IR (neat) 1860, 1790, 1640 cm^{-1}.

Compound **27** (27.6 mg, 0.134 mmol) was dissolved in THF (10 mL) and treated dropwise with compound **25** (50 mg, 0.10 mmol) in THF over 30 min. After the addition was completed, the mixture was allowed to stir for 16 h at room temperature. After the solvent was evaporated, the residue was crystallized from ether to provide **22** as white crystals, 14 mg (20%). This product had properties identical with those described before.

Acknowledgment. We gratefully acknowledge the support of the research by the NIH (Grant GM25845). The 300-MHz NMR spectrometer used was made available by grants from the NIH and the University of Notre Dame. Technical assistance was provided by Kathleen Peterson.

Registry No. **3**, 24277-39-2; **4**, 90194-99-3; **5**, 15255-86-4; **6**, 90195-00-9; **7**, 90219-04-8; **8**, 90195-01-0; **9**, 90195-02-1; **10**, 90195-03-2; **11**, 52816-28-1; **12**, 52816-29-2; **14**, 52816-30-5; **15**, 90195-04-3; **16**, 90195-05-4; **17**, 90195-06-5; **18**, 90195-07-6; **19**, 90195-08-7; **20**, 52816-32-7; **21**, 90195-09-8; **22**, 38532-33-1; **23**, 90195-10-1; **24**, 18928-00-2; **25**, 90195-11-2; **26**, 90195-12-3; *O*-benzylhydroxylamine hydrochloride, 2687-43-6; trichloroethyl chloroformate, 17341-93-4; di-*tert*-butyl dicarbonate, 24424-99-5; glutamic acid, 56-86-0.

Synthesis and Binding Studies of Crown Ethers Bearing Pharmacophoric Groups: Epoxy Lariat Crown Ethers

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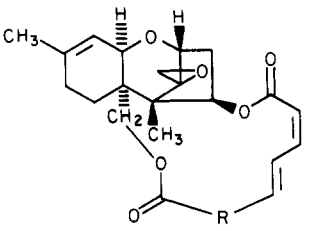
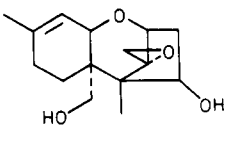
A series of lariat ethers (derivatives of 18-crown-6, 15-crown-5, and 12-crown-4) bearing pendant epoxy groups has been prepared and the homogeneous stability (binding) constants (K_s) with Na^+ and K^+ in MeOH have been measured. The epoxy groups appear to have only a marginal influence on complexation of K^+ in the larger ring compounds and do not enhance Na^+ binding. These epoxy lariat ethers exhibit no in vivo activity against P388 mouse leukemia at dose levels of 128 mg/kg and below.

Alkylating agents constitute an important class of compounds used in the treatment of cancer.[1] Many natural products with proven high antitumor activity are known to possess bioalkylating functionalities such as oxirane, α,β-unsaturated carbonyl, α-carbinol amide, and urethane groups.[2] During the past several years, a great deal of effort has been directed at establishing structure–activity relationships for natural products possessing anticancer activity.[3] One class that has been of interest to us is the trichothecenes,[4] which possess a 12,13-epoxide group. The epoxide appears to function as a bioalkylating center and is responsible for the potent biological activity associated with this series of fungal metabolites.

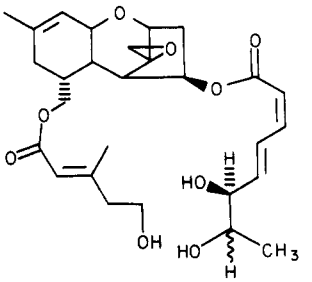
Our interests have been centered on the macrocyclic trichothecenes (e.g., **1**),[5a] which exhibit the highest cytotoxicity and cycostaticity of the trichothecenes. The role played by the macrocylic ring in the bioactivity of these compounds is not clear, although reduction of the diene system or loss of the macrolide chain by hydrolysis to give verrucarol (**2**) leads to trichothecenes of considerably lower activity.[5b,c] The nonmacrolide trichoverrins **3** and other related trichoverroids are about 2 orders of magnitude less cytotoxic than the macrocyclic trichothecenes, which



1



2



3

suggests that the macrolide ring in **1** plays an important role in potentiating the cytotoxicity of these compounds.[6]

Other macrocyclic antibiotics such as valinomycin, nonactin, gramicidin, antanamide, nystatin, and amphotericin B function as ionophores.[7] The macrolide antibiotic erythromycin requires potassium or ammonium ions in order to bind to the 50S subunit of bacterial ribosomes,[8,9] which suggests that perhaps cation complexation brings about

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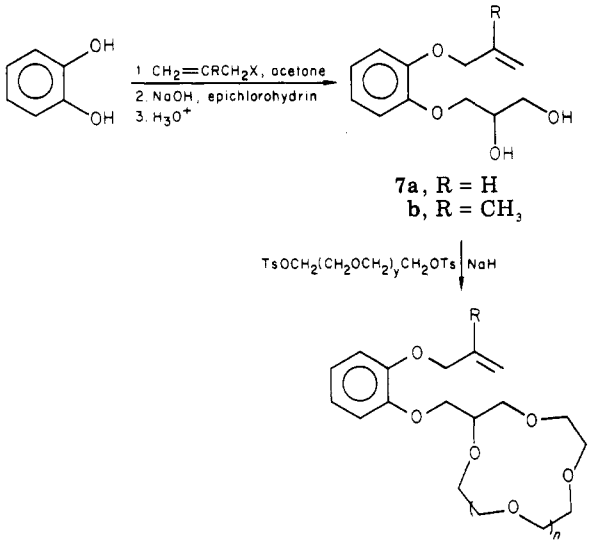
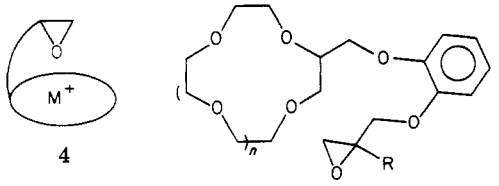
0022-3263/84/1949-2423$01.50/0

Scheme I



a conformational change in erythromycin which elicits the observed biological effect.

Recently, in an effort to develop crown ethers that mimic the behavior of naturally occurring ionophores such as valinomycin, some of us have synthesized representatives of a crown ether class we call the lariat ethers.[10] These are crown ethers that possess a side arm bearing a donor group which can aid in solvating a ring-bound metal ion. A lariat ether with an auxiliary oxirane ring should, if the oxygen-donor group is appropriately situated, coordinate more strongly to a macroring-bound metal cation than a crown ether lacking this functionality. The results of such additional binding (e.g., 4) should be activation of the



4

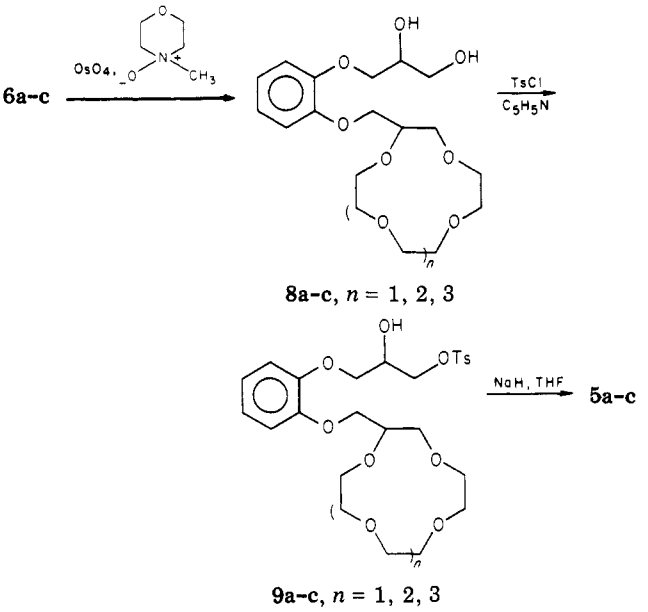
5a-c, R = H; n = 1, 2, 3
5d-f, R = CH_3; n = 1, 2, 3

oxirane to nucleophilic attack in the same fashion that intramolecular hydrogen bonding appears to activate certain epoxides.[11] Thus, lariat ethers possessing suitably disposed[10b] epoxide rings might display interesting biological activity. To test this possibility, we have synthesized a series of lariat ethers **5** possessing secondary donor epoxide groups, measured the stability constants of the Na^+ and K^+ complexes, and determined the in vivo activity of the compounds against P388 mouse leukemia.

Results and Discussion

The synthesis of the olefinic crown ethers **6b,c,e,f** starting from catechol is shown in Scheme I. Compounds **6a** and **6d** were prepared by condensation of diol **7** with triethylene glycol dichloride in the presence of lithium cation.[12] Epoxidation of the olefinic crown ethers **6d–f** (*m*-chloroperoxybenzoic acid, MCPBA) proceeded smoothly to give the diastereomeric epoxide mixtures **5d–f** in good yield. Epoxidation of crown ethers **6a–c** was unsuccessful under a variety of conditions.[13] The method ultimately developed for the preparation of epoxy crown ethers **5a–c** is shown in Scheme II.

Scheme II



Olefinic crowns **6a–c** were converted to the corresponding diols **8a–c** by treatment of the olefins with *N*-methylmorpholine *N*-oxide in the presence of catalytic

Table I. Stability Constants in Absolute Methanol at 25 ±1 °C

cmpd no.[a]	ring size	sidearm identity	binding constants,[b] log K_s for Na^+	K^+
	12	(12-crown-4)	1.70[c]	1.74[c]
5a[d]	12	glycidyl	1.43	1.81
5d	12	methylglycidyl	1.29	1.67
6a	12	allyl	1.54	1.59
6d	12	methallyl	1.54	1.58
	15	(15-crown-5)	3.24[c]	3.43[c]
5b	15	glycidyl	3.03	3.53
5e	15	methylglycidyl	3.02	3.44
6b	15	allyl	3.07	3.38
6e	15	methallyl	3.04	3.29
	18	(18-crown-6)	4.35[c]	6.08[c]
5c	18	glycidyl	3.76	5.40
5f	18	methylglycidyl	3.85	5.42
6c	18	allyl	3.87	5.52
6f	18	methallyl	3.87	5.55

[a] Sidearm refers to the ortho substituent on the (2-phenoxymethyl)-substituted crown ether. [b] Determined as previously reported.[10,17] [c] Values from ref 22 and are for the parent crowns with no sidearm. [d] Satisfactory analysis (±0.3 for C and H) were reported for compounds **5a–f** and **6a–f**.

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(13) Methods tried were the use of large excess of MCPBA, 1.2 equiv, and elevated temperature and 1.2 equiv of MCPBA in presence of Kishi's inhibitor[14a] in dichloroethane at elevated temperature. Use of 3,5-dinitroperbenzoic acid[14b] also proved ineffective. The bromohydrin route using *N*-bromoacetamide resulted in a ring brominated product.

(14) (a) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T.; Inoue, S.; Sugiuva, S.; Kakoi, H. *J. Am. Soc., Chem. Commun.* **1972**, 64. (b) Rastetter, W. H.; Richard, T. J.; Lewis, M. D. *J. Org. Chem.* **1978**, *43*, 3163.

osmium tetroxide.[15] The diols thus obtained were converted to the monotosylates **9a–c** which underwent NaH-mediated ring-closure to the desired epoxy crown ethers **5a–c**.[16] The use of NaOMe as base with **9b** results in methyl ether formation (displacement of TsO^- by MeO^-). The diastereomeric lariat ether epoxides could not be separated by HPLC on either normal or reversed-phase columns and were therefore used as diastereomeric mixtures for binding studies.

Since crown ethers are known to bind alkali and alkaline-earth metal cations, it was thought that binding constants for compounds **5** and **6** should be determined in anticipation of their being biologically active. It was hoped that the biological data would correlate in some discernible way to the activity. The marginal activity observed for these compounds makes such a correlation impossible, but the results of these binding studies are interesting in their own right and are presented in Table I.

In previous studies,[10,18] we have found that the presence of any carbon-pivot side arm, with or without a Lewis basic donor group, reduces cation binding to either sodium or potassium cation. Thus, the stability constant (log K_s) for the combination of Na^+ and 2-[(*m*-methoxyphenoxy)-methyl]-15-crown-5 is 2.89[18] compared to 3.24 for 15-crown-5.[22] When the arylmethoxy group is ortho, its oxygen can interact with a ring-bound cation and the loss of binding observed for the meta substituent is compensated. Log K_s for the ortho isomer of the above is 3.24,[22] the same as for the unsubstituted parent molecule.

The trend suggested above is largely followed by the 15 compounds for which data are presented in Table I. In each group, the unsubstituted crown-12, crown-15, or crown-18 shows the highest binding for that ring size. As expected, binding is low for all of the 12-membered rings and since experimental error is highest with these compounds, any conclusions drawn from subtle differences in binding are likely to be questionable if not in error.

In our previous surveys of other lariat ethers systems, we have noted that binding differences are usually more pronounced in the 15-membered ring systems than in the 18-crowns.[18] This is because 18-crown-6 is an especially effective binder for many cations[22] and therefore requires less support from a pendant side arm. There is relatively little difference in the cation binding among the 18-crowns. The equilibrium binding constants for the present compounds with Na^+ cation fall in the range 3.82 ± 0.06 and for K^+ binding are in the range 5.48 ± 0.08. Note that both of these stability constant values are significantly below the values observed for the parent compounds: 4.35 and 6.08, respectively.

If any differences in side-arm influences were observed, they would have been expected in the 15-membered ring systems. Instead, an even narrower range of Na^+ binding constants is observed than for the 18-membered ring systems. The only notable difference in binding at all is that K^+ binding seems to be slightly stronger with **5b** and **5e** than with **6b** and **6e**. This difference might support a secondary donor interaction with the ring-bound cation which should be stronger for glycidyl side arms than for allyl side arms. The differences are small at best and it is not clear that any significant conclusion regarding side-arm conformation can be drawn from the results obtained here.

The antitumor activity of epoxides has been investigated by a number of workers, and the general conclusion is that the synthetic compounds require the presence of two epoxy groups.[23] The hope that the presence of the crown ether ring would favorably influence a monoepoxide in terms of its in vivo anticancer activity was not realized; lariat epoxides **5a–f** all proved to be inactive in vivo at dose levels of 128 mg/kg and below against P388 mouse leukemia. Compound **5c** was toxic at 128 mg/kg. Activity might be realized if the epoxide group could be made more favorably disposed toward secondary binding as in a nitrogen-pivot system.[24]

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 281 spectrophotometer. Spectral bands are reported in reciprocal centimeters and are calibrated against the 1601-cm^{-1} band of polystyrene. Spectra were taken neat for liquids and in $CHCl_3$ for solids. ^1H NMR spectra were recorded on a Varian EM 360 spectrometer unless otherwise specified with $CDCl_3$ as the solvent and Me_4Si as internal standard. The chemical shifts are reported in δ units downfield from Me_4Si. The abbreviations br = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet together with the standard notations AB, ABX, etc., are used to described the spin multiplicity. Proton-decoupled ^{13}C NMR spectra were recorded at 50.4 MHz on an IBM WP-200 SY instrument unless otherwise specified. Electron-impact mass spectra were recorded on a Bell and Howell 492 instrument at 70 eV. Elemental analyses were performed by Dr. Franz Kasler of the University of Maryland. All new compounds gave satisfactory (±0.3%) elemental analyses. THF was distilled from CaH_2 prior to use. All other reagents used were of the highest grade commercially available. Thin-layer chromatograms (TLC) were carried out on Bakerflex Al_2O_3 IB-F sheets (7.5 × 2.5 cm) (J. T. Baker) and silica gel 60 F-254 precoated TLC plates (5 × 10 cm) (E. Merck). Aluminum oxide (neutral) (J. T. Baker 5-0537) was used for column chromatography. For the purification of epoxides the activity of Al_2O_3 was adjusted to II/III by the addition of the appropriate amount of water (4.5 mL/100 g).

3-[*o*-(Allyloxy)phenoxy]-1,2-propanediol (7a). A three-necked flask equipped with a magnetic stirring bar, a dropping funnel, and a reflux condenser was charged with 25.2 g (0.17 mol) of *o*-(allyloxy)phenol[19] and 62.9 g (4 equiv) of epichlorohydrin. The mixture was heated to 80 °C (oil bath temperature) with vigorous stirring. To this mixture was added dropwise 17 mL of 40% aqueous NaOH (1 equiv) during 1 h. The mixture was stirred for 24 h, cooled, and poured into water. The organic layer was washed with 10% aqueous NaOH, water, and brine and dried (Na_2SO_4). Evaporation of epichlorohydrin left the crude glycidyl ether which was stirred in 1.5 L of water with 0.2 mL of 70% $HClO_4$ at 80 °C for 24 h. The reaction mixture was cooled, neutralized with 5% Na_2CO_3 solution, and extracted with Et_2O (3 × 300 mL). The Et_2O extracts were washed with water and brine and dried (Na_2SO_4). Evaporation of Et_2O under vacuum gave the crude product, which was crystallized from dichloromethane–pentane to give 22.1 g (75%) of **7a**, mp 82 °C (lit.[16] mp 82–83 °C).

***o*-(Methallyloxy)phenol.** A three-necked flask equipped with a condenser, drying tube, mechanical stirrer, and addition funnel

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(24) Schultz, R. A.; Dishong, D. M.; Gokel, G. W. *J. Am. Chem. Soc.* **1982**, *104*, 625.

was purged with dry N_2 and charged with catechol (55 g, 0.5 mol), K_2CO_3 (42 g, 0.3 mol), KI (1 g), and acetone (500 mL). The mixture was heated to reflux while stirring. Methallyl chloride was added dropwise during 1 h, and heating was continued for another 24 h. The mixture was cooled and filtered, and the precipitate was washed with acetone (2 × 50 mL). The filtrate was reduced in vacuo, and the resulting crude product was dissolved in Et_2O (400 mL) and washed with water (3 × 200 mL) and 2 N NaOH until the organic layer showed no monoether on TLC (SiO_2, CH_2Cl_2). The aqueous NaOH washings were acidified by addition of cold 2 N HCl. The solution was extracted with Et_2O (3 × 150 mL), washed with water and brine, and dried (Na_2SO_4). Filtration followed by evaporation gave *o*-(methallyloxy)phenol: 41.6 g (50%); bp 71–75 °C (0.2 mm) (lit.[20] bp 78.5–83 °C (0.5 mm)); IR (neat) 3500, 1663 cm^{-1}; ^1H NMR δ 6.74 (4 H, s), 5.97 (1 H, br s), 4.96 (2 H, m), 4.33 (2 H, br s), 1.74 (3 H, s); ^{13}C NMR δ 145.9, 145.8, 140.5, 121.6, 119.9, 114.8, 112.8, 112.4, 72.5, 18.8.

3-[*o*-(Methallyloxy)phenoxy]-1,2-propanediol (7b). This compound was prepared (89% yield) by using the procedure described for **7a**. The intermediate 3-[*o*-(methallyloxy)phenoxy]-1,2-epoxypropane was characterized and has the following properties: bp 101–105 °C (0.1 mm); IR (neat) 1655 cm^{-1}; ^1H NMR (200 MHz) δ 6.95 (4 H, m), 5.11 (1 H, s), 4.98 (1 H, s), 4.49 (2 H, s), 4.16 (2 H, eight lines of AB of ABX, J_{AB} = 11.4 Hz, J_{AX} = 3.5 Hz, J_{BX} = 5.2 Hz), 3.4 (1 H, m) 2.89 (1 H, dd, $J_{1,2cis}$ = 4.2 Hz, J_{gem} = 4.8 Hz), 2.76 (1 H, dd, $J_{1,2trans}$ = 2.6 Hz, J_{gem} = 4.8 Hz); ^{13}C NMR δ 149.4, 148.9, 141.1, 122.2, 121.5, 115.9, 115.0, 112.5, 73.1, 70.6, 50.3, 44.7, 19.3.

Diol **7b** has the following properties: mp 90–92 °C; IR ($CHCl_3$) 3500, 1655 cm^{-1}; ^1H NMR δ 6.83 (4 H, s), 5.03 (1 H, br s) 4.94 (1 H, br s), 4.40 (2 H, s), 4.0 (3 H, m), 3.7 (3 H, m), 2.9 (1 H, br s), 1.8 (3 H, s); ^{13}C NMR δ 148.8, 148.4, 140.6, 122.1, 121.4, 115.2, 114.0, 112.9, 72.7, 72.0, 63.8, 19.3.

[[2-(Allyloxy)phenoxy]methyl]-12-crown-4 (6a). This compound was synthesized in an 18% yield from **7b** and triethylene glycol dichloride according to the literature procedure:[12] bp 161–167 °C (0.1 mm); IR (neat) 1650, 1130, 1110 cm^{-1}; ^1H NMR δ 6.7 (4 H, s), 5.7–6.4 (1 H, m), 5.1–5.6 (2 H, m), 4.4–4.7 (2 H, m), 3.5–4.2 (19 H, m); MS, *m/e* 338.

[[2-(Methallyloxy)phenoxy]methyl]-12-crown-4 (6d). This compound was synthesized by using the same procedure employed for preparing **7a** and was obtained in 16% yield: bp 165–170 °C (0.5 mm); IR (neat) 1660, 1130, 1105 cm^{-1}; ^1H NMR δ 6.90 (4 H, s), 5.0 (2 H, m) 4.4 (2 H, s), 3.4–4.2 (17 H, m), 1.8 (3 H, s); MS, *m/e* 352.

[[2-(Allyloxy)phenoxy]methyl]-15-crown-5 (6b). Compound **6b** was prepared by using the general procedure described in the literature[21] and was obtained in 45% yield after column chromatography on alumina using 2-propanol in hexane (0–3%): IR (neat) 1650, 1120 cm^{-1}; ^1H NMR δ 6.9 (4 H, s), 5.8–6.6 (1 H, m), 5.1–5.5 (2 H, m), 4.5 (2 H, br d, J = 5 Hz), 3.5–4.1 (21 H, m); MS, *m/e* 382.

[[2-(Methallyloxy)phenoxy]methyl]-15-crown-5 (6e). Compound **6e** was prepared and purified in the same manner as described for **6b** and was obtained in 52% yield: IR (neat) 1650, 1120 cm^{-1}; ^1H NMR δ 6.9 (4 H, s), 5.0 (2 H, m), 4.4 (2 H, s), 4.2–3.4 (21 H, m), 1.8 (3 H, s); MS, *m/e* 396.

[[2-(Allyloxy)phenoxy]methyl]-18-crown-6 (6c). Compound **6c** was prepared in the same manner as described for **6b** and was purified by using column chromatography on alumina using 2-propanol in hexane 0–3% and was obtained as a colorless oil in 23% yield: IR (neat) 1650, 1120 cm^{-1}; ^1H NMR δ 6.8 (4 H, s), 5.5–6.4 (1 H, m), 5.0–5.5 (2 H, m), 4.4 (2 H, br d, J = 5 Hz) 3.3–4.3 (25 H, m); MS, *m/e* 426.

[[2-(2′-Methyl-2-propenyloxy)phenoxy]methyl]-18-crown-6 (6f). Compound **6f** was synthesized in the same manner as described for **6b** and was purified by alumina chromatography and was obtained in 36% yield: IR (neat) 1650, 1120 cm^{-1}; ^1H NMR δ 6.8 (4 H, s), 4.9 (2 H, m, br s), 4.3 (2 H, s), 3.4–4.1 (25 H, m), 1.7 (3 H, s); MS, *m/e* 440.

Epoxidation of 6d–f. The appropriate olefinic crown ether was dissolved in $CHCl_3$, stirred with 1.2 equiv of *m*-chloroperoxybenzoic acid and 1.2 equiv of $NaHCO_3$ overnight (~15 h), and filtered. The filtrate was washed with 10% Na_2SO_3, saturated $NaHCO_3$, and water and dried over $MgSO_4$. Filtration followed by evaporation of $CHCl_3$ gave crude epoxides **5d–f** which were purified on a column of alumina by using 2-propanol–hexane (0–10%) to afford the diastereomeric mixture of epoxides in 65–90% yield. For **5d**: IR (neat) 3020, 2850, 1120 cm^{-1}; ^1H NMR δ 6.9 (4 H, s), 3.4–4.2 (19 H, m) 2.78 (2 H, AB, J_{AB} = 5), 1.5 (3 H, s); MS, *m/e* 368. For **5e**: IR (neat) 3020, 2860, 2830, 1120 cm^{-1}; ^1H NMR δ 6.9 (4 H, s), 3.7–4 (23 H, m), 2.8 (2 H, AB, J_{AB} = 5 Hz), 1.5 (3 H, s); MS, *m/e* 412. For **5f**: IR (neat) 3020, 2860, 2830, 1120 cm^{-1}; ^1H NMR δ 6.9 (4 H, s), 3.8–4.1 (27 H, m) 2.8 (2 H, AB, J_{AB} = 5 Hz), 1.5 (3 H, s); MS, *m/e* 456.

General Preparation of Epoxides 5a–c. The procedure described here is for the preparation of **5b**. The same method was used for preparing **5a** and **5c**. Olefin **6b** (1.91 g, 5 mmol) was dissolved in 65% aqueous acetone (3 mL). To this was added *N*-methylmorpholine *N*-oxide (0.75 g, 1.1 equiv) followed by 150 μL of 2.5% w/v solution of OsO_4 in *tert*-butyl alcohol. The mixture was stirred overnight at ambient temperature and Na_2SO_3 (500 mg) was added. Acetone (15 mL) was added to the reaction mixture, and the mixture was filtered through Celite. The Celite cake was washed with additional acetone (40 mL), and the washings were combined with filtrate and reduced in vacuo. The residue was acidified with 2 N HCl and extracted with dichloromethane. The dichloromethane extract was washed with water and dried ($MgSO_4$). Filtration followed by evaporation of dichloromethane gave **8b**, 1.99 g (95%): IR (neat) 3390 cm^{-1}; ^1H NMR δ 6.9 (4 H, s), 3.6–4.3 (28 H, m).

Preparation of 9b. To a stirred solution of diol **8b** (1.28 g, 3.1 mmol) in pyridine (10 mL) at 0 °C was added over a 5-min period an ice-cold solution of *p*-toluenesulfonyl chloride (590 mg, 3.1 mmol) in pyridine (10 mL). The reaction mixture was stirred overnight at ambient temperature, poured into ice–water (200 mL), acidified with 6 N HCl, and extracted with dichloromethane (3 × 70 mL). The combined dichloromethane extracts were washed with water and dried ($MgSO_4$). Filtration followed by evaporation of dichloromethane yielded **9b** (1.51 g, 86%): IR (neat) 3300, 1365, 1185 cm^{-1}; ^1H NMR δ 7.4 (4 H, AB, J_{AB} = 8 Hz) 6.8 (4 H, s), 3.2–4.3 (27 H, m), 2.4 (3 H, s).

Preparation of 5b. Sodium hydride (50% dispersion in mineral oil, 490 mg, 1.2 equiv) was washed with pentane (3 × 10 mL) and suspended in THF (20 mL). A solution of monotosylate **9b** (4.9 g 8.5 mmol) in THF (25 mL) was added dropwise over a period of 10 min to the suspension of NaH in THF. The mixture was stirred at ambient temperature for 1.5 h, and the solid was removed by filtration. The residue obtained after evaporation of solvent was taken up in dichloromethane (50 mL), washed with water, and dried ($MgSO_4$). Filtration followed by evaporation in vacuo yielded 3.9 g (80%) of crude epoxide which was further purified by column chromatography on alumina/1–3% 2-propanol in hexane: IR (neat) 3020, 2920, 2880, 1120 cm^{-1}; ^1H NMR δ 6.9 (4 H, s), 3.1–4.3 (24 H, m), 2.8 (2 H, m); MS, *m/e* 398.

[[2-(2,3-Epoxypropyloxy)phenoxy]methyl]-12-crown-4 (5a): IR (neat) 3020, 2920, 2888, 1120, 1095 cm^{-1}; ^1H NMR δ 7.0 (4 H, s), 3.3–4.6 (20 H, m), 2.8 (2 H, m); MS, *m/e* 354.

[[2-(2,3-Epoxypropyloxy)phenoxy]methyl]-18-crown-6 (5c): IR (neat) 3020, 2920, 2880, 1120 cm^{-1}; ^1H NMR δ 6.9 (4 H, s), 4.3–3.2 (28 H, m), 2.8 (2 H, m), MS *m/e* 442.

Measurement of log K_s. The values were determined in anhydrous methanol by Frensdorff's method[17] by using a Corning 476210 electrode for sodium and a Corning 476220 monovalent cation electrode for potassium. The temperature was maintained at 25 ± 1 °C in a water-free, nitrogen-purged drybox with di-*n*-butyl phthalate as the heat transfer medium. Emf changes were determined by using an Orion Model 701A Ionalyzer meter. The experimental error is ±0.02 log unit in log K_s.

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Registry No. **5a** (isomer 1), 90195-27-0; **5a** (isomer 2), 90195-33-8; **5b** (isomer 1), 90195-28-1; **5b** (isomer 2), 90195-34-9; **5c** (isomer 1), 90195-29-2; **5c** (isomer 2), 90195-35-0; **5d** (isomer 1), 90195-30-5; **5d** (isomer 2), 90195-36-1; **5e** (isomer 1), 90195-31-6;

5e (isomer 2), 90195-37-2; 5f (isomer 1), 90195-32-7; 5f (isomer 2), 90195-38-3; 6a, 90219-07-1; 6b, 90219-08-2; 6c, 90195-17-8; 6d, 90195-18-9; 6e, 90195-19-0; 6f, 90195-20-3; 7a, 6452-54-6; 7b, 90195-16-7; 8a, 90195-21-4; 8b, 90195-22-5; 8c, 90195-23-6; 9a, 90195-24-7; 9b, 90195-25-8; 9c, 90195-26-9; Na^+, 17341-25-2; K^+, 24203-36-9; *o*-(allyloxy)phenol, 1126-20-1; epichlorohydrin, 106-89-8; catechol, 120-80-9; methallyl chloride, 563-47-3; *o*-(methallyloxy)phenol, 4790-71-0; *o*-(allyloxy)phenyl glycidyl ether, 6452-72-8; 3-[*o*-(methallyloxy)phenoxy]-1,2-epoxypropane, 16479-39-3; triethylene glycol dichloride, 112-26-5.

Chemistry of (Glycidyloxy)propiolactones. An Intramolecular Transfer of Alkoxy Group in the Alcoholysis and Reduction Reactions

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An interesting intramolecular transfer of an acetal alkoxy group is observed in the alkaline alcoholysis and in reduction by $LiAlH_4$ of α-methyl-α-((1-*tert*-butoxy-2-methyl-2,3-epoxypropyl)oxy)-β-propiolactone (**3a**). With either methanol or ethanol and NaOH at 30 °C, the (glycidyloxy)propiolactone **3a** cleaves to produce α-methylglycidaldehyde and either methyl or ethyl α-*tert*-butoxy-β-hydroxyisobutyrate. Reduction with $LiAlH_4$ at 30 °C also cleaves **3a**, this time with partial reduction to give 2-methyl-2,3-epoxypropanol (**6**) and 2-methyl-2-*tert*-butoxypropane-1,3-diol (**7**). In each case the *tert*-butoxy group has been transferred to the α carbon of the β-lactone portion of **3a**.

Introduction

(Glycidyloxy)propiolactones are a new group of organic compounds which can be obtained by the reaction of α-methyl derivatives of glycidaldehyde **1** with aluminum alkoxides or alkylaluminium compounds.[1-3] (See Figure 1).

The chemistry of compounds **3a–h** is of particular interest due to their possessing three functional groups, i.e., oxirane and oxetanone rings and an acetal bond.

Depending on reaction conditions, the alcoholysis of β-lactones may lead to the formation of different products. The lactone group is known to react with alcohols in an alkaline medium to yield the corresponding β-hydroxy esters, while β-alkoxy acids, β-alkoxy esters, and polymeric products are additionally formed in an acidic medium.[4,5]

The alkaline or acidic alcoholysis of oxiranes leads to the formation of the corresponding hydroxy ethers, the reaction rate being higher in the acidic medium.[6]

The reduction of β-propiolactone to diol is thought to proceed by the acyl oxygen opening of the oxetanone ring.[7,8]

The reduction of monosubstituted oxiranes yields a mixture of secondary and primary alcohols. The yields and proportions of products are, however, dependent upon the type of oxirane used and also on the type and concentration of the reducing agent employed.[9,10] Epoxy aldehydes are reduced in the presence of sodium borohydride to epoxy alcohols, whereas in the presence of an excess of lithium aluminium hydride the corresponding diols are also formed.[11]

The present work is concerned with investigating the behavior of α-methyl-α-((1-*tert*-butoxy-2-methyl-2,3-epoxypropyl)oxy)-β-propiolactone (**3a**) during alkaline alcoholysis and reduction with $LiAlH_4$.

Results and Discussion

Alcoholysis of (Glycidyloxy)propiolactone 3a. Alcoholysis of the (glycidyloxy)propiolactone **3a** was carried out in an alkaline medium at 30 °C. Although both the oxirane ring and the acetal bond might be expected to be intact under these conditions, gas chromatographic data indicated the presence of two substances formed in the respective reactions of (glycidyloxy)propiolactone **3a** with corresponding alcohols **4**. The retention times of the first reaction products were the same, irrespective of the alcohol used. The retention times of the second peaks were found to depend on the kind of alcohol used and to increase for higher alcohols.

The two alcoholysis reaction products were separated by preparative GC. On the basis of elemental and instrumental analysis, the first product was indentified as 2-methyl-2,3-epoxypropanal (**1**), while the second one was found to be the β-hydroxy ester **5** appropriate to the alcohol used.

It was therefore clear that the alcoholysis reaction studied was accompanied by an unexpected intramolecular transfer of the alkoxy group. The reaction scheme consistent with the above findings is illustrated in Figure 2.

Reduction of (Glycidyloxy)propiolactone 3a. The quantitative reduction of (glycidyloxy)propiolactone **3a** with lithium aluminium hydride yielded a mixture of two products, both with gas chromatography retention times less than for **3a**. This indicates that (glycidyloxy)propiolactone **3a** was cleaved on reduction.

The two reduction products formed in the molar ratio close to unity were separated by gas chromatography.

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