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Structure, Synthesis and Absolute Configuration of Leptosphaerin, a Metabolite of the Marine Ascomycete *Leptosphaeria oraemaris*.

James D. White,*[1] Rodney A. Badger,[2] Hollis S. Kezar III, Alexander J. Pallenberg and Guy A. Schiehser

Department of Chemistry, Oregon State University, Corvallis, Oregon, 97331

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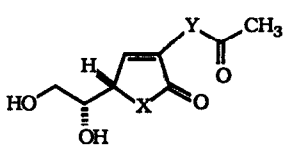
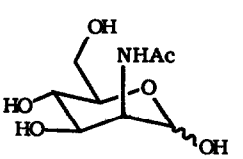
A structure **3** *erroneously deduced for the marine fungal metabolite leptosphaerin on the basis of spectroscopic evidence and an ambiguous x-ray analysis was disproved by synthesis. An alternative formulation* **1**, *including its absolute configuration, was confirmed by a stereospecific synthesis that began with condensation of the acetonide* **8** *of (R)-glyceraldehyde with the dianion from (Z)-N-methyl-2-benzyloxy-3-phenylthioacrylamide (***34***). The derived α-hydroxy lactone* **43** *was converted to the enamide moiety of leptosphaerin via decomposition of azidolactone* **45**. *Leptosphaerin is thus the γ-lactone of (4S,5R)-2-acetamido-4,5,6-trihydroxy-2-hexenoic acid and, as such, is a derivative of a D amino hexose.*

In the course of an examination of chemical constituents of higher marine fungi,[3] an isolate of the Ascomycete *Leptosphaeria oraemaris* (Linder) grown in artificial culture was found to yield a crystalline substance which was shown by high resolution mass spectrometry to possess the molecular formula $C_8H_{11}NO_5$. The physical properties of this material, named leptosphaerin, were similar to those of a product (**1**) claimed to be formed by oxidation of N-acetylmannosamine (**2**) with bromine,[4] but certain of our data could not be reconciled with this report. Moreover, attempts to reproduce the published oxidation of **2** led to a complex mixture from which no substance corresponding to **1** could be isolated. In view of these ambiguities, a detailed structural elucidation of leptosphaerin was undertaken which included both spectroscopic and x-ray crystallographic analyses,[5] and which initially led to its incorrect assignment as **3**. A synthesis of **3** revealed our error and was followed by a synthesis of leptosphaerin which conclusively established its structure and absolute configuration as shown in **1**.[6] We now describe details of the routes that led to **1** and **3**.



1 X=O, Y=NH
3 X=NH, Y=O



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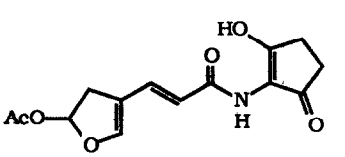

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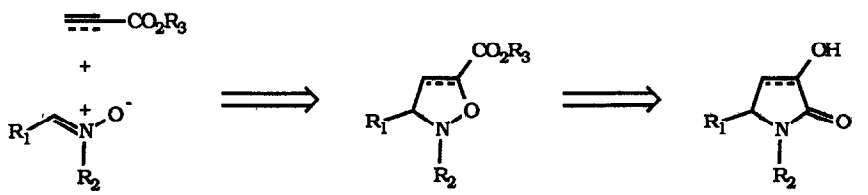
NMR evidence, including that derived from observation of spin-spin coupling of hydroxylic protons,[7] was compatible with either of the gross structures **1** or **3** for leptosphaerin but infrared absorptions at 1670 and 1745 cm^{-1} were taken as favoring **3**. An initial x-ray crystallographic analysis yielded a low quality set of diffraction data and misled us by "confirming" **3** as the structure for leptosphaerin. Contributing to the misinterpretation were difficulties associated with the placement of hydrogen atoms on the structure from the data available. As a result nitrogen and oxygen atoms were not securely identified even though the structure could be refined to a nominally acceptable level (R = 0.078). In this context, it is noteworthy that an analogous misassignment of nitrogen and oxygen atoms was made in the x-ray crystal structure of reductiomycin (**4**)[8] which was subsequently corrected through degradation and synthesis.[9] Regardless of our (erroneous) structural conclusion, the x-ray crystallographic analysis of leptosphaerin did provide useful stereochemical information by specifying its relative configuration as shown in **1** or **3**.

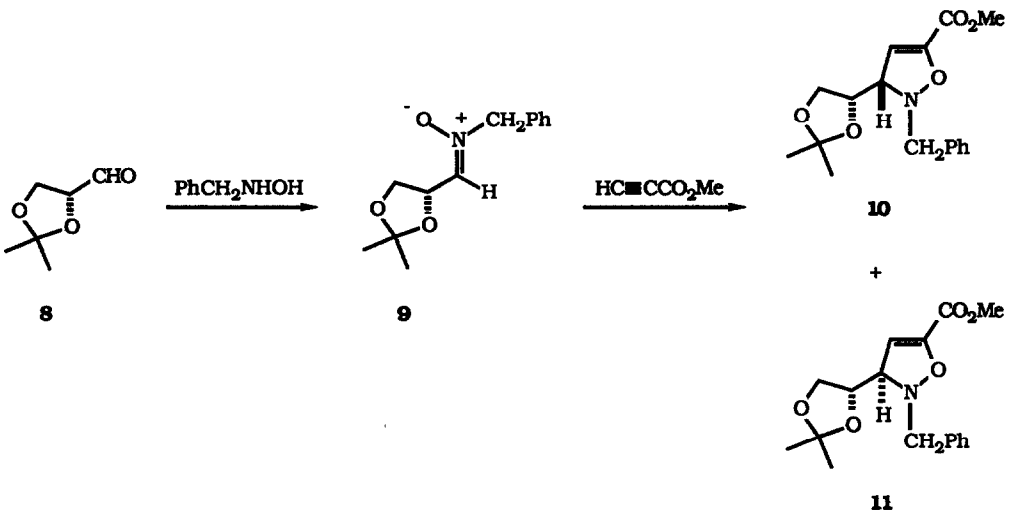
As a consequence of the spectroscopic and crystallographic evidence described above, **3** became the initial focus of our synthetic endeavors and, although the absolute configuration was not defined, it was arbitrarily assumed that leptosphaerin was derived from a hexose of the *D* series. This assumption specifies 4*S*,5*R* configuration for **3** and stipulates that a plan which assembles leptosphaerin by constructing the C(3)-C(4) bond must do so by a route that affords erythro C(4,5) geometry. A stereocontrolled approach to the α-keto γ-lactam moiety in the proposed structure (**3**) for leptosphaerin appeared feasible along lines established by Huisgen,[10] who has shown that nitrones (**5**) undergo cycloaddition to αβ-unsaturated esters to give 5-carboxy-isoxazolidines (**6**) which, upon hydrogenolysis, afford α-hydroxy γ-lactams (**7**). The stereochemical outcome of a dipolar cycloaddition using a chiral version of **5**, in which R_1 bears a stereogenic carbon α to the nitrone, was predicted to favor the desired erythro configuration based on the results of DeShong.[11] However, it was found that stereoselectivity is markedly dependent upon the nature of the substituents in the nitrone, as well as the dipolarophile, in these cases. The secondary stereochemical issue of exo-endo selectivity in the cycloaddition of **5** is less relevant here, since C(5) configuration of the isoxazolidine **6** would be lost at the subsequent α-keto lactam.[12]



5 **6** **7**

The acetonide **8**[13] of (*R*)-glyceraldehyde was prepared from D-mannitol and was condensed with N-benzylhydroxylamine to give the known nitrone **9**.[11] Our initial plan envisioned cycloaddition of **9** with methyl propiolate to give a $\Delta^{4,5}$-isoxazoline which, upon hydrogenolysis, was expected to yield an α-keto γ-lactam. In fact, the reaction of **9** with methyl propiolate in refluxing toluene gave a 1:1 mixture of erythro and threo isoxazolines **10** and **11**, respectively. Although these stereoisomers were readily separable by chromatography, their configurations could not be confidently assigned by NMR spectroscopy and each was therefore carried forward in the hope that a distinction would be possible at a later stage of the sequence. Hydrogenation

of **10** or **11** resulted not only in cleavage of the N-O bond and the N-benzyl group but in saturation of the C-C double bond as well. Consequently, in situ ring closure of the resulting amino ester gave, not an α-keto γ-lactam, but a mixture of stereoisomeric α-hydroxy lactams.



In contrast to its reaction with methyl propiolate, nitrone **9** underwent stereoselective cycloaddition with methyl acrylate to afford a 3:1 mixture of two products in virtually quantitative yield. Although these adducts could not be separated, subsequent transformations established that they were erythro and threo stereoisomers **12** and **13**, respectively. The major isomer **12** results from a diastereofacially selective addition by acrylate to the Z isomer of **9**[14] as illustrated in Figure 1. This stereoselectivity is in the same sense as that observed by DeShong[15] and gives rise to a *S,S* relationship between protons at C(3) and C(1'). The configuration of the ester substituent in **12** and **13** was not established, but on both electronic and steric grounds there should exist a strong preference for the "endo" transition state shown in figure 1,[15] leading to trans 2,5-disubstituted isoxazolidines.

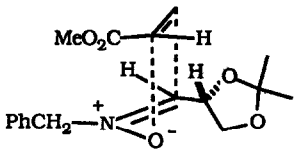
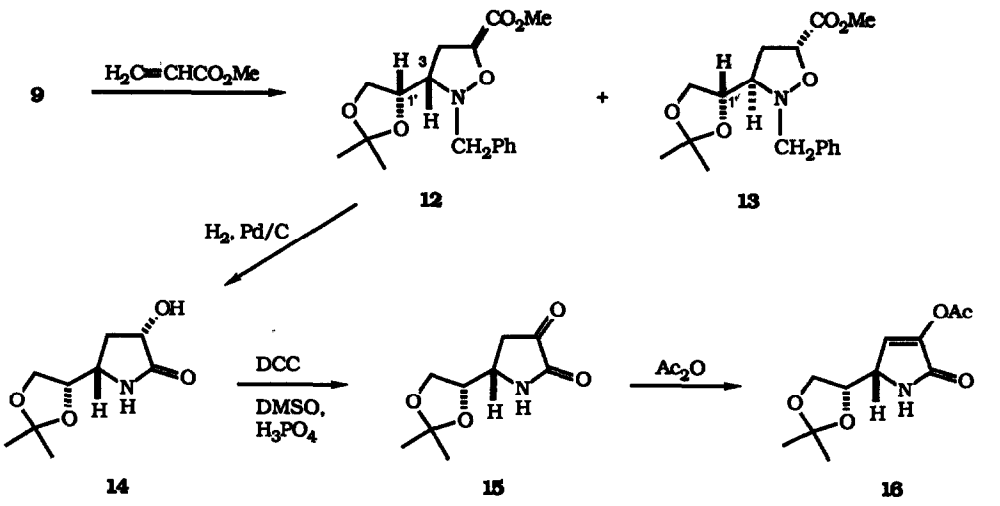


Figure 1. Transition state for the dipolar cycloaddition of **9** with methyl acrylate.

Hydrogenolysis of the mixture of **12** and **13** over palladium on charcoal resulted in scission of the isoxazolidine, removal of the benzyl substituent, and concomitant cyclization of the γ-amino ester to yield lactam **14**, easily separated by crystallization from its oily isomer. Pfitzner-Moffatt oxidation[16] of **14** furnished the unstable α-keto lactam **15** which was promptly acetylated to give the crystalline enol acetate **16**.[17] The ^{1}H NMR spectrum of **16**, which displayed a H(4)-H(5) coupling of 6 Hz, gave firm support to the assigned structure, yet was significantly different from that of the acetonide prepared from natural leptosphaerin. This



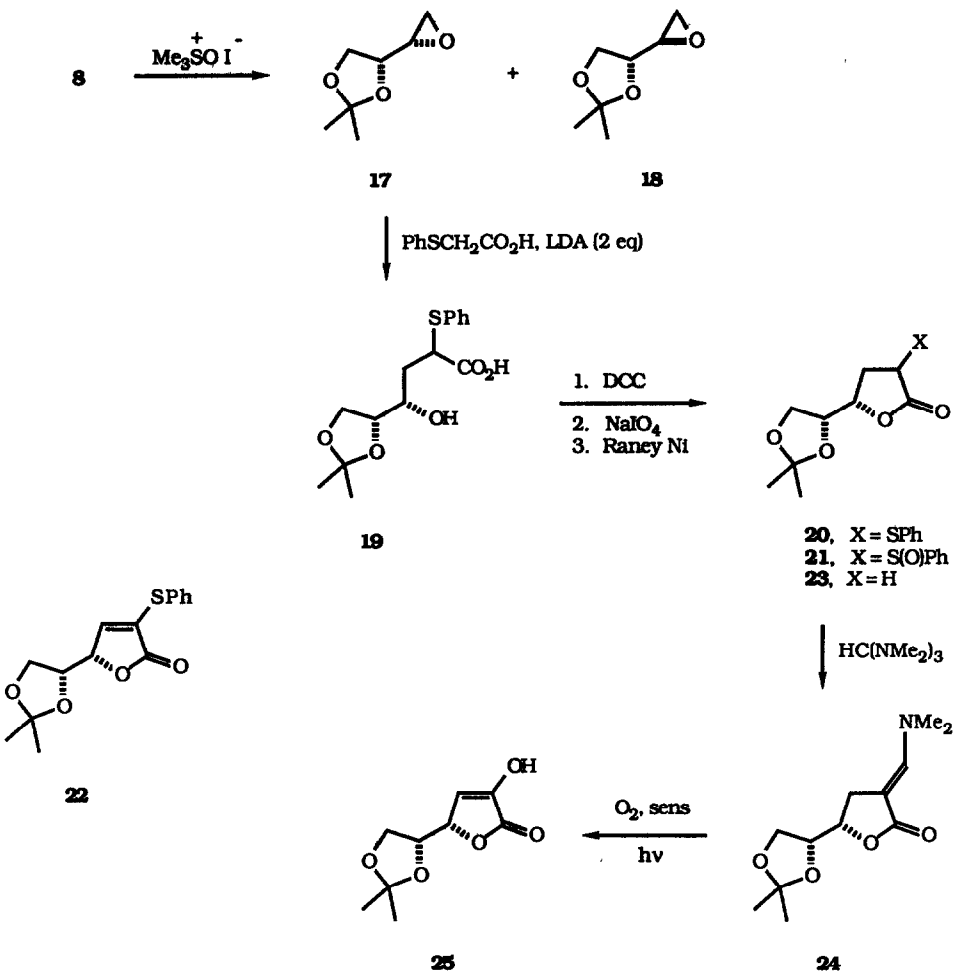
disparity was reinforced when the acetonide **16** was unmasked by acid-catalyzed hydrolysis. The diol obtained (**3**) was quite different from natural leptosphaerin in spectroscopic properties and tlc behavior.

The lack of identity between synthetic **3** and natural leptosphaerin left **1** as the only plausible structure for the metabolite. This formula posits leptosphaerin as a 2-aminohexose derivative and, as before, our plan for its synthesis was designed with the underlying assumption that it belonged to the *D* series of sugars.

Our starting point was again the acetonide **8** of (*R*)-glyceraldehyde, which was reacted with dimethylsulfoxonium methylide to produce a 5.3:1 mixture of erythro (**17**) and threo (**18**) epoxides, respectively. The predominant stereoisomer was assumed to be **17** on the basis of the classical Cram Rule selectivity principle, and conforms to previous observations of preferential si face attack at the carbonyl group of **8**.[18] Erythro epoxide **17** underwent clean alkylation with the lithio dianion of α-phenylthioacetic acid to give **19**, which was lactonized to cis and trans isomers of **20** with dicyclohexylcarbodiimide in the presence of (4-dimethylamino)-pyridine. Our original intention was to convert the phenylthio substituent of **20** to a keto group via Pummerer rearrangement of the corresponding sulfoxide (**21**), but this was thwarted by an intervening elimination to give the vinyl sulfide **22**. Consequently, an indirect method for preparing an α-keto lactone from **20** was investigated that took advantage of the singlet oxygenation of enamino lactones developed by Wasserman.[19]

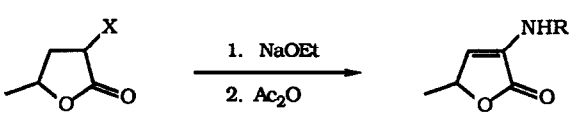
Hydrogenolysis of the mixture of sulfides **20** with Raney nickel afforded pure lactone **23** as an oil which condensed with tris(dimethylamino)methane to furnish the crystalline enamino lactone **24**. Photooxygenation of **24**, using Rose Bengal as sensitizer, led to a mixture of α-keto and enol lactones, with the enol tautomer **25** predominating. Further progress was stalled, however, when no means could be found for introducing the requisite nitrogen function into **25**. Attempts to condense this lactone with ammonia or a primary amine resulted in intractable mixtures, and hence an alternative approach was explored for elaborating the α-amino αβ-unsaturated γ-lactone unit of **1**.

A report by Kraatz et al.[20] that α-azido lactones undergo base-catalyzed decomposition to give α-enamino lactones was first examined with the model system **27**, prepared from α-bromo-γ-valerolactone (**26**)[21] by reaction with sodium azide. Exposure of an ethanol solution of **27** at 0 °C to a catalytic quantity of sodium



ethoxide led to rapid evolution of nitrogen and formation of **28**, acetylation of which produced the crystalline acetamide **29** in high yield.

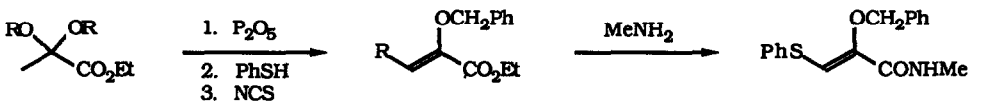
With these final stages of a putative route to **1** successfully tested, a complete sequence was available, in principle, from **23**. However, the lack of stereospecificity in the conversion of **8** to **17** and the necessity for a difficult chromatographic separation at an early stage of the pathway detracted from an otherwise appealing scheme. A publication by Schmidt[22] describing the dilithio dianion of (Z)-N-methyl-2-benzyloxy-3-phenyl



26, X = Br
27, X = N_3

28, R = H
29, R = $COCH_3$

thioacrylamide (**34**) and its highly diastereoselective, erythro condensation with aldehydes, such as the bis acetonide of arabinose, appeared to offer a means for circumventing this stereochemical obstacle, and **34** was therefore prepared by an established sequence[23] from ethyl pyruvate.



30, R = Et
31, R = CH_2Ph

32, R = H
33, R = SPh

34

The dibenzyl ketal **31** of ethyl pyruvate, conveniently obtained by transketalization of the diethyl ketal **30**,[24] underwent elimination with phosphorus pentoxide to give the α-benzyloxyacrylate **32**. Fluoride-catalyzed addition of thiophenol to **32**, followed by chlorination and Pummerer rearrangement, furnished **33** which condensed with methylamine to produce **34**. The dianion of **34**, prepared with two equivalents of lithium diisopropylamide at -78 °C and arbitrarily formulated as **35**, reacted with **8** to give a single, crystalline alcohol in good yield. Both Cram and Felkin-Anh[25] models for this addition predict si face attack by **35** at the aldehyde carbonyl of **8** (and hence erythro geometry for **36**), and this was confirmed by an x-ray crystal structure.[26] An ORTEP view of **36** is shown in figure 2.

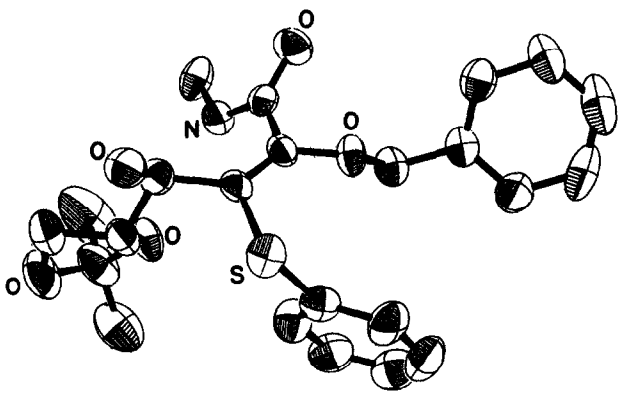
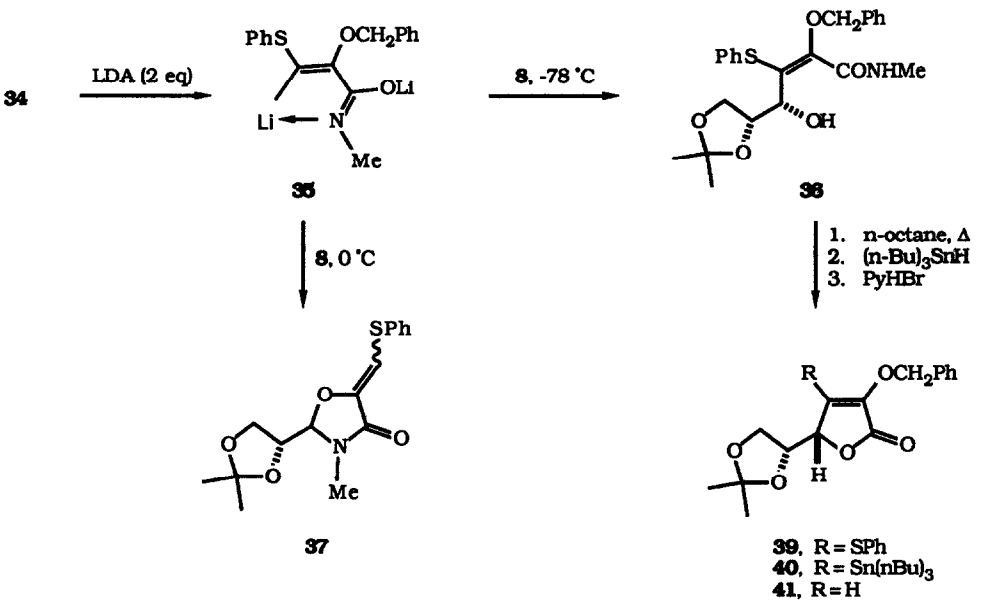


Figure 2. ORTEP plot of **36** determined by single crystal analysis showing erythro-C(4,5) configuration.

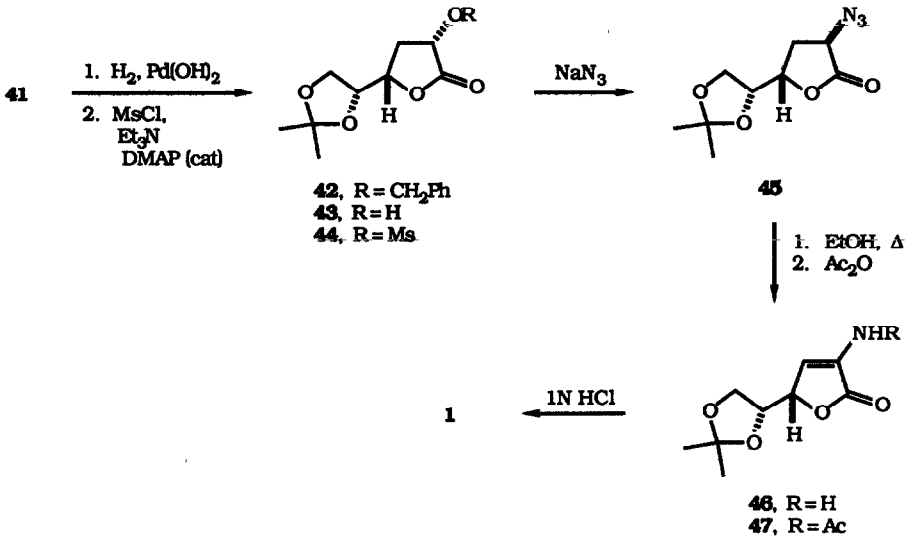
Interestingly, a quite different pathway is followed if the dianion **35** is first allowed to warm from -78 °C to 0 °C prior to addition of **8**. A product, $C_{16}H_{19}NO_4S$, was obtained which showed neither OH nor NH absorption in its infrared spectrum and from which protons due to the benzyloxy group were clearly absent in the NMR spectrum. The appearance of a new proton signal at δ 5.09 (d, J=7.5 Hz), along with spectral data from ^{13}C NMR, pointed to oxazolidone **37** as the structure of this unexpected product. Although **37** is highly crystalline, its configuration with respect to both the aminal carbon and vinyl sulfide geometry remain unknown. It was assumed at first that **37** arose from incomplete double deprotonation of **34** and that attack on

8 was initiated by the amide anion of **34**. However, when a solution of **35** in THF was brought to 0 °C and neutralized, the propiolamide **38** was virtually the sole product. We therefore believe that **37** originates from condensation of **8** with the anion of **38**, the latter resulting from elimination of benzyl oxide from dianion **35**. Suppression of this elimination by maintaining the reaction temperature at < 0 °C is therefore crucial to the successful preparation of **36**.

The hydroxy amide **36** underwent lactonization[27] to **39** in high yield in refluxing n-octane. In order to remove the phenylthio substituent from this lactone, **39** was next treated with tri-n-butylstannane.[22] The crystalline stannane **40** would not respond to protodestannylation[28] under conventional acidic catalysis without competing acetonide hydrolysis, but an effective means for this transformation was found when pyridine hydrobromide was employed. The crystalline lactone **41** was subjected to hydrogenolysis in the expectation that removal of the benzyl group would lead to the enol of the α–keto γ-lactone but, contrary to precedent,[22] the initial product was the benzyl ether **42**. It was subsequently found that saturation of the double bond of **41** was more rapid than hydrogenolysis of the benzyl group under a variety of conditions, with the



(presumed) cis disubstituted lactone **42** undergoing a slower hydrogenolysis to give the crystalline α-hydroxy lactone **43** in excellent yield. This serendipitous outcome was exploited by converting **43** to its mesylate **44** and then, by reaction with sodium azide, to the unstable α-azido lactone **45**. The latter was even more cooperative than the model system **27** in suffering spontaneous loss of nitrogen in refluxing ethanol to afford the enamine **46**. This amine was promptly acetylated to give a crystalline substance **47**, mp 128-129 °C, $[\alpha]_D^{22}$ -51°, that corresponded in every respect with the acetonide prepared from natural leptosphaerin.[29] Finally, when **47** was



subjected to hydrolysis, it afforded a quantitative yield of **1**, identical by comparison of mp, optical rotation, ^1H and ^{13}C NMR spectra and chromatographic behavior with leptosphaerin.

The synthesis of **1** confirms the structure and absolute configuration of leptosphaerin as (4*S*,5*R*)-2-acetamido-4,5,6-trihydroxy-2-hexenoic acid γ-lactone. It is thus a derivative of a *D* sugar, perhaps *D*-fructose. An x-ray crystallographic structure determination of leptosphaerin carried out subsequently yielded a data set which permitted unambiguous differentiation of oxygen and nitrogen atoms and thereby removed the error that had led to the incorrect assignment **3**.[30]

Experimental Section

All solvents were reagent grade and were distilled through glass. Solvents for reactions were dried by distillation from an appropriate drying agent shortly before use. THF, Et_2O, benzene, and toluene were distilled from potassium benzophenone ketyl under argon. Diisopropylamine, pyridine, DMSO, CH_2Cl_2, Et_3N, and DMF were distilled from CaH under argon. Starting materials and reagents were obtained from commercial suppliers unless otherwise noted.

Reaction flasks were oven-dried overnight at or above 165 °C or flame-dried and cooled in a desiccator over anhydrous $CaSO_4$ immediately prior to use. Syringes were oven-dried overnight and cooled in a desiccator as above. Removal of solvent was carried out at water aspirator pressure with a rotary evaporator and residual solvent was removed by vacuum pump.

Flash chromatography was performed using silica gel 60 (230-400 mesh ASTM) and an elution rate of approximately 5 cm per min. Analytical thin layer chromatography was carried out with precoated TLC plates (silica gel 60 F-254, 0.2 mm layer thickness) cut to a size of 2.6 x 6.7 cm.

Nuclear magnetic resonance (NMR) spectra were obtained at either 80 MHz or 400 MHz. Infrared spectra (IR) were recorded on either a FT instrument or a grating instrument. Optical rotations were determined with a polarimeter using cells of 1 decimeter pathlength and 1 mL capacity. Low and high resolution mass spectra (MS) were measured on Varian-MAT CH7 and Kratos MS-50 spectrometers using electron impact ionization at a

potential of 70 eV. Melting points were determined with a capillary melting point apparatus and are uncorrected.

Isolation of Leptosphaerin. 30 mL batches of a medium consisting of 10 g of glucose, 1 g of ammonium succinate, 1 g of Difco yeast extract, and 40 g of Rila marine mix diluted to 1 L with distilled water were placed in 125 mL Erlenmeyer flasks and autoclaved at 120 °C for 20 min. The media were inoculated from a stock culture of *L. oraemaris* and the flasks were shaken at 25 °C for 7 days. The contents were homogenized in a sterile blender, transferred to 500 mL Erlenmeyer flasks containing 150 mL of the medium used above, and incubated at 25 °C for a further 7 days on a rotary shaker. The cultures were harvested by suction filtration, which separated the medium from the mycelium. The culture filtrate was concentrated to dryness and was extracted 6 times with 150 mL of hexane. The residue was dissolved in 1 L of H_2O and was exhaustively extracted with EtOAc. The EtOAc extract of the culture filtrate was chromatographed on silica gel, using EtOAc as eluant. Evaporation of the first fractions yielded 25 mg of crystalline but slightly impure material. Preparative thin-layer chromatography (EtOAc) gave a UV active band (R_f 0.35) which was eluted from the silica with acetone. After evaporation of the solvent, recrystallization of the residual solid from EtOAc gave 16 mg of leptosphaerin as needles: $[\alpha]_D^{23}$ +38.8° (c 0.12, H_2O); mp 189.5-190.5 °C; UV (MeOH) λ_{max} 246 nm; IR (KBr) 3435, 3355, 3290, 1745, 1670, 1640, 1540, 1340, 1260, 1140, 1075, 1035, 870, and 780 cm^{-1}; ^1H NMR (acetone-d_6) δ 8.88 (1H, broad, exchanged with D_2O), 7.48 (1H, d, J=2 Hz), 5.09 (1H, dd, J=2,5 Hz), 4.25 (1H, ddd, J=4,6,7 Hz), 4.11 (1H, dd, J=7.9 Hz), 3.93 (1H, dd, J=4,8 Hz), 2.17 (3H, s); (DMSO-d_6) δ 10.12 (1H, broad, exchanged with D_2O), 7.45 (1H, d, J=2 Hz), 5.14 (2H, m, 1H exchanged with D_2O), 4.11 (1H, t, J=5 Hz, exchanged with D_2O), 3.72 (1H, m), 3.48 (2H, m), 2.08 (3H, s); MS (rel. intensity) m/z 201.057 (M^+, 2, Calcd for $C_8H_{11}NO_5$: 201.064), 141.037 (100, calcd for $C_6H_7NO_3$: 141.043), 123 (72), 99 (52), 98 (31), 70 (40), and 43 (78).

Leptosphaerin Diacetate. A solution of 5 mg (0.025 mmol) of leptosphaerin in 0.2 mL of Ac_2O containing a catalytic amount of pyridine was maintained at reflux for 1 h and then was allowed to stand at room temperature for 24 h. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic extract was washed with 1N HCl, 1N $NaHCO_3$, and H_2O, dried over $MgSO_4$ and concentrated in vacuo. The crude product was subjected to preparative tlc (silica gel); and the UV active band (R_f 0.69) was eluted with Et_2O to give 3 mg of leptosphaerin diacetate as a crystalline solid: mp 145-146 °C; IR (KBr) 3340, 3145, 1755, 1735, 1695, 1675, 1620, 1535, 1385, 1320, 1255, 1110, 1025, 965, 880, 835, 780, and 680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.12 (1H, broad), 7.45 (1H, d, J=2 Hz), 5.34 (2H, m), 4.33 (1H, dd, J=4,12 Hz), 4.08 (1H, dd, J=4,12 Hz), 2.17 (3H, s), 2.08 (3H, s), 2.05 (3H, s).

2-Benzyl-3-[1,2-O-(1-methylethylidene)]-5-carbomethoxy-4-isoxazoline (10 and 11). A solution of 235 mg (1.0 mmol) of **9** and 90 mg (1.0 mmol) of methyl propiolate in 5 mL of toluene was heated at relux for 1 h. Removal of the solvent gave 73% of a mixture of **10** and **11** which were separated by preparative tlc [benzene:EtOAc (9:1)].

10: R_f 0.52; IR (film) 1735 and 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (5H, s), 5.92 (1H, d, J=2 Hz), 4.28 (1H, d, J=12 Hz), 3.97 (5H, m), 3.80 (3H, s), 1.32 (3H, s), 1.26 (3H, s); MS m/z 319.143 (calcd for $C_{17}H_{21}NO_5$: 319.142).

11: IR (film) 1735 and 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (5H, s), 5.70 (1H, d, J=2 Hz), 4.35 (1H, d, J=13 Hz), 4.21 (1H, m), 3.98 (2H, m), 3.96 (1H, d, J=13 Hz), 3.81 (3H, s), 3.72 (1H, m), 1.28 (3H, s), and 1.26 (3H, s); MS m/z 319.140 (calcd for $C_{17}H_{21}NO_5$: 319.142).

2-Benzyl-3-[1,2-O-(1-methylethylidene)]-5-carbomethoxyisoxazolidine (12 and 13). A solution of 47 mg (0.2 mmol) of **9** in 4 mL of methyl acrylate was heated at reflux for 1 h. The solution was concentrated to a light syrup which was subjected to preparative tlc using benzene:Et_2O (1:2) as eluent. The band at R_f 0.75 was eluted to give 62 mg (97%) of a mixture of **12** and **13**: (IR (film) 1750, 1370, and 1360 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (5H, m), 4.87-4.47 (1H, m), 4.34-3.45 (6H, m), 3.77 (3H, s), 3.39-2.99 (1H, m), 2.85-2.26 (2H, m), 1.34 (3H, s), 1.32 (3H, s); MS m/z 321.156 (M^+, calcd for $C_{17}H_{21}NO_5$: 321.158).

3-Hydroxy-5-[1,2-O-(1-methylethylidene)]pyrrolidin-2-one (14). A solution of 1.50 g (4.80 mmol) of the mixture of **12** and **13** in 15 mL of ethanol was hydrogenolyzed over 300 mg of Pd/C (10%) at atmospheric pressure. After 18 h the solution was filtered through Celite and the solvent was removed under reduced pressure leaving a pale green syrup. This crystallized from acetone to give 477 mg (51%) of **14**: mp (decomp)

175 °C; IR (KBr) 3420, 3225, and 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.78 (1H, s), 4.46-3.65 (6H, m), 2.74-2.00 (1H, m), 1.87-1.53 (1H, m), 1.43 (3H, s), 1.33 (3H, s), MS m/z 201.102 (M^+, calcd for $C_9H_{15}NO_4$: 201.100).

Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.62; H, 7.57; N, 7.14.

3-Acetoxy-5-[1,2-O-(1-methylethylidene)]-3-pyrrolin-2-one (16). To a solution of 40 mg (0.2 mmol) of **14** in 3 mL of benzene:DMSO (9:1) was added 120 mg (0.6 mmol) dicyclohexylcarboditimide and 1 drop of polyphosphoric acid. The mixture was stirred at room temperature for 18 h, diluted with EtOAc and treated with 54 mg (0.6 mmol) of oxalic acid. The precipitate was removed by filtration and the filtrate was evaporated to dryness. The crude product **15** was dissolved in 3 mL of acetic anhydride containing a catalytic amount of pyridine and the solution was stirred at room temperature for 12 h. The reaction mixture was poured into ice-cold aqueous $NaHCO_3$ and was extracted with Et_2O. The combined ethereal extracts were dried and the solvent was removed to give **16**. Column chromatography on silica gel using EtOAc-MeOH (9:1) as eluent yielded 28 mg (58%) of **16**: mp 152-156 °C; IR 1770, 1720, and 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64 (1H, broad s, exchanged with D_2O), 6.89 (1H, t, J=2 Hz), 4.35 (1H, ddd, J=2,2,6 Hz), 4.16 (1H, q, J=6 Hz), 4.00 (1H, dd, J=6,8 Hz), 3.71 (1H, dd, J=5,8 Hz), 2.29 (3H, s), 1.46 (3H, s); MS m/z 241.097 (calcd for $C_{11}H_{15}NO_5$: 241.095).

Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.59; H, 6.11; N, 5.93.

3-Acetoxy-5-[1,2-O-(1-methylethylidene)]-3-pyrroline-2-one (3). To a solution of 10 mg (0.05 mmol) of **16** in 1 mL of 80% aqueous ethanol was added 10 mg of oxalic acid. The reaction mixture was maintained at 60 °C for 5 h. After removal of the solvent the crude residue was subjected to preparative tlc. Elution of the band at R_f 0.25 [EtOAc-MeOH (9:1)] with acetone gave **3**: IR 1770, 1720, and 1625 cm^{-1}; ^1H NMR (d_6-acetone) δ 7.56 (1H, broad s, exchanged with D_2O), 6.96 (1H, t, J=2 Hz), 4.30 (2H, m, 1H exchanged with D_2O), 3.75-3.30 (4H, m), 2.22 (3H, s); MS m/z 201.

Anal. Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.52; H, 5.76; N, 7.09.

1,2-Anhydro-3,4-O-(1-methylethylidene)-D-erythritol (17) and 1,2-anhydro-3,4-O-(1-methylethylidene)-D-threitol (18). Into a dry 250 mL three-neck Morton flask was placed 3.23 g (80.8 mmol) of fresh sodium hydride (60% dispersion in oil) and the solid was washed with several portions of dry hexane. The last traces of hexane were removed in vacuo and 17.8 g (80.8 mmol) of crushed trimethylsulfoxonium iodide was added. After flushing the flask with argon, 100 mL of dry DMSO was added dropwise over 20-30 min and the mixture was stirred vigorously for 40 min. To the resulting solution was added 9.55 g (67.57 mmol) of freshly distilled **8** in 10 mL of dry DMSO over 10 min. Periodic cooling of the reaction mixture was required to maintain it at room temp. After stirring for 4 h, the solution was diluted with 150 mL of H_2O and was extracted twice with 200 mL portions of Et_2O. The combined ether extracts were washed with satd aq NaCl, dried over Na_2SO_4, and carefully concentrated to give 9.6 g of a mixture of **17** and **18** as a yellow oil. Chromatography of the mixture on silica gel, eluting with hexane-ether (2:1), gave 4.77 g (50%) of **17** and 0.905 g (9.3%) of **18** as colorless oils.

17: $[\alpha]_D^{23}$ = +9.20° (c - 3.04 MeOH); ^1H NMR ($CDCl_3$) δ 1.37 (3H, s), 1.46 (3H, s), 2.62 (1H, dd, J=3,5 Hz), 3.82 (1H, dd, J=4,6 Hz), 3.00 (1H, m), 3.74-4.15 (3H, m).

Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.41; H, 8.30.

18: $[\alpha]_D^{23}$ = +5.94° (c = 2.02, MeOH); ^1H NMR ($CDCl_3$) δ 1.37 (3H, s), 1.47 (3H, s), 2.63 (1H, dd, J=3,5 Hz), 2.76 (1H, dd, J=4,6 Hz), 2.99 (1H, m), 3.79-4.09 (3H, m); MS m/z 144.

(4*S*,5*R*)-4-Hydroxy-5,6-O-(1-methylethylidene)-2-thiophenylhexanoic Acid (19). To a solution of 1.25 mL (8.93 mmol) of diisopropylamine in 2 mL of dry THF at -78 was added 5.76 mL (8.93 mmol) of nBuLi (1.4 M in hexane). After 5 min 2 mL of dry THF was added followed by a solution of 715 mg (4.25 mmol) of 2-thiophenylacetic acid in 4 mL of dry THF. A precipitate formed that redissolved during 15 min, after which a solution of 510 mg (3.54 mmol) of **7** in 3 mL of dry THF was added dropwise. The mixture was allowed to warm to room temperature and stirred for 18 h. After quenching with 3 mL of 2N NaOH the reaction mixture was extracted with 50 mL of Et_2O. The aqueous phase was acidified with 3N HCl to pH 1 and the resulting cloudy solution was extracted with 200 mL of Et_2O. The ethereal solution was washed with satd aq NaCl, dried over Na_2SO_4, and concentrated to give 1.19 g of impure **19** as a yellow oil. This was converted without purification to **20**.

Cis and Trans (4S,5R)-4-[5,6-O-(1-methylethylidene)]-2-thiophenylbutyrolactone (20). To a solution of 1.19 g of **19** in 15 mL of dry CH_2Cl_2 was added 876 mg (4.25 mmol) of dicyclohexylcarbodiimide and 3 mg of 4-(N,N-dimethylamino)pyridine. The mixture was stirred overnight, diluted with Et_2O and washed with H_2O and satd aq NaCl. The ethereal solution was dried over Na_2SO_4 and concentrated to give a brown oil. Chromatography on silica, eluting with hexane-Et_2O (1:1), afforded 897 mg (86% of **20** as a viscous, pale yellow oil: IR (film) 1762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (3H, s), 1.39 (3H, s), 1.92-2.95 (2H, m), 3.72-4.45 (5H, m), 7.19-7.63 (5H, m); MS (rel. intensity) m/z 294 (M^+, 59), 279 (47).

Anal. Calcd for $C_{15}H_{18}O_4S$: C, 61.22; H, 6.16. Found: C, 60.91; H, 5.99.

(4S,5R)-4-[5,6-O-(1-methylethylidene)]-γ-hexanolactone (23). To a slurry of Raney nickel (W-4) in 30 mL of refluxing EtOH was added 828 mg (2.82 mmol) of **20** in 10 mL of EtOH. After 2.5 h the reaction was allowed to cool to room temperature and filtered through celite. The filtrate was concentrated in vacuo and the residual oil was subjected to chromatography on silica. Elution with ether-hexane (3:1) furnished 404 mg (77%) of **23** as a colorless oil: $[\alpha]_D^{23}$ +4.9 (c 0.42, $CHCl_3$); IR (film) 1775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (3H, s), 1.41 (3H, s), 1.65-2.65 (4H, m), 3.55-4.55 (4H, m); MS m/z 171 (M^+ -CH_3).

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.91; H, 7.66.

(4S,5R)-2(E)-N,N-Dimethylaminomethylidene-4-[5,6-O-(1-methylethylidene)]-γ-hexanolactone (24). To a solution of 204 mg (1.09 mmol) of **23** in 1 mL of dry DMF was added 1 mL of tris(dimethylamino)methane. The solution was stirred overnight at 67 °C and then concentrated in vacuo to leave a brown oil. Chromatography of this oil on silica, eluting with ether, gave 224 mg (85%) of **24** as a colorless solid. A portion of this material was crystallized from ether-hexane to give **24**: ; mp 81.5-83.5 °C; $[\alpha]_D^{23}$ +22.6° (c 0.99, $CHCl_3$); IR($CHCl_3$) 1623, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (3H, s), 1.42 (3H, s), 3.01 (6H, s), 3.10 (2H, m), 3.82-4.40 (4H, m), 7.20 (1H, t, J=2 Hz); MS (rel intensity) m/z 241 (M^+, 80), 226 (43).

Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.80. Found: C, 59.73; H, 8.05; N, 6.06.

Reaction of 24 with Singlet Oxygen. A solution of 81 mg (0.34 mmol) of **24** in 30 mL of dry CH_2Cl_2 containing 5 mg of Rose Bengal was irradiated for 0.5 h at -78 °C through Pyrex with a sodium lamp as a stream of oxygen was passed through the solution. The pink solution was stirred with activated charcoal, filtered through Celite, and concentrated in vacuo to give 64 mg (94%) of a mixture of enol (**25**) and keto tautomers: IR ($CHCl_3$) 3550, 3350 (broad), 1770 (broad) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30-1.55 (6H, four s), 3.72-4.20 (3H, m), 4.75 (1H, dd, J=2,8 Hz), 6.30 (1H, d, J=2 Hz); MS (rel intensity) m/z 199 [$(M-1)^+$, 18], 185 (57).

2-Acetamido-γ-pent-2-enolactone (29). To a solution of 2 mg of Na in 3 mL of absolute EtOH at 0 °C was added dropwise a solution of 176 mg (1.25 mmol) of **27**[20] in 2 mL of absolute EtOH. Gas evolution began immediately. After stirring for 2 h at room temperature, the mixture was concentrated in vacuo and the crude **28** was taken up into 5 mL of CH_2Cl_2. This solution was cooled to 0 °C and 0.5 mL of Et_3N, followed by 1 mL of freshly distilled acetyl chloride, was added. The mixture was stirred at room temperature for 1 h, poured into ice-water, and extracted with CH_2Cl_2. The organic extract was washed with H_2O, dried over Na_2SO_4 and concentrated to give a yellow solid. This was crystallized from hexane-Et_2O to yield 163 mg (84%) of **29**: mp 118-121 °C; IR (KBr) 3360, 1755, 1700, 1655, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 and 6.15 (1H, d, J=2 Hz), 5.15 (1H, two overlapping 1, J=6 Hz), 2.17 (3H, s), 0.97 (3H, d, J=6 Hz); MS (rel intensity) m/z 155 (M^+, 29). 137 (19), 112 (63), 85 (21), 68 (22), 58 (31).

Anal. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.28; H, 5.57; N, 8.88.

(4R,5R)-(2Z)-N-Methyl-5,6-O-(1-methylethylidene)-3-S-phenyl-2-O-(phenylmethyl)-3-thio-erythro-hex-2-enonamide (36). To a stirred solution of 0.87 g, (8.59 mmol) of diisopropylamine in 25 mL of THF-HMPA (4:1) at -78 °C was added 5.1 mL (8.22 mmol) of a 1.6M solution of n-butyllithium in hexanes. The solution was stirred for 20 min at 0 °C and then cooled to -78 °C. A solution of 1.11g (3.73 mmol) of **34**[24] in 10mL of THF was added and the mixture was stirred at -78 °C for 2 h resulting in a yellow suspension. A solution of 0.486g (3.73mmol) of **8** in 10mL of THF was added and the mixture was allowed to warm to 0 °C over about 2 h, becoming clear at -50 °C. Upon reaching 0 °C the reaction mixture was quenched by the addition of 20 mL of satd aq NH_4Cl and diluted with 50 mL of ether. The layers were separated and the organic phase was washed

with water, dried over Na_2SO_4 and evaporated to give an amber oil. Chromatography of this oil on silica, eluting with EtOAc-hexane (1:1), gave 0.949g (59%) of **36** as a crystalline solid which was recrystallized from CH_2Cl_2-hexane to give needles: mp 105.5-106 °C; $[\alpha]_D^{22}$ -141° (c 3.1, $CHCl_3$); IR (film) 3320, 3060, 2940, 1655, 1382, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45-7.26 (10H, m), 6.77 (1H, d, J=5 Hz), 6.20 (1H, d, J=11 Hz), 5.02 (1H, d, J=11 Hz), 4.75 (1H, d, J=11 Hz), 4.37 (1H, dd, J=5,14 Hz), 4.09 (1H, m), 3.91 (1H, dd, J=5,9 Hz), 2.82 (3H, d, J=5 Hz), 1.37 (3H, s), 1.30 (3H, s); ^{13}C NMR ($CDCl_3$) δ 164.4, 146.1, 136.1, 133.5, 131.3, 129.2, 128.6, 128.51, 128.5, 128.2, 127.5, 109.6, 77.6, 73.3, 72.3, 68.0, 26.7, 26.1, 25.3; MS m/z 429 (M^+), 383, 280, 238, 101, 91.

Anal. Calcd for $C_{23}H_{27}NO_5S$: C, 64.31; H, 6.34; N, 3.26; S, 7.46. Found: C, 64.27; H, 6.18; N, 3.47; S, 7.58.

Oxazolidinone 37. To a solution of 0.533 g (5.27 mmol) of diisopropylamine in 20 mL of THF at -78 °C was added 3.5 mL (5.27 mmol) of a 1.5M solution of n-butyllithium in hexanes. The solution was stirred at 0 °C for 0.5 h, 0.45 g (2.51 mmol) of HMPA was added, and the solution was cooled to -78 °C. A solution of 0.751 g (2.51 mmol) of **34**[24] in 15 mL of THF was added and the mixture was stirred at 0 °C for 15 min and then cooled to -78 °C. A solution of 0.326 g (2.51 mmol) of freshly distilled **8** in 10 mL of THF was added and, after stirring the solution for 1 h at -78 °C, 10 mL of satd aq NH_4Cl was added. When the mixture had warmed to room temperature it was diluted with 50mL of Et_2O and the organic phase was separated, washed with water, and dried over Na_2SO_4. Evaporation of the solvent gave an amber oil. Chromatography of this oil on silica, with gradient elution using hexane-EtOAc (3:1 → 1:1), gave 453 mg (56%) of **37** as a colorless crystalline solid: mp 86-87 °C; IR (film) 3017, 1667, 1583, 1384, 1375, 761 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42-7.23 (5H, m), 6.25 (1H, s), 5.09 (1H, d, J=7 Hz), 4.14 (2H, m), 4.02 (1H, m), 3.10 (3H, s), 1.49 (3H, s), 1.37 (3H, s); ^{13}C NMR ($CDCl_3$) δ 160.1, 142.9, 134.3, 129.5, 129.2, 127.2, 110.9, 100.2, 91.4, 78.3, 65.8, 28.2, 26.7, 25.1; MS m/z 321, 220, 109.

Anal. Calcd for $C_{16}H_{19}NO_4S$: C, 59.79; H, 5.96; N, 4.36; S, 9.98. Found: C, 59.88; H, 5.94; N, 4.32; S, 9.96.

(4*R*,5*R*)-5,6-O-(1-methylethylidene)-3-S-phenyl-2-O-(phenylmethyl)-3-thio-γ-hex-2-enolactone (39). A solution of 21 mg (0.049 mmol) of **36** in 5 mL of n-octane was heated at reflux for 4 h and then evaporated to dryness in vacuo. The residual oil was passed through a pad of silica, eluting with hexane-EtOAc (1:1) to give 16.5 mg (87%) of **39** as a colorless oil: $[\alpha]_D^{21}$ -280° (c 2.2, $CHCl_3$); IR (film) 3060, 2980, 2930, 1765, 1625, 1380, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (10H, m), 5.37 (1H, d, J=12 Hz), 5.23 (1H, d, J=12 Hz), 4.84 (1H, d, J=4 Hz), 4.11 (1H, m), 3.78 (1H, dd, J=9,7 Hz), 3.53 (1H, dd, J=5,9 Hz), 1.34 (1H, s), 1.30 (1H, s); ^{13}C NMR ($CDCl_3$) δ 186.0, 141.8, 135.5, 134.5, 132.0, 129.8, 129.3, 128.5, 128.2, 128.0, 110.2, 77.8, 76.0, 72.0, 63.5, 25.8, 25.0; MS m/z 398 (M^+), 101, 91.

(4*R*,5*R*)-5,6-O-(1-methylethylidene)-2-O-(phenylmethyl)-γ-hex-2-enolactone (41). A solution of 0.80 g (2.0 mmol) of **39**, 1.10 g (13.7 mmol) of tri-n-butylstannane, and a trace of azobisisobutyronitrile (AIBN) in 30 mL of dry benzene was heated at reflux for 6 h. The resulting solution was cooled and concentrated to leave an oil. Chromatography of this oil on silica, eluting with hexane-EtOAc (10:1), gave a colorless oil which crystallized on standing. This material was dissolved in 50 mL of 1,1,2,2-tetrachloroethane and 0.58 g (3.62 mmol) of pyridine hydrobromide was added. The mixture was stirred overnight at 85 °C, cooled, and shaken with 50 mL of water. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic solutions were dried over Na_2SO_4 and concentrated. Chromatography of the residue on silica, with gradient elution using hexane-EtOAc (3:1 → 1:1), gave 0.42 g (79%) of **41** as a colorless crystalline solid which was recrystallized from CH_2Cl_2-hexane: mp 78.5-79 °C; IR (film) 2980, 1763, 1648, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36-7.25 (5H, m), 6.26 (1H, d, J=2 Hz), 5.03 (1H, d, J=12 Hz), 4.98 (1H, d, J=12 Hz), 4.70 (1H, dd, J=2,8 Hz), 4.09 (1H, dd, J=9,6 Hz), 4.02 (1H, dd, J=9,4 Hz), 3.85 (1H, m), 1.42 (3H, s), 1.33 (3H, s); ^{13}C NMR ($CDCl_3$) δ 167.0, 146.6, 134.6, 128.7, 128.6, 127.6, 116.1, 110.2, 78.4, 72.9, 66.6, 26.7, 24.9.

Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25. Found: C, 66.28; H, 6.22.

(4*S*,4*R*)-5,6-O-(1-methylethylidene)-2-hydroxy-γ-hexanolactone (43). A solution of 121 mg (0.42 mmol) of **41** in 3 mL of EtOH containing 53 mg of palladium hydroxide was stirred under an atmosphere of H_2 for 1 h. The suspension was filtered and the filtrate was concentrated. Chromatography of the residue on silica, eluting with hexane-EtOAc (1:1), gave 74 mg (88%) of **43** as a crystalline solid which was recrystallized from CH_2Cl_2-hexane: mp 89-90 °C; $[\alpha]_D^{21}$ -12.9° (c 2.0, $CHCl_3$); IR (film) 3400, 2980, 2930, 1785, 1380, 1370 cm^{-1}; ^1H NMR

($CDCl_3$) δ 4.56 (1H, ddd, J=4,10,10 Hz), 4.34 (1H, m), 4.21 (1H, m), 4.15 (1H, dd, J=6,9 Hz), 3.91 (1H, dd, J=5,9 Hz), 3.65 (1H, d, J=4 Hz), 2.75 (1H, m), 2.11 (1H, m), 1.45 (3H, s), 1.37 (3H, s); ^{13}C NMR ($CDCl_3$) δ 177.0, 110.3, 76.6, 76.5, 67.9, 66.3, 33.3, 26.5, 24.9.

Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.59; H, 7.02.

(4S,5R)-5,6-O-(1-methylethylidene)-2-methanesulfonyloxy-γ-hexanolactone (44). To a solution of 134 mg (0.664 mmol) of **43** and 1 mL of Et_3N in 10 mL of CH_2Cl_2 at 0 °C was added 152 mg (1.33 mmol) of methanesulfonyl chloride and a catalytic quantity of DMAP. After stirring for 0.5 h the mixture was diluted with 10 mL of water, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic extract was dried over $MgSO_4$ and concentrated. Chromatography of the residue on silica, eluting with hexane-EtOAc (1:1), gave 181 mg (97%) of **44** as a solid: $[\alpha]_D^{21}$ -8.85° (c 2, acetone); IR (film) 3021, 2993, 1800, 1375cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.38 (1H, dd, J=9,10 Hz), 4.38 (1H, ddd, J=6,6,10 Hz), 4.24-4.13 (2H, m), 3.91 (1H, dd, J=9,4 Hz), 3.28 (3H, s), 2.90 (1H, m), 2.41 (1H, ddd, J=10,10,13 Hz), 1.45 (3H, s), 1.36 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.7, 110.5, 76.6, 76.3, 73.6, 66.3, 39.8, 31.7, 26.6, 24.9.

Leptosphaerin Acetonide (46). To a solution of 98 mg (0.35 mmol) of **44** in 10mL of EtOH was added 68 mg (1.05 mmol) of sodium azide and the mixture was heated at reflux for 24 h. The resulting solution was evaporated to dryness and the residue was dissolved in 15 mL of CH_2Cl_2. To this solution at 0 °C were added 360 mg (3.6 mmol) of Et_3N, 91 mg (0.89 mmol) of acetic anhydride and a catalytic quantity of DMAP. The solution was stirred at 0 °C for 1 h and at room temperature for 2 h, and was diluted with 20 mL of H_2O. The layers were separated, the aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were dried over Na_2SO_4. Removal of the solvent yielded a colorless oil. Chromatography of this oil on silica, eluting with hexane-EtOAc (1:1), gave 57 mg (68%) of **46** as a crystalline solid which was recrystallized from CH_2Cl_2-hexane: mp 128-129 °C; $[\alpha]_D^{21}$ -57.3° (c 4.0, $CHCl_3$); IR (film) 3400, 2980, 2940, 1760, 1710, 1660, 1380, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.66 (1H, s), 7.56 (1H, d, J=2 Hz), 4.92 (1H, dd, J=2,7 Hz), 4.14-4.10 (1H, m), 4.03-3.98 (2H, m), 2.20 (3H, s), 1.46 (3H, s), 1.34 (3H, s); ^{13}C NMR ($CDCl_3$) δ 169.7, 169.3, 127.5, 126.8, 110.7, 81.7, 76.6, 66.4, 26.7, 25.1, 23.6; MS m/z 184, 101.

Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.78; H, 6.30; N, 5.86.

Leptosphaerin (1). A solution of 10 mg (0.04 mmol) of **46** in 2 mL of THF and 2 mL of 1N HCl at 0 °C was stirred for 1h and then allowed to warm to room temperature overnight. The mixture was evaporated to dryness and the residue was dissolved in 1 mL of MeOH. This solution was passed through silica and evaporated, and the residue was taken up into EtOAc. Chromatography of this solution on silica, eluting with EtOAc-hexane (3:1), gave 8 mg (99%) of **1**: mp 185-187 °C; $[\alpha]_D^{21}$ +40.0° (c 0.2, H_2O); ^1H NMR (acetone-d_6) δ 7.46 (1H, d, J=2 Hz), 5.06 (1H, dd, J=2,6 Hz), 4.23 (1H, ddd, J=4,6,7 Hz), 4.13 (1H, dd, J=9,7 Hz), 3.94 (1H, dd, J=4,9 Hz), 2.18 (3H, s); ^{13}C NMR (acetone-d_6) δ 170.1, 169.5, 128.0, 127.0, 81.9, 76.8, 66.1, 23.2.

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1. Fellow of the John Simon Guggenheim Memorial Foundation, 1988-89.
2. On leave from Southern Oregon State College, Ashland, Oregon.
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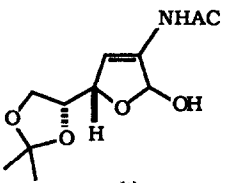

(i)

30. Personal communication from Professor J. C. Clardy.