Relative Stereochemistry of Multistriatin (2,4-Dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane)

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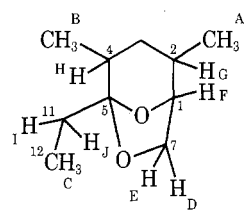
The stereochemical assignments for the C-2 and C-4 methyl groups in the four isomers of multistriatin (2,4-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane, 1α–1δ) were determined on the basis of chemical and spectrometric data. The stereospecific addition of *cis*-2-buten-1-ol to 2-methyl-1-penten-3-one (3) to give 1α and 1γ, and a similar addition of *trans*-2-buten-1-ol to 3 to give 1δ established the relative stereochemistry at C-2. Assignment of the C-2 and C-4 methyl group signals in the NMR spectra based on deuterium-labeled 1α–1δ and comparisons of chemical shift data led to the assignment of the relative stereochemistry at C-4. These assignments were supported by acid-catalyzed equilibration of 1α and 1γ and of 1β and 1δ. α-Multistriatin (1α) is one of the three essential components of the aggregation pheromone of the European elm bark beetle.

The bicyclic ketal α-multistriatin is one of three essential components of an aggregation pheromone for the European elm bark beetle, *Scolytus multistriatus* (Marsham), which is the principal vector of Dutch elm disease in the United States. In earlier work[1] we established the gross structure of multistriatin (1) and demonstrated that a mixture of α-multistriatin, 4-methyl-3-heptanol, and α-cubebene elicits aggregating behavior similar to that observed in the mass attack of *S. multistriatus* on beetle-infested elm trees.



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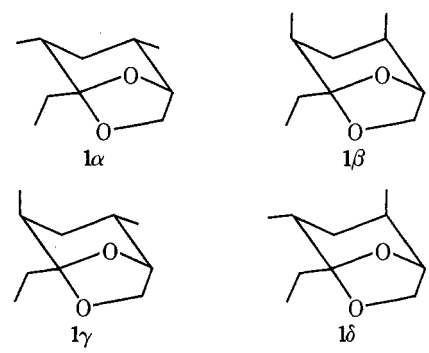
This pheromone was isolated from the air surrounding virgin female beetles boring in American elm (*Ulmus americana*) logs and is a potentially useful agent for monitoring and controlling beetle populations. The isolation procedure yielded two isomers of multistriatin, the biologically active α isomer (1α) and the inactive β form (1β). In addition to the two naturally occurring forms, two additional isomers, γ (1γ) and δ (1δ), are possible.

As part of a continuing study of the relationship between molecular structure and biological activity, we investigated the relative stereochemistry of the four multistriatin isomers, and in this report we provide evidence for the structural assignments of 1α–1δ.

The previously reported nonstereospecific synthesis of multistriatin gave four isomers (1α:1β:1γ:1δ 34:1:7:58) on GLC fractionation.[1] These isomers are characterized by



1α 1β 1γ 1δ

their MS, ir, and NMR spectra and by their gas chromatographic properties. The MS data for 1α–1δ exhibit no significant qualitative variations and only minor quantitative differences. Similarly, the ir data for 1α–1δ exhibit only minor variations at characteristic absorptions associated with CH, CC, and CO stretching frequencies. The four NMR spectra summarized in Tables I and II all show downfield signals for the three protons H_D, H_E, and H_F, a six-proton methylene envelope, and upfield signals for the three methyl groups. As shown in Figure 1, the isomer pair 1α,1γ clearly differs from the 1β,1δ pair in the patterns observed for the C-7 methylene protons, H_D and H_E. In the 1α and 1γ spectra, the two protons appear as two separate signals at approximately 3.7 (H_D) and 3.9 (H_E) ppm, respectively, whereas in 1β and 1δ both signals are observed at 3.9 ppm.

A stereospecific synthetic approach to the multistriatin isomers provided direct chemical evidence for the stereochemistry at C-2 relative to the bicyclic ketal ring system. The thermal addition of α,β-unsaturated aldehydes and ketones to α,β-unsaturated alcohols has been used as a one-

Table I
NMR Chemical Shifts (δ) for Multistriatin Isomers

Isomer	Multistriatin protons, chemical shifts[a] A	B	C	D	E	F
1α	0.81 (3 H, d)	0.81 (3 H, d)	0.94 (3 H, t)	3.68 (1 H, ddd)	3.89 (1 H, dd)	4.20 (1 H, m)
1β	1.24 (3 H, d)	1.10 (3 H, d)	0.93 (3 H, t)	3.85 (2 H, m)		4.26 (1 H, m)
1γ	0.80 (3 H, d)	1.01 (3 H, d)	0.92 (3 H, t)	3.65 (1 H, ddd)	3.94 (1 H, d)	4.19 (1 H, m)
1δ	1.15 (3 H, d)	0.81 (3 H, d)	0.94 (3 H, t)	3.85 (2 H, m)		4.22 (1 H, m)

[a] d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, m = multiplet.

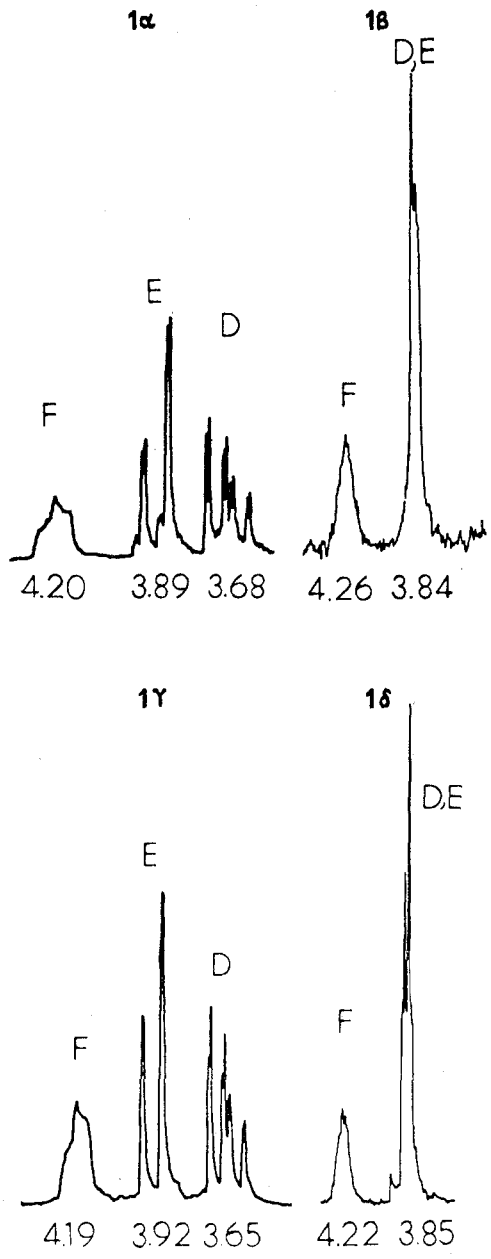
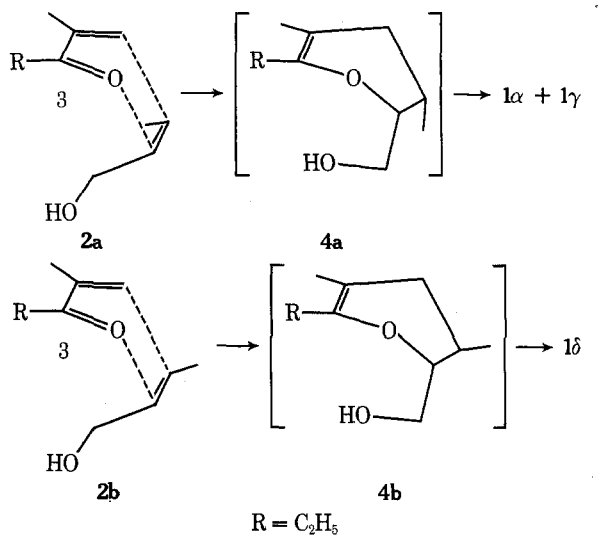


Figure 1. NMR spectra of protons D, E, and F for 1α, 1β, 1γ, and 1δ.

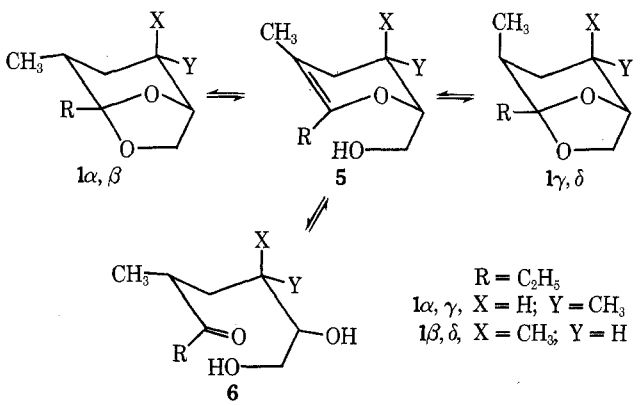
step synthesis of the dioxabicyclo[3.2.1]octane ring system.[2-4] We adopted a similar approach by adding 2-buten-1-ol (**2**) to 2-methyl-1-penten-3-one (**3**). Toluene solutions of the cis isomer (**2a**) and **3** and of the trans isomer (**2b**) and **3** were each heated to 270–290°, and the distribution of 1α–1δ was determined by preparative GLC, NMR, ir, and MS analysis. The results clearly showed that the addition of the cis alcohol (**2a**) to **3** gave 1α and 1γ (2:1) with the virtual exclusion of the 1β, 1δ isomer pair. However, when **2a** was replaced with the trans alcohol (**2b**), 1δ was formed with only trace quantities of 1α, 1γ, or 1β.

A one-step cycloaddition of **2a** or **2b** to **3** to give a dihydropyran intermediate (**4a** or **4b**) with subsequent ketal formation explains the stereospecificity observed in the formation of the multistriatin isomers and is consistent with previous findings associated with this type of reaction.[5,6] The stereospecific cycloaddition of **2a** to **3** should



give **4a**, and under the reaction conditions, ring closure would lead to products 1α and 1γ. Thus the C-2 methyl groups in 1α and 1γ must exist in the endo configuration. Similarly, the addition of **2b** to **3** would yield the 1β,1γ isomer pair, and the C-2 methyl groups would have the exo configuration. The failure to isolate 1β from the reaction mixture is probably related to the relative instability of this isomer.

Acid-catalyzed hydrolysis of the ketal to the keto glycol **6** via the dihydropyran intermediate **5** epimerizes the C-4 asymmetric center, leaving the configuration of C-2 unchanged. The result is that isomers with the same relative



configuration at C-2 are interconverted, whereas those with different configurations at C-2 are not. On equilibration in dilute phosphoric acid, GLC-purified isomer 1α yielded a 80:20 mixture of 1α and 1γ, but no 1β or 1γ; under the same conditions, pure isomer 1γ gave an identical equilibrium mixture. Similarly, equilibrating either 1β or 1γ yielded

Table II
NMR Coupling Constants for Multistriatin Isomers (Hz)

Isomer	J_{AG}	J_{BH}	$J_{CI,CJ}$	J_{DE}	J_{DF}	J_{EF}	J_{GD}
1α	7.0	7.0	7.0	7.0	5.0	0.8	0.8
1β	7.0	7.0	7.0	7.0[a]	5.0[a]	0.0[a]	0.0[a]
1γ	6.6	6.8	7.0	7.2	5.0	0.0	0.8
1δ	7.0	7.0	7.0	7.0[a]	5.0[a]	0.0[a]	0.0[a]

[a] Calculated.

a 95:5 mixture of 1γ and 1β with no 1α or 1γ. If C-4 is epimerized during the equilibration step, then isomers 1α and 1γ have one configuration at C-2, and 1β and 1δ have the opposite configuration at C-2.

The assumption that enolization occurred on C-4 and C-11 was verified by D–H exchange data. In the D–H exchange experiments, the equilibrating conditions were reproduced with D_3PO_4, and the mass spectrum of each isomer was recorded. In the NMR spectra, D–H exchange was accompanied by collapse to singlets of the C-12 methyl group triplet and *one* of the doublets associated with the C-2 and C-4 methyl groups. In the mass spectra, a molecular ion peak at *m/e* 173 and peaks at *m/e* 130 and 59, which were assigned to P − CH_3CDCH_2 and $CH_3CD_2CO^+$, respectively, point to the incorporation of one D atom at C-4 and two at C-11.

The differences in isomer ratios for the 1α,1γ pair and the 1β,1δ pair lend additional evidence for the stereochemical assignments. If we assume that the pyran ring exists primarily in the chair conformation, the C-2 endo methyl group is equatorial, with the C-4 group either axial or equatorial in the 1α,1γ isomer pair. In this case, both the equatorial–equatorial and the equatorial–axial isomers are relatively unhindered, and the 1α:1γ isomer ratios of 4:1 in equilibration and 2:1 in the stereospecific synthesis are consistent with these assignments. When the C-2 methyl group is exo as in the 1β,1δ isomer pair, the two methyl groups must exist either in a relatively unhindered axial–equatorial configuration or in the hindered axial–axial configuration. In the exo,exo isomer, the 1–3 axial–axial interaction could force the pyran ring into a boat conformation; however, the exo,exo isomer in either conformation should be significantly less stable than the exo,endo isomer. This difference in isomer stability is reflected in the 1:20 ratio observed on equilibration for the 1β,1δ isomers and the failure to observe 1β in the stereospecific synthesis. This evidence supports the assignment of the endo configuration at C-2 in 1α and 1γ and the exo configuration at C-2 for 1β and 1δ and also leads to the prediction that in 1β the methyl group is exo at C-4 and the corresponding C-4 methyl group in 1δ is endo.

An examination of the NMR shift data for the four isomers provides additional evidence for the assignments of the relative stereochemistry in the multistriatin isomers. Attention was focused on the two upfield doublets assigned to the C-2 and C-4 methyl groups, H_A and H_B, respectively. The signals for the two methyl groups could be distinguished by comparing spectra for the 4,11,11-trideuteriomultistriatin isomers in which the C-2 methyl group (H_A) appears as a doublet and the C-4 methyl group (H_B) and C-12 protons (H_C) give singlets. As shown in Table I, the exo C-2 methyl groups in 1β and 1δ and the C-4 exo methyl group in 1β exhibit chemical shifts of 1.15, 1.24, and 1.10 ppm, respectively, whereas the endo C-2 methyl groups in 1α and 1γ and the endo C-4 group in 1δ have shift values of 0.81, 0.80, and 0.81 ppm, respectively. The result of this comparison is that in all cases where the methyl group configuration is known or has been predicted, the endo methyl group signals are 0.29–0.44 ppm upfield from the exo methyl group signals. The pattern appears to be maintained in the case of the C-4 asymmetric center in the 1α,1γ pair in which the methyl group is endo in one isomer and exo in the other. Since the chemical shift for H_B is 0.81 ppm in 1α and 1.01 ppm in 1γ, the C-4 methyl group is assigned the endo configuration in 1α and the exo configuration in 1γ.

Interpretation of the observed splitting patterns for H_D and H_E was assisted by the use of spin–spin simulation experiments. As shown in Figure 1, the 1α,1γ pattern for protons H_D, H_E, and H_F exhibits an overall ABX form with a very small H_E–H_F coupling due to the dihedral angle of approximately 90° between these two protons.[7] The additional 0.8-Hz splitting in the H_D signal could be the result of long-range coupling between H_D and H_G.[8] This hypothesis was tested by simulating the H_D, H_E, H_F portion of the spectrum for 1α with chemical shift data from Table I, coupling constants from Table II, and a chemical shift value of 1.50 ppm for H_G. The simulated pattern for protons H_D and H_E agreed with the observed signals with respect to line position and relative line intensity. A second spin–spin simulation experiment demonstrated that the departure of the H_D, H_E pattern in 1β and 1δ from the pattern observed in the 1α,1γ isomer pair results from two factors. The coupling constants and chemical shift values for isomers 1α and 1γ were used as starting values for the 1β,1δ simulated spectra. When the chemical shift for H_D was increased by increments from 3.68 to 3.94 ppm the resulting spectra all contained more lines than the observed 1β,1δ spectra. When the J_{DG} value was changed from 0.8 to 0 Hz and the procedure repeated, the simulated spectrum duplicated the observed H_D, H_E pattern at an H_D value of 3.90 ppm. Thus, the observed differences in the H_D, H_E signals for the 1α,1γ and the 1β,1δ isomer pairs appear to result from a change in the J_{DG} value and in the chemical shift for H_D rather than from changes in the coupling of H_D, H_E, and H_F. This evidence indicates that the ring system conformation about C-1 and C-7 is relatively unchanged in the four isomers. Also the presence of long-range coupling in 1α,1γ and the absence of similar coupling in 1β,1δ provides spectral evidence for the relative configuration of the C-2 methyl group. The observed 0.8-Hz splitting in the H_D signal of 1α and 1γ could be the result of four-bond "W" coupling between H_D and H_G when the C-2 methyl group is in the endo configuration; and, conversely, this coupling would not be present in 1β and 1δ when the C-2 methyl group is exo.

The relative stereochemistry of the multistriatin isomers with respect to the C-2 and C-4 methyl groups can now be summarized as follows: 1α, 2 endo, 4 endo; 1β, 2 exo, 4 exo; 1γ, 2 endo, 4 exo; 1δ, 2 exo, 4 endo. Recent experiments have demonstrated that the naturally occurring 1α is optically active, and studies are currently in progress to establish the absolute configuration of carbons 2 and 4 in 1α and to measure the biological activity of the geometric isomers of multistriatin.

Experimental Section

Mass spectra were recorded on an Hitachi RMU-6E; the ir spectra in carbon tetrachloride solution on a Perkin-Elmer 621; and the Fourier transform ^1H NMR spectra in deuteriochloroform solution on a Varian XL-100 (unless otherwise indicated) as δ values with tetramethylsilane as an internal reference. The determination of coupling constants was assisted by the Varian 994029-B spin–spin simulation program and the 620 L computer. Preparative GLC was performed on a Varian Aerograph Series 2700 with glass columns containing 5% SE-30 on 60/80 DMCS Chromosorb G (10 mm × 3.6 m, He 100 ml/min, 140°), 5% Carbowax 20M on 60/80 DMCS Chromosorb G (6 mm × 6 m, He 60 ml/min), and 20% FFAP on 45/60 DMCS Chromosorb W (10 mm × 9.6 m, He 100 ml/min, 175°).

Nonstereospecific Synthesis of 1α–1δ. Compounds 1α–1δ were synthesized according to the method of Pearce et al.[1] The distillate (81–84°, 22 mm) was fractionated by GLC on Carbowax 20M at 140°, and four completely resolved peaks corresponding to 1δ, 1α, 1γ, and 1β with retention times of 14.4, 15.3, 16.5, and 18.0 min and relative areas of 58:34:7:1 were collected for ir, MS, and NMR analysis. The NMR data are summarized in Tables I and II, and a partial listing of the MS and ir data is as follows.

1α: MS *m/e* (rel intensity) 57 (100), 128 (9), 170 (4, M^+); ir 2960, 2930, 2880, 1455, 1375, 1358, 1172, 1122, 1030, 913, 894 cm^{-1}.

1β: MS *m/e* (rel intensity) 57 (100), 128 (10), 170 (5, M^+); ir 2980, 2950, 2890, 1465, 1380, 1360, 1235, 1060, 915, 910 cm^{-1}.

1γ: MS *m/e* (rel intensity) 57 (100), 128 (9), 170 (4, M^+); ir 3000, 2980, 2930, 1460, 1380, 1180, 1165, 1045, 1035, 1025, 905 cm^{-1}.

1δ: MS *m/e* (rel intensity) 57 (100), 128 (10), 170 (5, M^+); ir 2970, 2940, 2890, 1460, 1380, 1050, 915, 895 cm^{-1}.

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

Equilibration of 1α–1δ. A GLC-purified sample of 1α (1 mg) was refluxed in a mixture of 0.5 ml of 1 M phosphoric acid and 0.5 ml of tetrahydrofuran (THF) for 48 hr. The solution was saturated with sodium chloride, and the THF layer was removed, dried with anhydrous sodium carbonate, and fractionated by GLC as previously described. Reaction products were identified by GLC retention times and ir spectra of the GLC fractions. This procedure was repeated for 1β, 1γ, and 1δ.

D–H Exchange in 1α–1δ. The reaction product of the nonstereospecific synthesis (50 mg) was refluxed in a mixture of 2.5 ml of 1 M deuteriophosphoric acid and 2.5 ml of THF for 48 hr. The reaction product was separated by preparative GLC, and the mass spectra of the individual fractions with retention times corresponding to 1α–1δ were recorded. Each compound gave characteristic MS peaks at *m/e* 59, 130, and 173. To obtain 1β in sufficient quantities for NMR experiments, the ketal mixture (1 g) was refluxed for 3 days in 5 ml of 1 M deuteriophosphoric acid and 5 ml of THF, and the reaction product was fractionated on the FFAP column with retention times of 35.6, 41.6, 44.0, and 47.6 min for 1δ, 1α, 1γ, and 1β, respectively.

NMR Spectra of Trideuterio-1α–1δ. The NMR spectra were recorded for each of the deuterium-labeled isomers 1α–1δ; however, in 1α the signals at 1.0 ± 0.2 were not clearly resolved. The spectrum of 1α in carbon tetrachloride solution was subsequently recorded in the presence of freshly sublimed d_{27}-tris(2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-2,5-octanedione)europium(III). Spectra were recorded at 1α concentrations of 0.18, 0.12, 0.06, and 0.05 *M* with a constant shift reagent concentration of 0.006 *M*. At a 1α concentration of 0.06 *M*, all lines in the region of interest were clearly resolved.

Preparation of *cis*-2-Buten-1-ol (2a). The semihydrogenation of 2-butyn-1-ol (10 g) was performed in a Parr hydrogenation apparatus at 1–7 lb and 27° with methanol (260 ml) as the solvent and 5% palladium on barium sulfate (260 mg) poisoned with synthetic quinolone (260 mg) as the catalyst.[9,10] Distillation of the product gave **2a** (7.1 g, 71%): bp 56° (40 mm); NMR 1.95 (3 H, dd), 4.22 (2 H, m), 5.74 ppm (2 H, m), recorded on a Varian A-60. GLC analysis of the reduction products on Carbowax 20M at 120° gave resolved peaks for the cis and trans isomers **2a** and **2b** and on the basis of peak areas indicated a cis/trans ratio of 98:2.

Preparation of 2-Methyl-1-penten-3-one (3). A solution of paraformaldehyde (80 g, 2.6 mol), dimethylamine hydrochloride (224 g, 2.6 mol), and 3-pentanone (210 g, 2 mol) was refluxed for 3 hr in 400 ml of ethanol (95%) with 5 ml of hydrochloric acid.[11] Neutralization with potassium carbonate (450 g) followed by workup and subsequent methylation with methyl iodide (284 g, 2 mol) gave 480 g of a white quaternary ammonium salt. The salt was dissolved in 1 l. of water and stirred with 200 ml of ethyl ether and 200 ml of 4.3 *M* potassium hydroxide for 2 hr at room temperature.[12] The ether layer was replaced with a fresh 200-ml portion, and a second 200-ml aliquot of potassium hydroxide solution was added. Stirring was continued for an additional 2 hr and the ether was removed. The water was extracted twice with additional 200-ml portions of ether, and the combined extracts were dried over calcium sulfate. The ether was evaporated, and the product was distilled twice through a Vigreux column, yield 93.4 g (56%) of **3**: bp 37–38° (30 mm); NMR 1.10 (3 H, t), 1.88 (3 H, s), 2.70 (2 H, q), 5.74 (1 H, m), 5.94 ppm (1 H, d).

Stereospecific Synthesis of Multistriatin (1α and 1γ). A solution of **3** (6.8 g, 70 mmol), **2a** (5.8 g, 70 mmol), and 75 mg of hydroquinone in 7.5 ml of toluene was heated at 270–290° for 48 hr. The thermal additions were performed at autogenous pressure in glass tubes (6 mm × 60 cm, filled to ⅓ capacity), which were sealed under nitrogen and rocked continuously during the reaction. Vacuum distillation of the reaction product in a micro short path apparatus yielded three fractions; A, 30–55° (bath temperature) (1 mm); B, 80–100° (0.6 mm); and C, 80–100° (0.1 mm). GLC analysis on Carbowax 20M and NMR spectra of major components indicated that A contained toluene and **2a** (80% recovered), B contained a mixture of ketal isomers, and C contained only small amounts of the ketal isomers. Preparative GLC of fraction B on SE-30 gave a cluster of peaks between 17.6 and 25.6 min, which were collected and rechromatographed on Carbowax 20M at 140° for analytical determinations or on FFAP for large-scale purification. Peaks corresponding to 1α–1δ were collected, if present, and their identities verified by MS, NMR, and ir spectra. The purification sequence gave fractions corresponding to 1α and 1γ (2:1) with a total yield of 580 mg (5%). Yields of 1β and 1δ were less than 5% of the 1α + 1δ yield.

Stereospecific Synthesis of Multistriatin (1δ). The preceding procedure was repeated with **2a** being replaced with *trans*-2-buten-1-ol (**2b**). The purification scheme gave a major fraction (570 mg, 5%) with chromatographic and spectrometric properties corresponding to 1δ. Fractions corresponding to 1α, 1γ, and 1β were less than 5% of the 1δ yield.

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Registry No.—1α, 54815-06-4; 1β, 54832-20-1; 1γ, 54832-21-2; 1δ, 54832-22-3; **2a**, 4088-60-2; **2b**, 504-61-0; **3**, 25044-01-3; 2-butyn-1-ol, 764-01-2; 3-pentanone, 96-22-0.

References and Notes

(1) In a preliminary communication, G. T. Pearce, W. E. Gore, R. M. Silverstein, J. W. Peacock, R. A. Cuthbert, G. N. Lanier, and J. B. Simeone, *J. Chem. Ecol.*, **1**, 115 (1975), we reported that the major reaction product corresponded to the natural inactive isomer. We have since discovered that the natural isomer 1β isomerizes to 1δ on standing in $CDCl_3$ (100% D) and have determined that the natural inactive isomer corresponds to the least abundant synthetic isomer.
(2) C. W. Smith, D. G. Morton, and S. A. Ballard, *J. Am. Chem. Soc.*, **73**, 5270 (1951).
(3) Y. Naya and M. Kotake, *Tetrahedron Lett.*, 2459 (1967).
(4) G. W. Kinzer, A. F. Fentiman, T. F. Page, R. L. Foltz, J. P. Vite, and G. B. Pitman, *Nature (London)*, **221**, 477 (1969).
(5) For a review see J. Hamer, "1,4-Cycloaddition Reactions", Academic Press, New York, N.Y., 1967, p 217.
(6) A. Devaquet and L. Salem, *J. Am. Chem. Soc.*, **91**, 3793 (1969).
(7) R. M. Silverstein, R. G. Brownlee, T. E. Bellas, D. L. Wood, and L. E. Browne, *Science*, **159**, 889 (1968).
(8) Y. Gaoni, *J. Chem. Soc. B*, 382 (1968).
(9) R. L. Augustine, "Catalytic Hydrogenation", Marcel Dekker, New York, N.Y., 1965, p 69.
(10) L. F. Hatch and S. S. Nesbitt, *J. Am. Chem. Soc.*, **72**, 727 (1950).
(11) H. O. House, D. J. Reif, and R. L. Wasson, *J. Am. Chem. Soc.*, **79**, 2490 (1957).
(12) A. C. Cope and E. R. Trumbull, *Org. React.*, **11**, 317 (1960).