Stereochemical Dependence of Base-Catalyzed Cleavage of Cyclic Peroxy Ketals

Barry B. Snider,* Zhongping Shi, Steven V. O'Neil, Kevin D. Kreutter, and Tracy L. Arakaki

Department of Chemistry, Brandeis University, P. O. Box 9110, Waltham, Massachusetts 02254

Received November 29, 1993•

Base-catalyzed decomposition of cyclic peroxy ketals **1c**, **2c**, **14**, and **16** shows a strong stereochemical dependence. Isomers **2c** and **16** with a pseudoequatorial hydrogen undergo a fast antiperiplanar E2 elimination to afford ene diones **4** and **17** that react further. Ester **1c**, with a pseudoaxial hydrogen and a pseudoequatorial acetate side chain, reacts slowly to form the enolate, which undergoes an S_N2 reaction to give epoxide **3**. Peroxy ketals **14** and **15** are stable in base. Peroxy acetals **19** and **20** undergo a faster E2 elimination with loss of the pseudoequatorial acetal proton to provide alkoxide ester **21** that reacts further.

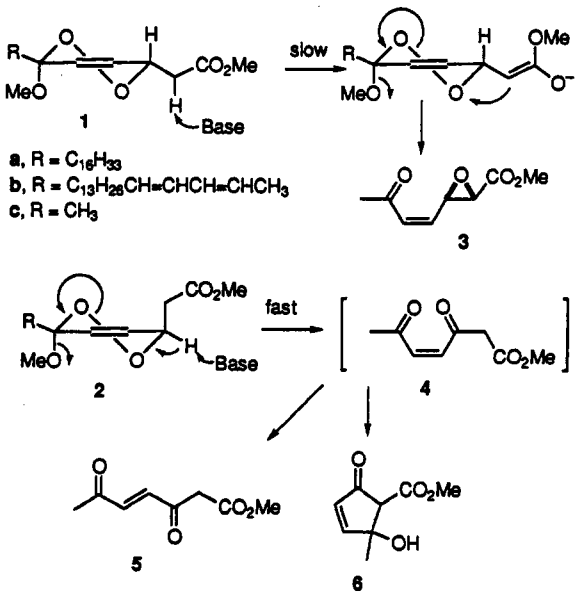
Introduction

We recently reported the first synthesis of plakorin (**1a**) and chondrillin (**2a**) based on the novel, efficient, nonsinglet oxygen photooxygenation of a conjugated enone in the presence of rose bengal lactone or copper sulfate.[1] These peroxy ketals are stable in acid, but, as first observed by Wells,[2] are extremely sensitive to inorganic bases and amines decomposing to unknown products. We were interested in determining the nature of the base-catalyzed decomposition pathway and the effect of peroxy ketal stereochemistry on the rate of the reaction.

These studies are of added interest because the biological activity of these peroxy ketals may be diminished by their instability to base. Alternatively, the biological activity may be due to the decomposition products rather than the peroxides themselves. The biological activity shows a strong dependence on the stereochemistry. Xestin A (**1b**) is 10 times as cytotoxic as xestin B (**2b**) toward P388 cells; xestin A is active against A549 cells while xestin B is inactive.[3] Similarly, chondrillin (**2a**) inhibits the growth of P388 and A549 cells at concentrations (IC_{50}) of 2.4 and 0.3 μg/mL, respectively.[4] The analogous values for synthetic (±)-chondrillin (**2a**) are 3.0 and 0.8 μg/mL, while those for synthetic (±)-plakorin (**1a**) are 1.0 and 1.2 μg/mL.[5] Thus as with the xestins, plakorin (**1a**) is more cytotoxic toward P388 cells than chondrillin (**2a**). Longley and co-workers have recently shown that chondrillin (**2a**) is a very effective inducer of EL-4 cell adherence at 0.4 μg/mL.[4] The analogous values for synthetic (±)-chondrillin (**2a**) and (±)-plakorin (**1a**) are 0.5 and 6.0 μg/mL, respectively.[5] Although plakorin is more cytotoxic toward P388 cells, chondrillin is a more effective inducer of EL-4 cell adherence.

Results and Discussion

We decided to examine the base-catalyzed decomposition of analogues **1c** and **2c** since the shorter side chain



should facilitate identification of the decomposition products. $CuSO_4$-sensitized photooxygenation of methyl 6-oxo-4(*E*)-heptenoate[6] as previously described[1] affords a 1.5:1 mixture of **1c** and **2c**. Base-catalyzed decomposition studies of the mixture were carried out in NMR tubes in CD_3OD or CD_3OD/D_2O (1:1 v/v) at an initial concentration of 0.071 M in **1c** plus **2c** and 0.28 M in pyridine or Et_3N. The rate of the reaction was determined by measuring the decrease in intensity of the alkene hydrogen peaks of **1c** and **2c** and the increase in intensity of the alkene hydrogen peaks of the products. Good data can be obtained from the mixture for both isomers under identical conditions because the peaks for **1c** and **2c** do not overlap. As expected, the reaction is first order in peroxy ketal.[7] Since base is not consumed, the reaction is pseudo first-order and a plot of $\ln[conc]/[conc]_0$ vs time is linear. The half-lives are shown in Table 1.

Decomposition of **2c** with Et_3N (entry 2) proceeds with a half-life of 16 min. Cyclopentenone **6** is formed rapidly but reacts further, decomposing after 2.5 h. The structure of **6** was assigned based on the absorptions at δ 7.70 (dd, 1, J = 5.7, 1.9) and δ 6.29 (d, 1, J = 5.7) that correspond closely to those of similar compounds.[8] Cyclopentenone

• Abstract published in *Advance ACS Abstracts*, March 1, 1994.

(1) (a) Snider, B. B.; Shi, Z. *J. Org. Chem.* **1990**, *55*, 5669. (b) Snider, B. B.; Shi, Z. *J. Am. Chem. Soc.* **1992**, *114*, 1790.

(2) Wells, R. J. *Tetrahedron Lett.* **1976**, 2637.

(3) Quiñoà, E.; Kho, E.; Manes, L. V.; Crews, P.; Bakus, G. J. *J. Org. Chem.* **1986**, *51*, 4260.

(4) Longley, R. E.; McConnell, O. J.; Essich, E.; Harmody, D. *J. Nat. Prod.* **1993**, *56*, 915.

(5) We thank Dr. Ross E. Longley, Division of Biomedical Marine Research, Harbor Branch Oceanographic Institution, Fort Pierce, Florida 34946 for carrying out these assays.

(6) Stork, G.; Sherman, D. H. *J. Am. Chem. Soc.* **1982**, *104*, 3758.

(7) (a) Kornblum, N.; DeLaMare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880. (b) Bell, R. P.; McDougall, A. O. *J. Chem. Soc.* **1958**, 1697.

0022-3263/94/1959-1726$04.50/0

Table 1. Rate of Base-Catalyzed Decomposition of Peroxy Ketals[a]

entry	peroxy ketal	solvent	base	half-life
1	1c	CD_3OD	Et_3N	12 h
2	2c	CD_3OD	Et_3N	16 min
3	1c	CD_3OD	pyridine	no reaction
4	2c	CD_3OD	pyridine	36 h
5	1c	CD_3OD/D_2O	pyridine	183 h
6	2c	CD_3OD/D_2O	pyridine	11 h
7	14	CD_3OD	Et_3N	no reaction
8	15	CD_3OD	Et_3N	no reaction
9	16	CD_3OD	Et_3N	77 min
10	16	CD_3OD	pyridine	240 h
11	19	CD_3OD	pyridine	46 h
12	20	CD_3OD	pyridine	17 h

[a] Decomposition studies were carried out on mixtures of stereoisomers in NMR tubes at an initial concentration of 0.071 M in peroxide and 0.28 M in pyridine or Et_3N.

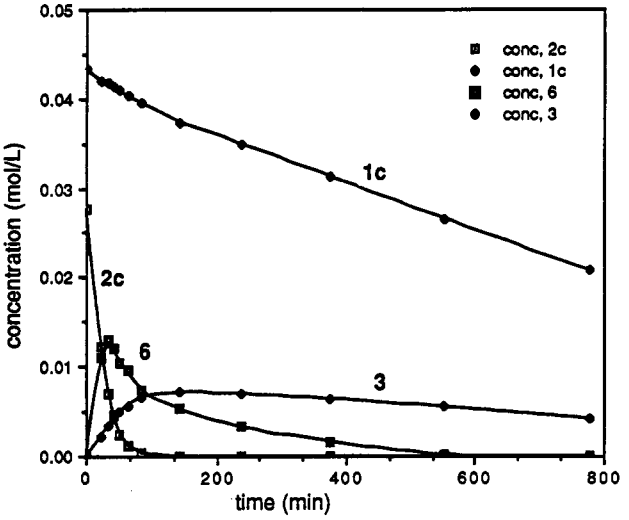
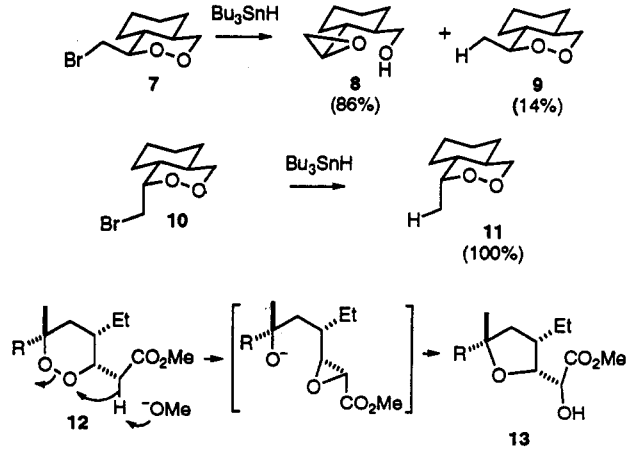


Figure 1. Decomposition of 1c and 2c in Et_3N/CD_3OD.

6 is probably formed by a base-catalyzed E2 elimination of 2c to afford cis ene dione 4, which undergoes a rapid base-catalyzed aldol condensation[9] to give 6. Isomer 1c (entry 1) reacts with Et_3N 45 times more slowly than 2c does with a half-life of 12 h to yield epoxide 3, whose structure was established by the NMR absorptions of the alkene hydrogens at δ 6.61 (dd, 1, J = 11.5, 1.0) and δ 5.72 (dd, 1, J = 11.5, 8.1), and the oxirane hydrogens at δ 4.54 (ddd, 1, J = 8.1, 1.7, 1.0) and δ 3.54 (d, 1, J = 1.7). The connectivity of the four protons was established by decoupling experiments. The chemical shifts and coupling constants correspond closely to those expected for a cis alkene attached to a trans epoxide.[10] Figure 1 shows the concentration of 1c, 2c, 3, and 6 as a function of time. These data make it clear that 2c decomposes to give mainly cyclopentenone 6, while 1c breaks down to afford predominantly epoxide 3. Neither 3 nor 6 can be isolated because they react further.

Why does 2c decompose much faster than 1c and why are different products formed from the two stereoisomers? An analysis of the stereoelectronic requirements for the base-catalyzed reaction and the preferred conformations of 2c and 1c provides an explanation for this unexpected observation. The alkyl groups on 1 and 2 prefer to be pseudoequatorial while the methoxy group prefers to be pseudoaxial due to the anomeric effect. Therefore, peroxy ketal 1 should strongly prefer the conformation shown because both alkyl groups are pseudoequatorial and the methoxy group is pseudoaxial. Peroxy ketal 2 should prefer the conformation shown to a lesser extent since one alkyl group must be pseudoaxial. This is confirmed by the vicinal coupling constants of 1.5 and 4.3 Hz, between the allylic hydrogen and alkene hydrogen in 1c and 2c, respectively.[11] The allylic hydrogen is antiperiplanar to the oxygen–oxygen bond in the preferred conformation of isomer 2c resulting in facile base-catalyzed E2 elimination. The allylic hydrogen is gauche to the oxygen–oxygen bond in the preferred conformation of isomer 1c so that E2 elimination cannot occur. However, enolization of the ester of 1c affords a pseudoequatorial enolate that is properly oriented for an S_N2 reaction to provide epoxide 3. Enolization of the ester of 2c will give a pseudoaxial enolate that is not properly oriented for an S_N2 reaction to provide an epoxide.

To the best of our knowledge there are no examples of the stereochemical dependence of E2 elimination reactions of peroxides.[12] A similar stereochemical dependence was described by Porter in an S_H2 reaction on a cyclic peroxide that proceeded to give an epoxide with an equatorial methylene radical but not with an axial methylene radical.[13] Treatment of 7 with Bu_3SnH provides 86% of epoxide 8 and 14% of reduced peroxide 9. The equatorial methylene radical derived from 8 is properly oriented for backside attack on the peroxide. Similar treatment of 10 affords only the reduced peroxide 11, since the axial methylene radical is not properly oriented for backside displacement on the peroxide. The formation of epoxides by attack of ester enolates on peroxides is also precedented in the sodium methoxide-catalyzed rearrangement of plakortin (12) to tetrahydrofuran 13[14] and in the work of Bartlett who generated peroxide enolates by intramolecular Michael additions of peroxides to unsaturated esters.[15]



The relative rate of decomposition of 1c and 2c is similar with the weaker base pyridine (Table 1, entries 3–6). In CD_3OD, 2c decomposes with a half-life of 36 h, while 1c reacts little after 1000 h. Peroxide 2c decomposes to methyl 3,6-dioxo-4(E)-heptenoate (5) with NMR absorptions at δ 6.96 (d, 1, J = 15.9) and δ 6.80 (d, 1, J = 15.9).[16] Presumably 4 is the initial product and isomerizes to 5,

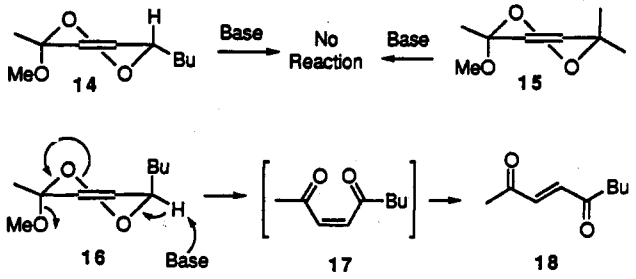
(8) Lolya, D. O.; Freimanis, Ya. F.; Vosekalna, I. A.; Liepinya, A. Ya. *J. Org. Chem. USSR (Engl. Transl.)* **1988**, *24*, 1280. *Zh. Org. Khim.* **1988**, *24*, 1422.

(9) Shono, T.; Hamaguchi, H.; Aoki, K. *Chem. Lett.* **1977**, 1053.

(10) (a) Kondo, S.; Miyamoto, M.; Naganawa, H.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1977**, *30*, 1143. (b) Ceroni, M.; Séquin U. *Helv. Chim. Acta* **1982**, *65*, 302. (c) Ku, T. W.; McCarthy, M. E.; Weichman, B. M.; Gleason, J. G. *J. Med. Chem.* **1985**, *28*, 1847. (d) Adams, W. R.; Trecker, D. J. *Tetrahedron* **1971**, *27*, 2631.

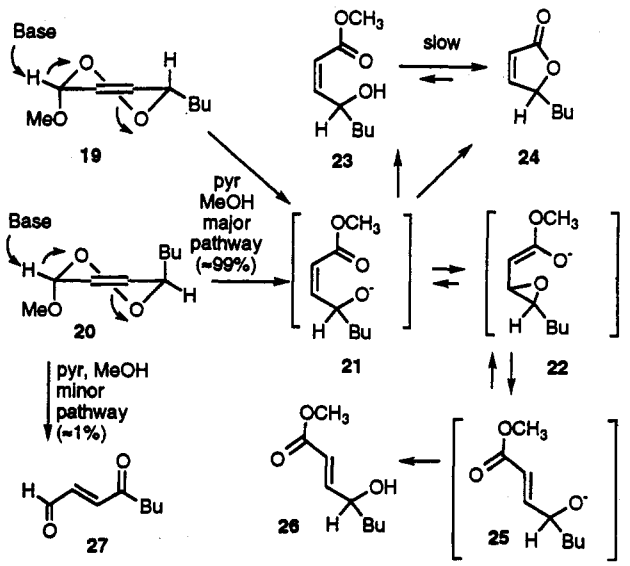
possibly by sequential Michael and retro-Michael reactions. Ene dione **5** reacts further and is no longer observable after 700 h. Decomposition is faster in 1:1 CD_3OD/D_2O; **2c** decomposes with a half-life of 11 h, while **1c** reacts with a half-life of 183 h. In this solvent mixture **2c** decomposes to **6**, which reacts further and is no longer observed after 70 h.

Peroxy ketal **15** and a 1.2:1 mixture of peroxy ketals **14** and **16**[1] were examined to determine the effect of the ester group on the rate of base-catalyzed decomposition (Table 1, entries 7–10).[17] Peroxy ketal **16**, with a hydrogen antiperiplanar to the oxygen–oxygen bond, decomposes with a half-life of 77 min with Et_3N and 240 h with pyridine in CD_3OD at the same concentrations used with **1c** and **2c**. ^1H NMR absorptions[16] characteristic of ene dione **18** were detected at δ 6.89 (d, 1, J = 16.3) and 6.81 (d, 1, J = 16.3) in the pyridine-catalyzed reaction. These results (entries 9 and 10 vs entries 2 and 4) indicate that the ester group of **2c** accelerates the E2 elimination approximately 5-fold over that of **16**, presumably due to the inductive effect of the ester group that will slightly increase the acidity of the abstracted proton.



Peroxy ketals **14**, with a pseudoaxial hydrogen β to the oxygen–oxygen bond, and **15**, with no hydrogens, are stable in Et_3N and CD_3OD and do not form epoxides analogous to **3**. The ester group should have a much greater effect on the rate of epoxide formation than it does on the rate of E2 elimination because the enolate of **1c** is an intermediate in the formation of **3**. Analogous anions are not accessible from peroxy ketals **14** and **15**.

Finally, we examined the pyridine-catalyzed decomposition of a 3:1 mixture of peroxy acetals **19** and **20** in CD_3OD. Both isomers react much more rapidly than **16** to provide unsaturated hydroxy esters rather than ene diones. Cis isomer **19** decomposes with a half-life of 46 h while the trans isomer **20** is somewhat more reactive, decomposing with a half-life of 17 h. The methoxy group is pseudoaxial in both stereoisomers due to the anomeric effect, so that the acetal hydrogen is pseudoequatorial and antiperiplanar to the oxygen–oxygen bond. Since the acetal hydrogen is more acidic than the other allylic hydrogen and is antiperiplanar to the oxygen–oxygen bond, base-catalyzed E2 elimination gives alkoxide **21**, which reacts further to afford a mixture of **23**, **24**, and **26**. These compounds were characterized by the following ^1H NMR absorptions. Cis hydroxy ester **23**: (CD_3OD/pyr) 6.17 (dd, 1, J = 11.7, 8.3), 5.78 (dd, 1, J = 11.7, 1.3); ($CDCl_3$) 6.30 (dd, 1, J = 11.7, 8), 5.86 (dd, 1, J = 11.9, 1.4), 4.90 (m, 1), 3.73 (s, 3).[18] Trans hydroxy ester **26**: (CD_3OD/pyr) 6.68 (dd, 1, J = 16.1, 4.3), 6.33 (dd, 1, J = 16.3, 1.3).[19] Lactone **24**: (CD_3OD/pyr) 7.70 (dd, 1, J = 5.7, 1.5), 6.12 (dd, 1, J = 5.7, 2.0); ($CDCl_3$) 7.45 (dd, 1, J = 5.7, 1.5), 6.11 (dd, 1, J = 5.7, 2), 5.05 (m, 1).[20] Trans enalone **27**, which will be formed from E2 elimination from the other side of peroxide **20** is a very minor product (≈1%) detected by the characteristic absorption of the aldehyde proton in $CDCl_3$ at δ 9.78 (d, 1, J = 6.9 Hz).[21]



The NMR spectra indicate that **23**, **24**, and **26** are formed in an initial 6:5:1 ratio after 19 h. This ratio changes only slowly with time. After 8 days, the ratio has changed to 5:7:1 indicating that hydroxy ester **23** slowly cyclizes to lactone **24**. The reaction was worked up and monitored in $CDCl_3$ for 8 d, during which time the ratio of products changed to 4:10:1. The cyclization of a hydroxy ester related to **23** to give lactones analogous to **24** under very mild conditions has been observed previously.[20a]

The formation of **23**, **24**, and **26** in a ratio that then changes only slowly as **23** cyclizes to **24** indicates that all three are primary products. Presumably, pyridine abstracts the more acidic acetal proton initiating E2 elimination to give alkoxide intermediate **21**. Protonation will provide cis hydroxy ester **23**. Attack of the alkoxide on the ester will afford lactone **24**. Michael addition of the alkoxide will give epoxy enolate **22** that can undergo ring opening after single bond rotation to afford trans alkoxide **25** that will be protonated to give **26**. The base-catalyzed opening of β,γ-epoxy esters to yield γ-hydroxy-α,β-unsaturated esters is well-known.[22] All three products

(11) For an extensive discussion of the conformation of 1 and 2 see ref 3.

(12) For a possibly related example of stereochemical dependence on the base-catalyzed decomposition of peroxides see: Matsumoto, M.; Kuroda, K.; Suzuki, Y. *Tetrahedron Lett.* **1981**, *22*, 3253.

(13) Porter, N. A.; Cudd, M. A.; Miller, R. W.; McPhail, A. T. *J. Am. Chem. Soc.* **1980**, *102*, 414.

(14) Bartlett, P. A.; Chapuis, C. *J. Org. Chem.* **1986**, *51*, 2799.

(15) Higgs, M. D.; Faulkner, D. J. *J. Org. Chem.* **1978**, *43*, 3454.

(16) Castagnino, E.; Corsano, S.; Strappaveccia, G. P. *Tetrahedron Lett.* **1985**, *26*, 93.

(17) A mixture of 14 and 16 shows no inhibitory activity against P388 cells at 5 μg/mL.[3]

(18) Tadano, K.-I.; Morita, M.; Hotta, Y.; Ogawa, S.; Winchester, B.; Cenci de Bello, I. *J. Org. Chem.* **1988**, *53*, 5209.

(19) Nakamura, E.; Inubushi, T.; Aoki, S.; Machii, D. *J. Am. Chem. Soc.* **1991**, *113*, 8980.

(20) (a) Jakubowski, A. A.; Guziec, F. S., Jr.; Sugiura, M.; Tam, C. C.; Tishler, M. *J. Org. Chem.* **1982**, *47*, 1221. (b) Miyashita, M.; Yamaguchi, R.; Yoshikoshi, A. *J. Org. Chem.* **1984**, *49*, 2857. (c) Chen, S.-Y.; Joullié, M. M. *J. Org. Chem.* **1984**, *49*, 2168.

(21) (a) Gunn, B. P. *Tetrahedron Lett.* **1985**, *26*, 2869. (b) Comasseto, J. V.; Brandt, C. A. *Synthesis* **1987**, 146. (c) Sharma, K. K.; Torssell, K. B. G. *Tetrahedron* **1984**, *40*, 1085. (d) MacLeod, J. K.; Bott, G.; Cable, J. *Aus. J. Chem.* **1977**, *30*, 2561.

23, 24, and 26 can thus be formed as primary products from alkoxide 21.

In conclusion, the base-catalyzed decomposition of peroxy ketals shows a strong stereoelectronic preference. Stereoisomers 2c and 16 in which a hydrogen is antiperiplanar to the oxygen–oxygen bond decompose rapidly to give ene diones 4 and 17. Stereoisomer 1c with the acetate side chain antiperiplanar to the oxygen–oxygen bond decomposes slowly to afford epoxy ester 3, while 14 with the hydrogen gauche to the oxygen–oxygen bond is base-stable. Both stereoisomeric peroxy acetals 19 and 20 decompose rapidly by E2 elimination with abstraction of the acetal proton that is antiperiplanar to the oxygen–oxygen bond to provide hydroxy esters 23 and 26 and lactone 24.

Experimental Section

Preparation of Peroxides. Peroxy ketals 14–16, 19, and 20 were prepared as previously described.[1b] Peroxy ketals 1c and 2c were prepared from methyl 6-oxo-4(*E*)-heptenoate[6] using the copper sulfate-sensitized procedure previously used to prepare 1a and 2a:[1b] ^{1}H NMR δ (1c) 6.05 (dd, 1, *J* = 10.1, 1.5), 5.87 (dd, 1, *J* = 10.1, 2.2), 5.00–5.06 (m, 1), 3.72 (s, 3), 3.40 (s, 3), 2.63 (dd, 1, *J* = 16.1, 7.4), 2.51 (dd, 1, *J* = 16.1, 6.6), 1.38 (s, 3); (2c) 6.14 (dd, 1, *J* = 10.1, 4.3), 5.90 (dd, 1, *J* = 10.1, 1.7), 4.75–4.83 (m, 1), 3.73 (s, 3), 3.41 (s, 3), 2.94 (dd, 1, *J* = 16.0, 8.1), 2.64 (dd, 1, *J* = 16.0, 5.3), 1.37 (s, 3); ^{13}C NMR δ (1c) 169.8, 129.2, 128.0, 98.0, 73.2, 51.8, 50.8, 36.1, 20.0; (2c) 170.6, 128.1, 127.6, 98.4, 73.4, 51.7, 50.6, 36.8, 20.5.

Preparation of Peroxides with a 350 nm Blacklight. The photooxygenation procedure we have developed[1b] uses a 275-W sun lamp that is no longer manufactured. We therefore explored alternate lamps for the photooxygenation. Excellent yields of peroxy hemiketals are formed with 350-nm long-wave UV lamps, while none of the desired product is formed with 254-nm or 300-nm UV lamps.

Oxygen was bubbled into a solution of 3-nonen-2-one (229 mg) and $CuSO_4$ (14 mg) in 150 mL of 19:1 CH_2Cl_2–MeOH in a Pyrex tube suspended in a multilamp photochemical reactor (Rayonet) equipped with 18 GE or Sylvania F8T5 BLB 350 nm lamps. The solution was irradiated for 17 h while being cooled by a fan. Additional solvent was added as needed every 5 h. The reaction was worked up as previously described and the crude mixture of peroxy ketals and hemiketals was treated with TsOH in MeOH to afford 14 and 16. Flash chromatography (15:1 hexane–EtOAc) gave 72% of a mixture of 14 and 16.

Base-catalyzed decompositions of 1c and 2c were carried out in NMR tubes and were monitored periodically by ^{1}H NMR at 300 MHz. Mixtures were ≈0.071 M in 1c and 2c [7 mg/0.5 mL of CD_3OD or 1:1 (v/v) CD_3OD/D_2O] and 0.28 M in pyridine (11 μL/0.5 mL) or Et_3N (19 μL/0.5 mL). The rate of decomposition was monitored by comparison of the peak height at δ = 6.05 (1c) and δ = 6.14 (2c) versus the CD_2HOD peak at δ = 3.35 for the pyridine reactions. A benzene standard was used for the Et_3N reaction. From the series of NMR spectra, a plot of ln-[conc]/[conc]$_0$ versus time was constructed and the half-lives were determined.

Base-Catalyzed Decomposition of 19 and 20. Distilled dry pyridine (11 μL) was added to a solution of peroxy acetals 19 and 20 (6 mg) in dry CD_3OD (0.5 mL) in an NMR tube. The concentration of the sample was 0.070 M in acetals 19 and 20 and 0.233 M in pyridine. The solution was monitored by ^{1}H NMR for 8 d by which time all of 19 and 20 had reacted. The solution was poured into water and extracted with three portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in $CDCl_3$ and monitored by ^{1}H NMR for 8 d. The half-lives of 19 and 20 were determined by comparing the peak heights at δ 4.6 for 19 and δ 4.2 for 20 to the methyl peak at δ 1.25 of a small amount of diethyl ether present in the solution.

Acknowledgment. We are grateful to the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. We thank Mr. Xinyi Huang for experimental assistance.

(22) (a) Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7550. (b) Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1691.