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ISOLATION OF THE BIOACTIVE TERPENE 7-DEACETOXY-OLEPUPUANE FROM THE TEMPERATE MARINE SPONGE *DYSIDEA* SP.

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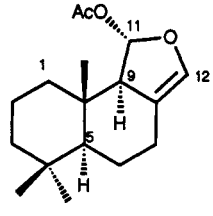
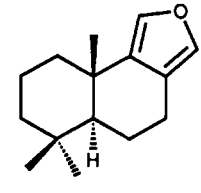
ABSTRACT.—A sesquiterpene ester **1** with a drimane skeleton has been isolated as the major metabolite of a temperate *Dysidea* sp.

Marine sponges of the genus *Dysidea* have occupied the attention of organic chemists because of their diverse chemistry, currently documented by over fifty papers in the chemical literature (1,2). Most workers have concentrated on the tropical species *Dysidea herbacea*, characterized by polychlorinated alkaloids and polybrominated diphenyl ethers in addition to terpenes, because the presence of symbiotic microorganisms may influence the chemical composition. As a result, the sesquiterpene metabolites alone can be considered genuine taxonomic markers for this genus (3). Temperate species of *Dysidea* are characterized by furans or quinols representing the many varied end-products of terpene biosynthesis. In this paper, we report the isolation of a bioactive drimane sesquiterpene, 7-deacetoxy-olepupuane [**1**], related to the marine products euryfuran (4,5) and olepupuane (6). Although the metabolite was recently isolated from nudibranchs of the genus *Dendrodoris* by Avila *et al.* (7), these workers did not provide complete spectroscopic characterization.

A biscuit-colored sponge identified as a *Dysidea* sp. was collected at Port Hacking, New South Wales, Australia. The EtOAc-soluble fraction from an EtOH extraction of diced sponge showed weak antimicrobial activity against *Staphylococcus aureus* and *Bacillus subtilis*. Tlc and nmr inspection showed that the extract contained a major terpene component in addition to sterols and fats. The metabo-



1



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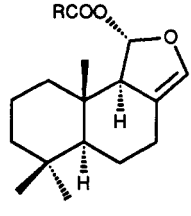
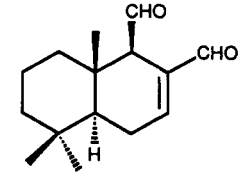


3 R=long chain alkyl



4

lite 7-deacetoxy-olepupuane [**1**] was isolated as a white solid, mp 83–85° and $[\alpha]_D$ −166.7° (c = 0.104, $CHCl_3$) following flash chromatography. The molecular formula of **1** was established as $C_{17}H_{26}O_3$ by hreims. The structure of **1** was fully deduced from ^1H nmr, including 2-D COSY-45 and NOESY spectroscopy, together with ^{13}C-nmr measurements, including one-bond C-H correlation. Nmr data for **1** are tabulated in Table 1; the ^{13}C values cited are in complete agreement with literature data (8). In the 2D COSY-45 experiment, long-range couplings were detected between H-9 and Me-13, between H_{ax}-1 and Me-13, and between H_{ax}-3 and Me-14, thus identifying these two axial methyl groups. A 1.8 Hz coupling between H-9 and H-11 suggested a trans relationship for these two protons. Cross peaks corresponding to an nOe between H-11 and Me-13, between H-11 and H_{eq}-1, and between H-9 and H-5 were detected in a 2D NOESY experiment and confirmed by nOe difference spectroscopy. These data identified the full relative stereochemistry of **1**. Acid treatment of **1** gave euryfuran [**2**] with ^1H nmr identical to that reported in the literature (4,5,8). The small sample size and instability of euryfuran precluded accurate measurement of the optical rotation; therefore the absolute stereochemistry could not be assigned. The absolute stereochemistry depicted was selected because *Dysidea* sp. is reported to contain (+)-euryfuran.

Purified 7-deacetoxy-olepupuane showed antimicrobial activity as described above together with antifungal activity against *Trichophyton mentagrophytes* and was cytotoxic to P388 cells in vitro (IC_{50} = 16.4 μg/ml). The isolation of a

TABLE 1. ^{13}C- and ^1H-nmr Assignments of 7-Deacetoxy-olepupuane [**1**].

Position	δ ^{13}C[a]	δ ^1H[b]
1	39.3 (t)	ax 1.08 (dddd, J = 12.9, 12.9, 3.6, <1 Hz)
		eq 1.62 (dddd, J = 12.9, 3.4, <1 Hz)[c]
2	18.3 (t)	ax 1.55 (ddddd, J = 13.8, 13.6, 12.9, 3.4, and 3.4 Hz)
		eq 1.45 (ddddd, J = 13.6, 3.8, 3.6 Hz)[c,d]
3	42.0 (t)	ax 1.17 (dddd, J = 13.8, 13.8, 3.8, and <1 Hz)
		eq 1.41 (dddd, J = 13.8, 3.4, <1 Hz)[d]
4	32.9 (s)	—
5	52.9 (d)	0.98 (dd, J = 12.5, 2.6 Hz)
6	22.5 (t)	ax 1.25 (dddd, J = 13.8, 12.7, 12.5, and 3.6 Hz)
		eq 1.69 (dddd, J = 12.7, 5.7, 2.6, and 1.1 Hz)
7	23.0 (t)	ax 1.98 (ddddd, J = 13.8, 13.7, 5.7, 1.9, and 1.9 Hz)
		eq 2.46 (ddd, J = 13.7, 3.6, and 1.1 Hz)
8	114.3 (s)	—
9	63.7 (d)	2.25 (bs, J = 1.8, 1.9, 1.9, <1 Hz)
10	36.8 (s)	—
11	98.1 (d)	6.27 (d, J = 1.8 Hz)
12	134.2 (d)	6.02 (dd, J = 1.9, 1.9 Hz)
13	13.7 (q)	0.78 (bs, J < 1 Hz)
14	21.5 (q)	0.80 (bs, J < 1 Hz, <1 Hz)
15	33.3 (q)	0.86 (s)
OAc	20.9 (q)	2.05 (s)
	169.6 (s)	

[a]Solution in $CDCl_3$ referenced to $CHCl_3$ at 77.0 ppm; 100 MHz. Assignments based on DEPT and XHCORR experiments.

[b]Solution in $CDCl_3$ referenced to $CHCl_3$ at δ 7.25; 400 MHz. Assignments based on COSY-45 and ^1H-^1H decoupling experiments.

[c,d]J values for coupling of H_{eq}-1 to H_{eq}-2 and of H_{eq}-2 to H_{eq}-3 not resolved.

bioactive sesquiterpene ester from *Dysidea* sp. is of interest as sesquiterpene esters **3** have been isolated from nudibranchs (7,9) where they are believed to represent detoxification products of the antifeedant cometabolite polygodial [**4**]. Although nudibranchs are known to derive defense chemicals from their sponge diets, both polygodial and the sesquiterpene esters **3** have been shown experimentally to be products of de novo nudibranch metabolism (10). Drimane sesquiterpenes represent a rare cyclization mode in marine sponges, having previously been reported only from a tropical collection of *Dysidea herbacea* (4) and from *Euryspongia* (5). The isolation of a drimane sesquiterpene ester from a sponge now raises the additional possibility that the nudibranch compounds could also have a dietary origin.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—These have been reported previously (11).

SPONGE.—The genus *Dysidea* has many species, some with cosmopolitan distributions, most with more restricted habitats. In temperate Australia several species have been recorded, but the descriptions are extremely poor and type specimens are not available. Until a revision of the genus is undertaken based upon collection of fresh material for comparison with Northern Hemisphere temperate *Dysidea* species, it is misleading to assign names or state that the species is new (P.R. Bergquist, personal communication). The present species (Australian Museum registry Number Z5089), a biscuit-colored sponge, growing in low ridges at −20 m, was collected offshore from Port Hacking, New South Wales, Australia in October 1986. The sponge tissue, although compressible, incorporates debris. The sponge surface is finely conulose; oscules (5 mm) are prominent. Other taxonomic markers conform to those recorded for the genus (12).

The sponge sample collected is morphologically different from the *Dysidea* sp. (FN 1762) collected from Diamond Head, Port Hacking, by the Roche group and reported to contain sesquiterpene metabolites (13). Sponge FN 1762 is a soft, encrusting sponge, usually pale pink in color, samples of which have also been collected by one of us (MJG) and found to contain furodysin, furodysinin, and thiofurodysin, together with acetate derivatives.

ISOLATION.—The wet sponge (58 g) was extracted with 95% EtOH (3 × 200 ml). After filtration and concentration in vacuo, the syrupy residue was partitioned between EtOAc (3 × 50 ml) and H_2O (50 ml). The combined EtOAc fractions were dried with Na_2SO_4 and evaporated to give a pale yellow oil (0.26 g). Flash chromatographic purification on silica using hexane-CH_2Cl_2 (3:1) afforded 7-deacetoxy-olepupuane [**1**], recrystallized from hexane/CH_2Cl_2 as white crystals, mp 83–85°; 0.11 g (0.17% of wet wt); $[\alpha]_D$ −166.7° (c = 0.104, $CHCl_3$); ir 2940, 2845, 1740, 1680, 1520, 1390, 1370, 1235 cm^{-1}; ^1H and ^{13}C nmr see Table 1; hreims 278.1882 ($C_{17}H_{26}O_3$ requires 278.1882), 218.1671 ($C_{15}H_{22}O$ requires 218.1671); eims *m/z* (intensity, %) $[M]^+$ 278 (<10), $[M - CH_2CO]^+$ 236 (<10), $[M - HOAc]^+$ 218 (17.6), 203 (48.2), 137 (17.2), 123 (24.6), 69 (64.2), 42 (100); cims (positive) *m/z* $[MH - HOAc]^+$ 219 (100%); (negative) *m/z* $[M - H - CH_2CO]^-$ 235 (100%).

CONVERSION TO EURYFURAN.—A solution of 7-deacetoxy-olepupuane (5.0 mg) in $CHCl_3$-MeOH (1:1) was treated with 10% H_2SO_4 (0.5 ml) at 0° for 12 h, then worked up with Et_2O to provide euryfuran (3.5 mg). Thermolysis of **1** on Si gel also provided euryfuran.

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