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THREE NEW *ent*-VALERENANE SESQUITERPENES
FROM AN OKINAWAN SOFT CORAL

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Three new sesquiterpenes named valerenenol (1), isovalerenenol (2), and anhydrovalerenenol (3), having a new carbon skeleton of *ent*-valerenane, were isolated from an Okinawan soft coral (unidentified sp., Xeniidae) and their absolute stereostructures were elucidated by chemical, physicochemical, and X-ray crystallographic analyses.

KEYWORDS— *ent*-valerenane sesquiterpene; valerenenol; isovalerenenol; anhydrovalerenenol; soft coral; Xeniidae; ¹H NMR; ¹³C NMR; X-ray analysis; CD

During studies on marine natural products,¹⁾ we isolated three new *ent*-valerenane sesquiterpenes from an Okinawan soft coral (unidentified sp., Xeniidae).

This paper describes the chemical characterization of these sesquiterpenes named valerenenol (1), isovalerenenol (2), and anhydrovalerenenol (3).

The acetone extract of a fresh soft coral collected in July at Kohamajima, Okinawa Prefecture was partitioned by an AcOEt-water solvent system. The AcOEt-soluble portion was subjected to HPLC and preparative GLC separation to furnish 1, 2, and 3 (32%, 2%, and 8% respectively).

The ¹H NMR spectrum (200 MHz, CDCl₃) of valerenenol (1), colorless oil, C₁₅H₂₆O,²⁾ [α]_D +123° (CHCl₃), IR (CHCl₃, cm⁻¹): 3610, showed signals due to two *sec.* CH₃ groups (δ 0.85, d, J=6.8 Hz, 8-CH₃; δ 0.93, d, J=7.3 Hz, 3-CH₃), two *tert.* CH₃ groups in an isopropanol moiety [δ 1.35, 1.37, both s, 12-(CH₃)₂], and one olefinic H (δ 5.42, br.s, 11-H).³⁾ The ¹³C NMR spectrum (50 MHz) of 1 showed the presence of a trisubstituted double bond (δc 140.7, s, 5-C; δc 134.4, d, 11-C) and a *tert.* OH group (δc 71.3, s, 12-C). Thus, 1 was considered to be a bicarbocyclic sesquiterpene.

Ozone oxidation of 1 gave an oily tetranor-derivative (4), C₁₁H₁₈O, [α]_D +17° (CHCl₃), which had a six-membered ring ketone function [IR (CCl₄): 1710; δc 215.2, s, 5-C]⁴⁾ and retained two *sec.* CH₃ groups (¹H and ¹³C NMR). *m*-Chloroperbenzoic acid oxidation of this ketone (4) furnished a seven-membered lactone (6), mp 59-60°C, C₁₁H₁₈O₂, IR (CHCl₃): no OH, 1716, which, on subsequent LiAlH₄ reduction, was

converted to a cyclopentane diol. (7), mp 77–78°C, $C_{11}H_{22}O_2$, δ 3.91 (1H, br.s, 4-H), 3.60 (2H, br.t, $J=6.4$ Hz, 5- H_2); δ 76.8 (d, 4-C), 63.5 (t, 5-C), which, after protection of the primary hydroxyl function by *t*-butyldimethylsilylation (giving 7a), was converted to a cyclopentanone (8), $C_{17}H_{34}O_2Si$, IR (CCl_4): 1740, δ 3.53 (2H, t, $J=6.5$ Hz, 5- H_2), δ 223.2 (s, 4-C), 63.5 (t, 5-C). $NaBH_4$ reduction of the ketone (8) yielded in 1:1 ratio 7a and the C-4 epimer (9), $C_{17}H_{36}O_2Si$, IR ($CHCl_3$): 3622, δ 3.29 (1H, br.t, $J=7.3$ Hz, 4-H), 3.55 (2H, br.t, $J=6.4$ Hz, 5- H_2), δ 83.3 (d, 4-C), 63.7 (t, 5-C).

It became clear from the ^{13}C NMR data for 7 and 9 that signals due to 4-C (δ 76.8, d), 10-C (14.3, q) and 8-C (33.4, d) of 7 appeared with higher δ values than 9 (δ 83.3, d; 17.8, q; 36.0, d, respectively) presumably due to steric compression⁵ by the 4-OH group of 7. Thus, the neighboring residues at C-3, C-4, and C-9 of the cyclopentane ring of 7 were assumed to be *cis*, whereas those in 9 were *trans* one by one.

Epoxidation followed by acidic treatment (2N HCl-benzene) of 7 quantitatively yielded an epimeric mixture of 5-ene-11,12-diol (10), the major product (colorless oil), $C_{15}H_{26}O_2$, IR ($CHCl_3$): 3611, 3573, δ 6.60 (1H, br.d, $J=7.3$ Hz, 6-H), 3.77 (1H, br.s, 11-H), 1.25, 1.18 (both 3H, s, 12-(CH_3)₂); δ 142.0 (s, 5-C), 125.8 (d, 6-C), 79.1 (d, 11-C), 73.8 (s, 12-C), 27.1, 24.9 (both q, 13-C, 14-C), which, on subsequent $NaIO_4$ degradation, was converted to the α,β -unsaturated trisnor-aldehyde (11), $C_{12}H_{18}O$, UV λ_{max}^{MeOH} 222 nm (ϵ 10100), δ 6.96 (1H, dd, $J=2.4, 6.8$ Hz, 6-H), 9.41 (1H, s, 11-H), δ 144.2 (s, 5-C), 152.2 (d, 6-C), 194.3 (d, 11-C). Isopropenyl acetate treatment of 11 furnished the enol-acetate (12), $C_{14}H_{20}O_2$, UV λ_{max}^{MeOH} 247 nm (ϵ 17300). The 1H NMR spectrum of 12 showed signals due to 7-H at δ 5.54 (ddd, $J_{7,6}=9.8, J_{7,8}=2.0, J_{7,9}=2.0$ Hz) and 6-H at δ 6.15 (dd, $J_{6,7}=9.8, J_{6,8}=2.0$ Hz), thus suggesting the $8\beta-CH_3$ configuration (assuming $4\alpha-H$ and $9\alpha-H$ for 7).

Based on the above-mentioned evidence together with biogenetic consideration, the structure 1 of an *ent*-valerenane skeleton was proposed except the geometry of the 5(11) double bond and the absolute stereochemistry. This was indicated by X-ray crystallographic analysis of the semicarbazone (13), mp 207–208°C, which was prepared from 11. The crystal data and intensity data were derived from measurements on a Syntex R3 four-circle diffractometer with graphite-monochromated Mo K α radiation. Crystal data: $C_{13}H_{21}N_3O$, orthorhombic, space group $P2_12_12_1$, $a=7.136(3)$, $b=13.142(9)$, $c=14.694(6)$ Å, $D_x=1.13$ g.cm $^{-3}$, $z=4$ and $\mu(Mo\ K\alpha)=0.8$ cm $^{-1}$. Intensity data for 952 reflections [$I>1.96\sigma(I)$] were collected using an ω -scan mode within 2θ less than 50°. Lorentz and polarization corrections were applied, but no absorption corrections were made. The structure was solved by the direct method using MULTAN on a Syntex XTL program. All the hydrogen atoms were found on a difference Fourier map. The refinement of atomic parameters was carried out by block-diagonal least-squares calculation. The final R-value was 0.056 assuming anisotropic thermal motions for non-hydrogen atoms and isotropic ones for hydrogen atoms. The molecular structure of 13 is illustrated in Fig. 1. The five-membered ring is an envelope type while the six-membered ring is in a distorted half chair form.

The physicochemical properties of isovalerenenol (2), colorless semisolid, $C_{15}H_{26}O$, $[\alpha]_D +45^\circ$ ($CHCl_3$), were very similar to those of 1. Since ozone oxida-

Fig. 1

Table I. ¹H NMR Data for 1 and 2

	4-H	6 α -H	11-H	3-CH ₃	8-CH ₃	12-(CH ₃) ₂
<u>1</u>	CDCl ₃ 3.70 (t, J=9.5)	—	5.42	0.93	0.85	1.37
	d ₅ -Py. 4.11	—	5.57	1.04	0.82	1.53, 1.54
<u>2</u>	CDCl ₃ 2.56 (t, J=8.5)	2.84 (ddd, J=15, 9.5, 5.5)	5.35	0.90	0.86	1.37
	d ₅ -Py. 2.56	3.14	5.53	0.95	0.82	1.53

tion of 2 yielded the same ketone (4) as was obtained from 1, 2 and 1 were shown to be geometrical isomers respectively at the 5(11) double bond.

In order to identify the 5(11)-geometry in 1 and 2, the solvent-induced shift⁶⁾ in the ¹H NMR spectra of both compounds was examined. As shown in Table I, 4-H in 1 and 6α-H in 2 were respectively observed at a lower field in d₅-pyridine than in CDCl₃. Thus, the 5(11) double bond in 1 was shown to be *Z*, while that in 2 was *E*. The ¹³C NMR data for 1 and 2 further supported the assignment by signals due to 4-C (δc 43.5 in 1; 53.0 in 2) and 6-C (δc 35.3 in 1; 25.3 in 2), which indicated the steric compression due to the C-11 isopropanol moiety onto C-4 in 1 and C-6 in 2.

The structure of anhydrovalerenenol (3), colorless oil, C₁₅H₂₄, [α]_D -150° (CHCl₃), IR (CHCl₃): no OH, UV λ_{max}^{MeOH} 232 nm (ε 7800), was based on its physico-chemical properties [e.g. δ1.75, 1.76 (both 3H, s, 12-(CH₃)₂), 5.50 (1H, s, 11-H), 5.66 (1H, br.d, J=4.6 Hz, 6-H); δc 127.7, 129.2 (both d, 11-C, 6-C), 131.2, 137.7 (both s, 12-C, 5-C)] and its ready formation from 1 by *p*.TsOH-acetone treatment.⁷⁾

In regard to the absolute stereochemistry of 1, 2, and 3, the CD spectral data for 4, 12, and the C-4 epimer of 4 (5), which was quantitatively prepared from 4 by alkaline treatment,⁸⁾ gave confirmative evidence: 4, [θ]₂₉₈ +2000 (pos. max.); 5, [θ]₂₈₈ -3800 (neg. max.); 12, [θ]₂₄₈ +35000 (pos. max.). The conformational examination using the Dreiding model disclosed that 3β-CH₃ and 8β-CH₃ in 4 were responsible for the less stable *cis*-indanone structure (4) than the *trans*-indanone structure (5). Furthermore, the helicity rule⁹⁾ applied to the CD data for 12 supported the absolute stereostructure.

The *ent*-valerenane sesquiterpenes elucidated in this paper are unprecedented examples having a new carbon skeleton, although a few valerenane-type sesquiterpenes were hitherto characterized from *Valeriana officinalis* L.¹⁰⁾

REFERENCES AND NOTES

- 1) For examples: a) I. Kitagawa, M. Kobayashi, and Y. Kyogoku, Chem. Pharm. Bull., 30, 2045 (1982); b) M. Kobayashi, T. Yasuzawa, Y. Kobayashi, Y. Kyogoku, and I. Kitagawa, Tetrahedron Lett., 22, 4445 (1981).
- 2) The molecular compositions of compounds with the chemical formulae were determined by elemental analyses and/or high resolution mass spectrometry.
- 3) The assignments of ¹H NMR signals were made on the basis of decoupling experiments in detail.
- 4) The ketone (4) was also obtained from 1 by OsO₄ oxidation and subsequent NaIO₄ degradation. Here again, 5 was not formed during the oxidation procedure.
- 5) M. Christl, H. J. Reich, and J. D. Roberts, J. Am. Chem. Soc., 93, 3463 (1971).
- 6) a) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, J. Am. Chem. Soc., 90, 5480 (1968); b) I. Kitagawa, M. Kobayashi, M. Hori, and Y. Kyogoku, Chem. Pharm. Bull., 29, 282 (1981).
- 7) Since the ¹³C NMR data for 2 resembled those for 11 and 13 except the signals due to their side chain carbons, the C-4 configuration in 1 was considered to be retained in 3 during the dehydration reaction. The ¹³C NMR data for C-4 isomeric 4 and 5 differed significantly from each other.
- 8) 4 was also unilaterally isomerized to 5 under strong acidic conditions (c.HCl-acetone), although it was unaffected under mild acidic conditions.
- 9) A. Moscovitz, E. Charney, U. Weiss, and H. Ziffer, J. Am. Chem. Soc., 83, 4661 (1961).
- 10) a) G. Büchi, T. L. Popper, and D. Stauffacher, J. Am. Chem. Soc., 82, 2962 (1960); b) G. I. Birnbaum, J. A. Findlay, and J. J. Krepsinsky, J. Org. Chem., 43, 272 (1978).

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