Table I. Physical Properties and Yields of Amino Alcohol Products

				HCl salt			
compd	$[\alpha]^{25}_D$, deg	c, solvent	mp, °C	$[\alpha]^{25}_D$, deg	c, solvent	mp, °C	yield, %[a]
2	+76.8	0.96, MeOH	oil			239–240	41
3	+22.1	1.2, MeOH	74–75			244–247	45
4	+86.7	1.3, MeOH	45–47			275–277	48
5	−15.5	1.0, MeOH	oil			201–203	51
6	+29.7[b,g]	1.5, EtOH	oil	+35.7[c]	0.86, H_2O	164–165	88
7	−32.9[g]	1.1, EtOH	oil	−34.1[d]	1.1, H_2O	163–164	82
8	+48.2[g]	1.0, MeOH	88–89				85
9	−48.5[g]	1.0, MeOH	85–86				71
10	+37.5[e]	5.0, H_2O	bp 96–98 (15 mm)				65
11	−37.9[f]	4.1, H_2O	bp 90–95 (12 mm)				74

[a] From the previous precursor. [b] This rotation may be slightly low due to the hygroscopic nature of this material. [c] Lit.[4b] +32.2 (c 0.9, H_2O). [d] Lit.[4b] −34.8 (c 1.6, H_2O). [e] Lit.[9] +38.2 (c, 5, H_2O). [f] Lit.[9] +39.8 (c 5, H_2O). [g] The enantiomeric excess of this sample was >96% as determined by 250-MHz ^1H NMR analysis of the amide formed from (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.

by 1.4 mL (78 mmol) of H_2O. The resulting suspension was rapidly stirred for 1 h at 25 °C and filtered through a short column of Celite and the column was subsequently washed with 30 mL of CH_2Cl_2. The combined filtrates were dried (K_2CO_3), concentrated, and separated by flash chromatography (4.8 × 15 cm column, hexane/ethyl acetate/Et_3N 4:1:0.2) to give, in the first fractions, 1.4 g (51%) of pure **5** as a colorless oil and, in later fractions, 1.3 g (48%) of **4** as a crystalline solid. **4**: mp 45–47 °C, mp (HCl salt) 271–277 °C dec; R_f 0.34 (hexane/ethyl acetate/Et_3N 1:1:0:1); IR ($CHCl_3$) 3200–3700, 1605, 1452, 1120, 1065 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.15–7.40 (m, Ph), 3.99 (q, J = 6.6 Hz, C*H*Me), 3.15 (app dt, J = 4.4, 10 Hz, OCH), 1.34 (d, J = 6.6 Hz, Me), 0.8–2.2 (m, 11 H). MS (isobutane, CI), m/e 220 (MH), 204, 142, 116, 98; $[\alpha]^{24}_{546}$ +103° (c 1.26, MeOH). Anal. Calcd (HCl salt) for $C_{14}H_{22}ClNO$: C, 65.75; H, 8.61; Cl, 13.89; N, 5.48. Found: C, 65.83; H, 8.67; Cl, 13.93; N, 5.46. **5**: mp (HCl salt) 201–203 °C; R_f 0.49 (hexane/ethyl acetate/Et_3N 1:1:0.1); IR ($CHCl_3$) 3200–3700, 1602, 1450, 1277, 1060 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.2–7.4 (m, Ph), 3.91 (q, J = 6.6 Hz, C*H*Me), 3.09 (ddd, J = 4.5, 9.8, 10.1 Hz, OCH), 2.32 (ddd, J = 3.9, 10.1, 10.3 Hz, NCH), 1.33 (d, J = 6.6 Hz, Me), 0.8–2.2 (m, 10 H); MS (isobutane CI) m/e 220 (MH), 204, 142, 116, 98; $[\alpha]^{24}_{546}$ −18.3 (c 1.0, MeOH). Anal. Calcd (HCl salt) for $C_{14}H_{22}ClNO$: C, 65.75; H, 8.61; Cl, 13.89; N, 5.48. Found: C, 65.86; H, 8.71; Cl, 13.99; N, 5.45.

(1*S*,2*S*)-*trans*-2-[(*R*)-(α-Methylbenzyl)amino]cyclopentanol (2) and (1*R*,2*R*)-*trans*-2-[(*R*)-(α-Methylbenzyl)amino]cyclopentanol (3). An identical sequence starting with 14.2 g of cyclopentene oxide provided 14 g (45%) of crystalline **3** [mp 74–75 °C, mp (HCl salt) 244–247 °C; R_f 0.33 (hexane/ethyl) acetate/Et_3N 1:1:0.1] and 13 g (41%) of pure **2** [colorless oil, mp (HCl salt) 239–240 °C; R_f 0.25 (hexane/ethyl acetate Et_3N 1:1:0.1].[3]

(1*R*,2*R*)-*trans*-2-Aminocyclopentanol (7). The general procedure of Anwer and Spatola was utilized.[7] A mixture of the HCl salt of **3** [prepared from 269 mg (1.31 mmol) of **3**], ammonium formate (420 mg, 6.6 mmol), 10% Pd/C (0.32 g), and dry *N*,*N*-dimethylformamide was heated at 110–120 °C for 4 h. After cooling to room temperature, the reaction mixture was filtered through Celite (~1 g), the filter cake was washed with MeOH (3 × 5 mL), and the combined filtrates were concentrated. The residue was partioned between $CHCl_2$ and saturated aqueous KOH and the organic layer was separated and dried (K_2CO_3). Concentration gave 109 mg (82%) of pure **7** as a colorless oil: mp (HCl salt) 163–164 °C, lit.[4b] mp 161–163 °C; optical rotations (HCl salt) $[\alpha]^{22}_D$ −34.1°, $[\alpha]^{22}_{546}$ −34.2°, $[\alpha]^{22}_{365}$ −76.0° (c 1.1, H_2O), lit.[4b] $[\alpha]^{20}_D$ −34.8° (c 1.6, H_2O); optical rotations (free base) $[\alpha]^{24}_D$ −32.9°, $[\alpha]^{24}_{546}$ −38.8° (c 1.1, EtOH), lit.[4b] $[\alpha]^{20}_D$ −33.3° (c 1.7, EtOH).

Amino alcohols **6**, **8**, and **9** were prepared in an identical fashion, and these results are summarized in Table I.

(1*S*,2*S*)-*trans*-2-(Dimethylamino)cyclohexanol (10). A solution of **8** (505 mg, 4.39 mmol), 37% HCHO (7 mL), and HCOOH (7 mL) was heated at reflux for 23 h and concentrated. The residue was partioned between Et_2O and 5 N NaOH, the organic layer was separated, the aqueous layer was washed with additional Et_2O, and the combined organic extracts were dried (K_2CO_3). Concentration and distillation of the residue [bulb to bulb; bp 96–98 °C, (15 mm)] gave 408 mg (65%) of pure **10**: $[\alpha]^{24}_D$ +37.5°, $[\alpha]^{24}_{546}$ +44.1°, $[\alpha]^{24}_{365}$ +186° (c 5.1, H_2O); lit.[9] $[\alpha]^{20}_D$ +38.2 (c 5, H_2O).

Amino alcohol **11** was prepared in an identical fashion (see Table I).

Acknowledgment. The financial support of the National Institutes of Health (NS-12389) is gratefully acknowledged. NMR and mass spectra were determined with spectrometers purchased with the assistance of NSF Departmental Instrumentation grants.

An Unusual β,γ-Epoxy γ-Lactone from the Sponge *Dysidea etheria*[1,2]

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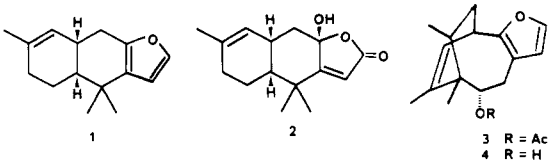
Received March 25, 1985

Our investigation of the secondary metabolites of the Bermudian sponge *Dysidea etheria* has resulted in the isolation and identification of a series of unusual ceramides[3] and a group of sesquiterpenes, including furodysinin (**1**), furodysinin lactone (**2**), and 5-acetoxy- and 5-hydroxynakafuran 8 (**3**, **4**).[4] In the course of reisolating quantities of 5-hydroxynakafuran 8 for stereochemical studies, we encountered a minor metabolite which exhibited some of the NMR spectral characteristics of furodysinin (**1**) but which was somewhat more polar.



This new sesquiterpene was readily purified by low-pressure adsorption and gel-permeation chromatography. Mass spectral analysis of the colorless oil revealed the molecular formula to be $C_{15}H_{20}O_3$. The presence of a γ-lactone (1783 cm^{-1}) and the absence of hydroxyl or additional carbonyl groups was evident from the IR spectrum; the remaining oxygen, then, had to constitute an ether linkage. A trisubstituted olefin was apparent from the ^{13}C NMR data, leaving the last three sites of unsaturation to be accommodated by two carbocyclic rings and a cyclic ether.

^1H NMR decoupling experiments (see Table I) provided part structure **5a**, which, together with the γ-lactone, 2

(1) Dedicated respectfully to Professor Paul J. Scheuer on the occasion of the seventieth anniversary of his birth.
(2) Contribution 1001 from the Bermuda Biological Station.
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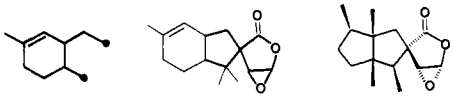
0022-3263/85/1950-4155$01.50/0

Table I. NMR Data for Dysetherin

carbon[a]	^{13}C NMR δ_{CCl_4}[b]	^{13}C NMR mult	^{1}H NMR δ_{CDCl_3}	^{1}H NMR $\delta_{C_6D_6}$	^{1}H NMR mult (J, Hz)[e]
1	47.50	s			
2	59.69	s			
3	39.06	t	2.10	1.65	dd (14.2, 8.5)
			1.59	1.08	dd (14.2, 9.9)
4	44.88	d	2.97	2.99	dddd (9.9, 8.5, 7.1, small)[d]
5	123.71	d	5.32	5.19	br dq (unresolved)
6	134.11	s			
7	21.21	t	1.88	1.65	br (unresolved)[f]
8	22.26	t	1.73	1.46	dddd (6.4)[d]
			1.49	1.22	dddd (5.7)[d]
9	31.11	d	2.31	2.31	ddd (7.1, 6.4, 5.7)
10	26.10[c]	q	1.18	0.95	s
11	28.72[c]	q	1.12	1.22	s
12	57.76	d	3.53	2.69	d (2.1)
13	76.14	d	5.45	4.62	d (2.1)
14	177.59	s			
15	23.71	q	1.65	1.59	br s (unresolved)[g]

[a] Numbering system is that employed for 7 is ref 7. [b] Assignments based on single frequency on resonance (SFORD) and gated decoupled (GD) experiments. [c] Assignments may be interchanged. [d] Some coupling constants not determined. [e] Determined in $CDCl_3$. [f] Coupled to H-8. [g] Coupled to H-5.

isolated methyl groups, and 2 quaternary sp^3 carbons, totaled 16 carbon atoms. So, it appeared that one of the quaternary carbons had to be in the lactone ring, suggesting a spirocyclic system. Only two hydrogens (δ 5.45 and 3.53, coupled by 2.1 Hz) and the ether oxygen remained unassigned. A consideration of similarities with furodysinin[4,5] and the proposed biogenesis of 1[5] resulted in the proposal of **5b** as the gross structure of this compound, for which we propose the trivial name dysetherin. Only one such naturally occurring β,γ-epoxy γ-lactone has been fully characterized, the sesquiterpene **6** from the liverwort *Ptychanthus striatus*.[6,7] The correlation of ^{1}H and ^{13}C NMR data for the nuclei in this unusual functional array in **5** and **6** was excellent.

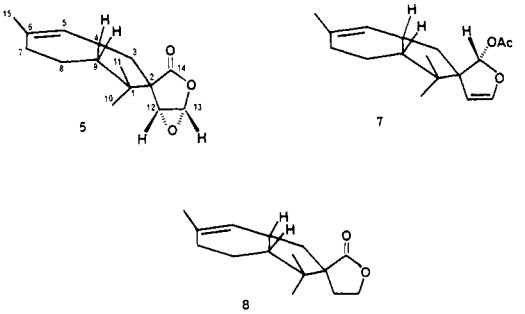


5a 5b 6

A cis configuration was proposed for the juncture of the carbocyclic rings, on the basis of the ^{1}H NMR coupling constants and the apparent relationship of dysetherin to furodysinin. A series of NMR experiments confirmed this hypothesis and established the relative stereochemistry at all five chiral centers as illustrated in **5**.

Comparison of ^{1}H NMR spectra of **5** in $CDCl_3$ and C_6D_6 revealed that the signals for the hydrogens on C-10, C-12, and C-13 were all shifted substantially upfield in C_6D_6 relative to $CDCl_3$, while the signals for hydrogens at C-4, C-9, and C-11 were virtually unchanged. These data suggested solvent complexation or coordination with the epoxide; the induced shifts confirmed that the ring juncture protons were, in fact, cis and indicated that they were on the opposite face of the carbocyclic system from the epoxide hydrogens. Difference NOE experiments disclosed a 10% enhancement of the signal for the epoxide proton on C-12 when the C-10 methyl group was irradiated, but no effect between the C-10 methyl and either ring juncture hydrogen. These results revealed a syn relationship of the epoxide hydrogens and the C-10 methyl and also indicated that this array was on the opposite face of the molecule from the ring juncture protons. Finally, a LIS experiment induced the greatest downfield shifts in the protons at C-3α, C-4, C-9, and C-11 [$\Delta\delta$ 1.27, 1.15, 1.21, and 1.12, respectively, at 1.0 equiv of Eu(fod)$_3$], indicating coordination of the lanthanide with the lactone moiety and a syn disposition of the carbonyl function with those shifted hydrogens. The induced shifts for the protons at C-3β, C-10, C-12, and C-13 were markedly less (δ 0.81, 0.62, 0.92, and 0.90, respectively). Taken together, these results led conclusively to structure **5** for dysetherin.

The structurally similar, albeit less oxidized, spirodysin (**7**) was isolated some time ago by Wells and his colleagues[8] from *Dysidea herbacea* collected near Queensland. The cis ring juncture in **7** was established by conversion to **1** by treatment with BF_3·Et_2O, and the relative configuration at C-14 was suggested from NOE experiments, but the stereochemistry at the spiro center (C-2) remained undefined. The redoubtable assignation of relative stereochemistry for **5** would strongly suggest a similar configuration for **7** as shown.



5 7

8

The Brussels group[9] has isolated two related spiro lactones, herbadysidolide (**8**), and its nor-secoderivative herbasolide from *D. herbacea* collected at Papua, New Guinea. The relative configuration of 8 was determined

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(8) Kazlauskas, R.; Murphy, P. T.; Wells, R. J. *Tetrahedron Lett.* **1978**, 4949.
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by X-ray crystallography and matches the assignments proposed herein for C-2, C-4, and C-9 in **5** and **7**.

Careful examination of three collections of *Dysidea etheria* has yielded no sign of spirodysin or herbadysidolide, although furodysinin is abundant and lesser amounts of the related furodysin[5,10] are always present. Dysetherin might represent an oxidative shunt in the biosynthetic pathway to this family of sesquiterpenes.

Experimental Section

The IR spectrum was recorded on a Beckman IR-20 spectrophotometer, while mass spectral analyses were performed on VG MM16F and 7070 EHF mass spectrometers. NMR spectra were obtained with a Bruker WM-250 Fourier transform spectrometer; chemical shifts are reported in δ units relative to Me_4Si (δ 0).

Collection and Extraction of *Dysidea etheria*. *Dysidea etheria* was collected in relatively shallow (2–5 m), calm inshore waters in Bermuda, primarily along the coastline of Harrington Sound, in August, 1983. The sponge was chopped and stored in acetone at −10 °C until extracted. The acetone was removed by suction filtration, and the sponge was ground with MeOH in a Waring blender. After removal of the MeOH by filtration, the marc was steeped in CH_2Cl_2 (thrice, 24 h each). The acetone and MeOH extracts were combined and reduced to an aqueous suspension, which was then equilibrated with the CH_2Cl_2 extracts. The CH_2Cl_2 phase was reduced, in vacuo, to a thick brown oil, 6.565 g (8.3% of dry weight).

Isolation of Dysetherin. The CH_2Cl_2-soluble extracts were chromatographed on Florisil (225 g, column 3 × 60 cm) with a hexane–EtOAc–MeOH gradient; 24 fractions were collected. Fraction 4, 492 mg, eluted with hexane–EtOAc (24:1), was permeated through Bio-Beads S-X4 (4 × 80 cm) with hexane–CH_2Cl_2–EtOAc (4:4:1) to give six fractions. Fraction 6, 93 mg, was chromatographed under low pressure (~10 psi of N_2) on silica gel (Whatman LPS-2, 2.5 × 34 cm) with a hexane–Et_2O gradient, yielding 12 fractions. Fraction 1, 48 mg, eluted with hexane–Et_2O (22:3), was permeated through Sephadex LH-20 (1.5 × 130 cm) with MeOH–CH_2Cl_2 (1:1). The seventh of seven fractions yielded dysetherin (**5**), 30 mg colorless oil: $[\alpha]_D$ −28.5° (*c* 0.85, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 2940, 1783, 1430, 1370, 1330, 1063 cm^{-1}; MS, *m/z* (relative intensity) 248.1407 (M^+, 6%, calcd for $C_{15}H_{20}O_3$ 248.1412), 233 (6), 215 (6), 203 (100), 189 (10), 159 (15); NMR data in Table I.

Acknowledgment. We thank Dr. Klaus Ruetzler for identifying the sponge. This investigation was supported by PHS Grant 1 R01 CA35905-01A1, awarded by the National Cancer Institute. The NMR spectrometer was acquired via NSF Grant CHE 79-26160 and the mass spectrometry facility was developed with funds from NSF Grant CHE 81-15565 and a grant from the M.J. Murdock Charitable Trust.

Registry No. **5**, 97920-19-9.

(10) Cardellina, J. H., II; Meng, M. W., unpublished data.

A Practical Access to Methyl 3,3-Dimethoxypropionates, *N*-Protected β-Aminoacrylates, and β-Aminoacrylonitrile Using an Electrochemical Procedure

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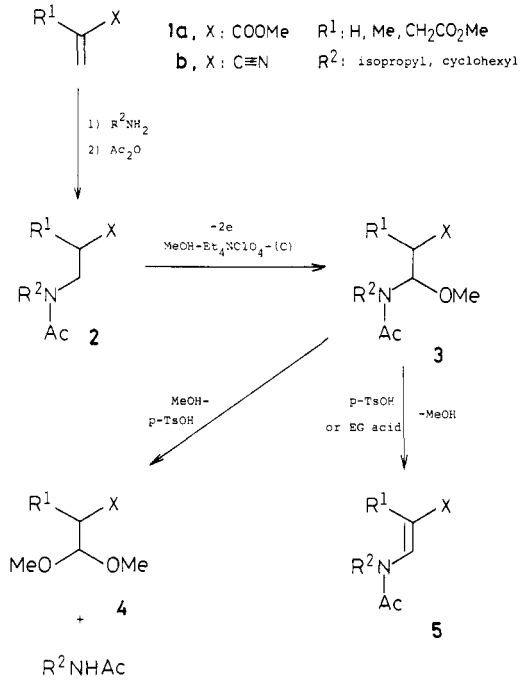
Methyl 3,3-dimethoxypropionate (**4a**, R^1 = H) is a sheltered form of the unstable methyl formylacetate and is useful for the synthesis of a variety of compounds including coumarins,[1] porphyrins,[2] and spermine metabolites.[3] Reported methods for the preparation of **4a** and its homologues involve (a) copper(I) triflate catalyzed addition of alcohol to ethyl propiolate,[4] (b) acetalization of ethyl formylacetate,[5] (c) AIBN initiated addition of carbon tetrachloride to ethyl vinyl ether,[6] (d) oxo reaction of acrylate with palladium catalyst in the presence of alkylnitrite,[7] and others.[8] These reported methods, however, are not satisfactory owing to high costs of their starting materials, low overall yields of the processes, or low efficiency of the transition-metal catalyst. We disclose here a facile preparative access to the acetal **4a** (R^1 = H) and its C(2) alkylated derivatives from methyl acrylate (**1a**, R^1 = H) and the related α,β-unsaturated esters (**1a**). In addition, the preparation of N-protected β-aminoacrylates **5a**[9] and β-aminoacrylonitriles **5b**, versatile intermediates for the preparation of a variety of nitrogen containing heterocycles,[10] is also described (Scheme I).

Scheme I



The electrochemical methoxylation at the α position of N-protected amines was employed as a means of obtaining the key precursors **3** of the desired products **4** and **5**. The procedure known as Ross–Eberson–Nyberg method[11g] has

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