

CHROMATOGRAPHIC METHODS FOR DETERMINING THE CONFIGURATION OF 1,2- AND 1,3- (UNSYMMETRICALLY SUBSTITUTED) DI-ALKYLGLYCEROL ETHERS

SUMMARY

The preparation of a series of 1,2- and 1,3-dialkylglycerol ethers as potential alternative substrates for biological and chemical studies is described. The absolute configurations of these compounds and their configurational purity can be determined by conversion into diastereomeric derivatives, the chromatographic properties of which are reported here. The gas-liquid chromatographic elution orders of the diastereomeric derivatives are discussed in relation to molecular size and shape.

INTRODUCTION

A resurgent interest in the chemistry of fungal lipases has led to a demonstration that these enzymes can be employed sometimes to resolve racemic secondary alcohols¹. In favorable cases this provides a facile method to obtain alcohols and esters in high configurational purity that have useful biological activity^{2,3} or are simply useful for organic synthesis. These observations appear to contrast with the data previously gathered in studies of hydrolyses of the lipase's natural substrate, triglycerides^{4,5}. The evaluations made have been limited, however, because the determination of configuration for mono-, di-, and triglycerides is quite laborious and not without some ambiguity⁶. We have been examining dialkylglycerol ethers and the corresponding esters (Fig. 1) as alternatives to di- and triglycerides, respectively, that we might more easily assess the stereobias in lipolytic reactions more precisely. Such "pseudolipids" have, in fact, been employed to study the transport properties of lipids⁷. In the present scheme, we expect that the stability of the ether links will assure the integrity of products formed by the lipolysis of an ester unit from a di-ether-ester of glycerol; *i.e.*, no further cleavage can occur due to lipase, nor can the familiar, and troublesome, intramolecular migration of an alkanoyl group occur.

In order to determine the stereochemical consequences of the reactions of such alcohols in esterification, or their esters in hydrolysis catalyzed by lipases, a method for configuration analysis was sought for the dialkylglycerol ethers. We report here the synthesis and characterization of 1,2- and 1,3-dialkylglycerol ethers, 1 and 2

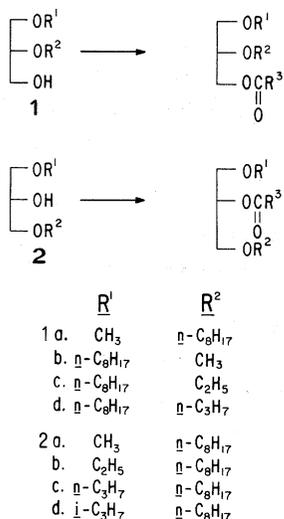


Fig. 1. Compounds prepared to study stereobias of lipase-catalyzed esterification and hydrolysis.

($R^3 = n$ -alkyl), the conversions of these alcohols to diastereomeric derivatives that are resolvable by gas-liquid chromatography (GLC), and discuss diastereomer elution order. The methodologies for synthesis and analysis are capable of extension and are expected to have broad application.

EXPERIMENTAL

GLC was performed with an SPB-1 column (30 m \times 0.25 mm I.D.), and an SP-2340 column (25 m \times 0.25 mm I.D.) (both purchased from Supelco, Bellefonte, PA, U.S.A.) with a 50:1 split ratio and helium carrier gas at a flow-rate adjusted to 18 cm/s. The instrument employed was a Shimadzu GC-mini-2 chromatograph, operated at the temperatures indicated in Tables I and II. High-performance liquid chromatography (HPLC) was performed using a Perkin-Elmer Model 2-LC pump, and a Waters Model 401 refractive index detector, and employing a silica gel column: LC-Si (15 cm \times 0.25 in. I.D.) from Supelco, with a flow-rate of 1.0 ml/min and solvent as indicated in Table II. Infrared data were recorded with a Perkin-Elmer 1310 spectrophotometer using 3% solutions in carbon tetrachloride. Mass spectra were obtained with a Hewlett-Packard HP-5995 GC/MS system employing an OV-1 column (30 m \times 0.25 mm I.D.) and isobutene for chemical ionization. 1H NMR and ^{13}C NMR spectra were obtained using a JEOL JNM-GX 400 Fourier transform (FT) NMR spectrometer with $[^2H]$ chloroform as the solvent and tetramethylsilane (TMS) as internal standard. The solvents employed were HPLC grade, and tetrahydrofuran (THF) was dried by distillation from lithium aluminum hydride (LAH). Hexamethylphosphoric triamide (HMPT) and dimethylformamide (DMF) were dried over M-13 molecular sieves. Sodium hydride (NaH) was a 44% oil dispersion (Ventron, Andover, MA, U.S.A.). Thin-layer chromatography (TLC) was performed with standard analytical plates of silica gel from Analtech (Newark, DE, U.S.A.).

TABLE I
GLC DATA FOR DIASTEREOMERIC CARBAMATES

Compound	SPB-1*		SP-2340**	
	α	k'	α	k'
2a-MBA***	1.028	3.57, 3.67	1.050	6.83, 7.17
2b-MBA	1.021	4.27, 4.36	1.040	6.17, 6.42
2c-MBA	1.017	5.27, 5.36	1.039	6.58, 6.83
2d-MBA	1.021	4.39, 4.48	1.022	5.42, 5.54
4-MBA	1.027	4.83, 4.96	1.200	5.92, 7.08
2a-NEA§	1.051	5.04, 5.30		
2b-NEA	1.040	5.52, 5.74		
2c-NEA	1.028	7.57, 7.78		
2d-NEA	1.034	5.87, 6.07		
4-NEA	1.045	5.39, 5.63		

* 260°C for MBA carbamates; 290°C for NEA carbamates.

** 240°C.

*** Chiral amine residue is (*S*)- α -methylbenzylamine (MBA).

§ Chiral amine residue is (*S*)- α -naphthylethylamine (NEA).

(*S*)- α -Methylbenzylamine (Hexcel, Zeeland, MI, U.S.A.), (*S*)- α -naphthylethylamine (Norse Labs., Santa Barbara, CA, U.S.A.), and (*S*)- α -naphthylethylethylisocyanate (Aldrich, Milwaukee, WI, U.S.A.) were used directly. Other reagents were purchased from Aldrich and used directly. Spectral data were consistent with the assignments of structure made for all new compounds. Selected data are presented below; refer to Fig. 2.

TABLE II
CHROMATOGRAPHIC DATA FOR DIASTEREOMERIC AMIDES

Compound	SPB-1*		SP-2340**		HPLC on silica gel***	
	α	k'	α	k'	α	k'
1a-MBA§	1.015	2.67, 2.71	1.079	5.30, 6.26	1.22	2.49, 3.03
1b-MBA	1.082	3.04, 3.29	1.083	5.08, 5.50	1.65	2.28, 3.76
1c-MBA	1.057	2.96, 3.13	1.039	4.33, 4.50	1.45	2.51, 3.64
1d-MBA	1.060	3.65, 3.87	1.036	4.42, 4.58		
1a-NEA§§	1.082	3.30, 3.57				
1b-NEA	1.112	3.83, 4.26			1.73	3.40, 5.89
1c-NEA	1.088	4.00, 4.35			1.45	2.30, 3.34
1d-NEA	1.072	4.70, 5.04			1.36	1.79, 2.43

* 260°C for MBA carbamates; 290°C for NEA carbamates.

** 240°C.

*** Solvent is ethyl acetate-hexane-tetrahydrofuran (15:83:2).

§ Chiral amine residue is (*S*)- α -methylbenzylamine.

§§ Chiral amine residue is (*S*)- α -naphthylethylamine.

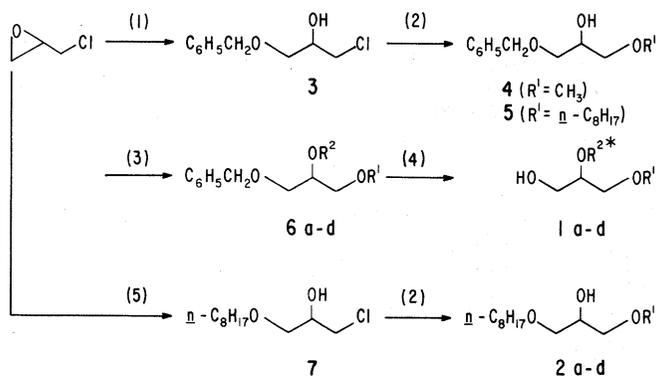


Fig. 2. Synthesis of 1,2- and 1,3-dialkylglycerol ethers. (1) $\text{C}_6\text{H}_5\text{CH}_2\text{OH}$, H^+ ; (2) NaOR' , $\text{R}'\text{OH}$; (3) NaH , THF ; R^2I ; (4) Na , $\text{C}_2\text{H}_5\text{OH}$; (5) $n\text{-C}_8\text{H}_{17}\text{OH}$, H^+ .

Preparation of chloroethers 3 and 7

Epichlorohydrin (20 ml, 0.26 mol) was allowed to react in benzyl alcohol (100 ml, 0.97 mol) containing 1 ml of sulfuric acid at *ca.* 50°C for 20 h. The reaction mixture was diluted with one volume of ether, washed sequentially with 1.25 *N* sodium hydroxide and water, and dried (magnesium sulfate). The solvent was removed by flash evaporation, benzyl alcohol was recovered by distillation at reduced pressure ($100\text{--}105^\circ\text{C}/30$ mm), and the chloroether 3 was obtained by further fractional distillation: 24.9 g (49%): b.p. $106\text{--}112^\circ\text{C}/0.6$ mm, IR 3580 cm^{-1} , $^1\text{H NMR}$ 3.3–3.5 (*ca.* 7H, m, CH_2Cl , CH_2O , CHOH), 4.54 (2H, s, ArCH_2O), 7.28–7.36 (5H, m, aryl H) ppm [chemical ionization mass spectrometry (CI-MS)] m/e 202 ($\text{M} + 1$), also 200, 126, 107, and 91 (base peak). Chloroether 7 was obtained in analogous fashion in 38% yield: b.p. $95\text{--}102^\circ\text{C}/0.5$ mm.

Synthesis of 1,3-dialkylglycerol ethers, 2a–d, 4, and 5

Compound 7 was allowed to react in absolute methanol with 3 equiv. of sodium methoxide under reflux for 16 h. The product was obtained by the usual workup and distilled to give an 84% yield of 2a: b.p. $95\text{--}98^\circ\text{C}/0.4$ mm, IR 3580 cm^{-1} , n_{D}^{20} 1.4382; $^1\text{H NMR}$ 0.87 (3H, t, CH_3), 1.28 (CH_2 envelope), 3.38 (3H, s, OCH_3), 3.3–3.6 (*ca.* 7H, CH_2O , CHOH) ppm; $^{13}\text{C NMR}$: 14.10, 22.66, 26.08, 29.25, 29.43, 29.60, 31.83, 59.18, 69.37, 71.72, 73.73 and 73.92 ppm; CI-MS m/e 219 ($\text{M} + 1$), 200 ($\text{M} - \text{H}_2\text{O}$), 173, 143, 111. The following compounds were obtained analogously in 65–90% yields using sodium hydride to generate the alkoxide of the required alcohol: 2b, b.p. $102\text{--}103^\circ\text{C}/0.6$ mm, n_{D}^{20} 1.4376; 2c, b.p. $116\text{--}124^\circ\text{C}/1.0$ mm, n_{D}^{20} 1.4385; 2d, b.p. $104\text{--}105^\circ\text{C}/0.5$ mm, n_{D}^{20} 1.4370; 4, b.p. $103\text{--}106^\circ\text{C}/0.4$ mm, n_{D}^{26} 1.5059; and 5, b.p. $160\text{--}173^\circ\text{C}/0.5$ mm, n_{D}^{26} 1.4859 (the latter compound distilled in a Hickman still).

Synthesis of trialkylglycerol ethers 6a–d

Compound 4 (5.5 g, 28.1 mmol) was converted to its sodio derivative in THF (50 ml) with sodium hydride (1.8 g, 40 mmol) that had been washed with hexane. 1-Iodooctane (9.7 ml, 50 mmol) was injected with 20 ml of HMPT, and the mixture was stirred for 16 h at $45\text{--}50^\circ\text{C}$. The reaction was worked up in the usual manner

using hexane. Because the product contained some unalkylated material (TLC), it was chromatographed over silica gel (40 g) and the triether was eluted with 5% ethyl acetate-hexane to yield 3.9 g of 6a (45%). A sample was distilled (Hickman): b.p. 170°C/0.5 mm, n_D^{26} 1.4770, IR 1125 $^{-1}$ cm, 13 C NMR 14.06, 22.62, 26.04, 29.24, 29.41, 30.04, 31.79, 59.20, 70.02, 70.55, 72.71, 73.33, 77.74, 127.51, 128.27 ppm, CI-MS m/e 307 (M-1), 277 (M+1-CH₃O), 193, 165, 105 (base peak). Preparations of triethers 6b-d were similar but excluded HMPT as a cosolvent and were conducted at ambient temperature. Thus were obtained from 5 in 85-90% yield: 6b, 170°C/0.3 mm, n_D^{26} 1.4753; 6c, 155-161°C/0.5 mm; 6d, 160-166°C/0.5 mm.

Synthesis of 1,2-dialkylglycerol ethers 1a-d

Triether 6a (3.7 g, 12 mmol) was placed in a vessel to which was added freshly cut sodium (4 g). Absolute ethanol was added in 10-ml portions and the mixture allowed to reflux until the sodium had been consumed. The mixture was cooled and acetic acid added to neutralize the base. The mixture was diluted with ether and filtered to remove most of the sodium acetate. After concentration, the residue was taken up in ether and washed with brine. After drying (magnesium sulfate) and concentrating, the organic product was distilled to give 2.09 g (80%) of 1a: b.p. 98-102°C/0.6 mm; n_D^{26} 1.4379; IR 3580 cm $^{-1}$; 13 C NMR 14.06, 22.62, 26.05, 29.22, 29.39, 30.01, 31.79, 59.29, 62.69, 70.37, 72.63 and 78.31 ppm. CI-MS m/e 219 (M+1), 187, 173, 156, 137. The 1,2-dialkylglycerol ethers 1b-d were obtained in 65-95% yields: 1b, b.p. 100-107°C/0.4 mm, n_D^{26} 1.4388; 1c, b.p. 99-101°C/0.4 mm, n_D^{20} 1.4411; 1d, b.p. 110-112°C/0.4 mm, n_D^{20} 1.4425.

Procedures to derivatize the dialkylglycerol ethers (Fig. 3)

1,2-Dialkylglycerol ethers (primary alcohols). The racemic alcohol (50-100 μ l) was dissolved in 10 ml of acetone and cooled in ice with stirring while Jones reagent⁸ was added dropwise until the orange color persisted. The mixture was diluted with two volumes of brine and extracted with three portions of ether totaling 100 ml. The ether extract was washed with brine, dried (magnesium sulfate), and concentrated to dryness (benzene was employed to azeotrope residual moisture using flash evaporation). The crude acid was converted to its acid chloride using thionyl chloride-DMF (0.2 ml/20 μ l) in anhydrous ether⁹. The crude acid halide was freed of ether and dissolved in 5 ml of methylene chloride. A solution of (*S*)- α -methylbenzylamine, or (*S*)- α -naphthylethylamine, (0.1 ml) and triethylamine (0.3 ml) in 5 ml of methylene chloride was added and the resulting mixture allowed to stand for 0.25 h. The mixture was washed with 1 *N* hydrochloric acid, and water; then the solvent

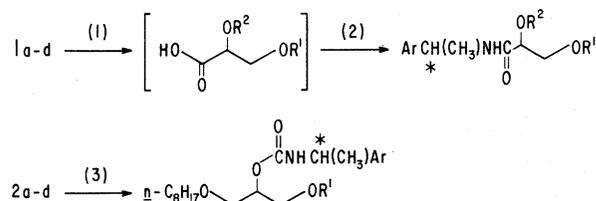


Fig. 3. Reactions to convert the dialkylglycerol ethers to diastereomers for analysis. (1) CrO₃, acetone; (2) SOCl₂, DMF, ether; (*S*)-ArCH(CH₃)NH₂; (3) (*S*)-ArCH(CH₃)NCO.

was removed. Although the amides so obtained could be analyzed directly, the following procedure was used as a protection for the GLC columns: the amides were passed through a disposable pipet that was half filled with silica gel in hexane (*ca.* 1 g). Elution was effected with 5 ml of 10% ethyl acetate–hexane followed by 20 ml of 20% solvent. No fractionation of the diastereomers was observed.

1,3-Dialkylglycerol ethers (secondary alcohols). These alcohols (10 μ l) were allowed to react with 20 μ l of (*S*)- α -methylbenzylisocyanate¹⁰, or (*S*)- α -naphthylethylisocyanate, in a screw-cap vial at 50–60°C for 1 h. Excess isocyanate was discharged with 0.1 ml of methanol (50–60°C for 0.25 h). The resulting carbamates were then diluted for analysis.

Absolute configuration of the eluting diastereomers (Fig. 4)

Synthesis of (S)-1-n-octyl-2-methylglycerol diether, (S)-1b (Fig. 4). A sample of the acetonide of glycerol (2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane) was obtained that was 82% ee (*S*)¹¹. This alcohol was benzylated, then hydrolyzed to give chiral 1-benzylglycerol ether, 8¹². Cyclization to epoxide 9¹² was followed by reaction with 1-octanol as described above for the reaction of epichlorohydrin to give a chiral 1,3-dialkylglycerol ether. This was converted to triether 10 as described for the racemic compound 6b, and the triether was finally debenzylated in the usual manner to provide a sample of (*S*)-1b, 82% ee, $\alpha_D^{20} = -2.02$ (ethanol, C = 5.7).

Synthesis of (R)-1-methyl-3-n-octylglycerol diether (Fig. 5). The chiral acetonide of glycerol was converted to the *n*-octyl ether, then hydrolyzed to the chiral 1-*n*-octylglycerol ether 12 as previously described. Compound 12 was monotosylated¹² and allowed to react with excess sodium methoxide in methanol to give a sample of (*R*)-2a; $\alpha_D^{25} = 7.9$ (ethanol, C = 6.67).

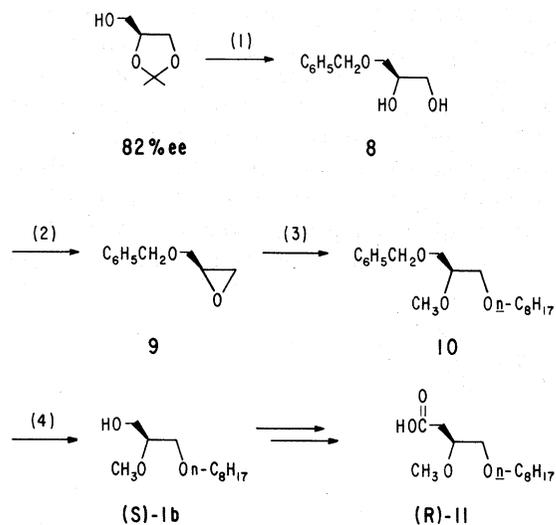


Fig. 4. Synthesis of (*R*)-2-methoxy-3-*n*-octyloxypropanoic acid. (1) NaH, THF, C₆H₅CH₂Cl; H₃BO₃; (2) *p*-TsCl, pyridine; NaOCH₃, CH₃OH; (3) *n*-C₈H₁₇OH, M⁺; NaH, THF, CH₃I; (4) Na, C₂H₅OH.

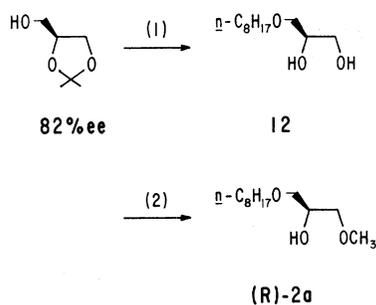


Fig. 5. Synthesis of (*R*)-1-methyl-3-*n*-octylglycerol diether. (1) NaH, THF, C₈H₁₇Br; H₃BO₃; (2) p-TsCl, pyridine; excess NaOCH₃, CH₃OH.

RESULTS AND DISCUSSION

Synthesis

The desired unsymmetrically substituted dialkylglycerols were synthesized starting with epichlorohydrin as shown in Fig. 2. Reaction of epichlorohydrin with benzyl alcohol gave 3-chloropropane-1,2-diol 1-benzyl ether, 3. Compound 3 was transformed to glycerol 1-benzyl 3-methyl diether, 4, by warming with sodium methoxide in methanol. The analogous 3-*n*-octyl ether, 5, was similarly prepared using sodium hydride in 1-octanol. The triethers 6a-d were then prepared by forming the alkoxides of the dialkylglycerols 4 and 5 and allowing these to react with the appropriate alkyl iodides in THF. After the triethers had been purified by column chromatography, the benzyl group was removed using sodium-ethanol to produce the 1,2-dialkylglycerols 1a-d.

The 1,3-dialkylglycerols could be prepared more directly. Reaction of epichlorohydrin with 1-octanol gave 3-chloropropane-1,2-diol 1-*n*-octyl ether, 7, that by reaction with sodium hydride in the appropriate alcohol yielded the diethers 2a-d.

Derivatization for analysis

Secondary alcohols in which the carbinol carbon is asymmetric frequently form separable diastereomeric carbamates by reaction with either α -methylbenzyl isocyanate, or the α -naphthylethyl analog. Such separations, including order of diastereomer elution and a conceptual model to explain relative retentions of diastereomers, have been discussed for both HPLC¹³⁻¹⁶ and GLC¹⁷. The 1,3-dialkylglycerols 2a-d were viewed as similar to simple dialkylcarbinols in which alkyl substituents were replaced by alkoxymethyl groups. These were converted to α -methylbenzyl and α -naphthylethyl carbamates with (*S*)- α -methylbenzyl isocyanate and (*S*)-naphthylethyl isocyanate, respectively (Fig. 3). The separation factors for these compounds on the nonpolar GLC phase, SPB-1, and polar SP-2340 are given in Table I. As expected, the separation factors were greater for the naphthyl derivatives. However, the retentions of the naphthyl carbamates were greater and this limited their usefulness. Separations were greater with the polar column, and better for those diastereomeric pairs that had alkyl substituents of large size difference. An example of the separations of the α -methylbenzyl carbamates is given in Fig. 6.

For primary alcohols in which the center of asymmetry is the adjacent carbon atom, separation after conversion to diastereomers is less assured. The α -naphthyl-ethyl carbamate of 1a was partially resolved by SP-2340, but 1b was not resolved at all. We therefore turned to chemical elaboration of the subject alcohols to produce a greater degree of functionalization at the asymmetric carbon. The 1,2-dialkyl ethers 1a–d were oxidized with Jones' reagent to the corresponding acids (Fig. 3). The conditions for the oxidation are quite mild and have been shown to occur without measurable racemization of a structurally similar compound, the 1,2-acetonide of glycerol¹⁸. The crude acids so obtained were exposed to thionyl chloride in anhydrous ether (catalytic DMF) to convert them to acid halides, that were then allowed to react directly with (*S*)- α -methylbenzylamine or the corresponding naphthyl compound. The sequence may seem lengthy, but several samples could be conveniently and simultaneously handled, and 50-mg samples were routinely processed with no effort made to determine minimum sample size.

Separations of diastereomeric pairs were evaluated with both the SPB-1 and SP-2340 phases (Table II). For the series 1b–d the separation factor was greatest when the relative size of the alkyl groups was largest, and a comparison of separations for the pairs 1a and 1b indicates that the effect of alkyl group size is maximal if the larger alkyl group is on the primary carbinol oxygen. These amides are also readily separated by HPLC on silica gel (Table II); separation factors tended to show the same variation with structure. An example of the separations of the α -methylbenzylamides by GLC is given in Fig. 7.

Elution order of diastereomers

The 1,2-acetonide of glycerol can be obtained from 1,2:5,6-di-*O*-isopropylidene-*D*-mannitol, by a sequence of reactions that involves oxidative cleavage of this readily available meso structure¹⁹. Depending upon reaction conditions, the desired acetonide is obtained with a strong configurational bias¹¹. This compound is a very

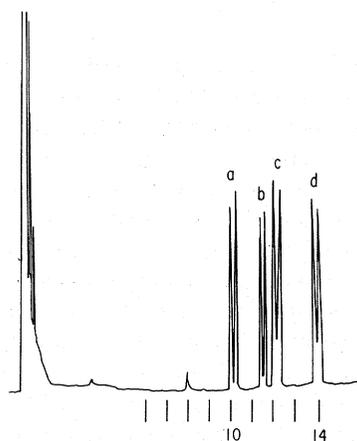


Fig. 6. α -Methylbenzyl carbamates of 2a–d superimposed. GLC, SPB-1 (30 m \times 0.25 mm I.D.) at 260°C. The *R,S*-diastereomer of a pair elutes first. Retention time is given in minutes.

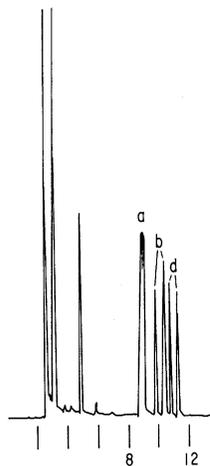


Fig. 7. α -Methylbenzylamides of 1a,b,d (alcohols oxidized first to acids). GLC, SPB-1 (30 m \times 0.25 mm I.D.) at 260°C. The *R,S*-diastereomer of a pair elutes first. The 1c diastereomers overlap 1b and d. Retention time is given in minutes. The amides from oxidized 1a are cleanly resolved on SP-2340 (Table II, $\alpha = 1.079$).

useful chiral synthon. Our sample was 82% ee (91:9) (*S*)-2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane. This was determined by oxidation to the acid and conversion to diastereomerically separable amides with (*S*)- α -methylbenzylamine¹⁸. This configurationally enriched material was employed as the chiral synthon from which were synthesized (a) a chiral 1,2-dialkylglycerol diether (Fig. 4), and (b) a chiral 1,3-dialkylglycerol diether (Fig. 5), that were employed as the basis for determining the absolute configurations of the stereoisomers being separated.

Benzylation of the 1,2-acetonide of glycerol (Fig. 4), followed by boric acid mediated hydrolysis of the ketal gave (*R*)-1-benzylglycerol ether, 8. Treatment of this vicinal diol with *p*-toluenesulfonyl chloride (*p*-TsCl) and pyridine in benzene followed by brief treatment with methoxide-methanol produced the epoxide 9. Compound 9 was allowed to react with 1-octanol in the presence of a trace of acid to give a 1,3-diether that was then methylated to the triether 10. Debenzylation led to (*S*)-1-octyl-2-methylglycerol diether, (*S*)-1b. The analytical protocol, oxidation of the primary carbinol to the corresponding carboxylic acid 11, produces the (*R*) configuration for that structure. The derivatization procedure gave a 92:8 ratio of diastereomers in which the earlier eluting peak (GLC) was the major (*R,S*) isomer. The elution order was the same on both polar and nonpolar GLC phases and was reversed on HPLC.

A complementary sequence of reactions was initiated by converting the acetonide to an octyl ether (Fig. 5) and then cleaving the ketal to produce (*R*)-1-*n*-octylglycerol ether, 12. Tosylation of the primary carbinol followed by reaction with excess methoxide-methanol gave (*R*)-1-methyl-3-*n*-octylglycerol diether, (*R*)-2a, presumably via the intermediacy of the epoxide. The analysis of the carbamates formed from (*S*)- α -methylbenzylamine gave a 9:1 ratio of diastereomers in which the earlier eluting GLC material was again the (*R,S*) isomer.

Pioneering work by Pirkle and co-workers^{15,16} and Helmchen and co-workers^{13,14} served as inspiration to generate pseudolipids such as 1 and 2 with the ex-

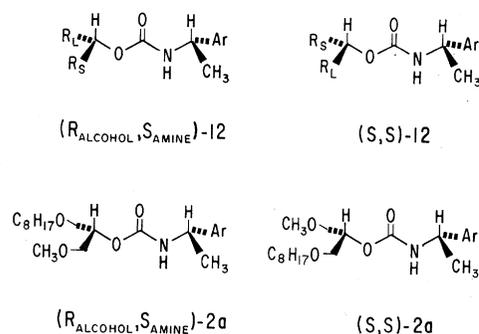


Fig. 8. Probable solution conformation preferences of carbamates. R_S = smaller alkyl group; R_L = larger alkyl group.

pectation that the derivatives described would indeed be separable. It is therefore instructive to compare the diastereomer elution orders for these derivatives with those of the simpler (non-ether) analogues for which the predictive models had been developed. In the carbamates the two asymmetric centers are attached by an array of atoms made coplanar in the lowest energy rotational conformation (Fig. 8). The alkyl (aryl) substituents on these centers extend to either side of this plane. Elution orders on HPLC are explained on the basis of a combination of hydrophobicity and steric bulk^{15,16}, while the GLC separations on nonpolar phases can be explained on the basis of molecular shape and are reversed from the HPLC order of elution¹⁷. Briefly, if the larger alkyl substituent (R_L) on the oxygen-bearing asymmetric center is opposed to the aryl group of the amine-based center (Fig. 8, R,S -12), the structure is cisoid (erythroid^{15,16}), and for unbranched hydrocarbon groups convention defines this structure (R,S). This structure is less extended than the (S,S) isomer that has the R_L and aryl groups across that central backbone (transoid). The less extended (R,S) isomer elutes first from GLC columns. Barring unforeseen specific bonding interactions, the situation for carbamates formed from 1,3-dialkylglycerol diethers is anal-

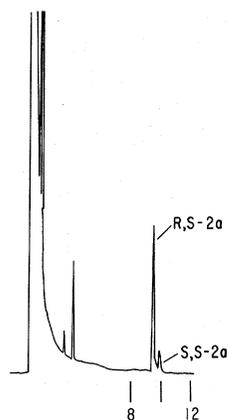


Fig. 9. Elution of (S)- α -methylbenzyl carbamate of (R)-1-methyl-3- n -octylglycerol (82% ee) on SP-2340 (30 m \times 0.25 mm I.D.) at 240°C. The (R,S)-diastereomer elutes first. Retention time is given in minutes.

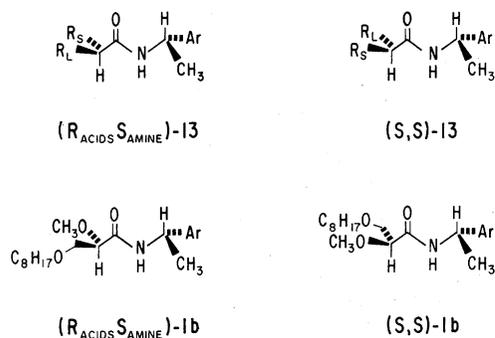


Fig. 10. Solution conformation preferences of amides 13 and analogous conformations for the diastereomers of 1b. R_S = smaller alkyl group; R_L = larger alkyl group.

ogous (Fig. 8). Although more penetrating studies are required to clearly define the solution conformation preferences of these new derivatives, the elution orders that one would predict from Pirkle's model appears to hold, and the (R,S) isomer elutes first from GLC columns (Fig. 9).

A similar picture has been devised for amides that are derived from α -branched carboxylic acids such as 13 (Fig. 10). The less extended, or cisoid, structure is the (S,S) -diastereomer, which elutes first on GLC. The analogy for 2,3-dialkoxypropanoic acids, *e.g.* 1b (Fig. 10), as ether versions of α -alkylalkanoic acids does not hold, however, the (R,S) isomer elutes first instead (Fig. 11). The separations obtained for these diastereomers are not simply diminished compared with those of type 13 as one might expect for weakened solution conformation preferences that tend to wash out the differences between diastereomers, but have been dramatically inverted. This implies another, probably pronounced rotational energy minimum for such molecules. The 1H NMR spectrum of amides 13 ($R_S = CH_3$; $R_L = aryl = phenyl$) offer evidence

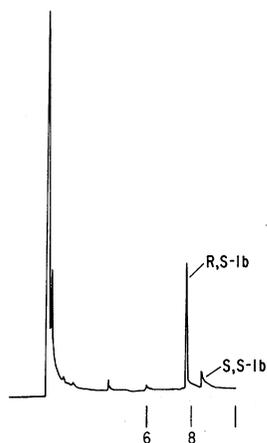
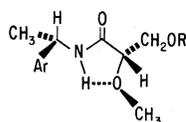


Fig. 11. Elution of (S) - α -naphthylethylamide of (R) -2-methoxy-3-*n*-octyloxypropanoic acid (82% ee) on SPB-1 (30 m \times 0.25 mm I.D.) at 290°C. The (R,S) -diastereomer elutes first. Retention time is given in minutes.



(*S,S*)-1b

R = *n*-C₈H₁₇
Ar = 1-Naphthyl

Fig. 12. Possible major conformation for (*S*)-1-(1'-naphthyl)ethylamide of (*S*)-2-methoxy-1-*n*-octyloxypropanoic acid showing basis for shielding of methoxyl protons by the naphthyl group.

for their conformations; methyl substituents that are opposed to aryl groups experience an upfield shift. Were (*R,S*)-1b in the conformation shown (Fig. 10) one would expect the methoxyl protons to be similarly affected and also that this diastereomer would be retained longer on GLC. In fact the reverse is true [¹H NMR for CH₃O:(*S,S*)-1b, 3.26 ppm; (*R,S*)-1b, 3.44 ppm]. One possible explanation for this is that the secondary ether oxygen is positioned to donate to the hydrogen of the amide nitrogen (Fig. 12). In this conformation it would be the (*S,S*) isomer that would exhibit a shielded methoxyl group. This structure is the more extended (aryl and aliphatic chain are on opposite sides of the central plane of the molecule) and could be expected to be retained longer on GLC.*

Summarizing, 1,2- and 1,3-dialkylglycerol ethers have been synthesized and chromatographic methods have been developed that permit an analysis of stereochemical configuration. Enzymatic esterifications of these monohydric alcohols can now be probed for stereochemical consequences using these compounds as more chemically stable analogs of 1,2- and 1,3-diglycerides. Other lipase-mediated reactions that would be both academically and industrially interesting include hydrolysis of the corresponding esters, as well as transesterifications. Such reactions could be similarly monitored for stereobias.

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We note that interchanging the methyl and octyl groups of each diastereomeric derivative of 1b to create the corresponding isomers of 1a does *not* change the configuration designations; *i.e.*, (*R,S*)-1b becomes (*R,S*)-1a. The relative size of the substituents on the asymmetric carbon, however, has become reversed. The predictive role of the model, of course, takes no cognizance of *R* and *S* designation, and a unifying model for these ethers would be obliged to predict a reversal of designators for elution order of diastereomeric pairs.

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