Mycothiazole, a Polyketide Heterocycle from a Marine Sponge†

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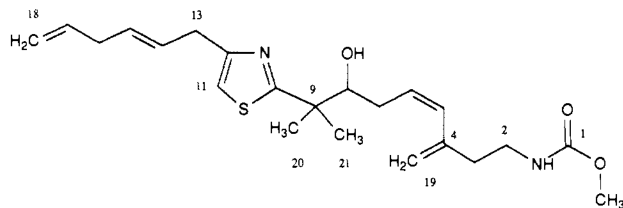
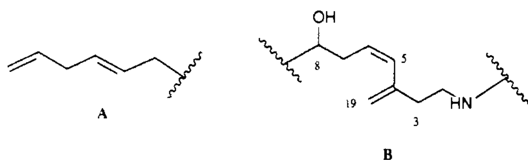
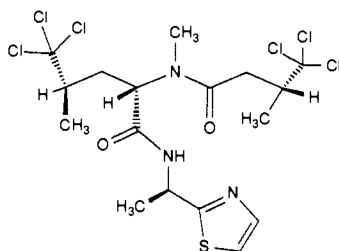
Abstract: The structure of an unusual thiazole containing compound, mycothiazole (**1**), was established after extensive NMR analysis. It was further confirmed by exhaustive interpretation of a HREIMS spectrum. Mycothiazole was isolated from *Spongia mycofijiensis* collected from Vanuatu and it exhibited anthelminthic activity (in vitro) while high toxicity was observed in mice. Even though the disubstituted thiazole ring system that is present in **1** has not been previously observed in natural products chemistry, comparisons of its carbon skeleton to that of latrunculin B suggest a possible route for its biogenesis.

Our recent studies of anthelminthic active extracts of soft-bodied sponges from Fiji have unveiled a diverse array of novel heterocycles, which may be derived from amino acids, such as jasplakinolide[1a] (jaspamide),[1b] the bengamides,[2] and the bengazoles.[3] We now extend this fascinating pattern by disclosing the structure of mycothiazole (**1**), isolated from *Spongia mycofijiensis*, which has no previous precedent among marine natural products. Its most unique feature is a thiazole ring, conceivably derived from cysteine, which is imbedded between two acyclic polyketide chains.



mycothiazole (1)





isodysidenin (2)

An examination of the anthelminthic active extract of the sponge–nudibranch pair *S. mycofijiensis*/*Chromodoris lochi* obtained from Fiji revealed latrunculin A and dendrolasin as major components.[4] By contrast, this pair from Vanuatu exhibited an entirely different profile of products because a ^{13}C NMR spectrum of the latter *S. mycofijiensis* extract demonstrated that dendrolasin was absent and latrunculin A was accompanied by two additional major metabolites, including mycothiazole. The specimens from Vanuatu, collected in January 1987, were similar to the material from Fiji except that the colonies were generally larger and more abundant. The sponge (1.7 kg, wet) was soaked (≈48 h, room temperature) in methanol (twice) and finally dichloromethane, and three separate dark viscous oils (respectively 1.96 g, 2.06 g, 2.50 g) were obtained in which mycothiazole could be directly seen only in the first oil by ^{13}C NMR spectroscopy. The isolation was begun by solvent partitioning of a portion of the first crude oil in aqueous methanol versus hexane, CCl_4, and then CH_2Cl_2. This procedure concentrated mycothiazole in the CCl_4 fraction, and additional purification involved flash chromatography followed by HPLC.

The molecular formula of $C_{22}H_{32}NO_3S$ (HREIMS = 404.2131, deviation of −0.2 mmu of calculated) with the unusual combination of sulfur, nitrogen, and oxygen was the first indication of mycothiazole's uniqueness. Careful analysis of ^1H–^1H COSY NMR spectra (Table I) in three different solvents ($CDCl_3$, benzene-d_6, DMSO-d_6) simultaneous with the evaluation of a ^1H–^{13}C (J = 140 Hz) COSY spectrum (Table I) permitted two substructures to be written, which accounted for four of the eight unsaturations. The ^1H–^1H COSY spectra revealed a carbon chain from C-13 to C-18, subgroup A, a 2(E),5-hexadienyl group (J = 18 Hz, benzene-d_6), a branched chain from C-2 to C-8, assembly B, which included a Z double bond (J = 12 Hz, benzene-d_6), and a terminal methylene group (C-19). Additional features included a CH_2NH group [DMSO-d_6; δ 2.94 (q, 2 H), 6.98 (t, NH)] and a CH_2C-H(OH) group [benzene-d_6; δ 2.30 (m, 1 H), 2.60 (dt, 1 H), 3.90 (dd, 1 H), 5.60 (brs, OH)]. Key long-range ^1H–^1H COSY NMR correlation peaks from H-19 to H-3,3′ and from H-19′ to H-5 verified the location of the diene moiety. Two additional substructures included a methoxy [$CDCl_3$; δ 51.8 (q), 3.56 (s)] and a geminal dimethyl [$CDCl_3$; δ 44.5 (s), 26.6 (q), 1.39 (s), 23.9 (q), 1.35 (s)]. The few unassigned atoms remained as C_4HNSO and included four sp^2 C's; however, at this point it was not clear either how many of these atoms were connected together or how they were linked to the other substructures. Vital new insights were provided from a ^1H–^{13}C (J = 9 Hz) COSY spectrum in DMSO-d_6, because of correlation peaks observed from the methoxy H's to the sp^2 C at δ 156.7, from the vinyl proton (δ 6.96, attached to δ 112.7) to each of the other two sp^2 C's at δ 177.7 and 154.3, and from the geminal dimethyl H's to the carbon at δ 177.7 and to the carbinol carbon (δ 77.7). New conclusions that could now be made included the following: the NH and OCH_3 were joined in a carbamate array, a disubstituted thiazole ring comprised of C-10, C-11, and C-12 was envisioned, and the C(Me_2) group must be attached to C-8 of substructure B. Additional support for the thiazole ring were diagnostic NMR parameters (Table II) including the ^1H shift and J_{CH} of H-11 [$CDCl_3$; δ_H 6.73 (J_{CH} = 194 Hz)] and ^{13}C shift of C-10 (δ 179.4).

It was apparent from ^1H–^{13}C NMR COSY data above and assignments in Table I that the C(Me_2) fragment was attached to the disubstituted oxazole at C-10. Even though a long range COSY NMR correlation was observed from H-11 to H-13,13′, it was not clear whether H-11 was α to the N or S of the thiazole

† Dedicated to Prof. Kurt Mislow (Princeton University) on the occasion of his 65th birthday.

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(2) Quiñoà, E.; Adamczeski, M.; Crews, P. *J. Org. Chem.* **1986**, *51*, 4494.
(3) Adamczeski, M.; Quiñoà, E.; Crews, P. *J. Am. Chem. Soc.*, in press.
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Table I. NMR[a] Data of Mycothiazole

atom no.	^{13}C δ (APT mult)		^{1}H δ (mult, *J* in Hz)		
	CDCl$_3$	DMSO-d_6	CDCl$_3$	DMSO-d_6	C$_6$D$_6$
01	157.1 (s)	156.7			
02	39.4 (t)	≈39.5	3.23 (m)	2.94 (q, 7)	3.35 (m)
			3.14 (m)		3.20 (dq, 12, 8, 8, 8)
03	37.1 (t)	37.0	2.29 (m)	2.11 (t, 7)	2.30 (m)
			2.18 (m)		2.10 (dt, 12, 6, 6)
04	142.4 (s)	142.5			
05	130.8 (d)	130.0	5.83 (m)	5.76 (m)	5.85 (d, 12.0)
06	130.8 (d)	130.9	5.65 (m)	5.54 (m)	5.72 (m)
07	30.6 (t)	31.3	2.39 (m)	2.20 (m)	2.60 (dt, 12, 8, 8)
			2.24 (m)	2.00 (m)	2.30 (m)
08	78.1 (d)	77.7	3.74 (dd, 10.2, 3.0)	3.60 (br t, 7)	3.90 (dd, 8.7, 2.4)
09	44.5 (s)	45.4			
10	179.4 (s)	177.7			
11	111.8 (d)	112.7	6.73 (t, 2)	6.96 (br s)	6.41 (s)
12	154.9 (s)	154.3			
13	29.4 (t)	29.3	3.46 (d, 7.2)	3.46 (d, 7)	3.42 (d, 7.2)
14	126.7 (d)	127.6	5.68 (br m)	5.65 (m)	5.68 (m)
15	128.8 (d)	128.0	5.50 (m)	5.46 (m)	5.62 (dt, 18.0, 5.7, 5.7)
16	31.5 (t)	31.3	2.84 (dt, 6.3, 6.3, 1.5)	2.86 (br t, 6)	2.75 (dt, 6, 6, 2)
17	136.4 (d)	136.7	5.73 (m)	5.80 (m)	5.76 (m)
18	115.0 (t)	115.1	4.96 (m)	5.03 (d, 18)	5.07 (dd, 17.1, 1.8)
			4.96 (m)	4.96 (d, 12)	5.03 (dd, 12.0, 1.8)
19	115.8 (t)	114.9	4.96 (m)	4.85 (br s)	5.03 (br s)
			4.83 (br s)	4.68 (br s)	4.94 (br s)
20	26.6 (q)	26.3	1.39 (s)	1.34 (s)	1.45 (s)
21	23.9 (q)	23.0	1.35 (s)	1.29 (s)	1.39 (s)
OMe	51.8 (q)	51.3	3.56 (s)	3.52 (s)	3.53 (s)
NH			not observed	6.98 (br t, 7)	5.72 (m)
OH			not observed	5.08 (br s)	5.60 (br s)

[a] Chemical shifts versus TMS for ^{1}H NMR spectroscopy at 300 MHz and ^{13}C NMR spectroscopy at 75 MHz; assignments were derived from a series of ^{1}H–^{1}H COSY, ^{1}H–^{13}C COSY (J = 140 Hz), and ^{1}H–^{13}C COSY (J = 9 Hz) spectra.

Table II. NMR Data for Predicting Thiazole Substitution Patterns

A. ^{13}C Chemical Shift Patterns

153.4 (C-2), 143.7 (C-4), 119.7 (C-5) — C; R-4 thiazole: 113–128 (C-5); R-5 thiazole: 137–152 (C-4)

B. ^{13}C–^{1}H Coupling Constant Patterns (Hertz)

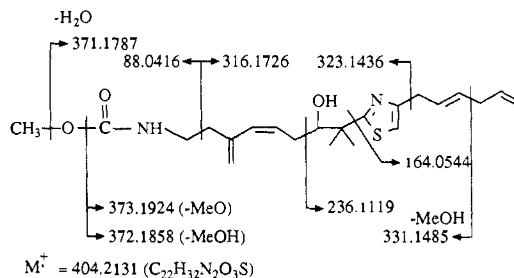
$^{1}J_{CH}$	$^{2}J_{CH}$	$^{3}J_{CH}$
C(2)H(2), 207–219	C(4)H(5), 15–17	C(2)H(4), 19.5–15.1
C(4)H(4), 180–191	C(5)H(4), 16	C(2)H(5), 8.5–6.2
C(5)H(5), 188–200		C(4)H(2), 7.2
		C(5)H(2), 3.6

$^{1}J_{CH}$ = 194 Hz; 113

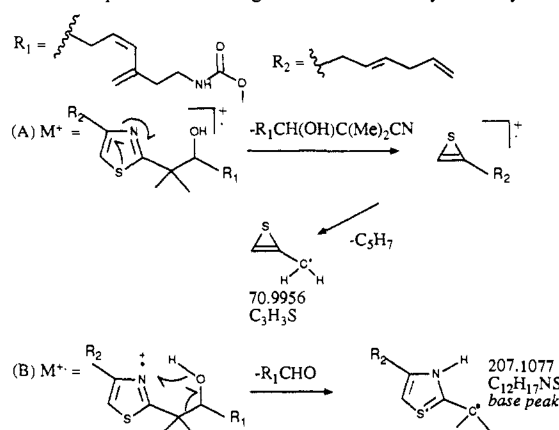
mycothiazole

ring. However, we have recently shown that ^{13}C NMR substituent increment shifts provide a simple way to determine when substituents are present at the C-4 or C-5 site in a 1,3-oxazole,[3] and a parallel analysis was applied to the thiazole group. A series of ^{13}C NMR shift increments for general structure C (Table II) were derived from literature data of various phenyl and alkyl substituted 1,3-thiazoles. Thus, a 2-alkyl or 2-aryl substituent imparts a shielding of 1 ppm or less at C-4 or C-5.[5,6] Furthermore, the β substituent effect across a C-4⋯C-5 trisubstituted thiazole double bond results in a small shift increment at the C(H) position ranging from +2 to −6 ppm for a wide range of substituents,[7] analogously to what happens across a double bond in a benzene ring. Consequently, the ^{13}C shift at the protonated carbon of the C-4⋯C-5 bond in structure C bearing nonpolar substituents at C-2 and/or C-5(4) are predicted to occur over a very different range as follows: δ 113–128 at C(H)-5 with C(R)-4, δ 137–152 at C(H)-4 with C(R)-5. The relevant ^{13}C shift in mycothiazole is δ 113 (C-11), and this requires the substitution pattern as shown in **1**. Thiazole ring J_{CH} coupling constants based on data from a series of sub-

Scheme I



Scheme II. Important MS Fragmentation Pathways for Mycothiazole



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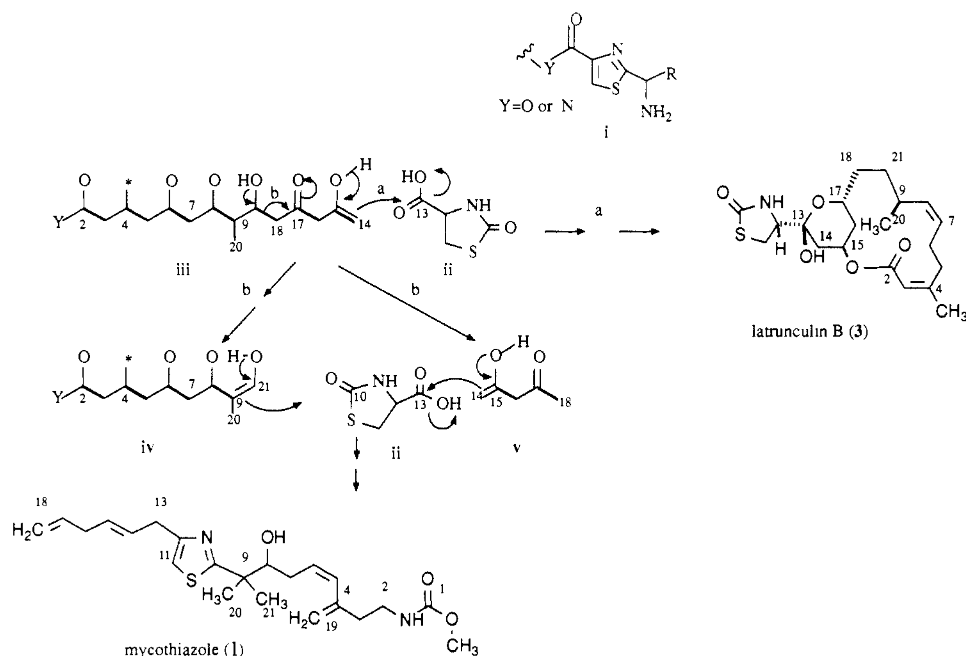
Scheme III



stituted thiazoles are also collected in Table II. They reveal the utility of $^1J_{CH}$ and $^3J_{CH}$ values for differentiating substitution patterns and the $^1J_{CH}$ = 194 Hz at C-11 observed in mycothiazole is consistent with the thiazole regiochemistry proposed above.

The HREI mass spectrum of mycothiazole contained numerous informative peaks between m/z 70 and 404, which are summarized in Schemes I and II. Fragmentation of each terminal group (Scheme I) was evident by m/z 323.1436 due to loss of subgroup A, m/z 316.1726 and 88.0416 owing to cleavage of the CH_3O-C(=O)$NHCH_2$, and m/z 164.0544 from detachment of the entire B chain including the dimethyls. Thiazoles undergo a ubiquitous EI induced ring contraction to a thietenyl cation (m/z 71)[8] as observed in Scheme II, path A, but this is of limited general diagnostic value because the m/z value of the key peak is very low. Alternatively, a series of fragmentations could be identified in which the thiazole ring was preserved as a cation, and these were more informative about the position and nature of the thiazole ring substituents. The most important of the latter is the fragmentation to the base peak at m/z 207.1077 by loss of neutral R_1CHO, and this intense ion is also important as it wholly supports the proposed proximity of the gem dimethyls to the thiazole ring.

Mycothiazole was completely active at 50 μg/mL in an anthelminthic (in vitro) assay against *Nippostrongylus braziliensis*. It was deadly to mice at 10 mg/kg when injected intraperitoneal, but no toxicity was seen by this route at 3 mg/kg. Mycothiazole is the first disubstituted thiazole to be reported from a marine sponge, as the only other examples of this functionality are the dysidenins,[9] exemplified by isodysidenin (**2**), which are all isolated from *Dysidea herbacea*. A small number of disubstituted thiazoles are known from other marine animals[10,11] and from terrestrial microorganisms.[12] Interestingly, the thiazole ring in all of these compounds is *always* present as general structure i (in Scheme III) which undoubtedly arises by condensation of cysteine with another amino acid.[13] Of relevance are Kashman's previous suggestions[14] that cysteine is a precursor of 2-oxo-4-thiazolidinecarboxylic acid (ii)[15] which adds to a heptaketide such as iii to generate a new bond from C-13 to C-14 yielding latrunculin B (**3**). A relationship between heptaketide iii, latrunculin B (**3**), and mycothiazole can be invisioned by inspecting the numbering (Scheme III) of their respective skeletons. A fragmentation of iii to iv and v followed by condensation of each of these to ii could generate the mycothiazole skeleton by the formation of new bonds from C-13 to C-14 and from C-10 to C-9.

Experimental Section

The NMR spectra were recorded on a JEOL FX-100 PFT spectrometer (99.5 MHz for ^1H NMR analysis and 25.0 MHz for ^{13}C NMR analysis) or on a GN-300 spectrometer (300 MHz for ^1H NMR analysis and 75 MHz for ^{13}C NMR analysis). Multiplicities of ^{13}C NMR peaks were determined from APT or DEPT data, and COSY experiments were done on the GN-300 instrument. Electron-impact mass spectrometry data were obtained on a Finnigan 4000 instrument (6000 LS7 computer system). High-resolution mass spectral data were obtained from the University of California, Berkeley, MS laboratory on a Kratos MS-50 spectrometer. High-performance liquid chromatography (HPLC) was done on a Waters ALC-201 instrument, with columns that include a Waters μPorasil, Whatman Partisil. All solvents were distilled and dried

(8) For example, see: (a) Tabacchi, T. *Helv. Chim. Acta.* **1974**, *57*, 324. (b) Demian, H.; Simiti, I.; Palibroda, N. *Org. Magn. Reson.* **1984**, *19*, 196.

(9) For literature to all six dysidenins and the proper assignment of their absolute stereochemistry, see: Willard, P. G.; de Laszlo, P. G. *J. Am. Chem. Soc.* **1985**, *107*, 199.

(10) There are eight thiazole-containing cyclic peptides from tunicates, which include the ulicyclamides, petallamides, lissoclinamides, and asicidacylamide. Their correct structures are summarized in Sessin, D. F.; Gaskell, S. J.; Ireland, C. M. *Bull. Soc. Chim. Belg.* **1986**, *95*, 853.

(11) There are two thiazole-containing cyclic peptides from a sea hare including (a) dolastin 3: Pettit, G. R; Kamano, Y.; Holzapqfel, C. W.; van Zyl, W. J.; Tuinman, A. A.; Herald, C. L.; Baczynaskyj, L.; Schmidt, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 7581. (b) dolastin 10: Pettit, G. R.; Kamano, Y.; Herald, C. L.; Tuinman, A. A.; Boettner, F. E.; Kizu, H.; Schmidt, J. M.; Baczynaskyj, L.; Tomer, K. B.; Bontmes, R. J. *J. Am. Chem. Soc.* **1987**, *109*, 6883.

(12) Thiazole-containing mold metabolites have been observed from two organisms. The largest number are from *Streptomyces*, and these include: (a) the thiostreptons (bramycin and thiactin): Hansens, O. D.; Albers-Schönberg, G. *J. Antibiot.* **1983**, *36*, 814. (b) The nosiheptides: Pascard, C.; Ducriux, A.; Lunel, J.; Prange, T. *J. Am. Chem. Soc.* **1977**, *99*, 6418. (c) The bottromycins: Schipper, D. *J. Antibiot.* **1983**, *36*, 107. (d) The siomycins: Kei, O.; Katsuya, K.; Kunoi, H.; Kazuo, T.; Yoshihiro, T.; Yohko, Y.; Hideo, O.; Kazuhiro, M.; Fuyuhiko, I.; Tatsuo, M. *Pept. Chem.* **1980**, *17*, 19. (e) Althiomycin: Bycroft, B. W.; Pinchin, R. *J. Chem. Soc., Chem. Commun.* **1975**, 121. (f) The bleomycins: *Bleomycin: Chemical, Biochemical, and Biological Aspects*; Hect. S. M., Ed.; Springer Verlag: Berlin, 1979. A smaller group are derived from *Bacillus*, and these include: (g) the thiocillins: Junichi, S.; Toshiyuki, K.; Yohko, Y.; Kazuo, T. *J. Antibiot.* **1981**, *34*, 1126. (h) The micrococcins: Brycroft, B. W.; Gowland, M. S. *J. Chem. Soc., Chem. Commun.* **1978**, 256.

(13) (a) Reference 12f. (b) Reference 11 in Pettit, G. R.; Kamano, Y.; Brown, P.; Gust, D.; Inoue, M.; Herald, C. L. *J. Am. Chem. Soc.* **1982**, *104*, 905.

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for HPLC use and were spectral grade for spectroscopy. Rotations were measured on a Perkin-Elmer 141 polarimeter.

Two-Dimensional NMR Procedures. Standard pulse sequences[16] were used for the homo COSY (ref 16b, Figure 37), and the hetero (ref 16b, Figure 35) experiments.

Isolation Procedures. The fresh *S. mycofijiensis* from Vanuatu (1.7 kg wet weight) was preserved and returned to University of California, Santa Cruz, for workup consisting of soaking (≈48 h, room temperature) in methanol (twice) and finally dichloromethane, and three separate dark viscous oils (respectively 1.96 g, 2.06 g, 2.50 g) were obtained. These oils were examined by ^{13}C NMR spectroscopy, which revealed a mixture of latrunculin A, mycothiazole, and other unidentified secondary metabolites (but no dendrolasin) in the first oil, while lipids and steroids were the major components of the other two oils. A portion of the first methanol extract crude oil (1.08 g) was then successively partitioned between equal volumes of aqueous MeOH (percent adjusted to produce a biphase solution) and a solvent series of hexanes (360 mg), CCl_4 (550 mg), and CH_2Cl_2 (170 mg). Analysis by ^{13}C NMR spectroscopy showed that mycothiazole and latrunculin A were major components of the CCl_4 partition fraction. This was then chromatographed (normal-phase flash column chromatography) with ethyl acetate–hexanes in a ratio of 5:95 with successive increases in ethyl acetate until pure ethyl acetate was attained. The fractions that displayed sharp, low-field signals in the ^1H NMR spectra were combined and further purified via preparative normal-phase HPLC (10 μm silica gel column; solvent = ethyl acetate–hexanes, 30:70) to yield (percents based on the crude oil used in the partition): mycothiazole (**1**) (68.7 mg, 6.3%, of shorter retention time) and latrunculin A (130.0 mg, 12.0%).

Mycothiazole (1): viscous oil $[\alpha]^{20}_D$ −3.8° (*c* 2.9, $CHCl_3$); IR (neat) 3600–3200, 2910, 1720, 1530, 1450, 1390, 1270, 1025 cm^{-1}; UV λ_{max} 235 (5270), 290 (1780); NMR data in Table I; HREIMS, *m/z*, in Schemes I and II and 220.1154 ($C_{13}H_{18}NS$), 192.0853 ($C_{11}H_{14}NS$), 166.0698 ($C_9H_{12}NS$), 140.0561 ($C_7H_{10}NS$).

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Registry No. 1, 114582-75-1.

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Total Synthesis of Zincophorin

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Abstract: The total synthesis of the title compound, which is a zinc-binding antibiotic, is described. The synthesis starts with aldehyde **4** and Grignard reagent **6**. The key steps are (i) the cyclocondensation of aldehyde **10** with diene **11** under the influence of magnesium bromide, (ii) the cyclocondensation of aldehyde **24** with diene **33** under the influence of $BF_3 \cdot OEt_2$, (iii) the carbon Ferrier reaction of glycal acetate **37** with (*E*)-crotyltrimethylsilane, and (iv) the reductive merger of aldehyde **2a** with sulfone **3**.

Many naturally occurring polyoxygenated ionophores have useful antiinfectious properties.[1] The primary mode of action seems to reside in the capacity of the ionophore to form lipophilic complexes with cations, thus affecting proton–cation exchange processes across biological membranes.[2] To date, the ionophoric antibiotics that have received the greatest attention are those with complex monovalent alkaline cations such as Li^+, Na^+, and K^+ or divalent alkaline earth cations such as Ca^{2+} and Mg^{2+}.

In this context a report in 1984 by an ICI group, describing the isolation of a zinc-sequestering antibiotic was of considerable interest.[3] This compound, zincophorin, was isolated from a strain of *Streptomyces griseus*. Apparently the same compound, previously called griseochellin, had been isolated from cultures of a modified strain of the same microorganism by Radics.[4] The constitution of griseochellin, though not its stereochemistry, was ascertained from extensive NMR measurements. The three-dimensional structure of zincophorin, also referred to as M144255, was determined to be structure **1** (including absolute configuration) by crystallographic measurements of its zinc–magnesium salt.[3]

Zincophorin exhibits strong in vitro activity against Gram-positive bacteria, as well as against *Clostridium coelchii*. A recent report, via the patent literature, registered the claim that griseochellin methyl ester exhibits a strong inhibitory action against influenza WSN/virus with sharply reduced host cell toxicity relative to the corresponding acid.[5]

In light of its novel structure and its profile of biological activity, zincophorin (griseochellin) provides an interesting context for chemical exploration, including total synthesis. It was not unnatural for our research group to undertake for itself the goal of a total synthesis of zincophorin. The most serious issues involved in such a venture would center around the introduction of the required configurations at the various oxygenated stereogenic centers. Our group had been involved with this type of objective, arising from its explorations into the Lewis acid induced aldehyde–siloxy diene cyclocondensation reaction and into the chemistry of pyranoid systems arising from such reactions.[6,7]

A plausible retrosynthetic disconnection point for a total synthesis of **1** would be the 16–17 double bond. In the forward sense, this double bond might be fashioned by reductive elimination of a β-hydroxy sulfone equivalent produced by the condensation of the anion of sulfone **3** with aldehyde **2** (P = unspecified blocking

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