Electronic Supplementary Information

Photocages for protection and controlled release of bioactive compounds

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Reagents and solvents

Avobenzone, (*S*)-ketoprofen, *N*-bromosuccinimide, cesium carbonate and anhydrous dimethylformamide were purchased from AK Scientific and Sigma-Aldrich, and used as received. Ethanol of HPLC grade used for steady-state photolysis and laser flash photolysis experiments was from Scharlau, whereas propylene glycol (Reagent-plus 99%, GC Grade) was purchased from Sigma-Aldrich.

Characterization

The ^1H and ^{13}C NMR spectra were measured by a 300 MHz instrument, and $CDCl_3$ was used as solvent for all the spectra. The solvent signal was taken as the reference using a chemical shift (δ) of ca. 7.26 ppm and 77.16 ppm, for ^1H NMR and ^{13}C NMR, respectively. Coupling constants (*J*) are given in Hz.

Exact mass values were determined by using a Waters ACQUITY™ XevoQToF spectrometer (Waters Corp.) connected to the UPLC system via an electrospray ionization (ESI) interface. The ESI source was operated in positive ionization mode with the capillary voltage at 3.0 kV. The temperature of the source and desolvation was set at 120°C and 500°C, respectively. The cone and desolvation gas flows were 10 L h^{-1} and 450 L h^{-1}, respectively. All data collected in Centroid mode were acquired using Masslynx™ software (Waters Corp.). Leucine-enkephalin was used as the lock mass generating an $[M+H]^+$ ion (*m/z* 556.2771) at a concentration of 500 pg/mL and a flow rate of 20 µL/min to ensure accuracy during the MS analysis.

Photophysical instrumentation

UV-Vis absorption. Spectra were registered on a Cary 50 spectrophotometer (Varian) using a quartz cuvette of 3 mL and 1 cm of optical path.

Steady-state photolysis. Simulated sunlight (SSL) irradiation, experiments were carried out with a Thermo Oriel Newport (A91192A) solar simulator equipped with a 1000 W Xe arc. Its output was adequately filtered to produce a spectrum approximating natural sunlight (1.5 G air mass filter). The spectral output was measured as ca. 1000 mW/cm^2.

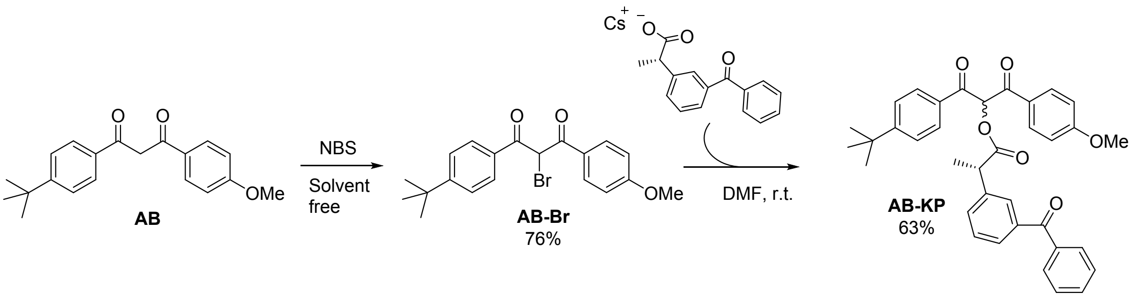
For preliminary studies monitoring the UV-Vis spectral changes as a function of SSL irradiation, deaerated or aerated ethanol solution of AB-KP at ca. 9 x 10^{-5} M were used. Finally, HPLC analysis was run by using SSL irradiation of AB-KP at 9.2 x 10^{-4} M or 7.1 x 10^{-4} M in deaerated ethanol or aerated propylene glycol, respectively.

Laser flash photolysis (LFP). Experiments were run with a pulsed Nd:YAG (L52137 V LOTIS TII) laser system instrument setting 355 nm as excitation wavelength. The pulse duration was of ca. 10 ns and the energy was adjusted at 21 mJ pulse^{-1}. The apparatus consisted of the pulsed laser, the Xe lamp, a 77250 Oriel monochromator, and a photomultiplier. The output signal from a Tektronix oscilloscope was transferred to a personal computer. The transient spectra were recorded at room temperature employing quartz cells of 1 cm optical path length. Experiments were performed for ethanol solutions of AB-KP (6.4 x 10-4 M) under air and N_2 atmosphere.

Femtosecond transient absorption spectroscopy. The transient absorption spectra were recorded using a typical pump−probe system. The femtosecond pulses were generated with a compact regenerative amplifier that produces pulses centered at 800 nm (∼100 fs, 1 mJ/pulse). The output of the laser was split into two parts to generate the pump and the probe beams. Thus, tunable femtosecond pump pulses were obtained by directing the 800 nm light into an optical parametric amplifier. In the present case, the pump was set at 355 nm and passed through a chopper prior to focus onto a rotating cell containing the solutions under study. The white light used as probe was produced after part of the 800 nm light from the amplifier travelled through a computer controlled 8 ns variable optical delay line and impinge on a CaF_2 rotating crystal. This white light is in turn, split in two identical portions to generate reference and probe beams that then are focused on the rotating cell containing the sample. The pump and the probe are made to coincide to interrogate the sample. A computer controlled imaging spectrometer is placed after this path to measure the probe and the reference pulses and obtain the transient absorption decays/spectra.

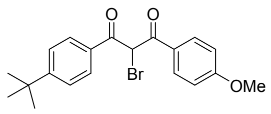
HPLC analysis. The irradiation mixtures were analyzed by reverse phase HPLC using a Varian ProStar instrument equipped with a diode array detector covering a detection range from 200 to 400 nm. A Mediterranea Sea C18 column (25 mm × 0.46 mm, 5 µm) was employed with an injection volume of 10 µL (removed from the cuvette at different irradiation times). The mobile phase was an isocratic mixture of water at pH 3 (20%) and acetonitrile (80%) at a flow rate of 0.7 mL/min. Different wavelengths were used to detect AB-KP ($\lambda_{detection}$ = 260 nm), KP ($\lambda_{detection}$ = 253 nm) or AB ($\lambda_{detection}$ = 357 nm).

Synthetic details



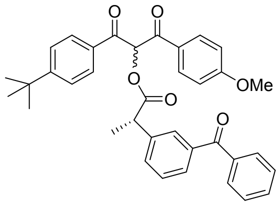
Scheme S1. Synthetic route for AB-KP

2-bromo-1-(4-(tert-butyl)phenyl)-3-(4-methoxyphenyl)propane-1,3-dione (AB-Br)



Two solids, avobenzone (AB, 1 g, 3.2 mmol) and N-bromosuccinimide (0.57 g, 3.2 mmol) were mixed under solvent free conditions in a mortar for 10 minutes. The mixture was left stand for 2 hours and then, mixed each 15 minutes during 2 h. Then, water was added and the solution was filtered under vacuum. The solid was left overnight to dry up. Purification was performed by flash chromatography using hexane:ethyl acetate as eluent (6:1, v:v). Colorless crystals of AB-Br were obtained (0.94 g) in a 76% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.99 (d, 2H, J=9Hz), 7.93 (d, 2H, J=9Hz), 7.46 (d, J=6Hz, 2H), 6.92 (d, J = 6Hz, 2H), 6.47 (s, 1H), 3.86 (s, 3H), 1.32 ppm (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 188.7 (CO), 187.7 (CO), 164.4 (C), 158.2 (C), 131.9 (CH), 131.3 (C), 129.3 (CH), 126.8 (C), 126.1 (CH), 114.3 (CH), 55.7 (CH_3), 53.3 (CH), 35.3 (C), 31.0 ppm (CH_3). **HRMS (ESI$^+$):** Calculated for $C_{20}H_{22}O_3Br$ [M+H]$^+$: 389.0752 found: 389.0753.

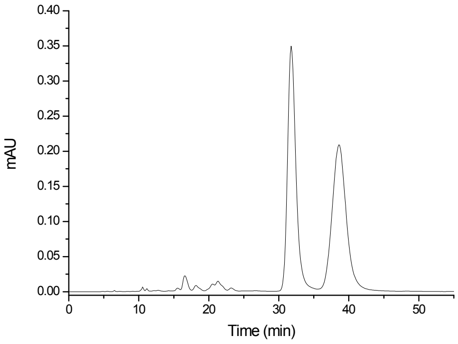
1-(4-(tert-butyl)phenyl)-3-(4-methoxyphenyl)-1,3-dioxoprop-2-yl (2S)-2-(3-benzoylphenyl)propanoate (AB-KP)



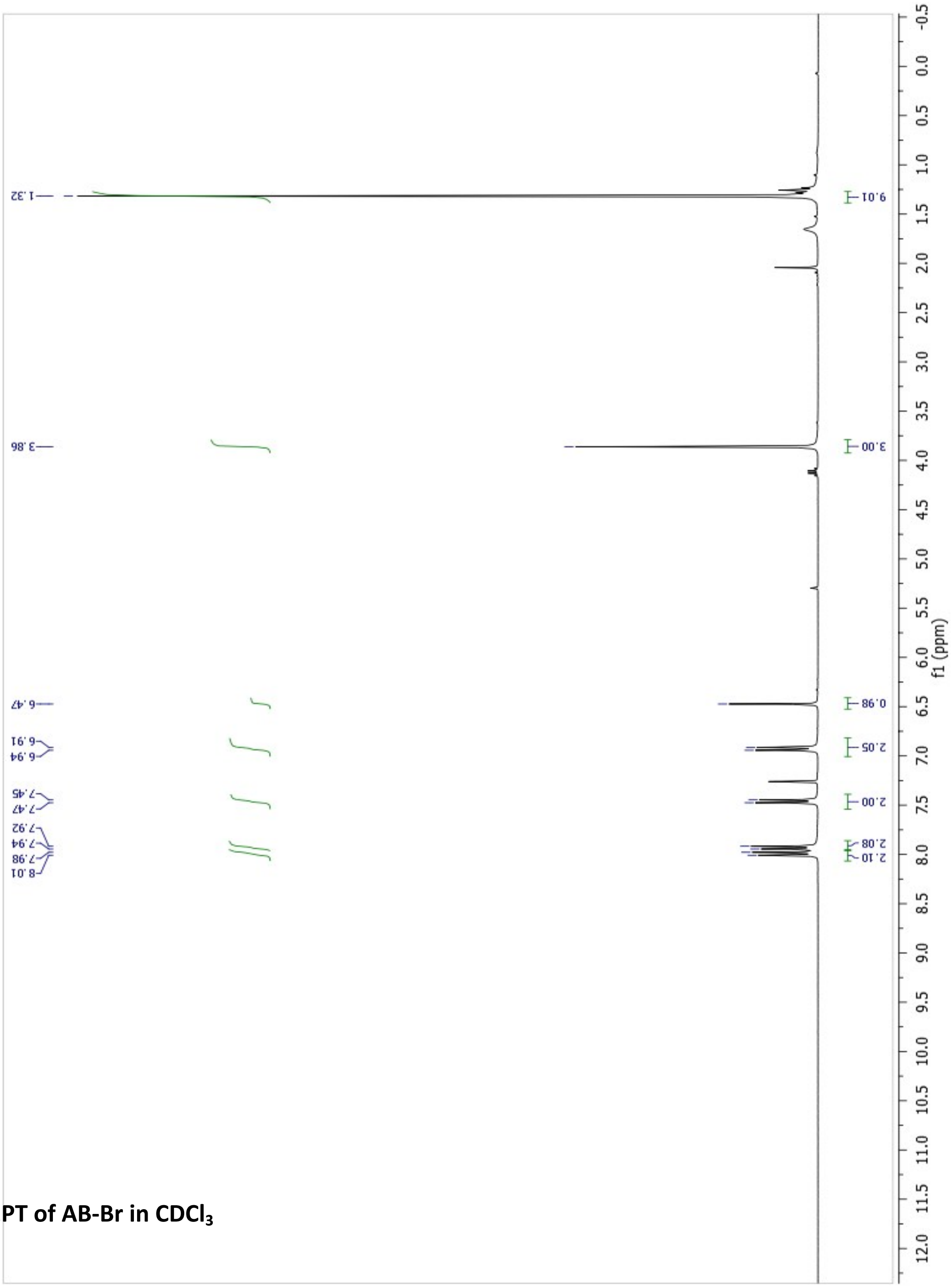
First, cesium (*S*)-ketoprofen salt was formed by titration of a (*S*)-ketoprofen water solution (8 mM) against a cesium carbonate water solution (4 mM) until pH stabilized at 7. Then, this salt (0.498 g, 1.29 mmol) dissolved in 5 mL of dimethylformamide was added to a flask containing Br-AB (0.2 g, 0.52 mmol). After 17 hours of stirring, the reaction turned orange. The solvent was directly evaporated and the reaction was purified by flash chromatography, hexane/ethyl acetate, (7:1, v:v). The product, a yellowish solid was obtained as a diastereoisomeric mixture in a 63% yield (0.18 g). **^{1}H NMR** (300 MHz, $CDCl_3$) δ

7.94-6.79 (m, 18H), 4.00 (q+q, J=7.1 Hz, 1H), 3.81 (s+s, 3H), 1.61 (d+d, *J* = 7.1 Hz, 3H), 1.28 ppm (s, 9H). **^{13}C NMR** (75 MHz, CDCl$_3$) *δ* 196.4 (CO), 196.3 (CO), 190.4 (CO), 190.3 (CO), 189.0 (CO), 172.4 (CO), 172.3 (CO), 164.3 (C), 158.1 (C), 158,0 (C), 139.8 (C), 138.0 (C), 137.9 (C), 137.4 (C), 132.5 (CH), 132.1 (CH), 132.0 (CH), 131.8 (CH), 131.7 (CH), 131.6 (C), 131.5 (C), 130.1 (CH), 129.6 (CH), 129.5 (CH), 129.1 (CH), 128.7 (CH), 128.3 (CH), 127.2 (C), 127.1 (C), 125.6 (CH), 113.9 (CH), 81.2 (CH), 81.1 (CH), 55.5 (CH$_3$), 45.2 (CH), 45.1 (CH), 35.2 (C), 30.9 (CH$_3$), 18.1 ppm (CH$_3$). **HRMS (ESI$^+$):** Calculated for $C_{36}H_{34}O_6Na$ [M+Na]$^+$: 585.2253, found: 585.2256.

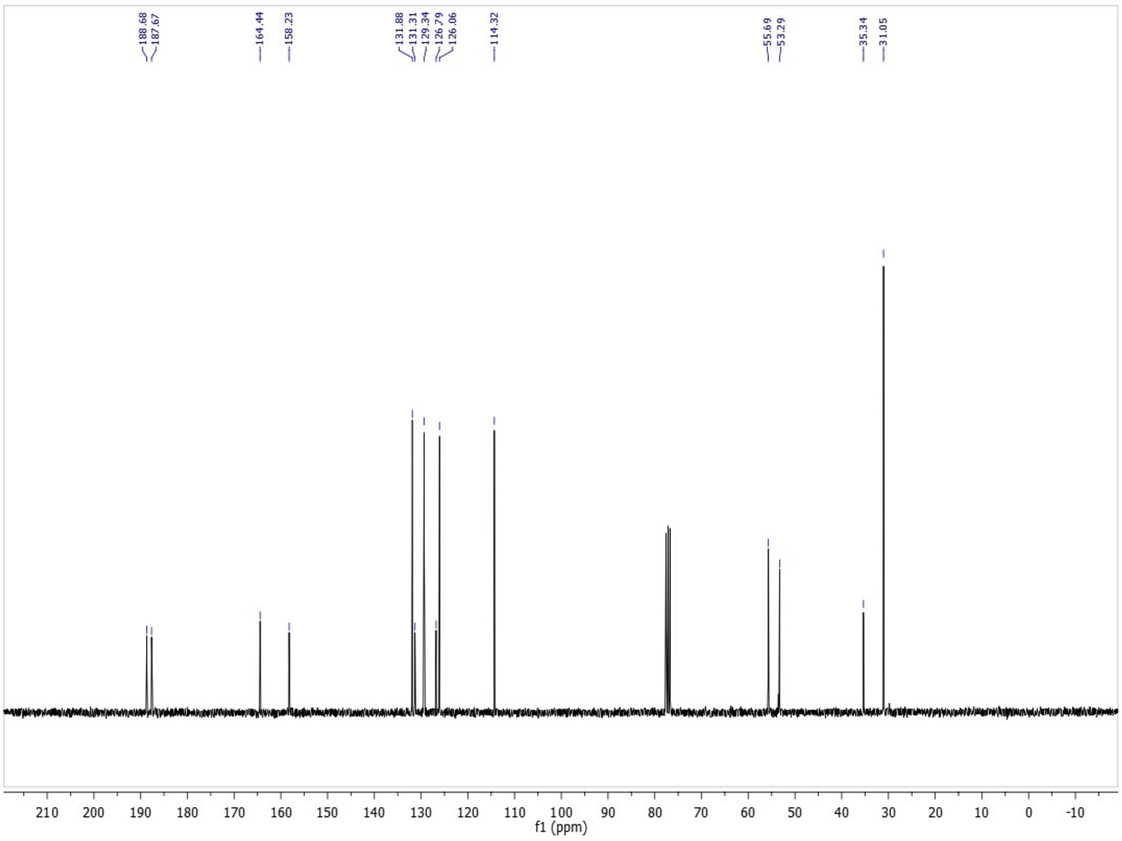
The presence of two diastereoisomers was confirmed by HPLC using a chiral column Kromasil 5-AmyCoat (4.6 x 250 mm, 5μ). The mobile phase was an isocratic mixture of hexane: isopropanol (80:20, v:v) at a flow rate of 0.7 mL/min; the detection wavelength was fixed at 260 nm. The AB-KP isomers (*R,S*) and (*S,S*) were present in 1:1 proportion (see chromatogram below).

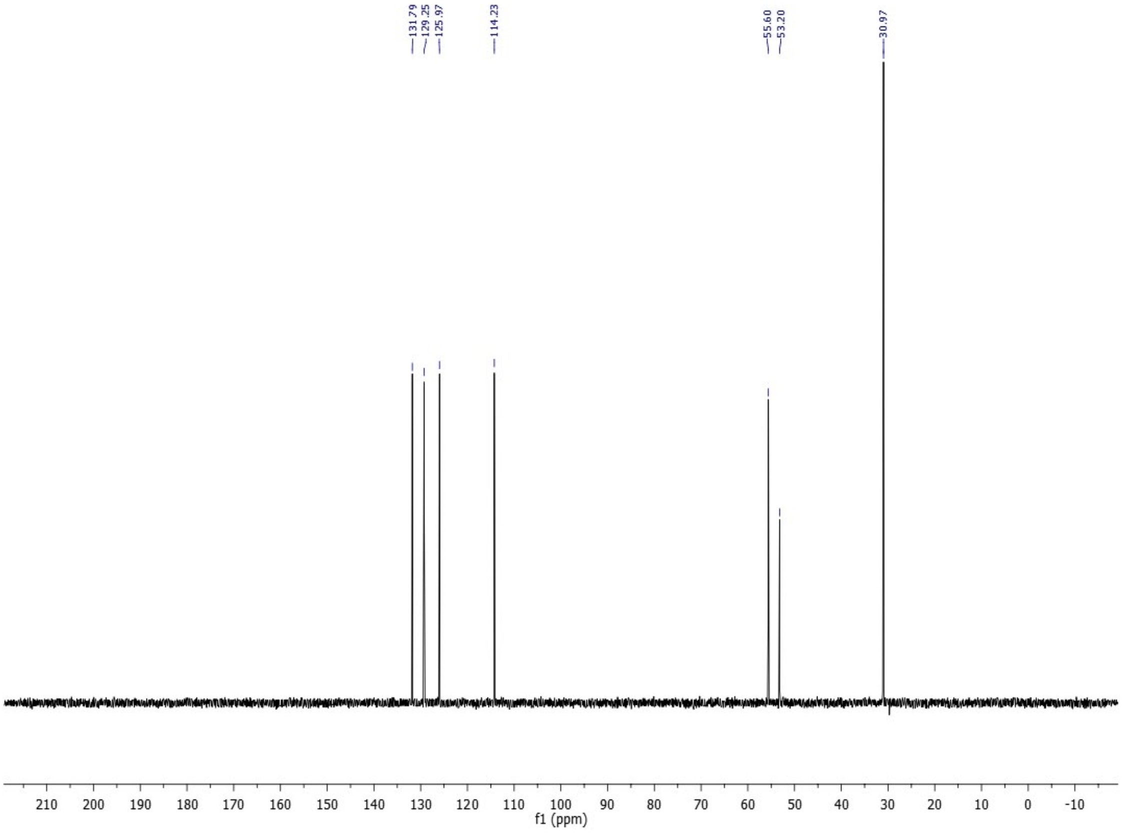


^{1}H NMR

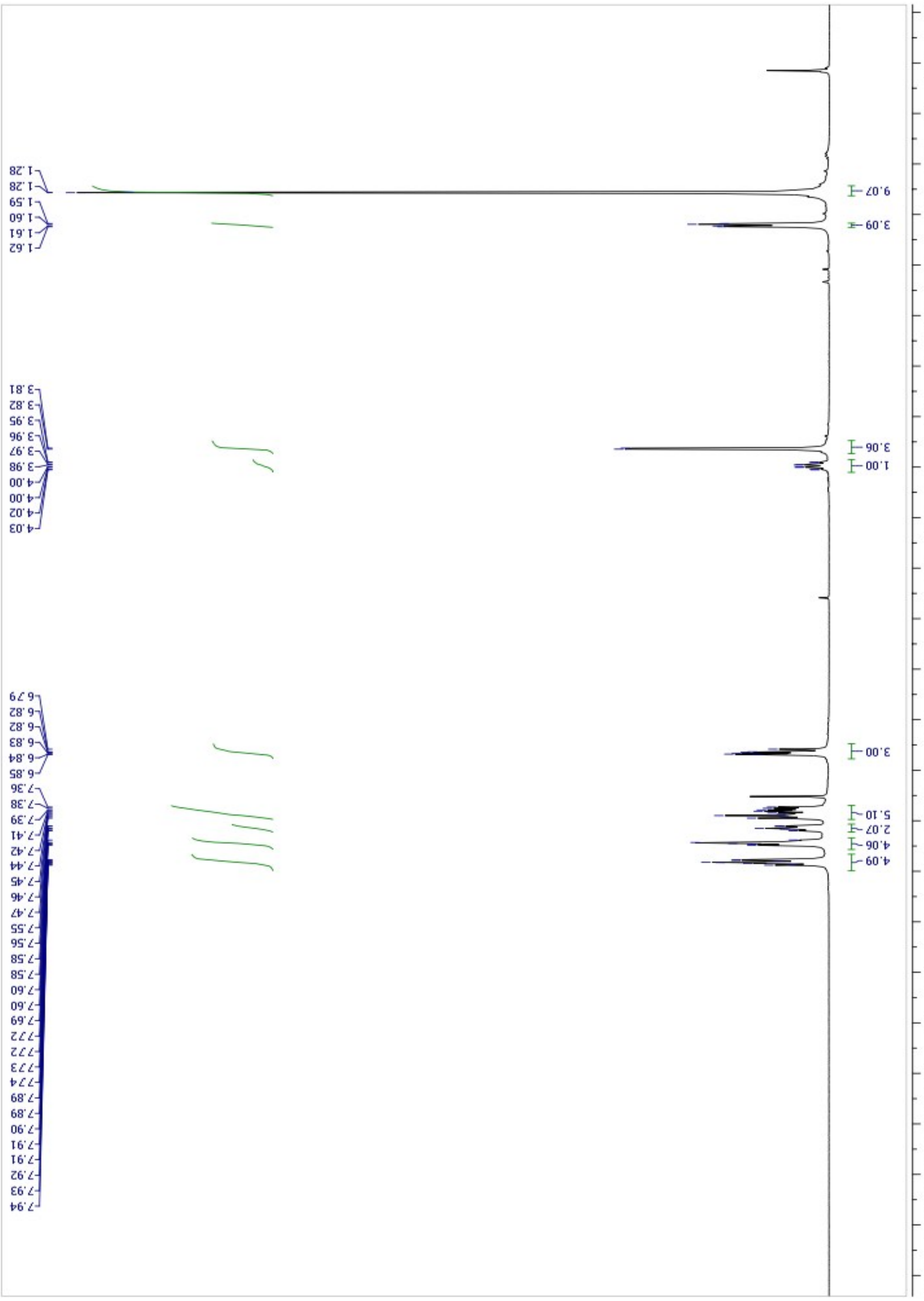


^{13}C NMR and DEPT of AB-Br in $CDCl_3$

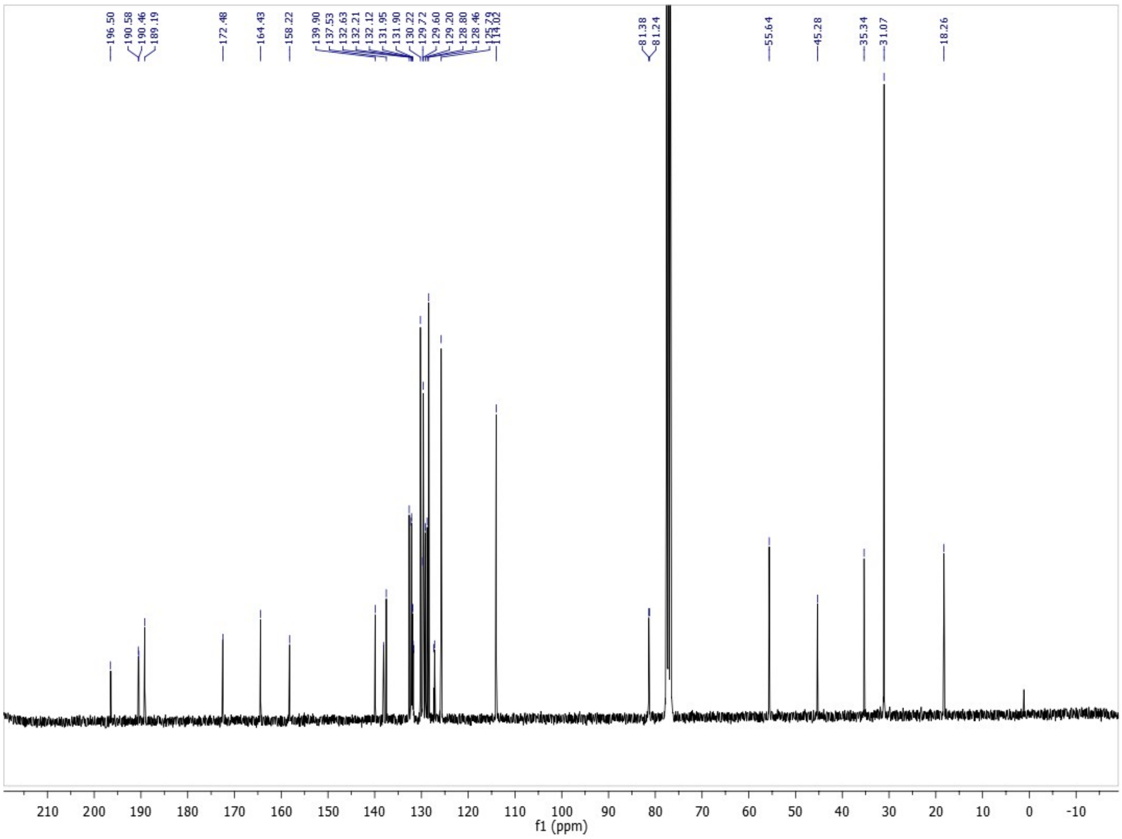


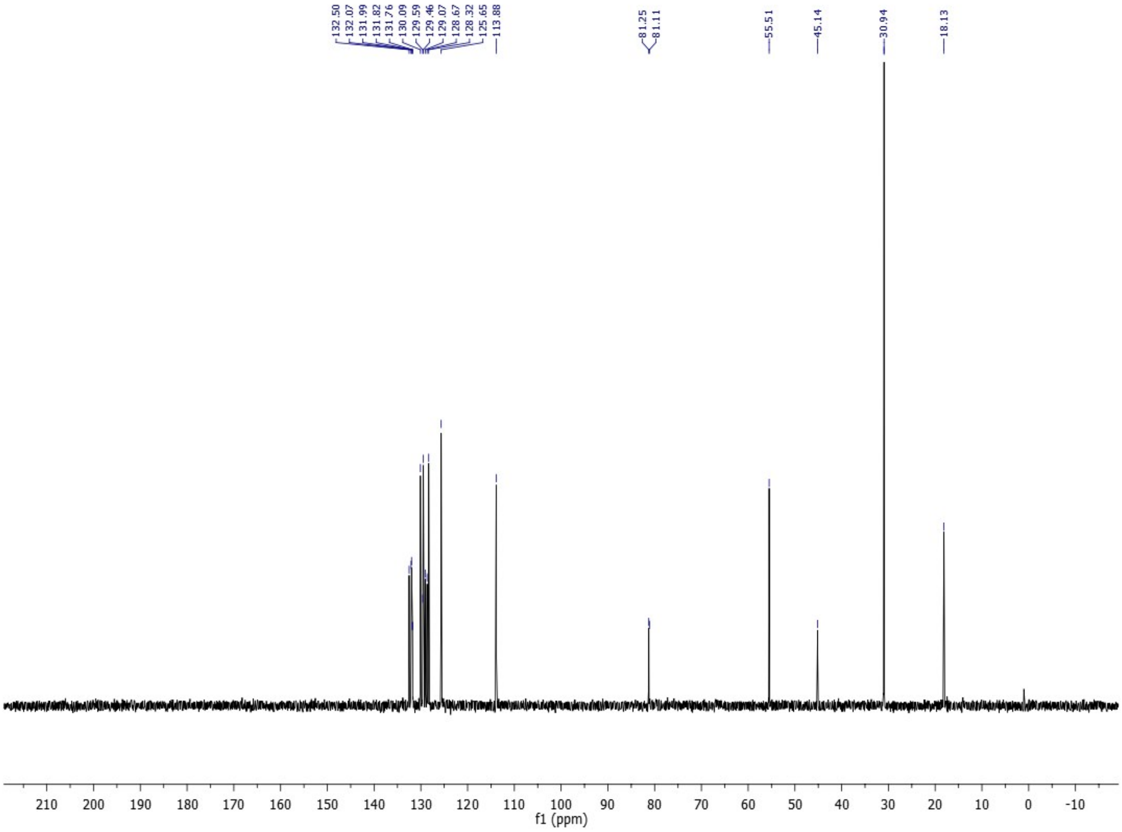


^{1}H NMR of AB-KP in CDCl$_3$



^{13}C NMR and DEPT of AB-KP in $CDCl_3$


196.50
190.58
190.46
189.19
172.48
164.43
158.22
139.90
137.53
132.63
132.21
132.12
131.95
131.90
130.22
129.72
129.60
129.20
128.80
128.46
125.79
114.02
81.38
81.24
55.64
45.28
35.34
31.07
18.26
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


132.50
132.07
131.99
131.82
131.76
130.09
129.59
129.46
129.07
128.67
128.32
125.65
113.88
81.25
81.11
55.51
45.14
30.94
18.13
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

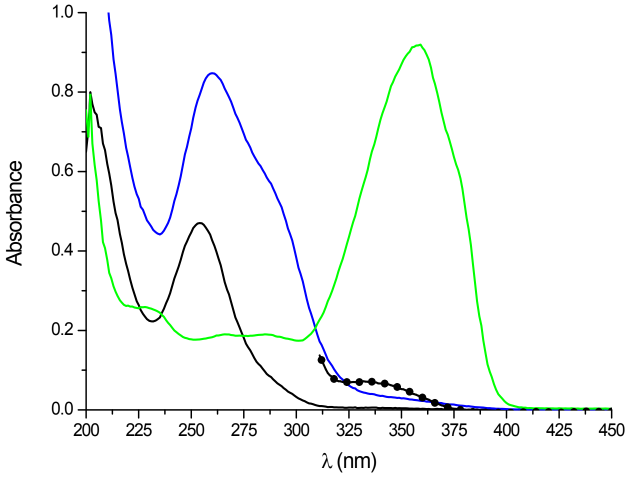
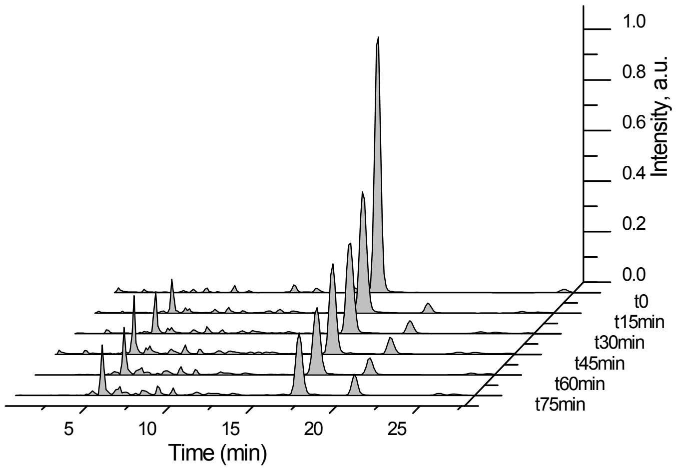


Figure S1. UV-Vis absorption spectra of 2 x 10^{-5} M KP (black line), AB-enol (green line) and AB-KP (blue line) and 7 x 10^{-4} M KP (black dots) in EtOH.

(A)



(B)

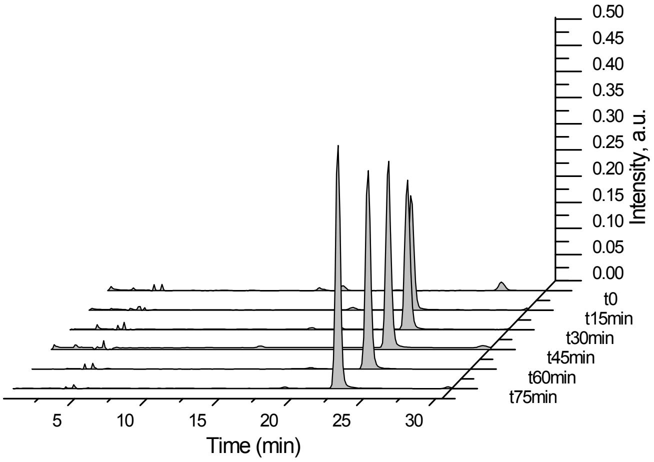


Figure S2. HPLC chromatograms registered at 260 nm (A) or 357 nm (B) of a deaerated ethanol solution of AB-KP (1.1 x 10^{-3} M) irradiated with SSL.

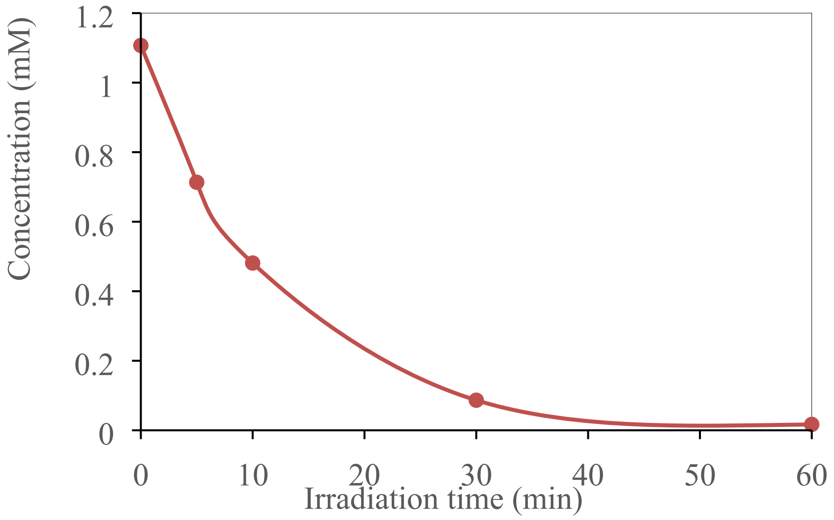
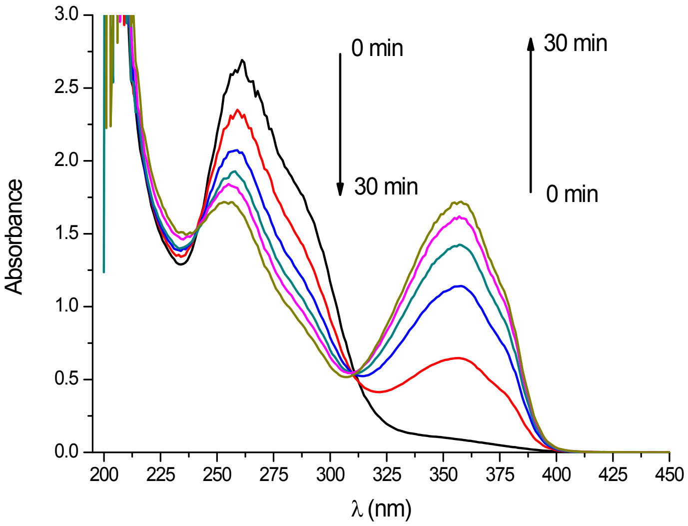


Figure S3. Time-dependent degradation of a deaerated ethanol solution KP (1.1 mM) alone.



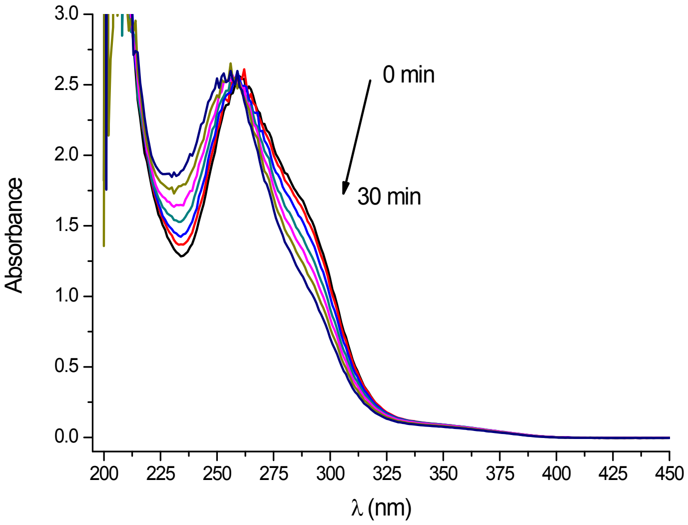


Figure S4. Simulated sunlight irradiation of AB-KP (9 x 10^{-5} M) in ethanol under N_2 (A) and air (B) followed by UV absorption.