3030, 3020, 2930, 1695, 1677, 1592, 1557 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 0.90 (m, 3H, CH_3), 1.00 (t, J = 7.4 Hz, 3H, CH_3), 1.27–1.58 (m, 8H, C_4H_4), 1.63–1.76 (m, 2H, CH_2), 2.74–2.79 (m, 2H, CH_2), 4.19–4.25 (m, 1H, CHOH), 4.55 (d, J = 6.0 Hz, 2H, OCH_2), 5.93 (dd, J = 6.0, 15.4 Hz, 1H, =CH), 6.04–6.13 (m, 1H, =CH), 7.61 (s, 1H. Ar-H), 7.73–7.83 (m, 2H, Ar-H), 8.19–8.27 (m, 2H, Ar-H), 10.23 (bs, 1H, CO_2H). δ_C (75 MHz, $CDCl_3$) 182.7, 182.2, 172.8, 158.8, 145.6, 137.7, 134.5, 134.8, 134.2, 133.8, 132.4, 131.2, 130.0, 127.3, 127.0, 126.1, 125.6, 74.8, 72.2, 37.1, 32.5, 31.7, 25.0, 23.2, 22.6, 14.1, 14.0. HRMS (EI) found MH+ 451.20948; $C_{27}H_{30}O_6H$+ requires 451.21152.

4-Bromo-1-hydroxy-2-propyl-9,10-anthraquinone 14. To a solution of **13** (22.5 mmol) in glacial acetic acid (11.2 ml) was added sodium acetate (67.4 mmol) and bromine (67.4 mmol). The reaction mixture was stirred under Ar at 50 °C for 4.5 hours and was considered complete when no starting material was visible by ^1H NMR. Distilled water (100 ml) was added to the reaction mixture, and it was cooled to 0 °C. The product was concentrated *via* vacuum filtration and dried *in vacuo* to give a yellow-orange powder (7.28 g, 94%). Mp 134.0–136.0 °C (CH_3OH). Found: C, 59.07; H, 3.76; Br, 23.07. Calcd. for $C_{17}H_{13}BrO_3$: C, 59.15; H, 3.80; Br, 23.15%. IR (nujol) 3300–2900, 3086, 3052, 2964, 2932, 1670, 1627, 1591, 1584 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.02 (t, J = 7.3 Hz, 3H, CH_3), 1.63–1.77 (m, 2H, CH_2), 2.69–2.74 (m, 2H, Ar-CH_2), 7.75 (s, 1H, Ar-H), 7.75–7.85 (m, 2H, Ar-H), 8.26–8.31 (m, 2H, Ar-H), 13.71 (s, 1H, Ar-OH). δ_C (75 MHz, $CDCl_3$) 188.4, 181.1, 161.6, 143.3, 140.3, 134.9, 134.2, 133.8, 132.2, 127.8, 127.6, 126.5, 116.9, 113.2, 31.6, 22.0, 13.9.

4-Cyano-1-hydroxy-2-propyl-9,10-anthraquinone 20. A solution of **16** (1.70 g, 4.46 mmol) in 12 : 7 : 1 AcOH–MeOH–H_2O (1.0 L) was photolyzed (MPL with UO_2 filter, hv > 340 nm) in a 1 L immersion well. The reaction was considered complete after 2 hours *via* TLC (alumina, CH_2Cl_2). The reaction solution was concentrated *in vacuo* and purified *via* flash chromatography (silica, 3 : 1 CH_2Cl_2–hexanes). The fractions containing product were combined and concentrated *in vacuo* to give a yellow solid (980.5 mg, 75%). Mp 185.0–186.0 °C (CH_3OH). Found: C, 74.22; H, 4.43; N, 4.87. Calcd. for $C_{18}H_{13}NO_3$ requires C, 74.22; H, 4.50; N, 4.81%. IR (nujol) 3250–2800, 3072, 3055, 2964, 2932, 2218, 1674, 1638, 1589, 1580 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.02 (t, J = 7.3 Hz, 3H, CH_3), 1.67–1.79 (m, 2H, CH_2), 2.73–2.80 (m, 2H,

Ar-CH_2), 7.81 (s, 1H, Ar-H), 7.84–7.91 (m, 2H, Ar-H), 8.30–8.39 (m, 2H, Ar-H), 13.62 (s, 1H, Ar-OH). δ_C (75 MHz, $CDCl_3$) 188.6, 180.1, 163.9, 141.1, 139.7, 135.5, 134.7, 133.7, 133.1, 133.3, 132.3, 128.0, 127.1, 118.2, 115.9, 102.3, 31.6, 21.9, 13.9.

1-(1-Phenylethyl)-9,10-anthraquinone 31. To a solution of **6** (1.32 g, 5.9 mmol) in dry THF (120 mL) under Ar in an oven dried flask was added, sequentially, Ph_3P (1.94 g, 7.4 mmol), 1-phenylethanol (1.07 g, 8.8 mmol) and DIAD (2.50 g, 10.3 mmol). The solution was stirred at 60 °C for 1 h. The solvent was removed *in vacuo* and the residue subjected to column chromatography over silica (hexanes–EtOAc). Compound **31** thus obtained was recrystallized from methanol to give yellow crystals (1.25 g, 3.8 mmol, 64%). (S)-**31** could be prepared using the same procedure but starting with (*R*)-1-phenylethanol instead of the racemate. Optical purity was determined by analytical HPLC. Mp 92.0–93.0 °C; found C, 80.34; H, 4.86. Calcd. for $C_{22}H_{16}O_3$: C, 80.46; H, 4.91%. IR (nujol) 3064, 3052, 3044, 2987, 2935, 1668, 1662, 1584, 1495 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.82 (d, J = 6 Hz, 3H), 5.53 (q, J = 6 Hz, 1H), 7.19 (d, J = 9 Hz, 1H), 7.28 (d, J = 9 Hz, 1H), 7.35 (t, J = 8 Hz, 2H), 7.51 (q, J = 7.5 Hz, 3H), 7.77 (dtd, J = 1.5 Hz, 3.9 Hz, 8 Hz, 2H), 7.89 (d, J = 6 Hz, 1H), 8.24 (dd, J = 1.5 Hz, 6 Hz, 1H), 8.34 (dd, J = 1.5 Hz, 4 Hz, 6 Hz, 1H); δ_C (300 MHz, $CDCl_3$) 183.7, 182.4, 158.9, 142.5, 135.9, 135.3, 134.6, 134.4, 133.3, 132.7, 129.0, 128.0, 127.4, 126.7, 125.9, 122.5, 121.5, 120.0. HRMS (EI) found MNa^+ 351.0982; $C_{22}H_{16}O_3Na^+$, requires 351.0992.

Relative quantum yields (rates) of 25, 15, 16, 17, 18, 29. UV–VIS spectra were taken of all compounds at 250 μM. Absorbances were normalized to the absorbance of **17** at 405 nm at a concentration of 5 mM. The molar absorptivities of **25**, **15**, **16**, **17**, **18**, and **29** were 1325, 792, 438, 870, 1876, 1345, respectively. The necessary concentrations of **25**, **15**, **16**, **18**, and **29** were calculated to be 2.75 mM, 4.60 mM, 8.31 mM, 4.0 mM, and 2.5 mM, respectively, using Beer's law. Experiments probing the heavy atom effect used 0, 28, 55, 110 mM iodoform, and 110 mM chloroform against **25**. All substrates were dissolved in 1 : 4 DMSO-*d6*–CD_3OD or 1 : 4 DMSO-*d6*–D_2O. Due to the lack of solubility of **16** in this solvent system at 8.31 mM, this substrate was diluted to 4.16 mM. 2,4,6-Trimethylbenzoic acid (1 equiv.) was added to each sample as an internal standard; the sodium salt of 2,4,6-trimethylbenzoic acid (1 equiv.) was used for the D_2O sample. Stock solutions of each sample were prepared; for each experiment, 500 μl was transferred to an NMR tube. Then, a 0 minute ^1H NMR was performed with a relaxation delay of 5 seconds and 64 scans. The aromatic protons of the internal standard (δ 6.87, 2H) were integrated against the benzyl signal (δ 5.05, 2H) of each substrate. The samples were irradiated with a monochromator by Oriel Instruments (model # 66901) equipped with a grating monochromator (model # 77250). The monochromator was set to 405 nm with a 10 nm bandpass. The samples were placed in a foiled chamber 20 cm from the slit. Time points of 4, 8, 12, 16 and 20 minutes were taken. All samples were run with and rates referenced to **25**.

Release of 4-HNE in aqueous solution. **24** (0.0819 mmol) was dissolved in a buffered solution (pH 5.0, 7.0, or 9.0; 32.7 mL) and irradiated with a Rayonet reactor (16 lamps with peak emission at 419 nm) for 2.5 hours. The aqueous solution was extracted with petroleum ether (3 × 60 ml). The petroleum ether was concentrated *in vacuo* to give 4-HNE. The aqueous layer was then diluted with diethyl ether and acidified with 1 N HCl. NaCl (s, 1 g) was added, and the aqueous layer was extracted with diethyl ether (2 × 60 ml). The organic extracts were combined, dried with $MgSO_4$, and concentrated *in vacuo* to give **33**. 1-Hydroxy-2-propyl-9,10-anthraquinone-4-carboxylic acid **33**. Mp 243.0–250.0 °C dec. δ_H (300 MHz, DMSO-*d6*, Me_4Si) 0.93 (t, J = 7.4 Hz, 3H, CH_3), 1.56–1.68 (m, 2H, CH_2), 2.65–2.70 (m, 2H, Ar-CH_2), 7.51 (s, 1H, Ar-H), 7.91–7.96 (m, 2H, Ar-H), 8.09–8.12 (m, 1H, Ar-H), 8.19–8.23 (m, 1H, Ar-H), 13.14 (bs, 1H, Ar-OH). δ_C (75 MHz, DMSO-*d6*) 188.8, 181.1, 170.2, 159.9, 137.9, 135.2, 135.0, 134.5, 133.2, 132.4, 127.1, 126.8, 126.5, 114.7, 31.0, 21.8, 13.8. HRMS (EI) found MNa+ 333.07492; $C_{18}H_{14}O_5Na$+ requires 333.07334.

Acknowledgements

This work was supported in part by NIH (R15GM070468–01) and NSF (CHE-0514576). The authors thank Drs Marcus Wright and Cynthia Day for spectroscopic assistance.

Notes and references

1 (*a*) A. Patchornik, B. Amit and R. B. Woodward, *J. Am. Chem. Soc.*, 1970, **92**, 6333–6335; (*b*) C. G. Bochet, *J. Chem. Soc., Perkin Trans. 1*, 2002, **2**, 125–142; (*c*) M. Schelhaas and H. Waldmann, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2056–2083; (*d*) C. G. Bochet, *Adv. Org. Synth.*, 2005, **1**, 3–23; (*e*) C. G. Bochet, *Pure Appl. Chem.*, 2006, **78**, 241–247; (*f*) A. del Campo, D. Boos, H. W. Spiess and U. Jonas, *Angew. Chem., Int. Ed.*, 2005, **44**, 4707–4712; (*g*) R. Glatthar and B. Giese, *Org. Lett.*, 2000, **2**, 2315–2317; (*h*) S. Peukert and B. Giese, *J. Org. Chem.*, 1998, **63**, 9045–9051; (*i*) R. S. Givens, P. G. Conrad II, A. L. Yousef and J.-I. Lee, *CRC Handbook of Organic Photochemistry and Photobiology (2nd Edition)*, 2004vol. 69, pp. 1–46; (*j*) R. S. Givens and J.-I. Lee, *J. Photosci.*, 2003, **10**, 37–48; (*k*) M. Mella, E. Fasani and A. Albini, *J. Org. Chem.*, 1992, **57**, 3051–3057; (*l*) E. Fasani, M. Freccero, M. Mella and A. Albini, *Tetrahedron*, 1997, **53**, 2219–2232; (*m*) S. Hashimoto, I. Kurimoto, Y. Fujii and R. Noyori, *J. Am. Chem. Soc.*, 1985, **107**, 1427–1429; (*n*) P. Wang, H. Hu and Y. Wang, *Org. Lett.*, 2007, **9**, 2831–2833; (*o*) S. Kantevari, C. V. Narasimhaji and H. B. Mereyala, *Tetrahedron*, 2005, **61**, 5849–5854; (*p*) W. Lin and D. S. Lawrence, *J. Org. Chem.*, 2002, **67**, 2723–2726; (*q*) A. Herrmann, *Angew. Chem., Int. Ed.*, 2007, **46**, 5836–5863; (*r*) R. Lage, X. X. Jaime and C. G. Bochet, *Org. Lett.*, 2005, **7**, 3545–3547; (*s*) A. Herrmann, *Spectrum*, 2004, **17**(2), 10–13; (*t*) B. Levrant and A. Herrmann, *Photochem. Photobiol. Sci.*, 2002, **1**, 907–919; (*u*) S. Rochat, C. Minardi, J. Y. de Saint-Laumer and A. Herrmann, *Helv. Chim. Acta*, 2000, **83**, 1645–1671; (*v*) A. Blanc and C. G. Bochet, *J. Org. Chem.*, 2003, **68**, 1138–1141; (*w*) P. K. Yong and A. Banerjee, *Org. Lett.*, 2005, **7**, 2485–2487.

2 T. J. Dougherty, C. H. Gomer, B. W. Henderson, G. Jori, D. Kessel, M. Korbelik, J. Moan and Q. Peng, *J. Natl. Cancer Inst.*, 1998, **90**, 889–905.

3 (*a*) Z. Huang, Q. Chen, A. Shakil, J. Beckers, H. Shapiro and F. W. Hetzel, *Photochem. Photobiol.*, 2003, **78**, 496–502; (*b*) B. W. Henderson and V. H. Fingar, *Cancer Res.*, 1987, **47**, 3110–3114; (*c*) J. Fuchs and X. X. Thiele, *Free Radical Biol. Med.*, 1998, **24**, 835–847.

4 R. G. Brinson and P. B. Jones, *Org. Lett.*, 2004, **6**, 3767–3770.

5 (*a*) L. J. Marnett and J. Plastaras, *Trends Genet.*, 2001, **17**, 213–220; (*b*) F. Chung, R. Nath, J. Ocando, A. Nishikawa and L. Zhang, *Cancer Res.*, 2000, **60**, 1507–1511; (*c*) J. P. Kehrer and S. S. Biswal, *Toxicol. Sci.*, 2000, **57**, 6–15; (*d*) E. Eder, S. Scheckenbach, C. Deininger and C. Hoffman, *Toxicol. Lett.*, 1993, **67**, 87–103; (*e*) B. Zarrouki, A. F. Soares, M. Guichardant, M. Lagarde and A. Geloen, *FEBS Lett.*, 2007, **581**, 2394–2400; (*f*) K. Chen, M. Kazachkov and P. H. Yu, *J. Neurol. Trans.*, 2007, **114**, 835–839; (*g*) D. Conklin, R. Prough and A. Bhatanagar, *Mol. BioSyst.*, 2007, **3**, 136–150; (*h*) K. Uchida, *Chem. Res. Toxicol.*, 2007, **20**, 3–5.

6 (*a*) H. Esterbauer, R. Schaur and H. Zollner, *Free Radical Biol. Med.*, 1991, **11**, 81–128; (*b*) A. Cerbone, C. Toaldo, S. Laurora, F. Briatore, S. Pizzimenti, M. U. Dianzani, C. Ferreti and G. Barrera, *Free Radical Biol. Med.*, 2007, **42**, 1661–1670.
7 (*a*) R. L. Blankespoor, R. L. De Jong, R. Dykstra, D. A. Hamstra, D. B. Rozema, D. P. VanMeurs and P. Vink, *J. Am. Chem. Soc.*, 1991, **113**, 3507–3513; (*b*) R. P. Smart, T. J. Peelen, R. L. Blankespoor and D. L. Ward, *J. Am. Chem. Soc.*, 1997, **119**, 461–465; (*c*) R. L. Blankespoor, R. P. Smart, E. D. Batts, A. A. Kiste, R. E. Lew and M. E. Vasnder Vilet, *J. Org. Chem.*, 1995, **60**, 6852–6859; (*d*) R. L. Blankespoor, T. DeVries, E. Hansen, J. M. Kallemeyn, A. M. Klooster, J. A. Mulder, R. P. Smart and D. A. Vander Griend, *J. Org. Chem.*, 2002, **67**, 2677–2681; (*e*) R. G. Brinson, S. C. Hubbard, D. R. Zuidema and P. B. Jones, *J. Photochem. Photobiol. A: Chem.*, 2005, **175**, 118–128.
8 (*a*) P. J. Wagner, *Acc. Chem. Res.*, 1989, **22**, 83–91; (*b*) X. X. Griesbeck and G. Axel, *Synlett*, 2003, 451–472; (*c*) R. Breslow, S. Kitabatake and J. Rothbard, *J. Am. Chem. Soc.*, 1978, **26**, 8156–8160; (*d*) H. E. Zimmerman and A. G. Kutateladze, *J. Am. Chem. Soc.*, 1996, **118**, 249–250; (*e*) H. E. Zimmerman and A. G. Kutateladze, *J. Org. Chem.*, 1995, **60**, 6008–6009; (*f*) H. E. Zimmerman and C. W. Carpenter, *J. Org. Chem.*, 1988, **53**, 3298–3305; (*g*) H. E. Zimmerman and A. P. Kamath, *J. Am. Chem. Soc.*, 1988, **110**, 900–911.
9 (*a*) J. N. Moorthy, S. L. Monahan, R. B. Sunoj, J. Chandrasekhar and C. Bohne, *J. Am. Chem. Soc.*, 1999, **121**, 3093–3103; (*b*) B. Giese, P. Wettstein, C. Stähelin, F. Barbosa, M. Neuberger, M. Zehnder and P. Wessig, *Angew. Chem., Int. Ed.*, 1999, **38**, 2586–2587; (*c*) P. Wagner and P. Klan, *J. Am. Chem. Soc.*, 1999, **121**, 9626–9635; (*d*) P. Wagner, M. A. Meador and B.-S. Park, *J. Am. Chem. Soc.*, 1990, **112**, 5199–5211.
10 See general experimental for CDC information.
11 R. Brinson, S. Hubbard, D. Zuidema and P. Jones, *J. Photochem. Photobiol. A: Chem.*, 2005, **175**, 118–128.
12 H. J. van Ramesdonk, B. H. Bakker, M. M. Groeneveld, J. W. Verhoeven, B. D. Allen, J. P. Tostron and A. Harriman, *J. Phys. Chem. A*, 2006, **110**, 13145–13150.
13 M. Tajima, H. Inoue and M. Hida, *Dyes Pigm.*, 1987, **8**, 119–127.