Reduction of Fatty Ester Δ^2-Isoxazoline Heterocycles. Preparation of Fatty Esters Containing the β-Hydroxy Ketone Moiety

James A. Kenar*

NCAUR, ARS, USDA, Food and Industrial Oil Research, Peoria, Illinois 61604

ABSTRACT: Fatty ester compounds containing the β-hydroxy ketone moiety were prepared in good yields from their corresponding fatty Δ^2-isoxazoline heterocyclic precursors by a reductive hydrogenolysis–hydrolysis procedure using Raney nickel as catalyst. By this methodology, C-17, C-18, and C-19 straight-chain fatty methyl esters containing the 10-hydroxy 12-keto moieties were prepared in 73, 83, and 92%, respectively, from their corresponding isoxazoline fatty ester compounds. Two other 10-hydroxy 12-keto C-12 and C-14 fatty ester compounds were prepared in 84 and 92% yield, respectively. The C-12 β-hydroxy ketone contains a phenyl ring at C-12, whereas the C-14 β-hydroxy ketone compound has two methyl substituents at C-13. GC–MS using electron impact ionization was used to determine the hydroxyl and ketone positions after conversion of the hydroxyl group into its corresponding trimethylsilyl ether. The precursor fatty ester Δ^2-isoxazolines used in this study are readily available in one step from a 1,3-dipolar cycloaddition reaction between nitrile oxides and methyl 10-undecenoate. This overall two-step sequence, 1,3-dipolar cycloaddition followed by reductive ring opening, represents a convenient method to construct fatty ester compounds in good yields containing the β-hydroxy ketone functionality, an outcome not easily accessible by other methods.

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KEY WORDS: Fatty ester β-hydroxy ketones, 1,3-cycloaddition, Δ^2-isoxazolines, mass spectrometry, methyl 10-hydroxy-12-ketomargarate, methyl 10-hydroxy-12-ketononadecanoate, methyl 10-hydroxy-12-ketostearate, nitrile oxides, Raney nickel, reductive hydrogenolysis–hydrolysis.

In pursuit of new strategies to functionalize fatty ester compounds and derive new oleochemicals with potentially useful chemical and physical properties, we have been interested in examining transformations available to fatty ester Δ^2-isoxazoline heterocycles (4,5-dihydroisoxazoles). Recently, a series of fatty ester Δ^2-isoxazoline compounds, **3**, containing the isoxazoline heterocycle in the alkyl chain, were prepared in good yields through a regioselective 1,3-dipolar cycloaddition reaction between methyl 10-undecenoate (**1**) and various nitrile oxides (**2**), generated *in situ* (Scheme 1).

*Address correspondence at NCAUR, ARS, USDA, 1815 N. University St., Peoria IL. 61604. E-mail: kenarja@ncaur.usda.gov

The Δ^2-isoxazoline heterocycle has found widespread application in organic chemistry due to its versatility as a synthetic intermediate, the ease with which it can be prepared, and the availability of starting materials needed for its preparation (2,3). The chemical transformations available to the Δ^2-isoxazoline heterocycle include alkylation (4), dehydrogenation to isoxazoles (5,6), and reductive cleavage to yield such functional groups as β-hydroxy carbonyls (7–12) or γ-amino alcohols (13). Because of the diverse chemical transformations available to the isoxazoline ring, fatty compounds possessing this heterocycle represent attractive intermediates from which to obtain new types of functionalized fatty compounds.

We now report on the Raney nickel-mediated reductive hydrogenolysis–hydrolysis of fatty ester isoxazoline precursors to prepare fatty ester compounds containing the β-hydroxy ketone functionality. This ring-opening reaction, in conjunction with the facile preparation of the fatty ester Δ^2-isoxazoline precursors, represents a straightforward method to prepare β-hydroxy ketone-containing fatty compounds in overall yields ranging from 48 to 78% for the two steps starting from methyl 10-undecenoate.

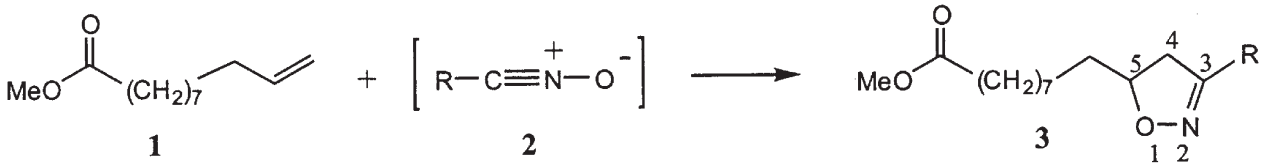
EXPERIMENTAL PROCEDURES

Materials. All Δ^2-isoxazolines were prepared as previously reported (1) and purified before use. Chemicals purchased from Aldrich Chemical Co. (Milwaukee, WI) were used without further purification unless otherwise noted. Methanol, THF, methylene chloride, hexane, and boric acid were obtained from Fisher Scientific Co. (Fairlawn, NJ) and Sylon BTZ trimethylsilyl silylating reagent was from Supelco (Bellefonte, PA).

NMR. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker ARX 400 spectrometer (Billerica, MA) with a 5-mm dual proton/carbon probe (400 MH ^{1}H/100.61 MHz ^{13}C) using $CDCl_3$ as solvent.

FTIR. IR spectra were obtained using a PerkinElmer (Norwalk, CT) Spectrum RX FTIR spectrophotometer. Samples were analyzed as either a film on NaCl plates (liquids) or in a KBr matrix (solids).

Melting points. Melting points were determined on a Fisher Johns melting point apparatus and are uncorrected.



1 **2** **3**

Substitutent	Yield
a R = $-(CH_2)_4CH_3$	65%
b R = $-(CH_2)_5CH_3$	63%
c R = $-(CH_2)_6CH_3$	64%
d R = *t*-butyl	85%
e R = phenyl	74%

SCHEME 1

GC. GC was performed with a Hewlett-Packard 5890 Series II gas chromatograph (Hewlett-Packard, Palo Alto, CA), equipped with an FID and an autosampler/injector. Analyses were conducted on a HP-5MS capillary column, 30 m × 0.25 mm i.d. (Hewlett-Packard). Column flow was 1.0 mL/min helium at a head pressure of 15 psi (776 torr); split ratio of 75:1; oven temperature 100°C for 2 min, then programmed to 210°C at 20°C/min, then to 250°C at 10°C/min and held 20 min at 250°C; injector and detector temperatures set at 280°C.

GC–MS. GC–MS analyses were conducted using a Hewlett-Packard 5890 Series II Plus GC (HP-5MS column: 30 m × 0.25 mm i.d.; Hewlett-Packard Co.) coupled with a Hewlett-Packard 5989B mass spectrometer. Electron ionization (EI) was performed at 70 eV using a mass range of 50–550 amu. GC conditions: helium head pressure 3 psi (155 torr); injector temperature set at 250°C; transfer line temperature set at 280°C; the oven temperature program was identical to that described in the GC section.

TLC. Analytical TLC was carried out on silica gel 60F254 (250 μm) plates purchased from Alltech Associates Inc. (Waukegan, IL). The eluent used to develop the plates was a 30:70 mixture of ethyl ether/hexane.

Representative procedure for the Raney nickel/boric acid reduction of Δ^2-isoxazolines to β-hydroxy ketones (8,9). To a solution of 5-(9-methyl nonanoate)-3-heptyl-Δ^2-isoxazoline, **3c** (151 mg, 0.446 mmol), in methanol (4.2 mL) and water (700 μL) (MeOH/H_2O = 6:1), was added boric acid (59.6 mg, 0.964 mmol) and a spatula tip (*ca.* 10–20 mg) of Raney nickel. The reaction vessel's atmosphere was replaced with hydrogen gas by repeated evacuation and flushing with hydrogen (six to ten times); a balloon filled with H_2 was used to maintain the reaction flask's H_2 atmosphere. The mixture was stirred vigorously for 22 h at room temperature (rt), and then filtered through a coarse glass frit into a separatory funnel containing water (10 mL) and CH_2Cl_2 (20 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated *in vacuo* to give 140 mg (92% yield) of an off-white solid that appeared pure by ^{1}H NMR. An analytical sample was obtained by recrystallization from methanol/H_2O to give **5c** as white crystals.

Representative procedure for the trimethylsilyl (TMS) derivatization of β-hydroxy keto fatty esters. In a small vial, the β-hydroxy ketone fatty ester (~10 mg) was dissolved in 500 μL of hexane. Sylon BTZ silylating reagent (50 μL) was added, the vial sealed then shaken, and the solution was allowed to stand for 10 min at 22°C. The resulting solution, without further preparation, was analyzed by GC and/or GC–MS.

^{1}H NMR of methyl 10-hydroxy-12-keto nonadecanoate (**5c**): δ 4.00 [broad *m*, 1H, $-CH_2CH(OH)CH_2-$], 3.65 (*s*, 3H, $-OCH_3$), 3.10–3.00 [broad *s*, 1H, –OH], 2.58 [*dd*, 1H, *J* = 17.5 and 2.8 Hz, –(HO)CHCH_2C(=O)–], 2.47 [*dd*, 1H, *J* = 17.6 and 9.1 Hz, –(HO)CHCH_2C(=O)–], 2.40 [*t*, 2H, *J* = 7.5 Hz, –(O=)CCH_2CH_2–], 2.28 (*t*, 2H, *J* = 7.5 Hz, –CH_2–CH_2–COOMe), 1.8– 1.1 (*m*, 24H, alkyl chain *H*), 0.86 (*t*, 3H, *J* = 6.9 Hz, –CH_2). ^{13}C NMR: δ 212.7 (*C*=O, ketone), 174.3 (*C*=O ester), 67.6 [–CH$_2$–H*C*(OH)–CH$_2$–], 51.4 (–O*C*H$_3$), 48.9, 43.7, 36.4, 34.1, 31.6, 29.5, 29.3, 29.1, 29.1, 29.1, 29.0, 25.4, 24.9, 23.6, 22.6, 14.0 (–CH$_3$). IR (KBr) cm^{-1}: 3406, 2954, 2923, 2849, 1738, 1703. m.p.: 50–51°C. Silylated derivative **6c** retention time 17.2 min, GC–MS (EI): *m/z* 415 (MH^+, 0.3 %), 399 ($M^+ - 15$, 24%), 315 ($M^+ - C_7H_{15}$, 15%), 273 ($M^+ - C_9H_{17}O$, 15%), 243 ($C_{13}H_{27}O_2Si$, 39%), 127 ($C_8H_{15}O$, 100%).

^{1}H NMR of methyl 10-hydroxy-12-keto heptadecanoate (**5a**): δ 4.00 [broad *m*, 1H, $-CH_2CH(OH)CH_2-$], 3.65 (*s*, 3H, $-OCH_3$), 3.06 (*s*, 1H, –O*H*), 2.58 [*dd*, 1H, *J* = 17.6 and 2.8 Hz, –(HO)CHCH_2C(=O)–], 2.47 [*dd*, 1H, *J* = 17.6 and 9.1 Hz, –(HO)CHCH_2C(=O)–], 2.40 [*t*, 2H, *J* = 7.5 Hz, –(O=)CCH_2–CH$_2$–], 2.28 (*t*, 2H, *J* = 7.5 Hz, –CH$_2$–CH_2–COOMe), 1.8–1.1 (*m*, 20H, alkyl chain *H*), 0.87 (*t*, 3H, *J* = 7.0 Hz, –CH_3). ^{13}C NMR: δ 212.6 (*C*=O, ketone), 174.3 (*C*=O ester), 67.6 [–CH$_2$–H*C*(OH)–CH$_2$–], 51.4 (–O*C*H$_3$), 48.9, 43.6, 36.4, 34.1, 31.3, 29.4, 29.3, 29.1, 29.1, 25.4, 24.9, 23.3, 22.4, 13.9 (–*C*H$_3$). IR (KBr) cm^{-1}: 3344, 3258, 2954, 2925, 2850, 1737, 1703. m.p.: 42–43°C. Silylated derivative **6a** retention time 14.2 min, GC–MS (EI): *m/z* 387 (MH^+, 0.9%), 371 ($M^+ - 15$, 21%), 315 ($M^+ - C_5H_{11}$, 11%), 273 ($M^+ - C_7H_{13}O$, 21%), 215 ($C_{11}H_{23}O_2Si$, 34%), and 99 ($C_6H_{11}O$, 100%).

^{1}H NMR of methyl 10-hydroxy-12-keto octadecanoate (**5b**): δ 4.00 [broad *m*, 1H, $-CH_2CH(OH)CH_2-$], 3.65 (*s*, 3H,

–OCH_3), 3.06 (broad *s*, 1H, –O*H*), 2.58 [*dd*, 1H, *J* = 17.5 and 2.8 Hz, –(HO)CHCH_2C(=O)–], 2.47 [*dd*, 1H, *J* = 17.5 and 9.1 Hz, –(HO)CHCH_2C(=O)–], 2.40 [*t*, 2H, *J* = 7.5 Hz, –(O=)C–CH_2CH$_2$–], 2.28 (*t*, 2H, *J* = 7.5 Hz, –CH$_2$–CH_2– COOMe), 1.8–1.1 (*m*, 22H, alkyl chain *H*), 0.86 (*t*, 3H, *J* = 6.8 Hz, –CH$_3$). ^{13}C NMR: δ 212.7 (*C*=O, ketone), 174.3 (*C*=O ester), 67.6 [–CH$_2$–H*C*(OH)–CH$_2$–], 51.4 (–O*C*H$_3$), 48.9, 43.7, 36.4, 34.1, 31.6, 29.5, 29.3, 29.1, 29.1, 28.8, 25.4, 24.9, 23.6, 22.5, 14.0 (–*C*H$_3$). IR (KBr) cm^{-1}: 3529, 3445, 2925, 2850, 1740, 1692. m.p.: 49.0–49.5°C. Silylated derivative **6b** retention time 15.7 min, GC–MS (EI): *m/z* 401 (MH$^+$, 0.4%), 385 (M$^+$ – 15, 31%), 315 (M$^+$ – C$_6$H$_{13}$, 17%), 273 (M$^+$ – C$_8$H$_{15}$O, 17%), 229 (C$_{12}$H$_{25}$O$_2$Si, 48%), and 113 (C$_7$H$_{13}$O, 100%).

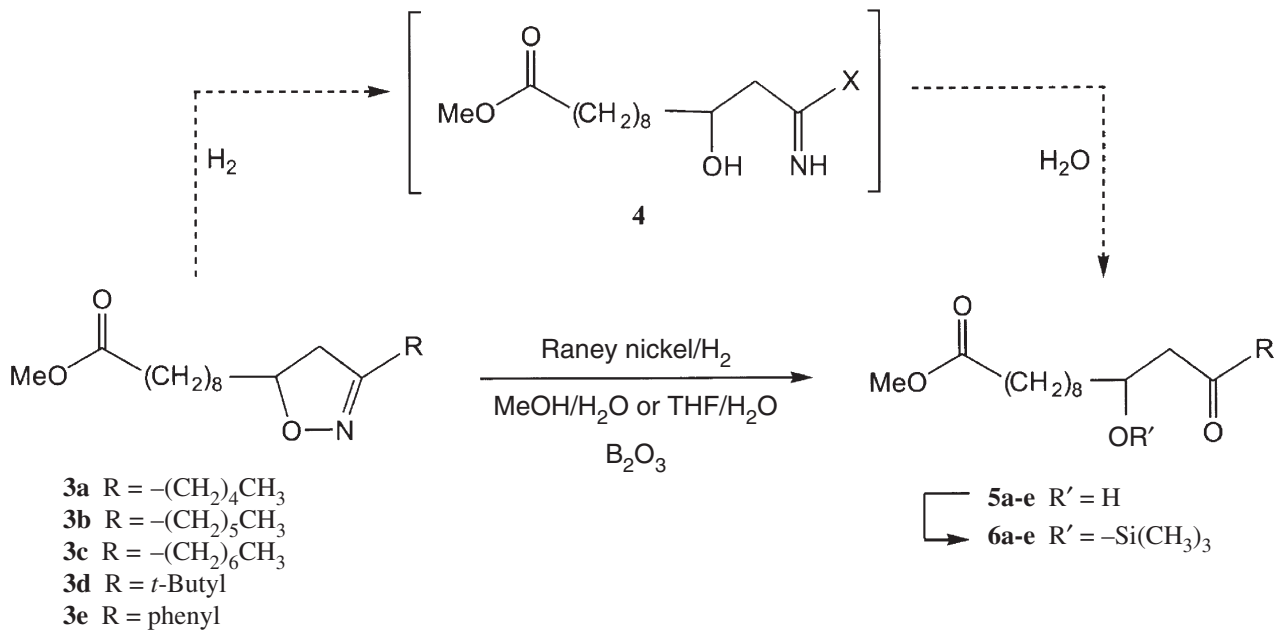
^{1}H NMR of methyl 13,13-dimethyl-10-hydroxy-12-keto tetradecanoate (**5d**): δ 4.00–3.90 [broad *m*, 1H, –CH$_2$C*H*(OH)CH$_2$–], 3.66 (*s*, 3H, –OCH_3), 3.0–2.7 (*s*, 1H, –O*H*), 2.68 (*dd*, 1H, *J* = 17.9 and 2.5 Hz, –(HO)CHCH_2C(=O)–], 2.52 [*dd*, 1H, *J* = 17.9 and 9.1 Hz, –(HO)CHCH_2C(=O)–], 2.29 (*t*, 2H, *J* = 7.5 Hz, –CH$_2$–CH_2–COOMe), 1.7–1.2 (*m*, 15H, alkyl chain *H*), 1.13 [*s*, 9H, C(CH_3)$_3$]. ^{13}C NMR: δ 218.0 (*C*=O, ketone), 174.4 (*C*=O ester), 67.8 [–CH$_2$–H*C*(OH)–CH$_2$–], 51.5 (–O*C*H$_3$), 44.4, 43.1, 36.5, 34.2, 29.6, 29.4, 29.2, 29.2, 26.3, 25.6, 25.0. IR (KBr) cm^{-1}: 3519, 2930, 2856, 1740, 1704. m.p.: *ca.* 10°C. Silylated derivative **6d** retention time 12.4 min, GC–MS (EI): *m/z* 373 (MH$^+$, 2%), 357 (M$^+$ – 15, 12%), 283 (M$^+$ – C$_3$H$_9$OSi, 11%), 273 (M$^+$ – C$_6$H$_{11}$O, 13%), 201 (C$_{10}$H$_{21}$O$_2$Si, 15%), 57 (C$_4$H$_9$, 100%).

^{1}H NMR of methyl 10-hydroxy-12-keto-12-phenyl dodecanoate (**5e**): δ 7.95–7.93 (*m*, 2H, aromatic *H*), 7.60–7.55 (*m*, 1H, aromatic *H*), 7.48–7.45 (*m*, 2H, aromatic *H*), 7.34 (*s*, 1H, –OH), 4.20 [broad *m*, 1H, –CH$_2$C*H*(OH)CH$_2$–], 3.65 (*s*, 3H, –OCH_3), 3.16 [*dd*, 1H, *J* = 17.7 and 2.6 Hz, –(HO)CHCH_2C (=O)–], 3.02 [*dd*, 1H, *J* = 17.7 and 9.0 Hz, –(HO)CHCH_2C (=O)–], 2.29 (*t*, 2H, *J* = 7.5 Hz, –CH$_2$–CH_2–COOMe), 1.9– 1.1 (*m*, 15H, alkyl chain *H*). ^{13}C NMR: δ 201.0 (*C*=O, ketone), 174.3 (*C*=O ester), 139.8 (aromatic *C*), 133.5 (aromatic *C*), 128.7 (aromatic *C*), 128.1 (aromatic *C*), 126.1 (aromatic *C*), 67.8 [–CH$_2$–H*C*(OH)–CH$_2$–], 51.4 (–O*C*H$_3$), 45.0, 36.5, 34.1, 29.6, 29.5, 29.4, 29.2, 29.1, 25.7, 25.5, 24.9. IR (KBr) cm^{-1}: 3378, 3060, 3024, 2930, 2850, 1741, 1682, 1597, 1581, 1449, 1436. m.p.: 48.5–50°C. Silylated derivative **6e** retention time 18.0 min, GC–MS (EI): *m/z* 392 (M$^+$, 1%), 377 (M$^+$ – 15, 26%), 302 (M$^+$ – C$_3$H$_{10}$OSi, 4%), 273 (M$^+$ – C$_8$H$_7$O, 7%), 221 (C$_{12}$H$_{17}$O$_2$Si, 41%), and 105 (C$_7$H$_5$O, 100%).

RESULTS AND DISCUSSION

Fatty compounds containing hydroxy (14) or keto (15–18) groups are well documented and have been thoroughly characterized (19,20). Several research groups have reported the synthesis of fatty compounds containing both a hydroxy and a keto group in the alkyl chain (21–23), although we could find no references describing fatty compounds containing the hydroxy and ketone moieties in a 1,3-position (β-hydroxy ketones) relative to one another. This work describes the second step of a facile two-step synthesis to prepare such compounds as well as their characterization.

Several methods based on AlCl$_3$ (11), titanous chloride (24), Raney nickel (7–12), ozone (11), or peracids (25) can be used to convert the isoxazoline ring into β-hydroxy carbonyl compounds by cleaving the isoxazoline's weak N-O bond. We utilized the Raney nickel procedure outlined by Curran and coworkers (7–9) because it appeared to be most suitable based on the mild reaction conditions and short reaction times. Scheme 2 depicts the general reaction sequence utilized to convert the fatty ester Δ^2-isoxazoline compounds,



SCHEME 2.

3, into their corresponding β-hydroxy carbonyl compounds, **5**. The mechanism purportedly proceeds through the intermediacy of β-hydroxy ketimine **4**, which is rapidly hydrolyzed to β-hydroxy carbonyl compound **5** by the water present in the reaction media (7–9).

Typically, the reactions are carried out at room temperature in a flask under a constant hydrogen atmosphere, at $MeOH/H_2O$ solvent ratios ranging between 5:1 and 6:1, with a catalytic amount of Raney nickel. Boric acid is added to buffer the reaction media and aid in the hydrolysis of the carbon–nitrogen double bond of intermediate **4**. The reaction proceeds smoothly, and TLC can be used conveniently to monitor the reaction's progress. Generally, the reactions are complete within 17–22 h. The reaction parameters and yields for the conversion of isoxazolines into β-hydroxy ketones are listed in Table 1. During the course of this research, no evidence of intermediate **4** was observed under the conditions utilized to perform the desired transformations.

The $MeOH/H_2O$ reaction medium was well suited for all the isoxazolines utilized except isoxazoline **3e**, which contained a phenyl ring. Initial attempts to reductively cleave this isoxazoline using $MeOH/H_2O$ at 6:1 failed because the addition of water prompted precipitation of the dissolved isoxazoline. Efficient reaction of **3e** with hydrogen (Raney nickel catalyst) was thus not possible due to the heterogeneous nature of the reaction mixture. By using THF (a better solvent with which to dissolve **3e**) rather than MeOH, the precipitation of **3e** was avoided and the reaction completed.

To confirm the structures of the β-hydroxy ketone fatty ester compounds and determine the position of the hydroxy and ketone moieties in their alkyl chains, the hydroxyl groups in **5a-e** were converted to their corresponding trimethylsilyl derivatives **6a-e** (Scheme 2) and subsequently analyzed by positive EI GC–MS. The electron impact mass spectra for **6b**, shown in Figure 1, illustrates the observed fragment ions derived from this molecule and is demonstrative of all the β-hydroxy ketone fatty ester compounds (**6a–e**) examined.

As can be seen for **6b**, the $[M]^+$ and $[M + H]^+$ molecular ions are in very low abundance, a commonly observed trend for trimethylsilyl-containing compounds (26). This was also found to be the case for **6a** and **6c–e**. Another prominent fragment ion, typically observed for compounds containing the trimethylsilyl group, is the $[M - CH_3]^+$ ion generated by loss of a methyl group from the silicon atom (26). In the case of **6b**, this cleavage gives an *m/z* 385 ion in 31% relative abundance (cleavage A, Fig. 1). Fragmentation along the fatty compound alkyl chain occurs selectively as evidenced by cleavages B and C α to the ketone moiety. Cleavage B (due to loss of a C_6H_{13} fragment) affords a $C_{16}H_{31}O_4Si$ *m/z* 315 fragment ion with a relative abundance of 17%. Likewise, cleavage at location C results in a $C_7H_{13}O$ fragment ion with *m/z* 113 and represents the base peak at 100% relative abundance. Cleavage also occurs predominantly α to the trimethylsilyl ether group at cleavage sites D and E. Cleavage at D gives loss of a $C_8H_{15}O$ fragment and results in a $C_{14}H_{29}O_3Si$ *m/z* 273 fragment ion in 17% relative abundance; cleavage at E (loss of $C_{10}H_{19}O_2$ fragment) gives a $C_{12}H_{25}O_2Si$ molecular ion with *m/z* 229 in 48% relative abundance. From these fragmentation patterns, the trimethylsilyl ether group and the ketone positions are readily established to be at the C-10 and C-12 carbons of the alkyl chain in **6b**, respectively. Similar interpretations of the mass spectra for compounds **6a** and **6c–e** indicate their trimethylsilyl ether and ketone groups, respectively, are located at the C-10 and C-12 carbons of the alkyl chain. Moreover, from these analyses it is apparent the hydroxy and ketone positions in fatty β-hydroxy ketones **5a–e** are located at the same positions along the alkyl chains as determined in **6a–e**.

TABLE 1
Reaction Conditions, Yields, Melting Points, and Selected ^{13}C NMR Signals of Fatty Ester β-Hydroxy Ketones, 5a–e

β-Hydroxy ketone	Reaction time (h)	Solvent system	Yield[a] (%)	m.p.[b] (°C)	^{13}C NMR signals[c] (ppm)	
					Carbinyl –C*H*(OH)–	Carbonyl –*C*(=O)–
5a, R = $-(CH_2)_4CH_3$	18	$MEOH/H_2O$ (5.8:1)	73	42–43	67.6	212.6
5b, R = $-(CH_2)_5CH_3$	20	$MEOH/H_2O$ (5.8:1)	83	49–49.5	67.6	212.7
5c, R = $-(CH_2)_6CH_3$	22	$MEOH/H_2O$ (6:1)	92	50–51	67.6	212.7
5d, R = *t*-Butyl	17	$MEOH/H_2O$ (5:1)	92	*ca.* 10	67.8	218
5e, R =Phenyl	21	THF/H_2O (5.8:1)	84	53–55	67.8	201

[a]Isolated yields.
[b]Melting points obtained from recrystallized samples.
[c]NMR spectrum obtained with $CDCl_3$ as solvent.

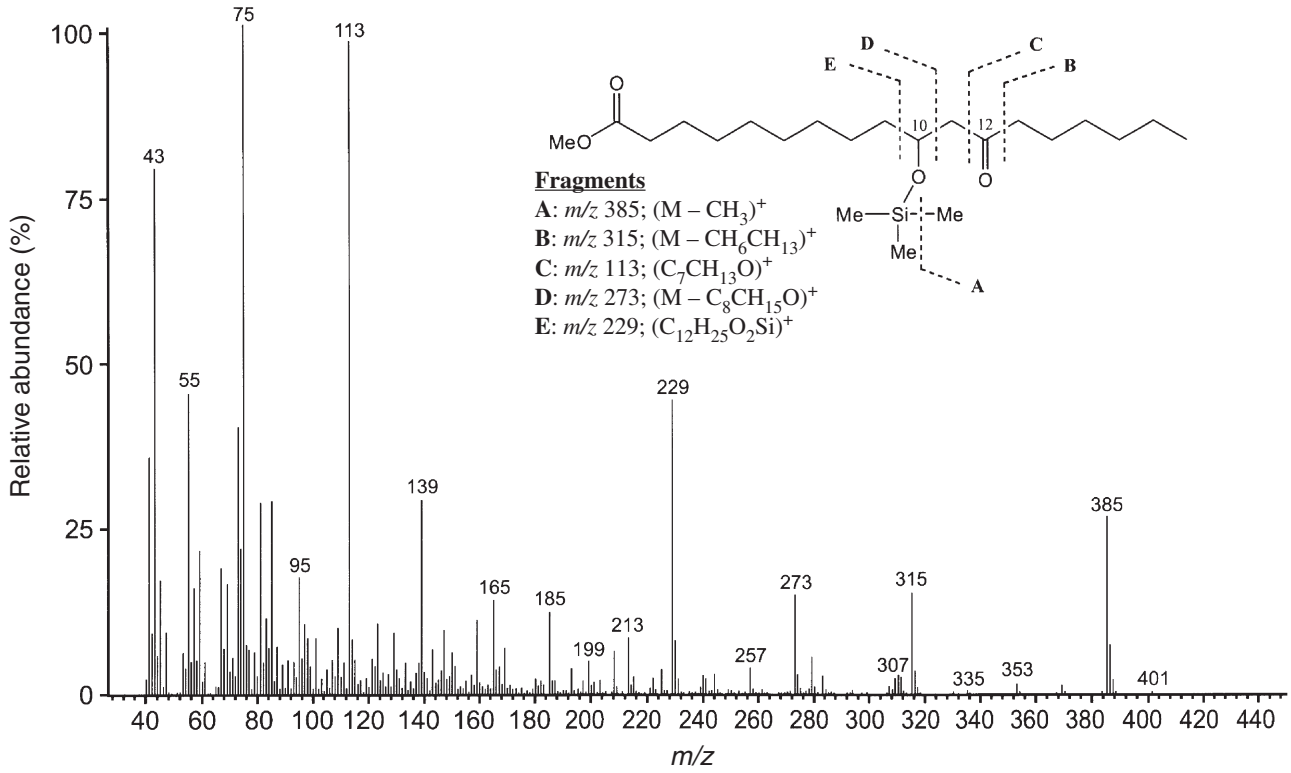


FIG. 1. Positive electron impact mass spectrum of trimethylsilylated fatty ester β-hydroxy ketone **6b**.

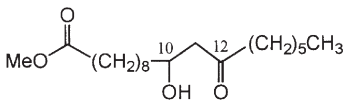
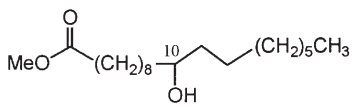
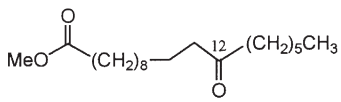
Also shown in Table 1 are the ^{13}C NMR signal assignments for the carbinyl [–*C*H(OH)–] and the carbonyl carbons [–*C*(=O)–] in the alkyl chain of the β-hydroxy ketone fatty compounds, **5a–e**. As can be seen, the carbinyl carbon's chemical shift is nearly identical regardless of the terminal R group. On the other hand, the carbonyl carbon's chemical shift is quite dependent upon the nature of the terminal R group, most likely because of its proximity to the R group. It is interesting to note the upfield (δ 201 ppm) and downfield (δ 218 ppm) chemical shifts between the carbonyl carbon in **5d** (R = *t*-butyl) and **5e** (R = phenyl), respectively, relative to the carbonyl carbon signal in **5a–c** (R = alkyl) at δ 212 ppm.

Insight into how the relative 1,3-proximity of the hydroxyl and ketone groups affects the ^{13}C chemical shifts for the carbinyl and carbonyl carbons can be gained by comparing the chemical shift data obtained for methyl 10-hydroxy-12-keto octadecanoate (**5b**) with the data presented by Tulloch for methyl 10-hydroxy-octadecanoate (19) and methyl 12-oxo-octadecanoate (20) as shown in Table 2.

As can be seen, the ^{13}C chemical shift for the C-10 carbinyl carbon in **5b** is moved upfield 4.2 ppm relative to the C-10 carbinyl carbon in methyl 10-hydroxy-octadecanoate, whereas the carbonyl carbon in **5b** is shifted downfield 1.8 ppm relative to methyl 12-oxooctadecanoate. By assuming all other interactions are equal, it appears the carbonyl group in **5b** is exerting a definite shielding effect on the C-10 hydroxy carbon, whereas the hydroxyl group is exerting only a slight (negligible) deshielding effect on the C-12 carbonyl carbon.

These Raney nickel-mediated reductions of fatty ester Δ^2-isoxazolines represent a convenient method to unmask the isoxazoline heterocycle and obtain fatty β-hydroxy ketone compounds in good overall yields. The isoxazoline ring opening

TABLE 2
Selected ^{13}C NMR Signals for the C-10 Carbinyl and C-12 Carbonyl Carbons of Methyl 10-Hydroxy-12-oxooctadecanoate (5b), Methyl 10-Hydroxy-Octadecanoate and Methyl 12-Oxooctadecanoate

	^{13}C NMR signals[a] (ppm)	
Fatty ester	C-10 Carbinyl	C-12 Carbonyl
 Methyl 10-hydroxy-12-oxooctadecanoate **5b**	67.6	212.7
 Methyl 10-hydroxy-12-octadecanoate	71.83[b]	—
 Methyl 12-oxo-octadecanoate	—	210.9[c]

[a]All ^{13}C NMR chemical shifts reported are from spectra obtained in $CDCl_3$.
[b]See Reference 19.
[c]See Reference 20.

combined with easy preparation of the precursor fatty ester Δ^2-isoxazoline compounds (derived from the reaction between methyl 10-undecenoate and nitrile oxides) makes this overall two-step procedure an attractive way to prepare fatty ester compounds containing the β-hydroxy ketone functionality, an outcome not readily accessible by other approaches.

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REFERENCES

1. Kenar, J.A., and S.Z. Erhan, Synthesis of Δ^2-Isoxazoline Fatty Acid Ester Heterocycles, *J. Am. Oil Chem. Soc. 78*:1045–1050 (2001).
2. Torssell, K.B.G., *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH, New York, 1988, pp. 14–49, 129–270.
3. Grundmann, C., Synthesis of Heterocyclic Compounds with the Aid of Nitrile Oxides, *Synthesis*:344–359 (1970).
4. Jäger, V., and W. Schwab, Syntheses *via* Isoxazolines II. Novel 4-Substituted 2-Isoxazolines by *endo*-Deprotonation/Alkylation, *Tetrahedron Lett. 34*:3129–3132 (1978).
5. Bianchi, G., and P. Grünanger, Conversion of 2-Isoxazolines to Isoxazoles, *Tetrahedron 21*:817–822 (1965).
6. Park, K.P., C.-Y. Shiue, and L.B. Clapp, Fused-Ring Isoxazolines and Their Isomers, *J. Org. Chem. 35*:2065–2067 (1970).
7. Curran, D.P., S.A. Scanga, and C.J. Fenk, Reduction of Δ^2-Isoxazolines. Synthesis of β-Hydroxy Acid Derivatives, *Ibid. 49*:3474–3478 (1984).
8. Curran, D.P., Reduction of Δ^2-Isoxazolines: A Conceptually Different Approach to the Formation of Aldol Adducts, *J. Am. Chem. Soc. 104*:4024–4026 (1982).
9. Curran, D.P., Reduction of Δ^2-Isoxazolines. 3. Raney-nickel Catalyzed Formation of β-Hydroxy Ketones, *Ibid. 105*:5826–5833 (1983).
10. Wollenberg, R.H., and J.E. Goldstein, Ring Annulation by Intramolecular Nitrile Oxide Cycloaddition, *Synthesis*:757–758 (1980).
11. Kozikowski, A.P., and M. Adamczyk, Methods for the Conversion of Isoxazolines to β-Hydroxy Ketones, *Tetrahedron Lett. 23*:3123–3126 (1982).
12. Kozikowski, A.P., and A.K. Ghosh, Diastereoselection in Intermolecular Nitrile Oxide Cycloaddition (NOC) Reactions: Confirmation of the "Anti-Periplanar Effect" Through a Simple Synthesis of 2-Deoxy-D-ribose, *J. Am. Chem. Soc. 104*:5788–5789 (1982).
13. Confalone, P.N., E.D. Lollar, G. Pizzolato, and M.R. Uskokovíc, Use of Intramolecular [3+2] Cycloaddition Reactions in the Synthesis of Natural Products. A Stereospecific Synthesis of (±)-Biotin from Cycloheptene, *Ibid. 100*:6291–6292 (1978).
14. Lower, E.S., Hydroxy Fatty Acids–Some General Aspects, *Riv. Ital. Sostanze Grasse, 74*:299–305 (1997).
15. Jie Ken Lie, M.S.F., and S.W.H. Cheung, Synthesis of Special Fatty Acids: A Review, in *Recent Developments in the Synthesis of Fatty Acid Derivatives*, edited by G. Knothe and J.T.P. Derksen, AOCS Press, Champaign, 1999, pp. 20–43.
16. Bogaert, M.P., T.M. Slaghek, H. Feil, and P.S.G. Tassignon, Organic Chemical Synthesis and Derivatization of Fatty Acids and Methyl Esters Obtained from *Ricinus* and *Dimorphotheca* Species: Some Industrially Feasible Preparations of New Fatty Acid–Based Products, in *Recent Developments in the Synthesis of Fatty Acid Derivatives*, edited by G. Knothe and J.T.P. Derksen, AOCS Press, Champaign, 1999, pp. 100–127.
17. Nakano, Y., and T. Foglia, Oxidation of Unsaturated and Hydroxy Fatty Acids by Ruthenium Tetroxide and Ruthenium Oxyanions, *J. Am. Oil Chem. 59*:163–166 (1982).
18. Lie Ken Jie, M.S.F., and C.K. Lam, Regiospecific Oxidation of Unsaturated Fatty Esters with Palladium(II) Chloride/*p*-Benzoquinone: A Sonochemical Approach, *Chem. Phys. Lipids 81*:55–61 (1996).
19. Tulloch, P., Carbon-13 NMR Spectra of All the Isomeric Methyl Hydroxy- and Acetoxyoctadecanoates, *Org. Magn. Reson. 11*:109–115 (1978).
20. Tulloch, P., Deuterium Isotope Effects and Assignment of ^{13}C Chemical Shifts in Spectra of Methyl Octadecanoate and the Sixteen Isomeric Oxooctadecanoates, *Can. J. Chem. 55*:1135–1142 (1977).
21. Ketola, M., and U. Leskinen, Chlorinated Long-Chain Fatty Acids. Their Properties and Reactions. XII. The Dechlorination Pathways of Sodium 9(10)-Chloro-1(9)-oxooctadecanoates in Aqueous Sodium Hydroxide Solution, *J. Am. Oil Chem. 62*:742–745 (1985).
22. Ahmed, S.M., M.S. Ahmad, F. Ahmad, and S.M. Osman, Oxymercuration–Demercuration of Hydroxy Acetylenic Acids, *Ibid. 61*:754–756 (1984).
23. Stoll, G., K. Worschech, and E. Grundt, Process for the Preparation of Ketones (e.g., oxo fatty esters) by Rearrangement of Epoxides (e.g., epoxidized fatty esters) in the Presence of Group I–III Iodides in the Absence of Solubilizing Agents, German Patent 4,018,262 (1991).
24. Mukerji, S.K., K.K. Sharma and K.B.G. Torssell, Addition of Nitrile Oxides to Olefins. Synthesis of Dihydrojasmone and Starting Material for Prostanoids. A Novel Route to Pyrroles, *Tetrahedron 39*:2231–2235 (1983).
25. Park, P.-U., and A.P. Kozikowski, Oxidation of Isoxazolines by Peracids—A Useful Route to β-Hydroxy Ketones and Acylated Diols, *Tetrahedron Lett. 29*:6703–6706 (1988).
26. Christie, W.W., *Gas Chromatography and Lipids, A Practical Guide*, The Oily Press, Dundee, Scotland, 1989, pp. 180–182.

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