zene–methanol (19:1) gave a partial separation in the form of an elongated band. Removal of the lower portion of this band followed by extraction with methanol–chloroform (1:1) and evaporation of the solvent gave pure β isomer **11** as colorless microcrystals: 95 mg, mp 125–140 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.31 and 1.55 (2 s, 6 H, isopropylidene CH_3), 3.32 (m, 2 H, H-5′,5″), 4.22 (m, 1 H, H-4′), 4.67–4.93 (m, 2 H, H-2′, H-3′), 4.99 (d, 1 H, H-1′).

Anal. Calcd for $C_{31}H_{30}N_2O_6$: C, 70.71; H, 5.74; N, 5.32. Found: C, 70.58; H, 5.80; N, 5.15.

From the upper layer portion of the elongated band in the thick layer chromatogram, only a mixture of the α and β isomers (**12** and **11**) was obtained.

5-(β-D-Ribofuranosyl)uracil (13, Pseudouridine). A mixture of **11** (105 mg, 0.2 mmol) and 10% methanolic HCl (2 ml) was stirred at room temperature for 15 min. During this time, a clear solution was obtained and then crystalline product **13** (20 mg) precipitated. The crystals were collected by filtration and washed with ether, mp 221–222 °C (lit.[15] mp for pseudouridine 220–221 °C). ^{1}H NMR spectrum (D_2O) of this product was identical with that of pseudouridine.[12]

From the filtrate a further quantity of **13** (26 mg) having the same melting point and ^{1}H NMR spectral characteristics was obtained upon dilution with 20 ml of ether. The combined yield was 92%.

Registry No.—**1**, 55726-19-7; **3**, 57100-24-0; **4**, 59464-13-0; **5**, 59464-14-1; **6**, 57100-19-3; **7**, 57100-18-2; **7** HCl, 59464-15-2; **8** HCl, 59464-16-3; **9**, 59464-17-4; **10**, 59464-18-5; **11**, 59464-19-6; **12**, 59464-20-9; **13**, 1445-07-4; (ethoxycarbonylmethylene)triphenylphosphorane, 1099-45-2; guanidine HCl, 15827-40-4; thiourea, 62-56-6.

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(1) This investigation was supported in part by funds from the National Cancer Institute, DHEW (Grants CA-08748, -18856, and -17805).
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(17) The previously reported extinction values for **7** and **8** are incorrect.

Synthesis and Absolute Configuration of Multistriatin

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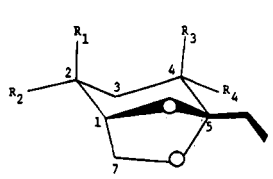
Multistriatin, 2,4-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane (**1**), was synthesized as a mixture of the four diastereomers **1**α–δ. The key step was the formation of 4,6-dimethyl-7-octen-3-one (**10**) by the alkylation of 3-pentanone with the tosylate (**7**) of 2-methyl-3-buten-1-ol via the metalloenamine synthesis. Epoxidation of **10** with *m*-chloroperoxybenzoic acid and intramolecular ketalization of the 4,6-dimethyl-7,8-epoxyocten-3-one (**11**) with $SnCl_4$ gave **1**, whose **1**α content was maximized by equilibration of **1**γ to **1**α with $SnCl_4$. Acid equilibration of **1** in the presence of excess peroxide leads to the formation of side products at the expense of the multistriatin isomers. Synthesis of **1** from (*S*)-(+)-2-methyl-3-butenoic acid gave (2*R*)-(−)-**1**α, which established the absolute configuration of natural (−)-**1**α as 1*S*:2*R*:4*S*:5*R*. The enantiomeric composition of synthetic (−)- and (+)-**1**α was determined by ^{13}C NMR with the chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III). Natural (−)-**1**α consisted of a single enantiomer.

α-Multistriatin, 2-*endo*,4-*endo*-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane (**1**α), is a novel component of the aggregation pheromone of the European elm bark beetle, *Scolytus multistriatus*.[1] In a previous publication,[2] we have determined the relative stereochemistry for each of the four possible pairs of multistriatin stereoisomers. We report here a synthesis of racemic **1**α–δ designed to confirm the gross structure of multistriatin and provide quantities of **1** sufficient

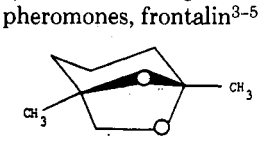


1

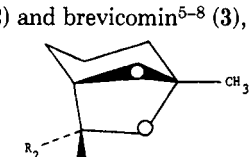
	R_1	R_2	R_3	R_4
1α :	H	CH_3	H	CH_3
1β :	CH_3	H	CH_3	H
1γ :	H	CH_3	CH_3	H
1δ :	CH_3	H	H	CH_3

for field tests. In addition, optically active (+)- and (−)-multistriatin stereoisomers (**1**α–δ) of known absolute configurations were synthesized by inclusion of a chiral intermediate (**5**) of known configuration into the synthetic scheme.

Previous syntheses of the 6,8-dioxabicyclo[3.2.1]octane ring system, including the synthesis of two other bark beetle pheromones, frontalin[3–5] (**2**) and brevicomin[5–8] (**3**), have been



(1S) **2**

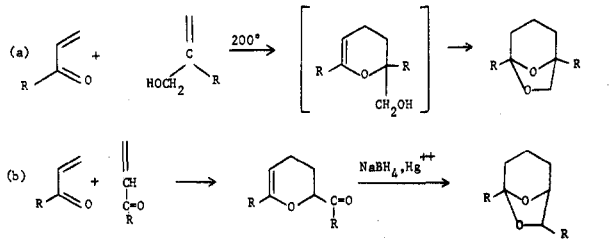


(1S) **3**

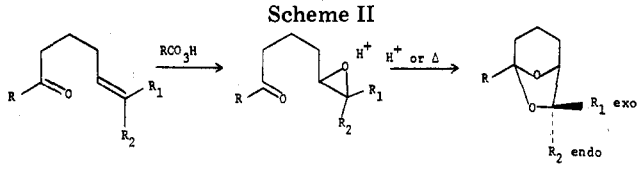
	R_1	R_2
exo :	CH_2CH_3	H
endo :	H	CH_2CH_3

accomplished by two main routes, Schemes I and II. Scheme I involves the Diels–Alder addition of an α,β-unsaturated carbonyl either to an α,β-unsaturated alcohol,[3,4,9] or to another α,β-unsaturated carbonyl that acts as the dienophile.[5,10,11] The first variation of this route (Scheme Ia), is thought to occur via a hydroxy dihydropyran intermediate[9] that cyclizes to the desired product under the conditions of the initial addition.

Scheme I



Scheme II

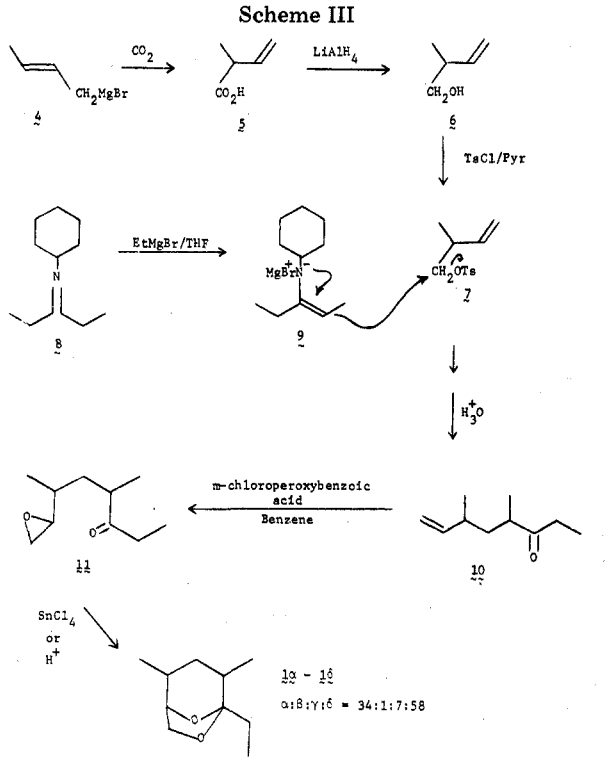


In the second variation (Scheme Ib), the initially formed keto dihydropyran is reduced to the corresponding alcohol, whereupon Lewis acid catalyzed ring closure yields the appropriately substituted 6,8-dioxabicyclo[3.2.1]octane ring. When applied to the synthesis of multistriatin (**1**), this route yielded only small amounts of **1** (5%) in a complex mixture of starting materials and reaction products.[2] Although the stereospecificity of the Diels–Alder reaction was helpful in assigning the relative configurations of the C-1 and C-2 carbons of **1**, this approach was not amenable to a large-scale synthesis.

An alternative approach (Scheme II), which was used in the present synthesis, involves the epoxidation of a δ-keto olefin, followed by thermal or acid-catalyzed cyclization of the keto epoxide.[7,8,12,13] The keto epoxide rearrangement is stereospecific by both thermal and acidic catalysis as evidenced by the stereospecific syntheses of *exo*- and *endo*-brevicomin from the cis and trans epoxides, respectively. This reaction[7,12,13] presumably involves attack of the carbonyl oxygen on the epoxide ring with inversion of the δ carbon.

Synthesis of Racemic Multistriatin. The key intermediate of our synthesis (Scheme III) was the keto olefin, 4,6-dimethyl-7-octen-3-one (**10**). The 2-methyl-3-butenyl moiety

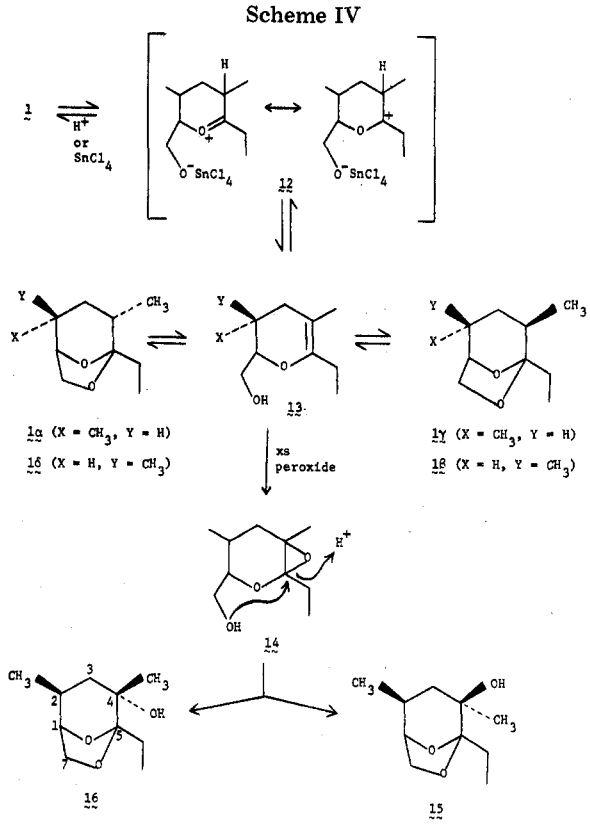
Scheme III



of **10** was introduced as the tosylate (**7**) of 2-methyl-3-butenol (**6**), which was synthesized by the carbonation of butenylmagnesium bromide (**4**) followed by reduction of the resulting 2-methyl-3-butenoic acid (**5**) with lithium aluminum hydride. Alkylation of the magnesium bromide salt (**9**) of the ketimine (**8**) formed from 3-pentanone and cyclohexylamine with the tosylate (**7**) in THF gave, after acid hydrolysis, **10** in 70% yield (distilled) from **6**.[14] The spectra of each of the GLC-purified diastereomers of **10** were nearly identical with minor variations observed only in the ir and NMR spectra. The infrared spectra each exhibited a peak at 1715 cm^{-1} corresponding to the C=O stretching frequency; strong absorptions at 995 and 915 cm^{-1} suggested the presence of a vinyl group, which was confirmed by a two-proton multiplet at 4.85–5.1 ppm and a one-proton multiplet at 5.4–5.8 ppm. The mass spectrum showed a molecular ion (M^+) at *m/e* 154, and an intense McLafferty rearrangement peak at *m/e* 86.

Epoxidation of **10** was accomplished with *m*-chloroperoxybenzoic acid in benzene, but refluxing the reaction mixture[15] gave only a 20–30% yield of cyclized product. Cyclization and equilibration[2] of the α/γ and β/δ pairs were effected by removal of excess peracid and treatment of a benzene solution of crude **11** with $SnCl_4$ (stirring at room temperature for 20 h and refluxing for 1 h). Under these conditions, cyclization occurred rapidly (<30 min), but the acid-catalyzed equilibrations of 1γ to 1α and of 1β to 1δ proceeded slowly, after ketalization was complete. Scheme IV depicts the acid-

Scheme IV



catalyzed cleavage of a C-5–O bond of **1** to give the resonance-stabilized oxonium ion **12** which, following loss of the C-4 proton, forms the hydroxy dihydropyran intermediate **13**.[16] Reversal of this process by reprotonation on either side of the double bond scrambles the stereochemistry at C-4, leaving C-2 unchanged. Thus, the thermodynamically more stable 1α and 1δ isomers predominate.

The MS, ir, and NMR spectra of two of the four synthetic ketal diastereomers separated by preparative GC were identical with those of natural 1α and 1β, while the spectra of the

Table I. Thermal Cyclization of Epoxy Ketones 11α–δ[a]

Time h	Epoxide 11α, % ketals (α:β:γ:δ)	11γ, % ketals (α:β:γ:δ)	11δ + 11β, % ketals (α:β:γ:δ)
2	29 (87:0:4:9)	73 (11:0:85:4)	64 (4:35:1:59)
11	100 (90:0:7:4)	100 (11:0:85:4)	100 (4:30:1:64)
33	100 (90:0:7:4)	100 (11:0:85:4)	100 (3:8:1:88)

[a] The designations α–δ refer to the multistriatin (1) isomer to which each epoxide cyclizes.

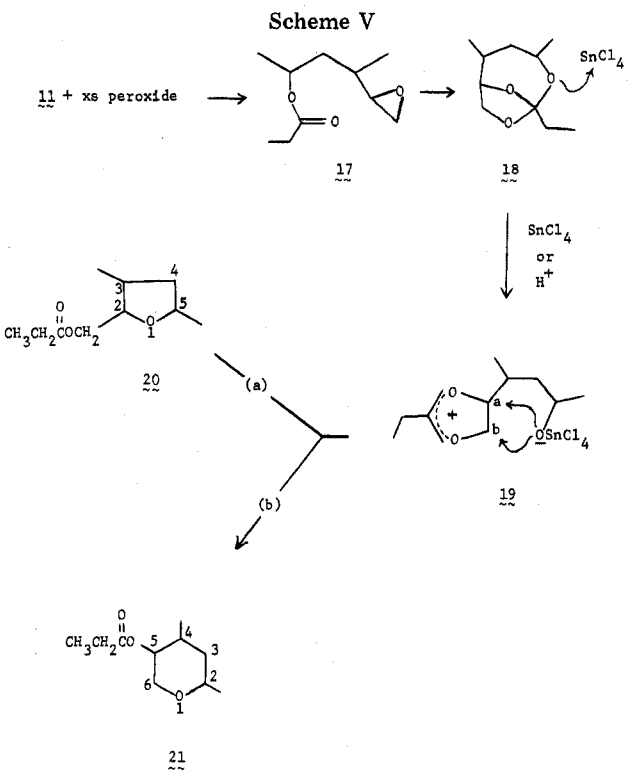
other two synthetic isomers were compatible with structures 1γ and 1δ. The total yield of ketals (1α–δ) from 10 was 63% following fractional distillation, with the biologically active 1α isomer representing 34% of the total multistriatin isomers.

The thermal cyclization of the epoxy ketone 11 was performed at 210 °C in sealed glass tubes on the diastereomers of 11 that were separated by preparative GC. Two of the epoxides were inseparable, and were cyclized as a binary mixture. The ir and NMR spectra of GC-separated samples of the epoxides confirmed that thermal cyclization did not occur on the gas chromatograph. Table I summarizes the results of the thermal cyclization, and shows that each individual epoxide gave mainly one diastereomer of multistriatin. Thus, the thermal ring closure was rapid, even though equilibration of the 1α/1γ pair did not occur and that of the 1β/1δ pair proceeded slowly. These results, in conjunction with those of the acid-catalyzed cyclization of 11, indicate that the initial ring closure in both cases does not affect the configuration of carbons adjacent to the carbonyl. Even though 13 is a likely intermediate in the equilibration process, it is not required in the intramolecular cyclization step.

If an acid catalyst is added to the mixture of crude epoxides without removal of excess peroxide, side products proliferate at the expense of the multistriatin isomers. Four of these side products were purified by preparative GLC and were identified by spectral analysis as 15, 16, 20, and 21. Epoxidation of 13 formed in the presence of acid leads via 14 to the hydroxy ketals 15 and 16 as shown in Scheme IV.[16] Elucidation of the relative stereochemistry of 15 and 16 was aided by the observation that only trace amounts of 1β and 1δ ketals were present in the reaction products relative to 1α and 1γ. The 1β/1δ pair were thus preferentially oxidized, which suggested that the methyl groups on C-2 of 15 and 16 are in the axial position since C-2 should not be affected by the reaction conditions employed. The NMR spectra of 15 and 16 supported this contention since the chemical shifts of the doublets of the methyl groups on C-2 in 15 and 16 (1.23 and 1.14 ppm, respectively) remained in the downfield region characteristic of the axial methyl group signals of 1β and 1δ.[2] In addition, the chemical shifts and splitting patterns for the C-1 and C-7 protons (3.5–3.8 and 4.1 ppm, respectively) closely resembled the C-1 and C-7 proton resonances of 1β and 1δ. The singlet of the methyl group on C-4 of 16 appeared at 0.2 ppm downfield from the same methyl singlet of 15, and is therefore assigned the axial position on the basis of the downfield shifts (0.15–0.2 ppm) observed in NMR spectra of 1α–δ of axial methyl signals relative to equatorial methyl signals.[2] The NMR spectra of 15 and 16 taken in Me_2SO displayed hydroxyl singlets at 4.06 and 4.02 ppm, respectively.

Tetrahydrofuran and pyran ester side products such as 20 and 21 are most likely the ultimate result of a Baeyer–Villiger oxidation by excess peroxide of the epoxy ketone 11 to the epoxy ester 17, which subsequently cyclizes in acid to the intermediate ortho ester 18 (Scheme V). Acid cleavage of 18

Scheme V



results in formation of a resonance-stabilized acetonium ion (19), while oxide attack at carbon a or b of 19 produces 20 or 21, respectively. Because the Baeyer–Villiger oxidation is catalyzed by acids, compounds such as 20 and 21 increased relative to the ketals if acid was applied directly to the epoxidation reaction mixture. These compounds were produced in smaller quantities under the optimum conditions whereby the acid was applied after removal of excess peroxide. The occurrence of side products analogous to 20 and 21 under similar conditions has been reported,[7] and the mechanism of their formation from ortho esters in the presence of Lewis acids has recently been elucidated with the use of ^{18}O-labeled precursors.[17]

Synthesis of Optically Active Multistriatin. Natural α-multistriatin (1α) produced by virgin female elm bark beetles is optically active ($[\alpha]^{25}D$ −47°) and has been shown to be optically pure by the use of the chiral shift reagent Eu(hfc)$_3$ in the ^1H NMR of 1α.[18] In the present study, optically active multistriatin isomers (1α–δ) were synthesized from *S*-(+)- and *R*-(−)-5 (70 and 60% optical purity, respectively), which were obtained by partial resolutions of racemic 5 with (+)- and (−)-α-methylbenzylamine. The absolute configurations of the enantiomers of 5 have been determined.[19] Each of these optically enriched acids was then used in the synthesis of 1α–δ as shown in Scheme VI. The steps employed were identical with those shown in Scheme III for the synthesis of racemic 1.

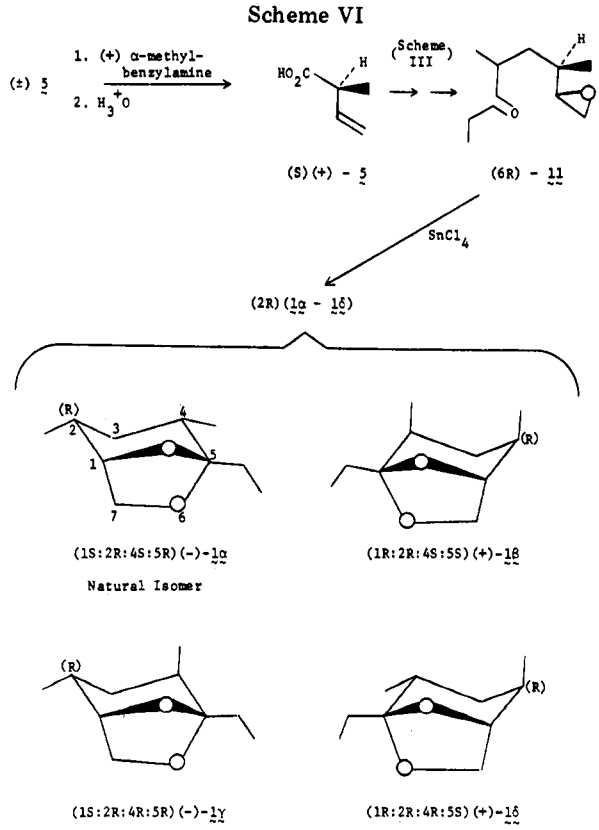
Each isomer of multistriatin (1α–δ) originating from *R*-(−)-5 and *S*-(+)-5 was purified by preparative GLC and shown to be optically active by ORD measurements in *n*-hexane (see Table II). The chiral center of 5 corresponds to C-2 in multistriatin (1), and therefore the multistriatin isomers (1α–δ) synthesized from *S*-(+)-5 all have the *R* configuration at C-2, whereas 1α–δ from *R*-(−)-5 are *S* at C-2. These assignments are based on the reasonable assumption that the configuration at C-2 remained intact because C-2 was not involved in any of the subsequent reactions. Furthermore, C-2 does not racemize during the acid-catalyzed equilibration step, as shown experimentally by the separate equilibrations of the α/γ and β/δ pairs.[2] The thermal conditions employed in the GLC purifications likewise did not lead to racemization at C-2

Table II. Specific Rotations ([α]^{25}D) of Stereoisomers of Multistriatin (1), Frontalin (2),[a] and *exo*-Brevicomin (3)[a]

	Configuration at chiral carbons				589 nm		365 nm	
	1	2	4	5	Obsd[b]	Calcd[c]	Obsd[b]	Calcd[c]
(−)-1α	*S*	*R*	*S*	*R*	−26	−47	−79	−142
(+)-1α	*R*	*S*	*R*	*S*	+21	+44	+62	+132
(−)	1β	*S*	*S*	*R*	*R*	−34	−73	−114
−242								
(+)-1β	*R*	*R*	*S*	*S*	+43	+78	+135	+241
(−)-1γ	*S*	*R*	*R*	*R*	−12	−21	−34	−51
(+)-1γ	*R*	*S*	*S*	*S*	+10	+21	+35	+75
(−)-1δ	*S*	*S*	*S*	*R*	−41	−87	−122	−260
(+)-1δ	*R*	*R*	*R*	*S*	+50	+89	+151	+270
(−)-2	*S*			*R*	−52.0			
(+)-2	*R*			*S*	+53.4			
(−)-3	*S*			*R*	−80.0			
(+)-3	*R*			*S*	+84.1			

[a] These values, obtained in ether, were reported by Mori for optically pure enantiomers.[21,22] [b] These values were observed in *n*-hexane for the synthetic stereoisomers of 1 purified by GLC. The concentrations varied between 0.057 and 0.48 M. [c] Calculated values of the optically pure (100%) stereoisomers of 1 based on the observed values, and the optical purities of 56 and 47% for the 2*R* and 2*S* stereoisomers, respectively.

Scheme VI



since each of the pure isomers remained unchanged following reinjection on the GLC column. Assignment of the *R* configuration to C-2 of the synthetic isomers of 1 originating from *S*-(+)-5 established the absolute configuration of all other chiral centers of 1α–δ (C-1, C-4, and C-5) by cognizance of the previously established relative stereochemistry of 1α–δ. Thus, the absolute configuration of both natural and synthetic (−)-α-multistriatin is 1*S*, 2*R*, 4*S*, and 5*R*, as shown in Scheme VI.

The determination of the optical purities of the synthetic (+)- and (−)-α-multistriatin by the use of Eu(hfc)$_3$ in the ^{1}H NMR spectra was not possible. Although natural (−)-1α did appear to be 100% optically pure by qualitative inspection of the Eu(hfc)$_3$-shifted ^{1}H NMR spectrum, a quantitative estimate of the optical purity by peak integration was prohibited by the broadening and multiplicity of the proton signals (C-7) exhibiting the largest enantiomeric split. This technique is of little value for optical purity measurements of synthetic (+)- or (−)-1α in cases of partial enantiomeric enrichment.

The recent report by Fraser[20] on the use of chiral shift reagents in ^{13}C NMR prompted our attempts to use this technique to determine the optical purities of synthetic (+)- and (−)-α-multistriatin. As shown in Figure 1, the noise-decoupled ^{13}C NMR spectra of racemic 1α, (−)-1α, and (+)-1α with Eu(hfc)$_3$ in benzene exhibit observable enantiomeric separations for eight of ten carbons, with the largest differences of 0.7–1.9 ppm observed for the C-1 resonances. The complexity caused by spin–spin splitting often encountered in ^{1}H spectra is absent in the broad-band proton decoupled ^{13}C NMR spectrum. Therefore, the shifted ^{13}C spectrum complements the corresponding ^{1}H spectrum by offering a greater acuity of enantiomeric resolution due to the singlet nature of the carbon-13 signals.

The optical purity of synthetic (+)- and (−)-1α was 47 and 56% respectively, based on peak integration of the ^{13}C NMR signals. Calculation of the specific rotations at 589 and 365 nm for the optically pure isomers of multistriatin (1α–δ) based on the optical purities and observed rotations of the synthetic stereoisomers demonstrated that the values for each pair of enantiomers were in good accord (see Table II). Comparison of the specific rotation of natural (−)-1α ([α]^{25}D −47°) with the values calculated for the optically pure enantiomers of 1α (−47 and +44°, Table II) supports the assignment of full enantiomeric purity for natural (−)-α-multistriatin.

The data of Table II also demonstrate that for all eight optically active stereoisomers of multistriatin, and the enantiomers of frontalin[21] and *exo*-brevicomin,[22] the sign of the plain curve observed in the ORD depends only on the absolute configuration of the 6,8-dioxabicyclo[3.2.1]octane ring system, and is independent of the alkyl substituents. Thus, the 1*S* rings of the multistriatin isomers (1α–δ) all exhibit minus plain curves as do (1*S*)-*exo*-brevicomin and (1*S*)-frontalin.

Experimental Section

General. Nuclear magnetic resonance spectra were recorded on a Varian XL-100 FT NMR spectrometer or a Varian A-60 NMR spectrometer. Infrared spectra were obtained on a Perkin-Elmer Model 621 spectrophotometer. Solution ir spectra were obtained with 40–60 μg samples in a Barnes 4-μl (1 mm path) ultramicro cavity cell mounted in a Perkin-Elmer 4X refractive beam condenser; a matched cavity cell and beam condenser were used for solvent compensation

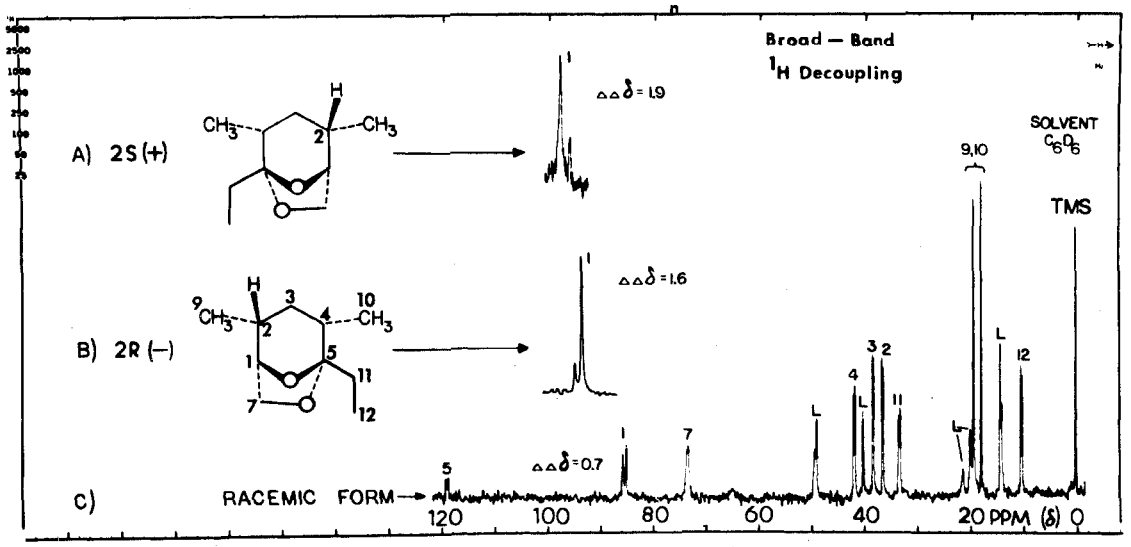


Figure 1. Noise-decoupled ^{13}C NMR spectra of 2*S*-(+)-1α, 2*R*-(−)-1α, and racemic 1α with Eu(hfc)$_3$ in benzene.

of the reference beam. Mass spectra were obtained at 70 eV ionization potential on a Perkin-Elmer Hitachi RMU-6E mass spectrometer modified with a direct inlet sampling system. Gas chromatography was performed on a Varian Aerograph series 2700 gas chromatograph, equipped with a flame ionization detector and modified for preparative GLC with a Brownlee-Silverstein thermal gradient collector. Optical rotary dispersion curves were measured on a JASCO ORD/UV-5 ORD recorder, in conjunction with a metal cylindrical cell (0.5 ml) consisting of a 10-mm metal spacer and pressure-sealed quartz windoes. Unless otherwise stated, all GLC analyses were performed as follows: 4% Carbowax 20M on Chromosorb G, 60/80 mesh, DMCS-AW, 6.3 m × 6 mm o.d., silanized glass; He flow 60 ml/min; column oven temperature, as indicated; detector temperature 200–210 °C; injector temperature 160–200 °C.

Microanalyses were carried out by Galbraith Laboratories, Knoxville, Tenn. All samples of the chiral NMR shift reagent, Eu(hfc)$_3$ (Aldrich Chemical Co.), were sublimed prior to use and prepared in a drybox under a nitrogen atmosphere. Solvents were reagent grade and were dried, when required, over Linde 4A molecular sieves. All reactions described below were performed under a positive pressure of dry nitrogen.

Synthesis of Racemic Multistriatin. 2-Methyl-3-butenoic acid (5) was prepared by the carbonation of butenylmagnesium bromide (4) as described by Lane et al.[23] Distillation of the crude acid gave pure **5**: bp 93–94 °C (33 mm) [lit.[23] bp 95.5 °C (35 mm)].

Anal. Calcd for $C_5H_8O_2$: C, 59.98; H, 8.05. Found: C, 60.02; H, 8.03.

2-Methyl-3-buten-1-ol (6). 2-Methyl-3-butenoic acid (121 g, 1.2 mol) was reduced with $LiAlH_4$ in ether and the crude alcohol was distilled to give 56.5 g (55%) of pure (99% by GC) **6**: bp 116–123 °C (755 mm) [lit.[19] bp 120 °C (756 mm)].

Anal. Calcd for $C_5H_{10}O$: C, 69.72; H, 11.70. Found: C, 69.59; H, 11.57.

2-Methyl-3-butenyl Tosylate (7). A cooled, stirred solution of **6** (65.7 g, 0.763 mol) in 600 ml of dry pyridine was treated with tosyl chloride (295 g, 1.54 mol), and stirring was continued until the tosyl chloride had completely dissolved. The reaction flask was then stoppered and placed in a refrigerator for 70 h. The reaction mixture was divided in half, with each half being poured over 1500 ml of crushed ice and extracted five times with 200 ml of ether. The total ether extracts were each washed three times with 200 ml of 1:1 HCl/H_2O and two times with 200 ml of salt water. The combined ether extracts were dried over $K_2CO_3/MgSO_4$ and concentrated by vacuum until no further weight loss occurred. The final product was 174 g (95%) of **7** as a light tan colored oil that was stored at 10 °C as a solution in 100 ml of dry THF: ir (film) 1190, 1175 cm^{-1} (s, SO_2OR), no O–H stretch absorption.

***N*-(1-Ethylpropylidine)cyclohexylamine (8).**[24] A solution of 3-pentanone (86.1 g, 1.0 mol), cyclohexylamine (99.8 g, 1.0 mol), and toluenesulfonic acid (100–200 mg) in 250 ml of dry benzene was refluxed in a Dean-Stark separator until 17.5 ml of H_2O was liberated (6 days). The benzene was removed, and the crude ketimine was distilled, yielding **8** (142 g, 85%): bp 100–101.5 °C (24 mm) [lit.[24] bp 102–104 °C (26 mm)]; ir (film) 1660 cm^{-1} (s, C=N), no absorption at the N–H or C=O stretching frequencies; NMR ($CDCl_3$) δ 1.06 (t, 3 H, J = 8 Hz), 1.2–1.9 (m, 10 H), 2.23 (q, 2 H, J = 8 Hz), 3.3 (m, 1 H, C=NCH).

Anal. Calcd for $C_{11}H_{21}N$: C, 78.97; H, 12.65; N, 8.37. Found: C, 77.91; H, 12.35; N, 8.08.

4,6-dimethyl-7-octen-3-one (10). A 260-ml solution of ethylmagnesium bromide in THF (2.67 M, 0.696 mol) was added dropwise to a stirred sample of the ketimine **8** (117 g, 0.696 mol) at room temperature followed by heating at reflux for 8 h. The reaction mixture was then cooled to 5 °C and a THF solution (100 ml) of the tosylate **7** (1.67 g, 0.696 mol) was added dropwise, followed by stirring at room temperature for 45 h, and at reflux for 1 h. At the conclusion of the stirring period, a white, milky precipitate had formed which dissolved upon addition of 10% HCl (700 ml, 3 × molar excess). Hydrolysis was continued at reflux temperature for 2.5 h, after which the solution was cooled and the resulting white precipitate was removed by filtration. The filtrate was extracted five times with ether (250 ml), and the combined ether extracts were then washed with 5% $NaHCO_3$ (4 × 250 ml) and salt water (2 × 250 ml). The ether extract was dried over $MgSO_4$, concentrated, and distilled to give pure (99% by GLC) **10** (75.9 g, 71%), bp 81–83 °C (23 mm).

The two diastereomeric forms of **10** were separable by preparative GLC (110 °C; retention times, 17.7 and 19.7 min from injection) and were collected separately for spectral analysis. The data for the second eluted peak are ir (CCl_4) 3080 (s, olefin), 2970 (s), 2935 (m), 2880 (m), 1715 (s, C=O), 1640 (m, C=C), 1460 (m), 1380 (m), 1105 (m), 995 (m, –CH=CH_2), 975 (m), 915 cm^{-1} (s, –CH=CH_2); NMR ($CDCl_3$) δ 0.94–1.12 (two d, one t, 9 H combined, J_d, J_t = 8 Hz), 1.15–1.85 (m, 2 H), 1.9–2.7 (m, 4 H, CH_2=CHC**H**, (CH_3)C**H**COC**H**$_2$$CH_3$, CH_2 q visible at 2.46, J = 8 Hz), 4.85–5.1 (m, 2 H, CH=C**H**$_2$), 5.4–5.8 (m, 1 H, C**H**=CH_2); mass spectrum *m/e* (rel intensity) 154 (13) (M^+), 97 (20), 86 (62), 57 (100), 55 (84). The ir, NMR, and mass spectra of the first eluted peak were nearly identical with those cited above.

Anal (distillate). Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.65; H, 11.59.

4,6-Dimethyl-7,8-epoxy-3-one (11). A sample of freshly opened *m*-chloroperoxybenzoic acid (85%, unassayed, 10% molar excess) was added slowly to a cooled (10–15 °C), vigorously stirred solution of the distilled ketone **10** (56.9 g, 0.369 mol) in 1 l. of dry benzene. Stirring of the mixture was continued for 5 h, while the temperature of the reaction mixture rose slowly to room temperature after removal of the ice bath. GLC analysis of a small aliquot of the reaction mixture indicated that 10–15% of the starting ketone **10** remained; an additional 15 g of peracid was added. Following an overnight stirring period, the mixture was cooled to 10 °C, and the precipitated *m*-chlorobenzoic acid was removed by filtration and washed with several portions of cold benzene. The combined filtrates were washed twice with 200 ml of 10% sodium metabisulfite, three times with 200 ml of 5% Na_2CO_3, and three times with 200 ml of salt water, and dried over $MgSO_4$. GLC analysis indicated that no appreciable amount of starting ketone (**10**) remained.

Preparative GLC (170 °C) of a portion of the benzene solution gave three separable peaks corresponding to the four diastereomeric forms of **11** (11α-δ), with the last two eluted epoxides partially coalesced to one peak. The composition, retention time, and percent of total epoxides for each of the collected fractions follow. Fraction 1: a 40/60

mixture of 11γ and an unidentified ester, 17.1–19.2 min, 41%. Fraction 2: pure 11α, 19.2–20.7 min, 15%. Fraction 3: a mixture of 11β and 11δ, 21.3–23.4 min, 43%. The spectral data for the collected fractions follow.

Fraction 1 (11γ): ir (CCl_4) 3040 (w), 2960 (m), 2920 (m), 1735 (s, OC=O), 1710 cm^{-1} (m, C=O), no C=C stretch absorption; NMR ($CDCl_3$) δ 0.9–2.9, complex; no olefin resonances.

Fraction 2 (11α): ir (CCl_4/CS_2) 3040 (w), 2960 (m), 2920 (m), 2870 (w), 1710 (s, C=O), no C=C stretch absorption, 1450 (m), 1370 (m), 1100 (m), 895 (w), 820 cm^{-1} (w); NMR ($CDCl_3$) δ 0.9–1.15 (two d, one t, 9 H combined), 1.15–2.0 (m, 2 H), 2.0–2.9 (m, 6 H combined); mass spectrum m/e (rel intensity) 170 (2), 128 (7), 96 (11), 71 (3), 57 (100), 55 (18), 41 (11), 29 (26).

Fraction 3 (11β + 11δ): ir (CS_2) 3040 (m), 2960 (s), 2920 (s), 2865 (m), 1710 (s, C=O), 1500–1400 (CS_2 interference), 1370 (m), 1000 (m), 900 (m), 835 (m); mass spectrum m/e (rel intensity) 170 (3), 128 (7), 96 (8), 71 (28), 57 (100), 55 (16), 41 (12), 29 (30).

2,4-Dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane (Multistriatin, 1α–δ). A. Acid-Catalyzed Cyclization of Epoxy Ketone 11. The dried benzene solution of crude epoxy ketone **11** was treated with a benzene solution of $SnCl_4$ (30 ml, 0.43 M, 0.013 mol), and stirring was continued for 20 h. The degree of cyclization and multistriatin isomer ratios were monitored during the reaction by analytical GLC (170 °C) of aliquots (0.5 ml) of the reaction solution, which were worked up according to the procedure given below. Analysis (GLC) of a trial run indicated that complete cyclization occurred in less than 30 min.

The reaction solution was poured over 6 N HCl/ice, and the benzene layer was washed with 5% Na_2CO_3 (3 × 250 ml) and salt water (2 × 250 ml). The above workup procedure produced a white precipitate that was difficult to remove from the organic phase. An improved workup procedure that did not produce this cumbersome precipitate was employed during the synthesis of optically active multistriatin (**1**) (see below). Fractional distillation of the yellow oil of crude ketals through a 25-cm Vigreux column at 6 mm gave four fractions as follows: fraction 1, bp 27–67 °C, 1.41 g, 88% **1** (by GLC); fraction 2, bp 67–82 °C, 36.4 g, >99% **1**; fraction 3, bp 82–91 °C, 2.3 g, 85% **1**; fraction 4, bp 91–96 °C, 1.35 g, 8% **1**. The total yield of multistriatin isomers (1α–δ) was 39.5 g, or 63% from the keto olefin **10**. The retention times and percent of total **1** for 1α–δ separated by preparative GLC (140 °C) of distillate fraction 2 are 1δ, 14.4 min, 57.5%; 1α, 15.3 min, 34%; 1γ, 16.5 min, 7%; and 1β, 18.0 min, 1.5%. The spectral data for the four isomers of multistriatin (**1**) have been previously reported.[2]

Anal (fraction 2). Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.32; H, 10.49.

Preparative GLC (170 °C) of distillate fraction 4 gave (retention time, percent of total fraction 4) multistriatin isomers (1α–δ), 7.2–9 min, 8%; 2,4-dimethyl-5-propionoxytetrahydropyran (**21**) (propionoxy group equatorial), 12.0–12.9 min, 30%; unidentified peaks, 12.9–16.8 min, 54%; 3,5-dimethyl-2-(methylpropionoxy)tetrahydrofuran (**20**), 16.8–17.7 min, 8%. The spectral data for **20** and **21** follow.

21: ir (CCl_4) 2970 (s), 2930 (s), 2870 (s), 2840 (s), 1735 (s, OC=O), 1460 (m), 1380 (m), 1355 (m), 1250 (m), 1175 (br, s, OC=O), 1100 (s), 1075 (s, C–O–C), 1020 (s, C–O–C); 885 cm^{-1} (m); NMR (CS_2)[25] δ 0.97 (d, 3 H, J = 6 Hz, C-4 CH_3), 1.07 [t, 3 H, J = 7 Hz, –OC(=O)CH_2CH_3], 1.09 (d, 3 H, J = 6 Hz, C-2 CH_3), 1.5–1.8 (m, 2–3 H), 2.21 [q, 2 H, J = 8 Hz, –OC(=O)CO_2CH_3], 2.91 (dd, 1 H, C-6 H_{ax}, $J_{gem} = J_{6_{ax}-5_{ax}}$ = 10 Hz), 3.21–3.42 (m, 1 H, C-2 H), 3.67–3.84 (dd, 1 H, C-6 H_{eq}, J_{gem} = 10, $J_{6_{eq}-5_{eq}}$ = 5 Hz), 4.12–4.40 (m, 1 H, C-5 H); mass spectrum m/e (rel intensity) no 186 (M^+), 184, 185 (<1), 171 (3), 112 (36), 99 (15), 97 (29), 68 (24), 57 (100), 55 (13), 45 (12), 43 (75), 41 (23), 29 (57).

20: ir (CCl_4) 2970 (s), 2930 (m), 2880 (m), 1738 (s, OC=O), 1455 (m), 1375 (m), 1350 (m), 1175 (s, OC=O), 1100, 1075 (br, m, C–O–C), 1000 cm^{-1} (w); NMR ($CDCl_3$) δ 0.97 (d, 3 H, J = 8 Hz, $CHCH_3$), 1.13 [t, 3 H, J = 8 Hz, OC(=O)CH_2CH_3], 1.20 (d, 3 H, J = 8 Hz, $CHCH_3$), 1.6–1.85 (m, 2 H), 2.20–2.6 [m, 3 H, q visible, J = 8 Hz, OC(=O)CH_2CH_3], 3.8–4.4 (m, 4 H, C-2 H, C-5 H, CH_2OC=O); mass spectrum m/e (rel intensity) no 186 (M^+), 171 (<1), 112 (14), 99 (71), 70 (19), 69 (11), 57 (46), 55 (25), 43 (100), 29 (35).

B. Thermal Cyclization of 11. The epoxides (11α–δ, ~100 μg each) were separated by preparative GLC as described above and collected in flame-sealed glass collection tubes (12 in. × 1.5 mm o.d.). The collection tubes were placed in an oven at 210 °C; the products were then rinsed from the tubes following the specified reaction time and analyzed by GLC (170 °C). The results given in Table I demonstrate that complete cyclization occurred within 11 h.

C. Epoxidation of 10 with Excess Peroxide Followed by Acid-Catalyzed Ketalization in Situ. A cooled (10–15 °C), vigorously stirred solution of keto olefin **10** (0.6 g, 3.9 mmol) in methylene chloride (10 ml) was treated with 85% m-chloroperoxybenzoic acid (1.0–1.1 g, 30–40% molar excess) and stirred for 5 h while the temperature of the mixture rose slowly to room temperature. The reaction mixture was then treated with two to three crystals of toluenesulfonic acid and heated to reflux for 2 h. The methylene chloride solution was washed with 10% Na_2CO_3, 10% sodium sulfite (2 × 10 ml), 5% Na_2CO_3 (2 × 10 ml), and salt water (2 × 10 ml), and was dried over $MgSO_4$. Preparative GLC (170 °C) of the crude reaction product in methylene chloride gave (retention time, percent of total reaction product) multistriatin isomers, 1α, 1γ, no 1β or 1δ, 7.2–9 min, 41%; tetrahydropyran and furan esters, including **20** and **21**, 12.6–18.0 min, 15%; 4-hydroxy-δ-multistriatin (**15**), 23.7–27.5 min, 21%; 4-hydroxy-β-multistriatin (**16**), 30.6–32.4 min, 23%. The spectral data for **15** and **16** follow.

15: ir (CCl_4) 3580 (m, O–H), 2960 (br, s), 2940 (s), 2880 (s), 1450 (br, m), 1370 (m), 1270 (m), 1180 (s), 1160 (m), 1105 (m), 1045 (s, O–C–O), 1020 (m), 925 cm^{-1} (s); NMR (CS_2)[25] δ 0.78 (t, 3 H, J = 8 Hz, (O–C–O)CH_2CH_3), 0.92 (br, s, 3 H, C-4 CH_3), 1.23 (d, 3 H, J = 8 Hz, C-2 CH_3), 1.25–1.95 (m, 6 H), 3.5–3.75 (m, ≈ 2 H, C-7 H_2), 4.10 (m, 1 H, C-1 H); (Me_2SO-d_6) δ 4.06 (s, 1 H, OH); chemical ionization mass spectrum[26] (CH_5^+) m/e (rel intensity) 187 (18) $(M + 1)^+$, 186 (2) $(M)^+$, 185 $(M - 1)^+$, 169 (100) $(M + 1 - H_2O)^+$, 123 (29), 69 (25).

16: ir (CCl_4) 3580 (m, OH), 2980 (s), 2940 (s), 2880 (s), 1460 (br, m), 1380 (m), 1355 (m), 1340 (m), 1220 (br, m), 1160 (s), 1130 (m), 1110 (m), 1055, 1050 (s, O–C–O), 1030 (s, O–C–O), 980 (m), 935 (s), 900 cm^{-1} (s); NMR (CS_2)[25] δ 0.78 (t, 3 H, J = 8 Hz, (O–C–O)CH_2CH_3), 1.11–1.35 (s, 3 H, C-4 CH_3, overlapping with d, 3 H, C-2 CH_3, J = 8 Hz), 1.3–1.9 (m, 6 H), 3.73 (d, 2 H, J = 3 Hz, C-7 H_2), 4.09 (m, 1 H, C-1 H); (Me_2SO-d_6) δ 4.02 (s, 1 H, –COH); chemical ionization mass spectrum[26] (CH_5^+) m/e (rel intensity) 187 (21) $(M + 1)^+$, 186 (3) $(M)^+$, 185 (10) $(M - 1)^+$, 169 (100) $(M + 1 - H_2O)^+$, 151 (22), 123 (42), 69 (32).

Note: The above procedure was carried out with a variety of acids, including H_2SO_4, H_3PO_3, $HClO_4$, and $SnCl_4$, with results that were qualitatively identical with those cited above. Only the ratio of side products and degree of oxidation varied with the acid used. The procedure cited was chosen to illustrate conditions which led to a maximum of side products.

Synthesis of Optically Active Multistriatin. Resolution of 5 with (+)- and (−)-α-Methylbenzylamine. (+)-α-Methylbenzylamine (13.0 g, 0.1 mol) and **5** (11.0 g, 0.1 mol) were dissolved in 80 ml of boiling acetone and allowed to cool to 20 °C and to stand for 14 h. Crystals were filtered from the acetone, washed with a small volume of ethyl ether, and vacuum dried. The amine salt was recrystallized five times from a minimum volume of acetone. The rate of cooling was controlled by placing the flask containing the hot acetone solution in a Dewar flask which contained water at 55 °C. The yield of the partially resolved amine salt was 2.1 g. This resolution process was repeated with (−)-α-methylamine as the resolving reagent, and 4.5 of the amine salt was obtained.

The free acids were recovered by decomposing the salts with 10 ml of 1 M hydrochloric acid for the (+) amine and 20 ml for the (−) isomer. The aqueous solutions were extracted four times with 15-ml portions of ethyl ether, and the extracts were dried with 4 Å sieves. Evaporation of the solvent gave 1.0 g of S-(+)-**5**, $[\alpha]^{20}D$ +28.8° (c 0.10, hexane), 70% optical purity; the (−) amine extract gave 2.1 g of R-(−)-**5**, $[\alpha]^{20}D$ 24.8° (c 0.42, hexane), 60% optical purity.

Synthesis of (+) and (−) Isomers of Multistriatin (1α–δ). The synthesis of (2R)-multistriatin (1α–δ) from (2S)-(+)-**5** (1.0 g, 70% optical purity) and of (2S)-multistriatin (1α–δ) from (2R)-(−)-**5** (2.1 g, 60% optical purity) was accomplished by the procedure described above (Scheme III). Intermediates were not distilled, and crude reaction products (following workup) were used directly in subsequent reactions. Workup of the final benzene/$SnCl_4$ solutions (35–50 ml) of ketals proceeded as follows. The solutions were washed with 10% NaOH (2 × 10 ml), 10% HCl (2 × 10 ml), 10% Na_2CO_3 (2 × 15 ml), and salt water (2 × 15 ml), dried over $MgSO_4$, and concentrated to give the crude (2R)- and (2S)-multistriatin isomers: (2R)-**1**, 0.73 g, 38% from (S)-(+)-**5**, 89% 1α–δ of total products by GLC (170 °C); (2S)-**1**, 1.87 g, 46% from (R)-(−)-**5**, 87% 1α–δ of total by GLC.

The individual multistriatin isomers (10–80 mg) were separated by preparative GLC (20% FFAP on Chromosorb W AW/DMCS, silanized glass column, 35 ft × 0.375 in. o.d., 120 ml He/min, 170 °C isothermal) and dissolved in n-hexane (Baker reagent grade, distilled) for ORD measurements. The ORD curves for all isomers (1α–δ) were plain curves; the quantitative data are given in Table II.

Determination of the Optical Purity of Synthetic (2R)-(−)- and (2S)-(+)-α-Multistriatin by ^{13}C NMR with the Chiral Shift Reagent Tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III) [Eu(hfc)$_3$]. Racemic (2R)- and (2S)-1α were separated from their respective mixtures of multistriatin isomers by preparative GLC as described above, and prepared for ^{13}C NMR with Eu(hfc)$_3$ in deuteriobenzene as follows: racemic 1α (117 mg),

molar ratio[27] Eu(hfc)$_3$/(2*R*)-1α 0.22, *c* (1α) 0.58 M, 1.2-ml solution in a 12-mm o.d. NMR tube with a vortex plug; (2*S*)-1α (120 mg), molar ratio Eu(hfc)$_3$/(2*S*)-1α 0.29, *c* (2*S*)-1α 2.2 M, 320 μl total solution in a 5-mm o.d. NMR tube; (2*R*)-1α (78 mg), molar ratio Eu(hfc)$_3$/(2*R*)-1α 0.26, *c* (2*R*)-1α 2.5 M, 185 μl total solution in a 5-mm o.d. tube.

The ^{13}C NMR spectra were obtained by pulsed Fourier transform NMR as follows: broad-band (noise modulated) ^{1}H decoupling, pulse width 78 μs, acquisition time 0.8 s, no pulse delay; transients, (racemic 1α) 62K; (2*R*)-1α 232K; (2*S*)-1α 71K. The changes in chemical shifts for the C-1 signals[28] in the presence of Eu(hfc)$_3$ were racemic 1α, $\Delta\delta$ 16.9, $\Delta\Delta\delta$ 1.9 ppm; (2*S*)-1$\alpha\Delta\delta$ 14.9, $\Delta\Delta\delta$ 1.6 ppm.

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Registry No.—(±)-1α, 54815-06-4; (−)-1α, 59014-03-8; (+)-1α, 59014-04-9; (±)-1β, 54832-20-1; (−)-1β, 59014-05-0; (+)-1β, 59014-06-1; (±)-1γ, 54832-21-2; (−)-1γ, 54832-22-3; (+)-1γ, 59014-07-2; (±)-1δ, 59014-08-3; (−)-1δ, 59014-09-4; (+)-1δ, 59014-10-7; (±)-**5**, 50304-40-0; (2*S*)-(+)-**5**, 59014-11-8; (2*R*)-(−)-**5**, 20626-49-7; **6**, 59014-12-9; **7**, 58977-11-0; **8**, 6125-73-1; **10** isomer I, 58977-12-1; **10** isomer II, 58977-13-2; **11**α, 58977-14-3; **11**β, 59014-13-0; **11**γ, 59014-14-1; **11**δ, 59014-15-2; **15**, 58977-15-4; **16**, 59014-16-3; **20**, 58977-16-5; **21**, 58977-17-6; tosyl chloride, 98-59-9; 3-pentanone, 96-22-0; cyclohexylamine, 108-91-8; (+)-α-methylbenzylamine, 3886-69-9; (−)-α-methylbenzylamine, 2627-86-3.

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(26) The chemical ionization mass spectra were run by Dr. J. Henion and his staff at the Department of Chemistry, Cornell University, Ithaca, N.Y. The system was a Finnigan Model 3300 GC-MS, GC Model 9500, interfaced with a Systems Industries 150 computer.
(27) The optimum molar ratio [Eu(hfc)$_3$/1α] for obtaining good enantiomeric separation was determined by previous runs at (E/1α) = 0.024 and 0.14.
(28) The assignment of the ^{13}C signals of 1α–γ will be discussed in a later publication.

Synthesis and Competitive Mechanism of Formation of Phenyl-Substituted 1,2-Azaborolidines and 1-Aza-5-borabicyclo[3.3.0]octanes[1]

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1,5-Diphenyl-1-aza-5-borabicyclo[3.3.0]octane, 1,2-diphenyl-1,2-azaborolidine, and propene were isolated as the major products of the reaction of triethylamine phenylborane with *N,N*-diallylaniline. These compounds were characterized by nuclear magnetic resonance, infrared, mass spectroscopy, and elemental analyses. Two mechanisms were proposed for the formation of propene and 1,2-diphenyl-1,2-azaborolidine. Triethylamine dideuteriophenylborane reacted with *N,N*-diallylaniline to give 3,7-dideuterio-1,5-diphenyl-1-aza-5-borabicyclo[3.3.0]octane, 3-deuterio-1,2-diphenyl-1,2-azaborolidine, and 3-deuteriopropene. These products are consistent with one of the proposed mechanisms, a concerted, facile elimination of propene. This elimination mechanism was supported by model studies of the transition states. Triethylamine phenylborane reacted with *N,N*-di-3-butenylaniline to give 1,2-diphenyl-1-(3-butenyl)-2-hydroazaboracyclohexane and 1,6-diphenyl-1-aza-6-borabicyclo[4.4.0]decane. No butene gas was eliminated, giving further support for the proposed mechanism. Several substituted derivatives of 1,5-diphenyl-1-aza-5-borabicyclo[3.3.0]octane and 1,2-diphenyl-1,2-azaborolidine were also prepared and characterized.

Previous studies[2,3] in our laboratories showed that the reaction of triethylamine phenylboranes with tertiary diallylamines yielded a new class of compounds, 1-aza-5-borabicyclo[3.3.0]octanes, as well as 1,2-azaborolidines. The formation of the azaborolidines was thought to occur with elimination of an allyl group from nitrogen, although no attempt was made to trap the evolved propene in the earlier work. We would now like to report mechanistic studies on this