112270-09-4; **V**, 112270-10-7; **VI**, 112270-11-8; **VII**, 16584-54-6; Me_2C=CHCOCH$(CO_2Et)_2$, 27761-58-6; MeCH=C(Me)COCH$(CO_2Et)_2$, 27761-60-0; MeCH=CHCOCH$(CO_2Et)_2$, 27761-57-5; *p*-hydroxyaniline, 123-30-8; *N*-methylaniline, 100-61-8.

Oxidized Nakafuran 8 Sesquiterpenes from the Sponge *Dysidea etheria*. Structure, Stereochemistry, and Biological Activity[1]

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We have been engaged for some time in a study of the metabolites of the distinctively blue-colored sponge *Dysidea etheria* and have previously reported the isolation of ceramides,[2] the sesquiterpenes furodysinin, furodysinin lactone,[3] and dysetherin,[4] and indoles[5] from the organic extracts of the sponge. Our study of the secondary metabolites of *D. etheria* has also resulted in the isolation of three additional new furanosesquiterpenes;[6] the complete structure elucidation and the biological testing of these compounds comprise this report.

Results and Discussion

Specimens of *Dysidea etheria* were collected from a variety of calm, shallow water locations in Bermuda on three occasions—October 1979, August 1982, and July 1984. The extraction of the 1979 and 1982 collections and subsequent crude fractionation of the extracts have been described earlier.[3] A nonpolar Florisil fraction, eluted with hexane–ethyl acetate (24:1), contained a pleasant smelling yellow oil. Gel permeation chromatography of this material through Bio-Beads S-X8 with dichloromethane–cyclohexane (3:2) yielded **1** as a colorless oil (5.5% of the total extract).

A 2,3-disubstituted furan was evident from the ^1H NMR doublets at δ 7.12 and 6.09 ($J \approx 1.5$ Hz) and ^{13}C NMR signals at δ 150.0 (s), 138.6 (d), 114.6 (s), and 113.7 (d). An acetate ester was indicated by a wealth of data: a three-proton singlet at δ 2.05, a ^{13}C NMR carbonyl signal at δ 170.0, a carbonyl stretch at 1735 cm^{-1} in the IR, and major mass spectral fragment ions at m/z 232 (M − 42) and 214 (M − 60). High resolution mass spectral analysis established $C_{17}H_{22}O_3$ as the molecular formula, suggesting that **1** was a sesquiterpene monoacetate.

^1H NMR decoupling experiments at 250 MHz led to two additional part structures, **1a** and **1b**, which accounted for all but two carbons in **1**, one quaternary (δ 44.4, s) and the other a quaternary methyl group (δ 1.02, s, and 17.5 q). The allylic methine in **1a** had to be connected to the furan ring to account for its chemical shift (δ 3.46, m). In **1b**, the chemical shift (δ 4.96, dd, J = 10, 6) of the X proton in the ABX system indicated that its carbon (δ 83.5) was the likely point of attachment of the acetate, while the AB methylene (δ 2.51, two overlapping 1 H, dd, J = 13, 10 and J = 13, 6) was connected to the furan. Assembly of all the pieces thus gave **1**.

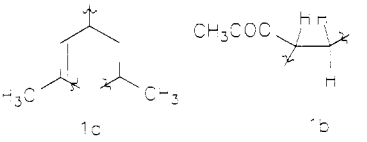
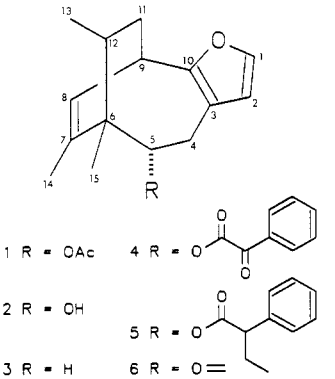


Table I. LIS Study of 5-Hydroxynakafuran 8 (2)

proton	slope[a]	$\Delta\delta^b$
H_1	0.017	0.67
H_2	0.024	0.97
H_{4a}	0.256	7.79
H_{4b}	0.206	7.11
H_5	0.348	13.35
H_8	0.081	3.16
H_9	0.060	2.33
H_{11a}	0.062	2.39
H_{11b}	0.065	2.51
H_{12}	0.103	4.00
H_{13}	0.047	1.79
H_{14}	0.120	4.69
H_{15}	0.151	5.82

[a] $\Delta\delta$ (y) vs mg of Eu(fod)$_3$ (x). [b] Extrapolated to 1 equiv of Eu(fod)$_3$.

Attempted hydrolysis of **1** with alcoholic KOH gave a low yield of **2** and considerable decomposition, but conversion to the alcohol was achieved in good yield by treatment with $Ba(OH)_2$.[7] The structure **2** was fully supported by loss of the acetate methyl and a shift of the heteroatom bearing methine from δ 4.96 (**1**) to 3.69 in the ^1H NMR of **2**, together with the mass spectral data (m/z 232, M^+, $C_{15}H_{20}O_2$).



1 R = OAc
2 R = OH
3 R = H
4 R = O
5 R = O
6 R = O=

Lanthanide-induced chemical shift studies of the alcohol **2** with Eu(fod)$_3$ supported the proposed structures and prescribed the relative configuration shown in **1** and **2**; Table I summarizes the relevant data. The difference in the induced shifts for H_1 and H_2 required placement of the furan oxygen as shown; in a similar fashion, the relative stereochemistry at C-5, C-6, and C-12 was deduced by comparison of the relative shifts induced for H_{12}, H_{13}, H_{14}, and H_{15}. The induced shifts for H_{14} and H_{15} are greater than those for H_{12} and H_{13}, indicating that the hydroxyl group is syn to the unsaturated bridge. The great difference between H_{12} and H_{13} required the methyl group to be positioned at a greater distance than the H_{12} methine from the lanthanide, resulting in the configuration shown. Analysis of the LIS data was aided significantly by the use of empirical force field calculations MM2[8] to determine

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the most stable conformation of the molecule. The sp^2 systems in **2** impart considerable rigidity to the molecule, so that the conformer possibilities include rotamers of the C_4–C_5–C_6 bonds with pseudoaxial and pseudoequatorial configurations of the oxygen functionality at C-5. The pseudoequatorial conformer was calculated to be 7.85, 1.87, and 58.65 kcal/mol more stable than the pseudoaxial conformer in **1**, **2**, and **6**, respectively.

The sponge metabolite **1** is, then, 5-acetoxynakafuran **8**, an oxidized representative of the rearranged sesquiterpene sekelton first found in the form of nakafuran 8 (**3**) by Schulte, Scheuer, and McConnell from *Dysidea fragilis* and its predator nudibranchs *Chromodoris maridadilus* and *Hypselodoris godeffroyama*[9] and isolated later from the nudibranch *Hypselodoris californiensis* by the Faulkner group.[10] Curiously, no **3** was found in any of our *D. etheria* collections, nor was it observed in our extracts of the nudibranch *Hypselodoris zebra*.[3] We did find the alcohol **2** in the *Hypselodoris zebra* extracts, although it was present only in small quantities in the 1979 *D. etheria* collection. The 1982 and 1984 collections, however, did contain more substantial amounts of **2**, indicating that it is not necessarily a product of biotransformation of **1** in the nudibranch but is more likely derived from the dietary source.

With the relative configuration of **1** and **2** established, the determination of absolute configuration via Prelog's atrolactic acid synthesis[11] was attempted. The benzoyl formate ester **4** was prepared in reasonable yield from **2**. Treatment of **4** with MeMgBr, however, gave a very poor yield of the Grignard adduct. Apparently, substantial steric crowding around the site of the neopentyl secondary hydroxyl was responsible for the low yield of Grignard product.

Reaction of **2** with racemic 2-phenylbutyric anhydride provided very poor yields of the ester **5**, but success with Horeau's method[12] was achieved by reaction of **2** with racemic 2-phenylbutyryl chloride. ^1H NMR analysis of the H-5 signals revealed a diastereoselectivity of about 6:1 in the ester **5**. The residual, unreacted 2-phenylbutyric acid was levorotatory, indicating the *S* configuration at C-5. The absolute configuration of **1** and **2**, then, is 5*S*,6*S*,9*R*,12*R*.

Conversion of **2** to **3** by reduction of the oxygen functionality at C-5 would permit assignment of absolute stereochemistry in the entire series **1**–**3**. Two approaches were contemplated—reductive elimination of a derived sulfonate ester or of the tosylhydrazone prepared from the ketone **6**. The tosylate **7** was formed in only low yields (~20%) and could not be reduced. The mesylate **8** could be obtained in more substantial yields, but treatment with hydride reducing agents under a variety of conditions[13] gave **2** and a complex mixture of unidentified elimination/rearrangement products. Oxidation of **2** with pyridinium dichromate gave the ketone **6** (*m/z* 230, $C_{15}H_{18}O_2$; 1705 cm^{-1}). The ^1H NMR ABX patterns of **1** and **2** gave way to an AB pattern at δ 3.52 and 3.17 (each 1 H, d, J = 12.9). The ketone yielded no tosylhydrazone in several tries but did prove identical with a very minor component found in the 1984 collection during the isolation of dysetherin.[4] It is unlikely that **6** is an artifact, since no oxidation of **2** was ever observed under a variety of chromatographic and storage conditions, including those used in the isolation of **6**.

Biological Testing

The organic soluble crude extracts of *D. etheria* elicited a slight life extension in the PS in vivo assay (T/C 118 @ 50 mg/kg) and differential toxicity to bacteria deficient in DNA repair capacity.[14] The alcohol **2** is not cytotoxic (ED_{50} is 22 μg/mL in the KB assay). The marginal antineoplastic activity of the extracts appears to be associated with cytotoxic polyoxygenated sterols,[15] but **1**, **2**, and **6** are responsible for some of the DNA repair activity. In the brine shrimp toxicity screen,[16] **1**, **2**, and **6** all showed some activity. The ketone **6** is the most active of the three compounds, with an LD_{50} of 38 μg/mL in the brine shrimp assay, and an MIC of 5 μg/mL against strains GW 900 and GW 902[17] in the differential DNA repair assay. Compounds **1** and **2** were roughly an order of magnitude less active in both assays.

None of the three nakafurans was phytotoxic to johnsongrass or leafy spurge in the nicked leaf assay.[18] Although **1** and **2** had exhibited some antifeedant activity toward grasshoppers,[19] none of the compounds caused any deleterious effects on the tobacco hornworm *Manduca sexta*. In fact, insects reared on diets containing 250 ppm **2** or **6** enjoyed slight weight gains in comparison to controls.

Experimental Section

General. NMR spectra were recorded on a Bruker WM-250 spectrometer; chemical shifts are reported in parts per million (δ, J = Hz) using $CDCl_3$ as solvent and internal standard. IR spectra were obtained with a Beckman IR-20 spectrophotometer. Mass spectra were recorded on VG Industries MM16F and 7070 EHF mass spectrometers. Optical rotations were measured on a Perkin Elmer 241MC polarimeter. The purity of all compounds was estimated to be ≥98% by analyses of ^1H NMR spectra.

Collection, Extraction, and Initial Fractionation. *Dysidea etheria* was collected from a variety of shallow water (2–8 m deep) habitats in Bermuda, primarily from Harrington Sound and Castle Harbour, in October 1979, August 1982, and July 1984; samples were stored in acetone at −5 °C prior to extraction. The separate collections were homogenized in a Waring blender and extracted with acetone (twice, 24 h each) and then with CH_2Cl_2 (thrice, 24 h each). The aqueous suspension remaining after evaporation of the acetone extracts was equilibrated with the CH_2Cl_2 extracts; the organic phase was then concentrated to a dark brown oil. The 1979 collection yielded 17.00 g of extract (from 210.7 g dry weight), the 1982 collection gave 17.45 g of extract (from 350.8 g dry weight), and the 1984 collection provided 51.79 g of extract (from 1234.5 g dry weight).

A portion of the extract from the first two collections was chromatographed on Florisil with a hexane–EtOAc–MeOH gra-

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dient. In each case, 13 fractions were collected; 4.8 g of the 1979 extract were used in one experiment, 17.4 g of the 1982 collection in another. A modified Kupchan partition scheme[19] was used to separate the 1984 extracts, yielding hexane (39.99 g), CCl_4 (5.35 g), $CHCl_3$ (5.76 g), EtOAc (0.20 g), and H_2O (0.49 g).

(5*S*,6*S*,9*R*,12*R*)-4,5,6,9-Tetrahydro-6,7,12-trimethyl-6,9-ethanocycloocta[*b*]furan-5-yl Acetate (5-Acetoxynakafuran 8, 1). A portion of fraction 2 (397 mg, eluted with hexane–EtOAc, 24:1) from the Florisil chromatography of the 1979 collection was permeated through Bio Beads S-X8 with CH_2Cl_2–cyclohexane (3:2), affording 1, 232 mg (0.4% dry weight), a colorless oil: $[\alpha]_D$ −31.1° (*c* 3.06, $CHCl_3$); ν_{max} (CCl_4) 3007, 2931, 1735, 1369, 1236, 1161, 851 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (1 H, d, J = 7 Hz), 1.02 (3 H, s), 1.20 (1 H, ddd, J = 12, 12, 4), 1.54 (1 H, ddq, J = 12, 6, 7), 1.69 (1 H, ddd, J = 12, 6, 4), 1.79 (3 H, br s), 2.05 (3 H, s), 2.46 (1 H, dd, J = 13, 10), 2.56 (1 H, dd, J = 13, 6), 3.46 (1 H, dt, J = 7.5, 4), 4.96 (1 H, dd, J = 10, 6), 6.00 (1 H, br d, J = 7.5), 6.09 (1 H, d, J = 1.5), 7.12 (1 H, d, J = 1.5); ^{13}C NMR ($CDCl_3$) δ 17.5 (q), 18.0 (q), 21.0 (q), 21.5 (q), 29.0 (t), 33.2 (d), 34.5 (d), 37.5 (t), 44.4 (s), 83.5 (d), 113.7 (d), 114.6 (s), 124.9 (d), 138.6 (d), 139.5 (s), 150.0 (s), 170.5 (s); high resolution EIMS, m/z 274.1568 (M^+, $C_{17}H_{22}O_3$ requires 274.1568); low resolution EIMS, (relative intensity) m/z 274 (40), 232 (16), 215 (16), 214 (59), 199 (100), 187 (11), 185 (10), 178 (9), 158 (21), 123 (23), 121 (45), 107 (26), 107 (15), 105 (11), 96 (22), 95 (37), 91 (16), 77 (14).

(5*S*,6*S*,9*R*,12*R*)-4,5,6,9-Tetrahydro-6,7,12-trimethyl-6,9-ethanocycloocta[*b*]furan-5-ol (5-Hydroxynakafuran 8, 2). A solution of 155 mg of $Ba(OH)_2{\cdot}8H_2O$ (0.49 mmol) in 80% EtOH (15 mL) was added to a 0.5-mL solution of 131 mg of 1 (0.48 mmol) in CH_2Cl_2. The mixture was stirred in a sealed flask at 55 °C for 3 h and then at room temperature overnight. The reaction mixture was neutralized with 4% HCl, the EtOH was removed, in vacuo, and the residual aqueous suspension was extracted with CH_2Cl_2 (5 × 10 mL). The combined CH_2Cl_2 phase was evaporated to give 114 mg of light brown oil; gel permeation through Bio Beads S-X8 with CH_2Cl_2–cyclohexane (3:2) gave 108 mg (97%) of 5-hydroxynakafuran 8 (2) as a colorless oil: $[\alpha]_D$ −65.3° (*c* 2.07, $CHCl_3$); ν_{max} (CCl_4) 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (1 H, d, J = 7 Hz), 1.19 (3 H, s), 1.26 (1 H, ddd, J = 12, 12, 4), 1.65 (2 H, m), 1.81 (3 H, br s), 2.53 (1 H, dd, J = 14.5, 5), 2.73 (1 H, dd, J = 14.5, 10), 3.45 (1 H, dt, J = 7.5, 4), 3.69 (1 H, dd, J = 10, 5), 5.99 (1 H, br d, J = 7.5), 6.13 (1 H, d, J = 1.5), 7.14 (1 H, d, J = 1.5); ^{13}C NMR ($CDCl_3$) δ 18.6 (q), 19.9 (q), 22.5 (q), 29.8 (t), 33.5 (d), 34.2 (d), 37.1 (t), 45.9 (s), 82.7 (d), 114.1 (d), 114.3 (s), 124.6 (d), 138.7 (d), 139.9 (s), 152.1 (s); high resolution EIMS, m/z 232.1465 (M^+, $C_{15}H_{20}O_2$ requires 232.1464) (M^+, 62) 217 (8), 214 (4), 199 (24), 137 (10), 136 (100), 122 (24), 121 (16), 108 (18), 107 (32), 105 (9), 91 (19), 77 (12), 69 (25), 43 (19).

Isolation of 5-Hydroxynakafuran 8 (2) from *Dysidea etheria*. Fraction 3 (1.23 g, eluted with hexane–EtOAc, 9:1) from the Florisil chromatography of the 1982 collection was permeated through Bio-Beads S-X4 (column 92 × 4 cm) with hexane–CH_2Cl_2–EtOAc (4:4:1). Six fractions were obtained; fractions 4 (84 mg) and 5 (274 mg) consisted primarily of 2 and dysetherin;[4] these fractions were combined and subjected to low pressure chromatography on silica gel (100 g Whatman LPS-2, 2.5 × 38 cm, ~15 psi N_2). Elution with hexane-Et_2O (3:1) gave 265 mg (0.02% dry weight), a colorless oil. This material was identical in all respects with the product obtained by hydrolysis of 5-acetoxynakafuran 8 (1).

2-Phenylbutanoyl Ester of 5-Hydroxynakafuran 8. Racemic 2-phenylbutyric acid (58 mg, 0.32 mmol) was dissolved in 1 mL of CH_2Cl_2 and 2 mL of $SOCl_2$ and the mixture was refluxed for 3 h. The mixture was then reduced in vacuo, and the residue was dissolved in 2 mL of dry pyridine; a solution of 36 mg of 2 (0.16 mmol) in dry benzene was added, along with 2 mg of (dimethylamino)pyridine. The flask was flushed with N_2, sealed, heated to 55 °C for 4 h, and then left at room temperature overnight. After the solvents were removed, in vacuo, the residue was partitioned between Et_2O and 5% $NaHCO_3$. The Et_2O phase was reduced to 71 mg of a yellow oil which was permeated through Sephadex LH-20 to give the ester 5, 26 mg (43%): $[\alpha]_D$ −33.4° (*c* 2.64, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.3–7.2 (5 H, br s), 7.08 (1 H, d), 6.04 (1 H, d), 6.90 (1 H, br d), 4.90 and 4.80 (each 1 H, dd, ratio ~6:1), 3.38 (1 H, ddd), 2.45 (1 H, dd), 2.30 (1 H, dd), 1.08 (1 H, m), 1.65 (3 H, br s), 1.70–1.40 (3 H, overlapping m), 1.20 (1 H, m), 0.90 (3 H, d), 0.86 (3 H, d), 0.62 (3 H, s); MS, m/z (relative intensity) 378 (M^+, 4), 231 (10), 214 (30), 199 (18), 119 (100), 91 (77).

The 5% $NaHCO_3$ phase was acidified with 5% HCl and extracted with CH_2Cl_2 (4 × 10 mL). The CH_2Cl_2 was reduced, in vacuo, to give 24.5 mg of 2-phenylbutyric acid: $[\alpha]_D$ −4.9° (*c* 2.45, $CHCl_3$); optical yield 20%.

(5*S*,6*S*,9*R*,12*R*)-6,9-Dihydro-6,7,12-trimethyl-6,9-ethanocycloocta[*b*]furan-5(4*H*)-one (5-Ketonakafuran 8, 6). A solution of 70.5 mg (0.30 mmol) of 2 in 1 mL of CH_2Cl_2 was added to a stirred suspension of 575.8 mg of pyridinium dichromate in 5 mL of dry pyridine and 2 mL of CH_2Cl_2 at 0 °C. After addition was complete, the temperature was allowed to rise to room temperature over 30 min. The mixture was reduced to a dark brown gum which was suspended in CH_2Cl_2 and filtered through a pad of silica gel and Celite. The filtrate yielded a brown oil upon evaporation. Gel permeation (Bio-Beads S-X8) of this oil gave 43 mg (62%) of 5-ketonakafuran 8 (6) as a colorless oil: $[\alpha]_D$ +35.1° (*c* 1.51, $CHCl_3$); ν_{max} (CCl_4) 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (1 H, d, J = 7 Hz), 1.20 (3 H, s), 1.38 (1 H, ddd, J = 12, 12, 4), 1.65 (1 H, ddd, J = 12, 6, 4), 1.74 (3 H, br s), 2.02 (1 H, ddq, J = 12, 6, 7), 3.17 (1 H, d, J = 12.9), 3.52 (1 H, d, J = 12.9), 3.67 (1 H, dt, J = 7.3, 4), 5.82 (1 H, br d, J = 7.3), 6.11 (1 H, d, J = 1.7), 7.15 (1 H, d, J = 1.7); ^{13}C NMR ($CDCl_3$) δ 19.0 (q), 20.2 (qa), 21.7 (q), 33.5 (t), 35.6 (d), 36.3 (d), 40.0 (t), 56.5 (s), 111.5 (d), 113.8 (s), 123.5 (d), 139.0 (d), 140.0 (s), 153.0 (s), 212.0 (s); MS, m/z (relative intensity) 230 (M^+, 27), 215 (8), 187 (29), 159 (15), 121, 49 (92), (50), 81 (100).

Isolation of 5-Ketonakafuran 8 (6) from *Dysidea etheria*. During the reisolation of dysetherin,[4] 1 mg (8 × 10^{-5} % dry wt) of 5-ketonakafuran 8 (6) was obtained from the CCl_4-soluble extracts of the 1984 collection by successive gel permeation chromatography through Bio-Beads S-X4 (hexane–CH_2Cl_2–EtOAc, 4:3:1), Sephadex LH-20 (CH_2Cl_2–MeOH, 1:1) and Bio-Beads S-X8 (CH_2Cl_2–cyclohexane, 3:2), followed by low pressure silica gel chromatography (hexane–MeO-*t*-Bu, 17:3). The ketofuran thus obtained was identical with the product of the oxidation of 2.

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Registry No. 1, 89837-73-0; 2, 89837-74-1; 5 (isomer 1), 112348-67-1; 5 (isomer 2), 112420-31-2; 6, 112348-68-2; $MeCH_2CH(Ph)CO_2H$, 7782-29-8; $MeCH_2CH(Ph)COCl$, 51260-63-0.

The Relationship between the Brønsted Acidities of Imides and Their Hydrogen-Bonding Acidities toward Oxygen Bases[1]

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It is known that for closely related acids and for closely related bases equilibrium constants for hydrogen bonding increase with the Brønsted acidity of the acids and the

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