Transformation of tricyclic makaluvamines from the marine sponge *Zyzzya fuliginosa* into damirones

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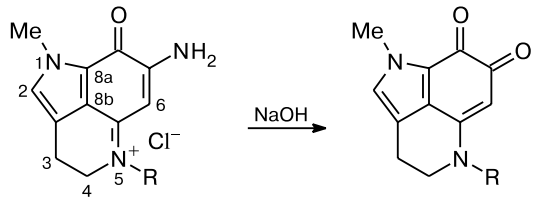
Makaluvamines H and C isolated from the marine sponge *Zyzzya fuliginosa* were transformed into damirones A and B, respectively, by alkaline hydrolysis. The crystal structure of damirone A was established by X-ray diffraction analysis.

Key words: marine sponge, *Zyzzya fuliginosa*; marine alkaloids; makaluvamines; damirones; alkaline hydrolysis; crystal and molecular structure, X-ray diffraction analysis.

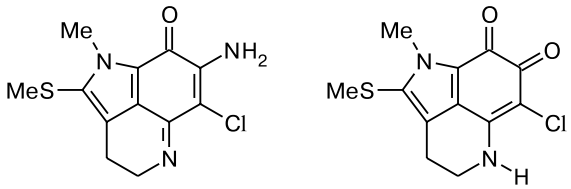
A series of alkaloids based on the pyrrolo[4,3,2-*de*]quinoline ring system were isolated from different marine sponges. This series of metabolites includes discorhabdins,[1—6] prianosins,[7,8] batzellines,[9] isobatzellines,[10] makaluvamines,[11—13] damirones,[13,14] veiutamine,[15] and epinardins.[16] Makaluvamines A—M and damirones A—C were isolated from sponges of the genus *Zyzzya* (order Poecilosclerida, family Iophonidae).[17] Tricyclic makaluvamines A—C, H, and I and damirones A—C are the simplest of this alkaloid series. When studying aromatic marine sponge metabolites, we isolated makaluvamines C, E, G, and H and damirones A and B from the Australian marine sponge *Zyzzya fuliginosa* (*Carter, 1879*).[18] A comparison of the compositions of ethanolic extracts of fresh and lyophilized sponges revealed that makaluvamines H (**1**) and C (**2**) prevailed in extracts from the fresh sponge, whereas damirones A (**3**) and B (**4**) were dominant in extracts from the lyophilized sponges. In our opinion, makaluvamines **1** and **2** were transformed into damirones **3** and **4**, respectively. In the present study, we demonstrated for the first time that this transformation proceeds readily under alkaline conditions.



1, **2** **3**, **4**

R = Me (**1**, **3**), H (**2**, **4**)

Treatment of compound **1** with an aqueous solution of NaOH at room temperature afforded compound **3** in high yield. It should be noted that the replacement of the amino group in isobatzelline A (**5**) by the oxygen atom proceeds through the diazonium salt to give batzelline A (**6**) in low yield.[10] The mass spectrum and melting point of compound **3** are identical with those of natural damirone A. Since the ^{1}H NMR spectra of compound **3** and natural damirone A measured in MeOH-d_4 differ only slightly, compound **3** was recrystallized to obtain crystals suitable for X-ray study. X-ray diffraction analysis confirmed the structure of semisynthetic damirone A (**3**) and revealed that the tricyclic system of **3** is virtually planar and is similar to the tricyclic system of batzelline A (**6**).[9]



5 **6**

Compound **2** was also treated with an aqueous alkali, which gave rise to compound **4**. The spectral and physicochemical characteristics of this compound are identical with those of natural damirone B. No melting point depression was observed for a mixed sample of both compounds.

Under the conditions of alkaline hydrolysis, compounds **1** and **2**, apparently, lose one proton to form *o*-iminoquinones, which are readily hydrolyzed to give *o*-quinones **3** and **4**, respectively. The transformation of the *p*-iminoquinoid system of makaluvamines **1** and **2** into the *o*-quinoid system of compounds **3** and **4**, respectively, leads to a considerable decrease in cytotoxicity

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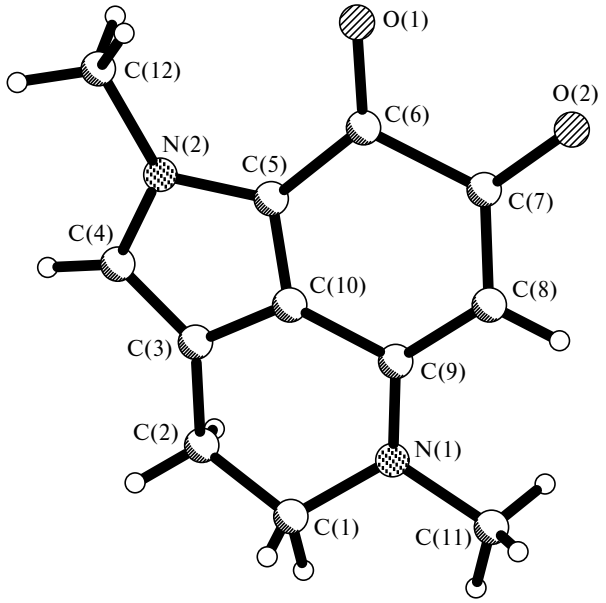

Fig. 1. Structure of molecule **3**.

against Ehrlich carcinoma cells. Thus ID_{50} for compounds **1** and **3** are 12.5 and 46.5 μg mL^{-1} and for compounds **2** and **4** are 26.5 and 50 μg mL^{-1}, respectively.

Experimental

The ^1H NMR spectra were recorded on a Bruker AVANCE DPX-300 spectrometer with $SiMe_4$ as the internal standard. The mass spectra were measured on an LKB-9000S mass spectrometer with direct inlet of the sample into the ion source; the ionizing voltage was 70 eV.

The isolation and identification of the compounds from the marine sponge *Z. fuliginosa* have been described earlier.[18]

Synthesis of damirone A (3) from makaluvamine H (1). A mixture of compound **1** (10 mg), $CHCl_3$ (5 mL), and 0.5 *M* aqueous NaOH (2 mL) was kept at ~20 °C for 10 min. Then the reaction mixture was extracted with $CHCl_3$ (2×15 mL). The combined organic extracts were washed with water (2×5 mL) and dried with Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on Sephadex LH-20 using the $CHCl_3$—MeOH solvent system (4 : 1). Damirone **3** was obtained in a yield of 7.4 mg (86%), m.p. 240—242 °C ($CHCl_3$) (*cf.* lit. data[14]: 240—242 °C). ^1H NMR (MeOH-d_4), δ: 2.78 (t, 2 H, H(3), J = 7.0 Hz); 3.07 (s, 3 H, N(5)Me); 3.59 (t, 2 H, H(4), J = 7.0 Hz); 3.90 (s, 3 H, N(1)Me); 5.29 (s, 1 H, H(6)); 6.62 (s, 1 H, H(2)). ^1H NMR ($CDCl_3$), δ: 2.85 (t, 2 H, H(3), J = 7.0 Hz); 3.06 (s, 3 H, N(5)Me); 3.57 (t, 2 H, H(4), J = 7.0 Hz); 3.93 (s, 3 H, N(1)Me); 5.29 (s, 1 H, H(6)); 6.62 (s, 1 H, H(2)). MS, *m/z*: 216 [M^+].

Synthesis of damirone B (4) from makaluvamine C (2). Analogous treatment of compound **2** (5 mg) afforded compound **4** (3.5 mg, 70%), m.p. >250 °C (MeOH) (*cf.* lit. data[14]: m.p. >250 °C). The melting point of a mixed sample with natural damirone B was higher than 250 °C. ^1H NMR (DMSO-d_6), δ: 2.78 (t, 2 H, H(3), J = 7.5 Hz); 3.03 (s, 3 H, NMe); 3.58 (t, 2 H, H(4), J = 7.5 Hz); 5.14 (s, 1 H, H(6)); 7.09 (s, 1 H, H(2)); 12.42 (s, 1 H, NH). MS, *m/z*: 202 [M^+].

Crystallographic data for compound 3. $C_{12}H_{12}N_2O_2$, M = 216.24; crystals are orthorhombic, space group *Pbca*; a = 7.3233(8), b = 15.903(2), c = 17.112(2) Å; α = 90, β = 90, γ = 90°; V = 1992.9(4) $Å^3$, Z = 8, d_{calc} = 1.44 g cm^{-3}, $F(000)$ = 912.

Crystals of **3** were grown from a solution in $CHCl_3$ by slow evaporation of the solvent. The X-ray diffraction data were collected from a prismatic crystal (0.36×0.23×0.12 mm) on a four-circle Bruker SMART CCD diffractometer (Mo-Kα radiation, λ = 0.71073 Å, graphite monochromator, ω scan technique) at ~21 °C with the use of the SMART and SAINT-Plus programs.[19] A total of 1762 independent reflections were measured of which 1315 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and refined anisotropi-

Table 1. Bond length (d) and bond angles (ω) in compound **3**

Bond	d/Å	Angle	ω/deg	Angle	ω/deg
O(1)—C(6)	1.223(1)	C(9)—N(1)—C(11)	119.5(1)	C(10)—C(5)—C(6)	121.9(1)
O(2)—C(7)	1.236(2)	C(9)—N(1)—C(1)	120.9(1)	O(1)—C(6)—C(5)	126.4(1)
N(1)—C(9)	1.344(2)	C(11)—N(1)—C(1)	116.6(1)	O(1)—C(6)—C(7)	119.7(1)
N(1)—C(11)	1.462(2)	C(4)—N(2)—C(5)	108.8(1)	C(5)—C(6)—C(7)	113.9(1)
N(1)—C(1)	1.474(2)	C(4)—N(2)—C(12)	125.7(1)	O(2)—C(7)—C(8)	123.8(1)
N(2)—C(4)	1.364(2)	C(5)—N(2)—C(12)	125.5(1)	O(2)—C(7)—C(6)	116.0(1)
N(2)—C(5)	1.376(2)	N(1)—C(1)—C(2)	115.1(1)	C(8)—C(7)—C(6)	120.2(1)
N(2)—C(12)	1.465(2)	C(3)—C(2)—C(1)	109.3(1)	C(9)—C(8)—C(7)	122.2(1)
C(1)—C(2)	1.526(2)	C(4)—C(3)—C(10)	105.8(1)	N(1)—C(9)—C(8)	127.6(1)
C(2)—C(3)	1.497(2)	C(4)—C(3)—C(2)	136.0(1)	N(1)—C(9)—C(10)	114.6(1)
C(3)—C(4)	1.380(2)	C(10)—C(3)—C(2)	118.2(1)	C(8)—C(9)—C(10)	117.8(1)
C(3)—C(10)	1.388(2)	N(2)—C(4)—C(3)	109.2(1)	C(5)—C(10)—C(3)	109.7(1)
C(5)—C(10)	1.379(2)	N(2)—C(5)—C(10)	106.5(1)	C(5)—C(10)—C(9)	123.8(1)
C(5)—C(6)	1.437(2)	N(2)—C(5)—C(6)	131.4(1)	C(3)—C(10)—C(9)	126.6(1)
C(6)—C(7)	1.563(2)				
C(7)—C(8)	1.415(2)				
C(8)—C(9)	1.380(2)				
C(9)—C(10)	1.449(2)				

cally by the full-matrix least-squares method with the use of the weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0733P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$. All calculations were carried out with the use of the SHELXTL/PC program package.[20] The hydrogen atoms were placed in geometrically calculated positions and refined isotropically. The structure was refined to $R(F^2) = 0.0389$, $wR(F^2) = 0.1116$, $S = 1.048$. The bond lengths and bond angles are given in Table 1.

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