# Plocamenols A−C, Novel Linear Polyhalohydroxylated Monoterpenes from *Plocamium cartilagineum*

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*Received September 28, 2001*

Three new minor linear polyhalohydroxylated marine monoterpenes, plocamenols A−C (**1**−**3**), have been isolated from the red alga *Plocamium cartilagineum*. The structure and relative stereochemistry of these compounds were determined on the basis of spectroscopic evidence.

*Plocamium cartilagineum* Dixon (Plocamiaceae, order Gigartinales) is a red alga that is found throughout the world, from tropical and subtropical areas to polar habitats such as Antarctica. This species is characterized by its interesting secondary metabolites, being a rich source of diverse polyhalogenated monoterpenes,[1−3] with a surprising degree of halogen incorporation, uncommon for small molecules having only 10 carbon atoms. Since the first halogenated monoterpenes were discovered in the digestive glands of the sea hare *Aplysia californica* in 1973[4] and subsequently in *Plocamium cartilagineum*,[5] the search for this type of compound from different sources was initially very intense. However, after 1985, interest decreased,[6] possibly due to the scanty prospects of finding new compounds, considering that over 150 monoterpenes with very different types of skeleton, including almost all the foreseeable ones, had been reported already from red algae. Nevertheless, the discovery of the important pharmacological properties of halomon[7,8] as well as the unusual incorporation of the oxygen[9] in the metabolic processes of several red algae,[10] is making it possible to characterize new structrural models.[11,12]

Most of the polyhalogenated metabolites within the marine monoterpene family (both cyclic and acyclic) are characterized by possessing a terminal 1-chloro-[13,14] or 1-bromovinyl[13,15] systems or the corresponding dehalo terminal double bond.[16] We have described[9,10] from *Pantoneura plocamioides* and *Plocamium cartilagineum* a series of novel oxane-derivatized monoterpenes (tetrahydropyran and tetrahydrofuran skeletons) possessing a regular chloro- or bromovinyl terminal and related compounds with an unusual chlorobromovinyl system.[17] In the present work, we report three minor interesting functionalized linear, ocimene-type, polyhalooxygenated monoterpenes, plocamenols A−C, **1**−**3**, from *P. cartilagineum* collected in Chile. Two of these, **1** and **2**, contain a terminal bromohydrin, and compound **3** is the corresponding keto derivative. Marine monoterpenes with these functionalities are not very common, and, until now, only one monoterpene ketone, plocamenone, and four marine monoterpenes, with a bromohydrin feature, have been isolated from Australian[18,19] and New Zealand[20,21] *Plocamium* species, respectively.

Vacuum flash chromatography of the ethyl acetate extract of the dried alga *P. cartilagineum* gave a fraction (75:25 hexane−ethyl acetate) from which compounds **1**−**3** were obtained by standard chromatographic procedures involving gel filtration, Si gel chromatography, and recycling-HPLC.

Plocamenol A, **1**, was isolated as a colorless oil. The EIMS showed peaks at *m*/*z* 344/346/348/350 $[M - H_2O]^+$, with relative intensities suggestive of two bromine atoms and one chlorine atom, which corresponded to the molecular formula $C_{10}H_{17}Br_2ClO_2$ $[M^+]$ (HRMS). Hydroxyl group absorption was observed at 3610 and 3580 $cm^{-1}$ in the IR spectrum.

The $^1H$ NMR spectrum of **1** (Table 1) showed signals corresponding to an olefinic proton ($\delta$ 5.70, 1H, t, $J$ = 7.1 Hz), a multiplet at $\delta$ 4.28 (1H, m), and a doublet of triplets at $\delta$ 3.63 (1H, dt, $J$ = 3.8, 8.3 Hz) attributed to methine protons joined to heteroatom. Two doublets of doublets at $\delta$ 3.52 (1H, dd, $J$ = 10.3, 4.3 Hz) and 3.46 (1H, dd, $J$ = 10.3, 7.8 Hz), and also two doublets at $\delta$ 3.80 and 4.28 (1H, d, $J$ = 10.6 Hz) that corresponded to the protons of two halomethylene groups, were observed. A methylene multiplet appeared at $\delta$ 2.44 (2H, m), and at high field, two methyl groups, one olefinic ($\delta$ 1.60, 3H, s) and another one geminal to halogen ($\delta$ 1.82, 3H, s), occurred. The presence of only two methyl groups suggested that the third methyl group, corresponding to a monoterpene skeleton, was oxidized as a halomethylene unit.

The $^{13}C$ NMR spectrum of **1** (Table 1) showed signals for 10 carbons. Multiplicities of the carbon signals were determined from the DEPT spectrum: two methyls at $\delta$ 12.4 and 25.9, three methylenes, one at $\delta$ 31.7 and two bearing halogen at $\delta$ 37.7 and 51.2, three methines (one olefinic at $\delta$ 123.9 and two bearing oxygen at $\delta$ 72.9 and 76.2), and two nonprotonated carbons at $\delta$ 137.1 and 73.3 were observed.

Chemical shift arguments and $^1H-^1H$ COSY correlations supported by MS data allowed the assignment of fragments

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10.1021/np010473z CCC: $22.00 
Published on Web 03/07/2002

**Table 1.** $^1$H, $^{13}$C, and HMBC Data of Compounds **1**−**3** [500 MHz, $\delta$ ppm, ($J$) Hz, $CDCl_3$]

| | **1** | | | **2** | | | **3** | | |
|---|---|---|---|---|---|---|---|---|---|
| no. | $\delta_H$ | $\delta_C$ | HMBC | $\delta_H$ | $\delta_C$ | HMBC | $\delta_H$ | $\delta_C$ | HMBC |
| 1 | 3.52 dd (10.3, 4.3) | 37.7 | C-2, C-3 | 3.55 dd (10.4, 4.0) | 38.2 | | 4.25 d (11.7) | 30.0 | |
| | 3.46 dd (10.3, 7.8) | | | 3.50 dd (10.4, 7.5) | | | 4.21 d (11.7) | | |
| 2 | 4.28 m | 76.2 | | 4.29 m | 75.7 | | | 192.6 | |
| 3 | | 137.1 | | | 137.1 | | | 136.7 | |
| 4 | 5.70 t (7.1) | 123.9 | C-2, C-5, C-6, Me-10 | 5.70 t (7.1) | 123.5 | Me-10 | 6.87 t (6.5) | 140.3 | C-2, Me-10 |
| 5 | 2.44 m | 31.7 | C-3, C-4, C-6, C-7 | 2.41 t (7.1) | 30.4 | C-3, C-4, C-6 | 2.67 ddd (3.1, 6.7, 15.9) | 33.2 | C-3, C-4, C-6 |
| | | | | | | | 2.59 ddd (6.7, 9.7, 15.9) | | |
| 6 | 3.63 dt (8.3, 3.8) | 72.9 | C-4, C-7 | 3.93 dt (7.4, 5.5) | 73.3 | | 3.77 dt (3.2, 10.5) | 72.6 | |
| 7 | | 73.3 | | | 74.6 | | | 73.8 | |
| 8 | 4.28 and 3.80 d (10.6) | 51.2 | C-6, C-7, Me-9 | 4.04 and 3.60 d (10.1) | 39.7 | C-6, C-7, Me-9 | 4.28 and 3.83 d (10.9) | 50.9 | C-6, C-7,Me-9 |
| 9 | 1.82 s | 25.9 | C-6,C-7, C-8 | 1.68 s | 25.5 | C-6,C-7, C-8 | 1.86 s | 25.8 | C-6,C-7, C-8 |
| 10 | 1.60 s | 12.4 | C-2, C-3, C-4 | 1.69 s | 12.6 | C-2, C-3, C-4 | 1.88 s | 12.1 | C-2, C-3, C-4 |
| O$H_2$ | 2.39 d (3.7) | | | 2.24 d (4.2) | | | | | |
| O$H_6$ | 2.04 d (7.6) | | | 1.93 d (7.3) | | | 1.90 s | | |

**Table 2.** $^1$H, $^{13}$C, and HMBC NMR Data of **1a** and **1** and $^1$H NMR Data of **2** [500 MHz, $\delta$ ppm, ($J$) Hz]

| | **1a** | | | **1** | | | **2** |
|---|---|---|---|---|---|---|---|
| no. | $\delta_H$[a] | $\delta_C$[a] | HMBC | $\delta_H$[b] | $\delta_C$[b] | HMBC | $\delta_H$[b] |
| 1 | 3.45 m | 31.8 | C-2, C-3 | 3.05 dd (5, 10.5) | 37.7 | C-2, C-3 | 3.01 m |
| 2 | 5.29 dd (5.5, 7.0) | 77.1 | C-1, C-3, C-4 Me-10, C=O | 3.85 m | 76.2 | | 3.81 m |
| 3 | | 134.2 | | | 137.4 | | |
| 4 | 5.56 t (7.0) | 124.6 | C-2, C-5, C-6, Me-10 | 5.34 t (6.8) | 123.8 | C-2, C-5, C-6, Me-10 | 5.32 t (6.6) |
| 5 | 2.58 m | 30.4 | C-3, C-4, C-6 | 2.17 ddd (9, 9, 14.8) | 31.9 | C-3, C-4, C-6 | 2.16 ddd (8.4, 9.5, 14.6) |
| | | | | 2.03 ddd (2.6, 6.5, 14.8) | | | 2.00 ddd (2.7, 6.4, 14.6) |
| 6 | 5.10 dd (4.8, 8) | 74.1 | C-4, C-5, C-8, C=O | 3.40 m | 73.0 | | 3.65 m |
| 7 | | 67.9 | | | 73.4 | | |
| 8 | 3.93 and 3.77 d (11.3) | 51.0 | C-6, C-7, Me-9 | 4.12 and 3.46 d (10.7) | 51.4 | C-6, C-7, Me-9 | 3.84 and 3.24 d (10.1) |
| 9 | 1.82 s | 26.5 | C-6, C-7, C-8 | 1.44 s | 25.6 | C-6, C-7, C-8 | 1.30 s |
| 10 | 1.69 s | 12.7 | C-2, C-3, C-4 | 1.32 s | 12.1 | C-2, C-3, C-4 | 1.28 s |
| *Me*CO | 2.09[c] | 20.7[c] | | | | | |
| *Me*CO | 2.08[c] | 20.8[c] | | | | | |
| Me*CO* | | 169.5 | | | | | |
| Me*CO* | | 169.6 | | | | | |
| O$H_2$ | | | | 1.88 d (3.9) | | | 1.61 d (4.4) |
| O$H_6$ | | | | 1.75 d (7.1) | | | 1.52 d (8.8) |

[a] $CDCl_3$. [b] $C_6D_6$. [c] Interchangeable signals.

**a**−**c** as shown in **1**. This, along with the olefinic unsaturation, is in keeping with the one degree of unsaturation required by the molecular formula. From the $^1$H−$^1$H COSY NMR spectrum of **1** it was possible to differentiate two discrete spin systems. The coupling between one of the protons bearing oxygen ($\delta$ 4.28) and the methylene protons at $\delta$ 3.52 and 3.46 established the connectivity of the H-1−H-2 fragment **a**. The signals corresponding to the olefinic proton at $\delta$ 5.70 and those assigned to the proton geminal to alcohol at $\delta$ 3.63 were coupled with both protons of the methylene at $\delta$ 2.44, establishing the connectivity of the H-4 to H-6 fragment **b**. HMQC and HMBC data were used to confirm the fragments **a**−**c** and to establish the connectivity between them. The linkage C-2/C-3 was secured by the correlations between H-1 and C-2, C-3 and also C-2 with H-4 and Me-10. C-6/C-7 was determined by the correlation between H-6 and C-7, and also by the correlations of H-8 with C-6, C-7, and Me-9 and by the correlation of H-5 with C-6 and C-7. The C-8/C-7/C-9 linkage was confirmed by the correlation of Me-9 with C-6, C-7, and C-8, and the correlation of C-7 with H-6 and H-8 with C-6 suggested the overall planar structure **1**, with the requisite of one degree of unsaturation. Because the $^1$H NMR signals due to the proton geminal to the alcohol on C-2 and one proton of the chloromethylene were superimposable ($\delta$ 4.28), **1** was acetylated in order to verify the correct HMBC correlations of the shifted H-2 geminal proton at $\delta$ 5.29 of the acetate **1a**. Analysis of the HMBC spectrum of **1a** as well that of the compound **1** run in benzene-$d_6$ (Table 2) agreed with the aforementioned correlations.

The molecular formula of plocamenol A contains two bromine atoms and one chlorine atom, and its $^{13}$C NMR spectrum enabled the regiochemistry[22] of the halogens in plocamenol A (**1**) to be established. It was deduced from the carbon chemical shift of the sp$^3$ halogen-bearing carbon at 51.2 ppm that this halogen atom was chlorine,[11,23] whereas the resonance at 37.7 ppm would correspond[23,24] to a bromomethylene. Thus, from a HMBC experiment, the halogen regiochemistries of both halomethylenes were established as shown in **1**. This was reinforced by analysis

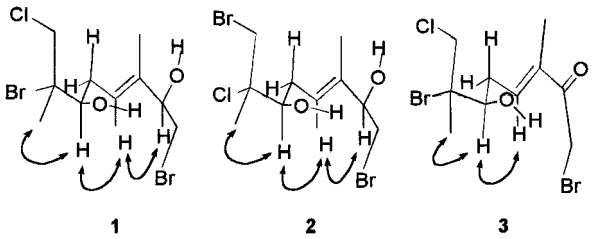

**Figure 1.** Selected NOE for plocamenols A−C (**1**−**3**).

of the MS of plocamenol A (**1**), which displayed peaks at *m*/*z* 185/187/189 which must correspond to a $C_4H_7BrClO$ fragment (HRMS). The *E* stereochemistry of the double bond was deduced from the $^{13}C$ NMR upfield chemical shift for C-10 ($\delta$ 12.4) due to a $\gamma$-effect[21,25] from both C-4, in a cis relationship, and the polar group at C-2. All these data supported the structure **1a** for plocamenol A.

Plocamenol B (**2**) was isolated as a colorless oil. The EIMS of compound **2** showed a fragment pattern $[M - H_2O]^+$ at *m*/*z* 344/346/348/350 similar to that in **1**, corresponding to the same molecular formula, $C_{10}H_{17}Br_2ClO_2$. Comparison of the $^1H$ NMR spectrum of **2** and **1** (Table 1) clearly indicated that both compounds have identical C-1−C-5 fragments, as could be seen from the almost equal chemical shift of the protons attached to the fragment as well as from the similar values of C-1−C-5 in the $^{13}C$ NMR spectrum (Table 1). In contrast, significant differences in the $^{13}C$ NMR chemical shift of the C-8 halomethylene groups (**1**, $\delta_{C-8}$ 51.2; **2**, $\delta_{C-8}$ 39.7) on the order of 11 ppm suggested that compound **2** has an attached bromine at C-8. The spectral evidence is fully consistent with the structure **2** for plocamenol A, with the substitution pattern of halogen on the isopropyl group representing the structural difference between **1** and **2**.

Plocamenol C (**3**) was isolated as an oil and was deduced to have the molecular formula $C_{10}H_{15}Br_2ClO_2$ by mass spectral analysis. Since the molecule contained two multiple bonds, a carbonyl (192.6 s), and a carbon−carbon double bond (136.7 s, 140.3 d), it had to be acyclic. The $^1H-^1H$ COSY spectrum allowed us to detect only one spin system attributable to fragment **b**, which is indicative of two halomethylene groups present in the molecule, a chloromethylene (50.9 t) and a bromomethylene (30.0 t), and must be discerned as shown in fragments **a** and **c**. This, together with the absorptions of an $\alpha,\beta$-unsaturated carbonyl group observed in the IR spectrum, suggested the overall planar structure **3**.

HMQC and HMBC data were used to confirm the fragments **a**−**c** and establish the connectivities between them. The linkage C-2/C-3 was secured by the correlations between C-2 with H-4 and Me-10, with C-6/C-7 determined by the correlations between C-6 and H-5, H-8, and Me-9. The C-8/C-7/C-9 linkage was confirmed by the correlations of Me-9 with C-6, C-7, and C-8 and corroborated by analysis of the MS, which displayed peaks at *m*/*z* 185/187/189 for a $C_4H_7BrClO$ fragment (HRMS). All these data supported structure **3** for plocamenol C.

The relative stereochemistries of the chiral centers were determined by 2D-NOESY experiments. Clear NOE effects between H-4 with H-2 and H-6 and also between H-6 with Me-9 were observed (Figure 1), suggesting a relative **R*, **R* configuration for the C-2 and C-6 chiral centers of compounds **1** and **2** and also a **R* configuration for the C-6 of **3**. 2D-NOESY experiments were run in chloroform-*d* for compounds **1a** and **3**, and for compounds **1** and **2** 2D-NOESY experiments were conducted in chloroform-*d* and also in benzene-$d_6$. We propose an **S* configuration for C-7 in compounds **1**−**3** on the basis of the similarities of the $^{13}C$ NMR chemical shifts of the C-9 methyl group (Me-9: $\delta_C$ ~25.7) compared with the data reported for C-7 (Me-9: $\delta_C$ ~25.3) in a series of related monoterpenes whose stereochemistries have been determined[21,26] by X-ray crystallography. Thus, we propose the stereochemistry shown in **1**−**3** respectively for plocamenols A−C.

Compounds **1** and **2**, along with costatol, are the first metabolites showing a double bond conjugate bromohydrin, and the incorporation of an additional oxygenated function enhances the number of new algal polyhalogenated and polyhydroxylated marine monoterpenes and encourages the study of habitat-dependent new metabolites from this and other species of red algae.

## Experimental Section

**General Experimental Procedures.** Optical rotations were measured on a Perkin-Elmer model 241 polarimeter using a Na lamp at 25 °C. IR spectra were obtained with a Perkin-Elmer 1650FT-IR spectrometer in $CHCl_3$ solution. $^1H$ NMR and $^{13}C$ NMR, HMQC, HMBC, NOESY, and $^1H-^1H$ COSY spectra were measured employing a Bruker AMX 500 instrument operating at 500 MHz for $^1H$ NMR and at 125 MHz for $^{13}C$ NMR, using TMS as internal standard. Two-dimensional NMR spectra were obtained with the standard Bruker software. EIMS and HRMS were taken on a Micromass Autospec spectrometer. Recycling-HPLC separations were performed with a Japan Analytical LC-908 instrument. The gel filtration column separation (Sephadex LH-20) used hexane−MeOH−$CHCl_3$ (3:1:1) as solvent. Merck Si gel 7734 and 7729 were used in column chromatography. The spray reagent for TLC was $H_2SO_4-H_2O$−AcOH (1:4:20).

**Plant Material.** *P. cartilagineum* was collected off the Chilean coast (V Región) using scuba diving. Voucher specimens have been deposited at the Museo de Historia Natural, Santiago de Chile (no. R23Pl35PLc-3).

**Extraction and Isolation of Monoterpenoids 1−3.** Air-dried *P. cartilagineum* (327 g, dry wt) was extracted with EtOAc at room temperature. The extract was concentrated to give a dark green residue (18.8 g) and chromatographed by flash chromatography on Si gel. The fraction eluted with hexane−EtOAc (75:25) (718 mg) was further separated by filtration chromatography to give a fraction (207 mg) which was chromatographed on a Si gel column to obtain a mixture (27 mg) of monoterpenes (**1**−**3**), which was separated by recycling-HPLC using chloroform as eluent.

**Plocamenol A (1):** colorless oil; $[\alpha]^{25}_D$ +22° (*c* 0.2, $CHCl_3$); IR $\nu_{max}$ 3610, 3580 $cm^{-1}$; $^1H$ and $^{13}C$ NMR, see Table 1 ($CDCl_3$) and Table 2 ($C_6D_6$); EIMS *m*/*z* 344/346/348/350 $[M - H_2O]^+$ (<1, 1, 1, <1), 265/267/269 $[M - H_2O - Br]^+$ (2, 2, <1), 251/253/255 $[M - CH_2Br - H_2O]^+$ (5, 7, 2), 185/187/189 (2, 3, 1), 160/162 (9, 9), 81 (100); HREIMS $[M - H_2O]^+$ 343.9164 (calcd for $C_{10}H_{15}{}^{79}Br^{79}Br^{35}ClO$, 343.9178); 265.0066 (calcd for $C_{10}H_{15}{}^{79}Br^{35}ClO$, 264.9994); 250.9802 (calcd for $C_9H_{13}{}^{79}Br^{35}ClO$, 250.9838); 184.9379 (calcd for $C_4H_7{}^{79}Br^{35}ClO$, 184.9368).

**Acetylation of 1.** A solution of compound **1** (3 mg) in dry $C_5H_5N$ (0.2 mL) was treated with $Ac_2O$ (0.3 mL), stirred at room temperature for 30 min, and then poured into 5% aqueous HCl and extracted with $CHCl_3$. The organic layer was washed with $H_2O$ and brine, dried ($Na_2SO_4$), and concentrated. The residue of acetate **1a** was purified using recycling-HPLC (Jaigel-sil column 20 × 250 mm), eluted with $CHCl_3$, affording **1a** (2.8 mg).

**Acetate 1a:** colorless oil; IR $\nu_{max}$ 1745 $cm^{-1}$; $^1H$ and $^{13}C$ NMR, see Table 2; EIMS *m*/*z* 367/369/371 $[M - Br]^+$ (2, 3, 1), 307/309/311 $[M - Br - AcOH]^+$ (15, 19, 5), 265/267/269 (7, 9, 2), 247/249/251 $[M - Br - 2AcOH]^+$ (10, 12, 5), 185/187 (100, 33); HREIMS $[M - Br]^+$ 367.0291 (calcd for $C_{14}H_{21}{}^{79}Br^{35}ClO_4$, 367.0312); 307.0107 (calcd for $C_{12}H_{17}{}^{79}Br^{35}ClO_2$, 307.0100); 246.9919 (calcd for $C_{10}H_{13}{}^{79}Br^{35}Cl$, 246.9889).

**Plocamenol B (2):** colorless oil; $[\alpha]^{25}_D$ +14 (*c*, 0.2, $CHCl_3$); IR $\nu_{max}$ 3610, 3580 $cm^{-1}$; $^1H$ and $^{13}C$ NMR, see Table 1 ($CDCl_3$)

and Table 2 ($C_6D_6$); EIMS *m/z* 344/346/348/350 $[M - H_2O]^+$ (<1, <1, <1, <1), 251/253/255 $[M - CH_2Br - H_2O]^+$ (2, 3, 1), 185/187/189 (2, 2, 1), 160/162 (7, 7), 81 (100); HREIMS $[M - H_2O]^+$ 343.8919 (calcd for $C_{10}H_{15}{}^{79}Br^{79}Br^{35}ClO$, 343.8992); 250.9655 (calcd for $C_9H_{13}{}^{79}Br^{35}ClO$, 250.9652); 187.9115 (calcd for $C_4H_7{}^{81}Br^{35}ClO$, 186.9162).

**Plocamenol C (3):** colorless oil; $[\alpha]^{25}{}_D$ +18 (*c*, 0.2, $CHCl_3$); IR $\nu_{max}$ 3610, 1700 $cm^{-1}$; $^1H$ and $^{13}C$ NMR, see Table 1; EIMS *m/z* 342/344/346/348 $[M - H_2O]^+$ (<1, 1, 1, <1), 281/283/285 $[M - Br]^+$ (2, 3, 1), 267/269/271 $[M - CH_2Br]^+$ (18, 23, 6), 205/207 (9, 9), 185/187/189 (10, 12, 3), 176/178 (67, 67), 97 (100); HREIMS $[M - H_2O]^+$ 343.9009 (calcd for $C_{10}H_{13}{}^{81}Br^{79}Br^{35}ClO$, 343.9001); 280.9889 (calcd for $C_{10}H_{15}{}^{79}Br^{35}ClO_2$, 280.9944); 266.9724 (calcd for $C_9H_{13}{}^{79}Br^{35}ClO_2$, 266.9787); 204.9817 (calcd for $C_7H_{10}{}^{79}BrO_2$, 204.9864); 184.9338 (calcd for $C_4H_7{}^{79}Br^{35}ClO$, 184.9369).

**Acknowledgment.** This work was supported by Programa Antártico Español (MCYT), FEDER (projects: 1FD97-0348-C03-03), FONDECYT (1990935), Subdirección General de Cooperación Internacional, and the Program of Cooperation between the Consejo Superior de Investigaciones Científicas (CSIC, Spain)-Universidad de Chile. A.R.D.-M. acknowledges a fellowship from the CICYT. We are grateful to Dr. Eliana Ramírez (Museo de Historia Natural, Chile) for the taxonomic classification of the alga.

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NP010473Z