Organoselenium-Mediated Cyclization of Hydroxyolefinic Fatty Acids and m-CPBA Oxidation of Selenium-Containing 1,4-Epoxy Acids

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Chlorophenylselenenylation methodology is shown to cause cyclization of naturally occurring β- and γ-hydroxyolefinic acids. The phenylseleno-substituted 1,4-epoxides (tetrahydrofurans) thus obtained are oxidized by m-chloroperbenzoic acid (m-CPBA). Reaction of phenylselenenyl chloride with methyl 12-hydroxyoctadec-*cis*-9-enoate (methyl ricinoleate) gave methyl 9,12-epoxy-10-phenylselenenyloctadecanoate in useful yields. A similar reaction of phenylselenenyl chloride with methyl 9-hydroxyoctadec-*cis*-12-enoate afforded a quantitative yield of methyl 9,12-epoxy-13-phenylselenenyloctadecanoate. Oxidation of selenium-containing 1,4-epoxy esters by m-chloroperbenzoic acid (1 equivalent) yielded the respective olefinic 1,4-epoxy esters, while 5 equivalent m-CPBA afforded the corresponding oxirane esters of epoxytetrahydrofurans in high yields. The structure of the individual reaction products have been established from analytical and spectral data and corroborated by a study of their mass spectra.

KEY WORDS: Methyl ricinoleate, methyl isoricinoleate, oxirane 1,4-epoxide, phenylselenenyl chloride and 1,4-epoxides.

Fatty acid epoxides have been isolated from natural sources (1), and a number of methods for their synthesis are available. Recently, intramolecular cyclization of appropriate hydroxyolefinic fatty acids using halogens and pseudohalogens has been considered an important route for the preparation of 1,4-epoxide (tetrahydrofurans) derivatives of fatty acids (2–4). These ethers are valuable intermediates for the synthesis of naturally occurring biologically active substances (5). Increasing interest in the chemistry of oxirane and 1,4-epoxy fatty acids prompted the need for the synthesis of a system containing both oxirane and 1,4-epoxide groupings in the fatty acid chain.

Organoselenium-mediated cyclization of a wider range of internal nucleophiles has received considerable attention in the literature (6). Selenium containing compounds are reported as antifungal and antibacterial agents (7,8). The *syn*-elimination of selenoxide constitutes a mild procedure for introduction of unsaturation. For this study we have chosen phenylselenenyl chloride; a versatile, mild and easy reagent to remove, for the cyclization of methyl ricinoleate (I) and methyl isoricinoleate (II). We made another choice of m-chloroperbenzoic acid (m-CPBA) for the oxidation of selenium containing cyclic acids. The reagent m-CPBA, when used in equimolar quantity, was found to oxidize the alkyl selenides (III, VI) to selenoxide, leading to the expected olefinic cyclic acids (VII, IX). However, an excess of m-CPBA (5 equivalent) reacted further with alkylselenides, giving the corresponding oxirane tetrahydrofuran (bicyclic) acids (VIII, X).

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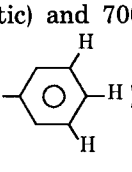
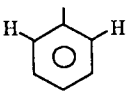
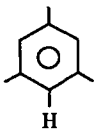
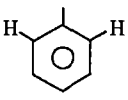
EXPERIMENTAL PROCEDURES

The homogeneity of the products were checked by TLC on silica gel plates. Infrared (IR) spectra were recorded as thin films or nujol mulls on a Pye Unicam SP-3-100 spectrophotometer (Pye Unicam, Cambridge, U.K.). Nuclear magnetic resonance (NMR) spectra was obtained with a Varian A60 spectrophotometer (Varian Associates, Palo Alto, CA). Chemical shifts were reported in relation to tetramethylsilane (TMS) in δ (ppm). The samples were run as 10% solution in $CDCl_3$. The abbreviations s, m, t and br stand for singlet, multiplet, triplet and broad, respectively. Mass spectra (MS) were measured on a JEOL JMS-D 300 instrument at 70 eV. In the MS study, only the structures justifying fragments have been included. The values quoted in brackets refer to the intensity of the fragment relative to the base peak (100). Compound (I) and (II) are isolated by Gunstone's procedure (9).

*Reaction of methyl 12-hydroxy-*cis*-9-octadecenoate (I) with PhSeCl.* Methyl 12-hydroxy-cis-9-octadecenoate (I, 1.56 g, 0.005 mol) was dissolved in dry acetonitrile (50 mL) and a solution of phenylselenenyl chloride (0.95 g, 0.005 mol) in 50 mL acetonitrile was added. After 30 min of stirring at room temperature, the reaction mixture was extracted with diethyl ether. The ethereal extract was washed with water and dried (anhydrous Na_2SO_4). The solvent was removed under reduced pressure to give a light yellow oil which showed three distinct spots on TLC. One product at a higher R_f, and other two at a lower R_f than the starting material were observed on a TLC plate. The oily mixture of products was chromatographed on a column of silica gel and eluted with petroleum ether/diethyl ether containing increasing amounts of diethyl ether as moving phase. Eluted material was monitored by TLC. Elution with petroleum ether/diethyl ether (96:4, v/v) gave III, (1.05 g, 45%) as a viscous oil. Analysis (Found: C, 64.2; H, 8.3%; Calcd. for $C_{25}H_{40}O_3Se$: C, 64.24; H, 8.57%).

Further elution with petroleum ether/diethyl ether (90:10, v/v) gave a viscous oil, IV, (0.55 g, 22%). Analysis (Found: C, 59.5; H, 8.2%; Calcd. for $C_{25}H_{41}O_3ClSe$: C, 59.58; H, 8.14%). IR(Neat) : 3300 (-OH), 1730 ($\underline{CO}OCH_3$), 1580, 1165, 1010, 740 (aromatic) and 700 cm^{-1} (C-Cl). NMR ($CDCl_3$) : δ 7.55 m (3H, ), 7.25 m (2H, ), 4.1 m (1H, $-C\underline{H}-$ Cl), 3.55 m 3.55 m (1H $-C\underline{H}-$ OH, merged in part to the ester signal), 3.6 s(3H, $COOC\underline{H}_3$), 3.1 m(1H, $C\underline{H}$-SePh), 2.42 br s(1H,

-CH-, D_2O exchangeable), 2.25 m(2H, C_{11} methylene
|
OH
protons), 1.25 br s (chain $-C\underline{H}_2-$) and 0.90 t (terminal $-C\underline{H}_3$).

The last product (V) was obtained by eluting with petroleum ether/diethyl ether (80:20, v/v) as a semisolid (0.25 g, 10%). Analysis (Found: C, 61.6; H, 8.8%; Calcd. for $C_{25}H_{42}O_4Se$: C, 61.83; H, 8.72%). IR (Neat) : 3300 (OH), 1735 ($C\underline{O}OCH_3$), 1578 (aromatic ring) and 1020 cm^{-1} (C-O str.). NMR ($CDCl_3$): δ 7.5 m (3H, H  H), 7.2 m(2H, ), 3.95 br m(1H, -C<u>H</u>-CH-), 3.15 br m(1H, -C<u>H</u>-), 3.7 s (3H, $COOC\underline{H}_3$), 3.6 m(1H, -C<u>H</u>-), methine proton, merged in part to the ester signal), 2.45 br s [2xCH-(O<u>H</u>)-, exchanged with D_2O], 2.25 m(2H, C_{11} methylene protons), 1.35 br s(chain-$C\underline{H}_2$-) and 0.90 t (terminal $-C\underline{H}_3$).

*Reaction of methyl 9-hydroxyoctadec-*cis*-12-enoate (II) with PhSeCl.* Methyl 9-hydroxyoctadec-*cis*-12-enoate (II, 1.56 g, 0.005 mol) was dissolved in dry acetonitrile (50 mL) and added to it a solution of PhSeCl (0.95 g, 0.005 mol) in 10 mL of CH_3CN. After 30 min of stirring, the product was extracted with diethyl ether. Removal of the solvent gave a light yellow oil. The compound gave a distinct spot at a higher R_f value than the substrate. The column chromatographic purification of reaction mixture on silica gel yielded only one product (VI), (2.29 g, 98%) as an oil. Analysis (Found: C, 63.6; H, 8.3% Calcd. for $C_{25}H_{40}O_3Se$: C, 64.24; H, 8.59%).

Reaction of methyl 9,12-epoxy-10-phenylselenenyloctadecanoate (III) with m-CPBA (1 equivalent). To a cooled (10°C) solution of methyl 9,12-epoxy-10-phenylselenenyloctadecanoate (III, 0.467 g, 0.001 mol) in CH_2Cl_2 (30 mL), m-CPBA (0.172 g, 0.001 mol) was added in small portions during 30 min, and the stirring was continued for another half hour. Reaction mixture was extracted with CH_2Cl_2 and shaken with a 10% solution of sodium bisulfite (15 mL) to destroy excess of m-CPBA. The organic layer was then shaken with 5% aqueous sodium bicarbonate, washed with water and dried (anhydrous Na_2SO_4). An oily reaction mixture was obtained which, on column chromatography using petroleum ether/diethyl ether (95:5, v/v), produced a product (VII) (0.303 g, 98%) as a viscous oil. Analysis (Found: C, 74.0; H, 11.0%; Calcd. for $C_{19}H_{34}O_3$: C, 73.50, H, 11.03%). Reaction with two equivalents of m-CPBA gave the same product, VII.

Reaction of methyl 9,12-epoxy-10-phenylselenenyloctadecanoate (III) with m-CPBA (5 equivalent). Reaction of III (0.467 g, 0.001 mol) with m-CPBA (0.860 g, 0.005 mol) was carried out for 30 min in dichloromethane. The reaction conditions were the same as detailed earlier. The analytical TLC plate showed a single spot at lower R_f value than the substrate. Silica gel column chromatographic purification using petroleum ether/diethyl ether (90:10, v/v) gave VIII (0.317 g, 97.5%). Analysis (Found: C, 70.0; H, 10.5%; Calcd. for $C_{19}H_{34}O_4$: C, 69.9; H, 10.49%).

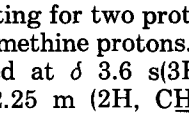
Methyl 9,12-epoxyoctadec-10-enoate (VII, 0.467 g, 0.001 mol) and m-CPBA (0.258 g, 0.0015 mol) in dichloromethane (30 mL) were allowed to react for 30 min. Completion of the reaction was evidenced by TLC. Final work up and purification by silica gel column chromatography afforded the product VIII (0.317 g, 97.5%) as a liquid.

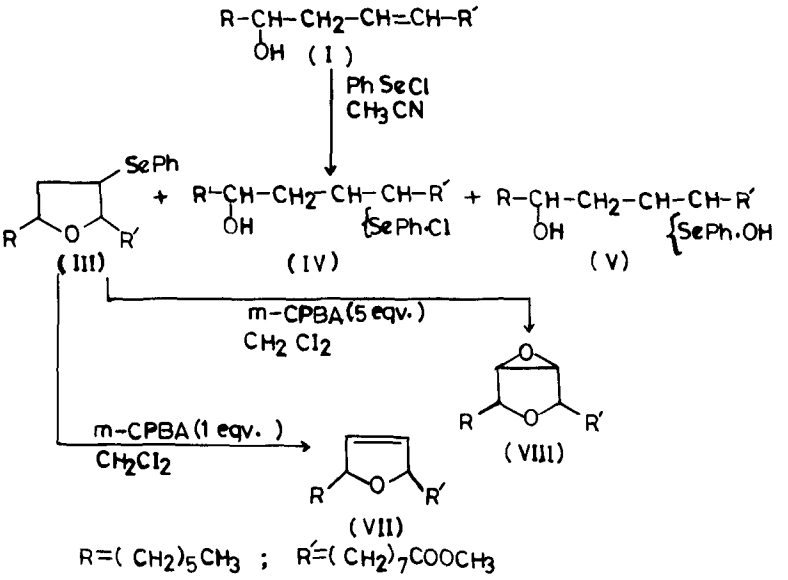
Reaction of methyl 9,12-epoxy-13-phenylselenenyloctadecanoate (VI) with m-CPBA (1 equivalent). Methyl 9,12-epoxy-13-phenylselenenyloctadecanoate (VI, 0.467 g, 0.001 mol) was added to CH_2Cl_2 (30 mL) and cooled (10°C) in ice bath. m-CPBA (0.172 g, 0.001 mol) was added to this ice-cooled stirred solution in portions over a 30-min period. Stirring was continued for another 30 min. A product of higher R_f value than the starting material was purified by silica gel column chromatography into IX (0.30 g, 98%) using petroleum ether/diethyl ether (95:5, v/v) as an eluant. Analysis (Found: C, 77.57; H, 11.0%; Calcd. for $C_{19}H_{34}O_3$: C, 77.50; H, 11.03%). The same results were obtained when 2 equivalents of m-CPBA were used.

Reaction of methyl 9,12-epoxy-13-phenylselenenyloctadecanoate (VI) with m-CPBA (5 equivalent). A reaction of methyl 9,12-epoxy-13-phenylselenenyloctadecanoate (VI, 0.476 g, 0.001 mol) and m-CPBA (0.860 g, 0.005 mol) was carried out under similar conditions as described for III. The reaction mixture on usual work up and its purification on silica gel with petroleum ether/diethyl ether (90:10, v/v) gave (0.317 g, 97.5%) as an oil (X). Analysis (Found: C, 70.0; H, 10.3%; Calcd. for $C_{19}H_{34}O_4$: C, 69.9; H, 10.5%).

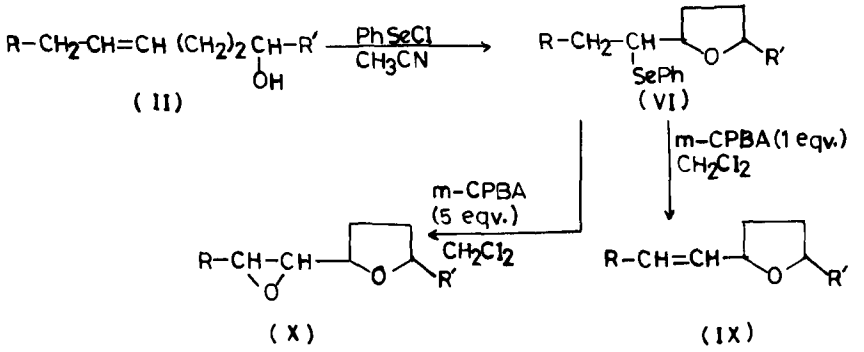
RESULTS AND DISCUSSION

This research is based on the phenylselenenyl chloride mediated cyclization of methyl 12-hydroxy-*cis*-9-octadecenoate (I) and methyl 9-hydroxy-*cis*-12-octadecenoate (II) and subsequent oxidation of phenylselenenyl substituted cyclic fatty compounds (III, VI). Complete conversion of substrates to products in both reactions occurred within 30 min (TLC analysis). Chromatographic behavior of the major product (III; Scheme 1) and only product (VI, Scheme 2), namely, higher R_f values than the substrates, indicated that the intramolecular cyclization through neighboring group participation had occurred as determined earlier (10,11).

The elemental analysis of the product (III) corresponded to $C_{25}H_{40}O_3Se$. The evidence in favor of a five-membered oxygen containing cyclic ring was initially derived from diagnostic IR bands at 1160 (1,4 epoxide) (12), 1070 and 1020 cm^{-1} (C-O). Monosubstituted benzene was evident from a band at 1575 cm^{-1}. The NMR spectrum of III provided further proof by showing signals at δ 7.5 m(3H) and 7.2 m(2H) for aromatic protons, a multiplet at δ 3.7 integrating for two protons assignable to C_9 and C_{12} furan ring methine protons. Other diagnostic signals were observed at δ 3.6 s(3H, $COOC\underline{H}_3$), 3.0 m(1H, -C<u>H</u>-SePh), 2.25 m (2H, $C\underline{H}_2$ α to the ester carbonyl), 1.85 (2H, ), 1.35 br s (chain



SCHEME 1



SCHEME 2

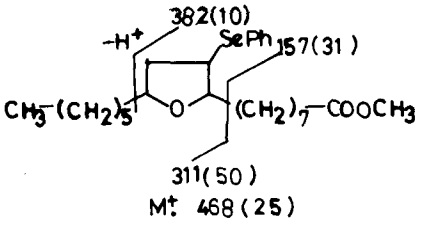


FIG. 1. MS fragmentation of III.

-C$\underline{H}_2$) and 0.9 t (terminal CH_3). The mass spectrum further confirmed the cyclic nature of III (Fig. 1).

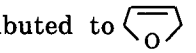
The molecular ion peak was present, *m/z* 468. An intense peak due to the loss of ester side chain from the molecular ion at 311 was present, therefore confirming the presence of phenylseleno group in the molecule. These spectral values are consistent with the structure (III) as methyl 9,12-epoxy-10-phenylselenenyloctadecanoate.

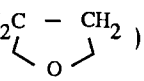
The compound (VI) was also analyzed for $C_{25}H_{40}O_3Se$ and its IR spectrum illustrated all the characteristic features of a 1,4-epoxide moiety and a monosubstituted benzene. The NMR spectrum showed signals at δ 7.5 m (3H) and 7.15 m(2H) for the benzene ring, 3.95 m(2H) for C_9, C_{12} methine protons of the oxygenated ring and one proton (broad multiplet) at 3.12 for C_{13} methine proton, α to a phenylseleno function. Another important peak at 1.85 m (4H) for C_{10}, C_{11} methylene protons was observed. The structure assigned from these data was methyl 9,12-epoxy-13-phenylselenenyloctadecanoate (VI).

Structures of two other isomeric products, formed in the reaction of I with phenylselenenyl chloride, were established as methyl 12-hydroxy-10(9)-chloro-9(10)-phenylselenenyloctadecanoate (IV) and methyl 12-hydroxy-10(9)-hydroxy-9(10)-phenylselenenyloctadecanoate (V) on the basis of their elemental and spectral values. The current understanding of this reaction's mechanism permits us to assign the *threo*-configuration (13-16). Spectral details are given in the experimental portion.

It has been established that oxidation of alkylphenylselenides to selenoxides with several oxidizing agents (17–19) results in selenoxide elimination leading to olefins. Phenylselenenyl-substituted cyclic fatty acids (III, VI) were treated with m-chloroperbenzoic acid (m-CPBA). The oxidation of III and VI with m-CPBA was affected with two stoichiometrics, i.e., 1 mole equivalent and 5 mole equivalent. The oxidation of III and VI with 1 mole equivalent produced the desired olefins, methyl 9,12-epoxyoctadec-10-enoate (VII) and methyl 9,12-epoxyoctadec-*trans*-13-enoate (IX), respectively. Similar reaction of III and VI, with 5 mole equivalent of m-CPBA produced epoxides, a methyl 9,12; 10,11-diepoxyoctadecanoate (VIII) and methyl 9,12; 13,14-diepoxyoctadecanoate (X), respectively.

However, pure products (VII and IX) reacted with only 1 mole m-CPBA to yield oxirane epoxides (VIII and X). Excess reagent (3 equivalent) in the reaction of III and VI with m-CPBA leads to the production of selenic acid (19). This oxidation takes place preferentially before the epoxidation of olefinic compounds, hence consumption of the excess reagent. The acid, being water soluble, is easily removed during work up.

The elemental analysis of VII corresponded to the formula $C_{19}H_{34}O_3$. The IR spectrum did not show any band in the region of 1578–1600 cm^{-1} for monosubstituted benzene and >C=C< function; but a diagnostic band at 1175 cm^{-1} was observed and attributed to  grouping. Its NMR exhibited a triplet at δ 5.67 integrating for two ethylenic protons, one each at C_{10} and C_{11}. A broad multiplet for two methine protons at δ 4.65 underneath the ester signal was attributed to 1,4-epoxide ring protons. MS (Fig. 2) further confirmed the previous findings. Molecular ion at *m/z* 310 was consistent with the molecular weight. Characteristic α-cleavage provided three mass ions at 239, 225 and 153.

The olefin (IX) analyzed for $C_{19}H_{34}O_3$. The IR spectrum exhibited characteristic bands similar to the other olefin (VII) in addition to a medium intensity band at 950 and a weak band at 1640 cm^{-1} assigned to the presence of *trans*-double bond and C=C stretching. The NMR spectrum displayed two multiplets ranging from δ 5.5–5.7 for two vinylic protons. It is obvious that both signals are, in part, merged with each other. The significant absorption was present at δ 4.1–4.3 (broad multiplet) integrating for the two C_9 and C_{12}-methine protons of the 1,4-epoxide ring. An equally significant multiplet at δ 2.0 for 1,4-epoxide ring methylene protons (4H, ) and C_{15} methylene protons α to the carbon-carbon double bond partly merged with the chain methylene protons.

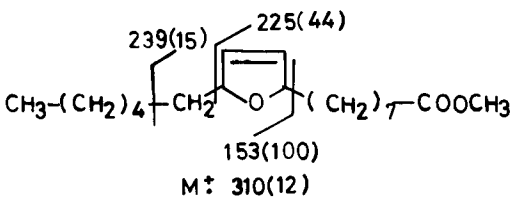
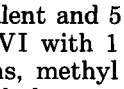
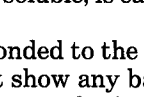
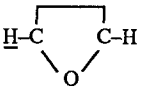
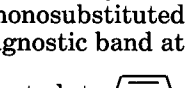


FIG. 2. MS fragmentation of VII.

The molecular ion (Fig. 3) was at *m/z* 310. Two significant mass ions present at *m/z* 267 and 253 arose from α- and β-cleavage.

The microanalysis of diepoxide (VIII) corresponded to the formula $C_{19}H_{34}O_4$. A positive picric acid TLC test (20) and the presence of IR bands at 1075 and 870 cm^{-1} for  indicated the presence of two different types of epoxy groups. The NMR spectrum had two characteristic broad multiplets, one for two methine protons (C_{10}, C_{11} epoxide ring) at δ 2.3–2.7 and the other for two C_9, C_{12} epoxide ring methine protons at δ 3.6–4.2. MS (Fig. 4) had the molecular ion at *m/z* 326. Two diagnostic mass ions present at *m/z* 241 and 169 substantiated the position and nature of the ring.

The other diepoxide (X) was analyzed for $C_{19}H_{34}O_4$. A positive picric acid TLC test and two IR absorptions at 885 (*trans*-epoxide) (9) and 1160 cm^{-1} for 1,4-epoxide were observed in favor of the structure. The compound (X) has exhibited diagnostic NMR signals at δ 3.6–4.1 m (2H, ), 2.5–2.8 m(2H, ), 2.0 m(6H,  , C-15 methylene). MS (Fig. 5) had molecular

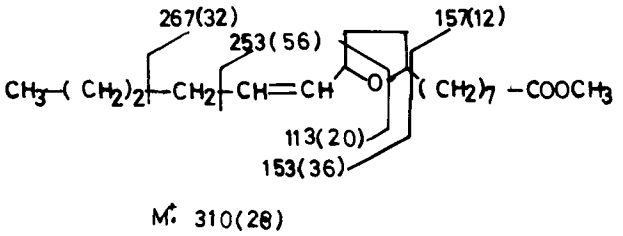


FIG. 3. MS fragmentation of IX.

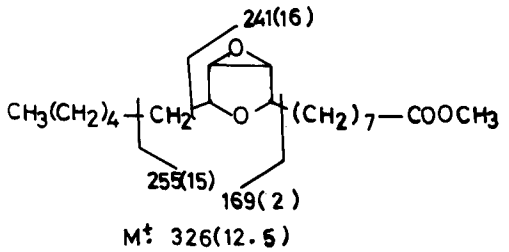


FIG. 4. MS fragmentation of VIII.

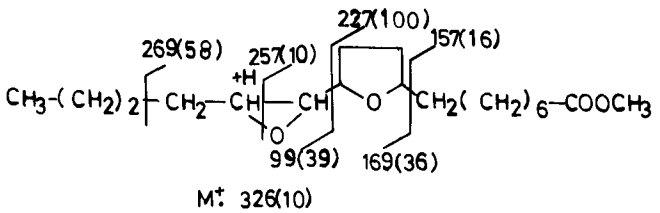


FIG. 5. MS fragmentation of X.

ion peak at *m/z* 326. Absence of an abundant ion at *m/z* 157 indicated that oxirane oxygen position is not at C_{12} and C_{13}, but the ion at *m/z* 269 proved it to be at C_{13} and C_{14}. Fragment at 269 has emerged from cleavage α to epoxide along with an ion at 257 arising from *trans*-annular fragmentation with concomitant hydrogen transfer.

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