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STRUCTURE OF NEW BROMODITERPENES, PINNATOLS, FROM THE MARINE RED ALGA LAURENCIA PINNATA YAMADA

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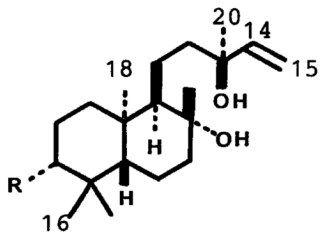
The structure of new bromoditerpenes named pinnatols A, B, C, and D, isolated from the title alga, was determined on the basis of the chemical and spectral data.

The title alga is a unique Laurencia species characterized by the fact that it contains marine phytosterols[1] with moulting hormone activity, bromoditerpenes[2] with an unusual skeleton (instead of halogenated sesquiterpenes usually isolated from the L. species[3]), and others.[4] Further examination of components of the alga led to isolation of a new bromoditerpene, named pinnatol A, and its dehydrated derivatives, named pinnatols B, C, and D. We report herein the isolation and structure elucidation of these diterpenes.

Neutral ether-soluble oil (30.8 g) obtained from the methanol extracts of the title alga (wet, 12 kg), collected at Onahama early in July (1982), was fractionated by chromatography over silica gel with benzene, ethyl acetate (EtOAc), and methanol as eluents. While fractions eluted with benzene:EtOAc (19:1), (9:1), and (4:1) afforded pinnatols B (43 mg), C (9 mg), and D (12 mg) (after HPLC over Radial Pak Silica, hexane:EtOAc = 98:2), pinnaterpene D[5] (13 mg) (after HPLC over μ-Porasil, hexane:EtOAc:acetonitrile = 94.5:5.0:0.5), and pinnaterpene C[2] (1.10 g) as the respective isolable major components, those eluted with benzene:EtOAc (1:1) yielded irieol C[2,6] (30 mg) (after HPLC over μ-Porasil, hexane:EtOAc = 3:2) and pinnatol A (1.50 g).[7]

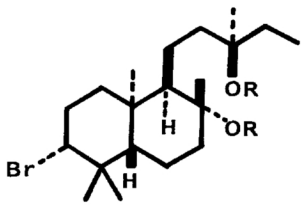
Pinnatol A (1), mp 49-51 °C, $[\alpha]_D$ +24.5° ($CHCl_3$),[8] exhibited the following spectra [EI-MS, m/z 370, 368 (M^+ - 18), 352, 350, and 71 (base); IR (KBr),[8] 3450, 1160, and 920 cm^{-1}; ^1H NMR ($CDCl_3$),[8] δ 0.96, 1.07, and 1.23 (each 3H, s), 1.29 (6H, s), 1.13 (1H, dd, J = 13 and 3, 5ax-H), 1.15 and 1.68 (each 1H, dt, J = 13, 4 and 4, 13, 1eq-H and 1ax-H), 1.73 (1H, dq, J = 4 and 13, 7ax-H), 2.08 and 2.30 (each 1H, dq, J = 13, 4 and 4, 13, 2eq-H and 2ax-H), 3.99 (1H, dd, J = 13 and 4, 3ax-H), 5.09, 5.22, and 5.88 (each 1H, dd, J = 11, 1, 17, 1, and 17, 11); ^{13}C NMR ($CDCl_3$), δ 17.7 (q), 20.2 and 23.3 (each t), 24.8, 28.2, and 30.6 (each q), 30.7 (t), 31.0 (q), 36.7 and 37.4 (each t), 39.0 and 39.5 (each s), 45.4 (t), 47.4, 59.2, and 69.7 (each d), 73.4 and 74.9 (each s), 112.1 (t), and 144.7 (d)] and gave its dihydro derivative[9] (2), mp 69-71 °C, $[\alpha]_D$ +18°, on hydrogenation (H_2-Pt in EtOH, room temp, 0.5 h) (≈100%), which was converted into the corresponding bis(trimethylsilyl) derivative (2a) (BSA, room temp, 9 h) (≈100%). The

molecular formula of 1 was determined to be $C_{20}H_{35}O_2Br$ by measurement of the high resolution (HR) EI mass spectrum of 2a (Found: m/z 532.2809 and 534.2709. Calcd for $C_{26}H_{53}O_2BrSi_2$: M^+, 532.2769 and 534.2749). Treatment of 1 with tributyltinhydride (with AIBN in C_6H_6, reflux, 10 h) afforded its debromo derivative (3), mp 53-54 °C, $[\alpha]_D$ +10°, (85%), which revealed five singlets (each 3H) at δ 0.82, 0.86, 1.22, 1.26, and 1.29 in the ^1H NMR spectrum; namely, only two of the five singlets were shifted to the higher field. These spectral data, coupled with spin decoupling experiments in the absence and presence of the shift reagent $Eu(fod)_3$ as well as examination of the EI mass spectra of 1 and 3 [absence of peaks at m/z 331 ($M^+ - C(CH_3)_3$), 329 ($M^+ - C(CH_3)_2OH$), 57, and 53], indicated the presence of the following structural units: CH_3-■, 4 × $-CH_2-$, 2 × $-\dot{C}H-$, 2 × CH_3-■-OH, CH_2=CH-■, and ■$(CH_3)_2$-CHBr-CH_2-CH_2-■.[10] The whole structure was elucidated by the transformation into the known compound.



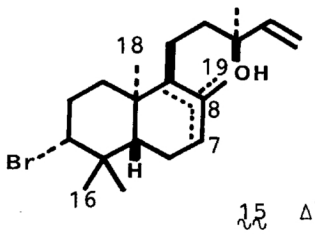
1 R=Br

3 R=H



2 R=H

2a R=Si$(CH_3)_3$



15 $\Delta^{8(19)}$

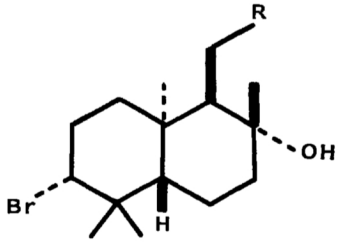
16 Δ^7

17 Δ^8

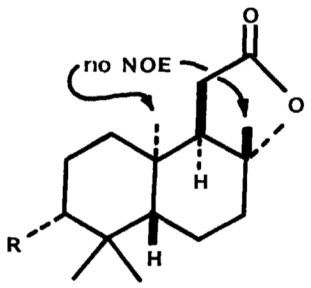
Compound 1 was oxidized with peracid (m-CPBA in CH_2Cl_2, reflux, 5 h) to yield a mixture of diastereoisomeric epoxides (93%), which on hydride reduction ($LiAlH_4$ in ether, -10 °C, 5 h) (93%) followed by oxidative cleavage [$Pb(OAc)_4$ in C_6H_6, room temp, 10 min] gave methyl ketone (4), mp 116-117 °C, $[\alpha]_D$ +25°, (79%), indicating the existence of a ■(CH_3)(OH)-CH=CH_2 moiety in 1. The ketone (4), after trimethylsilylation (BSA, 70 °C, 12 h) (75%) of the hydroxyl group, was submitted to Baeyer-Villiger oxidation (m-CPBA in $CHCl_3$, room temp, 10 d) to give acetate (75%), which on deprotection [$(C_4H_9)_4NF$ in THF, room temp, 1 h] was converted into hydroxy acetate (5), oil, (≈100%). The acetate (5) was hydrolyzed with base (5% NaOH in MeOH, room temp, 0.5 h) to give glycol (6), mp 154-155 °C, $[\alpha]_D$ +14°, (83%). Jones oxidation of 6 (room temp, 10 min) produced a mixture of hydroxy acid (7), oil, $[\alpha]_D$ -25°, and γ-lactone (8), mp 153-154 °C, $[\alpha]_D$ -29°, which was easily separated by preparative HPLC over μ-Porasil to give 7 and 8 in 67 and 25% yields, respectively: 7, IR, 3480, 1720, and 1275 cm^{-1}; ^1H NMR, δ 0.98, 1.08, 1.25, and 1.37 (each 3H, s), and 3.95 (1H, dd, J = 12 and 4.5, 3ax-H): 8, IR, 1765, 1390, and 940 cm^{-1}; ^1H NMR, δ 0.96, 1.08, 1.10, and 1.49 (each 3H, s), and 3.93 (1H, dd, J = 12 and 4.5). The former (7), when treated with p-toluenesulfonyl chloride in pyridine (room temp, 24 h), was converted into the latter (8) (75%). Reduction of 8 [$(C_4H_9)_3SnH$ and AIBN in C_6H_6, reflux, 12 h] afforded the debromo derivative (9), mp 87-88 °C, $[\alpha]_D$ +24.5°, (53%); ^1H NMR, δ 0.84, 0.92, 1.12, and 1.56 (each 3H, s). Treatment of 8 with acid[11] (H_2SO_4 in AcOH, 60-70 °C, 1 h) afforded two lactones (10), mp 149-150 °C, $[\alpha]_D$ +50°, (50%), and (11) (2%): 10, IR, 1760 cm^{-1}; ^1H NMR, δ 0.97, 1.13, 1.17, and 1.57 (each 3H, s), and 3.94 (1H, dd, J = 12.5 and 4.5, 3ax-H): 11, IR, 1760 cm^{-1}; ^1H NMR, δ 0.96, 1.01, 1.11,

and 1.33 (each 3H, s), and 3.96 (1H, dd, J = 12.5 and 4, 3ax-H). These spectra of 10 and 11 were identical with those of the known authentic (±)-cis-fused lactones,[12] confirming 8 to be a trans-fused lactone. A series of these transformations, coupled with measurement of the NOE difference spectra of 8, 10, and 11 (see the fomulas), establish that pinnatol A is represented by formula 1 (except the absolute configuration), because (i) 3 was identified neither as sclareol and 13-epi-sclareol[13] nor as their enantiomers, and (ii) 9 was not identical with 12-norambreinolide[14] (12) in respect to the spectral data.

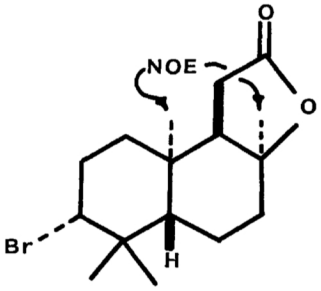
The absolute configuration was determined as shown by formula 1 on the following grounds: (i) acid treatment[11] (H_2SO_4 in AcOH, 60-70 °C, 10 h) of 9 resulted in epimerization at C-9 to give a new lactone (13), mp 93-94 °C, $[\alpha]_D$ +14°, (12%) [IR, 1775 cm^{-1}; ^1H NMR, δ 0.87, 0.91, 1.26, and 1.32 (each 3H, s)] with 9 (42%), which was identified as an enantiomer of the reported 8-epi-12-norambreinolide[11,14] [lit., mp 93 °C, 90-92 °C, and $[\alpha]_D$ -34.8° ($CHCl_3$)], (ii) ozonolysis (in $CHCl_3$, -40 °C) of 1 followed by hydride reduction ($NaBH_4$ in aq EtOH, 0 °C) yielded 13,14-glycol, which on treatment with thiophosgene (with DMAP, room temp, 12 h) formed the corresponding thiocarbonate (14), mp 140-141 °C, $[\alpha]_D$ +60°, (10%) [EI-MS, m/z 434, 432 (M^+), 133, 119, and 107; IR, 1325 cm^{-1}; ^1H NMR, δ 0.97, 1.08, 1.26, 1.31, and 1.58 (each 3H, s), 4.29 and 4.35 (each 1H, d, J = 8.5, 14-H)]. The thiocarbonate (14) showed a positive Cotton effect [CD (EtOH), 304 nm (Δε +4.32)],[15] indicating that the (S)-configuration is assigned to the 13-carbon atom.



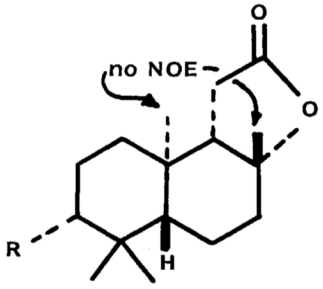
4 R=CH_2COCH_3
5 R=CH_2OCOCH_3
6 R=CH_2OH
7 R=COOH



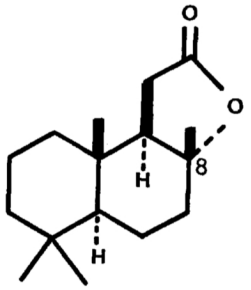
8 R=Br
9 R=H



10



11 R=Br
13 R=H



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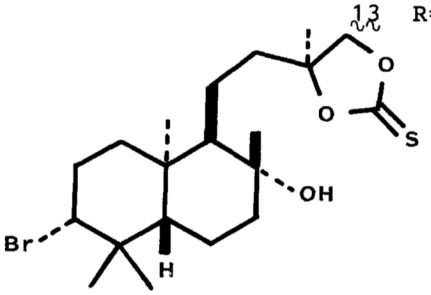

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Pinnatol B (15), mp 106.5-107.5 °C, $[\alpha]_D$ -7.6°, pinnatol C (16), oil, $[\alpha]_D$ +110.5°, and pinnatol D (17), oil, $[\alpha]_D$ -48.2°, were assigned formulas 15, 16, and 17, respectively, on the basis of the spectral data (MS, IR, ^{1}H NMR)[16] as well as dehydration of 1 at 150 °C (20 min, in a vacuum tube) leading to formation of 15 (4.1%) and 16 (4.6%) with 1 (45%).

Pinnatols A, B, and C are the first authentic examples of 9-epimeric labdane diterpenoids and thus represent a violation of the universality of the trans-anti ring skeletal arrangement.[17]

References

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5) This natural compound, mp 167.5-168 °C, $[\alpha]_D$ +16.1° ($CHCl_3$), was identical with the known synthetic sample (compound 5 in Ref. 2) in all respects. The reported value (oil, $[\alpha]_D$ +7.1°) in Ref. 2 should be revised.
6) B. M. Howard and W. Fenical, J. Org. Chem., 43, 4401 (1978).
7) The details of the isolation procedure will be described in a full paper.
8) Optical rotaions, IR and ^{1}H NMR spectra were measured in chloroform, chloroform, and [^{2}H]chloroform, respectively, unless otherwise stated.
9) All new compounds gave spectral data consistent with the assigned structures.
10) The abbreviation ■ denotes a quaternary carbon atom.
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15) A. H. Haines and C. S. P. Jenkins, J. Chem. Soc., 1971, 1438, J. de Pascual Teresa and A. F. Barrers, A. San Feliciano, M. Grande, and M. Medarde, Tetrahedron Lett., 1978, 4141.
16) 15, HR EI-MS, m/z 370.1684 and 368.1705; ^{1}H NMR, δ 0.96 (6H, s), 1.08 and 1.27 (each 3H, s), 4.52 and 4.71 (each 1H, t, J = 2): 16, HR EI-MS, m/z 370.1607 and 368.1619; ^{1}H NMR, δ 0.91, 1.03, 1.05, 1.29 (each 3H, s), and 1.65 (3H, br s): 17, HR EI-MS, m/z 370.1702 and 368.1729; ^{1}H NMR, δ 0.96, 0.98, 1.08, 1.29, and 1.56 (each 3H, s).
17) Cf., F. Orsini and F. Pellizoni, Tetrahedron Lett., 1977, 1085;, Y. Asakawa and T. Takemoto, ibid., 1977, 1407.

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