

Araguspongines K and L, New Bioactive Bis-1-oxaquinolizidine *N*-Oxide Alkaloids from Red Sea Specimens of *Xestospongia exigua*

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Received May 17, 2002

In addition to the previously reported (+)-araguspongine A, (+)-araguspongine C, (+)-araguspongine D, (–)-araguspongine E, and (+)-xestospongine B, two new *N*-oxide araguspongines, (+)-araguspongine K and (+)-araguspongine L, are described here. Their structures were established on the basis of spectral analyses including ¹H–¹⁵N HMBC. The promising in vitro antimalarial and antituberculosis activities of araguspongine C are reported.

The family of araguspongine/xestospongine alkaloids contains 13 members.^{1–6} Chemically, they are dimeric 2,9-disubstituted 1-oxaquinolizidines. Conformational aspects of the 1-oxaquinolizidine ring system have been studied via molecular modeling, NMR, and X-ray crystallographic analyses.^{1,7} Stereochemical complexities, *cis*- versus *trans*-decaline-like conformers and the relative configuration of variously substituted 1-oxaquinolizidines, have also been studied and explained.⁷

In these studies, it was concluded that *trans*-2,9-dialkylated 1-oxaquinolizidine rings reside predominantly in the *trans*-decaline-like conformer, while *cis*-dialkylated rings reside in the *cis*-decaline-like conformer. Moreover, the chemical shifts for H-10 in these *cis*-disubstituted compounds were typically in the range δ 3.8–4.2 and resonate as broad doublets with $J \approx 3$ Hz. This is nearly 1 ppm downfield to the shift for H-10 in the C-9 epimeric *trans*-disubstituted compounds, which typically appear as doublets with $J \approx 8$ Hz. These results were further confirmed via calculating isomer distribution obtained from alumina-catalyzed isomerization of araguspongines B, D, and E.¹

The 2,9-*trans* substituents in araguspongine D, having a *trans*-decaline-like conformation, are both of equatorial orientation, while the 2,9-*cis* substituents in araguspongine B, having a *cis*-decaline-like conformation, are also both of equatorial orientation. Thus, it was presumed that the isomerization of C-9 accompanied with inversion of a nitrogen lone pair of electrons 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 araguspongine D are isomerized by alumina treatment, the conformation of the resulting product, araguspongine B, will change to the thermodynamically stable *cis*-decaline-like conformation having equatorially oriented substituents at C-9 and C-9'.¹

Members of this family have been isolated principally from *Xestospongia exigua* (Kirkpatrick) and have been shown to possess a variety of pharmacological activities.

Araguspongines A,⁸ C,⁸ D,⁶ and E⁶ were isolated from *Haliclona exigua* (the correct taxonomic identity is *Xestospongia exigua*), and araguspongines A, D, and E and xestospongine B were obtained from Australian specimens of *Xestospongia exigua*.³ An undescribed species of *Xestospongia*⁴ yielded araguspongines A–H and J.⁴ Araguspongine A has been reported from an undescribed species of *Niphates*¹¹ from Singapore.

Araguspongines possess diverse important biological activities. For example, araguspongines A and C were shown to inhibit rat brain nitric oxide synthase activity in vitro.⁸ Araguspongines A, C, and J^{1,4} and xestospongine B³ exhibited stronger vasodilation activity than papaverine in the perfused model experiment using isolated mesenteric artery of SD-rat. They were also shown to be equally potent inhibitors of both inositol 1,4,5-triphosphate receptor-mediated Ca²⁺ release and endoplasmic reticulum-calcium pump.^{9,10}

Furthermore, several araguspongines were reported to possess other biological activities, including cytotoxicity,¹¹ antifungal activity,² and somatostatin and vasoactive intestinal peptide inhibition activity.¹²

As part of an ongoing research program at the Department of Pharmacognosy, College of Pharmacy, King Saud University, aimed at the discovery of bioactive diverse compounds from marine macrofauna and flora, it was decided to screen *Xestospongia exigua* (Kirkpatrick) for activity. As far as the original objectives were concerned, the study culminated in the isolation of the known (+)-araguspongine A (**1**), (+)-araguspongine C (**2**), (+)-araguspongine D, (–)-araguspongine E, and (+)-xestospongine B, in addition to two novel *N*-oxide araguspongines, (+)-araguspongine K (**3**) and (+)-araguspongine L (**4**), whose isolation, structure elucidation, and antimalarial and antituberculosis activities are the subject of this paper.

Results and Discussion

The frozen coarsely minced *X. exigua* sponge was percolated several times using 95% ethanol. The dried ethanol extract was partitioned between aqueous acetonitrile and hexane presaturated with each other. The acetonitrile fraction was chromatographed several times using flash silica gel to afford the known araguspongines A (**1**), C (**2**), D, and E and xestospongine B, in addition to the new araguspongines K (**3**) and L (**4**).

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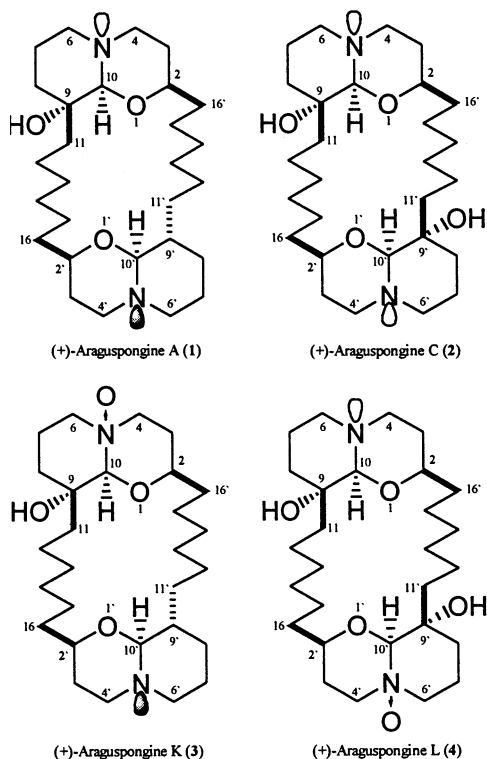
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The identity of the known compounds was established by direct comparison of their spectral data with those previously reported for (+)-araguspongine A,³ (+)-araguspongine C,⁴ (+)-araguspongine D,¹ (-)-araguspongine E,¹ and (+)-xestospongine B.³ Full NMR data of (+)-araguspongine A (Table 1) are reported here for the first time.

(+)-Araguspongine K (**3**) was isolated as colorless tiny needles in 0.0007% yield. It was shown to possess the molecular formula $C_{28}H_{50}O_4N_2$ as derived from the presence of an ion peak at m/z 478.3770 $[M]^+$ and NMR data. The IR spectrum showed an absorption band at 3410 cm^{-1} , indicative of the presence of a hydroxyl function, in addition to a Bohlmann band (2752 cm^{-1}). Therefore, the identity of **3** was concluded to be hydroxylated bis-1-oxaquinolizidine, with at least one oxaquinolizidine ring adopting a *trans*-decaline-like conformation. The ^{13}C NMR spectrum showed 28 carbon resonances distributed as 22 triplets, five doublets, and a singlet. Half of these resonances were similar to those of the *trans*-oxaquinolizidine half of araguspongine A (**1**) (Table 1).

Moreover, compound **3** is an *N*-oxide araguspongine as derived from ^1H - ^{15}N HMBC spectra, which showed an oxygenated nitrogen (N-5) resonating at δ_{N} 117.1. This nitrogen showed two two-bond correlations (^1H - ^{15}N) with a sharp singlet proton resonating at δ_{H} 4.24 (H-10), and H-6_{axial}, which resonated at δ_{H} 3.51 as a ddd ($J = 13.4, 13.4, 4.3\text{ Hz}$). H-10' resonated at δ_{H} 3.06 as a doublet ($J = 8.6\text{ Hz}$), a chemical shift and a coupling pattern and constant identical to those expected for a *trans*-decaline-like conformation of disubstituted oxaquinolizidines.⁷ The large coupling constant of H-10' ($J = 8.6\text{ Hz}$) indicated that H-9', resonating at δ_{H} 1.63, is axial and therefore with β disposition. On the other hand, H-2' resonated at δ_{H} 3.33 as a dd ($J = 10.7, 10.7\text{ Hz}$), and hence it must also be axial, however, with α disposition. These data were in full agreement with the previously mentioned observations about the relative stereochemistry of the 2,9-disubstituted *trans*-decaline-like conformation of oxaquinolizidines.^{3,7} These data along with key HMBC correlations (Table 1) suggested that compound **3** is araguspongine A *N*-oxide.

(+)-Araguspongine L (**4**) was also isolated as colorless tiny needles in 0.005% yield. High-resolution electrospray ionization mass spectroscopy (HRESIMS) of **4** gave a characteristic ion peak at m/z 494.3719 $[M]^+$ and was consistent with the molecular formula $C_{28}H_{50}O_5N_2$. The IR spectrum showed an absorption band for the hydroxyl group (3390 cm^{-1}) and was devoid of Bohlmann bands, indicating the relative stereochemistry of **4** as bis-*cis*-1-oxaquinolizidine. From the ^{13}C NMR data it was deduced that **4** has 28 carbon resonances, including 22 triplets, four doublets, and two singlets. Half of these resonances were ascribable to araguspongine C (**2**) (Table 2). The ^1H - ^{15}N HMBC spectrum showed two nitrogen atoms, one resonating at δ_{N} 43.1 (N-5) and the other resonating at δ_{N} 117.0 (N-5'), and hence, N-5' was concluded to be an *N*-oxide. This conclusion was further confirmed, from the HMBC (^1H - ^{15}N) spectra, due to the presence of $^2J_{\text{H-N}}$ cross-peaks between this nitrogen (N-5') and a sharp singlet proton resonating at δ_{H} 4.23 (H-10'), which correlated to a carbon resonating as a doublet at δ_{C} 98.6 (C-10'), and two protons resonating each as a ddd at δ_{H} 3.40 (H_{eq}-6') and δ_{H} 3.51 (H_{ax}-6') and correlated to a carbon resonating as a triplet at δ_{C} 68.4 (C-6').

The presence of the *N*-oxide moiety in this half of the molecule made its carbon resonances very similar to those of the *N*-oxide-containing half of compound **3**. Especially noteworthy are downfield shifts for C-4' (4.5 ppm), C-6' (23.8 ppm), and C-10' (8 ppm) when compared to carbons 4, 6, and 10, respectively, which indicated whatever moiety was added, it should have had a profound magnetic and electronic effect on this part of the molecule. Therefore, the identity of araguspongine L was established as araguspongine C *N*-oxide.

During the *in vitro* antimalarial activity test, araguspongines K and L were found to be inactive, unlike araguspongine C, which was active against *Plasmodium falciparum* African (D6) clone with IC_{50} 670 ng/mL and selectivity index > 7.1 and against *P. falciparum* Indochina (W2) clone with IC_{50} 280 ng/mL and selectivity index > 17.0 , while those of chloroquine were 7 and 220 ng/mL and those of artemisinin were 6 and 7 ng/mL against D6 and W2 clones, respectively. On the other hand, araguspongine C was submitted for antituberculosis activity evaluation and was shown to possess high activity against the H37Rv strain of *Mycobacterium tuberculosis* with $\text{MIC} = 3.94\text{ }\mu\text{M}$, while that of the positive control, rifampin, was $0.61\text{ }\mu\text{M}$.

Experimental Section

General Experimental Procedure. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. The IR spectra were recorded on a ATI Mattson Genesis Series FTIR spectrophotometer. The ^1H and ^{13}C NMR spectra were obtained on a Bruker DRX-400 spectrometer operating at 400 and 100 MHz, respectively. Both ^1H and ^{13}C NMR spectra were recorded in CDCl_3 , and the chemical shift values are expressed in δ (ppm) relative to the internal standard TMS. For the ^{13}C NMR spectra, spectral editing was determined by DEPT. 2D NMR data were obtained using the standard pulse sequence of the Bruker DRX-400 for COSY, HMQC, HMBC, and NOESY. The HRMS spectra were measured on a Bioapex FTMS with electrospray ionization.

^{15}N NMR. Inverse-detected ^{15}N NMR spectra were recorded using a Bruker DRX-500 spectrometer equipped with a 3 mm inverse-detected gradient probe. A gradient HMBC pulse sequence with 1 ms Gaussian *Z*-axis gradient pulses (70:30:50) was used, and a 100 ms delay for long-range coupling was used. Referencing of the indirectly detected ^{15}N dimension was accomplished using nitromethane as an external standard. A

Table 1. NMR Data of Araguspongines A (**1**) and K (**3**)^a

position	1		3		HMBC ^c
	δ_H (m, JHz)	δ_C , m	δ_H (m, JHz)	δ_C , m	
2	3.44 (dd, 10.7, 10.7)	76.2, d ^b	3.75 (dd, 10.7, 10.7)	77.2, d	10 ^d
3	1.50 (m)	26.0, t	1.32 (m)	31.9, t	4
4	1.61 (m)		1.55 (m)		
4	2.89 (m)	52.4, t	2.83 (br d, 9.6)	57.3, t	3, 6, 10
6	2.97 (br d, 8.5)		3.66 (ddd, 11.8, 11.8, 2.6)		
6	2.22 (br d, 8.4)	44.3, t	3.40 (br dd, 13.4, 3.0)	68.3, t	10
7	2.91 (m)		3.51 (ddd, 13.4, 13.4, 4.3)		
7	1.21 (m)	20.8, t	1.54 (m)	16.5, t	
8	1.66 (m)		1.55 (m)		
8	1.30 (m)	22.6, t	1.32 (m)	22.9, t	10
8	1.40 (m)		1.52 (m)		
9		70.7, s		72.5, s	10, 11
10	3.93 (s)	91.5, d	4.24 (s)	98.4, d	6
11	1.50 (m)	38.5, t	1.57 (m)	39.7, t	
11	1.54 (m)		1.58 (m)		
12	1.21 (m)	29.4, t	1.28 (m)	29.5, t	
12	1.51 (m)		1.58 (m)		
13	1.25 (m)	32.2, t	1.52 (m)	31.6, t	
13	1.42 (m)		1.72 (m)		
14	1.20 (m)	25.3, t	1.30 (m)	25.6, t	
14	1.52 (m)		1.50 (m)		
15	1.30 (m)	24.8, t	1.30 (m)	25.1, t	
15	1.60 (m)		1.52 (m)		
16	1.48 (m)	35.5, t	1.32 (m)	35.0, t	
16	1.57 (m)		1.57 (m)		
2'	3.23 (dd, 10.7, 10.7)	75.2, d	3.33 (dd, 10.7, 10.7)	75.4, d	3', 4', 10'
3'	1.48 (m)	32.3, t	1.48 (m)	32.4, t	
3'	1.55 (m)		1.66 (m)		
4'	2.65 (br d, 10.5)	54.2, t	2.72 (ddd, 11.1, 11.1, 4.2)	54.4, t	
4'	2.85 (br d, 14.2)		2.92 (ddd, 11.1, 2.9, 2.0)		
6'	1.88 (ddd, 11.4, 11.4, 2.8)	54.0, t	1.96 (ddd, 11.7, 11.7, 2.8)	54.3, t	9', 10'
6'	2.07 (ddd, 11.4, 2.8, 2.8)		2.18 (ddd, 11.7, 2.9, 2.9)		
7'	1.49 (m)	24.7, t	1.58 (m)	24.8, t	9'
7'	1.68 (m)		1.62 (m)		
8'	1.28 (m)	28.9, t	1.28 (m)	29.0, t	10'
8'	1.52 (m)		1.78 (m)		
9'	1.54 (m)	40.3, d	1.63 (m)	40.5, d	
10'	3.09 (d, 8.6)	95.5, d	3.06 (d, 8.6)	95.6, d	4'
11'	1.23 (m)	31.1, t	1.32 (m)	31.3, t	
11'	1.42 (m)		1.60 (m)		
12'	1.28 (m)	28.8, t	1.28 (m)	29.0, t	
12'	1.52 (m)		1.78 (m)		
13'	1.21 (m)	31.5, t	1.17 (m)	30.1, t	
13'	1.43 (m)		1.37 (m)		
14'	1.20 (m)	31.6, t	1.32 (m)	31.8, t	
14'	1.41 (m)		1.52 (m)		
15'	1.30 (m)	24.7, t	1.30 (m)	25.1, t	
15'	1.61 (m)		1.52 (m)		
16'	1.48 (m)	36.0, t	1.29 (m)	35.6, t	
16'	1.57 (m)		1.51 (m)		

^a Spectra recorded in CDCl₃. ^b ¹³C multiplicities were determined by DEPT 135°. ^c Two-bond and three-bond correlations. ^d Proton number.

GHMBC experiment was performed on nitromethane, and the ¹⁵N correlation was calibrated to 380.2 so that the chemical shifts are relative to liquid ammonia. This same calibration value was then used for araguspongines. The acquisition time was 24 h for each compound.

Sample Material. The sponge was collected from vertical reef slopes at -17 m at Bayadha, 4 miles north of Jeddah, on the Saudi Arabian Red Sea coast, in November 1999. The specimens are very similar to *Xestospongia exigua* (Kirkpatrick, 1900) (order Haplosclerida, family Petrosiidae), characterized in life by a dark reddish brown external coloration and cream interior, delicate skeletal architecture, and relatively small spicules. The sponge is massively encrusting (10 cm long × 10 cm wide × 5 cm thick) and the texture relatively crumbly and very sticky to the touch. The surface is irregular with small oscules on mounds on the surface. The skeleton is a delicate round-meshed reticulation of small oxea spicules ranging in length from 63 to 120 μm. A voucher specimen has

been deposited in the Natural History Museum, London (BMNH 2002.5.1.1).

Extraction and Isolation. The frozen, coarsely minced sponge (930 g) was percolated at room temperature with 95% EtOH (1 L × 3), and the extract was evaporated in vacuo to leave 58 g of residue. This residue was partitioned between 15% aqueous acetonitrile (1 L) and hexane (1 L × 3) presaturated with each other. The acetonitrile fraction was chromatographed, after evaporation, over flash Si gel (800 g, 10 × 30 cm), using increasing concentrations of MeOH in EtOAc as eluent, to yield partially pure compounds, which upon further chromatography yielded (+)-araguspongine K (7 mg) and (+)-araguspongine L (47 mg), in addition to the previously known araguspongines A (3 mg), C (257 mg), D (5 mg), and E (21 mg) and xestospongin B (2 mg).

(+)-Araguspongine K (3): colorless tiny needles; $[\alpha]_D^{25} +2.60^\circ$ (c 0.35, CHCl₃); IR neat (NaCl) ν_{\max} 3410, 2927, 2752 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz), see Table 1; ¹³C NMR

Table 2. NMR Data of Araguspongines C (**2**) and L (**4**)^a

position	2		4	
	δ_{H} (m, JHz)	δ_{C} , m	δ_{H} (m, JHz)	δ_{C} , m
2	3.56 (dd, 11.0, 11.0)	76.8, d ^b	3.74 (dd, 10.8, 10.8)	76.7, d
3	1.05 (m) 1.76 (m)	26.4, t	1.10 (m) 1.75 (m)	26.3, t
4	2.97 (ddd, 13.5, 3.5, 3.5) 3.11 (ddd, 13.5, 13.5, 3.5)	52.9, t	2.95 (ddd, 13.5, 3.8, 3.8) 3.09 (ddd, 13.5, 13.5, 3.0)	52.9, t
6	2.34 (br dd, 12.0, 3.0) 3.03 (ddd, 12.0, 12.0, 3.0)	44.6, t	2.32 (br dd, 11.7, 2.4) 3.00 (ddd, 11.7, 11.7, 2.6)	44.6, t
7	1.52 (m) 1.74 (m)	21.3, t	1.52 (m) 1.74 (m)	21.3, t
8	1.30 (m) 1.42 (m)	23.0, t	1.30 (m) 1.40 (m)	22.9, t
9		71.1, s		71.1, s
10	4.06 (s)	90.7, d	4.03 (s)	90.6, d
11	1.30 (m) 1.60 (m)	39.0, t	1.29 (m) 1.60 (m)	40.0, t
12	1.38 (m) 1.52 (m)	30.0, t	1.35 (m) 1.55 (m)	29.9, t
13	1.26 (m) 1.30 (m)	32.7, t	1.76 (m) 1.82 (m)	32.2, t
14	1.30 (m) 1.51 (m)	31.9, t	1.32 (m) 1.52 (m)	31.8, t
15	1.32 (m) 1.50 (m)	25.3, t	1.30 (m) 1.60 (m)	25.3, t
16	1.31 (m) 1.55 (m)	36.7, t	1.29 (m) 1.51 (m)	36.5, t
2'			3.53 (dd, 11.7, 11.7)	77.7, d
3'			1.32 (m) 1.55 (m)	30.3, t
4'			2.84 (br d, 12.4) 3.65 (ddd, 12.4, 12.4, 2.8)	57.4, t
6'			3.40 (ddd, 13.5, 3.2, 3.2) 3.51 (ddd, 13.5, 13.5, 4.2)	68.4, t
7'			2.65 (m) 2.68 (m)	16.7, t
8'			1.30 (m) 1.40 (m)	23.1, t
9'				72.7, s
10'			4.23 (s)	98.6, d
11'			1.31 (m) 1.58 (m)	38.9, t
12'			1.35 (m) 1.55 (m)	29.9, t
13'			1.76 (m) 1.82 (m)	32.7, t
14'			1.31 (m) 1.49 (m)	31.9, t
15'			1.30 (m) 1.60 (m)	25.4, t
16'			1.32 (m) 1.52 (m)	35.5, t

^a Spectra recorded in CDCl₃. ^b ¹³C multiplicities were determined by DEPT 135°.

(CDCl₃, 100 MHz), see Table 1; HRESIMS *m/z* 478.3770 [M]⁺ (calcd for C₂₈H₅₀O₄N₂ 478.3765).

(+)-Araguspongine L (4): colorless tiny needles: $[\alpha]_{\text{D}}^{25} +1.68^{\circ}$ (*c* 0.36, CHCl₃); IR neat (NaCl) ν_{max} 3390, 2928 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz), see Table 2; ¹³C NMR (CDCl₃, 100 MHz), see Table 2; HRESIMS *m/z* 494.3719 [M]⁺ (calcd for C₂₈H₅₀O₅N₂ 494.3714).

Bioassays. Araguspongines C, K, and L were submitted to the National Center for the Development of Natural Products, School of Pharmacy, the University of Mississippi, MS 38677, to evaluate their in vitro antimalarial activity against African (D6) and Indochina (W2) clones of *Plasmodium falciparum* using the previously reported method.¹³ Chloroquine and artemisinin were used as positive controls.

On the other hand, in vitro quantitative antituberculosis activity was evaluated at the Institute for Tuberculosis Research, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612, using the microplate-based Alamar Blue assay (MABA) protocol.¹⁴ It is a colorimetric oxidation–reduction assay that involves the addition of Alamar Blue dye as an indicator. It evaluates the metabolic activity of the microorganisms. The activity of the evaluated drug is expressed as minimum inhibitory concentration (μM). Araguspongine C was tested for its activity against *Mycobacterium tuberculosis* (H37Rv). Rifampin was used as a positive control.

Acknowledgment. S. G. Franzblau of the Institute for Tuberculosis Research, College of Pharmacy, University of Illinois at Chicago, is greatly acknowledged for evaluating the antimycobacterial activity. For financial support we acknowledge NIH, grant numbers R01A136596 and K02A101502, and the Research Center, College of Pharmacy, King Saud University, grant number C.P.R.C. 79.

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NP0202226