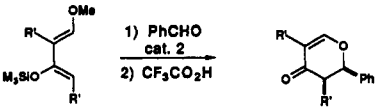


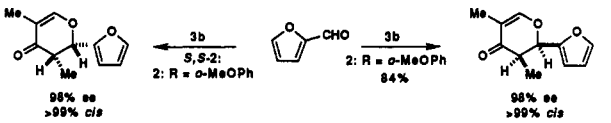
3 a: R' = H
b: R' = Me

4

configurations were determined by comparison of the specific rotation values with those of the literature.[7] Some of the results are summarized in Table I.

The new CAB catalyst disclosed herein exhibited the following characteristic features: (1) An extent of asymmetric induction is largely dependent on the structure of boric acid. In general, bulky phenylboric acid resulted in excellent asymmetric induction. Overly bulky substituents, however, led to the eminent loss of reactivity (entry 11), while the alkoxy substituents increased the reactivity of the catalyst without significant loss of selectivity. The catalyst derived from 2,4,6-trialkylphenylboric acid or *o*-alkoxyphenylboric acid thus reveals high reactivity and asymmetric induction with diene **3a** (entries 4 and 5) and **3b** (entries 12, 14, and 15), respectively. (2) Choice of alkoxyphenylboric acid is crucial for obtaining the high *diastereoselectivities* with diene **3b** (entries 12, 15, 16) which is in accord with our previous observation.[7] (3) Judging from the product configuration, CAB catalyst (from natural tartaric acid) should effectively cover the *si* face of carbonyl when coordinated, and the selective approach of nucleophiles from the *re* face should agree well with the results of previously reported CAB-catalyzed Aldol and Sakurai-Hosomi reactions.[3,4] (4) Since unnatural tartaric acid derivatives are equally accessible in optically pure form, the present method allows the synthesis of *both antipodal* products by choosing the handedness of the chiral auxiliary 1.

The power of the CAB catalytic reaction for the enantioselective route to carbon-branched pyranose derivatives is seen from the following example:[9]



We believe that the experimental results outlined above will stimulate further exciting advances for designer Lewis acid and offer essential information on the direction of future design of CAB catalyst.[10]

Acknowledgment. Support of this research by the Ministry of Education, Science and Culture of the Japanese Government and the Takeda Foundation are greatly appreciated.

(9) Danishefsky, S.; Maring, C. *J. Am. Chem. Soc.* **1985**, *107*, 7762.

(10) **General Procedure.** Ligand 1 (148 mg, 0.4 mmol) and phenylboric acid (48 mg, 0.40 mmol) were dissolved in dry propionitrile (2 mL), the resulting solution was stirred at 25 °C for 30 min, and the reaction system was cooled to -78 °C. Aldehyde (2.0 mmol) and then diene (2.4 mmol) were added successively and the reaction stirred a further 8 h at the same low temperature before being poured into 4 N HCl. The product was extracted with ether repeatedly, and the combined ether layers were dried and concentrated. The residue was dissolved in CH_2Cl_2 (20 mL), treated with trifluoroacetic acid (0.184 mL, 2.4 mmol), and stirred at 0 °C for 1 h. Usual workup, yielding crude adduct, was followed by column chromatography to give the pure pyrone.

The Total Synthesis of 15(*S*)-HPETE

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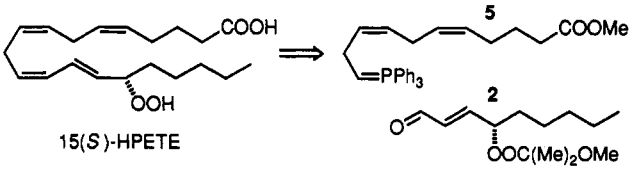
Summary: The total synthesis of 15(*S*)-HPETE in enantiomerically pure form is achieved through C=C bond formation in the presence of a masked hydroperoxide. Selective reduction of a peracid in the presence of a hydroperoxide affords a mild method for removal of an HPETE methyl ester.

The hydroperoxyeicosatetraenoic acids (HPETEs) are polyunsaturated hydroperoxides formed upon enzymatic peroxidation of arachidonic acid. These unstable natural products are the precursors of leukotrienes and lipoxins and may also contribute to carcinogenesis.[1] Despite the biomedical importance of HPETEs and other polyunsaturated hydroperoxides, there is as yet no broadly applicable method for their stereoselective synthesis in enantiomerically pure form. Lipoxygenase enzymes catalyze the stereoselective dioxygenation of specific polyunsaturated fats to the (*S*)-hydroperoxy-(*E,Z*)-diene unit found in HPETEs, but only a limited number of lipoxygenases

Scheme I



are readily available. The instability of the HPETEs and the apparent requirement for penultimate introduction of the labile hydroperoxide group have frustrated previous attempts at asymmetric chemical synthesis. For example, direct chemical dioxygenation of 1,4-dienes via autoxidation or singlet oxygenation produces a racemic mixture of hydroperoxide regioisomers while nucleophilic displacement of optically active sulfonates or phosphates with hydroperoxide nucleophiles proceeds with low stereospecificity.[2-4] Although the chromatographic resolution

(1) (a) Maycock, A.; Pong, S.-s.; Evans, J. F.; Miller, D. K. In *Leukotrienes and Lipoxygenases*; Rokach, J., Ed.; Elsevier: New York, 1989; pp 143-208. (b) Samuellson, B.; Dahlen, S.-E.; Lindgren, J. A.; Rouzer, C. A.; Serhan, C. N. *Science* **1987**, *237*, 1171-1176. (c) Marnett, L. J. In *Polycyclic Hydrocarbons and Carcinogenesis*; Harvey, R. G., Ed.; ACS Symposium Series 283; American Chemical Society: Washington, DC, 1985; pp 307-326.

(2) (±)-5-HPETE: Corey, E. J.; Albright, J. O.; Barton, A. E.; Hashimoto, S.-i. *J. Am. Chem. Soc.* **1980**, *102*, 1435-6. Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1983**, *24*, 999-1002. (±)11-HPETE: Just, G.; Luthe, C.; Viet, M. T. P. *Can. J. Chem.* **1983**, *612*, 712-719. 12(*S*)-HPETE (30% ee): Nagata, R.; Kawakami, M.; Matsuura, T.; Saito, I. *Tetrahedron Lett.* **1989**, *30*, 2817-20. (±)15-HPETE: Corey, E. J.; Marfat, A.; Falck, J. R.; Albright, J. O. *J. Am. Chem. Soc.* **1980**, *102*, 1433-35.

(3) Porter, N. A. *Acc. Chem. Res.* **1986**, *19*, 262-268.

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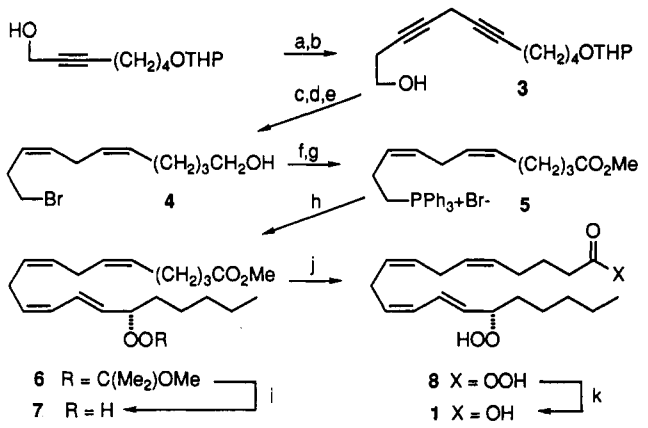
Scheme II[a]

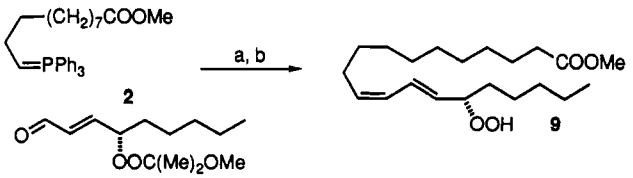


[a] Key: (a) Ph_3P, I_2 (72%); (b) 3-butynol, EtMgBr, CuBr·Me_2S (82%); (c) $Ni(OAc)_2$, $NaBH_4$, $H_2N(CH2)_2NH$, H_2 (68%); (d) CBr_4, imidazole, Ph_3P (96%); (e) TsOH, MeOH (95%); (f) H_2CrO_4 then CH_2N_2 (93%); (g) Ph_3P (100%); (h) $LiN(TMS)_2$, THF/HMPA, 2, (83%); (i) HOAc/H_2O (95%); (j) 2 equiv of LiOH, 4 equiv of H_2O_2, 3:1 THF/H_2O; (k) cycloheptene (82%, two steps).

of derivatized HPETEs has been recently reported, the isolation of purified racemic precursors is itself an arduous process best suited for milligram scale.[4,5] In the course of recent studies toward the synthesis of diene hydroperoxides, we demonstrated that an enzymatically derived γ-peroxy-α,β-unsaturated aldehyde could be coupled with Wittig or Horner–Emmons reagents to furnish optically active diene hydroperoxides in high enantiomeric excess.[6] We now report the application of this strategy to the synthesis of both 15(*S*)-HPETE and methyl 15(*S*)-hydroperoxy-11(*Z*),13(*E*)-eicosadienoate, a tetrahydroHPETE.

Our retrosynthetic strategy is shown in Scheme I. The eicosane skeleton of 15-HPETE (**1**) arises through Wittig coupling of aldehyde **2** with the ylide derived from 11-triphenylphosphonium 5(*Z*),8(*Z*)-undecadienoate methyl ester (**5**), ultimately derived from 5-hexynol. Aldehyde **2** is prepared from commercially available linoleic acid in three steps and 75% overall yield.[6] The total synthesis of 15(*S*)-HPETE is illustrated in Scheme II. The propargyl alcohol obtained upon protection and hydroxymethylation of 5-hexyn-1-ol is activated as the corresponding iodide and subjected to CuBr-catalyzed coupling with the dianion of 3-butyn-1-ol to afford diynol **3** in good yield.[7] Stereoselective diyne reduction with ethylenediamine-poisoned P2 Nickel furnishes the desired *Z,Z*-diene accompanied by 5% of an isomeric impurity; attempted reductions with $Pd/CaCO_3$ or $Pd/BaSO_4$ occur with significantly poorer stereospecificity.[8] The *Z,Z*-stereochemistry was confirmed by the observation of NOE enhancement between the bisallylic methylene and both flanking allylic positions. The minor impurity can be removed by HPLC after conversion to the corresponding bromide, and subsequent deprotection of the tetrahydropyranyl group provides bromo alcohol **4**. Although the Wittig reagent derived from **4** can be efficiently coupled with aldehyde **2** to afford a hydroperoxyeicosatetraene, the 5–8% of the 11*E* isomeric byproduct formed during olefination proved difficult to remove from the desired 5*Z*,8*Z*,11*Z*,13*E* product. Accordingly, alcohol **4** was converted to the corresponding methyl ester phosphonium salt **5** which underwent Wittig coupling with aldehyde **2** to furnish the perketalized 15-HPETE methyl ester **6** in 83% yield with ≥95% *Z* selectivity at the newly formed 11-olefin. Solvolysis of the perketal and HPLC purification of the resulting hydroperoxide provides 15(*S*)-HPETE methyl ester **7** ($[\alpha]_D$ = −2.5, MeOH) spectroscopically identical with enzymatically-derived material.[9,10] High-field NMR spectra of the diastereomeric perketals formed upon reaction with (−)-2-phenylcyclohexyl-2-propenyl ether demonstrated that the product was formed in >95% ee.[5]

Scheme III[a]



[a] Key: (a) $LiN(TMS)_2$, THF/HMPA, 2, (87%); (b) HOAc/H_2O, (85%).

The remaining step, deprotection of the methyl ester, proved unexpectedly difficult. Attempted saponification of hydroperoxyester **7** with LiOH/THF/H_2O, conditions successfully employed in our previous synthesis of a hydroperoxyoctadecadienoic acid, resulted in formation of substantial amounts of a yet unidentified hydroperoxide isomer.[6] Although this side reaction could be circumvented by first performing the saponification on perketal **6**, chromatographic removal of the small amount of 11*E* isomer proved difficult for the free acid. Fortunately, treatment of the hydroperoxy methyl ester **7** with LiOH and 4 equiv of H_2O_2 in 3:1 THF/H_2O cleanly furnishes the hydroperoxyeicosatetraene *peracid* **8**, which is selectively reduced with cycloheptene to afford 15(*S*)-HPETE (**1**, $[\alpha]_D$ = −4.6, MeOH) in 12 steps and 15% overall yield from commercially available starting materials.[10,11]

The broad applicability of this strategy is demonstrated by the remarkably rapid assembly of an unnatural tetrahydroHPETE, methyl 15(*S*)-hydroperoxy-11(*Z*),13(*E*)-eicosadienoate (**9**) (Scheme III). Wittig reaction between aldehyde **2** and the phosphonium salt derived from methyl 11-bromoundecanoate affords the eicosadienoate perketal in excellent yield. Deprotection and HPLC purification provides **9** ($[\alpha]_D$ = −3.3, MeOH) in excellent overall yield and >95% ee.

In summary, we have shown that the formation of carbon–carbon bonds in the presence of masked hydroperoxides allows the facile synthesis of an HPETE as well as an HPETE analogue. Application of this strategy to the

(4) Porter, N. A. Logan, J.; Knotoyiannidou, V. *J. Org. Chem.* **1979**, *44*, 3177–81.

(5) Porter, N. A.; Dussault, P.; Breyer, R. A.; Kaplan, J.; Morelli, J. *Chem. Res. Toxicol.* **1990**, *3*, 236–242. Dussault, P. H.; Porter, N. A. *J. Am. Chem. Soc.* **1988**, *110*, 6276–77. The diastereomeric perketals were quantified by integration of the methyl singlets at approximately 0.5 ppm in the ^1H NMR spectrum. The minor diastereomer was independently synthesized through the reaction of enzymatically derived hydroperoxide with racemic auxiliary.

(6) Dussault, P. H.; Lee, I. Q.; Kreifels, S. *J. Org. Chem.* **1991**, *56*, 4087–9.

(7) Heitz, M.-P.; Wagner, A.; Mioskowski, C.; Noel, J.-P.; Beaucourt, J.-P. *J. Org. Chem.* **1989**, *54*, 500–503.

(8) Brown, C. A.; Ahuja, V. K. *J. Chem. Soc., Chem. Commun.* **1973**, 553–4.

(9) New compounds were characterized by ^1H, ^{13}C, IR, and either HRMS or elemental analysis. Full experimental details are presented in the supplementary material. Hydroperoxides are isolated and stored in the presence of approximately 0.1% butylated hydroxytoluene (BHT).

(10) 15-HPETE was prepared enzymatically by a procedure similar to that of: Baldwin, J.; Davies, D. I.; Hughes, L.; Gutteridge, N. J. A. *J. Chem. Soc., Perkins Trans. 1* **1979**, 115–121, except that the crude peroxy acid was directly extracted with CH_2Cl_2; $[\alpha]_D$ = −4.4 MeOH. The corresponding methyl ester displayed $[\alpha]_D$ = −3.5, MeOH.

(11) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144.

synthesis of other hydroperoxide natural products is in progress.

Acknowledgment. This work was supported by the University of Nebraska Research Council and the American Cancer Society (CN-33). Mass spectra were obtained by Mr. Cliff Jacoby at the Midwest Center for Mass Spectroscopy, supported by NSF CHE-8620177.

Supplementary Material Available: Experimental procedures, spectral characterization, and ^1H NMR spectra of all new compounds (18 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Studies on the Biosynthesis of Aliphatic Lactones in *Sporobolomyces odorus*. Conversion of (*S*)- and (*R,S*)-13-Hydroxy-(*Z,E*)-9,11-octadecadienoic Acid into Optically Pure (*R*)-δ-Decalactone

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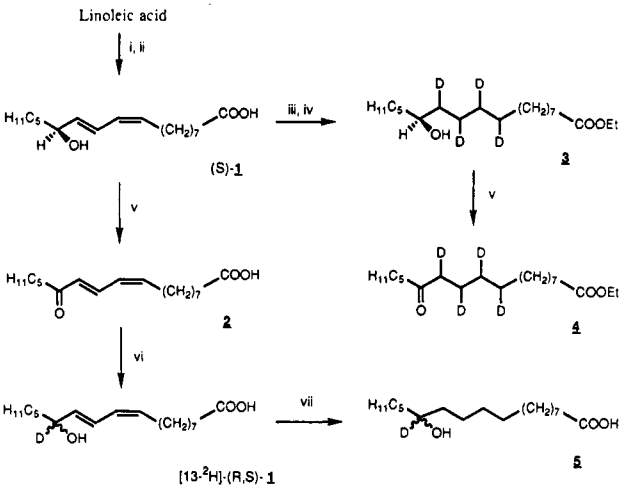
Summary: The mechanism of the biotransformations of (*S*)- and (*R,S*)-13-hydroxy-(*Z,E*)-9,11-octadecadienoic acid, **1**, into optically pure (*R*)-δ-decalactone, **12**, catalyzed by the yeast *Sporobolomyces odorus*, was studied, and an oxidation of the secondary hydroxy group followed by an enantioselective reduction of the keto acid intermediate was found to be responsible for the stereochemical outcome.

The yeast *Sporobolomyces odorus* excretes a series of aliphatic γ- and δ-lactones during growth,[1] which are known as important flavor compounds. Two main products (*R*)-γ-decalactone (>98% ee) and (*R*)-(*Z*)-6-dodecen-4-olide (84% ee), can be isolated from cultures of this organism. (*R*)-δ-**12** and (*S*)-(*Z*)-7-decen-5-olide accumulate in minor amounts and, after reaching maximum concentrations of 5 mg/L, both compounds are reabsorbed and degraded by the cells.[2] In the course of our studies on the biosynthesis of lactones in the yeast *Sp. odorus*, the transformation of [9,10,12,13-$^2H_4$]-linoleic acid into **12** could be detected. Additionally, ^{18}O labeled (*S*)-13-hydroperoxy- and 13-hydroxy-(*Z,E*)-9,11-octadecadienoic acid were generated by soybean lipoxygenase catalyzed hydroperoxidation of linoleic acid and administered to cell suspensions of *Sp. odorus*. This organism demonstrated the ability to transform both precursors into **12**.[2] These results indicate that a hydroperoxidation and a subsequent reduction are the initiating steps in the biosynthesis of (*R*)-**12**, which is formed by β-oxidation of the long-chain hydroxy acid. However, all lipoxygenases which have been isolated and characterized from plant sources or mammalian cells catalyze the hydroperoxidation of linoleic acid either stereospecifically, leading to the (*S*)-13-enantiomer (60–94% ee) or without stereospecificity.[3] Therefore, the mechanism of the conversion of enzymatically formed 13-hydroxy-(*Z,E*)-octadecadienoic acid (coriolic acid), **1**, into optically pure (*R*)-**12** remained unclear.

Recently, biotransformations of **1** into (*S*)-**12** (80% ee) with *Cladosporium suaveolens* were described.[4] The optically active lactone (78–82% ee) was also obtained when racemic coriolic acid was added to growing cultures of this organism. Studies using labeled (*S*)- (90% ee) and racemic 14-hydroxy-(*Z,E*)-10,12-nonadecadienoic acid as incubation substrates were also conducted. The degradation of both the optically active and the racemic precursor resulted first in the accumulation of (*S*)-γ-nonalactone. However, with continued fermentation the enantiomeric purity decreased, finally ending with a product mixture of predominantly (*R*)-configuration. Analysis of the chiral products by ^2H-NMR led to the hypothesis that different mechanisms are responsible for the degradation of each enantiomer of the substrate. Unequal rates in the formation and, later, in the catabolism of the products thus leads to the accumulation of optically active lactones.[4]

In this paper, stereochemical features of the transformation of (*S*)- and racemic **1** into optically pure (*R*)-**12**,

Scheme I. Synthetic Route Leading to the Precursors for the Feeding Experiments[a]



[a] Key: (i) soybean lipoxygenase;[7] (ii) $NaBH_4$; (iii) Pd/C, $^2H_2$; (iv) $EtOH/CH_3COCl$; (v) pyridinium chlorochromate;[8] (vi) NaB^2H_4; (vii) Pd/C, H_2.

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(1) Tahara, S.; Fujiwara, K.; Mizutani, J. *Agric. Biol. Chem.* **1973**, *37*, 2855. Tahara, S.; Mizutani, J. *Agric. Biol. Chem.* **1975**, *39*, 281. Tressl, R.; Apetz, M.; Arrieta, R.; Grünewald, K. *Flavors of Food and Beverages*; Academic Press: New York, San Francisco, London, 1978; p 145.

(2) Albrecht, W.; Heidlas, J.; Tressl, R. *Z. Naturforsch.* Submitted for publication.

(3) Vliegenthart, J. F. G.; Veldink, G. A. In *Free Radicals in Biology*; Pryor, W. A., Ed.; Academic Press: New York, 1982; Vol. V, p 29.

(4) Cardillo, R.; Fronza, G.; Fuganti, C.; Grasselli, P.; Mele, A.; Pizzi, D.; Allegrone, G.; Barbeni, M.; Pisiciotta, A. *J. Org. Chem.* **1991**, *56*, 5237.

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