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NANAIMOAL, A SESQUITERPENOID ALDEHYDE FROM THE DORID NUDIBRANCH ACANTHODORIS NANAIMOENSIS

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SUMMARY: Extracts of the dorid nudibranch Acanthodoris nanaimoensis contain the sesquiterpene nanaimoal (1). The structure of nanaimoal was inferred from its spectral data and the biogenetic isoprene rule. It was confirmed by an unambiguous synthesis of its p-bromophenylurethane derivative 10.

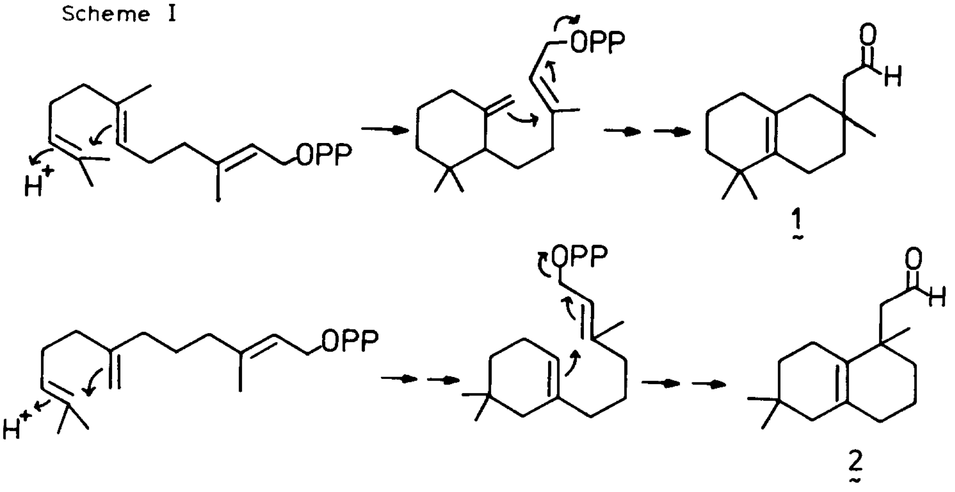
Terpenoid hydrocarbons bearing one or more aldehyde or aldehyde equivalent functionalities represent a growing subgroup of compounds among the many interesting metabolites isolated from nudibranchs[1]. Some of these aldehydic terpenoids, such as luteone[2], 2,6-dimethyl-5-heptenal[3], and apofarnesal[4] are responsible for the pleasant fruity odour of the nudibranchs from which they have been extracted. Others, such as polygodial[5] and olepuane[6], are fish antifeedants which are thought to act as chemical defense substances. In this paper we wish to report the structure of nanaimoal (1), a fragrant sesquiterpenoid aldehyde which has been isolated from the dorid Acanthodoris nanaimoensis.

Specimens of A. nanaimoensis were collected in Barkley Sound, British Columbia. Freshly collected animals were extracted whole in methanol for one to three days. The organic soluble fraction of the methanol extract was purified by column chromatography (Silica Gel, 5% Ethyl acetate/Pet. ether), and preparative gas chromatography to give one major (≈ 1.0 mg/animal) and two minor (≈ 0.5 mg/animal) isomeric sesquiterpenoid aldehydes.

Nanaimoal (1), the major component, had a molecular formula of $C_{15}H_{24}O$. Its mass spectrum showed an intense fragment ion at m/z 176 and a base peak at m/z 161 resulting from loss of ethanal via a McLafferty rearrangement followed by loss of a methyl group. The IR ($CHCl_3$) spectrum showed aldehydic C-H and C=O stretching bands at 2750 and 1710 cm^{-1} respectively. An ^1H NMR spectrum (400 MHz, $CDCl_3$) of nanaimoal contained aliphatic methyl signals at δ0.98 (s,6H) and 1.05 (s,3H), an isolated AB spin system at 1.77 (d,1H, J=17.3Hz) and 1.85 (d,1H, J=17.3Hz), four allylic protons at 1.81 (m,2H) and 2.02 (m,2H), and an isolated ABX spin system at 2.24 (dd,1H, J=3,14.5Hz), 2.29 (dd,1H, J=3,14.5Hz) and 9.84(t,1H, J=3Hz) ppm. The latter signals correspond to the ethanal fragment indicated by the mass spectral fragmentation pattern. A ^{13}C NMR spectrum (100 MHz, CDCl$_3$) of aldehyde 1 contained resonances at δ133.8 and 125.3 (both singlets in an SFORD experiment) appropriate for a tetrasubstituted olefin[7]. Examination of the spectral data for 1, indicates that it is a bicyclic sesquiterpenoid that contains three tertiary methyl groups, an ethanal side chain, a tetra-substituted olefin and six allylic protons of which two comprise an isolated geminal spin system.

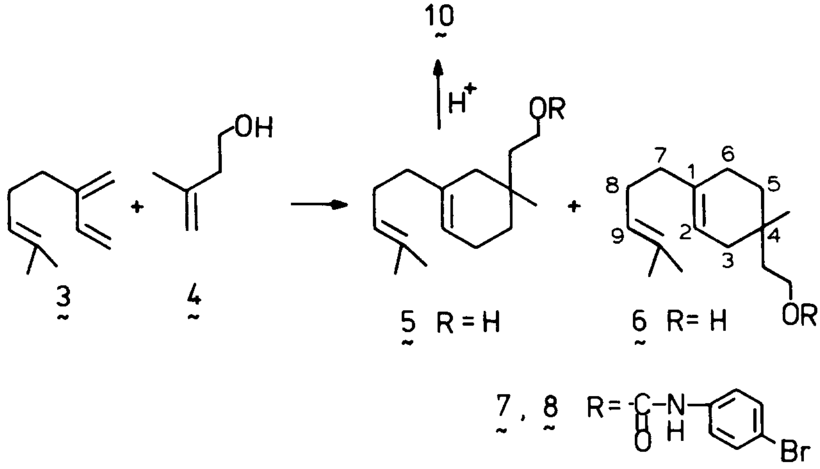
The biogenetic isoprene rule suggests two possible sesquiterpenoid structures 1 and 2 that are consistent with the above stated structural features of nanaimoal (see Scheme I). There are biogenetic precedents for the proposed first step in the formation of both compounds. Structure 1 can be rationally derived from an intermediate belonging to the well known monocyclofarnesane family[8], while structure 2 can be derived from an intermediate that has the carbon skeleton of the sponge metabolite pleraplysillin -1[9]. The proposed second cyclization reaction in the formation of structure 1 is analogous to the formation of ring C in the pimarane diterpenes[10].

Scheme I

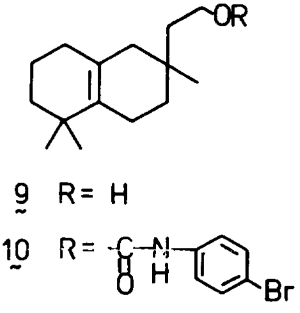


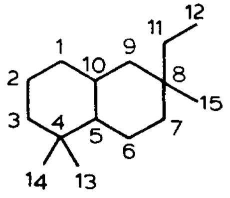
In the absence of any spectroscopic or degradative scheme that would unambiguously allow an assignment of either structure 1 or 2 to nanaimoal, we turned to synthesis. Our synthetic target, the p-bromophenylurethane 10, was chosen on the assumption that the large number of naturally occurring monocyclofarnesane sesquiterpenoids made the structure 1 most likely for nanaimoal. We prepared the urethane 10 from the natural product by first reducing the mixture of three isomeric naturally occuring aldehydes with sodium borohydride to give a mixture of three isomeric alcohols. The major alcohol, nanaimool (9)[11], could be easily separated from the two very minor components by radial thin layer chromatography (Harrison Chromatotron: Silica Gel, CHCl$_3$). Treatment of 9 with p-bromophenylisocyanate (benzene, reflux) gave a quantitative yield of the amorphous urethane 10. Compound 10 showed: MS M$^+$, m/z 419, 421; ^{1}HNMR (400 MHz, CDCl$_3$) δ 0.91 (s, 3H), 0.97 (s, 3H), 0.98 (s, 3H), 1.62 (bd, 1H, J = 17.2Hz), 1.76 (bd, 1H, J = 17.2Hz), 1.78 (bs, 2H), 1.98 (bs, 2H), 4.23 (m, 2H), 6.51 (bs, 1H), 7.39 (d, 2H), 7.27 (d, 2H); ^{13}C NMR (20 MHz, CDCl$_3$, only terpenoid carbons are listed) δ 19.0, 21.0, 24.3, 27.5, 27.7 30.4, 31.4, 33.3, 34.2, 39.2, 39.5, 43.5, 62.7, 125.7, 133.8

The carbon atoms found in the terpenoid fragment of urethane 10 could be readily assembled via a Diels-Alder reaction between myrcene (3) and 3-methyl-3-buten-1-ol (4) (225°C, 8 h, neat, 1 part 3 to 4 parts 4). Purification of the crude reaction mixture by flash chromotography (Silica Gel, 10% Ethyl acetate/Pet. ether) and radial tlc (Silica gel, 12% Ethyl acetate/ hexanes) gave the regioisomeric alcohols 5 and 6 in a very low but adequate yield. Routine inspection of the spectral data for these two regioisomers failed to allow an unambiguous structural assignment. They were therefore converted to their p-bromophenyl-urethane derivatives 7 and 8[12] and the structure of regiosomer 8 was verified by a difference Nuclear Overhauser Enhancement experiment. Irradiation of the C2 cyclohexene olefinic proton found in 8 at δ 5.29 ppm resulted in an NOE enhancement of the allylic protons on carbons 3 and 7. The allylic protons on C3 appear as two broadened doublets at δ 1.77 (bd, 1H, J = 17.6 Hz) and 1.90 (bd, 1H, J = 17.6 Hz) ppm in this difference NOE experiment. These same resonances are clearly visible in the normal 400 MHz 'H NMR spectrum of 8 and most of the broadening can be removed by a simple decoupling experiment in which the C2 olefinic resonance at δ 5.29 ppm is irradiated. Heating urethane 7 in 95% formic acid at 60°C for 12 h accomplished the required cyclization to give urethane 10 in excellent yield. Synthetic 10 was identical by HPLC, MS and 'H NMR comparison to the p-bromophenylurethane derivative prepared from nanaimoal (1).



Nanaimoal (1) has a new sesquiterpenoid carbon skeleton. We propose to name this skeleton nanaimoane and to number it as shown in 11. The structures of the two minor sesquiterpenoid aldehydes in A. nanaimoensis extracts are currently under investigation.





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Footnotes and References:

1) for examples see: a) Schulte, G.R.; Scheuer, P.J. *Tetrahedron* **1982**, *38*, 1857. b) Thompson, J.E.; Walker, R.P.; Wratten, S.J.; Faulkner, D.J. *ibid.* **1982**, *38*, 1865. c) Hellou, J.; Andersen, R.J.; Thompson, J.E. *ibid.* **1982**, *38* 1875.

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4) Isolated from *Anisodoris nobilis*. K. Gustafson unpublished results.

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6) Okuda, R.K.; Scheuer, P.J.; Hochlowski, J.E.; Walker, R.P.; Faulkner, D.J. *J. Org. Chem.* **1983**, *48*, 1866.

7) ^{13}C NMR data for nanaimoal 1 (100 MHz, CDCl$_3$) δ 19.4(t), 21.3(t), 25.9(q), 27.9(q, 2C), 31.6(t), 34.8(t), 39.8(t), 43.7(t), 53.7(t), 125.3(s), 133.8(s), 203.3(d). Due to a limited sample size we were unable to confidently assign values to the two quarternary carbons in 1.

8) a) Martin, J.D.; Darias, J. in "Marine Natural Products--Chemical and Biological Perspectives". Scheuer, P.J. Ed.; Academic Press: New York, 1978; Vol. 1, *Chapt.* 3. b) Minale, L. Ibid. *Chapter* 4.

9) Cimino, G.; De Stefano, S.; Minale, L.; Trivellone, E. *Tetrahedron* **1972**, *28*, 4761.

10) Geissman, T.A.; Crout, D.H.G. "Organic Chemistry of Secondary Plant Metabolism", Freeman Cooper: San Francisco, 1969, page 301.

11) nanaimool (9) shows: $[\alpha]_D+10.4^0$(MeOH); HRMS; M^+, m/z 222.1988 calc'd 222.1984; 'H NMR (400 MHz, CDCl$_3$) δ 0.88(s, 3H), 0.97 (s, 3H), 0.98 (s, 3H), 1.59 (bd, 1H, J = 17 Hz), 1.75 (bd, 1H, J = 17 Hz), 1.78 (bs, 2H), 1.97 (bs, 2H), 3.72 (m, 2H).

12) urethane 7 shows: HRMS, M^+, m/z 419.1447 calc'd 419.1460; 'H NMR (400 MHz, CDCl$_3$) δ 0.94 (s, 3H), 1.60 (bs, 3H), 1.68 (bs, 3H), 1.70 (bd, 1H, J = 17 Hz), 1.82 (bd, 1H, J = 17 Hz), 4.24 (m, 2H), 5.09 (bt, 1H, J = 7 Hz), 5.37 (bs, 1H), 6.51 (bs, 1H), 7.40 (d, 2H), 7.27 (d, 2H).

urethane 8 shows: HRMS, M^+, m/z 419.1443 calc'd 419.1460; 'H NMR (400 MHz, CDCl$_3$) δ 0.93 (s, 3H), 1.60 (s, 3H), 1.68 (s, 3H), 1.70 (bd, 1H, J = 17.6 Hz), 1.90 (bd, 1H, J = 17.6 Hz), 5.08 (bt, 1H, J = 7 Hz), 5.29 (bs, 1H), 4.24 (m, 2H), 6.51 (bs, 1H), 7.40 (d, 2H), 7.27 (d, 2H).

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