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ARAGUPETROSINE A, A NEW VASODILATIVE MACROCYCLIC QUINOLIZIDINE ALKALOID FROM AN OKINAWAN MARINE SPONGE XESTOSPONGIA SP.

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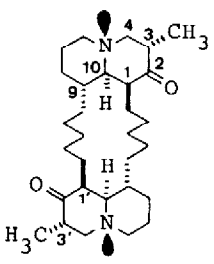
SUMMARY : A new vasodilative quinolizidine alkaloid named aragupetrosine A (7) was isolated from an Okinawan marine sponge Xestospongia sp. The absolute stereostructure of aragupetrosine A was elucidated to be 7 which was a hybrid of petrosin (1) and araguspongine F (12).

As a continuing study on bioactive marine natural products,[1] we recently isolated nine new vasodilative alkaloids named araguspongines A, B, C, D, E, F, G, H, and J from an Okinawan marine sponge Xestospongia sp. and elucidated the absolute stereostructures of araguspongines B (16), D (17) [(+)-D=xestospongin A[2]], E (18), F (12), G (13), H (14), and J (15) and the relative configuration of araguspongine C (19).[3] These alkaloids were characterized by having two 1-oxaquinolizidine moieties. Further investigation of the chemical constituents of the same marine sponge has led us to the isolation of another type of alkaloids having a 2-oxoquinolizidine moiety. In this paper, we report the absolute stereostructure elucidation of a new alkaloid named aragupetrosine A (7) together with the isolation of known alkaloids, petrosin (1) and petrosin A (5). We also comment a hypothetical biogenetic pathway for these alkaloids.

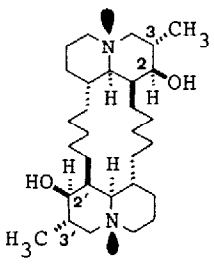
An acetone extract of the titled fresh marine sponge (4 kg collected in July at Aragusukujima, Okinawa Prefecture) was partitioned into a water-AcOEt mixture and the water phase was further partitioned with 1-butanol to afford araguspongines A~H and J.[3] The extract (30 g) obtained from the AcOEt phase was dissolved in aq. $(COOH)_2$ solution (pH 3) and extracted with AcOEt. The aqueous phase was then treated with aq. NH_4OH (to pH 10) and extracted again with AcOEt to furnish an alkaloid fraction (9.8 g). The alkaloid fraction (3 g) was subjected to silica gel column chromatography (benzene-acetone-NH_4OH), HPLC (ZORBAX ODS, $CHCl_3$-MeOH-CH_3CN-H_2O-NH_4OH), and preparative TLC (Aluminiumoxid $60F_{254}$, PSC-Fertigplatten, Merck) to give petrosin (1)(20 mg), petrosin A (5)(20 mg), and aragupetrosine A (7)(13 mg).

The physicochemical properties of 1[4] and 5[5] were identical with those of petrosin[6] and petrosin A[7] which were isolated from the Papua-New Guinean marine sponge Petrosia seriata. Braekman and Daloze[7] recently revised the structure of petrosin A as 5 with a mesomeric structure on the basis of the comparative ^1H NMR analysis with C_2 symmetrical petrosin (1) whose structure was determined by X-ray crystallographic analysis.[6]

In order to provide with the additional evidence for the mesomeric structure of petrosin A (5), we have carried out the following derivatization. Petrosin (1) was first reduced with $NaBH_3CN$ in EtOH (pH 2) at room temperature, and the resulting 2β,2'β-diol (2)(δ3.20, 2H, dd, J=4.5,10.7 Hz, 2,2'-H) was treated with (+)- and (-)-α-methoxy-α-trifluorophenylacetyl chloride (MTPA-Cl)[8] to furnish respectively a mixture (ca. 1:1) of two diastereomeric MTPA esters: 3a and 4a from (+)-MTPA-Cl and 4b and 3b from (-)-MTPA-Cl, which were separated by



petrosin (1)



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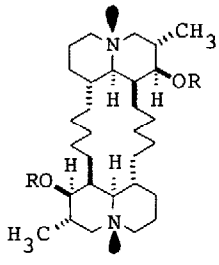
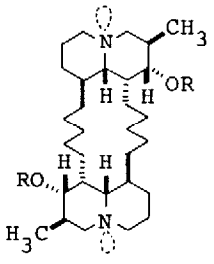
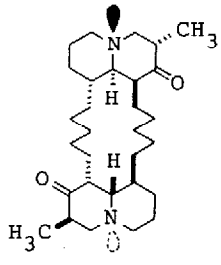


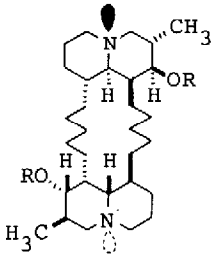
3a: R=(+)-MTPA
3b: R=(-)-MTPA



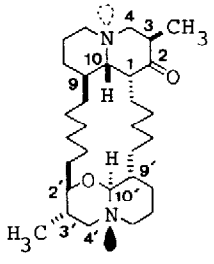
4a: R=(+)-MTPA
4b: R=(-)-MTPA



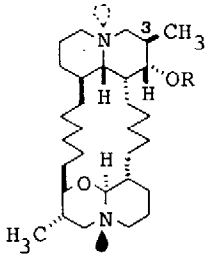
petrosin A (5)



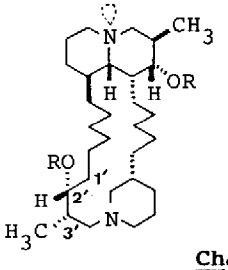
6a: R=(+)-MTPA
6b: R=(-)-MTPA



aragupetrosine A
(7)



8 : R= H
9a: R=(+)-MTPA
9b: R=(-)-MTPA



10 : R= H
11a: R=(+)-MTPA
11b: R=(-)-MTPA

Chart 1

HPLC (μ-PORASIL). The ^{1}H NMR spectra of 3a (δ0.76, 6H, d, J=6.4 Hz, 3,3'-CH_3) and 4a (δ0.87, 6H, d, J=6.4 Hz, 3,3'-CH_3) were identical with those of 4b and 3b, respectively. So that petrosin (1) isolated by us was shown to be an enantiomeric mexture (ca. 1:1). Next, petrosin A (5) was converted to the (+)- and (-)-MTPA esters (6a, 6b) as carried out for petrosin (1). The ^{1}H NMR spectrum of 6a was found identical with that of 6b which showed two doublet methyls at δ0.83 (J=6.4 Hz) and 0.73 (J=6.4 Hz). Consequently, petrosin A (5) has been further confirmed to possess a mesomeric structure.

Aragupetrosine A (7)[9] $C_{30}H_{52}N_2O_2$, $[\alpha]_D$ -18.8° ($CHCl_3$) showed carbonyl (1700 cm^{-1}) and Bohlmann absorptions[10] (2810, 2730 cm^{-1}) in its IR spectrum. The ^{1}H and ^{13}C NMR spectra of aragupetrosine A (7) showed ^{1}H and ^{13}C signals ascribable to one half moiety of petrosin (1) and the 3α-methyl-trans-1-oxaquinolizidine structure in araguspongine F (12). Detailed ^{1}H and ^{13}C NMR analysis, including homo and hetero COSY and HOHAHA of 7, disclosed the number of methylene chains from C-1 to C-9' together with the structures of 3β-methyl-trans-2-oxo-quinolizidine and 3'α-methyl-trans-1-oxaquinolizidine moieties.

The absolute stereostructure of aragupetrosine A (7), which gave a single peak on HPLC with a chiral column [CHIRALCEL OF (DAICEL), n-hexane-2-PrOH-Et_2NH], has been determined by the MTPA method.[8] The $NaBH_3CN$ reduction (in EtOH, pH 2, r.t.) of 7 furnished a 2α-ol (8) (δ_c 79.1, C-2; δ3.15, 1H, dd, J=10.7, 4.6 Hz, 2β-H_{ax}) which was converted to (+)- and (-)-MTPA esters (9a,[11] 9b[12]), whereas the $NaBH_3CN$ reduction (in aq. THF, pH 2, under reflux) of 7 furnished a 2α,2'-diol (10) [δ_c79.7 (C-2), 78.9 (C-2'); δ3.19 (1H, dd, J=10.4, 4.0 Hz, 2β-H_{ax}), 3.39 (1H, brt, J=ca. 7.3 Hz, 2'-H)] which was converted to (+)- and (-)-MTPA esters (11a,[13], 11b[14]). Comparisons of ^{1}H chemical shifts of 3-CH_3 and 1-H in 9a, 9b and 3'-CH_3

"optically pure"

	R^1	R^2
(+)-araguspongine F (12)	α-CH_3	H
(-)-araguspongine G (13)	β-CH_3	H
(+)-araguspongine H (14)	β-CH_3	α-CH_3
(-)-araguspongine J (15)	β-CH_3	β-CH_3

"enantiomeric mixture"

	R^1	R^2
araguspongine B (16)	○	○
araguspongine D (17) [(+)-D =xestospongin A]	●	●
araguspongine E (18)	○	●

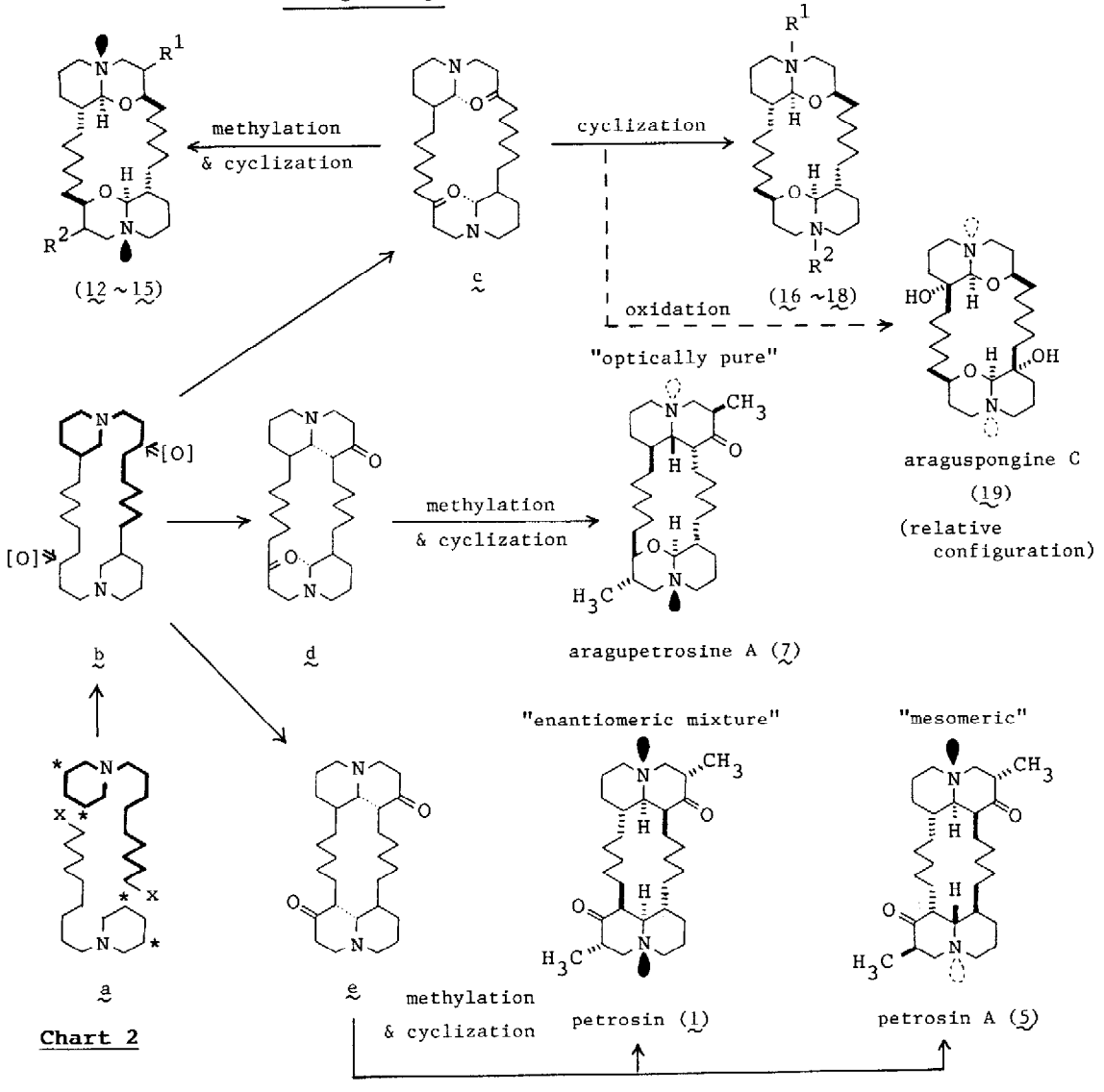


Chart 2

and 1'-H in 11a, 11b have led us to assign the 2S, 2'R configurations in 8 and 10, respectively and consequently, the absolute stereostructure of aragupetrosine A (7) has been determined as shown.

In 1986, Cimino et al. proposed a hypothetical biogenetic pathway for petrosin (1) and petrosin A (5) in connective with xestospongin A (17),[2] although those alkaloids were isolated from different kinds of marine sponges.[15] In the present study, all these alkaloids

were found together with araguspongines (12~19) and aragupetrosine A (7) in a single species of marine sponge. In regard to chemical processes which may occur in the marine sponge leading to these araguspongines and petrosins, a hypothetical pathway arrayed in Chart 2 seems to be attractive: initiated by dimerization of two C_9-C_5N units (a) followed by oxidation at the γ-position in b, and then cyclization and methylation. The fact, that araguspongines F (12), G (13), H (14), and J (15) were obtained as optically pure compounds while others as enantiomeric mixtures or a mesomeric compound, may be explained by presuming enantio-selective methylation to occur at C-3 prior to (or after) formation of the 1-oxaquinolizidine moieties.

Aragupetrosine A (7) showed vasodilative activity as well as araguspongines,[3] and petrosin (1) and petrosin A (5) showed two times stronger activities than papaverine in the perfusion model experiment using an isolated mesenteric artery of SD-rat.

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REFERENCES AND NOTES

1) a) The recent papers: I. Kitagawa, K. Hayashi, and M. Kobayashi, Chem. Pharm. Bull., 37, 849 (1989); b) I. Kitagawa, Yakugaku Zasshi, 108, 398 (1988).
2) M. Nakagawa, M. Endo, N. Tanaka, and G. Lee, Tetrahedron Lett., 25, 3227, (1984).
3) M. Kobayashi, K. Kawazoe, and I. Kitagawa, Chem. Pharm. Bull., to be published.
4) 1: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 3.04 (2H, dd, J=11.6,6.4 Hz, 4,4'-H_{eq}), 2.89 (2H, ddq, J=12.0,6.4,6.4 Hz, 3,3'-H), 2.53 (2H, ddd, J=11.6,3.7,3.7 Hz, 1,1'-H), 1.89 (2H, dd, J=12.0, 11.6 Hz, 4,4'-H_{ax}), 0.96 (6H, d, J=6.4 Hz, 3,3'-CH_3); ^{13}C NMR ($CDCl_3$, δ_c): 213.8 (C-2,2'), 70.4 (C-10,10'), 64.9 (C-4,4'), 56.0 (C-6,6'), 51.9 (C-1,1'), 40.5 (C-3,3'), 37.1 (C-9,9'), 11.3 (3,3'-CH_3).
5) 5: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 3.04 (2H, dd, J=11.3,6.4 Hz, 4,4'-H_{eq}), 2.54 (2H, ddd, J=9.5,4.3,4.3 Hz, 1,1'-H), 1.85 (2H, dd, J=11.3,11.3 Hz, 4,4'-H_{ax}), 0.94 (6H, d, J=6.4 Hz, 3,3'-CH_3); ^{13}C NMR ($CDCl_3$, δ_c): 213.9 (C-2,2'), 70.7 (C-10,10'), 64.9 (C-4,4'), 55.8 (C-6,6'), 51.5 (C-1,1'), 40.2 (C-3,3'), 35.9 (C-9,9'), 11.3 (3,3'-CH_3).
6) J. C. Braekman, D. Daloze, and P. M. Abreu, Tetrahedron Lett., 23, 4277 (1982).
7) J. C. Braekman and D. Daloze, Bull. Soc. Chim. Belg., 97, 519 (1988).
8) a) T. Kusumi, I. Ohtani, Y. Inouye, and H. Kakisawa, Tetrahedron Lett., 37, 4731 (1988); b) S. Takano, M. Takahashi, M. Yanase, Y. Sekiguchi, Y. Iwabuchi, and K. Ogasawara, Chem. Lett., 1988, 1827.
9) 7: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 3.03 (1H, dd, J=11.4,6.3 Hz, 4-H_{eq}), ca. 2.92 (1H, m, 3-H), 2.90 (1H, d, J=8.6 Hz, 10'-H), 2.86 (1H, ddd, J=9.2,9.2,2.0 Hz, 2'-H), 2.83 (1H, dd, J=10.7, 3.4 Hz, 4'-H_{eq}), 2.54 (1H, ddd, J=8.9,3.7,3.7 Hz, 1-H), 1.87 (1H, dd, J=11.4,11.4 Hz, 4-H_{ax}), 1.79 (1H, dd, J=10.7,10.7 Hz, 4'-H_{ax}), 0.95 (3H, d, J=6.4 Hz, 3-CH_3), 0.76 (3H, d, J=6.1 Hz, 3'-CH_3); ^{13}C NMR ($CDCl_3$, δ_c): 213.8 (C-2), 97.7 (C-10'), 83.2 (C-2'), 70.8 (C-10), 64.8 (C-4), 62.0 (C-4'), 55.9 (C-6), 53.7 (C-6'), 51.9 (C-1), 40.3 (C-3), 39.9 (C-9'), 36.7 (C-9), 34.7 (C-3'), 14.9 (3'-CH_3), 11.3 (3-CH_3), High-MS: Found=472.401, Calcd. for $C_{30}H_{52}N_2O_2$ =472.403.
10) F. Bohlmann, Angew. Chem., 69, 641 (1957).
11) 9a: FABMS: m/z 691$(M+H)^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ): 2.17 (1H, m, 1-H), 0.83 (3H, d, J=6.4 Hz, 3-CH_3), 0.77 (3H, d, J=6.4 Hz, 3'-CH_3).
12) 9b: FABMS: m/z 691$(M+H)^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ): 2.22 (1H, m, 1-H), 0.77 (3H, d, J=6.4 Hz, 3'-CH_3), 0.70 (3H, d, J=6.4 Hz, 3-CH_3).
13) 11a: FABMS: m/z 909$(M+H)^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ): 1.55 (1H, m, 1'-H), 0.91 (3H, d, J=6.4 Hz, 3'-CH_3), 0.84 (3H, d, J=6.4 Hz, 3-CH_3).
14) 11b: FABMS: m/z 909$(M+H)^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ): 1.53 (1H, m, 1'-H), 0.78 (3H, d, J=6.4 Hz, 3'-CH_3), 0.71 (3H, d, J=6.4 Hz, 3-CH_3).
15) G. Cimino, S. D. Stefano, G. Scognamiglio, G. Sodano, and E. Trivellone, Bull. Soc. Chim. Belg., 95, 783 (1986).

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