

Alkylglycidic Acids: Potential New Hypoglycemic Agents

Winston Ho,* Gene F. Tutwiler, Sandra C. Cottrell, Dave J. Morgans, Okan Tarhan,[†] and Richard J. Mohrbacher

Departments of Chemical Research and Biological Research, McNeil Pharmaceutical, Spring House, Pennsylvania 19477.
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A series of alkylglycidic acid analogues and derivatives were synthesized and tested for their ability to inhibit long-chain fatty acid oxidation in vitro and to lower blood sugar in rats. The extent of inhibition of carnitine acyl transferase, the enzyme at the mitochondrial membrane necessary to transport long-chain fatty acids into the mitochondria for subsequent β -oxidation, was determined for the series. Structure-activity relationships using in vitro inhibition of [1-¹⁴C]palmitic acid oxidation in rat hemidiaphragm muscle indicate that potent activity resides mainly in 2-alkyl (C₁₂-C₁₆) glycidates. Replacement of the oxirane ring with cyclopropyl, thiirane, or other rings diminishes activity, as does substitution of the glycidate ring at the 3-position. In vivo potency in the rat glucose tolerance test roughly parallels the hemidiaphragm results. The lead compound, methyl 2-tetradecylglycidate (8), is a potent hypoglycemic agent following oral administration to several animal species. The hypoglycemic analogues interfere with fatty acid oxidation by specific and irreversible inhibition of mitochondrial carnitine palmitoyl transferase-A.

It has generally been accepted that diabetes mellitus is primarily a disorder of carbohydrate metabolism. The observed concomitant disturbances of free fatty acid (FFA) metabolism were thought to be secondary effects brought on by the need for a tissue fuel other than carbohydrate. However, studies by Randle and co-workers¹⁻⁴ have demonstrated that the disturbances of carbohydrate metabolism characterized as "diabetic muscle" could be mimicked in normal muscle with increased oxidation of free fatty acids and ketones. They postulated that glucose and fatty acids control each other's release into the blood stream and their subsequent utilization in muscle. Thus, excessive free fatty acid oxidation might be a key factor underlying the decreased tolerance to glucose in diabetes.^{1,3}

If the hypothesis of Randle and co-workers is correct, then a rational and alternative approach to the treatment of diabetes mellitus would be to devise agents that would inhibit the abnormally high rate of fatty acid oxidation observed in diabetic patients. This approach was supported by the observation that hypoglycin, 4-pentenoic acid, (+)-decanoylcarnitine, and α -bromo fatty acids, all of which inhibit FFA oxidation in vitro, can induce hypoglycemia. However, these agents are not clinically useful⁴⁻⁸ due to nonselective inhibition of other enzymes, oral ineffectiveness, or toxicity.^{4,5,9}

We focused our efforts on inhibition of oxidation of fatty acids of chain length C₁₄-C₂₀ because (1) they are the predominant nutrient fatty acids and are utilized as energy substrates in "diabetic muscle",¹ and (2) there are steps in the oxidative pathway unique to these fatty acids²⁶ that might enable us to design inhibitors specific for these substrates.⁵ We embarked on a program to synthesize and evaluate novel fatty acid analogues as inhibitors of long-chain fatty acid oxidation for potential use as hypoglycemic agents.¹⁰ Some of our results have been previously reported.¹¹⁻¹⁵

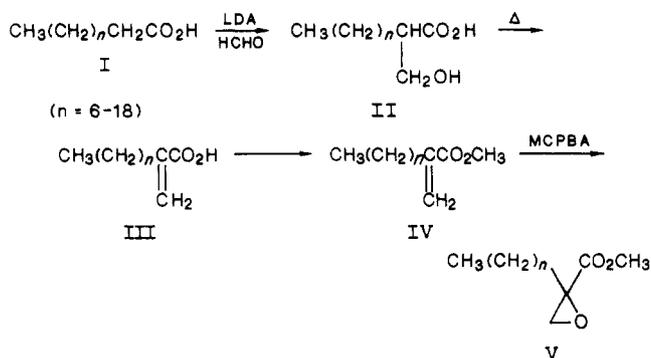
Chemistry. In general, 2-alkylglycidates (V) (Table I: 1-8, 11, 12, 16-22) were synthesized via epoxidation of the corresponding olefins (IV), which were readily prepared according to the method of Silbert¹⁶ (method A) or Gisser¹⁷ (method B) (Scheme I). Method B was the preferred method, giving purer products in large-scale preparations. Initial experiments utilizing the Darzens reaction to synthesize key glycidate 8 gave erratic, low yields. Further development of this method by our Department of Chemical Development demonstrated that 8 could be synthesized in consistently high yields.¹⁸

The synthesis of oleate 19 required the protection of the Δ^9 double bond of 2-methylene-9-octadecenoic acid (49).¹⁶

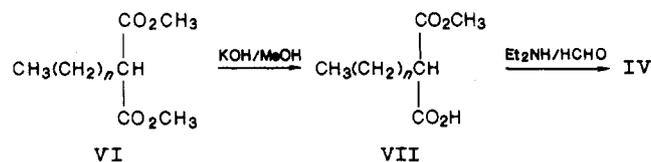
[†] Visiting Professor from the Middle East Technical University, Ankara, Turkey.

Scheme I

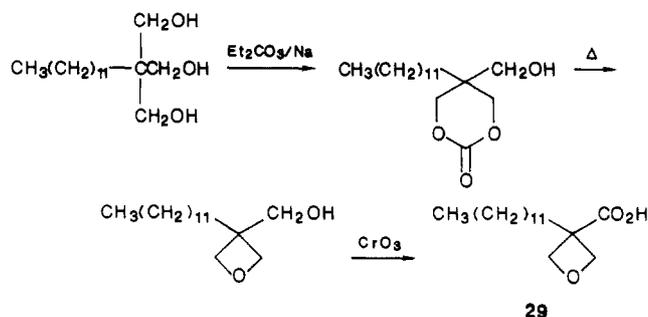
method A



method B



Scheme II



This was accomplished by regioselective addition of bromine to the Δ^9 double bond followed by esterification and

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Table I. Alkylglycidic Acids and Esters

no.	R	R ¹	R ²	R ³	yield, ^a %	mp or bp °C (mmHg)	formula	anal.	inhibn of CPT IC ₅₀ , μM	inhibn palmitate oxidn in vitro		rat glucose tolerance test	
										MEC, ^b μM	IC ₅₀ , μM	max % lowering at 100 mg/kg, po	min effec- tive dose, ^c mg/kg, po
1 ^d	CH ₃	OCH ₃	H	H	50	56 (28)	C ₅ H ₈ O ₃		inactive	inactive	inactive	inactive	inactive
2	C ₆ H ₁₃	OCH ₃	H	H	52	oil	C ₁₀ H ₁₈ O ₃	C, H	136	20	102	30	10
3	C ₁₀ H ₂₁	OCH ₃	H	H	56	31-33	C ₁₄ H ₂₆ O ₃	C, H ⁱ	0.68	0.5	1-5 ^e	32 (50)	10
4 ^f	C ₁₀ H ₂₁	OC ₂ H ₅	CH ₃	CH ₃	46	oil	C ₁₆ H ₃₂ O ₃			inactive	inactive	inactive	inactive
5	C ₁₁ H ₂₃	OCH ₃	H	H	51	30-31	C ₁₅ H ₂₈ O ₃	C, H	1.16	2.5	7	38	10
6	C ₁₂ H ₂₅	OCH ₃	H	H	45	38-42	C ₁₆ H ₃₀ O ₃	C, H	0.6	1	15	32	5
7	C ₁₃ H ₂₇	OCH ₃	H	H	49	38-39	C ₁₇ H ₃₂ O ₃	C, H	0.5	1	13	37	5
8	C ₁₄ H ₂₉	OCH ₃	H	H	59	44-46	C ₁₈ H ₃₄ O ₃	C, H	0.3	0.1	2	45 (75)	2-4
9	C ₁₄ H ₂₉	OH	H	H	74	77-79	C ₁₇ H ₃₂ O ₃	C, H	0.9	0.1	2.2	53	5 ^g
10	C ₁₄ H ₂₉	ONa	H	H	91	94-136	C ₁₇ H ₃₁ O ₃ · Na·2H ₂ O	C, H, H ₂ O		0.2	1	38 (60)	2.5
11	C ₁₄ H ₂₉	OCH ₂ C(OH) HC(OH)H ₂	H	H	90	61-63	C ₂₀ H ₃₇ O ₅	C, H		10	16	31 (25)	5
12	C ₁₄ H ₂₉	O- <i>n</i> -Bu	H	H	40	oil	C ₂₁ H ₄₀ O ₃	C, H		10	47	40	1.5
13	C ₁₄ H ₂₉	NH ₂	H	H	52	104-106	C ₁₇ H ₃₃ NO ₂	C, H, N		inactive	inactive	44	10
14	C ₁₄ H ₂₉	NHCH ₂ CH ₂ - OH	H	H	60	80-82	C ₁₉ H ₃₇ NO ₃	C, H, N		inactive	inactive	33	100
15	C ₁₄ H ₂₉	N(CH ₃) ₂	H	H	38	40-42	C ₁₉ H ₃₇ NO ₂	C, H, N		inactive	inactive	19	25
16	C ₁₄ H ₂₉	OCH ₃	CH ₃	CH ₃	38	39-40	C ₂₀ H ₃₈ O ₃	C, H	inactive	inactive	inactive	inactive	inactive
17	C ₁₄ H ₂₉	OCH ₃	CH ₃	H	42	oil	C ₁₉ H ₃₆ O ₃	C, H		inactive	inactive	inactive	inactive
18	C ₁₆ H ₃₃	OCH ₃	H	H	56	40-41	C ₂₀ H ₃₈ O ₃	C, H	1.04	10	100	16	25
19	7(<i>Z</i>)-C ₁₆ H ₃₁	OCH ₃	H	H	58	oil	C ₂₀ H ₃₆ O ₃	C, H	0.68	5	20	22	10
20	C ₁₈ H ₃₇	OCH ₃	H	H	50	58	C ₂₂ H ₄₀ O ₃	C, H		inactive		25	10
21	C ₂₂ H ₄₅	OCH ₃	H	H	68	60.5-61.5	C ₂₆ H ₅₀ O ₃	C, H	inactive	inactive	inactive	17	10
22	C ₆ H ₅ (CH ₂) ₁₀	OCH ₃	H	H	57	oil	C ₂₀ H ₃₀ O ₃	C, H ^j				36 (25)	10
23	CH ₃ (CH ₂) ₁₃	CH ₂ CH(CO ₂ CH ₃) ₂			70	40-41	C ₂₂ H ₄₀ O ₅	C, H	inactive	inactive	inactive	inactive	inactive
24	CH ₃ (CH ₂) ₁₃	(CH ₂) ₂ CO ₂ CH ₃			70	31	C ₂₀ H ₃₈ O ₃	C, H ^k	inactive	inactive	inactive	inactive	inactive
25 ^h	CH ₃ (CH ₂) ₁₃	CH ₂ OH			35	25	C ₁₇ H ₃₄ O ₂	C, H	inactive	inactive	inactive	inactive	inactive

^a Purified yield of epoxidation except compounds 11 and 14, which are crude yield. ^b Minimum effective concentration (lowest concentration giving a statistically significant ($p \leq 0.05$) inhibition). ^c Minimum dosage giving a statistically significant ($p < 0.05$) lowering at any time point. ^d Reference 23. ^e Range of concentration. ^f Reference 19. ^g Lowest dose tested. ^h Reference 24. ⁱ H: calcd, 10.81; found, 10.35. ^j C: calcd, 75.43; found, 74.96. ^k H: calcd, 11.73; found, 12.16.

epoxidation of the resultant dibromo acrylate and regeneration of the double bond using Zn dust in DMF.

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The 3,3-disubstituted glycidates 4 and 16 were prepared in low yield via the Darzens condensation, which involved reaction of acetone with the appropriate 2-bromoesters.¹⁹

The glycidamides 13-15 were readily obtained by converting the acid 9 to either a mixed anhydride or acid chloride intermediate with ethyl chloroformate or oxalyl chloride followed by treatment with the appropriate amines. Thioglycidate 26 was obtained in 40% yield by

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Table II. α -Substituted Palmitic Acid Analogues: $\text{CH}_3(\text{CH}_2)_n\text{ACO}_2\text{R}$

no.	<i>n</i>	A	R	mp, °C	formula	anal.
26	13		CH ₃	30–31	C ₁₈ H ₃₄ SO ₂	C, H
27	13		CH ₃	37–39	C ₁₉ H ₃₆ N ₂ O ₂	C, H, N
28	13		H	53–55	C ₁₈ H ₃₄ O ₂	C, H
29	11		H	37–38	C ₁₆ H ₃₀ O ₃	C, H
30 ^a	12		CH ₃	34–36	C ₁₇ H ₃₂ O ₃	
31	12		C ₂ H ₅	32–34	C ₁₉ H ₃₆ O ₃	C, H
32	13		CH ₃	49–50	C ₁₉ H ₃₈ O ₄	C, H
33	13		CH ₃	oil	C ₁₈ H ₃₄ Br ₂ O ₂	C, H, Br
34	13		CH ₃	oil	C ₁₈ H ₃₅ O ₂ Br	C, H, Br
35	13		CH ₃	oil	C ₁₉ H ₃₈ O ₂ S	C, H
36	13		H	59–62	C ₁₉ H ₃₈ O ₃	C, H
37	13		CH ₃	oil	C ₂₀ H ₄₀ O	C, H
38	13		CH ₃	35–36	C ₂₁ H ₄₀ O ₄ S	C, H, S
39	13		CH ₃	71–73	C ₂₀ H ₃₈ O ₅	C, H
40	13		H	115–120	C ₁₇ H ₃₄ O ₄	C, H ^b

^a Reference 25. ^b H: calcd, 11.33; found, 11.75.

the reaction of 8 with thiourea in methanol and sulfuric acid.²⁰ A byproduct, 32, was also isolated in 25% yield, apparently resulting from reaction of the oxirane ring with the methanol solvent. Oxetane 29 was synthesized from the triol²¹ (Scheme II) in 37% overall yield.

Biological Results and Discussion

In the cellular mechanism²⁶ of fatty acid oxidation, short- and long-chain fatty acids enter the cell from the bloodstream where they are esterified immediately to coenzyme A (CoA) esters by fatty acyl CoA synthetase. The CoA esters of long-chain fatty acids (C₁₂–C₂₀) cannot enter the mitochondrion directly where oxidation takes place; they must first be transesterified to their carnitine esters by carnitine palmitoyl transferase-A (CPT-A). The carnitine esters then pass into the mitochondrion where reesterification by carnitine palmitoyl transferase-B to their CoA esters occurs. The resulting fatty acyl-CoA esters then enter into the normal β -oxidative pathway. Short-chain fatty acids (shorter than nonanoic) can enter the mitochondrion directly without conversion to their carnitine esters. Thus, the transport of long-chain acids into the mitochondrion via their carnitine esters provides a locus of interference selective for long-chain fatty acids.

The active analogues (e.g., acid 9, Table I) are converted intracellularly to their CoA esters,^{14,15,22} which irrevers-

ibly^{22,27} inhibit CPT-A. Acid 9 and other active analogues inhibit the oxidation of long-chain fatty acids, but not short-chain fatty acids. This selective inhibition of long-chain fatty acid oxidation is observed in many tissues such as liver,¹³ kidney cortex slices,¹¹ adipose tissue,¹¹ and heart,²⁸ soleus,²⁹ and hemidiaphragm muscles.¹³ This inhibition results in a lowering of blood glucose and ketones (end product of fatty acid oxidation) in numerous species including rat,¹³ dog,¹³ monkey,³⁰ and guinea pig.³¹ Evi-

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dence presented previously from our laboratories^{11,14,15} indicates that the lowering of blood glucose by palmoxirate sodium (sodium salt of 9) and methyl palmoxirate (8) results from both inhibition of hepatic gluconeogenesis and stimulation of peripheral glucose utilization.^{11,14,29} The latter effect is postulated to be due to decreased availability of products of fatty acid oxidation, which are inhibitory of the glycolytic pathway in muscle.

In order to fully evaluate the structure-activity relationships (SAR) among the glycidate analogues, we have examined their inhibitory effect at the molecular enzyme level (CPT-A), tissue level (hemidiaphragm palmitic acid oxidation), and in vivo pharmacological level (glucose tolerance). The results are listed in Table I. With the exception of the thiirane analogue 26, which is slightly active, all of the substituted palmitic acid analogues listed in Table II are inactive, at least in inhibition of palmitate oxidation. The following structure-activity conclusions can be drawn: (1) Activity resides in the 2-alkylglycidates but not in the 3-alkylglycidates (5-8 vs. 30, 31). (2) Substitution in the 3-position of the long-chain 2-alkyl glycidates with alkyl groups diminishes activity, possibly due to steric effects (4, 16, 17). (3) Fatty acid chain lengths of C₁₂-C₁₆ seem to be optimal with maximum activity observed in chain length C₁₆ (8 vs. 18, 20, 21). The chain length range of our active analogues is similar to that of the natural fatty acyl-CoA substrates as reviewed by Hoppel.²⁶ Those results showed little or no CPT-A activity with fatty acid substrates of chain length less than C₈. Thus, the SAR results in Table I support our conclusions reported elsewhere²² that these glycidates inhibit at the fatty acyl-CoA substrate binding site of CPT-A. Also, compounds 1 and 2 were found not to inhibit the hemidiaphragm oxidation of their prototypic short-chain acids, acetic or octanoic, respectively.³⁰ (4) Introduction of unsaturation into the alkyl side chain does not affect activity (8 vs. 19). (5) Oxiranepropanoic acids are inactive, indicating that the 2-oxiranecarboxylate (glycidate) group is necessary for activity (8 vs. 23, 24). (6) The oxirane ring seems to be required for optimal activity; replacement of the oxirane ring with 4,5-dihydro-3H-pyrazole (27), cyclopropane (28), or oxetane (29) abolishes the activity. Thiirane analogue 26 is only slightly active. (7) Ring-opened compounds (32-40) are inactive. The biological activity of the enantiomers of methyl ester 8 and acid 9 will be reported elsewhere.³⁶

Palmitic acid analogues, ester 8 and acid 9, were studied more intensively^{11,13} and, in almost all experiments, were essentially identical in biological activity. Ester 8 also inhibited oxidation of other long-chain fatty acids such as oleic and stearic acids, which, like palmitic acid, are major substrates for mammalian fatty acid oxidation. Ester 8 was totally ineffective in preventing oxidation of shorter chain acids¹¹ such as octanoic acid or basic biochemical substrates such as citric, succinic, lactic, or pyruvic acids.

Ester 8 does not act as an insulin secretagogue as it fails to elevate insulin levels in the dog. Furthermore, it lowered blood glucose in diabetic mice (db/db)³⁵ and in animal models that are insulin deficient, i.e., streptozotocin diabetic rats, depancreatized dogs,¹³ and streptozotocin/all-oxan diabetic dogs.³² By contrast, the sulfonylurea insulin secretagogues, e.g., tolbutamide, are not active hypoglycemic agents in these models. In the fasted rat glucose tolerance test, ester 8 was 15-20 times more potent than tolbutamide.¹³ The fatty acid analogues demonstrated

Table III. 2-Methylenealkanoic Acids and Esters:
CH₂=CR₁CO₂R₂

no.	R ₁	R ₂	bp, °C (mmHg)	yield, ^a %	method
41 ^b	C ₆ H ₁₃	H	110-115 (0.2)	60	A
42 ^b	C ₁₀ H ₂₁	H	153-155 (0.2), 33-35 ^d	46	A
43 ^c	C ₁₁ H ₂₃	CH ₃	oil	62	B
44 ^b	C ₁₂ H ₂₅	H	146-150 (0.075)	68	A
45 ^b	C ₁₃ H ₂₇	H	155-160 (0.55), 46-48 ^d	52	A
46 ^b	C ₁₄ H ₂₉	H	170-177 (0.25), 53-54 ^d	77	A
47 ^b	C ₁₄ H ₂₉	CH ₃	150-155 (0.25)	79	A, B
48 ^b	C ₁₆ H ₃₃	H	160-170 (0.2), 59-63 ^d	43	A
49 ^b	Δ ^{7,8} C ₁₆ H ₃₁	H	190-195 (0.05)	53	A
50 ^c	C ₁₈ H ₃₇	CH ₃	39 ^d	70	B
51 ^c	C ₂₂ H ₄₅	CH ₃	50-51 ^d	59	B
52 ^c	C ₆ H ₅ ^e (CH ₂) ₁₀	CH ₃	oil	45	B

^aPurified yield of last step. ^bReference 16. ^cReference 17. ^dMelting point. ^eElemental analysis not done.

their hypoglycemic activity only in animals utilizing fatty acid oxidation as a major energy source and, therefore, were inactive in fed, nondiabetic animals.

Compounds 8 and 9 are the most potent and specific inhibitors of fatty acid oxidation yet reported. Compounds 8 (methyl palmoxirate) and 9 (as its sodium salt, palmoxirate sodium) produce hypoglycemic effects of long duration (10-15 h) when given orally to fasted rats,¹³ mice,³⁵ dogs,¹³ and monkeys³⁰ at single doses of 1-15 mg/kg, while multiple chronic dosing over several days gave similar activity at lower doses.

The alkylglycidates represent a new class of potentially useful oral hypoglycemic agents in which the lead compound, methyl palmoxirate, has shown hypoglycemic activity in initial clinical testing in a small group of type I diabetic patients.³³ Further clinical evaluation is under way.

Experimental Section

All melting points are uncorrected and were taken on Thomas-Hoover Uni-Melt or Laboratory Devices Mel-Temp melting point apparatuses in capillary melting point tubes. UV spectra were determined on a Carey 14 instrument and IR spectra on a Perkin-Elmer 552 infrared spectrophotometer. The 90-MHz ¹H NMR spectra were obtained on a Perkin-Elmer R-32 NMR spectrometer using Me₄Si as an internal standard. The spectral data for each compound supported the assigned structure, and all elemental and Karl-Fischer analyses were within 0.4% of calculated values.

Method A: General Procedure for the Preparation of 2-Methylenealkanoic Acids (III) and Esters (IV) (41-52) via Formylation of Fatty Acids. The procedure employed to synthesize III was essentially that described by Pfeffer and Silbert¹⁶ (Table III).

Methyl 2-Methylenehexadecanoate (IV) (47). A solution of 2-methylenehexadecanoic acid (14.6 g, 0.052 mol) and 15 mL of boron trifluoride methanol complex (51%) in 50 mL of absolute methanol was heated under reflux for 6 h. The mixture was concentrated to 1/2 volume and neutralized with NaHCO₃. The oily material was extracted into ether, washed with water, and dried over MgSO₄. The ether solvent was removed in vacuo to give 14.70 g (99% yield) of methyl 2-methylenehexadecanoate as an oil.

Method B: General Procedure for the Preparation of 2-Methylenealkanoate Esters (IV) via Alkylation of Malonic Ester. Dimethyl Tetradecylpropanedioate (VI). Diethyl malonate (29.06 g, 0.22 mol) was added to a freshly prepared solution of 4.83 g (0.21 mol) of sodium in MeOH (140 mL). The solution was heated under reflux for 5 minutes and cooled to 25 °C, and 1-bromotetradecane (55.46 g, 0.2 mol) was added. The mixture was heated to reflux for 2 h and neutralized with 1 N HCl after which the solvent was evaporated. Water (300 mL) was added, and the solution was extracted with ether (200 mL). After drying over Na₂SO₄ the ether solution was evaporated to yield 61 g of oily dimethyl tetradecylpropanedioate. It was purified

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by column chromatography to give 35 g (48%) of pure product, which crystallized: mp 34–36 °C.³⁴

Monomethyl Tetradecylpropanedioate (VII). To dimethyl tetradecylpropanedioate (1.0 g, 0.003 mol), in 10 mL of anhydrous MeOH, was added 5 mL of 1 N Ba(OH)₂ methanol solution. The mixture was stirred at 25 °C for 3 h. The precipitate was collected, washed with MeOH and ether, and air dried, giving 0.95 g of the barium salt. It was stirred in 10 mL of 1 N HCl and 30 mL of ether at 25 °C for 2 h. The ether layer was separated, washed with water, and dried over Na₂SO₄. Solvent removal under reduced pressure yielded 0.73 g of the half acid ester: mp 54–56 °C.

Methyl 2-Methylenehexadecanoate (47). To a solution of diethylamine (5.36 g, 0.073 mol) and 13.4 mL of 37% aqueous formaldehyde was added monomethyl tetradecylpropanedioate (4.24 g, 0.0134 mol). The mixture was heated to reflux for 30 min, cooled, and diluted with 20 mL of ether. The ether layer was separated, washed with water, dried over Na₂SO₄, and evaporated to yield 3.08 g (79%) of 95% pure material. This material could be purified further by distillation at 150–155 °C/0.25 mm.

General Procedure for the Preparation of Oxirane Esters (V) (1–8, 12, 16–22). **Methyl 2-Tetradecyloxirane-carboxylate (8).** A mixture of methyl 2-methylenehexadecanoate (8.9 g, 0.0316 mol), 3-chloroperbenzoic acid (10.9 g, 0.0632 mol), and 4,4'-thiobis[2-(1,1-dimethylethyl)-6-methylphenol] (0.2 g, 0.572 mmol) in 300 mL of dry 1,2-dichloroethane was heated at reflux temperature for 4 h, cooled, and filtered to remove 3-chlorobenzoic acid. The filtrate was concentrated to 1/3 its volume and filtered again. The filtrate was diluted with ether, washed with a saturated solution of K₂CO₃, water, and dried over Na₂SO₄. Removal of the solvent and recrystallization from methanol provided the oxirane (59%): mp 43–45 °C; IR (CHCl₃) V_{\max} 1735 cm⁻¹; NMR (CDCl₃) δ 0.90 (t, 3 H), 1.28 (s, 24 H), 1.6–2.2 (m, 2 H), 2.72–3.06 (q, oxirane protons), 3.75 (s, 3 H CO₂CH₃).

2-Tetradecyloxirane-carboxylic Acid (9). Sodium 2-tetradecyloxirane-carboxylate dihydrate 10 (3.1 g) in 75 mL of 1 N HCl solution was stirred for 4 h at room temperature. The solid was then taken up in ether, washed with water, and dried over Na₂SO₄. Removal of the ether solvent and recrystallization from acetone gave the acid 9 (2.5 g, 74%): mp 77–79 °C; IR (CHCl₃) V_{\max} 1775, 1715 cm⁻¹; NMR (CDCl₃) δ 0.88 (t, 3 H), 1.26 (s, 24 H), 1.5–2.2 (m, 2 H), 2.80–3.10 (q, 2 H, oxirane protons), 9.50 (s, 1 H, CO₂H).

Sodium 2-Tetradecyloxirane-carboxylate Dihydrate (10). To a freshly prepared solution of sodium (0.3 g, 0.014 g-atom) in 11 mL of absolute EtOH was added methyl 2-tetradecyloxirane-carboxylate (3.6 g, 0.012 mol) in 40 mL of absolute EtOH. The solution was cooled in an ice-water bath and water (0.24 g, 0.013 mol) was added. The reaction mixture was stirred at 25 °C for 15 h. The resulting thick solid was filtered, washed with ether, and dried (3.15 g, 91% yield): mp 92–136 °C. An analytical sample was obtained by several recrystallizations from MeOH/water (50:1): mp 94–136 °C; IR (Nujol) V_{\max} 3400, 3220, 1605 cm⁻¹; NMR (CD₃OD) δ 0.89 (t, 3 H), 1.28 (s, 24 H), 2.24 (m, 2 H), 2.59–2.80 (q, 2 H, oxirane protons), 4.73 (s, 4 H, water).

(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl 2-Tetradecyloxirane-carboxylate. To a stirred, ice-cooled solution of 9 (3.27 g, 11.5 mmol) in 40 mL of dry tetrahydrofuran (THF) under argon was added 1.21 g (12 mmol) of freshly distilled triethylamine. The reaction mixture was stirred in an ice bath for 2 h, after which 1.30 g (12.0 mmol) of ethyl chloroformate was added. After the reaction mixture was stirred in an ice bath for an additional 4 h, a solution of 276 mg (11.5 mmol) of dry, powdered sodium hydride in 22.0 g (0.166 mol) of 2,2-dimethyl-1,3-dioxolane-4-methanol was added dropwise. The reaction mixture was stirred at room temperature for 41 h. The solvent was removed in vacuo, and the resulting oil was dissolved in a mixture of 50 mL of ether, 50 mL of water, and 0.69 g (11.5 mmol) of acetic acid. The organic layer was washed with water, dried over MgSO₄, and concentrated to dryness to give 5.53 g of oil (53% pure by GC). The oil was purified by chromatography on silica gel with ether/hexane (1:9), followed by ether/hexane (1:4) to elute the desired product (810 mg, GC analysis indicated 94.7% purity).

2,3-Dihydroxypropyl 2-Tetradecyloxirane-carboxylate (11). To a stirred solution of 706 mg (1.77 mmol) of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl 2-tetradecyloxirane-carboxylate in 7.36 g (70.8 mmol) of trimethyl borate was added 717 mg (11.6 mmol)

of boric acid. The reaction mixture was heated on a steam bath for 20 min and was then concentrated in vacuo. The resulting oil was partitioned between ether and water. The organic layer (including some interfacial solid) was washed with water and 5% sodium sulfate solution, dried over MgSO₄, and concentrated to give 575 mg of crude solid (90.7%). Several samples similarly prepared were combined (944 mg) and purified by chromatography on 70 g of silica gel eluting with 2-butanone/cyclohexane (2:1) to give 844 mg of solid. Recrystallization from acetone (at –40 °C) and then from ether gave 217 mg of solid: mp (58 °C softens) 61–63.5 °C.

N-(2-Hydroxyethyl)-2-tetradecyloxirane-carboxamide (14). To oxirane-carboxylic acid 9 (0.2 g, 0.0007 mol) in 10 mL of anhydrous THF was added triethylamine (0.7 g, 0.0007 mol). The solution was stirred at 0 °C for 30 min, and ethyl chloroformate (76 mg, 0.0007 mol) was added. After the solution had been stirred at 0 °C for 3 h, ethanolamine 0.042 g (0.0007 mol) in 1 mL of THF was added. The mixture was stirred at room temperature for 16 h. The solvent was concentrated, diluted with water, and extracted with ether, and the ether layer was dried over Na₂SO₄. Solvent removal gave amide 14 in 60% yield (138 mg), which was recrystallized from acetone: mp 80–82 °C.

The amides 13 and 15 were prepared as described above for 14. Details are given in Table I.

Methyl 3,3-Dimethyl-2-tetradecyloxirane-carboxylate (16). To a stirred solution of methyl 2-bromopalmitate (2.07 g, 0.0059 mol) in 0.343 g of acetone (0.0059 mol) at 10–15 °C was added K-*t*-OBu (0.66 g, 0.0059 mol) in 10 mL of *t*-BuOH. The mixture was stirred at room temperature for 1 h. Ether (50 mL) was added, and the solution was washed with dilute HCl solution, water, and brine. The organic layer was dried over MgSO₄ and the solvent removed to give 1.84 g of crude product. This was purified by column chromatography on silica gel eluting with 5% ether in petroleum ether to give 0.73 g (38%) of white crystals: mp 39–40 °C.

Methyl 3-Methyl-2-tetradecyloxirane-carboxylate (17). To a solution of distilled diisopropylamine (5.06 g, 0.05 mol) and anhydrous THF (50 mL) at –78 °C under a nitrogen atmosphere was added dropwise 36 mL of 1.39 M *n*-butyllithium in hexane (0.05 mol), followed by dropwise addition of anhydrous HMPT (9.86 g, 0.055 mol). The solution was maintained at –78 °C for 1/2 h, and then methyl crotonate (5 g, 0.05 mol) was added dropwise. After 10 min, 1-bromotetradecane (15.3 g, 0.055 mol) was added. When the addition was complete, the system was allowed to warm to ≤–30 °C to achieve homogeneity and was maintained at this temperature for 1 h before being stirred at room temperature overnight. The solution was neutralized to pH 5 (1 N HCl) and extracted with ether. The organic layer was washed with water and brine and dried over Na₂SO₄, and the solvent was evaporated under reduced pressure. The crude product (9.0 g), a mixture of 1-bromotetradecane, the desired olefin and its nonconjugated isomer, was purified by column chromatography on silica gel to yield 1.13 g (12.6%) of methyl 2-ethylidenehexadecanoate as an oil. The oily ester was epoxidized without further purification, in a manner similar to the preparation of 8 followed by column chromatographic purification on silica gel (ether/petroleum ether, 1:4) to yield 17 (42%) as a homogeneous oil.

9,10-Dibromo-2-methyleneoctadecanoic Acid. To a solution of 2-methylene-9(*Z*)-octadecenoic acid¹⁶ (3.5 g, 0.012 mol) in CCl₄ (100 mL) at 0 °C was added bromine (1.90 g, 0.012 mol). The solvent was removed in vacuo and the residue taken up in ether, washed with water, and dried over Na₂SO₄. Removal of solvent gave 5.1 g (94%) of crude product, which was used without further purification in the following step.

Methyl 9,10-Dibromo-2-methyleneoctadecanoate. 9,10-Dibromo-2-methyleneoctadecanoic acid (5.1 g, 0.011 mol) and 5 mL of boron trifluoride methanolic solution (51%) in 50 mL of MeOH was heated under reflux for 6 h. The reaction was concentrated to 1/2 volume and neutralized to pH 7 with saturated NaHCO₃ solution. The solution was extracted with ether, washed with water, and dried over Na₂SO₄, and the solvent was removed to give 4.8 g (93%) of the ester, which was used in the next reaction.

Methyl 2-(7,8-Dibromohexadecyl)oxirane-carboxylate. A mixture of methyl 9,10-dibromo-2-methyleneoctadecanoate (3.8

g, 0.0081 mol), 3-chloroperbenzoic acid (2.76 g, 0.016 mol), and 4,4'-thiobis[2-(1,1-dimethylethyl)-6-methylphenol] (50 mg) in 50 mL of $\text{CH}_2\text{ClCH}_2\text{Cl}$ was heated at reflux for 4 h, cooled, and filtered. The filtrate was concentrated in vacuo, and 100 mL of petroleum ether was added. The insoluble solid was filtered and discarded. The filtrate was concentrated to dryness to give 4.29 g of oily residue. Chromatographic purification on silica gel eluted with 5% ether in petroleum ether gave 3.03 g (77%) of the dibromo epoxide as an oil.

Methyl 2-(7(Z)-Hexadecenyl)oxiranecarboxylate (19). A mixture of methyl 2-(7,8-dibromoheptadecyl)oxiranecarboxylate (3.32 g, 0.0069 mol), zinc dust (9.0 g, 0.14 g-atoms), and DMF (150 mL) was treated with anhydrous K_2CO_3 (1.5 g, 0.01 mol) and a few crystals of iodine. The mixture was maintained at 50 °C for 3.5 h. Ether (50 mL) was added, and the zinc dust was removed by filtration. The filtrate was washed with water and dried over Na_2SO_4 , and solvent was removed to yield 2.3 g of crude 19. Chromatographic purification on silica gel eluted with 5% ether in petroleum ether gave 1.30 g (58%) of pure 19 as an oil.

2-(Chloromethyl)-1-hexadecene. Methanesulfonyl chloride (2.25 g, 0.015 mol) was added slowly to a mixture of 2-methylene-1-hexadecanol (3.75 g, 0.015 mol), collidine (1.8 g, 0.015 mol), and lithium chloride (0.63 g, 0.015 mol) in 30 mL of DMF. The mixture was stirred at 25 °C for 2 h and heated at reflux for an additional 2 h. The reaction mixture was poured over ice and extracted with ether. The organic layer was washed with $\text{Cu}(\text{NO}_3)_2$ solution and water and dried over MgSO_4 . Solvent was removed, and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 15:85) to yield 3.5 g (87%) of the chloride as an oil.

Dimethyl (2-Methylenehexadecyl)propanedioate. A mixture of methyl malonate (0.13 g, 0.001 mol), 2-(chloromethyl)-1-hexadecene (0.27 g, 0.010 mol), potassium carbonate (0.138 g, 0.001 mol), and a catalytic amount of 18 crown-6 ether in 20 mL of toluene was heated under reflux for 48 h. The mixture was cooled, washed with water, and dried over MgSO_4 . The solvent was evaporated in vacuo to yield 0.25 g (69%) of 70% pure (GC) malonate, which was used in the next step.

Dimethyl [(2-Tetradecyloxiranyl)methyl]propanedioate (23). A mixture of 70% pure dimethyl (2-methylenehexadecyl)propanedioate (1.0 g, 0.0027 mol), 3-chloroperbenzoic acid (1.0 g, 0.0058 mol), and potassium carbonate (0.7 g, 0.005 mol) in 15 mL of CH_2Cl_2 was stirred at room temperature for 20 h. The mixture was filtered; ether was added to the filtrate, and the filtrate was washed with water and NaHCO_3 solution. After removal of the solvent the crude oxirane was purified by column chromatography on silica gel (hexane/ether, 1:1) to give 0.7 g of 23: mp 40–41 °C.

Methyl 2-Tetradecyloxiranepropanoate (24). A mixture of 70% pure dimethyl (2-methylenehexadecyl)propanedioate (6.9 g, 0.019 mol), sodium chloride (1.25 g, 0.019 mol), water (1.15 g), and 50 mL of dimethylsulfoxide was heated at 150–170 °C under nitrogen until the evolution of CO_2 ceased. Ether was added, and the solution was washed with water. The organic layer was separated, treated with charcoal, and dried over MgSO_4 . After evaporation of the solvent, the crude oily residue was purified by chromatography on silica gel to yield 3.4 g of 95% pure (GC) monoester. This was epoxidized with 3-chloroperbenzoic acid, following the general procedure, and purified via column chromatography on silica gel to give 24 in 70% yield: mp 31 °C.

2-Methylene-1-hexadecanol. To a solution of diisobutylaluminum hydride (DIBAL) (50 mL of a 1 M solution in toluene, 0.05 mol) in CH_2Cl_2 at –23 °C was added dropwise ester 47 (14.1 g, 0.05 mol) in 125 mL of CH_2Cl_2 . After 2 h, an additional 20 mL of DIBAL solution was added. The reaction mixture was stirred at –23 °C overnight and was neutralized carefully with 1 N HCl. After addition of 15 mL of water the organic layer was separated and concentrated to give an oily residue, which was purified by chromatography on silica gel (hexane/ether, 1:1) to yield 8.0 g of 2-methylene-1-hexadecanol: mp 35–36 °C.

2-Tetradecyloxiranemethanol (25). Epoxidation of 2-methylene-1-hexadecanol, in a manner similar to the preparation of 8, yielded 25 as a waxy solid, mp 25 °C, after column chromatographic purification on silica gel (hexane/ether, 1:1).

Methyl 2-Tetradecylthiiranecarboxylate (26) and Methyl 2-Hydroxy-2-(methoxymethyl)hexadecanoate (32). A mixture

of thiourea (1.27 g, 0.0167 mol), sulfuric acid (5 mL, 95–98%), absolute MeOH (400 mL), and 8 (5.0 g, 0.0167 mol) was stirred at 25 °C for 3 h. An additional 400 mL of MeOH was added, and the reaction mixture was made basic with NaHCO_3 . The solvent was removed under reduced pressure, and the residue was dissolved in ether; the solution was washed with water and dried over Na_2SO_4 . Removal of the solvent gave 5.77 g of a light-tan solid, which was a mixture of 26 and 32. The components were separated by chromatography on silica gel (hexane/ether, 93:3) to yield 2.1 g (40%) of 26 as a clear oil and 1.4 g (25%) of 32: mp 49–50 °C.

Methyl 4,5-Dihydro-3-tetradecyl-3H-pyrazole-3-carboxylate (27). To a solution of ester 47 (6.3 g, 0.023 mol) in 50 mL of ether was added ethereal diazomethane (excess). The reaction was kept at room temperature for 16 h. The solvent was removed to give 5.8 g (66%) of crude 27 (6.4 g), which was recrystallized from MeOH: mp 37–39 °C.

1-Tetradecylcyclopropanecarboxylic Acid (28). Pyrazole 27 (5.8 g, 0.018 mol) was heated at 150–160 °C in an oil bath for 3 hours, and the resulting residue was distilled at 120–125 °C/0.15 mm to give the cyclopropane ester (4.6 g, 87%). A 3.4-g (0.012 mol) sample of the cyclopropane ester in 50 mL of 5% methanolic solution of KOH was heated to reflux for 5 hours. The solvent was removed and the residue acidified with 10% HCl and extracted with ether. The ether layer was washed with water, dried over Na_2SO_4 , and evaporated to give a solid, which was recrystallized 3 times from MeOH to give 1.45 g (44%) of product: mp 53–55 °C.

3-Dodecyl-3-oxetanecarboxylic Acid (29). To a stirring mixture of ethyl carbonate (4.37 g, 0.037 mol) and sodium (0.45 g, 0.02 mol) heated to 80 °C was added 2-dodecyl-2-(hydroxymethyl)-1,3-propanediol²¹ (10 g, 0.0365 mol) in portions, allowing the triol to melt and the mixture to become homogeneous between additions. The mixture was then heated at 130–155 °C for 3.5 h during which time the EtOH distilled from the mixture. The pressure was gradually reduced to 100 mmHg over a 0.5-h period and more EtOH was distilled. The mixture was then heated at 180–200 °C for 1 h to decompose the cyclic carbonate. The oxetane alcohol was then distilled from the pot residue, bp 160–165 °C/0.05 mm, as a colorless oil, 6.92 g (74%). To a solution of 3-dodecyl-3-oxetanemethanol (3.0 g, 0.0117 mol) in acetone (100 mL) was added dropwise Jones reagent at 25 °C. The excess chromic acid was destroyed by adding several drops of isopropyl alcohol. Acetone solvent was removed. Ether (50 mL) and water were added. The ether layer was washed and dried over Na_2SO_4 . Removal of the solvent yielded 2.9 g of oil, which crystallized from petroleum ether to give 1.50 g (47%) of 29: mp 37–38 °C.

Ethyl 2-Methyl-3-tridecyloxiranecarboxylate (31). To a suspension of NaH (57% in mineral oil) (2.23 g, 0.053 mol), washed free of mineral oil) in 25 mL of dry glyme, under a nitrogen atmosphere, was added freshly distilled triethyl phosphonoacetate (10.8 g, 0.048 mol) in glyme (10 mL). The reaction was mildly exothermic and accompanied by H_2 evolution. After 1.25 h of stirring at room temperature, methyl iodide (6.8 g, 0.048 mol) in glyme (5 mL) was added dropwise. The system was maintained at ~50 °C for 1 h and then cooled to 10 °C. An additional 2.23 g (0.053 mol) of sodium hydride in glyme (25 mL) was added in bulk at room temperature. After 2 h, tetradecanal (10.2 g, 0.048 mol) in glyme (110 mL) was added dropwise over 1 h, and the reaction was left to stir overnight at room temperature. The reaction was poured onto ice and extracted into ether. The ether layer was washed with water and brine and dried over Na_2SO_4 . Evaporation gave 86% yield of crude olefin (72% pure by GC). Epoxidation of the olefin in a manner similar to the preparation of 8 followed by column chromatographic purification on silica gel (petroleum ether/ether, 4:1) yielded 2.9 g (58%) of 31: mp 32–34 °C.

Methyl 2-Bromo-2-(bromomethyl)hexadecanoate (33). To a solution of 47 (3.0 g, 0.0106 mol) in 100 mL of CCl_4 at 0 °C was added bromine (0.55 mL) in 15 mL of CCl_4 . The solution was stirred at 25 °C for 2 h, washed with Na_2CO_3 solution and water, and dried over Na_2SO_4 . After solvent removal, the residue was chromatographed on silica gel with 3% ether in petroleum ether to give 2.2 g (47%) of 33 as an oil.

Methyl 2-(Bromomethyl)hexadecanoate (34). A solution of 47 (2.8 g, 0.001 mol) in ether (50 mL) was treated with excess

hydrogen bromide gas. The solution was kept at 25 °C for 48 h. It was washed with K₂CO₃ solution and water and dried over MgSO₄. The solvent removal was evaporated under reduced pressure to give 3.22 g of crude product, which was chromatographed on silica gel and eluted with ether to yield 0.96 g (26%) of chromatographically homogeneous **34** as an oil.

Methyl 2-[(Methylthio)methyl]hexadecanoate (35). A solution of **47** (2.4 g, 0.0085 mol), methylmercaptan (0.42 g, 0.0085 mol) in MeOH (60 mL), and 0.75 mL of Triton B was stirred at 25 °C for 72 h. The solvent was removed and the residue dissolved in ether (50 mL). This was washed with water and dried over Na₂SO₄. Removal of the solvent yielded 2.7 g (96%) of **35** as an oil.

2-(1-Hydroxy-1-methylethyl)hexadecanoic Acid (36). To a stirred solution of THF (400 mL), diisopropylamine (24.75 g, 0.245 mol), and HMPA (40 mL, 0.22 mol) at -20 °C was added 150 mL of *n*-BuLi in hexane (1.6 M, 0.245 mol). Palmitic acid (25.64 g, 0.099 mol) in 200 mL THF was then added slowly while maintaining the reaction temperature below 0 °C. A milky white suspension resulted after the addition, and the mixture was warmed to 40 °C. Acetone (7.13 g, 0.123 mol) was added, and the solution was stirred at room temperature for 2 h. After acidification with 10% HCl, the organic layer was concentrated to dryness and the residue was taken up in ether (500 mL), washed with dilute HCl and water, and dried over Na₂SO₄. Solvent removal gave 19.3 g of material, which was recrystallized from acetone. The product was recovered in 41% yield: mp 59–62 °C. Esterification of **36** with CH₂N₂ gave **37** in 84% yield as a homogeneous oil.

Methyl 2-[(2-Methoxy-2-oxoethyl)thio]methyl]hexadecanoate (38). A solution of **47** (1.41 g, 0.005 mol), methyl thioglycolate (1.06 g, 0.01 mol) in methanol (10 mL), and 0.5 mL of Triton B (40% in MeOH) was stirred at room temperature for 16 h. After acidification with 10% HCl, ether (50 mL) was added and the separated organic layer was washed with water and dried over Na₂SO₄. After solvent removal under reduced pressure, the resulting oil was purified by column chromatography on neutral alumina by elution with petroleum ether to give 370 mg (19%) of **38**: mp 35–36 °C.

Methyl 2-(Acetyloxymethyl)-2-hydroxyhexadecanoate (39). To a stirred solution cooled to 0 °C of 3.0 g (0.01 mol) of **8** in 89 mL of glacial acetic acid was added, dropwise over 5 min, 0.9 mL (0.016 mol) of concentrated H₂SO₄. After the solution was stirred 6.5 h at 0–5 °C and 18 h at room temperature, 0.45 mL of concentrated H₂SO₄ was added and the solution was stirred an additional 24 h at 25 °C. The solution was cooled to 0–5 °C and treated slowly with 5 mL of 5 N NaOH. The reaction was evaporated in vacuo to a sludge, which was suspended in CH₂Cl₂/H₂O. Addition of a small volume of ether allowed separation of layers; the water layer was extracted several times with CH₂Cl₂. The combined organic layers were dried over K₂CO₃ and evaporated to give 2.9 g of a low-melting solid, which was recrystallized once from ether and 3 times from petroleum ether to give 1.1 g (30.7% yield) of white crystals: mp 71–73 °C.

2-Hydroxy-2-(hydroxymethyl)hexadecanoic Acid (40). A suspension of 20 g of **10** in 650 mL of water was refluxed for 17 h. The solid was filtered and dried to yield 16.2 g of **40** as the sodium salt. A mixture of 35 mL of 1 N HCl, 500 mL of ether, 50 mL of ethyl acetate, and 3.0 g of the sodium salt was stirred at room temperature for 4 h. The organic layer was separated, washed with water, and dried (Na₂SO₄). The solvent was removed to give 2.85 g of **40**, which was recrystallized from ethyl acetate: mp 115–120 °C.

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Registry No. 1, 58653-97-7; 2, 92708-68-4; 3, 85216-75-7; 4, 104156-85-6; 5, 104156-86-7; 6, 73472-13-6; 7, 73472-14-7; 8, 69207-52-9; 9, 68170-97-8; 10, 85216-79-1; 11, 85216-78-0; 12, 73472-22-7; 13, 73472-17-0; 14, 73472-21-6; 15, 73472-20-5; 16, 73472-23-8; 17, 73472-18-1; 18, 74416-77-6; 19, 69716-11-6; 20, 85216-76-8; 21, 104156-87-8; 22, 104156-88-9; 23, 104156-89-0; 24, 104156-90-3; 25, 70858-11-6; 26, 73472-15-8; 27, 104156-91-4; 28, 70858-10-5; 28 (R = CH₃), 104157-13-3; 29, 104156-92-5; 29 (alcohol), 104157-14-4; 30, 70858-12-7; 31, 104156-93-6; 32, 104156-94-7; 33, 104156-95-8; 34, 104156-96-9; 35, 104156-97-0; 36, 104156-98-1; 37, 104156-99-2; 38, 104157-00-8; 39, 104157-01-9; 40, 104157-02-0; 40-Na, 104157-16-6; 41, 3760-10-9; 41 (R₂ = CH₃), 3618-40-4; 42, 52756-21-5; 42 (R₂ = CH₃), 92319-59-0; 43, 104157-03-1; 44, 33785-92-1; 44 (R₂ = CH₃), 36986-32-0; 45, 104157-04-2; 45 (R₂ = CH₃), 73472-10-3; 46, 6818-50-4; 46 (R₂ = *n*-Bu), 73472-09-0; 47, 73472-08-9; 48, 6818-51-5; 48 (R₂ = CH₃), 53633-32-2; 49, 33780-98-2; 49 (R₂ = CH₃), 104157-10-0; 50, 38304-03-9; 51, 104157-05-3; 52, 104157-06-4; IV (*n* = 0), 80-62-6; VI (*n* = 13), 41240-57-7; VII (*n* = 13), 104157-07-5; CH₃-(CH₂)₉C(CO₂Et)=C(CH₃)₂, 104157-08-6; CH₃(CH₂)₁₃C(CO₂Me)=C(CH₃)₂, 104157-09-7; CH₃(CH₂)₁₃C(CO₂Me)=CHCH₃, 73472-12-5; diethyl malonate, 105-53-3; 1-bromotetradecane, 112-71-0; (2,2-dimethyl-1,3-dioxolan-4-yl)methyl 2-tetradecyloxiranecarboxylate, 85216-77-9; 2,2-dimethyl-1,3-dioxolane-4-methanol, 100-79-8; methyl crotonate, 18707-60-3; 9,10-dibromo-2-methyleneoctadecanoic acid, 69648-51-7; methyl 9,10-dibromo-2-methyleneoctadecanoate, 69648-52-8; methyl 2-(7,8-dibromohexadecyl)oxiranecarboxylate, 69648-53-9; 2-methylene-1-hexadecanol, 88393-66-2; 2-(chloromethyl)-1-hexadecene, 104157-11-1; dimethyl (2-methylenehexadecyl)propanedioate, 104157-12-2; methyl malonate, 108-59-8; 2-dodecyl-2-(hydroxymethyl)-1,3-propanediol, 88989-24-6; tetradecanol, 124-25-4; ethyl 2-methyl-2-hexadecenoate, 104157-15-5; palmitic acid, 57-10-3; methyl thioglycolate, 2365-48-2; methyl 2-bromopalmitate, 16725-35-2.