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SYNTHESIS, CHIROPTICAL PROPERTIES AND ABSOLUTE CONFIGURATION OF α-PHENYLGLYCIDIC ACID

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Abstract
The (+)- and (-) enantiomers of potassium α-phenylglycidate, an irreversible inhibitor of the enzyme mandelate racemase, were synthesized by resolution of the diastereomeric esters with R-(-)-2-octanol. Base-catalyzed ring-opening of the resolved α-phenylglycidate esters gave the enantiomers of 2,3-dihydroxy-2-phenylpropanoic acid, also obtained by resolution of the racemic dihydroxy acid using ephedrine. A comparison of the chiroptical properties of the esters of α-phenylglycidic and 2,3-dihydroxy-2-phenylpropanoic acids with those of the structurally similar atrolactic and mandelic acids and their 2-methoxy-derivatives showed that the (-)-methyl 2,3-dihydroxy-2-phenylpropanoate corresponding to the (+)-enantiomer of potassium α-phenylglycidate, as well as the esters of α-phenylglycidic acid derived from the same (+)-potassium salt, were all configurationally related to S-(+)-atrolactic and mandelic acids. The configurational assignments made on the basis of the chiroptical data were confirmed by lithium aluminum hydride reduction of the (-)-2-octyl S- and R-α-phenylglycidates, which led exclusively to the R-(-)- and S-(+)-2-phenyl-1,2-propanediols, respectively, previously related configurationally to R-(-)- and S-(+)-atrolactic acids.

Introduction

Enzymes exhibit remarkable stereospecificity for their physiological substrate. Except in the case of the interconversion of isomers, enzymes almost always will process a reaction with only one isomer[1]. Mandelate racemase, responsible for the racemization of either R- or S-mandelate, catalyzes its reaction with a surprising symmetry, i.e., the kinetic constants are nearly identical in either direction[2]. An exception to this symmetry became evident upon the incubation of the enzyme with the resolved enantiomers of potassium α-phenylglycidate (1 and 2) - active-site-directed irreversible inhibitors of the enzyme[3]. Therefore, it was of considerable interest and importance to assign the absolute configuration of these compounds.

This paper describes the resolution of α-phenylglycidic acid and the characterization of the enantiomers of the acid as the methyl esters and potassium salts. Ring-opening of the epoxide moiety to 2,3-dihydroxy-2-phenylpropanoic acid, and chiroptical comparison of these compounds with the structurally similar atrolactic and mandelic acids and their 2-methoxy derivatives, allowed configurational assignments to be made, which were confirmed by the conversion of α-phenylglycidate to 2-phenyl-1,2-propanediol of known configuration.

Results and Discussion.

Ethyl atropate was synthesized from ethyl phenylacetate and diethyl oxalate according to the procedure of Ames and Davey.[4] Saponification of the ester yielded the free acid which was esterified with excess R-(-)-2-octanol in the presence of a catalytic amount of sulfuric acid. After distillation the resulting octyl atropate was treated with a 50% excess of m-

chloroperbenzoic acid to yield the diastereomeric mixture of the R-(-)-2-octyl R,S-α-phenylglycidates. Preliminary work had indicated that these racemic epoxides could be separated as their diastereomeric R-(-)-octyl esters using either high or low pressure liquid chromatography.[5] Resolution employing the so-called Pirkle column[6] failed, while treatment of the free acid with resolving agents such as brucine or ephedrine was not favored because of the instability of epoxides towards acids and bases. The mixture was therefore fractionated using low pressure liquid chromatography, affording the diastereomeric R-(-)-2-octyl S- and R-α-phenylglycidates (3 and 4) as two overlapping peaks. Portions of the peaks were collected, concentrated, and reinjected onto the column. In this manner, it was possible to obtain compound 3 78% optically pure and 4 75% optically pure. Optical purity was determined by capillary gas chromatography which separated the two diastereomers.

The separated octyl α-phenylglycidates (3 and 4) were saponified with slightly more than one equivalent of potassium hydroxide to yield the desired enantiomeric potassium salts of α-phenylglycidic acid (1 and 2). The potassium salt of the R-(+)-enantiomer gave a specific rotation of +41°. More potassium hydroxide and a longer reaction period was used to obtain the potassium salt of the S-(-)-enantiomer, and it is therefore possible that some racemization occurred during this step, which would account for the lower specific rotation of this potassium salt. The enantiomeric salts (1 and 2) were separately converted into their methyl esters by complexing the salts with 18-crown-6 ether and dissolving the resulting complex in tetrahydrofuran; addition of iodomethane yielded oils which were subjected to "flash chromatography"[7] to afford the pure methyl α-phenylglycidate esters (5 and 6). An attempt to acidify the salts at low temperature, followed by treatment with diazomethane, resulted only in uncharacterized polymeric material. The methyl esters 5 and 6 did not have a measureable rotation at the D line. However, in order to show that racemization had not occurred during the methylation procedure, the methyl α-phenylglycidate (5) was saponified back to its precursor potassium salt (1) which was found to have a rotation in excess of 96% of its original value.

For configurational comparison 2,3-dihydroxy-2-phenylpropanoic acid [α-phenylglyceric acid (7)] was required. Ethyl R,S-α-phenylglycidate, synthesized according to Fee et al.,[8] and purified further by flash chromatography, was hydrolyzed in the presence of an excess of potassium hydroxide to yield potassium R,S-α-phenylglycerate which was in turn acidified to yield the free R,S-α-phenylglyceric acid.

The structural similarities between mandelic acid (8) and α-phenylglyceric acid suggested that (-)- and (+)- ephedrine, known to resolve racemic mandelic acid, could be used to resolve α-phenylglyceric acid. This proved to be the case, and (-)-ephedrine gave (after three crystallizations) a (-)-ephedrine (+)-α-phenylglycerate salt of constant melting point from which acid treatment produced (+)-α-phenylglyceric acid (17). In the same way (+)-ephedrine afforded an enantiomeric salt from which (-)-α-phenylglyceric acid (7) was obtained. The resolved (+)- and (-)-α-phenylglyceric acids (17 and 7) were treated with an excess of diazomethane to yield the optically active methyl esters (16 and 9), which were purified using flash chromatography.

The potassium salt (18) of R-(+)-α-phenylglyceric acid (17) was also produced directly from (-)-2-octyl R-α-phenylglycidate (4) by saponification in the presence of excess base. The NMR spectrum of the material produced by this reaction was identical to that of potassium R,S-α-phenylglycerate obtained earlier.

The chiroptical properties of (-)-methyl 2,3-dihydroxy-2-phenylpropanoate (9) were compared with those of the analogous R-(-)-methyl atrolactate 10 in the 200 to 250nm region, where earlier work[9] on α-hydroxy-substituted phenylacetic acids has shown that a correlation exists between the sign of the circular dichroism (CD) maxima and the absolute configuration. The CD spectra of (-)-9, R-(-)methyl atrolactate (10), and R-(-)-atrolactic acid (11) were found (Table) to be superimposable, showing strong negative CD maxima at 222nm and weak positive maxima at 240 to 246nm (Figs. 1 and 2). The corresponding R-(-)-mandelic acid (8) and its O-methyl ether R-(-)-2-methoxyphenylacetic acid (12) exhibited the same strong negative CD maxima at 224nm, but lacked the weak, oppositely-signed band in the 245nm region.

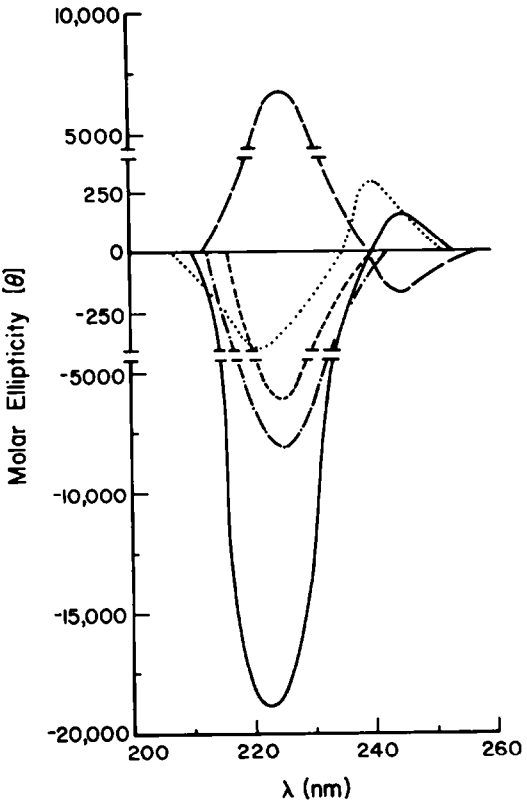


Fig. 1.

Circular dichroism spectra of R-(-)-2-octyl S-α-phenylglycidate 3 (•——•——•), R-(-)-2-octyl R-α-phenylglycidate 4 (———), methyl S-α-phenylglycidate 5 (– – – – –), methyl S-(-)-2,3-dihydroxy-2-phenylpropanoate 9 (————) and methyl R-(-)-atrolactate 10 (·····).

These results are in good agreement with data reported earlier [9] for α-hydroxyphenylacetic acids in which the Cotton effect (C.e.) observed at 220-225nm is assigned (on the basis of low temperature CD measurements) to the preferred (more highly populated) conformation A (see Fig. 3) which is energetically favored, whereas the smaller and oppositely-signed Cotton effect in the 240 to 245 nm region is associated with the much less highly populated conformation B, where Fig. 3 represents the octant projection of the carboxylic acids[9,10].

In the case of mandelic acid (8) and its O-methyl ether (12) only the 224 nm CD maximum is found, in agreement with the calculated preferred conformation A[11], while in compounds 10 and 11, the presence of a small percentage (2 to 7%) of the less populated rotamer B is indicated on the basis of the small C.e. at 240 to 245nm.

From the above chiroptical data, the S-configuration may be assigned to (-)-7 and (-)-9, showing them to be configurationally related to R-(-)-8, 10, 11, and 12.

The two enantiomeric methyl α-phenylglycidates (5) and (6) were next examined. The enantiomer 5 showed a strong negative CD maximum at 225nm [superimposable on that of R-(-)- methyl atrolactate (10)]; the lack of any observable C.e. in the 240 nm region indicated the absence of the second (minor) conformer. On the basis of the chiroptical data, 3 and 5 (and therefore the potassium salt 1) may be assigned the S-configuration and the enantiomers 4 and 6 (and therefore the potassium salts 18 and 2) the R-configuration.*

*Footnote: Configuration is now S because of change in priorities due to sequence rules in Cahn-Ingold-Prelog system.

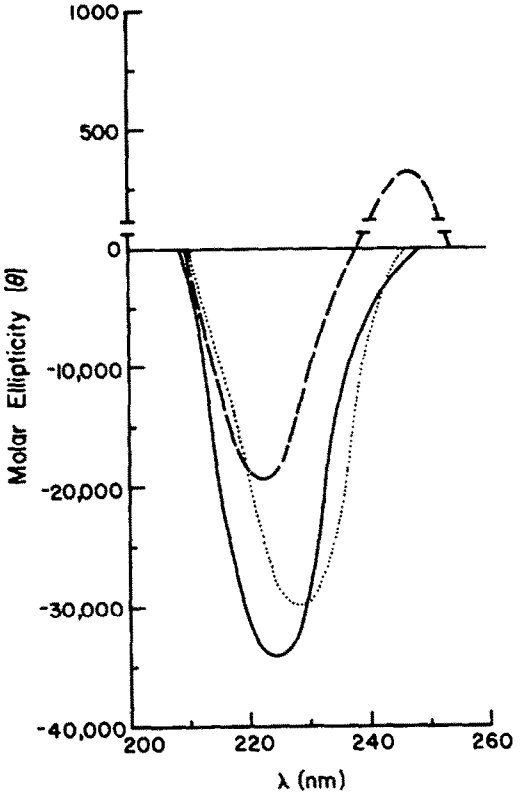


Fig. 2.

Circular dichroism spectra of R-(-)-mandelic acid 8 (———), R-(-)-atrolactic acid 11 (— — —) and (-)-menthyl R-(-)-2-methoxy-2-phenyl-propanoate 13 (·····).

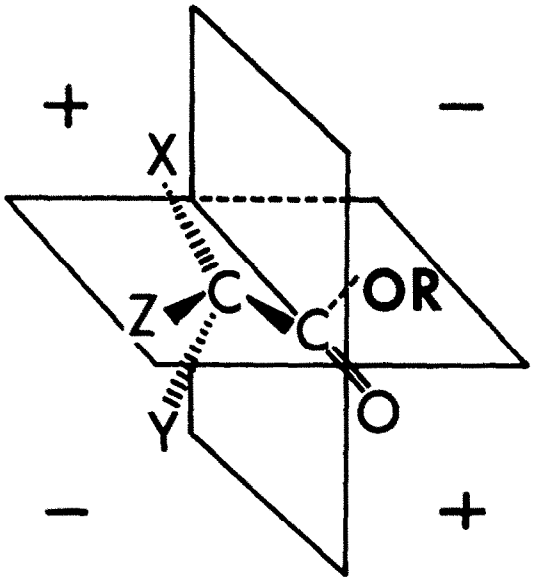


Fig. 3.

Octant projection for S-α-hydroxyphenylacetic acids.

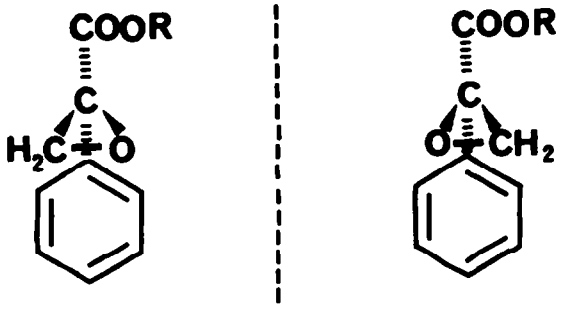
	Substituents			
CONFORMATION	X	Y	Z	R
A	C_6H_5	H	OH	H
B	OH	C_6H_5	H	H

The CD spectra of the diastereomeric R(-)-2-octyl esters 3 and 4 proved to be interesting. Compound 3 showed chiroptical properties superimposable on those of 5, i.e., a strong negative C.e. at 225nm and no CD maximum at 245nm, again suggesting the existence of a single conformer. Since the R-(-)-2-octanol chiral center has a transition in the $n \rightarrow \sigma^*$ region of the alcohol oxygen only (about 175nm), it will not interfere with the appearance of a transition in the 200-250 nm region.

The diastereomer 4 had a strong mirror image positive CD maximum at 225nm, and in addition showed a small negative CD at 253nm, pointing to the presence of a small (ca. 2.5%) percentage of a second conformer. Examination of molecular models suggests that this behavior of the two diastereomeric esters 3and 4 is due to the conformational effect caused by the R-(-)-2-octanol moiety present in both compounds.

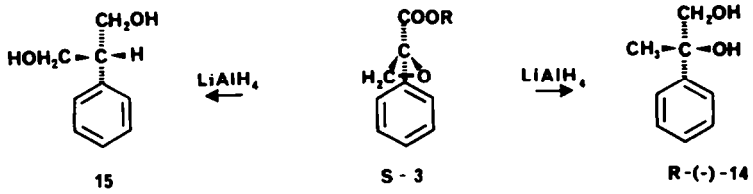
For comparison with the diastereomeric R-(-)-2-octyl esters 3 and 4, the chiroptical properties of the similarly constituted diastereomer (-)-menthyl R-(-)-2-methoxy-2-phenylpropanoate (13) were examined. This substance exhibited (Table) a strong negative C. e. at 228nm, superimposable on that of its parent compounds 10 and 11, but lacking the small positive C. e. at 245nm shown by these compounds. In this respect 13 therefore resembled its configurationally related diastereomeric analogue 3 which similarly existed in a single preferred conformation (Table).

Chemical evidence supporting the above configurational assignments based on chiroptical data was provided by the conversion, using $LiAlH_4$ reduction, of the octyl α-phenylglycidate esters 3 and 4 to 2-phenyl-1,2-propanediol of known absolute configuration.



1 R = K
3 R = (-)-2-octyl
5 R = CH_3

2 R = K
4 R = (-)-2-octyl
6 R = CH_3



15 S - 3 R-(-)-14

It is well known that lithium aluminum hydride will reduce epoxides to replace the carbon-oxygen bond with a carbon-hydrogen bond[12]. It is also established that the hydride will generally attack at the least hindered carbon atom[12]. In this case, the β-position will be the more vulnerable site to attack. With the simultaneous reduction of the ester to the primary alcohol, the reduction of the octyl esters 3 and 4 could lead either to the optically active product 14 or to the achiral product 15, which are easily distinguishable by the respective NMR spectra.

An NMR spectrum indicated that the product consisted entirely of 2-phenyl-1,2-propanediol (14), with no evidence for the presence of 15. This conclusion is based on six different reductions of either the racemic mixture or the isolated diastereomeric octyl esters. Reduction of R-(-)-2-octyl S-α-phenylglycidate (3) by $LiAlH_4$ gave R-(-)-2-phenyl-1,2-propanediol (14), while the diastereomeric ester 4 afforded the enantiomeric S-(+)-2-phenyl-1,2-propanediol.

Eliel and Freeman[13] established that the absolute configuration of (+)-2-phenyl-1,2-propanediol was S by a $LiAlH_4$ reduction of S(+)-atrolactic acid (11 indicates the R-isomer) of known optical purity and stereochemistry. Since application of the sequence rules had not changed the order of the priorities of the substituents, the (+)-2-phenyl-1,2-propanediol was assigned the S configuration.

Mitsui and Imaizumi[14] reduced the R-(-)- and S-(+)-methyl and ethyl atrolactates (e.g., 10) of known optical purity and configuration, with $LiAlH_4$ to produce the individual (+)- and (-)-2-phenyl-1,2-propanediols, and similarly concluded that the (+)-2-phenyl-1,2-propanediol had the same configuration as (+)-methyl atrolactate. In a like manner, the configuration of the (-)-2-phenyl-1,2-propanediol (14) was determined to be R.

The absolute configurations of R(-)-atrolactic acid (11) and its methyl ester (10) have been unequivocally assigned based on several different lines of evidence. First, a series of chemical interconversions, summarized by Cram et al.[15], and devised by Cram[16], Brewster[17], and McKenzie et al.[18], related the enantiomers of atrolactic acid to mandelic acid. Support for the assignments based on the conclusions was provided by Prelog's studies of asymmetric reactions of methyl Grignard reagent with the phenylglyoxylates of optically active alcohols of known configuration (e.g., menthol)[19]. Barth et al.[9] also confirmed these assignments by means of circular dichroism. Finally, Eliel et al.[20] reported their asymmetric synthesis of S(+)-atrolactic acid methyl ether which again reinforced the earlier assignments.

The configurational conclusions based on the chiroptical data in the Table are thus fully confirmed by the chemical evidence of the inter-relationship of both R(-)-methyl atrolactate (10) and 2-octyl (S)-α-phenylglycidate (3) to R(-)-2-phenyl-1,2-propanediol (14).

The subsequent hydrolysis of the octyl group in 3 and 4 leads to potassium S(-)-α-phenylglycidate (1) and potassium R(+)-α-phenylglycidate (2) - the two active-site-directed inhibitors used in the biochemical studies.[3] Since the hydrolysis does not alter the asymmetric center, the correlations made for the octyl esters can be extended to the potassium salts.

		CD Maximum Values[a]					
	SPECIFIC ROTATION[a]	220nm BAND		240nm BAND			
	$[\alpha]_D$,(c)	λ_{max}(nm), λ_o(nm)[b]		λ_{max}(nm), λ_o(nm)[b]		$[\theta]_{220}$ / $[\theta]_{240}$, %	
COMPOUND		[θ]		[θ]			
R-(-)-Mandelic acid (6)	-155° (0.23)	224 -34,200	208 248	--[c]		--	
R-(-)-2-Methoxy-phenylacetic acid (12)	-149.4° (1.0)	224 -26,400	208 247	--		--	
R-(-)-Atrolactic acid (11)	-37.6° (3.5)	222 -19,300	209 239	246 335	240 255	57.6/1,	98.3%
Methyl R-(-)-atrolactate (10)	-5.0° (4.9)	221 -4,000	206 236	240 295	236 252	13.5/1,	93.1%
(-)-Menthyl R-(-)-2-methoxy-2-phenylpropanoate (13)[e]	--	228 -29,800[f]	210 246	--		--	
Methyl S-α-phenylglycidate (5)	--	225 -5,950	216 240	--[c]		--	
R-(-)-2-Octyl S-α-phenylglycidate (3)	-22° (0.43)	225 -8,150	212 243	--[d]		--	
R-(-)-2-Octyl R-α-phenylglycidate (4)	-16° (0.4)	225 6,650	215 240	243 -170	240 257	39.1/1,	97.5%
Methyl S-(-)-2,3-dihydroxy-2-phenylpropanoate (9)	-12° (0.38)	222 -18,800	210 240	245 160	241[c] 254	117.5/1,	99.2%

a In 95% ethanol.

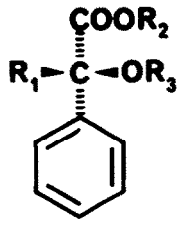
b At λ_o, [θ] = 0

c (+) Enantiomer shows mirror image CD spectrum.

d Above 240nm, shows only the ^1L_b band of C_6H_6 at 250 - 270 nm in agreement with the UV spectrum (250 -267nm, ε = 233).

e Mizuno, H. and Yamada, S., Chem. Pharm. Bull. (Japan), 23, 527 (1975).

f Corrected to optical purity



7 R_1=CH_2OH, R_2=R_3=H
8 R_1=R_2=R_3=H
9 R_1=CH_2OH, R_2=CH_3, R_3=H
10 R_1=R_2=CH_3, R_3=H
11 R_1=CH_3, R_2=R_3=H
12 R_1=R_2=H, R_3=CH_3
13 R_1=R_3=CH_3, R_2=(-)-menthyl

Experimental

General. All reagents except (+)-ephedrine were purchased from Aldrich Chemical Co. and were used without further purification. (+)-Ephedrine was obtained from Fluka AG Chemische Fabrik, Switzerland. Nuclear magnetic resonance spectra were determined on either a Varian FT-80 spectrometer or a 240 MHz widebore spectrometer equipped with Nicolet 1180 Data System, Cryomagnet Systems for magnet and probes, and custom built electronics. NMR spectra were expressed on the δ scale in parts per million downfield from an internal tetramethylsilane standard. The α rotation values were measured at the D line of sodium on a Perkin-Elmer 141 Polarimeter in a 1 dm polarimeter tube. The reported concentrations were expressed in g/100ml. Circular dichroic measurements were carried out on a Roussel-Jouan Mark II dichrograph at room temperature and were recorded in molar ellipticity units [θ] (degrees mol^{-1} cm^2). Enantiomers gave essentially (± 5%) mirror image curves. Gas chromatography was performed by Thomas Everhart using a Varian 1200 Gas Chromatograph modified with Grob injector enabling the instrument to accept a fused silica capillary column containing DB 1701 silicone. The column's dimensions were 0.32mm (i. d.) X 15 m. It was obtained from J & W Scientific Inc., Rancho Cordova, Calif. All melting points were uncorrected. Microanalyses were carried out by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley.

(-)-2-Octyl atropate. Ethyl atropate was synthesized according to the procedure of Ames and Davey[4]. The resulting ester was saponified to tropic acid and recrystallized; m.p. 103-105° (lit. 106-107°)[21]. The NMR spectrum showed contamination by ethyl phenylacetate. To 11.2 g (574.7 mmol) was added 76.9 g (591.3 mmol) of (-)-2-octanol. The mixture was heated at reflux for 44 hr. The desired ester distilled over a temperature range of 88-116° at 0.05 mm pressure. The NMR spectrum indicated that the product was contaminated with the octyl and ethyl phenylacetates. No further attempts were made at purification because it was possible to remove the contaminants in the following step in the reaction sequence. NMR ($CDCl_3$): δ 0.7-1.6 (brd m, 16H, octyl group), 3.55 (s, 2H, CH_2 of octyl and ethyl phenylacetates), 4.65-5.1 (brd m, 1H, CH), 5.8 (brd s, 1H, CH_2), 7.15-7.35 (brd m, 5H, Ph).

(-)-2-Octyl α-phenylglycidates (3 and 4). A solution of 6.7 g (25.8 mmol) of (-)-2-octyl atropate in 50 ml of CH_2Cl_2 was added dropwise to a rapidly stirring solution of 0.7 g (38.7 mmol) of 85% m-chlorobenzoic acid in 70 ml of CH_2Cl_2 at room temperature over 40 min. The solution was then heated at reflux for 38 hr. The mixture was cooled to room temperature, transferred to a separatory funnel, extracted with $NaHSO_3$ (1 X 100 ml of a 10% aq. soln.), followed by repeated washings with 10% $NaHCO_3$. The CH_2Cl_2 was dried over $MgSO_4$, filtered, and evaporated to dryness to yield a translucent, brown oil. The oil was dissolved in a mixture of 90% hexanes and 10% ethyl acetate and allowed to stand in a separatory funnel overnight. The mixture then separated into two layers of which the top was collected, dried over $MgSO_4$, filtered, and evaporated to dryness to yield a clear bronze oil.

The oil was made up in 10% (w/w) portions with 90% hexanes, 10% chloroform and injected in 1 ml aliquots onto a silica gel LoBar® Size B column. This low pressure liquid chromatography yielded first the (-)-2-octyl atropate with a retention time of 42-52.4 min, followed by octyl phenyl-acetate at 52.4-64 min, which, in turn, was followed by the diastereomeric mixture of the (-)-2-octyl α-phenylglycidates as 2 overlapping peaks at 78-112 min. The (-)-2- octyl R-α-phenylglycidate (4) was collected during the first 6 min (78-84 min) while the (-)-2-octyl S-α-phenylglycidate (3) was collected during the last 16 min (96-112 min). The 2 diastereomers were typically collected in round-bottom flasks and evaporated to dryness to yield oils which were made up as 10% (w/w) solutions with 90% hexames, 10% chloroform and then reinjected onto the LoBar® column. Upon reinjection 4 eluted as a broad peak between 68.1-96.3 min while 3 eluted between 100.5-140.7 min. Typically, the fraction eluting between 68.1-89.7 min was saved as 4 and the fraction eluting between 100.7-140.7 min was saved as 3. The optical purity of the oils was determined by GC analysis. Resolution of the diastereomers was obtained by using the fused silica capillary column starting at 120° and increasing the temperature by 4°/min. Compound 4 consisted of 75% R,R and 25% R,S while compound 3 was determined to be 78% R,S and 22% R,R. The helium carrier gas flow was maintained at 0.75 bar. Compound 4 eluted at 167.5° while 3 eluted at 168.5°. NMR ($CDCl_3$): δ 0.7-1.7 (brd m, 16H, octyl group), 2.87 (d, 1H, CH_2), 3.32 (d, 1H, CH_2), 4.7-5.1 (brd m, 1H, CH), 7.05-7.6 (brd m, 5H, Ph). (Found: C, 73.97; H, 8.49. $C_{17}H_{24}O_3$ requires: C, 73.87; H, 8.77%). (4): [α] = -16° (3): [α] = -22° (c = 0.40; 0.43, ethanol).

Still higher chemical purity of the octyl esters as determined by NMR analysis can be obtained by distillation of the oil in a micromolecular still. A clear oil distills at 0.1 mm pressure and bath temperature ca. 150°C (Found: C, 73.84; H, 8.84. $C_{17}H_{24}O_3$ requires : C, 73.87; H, 8.77%).

Potassium R(+)-α-phenylglycidate (2) was prepared by the saponification of 0.38 g (1.39 mmol) of 4 in a solution of 0.086 g (1.5 mmol) of KOH in 25 ml of 95% ethanol heated at reflux for 1.5 hr. The solution was evaporated to dryness to yield a gummy solid which solidified after being dried under vacuum for 3 hours.

After crystallization from EtOH-ether the hygroscopic crystals were collected in a sintered glass funnel and quickly transferred to a tared container and dried under vacuum in a desiccator. The crystals were stored below 0° C. in a desiccator to prevent decomposition (93.4 mg, 33%). The NMR (D_2O) corresponded to that of Fee et al.[8]: δ 3.3 (brd s, 2H, CH_2), 7.45 (brd s, 5H, Ph). [α] = +41° (c = 0.112, water).

Potassium S(-)-α-phenylglycidate (1) was synthesized by the hydrolysis of 0.52 g (1.88 mmol) of 3 in a solution of 0.12 g (2.13 mmol) of KOH in 30 ml of 95% ethanol by heating at reflux for 2 hr. The reaction yielded 85.7mg (22.5%) of product after work-up according to the procedure used

for the R(+)-isomer. The crystals were stored in a desiccator below 0° C. The NMR spectrum (D_2O) corresponded to that for the racemic sodium salt of Fee et al.[8]. $[\alpha]_D$ = -28° (c = 0.116, water).

Methyl R,S-α-phenylglycidate. A mixture of 0.50 g (2.48 mmol) of the R,S potassium salt synthesized according to Fee et al.[8] and 0.65 g (2.46 mmol) of 18-crown-6 ether was dissolved in 1 ml of water. The solution was evaporated to dryness to yield a crystalline glass. Most of the glass dissolved in 50 ml of tetrahydrofuran (freshly distilled after reflux over $LiAlH_4$), leaving a fine precipitate which dissolved upon the addition of 5.3 g (37.3 mmol) of iodomethane (freshly distilled after reflux over copper turnings). Immediately after addition, the solution turned yellow, followed by the precipitation of a solid. The reaction mixture was left to stir at room temperature overnight. It was then evaporated to dryness to yield both a solid and an oil. The mixture was dissolved in 90% hexanes, 10% ethyl acetate and filtered to yield an orange solution which was dried over $MgSO_4$, filtered, and evaporated to dryness to yield an oil. The oily residue was subjected to flash chromatography (90% hexanes, 10% ethyl acetate) on 50 g of silica gel to yield 0.32 g (71%) of pure ester. NMR ($CDCl_3$): δ 2.87 (d, 1H, CH_2), 3.37 (d, 1H, CH_2), 3.75 (s, 3H, CH_3), 7.2-7.55 (brd m, 5H, Ph). (Found: C, 67.58; H, 5.76. $C_{10}H_{10}O_3$ requires: C, 67.40; H, 5.67%).

Methyl R-α-phenylglycidate (6) was synthesized from 2 exactly according to the procedure used to prepare the racemic mixture. The NMR spectrum ($CDCl_3$) revealed approximately 15% impurity in the δ 1.05-1.5 region. No further attempt was made at purification. The reaction yielded 24.6 mg (21%). An α value was not measurable.

Methyl S-α-phenylglycidate (5) was synthesized from 1 according to the procedure used to prepare the racemic mixture. The reaction yielded 45.3 mg (60%) of a clear oil after flash chromatography. An α value was not measurable. Consequently, in order to ensure that significant racemization had not occurred during the reaction, 22.5 mg (0.13 mmol) of 5 was heated at reflux for 1.5 h in an ethanolic solution of 5.8 mg (0.15 mmol) of KOH. After rotary evaporation of the solution, crystals were obtained. $[\alpha]_D$ = -27° (c = 0.23, water) (starting material $[\alpha]_D$ = -28°).

Methyl R(+)-2,3-dihydroxy-2-phenylpropanoate (16). Ethyl atropate was prepared according to Ames and Davey[4] and then subjected to flash chromatography (90% hexanes, 10% ethyl acetate) on 50 g of silica gel in 1.0 g portions to remove the ethyl phenylacetate. NMR ($CDCl_3$): δ 1.2 (t, 3H, CH_3), 2.87 (d, 1H, CH_2), 3.32 (d, 1H, CH_2), 4.2 (q, 2H, CH_2), 7.2-7.5 (brd m, 5H, Ph). The pure oil was treated with m-chloroperbenzoic acid as described above and saponified to yield potassium α-phenylglycidate, which was, in turn, hydrolyzed to yield potassium α-phenylglycerate. NMR (D_2O): δ 4.05 (1, 2H, CH_2), 7.25-7.6 (brd m, 5H, Ph). Potassium phenylglycerate (1.8 g, 8.2 mmol.) was dissolved in 9 ml of water, acidified to pH 1 with conc. HCl, extracted with ether (8 X 15 ml), dried over $MgSO_4$, filtered, and evaporated to dryness to yield racemic α-phenylglyceric acid, m.p. 146-148° (lit. 148-150°)[22]. The free acid (1.3 g, 7.14 mmol) and (-)-ephedrine (1.3 g, 7.87 mmol) were dissolved in 10 ml of 100% ethanol. After 3 crystallizations, 0.3 g of the (-)-ephedrine (+)-α-phenylglycerate salt was recovered by filtration, m.p. 96-97°. The salt was dissolved in water, acidified with conc. HCl, and extracted with ether to yield 122 mg of the (+)-acid (7) (9.4% yield). $[\alpha]_D$ = + 22° (c = 0.25, ethanol).

Diazomethane was generated from Diazald®, collected as an ethereal solution, and added in portions to a chilled solution of 122 mg of phenylglyceric acid in 25 ml of ether until the yellow color persisted. The reaction mixture was left to stir at room temperature overnight. Then it was extracted with saturated $NaHCO_3$ (1X100 ml), dried over $MgSO_4$, filtered, and evaporated to dryness to yield an oil. The oily residue was then subjected to flash chromatography (75% hexanes, 25% ethyl acetate) on 20 g of silica gel to yield 56 mg (43%) of white crystals, m.p. 63-65°. NMR ($CDCl_3$): δ 2.55-3.0 (brd s, 2H, CH_2), 7.2-7.6 (brd m, 5H, Ph). (Found: C, 61.41; H, 6.08. $C_{10}H_{12}O_4$ requires: C, 61.22; H, 6.18%). $[\alpha]_D$ = + 14° (c = 0.40, ethanol).

Methyl S(-)-2,3-dihydroxy-2-phenylpropanoate (9). S(-)-α-Phenylglyceric acid (17) was obtained from the racemic acid after three crystallizations of the salt formed with (+)-ephedrine (m.p. (+)-ephedrine (-)-α-phenylglycerate, 96-102°). The free (-)-acid [83.6 mg, 0.46 mmol, $[\alpha]$ = - 22° (c = 0.29, ethanol)] was esterified with diazomethane and then subjected to flash chromatography (75% hexanes, 25% ethyl acetate) on 25 g of silica gel to yield 77.4 mg (86%) of white crystals, m.p. 61-63°. The NMR spectrum ($CDCl_3$) was identical to that of the R(+) isomer. (Found: C, 61.13; H, 6.15. $C_{10}H_{12}O_4$ requires C, 61.22; H, 6.18%). $[\alpha]$ = - 12° (c = 0.38, ethanol).

R,S-1,2-Dihydroxy-2-phenylpropane. To a chilled solution of 146.6 mg (3.86 mmol) of $LiAlH_4$ in 200 ml of tetrahydrofuran (freshly distilled after reflux over $LiAlH_4$) was added a solution of 266.1 mg (0.96 mmol) of (-)-2-octyl R,S-α-phenylglycidate in 30 ml of the tetrahydrofuran over a 20 minute period. The solution was heated at reflux for 4 hr. The reaction vessel was then immersed in an ice bath, and the excess $LiAlH_4$ was destroyed by the addition of 0.15 ml water, 0.15 ml of a 15% aq. NaOH solution, and 0.45 ml water from a syringe. The solution was filtered and evaporated to dryness to yield an oily residue. The residue was subjected to flash chromatography (50% hexanes, 50% ethyl acetate) on 50 g of silica gel to yield 63.8 mg (44%) of an oil which solidified upon standing. NMR ($CDCl_3$): δ 1.4 (s, 3H, CH_3), 2.5-3.0 (brd s, 1H, OH, collapses upon the addition of 1 drop of D_2O), 3.1-3.7 (brd s, 3H, CH_2OH), 7.1-7.4 (brd m, 5H, Ph). (Found: C, 70.73; H, 7.82. $C_9H_{12}O_2$ requires: C, 71.02; H, 7.96%).

S(+)-1,2-Dihydroxy-2-phenylpropane was prepared by reducing 4 resulting in 77.7 mg (56%) of product after flash chromatography. The NMR spectrum ($CDCl_3$) was similar to that of the racemic mixture except that there were some minor impurities in the δ 1.85-2.2 region. Two rotations measured in two different solvents showed the compound to be dextrorotatory corresponding to the S configuration as determined by Eliel and Freeman[13] and by Mitsui and Imaizumi[14]. $[\alpha]_D$ = 3.0° (c =

1.55, ether) (Lit. $[\alpha]_D$ = 8.42, c = 6.8[13]; $[\alpha]_D$ = 3.25° (c = 1.24, ethanol) (Lit. $[\alpha]_D$ = 5.4, c = 8.9)[14].

R(-)-1,2-Dihydroxy-2-phenylpropane (14) was prepared by reducing 3 to yield 33.2 mg (25%) of 14 after flash chromatography. The NMR spectrum ($CDCl_3$) was similar to that for the racemic mixture with a small amount of impurity in the δ 2.4 region. $[\alpha]_D$ = -4° (c = 0.66, ether).

Potassium R(+)-2,3-dihydroxy-2-phenyl propanoate (18) was prepared by the base hydrolysis of 4. Typically, 0.51 g (1.85 mmol) of 4 was hydrolyzed in a solution of 0.21 g (3.74 mmol) of KOH in 10ml of 95% ethanol heated at reflux for 1.5 hrs. After cooling to room temperature, the solution was evaporated to dryness to yield a solid. Recrystallization from ether/EtOH yielded 0.05 g (14%) of compound 18. The NMR spectrum (D_2O) was identical to that reported for potassium R,S-α-phenylglycerate. $[\alpha]_D$ = 26° (c = 0.1, water).

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