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Absolute Stereochemistry of Isosaraine-1 and Isosaraine-2

Yuewei Guo, Enrico Trivellone, Gennaro Scognamiglio and Guido Cimino

Istituto per la Chimica di Molecole di Interesse Biologico-CNR,[1] Via Toiano, 6 - 80072, Arco Felice (Na), Italy

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Abstract: The absolute stereochemistry of the quinolizidone systems present in the marine macrocyclic alkaloids isosaraine-1 (**3**) and isosaraine-2 (**4**), minor metabolites of the Mediterranean sponge *Reniera sarai*, has been established by applying advanced Mosher's method to the alcohol derivatives (**5** and **6**).

The sponge *Reniera sarai*, order Haplosclerida, is widely present in the Bay of Naples, Italy. Its metabolic pattern is heavily characterized by a series of complex polycyclic diamine alkaloids, saraines, which possess interesting phase transfer catalytic properties[2] and biological activities.[3]

Up to now, nine macrocyclic alkaloids, saraines A-C,[4-6] saraines 1-3,[2,7] and isosaraines 1-3,[7-9] have been isolated and structurally characterized by our group. Two different skeletons were exhibited by saraines A-C (examplified by saraine-A, **1**) and saraines 1-3 (examplified by saraine-2, **2**) whereas isosaraines -1 (**3**), -2 (**4**), and -3[7] were characterized by having the same framework of saraines 1-3 but displaying inverted stereochemistry at the chiral centers C-1, C-2, and C-9. Very recently, the absolute stereochemistry of the quinolizidone moiety of saraines -1 and -2 have been established,[7] while the absolute configurations of isosaraines remain undefined. In particular, the stereochemical relationships between saraines 1-3 and isosaraines 1-3 are extremely relevant in the light of the recent paper[10] reporting the total synthesis of racemic petrosin (**7**) identical to the natural compound. The authors stated that being uncommon for natural products to be biosynthesized in racemic form, the presence in *Petrosia seriata* of racemic alkaloids could be due to some post-biosynthetic equilibrations. Of course, the chiral centers α to the carbonyl can be very easily epimerized whereas the more remote stereocenters might epimerize by retro-Mannich-Mannich and immonium ion-enamine equilibria (**Scheme 1**). According to this hypothesis, isosaraines 1-3 could biosynthetically derive from saraines 1-3. Because of this, it is very relevant to establish their absolute stereostructure. For a better understanding of both chemistry and biogenetic origin of saraines, we have recently studied the absolute stereochemistry of isosaraines. This paper describes the elucidation of the absolute stereochemistry of isosaraines -1 (**3**) and -2 (**4**).

Isosaraine-1 (**3**) was first subjected to reduction with $NaBH_4$ to afford the derivative **5** as a single product. The structure of **5**[11] was fully analyzed by detailed NMR analysis confirming the relative configurations at C-1, C-2, C-9 and C-10. Moreover, ^1H- and ^{13}C-NMR spectra allowed to assign an oxymethine (δ_H 3.60, δ_C 72.5) at C-8 suggesting that **5** was the 8-hydroxy-isosaraine-1. The equatorial orientation of the hydroxy group was determined on the basis of decoupling experiments. In fact, irradiation at

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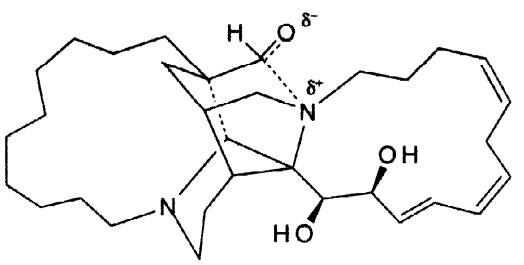
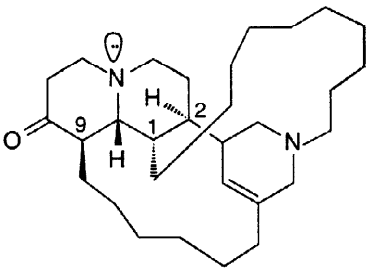
H-9 (δ_H 1.88, δ_C 42.6) simplified the H-8 multiplet to a double doublet exhibiting axial-axial (J = 9.9 Hz) and axial-equatorial (J = 4.3 Hz) couplings with the vicinal H_2-7 protons.



1



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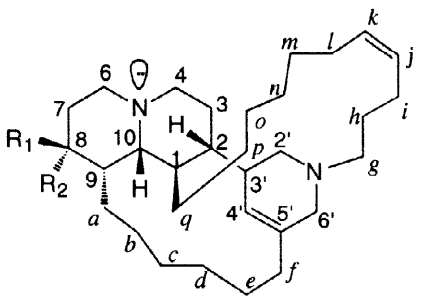
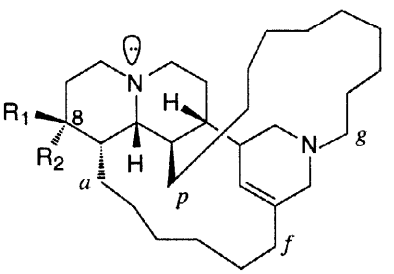
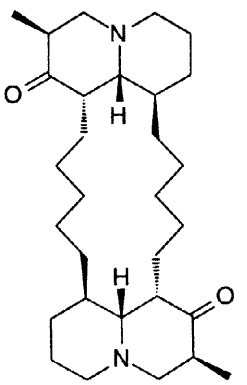


3: R_1=R_2=O
5: R_1=H, R_2=OH
5S: R_1=H, R_2=(*S*)-OMTPA
5R: R_1=H, R_2=(*R*)-OMTPA



4: R_1=R_2=O
6: R_1=H, R_2=OH
6S: R_1=H, R_2=(*S*)-OMTPA
6R: R_1=H, R_2=(*R*)-OMTPA



7

Treatment of **5** with *R*-(-)- and *S*-(+)-α-methoxy-α-(trifluromethyl)phenylacetyl chloride (MTPA-Cl) yielded the corresponding *S* (**5S**)- and *R* (**5R**)-MTPA esters, respectively.

Table 1. Selected ^{1}H-NMR Chemical Shifts[a] for the MTPA Esters of the Reductive Products of Isosaraines 1-2 (**5** and **6**) and $\Delta\delta$ ($\delta_{S\text{-MTPA ester}}$ - $\delta_{R\text{-MTPA ester}}$)[b]

H	5S	5R	$\Delta\delta$	6S	6R	$\Delta\delta$
4a	2.67	2.66	+5	2.69	2.69	0
4b	1.85	1.85	0	1.87	1.87	0
6a	2.81	2.78	+15	2.81	2.79	+10
6b	2.00	1.98	+10	2.00	2.00	0
7a	1.86	1.76	+50	1.85	1.76	+45
7b	1.80	1.76	+20	1.81	1.76	+25
8	4.93	4.93	0	4.93	4.92	+5
9	1.94	1.99	-25	1.98	2.02	-20
10	1.81	1.83	-10	1.70	1.72	-10
1	1.62	1.63	-5	1.56	1.58	-10
2	1.50	1.51	-5	1.92	1.92	0
a_1	1.59	1.53	-30	1.52	1.56	-20
a_2	1.59	1.53	-30	1.27	1.32	-25
b_1	1.19	1.22	-15	1.12	1.20	-40
b_2	1.19	1.22	-15	0.89	1.00	-55

[a] Bruker AMX 500 MHz; $CDCl_3$; δ values referred to $CHCl_3$ (δ 7.26 ppm); The assignments were aided by ^{1}H-^{1}H COSY, TOCSY and ^{1}H-^{13}C HETCOR.

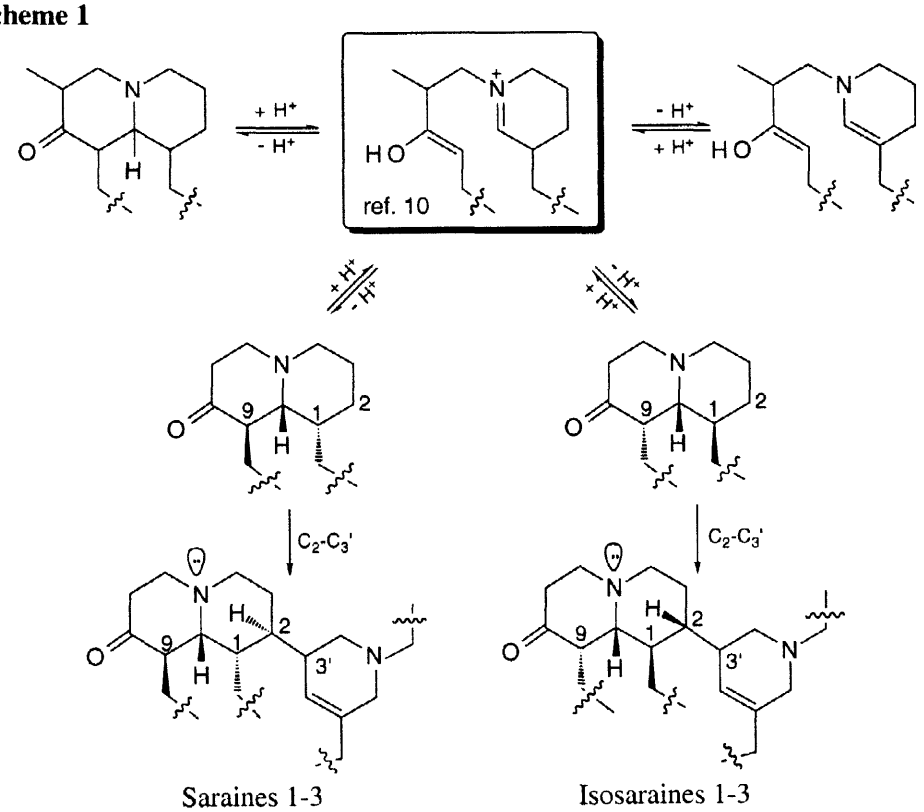
[b] $\Delta\delta$ values are given in Hz.

The ^{1}H-NMR chemical shifts of **5S** and **5R** were carefully assigned by extensive interpretation of ^{1}H-^{1}H COSY, TOCSY, and ^{1}H-^{13}C HETCOR spectra. The proton chemical shift differences ($\Delta\delta=\delta_{S\text{-MTPA-ester}}-\delta_{R\text{-MTPA-ester}}$) for the protons near to the chiral center C-8 are listed in **Table 1.**

Analogously with the Mosher esters of equatorial 8-hydroxy-saraine-2,[7] positive $\Delta\delta$ values were observed for H_2-7 and H_2-6 which were located on the right side of the MTPA plane, whereas negative values were observed for H-9, H_2-*a*, H_2-*b*, H-1, and H-2 which were located on the left side of the MTPA plane. According to MTPA determination rule,[12] the absolute stereochemistry of C-8 was assigned as *R*. Consequently, the absolute configurations at C-1, C-2, C-9, and C-10 of isosaraine-2 were concluded to be *R*, *R*, *S*, and *R*, respectively. Of course, it is impossible to determine the absolute stereochemistry at C-3', joining point of two independent heterocyclic systems.

In a similar manner, isosaraine-2 (**4**) was reduced to **6**[13] which was subsequently esterified by reacting with *R*(-)- and *S*(+)-MTPA chloride affording the pair of Mosher esters **6S** and **6R**. The $\Delta\delta$ values [$\Delta\delta=\delta_{S(\mathbf{6S})}-\delta_{R(\mathbf{6R})}$] of the protons near the chiral center C-8, as reported in **Table 1**, were very similar to those observed for Mosher esters (**5S** and **5R**) of 8-hydroxy-isosaraine-1 (**5**) leading to the same assignments 1*R*, 2*R*, 8*R*, 9*S*, 10*R* for all the chiral centers of the quinolizidine moiety. The limited amounts of isosaraine-3 prevented from establishing its absolute stereochemistry by using the same procedure as mentioned above. However, considering that it is a superior homologue of **3** and **4**, it probably displays the same absolute configuration (1*R* 2*R*, 9*S*, 10*R*).

Scheme 1



Plausible biosyntetic pathway of saraines 1-3 and isosaraines 1-3 according to ref. 10

On the basis of the knowledge of both absolute stereochemistry of saraines 1-2 and isosaraines 1-2, it is fascinating to suggest a more insightful biogenetic pathway for them. The hypothesis proposed by **Heathcock *et al*** for petrosins[10] can, as shown in **Scheme 1**, justify the epimerization of the stereocenters C-1 and C-9 that might occur by retro-Mannich-Mannich and immonium ion-enamine equilibria while the configuration of the more remote stereocenter C-2 might be controlled, in a subsequent step when there is the coupling between C-2 and C-3', by the steric bulk of the alkyl chain at C-1 and the tetrahydropyridine ring at C-2. As a consequence, a *trans* orientation of the substituents at C-1 and C-2 is favoured in both saraines 1-3 and, with inverted configuration, isosaraines 1-3.

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REFERENCES AND NOTES

1. Associated to the National Institute for the Chemistry of Biological System (CNR).
2. Cimino, G.; De Stefano, S.; Scognamiglio, G.; Trivellone, E. *Bull. Soc. Chim. Belg.* **1986**, *95*, 783-800.
3. Caprioli, V.; Cimino, G.; De Giulio, A.; Madaio, A.; Scognamiglio, G.; Trivellone, E. *Comp. Biochem. Physiol.* **1992**, 103B, 293-296.
4. Cimino, G.; Mattia, C. A.; Mazzarella, L.; Puliti, R.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *Tetrahedron* **1989**, *45*, 3863-3972.
5. Cimino, G.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *J. Nat. Prod.* **1990**, *53*, 1519-1525.
6. Guo, Y.-W.; Madaio, A.; Scognamiglio, G.; Trivellone, E.; Cimino, G. *Tetrahedron* **1996**, *52*, 8341-8348.
7. Guo, Y.-W.; Madaio, A.; Scognamiglio, G.; Trivellone, E.; Cimino, G. *Tetrahedron* **1996**, *52*, 14961-14974.
8. Cimino, G.; Spinella, A.; Trivellone, E. *Tetrahedron Lett.* **1989**, *30*, 133-136.
9. Cimino, G.; Fontana, A.; Madaio, A.; Scognamiglio, G.; Trivellone, E. *Magn. Reson. Chem.* **1991**, *29*, 327-332.
10. Scott, R. W.; Epperson, J. R.; Heathcock, C. H. *J. Am. Chem. Soc.* **1994**, *116*, 8853-8854.
11. Spectral data of equatorial 8-hydroxy-isosaraine-1 (**5**): Amorphous powder, $[\alpha]_D$ -27.9° (*c* 0.46, $CHCl_3$); EIMS, *m/z* (%): 468 (M^+, 100), 329 (35); ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.65 (m, H-1), 1.49 (m, H-2), 1.68, 1.54 (m, H_2-3), 2.70 (m, H-4a), 1.84 (m, H-4b), 2.78 (m, H-6a), 1.92 (m, H-6b), 1.67, 1.62 (m, H_2-7), 3.62 (ddd, *J*=9.9, 6.0, 5.1 Hz, H-8_{ax}), 1.88 (m, H-9eq), 1.73 (m, H-10ax), 2.72 (br d, *J*=10.5 Hz, H-$2'_{eq}$), 2.29 (m, H-$2'_{ax}$), 2.16 (m, H-3'), 5.46 (br s, H-4'), 3.14 (d, *J*=16.5 Hz, H-6'a), 2.40 (d, *J*=16.5 Hz, H-6'b), 1.32, 1.26 (m, H_2-*a*), 1.16 (m, H_2-*b*), 1.37 (m, H_2-*d*), 1.53, 1.02 (m, H_2-*e*), 1.86, 1.76 (m, H_2-*f*), 2.32 (m, H_2-*g*), 1.50 (m, H_2-*h*), 2.10, 1.90 (m, H_2-*i*), 5.56 (m, H-*j*), 5.27 (m, H-*k*), 2.20, 2.05 (m, H_2-*l*), 1.43 (m, H_2-*n*), 2.39, 1.27 (m, H_2-*q*); ^{13}C-NMR ($CDCl_3$) δ(ppm): 34.4 (d, C-1), 41.7 (d, C-2), 32.3 (t, C-3), 54.3 (t, C-4), 55.4 (t, C-6), 30.0 (t, C-7), 73.2 (d, C-8), 43.9 (d, C-9), 68.1 (d, C-10), 55.4 (t, C-2'), 42.5 (d, C-3'), 119.5 (d, C-4'), 137.8 (s, C-5'), 55.0 (t, C-6'), 24.8 (t, C-*a*), 29.7 (t, C-*b*), 25.8 (t, C-*d*), 24.2 (t, C-*e*), 33.8 (t, C-*f*), 58.0 (t, C-*g*), 28.5 (t, C-*h*), 26.0 (t, C-*i*), 129.4 (t, C-*j*), 130.8 (t, C-*k*), 24.9 (t, C-*l*), 27.7 (t, C-*m*), 30.9 (t, C-*q*).
12. Ohtani, I.; Kusumi, T.; Kashman. Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092-4097 and references cited therein.
13. Spectral data of equatorial 8-hydroxy-isosaraine-2 (**6**): Amorphous powder, $[\alpha]_D$ -37.9° (*c* 1.2, $CHCl_3$); EIMS, *m/z* (%): 456 (M^+, 100), 329 (32); ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.73 (m, H-1), 1.55 (m, H-2), 1.70, 1.55 (m, H_2-3), 2.70 (m, H-4a), 1.83 (m, H-4b), 2.77 (br d, H-6a), 1.92 (m, H-6b), 1.68, 1.63 (m, H_2-7), 3.60 (ddd, *J*=9.9, 6.1, 4.1 Hz, H-8_{ax}), 1.89 (m, H-9eq), 1.70 (m, H-10ax), 2.53 (m, H-2'a), 2.69 (m, H-2'b), 2.29 (br s, H-3'), 5.50 (s, H-4'), 3.18 (d, *J*=16.5 Hz, H-6'a), 2.49 (m, H-6'b), 1.50, 1.37 (m, H_2-*a*), 1.24 (m, H_2-*b*), 1.57, 1.08 (m, H_2-*e*), 1.88, 1.85 (m, H_2-*f*), 2.56, 2.47 (m, H_2-*g*), 1.62, 1.43 (m, H_2-*h*), 1.38 (m, H_2-*i*), 1.26, 1.17 (m, H_2-*o*), 2.21, 2.17 (m, H_2-*p*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 34.1 (d, C-1), 38.6 (d, C- 2), 31.9 (t, C-3), 54.5 (t, C-4), 55.3 (t, C-6), 30.5 (t, C-7), 73.2 (d, C-8), 42.6 (d, C-9), 66.8 (d, C-10), 55.0 (t, C-2'), 42.6 (d, C-3'), 119.8 (d, C-4'), 137.9 (s, C-5'), 54.2 (t, C-6'), 24.0 (t, C-*a*), 29.5 (t, C-*b*), 26.7 (t, C-*e*), 33.6 (t, C-*f*), 57.1 (t, C-*g*), 23.4 (t, C-*h*), 26.9 (t, C-*i*), 22.3 (t, C-*o*), 28.9 (t, C-*p*).