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Unveiling the Role of Molecule-Assisted Homolysis: A Mechanistic Probe into the Chemistry of a Bicyclic Peroxide

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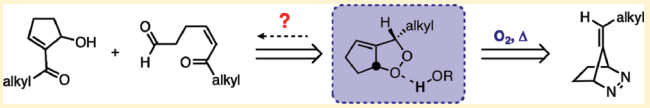
Supporting Information

ABSTRACT: Unlike the reaction of aryl-substituted diazenes, pyrolysis of alkyl-substituted diazenes in the presence of molecular oxygen generates an unexpectedly complex product mixture. Using deuterium labeling studies, in conjunction with quantum calculations, a reasonable mechanistic hypothesis for the decomposition of the resultant [3.3.0] peroxide, and subsequent formation of the keto-alcohol and *Z*-configured *α,β*-unsaturated keto-aldehyde, is proposed. Surprisingly, molecule-assisted homolysis plays a key role in this transformation, the details of which are discussed herein.

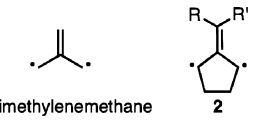


INTRODUCTION

Organic peroxides are an important structural motif; they are commonly used in the initiation of industrial polymerization processes,[1] as key precursors in the synthesis of biologically active natural products,[2] and even as an active ingredient in personal care products, such as acne medication.[3] Alkyl peroxyl radicals have long been under scrutiny. While many of these reactive oxygen species are considered toxic,[4] evidence suggests that others are biologically relevant in the fight against diseases such as malaria.[5] Although peroxides are traditionally thought of as being unstable, even hazardous substances, this need not be the case. In this paper, we describe the chemistry of two remarkably stable bicyclic peroxides and delve into the factors that eventually lead to cleavage of the peroxide bond. We have come to appreciate the role that seemingly innocent components of a reaction mixture can have in promoting reactivity and discuss our results in terms of a well-known, but not always fully appreciated, phenomenon called molecule-assisted homolysis.

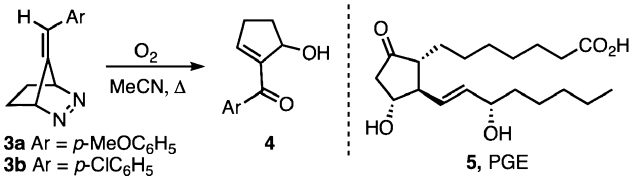
The diradical trimethylenemethane (TMM), **1**, has been a source of interest to researchers for many years.[6] The parent diyl was first generated and studied by Dowd in 1966[7] and was later shown to possess a triplet ground state, in accord with predictions based upon Hückel calculations and Hund's rule.[8] 2-Alkylidenecyclopentane-1,3-diyl analogues, e.g., **2**, of the parent system were first investigated by Berson and co-workers.[9] Later, our group uncovered their synthetic utility and discovered several unanticipated reactivity patterns, including the ability to cleave DNA and engage in intramolecular atom-transfer pathways.[10] On several occasions, molecular oxygen has been used to selectively probe the triplet chemistry of these diyls. It was used, for example, in determining the spin state responsible for formation of the linear and bridged cyclo-addition products in the so-called intramolecular diyl trapping reaction.[11]

Some time ago, we reported that the reaction of the diyl produced upon heating the aryl-substituted diazene, **3a,b**, in the presence of a continuous stream of molecular oxygen led to the formation of keto-alcohol **4** in a 70−75% isolated yield (note Scheme 1).[12] Given its structural similarity to prostaglandins such as **5**, it was envisioned that by starting with a suitably alkyl-substituted diazene one might be able to use the oxygen trapping reaction to access prostanoids. Toward that end, we then elected to investigate the isopropyl-substituted diazene.[13] As the subsequent discussion shows, its chemistry and that of other alkyl-substituted systems proved more complex than anticipated.



1, trimethylenemethane **2**

Scheme 1. The Reaction of Aryl-Substituted Diyls with Oxygen



3a Ar = *p*-$MeOC_6H_5$
3b Ar = *p*-ClC_6H_5

4

5, PGE

To mitigate volatility problems that were encountered using the low molecular weight isopropyl-substituted diazene, and in preparation for a detailed mechanistic analysis, the *n*-heptyl-substituted diazene, **9**, was synthesized and its chemistry subsequently explored. Herein we report a mechanistic investigation of its behavior in the presence of oxygen, highlighting in particular the unforeseen role of molecule-assisted homolysis (MAH) in the conversion of peroxide **11** into keto-alcohol **10** and keto-aldehyde **12**.

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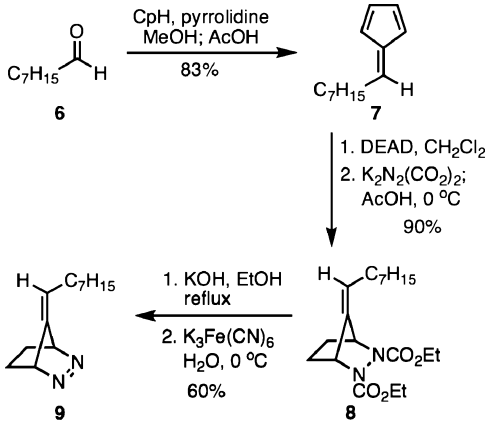
RESULTS AND DISCUSSION

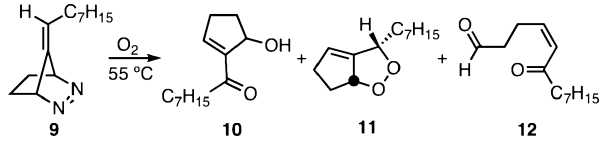
Synthesis of Diazene 9 and Initial Oxygen Trapping Results. Fulvene 7 was prepared from octanal using the Stone–Little procedure (Scheme 2).[14] The fulvene was converted to the [2.2.1] biscarbamate, **8**, through a Diels–Alder reaction with DEAD and subsequent diimide reduction of the resulting $\Delta^{(4,5)}$ π-bond. Diazene **9** was then generated by saponification of the biscarbamate with KOH in refluxing ethanol, followed by oxidative decarboxylation using aqueous $K_3Fe(CN)_6$.[15]

Scheme 2. Synthetic Route Used To Assemble Diazenes



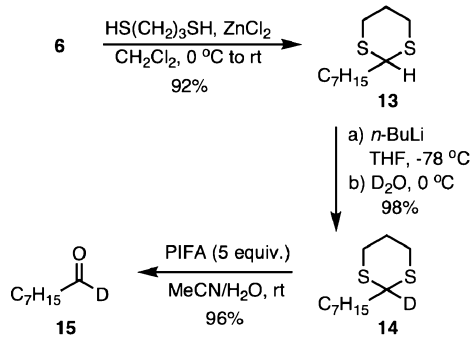
Thermolysis was accomplished by heating **9** in a solution of acetonitrile to 55 °C in the presence of a continuous stream of oxygen (Scheme 3). Three major products, viz., the expected keto-alcohol, **10**, as well as a [3.3.0] peroxide, **11**,[16,17] and a *Z*-substituted α,β-unsaturated keto-aldehyde, **12**, were isolated and characterized.[18] As the ensuing discussion will show, the relative amounts of each varied as a function of (a) time, (b) concentration of the starting diazene, and (c) the amount of keto-alcohol **10** present at any one time. While the crude reaction mixture contained a variety of additional products, these three accounted for 76% of the isolated mass. To minimize the formation of secondary products, we quenched the reactions at less than complete conversion. As a result, recovered starting material accounted for an additional 14% of the isolated mass. The three products, **10**–**12**, formed the focus of our subsequent investigations. To assist in the elucidation of a reasonable mechanistic hypothesis, the order in which the products formed was determined. The peroxide, **11**, was the first to form, followed by the keto-alcohol, **10**, and finally the keto-aldehyde, **12**. From this information, we suspected that the peroxide might serve as the precursor of the other two products.

Scheme 3. Major Products Formed in the Presence of Oxygen



Deuterium Labeling and Initial Thermolysis Results. To assist in determining the origin of these substances, the deuterium labeled diazene, **9-d$_1$**, was synthesized in the manner portrayed in Scheme 4. Thus, octanal, **6**, was converted to the dithiane, **13**, with 1,3-propanedithiol, using $ZnCl_2$ as a Lewis acid. Deuterium exchange to form **14** was accomplished by deprotonation with *n*-BuLi and a subsequent quench with D_2O.[19] An efficient deprotection of **14** using PIFA yielded octanal-d_1, **15**;[20] its subsequent conversion to the deuterated diazene, **9-d$_1$**, followed the protocol illustrated in Scheme 2.

Scheme 4. Insertion of the Deuterium Label



Thermolysis of the deuterated diazene, **9-d$_1$**, was conducted under the same conditions as its protio-counterpart, **9**. The location of the deuterium label in each of the three products was determined spectroscopically and the results are illustrated in Figure 1.[21] Examination of the structures for keto-alcohol **10-d$_1$** and enone **12-d$_1$** clearly reveals that the label has moved; but how, and when? From these results, one can envision that the presence of dioxolane **11-d$_1$** is simply a result of the triplet diyl being trapped by the molecular oxygen.

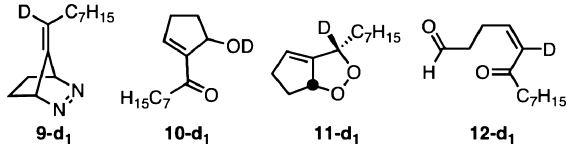


Figure 1. Location of the deuterium label in the products formed from the reaction of the deuterated diazene, **9-d$_1$**, with oxygen.

Unanticipated Concentration Effects. One of the more intriguing aspects of our initial findings was the dramatically different time needed for the conversion of the deuterated substrate, **9-d$_1$**, to the products relative to its protio-analogue, **9**. This was obvious even when assessed qualitatively by TLC. In the protio case, for example, all three products were observed in approximately 2.5 h, with peroxide **11** appearing after 1 h and **10** and **12** appearing after 1.5 and 2 h, respectively. In contrast, the deuterated substrate, **9-d$_1$**, required 2 h before the peroxide, **11-d$_1$**, was visible by TLC, and even after an additional 2 h of heating, no keto-alcohol or keto-aldehyde was observed.

To investigate further this unanticipated outcome, separate experiments were performed starting with the protio and deuterated diazenes **9** and **9-d$_1$**, respectively. The amount of peroxide (**11** and **11-d$_1$**) formed was measured as a function of time using ^{1}H NMR. Two diazene concentrations were examined, *viz.*, 0.025 and 0.05 M, the latter representing a 10-fold increase relative to the concentration normally used. Figure 2 compares the results for the two systems at a starting diazene concentration of 0.05 M (note the black and red curves in Figure 2). Notably after 2.5 h, there is nearly 20% more peroxide present when starting from the deuterated substrate,

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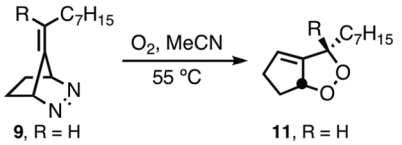


9, R = H
9-d$_1$, R = D

11, R = H
11-d$_1$, R = D

	from 0.05 M diazene:	
time (h)	**11** (%)	**11-d$_1$** (%)
0.5	9.4	10.
1.0	18	27
1.5	27	37
2.0	33	48
2.5	37	56

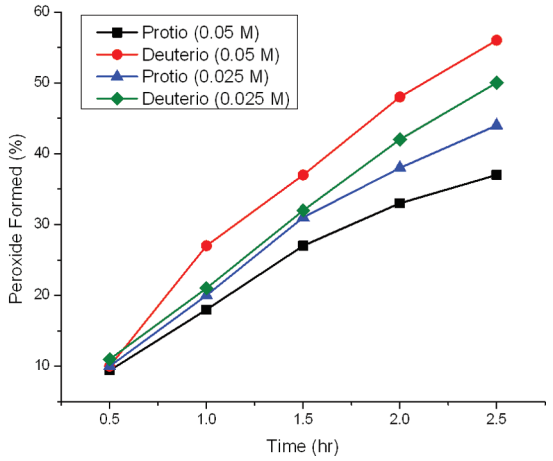
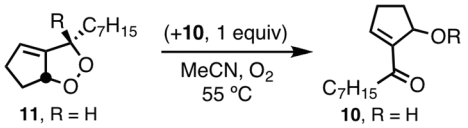


Figure 2. Profile for the percentage of peroxide formed from pyrolysis of protio- and deuterated diazene **9** and **9-d$_1$** as a function of time and concentration of the diazene.



11, R = H
11-d$_1$, R = D

10, R = H
10-d$_1$, R = D

	10 (%)		**10-d$_1$** (%)	
time (h)	from: **11**	**11** + **10**	**11-d$_1$**	**11-d$_1$** + **10**
0.5	3.5	6.4	2.4	5.2
1.0	4.1	16	3.1	6.8
1.5	6.6	44	4.1	9.0
2.0	8.3	50.	5.0	9.7
2.5	11	65	5.2	12

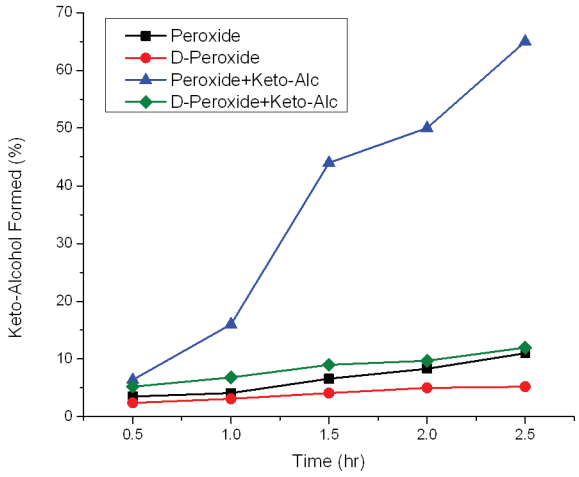


Figure 3. Profile for the percentage of keto-alcohol generated from the pyrolysis of a 0.05 M solution of peroxide in the absence and presence of added **10**.

9-d$_1$, compared with its protio-counterpart, **9**. Why is this so? One option, discussed below, is that the deuterated peroxide, **11-d$_1$**, accumulates because its rate of conversion to the other two products is considerably slower than that of its protio-analogue.

Since we suspected that **11-d$_1$** was the precursor of the other two products, we reheated it to the same temperature in an oxygen-rich solution similar to that used during its genesis, anticipating its facile conversion to **10-d$_1$** and **12-d$_1$**. Such was not the case. Only after prolonged heating (8 h) at elevated temperatures (85 °C) did we observe any sign of a reaction. This impasse led us to wonder whether there was something "special" about the reaction medium that existed as the products were being formed during the reaction with oxygen.

Molecule-Assisted Homolysis. In 1973, Nugteren and Hazelhof reported that the prostaglandin endoperoxide 9α,11α-epidioxy-15(*S*)-hydroxy-13-*trans*-prostenoic acid decomposed with a half-life of only 30 min in an aqueous medium, while in organic solvents the half-life increased to 2 h.[22] Their observation is not unprecedented.[23] It is known, for example, that peroxides are particularly sensitive to bond homolysis in the presence of hydrogen-bond donors and subsequent transformations are often accelerated.[24] We suspected that a similar molecule-assisted homolysis (MAH) pathway might be playing a role in the chemistry of peroxides **11** and **11-d$_1$**. Could it be, for example, that the conversion of the protio-peroxide **11** to the keto-alcohol **10** is facilitated as the concentration of the latter increases?

To explore this hypothesis, we first verified that the [3.3.0] peroxide was the sole precursor to keto-alcohol **10** and keto-aldehyde **12**.[25] With that accomplished, we then used ^{1}H NMR to examine the chemistry of the peroxides as a function of time. To determine whether the presence of keto-alcohol **10** assisted the subsequent transformation of the peroxide, we compared the amount of keto-alcohol **10** and **10-d$_1$** produced when the peroxide was heated, both in its presence and absence. As indicated by the data listed in columns two and three of the table in Figure 3 (note particularly, the values at 2.5 h) and illustrated in the graph, the addition of an equivalent of keto-alcohol *afforded a dramatic increase* in the amount of keto-alcohol generated from the protio-peroxide, **11**.[26] This is consistent with the notion that the keto-alcohol assists in, and increases the rate of conversion of peroxide **11** into keto-alcohol **10**, perhaps through hydrogen-bonding to the peroxide unit in the manner portrayed by **16**. Comparison of the entries in columns three and five of the table in Figure 3 reveals that although the addition of keto-alcohol to the deuterated peroxide, **11-d$_1$**, leads to some **10-d$_1$** formation, the amount

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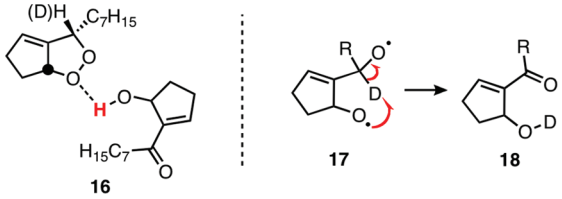
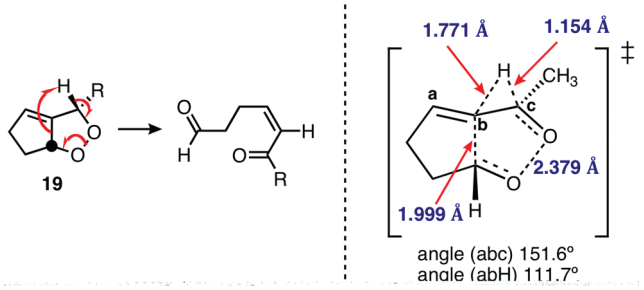
is significantly less than that of the protio-counterpart. While the added keto-alcohol presumably facilitates cleavage of the peroxide bond, the rate of C−D cleavage in the atom transfer step portrayed by the conversion of **17** to **18** is presumably too slow to allow the amount of keto-alcohol to grow significantly during the time frame of the investigation.



Formation of the Keto-aldehyde 12. One of the more challenging aspects of the present investigation was to determine a reasonable mechanism for the conversion of the peroxide, **11**, into the keto-aldehyde, **12**, in a manner that accounts for the *Z*-configuration. Of the options illustrated in Scheme 5, we find that neither pathway *a* involving oxetane **20**, nor pathway *b* involving allene oxide[27] **21** suffice since each leads to an *E*- rather than *Z*-configuration. A similar problem exists for pathways *c* and *d*, each involving a vinyl radical (e.g., **22** or **23**) since rapid equilibration would ensure formation of the more stable *E*-configuration.[28]

We propose that the enone is generated via a *concerted six-electron process* involving cleavage of the peroxide bond in concert with opening of the bridging C−C bond and H-atom transfer in the manner portrayed in Scheme 6. Quantum calculations at the UB3LYP/6-31+G(d) level provide evidence in accord with our predictions. Once we identified a transition structure, an intrinsic reaction coordinate (IRC) calculation was performed in order to supply additional credibility to our proposal. The calculations point to an exothermic transformation with a transition state 36.6 kcal/mol above the equilibrium geometry of the starting peroxide, **19** (Scheme 6). In the transition structure the peroxide bond has lengthened to 2.379 Å while the length of the bridging C−C bond has increased to 1.999 Å. The H-atom transfer to form the *α,β*-unsaturated ketone is just beginning as is evidenced by the finding that the length of the C−H bond undergoing cleavage is 1.154 Å while that to which the migration terminates is 1.731 Å. Most interesting, however, is the angle about the emergent sp^2 center. As the a−b−c angle of the sp^2 center at *b* changes from 139° in the starting material to the *Z*-configuration found in the product, it must pass through a linear geometry. The calculated value of 152° in the transition structure indicates significant progress toward that end.

Scheme 6. Concerted Six-Electron Pathway Leading to the *Z*-Enone



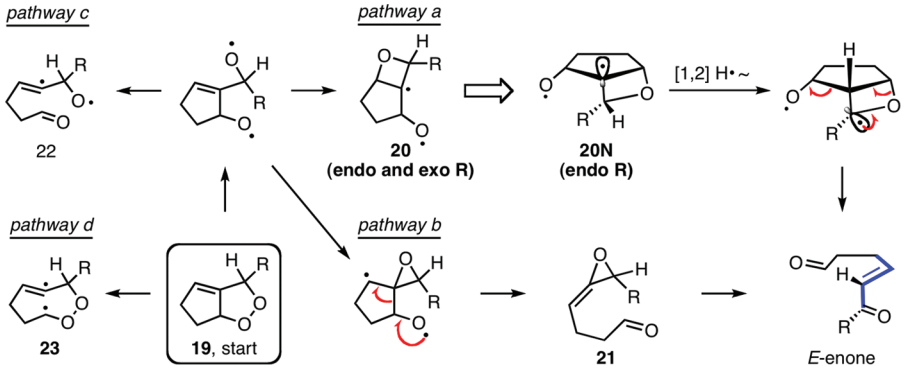
CONCLUSION

The importance of the peroxide functionality is apparent by its widespread presence from biological to industrial applications. As such, the role that seemingly innocuous reaction components have on the decomposition of an otherwise notably stable peroxide bond is significant. When aryl-substituted trimethylenemethane diradical precursors are heated in the presence of molecular oxygen, keto-alcohols like **4** are produced cleanly. The chemical landscape changes dramatically when alkyl-substituted substrates are used. In these instances, a thermally stable [3.3.0] bicyclic peroxide is isolable in addition to the expected keto-alcohol and, interestingly, a *Z*-configured *α,β*-unsaturated keto-aldehyde. Deuterium labeling studies were used to facilitate the elucidation of a mechanism for the transformation of the peroxide to the other two products. In the course of these studies, an unanticipated concentration effect was observed: it is only when heated in the presence of an additive, in this case keto-alcohol **10**, that the deuterated peroxide, **11-d$_1$**, is converted to the other two products. Such is not the case for the protio-counterpart, **11**, in which decomposition is unassisted in the absence of, and accelerated in the presence of, **10**. Further inquiry uncovered molecule-assisted homolysis of the peroxide bond via hydrogen-bonding with the keto-alcohol and the existence of a kinetic isotope effect.

EXPERIMENTAL SECTION

General Procedures. In reactions where water was not present as a solvent, reagent, or byproduct, all glass vessels were flame-dried unless otherwise noted. A slight positive pressure of dry argon was maintained via rubber septum seal during the course of the reaction.

Scheme 5. Mechanistic Options That Fail To Deliver the *Z*-Configuration Found in the Product Enone



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Reagents were purchased from commercial vendors and used as received unless otherwise stated. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. Methanol (MeOH) was distilled from $Mg(OMe)_2$. Ethanol (EtOH) was distilled from $Mg(OEt)_2$. Dichloromethane (CH_2Cl_2) and acetonitrile (MeCN) were distilled from CaH_2. Pyrrolidine was distilled from $Ba(OH)_2$ at atmospheric pressure. Reactions were monitored by analytical thin-layer chromatography on hard layer silica gel-60F-250. Visualization was effected by ultraviolet light (254 nm), followed by staining (*p*-anisaldehyde). Removal of solvents was typically accomplished using a rotary evaporator. Silica gel (60, particle size 0.043−0.063 mm) was used for flash column chromatography. NMR spectra were recorded on a 400, 500, or 600 MHz instrument and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations (or combinations thereof) are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet.

5-Octylidenecyclopenta-1,3-diene (6-Heptylfulvene) (7). To a solution of octanal (100. mg, 0.780 mmol, 1.0 equiv) in dry methanol (0.780 mL, 1.0 M) was added freshly cracked cyclopentadiene (0.159 mL, 1.95 mmol, 2.5 equiv). At room temperature, freshly distilled pyrrolidine (0.0960 mL, 1.17 mmol, 1.5 equiv) was added. The reaction was stirred at room temperature until determined to be complete by TLC (approximately 15 min). Glacial acetic acid (0.0730 mL, 1.25 mmol, 1.6 equiv) was added slowly to the reaction mixture. The crude reaction mixture was poured into water (2 mL) and extracted with ether (3 × 2 mL). The combined organic extracts were washed with $NaHCO_3$ (5 mL), water (5 mL), and brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo. The fulvene was purified by flash column chromatography, eluting with 100% pentane, to afford the product (125 mg, 0.709 mmol, 91%) as a bright yellow liquid. TLC: (100% pentane) R_f^{SM} = 0.05 (red), R_f^{PROD} = 0.6 (blue, UV). ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.55 (dt, J = 3.6, 1.7 Hz, 1H), 6.52−6.51 (m, 1H), 6.46 (t, J = 5.6 Hz, 1H), 6.43 (t, J = 8.0 Hz, 1H), 6.21 (dt, J = 5.1, 1.7 Hz, 1H), 2.52 (t, J = 7.5 Hz, 2H), 1.55−1.52 (m, 2H), 1.35−1.28 (m, 8H), 0.89 (t, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 146.1, 143.7, 133.1, 130.9, 125.8, 119.4, 32.0, 31.3, 29.7, 29.5, 29.3, 22.9, 14.3. IR (neat, cm^{-1}): 3101.64, 3070.78, 2955.04, 2924.18, 2781.44, 1651.12, 1458.23, 1377.22, 1338.64, 1134.18, 898.86, 817.85. HRMS (EI): calcd for $[C_{13}H_{20}]^+$ 176.1565, found 176.1564.

***N,N′*-Dicarbethoxy-2,3-diaza-7-(octylidene)bicyclo[2.2.1]-heptane (8).** A solution of fulvene (80.0 mg, 0.454 mmol, 1.0 equiv) in dry dichloromethane (1.82 mL, 0.25 M) was prepared. Diethyl azodicarboxylate (0.0750 mL, 0.477 mmol, 1.05 equiv) was added at room temperature. The reaction was stored in the freezer at 0 °C. After 12 h, dipotassium azodicarboxylate (881 mg, 4.54 mmol, 10 equiv) was added to the solution. For reactions of >1 g, a mechanical stirrer was installed. The reaction was cooled to 0 °C. Glacial acetic acid (0.400 mL, 6.81 mmol, 15 equiv) was added dropwise to the reaction mixture over 45 min. The reaction mixture was stirred for an additional 4 h at 0 °C and then filtered through a sintered glass funnel, which was subsequently rinsed with ether (10 mL). The crude reaction mixture was neutralized with $NaHCO_3$ (15 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude biscarbamate was carried on to the next reaction as a foamy white solid (158 mg, 0.448 mmol, 98%). Due to "dynamic" processes involving the ethyl carbamate moiety, significantly broadened signals appeared in the NMR; thus, characteristic peaks were identified and no further characterization was carried out. TLC: *step 1*: (50% ether in pentane) R_f^{SM} = 0.99 (blue, UV), R_f^{DEAD} = 0.6 (yellow), R_f^{PROD} = 0.3 (purple); *step 2*: (50% ether in pentane) R_f^{PROD} = 0.3 (blue). ^{1}H NMR (600 MHz; $CDCl_3$): δ 6.56 (s, 2H), 5.30 (d, J = 0.4 Hz, 1H), 4.18 (q, J = 7.1 Hz, 6H), 2.03 (dt, J = 12.2, 6.4 Hz, 2H), 1.85 (t, J = 0.6 Hz, 2H), 1.25 (m, 18H), 0.85 (d, J = 7.1 Hz, 3H).

2,3-Diaza-7-(octylidene-*1-d*)-bicyclo[2.2.1]hept-2-ene (9). A solution of biscarbamate (158 mg, 0.448 mmol, 1.0 equiv) in dry ethanol (4.48 mL, 0.10 M) was prepared in a three-neck round-bottomed flask and degassed by bubbling Ar through the solution while stirring for 30 min. Potassium hydroxide pellets (447 mg, 7.97 mmol, 17.8 equiv) were added at room temperature. A reflux condenser was attached, and the reaction mixture was heated to reflux for 2.5 h. The yellow-colored solution was then cooled to 0 °C. An addition funnel was attached, and a solution of potassium ferricyanide powder (481 mg, 1.46 mmol, 3.25 equiv) in deionized water (3.84 mL, 0.38 M) was added dropwise over 30 min. The reaction was stirred for an additional 2.5 h at 0 °C. The mustard yellow, chalky mixture was then poured into water (20 mL) and ether (20 mL). If necessary, additional water was added to completely dissolve any remaining solids in order to avoid emulsion formation during extraction. The aqueous layer was extracted with ether (7 × 10 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The diazene was purified by flash column chromatography, eluting with a 15−25% ether/pentane gradient as a light yellow oil (480. mg, 0.232 mmol, 52%). TLC: *step 1:* (50% ether in pentane) R_f^{SM} = 0.3 (blue), R_f^{PROD} = 0.0 (white/no stain); *step 2:* (25% ether in pentane) R_f^{PROD} = 0.5 (lime green, UV). ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.41 (d, J = 2.2 Hz, 1H), 5.13 (dt, J = 4.6, 2.6 Hz, 2H), 2.04−1.92 (m, 2H), 1.71−1.60 (m, 2H), 1.36−1.21 (m, 10H), 1.15−1.10 (m, 2H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C NMR (150 MHz; $CDCl_3$): δ 144.8, 117.9, 77.1, 72.9, 32.0, 29.6, 29.3, 29.2, 29.2, 22.9, 21.8, 21.3, 14.3. IR (neat, cm^{-1}): 3018.70, 2926.11, 2854.74, 1479.45, 1456.30, 1377.22, 1284.63, 1273.06, 1112.96. HRMS (ESI) calcd for $[(C_{13}H_{22}N_2) + Na]^+$ 229.1681, found 229.1678.

Pyrolysis of Diazene 9 in the Presence of Molecular Oxygen: Formation of 10−12. A round-bottomed flask containing an internal tube with a sintered glass tip of medium porosity (Figure S1, Supporting Information) and condenser were dried in a vacuum oven overnight and subsequently cooled under argon. A solution of diazene (175 mg, 0.848 mmol, 1.0 equiv) in dry acetonitrile (17.0 mL, 0.05 M) was added to the reaction vessel, and oxygen was bubbled through the solution for 10 min. The solution was heated to 55 °C, with continuous oxygen flow, until the presence of compounds **10−12** were visualized by TLC. After cooling to room temperature, the crude acetonitrile solution was extracted with pentane (5 × 20 mL) to avoid heating and further reaction progress during evaporation of the solvent. The combined pentane extracts were concentrated in vacuo. The products (135 mg, 0.642 mmol, 76%) were separated and purified by, first, performing a prep-TLC with 5% ether in pentane to isolate the peroxide and then 10% ether in pentane to isolate the keto-alcohol and keto-aldehyde. Recovered starting material accounted for an additional 25.0 mg (14%) of the recovered mass and was isolated in the first prep-TLC. TLC: (25% ether in pentane) R_f^{SM} = 0.5 (lime green, UV), $R_f^{PEROXIDE}$ = 0.95 (brown, light UV), $R_f^{KETO\text{-}ALD}$ = 0.25 (blue, UV), $R_f^{KETO\text{-}ALC}$ = 0.2 (maroon, UV).

2-Heptyl-3,4-dioxabicyclo[3.3.0]oct-1(8)-ene (11). 32.0 mg, 0.152 mmol, 18% yield. ^{1}H NMR (600 MHz; $CDCl_3$): δ 5.58 (dq, J = 3.5, 1.8 Hz, 1H), 5.34−5.31 (m, 1H), 4.57−4.54 (m, 1H), 2.89 (dtdd, J = 16.0, 8.0, 3.8, 2.0 Hz, 1H), 2.76 (ddddd, J = 16.0, 8.0, 3.3, 2.2, 1.1 Hz, 1H), 2.21−2.17 (m, 1H), 1.81 (dtd, J = 12.6, 9.3, 7.3 Hz, 1H), 1.74−1.63 (m, 2H), 1.48−1.39 (m, 2H), 1.34−1.23 (m, 8H), 0.87 (t, J = 7.1 Hz, 3H). ^{13}C NMR (150 MHz; $CDCl_3$): δ 157.1, 121.7, 91.6, 78.5, 38.8, 34.6, 32.0, 30.6, 29.7, 29.4, 26.3, 22.9, 14.3; IR (neat, cm^{-1}): 3063.06, 2928.04, 2854.74, 1620.26, 1558.54, 1500.67, 1458.23, 1049.31. HRMS (ESI): calcd for $[C_{13}H_{22}O_2 + Na]^+$ 233.1517, found 233.1521.

1-(5-Hydroxycyclopent-1-enyl)octan-1-one (10). 91.0 mg, 0.434 mmol, 51% yield. ^{1}H NMR (600 MHz; $CDCl_3$): δ 6.83 (t, J = 2.5 Hz, 1H), 5.12 (t, J = 6.0 Hz, 1H), 3.10 (s, 1H), 2.71−2.63 (m, 3H), 2.46−2.40 (m, 1H), 2.34−2.29 (m, 1H), 1.84−1.79 (m, 1H), 1.61 (dd, J = 14.7, 7.4 Hz, 2H), 1.32−1.21 (m, 8H), 0.87 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 201.1, 145.7, 132.8, 75.9, 39.3, 31.9, 31.5, 31.3, 29.5, 29.3, 24.6, 22.8, 14.3; IR (neat, cm^{-1}): 3468.11, 3059.20, 2955.04, 2928.04, 2854.74, 1662.69, 1616.40, 1462.09, 1377.22, 1180.47, 1053.17, 983.73. HRMS (FI) calcd for $[C_{13}H_{22}O_2]^+$ 210.1620, found 210.1611.

(*Z*)-6-Oxotridec-4-enal (12). 12.0 mg, 0.0571 mmol, 7% yield. ^{1}H NMR (600 MHz; $CDCl_3$): δ 9.76 (t, J = 1.4 Hz, 1H), 6.17 (dt, J = 11.4, 1.4 Hz, 1H), 6.07 (dt, J = 11.4, 7.5 Hz, 1H), 2.89 (qd, J = 7.3, 1.3 Hz, 2H), 2.60 (td, J = 7.1, 1.3 Hz, 2H), 2.44 (t, J = 7.4 Hz, 2H), 1.57 (t, J = 7.2 Hz, 2H), 1.28−1.24 (m, 8H), 0.86 (t, J = 6.9 Hz, 3H). ^{13}C

NMR (150 MHz; $CDCl_3$): δ 202.0, 201.7, 145.4, 127.9, 44.5, 43.4, 31.9, 29.4, 29.3, 24.2, 22.8, 22.5, 14.3. IR (neat, cm^{-1}): 3060.11, 2955.04, 2928.04, 2854.74, 2723.58, 1720.56, 1689.70, 1654.98, 1620.26, 1458.23, 1408.08, 1130.32, 1076.32. HRMS (ESI) calcd for $[(C_{13}H_{22}O_2) + Na]^+$ 233.1517, found 233.1515.

2-Heptyl-1,3-dithiane (13). A solution of octanal (12.2 mL, 78.0 mmol, 1.0 equiv) in dry dichloromethane (78.0 mL, 1.0 M) was prepared. Propane-1,3-dithiol (7.83 mL, 78.0 mmol, 1.0 equiv) was added, and the resulting mixture was stirred at room temperature for 1 h. Zinc chloride (5.21 g, 38.2 mmol, 0.49 equiv) was added portionwise at 0 °C, and the reaction mixture was allowed to warm to room temperature slowly. After being stirred for an additional 15 h, the colorless, cloudy solution was washed with water (3 × 20 mL), a 7% KOH solution (3 × 20 mL), and water (3 × 20 mL). The crude reaction mixture was dried over Na_2SO_4, filtered, and concentrated in vacuo. No purification of the crude product was necessary, yielding the dithiane as a pale yellow liquid (17.0 g, 77.8 mmol, 99%). TLC: (10% ether in pentane) R_f^{SM} = 0.4 (blue), R_f^{PROD} = 0.5 (yellow). ^1H NMR (500 MHz; $CDCl_3$): 4.04 (t, *J* = 6.9 Hz, 1H), 2.90−2.79 (m, 4H), 2.13−2.08 (m, 1H), 1.89−1.80 (m, 1H), 1.75−1.71 (m, 2H), 1.52−1.46 (m, 2H), 1.31−1.22 (m, 8H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 47.9, 35.7, 32.0, 30.8, 29.4, 29.3, 26.9, 26.3, 22.9, 14.3. IR (neat, cm^{-1}): 2951.19, 2928.04, 2854.74, 1462.09, 1419.66, 1377.22, 1273.06, 1180.47, 906.57. HRMS (FI) calcd for $[C_{11}H_{22}S_2]^+$ 218.1163, found 218.1139.

2-Heptyl-1,3-dithiane-*2-d* (14). A solution of dithiane (5.00 g, 22.9 mmol, 1.0 equiv) in dry THF (58.7 mL, 0.39 M) was prepared and cooled to −78 °C. A 2.05 M solution of *n*-BuLi in hexanes (11.7 mL, 24.0 mmol, 1.05 equiv) was added dropwise, and the resulting mixture was allowed to warm to room temperature slowly. After being stirred for 1.5 h, the reaction mixture was cooled to 0 °C, and deuterium oxide (3.92 mL, 196 mmol, 8.55 equiv) was added all at once. The crude reaction was warmed to room temperature and extracted with ether (3 × 15 mL). The combined organic extracts were washed with water (3 × 25 mL), a 7% KOH solution (3 × 25 mL), and water (3 × 25 mL). The crude reaction mixture was dried over Na_2SO_4, filtered, and concentrated in vacuo. The deuterated dithiane from three 5.00 g reactions was combined and distilled (115−118 °C, 5 Torr), yielding a clear, colorless liquid (13.4 g, 61.1 mmol, 89%). ^1H NMR (500 MHz; $CDCl_3$): δ 2.90−2.79 (m, 4H), 2.11 (dtt, *J* = 14.1, 4.7, 2.4 Hz, 1H), 1.90−1.81 (m, 1H), 1.81−1.71 (m, 2H), 1.49 (quintet, *J* = 7.5 Hz, 2H), 1.32−1.21 (m, 8H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 47.9, 35.6, 31.9, 30.7, 29.4, 29.2, 26.8, 26.3, 22.8, 14.3. IR (neat, cm^{-1}): 2953.12, 2924.18, 2853.78, 1456.30, 1421.58, 1274.99. HRMS (FI): calcd for $[C_{11}H_{21}DS_2]^+$ 219.1226, found 219.1220.

Octanal-*1-d* (15). To a solution of deuterated dithiane (100. mg, 0.456 mmol, 1.0 equiv) in a 9:1 mixture of acetonitrile and water (0.460 mL, 1.0 M) was added PIFA (391 mg, 0.912 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature until found to be complete by TLC (approximately 35 min). The light yellow solution was neutralized with $NaHCO_3$ and extracted with ether (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The deuterated octanal was purified by flash column chromatography, eluting with 5%−10% gradient of ether in pentane as a light yellow oil (56.0 mg, 0.433 mmol, 95%). TLC: (10% ether in pentane) R_f^{SM} = 0.5 (yellow), R_f^{PROD} = 0.4 (blue). ^1H NMR (500 MHz; $CDCl_3$): δ 2.41 (t, *J* = 7.4 Hz, 2H), 1.62 (quintet, *J* = 7.2 Hz, 2H), 1.31−1.25 (m, 8H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 203.0, 44.10, 43.9, 31.8, 29.2, 22.8, 22.3, 14.3. IR (neat, cm^{-1}): 2955.04, 2924.18, 2853.78, 1715.74, 1464.02, 1456.30, 1378.18. HRMS (EI): calcd for $[C_8H_{15}DO]^+$ 129.1264, found 129.1268.

5-(Octylidene-*1-d*)cyclopenta-1,3-diene (6-Heptylfulvene-*6-d*). See the experimental methods for compound 7 (60.0 mg, 0.338 mmol, 74%). ^1H NMR (500 MHz; $CDCl_3$): δ 6.55−6.51 (m, 2H), 6.47−6.41 (m, 1H), 6.21 (dt, *J* = 5.1, 1.7 Hz, 1H), 2.52 (t, *J* = 7.1 Hz, 2H), 1.53 (quintet, *J* = 7.4 Hz, 2H), 1.37−1.26 (m, 8H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 145.9, 143.6, 133.1, 130.8, 125.7, 119.3, 32.0, 31.2, 29.7, 29.6, 29.4, 22.9, 14.4. IR (neat, cm^{-1}): 3099.71, 3073.67, 2956.01, 2925.15, 2854.74, 1637.62, 1470.77, 1455.34, 1362.75, 1078.24, 886.32, 771.55, 765.77. HRMS (FI) calcd for $[C_{13}H_{19}D]^+$ 177.1628, found 177.1634.

***N,N′*-Dicarbethoxy-2,3-diaza-7-(octylidene-*1-d*)bicyclo-[2.2.1]heptane.** The procedure is the same as that for **8** with exception that the second step, starting with the addition of dipotassium azodicarboxylate, is carried out after 1 h instead of 12 h. The crude biscarbamate was used in the next reaction as a foamy white solid (151 mg, 0.427 mmol, 130%). Due to "dynamic" processes of the ethyl carbamate subunit, significantly broadened signals appeared in the NMR; thus, characteristic peaks were identified and no further characterization was carried out. TLC: *step 1*: (50% ether in pentane) R_f^{SM} = 0.99 (blue, UV), R_f^{DEAD} = 0.6 (yellow), R_f^{PROD} = 0.3 (purple); *step 2*: (50% ether in pentane) R_f^{PROD} = 0.3 (blue). ^1H NMR (400 MHz; $CDCl_3$): δ 6.56 (s, 2H), 4.21 (q, *J* = 7.1 Hz, 4H), 2.05 (td, *J* = 7.1, 2.1 Hz, 2H), 1.89−1.80 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 18H), 0.87 (t, *J* = 6.9 Hz, 3H). HRMS (ESI) calcd for $[(C_{19}H_{31}DN_2O_4) + Na]^+$ 376.2323, found 376.2314.

2,3-Diaza-7-(octylidene-*1-d*)bicyclo[2.2.1]hept-2-ene (9-d_1). See the experimental for compound **9** (30.0 mg, 0.145 mmol, 68%). ^1H NMR (500 MHz; $CDCl_3$): δ 5.39 (d, *J* = 2.6 Hz, 1H), 5.12−5.11 (m, 1H), 2.02−1.91 (m, 2H), 1.66−1.62 (m, 2H), 1.33−1.22 (m, 10H), 1.11 (dd, *J* = 9.4, 1.8 Hz, 2H), 0.89 (t, *J* = 14.0 Hz, 3H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 144.6, 117.8, 72.9, 32.1, 30.0, 29.6, 29.3, 29.2, 29.16, 22.9, 21.8, 21.4, 14.4. IR (neat, cm^{-1}): 3017.73, 2950.22, 2925.15, 2853.78, 1455.34, 1277.88, 1113.93, 925.86. HRMS (ESI) calcd for $[C_{13}H_{21}DN_2 + Na]^+$ 230.1743, found 230.1740.

Pyrolysis of Diazene 9-d_1 in the Presence of Molecular Oxygen: Formation of 10-d_1, 11-d_1, and 12-d_1. See the experimental methods for compound **9** (63.0 mg, 0.300 mmol, 67%).

2-Heptyl-3,4-dioxabicyclo[3.3.0]oct-1(8)-ene-*2-d* (11-d_1). 33.0 mg, 0.157 mmol, 39%. ^1H NMR (600 MHz; $CDCl_3$): δ 5.59 (t, *J* = 1.7 Hz, 1H), 5.34−5.31 (m, 1H), 2.93−2.87 (m, 1H), 2.79−2.74 (m, 1H), 2.20 (dt, *J* = 12.7, 6.3 Hz, 1H), 1.85−1.80 (m, 1H), 1.69 (dqd, *J* = 18.3, 9.2, 5.5 Hz, 2H), 1.49−1.41 (m, 2H), 1.35−1.27 (m, 8H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (150 MHz; $CDCl_3$): δ 157.0, 121.8, 91.5, 78.5, 38.8, 34.5, 32.0, 30.6, 29.7, 29.4, 26.2, 22.9, 14.3. IR (neat, cm^{-1}): 3056.98, 2927.91, 2861.63, 1463.79, 1317.55, 1045.96, 817.67. HRMS (ESI): calcd for $[C_{13}H_{21}DO_2 + Na]^+$ 234.1580, found 234.1577.

1-(5-Hydroxycyclopent-1-enyl)octan-1-one (10-d_1). 16.0 mg, 0.0761 mmol, 19%. ^1H NMR (600 MHz; $CDCl_3$): δ 6.84 (t, *J* = 2.6 Hz, 1H), 5.14−5.12 (m, 1H), 3.09 (s, 1H), 2.67 (td, *J* = 7.5, 3.2 Hz, 3H), 2.48−2.42 (m, 1H), 2.33 (dddd, *J* = 13.7, 8.8, 7.9, 4.1 Hz, 1H), 1.86−1.80 (m, 1H), 1.65−1.60 (m, 2H), 1.31−1.25 (m, 8H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz; $CDCl_3$): δ 201.1, 146.0, 145.8, 75.9, 39.3, 31.9, 31.5, 31.3, 29.5, 29.3, 24.6, 22.8, 14.3. IR (neat, cm^{-1}): 3441.12, 3028.34, 2955.04, 2928.04, 2050.88, 1666.55, 1651.12, 1616.40, 1512.24, 1458.23, 1373.36, 1049.31. HRMS (ESI): calcd for $[C_{13}H_{22}O_2 + Na]^+$ 233.1517, found 233.1519.

(*Z*)-6-Oxotridec-4-enal-*5-d* (12-d_1). 14.0 mg, 0.0665 mmol, 17%. ^1H NMR (600 MHz; $CDCl_3$): δ 9.78 (t, *J* = 1.4 Hz, 1H), 6.08 (dd, *J* = 9.5, 4.6 Hz, 1H), 2.92−2.88 (m, 2H), 2.62 (td, J = 7.08, 2.35 Hz, 2H), 2.45 (t, *J* = 7.4 Hz, 2H), 1.61−1.57 (m, 2H), 1.30−1.25 (m, 8H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (150 MHz; $CDCl_3$): δ 202.0, 201.7, 145.3, 127.9, 44.5, 43.4, 31.9, 29.4, 29.3, 24.1, 22.8, 22.4, 14.3. IR (neat, cm^{-1}): 3024.48, 2955.04, 2924.18, 2854.74, 2816.16, 2715.86, 1728.28, 1681.98, 1612.54, 1408.08, 1373.36, 1149.61, 1080.17. HRMS (ESI) calcd for $[(C_{13}H_{21}DO_2) + Na]^+$ 234.1580, found 234.1580.

General Procedure for ^1H NMR Analysis of Peroxide or Diazene Decomposition. A J Young NMR tube was dried in a vacuum oven overnight and subsequently cooled under argon. A solution of the substrate in dry acetonitrile-d_3 was added to the NMR tube, and oxygen was bubbled through the solution for 20 min. The NMR tube was sealed, and an initial ^1H NMR spectrum was obtained as a baseline measurement. The solution was heated to 55 °C in an oil bath, and subsequent ^1H NMR spectra were recorded at 30-min intervals with an ice bath "quench" before each analysis.

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Quantum Calculations. Calculations carried out at UCSB used Spartan 08 for Macintosh software.[29] Geometries were optimized using the B3LYP/6-31+G(d) method.[30] The transition structure was characterized by a frequency calculation for which there was one and only one imaginary frequency. That the transition structure was an accurate representation for the conversion of the peroxide to the unsaturated keto-aldehyde was verified using an intrinsic reaction coordinate (IRC) calculation that was carried out by Professor D. J. Tantillo at UC Davis.[31]

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all synthesized compounds, a 2D NOESY spectrum for compound **11**, and computational details. 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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