# XESTODIOL, A NEW APOCAROTENOID FROM THE SPONGE
XESTOSPONGIA VANILLA

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Marine sponges belonging to the genus *Xestospongia* have been the source of a number of extremely interesting secondary metabolites. These include a family of brominated acetylenic fatty acids (1,2), a group of pentacyclic hydroquinones and quinones (3,4), a family of macrocyclic bis(1-oxaquinolizidines) (5), and a series of steroids with unusual side-chain alkylation patterns (6). We now wish to report the isolation of xestodiol [1], a new apocarotenoid, from the extracts of *Xestospongia vanilla* de Laubenfels.[1]
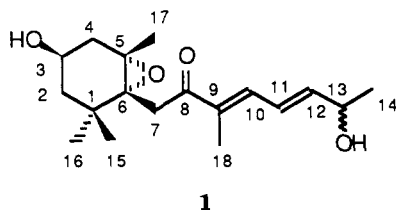
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X. vanilla was collected by hand using scuba equipment in several exposed surge channels along the shoreline of the Deer Group of Islands in Barkeley Sound, British Columbia. Freshly collected sponge was immediately immersed in MeOH. The organic soluble portion of the MeOH extract was fractionated by Sephadex LH 20, Si gel flash, and reverse phase high performance chromatographies to give pure xestodiol [1].

Xestodiol [1], obtained as a clear oil, gave a molecular ion at m/z 308.1981 daltons in the hreims appropriate for a molecular formula of $C_{18}H_{28}O_4$ (dev. -0.6 mmu). All eighteen carbon atoms were readily apparent in the ^{13}C-nmr spectrum of 1 (Table 1), and an APT

spectrum showed 26 protons attached to carbon atoms. A strong band at 3369 cm^{-1} in the ir spectrum of 1 suggested that the remaining two protons were attached to alcohol oxygen atoms. Three of the five degrees of unsaturation required by the molecular formula of xestodiol could be accounted for by the conjugated ketone and two olefinic bonds that were evident from ^{13}C-nmr resonances at δ 198.0, 145.5, 137.5, 136.0, and 124.3 ppm. There was no evidence for additional carbonyl functionalities in xestodiol, so the remaining oxygen atom had to be present as an ether. ^{13}C-nmr resonances at δ 66.2 (s) and 67.0 (s) ppm indicated that the ether was a fully substituted epoxide. The final degree of unsaturation had to be a carbocyclic ring.

A number of structural fragments could be routinely assembled from evidence present in the richly detailed and highly dispersed ^1H-nmr spectrum of 1. Coupling patterns and double resonance experiments revealed a conjugated diene that had a 1-hydroxyethyl substituent attached to one terminus and two nonhydrogen substituents attached to the other terminus (Table 1: H_{10} to H_{14}). An olefinic methyl (δ 1.92 ppm, s, 3H) and the conjugated ketone carbonyl comprised the two non-hydrogen substituents. The chemical shifts of a pair of spin-isolated geminal protons (δ 2.59, d, $J=18.3$ Hz and 3.65 ppm, d, $J=18.3$ Hz) suggested that the methylene carbon to which they were attached was adjacent to the ketone. A 15.0 Hz coupling between the olefinic protons resonating at δ 6.18 and 6.64 ppm, and the observation of nOes between both of the methylene resonances at δ 2.59 and 3.65 and the olefinic resonance at 7.04 ppm demonstrated that

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TABLE 1.   Nmr Assignments for Xestodiol [1] and Fucoxanthin [2]

Carbon atom	Xestodiol		Fucoxanthin (10,11)	
	$^1H^a$	$^{13}C^b$	^1H	$^{13}C^c$
1	—	35.3	—	35.2
2	1.52, ddd, J=12.6, 3.2, 1.5 Hz 1.68 —	40.9^d	—	40.9
3	3.82, m	64.3^e	—	64.2
4	1.79, dd, J=14.6, 9.3 Hz 2.34, ddd, J=14.6, 4.6, 1.5 Hz	41.7^d	—	41.8
5	—	66.2^f	—	66.2
6	—	67.0^f	—	67.2
7	2.59, d, J=18.3 Hz 3.65, d, J=18.3 Hz	47.2^d	2.55 3.60	47.3
8	—	198.0	—	197.9
9	—	136.0	—	134.5
10	7.04, d, J=11 Hz	145.5^g	—	145.1
11	6.64, ddd, J=1.3, 11, 15 Hz	124.3^g	—	123.4
12	6.18, dd, J=5.5, 15 Hz	137.5^g	—	139.2
13	4.51, quintet, J=5.5 Hz	68.3^e	—	—
14	1.37, d, J=5.5 Hz	21.2^h	—	—
15	0.96, s	23.5^h	0.97	21.5
16	1.04, s	25.1^h	1.03	25.0
17	1.22, s	28.2^h	1.20	28.2
18	1.92, s	11.8	1.92	11.9

^{a}Recorded in CDCl$_3$ at 400 MHz.
^{b}Record in CDCl$_3$ at 75 MHz.
^{c}The ^{13}C-nmr spectrum of fucoxanthin [2] has not been fully assigned (11). We have simply listed the values in the spectrum of 2 which correspond to resonances in the spectrum of 1.
^{d,e,f,g,h}Assignments may be interchanged.

both the double bonds had the E configuration. The structural fragment identified by the above experiments was assigned to the side chain of xestodiol [1] extending from C$_7$ to C$_{14}$.
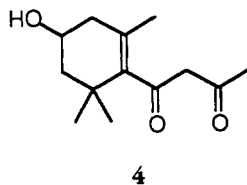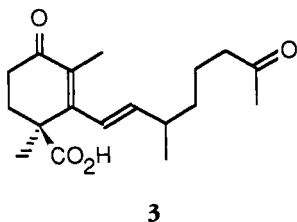
A five proton spin system consisting of a central carbinol methine proton (δ 3.82 ppm, m) flanked by two sets of non-equivalent geminal protons (δ 1.52, ddd, J=12.6, 3.2, 1.5 Hz; 1.68 (submerged): 1.79, dd, J=14.6, 9.3 Hz; 2.34, ddd, J=14.6, 4.6, 1.5 Hz) was also readily apparent. The coupling constants observed for this system suggested that the carbon atoms bearing the protons were part of a cyclohexane ring fixed in a chair-like conformation,

and that the alcohol functionality on the central carbon was equatorial. Methyl resonances at δ 0.96 (s) and 1.04 (s) ppm were assigned to a gem-dimethyl moiety, and a methyl resonance at δ 1.22 (s) ppm was assigned to a methyl group attached to a carbon bearing an oxygen atom. Biogenetic reasoning guided the assembly of all the fragments of xestodiol into the terpenoid structure 1. Support for the proposed constitution of 1 and assignment of the relative stereochemistry of the chiral centers in the cyclohexane ring came from a comparison of the ^{1}H- and ^{13}C-nmr data of xestodiol [1] with the values reported for fucoxanthin [2] (7-10) (Table 1). A series of nOe experi-

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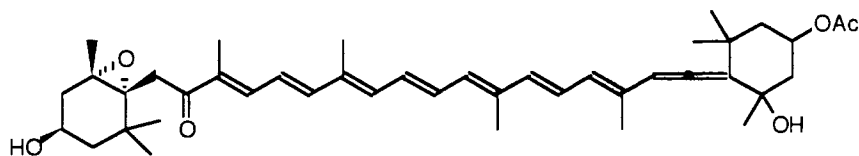
ments (see Experimental) supported the stereochemical assignment.

Apocarotenoids are well known from terrestrial sources (11). Trisporic acid B [**3**], one member of a family of extensively studied fungal hormones that have the same carbon skeleton as **1**, is a typical example (12). Xestodiol [**1**] and the dinoflagellate metabolite **4** (13) are, to the best of our knowledge, the only examples of apocarotenoids isolated from marine organisms. The biogenetic origin of xestodiol [**1**], like that of many terrestrial apocarotenoids, is unclear. It may be formed by degradation of a carotenoid, or it may be formed directly by de-novo biosynthesis from mevalonic acid.

The CH_2Cl_2 and EtOAc solutions were dried over Na_2SO_4, evaporated in vacuo, and combined. The combined organic extracts were fractionated on LH 20 (eluent: MeOH-CH_2Cl_2, 9:1). Fractions showing a uv (254 nm) absorbing tlc spot (Si gel, eluent: Et_2O, Rf 0.29) which charred a bright yellow with H_2SO_4 were combined and further fractionated using gradient flash chromatography (gradient: 100% CH_2Cl_2 to 100% EtOAc in 10% increments). Again the fractions showing the bright yellow tlc spot were combined. The combined flash fractions were purified by preparative reverse phase hplc (eluent: MeOH-H_2O, 7:3) to give pure xestodiol [**1**] (5 mg, 3×10^{-4}% of dry wt.).

XESTODIOL [**1**].—Clear oil; $[\alpha]D - 27°$ ($c=0.5$, MeOH); uv (MeOH) λ max 276 nm (ϵ 16, 100); ir (neat) 3370, 2966, 1664, 1637 cm^{-1}; ^{1}H nmr (see Table 1); ^{13}C nmr (see Table 1); ms M$^+$ 308.1981 ($C_{18}H_{28}O_4$, deviation -0.6 mmu), 290, 263, 247.

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EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.— Nmr spectra were recorded on Varian XL 300 and Bruker WH-400 spectrometers. TMS was used as an internal standard. Low resolution mass spectra were recorded on an AEI MS902 spectrometer and high resolution mass spectra on an AEI MS50 spectrometer. Ir spectra were recorded on a Perkin-Elmer 1710 Fourier transform spectrometer. Uv spectra were recorded on a Bausch and Lomb Spectronic 2000 instrument. Optical rotation measurements were recorded on a Perkin-Elmer 141 polarimeter.

Merck Si gel (230-400 mesh) was used for flash chromatography, and a Whatman Magnum 9 Partisil 10 ODS-3 column was used for preparative hplc. Sephadex LH 20 was used for molecular exclusion chromatography.

Freshly collected sponge (voucher sample is deposited in the Department of Oceanography, UBC) (dry weight 1.6 kg) was immersed in MeOH (21), homogenized in a Waring blender, and allowed to extract for 2 days at room temperature. Vacuum filtration of the homogenate gave a filtrate which was concentrated in vacuo. The concentrate was suspended in H_2O (11) and sequentially extracted with CH_2Cl_2 (750 ml x 3) and EtOAc (750 ml x 3) in a separatory funnel.

THE NOE RESULTS.—Irrad 3.82 (H3), obsvd. 2.34 (H4α), 1.52 (H2α), 1.04 (Me16); irrad 3.65 (H7), obsvd. 7.04 (H10), 2.59 (H7'), 0.96 (Me15), 1.04 (Me16); irrad 2.59 (H7'), obsvd. 7.04 (H10), 3.65 (H7), 1.22 (Me17); irrad. 1.52 (H2α), obsvd. 3.82 (H3); irrad 1.22 (Me17), obsvd. 2.59 (H7'), 2.34 (H4β), 1.79 (H4α); irrad 1.04 (Me16), obsvd. 3.82 (H3), 3.65 (H7), 2.59 (H7', neg.), 1.52 (H2α); irrad 0.96 (Me15), obsvd. 3.65 (H7), 2.59 (H7', neg.), 1.52 (H2α); irrad 6.18 (H12), obsvd. 4.51 (H13), 7.04 (H10), 3.65 (H7, neg.), 2.59 (H7', neg.).

ACKNOWLEDGMENTS

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