Synthesis of Tetrahydrofuran Ring Containing Oligoethylene Glycol Ethers from the Seed Oil of *Vernonia anthelmintica*

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ABSTRACT: A tetrahydrofuran ring containing oligoethylene glycol ethers has been synthesized from the seed oil of *Vernonia anthelmintica*. The seed oil was reacted with mono-, di-, and triethylene glycols in the presence of boron trifluoride etherate, followed by saponification and esterification (MeOH/H$^+$). The oligoethylene glycol ethers thus obtained were epoxidized with perbenzoic acid. The 9,10-epoxy oligoethylene glycol ethers so formed were intramolecularly cyclized in dry benzene using boron trifluoride etherate as a catalyst to yield the tetrahydrofuran ring containing oligoethylene glycol ethers; methyl 9,12-epoxy,10-hydroxy-13-[2-hydroxyethyl-1-oxy]; methyl 9,12-epoxy,10-hydroxy-13-[5-hydroxy-3-oxapentyl-1-oxy] and methyl 9,12-epoxy,10-hydroxy-13-[8-hydroxy-3,6-dioxaoctyl-1-oxy]octadecanoates, respectively.

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KEY WORDS: Boron trifluoride etherate, ethylene glycols (mono-, di-, and tri-), methyl esters, polyethers, synthesis, 2,3,5-trisubstituted tetrahydrofurans, trivernolin, *Vernonia anthelmintica.*

Tetrahydrofuran is by far the most important of the reduced furans. The compound itself is a major solvent, and the nucleus that occurs in the ribose and deoxyribose sugar units is an integral part of the nucleic acids RNA and DNA. Tetrahydrofurans are widely distributed in nature and are key structural components of a variety of ionophores (1) and polyether antibiotics (2). The synthesis of reduced furans has been reviewed in detail (3). The electrophilic cyclization of γ,δ-unsaturated alcohols to tetrahydrofurans is a versatile method for the synthesis of these compounds and has been well utilized for the synthesis of similar compounds from γ,δ-hydroxy unsaturated fatty acids. Haloetherification with *N*-halosuccinimide is a good general high-yielding route to cyclic haloethers (4). Substituted tetrahydrofurans and tetrahydropyrans have also been formed previously in the reaction of threo- and erythro- isomers of methyl 9,10;12,13-diepoxy octadecanoate (5).

Vernonia anthelmintica is an annual herb. Air-dried seeds of the plant contain about 30% oil, whose major fatty acid is vernolic (*cis*-12,13-epoxy-*cis*-9-octadecenoic) acid (70–80%) (6). The high vernolic acid content makes it a viable starting material for making a number of industrial derivatives, such as oil-based paints, toughened epoxy resins, lubricants, adhesives, insect repellents (7), oligoethylene glycols (8), and 12-aminododecanoic and 11-aminoundecanoic acids (9).

In the present study we report that the vernoleic acid-based oligoethylene glycol ethers [1a–c] (8) undergo perbenzoic acid-mediated epoxidation to epoxides [2a–c], which on BF$_3$-etherate catalyzed intramolecular cyclization provide tetrahydrofuran derivatives [3a–c], as shown in Scheme 1. These derivatives may find applications as emulsifiers (10), etc.

EXPERIMENTAL PROCEDURES

Oligoethylene glycol ethers ([1a–c]; obtained as a mixture of positional isomers) were prepared by the previously reported method (8). BF$_3$-etherate was purchased from Fluka (Buchs, Switzerland) and was used without further purification. The benzene procured commercially was purified and dried over sodium metal. Perbenzoic acid was prepared from benzoylperoxide (11) purchased from CDH, Mumbai, India. Benzoylperoxide was recrystallized from $CHCl_3/CH_3OH$ (1:2, vol/vol) before use.

Thin-layer chromatography (TLC) was carried out on silica gel-G coated (0.25 mm thick) plates with petroleum ether/diethylether/acetic acid (80:20:1 or 60:40:1) as the mobile phase. Spots were visualized with iodine. Infrared (IR) spectra were recorded on a Shimadzu DR-8001 (Kyoto, Japan) Fourier transform infrared instrument. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra on a Bruker-AC 200 Fourier transform NMR spectrometer (Switzerland) in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra were recorded on a Shimadzu 2000 QP gas chromatograph–mass spectrophotometer.

Synthesis of epoxy oligoethylene glycol ethers [2a–c]. To the oligoethylene glycol ethers ([1a–c]; 5.0 g; 13.4, 11.7, and 10.8 mmol) was added a solution of perbenzoic acid (2.20 g, *ca.* 16.0 mmol) in 50 mL chloroform. The solution was kept at 0°C for 24 h in a freezer with occasional shaking during the first hour. After 24 h only a slight excess of the perbenzoic acid was left. The reaction mixture was stirred with 20 mL of a saturated solution of sodium carbonate to remove all

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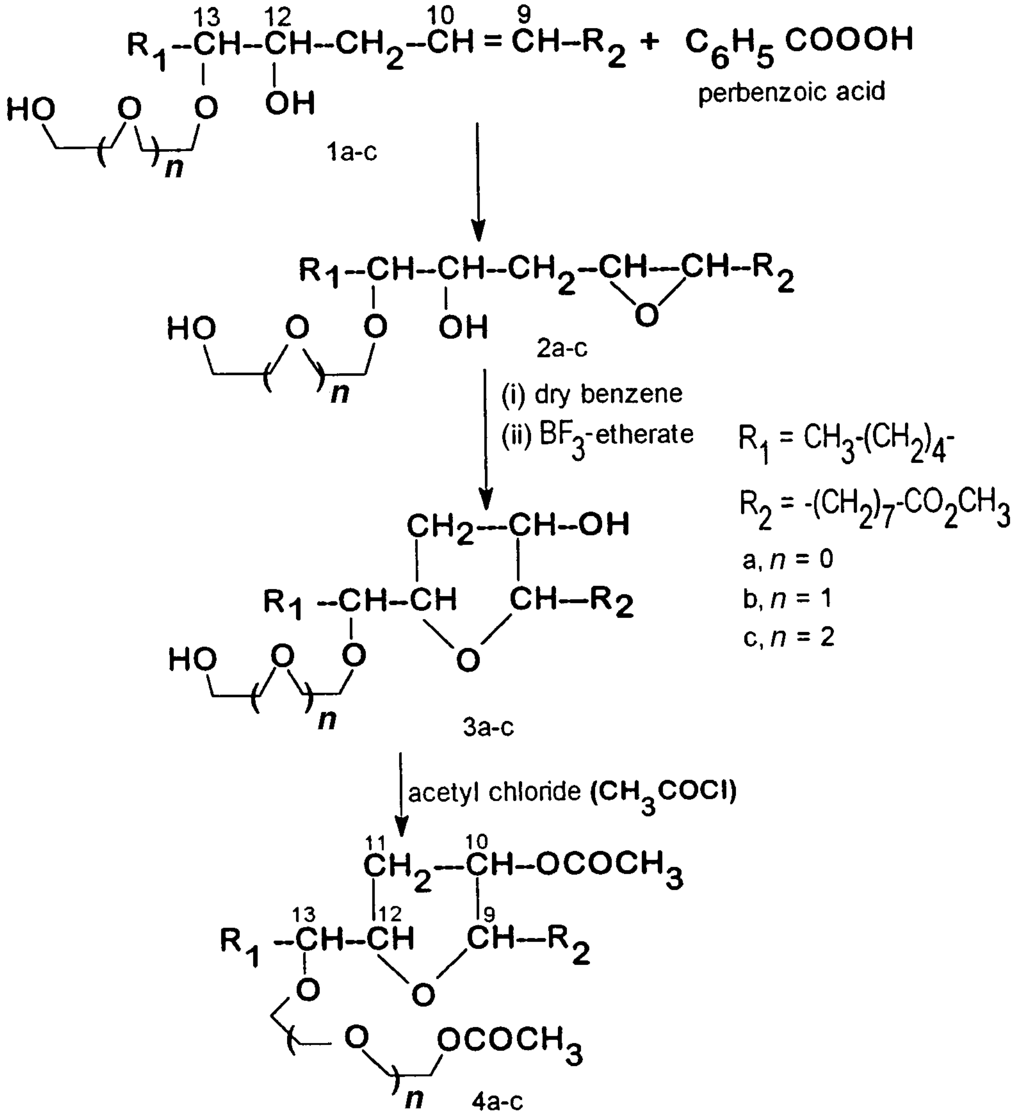

SCHEME 1

the benzoic acid, followed by washing with water and drying over anhydrous sodium sulfate. The chloroform was distilled off under reduced pressure on a water bath. The crude epoxide [2a–c] was used as such without any further purification for the intramolecular cyclization (Scheme 1).

Synthesis of tetrahydrofurans [3a–c]. The epoxidized glycol ethers [2a–c] (2.0 g) were refluxed in dry benzene (50 mL) using 0.5 mL BF_3-etherate as a catalyst (Scheme 1). The reaction was monitored by TLC and was completed in 1 h. The crude product was purified using silica gel column chromatography (using increasing amounts of diethyl ether in petroleum ether as eluent) to afford the tetrahydrofurans [3a–c] in more than 80% yield (as assessed from the TLC).

Acetylation of tetrahydrofurans [3a–c]. To 1.5 g of tetrahydrofurans ([3a–c]; 3.9, 3.7, 3.1 mmol, respectively) in 250 cc round-bottom flask was added 10 mL acetyl chloride. The reaction started instantaneously in cold (*ca.* 15°C). The reaction mixture was warmed on a water bath for 5 min followed by the distillation of excess acetyl chloride. To the reaction mixture was added 50 mL of water to destroy the remaining acetyl chloride. The acetylated product was extracted with chloroform, washed with 10% solution of sodium carbonate and water, and dried over anhydrous sodium sulfate. The chloroform was distilled to give the crude acetylated products [4a–c] in quantitative yields. The products were purified by silica gel column chromatography, using increasing amounts of diethyl ether in petroleum ether (40–60) as the mobile phase.

RESULTS AND DISCUSSION

The oligoethylene glycol ethers [1a–c], in addition to two hydroxyl groups, contain a double bond and a carboxylate functional group that can further undergo transformations to provide industrially useful products, including the heterocyclic crown ethers and the tetrahydrofurans. In the present study the olefinic double bond was converted into an epoxy ring by the action of perbenzoic acid (Scheme 1). The infrared spectra of these products [2a–c] gave strong stretchings at 1240 and 845 cm^{-1} for the C-O-C and C-C bonds of the epoxide ring. In the proton NMR of the epoxide no olefinic protons were observed, in addition, epoxide ring protons attached to C-9 and C-10 were observed at δ 2.8 as a multiplet (Table 1).

The epoxides [2a–c] on refluxing in dry benzene (50 mL) in the presence of BF_3-etherate (0.5 mL) for 1 h yielded the heterocyclic products [3a–c]. The infrared spectra (Table 1) of [3a–c] gave a strong absorption at 3450 cm^{-1} for the OH-stretching, while the carbonyl of the ester was observed at 1740 cm^{-1}. A strong C-O tetrahydrofuran ring stretching was observed at 1240 cm^{-1} along with a number of C-O stretchings at 1180, 1080, and 1030 cm^{-1}.

In the proton NMR of [3a–c], the protons attached to C-9 and C-12 (a part of the tetrahydrofuran ring) were observed at δ 3.8 as a multiplet (Table 1) while the protons attached to C-11 were observed at δ 1.6. The spectral data of these compounds were not sufficient to distinguish whether the product formed is a crown ether, a tetrahydrofuran ring containing polyether, or an open-chain tetrahydroxy compound, as these compounds show similar chemical shifts.

To establish the structure of the products [3a–c], these products were further reacted with acetyl chloride to yield the respective diacetates [4a–c]. The signal at 3500–3400 cm^{-1} was absent in the IR spectra of these products, indicating the absence of hydroxy group. The C-O, ring, and open-chain stretchings were observed at similar wavenumbers as in the case of [3a–c]. The ^{1}H NMR spectra of these compounds clearly established that the product formed is a tetrahydrofu-

TABLE 1
IR and ^{1}H NMR Spectral Features of the Products

Prod. no.	Yield (%)	Molecular formula	IR (cm^{-1}) neat	^{1}H NMR (δ ppm) $CDCl_3$
2a	>90	$C_{21}H_{40}O_6$	3450 (OH, str); 1740 (C=O, ester str); 1240, 845 (C-O-C, epoxide str); 1180, 1080, 1030 (C-O, str)	3.6–3.4 (*m* , 9H,$C\underline{H}_2O$ + $C\underline{H}_2OH$ + $C\underline{H}O$ + $C\underline{H}OH$ + CO_2CH_3); 2.8 (*m*, 2H, 2 × $C\underline{H}$-O ring); 2.2 (*t*, 2H, $C\underline{H}_2$-CO_2); 1.6 (*m*, 2H, $C\underline{H}_2$-CH_2-CO_2); 1.3 (*br.s*, 18H, -$C\underline{H}_2$- chain); 0.9 (*dt*, 3H, terminal $C\underline{H}_3$)
2b	>90	$C_{23}H_{44}O_7$	3450 (OH, str); 1740 (C=O, ester str); 1240, 845 (C-O-C, epoxide str); 1180, 1080, 1030 (C-O, str)	3.6–3.4 (*m*, 13H, 3 × $C\underline{H}_2O$ + $C\underline{H}_2OH$ + $C\underline{H}O$ + $C\underline{H}OH$ + $CO_2C\underline{H}_3$); 2.8 (*m*, 2H, 2 × $C\underline{H}O$ ring); 2.2 (*t*, 2H, $C\underline{H}_2$-CO_2); 1.6 (*m*, 2H, $C\underline{H}_2$-$C\underline{H}_2$-CO_2); 1.3 (*br.s*, 18H, -$C\underline{H}_2$- chain); 0.9 (*dt*, 3H, terminal $C\underline{H}_3$)
2c	>90	$C_{25}H_{48}O_8$	3450 (OH, str); 1740 (C=O, ester str); 1240, 845 (C-O-C, epoxide str); 1180, 1080, 1030 (C-O, str)	3.6–3.4 (*m*, 17H, 5 × $C\underline{H}_2O$ + $C\underline{H}_2OH$ + $C\underline{H}O$ + $C\underline{H}OH$ + $CO_2C\underline{H}_3$); 2.8 (*m*, 2H, 2 × $C\underline{H}O$ ring); 2.2 (*t*, 2H, $C\underline{H}_2$-CO_2); 1.6 (*m*, 2H, $C\underline{H}_2$-CH_2-CO_2); 1.3 (*br.s*, 18H, -$C\underline{H}_2$- chain); 0.9 (*dt*, 3H, terminal $C\underline{H}_3$)
3a	>80	$C_{21}H_{40}O_6$	3500 (OH, str); 1740 (C=O, ester str), 1240 (C-O ring str), 1180, 1080, 1030 (C-O, str)	3.8 (*m*, 2H, 2 × $C\underline{H}O$ ring); 3.6–3.4 (*m*, 9H, $C\underline{H}_2O$ + $C\underline{H}_2OH$ + $C\underline{H}O$ + $C\underline{H}OH$ + $CO_2C\underline{H}_3$); 2.2 (*t*, 2H, $C\underline{H}_2$-CO_2); 1.6 (*m*, 4H, $C\underline{H}_2$-CH_2-CO_2 + $C\underline{H}_2$ ring); 1.3 (*br.s*, 18H, -$C\underline{H}_2$- chain); 0.9 (*dt*, 3H, terminal $C\underline{H}_3$)
3b	>80	$C_{23}H_{44}O_7$	3500 (OH, str); 1740 (C=O, ester str), 1240 (C-O ring str), 1180, 1080, 1030 (C-O, str)	3.8 (*m*, 2H, 2 × $C\underline{H}O$ ring); 3.6–3.4 (*m*, 13H, 3 × $C\underline{H}_2O$ + $C\underline{H}_2OH$ + $C\underline{H}O$ + $C\underline{H}OH$ + $CO_2C\underline{H}_3$); 2.2 (*t*, 2H, $C\underline{H}_2$-CO_2); 1.6 (*m*, 4H, $C\underline{H}_2$-CH_2-CO_2 + $C\underline{H}_2$ ring); 1.3 (*br.s*, 18H, -$C\underline{H}_2$- chain); 0.9 (*dt*, 3H, terminal $C\underline{H}_3$)
3c	>80	$C_{25}H_{48}O_8$	3500 (OH, str); 1740 (C=O, ester str), 1240 (C-O ring str), 1180, 1080, 1030 (C-O, str)	3.8 (*m*, 2H, 2 × $C\underline{H}O$ ring); 3.6–3.4 (*m*, 17H, 5 × $C\underline{H}_2O$ + $C\underline{H}_2OH$ + $C\underline{H}O$ + $C\underline{H}OH$ + $CO_2C\underline{H}_3$); 2.2 (*t*, 2H, $C\underline{H}_2$-CO_2); 1.6 (*m*, 4H, $C\underline{H}_2$-CH_2-CO_2 + $C\underline{H}_2$ ring); 1.3 (*br.s*, 18H, -$C\underline{H}_2$- chain); 0.9 (*dt*, 3H, terminal $C\underline{H}_3$)
4a	>95	$C_{25}H_{44}O_8$	1740 (C=O, ester str), 1242 (C-O ring str), 1180, 1160, 1080, 1030 (C-O, str)	4.8 (*m*, 1H, $C\underline{H}$-OC=O); 4.2 (*m*, 2H, $C\underline{H}_2$-OC=O); 3.8 (*m*, 2H, 2 × $C\underline{H}O$ ring); 3.65 (*br.s*, 6H, $C\underline{H}_2O$ + $C\underline{H}O$ + $CO_2C\underline{H}_3$); 2.2 (*t*, 2H, $C\underline{H}_2$-CO_2); 2.0 (*s*, 6H, 2 × $CO_2C\underline{H}_3$); 1.6 (*m*, 4H, $C\underline{H}_2$-CH_2-CO_2 + $C\underline{H}_2$ ring); 1.3 (*br.s*, 18H, -$C\underline{H}_2$- chain); 0.9 (*dt*, 3H, terminal $C\underline{H}_3$)
4b	>95	$C_{25}H_{44}O_8$	1740 (C=O, ester str), 1242 (C-O ring str), 1180, 1160, 1080, 1030 (C-O, str)	4.8 (*m*, 1H, $C\underline{H}$-OC=O); 4.2 (*m*, 2H, $C\underline{H}_2$-OC=O); 3.8 (*m*, 2H, 2 × $C\underline{H}O$ ring); 3.65 (*br.s*, 10H, 3 × $C\underline{H}_2O$ + $C\underline{H}O$ + $CO_2C\underline{H}_3$); 2.2 (*t*, 2H, $C\underline{H}_2$-CO_2); 2.0 (*s*, 6H, 2 × $CO_2C\underline{H}_3$); 1.6 (*m*, 4H, $C\underline{H}_2$-CH_2-CO_2 + $C\underline{H}_2$ ring); 1.3 (*br.s*, 18H, -$C\underline{H}_2$- chain); 0.9 (*dt*, 3H, terminal $C\underline{H}_3$)
4c	>95	$C_{25}H_{44}O_8$	1740 (C=O, ester str), 1242 (C-O ring str) 1180, 1160, 1080, 1030 (C-O, str)	4.8 (*m*, 1H, $C\underline{H}$-OC=O); 4.2 (*m*, 2H, $C\underline{H}_2$-OC=O); 3.8 (*m*, 2H, 2 × $C\underline{H}O$ ring); 3.65 (*br.s*, 14H, 5 × $C\underline{H}_2O$ + $C\underline{H}O$ + $CO_2C\underline{H}_3$); 2.2 (*t*, 2H, $C\underline{H}_2$-CO_2); 2.0 (*s*, 6H, 2 × $CO_2C\underline{H}_3$); 1.6 (*m*, 4H, $C\underline{H}_2$-CH_2-CO_2 + $C\underline{H}_2$ ring); 1.3 (*br.s*, 18H, -$C\underline{H}_2$- chain); 0.9 (*dt*, 3H, terminal $C\underline{H}_3$)

ran ring containing polyether, as indicated by a multiplet integrating for one proton at δ 4.8 for C<u>H</u>-$OCOCH_3$ and a multiplet integrating for two protons at δ 4.2 for -C<u>H</u>$_2$-$OCOCH_3$. The signal at δ 4.2 would have been absent, while the signal at δ 4.8 would have been accountable for two protons if the molecules formed were crown ethers; the signals at δ 4.2 and δ 4.8 would have been accountable for three protons if the compounds formed were open-chain tetrahydroxy ethers.

The structures of these products were further clarified by the ^{13}C (Fig. 1) and mass (Fig. 2) spectra. The carbons directly attached to the oxygen atoms of the tetrahydrofuran ring, C-9 and C-12, were observed at δ 80.0 and 80.65 ppm, respectively, indicating the formation of the tetrahydrofuran ring. The carbon attached to open-chain ether oxygen was observed at δ 74.62 ppm. Similarly, the carbon attached to the acetyl group inside the ring, C-10, was observed at δ 81.94 and C-11, and the ring methylene carbon was observed at δ 33.8 ppm. The carbon attached to the acetyl group and outside the ring was observed at its normal chemical shift of δ 63.34 ppm.

The chemical shifts for C-9 and C-12 would have been between δ 70.0 and δ 75.0 ppm (12) if the compound formed was either a crown ether type or an open-chain tetrahydroxy molecule. In the DEPT (Distortionless Enhancement by Polarization Transfer) experiment, the signals at δ 170.58 and 173.65 (quaternary carbons) were absent. At the same time, the polarities of the signals at δ 14.04, 20.99, and 51.19 (primary carbons) and δ 74.62, 80.0, 80.65, and 81.94 (tertiary carbons) were reversed, which further supported the above assignment of chemical shifts to various carbons. Only one signal was observed for carbons 9, 10, 11, 12, and 13 in the ^{13}C NMR spectra, which shows the formation of one isomer.

In the mass spectra (Fig. 2) of the products [4b and c] the parent ion was invariably absent. This may be due to intensive functionalization of the molecule and the presence of

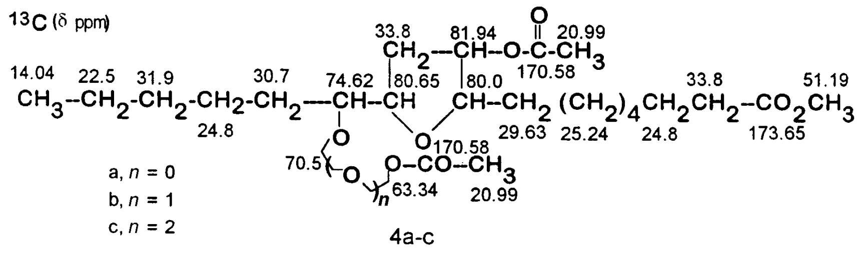

FIG. 1. Chemical shifts of ^{13}C nuclear magnetic resonance spectrum of the product [4a-c] ($CDCl_3$).

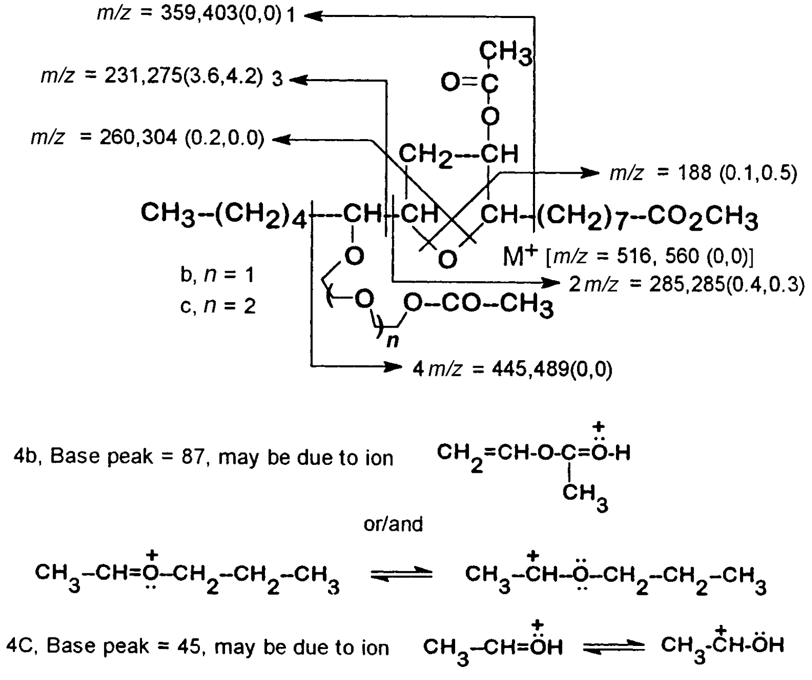

FIG. 2. Mass spectral fragmentation pattern of products [4b and 4c]. Items in parentheses are the intensities relative to base peak.

various labile groups like acetate ion and ether linkages, which can easily be lost from the molecule. The most predominant ions observed by α-cleavage between various carbons are indicated in Figure 2.

The cleavage of the tetrahydrofuran ring on both sides of the oxygen gave ions at *m/z* 188 (intensity relative to base peak, 0.1% [4b] and 0.5% [4c]) and *m/z* 260 ([4b], 0.2%). The loss of the methoxide ion (31) from the ion at *m/z* 188 gave an ion at *m/z* 157 ([4b], 0.8%; [4c], 1.4%) while the loss of acetic acid (60) from the ion at *m/z* 260 [4b] gave an ion at *m/z* 200 (0.1%) and the similar loss from the ion *m/z* 304 [4c] gave an ion at *m/z* 244 (0.4%). The other α-cleavage ions and ions after the loss of labile groups were also observed and supported the assigned structure. The base peaks were observed at *m/z* 87 [4b] and at *m/z* 45 [4c], as normally found for molecules containing aliphatic ether linkages (12), which further supported the assigned structure.

Thus, the diols [1a–c], obtained from the trivernolein, were easily converted to the respective epoxides [2a–c] by perbenzoic acid-mediated epoxidation reaction. The epoxides [2a–c] undergo Lewis acid-catalyzed intramolecular cyclization through the reaction of the backbone hydroxyl group, while the primary hydroxyl group of the glycol part did not participate in the reaction. These results can significantly be attributed to the ease in formation of five-membered ring over larger (8-, 11-, or 14-membered) crown ether rings. Thus the tetrahydrofuran ring containing oligoethylene glycol ethers have been synthesized from the seed oil of *Vernonia anthelmintica.*

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