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TWO SESQUITERPENE FURANS WITH NEW CARBOCYCLIC RING SYSTEMS AND RELATED THIOL ACETATES FROM A SPECIES OF THE SPONGE GENUS DYSIDEA

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Recent investigations of marine species have yielded a plethora of terpenes containing novel carbocyclic ring systems[1]. One of the richest sources of terpenoid compounds was the sponge Dysidea pallescens from which an array of related furanoid sesquiterpenes with new carbocyclic carbon skeletons were isolated of which (1) and (2) are examples. The sponges Pleraplysilla spinifera and Microciona toxistyla have also yielded furanoid sesquiterpenes and this work by the Minale group has been reviewed[2].

We now report the isolation of four new furanoid sesquiterpenes from a Dysidea species collected near Cronulla, New South Wales, Australia. Extraction of the freeze dried sponge with dichloromethane followed by chromatography and HPLC on silica gel gave two new uniquely cyclised sesquiterpenes furodysin (3) and furodysinin (4) in yields of 0.3% and 0.9% respectively. Thiofurodysin acetate (5) and thiofurodysinin acetate (6) were obtained from more polar fractions in yields of 0.1% and 2% respectively. To our knowledge this is the first report of the isolation of terpene thiol derivatives from natural sources.

Furodysin (3) separated from hexane as large prisms mp. 75°, $[\alpha]_D$ +36° (c = 0.5, $CHCl_3$) and the formula $C_{15}H_{20}O$ was established by high resolution mass spectrometry with fragment ions at m/e 201 and 122 (P^+, $C_8H_{10}O$). The ^1H n.m.r. spectrum of (3) in CCl_4 indicated the presence of α- and β-furan protons at δ7.03 (1H,d,J 2Hz) and 5.90 (1H,d,J 2Hz). Further features included a very broad vinylic proton doublet at δ5.50 (1H,J 6Hz), the A and B portion of an ABX system at δ2.48 (1H,dd,J 17, 5.5Hz) and 2.1 (1H,dd,J 17, 12Hz), a vinylic methyl group at δ1.61 and a sharp six proton singlet at δ1.23. The ^{13}C n.m.r. (δ156.8 (s), 140.4 (d), 133.0 (s), 126.5 (d), 113.0 (s), 109.8 (d), 45.7 (d), 34.6 (s), 31.7 (2C), 30.8, 27.4 (t), 23.8 (q), 23.3 (q), 19.6 (t)) in $CDCl_3$ supported the presence of a furan and one trisubstituted double bond and furodysin (3) was therefore tricyclic.

Double irradiation studies in the ^1H n.m.r. of (3) supported the partial structure $-C(CH_3)=CH-CH-CH_2-C=$ and, assuming an unrearranged farnesyl pyrophosphate precursor, the very strong $C_8H_{10}O$ base peak in the mass spectrum suggested structure (3) for furodysin.

This was confirmed and the relative stereochemistry of furodysin established by a single crystal X-ray structure determination[3]. Figure 1 is a stereoprojection of the molecule.

Furodysinin (4), the major non-polar furanoid isolated from the sponge separated from hexane as large colourless needles mp. 55°, $[\alpha]_D$ +64° (c = 0.5, $CHCl_3$). It was shown to be isomeric with (3) by high resolution mass spectrometry and the remainder of the mass spectrum was qualitatively very similar to that of (3) with a dominant fragment ion at m/e 122. The ^1H n.m.r. spectrum of (4) was also very similar to that of (3) as follows:- δ6.98 (1H,bs); 6.01 (1H,d,J 2Hz); 5.50 (1H,bd,J 6Hz), 2.64 (1H,dd,J 17.5, 5.5Hz), 2.56 (1H,m), 2.19 (1H,dd,J 17.5, 12.5Hz), 1.60 (3H, bs) and 1.15 (6H,s). The ^{13}C n.m.r. of (4) was also qualitatively similar to that of (3) as follows:- δ($CDCl_3$): 147.3 (s); 140.4 (d), 133.4 (s), 126.2 (d), 124.5 (s), 108.0 (d), 44.7 (d), 33.1 (s), 32.9, 31.8, 31.3, 27.7, 26.3, 23.2 and 19.3 (t).

A single crystal X-ray structure showed that furodysinin (4) was not epimeric with (3) but had a unique rearranged sesquiterpene skeleton[4]. Figure 2 is a stereoprojection of the molecule.

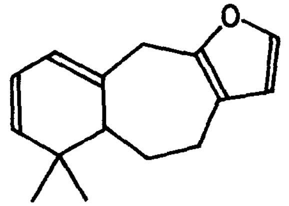
The carbocyclic ring system of furodysinin (4) probably arises by a rearrangement of a monocyclic or bicyclic precursor. A precursor such as (7) would produce (3) or (4) by alternative migration of the appropriate bond. Recently we have isolated (7) from a collection of the sponge D. herbacea and find that BF_3 catalysed rearrangement gives a 1:1 mixture of (3) and (4).

Thiofurodysinin acetate (6) was separated from thiofurodysin acetate (5) by HPLC on silica gel. The ratio of rearranged thiol acetate (6) to the regular terpenoid thiol acetate (5) was far greater (20:1) than that of (4) to (3) (3:1).

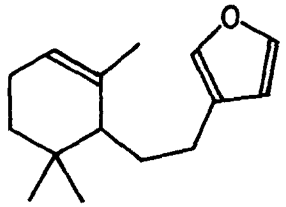
Thiofurodysinin acetate (6) was an oil $[\alpha]_D$ +52° (c = 0.5, $CHCl_3$). The relationship to (4) was first suggested by t.l.c. visualisation characteristics[5] and similarities of the ^1H and ^{13}C n.m.r. spectra. [^1H n.m.r. (CCl_4); δ6.98 (1H,bs); 6.01 (1H,d,J 1.5Hz), 5.78 (1H,bd, 6Hz), 3.39 (2H,s); 2.66 (1H,dd,J 17, 6Hz); 2.60 (1H,m); 2.21 (3H,s); 1.13 (6H,s): ^{13}C n.m.r. ($CDCl_3$); δ195.4 (s), 146.9 (s), 140.6 (d), 132.8 (s), 130.0 (d), 124.7 (s), 108.2 (d), 44.3 (d), 35.7 (t), 32.9 (2C), 31.3, 30.5, 29.0, 27.3, 26.2, 19.1 (t)]. The high resolution mass spectrum established the formula $C_{17}H_{22}O_2S$ and major fragment ions occurred at m/e 275, 215, 199 and the dominant fragment ion at 122.

These data suggested that thiofurodysinin acetate (6) had the same carbocyclic skeleton as (4) with the conversion of the vinylic methyl group of (4) to a $-CH_2-S-Ac$ group in (6). The presence of a thiol acetate group was established by comparison of the i.r. and ^{13}C n.m.r. absorptions of (6) (1695 cm^{-1} and δ195.4 respectively) with those of ethanedithiol diacetate (1695 cm^{-1} and δ194.4 respectively). Treatment of (6) with Raney nickel in ethanol for five minutes gave an inseparable mixture of (4) and (8). The same mixture was formed in identical ratio when (4) was treated with Raney nickel under the same conditions.

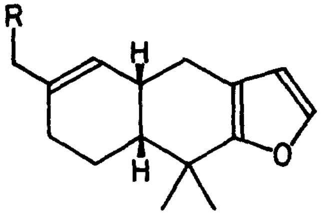
Thiofurodysin acetate (5) was also isolated as an oil and the formula $C_{17}H_{22}O_2S$ was confirmed by high resolution mass spectrometry and the fragmentation pattern was almost identical to that of (6). The ^1H n.m.r. spectrum [δ(CCl_4) 6.98 (1H,d,J 1.5Hz), 5.86 (1H,d,J 1.5Hz), 5.77 (1H,bd, 6Hz), 3.43 (2H,s), 2.70 (1H,m), 2.50 (1H,dd,J 16, 6Hz), 2.23 (3H,s), 1.22 (6H,s)] suggested the same relationship of (5) to (3) as found between (6) and (4). This was confirmed by the treatment of (5) with Raney nickel to give the same mixture of products as that obtained from (3) under the same conditions.



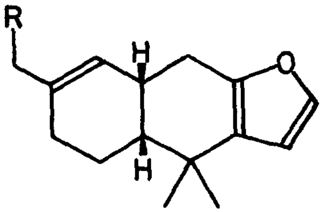
(1)



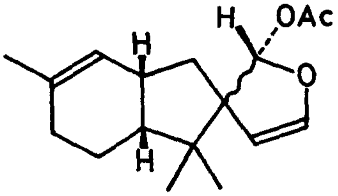
(2)



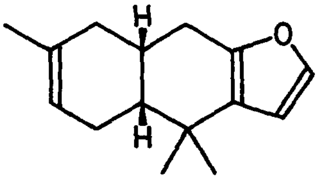
(3) R = H
(5) R = AcS



(4) R = H
(6) R = AcS



(7)



(8)

Figure 1. Stereoprojection of furodysin (3)

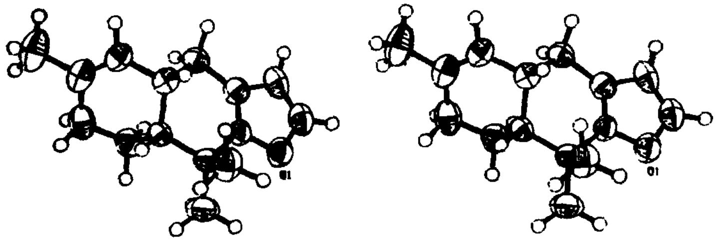
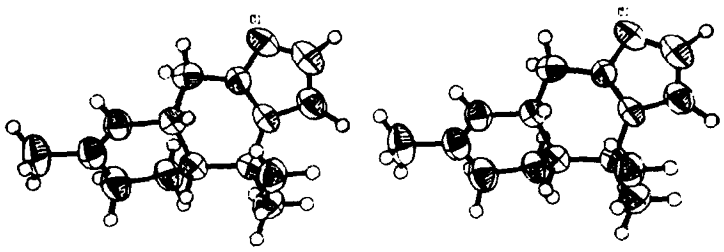


Figure 2. Stereoprojection of furodysinin (4)



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3. The colourless crystals of (3) have the space group $P2_12_12_1$ with a = 16.604, b = 6.158, c = 12.545 Å. Intensities were measured to $\theta < 28°$ with PDP8 controlled Hilger and Watts four circle diffractometer using filtered MoKα radiation. Independent data were obtained for 1800 planes and 929 of these had $\sigma I > 2.5$ (I) and were used in the refinement. The structure was solved by MULTAN[7] and the other calculations were done with SHELX[8]: refinement by full matrix converged at R = 0.069.

4. The colourless crystals of (4) have the space group $P2_12_12_1$ with a = 16.894 (5), b = 6.237 (2), c = 12.156 (4) Å. V = 1280.844 Å^3, Z = 4, D_{calc} = 1.12 g. cm^{-3}, $F(000)$ = 472, T = 293°K, μ = 0.36 cm^{-1}, crystal size: .35 x .35 x .4 mm^3. Intensities were collected on a Hilger and Watts four circle diffractometer Y 290/PDP 8, with Zirconium filtered MoKα radiation λ = 0.71069 Å and the $\omega - 2\theta$ scan mode. Of 1563 independent planes 1015 with $I > 2\sigma(I)$ were used in the structure determination. The phase problem was solved with the SHELX-System[8]. The full matrix least squares refinement was carried out with anisotropic temperature factors for the heavier atoms to convergence at R = 6.45%.

5. All four compounds (3)-(6) visualized on t.l.c. with 1% vanillin-sulphuric acid appear as rose pink spots. The colours of (4) and (6) change to blue-grey after some hours but those of (3) and (5) remain unchanged.

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