# A Highly Regioselective Synthesis of δ-Lactones from Meadowfoam Fatty Acids

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**ABSTRACT:** Meadowfoam fatty acids, when treated with mineral acid catalysts in the presence of polar nonparticipating solvents, undergo a facile ring closure to form δ-lactones. Perchloric and sulfuric acids catalyze the cyclization at concentrations of 0.6–13 mole equivalents, both neat and in the presence of solvent. Under constant acid concentrations, methylene chloride was found to increase the rate of reaction, the regioselectivity for the formation of δ-lactone, and the overall yield. In the absence of solvent, increased acid concentration improved the yield of lactone but reduced regioselectivity for the δ-isomer. Solvent polarity plays a significant role in the regioselectivity of the cyclization for δ-lactone, with solvents of higher dielectric strength providing larger δ/γ ratios (38:1) and higher yields up to 92%.

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**KEY WORDS:** δ-Eicosanolactone, γ-eicosanolactone, lactone, meadowfoam fatty acids, perchloric acid, regioselective lactonization, sulfuric acid.

Meadowfoam (*limnanthes*) is a developing oilseed crop currently grown in the Pacific Northwestern United States. This winter annual crop is an economical and environmental alternative to the grass seed industry currently located in the Willamette valley of Oregon.

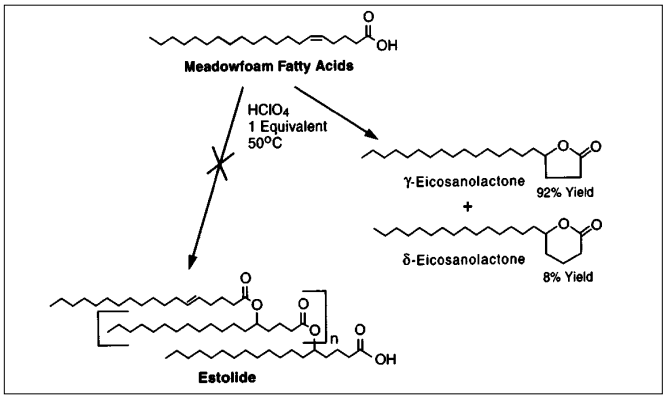
Meadowfoam oil is composed of long-chain fatty acids (1) with 5-eicosenoic acid (64%) as the major fatty acid. The other main components are 5,13-docosadienoic acid (19%), 5-docosenoic acid (3%), and 13-docosenoic acid (10%). This unique combination of monoenoic fatty acids makes for a very oxidatively stable oil with an Active Oxygen Method (AOM, AOCS Method Cd 12-57) value of 200 as compared to other vegetable oils such as soybean oil and high oleic sunflower oil which have AOM values of 14 and 90, respectively (2).

Meadowfoam oil and its fatty acids have been utilized recently in the development of novel materials with potential uses as industrial agents. The oil has been vulcanized and the resultant factice exhibits good properties in rubber applications (3–5). The fatty acids have been converted to amides (6), dimer acids (7), and estolides (8,9). Of particular interest was the acid-catalyzed process (9) for the production of estolides where, under certain reaction conditions (Scheme 1), no estolide was formed but large yields (50–90%) of lactones were obtained. The monomer mixture from the estolide reaction contained nearly equal amounts of γ- and δ-lactones. The presence of substantial quantities of δ-lactone within this monomer fraction prompted us to begin an investigation into the possible synthesis of δ-lactone from meadowfoam fatty acids.

γ-Lactones have been synthesized previously (10) from meadowfoam fatty acids and mineral acid catalysts utilizing methodology developed by Swern *et al.* (11) and Shepherd and Showell (12). Swern developed a methodology for a perchloric acid-catalyzed isomerization of oleic acid into γ-stearolactone (Scheme 2). However, Swern's process did not produce δ-lactones due to the vigorous reaction conditions necessary to isomerize the Δ9 double bond of oleic acid to the Δ4 position where facile ring closure to γ-lactone occurred.

Other acid-catalyzed lactonizations reported in the literature are summarized in Table 1. Ansell and Palmer (13,14) conducted a series of reactions in which he studied the formation of δ- and γ-lactones from short-chain unsaturated acids. He obtained lactone yields ranging from 5–50% with an optimum yield of 32% δ-lactone and a regioselectivity of 19:1 for δ-lactone.

Fujita *et al.* (15) utilized a stabilized tertiary carbocation in the cyclization of 5-methyl hex-4-enoic acid with sulfuric




**SCHEME 1**

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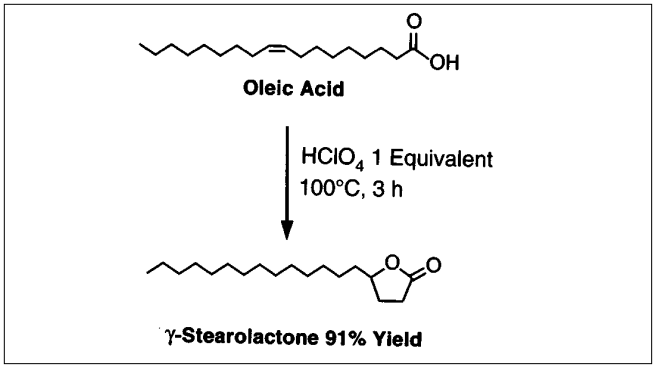


SCHEME 2

acid, which is the only published report of a high yielding (82%) cyclization to δ-lactone. Mechanistically, protonation of 5-methyl hex-4-enoic acid yields the stable tertiary carbocation, which is captured intramolecularly by the carboxyl group to form δ-lactone. In all other cases, the γ-lactone is the product isolated in high regioselectivity and yield due to the thermodynamic stability of the 5-membered ring (16).

Other workers explored the use of ion exchange resins (17) where γ-lactone was synthesized exclusively at 100°C, even in the presence of solvents. Nakano and Foglia (18) report the synthesis of small amounts of δ-lactone from unsaturated acids with *p*-toluene sulfonic acid in the presence of an aromatic solvent at room temperature.

In light of these findings, we set out to synthesize δ-eicosanolactone from meadowfoam fatty acids by taking advantage of the natural proximal relationship of the Δ5 double bond and carboxyl group. The initial stage of the mechanism would be the protonation of the Δ5 double bond to form a carboxylate stabilized carbocation (Fig. 1). Subsequent ring closure to the δ-lactone can occur readily as well as proton elimination or hydride migration which would lead to unsaturated fatty acid or γ-lactone, respectively. Control of these reaction pathways by neighboring group participation of the carboxylic acid functionality and kinetic control will be needed for the regioselective formation of δ-lactone.

## EXPERIMENTAL PROCEDURES

*Materials.* Meadowfoam fatty acids were obtained by hydrolysis of meadowfoam oil supplied by the Fanning Corp. (Chicago, IL) and the Oregon Meadowfoam Growers Association (Salem, OR). Perchloric acid and *bis*(trimethylsilyl)-trifluoroacetamide (BSTFA) were purchased from Aldrich Chemical Co. (Milwaukee, WI). Concentrated sulfuric acid was obtained from J.T. Baker Chemical Co. (Phillipsburg, NJ). Potassium hydroxide, methanol, hexane (for extraction and high-pressure liquid chromatography, HPLC) and acetone (for HPLC) were obtained from Fisher Scientific Co. (Fairlawn, NJ). Boron triflouride/methanol complex (14% wt/vol) and reference fatty acid methyl esters (FAME) were purchased from Alltech Associates, Inc. (Deerfield, IL). Tetrahydrofuran (THF), monobasic phosphate, and dibasic phosphate were obtained from EM Science (Gibbstown, NJ). Triphenylphosphine was purchased from Eastman Kodak (Rochester, NY). Filter paper was obtained from Whatman (Maidstone, England).

*Instrumentation.* HPLC analyses were performed on a Spectra-Physics 8800 ternary pump (San Jose, CA) with a Spectra System AS3000 autosampler/injector from Thermo Separation Products (Fremont, CA) coupled to an evaporative light-scattering detector (ELSD) from Varex (Burtonsville, MD). A Dynamax (250 mm × 4.6 mm, 60Å, 8 μm) silica column purchased from Rainin Instrument Co. (Woburn, MA) was used to separate the reaction mixtures. Components were eluted from the column with a hexane/acetone 80:20 mixture at a flow rate of 1 mL/min with the ELSD drift tube set at 35°C, the nebulizer set at 10 psi $N_2$, and a flow rate of 1.50 standard liters per minute (SLPM). Retention times for eluted peaks: fatty acids, 4.4; min, γ-eicosanolactone, 4.6 min; and δ-eicosanolactone, 4.9 min.

*Gas chromatography (GC).* GC was performed with a Hewlett-Packard 5890 Series II gas chromatograph (Palo

**TABLE 1**
**Literature Summary of Lactonization Conditions**

| Fatty acid | Catalyst | Equivalent | Solvent | Temperature (°C) | γ-Lactone | δ-Lactone | Yield | Reference number |
|---|---|---|---|---|---|---|---|---|
| Hex-5-enoic | $H_2SO_4$ | 21.8 | Acid | 20 | 1 | 2.2 | 33 | 13 |
| Octa-7-enoic | $H_2SO_4$ | 21.8 | Acid | 20 | 1 | 2 | 43 | 13 |
| Hex-5-enoic | $H_2SO_4$ | 11.0 | Acid/$H_2O$ | 150 | 49 | 1 | 50 | 13 |
| Hex-5-enoic | $CF_3CO_2H$ | 16.9 | Acid | 150 | 1 | 4.5 | 28 | 13 |
| Hept-5-enoic | $H_2SO_4$ | 12.5 | Acid/$H_2O$ | 150 | 24 | 1 | 44 | 13 |
| Hept-5-enoic | $CF_3CO_2H$ | 18.7 | Acid | 150 | 1 | 19.0 | 32 | 13 |
| Hept-6-enoic | $H_2SO_4$ | 12.5 | Acid/$H_2O$ | 150 | 32.3 | 1 | 30 | 13 |
| Hept-6-enoic | $CF_3CO_2H$ | 18.7 | Acid | 150 | 1 | 4.5 | 5 | 13 |
| 4-Acyloxy hex-5-enoic | Amberlyst | NA | Solvents | 100 | 100 | NA | 74 | 16 |
| 5-Methyl hex-4-enoic | $H_2SO_4$ | 1.0 | Benzene | 80 | NA | 100 | 82 | 14 |
| Oleic | $HClO_4$ | 1.0 | Acid | 85 | 19 | 1 | 93 | 11 |
| Oleic | *p*-tolunesulfonic | 6.0 | Aromatic | 25 | 1 | 2.3 | 50 | 17 |
| Eicos-5-enoic | $HClO_4$ | 1.4 | Acid | 85 | >100 | NA | 75 | 18 |
| Eicos-5-enoic | *p*-toluene sulfonic | 1.0 | Neat | 130 | >100 | NA | 89 | 18 |

Alto, CA) equipped with a flame-ionization detector and an autosampler/injector. Analyses were conducted on two columns: an SP 2330, 30 m × 0.25 mm i.d. (Supelco, Bellefonte, PA) and a CPSIL-5, 15 m × 0.25 mm i.d. (Chrompack, Bridgewater, NJ). Saturated C8-C30 FAME provided standards for calculating equivalent chainlength (ECL) values.

SP 2330 analysis conditions for standard FAME analysis: column flow 1.48 mL/min with a helium head pressure of 25 psi; split ratio 40:1; programmed ramp 180 to 250°C at 3°C/min with a 2 min hold at 250°C; injector and detector temperatures set at 250°C.

SP 2330 analysis of aldehydes, dialdehydes, and aldehyde–esters from ozonolytic cleavage of unsaturated FAME: gas flow, injector, and detector conditions as previously described; programmed ramp 50 to 250°C at 5°C/min, hold 5 min at 250°C. CPSIL-5 analysis conditions: column flow 0.77 mL/min with 10 psi helium head pressure; split ratio 75:1; programmed ramp 170 to 250°C at 3°C/min, hold 2 min at 250°C; injector and detector temperatures set at 250°C.

CPSIL-5 analysis of aldehydes, dialdehydes, and aldehyde–esters from ozonolytic cleavage of unsaturated FAME: gas flow, injector and detector conditions as described above; programmed ramp 35 to 250°C at 3°C/min.

GC–mass spectrometry (MS) was performed with a Hewlett-Packard 5890A GC using a 15 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 270°C at 3°C/min. MS conditions: mass range 50 to 550 amu; electron multiplier 200 volts relative. δ-Eicosanolactone retention time 14.5 min, MS: *m/e* 310 ($M^+$, 2%), 292 ($M^+ - 18$, 12%), 99 ($C_5H_7O_2$, 100%). γ-Eicosanolactone retention time 15.2 min, MS: *m/e* 310 ($M^+$, 1%), 292 ($M^+ - 18$, 7%) and 85 ($C_4H_5O_2$, 100%).

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

$^1$H NMR of δ-eicosanolactone: δ 4.27–4.24 (*m*, 1 H), 2.59–2.53 (*m*, 1 H), 2.46 –2.40 (*m*, 1 H), 1.92–1.81 (*m*, 3H), 1.69–1.66 (*m*, 1 H), 1.58–1.47 (*m*, 4 H), 1.30–1.15 (*m*, 27 H) and 0.86 ppm (*t, J* = 6.7 Hz, 3 H). $^{13}$C NMR of δ-eicosanolactone: δ 172.0 (*s*), 80.6 (*d*), 35.8 (*t*), 31.9 (*t*), 29.7 (*t*), 29.6 (*t*), 29.5 (*t*), 29.5 (*t*), 29.4 (*t*), 29.4 (*t*), 29.3 (*t*), 27.8 (*t*), 24.9 (*t*), 22.7 (*t*), 18.5 (*t*) and 14.1 ppm (*q*).

$^1$H NMR of γ-eicosanolactone: δ 4.47 (*p, J* = 7.4 Hz, 1 H), 2.52 (*dd, J* = 9.4 Hz, 2.5 Hz, 2 H), 2.29 (*h, J* = 6.5 Hz, 1 H) 2.05–1.00 (*m*, 31 H) and 0.87 ppm (*t, J* = 6.2 Hz, 3 H). $^{13}$C NMR of γ-eicosanolactone: δ 174.0 (*s*), 81.0 (*d*), 35.6 (*t*), 31.9 (*t*), 29.7 (*t*), 29.5 (*t*), 29.5 (*t*), 29.4 (*t*), 28.9 (*t*), 28.0 (*t*), 25.2 (*t*), 22.7 (*t*) and 14.1 ppm (*q*).

*Methods.* Lactonization reactions conducted without solvent or below the solvent's boiling point were carried out in a constant temperature reactor maintained ±0.1°C of desired set point. Higher temperature reactions were run at the solvent's boiling point in a round-bottom flask fitted with a reflux condenser. Mixing of the reactants was maintained by magnetic stirring throughout the course of the reaction. The product distribution was monitored by HPLC and/or GC, as described above. All reactions exploring the mechanism of the ring closure were performed with 2.02 g of meadowfoam fatty acids (6.5 mmoles) under the general conditions just described or as outlined in Tables 2 and 3. Completed reactions were quenched with base (0.5 M $Na_2HPO_4$) until a neutral pH water wash was obtained. The base wash resulted in a color change from black to yellow coinciding with neutralization of the equivalent amount of acid present in the reaction mixture. Purification of the δ-lactone was accomplished by crystallization from hexane or by kugelrohr distillation (140–180°C at 0.1–0.5 mm Hg) to give a white crystalline solid, m.p. 41.5–50.5°C.

*Methyl ester synthesis*. Methyl esters of fatty acids were prepared by refluxing 10 mg of sample in 2 mL of 14% (wt/vol) $BF_3$/methanol over a steam bath. After 5 min the reaction mixture was poured into a separatory funnel with 5 mL of hexane and washed with 2 × 5 mL of saturated NaCl solution, then dried over $Na_2SO_4$, filtered and injected into the GC. Treatment of the δ-lactones under these reaction conditions resulted in their ring opening to 5-hydroxy methyl esters.

*Trimethylsilyl (TMS) derivatization of 5-hydroxy methyl esters.* Hydroxy methyl esters (~10 mg) were dissolved in 2 drops of pyridine and 0.1 mL of BSTFA. This solution was then placed in a sealed vial for 5 min at 60°C. Hexane (1 mL) was added, and the resulting solution washed with 2 × 1 mL of 5% $H_2SO_4$ solution and dried over $Na_2SO_4$. The hexane layer was filtered, placed in a sealed GC vial, and injected onto the GC and GC–MS.

*Ozonolysis of δ-22:1 lactone.* Ozonolysis was performed as described in a previous publication (19) on a 10 mg sample. The isolated lactone was cleaved with ozone and analyzed on the polar SP 2330 and nonpolar CPSIL-5 GC columns under the conditions outlined above. Methyl oleate, methyl linoleate, and meadowfoam fatty acids were also reacted with ozone and analyzed under the same conditions to serve as appropriate standards. GC–MS confirmed aldehyde assignments.

## RESULTS AND DISCUSSION

Meadowfoam oil was hydrolyzed, and the resultant fatty acids were distilled under vacuum. The fatty acids from distillation contained 91% Δ5 and Δ5,13 unsaturated fatty acids (9) and the remaining portion was mainly erucic acid. Since work by Brown *et al.* (16) have shown that the γ-lactone ring structure is the thermodynamically more stable ring system, a set of experiments was devised, using kinetic control, to produce a highly regioselective ring closure of unsaturated acids to δ-lactone. These results are reported in Table 2. Initial reactions were run in the absence of solvent with molar equivalents (mole of substrate per mole of catalyst protons) of acid and gave moderate yields of lactones (entries 5 and

**TABLE 2**
**Lactonization Reaction Conditions[a]**

| Number | Acid | Equivalent | Solvent | % Solvent (w/w) | Temperature | δ/γ[b] | %Lactones[c] |
|---|---|---|---|---|---|---|---|
| 1 | $HClO_4$ | 2.01 | $CH_2Cl_2$ | 500 | R.T. | 38.5 | 74.7 |
| 2 | $HClO_4$ | 2.01 | $CH_2Cl_2$ | 250 | R.T. | 25.7 | 77.8 |
| 3 | $HClO_4$ | 2.01 | $CH_2Cl_2$ | 100 | R.T. | 16.2 | 80 |
| 4 | $HClO_4$ | 2.01 | $CH_2Cl_2$ | 50 | R.T. | 7.8 | 82.9 |
| 5 | $HClO_4$ | 2.01 | None | 0 | R.T. | 7.7 | 77.6 |
| 6 | $HClO_4$ | 3.18 | $CH_2Cl_2$ | 50 | R.T. | 10.4 | 88.5 |
| 7 | $HClO_4$ | 4.02 | $CH_2Cl_2$ | 100 | R.T. | 12.5 | 91.7 |
| 8 | $HClO_4$ | 6.96 | $CH_2Cl_2$ | 250 | R.T. | 16.4 | 91.4 |
| 9 | $HClO_4$ | 12.9 | $CH_2Cl_2$ | 500 | R.T. | 20.7 | 87.6 |
| 10 | $HClO_4$ | 1.35 | None | 0 | R.T. | 9.9 | 68.3 |
| 11 | $HClO_4$ | 1.02 | None | 0 | R.T. | 13 | 46.8 |
| 12 | $HClO_4$ | 0.57 | None | 0 | R.T. | 19.2 | 22.6 |
| 13 | $H_2SO_4$ | 1 | $CH_2Cl_2$ | 500 | 35°C | 34.9 | 35.8 |
| 14 | $H_2SO_4$ | 2 | $CH_2Cl_2$ | 500 | 35°C | 11.3 | 62.9 |
| 15 | *p*-TSA[d] | 1 | $CH_2Cl_2$ | 500 | 35°C | NA | 0 |
| 16 | Amberlyst | 0.5 | $CH_2Cl_2$ | 500 | 35°C | NA | 0 |
| 17 | $HClO_4$ | 1 | Hexane | 500 | Reflux | 0.15 | 75.9 |
| 18 | $HClO_4$ | 1 | Cyclohexane | 500 | Reflux | 0.06 | 95.5 |

[a]Reactions were run for 24 h with magnetic stirring.
[b]Ratios determined on the crude reaction mixture by GC (SP2330 30 m × 0.25 mm i.d.).
[c]Yield determined on the methyl esters by GC (SP2330 30 m × 0.25 mm i.d.).
[d]*p*-TSA is *p*-toluene sulfonic acid.

10–12). The critical difference between this set of experiments and those found in Table 1 is the reduction in the temperature of the reaction. This control provided a dramatic increase in the regioselectivity of the reaction in favor of δ-lactones with δ/γ ratios approaching 20:1. Contrast these results to entries 17 and 18 of Table 2 where higher temperatures, even in the presence of solvent, provided high regioselectivity for γ-lactone.

Figure 1 is an energy coordinate diagram depicting a plausible reaction path for the ring closure of δ and γ-lactones. The initial step in the reaction is a large endothermic step for the formation of a carbocation at the C-5 position. Capture of the carbocation in an intramolecular process by the carboxyl group will lead to the kinetic product, δ-lactone. If the reaction contains sufficient energy, this species will be protonated and establish an equilibrium with the starting unsaturated fatty acid. Since the carbocation can lose a proton at C-6 or at C-4, double-bond migration occurs and has been demonstrated elsewhere (11,12). Under thermodynamically controlled conditions, the carbocation formed at C-4 will be captured by the carboxyl group to form the more stable γ-lactone, with the thermodynamic equilibrium favoring this product. Results shown in Table 1 demonstrate this equilibrium in the case of 5-enoic acids, where the reactions were carried out at higher temperatures. In contrast, our results at the lower temperatures provided a good regioselectivity for the δ-lactone.

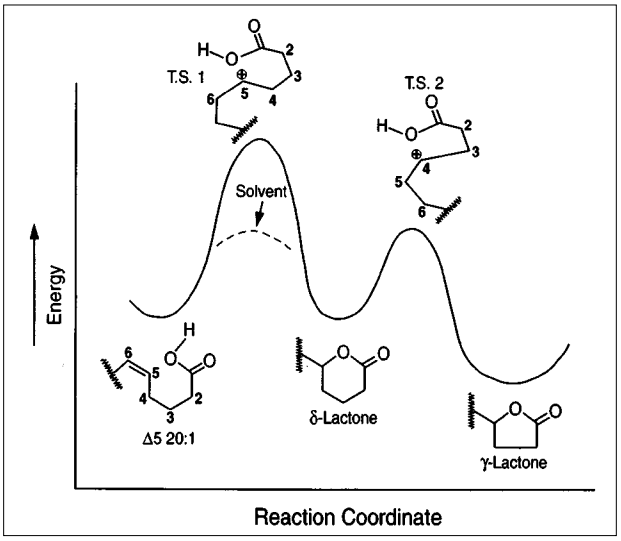


**FIG. 1.** Reaction coordinate diagram for the synthesis of lactones. T.S. 1, transition state 1; T.S. 2, transition state 2.

Enhanced regioselectivity might be expected by performing the reaction in a polar nonparticipating solvent, which could stabilize the polar transition state by creating a sphere of higher dielectric solvent to delocalize the developing charge. The net result of charge delocalization would be a lower activation energy necessary to reach the transition state leading to δ-lactone. Therefore, kinetic control of the lactonization reaction is favored by lowering the transition state energy leading to δ-lactone formation relative to the activation barrier for bond migration leading to γ-lactone.

The kinetic control theory was tested by three independent sets of experiments. First, the effect of dielectric strength on δ/γ regioselectivity and yield was studied. Second, the effect of concentration of a nonparticipating polar solvent on regioselectivtiy was examined under constant acid catalyst concentration. Lastly, the effect of acid concentration on regioselectivity was examined.

*Effect of dielectric strength on δ-lactone regioselectivity.* A strong correlation was observed between solvent polarity and both regioselectivity and reaction yield (Table 3). Polar solvents greatly improve both the regioselectivity and the yield. Solvation of the developing carbocation at C-5 would lower the transition state energy (T.S. 1, Fig. 1) and reduce the acidity of the α-hydrogens at C-4 and C-6, thus diminishing the competing hydrogen migration pathway which leads to γ-lactone, all of these effects together promote the formation of δ-lactone.

*Effect of $CH_2Cl_2$ on the regioselectivity of the lactonization reaction.* A linear relation was observed for the percentage $CH_2Cl_2$ vs. the ratio of δ:γ-lactone with a slope of 0.064 and a δ/γ intercept ratio of 7.67. Increased solvent will also promote intramolecular cyclization by diluting out bimolecular processes, such as deprotonation by weak bases of the vicinal protons to the carbocation. In addition to the dilution effect, solvent polarity will stabilize the transition state up to a point of maximum solvation and then level out. This maximum stabilization was not observed in this study (Figs. 2 and 3), possibly due to the reduction in bimolecular reactions through solvent dilution.

*Effect of acid concentration on δ-lactone formation*. To examine this effect, we performed the reaction under equivalent acid concentrations both with and without solvent, and these results are shown in Figure 2. The concentration of the acid in solution has a large influence on the regioselectivity of the lactonization reaction with lower acid concentrations giving higher δ/γ ratios. The solvent also influences regioselectivity, even more then acid concentrations, at all acid concentrations below 2.5 molal, demonstrating the stabilizing effect of the polar solvent on the transition state.

Under constant acid concentration, varying only the percentage solvent (Fig. 3), the lactone yield increases to ~92% (19.5:1 for δ/γ) with 100–250% methylene chloride then falls to 87% (20.7:1.0 for δ/γ) at higher $CH_2Cl_2$ concentrations. The δ/γ-lactone ratio increases steadily across the range of $CH_2Cl_2$ concentrations (Fig. 3), even in the presence of a constant concentration of weak bases that are capable of vicinal deprotonation which will result in unsaturated acids, indicating the pronounced effect of charge delocalization.

*Study on the lactonization of Δ5,13 22:2 concentrated from meadowfoam.* A meadowfoam fatty acids concentrate of the Δ5,13 22:2 (70%) was obtained by the fractional crystallization method of Chang and Rothfus (20). This concentrate of 22:2 fatty acid was lactonized with perchloric acid in methylene chloride to yield 86% lactone. Ozonolysis of the resulting 22:1 lactones indicated extensive double-bond isomerization along the chain during lactonization, yielding residual double bonds from Δ6 to Δ17 (Table 4). These results further confirm the ease of bond migration under these reaction conditions and the trapping efficiency of the carboxyl group in the stabilization of the carbocation (14).

*Stability and analysis of δ-lactones.* Some of the appeal for the synthesis of δ-lactones lies in their facile ring opening to nucelophiles, both with and without catalysts. Complete details of this work will be reported in a subsequent publication. However, due to the lability of the ring, purification, and analysis of the δ-eicosanolactone proved to be challenging in the initial stages of this investigation. The δ-lactone is quite sensitive to distillation, especially in the presence of small amounts of residual acid, which cause dehydration to the unsaturated fatty acids. Similarly, HPLC conditions that use

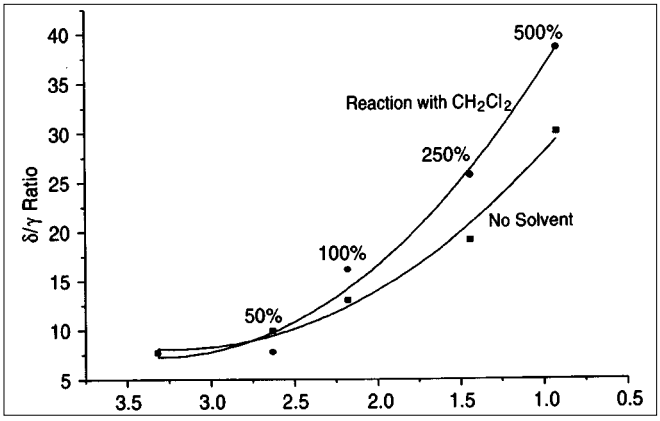


**FIG. 2.** Effect of perchloric acid concentration on the ratio of δ- to γ-lactone reactions catalyzed by $HClO_4$ at room temperature for 24 h. Percentage $CH_2Cl_2$ by mass. Ratio determined by gas chromatography.

**TABLE 3**
**Effect of Solvent Dielectric Strength on δ-Lactone Formation[a]**

| Solvent | Dielectric constant (ε) | δ to γ Ratio[b] | Yield[c] |
|---|---|---|---|
| Hexane | 1.89 | 6.4 | 32.9 |
| Cyclohexane | 2.02 | 12.8 | 13.1 |
| $CHCl_3$ | 4.81 | 21.7 | 52.3 |
| $CH_2Cl_2$ | 9.08 | 17.7 | 81.6 |

[a]Reactions run with 500% (w/w) solvent at 35°C with 1.0 mole equivalent of $HClO_4$ for 24 h.
[b]Ratios determined on the crude reaction mixture by GC (SP2330 30 m × 0.25 mm i.d.).
[c]Yield determined on the methyl esters by GC (SP2330 30 m × 0.25 mm i.d.).

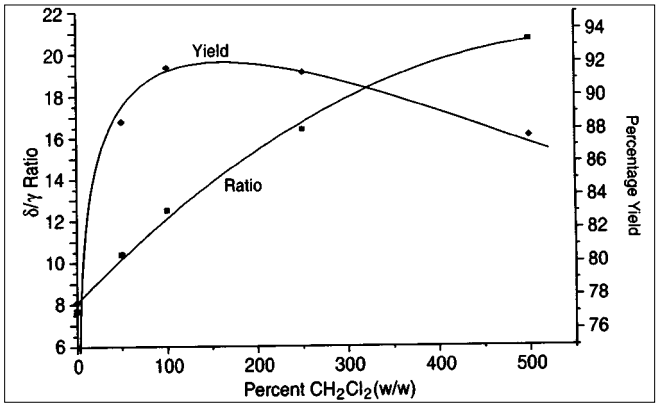


**FIG. 3.** Effect of $CH_2Cl_2$ on the δ- to γ-lactone ratio and yield under constant acid concentration. Reactions catalyzed by $HClO_4$ at 3.32 molal at room temperature, yield and ratio determined by gas chromatography after 24 h.

**TABLE 4**
**Olefin Position of 22:1 Lactone**

| Olefin position[a] | Normalized mole percentage[b] |
|---|---|
| 6 | 0.63 |
| 7 | 2.27 |
| 8 | 3.36 |
| 9 | 4.87 |
| 10 | 6.86 |
| 11 | 9.63 |
| 12 | 12.88 |
| 13 | 15.75 |
| 14 | 15.69 |
| 15 | 13.85 |
| 16 | 8.72 |
| 17 | 5.5 |

[a]Olefin position determined by aldehyde fragment from ozonolysis.
[b]Ratios determined on the crude reaction mixture by GC (SP2330 30 m × 0.25 mm i.d.) with calibration of the detector output to account for the different response factors for the varying chainlength of the aldehydes.

acetic acid as a mobile phase modifier also result in dehydration on column to the unsaturated fatty acids. The dehydration is highly dependent on sample concentration, with dilute samples (<0.1 mg/mL) having relatively large amounts of dehydration. In contrast, HPLC elution schemes that use hexane, acetone, or acetonitrile provided clean separation of all components without dehydration or ring opening to hydroxy fatty acids in both normal and reverse-phase HPLC separations.

GC analysis of the lactones is straightforward and provides good separations from normal fatty acids on polar columns with ECL values of 31.6 for δ-eicosanolactone and 30.6 for γ-eicosanolactone. We utilized this large separation to determine the δ/γ ratios for all experiments by running the crude reaction mixtures on the GC. To determine the yield of lactone, the reaction mixtures were treated with $BF_3$/methanol to convert the residual fatty acids to methyl esters. The derivatized samples were then analyzed on a polar phase SP2380 GC column, and quantitation of fatty esters vs. lactones was made. Note that the lactone will be converted to hydroxy methyl esters under the derivatizing conditions, but will spontaneously ring close in the hot injection port of the GC. Cyclization of 4 and 5 hydroxy methyl esters was also observed by Tulloch (21) upon attempted analysis by GC. However, when the hydroxy methyl esters are silylated, analyses of the TMS ethers can be obtained (9).

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