Tetrahedron Letters 50 (2009) 3202–3204

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Plakoridine C, a novel piperidine alkaloid from an Okinawan marine sponge *Plakortis* sp.

Yuichiro Ishiguro [a], Takaaki Kubota [a], Kan'ichiro Ishiuchi [a], Jane Fromont [b], Jun'ichi Kobayashi [a,*]

[a] Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan
[b] Western Australian Museum, Locked Bag 49, Welshpool DC, WA 6986, Australia

ARTICLE INFO

Article history:
Received 9 December 2008
Revised 26 January 2009
Accepted 29 January 2009
Available online 1 February 2009

Keywords:
Sponge
Plakortis sp.
Piperidine alkaloid
Plakoridine C

ABSTRACT

A new piperidine alkaloid plakoridine C (**1**) has been isolated from an Okinawan marine sponge *Plakortis* species, and the structure was elucidated from spectroscopic data. Plakoridine C (**1**) is a new alkaloid possessing a piperidine ring connected to a β-keto-γ-lactone through a double bond.

Marine sponges of the genus *Plakortis* are known to be a rich source of unique peroxy aliphatic acids and esters.[1] During our search for new metabolites from Okinawan marine sponges, we have isolated some polyketide with unique skeletons from the genus *Plakortis*.[2–7] Recently, we investigated extracts of an Okinawan marine sponge *Plakortis* sp. (SS-11) and isolated plakoridine C (**1**), a new alkaloid possessing a piperidine ring connected to a β-keto-γ-lactone through a double bond. Herein, we describe the isolation and structure elucidation of **1**.

The sponge *Plakortis* sp. (SS-11) collected off Manzamo, Okinawa, was extracted with MeOH. EtOAc-soluble materials of the extract were subjected to silica gel column chromatographies to yield plakoridine C (**1**, 0.00015%, wet weight), together with known compounds, manzamenones A, D, J, and K,[2,6,8,9] plakorin,[10] chondrillin,[11] and plakevulin A.[7,12]

Plakoridine C (**1**) was obtained as a colorless amorphous solid.[13] The ESIMS spectrum of plakoridine C (**1**) showed the pseudomolecular ion peak at *m/z* 470 $(M+Na)^+$, and the molecular formula of **1** was revealed to be $C_{27}H_{45}NO_4$ by HRESIMS data [*m/z* 470.3230 $(M+Na)^+$, Δ −1.6 mmu]. UV absorptions [λ_{max} 289 nm (ε 18,400) and 229 nm (ε 11,900)] suggested the presence of conjugated system, while IR absorptions indicated the existence of carbonyl (1737 and 1712 cm^{-1}) functionalities. Several pairs of signals were observed in the ^1H and ^{13}C NMR spectra of **1** with a ratio of approximately 1:1, suggesting that **1** is an epimeric or isomeric mixture. Despite many attempts, further separation of **1** was not accomplished by semi-preparative HPLC. Therefore, structural elucidation of **1** was carried out using the mixture.

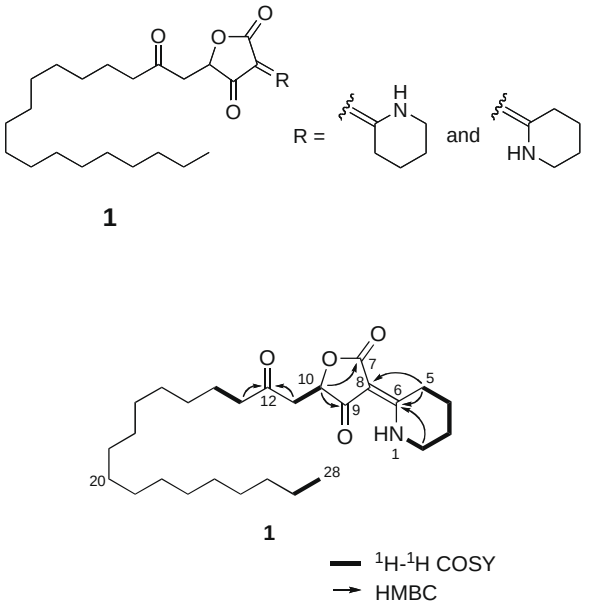


Figure 1. Selected 2D NMR correlations for plakoridine C (**1**). *E*-isomer was depicted for descriptive purposes.

* Corresponding author. Tel.: +81 11 706 3239; fax: +81 11 706 4989.
E-mail address: jkobay@pharm.hokudai.ac.jp (J. Kobayashi).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.01.135

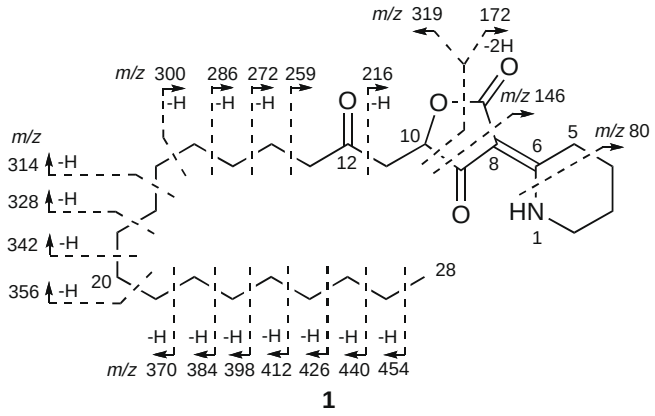


Figure 2. Fragmentation patterns observed in positive ion ESIMS/MS spectrum of plakoridine C (**1**) [precursor ion, *m*/*z* 470 $(M+Na)^+$]. *E*-isomer was depicted for descriptive purposes.

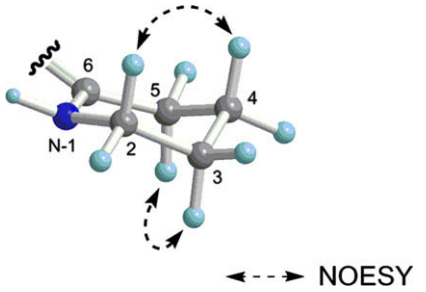


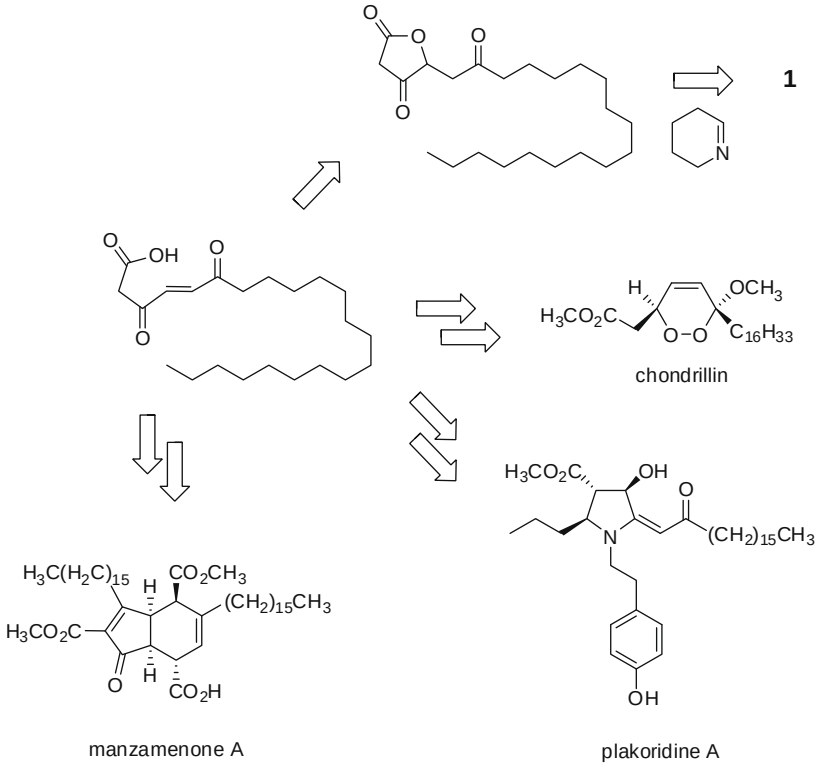
Figure 3. Selected NOESY correlations and the conformation of piperidine ring in plakoridine C (**1**).

The ^1H and ^{13}C NMR spectra of **1** implied the presence of two keto groups and an ester carbonyl group, a tetrasubstituted olefin, and a long aliphatic chain. The HN-HMQC spectrum of **1** revealed that two proton signals (δ_H 11.03 and 10.20) were ascribed to a proton attached to a nitrogen atom (δ_N −238.4).[14] Analyses of the ^1H–^1H COSY and the HMQC spectra of **1** disclosed connectivities of N-1 to C-5, C-10 to C-11, C-13 to C-14, and C-27 to C-28 (Fig. 1). HMBC correlations for H-2 and H-5 to C-6 revealed the presence of a piperidine ring (N-1 to C-6), while connectivities of N-1, C-5, and C-8 to C-6 were implied by the HMBC cross-peak for H-5 to C-8 (Fig. 1). Connections of C-10 to an ester carbonyl carbon through an oxygen atom and a keto carbonyl carbon were indicated by HMBC correlations of H-10 to C-7 and C-9. In addition, HMBC cross-peaks for H_2-11 and H_2-13 to C-12 suggested connections of C-11 and C-13 to another keto carbonyl carbon (C-12).

Analysis of the ESIMS/MS spectrum of **1** revealed connectivities from C-14 to C-27 (Fig. 2). These fragmentation patterns also supported the structure of plakoridine C (**1**) elucidated from 2D NMR data.

The conformation of a piperidine ring in **1** was deduced from NOESY correlations between H-2 and H-4, and H-3 and H-5 as shown in Figure 3.

According to the structure of **1** based on these data, it was revealed that **1** is a mixture of inseparable geometrical isomers at the C-6–C-8 double bond (*E*/*Z*, ca. 1:1).[15] Furthermore, the specific optical rotation, $[\alpha]_D^{21}$ ~0 (*c* 1.0, $CHCl_3$), and the CD spectrum, which was flat between 200 and 400 nm, suggested that **1** was racemic mixture of enantiomers at C-10 of *E* and *Z* isomers. Chiral HPLC analysis of **1** [CHIRALCEL® OD-H, Daicel Chemical Industries, Ltd, 4.6 × 250 mm; eluent, *n*-hexane/*i*-propanol, 70:30; flow rate, 0.5 mL/min; UV (289 nm) and chiral detection] resulted in separation of (+)-plakoridine C (t_R 26.3 min) and (−)-plakoridine C (t_R 27.9 min), and revealed that the ratio of (+)- and (−)-forms of plakoridine C (**1**) was ca. 1:1.



Scheme 1. Plausible biogenetic path for plakoridine C (**1**).

A plausible biogenetic path for plakoridine C (**1**) is proposed as shown in Scheme 1. Plakoridine C (**1**) seems to be generated from a piperideine and a 3,6-dioxo-4-docosenoic acid, which has been proposed to be a common key intermediate for metabolites of *Plakortis* sponges such as chondrillin,[11] plakoridine A,[5] and manzamenone A.[2,8,9]

Plakoridine C (**1**) is a new alkaloid possessing a piperidine ring connected to a β-keto-γ-lactone through a double bond. Plakoridine C (**1**) did not show cytotoxicities against P388 and L1210 murine leukemia, and KB human epidermoid carcinoma cells (IC_{50} > 10.0 μg/mL) in vitro.

Acknowledgments

We thank Mr. Z. Nagahama for his help in sponge collection, Dr. E. Fukushi, Graduate School of Agriculture, Hokkaido University, for measurements of HN-HMQC and HMBC spectra of **1**, and Ms. S. Oka, Center for Instrumental Analysis, Hokkaido University, for measurements of ESIMS and ESIMS/MS. This work was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References and notes

1. Blunt, J. W.; Copp, B. R.; Hu, W.-P.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2008**, *25*, 35–94. and references cited therein.
2. Tsukamoto, S.; Takeuchi, S.; Ishibashi, M.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 5255–5260.
3. Kobayashi, J.; Tsukamoto, S.; Takeuchi, S.; Ishibashi, M. *Tetrahedron* **1993**, *27*, 5955–5960.
4. Ishibashi, M.; Takeuchi, S.; Kobayashi, J. *Tetrahedron Lett.* **1993**, *34*, 3749–3750.
5. Takeuchi, S.; Ishibashi, M.; Kobayashi, J. *J. Org. Chem.* **1994**, *59*, 3712–3713.
6. Takeuchi, S.; Kikuchi, T.; Tsukamoto, S.; Ishibashi, M.; Kobayashi, J. *Tetrahedron* **1995**, *51*, 5979–5986.
7. Tsuda, M.; Endo, T.; Perpelescu, M.; Yoshida, S.; Watanabe, K.; Fromont, J.; Mikami, Y.; Kobayashi, J. *Tetrahedron* **2003**, *59*, 1137–1141.
8. Al-Busafi, S.; Drew, M. G. B.; Sanders, T.; Whitehead, R. C. *Tetrahedron Lett.* **1998**, *39*, 1647–1650.
9. Al-Busafi, S.; Whitehead, R. C. *Tetrahedron Lett.* **2000**, *41*, 3467–3470.
10. Murayama, T.; Ohizumi, Y.; Nakamura, H.; Sasaki, T.; Kobayashi, J. *Experientia* **1989**, *45*, 898–899.
11. Wells, R. J. *Tetrahedron Lett.* **1976**, *17*, 2637–2638.
12. Kuramochi, K.; Saito, F.; Takeuchi, R.; Era, T.; Takemura, M.; Kobayashi, J.; Sakaguchi, K.; Kobayashi, S.; Sugawara, S. *Tetrahedron* **2006**, *62*, 8006–8015.
13. *Plakoridine C* (**1**): colorless amorphous solid; UV (MeOH) λ_{max} 289 nm (ε 18,400), 229 nm (ε 11,900); IR (film) ν_{max} 1737, 1712, 1664, 1647, and 1604 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 11.03 (0.5H, br s NH), 10.20 (0.5H, br s NH), 4.84 (0.5H, dd, 8.0, 3.5 Hz, H-10), 4.79 (0.5H, dd, 8.0, 3.5 Hz, H-10), 3.49 (2H, m H_2-2), 3.14 (1H, m, H-5a), 3.09 (1H, m, H-5b), 2.94 (1H, dd, 15, 3.5 Hz, H-11a), 2.75 (1H, dd, 15, 8.0 Hz, H-11b), 2.43 (2H, m, H_2-13), 1.87 (2H, m, H_2-3), 1.81 (2H, m, H_2-4), 1.56 (2H, m, H_2-14), 1.10–1.30 (26H, br s, H_2-15–H_2-27), 0.88 (3H, t, 10.2 Hz, H_3-28) δ_C 206.4 (1C, C-12), 198.0 (0.5C, C-9), 194.5 (0.5C, C-9), 175.3 (0.5C, C-7), 171.3 (0.5C, C-7), 171.3 (0.5C, C-6), 170.7 (0.5C, C-6), 90.5 (0.5C, C-8), 89.0 (0.5C, C-8), 78.2 (0.5C, C-10), 76.5 (0.5C, C-10), 43.6 (1C, C-11), 43.4 (1C, C-13), 42.1 (1C, C-2), 22.6-31.8 (13C, C-15–C-27), 26.3 (0.5C, C-5), 25.7 (0.5C, C-5), 23.4 (1C, C-14), 20.9 (1C, C-3), 17.4 (1C, C-4), 14.0 (1C, C-28); ESIMS (pos.) *m/z* 470 [$(M+Na)^+$]; HRESIMS (pos.) *m/z* 470.3230 [$(M+Na)^+$, calcd for $C_{27}H_{45}NO_4Na$, 470.3246].
14. The ^{15}N signal of formamide (−267.5 ppm with respect to CH_3NO_2, 0 ppm) was used as a reference for ^{15}N chemical shifts.
15. Ghosal, S.; Chaudhuri, R. K.; Tiwari, M. P.; Singh, A. K.; Wehrli, F. W. *Tetrahedron Lett.* **1974**, *15*, 403–406.