Enantioselective Formation of an α, β-Epoxy Alcohol by Reaction of Methyl 13(*S*)-Hydroperoxy-9(*Z*),11(*E*)-octadecadienoate with Titanium Isopropoxide

ABSTRACT: Methyl 11(*R*),12(*R*)-epoxy-13(*S*)-hydroxy-9(*Z*)-octadecenoate (*threo* isomer) was generated from linoleic acid by the sequential action of an enzyme and two chemical reagents. Linoleic acid was treated with lipoxygenase to yield its corresponding hydroperoxide [13(*S*)-hydroperoxy-9(*Z*),11(*E*)-octadecadienoic acid]. After methylation with CH_2N_2, the hydroperoxide was treated with titanium (IV) isopropoxide [Ti(O-*i*-Pr)$_4$] at 5°C for 1 h. The products were separated by normal-phase high-performance liquid chromatography and characterized with gas chromatography–mass spectrometry, infrared spectroscopy, and nuclear magnetic resonance spectroscopy. Approximately 30% of the product was methyl 13(*S*)-hydroxy-9(*Z*),11(*E*)-octadecadienoate. Over 60% of the isolated product was methyl 11(*R*),12(*R*)-epoxy-13(*S*)-hydroxy-9(*Z*)-octadecenoate. After quenching Ti(O-*i*-Pr)$_4$ with water, the spent catalyst could be removed from the fatty products by partitioning between CH_2Cl_2 and water. These results demonstrate that Ti(O-*i*-Pr)$_4$ selectively promotes the formation of an α-epoxide with the *threo* configuration. It was critically important to start with dry methyl 13(*S*)-hydroperoxy-9(*Z*),11(*E*)-octadecadienoate because the presence of small amounts of water in the reaction medium resulted in the complete hydrolysis of epoxy alcohol to trihydroxy products.
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KEY WORDS: Epoxide, hydroperoxide, linoleic acid, lipoxygenase, titanium isopropoxide.

Fatty epoxy alcohols serve as intermediates in the facile conversion of common fats and oils to useful polar materials. Epoxy alcohols can be produced from fatty acid hydroperoxides by nonenzymatic catalysis with strong acid, ferrous iron, or hematin (1). They can also be produced from fatty acid hydroperoxides enzymatically by epoxygenase (2), lipoxygenase (3), or cytochrome P450-dependent mixed-function oxidases (4). Chemical methodology for the introduction of epoxides includes the Sharpless method (5) by using titanium complexes and a hydroperoxide donor and the Jacobsen method (6) with a manganese complex and sodium hypochlorite. Much work has been devoted to the investigation of heterogeneous titanium catalysts for epoxide formation with hydrogen peroxide or an organic hydroperoxide as the oxygen donor (7,8). Recently, it has been shown that complexes of titanium, vanadium, and molybdenum in the presence of singlet oxygen directly convert unsaturated compounds to epoxy alcohols (9,10). It has been postulated that the latter materials are formed through the intermediacy of metal–hydroperoxide complexes.

We have investigated the possibility of forming fatty acid epoxy alcohols with a titanium catalyst, starting with the methyl ester of the hydroperoxide of linoleic acid [methyl 13(*S*)-hydroperoxy-9(*Z*),11(*E*)-octadecadienoate, Me-HPODE], derived enzymatically with soybean lipoxygenase. The advantage of using enzymatically formed Me-HPODE is that approximately 97% of the hydroperoxide is in the 13(*S*) configuration, whereas chemically formed Me-HPODE is a mixture of the 13(*R,S*) and 9(*R,S*) species (11). Previously, Hamberg (12) showed that Me-HPODE converts to two diastereomeric α,β-epoxy alcohols in the presence of vanadium oxyacetylacetonate.

MATERIALS AND METHODS

Materials. Soybean (*Glycine max* L. Merr.) lipoxygenase (Lipoxidase, Type 1-B), linoleic acid, and silica gel (70–230 mesh) were purchased from Sigma (St. Louis, MO). Titanium(IV) isopropoxide [Ti(O-*i*-Pr)$_4$] and vanadyl acetylacetonate [VO(acac)$_2$] were purchased from Aldrich (Milwaukee, WI). Celite 545 was purchased from Fisher Scientific (Pittsburgh, PA). Water was purified to a resistance of 18 mΩ-cm in a Barnstead (Dubuque, IA) NANOpure system. All other reagents were of the highest purity available.

Me-HPODE formation. Linoleic acid (80 mg) was placed in a 125-mL Erlenmeyer flask, along with 80 mL 0.2 M borate buffer, pH 9.0. The flask was packed in ice and stoppered with a rubber septum. The contents were stirred gently for 0.5 h while oxygen was slowly bubbled into the buffer through a metal syringe needle. Four 50-μL aliquots of a lipoxygenase solution (32 mg/mL) in borate buffer were added at 30-min intervals. The pH of the reaction medium was lowered to 3 with 1 M HCl, and HPODE was extracted with 2 × 50 mL diethyl ether. The diethyl ether was dried over potassium sulfate, and the diethyl ether was removed under a stream of nitrogen. HPODE was dissolved in 5 mL CH_2Cl_2 and treated with diazomethane to give the methyl ester.

Titanium treatment. Me-HPODE (27 mg, 83 μmol), dissolved in 4.7 mL CH_2Cl_2, was treated with 63 μL (212 μmol) Ti(O-*i*-Pr)$_4$ for 1 h at 5 C. The reaction was quenched by the addition of 0.3 mL H_2O, and the reaction mixture was allowed to stand for 30 min at room temperature. The solid matter was removed by filtration through Celite. After washing the Celite with 10 mL diethyl ether, the filtrate and wash were combined, and the solvent was removed under a stream of dry nitrogen. The residue was dissolved in 6 mL CH_2Cl_2.

After establishing reaction conditions for synthesis of alcohol epoxide, a larger-scale synthesis was conducted: Me-HPODE (1.9 g, 5.8 mmol), dissolved in 300 mL CH_2Cl_2, was treated with Ti(O-*i*-Pr)$_4$ (1.1 mL, 3.7 mmol) for 1 h at 5°C. Spent Ti(O-*i*-Pr)$_4$ was removed with four 100-mL water washes. Each water fraction was back-washed with 100 mL CH_2Cl_2, and the CH_2Cl_2 fractions were combined prior to the next aqueous wash.

Vanadium treatment. Me-HPODE (95 mg, 291 μmol), dissolved in 14 mL CH_2Cl_2, was treated with 26 μL (1.5 μmol) VO(acac)$_2$ for 1 h at 5°C. The reaction mixture was diluted with 50 mL diethyl ether and washed with water (3 × 30 mL). After drying over potassium sulfate, the solvent was removed under a stream of nitrogen.

High-performance liquid chromatography (HPLC). Reaction products were separated on a Dynamax Macro HPLC Si column (300 × 10 mm) (Rainin, Emeryville, CA), installed on a Waters (Milford, MA) LCM1 HPLC instrument. It was equipped with a Waters 996 photodiode array detector in tandem with a Varex evaporative light-scattering detector MK III (Alltech, Deerfield, IL) and operated at a temperature of 40°C with N_2 as the nebulizing gas at a flow rate of 1.5 L/min. Mobile phase composition and linear gradient were hexane/isopropanol (97:3) to (94:6) over 28 min. The flow rate was 2 mL/min.

Gas chromatography–mass spectrometry (GC–MS). Generally, samples were analyzed before and after treatment with *N,O*-bis(trimethylsilyl) trifluoroacetamide (BSFTA; Pierce, Rockford, IL). Mass spectra were obtained on a Hewlett-Packard (HP) (Wilmington, DE) 5890 Series II Plus gas chromatograph, equipped with an HP 5972 mass-selective detector set to scan from *m/e* 10 to 600 at 1.2 scans/s. A capillary column (HP-5MS, 30 m × 0.25 mm), coated with 0.25 μm 5% cross-linked phenyl methyl silicone, was used to separate the products. The oven temperature was increased from 80 to 230°C at 10°C/min. The injector port temperature was 230°C, and the detector transfer line temperature was 240°C.

Nuclear magnetic resonance spectrometry (NMR). Spectra were obtained on a Varian Unity Plus 400 MHz NMR spectrometer in either 99 atom% *p*-dioxane-d_8 or 99.6 atom% benzene d_6 (Cambridge Isotope Labs, Woburn, MA). Typical acquisition conditions for the proton spectra were 9,600 data points; 4 kHz spectral width; 2.2 s recycle time. For carbon spectra, typical acquisition conditions were 60,000 data points; 25 kHz spectral width; 21.7 s recycle time. The 90° pulse was measured for both proton and carbon spectra prior to acquisition. All spectra were recorded at 30°C.

RESULTS AND DISCUSSION

Me-HPODE was incubated with Ti(O-*i*-Pr)$_4$, and the products were analyzed by HPLC and GC–MS. Low reaction temperatures and short reaction times favored production of alcohol epoxide. Shown in Figure 1 is the normal-phase HPLC profile of an incubation conducted at 5°C for 1 h. The peaks corresponding to minor products A were collected together. Their mass spectra were consistent with them being a mixture of methyl linoleate and conjugated methyl linoleate.

Product B constituted approximately 30% of the total product. Product B was identified as methyl 13-hydroxy-9,11-octadecadienoate by comparison of its mass spectrum to that of an authentic standard purchased from Oxford Biomedical Research (Oxford, MI). The mass spectrum of product B showed ions at *m/z* 310 (M), 292 (M – 18; loss of H_2O), and 279 (M – 31). After preparation of the $(CH_3)_3Si$ derivative, the mass spectrum showed ions at *m/z* 382 (M), 367 (M – 15; loss of CH_3), 311 $[(CH_3)_3SiO^+{=}CH{-}CH{=}CH{-}CH{=}CH{-}(CH_2)_7COOCH_3]$ and 225 $\{CH_3(CH_2)_4CH[OSi(CH_3)_3]{-}CH{=}CH{-}CH{=}CH^+\}$. Prior work has shown that the ion at *m/z* 225 is diagnostic for an *n*-6 hydroxy fatty acid with polyunsaturation (14). The ultraviolet/visible (UV/VIS) spectrum showed an absorption peak with λ_{max} 234 nm. Absorption at 234 nm demonstrates that the double bonds are conjugated (14).

The neat infrared spectrum of product B showed absorbances at 3500 cm^{-1} (hydrogen-bonded hydroxyl), 1740 cm^{-1} (ester carbonyl), and 985 and 951 cm^{-1} (double bonds conjugated with a *cis,trans* configuration) (15).

The decoupled ^{13}C NMR ($C_4D_8O_2$, 100 MHz) spectrum of product B showed important signals at δ 52.5 (OCH_3), 73.5 (C-13), 126.4, 130.4, 133.2, 139.8 (C=C), and 175.1 [*C*(O)OCH_3].

Important signals in the ^1H NMR ($C_4D_8O_2$, 400 MHz) spectrum of product B are shown in Table 1. The coupling constant $J_{9\text{-}10}$ was 10.8–11.0 Hz, and $J_{11\text{-}12}$ was 15.2 Hz, demonstrating that the $C_{9\text{-}10}$ double bond was *cis*, and the $C_{11\text{-}12}$ double bond was *trans*: J = 5–14 Hz for *cis* protons and 12–18 Hz for *trans* protons (16). By assuming that the configuration of C-13 has not changed, product B is methyl 13(*S*)-hydroxy-9(*Z*),11(*E*)-octadecadienoate (methyl ester of coriolic acid).

Major product C accounted for approximately 67% of the total product. Its mass spectrum showed an ion at *m/z* 288 [M – (18 + 31)]. After formation of the $(CH_3)_3Si$ derivative, its mass spectrum showed ions at *m/z* 383 (M – 15), 367 (M – 31), 327 (M – 71), 270 [M – 128; rearrangement with expulsion of $\cdot CO{-}CH(O\cdot){-}(CH_2)_4{-}CH_3$] (17) and 173 $[(CH_3)_3SiO^+{=}CH{-}(CH_2)_4{-}CH_3]$. The UV/VIS spectrum showed absorbance below 210 nm. Thus, the data show that compound C is a monounsaturated 18-carbon epoxy alcohol methyl ester with the hydroxyl group at C-13.

The neat infrared spectrum of product C showed a broad band centered at 3425 cm^{-1} (hydrogen-bonded hydroxyl), 1739 cm^{-1} (ester carbonyl), and 890 cm^{-1} (*trans* epoxide). No absorption band appeared in the region 900–1000 cm^{-1}, excluding the presence of *trans* double bonds (16).

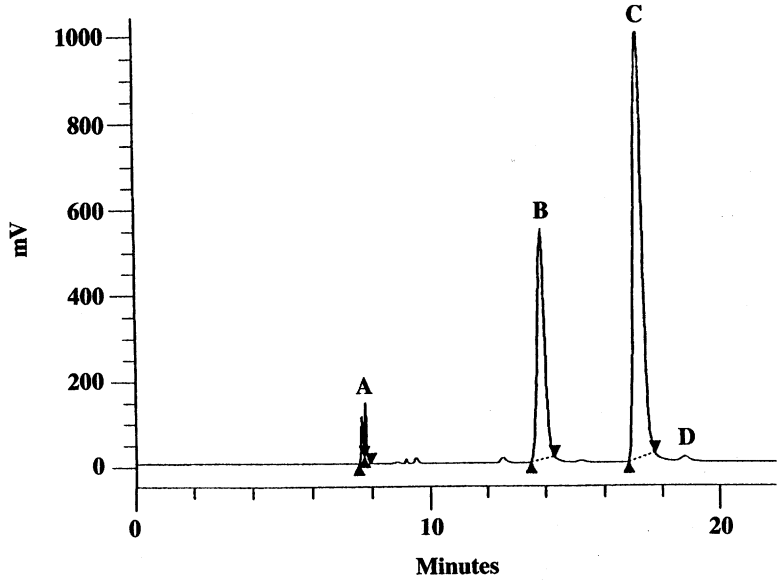

FIG. 1. Normal-phase high-performance liquid chromatographic analysis of the products obtained by the treatment of methyl 13(*S*)-hydroperoxy-9(*Z*),11(*E*)-octadecadienoate with Ti(*O*-*i*-Pr)$_4$. Structural analyses, as discussed in the text, resulted in the following elucidations: A, methyl linoleate and its conjugated isomer; B, methyl 13(*S*)-hydroxy-9(*Z*),11(*E*)-octadecadienoate; C, methyl 11(*R*),12(*R*)-epoxy-13(*S*)-hydroxy-9(*Z*)-octadecenoate; D, trihydroxy hydrolysis product of C.

The decoupled ^{13}C NMR (100 MHz) spectrum of product C is shown in Figure 2. Important signals in the spectrum obtained in C_6D_6 are δ 51.6 (OCH_3), 52.9 (C-12), 63.7 (C-11), 71.6 (C-13), and 174.2 [$C(O)OCH_3$]. The solvent signal partially obscured those from the double-bond carbons. Thus, the ^{13}C NMR spectrum was also obtained in $C_4D_8O_2$ to give the signals for the double bond: δ 129.4 (C-10) and 137.5 (C-9). Because there are only two signals for the epoxide carbons, two signals for the double-bond carbons, and one signal for the alcoholic carbon, product C is predominantly one structural isomer.

The ^{1}H NMR (C_6D_6, 400 MHz) spectrum of product C is shown in Figure 3. Important signals are listed in Table 1. The coupling constant $J_{9\text{-}10}$ was 11–11.2 Hz, demonstrating that the double bond is in the *cis* configuration: J = 5–14 Hz for *cis* protons and 12–18 Hz for *trans* protons (16). The coupling constant $J_{11\text{-}12}$ was 2.2–2.3 Hz, demonstrating that the configuration of the epoxide group is *trans*: J = 4.3 for *cis* and 2.1–2.4 for *trans* (18). The coupling constant $J_{12\text{-}13}$ is 4.6 Hz, indicating that the relationship between the adjacent protons of the alcohol and the epoxide is *threo*: J = 5 for *threo* and 3.25 for *erythro* (19). An analogous coupling constant, reported for the *threo* derivative of an alcoholic epoxide derived from the action of the fungus *Saprolegnia parasitica* upon arachidonic acid, was 4.5 Hz (20). In support of the *threo* as-

TABLE 1
Diagnostic ^{1}H NMR Chemical Shifts and Coupling Constants of Products B and C[a]

Chemical shift (δ)	Number of protons	Appearance	Assignment	Coupling constant (Hz)
Product B				
4.13	1H	*br s*	H-13	
5.48	1H	*dt*	H-9	$J_{8\text{-}9}$ = 7.7, $J_{9\text{-}10}$ = 10.8
5.75	1H	*dd*	H-12	$J_{11\text{-}12}$ = 15.2, $J_{12\text{-}13}$ = 6.4
6.06	1H	t	H-10	$J_{10\text{-}11}$ = 11.0
6.55	1H	*dd*	H-11	$J_{10\text{-}11}$ = 11.2, $J_{11\text{-}12}$ = 15.2
Product C				
2.97	1H	*dd*	H-12	$J_{11\text{-}12}$ = 2.2, $J_{12\text{-}13}$ = 4.6
3.60	1H	*br s*	H-13	
3.88	1H	*dd*	H-11	$J_{10\text{-}11}$ = 8.7, $J_{11\text{-}12}$ = 2.3
5.39	1H	*dd*	H-10	$J_{9\text{-}10}$ = 11.0, $J_{10\text{-}11}$ = 9.0
5.80	1H	*dt*	H-9	$J_{8\text{-}9}$ = 7.5, $J_{9\text{-}10}$ = 11.2

[a]NMR, nuclear magnetic resonance.

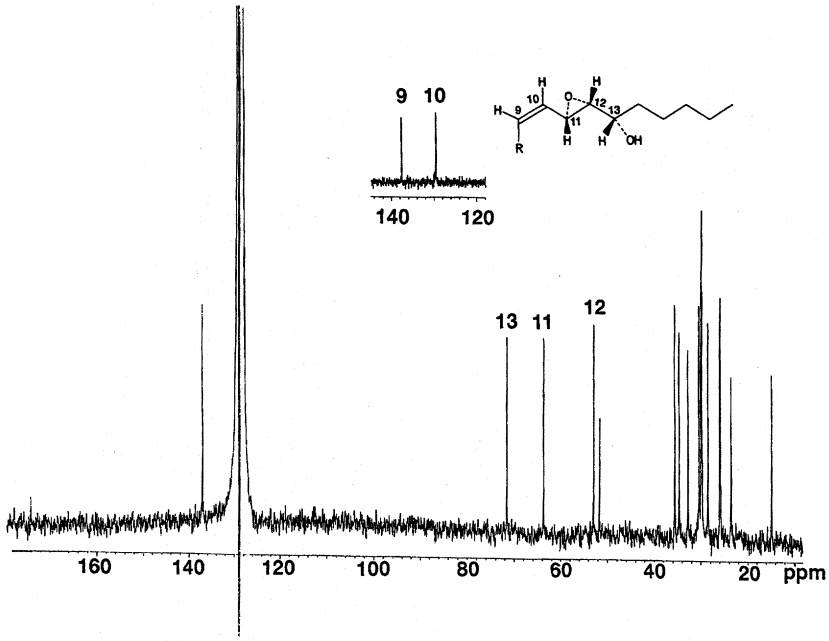

FIG. 2. ^{13}C-nuclear magnetic resonance spectrum of methyl 11(*R*),12(*R*)-epoxy-13(*S*)-hydroxy-9(*Z*)-octadecenoate.

signment, H-13 resonates at 3.60 ppm: 3.8 ± 1 ppm for *erythro* and 3.5 ± 1 ppm for *threo* (21).

From all data, we concluded that the stereochemical structure of product C is methyl 11(*R*),12(*R*)-epoxy-13(*S*)-hydroxy-9(*Z*)-octadecenoate (Figs. 2 and 3).

Minor product D is formed from C when the epoxide is hydrolyzed. This was inadvertently shown when the reaction was conducted with a wet sample of Me-HPODE: Product D was the major product formed. The mass spectrum of the $(CH_3)_3Si$ derivative of D showed ions at *m/z* 530 (M − 31), 400 (M − [71 + 90]; loss of $\bullet(CH_2)_4CH_3$ and $(CH_3)_3SiOH$), 285, 275 $\{(CH_3)_3SiO^+{=}CH\text{-}CH[OSi(CH_3)_3](CH_2)_4CH_3\}$, and 173. The UV/VIS spectrum showed end absorbance below 210 nm. Thus, the data demonstrate that product D is an 18-carbon trihydroxy methyl ester with a single double bond.

Larger amounts of product were subjected to HPLC analysis, and minor peaks were collected to determine if the *erythro* or other structural epoxy alcohol isomers were being formed.

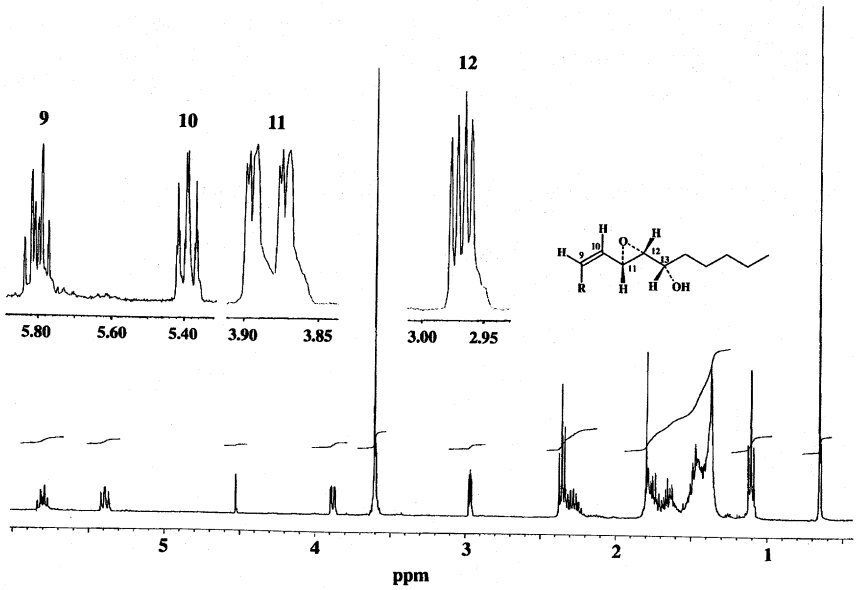

FIG. 3. ^{1}H-nuclear magnetic resonance of methyl 11(*R*),12(*R*)-epoxy-13(*S*)-hydroxy-9(*Z*)-octadecenoate.

No other isomers were detected. One minor product identified was methyl 13-keto-9,11-octadecadienoate (13), *m/z* 308 (M), 277 (M – 31), 252 (M – 56; β-cleavage with loss of $\cdot CH_2{=}CH{-}CH_2{-}CH_3$), 237 [M – 71; α-cleavage with loss of $\cdot(CH_2)_4CH_3$], 209 [M – 99; α-cleavage with loss of $\cdot C({=}O){-}(CH_2)_4CH_3$], 177 (209 – 32), and 151 $\{[(CH{=}CH)_2{-}C({=}O){-}(CH_2)_4CH_3]^+\}$. The UV/VIS spectrum contained an absorption peak at λ_{max} 271 nm.

As an additional check on the findings, Me-HPODE was subjected to the action of $VO(acac)_2$, because prior work had shown that both the *erythro* and *threo* epoxy alcohol isomers were formed by the action of this catalyst (12). HPLC and GC–MS analysis of the products derived from the action of $VO(acac)_2$ showed that two products had mass spectra identical to that of epoxy alcohol C. The *threo* epoxy alcohol eluted at 17.6 min, and the *erythro* isomer (*vide ante*) eluted at 14.6 min. The *erythro* and *threo* isomers constituted approximately 70% of the product, and the ratio of *erythro* to *threo* was 1.0:1.1. A minor product had a mass spectrum identical to that of alcohol B.

The results of the study with $VO(acac)_2$ showed that the *erythro* isomer of the epoxy alcohol and the alcohol B elute closely during HPLC analysis. If the *erythro* isomer of the epoxy alcohol had been produced by $Ti(O\text{-}i\text{-}Pr)_4$ catalysis, this isomer would have been collected along with alcohol B when the sample was obtained for NMR analysis. Examination of the ^{13}C NMR of alcohol B in the region where epoxide carbons resonate revealed no discernible signals. From consideration of the signal-to-noise ratio, an estimate for the upper limit of the yield of the *erythro* isomer by $Ti(O\text{-}i\text{-}Pr)_4$ is 3%. Thus, the results demonstrate that $Ti(O\text{-}i\text{-}Pr)_4$ is more *threo*-selective than $VO(acac)_2$. There have been few studies on the direct action of $Ti(O\text{-}i\text{-}Pr)_4$ on unsaturated hydroperoxides. However, the transfer of oxygen from saturated hydroperoxide to α,β-unsaturated alcohol has been intensively studied (10). These studies also showed that $Ti(O\text{-}i\text{-}Pr)_4$ is more *threo* selective than $VO(acac)_2$ (22).

Larger-scale reaction. No technical difficulties were encountered when conducting the $Ti(O\text{-}i\text{-}Pr)_4$ reaction on a larger scale, except that removal of spent $Ti(O\text{-}i\text{-}Pr)_4$ by filtration over Celite gave unsatisfactory results; the Celite readily clogged. Attempts to remove the spent titanium catalyst by partitioning between diethyl ether and water were also unsuccessful because the spent catalyst congregated in the lower portion of the diethyl ether layer. Satisfactory separation of the spent catalyst from the fatty products was achieved by partitioning the reaction products between CH_2Cl_2 and water. Although the spent catalyst is insoluble in water, it remained suspended in the aqueous phase above the CH_2Cl_2 layer. When 1.9 g Me-HPODE was treated with $Ti(O\text{-}i\text{-}Pr)_4$, 1.48 g of product was recovered after removal of the spent catalyst. Of this recovered product, 63% was the *threo* alcohol epoxide isomer C.

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