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MARINE NATURAL PRODUCTS: DACTYLOL, A NEW SESQUITERPENE ALCOHOL FROM A SEA HARE[1]

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Abstract—A new sesquiterpene alcohol, dactylol, having an uncommon bicyclo [6.3.0] undecane skeleton has been isolated from the sea hare *Aplysia dactylomela*. Chemical degradation and NMR studies using a shift reagent established the structure and relative stereochemistry. The absolute configuration was derived from ORD/CD data of a substituted cyclopentanone degradation product.

Sea hares have yielded a variety of novel natural products.[2,3] We have previously reported the isolation of sesquiterpene ethers[4] and halogenated non-terpenoid ethers[5] from a Caribbean sea hare, *Aplysia dactylomela*. Pharmacological testing has established[5] that dactylyne, one of the halogenated non-terpenoid ethers, significantly prolongs pentobarbital hypnosis in mice, apparently by inhibiting pentobarbital metabolism. In our continuing search for biologically active compounds from this animal we have isolated a new sesquiterpene alcohol, dactylol, 1. Its fused 8,5 ring skeleton is uncommon for sesquiterpenoids.[6]

Dactylol was initially isolated[2b,c] by repeated chromatography of the crude hexane extracts of whole, dried animals, using Florisil and then TLC mesh silica gel. Subsequently we have obtained dactylol from isopropyl alcohol extracts of the digestive glands of *A. dactylomela* as follows. The concentrated alcohol extracts were extracted with dichloromethane, then the dichloromethane solubles were partitioned between hexane and 10% aqueous methanol. The hexane solubles were distilled at low temperature, and the fraction distilling from 53° to 67° at 5 microns which contained dactylol was chromatographed over Sephadex LH-20 and silica gel. Fractions rich in dactylol were resolved with high pressure liquid chromatography using a Partisil 10 column to give pure dactylol; m.p. 50.3–51.5°C, $[\alpha]_D + 22.5$, after recrystallization from hexane.

Dactylol, $C_{15}H_{26}O$ (combustion and mass spectral analysis) was characterized as a tertiary alcohol by virtue of hydroxyl absorption at 3500 cm^{-1} in its IR spectrum and a quaternary carbon signal at δ 83.3 in the ^{13}C NMR spectrum. The ^{13}C NMR spectrum also revealed that there are only two unsaturated carbons (δ 125.5, d; 135.4, s) in dactylol, indicative of one trisubstituted double bond; hence a bicyclic carbon skeleton was indicated.

The ^1H NMR spectrum of dactylol, 1, see Fig. 1a, contains signals for two quaternary methyl groups (δ 0.88, 6H, s), one secondary methyl (δ 0.92, d, overlapped with the δ 0.88 signal) and one vinyl methyl group (δ 1.80). Since the vinyl methyl group is coupled with a complex triplet at δ 5.45, a $-CH_2-CH=C(CH_3)-$ unit was indicated. Expansion of this partial formula to $-CH_2-CH=C(CH_3)-CH_2-\dot{C}(OH)-$ was suggested by the presence of an AB quartet in the allylic region (δ 2.10, 2.35, J = 14).

The above partial formula could be developed still further from NMR spectra taken in the presence of 0.45 mole ratio of Eu(fod)$_3$. Under these conditions signals for each of the non-equivalent protons in dactylol could be identified, see Fig. 1(b) and structure 1'. The AB quartet originally found at δ 2.10 and 2.35 was shifted to δ 6.56 and 8.44, thus substantiating the proposed position of the hydroxyl group. Decoupling revealed that the two allylic methylene protons (δ 3.3, 4.9) coupled to the olefinic proton (δ 7.1, J = 8, 10) interact further only with each other (J = 13). Such a limited spin system could be accounted for by joining this allylic methylene group to a quaternary carbon, i.e. one bearing the geminal dimethyl groups. Spectral evidence for a second quaternary carbon in dactylol was derived from the Eu(fod)$_3$ shifted ^{13}C NMR spectrum which possessed only two quaternary carbon signals, δ 93.94 (carbinol carbon) and 36.41. Thus the partial structure for dactylol could be expanded to $-C(CH_3)_2-CH_2-CH=C(CH_3)-CH_2-\dot{C}(OH)-$.

Chemical degradation confirmed the above partial structure and established the ring sizes. Permanganate-periodate oxidation[7] of dactylol afforded a hydroxy keto acid, 2a (IR 3600, 1700 cm^{-1}) which upon esterification (CH_2N_2) yielded a hydroxy keto ester, 2b. These products retained all of the original carbons of the

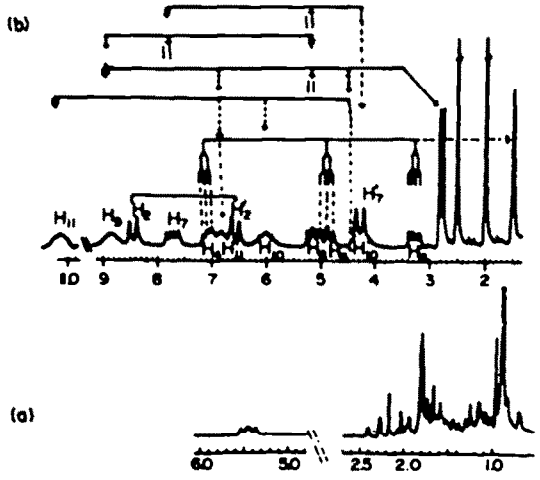
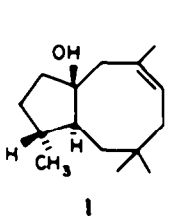
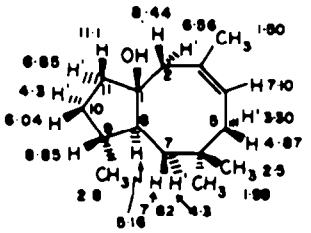


Fig. 1. 100 MHz ^1H NMR spectra of dactylol: (a) CCl_4; (b) CCl_4/0.45 mole ratio Eu(fod)$_3$.

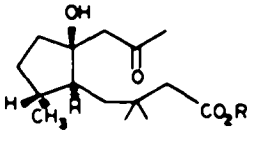


1

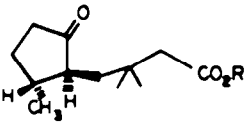


1'

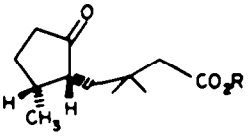
Chemical Shifts with Eu(fod)$_3$



2a
2b



3a
3b



4a
4b

a R=H
b R=CH$_3$

natural product and so confirmed that the double bond was contained within a ring. The ^{1}H NMR spectrum of **2b** exhibited an AB quartet (δ 2.42, 2.76, J = 17) appropriate for the non-equivalent protons of the acetone side chain. In addition, the expected signals for methyl ketone, methyl ester, secondary methyl, and two quaternary methyl groups were observed.

Treatment of **2b** with sodium carbonate in methanol induced the retro-aldol removal of acetone as expected for this structure, and afforded an 85:15 mixture of the epimeric keto esters **3b** and **4b**. The keto ester mixture showed carbonyl absorption at 1750 cm^{-1} indicative of the presence in **3b** and **4b** of a cyclopentanone moiety which had been unmasked in the retro-aldol reaction. Confirmation of the cyclopentanone feature was obtained by basic hydrolysis of **2b** in aqueous methanol which gave a keto acid mixture (**3a**, **4a**) that exhibited infrared absorption characteristic of both cyclopentanone (1750 cm^{-1}) and carboxyl (1715 cm^{-1}) functionalities. One of the rings in dactylol is thus established as five-membered and hence the second is eight-membered.

The gross structures of keto esters **3b** and **4b** were confirmed by mass spectral and NMR data. The isomers gave virtually identical low resolution mass spectra (GC/MS). The high resolution mass spectrum of the mixture of epimers showed significant peaks corresponding to $(-CH_2-CO_2CH_3)^+$, $((CH_3)_2C-CH_2-CO_2CH_3)^+$, and (2-methylene-3-methylcyclopentanone)$^+$ fragments, in agreement with the proposed structure. NMR analysis of the mixture confirmed that the keto esters possessed one secondary and two quaternary methyl groups, and a set of methylene protons (δ 2.17, s) deshielded by an ester group. On thermodynamic grounds the predominant product is assigned the *trans* structure **3b**, and the minor component the epimeric *cis* structure **4b**.

The locus of the secondary methyl group on the cyclopentane ring and the relative stereochemistry of **1** were ascertained from decoupling of the europium shifted ^{1}H NMR spectrum. The protons that resonated at δ 11.1, 6.85, 6.04, and 4.3 (brd underlying band) were shown to be mutually coupled, and two of these protons (δ 6.04 and 4.3) were further coupled to the methine hydrogen (δ 8.85) adjacent to the 2° methyl group. This confirms the $-C(OH)-CH_2-CH_2-CH(CH_3)-$ sequence in the five membered ring, and is in accord with the expectation that the proton absorbing at δ 11.1 is adjacent to the 3° hydroxyl group. The methine hydrogen, δ 8.85, is also coupled to the proton absorbing at δ 5.16 (J = 8–10), and the latter in turn is coupled to the proton that resonates at δ 7.62 (J = 8, 15). The 15 Hz (geminal) coupling in the δ 7.62 signal is due to interaction with the δ 4.3 proton (d, J = 15). These interactions and chemical shifts are consistent with the structure **1**, in which the methine proton (δ 8.85) at C_9 is *cis* to the OH, and the $C_{8,9}$ protons are *trans* to each other. The lack of observable coupling between the protons absorbing at δ 4.3 and 5.16 is attributed to a near 90° dihedral angle existing between them, which is best accounted for by a *trans* ring juncture. A *cis* ring juncture would be expected to result in a much lower field absorption for the ring juncture methine hydrogen in the presence of europium. Hence the relative stereochemistry shown in **1** was established for dactylol.

Analysis of the circular dichroism data for the *trans* keto ester **3b**, leads to an absolute configurational assignment for dactylol. The CD curve of **3b** shows a strong positive Cotton effect (θ = +11,316; max., 295 nm) in contrast to the strong negative Cotton effect reported[8] for (*R*)-2-methylcyclopentanone and (2*R*, 3*S*) - *trans* - 2, 3 - dimethylcyclopentanone. Hence **3b** is assigned the 2*S*, 3*R* configuration and, accordingly, the absolute configuration of dactylol is 1*S*, 8*S*, 9*R* as depicted in formula **1**.

The CD curve of the minor *cis* isomer **4b** exhibits the negative Cotton effect (θ = −7,367; max, 294 nm) anticipated from literature analogs[8] and supports the 2*R*, 3*R* configuration for **4b**.

Dactylol represents a new carbon skeleton among sesquiterpenes. The [6.3.0] bicyclic ring system in dactylol is uncommon among sesquiterpenes, the most closely related ring skeleton being that of aromadendrene and related compounds.[9] Appropriate opening of the cyclopropane ring of aromadendrene would produce the ring system of **1**.

Dactylol has a rearranged isoprenoid skeleton. The proposed structure is one of twenty-nine generated by

the CONGEN computer program[9] from the structural segments deduced from chemical and spectral data. None of the eight computer generated structures containing only regular isoprene units satisfied all of the spectral and degradative data.

The likely dietary source of dactylol found in *A. dactylomela* is the red alga *Laurentia poitei*. Dactylol has been isolated by Fenical[10] from samples of this alga collected in the Florida Keys.

EXPERIMENTAL[11]

Isolation of dactylol. Sea hares were collected and extracted as described previously.[3b,c] The combined fractions 15–18 (6.3 g) from the Florisil chromatography described earlier were rechromatographed on TLC mesh silica gel (60 g) using a benzene-hexane (7:3 v/v) mixture as eluant. Pooling of several fractions exhibiting similar TLC profiles gave 238 mg of impure dactylol which was rechromatographed to afford 109 mg of crystalline alcohol.

Dactylol was also obtained from the isopropyl alcohol extracts from a batch of animals collected at Bimini, Bahamas in 1975. The alcohol was decanted, filtered, and concentrated at reduced pressure. The concentrate was suspended in water (final volume 1200 ml) and extracted with dichloromethane continuously for 24 h. Evaporation of the dichloromethane yielded a dark green oil (388 g).

A 250 g portion of the dichloromethane extract was dissolved in 1500 ml of methanol–water (9:1) and extracted with hexane three times (150, 2 × 700 ml). Evaporation of the combined hexane extracts gave a dark, viscous residue (170 g).

A 32.1 g portion of the hexane extract was distilled at 53–67° and 5 μ to yield an orange distillate (9.58 g). This was chromatographed on a column of Sephadex LH–20 (450 g) in chloroform-methanol (1:1). TLC analysis of fractions revealed that dactylol occurred predominantly in an 85 ml fraction (3.93 g) that began to elute 600 ml after the void volume. A 3.82 g portion of this fraction was adsorbed on a column of Bio-Sil A (100 g, Bio-Rad Laboratories, Richmond, Calif.) and eluted with toluene in 30-ml fractions. Fractions 13–18 were combined as indicated by TLC analysis and evaporated to give 944 mg of a pale yellow, viscous oil. This was subjected to HPLC separation on Partisil–10 using hexane–THF (9:1) to yield 134 mg of crystalline dactylol. The estimated yield of dactylol from digestive glands was 0.09%.

Recrystallization of dactylol from hexane gave an analytical sample, m.p. 50.3–51.5°C, $[\alpha]_D$ + 22.5° (c 1.76, $CHCl_3$); IR (neat) 3600, 3500, 3090, 3070, 3040, 2960, 2870, 1460, 1370, 1360, 1265 cm^{-1}. 100 MHz ^1H NMR (CCl_4) δ 0.91 (s, 6H, quaternary methyls); 0.95 (d, 3H, sec. methyl), 1.83 (brd s, 3H, vinyl methyl), 2.12, 2.37 [AB q, 2H, J = 14, $>C{=}C(CH_3)\text{–}CH_2\text{–}\dot{C}(OH)\text{–}$], 5.47 (complex t, 1H, olefinic proton); ^{13}C NMR [$CDCl_3$, 0.45 mole ratio Eu(fod)$_3$] δ 20.11 (q), 28.569 (q), 29.484 (q), 29.775 (q), 32.195 (t), 36.412 (s), 38.978 (t), 40.506 (t), 42.083 (t), 45.860 (t), 46.517 (d), 54.797 (d), 93.944 (s), 126.485 (d), 137.292 (s); mass spectrum (70 eV) *m/e* (rel intensity) M^+ 222 (10), 207 (3), 204 (5), 189 (4), 161 (4), 153 (100) base peak, 111 (53), 110 (45), 97 (35), 81 (24), 69 (47), 55 (50), 43 (20), and 41 (48). Anal. Calc. for $C_{15}H_{26}O$: C, 81.02; H, 11.78. Found: C, 81.05, H, 11.90%.

Conversion of dactylol to **2a** *and* **2b**. The procedure of Lemieux-von Rudloff was used.[7] Stock oxidant solution (40 ml) was added in 10 ml portions to dactylol (100 mg) dissolved in a water-*t*-butyl alcohol (150 ml:30 ml) mixture. The pH was adjusted to 7.8 with solid K_2CO_3 after the addition of each aliquot of oxidant. The final reaction mixture was acidified to pH 4.0 using 1 M H_2SO_4 and treated with powdered sodium metabisulfite to convert all the periodate, iodate and iodine into iodide (a dark red color develops initially, but this soon disappears as more metabisulfite is added and a nearly colorless solution is finally obtained). The solution was basified with 5% potassium hydroxide, the butanol was removed on a rotary evaporator, and the concentrated solution was acidified and extracted several times, first with ether and then ethyl acetate. The organic layers were combined, dried and evaporated to give 104 mg (86%) of a clear oil: IR (CCl_4) 3520, 1710 (brd) cm^{-1}; ^1H NMR (CCl_4) δ 1.03, 1.04 (s, 6H, overlapping d, 3H, quaternary and secondary methyls), 2.15 (s, 3H, $-COCH_3$), 2.22 (s, 2H, $-CH_2\text{–}CO_2H$), 2.44, 2.78 [AB q, 2H, $-CO\text{–}CH_2\text{–}C(OH)\text{–}$].

Treatment of the hydroxy keto acid **2a** with diazomethane in ether afforded the ester **2b** as an oil in quantitative yield; IR (CCl_4) 3600, 1735 cm^{-1}; NMR (100 MHz, CCl_4), δ 1.00 (s, 6H), 1.03 (d, 3H), 2.10 (s, 3H), 2.19 (s, 2H, $-CH_2\text{–}CO_2H$), 2.42, 2.76 [AB q, 2H, J = 17, $-CO\text{–}CH_2\text{–}\dot{C}(OH)\text{–}$]; M^+ 284 (2), 252 (2), 224 (4), 211 (6), 195 (10), 153 (23), 135 (18), 115 (30), 97 (23), 74 (10), 73 (34), 69 (32), 55 (55), 43 (100).

Conversion of **2b** *to* **3b**, **4b**. An 18 mg sample of **2b** in 2 ml of methanol saturated with sodium carbonate was allowed to stand at room temperature overnight. The reaction mixture was diluted with water (5 ml) and extracted five times with ether. The combined ether layers were dried ($MgSO_4$) and evaporated to give a keto ester product judged by GC analysis (Column A) to be 85% **3b** and 15% **4b**. The keto ester mixture showed the following spectral properties: IR (CCl_4) 1748 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 1.00 (s, 6H, quaternary methyls), 1.16 (d, secondary methyl), 2.17 (s, 2H, $-CH_2\text{–}CO_2CH_3$), 3.56 (s, 3H, OCH_3); MS [*m/e* (elemental composition, millimass error, fragment assignment)] 226.15845 ($C_{13}H_{22}O_3$, +1.56, M^+), 194.12994 ($C_{12}H_{18}O_2$, −0.73, $M^+ - CH_3OH$), 179.10678 ($C_{11}H_{15}O_2$, −0.41, $M^+ - CH_3 + CH_3OH$), 153.12947 ($C_{10}H_{17}O$, +1.53, $M^+ - CH_2\text{–}CO_2CH_3$), 115.07636 [$C_6H_{11}O_2$, +0.46 [$C(CH_3)_2\text{–}CH_2\text{–}CO_2CH_3]^+$], 111.07934 [$C_7H_{11}O$, −1.64, $M^+ - C(CH_3)_2\text{–}CH_2\text{–}CO_2CH_3$], 97.06685 ($C_6H_9O$, +1.51, *m/e* 111–$CH_2$), 83.04842 [$C_5H_7O$, −1.26, ($\Delta^2$-cyclopentenone)$^+$], 73.06436 [$C_4H_9O$, −0.97, $(-CH_2\text{–}CO_2CH_3)^+$].

The keto alcohol ester **2b** also underwent a retro-aldol reaction to give **3b** and **4b** during chromatography over neutral alumina and on gas chromatographic analysis. Preparative gas chromatography of approximately 10 mg of **2b** (injection temp. 260°C; col. temp., 175°C, column A) afforded 4 mg of an ~85/15 mixture of **3b** and **4b** as determined by reinjection on an analytical column (col. B).

Conversion of **2a** *to* **3a** *and* **4a**. A 52 mg sample of **2a** was stirred at room temperature for two days in 2 ml of aqueous methanol (1:1 v/v) saturated with sodium carbonate. The reaction mixture was extracted five times with small portions of ether which were combined, dried ($MgSO_4$) and evaporated to give trace amounts of **3b** (IR, NMR, GC). The basic aqueous methanolic phase was diluted with a little water, acidified cautiously with 1 N HCl, and extracted five times with ether. The combined ether extracts were dried and evaporated to give a mixture of **3a** and **4a**: IR (CCl_4) 1750, 1715 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.03 (s, 6H), 1.13 (d, 3H), 2.23 (s, 2H, $-CH_2\text{–}CO_2H$).

Conversion of **2A** *to* **3a** *and* **4a**. A 52 mg sample of **2a** was dissolved in 5% aqueous sodium carbonate (25 ml) and stirred at room temp. for 15 h. Acidification to pH 3.6 followed by extraction with ether afforded a product whose NMR indicated that the retro-aldol reaction was incomplete. The sample was again dissolved in 5% sodium carbonate solution and warmed at 70° in a sealed vial for 20 h. The reaction mixture was extracted with ether to remove traces of neutral components, then acidified with 1 M H_2SO_4 to pH 3.7, and extracted again to give 47 mg of the acid mixture **3a/4a**. The ^1H NMR of this product was the same as that of **3a/4a** derived from aqueous basic hydrolysis of **2b** (see above).

Preparation of pure **3b** *and* **4b**. The acid mixture **3a/4a** was converted quantitatively by treatment with diazomethane to the ester mixture **3b/4b**. Preparative gas chromatography (column B) yielded pure samples of **3b** and **4b** for ORD and CD measurements. For the major isomer **3b**: CD (0.0043 M, EtOH) $[\theta]_{332}$ 0; $[\theta]_{295/296}$ + 11,316 (max); $[\theta]_{343}$ 0; ORD (0.0043 M, EtOH) $[\theta]_{650}$ + 106; $[\theta]_{589}$ + 141; $[\theta]_{546}$ + 180; $[\theta]_{436}$ + 448; $[\theta]_{365}$ + 1,247; $[\theta]_{312/313}$ + 6,928; $[\theta]_{294/297}$ 0, $[\theta]_{275}$ − 8,372; $[\theta]_{231/238}$ − 5,196; $[\theta]_{200}$ − 10,162.

For **4b**: CD (0.002 M EtOH) $[\theta]_{329}$ 0; $[\theta]_{304/305}$ − 5,893 (inflection); $[\theta]_{294/295}$ − 7,367 (max); $[\theta]_{260}$ 0; ORD (0.002 M,

EtOH) $[\theta]_{630}$ – 189; $[\theta]_{589}$ – 236; $[\theta]_{546}$ – 297; $[\theta]_{436}$ – 603; $[\theta]_{365}$ – 1,282; $[\theta]_{330/311}$ – 5,304; $[\theta]_{320/290}$ O; $[\theta]_{279/275}$ + 4,008; $[\theta]_{220}$ O.

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[10]W. H. Fenical, Scripps Institute of Oceanography, LaJolla, California unpublished results. We thank Dr. Fenical for communicating his results to us while our work was in progress.

[11]Melting points are uncorrected. IR spectra were taken on Beckman IR-8 or Acculab 3 spectrophotometers. NMR spectra were acquired on Varian T-60 or XL-100 instruments in the solvents specified; signals are reported in parts per million (δ) downfield from internal tetramethylsilane. Mass spectra were obtained on Hitachi RMU-7, Finnegan 3000 D, and CEC (Dupont, Monrovia, Calif.) 110 mass spectrometers. A Gaertner polarimeter was used for obtaining the optical rotation; a JASCO, Inc., Model J-20 spectropolarimeter was employed for optical rotatory dispersion and circular dichroism measurements. Micro-analyses were obtained from Mr. E. Meier, Department of Chemistry, Stanford University, Stanford, California. Chromatographic adsorbents used were Florisil (Fisher, 100-200 mesh) and silic acid (Mallinckrodt, silicAR CC-7, Brinkman TLC mesh, and Whatman Inc., 10 μ microparticulate silica gel: Partisil 10). Gas chromatographic columns used were: (A) 8.5 ft × 8 mm ID glass, 10% OV-225 on 60-80 mesh chromasorb W; (B) 6 ft × 1/8 in. OD ss, 3% OV-225 on 80-100 mesh chromasorb W.