be placed at C-1. Incidentally, non-sulfated polyprenylhydroquinones were isolated from the Mediterranean sponge *Ircinia spinosula*[11].

Compound **1** is inhibitory not only against H,K-ATPase with an IC_{50} of 4.6×10^{-6} M but also against secretion of gastric acid in rats (po. 54% inhibition at 300 mg/kg). However, no antiulcer activity in rats was observed at 300 mg/kg. It should also be noted that **1** inhibits phospholipase A_2 with an IC_{50} of 1.8×10^{-6}M[12].

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(+)-Curcuphenol and dehydrocurcuphenol, novel sesquiterpenes which inhibit H,K-ATPase, from a marine sponge *Epipolasis* sp.[1]

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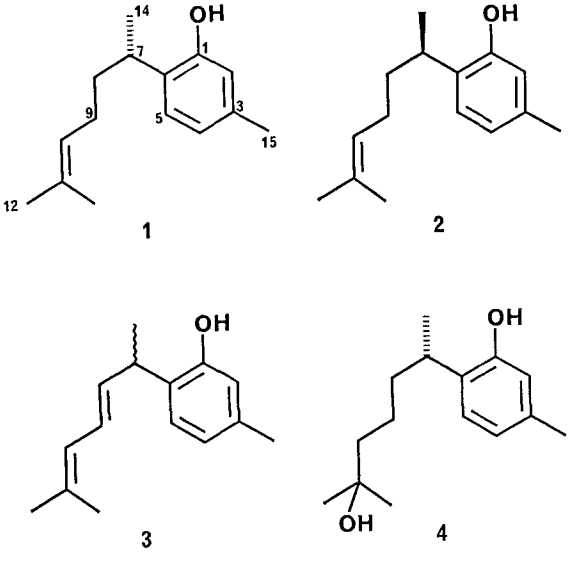
Summary. Two H,K-ATPase inhibitors and an inactive related compound have been isolated from a marine sponge *Epipolasis* sp. They are aromatic sesquiterpene α-curcumenes.
Key words. Marine sponge; *Epipolasis;* curcuphenol; H,K-ATPase inhibitor; gastric secretion.

In the course of our search for bioactive metabolites from Japanese marine invertebrates, we found that the lipophilic extract of a marine sponge *Epipolasis* sp.[2] collected on Hachijojima Island of the Izu Archipelago showed strong inhibitory activity against H,K-ATPase[3]. From this sponge we have isolated two active substances, (+)-curcuphenol (**1**) and dehydrocurcuphenol (**3**), and a closely-related inactive sesquiterpene (**4**).

The ethanol extract of the frozen animal (1 kg) was partitioned between ether and water. The ether layer was subjected to silica gel column chromatography (*n*-hexane/ethyl acetate) followed by gel-filtration on Toyopearl HW-40S (Toyo Soda Co.) with $CHCl_3$-MeOH (1:1). The main active fraction was purified by reversed-phase HPLC on a YMC ODS column (Yamamura Chem. Co.) with 30% aq CH_3CN to give **1** (300 mg) and **3** (13 mg), both as yellowish oils.

Compound **1**, $[\alpha]_D^{23}$ +29.1°, (*c* 3.13, $CHCl_3$), possessed the molecular formula $C_{15}H_{22}O$ which was established by high resolution EIMS (*m/z* 218.1662, *Δ* −0.7 nm). An IR band at 3450 cm^{-1} together with characteristic UV absorption at λ_{max}(MeOH) 278 nm (ε 2500) indicated the presence of a phenol[4]. The ^1H NMR spectrum consisted of a secondary methyl (*δ* 1.21, 3H, br d, *J* = 7 Hz), two olefinic methyls (*δ* 1.65, 1H, s; 1.50, 1H, s), two methylenes (*δ* 1.90, 4H, m), a methine (*δ* 3.00, 1H, m), a trisubstituted double bond (*δ* 5.15, 1H, dd, *J* = 7, 7 Hz) and three aromatic signals for a 1,2,4-trisubstituted benzene ring (*δ* 6.60, 1H, br s; 6.70, 1H, br d, *J* = 7 Hz; 7.05, 1H, d, *J* = 7 Hz), which were supported by the ^{13}C NMR data (table). These structural features were in good agreement with those reported for (−)-curcuphenol (**2**)[5], an antimicrobial sesquiterpene, isolated from a Caribbean gorgonian *Pseudopterogorgia rigida,* $[\alpha]_D$ −7.0°. Recently, an $[\alpha]_D$ value of −23.6° was reported for synthetic (−)-curcuphenol[6], which indicates that our compound must possess the opposite (*S*) configuration at C-7. Therefore, **1** is (*S*) or (+)-curcuphenol.

Compound **3**, $[\alpha]_D^{23}$ −1.2° (*c* 0.48, $CHCl_3$), showed λ_{max}(MeOH) 232 (ε 9600) and 278 nm (ε 2500), indicating the presence of a diene chromophore in addition to a phenol system[4]. The molecular ion peak at *m/z* 216 in EIMS together with other spectral data suggested the dehydrocurcuphenol structure. The ^1H NMR spectum (table) including intensive decoupling experiments led to 8,9-dehydrocurcuphenol for



Assignments of ^1H and ^{13}C NMR signals for **1**, **3**, and **4***

	1 ^1H NMR (δ)	^{13}C NMR (δ)	**3** ^1H NMR (δ)	**4** ^1H NMR (δ)	^{13}C NMR (δ)
C-1		152.8s			153.9s
C-2	6.60br s	116.4d	6.64br s	6.59br s	116.2d
C-3		131.6s			131.8s
C-4	6.70br d(7)**	121.8d	6.73br d(7)	6.70br d(7)	120.9d
C-5	7.05br d(7)	126.9d	7.04br d(7)	7.04d(7)	126.9d
C-6		136.4s			135.8s
C-7	3.00m	31.5d	3.18m	3.14m	31.1d
C-8	1.90m	26.2t	5.73dd(14, 6)	1.45m	22.1t
C-9	1.90m	37.4t	6.38brdd(14, 9)	1.45m	37.6t
C-10	5.15dd(7, 7)	124.8d	5.87m	1.45m	43.4t
C-11		130.4s			71.6s
C-12	1.65s	25.7q	1.74s	1.18s	29.0q
C-13	1.50s	17.7q	1.74s	1.18s	28.4q
C-14	1.21d(7)	21.2q	1.40d(7)	1.23d(7)	21.0q
C-15	2.25s	20.8q	2.26s	2.25s	20.7q

* Measured in $CDCl_3$; ** coupling constant in Hz.

3. *E* geometry for the $\Delta^{8,9}$ double bond was deduced from a coupling constant of 14 Hz between H-8 and H-9. Due to the instability as well as scarcity of **3**, the stereochemistry at C-7 has not been determined.

A more polar fraction obtained by silica gel column chromatography was purified by reversed-phase HPLC to yield **4** (290 mg). Compound **4**, $[\alpha]_D^{23}+1.3°$ (*c* 5.92, $CHCl_3$), has a UV spectrum [λ_{max}(MeOH) 278 nm (ε 2000)], which is superimposable on that of **1**, while the IR spectrum showed more intense OH absorption than did **1**. The molecular formula of $C_{15}H_{24}O_2$ was obtained by EIMS(*m/z* 236) as well as by ^1H and ^{13}C NMR (table). The ^1H NMR spectrum revealed no signals for olefinic protons or two olefinic methyls, which were seen in **1**. Instead, there were a methyl singlet (6H) at δ 1.18 and a 6H broad multiplet centered at δ1.45. The ^{13}C NMR spectrum also secured these structural features; an oxygen-bearing quaternary carbon at δ71.6, three methylene carbons at δ22.1, 37.6, and 43.4, and two methyl signals at δ28.4 and 29.0. These spectral features led us to assign an 11-hydroxy-10,11-dihydrocurcuphenol structure to **4**. This structure, including the configuration at C-7, was confirmed by chemical conversion of **4** with $SOCl_2$/py (rt, overnight)[7] to **1**, which was identical with natural **1** in every respect. Thus **4** possesses 7*S* configuration.

(+)-Curcuphenol and dehydrocurcuphenol inhibit the activity of gastric H,K-ATPase with an IC_{50} of 8.3×10^{-6} M and 2.3×10^{-5} M, respectively, while **4** is inactive. The two active compounds also inhibited gastric acid secretion in rats. (+)-Curcuphenol and dehydrocurcuphenol are the first marine natural products that inhibit H,K-ATPase activity. It is interesting that the sponge sesquiterpenes had stereochemistry (*S*) opposite to the gorgonian analog.

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Insecticidal organophosphates: Nature made them first

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Summary. Out of the three most important classes of synthetic insecticides only the carbamates and pyrethroids were known to have ancestors in nature. Now two organophosphates (which are quite good insecticides and very potent acetylcholinesterase inhibitors, e.g. comparable to carbofuran) have been isolated from *Streptomyces antibioticus* strain DSM 1951.
Key words. Organophosphates; natural insecticides; acetylcholinesterase inhibitors; *Streptomyces*.

Today, organophosphates, carbamates and pyrethroids are the three most important classes of synthetic insecticides. The first two interfere with nervous transmission by inhibiting the acetylcholinesterases (AChE), the last by blocking the sodium channels. The first insecticidal organophosphates were invented by Schrader and Kükenthal in 1937[1]. On the other hand, the first insecticidal carbamates were synthesized on purely chemical grounds[2], and as analogues of physostigmine[3], a toxic alkaloid from the seeds of the vine *Physostigma venenosum*[4]. Earlier experiments[5] had indicated that physostigmine interfered with the AChE in the same way as the organophosphates. The third class, the pyrethroids, is derived form the natural pyrethrins, a mixture of insecticidal esters obtained from the flowers of certain *Chrysanthemum* species, especially *C. cinerariaefolium*. The first written accounts date back to the 17th century and commercial production of an insecticidal powder ground from the heads of these flowers started around 1840[6].