**Registry No.**—L-Valyl-L-leucyl-L-threonine amide, 69462-04-0; benzylcarbonyl-L-valyl-L-leucyl-L-threonine methyl ester, 69462-05-1; L-prolyl-$N^{\epsilon}$-*p*-nitrobenzyloxycarbonyl-L-lysylglycine ethyl ester trifluoroacetate salt, 69470-11-7; $N^{\alpha}$-*tert*-butoxycarbonyl-$N^{\epsilon}$-*p*-nitrobenzyloxycarbonyl-L-lysine *p*-nitrophenyl ester, 33662-24-7; ethyl glycinate, 459-73-4; *tert*-butyloxycarbonyl-L-proline *o*-nitrophenyl ester, 38605-56-0; *N*-*tert*-butyloxycarboxy-L-prolyl-$N^{\epsilon}$-*p*-nitrobenzyloxycarbonyl-L-lysylglycine ethyl ester, 69462-06-2; FMOC-L-alanine *p*-nitrophenyl ester, 69462-07-3; *p*-nitrophenol, 100-02-7; L-proline *tert*-butyl ester, 2812-46-6.

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(19) The 3-peptide with Val as the N-terminal residue was chosen because it allowed comparison with the effect of L-valine *tert*-butyl ester. (Also, this peptide amide was available in our laboratory.) A peptide with proline at its N-terminal seemed to be desirable for the same reasons. The tripeptide ester used was prepared from a dipeptide at hand.
(20) At this point it should be remembered that in syntheses in which the FMOC group is used for the protection of α-amino functions, removal of the protection does not result in a salt of the liberated amine and accordingly no need exists for the addition of a tertiary amine.
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# Highly Stereoselective Synthesis of (±)-α-Multistriatin


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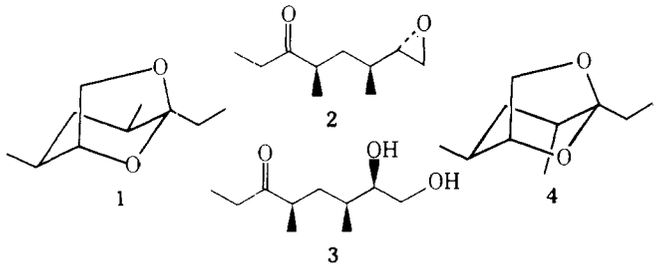
*Erythro*-2,4-Dimethyl-5-hexenoic acid (**7**), available from *meso*-2,4-dimethylglutaric anhydride, is functionalized in a highly stereoselective manner by iodolactonization. Subsequent methanolysis of the iodo lactone **9** and conversion of the ester to the ethyl ketone provide the desired cyclization substrate **2**. Lewis acid catalyzed cyclization of **2** then affords (±)-α-multistriatin of more than 95% purity in a sequence which necessitates no column or vapor phase chromatography purification steps.


Multistriatin (**1**) has been the target of a number of synthetic endeavors[1] because it is one of the three components of the aggregation pheromone of the European elm bark beetle, *Scolytus multistriatus* Marsham, the primary vector of Dutch elm disease in Europe and North America. With one exception,[1a] all of the reported syntheses entail the construction of the keto epoxide **2**[1c,e] or the keto diol **3**[1b,d] prior to cyclization. None of the syntheses of α-multistriatin is stereospecific in the sense of controlling the relative configurations of the chiral centers, although enantiomerically pure (−)-α-multistriatin has been synthesized from appropriate optically active precursors.[1c-e] In the Diels–Adler approach of Gore, Pearce, and Silverstein[1a] and the route developed by Elliot and Fried,[1b] the relative stereochemistry of carbons 1 and 2 of multistriatin is introduced specifically; however, the natural α isomer is obtained as a mixture with the γ isomer (**4**) after acid-catalyzed equilibration (α/γ = 80:20[1a] or 85:15[1b]). We have completed a synthesis of (±)-α-multistriatin, via the keto epoxide **2**, in which all of the relative stereochemistry is introduced with high selectivity and which provides material of greater than 95% purity without VPC purification at any stage.




1 2 3 4

The addition of dilithiomethyl phenyl sulfone[2] to the readily available *meso*-2,4-dimethylglutaric anhydride (**5**),[3] followed by sodium borohydride reduction and lactonization, gave the sulfonyl lactone **6** as a mixture of isomers. Sodium amalgam reduction[4] of this material then provided the olefinic acid **7** in 66% overall yield from the anhydride **5**. Although this was an efficient process, the acid **7** was occasionally contaminated with varying amounts of the threo isomer, apparently arising from epimerization during the borohydride reduction step, and an alternative stereospecific synthesis was required. The aldehyde ester **8**[5] is available in 80% yield from the anhydride **5** by Rosenmund reduction of the half ester acid chloride. Wittig methylenation of this material and subsequent ester hydrolysis afford the olefinic acid **7** without sig-

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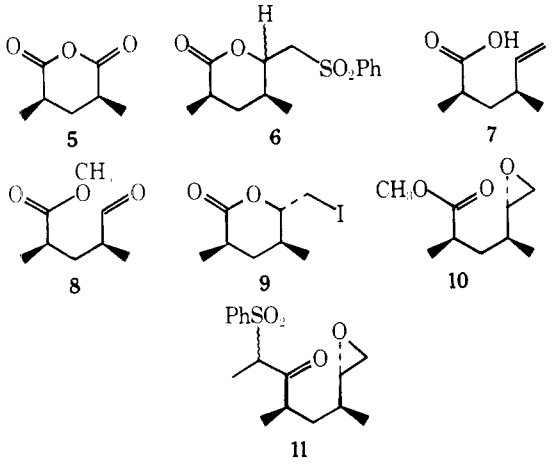
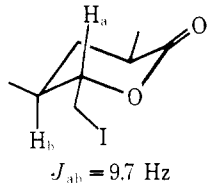



nificant (<3% by $^{13}C$ NMR) contamination by its diastereomer.

Acid **7** is converted to the iodo lactone **9** in 85–90% yield with 3 equiv of iodine in acetonitrile at 0 °C for 3.5 h, accomplishing the crucial functionalization of the double bond in a highly stereoselective manner.[6] Careful VPC analysis indicated that iodo lactone produced in this fashion is contaminated with <5% of isomeric material, reflecting the thermodynamic control exerted by these iodolactonization conditions. If the cyclization reaction is performed under conditions of kinetic control (*N*-iodosuccinimide in chloroform), up to 23% of the all-cis isomer is obtained. The all-equatorial stereochemistry of the iodo lactone **9** was clearly shown by 180-MHz $^1H$ NMR, which revealed an axial–axial coupling constant of 9.7 Hz between the adjacent methine hydrogens.




Addition of a sulfonyl-stabilized carbanion directly to the iodo lactone **9** led to complex mixtures from which the epoxy β-keto sulfone **11** could be isolated in only poor yield. Alkaline methanolysis of **9** leads to the epoxy ester **10** in high yield, however, and this compound reacts smoothly with 2 equiv of α-lithioethyl phenyl sulfone at 0 °C to afford the desired β-keto sulfone **11**. Aluminum amalgam reduction[7] then provides the ethyl ketone **2**.

The crude reduction product (**2**) is rapidly isomerized[1c,e] by stannic chloride in benzene at 0 °C to give (±)-α-multistriatin in 50% yield from the epoxy ester **10** after simple bulb-to-bulb distillation. The spectral properties (notably $^{13}C$ NMR and $^1H$ NMR) of this compound are identical with those reported for α-multistriatin.[1a,8] Furthermore, VPC and 180-MHz $^1H$ NMR analysis indicate that this material is >95% pure with respect to contamination by other isomers or other impurities.

## Experimental Section

Routine $^1H$ NMR spectra were recorded on a Varian T-60 spectrometer; high-field (180-MHz) $^1H$ NMR spectra were acquired on a system equipped with a Bruker magnet and a Nicolet computer. The spectra are reported as: chemical shift in parts per million (multiplicity, intensity, assignment). $^{13}C$ NMR spectra were acquired on a Nicolet TT-23 system; the reported chemical shifts (ppm) are referenced to $CDCl_3$ as 77.0 ppm. Analytical VPC was performed on 6 ft × ⅛ in. columns using nitrogen as the carrier gas and OV-101 or Carbowax 20M on 100–200 mesh GasChrom Q; preparative VPC was performed on 6 ft × ¼ in. SE-30 columns eluted with helium. Ether and tetrahydrofuran (THF) were dried by distillation from sodium benzophenone ketyl, and acetonitrile was Aldrich Gold Label grade dried over Linde 4Å molecular sieves.

**(2*R**,4*S**)-2,4-Dimethyl-5-hexenoic Acid (7).** A solution of methylenetriphenylphosphorane was generated at 0 °C from 11.25 g (31.5 mmol) of methyltriphenylphosphonium bromide, 100 mL of ether, and 130 mmol of a 1.55 M solution of *n*-butyllithium in hexane. After stirring for 0.5 h at room temperature, the ylide solution was added over a 1-h period to a solution of 5.17 g (30 mmol) of ethyl (2*R**, 4*S**)-2,4-dimethyl-5-oxopentanoate[5] (**8**) in 50 mL of ether at −78 °C. When the addition was complete, the slurry was brought to room temperature and stirred for 16 h. The mixture was filtered, the precipitated triphenylphosphine oxide–lithium bromide complex was washed with ether, and the combined ether solutions were washed with 0.5 N HCl, water, and brine, concentrated under reduced pressure to a volume of about 20 mL, and added to a refluxing solution of 100 mL of ethanol and 30 mL of 1 N NaOH. After 3 h, the bulk of the ethanol was removed under reduced pressure and the solution was diluted with water and washed with two portions of $CH_2Cl_2$. The aqueous layer was acidified and extracted three times with $CH_2Cl_2$, and the combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give 2.1 g of the acid **7**. A similar workup of the triphenylphosphine oxide precipitate afforded an additional 0.22 g of material, for a combined yield of 54%: IR 1705 (C=O), 2500–3600 ($CO_2H$) $cm^{-1}$; $^1H$ NMR δ 1.03 (d, 3), 1.20 (d, 3), 1.7–2.3 (m, 4), 4.9 (m, 2, $=CH_2$), 5.5 (m, 1, –CH=), 11.75 (s, 1); $^{13}C$ NMR δ 16.6, 20.4, 35.7, 37.2, 40.1, 113.4, 143.3, 183.4 (the 2*R**,4*R** diastereomer shows resonances at δ 17.5, 20.3, 36.0, 37.4, 40.4, 113.5, 143.5, and 183.3). A sample was purified for analysis by preparative VPC (190 °C, 30% SE-30). Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.29, H, 9.76.

**(3α,5α,6β)-3,4,5,6-Tetrahydro-6-(iodomethyl)-3,5-dimethylpyran-2-one (9).** A mixture of 2.09 g (14.7 mmol) of olefinic acid **7**, 50 mL of acetonitrile, and 11.2 g (44.1 mmol) of iodine was stirred at 0 °C for 3.5 h, and then partitioned between saturated $NaHCO_3$ (50 mL) and ether (100 mL). The organic layer was decolorized with aqueous $Na_2S_2O_3$, washed with water and brine, dried ($MgSO_4$), and concentrated to give 3.33 g (85% yield) of the iodo lactone **9**. VPC analysis (97 °C, 3% OV-101, 30 mL/min) showed two isomers of retention time 11.3 and 12.5 min, in a ratio of less than 1:20, respectively: IR ($CHCl_3$) 1735 (C=O) $cm^{-1}$; $^1H$ NMR (180-MHz) δ 1.00 (d, 3), 1.29 (d, 3), 1.52 (ddd, 1, $J$ = 13 Hz, H(4)-axial), 2.0 (m, 1, H(4)-equatorial), 2.57 (ddq, 1, H(3)), 3.41, 3.55, 3.64, and 1.92 (ABCX, 4, $J_{AB}$ = 11.2, $J_{BC}$ = 2.9, $J_{AC}$ = 3.4, $J_{CX}$ = 9.7 Hz; A, B = $CH_2I$, C = H(6), X = H(5)); $^{13}C$ NMR δ 9.6, 16.6, 16.7, 34.2, 35.9, 36.1, 83.1, 173.0. The analytical sample was purified by preparative VPC (180 °C, 10% SE-30). Anal. Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89; I, 47.34; Found: C, 35.97; H, 4.94; I, 47.06.

**Methyl (2*R**,4*S**,5*S**)-5,6-Epoxy-2,4-dimethylhexanoate (10).** A mixture of the iodo lactone **9** (3.33 g, 12.4 mmol), 180 mL of methanol, and 1.45 g (13.7 mmol) of anhydrous powdered $Na_2CO_3$ was stirred at room temperature for 11 h in the dark. The solution was then concentrated under reduced pressure and partitioned between water and ether, and the ether layer was washed with water and brine, dried ($MgSO_4$), and evaporated to give 1.97 g (92% yield) of the epoxy ester **10**: IR 1735 (C=O), 2990 (CH), 3050 (epoxy CH); $^1H$ NMR δ 0.9–2.0 (m, 10), 2.0 (m, 3, epoxide), 3.67 (s, 3, $OCH_3$). The analytical sample was purified by preparative VPC (180 °C, 30% SE-30). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.68; H, 9.27.

**(±)-α-Multistriatin (1).** A solution of α-lithioethyl phenyl sulfone was generated by adding 24.0 mmol of a 1.55 M *n*-butyllithium/hexane solution to 4.09 g (24.0 mmol) of ethyl phenyl sulfone in 75 mL of THF at −78 → 0 °C. This solution was added over a 1-h period to the epoxy ester **10** (1.97 g, 11.44 mmol) in 75 mL of THF at 0 °C. The mixture was partitioned between saturated $NH_4Cl$ (50 mL) and ether (100 mL), and the organic layer was washed with water and brine (20 mL each) and evaporated to give 5.46 g of the β-keto sulfone **11**, mixed with ethyl phenyl sulfone.

From a similar preparation, an analytical sample of the β-keto sulfone **11** was isolated by column chromatography (silica gel, 1:1 ether/hexane): IR 1310 ($SO_2$), 1590 (aryl), 1715 (C=O), 3075 (CH) $cm^{-1}$; $^1H$ NMR δ 2.6 (m, 3, epoxide), 4.45 (q, 1, SOCHCO). Anal. Calcd for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.14; S, 10.33. Found: C, 61.60; H, 7.14; S, 10.18.

The mixture of β-keto sulfone **11** and ethyl phenyl sulfone was dissolved in 200 mL of 10% aqueous THF and heated at reflux with 2.88 g (0.11 g-atom) of freshly amalgamated aluminum foil for 1.5 h.[7] The mixture was filtered through Celite, concentrated, and extracted with ether. The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford a mix-

ture of ethyl phenyl sulfone and the epoxy ketone **2** which was used directly in the next step.

The crude reduction product was diluted with 50 mL of benzene, cooled in an ice bath, and treated with 0.36 mL of a 1 M solution of $SnCl_4$ in benzene. After 3 min, the mixture was partitioned between ether and 2 N NaOH, and the organic layer was washed with 2 N NaOH, 1 N HCl, saturated $NaHCO_3$, and brine. After drying over $MgSO_4$, the solvent was removed under reduced pressure. The (±)-α-multistriatin was separated from the ethyl phenyl sulfone by bulb-to-bulb distillation using a Büchi Kugelrohr oven [90 °C (7 torr)], providing 980 mg (50% overall yield from the epoxy ester **10**) of material of >95% chemical and stereochemical purity by VPC (100 °C, 15% Carbowax) and 180-MHz $^1H$ NMR analysis. The spectral properties (IR, $^{13}C$ NMR, and 180-MHz $^1H$ NMR) corresponded to those reported for the α isomer of multistriatin.[1,8]

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**Registry No.**—**1**, 54815-06-4; **2**, 59014-13-0; **7**, 69291-66-3; **8**, 69291-67-4; **9**, 69291-68-5; **10**, 69291-69-6; **11**, 69291-70-9; methylenetriphenylphosphorane, 3487-44-3; α-lithioethyl phenyl sulfone, 69291-71-0; ethyl phenyl sulfone, 599-70-2.

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# Use of $^{15}N$–$^1H$ and $^{15}N$–$^{13}C$ Coupling Constants for the Measurement of Uracil Monoanion Tautomerism[1]

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*Received December 5, 1978*

We have measured the proton and carbon-13 couplings to nitrogen-15 ($J_{H_6,N_1}$, $J_{H_5,N_1}$, $J_{H_5,N_3}$, and $J_{C_6,N_1}$) for uracil-1,3-$^{15}N_2$, its *N*-deuteriomethyl derivatives (I–IV), and the corresponding monoanionic species (Ia ⇌ Ib, IIa, and IIIb). These parameters were found to be sensitive probes for the determination of the uracil monoanion tautomeric equilibrium (Ia ⇌ Ib) by reference to the fixed tautomer models, IIa and IIIb. Similar measurements were performed employing $J_{H_5,H_6}$, $\delta_{H_6} - \delta_{H_5}$, and $\delta_{C_6} - \delta_{C_5}$. The population of the $N_1H$ tautomer (Ia), based upon the weighted average derived from four of these coupling constants, is 48.5%. If a correction is made for the effect of *N*-methyl substituents on the tautomer models, IIa and IIIb, the weighted average is 52.2%. The above population determinations are in excellent agreement with those made previously using other methods. The potential of this approach in the study of similar equilibria for oligonucleotides is discussed.

The investigation of chemical tautomerism is of considerable importance in the study of heterocyclic molecules. In many instances, the determination of the structure of such tautomeric species and their relative stabilities is of considerable biological importance. A wide range of chemical and spectroscopic methods (e.g., IR, UV, and NMR) have already been applied to this problem, with varying degrees of success. For the most part, these studies are based upon the assumption that substitute fixed tautomer parameters, which can be obtained from two or more partially methylated derivatives, are good models for the otherwise unmeasurable intensive parameters of the corresponding tautomeric species.

It is known that $^{15}N$–$^1H$ and $^{15}N$–$^{13}C$ coupling constants are sensitive to changes in hybridization of the nitrogen in question and that such variations are likely to be both large and highly specific when the parameter is measured for each tautomeric species. Recently, this approach has been applied successfully to the problem of histidine tautomerism.[2]

We have now applied this method to the quantitative measurement of uracil monoanion tautomerism. The use of this system permits a direct comparison of our results with those obtained by other methods.

## Experimental Section

We have prepared uracil-1,3-$^{15}N_2$ (I) from urea-$^{15}N_2$, 99.6% $^{15}N$ (KOR Isotopes, Cambridge, Mass.), and propiolic acid (Aldrich) in 77% yield, according to the procedure employed by Harada and Suzuki for the synthesis of the nonlabeled material.[3a] The uracil-1,3-$^{15}N_2$ was randomly alkylated with 1 equiv of dimethyl-$d_6$ sulfate, 99% *d* (Aldrich), in the presence of 1 equiv of aqueous sodium hydroxide to yield a mixture of 1-methyl-$d_3$-uracil-1,3-$^{15}N_2$ (II), 3-methyl-$d_3$-uracil-1,3-$^{15}N_2$ (III), and 1,3-dimethyl-$d_6$-uracil-1,3-$^{15}N_2$ (IV), which was separated chromatographically. Each of the components was identified by comparison of its UV spectra in neutral and alkaline pH's with those derived from authentic samples of the corresponding nonlabeled derivatives. UV measurements were performed on a Varian Superscan 3 spectrophotometer. The experimental details of these isotopic syntheses and the separation procedures used will be reported elsewhere.[3b]

NMR measurements were performed in $D_2O$ solution on a JEOL-PFT-100 spectrometer, operating at ambient probe temperature, 22 °C. Field stabilization was provided through internal $^2H$ lock on the deuterated solvent. Measurements of the monoanionic species were made at pD ≅ 12.0.[4] Under these conditions uracil and its monomethyl derivatives should exist solely as the monoanionic forms, as calculated from the known $pK_a$'s of these molecules.[5,6] The pD adjustments were made by adding 5-μL aliquots of 10% NaOD solution from a micropipet and monitoring changes with an Ingold 6025-02 combination microelectrode and a Beckman Research pH meter. For the analysis of the proton spectra, all coupling constants were extracted directly from the average of the appropriate repeated spacings, as $J/\Delta\gamma \ll 0.1$ in all such cases, allowing a first-order treatment.[7]

## Results and Discussion

We have measured the $^{15}N$–$^1H$ and $^{15}N$–$^{13}C$ coupling constants from the proton and natural abundance $^{13}C$ NMR spectra, respectively, for both the neutral (I–IV) and the

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