°C for the threo acid and mp 115 °C for the erythro isomer. Stereoisomeric purity of **6** was shown by elution of a single peak on GLC under conditions that separated the (5*RS*,6*SR*) and (5*RS*,6*RS*) isomers, obtained by Collins oxidation of **6** and reduction of the resulting ketone by $NaBH_4$.

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Stereocontrolled Synthesis of α-Multistriatin, an Essential Component of the Aggregation Pheromone for the European Elm Bark Beetle

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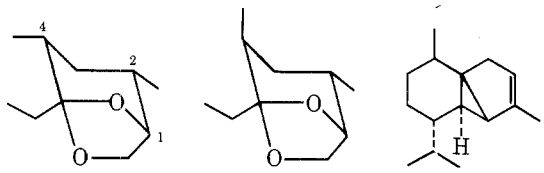
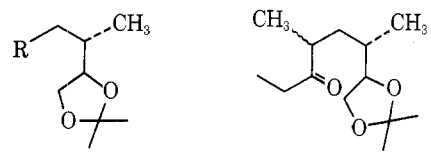
A practical stereocontrolled synthesis of an 85:15 equilibrium mixture of α- and γ-multistriatin (**1**) in an overall yield of 73% is described. α-Multistriatin is one of the three essential components of the aggregation pheromone of the European elm bark beetle. The dioxolane **3** which is available in 90% yield from (*Z*)-2-butene-1,4-diol in both the racemic and enantiomeric forms is converted as the racemate to the iodide **5** and the latter used in the alkylation of the anion of 3-pentanone. Hydrolytic cleavage of the resulting acetonide **6** furnishes the racemic multistriatins in 80% yield from **3**. The use of optically active **3** in this synthesis should furnish the as yet unknown absolute configuration of the natural pheromone.

The aggregation pheromone for the European elm bark beetle, *Scolytus multistriatus* (Marsham), which is the principal vector of Dutch elm disease in the United States, has recently been characterized as a three-component mixture by Silverstein et al.[1] One of the active components has been named α-multistriatin by these authors and has been assigned structure **1**.[2] The other two components are (−)-4-methyl-3-heptanol and (−)-α-cubebene (**2**). The first two components are beetle-produced pheromones, the third a host-produced synergist. The possible uses of a mixture of the three as a control of the elm bark beetle makes α-multistriatin an interesting target for chemical synthesis.



1α **1γ** **2**



3, R = OH
4, R = tosyl
5, R = I

6

Of the two previous syntheses by Silverstein and associates the first, a nonstereospecific approach, served to elucidate and confirm the structure of the molecule; the second was designed to prove its stereochemistry. Although stereocontrolled, it proceeded in less than 2.5% overall yield.[2]

The synthesis reported in this paper yields multistriatin as an 85:15 mixture of α and γ isomers (as does that of Silverstein et al.[2]) in an overall yield of 73% from commercially available (*Z*)-2-butene-1,4-diol. The crucial step is the alkylation of 3-pentanone with the iodide **5**, which possesses the correct threo configuration at C-1 and C-2 of both α- and γ-multistriatin.[3] The iodide **5** was obtained in quantitative yield by classical procedures from the dioxolane **3**. The synthesis of the latter in four steps in 90% yield is described in the preceding paper.[4,5] The alkylation reaction of 3-pentanone with the iodide **5** could be accomplished in low yield via the pyrrolidine enamine,[6] or the magnesium salt of the *tert*-butylimine.[7] The preferred method was reaction of the enolate (5 equiv; prepared from the ketone with lithium diisopropylamide) and the iodide in THF for 3 days at room temperature. This method afforded approximately 85% of the mixture of diastereomeric ketones **6**, and 15% of recovered iodide. The acetonide grouping was removed and the molecule cyclized by treatment with 1 N HCl in 2:1 acetonitrile–H_2O for 18 h, which provided multistriatin (**1**) in quantitative yield in an 85:15 ratio of α and γ isomers, shown by ^1H NMR at 270 MHz and GLC to be identical with the equilibrium mixture obtained by Silverstein et al.[2]

That no detectable amounts of the β or δ isomers were formed in this sequence of reactions attests to the stereospecificity of the epoxide opening reaction with dimethyllithium cuprate,[4,5] a key reaction in the synthesis of the dioxolane **3**.

Since this compound has been obtained in optically active form of known absolute configuration,[4] this synthesis also constitutes a total synthesis of optically active α- and γ-multistriatin. Completion of the synthesis with optically active **3** will at the same time establish the as yet unknown absolute configuration of the natural pheromone.

Experimental Section

Ir spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Liquid samples were run as a thin film between NaCl plates. NMR spectra were determined as solutions in $CDCl_3$ with Me_4Si as an internal standard. Chemical shifts are reported in δ, coupling constants (*J*) are reported in hertz; the abbreviations s, d, t, q, and m signify singlet, doublet, triplet, quartet, and multiplet, respectively. ^1H NMR spectra were recorded on a Bruker HX-270

(270 MHz) spectrometer in the pulsed Fourier transform mode. ^{13}C NMR spectra were recorded on a Bruker HX-90E spectrometer operating at 22.63 MHz in the pulsed Fourier transform mode. Free induction decay data were accumulated and processed with a Nicolet 1089 computer. Low-resolution mass spectra were determined using a Finnigan 1015 quadrupole mass spectrometer equipped with VPC, gas and solid probe inlets; the data were recorded and processed by a Systems Industries Computer Interface System/150, and plotted as bar graphs. High-resolution mass spectra were determined on an AEI MS-9 spectrometer fitted with a PDP-8/I computer system for data analysis. High-pressure liquid chromatography was carried out using Quantum Industries TLC grade silica gel (no binder) in glass columns. Separation of multistriatin isomers was carried out using an F and M Model 400 gas chromatograph with a 6 ft × 0.125 in. glass column containing 1.5% Carbowax 20M on 100/120 Chromosorb G at 80 °C.

(2′*RS*,4*SR*)-2′-(2,2-Dimethyl-1,3-dioxacyclopent-4-yl)-1′-propyl Tosylate (4). To a solution of 503.5 mg (3.14 mmol) of the acetonide alcohol **3** in 8 ml of pyridine, cooled to 0 °C, was added 1.1996 g (6.3 mmol) of tosyl chloride and the solution stirred at 0 °C for 2 h and then at room temperature for 3 h. Cold H_2O (50 ml) was added and the liquid extracted with 4 × 35 ml of ether. The ether layers were combined, washed with 2 × 35 ml of 5% HCl and 3 × 50 ml of saturated $NaHCO_3$, and dried over $MgSO_4$. Evaporation of the ether gave 978.2 mg (99%) of an oil that was 99% pure by NMR. This material was thermally unstable when kept neat at room temperature, and was therefore used immediately in the next reaction. ^1H NMR δ 7.60, AA′BB′, 4 H (aromatic protons); 4.03, m, 1 H (CHO); 3.95, d, J = 6.5 Hz, 2 H (CH_2OTs); 3.91, m, 1 H ($OCHCH_2O$); 3.60, t, J = 6.7 Hz, 1 H ($OCHCH_2O$); 2.45, s, 3 H (CH_3Ar–); 1.98, septet, J = 6.5 Hz, 1 H (CH_3CH); 1.32, s, 3 H (acetonide CH_3); 1.28, s, 3 H (acetonide CH_3); 0.95, d, J = 6.5 Hz, 3 H (CH_3CH). ^{13}C NMR δ 144.8, s (para C); 132.9, s (sulfur-bearing C); 129.9, d (meta C's); 127.9, d (ortho C's); 108.8, s (C-2 of dioxolane); 76.2, d (C-4 of dioxolane); 72.1, t (C-1 of propyl); 67.1, t (C-5 of dioxolane); 36.0, d (C-2 of propyl); 26.2, q (methyl of dioxolane cis to alkyl chain); 25.2, q (methyl of dioxolane trans to alkyl chain); 21.6, q (tosyl methyl); 11.8, q (C-3 of propyl). Ir 1361, 1186 (SO_2OR); 971; 820 cm^{-1} (para-disubstituted benzene). Mass spectrum (10% cutoff) m/e 299, 1.9% ($M^+ - CH_3$); 172, 65% ($TsOH^+$); 155, 10% (Ts^+); 107, 44%; 91, 100% ($PhCH_2^+$); 65, 56%; 57, 55% ($CH_3COCH_2^+$); 43, 14% ($CH_3C{\equiv}O^+$).

(2′*RS*,4*SR*)-2′-(2,2-Dimethyl-1,3-dioxacyclopent-4-yl)-1′-iodopropane (5). A solution of 394.7 mg of the tosylate **4** in 5 ml of distilled acetone and 502.3 mg of NaI was stirred for 18 h, and the resulting precipitate filtered. An additional 201.3 mg of NaI was added, and the mixture stirred for 30 more h, after which it was filtered, and the filtrate poured into 50 ml of H_2O and extracted with 4 × 50 ml of ether. The combined layers were washed with 50 ml of 10% Na_2SO_3 and dried over $MgSO_4$, and the ether was evaporated. The resulting pale yellow oil was distilled at 20 mTorr at 55 °C in a microstill to give 340 mg (99%) of a clear oil. The oil decomposed to a black tar when allowed to remain at room temperature in air for 24 h, or upon heating above 60 °C. It could be stored for at least 6 months in hexane over copper wire. ^1H NMR δ 4.08, m, 1 H ($CHOCH_2$); 4.06, m, 1 H (CH_2O); 3.63, m, 1 H (CH_2O); 3.26, d of d, J = 6, 12.4 Hz, 1 H (CH_2I); 3.03, d of d, J = 7.2, 12.4 Hz, 1 H (CH_2I); 1.76, m, 1 H (CH_3CH); 1.41, s, 3 H (acetonide CH_3); 1.34, s, 3 H (acetonide CH_3); 1.09, d, J = 6 Hz, 3 H (CH_3CH). ^{13}C NMR δ 108.6, s (C-2 of dioxolane); 78.3, d (C-4 of dioxolane); 66.8, t (C-5 of dioxolane); 38.3, d (C-2 of propane); 26.3, q (methyl of dioxolane cis to alkyl group); 25.2, q (methyl of dioxolane trans to alkyl group); 16.2, q (C-3 of propane); 10.7, t (C-1 of propane). Ir 2950 (CH); 1490, 1480 (methyls); 1205; 1065 (C–O–C); 862 cm^{-1}. Mass spectrum (20% cutoff) m/e 270, 0.02% (M^+); 255, 38% ($M^+ - CH_3$); 195, 20%; 101, 40% (2,2-dimethyl-1,3-dioxacyclopent-4-yl ion); 43, 100%, ($CH_3C{\equiv}O^+$). High-resolution MS, calcd for $C_8H_{15}IO_2$ ($M^+ - I$), 143.1072; found, 143.1077, 143.1065.

(2′*RS*,4*SR*)-2′-(2,2-Dimethyl-1,3-dioxacyclopent-4-yl)-4′-ξ-methylhept-5′-one (6). To a dry 25-ml flask were added under N_2 0.7 ml (5.0 mmol) of freshly distilled diisopropylamine, 3 ml of dry THF, and a stirring bar. After cooling to −78 °C, 3.75 ml of a 1.3 M n-BuLi solution was added, and the contents of the flask stirred for 30 min. Then 0.52 ml (4.94 mmol) of freshly distilled diethyl ketone in 5 ml of THF was added and the solution stirred for 0.5 h while warming to −40 °C. A solution of 270 mg (1 mmol) of the iodide **5** in 5 ml of THF was added and the solution stirred for 3 days at room temperature. The yellow mixture was then poured into 30 ml of saturated NaCl, and the H_2O layer extracted with 4 × 20 ml of ether. The ether layers were combined, washed with 2 × 50 ml of 10% HCl and 50 ml of saturated $NaHCO_3$, and dried over $MgSO_4$. The ether was evaporated and the residue of 249 mg was chromatographed on 18.6 g of silica gel. Iodide **5** (38.2 mg, 14%) was eluted with 5% EtOAc in hexane. Thereafter 193.8 mg of the desired ketone **6** (84%) was eluted with 8% EtOAc in hexane. This material was a mixture of two diastereomers as shown by NMR, which could not be separated by GLC. A sample was distilled at 90 °C (bath temperature) at 180 mTorr. ^1H NMR δ 4.01, complex q, 1 H (CHO); 3.87, m, 1 H (CH_2O); 3.61, m, 1 H (CH_2O); 2.73, m (C-4′ H); 2.65, m, 1 H (C-2′ H); 2.49, q, 2 H (C-6′ H_2); 1.70, m, 2 H (C-3′ H_2); 1.34, s, 3 H (acetonide CH_3); 1.26, s, 3 H (acetonide CH_3); 1.09, d, J = 7 Hz, 3 H (C-4′ CH_3); 1.05, t, J = 7 Hz, 3 H (C-7′); 0.94, d, J = 7 Hz, 3 H (C-1′). The resonance at δ 0.94 is split into two doublets in a 60:40 ratio separated by less than 2 Hz at 270 MHz; the resonance at δ 1.34 is also so split. Ir 2980–2930 (CH); 1748 (CO); 1374 (CH_3); 1064 (C–O–C); 875–860 cm^{-1}. Mass spectrum (10% cutoff) m/e 228, 0.04% (M^+); 213, 2.7% ($M^+ - CH_3$); 101, 23% (2,2-dimethyl-1,3-dioxacyclopent-4-yl ion); 97, 43%; 57, 100% ($CH_3CH_2C{\equiv}O^+$); 43, 66% ($CH_3C{\equiv}O^+$). High-resolution MS, calcd for $C_{12}H_{21}O_3$ ($M^+ - CH_3$), 213.1491; found, 213.1490.

Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.17; H, 10.31.

(±)-α (and γ-) Multistriatin (2,4-Dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane) (1). To a solution of 150.0 mg (0.66 mmol) of 2′-(2,2-dimethyl-1,3-dioxacyclopent-4-yl)-4′-methylhept-5′-one (**6**) in 2 ml of CH_3CN 1 ml of aqueous 10% HCl was added. The solution was stirred for 18 h at room temperature and then 2 g of NaCl was added to saturation. It was poured into 30 ml of saturated NaCl solution and extracted with 4 × 20 ml of ether. The ether layers were combined and washed with 40 ml of saturated $NaHCO_3$ and dried over $MgSO_4$ and the solvent was removed. This left a clear oil that was distilled in a microstill: 110.2 mg (98%) were collected at bath temperature, 90 °C at 20 Torr. This material was shown to be an 85:15 mixture of α:γ-multistriatin by 270-MHz ^1H NMR and by GLC. The identity of the synthetic material with α-multistriatin was established by the very characteristic NMR, the infrared, and low-resolution mass spectra, all of which were the same as the data published by Silverstein et al.[2] ^1H NMR δ 4.20, m, 1 H (C-1 H); 3.89, d of d, J = 7.0, 0.8 Hz, 1 H (C-7 H); 3.68, d of d, J = 7.0, 5.0 Hz, 1 H (C-7 H); 2.06, m, 1 H; 1.83, m, 1 H; 1.73, q, 2 H (CH_2CH_3); 1.61, m, 1 H; 0.94, t, J = 7.0 Hz, 3 H (CH_2CH_3); 0.81, d, 6 H, J = 7 Hz (C-2 and C-4 methyls). Ir 2960–2880 (CH); 1453, 1379, 1361 (CH); 1172, 1124, 1031 (C–O–C); 912, 894 cm^{-1} (ring). Mass spectrum (10% cutoff) m/e 170, 3% (M^+); 128, 11%; 57, 100% ($CH_3CH_2C{\equiv}O^+$). High-resolution MS, calcd for $C_{10}H_{18}O_2$, 170.1307; found, 170.1307.

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Registry No.—(±)-α-**1**, 54815-06-4; (±)-γ-**1**, 54832-21-2; **3**, 58967-01-4; **4**, 58967-02-5; **5**, 58967-03-6; **6**, 58967-04-7; tosyl chloride, 98-59-9; diisopropylamine, 108-18-9; diethyl ketone, 96-22-0.

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