as a consequence form a variety of internucleotide linkages such as phosphoramidates, azoamidates, and esters. Moreover, by oxidation with *tert*-butylhydroperoxide or sulfur, **1a** also forms either the dinucleoside phosphate or thiophosphate triester, respectively, without loss of the 2-cyano-1,1-dimethylethyl protecting group (unpublished observation). Since phosphite triesters are intermediates in solid phase oligonucleotide synthesis via the phosphoramidite method,[14] this approach can now be extended so that one synthon, the deoxynucleoside 3′-phosphoramidite having a 2-cyano-1,1-dimethylethyl (or perhaps *o*-methylbenzyl) protection group, is used to introduce several phosphate analogues uniquely at specific sites in any combination with natural internucleotide linkages.

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The Resolution of Racemic Hydroperoxides: The Preparation of Optically Pure Hydroperoxide Natural Products[1]

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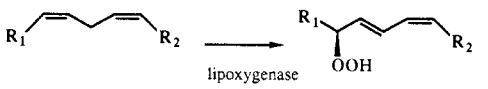
Lipoxygenase enzymes[3] catalyze the conversion of polyunsaturated fatty acids to fatty acid hydroperoxides and these hydroperoxides serve as important intermediates in the formation of diverse compounds of biological importance (Scheme I). A new stereocenter is generated in the lipoxygenase reaction, and fatty acid hydroperoxides isolated from natural sources are essentially one enantiomer if they are formed enzymatically.[3,4] Nonenzymatic autoxidation of fatty acid substrates also gives fatty acid hydroperoxides,[5] but racemic mixtures are formed in this process.[4]

Despite the importance of unsaturated hydroperoxides in chemistry, biology, and medicine, no general method for the preparation of these labile compounds has been reported. Although the natural products can be obtained from enzymatic sources, unnatural enantiomers are unavailable because all chemical syntheses described give racemic mixtures.[6-8] We report here what appears to be a general solution to this problem, the resolution of unsaturated hydroperoxide enantiomers by liquid chromatography of diastereomeric derivatives. This method allows, for the first time, the nonenzymatic preparation of optically pure allylic or dienylic hydroperoxide natural products.

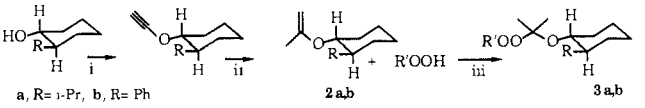
Preliminary screens of several hydroperoxide derivatives of the structure R-OO-CR′XOR″, **1**, were carried out. Peracetals **1** (R′ = alkyl or H, X = H) are readily formed[9] and stable to chromatography but require harsh conditions for deprotection,[10] while perortho esters[11] (R′ = H, aryl or alkyl and X = OR″) and peraminals[12] are unstable to chromatography. Perketals **1** with R′ = X = alkyl are readily prepared[13,14] from hydroperoxides, are stable to normal or reverse-phase chromatography, and can be deprotected under very mild acid conditions.

We have had the most success with resolution utilizing the vinyl ethers **2a** and **2b**, prepared from menthol and (-)-*trans*-2-phenylcyclohexanol[15] (Scheme II). Standard procedures for vinyl ether synthesis directly from the alcohol were unsuccessful, but the path through the acetylenic ether gave **2a** in 58% and **2b** in 84% yield for the two steps.[16] The perketals **3** could be prepared from **2** and hydroperoxide with pyridinium *p*-toluenesulfonate (PPTS) catalyst in yields of 92-100%. Hydroperoxide **4** was converted to the perketal **3a**, and **4**-**7**[17] (R = Me) were reacted with **2b** to give the corresponding perketals **3b**. In each case

Scheme I



Scheme II[a]



[a] (i) a Cl_3C_2H, KH, imidazole, b *n*-BuLi, (ii) MeMgBr/CuBr, (iii) PPTs/CH_2Cl_2.

Table I. Data for Hydroperoxide Resolution

racemic hydroperoxide	diastereomeric perketal ratio[a]	diastereomeric perketal yield[b]	resolved hydroperoxides yield[c]	resolved hydroperoxides ee[d]	resolved hydroperoxides rotation[e]
4	>99/1	77	85	97	+104 (*R*)
	1.5/98.5	76	89	95	-102 (*S*)
5 (R = Me)	>99/1	53	92	99	-1.9 (*R*)
	3.5/96.5	56	95	93	+1.6 (*S*)
6 (R = Me)	>98/2	91	90	96	-8.7 (*R*)
	>99/1	93	91	99	+9.1 (*S*)
7 (R = Me)	99/1	60	74	98	-4.3 (*R*)
	>99/1	59	64	98	+3.6 (*S*)

[a] Each pair of diasteromeric perketals is listed in order of reverse-phase chromatographic elution. [b] Yield of purified diastereomer based on 50% of racemic hydroperoxide. [c] Purified hydroperoxide isolated from hydrolysis of resolved perketals. [d] Assessed by HPLC on reformed perketal for **5**, **6**, and **7**; capillary GC of alcohol Mosher ester of **4**. Perketals derived from **4** were prepared from auxiliary of only 97% ee. [e] Measured in chloroform (c = 0.5-0.9).

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(17) In a representative procedure, 1 mmol of hydroperoxide is dissolved in 5-10 mL of dry CH_2Cl_2. Enol ether (1.2 equiv) is added along with 2-5% of PPTS. After the reaction is judged complete by TLC (usually 5-15 min), a small amount of $KHCO_3$ is added. Several volumes of CCl_4 are added, and the CH_2Cl_2 is removed (rotary evaporator or argon stream). The resulting solution is directly loaded onto a flash column of 230-400 mesh silica, and the perketal eluted with EtOAc/petroleum ether, typically in approximately 95% yield.

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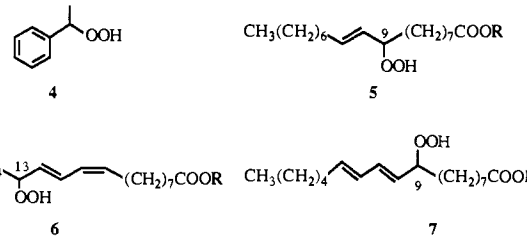

examined, the readily formed perketals were stable to chromatography under appropriate conditions, and the perketal protecting group could be removed with acetic acid/THF/water. Although the perketals are completely stable to normal-phase chromatography, some decomposition occasionally occurs in reverse-phase solvents such as acetonitrile/water or methanol/water unless 0.01% Et_3N is added.

Separation of the menthol derivatives **3a** was acceptable on analytical reverse-phase columns but troublesome on a preparative scale. In contrast to the menthol auxiliary, the diastereomeric perketals **3b** derived from (−)-phenylcyclohexanol generally gave base line separation on normal or reverse-phase chromatography, and hundreds of mg quantities of the diastereomers could be isolated with isomeric purities of 96% or better.[18] After recovery of hydroperoxides **4–7** from the perketal by hydrolysis with acetic acid/THF/water, the optical purity of the hydroperoxide was assayed by rederivatization with **2b** and analytical chromatography or by comparison of the specific rotation of the resolved enantiomers with a known natural product.[19] For **4** and **6**, reduction of the hydroperoxide to the corresponding alcohol and conversion of the alcohol to its Mosher ester followed by spectroscopic or chromatographic analysis was used to confirm the purity of the hydroperoxides.[20] No evidence for racemization during deprotection was observed. Properties of the perketals and resolved isomers are presented in Table I.

The hydroperoxides **5** and **6** are of particular interest. The fatty acid alcohol ($[\alpha]_D = -2.14°$ in EtOH, methyl ester) derived from **5** has recently been obtained from the timothy plant fungus *Epichloe typhina*.[21] Enzymatic formation of **5** is unexpected since all known lipoxygenase enzymes require at least diene substrates for activity. The hydroperoxide **5** resulting from the initially eluting perketal could be resolved to 99% ee and the derived alcohol (R = Me) had $[\alpha]_D = -4.6°$ (EtOH), indicating that the material isolated from *Epichloe typhina* is not optically pure. The *S* enantiomer of hydroperoxide **6** (R = H), a natural product resulting from the action of soybean lipoxygenase on linoleic acid,[3] could be prepared in one pot from the corresponding perketal by LiOH hydrolysis of the methyl ester followed by acidification to give the deprotected free acid hydroperoxide which was identical with the lipoxygenase product in every respect.

The use of chiral perketal derivatives to resolve hydroperoxides may have widespread application. We have yet to study a hydroperoxide (seven total) that could not be resolved by chromatography of one of the perketal derivatives.

(18) The 96% figure and the purities quoted in Table I are drawn from preparative (150–750 mg) resolutions. Chromatographic conditions: Rainin 21 mm × 25 cm C18 Dynamax (8μ), 15–50 mg/injection, 9 mL/min. Perketal **4**: 950/50/0.1 $CH_3CN/H_2O/Et_3N$, 21.2, 23.2 min (α = 1.15). **5**: 0.01% Et_3N/MeOH, 33.0, 34.2 min (α = 1.05). **6**: CH_3CN, 51.3, 55.7 min (α = 1.1). **7**: CH_3CN, 58.72, 64.45 (α = 1.11). Recovery of perketals was 60–90%. It should be noted that base line (100%) separations are often achieved during analytical separations by using two Altex Ultrasphere 4.6 mm × 25 cm C-18 columns in series.

(19) Perketals were deprotected in 4:2:1 THF/HOAC/H_2O in the presence of 0.1% butylated hydroxytoluene (BHT) within 4–8 h at room temperature. Hydroperoxide **4** was extracted from water with ether; **5–7** were isolated by removal of solvent in vacuo. The hydroperoxides were separated from hydrolyzed auxiliary by flash chromatography on 230–400 mesh silica in ether/petroleum ether and concentrated in the presence of 0.1% BHT.

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Principal Component Self-Modeling Analysis Applied to Conformational Equilibration of 1,3-Butadiene Vapor. UV Spectra and Thermodynamic Parameters of the Two Conformers

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1,3-Butadiene exists as a mixture of two conformations separated by a small energy barrier.[1] The more stable is planar *s-trans*-1,3-butadiene, while the less stable *s-cis*-1,3-butadiene, planar or twisted, has been the topic of many recent experimental[2] and theoretical[3] investigations. The UV absorption spectrum of the minor conformer in an Ar matrix at 20 K was estimated by subtraction of the spectrum of the s-trans conformer from a spectrum obtained by irradiation of 1,3-butadiene at 214 nm, assuming that only the s-trans conformer absorbs at 200 nm.[4] A Gaussian shape spectrum resulted with λ_{max} significantly red shifted from that of the s-trans conformer, 226 and 212 nm, respectively, leading to a preference for the planar s-cis geometry.[4]

In this paper we report the resolution of UV absorption spectrothermal matrices of 1,3-butadiene vapor by using our modified principal component analysis (PCA)-self modeling (SM) method.[5]

Two sets of 90 UV spectra were measured in the 5.0 to 93.0 °C temperature range with a Perkin Elmer λ5 spectrophotometer interfaced to a PC's Limited 80286/87 (12 MHz) microcomputer. Spectral set **A**, consisting of spectra in the 250–226 nm range in 0.2-nm increment, was obtained with a high 1,3-butadiene partial pressure (air was not excluded). The second set **B**, consisting of spectra in the 246–196 nm range in 0.4-nm increments, was obtained with a lower partial pressure of 1,3-butadiene vapor. PCA treatment of matrix **A** gave eigenvalues corresponding to a two-component system. The coefficients (α_i, β_i) for the experimental spectra adhered closely to the normalization line, Figure 1. A narrow range of pure component coefficients for the s-trans conformer was found readily because only the minor conformer contributes significantly at the high λ part of the spectrum. Minor conformer coefficients were determined by applying the constraint that they correspond to the best fit of the fractional contributions to the van't Hoff equation

$$\ln \frac{\chi_{s\text{-}cis}}{\chi_{s\text{-}trans}} = -\frac{\Delta H}{RT} + \frac{\Delta S}{R} + \ln \frac{\Sigma\epsilon_{s\text{-}cis}}{\Sigma\epsilon_{s\text{-}trans}} \qquad (1)$$

where ΔH and ΔS are enthalpy and entropy differences for the s-trans $\rightleftarrows$ s-cis equilibrium and $\Sigma\epsilon_{s\text{-}cis}$ and $\Sigma\epsilon_{s\text{-}trans}$ are sums of absorptivity coefficients over the λ range monitored. Plots of standard deviation of fit, σ (Figure 1) versus combination coefficient β, show a minimum defining the optimum β value (for a given β, α is defined by the normalization equation). The van't Hoff plot corresponding to this limit gives $\Delta H = 2.950 \pm 0.002$ kcal/mol, Figure 2. Since the limit for the s-cis conformer depends on the pure component coefficients selected for the s-trans conformer, region R on normalization line, we estimate that a more realistic uncertainty range for ΔH is ±0.15 kcal/mol. Our value falls within the range, 2.3–3.3 kcal/mol, from previous determinations.[1c,6]

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