Reactions of Dioxiranes with Selected Oleochemicals

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ABSTRACT: Reaction of fatty acids with dimethyldioxirane in acetone produces ketoacids in 9–12% yields in which the ketone carbonyl is distributed along the fatty chain. The n-1 position appears to be preferred. Lactones of hydroxy fatty acids are oxidized by this reagent, but in low yields, to the corresponding ketoacids. Biphasic epoxidations with methylethyldioxirane in 2-butanone were conducted with methyl oleate and methyl ricinoleate to give the corresponding epoxides in high yield, and olive oil and tallow were cleanly epoxidized by this procedure as well.
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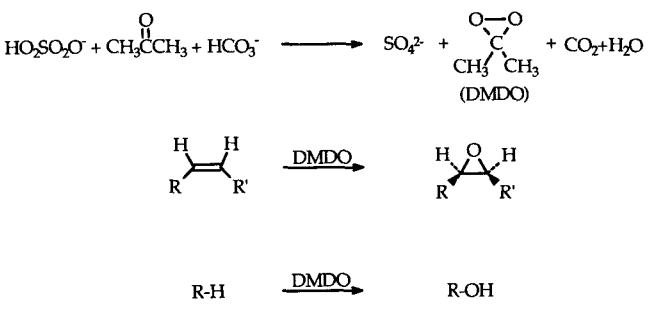
KEY WORDS: Chain functionalization, dioxirane, epoxidation, oleic acid, ricinoleic acid, tallow.

Oxygenated fatty acids are employed industrially as lubricants and as secondary plasticizers (1). Recent interest in generating oxygenated fatty acids has been manifested in essentially two approaches. Materials for which there are established uses are prepared by novel procedures. Alternatively, new structures are synthesized that might warrant evaluation. For example, peracid epoxidation of lesquerella oil (2), examination of the synthetic potential of a hydratase (3,4) and a lipoxygenase (5,6), exploiting the 1,3-positional selectivity of a lipase to reap a hydroxylated fatty acid (7,8), and evaluating lipase discrimination against such fatty acids (9) constitute efforts to provide new procedures for obtaining useful compounds. By contrast, allylic oxidation with SeO_2 (10) and uncovering new microbial oxidations (11) will provide new materials whose potential can then be explored. In this context, dioxiranes, three-membered rings containing two oxygens, may be able to furnish new chemistry for the fats and oils industries in both senses.

Oxone™ is a stable and inexpensive inorganic salt complex, the oxidizing component of which is the monopotassium salt of peroxysulfuric acid. This material has been studied intensively as a source of dioxiranes (12–14). Comprehensive and authoritative reviews set forth the preparations and basic chemistry of this type of compound, which is formed from ketones as a result of reaction with the peroxysulfate anion (Scheme 1; generation of dimethyldioxirane and its reactions with alkenes and hydrocarbons). The most studied member of the family is dimethyldioxirane (DMDO); it is obtained as an acetone solution by low vacuum co-distillation of a reaction mixture containing aqueous Oxone™ and $NaHCO_3$ with excess acetone. Alternatively, one can generate and use DMDO directly in biphasic systems with a phase transfer catalyst.

Among the many examples of oxidations by DMDO that would interest the oleochemist are alkene epoxidations and C–H insertion reactions. Of particular interest are examples of epoxidations in situations where peracids fail (15). The byproducts from DMDO are acetone and other low-boiling organics that form from autodecomposition, such as methyl acetate and acetol (16). The waste aqueous solution contains K_2SO_4. By comparison, peracid epoxidations might be inappropriate for acid-sensitive compounds, and the industrial use of acetic and formic acids in conjunction with H_2O_2 results in materials having oxirane values that are 15–20% lower than theoretical (1). Moreover, some peracids, such as m-chloroperbenzoic acid, are used frequently in a halogenated organic solvent and produce the organic acid as a by-product. This is a material that must be recovered and either disposed of or recycled.

The most exciting prospect is the direct functionalization of hydrocarbons to generate alcohols and ketones. For example, DMDO will react stereospecifically with stereoisomeric 1,2-dimethylcyclohexanes and decalins to produce tertiary al-



SCHEME 1

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cohols with retention of configuration (17). We report here an initial evaluation of the C–H insertion reaction using selected fatty acids and the epoxidations of several unsaturated fatty acid esters. A useful biphasic synthetic procedure for the epoxidation reactions is described.

MATERIALS AND METHODS

Materials. Acetone and 2-butanone were high-performance liquid chromatography (HPLC)-grade; other ketones were reagent-grade and used directly. These materials were purchased from Aldrich Chemical Company (Milwaukee, WI) as were the following: Oxone™, 18-crown-6, all fatty acids, methyl oleate, 4-oxopentanoic acid, 4- and 5-hydroxyalkanoic acid lactones (C6–C11), and 5-oxononanedioic acid. Methyl ricinoleate and its epoxide were generous gifts of Dr. R. Benedict of our laboratory. Gas–liquid chromatography (GLC) was performed with: (i) a Chrompack–Packard Model 438A instrument (Avondale, PA) using a split (50:1) capillary column injector, He carrier gas, and either an SP2330 column (0.25 mm × 30 m) or a Supelcowax column (0.25 mm × 30 m) from Supelco (Bellefonte, PA); and (ii) a Hewlett-Packard Model 5610 chromatograph with on column injection, He carrier, and a DBl-HT capillary column (0.32 mm × 15 m) from J&W Scientific (Folsom, CA). Triglycerides and their epoxidation products were analyzed using an initial oven temperature of 110°C followed by a rise of 20°C/min to a final temperature of 350°C which was held for 18 min. Both systems had flame-ionization detectors. Mass spectra were obtained on a Hewlett-Packard 5989A MS Engine operated in the electron impact mode. The ion source temperature was 280°C, and the spectral mass range was *m/z* 80 to *m/z* 1000. Samples were introduced into the spectrometer *via* an SP2330 capillary column (0.25 mm × 15 m). Thin-layer chromatography (TLC) was performed with analytical silica gel plates from Alltech Associates, Inc. (Deerfield, IL).

Preparation of methyl 4- and 5-oxoalkanoates. The following procedures were used to synthesize reference oxoesters that were compared to those in mixtures obtained by oxidation of fatty acids with DMDO/acetone followed by methylation. Thus, δ-decanolactone (200 μL) was warmed in MeOH (5 mL) containing a few mg of NaOMe for 2–3 h. The solution was diluted with ice water and extracted with ether. The organic phase was washed with water, dried ($MgSO_4$), and stripped of solvent using benzene as a chaser. The residue was then oxidized to the 5-oxoester in CH_2Cl_2 (3 mL) with 0.2 g of pyridinium chlorochromate (PYCC) for 1 h at room temperature. The mixture was diluted with ether and passed through a short column of Florisil (Aldrich Chemical Co.) to give methyl 5-oxodecanoate: infrared (IR) 1735, 1710 cm^{-1}; *m/z* 169 $(M - 31)^+$, 129 $(CH_3O_2C[CH_2]_3C = O)^+$, and 99 $(CH_3[CH_2]4C = O)^+$. The γ-lactones produced mixtures containing a preponderance of the lactone, and so were handled as follows: γ-decanolactone (1.70 g, 10 mmol) was warmed in a solution of NaOH (10 mmol) in 10% aq. MeOH for 2 h. The mixture was concentrated, and traces of MeOH and water removed by evaporating with benzene. The sodium salt was suspended in CH_2Cl_2 and treated with an excess of PYCC as above. The mixture was acidified with 2N HCl and extracted with ether to recover the oxoacid. Esterification in BF_3–MeOH and the conventional workup provided the oxoester contaminated with *ca.* 10% of the γ-lactone. A sample was purified by flash chromatography (7.5% ethyl acetate–hexane): 1735, 1715 cm^{-1}; *m/z* 169 $(M - 31)^+$, 115 $(CH_3O_2C[CH_2]_2C = O)^+$ and 113 $(CH_3[CH_2]_5C = O)^+$.

Preparation and use of DMDO in acetone. The original preparation of Murray and Jeyaraman (18) as simplified by Crandall *et al.* (19) was employed here. The solutions were stored at –20°C over freshly ground $CaSO_4$ and used within a week. The titer was presumed to be 0.08–0.1 M, and the reagent was used in excess. Solutions of substrate (organic acids, esters and lactones), 0.10 mmol, in 10–12 mL of DMDO–acetone were capped and stored in the dark for 20–24 h. Aliquots of reaction mixtures of the acids were esterified (CH_2N_2), and these solutions were then analyzed by GLC as were the other ester and lactone product solutions. The relative amounts of oxidized esters were estimated by GLC peak areas (average of three injections each of duplicate oxidations) without corrections for response factors. Mass spectra of the oxidation products from methyl decanoate were consistent with assignments, and the peak assigned to methyl 9-oxodecanoate gave a mass spectrum matching that found in the Wiley 138L database.

Biphasic oxidations. The procedure for epoxidizing methyl oleate is typical and is patterned after procedures reported by Curci and co-workers (20): methyl oleate (1.50 g, 5.00 mmol) was vigorously stirred in a solution of 2-butanone (20 mL) containing $NaHCO_3$ (3.7 g) and 18-crown-6 (0.3 g) in the dark at ambient temperature, while a solution of Oxone™ (7.40 g, 12.0 mmol) in 30–35 mL of distilled water was added dropwise during 10 min. Stirring was continued for 2 h after which water (100 mL) was added, and the phases were separated. The aqueous phase was extracted with 30 mL of ether, and the combined organic phase was washed with 2 × 25 mL of water. The organic solution was dried ($MgSO_4$), and the solvent was removed. Distillation of the residue in a molecular still with bath temperature 160–170°C/0.20 mm provided 1.26 g of product (80%). The methyl *cis*-9,10-epoxystearate so obtained was identical in all respects to a known sample. The crude product contained no methyl oleate (GLC). Oxidations of methyl linoleate and methyl linolenate were conducted using the same stoichiometric ratio of Oxone™ to alkene (2.4:1). The products were mobile liquids: TLC (30% ethyl acetate–hexane); epoxide of methyl oleate (R_f = 0.61); diepoxides of methyl linoleate (R_f = 0.49); triepoxides of methyl linolenate (R_f = 0.30). These materials aided in identifying peaks in chromatograms of methyl esters of epoxidized olive oil and tallow.

Similarly, methyl ricinoleate (1.57 g, 5.00 mmol) gave methyl 12-hydroxy-9,10-epoxystearate (1.42 g, 86%) after flash chromatography (20% ethyl acetate–hexane) that was >98% pure by GLC comparison with a sample pre-

pared from methyl ricinoleate with *m*-chloroperbenzoic acid in CH_2Cl_2.

Olive oil (1.45 g, *ca.* 5 mmol of alkene) was oxidized and the product oil recovered as above. The oleic acid had been consumed as judged by GLC of methyl esters formed by transesterification in methanol containing a trace of $NaOCH_3$ as well as by examination by GLC of the triglyceride content itself.

Tallow (0.72 g) was converted with the amounts of reagents listed above to an oil now devoid of its original unsaturated fatty acid content, namely, principally, 14:1, 16:1, 18:1 and 18:2 as judged by GLC analysis of the triglycerides and the related methyl esters.

RESULTS AND DISCUSSION

Oxidation of fatty acids. Acetone solutions of DMDO were prepared from Oxone^{TM}/$NaHCO_3$ as previously described (18) using the simplified procedure of Crandall *et al.* (19). These solutions were stored at –20°C and used within a few days. Treatment of fatty acids (C5 to C12) with these solutions at room temperature and in the dark for 16–24 h produced mixtures of ketoacids (oxoacids) that were assigned structures based on GLC analysis of methyl esters (CH_2N_2) (see Materials and Methods section). The principal products of these oxidations were the oxoacids; evidently the alcohols that were initially formed oxidized rapidly to the ketones. Typically, 9–12% yields of oxoacids are obtained by this procedure. The distribution of positional isomers was such that essentially no 2- or 3-oxoacids were observed, and the proportion of a particular position isomer gradually increased from C4 to n-1. For example, decanoic acid produced a mixture of oxodecanoic acids (Fig. 1 shows the methyl esters) in which the 9-oxodecanoic acid predominated. The proportions of isomers were: C4(9%), C5(13%), C6(16%), C7(17%), C8(18%) and C9(27%). The 4- and 5-oxodecanoic acids were obtained by methods outlined in Scheme 2 [oxidations of decanoic acid, and γ- and δ-decanolactones with dimethyldioxirane in acetone: (1) DMDO/acetone; (2) CH_2N_2; (3) NaOH, MeOH; (4) pyridinium chlorochromate; and (5) BF_3-MeOH] from commercially available lactones, and gas chromatography/mass spectrometry (GC/MS) data were consistent with assignments as methyl oxodecanoates. Additionally, DMDO/acetone treatment of these lactones also produced the corresponding oxoacids though the yields were variable and sometimes quite low (>5%). Results with the other fatty acids were similar, namely a relatively low conversion occurred corresponding to the consumption of about 20% of the oxidizing agent with the generation of several positional isomers. The nature of the hydrogen abstraction process is probably a concerted insertion of oxygen into a C–H bond rather than one involving the intermediacy of a discrete free radical (17). Nevertheless, some similarity exists between dioxirane oxidations of hydrocarbons (17), our results with fatty acids and radical chlorinations of hydrocarbons (21) in that the reactions have electrophilic character. Thus, the functionalization

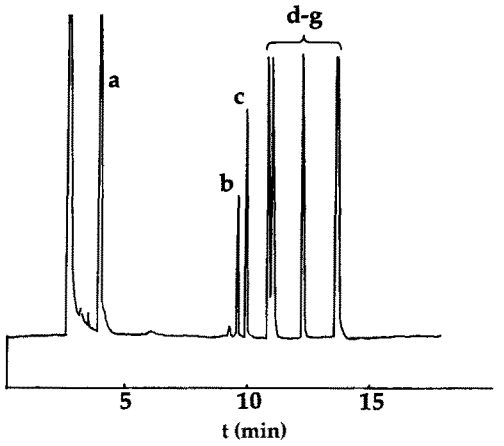
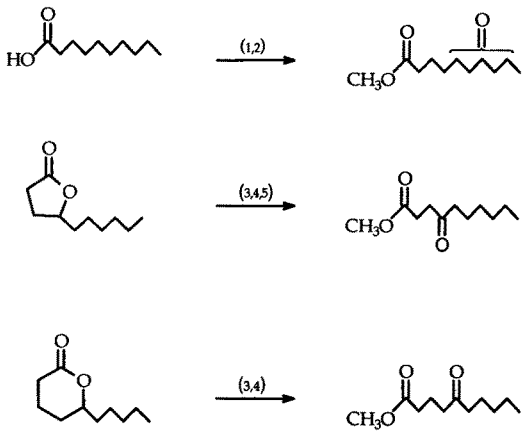


FIG. 1. Gas–liquid chromatography of methyl esters of the oxoacids formed by treating decanoic acid with dimethyldioxirane/acetone using a Supelcowax column (0.25 mm i.d. × 30 m; Supelco, Bellefonte, PA) at 170°C: (a) methyl deeanoate; (b) 4-oxoester; (c) 5-oxoester; and (d–g) 6–9 oxoesters.



SCHEME 2

tends to occur away from the electrophilic centers of the molecule attacked. Unfortunately, in the case of fatty acids, that effect is not sufficiently dramatic to produce a highly skewed distribution of oxoacids. Since methyl octanoate gave almost identical results to those of octanoic acid, it appears that the carboxyl group has no particular adverse effect upon the oxidation. The low yields we observed in the oxidations of fatty acids (and of the lactones) probably reflect autodecomposition of the DMDO (16) which competes successfully with the relatively high energy requirements for C–H insertion in a chain of undifferentiated methylene groups. We should point out that the dioxirane obtained from 1,1,1-trifluoroacetone is much more reactive in C–H insertion reactions (22), but this ketone is very much more expensive.

Diacids of chainlength C6 to C12 were exposed to DMDO/acetone as was dimethyl azelate with the hope that the effect of two electrophilic groups would concentrate the sites of oxidation to the center of the chain. No products of oxidation were observed, however.

Dioxiranes have also been prepared and used directly under biphasic conditions using phase transfer catalysts, such as 18-crown-6 and tetrabutylammonium bisulfate (20). Accordingly, DMDO was generated from Oxone™ in a mixture of phosphate buffer at pH 7.4 containing 18-crown-6 and methylene chloride containing methyl octanoate. However, only trace amounts of oxoesters were formed by this procedure.

Epoxidation of unsaturated fatty acids. In sharp contrast to the slow oxidation of methylene groups, the oxidation of methyl oleate to the corresponding *cis*-epoxide occurred cleanly and completely at 25°C within 0.5 h with DMDO/acetone. A procedure that used the DMDO directly in a biphasic mixture, however, seemed more attractive for synthetic purposes. Reactions were conducted varying the amount of Oxone™, nature of co-solvent and reaction time. In addition, agitation of the mixture was also important. Complete conversion of methyl oleate to its epoxide was obtained for DMDO with a 10:1 molar ratio of Oxone™ to alkene in benzene or 25:1 in CH_2Cl_2. A better preparation used 2-butanone as both the ketone component and the solvent. Complete reaction occurred presumably *via* methyl ethyldioxirane (MEDO) within 1 h with a ratio of Oxone™ to alkene of 2.5:1. Because the procedures are simple and the conditions are not likely to jeopardize groups that are sensitive to acids and bases, MEDO may prove useful as a general epoxidizing agent for unsaturated fatty acids and their derivatives, including those fatty acids with methylene-interrupted unsaturation. Methyl linoleate produced a mixture containing 10% monoepoxides and a 64:36 ratio of diastereomeric diepoxides when treated with the same (2.4:1) stoichiometric ratio of oxidant to double bond. The oxidation of methyl linolenate gave mono- (8%), di-(16%) and triepoxides (76%). These preparations gave excellent material recovery and showed little polymeric materials (TLC). No effort was made to obtain optimal conditions for these conversions; currently more detailed studies are being performed on natural triglycerides that are higher in polyunsaturated fatty acid (PUFA) content.

Ricinoleic acid, (R)-12-hydroxy-Z-9-octadecenoic acid, is a commercially important fatty acid having both a hydroxyl group and unsaturation. An epoxide of this acid provides additional chemical potential to the material. Moreover, the nature of the epoxidation process could be altered by the presence of a proximate hydroxyl group resulting in a stereo-bias for the product epoxyalcohol. The possibility of generating two new stereocenters in response to an existing one (the hydroxyl-bearing carbon) is most intriguing, since it would provide access to a versatile chemical structure with useful chirality for much more highly valued end products.

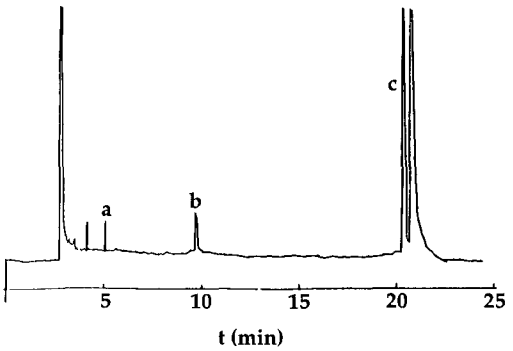


FIG. 2. Gas–liquid chromatography of oxidation product of methyl ricinoleate with methyl ethyldioxirane at 5°C; column as in Figure 1 (260°C): (a) corresponding ketone, (b) methyl ricinoleate; and (c) diastereomeric epoxides.

The reaction of DMDO/acetone solutions with methyl ricinoleate were not encouraging. A ketone that was apparently doubly unsaturated ($[M]^+ = 308$, $[M - 31]^+ = 177$), (not identical to the product of oxidation of the alcohol group of methyl ricinoleate) as well as the expected epoxyketone ($[M]^+ = 326$, $[M - 31]^+ = 295$) were produced (*ca.* 1:2) with no epoxyalcohol in the product mixture. The indication was that the alcohol group oxidized faster than oxygen was transferred to the alkene double bond and that the resulting β,γ-unsaturated ketone was subject to desaturative oxidation in addition to epoxidation. The competition between epoxidation of an alkene and oxidation of an alcohol has been described in the case of allylic alcohols (23); ketone formation was suppressed by acetylating the alcohol. The biphasic reactions (acetone–benzene, or a ketone as the solvent), however, did indeed produce the diastereomeric epoxyalcohols (Fig. 2). The percent conversions and product ratios are given in Table 1. The best conversion to epoxyalcohol was with methyl ethyl ketone though the diastereomer ratio was not >2: 1 in any instance. Increasing the steric bulk around the dioxirane by altering ketone structure generally reduced oxidative conver-

TABLE 1
Products of Oxidation of Methyl Ricinoleate Under Biphasic Conditions with Several Dioxiranes

Ketone[a]	Methyl ricinoleate	Corresponding ketone	Epoxyalcohol[b]	Epoxyketone
Acetone[c]	3.0	2.9	79(43:57)	18
2-Butanone	2.6	0.7	93(45:55)[d]	4.1
4-Methyl-2-pentanone	98	0.4	1.5(.33:67)	0
Cyclohexanone	51	0	49(41:59)	0

[a]The following ketones produced no oxidized materials: 3-pentanone, cyclopentanone, 2,4-dimethyl-3-pentanone, 2-ethylcyclohexanone, acetophenone.
[b]Ratio of diastereomers.
[c]Benzene used as the organic solvent.
[d]Reaction at 5°C gave a ratio of 42:58, and essentially no epoxylketone.

sion of the methyl ricinoleate. A number of ketones gave no products of oxidation at all (see Table 1). Since some of the dioxiranes formed from these ketones have in fact been described (23), the tentative conclusion is that these dioxiranes are more disposed to radical fragmentation (16).

Epoxidation of natural triglycerides. Because epoxidation of unsaturated fatty acids is synthetically useful, we briefly examined the epoxidations of olive oil and tallow. The crude products were clear, colorless oils. The GLC of the methyl esters (Figs. 3 and 4) indicated that the major unsaturated fatty acid, oleic acid, had been consumed. The epoxides of palmitoleic and oleic acids appeared in the products. A more thorough investigation of triglyceride epoxidation is planned.

In summary, Oxone™ is an inexpensive oxidant that is easily handled and with demonstrated utility in synthetic organic chemistry. Reaction with C–H bonds presumably generated alcohols that were then further oxidized to ketones, thus converting fatty acids/esters into ketoacids/esters, albeit in low yields. Lactones of hydroxyfatty acids were oxidized to the corresponding ketoacids by DMDO in acetone. Epoxidations of unsaturated fatty acid esters are best accomplished using Curci *et al.'s* (20) biphasic method employing 2-butanone as the solvent (MEDO as the oxidant). This procedure also converted methyl ricinoleate, a homoallylic hydroxyfatty acid ester, to the epoxyalcohol while DMDO/acetone gave only ketone and ketoepoxide as products. Oxone–dioxirane chemistry may be useful in the fats and oils industries.

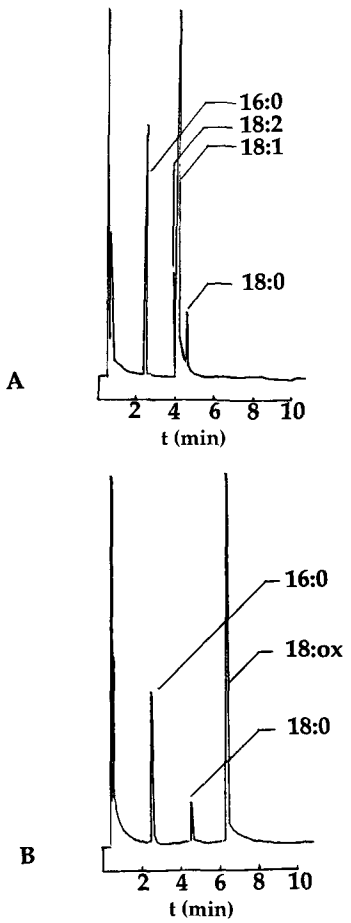


FIG. 3. Gas–liquid chromatography of (A) methyl esters of olive oil, and (B) methyl esters of methyl ethyldioxirane-oxidized olive oil using a DB-HT1 column (0.32 mm × 15 m) programmed from 130 to 180°C at 5°C/min.

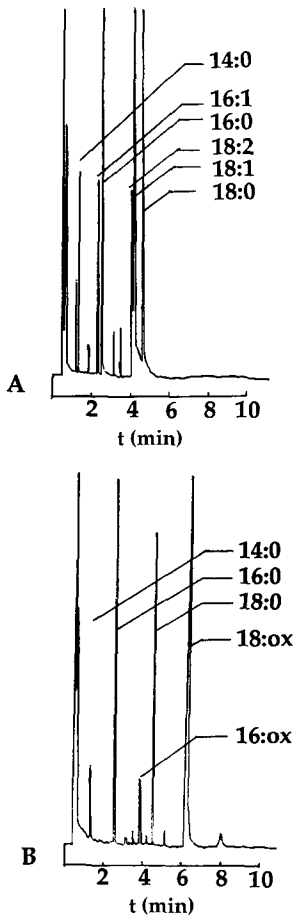


FIG. 4. Gas–liquid chromatography of (A) methyl esters of tallow, and (B) methyl esters of methyl ethyldioxirane-oxidized tallow with column and conditions as noted in Figure 3.

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