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MINOR C-21 FURANOTERPENES FROM THE SPONGES *SPONGIA OFFICINALIS* AND *HIPPOSPONGIA COMMUNIS*

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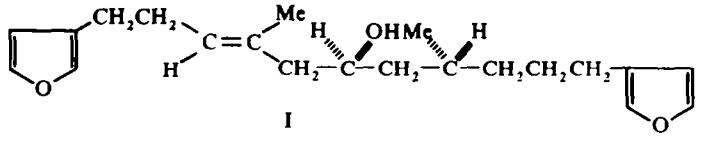
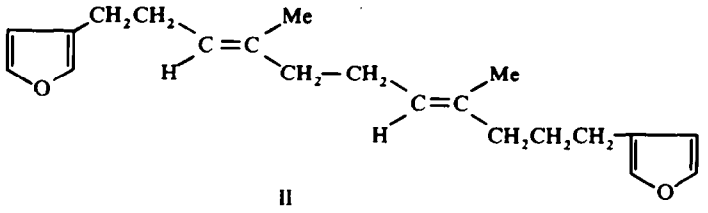
Abstract—Five more difuranoterpenes having the same carbon skeleton as furospongin-1, have been identified in the sponges *Spongia officinalis* and *Hippospongia communis*, namely anhydrofurospongin-1 (II), furospongin-2 (III), isofurospongin-2 (IV), dihydrofurospongin-2 (V) and tetrahydrofurospongin-2 (VI).

IN A PREVIOUS PAPER[1] we reported the presence of furospongin-1 (I), apparently an oxidised linear sesterterpenoid, in the sponges *Spongia officinalis* and *Hippospongia communis*. We have now isolated five new C-21 furanoterpenes, present in smaller amounts and closely related to furospongin-1 (I), and have named them anhydrofurospongin-1 (II), furospongin-2 (III), isofurospongin-2 (IV), dihydrofurospongin-2 (V) and tetrahydrofurospongin-2 (VI).



I



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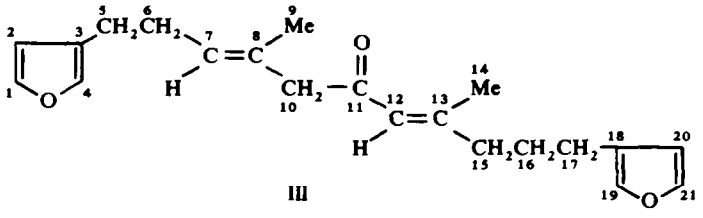

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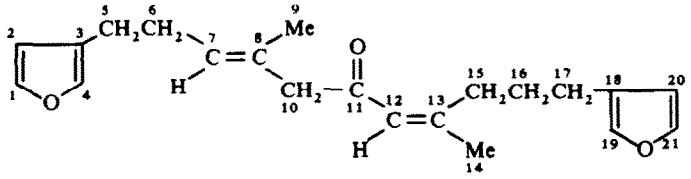

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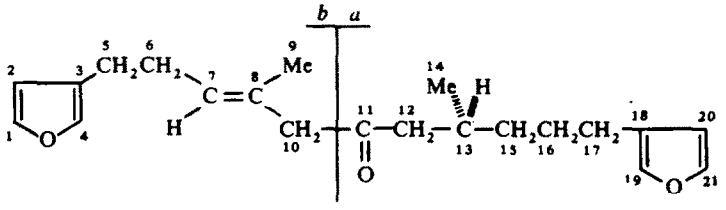
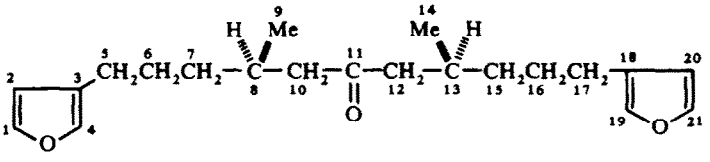


V

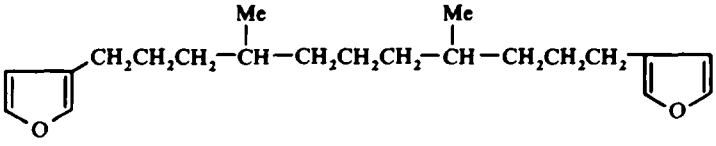


VI

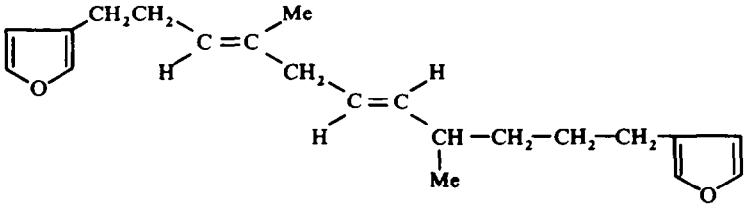
Anhydrofurospongin-1 (II). $C_{21}H_{28}O_2$. is a colourless. optically inactive oil. Its NMR spectrum shows the presence of 2 β-methylene-substituted furan rings [two broad singlets at δ 7·22 (2H) and 7·09 (2H). attributable to four α-hydrogens. a broad singlet at δ 6·15 (2H) due to two β-protons. and one four-proton triplet (J = 6 Hz) at δ 2·34 assignable to two methylene groups attached to the furan rings] and also of two —CH=CMe—groupings [six-proton singlet at δ 1·58 broadened by long range coupling (Me *trans* to the olefinic protons in an isoprene residue)[2] and a two-proton broad multiplet at δ 5·08]. In addition a broad multiplet (8H) at δ 2·00 (C=C—CH_2) and a two-proton signal at δ 1·65 (m. —$CH_2C\underline{H}_2CH_2$—) account for all the hydrogens in the molecule.

The presence of furan rings is also revealed by the IR spectrum (ν_{max} 3140. 1570. 1500. 1165. 1065. 1020. 875. 780 cm^{-1})[3,4] mass spectrum [ions at m/e 67 ($C_4H_3O^+$) and 81 (base peak. $C_4H_3OCH_2^+$)] and UV spectrum (λ_{max} 220 nm. ε 8.900 in cyclohexane).

Anhydrofurospongin-1 (II) yielded a mixture of reduction products by catalytic hydrogenation under various mild reaction conditions.[4] In order to obtain the tetrahydroderivative (VII) selectively. both from anhydrofurospongin-1 (II) and from the dehydration product (VIII)[1] of furospongin-1 we resorted to metal-catalysed transfer-hydrogenation.[5] Using decalin and Pd/C under reflux for 2 hr we obtained the same tetrahydroderivative. (VII: M^+ 316). in good yield. from both (II) and (VIII). as demonstrated by MS. TLC and GLC. Therefore. as anhydrofurospongin-1 (II) has the same framework as VIII.[1] our next concern was to establish the position of



VII



VIII

the two double bonds in this natural compound. This problem was solved by ozonolysis of anhydrofurospongin-1 which gave, in agreement with structure II, succinic, levulinic and 5-oxohexanoic acids. Prominent peaks in the mass spectrum of II at *m/e* 163 [$C_4H_3OCH_2CH_2CH_2C(CH_3)$=$CHCH_2^+$] and 149 [$C_4H_3OCH_2CH_2CH$=$C(CH_3)CH_2^+$] confirm the assigned structure.

Furospongin-2 (III). $C_{21}H_{26}O_3$ (M^+ at *m/e* 326). a colourless oil. $[\alpha]_D = 0°$. shows UV (λ_{max}242 nm. ε 18.200) and IR (ν_{max}1670 and 1610 cm^{-1}) absorption spectra characteristic of an α,β-unsaturated ketone. The presence of an α,β-unsaturated ketone is also indicated by the one-proton broad singlet at δ 6·05 (H-12) and the three-proton doublet (J = 1·3 Hz) at δ 2·11 (Me on C-13), coupled to each other as demonstrated by double resonance experiments: on irradiation of the vinylic proton signal at δ 6·05 the doublet at δ 2·11 collapses to a singlet and the reverse experiment (irradiation at δ 2·11) causes the broad singlet at δ 6·05 to sharpen. In addition, the low-field resonance of the vinylic Me group (δ 2·11) suggests that it may be *cis* to the > CO group.[6]

The NMR spectrum also shows the presence of two β-methylene-substituted furan rings (Experimental). a H_2C—CH=CMe— grouping [(δ 5·31. 1H. t. J = 6 Hz) and (δ 1·60, 3H, bs; Me *trans* in an isoprene residue)[2]] and a methylene group, the protons of which resonate as a singlet at low-field [δ 3·03. >C=C(Me)—$C\underline{H}_2$—CO—]. The remaining signals at δ 2·16 (bm. 4H) and at δ 1·75 are attributable to three —CH_2—. two of which (δ 2·16) must be linked to a double bond. All this spectral information. together with biogenetic considerations. suggests structure III for furospongin-2. This was confirmed by $NaBH_4$-pyridine reduction[7] of the natural compound. which gave. in good yield. an alcohol with spectral (UV. IR. NMR and MS) and chromatographic (TLC on silica gel) properties identical with those of furospongin-1 (I).[1] Prominent peaks in the mass spectrum of III at *m/e* 177 and 149. corresponding to cleavages of the bonds adjacent to the keto group. agree with the suggested structure.

Isofurospongin-2 (IV). $C_{21}H_{26}O_3$. shows UV. IR and mass spectra identical with those of furospongin-2 (III). The NMR spectrum is almost identical; the only difference

being a shift of the Me resonance at δ 2·11 in the spectrum of furospongin-2 to 1·83 in that of isofurospongin-2. From this evidence we conclude that furospongin-2 (III) and isofurospongin-2 (IV) differ only in the configuration of the $\Delta^{12,13}$ double bond. Accordingly isofurospongin-2 can be represented by IV; the higher field resonance of Me on C-13 (δ 1·83) agrees with the assigned stereochemistry (Me *trans* to >CO) and further supports the configuration of the 12. 13 double bond for furospongin-2 (III). On $NaBH_4$–pyridine reduction. isofurospongin-2 gave. as expected. an alcohol indistinguishable from furospongin-1 (I). when compared by TLC. IR and MS.

Dihydrofurospongin-2 (V). $C_{21}H_{28}O_3$. M^+ 328. $[\alpha]_D = -0{\cdot}91°$ ($CHCl_3$). λ_{max} 220 (8.900) nm. possesses a keto group (ν_{max} 1710 cm^{-1}). two β-methylene-substituted furan rings and a —H_2C—CH=CMe group (NMR in Experimental). thus accounting for all the unsaturation in the molecule. Moreover. a singlet (2H) at δ 2·90 in the NMR spectrum and prominent peaks in the mass spectrum at *m/e* 179 and 149 corresponding to the fragments *a* and *b* (V) indicate the presence in the molecule of the unit —H_2C—CH=C(Me)—CH_2—CO— and suggest structure V. apart from the stereochemistry. for dihydrofurospongin-2. Furospongin-1 (I). when oxidised with the CrO_3–pyridine complex. gave a ketone. $[\alpha]_D = -1{\cdot}04°$ identical in all respects with dihydrofurospongin-2. thus establishing the structure and the absolute configuration for the latter. as formulated in V.

Tetrahydrofurospongin-2 (VI). $C_{21}H_{30}O_3$. M^+ 330. $[\alpha]_{589,\,578,\,546,\,436,\,365} = 0°$. λ_{max} 220 (ε. 10.700) nm. ν_{max} 1710 (>C=O. ketone) is a colourless oil. The NMR spectrum indicates the presence of two β-methylene-substituted furan rings (Experimental) and of two *sec* Me groups at δ 0·85 (d. J = 6 Hz). The fact that tetrahydrofurospongin-2 exhibits no optical rotation. coupled with the NMR data (two *sec* Me groups). suggests that this natural compound possesses a symmetrical structure. the two halves being mirror images. If this is correct the CO group would be situated in the central part of the molecule: this is supported by the mass spectrum in which only one peak (*m/e* 179) corresponding to the cleavage of the bonds adjacent to the CO group. could be observed.

The structure VI. apart from stereochemistry. for tetrahydrofurospongin-2 was also confirmed by Pd/C transfer-hydrogenation of dihydrofurospongin-2 (V) in refluxing decalin which afforded a reduced ketone (mixture of diastereoisomers). identical with tetrahydrofurospongin-2. when compared by GLC. NMR and MS. As far as the stereochemistry of tetrahydrofurospongin-2 is concerned. the fact that it exhibits no optical rotation (rotations were measured at five different wave lengths) indicates that the natural compound is either a racemate or. more probably. the *meso*-diastereoisomer as formulated in VI.

EXPERIMENTAL

Instrumental techniques were given in the previous paper.[1]

Isolation of anhydrofurospongin-1 (II), *furospongin-2* (III), *tetrahydrofurospongin-2* (VI), *dihydrofurospongin-2* (V) *and isofurospongin-2* (IV) *from* Spongia officinalis

The extraction of fresh material (350 g. dry weight after extraction) and the subsequent chromatography in benzene on silica gel of the crude extract was described previously.[1]

Anhydrofurospongin-1 (II). Fractions 2–3 were further chromatographed in light petroleum (40–70°) over SiO_2 (20 g; ϕ 1·1) to give 30 mg of *anhydrofurospongin-1* (II) (fractions 46–49; fractions of 10 ml were collected) as an oil. $[\alpha]_D = 0°$: UV $\lambda_{max}^{C_6H_{12}}$ 220 nm. ε 8.900; IR (liquid film) 1620 (>C=C<) and

1570. 1500. 1165, 1065. 1020. 875. 780 (furan rings) cm^{-1}; NMR δ (CCl_4) 7·22 (2H. bs. furan α-H). 7·09 2H. bs. furan α-H), 6·15 (2H. bs. furan β-H). 5·08 (2H. bm. CH=C). 2·34 (4H. bt. J = 6 Hz. C_4H_3O—C<u>H</u>$_2$—). 2·00 (8H. bm. C=C—C<u>H</u>$_2$). 1·65 (2H. bm. $CH_2C\underline{H}_2CH_2$) and 1·58 (6H. bs. *trans* MeC=C); MS. *m/e* (%) 312 (35. M^+). 135 (70). 95 (55). 81 (100). and 67 (25). (Found: C. 80·28; H. 8·78. $C_{21}H_{28}O_2$ requires: C. 80·73; H. 9·03%).

Furospongin-2 (III). Fraction 12 (40 mg) was subjected to prep TLC (2 runs) using benzene light petroleum (40–70°) (9:1). The band (R_f 0·4) (blue in UV light) was scraped off and eluted with $CHCl_3$ to yield *furospongin*-2 (III) (27 mg). $[\alpha]_D$ = 0°: UV $\lambda_{max}^{C_6H_{12}}$ 220 and 242 nm. ε 11.400 and 8.200; IR $\nu_{max}^{CHCl_3}$ 1670 (>C=O. α.β-unsaturated ketone). 1610 (>C=C<. α.β-unsaturated ketone) and 1570. 1500. 1165. 1065. 1020. 875 (furan rings) cm^{-1}: NMR δ ($CDCl_3$) 7·36 (2H. bs: furan α-H). 7·25 (2H. bs; furan α-H). 6·12 (2H. bs; furan β-H). 6·05 (1H. bs. H-12). 5·31 (1H. bt. J = 6 Hz. H-7). 3·03 (2H. s. H_2-10). 2·43 (4H. t. J = 6 Hz. H_2-5. and H_2-17). 2·27–2·06 (4H. bm. H_2-6 and H_2-15). 2·12 (3H. d. J = 1·3 Hz. Me on C-13). 1·75 (2H. bm. H_2-16) and 1·60 (3H. bs. *trans* Me on C-8); MS. *m/e* (%) 326 (15. M^+). 311 (10). 177 (5). 149 (40). 95 (80). 81 (100) and 67 (35). (Found: C. 76·97; H. 8·23. $C_{21}H_{26}O_3$ requires C. 77·30; H. 7·97%).

Tetrahydrofurospongin-2 (VI). *dihydroforospongin*-2 (V) *and isofurospongin*-2 (IV). Fractions 7–11 (250 mg) were rechromatographed on a SiO_2 (40 g) column (ϕ1 cm) using benzene-light petroleum (40–70°) (7:3). Fractions of 40 ml were collected and monitored by TLC using *p*-(dimethylamino)benzaldehyde in conc HCl–EtOH as a spray.

Fractions 50–54 gave. on evaporation. *tetrahydrofurospongin*-2 (VI) (50 mg) as an oil. $[\alpha]_{589,\,578,\,546,\,436,\,365}$ = 0° ($CHCl_3$); UV. $\lambda_{max}^{C_6H_{12}}$ 220 nm ε 10.700; IR (liquid film) 1710 (>C=O) and 1560. 1500. 1160. 1065. 1025. 875 and 780 (furan rings) cm^{-1}; NMR δ (CCl_4) 7·25 (2H. bs; furan α-H). 7·12 (2H. bs; furan α-H). 6·14 (2H. bs; furan β-H). 2·36 (4H. t. J = 6 Hz. H_2-5 and H_2-17). 2·12 (4H. m. H_2-10 and H_2-12). 1·85 (2H. bm. H-8 and H-13). 1·51 (4H. m. H_2-6 and H_2-16). 1·26 (4H. m. H_2-7 and H_2-15) and 0·85 (6H. d. J = 6 Hz. Me on C-8 and C-13); the coupling between the signals at δ 2·36 and 1·51 was confirmed by double irradiation: MS. *m/e* (%) 330 (25. M^+). 179 (20). 95 (35). 81 (100) and 67 (20). (Found: C. 76·10; H. 8·91. $C_{21}H_{30}O_3$ requires: C. 76·33; H. 9·09%).

Fractions 60–66 gave. on evaporation. *dihydrofurospongin*-2 (V) (65 mg). as an oil. $[\alpha]_D$ = −0·91° ($CHCl_3$): UV. $\lambda_{max}^{C_6H_{12}}$ 220 nm ε 8.900: IR. (liquid film) 1710 (>C=O) and 1570. 1500. 1160. 1065. 1020. 875 and 775 (furan rings) cm^{-1}: NMR δ (CCl_4) 7·23 (2H. bs: furan α-H). 7·14 (2H. bs: furan α-H). 6·16 (2H. bs; furan β-H). 5·22 (1H, bt, J = 6 Hz, H-7), 2·90 (2H, s, H_2-10), 2·46–2·05 (8H, m, H_2-5, H_2-17, H_2-12 and H_2-6). 1·90 (1H. bm. H-13). 1·56 (3H. bs. *trans* Me on C-8). 1·54 (2H. m. H_2-16 overlapping the Me signal). 1·26 (2H. bm. H_2-15) and 0·84 (3H. d. J = 7 Hz. Me on C-13); MS. *m/e* (%) 328 (10. M^+). 179 (35). 149 (20). 95 (15). 81 (100) and 67 (15). (Found: C. 76·68; H. 8·21. $C_{21}H_{28}O_3$ requires: C. 76·82; H. 8·53%).

Fractions 55–59 left a residue on evaporation which was found by TLC to be a mixture. By multiple development prep TLC (2 runs). using CCl_4–ether (96:4). it could be resolved into three compounds. The slowest moving bands were dihydrofurospongin-2 (17 mg) and tetrahydrofurospongin-2 (12 mg). The fastest moving band (blue in UV light) was scraped off and eluted with $CHCl_3$ to give isofurospongin-2 (IV) (15 mg): UV. $\lambda_{max}^{C_6H_{12}}$ 220 and 242 nm ε 10.400 and 8.000; IR. (liquid film) 1680 (>C=O. α.β-unsaturated ketone). 1615 (>C=C<, α,β-unsaturated ketone) and 1570, 1500, 1165, 1065, 1025, 875 and 725 (furan rings) cm^{-1}; NMR. (CCl_4) 7·24 (2H. bs; furan α-H). 7·15 (2H. bs; furan α-H). 6·19 (2H. bs. furan β-H). 5·98 (1H. bs. H-12). 5·27 (1H. bt. J = 6 Hz. H-7). 2·96 (2H. s. H_2-10). 2·46 (8H. m. H_2-5. H_2-17. H_2-6. H_2-15). 1·83 (3H. d. J = 1 Hz. Me on C-13). 1·75 (2H. m. H_2-16) and 1·59 (3H. bs. *trans* Me on C-8); MS. *m/e* 326 (M^+).

Isolation of (II). (III). (IV). (V) *and* (VI) *from* Hippospongia communis. Working up as above. starting from fresh material (110 g. dry weight after extraction). yielded anhydrofurospongin-1 (II. 40 mg). furospongin-2 (III. 100 mg). isofurospongin-2 (IV. 15 mg). dihydrofurospongin-2 (V. 85 mg). tetrahydrofurospongin-2 (VI. 35 mg) together with furospongin-1 (I. 350 mg).

Metal-catalysed transfer-hydrogenation of VIII *and anhydrofurospongin*-1 (II) VIII[1] (30 mg), 10% Pd/C (15 mg) and decalin (1 ml) were refluxed for 2 hr. Removal of catalyst and solvent left a residue chromatographed on a SiO_2 (5 g) column (ϕ 0·5 cm). Elution with light petroleum (40–70°) yielded the *tetrahydro derivative* (VII) as an oil (23 mg). M^+ at *m/e* 316; NMR. δ (CCl_4) 7·25 (2H. bs. furan α-H). 7·11 (2H. bs. furan α-H). 6·16 (2H. bs. furan β-H). 2·35 (4H. t. J = 6 Hz. C_4H_3O—C<u>H</u>$_2$). 1·60–1·24 (16H. C<u>H</u>$_2$ and C<u>H</u>) and 0·85 (6H. d. J = 6 Hz. Me).

Anhydrofurospongin-1 (II; 10 mg) was similarly treated with Pd/C and decalin to give a product identical (MS. TLC and GLC) with VII.

Ozonolysis of anhydrofurospongin-1 (II). Anhydrofurospongin-1 (20 mg) in EtOAc (5 ml) was ozonized (2%

O_3) for 3 hr at $-15°$. After evaporation of solvent *in vacuo*, the ozonide was decomposed with water containing a few drops of H_2O_2. The mixture was extracted continuously for 5 hr with ether. The extract was concentrated and treated with CH_2N_2. After removal of solvent, the degradation products were analysed by GLC (5% SE-30 and 10% DEGS at 100° and 175°, respespectively) and found to comprise methyl succinate, methyl levulinate and methyl 5-oxo-hexanoate, by comparison with authentic samples.

$NaBH_4$-pyridine reduction of furospongin-2 (III) and isofurospongin-2 (IV). Furospongin-2 (50 mg), $NaBH_4$ (25 mg) and pyridine (5 ml) were kept at room temp for 24 hr. Water (20 ml) was added to the mixture, which was extracted with light petroleum (50 ml in 3 portions). The light petroleum soln was washed, dried (Na_2SO_4) and evaporated to give crude product, chromatographed on SiO_2 in benzene to yield furospongin-1 (I) (38 mg) identified by UV, IR, NMR, MS and TLC.

Isofurospongin-2 (25 mg), when treated with $NaBH_4$ and pyridine as described above, also yielded furospongin-1 (I) (13 mg), characterized by IR, MS and TLC.

CrO_3-pyridine oxidation of furospongin-1 (I). Furospongin-1 (200 mg) in pyridine (0·6 ml) cooled to 15° was added to the CrO_3-pyridine complex (4 ml).[8] The mixture was left at room temp for 3 days, poured into water, and ether extracted. The extract (189 mg) was purified by chromatography on SiO_2 (35 g) in benzene to give a product (140 mg). $[\alpha]_D = -1·04°$ ($CHCl_3$), identical (UV, IR, NMR and MS) with dihydrofurospongin-2 (V).

Metal-catalysed transfer-hydrogenation of dihydrofurospongin-2 (V). Dihydrofurospongin-2 (50 mg) was refluxed with 10% Pd/C (25 mg) and decalin (2 ml) for 2 hr. Working up as described above followed by chromatography in light petroleum–benzene (1:1) on SiO_2 (10 g) gave a product (30 mg). $[\alpha]_D = -0·85°$ ($CHCl_3$), identical (NMR, MS and GLC) with tetrahydrofurospongin-2.

REFERENCES

1 G. Cimino, S. De Stefano, L. Minale and E. Fattorusso, *Tetrahedron* **28**, 333 (1972)
2 R. B. Bates and D. M. Gale, *J. Am. Chem. Soc.* **82**, 5749 (1960); R. B. Bates, D. M. Gale and B. J. Gruner, *J. Org. Chem.* **28**, 1086 (1963)
3 T. Kubota, *Tetrahedron* **4**, 82 (1958)
4 A. Quilico, F. Piozzi and M. Pavan, *Ibid.* **1**, 177 (1957)
5 E. A. Brande, R. P. Linstead and P. W. D. Mitchell, *J. Chem. Soc.* 3578 (1954)
6 L. M. Jackman and R. H. Wiley, *Ibid.* 2881 (1960)
7 W. R. Jackson and A. Zurquivah, *Ibid.* 5280 (1965)
8 R. H. Cornforth, J. W. Cornforth and G. Popjak, *Tetrahedron* **18**, 1351 (1962)

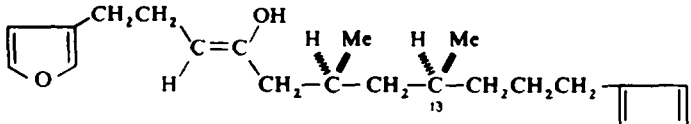
Note added in proof: The stereochemistry at C-13 of dihydrofurospongin-2 (V) was established on the basis of the correlation with furospongin-1 (I).

Originally, the configuration of furospongin-1 (I)* at C-13 was proposed on the basis that (+) α-methyladipic acid obtained on degration possessed R configuration.†

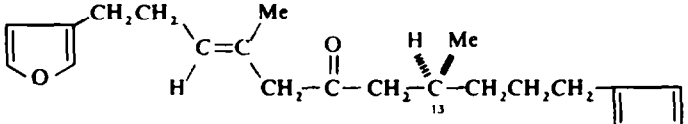
More recently, C. F. Wong *et al.*‡ have revised the stereochemistry of α-methyladipic acid, synthesizing the (−) (*R*)-isomer; therefore, the asymmetric centre C-13 of furospongin-1 (I) and accordingly of dihydro-

* *Tetrahedron* **27**, 4673 (1971)
† T. Kaneko et al., *Bull. Chem. Soc. Japan* **35**, 1149 (1962).
‡ *J. Org. Chem.* **35**, 517 (1970)

furospongin-2 (V) must have *S* configuration and consequently, the full structures, I and V, must be changed as depicted in a and b, respectively.



a, furospongin-1



b, dihydrofurospongin-2