140. New Furano-sesquiterpenoids from Mediterranean Sponges

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A mixture of sponges of the East Pyrenean Mediterranean is shown to contain the known sponge products longifolin (**1**), avarol ((+)-**3**), and avarone (**4**) and the terrestrial-plant product sesquirosefuran (**2**), besides to the new furano-sesquiterpenoids tavacfuran (= 3-methyl-2-[(3′*Z*)-3′-methyl-4′-(4″-methyl-2″-furyl)-3′-butenyl]furan; **5**) and tavacpallescensin (= 5,10-dihydro-6,9-dimethyl-4*H*-benzo[5,6]cyclohepta[1,2-*b*]furan; **6**) and the new furano-butenolide sesquiterpenoids tavacbutenolide-1 (= (±)-4-ethoxy-2-methyl-4-[(2′*E*)-2′-methyl-4′-(3″-methyl-2″-furyl)-2′-butenyl]-2-buten-4-olide; (±)-**7**) and tavacbutenolide-2 (= (±)-4-ethoxy-3-methyl-4-[(2′*E*)-3′-methyl-4′-(4″-methyl-2″-furyl)-2′-butenyl]-2-buten-4-olide; (±)-**8**). Structural assignments are based on NMR data and on the synthesis of the (*E*)-isomer of **5**. The sponge *Dysidea tupha* of the same area is also shown to contain the two sesquiterpenoids *ent*-furodysinin ((−)-**14**), which is enantiomeric to a product of a *Dysidea* sp. of Australian waters, and tuphabutenolide ((+)-**15**).

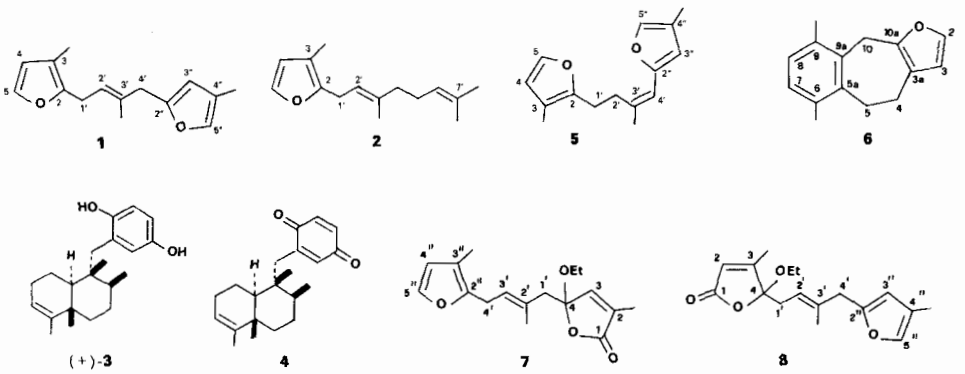
1. Introduction. – New furano-sesquiterpenoids of a wide variety of skeleton types have been isolated during the last decade from marine sponges of the class Demospongiae, subclass Ceractinomorpha [1] mainly of the family Dysideidae, order Dictyoceratida [2], but also from *Pleraplysilla spinifera,* order Dendroceratida [3], and *Microciona toxystila,* order Poecilosclerida [4].

We report here on some new furano-sesquiterpenoids and related butenolides isolated from what was collected and investigated as a mixture of sponges of the East Pyrenean area. Judging from the known compounds which have been isolated, this sponge mixture likely contains *Pleraplysilla spinifera* [3] and *Dysidea avara* [5], which are common hosts of this marine area. However, the new compounds which have also been isolated suggest the presence in our sponge mixture of other undetermined sponges as well.

A parallel investigation of the sponge *Dysidea tupha* poses problems of enantiomerism with sesquiterpenoids previously isolated from sponges of the same genus [6] [7].

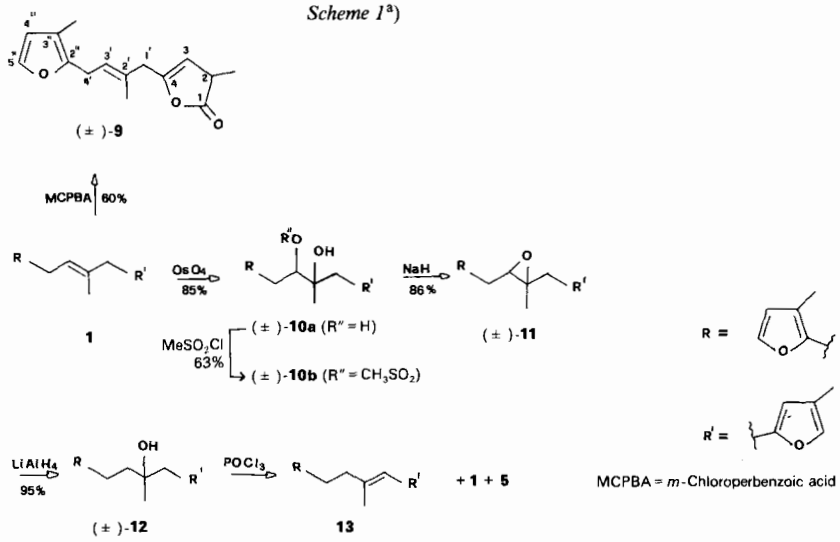
2. Results and Discussion. – Our mixture of sponges proved to contain the two known linear furano-sesquiterpenoids longifolin (**1**) and sesquirosefuran (**2**) and the two known rearranged drimanes avarol ((+)-**3**) and avarone (**4**) of mixed biogenesis. Compounds **3** and **4** have been previously isolated from a non-better described Mediterranean [8] collection of *D. avara,* whereas **1** was initially isolated from the terrestrial Japanese plant *Actinodaphne longifolia* (BLUME) (which also contains **2** [9]) and later from either the marine sponge *Pleraplysilla spinifera* [3a] and the nudibranch *Glossodoris gracilis* [3b].

Our mixture of sponges proved also to contain the new furano-sesquiterpenoids **5** and **6** and the new furano-butenolide sesquiterpenoids **7** and **8**. The isomer **5** of longifolin, which is named 'tavacfuran' from the place of collection of our sponge mixture, is



interesting for having the unusual situation, as regards terpenoids[1]), of an olefinic bond in the (*Z*)-configuration conjugated to a furan ring. The structure of **5** was deduced from NMR and UV data by comparison with **1**[2]). However, from this analysis the (*Z*)-configuration only rested on the ^{13}C-NMR low-field resonance (24.7 ppm) of the CH_3 group at the olefinic bond [10] whilst, owing to the complex environment around the conjugated olefinic bond, a comparison with the (*E*)-isomer of **5** would be both desirable and interesting. Therefore, we have undertaken the synthesis of the (*E*)-isomer of **5**.

Scheme 1[a])



[a]) Yields take into account recovered starting material.

[1]) Conjugated furans with either acetylenic or (*E*)-olefinic bonds at the C(*β*)-atom are well known from terrestrial plants [11].

[2]) Spectral ^{1}H-NMR assignment of **5** mainly rests on both double-resonance experiments and marked solvent effects of C_6D_6 with respect to $CDCl_3$. Full spectral ^{13}C-NMR assignments of both **1** and **5** were made possible by the comparison with **7** which mainly differs with respect to the butenolide moiety.

Initial attempts directed at isomerizing the rather unstable natural longifolin (**1**) with either oxalic acid or $BF_3 \cdot Et_2O$ [12] under mild conditions left **1** unchanged. Transition-metal complexes were not assayed owing to presumably [13] harsh conditions for **1**. We, therefore, envisaged to transpose the double bond into the conjugated position *via* oxygenation/β-elimination. Attempts directed at epoxidizing **1** with a peracid failed as the α,γ-disubstituted furan ring was oxydized instead giving (±)-**9** *(Scheme 1)*. This is not too surprising in view of lack of systematization of these reactions [14]. Therefore, we turned to the idea of saturating the central chain of **1** while placing a leaving group at C(3') in the hope that a product-determined β-elimination would preferentially place a (*E*)-double bond at the conjugated C(3'),C(4') position. This was accomplished, as shown in *Scheme 1*, by hydroxylation of the double bond of **1** with osmium tetroxide to give (±)-**10a** which was mesylated at the secondary alcoholic function to give (±)-**10b**. The latter, on treatment with NaH, gave the epoxide (±)-**11** which was reduced to the tertiary alcohol (±)-**12** by $LiAlH_4$. Though yields were good up to this point; to our disappointment, the final β-elimination step proved non-regioselective under a variety of conditions. However, $POCl_3$-induced elimination with (±)-**12** gave, besides **5**, **1** and an uninvestigated product, the desired **13** in sufficient amount to determine that the ^{13}C-NMR resonance of CH_3–C(3') is at higher field (18.5 ppm) than with **5**. In accordance, on going from **5** to **13** C(3) undergoes a marked low-field shift for release of steric crowding in **5**. Beyond proving the (*Z*)-configuration of **5**, **13** and **5** constitute useful models for future assessments by ^{13}C-NMR spectroscopy of the configuration of conjugated furanoterpenoids.

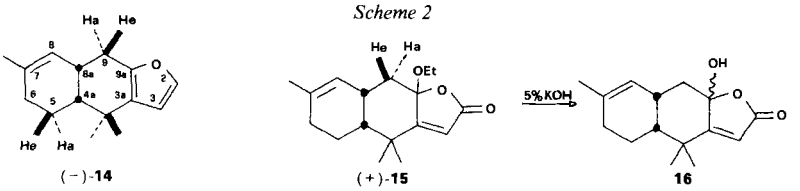
The structures of the two butenolides 'tavacbutenolide-1' (**7**) and 'tavacbutenolide-2' (**8**) were secured from a detailed evaluation of the NMR data in comparison with **1**. Most likely **7** and **8** have incorporated the ethoxy group from the solvent during extraction.

Structure **6** for 'tavacpallescensin' was deduced from NMR data in comparison with both pallescensin-E, which is the 6,7-dimethyl isomer isolated from the Mediterranean *Dysidea pallescens* [2b], and the unnatural stereoisomer of pallescensin-E with the furan O-atom in place of C(3) [2c]. In fact, deshielding of the isolated methylene protons (CH_2(10)) and the clear A_2B_2 pattern of the two vicinal CH_2 groups, strongly support structure **6**.

Sesquirosefuran (**2**), which we have detected for the first time in the marine environment, is a conceivable precursor of **6**. Joining in **2** the CH_3 group at C(3) with one at C(7'), and C(2')–C(7') coupling followed by a 1,2-CH_3 migration formally accounts for the biogenesis of **6**. Alternatively, allylic oxidation at C(7) of pallescensin-F [2b], followed by sequential CH_3 migrations, could also formally explain the formation of **6**. However, pallescensin-F, though being a likely precursor of pallescensin-E [2b], has not been isolated from our sponge mixture.

Structure (–)-**14** (or its enantiomer) for a product that we have isolated from *D. tupha* rests on detailed 1D- and 2D-NMR data which exactly match those less detailed reported

Scheme 2



(–)-**14** (+)-**15** **16**

for furodysinin, isolated from a *Dysidea* sp. of Australian waters [6], and the structure of which was unequivocally proven by X-ray diffraction analysis [6]. However, it is interesting that the product of *D. tupha* has the opposite optical rotation of furodysinin so that the two products from different species of the genus *Dysidea* must be enantiomeric. Therefore, (−)-**14** is appropriately named '*ent*-furodysinin'.

D. tupha has now been proved to contain also tuphabutenolide ((+)-**15**), the structure of which was derived from NMR and IR analysis in comparison with (−)-**14**. Also, what appears from NMR data to be the hydroxy analogue **16** of (+)-**15** was previously isolated from the Bermudian *Dysidea etheria* and named furodysinin lactone [7][3]). The latter sponge was also previously shown to contain furodysinin for which, as well as for furodysinin lactone, no chiroptical data were reported [7]. Therefore, for the time being it is precluded to know whether the Bermudian *D. etheria* [7] contains (+)-**14**, as the Australian *Dysidea* sp. [6], or rather (−)-**14**, as the East Pyrenean *D. tupha*. In this situation we have not undertaken the separation of the diastereoisomeric mixture **16** obtained by saponification of (+)-**15** *(Scheme 2)*, as there would be no chiroptical comparison with furodysinin lactone of *D. etheria* [7].

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Experimental Part

1. *General.* Syntheses were carried out in dried solvents under N_2. Org. extracts were dried over Na_2SO_4, and yields take into account recovered starting material. All evaporations were carried out at reduced pressure. Flash chromatography was carried out by suction with *Merck LiChroprep-Si-60*, 15–25 μm, and TLC on *Merck-60-F-254* silica-gel plates. Silica-gel HPLC and reverse-phase HPLC were performed with 25 × 1 cm *Merck-LiChrosorb* columns and *Si-60* (7 μm) or *RP-18* (7 μm), resp., with 5 ml/min solvent flux, monitoring by UV absorption at 225 nm. Reverse-phase eluates were extracted with either hexane or pentane, and the resulting org. phase was dried over phase-separation filters. For polarimetric investigations, a *JASCO-DIP-181* polarimeter was utilized. UV (λ_{max} in nm, ε in mol^{-1} l cm^{-1}) and IR ($\tilde{\nu}_{max}$ in cm^{-1}): *Beckmann-DB-4* and *Perkin-Elmer-337* spectrometer, resp. NMR: *Varian-CFT20* (^{13}C-NMR at 20 MHz with a microinsert, ^{1}H-NMR at 80 MHz) or, for compound (−)-**14** only, *Varian-XL-200* (^{1}H-NMR at 200 MHz) spectrometer; δ's (ppm) relative to internal Me_4Si (= 0 ppm) and J's in Hz; multiplicities for ^{13}C-NMR were obtained by off-resonance decoupling. MS (EI): home-made spectrometer built on a *ELFS-4-162-8-Extranuclear* quadrupole.

2. *Isolations.* A fresh sponge mixture (collected at Roche Tavac, Eastern Pyrenean Sea, at a depth of 25 m, on July 26th, 1983) freed of H_2O by hand pressing was soaken in 95% EtOH, homogenized, and paper filtered by repeatedly adding fresh 95% EtOH to the residue on the filter (dry residue sponge weight 240 g). The EtOH extract was evaporated at r.t. at reduced pressure and repeatedly extracted with hexane. The extracts were evaporated at reduced pressure to leave 2.1 g of oily residue which was first subjected to flash chromatography on 130 g of silica gel starting with hexane and following with increasing percentages of AcOEt. Monitoring the eluates by TLC with either a 254-nm UV lamp or the *Ehrlich* reagent or, finally, $Ce(SO_4)_2$, gave a less polar and a more polar series of eluates. The first one was subjected to silica-gel HPLC (hexane), each of the resulting fractions containing partly separated **2**, **5**, **6**, and **1**, in the order of increasing polarity, being then further subjected to reverse-phase HPLC ($MeCN/H_2O$ 78:22) to get, on hexane extraction and evaporation of the extracts at r.t. at reduced pressure, pure **2** (0.006 g), **5** (0.050 g), **6** (0.004 g), and **1** (*ca.* 1 g). The more polar eluates from the flash chromatography were subjected to reverse-phase HPLC ($MeOH/H_2O$ gradient elution) to get first a partially separated mixture which

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[3]) γ-Hydroxybutenolide terpenoids have already been isolated from other sponges belonging to the Dictyoceratida [7] [15].

was further separated by silica-gel HPLC (hexane/(i-Pr)$_2$O 75:25) to get pure **8** (0.002 g) and **7** (0.013 g). Subsequent HPLC reverse-phase eluates contained pure (+)-**3** and **4** which were deliberately only in part recovered, 0.030 g and 0.010 g, resp. The order of increasing polarity on silica gel is **4**, **7**, **8**, and (+)-**3**.

A collection of *D. tupha*, taken at Roche Torreille at a depth of 30 m in August 1984, and which proved identical to a previous collection of July 1983 in the same area, was similarly extracted to give 0.71 g of oily residue. Gradient-elution flash chromatography (hexane to AcOEt) gave first (−)-**14** and then (+)-**15** which were further purified by silica gel (hexane) and reverse-phase (CH_3CN/H_2O 75:25) HPLC, resp., leading to (−)-**14** (0.003 g) and (+)-**15** (0.012 g).

3. *Longifolin* (= *3-Methyl-2-[(2'E)-3'-methyl-4'-(4''-methyl-2''-furyl)-2'-butenyl]furan*; **1**). ^{1}H-NMR ($CDCl_3$): 1.71 (br. *s*, CH_3–C(3')); 1.96 (br. *s*, CH_3–C(4''), CH_3–C(3)); 3.27 (*s*, 2H–C(4')); 3.32 (*d*, *J* = 7.4, 2H–C(1')); 5.26 (br. *t*, *J* = 7.4, H–C(2')); 5.88 (br. *s*, H–C(3'')); 6.15 (*d*, *J* = 1.7, H–C(4)); 7.06 (br. *s*, H–C(5'')); 7.21 (*d*, *J* = 1.7, H–C(5)). ^{1}H-NMR (C_6D_6): 1.60 (br. *d*, *J* = 0.9, CH_3–C(3')); 1.78 (*d*, *J* = 1.3, CH_3–C(4'')); 1.80 (*s*, CH_3–C(3)); 3.17 (*s*, 2H–C(4')); 3.22 (*d*, *J* = 7.6, 2H–C(1')); 5.46 (br. *t*, *J* = 7.6, H–C(2')); 5.76 (br. *s*, H–C(3'')); 5.99 (*d*, *J* = 1.8, H–C(4)); 6.92 (*m*, H–C(5'')); 7.07 (*d*, *J* = 1.8, H–C(5)). ^{13}C-NMR (C_6D_6): 9.7 (*q*, CH_3–C(4''), CH_3–C(3)); 15.9 (*q*, CH_3–C(3')); 25.7 (*t*, C(1')); 38.7 (*t*, C(4')); 109.2 (*d*, C(3'')); 113.2 (*d*, C(4)); 113.9 (*s*, C(4'')); 120.7 (*s*, C(3)); 122.9 (*d*, C(2')); 133.4 (*s*, C(3')); 138.2 (*d*, C(5'')); 140.1 (*d*, C(5)); 149.9 (*s*, C(2)); 154.5 (*s*, C(2'')). MS: 230 (20, M^+), 135 (100), 95 (25).

4. *Tavacfuran* (= *3-Methyl-2-[(3'Z)-3'-methyl-4'-(4''-methyl-2''-furyl)-3'-butenyl]furan*; **5**). Optically inactive, colourless liquid. UV (MeOH): 205 (6500), 224 (6800), 264 (12400), 272 (13600), 284 (10000). IR (film): 885*s*, 1080*s*, 1650*m*. ^{1}H-NMR ($CDCl_3$): 1.84 (*d*, *J* = 1.4, CH_3–C(3')); 1.97 (*s*, CH_3–C(3)); 2.00 (*d*, *J* = 1.2, CH_3–C(4'')); 2.69 (*m*, 2H–C(2'), 2H–C(1')); 6.04 (br. *s*, H–C(4'), H–C(3'')); 6.15 (*d*, *J* = 1.8, H–C(4)); 7.09 (br. *s*, H–C(5'')); 7.22 (*d*, *J* = 1.9, H–C(5)). ^{1}H-NMR (C_6D_6): 1.64 (*d*, *J* = 1.3, CH_3–C(3')); 1.78 (*d*, *J* = 1.0, CH_3–C(4'')); 1.83 (*s*, CH_3–C(3)); 2.76 (*s*, 2H–C(2'), 2H–C(1')); 6.02 (br. *s*, H–C(3''), H–C(4)); 6.08 (*m*, H–C(4')); 6.92 (br. *s*, H–C(5'')); 7.10 (*d*, *J* = 1.9, H–C(5)). ^{13}C-NMR (C_6D_6): 9.6 (*q*, CH_3–C(3), CH_3–C(4'')); 24.7 (*q*, CH_3–C(3')); 24.8 (*t*, C(1')); 33.0 (*t*, C(2')); 110.5 (*d*, C(3'')); 113.1 (*d*, C(4)); 114.1 (*s*, C(4'')); 115.8 (*d*, C(4')); 121.4 (*s*, C(3)); 137.4 (*s*, C(3')); 137.9 (*d*, C(5'')); 140.0 (*d*, C(5)); 151.1 (*s*, C(2)); 153.6 (*s*, C(2'')). MS: 230 (47, M^+), 135 (100), 107 (28), 95 (40), 91 (30).

5. *Tavacbutenolide-1* (= *(±)-4-Ethoxy-2-methyl-4-[(2'E)-2'-methyl-4'-(3''-methyl-2''-furyl)-2'-butenyl]-2-buten-4-olide*; *(±)-***7**). Optically inactive, colourless liquid. UV (MeOH): 225 (6500). IR (film): 1758*s*. ^{1}H-NMR ($CDCl_3$): 1.15 (*t*, *J* = 7.0, CH_3CH_2O); 1.75 (br. *s*, CH_3–C(2')); 1.88 (*d*, *J* = 1.6, CH_3–C(2)); 1.94 (*s*, CH_3–C(3'')); 2.60 (br. *s*, 2H–C(1')); 3.25 (*d*, *J* = 6.8, 2H–C(4')); 3.33, 3.47 (*B* and *A* of *ABX*$_3$, J_{AB} = 9.5, $J_{AX} = J_{BX}$ = 7.0, CH_3CH_2O); 5.32 (br. *t*, *J* = 6.8, H–C(3')); 6.14 (*d*, *J* = 1.8, H–C(4'')); 6.68 (*q*, *J* = 1.6, H–C(3)); 7.19 (*d*, *J* = 1.8, H–C(5'')). ^{1}H-NMR (C_6D_6): 0.93 (*t*, *J* = 7.0, CH_3CH_2O); 1.56 (*d*, *J* = 1.7, CH_3–C(2)); 1.66 (br. *s*, CH_3–C(2')); 1.78 (*s*, CH_3–C(3'')); 2.47 (br. *s*, 2H–C(1')); 3.13 (*d*, *J* = 6.7, 2H–C(4')); 2.95, 3.21 (*B* and *A* of *ABX*$_3$, J_{AB} = 9.3, $J_{AX} = J_{BX}$ = 7.0, CH_3CH_2O); 5.27 (br, *t*, *J* = 6.7, H–C(3')); 6.00 (*m*, H–C(4''), H–C(3)); 7.07 (*d*, *J* = 1.8, H–C(5'')). ^{13}C-NMR (C_6D_6): 9.7 (*q*, CH_3–C(3'')); 10.2 (*q*, CH_3–C(2)); 15.2 (*q*, CH_3CH_2O)); 17.7 (*q*, CH_3–C(2')); 25.5 (*t*, C(4')); 47.5 (*t*, C(1')); 59.0 (*t*, CH_3CH_2O); 108.4 (*s*, C(4)); 113.1 (*d*, C(4'')); 121.5 (*s*, C(3'')); 126.8 (*d*, C(3')); 130.6 (*s*, C(2)); 133.4 (*s*, C(2')); 140.2 (*d*, C(5'')); 145.9 (*d*, C(3)); 149.7 (*s*, C(2'')); 170.7 (*s*, C(1)). MS: 244 (2, M^+ − EtOH), 149 (7), 141 (57), 113 (100), 95 (32).

6. *Tavacbutenolide-2* (= *(±)-4-Ethoxy-3-methyl-4-[(2'E)-3'-methyl-4'-(4''-methyl-2''-furyl)-2'-butenyl]-2-buten-4-olide*; *(±)-***8**). Optically inactive, colourless liquid. ^{1}H-NMR ($CDCl_3$): 1.20 (*t*, *J* = 7.0, CH_3CH_2O); 1.62 (br. *s*, CH_3–C(3')); 1.95 (*d*, *J* = 1.6, CH_3–C(3)); 1.96 (br. *s*, CH_3–C(4'')); 2.62, 2.72 (*B* and *A* of *ABX*, J_{AB} = 14.0, $J_{AX} = J_{BX}$ = 6.8, 2H–C(1')); 3.21 (br. *s*, 2H–C(4')); 3.27, 3.59 (*B* and *A* of *ABX*$_3$, J_{AB} = 9.5, $J_{AX} = J_{BX}$ = 7.0, CH_3CH_2O); 5.14 (br. *t* as *X* of *ABX*, $J_{AX} = J_{BX}$ = 6.8, H–C(2')); 5.84 (br. *s*, H–C(3'')); 5.87 (*m*, H–C(2)); 7.04 (*m*, H–C(5'')).

7. *Sesquirosefuran* (**2**). ^{1}H-NMR and MS data closely corresponding to literature data [8].

8. *Tavacpallescensin* (= *5,10-Dihydro-6,9-dimethyl-4H-benzo[5,6]cyclohepta[1,2-b]furan*; **6**). Optically inactive, colourless oil. UV (MeOH): 222 (11400). ^{1}H-NMR ($CDCl_3$): 2.35 (*s*, CH_3–C(6), CH_3–C(9)); 2.70 (*m*, 2H–C(4)); 3.02 (*m*, 2H–C(5)); 4.05 (br. *s*, 2H–C(10)); 6.10 (*d*, *J* = 1.8, H–C(3)); 6.93 (*s*, H–C(7), H–C(8)); 7.16 (*d*, *J* = 1.8, H–C(2)). ^{1}H-NMR (C_6D_6): 2.10, 2.13 (2*s*, CH_3–C(6), CH_3–C(9)); 2.40 (B_2 of A_2B_2, 2H–C(4)); 2.76 (A_2 of A_2B_2, 2H–C(5)); 3.94 (br. *s*, 2H–C(10)); 5.94 (*d*, *J* = 1.8, H–C(3)); 6.88, 6.80 (*AB*, J_{AB} = 8.0, H–C(7), H–C(8)); 7.03 (*d*, *J* = 1.8, H–C(2)). ^{13}C-NMR (C_6D_6): 20.0, 20.3 (2*q*, CH_3–C(6), CH_3–C(9)); 24.4 (*t*, C(4)); 27.4, 28.0 (2*t*, C(5), C(10)); 112.5 (*d*, C(3)); 117.9 (*s*, C(3a)); 128.3, 128.6 (2*d*, C(7), C(8)); 132.1, 133.2 (2*s*, C(6), C(9)); 138.1, 139.5 (2*s*, C(5a), C(9a)); 139.3 (*d*, C(2)); 148.6 (*s*, C(10a)). MS: 212 (88, M^+), 197 (100), 169 (29), 115 (9).

9. *Avarol* ((+)-**3**). $[\alpha]_d = +8.2°$ ($c = 1.44$, $CHCl_3$). The ^{1}H-NMR data matched those in [5].

10. *Avarone* (**4**). The ^{1}H-NMR data matched those in [5]. We have not measured $[\alpha]_D$ since no comparison with previously isolated **4** could be made [5].

11. *Peracid Oxydation of* **1**. To a soln. of **1** (0.052 g, 0.23 mmol) in 1 ml of CH_2Cl_2 was added 85% *m*-chloroperbenzoic acid (0.052 g) in 1.5 ml of CH_2Cl_2 at r.t. After 3 h, $NaHSO_3$ was added followed by $NaHCO_3$, and the mixture was extracted with Et_2O, dried over Na_2SO_4, evaporated, and the residue subjected to reverse-phase HPLC with MeOH/H_2O 7:3 to give *(±)-2-methyl-4-[(2'E)-2'-methyl-4'-(3"-methyl-2"-furyl)-2'-butenyl]-3-buten-4-olide* ((±)-**9**; 0.005 g, 60%) besides unreacted **1** (0.043 g). (±)-**9**: ^{1}H-NMR ($CDCl_3$): 1.32 (*d*, $J = 7.6$, CH_3–C(2)); 1.75 (br. *s*, CH_3–C(2')); 1.96 (*s*, CH_3–C(3")); 2.98 (br. *s*, 2H–C(1')); 3.31 (br. *d*, $J = 6.9$, 2H–C(4')); 5.16 (br. *s*, H–C(3)); 5.43 (br. *t*, $J = 6.9$, H–C(3')); 6.15 (*m*, H–C(4")); 7.21 (*m*, H–C(5")).

12. *Synthesis of* **13**, *the (E)-Isomer of* **5**. To a soln. of **1** (0.182 g, 0.78 mmol) in 6 ml of pyridine OsO_4 (0.2 g, 0.78 mmol) was added and the resulting soln. stirred at r.t. for 2 h. Then, 0.60 g of $NaHSO_3$ in 20 ml of H_2O/pyridine 5:1 were added, and the resulting soln. was extracted with CH_2Cl_2. The org. phase was shaken with aq. $CuSO_4$, then with H_2O, dried, and evaporated, and the residue was subjected to flash chromatography with hexane/AcOEt 8:2. The first eluates gave unreacted **1** (0.030 g) whilst subsequent eluates gave *2-methyl-4-(3'-methyl-2'-furyl)-1-(4"-methyl-2"-furyl)-2,3-butanediol* ((±)-**10a**; 0.149 g, 85%). White solid. ^{1}H-NMR ($CDCl_3$): 1.21 (*s*, CH_3–C(2)); 1.99 (*s*, CH_3–C(4"), CH_3–C(3')); 2.3 (*d*, $J = 3.4$) and 2.4 (*s*, 2 OH); 2.76 (*m*, 2H–C(4)); 2.85 (br. *s*, 2H–C(1)); 3.72 (*m*, H–C(3)); 5.99 (br. *s*, H–C(3")); 6.19 (*m*, H–C(4')); 7.10 (br. *s*, H–C(5")); 7.25 (*m*, partly covered by solvent signal, H–C(5')). MS: 246 (1, $M^+ - H_2O$), 151 (12), 95 (100).

To a soln. of (±)-**10a** (0.144 g, 0.54 mmol) in 1.2 ml of pyridine was added 42 µl of CH_3SO_2Cl, and the soln. was stirred at 0° overnight. Then, 0.01M aq. HCl was added, the mixture extracted with Et_2O, and the org. phase washed with H_2O, dried, and evaporated to give *3-hydroxy-3-methyl-1-(3'-methyl-2'-furyl)-4-(4"-methyl-2"-furyl)-2-butanyl methanesulfonate* ((±)-**10b**; 0.117 g, 63%). Oil. ^{1}H-NMR ($CDCl_3$): 1.25 (*s*, CH_3–C(3)); 1.99 (*s*, CH_3–C(4"), CH_3–C(3')); 2.59 (*s*, CH_3SO_2); 2.88 (br. *s*, 2H–C(4)); 3.00 (*m*, 2H–C(1)); 4.80 (*dd*, $J = 13.2$, 7.2, H–C(2)); 6.07 (br. *s*, H–C(3")); 6.18 (*m*, H–C(4')); 7.13 (br. *s*, H–C(5")); 7.28 (*m*, partly covered by solvent signal, H–C(5')).

To a soln. of NaH (0.008 g, 0.33 mmol) in 1.5 ml of THF was added the equimolar amount of (±)-**10b** and the soln. was refluxed for 3 h. The mixture was evaporated, and, after addition of H_2O, extracted with Et_2O. The org. phase was washed with H_2O, dried, and evaporated, and the residue flash chromatographed with hexane to give first *2-[2',3'-epoxy-3'-methyl-4'-(4"-methyl-2"-furyl)butyl]-3-methylfuran* ((±)-**11**; 0.055 g, 86%), followed by unreacted (±)-**10b** (0.026 g). (±)-**11**: Colourless oil. ^{1}H-NMR ($CDCl_3$): 1.25 (*s*, CH_3–C(3')); 1.98 (*s*, CH_3–C(4") and CH_3–C(3)); 2.96 (*m*, 2H–C(4'), H–C(2'), 2H–C(1')); 5.97 (br. *s*, H–C(3")); 6.18 (*m*, H–C(4')); 7.10 (br. *s*, H–C(5")); 7.25 (*m*, partly covered by solvent signal, H–C(5)). MS: 246 (2, M^+), 151 (50), 95 (100).

To a soln. of $LiAlH_4$ (0.033 g, 0.84 mmol) in 2.5 ml of THF was added (±)-**11** (0.054 g, 0.21 mmol) in 0.5 ml of THF, and the soln. was refluxed for 2 h. Excess hydride was destroyed with H_2O, the mixture filtered, and the filtrate extracted with Et_2O. The org. layer was washed with H_2O, dried, and evaporated and the residue flash chromatographed with hexane/AcOEt 8:2 to give *2-methyl-4-(3'-methyl-2'-furyl)-1-(4"-methyl-2"-furyl)-2-butanol* ((±)-**12**; 0.052 g, 95%). Oil. ^{1}H-NMR ($CDCl_3$): 1.22 (*s*, CH_3–C(2)); 1.76 (*m*, 2H–C(3)); 1.96, 1.99 (2*s*, 2 CH_3); 2.70 (*m*, 2H–C(4)); 2.77 (br. *s*, 2H–C(1)); 5.98 (br. *s*, H–C(3")); 6.14 (*m*, H–C(4')); 7.10 (br. *s*, H–C(5")); 7.20 (*m*, H–C(5')). MS: 230 (1, $M^+ - H_2O$), 135 (7), 95 (100).

To a soln. of (±)-**12** (0.049 g, 0.20 mmol) in 2 ml of pyridine was added, at 0°, 47 µl of freshly distilled $POCl_3$, and the soln. was stirred at r.t. overnight. After addition of H_2O, the mixture was extracted with Et_2O, the org. phase washed with H_2O, dried, and evaporated, and the residue (0.035 g) subjected to reverse-phase HPLC with CH_3CN/H_2O 82:18 to give, in roughly equal amounts, first **1**, followed, in the given order, by an uninvestigated product, **13**, and **5**. This sample of **13** was further subjected to HPLC to give 0.004 g of pure *3-methyl-2-[(3'E)-3'-methyl-4'-(4"-methyl-2"-furyl)-3'-butenyl]furan* **13**. Colourless oil. ^{1}H-NMR ($CDCl_3$): 1.94 (*s*, CH_3–C(3)); 1.97 (br. *s*, CH_3–C(3')); 2.01 (*d*, $J = 1.1$, CH_3–C(4")); 2.35 (*m*, 2H–C(2')); 2.70 (*m*, 2H–C(1')); 6.02 (*d*, $J = 1.1$, H–C(3")); 6.04 (br. *s*, H–C(4')); 6.14 (*d*, $J = 1.9$, H–C(4)); 7.09 (br. *s*, H–C(5")); 7.21 (*d*, $J = 1.9$, H–C(5)). ^{1}H-NMR (C_6D_6): 1.77 (*s*, CH_3–C(3), CH_3–C(4")); 1.88 (br. *s*, CH_3–C(3')); 2.37 (*m*, 2H–C(2')); 2.57 (*m*, 2H–C(1')); 5.96 (br. *s*, H–C(3")); 5.98 (*d*, $J = 1.9$, H–C(4)); 6.11 (br. *s*, H–C(4')); 6.92 (br. *s*, H–C(5")); 7.08 (*d*, $J = 1.9$, H–C(5)). ^{13}C-NMR (C_6D_6): 9.7 (*q*, CH_3–C(4"), CH_3–C(3)); 18.5 (*q*, CH_3–C(3')); 25.4 (*t*, C(1')); 39.7 (*t*, C(2')); 110.9 (*d*, C(3")); 113.0 (*d*, C(4)); 114.2 (*s*, C(4")); 115.6 (*d*, C(4')); 121.4 (*s*, C(3)); 136.9 (*s*, C(3')); 137.9 (*d*, C(5")); 140.1 (*d*, C(5)); 150.8 (*s*, C(2)); 154.1 (*s*, C(2")). MS: 230 (1, M^+), 135 (26), 107 (18), 95 (100), 91 (28).

13. ent-*Furodysinin* *(= (−)-4,4a,5,6,8a,9-Hexahydro-4,4,7-trimethyl-cis-naphtho[2,3-b]furan; (−)-***14**). $[\alpha]_D = -47.8°$ ($c = 0.096$, $CHCl_3$). ^{1}H-NMR (200 MHz, C_6D_6): 1.13, 1.15 (2*s*, 2 CH_3–C(4)); 1.22 (*m*, H_a–C(5));

1.42 (*m*, H–C(4a)); 1.52 (*m*, H_e–C(5)); 1.56 (br. *s*, CH_3–C(7)); 1.82 (*m*, 2H–C(6)); 2.35 (br. *dd*, J_{gem} = 15.4, *J*(9,8a) = 10.0, H_a–C(9)); 2.54 (*m*, H–C(8a)); 2.71 (*dd*, J_{gem} = 15.4, *J*(9,8a) = 5.7, H_e–C(9)); 5.47 (br. *d*, *J*(8,8a) = 5.8, H–C(8)); 6.14 (*d*, *J*(2,3) = 2.0, H–C(3)); 7.13 (br. *s*, H–C(2)). ^{1}H-COSY experiments at low resolution showed correlations confirming all above ^3J's. MS: 216 (19, M^+), 201 (2), 122 (100, probably by scission at C(8a)–C(9) and C(4a)–C(4): *retro-Diels-Alder*-oxygenated fragment).

14. *Tuphabutenolide (= (+)-9a-Ethoxy-4a,5,6,8a,9,9a-hexahydro-4,4,7-trimethyl-4*H-cis-*naphtho[2,3-b]-furan-1-one;* (+)-**15**). Colourless oil. $[\alpha]_D$ = +221.6° (*c* = 0.50, MeOH). UV (MeOH): 228 (8100). IR (film): 1750. ^{1}H-NMR ($CDCl_3$): 1.18 (*t*, *J* = 7.0, CH_3CH_2O); 1.22, 1.35 (2*s*, 2 CH_3–C(4)); 1.61 (br. *s*, CH_3–C(7)); 1.5–2.2 (series of *m*, H–C(4a), 2H–C(5), 2H–C(6), H_a–C(9)); 2.34 (*dd*, J_{gem} = 12.2, *J*(9,8a) = 3.7, H_e–C(9)); 2.7 (*m*, H–C(8a)); 3.22, 3.53 (*B* and *A* of ABX_3, J_{AB} = 10.0, $J_{AX} = J_{BX}$ = 7.0, CH_3CH_2O); 5.35 (br. *d*, *J*(8,8a) = 5.7, H–C(8)); 5.77 (*s*, H–C(3)). ^{13}C-NMR (C_6D_6): 14.9 (*q*, CH_3CH_2O); 18.7 (*t*, C(5)); 23.3 (*q*, CH_3–C(7)); 25.1, 25.9 (2*q*, 2 CH_3–C(4)); 30.5 (*d*, C(8a)); 31.3 (*t*, C(6)); 38.5 (*s*, C(4)); 41.0 (*t*, C(9)); 47.8 (*d*, C(4a)); 58.4 (*t*, CH_3CH_2O); 107.0 (*s*, C(9a)); 117.6 (*d*, C(3)); 124.2 (*d*, C(8)); 133.9 (*s*, C(7)); 168.8 (*s*, C(3a)); 172.4 (*s*, C(2)). MS: 276 (0.1, M^+), 230 (100, M^+ – EtOH), 215 (46, 230 – Me), 202 (40, 230 – CO), 187 (19), 174 (12), 136 (20), 91 (18), 41 (15).

15. *Hydrolysis of (+)-***15**. A soln. of (+)-**15** (0.005 g) in 2 ml of 5% KOH in MeOH was refluxed for 1 h, then cooled and slightly acidified with 2M H_2SO_4. The crude mixture of diastereoisomers **16** was extracted with Et_2O and separated by TLC with hexane/Et_2O 6:4. ^{1}H-NMR ($CDCl_3$, **16**): 4*s* for 4 CH_3 at sat. C-atoms.

REFERENCES

[1] P.R. Bergquist, R.J. Wells, in 'Marine Natural Products – Chemical and Biological Perspectives', Ed. P.J. Scheuer, Academic Press, New York, 1983, Vol. V, p. 1; L. Minale, ibid., 1978, Vol. I, p. 175; L. Minale, G. Cimino, S. De Stefano, G. Sodano, in 'Progress in the Chemistry of Organic Natural Products', Eds. W. Herz, H. Grisebach, and G.W. Kirby, Springer Verlag, Wien, 1976, Vol. 33, p. 1.

[2] a) G. Guella, A. Guerriero, F. Pietra, *Helv. Chim. Acta* **1985,** *68*, 39; b) G. Cimino, S. De Stefano, A. Guerriero, L. Minale, *Tetrahedron Lett.* **1975,** 1421; c) R. Baker, R.J. Sims, *J. Chem. Soc., Perkin Trans. 1* **1981,** 3087.

[3] a) G. Cimino, S. De Stefano, L. Minale, E. Trivellone, *Tetrahedron Lett.* **1975,** 3727; b) G. Cimino, S. De Stefano, S. De Rosa, G. Sodano, G. Villani, *Bull. Soc. Chim. Belg.* **1980,** *89*, 1069.

[4] G. Cimino, S. De Stefano, A. Guerriero, L. Minale, *Tetrahedron Lett.* **1975,** 3723.

[5] L. Minale, R. Riccio, G. Sodano, *Tetrahedron Lett.* **1974,** 3401; S. de Rosa, L. Minale, R. Riccio, G. Sodano, *J. Chem. Soc., Perkin Trans. 1* **1976,** 1408.

[6] R. Kazlauskas, P.T. Murphy, R.J. Wells, J.J. Daly, P. Schoenholzer, *Tetrahedron Lett.* **1978,** 4951.

[7] S.H. Grode, J.H. Cardellina II, *J. Nat. Prod.* **1984,** *47*, 76.

[8] G. Cimino, in 'Marine Natural Products Chemistry', Eds. D.J. Faulkner and W.H. Fenical, Plenum Press, New York, 1977, p. 78.

[9] N. Hayashi, H. Komae, S. Eguchi, M. Nahayama, S. Hayshi, T. Sakao, *Chem. Ind.* **1972,** 572.

[10] P.A. Couperus, A.D.H. Clague, J.P.C.M. van Dongen, *Org. Magn. Reson.* **1976,** *8*, 4266.

[11] G. Pattenden, in 'Fortschritte der Chemie Organischer Naturstoffe', Eds. W. Herz, H. Grisebach, and G.W. Kirby, Springer Verlag, Wien, 1978, p. 140.

[12] G.H. Whitham, in 'Comprehensive Organic Chemistry', Eds. D.H.R. Barton and W.D. Ollis, Pergamon Press, Oxford, 1979, Vol. 1, p. 167.

[13] H.M. Colquhun, J. Holton, D.J. Thompson, M.V. Twigg, 'New Pathways for Organic Synthesis. Practical Applications of Transition Metals', Plenum Press, New York, 1984.

[14] S.P. Tanis, P.M. Herrington, *J. Org. Chem.* **1983,** *48*, 4572; Y.S. Rao, *Chem. Rev.* **1976,** *76*, 625.

[15] G. Cimino, S. De Stefano, L. Minale, *Experientia* **1974,** *30*, 18.