Cytotoxic Amides from the Octocoral *Telesto riisei*

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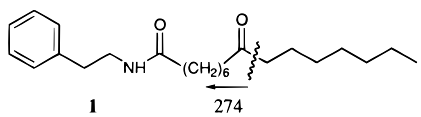
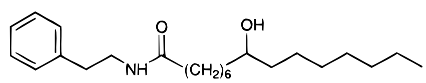
Two new acyl derivatives of *β*-phenylethylamine, *N*-(2-phenylethyl)-9-oxohexadecacarboxamide (**1**) and *N*-(2-phenylethyl)-9-hydroxyhexadecacarboxamide (**2**), and two new tetrahydroxysterols, cholestane-3*β*,5α,6*β*-26-tetrol 27-acetate (**3**) and cholestane-3*β*,5α,6*β*-26-tetrol (**4**), have been isolated from the coelenterate *Telesto riisei* collected in Chuuk, Federated States of Micronesia. Structures were determined from spectroscopic data. All new compounds were mildly toxic to murine leukemia cells (P-388) in culture.

Numerous species of soft corals (Alcyonaceae) and gorgonians (Gorgonaceae) abound on tropical reefs, and these octocorals have been the source of a vast array of secondary metabolites.[1] In contrast, the octocoral order Telestaceae contains few members, and chemical investigation of only one species, *Telesto riisei* Duchassaing and Michelotti (family Telestidae), has been reported. An initial report[2] described two new pregnane derivatives from *T. riisei* collected in Enewetak, whereas later reports[3,4] on specimens collected in Hawaii have described 19 punaglandins, highly functionalized prostanoids. In our search for anticancer agents we have investigated *T. riisei* collected at Chuuk Atoll, Federated States of Micronesia. We report here two cytotoxic amides and two new hydroxy sterols from this octocoral.

Frozen specimens were soaked first in MeOH and then MeOH−CH_2Cl_2 (1:1). The combined extracts were dissolved in MeOH−H_2O (9:1) and partitioned against hexane. The defatted alcohol solution was diluted with H_2O to MeOH:H_2O (7:3) and then extracted with CH_2Cl_2. The CH_2Cl_2 solubles were cytotoxic to P-388 leukemia cells and were fractionated successively by LH-20, Si gel, and finally reversed-phase HPLC to give the amides **1** and **2** and sterols **3** and **4**.



1



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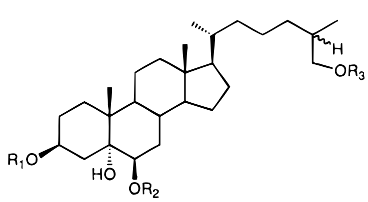

	R_1	R_2	R_3
3	H	H	Ac
4	H	H	H
5	Ac	Ac	Ac

Amide **1** was obtained as a white solid, mp 85 °C, and its formula was confirmed as $C_{24}H_{39}NO_2$ by HREIMS. The presence of ketone and amide groups was revealed by IR [3316 (NH); 1707 (ketone); 1638 cm^{-1} (amide)] and ^{13}C-NMR (*δ* 173.08, 206.39) data. A five-proton multiplet at *δ* 7.23 revealed the presence of a monoalkyl-substituted phenyl group.

The ^1H-NMR spectrum contained a coupled spin system (COSY analysis) corresponding to C(O)NHCH_2-CH_2− [*δ* 4.41 (^1H, br s, exchangeable), 3.49 (2H, q, J = 6.9 Hz), 2.79 (2H, t, J = 6.9 Hz)]. This unit was confirmed to be part of a phenylethylamine moiety by the correlations observed in an HMBC experiment between the *δ* 2.79 signal and carbons (*δ* 138.93, s; 128.62, d) of the phenyl group. Further support for the phenylethylamine amide moiety was gleaned from an intense peak (base peak) in the EIMS at *m/z* 104, corresponding to a charged styrene unit resulting from a McLafferty cleavage of **1**.

The best dispersion of methylene proton signals was obtained in C_6D_6. In this solvent, a methylene triplet at *δ* 1.80 (J = 7.5 Hz), corresponding to the protons adjacent to the amide carbonyl group, showed correlation to a methylene pentet at *δ* 1.65. An overlapping pair of methylene triplets at *δ* 2.07 (J = 7.5 Hz) and 2.04 (J = 7.0 Hz) were correlated to partially overlapping methylene pentets at *δ* 1.60 and 1.54. The latter signals were further coupled to the methylene envelopes at *δ* 1.28. The data are consistent with methylene groups flanking a ketone in an extended methylene chain. One conventional methyl triplet was observed at *δ* 0.87.

The location of the ketone group in the aliphatic chain was deduced by analysis of the mass spectrum, in particular, a strong $M^+ - 99$ peak at *m/z* 274 corresponding to the loss of C_7H_{15} (see structure). The combined spectral data confirm formula **1**.

Amide **2** was an optically active, white solid, mp 78 °C, $[\alpha]^{25}D$ −2.68, with a molecular weight of 375 as confirmed by LREIMS and LRFABMS [*m/z* 398 for $(M + Na)^+$]. An $M^+ - H_2O$ peak at *m/z* 357 in the LREIMS suggested the presence of an alcohol group. The IR revealed absorptions compatible with both hydroxyl and amide groups (3308, 1638 cm^{-1}). The ^1H-NMR spectrum contained all the signals present in **1** for the phenylethylamine moiety and methylene group adjacent to the amide carbonyl (*δ* 1.78, t). A methine signal at *δ* 3.48 (C_6D_6) and the lack of the methylene absorptions at ∼*δ* 2 ppm corresponding to protons adjacent to a ketone suggested that **2** was the alcohol analogue of **1**. This was confirmed when oxidation of **2** with CrO_3/Py

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in CH_2Cl_2 yielded a product whose ^{1}H-NMR and MS were the same as those of **1**.

The formula for compound **3** was confirmed as $C_{29}H_{50}O_5$ by HRFABMS [501.3556 for $(M + Na)^+$]. The IR spectrum contained absorptions indicative of hydroxyl groups (3117–3468 cm^{-1}), and a split carbonyl absorption at 1713, 1729, and strong absorption at 1230 cm^{-1} combined with a singlet methyl proton NMR signal at δ 1.95 indicated the presence of an acetate group. No olefinic carbon signals were observed in the ^{13}C-NMR spectrum, and hence, **3** was determined to be tetracyclic.

The ^{1}H-NMR spectrum of **3** in CD_3OD exhibited various peaks characteristic of a 3β,5α,6β-trihydroxysterol moiety,[5] a common feature in marine polyhydroxysterols.[6] These included methyl singlets at δ 0.67 (H-18) and 1.11 (H-19), two overlapping methyl doublets at 0.90/0.89 (J = 6 Hz, H-21, 27, respectively), a broad one-proton mutiplet at δ 3.96 (H-3), and a broad singlet at δ 3.42 (H-6). The signal for H-27 was doubled owing to stereoisomerism at C-25, see below. The 3β,5α,6β-hydroxylation pattern was supported by measuring the NMR spectrum in pyridine-d_5 and noting that a significant downfield shift occurred for H-3 (δ 4.84) and H-19 (δ 1.63).[7,8] Also, the H-3 signal was coupled to a pair of sharp double doublets at δ 2.30 (1 H, J = 5.1, 12.6 Hz) and 2.94 (1 H, t, J = 12.6 Hz), which were also mutually coupled (COSY) as expected for H-4α and H-4β, respectively, in a 5α-hydroxylated sterol. The remaining downfield signals occurred at δ 3.81, 3.82 (overlapping pair of double doublets, 1 H, J = ~6, ~11 Hz for each pair) and 3.90, 3.91 (overlapping pair of double doublets, 1 H, J = ~6′, ~11 Hz). The COSY spectrum revealed that the double doublet sets were coupled with each other and also to a signal at δ 1.82, which in turn correlated to the doubled secondary methyl signal at δ 0.89. Thus, the 3.81–3.91 signals could be assigned to a hydroxy methyl group at C-26. The doubling of the hydroxymethylene and H-27 signals indicates that **3** consists of a stereoisomeric mixture (25*R*/25*S*). The possibility that the signal doubling for H-26 and H-27 was due to conformational isomerism was contraindicated by the observation that the multiplicity of these signals did not change when the spectrum was measured at elevated temperatures (50 °C, MeOD). The downfield shift of the C-26 protons relative to other reported examples[5] reveals that the oxygen at this position is acetylated.

The ^{13}C-NMR data for **3** (see Table 1) are consistent with this assignment and compare favorably with data for related sterols.[5] The presence of a C-25 epimeric mixture was evident from the doubling of various peaks, including those assigned to C-26 (δ 70.46, 70.61), C-27 (δ 19.18, 19.23), and C-25 (δ 37.21, 37.35). Conventional cholesterol configurations are assumed for the steroid nucleus and side chain, except for C-25, inasmuch as the carbon chemical shifts match those of known sterols.[5]

The LRFABMS of **4** exhibited a peak at m/z 459 consistent with the formula $C_{27}H_{48}O_4Na$, and HREIMS showed a peak at m/z 418.0275 corresponding to $C_{27}H_{46}O_3$ (calcd 418.0215), hence, the latter was assumed to represent $[M - H_2O]^+$. The IR spectrum contained absorptions for hydroxyl groups but not for any carbonyl functionality. The ^{1}H-NMR spectrum was very similar to that of **3**, except that the acetate methyl signal was missing and the signals for H-26,26′ were

Table 1. ^{13}C-NMR Data of Steroids **3** and **4** (δ)[a]

carbon position	**3**(δ)[b]	**4**(δ)
1	31.68	31.67
2	33.48	33.47
3	68.33	68.32
4	41.51	41.49
5	76.82	76.81
6	76.55	76.51
7	35.3	35.27
8	31.63	31.61
9	46.59	46.56
10	39.32	39.3
11	22.34	22.29
12	41.47	41.43
13	43.94	43.91
14	57.47	56.46
15	25.21	25.21
16	29.31	29.33
17	57.67	57.67
18	12.6	12.59
19	17.09	16.99
20	33.75, 33.83	34.74, 34.89
21	17.29	17.21, 17.3
22	37.21, 37.35	37.06, 37.15
23	24.40, 24.32	24.52, 24.58
24	34.82, 34.92	36.87, 36.93
25	36.99, 37.09	37.36, 37.48
26	70.45, 70.61	68.39, 68.57
27	19.17, 19.27	19.12, 19.23
28	173	
29	20.76	

[a] Recorded at 75 MHz in CD_3OD. [b] Assignments aided by DEPT technique and analogy to literature values.[5]

shifted upfield slightly to δ 3.1–3.3. The ^{13}C-NMR spectrum of **4** was also nearly identical to that of **3** except that signals for the acetate group were missing and the doubled signal for C-26 was observed at slightly higher field, δ 68.57, 68.40. Thus **4** was taken to be the alcohol analogue of **3**. Acetylation of **3** and **4** yielded what was judged to be a common triacetyl derivative, **5**, by TLC, MS, and ^{1}H-NMR analysis.

Amides **1** and **2** and sterols **3** and **4** were all cytotoxic to murine leukemia cells (P-388), ED50 (μg/ml) 2.1 (**1**), 2.2 (**2**), 2.4 (**3**), 1.3 (**4**).

Experimental Section

General Experimental Procedures. Reagent-grade solvents were distilled before use for extraction and isolation procedures. ^{1}H-NMR spectra were recorded on Varian-VXR-300 and VXR-500 spectrometers in $CDCl_3$, C_6D_6, CD_3OD or C_5D_5N. Chemical shift values were referenced to the residual protiated solvent peaks at, respectively, δ 7.24, 7.15, 3.30, and 8.71. LRMS were recorded on a Hewlett Packard 5985 mass spectrometer. HRMS measurements were obtained on a VG ZAB-E mass spectrometer. IR spectra were measured with a Bio Rad FTS-7 Ft-ir spectrometer. HPLC was performed using Waters 501 pumps, model 660 solvent programmer, and dual cell refractometer.

Extraction and Isolation of 1–4. Specimens of *T. riisei* were collected at a depth of ca. 15 m from Northeast Pass, Chuuk, Federated States of Micronesia, July 1991, and stored −20 °C until used. A voucher specimen, 46-T-91, is kept at the University of Oklahoma Chemistry Department. Thawed specimens (653 g, wet weight) were extracted first with MeOH (500 mL × 2) and then $MeOH-CH_2Cl_2$ (1:1) (500 mL × 2). The combined extracts were concentrated under vacuum at

35 °C to obtain 5.3 g of crude extract. The crude extract was dissolved in 200 mL of MeOH-H_2O (9:1) and partitioned twice against equal volumes of hexane. The alcohol solution was diluted with H_2O to MeOH-H_2O (7:3) and extracted twice with equal volumes of CH_2Cl_2. The CH_2Cl_2-soluble fraction (2.8 g) was chromatographed over Sephadex LH-20 (75 cm × 2.5 cm column) using $CH_3OH-CH_2Cl_2$ (1:1), and 17 (ca. 100 mL) fractions were collected. These fractions were combined based on their behavior on Si gel TLC [$CH_3OH-CHCl_2$ (1:19)] into two major fractions containing 1.3 g (early eluates) and 3.82 g (later eluates). The later eluates exhibited cytotoxic activity (ED50 = 11 μg/mL) against P-388 murine leukemia cells and were chromatographed on Si gel (120−240 mesh, 40-cm × 2.5 cm column) and eluted under gravity using a step gradient: hexane−CH_2Cl_2 (3:1, 1:1, 0:1) and CH_2Cl_2−MeOH (19:1, 9:1, 4:1). Eighteen 300-mL fractions, were collected and these were combined into 10 fractions. Fractions 5, 7, 8, and 9 displayed cytotoxic activity (ED_{50} = 7−11 μg/mL). Fraction 5 (12 mg, ED50 = 7 μg/mL) was resolved on a reversed-phase C-18 (Whatman Partisil-5 ODS-3, 250 × 9.5 mm) column using gradient elution in CH_3OH:H_2O (1:1 to 1:0 in 40 min) and detected by UV absorbance at 254 nm to give two major components. These were further purified on a C-18 analytical column (Rainin Microsorb 250 × 4.6 mm) using MeOH−H_2O (23:77) with RI detection to obtain pure **1** (11 mg) and **2** (14 mg). Fraction 8 was purified by HPLC over C-18 (as above) in MeOH−H_2O (4:1), followed by another chromatography on C-18 using *n*-propanol−CH_3CN−H_2O (5:6:5) to give compound **3** (8.0 mg). Fraction 9 was resolved by HPLC over C-18 (as above) in MeOH−CH_3CN−H_2O−THF (5:5:6:1) to yield compound **4** (10.0 mg).

***N*-[2-Phenylethyl]-9-oxo-hexadecacarboxamide (1):** white crystalline solid; mp 85 °C; IR ν max (neat) 3316 (−NH), 1707 (C=O), 1638 (O=C-NH) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.87 (3 H, t, J = 7.1 Hz, H-16), 1.22 (14 H, br s, H-4−6 and H-12−15), 1.55 (6 H, m, H-3,7,11), 2.08 (2 H, t, J = 7.8 Hz, H-2), 2.35 (2 H, t, J = 7.5 Hz, H-10), 2.36 (2 H, t, J = 7.5 Hz, H-8), 2.79 (2 H, t, J = 6.9 Hz, H-2′), 3.49 (2 H, q, J = 6.9 Hz, H-1′), 4.41 (1 H, br s, -N-H), 7.23 (5 H, m, phenyl); ^{1}H-NMR (C_6D_6, 500 MHz) δ 0.87 (3 H, t, J = 7.1 Hz, H-16), 1.23 (2H, heptet, H-15), 1.28 (14 H, br s, H-4-6 and H-12−15), 1.54 (2 H, pentet, H-11), 1.61 (2 H, pentet, H-7), 1.65 (2 H, m, H-3), 1.81 (2 H, t, J = 7.2 Hz, H-2), 2.05 (2 H, t, J = 7.5 Hz, H-10), 2.07 (2 H, t, J = 7.2 Hz, H-8), 2.53 (2 H, t, J = 6.9 Hz, H-2′), 3.38 (2 H, q, J = 6.9 Hz, H-1′), 4.57 (1 H, br s, N-H), 7.16 (5 H, m); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 13.87 (C-16), 22.3 (C-15), 23.86, 25.70, 26.0, 29.22, 29.26, 29.35, 35.73, 36.84, 40.4 (C-1′), 42.53, 42.80 (C-8 and C-10), 126.49 (C-6′), 128.62, (C-4′ and C-8′), 128.76 (C-5′ and C-7′), 138.93 (C-3′), 173.08 (C-1), 206.39 (C-9); HREIMS *m/z* found 373.2968 (calcd for $C_{24}H_{39}NO_2$, 373.2981); EIMS (70 ev) *m/z* (rel int) 373 (1.1) M^+, 282 (16.9) $[M - C_6H_5CH_2]^+$, 288 (2.5) $[C_6H_5CH_2OH_2NHCO(CH_2)_7C{=}O]^+$, 274 (21) $[M - C_7H_{15}]^+$, 253 (69) $[M - C_6H_6CH_2CH_2NH]^+$, 176 (9) $[C_6H_5CH_2CH_2NHCO(CH_2)_2]^+$, 163 (13) $[C_6H_5CH_2CH_2NHC(OH)CH_2]^+$, 104 (100) $[C_6H_5CHCH_2]^+$, 91 (13.5) $[C_6H_5CH_2]^+$, 85 (29), 69 (16).

***N*-(2-Phenylethyl)-9-hydroxyhexadecacarboxamide (2):** white crystalline solid, mp 78 °C; $[\alpha]^{25}{}_D$ −2.68 (*c* 0.41, $CHCl_3$); IR ν max (neat) 3310 (N-H), 1641 (CONH); ^{1}H-NMR (C_6D_6, 300 MHz) δ 0.97 (3 H, t, J = 7.5 Hz, H-16), 1.35 (22 H, br s, H-4 to H-8 and H-10 to H-15), 1.64 (2 H, m, H-3), 1.78 (2 H, t, J = 6.9 Hz, H-2), 2.58 (2 H, t, J = 6.9 Hz, H-2′), 3.33 (2 H, q, J = 6.9 Hz, H-1′), 3.48 (1 H, br m, H-9), 4.51 (br s, NH), 7.16 (5 H, m, phenyl); EIMS (70 ev) *m/z* (rel. int.) 375 (2.2) $[M]^+$ 373 (2.7) $[M - 2\ H]^+$, 357 (4.7) $[M - H_2O]^+$, 266 (24.7) $[M - H_2O - C_6H_5CH_2]^+$, 253 (21.7) $[M - C_6H_6CH_2CH_2NH]^+$, 176 (9.4) $[C_6H_5CH_2CH_2NHCOCH_2]^+$, 163 (13.9) $[C_6H_5CH_2CH_2NHCOHCH_2]^+$, 104 (100) $[C_6H_5CHCH_2]^+$.

Cholestane-3β,5α,6β,26-tetrol 26-acetate (3): white crystalline solid; mp 200−202 °C; $[\alpha]^{25}{}_D$ 3.52° (*c* 0.34, MeOH); IR ν max (neat), 3117 (-OH), 1729, 1713 (acetate-carbonyl) cm^{-1}; ^{1}H-NMR (CD_3OD, 500 MHz) δ 0.67 (3 H, s, H-18), 0.890 and 0.896 (3 H, pair of d, J = 7.0 and 6.5 Hz respectively, H-27 isomers), 0.90 (3 H, d, J = 6.0 Hz, H-21), 1.11 (3 H, s, H-19), 1.82 (1 H, m, H-25), 2.01 (3 H, s, CH_3-C=O), 3.42 (1 H, brd s, H-6α) 3.81 and 3.82 (1 H, pair of dd, J = ca. 6, ca. 11 Hz, H-26), 3.90 and 3.91 (1 H, pair of dd, J = ca. 6, ca. 11 Hz, H-26′), 3.96 (1 H, heptet, H-3α); ^{1}H-NMR (C_5D_5N, 300 MHz) δ 0.71 (3 H, s, H-18), 0.90 and 0.91 (3 H, d ea, J = 6.9, 6.6 Hz, respectively, H-27 isomers), 0.94 (3 H, d, J = 6.6 Hz, H-21), 1.63 (3 H, s, H-19), 1.78 (1 H brd m, H-25), 2.02 (3 H, s, CH_3-C=O), 2.30 (1 H, dd, J = 5.1, 12.6 Hz, H-4α), 2.94 (1 H, t, J = 12.6, Hz, H-4β), 3.92 (1 H, dd, J = ca. 6, ca. 11 Hz, H-26), 4.06 (1 H, mult., H-26′), 4.14 (1 H, brd s, H-6α), 4.84 (1 H, m, H-3α); ^{13}C-NMR (CD_3OD, 75 MHz) see Table 1; HRFABMS found *m/z* 501.3553 (calcd for $C_{29}H_{50}O_5Na$ 501.3556; EIMS (70 ev) *m/z* (rel int) 478 (2.3) M^+, 460 (15) $[M - H_2O]^+$, 442 (100) $[M - 2H_2O]^+$, 424 (34.6) $[M - 3H_2O]^+$, 416 (2.1) $[M - CH_3COOH - H_2O]^+$, 398 (4.4) $[M - CH_3COOH - 2H_2O]^+$.

Cholestane-3β,5α,6β,-26-tetrol (4): white crystalline solid, mp 212−214 °C; $[\alpha]^{25}{}_D$−70° (*c* 0.02, MeOH); IR ν max (neat) 3125 (−OH), cm^{-1}; ^{1}H-NMR (CD_3OD, 300 MHz), δ 0.61 (3 H, s, H-18), 0.81−0.84 (3 H, d ea, H-21 and H-27 isomers), 1.10 (3 H, s, H-19), 1.93 (1 H, t, J = 12.4 Hz, H-4β; coupled with δ 3.92), 3.1−3.3 (2 H, 2 pair of dd overlapped with each other and solvent peak H-26,26′), 3.41 (1 H, br s, H-6α), 3.92 (1 H, m, H-3α); ^{13}C-NMR (CD_3OD, 75 MHz), see Table 1; HREIMS found *m/z* 418.0275 [$M^+ - H_2O$ ion], (calcd for $C_{27}H_{46}O_3$ 418.0215); LREIMS *m/z* (rel int), 418 (13.8) $[M - H_2O]^+$, 400 (62.1) $[M - 2H_2O]^+$, 382 (23.2) $[M - 3H_2O]^+$, 364 $[M - 4H_2O]^+$, 278 (47.5), 251.

Oxidation of 2 into 1. A 5% solution of dipyridinechromium (VI)oxide[9] in CH_2Cl_2 was added to 6 mg of **2** dissolved in 1 mL of CH_2Cl_2 (6:1 final molar ratio) and stirred for 2 h at room temperature. The reaction mixture was partitioned against an equal amount of H_2O, and the organic phase was dried (Na_2SO_4) and chromatographed on Si gel using MeOH-CH_2Cl_2 (2:23) to isolate 4.2 mg of **1** (70% yield).

Acetylation of 3 and 4. Acetic anhydride:pyridine (1:1, v/v) 3 mL was added to 3 mg quantities of **3** and **4**. Each solution was stirred at room temperature for 12 h. The reaction mixtures were evaporated and chromatographed on Si gel using Me_2CO-hexane (1:9) to obtain the acetylated derivative **5**: 1.8 mg from **3**; 2.1 mg from **4**.

Cholestane-3β,5α,6β,26-tetrol 3,6,26-triacetate (5): amorphous powder; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.67

(3 H, s, H-18), 0.87−0.94 (3 H, d ea., overlapped doublets of H-21 and H-27), 2.0, 2.02, 2.04 (3 H ea., $CH_3C{=}O$), 3.82 and 3.84 (1 H pr of dd, H-26), 3.91 and 3.92 (1 H, pr of dd, H-26′), 4.65 (1 H, br s, H-6α), 5.11 (1 H, heptet, H-3α); HRFABMS found *m/z* 584.9920, calcd for $C_{33}H_{54}O_7Na^+$, 584.9973; LRFABMS *m/z* 585.4 $[M + Na]^+$, 545.4 $[M - H_2O + H]^+$.

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