Marine Terpenes and Terpenoids. XIV.[1] Absolute Configuration and Acid-Catalyzed Transformation of (−)-12,13-Didehydrofurospongin-1 Isolated from an Arabian Sea Sponge, *Fasciospongia cavernosa* SCHMIDT

Masaru KOBAYASHI,*[,a] Ramadas CHAVAKULA,[b] Osamu MURATA[a] and Nittala S. SARMA*[,b]

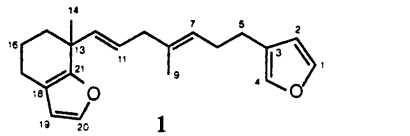
Faculty of Pharmaceutical Sciences, Hokkaido University,[a] Kita-ku, Sapporo 060, Japan and School of Chemistry, Andhra University,[b] Visakhapatnam 530 003, India. *Received August 27, 1991*

Three furanoterpenes, one having a furanocyclohexane ring (1) and two methyl ethers (2 and 3), and 12,13-didehydrofurospongin-1 (4a) were isolated from the lipid extract of the sponge, *Fasciospongia cavernosa* SCHMIDT. The absolute configuration of 4a at C-11 was shown to be (*S*), opposite to that reported for furospongin-1 (5). Compound 4a was found to be quite labile in acidic media and was converted, at room temperature, to 1 ($HClO_4$ in dioxane) or to a mixture of 1, 2 and 3 ($HClO_4$ in MeOH). These results suggest that 1, 2 and 3 are at least partly artefacts formed from 4a during the isolation process.

Keywords sponge; *Fasciospongia cavernosa*; furanoterpene; (−)-12,13-didehydrofurospongin-1; acid-catalyzed cyclization

Some C_{21} terpenoids having furyl groups were among the earliest examples of unique sponge metabolites to be found.[2] Examination of the lipid extract of the sponge *Fasciospongia cavernosa* SCHMIDT, collected off the coast of the Lakshadweep Islands, Arabian Sea, resulted in the isolation of four C_{21} furanoterpenes in fairly high yields [**1** (102 mg), a mixture of **2** and **3** (134 mg), and **4a** (615 mg) from 2 kg of the dried material]. Compounds **2** and **3** showed identical mobilities on silica gel column chromatography but were easily separable by chromatography on a 7.5% silver nitrate-impregnated silica gel column.

The least polar compound **1** showed the molecular formula $C_{21}H_{26}O_2$ by high-resolution mass spectroscopy (HR-MS). The signals having small coupling constants at δ 6.17, 6.26, 7.19, 7.26 and 7.33 in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum indicated that **1** is a C_{21} furanoterpene having two furyl groups.[3] Simultaneous occurrence of **2**, **3** and **4a** (*vide infra*) suggested that the two furyl groups are located at both ends of the chain. The ^{1}H-NMR spectrum showed the simultaneous presence of one trisubstituted *E*-double bond (5.15, 1H, br t, J=7.0 Hz) linked to a methyl group [δ 1.53, 3H, br s; carbon-13 nuclear magnetic resonance (^{13}C-NMR), δ 16.1] and an *E*-disubstituted double bond (δ 5.06, dt, J=15.0, 7.0 Hz and 5.45, dt, J=15.0, 1.5 Hz), both unconjugated. The signals of the two α,α'- and one β-protons (δ 6.26, 7.19, 7.33) are typical of a β-substituted furyl group,[3] but the other furan moiety showed signals of one α-proton and one β-proton (δ 6.17 and 7.26), indicating it to be substituted at both α' and β'. Unlike other C_{21} furanoterpenes, **1** contained one tertiary methyl group (δ 1.33, s). The molecular formula and the number of unsaturations indicate the presence of an extra carbocyclic ring in the molecule. Based on the conventional biogenesis and the spectroscopic facts cited above, the structure of **1** was deduced to contain a furanocyclohexane moiety, formed by the cyclization of C-13 and C-21 of the linear C_{21} furanoterpene with an *E*-disubstituted double bond at C-11. The ^{1}H-NMR data of **1** resembled those of the tetronic acid derivative **6**[4] isolated from sponges of *Spongenella* sp. and *Hippospongia* sp., the only available example having the same partial structure. The ^{13}C-NMR data of **1** (Experimental), with regard to C-11 to C-21, showed a good agreement to the corresponding signals of **6**, within a deviations of less than 0.3 ppm.



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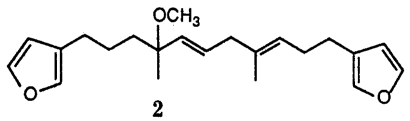

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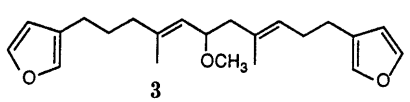

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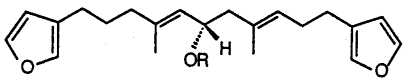
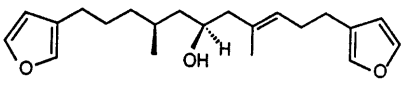


4a : R = H
4b : R = (-)-MTPA
4c : R = (+)-MTPA



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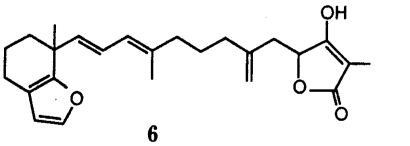


6

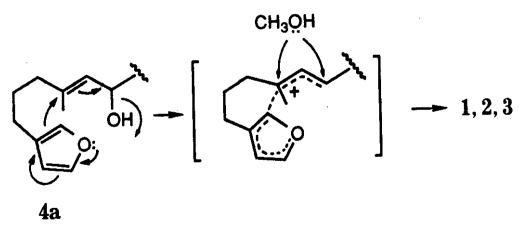
Chart 1

Compounds **2**, **3** and **4a** were considered to be linear C_{21} terpenes having two β-substituted furyl groups as indicated by the typical ^{1}H- and ^{13}C-NMR signals (Experimental). Compound **2** was an isomer of **3**, with tertiary methyl (δ 1.21, s) and methoxyl (δ 3.11, 3H, s) groups, and an *E*-disubstituted double bond (δ 5.35, 1H, br d, J=16.0 Hz, 5.48, 1H, dt, J=16.0, 7.0 Hz) as in **1**. Virtually the same ^{13}C-NMR signals due to C-1 to C-12 as those of **1** indicated **2** to be a furanoterpene bearing a methoxyl group at C-13.

Compound **3** and the predominant compound **4a** were closely related, except that the secondary hydroxyl group

of **4a** was converted to the methyl ether in **3**. The ^{1}H-NMR spectrum of **4a** showed the signal of an allylic hydroxymethine proton adjacent to a methylene group (δ 2.15, 2H, br d, J=7.0 Hz; 4.43, 1H, dt, J=8.5, 7.0 Hz; 5.16, 1H, dq, J=8.5, 1.5 Hz). These and other ^{1}H- and ^{13}C-NMR signals (Experimental) were found to be identical with those reported for the known compound 12,13-didehydrofurospongin-1 (**4a**), recently isolated in a minute amount from a Pacific sponge, *Carteriospongia flavellifera*, by Schmitz and Chang.[5] The authors did not state the specific rotation, or the absolute configuration. The absolute configuration of furospongin-1 (**5**) itself was reported as (*S*) in the earlier study, using Horeau's method.[6] However, this method seems to be inappropriate for furospongin-1 (**5**), whose asymmetric carbinyl carbon is linked to two methylene groups, since the nature of the substituent effect and the influence of steric hindrance on the racemic acid anhydride are not clear.[7] In the present work, compound **4a** was subjected to the MTPA (2-methoxy-2-trifluoromethylphenylacetic acid) ester method developed by Kusumi *et al.* and Takano *et al.*[8] Compounds such as **4a** seem to be very suitable for examination by this method, since the two linear substituents (C-1 to C-10 and C-12 to C-21) are elongated in opposite directions, so that the plane which involves the C-11 carbinyl methine and the ester carbonyl group would exactly bisect these two segments.[8c] The alcohol **4a** was converted to (*S*)- and (*R*)-MTPA esters (**4b** and **4c**). The $\Delta\delta'_S$ ($\delta_{S(-)}-\delta_{R(+)}$) observed for 7-H, 10-$H_a$, 10$H_b$ were -0.09, -0.04, -0.06 ppm, while those observed for 12-H, 16-H_2 were $+0.14$ and $+0.04$ ppm, respectively. The C-10 methylene protons (H_a and H_b) were sterically equivalent in the parent alcohol **4a** and appeared as a 2H broad doublet. In the methyl ether **3** and the MTPA esters **4b** and **4c**, however, the bulkiness of the C-11 substituents makes them non-equivalent, due to the restricted rotation about the C-10,11 bond, and the 10-H_2 signals were split into two double doublets (Experimental). From the MTPA determination rule,[8c] the positive and negative $\Delta\delta'_S$ observed for the signal of the protons in the left and the right segments, respectively, show clearly that the absolute configuration of **4a** at C-11 is (*S*), which is enantiomeric to that reported for furospongin-1 (**5**).[6,9]

Although compounds **1**, **2** and **3**, isolated from the sponge, were weakly optically active, their structures led us to suspect the stability of the allylic alcohol **4a**. In fact, during collection, the organism was stored in MeOH until transportation to the laboratory. The crude extract of these organisms is liable to liberate various acidic molecular species which may catalyze side-reactions. When kept in $CHCl_3$–MeOH (2:1) at room temperature for one month, about one-tenth of **4a** was converted to a **2**, **3** mixture, but the formation of **1** was minimal. However, on brief treatment in acidic media, *e.g.* dilute $HClO_4$ in MeOH for 1 h, it was converted completely into equal amounts of **1** and a mixture of **2** and **3** (Chart 2). Treatment of **4a** at room temperature with aqueous $HClO_4$ in dioxane overnight gave **1** in 66% yield. Compound **4a** was stable in freshly distilled CH_2Cl_2, but was converted rapidly to **1** in 96% yield when dissolved in *ca.* one-year-old CH_2Cl_2, presumably catalyzed by residual HCl. The distinctly different patterns of ^{1}H-NMR spectra of the MTPA esters **4b** and **4c** indicate that **4a** is enantiomerically pure. Compounds **1**, **2** and **3**, derived from **4a**, are in contrast expected to be racemic in view of their virtually negligible specific rotations, within the range of experimental error, and indicate the intermediacy of a furyl-associated cation (Chart 2). The observed instability of **4a** suggests that at least a portion of **1**, **2** and **3** isolated from the sponge extract represents artefacts. The cyclization process of **4a** to **1** would also account for the biogenesis, or the artificial formation, of **6** recorded in the previous reports.[4]



4a

Chart 2

Experimental

Optical rotations were determined in $CHCl_3$ on a JASCO DIP-370 digital polarimeter. NMR spectra were determined in $CDCl_3$ solution on a JEOL JMN GX-400 spectrometer at 400 MHz (^{1}H) and on a JEOL JMN FX-90Q spectrometer at 22.5 MHz (^{13}C) with tetramethylsilane (^{1}H, δ 0.00) and $CDCl_3$ (^{13}C, center peak δ 77.1) as internal standards. Mass spectra (MS) were determined on a JEOL JMS D300 mass spectrometer. Chromatography was done by flash column chromatography[10] using silica gel (Wako gel C-300, 200—300 mesh, Wako Pure Chemical Industries).

Isolation of Furanoterpenes 1, 2, 3 and 4a The sponge (2 kg, dry weight), *F. cavernosa*, collected on the Arabian Sea coast at Kalpeni Island, Lakshadweep, India, during December, 1989, was immediately placed in MeOH for transportation to the laboratory. The material was extracted with ethyl acetate in a Soxhlet apparatus and the crude residue (30 g) was subjected to column chromatography. Elution with 2% ethyl acetate in hexane gave **1** (102 mg) and a mixture of **2** and **3** (134 mg). Further elution with 5% and 8% ethyl acetate in hexane gave **4a** (615 mg). A portion (50 mg) of the mixture of **2** and **3** was submitted to chromatography over a column of 7.5% silver nitrate-impregnated silica gel. Elution with 2.5% ethyl acetate–hexane gave first **2** (25.1 mg), and then **3** (19.7 mg).

Compound 1 Oil, $[\alpha]_D^{28}$ +5° (c=0.88), ^{1}H-NMR δ: 1.33 (3H, s, 14-H_3), 1.53 (3H, br s, 9-H_3), 2.23 (2H, br q, J=7.0 Hz, 6-H_2), 2.64 (2H, br d, J=7.0 Hz, 10-H_2), 5.06 (1H, dt, J=15.0, 7.0 Hz, 11-H), 5.15 (1H, br t, J=7.0 Hz, 7-H), 5.45 (1H, dt, J=15.0, 1.5 Hz, 12-H), 6.17 (1H, d, J=2.0 Hz, 19-H), 6.26 (1H, br s, 2-H), 7.19 (1H, br s, 4-H), 7.26 (1H, br s, 20-H), 7.33 (1H, t, J=1.0 Hz, 1-H). ^{13}C-NMR δ: C-1 (142.5), C-2 (111.1), C-3 (124.9), C-4 (138.7), C-5 (25.0), C-6 (28.6), C-7 (127.1), C-8 (134.9), C-9 (16.1), C-10 (42.7), C-11 (124.3), C-12 (138.9), C-13 (38.4), C-14 (26.0), C-15 (38.4), C-16 (20.1), C-17 (22.6), C-18 (116.6), C-19 (110.1), C-20 (140.6), C-21 (154.7). MS m/z: 310 (M^+), 295, 161, 147, 135, 121 (base peak). High-resolution MS [Found (Calcd)] m/z: $C_{21}H_{26}O_2$ (M^+), 310.1914 (310.1933).

Compound 2 Oil, $[\alpha]_D^{28}$ +12° (c=0.30). ^{1}H-NMR δ: 1.21 (3H, s, 14-H_3), 1.57 (3H, br s, 9-H_3), 2.25 (2H, br q, J=7.5 Hz, 6-H_2, 2.40 (2H, m), 2.45 (2H, br t, J=7.5 Hz), 2.71 (1H, br d, J=7.0 Hz, 10-H_2), 3.11 (3H, s, OMe), 5.19 (1H, tq, J=7.0, 1.0 Hz, 7-H), 5.35 (1H, br d, J=16.0 Hz, 12-H), 5.48 (1H, dt, J=16.0, 7.0 Hz, 11-H), 6.26, 6.27 (each 1H, br s, 2, 19-H), 7.20 (2H, br s, 4, 21-H), 7.33 (2H, br s, 1, 20-H). ^{13}C-NMR δ: C-1, 20 (142.5, 142.6), C-2, 19 (111.0, 111.1), C-3, 18 (124.8, 124.9), C-4, 21 (138.8, 138.9), C-5, 16 (24.9, 25.2), C-6 (28.5), C-7 (129.1), C-8 (134.5), C-9 (16.2), C-10 (42.8), C-11 (124.7), C-12 (136.0), C-13 (76.9), C-14 (21.8), C-15 (39.9), C-17 (24.3), OMe (49.9). MS m/z: 342 (M^+), 327, 310, 295, 233, 216, 201, 193, 161. High-resolution MS [Found (Calcd)] m/z: $C_{22}H_{30}O_3$ (M^+), 342.2178 (342.2195).

Compound 3 Oil, $[\alpha]_D^{28}$ +13° (c=0.22). ^{1}H-NMR δ: 1.61 (3H, br s), 1.65 (3H, d, J=1.5 Hz), 1.67 (2H, quint, J=7.0 Hz, 16-H_2), 2.06, 2.32 (each 1H, dd, J=14.0, 7.0 Hz, 10-H_a and 10-H_b), 2.32 (2H, br q, J=7.5 Hz, 6-H_2), 2.06, 2.39, 2.43 (each 2H, br t, J=7.5 Hz, 5, 15, 17-H_2), 3.23 (3H, s, OMe), 4.01 (1H, dt, J=9.0, 7.0 Hz, 11-H), 5.01 (1H, br d, J=9.0 Hz, 12-H), 5.20 (1H, br t, J=7.0 Hz, 7-H), 6.26 (2H, br s, 2, 19-H), 7.19, 7.20 (each 1H, br s, 4, 21-H), 7.32, 7.35 (each 1H, br t, J=1.5 Hz, 1, 20-H). ^{13}C-NMR δ: C-1, 20 (142.5, 142.7), C-2, 19 (111.0, 111.1), C-3, 18 (124.9),

C-4, 21 (138.8), C-5 (24.9), C-6, 16 (28.1, 28.5), C-7, 12 (126.2, 126.4), C-8 (132.4), C-9, 14 (16.6), C-10 (45.8), C-11 (76.1), C-13 (139.0), C-15 (39.2), C-17 (24.3), OMe (55.6). MS *m/z*: 342 (M^+), 327, 310, 295, 233, 216, 201, 193, 161. High-resolution MS [Found (Calcd)] *m/z*: $C_{22}H_{30}O_3$ (M^+), 342.2215 (342.2195).

Compound 4a Oil, $[\alpha]_D^{28}$ −8° (*c*=0.92). ^{1}H-NMR δ: 1.64 (3H, br s), 1.67 (3H, d, *J*=1.5 Hz), 2.15 (2H, br d, *J*=7.0 Hz, 10-H_2), 2.29 (2H, br q, *J*=7.5 Hz, 6-H_2), 2.03, 2.39, 2.48 (each 2H, br t, *J*=7.5 Hz, 5, 15, 17-H_2), 4.43 (1H, dt, *J*=8.5, 7.0 Hz, 11-H), 5.16 (1H, dq, *J*=8.5, 1.5 Hz, 12-H), 5.27 (1H, br t, *J*=7.0 Hz, 7-H), 6.26 (2H, br s, 2, 19-H), 7.20 (2H, br s, 4, 21-H), 7.34 (2H, br s, 1, 20-H). ^{13}C-NMR δ: C-1, 20 (142.5), C-2, 19 (110.9), C-3, 18 (124.6, 124.8), C-4, 21 (138.8), C-5 (24.8), C-6, 16 (27.9, 28.4), C-7, 12 (127.6, 127.7), C-8 (132.2), C-9, 14 (16.2, 16.3), C-10 (48.0), C-11 (66.0), C-13 (137.6), C-15 (38.9), C-17 (24.3). MS *m/z*: 328 (M^+), 310, 256, 229, 179, 161, 150. High-resolution MS [Found (Calcd)] *m/z*: $C_{21}H_{26}O_2$ ($M^+ - H_2O$), 310.1912 (310.1933).

(*S*)- and (*R*)-MTPA Esters of Compound 4a (a) A solution of **4a** (7.0 mg) in CH_2Cl_2 (0.5 ml) was treated at room temperature with (*S*)-MTPA (30 mg), dicyclohexylcarbodiimide (DCC) (30 mg) and dimethylaminopyridine (10 mg) for 2 h. The mixture was charged on a column of silica gel. Elution with 2.5% ethyl acetate in hexane gave the (*S*)-MTPA ester (**4b**, 9.3 mg) as an oil, $[\alpha]_D^{30}$ −22° (*c*=1.86). ^{1}H-NMR δ: 1.66 (2H, quint, *J*=7.5 Hz, 16-H_2), 1.57 (3H, br s), 1.76 (3H, d, *J*=1.5 Hz), 2.06, 2.36, 2.37 (each 2H, br t, *J*=7.5 Hz), 2.20 (1H, dd, *J*=14.0, 6.5 Hz, 10-H_a), 2.39 (1H, dd, *J*=14.0, 8.0 Hz, 10-H_b), 3.52 (1H, d, *J*=1.0 Hz, OMe), 5.16 (1H, br t, *J*=7.0 Hz, 7-H), 5.18 (1H, dq, *J*=9.5, 1.0 Hz, 12-H), 5.87 (1H, ddd, *J*=9.5, 8.0, 6.5 Hz, 11-H), 6.23 (2H, br s), 7.16, 7.19 (each 1H, br s). (b) Treatment of 7.3 mg of **4a** with (*R*)-MTPA according to the same procedure as in (a) gave the (*R*)-MTPA ester (**4c**, 10.6 mg). Oil, $[\alpha]_D^{30}$ +29° (*c*=2.12). ^{1}H-NMR δ: 1.62 (2H, quint, *J*=7.5 Hz, 16-H_2), 1.64, 1.76 (each 3H, br s), 2.02, 2.34, 2.40 (each 2H, br t, *J*=7.5 Hz), 2.24 (1H, dd, *J*=14.0, 6.0 Hz, 10-H_a), 2.45 (1H, dd, *J*=14.0, 8.0 Hz, 10-H_b), 3.52 (3H, br s, OMe), 5.04 (1H, br d, *J*=9.0 Hz, 12-H), 5.25 (1H, br t, *J*=7.0 Hz, 7-H), 5.85 (1H, ddd, *J*=9.0, 8.0, 6.5 Hz, 11-H), 6.23, 6.24 (each 1H, br s), 7.17 (2H, br s).

Acid Treatment of 4a (a) A solution of **4a** (5.2 mg) in 0.5 ml of MeOH was treated with 15 μl of $HClO_4$ solution, made from 0.15 ml of 70% perchloric acid and 5 ml of H_2O. The mixture was concentrated, and diluted with Et_2O. Column chromatography of the mixture, after usual work-up, with 2.5% ethyl acetate–hexane gave **1** ($[\alpha]_D^{30}$ 0° (*c*=0.54), 2.7 mg) and an equal mixture ($[\alpha]_D^{30}$ 0° (*c*=0.56), 2.8 mg) of **2** and **3**, whose ^{1}H-NMR spectra were identical with those of **1** and a **2**, **3** mixture, isolated from the sponge. (b) A solution of **4a** (3.2 mg) was treated in dioxane (0.2 ml) with 15 μl of the $HClO_4$ solution overnight. Chromatography of the mixture as in (a) gave 2.0 mg of **1** (66%). (c) **4a** (11.6 mg) was dissolved in CH_2Cl_2 (0.5 ml) which had not been distilled for *ca.* one year. The solution turned violet within 30 min. Evaporation of the solvent and chromatography of the residue as in (a) gave **1** ($[\alpha]_D^{30}$ 0° (*c*=2.12), 10.6 mg, 96%).

Acknowledgment The authors thank the Department of Science and Technology, Government of India, for financial assistance (SP/S1/G15/86) and Dr. P. A. Thomas, VR Center of CMFRI, Vizhinjam, India for the identification of the sponge.

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