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New Marine Furanosesquiterpenoids, Tubipofuran and 15-Acetoxytubipofuran from the Stolonifer Tubipora musica Linnaeus

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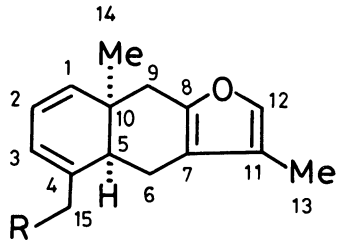
New bioactive furanosesquiterpenoids, tubipofuran and 15-acetoxytubipofuran, were isolated from the Japanese stolonifer Tubipora musica Linnaeus. Their structures were determined on the basis of spectral data and chemical reactions.

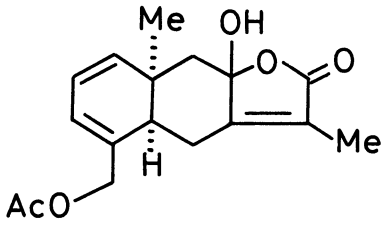
Recently bioactive marine natural products such as antitumor prostanoids[1,2] isolated from stolonifer have been received attention. During the course of our investigation[1] on bioactive substances from Japanese stolonifer, we have isolated two new furanosesquiterpenoids, tubipofuran (1) and 15-acetoxytubipofuran (2), from Tubipora musica Linnaeus. These compounds showed an ichtyotoxicity toward a killifish Orizias latipes (15 μg/ml for 1 and 20 μg/ml for 2), and 2 showed a cytotoxicity against B-16 melanoma cells in vitro (IC_{50} 33 μg/ml). This paper describes isolation and structure elucidation of these sesquiterpenoids.

The methanol extract of Tubipora musica (wet weight 2.8 kg), collected at the coral reef of Ishigaki Island (Okinawa, Japan), was suspended in water and then extracted with ethyl acetate. The ethyl acetate extract (11 g) was chromatographed on a silica gel column, and the fraction (4.1 g) obtained by elution with hexane was further chromatographed on a silica gel column using hexane/ethyl acetate (30:1) as an eluent, giving tubipofuran (1)[3] ($C_{15}H_{18}O$, colorless oil, 13 mg), furanodiene[4] (32 mg) and 15-acetoxytubipofuran (2) ($C_{17}H_{20}O_3$, colorless oil, 150 mg), respectively, in order of increasing polarity.



1 R = H

2 R = OAc



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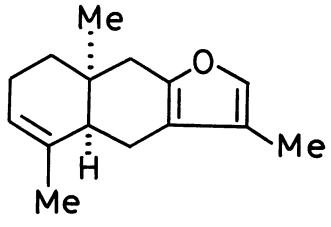

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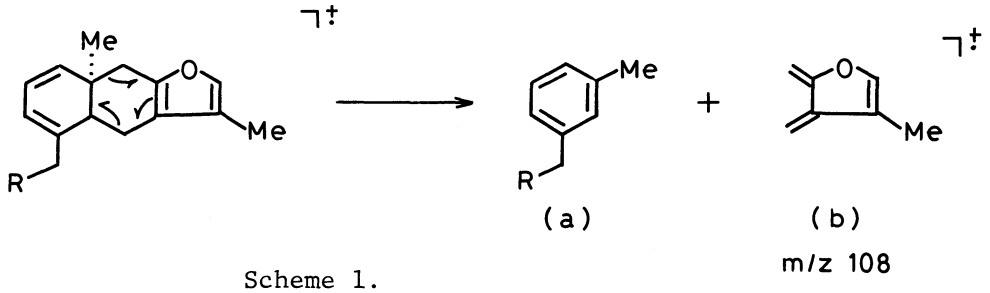
The spectral data of 1 and 2 as shown in the Table 1 are very similar to each other. The presence of a homoannular diene system in both compounds was indicated by the UV spectra [λ_{max} 263 nm (ε 3900) for 1 and 262 nm (ε 4300) for 2], and the presence of a 2,3,4-trisubstituted furan moiety in 1 and 2 was shown by the following data: 1, UV 216 nm (ε 5400), ^{1}H-NMR δ_{ppm} 7.00 (1H, q, J=1.1 Hz); 2, UV 215 nm (ε 5500), ^{1}H-NMR δ 7.00 (1H, sextet, J=1.1 Hz). The mass spectra of both compounds showed a peak at m/z 108.0565 (calcd for C_7H_8O 108.0574, a base peak) due to the fragment ion (b) caused by retro-Diels-Alder fragmentation as shown in the Scheme 1.



Scheme 1.

The ^{1}H- and ^{13}C-NMR spectra of 1 showed the signals due to a methyl [^{1}H-NMR δ 1.13 (3H, s)], two olefinic methyls [^{1}H-NMR δ 1.86 (3H, brs), 1.90 (3H, d, J=1.2 Hz)], two methylenes [^{13}C-NMR δ 23.1 (t), 35.0 (t)], a methine [^{13}C-NMR δ 44.1 (d)], and a quaternary carbon [^{13}C-NMR δ 35.7 (s)] in addition to the signals attributed to the monosubstituted homoannular diene system [^{1}H-NMR δ 5.42 (1H, dd, J=0.9, 9.5 Hz), 5.61 (1H, brd, J=5.2 Hz), 5.81 (1H, dd, J=5.2, 9.5 Hz)] and the 2,3,4-trisubstituted furan moiety. The ^{1}H- and ^{13}C-NMR spectra of 2 were very similar to those of 1, except for the presence of the signals due to $-CH_2OCOCH_3$ [^{1}H-NMR δ 2.08 (3H, s), 4.63 (1H, brd, J=13.0 Hz), 4.70 (1H, dd, J=1.2, 13.0 Hz), ^{13}C-NMR δ 66.4 (t), 170.7 (s)] instead of the olefinic methyl signal on the diene system present in 1.

These spectral data suggested the structures 1 and 2 for both compounds, although the structures with the furan moiety linked in the opposite direction were not excluded. The following chemical conversions established the structures 1 and 2 unambiguously. Oxidation[5] of 2 with m-chloroperbenzoic acid gave the lactone alcohol 3,[6] whose ^{1}H-NMR spectrum showed a long-range coupling (J=1.5 Hz) between the olefinic methyl [δ 1.81 (d)] on the lactone ring and C-6 proton [δ 2.38 (ddq)]. The presence of this long-range coupling in 3 was reasonably explained only in the case of structure 2 for 15-acetoxytubipofuran. Furthermore reduction of 1 and 2 with lithium in liquid ammonia gave the same compound 4[7] [^{1}H-NMR δ 1.71 (3H, d, J=1.8 Hz), 5.28 (1H, brs, H-3)]. Thus the structure 1 was assigned for tubipofuran.

The cis stereochemistry between the angular C-5 and C-10 positions for 1 and 2 was determined by the measurement of the ^{1}H -^{1}H long-range correlation 2-D NMR spectrum of 2; the W-shape long-range coupling was observed between H-1 [δ 5.58 (brd)] and H-5 [δ 2.16 (m)]. This was explainable only in the case of cis stereochemistry with the nonsteroidal conformation in 2 shown in Fig. 1.

The absolute stereochemistry of 1 and 2 was elucidated by application of the diene helicity rule[8] in CD measurement. The CD spectra of 1 and 2 (in hexane)

Table 1. Physical Data of 1 and 2

	1	2
$[\alpha]_D$ ($CHCl_3$)	+ 5.7° (c 0.6)	+ 10.7° (c 0.5)
MS m/z	214 (M^+, 6%) 209 (M-Me, 2%) 108 (100%)	272 (M^+, 44%) 213 (M-AcO, 42%) 212 (M-AcOH, 32%) 197 (M-Me-AcOH, 60%) 108 (100%)
UV λ_{max}^{EtOH} (nm)	216 (ε 5400) 263 (ε 3900)	215 (ε 5500) 262 (ε 4300)
IR $\nu_{max}^{CHCl_3}$ (cm^{-1})	1645 1585 1100 855	1730 1650 1565 1240 1100 870
^{1}H-NMR (400 MHz) $\delta_{ppm}^{CDCl_3}$	1.13 (3H,s,14-Me) 1.86 (3H,brs,15-Me) 1.90 (3H,d,J=1.2 Hz,13-Me) 2.01 (1H,dd,J=5.8, 8.6 Hz,H-5) 2.19 (1H,dddd,J=2, 2.9, 8.6, 15.9 Hz,H-6) 2.44 (1H,brd,J=16.5 Hz,H-9) 2.53 (1H,tdd,J=1.2, 5.8, 15.9 Hz,H-6) 2.63 (1H,brd,J=16.5 Hz,H-9) 5.42 (1H,dd,J=0.9, 9.5 Hz,H-1) 5.61 (1H,brd,J=5.2 Hz,H-3) 5.81 (1H,dd,J=5.2, 9.5 Hz,H-2) 7.00 (1H,q,J=1.1 Hz,H-12)	1.15 (3H,s) 1.89 (3H,d,J=1.3 Hz) 2.08 (3H,s) 2.14-2.24 (2H,m) 2.51 (1H,dd,J=2.7, 16.6 Hz) 2.56 (1H,dd,J=3.4, 13.4 Hz) 2.65 (1H,brd,J=16.6 Hz) 4.63 (1H,brd,J=13.0 Hz) 4.70 (1H,dd,J=1.2, 13.0 Hz) 5.58 (1H,brd,J=8.6 Hz) 5.85-5.90 (2H,m) 7.00 (1H,sextet,J=1.1 Hz)
^{13}C-NMR (25 MHz) $\delta_{ppm}^{CDCl_3}$	8.1 (q) 22.3 (q) 23.1 (t) 26.0 (q) 35.0 (t) 35.7 (s) 44.1 (d) 117.8 (d) 118.5 (s) 118.6 (s) 124.0 (d) 134.7 (d) 136.4 (d) 140.7 (s) 149.6 (s)	8.0 (q) 20.8 (q) 23.7 (t) 25.8 (q) 35.2 (t) 35.9 (s) 40.4 (d) 66.4 (t) 118.96(s) 119.03(s) 121.1 (d) 123.3 (d) 136.6 (d) 137.9 (s) 138.3 (d) 149.5 (s) 170.7 (s)

showed a positive Cotton effect due to the helical diene system at 263 nm ($\Delta\varepsilon$ + 0.56) for 1 and 270 nm ($\Delta\varepsilon$ + 3.0) for 2, respectively. The positive sign of these Cotton effect coincided with the positive chirality of the diene system predicted from the absolute structure of 1 and 2 as shown in Fig. 1.

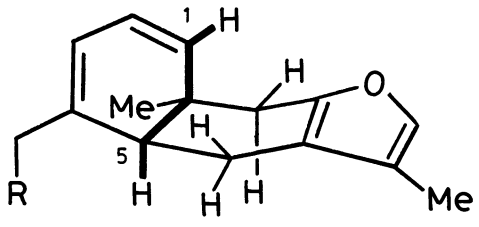


Fig. 1. Conformation of 1 (R = H) and 2 (R = OAc).

The compounds reported here are the first examples of eudesmane-type furanosesquiterpenoids having a cis-fused A/B ring with a homoannular 1,3-diene system from natural sources.

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References

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3) All new compounds gave satisfactory high resolution mass measurement.

4) H.Hikino, K.Agatsuma, and T.Takemoto, Tetrahedron Lett., 1968, 931; R.R.Izac, M.M.Bandurraga, J.M.Wasylik, F.W.Dunn, and W.Fenical, Tetrahedron, 38, 301 (1982).

5) K.Takeda, H.Minato, M.Ishikawa, and M.Miyawaki, Tetrahedron, 20, 2655 (1964).

6) 3; IR($CHCl_3$) 3560, 3300, 1745, 1730, 1690 cm^{-1}; ^{1}H-NMR (400 MHz,$CDCl_3$) δ_{ppm} 0.98 (3H,s), 1.60 (1H,d,J=13.9 Hz), 1.81 (3H,d,J=1.5 Hz), 1.88 (1H,ddd,J=1.3, 4.2, 12.1 Hz), 2.10 (3H,s), 2.38 (1H,ddq,J=13.4, 12.1, 1.5 Hz), 2.46 (1H,d, J=13.9 Hz), 2.67 (1H,dd,J=4.2, 13.4 Hz).

7) 4; ^{1}H-NMR (400 MHz,$CDCl_3$) δ_{ppm} 1.04 (3H,s), 1.71 (3H,d,J=1.8 Hz), 1.91 (3H,d, J=1.1 Hz), 5.28 (1H,brs), 7.04 (1H,brs).

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