Tetrahedron Letters Vol. 21, pp 797 - 800
0040-4039/80/0222-0797$02.00/0

FARNESIC ACID GLYCERIDES

FROM THE NUDIBRANCH *ARCHIDORIS ODHNERI*

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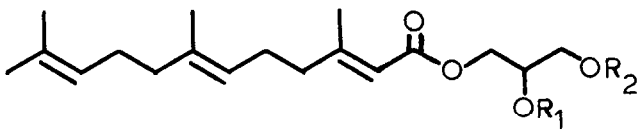
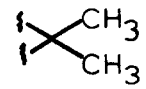
Summary: The dorid nudibranch *Archidoris odhneri* produces (all *E*)-2,3-dihydroxypropylfarnesate and its two monoacetoxy derivatives.

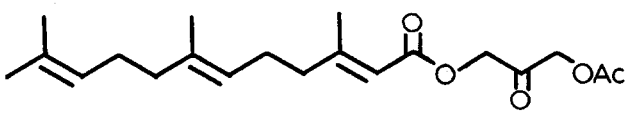
Dorid nudibranchs lack the protection of a hard shell usually associated with members of the phylum mollusca. It has been frequently suggested that these soft bodied animals rely instead on chemical defensive substances to ward off predators[1]. Recent studies have revealed the presence of biologically active metabolites in nudibranch extracts lending credence to the speculations about chemical defense mechanisms[2]. As part of a program aimed at discovering bioactive substances in British Columbia marine invertebrates we have examined methanol extracts of several dorid nudibranchs.

Specimens of *Archidoris odhneri*[3] were collected by SCUBA at 5-10m depth off Dixon Island, in Barkley Sound, B.C. Freshly collected whole animals were immediately immersed in methanol. Concentration of the methanol supernatants followed by a partition between ethyl acetate and water produced an organic extract which could be trivially separated into two major components by silica ptlc (EtOAc). The more polar component (R_f 0.4), (all *E*)-2,3-dihydroxypropylfarnesate 1, was obtained as a colourless oil (5 mg/animal), IR(neat) 3350, 1690, 1640, 1430, 1380, 1220, 1145, 1055 and 870 cm^{-1}; MS (M^+ 310.2150, calc'd for $C_{18}H_{30}O_4$ 310.2144, 219 ($M^+ - C_3H_7O_3$), 218 ($M^+ - C_3H_8O_3$); ^{1}HNMR ($CDCl_3$, 270 MHz) δ 1.60 (s,6H), 1.67 (s,3H), 1.90→ 2.22 (complex multiplet, 11H), 2.96 (br, 2H, exchanges), 3.60 (dd,J=6,13,1H), 3.70 (dd,J=6,13,1H), 3.94 (m,1H), 4.19 (m, 2H), 4.91 (br m,2H), 5.70 (m,1H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 16.04, 17.67, 19.05, 25.64, 26.01, 26.74, 39.68, 41.08, 63.48, 64.58, 70.51, 114.85, 122.79, 124.24, 131.41, 136.34, 161.86 and 167.10.

The presence of an $\alpha\beta$ unsaturated ester moiety in 1 could be readily deduced from the IR spectrum (1690 cm^{-1}) and the ^{13}C NMR (δ 167.10 



1 $R_1 = R_2 = H$
2 $R_1 = H$ $R_2 = Ac$
3 $R_1 = Ac$ $R_2 = H$
4 $R_1 = R_2 = Ac$
5 $R_1, R_2 =$ 



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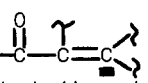
and 161.86 (). A strong acyl cleavage observed in the mass spectrum indicated that the alcohol residue in the ester should have a molecular formula of $C_3H_7O_3$ and the ^{1}HNMR pointed to a glycerol residue (δ 3.60 (dd,J=6,13, 1H), 3.70 (dd,J=6,13,1H), 3.94 (m,1H) and 4.19 (m,2H)). The strong resemblance between the ^{1}HNMR of 1 and that of methyl farnesate[4] indicated that farnesic acid was the acyl component of the ester. This structural hypothesis was proven by chemical degradation. Reduction of 1 with excess DIBAL (benzene, rt, 2hr) gave a quantitative yield of (all *E*)farnesol[5]. Treatment of 1 with 2,2-dimethoxypropane (pTsOH, rt, 2hr) generated the acetonide 5[6] which could be hydrolyzed with base (20% KOH/MeOH, reflux, 6hr) to give glycerol aceton-

ide which was identical to an authentic sample[7]. Acetylation (Ac_2O, pyridine, 24hr, rt) of 1 generated the diacetate 4, MS (M^+ 394.2334, calc'd for $C_{22}H_{34}O_6$ 394.2356); IR ($CHCl_3$) 1740-1700 br cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.59(s,6H), 1.66(s,3H), 2.06(s,3H), 2.07(s,3H), 1.90-2.25(complex multiplet, 11H), 4.19(m, 2H), 4.27(m,2H), 5.07(m,2H), 5.26(m,1H), and 5.65(m,1H).

The least polar band (R_f 0.7) from the EtOAc ptlc could be further fractionated via ptlc ($CHCl_3$/MeOH, 25:1) to give (all *E*)-2-hydroxy-3-acetoxypropylfarnesate 2 (10 mg/animal) and its positional isomer (all *E*)-3-hydroxy-2-acetoxypropylfarnesate 3 (.5 mg/animal). The major isomer 2 was obtained as a colourless oil, IR(neat) 3450, 1720-1690 br, 1640, 1445, 1380, 1220, 1145, 1050 and 870 cm^{-1}; MS (M^+ 352.2225, calc'd for $C_{20}H_{32}O_5$ 352.2227), 219 ($M^+ - C_5H_9O_4$), 218 ($M^+ - C_5H_{10}O_4$), ^1H NMR ($CDCl_3$, 270 MHz) δ 1.60(s,6H), 1.67(s,3H), 1.92-2.22(m,11H), 2.09(s,3H), 2.85 (br, exchanges, 1H), 4.15(m,5H), 5.07(br m, 2H), 5.69(m,1H), ^{13}C NMR ($CDCl_3$, 20 MHz) δ 16.02, 17.66, 19.04, 20.75, 25.65, 26.01, 26.72, 39.69, 41.08, 64.53, 65.42, 68.42, 114.82, 122.81, 124.26, 131.36, 136.31, 161.75, 166.70 and 171.03. The strong similarities between the spectral data of 1 and 2 suggested that 2 was merely a monoacetylated derivative of 1. This was confirmed by converting 2 (Ac_2O, pyridine, rt, 24hr) to the diacetate 4. Oxidation of 2 (pyridine·HCl·CrO_3, CH_2Cl_2) to the ketone 6[8] demonstrated that the glycerol fragment was 1,3 diacylated.

Compound 3, a colourless oil, showed IR ($CHCl_3$) 3500, 1730-1700 br, 1645, 1445, 1380, 1240, 1215, 1155, 1060 and 875 cm^{-1}; MS (M^+ 352.2220, calc'd for $C_{20}H_{32}O_5$ 352.2227), 219 ($M^+ - C_5H_9O_4$), 218 ($M^+ - C_5H_{10}O_4$) and ^1H NMR ($CDCl_3$, 100 MHz) δ 1.60(s,6H), 1.68(s,3H), 2.0→ 2.3(m,11H), 2.13(s,3H), 3.76(d,J=6, 2H), 4.34(d,J=6,2H), 5.12(m,3H), 5.74(m,1H). The spectral data for 3 suggested that it was a positional isomer of 2 in which the 3-hydroxy group of the glycerol residue was nonacylated (^1H NMR δ 3.76(d,J=6,2H)). This was confirmed by converting 3 into the diacetate 4 (pyridine, Ac_2O, rt).

A second collection of *A odhneri* (two animals) was extracted by immersing the whole animals in chloroform (12 hr, rt). The decanted extraction solvent was evaporated in vacuo (30°) to give a crude residue which was purified by silica ptlc ($CH_3C{\equiv}N/CHCl_3$, 15:85) to give the monoglyceride 1 and the diglycerides 2 and 3. Thus it is clear that 1, 2 and 3 have not arisen from methanolysis of more highly substituted glycerides during the extraction procedure.

(All *E*)-2,3-dihydroxypropylfarnesate 1 shows moderate in-vitro antibiotic activity against *Staphylococcus aureus*, while its monoacetates 2 and 3 are totally inactive. To the best of our knowledge 1, 2 and 3 represent the first reported natural occurrence of glycerides containing farnesic acids.

Acknowledgements

This work was supported by the Natural Science and Engineering Research Council of Canada. The authors would like to thank Sheila McDonald, Mike LeBlanc and the staff of the Bamfield Marine Station for assistance in collecting *Archidoris odhneri*.

References and Footnotes

1. See for example "Between Pacific Tides", E.F. Rickets and J. Calvin, Stanford University Press, fourth edition, 1968, pages 118 and 119.
2. a) C. Ireland and D.J. Faulkner, Bioorganic Chemistry, 7, 125 (1978).
   b) B.J. Burreson, P.J. Scheuer, J. Finer and J. Clardy, JACS, 97, 4763 (1975).
3. *Archidoris odhneri* was identified by Sandra Millen, Zoology Dept., U.B.C.
4. F.W. Sum and L. Weiler, JACS, 101, 4401 (1979).
5. Authentic (all *E*)farnesol was obtained by DIBAL reduction of synthetic (all *E*)methylfarnesate. See ref. 4.
6. Satisfactory spectral data were obtained for this compound.
7. Prepared from glycerol by treatment with acetone, a catalytic amount of p-toluenesulfonic acid and anhydrous magnesium sulfate at room temperature for three days.
8. Ketone 6 showed MS (M^+ 350.2115, calc'd for $C_{20}H_{30}O_5$ 350.2137), 219(M^+ - $C_5H_7O_4$), 218(M^+ - $C_5H_8O_4$); IR ($CHCl_3$) 1735(sh), 1715br, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.61(s,6H), 1.69(s,3H), 2.0→ 2.25(m,11H), 2.16(s,3H), 4.77(s,2H), 4.80(s,2H), 5.11(m,2H), 5.80(m,1H).

(Received in USA 18 September 1979)