# Enantioselective Synthesis of Reported Hippospongic Acid A

Hideaki Hioki, Hidenori Ooi, Yumi Mimura, Suzuyo Yoshio, and Mitsuaki Kodama*
Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan
E-mail: QWH02611@niftyserve.or.jp

*Received 14 April 1998*

**Abstract** : Total synthesis of hippospongic acid A, an inhibitor of gastrulation of starfish embryos, has been studied. A compound having the structure assigned to hippospongic acid A was synthesized enantioselectively. The spectral data of the synthetic compound were slightly different from those of the natural product and an alternative structure was proposed for the natural product.

Hippospongic acid A (**1**) isolated from a marine sponge, *Hippospongia* sp., is an attractive natural product because it exhibits potent inhibitory activity in gastrulation of starfish embryos.[1] In addition, a biogenetically irregular triterpene structure (tail-to-tail coupling of geranylgeranyl and geranyl diphosphates) has been assigned on the basis of spectral analysis. The absolute stereochemistry has not been determined yet. Rhopaloic acid A (**2**) isolated from a marine sponge, *Rhopaloeides* sp., has a related norsesterterpene structure and exhibits potent cytotoxicity against some human tumor cell lines and inhibitory activity in gastrulation of starfish.[2] From the interests in biological activity and a new triterpene carbon skeleton, we investigated the total synthesis of hippospongic acid A.

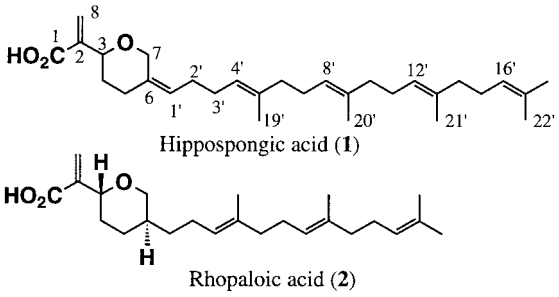
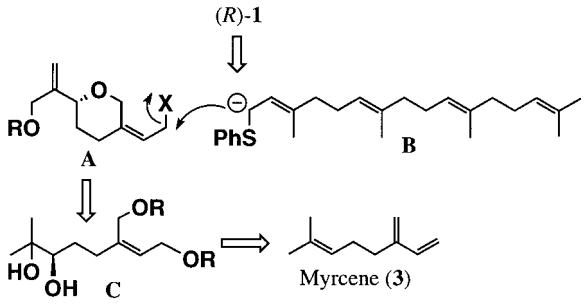



**Figure 1**

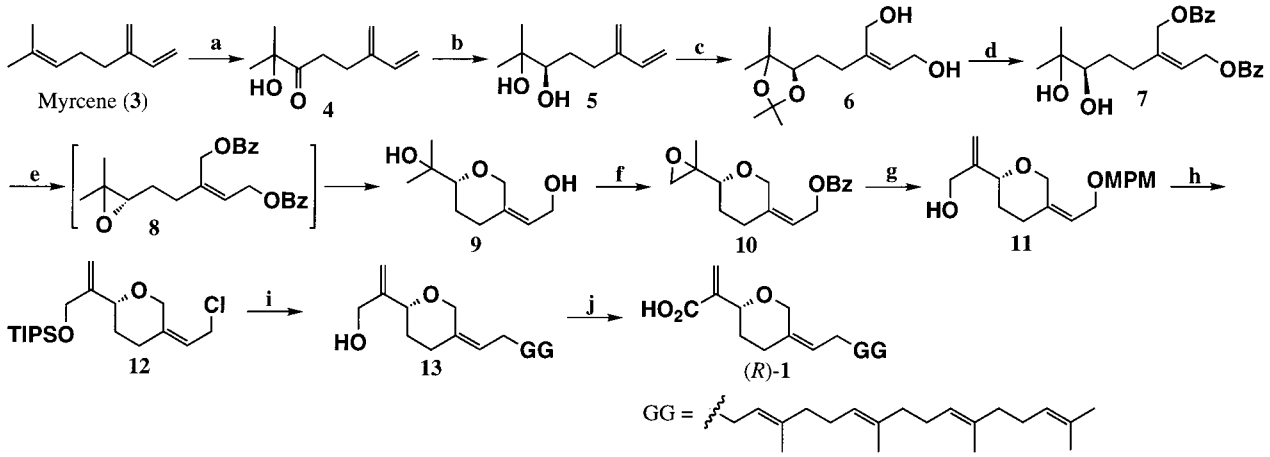
In this communication we describe the enantioselective synthesis of a compound having the structure assigned to hippospongic acid A. Furthermore, we propose an alternative structure for the natural product on the basis of a comparison of the spectral data of the synthetic and natural compounds.

Our synthetic strategy consists of a coupling of a geranylgeranyl unit (**B**) and a hydropyran ring unit (**A**), the latter of which is synthesized enantioselectively from myrcene (**3**) using baker's yeast reduction as the chirality induction method (Scheme 1) .




**Scheme 1**

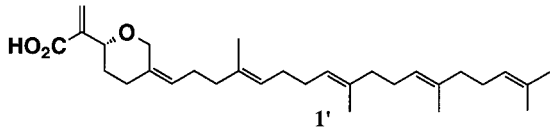
For the synthesis of the hydropyran unit (**A**), myrcene (**3**) was first converted into α-hydroxyketone **4** in three steps in 36% overall yield (Scheme 2). Treatment of **4** with baker's yeast[3] at room temp. yielded (*R*)-diol **5** (96% yield) in high enantiomeric purity.[4] After the diol part was protected as an acetonide, **5** was subjected to photosensitized oxidation in DMF using hematoporphyrin as a sensitizer. The endoperoxide thus obtained in good yield was reduced with $NaBH_4$ at 50 °C to give 1,4-diol **6** in 46% yield from **5**. The diol part in **6** was protected as bisbenzoate and the acetonide group was hydrolyzed. The resulting 1,2-diol **7** was then converted into epoxide **8**. Hydrolysis of the




**a**. i) *m*CPBA, ii) $HClO_4$ in aq. THF, iii) Swern oxid.; **b**. Baker's yeast; **c**. i) DMP, PPTS, ii) $O_2$/*hv*, hematoporphyrin, DMF, iii) $NaBH_4$; **d**. i) BzCl, Py, ii) *p*-TsOH; **e**. i) MsCl, Py, ii) $K_2CO_3$, iii) NaOH; **f**. i) BzCl, $Et_3N$, ii) MsCl, $Et_3N$, DMAP, iii) *m*CPBA; **g**. i) NaOH, ii) MPM-Cl, NaH, iii) $(i\text{-PrO})_3Al$ in refluxing Tol; **h**. i) TIPS-Cl, imid., ii) DDQ, iii) NCS, $Me_2S$; **i**. i) GG-SPh, *n*-BuLi, DABCO, ii) Na, *n*-BuOH, iii) *n*-$Bu_4NF$; **j**.i) $MnO_2$, ii) $NaClO_2$, *t*-BuOH, 2-methyl-2-butene

**Scheme 2**

benzoates of **8** with alkali resulted in the concomitant formation of a hydropyran ring to give **9** (69% from **6**). Benzoylation, dehydration[6] through mesylate, and epoxidation afforded epoxide **10** as a diastereomeric mixture (29% for three steps). After the protective group was changed to *p*-methoxybenzylether, the oxirane ring was opened with aluminum triisopropoxide in refluxing toluene to give allylic alcohol **11** in 60% yield from **10**, which was converted into the chloride **12** in three steps (84%). Thus obtained chloride **12** was reacted with the lithio-anion of geranylgeranyl phenyl sulfide (GG-SPh) in the presence of DABCO and the resulting coupling product was subjected to desulfurization using the Bouveault-Blanc conditions and then deprotection of silylether to yield **13** (61% yield after purification by $AgNO_3$-impregnated silica-gel chromatography) having the desired carbon skeleton. Finally, **13** was converted into (*R*)-**1** ($[\alpha]_D^{23}$ +47.1°; *lit.* $[\alpha]_D^{25}$ +37°) in a two step reaction in 69% yield. Thus, we achieved the enantioselective synthesis of a compound corresponding to the reported hippospongic acid A. The $^1H$ and $^{13}C$ NMR spectra of the synthetic compound[7] were similar to those of the natural product. However, the multiplet at 2.15 ppm (H-2' ) which appeared in the $^1H$ NMR spectrum (500 MHz) of the natural product was not observed as a separate signal in the spectrum (600 MHz) of the synthetic compound. Moreover, the $^{13}C$ NMR signals observed at 125.0, 28.3, and 25.7 ppm in the spectrum of the natural product appeared at 123.5, 27.3 and 26.6 ppm, respectively, in the synthetic compound. These facts revealed that the structures of natural product and synthetic compound are quite similar, but not identical. Since the $^{13}C$ NMR signals described above are assignable to C-4', C-2', and C-3', we propose an alternative structure **1'** possessing a normal triterpene carbon skeleton for hippospongic acid A. Work on confirmation of the new structure by synthesis is currently in progress.




**1'**

**Figure 2**

**Acknowledgments** We are grateful to Dr. Shinji Ohta, Hiroshima University, for the spectra of natural hippospongic acid A. This work was partially supported by a Grant-in-Aid for Scientific Research (No. 08680642) from the Ministry of Education, Science and Culture of Japan.

**References and Notes**

(1) Ohta, S.; Uno, M.; Tokumasu, M.; Hiraga, Y.; Ikegami, S. *Tetrahedron Lett*. **1996**, *37*, 7765.

(2) Ohta, S.; Uno, M.; Yoshimura, M.; Hiraga, Y.; Ikegami, S. *Tetrahedron Lett*. **1996**, *37*, 2265. For the synthesis of **2**, see Takagi, R.; Sasaoka, A.; Kojima, S.; Ohkata, K. *J. Chem. Soc., Chem. Commun*. **1997**, 1887; Snider, B. B.; He, F. *Tetrahedron Lett*. **1997**, *38*, 5453.

(3) Kodama, M.; Minami, H.; Mima, Y.; Fukuyama, Y. *Tetrahedron Lett*. **1990**, *31*, 4025; Kodama, M.; Yoshio, S.; Yamaguchi, S.; Fukuyama, Y.; Takayanagi, H.; Morinaka, Y.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett*. **1993**, *34*, 8453.

(4) The absolute configuration of **5** was determined by modified Mosher's method.[5] The optical purity was >98% ee as analyzed by GC using chiral Column.

(5) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakizawa, H. *J. Am. Chem. Soc*. **1991**, *113*, 4092; Kusumi, T. *J. Syn. Org. Chem. Jpn*. **1993**, *51*, 462.

(6) Various dehydration conditions including $SOCl_2$ in pyridine, $POCl_3$ in pyridine have been examined, but the yields of the desired exomethylene derivative were less than 35% because of the formation of an unstable product (probably a compound containing a tetrasubstituted double bond).

(7) Spectral data of synthetic (*R*)-**1**: $^1H$ NMR (600 MHz, $CDCl_3$) 1.43 (1H, m, H-4), 1.60 (12H, s, $H_3$-19', $H_3$-20', $H_3$-21', $H_3$-22'), 1.68 (3H, s, $H_3$-18'), 1.95-2.01 (6H, m, $H_2$-6', $H_2$-10', $H_2$-14'), 2.01-2.12 (11H, m, H-4, $H_2$-2', $H_2$-3', $H_2$-7', $H_2$-11', $H_2$-15'), 2.31-2.41 (2H, m, $H_2$-5), 3.90 (1H, d, *J* = 12.6 Hz, H-7), 4.32 (1H, d, *J* = 10.1 Hz, H-3), 4.72 (1H, d, *J* = 12.6 Hz, H-7), 5.07-5.14 (4H, m, H-4', H-8', H-12', H-16'), 5.26 (1H, t, *J* = 7.0 Hz, H-1'), 5.97 (1H, s, H-8), 6.34 (1H, s, H-8); $^{13}C$ NMR (150 MHz, $CDCl_3$) 170.1 (C-1), 140.6 (C-2), 135.8, 135.0, 134.9 (C-5', C-9', C-13'), 132.6 (C-6), 131.2 (C-17'), 127.1 (C-8), 125.0 (C-1'), 124.4, 124.2, 124.2, 123.5 (C-4', C-8', C-12', C-16'), 75.6 (C-3), 67.1 (C-7), 39.7 (C-6', C-10', C-14'), 33.7 (C-4), 32.9 (C-5), 28.2, 27.3 (C-2', C-3'), 26.8, 26.7, 26.6 (C-7', C-11', C-15'), 25.7 (C-18'), 17.7 (C-22'), 16.1, 16.0, 16.0 (C-19', C-20', C-21').