Electrophilic Substitution at Saturated Carbon. XLI. Equilibrium Constants, Absolute Configurations, and Maximum Rotations of *cis*- and *trans*-1,2-Dimethyl-2-phenylcyclopentanols and Their Base-Catalyzed Cleavage Products[1]

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Abstract: Racemic 2-methyl-2-phenylhexanedioic acid (I) was resolved, both enantiomers (−)-(*R*)-I and (+)-(*S*)-I being brought to maximum rotation. Both enantiomers were esterified to give dimethyl esters (−)-(*R*)-II and (+)-(*S*)-II. When subjected to a Dieckman condensation, (−)-(*R*)-II gave a β-keto ester, hydrolysis and decarboxylation of which produced (+)-(*R*)-2-methyl-2-phenylcyclopentanone, (+)-(*R*)-III. Treatment of this ketone with methyllithium gave carbinol in the proportion of 75% (−)-(1*R*,2*R*)-1,2-dimethyl-2-phenylcyclopentanol [(−)-(1*R*,2*R*)-IV] and 25% (−)-(1*S*,2*R*)-1,2-dimethyl-2-phenylcyclopentanol [(−)-(1*S*,2*R*)-*trans*-IV]. The relative configurations of these diastereomers were determined from their physical properties. These diastereomers were equilibrated at 25° in dimethyl sulfoxide–dimsylsodium to give an equilibrium constant (approached from both sides) of *trans*/*cis* = 2.51. At 37° with potassium *t*-butoxide in *t*-butyl alcohol–dimethyl sulfoxide, *trans*/*cis* = 2.22. Use of optically active diastereomers resulted in equilibrium mixture of the two racemates. Thus, epimeric equilibration occurred at both asymmetric centers undoubtedly through trismethyleneketo carbanions as intermediates. Cleavage of optically pure ketone, (+)-(*R*)-III, in *t*-butyl alcohol–potassium *t*-butoxide gave 61% optically pure (+)-(*S*)-5-phenylhexanoic acid [(+)-(*S*)-V]. The enantiomer, (−)-(*R*)-V, was synthesized by a twofold Arndt–Eistert reaction from optically pure (−)-(*R*)-3-phenylbutanoic acid [(−)-(*R*)-VI] of known absolute configuration. Optically pure (−)-(*R*)-V was converted with methyllithium to (−)-(*R*)-6-phenyl-2-heptanone [(−)-(*R*)-VII] which with more methyllithium gave (−)-(*R*)-2-methyl-6-phenyl-2-heptanol [(−)-(*R*)-VIII]. This alcohol, (−)-(*R*)-VIII, also was prepared from (+)-(*S*)-I. Esterification of (+)-(*S*)-I gave diester (+)-(*S*)-II which was treated with excess methyllithium to give optically pure (−)-(*S*)-3-phenyl-2,3,7-trimethyl-2,7-octanediol [(−)-(*S*)-IX]. This material, when treated with potassium *t*-butoxide–*t*-butyl alcohol, underwent cleavage to give (−)-(*R*)-2-methyl-6-phenyl-2-heptanol [(−)-(*R*)-VIII] with 88% net retention, with potassium *t*-butoxide in dioxane to give (−)-(*R*)-VIII with 78% net retention, and with potassium diethylene glycoxide in diethylene glycol to give (+)-(*S*)-VIII with 24% net inversion. The stereochemical courses of these reactions were assigned by analogy with similar cleavage reactions whose starting materials and products have been configurationally related by an independent means. The reactions complete a cycle of configurational relationships. The absolute configurations and maximum rotations of all of the above compounds were assigned based on these interconversions and ultimately on the known absolute configuration of (−)-(*R*)-3-phenylbutanoic acid. The configurational relationships indicate that cyclic ketone (+)-(*R*)-III cleaved to (+)-(*S*)-V with 61% net retention of configuration.

The stereochemical course of the S$_E$1 reaction with carbon as leaving group, proton donors as electrophiles, and phenyl or sulfonyl as carbanion-stabilizing groups has been subjected to systematic study in open-chain systems.[2]

The stereochemical course of the base-catalyzed cleavage of cyclic and bicyclic alcohols and ketones has also been examined,[3] and were found to be different from their open-chain counterparts. The reactions studied all involve carbanions as intermediates which are stabilized by phenyl, by sulfonyl, or by being in a three-membered ring. Particularly in those cases in which the carbanions are stabilized by aryl or sulfonyl groups, the open-chain systems are prone to undergo substitution with inversion under conditions that cyclic systems give retention. These observations suggest that the carbonyl leaving group may be a more effective shield for the carbanion when the carbanion and leaving group are tied together by a methylene bridge than when they are free to become completely separated.

This and the adjacent paper report results of a study of the stereochemical course of cleavage, epimerization, and racemization of a cyclic system capable of generating a carbanion stabilized by a phenyl group. Optically active 2-methyl-2-phenylcyclopentanone ((+)-III), (−)-*cis*-1,2-dimethyl-2-phenylcyclopentanol ((−)-*cis*-IV), and (−)-*trans*-1,2-dimethyl-2-phenylcyclopentanol ((−)-*trans*-IV) were selected for study for the following reasons. (1) The compounds are cyclic analogs of open-chain ketones and alcohols whose cleavage has

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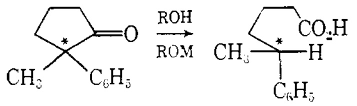
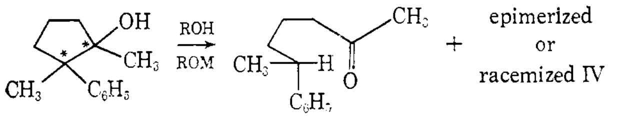
(1) This research was sponsored by the U. S. Army Research Office, Durham, N. C. The authors extend their thanks.

(2) (a) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 138; (b) D. J. Cram, F. Hauck, K. R. Kopecky, and W. D. Nielsen, *J. Am. Chem. Soc.*, **81**, 5767 (1959); (c) D. J. Cram and B. Rickborn, *ibid.*, **83**, 2178 (1961); (d) D. J. Cram, J. L. Mateos, F. Hauck, A. Langemann, K. R. Kopecky, W. D. Nielsen, and J. Allinger, *ibid.*, **81**, 5774 (1959); (e) D. J. Cram, K. R. Kopecky, F. Hauck, and A. Langemann, *ibid.*, **81**, 5754 (1959); (f) D. J. Cram and A. S. Wingrove, *ibid.*, **85**, 1100 (1963).

(3) (a) A. Nickon, J. L. Lambert, R. O. Williams, and N. H. Werstiuk, *ibid.*, **88**, 3354 (1966); (b) C. H. DePuy, F. W. Breitbiel, and K. R. DeBruin, *ibid.*, **88**, 3347 (1966); (c) C. H. DePuy, *Accounts Chem. Res.*, 1, 33 (1968); (d) P. G. Gassman, J. T. Lumb, and F. V. Zalar, *J. Am. Chem. Soc.*, **89**, 946 (1967); (e) S. Masamune, *Tetrahedron Letters*, 945 (1965); (f) A. S. Monahan, *J. Org. Chem.*, **33**, 1441 (1968); (g) E. J. Corey and T. H. Lowry, *Tetrahedron Letters*, 793 (1965); (h) E. J. Corey and T. H. Lowry, *ibid.*, 803 (1965).

been thoroughly studied previously.[2a,b,e] (2) The presence of the two adjacent asymmetric centers in *cis*- and *trans*-IV allowed examination of the possibility that keto carbanions could be generated which recombined with modified configurations (epimerization or racemization) at rates competitive with that of proton capture. (3) These compounds could be readily prepared in an optically active state, and their configurations and maximum rotations and those of their cleavage products readily determined. This paper reports the preparation and determination of maximum rotations and configurations of ketone III, of carbinols IV, and of their cleavage products, V and VII, respectively. The next paper reports the results of an investigation of the cleavage, epimerization, and racemization of these compounds.


III V



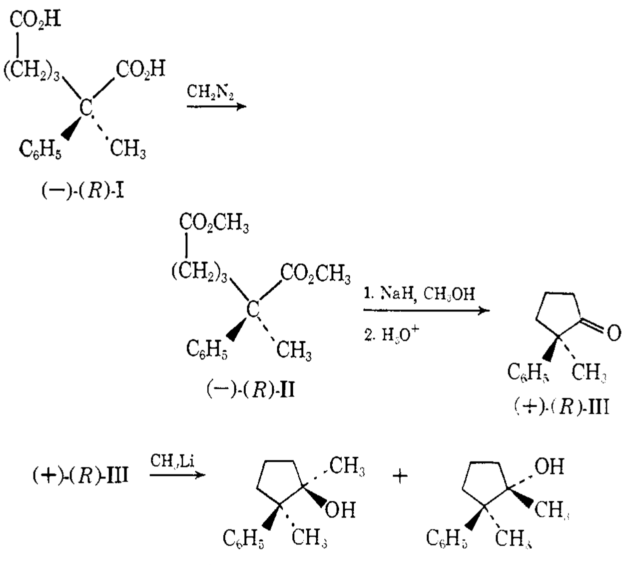
cis- or *trans*-IV VII

Syntheses, Maximum Rotations, and Configurations. Both enantiomers of diacid I of maximum rotation[4] were prepared, and (−)-(*R*)-I was converted to *cis*- and *trans*-IV by conventional reactions[5] (see formulas). The specific rotation of ketone (+)-(*R*)-III was large, but not subject to the same solvent dependence observed by others[6] for the rotation of (+)-2-phenylcyclopentanone. Steric approach control[7] appeared to dominate the course of reaction of methyllithium with ketone III since 75% *cis*-IV and 25% *trans*-IV were produced.

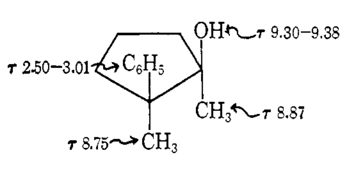
The diastereomeric structural assignments of *cis*- and *trans*-IV were made on the basis of comparisons of their physical properties. The predominant isomer is given the experimental designation of α, and the other isomer the designation of β. The α isomer moved faster on tlc and glpc than the β. This behavior suggested that in the α isomer the phenyl and hydroxyl groups were hydrogen bonded and *cis* to one another. Spectral evidence[3b,8] confirmed this assignment.

The nmr and infrared spectra of α and β isomers were determined in carbon tetrachloride solution. The absorption bands in the nmr were assigned (see formulation) making use of analogies between chemical shifts and structural features of α- and β-IV on the one hand, and the chemical shifts and established configurational features of *cis*- and *trans*-1-methyl-2-phenylcyclopropanecarboxylic acids and derived compounds on the other.[3b] Particularly useful in making structural assignments were the upfield shifts of the methyl protons *cis* to the shielding phenyl group in β-IV, and of the hydroxyl proton *cis* to the hydrogen-bonding phenyl group in α-IV (in each case relative to the corresponding shifts in the *trans* isomer). Added weight to these structural assignments is found in the effect of concentration of α- and β-IV on the chemical shift of the hydroxyl proton. In the spectrum of α-IV, a change in concentration from 7.72 mol% (carbon tetrachloride) to 4.02 mol % moved the hydroxyl proton band only 0.08 ppm upfield. In the spectrum of β-IV, a change in concentration from 8.70 to 4.34 mol % moved the hydroxyl proton band 0.45 ppm upfield. Clearly, the concentration-insensitive band involves the isomer in which the hydroxyl group undergoes little intermolecular hydrogen bonding because of intramolecular hydrogen bonding with a *cis*-phenyl group. Thus, α-IV must possess the structure with the hydroxyl and phenyl *cis* (two methyl groups *cis*), and β-IV, the structure with the hydroxyl and phenyl groups *trans* (two methyl groups *trans*).

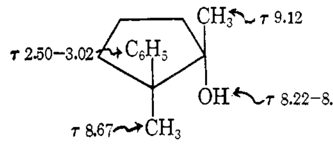
Additional confirmation of structure is found in the



(−)-(*R*)-I
(−)-(*R*)-II
(+)-(*R*)-III
(+)-(*R*)-III
(−)-(1*R*, 2*R*)-*cis*-IV 75%
(−)-(1*S*, 2*R*)-*trans*-IV 25%



infrared bands at 3588 and 3550 cm^{-1}
α-IV



infrared band at 3636 cm^{-1}
β-IV

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(4) M. S. Newman and R. D. Clossom, *J. Am. Chem. Soc.*, **66**, 1553 (1944).

(5) (a) P. K. Banerjee and P. R. Shafer, *ibid.*, **72**, 1931 (1950); (b) W. S. Johnson, A. R. Jones, and W. P. Schneider, *ibid.*, **72**, 2395 (1950).

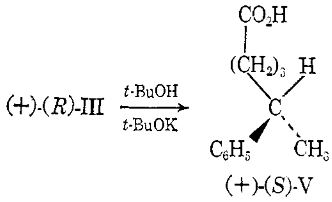
(6) K. Mislow and C. L. Hamermesh, *ibid.*, **77**, 1590 (1955).

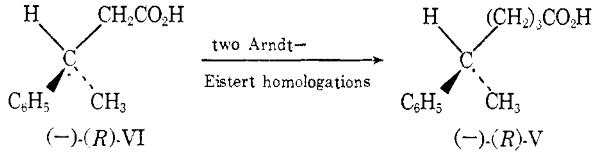
(7) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *ibid.*, **78**, 2579 (1956).

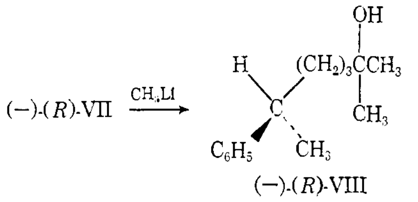
(8) (a) P. von R. Schleyer, C. Wintner, D. S. Trifan, and R. Bacskai, *Tetrahedron Letters*, No. 14, 1 (1959); (b) P. von R. Schleyer, D. S. Trifan, and R. Bacskai, *J. Am. Chem. Soc.*, **80**, 6691 (1958); (c) I. M. Goldman and R. O. Crisler, *J. Org. Chem.*, **23**, 751 (1958); (d) Z. Yoshida and E. Osawa, *J. Am. Chem. Soc.*, **88**, 4019 (1966).

infrared spectra of very dilute solutions (0.0215 *M*) of α- and β-IV in carbon tetrachloride. In the O–H stretching region, α-IV exhibited two peaks at 3588 and 3550 cm^{-1} characteristic of π-hydrogen bonding to an adjacent phenyl.[8] The β isomer provided only one peak at 3636 cm^{-1} in addition to broad absorption due to dimer.

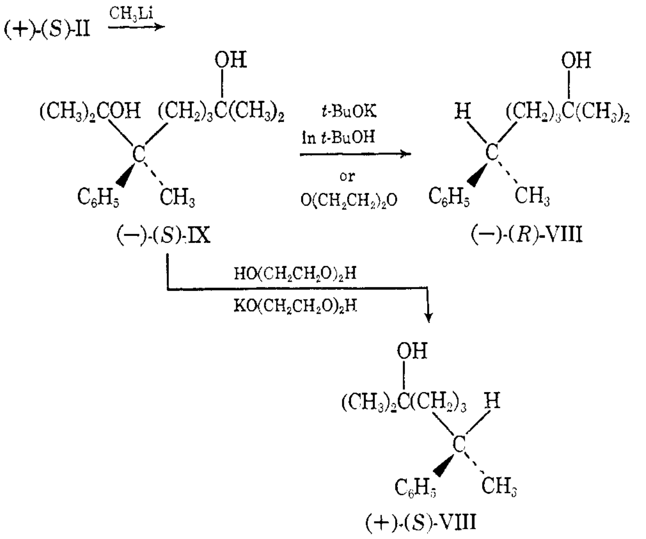
Ketone (+)-(*R*)-III, when heated with potassium *t*-butoxide–*t*-butyl alcohol, gave (+)-(*S*)-5-phenylhexanoic acid [(+)-(*S*)-V] in 43% yield with 61% net retention of configuration. The maximum rotation and absolute configuration of this acid was determined by synthesis of its enantiomer from optically pure (−)-(*R*)-3-phenylbutanoic acid [(−)-(*R*)-VI] by two successive Arndt–Eistert homologation reactions.[9] The maximum rotation[10] and absolute configuration[11] of (−)-(*R*)-VI are established, and the Arndt–Eistert reaction is known to go with retention of configuration.[12]







The absolute configurations of the stereomers of I, II, III, and IV were established by closing a cycle of interconversions. Optically pure acid (−)-(*R*)-V was converted with methyllithium to (−)-(*R*)-6-phenyl-2-heptanone [(−)-(*R*)-VII] which with more methyllithium gave (−)-(*R*)-2-methyl-6-phenyl-2-heptanol [(−)-(*R*)-VIII]. This same alcohol, (−)-(*R*)-VIII, was prepared from diacid (+)-(*S*)-I as follows. Esterification of (+)-(*S*)-I gave diester (+)-(*S*)-II, a nearly optically pure sample of which was treated with excess methyllithium to give (−)-(*S*)-3-phenyl-2,3,7-trimethyl-2,7-octanediol [(−)-(*S*)-IX]. This compound was crystallized to maximum rotation (sharp melting point), and was submitted to base-catalyzed cleavage reactions to give alcohol VIII under conditions that in similar systems gave high retention of configuration, and under a second set of conditions that in similar systems gave net inversion of configuration.[2a,d] Thus, treatment of optically pure (−)-(*S*)-IX with potassium *t*-butoxide–*t*-butyl alcohol gave (−)-(*R*)-VIII with 88% net retention of configuration, with potassium *t*-butoxide in dioxane to give (−)-(*R*)-VIII with 78% net retention, and with potassium diethylene glycoxide in diethylene glycol to give (+)-(*S*)-VIII with 24% net inversion. The assignment of relative configurations of IX and VII depend on knowledge of the stereochemical course of the reaction IX → VIII. In a number of other open-chain β-phenyl alcohols the cleavage reaction was found to go with 80–99% net retention in *t*-butyl alcohol or dioxane, and with 20–60% net inversion in the glycols or methanol.[2a,d] The facts that use of the two types of solvents for cleavage of (−)-(*S*)-IX gave VIII of opposite configurations, and that the relatively nonpolar solvents gave the higher stereospecificity, point conclusively to (−)-(*S*)-IX behaving similarly to the open-chain β-phenyl alcohols studied previously. Thus, the assignment of both the predominant stereochemical course of the reaction, IX → VIII, and the relative configurations of IX and VIII is made on the basis of substantial analogy.



These reactions provide absolute configurations and maximum rotations for compounds I–IX. The assignments of configurations to ketone III and to its cleavage product, acid V, were not dependent on knowing the stereochemical course of the cleavage reaction. Indeed, knowledge of these configurations establishes that the cleavage reaction went with predominating retention (61% net) of configuration. This reaction will be discussed in the next paper of this series.

Epimeric and Enantiomeric Equilibration of Alkoxides of Optically Active (−)-*cis*- and (−)-*trans*-1,2-Dimethyl-2-phenylcyclopentanols. Epimeric and enantiomeric equilibrations of alkoxides of optically pure (−)-*cis*-IV and (−)-*trans*-IV were accomplished by dissolving each isomer in a dimsylsodium solution in dimethyl sulfoxide at 25°. Equilibration was complete in a few hours. A small amount of 6-phenyl-2-heptanone (VII) as cleavage product was formed in most runs. Since the retention times on glpc of *cis*-IV and ketone VII were identical, the reaction products were reduced with lithium aluminum hydride and

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(9) A. L. Wilds and A. L. Meader, *J. Org. Chem.*, 13, 763 (1948).

(10) D. J. Cram, *J. Am. Chem. Soc.*, 74, 2137 (1952).

(11) (a) J. H. Brewster and M. W. Kline, *ibid.*, 74, 5179 (1952); (b) J. A. Mills and W. Klyne, *Progr. Stereochem.*, 1, 177 (1954).

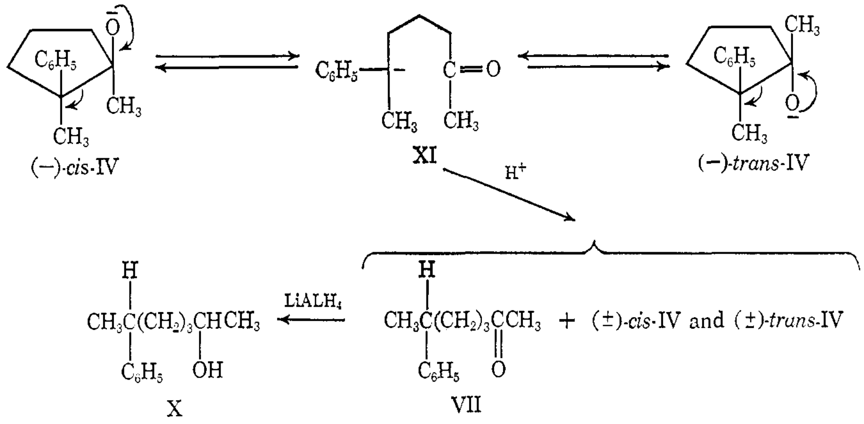
(12) K. B. Wiberg and T. W. Hutton, *J. Am. Chem. Soc.*, 78, 1640 (1956).

Table I. Equilibration of Sodium Alkoxides of *cis*- and *trans*-1,2-Dimethyl-2-phenylcyclopentanols (*cis*- and *trans*-IV) and Generation of 6-Phenyl-2-heptanone (VII) in Dimethyl Sulfoxide

Run no.	Starting material: Nature	Starting material: Concn, *M*	Base: Nature	Base: Concn, *M*	Time, hr	Temp, °C	Total[a] yield, %	%[b] *trans*-IV	%[b] *cis*-IV	%[c] X	*K* (*trans*-IV/*cis*-IV)
1	(−)-*cis*-IV[d]	0.0029	$NaCH_2SOCH_3$	0.025	10	25	48	72.4[e]	27.6[e]	0.9	2.62
2	(−)-*trans*-IV[d]	0.0027	$NaCH_2SOCH_3$	0.025	10	25	51	71.5	28.5	<0.1	2.51
3	(−)-*cis*-IV[d]	0.0029	$NaCH_2SOCH_3$	0.021	11	25	62	71.3[e]	28.7[e]	8	2.48
4	(−)-*trans*-IV[d]	0.0029	$NaCH_2SOCH_3$	0.021	11	25	51	70.8[e]	29.2[e]	6	2.42
5	(±)-*cis*-IV	0.0033	KOBu-*t*[f]	0.16	46	37		69.0	31.0	28	2.22
6	(±)-*trans*-IV	0.0033	KOBu-*t*[f]	0.16	46	37		69.0	31.0	28	2.22
7	(±)-*cis*-IV	0.0021	$NaCH_2SOCH_3$	0.0025	10	75		60.5	39.5	15	1.53

[a] Glpc with an internal standard. [b] Glpc analysis based on *cis*-IV + *trans*-IV = 100%. [c] Glpc based on *cis*-IV + *trans*-IV + 6-phenyl-2-heptanol = 100%. [d] Optically pure compounds. [e] These compounds were each found to have $[\alpha]^{25}{}_{546}$ 0.00° (*c* 1.5, benzene). [f] Solutions were 1.8 *M* in *t*-BuOH.

analyzed by glpc. Then, the three alcohols were separated by elution chromatography. The total yields (internal standard in glpc) were only 48–62%. The remaining 38–52% was lost either in isolation (small amount) or as condensation product of ketone VII, either with itself or dimethyl sulfoxide. From either *cis*- or *trans*-IV approximately the same balance of diasteromers was obtained, demonstrating that equilibrium was reached. At 25° an average equilibrium constant of $K = trans/cis = 2.51$ was obtained. Racemic *cis*- and *trans*-IV were also found to equilibrate at 37° in a solution of potassium *t*-butoxide in dimethyl sulfoxide, 1.8 *M* in *t*-butyl alcohol (runs 5 and 6). The same product composition was obtained from each isomer, and $K = trans/cis = 2.22$. A lower value of $K = 1.53$ was obtained at 75° from *cis*-IV in dimethyl sulfoxide–dimsylsodium solution. Thus, the difference in free energy between the diastereomeric alkoxides is about 550 cal/mol at 25°, and decreases to about 250 cal/mol at 75°. Table I reports the conditions for equilibrations and the results.



In those runs (1–4 and 7) made with dimsylsodium as base, the equilibrium constant must have been between the sodium alkoxides rather than between the diastereomeric alcohols themselves since tertiary alcohols even in dimethyl sulfoxide are considerably more acidic than dimethylsulfoxide itself.[13] Thus, the *trans*-alkoxide is the more thermodynamically stable of the two isomers. This fact suggests that the alkoxide group or the sodium alkoxide ion pair (whichever species predominates) is more stable when *trans* to the phenyl group. The data suggest that either the methyl group is in effect smaller than oxygen and its solvation shell, or that the π electrons of the phenyl and the electron pairs on oxygen repel one another enough to overcome an otherwise favorable steric situation. What is more surprising is that *trans*-IV itself is slightly more stable than *cis*-IV. In runs 5 and 6, enough *t*-butyl alcohol was present (1.8 *M*) compared to cyclopentanol (0.0033 *M*) to make the equilibrium concentration of cyclopentoxide extremely low. Thus, the equilibrium constant measured in runs 5 and 6 was that of the diastereomeric alcohols rather than their alkoxides. Apparently, the repulsive forces between the phenyl and hydroxyl groups in this good hydrogen-bonding solvent (DMSO) outweigh the attractive forces (hydrogen bonding) enough to compensate for the usually smaller size of hydroxyl as compared to methyl. Possibly in a nonhydrogen bonding solvent, *cis*-IV would be more stable than *trans*-IV.

In those runs (1, 3, and 4) made at 25° with optically pure starting materials, the diastereomers *cis*- and *trans*-IV were found to be completely racemic. Thus, both asymmetric centers of the starting alcohols lost their configurational history during the reaction. This result, coupled with the production of ketone VII, indicates that the equilibration involved the trimethyleneketo carbanion XI as intermediate, and this species lost its asymmetry and partitioned between racemic *cis*- and *trans*-IV and open-chain ketone VII. Production of ketone involved proton donation to the benzyl carbon. In runs 1–4 and 7, the proton must have come either from dimethyl sulfoxide or the methyl or methylene groups α to the carbonyl or both. The yield of isolated open-chain product was higher in runs 5 and 6 which involved potassium *t*-butoxide as base.

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(13) Reference 2a, p 41.

In these runs the medium was 1.8 *M* in *t*-butyl alcohol, and, thus, a more acidic proton donor was present than in the other runs. Possibly, the keto carbanion XI was more efficiently intercepted than when this type of proton donor was absent (runs 1–4). However, this interpretation is clouded by the possibility that more condensation product was formed in runs 1–4 and 7 from ketone VII than in runs 5 and 6. A more complete discussion of mechanism is deferred to the next paper of this series.

Experimental Section

General. Nuclear magnetic resonance spectra were recorded with a Varian A-60 instrument. Solvent for all spectra was spectral grade carbon tetrachloride with 2–5% added tetramethylsilane. The infrared spectra were recorded with a Beckman IR-5 machine with the exception of the π-hydrogen-bonding analysis of the diastereomeric 1,2-dimethylcyclopentanols. This was performed on a Beckman IR-4 instrument with LiF optics. The solvent was carbon tetrachloride unless otherwise stated. All rotations were taken on a Perkin-Elmer Model 141 polarimeter. Reagent grade benzene was dried over sodium wire. The absolute ethanol (USI, USP grade) was stored over molecular sieves (Linde, Type 4A) in a glass bottle sealed with a securely fastened serum cap. All melting points were taken in a Hershberg apparatus and are uncorrected unless otherwise stated. All boiling points are uncorrected. Granular, anhydrous sodium sulfate was uniformly used as drying agent; brine refers to a saturated aqueous solution of sodium chloride. Thin layer chromatographic analyses (tlc) were carried out with silica gel G (prepared by E. Merckag (Germany) according to Stahl) on glass plates. Visualization was accomplished with 10% (w/v) phosphomolybdic acid in ethanol. Mass spectra were obtained on an Associated Electronic Industries MS9 mass spectrometer. Samples were introduced through the glass inlet system preheated to 158°.

Resolution of 2-Methyl-2-phenylhexanedioic Acid (I) with Brucine. To a mixture of racemic 2-methyl-2-phenylhexanedioic acid (414 g, 1.75 mol, mp 113.6–114.3°, lit.[4] mp 113.7–114.6°) and brucine (1380 g, 3.50 mol) was added *ca.* 3.5 l. of reagent acetone. The slurry was brought to reflux on a steam bath and enough water (7% by volume) added to completely dissolve the disalt. The progress of the resolution was monitored *via* rotations of the derived acid in absolute ethanol. Although three recrystallizations gave a small amount of diacid of high optical purity, $[\alpha]^{25}_{546}$ – 25.5° (*c* 5.29, ethanol) and sharp melting point (126.3–127.6°), the more efficient triangle method[14] was employed. This procedure yielded 402 g of salt which was converted to the diacid in the following manner.

Dibrucine salt (402 g, 0.730 equiv) was dissolved in 1.8 l. of 50% aqueous acetone. Solid sodium carbonate (115 g, 1.1 mol) was added to the homogeneous solution and the acetone evaporated. The alkaloid precipitated from the stirred solution. The solution was decanted and the solid slurried with dilute sodium hydroxide solution. The combined aqueous layers were washed with five 250-ml portions of chloroform, then neutralized with concentrated sulfuric acid–ice. An equal volume of dichloromethane was added and the organic layer separated, washed with brine, and dried. This was repeated five more times to yield 72.9 g of light brown solid (84.7% yield). The diacid was recrystallized from 2.5 l. of carbon tetrachloride to yield light yellow crystals (53.1 g). A small sample was dried in an Abderhalden drying pistol at 100° (0.1 mm) for 12 hr: $[\alpha]^{25}_{546}$ –25.6° (*c* 5.06, ethanol). A treatment with Norit failed to remove the color. The diacid (53.1 g) was dissolved in 0.5 l. of diethyl ether. A brown gum was removed by filtration and the volume of the solution condensed to 200 ml. A white crystalline solid (29.6 g) was recovered of slightly higher rotation ($[\alpha]^{25}_{546}$ –25.65° (*c* 5.27, ethanol)) and sharp melting point, 126.3–127.5°. The mother liquors from the carbon tetrachloride and diethyl ether were upgraded to give an additional 45.3 g of the levorotatory diacid of identical optical purity, total yield 36.2%, based on one enantiomer.

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.20; H, 6.65.

Resolution of 2-Methyl-2-phenylhexanedioic Acid (I) with Strychnine. The mother liquors from the brucine resolution (enriched in the dextrorotatory isomer) were converted by the procedure outlined above to 153.1 g of (+)-diacid. The enriched racemate (0.648 mol) was added to strychnine (434 g, 1.30 mol), dissolved in 4.6 l. of 83:17 (v/v) ethanol–water. The solution was refluxed on a steam bath until homogeneous. The recovered disalt was recrystallized again and converted to the acid. The conversion of the distrychnine salt (316 g) to the diacid was performed in a manner completely analogous to the one detailed above to give 69.1 g of the dextrorotatory diacid (83.7% recovery).

The diacid was dissolved in diethyl ether and filtered and the solution concentrated to 250 ml. The first crop of crystals (45.1 g) was light yellow: $[\alpha]^{25}_{546}$ +25.1° (*c* 5.24, ethanol); mp 126.7–128.0°. A second crop (11.63 g) had a sharper melting point (126.7–127.7°) and a slightly higher rotation: $[\alpha]^{25}_{546}$ +25.55° (*c* 5.22, ethanol). Concentration of the mother liquors gave 7.24 g of a white solid: $[\alpha]^{25}_{546}$ +25.25° (*c* 5.42, ethanol); mp 126.4–127.7°.

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.06; H, 6.67.

Racemic Dimethyl 2-Methyl-2-phenylhexanedioate ((±)-(II)). The procedure of Clinton and Laskowski[15] was employed but the reaction time was significantly extended. A mixture of 18 ml (0.45 mol) of pure methanol, 50 ml of dry 1,2-dichloroethane, 0.5 ml of concentrated sulfuric acid, and 11.3 g (0.048 mol) of 2-methyl-2-phenylhexanedioic acid was stirred at reflux for 48 hr. Additional methanol was added during the course of the reaction. Water produced during the reaction formed a second layer. The cooled reaction mixture was diluted with water and the diester extracted with dichloromethane. The organic layer was washed with water, 5% sodium bicarbonate solution, water, brine, and dried. The solvent was removed at aspirator vacuum, and the oil fractionated to give 8.99 g (72% yield) of dimethyl ester, mp 124–125° (0.37 mm); the infrared spectrum showed no absorption in the 2.8–3.1-μ region: ir (carbon tetrachloride) 5.75 (C=O), 7.33, 7.43 (CH_3), 8.35, and 8.55 μ (CO_2CH_3); nmr (carbon tetrachloride) τ 2.72 (aromatic CH, s, 5), 6.45 (CO_2CH_3, s, 6), 8.40 ($-(CH_2)_3-$, m, 6), and 8.48 (CH_3, s, 3). When the reaction was first run and stopped after 9 hr, a compound was isolated with an ir spectrum indicative of monoacid–monoester.

(–)-(*R*)-Dimethyl-2-methyl-2-phenylhexanedioate ((–)-II). Excess diazomethane[16] in dry ether was distilled into a 500-ml, side-arm filter flask containing a magnetically stirred solution of 15 g of (–)-2-methyl-2-phenylhexanedioic acid ($[\alpha]^{25}_{546}$ –25.65° (*c* 5.22, ethanol); mp 126.3–127.5°) in *ca.* 200 ml of anhydrous diethyl ether. The temperature of the solution was held at 5–10° by external cooling. The yellow solution was stirred for 12 hr. Formic acid was added dropwise until gas evolution ceased. The ether solution was concentrated on the steam bath, filtered through glass wool to remove the solid polymethylene, washed with dilute sodium bicarbonate, and then washed with brine. The solution was dried, and the solvent was removed to yield 16.64 g of a viscous yellow oil. The reaction was repeated on the same scale. The oily diester from both runs was combined and vacuum distilled through a Vigreux column to give 31.83 g of a colorless oil (95.0% yield): bp *ca.* 144° (0.4 mm); $[\alpha]^{25}_{546}$ –28.5° (*c* 5.57, ethanol), $n^{25}D$ 1.5012; ir 5.75, 5.85 (C=O), 6.22 (C=C), 8.35, and 8.55 μ (CO_2CH_3); nmr (carbon tetrachloride) τ 2.80 (aromatic C–H, 5), 6.48 (CO_2CH_3, s, 6), and 8.48 (CH_3, s. 3); tlc (1:1 (v/v) ethyl acetate–cyclohexane) showed only one spot, (R_f *ca.* 0.7) when the plate was visualized in an iodine chamber.

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.02; H, 7.65.

Material stored under oxygen-free dry nitrogen in an aluminum foil wrapped flask sealed with wax proved homogeneous to tlc (3:1 pentane–diethyl ether) after several months.

(+)-(*R*)-2-Methyl-2-phenylcyclopentanone ((+)-III). The following modified procedure was employed.[5a,b] A solution of 37.57 g (0.1421 mol) of optically pure dimethyl (–)-2-methyl-2-phenylhexanedioate ($[\alpha]^{25}_{546}$ –28.5° (*c* 5.43, ethanol); $n^{25}D$ 1.5012) in 175 ml of sodium-dried benzene and 1.5 ml of dry methanol was added dropwise over a period of 4 hr to a well-stirred, refluxing mixture of 27.6 g (0.604 mol) of a 52.6% sodium hydride dispersion

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(14) K. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 110.

(15) R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, 70, 3135 (1948).

(16) Th. J. de Boer and H. J. Backer, "Organic Synthesis," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 250.

in mineral oil (Metal Hydrides) and 265 ml of dry benzene. The course of the reaction was followed by glpc (20% SE 30 on 60–80 mesh Firebrick, 190°, 60 cc of helium/min). After a total of 11 hr at reflux, an aliquot was removed, quenched, and analyzed by glpc to contain 97.1% β-keto methyl ester and 2.9% starting material. The reaction vessel was immersed in an ice–water bath and a solution of 150 ml of concentrated hydrochloric acid and ice added slowly. Additional water was added to dissolve precipitated salt, and the layers were separated. The benzene layer was washed twice with saturated sodium bicarbonate, water, brine, and dried. The extraction was repeated with three, 200-ml portions of benzene. The solvent was removed at reduced pressure to yield 51.9 g of tan oil, of which *ca.* 13 g could be mineral oil. The material was not purified further but carried onto the next step. The crude β-keto methyl ester was hydrolyzed and decarboxylated in a mixture of glacial acetic acid (500 ml), concentrated hydrochloric acid (150 ml), and water (75 ml). The mixture was stirred at reflux for 14 hr, and the solvents were evaporated under vacuum from the hot solution. The resulting red-brown oil was cooled, and 50% potassium hydroxide solution added until the solution was weakly alkaline. Ethanol (50 ml) and 10% potassium hydroxide (75 ml) were added; the red solution was stirred at reflux for 2 hr. External cooling was applied, and the product extracted with three 200-ml portions of 50% ether–pentane. The combined organic layers were washed with saturated sodium bicarbonate, water, brine, and dried. The solvent was removed and the crude product (35.05 g) was found to be free of precursors by tlc. The tan oil was fractionated at reduced pressure to give 20.33 g (82% over-all) of colorless oil: bp 80–83° (0.63 mm), n^{25}_{D} 1.5342; ir (carbon tetrachloride) 5.75 μ (C=O); nmr (carbon tetrachloride) τ 2.70 (aromatic CH, m, 5), 7.98 ($-(\mathrm{CH_2})_3-$, m, 6), and 8.72 ($\mathrm{CH_3}$, s, 3); $[\alpha]^{25}_{\mathrm{D}}$ +95.30°, $[\alpha]^{25}_{546}$ +113.9°, $[\alpha]^{25}_{365}$ +357.9° (*c* 3.89, ethanol); $[\alpha]^{25}_{\mathrm{D}}$ +92.60°, $[\alpha]^{25}_{546}$ +111.0°, $[\alpha]^{25}_{365}$ +346.1° (*c* 3.97, toluene); mass spectrum (70 eV) *m/e* (relative intensity) 175 (6), 174 (41), 131, (19), 118 (100), 117 (25), 78 (12), 77 (11), and 28 (12).

Anal. Calcd for $\mathrm{C_{12}H_{14}O}$: C, 82.72; H, 8.10. Found: C, 82.57; H, 8.20.

Preparation and Separation of the Optically Pure *cis*- and *trans*-1,2-Dimethyl-2-phenylcyclopentanols ((−)-*cis*- and (−)-*trans*-IV). A solution of methyllithium, 370 ml of 1.7 *M* solution in diethyl ether (Foote Mineral Co.), was added under nitrogen to a dry flask immersed in a Dry Ice–acetone bath maintained at *ca.* −28°. A solution of 20.22 g (0.116 mol) of (+)-2-methyl-2-phenylcyclopentanone ($[\alpha]^{25}_{546}$ +113.9°, *c* 3.89, ethanol) in 210 ml of dry ether was added dropwise over a space of 2.5 hr. The colorless solution was stirred an additional 3 hr at *ca.* −26°, then the reaction was allowed to slowly come to *ca.* 15° over a 12-hr period. The temperature was lowered to 0–5°, and an ice–water solution was added slowly (2 hr). The ice bath was removed and excess water added until the aqueous solution was homogeneous. The reaction mixture was poured into a separatory funnel, and the products were extracted with three, 250-ml portions of ether. The combined organic layers were washed twice with water, brine, and dried. The solvent was removed at aspirator vacuum and benzene added to remove last traces of moisture.

Analysis of the crude reaction mixture on glpc (Aerograph A-90P, 6 ft × 0.25 in. aluminum column of 10% potassium hydroxide–10% Carbowax 4000 on 60–80 mesh Chromosorb W NAW, column 152°, flow rate of 62.5 cc of helium/min) indicated 22% of starting material. The diastereomeric alcohols were in the ratio of 74.6:25.4. The epimer of shorter retention time also moved faster on tlc and was designated α, the slower, β. The reaction mixture was recycled under the same conditions but the addition time was doubled. After quenching and work-up, a crude yield of 22.2 g was obtained. Analysis of the mixture by glpc indicated only 4.3% of starting material. The retention times of ketone and the α- and β-alcohols on glpc were as follows: ketone, 37.3 min; α-alcohol, 45.6 min; β-alcohol, 69.0 min.

The total mixture of epimeric alcohols and ketone was subjected to elution chromatography on 2884 g of 60–200 mesh silica gel. The column was prepared in 1:100 ether–pentane and measured 146 cm in height and 69 mm in diameter; 22.15 g of the crude mixture in 1:100 ether–pentane was placed on the column. A total of 206 fractions was taken. Fractions 1–57 (*ca.* 300 ml each) were taken as the solvent was varied from ether–pentane compositions of 1:100, 3:97, 5:95, and 7.5:92.5. All these fractions contained noncrystalline oils with R_f's greater than 2-methyl-2-phenylcyclopentanone. The next 90 fractions involved 10:90 ether–pentane. The 73rd fraction contained ketone contaminated by material of greater R_f. Fractions 80–85 contained pure ketone. The ketone appeared in the next six fractions. Fraction 91 contained alcohol (α isomer) with a trace of ketone by tlc. Fractions 95–148 netted 13.18 g of pure α isomer. Fractions 164–201 contained 4.98 g of pure β isomer.

By tlc only fractions 149–163 (0.926 g) contained both isomers. A total of 98% of all material placed on the column was recovered. The total yield of alcohol recovered was 87%. Each isomer was flash distilled. Physical measurements, including spectra, were taken on distilled material. Rotations were taken in both dry ethanol and benzene. The rotations observed for α (which behaved like a hydrocarbon) were *ca.* 10% larger in benzene. The β isomer (which behaved like an alcohol) showed a 50% increase in its observed rotations when benzene was used in place of ethanol. Consequently, all rotations were taken in benzene (*c* 2.5–2.8): α isomer, $[\alpha]^{25}$'s at 589, 578, 546, 436, and 365 mμ were −106.1, −110.8, −127.5, −227.6, and −380.7°, respectively; β isomer, $[\alpha]^{25}$'s at 589, 578, 546, 436, and 365 mμ were −43.18, −45.19, −51.97, −93.38, and −159.4°, respectively.

The detection of a trace amount of one isomer in the presence of the other was most easily accomplished by tlc (silica gel G, 3:1 pentane–ether). Phosphomolybdic acid solutions (10% w/v) in ethanol or iodine were both acceptable for visualization. Since iodine can dehydrate alcohols, this reagent proved particularly sensitive to trace (< 0.1%) amounts of either epimer.

Anal. Calcd for $\mathrm{C_{13}H_{18}O}$ (α): C, 82.06; H, 9.53. Found: C, 82.20; H, 9.58.

Anal. Calcd for $\mathrm{C_{13}H_{18}O}$ (β): C, 82.06; H, 9.53. Found: 82.19; H, 9.54.

(−)-(*R*)-5-Phenylhexanoic Acid ((−)-V). Racemic 3-phenylbutyric acid[17] was resolved *via* its menthol ester,[10] and the derived acid was treated with optically pure (+)-α-phenylethylamine Three crystallizations of the resulting salt from 1:1 ethanol–water gave acid of unchanged optical purity: n^{25}_{D} 1.5147, α^{25}_{D} −56.96 ± 0.02°, α^{25}_{546} −68.38 ± 0.02° (*l* 1 dm, neat); $[\alpha]^{25}_{\mathrm{D}}$ −57.95 ± 0.02°, $[\alpha]^{25}_{546}$ −69.36 ± 0.02° (*c* 3.04, benzene). By tlc, the acid was chemically pure. The optically pure (−)-3-phenylbutyric acid was submitted to two successive modified Arndt–Eistert reactions.[9]

A mixture of 10.7 g of the acid and 25 ml of redistilled thionyl chloride was allowed to stand at 25° for 12 hr, and then excess reagent was removed at 25° (25 mm). Sodium-dried benzene was added and the residue distilled to give 11.17 g of 3-phenylbutyroyl chloride (bp 88° (3.4 mm)); ir (carbon tetrachloride) 5.55 μ (C=O). The acid chloride was dissolved in 50 ml of dry ether and added dropwise over a period of 2 hr to an ice-cold solution of *ca.* 7.7 g of diazomethane in 250 ml of ether. The reaction mixture was stirred as the temperature slowly rose to 25° over a space of 12 hr. The excess diazomethane and ether were evaporated at 10° under reduced pressure. The oily residue was filtered through glass wool and the yellow oil stirred at 0.3 mm for 2 hr to yield 11.3 g (90.1%): ir (carbon tetrachloride), 4.74 ($\mathrm{CH}N_2$), 4.76 ($\mathrm{C}H_2\mathrm{N_2}$), 5.78 ($-\mathrm{C}O\mathrm{CH_2Cl}$), 6.08 ($-\mathrm{C}O\mathrm{CHN_2}$), and 7.45 μ; nmr (carbon tetrachloride) τ 2.82 (aromatic CH, singlet with fine structure, 5), 4.83 ($\mathrm{C}H\mathrm{N_2}$, s, 1), 6.45–6.97 (–CH, m, 1), 7.52 ($-\mathrm{CH_2}-$, ABX, 2), and 8.77 ($\mathrm{CH_3}$, d, 3, $J = 7$ Hz). The crude diazoketone was rearranged in the next step without further purification. An equimolar mixture of pure benzyl alcohol and γ-collidine was brought to 174° (Wood's metal bath). To this solution was added dropwise, over a period of 2.5 min, a neat solution of the diazoketone. The molar ratio of diazoketone to amine was 1:5. After an induction period of a few seconds, nitrogen was evolved in an exothermic reaction and the temperature rose 7°. The reaction mixture was heated for 5 min after gas evolution ceased and cooled; cold concentrated hydrochloric acid was added. The product was extracted with two 100-ml portions of ether. The combined organic layers were washed with dilute hydrochloric acid, water, brine, and dried. The solvent was removed, and the benzyl ester was hydrolyzed by refluxing with a solution of 55 ml of 50% potassium hydroxide and 50 ml of methanol for 4 hr. The dark, opaque solution was cooled, washed with 1:1 ether–pentane, and acidified with cold, dilute hydrochloric acid. The aqueous mixture was concentrated at reduced pressure and the product extracted with ether. The ether solution was dried and evaporated, and the residual oil distilled to give 7.42 g (75% yield) of 4-phenylpentanoic acid, bp 140° (*ca.* 1 mm). The methyl region in the nmr was examined at a sweep width of 50 cps. The broad doublet observed at 500-cps sweep width was resolved into two doublets.

Analysis of the methyl ester on glpc (Aerograph A-700, 6 ft ×

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[17] G. Baddeley and W. Pickles, *J. Chem. Soc.*, 2855 (1957).

0.25 in. aluminum column of 10% SE 30 on silanized Chromosorb W, column temperature 175°, flow rate of 145 cc of helium/min) showed the ester to be a mixture of 83.9% methyl pentanoate, 9.7% methyl butyrate, and 6.4% two other unidentified substances. The difference between the volatility of 4-phenylpentanoate and that of 3-phenylbutyrate is not great, but the boiling point of methyl 5-phenylhexanoate is significantly higher than the two lower homologs. Thus, purification of the phenylhexanoate was more feasible. Optically active 4-phenylpentanoic acid contaminated by *ca.* 17% 3-phenylbutyric acid was homologated again by the modified Arndt–Eistert procedure described above.

A 41.5% yield of (−)-5-phenylhexanoic acid was obtained. Careful vacuum fractionation on a Nester–Faust annular Teflon spinning-band distillation column yielded a light yellow oil: bp 168° (1.2 mm) [lit.[18] bp 156° (*ca.* 1 mm)]; ir (carbon tetrachloride) 2.5–4.2 μ (OH) and 5.85 (C=O); nmr (carbon tetrachloride) τ −1.20 (OH, s, 1), 2.88 (aromatic CH, singlet with fine structure, 5), 7.77–8.70 (-$(CH_2)_3$-, -CH, m, 7), and 8.84 (CH_3, d, 3, J = 7 Hz); $n^{25}D$ 1.5091; $\alpha^{25}D$ −26.24 ± 0.02°, $\alpha^{25}{}_{546}$ −31.56. ± 0.02° (*l* 1 dm, neat). The methyl ester was analyzed on glpc (Aerograph A-700, 6 ft × 0.25 in. aluminum column of 10% SE 30 on silanized Chromosorb W, column temperature 175°, flowrate of helium 145 cc/min). The results are as follows: methyl 3-phenylbutanoate, <0.1%, retention time 6.3 min; methyl 4-phenylpentanoate, 1.1%, 10.6 min; methyl 5-phenylhexanoate, 98.8%, 16.9 min.

Esterification of the (−)-5-phenylhexanoic acid with methanol in 1,2-dichloroethane[15] gave a 94% yield after distillation. Preparative glpc (Aerograph A-90P, 30% SE 30 on 60–80 mesh Chromosorb W, column temperature 212°, flow rate of 98 cc of helium/min) gave a 51.4% yield of chemically pure ester: homogeneous on tlc, and analytical glpc (20% SE 30 on 60–80 Firebrick, 170°, helium). Saponification of the ester with 10% sodium hydroxide in 3:1 water–methanol gave the acid in 90% yield: $[\alpha]^{25}D$ −24.0 ± 0.02°, $[\alpha]^{25}{}_{546}$ −29.0 ± 0.02° (*c* 3.04, benzene); $\alpha^{25}D$ −26.47 ± 0.02°, $\alpha^{25}{}_{546}$ −31.93 + 0.02° (*l* 1 dm, neat); $n^{25}D$ 1.5093. The infrared and nmr spectra were essentially unchanged. Only the specific and observed rotations were significantly altered. This compound was analyzed as its methyl ester.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.82; H, 9.00.

Hill and Carlson[18] calculated the maximum rotation of 5-phenylhexanoic acid from Levene and Marker's data,[19] but mistook specific for observed rotation of (+)-3-phenyl-1-bromobutane (neat).[10] Our observed rotation and that properly calculated from past data[10,19] are within experimental error of one another ($\alpha^{25}D$ −26.47 and −27.00°, neat, respectively).

(−)-(*R*)-6-Phenylheptanone ((−)-VII). A modified procedure[20] was used. To a well-stirred solution of 1.09 g (5.63 mmol) of optically pure (−)-5-phenylhexanoic acid in 20 ml of ether maintained at *ca.* −12° was added 10 ml of a 1.6 *M* ethereal solution of methyllithium over a period of 30 min. An equivalent volume of methyllithium was added in the next 15 min. The resulting slurry was stirred for 3.5 hr. The temperature rose to 12°. The slurry was quenched at −20° by dropwise addition of ether saturated with ice water. The solution was stirred overnight, excess water was added, and the white solid dissolved. The product was extracted with ether. The organic layer was washed with water, brine, dried, and evaporated to a yellow oil. From the water layer was recovered 40 mg of starting acid. By glpc (20% SE 30 on 60-80 Firebrick), the crude product was a mixture of 69.3% ketone and 30.7% alcohol.

The alcohol–ketone mixture was subjected to elution chromatography on 185 g of silica gel. The column was prepared in 1:99 ether–pentane and measured 67.5 cm in height and 32 mm in diameter. The column was washed with 3 l. of 1:99 ether–pentane, and the ketone was eluted with 3:97 ether–pentane. Evaporation of the solvent yielded 0.452 g (42.3% yield) of optically pure (−)-ketone as a liquid which was flash distilled: bp 90–92° (1 mm) [lit.[21] bp 136–140° (13 mm)]; $n^{25}D$ 1.4997; ir (carbon tetrachloride) 5.81 μ (C=O); nmr (carbon tetrachloride) τ 2.86 (aromatic CH, singlet with fine structure, 5), 7.43 (-CH, m, 1, J = 7 Hz), 7.79 ($CH_2C{=}O$, m, 2), 8.12 (-C(=O)CH_3, s, 3), 8.53 (-$(CH_2)_2$-, m, 4), and 8.82 (CH_3, d, 3, J = 7 Hz); $[\alpha]^{25}D$ −21.6 ± 0.2°; $[\alpha]^{25}{}_{546}$ −26.1 ± 0.2° (*c* 1.85, benzene).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.25; H, 9.52.

The alcohol was eluted with 1:9 ether–pentane and obtained in 33.5% yield as an oil. A 16% impurity (probably the aldol dimer of the ketone) was present. Attempts at a chemical separation were unsuccessful. Careful elution chromatography lowered the impurity, but the alcohol was still not homogeneous by tlc. A glpc separation was possible but the above manipulations wasted enough material to make it inefficient. The (−)-alcohol was obtained by careful addition of the (−)-ketone to methyllithium.

(−)-(*R*)-2-Methyl-6-phenyl-2-heptanol ((−)-VIII). An ethereal solution of methyllithium, 10 ml, 1.7 *M*, was placed in a nitrogen-filled flask immersed in a methanol–ice bath at *ca.* −19°. To this solution, 0.203 g (1.06 mmol) of optically pure (−)-6-phenyl-2-heptanone dissolved in 25 ml of ether was added over a 1.67-hr period. After addition was complete, the reaction mixture was stirred for 12 hr as the temperature slowly rose to +12°. The solution was cooled to −10°, and water and then saturated ammonium chloride were added. The product was extracted from the homogeneous solution with ether–dichloromethane. The solvents were washed with water and brine, dried, and removed at reduced pressure to yield 0.211 g (96% yield) of an oil. By tlc no starting material was visible (2,4-DNPH spray). The oil was chromatographed on 37 g of silica gel and the optically pure (−)-alcohol eluted with 1:10 ether–pentane. The product was flash distilled in a micro Hickman flask, bp 95–98° (*ca.* 0.19 mm): ir (carbon tetrachloride) 2.78 and 2.88–3.05 μ (OH); nmr (carbon tetrachloride) τ 2.84 (aromatic CH, singlet with fine structure, 5), 7.39 (-CH, m, 1, J = 6.5 Hz), 7.62 (OH, s, 1), 8.20–9.33 ($(CH_2)_3$, m, 6), 8.78 (-CCH_3, d, 3, J = 6.5 Hz), and 8.94 (-C(OH)$(CH_3)_2$, s, 6); $n^{25}D$ 1.5040; $[\alpha]^{25}D$ −25.7 ± 0.2°; $[\alpha]^{25}{}_{546}$ −30.5 ± 0.2° (*c* 1.482, benzene); $[\alpha]^{25}D$ −27.36 ± 0.02°; $[\alpha]^{25}{}_{546}$ −32.74 ± 0.02° (*c* 3.77, ethanol).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.53; H, 10.71.

(−)-(*S*)-3-Phenyl-2,3,7-trimethyl-2,7-octanediol ((−)-IX). A solution of 93.5% optically pure dimethyl 2-methyl-2-phenylhexanedioate, 4.06 g or 0.0154 mol, ($[\alpha]^{25}{}_{546}$ +26.65° (*c* 5.10, ethanol), $n^{25}D$ 1.5009) was added (45 min) to excess methyllithium in ether stirred at *ca.* −20°. The crude product was isolated in the usual way and recycled. The product isolated showed only weak absorption in the carbonyl region of the ir. By tlc (1:1 ethyl acetate–cyclohexane) only a trace of starting material was present (R_f 0.56) in addition to two slower moving spots (R_f 0.27 and 0.36), glycol and monoketone, respectively. The crude oil (5.12 g) was subjected to elution chromatography on 589 g of silica gel activated at 150° for 24 hr. The column was prepared in 1:1 ether–pentane and measured 93 cm in height and 52 mm in diameter. Fractions (92) were taken as the solvent was varied from 1:1 to 3:1 ether–pentane and finally pure ether. Fractions 34–47 netted 0.107 g of a clear colorless oil that corresponded to the faster of the two major components visible by tlc. The infrared and nmr spectra were definitive for 7-hydroxy-3,7-dimethyl-3-phenyl-2-octanone: ir (chloroform) 2.75 and 2.95 (OH) and 5.85 μ (C=O); nmr (carbon tetrachloride) τ 2.78 (aromatic CH, singlet with fine structure, 5), 8.18 ($CH_3C{=}O$, s, 3), 8.65 ($\geqslant CCH_3$, s, 3), 8.74 (OH, s, 1), and 8.90 ($\geqslant COH(CH_3)_2$, s, 6). Fractions 48–58 contained 0.535 g of a waxy solid contaminated by a small amount of faster moving material. Fractions 59–92 netted 2.15 g of a semisolid which was homogeneous to tlc (1:100 methanol–ether). This waxy solid had the flow properties of cold maple syrup. A sample was dissolved in ethanol, and the following specific rotations were calculated: $[\alpha]^{25}{}_{578}$ −10.72°, $[\alpha]^{25}{}_{546}$ −12.20° (*c* 5.27, ethanol). This material was fractionally crystallized to constant melting point, and probably to optical purity, mp 67.2–67.9°; $[\alpha]^{25}{}_{578}$ −12.1°, $[\alpha]^{25}{}_{546}$ −16.25° (*c* 5.26, ethanol); ir (deuteriochloroform) 2.79 and 2.90 μ (OH); nmr (deuteriochloroform) τ 2.70 (aromatic CH, singlet with fine structure, 5), 8.62 ($\geqslant CCH_3$, s, 3), 8.87 and 8.95 ($\geqslant CCOH(\mathit{CH}_3)_2$, 2s, 6), and 8.92 ($-COH(\mathit{CH}_3)_2$, s, 3). The resonance of the hydroxyl proton was hidden under that of the methyls.

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.39; H, 10.50.

Racemic material similarly prepared gave mp 66.0–67.5° and the same spectral characteristics.

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.42; H, 10.68.

Cleavage Reactions. Conditions for the retro-grade condensation reactions of glycol IX were obtained for the racemic material

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(18) R. K. Hill and R. M. Carlson, *J. Am. Chem. Soc.*, **87**, 2772 (1965).

(19) P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **100**, 685 (1933).

(20) J. D. Billimoria and N. F. MacLagan, *J. Chem. Soc.*, 3067 (1951).

(21) C. D. Nenitzescu and I. G. Gavat, *Ann. Chem.*, **519**, 270 (1935).

by running a series of sealed-tube reactions under varied conditions of temperature and reaction time. The progress of the reaction was followed by tlc with authentic samples. All reactions were run on a 25-mg scale in 0.3–0.4 ml of solvent. The *t*-butyl alcohol and diethylene glycol were purified according to previously published procedures.[2b] Dioxane was purified by the method of Fieser.[22] Reactions were run in clean, dry ampoules under pure, dry nitrogen.

Cleavage of (−)-(*S*)-3-Phenyl-2,3,7-trimethyl-2,7-octanediol ((−)-IX) in Dioxane–Potassium *t*-Butoxide. To a nitrogen-filled tube, 0.235 g (0.89 mmol) of (−)-(*S*)-3-phenyl-2,3,7-trimethyl-2,7-octanediol and 0.281 g (2.5 mmol) of potassium *t*-butoxide (MSA Research Corp., Callery, Pa.) was added and washed down with 4 ml of pure dioxane. A serum cap was added and the nonhomogeneous solution was frozen (−78°), evacuated, and sealed. The ampoule was warmed under a stream of warm water, but the solution was not homogeneous. The tube was immersed up to meniscus in a stirred bath at 148–149.5° for 40.5 hr. The tube was etched and contained a white flocculent solid. When the mixture was cooled, it completely solidified. The contents of the tube were transferred to a separatory funnel containing 40 ml of water and an equal volume of 1:1 ether–pentane. The tube was washed out with copious volumes of solvent. The layers were separated. The organic layer was filtered through glass wool, washed with three portions of water, brine, and dried. The aqueous layers were extracted two more times with pentane. Removal of solvent left 0.173 g of crude oil. Only product alcohol and two spots of faster R_f were visible by tlc (10% phosphomolybdic acid in ethanol). The crude product was subjected to elution chromatography on 21 g of 80–200 mesh silica gel. The desired product (2-methyl-6-phenyl-2-heptanol) was eluted with 1:9 ether–pentane, and solvent removed to give 0.118 g (65% yield) of a colorless oil, homogeneous by tlc. This material was distilled in a micro Hickman flask at 0.03 mm pressure. The infrared and nmr spectra were superimposable with those of an authentic sample (see Table II for polarimetric readings).

Table II

$\alpha^{25}{}_{\text{obsd}}$, deg	$[\alpha]^{25}{}_{\lambda}$,[a] deg	λ, mμ	% optical purity[b]
−0.959	−22.4	578	78.79
−1.098	−25.64	546	78.29
−1.909	−44.57	436	78.03
−3.100	−72.38	365	77.75
		Av	78.09

[a] *c* 4.33, ethanol; $n^{25}{}_{D}$ 1.5040. [b] Compared to optically pure alcohol (*c* 3.77, ethanol).

Cleavage of (−)-(*S*)-3-Phenyl-2,3,7-trimethyl-2,7-octanediol ((−)-IX) in *t*-Butyl Alcohol–Potassium *t*-Butoxide. To a nitrogen-filled tube, 0.235 g (0.89 mmol) of (−)-(*S*)-3-phenyl-2,3,7-trimethyl-2,7-octanediol and 4 ml of *t*-butyl alcohol, 0.493 *M*, in potassium *t*-butoxide were added. The ampoule was frozen, evacuated, sealed, and placed in an oil bath maintained at 148–149.5° for 40.5 hr. The solution was homogeneous before and after the run. The work-up was completely analogous to that described above. The desired alcohol was purified by elution chromatography to give 0.199 g of oil (68%) homogeneous to tlc. A trace amount of 2-phenylpentane was identified by comparison with an authentic sample. The alcohol was distilled in a micro Hickman flask at 0.03 mm pressure. The nmr spectrum of this material was identical with that of an authentic sample (see Table III for specific rotations).

Table III

$\alpha^{25}{}_{\text{obsd}}$, deg	$[\alpha]^{25}{}_{\lambda}$,[a] deg	λ, mμ	% optical purity[b]
−0.900	−23.9	589	87.51
−0.940	−25.0	578	87.44
−1.077	−28.65	546	87.51
−1.876	−49.91	436	87.88
		Av	87.46

[a] *c* 3.80, ethanol; $n^{25}{}_{D}$ 1.5039. [b] Compared with optically pure alcohol (*c* 3.77, ethanol).

Cleavage of (−)-(*S*)-3-Phenyl-2,3,7-trimethyl-2,7-octanediol ((−)-IX) in Diethylene Glycol–Potassium Diethylene Glycoxide. To a dry ampoule filled with pure nitrogen, 0.224 g (8.5 mmol) of (−)-(*S*)-3-phenyl-2,3,7-trimethyl-2,7-octanediol and 5 ml of diethylene glycol, 0.342 *M* in potassium glycoxide, were added. The tube was frozen, evacuated, sealed, and placed in a Wood's metal bath at 186 ± 1° for 40.25 hr. Work-up in the usual manner netted 0.198 g of oil which contained a trace amount of starting glycol (tlc), as well as an equally small amount of 2-phenylpentane. The entire crude reaction mixture was subjected to elution chromatography. Fractions 16–21 gave 0.111 g of a homogeneous oil with a nmr spectrum indicative of 2-methyl-6-phenyl-2-heptanol. The oil was flash distilled in a micro Hickman flask (see Table IV for specific rotations obtained on this material).

Table IV

$\alpha^{25}{}_{\text{obsd}}$, deg	$[\alpha]^{25}{}_{\lambda}$,[a] deg	λ, mμ	% optical purity[b]
+0.097	+6.10	589	23.75
+0.102	+6.38	578	23.92
+0.116	+7.32	546	23.98
+0.204	+12.8	436	23.57
+0.332	+20.9	365	23.22
		Av	23.7

[a] *c* 1.5722, benzene; $n^{25}{}_{D}$ 1.5037. [b] Based on specific rotation of optically pure alcohol (*c* 1.4820, benzene).

Cleavage of (+)-(*R*)-2-Methyl-2-phenylcyclopentanone ((+)-III) in *t*-Butyl Alcohol. The ampoule technique was necessary since the boiling point of the solvent was exceeded. Optically pure (+)-2-methyl-2-phenylcyclopentanone (0.506 g, 0.0029 mol) was syringed into a clean Carius tube that had been evacuated while hot and then filled with oxygen-free, dry nitrogen. A solution of 15 ml of *t*-butyl alcohol, 0.444 *M* in potassium *t*-butoxide, was pipetted into the tube which was then immersed in a Dry Ice–acetone bath and sealed under vacuum. The tube was warmed in a stream of water, shaken to ensure homogeneity, and then immersed up to the meniscus in a stirred oil bath maintained at 165 ± 1°. After 22.6 hr the tube was removed, frozen, and opened. A gas, probably isobutylene, escaped upon opening. The contents of the ampoule were transferred to a separatory funnel containing 25 ml of 1:20 methanol–water and 25 ml of 1:1 ether–pentane. The ampoule was then washed with copious amounts of these solvents. The layers were separated and the organic phase shaken with two portions of 1:20 methanol–water, brine, and dried. Solvents were removed to give 0.314 g of a light yellow oil. By tlc (3:1 pentane–ether) the oil was a mixture of starting material, *t*-butyl 5-phenylhexanoate, and a slower moving material, presumably dimer of starting material. Analysis of the nonacidic mixture by glpc (Aerograph A90P, 6 ft × 0.25 in. aluminum column of 5% SE 30 on Chromosorb W, HMDS at 210°, flow rate of helium 60 cc/min) showed the presence of 11.2% 2-methyl-2-phenylcyclopentanone and 14.2% *t*-butyl ester; yields are absolute. The ir spectrum in carbon tetrachloride showed no hydroxyl absorption in the 2.8–4.2-μ region: ir (carbon tetrachloride) 5.75, (C=O), 5.85 (CO_2R'), 6.02, 6.15, 6.25 (C=C), 7.30 (CH_3), and 8.16 μ $(CH_3)_3$.

The combined aqueous layers were saturated with sodium chloride and neutralized with excess cold concentrated hydrochloric acid. The product acid was extracted with three portions of dichloromethane. Solvent was dried, then removed to give a yellow oil. This oil was dissolved in 5% sodium bicarbonate containing 15% methanol. This mixture was shaken with two 25-ml portions of 1:1 ether–pentane. The aqueous solution was carefully made strongly acidic with cold concentrated hydrochloric acid. The oil which separated was taken up in dichloromethane which was shaken with brine and dried. Solvent was removed to give 0.239 g of 5-phenylhexanoic acid (43% yield). The oil was flash distilled in a micro Hickman flask: bp 123–125° (pot) at 0.08 mm [lit.[19] bp 156° (1–2 mm)]; $[\alpha]^{25}{}_{D}$ +14.8°, $[\alpha]^{25}{}_{546}$ +17.7° (*c* 2.79, benzene); $n^{25}{}_{D}$ 1.5082; ir (carbon tetrachloride) 2.8–4.2 (OH), 5.85 (C=O), and 6.22 μ (C=C); nmr (carbon tetrachloride) −1.17 (OH, s, 1), 2.88 (aromatic CH, singlet with fine structure, 5), 7.15–8.03 (CH, CH_2CO, m, 3), 8.17–8.67 ($-(CH_2)_2-$, m, 4), and 8.79 (CH_3, d, 3, J = 7 Hz). A sample of the acid dissolved in ethanol gave a negative test with 2,4-dinitrophenylhydrazine.

Equilibration of (−)-(1*R*,2*R*)- and (−)-(1*S*,2*R*)-1,2-Dimethyl-2-

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[22] L. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1957, p 285, procedure A.

phenylcyclopentanol [(−)-*cis*- and (−)-*trans*-IV] in Dimethyl Sulfoxide at 25°. Pure dimethyl sulfoxide (Crown Zellerbach Corp.), 400 ml, was transferred *via* dry pipet to a previously dried 500-ml, three-necked flask equipped with a pressure-equilibrating dropping funnel, nitrogen inlet, and Teflon stirring bar. Teflon sleeves were used. Optically pure (−)-*cis*-1,2-dimethyl-2-phenylcyclopentanol, 0.237 g, and a few crystals of triphenylmethane (mp 93.1–93.9°) were added, and the contents thermostated at 25.5°. A dimsylsodium solution was prepared under an atmosphere of oxygen-free nitrogen from 0.310 g of sodium amide in 40 ml of pure dimethyl sulfoxide. The ammonia produced was removed by bubbling a fine stream of pure dry nitrogen through the solution until a strip of wet litmus paper did not change color. The dimsylsodium was rapidly added to the alcohol in dimethyl sulfoxide (*ca.* 30 sec). The solution became deep red. The joints were sealed with melted wax, and the flask was immersed in a water bath held at 25.5° for 11 hr. The light pink solution was poured into a rapidly stirred mixture of 1 l. of ice and water. The resulting colorless solution was transferred to a separatory funnel containing 400 ml of 1:1 ether–pentane and 400 ml of water. The layers were separated and the organic phase was washed with two, 50-ml portions of water and brine and then dried. The aqueous layer was shaken with three more 400-ml portions of 1:1 ether–pentane which were treated as above. The solvents were removed at aspirator vacuum at 25°. The residual oil was dissolved in *ca.* 50 ml of dry ether.

By tlc a ketone, epimeric alcohols, olefin, and aldol dimer were present. An ice bath at *ca.* 0° was applied and 1.1 g of powdered lithium aluminum hydride (Metal Hydrides) added portionwise. The slurry was stirred for 12 hr as the temperature slowly rose to 25°. The flask and its contents were again cooled to *ca.* 0°, and the mixture was hydrolyzed with water, 10% sodium hydroxide, and water. The resulting granular, white precipitate was stirred an additional hour and the solvent decanted. The salts were triturated with dichloromethane and ether. The combined organic phases were washed with water (until the aqueous layer was neutral) and brine and dried. The solvents were removed, pure octadecane (Matheson Coleman and Bell) (0.106 g) was added, and the solution was diluted to 1 ml with ether.

Analyses by glpc were performed (see next section) and the results recorded in Table I. No material of retention time longer than 6-phenyl-2-heptanol was found (analysis time 200 min). Each peak was collected and checked by tlc to be one component. The cyclic olefin, 1,2-dimethyl-2-phenylcyclopentene, was present to the extent of 8–10%.

The solvent was removed from the crude mixture and the residual oil subjected to elution chromatography on 36 g of silica gel packed in pentane. The column measured 30 cm in height and 15 mm in width. The hydrocarbon standard was eluted with 300 ml of pure pentane.

Fractions 9–11 netted 40.2 mg of a crystalline solid, *cis* isomer (α). Then, the ratio of ether:pentane was changed from 5:95 to 10:90. Fractions 18–22 contained 50.4 mg of a crystalline solid, *trans* isomer (β). The column was next eluted with 30:70 ether–pentane, then pure ether. Fractions 19–31 contained 6-phenyl-2-heptanol contaminated by some of the β isomer. Fraction 33 was eluted with pure methanol and contained two compounds. Analysis of fraction 33 *via* ir indicated that it was a mixture of α,β-unsaturated ketone. The spectrum was too weak to assign stereochemistry: ir (carbon tetrachloride) 2.78–3.2, 5.75, 5.78, 5.85, 6.02, 6.1–6.2, and 6.22 μ.

The samples of both pure diastereomers were dissolved in dry benzene and analyzed polarimetrically at the mercury green line (546 mμ): for α isomer, $\alpha^{25}_{\text{obsd}}$ −0.001 ± 0.002° (*c* 2.60, benzene); for β isomers, $\alpha^{25}_{\text{obsd}}$ +0.002 ± 0.002° (*c* 1.15, benzene).

The equilibration of (−)-*trans*-1,2-dimethyl-2-phenylcyclopentanol was carried out in a completely analogous way. After glpc analysis (next section) and chromatography, the following polarimetric readings were taken at the mercury green line: for α isomer, $\alpha^{25}_{\text{obsd}}$ −0.002 ± 0.002° (*c* 1.47, benzene); for β isomer, $\alpha^{25}_{\text{obsd}}$ −0.002 ± 0.002° (*c* 2.40, benzene).

Analysis of Diastereomeric 1,2-Dimethyl-2-phenylcyclopentanols and Their Cleavage Products by Gas–Liquid Partition Chromatography. Samples corresponding to each peak were collected in capillary tubes and analyzed for purity by tlc. Complete base-line separation of the epimers was achieved on a 6 ft × 0.25 in. aluminum column packed with 10% potassium hydroxide–10% Carbowax 4000 on 60–80 mesh Chromosorb W NAW.

The column was installed in a Wilkens A90P gas chromatograph (thermal conductivity detection) coupled to a Leeds and Northrop 1-mV recorder equipped with a disk integrator. Column oven temperature ranged between 145 and 155°. Injector and detector oven temperatures were 150 and 178°, respectively, and the flow of helium carrier gas was *ca.* 60 cc/min.

Analysis of a mixture of the *cis* and *trans* epimers in the presence of 6-phenyl-2-heptanone gave only two peaks. By tlc the *cis* epimer and the heptanone were shown to possess the same retention times. Reduction of the ketone to 6-phenyl-2-heptanol afforded a mixture that could be separated on this column. The retention time of the heptanol was greater than the *trans* epimer.

Standard mixtures of the diastereomers were made up and analyzed by glpc to contain ±0.1% of the weighed amounts. Analyses involving sliding base lines were most easily carried out by the cut-and-weigh technique. Tracings of peaks were done on Albanene tracing paper (K & E No. 10-5351) with a hard drawing pencil. An internal standard, either heptadecane or octadecane was added to the crude sample in a 1-ml volumetric flask and ether added to the mark. Under the conditions detailed above, *cis*-1,2-dimethyl-2-phenylcyclopentanol was eluted in *ca.* 43 min. Retention time ratios, relative to *cis*-1,2-dimethyl-2-phenylcyclopentanol, were *trans*-1,2-dimethyl-2-phenylcyclopentanol, 1.58; 6-phenyl-2-heptanol, 1.75.

Equilibration of *cis*- and *trans*-1,2-Dimethyl-2-phenylcyclopentanol in Dimethyl Sulfoxide, 1.8 *M* in *t*-Butyl Alcohol and 0.164 *M* in Potassium *t*-Butoxide at 37°. To a previously dried, three-necked flask equipped with nitrogen inlet and outlet (Teflon sleeves) were placed 61 mg (0.32 mmol) of racemic *trans*-1,2-dimethyl-2-phenylcyclopentanol, 80 ml of pure dimethyl sulfoxide, and 16 ml of *t*-butyl alcohol, 0.980 *M* in potassium *t*-butoxide. The resulting straw-yellow solution was shaken vigorously under an atmosphere of nitrogen. The homogeneous solution was placed in an oil bath at 37°. After 22 hr, an aliquot was removed with a syringe. The aliquot was quenched with ice-water and the products were extracted with 1:1 ether–pentane. The organic phases were each shaken with two 10-ml portions of water and then brine. The combined organic phases were dried, and the solvent was removed at reduced pressure. The residual oil was analyzed by tlc to contain both isomeric alcohols in addition to open-chain ketone VII. The crude oil was dissolved in 20 ml of dry ether and 0.3 g of lithium aluminum hydride added, portionwise. The slurry was stirred at 25° for 12 hr. Water (0.3 ml), then 0.3 ml of 10% sodium hydroxide, and finally 0.9 ml of water were added dropwise. The solution was stirred until a white granular solid formed. The solution was decanted; the solid was triturated with ether and dichloromethane. Finally, the slurry was filtered through Celite. The combined organic layers were washed with water and brine and dried. By tlc ketone VII had been completely converted into the secondary alcohol, 6-phenyl-2-heptanol (X). By glpc the following results were obtained: *cis*-IV, 25.1%; *trans*-IV, 70.4%; X, 4.5%.

After a total of 46.25 hr, another aliquot was removed; the products were extracted and reduced with lithium aluminum hydride. The basic work-up and product extraction were performed as described above. The results were as follows: *trans*-IV, 50.1%; *cis*-IV, 22.5%; X, 27.5%.

A sample of *cis*-IV was epimerized and equilibrated under the same conditions as those employed for the *trans*-IV to give 22.3% *cis*-VI, 49.7% *trans*-IV, and 28.1% X. The possibility exists that some of the phenyl-2-heptanone was lost as higher aldol condensation products. By tlc no material of R_f less than that of 6-phenyl-2-heptanol was visible.