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A New Synthon for Optically Active Diene Hydroperoxides

Patrick Dussault,* In Quen Lee, and Scott Kreifels

Department of Chemistry, University of Nebraska—Lincoln, Lincoln, Nebraska 68588-0304

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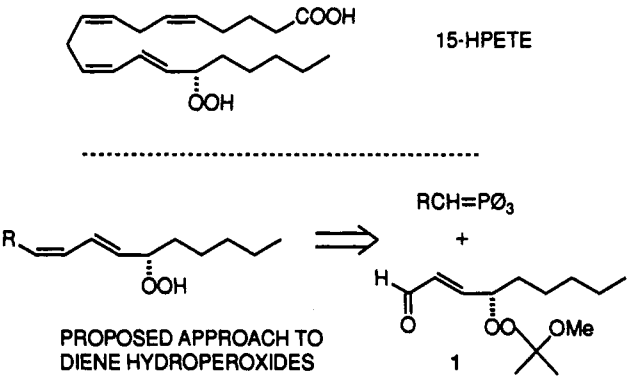
Summary: The olefination of an enzymatically derived γ-peroxy-α,β-unsaturated aldehyde (1) allows the synthesis of optically active diene hydroperoxides in high enantiomeric excess. The application of this method to the synthesis of 13(*S*)-hydroperoxy-9(*Z*),11(*E*)-octadecadienoic acid methyl ester is presented.

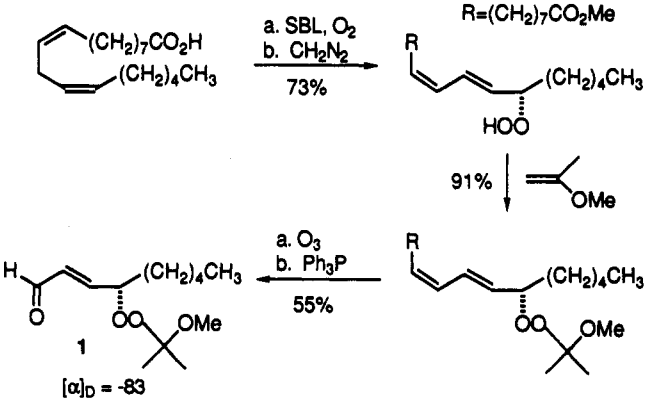
Diene hydroperoxides resulting from the peroxidation of polyunsaturated fatty acids are an important class of biomolecules. For example, the enzymatic peroxidation of arachidonic acid to hydroperoxyeicosatetraenoic acids (HPETEs) is an integral step in the biosynthesis of leukotrienes and lipoxins, known mediators of anaphalyxis and inflammation.[1-3] However, in spite of the biomedical importance of diene hydroperoxides, only a limited number of methods are available for their racemic synthesis and few general methods exist for the synthesis of single enantiomers. Consequently, few diene hydroperoxides are available in optically active form.

Synthetic approaches to optically active diene hydroperoxides have been hampered by the perceived requirement for penultimate introduction of the labile hydroperoxide group. For example, common preparative methods for final-step dioxygenation, such as autoxidation or singlet oxygenation of 1,4-dienes, produce a racemic mixture of hydroperoxide regioisomers.[4] Lipoxygenase enzymes catalyze the aerobic oxidation of (*Z*,*Z*)-1,4-dienes to (*S*)-hydroperoxy (*E*,*Z*)-2,4-dienes in high enantiomeric excess but are restricted to a limited class of substrate.[3] The displacement of optically active sulfonates or phosphates with hydroperoxide nucleophiles proceeds with poor stereospecificity.[5] Although the resolution of racemic diene hydroperoxides has recently been reported, synthetic approaches to the racemates themselves are often arduous.[6]

Scheme I



Scheme II



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(5) Nagata, R.; Kawakami, M.; Matsuura, T.; Saito, I. *Tetrahedron Lett.* **1989**, *30*, 2817–20 and references within.

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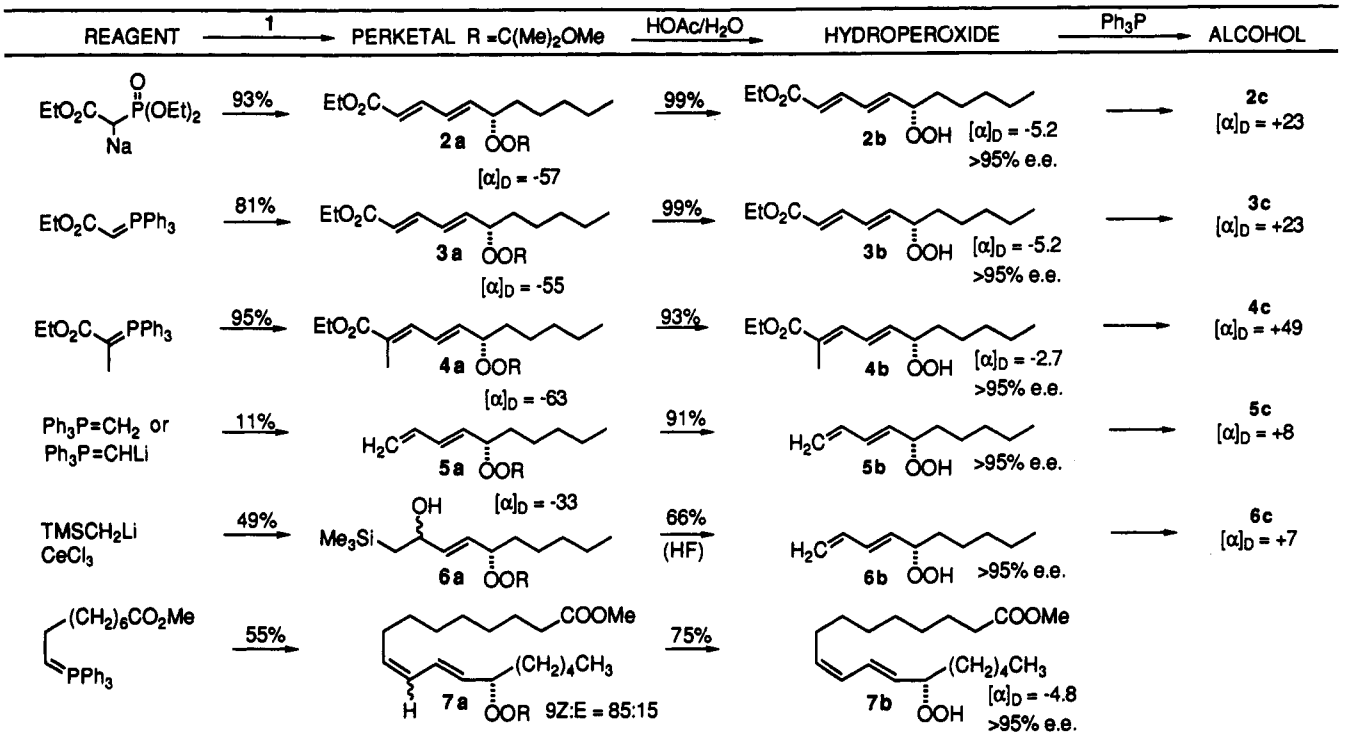
Scheme III. Olefination of Aldehyde 1[11]



We recently reported a new strategy for the stereoselective synthesis of unsaturated hydroperoxides based upon olefination of aldehydes containing a ketalized hydroperoxide.[7] We reasoned that application of this methodology to an optically active γ-peroxy-α,β-unsaturated aldehyde would provide an attractive route to a variety of optically active diene hydroperoxides (Scheme I). We report herein the stereospecific synthesis of optically active diene hydroperoxides via Wittig, Horner–Emmons, or Peterson olefination of aldehyde 1.

Lipoxygenase-catalyzed dioxygenation of commerically available linoleic acid (soybean lipoxygenase, pH 9 buffer, O_2) provides, after treatment with diazomethane, a 65% isolated yield of methyl 13(*S*)-hydroperoxy-9(*Z*),11(*E*)-octadecadienoate.[8] Acid-catalyzed ketalization with 2-methoxypropene affords a nearly quantitative yield of the diene perketal as a refrigerator-stable compound.[7] Selective ozonolysis of this diene to the Sudan III endpoint results in a 50–60% yield of 1 after chromatography[9,10] (Scheme II). The corresponding saturated peroxyaldehyde is available through prolonged ozonolysis, but all work described herein concerns use of the unsaturated aldehyde.

Olefination of peroxyaldehyde 1 with various nucleophilic reagents is shown in Scheme III.[11] Reaction with stabilized Wittig ylides such as (carbethoxymethylene)-triphenylphosphorane or (carbethoxyethylidene)triphenylphosphorane proceeds in high yield to provide the dienoate perketals **3a** and **4a**.[11,12] Reaction with the sodium salt of triethyl phosphonoacetate also proceeds, despite the increased basicity of the reagent, to furnish dienoate perketal **3a** in high yield.

Reaction of the perketal aldehyde with either methylenetriphenylphosphorane, the corresponding ylide anion, or the Peterson reagent (Me_3SiCH_2Li) furnishes simple diene **5a** in low yield.[13,14] Fortunately, Johnson's variant of the Peterson olefination ($Me_3SiCH_2Li/CeCl_3$) furnishes the desired β-hydroxy silane **6a** in 49% yield.[14] Attempted elimination of Me_3SiOH under basic conditions results only in decomposition, but treatment with HF/CH_3CN induces simultaneous elimination and perketal deprotection to produce the desired diene hydroperoxide (**6b**) in >30% overall yield for the two-step transformation. The last entry in Scheme III illustrates the potential of this methodology toward natural product synthesis. Reaction of aldehyde 1 with the ylide derived from methyl 9-bromononanoate furnishes a 55% yield of perketal **7a** as an 85:15 9*Z*:9*E* mixture. Perketal removal and HPLC purification afforded 13(*S*)-hydroperoxy-9(*Z*),11(*E*)-octadecadienoic acid methyl ester (**7b**), identical in every respect with enzymatically derived material.[8,15]

(6) Dussault, P. H.; Porter, N. A. *J. Am. Chem. Soc.* **1988**, *110*, 6276–77. The diastereomeric perketals were quantified either by integration of the methyl singlets in the ^1H NMR spectrum or more accurately by RP-HPLC (C-18, 4.6 × 250 mm, CH_3CN).

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(10) Ozonolyses were conducted as reported in ref 7. The crude peroxy aldehyde was purified by column chromatography or HPLC.

(11) All perketals and hydroperoxides have been characterized by ^1H, ^{13}C, and IR. Peroxides **2a**, **2b**, **3a**, **3b**, **4b**, and **7b** have been characterized by HRMS, as have the corresponding alcohols **2c**, **3c**, **4c**, **5c**, and **6c**. Full experimental details are presented in supplementary material. Hydroperoxides are isolated and stored in the presence of approximately 0.1% butylated hydroxytoluene (BHT).

(12) Sample Wittig olefination (stabilized ylides): To a solution of 216 mg (1.06 mmol) of perketal aldehyde 1 in toluene was added, over a 15-min period, (carbethoxymethylene)triphenylphosphorane (442 mg, 1.27 mmol). The reaction was stirred overnight, concentrated in vacuo, and directly subjected to chromatography on silica gel with 20% ethyl acetate/hexane to afford a 81% yield of the peroxy dienoate. Other olefinations (nonstabilized ylides, ylide anions, phosphonates): A 0.5 M solution of the perketal aldehyde in dry toluene was slowly added via canula to a −78 °C solution of the ylide, ylide anion, or phosphonate; isolation and purification were performed as before. The use of a standard aqueous workup facilitated product recovery during the Horner–Emmons olefination. The Peterson olefination was conducted as in ref 14. The ylide derived from methyl 9-bromononanoate was formed with $LiN(TMS)_2$ in THF at 0 °C and immediately cooled to −78 °C before addition of the aldehyde.

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(15) The 9*Z*/9*E* isomers of hydroperoxide **7b** were separated by HPLC (5% ethyl acetate/hexane).

Perketals **2a**, **3a**, **4a**, **5a**, and **7a** are deprotected to the corresponding hydroperoxides (**2b–7b**) in high yield upon acidic solvolysis.[7] Enantiomeric excesses were determined after quantitative ketalization of the hydroperoxides with the 2-propenyl ether of (−)-*trans*-2-phenylcyclohexanol.[6] The ratio of diastereomeric perketals is easily quantified by ^{1}H NMR or RP-HPLC.[6] In all cases, the produce hydroperoxides are found to be >95% ee.

Our preliminary studies clearly show that the stereoselective synthesis of optically active dienyl hydroperoxides is possible through construction of C=C double bonds in the presence of a masked peroxide. Investigations into the application of this new transformation towards the synthesis of HPETEs and other diene hydroperoxide natural products are in progress.

Caution. Although we have not encountered any specific dangers in the course of this work, standard precautions for handling peroxides (avoidance of heat, light, or metal salts, work behind shields, use of a stabilizer[11]) should be followed whenever possible.

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Supplementary Material Available: Spectroscopic and analytical data for compounds **1**, **2a–c**, **3a–c**, **4a–c**, **5a–c**, **6a–c**, and **7a,b** (10 pages). Ordering information is given on any current masthead page.

Specific Complexation with Mono- and Disaccharides That Can Be Detected by Circular Dichroism

Kazuhiko Tsukagoshi and Seiji Shinkai*

Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Fukuoka 812, Japan

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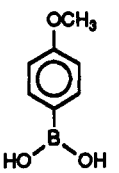
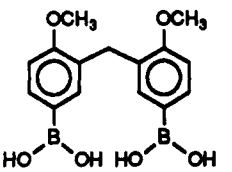
Summary: For the development of receptor molecules that can recognize sugar molecules, we newly synthesized 2,2′-dimethoxydiphenylmethane-5,5′-diboronic acid (**2**). It was shown that in the presence of **2**, D-glucose, D-maltose, D-cellobiose, and D-lactose result in a CD band at 275 nm. The results indicate that the CD spectroscopic method using **2** as a receptor molecule serves as a new sensory system for sugar molecules.

The development of receptor molecules that can precisely recognize and specifically bind guest molecules has been the focus of much recent attention.[1,2] In the design of such artificial receptor molecules, hydrogen-bonding interactions play a central role.[3–8] For example, Rebek et al.[3] synthesized model receptors that have carboxylate functions in a molecular cleft. Hamilton et al.[4] synthesized macrocyclic receptors that feature a 2,6-diaminopyridine unit as a recognition site. It was recently demonstrated that recognition through the hydrogen-bonding interactions is also effective for sugars and cyclodextrins.[9,10] However, more precise molecular recognition may be achieved through the formation of covalent bonds rather than through noncovalent interactions. It is known that boronic acids form cyclic esters with saccharides, particularly with those including *cis*-diol groups.[11] Wulff et al.[12] demonstrated that certain saccharide molecules are precisely recognized by two benzeneboronic acids immobilized in polymer matrices. In this paper, we report the specific complexation of benzeneboronic acid derivatives **1** and **2** with mono- and disaccharides. One can expect that these compounds will become CD (circular dichroism) active only when they form "specific" complexes with saccharide molecules.



1



2

Compounds **1** and **2** were synthesized by the treatment of *p*-bromoanisole and bis(2-methoxy-5-bromophenyl)-

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