Synthesis of Chloroalkoxy Eicosanoic and Docosanoic Acids from Meadowfoam Fatty Acids by Oxidation with Aqueous Sodium Hypochlorite

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ABSTRACT: Chloroalkoxy substituted C_{20} and C_{22} fatty acids can be synthesized from the unsaturated fatty acids in meadowfoam oil by reaction of the fatty acids with primary or secondary alcohols and an aqueous sodium hypochlorite solution (commercial bleach). The reactions are conducted at room temperature for 3 h. Chlorohydroxy fatty acid derivatives are formed as by-products owing to the presence of water in the reaction mixture. Chlorinated δ-lactones are also produced by direct reaction of sodium hypochlorite with the Δ5 unsaturated fatty acids present in meadowfoam or by ring closure of the 6-chloro-5-hydroxy fatty acids. The product yield of chloroalkoxy fatty acids is dependent on the nature and volume of the alcohol used in the reaction, as well as the concentration and pH of the sodium hypochlorite solution. Primary alcohols such as methanol and butanol produce maximal yields (50–60%) of chloroalkoxy fatty acids whereas the secondary alcohol 2-propanol gives a 30% yield. Chloroalkoxy fatty acid yields can be increased to 75–80% by elimination of water from the reaction mixture through a procedure that partitions sodium hypochlorite from water into hexane/ethyl acetate mixtures. All of the reaction products were fully characterized using nuclear magnetic resonance and gas chromatography–mass spectrometry.

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Meadowfoam (*Limnanthes alba*) is a developing oilseed crop that is well suited to the Pacific Northwest where a large portion of the current commercial acreage is grown. Interest in meadowfoam has developed owing to the unique long-chain unsaturated fatty acids present in the oil. The oil is composed of 63% 5-eicosenoic acid, 4% 5-docosenoic acid, 12% 13-docosenoic acid, and 17% 5,13-docosadienoic acid as triglycerides. Meadowfoam oil also has an unusually high oxidative stability compared to most other vegetable oils (1).

Previous studies on meadowfoam oil and the fatty acids hydrolyzed from the oil have resulted in the production of several novel compounds. Vulcanization of the oil leads to production of factice which has been used in rubber applications (2–4). Burg and Kleiman have synthesized amides and dimer acids from meadowfoam fatty acids (5,6). Estolide, a type of oligomeric ester, has also been synthesized (7,8). The unique Δ5 position of the double bond, the major olefin of meadowfoam fatty acids, has also lead to the production of δ-lactones and 5-hydroxy fatty acids (9,10). Finally, previous work in our laboratory resulted in the synthesis of 5-alkoxy eicosanoates by reaction of the meadowfoam derivatives, δ-eicosanolactone, and 5-hydroxy eicosanoic acid, with an alcohol in the presence of an acid catalyst (11,12).

To explore the alkoxylation of meadowfoam fatty acids further, we examined the use of sodium hypochlorite and an alcohol to produce novel chloroalkoxy derivatives directly from the fatty acid. Sodium hypochlorite, a common inexpensive oxidant, provides adequate functionality to allow alkoxylation reactions to proceed *in situ* while also providing further derivatization of the alkoxy fatty acid by addition of a chlorine atom adjacent to the alkoxy substituent. Unlike the previous synthesis of 5-alkoxy eicosanoates (11,12), the hypochlorite reaction is not restricted to derivatives of fatty acids that contain double bonds in the 5 position.

In the past, chloroalkoxy derivatives of unsaturated compounds have been synthesized by reaction with premade alkyl hypochlorites (13). Unfortunately, the only alkyl hypochlorites that are stable enough to be isolated are *tert*-butyl, *tert*-amyl, and ethyl hypochlorites. Other chloroalkoxy derivatives have been made by reaction of an alkene with alkyl hypochlorites generated *in situ* by the reaction of chlorine or several different chlorine species such as hypochlorous acid, chlorine monoxide, alkyl hypochlorite, or sodium hypochlorite with a solution of the alcohol of interest (13).

There are several literature references for the use of chlorine gas and alcohol to generate chloroalkoxy, substituted compounds from unsaturated compounds (14,15). However, the use of chlorine can lead to production of a dichloro side product. This problem can be resolved by using premade *tert*-butyl hypochlorite in alcohol. By this method, chloroalkoxy derivatives such as chloroethoxy, 1-propoxy, 2-propoxy, butoxy, *tert*-butoxy, phenoxy, and acetoxy compounds have all been synthesized from unsaturated compounds (15,16). Al-

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though there has been a study conducted on the bromoalkoxylation of conjugated diene fatty acids by treatment with *tert*-butyl hypobromite (17), a reference to the synthesis of chloroalkoxy fatty acids by utilization of bleach and alcohol could not be found.

To avoid the use of preformed alkyl hypochlorite and the restrictions this reagent imparts, we set out to investigate the use of sodium hypochlorite and alcohols in chloroalkoxylations. This investigation details the effect of the nature of the alcohol, reactant concentration, and pH on the production of chloroalkoxy derivatives of meadowfoam fatty acids. A comparison was made between the efficacy of commercial bleach and of sodium hypochlorite extracted from bleach prior to chloroalkoxylation.

EXPERIMENTAL PROCEDURES

Materials. Meadowfoam oil was provided by The Fanning Corp. (Chicago, IL) and split into fatty acids by the Witco Chemical Co. (Greenwich, CT). Concentrated (75%) 5,13-docosadienoic acids were obtained by Chang's method of low-temperature crystallization of meadowfoam fatty acids (18). Chang's method was also used to precipitate concentrated (99%) 13-docosenoic acid from fatty acids obtained from crambe seed oil. Methanol, 1-butanol, 2-propanol, hexane, and sulfuric acid were obtained from Fisher Scientific Co. (Fairlawn, NJ). Ethyl acetate, potassium hydroxide, and potassium iodide were purchased from J.T. Baker (Phillipsburg, NJ). Acetic acid, sodium phosphate monobasic monohydrate, and sodium phosphate dibasic monohydrate were acquired from EM Science (Gibbstown, NJ). Sodium thiosulfate pentahydrate, potassium iodate, *tert*-butyldimethylsilyl (TBDMS) trifluoromethanesulfonate, and *N,O*-bis(trimethylsilyl)acetamide were purchased from Aldrich Chemical Co. (Milwaukee, WI). Pyridine was purchased from Mallinckrodt (Paris, KY). Soluble starch was purchased from Difco Laboratories (Detroit, MI), and 5% NaOCl solution was manufactured by the Clorox Company (Oakland, CA).

Methods. Methanol and 1-butanol reaction products were esterified and analyzed by gas chromatography (GC) with a Hewlett-Packard 5890 Series II gas chromatograph (Palo Alto, CA) equipped with a flame-ionization detector and autosampler/injector. A Supelco SPB20 2.5 m ∞ 0.32 mm i.d. column (Bellefonte, PA) with a flow of 3.9 mL/min, a helium head pressure of 2.5 psi, and a split ratio of 8:1 was utilized. Products were separated with a programmed temperature ramp of 150 to 250°C at 10°C/min, then 250 to 300°C at 20°C/min with the injector and detector set at 300°C. Retention times for eluted peaks: methyl 5,6-chloromethoxy eicosanoate positional isomers, 4.6 min; methyl 5,6-chlorhydroxy eicosanoate positional isomers, 5.0 min; methyl 5,6-chlorobutoxy eicosanoate positional isomers, 5.8 min; methyl 5,6-chloromethoxy docosanoate and methyl 13,14-chloromethoxy docosanoate positional isomers, 6.0 min; methyl 5,6-chlorohydroxy docosanoate and methyl 13,14-chlorohydroxy docosanoate positional isomers, 6.4 min; methyl 5,6-chlorobutoxy docosanoate and methyl 13,14-chlorobutoxy docosanoate positional isomers, 7.1 min; methyl 5,6-chloromethoxy-13,14-chloromethoxy docosanoate positional isomers, 8.2 and 8.5 min; and methyl 5,6-chlorobutoxy-13,14-chlorobutoxy docosanoate positional isomers, 9.5 and 10 min. GC standard curves were obtained for methyl 5,6-chlorohydroxy eicosanoate and methyl 5,6-chloromethoxy eicosanoate isomers and used to determine normalized percentage yields of all C_{20} and C_{22} reaction products.

The free fatty acid–2-propanol reaction products were analyzed by high-performance liquid chromatography (HPLC). The HPLC system consisted of a Thermo Separations Products instrument with a P2000 binary pump and an AS2000 autosampler/injector (Freemont, CA) coupled with an evaporative light-scattering Varex Mark III detector (ELSD III; Alltech Associates, Deerfield, IL). Product separation was performed on a Dynamax silica column (25 cm ∞ 4.6 mm, 60Å, 8 μm) purchased from Rainin Instrument Co. (Woburn, MA) with a hexane/ethyl acetate gradient elution at 1 mL/min. The gradient consisted of 95:5 hexane/ethyl acetate to 70:30 in 17 min, held for 3 min, then back to 95:5 in 0.1 min and held for 10 min. Retention times for eluted peaks were: 5,6-chloro-2-propoxy docosanoic acid and 13,14-chloro-2-propoxy docosanoic acid positional isomers, 11.2 min; 5,6-chloro-2-propoxy eicosanoic acid positional isomers, 12.6 min; 5,6-chloro-2-propoxy-13,14-chloro-2-propoxy docosanoic acid positional isomers, 13.3 min; 5,6-chlorohydroxy docosanoic acid and 13,14-chlorohydroxy docosanoic acid positional isomers, 15.5 min; 6-chloro-δ-eicosanolactone, 17.2 min; 5-chloro-6-hydroxy eicosanoic acid, 21.1 min; and 6-chloro-5-hydroxy eicosanoic acid, 22.1 min. HPLC standard curves were obtained for 5-chloro-6-hydroxyeicosanoic acid, 6-chloro-δ-eicosanolactone, and 5,6-chloromethoxy eicosanoic acid isomers and used to determine normalized percentage yields of all C_{20} and C_{22} 2-propanol reaction products.

Methane chemical ionization (CI) GC–mass spectrometry (MS) was performed with a Hewlett-Packard 5890A gas chromatograph with a Supelco SPB1 30 m ∞ 0.2 mm i.d. column and a Hewlett-Packard 5970 mass selective detector. The gas chromatograph was operated by electronic pressure control to vary helium head pressure and maintain a 1 mL/min flow rate. The injector temperature and transfer line were set at 250 and 300°C, respectively, and the split ratio was 20:1. A programmed temperature ramp of 70 to 200°C at 30°C/min, then 200 to 330°C at 7°C/min, held for 2 min was used. The MS electron multiplier was operated at 200 volts relative, and the mass range was 50–550 amu.

Electron ionization (EI) GC–MS was performed with a Hewlett-Packard 5890A gas chromatograph with a Supelco SPB1 30 m ∞ 0.2 mm i.d. column and a Hewlett-Packard 5970 mass selective detector. The gas chromatograph was operated by electronic pressure control to vary helium head pressure and maintain a constant 1 mL/min flow rate. The injector temperature and transfer line were set at 250 and 300°C, respectively, and the split ratio was 20:1. A pro-

grammed temperature ramp of 70 to 150°C at 30°C/min, 150 to 250°C at 5°C/min, and finally 250 to 300°C at 10°C/min was used. The MS electron multiplier was operated at 200 volts relative, and the mass range was 50–550 amu. To improve chromatography, all fatty acid samples were converted to methyl esters prior to EI or CI GC–MS analysis.

^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR experiments were performed on a Bruker ARX 400 (Karlsruhe, Germany) with a 5-mm dual proton/carbon probe (400 MHz ^{1}H/100.61 MHz ^{13}C). $CDCl_3$ was used as the solvent in all experiments.

Melting points were obtained on a Thomas Hoover capillary melting point apparatus (Svedesboro, NJ).

Formulas corresponding to compound numbers are given in Scheme 3.

^{1}H NMR of 5,6-chloromethoxy eicosanoic acid positional isomers (**1a**, **2a**): δ 3.96 (*m*, –C*H*–Cl, 1H), 3.41 and 3.40 (*s*, –CH–OC*H*$_3$, 3H), 3.25 (*m*, –C*H*–OCH$_3$, 1H), 2.39 (*t, J* = 7.0 Hz, HO_2C–C*H*$_2$–, 2H), 1.78–1.24 (*m*, 30H), and 0.86 ppm [*t, J* = 6.8 Hz, –$(CH_2)_{13}$–C*H*$_3$, 3H]. ^{13}C NMR: δ 179.38 and 179.23 (–*C*=O), 83.97 and 83.88 (–*C*H–OCH$_3$), 63.06 and 62.74 (–*C*H–Cl), 58.51 and 58.46 (–O*C*H$_3$), 33.87, 32.73, 32.38, 31.91, 29.84, 29.67, 29.58, 29.56, 29.46, 29.34, 29.28, 29.13, 26.91, 25.88, 22.68, 22.13, 21.20, and 14.11 ppm [–$(CH_2)_{13}$–*C*H$_3$]. CI MS spectra of the methyl esters of 5,6-chloromethoxy eicosanoic acid positional isomers (**1a**, **2a**): *m/z* 421 (M + $C_2H_5^+$ with ^{37}Cl, 2%), 419 (M + $C_2H_5^+$, 5%), 393 (M + H^+ with ^{37}Cl, 3%), 391 (M + H^+, 11%), 359 (loss of $HOCH_3$, 41%), 355 (loss of HCl, 51%), 323 (loss of $HOCH_3$ and HCl, 41%), 291 (loss of 2 ∞ $HOCH_3$ and HCl, 13%), 241 [loss of –$CHCl(CH_2)_3CO_2CH_3$, 26%], and 145 [loss of –$CHCl(CH_2)_{13}CH_3$, 100%].

^{1}H NMR of 5,6-chlorobutoxy eicosanoic acid positional isomers (**1b**, **2b**): δ 3.95 (*m*, –C*H*–Cl, 1H), 3.49 (*m*, –CH–OC*H*$_2$CH$_2$CH$_2$CH$_3$, 2H), 3.33 (*m*, –C*H*–OCH$_2$CH$_2$CH$_2$CH$_3$, 1H), 2.39 (*t, J* = 6.9 Hz, HO_2C–C*H*$_2$–, 2H), 1.70–1.24 (*m*, 34H), 0.90 (*t, J* = 7.4 Hz, –OCH$_2$CH$_2$CH$_2$C*H*$_3$, 3H), and 0.86 ppm [*t, J* = 7.0 Hz, –$(CH_2)_{13}$–C*H*$_3$, 3H]. ^{13}C NMR: δ 179.50 and 179.33 (–*C*=O), 82.46 and 82.35 (–*C*H–OCH$_2$CH$_2$CH$_2$CH$_3$), 70.65 and 70.61 (–OCH$_2$CH$_2$CH$_2$CH$_3$), 63.20 and 62.87 (–*C*H–Cl), 32.38, 32.20, 31.91, 29.81, 29.67, 29.64, 29.56, 29.45, 29.35, 29.24, 29.10, 26.92, 26.00, 22.68, 22.19, 19.30, 14.10 [–$(CH_2)_{13}$–*C*H$_3$], and 13.85 ppm (–OCH$_2$CH$_2$CH$_2$*C*H$_3$). EI MS spectra of the methyl esters of 5,6-chlorobutoxy eicosanoic acid positional isomers (**1b**, **2b**): *m/z* 283 [loss of –$CHCl(CH_2)_3CO_2CH_3$, 18%], 187 [loss of –$CHCl(CH_2)_{13}CH_3$, 100%], and 57 [$^+(CH_2)_3CH_3$, 50%].

^{1}H NMR of 5,6-chloro-2-propoxy eicosanoic acid positional isomers (**1c**, **2c**): δ 3.90 (*m*, –C*H*–Cl, 1H), 3.64 [*m*, –CH–OC*H*$(CH_3)_2$, 1H], 3.42 [*m*, –CH–OC*H*$(CH_3)_2$, 1H], 2.38 (*m*, HO_2C–C*H*$_2$–, 2H), 1.94–1.24 (*m*, 30H), 1.14 [*m*, –OCH(C*H*$_3)_2$, 6H], and 0.86 ppm [*t, J* = 7.0 Hz, –$(CH_2)_{13}$–C*H*$_3$, 3H]. ^{13}C NMR: δ 179.25 and 179.09 (–*C*=O), 80.21 and 80.01 [–*C*H–OCH$(CH_3)_2$], 71.24 [–O*C*H$(CH_3)_2$], 63.41 and 63.02 [–*C*H–Cl], 33.94, 31.91, 31.48, 29.64, 29.60, 29.57, 29.45, 29.35, 29.06, 29.03, 26.05, 23.24, 23.18, 22.68, 22.46, 22.37, 21.39, and 14.10 ppm [–$(CH_2)_{13}$–*C*H$_3$]. Melting point of 6-chloro-5-hydroxy eicosanoic acid (**3**): 48.0–49.0°C. EI MS spectra of the methyl esters of 5,6-chloro-2-propoxy eicosanoic acid positional isomers (**1c**, **2c**): *m/z* 269 [loss of –$CHCl(CH_2)_3CO_2CH_3$, 11%], 227 [loss of –$CHCl(CH_2)_3CO_2CH_3$ and –$CH(CH_3)_2$, 40%], 173 [loss of –$CHCl(CH_2)_{13}CH_3$, 94%], and 131 [loss of –$CHCl(CH_2)_{13}CH_3$ and –$CH(CH_3)_2$, 100%].

^{1}H NMR of 6-chloro-5-hydroxy eicosanoic acid (**3**): δ 3.88 (*m*, –C*H*–Cl, 1H), 3.62 (*m*, –C*H*–OH, 1H), 2.41 (*m*, HO_2C–C*H*$_2$–, 2H), 1.85–1.60 (*m*, 7H), 1.30–1.24 (*m*, 23H), and 0.86 ppm [*t, J* = 6.9 Hz, –$(CH_2)_{13}$–C*H*$_3$, 3H]. ^{13}C NMR: δ 178.78 (–*C*=O), 73.90 (–*C*H–OH), 68.92 (–*C*H-Cl), 34.77, 34.59, 34.12, 33.77, 33.52, 31.87, 29.63, 29.61, 29.57, 29.50, 29.41, 29.30, 29.07, 26.90, 25.57, 22.63, 20.81, and 14.05 ppm [–$(CH_2)_{13}$–CH_3]. EI MS spectra of the TBDMS derivative of the methyl ester of 6-chloro-5-hydroxy eicosanoic acid (**3**): *m/z* 433 [loss of $^+C(CH_3)_3$, 1%], 323 [loss of HCl and $HOSi(CH_3)_2C(CH_3)_3$, 2%], 291 [loss of HCl, $HOCH_3$, and $HOSi(CH_3)_2C(CH_3)_3$, 11%], and 245 [loss of –$CHCl(CH_2)_{13}CH_3$, 100%].

^{1}H NMR of 5-chloro-6-hydroxy eicosanoic acid (**4**): δ 3.90 (*m*, –C*H*–Cl, 1H), 3.62 (*m*, –C*H*–OH, 1H), 2.41 (*m*, HO_2C–C*H*$_2$–, 2H), 1.89–1.52 (*m*, 6H), 1.30–1.24 (m, 24H), and 0.86 ppm [*t, J* = 6.9 Hz, –$(CH_2)_{13}$–C*H*$_3$, 3H]. ^{13}C NMR: δ 178.34 (–*C*=O), 73.89 (–*C*H–OH), 68.06 (–*C*H–Cl), 34.77, 34.60, 34.12, 33.16, 31.88, 29.64, 29.60, 29.53, 29.49, 29.41, 29.31, 29.07, 29.60, 25.57, 22.64, 21.83, and 14.05 ppm [–$(CH_2)_{13}$–C*H*$_3$]. EI MS spectra of the TBDMS derivative of the methyl ester of 5-chloro-6-hydroxy eicosanoic acid (**4**): *m/z* 433 [loss of $^+C(CH_3)_3$, 21%], 341 [loss of –$CHCl(CH_2)_3CO_2CH_3$, 100%], 323 [loss of HCl and $HOSi(CH_3)_2C(CH_3)_3$, 12%], and 291 [loss of HCl, $HOCH_3$, and $HOSi(CH_3)_2C(CH_3)_3$, 26%]. Melting point of 5-chloro-6-hydroxy eicosanoic acid (**4**): 48.0–50.5°C.

^{1}H NMR of 6-chloro-δ-eicosanolactone (**5**): δ 4.45 (*m*, –C*H*–O–C=O, 1H), 3.91 (*m*, –C*H*–Cl, 1H), 2.60–2.47 (*m*, –C*H*$_2$–CO_2–, 2H), 1.98–1.79 (*m*, 5H), 1.55 (*m*, 2H), 1.24 (*m*, 23H), and 0.86 ppm [*t, J* = 6.8 Hz, –$(CH_2)_{13}$–CH_3]. ^{13}C NMR: δ 170.66 (–*C*=O), 81.41 (–*C*H–O–C=O), 63.23 (–CH–Cl), 33.39, 31.90, 29.69, 29.65, 29.63, 29.58, 29.51, 29.42, 29.33, 29.01, 26.72, 24.22, 22.67, 18.44, and 14.11 ppm [–$(CH_2)_{13}$–*C*H$_3$]. CI MS of 6-chloro-δ-eicosanolactone (**5**): *m/z* 375 (M + $C_2H_5^+$ with ^{37}Cl , 6%), 373 (M + $C_2H_5^+$, 19%), 347 (M + H^+ with ^{37}Cl, 23%), 345 (M + H^+, 75%), 309 (loss of HCl, 73%), 291 (loss of H_2O and HCl, 69%), and 99 [loss of –$CHCl(CH_2)_{13}CH_3$, 100%]. Elemental analysis was performed by Desert Analytics Laboratory (Tucson, AZ). Analysis of 6-chloro-δ-eicosanolactone (**5**). Calculated for $C_{20}H_{37}O_2Cl$: C, 69.72; H, 10.83; Cl, 10.16. Found: C, 69.54; H, 10.68; Cl, 9.97. Melting point of 6-chloro-δ-eicosanolactone (**5**): 63.0–65.0°C.

CI MS spectra of the methyl esters of chloromethoxy docosanoic acid positional isomers (**6a**, **7a**, **10a**, **11a**): *m/z* 449 (M + $C_2H_5^+$ with ^{37}Cl, <1%), 447 (M + $C_2H_5^+$, <1%), 421 (M + H^+ with ^{37}Cl, 1%), 419 (M + H^+, 10%), 383 (loss of HCl, 46%), 351 (loss of $HOCH_3$ and HCl, 100%), 319

(loss of 2 ∞ $HOCH_3$ and HCl, 46%), 269 [loss of $–CHCl(CH_2)_3CO_2CH_3$, 8%], 257 [loss of $–CHCl(CH_2)_5CH_3$, 35%], and 157 [loss of $–CHCl(CH_2)_{11}CO_2CH_3$, 69%].

^{1}H NMR of 13,14-chlorobutoxy docosanoic acid positional isomers (**10b**, **11b**): δ 3.94 (*m*, –C*H*–Cl, 1H), 3.48 (*m*, $–CH–OCH_2CH_2CH_2CH_3$, 2H), 3.31 (*m*, $–CH–OCH_2CH_2CH_2CH_3$, 1H), 2.33 (*t, J* = 7.2 Hz, $HO_2C–CH_2–$, 2H), 1.65–1.25 (*m*, 38H), 0.90 (*t, J* = 7.3 Hz, $–OCH_2CH_2CH_2CH_3$, 3H), and 0.86 ppm [*t, J* = 6.8 Hz, $–(CH_2)_7–CH_3$, 3H]. ^{13}C NMR: δ 178.97 (–*C*=O), 82.58 ($–CH–OCH_2CH_2CH_2CH_3$), 70.56 ($–OCH_2CH_2CH_2CH_3$), 63.77 (–*C*H–Cl), 32.71, 32.22, 31.84, 29.91, 29.63, 29.52, 29.40, 29.22, 29.11, 29.04, 26.90, 26.00, 22.64, 19.30, 14.08 [$–(CH_2)_7–CH_3$], and 13.86 ppm ($–OCH_2CH_2CH_2CH_3$).

^{1}H NMR of 13,14-chloromethoxy docosanoic acid positional isomers (**10a**, **11a**): δ 3.95 (*m*, –C*H*–Cl, 1H), 3.41 (*s*, $–CH–OCH_3$, 3H), 3.23 (*m*, $–CH–OCH_3$, 1H), 2.33 (*t, J* = 7.5 Hz, $HO_2C–CH_2–$, 2H), 1.77–1.25 (*m*, 34H), and 0.86 ppm [*t, J* = 7.0 Hz, $–(CH_2)_7–CH_3$, 3H]; ^{13}C NMR: δ 179.74 (–*C*=O), 84.10 ($–CH–OCH_3$), 63.65 (–*C*H–Cl), 58.45 ($–OCH_3$), 33.98, 33.13, 31.84, 29.96, 29.67, 29.66, 29.51, 29.43, 29.38, 29.24, 29.20, 29.15, 29.02, 26.92, 25.90, 24.65, 22.64, and 14.09 ppm [$–(CH_2)_7–CH_3$]. EI MS spectra of the methyl esters of 13,14-chlorobutoxy docosanoic acid positional isomers (**10b**, **11b**): *m/z* 299 [loss of $–CHCl(CH_2)_7CH_3$, 37%], 199 [loss of $–CHCl(CH_2)_{11}CO_2CH_3$, 100%], and 57 [$^+(CH_2)_3CH_3$, 80%].

^{1}H NMR of 13,14-chloro-2-propoxy docosanoic acid positional isomers (**10c**, **11c**): δ 3.90 (*m*, –C*H*–Cl, 1H), 3.64 [*m*, $–CH–OCH(CH_3)_2$, 1H], 3.41 [*m*, $–CH–OCH(CH_3)_2$, 1H], 2.33 (*t, J* = 7.5 Hz, $HO_2C–CH_2–$, 2H), 1.68–1.18 (*m*, 34H), 1.14 [*m*, $–OCH(CH_3)_2$, 6H], and 0.86 ppm [*t, J* = 6.9 Hz, $–(CH_2)_7–CH_3$, 3H]. ^{13}C NMR: δ 179.82 (–*C*=O), 80.42 [$–CH–OCH(CH_3)_2$], 71.19 [$–OCH(CH_3)_2$], 63.90 (–CH–Cl), 32.15, 31.85, 29.70, 29.67, 29.55, 29.52, 29.42, 29.40, 29.28, 29.22, 29.08, 29.04, 27.06, 26.07, 24.67, 23.22, 22.65, 22.48,and 14.09 ppm [$–(CH_2)_7–CH_3$]. EI MS spectra of the methyl esters of 13,14-chloro-2-propoxy docosanoic acid positional isomers (**10c**, **11c**): *m/z* 285 [loss of $–CHCl(CH_2)_7CH_3$, 9%], 243 [loss of $–CHCl(CH_2)_7CH_3$, and $–CH(CH_3)_2$, 70%], 185 [loss of $–CHCl(CH_2)_{11}CO_2CH_3$, 75%], and 143 [loss of $–CHCl(CH_2)_{11}CO_2CH_3$ and $–CH(CH_3)_2$, 100%].

^{1}H NMR of 13,14-chlorohydroxy docosanoic acid positional isomers (**12**, **13**): δ 3.88 (*m*, –C*H*–Cl, 1H), 3.62 (*m*, –C*H*–OH, 1H), 2.32 (*t, J* = 7.5 Hz, $HO_2C–CH_2–$, 2H), 1.78 (*m*, 2H), 1.65–1.25 (*m*, 32H), and 0.86 ppm [*t, J* = 6.9 Hz, $–(CH_2)_7–CH_3$, 3H]. ^{13}C NMR: δ 179.87 (–*C*=O), 73.91 (–*C*H–OH), 69.06 (–*C*H–Cl), 34.88, 34.62, 34.01, 31.82, 29.53, 29.47, 29.40, 29.35, 29.22, 29.20, 29.17, 29.11, 29.08, 29.00, 26.65, 25.58, 24.64, 22.64, and 14.09 ppm [$–(CH_2)_7–CH_3$]. EI MS spectra of the trimethylsilyl (TMS) derivatives of the methyl esters of 13,14-chlorohydroxy docosanoic acid positional isomers (**12**, **13**): *m/z* 315 [loss of $–CHCl(CH_2)_7CH_3$, 53%], 215 [loss of $–CHCl(CH_2)_{11}CO_2CH_3$, 100%], and 73 [$^+Si(CH_3)_3$, 46%]. Melting point of 13,14-chlorohydroxy docosanoic acid positional isomers (**12**, **13**): 50.5–54.0°C.

^{1}H NMR of 5,6-chloromethoxy-13,14-chloromethoxy docosanoic acid positional isomers (**14a**, **15a**, **16a**, **17a**): δ 3.95 (*m*, 2 ∞ –C*H*–Cl, 2H), 3.40 (*s*, 2 ∞ $–CH–OCH_3$, 6H), 3.23 (*m*, 2 ∞ $–CH–OCH_3$, 2H), 2.39 (*t, J* = 7.0 Hz, $HO_2C–CH_2–$, 2H), 1.77–1.25 (*m*, 30H), and 0.86 ppm [*t, J* = 7.0 Hz, $–(CH_2)_7–CH_3$, 3H]. ^{13}C NMR: δ 179.02 and 178.85 (–C=O), 84.12 and 84.09 and 83.95 ($–CH–OCH_3$), 63.58 and 63.01 and 62.70 (–*C*H–Cl), 58.53 and 58.47 ($–OCH_3$), 34.89, 33.07, 31.84, 29.94, 29.68, 29.51, 29.46, 29.42, 29.28, 29.24, 29.16, 29.02, 26.93, 26.84, 26.81, 25.91, 22.64, 22.13, and 14.09 ppm [$–(CH_2)_7–CH_3$]. CI MS spectra of the methyl esters of 5,6-chloromethoxy-13,14-chloromethoxy docosanoic acid positional isomers (**14a**, **15a**, **16a**, **17a**): *m/z* 513 ($M + C_2H_5^+$ with ^{37}Cl, <1%), 511 ($M + C_2H_5^+$,<1%), 485 ($M + H^+$ with ^{37}Cl, 1%), 483 ($M + H^+$, 3%), 451 (loss of $HOCH_3$, 6%), 447 (loss of HCl, 42%), 419 (loss of $2HOCH_3$, 5%), 415 (loss of $HOCH_3$ and HCl, 19%), 411 (loss of 2 ∞ HCl, 5%), 383 (loss of 2 ∞ $HOCH_3$ and 2 ∞ HCl, 16%), 379 (loss of $HOCH_3$ and 2 ∞ 2HCl, 15%), 347 (loss of 2 ∞ $HOCH_3$ and 2 ∞ HCl, 59%), 157 [loss of $–CHCl(CH_2)_6CHClCHOCH_3(CH_2)_3CO_2CH_3$, 82%], and 145 [loss of $–CHCl(CH_2)_6CHClCHOCH_3(CH_2)_7CH_3$, 100%].

^{1}H NMR of 5,6-chlorobutoxy-13,14-chlorobutoxy docosanoic acid positional isomers (**14b**, **15b**, **16b**, **17b**): δ 3.95 (*m*, 2 ∞ –C*H*–Cl, 2H), 3.48 (*m*, 2 ∞ $–CH–OCH_2CH_2CH_2CH_3$, 4H), 3.33 (*m*, 2 ∞ $–CH–OCH_2CH_2CH_2CH_3$, 2H), 2.39 (*t, J* = 7.0 Hz, $HO_2C–CH_2–$, 2H), 1.68–1.24 (*m*, 38H), 0.90 (*t, J* = 7.3 Hz, 2 ∞ $–OCH_2CH_2CH_2CH_3$, 6H), and 0.86 ppm [*t, J* = 7.0 Hz, $–(CH_2)_7–CH_3$, 3H]. ^{13}C NMR: δ 178.97 (–*C*=O), 82.60 and 82.43 and 82.35 ($–CH–OCH_2CH_2CH_2CH_3$), 70.67 and 70.62 and 70.59 ($–OCH_2CH_2CH_2CH_3$), 63.77 and 63.74 and 63.14 and 62.83 (4 ∞ –*C*H–Cl), 32.67, 32.22, 32.20, 31.85, 29.92, 29.64, 29.41, 29.23, 29.13, 26.94, 26.89, 26.01, 22.65, 22.19, 19.31, 14.10 [$–(CH_2)_7–CH_3$], and 13.87 ppm ($–OCH_2CH_2CH_2CH_3$). EI MS spectra of the methyl esters of 5,6-chlorobutoxy-13,14-chlorobutoxy docosanoic acid positional isomers (**14b**, **15b**, **16b**, **17b**): *m/z* 199 [loss of $–CHCl(CH_2)_6CHClCH(O(CH_2)_3CH_3)(CH_2)_3CO_2CH_3$, 69%], 187 [loss of $–CHCl(CH_2)_6CHClCH(O(CH_2)_3CH_3)(CH_2)_7CH_3$, 83%], and 57 [$^+(CH_2)_3CH_3$, 100%].

^{1}H NMR of 5,6-chloro-2-propoxy-13,14-chloro-2-propoxy docosanoic acid positional isomers (**14c**, **15c**, **16c**, **17c**): δ 3.90 (*m*, 2 ∞ –C*H*–Cl, 2H), 3.64 [*m*, 2 ∞ $–CH–OCH(CH_3)_2$, 2H], 3.41 [*m*, 2 ∞ $–CH–OCH(CH_3)_2$, 2H], 2.39 (*t*, $HO_2C–CH_2–$, 2H), 1.66–1.21 (*m*, 32H), 1.14 [m, $–OCH(CH_3)_2$, 11H], and 0.86 ppm [*t, J* = 6.8 Hz, $–(CH_2)_7–CH_3$, 3H]. ^{13}C NMR: δ 80.41 and 80.16 and 79.99 [$–CH–OCH(CH_3)_2$], 71.23 and 71.20 [$–OCH(CH_3)_2$], 63.84 and 62.9 (–*C*H–Cl), 32.12, 31.85, 29.66, 29.55, 29.41, 29.26, 29.23, 29.08, 29.01, 28.90, 27.04, 26.07, 23.23, 21.42, and 14.10 ppm [$–(CH_2)_7–CH_3$]. EI MS spectra of the methyl esters of 5,6-chloro-2-propoxy-13,14-chloro-2-propoxy docosanoic acid positional isomers (**14c**, **15c**, **16c**, **17c**): *m/z* 185 [loss of $–CHCl(CH_2)_6CHClCH(OCH(CH_3)_2)(CH_2)_3CO_2CH_3$, 61%], 173 [loss of $–CHCl(CH_2)_6CHClCHOCH(CH_3)_2(CH_2)_7CH_3$,

69%], 143 [loss of –CHCl(CH_2)$_6$CHClCH(O(CH_3)$_2$)(CH_2)$_3$$CO_2CH_3$ and –CH(CH_3)$_2$, 100%], and 31 [loss of –CHCl(CH_2)$_6$-CHClCH(OCH(CH3)2)(CH2)7CH3 and CH(CH3)2, 86%].

Reaction of bleach and alcohol with meadowfoam fatty acids. A study of this reaction was conducted with methanol, butanol, and 2-propanol. The bleach and alcohol concentrations were varied as detailed in Table 1, with addition of a volume of acetic acid that was 10% of the volume of the bleach solution. In each reaction, meadowfoam fatty acids (2 g, 6.45 mmole) were placed in a round-bottomed flask with the desired amount of the appropriate alcohol and stirred magnetically. The acetic acid and bleach were mixed in a separate vial and then immediately added to the meadowfoam fatty acids and alcohol. The reaction flask was fitted with a stopper and left to stir at room temperature for 3 h. The reaction mixture was then poured into a separatory funnel, diluted with hexane, and washed with sodium metabisulfite until a KI test strip showed that subsequent sodium chloride washes were negative for oxidant (positive KI strip is black). The hexane layer was then washed with 0.5 M $Na_2HPO_4 \cdot H_2O$ and a pH 5 buffer consisting of 0.85 g $Na_2HPO_4 \cdot H_2O$ and 129.7 g $NaH_2PO_4 \cdot H_2O$ in 1 L of water until subsequent sodium chloride washes had a pH of 4–5. The hexane layer was then dried over sodium sulfate and gravity-filtered through #1 Whatman filter paper (Clifton, NJ). The hexane and alcohol were then removed *in vacuo*. All reactions were performed in duplicate.

The series of reactions at varying pH levels (Figs. 1,2) were conducted with 1.5 equivalents of NaOCl, 25 mL of alcohol, and varying amounts of acetic acid or potassium hydroxide as specified in Table 2. As with the acetic acid, the potassium hydroxide pellets were added to the bleach solution and dissolved prior to addition to the meadowfoam fatty acid/alcohol mixture. The pH values of the bleach/acetic acid or bleach/KOH solutions were determined with a Beckman

TABLE 1
Effect of Alcohol Volume and NaOCl Equivalents on Product Distribution[a]

Alcohol	Alcohol volume	Alcohol equivalents	NaOCl eq.[b]	Chloroalkoxy fatty acids[c] (%)	Chlorohydrin fatty acids[d] (%)	Meadowfoam fatty acids (%)
Methanol	5	19.0	1.5	44.9	53.0	2.1
Methanol	10	38.2	1.5	54.1	42.8	3.1
Methanol	15	57.4	1.5	55.8	42.1	2.1
Methanol	20	76.5	1.5	58.6	39.0	2.4
Methanol	25	95.7	1.5	62.5	34.6	2.9
Methanol	25	95.7	1	50.1	28.3	21.6
Methanol	25	95.7	2	62.0	36.7	1.3
Methanol	25	95.7	2.5	63.4	35.8	0.8
Methanol	25	95.7	3	63.1	35.7	1.2
Butanol	5	8.5	1.5	50.9	48.4	0.7
Butanol	10	16.9	1.5	58.9	40.5	0.6
Butanol	15	25.4	1.5	57.5	41.1	1.4
Butanol	20	33.9	1.5	57.2	41.7	1.1
Butanol	25	42.3	1.5	59.5	38.9	1.6
Butanol	50	84.6	1.5	57.6	22.3	20.1
Butanol	25	42.3	1	48.2	29.3	22.5
Butanol	25	42.3	2	58.3	40.0	1.7
Butanol	25	42.3	2.5	59.2	39.2	1.6
Butanol	25	42.3	3	62.8	35.9	1.3
2-Propanol	5	10.1	1.5	33.0	65.5	1.5
2-Propanol	10	20.2	1.5	31.2	67.7	1.1
2-Propanol	15	30.4	1.5	29.6	69.3	1.1
2-Propanol	20	40.5	1.5	30.1	69.0	0.9
2-Propanol	25	50.6	1.5	29.3	70.0	0.7
2-Propanol	25	50.6	1	25.0	50.8	24.0
2-Propanol	25	50.6	2	29.6	69.5	0.9
2-Propanol	25	50.6	2.5	29.0	69.5	1.5
2-Propanol	25	50.6	3	29.5	69.9	0.6

[a]Reactions consisted of (2 g, 6.45 mmoles) meadowfoam fatty acids, the appropriate alcohol in the volume specified, a bleach solution containing the molar equivalents specified, and a volume of acetic acid that was 10% of the bleach volume (2.4 equiv. H^+ per mole of NaOCl).
[b]Molar equivalent based on the moles of meadowfoam fatty acid.
[c]Methanol and butanol reactions: sum of the normalized gas chromatographic (GC) percentage yields of the methyl esters of the chloroalkoxy products from 20:1, 22:1 and 22:2 fatty acids. 2-Propanol reactions: sum of the normalized high-performance liquid chromatographic (HPLC) percentage yields of the chloroalkoxy products from 20:1, 22:1, and 22:2 fatty acids.
[d]Methanol and butanol reactions: sum of the normalized GC percentage yields of the methyl esters of the chlorohydroxy products from 20:1, 22:1 fatty acids and 6-chloro-δ-eicosanolactone. 2-Propanol reactions: sum of the normalized HPLC percentage yields of the chlorohydroxy products from 20:1, 22:1 fatty acids and 6-chloro-δ-eicosanolactone.

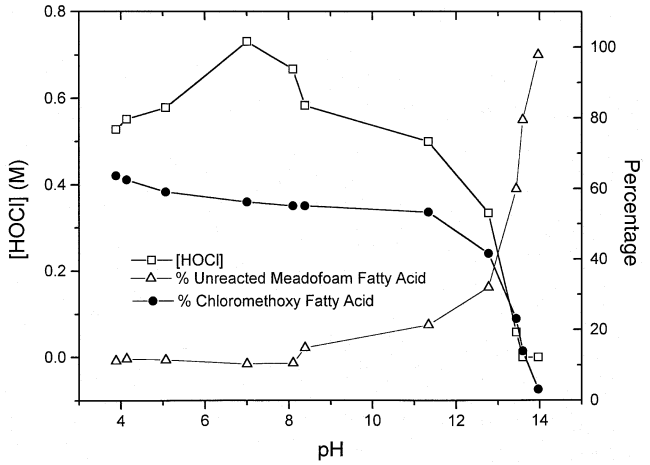


FIG. 1. Chloromethoxy fatty acid production as a function of pH and hypochlorous acid concentration.

pH meter (Fullerton, CA). The reactions with varying amounts of acetic acid and KOH proceeded as described above except that once the potassium hydroxide reactions were complete they were diluted in hexane and washed with sodium metabisulfite, then 1 M sulfuric acid in water was added to adjust the pH to between 4 and 5. All reactions were performed in duplicate.

Reaction of extracted sodium hypochlorite with meadowfoam fatty acids. To eliminate as much water as possible from the reaction, sodium hypochlorite was extracted from an acetic acid/bleach mixture with each of the solvent solutions listed in Table 3. In each reaction 2 g (6.45 mmole) of meadowfoam fatty acids was stirred magnetically with 25 mL of methanol in a round-bottomed flask. A bleach solution containing two molar equivalents of sodium hypochlorite was mixed in a separatory funnel with a volume of acetic acid which was 10% of the bleach volume. Four 15-mL extractions of the bleach/acetic acid mixture were then performed with the solvent mixture of interest. After the final extraction,

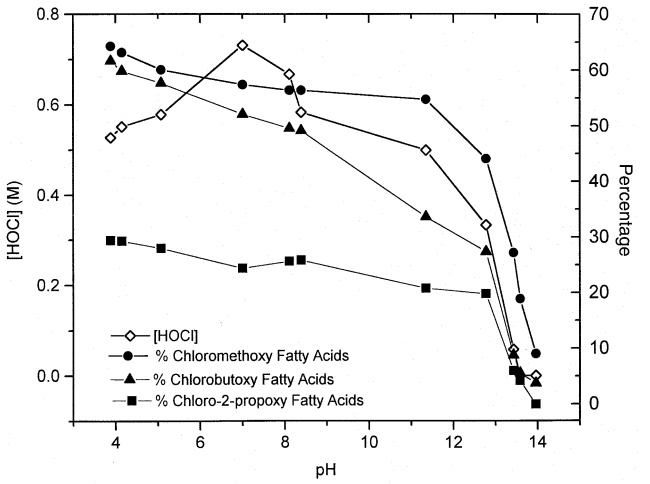


FIG. 2. Chloroalkoxy fatty acid production as a function of pH and hypochlorous acid concentration.

TABLE 2
pH and Hypochlorous Acid Concentration of Bleach/Acetic Acid and Bleach/Potassium Hydroxide Solutions

CH_3CO_2H (M)	KOH (M)	Observed pH[a]	Calculated [HOCl][b] (M)
0	1.3965	13.96	0
0	0.5985	13.59	0
0	0.32	13.43	0.0581
0	0.4256	12.77	0.3341
0	0.1596	11.34	0.5000
0.0869	0	8.38	0.5846
0.1730	0	8.10	0.6677
0.4261	0	7.00	0.7312[c]
0.8318	0	5.07	0.5792[c]
1.5881	0	4.14	0.5528[c]
2.2785	0	3.88	0.5288[c]

[a]pH of the bleach/CH_3CO_2H and bleach/KOH solutions were measured with a pH meter.
[b]HOCl concentrations were calculated based on the NaOCl molarity of the bleach solution.
[c]The molar equivalents of HOCl remain the same but concentration decreases owing to increased volume of the bleach/CH_3CO_2H solution.

the combined HOCl-laden solvent was dried over sodium sulfate and filtered through Whatman #1 filter paper into a round-bottomed flask containing the meadowfoam fatty acids and methanol. The mixture was then stoppered and allowed to react for 1 h. The workup was conducted as described for the nonextracted bleach/acetic acid reactions. All reactions were performed in duplicate.

*Synthesis of C_{20} and C_{22} chlorohydroxy fatty acids (**3**, **4**, **12**, **13**) and 6-chloro-δ-eicosanolactone (**5**).* For reference in compound characterization, the chlorohydrin and chlorolactone derivatives of unsaturated fatty acids were selectively formed by reaction of the unsaturated fatty acids with bleach in the presence of ethyl acetate. The 5,6-chlorohydroxy eicosanoic acid positional isomers (**3**, **4**) and 6-chloro-δ-eicosanolactone (**5**) were synthesized by first mixing meadowfoam fatty acids (2 g, 6.45 mmole) with 20 mL of ethyl acetate. Two equivalents of NaOCl was then added, and the

TABLE 3
Effect of Solvent-Extracted NaOCl on Product Distribution[a]

Ethyl acetate (%)	Hexane (%)	Chloromethoxy[b] (%)	Chlorohydrin[c] (%)	Unreacted fatty acid (%)
0	0	62.0	36.7	1.3
100	0	76.2	22.5	1.3
75	25	79.7	18.8	1.5
50	50	82.8	15.9	1.3
25	75	80.9	17.6	1.5
0	100	33.2	2.5	64.3

[a]Each reaction contained 2 g of meadowfoam fatty acids, 25 mL of methanol, and the solvent from 4 ∞ 15 mL extractions of a bleach solution containing two molar equivalents of sodium hypochlorite and a volume of acetic acid that was 10% of the bleach volume.
[b]Sum of the normalized HPLC percentage yields of the chloromethoxy products from 20:1, 22:1, and 22:2 fatty acids.
[c]Sum of the normalized HPLC percentage yields of the chlorohydroxy products from 20:1, 22:1 fatty acids and 6-chloro-δ-eicosanolactone. For abbreviation see Table 1.

reaction was fitted with a stopper and left to stir for 20 h. The reaction was then diluted in 150 mL of hexane and washed with 20 mL of sodium metabisulfite to remove any excess oxidant. The hexane layer was then washed with 1 M H_2SO_4 and pH 5 Na_2HPO_4/NaH_2PO_4 buffer until subsequent sodium chloride washes gave a pH between 4 and 5. The hexane layer was dried over sodium sulfate, gravity-filtered through #1 Whatman filter paper, and hexane and ethyl acetate were removed *in vacuo*. The product was a pale yellow oil which developed crystals upon standing. This solid was recrystallized from the oil with hexane. Flash column chromatography was performed on the crystals to isolate the 6-chloro-δ-eicosanolactone and the 5,6-chlorohydroxy eicosanoic acid positional isomers. The same reaction method was utilized for the synthesis of 13,14-chlorohydroxy-docosanoic acid positional isomers (**12**, **13**) with 13-docosenoic acid serving as the starting material.

Determination of NaOCl Concentration in Clorox bleach. The Clorox bleach solution was titrated for NaOCl concentration with a solution made from 10 g of $Na_2S_2O_3 \cdot 5H_2O$ in 400 mL of deionized water (19). The $Na_2S_2O_3$ solution was standardized by titrating a solution of 102 mg of KIO_3, 2 g KI, 5 mL of a 50% solution of H_2SO_4, and 50 mL of water. When this purple solution changed to yellow, 1 mL of a 1% soluble starch solution was added which reproduced a purple color. Additional $Na_2S_2O_3$ solution was added until the solution was clear. The concentration of the $Na_2S_2O_3$ solution was then calculated based on the volume of $Na_2S_2O_3$ added and the reaction of 1 mol of KIO_3 with 6 mol of $Na_2S_2O_3$. A solution of 1 mL of bleach, 2 g of KI, 2 mL of 6 M HCl, and 50 mL of deionized water was then titrated with the standardized $Na_2S_2O_3$ in the same manner as the KIO_3 titration. The concentration of NaOCl was then determined by the volume of $Na_2S_2O_3$ added and the reaction of 1 mol of NaOCl with 2 mol of $Na_2S_2O_3$. Since the NaOCl solution degrades over time, the bleach was titrated on several occasions. The initial concentration of NaOCl in the bleach was determined to be 0.7220 M which is a 5.37% solution of NaOCl and is very close to the manufacturer's reported concentration of 5.25%. The bleach was titrated again 6 mon later and the concentration was determined to be 0.6090 M which is a 4.53% NaOCl solution. Three months later the concentration was down to 0.6035 M NaOCl. The amount of bleach solution added to the reactions was determined by the equivalents desired and the NaOCl concentration determined most recently.

Esterification of fatty acid products for analysis. To improve the quality of the GC used in analyzing the methanol and 1-butanol products and in obtaining GC–MS data, small samples of the fatty acid products were converted to methyl esters by treatment with a 1 M solution of sulfuric acid in methanol at 100°C for 15 min. The esterification product was then diluted in hexane and rinsed with 0.5 M Na_2HPO_4 to consume any excess acid. The hexane layer was then dried over sodium sulfate and analyzed by GC or GC–MS.

Isolations and characterizations. GC analysis of the reaction products revealed the presence of chloroalkoxy, chlorohydroxy and chlorolactone derivatives of 20:1, 22:1, and 22:2 fatty acids. Characterization of all 20:1 chloroalkoxy products was performed on the compounds isolated by preparative HPLC or flash column chromatography directly from the meadowfoam fatty acid reaction mixture. Characterization of the 22:1 and 22:2 chloroalkoxy products was performed on material that was isolated from reactions with concentrated 13-docosenoic acid and 5,13-docosadienoic acids. Characterization of the chlorohydroxy and chlorolactone derivatives was performed on products obtained by reaction of meadowfoam fatty acids, concentrated 13-docosenoic acid, and concentrated 5,13-docosadienoic acid with bleach in the presence of ethyl acetate instead of alcohol.

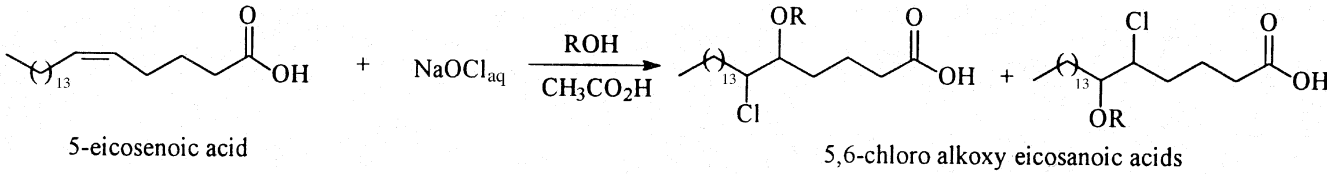
TMS and TBDMS derivatization of chlorohydroxy fatty acids. To improve chromatography and enhance MS fragmentation, small samples (1 mg) of the C_{20} and C_{22} chlorohydroxy fatty acids were converted to methyl esters and then reacted with 50 μL of either *N,O*-bis(trimethylsilyl)acetamide or TBDMS trifluoromethanesulfonate in pyridine (200 μL) at 100°C for 30 min to produce the TMS and TBDMS chlorohydroxy ester derivatives, respectively. Prior to GC–MS analysis, the products were diluted in hexane and run through a small Pasteur pipet which was plugged and filled with silica gel to remove any excess silylating reagent.

RESULTS AND DISCUSSION

Synthesis of novel 5-alkoxy eicosanoates from meadowfoam fatty acid derivatives, 5-hydroxy eicosanoic acid and δ-eicosanolactone, was previously accomplished in our laboratory. To examine the alkoxylation of meadowfoam fatty acids further, we conducted a study concerning the direct formation of alkoxy fatty acids from unsaturated fatty acids. After review of the technology pertaining to alkoxylation, we determined that the most practical approach would be addition of household bleach (5% sodium hypochlorite) to a solution of meadowfoam fatty acids in alcohol. The product, a chloroalkoxy fatty acid, would be unique in that the substituent alkoxy group would be adjacent to a chlorine atom.

Formation of chloroalkoxy fatty acids from 5-eicosenoic acid is depicted in Scheme 1. Acetic acid is added to ensure that the carboxylate group of the fatty acid remains protonated during the course of the reaction. Bleach is a complex mixture of sodium hypochlorite and various chlorine species, therefore, the acetic acid also reacts with sodium hypochlorite to produce hypochlorous acid. Excess acetic acid serves an additional role in the transition state of this reaction by forming protonated hypochlorous acid which can react with the carbon-carbon double bond to produce a chloronium ion as shown in Scheme 2 (20). The alcohol then attacks the chloronium ion to produce both positional isomers of the chloroalkoxy eicosanoic acid. Reaction can occur at either of the two carbon-carbon double bonds of the meadowfoam C_{20} and C_{22} fatty acids to produce chloroalkoxy derivatives.

The nature of the alcohol (primary or secondary) and its chain length are just two of the factors that affect the



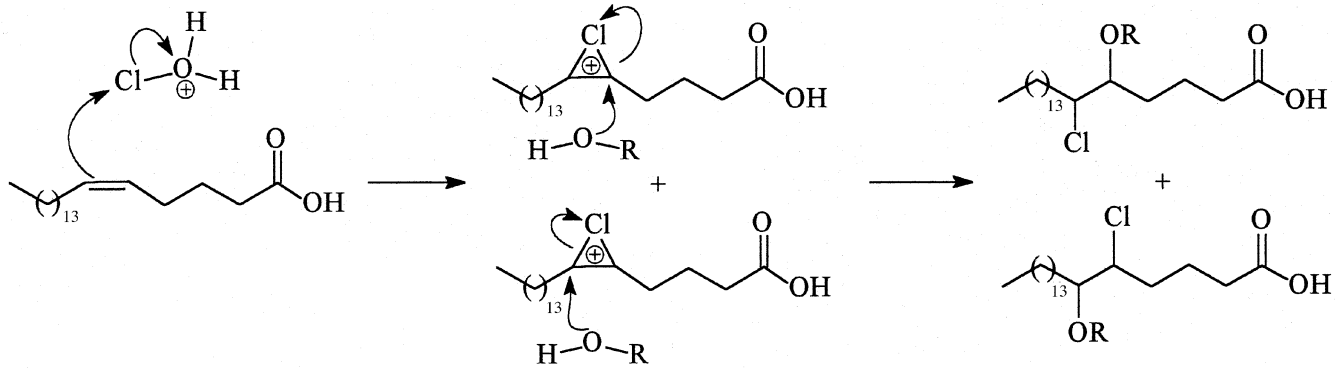
SCHEME 1

chloroalkoxylation reaction. Therefore, a range of alcohols, including methanol, butanol and 2-propanol, were utilized to study the chloroalkoxylation reaction. Use of these alcohols led to formation of chloromethoxy, chlorobutoxy, and chloro-2-propoxy fatty acids.

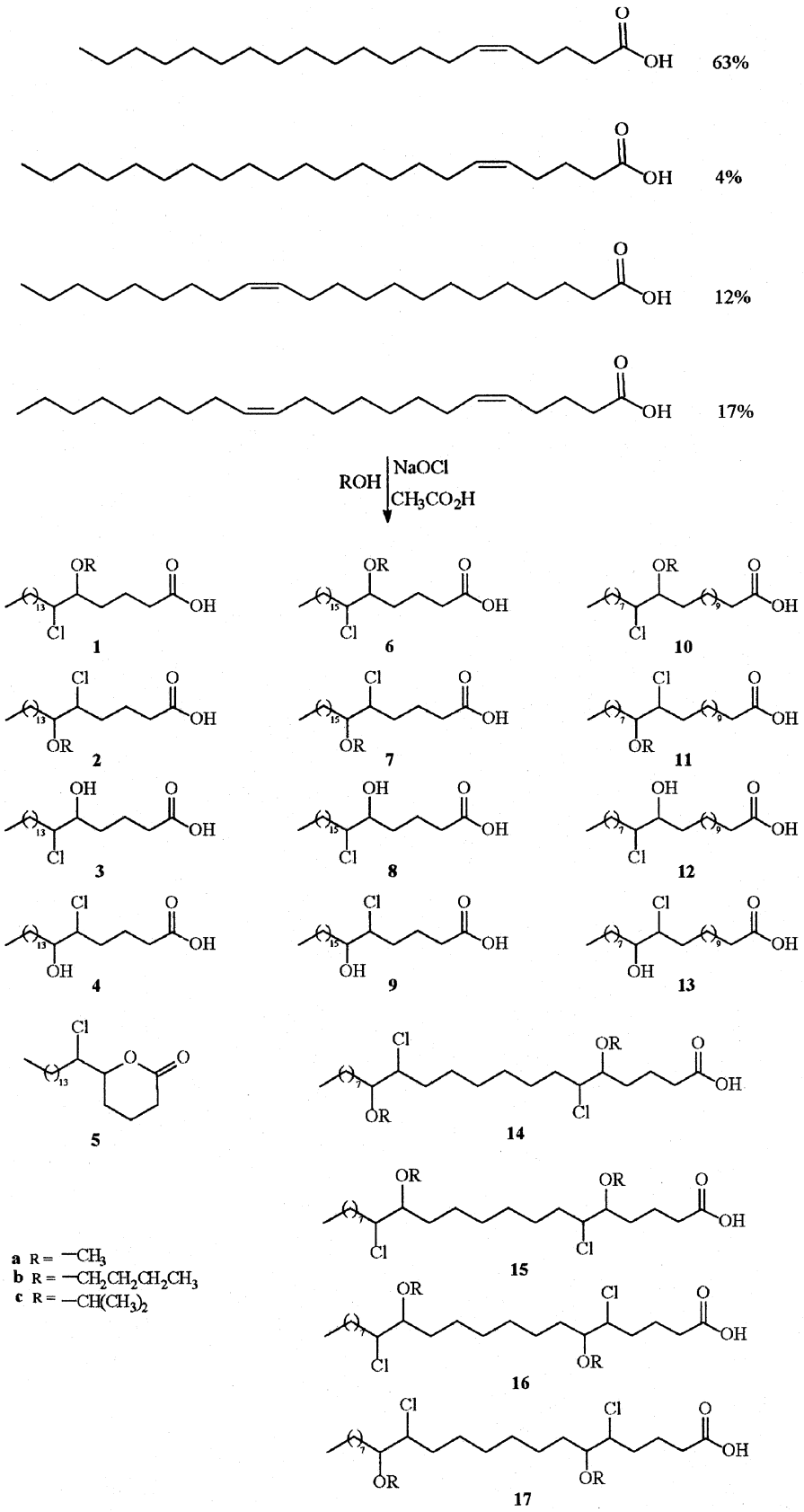
We found that the chloroalkoxylation reaction produced a mixture of products as detailed in Scheme 3. With each alcohol, we successfully produced 5,6-chloroalkoxy eicosanoic acid isomers **1** and **2**, 5,6-chloroalkoxy docosanoic acid isomers **6** and **7**, 13,14-chloroalkoxy docosanoic acid isomers **10** and **11**, and bis-chloroalkoxy docosanoic acid isomers **14**, **15**, **16,** and **17**. However, several inherent characteristics of the reactants led to formation of 5,6-chlorohydroxy eicosanoic acid isomers **3** and **4**, 5,6-chlorohydroxy docosanoic acid isomers **8** and **9**, 13,14-chlorohydroxy docosanoic acid isomers **12** and **13,** and 6-chloro-δ-eicosanolactone (**5**) which reduced chloroalkoxy yields substantially.

The chlorohydroxy formation can be attributed to the nature of the bleach solution. The bleach used in each series of reactions was a 5% aqueous solution of sodium hypochlorite. Therefore, there is a sufficient concentration of water available to compete against the alcohol for attack of the chloronium ion. When the water successfully reacts with the chloronium ion, the result is the production of chlorohydrins **3** and **4** (Scheme 4). The chlorohydroxy fatty acids can be selectively synthesized by eliminating alcohol from the reaction and substituting ethyl acetate as the solvent. Formation of the by-product, 6-chloro-δ-eicosanolactone (**5**), can be attributed to the 5-position of the double bond. As Scheme 5 shows, 6-chloro-δ-eicosanolactone (**5**) is produced from attack of the chloronium ion by the hydroxy oxygen of the carboxylic acid. Intramolecular ring closure to lactone is expected from unsaturated carboxylic acids with the double bond in the fourth and fifth position owing to the relative ease of cyclization to γ- and δ-lactones (21,22). This intramolecular side reaction is also a strong competitor against formation of chloroalkoxy derivatives because it is a unimolecular process which has a rate independent of concentration. Formation of **5** occured in all cases but was not readily quantifiable from the chlorohydrins generated from the complex mixture of meadowfoam fatty acids. Therefore, derivatization of the reaction mixtures was necessary to obtain standardized analysis for all independent functional groups produced by the reaction. Consequently, chlorolactone was converted to 6-chlor-5-hydroxy fatty esters and reported as such.

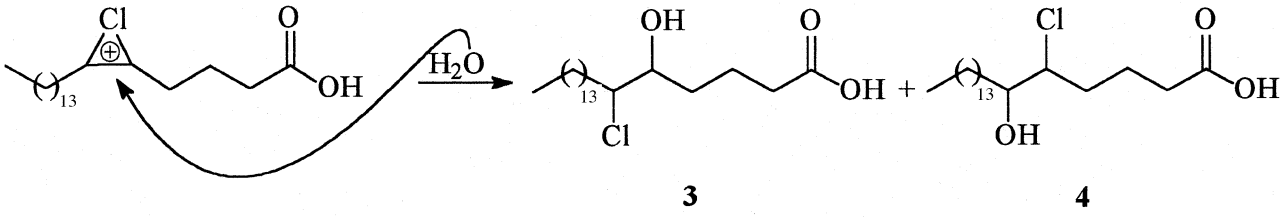
To develop a reaction method which minimized formation of the chlorhydrin and chlorolactone by-products, we analyzed the effects of varying NaOCl concentration on product distribution by comparison of normalized GC and HPLC percentage yields from reactions of meadowfoam fatty acids in methanol, 1-butanol, or 2-propanol. Table 1 shows the effect of NaOCl concentration on normalized percentage yields of chloromethoxy and chlorohydrin products obtained by GC analysis of reaction mixtures as their methyl esters. Upon esterification, the chlorolactone product is converted to methyl 6-chloro-5-hydroxy eicosanoate and therefore the percentage yield of chlorolactone is included in the percentage yield of chlorohydrin methyl esters. The data show that a 1:1 molar ratio of NaOCl to meadowfoam fatty acids is not sufficient for a complete reaction since 21.6% of the meadowfoam fatty acids remained unreacted. This is not surprising since 17.6% of the fatty acids are dienes and contain twice the number of reactive sites. As the NaOCl concentration is increased to 1.5 equivalents, the meadowfoam fatty acids are consumed and the percentage yield of chloromethoxy products jumps to 62.5%. Unfortunately the chlorohydroxy by-product also increases to 34.6%. After all of the meadowfoam fatty acids are consumed, NaOCl concentration has little effect on chloro-



SCHEME 2


63%
4%
12%
17%
ROH
NaOCl
CH_3CO_2H
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
a R = $-CH_3$
b R = $-CH_2CH_2CH_2CH_3$
c R = $-CH(CH_3)_2$

SCHEME 3



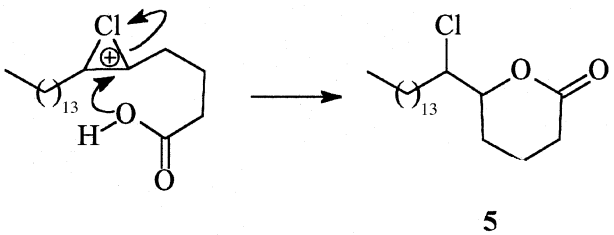
3 4

SCHEME 4

methoxy product yield. Upon increasing the NaOCl concentration from 1.5 to 3 equivalents, formation of chloromethoxy and chlorohydroxy products remain constant at approximately 63 and 35%, respectively.

The effect of NaOCl concentration on the production of chlorobutoxy fatty acids is also shown in Table 1. Again, GC-normalized percentage yields of methyl esters were utilized, and therefore chlorolactone production is included in the percentage yield of chlorohydrin methyl esters. As with methanol, complete consumption of meadowfoam fatty acids is not achieved until 1.5 equivalents of NaOCl are added. There is also no net effect on chlorobutoxy product formation as the NaOCl concentration is increased from 1.5 to 3 equivalents. One interesting note is that the chlorobutoxy product yield levels off at 59% which is four percentage points lower than the maximum chloromethoxy acid yield. The decrease in chloroalkoxy product formation when 1-butanol is used could be attributed to the 1-butanol being a larger attacking species and therefore encountering more steric hindrance as it approaches the chloronium ion. Water would therefore find it easier to compete against butanol for capture of the chloronium species and more chlorohydroxy by-products would result. Also, unlike methanol, butanol is not totally miscible with water and the reaction must occur in two phases. Therefore, the movement of the hypochlorite species between the 1-butanol and water layers may affect product distribution and chloroalkoxy production.

Leveling off of the chloroalkoxy yield at 1.5 equivalents of NaOCl is also apparent when 2-propanol is utilized. Unfortunately, the 29% maximum yield of the chloro-2-propoxy product is substantially lower and is essentially one-half that of the chloromethoxy yield. One explanation of this large discrepancy in yield is that 2-propanol is a secondary alcohol, and the two alkyl groups provide even more steric hindrance than in the butanol case. This demonstrates the poor nucleophilicity of secondary alcohols. Consequently, competition by water in the 2-propanol reaction results in a 70% yield of chlorohydrins.



5

SCHEME 5

The effects of alcohol volume on product distribution were analyzed by comparison of normalized GC and HPLC percentage yields from reactions of meadowfoam fatty acids in varying amounts of methanol, 1-butanol, or 2-propanol with 1.5 molar equivalents of NaOCl. As Table 1 shows, the chloromethoxy yield increases by 39.2% as the amount of methanol increases to 25 mL. Water and methanol are miscible and therefore strong competitors, and an increase in methanol concentration will result in an increase of the chloromethoxy product. The 1-butanol series shows a similar trend, with a 16.9% increase in the chloroalkoxy percent yield as the volume of alcohol is increased from 5 to 25 mL.

Varying the 2-propanol concentration has the opposite effect on chloroalkoxy production. As 2-propanol volume increases the percentage yield of chloro-2-propoxy compounds decreases from 33.0 to 29.3%, an 11.2% decrease. 2-Propanol and methanol are both miscible with water. The key difference between methanol and 2-propanol is that meadowfoam fatty acids are more soluble in 2-propanol. When 5 mL of 2-propanol, meadowfoam fatty acids, and NaOCl were reacted, two phases resulted. However, when the volume of 2-propanol was increased, the reaction became homogeneous. Consequently, the homogeneous reaction allowed a greater concentration of water to come in contact with the fatty acids and an increased yield of chlorohydrins resulted. Increased chlorohydrin production is also aided in this homogeneous 2-propanol reaction by the lower nucleophilicity of the secondary alcohol as compared to the primary alcohols.

The effects of bleach solution pH on product distribution were studied by reacting 2 g of meadowfoam fatty acids in 25 mL of methanol, 1-butanol, or 2-propanol with 1.5 molar equivalents of bleach with acetic acid or potassium hydroxide added to vary the pH from 3.9 to 14.0. As Table 2 shows, the amount of acetic acid was varied from 0% to 15% of the bleach volume (0–36 equiv) which corresponds to a pH range of 11.3–3.9. In order to study the effects of a more basic bleach solution, potassium hydroxide was added to the bleach in amounts varying from 0.1 to 1.0 g which extended the pH range to 14.0.

Figure 1 depicts hypochlorous acid concentration and chloromethoxy product yield as a function of pH. At pH levels below 5, which correspond to a volume of acetic acid equal to 5–15% of the bleach volume, the chloromethoxy

product yield is highest at 63%. At these pH levels, excess acetic acid beyond the amount needed to protonate all of the NaOCl present has been added. Therefore, the excess acid can generate protonated HOCl which would react readily with an unsaturated compound to form the chloronium ion and water. This increased reactivity of the protonated hypochlorous acid would lead to an increased yield of chloromethoxy acid.

At pH levels between 7 and 12, which correspond to a volume of acetic acid equal to 2.5–0% of the bleach volume, the chloromethoxy yield slowly decreases to 53%. Addition of 2.5% acetic acid is sufficient for protonation of 58% of the total NaOCl in solution. The remaining 42% of the NaOCl can remove a proton from the fatty acids in the reaction. Therefore, all of the NaOCl is converted to HOCl but there is no excess acetic acid present to generate protonated HOCl. The reactive species is then HOCl and since H_2O is a better leaving group than ^{-}OH, the reactivity of the HOCl is not as great as the reactivity of protonated HOCl and chloromethoxy product yield decreases slightly. When 0–1% acetic acid vol/vol is added, the amount of acetic acid and fatty acid is insufficient for complete protonation of NaOCl. Therefore, the chloromethoxy product yield decreases not only because of the lower reactivity of HOCl but also because of the decrease in HOCl concentration.

Within the pH range of 12–14, which corresponds to the addition of 0.12–1.05 g KOH, the chloromethoxy product yield drastically drops off to 3%. When 0.12–0.32 g of KOH is present, some protonated fatty acid is still available to form small amounts of HOCl. Therefore some reaction can still take place. When 0.45 to 1.05 g of KOH is added, there is enough hydroxide ion present to deprotonate all of the fatty acid. Therefore, essentially no HOCl is formed and very little reaction takes place since ^{-}OCl would not readily dissociate to O^{2-} and Cl^{+}.

The variation of chloroalkoxy production as a function of pH and hypochlorous acid concentration was also studied with 1-butanol and 2-propanol. Figure 2 illustrates the loss of product formation at high pH levels and low HOCl concentrations for chloromethoxy, chlorobutoxy, and chloro-2-propoxy fatty acids.

To determine if chloroalkoxy yield could be increased by reducing the amount of water present in the reaction, we conducted a study on the reactivity of solvent-extracted HOCl. A series of reactions were performed in methanol with HOCl that was extracted from a bleach/acetic acid mixture with varying amounts of hexane and ethyl acetate as listed in Table 3.

In each case, four 15-mL quantities of the appropriate solvent mixtures were used to extract hypochlorite species from a mixture of a bleach solution containing 2 equivalents of NaOCl and a volume of acetic acid that was 10% of the bleach volume.

As Table 3 shows, extraction of NaOCl into 100% ethyl acetate increases chloromethoxy yield by approximately 30%. Ethyl acetate is partially miscible with water, therefore there is enough interaction between the water/ethyl acetate layers to allow transfer of the hypochlorite species into the ethyl acetate layer. When the ethyl acetate layer is dried and added to the reaction, a large majority of the water is left behind and chlorohydrin production is reduced. As hexane is added to the ethyl acetate, the percentage of chloromethoxy products increases and reaches a maximum of 82.8% at a ratio of 50:50 ethyl acetate/hexane. This increase in chloromethoxy production at the expense of chlorohydrin can be attributed to the ability of hexane to lower the miscibility of ethyl acetate and water. The presence of the hexane in the ethyl acetate sufficiently decreases the amount of residual water in the extracted solvent layer but still allows sufficient extraction of the hypochlorite species. When 100% hexane is used to extract the hypochlorite species, the majority of meadowfoam fatty acids (64.3%) is left unreacted. In comparison to ethyl acetate, only a small amount of the hypochlorite species is extracted into 100% hexane due to the poor solubility of HOCl in hexane, therefore, incomplete consumption of the starting material results.

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