Articles

Conformational Considerations in 1-Oxaquinolizidines Related to the Xestospongin/Araguspongine Family: Reassignment of Stereostructures for Araguspongines B and E

Thomas R. Hoye,* Jeffrey T. North, and Letitia J. Yao[1]

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

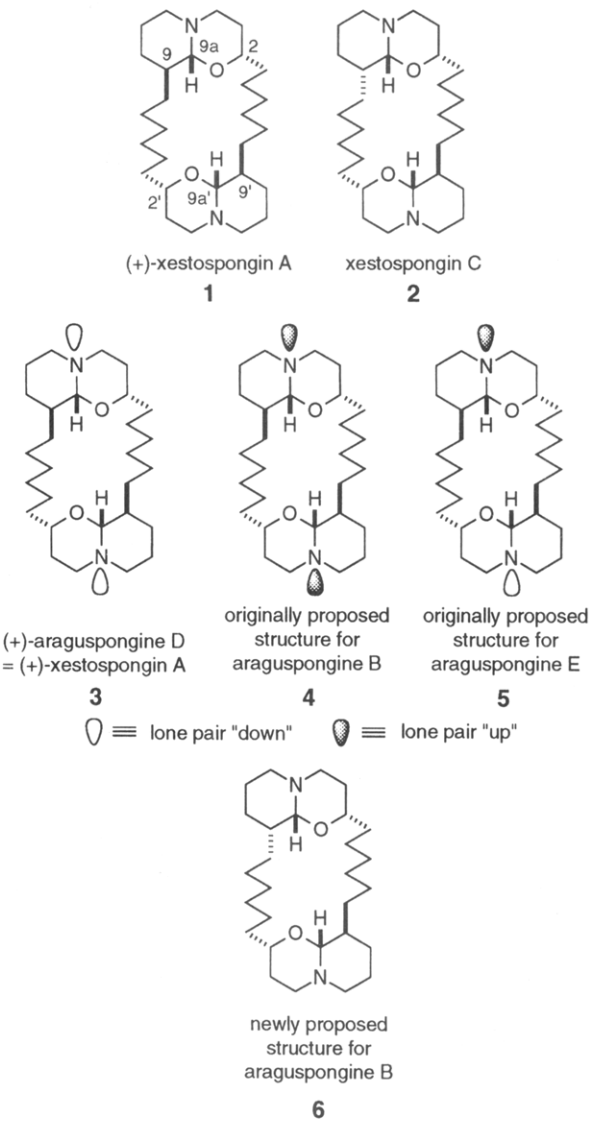
Received July 6, 1994[⊗]

Conformational aspects of the 1-oxaquinolizidine ring system found in the xestospongin/araguspongine family of natural products has been studied by molecular modeling and NMR spectroscopy. Stereochemical complexities [e.g., (i) *cis*- vs *trans*-decalin-like conformers and (ii) relative configuration of variously substituted 1-oxaquinolizidines] associated with this bridgehead nitrogen-containing skeleton are discussed. Experimental equilibrium values are rationalized. Reassignment of the stereostructures for araguspongines B (from **4** to **6**) and E (from **5** to **2**) is made in light of the above.

Xestospongins A and C (**1** and **2**) were originally isolated from the Australian sponge *Xestospongia exigua* by Nakagawa and Endo in 1984.[2] The structure of xestospongin C (**2**) was determined crystallographically while that of xestospongin A (**1**) was assigned by spectroscopic comparison with the data from **2**. Xestospongin C (**2**) lacks symmetry; its C(9)-epimer, xestospongin A (**1**), is C_2-symmetric. These alkaloids contain a pair of the conformationally interesting 1-oxaquinolizidine (hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine) ring systems.

In 1989 Kitagawa *et al.* isolated araguspongines A−H and J from the Okinawan marine sponge *Xestospongia* sp.[3] They found that araguspongine D (**3**) was identical to xestospongin A (**1**).[4] Two of the other araguspongines, B and E,[4] have the same constitution as araguspongine D (**3**)/xestospongin A (**1**). These were assigned the structures shown as **4** and **5**, respectively.[3] The only difference among structures **3-5** is the relative orientation of the bridgehead nitrogen lone pairs of electrons with respect to the stereogenic carbon centers resident on the bis-1-oxaquinolizidine rings.[3] That is, the relative configurations of the stereogenic nitrogen atoms differ among **3-5**, but the configurations of all remaining stereocenters [i.e., C(2) vs C(9) vs C(9a) vs C(2′) vs C(9′) vs C(9a′)] are identical. In conjunction with the isolation and structural studies, it was observed that araguspongines B and E each could be isomerized to araguspongine D (**3**) when exposed to alumina at 80 °C.

We have studied intermediates containing the 1-oxaquinolizidine ring system[5] in conjunction with a recently described total synthesis of xestospongin A.[6,7] We describe here various conformational aspects of this system. Among other things, the understanding we have gained



⊗ Abstract published in *Advance ACS Abstracts,* October 15, 1994.

(1) National Science Foundation Graduate Fellow (1989−1992); DuPont Fellow (1993−1994).

(2) Nakagawa, M.; Endo, M.; Tanaka, N.; Gen-Pei, L. *Tetrahedron Lett.* **1984**, *25*, 3227.

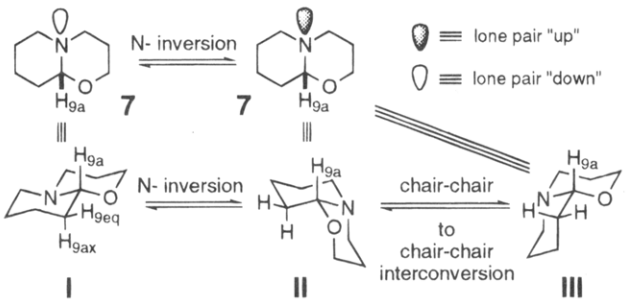
(3) Kobayashi, M.; Kawazoe, K.; Kitagawa, I. *Chem. Pharm. Bull.* **1989**, *37*, 1676.

(4) Each of araguspongines D, B, and E were isolated as a mixture of enantiomers that were separated in every case by HPLC (Chiralcel OF column).[3] For ease of comparison, structures for the araguspongines shown here are the same antipodes as those for the xestospongins, for which only a single enantiomer was isolated.[2]

(5) Hoye, T. R.; North, J. T. *Tetrahedron Lett.* **1990**, *31*, 4281.

0022-3263/94/1959-6904$04.50/0

Scheme 1



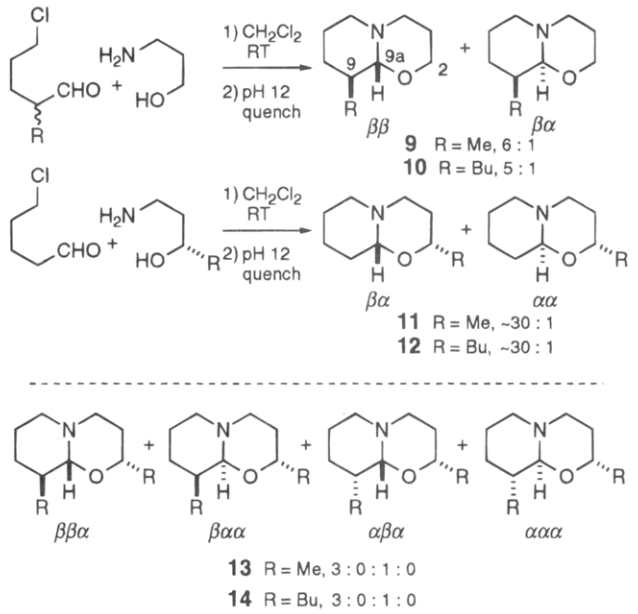
leads us to now propose an alternative structure, **6**, for araguspongine B (originally assigned **4**) and to suggest that araguspongine E (originally assigned **5**) is, in fact, identical to xestospongin C (**2**).

It is helpful to first define some stereochemical considerations. The parent 1-oxaquinolizidine (**7**) ring system can access several conformational isomers (see **I-III** in Scheme 1). The *trans*-decalin-like conformer **I** is transformed into the *cis*-decalin-like conformer **II** by bridgehead nitrogen atom inversion. Chair−chair conformational interconversions within both rings of **II** generate the alternative *cis*-decalin-like conformer **III**. Proton NMR spectral data for 1-oxaquinolizidine (**7**) suggest that **I-III** are in rapid equilibrium and that the dominant contributor to the conformational equilibrium for this unsubstituted parent (**7**) is the *trans*-decalin-like isomer **I**. Thus, H(9a) exhibits coupling to H(9ax) of 8.5

Hz and to H(9eq) of 2.5 Hz, consistent with the dihedral angles in either **I** or **II**, but not those in **III**. Furthermore, H(9a) also is highly shielded (δ 3.41), consistent with the presence of two sets of nonbonding electrons antiperiplanar to the C(9a)−H(9a) bond uniquely found in **I**. Notice that this suggests that the greater degree of anomeric stabilization expected for **III** (double) relative to either **I** (single) or **II** (single) is energetically insufficient to override the enthalpic destabilization that accompanies the additional axial substituent present in either of the *cis*-decalin-like conformers **II** or **III**. Later we describe aspects of the molecular mechanics energetics of this system. This situation is similar to that previously described for the isomeric 3-oxaquinolizidine structure **8**.[8]

An independent stereochemical issue is whether the relative configurations of the two appendages of the macrocyclic ring at C(2) and C(9) on any single 1-oxaquinolizidine ring have a *trans*-dialkylated or a *cis*-dialkylated orientation. All of our (principally NMR-based) observations are consistent with the notions that (i) *trans*-dialkylated rings reside, coincidentally, to a large extent in the *trans*-decalin-like conformation **I** [cf. both of the identical 1-oxaquinolizidine rings in **1**, the "bottom" ring in **2**, and the dimethylated model compound **13**$\beta\beta\alpha$

Scheme 2



(Scheme 2)] and (ii) *cis*-dialkylated rings reside, also coincidentally, to a large extent in the *cis*-decalin-like conformation **III** [cf. the "top" ring in **2** and the dimethylated model compound **13**$\alpha\beta\alpha$ (Scheme 2)]. The chemical shifts for proton H(9a) in these *cis*-disubstituted compounds are typically in the range of $\delta = 3.8-4.2$ ppm and appear as broad doublets with $J \approx 3$ Hz. This is nearly 1 ppm downfield of the shift for H(9a) in the C(9)-epimeric *trans*-disubstituted compounds, which typically appear as broad doublets with $J \approx 8$ Hz.

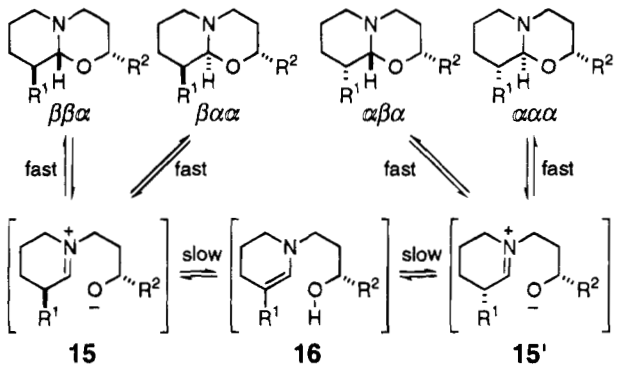
We have previously described the synthesis of derivatives of **7** containing C(9)-monomethyl, C(2)-monomethyl, and C(2),C(9)-dimethyl substituents, as well as their *n*-butylated analogs (Scheme 2).[5] In the following discussion α and β refer to the "down" vs "up" orientation, respectively, of the alkyl substituents at C(2) and C(9) and of the hydrogen atom at C(9a). Thus, a 6:1 mixture (^{1}H NMR) of the 9-methylated diastereomers **9**$\beta\beta$/**9**$\beta\alpha$ or a 5:1 mixture (^{1}H NMR) of the 9-butylated diastereomers **10**$\beta\beta$/**10**$\beta\alpha$ was generated when the 2-methyl- or 2-butyl-5-chlorovaleraldehyde was condensed with 1,3-aminopropanol. This equilibrium mixture was not separable by either liquid or gas chromatography, suggesting that ring opening of the 1,3-oxazine ring within **9** or **10** was both rapid and reversible (see later discussion). In an analogous fashion, the 2-methylated and 2-butylated diastereomeric pairs **11**$\beta\alpha$/**11**$\alpha\alpha$ and **12**$\beta\alpha$/**12**$\alpha\alpha$ (from 5-chlorovaleraldehyde and 1-amino-3-butanol or -3-heptanol, respectively) were each generated as equilibrium mixtures as detected (only) by ^{13}C NMR analysis. The ratio was estimated to be ~30:1, but this value is much less precise than those K_{eq}'s of <10 for **9**, **10**, **13**, and **14**, which were measured by integration of ^{1}H NMR resonances. Finally, the 2,9-dimethylated and 2,9-dibutylated derivatives **13**$\beta\beta\alpha$/**13**$\alpha\beta\alpha$ and **14**$\beta\beta\alpha$/**14**$\alpha\beta\alpha$ were each isolated as 3:1 mixtures. In the case of these *di*substituted 1-oxaquinolizidines it proved possible to separate the diastereomers by liquid chromatography on silica gel. Only two ($\beta\beta\alpha$ and $\alpha\beta\alpha$) of the four possible diastereomers of **13** and **14** were observed. It should be noted that we earlier described[5] the equilibration of isomers of **13** in D_2O as their hydrobromide salts and observed essentially a single diastereomer in the proton NMR spectrum. As has been verified and correctly

(6) Hoye, T. R.; North, J. T.; Yao, L. J. *J. Am. Chem. Soc.* **1994**, *116*, 2617.

(7) For other studies related to the synthesis of xestospongin A, see: (a) Ahn, K. H.; Lee, S. J. *Tetrahedron Lett.* **1992**, *33*, 507. (b) Börjesson, L.; Welch, C. J. *Tetrahedron* **1992**, *48*, 6325.

(8) (a) Blackburne, I. D.; Katritzky, A. R.; Read, D. M.; Chivers, P. J.; Crabb, T. A. *J. Chem. Soc., Perkin Trans. 2* **1976**, 418. (b) Crabb, T. A.; Newton, R. F. *Tetrahedron* **1968**, *24*, 4423.

Scheme 3



pointed out by Ahn and Lee,[7a] this equilibrium under acidic aqueous conditions differs significantly from that of the neutral (free-base) system.

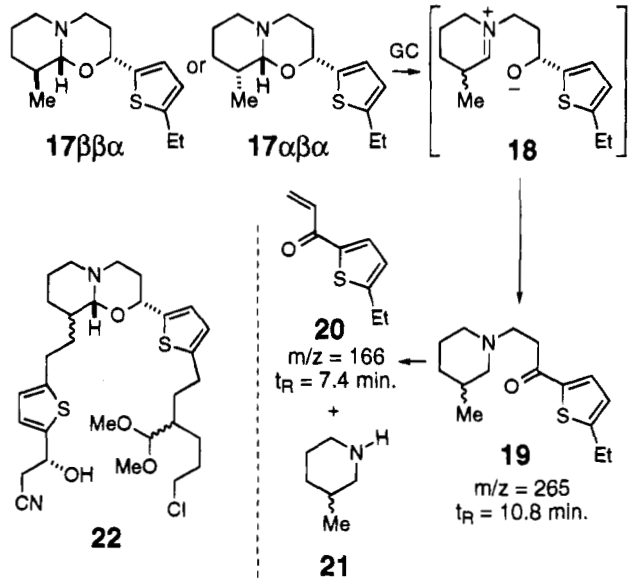
Equilibrium considerations within each set of substituted 1-oxaquinolizidines are very informative. Every attempt to purify a mixture of *mono*substituted 1-oxaquinolizidines **9-12** on silica gel (HPLC, MPLC, or flash) resulted in recovery of the same ratio of diastereomers [or C(9a)-epimers]. Thus, all spectroscopic data reported here for monosubstituted 1-oxaquinolizidines are extracted from mixtures of major and minor diastereomers. This facile diastereomerization within each of the monosubstituted pairs (i.e., R^1 = alkyl, R^2 = H or R^1 = H, R^2 = alkyl) was consistent with a rapid and reversible ring opening at the aminal carbon to the iminium ion **15** (or **15′**) as shown in the left (or right) half of Scheme 3.

By contrast, the two observed diastereomers of the 2,9-*di*substituted 1-oxaquinolizidines **13** and **14** were separable on silica gel. This implies that a kinetically less accessible pathway is required for isomerization of the two alkyl-bearing stereogenic centers, C(2) vs C(9). Thus, either of the epimeric iminium ions **15** or **15′** can lose a proton and form the enamine **16** in what is apparently a slower step than iminium ion formation itself. Carbinol **16** contains a single stereogenic center. Reprotonation of that enamine from either face and reclosure to the oxazine then provides a mechanism for interconversion of all four diastereomers of **13** and **14**.

Another observation, made during capillary gas chromatographic/mass spectroscopic analysis of the disubstituted 1-oxaquinolizidine **17**, a model compound studied in conjunction with our recent xestospongin A synthesis work,[6] was consistent with the intermediacy of zwitterions like **15**/**15′**. Thus, independent GC–MS analysis of each of the diastereomers **17**ββα and **17**αβα gave rise to two peaks of the same retention times and mass spectral fragmentation patterns (Scheme 4). The first peak was a low molecular weight product assigned, on the basis of its mass spectrum, as the vinyl ketone **20**. The second peak had the mass of each analyte, but the fragmentation pattern was consistent with the structure of the ketone **19**, which contains only one stereogenic center. A mechanism that accounts for this involves thermal generation (injection port) of zwitterion **18**, intramolecular hydride transfer to produce the ketone **19**, and subsequent thermal elimination of 3-methylpiperidine **21**.

Equilibration studies with thiophene-substituted **17** established conditions required to isomerize the ββα- and αβα-epimers; heating either diastereomer at 80 °C in $CDCl_3$ containing triethylamine smoothly interconverted the two. In this instance an equilibrium value of 3.9 was observed for **17**ββα/**17**αβα. These conditions were also

Scheme 4



used to equilibrate the ββα- and αβα-epimers of the key intermediate **22** in our xestospongin synthesis (K_{eq} = 2.3).[6]

One aspect of this family of equilibrium values (Scheme 2) was counterintuitive. The major isomer in 2- and 9-monoalkyl-1-oxaquinolizidines predominated by ~30:1 (**11** and **12**) and 5–6:1 (**9** and **10**), respectively. We therefore expected the equilibrium constants for the 2,9-dialkyl-1-oxaquinolizidines (**13**, **17**, and **22**) to vastly favor the *trans*-dialkyl isomer having the ββα relative configuration. This is clearly not the case; all *trans*-dialkyl:*cis*-dialkyl equilibrium ratios for these compounds are only 2.3–3.9:1. We turned to molecular mechanics for insight.

Force-field calculations were performed for the different conformations, **I-III**, of all of the diastereomers of the methyl-substituted oxaquinolizidines **9**, **11**, and **13** as well as for 6-methyl-1-oxaquinolizidine (**23**). Synthesis of this monomethyl isomer was very recently described, and the **23**αβ/**23**αα diastereomers were isolated in a 3:1

23αβ 3.0 : 1.0 **23**αα

ratio.[9] We suspect that this again represents the thermodynamic ratio of these C(6)-epimers. For the calculations we considered implementing the aminal parameter set recently reported by Fuchs and Senderowitz for MMP2.[10] However, since we were also interested in examining the effect of solvation on the relative energies of the various conformations, we elected to use the modified MM2 forcefield within Macromodel. In this forcefield the aminal N is treated as a simple aliphatic amine nitrogen atom. Monte Carlo conformational searches were performed on each of the conformations shown in Figures 1–4. In each case the global minimum has both 6-membered rings in chairlike conformations

(9) Cossy, J.; Guha, M.; *Tetrahedron Lett.* **1994**, *35*, 1715.
(10) Senderowitz, H.; Aped, P.; Fuchs, B. *J. Comput. Chem.* **1993**, *14*, 944.

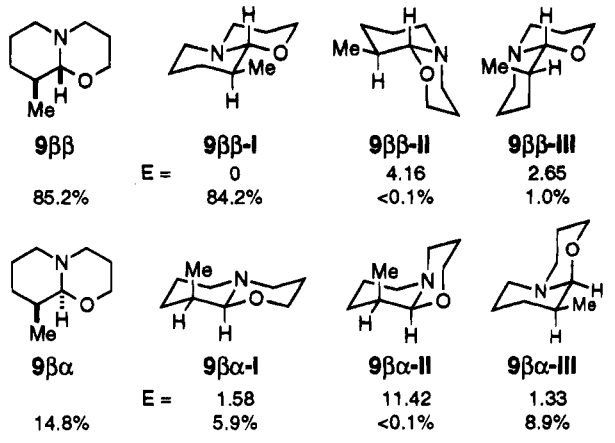


Figure 1. MM2-energies of 9-methyl-1-oxaquinolizidine (**9**). The top number indicates the energy (kcal/mol) in chloroform relative to the most stable species. The bottom number indicates the percentage of each in the Boltzmann equilibrium distribution among all six species.

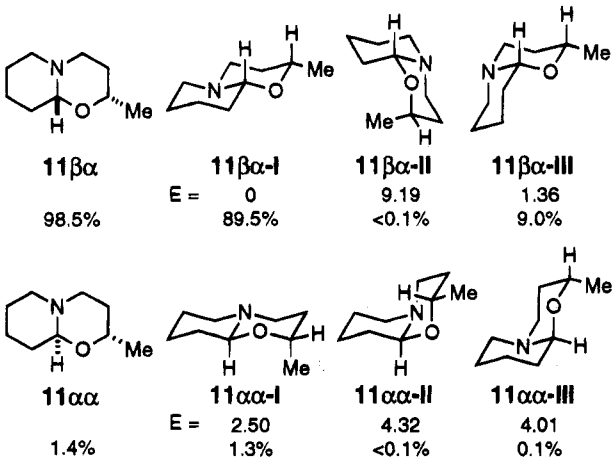


Figure 2. MM2-energies of 2-methyl-1-oxaquinolizidine (**11**). The top number indicates the energy (kcal/mol) in chloroform relative to the most stable species. The bottom number indicates the percentage of each in the Boltzmann equilibrium distribution among all six species.

and is substantially below the next lowest energy conformer, which always had at least one ring in a distorted, nonchair array. Boltzmann analysis of the energies in chloroform for conformations **I-III** for each diastereomer of **9**, **11**, **13**, and **23** led to the calculated equilibrium values collected in Table 1. A qualitative match between the calculated and observed K_{eq}'s can be seen, suggesting that this approach is valid for estimating relative stabilities of unknown 1-oxaquinolizidines. Adding a 500 cal/mol correction term for the additional anomeric stabilization energy uniquely present in conformers **III** did not universally improve the agreement; the calculated K_{eq}'s for **23** and **13** were more well matched, but that for **9** was less. Nonetheless, these calculations demonstrate that the unexpectedly small K_{eq} for the 2,9-dialkyl-1-oxaquinolizidines arises from the accessibility of both *trans*- and *cis*-decalin-like conformations.

The lowest energy conformation for each of the isolated model 1-oxaquinolizidines **9**, **11**, **13**, or **23** has the substituent(s) oriented in an equatorial position. By contrast, the originally reported structures for araguspongines B (**4**) and E (**5**) necessarily have one axial substituent regardless of which *cis*-fused decalin conformer predominates (cf. **13**$\beta\beta\alpha$-II and **13**$\beta\beta\alpha$-III). We

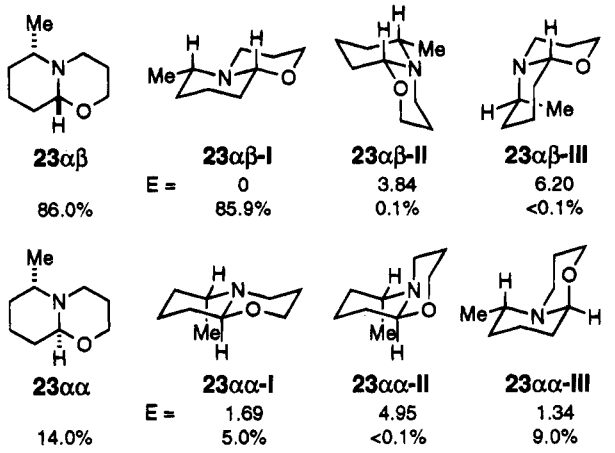


Figure 3. MM2-energies of 6-methyl-1-oxaquinolizidine (**23**). The top number indicates the energy (kcal/mol) in chloroform relative to the most stable species. The bottom number indicates the percentage of each in the Boltzmann equilibrium distribution among all six species.

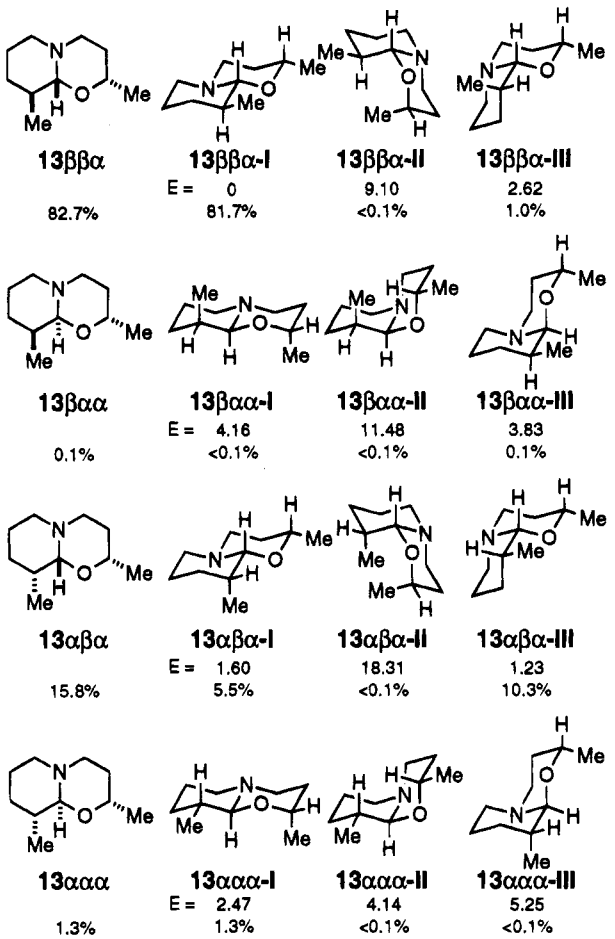


Figure 4. MM2-energies of 2,9-dimethyl-1-oxaquinolizidine (**13**). The top number indicates the energy (kcal/mol) in chloroform relative to the most stable species. The bottom number indicates the percentage of each in the Boltzmann equilibrium distribution among all 12 species.

have reconsidered these structures vis-a-vis that of araguspongine D (**3**). Structure **3** has two *trans*-decalin-like rings, structure **4** has two *cis*-decalin-like rings, and structure **5** has one of each. However, all have a *trans*-dialkyl relationship between the macrocyclic appendages on any one 1-oxaquinolizidine ring. Xestospongin C (**2**), like the originally proposed structure **5** for araguspongine

Table 1. Observed vs Calculated Equilibrium Values in Chloroform for the Series of Mono- and Dimethylated-1-Oxaquinolizidines.

		K_{eq}		
			calcd	
compd	ratio	obsd	uncorrected	corrected[a]
9-methyl (**9**)	[**9**ββ]/[**9**βα]	6	5.8	3.3
2-methyl (**11**)	[**11**βα]/[**11**αα]	~30	66.5	68.3
6-methyl (**23**)	[**23**αβ]/[**23**αα]	3	6.2	3.3
2,9-dimethyl (**13**)	[**13**ββα]/[**13**αβα]	3	5.2	2.9

[a] The energies of **III** were lowered by 0.5 kcal/mol and the K_{eq}'s were redetermined following Boltzmann analysis.

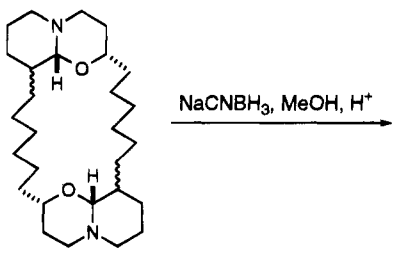
E, also has one *trans*- and one *cis*-decalin-like 1-oxaquinolizidine ring. However, xestospongin C has a *cis* relationship of the C(2)- and C(9)-substituents on the *cis*-decalin-like 1-oxaquinolizidine ring, as supported both by its X-ray structure and solution NMR data.

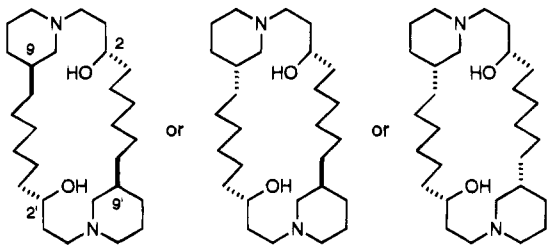
The Kitagawa group described isomerization experiments in which aragusponge E and aragusponge B were individually converted into aragusponge D when heated to 80 °C in the presence of alumina. This conversion was attributed to nitrogen lone-pair inversion (i.e., **5** to **3** and **4** to **3**, respectively). However, this observation can also be explained by the iminium ion/enamine epimerization mechanism shown in Scheme 3 (cf. **15** to **16** to **15′**). In other words, if aragusponges E and B have structures **2** and **6**, respectively, and as we now propose, they would also be expected to epimerize to aragusponge D (**3**) when heated in the presence of a base catalyst (cf. 80 °C, $CDCl_3$, Et_3N for isomerizations of **17** and **22**).

The published ^1H and ^{13}C NMR spectral data for xestospongin C[2,11] (**2**) and aragusponge E[3] (originally **5**) are reproduced in Tables 2 and 4, respectively. The proton and carbon chemical shift values are similar. Although the reader may be concerned about the magnitude of the differences in chemical shifts, we note that the variations are systematic ($\Delta\delta_H$'s of 0.1−0.7 ppm and $\Delta\delta_C$'s of 0.3−1.03 ppm). We attribute these discrepancies to differences in spectral referencing protocols. This explanation is reinforced by the comparable magnitude of discrepancies that was observed among the chemical shifts reported for natural xestospongin A (**1**)[2,11] and aragusponge D (**3**)[3] when compared with our synthetic sample of **1/3** (Table 3).[6]

The reassignment of aragusponge E as structure **2** necessitates the reassignment of aragusponge B (originally **4**) as **6**. As noted above, aragusponge B also can be isomerized to xestospongin A/aragusponge D (**1/3**).[3] The reported NOE study of aragusponge B demonstrated the proximity among protons H(2), H(4ax), and H(9a) (Figure 5);[3] this observation is consistent with either of structures **4** or **6**. The simplicity of the ^1H (Table 2) and ^{13}C NMR (Table 4) spectral data for aragusponge B suggest that it is a C_2-symmetric molecule. Moreover, the chemical shifts match quite closely those attributed to the *cis*-disubstituted/*cis*-decalin-like half of the unsymmetrical aragusponge E/xestospongin C (**2**). Thus, structure **6** is consistent with all of the reported chemical and spectroscopic data for aragusponge B.

There is further evidence to support this new assignment of structures **2** and **6** for aragusponges E and B, respectively. Kawazoe described[12] the sodium cyanoborohydride reduction of each of the aragusponges D, E, and B in acidic methanol. Each isomer gave rise to one of three distinct, diastereomeric compounds; these were again originally assigned as nitrogen invertomers (on the piperidine rings), each having the *constitution* of macrocycles **24**.[12] We expect that the originally assigned





24D **24E** **24B**

aragusponge structures **3**−**5** would have given the same compound (i.e., **24D**) upon $NaCNBH_3$ reduction because of rapid N-inversion. However, each of the isolated isomers of **24** was stable when heated with alumina at 80 °C.[12] We therefore speculate that these three compounds have the structures **24D**, **24E**, and **24B**, respectively. That is, that they retain the configurational relationships among C(2), C(9), C(2′), and C(9′) present in the newly assigned aragusponge structures **3**, **2**, and **6**, respectively.

In conclusion, a self-consistent framework for understanding the many stereochemical and conformational issues that are associated with the xestospongin/aragusponge family of 1-oxaquinolizidine-containing alkaloids is presented. Arguments based on this understanding provide strong evidence that the structures of aragusponges B and E possess structures **6** and **2**.

Experimental Section

For the oxaquinolizidines **7** and **9-14**, either the major isomer (or the inseparable mixture of isomers) in each instance was further characterized by high-resolution mass spectrometry and ^{13}C NMR and IR spectroscopy. Only the ^1H NMR data in $CDCl_3$ are reported here.

Representative Procedure for Preparation of 1-Oxaquinolizidines: Synthesis of (±)-(2*R,9*S**,9a*R**)-Hexahydro-2-(5-ethyl-2-thienyl)-9-methyl-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine (17ββα) and (±)-(2*R**,9*R**,9a*R**)-Hexahydro-2-(5-ethyl-2-thienyl)-9-methyl-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine (17αβα).** (±)-α-(2-Aminoethyl)-5-ethyl-2-thiophenemethanol (9.6 mmol, 1.80 g) was dissolved in CH_2Cl_2 (50 mL). (±)-5-Bromo-2-methylpentanal (7.9 mmol, 1.42 g) in CH_2Cl_2 (50 mL) was added at rt. The reaction mixture turned bright yellow and water droplets formed on the sides of the flask. The reaction was stirred overnight (~12 h) at rt, slowly

(11) Copies of ^1H NMR spectra recorded in $CDCl_3$ for xestospongins A and C were kindly provided by Dr. M. Nakagawa.

(12) Kawazoe, K. Ph. D. Dissertation, Osaka University, 1989.

Table 2. Comparison of ^{1}H NMR Spectral Data (J in Hz) for Xestospongin C, Araguspongine E, and Araguspongine B

assign.[a]	xestospongin C (**2**) ^{1}H NMR ($CDCl_3$, 360 MHz)[b]			araguspongine E (old **5**; new **2**) ^{1}H NMR ($CDCl_3$, 500 MHz)[c]			araguspongine B (old **4**; new **6**) ^{1}H NMR ($CDCl_3$, 500 MHz)[c]		
H(9a)	4.28	br d	J = 2.6	4.24	br s		4.30	d	J = 2.8
H(2)	3.52	br t	J = 11.0	3.48	br t	$J \approx 10.7$	3.53	br t	J = 11
H(2′)	3.33	br t	J = 10.3	3.30	br t	$J \approx 10.7$			
H(4ax)	3.18	ddd	J = 12.7, 12.7, 3.6	3.13	br t	$J \approx 14.1$	3.18	ddd	J = 13.7, 13.4, 3.1
H(9a′)	3.07	d	J = 7.4	~3.00	m	2H			
H(6eq)	3.05	m	1 H						
H(4eq)	2.98	m	2 H	2.91	br dd	$J \approx 14.2, 3.4$	2.95	ddd	J = 13.7, 3.1, 1.5
H(4′eq)	2.89			2.88	br d	$J \approx 1.1$			
H(6′eq)	2.75	br d	J = 11.5						
H(6ax)	2.39	br d	J = 11.0						
H(4′ax)	2.17	ddd	J = 12.2, 12.2, 3.1	2.12	ddd	J = 12.2, 12.2, 3.4			
H(6′ax)	1.97	ddd	J = 11.5, 11.5, 3.1						
	1.8–1.0	m							
	1.03	br d	J = 12.0						

[a] Primed numbers denote the *trans*-1-oxaquinolizidine ring. [b] Obtained from spectrum in $CDCl_3$ provided by Nakagawa. [c] Reference 3.

Table 3. ^{1}H NMR Spectral Data (J in Hz) for Natural Araguspongine D and Xestospongin A and for Synthetic Xestospongin A

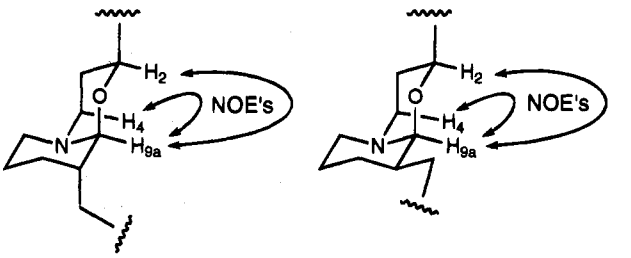
assign.	araguspongine D ^{1}H NMR ($CDCl_3$, 500 MHz)[a]			xestospongin A ^{1}H NMR ($CDCl_3$, 360 MHz)[b]			xestospongin A, synthetic sample ^{1}H NMR ($CDCl_3$, 500 MHz)[c]		
H(2)	3.35	br d	$J \approx 10.7$	3.34	br t	J = 10.8	3.29	br t	J = 10.7
H(9a)	3.06	d	J = 8.2	3.06	d	J = 8.6	3.01	d	J = 7.9
H(4eq)	2.94	ddd	J = 11.8, 4.0, 1.8	2.93	ddd	J = 11.2, 4.3, 2.2	2.89	ddd	J = 12.2, 3.7, 1.8
H(6eq)	2.76	br d	$J \approx 11.6$	2.75	br d	J = 10.8	2.71	br d	J = 11.6
H(4ax)	2.18	ddd	J = 12.0, 11.8, 3.1	2.18	ddd	J = 12.1, 12.1, 3.2	2.13	ddd	J = 12.2, 12.2, 3.1
H(6ax)	1.96	ddd	J = 11.6, 11.6, 2.7	1.98	ddd	J = 11.9, 11.9, 3.9	1.93	ddd	J = 11.6, 11.6, 3.1
others				1.8–1.0	m		1.7–1.0	m	

[a] Reference 3. [b] Obtained from spectrum at 360 MHz provided by Nakagawa. [c] Reference 6; shifts are referenced to TMS = 0.00 ppm.

Table 4. ^{13}C NMR data in $CDCl_3$ for Xestospongins C and A (at 90 MHz) and Araguspongines B, D, and E (at 125 MHz)

assign.[a]	xesto C[b] **2**	aragu E[c] old **5**; new **2**	aragu B[c] old **4**; new **6**	xesto A[b] **1**	aragu D[c] **3** (= **1**)
C(9a′)	96.22	95.7		96.32	95.9
C(2′)	75.50	75.2		75.35	75.3
C(6′)	54.85	54.2		54.55	54.3[d]
C(4′)	54.85	53.9		53.85	54.1[d]
C(9′)	41.43	40.4		40.95	40.6
C(9a)	88.18	87.4	87.5		
C(2)	76.18	75.7	76.0		
C(4)	53.26	52.6	52.8		
C(6)	46.03	45.3	45.3		
C(9)	40.84	40.1	40.5		
C(3)	26.41				

[a] Primed numbers denote the *trans*-1-oxaquinolizidine ring. [b] Reference 2. [c] Reference 3. [d] C(6′) and C(4′) were not differentiated.



trans-disubstituted ring in *cis*-decalin-like conformer as in **4**

cis-disubstituted ring in *cis*-decalin-like conformer as in **6**

Figure 5. NOE's in araguspongine B[3] are consistent with either structure **4** or **6**.

turning orange. The reaction was quenched with 5% aqueous NaOH (~50 mL) and stirred for 20 min. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, washed (5% aqueous NaOH and saturated aqueous NaCl), dried ($MgSO_4$), and concentrated to leave 2.25 g of a yellow oil that was a 2.1:1 mixture of diastereomers. Purification by MPLC (2:1::Hex:EtOAc with 3% triethylamine) gave **17**$\beta\beta\alpha$ (3.4 mmol, 0.89 g, 42% yield) and **17**$\alpha\beta\alpha$ (1.6 mmol, 0.43 g, 20% yield). **17**$\beta\beta\alpha$: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, J = 3.4 Hz, Ar-H_3), 6.63 (dd, J = 3.4 and 0.9 Hz, Ar-H_4), 4.55 [dd, J = 11.4 and 2.2 Hz, H(2)], 3.14 [d, J = 8.0 Hz, H(9a)], 3.02 [ddd, J = 11.3, 5.2, and 2 Hz, H(4eq)], 2.80 [q, J = 7.4 Hz, CH_2CH_3), 2.84–2.76 [m, H(6eq)], 2.36 [ddd, J = 11.3, 11, and 2.2 Hz, H(4ax)], 2.16 [dddd, J = 13.0, 11.4, 11, and 2.2 Hz, H(3ax)], 2.15–2.00 [m, H(6ax)], 1.88 [dddd, J = 13.0, 5.2, 2.2, and 2 Hz, H(3eq)], 1.78–1.54 [m, H(9, 7eq, 7ax, and 8eq)], 1.28 (dt, J = 7.4 and 0.9 Hz, CH_2CH_3), 1.10 [dddd, J = 12.0, 12.0, 12.0, and 4.3, H(8ax)], and 0.98 (d, J = 5.9 Hz, $CHCH_3$); ^{1}H NMR (300 MHz, d_6-benzene): δ 6.73 (d, J = 3.5 Hz, Ar-H_3), 6.51 (d, J = 3.5 Hz, Ar-H_4), 4.45 [brd, J = 11.4 Hz, H(2)], 3.04 [d, J = 8.4 Hz, H(9a)], 2.69 [ddd, J = 11.4, 3.3, and 2.1 Hz, H(4eq)], 2.61–2.53 [m, H(6eq)], 2.56 (q, J = 7 Hz, CH_2CH_3), 2.16 [dddd, J = 11.7, 11.4, 11.4, and 3.3 Hz, H(3ax)], 2.05 [ddd, J = 11.4, 11.4, and 2.7 Hz, H(4ax)], 1.85 [ddd, J = 11.7, 11.7, and 2.7 Hz, H(6ax)], 1.90–1.82 [m, H(9)], 1.65–1.50 [m, H(8eq, 3eq, and 3ax)], 1.35–1.29 [m, H(7ax)], 1.08 (t, J = 7 Hz, CH_2CH_3), 1.05 (d, J = 6.6 Hz, $CHCH_3$), and 0.92 [dddd, J = 12.0, 12.0, 12.0, and 3.3 Hz, H(8ax)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 142.5, 123.0, 122.4, 98.6, 75.1, 53.7, 53.6, 35.8, 32.7, 31.9, 24.4, 23.3, 17.4, and 15.8; ^{13}C NMR (75 MHz, d_6-benzene) δ 146.4, 143.8, 123.0, 122.7, 98.8, 75.6, 53.9, 53.8, 36.1, 33.5, 32.2, 24.9, 23.7, 17.6, and 16.1; IR (neat, thin layer) 2930s, 2870m, 2850m, 2810m, 2750m, 2710w, 2670w, 1500w, 1470m, 1460m, 1400m, 1380m, 1350m, 1320m, 1300m, 1280s, 1250w, 1240w, 1210m, 1150m, 1140s, 1090s, 1080s, 1040m, 1030m, 1010w, 980w, 950m, 900w, 890w, 860w, 840w, 820m, and 810m cm^{-1}; GC/LRMS (EI) t_R = 10.85 min; m/z 265 (M^+, 34), 151 (60), 140 (25), 139 (26), 138 (49), 125 (39), 123 (100), 112 (51), 111 (73), 110 (33), 98 (22), 97 (54), 96 (22), 82 (33), 69 (23), 55 (25), 45 (20), 42 (41), 41 (37), and 39 (21); HRMS (CI, isobutane) calcd for $C_{15}H_{24}NOS$ acc mass $(M + H)^+$ 266.1579, Obsd mass $(M + H)^+$ 266.1585. Anal. Calcd for $C_{15}H_{23}NOS$: C, 67.89; H, 8.72. Found: C, 68.09; H, 8.63.

17$\alpha\beta\alpha$: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, J = 3.4 Hz, Ar-H_3), 6.62 (d, J = 3.4 Hz, Ar-H_4), 4.71 [dd, J = 11.3 and 2.6

Hz, H(2)], 4.12 [brs, H(9a)], 3.07–2.99 [m, H(4eq), H(4ax), H(6eq)], 2.80 (q, J = 7.5 Hz, CH_2CH_3), 2.35–2.28 [m, H(6ax)], 2.21–2.08 [m, H(3ax)], 1.85–1.72 [m, H(9 and 7eq)], 1.60–1.54 [m, H(3eq and 7ax)], 1.48–1.44 [m, H(8eq and 8ax)], 1.29 (t, J = 7.5 Hz, CH_2CH_3), and 1.00 (d, J = 6.9 Hz, $CHCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.4, 143.5, 122.3$^+$, 122.3$^-$, 92.1, 75.6, 52.7, 34.6, 28.7, 27.4, 24.0, 23.4, 16.0, and 15.8; IR (neat, thin layer) 3070w, 2970s, 2930s, 2900s, 2860s, 2810m, 2760m, 2740m, 2670w, 1490w, 1470m, 1460m, 1390m, 1340w, 1350m, 1320m, 1300m, 1280m, 1260w, 1230m, 1220w, 1190w, 1160m, 1140m, 1130m, 1080m, 1050m, 1040w, 1030m, 990w, 980w, 960m, 920m, 850w, 830w, and 800m cm^{-1}; GC/LRMS (EI) t_R = 10.83 min; m/z 265 (M^+, 42), 153 (16), 152 (24), 151 (78), 140 (28), 139 (27), 138 (48), 126 (15), 125 (52), 124 (15), 123 (100), 112 (66), 111 (98), 110 (47), 98 (33), 97 (73), 96 (33), 82 (38), 77 (16), 69 (26), 68 (16), 56 (16), 55 (26), 45 (20), 44 (24), 43 (15), 42 (57), 41 (52), and 39 (18).

As described in the text, fragmentation to compounds **20** (and, presumably, **21**) was observed during GC–MS analysis of **17**: GC/LRMS (EI) of **20** t_R = 7.42 min; m/z 166 (M^+, 54), 151 (20), 139 (100), 55 (11), and 45 (10).

(±)-Hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine (7): ^1H NMR (200 MHz, $CDCl_3$) δ 7.257 ($CDCl_3$), 4.02 [ddd, J = 11.3, 4.8, and 1 Hz, H(2eq)], 3.51 [ddd, J = 11.3, 11.3, and 2.5 Hz, H(2ax)], 3.41 [dd, J = 8.5 and 2.5 Hz, H(9a)], 2.91 [dddd, J = 12, 4, 2, and 1 Hz, H(4eq)], 2.80 [ddt, J = 12, 1, and 3 Hz, H(6eq)], 2.31 [ddd, J = 12, 12, and 3 Hz, H(4ax)], 2.18–1.95 (m, 2H), and 1.78–1.23 (m, 7H).

(±)-(9*R,9a*S**)-Hexahydro-9-methyl-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine (9$\beta\beta$)**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.250 ($CDCl_3$), 3.93 [ddd, J = 11.5, 4.9, and 1 Hz, H(2eq)], 3.33 [dt, J = 2.4 and 11.5 Hz, H(2ax)], 2.84–2.79 [m, H(4eq)], 2.80 [d, J = 8.4 Hz, H(9a)], 2.63 [dddd, J = 11.5, 5.9, 2.6, and 1 Hz, H(6eq)], 2.09 [dt, J = 2.8 and 11.8 Hz, H(4ax)], 2.01–1.85 [m, 1H and H(6ax)], 1.64–1.24 (m, 5H), 0.96 [dq, J = 4.0 and 12.5 Hz, H(8ax)], and 0.82 (d, J = 6.5 Hz, CH_3).

(±)-(9*R,9a*R**)-Hexahydro-9-methyl-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine (9$\beta\alpha$)**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.250 ($CDCl_3$), 4.04–3.93 [m, H(2eq)], 3.83 [brd, J = 2.9 Hz, H(9a)], 3.54 [dt, J = 5 and 12 Hz, H(2ax)], and 2.95–2.65 [m, H(4ax, 4eq, and 6eq)].

(±)-(9*R,9a*S**)-Hexahydro-9-butyl-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine (10$\beta\beta$)**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.250, ($CDCl_3$), 4.08 [dt, J = 11.8 and 7.1 Hz, H(2eq)], 3.44 [dt, J = 2.8 and 11.8 Hz, H(2ax)], 3.00 [d, J = 8.3 Hz, H(9a)], 2.93 [ddd, J = 11.2, 1, and 1 Hz, H(4eq)], 2.75 [ddd, J = 11.3, 1, and 1 Hz, H(6eq)], 2.23 [dt, J = 2.7 and 11.2 Hz, H(4ax)], 2.18–0.84 (m, 14H), and 0.87 (t, J = 6.6 Hz, CH_3).

(±)-(9*R,9a*R**)-Hexahydro-9-butyl-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine (10$\beta\alpha$)**: ^1H NMR (200 MHz, $CDCl_3$) δ 4.19–4.00 [m, H(2eq and 9a)], 3.70 [dt, J = 3 and 11 Hz, H(2ax)], and 3.20–2.88 [m, H(4ax, 4eq, and 6eq)].

(±)-(2*R,9a*S**)-Hexahydro-2-methyl-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine (11$\beta\alpha$)**: ^1H NMR (300 MHz, $CDCl_3$) δ 3.56 [ddq, J = 12.4, 2.5, and 6.2 Hz, H(2ax)], 3.45 [dd, J = 8.9 and 2.9 Hz, H(9a)], 2.92 [ddd, J = 11.8, 4.3, and 2.3 Hz, H(4eq)], 2.83 [ddt, J = 11.5, 1.5, and 3.5 Hz, H(6eq)], 2.33 [dt, J = 3.3 and 11.8 Hz, H(4ax)], 2.08 [dt, J = 4.0 and 11.5 Hz, H(6ax)], 1.82–1.31 (m, 8H), and 1.22 (d, J = 6.2 Hz, CH_3).

(±)-(2*R,9a*S**)-Hexahydro-2-butyl-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine (12$\beta\alpha$)**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.252 ($CDCl_3$), 3.37–3.29 [m, H(2ax)], 3.36 [dd, J = 8.9 and 2.9 Hz, H(9a)], 2.90 [ddd, J = 11.7, 4.4, and 2.3 Hz, H(4eq)], 2.78 [ddt, J = 11.5, 1.5, and 3.7 Hz, H(6eq)], 2.25 [dt, J = 3.4 and 11.7 Hz, H(4ax)], 2.02 [dt, J = 3.7 and 11.5 Hz, H(6ax)], 1.80–1.23 (m, 14H), and 0.86 (t, J = 7.1 Hz, CH_3)].

(±)-(2*R,9*R**,9a*S**)-Hexahydro-2,9-dimethyl-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine (13$\beta\beta\alpha$)**: ^1H NMR (200 MHz, $CDCl_3$) δ 3.49 [ddq, J = 12.4, 2.9, and 6.2 Hz, H(2ax)], 2.95 [d, J = 8.2 Hz, H(9a)], 2.92 [ddd, J = 11.6, 4.4, and 2.5 Hz, H(4eq)], 2.78 [ddt, J = 11.6, 1, and 3 Hz, H(6eq)], 2.22 [dt, J = 3.8 and 11.6 Hz, H(4ax)], 2.06 [dt, J = 3.6 and 11.6 Hz, H(6ax)], 1.79 –1.51 (m, 6H), 1.26–0.94 [m, H(8ax)], 1.22 [d, J = 6.2 Hz, $OCHCH_3$], and 0.96 [d, J = 6.5 Hz, $CHCHCH_3$].

(±)-(2*R,9*S**,9a*S**)-Hexahydro-2,9-dimethyl-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine (13$\alpha\beta\alpha$)**: ^1H NMR (200 MHz, $CDCl_3$) δ 3.89 [brd, J = 2.7 Hz, H(9a)], 3.57 [ddq, J = 12.3, 2.5, and 6.2 Hz, H(2ax)], 2.99–2.73 [m, H(4ax, 4eq, and 6eq)], 2.03 [ddd, J = 11, 6, and 2 Hz, H(6ax)], 1.80–1.37 (m, 1H), 1.19 [d, J = 6.2 Hz, $OCHCH_3$], and 0.97 [d, J = 7.0 Hz, $CHCHCH_3$].

(±)-(2*R,9*R**,9a*S**)-Hexahydro-2,9-dibutyl-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine (14$\beta\beta\alpha$)**: ^1H NMR (200 MHz, $CDCl_3$) δ 3.25 [dddd, J = 11, 7, 4, and 1 Hz, H(2ax)], 2.98 [d, J = 8.5 Hz, H(9a)], 2.93 [ddd, J = 11.7, 4.6, and 2.7 Hz, H(4eq)], 2.73 [ddd, J = 11.6, 5.3, and 3.5 Hz, H(6eq)], 2.18 [dt, J = 3.9 and 11.7 Hz, H(4ax)], 2.01 [dt, J = 4 and 11.6 Hz, H(6ax)], 1.95–0.70 (m, 19H), and 0.80–0.63 (m, CH_3 and CH_3).

(±)-(2*R,9*S**,9a*S**)-Hexahydro-2,9-dibutyl-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine (14$\alpha\beta\alpha$)**: ^1H NMR (200 MHz, $CDCl_3$): δ 4.09 [brd, J = 2.7 Hz, H(9a)], 3.41 [dddd, J = 12, 7.9, 3.0, and 1.6 Hz, H(2ax)], 3.08–2.77 [m, H(4ax, 4eq, and 6eq)], 2.32 [dt, J = 11.0 and 4.0 Hz, H(6ax)], 1.80–1.05 (m, 19H), and 0.82–0.64 (m, CH_3 and CH_3).

Acknowledgment. This work was supported by Grant GM 39339 awarded by the DHHS. We thank Professor Isao Kitagawa for a copy of relevant information from the thesis of Dr. Kazuyoshi Kawazoe, Dr. Masashi Nakagawa for $CDCl_3$ spectral data of xestospongins A and C, and Dr. Hanoch Senderowitz, Mr. Toshihiro Hashimoto, and Mr. Michael J. Mayer for helpful discussions.