Synthesis of δ-Eicosanolactone and δ-Docosanolactone Directly from Meadowfoam Oil

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ABSTRACT: δ-Eicosanolactone and δ-docosanolactone were synthesized directly from the triacylglycerides of meadowfoam *(Limnanthes)* oil. Perchloric and sulfuric acids were used in stoichiometric quantities (0.5–4.0 mol equiv) to cyclize triglyceride to δ-lactone. When the reactions were run in the absence of solvent at 40°C, δ-lactone yields ranged from 17–75% where δ/γ ratios ranged from 6:1 to 10.4:1. Sulfuric and perchloric acids gave similar yields for their individually optimized reactions. Perchloric acid-catalyzed reactions required less acid to produce similar amounts of δ-lactone ($HClO_4$ at 2.0 mol equiv gave 73% yield vs. H_2SO_4, which gave 75% yield at 2.5 mol equiv). The use of polar nonparticipating solvents during the reaction had little impact on δ-lactone formation or δ/γ ratio. Higher perchloric acid concentrations provided higher δ-lactone yields with δ/γ ratios remaining nearly constant. The effect of sulfuric acid on δ-lactone yield and δ/γ ratio was more direct; higher acid concentration improved both. Both crystallization and short path distillation improved δ-lactone quality, but short path distillation gave higher recovered yields. The δ-lactones were converted to their corresponding 5-hydroxy acids in the same reaction vessel, separated, and cyclized back to δ-lactones upon heating under vacuum. This provided a convenient method for δ-lactone purification.

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KEY WORDS: δ-Docosanolactone, δ-eicosanolactone, 5-hydroxydocosanoic acid, 5-hydroxyeicosanoic acid, meadowfoam.

Meadowfoam *(Limnanthes)* is a developing oilseed crop grown on a commercial scale in the Willamette Valley of Oregon. Acreage peaked in 1997 with 8000 acres under cultivation, which resulted in a surplus oil supply and subsequent reduction in acreage through the 2000 crop season when no acreage was grown for oil production. The oil and its derivatives are used almost exclusively in cosmetics (1–11). The cost of the oil ($7–8/lb) is somewhat prohibitive for good market penetration in many areas, but niche markets that utilize unique or improved functionality are still viable. To this end, our group has been developing derivatives (12–17) to expand the potential market for meadowfoam oil.

Meadowfoam is composed of unique long-chain fatty acids with 5-eicosenoic acid (62%) as the major fatty acid. The other main components are 5,13-docosadienoic acid (19%), 5-docosenoic acid (3%), and 13-docosenoic acid (10%). Meadowfoam's high level of Δ5 unsaturated fatty acids provides a useful synthetic handle for stabilized carbocation manipulations at the olefinic site. The synthesis of δ-lactones from meadowfoam fatty acids (15) has lead to a number of potentially useful products (16,17) *via* the facile ring opening of the δ-lactone ring system (18).

The lactonization of 5-eicosenoic acid was dependent on the development and stabilization of a carbocation at the Δ5 position followed by capture with the carboxylate functionality. Polar solvent stabilized the developing carbocation, which provided good yields and regioselectivity for the δ-lactone over the γ-lactone (15). Other olefin positions under lactonization conditions typically yield the γ-lactone as the predominant product (19,20). However, recent efforts (21) showed that a remote olefin can be isomerized and captured by the carboxylate to form the kinetic δ-lactone product in good yield (85%) and regioselectivity (δ/γ, 15.0:1.0).

In light of the ease of Δ5-olefinic acid cyclizations, we envision that δ-lactone may be obtainable directly from the meadowfoam triglycerides with liberation of glycerol as a byproduct. In addition, synthesis of δ-lactone directly from the oil has particular economic advantages by elimination of fatty acid production costs. The triglyceride molecule presents some challenges synthetically because of poorer water miscibility compared to fatty acids and increased steric bulk during the cyclization step.

EXPERIMENTAL PROCEDURES

Materials. Meadowfoam oil was a generous gift from the Fanning Corp. (Chicago, IL). Perchloric acid was purchased from Aldrich Chemical Co. (Milwaukee, WI). Concentrated sulfuric acid, sodium hydroxide, hexane, methylene chloride, toluene, acetonitrile, and acetone were obtained from Fisher Scientific Co. (Fair Lawn, NJ). Monobasic phosphate and dibasic phosphate were obtained from EM Science (Gibbstown, NJ).

Instrumentation. High-performance liquid chromatography (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 III) from Alltech Associates Inc. (Deerfield, IL). A Dynamax C8 column (250 mm × 4.6 mm, 60Å, 8 µm) purchased from Varian Associates (Walnut Creek, CA) was used to separate the reaction mixtures. Components were eluted from the

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TABLE 1
Sulfuric Acid Lactonization Conditions

Entry	Acid (mol equiv.)	Solvent	Solvent percentage (vol/wt)	Temperature (°C)	Time (min)	δ-Lactone (%)[a]	γ-Lactone (%)[a]	Ratio δ/γ
A	0.5	None	0	40	1020	17	7	2.4
B	1.0	None	0	40	1200	29	19	1.5
C	1.5	None	0	40	1200	61	7	8.7
D	2.0	None	0	40	1230	75	6	9.7
E	2.5	None	0	40	600	75	8	9.4
F	3.0	None	0	40	300	71	7	10.1
G	4.0	None	0	40	240	64	12	5.3
H	0.5	None	0	60	675	20	8	2.5
I	2.0	CH_2Cl_2	100	40	240	73	8	9.1
J	2.0	CH_2Cl_2	500	40	1200	73	7	10.4
K	2.0	Toluene	100	40	615	67	11	6.1
L	2.0	Toluene	500	40	1320	51	5	10.2
M	0.5	Toluene	500	80	1440	22	13	1.7
N	2.5	H_2O[b]		40	1440	68	20	3.4

[a] All yields reported are from C8 high-performance liquid chromatography normalized percentages based on regression analysis of authentic standards compared to an internal standard.

[b] H_2O was added at 0.5 mole equivalents.

column with the following acetonitrile/acetone gradient: 0–3 min, 80:20; 7–10 min, 0:100; 12–16 min, 80:20. A set flow rate of 1 mL/min was used with the ELSD III drift tube set at 50°C, the nebulizer set at 20 psi N_2, and a flow rate of 2.0 standard liters per minute (SLPM). Retention times for eluted peaks were: δ-eicosanolactone, 4.75 min; γ-eicosanolactone, 5.2 min; octacosane 10.8 min; and meadowfoam oil 11.60 min. Octacosane was used as an internal standard in the reaction, and all yields reported were generated from standard curves of authentic samples as normalized percentages.

Lactone optimization study. Lactonization reactions were carried out in a jacketed reactor connected to a recirculating, constant-temperature bath maintained at ±0.1°C of the setpoint. Mixing of the reactants was maintained by magnetic stirring throughout the course of the reaction. Reactions were performed with 10.0 g of meadowfoam oil (10.0 mmol) under the general conditions just described with varying equivalents of acid and temperature as reported in Tables 1 and 2. Reactions were monitored by C8 HPLC. In addition, reactions were spiked with octacosane as an internal standard for quantitation using standard ELSD III response curves as described previously.

H_2SO_4-catalyzed reaction. Meadowfoam oil (100 g, 0.1 mol) was placed in a jacketed reactor connected to a constant temperature circulating bath maintained at 40°C. The flask was fitted with a reflux condenser and an overhead stir motor with a glass shaft and Teflon blade for mixing reactants. Water (0.54 mL, 0.030 mol) was added to the flask and the mixture equilibrated at 40°C. Concentrated H_2SO_4 (16.2 mL, 0.300 mol) was added all at once to the flask with stirring. After 24 h the reaction was neutralized with sodium hydroxide (36 g, 0.900 mol in 125 mL H_2O/25 mL ethanol) while the reaction was stirred vigorously at 40°C. The solution turned light yellow from black upon neutralization. The strongly basic solution was neutralized with 30 mL of 6 M HCl and the oil layer centrifuged from the water layer (water layer pH = 4). A solid layer, between the organic and water layers, was also obtained (8 g was 29% 5-hydroxy fatty acids, 14% δ-lactones, with the balance being meadowfoam oil). The top oil layer was decanted and concentrated on a rotating

TABLE 2
Perchloric Acid Lactonization Conditions

Entry	Acid (mol equiv.)	Solvent	Solvent percentage (vol/wt)	Temperature (°C)	Time (min)	δ-Lactone (%)[a]	γ-Lactone (%)[a]	Ratio δ/γ
O	0.5	None	0	40	540	32	16	2.0
P	1.0	None	0	40	420	58	6	9.7
Q	1.5	None	0	40	1290	69	14	4.9
R	2.0	None	0	40	300	73	10	7.3
S	2.5	None	0	40	300	73	14	5.2
T	3.0	None	0	40	660	70	12	5.8
U	4.0	None	0	40	1440	59	13	4.5
V	0.5	None	0	60	1440	62	8	7.8
W	2.0	CH_2Cl_2	100	40	675	75	9	8.3
X	2.0	CH_2Cl_2	500	40	1440	73	12	6.1

[a] All yields reported are from C8 HPLC normalized percentages based on regression analysis of authentic standards compared to an internal standard.

solvent evaporator (rotovap) to give 83 g of crude oil. Wiped film short path distillation of the oil layer on a UIC molecular still (Joliet, IL) at 160°C oil bath temperature, with the cold finger maintained at 50°C, the wiper motor set to 200 rpm, and a flow rate of 1 drop/s under 6×10^{-2} torr pressure, gave 51 g of distilled lactone (pale yellow) and 29 g of residue (brown oil). δ-Lactone was isolated in a 66% yield based on 84% Δ5-unsaturation. δ-Lactone was compared by nuclear magnetic resonance (NMR) and gas chromatography–mass spectrometry (GC–MS) to an authentic sample (15) and had an identical spectrum.

Perchloric acid synthesis. Meadowfoam oil (100 g, 0.10 mol) was treated with $HClO_4$ (17.3 mL, 0.20 mol) at 40°C in 200 mL of CH_2Cl_2 using the same apparatus as the sulfuric acid reaction. After 22 h the reaction was neutralized with sodium hydroxide (40 g, 1.00 mol in 200 mL H_2O) while the mixture was stirred vigorously at 20°C. The solution turned light yellow with a white paste upon neutralization. A Dean-Stark trap was placed on the flask, and the reaction mixture was warmed to 80°C to remove CH_2Cl_2. When solvent removal neared completion, 200 mL of H_2O was added. Also, 200 mL of ethanol was incrementally added to abate foaming. The mixture was then warmed to 90°C, at which point the solution became clear. After 1 h at 90°C the mixture was cooled to room temperature, and the contents were poured into a 2-L Erlenmeyer flask that contained 810 mL of 1 M HCl cooled in an ice bath. The resulting mixture had a pH of 1. The mixture was cooled to 17°C, then vacuum filtered through a #54 Whatman filter paper using a Buchner funnel. The white crystals were washed with 3 × 250 mL of pH = 5 phosphate buffer. The wet crystals were dissolved in ethyl acetate over a steam bath, and the residual water was removed by pipette. The oil was concentrated on the rotovap. Wiped film short path distillation, as described in the sulfuric acid reaction, gave 52 g of distilled lactone (pale yellow) and 43 g of residue (brown oil). We obtained a 66% yield of δ-lactone based on 84% Δ5-unsaturation. The isolated δ-lactone had the same properties as the sulfuric acid reaction product.

Synthesis of 5-hydroxy fatty acids. Meadowfoam oil (10 g, 0.010 mol) was treated with $HClO_4$ (2.3 mL, 0.030 mol) at 40°C in 50 mL of CH_2Cl_2 under the same conditions as described for the sulfuric acid reaction. After 3 h the reaction was neutralized with sodium hydroxide (4.3 g, 0.76 mol in 40 mL H_2O and 10 mL of ethanol) while the mixture was stirred vigorously at 20°C. The solution turned light yellow with the formation of a white paste upon neutralization. A Dean-Stark trap was placed on the flask, and the mixture warmed to 80°C to remove CH_2Cl_2. The reaction mixture was warmed to 90°C, and the solution became clear. After 3 h at 90°C the mixture was cooled in an ice bath. Acetic acid (1.93 g, 0.320 mol) was added, and the resulting crystals were removed by vacuum filtration through #54 Whatman filter paper on a Buchner funnel. The gelatinous wet crystals were dissolved in ethyl acetate over a steam bath, and the residual water was removed in a separatory funnel. The solution was placed in a freezer at −10°C overnight then vacuum filtered through #54 Whatman filter paper on a Buchner funnel. We obtained 5.26 g (0.160 mol) of 5-hydroxy fatty acids, a 63% yield of 5-hydroxy fatty acids based on 84% Δ5-unsaturation of the oil.

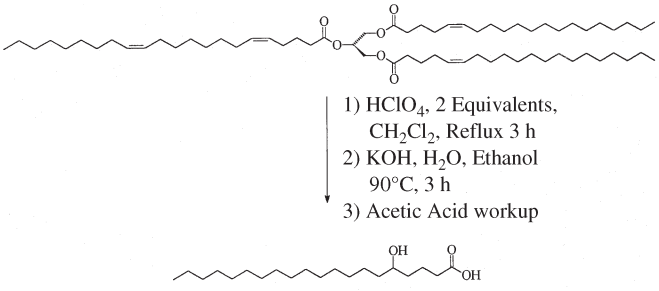
RESULTS AND DISCUSSION

δ-Eicosanolactone and δ-docosanolactone were synthesized using mineral acids from meadowfoam oil with the conditions for sulfuric acid reactions summarized in Table 1. All reactions were run in a jacketed reactor connected to a circulating bath for temperature control. Reactions A–G explored the role of acid concentration on δ-lactone yield and δ/γ ratio at a constant temperature. Reaction E (H_2SO_4, 2.5 mol equiv) gave a 75% yield of δ-lactone, the highest yield of all the sulfuric acid reactions studied. However, the δ/γ ratio of 9.4:1 for reaction E was outperformed by several other reactions but the general trend for sulfuric acid-catalyzed reactions gave δ/γ ratios <10. Addition of a polar nonparticipating solvent in a prior study (15) greatly improved both δ-lactone yield and δ/γ ratios. Reactions I–L explored the use of solvent on δ-lactone yield and ratio. When methylene chloride was added to the reaction mixture, 100% vol/wt (reaction I vs. D), the reaction time was shortened considerably, but the δ-lactone yield and ratio were not significantly improved. At higher methylene chloride levels (reaction J) the reaction time increased due to catalyst dilution, but δ-lactone yield and ratio were not improved. When toluene, a slightly less polar solvent than methylene chloride (reactions K and L), was used, longer reaction times were observed, coupled with depressed δ-lactone yields. Increased reaction temperature (reactions H and M) caused a reduction in δ-lactone yield and δ/γ ratio.

When 0.5 mol equiv of water were added to the sulfuric acid reaction, the yield fell slightly from 75% (reaction E) to 68% (reaction N) with a dramatic decrease in the δ/γ ratio, 9.4:1 to 3.4:1.

Perchloric acid lactonization conditions are shown in Table 2. Both the 2.0 and 2.5 equivalent reactions, R and S, gave the highest δ-lactone yields, which are similar to the best sulfuric acid case (reaction E). The δ/γ ratio for the perchloric acid reactions ranged from 2.0–9.7:1 but the general trend for δ/γ ratio was <5:1, which was significantly lower than the ratios observed for the sulfuric acid-catalyzed reactions. Addition of methylene chloride increased reaction times with no significant increase in yield and only a slight increase in δ/γ ratio. Reactions with solvent were more difficult to neutralize and δ-lactone isolation was more problematic due to violent foaming during the final stages of solvent removal.

Hydroxy fatty acids were isolated directly from meadowfoam as outlined in Scheme 1. The δ-lactones formed were treated *in situ* with caustic in water. Ethanol was added to abate foaming during neutralization and solvent removal. One critical aspect to isolation of the 5-hydroxy fatty acids was to properly adjust the pH of the water layer to 5. Adjustment of the pH was accomplished by careful neutralization of the reaction medium with acetic acid or by washing the resultant crystals with copious amounts of pH 5 buffer solution. The



5-Hydroxyeicosanoic acid

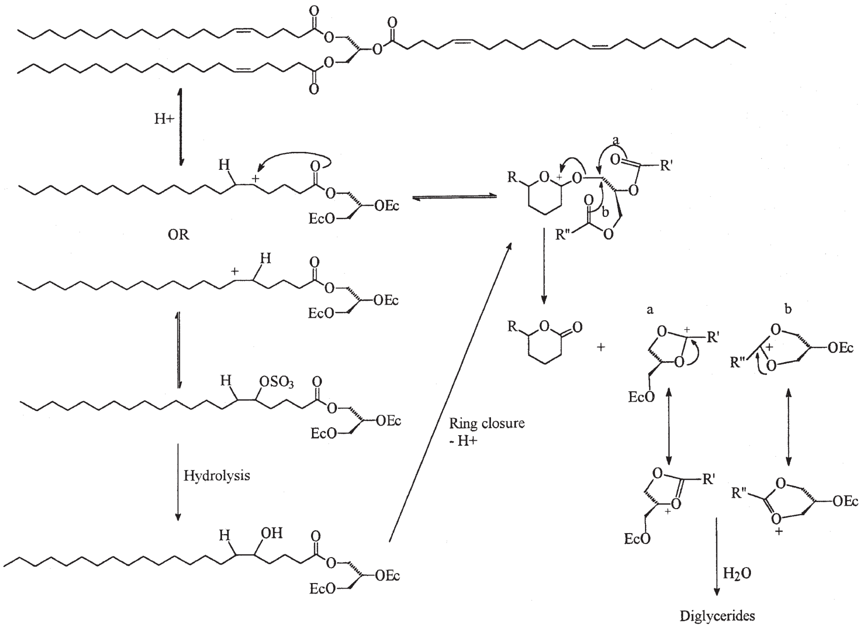
SCHEME 1

wet crystals were extracted into hot ethyl acetate to separate water from the 5-hydroxy fatty acids and recrystallized to high purity. If the pH of the crystals was too acidic, cyclization of the 5-hydroxy fatty acids to δ-lactone occurred spontaneously during recrystallization attempts. When the pH was greater than six, partial soaping of the fatty acids occurred and made crystallization difficult.

Lactonization of Δ5-unsaturated triglyceride most likely proceeds through a carbocation intermediate *via* protonation of the olefin (Scheme 2). A Δ5- or Δ6-carbocation results from this protonation step. The Δ6-cation, if captured by the carboxylate, gives a seven-membered ring that is unfavorable thermodynamically (22). Therefore, positional isomerization *via* deprotonation of adjacent hydrogens becomes the favorable path and results in an equilibrium between isomerized starting material and cation. The olefin then migrates back and forth along the chain as previously observed (16,21).

When protonation occurs at the Δ6 position to produce the Δ5 cation, capture by the carboxylate gives a kinetically stable six-membered ring. The resulting cation can be further stabilized through the resonance structures shown in paths *a* and *b* of Scheme 2. These resonance structures further disperse the cationic charge across six oxygen and three carbon atoms, stabilizing the transition state cation. Capture of the cation by water releases the δ-lactone from the triglyceride with diglycerides as the by-product. Diglycerides were not isolated from the lactonization reactions. However, HPLC traces had small peaks with retention times that corresponded to diglyceride standards.

Reactions catalyzed with concentrated sulfuric acid follow a mechanism that is slightly more complex. Concentrated sulfuric acid in the absence of additional water (2.5 mol equiv, reaction E) has 0.27 mol equiv of residual water within the acid. This quantity of water is insufficient to liberate all of the ring-closed products from the glyceride. Sulfate esters most likely play an intermediate role in initial capture of the cation to form sulfonated fatty acids, which have been identified in other studies (21). The sulfonated fatty acids, upon neutralization, liberate hydroxy fatty acids that, under the reaction conditions, close to form δ-lactones. The sulfate may also serve to liberate the ring closed glyceride *via* formation of a glycerol-sulfate ester that hydrolyzes upon neutralization to form glycerol. Additional water at the 0.5 mol equiv level did not improve the yield of the lactonization or the δ/γ ratio, but the rate of the reaction was reduced. The critical role of water in this hydrolysis of δ-lactone from glyceride is yet to be fully understood.



Ec = 5-Eicosenoyl, 5-Docosenoyl, 13-Docsenoyl or 5,13-Docosdienoyl
R = $-(CH_2)_{14}CH_3$
R' = R" = $-(CH_2)_3CHCH(CH_2)_{14}CH_3$, $-(CH_2)_3CHCH(CH_2)_{16}CH_3$, $-(CH_2)_{11}CHCH(CH_2)_7CH_3$
or $-(CH_2)_3CHCH(CH_2)_6CHCH(CH_2)_7CH_3$

SCHEME 2

5-Hydroxy fatty acids were isolated directly from meadowfoam oil by utilizing the labile nature of the δ-lactone to nucleophiles (18). The optimal δ-lactone reaction was conducted, then the reaction mixture was immediately treated with sodium hydroxide to open the δ-lactone ring *in situ*. The process for ring opening yielded a 5-hydroxy soap, which, upon careful neutralization, gave the 5-hydroxy fatty acids. Care was taken in adjusting the pH, because spontaneous ring closure to δ-lactone occurs under even slightly acidic conditions. We utilized the spontaneous ring closure of 5-hydroxy fatty acids to obtain cleaner lactones; isolation of the δ-lactone directly from the reaction was more problematic because of poor crystal formation.

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