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SESQUITERPENES FROM THE SPONGE *DYSIDEA ETHERIA* AND THE NUDIBRANCH *HYPSELODORIS ZEBRA*[1]

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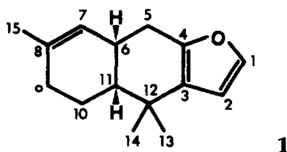
ABSTRACT.—A new sesquiterpene lactone, furodysinin lactone, has been isolated from the sponge *Dysidea etheria*, along with the known furodysinin. The lactone was identified by detailed analysis of spectral data and by chemical correlation with furodysinin. The relative configuration of the newly discovered lactone was determined by lanthanide-induced chemical shift studies.

Subsequent examination of the nudibranch *Hypselodoris zebra*, a predator of *D. etheria*, revealed the presence of high concentrations of several furanosesquiterpenes, including the known furodysinin and euryfuran, along with 5-acetoxy- and 5-hydroxy-nakafuran-8, both found previously in the *Dysidea* extracts. The feeding-deterrent properties of these compounds are discussed.

Interest in chemical communication in the marine biosphere has increased markedly over the past few years. Recent reports (1-4) have concentrated principally on the relationships between sponges and nudibranches, frequent predators of sponges. As part of our continuing study of invertebrates from Bermudian waters (5-7), we have examined the chemical constituents of the sponge *Dysidea etheria* de Laubenfels and its predator, the nudibranch *Hypselodoris zebra* Heilprin. Described in this report are sesquiterpenes found in both organisms.

Dysidea is a large genus widely distributed in tropical and subtropical waters around the world; *D. etheria* is a soft-bodied, bright blue sponge conspicuous in the low-light zones of the reef systems in Bermuda and the Caribbean. The nudibranch *H. zebra* was frequently observed grazing on *D. etheria* in Bermudian waters. When a single specimen of *H. zebra* was dissected and offered in separate portions to *Abudefduf saxatilis*, an omnivorous scavenger fish common on Bermuda's reefs, only the gonads were consumed. The digestive tract and outer skin were categorically rejected by the fish.

Chromatography of the CH_2Cl_2 soluble extracts of *D. etheria* on Florisil gave 15 fractions. The most nonpolar fraction consisted primarily of one furanosesquiterpene; gel permeation and flash chromatography of this material gave a colorless oil that solidified in the cold. Mass spectral analysis revealed a molecular formula of $C_{15}H_{20}O$, and the fragmentation pattern, together with the ^1H-nmr and inverse gated ^{13}C-nmr data, left no doubt that this compound was the rearranged sesquiterpene furodysinin (**1**) (8).



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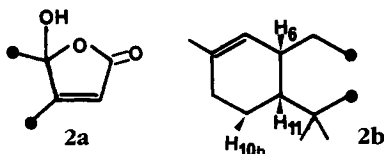
Gel permeation chromatography and subsequent reversed phase hplc of relatively polar fractions eluted with EtOAc and small percentages of MeOH in EtOAc yielded small quantities of a colorless solid, subsequently shown to be the sesquiterpene lactone **2**.

Inspection of the ^{13}C-nmr spectral data for **2** revealed the presence of one carbonyl, two olefinic linkages, a quaternary sp^3 carbon substituted by two heteroatoms (δ

[1]Contribution #910 from the Bermuda Biological Station. Part of this work was presented at the 23rd Annual Meeting of the American Society of Pharmacognosy, Pittsburgh, PA, August 1982.

104.91), one other quaternary carbon, two methines, three methylenes, and three methyl groups. The total of 15 carbons, including three methyl groups, indicated a probable sesquiterpene. Accurate mass spectral measurements delineated a molecular formula of $C_{15}H_{20}O_3$. The carbonyl and two carbon-carbon double bonds left three sites of unsaturation, which were attributed to a tricyclic skeleton.

From the ^{1}H-nmr data, the two olefinic protons, a singlet at δ 5.67 and a broad doublet at δ 5.36, had to be on separate trisubstituted double bonds. A broad D_2O exchangeable singlet at δ 3.5 was assigned to a hydroxyl group (3580, 3330 cm^{-1}). An unsaturated γ-lactone [1745 cm^{-1} and λ max 221 nm (ε=8700)] accounted for one ring and the other oxygens, meaning that the quaternary carbon at δ 104.91 bore both the hydroxyl group and the lactone oxygen, as illustrated in **2a**.



Spin-spin decoupling and other nmr experiments suggested part of structure **2b**; the ^{1}H-nmr assignments are presented in Table 1. The coupling constant between H_6 and H_{11} could not be measured directly because H_6 was represented by a poorly defined, broad multiplet at δ 2.80, and H_{11} was overlapped by signals for H_{15} and H_{10b}. However, decoupling experiments conducted during the lanthanide-induced chemical shift (LIS) study (see below) suggested a coupling of ~2.5 Hz between these protons, indicating a *cis*-juncture of the two carbocyclic rings. Somewhat perplexing at first glance was the coupling between H_6 and H_{10b}, but construction of a Dreiding model illustrated that when the dihedral angle between H_6 and H_{11} was minimized, H_6 and H_{10b} were aligned quite properly for W-coupling. The two methyl singlets (δ 1.38, 1.21), ir absorptions at 1371 and 1348 cm^{-1}, and a fully substituted sp^3 carbon (δ 38.47) were ample evidence for a geminal dimethyl group and accounted for the remaining elements in the molecule.

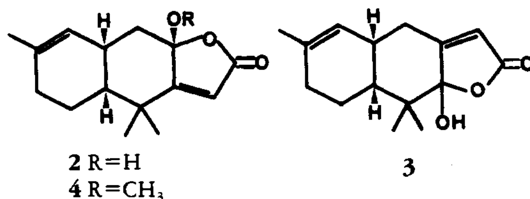
TABLE 1. ^{1}H-nmr Assignments for Furodysinin Lactone

Hydrogen	Chemical shift (δ)	Multiplicity	Coupled to (*J*, Hz)
H_2	5.67	s	—
OH	3.5	br s	—
H_{5a}	1.57	dd	H_{5b} (14), H_6 (13)
H_{5b}	2.28	dd	H_{5a} (14), H_6 (3.8)
H_6	2.80	m	H_{5a} (13), H_7 (5.7) H_{5b} (3.8), H_{10b} (3.7)[a] H_{11} (2.5)
H_7	5.36	br dd	H_6 (5.7), $H_{9a,b}$ (1.4)
$H_{9a,b}$	1.96	overlapping m	H_{10a} (9.5), H_7 (1.4)
H_{10a}	1.12	br ddd	H_{10b} (12.6), H_{11} (12.6) $H_{9a,b}$ (9.5 plus unresolved, small)
H_{10b}	1.70	br ddd	H_{10a} (12.6), H_6 (3.7)[a] H_{11} (3.1) $H_{9a,b}$ (unresolved, small)
H_{11}	1.63[b]	m	H_{10a} (12.6), H_{10b} (3.1), H_6 (2.5)
H_{13}	1.38	s	
H_{14}	1.21	s	
H_{15}	1.61	br s	

[a]W-coupling.

[b]Not resolved in normal spectrum; chemical shift of H_{11} obtained by extrapolation to zero equivalents Eu(fod)$_3$; after addition of 0.554 Eq, an apparent dt (*J*= 13.3, 2.5, 2.5).

The identified substructures could be assembled to give **2** or **3**. In either case, the ring juncture of the two carbocyclic rings had to be *cis* because of the observations described above. While structure **3** was originally favored because it, rather than **2**, obeyed the head-to-tail isoprene rule, two subsequent experiments rigorously established **2** as the correct structure of this new compound.



2 R=H
4 R=CH_3
3

In order to define the possible relationship between furodysinin and the newly discovered lactone, the oxidation of **1** was undertaken. Photo-induced oxygenation of **1** in MeOH (9) gave exclusively a ketal-lactone ultimately shown to be **4** (δ 3.12, 3H, s). The ketal could not be hydrolyzed to the hydroxy lactone under a variety of conditions (4% HCl at room temperature for 8 h; 4% HCl at 50°C for 2.5 h; 4% HCl at reflux for 2.25 h). Repetition of this oxidation, using THF-H_2O in place of the MeOH, gave only intractable tars and recovered starting material. The conversion was finally achieved by a two-step oxidation with *meta*-chloroperbenzoic acid, followed by Jones reagent. The sole product of this sequence gave a ^{1}H-nmr spectrum superimposable with that of the natural lactone, indicating exclusive formation of the diastereomer of **2** (epimer at C-4) represented by the natural product.

The ^{13}C-nmr assignments for **1** and **2** are presented in Table 2. The assignments for furodysinin lactone followed from an off-resonance decoupling experiment, irradiating at δ −2.2, and three single frequency off-resonance decoupling experiments (SFORD), irradiating at δ 2.80, 2.28, and 1.12. The assignments for furodysinin were not as simple to ascertain. The six sp^2 carbons were assigned with the aid of an off-resonance decoupling experiment, but the upfield region, because of the congestion of the four signals between δ 33.2 and 31.2, required additional experimentation for full assignment. The off-resonance decoupled spectrum provided the multiplicity of five sp^3 carbons, a spin-echo experiment $(0.5/J)$[2] identified the quaternary carbon (δ 33.13), and a second spin-echo experiment $(1/J)$[2] established the remaining CH_2 (δ 31.69) and indicated that the resonances at δ 31.22 and 32.85 were due to either methine or methyl groups (see Figure 1). Correlation of the ORD and spin-echo data indicated that the signal at δ 31.22 was the methine, while that at δ 32.85 was the methyl. An SFORD, irradiating at δ 1.61, identified the allylic methyl (δ 23.12), and another SFORD, irradiating at δ 2.65, confirmed the resonance at δ 31.22 as the methine.

A LIS was undertaken to establish the full relative configuration of **2**. A full equivalent of $Eu(fod)_3$ was added in increments to a $CDCl_3$ solution of the lactone and a ^{1}H-nmr spectrum recorded after each addition. Figure 2 is a plot of induced chemical shift *versus* equivalents of shift reagent added.

The assignment of relative configuration of polycyclic systems from LIS data is rarely straightforward. In this case, analysis was rendered particularly difficult because the hydroxyl group did not appear to be the site of chelation, as might be expected. This assumption was based on the observation that the hydroxyl proton did not undergo the exceedingly large shifts attributed to pseudocontact with the lanthanide.

In order to determine, first, the site of chelation and, then, the relative configura-

[2]An echo delay of $0.5/J$ (J is ^{13}C-H coupling constant) will give a spectrum exhibiting only quaternary carbons (defined as the positive phase); a $1/J$ spectrum will show quaternary and methylene carbons as the positive and methine and methyl carbons as the negative phase (10).

TABLE 2. ^{13}C-nmr Assignments, Furodysinin Lactone, and Furodysinin

Carbon #	Furodysinin Lactone		Furodysinin			
					J-Modulated Spin-Echo	
	δ	ORD	δ	ORD	0.5/*J*	*J*
1	174.76	s	140.51	d		
2	115.27	d	108.20	d		
3	169.82	s	124.71	s		
4	104.91	s	147.48	s		
5	41.17	t	27.56	t		pos
6	30.37	d	31.22			neg[c]
7	123.54	d	126.18	d		
8	134.49	s	133.62	s		
9	30.96	t	31.69			pos
10	18.65	t	19.26	t		pos
11	47.33	d	44.60	d		neg
12	38.47	s	33.13		s	pos
13	25.28[a]	q	32,85[b]			neg[d]
14	26.84[a]	q	26.21[b]	q		neg
15	22.98	q	23.12	q		neg

[a]Assignments interchangeable.
[b]Assignments interchangeable.
[c]A methine (see text).
[d]A methyl (see text).

tion of the three chiral centers in **2**, the PDIGM program of Willcott and Davis (11) was utilized. From Dreiding models of **2**, Cartesian coordinates were generated by projection onto the xy plane; z coordinates were measured directly. Because the *cis*-ring juncture between the two cyclohexane rings was clearly defined from the chemical cor-

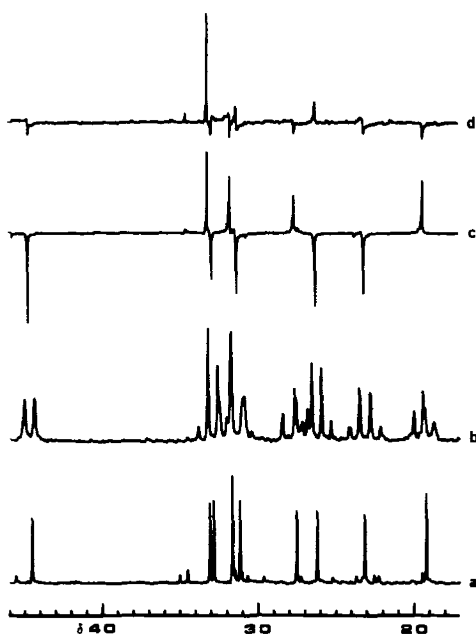


FIGURE 1. Highfield region, ^{13}C-nmr spectra of furodysinin (**1**); a) the inverse gated spectrum; b) the off-resonance decoupled spectrum; c) the 1/*J* *J*-modulated spin-echo spectrum; d) the 0.5/*J* *J*-modulated spin-echo spectrum.

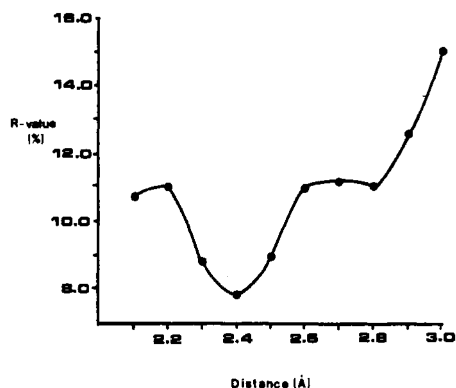


FIGURE 2. Plot of $\Delta\delta$ *versus* equivalents $Eu(fod)_3$, furodysinin lactone (**2**).

relation with **1**, it was necessary to compare only the two diastereomers epimeric at the hemiketal carbon. However, any of the three oxygens might serve as the site of chelation of the lanthanide with a lone pair of electrons; so, each of these possibilities had to be evaluated. The best fit for the LIS data indicated complexation of the europium with the carbonyl oxygen at a distance of 2.4 Å in the isomer with the hydroxyl *cis* to the ring juncture protons as shown in **2**; the minimum *R* value was 7.98%. The C-4 epimer gave a minimum *R* value of 16.83%. No other combination of relative configuration and site of complexation resulted in minimum *R* values under 28.5%. Figure 3 illustrates the graphical relationship of the *R* values obtained for **2** with the distance between the europium and carbonyl oxygen atom.

Consideration of steric effects provided a suitable explanation for the failure of the $Eu(fod)_3$ to chelate with the hydroxyl group. The molecular model suggested the likeli-

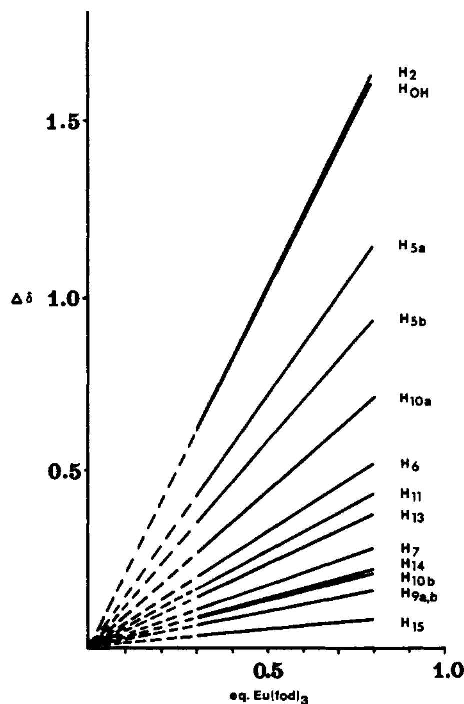


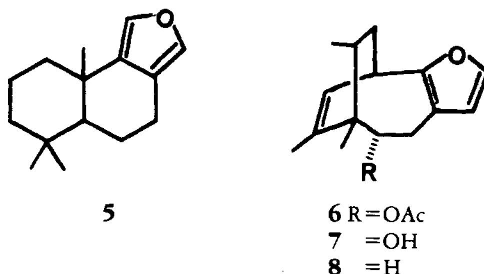
FIGURE 3. Plot of *R*-value *versus* europium-oxygen distance (11), furodysinin lactone (**2**).

hood of intramolecular hydrogen bonding of the hydroxyl with a non-bonding electron pair on the lactone oxygen. This idea was supported by the sharpness and constancy of chemical shift of the hydroxyl hydrogen in the ^{1}H-nmr; variation in sample concentration exhibited no effect on chemical shift. Such a configuration would preclude access of the lanthanide to the lone pairs of the hydroxyl oxygen and to one pair on the lactone oxygen; the net result would be that the carbonyl oxygen should become the primary complexation site.

The Eu(fod)$_3$ shift reagent induced identical chemical shift changes in the lactone prepared by oxidation of furodysinin, confirming that a single diastereomer, identical to the natural product, was produced in the course of the oxidation.

In order to determine whether the antifeedant activity of the body parts of *H. zebra* might be due to metabolites obtained by ingestion of *D. etheria*, specimens of the nudibranch were collected in Harrington Sound and Castle Harbour. Extraction of those nudibranchs gave very limited quantities of extract; the extract, however, contained a significant percentage (36%) of sesquiterpenes.

Gel permeation chromatography of this extract through Bio-Beads S-X8 with cyclohexane-CH_2Cl_2 (2:3) yielded a mixture of furodysinin (**1**), euryfuran (**5**), and 5-acetoxy-nakafuran-8 (**6**), as major constituents and 5-hydroxy-nakafuran-8 (**7**), as a minor constituent of the extract. The identity of furodysinin and the two nakafuran-8 derivatives (12-14) were secured by direct comparison with the furanosesquiterpenes isolated earlier from the sponge; euryfuran was identified by comparing its mass spectral and ^{1}H-nmr data with those reported in the literature (15-17).[3]



Both furodysinin and euryfuran have been identified previously as feeding deterrents in nudibranchs (2, 15) and likely serve the same function in *H. zebra*. Similar activity has been reported for nakafuran-8 (**8**) (18). Curiously, euryfuran is absent in *D. etheria*. We have been unsuccessful thus far in efforts to identify a dietary source of this compound. Recently it has been shown that precursors of euryfuran are synthesized *de novo* by the nudibranch *Dendrodoris limbata* (19).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—The nmr spectra were obtained with a Brüker WM-250 Fourier Transform Spectrometer. Chemical shifts are expressed as δ units, relative to TMS (δ=0), using $CDCl_3$ as solvent and internal standard. The ir spectra were obtained on a Beckman IR-20 and uv spectra with a Varian G34 Spectrophotometer. Mass spectra were recorded with Kratos MS-25 and VG MM16F spectrometers operating at 70 eV in the electron impact mode.

COLLECTION AND EXTRACTION OF *DYSIDEA ETHERIA*.—*D. etheria* was collected from a variety of shallow-water (2-8 m deep) habitats in Bermuda, primarily in Harrington Sound, in October 1979 and August 1982, and stored in Me_2CO prior to extraction. The 1979 collection (dry weight, 210.7 g) was homogenized in a Waring Blender and extracted with Me_2CO (twice, 24 h each), then with CH_2Cl_2

[3]There is an apparent typographical error in reference 15 regarding the ^{1}H-nmr data of euryfuran (**5**). We find chemical shifts of δ 0.90 and 0.93 for two of the methyl groups in **5**, consistent with the data reported in references 16 and 17, while reference 15 reports those signals at δ 0.90 and 0.99.

(thrice, 24 h each). The aqueous suspension remaining after evaporation of the Me_2CO extracts was equilibrated with the CH_2Cl_2 extracts; the organic phase was concentrated to yield 17.5 g of a brown oil (8.3% of dried weight).

Initial separation was accomplished by chromatography of 7.3 g of the crude extract on 275 g of Florisil with a hexane-EtOAc-MeOH gradient; 15 fractions were obtained. Fraction 1, eluted with hexane and hexane-EtOAc (49:1), was a nearly colorless oil with a pleasant aroma (912 mg); and fraction 10, eluted with EtOAc-MeOH (97:3) was a brown gum (272 mg).

ISOLATION OF FURODYSININ.—A portion of Florisil fraction 1 (210 mg) was further purified on silica gel (30 g, 70-230 mesh); hexane eluted 146 mg of a colorless oil. Additional separation was accomplished by gel permeation through Bio-Beads S-X8 (2× 125 cm); elution with CH_2Cl_2-cyclohexane (3:2) yielded one major fraction (118 mg), which was submitted to flash chromatography (100 g silica gel, 37-53μ). Hexane eluted one major fraction (109 mg), whose ^{1}H-nmr and ^{13}C-nmr spectra were identical with those reported (8) for furodysinin (**1**); ν max ($CHCl_3$) 2861, 2838, 1632, 1377, 1361 cm^{-1}; λ max (EtOH) 223 nm (ϵ=8300).

ISOLATION OF FURODYSININ LACTONE.—Florisil fraction 10 was permeated through Sephadex LH-20 (2× 125 cm) with CH_2Cl_2-MeOH (1:1); six fractions were obtained. The sixth fraction was further separated by hplc on an Ultrasphere-ODS column; elution with acetonitrile-H_2O (3:2) yielded 12 mg of furodysinin lactone (**2**): λ max (EtOH) 221 nm (ϵ=8700); ν max $CHCl_3$ 3580, 3330, 2925, 2890, 2857, 1745, 1640 cm^{-1}; ms: *m/z* (rel. int.) 248 (M^+, 6), 230 (95), 215 (66), 202 (30, 187 (25), 159 (20), 140 (63), 112 (97), 93 (100), 79 (66), 67 (71); hrms: *m/z* 248.1404 (M^+, $C_{15}H_{20}O_3$ requires 248.1412), 93.0715 (C_7H_9 requires 93.0705).

OXIDATION OF FURODYSININ.—To a stirred mixture of 113 mg furodysinin (**1**) in 2.5 ml CH_2Cl_2, 120 mg *m*-chloroperbenzoic acid were added over 10 min at room temperature. The mixture was then heated to 35° for 30 min. The CH_2Cl_2 was evaporated, and the residue was taken up in 2 ml Me_2CO; 1.5 ml of Jones reagent was then added over 25 min at 0°. After the mixture was heated to 30° and stirred for an additional half hour, the reaction was quenched with *iso*-PrOH. The mixture was then filtered twice through Hyflo-Super Cel and evaporated; the residue was suspended in CH_2Cl_2, washed with 5% $NaHCO_3$, dried over $MgSO_4$, and concentrated again to yield 39 mg of a light brown gum, which was purified by gel permeation chromatography through Bio-Beads S-X8 with CH_2Cl_2-cyclohexane (3:2) to yield 27 mg of furodysinin lactone (**2**) (21% yield), identical in all respects with the natural product.

PHOTOOXIDATION OF FURODYSININ.—In a test tube, 188 mg of furodysinin (**1**) were dissolved in 2.5 ml MeOH and 3.5 ml CH_2Cl_2; a catalytic amount of Rose bengal was then added. Oxygen was bubbled through the mixture, which was immersed in cold H_2O during illumination by a Sylvania 300-watt bulb for 4 h (10). The mixture was then reduced *in vacuo*, dissolved in CH_2Cl_2, and washed with distilled H_2O. The organic phase was evaporated and permeated through Sephadex LH-20 with CH_2Cl_2-MeOH (1:1) to yield 148 mg of the 4-*O*-methyl-furodysinin lactone (**4**); ^{1}H-nmr: δ 5.78 (1H, s), 5.30 (1H, br dd, *J*=5.7, 1.5), 312 (3H, s), 2.70 (1H, m), 2.30 (1H, dd, *J*= 13.8, 4), 1.96 (2H, m), 1.96 (2H, m), 1.69 (1H, br ddd, *J*= 12.6, 3.7, 3.1), 1.59 (3H, br s), 1.55 (1H, dd, *J*= 14, 14), 1.31 (3H, s), 1.20 (3H, s), 1.10 (1H, br ddd, *J*= 12.6, 12, 9.5).

COLLECTION AND EXTRACTION OF *HYPSELODORIS ZEBRA*.—Five specimens of *H. zebra* were collected in Shark's Hole and Church Bay, Harrington Sound, and under the airport causeway in Castle Harbour, Bermuda; the nudibranchs were stored in acetone prior to extraction. The animals (dry weight 1.5 g) were extracted with Me_2CO (twice, 24 h), then with CH_2Cl_2 (thrice, 24 h). The aqueous suspension remaining after evaporation of the Me_2CO extracts was equilibrated with the CH_2Cl_2 extracts; the organic phase was concentrated to yield 192 mg of a pleasant-smelling, orange oil.

ISOLATION OF FURANOSESQUITERPENES.—The organic extract (192 mg) was initially separated by gel permeation chromatography on Bio-Beads S-X8 (125× 2 cm); elution with cyclohexane-CH_2Cl_2 (2:3) yielded seven fractions. The fifth fraction (71 mg) was further purified by permeation through Sephadex LH-20 (125× 2 cm); elution with CH_2Cl_2-MeOH (1:1) yielded five fractions. The third fraction's (54 mg) ^{1}H-nmr spectrum indicated a mixture of furodysinin (**1**), euryfuran (**5**), and 5-acetoxy-nakafuran-8 (**6**). Analysis by gc-ms (5% SE-30, 6′× ⅛″, 130°-220°, 10°/min) indicated that the ratio of furodysinin (*m/z* 216, 122 base peak) to euryfuran (*m/z* 218, 203 base peak) to 5-acetoxy-nakafuran-8 (*m/z* 274, 232, 43 base peak) was ~2:1:1. The sixth fraction (16 mg) from the initial Bio-Beads S-X8 separation had an nmr spectrum identical to that of a mixture of furodysinin, 5-hydroxy-nakafuran-8 (**7**) and euryfuran. Analysis by gc-ms (6′× ⅛″, 5% SE-30, 150°-200°, 10°/min) indicated that the ratio of euryfuran to furodysinin to 5-hydroxy-nakafuran-8 (*m/z* 232, 136 base peak) was ~3:2:1.

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