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The Structure and Probable Biogenesis of Helianane, a Heterocyclic Sesquiterpene, from the Indo-Pacific Sponge *Haliclona ?fascigera*

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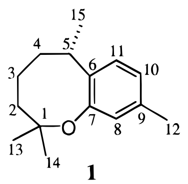
Sponges, as well as a host of other organisms, both marine and terrestrial, are a source of functionalized aromatic bisabolene sesquiterpenes. The first of these compounds reported from a marine organism[1,2] was α-curcumene (configuration or rotation not specified)[2] isolated from gorgonians in the 1970s, and at that time (*R*)-(−)-α-curcumene was a well-known plant constitutent. The closely related alcohol analog, (*R*)-(−)-curcuphenol (**3**), was subsequently described almost simultaneously from gorgonians, especially *Pseudopterogorgia rigida*, and terrestrial plants, including *Lasianthaea podocephala*.[3] Eventually, its optical antipode, (*S*)-(+)-curcuphenol (**3**), was also obtained from several different sponges.[4−6] Additional aromatic bisabolenes have been reported such as (*R*)-(−)-curcuquinone (**4**)[2] from marine gorgonians and (*S*)-(+)-curcuphenol (**3**), a metabolite of sponges gathered from widely differing regions including the Bahamas (*Didiscus flavus*),[4] Japan (*Epipolasis sp.*),[5] and Australia (*Arenochalina sp.*).[6] We have also found known compounds (+)-curcuphenol (**3**)[4] and (+)-curcudiol (**5**)[4] as constituents of the Caribbean sponge *D. flavus*. Some compounds of this family are bioactive, and the most noteworthy is (−)-curcuphenol (**3**), which exhibits antifungal activity (*Candida albicans*) and inhibition of H/K-ATPase. It is also cytotoxic against P-388 murine leukemia, A-549 lung, HCT-8 colon, and MDAMB mammary cancer cell lines.[7] The various total syntheses, especially of (+)-curcudiol, of (+)-curcuphenol, or of (±)-curcudiol, (±)-curcuhydroquinone, and (±)-curcuquinone[8−10] collectively represent another milestone in the research on these aromatic bisabolenes.

Less well-known are compounds possessing both an aromatic bisabolene moiety and a heterocyclic ring. To date the singular example in the literature is (−)-heliannuol A (**2**), whose complete structure was reported in 1994.[11] This sunflower-derived metabolite has a benzenoid moiety fused to an eight-membered ether ring. In the short report below we describe the structure of (+)-helianane (**1**) as an additional new member of this class.

The sponge we examined was classified as a *Haliclona ?fascigera*. The initial processing of the freshly collected material was according to procedures described previously,[12] which afforded a methanol soluble crude oil (4.19 g) and subsequently a methylene chloride solvent partition fraction (278 mg). Final purification was straightforward as it simply involved step gradient (EtOAc/hexane) silica gel chromatography to afford pure helianane (**1**), whose general features were established once the molecular formula was in hand. Both the ^{13}C APT NMR spectrum and HRFABMS data, m/z 219.1746 (0.3Δ mmu of calcd), generated the same molecular formula, $C_{15}H_{22}O$, indicating five degrees of unsaturation. A trisubstituted benzene ring was identified from the six ^{13}C NMR (Table 1) resonances between δ 116 and 135. The annelation of the one additional ring as well as the substitution pattern within the benzene ring was quickly established. Two ortho protons, H11 and H10, were recognized by their mutual coupling of $J = 8$ Hz. The broadened singlet proton resonance of H8 meant that it was meta to H10 and ortho to $CH_3$12 as established by the heteronuclear multiple bond correlation (HMBC) data in Table 1. Additionally, the HMBC correlations from C12 to H10 and to H8 and from C9 to H11 further confirmed the substitution pattern of the three benzene ring protons and the methyl group. Another benzene ring substituent was defined by HMBC correlations from C6 to H4, H5, and $CH_3$15. Working further outward the $^1H-^1H$ COSY correlations defined the spin system including $CH_3$15 to $CH_2$2. Finally, HMBC correlations from the quaternary carbon C1 to $CH_2$2, $CH_3$13, and $CH_3$14 established the terminus of this array. An ether functionality provided the only possible bridge from C1 to C7 in that each of these carbons had to be attached to oxygen because of their relatively lowfield carbon resonances: C1 (δ 71.6) and C7 (δ 153).



1
helianane

The stereochemical and conformational properties of **1** were examined next. There is an approximate relationship between the absolute stereochemistry of the C-CH_3 group and the *d*/*l* optical rotation in aromatic bisabolene derivatives having this as the *only* chiral center. Examples of the straightforward pattern include (*R*)-(−)-α-curcumene,[2] (*R*)-(−)-curcuphenol (**3**),[2] and (*R*)-(−)-curcuquinone (**4**)[2] versus (*S*)-(+)-curcudiol (**5**),[4] (*S*)-(+)-curcuphenol (**3**),[4] and an unnamed (*S*)-(+)-11-hydroxy curcuphenol derivative.[6] Applying this pattern to (+)-helianane (**1**) allows a *provisional* 5*S* designation for the stereochemistry in (+)-**1**. Turning to the second issue, the eight-membered ring of **1** appears to be conformationally mobile. The small difference in the ^{13}C shifts of the ring methyls, Me-13 (δ 29.8) and Me-14 (δ 28.9), as

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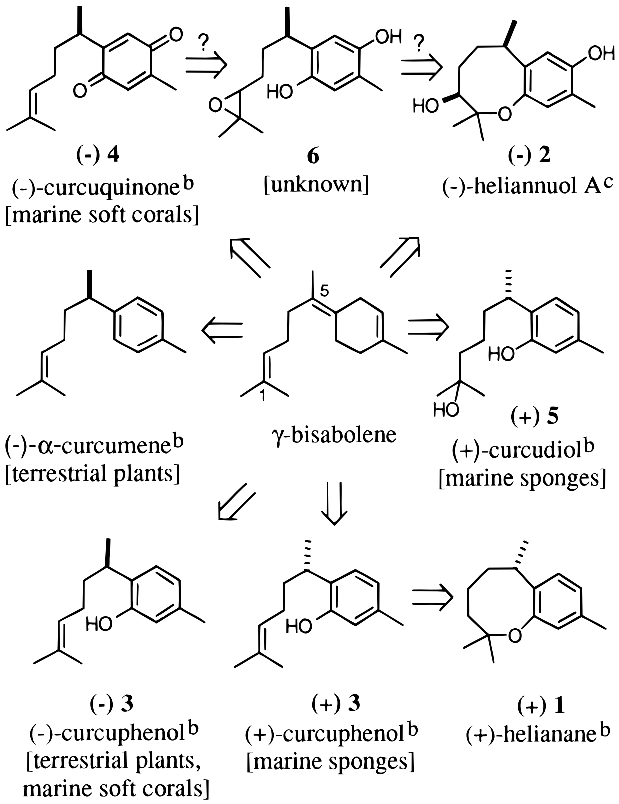
Table 1. NMR Data of Helianane (1) at 500/125 MHz ($CDCl_3$)

atom no.	^{13}C	^1H [δ mult, J (Hz)]	COSY	HMBC
1	71.6 s			H13, H14, H2, H2′
2	43.4 t	1.48 m	H3, H3′	H13, H14, H4, H4′
2′		1.55 m		
3	22.2 t	1.35 m	H4, H4′, H2, H2′	H2, H2′
3′		1.35 m		
4	37.8 t	1.53 m	H5, H3, H3′	H5, H3, H3′, H15
4′		1.67 dq, $J = 14, 7$		
5	31.4 d	3.10 sext, $J = 7$	H4, H4′, H15	H4, H4′, H15, H3, H3′, H11
6	130.6 s			H15, H4, H4′, H5, H8, H10
7	153.1 s			H5, H11
8	116.4 d	6.60 bs		H12, H10
9	136.5 s			H12, H11
10	121.7 d	6.73 bd, $J = 8$	H11	H12, H8
11	126.9 d	7.04 d, $J = 8$	H10	H5
12	21.0 q	2.27 s		H10, H8
13	29.8 q	1.21 s		H14
14	28.9 q	1.88 s		H13, H2, H2′
15	21.1 q	1.25d, $J = 7$	H5	H5, H4, H4′

opposed to a large divergence in A-ring *gem*-dimethyl carbon NMR shifts[13] in polycyclic terpenoids provides one indication of the ring dynamics. Also, the D NMR results published for heliannuol A (**2**), whose geminal methyls were almost identical in their ^{13}C NMR chemical shifts, represents definitive evidence on this point.[11]

The ring system of helianane does not have a prior precedent in a marine natural product. However, it is close in structure to the recently discovered sunflower-derived bioactive sesquiterpenes headed by (−)-heliannuol A (**2**).[11a] The structure of **2** was secured by X-ray analysis, but only relative 2S*,5R* stereochemistry was reported and the hypothetical compound **6** (without stereochemistry) was outlined as a logical precursor to it.[11b] An interesting circumstance appears to be associated with the initial chirality that arises during the conversion of γ-bisabolene to its aromatic derivatives. The chiral center at C5 emerges along two antipodal directions: one in plants or marine soft coral compounds as 5R and another in marine sponge metabolites as 5S. These relationships are summarized in Scheme 1 and are consistent with our provisional assignment of 5S stereochemistry in (+)-helianane (**1**) and further hint that 5R stereochemistry might be appropriate for (−)-heliannuol A (**2**) and related compounds heliannuol B and D.

Scheme 1. Relationships between Possible Biogenesis Routes to (−)-Heliannuol A (2) and Helianane (1)[a]



[a] Extends the proposal of ref 10. [b] Designates absolute stereochemistry. [c] Designates relative, not absolute, stereochemistry.

Experimental Section

General Experimental Procedures. NMR spectra were recorded at 500 MHz (^1H) and 125 MHz (^{13}C) in $CDCl_3$. Carbon multiplicities were determined using DEPT-135 data. Atom connectivities were determined using heteronuclear multiple quantum coherence (HMQC), HMBC, and $^1H-^1H$ COSY data. Both low- and high-resoltuion FABMS data were obtained as were optical rotations in CH_2Cl_2. Flash chromatography was carried out on silica gel (200−400 mesh).

Animal Materials. The sponge *Haliclona ?fascigera*[14,15] (family Chalinidae; order Haploscelerida, coll no. 95503), collected in the Togian Islands of Tomini Bay, North Sulawesi, Indonesia, was identified by Dr. M. C. Diaz (UCSC). The sponge was found growing as thin erect fans, 2−3 mm thick, with a smooth surface and soft consistency. The color of the sponge underwater was pink−gray externally and gray internally. Round oscules (1 mm in diameter) were regularly dispersed on one side of the fan. Fusiform oxeas 80−90 × 3−4 μm (length by width) form the skeleton, which is a basic isotropic unispicular reticle both in the ectosome and choanosome. In the choanosome, multispicular tracts (2−8 spicules in cross section, 16−40 μm in width) run parallel to the surface crisscrossing each other in an irregular fashion. The species is very similar to *Haliclona fascigera*; however, these specimens were found growing as fans, while *H. fascigera* is tubular.[15] A voucher, as well as an underwater photograph, are in the UCSC sponge collection archives and are available from P.C.

Extraction and Isolation. The sponge (0.08 kg, dry wt.) was preserved and processed according to our standard procedures.[12] The methylene chloride partition fraction afforded a semipure extract (280 mg) of which 150 mg was subjected to flash chromatography on silica gel and eluted with *n*-hexane−EtOAc mixtures of increasing polarity to afford 24.4 mg of pure helianane (**1**).

Helianane (1). Sesquiterpene **1** was obtained as an amorphous amber solid: $[\alpha]_D$ +8.0° (c 1.01, CH_2Cl_2); UV (CH_2Cl_2) λ_{max}

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(log ϵ) 230 (3.58), 276 (3.65), 282 (sh, 3.66) nm; IR (CH_2Cl_2) ν_{max} 2966, 1454, 1149, 937, 814; LRFABMS *m/z* $[M + H]^+$ 219 (67),-161 (21),149 (25),135 (100), 121 (42); HRFABMS *m/z* $[M + H]^+$ 219.1746 (calcd for $C_{15}H_{23}O$, 219.1749); see Table 1 for ^1H and ^{13}C NMR.

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