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THE SYNTHESIS AND ABSOLUTE CONFIGURATION OF (+)-LEPTOSPHAERIN

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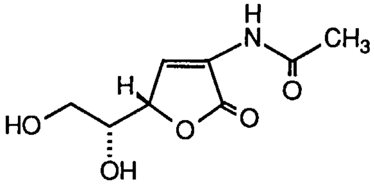
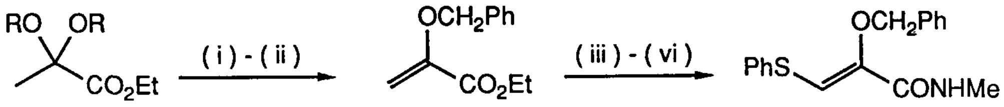
Summary. A synthesis of (+)-leptosphaerin (**1**), a metabolite of the marine ascomycete Leptosphaeria oraemaris (Linder), was accomplished from (R)-glyceraldehyde by a route that confirms the structural assignment and establishes the absolute configuration of **1** as (4S,5R).

The marine ascomycete Leptosphaeria oraemaris (Linder) produces a metabolite, leptosphaerin, whose structure and relative configuration have been established from spectral evidence and a single crystal x-ray analysis as **1**.[1] On the arbitrary assumption that leptosphaerin is a member of the D series of 2-aminohexoses,[2] its absolute configuration would also be represented by **1** and, in order to verify this, we undertook an enantioselective synthesis of the metabolite.



1

Ethyl 2-benzyloxyacrylate (**4**), prepared from the diethyl ketal **2**[3] of ethyl pyruvate, subsequent transketalization to **3** and elimination,[4] was converted to the amide **5** by the procedure of Schmidt and Betz.[5] The dilithio dianion of **5** has been shown to react with an arabinose derivative to give a γ-hydroxy-$\alpha\beta$-unsaturated amide with high diastereoselectivity[4] and, when this protocol was applied to the acetonide **6**[6] of R-(+)-glyceraldehyde at -78°C, smooth addition occurred to yield a crystalline product. The Felkin-Anh model[7] for the transition state of this addition leads to the prediction that attack by the dianion of **5** should take place at the si face of **6** leading to erythro (ie 4R) stereochemistry for **7**. This was verified by a single crystal x-ray analysis of **7**, which revealed the relative configuration shown in figure 1.[8] By contrast, when the dianion of **5** reacted with **6** at 0°C the oxazolidinone **8** was obtained in 56% yield.



2 R = Et
3 R = CH_2Ph

4

5

(i) $PhCH_2OH$, $KHSO_4$, 77%; (ii) P_2O_5, DMF, 82%; (iii) PhSH, nBu_4NF, 44%; (iv) NCS, CCl_4; (v) Et_3N, $CHCl_3$; (vi) $MeNH_2$, MeOH, 65%(3 steps).

Upon exposure to refluxing n-octane, **7** underwent loss of methylamine to give γ-lactone **9** in good yield.[9] The phenylthio group of **9** was removed via the tri-n-butylstannyl derivative **10** and protodestannylation with pyridine hydrobromide. Hydrogenolysis of the resulting enol ether **11** over palladium hydroxide in the hope of obtaining an α-keto lactone gave instead the alcohol **12** as a single (presumably cis) epimer. Fortunately, this outcome presented no obstacle to elaboration of the enamide moiety of leptosphaerin, since azide displacement of the mesylate **13** was followed by spontaneous loss of nitrogen from the intermediate α-azidolactone to provide the enamine **14** in good yield.[10] Acetylation of **14** gave the amide **15**, from which the acetonide was removed by careful hydrolysis. The resulting product was identical with natural leptosphaerin isolated from *L. oraemaris* by comparison of chromatographic behaviour, melting point, optical rotation,[11] and infrared and NMR spectra.

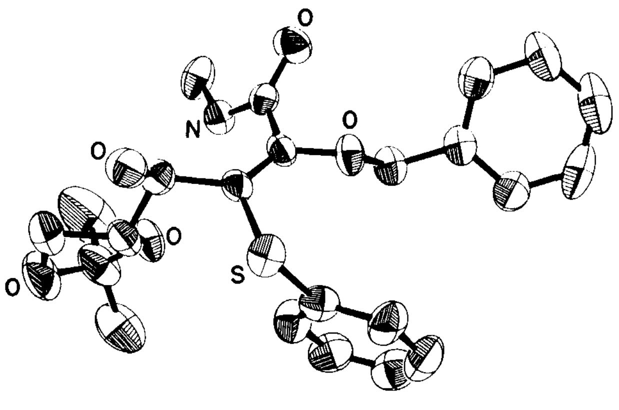
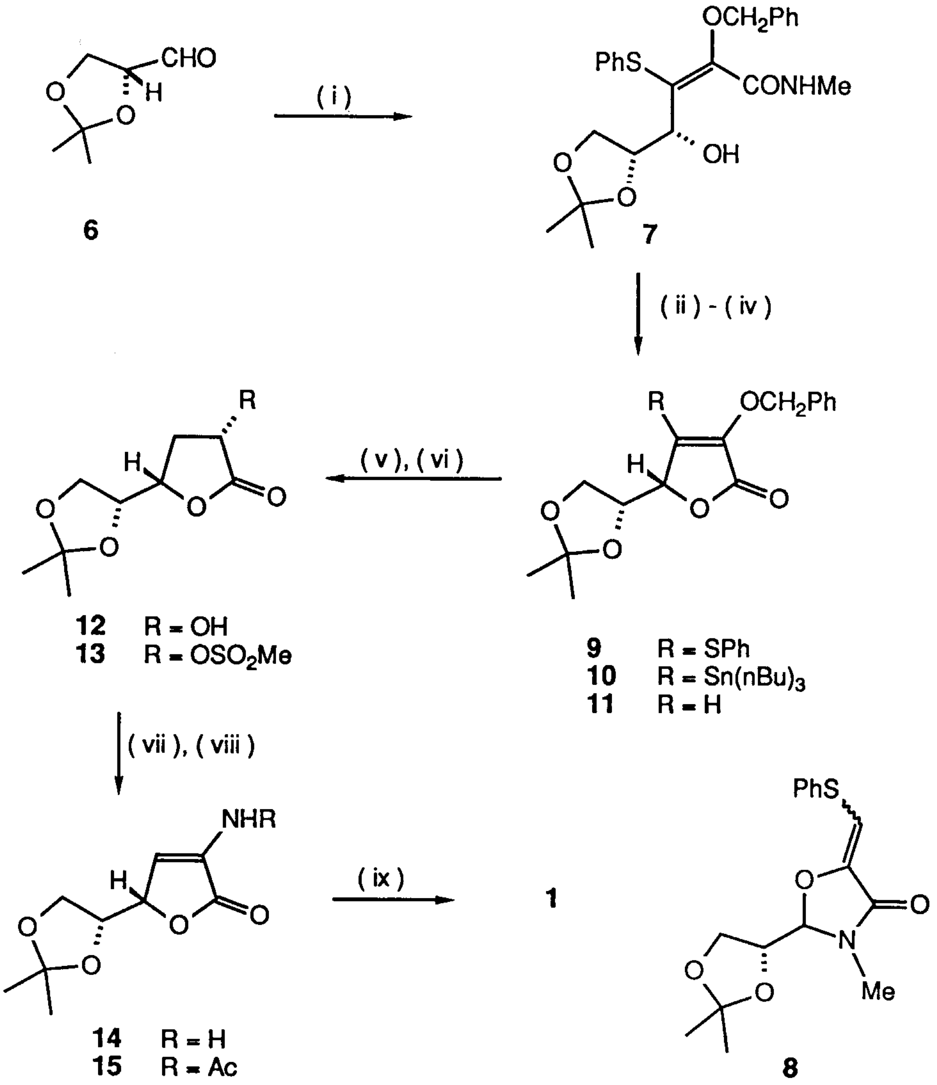


Figure 1. X-Ray Crystal Structure of **7**



(i) **5** (1 eq.), 2.2 eq. LDA, THF, HMPA, 59%; (ii) n-octane, reflux, 87%; (iii) n-Bu_3SnH, AIBN, PhH; (iv) pyr.HBr, 79% from **9** ; (v) H_2, $Pd(OH)_2$, 100%; (vi) MsCl, Et_3N, 97%; (vii) NaN_3, EtOH; (viii) Ac_2O, Et_3N, 68% from **13** ; (ix) HCl, THF, H_2O, 90%.

Leptosphaerin is thus the γ-lactone of 2-acetamido-2,3-dideoxy-D-erythro-hex-2-enoic acid. Its absolute configuration suggests a biogenetic origin in a hexose of D-glucose configuration, perhaps via transamidation of fructose.

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(11) Synthetic leptosphaerin had $[\alpha]_D$ +40° (c 0.2, H_2O) and mp 185-187°C.

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