# *Communications to the Editor*

## A Baeyer−Villiger Approach to $^{18}$O-Labeled Peroxides: A Protected Form of Unsymmetrically Labeled Hydrogen Peroxide

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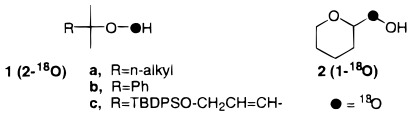
Peroxides and hydroperoxides are reactive compounds that play an important role in many chemical and biochemical transformations.[1] These compounds, derived from molecular oxygen, superoxide, or hydrogen peroxide, are formed in the free radical oxidation of organic precursors, and they are versatile intermediates in the chemical synthesis and biosynthesis of a host of important compounds. Mechanistic studies involving peroxides benefit from the availability of unsymmetrically labeled compounds,[2] and we have recently reported on the synthesis and study of three such labeled compounds **1a**−**c**, all of which are tertiary hydroperoxides.[2,3] The strategy applied in the synthesis of **1a**−**c**

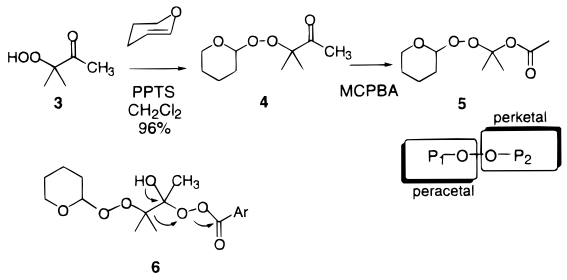



is inappropriate for use in the preparation of primary and secondary peroxides,[4] and there are, to our knowledge, no procedures reported that lead to such unsymmetrically labeled compounds. In the pursuit of a general solution to the preparation of unsymmetrically labeled peroxides, we have sought a specifically labeled form of protected hydrogen peroxide, $P_1$-●-OH, where $P_1$ is a protecting group and ● is an isotope of oxygen. Access to $P_1$-●-OH could logically come from a doubly protected species, $P_1$-●−O−$P_2$ if one of the protecting groups could be preferentially removed.

We report here a successful synthesis of the tetrahydropyran-protected hydroperoxide **2 (1-$^{18}$O)**,[5] that proceeds through a diprotected form of hydrogen peroxide. In this synthesis, the removable protecting group $P_2$ is revealed by a Baeyer−Villiger reaction on an α-ketoperoxide. Both **2** and the Baeyer−Villiger strategy may prove to be generally useful for the preparation of a variety of specifically labeled peroxide compounds.

Preliminary experiments to find a diprotected form of hydrogen peroxide were performed on unlabeled methyl ketone-hydroperoxide, **3**, prepared from the base-catalyzed autoxidation of 3-methyl-2-butanone.[6] The hydroperoxide **3** proved to be a reluctant substrate for further reaction. Alkylation under standard basic or silver ion catalyzed conditions failed to give any alkylated product,[7] but reaction of **3** with vinyl ethers did proceed in excellent yield. Thus, as shown in Scheme 1, dihydropyran reacted with **3** to give the THP peracetal **4** in over 95% isolated yield. Reaction of **4** under standard Baeyer−Villiger conditions, *m*-chloroperbenzoic acid[8] with sodium bicarbonate as a buffer, yielded **5** in 70−80% yield. The peroxide **5** is a diprotected hydrogen peroxide with $P_1$, a peracetal-protecting group, expected to be more stable to acid-catalyzed deprotection than $P_2$, a perketal-protecting group.

**Scheme 1**




The Baeyer−Villiger transformation of **4** is of some interest. Groups that stabilize positive charge generally migrate preferentially, and migrations are thought to be concerted with loss of the leaving group. Product perketal **5** will result if collapse of the tetrahedral intermediate **6** proceeds with migration of the group α to the peroxide. Carbocations α to peroxides are stabilized by resonance and should, therefore, migrate preferentially over the methyl group.[9] An alternate Grob-type fragmentation pathway for **6** can, of course, be written, but we have found no indication that this pathway competes with the Baeyer−Villiger route (see ref 11 for an analogous Grob process).

With a di-protection scheme in place for hydrogen peroxide, routes to unsymmetrically labeled **4** were investigated. A synthesis of the unsymmetrically labeled *tert*-butyl α-hydroperoxyisobutyrate, **7**, had been previously developed,[2,10] and this compound was therefore chosen as a starting material since it can be prepared in gram quantities.[10] This approach permits the known hydroxamate ester-NOCl procedure to be used to incorporate an $^{18}$O-label, which originates from $H_2{}^{18}O$.

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

(2) Lowe, J. R.; Porter, N. A. *J. Am. Chem. Soc.* **1997**, *119*, 9, 11534.

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

(4) The synthesis of **1 a**−**c** proceeds through the corresponding perester intermediates. Primary and secondary peresters undergo fragmentation to give carboxylic acids and aldehydes or ketones.

(5) We identify the position of the label by assigning priorities to the two oxygens in the usual way.

(6) (a) Gersmann, J. R.; Bickel, A. F. *J. Chem. Soc. B* **1971**, 2230. (b) Adam, W.; Catalani, L. H.; Saha-Moller, C. R.; Will, B. *Synthesis* **1989**, 121.

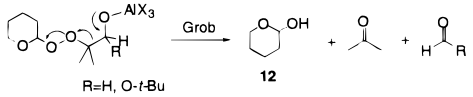
(7) The starting hydroperoxide was immediately consumed in these reactions, pointing to base-induced decomposition to give acetone and acetic acid. See Richardson, W. H.; Hodge, V. F.; Stiggall, D. L.; Yelvington, M. B.; Montgomery, F. C. *J. Am. Chem. Soc.* **1974**, *96*, 6652.

(8) . MCPBA used was purified to greater than 95% by the method described in Perrin, D. D.; Armarego, W. F. L. In *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Toronto, Canada, 1988.

(9) Carbocations α to peroxides are formed in transformations which start from perketals and utilize $SnCl_4$ or $TiCl_4$ as Lewis acids to initiate the chemistry. Dussault, P. H.; Lee, I. Q. *J. Am. Chem. Soc.* **1993**, *115*, 6458.

(10) Porter, N. A.; Caldwell, S. E.; Lowe, J. R. *J. Org. Chem.* **1998**, *63*, 5547−5554.

(11) This product could result by direct reduction of the hydroperoxide by Dibal-H or by a Grob fragmentation process on an appropriate intermediate, as shown below. The formation of **12** in these reactions was, however, not investigated thoroughly.

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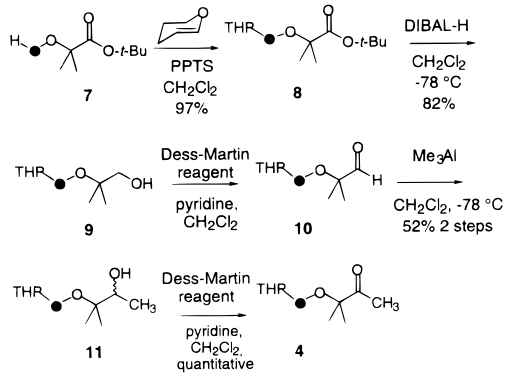
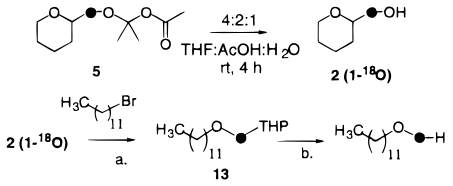
**Scheme 2**




The initial steps involving protection and Dibal-H reduction have ample precedent, see Scheme 2.[2,10] Thus labeled **7**, prepared as previously described,[2,10] was protected as a THP, and **8** was reduced with Dibal-H in methylene chloride at low temperature to give the alcohol **9**. It is of interest to note that performing this reduction in THF or ether resulted in a significant amount of the six-membered ring lactol **12** as a byproduct.[11] Hexane was a somewhat better solvent than THF or ether; however, $CH_2Cl_2$ was far superior, giving no $\delta$-lactol. Oxidation of alcohol **9** was accomplished by the Dess−Martin periodinane[12] with pyridine, to give the aldehyde **10** which was unstable to chromatography and was not purified further. In attempting to form the carbinol **11**, we found that reaction of aldehyde **10** with methyl Grignard or methyllithium rapidly produced $\delta$-lactol. Reaction of **10** with trimethylaluminum proceeded cleanly in methylene chloride at low temperature. Interestingly, no reaction occurred with $Me_3$-Al and **10** in anhydrous hexane, THF, or ether. Because of the stereogenic center contained in the THP linkage, the products **11** are formed as a mixture of diastereomers, which are easily separated by flash column chromatography. The combined alcohols **11** were oxidized to the corresponding ketone **4** labeled at the oxygen bearing the THP, and the Baeyer−Villiger reaction produced labeled **5**.

Reaction of **5** under conditions used to remove perketal protecting groups, 4:2:1 THF/AcOH/$H_2O$, yielded the THP-protected hydrogen peroxide, **2** with yields in excess of 90%[13] This experiment verifies the selective protection scheme and the Baeyer−Villiger approach to diprotected hydrogen peroxide and provides the versatile synthetic intermediate **2**. Scheme 3 illustrates a typical transformation starting from **2** that provides,

**Scheme 3**




a. CsOH:$H_2O$, DMF, 84%; b. TsOH, MeOH:THF (2:1), 100%

in this case, a labeled primary hydroperoxide. Reaction of **2** with dodecyl bromide and cesium hydroxide, according to the method of Dussault and co-workers,[14] gives the dodecyl THP-protected peroxide **13** in 84% yield.

The final deprotection (the $P_1$ protecting group in this case) of **13** was achieved with stoichiometric *p*-toluenesulfonic acid in MeOH/THF (2:1) and this resulted in a quantitative cleavage of the THP peracetal to give (2-$^{18}$O) dodecyl hydroperoxide, labeled in the terminal oxygen.[15] The position and the extent of the label was determined by reaction of the hydroperoxide with triphenylphosphine, followed by determination of the isotopic composition of the triphenylphosphine oxide so formed. In this way, it was determined that the terminal label in the precursor **7** (see Scheme 2) was delivered undiluted to the terminal oxygen of the product of the sequence, dodecyl hydroperoxide.[16] Transformations of **2** similar to those shown in Scheme 3 but with a secondary bromide, PhCH($CH_3$)Br, provided the secondary hydroperoxide, PhCH($CH_3$)OOH, albeit in lower overall yield (see Supporting Information). Indeed, **2** should prove to be a versatile intermediate in the preparation of several unsymmetrically labeled peroxidic compounds, and synthetic and mechanistic studies taking advantage of this opening are ongoing.[17,18]

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**Supporting Information Available:** Experimental procedures and characterization data for compounds (9 pages, print/PDF) are included. See any current masthead page for ordering information and Web access instructions.

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(12) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899, (c) Meyer, S. D.; Schrieber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

(13) Compound **2** is a known compound. Milas, N. A.; Peeler, R. L.; Mageli, O. L. *J. Am. Chem. Soc.* **1954**, *76*, 2322.

(14) (a) Dussault, P. H.; Sahli, A.; Westermeyer, T. *J. Org. Chem.* **1993**, *58*, 5469. (b) Dussault, P. H.; Sahli, A. *Tetrahedron Lett.* **1990**, *60*, 784.

(15) Dussault, P. H. *Synlett*, **1995**, 997.

(16) Starting material **7** had 11% $^{18}$O label in the terminal hydroperoxide position. The product dodecyl hydroperoxide reacted with triphenylphosphine to give the phosphine oxide that had *m*/*z* 279 = 1000 (M + $H^+$); 280 = 200 and 281 = 130. Unlabeled triphenylphosphine oxide has *m*/*z* 279 = 1000; 280 = 203 and 281 = 21. This confirms the 11% isotope incorporation in the final hydroperoxide. The acetate derivative of dodecanol, the other product of the reaction of the hydroperoxide with triphenylphosphine gives a normal isotope distribution pattern.

(17) All organic peroxides should be treated as though they are potentially explosive although we have had no events with the compounds reported here.

(18) Abbreviations: THP, tetrahydropyranyl; PPTS, pyridinium *p*-toluene sulfonate; THF, tetrahydrofuran; DMF, dimethylformamide.