3990-93-0; 4-isopropenylcyclohexene, 26325-89-3; 2-methyl-1,12-dodecadiene, 34386-65-7; 2-methyl-1-decene, 13151-27-4; 1-isopropenyl-4-methylenecyclohexane, 499-97-8; 1-isopropenyl-4-ketocyclohexyltrimethylene dithioacetal, 70813-54-6; 1-isopropenyl-4-ketocyclohexyl ethylene acetal, 70850-38-3; 1-isopropenyl-4-(2'-tetrahydrofuranoxy)cyclohexane, 70813-55-7; 1-isopropenyl-4-ketocyclohexane, 22460-53-3; 2-methyl-3,3-diphenylpropene, 70813-56-8; $EtO_2C(CH_2)_2CO_2Et$, 123-25-1; $EtO_2C(CH_2)_3CO_2Et$, 818-38-2; $EtO_2C(CH_2)_4CO_2Et$, 141-28-6; $EtO_2C(CH_2)_5CO_2Et$, 2050-20-6; $MeO_2C(CH_2)_{10}CO_2Me$, 1731-79-9; $CH_3C(=CH_2)(CH_2)_2C(=CH_2)CH_3$, 627-58-7; $CH_3C(=CH_2)(CH_2)_3C(=CH_2)$, 51708-83-9; $CH_3C(=CH_2)(CH_2)_4C(=CH_2)CH_3$, 59840-10-7; $CH_3C(=CH_2)(CH_2)_5C(=CH_2)CH_3$, 20054-25-5; $CH_3C(=CH_2)(CH_2)_{10}C(=CH_2)CH_3$, 22080-36-0; 1-ethoxy-1-(2-naphthyl)ethene, 70813-57-9; 1-(2-naphthyl)ethanone, 93-08-3; $CH_3(CH_2)_7C(=CH_2)OCH_3$, 54123-72-7; 1-methylethyl *o*-methoxybenzoate, 944-95-6; 1,1-dimethylethyl *o*-methoxybenzoate, 16537-20-5; 2,2-dimethylpropyl *o*-methoxybenzoate, 66702-44-1; methyl benzoate, 93-58-3; 1-methylethyl benzoate, 939-48-0; ethyl *p*-methoxybenzoate, 94-30-4; methyl *p*-bromobenzoate, 619-42-1; ethyl 3-pyridylcarboxylate, 614-18-6; methyl 4-pyridylcarboxylate, 2459-09-8; methyl *n*-nonylcarboxylate, 110-42-9; ethyl benzoate, 93-89-0; ethyl acetate, 141-78-6; methyl *p*-methylbenzoate, 99-75-2; (*Z*)-5-phenyl-4-nonene-1,9-dicarboxylic acid, 70813-58-0; (*E*)-5-phenyl-4-nonene-1,9-dicarboxylic acid, 70813-59-1; 4-nonene-1,9-dicarboxylic acid, 70813-60-4; 9-(ethoxycarbonyl)nonyltriphenylphosphonium iodide, 70813-61-5; 9-(ethoxycarbonyl)nonyltriphenylphosphorane, 70813-62-6; 5-(triphenylphosphonio)pentanoic acid iodide, 70813-63-7; sodium 5-(triphenylphosphonio)pentanoate, 41723-91-5; 3-(2-methyl-1,3-dioxolan-2-yl)propyltriphenylphosphonium iodide, 70813-64-8; 3-(2-methyl-1,3-dioxolan-2-yl)propylidenetriphenylphosphorane, 3054-93-1; ethyl 10-chlorodecanoate, 70813-65-9; triphenylphosphine, 603-35-0.

Synthesis and Stereochemistry of Ethyl (*E*)-3-Methyl-3-phenylglycidate and (*E*)- and (*Z*)-1,3-Diphenyl-2-buten-1-one Oxide

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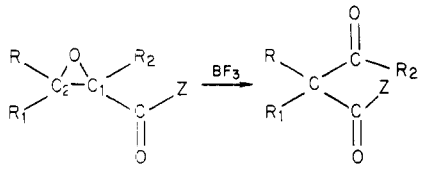
The absolute configurations of (+)-(2*S*,3*R*)-Ethyl (*E*)-3-methyl-3-phenylglycidate (1) and (+)-(2*S*,3*R*)-(*E*)- and (−)-(2*S*,3*S*)-(*Z*)-1,3-diphenyl-2-buten-1-one oxide (dypnone oxide) have been assigned. The resolution of sodium (*E*)-3-methyl-3-phenylglycidate (4) and an asymmetric epoxidation of 1,3-diphenyl-2-buten-1-one are described.

When 1,2-epoxycarbonyl compounds are treated with Lewis acids, 1,3-dicarbonyl products may be formed from the 1,2 migration of the carbonyl group (eq 1).[2,3] Carbonyl

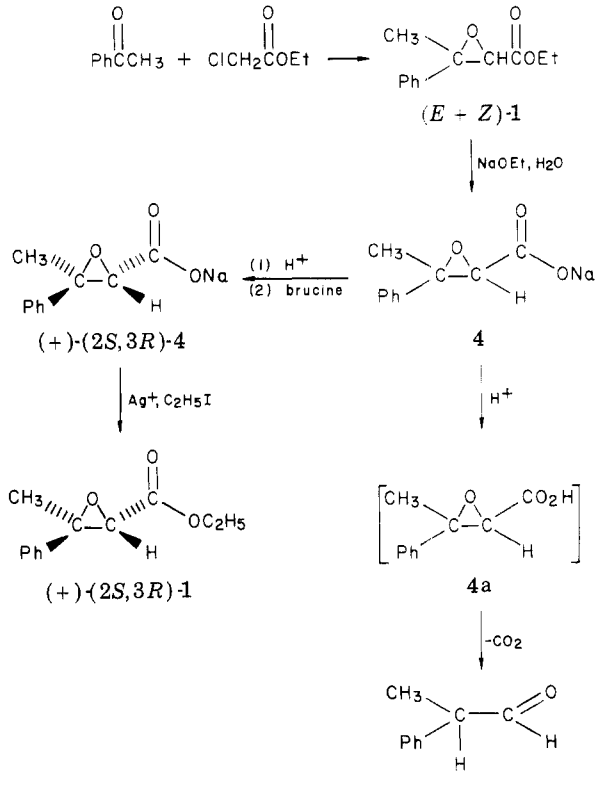


(1)

migrations have been observed with epoxy ketones,[4] esters,[5] and thiol esters.[6] These intramolecular[7] rearrangements have been established to be concerted processes that proceed with complete inversion of configuration at the migration terminus.[8] We have been able to ascertain the overall stereochemistry of these transformations by employing model substrates in optically active form and establishing the absolute configuration and optical purity of both starting material and rearrangement products (eq 1).

An examination of the literature revealed that very few derivatives of glycidic acids have been prepared in optically active form.[9] Fortunately, the optically active glycidic ester 1 had been reported and its absolute configuration assigned.[10] We chose (+)-sodium 2-methyl-2-phenylglycidate as the pivotal intermediate in our mechanistic scheme since it is the precursor to 1 and we felt that we could devise a method to stereospecifically convert it to

Scheme I



(1) National Science Foundation Predoctoral Fellow.

(2) (a) Blaise, E. E.; Courtot, A. *Bull. Soc. Chim. Fr.* **1906**, *35*, 360, 589. (b) For a review of alkoxycarbonyl rearrangements see: Acheson, R. M. *Acc. Chem. Res.* **1971**, *4*, 177.

(3) Pocker, Y. "Molecular Rearrangements"; DeMayo, P., Ed.; Interscience: New York, N.Y., 1963; Vol. 1, p 1.

(4) House, H. O. *J. Am. Chem. Soc.* **1954**, *76*, 1235.

(5) (a) Singh, S. P.; Kagan, J. *J. Am. Chem. Soc.* **1969**, *91*, 6198. (b) Kagan, J.; Agdeppa, D. A.; Singh, S. P.; Mayers, D. A.; Bayajian, C.; Pourker, C.; Firth, B. E. *Ibid.* **1976**, *98*, 4581.

(6) Gorski, G. A.; Dagli, D. J.; Wemple, J. *J. Am. Chem. Soc.* **1976**, *98*, 4585.

(7) House, H. O. *J. Am. Chem. Soc.* **1956**, *78*, 2298.

(8) (a) Domagala, J. M.; Bach, R. D.; Wemple, J. *J. Am. Chem. Soc.* **1976**, *98*, 1975. (b) Domagala, J. M.; Bach, R. D. *Ibid.* **1978**, *100*, 1605. (c) Domagala, J. M.; Bach, R. D. *Ibid.* in press.

(9) (a) Harada, K. *J. Org. Chem.* **1966**, *31*, 1407. (b) Harada, K. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2311. Harada, K.; Ohhashi, J. *Ibid.* **1967**, *40*, 2977.

(10) Abidi, S. L. Ph.D. Thesis, University of Maine, 1969 (University Microfilm 70-12, 389).

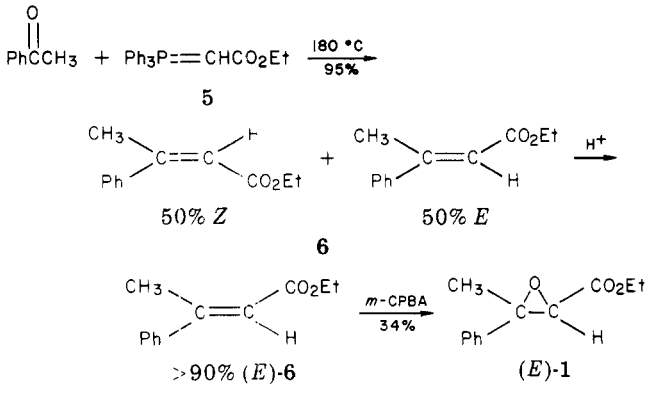
0022-3263/79/1944-3168$01.00/0

Table I. Optical Purity Determinations for (+)-Ethyl (*E*)-3-Methyl-3-phenylglycidate (1) and (+)-Methyl (*E*)-3-Methyl-3-phenylglycidate (7)

compd	proton type	chem shift, Hz (+)-(2*S*,3*R*)	chem shift, Hz (−)-(2*R*,3*S*)	optical purity, %	$[\alpha]^{25}_D$,[a] deg
1	C_β-CH_3	163	156	racemic	0
		260		100	113.8
7	C_α-H	303	299	racemic	0
		313	309	44	53.4
		314		100	114.7
7	CO_2CH_3	272	268	racemic	0
		275	269	48	53.4
		273		100	114.7

[a] Specific rotations were taken in $HCCl_3$ by using Eu-Opt.[16]

Scheme II



dypnone oxides **2** and **3**. This would be highly desirable since it is not always a trivial matter to determine the absolute configuration of such acid- and base-sensitive molecules. In this paper we disclose the synthesis, absolute configuration, and optical purity of ethyl (*E*)-3-methyl-3-phenylglycidate (**1**) and (*E*)- and (*Z*)-1,3-diphenyl-2-buten-1-one oxides (**2** and **3**).

Results and Discussion

(+)-(2*S*,3*R*)-Ethyl (*E*)-3-Methyl-3-phenylglycidate (1). Optically active glycidic ester **1** was prepared by the synthesis outlined in Scheme I. The racemic ester **1** was obtained by a Darzen condensation as a mixture of *Z* and *E* isomers,[11] which was enriched in the *E* isomer by distillation. The *E*-enriched glycidate **1** was saponified to the sodium salt **4**, which was recrystallized from dioxane–water to remove the remaining *Z*-sodium glycidate. Since the overall yield of (*E*)-**4** was lowered, after the required removal of the *Z* isomer, an alternate synthesis of the racemic (*E*)-ethyl glycidate **1** was developed (Scheme II).

The reaction of acetophenone and the phosphorane **5** was accomplished in high yield at 180 °C.[12] The ethyl β-methylcinnamate **6** was obtained as a mixture of *E* and *Z* isomers, which were equilibrated with sulfuric acid to predominantly (*E*)-**6**. Epoxidation of **6** with *m*-chloroperbenzoic acid[13] gave **1** isomerically pure, but in relatively low yield. Both schemes afforded **1** in comparable overall yield.

The sodium (*E*)-3-methyl-3-phenylglycidate (**4**) was resolved[10] with brucine through its corresponding glycidic acid (**4a**), which was prone to rapid decarboxylation even at low temperature to give 2-phenylpropanal.[14] To circumvent this problem, the glycidic acid was generated at 0 °C and mixed with brucine immediately. It was found that recrystallizing the brucine–glycidic acid salt to constant rotation from ethanol[10] was not as effective in separating the diastereomers as the combined treatment of the complex with Norit and precipitation from ethanol with petroleum ether. The latter method appeared to be more reproducible and gave higher yields of resolved sodium salt **4**. The optically active (+)-sodium glycidate was liberated from the brucine salt by the action of aqueous sodium hydroxide.

The (+)-sodium glycidate, $[\alpha]^{25}_D$ 85.6°, was converted to the (+)-ethyl glycidate **1** in high yield by the reaction of its silver salt with ethyl iodide.[15] The specific rotation of **1**, $[\alpha]^{25}_D$ 113.8° ($HCCl_3$), was lower than the reported[10] value of $[\alpha]^{25}_D$ 128.8°, but no further purification was attempted since spectral data did not show any signs of impurity. The optical purities of all samples of (+)-ethyl glycidate were determined by using NMR chiral shift reagents,[16-18] which separated (9 Hz) the enantiomeric oxirane methyl resonances into well-resolved singlets. Analysis of the (+)-glycidic ester, $[\alpha]^{25}_D$ 113.8°, by this technique indicated the presence of only one enantiomer and established the optical purity as 100%. The same methodology was used to obtain (+)-methyl (*E*)-3-methyl-3-phenylglycidate (**7**), $[\alpha]^{25}_D$ 114.3°, from **4** ($[\alpha]^{25}_D$ 85.6°); it too was shown to be optically pure. The optical purity determinations are summarized in Table I.

Optically Active Dypnone Oxide. We had envisioned that optically pure (+)-sodium 3-methyl-3-phenylglycidate (**4**) would be an ideal precursor to optically pure (*E*)-dypnone oxide (**2**), because of the variety of methods available for the conversion of a carboxyl functional group to a ketone. The methodology for preparing ketones from carboxylic acids by organolithium reagents has been reviewed.[19] Since the glycidic acid **4a** was unstable, we attempted to prepare the lithium salt (**4b**), an equally useful substitute, via an exchange reaction with lithium chloride in acetone. This technique worked well for racemic *Z* sodium salt **4**, but the *E* isomer would not readily exchange. The insolubility of the (*Z*)-sodium glycidate **4** in acetone, tetrahydrofuran, and ether was demonstrated by the total recovery of (*Z*)-**4** after Soxhlet extraction with these solvents for 48 h. Indeed, Soxhlet extraction with acetone proved to be an excellent method for the separation of the *Z* from the *E* sodium salt. The *Z* lithium salt

(11) House, H. O.; Blaker, J. W.; Madden, D. A. *J. Am. Chem. Soc.* **1958**, *80*, 6386.
(12) Fodor, G.; Tomoskozi, I. *Tetrahedron Lett.* **1961**, 579.
(13) Valente, V. R.; Wolfhagen, J. L. *J. Org. Chem.* **1966**, *31*, 2509.
(14) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: New York, N.Y., 1965; p 242.
(15) Royals, E. E. "Advanced Organic Chemistry"; Prentice-Hall: Englewood Cliffs, N.J., 1954; p 604.
(16) The shift reagent employed was "Eu-Opt" (Ventron).
(17) (a) Goering, H. L.; Eikenberry, J. N.; Koermer, G. S. *J. Am. Chem. Soc.* **1971**, *93*, 5913. (b) Whitesides, G. M.; Lewis, D. W. *Ibid.* **1970**, *92*, 6980; **1971**, *93*, 5914.
(18) The apparent detectability limit of the NMR spectrometer was 2–3%. The error in determining enantiomer areas was ±2%, which defines an error of ±4% in optical purity values.
(19) Jorgenson, M. J. *Org. React.* **1970**, *18*, 1.

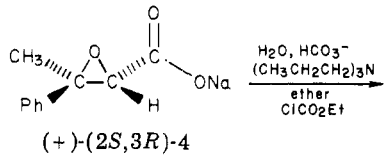
Table II. Optical Purity Determination for (Z)- and (E)-Dypnone Oxide

compd	source	proton type	chem shift,[a] Hz (+)	chem shift,[a] Hz (−)	optical purity, %	$[\alpha]^{25}_D$, deg	$[\alpha]^{25}_D$, for 100% optical purity,[b] deg
(E)-2[c]	9	CH	340	328	racemic	0	
		CH_3	190	177	racemic	0	
	(+)-4	CH	385		100.0	147.2	147.2
		CH_3	236		100.0	147.2	147.2
	9[d]	CH	380	364	41.2	−71.27	−173.0
(Z)-3[e]	9	CH	297	307	racemic	0	
		CH_3	113	121	racemic	0	
	3[f]	CH_3	112	117	4.0	−6.46	−161.5
cis-3	9[c]	CH	300	308	25.7	−42.75	−166.3

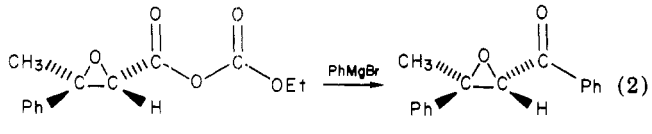
[a] Chemical shift of (+) and (−) enantiomers relative to Me_4Si as measured by standard size side-banding techniques. [b] Calculated by dividing the observed rotation by the optical purity. [c] The configuration of (+)-(E)-dypnone oxide is 2S,3R. [d] From asymmetric epoxidation. [e] The configuration of (+)-(Z)-dypnone oxide is 2R,3R. [f] From the resolution of (Z)-3 with acetate cellulose.

4b was converted to (Z)-dypnone oxide (**2**) in good yield with phenyllithium. Treatment of (E)-**4**, in tetrahydrofuran and HMPA, directly with phenyllithium afforded only 2% of (E)-dypnone oxide and 85% of unreacted **4**. Attempts to prepare the acid chloride[20] of **4a** met with only moderate success and its reaction with diphenylcadmium[21] gave a plethora of products.[22] Similar results were observed when we attempted to convert **1** to the phenyl ketone with phenyllithium at −78 °C. These problems have been encountered previously with other glycidic esters and α-oxido ketones in reactions with Grignard reagents.[22,23]

We therefore considered using a mixed carbonate as an activating group. This functional group should be derivable from the E sodium salt **4** and ethyl chloroformate.[24a] Furthermore, these mixed carbonates are relatively stable and had been converted to ketones with organocadmium reagents.[24b] Taking advantage of the water solubility of (E)-**4**, we prepared the mixed-carbonate **8** in quantitative yield in a two-phase process (eq 2). The



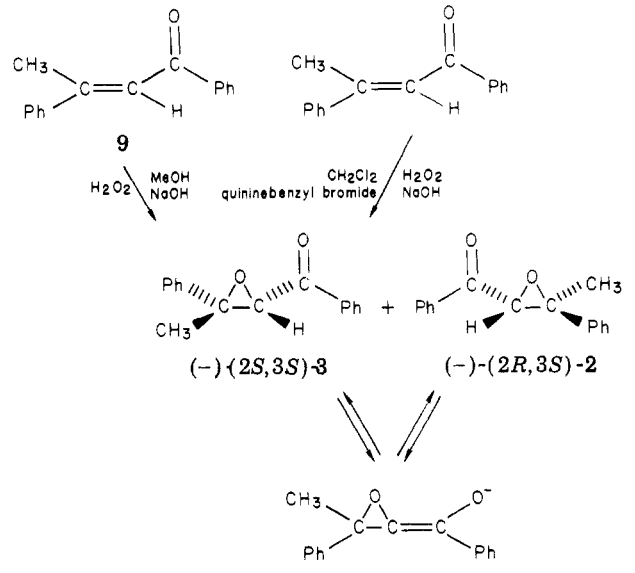
(+)-(2S,3R)-4



(+)-(2S,3R)-8 (+)-(2S,3R)-2

sodium salt was dissolved in water buffered with sodium bicarbonate and stirred with ethyl ether containing an excess of ethyl chloroformate. Tri-n-propylamine was a suitable phase-transfer catalyst. The infrared spectrum of **8** displayed two prominent bands at 1830 and 1765 cm^{-1}, which are typical of a mixed-carbonate functional group.[24a] The mixed-carbonate **8** reacted smoothly at −78 °C with phenylmagnesium bromide to give dypnone oxide in 40–50% isolated yield, after purification by preparative TLC. When this reaction sequence was applied to optically pure (+)-(2S,3R)-**4**, $[\alpha]^{25}_D$ 85.6°, (+)-(E)-dypnone oxide was obtained in 50% yield, $[\alpha]^{25}_D$ 147.2° ($HCCl_3$). It was assumed that the absolute configuration of the (+)-(E)-dypnone oxide was identical with that of the (+)-(E)-sodium glycidate, although this was independently proven (vide infra). The optical purities and rotations from several preparations of dypnone oxide are given in Table II.

Scheme III



Although the synthesis of optically active (E)-dypnone oxide from resolved (+)-sodium glycidate **4** was successful, it was not amenable to large-scale preparation. In addition, a source of optically active (Z)-dypnone oxide would ultimately be required, and a process for producing both Z and E isomers of **2** and **3** in optically active form would be valuable. Therefore, two alternate methods were utilized in the preparation of optically active dypnone oxide. The first method employed the direct resolution of racemic dypnone oxide. This was partially accomplished by chromatographing dypnone oxide, with benzene or ethanol eluent, through cellulose acetate.[25] However, the optical purities obtained for both **2** and **3** were less than 4% (Table II).

The second approach available was to prepare dypnone oxide from dypnone (**9**) by asymmetric epoxidation. Racemic (Z)- and (E)-dypnone oxides were customarily prepared by treatment of dypnone[26] with alkaline hydrogen peroxide.[27] The yield of this reaction was generally

(20) (a) Padwa, A.; Das, N. C. *J. Org. Chem.* **1969**, *34*, 816. (b) Speziale, A. J.; Frazier, H. W. *Ibid.* **1961**, *26*, 3176. Cason, J. "Organic Syntheses", Collect. Vol. III; Wiley: New York, N.Y. 1955; p 169.

(21) (a) Cole, W. C.; Julian, P. L. *J. Am. Chem. Soc.* **1945**, *67*, 1369. (b) Hoehn, W. M.; Moffett, R. B. *Ibid.* **1945**, *67*, 740. (c) Dauben, W. G.; Tilles, H. *J. Org. Chem.* **1950**, *15*, 785.

(22) Pierre, J. L. *Ann. Chim. (Paris)* **1966**, ser. 14, 1, 159.

(23) Kolher, E. P.; Richtmyer, N. K.; Hester, W. F. *J. Am. Chem. Soc.* **1931**, *53*, 205.

(24) (a) Tarbell, D. S.; Leister, N. A. *J. Org. Chem.* **1958**, *23*, 1149. (b) Tarbell, D. S.; Price, J. A. *Ibid.* **1957**, *22*, 245.

(25) Ready to use powder available from Alupharm Chemicals.

(26) Calloway, H. O.; Green, L. D. *J. Am. Chem. Soc.* **1937**, *59*, 809.

high, with short reaction times (45 min) giving predominantly (*E*)-**3** and longer times giving mostly (*Z*)-**3**, but with lower overall yield. This result was explained by House, who demonstrated that **2** and **3** were interconverted in the basic medium, probably via an enolate anion (Scheme III).

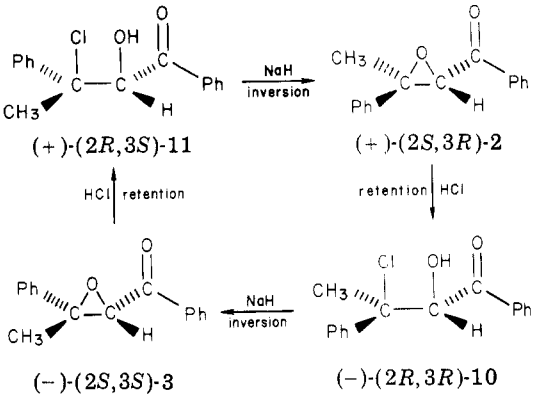
Wynberg[28] has performed asymmetric epoxidations by using the quaternary ammonium salt of quinine and benzyl chloride[29] and alkaline hydrogen peroxide in a two-phase system. He reported the conversion of α,β-unsaturated ketones to their corresponding epoxides in high optical yields.[28] Using this method, we allowed dypnone (**9**) to stir in methylene chloride with alkaline hydrogen peroxide (pH 11) for 96–120 h in the presence of a catalytic amount of quininebenzyl bromide to produce (−)-(*Z*)-dypnone oxide (29%) in 26% optical yield and (−)-(*E*)-dypnone oxide (49%), whose optical purity was 22%. The procedure was adaptable to the large-scale synthesis of the (*Z*)- and (*E*)-dypnone oxides. In practice the yield of (*E*)-dypnone oxide was less and the optical purity higher than indicated above, because the racemate crystallized out of solution leaving the mother liquor enriched in the (−) enantiomer. Thus, crystallization of the crude (*E*)-oxide **2**, from the epoxidation, gave 40% racemic **2**, with 9% of (−)-(*E*)-dypnone oxide of 53% optical purity recovered from the mother liquor. The optical purity of the (*Z*)-dypnone oxide did not change during purification.

A major difficulty encountered during these experiments was the rapid interconversion of (*Z*)- and (*E*)-dypnone oxides, whose composition at equilibrium was about 70% *E* and 30% *Z*. This isomerization made it difficult to correlate optical purities with percent yield. Control experiments did indicate that optically active (*Z*)-oxide was not racemized during the isomerization process. The rotations and optical purities are given in Table II.

Absolute Configuration of Dypnone Oxide. Since (+)-(*E*)-dypnone oxide had the 2*S*,3*R* configuration, based on the (+)-(*E*)-sodium glycidate **4** from which it was prepared, the (−)-(*E*)-dypnone oxide from the asymmetric epoxidation must have the 2*R*,3*S* configuration. The absolute configuration of (−)-(*Z*)-dypnone oxide remained to be determined. To accomplish this, we sought a method that could unambiguously interconvert the (*E*)- and (*Z*)-dypnone oxides by a pathway of known specificity. We successfully employed a reaction sequence reported by Wasserman[30] that involved a chlorohydrin intermediate.

The stereochemistry of epoxide ring opening with protic acid has been the subject of intensive studies.[31] Certain epoxides have been shown to ring open with complete inversion of configuration, while others cleave with complete retention.[31,32] Both the (*Z*)- and (*E*)-dypnone oxides, when cleaved with HCl, belong to the latter category. There are at least nine other epoxides for which this mode of addition has been observed, *all of which contain a phenyl substituent on the oxirane ring.*[7,33] The mechanism of epoxide cleavage, with retention of configuration, is not fully understood, but Brewster's suggestion[33b] seems plausible. He proposed that as the epoxide was protonated and began to open, the nucleophile attacked the incipient carbenium ion from the solvent cage on the top face of the epoxide (retention), where the positive charge of the system was localized. According to this hypothesis, retention should be observed (a) when the incipient carbenium ion is tertiary or stabilized by a phenyl group, (b) when nonpolar, or nonionizing solvents are used, increasing the likelihood of aggregates, and (c) when S_N2 mechanisms are unlikely because of steric congestion at the carbon from which cleavage has taken place. Our substrates and reaction conditions meet these criteria.

Scheme IV



When (*E*)- or (*Z*)-dypnone oxide was treated with glacial acetic acid saturated with gaseous hydrogen chloride for 2 h at 20 °C, the corresponding chlorohydrins **10** and **11** were formed, with 100% retention of configuration.[30] Both chlorohydrins have been fully characterized and can be distinguished from each other by NMR and IR spectroscopy. When optically pure (*E*)-dypnone oxide (**2**) was subjected to HCl cleavage in acetic acid, (−)-(2*R*,3*R*)-3-chloro-1,3-diphenyl-2-hydroxy-1-butanone (**10**), $[\alpha]^{25}_D$ −7.99° ($HCCl_3$), was formed with 100% retention of configuration. Likewise, when (−)-(2*S*,3*S*)-(*Z*)-dypnone oxide, of 22% optical purity,[16] was subjected to the same reaction conditions (+)-(2*R*,3*S*)-**11** was formed with complete retention (Scheme IV). The optical purities of **10** and **11** were established by silver-catalyzed rearrangement[8c] of (−)-**10** to optically pure[8b] (−)-(*S*)-1,2-diphenyl-2-methyl-1,3-propanedione (**12**) and (+)-**11** to dione (+)-**12** of 22.3% optical purity.[16-18]

Using the conditions described above, we were able to obtain (−)-(2*R*,3*R*)-**10** in 50% yield from (+)-(2*S*,3*R*)-(*E*)-dypnone oxide (38% optical purity). Treatment of (−)-**10**, without isolation, with sodium ethoxide in tetrahydrofuran produced (−)-(*Z*)-dypnone oxide, whose absolute configuration must be 2*S*,3*S*, because of the inversion of configuration at C_3 attending epoxide formation (Scheme IV). These data corroborate the earlier stereochemical studies of Wasserman[30] on racemic compounds.

Capitalizing on the complete stereospecificity attending the formation of the (−)-chlorohydrin (**10**), we employed this compound to verify the stereospecificity of oxirane cleavage and the absolute configuration assigned to (+)-(*E*)-**2**, which was based on the assignment of 2*S*,3*R* to the (+)-*trans*-sodium glycidate[10] **4**. When the (−)-chlorohydrin **10** (53.2% optical purity based on (+)-(*E*)-**2** from which it was prepared) was oxidized under mild conditions with periodic acid, (−)-2-chloro-2-phenylpropanal (**13**), $[\alpha]^{25}_D$ −10.1° (C_6H_6), was obtained in moderate yield. The (−)-aldehyde **13** was oxidized with chromium trioxide in acetone to the corresponding (−)-(*R*)-2-chloro-2-phenylpropionic acid[34] (**14**), $[\alpha]^{25}_D$ −13.4°

(27) Wasserman, H. H.; Aubrey, N. E.; Zimmerman, H. E. *J. Am. Chem. Soc.* **1953**, *75*, 96.
(28) Helder, R.; Hummelen, J. C.; Laane, R. W.; Wiering, J. S.; Wynberg, Hans *Tetrahedron Lett.* **1976**, 1831.
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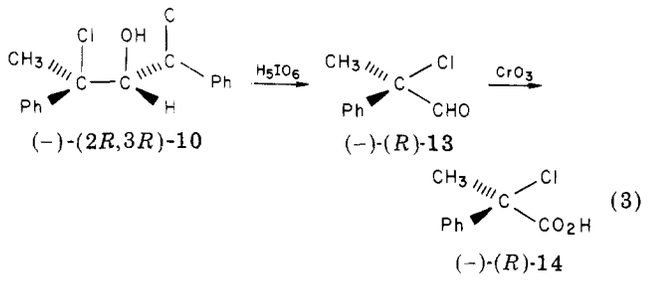
(C_6H_6). On the basis of the published rotation ($[\alpha]^{25}_D$ −26°), the optical purity of the (−)-acid **14** was 51%. This sequence of reactions (eq 3) established that C_3 (β carbon)



(−)-(2*R*,3*R*)-10 (−)-(*R*)-13 (−)-(*R*)-14 (3)

in (*E*)-dypnone oxide, and in the (+)-sodium glycidate **4**, has the *R* configuration. The rigid epoxide ring defines the α carbon as the *S* configuration in the *E* isomer of this series. The absolute configurations given for (+)- and (−)-(*E*)-dypnone oxide and (−)-(*Z*)-dypnone oxide have thus been independently determined and are in complete agreement with the assignments made for the (+)-sodium salt **4**.[10]

Experimental Section

Ethyl (*E*)- and (*Z*)-3-Methyl-3-phenylglycidate (1). In a modification of the procedure of House,[35a] 113.0 g (1.00 mol) of potassium *tert*-butoxide in 800 mL of dry *tert*-butyl alcohol was added, over 2 h at 0 °C, to 122.8 g (1.00 mol) of ethyl chloroacetate and 120.0 g (1.00 mol) of acetophenone. After an additional 2 h of stirring at room temperature, the *tert*-butyl alcohol was removed in vacuo at 50–60 °C. The oily residue was diluted with ethyl ether (400 mL) and extracted with water. The etheral layer was dried ($MgSO_4$) and concentrated. Distillation afforded approximately 100 g of *Z*-enriched **1**, bp 82–90 °C (0.2 mm), and a second fraction of about 100 g of *E*-enriched **1**, bp 90–104 °C (0.2 mm). Analysis of the crude mixture by NMR, before distillation, revealed that the ratio of (*E*)-**1** to (*Z*)-**1** was 1:1.

(+)-(2*S*,3*R*)-Ethyl (*E*)-3-Methyl-3-phenylglycidate (1). A. From Silver (*E*)-3-Methyl-3-phenylglycidate. To 1.00 g (5.00 mmol) of sodium glycidate (**4**) in 5 mL of water was added 0.87 g (5.0 mmol) of silver nitrate in 7 mL of water. The thick, white solid which formed immediately was isolated after 10 min by vacuum filtration and dried for 24 h (0.2 mm). The dry silver salt (mp 155–156 °C dec) was suspended in 10 mL of ethyl ether and 5 mL of ethyl iodide. The mixture was stirred for 16 h and silver salts were removed by filtration. The ethereal filtrate was concentrated affording 0.81 g (79%) of (*E*)-**1**: NMR (CCl_4) δ 7.38 (s, 5 H, C_6H_5), 4.28 (q, 2 H, J = 7 Hz, OCH_2CH_3), 3.31 (s, 1 H, CH), 1.73 (s, 3 H, CCH_3), 1.31 (t, 3 H, J = 7 Hz, OCH_2CH_3); IR (neat)[35b] 2982, 1751, 1732, 1205 cm^{-1}.

The above procedure was used to convert 1.50 g (7.50 mmol) of (+)-(2*S*,3*R*)-(*E*)-**4**, $[\alpha]^{25}_D$ 85.7° (*c* 2.4, H_2O), to 1.14 g (74%) of (+)-(2*S*,3*R*)-**1**, $[\alpha]^{25}_D$ 113.8° (*c* 1.7, $HCCl_3$) (lit.[10] $[\alpha]^{25}_D$ 128.8°). The spectral properties of this material were identical with those of racemic *trans*-**1**. Analysis by NMR, using a chiral shift reagent,[16-18] indicated the presence of only one enantiomer. When 60 mg of the same sample was mixed with 19.5 mg of racemic material, NMR analysis[16] showed the ratio of the enantiomeric oxirane methyl singlets was 86:14. The calculated ratio based on 100% optical purity was 88:16.

B. Wittig Reaction. Following the procedure of Fodor and Tomoskozi,[12] 17.0 g (48.9 mmol) of the carbethoxyphosphorane **5** and 7.03 g (58.6 mmol) of acetophenone yielded 8.48 g (91.4%) of a 1:1 mixture of *cis*- and *trans*-ethyl β-methylcinnamates (**6**); bp 70–82 °C (0.2 mm). The ratio of (*Z*)- to (*E*)-**6** was determined by GLC (SE 30, 140 °C). The mixture was treated for 2 h with concentrated sulfuric acid at room temperature, diluted with ethyl ether, and extracted with water and saturated sodium bicarbonate. The ether layer was dried ($MgSO_4$) and concentrated to 8.33 g (98%) of ethyl (*E*)-3-methylcinnamate (**6**): NMR (CCl_4) δ 7.5–7.0 (m, 5 H, C_6H_5), 6.12 (m, 1 H, C=CH), 4.17 (q, 2 H, J = 7 Hz, OCH_2CH_3), 2.55 (d, 3 H, J = 1 Hz, C=CCH_3), 1.22 (t, 3 H, J = 7 Hz, OCH_2CH_3); IR (neat) 2989, 1709, 1625, 1165 cm^{-1}. Analysis by GLC (SE 30, 140 °C) showed only a trace of (*Z*)-**6**.

Epoxidation of the *trans*-Cinnamate (6). The epoxidation of (*E*)-**6** was accomplished by using a reported procedure[13] with chloroform used as a cosolvent with methylene chloride. Thus 33.0 g (17.4 mmol) of (*E*)-**6** and 36.0 g (17.8 mmol) of *m*-chloroperbenzoic acid produced 12.5 g (34.2%) of (*E*)-**1**, whose spectral properties were identical with those of authentic material.

Ethyl (*Z*)-3-Methyl-3-phenylglycidate (1). The *Z* isomer of **1** was obtained from a mixture of (*Z*)- and (*E*)-ethyl 3-methyl-3-phenylglycidates (**1**) by purification by high-pressure LC (Porasil), using hexane–ethyl acetate eluent: NMR (CCl_4) δ 7.35 (m, 5 H, C_6H_5), 3.81 (q, 2 H, J = 7 Hz, OCH_2CH_3), 3.51 (s, 1 H, CH), 1.66 (s, 3 H, CCH_3), 0.81 (t, 3 H, J = 7 Hz, OCH_2CH_3).

(+)-(2*S*,3*R*)-Methyl (*E*)-3-Methyl-3-phenylglycidate (7). In a procedure similar to that used for the preparation of **1** from the sodium glycidate **4**, (*E*)-**7** was obtained in 85% yield by treatment of silver (*E*)-3-methyl-3-phenylglycidate with methyl iodide: NMR (CCl_4) δ 7.36 (s, 5 H, C_6H_5), 3.77 (s, 3 H, OCH_3), 3.33 (s, 1 H, CH), 1.70 (s, 3 H, CCH_3); IR (neat) 1754, 1738, 1210 cm^{-1}.

As described above, 45 mg (0.22 mmol) of (+)-(2*S*,3*R*)-**4**, $[\alpha]^{25}_D$ 85.7°, was converted to 35 mg (81%) of (+)-(2*S*,3*R*)-**7**, $[\alpha]^{25}_D$ 114.3° (*c* 1.4, $HCCl_3$). The optical purity of this material was established as 100% by NMR analysis.[16,18]

Sodium (*E*)-3-Methyl-3-phenylglycidate (4). A solution of 94.0 g (0.460 mol) of a mixture of (*Z*)- and (*E*)-ethyl glycidates **1** (1:1) in 100 mL of absolute ethanol was added, over 20 min, to 350 mL of ethanolic sodium ethoxide (0.460 g-atom of sodium) at 0 °C, under a positive pressure of argon. After the mixture had stirred for several minutes, 10 mL of water was slowly added at 0 °C and the mixture was stirred for an additional 2 h at room temperature. The crude salt, 82 g, was isolated by vacuum filtration. Recrystallization from dioxane–water (water being added in just sufficient quantity to achieve solution at 100 °C) afforded 34 g (37%) of (*E*)-**4**: mp 252–253 °C dec (lit.[36] mp 255 °C); NMR (D_2O–acetone-d_6, external Me_4Si) δ 7.15–6.85 (m, 5 H, C_6H_5), 3.50 (s, 1 H, CH), 1.39 (s, 3 H, CCH_3); IR (Nujol) 1610 cm^{-1}.

Resolution of Sodium (*E*)-3-Methyl-3-phenylglycidate (4). In a modification of a reported procedure,[10] 12.0 g (60.0 mmol) of (*E*)-**4** was dissolved in 75 mL of water and 60 mL of ethyl ether in a two-phase system. The solution was cooled to −5 °C and 82.4 mL of 0.73 M hydrochloric acid, at 0 °C, was added in 2–3 min with rapid stirring. After the addition of acid was complete, the etheral layer was separated and stored at −10 °C. The water layer was again extracted with 60 mL of ether, and the ethereal fractions were combined, dried (Na_2SO_4), and kept at −35 °C. This solution of the glycidic acid **4a** must be used as soon as possible after drying.

To the solution of **4a**, after removal of the desiccant by rapid filtration, was added 28 g (60 mmol) of brucine tetrahydrate, dissolved in 70 mL of benzene–absolute ethanol (1:1), at 55 °C with rapid stirring. The oily residue initially formed slowly dissolved, and a white powder gradually appeared as the mixture was stirred an additional 6 h. Vacuum filtration afforded 12.3 g (77%) of the (+)-brucine–glycidic acid salt: mp 180–182 °C; $[\alpha]^{25}_D$ 3.12° (*c* 1.7, $HCCl_3$). The brucine complex was recrystallized from 225 mL of hot absolute ethanol. After 8 h, filtration gave 4.60 g of the brucine salt: mp 183–185 °C; $[\alpha]^{25}_D$ 15.0° (*c* 2.0, $HCCl_3$). A second recrystallization from ethanol yielded 2.34 g of salt (mp 185–189 °C; $[\alpha]^{25}_D$ 16.9° (*c* 1.1, $HCCl_3$)) and a third gave 1.75 g (mp 188–191 °C (lit.[10] mp 192–193 °C); $[\alpha]^{25}_D$ 19.5° (*c* 1.1, $HCCl_3$) (lit.[10] $[\alpha]^{25}_D$ 19.5°)). This method of resolution was

(34) The absolute configurations of (−)-(*R*)-2-chloro-2-phenylpropionic acid (**14**) and (−)-(*R*)-atrolactic acid ($Ph(CH_3)COHCO_2H$) have been related by: McKenzie, A.; Clough, G. W. *J. Chem. Soc.* **1910**, *97*, 1016. The assignments of absolute configuration for atrolactic acid were reported by Brewster[33b] with a summary of related work. Confirmation of McKenzie's interreltaionships was reported by: Cowdrey, W. A.; Hughes, E. D.; Ingold, C. K.; Masterman, S.; Scott, A. D. *J. Chem. Soc.* **1937**, 1252.

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not always reproducible, especially when performed on a large scale.

An alternate method of resolution involved the dissolution of 12.3 g (21.3 mmol) of brucine salt in 200 mL of hot absolute ethanol with approximately 1 g of charcoal (Norit). This solution was boiled for 5 min and then gravity filtered, while hot, to yield upon cooling a clear, colorless solution. To this solution was added approximately 100 mL of petroleum ether (bp 30–45 °C) in small portions allowing crystallization to begin. Filtration of the fine, white solid gave 6.23 g of brucine salt; $[\alpha]^{25}_D$ 15.4° (*c* 1.9, $HCCl_3$). This salt was recrystallized from 100–150 mL of absolute ethanol and 200 mL of petroleum ether as described above to give 2.96 g of the brucine salt; $[\alpha]^{25}_D$ 19.6° (*c* 1.3, $HCCl_3$).

To 6.13 g (0.011 mol) of the brucine salt, $[\alpha]^{25}_D$ 15.4°, in 80 mL of chloroform was added, at 0 °C with rapid stirring, 10.6 mL of 1.0 M sodium hydroxide in 25 mL of water, and the mixture was stirred for 30 min. After the mixture had come to room temperature, the water layer was separated and the organic layer reextracted with 25 mL of water. The combined extracts were concentrated in vacuo at 75 °C, giving 2.04 g (96%) of (+)-(2*S*,3*R*)-**4**; $[\alpha]^{25}_D$ 58.7° (*c* 1.8, H_2O).

Mixed Carbonate of (*E*)-3-Methyl-3-phenylglycidate (8). To 1.0 g (5.0 mmol) of sodium glycidate **4** dissolved in 16 mL of water were added 25 mL of ethyl ether, 0.24 mL (0.25 equiv) of tri-*n*-propylamine, and 0.632 g of sodium bicarbonate followed by slow addition of 2 mL of ethyl chloroformate. The two phases were stirred vigorously for 4 h. The phases were then separated, and the water layer was extracted with 50 mL of ethyl ether. The combined etheral fractions were then washed with 10% hydrochloric acid. The etheral layer was dried (Na_2SO_4 only) and concentrated giving 1.14 g (92%) of the *E* mixed-carbonate **8** as a pink oil: NMR (CCl_4) δ 7.36 (s, 5 H, C_6H_5), 4.33 (q, 2 H, *J* = 7 Hz, OCH_2CH_3), 3.43 (s, 1 H, CH), 1.78 (s, 3 H, CH_3), 1.35 (t, 3 H, *J* = 7 Hz, OCH_2CH_3); IR (neat) 1830, 1765, 1250, 1115 cm^{-1}. The (*Z*)-carbonate could be made under identical conditions but was never separated from the *E* isomer: NMR (CCl_4) δ 7.35 (s, 5 H, C_6H_5), 4.10 (q, 2 H, *J* = 7 Hz, OCH_2CH_3), 3.73 (s, 1 H, CH), 1.68 (s, 3 H, CCH_3), 1.28 (t, 3 H, *J* = 7 Hz, OCH_2CH_3); IR (neat) 1825, 1770 cm^{-1}. The mixed carbonates of both isomers were unstable to GLC, silica gel, and heat.

(+)-(2*S*,3*R*)-(*E*)-Dypnone Oxide (2). To 0.346 g (0.014 g-atom) of magnesium turnings and 75 mL of dry ethyl ether was added, under anhydrous conditions, 2.26 g of bromobenzene. The mixture was gently refluxed for 1 h and poured with a U-tube into a dropping funnel equipped with a side arm, under a positive pressure of argon. The Grignard reagent was added to a solution of 3.0 g (12.0 mmol) of *E* and *Z* mixed-carbonate **8** in 50 mL of dry ethyl ether at −78 °C over 30 min. When the addition was complete, the mixture was allowed to stir for an additional 1 h and was then poured into a saturated ammonium chloride solution. The phases were separated, and the aqueous layer was extracted twice with 50 mL of ether. The ethereal fractions were combined, dried ($MgSO_4$), and concentrated. Biphenyl and benzophenone impurities were separated from the dypnone oxides by column chromatography, using benzene–hexane (1:1). The dypnone oxides were eluted with benzene giving, upon crystallization from hexane–ethyl acetate (99:1), 1.71 g (14%) of (*E*)- and (*Z*)-dypnone oxide (58:42), whose spectral properties were identical with those of authentic samples.

The above procedures were used to obtain 592 mg (50%) of (+)-(2*S*,3*R*)-(*E*)-dypnone oxide, $[\alpha]^{25}_D$ 147.2° (*c* 1.3, $HCCl_3$), from 1.00 g (5.00 mmol) of (+)-(2*S*,3*R*)-sodium (*E*)-3-methyl-3-phenylglycidate (**4**), $[\alpha]^{25}_D$ 85.6°. The optical purity was 100% as determined by NMR analysis.

(−)-(2*S*,3*S*)-*cis*-Dypnone Oxide (3). To 81 mg (1.2 equiv) of sodium hydride (57% dispersion), washed several times with pentane, in 15 mL of dry tetrahydrofuran (THF) was added 1.6 mL of absolute ethanol. The mixture was cooled to 0 °C, and 440 mg (1.60 mmol) of the chlorohydrin **10** in 25 mL of dry THF was added over 30 min. The mixture was stirred at 0 °C for 30 min and at 25 °C for 1.25 h. The mixture was then diluted with methylene chloride and extracted with water. The methylene chloride layer was separated, dried ($MgSO_4$), and concentrated to a thick yellow oil, which crystallized upon addition of 80% ethanol (approximately 5 mL). The solid was filtered and dried to give 125 mg of crude (*Z*)-dypnone oxide. Recrystallization from ethanol–water gave 90 mg (24%) of (*Z*)-dypnone oxide; mp 161–163 °C (lit.[30] mp 162–163 °C). Spectral properties were identical with those of authentic material.

The procedure described above was used in the conversion of 440 mg (1.60 mmol) of (−)-(2*S*,3*R*)-**10** (28% optical purity based on the (*E*)-dypnone oxide from which it was prepared) with sodium hydride in THF–ethanol to 123 mg of a crude white solid; mp 151–156 °C. Trituration of the white solid in ethanol–water (50:50) and drying (0.2 mm) gave 88 mg (22%) of (−)-(2*S*,3*S*)-(*Z*)-dypnone oxide: mp 160–163 °C; $[\alpha]^{25}_D$ −38.5° (*c* 1.1, $HCCl_3$).

(*Z*)- and (*E*)-Dypnone Oxides from the Asymmetric Epoxidation of Dypnone (9). To 6.00 g (27.0 mmol) of dypnone[26] (**9**) in 60 mL of methylene chloride and 24.8 mL of 30% hydrogen peroxide (8.0 equiv) was added 224 mg (0.017 equiv) of quininebenzyl bromide dissolved in 8 mL of distilled water. The pH of the aqueous layer was adjusted to 10.5 by the addition of 12 M of sodium hydroxide. The mixture was rapidly stirred for 120 h. Every 24 h, a fresh solution of 24.8 mL of hydrogen peroxide and 224 mg of quininebenzyl bromide was added to the mixture and the pH was adjusted to 10.5. After 96–120 h, the layers were separated and the methylene chloride was dried ($MgSO_4$) and concentrated to give a thick oil which crystallized upon addition of pentane. The pentane was removed in vacuo and a 50-mg portion of the solid was analyzed by NMR. Integration of the methine hydrogens at δ 4.15 (trans) and δ 4.31 (cis) determined the trans–cis ratio to be 69:31. Addition of a chiral shift reagent (Eu-Opt)[16] effected the separation of the enantiomeric resonances of both (*Z*)- and (*E*)-dypnone oxides. Integration of the *E* oxide's enantiomeric methines at 368 and 352 Hz determined the optical purity of the (*E*)-dypnone oxide to be 22%. Similarly, the enantiomeric methines of the *Z* oxide at 282 and 276 Hz were integrated, and the optical purity was determined to be 26%.

The remaining 5.91 g of solid was subjected to Soxhlet extraction with pentane for 3 h or until the weight loss of the remaining solid became constant.

The solid was recrystallized from ethanol–water giving 1.88 g (29%) of (*Z*)-dypnone oxide (mp 158–159 °C; $[\alpha]^{25}_D$ −38.5° (*c* 1.8, $HCCl_3$)), whose spectral properties were identical with those of authentic material. The optical purity was established at 21.8% by integration of the enantiomeric methine singlets at 300 and 308 Hz.

The pentane was concentrated and the residual solid was recrystallized from heptane–ethyl acetate (99:1) to give 2.48 g (39%) of racemic (*E*)-dypnone oxide: mp 91.5–92.0 °C; $[\alpha]^{25}_D$ 0.0° (*c* 1.1, $HCCl_3$). The mother liquor from the recrystallization was concentrated and the residual oil was purified by preparative TLC (silica gel), using hexane–ethyl acetate (9:1), affording 0.588 g (9%) of (−)-(*E*)-dypnone oxide as an oily solid; $[\alpha]^{25}_D$ −78.0° (*c* 1.4, $HCCl_3$).

3-Chloro-1,3-diphenyl-2-hydroxy-1-butanone (10). In a modification of the procedure of Wasserman and Aubrey,[30] 7.00 g (29.0 mmol) of (*E*)-dypnone oxide was added to a cold solution of 100 mL of glacial acetic acid saturated with hydrogen chloride gas. The mixture was stirred at 5–10 °C for 1.5 h and then at room temperature for 0.5 h. The solution was poured over 200 g of ice and 200 mL of methylene chloride, and the acid was cautiously neutralized with 12 M sodium hydroxide. The organic layer was separated and the basic water layer was extracted two times with methylene chloride. The combined extracts were dried ($MgSO_4$) and concentrated to give a faint yellow solid. This powder was recrystallized from *n*-heptane to yield 6.78 g (84%) of the chlorohydrin **10**: mp 99–100 °C (lit.[30] mp 98–99 °C); NMR ($DCCl_3$) δ 7.9–7.0 (m, 10 H, aromatic), 5.5 (s, 1 H, CHOH), 3.75 (s, 1 H, OH), 2.0 (s, 3 H, CCH_3); IR (Nujol) 3490, 1670 cm^{-1}. Depending on the dryness of the sample, the singlets at δ 5.5 and 3.75 were often observed as doublets (*J* = 8 Hz) due to coupling between the methine and hydroxy protons.

(−)-(2*R*,3*R*)-3-Chloro-1,3-diphenyl-2-hydroxy-1-butanone (10). To a cold solution of 15 mL of glacial acetic acid saturated with hydrogen chloride gas was added 200 mg (0.84 mmol) of optically pure (+)-(2*S*,3*R*)-**2**. Workup as described above gave 147 mg of an oil, which slowly solidified upon standing. Recrystallization from *n*-heptane afforded 100 mg (43%) of (−)-(2*R*,3*R*)-chlorohydrin **10**: mp 98–99 °C (lit.[30] mp 98–99 °C); $[\alpha]^{25}_D$ −7.99° (*c* 1.1, $HCCl_3$).

3-Chloro-1,3-diphenyl-2-hydroxy-1-butanone (11). Chlorohydrin **11** was prepared by using the identical conditions described for the preparation of the chlorohydrin **10**. Thus, 7.00 g (29.0 mmol) of (*Z*)-dypnone oxide afforded 7.18 g (89%) of **11**: mp 101–102 °C (lit.[30] mp 100–101 °C); NMR ($DCCl_3$) δ 7.9–7.1 (m, 10 H, aromatic), 5.4 (d, 1 H, J = 8 Hz, CHOH), 4.1 (d, 1 H, J = 8 Hz, CHOH), 2.1 (s, 3 H, CCH_3); IR (Nujol) 3450, 1680 cm^{-1}.

(+)-(2*R*,3*S*)-3-Chloro-1,3-diphenyl-2-hydroxy-1-butanone (11). The (+)-(2*R*,3*S*)-chlorohydrin **11** was obtained in 91% yield from (−)-(2*S*,3*S*) (*Z*)-dypnone oxide of 21.6% optical purity ($[\alpha]^{25}_D$ −37.91° (*c* 1.1, $HCCl_3$)) by using the conditions employed for the preparation of racemic **11**. Recrystallization from heptane continued to raise the specific rotation from $[\alpha]^{25}_D$ 40.6° (*c* 1.0, $HCCl_3$) after the first recrystallization to $[\alpha]^{25}_D$ 63.5° (*c* 1.3, $HCCl_3$) after the third.

Degradation of 3-Chloro-1,3-diphenyl-2-hydroxy-1-butanones 10 and 11. 2-Chloro-2-phenylpropanal from 10. To 900 mg (3.28 mmol) of the chlorohydrin **10** were added 42 mL of acetic acid and 42 mL of dry ethyl ether. The mixture was cooled to 0 °C and 822 mg (1.1 equiv) of fresh, dry periodic acid (H_2IO_6) was added. After 2.5 h of vigorous stirring (a cloudy suspension was visible after 45 min), the mixture was poured into a large excess of methylene chloride, and ice was added, followed by enough 12 M sodium hydroxide to neutralize the acid. The methylene chloride was separated, dried ($MgSO_4$), and concentrated, giving 880 mg of a yellow oil, which was purified by GLC (FFAP, 140 °C) affording 215 mg (39%) of aldehyde **13**: NMR ($DCCl_3$) δ 9.5 (s, 1 H, CHO), 7.47 (s, 5 H, C_6H_5), 1.97 (s, 3 H, CCH_3); IR (neat) 2710, 1730 cm^{-1}.

(−)-(*R*)-2-Chloro-2-phenylpropanal (13). The procedure above was used in conversion of 1.10 g (4.00 mmol) of (−)-(2*S*,3*R*)-**10** (53.2% optical purity based on (−)-(2*S*,3*R*)-**2** from which it was prepared) to 274 mg (41%) of (−)-(*R*)-**13**; $[\alpha]^{25}_D$ −10.1° (*c* 3.6, C_6H_6). The spectral properties of this sample were identical with those of racemic **13**.

2-Chloro-2-phenylpropanal (13) from 11. To 600 mg (2.18 mmol) of the chlorohydrin **11** in 20 mL of acetic acid was added 548 mg (1.1 equiv) of fresh dry periodic acid. The mixture was stirred for 15 min (becoming cloudy after 3 min) and was diluted with methylene chloride, ice, and enough 12 M sodium hydroxide to completely neutralize the acid. The methylene chloride was separated, dried ($MgSO_4$), and concentrated to give 3.36 mg (91%) of the aldehyde **13**, whose spectral properties were identical with those of **13** obtained from **10**.

2-Chloro-2-phenylpropionic Acid (14). To 336 mg (1.99 mmol) of 2-chloro-2-phenylpropanal (**13**) in 20 mL of dry acetone were added 0.3 g of concentrated sulfuric acid and 280 mg (1.4 equiv) of chromium trioxide. After 45 min of stirring, the mixture was poured into 150 mL of methylene chloride and extracted with cold 1 M sulfuric acid. The methylene chloride was separated, dried ($MgSO_4$), and concentrated, giving a thick yellow-brown oil, which crystallized when mixed at low temperature with petroleum ether (30–50 °C) to yield 160 mg (43%) of the acid **14**. This material was recrystallized from hexane, giving 130 mg (35%) of **14**: mp 72–73 °C (lit.[34] mp 75–76 °C); NMR ($DCCl_3$) δ 11.8 (bs, 1 H, CO_2H), 7.4 (m, 5 H, C_6H_5), 2.13 (s, 3 H, CCH_3; IR (Nujol) 1718 cm^{-1}. Anal. Calcd for $C_9H_9O_2Cl$: C, 58.55; H, 4.88. Found: C, 58.57; H, 4.90. The purification of **14** was very difficult. Both column chromatography and GLC (FFAP, SE 30, 160 °C) effect dehydrochlorination to 2-phenylpropenoic acid; mp 104–106 °C (lit.[37] mp 106–107 °C).

(−)-(*R*)-2-Chloro-2-phenylpropionic Acid (14). The above procedure was used in conversion of 190 mg (1.13 mmol) of (−)-(*R*)-**13**, $[\alpha]^{25}_D$ −10.1°, to 90 mg (43%) of (−)-(*R*)-**14**: mp 69–70 °C; $[\alpha]^{25}_D$ −11.7° (*c* 2.8, C_6H_6). Trituration with pentane raised the specific rotation to $[\alpha]^{25}_D$ −13.4° (*c* 4.1, C_6H_6) [lit.[34] $[\alpha]^{25}_D$ −26.0° (C_6H_6)].

Interconversion of (*E*)- and (*Z*)-Dypnone Oxides under the Reaction Conditions of Asymmetric Induction. (*E*)- to (*Z*)-Dypnone Oxide. To 100 mg (0.420 mmol) of (*E*)-dypnone oxide in 7 mL of methylene chloride were added 25 mL of an aqueous solution of 56 mg (0.135 equiv) of quininebenzyl bromide, 1 mL of 30% hydrogen peroxide, and enough sodium hydroxide to attain pH 12. The mixture was rapidly stirred for 96 h. The layers were separated and the methylene chloride was dried ($MgSO_4$) and concentrated. Analysis by NMR indicated the presence of both (*E*)- and (*Z*)-dypnone oxides in a ratio of 82.5:17.5.

Isomerization of Optically Active (*Z*)-Dypnone Oxide. When 200 mg of (−)-(*Z*)-dypnone oxide, $[\alpha]^{25}_D$ −36.7° (*c* 1.1, $HCCl_3$), was treated under conditions similar to those described above, the ratio of (*E*)- to (*Z*)-dypnone oxides was 70:30. The recovered crude (−)-(*Z*)-dypnone oxide was recrystallized from ethanol–water, giving 56 mg (28%) of (*Z*)-**3**; $[\alpha]^{25}_D$ −39.0° (*c* 1.5, $HCCl_3$).

Quininebenzyl Bromide. Following the procedure for quininebenzyl chloride,[29] 2.00 g (5.8 mmol) of quinine monohydrate was dissolved in 70–100 mL of refluxing acetone and treated with 1.05 g (1.05 equiv) of benzyl bromide, and the mixture was refluxed for 24 h. The residue remaining after removal of the acetone was dissolved in a small amount of absolute ethanol. Within minutes, a precipitate began to form and ethyl ether was added slowly to complete the process. The solid was isolated by vacuum filtration, giving 2.82 g of crude salt, which was recrystallized from absolute ethanol affording 1.95 g (70%) of yellow cubes: mp 164–169 °C dec; IR (Nujol) 3320, 3200, 1620, 1590 cm^{-1}. Anal. Calcd for $C_{27}H_{31}O_2N_2Br$: C, 65.45; H, 6.26. Found: C, 65.17; H, 6.18.

Determination of Optical Purity. All samples whose optical purities were to be determined were weighed directly into the NMR tubes. Typical sample sizes were 30–60 mg. For all determinations, carbon tetrachloride or deuterated chloroform (approximately 0.5 mL, 4% Me_4Si) was used. After preliminary analysis, the europium shift reagent $Eu(C_{11}H_{19}O_2)_3$ was added directly and the tube shaken until all solids were dissolved. The spectra were examined for the extent of chemical shift and diastereomeric separation, and then the diastereomeric signals were integrated five times. The chemical shifts were obtained relative to Me_4Si by using a side-banding technique. From the results of multiple analyses of the same sample, it was found that the relative error in determining optical purities by this method was ±4%.

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Registry No. (±)-(*E*)-**1**, 59492-58-9; (±)-(*Z*)-**1**, 70774-46-8; (2*S*,3*R*)-**1**, 33530-46-0; (2*S*,3*S*)-**1**, 59492-57-8; (±)-(*E*)-**2**, 70774-47-9; (±)-(*Z*)-**2**, 70774-48-0; (2*R*,3*S*)-**2**, 63257-42-1; (2*S*,3*R*)-**2**, 63257-41-0; (2*S*,3*S*)-**3**, 63257-44-3; (±)-(*E*)-**4** sodium salt, 68330-59-6; (±)-(*E*)-**4** silver salt, 70729-28-1; (2*S*,3*R*)-**4**, 59492-56-7; (2*S*,3*R*)-**4a** brucine, 68330-57-4; **5**, 1099-45-2; (*E*)-**6**, 1504-72-9; (*Z*)-**6**, 13979-22-1; (±)-(*E*)-**7**, 70729-29-2; (2*S*,3*R*)-**7**, 70774-49-1; (2*R*,3*S*)-**7**, 70774-50-4; (±)-(*E*)-**8**, 70774-51-5; (±)-(*Z*)-**8**, 70774-52-6; **9**, 22573-24-6; (2*S*,3*R*)-**10**, 70729-30-5; (2*R*,3*R*)-**10**, 66364-97-4; (2*R*,3*S*)-**11**, 70774-53-7; (±)-**11**, 70774-54-8; (*R*)-**13**, 70729-31-6; (±)-**13**, 70774-55-9; (*R*)-**14**, 51117-40-9; (±)-**14**, 70729-32-7; ethyl chloroacetate, 105-39-5; acetophenone, 98-86-2; bromobenzene, 108-86-1; 2-phenylpropenoic acid, 492-38-6; benzyl bromide, 100-39-0; quininebenzyl bromide, 69212-47-1; quinine, 130-95-0.

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