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Revised Structure, Synthesis and Absolute Configuration of Hippospongic Acid A

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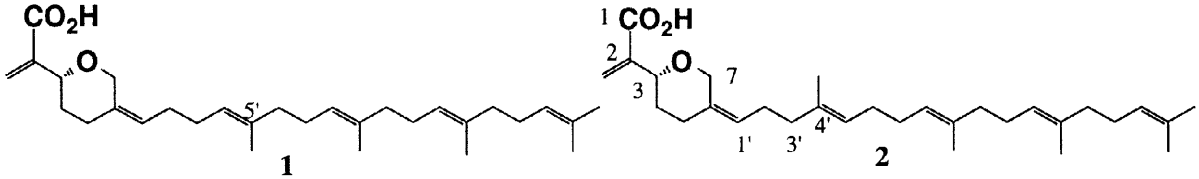
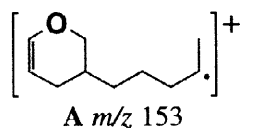
Abstract: The structure of hippospongic acid A was reinvestigated and new evidence supporting the revised structure previously proposed was obtained. The structure, including absolute configuration, was established by the enantioselective synthesis.

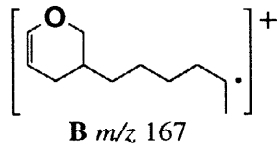
Hippospongic acid A, isolated from a marine sponge of *Hippospongia* sp., is a triterpene ether possessing inhibitory activity for gastrulation of starfish embryos. Previously, our Hiroshima group has reported that hippospongic acid A is formulated as the structure **1**.[1] Recently, Tokushima group has synthesized the compound corresponding to **1** and found that the NMR spectra of the synthetic compound were apparently different from those of the natural product. Careful examination of NMR spectra led us to propose an alternative structure **2** having a normal triterpene carbon skeleton.[2] In order to determine the structure of the interesting natural product, we reinvestigated the structure of hippospongic acid A and were able to obtain the evidence supporting the structure **2**. Furthermore, we confirmed the revised structure **2** for hippospongic acid A by the enantioselective synthesis. The results are described in this communication.



At first, we searched for some related marine sponges to obtain an adequate amount of hippospongic acid A and isolated 15 mg of the natural product from a marine sponge of *Rhopaloeides* sp.,[3] the source of another gastrulation inhibitor, rhopaloic acid A.[4] Hippospongic acid A was then converted (H_2/Pd-C) to a perhydro-derivative, whose EIMS showed a peak having medium intensity at *m/z* 153 corresponding to the fragment ion **A** (not *m/z* 167 due to the **B**). In addition, in the HMBC spectrum a cross peak was observed between H-1'(5.23 ppm) and a methylene carbon at 39.7 ppm (C-3'). If the methyl group ispresent at C-5' as in **1**, the C-3' carbon signal should appear at higher field (around at26 ppm) due to the steric compression of the methyl group. Both findings supported the location of the methyl group at C-4' as in the structure **2**.



A *m/z* 153



B *m/z* 167

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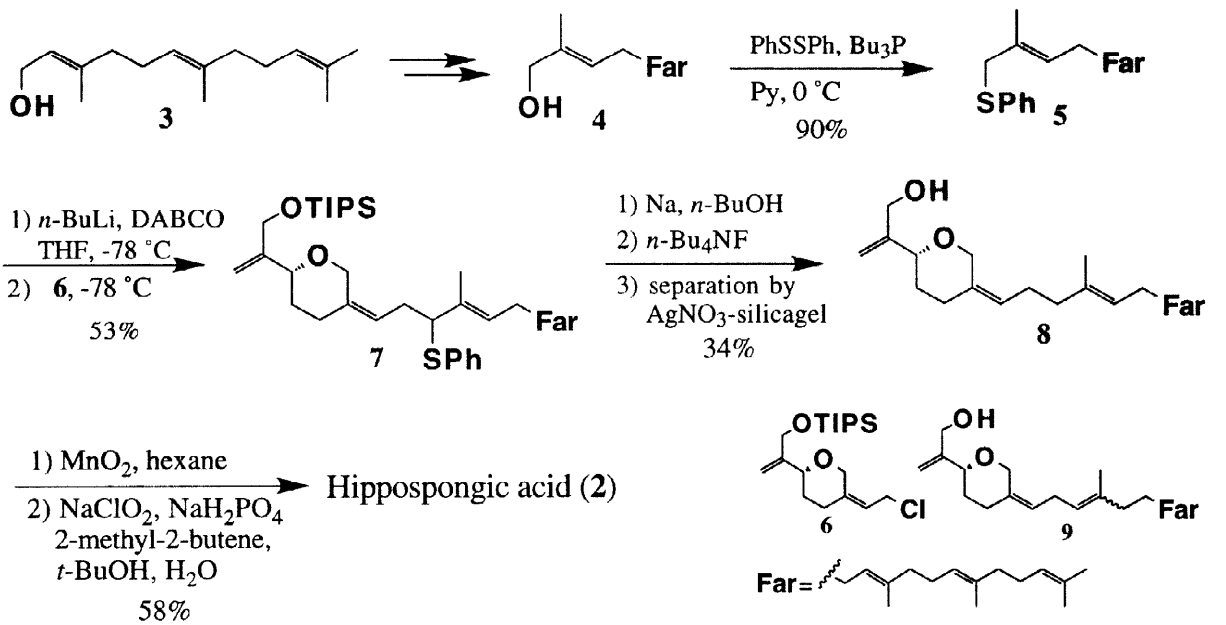
In order to confirm the structure, the compound **2** was synthesized enantioselectively. Thus, allylic alcohol **4**[5] obtained from farnesol **3**, was converted into sulfide **5**. The lithio-anion of **5** was coupled with the allylic chloride **6** which has been synthesized by us in high optical purity.[2] Desulfurization of **7** followed by deprotection of the silyl group and separation by $AgNO_3$-impregnated silica gel chromatography afforded alcohol **8** together with the isomer **9** (**8** : **9** = ca. 3 : 1). Two-step oxidation of the allylic alcohol part in **8** yielded carboxylic acid **2** whose ^1H and ^{13}C NMR spectra[6] as well as IR and mass spectra were identical to those of natural hippospongic acid A. Since the optical rotation of synthetic **2** $[[\alpha]_D^{20}$ +41.4° (*c* 0.22, $CHCl_3$)] has the same sign as that of the natural product ($[\alpha]_D$ +37°) ,[1] the structure of hippospongic acid A including its absolute configuration was determined as **2**.



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References and Notes

1. Ohta, S.; Uno, M. ; Tokumasu, M.; Hiraga, Y.; Ikegami, S. *Tetrahedron Lett.* **1996**, 37, 7765.
2. Hioki, H.; Ooi, H.; Mimura, Y.; Yoshio, S.; Kodama, M. *SYNLETT* **1998**, 729.
3. Isolation was performed according to the same procedure reported previously.[1]
4. Ohta, S.; Uno, M.; Yoshimura, M.; Hiraga, Y.; Ikegami, S. *Tetrahedron Lett.* **1996**, 37, 2265.
5. Zheng, Y. F.; Oehlschlager, A. C.; Hartman, P. G*J. Org. Chem.* **1994**, 59, 5803.
6. ^{13}C NMR (ca. 0.1 mol/l): δ ($CDCl_3$) 170.0 (C-1), 140.7 (C-2), 135.2, 134.9, and 134.4 (C-4', C-9', C-13'), 132.5 (C-6), 131.2 (C-17'), 127.1 (C-8), 124.9×2, 124.4 , 124.2×2 (C-1', C-5', C-8', C-12', C-16'), 75.6 (C-3), 67.1 (C-7), 39.7×3 (C-3', C-10', C-14'), 33.7 (C-4), 32.9 (C-5), 28.3 and 28.2 (C-6', C-7'), 26.8 and 26.6 (C-11', C-15'), 25.7 and 25.6 (C-2', C-18'), 17.6 (C-22'), 16.1 and 16.0×2 (C-19', C-20', C-21'). ^{13}C NMR signals of C-1 (1.9 ppm), C-2 (0.4 ppm), and C-3 (0.5 ppm) showed a concentration-dependent behavior probably due to the hydrogen bonding. The ^{13}C NMR spectra of synthetic and natural compounds were identical within ±0.1 ppm at the concentration of ca. 0.1 and 0.01 mol/l, respectively.