Highly Selective Asymmetric Synthesis of 2-Hydroxy Fatty Acid Methyl Esters Through Chiral Oxazolidinone Carboximides

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ABSTRACT: Highly selective asymmetric synthesis of 2-hydroxy fatty acid methyl esters has been accomplished through chiral imide enolates. Five chiral oleic acid imides were prepared by reaction of oleic acid with pivaloyl chloride followed by reaction with five different lithiated chiral oxazolidinones including (*R*)-(+)-4-benzyl-2-, (*S*)-(–)-4-benzyl-2-, (4*R*,5*S*)-(+)-4-methyl-5-phenyl-2-, (4*S*,5*R*)-(–)-4-methyl-5-phenyl-2-, and (*R*)-(+)-4-isopropyl-2-oxazolidinones in 88–92% yields. The chiral imides were reacted with $NaN(Me_3Si)_2$ at –78°C to give enolates, which subsequently reacted with 2-(phenylsulfonyl)-3-phenyloxaziridine to give hydroxylated products in 78–83% yields. Methanolysis of the hydroxylated products with magnesium methoxide gave methyl 2-hydroxyoleate. Enantiomeric excesses (ee) of the products were determined to be very high (98–99% ee) by ^1H nuclear magnetic resonance study after esterification of the hydroxy group with (*S*)-(+)-*O*-acetylmandelic acid. Enantioselective hydroxylation of other fatty acids including elaidic, petroselinic, vaccenic, and linoleic was evaluated under the similar conditions using (4*R*,5*S*)-(+)-4-methyl-5-phenyl-2-oxazolidinone as a chiral auxiliary to give 98% ee values for all cases.

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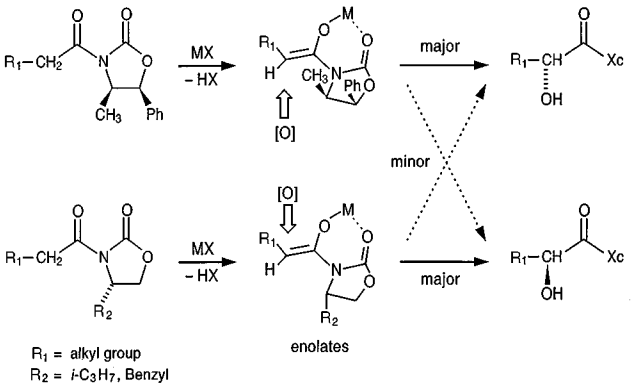
KEY WORDS: Asymmetric, chiral imide, enantioselective, fatty acid, hydroxylation, oleic acid, oxazolidinone.

Hydroxy fatty acids are of great interest because of their usefulness as lubricants, surfactants, plasticizers, and components in detergents, coatings, and paints (1). The value of a hydroxy fatty acid is often much enhanced when it exhibits a variety of biological activities such as hormone secretion, ion transport, cell proliferation, and other inflammatory responses (2). The biological activity of a hydroxy fatty acid depends on the number, position, and stereochemistry of the hydroxy groups. 2-Hydroxy fatty acids occur naturally in sphingolipids, as components of wool wax and skin lipids, and in a few unusual seed oils (3) and show antimicrobial activities (4).

Since chiral 2-hydroxy carboxylic acids are important building blocks for the synthesis of optically active materials, efforts have been made for enantioselective preparation of 2-hydroxy acids using enzymatic (5–8) and chemical (9–12) methods. Among the enzymatic methods recently reported are the enantioselective α-hydroxylation of carboxylic acids, including some fatty acids, with an α-oxidative enzyme system from peas (*Pisum sativum*) (7,8). The method is effective for some substrates but not for substrates containing a double bond such as oleic acid.

Several chemical methods for asymmetric α-hydroxylation of carboxylic acids by use of MoO_5/pyridine/hexamethylphosphorus triamide (MoOPH) with a camphor-based chiral auxiliary (10) and 2-sulfonyloxaziridines with chiral amides (11) or imides (12) have been reported. Among them the method developed by Evans *et al*. (12) with oxazolidinones as chiral auxiliaries and 2-(phenylsulfonyl)-3-phenyloxaziridine as an oxidant has been most widely applied in syntheses. In the method when a chiral oxazolidinone carboximide of a carboxylic acid is deprotonated at the α-position and the resulting enolate reacts with electrophilic oxygen, the chiral oxazolidinone group controls the direction of the attack from the less hindered face (Scheme 1). Although oxazolidinones with different structural features were used, the diastereomeric excesses (de) reported generally ranged from 80 to 90% for R_1 = Et, Ph, and CH_2Ph. When bulkier R_1 groups such as t-C_4H_9 and i-C_3H_7 were used, the de were higher (98% de).

Development of facile synthetic methods for the preparation of enantiomerically pure 2-hydroxy fatty acids would be critical for their utilization in industrial applications, especially in physiological applications. Herein, we report the successful chiral auxiliary-induced asymmetric synthesis of



SCHEME 1

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2-hydroxy fatty acid methyl esters containing double bonds by use of the method of Evans *et al*. (12).

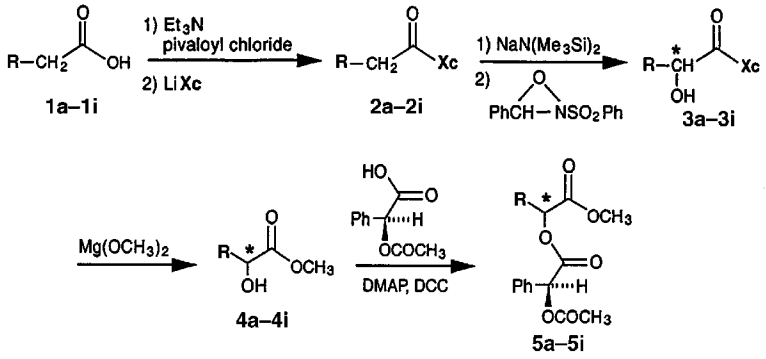
EXPERIMENTAL PROCEDURES

Materials. All fatty acids (99% pure) were purchased from Nu-Chek-Prep, Inc. (Elysian, MN), and all solvents were obtained from Fisher Scientific Co. (Fairlawn, NJ) and used without further purification except tetrahydrofuran (THF), which was freshly distilled from sodium metal and benzophenone ketyl before use. Unless otherwise specified, all other chemicals were purchased from Aldrich Chemical Co. (Milwaukee, WI), and used without further purification.

Analysis. ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR were performed with a Bruker (Rheinstetten, Germany) ARX 400 spectrometer. Fourier transform-infrared (IR) spectra were obtained with a PerkinElmer (Bucks, England) Spectrum RX FT-IR System as film on NaCl plates. Gas chromatography–mass spectrometry (GC–MS) analysis was conducted on a Hewlett-Packard (Palo Alto, CA) 5890/5970 benchtop GC–MS system, operated with electron ionization (EI) and equipped with a J&W Scientific (Folsom, CA) HP-5MS column (30 m × 0.25 mm i.d.). Derivatizations for GC–MS were carried out by silylating at ambient temperature with a Supelco (Bellefonte, PA) Sylon BTZ mixture that contained trimethylchlorosilane, *N,O*-bis(trimethylsilyl)acetamide and *N*-trimethylsilylimidazole. Preparative thin-layer chromatography (TLC) was carried out on silica gel 60F254 (2-mm thick).

Synthesis. As shown in Scheme 2, fatty acids **1a**–**1i** underwent reactions to give methyl esters of 2-hydroxy fatty acids **4a**–**4i**, which were transformed to chiral esters **5a**–**5i** for NMR study. The following are the procedures for each reaction. ^{1}H NMR, ^{13}C NMR, and IR spectra of all products are summarized in Table 1.

Synthesis of oxazolidinone carboximides. To a stirred solution of fatty acid (3.53 mmol) and 0.59 mL (4.23 mmol) of triethylamine in THF (30 mL) was added 0.46 mL (3.72 mmol) of pivaloyl chloride at –78°C, and the mixture was stirred for 10 min at –78°C and 30 min at 0°C. The resulting



Compound	R	Xc
a	$CH_3(CH_2)_7CH{=}CH(CH_2)_6$ *cis-*	
b	$CH_3(CH_2)_7CH{=}CH(CH_2)_6$ *cis-*	
c	$CH_3(CH_2)_7CH{=}CH(CH_2)_6$ *cis-*	
d	$CH_3(CH_2)_7CH{=}CH(CH_2)_6$ *cis-*	
e	$CH_3(CH_2)_7CH{=}CH(CH_2)_6$ *cis-*	
f	$CH_3(CH_2)_7CH{=}CH(CH_2)_6$ *trans-*	
g	$CH_3(CH_2)_{10}CH{=}CH(CH_2)_3$ *cis-*	
h	$CH_3(CH_2)_5CH{=}CH(CH_2)_8$ *trans-*	
i	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_6$ *cis- cis-*	

SCHEME 2

TABLE 1
^{1}H NMR, ^{13}C NMR, and IR Spectra of Products[a]

Compound	^{1}H NMR (ppm)	^{13}C NMR (ppm)	IR (cm^{-1})
2a, 2b	0.85–0.89 (*m*, 6H), 1.26–1.40 (*m*, 20H), 1.67 (*m*, 2H), 2.00 (*m*, 4H), 2.93 (*m*, 2H), 4.75 (*m*, 1H), 5.34 (*m*, 2H), 5.65 (*d*, 1H, *J* = 7.3 Hz), 7.28–7.42 (*m*, 5H)	14.1, 14.6, 22.6, 24.3, 27.2 (*d*), 29.1 (*d*), 29.3 (*t*), 29.5, 29.7, 29.8, 31.9, 35.6, 54.7, 78.9, 125.6, 128.7 (*d*), 129.7, 129.9, 133.3, 153.0, 173.1	1786 and 1703 (C=O), 1456 (C-N), 1345 and 1197 (C-O)
2c, 2d	0.87 (*t*, 3H, *J* = 7.1 Hz), 1.26–1.32 (*m*, 20H), 1.68 (*m*, 2H), 2.00–2.03 (*m*, 4H), 2.75 (*dd*, 1H, J_1 = 13.3 Hz, J_2 = 10.0 Hz), 2.92 (*m*, 2H), 4.66 (*m*, 1H), 5.34 (*m*, 2H), 7.19–7.34 (*m*, 5H)	14.1, 22.6, 24.2, 27.2 (*d*), 29.1 (*d*), 29.3 (*t*), 29.5, 29.7 (*d*), 31.9, 35.5, 37.9, 55.1, 77.3, 127.3, 128.9, 129.4, 129.7, 130.0, 135.3, 153.4, 173.4	1786 and 1703 (C=O), 1455 (C-N), 1385 and 1210 (C-O)
2e	0.85–0.91 (*m*, 9H), 1.25–1.30 (*m*, 20H), 1.64 (*m*, 2H), 1.97–2.30 (*m*, 4H), 2.36 (*m*, 1H), 2.84–2.96 (*m*, 2H), 4.17–4.27 (*m*, 2H), 4.40–4.43 (*m*, 1H), 5.31–5.34 (*m*, 2H)	14.1, 14.6, 17.9, 22.6, 24.4, 27.1 (*d*), 28.3, 29.0, 29.1, 29.2 (*d*), 29.4, 29.6, 29.7, 31.8, 35.5, 58.3, 63.2, 129.7, 129.9, 154, 173.3	1786 and 1704 (C=O), 1465 (C-N), 1386 and 1206 (C-O)
2f	0.85–0.89 (*m*, 6H), 1.24–1.39 (*m*, 20H), 1.65 (*m*, 2H), 1.95 (*m*, 4H), 2.91 (*m*, 2H), 4.75 (*m*, 1H), 5.36 (*m*, 2H), 5.64 (*d*, 1H, *J* = 7.3 Hz), 7.30–7.42 (*m*, 5H)	14.1, 14.5, 22.6, 24.2, 28.9, 29.0, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 31.8, 32.5 (*d*), 35.6, 54.7, 78.9, 125.6, 128.6, 128.7, 130.2, 130.4, 133.3, 153.0, 173.1	1786 and 1701 (C=O), 1457 (C-N), 1346 and 1196 (C-O)
2g	0.85–0.89 (*m*, 6H), 1.25–1.44 (*m*, 20H), 1.67 (*m*, 2H), 2.00–2.07 (*m*, 4H), 2.92–2.96 (*m*, 2H), 4.75 (*m*, 1H), 5.34 (*m*, 2H), 5.65 (*d*, 1H, *J* = 7.3 Hz), 7.30–7.41 (*m*, 5H)	14.1, 14.5, 22.6, 23.9, 26.2, 26.9, 27.2, 29.1, 29.3, 29.5, 29.6 (*t*), 31.9, 35.5, 54.7, 78.9, 125.6, 128.6, 128.7, 129.0, 130.4, 133.3, 153.0, 173.0	1786 and 1701 (C=O), 1457 (C-N), 1346 and 1196 (C-O)
2h	0.85–0.88 (*m*, 6H), 1.27–1.39 (*m*, 20H), 1.64–1.66 (*m*, 2H), 2.00–2.02 (*m*, 4H), 2.88–2.96 (*m*, 2H), 4.75 (*m*, 1H), 5.32–5.34 (*m*, 2H), 5.65 (*d*, 1H, *J* = 7.3 Hz), 7.30–7.42 (*m*, 5H)	14.1, 14.5, 22.6, 24.2, 27.1 (*d*), 28.9, 29.0, 29.2, 29.3, 29.4 (*d*), 29.6, 29.7, 31.7, 35.6, 54.7, 78.9, 125.6, 128.6, 128.7, 129.8 (*d*), 133.3, 153.0, 173.1	1787 and 1703 (C=O), 1457 (C-N), 1347 and 1197 (C-O)
2i	0.85–0.89 (*m*, 6H), 1.29–1.40 (*m*, 14H), 1.75 (*m*, 2H), 2.03–2.05 (*m*, 4H), 2.76 (*t*, 2H, *J* = 6.5 Hz), 2.90 (*m*, 2H), 4.75 (*m*, 1H), 5.28–5.36 (*m*, 4H), 5.65 (*d*, 1H, *J* = 7.3 Hz), 7.30–7.41 (*m*, 5H)	14.0, 14.5, 22.5, 24.2, 25.6, 27.1, 29.0, 29.1, 29.2, 29.3, 29.5, 31.5, 35.6, 54.7, 78.9, 125.6, 127.9, 128.0, 128.6, 128.7, 130.0, 130.1, 133.3, 153, 173.1	1786 and 1702 (C=O), 1456 (C-N), 1346 and 1197 (C-O)
3a,3b	0.87 (*t*, 3H, *J* = 7.0 Hz), 0.94 (*d*, 3H, *J* = 6.6 Hz), 1.27–1.35 (*m*, 18H), 1.50–1.57 (*m*, 3H), 1.81 (*m*, 1H), 2.00 (*m*, 4H), 3.33 (*d*, 1H, *J* = 8.1 Hz), 4.78 (*m*, 1H), 5.03 (*m*, 1H), 5.32 (*m*, 2H), 5.73 (*d*, 1H, *J* = 7.1 Hz), 7.30–7.44 (*m*, 5H)	14.1, 14.2, 22.6, 25.2, 27.1, 27.2, 29.1 (*d*), 29.3 (*d*), 29.5, 29.6, 29.7, 31.8, 34.5, 55.4, 70.9, 79.8, 125.5, 128.8, 128.9, 129.7, 130.0, 132.6, 152.6, 175.1	3513 (O-H), 1790 and 1699 (C=O), 1457 (C-N), 1347 and 1197 (C-O)
3c, 3d	0.87 (*t*, 3H, *J* = 7.1 Hz), 1.25–1.31 (*m*, 18H), 1.49–1.57 (*m*, 3H), 1.82 (*m*, 1H), 1.99 (*m*, 4H), 2.83 (*dd*, 1H, J_1 = 13.5 Hz, J_2 = 9.4 Hz), 3.29 (*dd*, 1H, J_1 = 13.5 Hz, J_2 = 3.9 Hz), 3.42 (*d*, 1H, *J* = 8.0 Hz), 4.25 (*m*, 2H), 4.65 (*m*, 1H), 4.98 (*m*, 1H), 5.33 (*m*, 2H), 6.20–7.36 (*m*, 5H)	14.1, 22.6, 25.2, 27.1, 27.2, 29.1 (*d*), 29.3 (*d*), 29.5, 29.6, 29.7, 31.8, 34.2, 37.4, 55.5, 66.8, 70.8, 127.5, 129.0, 129.4, 129.7, 129.9, 134.7, 153.1, 175.0	3510 (O-H), 1789 and 1696 (C=O), 1456 (C-N), 1352 and 1212 (C-O)
3e	0.84–0.93 (*m*, 9H), 1.25–1.51 (*m*, 23H), 1.75 (*m*, 1H), 1.96–1.99 (*m*, 4H), 2.42 (*m*, 1H), 3.44 (*d*, 1H, *J* = 8.1 Hz), 4.26–4.34 (*m*, 2H), 4.38–4.41 (*m*, 1H), 4.96 (*m*, 1H), 5.28–5.34 (*m*, 2H)	14.1, 14.4, 17.9, 22.6, 25.2, 27.1 (*d*), 28.1, 29.1 (*d*), 29.2, 29.4, 29.6, 29.7, 31.8, 34.1, 58.9, 64.0, 70.7, 129.7, 129.9, 153.8, 174.9	3511 (O-H), 1789 and 1696 (C=O), 1457 (C-N), 1303 and 1204 (C-O)
3f	0.87 (*t*, 3H, *J* = 7.1 Hz), 0.93 (*d*, 3H, *J* = 6.6 Hz), 1.25–1.34 (*m*, 21H), 1.78 (*m*, 1H), 1.95 (*m*, 4H), 3.33 (*d*, 1H, *J* = 8.1 Hz), 4.73 (*m*, 1H), 5.03 (*m*, 1H), 5.37 (*m*, 2H), 5.73 (*d*, 7.1 Hz), 7.30–7.43 (*m*, 5H)	14.1, 14.2, 22.6, 25.2, 26.2, 29.0, 29.1, 29.3, 29.4, 29.5, 29.6, 31.8, 32.5, 32.6, 34.5, 55.4, 70.9, 79.8, 125.5, 128.8, 128.9, 130.1, 130.4, 132.6, 152.6, 175.1	3510 (O-H), 1790 and 1697 (C=O), 1457 (C-N), 1347 and 1197 (C-O)

(*Continued*)

TABLE 1 (Continued)

Compound	^{1}H NMR (ppm)	^{13}C NMR (ppm)	IR (cm^{-1})
3g	0.86 (*t*, 3H, *J* = 7.1 Hz), 0.94 (*d*, 3H, *J* = 6.6 Hz), 1.24–1.30 (*m*, 18H), 1.57 (*m*, 3H), 1.84 (*m*, 1H), 2.00–2.01 (*m*, 4H), 3.36 (*d*, 1H, *J* = 8.0 Hz), 4.73 (*m*, 1H), 5.08 (*m*, 1H), 5.36 (*m*, 2H), 5.73 (*d*, 1H, *J* = 7.1 Hz), 7.30–7.43 (*m*, 5H)	14.1, 14.2, 22.6, 25.3, 26.8, 27.2, 29.3 (*d*), 29.5, 29.6 (*t*), 29.7, 31.9, 34.1, 55.4, 70.8, 79.8, 125.5, 128.8, 128.9, 130.6 (*d*), 132.6, 152.6, 170.0	3510 (O-H), 1791 and 1699 (C=O), 1457 (C-N), 1347 and 1197 (C-O)
3h	0.87 (*t*, 3H, *J* = 7.1 Hz), 0.93 (*d*, 3H, *J* = 6.6 Hz), 1.24–1.34 (*m*, 21H), 1.79 (*m*, 1H), 2.00 (*m*, 4H), 3.35 (*br s*, 1H), 4.73 (*m*, 1H), 5.05 (*m*, 1H), 5.37 (*m*, 2H), 5.73 (*d*, 7.1 Hz), 7.30– 7.43 (*m*, 5H)	14.1, 14.2, 22.6, 25.2, 27.1 (*d*), 28.9, 29.2 (*d*), 29.4 (*d*), 29.7 (*d*), 31.7, 34.6, 55.4, 70.9, 79.8, 125.5, 128.8, 128.9, 129.8, 129.9, 132.6, 152.6, 175.1	3510 (O-H), 1789 and 1700 (C=O), 1457 (C-N), 1347 and 1197 (C-O)
3i	0.88 (*t*, 3H, *J* = 7.1 Hz), 0.93 (*d*, 3H, *J* = 6.6 Hz), 1.28–1.36 (*m*, 12H), 1.53 (*m*, 3H), 1.81 (*m*, 1H), 2.04 (*m*, 4H), 2.75 (*t*, 2H, *J* = 6.5 Hz), 3.34 (*d*, 1H, *J* = 8.0 Hz), 4.73 (*m*, 1H), 5.03 (*m*, 1H), 5.33–5.36 (*m*, 4H), 5.73 (*d*, 1H, *J* = 7.1 Hz), 7.30–7.42 (*m*, 5H)	14.0, 14.2, 22.5, 25.2, 25.6, 27.1 (*d*), 29.1 (*d*), 29.3, 29.5, 31.5, 34.5, 55.4, 70.9, 79.8, 125.5, 127.8, 128.0, 128.8, 128.9, 130.0, 130.2, 132.6 152.6, 175.1	3510 (O-H), 1789 and 1700 (C=O), 1457 (C-N), 1347 and 1197 (C-O)
4a, 4b, 4c, 4d, 4e	0.90 (*t*, 3H, *J* = 7.0 Hz), 1.29–1.43 (*m*, 20 H), 1.62–1.67 (*m*, 1H), 1.76–1.80 (*m*, 1H), 2.00– 2.05 (*m*, 4H), 2.75 (*d*, 1H, *J* = 4.4 Hz), 3.81 (*s*, 3H), 4.20 (*m*, 1H), 5.35–5.38 (*m*, 2H)	14.0, 22.6, 24.7, 27.1, 27.2, 29.1, 29.2, 29.5, 29.6, 29.7, 31.9, 34.4, 52.3, 70.5, 129.7, 130.0, 175.8	3503 (O-H), 1740 (C=O), 1214 (C-O)
4f	0.90 (*t*, 3H, *J* = 7.0 Hz), 1.28–1.46 (*m*, 20 H), 1.63–1.67 (*m*, 1H), 1.76–1.82 (*m*, 1H), 1.95–2.00 (*m*, 4H), 2.73 (*br s*, 1H), 3.81 (*s*, 3H), 4.19–4.22 (*m*, 1H), 5.38–5.41 (*m*, 2H)	14.0, 22.6, 24.7, 28.9, 29.1 (*d*), 29.3, 29.4, 29.5, 29.6, 31.9, 32.5, 32.6, 34.4, 52.3, 70.5, 130.1, 130.5, 175.8	3504 (O-H), 1740 (C=O), 1216 (C-O)
4g	0.90 (*t*, 3H, *J* = 7.0 Hz), 1.27–1.55 (*m*, 20 H), 1.63–1.68 (*m*, 1H), 1.78–1.84 (*m*, 1H), 2.00–2.10 (*m*, 4H), 2.70 (*br s*, 1H), 3.80 (*s*, 3H), 4.20–4.22 (*m*, 1H), 5.33–5.42 (*m*, 2H)	14.0, 22.6, 24.8, 26.7, 27.2, 29.3 (*d*), 29.5, 29.6 (*d*), 29.7, (*d*), 31.9, 34.0, 52.4, 70.4, 128.9, 130.7, 175.7	3503 (O-H), 1740 (C=O), 1218 (C-O)
4h	0.90 (*t*, 3H, *J* = 7.0 Hz), 1.24–1.39 (*m*, 20 H), 1.59–1.65 (*m*, 1H), 1.78–1.82 (*m*, 1H), 2.01–2.07 (*m*, 4H), 2.73 (*br s*, 1H), 3.81 (*s*, 3H), 4.20–4.23 (*m*, 1H), 5.35–5.38 (*m*, 2H)	14.0, 22.6, 24.7, 27.2 (*d*), 28.9, 29.2, 29.4, 29.7 (*t*), 31.8, 31.9, 34.4, 52.3, 70.5, 129.8, 129.9, 175.9	3472 (O-H), 1734 (C=O), 1221 (C-O)
4i	0.90 (*t*, 3H, *J* = 7.0 Hz), 1.29–1.40 (*m*, 16H), 1.67–1.72 (*m*, 1H), 1.80–1.84 (*m*, 1H), 2.04–2.10 (*m*, 4H), 2.77 (*m*, 1H), 3.81 (*s*, 3H), 4.20 (*m*, 1H), 5.34–5.40 (*m*, 4H)	14.0, 22.5, 24.7, 25.6, 27.1, 27.2, 29.1, 29.2, 29.3, 29.5, 31.5, 34.4, 52.3, 70.5, 127.9, 128.1, 130.0, 130.2, 175.8	3462 (O-H), 1739 (C=O), 1218 (C-O)
5a, 5c, 53	0.87 (*t*, 3H, *J* = 7.1 Hz), 1.13–1.29 (*m*, 20 H), 1.75 (*m*, 2H), 1.97 (*m*, 4H), 2.18 (*s*, 3H), 3.71 (*s*, 3H), 5.00 (*dd*, 1H, J_1 = 6.8 Hz, J_2 = 6.3 Hz), 5.31–5.34 (*m*, 2H), 6.04 (*s*, 1H), 7.36–7.50 (*m*, 5H)	14.1, 20.6, 22.6, 24.6, 27.0, 27.2, 28.6, 28.8, 29.3, 29.4, 29.5, 30.8, 31.8, 52.3, 72.9, 74.2, 127.7, 128.6, 128.7, 129.3, 129.5, 130.0, 168.3, 170.0 (*d*)	1752 (C=O), 1228 (C-O)
5b, 5d	0.87 (*t*, 3H, *J* = 7.1 Hz), 1.26–1.36 (*m*, 20 H), 1.80–1.83 (*m*, 2H), 1.97–2.02 (*m*, 4H), 2.19 (*s*, 3H), 3.54 (*s*, 3H), 5.07 (*dd*, 1H, J_1 = 7.5 Hz, J_2 = 5.1 Hz), 5.32–5.35 (*m*, 2H), 5.99 (*s*, 1H), 7.38–7.51 (*m*, 5H)	14.1, 20.6, 22.6, 24.8, 27.0, 27.2, 28.8 (*d*), 29.3 (*d*), 29.4, 29.5, 29.7, 30.8, 31.8, 52.0, 73.1, 74.2, 127.8, 128.6, 129.2, 129.6, 130.0, 133.1, 168.3, 169.7, 170.2	1751 (C=O), 1231 (C-O)
5f	0.86 (*t*, 3H, *J* = 7.1 Hz), 1.12–1.32 (*m*, 20 H), 1.74 (*m*, 2H), 1.90–1.96 (*m*, 4H), 2.18 (*s*, 3H), 3.70 (*s*, 3H), 5.00 (*t*, 1H, *J* = 6.8 Hz), 5.34–5.37 (*m*, 2H), 6.04 (*s*, 1H), 7.36–7.50 (*m*, 5H)	14.1, 20.6, 22.6, 24.7, 28.5, 28.7, 29.1, 29.2, 29.3, 29.4, 29.6, 30.8, 31.8, 32.4, 32.5, 52.3, 72.9, 74.2, 127.7, 128.7 (*d*), 129.3, 130.0, 133.6, 168.3, 169.9 (*d*)	1755 (C=O), 1228 (C-O)

(*Continued*)

TABLE 1 (Continued)

Compound	^{1}H NMR (ppm)	^{13}C NMR (ppm)	IR (cm^{-1})
5g	0.86 (*t*, 3H, *J* = 7.1 Hz), 1.18–1.30 (*m*, 20H), 1.75–1.77 (*m*, 2H), 1.89–1.93 (*m*, 4H), 2.18 (*s*, 3H), 3.70 (*s*, 3H), 5.02 (*dd*, 1H, J_1 = 8.3 Hz, J_2 = 7.6 Hz), 5.15 (*m*, 1H), 5.53 (*m*, 1H), 6.04 (*s*, 1H), 7.36–7.50 (*m*, 5H)	14.1, 20.6, 22.6, 24.7, 26.2, 27.1, 29.3 (*d*), 29.5 (*t*), 29.6 (*d*), 30.4, 31.8, 52.3, 72.9, 74.2, 127.7, 128.3, 128.7, 129.3, 130.8, 133.6, 168.3, 169.8, 170.0	1755 (C=O), 1228 (C-O)
5h	0.87 (*t*, 3H, *J* = 7.1 Hz), 1.12–1.31 (*m*, 20 H), 1.74 (*m*, 2H), 2.00 (*m*, 4H), 2.18 (*s*, 3H), 3.71 (*s*, 3H), 5.00 (*t*, 1H, *J* = 6.8 Hz), 5.34 (*m*, 2H), 6.04 (*s*, 1H), 7.37–7.50 (*m*, 5H)	14.1, 20.6, 22.6, 24.6, 27.1, 27.2, 28.7, 28.9, 29.1 (*d*), 29.2, 29.7 (*d*), 30.8, 31.7, 52.3, 72.9, 74.2, 127.7, 128.7, 129.2, 129.7, 129.9, 133.6, 168.3, 170.0 (*d*)	1752 (C=O), 1228 (C-O)
5i	0.88 (*t*, 3H, *J* = 7.0 Hz), 1.13–1.30 (*m*, 14 H), 1.75 (*m*, 2H), 2.00–2.05 (*m*, 4H), 2.18 (*s*, 3H), 2.75 (*m*, 2H), 3.70 (*s*, 3H), 5.00 (*dd*, 1H, J_1 = 6.8 Hz, J_2 = 6.3 Hz), 5.32–5.37 (*m*, 4H), 6.04 (*s*, 1H), 7.37–7.50 (*m*, 5H)	14.1, 20.6, 22.5, 24.6, 25.5, 27.0, 27.1, 28.6, 28.8, 29.3 (*d*), 30.8, 31.4, 52.3, 72.9, 74.2, 127.7, 127.8, 128.0, 128.7, 129.3, 129.8, 130.2, 133.6, 168.3, 169.3, 169.9	1754 (C=O), 1228 (C-O)

[a]NMR, nuclear magnetic resonance; IR, infrared.

white slurry was cooled to −78°C and then a solution of lithiated oxazolidinone [obtained by adding 1.41 mL (3.53 mmol) of 2.5 M *n*-BuLi in hexane to a solution of 0.63 g (3.55 mmol) of oxazolidinone in 20 mL of THF at −78°C and stirred for 15 min] was added. The mixture was stirred for 15 min at −78°C and then warmed to room temperature (45 min). The reaction was quenched with 10 mL of 1 N aqueous $NaHSO_4$ solution. After adding water (30 mL), the mixture was extracted with dichloromethane (30 mL), washed with 5% aqueous $NaHCO_3$ and with saturated aqueous NaCl solution, and then dried over $MgSO_4$. Column chromatography on alumina with EtOAc/hexane (1:10) afforded a pure product as a colorless oil in 87–92% yields.

*Hydroxylation of **2a–2i***. To a stirred solution of 2.26 mmol of the chiral carboximide in THF (20 mL) at −78°C was added 2.50 mL (2.50 mmol) of 1.0 M NaN(trimethylsilyl)$_2$ in THF during a period of 15 min, and the mixture was stirred for 20 min at −78°C. To this solution was added a precooled (−78°C) solution of 0.89 g (3.40 mmol) of 2-(phenylsulfonyl)-3-phenyloxaziridine (13) in THF (20 mL). The solution was stirred for 2 min at −78°C and then quenched by rapid addition of 10-camphorsulfonic acid (2.60 g, 11.2 mmol) in THF (20 mL). The mixture was stirred at room temperature for 30 min and diluted with dichloromethane (20 mL). The mixture was washed with water, 5% aqueous $NaHCO_3$, and saturated aqueous NaCl solution and then dried over $MgSO_4$. Column chromatography on alumina with hexane/CH_2Cl_2/EtOAc (10:2:1) and then with 10% MeOH in CH_2Cl_2 gave a crude product. The second chromatography on silica gel with hexane/EtOAc (6:1) gave a pure product as a colorless oil in 68–83% yields.

*Methanolysis of **3a–3i***. To a solution of 0.11 mmol of a 2-hydroxy fatty acid carboximide in methanol/dichloromethane (1:1, 6 mL) was added 0.33 mL of 8% magnesium methoxide in methanol at 0°C. The mixture was stirred at 0°C for 30 min, and dichloromethane (30 mL) was added. The mixture was washed with 0.5 N HCl (30 mL), 5% aqueous $NaHCO_3$, and saturated aqueous NaCl solution, dried over $MgSO_4$, and evaporated. The residue was passed through a short silica gel column with hexane/EtOAc (6:1) as eluent to give the methyl ester of 2-hydroxy fatty acid as a colorless oil in 90–97% yields. EI–MS spectra of the silylated derivatives of products are summarized here.

4a, **4b, 4c, 4d,** and **4e**: *m/z* 384 (M^+, 18%), 369 ($M^+ - CH_3$, 100%), 325 ($M^+ - COOCH_3$, 91%). **4f**: *m/z* 384 (M^+, 22%), 369 ($M^+ - CH_3$, 100%), 325 ($M^+ - COOCH_3$, 68%). **4g**: *m/z* 384 (M^+, 21%), 369 ($M^+ - CH_3$, 100%), 325 ($M^+ - COOCH_3$, 77%). **4h**: *m/z* 384 (M^+, 17%), 369 ($M^+ - CH_3$, 80%), 325 ($M^+ - COOCH_3$, 100%). **4i**: *m/z* 382 (M^+, 26%), 367 ($M^+ - CH_3$, 100%), 323 ($M^+ - COOCH_3$, 68%).

*Esterification of **4a–4i** with (*S*)-(+)-O-acetylmandelic acid*. The methyl ester of hydroxy fatty acid (0.10 mmol) was dissolved in dichloromethane (3 mL, dried over $MgSO_4$), and (*S*)-(+)-*O*-acetylmandelic acid (30 mg, 0.15 mmol), 4-(dimethylamino)pyridine (DMAP, 3.4 mg, 0.03 mmol), and dicyclohexylcarbodiimide (DCC, 31 mg, 0.15 mmol) were sub-

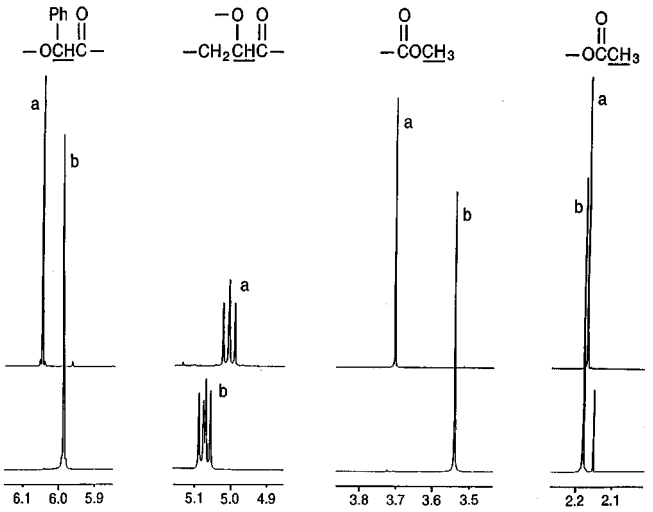


FIG. 1. Chemical shift differences in ^{1}H nuclear magnetic resonance spectra of diastereomers, (a) **5a** and (b) **5b**.

sequently added at 0°C. The mixture was stirred at 0°C for 30 min and at room temperature for 30 min. Hexane (10 mL) was added, and the insoluble solid was removed by filtration. Preparative TLC on silica gel with hexane/EtOAc (4:1) gave an enantiomerically pure product as a colorless oil in 95–98% yields.

RESULTS AND DISCUSSION

For the initial stage of this study, 2-(phenylsulfonyl)-3-phenyloxaziridine as an oxidant, oleic acid as a substrate, and five different commercially available chiral auxiliaries including (*R*)-(+)-4-benzyl-2-, (*S*)-(−)-4-benzyl-2-, (4*R*,5*S*)-(+)-4-methyl-5-phenyl-2-, (4*S*,5*R*)-(−)-4-methyl-5-phenyl-2-, and (*R*)-(+)-4-isopropyl-2-oxazolidinones were chosen. As shown in Scheme 2, oleic acid carboximides **2a**–**2e** were prepared by reaction of the oleic acid with triethylamine and pivaloyl chloride in THF followed by reaction with a lithiated oxazolidinone in 88–92% yields. Asymmetric hydroxylation of the carboximides **2a**–**2e** was carried out by reaction with $NaN(Me_3Si)_2$ at −78°C to give their corresponding enolates and then reaction of the enolates with 2-(phenylsulfonyl)-3-phenyloxaziridine to give hydroxylated products **3a**–**3e** in 68–83% yields.

Determination of de for **3a**–**3e** was initially attempted using GC–MS, but the molecule was decomposed at the elevated temperature needed to perform the analysis. Therefore, products **3a**–**3e** were transformed to methyl 2-hydroxyoleate (**4a**–**4e**) by the reaction with magnesium methoxide in methanol. A literature method (14) was used to determine the enantiomeric excess (ee) of methyl 2-hydroxyoleate (**4a**–**4e**) using ^{1}H NMR. Esterification reaction of **4a**–**4e** with (*S*)-(+)-*O*-acetylmandelic acid, DMAP, and DCC gave the chiral esters **5a**–**5e** in 88–99% yields. Pure **5a** and **5b** were isolated by preparative TLC, and the proton NMR (400 MHz) spectra are shown in Figure 1. The ^{1}H NMR spectra of diastereomers **5a** and **5b** have different chemical shifts, especially, for the four peaks that appear in the regions of 5.9–6.1, 4.9–5.1, 3.5–3.8, and 2.1–2.2 ppm. Among them, the methyl ester singlets which appeared at 3.71 ppm for **5a** (*R*-configuration at C2) and 3.54 ppm for **5b** (*S*-configuration at C2) were used to determine the enantioselectivities due to their large chemical shift differences. The absolute configuration of the products was confirmed by comparison to ^{1}H NMR spectra of the authentic reference compounds, methyl (*R*)-(+)-lactate and (*S*)-(−)-lactate. The chiral ester obtained by esterification of methyl (*R*)-(+)-lactate with (*S*)-(+)-*O*-acetylmandelic acid gave peaks at 6.01 (singlet), 5.09 (double doublets), 3.70 (singlet), and 2.16 (singlet) while the chiral ester of methyl (*S*)-(−)-lactate gave peaks at 5.97 (singlet), 5.16 (double doublets), 3.55 (singlet), and 2.18 (singlet).

To determine the ee of methyl 2-hydroxyoleate (**4a**–**4e**), the relative amounts of diastereomers in the chiral esters **5a**–**5e** were calculated using the proton NMR before isolation of one diastereomer. As shown in Table 2 (Entries 1–5), the % ee of **4a**–**4e** were very high (98–99%), presumably because of the relatively bulky, long alkyl chain of the oleic acid with no noticeable difference between the chiral auxiliaries. During the entire reaction sequence, no isomerization of the *cis*-alkene was detected by NMR or TLC.

To examine the utility of this asymmetric hydroxylation method to other fatty acids, elaidic (9*E*-), petroselinic (6*Z*-), vaccenic (11*E*-), and linoleic (9*Z*-, 12*Z*-) acids were reacted under similar conditions with (4*R*,5*S*)-(+)-4-methyl-5-phenyl-

TABLE 2
Reaction Yields and Enantiomeric Excesses (ee) Values

Entry	Yields (%)	Configuration at C2 of 3, 4, and 5	ee (%) of 4
1	**2a** (90), **3a** (83), **4a** (93), **5a** (99)	*R*	99
2	**2b** (90), **3b** (78), **4b** (90), **5b** (98)	*S*	98
3	**2c** (88), **3c** (81), **4c** (93), **5c** (98)	*R*	99
4	**2d** (92), **3d** (82), **4d** (90), **5d** (98)	*S*	98
5	**2e** (91), **3e** (68), **4e** (93), **5e** (99)	*R*	98
6	**2f** (88), **3f** (77), **4f** (97), **5f** (95)	*R*	98
7	**2g** (87), **3g** (74), **4g** (95), **5g** (98)	*R*	98
8	**2h** (92), **3h** (72), **4h** (95), **5h** (97)	*R*	98
9	**2i** (90), **3i** (70), **4i** (96), **5i** (98)	*R*	98

2-oxazolidinone as a chiral auxiliary to give **5f–5i** in high yields (Scheme 1). As shown in Table 2 (Entries 6–9), their ee of **4f–4i** are 98% with no observable double-bond isomerization for all cases.

The position of the hydroxy group in the products was confirmed by ^{13}C NMR and mass spectra. The chemical shifts of the C-2 (70.5 or 70.4 ppm) in the methyl esters of 2-hydroxy fatty acids **4a–4i** are consistent with the values in the literature (15). Further confirmation was obtained by silylating the methyl esters of 2-hydroxy fatty acids **4a–4i** with a silylating reagent (Supelco Sylon BTZ mixture) followed by GC–MS analyses. The EI mass spectra of the silylated products obey a fragmentation pattern of 2-hydroxy fatty acids in the literature (16). The typical peaks for silylated 2-hydroxy fatty acids by loss of CH_3 (m/z = 369 for **4a–4h**, m/z = 367 for **4i**) and loss of $COOCH_3$ (m/z = 325 for **4a–4h**, m/z = 323 for **4i**) were obtained in the EI mass spectra.

This research provides a convenient route to enantiomerically pure 2-hydroxy fatty acid methyl esters and could be similarly applied to prepare other functionalized fatty acid esters such as 2-amino fatty acid esters and 2-halo fatty acid esters.

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REFERENCES

1. Yang, W., L. Dostal, and J.P.N. Rosazza, Stereospecificity of Microbial Hydrations of Oleic Acids to 10-Hydroxystearic Acid, *Appl. Environ. Microbiol. 59*:281–284 (1993).
2. Spector, A.A., J.A. Gordon, and S.A. Moore, Hydroxyeicosatetraenoic Acids (HETEs), *Progr. Lipid Res. 27*:271–323 (1988).
3. Gunstone, F.D., Hydroxy Acids, in *The Lipid Handbook*, edited by F.D. Gunstone, J.L. Harwood, and F.B. Padley, Chapman and Hall, London, 1992, pp. 15–16.
4. Kurtzman, C.P., R.F. Vesonder, and M.J. Smuley, Formation of Extracellular C_{14}–C_{18} 2-*D*-Hydroxy Fatty Acids by Species of *Saccharomycopsis*, *Appl. Microbiol. 24*:650–652 (1973).
5. Nakamura, K., K. Inoue, K. Ushio, S. Oka, and A. Ohno, Stereochemical Control on Yeast Reduction of α-Keto Esters. Reduction by Immobilized Bakers' Yeast in Hexane, *J. Org. Chem. 53*:2589–2593 (1988).
6. Wong, C.-H., and J.R. Matos, Enantioselective Oxidation of 1,2-Diols to L-α-Hydroxy Acids Using Coimmobilized Alcohol and Aldehyde Dehydrogenases as Catalysts, *Ibid. 50*:1992–1994 (1985).
7. Adam, W., W. Boland, J. Hartmann-Schreier, H.-U. Humpf, M. Lazarus, A. Saffert, C.R. Saha-Moller, and P. Schreier, α-Hydroxylation of Carboxylic Acids with Molecular Oxygen Catalyzed by the α-Oxidase of Peas (*Pisum sativum*): A Novel Biocatalytic Synthesis of Enantiomerically Pure (*R*)-2-Hydroxy Acids, *J. Am. Chem. Soc. 120*:11044–11048 (1998).
8. Adam, W., W. Lazarus, A. Saffert, C.R. Saha-Moller, and P. Schreier, Enantioselective α-Hydroxylation of Carboxylic Acids with Molecular Oxygen Catalyzed by the α-Oxidation Enzyme System of Young Pea Leaves (*Pisum sativum*): A Substrate Selectivity Study, *Tetrahedron: Asymmetry 7*:2287–2292 (1996).
9. Corey, E.J., J.O. Link, and Y. Shao, Two Effective Procedures for the Synthesis of Trichloromethyl Ketones, Useful Precursors of Chiral α-Amino and α-Hydroxy Acids, *Tetrahedron Lett. 33*: 3435–3438 (1992).
10. Gamboni, R., P. Mohr, N. Waespe-Sarcevic, and C. Tamm, Asymmetric Synthesis of α-Hydroxy-Ester *via* Ester Enolates, *Ibid. 26*:203–206 (1985).
11. Davis, F., and L.C. Vishwakaram, Asymmetric Synthesis of α-Hydroxy Carboxylic Acids: Direct Oxidation of Chiral Amide Enolates Using 2-Sulfonyloxaziridines, *Ibid. 26*:3539–3542 (1985).
12. Evans, D.A., M.M. Morrissey, and R.L. Dorow, Asymmetric Oxygenation of Chiral Imide Enolates. A General Approach to the Synthesis of Enantiomerically Pure α-Hydroxy Carboxylic Acid Synthons, *J. Am. Chem. Soc. 107*:4346–4348 (1985).
13. Davis, F.A., S. Chattopadhyay, J.C. Towson, S. Lal, and T. Reddy, Chemistry of Oxaziridines. 9. Synthesis of 2-Sulfonyl- and 2-Sulfamyloxaziridines Using Potassium Peroxymonosulfate (Oxone), *J. Org. Chem. 53*:2087–2089 (1988).
14. El-Shearkaway, S.H., W. Yang, L. Dostal, and J.P.N. Rosazza, Microbial Oxidation of Oleic Acid, *Appl. Environ. Microbiol. 58*:2116–2122 (1992).
15. Tulloch, A.P., Carbon-13 NMR Spectra of All the Isomeric Methyl Hydroxy- and Acetoxyoctadecanoates, *Org. Magn. Reson. 11*:109–115 (1978).
16. Nicolaides, N., V.G. Soukup, and E.C. Ruth, Mass Spectrometric Fragmentation Patterns of Acetoxy and Trimethylsilyl Derivatives of All the Positional Isomers of the Methyl Hydroxypalmitates, *Biomed. Mass Spectrom. 10*:441–449 (1983).

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