Preparation of Unsymmetrically Labeled Hydroperoxides. A Hydroxamate Ester−Nitrosation Approach

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Reaction of *O*-tertiary alkyl arylhydroxamate esters with nitrosyl chloride gives *O*-tertiary alkyl aryl peresters that can be hydrolyzed to the hydroperoxide. If the hydroxamate ester carbonyl oxygen or nitrosyl chloride is labeled with ^{18}O, the label appears in the product hydroperoxide's terminal oxygen. This strategy, which derives from the pioneering work of Koenig, permits the preparation of a variety of (2-^{18}O) hydroperoxides, including tertiary alkyl and cumyl hydroperoxides. *tert*-Butyl α-hydroperoxyisobutyrate, **27**, prepared in this way with an ^{18}O label in the terminal oxygen, serves as a useful precursor for the preparation of other unsymmetrically labeled peroxides and hydroperoxides. Hydroperoxide **27** is protected as a perketal with 2-methoxypropene, and a six-step sequence involving Dibal-H reduction, oxidation (PDC), and Wittig chemistry provides the allylic hydroperoxide **12** that is used in mechanistic studies. Hydroxamate esters that give peresters prone to undergo the Criegee rearrangement upon reaction with NOCl do not give useful yields of product hydroperoxides in the transformation and one hydroxamate ester **17** that reacts via an allylalkoxyl radical gives epoxides **20a** and **20b** as the major isolable products of reaction.

Alkyl hydroperoxide chemistry is of significance to many areas of organic and biological chemistry. The mechanisms of reactions involving hydroperoxides have been extensively studied by a variety of techniques, and these studies have provided a basic framework for understanding autoxidation and other reactions involving hydroperoxides.[1] One aspect of hydroperoxide reactions which has never been addressed is the specific fate of individual oxygens of the functional group in the reactions of these important compounds. Such studies have not been possible because there has been no method for distinguishing between the two oxygens of a hydroperoxide.

Hydroperoxides specifically labeled with ^{18}O in only one of the two peroxyl oxygens would provide a unique and powerful tool for studying hydroperoxide reaction mechanisms. The potential uses of such specifically labeled hydroperoxides are numerous and of broad scope. Such compounds would be useful for the study of the mechanisms of nucleophilic attack on alkyl hydroperoxides, metal-catalyzed oxidations involving alkyl hydroperoxides, reactions of peroxyl radicals, and biological reactions involving hydroperoxide intermediates.

The preparation of unsymmetrically labeled hydroperoxides has proven to be a challenging problem, due to the difficulty in distinguishing synthetically between two atoms which are otherwise identical. Alkyl hydroperoxides are generally prepared through C−O bond formation, and syntheses utilize reagents such as molecular oxygen or hydrogen peroxide in which the O−O bond is already intact.[1b] For example, the reaction of hydrogen peroxide with alkyl halides,[2] the singlet oxygenation of alkenes,[3] and the autoxidation of hydrocarbons all result in the formation of hydroperoxides. By carrying out these reactions with either $H^{18}O^{16}OH$ or $^{16}O^{18}O$, unsymmetrically labeled hydroperoxides may be prepared, but the hydroperoxides formed in these reactions consist of a mixture of $R^{16}O^{18}OH$ and $R^{18}O^{16}OH$. Such a mixture would not be useful in mechanistic studies, unless some means could be found to separate the isotopic compounds.[4]

Construction of the O−O bond in a peroxide or hydroperoxide synthesis would provide the possibility of separately labeling each oxygen of the functional group, but there are few examples of O−O bond-making reactions. Perhaps the only convincing example of nucleophilic attack by oxygen on oxygen that forms an O−O bond occurs in the ketone-catalyzed decomposition of caroate (HSO_5^-) that leads to the formation of dioxiranes.[5] Such reactions are not general, however, and no examples could be found of analogous nucleophilic transformations leading to acyclic peroxides (or for that matter, we found no reports of cyclic peroxide synthesis by this approach other than the dioxiranes).[6]

In contrast to the paucity of examples of nucleophilic peroxide bond formation, there are numerous examples of oxygen−oxygen bond formation by radical coupling reactions. For example, termination of autoxidation occurs through the free radical coupling of two peroxyl radicals to generate an unstable tetroxide intermediate. Radical-mediated peroxide bond formation also occurs in the homolytic decomposition of compounds such as diacyl

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(1) (a) Davies, A. G. In *Organic Peroxides*; Davies, A. G., Ed.; Butterworth: London, 1961; p 128. (b) Porter, N. A. In *Organic Peroxides*; Ando, W., Ed.; John Wiley & Son, Ltd.: Chichester, England, 1992; p 101. (c) Hiatt, R. In *Organic Peroxides*; Swern, D., Ed.; John Wiley & Sons: New York, 1971; Vol. II; p 60. (d) Plesinicar, B. In *The Chemistry of Peroxides*; Patai, S., Ed.; John Wiley & Sons Ltd.: Chichester, 1983; p 521.

(2) Cookson, P. G.; Davies, A. G.; Roberts, B. P. *J. Chem. Soc., Chem Commun.* **1976**, 1022.

(3) Foote, C. S.; Uhde, G. *Org. Photochem. Synth.* **1971**, *1*, 60.

(4) We have attempted, without success, to separate such hydroperoxide mixtures by pH controlled reverse-phase HPLC, S. E. Caldwell, Duke University Thesis, 1995. For reports of chromatographic separation of isotopically labeled benzoic acids, see: (a) Tanaka, N.; Araki, M. *J. Am. Chem. Soc.* **1985**, *107*, 7780. (b) Tanaka, N.; Yamaguchi, A.; Araki, M. *J. Am. Chem. Soc.* **1985**, *107*, 7781. (c) Tanaka, N.; Araki, M. *J. Chromatogr.* **1986**, *352*, 307.

(5) (a) Edwards, J. O.; Pater, P. H.; Curci, R.; Furia, F. D. *Photochem. Photobiol.* **1979**, *30*, 63. (b) The case for dioxirane synthesis contained in ref 5a was made complete by the isolation (in solution) of the dioxirane. Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.

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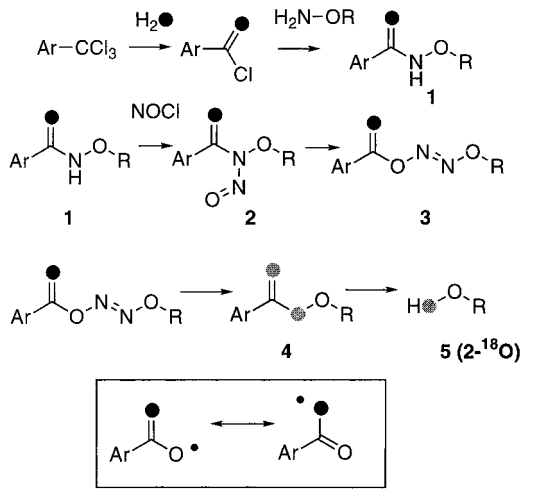
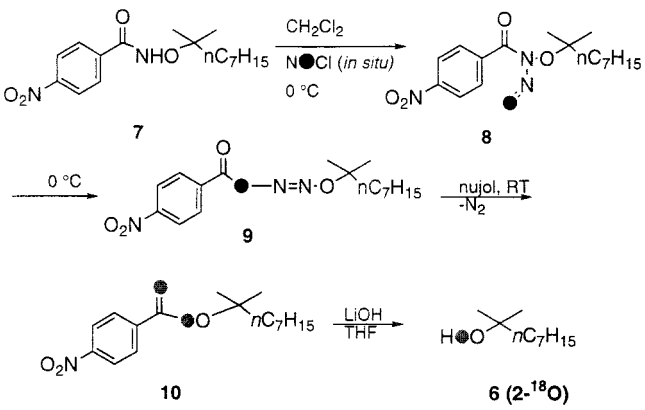
Scheme 1



Scheme 2



peroxides and peresters, where radical coupling of caged benzoyloxy or benzoyloxy−alkoxyl radical pairs has been demonstrated.[8]

Yet another example of free radical mediated oxygen−oxygen bond formation occurs in the decomposition of *N*-nitroso hydroxamate esters. These compounds, prepared by nitrosation of the corresponding hydroxamates, decompose to give peresters and other products that result from an apparent acyloxyl−alkoxyl radical pair. Koenig, Hoobler, and Deinzer[9] clarified the steps involved in this complex reaction sequence in a series of pioneering experiments, and their research provides the foundation of our strategy for the preparation of unsymmetrically labeled hydroperoxides, which we describe herein.[10]

Results and Discussion

The synthetic strategy for the preparation of a labeled hydroperoxide is presented in Scheme 1. Label in the hydroperoxide product **5** could in principle be derived from either of the oxygens on the hydroxamate ester, **1**, or from the nitrosating agent, NOCl. In practice, we have confined our source of label to the carbonyl oxygen of **1** or to labeled nitrosyl chloride, ^{18}O label for both of these compounds coming from $H_2(^{18}O)$. Carbonyl-labeled **1** can be prepared by reaction of *O*-alkylhydroxylamine with labeled aryloyl chloride. This acid chloride is prepared from labeled water and the appropriate trichloromethyl aromatic compound as shown in the scheme. Introduction of label in this way is reasonably efficient since the sequence leading from labeled water through benzoyl chloride to **1** occurs in excellent overall yield. The preparation of labeled nitrosyl chloride by exchange of label into sodium nitrite and its subsequent reaction with concentrated aqueous $(H_2{}^{18}O)$/ HCl uses label much less efficiently. We include procedures involving this strategy here since a terminally labeled hydroperoxide with high isotopic enrichment would require the use of both labeled aryloyl chloride and nitrosyl chloride.

In this synthetic approach to unsymmetrically labeled hydroperoxides, the label is carried undiluted from water to the acyl hyponitrite, **3** (undiluted labeled oxygen is indicated by ● in the scheme). The conversion of **3** to **4** occurs by fragmentation of the hyponitrite to give molecular nitrogen and the acyloxyl−alkoxyl radical pair. In this pair, the acyloxyl oxygens become equivalent and the label is scrambled between the carbonyl and peroxo positions of the perester **4**. This exchange is shown in the inset in Scheme 1. If unlabeled NOCl is used in the procedure, the product hydroperoxide formed has 50% of the original label in the terminal position of the hydroperoxide, **5**, as shown in structures **4** and **5**. The terminally labeled hydroperoxide is designated in the formula by (2-^{18}O). Proximally labeled hydroperoxide is designated (1-^{18}O) since this oxygen has higher priority by virtue of its substitution.

Koenig's original studies of the hydroxamate rearrangement all involved the use of *O*-*tert*-butyl hydroxamates that give *tert*-butyl peresters upon reaction with NOCl. Hydrolysis (or methanolysis) of the perester was attempted by Koenig, and his studies provided indirect evidence for formation of *tert*-butyl hydroperoxide, which was never isolated.[11]

2-Methyl-2-nonyl Hydroperoxide ^{18}O Labeled in the Terminal Peroxide Position, 6 (2-^{18}O). Koenig's original work on the hydroxamate rearrangement led to *tert*-butyl peresters of several aromatic acids. We repeated Koenig's experiments and hydrolyzed the peresters but found that isolation of *tert*-butyl hydroperoxide was indeed difficult on reactions carried out on a small scale, a necessity when working with labeled precursors. In response to this, we adjusted our target and carried out experiments directed at preparing *tert*-alkyl hydroperoxides that are less volatile than the *tert*-butyl compound.

We describe here our strategy for preparing 2-methyl-2-nonyl hydroperoxide **6** labeled with ^{18}O in the terminal oxygen starting from hydroxamate ester **7**. In this experiment, we used N^{18}OCl as a source of label as outlined in Scheme 2. The most consistent results were

(6) After our first report of the preparation of an unsymmetrically substituted hydroperoxide, see ref 7, a report appeared of the use of HOF to convert *tert*-butyl alcohol to *tert*-butyl hydroperoxide. HOF is reactive with a number of organic functional groups and would likely not be useful as a general reagent for the preparation of hydroperoxides, Zang, Y.; Kim, J.; Dong, Y. H.; Wilkinson E. C.; Appelman, E. H.; Que, L. *J. Am. Chem. Soc.* **1997**, *119*, 4197.

(7) Caldwell, S. E.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 8676.

(8) (a) Koenig, T.; Deinzer, M.; Hoobler, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 938. (b) Martin, J. C.; Hargis, H. *J. Am. Chem. Soc.* **1969**, *91*, 5399.

(9) (a) Koenig, T.; Hoobler, J. A.; Mabey, W. R. *J. Am. Chem. Soc.* **1972**, *94*, 2514. (b) Koenig, T.; Deinzer, M. *J. Am. Chem. Soc.* **1966**, *88*, 4518. (c) Koenig, T.; Deinzer, M. *J. Am. Chem. Soc.* **1968**, *90*, 7014. (d) Koenig, T. *Tetrahedron Lett.* **1973**, 3487.

(10) Preliminary reports of some of the transformations reported here have appeared, see ref 7 and Lowe, J. R.; Porter, N. A. *J. Am. Chem. Soc.* **1997**, *119*, 11534.

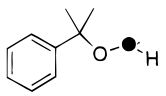
(11) Koenig reacted the methanolysis product mixture with benzoyl chloride and found *tert*-butyl perbenzoates as a product.

obtained by generating nitrosyl chloride in situ by bubbling HCl(g) into a two-phase reaction solution consisting of 2.88 M $NaNO_2$ and *N*-*p*-nitrobenzoyl-*O*-2-methyl-2-nonylhydroxylamine **7** in dichloromethane. The progression of the reaction could be monitored by ^1H NMR. Although the chemical shift of the geminal dimethyl proton singlet overlapped somewhat with the other protons of the nonyl chain, it was clearly distinguishable. The chemical shifts for the products of the nitrosation (acetone insert tube, TMS reference) are as follows: 2-methyl-2-nonyl hydroxamate ester **7**, 1.33 ppm; *N*-nitroso derivative **8**, 1.21 ppm; hyponitrite **9**, 1.43 ppm; perester **10**, 1.34 ppm.

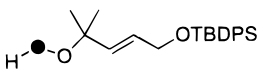
Perester **10** isolated by this procedure after reaction with labeled NOCl (generated in situ from $NaN^{18}O_2$, prepared in an exchange reaction of $Na^{16}O_2$ with $H_2{}^{18}O$)[12] was obtained in yields that ranged from 22 to 32%. Analysis of the perester by mass spectrometry indicated that the extent of ^{18}O incorporation was 54%. ^{13}C NMR analysis of the acyl carbon revealed three peaks, with chemical shifts of 162.397, 162.417, and 162.429, while analysis of the ether type carbon revealed a single peak at 86.97 ppm. In general, substitution with ^{18}O causes an upfield shift in the ^{13}C NMR spectra of directly attached carbons.[13] The results are consistent with a mixture of peresters labeled with ^{18}O in one of the oxygens attached to the carbonyl carbon along with unlabeled perester.

Hydrolysis of 2-methyl-2-nonyl-*p*-nitroperbenzoate **10** was carried out with $LiOH{\bullet}H_2O$ in THF−water. Hydrolysis of the ^{18}O-labeled perester yielded 2-methyl-2-nonyl hydroperoxide **6 (2-^{18}O)** in 52% yield. Mass spectrometry analysis of the hydroperoxide indicated that the extent of ^{18}O incorporation was 26%. The fragment ion $m/z = 157$ resulting from the loss of H_2O from MH^+ contained no evidence of isotopic oxygen. A single peak was observed at 82.959 ppm for the carbon adjacent to the hydroperoxyl group by ^{13}C NMR analysis. This suggests a product hydroperoxide labeled with ^{18}O in its terminal oxygen only, the expected result from nitrosation with $N^{18}OCl$. Approximately half of the ^{18}O present in the perester remained in the hydroperoxide after hydrolysis, indicating that randomization of the ^{18}O label at the stage of hyponitrite to perester was essentially 100%.

With the Koenig approach to unsymmetrically labeled hydroperoxide established for a tertiary alkyl hydroperoxide, we next turned our attention to the preparation of labeled cumyl hydroperoxide **11** and the allylic hydroperoxide **12**. Cumyl hydroperoxide is of interest since it



11 (2-^{18}O)



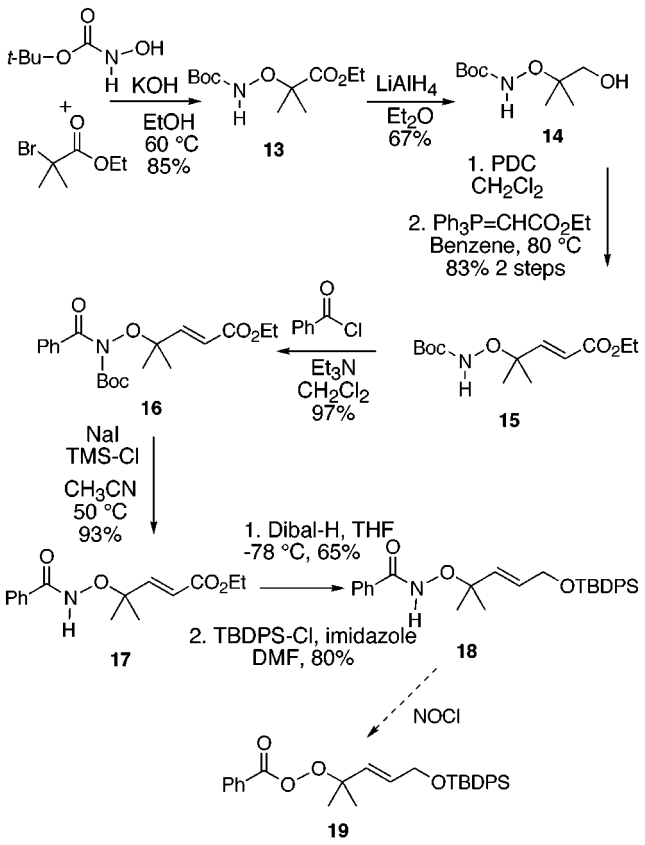
12 (2--^{18}O)

lies on one of the commerically important routes to phenol, and **12** labeled in the terminal position has provided important mechanistic insight into the nature of the Schenk hydroperoxide rearrangement.[10]

Cumyl Hydroperoxide ^{18}O Labeled in the Terminal Peroxide Position, 11 (2-^{18}O). Labeled *N*-benzoyl-*O*-cumylhydroxylamine (66% ^{18}O in the benzoyl carbonyl)

(12) Rajendran, G.; Etten, R. L. V. *Inorg. Chem.* **1986**, *25*, 876.
(13) Risley, J. M.; Etten, R. L. V. *J. Am. Chem. Soc.* **1980**, *102*, 4609.

Scheme 3



was converted to cumyl perbenzoate by the procedures described for preparation of the tertiary alkyl hydroperoxide. Attempts to purify the perester reaction product, cumyl perbenzoate, resulted in decomposition, and hydrolysis (LiOH, THF, H_2O) was therefore carried out on the crude mixture that resulted from the nitrosation. Chromatographically pure cumyl hydroperoxide was isolated in ~25% yield in the sequence from hydroxamate ester to hydroperoxide. Analysis by GC/CIMS indicated that the incorporation of ^{18}O into cumyl hydroperoxide **11 (2-^{18}O)** was 49% if labeled NOCl was used in the transformation, while hydroperoxide with 33% label was obtained in the conversion of labeled hydroxamate ester with unlabeled NOCl. Reaction of the hydroperoxides with triphenylphosphine resulted in triphenylphosphine oxide with essentially all of the label transferred from the hydroperoxide. Analysis of the hydroperoxide by carbon NMR with increased digitization gave a single peak for the hydroperoxyl carbon.

Synthesis of the Unsymmetrically ^{18}O-Labeled Allyl Hydroperoxide, 12 (2-^{18}O). Three approaches were ultimately required to complete the synthesis of terminally labeled **12**. All three approaches are reported here because the series of experiments involved gave interesting and instructive results. The first approach anticipated a nitrosation reaction on a fully functionalized hydroxamate ester, **18**, which would lead directly to the desired hydroperoxide upon hydrolysis.

Hydroxamate ester **18** was synthesized according to Scheme 3. *tert*-Butyl *N*-hydroxycarbamate was coupled to ethyl α-bromo isobutyrate in ethanolic potassium hydroxide to give the Boc-protected alkoxylamine derivative **13**. Precedent for this reaction comes directly from the literature for the corresponding ethyl carbamate

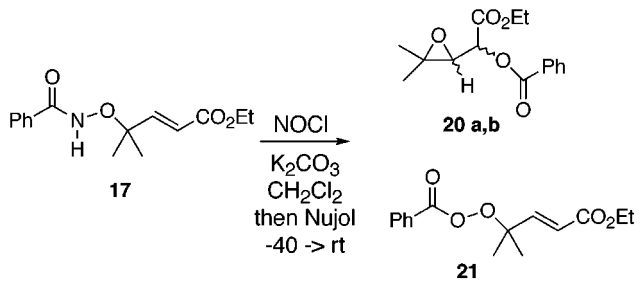
derivative.[14] Reaction with lithium aluminum hydride selectively reduced the ethyl ester, again according to literature precedent, to give alcohol **14**. The carbamate remains untouched in this reaction presumably because the loss of the relatively acidic proton forms a "protective anion" in this region.[15] Oxidation with PDC gave the aldehyde which was not purified but subjected to a Wittig olefination reaction to give the (*E*)-unsaturated ester **15**. Only a minor amount of the (*Z*)-olefin could be detected in this reaction, and it is effectively removed by column chromatography. Acylation with benzoyl chloride proceeded in 97% yield to give **16**, and the Boc group was subsequently removed with the in situ generation of trimethylsilyl iodide[16] to give hydroxamate ester **17**. It should be noted that attempted removal of the Boc protecting group from **15**, and all other related derivatives leading to free alkoxylamines, resulted in decomposition. The allylic alcohol was obtained by selective reduction of the α,*β*-unsaturated ester with diisobutylaluminum hydride at −78 °C, and reaction with chloro *tert*-butyldiphenylsilane gave the desired hydroxamate ester **18**.

The successful synthesis of **12** from **18** went uncelebrated, however, because attempted reaction of **18** with NOCl failed to give the anticipated perester **19**. The reaction was also performed and immediately followed by in situ hydrolysis with LiOH:H_2O, although this did not result in the isolation of any of the desired hydroperoxide **12**. Several attempts were made with many different conditions of nitrosation including the use of $NOBF_4$, a solid commercial nitrosating agent, but under no conditions attempted was perester **19 i**solated. The products from the nitrosation reactions included those due to loss of silicon and presumably from the addition of NOCl across the olefin, although these products were not found. Synthesis of **19**, from independently prepared **12** and benzoyl chloride, was also unsuccessful. We note that Criegee rearrangement of peresters such as **19** would be expected to be facile, and syntheses proceeding through this intermediate may have this rearrangement as the root cause of failure.[17−19]

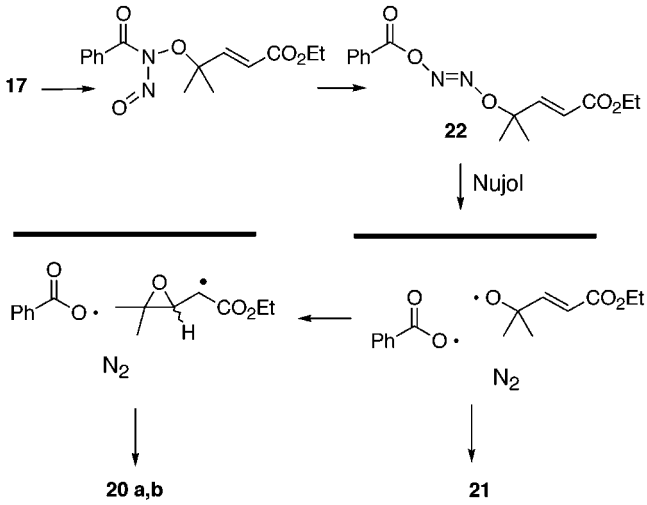
An alternative approach to the synthesis of labeled **12 w**as to form the labeled perester at an earlier stage in the synthesis and to carry out further manipulations on the resulting labeled hydroperoxide in a protected form. On the basis of literature precedents for Criegee rearrangements, we anticipated that the perester substituted with electron deficient groups on the alkyl side of the perester would be less likely to rearrange than would **19**. With this in mind, hydroxamate ester **17** was investigated next in reactions with NOCl.

The results from the nitrosation of **17** are presented in Scheme 4. The major products isolated were determined to be a 9:1 mixture (by ^{1}H NMR) of diastereomeric epoxides **20a** and **20b** and the desired perester **21**. The mixture was obtained in 39% combined yield, but was found to be inseparable by flash column chromatography. Instead, normal-phase HPLC was found to be successful

Scheme 4



Scheme 5



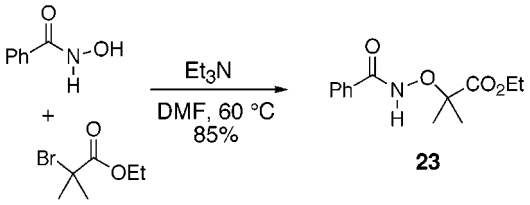
in separating **20a**,**b** from **21** for characterization purposes. Products **20** were determined to be a 1:1 mixture by ^{1}H NMR and by GC.

The formation of epoxides **20** and perester **21** is rationalized in Scheme 5. Upon reaction to give the *N*-nitroso product, it is proposed that the formation of the hyponitrite **22** occurs as expected. Upon thermal decomposition of **22**, radicals are subsequently formed in the solvent cage as shown in Scheme 5 and the intermediate alkoxyl can undergo a well-known oxiranyl rearrangement.[20] In-cage coupling of benzoyloxyl and the alkoxyl radical gives the perester **21**, while coupling of benzoyloxyl and the prochiral oxiranyl radical gives a 1:1 mixture of epoxides **20a,b**.

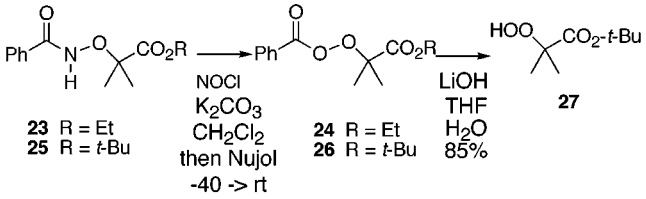
All efforts to alter this 9:1 product ratio failed and resulted only in decreased yields. Hyponitrite **22** was found to be relatively stable at 0 °C. Decompositions carried out at temperatures elevated slightly above room temperature resulted in the same 9:1 ratio as judged by NMR, but with lower yields. Only 11% of the 9:1 mixture was obtained from decomposition of **22** at 30 °C, and 10% was obtained at 40 °C. This is in comparison to the 39% yield for decompositions of **22** at room temperature. Another important aspect of these results is that the formation of products **20a,b** and **21** must be from in-cage recombination processes, therefore consistent with the postulated pathway in Scheme 5. These results are also consistent with a significant cage effect for the formation of the products.

(14) Rudchenko, V. F.; Shevchenko, V. I.; Kostanovskii, R. G. *Chem. Heterocycl. Cmpd.* **1989**, *25*, 330.
(15) Riddell, F. G.; Berry, M. H.; Turner, E. S. *Tetrahedron* **1978**, *34*, 1415.
(16) Hermkins, P. H. H.; Marseveen, J.; Ottenheim, H. C. J.; Kruse, C. G.; Scheeren, H. W. *J. Org. Chem.* **1990**, *55*, 3998.
(17) Creigee, R. *Ber. Dsch. Chem. Ges.* **1944**, *77*, 722.
(18) Denney, D. B.; Denney, D. G. *J. Am. Chem. Soc.* **1957**, *79*, 4806.
(19) Bartlett, P. D.; Kice, J. L. *J. Am. Chem. Soc.* **1953**, *75*, 5591.
(20) (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in the Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, p 162. (b) Krishnamurthy, V.; Rawal, V. *J. Org. Chem.* **1997**, *62*, 1572. (c) Ziegler, F. E.; Peterson, A. K. *J. Org. Chem.* **1995**, *60*, 2666.

Scheme 6



Scheme 7



Although the desired perester **21** was not obtained in a synthetically useful yield, the conversion of **17** to **20** and **21** showed more promise than the attempt with **19** described earlier. Furthermore, the direct isolation of perester **21** proved to indicate its stability, as it did not appear to undergo destructive rearrangement. This favorably demonstrates that hydroxamate esters which contain groups with a reduced capability to migrate in a Criegee rearrangement can act as good nitrosation candidates. On the basis of these discoveries, we stepped backward in the synthesis and investigated another, less advanced hydroxamate ester.

The next logical candidate was hydroxamate **23**, the corresponding hydroxamate ester derived from **13** (Scheme 6). Unlabeled **23** was synthesized by coupling of benzohydroxamic acid with the same α-bromo ester used previously.

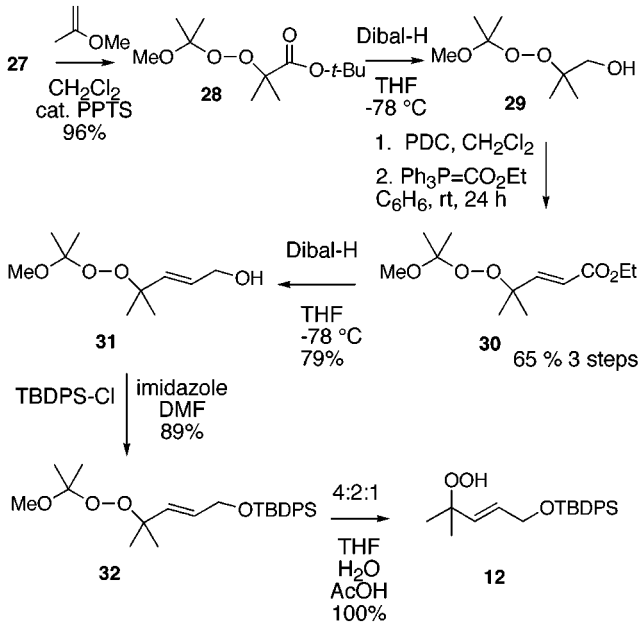
When subjected to the standard nitrosation conditions, **23** was converted to perester **24** which can be isolated from the reaction mixture, in 39% yield (Scheme 7). At this point, hydrolysis of **24** to the corresponding hydroperoxide was not attempted because it was anticipated that a peroxylactonization would occur and compromise the synthesis.[21] Consequently, hydroxamate ester **25** was synthesized in order to avoid formation of a peroxylactone upon hydrolysis. Nitrosation of **25** gave the novel perester **26** in 40% yield as a white solid melting at 72 °C and giving the correct elemental analysis. Hydrolysis of **26** with lithium hydroxide afforded the known hydroperoxide **27**[22] as a crystalline solid in 85% yield.

Collectively, these results show that it is possible to predict a successful nitrosation candidate based upon the stability of the resulting perester, provided that further reactions with NOCl are not possible. Hydroxamate ester **25** was therefore used from this point on as a means to incorporate the oxygen−oxygen bond required in the synthesis of unsymmetrically labeled hydroperoxides.

(21) The implicated peroxylactone, shown below, has been shown to be involved in chemiluminesence. See: (a) Sawaki, Y.; Ogata, Y. *J. Org. Chem.* **1977**, *42*, 40. (b) Adam, W.; del Fierro, J. *J. Org. Chem.* **1978**, *43*, 1159. Furthermore, nucleophiles react with the peroxylactone at the terminal oxygen rather than at the carbonyl carbon. See: Adam, W.; Blancafort, L. *J. Org. Chem.* **1997**, *62*, 1623.

(22) Gersmann, H. R.; Bickel, A. F. *Chem. Soc. B* **1971**, 2230.

Scheme 8



With hydroperoxide **27** in hand via a nitrosation procedure, it remained to extend its synthesis to the allyl hydroperoxide **12 (2-^{18}O)**. For these exploratory purposes, a significant amount of **23** was required. Since the nitrosation procedure is somewhat tedious and low yielding, an independent synthesis was sought in order to obtain 1−2 g of the hydroperoxide. *tert*-Butyl isobutyrate was therefore subjected to base-induced autoxidation to give **27** in 35% yield by a known procedure.[22]

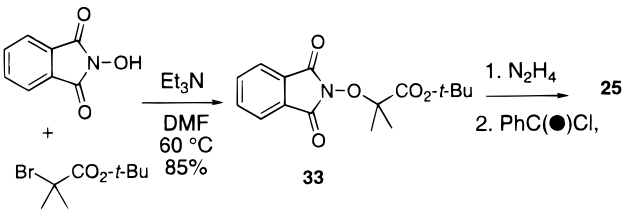
Conversion of **27** to **12** is shown in Scheme 8. The sequence begins with standard hydroperoxide protection; thus reaction with 2-methoxypropene gave the methoxy perketal derivative **28**.[23] Reduction of **28** to the corresponding alcohol was realized with Dibal-H to give **29** and was followed by oxidation with PDC and reaction with the stabilized ylid to give the unsaturated ester **30**. A second Dibal-H reduction and derivatization with TBDPS-Cl gave the allylic silyl ether **32**. Removal of the protecting group was accomplished with acetic acid, according to the method of Dussault and co-workers,[23] and the desired allylic hydroperoxide **12** was isolated in quantitative yield and stored as a dilute solution (0.01M) stabilized with 5% BHT. It should be noted that without BHT, hydroperoxide **12** does undergo rearrangement in dilute solutions upon standing in common room light over prolonged periods of time (1 week).[10] Therefore, its purification from BHT by chromatography is necessary just prior to use.

With a capable synthesis of **12** in hand, it remained to complete the synthesis with the ^{18}O label. Coupling of *N*-hydroxy phthalimide with the same *tert*-butyl α-bromo ester gave the phthalimide **33** in 85% yield.[24] The phthalimide amine protecting group was more compatible in this synthesis, as compared to Scheme 3 which started from Boc-NH-OH. The free alkoxylamine was generated from **33** under standard conditions with hydrazine hy-

(23) (a) Dussault, P. *Synlett* **1995**, 997. (b) Dussault, P.; Sahli, A.; Westermeyer, T. *J. Org. Chem.* **1993**, *58*, 5469; (c) Dussault, P.; Lee, I. Q. *J. Org. Chem.* **1993**, *58*, 6458. (d) Dussault, P.; Lee, H.-J.; Niu, J. *J. Org. Chem.* **1995**, *60*, 784.

(24) Fujii, T.; Wu, C. C.; Ymada, S. *Chem. Pharm. Bull.* **1967**, *15*, 345.

Scheme 9



drate and was not purified but subjected to acylation with ^{18}O benzoyl chloride to give labeled hydroxamate ester **25** in 71% yield over the two steps (Scheme 9). Labeled benzoyl chloride was prepared from trichlorotoluene and 97% $H_2{}^{18}O$. Mass spectral analysis showed **25** to have greater than 95% ^{18}O incorporation.

Gram quantities of labeled perester **26** were accumulated by 1.0 g scale nitrosation reactions of **25** according to Scheme 7 in yields ranging from 28 to 40%. Lithium hydroxide hydrolysis of **26** afforded the unsymmetrically labeled hydroperoxide **27 (2-^{18}O)** which was not analyzed for ^{18}O incorporation at this point but which was converted to the unsymmetrically labeled allyl hydroperoxide **12** according to Scheme 8. Reaction of **12** with Ph_3P followed by GC/MS analysis of the resulting tertiary alcohol and $Ph_3P{=}\bullet$ showed **12** to be labeled with 44% ^{18}O in the terminal oxygen. The seven-step sequence from **27** to **12** was achieved in 44% overall yield.

Summary

Several unsymmetrically labeled hydroperoxides can be accessed by the Koenig approach, and these hydroperoxides are useful intermediates in sequences that lead to more complex peroxide products. Nitrosation of hydroxamate esters provides the unsymmetrically labeled perester if substituents on the alkyl group do not promote Criegee rearrangement. While the synthesis of several unsymmetrically labeled hydroperoxides is possible by this strategy, there are limitations to the approach that emphasize the need for a more general solution to the problem. Among these limitations is the fact that the nitrosation works only with tertiary alkyl esters of aryloylhydroxamic acids since peresters of secondary hydroperoxides fragment to give ketones and carboxylic acids.

Experimental Section

Reactions involving hydroperoxides were monitored by TLC using a stain of 1.5 g of *N*,*N*′-dimethyl-*p*-phenylenediamine dihydrochloride/25 mL of H_2O/125 mL of MeOH/1 mL of AcOH. Hydroperoxides and peresters yield an immediate pink color, while perketals and peracetals exhibit a green-red color after standing unless otherwise noted. In general, hydroperoxides and perketals were stored as dilute solutions in hexane at −80 °C and were never exposed to temperatures above 40 °C. All NMR spectra of ^{18}O labeled compounds were found to match their corresponding unlabeled compounds and were not characterized further unless mass spectral analysis was appropriate and noted. Elemental analyses were performed by Atlantic Microlab Inc. (Norcross, GA). High-resolution mass spectral analyses were performed in the Duke University Mass Spectrometry Center using a JEOL JMS-SX102A spectrometer.

^{18}O-Labeled Benzoyl Chloride. Trichlorotoluene (7.79 mL, 55.0 mmol) and $H_2{}^{18}O$ (97%, 1.0 g, 50.0 mmol) were mixed in a thick-walled sealed tube and heated to 110 °C for 2 days.[25] The heterogeneous reaction mixture turned into a homogeneous yellow solution. The reaction vessel was cooled to room temperature and carefully opened to the air. HCl gas was released, and the solution was further purged with a stream of Ar. The benzoyl chloride, containing a 10% trichlorotoluene impurity, was used without further purification and was determined to have greater than 95% ^{18}O incorporation by mass spectrometry: GC/MS (MH^+) 144.

Typical Nitrosation Procedure with NOCl. Synthesis of *tert*-Butyl α-(Peroxybenzoyl)isobutyrate, 26. In a three-necked 100 mL reaction flask, hydroxamate ester **25** (1.0 equiv, 1.0 g, 3.55 mmol) was dissolved in CH_2Cl_2 (14 mL, 0.25 M) and K_2CO_3 (10.0 equiv, 4.90 g, 35.5 mmol) was added. This flask was cooled to −40 °C. A drying tube was attached to one arm of the flask, a second was stoppered with a glass stopper, and to the third was attached a glass tube packed with KCl and K_2CO_3 leading to a second two-necked flask. In this second flask was placed 7.0 mL (20.0 equiv) of concentrated HCl. An aqueous solution of $NaNO_2$ (5.0 equiv, 1.22 g in 6.10 mL of H_2O, 2.88 M) was dripped into the HCl and an orange gas was immediately generated. A stream of argon was used to transfer the NOCl gas to the reaction flask. Upon complete addition of the $NaNO_2$ solution, the reaction flask was brought to 0 °C for 30 min. The cooled reaction was then rapidly filtered through a plug of K_2CO_3 into a flask cooled to 0 °C and containing 7.0 mL of Nujol (0.5M). The CH_2Cl_2 was removed under high vacuum while keeping the reaction below 0 °C. The Nujol solution was then allowed to warm to room temperature overnight. Evolution of N_2 was visible.

The perester **26** was recovered by column chromatography. The entire Nujol mixture was loaded onto the column, and elution with hexanes (300 mL) was follwed by 10% EtOAc/hexanes to yield 387 mg (39%) of a white solid: mp 72−3 °C; R_f 0.20 (10% EtOAc/hexanes); IR ($CDCl_3$) 3154, 2982, 2933, 1760, 1728, 1383, 1369, 1235, 1146, 907, 729 cm^{-1}; ^1H NMR δ 7.87 (d, 2H), 7.54 (t, 1H), 7.43 (t, 2H), 1.55 (s, 6H), 1.40 (s, 9H); ^{13}C NMR δ 170.47, 162.80, 137.85, 128.42, 127.98, 127.09, 85.01, 81.18, 27.95, 21.91. Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.01; H, 7.26.

***N*-*p*-Nitrobenzoyl-*O*-2-methyl-2-nonylhydroxylamine, 7.** *O*-2-Methyl-2-nonylhydroxylamine hydrochloride (1.32 g, 6.3 mmol, 0.35 M), imidazole (1.12 g, 16.4 mmol), THF (10 mL), and absolute ethanol (8 mL) were added to a 50 mL two-necked flask under argon. The reaction was cooled to 0 °C, and *p*-nitrobenzoyl chloride (1.87 g, 10.1 mmol) was added by spatula in small portions over 15 min. The reaction was kept at 0 °C for 8 h and then put in refrigerator overnight, and it was worked up by stripping the solvent and dissolving the residue in chloroform (200 mL). The organic solution was washed with water (2 × 50 mL), 1.5 M HCl (1 × 50 mL), and then water again (1 × 50 mL). The solution was dried over magnesium sulfate. Purification by flash chromatography (0−10% ethyl acetate in hexane) afforded *N*-*p*-Nitrobenzoyl-*O*-2-methyl-2-nonylhydroxylamine, **7** (1.90 g, 5.9 mmol), a white solid, in 94% yield: mp 96−97°; R_f 0.33 (70:30 hexane:ethyl acetate); ^1H NMR (300 MHz, CD_3CN) δ 9.35 (br s, 1H), 8.26 (d, 2H), 7.92 (d, 2H), 1.56 (m, 2H), 1.28 (br, 10H), 1.23 (s, 6), 0.87 (t, 3H); ^{13}C NMR (300 MHz, CD_3CN) δ 150.7, 139.7, 129.6, 124.5, 82.0.2, 40.2, 32.57, 32.51, 30.89, 30.00, 24.83, 24.71, 23.36, 14.35; DIP/CIMS (CH_4/NH_3) *m*/*z* 323 (MH^+). Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.44; H, 8.18; N, 8.74.

2-Methy-2-nonyl-*p*-nitroperbenzoate, 10. *N*-*p*-Nitrobenzoyl-*O*-2-methyl-2-nonylhydroxylamine (200 mg, 621 μmol, 0.08 M) was reacted with NOCl as described in the general procedure. Purification of the product mixture by flash chromatography (0−10% ethyl acetate in hexane) yielded 2-methy-2-nonyl-*p*-nitroperbenzoate (64.4 mg, 199 μmol), a yellow oil, in 32% yield. DIP/CIMS analysis indicated that the percent ^{18}O incorporation into the perester was 54% (The relative intensity of *m*/*z* 341:343 ($M + NH_4^+$) was 847:1000.) Increased digitization NMR analysis of the acyl carbon and the ether carbon confirmed that the ^{18}O label was in the acyl oxygen only. The signal for the acyl carbon at 162.4 ppm was

(25) For the preparation of labeled benzoic acid see, Ponticorvo, L.; Rittenberg, D. *J. Am. Chem. Soc.* **1954**, *76*, 1705.

split into three peaks (at 162.397, 162.417, 162.429), while the ether carbon at 86.97 ppm was a single peak (conditions of analysis: 64 000 data points covered a sweep width of 7012.6 Hz) **10**: R_f 0.38 (80:20 hexane:ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 8.7 Hz, 2H), 8.102 (d, J = 8.7 Hz, 2H), 1.66 (m, 2H), 1.36 (s, 6H), 1.26 (br m, 10H), 0.85 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.41, 150.61, 133.16, 130.36, 130.16, 123.90, 123.64, 86.97, 39.01, 31.80, 30.02, 29.21, 24.38, 24.33, 23.92, 22.68, 14.13; DIP/CIMS (CH_4/NH_3) m/z 341 (M + NH_4^+), 343 (M + NH_4^+).

2-Methyl-2-nonyl hydroperoxide, 6. 2-Methyl-2-nonyl-*p*-nitroperbenzoate, **10** (64.4 mg, 199 μmol, 0.07 M), was added to a 25 mL round-bottom flask with THF (2.5 mL), water (0.38 mL), and LiOH•H_2O (25 mg, 594 μmol, 0.21 M). The reaction was stirred at room temperature for 2 h. THF was removed under vacuum, and ether (50 mL) was added to the residue. The solution was washed with saturated sodium bicarbonate (2 × 20 mL), and the organic layer was dried over magnesium sulfate. 2-Methyl-2-nonyl hydroperoxide (18 mg, 103 μmol) was isolated in 52% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, 1H), 1.50 (m, 2H), 1.26 (br s, 10H), 1.19 (s, 3H), 0.86 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.96, 38.49, 31.83, 30.11, 29.27, 23.99, 23.79, 22.65, 14.09; GC/CIMS (CH_4/NH_3) (DIP) m/z 192 (36, M + NH_4^+), 194 (100, M + NH_4^+).

Ethyl α-[*N*-(*tert*-Butoxycarbonyl)aminooxy]isobutyrate, 13. This compound was prepared in 85% yield as described[14] to give **13** as a colorless oil which was analytically pure and used without further purification: ^{1}H NMR δ 7.56 (bs, 1H), 4.29 (q, 2H), 1.56 (s, 6H), 1.55 (s, 9H), 1.38 (t, 3H); ^{13}C NMR δ 173.78, 156.78, 83.48, 81.46, 61.22, 28.11, 22.87, 14.08. Anal. Calcd for $C_{11}H_{21}NO_5$: C, 53.42; H, 8.56; N, 5.66. Found: C, 53.18; H, 8.45; N, 5.83.

2-Methyl-2-[*N*-(*tert*-butoxycarbonyl)aminooxy]propanol, 14. This compound prepared by literature methods[15] precipitated as a white fluffy solid (67%) which was analytically pure and used without further purification: mp 106−7 °C; IR ($CDCl_3$) 3661, 3638, 3376, 2982, 1726, 1468, 1383, 908 cm^{-1}; ^{1}H NMR δ 6.87 (bs, 1H), 3.39 (s, 2H), 1.47 (s, 6H), 1.19 (s, 9H); ^{13}C NMR δ 159.10, 83.27, 82.58, 65.45, 28.06, 21.29. Anal. Calcd for $C_9H_{19}NO_4$: C, 52.66; H, 9.33; N, 6.82. Found: C, 52.65; H, 9.38; N, 6.80.

Typical Oxidation and Wittig Olefination Procedure. Ethyl 4-Methyl-4-[*N*-(*tert*-butoxycarbonyl)aminooxy]-2-penteneoate, 15. Alcohol **14** (1.14 g, 5.6 mmol), in 5.0 mL of CH_2Cl_2, was added at room temperature to a mixture of pyridinium dichromate (5.26 g, 14.0 mmol), molecular sieves, and CH_2Cl_2 (28 mL). The reaction was stirred at room temperature for 18 h. Filtration through Celite was followed by washes with EtOAc. The combined organic layers were concentrated under reduced pressure to yield the crude aldehyde, which was unstable to chromatography. It was carried through to the Wittig olefination without purification. A solution of crude aldehyde and (carboethoxymethylene)triphenylphosphorane (1.95 g, 5.6 mmol) in benzene (23 mL) was brought to reflux for 12 h. Evaporation of the solvent was followed by chromatography on silica gel (10% EtOAc/hexane/0.1 Et_3N) to give 933 mg of a faint yellow oil (61%): R_f 0.28 (20% EtOAc/hexane); ^{1}H NMR δ 6.99 (d, 2H, J = 15.9 Hz), 6.78 (bs, 1H), 5.92 (d, 2H, J = 15.9 Hz), 4.20 (q, 2H), 1.47 (s, 9H), 1.39 (s, 6H), 1.29 (t, 3H); ^{13}C NMR δ 166.15, 152.21, 150.76, 120.48, 81.38, 81.17, 60.24, 27.93, 27.85, 24.03, 13.97. Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.12; H, 8.48; N, 5.12. Found: C, 56.99; H, 8.50; N, 5.19.

Ethyl 4-Methyl-4-[*N*-(*tert*-butoxycarbonyl)-*N*-(benzoyl)aminooxy]-2-penteneoate, 16. This compond was obtained as a yellow oil: R_f 0.35 (20% EtOAc/hexane); ^{1}H NMR δ 7.55−7.26 (m, 5H), 7.05 (d, 1H, J = 16.2 Hz), 5.86 (d, 1H, J = 16.2 Hz), 4.05 (q, 2H), 1.35 (bs, 6H), 1.14 (s, 9H), 1.12 (t, 3H); ^{13}C NMR δ 171.82, 166.04, 152.38, 149.82, 135.54, 132.23, 130.55, 128.67, 128.30, 128.13, 121.34, 84.55, 84.44, 60.54, 27.43, 14.15. Anal. Calcd for $C_{20}H_{27}NO_6$: C, 63.65; H, 7.21; N, 3.71. Found: C, 63.47; H, 7.23; N, 3.76.

Ethyl 4-Methyl-4-[*N*-(benzoyl)aminooxy]-2-penteneoate, 17. The Boc-protected hydroxamate **16** (557 mg, 1.47 mmol) was dissolved in CH_3CN (5.0 mL), and sodium iodide was added (881 mg, 5.88 mmol). Chlorotrimethylsilane (0.560 mL, 4.41 mmol) was added dropwise at room temperature with stirring. The reaction mixture was brought to reflux for 5 h. Workup involved cooling in an ice bath, the addition of MeOH, and stirring for 30 min. The mixture was extracted with ether (3 × 100 mL) and washed with saturated NaCl (2 × 200 mL). The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to yield a dark red oil. This material was purified by chromatography on silica gel (10% EtOAc/hexane/0.1% Et_3N) to give 329 mg (81%) of a pale yellow solid: mp 70−72 °C; R_f 0.20 (20% EtOAc/hexane); IR ($CDCl_3$) 3661, 3154, 2984, 1711, 1698, 1382, 911, 739 cm^{-1}; ^{1}H NMR δ 8.42 (bs, 1H), 7.71 (d, 2H), 7.52 (t, 1H), 7.42 (t, 2H), 7.05 (d, 1H, J = 16.2 Hz), 6.00 (d, 1H, J = 16.2 Hz), 4.20 (q, 2H), 1.49 (s, 6H), 1.29 (t, 3H); ^{13}C NMR δ 167.86, 166.30, 150.18, 132.08, 132.02, 128.67, 127.13, 125.76, 82.93, 60.71, 24.34, 14.17; HRMS (calcd for $C_{15}H_{20}NO_4$) 278.1392, found 278.1384.

4-Methyl-4-[*N*-(benzoyl)aminooxy]-2-pentenol. See the synthesis of **29** for a representative procedure. This compound was obtained as a white solid: R_f 0.10 (50% EtOAc/hexane); mp 101 °C; IR ($CDCl_3$) 3661, 3433, 3154, 2982, 1724, 1467, 1381, 898, 715 cm^{-1}; ^{1}H NMR δ 9.0 (bs, 1H), 7.74 (d, 2H), 7.42 (t, 1H), 7.39 (t, 2H), 5.93 (m, 2H), 4.15 (m, 2H), 1.47 (s, 6H); ^{13}C NMR δ 167.31, 133.87, 132.09, 131.63, 130.51, 128.35, 127.16, 83.23, 62.22, 24.25. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.26; H, 7.26; N, 5.89.

1-*tert*-Butyldiphenylsilyloxy-4-methyl-4-[*N*-(benzoyl)-aminooxy]-2-pentene, 18. This compound was obtained as a colorless oil according to the procedure described for compound **32**: R_f 0.20 (20% EtOAc/hexane); ^{1}H NMR δ 8.08 (bs, 1H), 7.76 (m, 6H), 7.48 (m, 9H), 5.94 (m, 2H), 4.37 (d, 2H), 1.53 (s, 6H), 1.17 (s, 9H); ^{13}C NMR δ 165.90, 135.52, 135.45, 133.43, 132.87, 131.73, 130.66, 129.69, 128.56, 127.64, 127.03, 83.25, 63.82, 26.79, 24.50, 19.17; HRMS (calcd for $C_{29}H_{35}SiNO_3$) 474.2464, found 474.2469.

Typical Nitrosation with $NOBF_4$. Synthesis of 20a,b and 21. Hydroxamate ester **17** (1.0 equiv, 100 mg, 0.358 mmol) was dissolved in CH_2Cl_2 (3.5 mL, 0.1 M), K_2CO_3 (10.0 equiv, 494 mg, 3.58 mmol) was added, and the reaction was cooled to −40 °C. Solid $NOBF_4$ (1.1 equiv, 46 mg, 0.393 mmol) was added, and the reaction was stirred at −40 °C for 30 min and then brought to 0 °C for 30 min. The reaction mixture was kept below 0 °C and quickly filtered through a plug of K_2CO_3 into a cooled flask containing 0.7 mL (0.5 M) of Nujol. The CH_2Cl_2 was removed under high vacuum at 0 °C, and the Nujol reaction solution was allowed to warm to room temperature overnight. The evolution of N_2 was visible.

The products were recovered by column chromatography on silica gel. The entire Nujol solution was loaded onto the column, and elution with hexanes (200 mL) was followed by 10% EtOAc/hexane. A single spot which was both UV active and stained peroxide positive was concentrated to give 39 mg (39%) of a mixture of **20a,b** and **21** (9:1 by ^{1}H NMR). This mixture was separated by HPLC (normal phase, 1.0% 2-propanol/hexane). The diastereomeric epoxides **20a,b** eluted first and were found to be inseparable: ^{1}H NMR δ 8.13 (m, 2H), 7.62 (m, 1H), 7.48 (m, 2H), 5.11 (d, 1H, J = 8.7 Hz), 5.02 (d, 1H, J = 8.7 Hz), 4.33 (q, 2H), 3.28 (d, 1H, J = 9.0 Hz), 3.25 (d, 1H, J = 9.0 Hz), 1.60 (s, 3H), 1.54 (s, 3H), 1.43 (s, 6H), 1.29 (t, 3H); ^{13}C NMR δ 167.64, 166.67, 165.16, 164.56, 132.95, 132.78, 129.34, 129.29, 127.84, 72.66, 70.90, 61.30, 61.22, 60.88, 60.25, 58.57, 58.10, 23.94, 23.54, 19.32, 18.11, 13.48, 13.40; GC/MS (7.03 min MH^+) 279, (7.15 min MH^+) 279. The perester **21** eluted second: ^{1}H NMR δ 7.94 (d, 2H), 7.62 (m, 1H), 7.47 (m, 2H), 7.12 (d, 1H, J = 16.2 Hz), 6.09 (d, 1H, J = 16.2 Hz), 4.23 (q, 2H), 1.57 (s, 6H), 1.32 (t, 3H).

***tert*-Butyl α-[*N*-(Benzoyl)aminooxy]isobutyrate, 25.** Benzohydroxamic acid (3.15 g, 22.9 mmol) and *tert*-butyl-2-bromoisobutyrate (5.12 g, 22.9 mmol) were dissolved in DMF (46 mL) at room temperature. Triethylamine (3.20 mL, 22.9 mmol) was added, and the reaction was brought to 60 °C and stirrred for 28 h. The cooled reaction mixture was poured into H_2O (500 mL) and extracted with ether (3 × 150 mL). The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to yield a mixture of oils and solids.

The product was crystallized with pentane (5.50 g, 86%): R_f 0.25 (20% EtOAc/hexane); mp 68 °C; IR ($CDCl_3$) 3638, 3398, 3154, 2984, 1726, 1690, 1454, 1143, 910 cm^{-1}; ^1H NMR δ 9.26 (bs, 1H), 7.70 (d, 2H), 7.51 (m, 1H), 7.42 (m, 2H), 1.54 (s, 6H), 1.49 (s, 9H); ^{13}C NMR δ 172.93, 131.28, 128.01, 127.63, 126.32, 83.65, 81.68, 27.29, 22.31; GC/MS (MH^+) 280. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.44; H, 7.55; N, 5.01.

Hydrolysis of *tert*-Butyl α-(peroxybenzoyl)isobutyrate. *tert*-Butyl α-hydroperoxyisobutyrate, 27. Perester **26** (40 mg, 0.142 mmol) was dissolved in THF (1.4 mL) and H_2O (1.4 mL) and cooled in an ice bath. Lithium hydroxide (1:1 LiOH:H_2O, 18 mg, 0.426 mmol) was added, and the reaction was stirred for 12 h. The reaction was poured in saturated $NaHCO_3$ and extracted with ether several times. The organic extracts were combined, dried over Na_2SO_4, and concentrated at 25 °C to a solid material which could be crystallized with pentane (−80 °C) or purified by chromatography on silica gel (10% EtOAc/hexane). Then 20 mg of hydroperoxide was recovered (83%): R_f 0.39 (20% EtOAc/hexane); mp 47 °C; IR (neat) 3427 bs, 2982, 2937, 1723, 1146, 790 cm^{-1}; ^1H NMR δ 9.22 (s, 1H), 1.46 (s, 9H), 1.41 (s, 6H); ^{13}C NMR δ 82.83, 81.71, 27.28, 21.89. Anal. Calcd for $C_8H_{16}O_4$: C, 54.43; H, 9.15. Found: C, 54.75; H, 9.04.

***tert*-Butyl α-[(1-Methoxy-1-methylethyl)dioxy]isobutyrate, 28.** Hydroperoxide **27** (1.58 g, 8.96 mmol) was dissolved in CH_2Cl_2 (18 mL) and cooled to 0 °C. 2-Methoxypropene (1.71 mL, 17.90 mmol) was added, followed by a catalytic amount of pyridinium *p*-toluenesulfonate, and the reaction mixture was stirred for 4 h. The solvent was removed under reduced pressure, and the crude yellow oil was subjected to purification by chromatography on silica gel (10% EtOAc/hexane) to give 2.13 g (96%) of a colorless liquid: R_f 0.40 (10% EtOAc/hexane); IR (neat) 2941, 2873, 1731, 1367, 1258, 1148, 905 cm^{-1}; ^1H NMR δ 3.29 (s, 3H), 1.43 (s, 9H), 1.37 (s, 6H), 1.34 (s, 6H); ^{13}C NMR δ 171.78, 103.17, 81.36, 79.97, 48.23, 30.87, 27.21, 22.10. Anal. Calcd for $C_{12}H_{24}O_5$: C, 58.04; H, 9.74. Found: C, 57.98; H, 9.74.

Typical Reduction with Diisobutylaluminum Hydride. 2-[(1-Methoxy-1-methylethyl)dioxy]-2-methylpropanol, 29. Ester **28** (1.45 g, 5.86 mmol) was dissolved in CH_2Cl_2 (15 mL), and the reaction was cooled to −78 °C. DIBAL-H (1.0 M solution in hexanes, 14.6 mL, 14.6 mmol) was added, and the mixture was stirred at −78 °C for 6 h. The reaction was allowed to warm to room temperature and then quenched with saturated NH_4Cl (450 μL). The slurry was filtered and washed with copious amounts of EtOAc. The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to yield a colorless liquid. This material was purified by chromatography on silica gel (30% EtOAc/hexane) to give 695 mg (67%) of a colorless oil: R_f 0.45 (30% EtOAc/hexane); ^1H NMR δ 3.46 (d, 2H), 3.27 (s, 3H), 2.74 (t, 1H), 1.35 (s, 6H), 1.15 (s, 6H); ^{13}C NMR δ 103.72, 81.15, 66.30, 49.17, 22.02, 20.78. Anal. Calcd for $C_8H_{18}O_4$: C, 53.91; H, 10.18. Found: C, 54.06; H, 10.24.

Ethyl 4-[(1-Methoxy-1-methylethyl)dioxy]-4-methyl-2-pentenoate, 30. This compound was prepared according to the procedure given for **15** except the olefination was performed at room temperature for 24 h. Ester **30** is a colorless liquid: ^1H NMR δ 7.04 (d, 1H, J = 16.0 Hz), 5.90 (d, 1H, J = 16.0 Hz), 4.20 (q, 2H), 3.27 (s, 3H), 1.36 (s, 6H), 1.35 (s, 6H), 1.26 (t, 3H); ^{13}C NMR δ 151.58, 119.07, 104.94, 103.27, 79.40, 58.75, 48.54, 23.91, 22.18, 13.56. Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.51; H, 9.00. Found: C, 58.24; H, 8.93.

4-[(1-Methoxy-1-methylethyl)dioxy]-4-methyl-2-pentene-1-ol, 31. This compound was prepared in 79% yield according to the procedure outlined above: ^1H NMR δ 5.85 (m, 2H), 4.19 (d, 2H), 3.48 (s, 3H), 1.35 (s, 6H), 1.34 (s, 6H); ^{13}C NMR δ 135.59, 127.49, 102.97, 79.52, 62.61, 24.22, 22.22. Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.68; H, 9.89.

1-*tert*-Butyldiphenylsilyloxy-4-[(1-methoxy-1-methylethyl)dioxy]-4-methyl-2-pentene, 32. The allylic alcohol **31** (110 mg, 0.538 mmol) and imidazole (80 mg, 1.18 mmol) were dissolved in DMF (1.5 mL) at room temperature. *tert*-Butylchlorodiphenylsilane (0.154 mL, 0.592 mmol) was added and the reaction stirred at room temperature for 6 h. Workup involved washing with H_2O (100 mL) and extracting with ether (3 × 50 mL). The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to yield a pale yellow oil. This material was purified by chromatography on silica gel (5% EtOAc/hexane) to give 212 mg (89%) of a colorless oil: R_f 0.25 (10% EtOAc/hexane); ^1H NMR δ 7.80 (m, 4H), 7.50 (m, 6H), 6.03 (d, 1H, J = 15.0), 5.78 (dt, 1H, J = 15.0, 4.5), 4.33 (d, 2H, J = 4.5), 3.40 (s, 3H), 1.48 (s, 6H), 1.44 (s, 6H), 1.17 (s, 9H); ^{13}C NMR δ 134.87, 133.06, 128.92, 126.93, 102.84, 79.56, 63.47, 26.13, 24.32, 22.28, 18.58. Anal. Calcd for $C_{26}H_{38}O_4Si$: C, 70.55; H, 8.65. Found: C, 70.89; H, 8.70.

5-*tert*-Butyldiphenylsilyloxy-2-hydroperoxy-2-methyl-3-pentene, 12. The protected hydroperoxide **32** (100 mg, 0.225 mmol) was dissolved in 5.0 mL of a 4:2:1 mixture of THF:AcOH:H_2O with a few crystals of BHT. The reaction was stirred at room temperature overnight. Workup involved adding solid $NaHCO_3$ to the cooled reaction, followed by washes with H_2O and extraction with ether (3 × 50 mL). The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to yield a colorless oil (84 mg, 100%). This material was stored as a 1.0 M solution in hexane with 0.01 M BHT and purified by HPLC (normal phase, 1.0% 2-propanol/hexane) just prior to use: R_f 0.40 (20% EtOAc/hexane); ^1H NMR δ 7.68 (m, 4H), 7.41 (m, 6H), 7.29 (s, 1H), 5.77 (m, 2H), 4.25 (d, 2H), 1.32 (s, 6H), 1.08 (s, 9H); ^{13}C NMR δ 140.0, 132.90, 132.43, 130.05, 129.04, 126.98, 82.28, 63.28, 26.16, 23.51, 18.54.

5-*tert*-Butyldiphenylsilyloxy-2-methyl-3-pentene-1-ol. The hydroperoxide was further characterized by derivitization to the corresponding alcohol with triphenylphosphine: ^1H NMR δ 7.70 (m, 4H), 7.43 (m, 6H), 5.85 (d, 1H, J = 16.5 Hz), 5.74 (dt, 1H, J = 20.1, 4.5 Hz), 4.24 (d, 2H, J = 4.5 Hz), 1.32 (s, 6H), 1.09 (s, 9H); GC/CIMS m/z 372 ($M + NH_4^+$).

***tert*-Butyl α-(Phthalimidooxy)isobutyrate, 33.** For preparation of this compound see unlabeled **25**: R_f 0.25 (20% EtOAc/hexane); mp 100 °C; IR ($CDCl_3$) 3154, 2986, 2901, 1794, 1738, 1468, 1185, 913, 789 cm^{-1}; ^1H NMR δ 7.80 (m, 2H), 7.74 (m, 2H), 1.56 (s, 6H), 1.49 (s, 9H); ^{13}C NMR δ 169.24, 163.89, 133.85, 128.33, 122.86, 86.45, 81.45, 27.10, 22.73. Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.58. Found: C, 63.02; H, 6.31; N, 4.63.

^{18}O-Labeled 25. The pthtalimide derivative **33** (14.0 g, 45.9 mmol) was dissolved in CH_2Cl_2 (115 mL) and MeOH (115 mL). Hydrazine hydrate (55%, 6.49 mL, 114.6 mmol) was added and the reaction brought to reflux for 3 h. The reaction was cooled, and 5% Na_2CO_3 (1000 mL) was added followed by extraction with ether (5 × 250 mL). The combined ether extracts were dried over $MgSO_4$ and concentrated to a viscous and somewhat hygroscpoic yellow oil. The crude alkoxylamine was used without further purification: ^1H NMR δ 5.32 (bs, 2H), 1.49 (s, 9H), 1.35 (s, 6H); ^{13}C NMR δ 172.89, 80.76, 79.82, 27.15, 22.40. The yellow oil was dissloved in a solution of CH_2Cl_2:THF (1:1 80 mL), and imidazole (8.16 g, 120 mmol) was added with stirring. The reaction was cooled to 0 °C, and ^{18}O-benzoyl chloride (4.70 g, 40 mmol, with 10% trichlorotoluene impurity) was added dropwise via an addition funnel with an additional 10 mL of CH_2Cl_2. The reaction was allowed to warm to room temperature and stirred for 12 h. Workup involved washing the reaction with saturated $NaHCO_3$ (800 mL) and extracting with ether (4 × 200 mL). The combined organic layers were condensed under reduced pressure to give a yellow oil. This oil was purified by column chromatography on silica gel (20% EtOAc/hexane) to yield a material which in cold pentane crystalized to a white solid (8.11 g, 72%) and was determined to have greater than 95% ^{18}O incorporation by mass spectrometry: GC/MS (MH^+) 282. All other spectral data matches the unlabeled compound.

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