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XESTENONE, A NEW BICYCLIC C19 TERPENOID FROM THE MARINE SPONGE *XESTOSPONGIA VANILLA*

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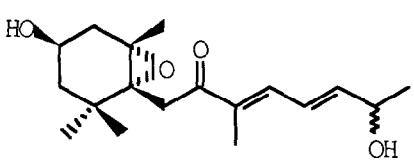
Abstract *The structure of xestenone (2), a degraded terpenoid isolated from the sponge* Xestospongia vanilla, *has been solved by a combination of spectroscopic analysis and chemical interconversions.*

Chemical studies on marine sponges belonging to the genus *Xestospongia* have yielded a biogenetically diverse group of secondary metabolites. These include brominated acetylenic fatty acids[1], pentacyclic hydroquinones and quinones[2], macrocyclic bis(1-oxaquinolizidines)[3], steroids with unusual side chain alkylation patterns[4], and isoquinoline alkaloids[5]. We recently reported the isolation of xestodiol (**1**), a C18 apocarotenoid, from *Xestospongia vanilla* [6] and we now wish to report the the isolation of xestenone (**2**), a C19 terpenoid with a new bicyclic carbon skeleton, from the same sponge.



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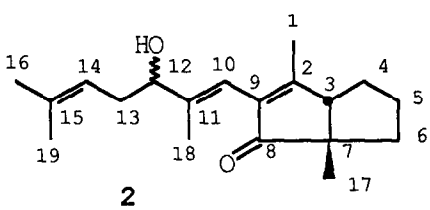


2

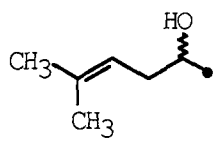
X. vanilla (0.8kg dry wt.) was collected in exposed surge channels along the shoreline of the Deer Group of islands in Barkley Sound, British Columbia. Freshly collected sponge was homogenized with methanol in a Waring blender and extracted at room temperature. The organic soluble portion of the methanol extract was fractionated by Sephadex LH 20 ($MeOH/CH_2Cl_2$, 9:1), gradient silica gel flash (CH_2Cl_2 to MeOH/EtOAc,1:4), silica gel preparative thin layer (Et_2O) and reverse phase preparative thin layer ($MeOH/H_2O$, 8:2) chromatographies to give pure xestenone (**2**) (12.9mg) as an optically active clear oil[7].

The HRMS of xestenone showed a parent ion at m/z 288.2024 daltons appropriate for a molecular formula of $C_{19}H_{28}O_2$ (ΔM -0.6 mmu) requiring six sites

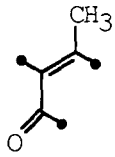
of unsaturation. Resonances that could be assigned to three olefins, two tri-substituted and one tetra-substituted, and a ketone were present in the ^{13}C nmr spectrum of **2** (Table 1). The absence of additional unsaturated functionality required that xestenone contain two rings.

A strong band at 3416 cm^{-1} in the IR spectrum of **2** was assigned to an OH stretch and a ^{13}C resonance at δ 76.3 (CH) indicated that the alcohol was secondary. The carbinol methine proton was found at δ 4.17 in the ^{1}H nmr spectrum of xestenone and a series of decoupling experiments showed that it was coupled to a pair of methylene protons at δ 2.34 which were in turn coupled to an olefinic proton at δ 5.16. Irradiation of the olefinic proton at δ 5.16 induced an nOe into a methyl resonance at δ 1.73. The above evidence, in conjunction with the observation of a fragment ion (base peak) at m/z 219 daltons ($M^+ - C_5H_9$) in the mass spectrum of **2**, suggested the partial structure **A**. In accordance with the presence of a secondary alcohol, xestenone formed a monoacetate when treated with acetic anhydride in pyridine[8].

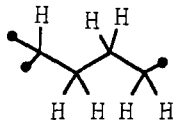
Fragments of Xestenone



A



B



C

A very deshielded olefinic resonance (δ 172.6) in the ^{13}C nmr spectrum, a deshielded olefinic methyl resonance (δ1.92) in the ^{1}H nmr spectrum and a carbonyl stretching band at 1698cm^{-1} in the IR spectrum of **2** were tentatively assigned to an αβ unsaturated ketone with a β methyl substituent (fragment **B**). Evidence obtained from ^{1}H-^{1}H decoupling , double quantum filtered COSY, ^{1}H 2D J-resolved and HETCOR experiments (see H3 to H6 & H6' in Table 1) established the existence of fragment **C** in xestenone. The remaining atoms of **2** could be accounted for by a second trisubstituted olefin having one methyl attachment (COSY showed allylic coupling between an olefinic proton at δ 5.92 and the olefinic methyl at δ1.53) and a methyl (δ1.20,s) attached to a quaternary carbon (δ 54.7).

Biogenetic reasoning guided the assembly of the fragments into the proposed terpenoid structure **2** for xestenone. A strong nOe (12% enhancement) between the carbinol methine proton at δ 4.17 (H12) and the olefinic proton at δ 5.92 (H10) supported the attachment of fragment **A** to the second trisubstituted olefin and established the C10-C11 olefin stereochemistry as E. Similarly, a nOe (3% enhancement) between the deshielded C1 olefinic methyl at δ 1.92 and the olefinic proton at δ 5.92 (H10) supported the attachment of the side chain to the α carbon of the αβ unsaturated ketone. A SINEPT experiment, optimized for polarization transfer through a J ^{13}C-^{1}H of 7Hz, showed three bond coupling between the olefinic proton at δ5.92 (H10) and carbons at δ 76.3 (C12) and δ 172.3 (C2) in agreement with the proposed structure. A strong nOe (14% enhancement) between the methyl

protons on C17 (δ 1.20) and the methine proton at C3 (δ 2.70) established that the five membered rings were *cis* fused.

Reduction of xestenone with sodium borohydride gave diol **3** as one of several products. The mass spectrum of **3** failed to show a parent ion but did show strong fragment ions at m/z 274 ($M^+ - H_2O$) and 223 ($M^+ - C_5H_9$) daltons indicating that four hydrogen atoms had been added. Decoupling experiments showed that an allylic methine proton (H9, δ 2.96) in the ^1H nmr spectrum of diol **3** was coupled to a new carbinol methine proton (H8, δ3.72), to an olefinic proton (H10, δ 5.71), and to another aliphatic methine (H2, δ 2.09) which was in turn coupled to a methyl doublet ($CH_3$1, δ 0.94). This set of experiments confirmed the attachment of the side chain to the α carbon and a methyl group to the β carbon of the αβ unsaturated ketone fragment of xestenone (**2**). Further decoupling showed that H2 (δ 2.09) was coupled to a methine proton at δ 1.85 assigned to H3 in diol **3**, thereby confirming the attachment of fragment **C** to the β carbon of the αβ unsaturated ketone portion

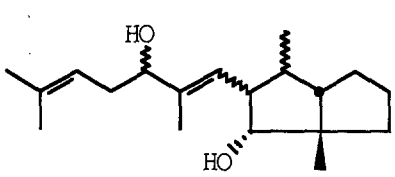
Table 1 ^1H and ^{13}C nmr assignments for xestenone (**2**) and the reduction product **3**. Chemical shifts are reported in ppm from internal TMS.

	Xestenone (**2**)[a]		Diol **3**[b]
	^1H	^{13}C[c]	^1H
C#			
1	1.95,s	16.7(CH_3)	0.94,d,J=7.4Hz
2	-	172.3(C)	2.09,ddq,J=7.3,7.3,6.6Hz
3	2.70,bd,J=9.3Hz	56.6(CH)	1.85,ddd,J=6.6,6.6,6.6Hz
4	1.8,m ; 1.7,m	28.8(CH_2)	-
5	1.6,m ; 1.2,m	24.7(CH_2)	-
6	1.93,dd,J=12,6Hz 1.34,ddd,J=12,12,6Hz	37.4(CH_2)	-
7	-	54.7(C)	-
8	-	212.9(C)	3.72,bd,J=6.6Hz
9	-	137.3#(C)	2.96,ddd,J=10.5,6.6,6.6Hz
10	5.92,bs	115.6(CH)	5.71,bd,J=10.5Hz
11	-	144.3#(C)	-
12	4.17,t,J=6.9Hz	76.3(CH_2)	3.96,dd,J=6.2,6.2Hz
13	2.34,t,J=6.9Hz	33.9(CH_2)	-
14	5.16,bt,J=6.9Hz	119.9(CH)	5.17,dd,J=7.5,7.5Hz
15	-	134.4#(C)	-
16	1.73,bs	25.9(CH_3)	1.66,bs#
17	1.20,s	22.5(CH_3)	1.11,s
18	1.53,bs	14.4(CH_3)	1.51,s#
19	1.65,bs	18.0(CH_3)	1.58,bs#

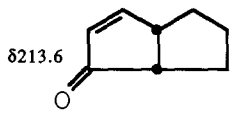
a) Recorded in $CDCl_3$. b) Recorded in d_6-Benzene. c) Proton attachments determined with APT. # May be interchanged.

of **2**. A nOe experiment established that the C8 hydroxyl was *trans* to the C7 methyl in **3**. We were not able to assign the relative configurations at C2 and C9.

Spectral data reported for the two model compounds **4**[9] and **5**[10] (shown below) is in excellent agreement with that found for xestenone (**2**).



3



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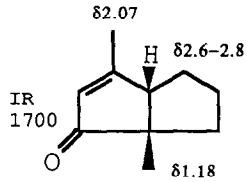

5

Xesteneone is apparently a degraded diterpenoid. To the best of our knowledge, its carbon skeleton is not related to that of any previously reported diterpenoid or nor-diterpenoid. Xestodiol (**1**) and xestenone (**2**) represent the first examples of obvious terpenoid metabolites from the genus *Xestospongia*; however, halenaquinone[2] and related compounds could conceivably be formed by a mixed terpenoid-benzenoid biogenesis similar to that proposed for averol[11].

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7. The $[\alpha]_D$ for xestenone is essentially 0° (c= 1.0, MeOH). The CD spectrum of xestenone showed a positive Cotton effect at λ= 324nm ([Θ] = +900 ; MeOH) and a negative Cotton effect at 257nm ([Θ] = -3,000) and the UV spectrum showed λ_{max} 258nm (sh, MeOH; ε = 6,400).
8. Xestenone monoacetate showed: ^{1}H nmr ($CDCl_3$) δ 1.19(s,3H), 1.54(s,3H), 1.63(s,3H), 1.70(s,3H), 1.93(s,3H), 2.06(s,3H), 5.22 (t, J=6.6Hz, H12).
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