ISOMERIZATION OF DIMERIC 2,9-DISUBSTITUTED 1-OXA-QUINOLIZIDINE ALKALOIDS AND STRUCTURAL REVISION OF ARAGUSPONGINES B AND E, ISOLATED FROM A MARINE SPONGE OF *XESTOSPONGIA* SP.[1]

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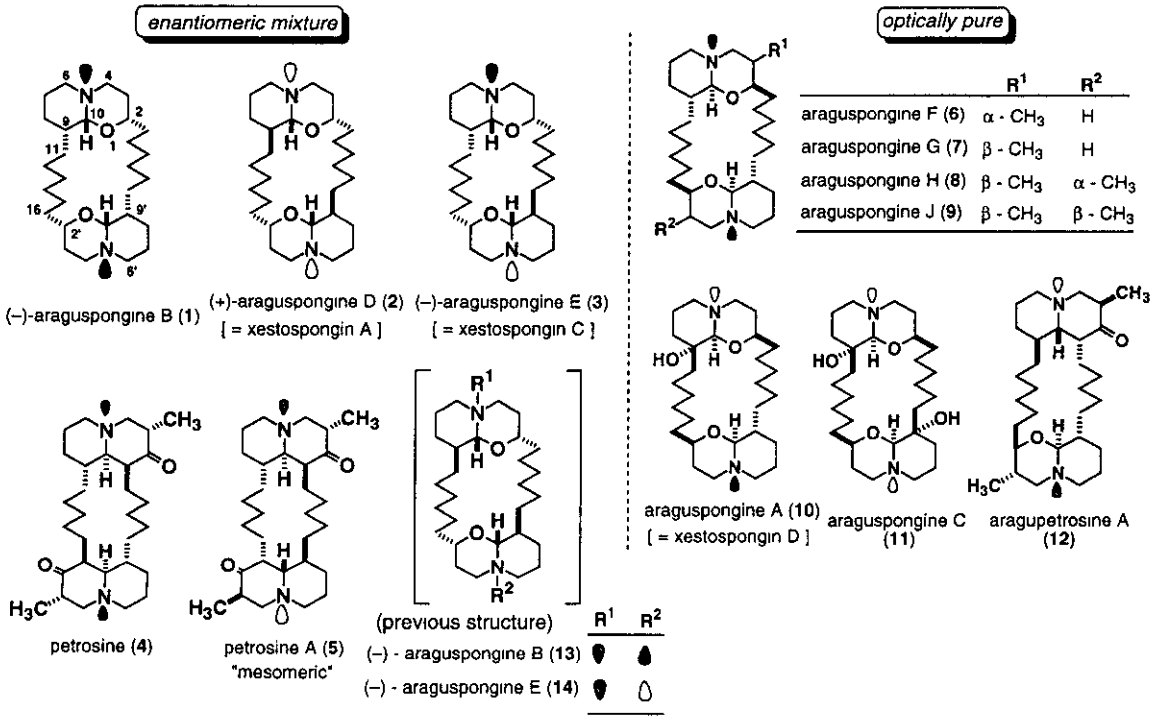
Abstract - Isomerization reaction of araguspongines B (**1**), D (**2**), and E (**3**) having dimeric 2,9-disubstituted 1-oxaquinolizidine moiety was studied in detail. Conformational aspects of **1**, **2**, and **3** were also analyzed on the basis of NMR and X-ray crystallographic analysis. The C-9 stereochemistry of **1** and **3** was revised.

In a continuing search for new bioactive substances from marine organisms,[1] we have isolated ten new dimeric quinolizidine alkaloids named araguspongines A (**10**), B (**13**), C (**11**), D (**2**), E (**14**), F (**6**), G (**7**), H (**8**), and J (**9**) and aragupetrosine A (**12**) together with two known dimeric 2-oxoquinolizidine alkaloids, petrosin (**4**)[3] and petrosin A (**5**)[4] from an Okinawan marine sponge of *Xestospongia* sp.[5,6] These alkaloids were characterized as a macrocyclic dimer of 2,9-disubstituted 1-oxaquinolizidine and we have determined the absolute stereostructures of those new alkaloids on the basis of chemical and physico-chemical analysis. Very interestingly, araguspongines A (**10**), C (**11**), F (**6**), G (**7**), H (**8**), J (**9**), and aragupetrosine A (**12**) were respectively obtained as a single enantiomer while the others as an enantiomeric mixture or as a mesomeric compound (Scheme 1). It is presumed that enantioselective oxidation or methylation occurred at C-9 or C-3 prior to (or after) formation of the intermediary 1-oxaquinolizidine moieties. Araguspongines C (**11**), D (**2**), E (**14**), J (**9**), and aragupetrosin A (**12**) were shown to exhibit stronger vasodilative activities than papaverine in the perfusion model experiment using an isolated mesenteric artery of SD-rat.

By treatment with alumina [Al_2O_3 60 F_{254} (Type E, Merck)] at 80° C, (-)-araguspongine B (**13**) was isomerized to (+)-araguspongine D (**2**)(= enantiomer of xestospongin A[7]).[5] Accordingly, we concluded that araguspongine B (**13**) is the stereoisomer of araguspongine D (**2**) with respect to the electron lone-pairs of 5,5'-nitrogens. After that, several synthetic studies of 1-oxaquinolizidine moiety have been reported.[8] Hoye and his group have succeeded in the total synthesis[9] of (+)-araguspongine D (**2**) and suggested that araguspongines B and E are the respective C-9 and/or C-9' stereoisomers (**1**) and (**3**) (= xestospongin C[7]) of araguspongine D (**2**) on the basis of synthetic and molecular mechanic study.[10]



Scheme 1

From the analysis of the isomerization reaction and conformation of araguspongines B, D, and E and the X-ray crystallographic analysis of araguspongine B, we also reached the structural revision of araguspongines B (**1**) and E (**3**). In this paper, we describe the details of the analysis of the isomerization reaction and the conformational analysis of araguspongines B (**1**), D (**2**), and E (**3**).

Araguspongine B (**1**) and D (**2**) showed 14 carbon signals in the ^{13}C-NMR spectrum, suggesting that **1** and **2** have C_2 symmetry. Araguspongine E (**3**) showed ^{1}H and ^{13}C signals ascribable to one half moiety of both araguspongines B (**1**) and D (**2**) in the ^{1}H- and ^{13}C-NMR spectra. From the detailed analysis by 2D-NMR (COSY, HMBC, C-H COSY, and COLOC experiment), each ^{1}H and ^{13}C signal for **1**, **2**, and **3** was assigned as shown in Table 1. On the basis of NOE correlation and coupling constant, it was clarified that the 2,9-disubstituted 1-oxaquinolizidine moiety of araguspongine B (**1**) has *cis*-decaline-like

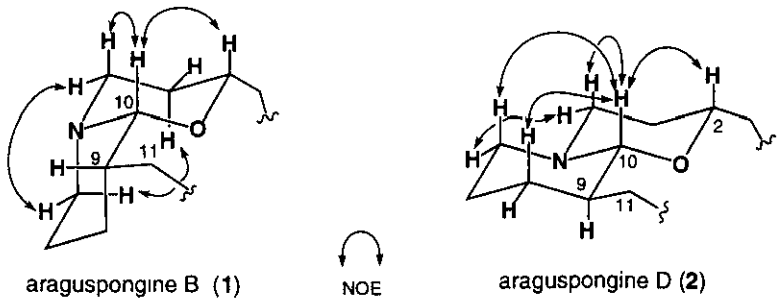


Figure 1 NOE Data for Araguspongines B (**1**) and D (**2**)

Table 1. ^{1}H- and ^{13}C-NMR Data for Araguspongines B (**1**), D (**2**), and E (**3**) (*500 MHz in $CDCl_3$, ** 68 MHz in $CDCl_3$, J value in Hz)

Atom	**1**			**2**			**3**		
No	δc**		δ*	δc**		δ*	δc**		δ*
2	76.0		3.53 (br t, 11)	75.2		3.35 (br t, 11)	75.8		3.53 (br t, 11)
3	26.3	ax	1.73	32.2		1.68, 1.49	26.3	ax	1.74
		eq	1.03 (br d, 13.5)					eq	1.03 (br d, 13.5)
4	52.7	ax	3.18 (ddd, 3.5, 13.5, 13 5)	54.3	ax	2.18 (ddd, 3.5, 12, 12)	52.8	ax	3.19 (br t, 13.5)
		eq	2 95 (dd, 3.5, 13.5)		eq	2.93 (ddd, 1.5, 4.5, 12)		eq	2.96 (dd, 2.5, 13.5)
6	45.2	ax	3.06 (ddd, 2.5, 11.5, 11.5)	54.0	ax	1.98 (ddd, 3.5, 12, 12)	45.3	ax	3.06 (ddd, 3 5, 11, 11)
		eq	2.40 (br d, 11 5)		eq	2.75 (br d, 12)		eq	2 46 (br d, 11)
7	25.7		1 68, 1.57	24.9		1.65, 1.58	25.7		1.67, 1.60
8	26.5		1.36	28.9	ax	1.67 (dddd, 4.5, 13, 13, 13)	26.5		1.35
			1.27			1.24			1.29
9	40.4		1.59	40.5		1.61	40.2		1.59
10	87.4		4.30 (d, 2.5)	95.8		3.06 (d, 8.5)	87.4		4.30 (br s)
11	33.0		1 47, 1.11	31.2		1.59, 1.35	32.9		1.50, 1.12
12	27 3		1.40, 1.10	28.7		1.40, 1 18	27.1		1.38, 1.13
13	31.8		1.31, 1.14	31.6		1.30, 1.18	31 6		1.31, 1.17
14	29.5		1.39, 1.17	25.2		1 26, 1.16	29.4		1.36, 1 20
15	24.8		1.59, 1.30	25.3		1.58, 1.35	25.3		1.57, 1.34
16	36 2		1.57, 1.30	35.4		1.60, 1.40	35.6		1.58, 1.38
2'							75.3		3.35 (brt, 11)
3'							32.3		1.67, 1 48
4'							54.3	ax	2.17 (ddd, 3.5, 12, 12)
								eq	2.93 (ddd, 1.5, 4.5, 12)
6'							54.1	ax	1.98 (ddd, 3.5, 12, 12)
								eq	2.75 (br d, 11)
7'							25.0		1.65, 1 57
8'							28.9		1.66, 1.23
9'							40.6		1.60
10'							95.8		3.07 (d, 8.5)
11'							31.1		1 60, 1.32
12'							28.8		1.40, 1 17
13'							31.6		1.31, 1.17
14'							25.1		1.35, 1.25
15'							24.7		1.69, 1.29
16'							36.0		1.57, 1 32

conformation while that of araguspongine D (**2**) has *trans*-decaline-like conformation as shown in Figure 1. However, in the case of araguspongine B (**1**), the coupling constant between H-9 and H-10 protons was observed as J= 2.5 Hz. Furthermore, the chemical shifts of H-9 , H_2-7, and H_2-11 protons are very close to those of other methylene protons and no NOE information was obtained for H-9 proton. It was, therefore, difficult to assign the relative configuration of the C-9 position.

In order to confirm the stereochemistry of the C-9 position of araguspongine B, we first analyzed the isomerization reaction among araguspongines B, D, E by alumina treatment. The solution of araguspongine E (**3**) in ethylenedichloride containing deuterium-labeled water (D_2O) was treated with dry Al_2O_3 under reflux for 5 h to furnish the deuterized araguspongines B (**1a**), D (**2a**), and E (**3a**) in 55:35:10 ratio (Figure 2). Each deuterized araguspongine B (**1a**), D (**2a**), and E (**3a**) showed the pseudo molecular

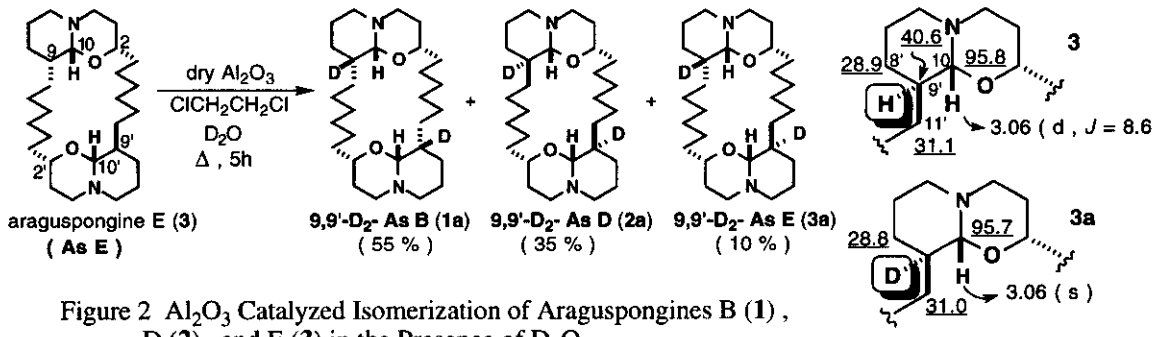


Figure 2 Al_2O_3 Catalyzed Isomerization of Araguspongines B (**1**) , D (**2**) , and E (**3**) in the Presence of D_2O

[(M+ H)$^+$] ion peak at *m/z* 449 ($C_{28}H_{49}D_2N_2O_2$) in FAB MS. Furthermore, in the ^{1}H-NMR spectra of **1a**, **2a**, and **3a**, H-9 and H-9' signals for these compounds were missing and 10-H and 10'-H signals were observed as a singlet at δ 4.30 in **1a**, δ 3.06 in **2a**, and δ 4.30 and δ 3.06 in **3a**, respectively. In the ^{13}C-NMR spectra of **1a**, **2a**, and **3a**, the C-9 and C-9' signals changed to small complex signals and the high-field shift of *ca* 0.1 ppm was observed at C-8,8', C-10,10', C-11,11' signals for these compounds. Thus, it was clarified that the H-9 and H-9' protons were exchanged with deuterium and the isomerization at the C-9 and C-9' through alumina treatment is possible.

Next, in order to clarify whether this isomerization is an equilibrium reaction or not, we analyzed the time course of the isomerization reaction among araguspongines B (**1**), D (**2**), and E (**3**) as shown in Table 2. After 24 h, aragusponge E (**3**) was converted to a mixture of **1**, **2**, and **3** (58:36:6 ratio) by alumina treatment. Araguspongines B (**1**) and D (**2**) were also converted to a similar mixture of **1**, **2**, and **3** under the same reaction conditions, respectively.

Table 2. Time Course of Distribution of Araguspongines in Isomerization Reaction

Starting material	Aragusponge D (As D)	Aragusponge E (As E)	Aragusponge B (As B)
products	As D As E As B	As D As E As B	As D As E As B
5 min	81 : 18 : 1	30 : 68 : 2	23 : 27 : 50
20 min	75 : 23 : 2	50 : 44 : 6	41 : 41 : 18
1 h	69 : 28 : 3	51 : 44 : 5	54 : 35 : 11
24 h	56 : 38 : 6	58 : 36 : 6	57 : 35 : 8

reaction condition : Al_2O_3 in $ClCH_2CH_2Cl$, reflux

Furthermore, we examined this isomerization reaction using different catalysts. As shown in Table 3, it was found that the isomerization of aragusponge E (**3**) also proceeded by aluminum isopropoxide [Al(O^{i}Pr)3], trimethyl borate [B(OMe)3], and titanium tetraisopropoxide [Ti(O^{i}Pr)4], while **3** was not converted to **1** and/or **2** in the cases of $AlCl_3$, $ZnCl_2$, BBr_3, and $CuCl_2$ treatment. These results

Table 3. Metal Salt Catalyzed Isomerization of Aragusponginе E (**3**)

	As D (**2**)		As E (**3**)		As B (**1**)	Recovered yield (%)
Al_2O_3	55	:	37	:	8	92
$Al(O^iPr)_3$	56	:	36	:	8	95
$B(OMe_3)_3$	53	:	40	:	7	91
$Ti(O^iPr)_4$	81	:	16	:	3	84

reaction condition : in $ClCH_2CH_2Cl$, reflux for 1 h

suggested that this isomerization reaction is an equilibrium reaction and proceeds through iminium (**i** and **iii**) and enamine (**ii**) intermediates as shown in Figure 3.

The isomer distribution (**1**-**3**) obtained by ring closure is presumably in accordance with the thermodynamic stability of individual isomers. The 2,9-*anti* substituents in aragusponginе D (**2**) having *trans*-decaline-like conformation are both equatorial orientation, while the presumable 2,9-*syn* substituents in aragusponginе B (**1**) having *cis*-decaline-like conformation are also both equatorial orientation. Thus, it was presumed that the isomerization of the C-9 position accompanied with inversion of a nitrogen lone-pair must occur by alumina treatment of the dimeric 2,9-disubstituted 1-oxaquinolizidine moiety. In other words, if both C-9 and C-9' substituents in **2** are isomerized by alumina treatment, the conformation of the resulting product (=aragusponginе B (**1**)) will change to thermodynamically stable *cis*-decaline-like conformation having equatorial orientated substituents at C-9 and C-9' as shown in Figure 1.

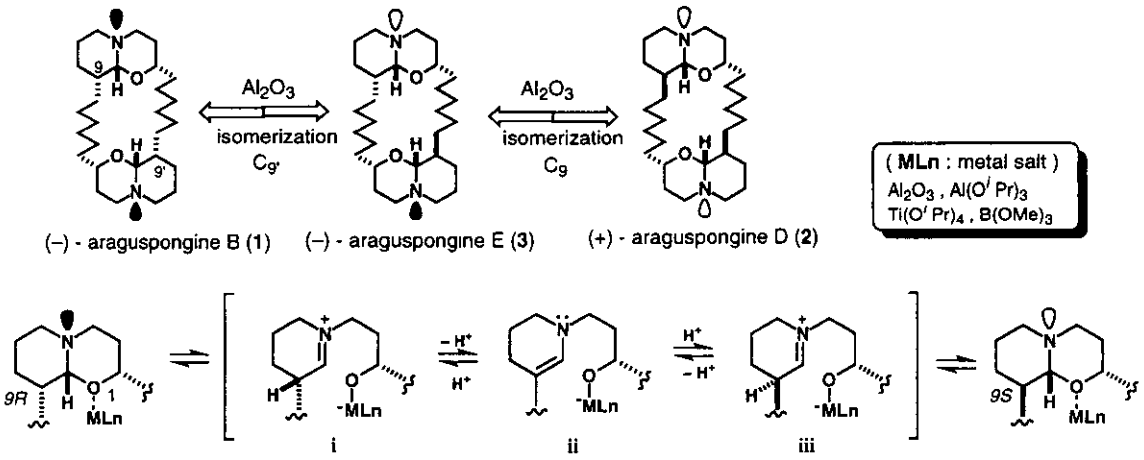


Figure 3 Plausible Reaction Mechanism for Isomerization in Aragusponginеs B (**1**), D (**2**), and E (**3**)

In order to confirm this presumption, we carried out X-ray crystallographic analysis of aragusponginе B (**1**). The single structure, which was solved by the direct method, was refined to R =0.068. The molecular conformation is shown in Figure 4. The X-ray analysis elucidated that **1** corresponds to 9 *R* configuration of (-)-aragusponginе B.

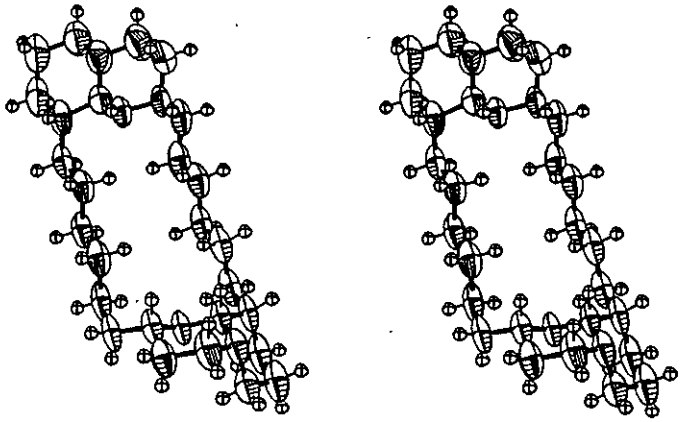
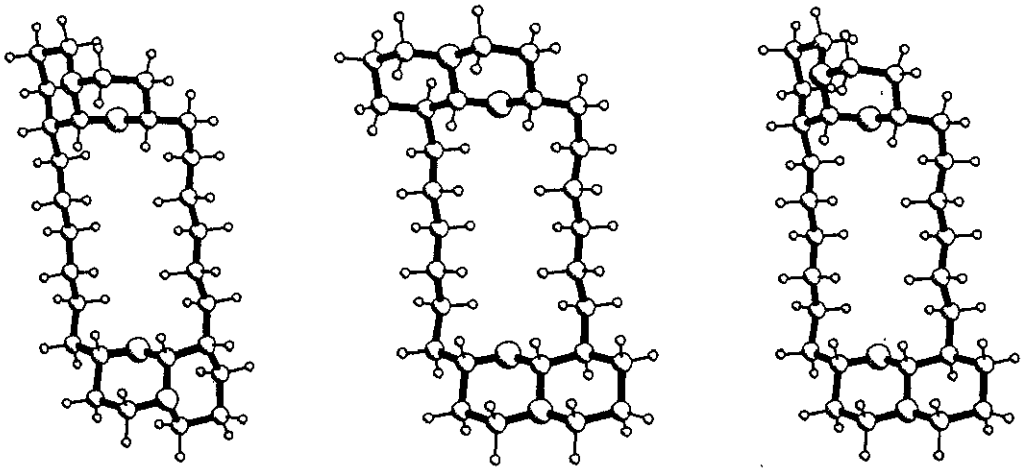


Figure 4 Stereoscopic View of Araguspongine B (**1**)

From the stereoview of Figure 4, the *cis*-decaline-like conformation for **1** having a 2,9-*syn*-disubstituted 1-oxaquinolizidine moiety was supported. On the basis of the structural correlation among araguspongines B, D, and E, it was clarified that (-)-araguspongine E (**3**) has 9 *R*, 9' *S* configurations and is the same compound as xestospongin C,[7] whose relative stereostructure has been determined by X-ray crystallographic analysis.

On the basis of crystallographic data of araguspongine B (**1**) and xestospongin C (**3**), we performed molecular mechanics calculations to compare thermodynamic stability among araguspongines B (**1**), D (**2**), and E (**3**). As shown in Figure 5, the energy-refined conformations by the molecular mechanics calculations showed good agreement with those obtained by X-ray crystallographic analysis and NMR analysis. The total energies of **1** and **3** were 1.37 and 0.60 kcal/mol unstable compared to that of **2**, respectively. These data supported the isomerization ratio among araguspongines B (**1**), D (**2**), and E (**3**) by alumina treatment as shown in Table 2.



Araguspongine B (**1**) Araguspongine D (**2**) Araguspongine E (**3**)

Figure 5 Energy-Refined Conformations of **1**, **2** and **3** by Molecular Mechanics Calculations

EXPERIMENTAL SECTION

The ^{1}H- and ^{13}C-NMR spectra were measured with a JEOL GX-500 (500 MHz) spectrometer and with Me_4Si (0 ppm) as the internal standard. The FAB MS were recorded on a JEOL JMS SX-102 mass spectrometer. For HPLC, a JASCO 887-PU Intelligent Pump module was used with a JASCO 875-UV Intelligent UV/Vis detector. Thin-layer chromatography (TLC) was conducted on precoated Kieselgel 60 F_{254} plates (0.25 mm, Merck) and detection of the spots was carried out by spraying 1% $Ce(SO_4)_2$/10% H_2SO_4 on the TLC plates followed by heating.

Isomerization of Araguspongines B (1), D (2), and E (3) A solution of **1** (10 mg) in $ClCH_2CH_2Cl$ (2 mL) was treated with alumina (Al_2O_3 60 F_{254}, Merck) (20 mg) under reflux. An aliquot of the reaction mixture was taken and filtered. After evaporation of the solvent, the product was analyzed by HPLC (Mightysil ODS, MeOH-H_2O=20:1 containing 0.1% Et_2NH). Each peak was identified with the authentic sample. The reaction products from **2** and **3** were also analyzed by the same method.

Deuteration Experiment in Isomerization of Araguspongine E (3) A solution of **3** (30 mg) in $ClCH_2CH_2Cl$ (2 mL)-99.996% D_2O (0.06 mL) mixture was treated with alumina (Al_2O_3 60 F_{254}, Merck)(73 mg) under reflux for 5 h. The reaction mixture was poured into sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by HPLC (Mightysil ODS) to furnish **1a** (2 mg), **2a** (11 mg), and **3a** (7 mg).

1a: FAB MS : *m/z* 449 $(M+H)^+$. HR-FAB MS *m/z* : Calcd for $C_{28}H_{49}D_2N_2O_2$: 449.4076. Found: 449.4098. ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 4.30 (s, H-10), 3.54 (br t, *J*=*ca.*11 Hz, H-2), 3.19 (ddd, *J*=3.5, 13, 13, H-4ax), 3.06 (dt-like, *J*=*ca.*3.5, 13, H-6ax), 2.96 (dd, *J*=3.5, 13.5, H-4eq), 2.41 (br d, *J*=*ca.*13, H-6eq). ^{13}C-NMR (68 MHz, $CDCl_3$, δc): 76.0 (C-2), 26.3 (C-3), 52.7 (C-4), 45.2 (C-6), 25.7 (C-7), 26.4 (C-8), 87.4 (C-10), 32.9 (C-11), 27.3 (C-12), 31.8 (C-13), 29.5 (C-14), 24.8 (C-15), 36.2 (C-16).

2a: FAB MS : *m/z* 449 $(M+H)^+$. HR-FAB MS *m/z* : Calcd for $C_{28}H_{49}D_2N_2O_2$: 449.4076. Found: 449.4082. ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 3.35 (br t, *J*=*ca.*11 Hz, H-2), 3.06 (s, H-10), 2.93 (ddd, *J*=1.5, 4.5, 12, H-4eq), 2.75 (br d, *J*=*ca.*12, H-6eq), 2.18 (ddd, *J*=3.5, 12, 12, H-4ax), 1.98 (ddd, *J*=3.5, 12, 12, H-6ax). ^{13}C-NMR (68 MHz, $CDCl_3$, δc): 75.2 (C-2), 32.2 (C-3), 54.3 (C-4), 54.0 (C-6), 24.9 (C-7), 28.8 (C-8), 95.8 (C-10), 31.1 (C-11), 28.8 (C-12), 31.6 (C-13), 25.1 (C-14), 25.3 (C-15), 35.4 (C-16).

3a: FAB MS : *m/z* 449 $(M+H)^+$. HR-FAB MS *m/z* : Calcd for $C_{28}H_{49}D_2N_2O_2$: 449.4076. Found: 449.4067. ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 4.29 (s, H-10), 3.53 (br t, *J*=*ca.*11 Hz, H-2), 3.35 (br t, *J*=*ca.*11, H-2'), 3.18 (br t, *J*=*ca.*13, H-4ax), 3.06 (s, H-10'), 3.06 (dt-like, *J*=*ca.* 2.5, 11, H-6ax), 2.96 (dd, *J*=3.5, 13, H-4eq), 2.93 (ddd, *J*=1.5, 4.5, 12, H-4'eq), 2.75 (br d, *J*=*ca.*12.5, H-6'eq), 2.40 (br d, *J*=*ca.*11, H-6eq), 2.17 (ddd, J=3, 12, 12, H-4'ax), 1.98 (ddd, *J*=3.5, 12, 12, H-6'ax). ^{13}C-NMR (68

MHz, $CDCl_3$, δc): 75.8 (C-2), 26.3 (C-3), 52.8 (C-4), 45.3 (C-6), 25.7 (C-7), 26.4 (C-8), 87.4 (C-10), 32.8 (C-11), 27.1 (C-12), 31.6 (C-13), 29.4 (C-14), 25.3 (C-15), 35.6 (C-16), 75.4 (C-2'), 32.3 (C-3'), 54.3 (C-4'), 54.1 (C-6'), 24.9 (C-7'), 28.8 (C-8'), 95.8 (C-10'), 31.0 (C-11'), 28.8 (C-12'), 31.6 (C-13'), 25.1 (C-14'), 24.7 (C-15'), 36.0 (C-16').

Isomerization Reaction of Araguspongine E (3) Using Different Catalysts A solution of **3** (4.5 mg, 0.01 mmol) in $ClCH_2CH_2Cl$ (0.5 mL) was treated with several kinds of metal salt (0.02 mmol) [$Al(O^iPr)_3$, $B(OMe)_3$, $Ti(O^iPr)_4$, $AlCl_3$, $ZnCl_2$, BBr_3, or $CuCl_2$] under reflux for 1 h. Each reaction mixture was poured into sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the crude product was analyzed by HPLC (Mightysil ODS, MeOH-H_2O=20:1 containing 0.1% Et_2NH).

X-ray Crystallographic Analysis of Araguspongine B (1) Araguspongine B (**1**) (mp 132-133 °C) was recrystallized from Et_2O. X-ray data were collected with a Rigaku AFC-5R diffractometer by using the graphite-monochromated Cu-Ka radiation (l=1.5418 Å) at 293 K. Details for cell parameter determination and the reflectional intensity data collection are summarized below. Intensity data within $2°\leq 2q \leq 130°$ were measured by employing a w-2q scan mode. Four standard reflections monitored every 100 reflections showed no significant time-dependence (< ±2%).
The crystal structure was solved by the direct method with the *MULTAN87* program.[11] The positional parameters of non-H atoms were refined by full-matrix least-squares with anisotropic temperature parameters using the SHELX76 program.[12] The positions of the H atoms were located on the difference Fourier map and were included in the subsequent refinements with isotropic temperature parameters. The atomic scattering factors and terms of anomalous dispersion corrections were taken from *International Tables for X-Ray Crystallography.*[13] The crystallographic calculations were performed using a CRYSTAN GM soft package.[14]

Crystal Data and Data Collection of 1[15] Formula: $C_{28}H_{50}N_2O_2$, MW = 446.72. Monoclinic, a (Å) = 9.120(2), b (Å) = 9.820(1), c (Å) = 15.490(1), β=100.96(1)°, V ($Å^3$) = 1362.0(3). Space group $P2_1$, Z = 2, D_X = 1.089 $g \cdot cm^{-3}$, μ(Cu-Kα)(cm^{-1}) = 4.86. Crystal size (mm^3): 1.0x0.4x1.0. No. of data with ($F_o < 3\sigma(F_o)$) = 2213. No. of variables = 337. R_F = 0.068. R_{wF} = 0.108. Goodness of fit = 1.106.

Molecular Mechanics Calculation All energy calculations were carried out with the molecular mechanics force field (MMFF) program[16] within the CHEMLAB-II system[17] operating on a MicroVAX-II computer. The empirical energy function used to obtain the energy-minimized structures included harmonic potential energy terms for bond lengths, bond angles, bond dihedral angles, torsion angles, and van der Waals and electrostatic terms for nonbonded interactions and hydrogen bonding potentials. The starting atomic coordinates for energy minimization calculations were constructed by using the bond lengths and angles of crystallographic data of araguspongine B (**1**) and xestospongin C (**3**).[7]

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. This paper constitutes Part XXXIX of our studies on Marine Natural Products. Part XXXVIII: M. Kobayashi, S. Aoki, K. Gato, and I. Kitagawa, *Chem. Pharm. Bull.*, 1996, **44**, 2142.

2. Present address: *Faculty of Pharmaceutical Sciences, Kinki University, Kowakae, Higashiosaka, Osaka 577, Japan.*

3. J. C. Braekman, D. L. Daloze, and P. M. Abreu, *Tetrahedron Lett.*, 1982, **23**, 4277.

4. J. C. Braekman and D. L. Daloze, *Bull. Soc. Chim. Belg.*, 1988, **97**, 519.

5. M. Kobayashi, K. Kawazoe, and I. Kitagawa, *Chem. Pharm. Bull.*, 1989, **37**, 1676.

6. M. Kobayashi, K. Kawazoe, and I. Kitagawa, *Tetrahedron Lett.*, 1989, **30**, 4149.

7. M. Nakagawa, M. Endo, M. Tanaka, and G. Lee, *Tetrahedron Lett.*, 1984, **25**, 3227. The relative stereostructures of these compounds have been elucidated. The stereoview of xestospongin C supports that the 2,9-*syn*-disubstituted 1-oxaquinolizidine moiety has *cis*-decalin-like conformation while the 2,9-*anti*-disubstituted 1-oxaquinolizidine moiety has *trans*-decaline-like conformation.

8. K. H. Ahn and S. J. Lee, *Tetrahedron Lett.*, 1992, **33**, 507; L. Börjesson and C. J. Welch, *Tetrahedron*, 1992, **48**, 6325; N. Bentley, G. Singh, and O. W. Howarth, *Tetrahedron*, 1993, **49**, 4315; L. Börjesso, I. Csöregh, and C. J. Welch, *J. Org. Chem.*, 1995, **60**, 2989.

9. T. R. Hoye, J. T. North, and L. J. Yao, *J. Am. Chem. Soc.*, 1994, **116**, 2617.

10. T. R. Hoye, J. T. North, and L. J. Yao, *J. Org. Chem.*, 1994, **59**, 6904.

11. T. Debaerdemaeker, G. Germain, P. Main, C. Tate, and M. M. Woolfson, MULTAN87, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data, Universities of York, England, and Louvain, Belgium, 1987.

12. G. M. Sheldrick, SHELX76, Program for Crystal Structure Determination, University of Cambridge, England, 1976.

13. 'International Tables for X-Ray Crystallography,' Vol. 4, Kynoch Press, Birmingham, England, 1974.

14. CRYSTAN GM, A Computer Program for the Solution and Refinement of Crystal Structures from X-ray Diffraction Data, Version 6.1, MAC Science Co., Ltd., 1984.

15. Lists of structure factors, anisotropic thermal parameters of non-H atoms, H-atom coordinates and their isotropic thermal parameters, bond lengths and angles, torsion angles, and intermolecular distances less than 3.4 Å have been deposited at the Cambridge Crystallographic Data Centre.

16. A. J. Hopfinger and R. A. Pearlstein, *J. Comput. Chem.*, 1984, **5**, 486.

17. Chemical Modeling Laboratory-II (CHEMLAB-II); Molecular Design Limited, San Leandro, CA, 1986.

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