Synthesis of Secondary Ethers Derived from Meadowfoam Oil

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ABSTRACT: Secondary ethers can be obtained from meadow-foam-derived delta lactones or 5-hydroxy fatty acids by using Lewis or Brønsted acid catalysts in good yield (70–90%). The conversion of δ-lactone or 5-hydroxy fatty acid to 5-ethers is performed under atmospheric pressure between 67 and 125°C with 0.5–6.4 mole equivalents of acid catalyst in the presence of 2–40 equivalents of alcohol and a reaction time of 1–140 h. Acid catalysts include mineral acids, such as perchloric and sulfuric; Lewis acids, such as boron trifluoride; and heterogeneous catalysts, such as clays and ion-exchange resins. Primary alcohols, such as methanol, butanol, decanol, and oleyl alcohol, or branched-chain alcohols, such as 2-ethylhexanol, can be used to make secondary ether fatty esters. The 5-ether fatty esters and the process for their formation have not been previously known and appear to be limited to structures where stabilized cations can be formed. The novel ethers were fully characterized by nuclear magnetic resonance and gas chromatography–mass spectrometry.
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KEY WORDS: 5-Alkoxy, branched-chain alcohols, 5-eicosenoic acid, esters, fatty acids, Lewis acids, meadowfoam, mineral acids, montmorillonite, secondary ethers, stabilized cations.

Meadowfoam is a developing new crop that is currently grown on a commercial scale in the Willamette Valley of Oregon. The meadowfoam triglycerides are composed of long-chain fatty acids, with 5-eicosenoic acid (63%) as the major fatty acid. The other main components are 5,13-docosadienoic acid (17%), 5-docosenoic acid (4%), and 13-docosenoic acid (12%). This unique combination of monoenoic fatty acids makes for an oxidatively stable oil with an oxidative stability index (OSI) time of 246.9 h. Other vegetable oils, such as soybean oil and high-oleic sunflower oil, have OSI times of 19.9 and 49.8 h, respectively (1).

Meadowfoam's unique fatty acid composition, particularly the Δ5 unsaturated fatty acids, has been exploited for the production of novel estolides (2) and δ-lactones (3) (Scheme 1). Because of the unique chemistry of the Δ5-position on the fatty acid backbone, unusual oxidative stabilization of the fatty acid is imparted (1), as well as enhanced reactivities in cationic reaction pathways (4). The facile ring opening of the δ-lactone has potential for the development of a whole new class of novel hydroxylated fatty acid derivatives.

In the course of examining the ring opening of the δ-lactone with methanol to form methyl 5-hydroxy eicosanoate (Scheme 2), we noted the formation of a 5-alkoxy ester in moderate yield (62%). Typically, secondary (2°) ethers are difficult to synthesize in good yield. The development of secondary ethers from fats is usually achieved from halo (5) or epoxy lipids (6). Madrigal *et al.* (7) have described a synthesis of ether fatty acids derived from unsaturated fatty acids. This reaction provided low yields (1–34%) of the Δ9–Δ15 alkoxy adducts from a sulfuric acid-catalyzed reaction with C_1 to C_6 alkyl alcohols. Ballantine *et al.* (8,9), with the use of small-chain alkyl alcohols, were able to synthesize 2° ethers in low yields with cation-exchanged sheet silicates in conjunction with large quantities of the undesirable alkene dehydration product (15–88%). Good ether yields (34–88%) were only achieved when a 3° stabilized benzyl cation was condensed with an alcohol (10).
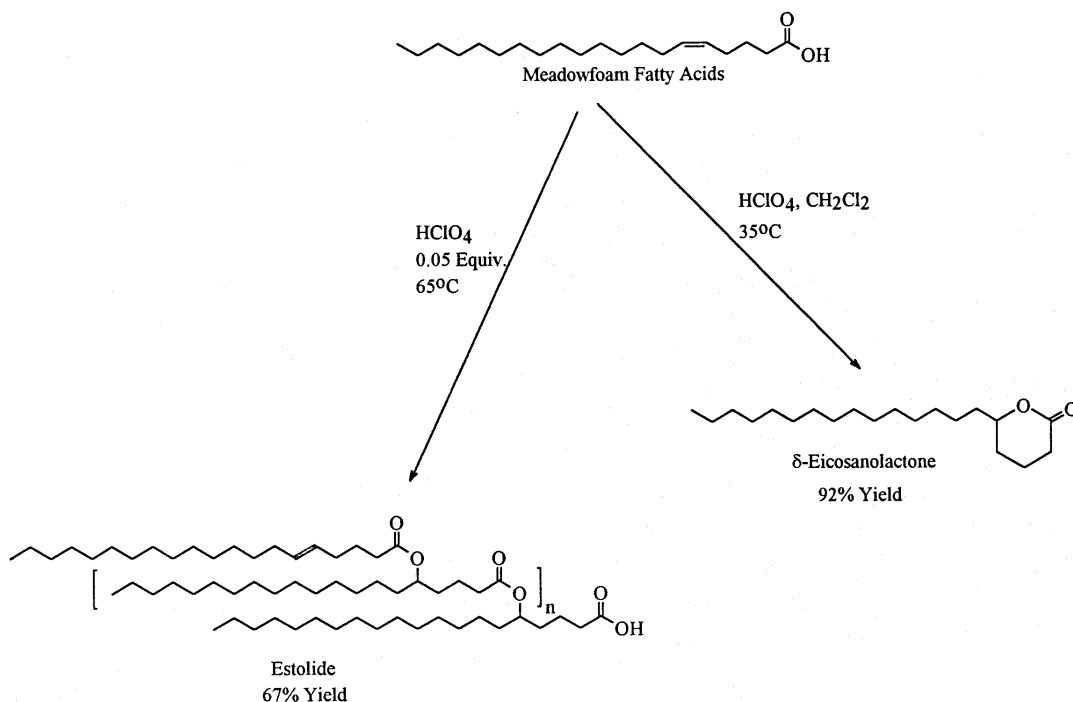
This investigation will examine the role of a proximally located carboxylic acid functionality on the stability of a developing cation and its impact on the formation of 2° ethers. δ- and γ-lactones, derived in a single-step reaction from unsaturated meadowfoam fatty acids, will serve as starting materials for this ether synthesis.

EXPERIMENTAL PROCEDURES

Materials. δ-Lactone and 5-hydroxy fatty acids were obtained from meadowfoam fatty acids by the method of Isbell and Plattner (3). Meadowfoam oil was supplied by The Fanning Corp. (Chicago, IL). Methanol, butanol, acetone, and sulfuric acid were purchased from Fisher Scientific Co. (Fairlawn, NJ). Acetonitrile was obtained from EM Science (Gibbstown, NJ). Decyl alcohol, 2-ethylhexyl alcohol, perchloric acid 70%, montmorillonite K-10 clay, boron trifluoride gas, Amberlyst XN-1010 strongly acidic resin, Dowex strongly acidic resin, and silica gel 60-Å were purchased from Aldrich Chemical Co. (Milwaukee, WI). Saturated fatty acid methyl ester (FAME) standards and BF_3/methanol (14% wt/vol) were obtained from Alltech Associates (Deerfield, IL).

Instrumentation. Gas chromatography (GC) was performed with a Hewlett-Packard 5890 Series II gas chromatograph (Palo Alto, CA), equipped with a flame-ionization de-

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Meadowfoam Fatty Acids

HClO$_4$
0.05 Equiv.
65°C

HClO$_4$, CH$_2$Cl$_2$
35°C

δ-Eicosanolactone
92% Yield

Estolide
67% Yield

SCHEME 1

tector and an autosampler/injector. Analyses were conducted on an SP 2380, 30 m × 0.25 mm i.d. (Supelco, Bellefonte, PA). Saturated C$_8$–C$_{30}$ FAME provided standards for calculating equivalent chainlength (ECL) values, which were used to make FAME assignments.

SP 2380 analysis: column flow 1.2 mL/min with a helium head pressure of 15 psi; split ratio 40:1; programmed ramp 180 to 250°C at 3°C/min, hold 2 min at 250°C; injector and detector temperatures set at 250°C. Retention times for eluted peaks with ECL values in parentheses: methyl 5-eicosenoate

Methanol
BF$_3$
Reflux

Methyl 5-hydroxyeicosanoate

+

Methyl 5-methoxyeicosanoate

62%
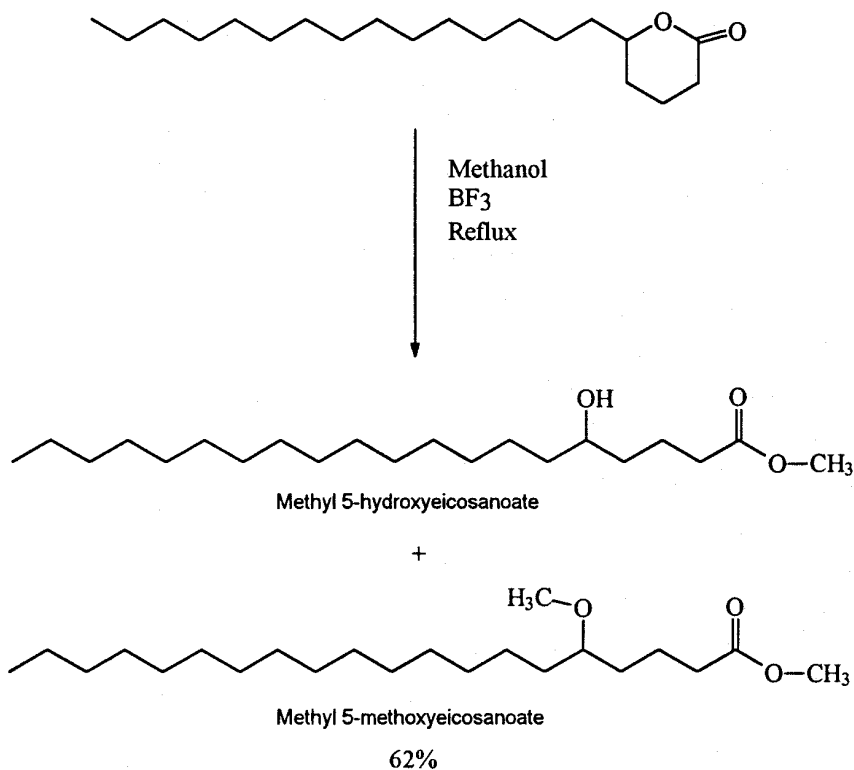
SCHEME 2

3.3 min (20.34), butyl 5-eicosenoate 5.2 min (22.41), methyl 5-methoxyeicosanoate 5.5 min (22.79), butyl 5-butoxye-icosanoate 9.4 min (26.25), γ-lactone 15.7 min (30.94), and δ-lactone 17.1 min (31.94).

High-performance liquid chromatography (HPLC). HPLC analyses were performed on a Thermo Separation Products (Fremont, CA) instrument with a P2000 binary pump and an AS2000 autosampler/injector, coupled to an evaporative light scattering Varex Mark III detector (ELSD III, Alltech Associates). A Dynamax C_8 (Rainin Instrument Co., Woburn, MA) column (250 mm × 4.6 mm, 60 Å, 8 µm) was used to separate the decyl reaction mixtures. Components were eluted from the column with a gradient elution at a flow rate of 1 mL/min. Acetonitrile/acetone gradient: 0 min, 70:30; 8 min, 40:60; 12 min, 40:60; 12.1 min, 70:30, and 15 min, 70:30. Retention times for eluted peaks were: δ-lactone 4.0 min, decyl 5-hydroxyeicosanoate 4.6 min, decyl 5-eicosenoate 5.2 min, and decyl 5-decoxyeicosanoate 6.9 min.

HPLC of 2-ethylhexyl ethers. A Dynamax C_8 column (250 mm × 4.6 mm, 60 Å, 8 µm) was used to separate the 2-ethylhexyl ether reaction mixtures. Components were eluted from the column under isocratic conditions of acetonitrile/acetone 95:5 at a flow rate of 1 mL/min. Retention times for eluted peaks were: 5-hydroxyeicosanoic acid 4.2 min, δ-lactone 4.2 min, 2-ethylhexyl 5-hydroxyeicosanoate 4.6 min, 2-ethylhexyl 5-eicosenoate 6.1 min, 2-ethylhexyl 5-(2-ethylhexoxy)-eicosanoate 8.9 min.

GC–mass spectrometry (GC–MS). GC–MS was performed with a Hewlett-Packard 5890A GC with a 30 m × 0.25 mm i.d DB-1 column (J&W Scientific, Folsom, CA) and a Hewlett-Packard 5970 mass-selective detector. GC conditions: helium head pressure 5 psi; split ratio 50:1; injector temperature set at 250°C; transfer line temperature set at 250°C; programmed ramp from 170 to 250°C at 5°C/min. MS conditions: mass range 50 to 550 amu; electron multiplier 200 volts relative.

MS spectra of methyl 5-methoxyeicosanoate: *m/e* 255 ($C_{17}H_{35}O$, 5.5%), 145 ($C_7H_{13}O_3$, 100%), 113 (32.0%), and 71 (32.9%).

MS spectra of butyl 5-butoxyeicosanoate: *m/e* 439 [$(M - H)^+$, <1%], 383 [loss of $CH_3(CH_2)_2CH_2$–O–, 2%], 368 [loss of –$(CH_2)_3CH_3 + H$, 4%], 367 [loss of –$(CH_2)_3CH_3$, 4%], 229 [loss of $CH_3(CH_2)_{13}CH_2$–, 100%], 173 ($C_9H_{17}O_3$, 16%), and 99 ($C_5H_7O_2$, 90%).

MS spectra of butyl 4-butoxyeicosanoate: *m/e* 383 [loss of $CH_3(CH_2)_2CH_2$–O–, 4%], 368 [loss of –$(CH_2)_3CH_3 + H$, 4%], 311 [loss of $CH_2CH_2C(O)$–O–$(CH_2)_3CH_3$, 12%], 215 [loss of $CH_3(CH_2)_{14}CH_2$-, 100%], 159 ($C_8H_{15}O_3$, 21%), and 85 ($C_4H_5O_2$, 76%).

MS spectra of 2-ethylhexyl 5-(2-ethylhexoxy)-eicosanoate: *m/e* 424 (loss of 2-ethylhexyl, <1%), 341 [loss of $CH_3(CH_2)_{13}CH_2$–, 34%], 241 (25%), 229 ($C_{13}H_{25}O_3$, 16%), 99 ($C_5H_7O_2$, 39%), and 57 [–$(CH_2)_3CH_3$, 100%].

Nuclear magnetic resonance (NMR). ^{1}H NMR and ^{13}C NMR were performed with a Bruker ARX 400 with a 5-mm dual proton/carbon probe (400 MHZ ^{1}H/100.61 MHZ ^{13}C) with $CDCl_3$ as the solvent in all experiments.

^{1}H NMR of methyl 5-methoxyeicosanoate: δ 3.65 (*s*, O=C–O–C*H₃*, 3H), 3.29 [*s*, *H₃C*–O–CH–(CH₂)₂–, 3H], 3.12 [*p*, H₃C–O–C*H*–(CH₂)₂–, 1H], 2.31 [*t*, –C*H₂*C(O)–O–, 2H], 1.50–1.35 (*m*, 4H), 1.35–1.20 (*m*, 28H), and 0.86 ppm (*t*, *J* = 6.7 Hz, –C*H₃*, 3H). ^{13}C NMR of methyl 5-methoxyeicosanoate: δ 174.1 (*s*, –*C*=O), 80.5 [*d*, H₃C–O–*C*H–(CH₂)₂–], 56.4 [*q*, *H₃C*–O–CH–(CH₂)₂–], 51.4 (*q*, O=C–O–*C*H₃), 34.1 (*t*), 33.3 (*t*), 32.8 (*t*), 31.9 (*t*), 29.8 (*t*), 29.7 (*t*), 29.3 (*t*), 25.2 (*t*), 22.7 (*t*), 20.8 (*t*), and 14.1 ppm [*q*, –(CH₂)₁₄–*C*H₃].

^{1}H NMR of methyl 5-eicosenoate: δ 5.36 (*m*, –*H*C=C*H*–, 2H), 3.65 (*s*, O=C–O–C*H₃*, 3H), 2.28 [*t*, *J* = 7.5 Hz, –C*H₂*C(O)–O–, 2H], 2.08–1.92 (*m*, –C*H₂*–CH=CH–C*H₂*–, 4H), 1.35–1.20 (*m*, 28H) and 0.86 ppm (*t*, *J* = 6.6 Hz, –C*H₃*, 3H). ^{13}C NMR of methyl 5-eicosenoate: δ 174.2 (*s*, –*C*=O), 131.7 (*d*, –*C*H=CH–), 128.7 (*d*, –CH=*C*H–), 51.4 (*q*, O=C–O–*C*H₃), 33.3 (*t*), 32.6 (*t*), 31.9 (*t*), 29.7 (*t*), 29.6 (*t*), 29.5 (*t*), 29.5 (*t*), 29.4 (*t*), 29.3 (*t*), 29.3(*t*), 29.2 (*t*), 24.9 (*t*), 24.7 (*t*), 22.7 (*t*) 22.7 (*t*), and 14.1 ppm [*q*, –(CH₂)₁₄–*C*H₃].

^{1}H NMR of butyl 5-butoxyeicosanoate: δ 4.05 (*t*, *J* = 6.7 Hz, 2H, –C*H₂*CO₂C*H₂*CH₂–), 3.38 [*m*, 2H, –CH₂C*H₂*–O–CH(CH₂)₂–], 3.18 [*m*, 1H, –CH₂CH₂–O–C*H*(CH₂)₂–)], 2.29 (*t*, *J* = 7.4 Hz, 2H, –C*H₂*CO₂CH₂CH₂–), 1.65–1.2 (*m*, 40H), 0.86 ppm (*m*, 9H, –C*H₃*). ^{13}C NMR of butyl 5-butoxyeicosanoate: δ 173.8 (*s*, C=O), 79.0 [*d*, –CH₂CH₂–O–*C*H(CH₂)₂–], 68.7 [*t*, –CH₂*C*H₂–O–CH(CH₂)₂–], 64.1 (*t*, –CH₂CO₂*C*H₂CH₂–), 34.4 (*t*, –*C*H₂CO₂CH₂CH₂–), 33.9 (*t*), 33.4 (*t*), 32.3 (*t*), 31.9 (*t*), 30.7 (*t*), 29.8 (*t*), 29.7, (*t*), 29.6 (*t*), 25.3 (*t*), 22.6 (*t*), 21.0 (*t*), 19.4 (*t*), 19.1 (*t*), 14.1 (*q*), 13.9 (*q*), and 13.7 ppm (*q*).

^{1}H NMR of butyl 5-eicosenoate: δ 5.36 (*m*, –*H*C=C*H*–, 2H), 4.05 (*s*, O=C–O–C*H₂*–CH₂–, 2H), 2.27 [*t*, *J* = 7.6 Hz, –C*H₂*C(O)–O–, 2H], 2.08–1.92 (*m*, –C*H₂*–CH=CH–C*H₂*–, 4H), 1.67 (*m*, –OCH₂C*H₂*CH₂CH₃, 2H), 1.59 (*m*, –OCH₂C*H₂*CH₂CH₃, 2H), 1.35–1.20 (*m*, 28H), 0.92 [*t*, *J* = 7.4 Hz, –(CH₂)₃C*H₃*], and 0.86 ppm [*t*, *J* = 6.6 Hz, –(CH₂)₁₄C*H₃*, 3H]. ^{13}C NMR of butyl 5-eicosenoate: δ 173.9 (*s*, –*C*=O), 131.7 (*d*, –*C*H=CH–), 128.8 (*d*, –CH=*C*H–), 64.1 (*t*, O=C–O–*C*H₂–), 34.4 (*t*), 33.7 (*t*), 32.6 (*t*), 32.5 (*t*), 31.9 (*t*), 30.7 (*t*), 29.7 (*t*), 29.6 (*t*), 29.5 (*t*), 29.5 (*t*), 29.4 (*t*), 29.3 (*t*), 29.2 (*t*), 29.1 (*t*), 24.8 (*t*), 22.7 (*t*), 19.1 (*t*), 14.1 [*q*, –(CH₂)₁₄–*C*H₃], and 13.7 ppm [*q*, –O(CH₂)₃–*C*H₃].

^{1}H NMR of 2-ethylhexyl 5-(2-ethylhexoxy)-eicosanoate: δ 3.97 [*dd*, *J* = 2.4 Hz, 3.3 Hz, O=C–OC*H₂*CH(CH₂)₂–, 2H], 3.25 [*m*, –OC*H₂*CH(CH₂)₂–, 2H], 3.17 [*m*, –OC*H*(CH₂)₂–, 1H], 2.30 (*t*, *J* = 7.4 Hz, –C*H₂*CO₂CH₂–, 2H), 1.75–1.20 (*m*, 48H), and 0.87 ppm (*m*, 17H). ^{13}C NMR of 2-ethylhexyl 5-(2-ethylhexoxy)-eicosanoate: δ 173.9 (*s*, C=O), 79.1 [*d*, –O*C*H(CH₂)₂–], 71.4 [*t*, –O*C*H₂CH(CH₂)₂–], 66.6 [*t*, O=C–O*C*H₂CH(CH₂)₂–)], 40.1 and 38.7 [*d*, –OCH₂*C*H(CH₂)₂–], 34.54 (*d*), 33.8 (*d*), 33.4 (*d*), 31.9 (*d*), 30.4 (*d*), 29.8 (*d*), 29.7 (*d*), 29.3 (*d*), 28.9 (*d*), 25.3 (*d*), 23.7 (*d*), 23.1 (*d*), 22.9 (*d*), 22.7 (*d*), 21.1 (*d*), 14.1 [*q*, –(CH₂)₁₄–*C*H₃], and 11.0 ppm [*q*, –CH–(CH₂)₃–*C*H₃)].

^{1}H NMR of decyl 5-decoxyeicosanoate: δ 4.04 [*t*, *J* = 6.75 Hz, –OC*H₂*(CH₂)₂CH₃, 2H], 3.37 [*t*, *J* = 6.73 Hz, –CH₂C*H₂*–

OCH(CH$_2$–)$_2$, 2H], 3.18 [p, –CH$_2$CH$_2$–OCH(CH$_2$–)$_2$, 1H], 2.31 (t, J = 7.5 Hz, –CH$_2$CO$_2$CH$_2$–, 2H), 1.72–1.20 (m, 64H) and 0.86 ppm (t, J = 7.1 Hz, –CH$_3$, 9H). ^{13}C NMR of decyl 5-decoxyeicosanoate: δ 173.8 (s, C=O), 79.0 [d, –CH$_2$CH$_2$–O–CH(CH$_2$)$_2$–], 68.9 [t, –CH$_2$CH$_2$–O–CH(CH$_2$)$_2$–], 64.4 (t, –CH$_2$CO$_2$CH$_2$CH$_2$–), 34.4 (t, –CH$_2$CO$_2$CH$_2$CH$_2$–), 33.9 (t), 33.4 (t), 33.4 (t), 31.9 (t), 30.2 (t), 29.8 (t), 29.7 (t), 29.6 (t), 29.5 (t), 29.3 (t), 29.2 (t), 28.6 (t), 26.3 (t), 25.9 (t), 25.4 (t), 22.7 (t), 21.0 (t), and 14.1 ppm (q).

^{1}H NMR of oleyl 5-oleyloxyeicosanoate: δ 5.33 (m, –CH=CH–, 2H), 4.04 [t, J = 6.7 Hz, –OCH$_2$(CH$_2$)$_8$–, 2H], 3.37 [t, J = 6.7 Hz, –CH$_2$CH$_2$–OCH(CH$_2$–)$_2$, 2H], 3.24 [p, –CH$_2$CH$_2$–OCH(CH$_2$–)$_2$, 1H], 2.30 (m, –CH$_2$CO$_2$CH$_2$–, 2H), 2.05 (m, 2H), 1.77–1.20 (m, 92H) and 0.87 ppm (t, J = 4.0 Hz, –CH$_3$, 9H).

Methods. A series of reactions was conducted to examine the production of 5-alkoxy eicosanoates from δ-lactones, γ-lactones, or 5-hydroxy fatty acid. δ-Lactone, γ-lactone, or 5-hydroxy fatty acid (0.5 g) was dissolved in the appropriate alcohol (5 mL) and reacted under the conditions listed in Tables 1 and 2. Mixing was maintained throughout the course of the reaction by magnetic stirring. The reaction vessels were fitted with reflux condensers to recycle volatile alcohols back into the reaction mixture. Temperature was maintained at ±1°C of the desired set point *via* a temperature controller and a thermocouple that was immersed in the reaction mixture, except for those reactions that were conducted at the alcohol's boiling point where reflux maintained the temperature. Isolation and workup of the reaction are listed below, based on the catalyst employed. All reaction mixtures, subsequent to the workup, were concentrated *in vacuo,* then kugelrohr-distilled at 160–180°C at 0.2 mm Hg to remove unsaturated byproducts and excess alcohol.

After the reaction of δ-lactone and BF$_3$/alcohol had reached completion, the crude reaction mixture was poured into a separatory funnel and diluted with 50 mL hexane, washed 2 × 10 mL with saturated NaCl solution, dried over Na$_2$SO$_4$, and gravity-filtered through a #1 Whatman (Maidstone, England) filter paper.

After the reaction with montmorillonite K-10 clay reached completion, the crude reaction mixture was diluted in 50 mL of hexane and filtered through #1 Whatman filter paper in a Buchner funnel and vacuum filtration flask.

After the reaction with mineral acids reached completion, the crude reaction mixture was poured into a separatory funnel and diluted with 50 mL of hexane, washed 2 × 10 mL with 0.5 M Na$_2$HPO$_4$ solution, dried over Na$_2$SO$_4$, and gravity-filtered through a #1 Whatman filter paper.

BF$_3$ alcoholates. BF$_3$/methanol was purchased from Alltech as a 14% wt/vol solution; all other BF$_3$ solutions were made as described below. Solutions of BF$_3$ were made by placing 100 g of the desired alcohol in a flask, fitted with a fritted-glass bubbler. The flask was then cooled in an ice-bath and placed on a top-loading balance. BF$_3$ gas was passed through the solution until the appropriate weight gain was observed. Extreme care must be taken when using BF$_3$ gas because the gas is poisonous and draw-back of the alcohol into the gas cylinder could result in an explosion. An appropriate dry trap must be placed between the cylinder and the flask that contains the alcohol to prevent pull-back of the alcohol into the cylinder. In addition, the effluent gas above the alcohol should be passed through a dry trap (prevents water pull-

TABLE 1
Etherification Reactions of δ-Lactone and 5-Hydroxy Fatty Acid

Entry	Substrate	Alcohol	Acid catalyst	Acid equiv.[a]	Temperature (°C)	Time (h)	Ether (%)[b]	Alkene (%)[b]	5-OH (%)[b]	δ-Lactone (%)[b]
A	δ-Lactone[c]	CH$_3$OH	5% BF$_3$[d]	2.3	67	46	59	7	0	30
B	δ-Lactone	CH$_3$OH	10% BF$_3$	4.5	67	23	71	10	0	19
C	δ-Lactone	CH$_3$OH	10% BF$_3$	4.5	67	44	79	9	0	11
D	δ-Lactone	CH$_3$OH	14% BF$_3$	6.4	67	24	86	10	0	3
E	δ-Lactone	CH$_3$OH	Fe^{+3} Clay[e]	0.1 g	67	23	1	14	1	84
F	δ-Lactone	CH$_3$OH	H$_2$SO$_4$[f]	17.0	67	21	26	39	1	34
G	δ-Lactone	CH$_3$OH	HClO$_4$[g]	0.35	67	25	4	5	91	0
H	δ-Lactone	Decanol	Fe^{+3} Clay	0.1 g	100	96	91	6	3	0
I	δ-Lactone	Decanol	Fe^{+3} Clay	0.1 g	125	24	84	12	1	0
J	δ-Lactone	Decanol	5% BF$_3$	2.3	85	5	80	8	0	0
K	δ-Lactone	Decanol	10% BF$_3$	4.5	85	24	93	7	0	0
L	δ-Lactone	2-Ethylhexyl	Fe^{+3} Clay	0.1 g	120	22	84	11	5	0
M	5-Hydroxy[h]	2-Ethylhexyl	5% BF$_3$	0.4	110	3	75	22	0	0
N	5-Hydroxy	2-Ethylhexyl	5% BF$_3$	1.0	120	18	80	14	5	0
O	5-Hydroxy	2-Ethylhexyl	HClO$_4$	0.3	80	28	78	7	15	0
P	δ-Lactone	Oleyl[i]	Fe^{+3} clay	0.1 g	150	20	~50	NA	NA	~50

[a]Moles of acid catalyst with respect to moles of substrate.
[b]Normalized mass percentage, gas chromatography analysis for methyl, 2-ethyl hexyl, high-performance liquid chromatography for oleyl.
Materials: [c]δ-Lactone, a mixture of C$_{20}$ and C$_{22}$ δ-lactones, derived from meadowfoam fatty acids; [d]BF$_3$, boron trifluoride complex as weight of BF$_3$ per volume (wt/vol) of butanol; [e]Fe^{+3} clay, an iron (III) cation-exchanged K-10 clay; [f]H$_2$SO$_4$, concentrated sulfuric acid; [g]HClO$_4$ is 70% perchloric acid; [h]5-hydroxy fatty acid, a mixture of C$_{20}$ and C$_{22}$ 5-hydroxy fatty acids, derived from meadowfoam δ-lactones. [i]Reaction followed by thin-layer chromatography only. Products isolated by flash column chromatography.

TABLE 2
Etherification Reactions with Butanol

Entry	Substrate	Acid catalyst	Acid equiv.[a]	Temperature (°C)	Time (h)	Ether (%)[b]	Alkene (%)[b]	5-Hydroxy (%)[b]	Lactone (%)[b]
A	δ-Lactone[c]	BF_3[d]	4.5	85	19	84	13	0	3
B	5-Hydroxy[e]	BF_3	4.5	85	22	82	14	0	3
C	γ-Lactone[f]	BF_3	4.5	85	22	21	1	0	78
D	γ-Lactone	BF_3	4.5	85	94	76	8	0	15
E	MFA[g]	BF_3	4.5	85	17	0	100	0	0
F	δ-Lactone	BF_3	4.5	20	120	2	2	0	96
G	δ-Lactone	BF_3	4.5	60	141	28	4	0	66
H	δ-Lactone	BF_3	4.5	70	66	43	8	0	49
I	δ-Lactone	BF_3	4.5	80	45	83	12	0	4
J	δ-Lactone	BF_3	4.5	90	20	83	14	0	3
K	δ-Lactone	BF_3	4.5	117	1	75	25	0	0
L	γ-Lactone	BF_3	4.5	117	23	74	13	0	12
M	δ-Lactone	K-10 Clay[h]	0.1 g	117	24	64	21	0	13
N	δ-Lactone	Fe^{+3} Clay[i]	0.1 g	117	21	70	17	2	10
O	δ-Lactone	Amberlyst[j]	0.1 g	117	22	53	45	0	1
P	δ-Lactone	Dowex[k]	0.1 g	117	22	40	32	7	20
Q	5-Hydroxy	H_2SO_4[l]	2	110	18	67	33	0	0
R	5-Hydroxy	p-TSA[m]	1	90	1	52	26	12	6
S	5-Hydroxy	$HClO_4$[n]	1	90	44	72	20	5	2
T	5-Hydroxy	$HClO_4$/H[o]	0.5	92	5	64	24	12	0
U	5-Hydroxy	$HClO_4$/T[p]	0.5	98	2	48	41	11	0
V	5-Hydroxy	$HClO_4$/D[q]	0.5	92	4	18	27	55	0

[a]Moles of acid catalyst with respect to moles of substrate.
[b]Normalized mass percentage by gas chromatography.
Materials: [c]δ-Lactone, a mixture of C_{20} and C_{22} δ-lactones, derived from meadowfoam fatty acids; [d]BF_3, boron trifluoride complex as weight of BF_3 per volume (wt/vol) of butanol; [e]5-hydroxy fatty acid, a mixture of C_{20} and C_{22} 5-hydroxy fatty acids, derived from meadowfoam δ-lactones.; [f]γ-lactone, a mixture of C_{20} and C_{22} γ-lactones, derived from meadowfoam fatty acids; [g]MFA, meadowfoam fatty acids; [h]K-10 clay, montmorillonite K-10 acid activated clay, obtained from Aldrich Chemical Co. (Milwaukee, WI); [i]Fe^{+3} clay, an iron (III) cation-exchanged K-10 clay; [j]Amberlyst, a strongly acidic sulfonic acid-based ion exchange resin; [k]Dowex (Aldrich Chemical Co.), a strongly acidic sulfonic acid-based ion exchange resin; [l]H_2SO_4, concentrated sulfuric acid; [m]p-TSA, p-toluenesulfonic acid; [n]$HClO_4$ is 70% perchloric acid. [o]This is a reaction performed in 10 mL heptane, [p]toluene, or [q]dioxane.

back into the alcohol) and then through a water solution to prevent escape of excess BF_3.

RESULTS AND DISCUSSION

The facile rate of ring opening of δ-lactones with nucleophiles (4) prompted us to react a variety of alcohols to form 5-hydroxy esters (Isbell, T.A., unpublished results), as depicted in Scheme 1. During the course of this study, we noted the formation of a secondary ether as a minor by-product in some instances and as the major product in others. The synthesis of a 2° ether from an alcohol is typically fraught with the problem of dehydration to the alkene as the major pathway (7–10) unless a stabilized cation transition state can be obtained. The unique stability of the Δ5 fatty acid in oxidative stability tests (1) and its unusual reactivity to form δ-lactone, the kinetic product (3), over the thermodynamically favored γ-lactone (10,11) indicate that unique cationic stabilization is possible at the Δ5 position by the proximally located carboxylic acid functionality. Utilization of this stability provided good yields of a variety of 2° ethers, which are reported in Tables 1 and 2.

The etherification reaction is general for primary alcohols and demonstrates that δ-lactones have good reactivity with alcohol, from methanol through oleyl alcohol. Alcohols branched at the β-position, such as 2-ethylhexyl, also pro-

vided good yields of ethers. However, attempts to synthesize ethers with 2° alcohols as the nucleophile provided only 5-hydroxy esters. Etherification reactions with methanol proved to be the most challenging. Etherifications in methanol were temperature-restricted by its low boiling point and the reduced solubility of the δ-lactone in methanol. However, the methanol series (entries A–D, Table 1) demonstrated that acid concentration plays a significant role in the formation of ethers, with stronger acid concentrations providing higher yields of ether during shorter reaction times. Other catalysts failed to provide significant yields of ether with methanol.

The montmorillonite-cation exchanged clays gave good to excellent yields (70 to 91%) for all alcohols except methanol, but generally required higher temperatures to achieve catalytic activity. All clay catalysts, however, failed to provide reproducible yields in larger-scale reactions.

A thorough examination of the factors that influence the etherification of δ-eicosanolactone or its corresponding 5-hydroxy acid is reported in Table 2. Initially, etherification of δ-lactone was compared to 5-hydroxy fatty acid, meadowfoam fatty acids, and γ-lactone (entries A–E, Table 2). δ-Lactone and 5-hydroxy fatty acid gave nearly identical results under the same reaction conditions. Rate, yield, and degree of dehydration are experimentally equivalent. These data suggest that both δ-lactone and 5-hydroxy fatty acid pass through the

same transition state during the course of the reaction. γ-Lactone provided good yields of ether (entries C, D, and L, Table 2), even though at a much slower rate. The γ-lactone's slow rate of conversion to ether is in good agreement with Brown and colleagues' predictions (12) on the stability of the five-membered ring and the demonstrated rates of ring opening of lactones with nucleophiles (4). Interestingly, meadowfoam fatty acids with Δ5 unsaturation could not be converted to ethers and remained unchanged during the reaction. This indicates that the catalyst is coordinated to the oxygen at the Δ5 position, developing a δ+ charge at this site, but a full carbocation appears not to have developed. Furthermore, the ether remains solely at the Δ5 position with no evidence of migration from this position, as determined by GC–MS of the isolated ethers (see below), further decreasing the probability that a full carbocation was developed.

Temperature enhances the rate of etherification (entries F–L, Table 2). Higher temperatures induce faster rates of reaction but at the cost of secondary reaction mechanisms that lead to dehydration. Even γ-lactone has a good rate at 117°C, but the amount of dehydration at this temperature is nearly double the dehydration in the same reaction carried out at 85°C. The optimum reaction temperature for etherification of δ-lactone appears to be 90°C, where rate and dehydration are at reasonable values for production of ether. Weaker catalysts, such as the iron (III) clay, however, require higher tempera-

ture (100 to 125°C) to achieve good rates (entries H and I, Table 1, and entry N, Table 2).

The iron (III) cation-exchanged clay was significantly more catalytic than its parent montmorillonite K-10 clay. The other heterogenous solid catalysts, Amberlyst and Dowex strongly acidic ion exchange resins, severely dehydrated the δ-lactone, which is typical of sulfonic acid-based materials. Sulfonic acid dehydration was further exemplified by sulfuric and p-toluene sulfonic acids, where 26 to 45% olefin was obtained with these catalysts (entries M–R, Table 2).

Perchloric acid provided good conversion to ether (72%) from the 5-hydroxy fatty acid, with 20% dehydration to the alkene. Co-solvents in the $HClO_4$ reaction diminished the yield of ether but appeared to enhance the rate. The more polar the solvent, the greater the tendency to dehydrate (entries T–V, Table 2). Heptane gave the best yield in this series, and the more polar toluene and dioxane provided dehydration as the major pathway. Increased solvent polarity would create a dipolar environment in the solution. Consequently, the dipolar environment would allow a greater degree of charge separation and a more carbocation-like transition state. Therefore, as the transition state becomes carbocation-like, loss of adjacent protons into the carbocation center becomes likely.

Mechanism of etherification reaction. The mechanism of the etherification reaction is depicted in Scheme 3. In the mechanism shown, H+ will represent the acid catalyst pres-
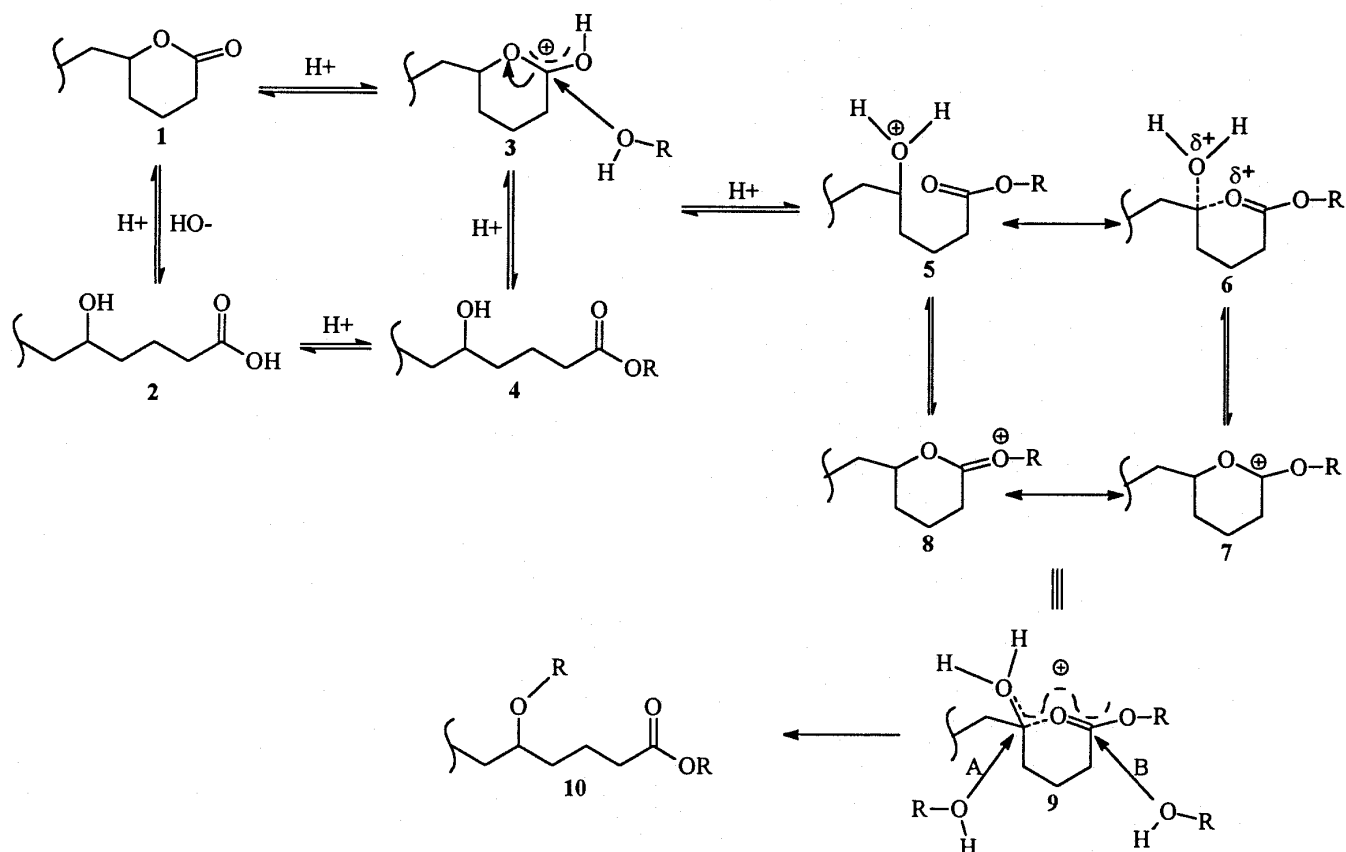
SCHEME 3

ent, whether that be Brøsted or Lewis acid, because both types of catalyst will act to activate the carboxylate functionality. The δ-lactone and the 5-hydroxy fatty acid must pass through a similar transition state because their reaction parameters are nearly identical. Furthermore, we found that the intramolecular cyclization of 5-hydroxy fatty acid to δ-lactone is fast, even at room temperature and under low acid concentrations. Scheme 3 depicts a probable mechanistic pathway for the etherification reaction. Intramolecular conversion between δ-lactone **1** and 5-hydroxy acid **2** is a fast process, with the acid-catalyzed reaction favoring the δ-lactone and the base-catalyzed reaction providing the 5-hydroxy fatty acid. In the presence of an acid catalyst, a near instantaneous conversion of **1** to 5-hydroxy ester **4** is observed (4). Consequently, **2** could be converted to its ester under normal ester mechanistic pathways, but the rapid conversion of **2** to **4** suggests that δ-lactone **1**, even though δ-lactone was not detected initially in our reactions with **2**, served as an intermediate to ester **4**. Over the period of several hours at low temperatures (<60°C), 5-hydroxy ester **4** will ring-close back to δ-lactone.

Protonation of ester **4** will yield cation **5**, which has three other stabilized forms **6**, **7**, and **8**. In effect, the cation is dissipated over 5 atoms as depicted in the hybrid resonance form **9**. Capture of cation **9** by the alcohol in path A will yield ether **10**. Conversely, capture of cation **9** by the al-

cohol in path B will provide ester interchange with no net effect.

The ester functionality, R, most likely will release electron density into the cation as well, further diminishing its charge. All these factors taken into consideration will provide a stable transition state that minimizes cationic charge and reduce the probability of elimination to form the dehydrated alkene fatty acid, which is the major mechanistic pathway in other 2° alcohol/ether syntheses.

The Brønsted acids, perchloric and sulfuric, have lower conversion to ether and higher olefin products, compared to the Lewis acid catalysts. The reduced yield of ether with Brønsted acids is most likely a result of deprotonation of the developing cation by the stronger conjugate bases, i.e., HSO_4^-, as compared to the conjugate bases of the Lewis acids, such as boron trifluoride and iron clay. The stronger the conjugate base, the more likely proton abstraction will occur in the transition state. Consequently, proton abstraction leads to olefin production.

Characterization of ethers. GC–MS cleavages are distinct for the ethers and provide strong evidence for their structural configuration. Figure 1 shows GC–MS spectra of the two positional ethers, 5-butoxy from δ-lactone and 4-butoxy from γ-lactone. The base peak in both spectra shows cleavage around the ether functionality toward the carboxylate terminus to provide the oxonium stabilized radical cation 229 amu for the
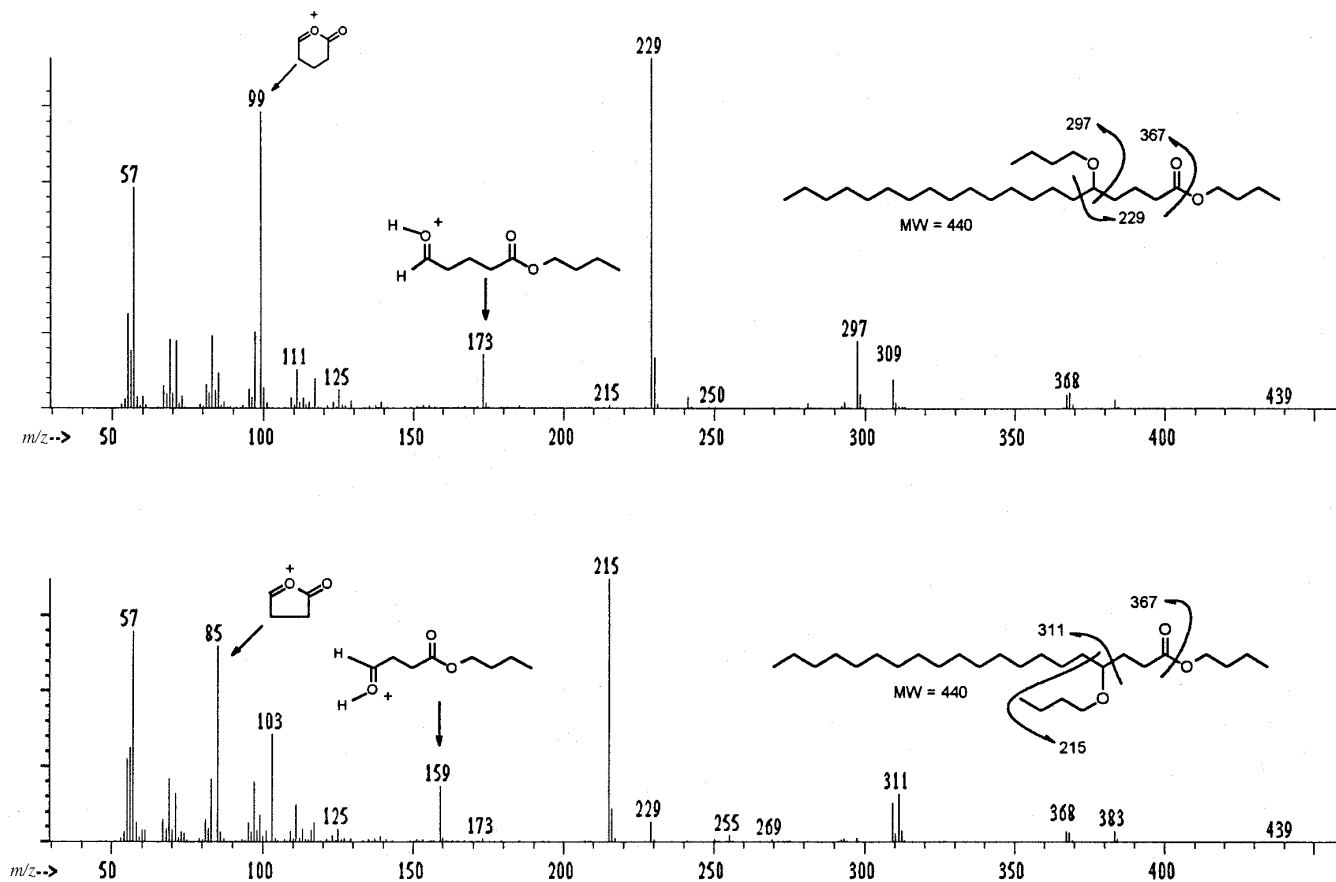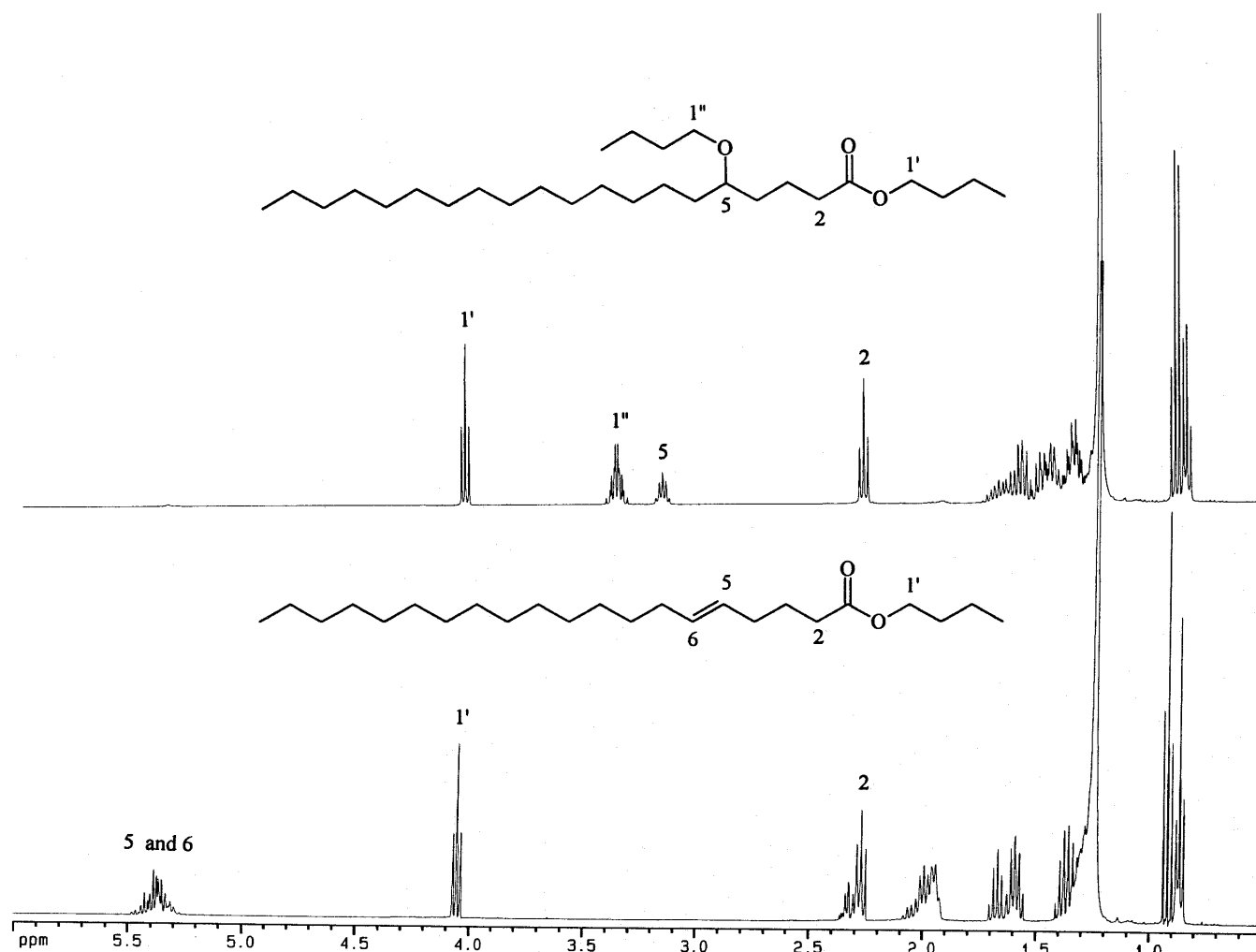

FIG. 1. Mass spectrum of 5- and 4-butoxy ethers.

FIG. 2. Comparison of ^{1}H nuclear magnetic resonance of 5-butoxy ether and unsaturated butyl ester.

5-butoxy and 215 amu for the 4-butoxy ethers. The other ether fragment, resulting from cleavage at the ether toward the alkyl terminus, is much weaker, and yields fragments 297 and 311 amu from 5- and 4-butoxy, respectively. Other key fragments are the cyclized oxonium fragments at 99 and 85 amu, which are the major fragments for Δ6 and Δ5 oxygenated fatty acids and/or δ- and γ-lactones, respectively. The MS spectra provide evidence (no 159 amu and few 215 amu fragments in the 5-butoxy spectrum) that the etherification reaction yields only one regioisomer. Because other regioisomers are absent, this indicates that the cation is held at the position of generation, and migration from this site does not occur due to the stability of the Δ5 position. The minor fragment at 215 amu in the 5-butoxy spectrum is most likely due to the small amount of γ-lactone (~1%) in the starting δ-lactone. Similarly, the 229 amu peak in the 4-butoxy spectrum is from a small amount of δ-lactone present in the starting γ-lactone. If cation migration had occurred, it would have proceeded in both directions (13), and Δ6 ethers would have resulted. Therefore, a nearly equal amount of Δ4 and Δ6 ethers

would be produced from the etherification reaction to result in MS fragments at 187 and 243 amu; neither of these fragments is present in these spectra.

NMR analysis of the ethers is shown in Figure 2, where the 5-butoxy ester is compared to the major by-product, the unsaturated ester. The NMR assignments were derived from the ^{1}H, ^{13}C, DEPT (indicates the number of hydrogens attached to a carbon), COSY (determines the coupling between adjacent protons) and HETCOR (determines which hydrogens are attached to each carbon) spectra. The prominent recurring feature of the ethers is the ^{1}H NMR methine signal of the ether at 3.15 ppm, labeled as resonance 5. The methylene of the ether (3.35 ppm) also has a significantly different chemical shift than the corresponding ester methylene (4.05 ppm). In addition, the ester contains unsaturated signals at 5.4 ppm.

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oil, which provided the material for the synthesis of δ-lactones and hydroxy fatty acids.

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