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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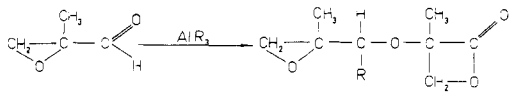
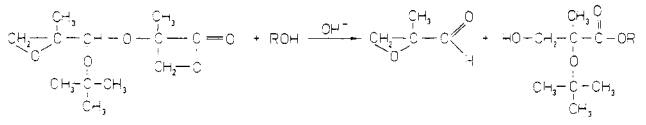


1 2 3

2,3, a: R = O-C4H9t e: R = O-C4H9n i: R = i-C4H9
b: R = O-C2H5 f: R = O-C4H9s j: R = n-C4H9
c: R = O-C3H5n g: R = O-CH2C3H5i k: R = C2H5
d: R = O-C3H7i h: R = O-CH3

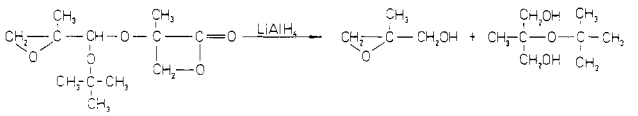
Figure 1. Preparation of (glycidyloxy)propiolactones.



3a 4 1 5

4,5, c: R = CH3
b: R = C2H5

Figure 2. Alcoholysis of (glycidyloxy)propiolactone **3a**.



3a 6 7

Figure 3. Reduction of (glycidyloxy)propiolactone **3a**.

Elemental and instrumental analyses showed the two products to be 2-methyl-2,3-epoxypropanol (**6**) and 2-methyl-2-*tert*-butoxypropane-1,3-diol (**7**).[12] The reaction scheme is shown in Figure 3.

The lactone ring opening was thus shown to proceed as in the reduction of the β-propiolactone.[8] It was found, however, that as in the alkaline alcoholysis reaction, transfer of the alkoxy group to the carbon atom of the lactone ring occurs, which leads to the cleavage of the acetal bond. The oxirane ring does not undergo reduction under the above conditions. However, with an excess of $LiAlH_4$, after a reaction time longer than specified in the Experimental Section the epoxy alcohol **6** undergoes further reduction to 2-methylpropane-1,2-diol (**8**).

$$(CH_3)_2C(OH)CH_2OH$$
8

In particular, after a 9-h reduction of (glycidyloxy)propiolactone **3a** with excess $LiAlH_4$ (molar ratio 1:3), the following composition of the reaction products was determined by GC analysis (mol %): **6**, 10.7%; **8**, 33.4%; **7**, 55.9%.

It was therefore found, that the composition of the reduction products of the (glycidyloxy)propiolactone **3a** can be changed depending on the reaction conditions employed.

Conclusions

The intramolecular transfer of an acetal alkoxy group has been observed during the alkaline alcoholysis (Figure 2) and the reduction (Figure 3) of (glycidyloxy)propiolactone **3a**. The oxirane ring proved stable under selected reaction conditions. This interesting intramolecular transfer merits further study directed toward elucidation of a reaction mechanism. It also suggests there may be other unusual properties of this class of trifunctional compounds.

Experimental Section

Gas chromatographic separations were made on a Varian 2800 gas chromatograph equipped with a preparative unit and an electronic integrator. The quantitative and qualitative GC analyses were carried out in the following conditions: a 2-mm i.d. glass column, 2 m long, packed with Carbowax 20 MTA 10% in Chromosorb WDMSC; injector temperature, 225 °C; detector temperature, 250 °C. The column temperature was changed in the range of from 100 °C to 195 °C at the rate of 8 deg/min., and argon was the carrier gas (flow rate of 25 mL/min). A flame ionization detector (FID) was used. The preparative separations were run on a 7-mm i.d., 3 m long, glass column packed with Carbowax 20M 20% on Chromosorb W, 30–60 mesh. The IR spectra were recorded on a UR-20 Carl Zeiss Jena spectrophotometer. The ^1H NMR spectra were recorded on a Varian XL-100 spectrometer, using Me_4Si as an internal standard. The GC–MS data were obtained on a Varian MAT711 mass spectrometer at 70 eV, with ion source temperature of 200 °C.

Reagents. α-Methyl-α-((1-*tert*-butoxy-2-methyl-2,3-epoxypropyl)oxy)-β-propiolactone (**3a**) was obtained by the method described previously.[1,2] 2-Methyl-2,3-epoxypropanol (serving as a reference compound) was obtained by the selective oxidation of 2-methyl-2-propen-1-ol with cumene hydroperoxide (98%) in the presence of V_2O_5[13] and by the selective reduction of 2-methyl-2,3-epoxypropanal with sodium borohydride.[11] Lithium aluminium hydride (pure) was supplied by L.C.B., Belgium.

Alcoholysis of α-Methyl-α-((1-*tert*-butoxy-2-methyl-2,3-epoxypropyl)oxy)-β-propiolactone (3a). **3a** (1 mL, 4.5 mmol) was added slowly (syringe), over a 30-min period, to a stirred solution of 9.02 mg of NaOH in 27 mmol of the desired alcohol in a flask fitted with a glass stirrer, thermometer, and reflux condenser. The reaction temperature was maintained at 30 °C with a water bath. After further stirring and heating for 1.5 h, the alkali was neutralized with HCl in EtOH. The solution was then filtered and concentrated at reduced pressure. The components of the resulting oil were separated using preparative GC and the following two substances were collected.

2-Methyl-2,3-epoxypropanal (1): yield, 268 mg (69.3%); IR (capillary cell) ν_{max} 3000, 2840, 1740, 1720, 1445, 1400, 1325, 1150, 1085, 1025, 870, 810 cm^{-1}; MS, *m/e* 86 (M^+) (9), 85 (M − 1) (21), 57 (81), 55 (13), 43 (82), 39 (26), 31 (24), 29 (89), 28 (22), 27 (100), 26 (34); ^1H NMR (C_6D_6) δ 1.20 (s, 3, CH_3–C), 2.90, 2.99 (AB q, 2, J = 8 Hz, CH_2OCCH_3), 8.81 (s, 1, CHO). Anal. Calcd for $C_4H_6O_2$: C, 55.81; H, 7.03. Found: C, 55.64; H, 7.05.

Methyl 2-methyl-2-*tert*-butoxy-3-hydroxypropanoate (5a): yield, 510 mg (60.0%); IR (capillary cell) ν_{max} 3520, 3480, 2960, 2872, 2840, 1760, 1467, 1250, 1175, 1140 cm^{-1}; MS, *m/e* (molecular ion was not detected), 117 (8), 104 (51), 85 (9), 75 (20), 59 (16), 58 (7), 57 (100), 43 (29), 41 (21), 29 (20); ^1H NMR ($CDCl_3$) δ 1.08 [s, 9, $C(CH_3)_3$], 1.32 (s, 3, CCH_3), 3.44 (s, 1, CH_2–O*H*), 3.28, 3.59 (AB q, 2, J = 8 Hz, CH_2OH), 3.72 (s, 3, O–CH_3). Anal. Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.54. Found: C, 56.85; H, 9.56.

Ethyl 2-methyl-2-*tert*-butoxy-3-hydroxypropanoate (5b): yield, 580 mg (63.2%); IR (capillary cell) ν_{max} 3520, 3480, 2960, 2890, 2870, 1750, 1470, 1250, 1175, 1140 cm^{-1}; MS, *m/e* (molecular ion was not detected), 131 (10), 118 (45), 90 (22), 85 (10), 75 (36), 59 (12), 57 (100), 43 (18), 41 (22), 29 (27); ^1H NMR (C_6D_6) δ 0.86 (t, 3, J = 7 Hz, OCH_2CH_3), 0.89 [s, 9, $C(CH_3)_3$], 1.25 (s, 3, CCH_3), 3.14, 3.43 (AB q, 2, J = 9 Hz, CCH_2OH), 3.45 (s, 1, CH_2OH), 3.89 (q, 2, J = 7 Hz, OCH_2CH_3). Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.68; H, 9.85.

Ester **5b** reacted with trichloroacetyl isocyanate forming a urethane which has the following ^1H NMR spectrum: ^1H NMR (C_6D_6) δ 0.82 [s, 9, $C(CH_3)_3$], 0.83 (t, 3, J = 7 Hz, OCH_2CH_3), 2.06 (s, 3, CCH_3), 3.54, 3.69 (AB q, 2, J = 10 Hz, $CH_2OCONHCCl_3$), 3.90 (q, 2, J = 7 Hz, OCH_2CH_3), 8.32 (s, 1, CONHCO).

(12) In the ^1H NMR spectrum of this compound the uneqiuvalency of the protons of the CH_2OH groups is observed. This is most probably due to intramolecular hydrogen bonding, and also to steric hindrance. The isomeric optically active 2-methyl-3-*tert*-butoxypropane-1,2-diol has been obtained by the alkaline *tert*-butanolysis of the (−)-2-methyl-2,3-epoxypropanol (prepared according to Sharpless et al.[14]) and it was found that the retention time of this diol was different than that of the diol **7**.

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Reduction of α-Methyl-α-((1-*tert*-butoxy-2-methyl-2,3-epoxypropyl)oxy)-β-propiolactone (3a). Lithium aluminium hydride (0.5 g) in 10 mL of absolute ether was put into a flask containing a magnetic stirring bar and fitted with a septum and protected by a calcium chloride tube. A solution of 2 mL (9 mmol) of **3a** in 5 mL of absolute ether was added, with continous stirring, over a period of 30 min. The mixture was then stirred for a further 4 h. The excess $LiAlH_4$ was destroyed by careful addition of ice–water, until hydrogen was no longer evolved, and 5 mL of 10% sulphuric acid was added to dissolve the precipitated aluminium hydroxide. The layers were separated, the aqueous layer extracted with ether three times, and the combined organic phases were then washed with sodium chloride, dried over magnesium sulfate, filtered, and concentrated by evaporation of the ether. The components of the mixture thus obtained were separated using PGC, and the following substances were collected.

2-Methyl-2,3-epoxy-1-propanol (6): yield, 362 mg (47.3%); IR (capillary cell) ν_{max} 3420, 2980, 2940, 2870, 1450, 1380, 1200, 1090 cm^{-1}; MS *m/e* 88 ($M^+ - 1$) (34), 75 (23), 74 (25), 59 (31), 58 (11), 57 (100), 43 (22), 41 (29), 39 (7), 31 (5), 29 (20); ^1H NMR (CCl_4) ν 1.3 (s, 3, CH_3), 2.53, 2.79 (AB q, 2, J = 5 Hz, CH_2OCCH_3), 3.56, (s, 2, CH_2OH), 3.97 (s, 1, CH_2OH). Anal. Calcd for $C_4H_8O_2$: C, 54.53; H, 9.15. Found: C, 54.42; H, 9.22.

2-Methyl-2-*tert*-butoxypropane-1,3-diol (7): yield, 1.092 g (74.9%); IR (capillary cell) ν_{max} 3450, 2970, 2870, 1370, 1250, 1100 cm^{-1}; MS, *m/e* (molecular ion was not detected) 105 (45), 75 (73), 59 (22), 58 (16), 57 (100), 56 (5), 43 (14), 41 (21), 31 (7), 29 (15); ^1H NMR (CCL_4) δ 1.05 (s, 3, CH_3–C), 1.16 [s, 9, $C(CH_3)_3$], 3.25 (s, 2, CCH_2OH), 3.32, 3.46 (AB q, 2, J = 12 Hz, CCH_2OH), 3.81 (s, 2, CH_2OH). Anal. Calcd for $C_8H_{18}O_3$: C, 59.23; H, 11.18. Found: C, 59.35; H, 11.20.

Diol **7** reacted with acetic anhydride forming a diacetate with a PMR spectrum that confirmed the structure of **7**: ^1H NMR ($CDCl_3$) δ 1.09 (s, 3, CCH_3), 1.12 [s, 9, $C(CH_3)_3$], 2.04 [s, 6, $C(O)CH_3$], 3.95 (s, 4, CH_2O).

The reduction of **3a** with excess $LiAlH_4$ (mol ratio 1:3) leads in addition to compounds **6** and **7** to the formation of 2-methylpropane-1,3-diol (**8**): IR (capillary cell) ν_{max} 3380, 2980, 2940, 2880, 1480, 1390, 1370, 1230, 1170, 1065, 990 cm^{-1}; ^1H NMR (CCl_4) δ 1.11 [s, 6, $C(CH_3)_3$], 3.30 (s, 2, CH_2OH), 3.43 (s, 2, OH). Anal. Calcd for $C_4H_{10}O_2$: C, 53.29; H, 11.20. Found: C, 53.15; H, 11.24.

Registry No. **1**, 52788-68-8; **3a**, 67872-66-6; **5a**, 89346-43-0; **5b**, 89346-44-1; **5b** (urethane derivative), 89346-45-2; **6**, 872-30-0; **7**, 89346-46-3; **7** (diacetate), 89346-47-4; **8**, 2163-42-0.

Synthesis of 3-Hydroxy-3-(hydroxymethyl)-5-methylcyclohexane-1,2-dione Dibenzoate, a Reported Hydrolytic Degradation Product of Leucogenenol

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2-Hydroxy-2-(hydroxymethyl)cyclohexanone (**3a**), 2-hydroxy-2-(hydroxymethyl)-4-methylcyclohexanone (**3b**), and 2-hydroxy-2-(hydroxymethyl)-5-methylcyclohexanone (**6**) were converted with MoO_5·pyridine·HMPA (MoOPH) into the respective 6-hydroxy analogues, which were oxidized with trifluoroacetic anhydride–Me_2SO–Et_3N to the corresponding α-diones **1a**, **1b**, and **9**. The title compound **1b** was not identical with a compound reported to have the same structure obtained by Rice through the degradation of leucogenenol.

For a projected (but now abandoned, at least temporarily) study of the biosynthesis of leucogenenol, a so-called thymothyroid hormone[1] of unknown structure[2-4] isolated from *Penicillium gilmanii*[3] and from various animal (including human) tissues,[5,6] we required the leucogenenol degradation product **1b**. Although a synthesis of this dione has previously been reported,[7] the method used was rather lengthy (eight steps from 5-methyl-1,3-cyclohexanedione). We therefore developed, and now report, the alternative synthetic route, shown in Scheme I, to **1b** (only one diastereomer of **1b** being obtained). The method developed is a useful route to cyclohexane-1,2-diones and was also used for the synthesis of diones **1a** and **9**.

Because of the commercial avaiability of **2a**, the route leading to **1a** was first attempted. Treatment of **2a** with trioxymethylene and alkali by a modification of a published method[8] gave **3a**, which was converted by treatment with excess benzoyl chloride in pyridine at 70 °C into the dibenzoate **4a**.[9] Treatment of **4a** with MoO_5·pyridine·HMPA (MoOPH)[10] gave a good yield of the α-hydroxy analogue **5a**, apparently a single stereoisomer (of unknown stereochemistry) as suggested by the NMR spectrum that showed a clean AB pattern for the CH_2O protons. Finally, oxidation of **5a** by treatment with trifluoroacetic anhydride–Me_2SO–Et_3N[11] gave the desired **1a** in fair yield. As expected, the compound was essentially completely enolized, showing a vinylic proton signal at δ 6.23.

† Worcester Foundation for Experimental Biology.
‡ Cornell University.

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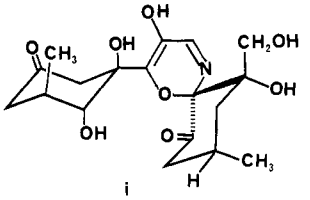
(2) The structure i for leucogenenol was proposed by Rice,[3] largely on the basis of degradative chemistry. However, this structure was recently



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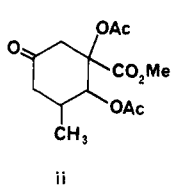

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shown to be untenable by Salomon et al.,[4] who synthesized all possible diastereomers of one of the degradation products having a proposed structure ii. None of the synthetic compounds was identical with the degradation product reported by Rice.[3]

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