Cyclic Fatty Esters: Synthesis and Characterization of Methyl ω -(6-Alkyl-3-Cyclohexenyl) Alkenoates[1]

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ABSTRACT

Diunsaturated C_{18} cyclic fatty acid methyl esters of known structure and configuration were synthesized as model derivatives of cyclic fatty acids formed in heat-abused vegetable oils for characterization and further biological evaluation. The Wittig reaction was used to prepare 5 pure methyl esters: (a) 12-(3-cyclohexenyl)-11-dodecenoate, (b) 11-(6-methyl-3-cyclohexenyl)-10-undecenoate, (c) 10-(6-ethyl-3-cyclohexenyl)-9-decenoate, (d) 9-(6-propyl-3-cyclohexenyl)-8-nonenoate and (e) 8-(6-butyl-3-cyclohexenyl)-7-octenoate. Diels-Alder cycloaddition reactions between 1,3-butadiene and appropriate (E)-2-alkenals produced 3-cyclohexenal intermediates. The appropriate methyl ω-bromoesters and their triphenylphosphonium bromides were made and converted to their respective ylids with $NaOCH_3$ in DMF. The appropriate 3-cyclohexenals and phospho-ylids were reacted, and the desired cyclic ester products were isolated in crude yields of 30-83% as liquids and fractionally distilled. The crude cyclic esters were purified either by preparative TLC or by saponification-esterification. Double bonds in purified cyclic esters were *trans*-isomerized and hydrogenated. Each derivative was characterized by IR, ^{1}H-NMR, ^{13}C-NMR, capillary GLC and GC-MS. On the basis of these analyses, no positional isomers were detected, Z-unsaturated isomers were produced in better than 90% purity, and the alkyl and ester ring substituents were predominantly *trans* to each other.

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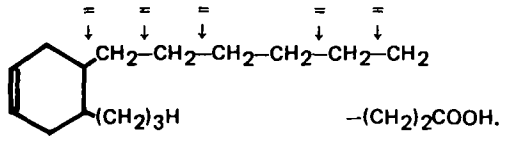
The formation of cyclic fatty acids in thermally abused cooking oils has been well documented, and investigations concerning their toxicity and that of heat-abused vegetable oils have been reviewed (1-3). According to previous investigations, monomeric cyclic acids caused quick deaths of experimental animals. The monomeric cyclic acids, unlike the dimeric or polymeric, have the greatest potential for harm because they are absorbed more readily by the digestive and lymphatic systems (4) and may be included in body fat along with natural fatty acids.

During the last 20 years, many studies indicated that 1,2-disubstituted, 6-membered ring compounds were the principal, cyclic components of heat-abused oils (1-3). Even with the most abused oils, however, the concentration of cyclic acids was too low and the isomeric distribution too large to permit practical isolation of any pure compound for direct characterization and definitive feeding studies (2,3).

The specific structures of the toxic, monomeric cyclic acids found in heat-abused vegetable oils are still unknown. On the basis of gas chromatographic studies, McInnes et al. (5) proposed the generalized cyclohexene structure, which included a complicated mixture of isomers:



Possible double bond positions are indicated by arrows. The unsaturation in the ring and the chain was not conjugated, according to McInnes. Later investigators (3,6,7) noted that the 6-membered ring was not formed exclusively, and the respective length of the substituent chains and position of the double bonds varied. Other questions that remain unanswered include: what biological effects are produced by the pure cyclic compounds, and can specific, unsaturated cyclic acids or esters be determined in heated oils. A synthetic program was initiated to address these questions. This paper reports the synthesis and characterization of a family of diunsaturated, C_{18} fatty esters having the 1,6-disubstituted-3-cyclohexenyl ring. These synthetic compounds will be evaluated biologically later.

RESULTS AND DISCUSSION

Synthesis and Stereochemistry

One monosubstituted- and four 1,6-disubstituted-3-cyclohexenyl methyl esters (1_n, where n = 0 to 4) with unsaturation α to the ring on the ester substituent were prepared as new compounds according to Scheme 1. The chain

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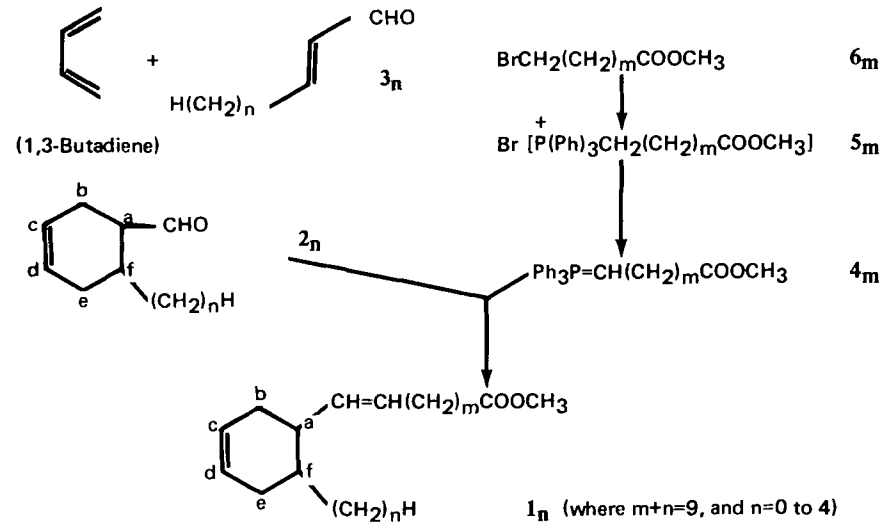


SCHEME 1. Subscript n refers to a specific cyclic ester (1_n) or cyclohexenal (2_n); e.g., 1_0 has no alkyl substituent.

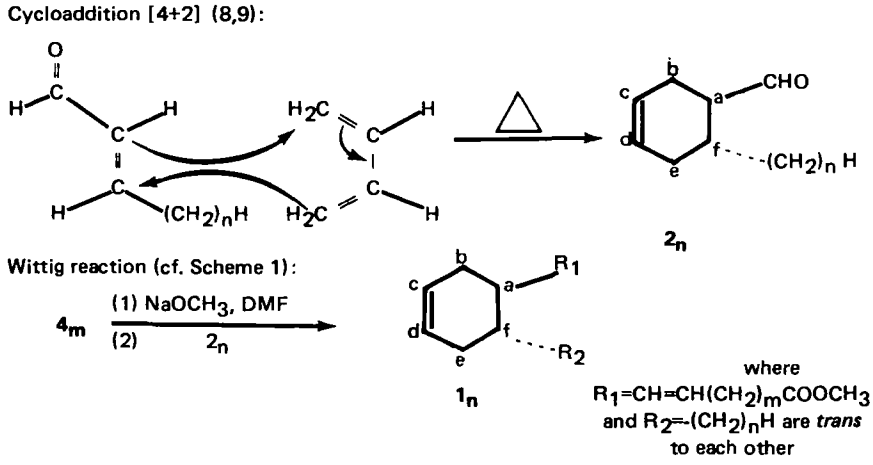
lengths of the ester and alkyl substituents were varied to determine their effect on physicochemical properties and analytical separations. Although the monosubstituted cyclohexenyl ester 1_0 is not expected in heated fats, it was synthesized as a reference compound.

Methyl 9-(6-propyl-3-cyclohexenyl)-8-nonenoate (cyclic ester 1_3) was our principal synthetic target for later feeding studies because previous work (3) indicated the ester with (n = 3) to be the most abundant isomer. The corresponding monounsaturated cyclohexenyl ester was another synthetic target. A monounsaturated cyclic ester was recently synthesized by Graille et al. (8) by a different route, which included a Diels-Alder cycloaddition step. According to the "Alder rules," the cycloaddition of E-unsaturated aldehydes 3_n with butadiene will give a *trans*-adduct (9). Therefore, the cyclic esters expected from our synthesis have ring substituents *trans* to each other (Scheme 2). To avoid confusion in this paper, *cis* and *trans* refer to the disubstituted cyclohexene ring isomers and the geometric double bond isomers are called Z (*cis*) or E (*trans*) isomer. After the final Wittig reaction step, the double bond in the side chain would be predominantly Z configuration under our reaction conditions, and the ring substituents would retain their *trans* relationship as indicated in Scheme 2.

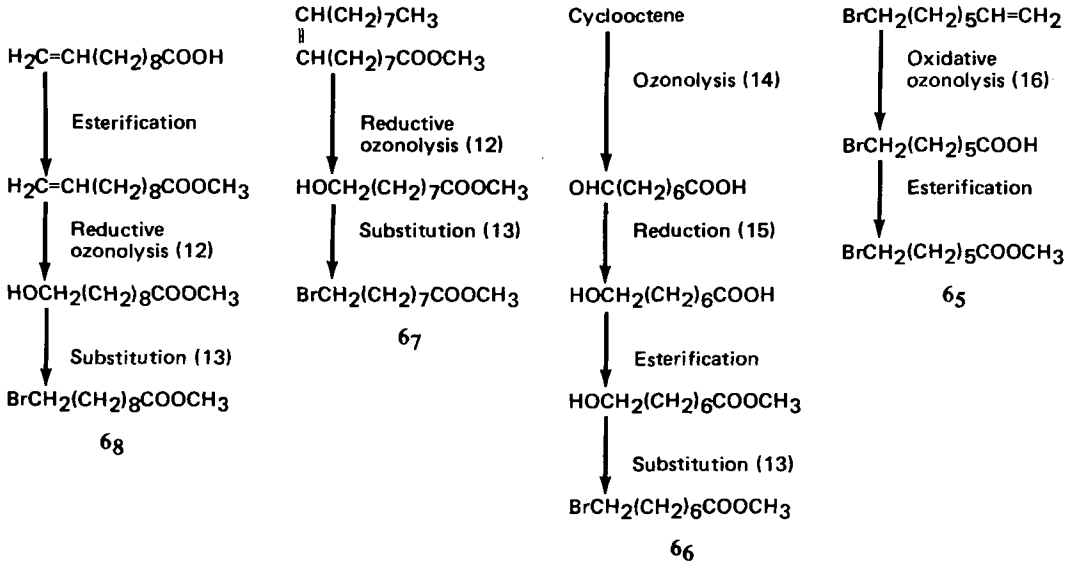
Diels-Alder cycloaddition (9) of butadiene and (E)-2-alkenals gave the cyclohexenal intermediates 2_n, which were reacted with the appropriate phospho-ylid 4_m in a Wittig reaction (10) to produce Z-unsaturated cyclic esters 1_n predominantly (Scheme 1). Both reactions as used are stereoselective. By using NaOEt in dimethylformamide (DMF) to generate the ylid from its phosphonium halide and then adding an appropriate aldehyde, Bergelson et al. (11) previously showed that the Wittig reaction formed Z-unsaturated isomers of fatty acids in better than 90% isomeric purity.

Those ω-bromoacids or -bromoesters 6_m (Scheme 1) that were not commercially available were made according to Scheme 3. The phosphonium bromides 5_m were prepared in better than 97% yields by refluxing an acetonitrile solution of Ph_3P and bromoester 6_m for ca. 36 hr. The phospho-ylids 4_m generated from their phosphonium bromides 5_m were reacted directly with the cyclohexenals 2_n by the method of Bergelson et al. (11).

When crude, cyclic ester 1_0 (Scheme 1) was isolated by the method of Bergelson et al. (11), which called for treatment with Al_2O_3, the product was still contaminated with Ph_3P or similar P-containing compound. This P impurity was removed completely by saponification-esterification (17), but the yield was reduced considerably. The colored, purified product 1_0 became clear after a short-path distillation. Gas chromatography-mass spectrometry (GC-MS) and capillary GLC indicated that it was composed of 2 isomers (M^+, m/z 292.3) in the ratio



SCHEME 2



SCHEME 3

93.2:6.2 (Fig. 1, curve I). IR showed only Z couble bonds. To confirm this double bond configuration, cyclic ester 1_0 was *trans*-isomerized with *p*-toluenesulfinic acid (p-TSIA) catalyst (18). This treatment changed the GLC peak ratio to 21.6:77.2 (Fig. 1, curve II). Therefore, the predominant isomer of 1_0 had Z unsaturation. After hydrogenation of 1_0, capillary GLC indicated 96% saturated cyclic ester and ca. 2% of 1_0 remaining (Fig. 1, curve III). The results were confirmed by IR, NMR and GC-MS.

Cyclic esters $1_{1\text{-}4}$ were adequately purified by TLC or on a larger scale by saponification-esterification, and the resulting products showed no evidence of isomerization by spectroscopic or chromatographic analyses. In contrast, when Graille et al. (8) purified their intermediate keto ester by saponification with KOR and re-esterification, they reported positional isomerization. Apparently, their keto ester was susceptible to isomerization under their conditions.

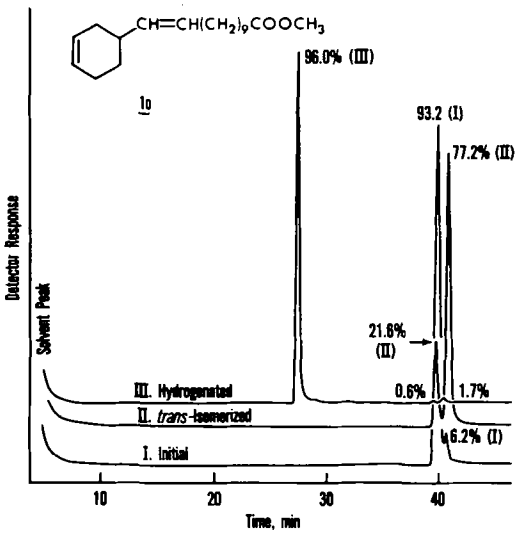


FIG. 1. Capillary GLC of cyclic fatty ester 1_0.

Capillary GLC Characterization

An equivalent chain length (ECL) for each cyclic ester was determined by the capillary GLC method of Scholfield (19) to determine how they would be resolved from other fatty acids in heated fats. On the basis of ECL (Table 1), cyclic isomers 1_0 and 1_1 corresponded to conjugated methyl octadecadienoates (E,E- or E,Z-9,11-; E,Z- or E,E-10,12- or E,E-11,13-); cyclic isomers 1_3 corresponded to methyl 9,12, 15-octadecatrienoates, and cyclic isomers 1_4 corresponded to nonconjugated E,E-12,15- and E,Z-12,15-octadecadienoates in 2 instances and to a Z,E,E,-9,12,15-octadecatrienoate in the other instance (19). The cyclic isomers 1_2 were intermediate between the nonconjugated octadecatrienoates and the conjugated octadecadienoates. For the monosubstituted cyclic ester 1_0, the E unsaturated ester had longer retention than the Z, but with the disubstituted ester 1_3 this order was reversed. As expected with a polar Silar 10C column, the saturated derivatives had lower retention times than the unsaturated cyclic esters. Also, for both the saturated and unsaturated cyclic esters, retention increased as the length of alkyl chain decreased.

Spectral Characterization

IR spectra of the cyclohexenals 2_n and cyclic esters 1_n displayed absorption bands consistent with the expected structures (Scheme 1): Z unsaturation at 1660 and 660 cm^{-1} (5,20); aldehyde (1728 cm^{-1}) or methyl ester (1747 cm^{-1}), respectively; and chain methylenes (725 cm^{-1}). An absorption band for E CH=CH (965 cm^{-1}) was observed only after cyclic esters 1_0 and 1_3 were isomerized with *p*-toluenesulfinic acid (18). Although the conversion of methyl oleate into methyl elaidate with this reagent was ca. 80%, the isomerization of cyclic ester 1_3 from Z to E unsaturation under the same conditions was only ca. 12%, according to capillary GLC (Fig. 2, curves I and II). The double bond in the side chain of 1_3 would be expected to isomerize with much difficulty because of steric hindrance by the α-alkyl substituent. This steric hindrance is confirmed by the greater degree of isomerization (ca. 77%) observed under the same conditions for the monosubstituted cyclic ester 1_0 (Fig. 1, curves I and II).

^{1}H-NMR data (Table 2) were consistent with those expected from structures of cyclohexenals 2_n and cyclic esters 1_n (Scheme 1). Our assignments for the diunsaturated cyclic ester 1_3 were in good agreement with those of Graille et al. (8) for their monounsaturated cyclic ester. ^{1}H-NMR of cyclohexenals $2_{1\text{-}3}$ (Table 2) showed evidence for mixtures of conformational isomers, e.g., 2 different -CHO resonances (δ 9.66 and 9.74) for 2_1 in a ratio of 2:1 (axial:equatorial). Apparently, the longer the alkyl branch, the more favored was the axial -CHO conformation. Examination of a molecular model of 2_1 demonstrated that the *trans* configuration can exist either as a half-chair form (conformer) with axial-axial (a_{CHO} a_R) and equatorial-equatorial (e_{CHO} e_R) substituents, or as a boat form with a_{CHO} e_R and e_{CHO} a_R substituents. Similarly, the *cis* configuration can assume either a half-chair form with a_{CHO} e_R and e_{CHO} a_R, or a boat form with a_{CHO} a_R and e_{CHO} e_R substituents. With either *trans* or *cis* configuration, the axial and equatorial CHO substituent would seem equally probable if conformational interconversions were purely random and not influenced by other factors. Thermodynamic considerations (21) and NMR data (8) strongly suggest that the half-chair form is much preferred over the boat form. The literature is controversial regarding the stability and preference of an axial CHO over an equatorial CHO in the half-chair conformation. For example, Kugatova-Shemyakina et al. (22,23) concluded from reactivity and spectral studies that axial CHO interacts with the ring double bond (a "supra-annualar effect") forming an intramolecular pi-complex that favors axial CHO. However, Zefirov et al. (24) concluded from heteronuclear double resonance studies that the equatorial CHO is favored.

^{13}C-NMR data for the cyclohexenals 2_n and

TABLE 1

Capillary Gas Liquid Chromatography[a]

Compound[b]	Peak (stereoisomer)	Relative area (%)[c]	ECL
1_0	1 (Z)	93.2	21.50
	2 (E)	6.2	21.57
1_1	1	2.1u	20.60
	2	61.1u	20.66
	3	2.8	20.75
	4	30.5	21.11
1_2	1	3.3	20.49
	2	70.5	20.59
	3	24.3	20.89
1_3	1	0.8	19.94
	2	77.1	20.07
	3	21.1	20.42
1_4	1	0.8	19.67
	2	75.2	19.81
	3	20.8	20.13
trans-Isomerized 1_0	1 (Z)	21.6	21.48
	2 (E)	77.2	21.58
Hydrogenated 1_0	1	96.0	20.09
	2	0.6	–
	3	0.6	21.46
	4	1.7	21.55
Hydrogenated 1_1	1	1.6u	19.44
	2	61.5u	19.55
	3	28.0	20.10
	4	1.9	20.19
	5	1.4u	20.34
trans-Isomerized 1_3	1 (E)	12.9	19.94
	2 (Z)	77.7	20.08
	3 (Z)	9.4	20.37
Hydrogenated 1_3	1	0.9u	18.76
	2	13.6	18.82
	3	60.9u	19.04
	4	0.8u	19.26
	5	21.6u	19.35
	6	0.9	19.53

[a]Ref. 19.

[b]See Scheme 1.

[c]u = unresolved.

the cyclic esters 1_n are given in Tables 3 and 4. Only cyclohexenal 2_1 gave a spectrum with resonances attributable to a *cis* ring isomer (designated by [*c*] in Table 3) showing a mixture of the *cis* and *trans* ring isomers. The commercial source of cyclohexenal 2_1 could explain this isomeric mixture. Reaction conditions different than ours, such as acid catalysis, higher temperatures or longer reaction times, generated mixtures of the *cis*- and *trans*-disubstituted-3-cyclohexene isomers (27,28). In the present work, all cyclohexenals showed one peak on GLC, except the commercial cyclohexenal 2_1 which gave 2 peaks in the ratio of 2:1. As expected, a mixture of *cis* and *trans* ring isomers was also indicated by ^{13}C-NMR for cyclic ester 1_1 derived from 2_1; more ring resonances were observed for 1_1 than for the other cyclic esters. The resonances for the *cis* ring were not observed in the spectra of the other cyclohexenals and cyclic esters and, therefore, supported our previous assessment that the *trans* ring isomer was formed by the Diels-Alder cycloaddition (Scheme 2).

Chemical shift assignments for the ester chain moiety A and the alkyl moiety D in Table 4 are based on the literature (29). The assignments for moiety B and ring moiety C are ten-

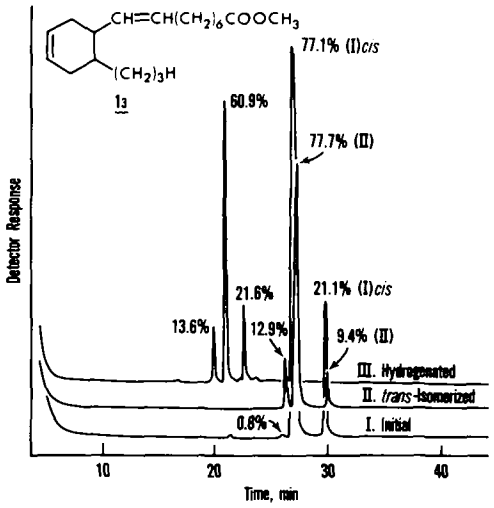


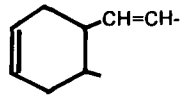
FIG. 2. Capillary GLC of cyclic fatty ester 1_3.

tative and based on comparisons with similarly substituted cyclic compounds (25,26), and our cyclohexenals 2_n. The assignments for E double bond in moieties B and C are based on its appearance after the cyclic esters were isomerized with *p*-TSIA.

GC-MS Characterization

After hydrogenation, cyclic esters 1_0, 1_1 and 1_3 showed characteristic MS fragments (Fig. 3 and Table 5) conforming to those reported in the literature (30,31). The skeletal structures of 1_0, 1_1 and 1_3 were thus confirmed. In addition to the fragments listed in Table 5, characteristic aliphatic methyl ester fragments (m/z 59, 74 and 87) and chain/ring fragments (m/z 41, 43, 55, 69, 83 and 97) were recorded with relative intensities exceeding 10% (32).

The diunsaturated cyclic esters 1_n gave more intense molecular ion (M^+) peaks than their saturated derivatives. Because of the double bond alpha to the cyclohexenyl ring in cyclic esters 1_n, the B-type fragmentation of Figure 3 was very weak or absent as would be expected between a saturated and unsaturated carbon. Otherwise, the characteristic A-D fragmentations were observed (Table 6). However, several new relatively intense fragmentations (m/z 238, 206 and 164) were characteristic of the diunsaturates 1_n. The fragment at m/z 238 and one at m/z 54 were attributed to a homolytic, retro Diels-Alder reaction, as illustrated in Figure 3, characteristic of cyclic olefins (32). Loss of CH_3OH (m/z 32) from m/z 238 would account for m/z 206. A McLafferty rearrangement on m/z 238 and resulting loss of m/z 74 would explain the m/z 164 fragment. In addition to the characteristic aliphatic methyl ester fragments and alkyl fragments, relatively intense peaks due to m/z 79-82 were noted due to fragmentation of the cyclohexenyl ring. Moderately intense peaks at m/z 107-110 were attributed to the



fragment and its rearrangements.

The cyclic esters $1_{0\text{-}4}$ and cyclohexenals $2_{2\text{-}4}$ are new compounds. The study of their selective reactions (e.g., isomerizations and hydrogenations), isolation and identification of specific geometric or stereoisomers is the subject of another paper.

EXPERIMENTAL

Materials and Methods

Commercial products included: 6-methyl-3-cyclohexene carboxaldehyde (cyclohexenal 2_1: bp, 77 C/25 mm; lit. [33] 75 C/22 mm) (K&K labs, Plainview, NY), 1,2,3,6-tetrahydrobenzaldehyde (cyclohexenal 2_0; 99%: bp, 63.5-65.5 C/23 mm; lit. [34] 58 C/17 mm), (E)-2-hexenal (3_3; 99%: bp, 54 C/23 mm; lit. [35], 50.5-51.5/20 mm), 11-bromoundecanoic acid (99+%), undecylenic acid (99%), cyclooctene (95%), triphenylphosphine (99%) and sodium methoxide (anhydrous powder) (Aldrich Chemical Co., Milwaukee, WI); (E)-2-pentenal (3_2: bp, 50-51 C/23 mm; lit. [36], 56 C/65 mm), (E)-2-heptenal (3_4: bp, 71-72 C/21 mm; lit. [37], 61-62 C/15 mm), 8-bromo-1-octene, sodium borohydride (98%) and 6-bromohexanoic acid (Alfa Products, Danvers, MA); 1,3-butadiene (99.5% min) (Matheson, East Rutherford, NJ) and bromine (J.T. Baker Chem. Co., Phillipsburg, NJ). All aldehydes were kept under N_2 and freshly distilled before use. Carboxylic acids were esterified in methanol containing conc. H_2SO_4 or HCl. The cyclic esters 1_0, 1_1 and 1_3 (ca. 50 mg) were hydrogenated with PtO_2 in 2-5% EtOH solution under ambient conditions. The cyclic esters 1_0 and 1_3 (ca. 250 mg) were isomerized with *p*-TSIA catalyst (18).

IR spectra were recorded on a Perkin-Elmer 621 spectrometer. ^{1}H-NMR spectra were determined on a Varian XL-100 Spectrometer using $CDCl_3$ as the solvent with Me_4Si as internal standard. ^{13}C-NMR was run on a Bruker WH-90 Fourier Transform spectrometer at 22.63 MHz, and $CDCl_3$served as the internal deuterium lock

TABLE 2

^{1}H-NMR Chemical Shifts (δ, ppm from TMS), in $CDCl_3$

Group proton	n = 0	n = 1	n = 2	n = 3	n = 4
			3-Cyclohexenals 2_n (Scheme 1):		
$-CH_3$	–	1.02 (m, 3)[a]	0.93 (m, 3)	0.92 (m, 3)	0.89 (m, 3)
$-(CH_2)_n-$	–	–	ca. 1.07-1.57 (m, 2)	1.37 (m, 4)	1.36 (m, 6)
-CH-CH- (a,f)	ca. 1.4-2.0 (m, 2)	ca. 1.5-2.0 (m, 2)	ca. 1.5-2.0 (m, 2)	ca. 1.5-2.0 (m, 2)	ca. 1.5-2.0 (m, 2)
$-CH_2-$ (b,e)	ca. 2.0-2.4 (m, 4)	ca. 2.0-2.4 (m, 4)	ca. 2.0-2.7 (m, 5)	ca. 2.0-2.6 (m, b)	ca. 2.0-2.6 (m, 5)
-CH=CH- (c,d)	5.71 (m, 2)	5.68 (m, 2)	5.67 (m, 2)	5.67 (m, 2)	5.66 (m, 2)
-CHO[b]	9.69 (d, 1)	9.66 (d, 0.67)[b]	9.64 (d, 0.75)[b]	9.64 (d, 0.9)[b]	9.64 (d, 1)
		9.74 (d, 0.33)[b]	9.75 (d, 0.25)[b]	9.75 (d, 0.1)[b]	
			Cyclic fatty methyl esters 1_n (Scheme 1):		
$-CH_3$	–	0.90 (m, 3)[c]	0.88 (m, 3)	0.87 (m, 3)	0.87 (m, 3)
$-(CH_2)_x$	1.29 (m, ca. 12)	1.29 (m, ca. 12)	1.32 (m, 9)	1.32 (m, ca. 10)	1.32 (m, 10)
CH-CH (a,f)	1.62 (m, ca. 4)	1.60 (m, ca. 4)	1.61 (m, 4)	1.64 (m, ca. 4)	1.64 (m, 5)
$-CH_2-$ (b,e)	2.05 (m, 4-5)	2.00 (m, 4-5)	2.00 (m, 4)	2.00 (m, ca. 4)	2.00 (m, 5)
$-CH_2COO-$	2.29 (t, 2)	2.30 (t, ca. 3)	2.30 (t, ca. 3)	2.29 (t, ca. 3)	2.29 (t, ca. 3)
CH_3O-CO-	3.65 (s, 3)	3.66 (s, 3)	3.66 (s, 3)	3.66 (s, 3)	3.66 (s, 3)
-CH=CH-	5.28 (m, 2)	5.26 (m, 2)	5.26 (m, 2)	5.26 (m, 2)	5.28 (m, 2)
-CH=CH- (c,d)	5.67 (d, 2)	5.65 (d, 2)	5.66 (m, 2)	5.64 (m,2) 5.66	5.64 (m, 2)

[a]Most likely a doublet overlapping a doublet, because a mixture of 2 ring isomers is indicated (by gas chromatography).

[b]The 2 aldehyde resonances (axial and equatorial -CHO) suggest a mixture of conformational isomers.

[c]Most likely a doublet overlapping a doublet.

TABLE 3

^{13}C-NMR Chemical Shifts (ppm, rel. TMS) for 3-Cyclohexenals 2_n (Scheme 1), in $CDCl_3$

Carbon	n = 0	n = 1[a]	n =2	n = 3	n = 4
-CHO	203.7	204.6	204.9	204.6	204.9
a	46.1	50.0 (*c*) 52.5 (*t*)	50.4	50.8	50.7
b	23.9[b]	22.8 (*c*) 23.9 (*t*)	23.3	23.3	23.2
c	125.0	124.1 (*c*) 124.6 (*t*)	124.0	124.1	124.0
d	127.3	126.0 (*c*) 126.4 (*t*)	126.3	126.3	126.3
e	24.6[b]	32.1 (*c*)[b] 32.2 (*t*)[b]	34.3	32.4	32.5
f	22.4	27.8 (*c*) 28.1 (*t*)	28.3	28.8	28.8
$-CH_2-$	–	–	26.5	36.1	33.5
$-CH_2-$	–	–	–	20.0	29.0
$-CH_2-$	–	–	–	–	22.8
$-CH_3$	–	16.2 (*c*) 19.7 (*t*)	11.2	14.2	14.0

[a]Resonances attributed to either: (*c*) = *cis*-1,6-disubstituted, -3-cyclohexene ring or (*t*) = *trans*-1,6-disubstituted-3-cyclohexene ring (cf. refs. 25,26 and text).

[b]These assignments are tentative and may be reversed.

with Me_4Si as internal reference.

Analyses by GLC were run on a Hewlett-Packard Model 5710A gas chromatograph (FID, 300 C; injection port 260 C or on-column) with a 6 ft × 1/8 in. s.s. column of 10% SP2330 (Supelco, Inc. Bellefonte, PA) on 100-120 mesh Chromosorb WAW. Methyl cyclic fatty esters, ω-hydroxyesters and ω-bromoesters were analyzed isothermally at 190 C, and the ω-aldehyde esters at 150 C. For other aldehydes, however, the column temperature was held at 80 C for 16 min and then programmed at 8 C/min to 130 C. The procedure for capillary GLC of the fatty methyl esters was described by Scholfield (19).

GC-MS was run on a Nuclide 12-90 DF mass spectrometer with 70 eV impact ionization and equipped with an all-glass jet separator (source temperature, 200 C). Output of the MS was to a Finnigan INCOS 2000 computer system repeatedly scanning masses 15-370 every 8 sec. A Bendix 2600 gas chromatograph interfaced with the MS was used with a 6 ft × 2 mm glass column packed with 3% JXR on Gas Chrom Q, 100-120 mesh. The column was held at 190 C for 4 min, then programmed at 2 C/min to 250 C, with a 20 ml/min flow of carrier gas (He); injection temperature was 210 C and detector temperature was 235 C.

Precoated plates of silica gel with fluorescent indicator, 0.25 mm thick, were used for analytical TLC. For preparative TLC, plates of silica gel, 0.50 mm thick, with fluorescent indicator but no binder, were used. The developing solvent was either 1:5 (v/v) ether/hexane for the cyclic fatty esters or 1:2 (v/v) ether/hexane for the intermediates. Developed spots were generally visualized by charring with 50% H_2SO_4 after UV detection for phenylphosphine impurities.

Methyl 10-Hydoxydecanoate

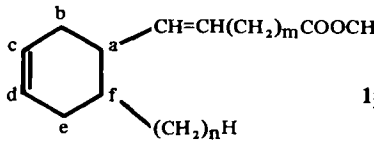
Methyl 10-undecenoate was prepared by conventional esterification of undecylenic acid. The distilled ester (99.9% by GLC) was ozonized in MeOH and the products were reduced with $NaBH_4$ (12) to give 145.3 g (68% yield) of the crude hydroxyester (93.7% by GLC), which was distilled through a Vigreux column (bp 152-156 C/11 mm; lit. [38], 154 C/17 mm). The distillate (96-97% purity by GLC) was purified further by low-temperature crystallization to yield clear, colorless liquid (99+% hydroxyester by GLC). IR (KBr neat): 3650-3100 (-OH), 1742 (ester C=O), (1250, 1197 and 1170 [Me ester C-O-C]) and 720 ($-[CH_2]_n-$) cm^{-1}.

Methyl 9-Hydroxynonanoate

Methyl oleate (99% by GLC, 40.0 g, 0.1439

TABLE 4

^{13}C-NMR Chemical Shifts (δ, ppm) for Cyclic Fatty Methyl Esters 1_n (cf. Scheme 1) in $CDCl_3$



1_n (where m+n=9; n=0 to 4)

Compound	Assignments					
A.	CH_3	OOC	CH_2	CH_2	$(CH_2)_{m-3}$	
1_{0-4}	51.3	174.2	34.2	25.0	(28.9-29.5)[a]	
B.	CH_2	CH=CH				
1_0	27.5 32.6 (E)[b]	128.9 128.6 (E)[b]	135.2 135.4 (E)[b]			
1_1	27.6	129.5	134.3			
1_2	27.5	129.2	134.4			
1_3	27.5 32.4 (E)[b]	129.2 129.8 (E)[b]	134.6 134.9 (E)[b]			
1_4	27.4	129.0	134.7			
C.	Ring Carbons:					
	a	b	c	d	e	f
1_0	32.2 36.7[b]	30.0	126.4	126.9	24.8	31.9
1_1	35.2[c] 38.9	30.0	125.4[c] 126.3	126.7[c] 130.9	32.4	–[a]
1_2	37.2	30.1	126.0	126.6	32.3	–[a]
1_3	37.5 42.8[b]	30.7	126.0 126.6[b]	126.7 129.2[b]	32.3	–[a]
1_4	37.5	30.7	125.9	126.6	32.3	–[a]
D.	CH_2	CH_2	CH_2	CH_3		
1_0	–	–	–	–		
1_1	–	–	–	17.3[c] 20.2		
1_2	–	–	26.8	11.0		
1_3	–	36.7	19.8	14.4		
1_4	37.4	–[a]	23.0	14.1		
	Unassigned resonances:					
1_1	31.3, 32.9, 33.9					
1_2	29.9, 39.2, 125.5, 126.5, 130.3					
1_3	27.7, 30.5[b], 31.1, 32.0, 125.6, 126.5, 130.6					
1_4	29.6, 31.9, 32.6, 36.8, 130.1, 130.6					

[a]Assignment to chain methylenes. Individual assignments are not possible.

[b]Resonances observed only after reaction with *p*-toluenesulfinic acid (conversion of acyclic [Z]-CH=CH to [E]-CH=CH) (18).

[c]The *cis* ring isomer (i.e., *cis*-1,6-disubstituted-3-cyclohexene) was indicated by these resonances.

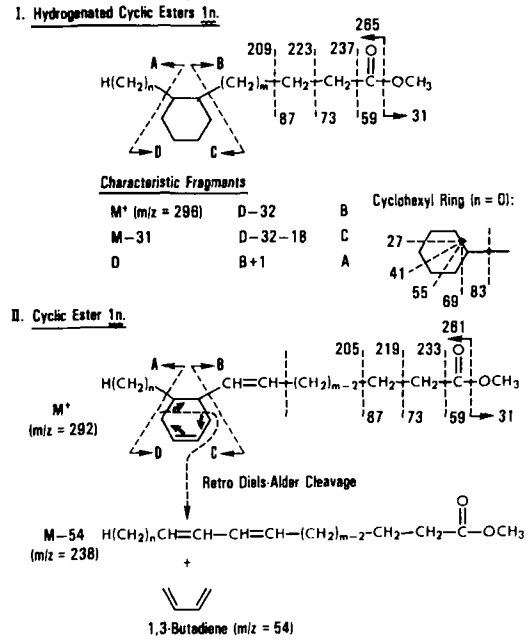


FIG. 3. Characteristic mass fragmentations of hydrogenated (I) and nonhydrogenated (II) cyclic esters 1_n (Scheme 1).

TABLE 5

GC-MS Fragmentations of Hydrogenated Cyclic Fatty Methyl Esters 1_n (Scheme 1)

Compound	Ion fragment (cf. Fig. 3):m/z (% rel. intensity)									
	M+	M-31	D	D-32	D-32-18	B+1	B	C	A	(Base)
1_0	296 (27)	265 (4)	296 (27)	264 (<3)	246 (<1)	214 (<5)	213 (<5)	83 (41)	–	74 (100)
1_1	296 (19)	265 (5)	281 (0)	249 (0)	231 (0)	200 (17)	199 (14)	97 (97)	15 N.D.	55 (100)
1_3	296 (11)	265 (3)	253 (22)	221 (17)	203 (11)	172 (16)	171 (3)	125 (43)	43 (29)	69 (100)

TABLE 6

GC-MS Fragmentations of Diunsaturated Cyclic Fatty Methyl Esters 1_n (Scheme 1)

Compound	Ion fragment (cf. Fig. 3):m/z (% rel. intensity)										
	M+	M-31	D	D-32	D-32-18	B+1	B	C	A	(Base)	M-54
1_0	292 (32)	261 (18)	292 (32)	260 (3)	242 –	212 –	211 –	81 (67)	– –	94 (100)	238 (11)
1_1	292 (46)	261 (5)	277 (1)	245 –	227 –	197 –	196 (2)	96 (31)	15 –	94 (100)	238 (45)
1_2	292 (33)	261 (9)	263 (14)	231 (13)	213 (2)	183 (1)	182 (5)	110 (32)	29 –	67/79 (100)	238 (72)
1_3	292 (16)	261 (3)	249 (5)	217 (5)	199 –	169 –	168 (3)	124 (7)	43 (29)	67 (100)	238 (38)
1_4	292 (39)	261 (3)	235 (6)	203 (6)	185 (3)	155 (1)	154 (3)	138 (3)	57 (11)	67 (100)	238 (83)

mol) was reductively ozonized (12) to yield a mixture (39.70 g) of crude hydroxyester and nonanol. Vacuum distillation (28.77 g) through a Vigreux column gave the hydroxyester (17.71 g; bp 89-95 C/0.05 mm) in 95.4% purity (<3% nonanol by GLC); lit. (39), bp 82-95 C/0.05 mm (90% purity). IR (KBr neat): 3650-3100 (-OH), 1742 (ester C=O), (1242, 1198 and 1172 [Me ester C-O-C]) and 722 (-$[CH_2]_n$-) cm^{-1}.

Methyl 8-Hydroxyoctanoate

Cyclooctene (99.0 g, 0.853 mol) was ozonized in cyclohexane (1150 g) and glacial HOAc (145 g), and the ozonide was treated with acetic anhydride and sodium acetate (14) to obtain crude 8-oxooctanoic acid, 114.9 g. The fractionally distilled aldehydic acid (bp 125-127 C/0.08 mm; 97+%), 41.3 g (0.261 mol), was selectively reduced with $NaHCO_3$ and $NaBH_4$ (15) to give 27.3 g of crude 8-hydroxyoctanoic acid as white solid. The hydroxyacid was then esterified ($CH_3OH+H_2SO_4$) and distilled to give a clear, colorless liquid (bp 93-95 C/0.22 mm; 98+%); lit. (40), bp 137-138 C/8 mm. IR (KBr neat): 3650-3100 (-OH), 1742 (ester C=O), (1250, 1200 and 1172 [Me ester C-O-C]) and 727 (-$[CH_2]_n$-) cm^{-1}.

Methyl ω-Bromoalkanoates (6_m)

11-Bromoundecanoic acid was converted to its methyl ester **69** by conventional esterification. Methyl 10-bromodecanoate (**68**), methyl 9-bromononanoate (**67**) and methyl 8-bromooctanoate (**66**) were prepared from their respective ω-hydroxyesters by bromination of the -OH group, using $Ph_3P{\cdot}Br_2$ reagent (13).

An oxidative ozonolysis procedure for olefins (17) was adapted to synthesize methyl 7-bromoheptanoate (**65**). 8-Bromo-1-octene (13.37 g, 0.070 mol) in MeOH (450 ml) was ozonized at 5-10 C; then N_2 was bubbled through the stirred solution as it warmed to room temperature (RT). After removing the MeOH, the residue was transferred with 91% formic acid (225 ml) and cooled to 15 C. Cold 30% H_2O_2 (35 ml) was added by drops to the stirred solution, which was then allowed to warm to RT and heated gradually in 3 hr to 75 C. The cooled reaction mixture was extracted with petroleum ether, washed, dried, filtered and stripped of solvent. Esterification with MeOH and H_2SO_4 gave the crude bromoester **65** (5.0 g). Short-path distillation with dimethyl sebacate as chaser gave the bromoester (bp 65-71 C/0.19 mm; lit. [41], bp 112 C/5 mm) in 92.4% purity.

Boiling points for the other methyl ω-bromoesters were (11-) 106-108 C/0.10 mm; (10-) 104-114 C/0.20 mm; (9-) 92 C/0.25 mm; and (8-) 83-84 C/0.20 mm. Literature boiling points (41): 176 C/14 mm, 165 C/12 mm, 131 C/2 mm and 124 C/6 mm, respectively.

IR (KBr, neat): 1742 (ester C=O), (ca. 1250, 1200 and 1172 [Me ester C-O-C]), 725 (-$[CH_2]_m$-), 641 (C-Br) and 560 (C-Br) cm^{-1}. A mixture of these homologous C_6-C_{11} ω-bromo-esters showed on GLC the expected linear relationship between carbon number and log of retention time.

(ω-Carbomethoxyalkyl)triphenylphosphonium Bromides (5_m)

The following procedure for 10-methoxycarbonyldecyl)triphenylphosphonium bromide (**50**) is generally representative of that used for the other phosphonium bromides (**58-5**). However, phosphonium bromides (**57-5**) could not be crystallized and were isolated as viscous, transparent gums.

A mixture of Ph_3P (82.8 g, 0.316 mol), bromoester **60** (75.4 g, 0.270 mol) and CH_3CN (300 ml) was stirred magnetically and heated under N_2. After 36 hr reflux, the solution was concentrated on a rotary evaporator and crystallized from ether after 4 repetitive extractions by kneading it in the ether (10 vol) and decanting. Final weight of **59** was 139.9 g (95.9% yield). IR (KBr disc): 1740 (ester C=O), (1248, 1190 and 1170 [Me ester C-O-C]), 725 (-$[CH_2]_9$-), 691 (C-Br) cm^{-1}.

By the same procedure, bromide **58** (144.3 g; 92% yield) was obtained from bromoester **68** (85.6 g); bromide **57** (13.60 g, 98.1% yield) from bromoester **67** (8.00 g); bromide **56** (40.1 g, 100.3% yield) from bromoester **66** (18.8 g) and bromide **55** (12.4 g, 95.0% yield) from bromoester **65** (6.00 g).

6-Alkyl-3-Cyclohexenals (2_{3-4}).

The following procedure for 6-propyl-3-cyclohexenal (**23**) from 1,3-butadiene and (E)-2-hexenal (**33**) was typical.

A 250-ml Hastelloy autoclave (rocker type) was evacuated and charged with (E)-2-hexenal (18.3 g, 0.186 mol) through the inlet tube and attached syringe needle. The autoclave was then chilled in Dry Ice/acetone and re-evacuated. The inlet tube needle was inserted through a 2-hole, crown cap and gasket into a tared pressure bottle (Lab Glass, Inc., Vineland, NJ) containing liquefied 1,3-butadiene (cooled in Dry Ice/CCl_4). The valve on the inlet tube was opened, and the butadiene (33.6 g, 0.521 mol) was transferred into the autoclave. After standing

overnight at RT, the autoclave was agitated and heated to 165 C for 5 hr. The cooled contents were transferred with ether, and the solution was concentrated on a rotary evaporator to a clear, pale-yellow liquid (39.4 g; 61% cyclohexenal, 33% hexenal, and 6% unknown byproducts by GLC). Distillation of the concentrate (28.3 g) with a Vigreux column (4.5 x 0.5 in.) afforded a main fraction 11.6 g; bp 94-97 C/13 mm; 94+% cyclohexenal 2_3 by GLC.

Similarly prepared were: 6-butyl-3-cyclohexenal (2_4, 5.21 g, bp 47-54 C/0.04 mm, 98% purity by GLC; crude yield, 43.7%) from (E)-2-heptenal; and 6-ethyl-3-cyclohexenal (2_2, 11.03 g, bp 33-40 C/0.24-0.20 mm, 96+% by GLC) from (E)-2-pentenal. Cyclohexenals 2_{2-4} are new compounds.

IR (neat) for cyclohexenals 2_n: 3025 (CH=CH), 1728 (aldehyde C=O), 1660 and 660 (Z CH-CH); except 2_0, 1650 and 652 (Z CH=CH) cm^{-1}. NMR (cf. Table 2). All commercial E-2-alkenals were freshly distilled before use and showed high E-purity by GLC and IR. Any isomerization would not be expected before cycloaddition because no thermal isomerization of E-crotonaldehyde was observed even at 240 C (27).

Methyl ω-(6-Alkyl-2-Cyclohexenyl) Alkenoates (1_n)

The preparation of methyl 9-(6-propyl-3-cyclohexenyl)-8-nonenoate (1_3) was typical of the other cyclic ester 1_n syntheses.

Phosphonium bromide 5_6 (39.5 g, 0.0791 mol) in dry DMF (100 ml) was stirred magnetically under N_2, cooled (ca. 5 C) in an ice bath, and $NaOCH_3$ (4.83 g, 0.0894 mol) was added quickly. The initially colorless solution turned orange-brown. After 45 min, a solution of cyclohexenal 2_3 (10.59 g, 0.0695 mol) in DMF (20 ml) was added by drops (ca. 10 min). The color of the reaction became light tan or cream, and the mixture was stirred overnight under N_2 after removing the ice bath. The mixture was concentrated (at 40 C/1.0-0.5 mm) on a rotary evaporator to a brown residue (56.3 g), which was slurried in ether (100 ml), filtered and concentrated. The resulting brown residue was chromatographed through neutral alumina (48 g) in hexane (100 ml) followed by ether (100 ml). GLC indicated that the hexane eluate contained mainly cyclic ester 1_3 (96+% pure; crude yield, 79.8%), and the ether eluate contained mostly cyclohexenal 2_3 (ca. 83% pure). A short-path distillation gave a clear, nearly colorless fraction (10.80 g; bp 126-133 C/0.04 mm; 98.5% 1_3 by GLC), which was still contaminated wih PH_3P according to NMR and TLC. The impurity was completely removed by preparative TLC. The saponification-esterification procedure of Bergelson et al. (17) was used to purify larger quantities of 1_3. From 3.0 g of distilled 1_3, we obtained by the saponification-esterification a clear, pale-yellow liquid (1_3, 2.12 g; 98+% by GLC), free of phenylphosphines according to TLC. Boiling points of the purified cyclic esters were: 1_0, 125-128 C/0.02 mm; 1_1, 127-132 C/0.05 mm; 1_2, 125-127 C/0.04 mm; 1_3, 125-129 C/0.05 mm; 1_4, 124-130 C/0.09 mm.

IR (KBr, neat) for cyclic esters 1_n: 3020 (CH=CH), 1748 (ester C=O), 1660 (Z CH=CH), (1250-1255, 1198 and 1172 [Me ester C-O-C]), 725 (-$[CH_2]_4$-) and 660 (Z CH=CH) cm^{-1}; except 1_0, which had 1653 and 655 cm^{-1} for Z CH=CH.

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REFERENCES

1. Artman, N.R. (1969) Adv. Lipid Res. 7, 245-329.
2. Perkins, E.G. (1976) Rev. Fr. Corps Gras 23, 257-262 and 313-322.
3. Potteau, B., Dubois, P., and Rigaud, J. (1978) Ann. Technol. Agri. 27, 655-679.
4. Combe, N., Constantin, M.J., and Entressangles, B. (1981) Lipids 16, 8-14.
5. McInnes, A.G., Cooper, F.P., and MacDonald, J.A. (1961) Can. J. Chem. 39, 1906-1914.
6. Hutchinson, R.B., and Alexander, J.C. (1963) J. Org. Chem. 28, 2522-2526.
7. Michael, W.R. (1966) Lipids 1, 365-368.
8. Graille, J., Bonfand, A., Perfetti, P., and Naudet, M. (1980) Chem. Phys. Lipids 27, 23-41.
9. Holmes, H.L. (1948) in Organic Reactions (Adams, R. ed.), Vol. 4, pp. 60-173, John Wiley and Sons, New York, NY.
10. Gosney, I., and Rowley, A.G. (1980) in Organophosphorous Reagents in Organic Synthesis (Cadogan, J.I.G., ed.), pp. 17-53, Academic Press, Inc. New York, NY.
11. Bergelson, L.D., Vaver, V.A., YuKovtun, V., Senyavina, L.B., and Shemyakin, M.M. (1962) Zh. Obsshch. Khim. 32, 1802-1807; C.A. (1963) 58, 4415g.
12. Diaper, D.G.M., and Mitchell, D.L. (1960) Can. J. Chem. 38, 1976-1982.
13. Schaefer, J.P., Higgins, J.G., and Shenov, P.K. (1968) Org. Synth. 48, 51-53.
14. Siclari, F. (1974) U.S. Patent 3,856,833.
15. Siclari, F. (1980) U.S. Patent 4,192,813.
16. Ackman, R.G., Retson, M.E., Gallay, L.R., and Vandenheuvel, F.A. (1961) Can. J. Chem. 39, 1956-1963.
17. Bergelson, L.D., Vaver, V.A., Bezzubov, A.A., and Shemyakin, M.M. (1962) Zh. Obshch. Khim. 32, 1807-1811; C.A. (1963) 58, 4416c.
18. Gibson, T.W., and Strassburger, P. (1976) J. Org. Chem. 41, 791-793.

19. Scholfield, C.R. (1981) J. Am. Oil Chem. Soc. 58, 662-663.
20. MacDonald, J.A. (1956) J. Am. Oil Chem. Soc. 33, 394-496.
21. Eliel, E.L. (1962) Stereochemistry of Carbon Compounds, McGraw-Hill Book Company, Inc., New York, NY.
22. Kugatova-Shemyakina, G.P., Nikolaev, G.M., and Andreev, V.M. (1967) Tetrahedron 23, 2721-2733.
23. Kugatova-Shemyakina, G.P., and Nikolaev, G.M. (1967) Tetrahedron 23, 2987-2995.
24. Zefirov, N.S., Sergeev, N.M., and Gurvich, L.G. (1970) Dokl. Akad. Nauk SSSR 190, 345-347.
25. Johnson, L.F., and Jankowski, W.C. (1972) Carbon-13 NMR Spectra, Spectrum No. 272, John Wiley & Sons, Inc., New York, NY; and Sadtler Standard Carbon-13 NMR Indexes (1977), Vol. 5, Spectrum No. 896, Sadtler Research Laboratories, Inc., Philadelphia, PA.
26. Nakagawa, K., Sawai, M., Ishii, Y., and Ogawa, M. (1977) Bull. Chem. Soc. Jpn. 50, 2487-2488.
27. Kugatova-Shemyakina, G.P., and Nikolaev, G.M. (1967) Zh. Org. Khim. 3, 1448-1455.
28. Miyajima, S., and Inukai, T. (1972) Bull. Chem. Soc. Jpn. 45, 1553-1554.
29. Bus, J., Sies, I., and Lie Ken Jie, M.S.F. (1976) Chem. Phys. Lipids 17, 501-518.
30. Friedrich, J.P. (1967) J. Am. Oil Chem. Soc. 44, 244-248.
31. Oshima, M., and Ariga, T. (1975) J. Biol. Chem. 250, 6963-6968.
32. Silverstein, R.M., Bassler, G.C., and Morrill, T.C. (1974) Spectrometric Identification of Organic Compounds, 3rd edn., pp. 5-71, John Wiley & Sons, Inc., New York, NY.
33. Diels, O., and Alder, K. (1929) Justus Liebigs Ann. Chem. 470, 62-103.
34. Sobecki, W. (1910) Chem. Ber. 43, 1038-1041.
35. Winter, M., and Goutschi, F. (1962) Helv. Chim. Acta 45, 2567-2575.
36. Prevost, C. (1944) Bull. Soc. Chim. Fr. 11, 218-225.
37. Delaby, R., and Guillot-Allegre, S. (1931) Compt. Rend. 192, 1467-1469.
38. Lycan, W.H., and Adams, R. (1929) J. Am. Chem. Soc. 51, 625-629.
39. Pryde, E.H., Theirfelder, C.M., and Cowan, J.C. (1976) J. Am. Oil Chem. Soc. 53, 90-93.
40. Chuit, P., and Hausser, J. (1929) Helv. Chim. Acta 12, 463-492.
41. Hunsdiecker, H., and Hunsdiecker, C. (1942) Chem. Ber. 75, 291-297.

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