and **6b** under the reaction conditions. Since it is reasonable to assume that none of the eight possible 7-cis[12] isomers were present, what is described as a new isomer can only be the 9-cis,11-cis,13-cis isomer as assigned (see below) or the 9-cis,11-cis isomer. No other retinol besides **6a**, **3a**, and **6b** could be detected during high-pressure LC separation runs. The conclusion then is that **6a**, **3a**, and **6b** are primary products produced competitively. Since the three products are produced in about a 1:1:1 ratio (by weight and by integration of the RI detector trace), it is apparent that formation of 9-trans and 13-cis isomers is slightly favored. The 11-cis linkage is predetermined by the cyclic nature of these competing and presumably concerted sigmatropic shift processes.

In order to further support the stereostructure of the new retinol (**3a**), it was oxidized (MnO_2, 30-fold excess, low-boiling petroleum ether, 1 h, 4 °C; short Celite column chromatography, ether) in 82% yield to the aldehyde **3b**.[13] The ^1H NMR spectrum of the latter was clearly distinguishable from that of 9-*cis*,11-*cis*-retinal, whose spectrum was kindly provided by Professor R. S. H. Liu.[14] The ^1H NMR spectrum of **3b** is characterized by an aldehyde proton signal at τ 0.32 (d, $J \sim 7.8$ Hz); the only other retinal with such a high-field aldehyde proton chemical shift is the 11-cis,13-cis isomer: τ 0.29 (d, $J \sim 8.1$ Hz).[14] Signals assigned to H_{10} [τ 3.91 (d, $J \sim 11.7$ Hz)], H_{11} [τ 3.15 (t, $J \sim 11.7$ Hz)], and H_{12} [τ 3.98 (d, $J \sim 11.7$ Hz)][15] suggest a 10-*s*-trans conformation for **3b**. The most remarkable spectral property of **3b** is its electronic spectrum [λ_{max} (95% EtOH) 302 nm (ϵ 14 300); λ_{max} (hexane) 302 nm (ϵ 15 500)] since all other retinals absorb above 360 nm.[16] Moreover, the corresponding alcohol **3a** actually exhibits its maximum slightly to the red [λ_{max} (95% EtOH) 306 nm (ϵ 24 500)] of the aldehyde! The tetraene **7** should exhibit a maximum at 290 nm.[17] Thus, both **3a** and **3b** are probably very highly twisted about the Δ^{12} single bond.[17] When **3b** is warmed mildly, it isomerizes to 9-*cis*,13-*cis*-retinal ($t_{1/2} \sim 2$ h in $CDCl_3$ at 45 °C, by ^1H NMR)[18] through successive electrocyclic ring-closing and then ring-opening processes similar to those previously described.[12]

Although the stereoselectivity and yields of the vinylallene scheme for preparing retinoids are not high, the method is gratifyingly specific for producing the difficult-to-obtain 11-cis isomers. This feature should make it a useful method for producing these key stereoisomers of analogues in adequate quantities for vision research.

Acknowledgment. The U.S. Public Health Service (NIH Grant EY-02452), the University of California Cancer Research Coordinating Committee (Grant 79R4), and the Intramural Research Fund, University of California, Riverside, provided financial support for this project. We also gratefully acknowledge the gifts of chemicals provided by Hoffmann-La Roche (Nutley) and by Badische-Anilin Und Soda-Fabrik, A. G. (Ludwigshafen). Professor Robert S. H. Liu kindly provided the spectral data for the yet unpublished 9-*cis*,11-*cis*-retinal.

Supplementary Material Available: Spectral and analytical data (5 pages). Ordering information is given on any current masthead page.

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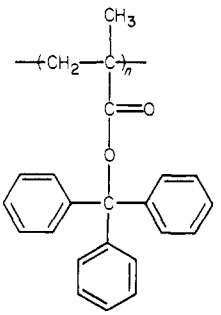
(12) For leading references, see: Kini, A.; Matsumoto, H.; Liu, R. S. H. *J. Am. Chem. Soc.* **1979**, *101*, 5078.
(13) For examples of related oxidations, see ref 3a and 12.
(14) (a) Patel, D. J. *Nature (London)* **1969**, *221*, 825: (b) Professor R. S. H. Liu has kindly provided detailed tables of ^1H NMR spectral parameters for all previously reported retinals, including unpublished data from his own laboratory.
(15) The signals attributed to H_{10} and H_{12} may be reversed.
(16) Zechmeister, L. "*Cis-Trans* Isomeric Carotenoids, Vitamins A and Arylpolyenes", Academic Press: New York, 1962; p 126.
(17) The 290-nm value was obtained from a simple Woodward's Rules calculation, assuming a base value of 255 nm for the $\Delta^{5,7,9}$ triene chromophore: Baas, J. L.; Davies-Fidder, A.; Visser, F. R.; Huisman, H. O. *Tetrahedron* **1966**, *22*, 265. The λ_{max} value of the aldehyde **3b** is significantly more highly perturbed (ref 16: 368–381 nm for other isomers) than that of the alcohol **3a** (ref 16: 312–328 nm). The aldehyde **3b** may more easily accommodate chromophore splitting(deconjugation by twisting about the Δ^{12} bond) to minimize steric congestion by virtue of added delocalization energy gained by the presence of the aldehyde and the linearly positioned (in a hyperconjugative sense) C_{13} methyl. *all-trans*- and 9-*cis*,11-*cis*,13-*cis*-retinoic acids exhibit UV maxima at 359 nm (ϵ 43 000) and 348 nm (ϵ 26 400), respectively (private communication to an anonymous referee from Dr. M. Klaus, F. Hoffmann-La Roche, Basel, Switzerland).
(18) The 11-*cis*,13-*cis*-retinal isomerizes to 13-*cis*-retinal under the same conditions with a similar half-life.

Resolution of Racemic Compounds by Optically Active Poly(triphenylmethyl methacrylate)

Sir:

We have recently reported the preparation of optically active, isotactic poly(triphenylmethyl methacrylate) (PTrMA) by chiral



PTrMA

anion catalysts such as (−)-sparteine–butyllithium complex.[1] This is the first example of the optically active vinyl polymer, the chirality of which is caused only by helicity. The polymer of high molecular weight shows high crystallinity and is insoluble in common organic solvents. This communication describes the liquid chromatographic resolution of various racemic compounds such as alcohol, ester, amine, and hydrocarbon by insoluble, optically active (+)-PTrMA.

The resolutions of racemic compounds have been achieved by column chromatography with naturally occurring or synthetic polymers as optically active adsorbents.[2] Most synthetic adsorbents were prepared either by attaching chiral molecules onto insoluble supports or by polymerizing (or binding) chiral molecules in the presence of cross-linking agents. Optically active PTrMA is a new type of synthetic chiral adsorbent and is easily prepared by a small amount of a chiral anionic catalyst.

Triphenylmethyl methacrylate (20.0 g, 60.7 mmol) was dissolved in dry toluene (400 mL) under nitrogen and cooled to −78 °C. To this solution was added a toluene solution of (−)-sparteine (0.342 g, 1.46 mmol) and butyllithium (1.21 mmol) with a syringe. After 24 h, the reaction mixture was poured into methanol (4 L), and the insoluble polymer was separated with a centrifuge. The polymer was grained and extracted with tetrahydrofuran (700 mL). The insoluble polymer was separated with a centrifuge and dried under vacuum, yield 19.4 g (96.8%). The specific rotation, $[\alpha]^{20}_D$ of this polymer is considered to be greater than +250° on the basis of the data reported previously.[1] The $\overline{DP}$ of the polymer was estimated to be 220 from a gel-permeation chromatogram of the poly(methyl methacrylate) derived from (+)-PTrMA.[1] The polymer was grained to small particles, which swelled 2–4 times

(1) Okamoto, Y.; Suzuki, K.; Ohta, K.; Hatada, K.; Yuki, H. *J. Am. Chem. Soc.* **1979**, *101*, 4763.
(2) (a) Boyle, P. H. *Q. Rev., Chem. Soc.* **1971**, 323. (b) Sousa, L. R.; Sogah, G. D. Y.; Hoffman, D. H.; Cram, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 4569, and references cited therein. (c) Harada, A.; Furue, M.; Nozakura, S. *J. Polym. Sci., Polym. Chem. Ed.* **1978**, *16*, 189. (d) Wulff, G.; Vesper, W. *J. Chromatogr.* **1978**, *167*, 171. (e) Blaschke, G.; Kraft, H.-P. *Makromol. Chem., Rapid Commun.* **1980**, *1*, 85.

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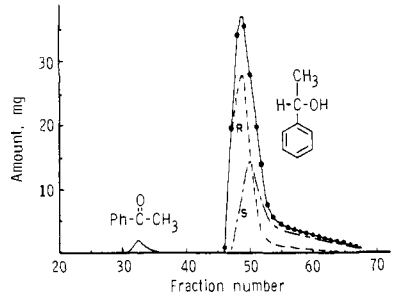


Figure 1. Resolution of racemic 1-phenylethyl alcohol by (+)-PTrMA. Column, 80.6 cm × 1.16 cm (i.d.); (+)-PTrMA, 32 g (200–250 mesh); sample, 219 mg; solvent, hexane; flow rate, 0.10 mL/min; one fraction, 5 mL; room temperature.

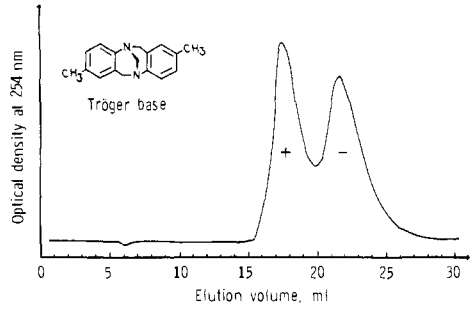
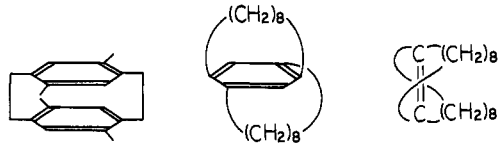


Figure 2. Resolution of racemic Tröger base by (+)-PTrMA.[8] Column, 50 cm × 0.46 cm (i.d.); (+)-PTrMA, 3.5 g (less than 250 mesh); sample, 0.21 mg; solvent, cyclohexane/THF (99:1 v/v); flow rate, 0.20 mL/min; room temperature.

when hexane was used as the solvent of chromatography.

An example of the chromatographic resolution is shown in Figure 1.[3] (*RS*)-1-Phenylethyl alcohol was partially resolved and well separated from acetophenone, which was present as an impurity. The fraction of the alcohol that was initially eluted (26%) consisted of 81% of the (*R*)-(+) enantiomer and 19% of the (*S*)-(−) enantiomer, and its optical purity was 62%.

The results of the resolution of various racemic compounds are shown in Table I. The resolution was carried out in a way similar to that shown in Figure 1. 1-Phenylethyl alcohol, styrene oxide, and menthyl benzoate were resolved to similar extents. These compounds have different functional groups, but all contain a phenyl group. In the case of menthol, the (+) enantiomer showed a higher mobility, contrary to its benzoate. A large cyclic ketone, muscone, and 2-phenylbutane were resolved only slightly. The three hydrocarbons, tetramethyl[2.2]paracyclophane (**1**), [8]-



1 2 3

[8]paracyclophane (**2**), and "trans"-bicyclo[8.8.0]octadeca-1-(10)-ene (**3**), were partially resolved.[5] The specific rotations of **1** and **2** were greater than the values found in the literature.[6,7] No optical data are available for **3**.

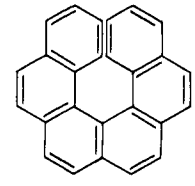
Table I. Chromatographic Resolution of Racemic Compounds by (+)-PTrMA[a]

racemic sample	column[b]	sample eluted,[c] wt %	config or sign	optical yield, % ($[\alpha]^{25}_D$)[d]
1-phenylethyl alcohol	I	26	*R*	62
menthol	I	17	+	32[e]
menthyl benzoate	I	31	−	71[f]
styrene oxide	I	25	*S*	53[g]
muscone	I	47	*R*	2[h]
2-phenyl-butane	I	38	*S*	2[i]
1	II	11	−	(−22°)
2	II	10	+	(+8.6°)
3	I	37	+	(+10.3°)

[a] See ref 3. [b] I, 80.6 cm × 1.16 cm (i.d.); II, 37.5 cm × 0.95 cm (i.d.). About 200 mg of sample was used for I and about 70 mg for II. [c] The weight percentage of the sample eluted initially. [d] See ref 4. [e] From $[\alpha]^{25}_D$ −47° (benzene): Dasannacharya, B. *J. Am. Chem. Soc.* **1924**, *46*, 1629. [f] From $[\alpha]^{25}_{365}$ −182° (hexane): Rupe, H. *Justus Liebigs Ann. Chem.* **1903**, *327*, 188. [g] From $[\alpha]^{25}_{365}$ +17.5° (hexane): Biggs, J.; Chapman, N. B.; Wray, V. *J. Chem. Soc. B* 1971, 72. [h] From $[\alpha]^{17}_D$ −13.0° (neat): Ruzicka, L. *Helv. Chim. Acta* **1926**, *9*, 721. [i] From $[\alpha]^{25}_D$ +27° (neat): Harrison, P. W. B.; Kenyon, J.; Shepherd, J. R. *J. Chem. Soc.* **1926**, 658.

Figure 2 shows the resolution of a tertiary diamine Tröger base obtained by high-performance liquid chromatography with a cyclohexane/THF (99:1) mixture as solvent.[8] The base was almost completely resolved. The ratio of the retention volume of the (−) isomer to that of the (+) isomer was 1.23, which corresponds to the resolution factor of 1.36 [the ratio $(V_A - V_0)/(V_B - V_0)$; V_A = retention volume of less mobile enantiomer, V_B = retention volume of more mobile enantiomer, and V_0 = dead volume)]. When hexane was used as solvent, strong tailing was observed. The Tröger base was first resolved by Prelog and Wieland[9] with a lactose column [88 cm × 7.5 cm (i.d.)]. The first fraction of the eluate contained the (+) isomer, the optical purity of which was 27%.

In the resolution of hexahelicene (**4**) by the (+)-PTrMA column, tailing was so strong that a clear peak did not appear.



4

Therefore, a more simple method was applied for the resolution of **4**. Insoluble (+)-PTrMA (77.2 mg)[10] was mixed with **4** (5.43 mg) in hexane (7.1 mL) and stirred for 3 h at room temperature. Then the polymer was separated from the solution, which contained 2.96 mg of (−)-**4**. Its specific rotation, $[\alpha]^{25}_D$, was −687° (OP 18.5%) in hexane.[11] The polymer was extracted three times with 7.1 mL of hexane. The first extract contained (−)-helicene (1.19 mg), $[\alpha]^{25}_D$ −190° (OP 5.1%); the second (+)-helicene (0.33 mg), $[\alpha]^{25}_D$ +1200° (OP 32%); and the third (+)-helicene (0.12 mg), $[\alpha]^{25}_D$ +2100° (OP 57%). The resolution of **4** was first carried out by Newman and Lednicer with optically active com-

(3) The amount of alcohol in each fraction was determined on a Hitachi 124 spectrophotometer. The optical rotation of the alcohol was measured in a 10-cm cell on a JASCO DIP-181 digital polarimeter; its precision of reading was ±0.001°. The optical purity of the alcohol was estimated on the basis of an optical rotation of $[\alpha]^{25}_{365}$ + 195° (hexane) for the optically pure (*R*)-(+) isomer, which was obtained in our group.

(4) Optical purity was calculated from the specific rotations shown at footnotes. The differences of the solvents were ignored in the cases of menthol, muscone, and 2-phenylbutane. Our rotation was measured in hexane.

(5) These three hydrocarbons and hexahelicene (**4**) were provided by Professor Masao Nakazaki and Dr. Koji Yamamoto in our department.

(6) Longone, D. T.; Reets, M T. *Chem. Commun.* **1967**, 46.

(7) Nakazaki, M.; Yamamoto, K.; Ito, M.; Tanaka, S. *J. Org. Chem.* **1977**, *42*, 3468.

(8) Tröger base (mp 135–136 °C) was used. The chromatography was done with a JASCO FLC-A10 instrument and a UV detector, JASCO UV-254-II.

(9) Prelog, V.; Wieland, P. *Helv. Chim. Acta* **1944**, *27*, 1127.

(10) (+)-PTrMA was extracted with hexane (10 mL) for 3 h. The rotation, α^{25}_D of the extract was 0.000 ± 0.001° in a 10-cm cell.

(11) The optical purity of **4** was calculated on the basis of $[\alpha]^{25}_D$ +3707° (chloroform).[12] The difference in solvents was ignored. The concentration of **4** was estimated spectrophotometrically.

plexing agents, e.g., Newman's chiral aromatic nitro compound.[12] After three recrystallizations of the complex in benzene/ethanol, they obtained an isomer $[[\alpha]^{27}_D$ -123° (OP 3.3%)] in 22% yield.

Optically active PTrMA seems to be very useful for the resolution of many racemic compounds, particularly aromatic hydrocarbons, the resolution of which is rather difficult by the usual method.

Acknowledgment. We are grateful to Professor M. Nakazaki and Dr. K. Yamamoto in our department for providing us with valuable hydrocarbons. We also thank Daicel Chemical Industries Ltd. for giving us several racemic compounds.

(12) Newman, M. S.; Lednicer, D. *J. Am. Chem. Soc.* **1956**, *78*, 4765.

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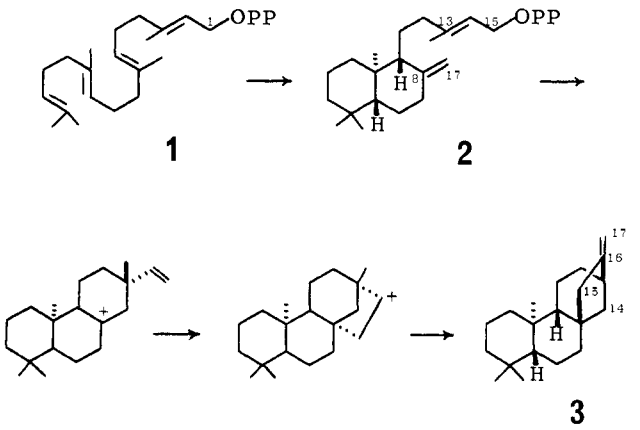
Stereochemistry of the Enzymatic Cyclization of Copalyl Pyrophosphate to Kaurene in Enzyme Preparations from *Marah macrocarpus*

Sir:

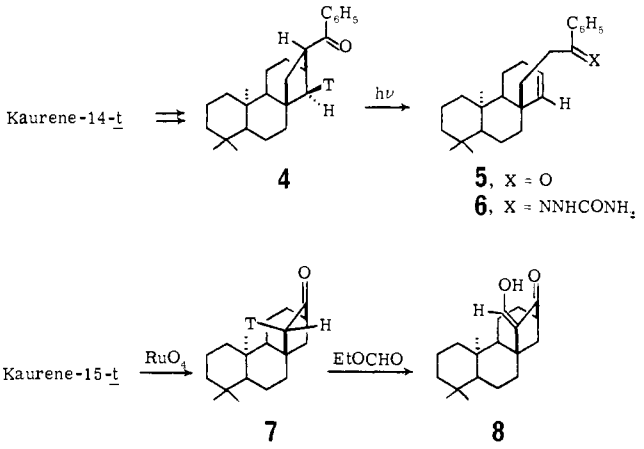
The biosynthesis of (-)-kaurene (**3**) is of considerable interest since this diterpene hydrocarbon is a key intermediate in the biosynthesis of the gibberellin plant growth regulating substances[1] and is a representative member of a biogenetically novel family of tetra- and pentacyclic diterpenoids.[2] The essential features of the commonly accepted biogenetic pathway to kaurene from geranylgeranyl pyrophosphate (**1**) shown in Scheme I were first proposed by Wenkert in 1955.[3] The results of tracer studies on gibberellin biosynthesis[1,4] are in accord with this pathway, and the intermediacy of copalyl pyrophosphate (**2**) has been established.[5] In this communication, we describe experiments which elucidate the stereochemistry of the cyclization of **2** to **3** with respect to C-15 and C-17 of the former in soluble enzyme preparations from *Marah macrocarpus*.[6]

Oxidation of (*R*,*S*)-geranylgeraniol-*1-t* (MnO_2, hexane, 0 °C)[7] followed by stereospecific reduction of the labeled aldehyde with liver alcohol dehydrogenase and NAD^+ (0.1 M PO_4 buffer, pH 7.5, 0.57 M C_2H_5OH, Tween 80, 30 °C, 19 h)[8] provided (*S*)-geranylgeraniol-*1-t* in 65% yield.[9] The corresponding pyrophosphates (43.4 and 9.8 mCi/mmol, respectively) of the *R*,*S* and *S* alcohols were prepared[7a] and separately incubated with a reconstituted lyophilisate isolated from the endosperm of immature *M. macrocarpus* seeds which is known to contain kaurene synthetase activity.[6] The incubation conditions were as follows: 0.1 M Tris buffer, pH 7.4, 0.01 M PO_4, 2 mM $MgCl_2$, 27.5 mg of lyophilisate/mL, 20 μM substrate, 30 °C, 8.5-25 h. Kaurene was isolated by extraction, purified by preparative TLC, diluted with ca. 100 mg of nonradioactive kaurene,[12] and crystallized to constant specific activity (20.0 and 7.16 μCi/mmol, respectively). The incorporation of radioactivity into kaurene was 31-49% in three incubations.

Scheme I



Scheme II



The samples of kaurene-*14-t* were converted to the exo phenyl ketone **4** (mp 166 °C)[13] in five steps,[14] and the latter upon irradiation to low conversion (Rayonet reactor, *t*-C_4H_9OH, 3 h) afforded unsaturated ketone **5** (mp 96-97 °C, 20-30%), the semicarbazone (**6**, mp 196-197 °C) of which was recrystallized to constant specific activity (Scheme II). Whereas **4** (5.09 μCi/mmol) derived from the *R*,*S* pyrophosphate gave rise to **6** retaining 59% of the original radioactivity, **4** (2.1 μCi/mmol), originating from the *S* substrate, produced **6** which had lost 99% of the tritium label (0.02 ± 0.005 μCi/mmol). Since Norrish II photofragmentation reactions occur via intramolecular γ-hydrogen transfer,[15] it follows that the tritium in kaurene biosynthesized

(1) For a recent review, see: P. Hedden, J. MacMillan, and B. O. Phinney, *Annu. Rev. Plant Physiol.*, **29**, 149-192 (1978).

(2) For a review, see: R. McCrindle and K. H. Overton in "Rodd's Chemistry of Carbon Compounds", 2nd ed., S. Coffey, Ed., Elsevier, Amsterdam, 1969, Vol. II, Part C, pp 373-402.

(3) E. Wenkert, *Chem. Ind. (London)*, 282 (1955).

(4) J. R. Hanson, *Fortschr. Chem. Org. Naturst.*, **29**, 395 (1971).

(5) (a) I. Shechter and C. A. West, *J. Biol. Chem.*, **244**, 3200 (1969); (b) R. R. Fall and C. A. West, *ibid.*, **246**, 6913 (1971).

(6) C. D. Upper and C. A. West, *J. Biol. Chem.*, **242**, 3285 (1967); M. O. Oster and C. A. West, *Arch. Biochem. Biophys.*, **127**, 112 (1968).

(7) (a) R. M. Coates, R. A. Conradi, D. A. Ley, A. Akeson, J. Harada, S.-C. Lee, and C. A. West, *J. Am. Chem. Soc.*, **98**, 4659 (1976); (b) R. M. Coates, D. A. Ley, and P. L. Cavender, *J. Org. Chem.*, **43**, 4915 (1978).

(8) (a) D. E. Gregonis and H. C. Rilling, *Biochemistry*, **13**, 1538 (1974); A. R. Battersby, J. Staunton, and H. R. Wiltshire, *J. Chem. Soc., Perkin Trans. 1*, 1156 (1975); (b) we are grateful to R. A. Conradi for developing this procedure.

(9) Although the stereospecificity of liver alcohol dehydrogenase for delivery of hydrogen to the *re* face of citral and farnesal has been established,[10] the stereochemistry of (*S*)-geranylgeraniol-*1-d* prepared by the same procedures was independently verified by the NMR method of Gerlach and Zagalak.[11]

(10) C. Donninger and G. Ryback, *Biochem. J.*, **91**, 11 P (1964); K. H. Overton and F. M. Roberts, *ibid.*, **144**, 585 (1974); K. Imai and S. Marumo, *Tetrahedron Lett.*, 4401 (1974).

(11) H. Gerlach and B. Zagalak, *J. Chem. Soc., Chem. Commun.*, 274 (1973).

(12) We are grateful to Drs. A. O. Geiszler and M. A. Nyman, Abbott Laboratories, North Chicago, Illinois, for providing the natural (-)-kaurene used in this research.

(13) The IR and NMR spectra of all compounds described in this work were fully consistent with the structure shown or implied. Only key data are cited. Satisfactory combustion analyses were obtained for all new, crystalline compounds reported.

(14) The following sequence of reactions afforded phenyl ketone **4** in 75% overall yield: (i) epoxidation (*m*-$ClC_6H_4CO_3H$, $CHCl_3$, 0 °C); (ii) rearrangement to *endo*-kauran-17-al ($BF_3{\cdot}Et_2O$, C_6H_6, 25 °C); (iii) Grignard addition (C_6H_5MgBr, ether, reflux); (iv) oxidation (Collins reagent, CH_2Cl_2, 25 °C); (v) epimerization ($NaOC_2H_5$, C_2H_5OH, 25 °C, 2 h).

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