point of 225–227 °C exhibited spectral and chromatographic behavior identical with that of the synthetic material described above.

**Acknowledgment.** We thank the National Institutes of Health, the National Science Foundation, the Alfred P. Sloan Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Hoffmann-La Roche Foundation, and the Shermann-Clark Fund for support of this work.

## References and Notes

(1) For isolation and structure proof of eburnamonine, see (a) M. F. Bartlett, W. I. Taylor, and Raymond-Hamet, *C.R. Hebd. Seances Acad. Sci., Ser. C*, **249**, 1259 (1959); (b) M. F. Bartlett and W. I. Taylor, *J. Am. Chem. Soc.*, **82**, 5941 (1960); (c) J. Mokrý, I. Kompiš, and P. Šefčovič, *Tetrahedron Lett.*, 433 (1962).

(2) (a) E. Schlittler and R. Furlenmeier, *Helv. Chim. Acta*, **36**, 2017 (1953); (b) J. Trojánek, O. Štrouf, J. Holubek, and Z. Čekan, *Tetrahedron Lett.*, 702 (1961); (c) J. Mokrý, M. Shamma, and H. E. Soyster, *ibid.*, 999 (1963); (d) M. F. Bartlett, R. Sklav, A. F. Smith, and W. I. Taylor, *J. Org. Chem.*, **28**, 2197 (1963); (e) J. Trovjánek, Z. Koblicová, and K. Bláha, *Chem. Ind. (London)*, 1261 (1965).

(3) (a) M. F. Bartlett, W. I. Taylor, and Raymond-Hamet, *C.R. Hebd. Seances Acad. Sci., Ser. C*, **240**, 1470 (1955); (b) E. A. Trutneva and V. V. Berezhinskaya, *Farmakol. Toksikol.*, **29**, 171 (1966).

(4) (a) L. Szporny and K. Szász, *Arch. Exp. Pathol. Pharmakol.*, **236**, 296 (1959); (b) Z. Szabo and Z. Nagy, *Arzneim.-Forsch.*, **10**, 811 (1960); (c) L. Szporny and P. Gorog, *Arch. Int. Pharmacodyn. Ther.*, **138**, 451 (1962); (c) M. Foldi, F. Obal, and G. Szeghy, *Med. Welt*, **37**, 2122 (1965); (d) F. Solti, *Ther. Hung.*, **13**, 101 (1965).

(5) For total syntheses of eburnamonine and related alkaloids, see E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **87**, 1580 (1965); also see ref 1b. Very recently, a new and elegant approach to these substances has been reported by E. Wenkert, T. Hudlický, and H. D. Hollis Showalter, *ibid.*, **100**, 4893 (1978).

(6) For total syntheses of vincamine, see (a) J. F. D. Barton and J. Harley-Mason, *Chem. Commun.*, 298 (1965); (b) K. H. Gibson and J. E. Saxton, *ibid.*, 799, 1490 (1969); (c) K. H. Gibson and J. E. Saxton, *J. Chem. Soc., Perkin Trans. 1*, 2776 (1972); (d) C. Thal, T. Sevenet, H. P. Husson, and P. Potier, *C.R. Hebd. Seances Acad. Sci., Ser. C*, **275**, 1295 (1972); (e) Atta-ur-Rahman, *J. Chem. Soc., Perkin Trans. 1*, 731 (1972); (f) C. Szántay, L. Szabo, and G. Kalaus, *Tetrahedron Lett.*, 191 (1973); (g) C. Thal, T. Imbert, H. P. Husson, and P. Potier, *Bull. Soc. Chim. Fr.*, 2010, 2013 (1973); (h) G. Hugel, J. Levy, and J. LeMen, *C.R. Hebd. Seances Acad. Sci., Ser. C*, **274**, 1350 (1972); (i) D. L. Coffen, D. A. Katonak, and F. Wong, *J. Am. Chem. Soc.*, **96**, 3966 (1974); (j) P. Pfäffli, W. Oppolzer, R. Wenger, and H. Hauth, *Helv. Chim. Acta*, **58**, 1131 (1975); (k) C. Szántay, L. Szabo, and G. Kalaus, *Tetrahedron*, **33**, 1803 (1977); (l) W. Oppolzer, H. Hauth, P. Pfäffli, and R. Wenger, *Helv. Chim. Acta*, **60**, 1801 (1977). For the original synthesis of vincamine, see M. E. Kuehne, *J. Am. Chem. Soc.*, **86**, 2946 (1964).

(7) (a) For a preliminary report of this methodology leading to eburnamonine, see J. L. Herrmann, G. R. Keiczykowski, S. E. Normandin, and R. H. Schlessinger, *Tetrahedron Lett.*, 801 (1976). (b) For a preliminary description of the synthesis of vincamine prepared in this manner, see J. L. Herrmann, R. J. Cregge, J. E. Richman, C. L. Semmelhack, and R. H. Schlessinger, *J. Am. Chem. Soc.*, **96**, 3702 (1974).

(8) Wenkert and Wickberg prepared **3** starting from diethyl ethylmalonate; see ref 5.

(9) R. J. Cregge, J. L. Herrmann, C. S. Lee, J. F. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 2425 (1973).

(10) Originally, 10 equiv of potassium hydride were used for this reaction; see ref 7b.

(11) A convenient and high yield preparation of this compound is described by K. D. Gundermann and H. Schulze, *Chem. Ber.*, **94**, 3254 (1961). For the application of this acrylate derivative in conjugate addition reactions, see R. J. Cregge, J. L. Herrmann, and R. H. Schlessinger, *Tetrahedron Lett.*, 2063 (1973).

(12) The inspiration for this intended sequence stemmed from similar work reported by Saxton.[6b]

(13) We thank Professor M. P. Cava, Department of Chemistry, University of Pennsylvania, for a generous sample of naturally occurring racemic vincamine.

(14) Melting points were taken on a Fisher-Johns melting point block and are reported uncorrected. Analyses were performed by Spang Microanalytical Laobratories, Ann Arbor, Mich. Reactions were run in either insulated cryostats (for temperatures of <0 °C) or thermostated silicone oil baths with a temperature accuracy of 1°. Solvents were evaporated to dryness using a rotary evaporator at steam-bath temperatures and reduced pressures. Anhydrous solvents were distilled immediately before use. Tetrahydrofuran, diethyl ether, and 1,2-dimethoxyethane were distilled from lithium aluminum hydride, *tert*-butyl alcohol was distilled from calcium hydride, and methanol was distilled from magnesium turnings. Other solvents were at least reagent grade and used as received. Reagents were distilled at least once prior to use. Amines were distilled from calcium hydrogen under a nitrogen atmosphere. Hydrogenations were carried out in a slanted manifold all glass apparatus at 1 atm at 0 °C. The system was evacuated by a water aspirator and then filled with hydrogen while stirring (this was repeated four times). Thin layer chromatography was performed on microscope slides coated by dipping in a slurry of either silica gel G or silica gel HF-254 (Brinkman) suspended in chloroform. High pressure liquid phase chromatography was performed on a Water's Associates ALC-202 instrument equipped with both ultraviolet and differential refractometer detectors. Vapor phase chromatography was performed on a Hewlett-Packard 5700A instrument with TC detector and HP-5702A temperature programmer. Column chromatography was carried out using Brinkmann alumina. Infrared spectra were recorded on either a Perkin-Elmer 700 or a Perkin-Elmer 467 spectrophotometer. Nuclear magnetic resonance spectra were recorded on either a JEOLCO C-60 HL or a JEOLCO MH-100 spectrometer using deuteriochloroform as solvent and tetramethylsilane as internal reference, and are expressed as $\delta$ values, with the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Ultraviolet spectra were recorded on a Perkin-Elmer Digital 602 spectrophotometer.

# A Total Synthesis of Racemic Avenaciolide

**John L. Herrmann, Mitchel H. Berger, and R. H. Schlessinger***

*Contribution from the Department of Chemistry, University of Rochester, Rochester, New York 14627.* *Received August 30, 1978*

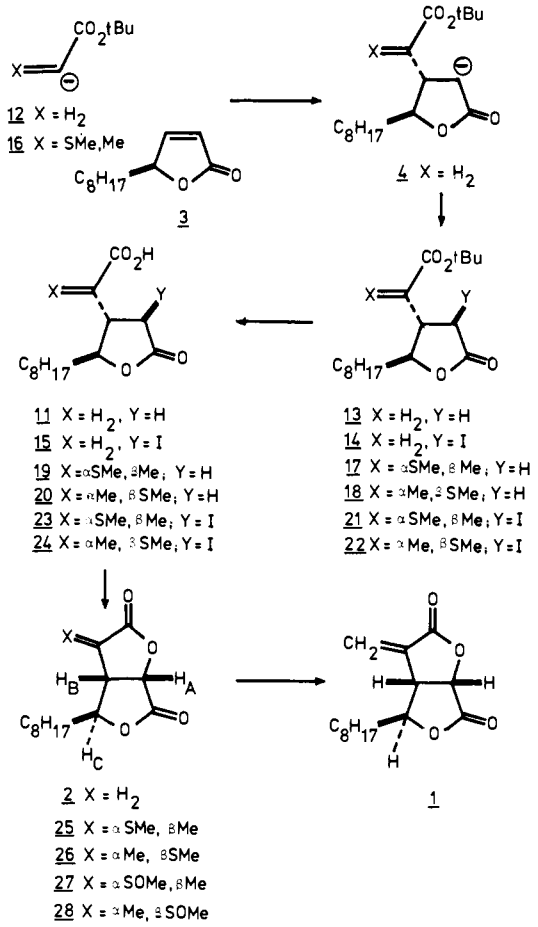
**Abstract:** A stereospecific total synthesis of racemic avenaciolide (**1**) has been realized in 64% overall yield starting from 5-*n*-octyl-2(5*H*)-furanone (**3**). The salient features of this synthesis include stereospecific substitution of both the $\beta$ and $\alpha$ positions of **3** via a conjugate addition–halogenation sequence, and transformation of an $\alpha$-methyl-$\alpha$-thiomethylbutyrolactone into an $\alpha$-methylene butyrolactone. The anion derived from ethyl propiolate has been utilized for the efficient synthesis of several 5-substituted 2(5*H*)-furanones.

## Introduction

Avenaciolide (**1**) is an antifungal agent first isolated by Turner from *Aspergillus avenaceaus*[1] and later by others from *Aspergillus fischeri*.[2] The structure of **1**, deduced by Turner from both degradation and nuclear magnetic resonance studies,[3] is an unusual $\alpha$-methylene bis(butyrolactone) system containing three chiral centers. The structurally novel nature of avenaciolide has prompted a measure of synthetic activity resulting in the description of three total syntheses.[4] Johnson was the first to synthesize **1**, beginning with tricarballylic acid,[4a] whereas Fraser-Reid prepared optically active **1** starting from D-glucose.[4c] These interesting and elegant syntheses, while starting from widely divergent substances, proceed to avenaciolide through a common intermediate, bislactone **2**.

Our own synthetic strategy involved a multiple-bond-forming process which combined one nucleophile with two electrophiles under aprotic conditions.[4b] This methodology, applied to an unsaturated carbonyl system, would yield a new carbonyl substance substituted in both the $\beta$ and $\alpha$ positions.

0002-7863/79/1501-1544$01.00/0 




In addition, stereochemistry of a usable synthetic nature could accrue from such a reaction, particularly if the unsaturated carbonyl residue were contained in a ring.[5]

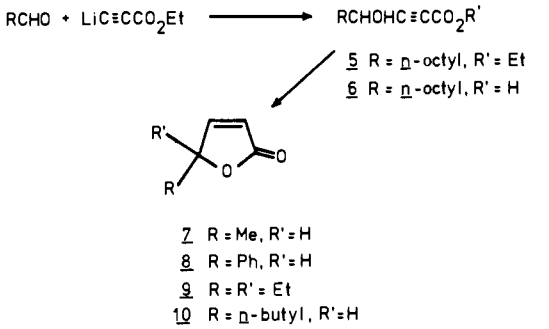
The most obvious reaction sequence to avenaciolide in light of such considerations would require conjugate addition of an acetate ester enolate onto the furanone **3** followed by trapping of the resulting lactone enolate, **4**, with an electrophile such as bromine or iodine. Establishment of the second lactone ring could, in principle, be carried out by hydrolysis of the acetate residue to the free acid followed by lactonization. In this case, the Johnson intermediate **2** would be obtained.

Implicit in this scheme is the stereochemical course of these reactions which demands addition of the acetate anion to occur trans to the $C_8$ side chain of **3**. In addition, halogenation of the lactone enolate **4** must occur trans to the newly introduced acetate residue. Molecular models suggested the stereochemical aspects of this reaction scheme to be reasonable; furthermore, the work of Rathke suggested that halogenation of a lactone enolate would be possible.[6] Unprecedented at that time, however, both in terms of existing literature and our own laboratory experience, was the viability of realizing conjugate addition of a simple ester enolate to a furanone under aprotic reaction conditions.[7] We addressed ourselves to the latter problem first by preparing the furanone **3** and then by investigating its behavior in the conjugate addition reaction.

## Results

i. **Preparation of 5-Substituted 2(5*H*)-Furanones.** Nobuhara has prepared furanone **3** along with a number of analogues of this system.[8] Nobuhara's sequence calls for the reaction of an aldehyde with the sodium salt of acetylene followed by carbonation of the magnesium salt of the resulting acetylenic alcohol. Reduction of the acetylene with concurrent lactonization yields the desired furanone. While we were able to reproduce the Nobuhara synthesis of this furanone, we found the carbonation step to be highly capricious. As a result, we developed an alternative and somewhat shorter means of preparing 5-substituted furanones starting from ethyl propiolate.

Bachmann has described the reaction of sodio methyl propiolate with ketones.[9] Unfortunately, these reactions gave low yields of the desired addition products, a phenomenon also observed by several others.[10] The preceding work with propiolate anions used either the sodium or potassium salts. It occurred to us that the lithium salt of a propiolate ester might better serve in this reaction by suppressing the base behavior of the propiolate anion. This surmise proved correct for the lithium salt of ethyl propiolate which, when reacted with nonanal, afforded an excellent yield of the corresponding hydroxy ester **5**. The reduction-lactonization conversion of **5** into




**3** required some experimentation to achieve reproducible and efficient results, but eventually the following methodology was adopted. Ester **5** was saponified in methanolic potassium hydroxide solution; the resulting acid, **6**, was then hydrogenated in methanol and quinoline using 5% palladium-on-barium sulfate. Acidification of the hydrogenate solution gave **3** directly in good overall yield. The preparations of several 5-substituted 2(5*H*)-furanones, in addition to **3**, are reported in the Experimental Section (compounds **7, 8, 9,** and **10**).[11]

ii. **Preparation of the Bislactone 2. A Necessary Diversion.** Of the premises upon which our intended synthesis of avenaciolide was based, none was more vital than trans-1,4 addition of an acetate enolate to the furanone **3**. The experimental viability of this prerequisite was tested with an attempt to prepare the lactone acid **11** and subsequently the bislactone **2**. Gratifyingly, addition of the enolate of *tert*-butyl acetate (**12**) to the furanone **3** resulted in the high yield formation of the conjugate addition product **13**. Acid-catalyzed removal of the *tert*-butyl ester portion of **13** gave a lactone acid, which after five recrystallizations gave a 70% yield of material (mp 53–54.5 °C). Johnson reports this lactone acid, **11,** to have a melting point of 55–56 °C.[4a] Spectral and chromatographic data for our lactone acid compared favorably with those reported;[4a] yet, unconvinced of the stereochemical purity of our material, we converted it into the bislactone **2**. This transformation was carried out with the aid of a procedure described by Rathke.[12] Thus, our lactone acid was treated with 2 equiv of lithium diisopropylamide to form its corresponding carboxyl and lactone anions, which were then coupled with cupric bromide. This reaction, based on chromatographic and spectral data, yields a mixture of bislactones **2**, which are epimeric with respect to the *n*-octyl side chain.

An alternative attempt to prepare **2** was also carried out in the following manner. The anion of *tert*-butyl acetate again was added to **3**, but, in this case, the resulting lactone enolate, **4**, was quenched by addition of iodine.[6] The resulting iodolactone ester **14** was hydrolyzed to its corresponding iodolactone acid **15** and this product lactonized with sodium hydride in benzene solution. A mixture of bislactones (epimeric at the *n*-octyl side chain) also was obtained in this case; however, the yield of bislactonic products was much higher than that ob-

served for the copper coupling reaction. The latter result, together with $^1$H NMR data obtained from the iodolactone ester **14**, suggested to us that iodonation trans to the acetate residue had occurred in a reasonably stereospecific manner. Clearly then, to develop a viable synthesis of avenaciolide, we needed only to secure the stereochemistry of 1,4 addition to the furanone **3**.

iii. **Preparation of Avenaciolide (1).** The obvious solution to overcome the problem of stereoselectivity during the 1,4 addition of acetate to the furanone **3** would be to increase the bulk of the acetate component. Presumably, this would lead to greater steric interaction between the entering nucleophile and the *n*-octyl side chain of **3**, resulting in a higher proportion of trans addition product. Coupled with the above consideration was our desire to utilize this additional steric bulk subsequently to formulate the $\alpha$-methylenelactone residue present in the natural product. Hence, we redefined our acetate nucleophile as a latent "methylene anion" equivalent.[13] Of several possibilities deliberated in this regard, the simplest solution, based on prior laboratory experience, seemed to be the anion derived from *tert*-butyl 2-thiomethylpropionate (**16**). Assuming that this anion added to **3** in a trans fashion, the resulting adduct could be lactonized in a manner similar to that used for the acetate series. Finally, the desired $\alpha$-methylene residue could be created via an elimination reaction involving the thiomethyl group.[14] The simplicity and potential soundness of this scheme appealed to us, and we forthwith began a construction of **1**.

Addition of furanone **3** to a solution of the lithium salt of *tert*-butyl 2-thiomethylpropionate followed by quenching with aqueous ammonium chloride gave a mixture of adducts identifiable as compounds **17** and **18**. Acid-catalyzed hydrolysis of **17** and **18** gave the corresponding acids **19** and **20**. The $^1$H NMR spectra of compounds **17–20** suggested that exclusive trans addition of **16** to **3** had occurred.

Conjugate addition of **16** to **3** followed by quenching with iodine gave a mixture of the adducts **21** and **22**. The juxtaposition of the *n*-octyl, 2-thiomethylpropionate, and iodine substituents in these compounds clearly was all-trans as revealed by their $^1$H NMR spectra as well as by their ultimate conversion into avenaciolide. Lactonization of a mixture of **21** and **22** was achieved in the following manner. The iodolactone esters were heated in benzene containing a small amount of *p*-toluenesulfonic acid to give the iodolactone acids **23** and **24**. Without workup, this reaction mixture was stirred with aqueous sodium bicarbonate at room temperature to afford a mixture of the bislactones **25** and **26** in 83% overall yield from **3**.

Although carried to avenaciolide as a mixture, these bislactones could be readily separated and their structures assigned on the basis of spectral data. Compounds **25** and **26** show methyl singlets $\delta$ at 1.58 and 1.62, respectively. The thiomethyl group for both compounds appears at $\delta$ 2.22. A chemical shift of $\delta$ 5.03 (d) was observed for the $H_A$ proton of **25** ($J_{AB}$ = 9 Hz), whereas a value of $\delta$ 5.01 (d) ($J_{AB}$ = 7 Hz) was observed for $H_A$ in **26**. The $H_B$ proton of **25** is a doublet of doublets ($J_{AB}$ = 9 Hz and $J_{BC}$ = 3 Hz) at $\delta$ 3.10. Compound **26** also shows $H_B$ as a doublet of doublets ($J_{AB} = J_{BC}$ = 7 Hz) at $\delta$ 2.73. Proton $H_C$ occurs in both materials as a doublet of triplets: for **25**, $\delta$ 4.83 ($J_{BC}$ = 3 Hz, $J_{C\text{-methylene}}$ = 7 Hz); for **26**, $\delta$ 4.47 ($J_{BC}$ = 7 Hz, $J_{C\text{-methylene}}$ = 7 Hz). These data are consistent for the structural assignments given to **25** and **26**—not surprisingly, both **25** and **26** show virtually identical infrared spectra.

With the bislactones **25** and **26** "in hand", we then began to seek a means of transforming these materials into our final goal. We had envisaged a two-step process for this conversion: the first reaction involved oxidation of the thiomethyl residue into its corresponding sulfoxide analogue, while the second consisted of anhydride-mediated elimination of the elements of MeSOH.[14] Our initial oxidation experiments were carried out on **25** and **26** separately. As might be expected, **26** undergoes oxidation to the sulfoxide **28** with *m*-chloroperbenzoic acid at a rate much faster than **25** is converted into **27**. A mixture of sulfides **25** and **26** also was oxidized to the sulfoxides **27** and **28**.

We were now ready to carry out the final elimination process leading to **1**, and our first attempts at realizing this reaction were performed using the sulfoxide **27**.[15] On heating at 140 °C in acetic anhydride, **27** gave **1** in 85% crude yield. However, sulfoxide **28**, when subjected to the same reaction conditions, only gave a 44% crude yield of **1**. A mixture of **27** and **28** afforded a 60% unpurified yield of avenaciolide. To salvage this somewhat unfortunate situation, a mixture of **27** and **28** was heated to 140 °C with succinic anhydride instead of acetic anhydride. In this case, an 80% crude yield of **1** was obtained which on crystallization from ether–petroleum ether afforded pure racemic **1** in 73.3% yield. The synthetic substance was found identical in all respects, except optical rotation, with authentic avenaciolide.[16]

Quite different in design from those reported by Johnson and by Fraser-Reid, the above synthesis of avenaciolide, in our judgment, clearly demonstrates the power of this type of multiple-bond-forming methodology. In the latter regard, we note that a wide variety of natural products have yielded to synthesis by employment of this methodology since the original illustration of this strategy was detailed so elegantly by Stork.[5]

## Experimental Section[17]

**Ethyl Propiolate.** To a solution of propiolic acid (50 g, 0.715 M) in absolute ethanol (150 mL) at ice-bath temperature was added dropwise sulfuric acid (15 g) (5 min). The reaction was stirred at 22 °C for 50 h and then poured over ~200 g of ice and water. The product was extracted with ether (5 × 40 mL), washed with saturated $NaHCO_3$ (4 × 30 mL), dried ($Na_2SO_4$ and $MgSO_4$), and then distilled to give a pale yellow oil (39.0 g, 56% yield). Redistillation from calcium chloride gave 36.1 g (52% yield) of a colorless oil: bp 116–118 °C (lit.[18] bp 118 °C); IR ($CHCl_3$) 3300, 1715 cm$^{-1}$; NMR ($CDCl_3$) $\delta$ 1.35 (t, 3 H), 2.96 (s, 1 H), 4.35 (q, 2 H).

**Ethyl 4-Hydroxy-2-dodecynoate (5).** To a solution of lithium diisopropylamide (0.06 M, 1.0 equiv) in tetrahydrofuran (60 mL, 1.0 M) at −70 °C was added ethyl propiolate (5.88 g, 0.060 M) at such a rate as to maintain the internal temperature below −60 °C. The resulting yellow solution was stirred at −70 °C for 70 min. Nonanal (7.52 g, 0.60 M) was then added dropwise at −70 °C, and then the reaction was stirred at −70 °C for 22 h. The reaction was made acidic by addition of 50% HCl at −70 °C. The reaction mixture was then allowed to reach 4 °C, and the product was then extracted with ether (4 × 30 mL), washed with saturated $NaHCO_3$ (4 × 20 mL) and saturated NaCl (1 × 20 mL), dried ($MgSO_4$), and evaporated to give a yellow orange oil (14.5 g, 98% yield). Distillation gave a pale yellow oil (80% recovery): bp 134–138 °C ($10^{-3}$ Torr); IR ($CHCl_3$) 3600, 3400, 2240, 1710 cm$^{-1}$; NMR ($CDCl_3$) $\delta$ 0.90 (t, 3 H), 1.32 (m, 15 H), 1.76 (m, 2 H), 3.35 (s, 1 H), 4.34 (q, 2 H), 4.59 (s, 1 H); UV $\lambda_{max}^{MeOH}$ 215 nm ($\epsilon$ 3000); mass spectrum *m/e* 240 (parent).

**4-Hydroxy-2-dodecynoic Acid (6).** To a solution of crude ethyl 4-hydroxy-2-decynoate (14.5 g, 0.059 M) in methanol (60 mL, 1.0 M) at 0 °C was added dropwise a solution of 20% aqueous KOH (20 mL, 0.072 M). After the addition was complete, the reaction was stirred at 22 °C for 1 h. The reaction was poured over an ice–water mixture (100 mL) and extracted with ether (2 × 40 mL). The aqueous layer was then made acidic (pH 1) with cold concentrated HCl. The product was extracted with methylene chloride (5 × 50 mL), dried ($MgSO_4$), and evaporated to give a yellow oil (10.5 g, 85% yield) which crystallized on standing. Recrystallization from ether–petroleum ether gave white plates: 9.87 g, 80% yield; mp 64–66 °C; IR ($CHCl_3$) 3600, 3400, 2240, 1695 cm$^{-1}$; NMR ($CDCl_3$) $\delta$ 0.90 (t, 3 H), 1.31 (s, 12 H), 1.65 (m, 2 H), 4.60 (t, 1 H), 7.75 (s, 2 H); mass spectrum *m/e* 212 (parent).

**5-*n*-Octyl-2(5*H*)-furanone (3).** To a solution of 4-hydroxy-2-dodecynoic acid (4.24 g, 0.020 M) in methanol was added 5% Pd/$BaSO_4$ (82 mg, 2% by weight) and quinoline (76 mg, 93%, $\mu$L/mg to cata-

lyst). Reaction was placed on hydrogenator and, after taking up the theoretical amount of hydrogen, was filtered and evaporated. The resulting oil was dissolved in ether (100 mL) and shaken in a separatory funnel with concentrated HCl (3 mL), washed with water (1 × 20 mL) and saturated $NaHCO_3$ (3 × 20 mL), dried ($MgSO_4$), and evaporated to give a yellow oil (3.72 g, 95% yield). Distillation of this material gave a colorless liquid which solidified on standing (3.52 g, 95% yield): bp 94–96 °C ($10^{-4}$ Torr) (lit.[8] bp 152–153 °C (6 mm); mp 34–36 °C; IR ($CHCl_3$) 1755, 1605 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.90 (t, 3 H), 1.32 (s, 12 H), 1.75 (m, 2 H), 5.19 (m, 1 H), 6.28 (dd, 1 H), 7.41 (dd, 1 H); UV $\lambda_{max}^{MeOH}$ 217 nm ($\epsilon$ 14 500); mass spectrum *m/e* 196 (parent). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.50; H, 10.21.

**5-Methyl-2(5*H*)-furanone (7).** Following the same procedure outlined above for the preparation of **3**, ethyl 4-hydroxy-2-pentynoate was prepared as a colorless oil: bp 36–39 °C ($10^{-3}$ Torr); IR ($CHCl_3$) 3600, 2240, 1710 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.29 (t, 3 H), 1.50 (d, 3 H), 3.90 (s, 1 H), 4.29 (q, 2 H), 4.67 (t, 1 H); mass spectrum *m/e* 142 (parent).

This ester was hydrolyzed, as above, to give 4-hydroxy-2-pentynoic acid as a crystalline solid: mp 62–65 °C (lit.[19] mp 66–67 °C); IR ($CHCl_3$) 3500, 2240, 1700 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.52 (d, 3 H), 4.52 (q, 1 H), 5.92 (s, 2 H); mass spectrum *m/e* 114 (parent).

Hydrogenation of this acid, as previously described, gave **7** as an oil: bp 65 °C (2.5 Torr) (lit.[20] bp 84 °C (10 Torr)); IR ($CHCl_3$) 1760, 1600 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.46 (d, 3 H), 5.13 (m, 1 H), 6.06 (d, 1 H), 7.46 (d, 1 H); UV $\lambda_{max}^{MeOH}$ 214 nm ($\epsilon$ 9800); mass spectrum *m/e* 98 (parent). Anal. Calcd for $C_5H_6O_2$: C, 61.22; H, 6.71. Found: C, 61.51; H, 7.01. The overall yield of **7** was 65%.

**5-Phenyl-2(5*H*)-furanone (8a) and 5-Phenyl-2(3*H*)-furanone (8b).** Prepared from ethyl 4-hydroxy-4-phenyl-2-butynoate (oil): bp 95–98 °C (4 × $10^{-4}$ Torr)); IR ($CHCl_3$) 3590, 2240, 1710 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.27 (t, 3 H), 3.46 (d, 1 H), 4.20 (q, 2 H), 5.47 (d, 1 H), 7.36 (m, 5 H); mass spectrum *m/e* 204 (parent).

This material was hydrolyzed into its corresponding acid which without characterization was hydrogenated to give a mixture of **8a** and **8b**. Sublimation of this mixture gave pure **8b** as a yellow crystalline solid: mp 90–91 °C (lit.[21] mp 91–92 °C)); IR ($CHCl_3$) 1800 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 3.38 (d, 2 H), 5.76 (t, 1 H), 7.35 (m, 3 H), 7.58 (m, 2 H); mass spectrum *m/e* 160 (parent). The overall yield of **8b** was 44%.

**5,5-Diethyl-2(5*H*)-furanone (9).** **9** was prepared from ethyl 4-ethyl-4-hydroxy-2-hexynoate: bp 62–65 °C (5 × $10^{-4}$ Torr) (lit.[8] bp 87–88 °C (7 Torr)); IR ($CHCl_3$) 3600, 2240, 1710 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.05 (t, 6 H), 1.30 (t, 3 H), 1.69 (q, 4 H), 2.66 (s, 1 H), 4.22 (q, 2 H); mass spectrum *m/e* 184 (parent).

This material was hydrolyzed to 4-ethyl-4-hydroxy-2-hexynoic acid: mp 56–59 °C; IR ($CHCl_3$) 3600, 2240, 1705 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.05 (t, 6 H), 1.30 (t, 3 H), 1.69 (q, 4 H), 2.66 (s, 1 H), 4.22 (q, 2 H); mass spectrum *m/e* 184 (parent).

On hydrogenation this acid afforded **9**: bp 34–37 °C ($10^{-3}$ Torr) (lit.[8] bp 122–124 °C (19 Torr)); IR ($CHCl_3$) 1755 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.89 (t, 6 H), 1.81 (m, 4 H), 6.02 (d, 1 H), 7.25 (d, 1 H); UV $\lambda_{max}^{MeOH}$ 214 nm ($\epsilon$ 15 500); mass spectrum *m/e* 140 (parent). Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.57; H, 8.61. The overall yield of **9** was 56%.

**5-Butyl-2(5*H*)-furanone (10).** **10** was prepared from ethyl 4-hydroxy-2-octynoate: bp 56–58 °C ($10^{-3}$ Torr); IR ($CHCl_3$) 3600, 2240, 1710 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.91 (t, 3 H), 1.35 (m, 9 H), 3.69 (s, 1 H), 4.23 (q, 2 H), 4.49 (q, 1 H); mass spectrum *m/e* 184 (parent).

This material was hydrolyzed to 4-hydroxy-2-octynoic acid: mp 84–85 °C; IR ($CHCl_3$) 3600, 2240, 1700 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.91 (t, 3 H), 1.51 (m, 6 H), 4.40 (t, 1 H), 6.00 (s, 2 H); mass spectrum *m/e* 156 (parent).

This material was hydrogenated to give **10**: bp 48–50 °C (5 × $10^{-4}$ Torr) (lit.[8] bp 121–125 °C (10 Torr)); IR ($CHCl_3$) 1755, 1600 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.91 (t, 3 H), 1.60 (m, 6 H), 5.05 (m, 1 H), 6.09 (d, d, 1 H), 7.47 (d, m, 1 H); UV $\lambda_{max}^{MeOH}$ 217 nm ($\epsilon$ 14 500); mass spectrum *m/e* 140 (parent). Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.62; H, 8.42. The overall yield of **10** was 57%.

***tert*-Butyl Tetrahydro-2-octyl-5-oxo-3-furanacetate (13).** To a solution of lithium diisopropylamide (1.0 mM) in tetrahydrofuran (1.0 mL) at −70 °C was added *tert*-butyl acetate (116 mg, 1.0 mM). After stirring for 20 min at −70 °C, a solution of **3** (196 mg, 1.0 mM) in tetrahydrofuran (1.0 mL) was added at a rate of 6 drops/min. Stirring was continued for an additional 3 h and the reaction was then quenched at −70 °C with saturated $NH_4Cl$ (1.0 mL). The product was extracted with methylene chloride (3 × 5 mL), dried over $MgSO_4$, and evaporated to give a colorless oil in 96% yield (300 mg): IR ($CHCl_3$) 1770, 1730 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.89 (t, 3 H), 1.42 (m, 14 H), 1.45 (s, 9 H), 2.45 (m, 5 H), 4.23 (d, t, 1 H); mass spectrum *m/e* 312 (parent).

**Tetrahydro-2-octyl-5-oxo-3-furanacetic Acid (11).** A solution of **13** (312 mg, 1.0 mM) and *p*-toluenesulfonic acid (*p*-TSA, 30 mg, 10% by weight) in benzene (7.0 mL) was brought to reflux (100 °C). The reflux condensor was removed to allow some benzene to distil off. After 2.0 mL of benzene had been removed, the reaction was allowed to reflux for 4 h. The reaction mixture was cooled and the product extracted with saturated $Na_2CO_3$ (3 × 4 mL). The aqueous phase was washed with ether (5 mL) and then acidified with cold concentrated HCl. The product was extracted from this acid solution with methylene chloride (4 × 4 mL), dried ($MgSO_4$), and evaporated to give an off-white powder: 243 mg, 91% yield; mp 42–45 °C. Five recrystallizations from petroleum ether gave 183 mg (72% yield) of a white powder: mp 53–54.5 °C (lit.[4a] mp 55–56 °C)); IR ($CHCl_3$) 3600–2600, 1760, 1700 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.90 (t, 3 H), 1.45 (m, 14 H), 2.56 (m, 5 H), 4.17 (m, 1 H); mass spectrum *m/e* 256 (parent).

**3-Hydroxy-3-(1-hydroxynonyl)glutaric Acid Bis-γ-lactone (2).** To a solution of lithium diisopropylamide (0.125 mM) in tetrahydrofuran (0.50 mL) at −70 °C was added a solution of **11** (30 mg, 0.117 mM) in tetrahydrofuran (0.50 mL) followed by HMPA (22 mg, 0.125 mM). The reaction was stirred for 5 min at −70 °C, followed by stirring for 30 min at 0 °C, whereupon it was recooled to −70 °C and cupric bromide ($CuBr_2$, 112 mg, 0.50 mM) was added. After stirring for 2.5 h at −70 °C, the reaction mixture was quenched with 10% HCl (1.0 mL) and ether (3.0 mL) was then added. The ether solution was separated, dried, and evaporated to dryness. The resulting residue was treated with saturated $NaHCO_3$ (2.0 mL) and the product extracted with ether–hexane (1:3, 5 × 3 mL), washed with saturated $NaHCO_3$ (1.0 mL), dried over $MgSO_4$, and evaporated to give an orange brown oil (20 mg, 69% yield). High pressure liquid chromatographic (LC) analysis of the product (6-ft Porasil II, 1:1 isooctane–chloroform, 2.0 mL/min) showed the presence of two compounds. The chromatographic data is supported by the following spectroscopic data which clearly indicate that the predominate isomer of the mixture has the *n*-octyl side chain trans to the lactone ring junction: IR ($CHCl_3$) 1785, 1795 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.89 (t, 3 H), 1.34 (m, 14 H), 2.96 (m, 3 H), 4.35 (m, 1 H), 5.01 (d, 1 H); mass spectrum *m/e* 254 (parent).

***tert*-Butyl Tetrahydro-4-iodo-octyl-5-oxo-3-furanacetate (14).** To a solution of lithium diisopropylamide (2.0 mM) in tetrahydrofuran (2.0 mL) at −70 °C was added *tert*-butyl acetate (232 mg, 2.0 mM). The reaction mixture was stirred for 20 min before a solution of **3** (352 mg, 1.8 mM) in tetrahydrofuran (2.0 mL) was added at a rate of 6 drops/min at −70 °C. The reaction mixture was stirred for 3 h at −70 °C. Iodine solution (freshly sublimed, 528 mg, 2.08 mM) in tetrahydrofuran (2.0 mL) was added at −70 °C. The reaction mixture was stirred for 20 min and quenched at −70 °C with concentrated HCl (24 drops) and $NaHSO_3$ (100 mg). The product was extracted with ether (3 × 6 mL) while still cold, washed with cold saturated $NaHSO_3$ (1 × 5 mL), cold saturated $NaHCO_3$ (5 mL), dried ($MgSO_4$), and evaporated to give a pale yellow oil in 97% yield (775 mg): IR ($CHCl_3$) 1765, 1720 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.89 (t, 3 H), 1.34 (m, 14 H), 1.49 (s, 9 H), 2.55 (m, 3 H), 4.12 and 4.45 (m, 1 H), 4.78 and 4.97 (d, 1 H); mass spectrum *m/e* 438 (parent). The integrations of the above methine peaks show what seems to be an isomer ratio of 84:16, the predominate isomer having the desired trans,anti,trans configuration.

**Tetrahydro-4-iodo-2-octyl-5-oxo-3-furanacetic Acid (15).** A solution of *p*-TSA (13.8 mg, 15% by weight) in benzene (7.0 mL) was dried by heating the solution to reflux and removing the condensor and allowing 2.0 mL of benzene to distil off (under $N_2$). Compound **14** (92 mg, 0.21 mM) was added and the reaction then refluxed (100 °C) for 3 h. The reaction mixture was cooled to 22 °C, saturated $NaHCO_3$ (3.0 mL) was added, and the reaction mixture was stirred for an additional 30 min. The organic layer was removed, dried ($MgSO_4$), and evaporated to give an orange oil (14 mg, 10%). This material was spectroscopically and chromatographically identical with **2**. The aqueous phase was acidified with concentrated HCl and the product was extracted with methylene chloride (4 × 4 mL), dried over $MgSO_4$, and evaporated to give 72 mg (90% yield) of a deep yellow

oil, **15**; IR ($CHCl_3$) 3600–2600, 1760, 1710 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.89 (t, 3 H), 1.35 (m, 14 H), 2.70 (m, 3 H), 4.15 (m, 1 H), 5.00 (d, 1 H); mass spectrum *m/e* 382 (parent).

**2-Hydroxy-3-(1-hydroxynonyl)glutaric Acid Bis-γ-lactone (2).** To a suspension of NaH (57% oil dispersion, 2.26 mg, $5.35 \times 10^{-2}$ mM) in tetrahydrofuran (0.30 mL) at 22 °C was added **15** (20 mg, 0.525 mM). The reaction was stirred for 5 h at 22 °C. Reaction mixture was then poured into water (2.0 mL) and the product was extracted with ether (3 × 5 mL), dried ($MgSO_4$), and evaporated to give a yellow oil (10.5 mg, 71% yield) which was spectroscopically and chromatographically identical with the bislactone **2**.

***tert*-Butyl Propionate.** To a solution of *tert*-butyl alcohol (65 g, 0.88 M) and *N,N*-dimethylaniline (111 g, 0.88 M) in ether (50 mL) at 22 °C was added propionyl chloride (74.3 g, 0.81 M). The reaction was stirred for 12 h at 22 °C. Water (100 mL) was added and the product was extracted with ether (2 × 100 mL), washed with 10% $H_2SO_4$ (6 × 50 mL), saturated $NaHCO_3$ (3 × 50 mL), and saturated NaCl (1 × 50 mL), dried over $MgSO_4$, and then distilled to give 70 g (70% yield) of a colorless liquid: bp 117–119 °C (lit.[22] bp 120–121 °C); IR ($CHCl_3$) 1720 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.07 (t, 3 H), 1.44 (s, 9 H), 2.22 (q, 2 H).

***tert*-Butyl 2-Thiomethylpropionate.** To a solution of lithium diisopropylamide (0.11 M) in tetrahydrofuran (11 mL) at −70 °C was added *tert*-butyl propionate (13 g, 0.10 M). The reaction was stirred for 20 min at −70 °C whereupon dimethyl disulfide (14.1 g, 0.15 M) was added. The reaction was stirred at −70 °C for 1 h and then quenched with 6 N HCl (19 mL). The product was extracted with ether (3 × 25 mL), washed with saturated $NaHCO_3$ (2 × 10 mL), dried over $MgSO_4$, and evaporated to give a colorless oil (16.5 g, 94% yield). Distillation afforded 14.3 g (81% yield) of a colorless oil: bp 70–72 °C (16 Torr); IR ($CHCl_3$) 1720 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.40 (d, 3 H), 1.44 (s, 9 H), 2.14 (s, 3 H), 3.12 (q, 1 H); mass spectrum *m/e* 176 (parent).

**Preparation of the *tert*-Butyl-3-(1-hydroxynonyl)-2-methyl-2-thiomethylglutaric Acid 5γ-Lactones (17 and 18).** To a solution of lithium diisopropylamide (0.25 mM) in tetrahydrofuran (0.25 mL) at −70 °C was added *tert*-butyl 2-thiomethylpropionate (44 mg, 0.25 mM). The reaction mixture was stirred for 20 min at −70 °C. Then a solution of **3** (49 mg, 0.25 mM) in tetrahydrofuran (0.25 mL) was added at a rate of 6 drops/min at −70 °C. The reaction mixture was stirred for 3 h and then quenched at −70 °C with saturated $NH_4Cl$ (1.0 mL). The product was extracted with methylene chloride (3 × 5 mL), dried over $MgSO_4$, and evaporated to give a pale yellow oil (93 mg, 100% yield): IR ($CHCl_3$) 1770, 1715 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.89 (t, 3 H), 1.40 (m, 14 H), 1.51 (s, 9 H), 2.08 (m, 3 H), 2.75 (m, 3 H), 4.25 and 4.58 (m, 1 H); mass spectrum *m/e* 372 (parent).

**Preparation of the 3-(1-Hydroxynonyl)-2-methyl-2-thiomethylglutaric Acid 5γ-Lactones (19 and 20).** To a predried solution of *p*-TSA (15 mg, 15% by weight) in benzene (2.5 mL) at 22 °C was added a mixture of the lactone esters **17** and **18** (93 mg, 0.25 mM). Reaction was heated at reflux (110 °C) for 3 h and then cooled, and the product extracted with saturated $NaHCO_3$ (4 × 2 mL). The aqueous phase was acidified (concentrated HCl), and the product was extracted with methylene chloride (4 × 3 mL), dried over $MgSO_4$, and evaporated to give a colorless semicrystalline oil (71 mg, 90% yield): IR ($CHCl_3$) 3600–2400, 1775, 1705 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.89 (t, 3 H), 1.46 (m, 17 H), 2.16 (m, 3 H), 2.83 (m, 3 H), 4.34 and 4.66 (m, 1 H); mass spectrum *m/e* 316 (parent).

**Preparation of the *tert*-Butyl 3-(1-Hydroxynonyl)-4-iodo-2-methyl-2-thiomethylglutaric Acid 5γ-Lactones (21 and 22).** To a solution of lithium diisopropylamide (2.0 mM) in tetrahydrofuran (2.0 mL) at −70 °C was added *tert*-butyl 2-thiomethylpropionate (352 mg, 2.0 mM). The reaction was stirred for 20 min at −70 °C. Then a solution of **3** (392 mg, 2.0 mM) in tetrahydrofuran (2.0 mL) was added at a rate of 6 drops/min at −70 °C. The reaction mixture was stirred for 3 h at −70 °C. Then a solution of iodine (608 mg, 2.4 mM) in tetrahydrofuran (2.0 mL) was added at −70 °C. The reaction mixture was stirred for 25 min and then quenched at −70 °C with concentrated HCl (1.3 mL). The product was extracted with cold ether (4 × 5 mL), washed with cold saturated $NaHSO_3$ (2 × 3 mL) and saturated $NaHCO_3$ (2 × 3 mL), dried over $MgSO_4$, and evaporated to give a pale yellow oil (980 mg, 97% yield): IR ($CHCl_3$) 1770 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.90 (t, 3 H), 1.43 (m, 14 H), 1.54 (s, 9 H), 2.16 (m, 3 H), 3.03 and 3.17 (m, 1 H), 4.16 and 4.80 (d, m, 1 H), 4.64 and 4.95 (d, 1 H); mass spectrum *m/e* 499 (parent).

**Preparation of the 3-(1-Hydroxynonyl)-4-hydroxy-2-methyl-2-thiomethylglutaric Acid Bis-γ-lactones (25 and 26). Method A.** To a predried solution of *p*-TSA (148 mg, 15% by weight) in benzene (20 mL) at 22 °C was added a mixture of the iodolactone esters **21** and **22** (980 mg, 1.96 mM). The reaction mixture was refluxed (100 °C) for 3 h and then cooled to 22 °C. Saturated $NaHCO_3$ (7 mL) was added, and the reaction mixture was stirred for 45 min at 22 °C. The product was extracted with ether (3 × 10 mL), decolorized (activated charcoal), dried over $MgSO_4$, and evaporated to give a light brown oil (565 mg, 91.5% yield). Preparative LC on 6-ft Porasil II (elution with 25% chloroform–75% isooctane (2.0 mL/min)) gave two materials, **25** and **26**, which were isomeric with respect to the configuration of the thiomethyl group. Spectroscopic data for these two substances follow: **25**: IR ($CHCl_3$) 1795, 1785 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.89 (t, 3 H), 1.43 (m, 14 H), 1.62 (s, 3 H), 2.22 (s, 3 H), 3.10 (dd, 1 H), 4.84 (dt, 1 H), 5.03 (d, 1 H). **26**: IR ($CHCl_3$) 1795, 1785 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.89 (t, 3 H), 1.43 (m, 14 H), 1.58 (s, 3 H), 2.22 (s, 3 H), 2.73 (dd, 1 H), 4.47 (dt, 1 H), 5.01 (d, 1 H). **25** and **26**: mass spectrum *m/e* 314 (parent).

**Method B.** A solution of iodolactone esters **21** and **22** (76.0 mg, 0.152 mM) in dimethyl sulfoxide (29 mg, 0.46 mM) was heated at 140 °C for 15 min, cooled, and then poured over water (1.0 mL). The product was extracted with methylene chloride (3 × 5 mL), washed with water (3 mL), dried ($MgSO_4$), and evaporated to give a brown oil (45 mg, 96% yield) which was spectroscopically and chromatographically identical with the bis-γ-lactones **25** and **26** previously prepared.

**Preparation of the 3-(1-Hydroxynonyl)-2-methyl-2-sulfinylmethylglutaric Acid Bis-γ-Lactones (27 and 28).** To a solution of bis-γ-lactones **25** and **26** (118 mg, 0.376 mM) in methylene chloride (0.40 mL) at 0 °C was added a 0.5 M solution of *m*-chloroperbenzoic acid in methylene chloride (0.90 mL, 0.45 mM, 1.2 equiv). The reaction mixture was stirred for 30 min at 0 °C. The product was washed with saturated $NaHCO_3$ (3 × 1.0 mL), dried ($MgSO_4$), and evaporated to give a dark yellow oil (119 mg, 96% yield): IR ($CHCl_3$) 1785, 1060 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.90 (t, 3 H), 1.48 (m, 17 H), 2.67 (s, 3 H), 4.45 (m, 0.5 H), 5.06 (m, 1.5 H); mass spectrum *m/e* 330 (parent).

**Avenaciolide (1). Method A.** A solution of sulfoxides **27** and **28** (15 mg, 0.045 mM) in acetic anhydride (1.0 mL) was heated under $N_2$ at 140 °C for 30 min. The reaction mixture was cooled and evaporated to dryness to give a brown oil (13 mg, 100% yield) which was a mixture containing avenaciolide (60% by integration) and bis-γ-lactones **27** and **28** (15%). All other spectroscopic and chromatographic data agreed with NMR data.

**Method B.** A mixture of sulfoxides **27** and **28** (39.8 mg, 0.124 mM) and succinic anhydride (12 mg, 0.12 mM) was heated under $N_2$ at 140 °C for 30 min. The reaction mixture was cooled and evaporated to dryness and the excess succinic anhydride was then removed by sublimation. The residue was extracted with ether (10 mL), washed with cold 10% HCl (2 × 4 mL) followed by cold $NaHCO_3$ (2 × 3 mL), dried over $MgSO_4$, and evaporated to give a light tan semicrystalline oil (10 mg, 100% yield). Three of these reaction mixtures were combined and recrystallized from ether–petroleum ether to give a white solid (22 mg, 73.3% yield, mp 55–56 °C) identical spectroscopically and chromatographically with *dl*-avenaciolide: IR ($CHCl_3$) 1770, 1665 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.89 (t, 3 H), 1.40 (m, 14 H), 3.56 (m, 1 H), 4.41 (m, 1 H), 5.00 (d, 1 H), 5.84 (d, 1 H), 6.42 (d, 1 H); mass spectrum *m/e* 266 (parent).

**Acknowledgment.** We thank the National Institutes of Health, the National Science Foundation, the Alfred P. Sloan Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Shell Corporation for support of this work.

## References and Notes

(1) D. Brookes, B. K. Tidd, and W. B. Turner, *J. Chem. Soc.*, 5385 (1963).
(2) J. J. Ellis, F. H. Stodola, R. F. Vesonder, and C. A. Glass, *Nature (London)*, **203**, 1382 (1964).
(3) D. Brookes, S. Sternhell, B. K. Tidd, and W. B. Turner, *Aust. J. Chem.*, **18**, 373 (1967).
(4) (a) W. L. Parker and F. Johnson, *J. Am. Chem. Soc.*, **91**, 2708 (1969), and W. L. Parker and F. Johnson, *J. Org. Chem.*, **38**, 2489 (1973); (b) J. L. Herrmann, M. H. Berger, and R. H. Schlessinger, *J. Am. Chem. Soc.*, **95**, 7923 (1973); (c) R. C. Anderson and B. Fraser-Reid, *ibid.*, **97**, 3870 (1975).
(5) To our knowledge, the first and most elegant example of this type of methodology was reported by G. Stork, *Pure Appl. Chem.*, 383 (1968).

(6) W. M. Rathke and A. Lindert, *Tetrahedron Lett.*, 3995 (1971).
(7) Since this synthesis was initially described,[4b] we, as well as others, have utilized this type of reaction sequence in problems of total synthesis. For examples, see (a) R. E. Damon and R. H. Schlessinger, *Tetrahedron Lett.*, 4551 (1975); (b) F. E. Ziegler and J. A. Schwartz, *ibid.*, 4643 (1975); (c) R. E. Damon and R. H. Schlessinger, *ibid.*, 1561 (1976); (d) R. E. Damon, R. H. Schlessinger, and J. F. Blount, *J. Org. Chem.*, **41**, 3772 (1976); (e) F. E. Ziegler and J. A. Schwartz, *ibid.*, **43**, 985 (1978).
(8) A. Nobuhara, *Agric. Biol. Chem.*, **34**, 1745 (1970).
(9) W. E. Bachmann and E. K. Raunio, *J. Am. Chem. Soc.*, **72**, 2533 (1950).
(10) (a) E. K. Raunio and L. P. Remsberg, *J. Org. Chem.*, **25**, 1436 (1950); (b) H. O. House, W. L. Roelofs, and B. M. Trost, *ibid.*, **31**, 646 (1966).
(11) The yields reported for these furanones have not been optimized.
(12) M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, **93**, 4065 (1971).
(13) An interesting "methylene anion" of this type has recently been described by (a) J. P. Marino and D. M. Floyd, *J. Am. Chem. Soc.*, **96**, 7138 (1974); (b) J. P. Marino and D. M. Floyd, *Tetrahedron Lett.*, 3897 (1975); (c) J. P. Marino and J. S. Farina, *ibid.*, 3901 (1975).
(14) Shortly before this synthesis was published, B. M. Trost and T. N. Salzmann, *J. Am. Chem. Soc.*, **95**, 6843 (1973), published a similar type of elimination reaction leading to unsaturated carbonyl systems. We thank Professor Trost for a preprint of his work prior to its publication.
(15) This sulfoxide was used initially because we assumed that loss of the elements of MeSOH would require cis geometry between the MeSO and H residues. Clearly, with this reaction constraint, **27** can lose the elements of MeSOH only toward the methyl group.
(16) The authors thank Drs. F. Johnson, J. J. Ellis, and F. H. Stodola for their generous gifts of *l*-avenaciolide.
(17) Melting points were taken on a Fisher-Johns melting point block and are reported uncorrected. Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Reactions were run in either insulated cryostats (for temperatures <0 °C) or thermostated silicone oil baths with a temperature accuracy of 1 °C. Solvents were evaporated to dryness using a rotary evaporator at steam-bath temperatures and reduced pressures. Anhydrous solvents were distilled immediately before use. Tetrahydrofuran, diethyl ether, and 1,2-dimethoxyethane were distilled from lithium aluminum hydride, *tert*-butyl alcohol was distilled from calcium hydride, and methanol was distilled from magnesium turnings. Other solvents were at least reagent grade and used as received. Reagents were distilled at least once prior to use. Amines were distilled from calcium hydride under a nitrogen atmosphere. Hydrogenations were carried out in a slanted manifold all-glass apparatus at 1 atm at 0 °C. The system was evacuated by a water aspirator and then filled with hydrogen while stirring (this was repeated four times). Thin layer chromatography was performed on microscope slides coated by dipping in a slurry of either silica gel G or silica gel HF-254 (Brinkman) suspended in chloroform. High pressure liquid phase chromatography was performed on a Water's Associates ALC-202 instrument equipped with both an ultraviolet and differential refractometer detectors. Vapor phase chromatography was performed on a Hewlett-Packard 5700A instrument with TC detector and HP-5702A temperature programmer. Infrared spectra were recorded on either a Perkin-Elmer 700 or a Perkin-Elmer 467 spectrophotometer. Nuclear magnetic resonance spectra were recorded on either a JEOLCO C-60 HL or a JEOLCO MH-100 spectrometer using deuteriochloroform as solvent and tetramethylsilane as internal reference and are expressed as $\delta$ values, with the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Ultraviolet spectra were recorded on a Perkin-Elmer Digital 602 spectrophotometer.
(18) W. H. Perkin and J. L. Simonsen, *J. Chem. Soc.*, **91**, 155 (1907).
(19) L. J. Haynes and E. R. H. Jones, *J. Chem. Soc.*, 503 (1946).
(20) G. O. Schenk, *Angew. Chem.*, **64**, 12 (1952).
(21) J. Thiele and F. Straus, *Justus Liebigs Ann. Chem.*, **319**, 155 (1901).
(22) C. R. Hauser, B. F. Hudson, B. Abramovitch, and J. C. Shivers, "Organic Syntheses", Collect. Vol. III, Wiley, New York, 1955, p 144.

# Organic Structure Characterization by Natural-Abundance Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy. *Rauwolfia* Alkaloids and Model Compounds[1]

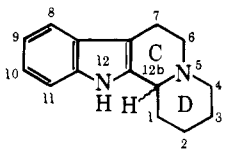
**Samuel N. Y. Fanso-Free,[2a] George T. Furst,[2a] P. R. Srinivasan,[2a] Robert L. Lichter,*[2a] Randall B. Nelson,[2b] Jill A. Panetta,[2b] and Gordon W. Gribble[2b,c]**

*Contribution from the Department of Chemistry, Hunter College of the City University of New York, New York, New York 10021, and the Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755.* *Received September 7, 1978*

**Abstract:** $^{15}N$ chemical shifts of yohimbine, reserpine, and several structurally related alkaloids and model compounds as well as those of several trifluoroacetate salts have been obtained at the natural-abundance level. Both the nature of the quinolizidine ring fusion at N-5 and substituents in a $\gamma$-gauche conformation markedly affect $^{15}N$ resonance positions. The latter factor induces shieldings of magnitudes (7–12 ppm) comparable to those observed in $^{13}C$ NMR. Where $\gamma$ effects are absent, a cis-fused quinolizidine nitrogen is shielded by 13–15 ppm compared with a trans-fused one. Protonation deshields nitrogens in both series, but the displacement is larger for the cis-fused case and serves to characterize this geometry. Hyperconjugation between the nitrogen lone pair and adjacent antibonding C–H orbitals is tentatively proposed to rationalize the shift difference between the cis and trans cases. The structure of sparteine is confirmed as existing in the all-trans configuration. Nitrogen resonance positions are solvent sensitive in a predictable manner.

## Introduction

Nuclear magnetic resonance (NMR) spectroscopy has proven to be a highly effective tool in elucidating structures of natural products. Both $^{1}H^{3}$ and $^{13}C^{4}$ NMR have been employed extensively for this purpose; the latter has been especially useful in characterizing subtle differences in geometry. Neither technique, of course, can give explicit information about the nature of any constituent nitrogen atoms, which in many cases markedly determine the properties of these substances. With the demonstration that nitrogen-15 spectra of several classes of compounds can be obtained at the natural-abundance level within reasonable time periods,[5,6] natural-abundance $^{15}N$ NMR is expected to play an increasingly important role in structure elucidation despite the low isotopic natural abundance (0.365%) and sensitivity (0.1% relative to an equal number of protons). We have used this approach to characterize the nitrogen resonance positions of representatives of the *Rauwolfia* family of indole alkaloids, because these were expected to allow distinctions to be made between effects of substituents and effects of bridgehead nitrogen geometry in the indoloquinolizidine skeleton (**1**). We have found that nitrogen resonance positions at N-5 reflect both factors in a very




**1**

0002-7863/79/1501-1549$01.00/0 