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Acantholactone, a new manzamine related alkaloid with an unprecedented δ-lactone and ε-lactam ring system

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Abstract

A new manzamine-related alkaloid with unprecedented δ-lactone and ε-lactam rings called acantholactone (**2**), was isolated from the Indonesian sponge *Acanthostrongylophora* sp. The relative configuration of the two new ring systems was established through detailed analysis of NOESY correlations combined with molecular modeling studies. The absolute configuration of **2** was determined as 12*S*, 24*R*, 25*R*, 26*R* by comparing the computed electronic circular dichroism (ECD) spectra with experimental values.

Keywords

Manzamine alkaloids

The manzamine alkaloids have proven to be a source of promising biological activities as well as fascinating and novel chemical structures.[1] Since the discovery of manzamine A (**1**),[2] over 80 related structures have been reported[3] including the novel structures: dimer kauluamine,[4] dimer neo-kauluamine,[5] manadomanzamines A and B,[6] and zamamidines A and B.[7]

As a part of our lead optimization of **1** against malaria and other targets, a large scale purification method that enables the isolation of pure **1** and related alkaloids in gram quantities[1a] from the Indonesian sponge *Acanthostrongylophora* sp. was developed. We investigated the polar fractions and isolated the new manzamine acantholactone. Herein, we report the isolation and structure elucidation of **2**.

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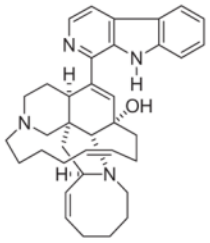
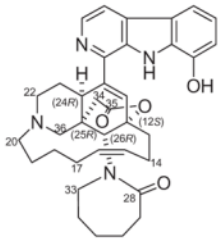
Supplementary data

Supplementary data (copies of the 1D and 2D spectra of acantholactone and experimental details of the isolation and the computational part)associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.140.

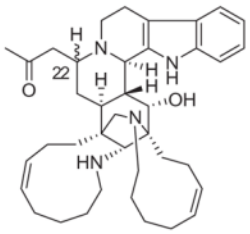
The sponge, *Acanthostrongylophora* sp., was collected from Indonesia and successively extracted with acetone. The crude acetone extract was subjected first to an acid–base[1a] process to obtain the total alkaloids content. Silica gel fractionation and purification of the more polar fractions by successive RP-HPLC resulted in the isolation of the new manzamine acantholactone (**2**) as well as the known manzamines manzamine A (**1**),[2] 8-hydroxymanzamine A,[8] manzamine F,[7] 12,34-oxamanzamine E,[9] and 31-keto-12,34-oxa-32,33-dihydroircinal A.[8]



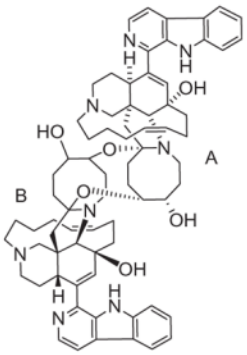
manzamine A (**1**)



acantholactone (**2**)



manadomanzamine A : 22b-H
manadomanzamine B : 22a-H



neo-kauluamine

Acantholactone (**2**)[10] was obtained as a pale yellow powder from DCM, and it was revealed to have a molecular formula of $C_{36}H_{43}N_4O_4$ by HRESIMS (*m/z* 595.3416 $(M+H)^+$) combined with ^1H and ^{13}C NMR data (Table 1). The ^1H NMR resonances at δ 8.28 (1H, d, J = 5.2), 8.04 (1H, d, J = 5.2 Hz), 7.73 (1H, d, J = 7.5 Hz), 7.17 (1H, t, J = 8.0 Hz), and 7.09 (1H, d, J = 7.2 Hz) combined with ^{13}C NMR resonances at 136.9, 121.7, 116.5, 113.7, and 113.4 confirmed the presence of an 1,8-disubstituted β-carboline moiety with a hydroxy group at C-8 (144.4). HMBC correlation of H-11 (δ_H 6.09, δ_C 121.4) to C-12 (83.6), C-26 (70.9), C-10 (140.2), and C-24 (44.0) confirmed that the β-carboline moiety is coupled with the typical cyclohexene ring found in many manzamine alkaloids. The presence of the piperidine ring was confirmed by the HMBC correlations of H-26 (δ_H 3.86, δ_C 70.9) to C-36 (70.7), C-25 (46.8), and C-24 (44.0). The ^{13}C NMR resonance at 56.6 (δ_H 4.69, 3.97) was assigned to C-20 which showed HMBC correlations with the other two α-carbons of *N*-21 (C-22, 61.0; C-36, 70.7) in the piperidine ring. The presence of the 13-membered ring in the molecule was confirmed by the ^1H–^1H-COSY and HMBC correlations of the two olefinic ^1H NMR resonances, H-15 (δ_H 5.47, δ_C 131.4) and H-16 (δ_H 5.50, δ_C 131.8). The unprecedented δ-lactone ring was established based on the HMBC correlations of H-34 (δ_C 36.4) methylene resonances at δ 3.04 and 2.90 to C-24 (δ_H 4.07, 44.0), C-25 (46.8), and C-35 (ester carbonyl) (173.9). The downfield chemical shifts of C-12 (83.6), C-25 (46.8), C-36 (70.7), and C-26 (70.9) with the HMBC correlations confirmed the δ-lactone ring to be connected between C-12 and C-26. The ^{13}C NMR spectra showed an additional carbonyl

group which was shown to be the amidic carbonyl at C-28 of the ε-lactam ring based on the HMBC correlations of H-26 (δ_H 3.86, δ_C 70.9), H-33 (δ_H 3.80, 3.58; δ_C 55.8), and H-29 (δ_H 1.92, 1.67; δ_C 29.3) to the C-28 carbonyl (179.6). The relative configuration of acantholactone (**2**) was deduced from the detailed analysis of the NOESY spectrum (Table 1, 2Fig. 1). The chair-boat conformation of the piperidine and the cyclohexene rings was assigned based on the NOESY correlations of H-24, H-26, and H-22. The new δ-lactone ring was assigned as α-orientation relative to the cyclohexene ring based on the NOESY correlations of H-24/H-36. The NOESY correlation between H-20 and H-33 suggested the α-conformation of the ε-lactam ring as seen in the 3D structure of the most stable conformer of (Fig. 2).

The absolute configuration of acantholactone (**2**) was established by comparing the computed electronic circular dichroism (ECD) spectra with experiment (Fig. 3). As a result of conformational analysis, six low-energy conformations were generated using the Merck Molecular Force Field (MMFF) calculations followed by the PM6 semi-empirical optimizations. The optimized structures were then used for the hybrid density-functional theory (DFT) calculation at the B3LYP/6-31G(d,p) level for the gas phase and for acetonitrile (using the Polarizable Continuum Model (PCM)).[11] The DFT optimized structures were subsequently used for the TDDFT excited-state calculations at the BHANDHLYP/TZVP level for the gas phase and for acetonitrile (PCM). The obtained rotational strengths were Boltzmann averaged and fitted to Gaussian functions with the calculated excitation energies to simulate ECD curves of **2** which were then overlaid with the experimental ECD spectrum for comparison. Based on the relative configuration elucidated by the NMR experiments, the absolute configuration of acantholactone (**2**) was thus assigned as 12*S*, 24*R*, 25*R*, 26*R*.

Acantholactone (**2**) is the first manzamine-related alkaloid with a unique ε-lactam as well as δ-lactone rings. The fact that the manzamine family showed a diverse range of biological activities makes acantholactone a good candidate for evaluation against malaria, neuroprotection, and TB. However, the low isolated yield of **2** from the sponge extract limited its biological evaluation. This will encourage the synthetic community to develop efficient synthetic routes that will enable the biological evaluation of **2**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References and notes

1. For reviews on manzamine alkaloids: Peng J, Rao KV, Choo YM, Hamann MT. Fattorusso E, Taglialatela-Scafati O. Manzamine Alkaloids. Modern Alkaloids. Wiley-VCH, GmbH, KgaAWeinheim, Germany2007:189–232.Hamann MT. Curr Pharm Des. 2007; 13:653–660. [PubMed: 17346180]
2. Sakai R, Higa T, Jefford CW, Bernardinelli G. J Am Chem Soc. 1986; 108:6404–6405.
3. Hu, J.; Hamann, MT.; Hill, RT.; Kelly, M. Alkaloids. Vol. 6. Elseiver Science; San Diego, USA: 2003. p. 207-285.

4. Ohtani II, Ichiba T, Isobe M, Kelly-Borges M, Scheuer PJ. J Am Chem Soc. 1995; 117:10743–10744.
5. El-Sayed KA, Kelly M, Kara UAK, Ang KKH, Katsuyama I, Dunbar DC, Khan AA, Hamann MT. J Am Chem Soc. 2001; 123:1804–1808. [PubMed: 11456797]
6. Peng J, Hu J, Kazi AB, Li Z, Avery M, Peraud O, Hill RT, Franzblau SG, Zhang F, Schinazi RF, Wirtz SS, Tharnish P, Kelly M, Wahyuono S, Hamann MT. J Am Chem Soc. 2003; 125:13382–13386. [PubMed: 14583033]
7. Takahashi Y, Kubota T, Fromont J, Kobayashi J. Org Lett. 2009; 11:21–24. [PubMed: 19053818]
8. Rao KV, Kasanah N, Wahyuono S, Tekwani BL, Schinazi RF, Hamann MT. J Nat Prod. 2004; 67:1314–1318. [PubMed: 15332848]
9. Rao KV, Donia MS, Peng J, Garcia-Palomero E, Alonso D, Martinez A, Medina M, Franzblau SG, Tekwani BL, Khan SI, Wahyuono S, Willett KL, Hamann MT. J Nat Prod. 2006; 69:1034–1040. [PubMed: 16872140]
10. Acantholactone (**2**) 4 mg; yellow powder (DCM); $[\alpha]_D^{25}$ 31.6 (c 0.045, MeOH); UV (MeOH) λ_{max} 352, 292, 255, 234 nm; CD (CH_3CN) λ_{max} 306 nm ($\Delta\varepsilon$+0.0084), 274 nm ($\Delta\varepsilon$−0.0047), 244 nm ($\Delta\varepsilon$−0.0065), 230 nm ($\Delta\varepsilon$−0.0075); NMR data, see Table 1; HRESIMS m/z 595.3416 (calcd for $C_{36}H_{43}N_4O_4$, $(M+H)^+$, 595.3498).
11. (a) Becke AD. J Chem Phys. 1993; 98:1372–1377.(b) Schaefer A, Horn H, Ahlrichs R. J Chem Phys. 1992; 97:2571–2577.(c) Schaefer A, Huber C, Ahlrichs R. J Chem Phys. 1994; 100:5829–5835.(d) Wang J, Zhai WZ, Zou Y, Zhu JJ, Xiong J, Zhao Y, Yang GX, Fan H, Hamann MT, Xia G, Hu JF. Tetrahedron Lett. 2012; 53:2654.

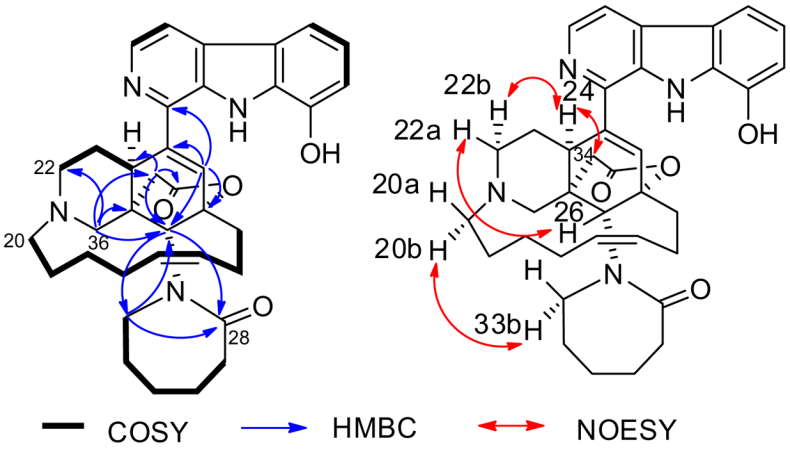

Figure 1.
Selected 2D correlations of acantholactone (**2**).

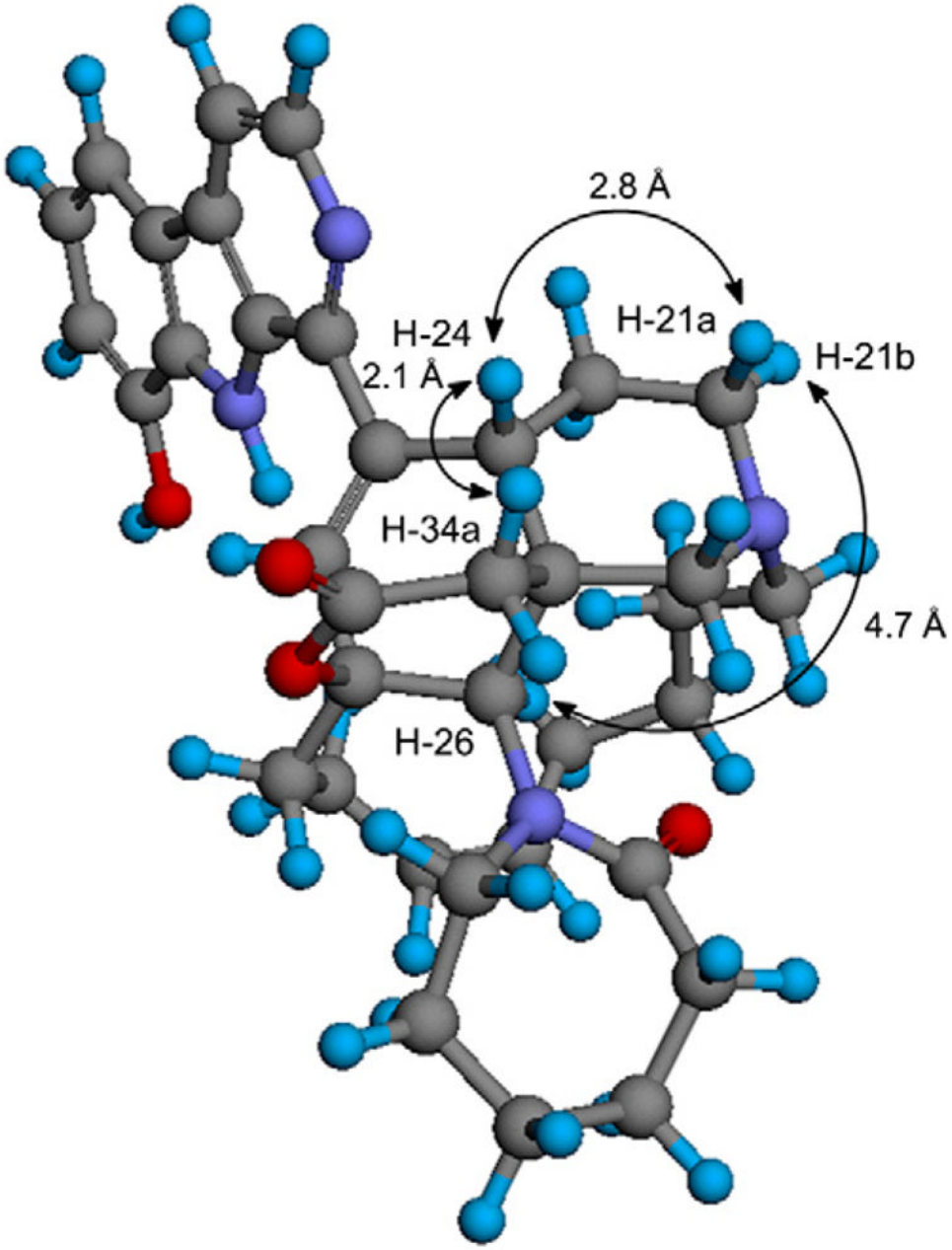

Figure 2.
3D structure of the most stable conformer of acantholactone (**2**) in acetonitrile with the key NOESY correlations and the distance between the hydrogen atoms.

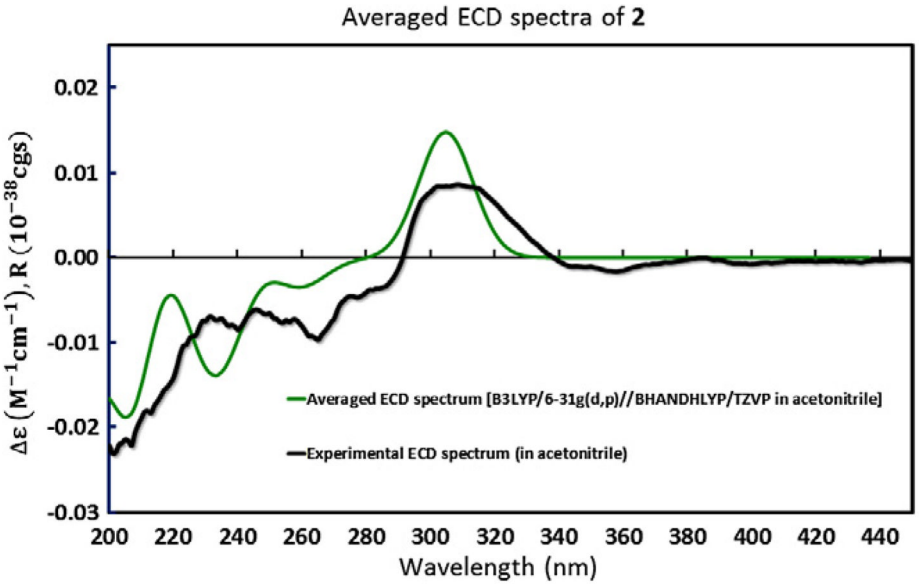

Figure 3.
Computed ECD curve (in acetonitrile) overlaid with the experimental ECD spectrum of **2.**

Table 1

^{1}H, ^{13}C NMR, and 2D data of **2** (δ in ppm, J in Hz)[a]

Position	Acantholactone (2)[b]				
	^{13}C NMR	^{1}H NMR	HMBC	COSY	NOESY
1	147.5 s	–	–	–	
3	136.9 d	8.28 d, 5.2	3, 4a, 10	4	4, 6, 7, 11, 15, 16
4	116.5 d	8.04 d, 5.2	3, 4a	3	3, 6, 7, 11
4a	131.2 s	–	–	–	
4b	131.0 s	–	–	–	
5	113.4 d	7.73 d, 7.5	4b, 6, 7	6	6, 7, 11
6	121.7 d	7.17 t, 8.0	8a, 8b	5	5, 11, 15, 16
7	113.7 d	7.09 d, 7.2	5, 8, 9	6	5, 11, 15, 16
8	144.4 s	–	–	–	
8a	121.9 s	–	–	–	
9b	132.2 s	–	–	–	
10	140.2s	–	–	–	
11	121.4 d	6.09 s	10, 12, 24, 26	–	3, 4, 5, 6, 7, 24, 26
12	83.6 s	–	–		
13	39.1 t	2.94 m, 2.57 m	26	14	
14	28.7 t	1.91 m, 1.81 m		13, 15	
15	131.4 d	5.47 dd, 9.5. 4.8	14, 16	14, 16	26, 24, 17, 16
16	131.8 d	5.50 m	15, 17		26, 24, 17, 15
17	25.5 t	1.77 m, 1.65 m	16	16, 17a	16, 15
18	27.5 t	2.47 m, 2.26 m			
19	23.0 t	1.91 m, 1.74 m			
20	56.6 t	4.69 d, 14, 3.97 m	19, 18	20a, 19	
21	-	–	–	–	
22	61.0 t	4.55 m, 3.57 m	36, 23, 20	23	
23	30.5 t	2.17 m, 1.51 m	24	22, 24	
24	44.0 d	4.07 d, 4.1	12, 22, 25, 26	23	34, 16, 15, 11
25	46.8 s	–	–	–	

Position	Acantholactone (2)[b]				
	^{13}C NMR	^{1}H NMR	HMBC	COSY	NOESY
26	70.9 d	3.86 s	12, 13, 24, 33, 36	–	22
28	179.6 s	–	–	–	
29	29.3 t	1.92 m, 1.67 m	28		
30	24.0 t	1.87 m, 1.64 m			
31	26.1 t	1.76 m, 1.62 m			
32	23.6 t	1.91 m, 1.74 m			
33	55.8 t	3.80 d,12, 3.58 m	26, 28, 32	32	
34	36.4 t	3.04 d, 18, 2.90 d, 18	24, 26, 35	–	26, 24
35	173.9 s	–	–	–	
36	70.7 t	3.77 m, 3.49 m	12, 22, 25, 26,34	36	

[a] 400 MHz for ^{1}H and 100 MHz for ^{13}C NMR. Carbon multiplicities were determined by DEPT135 experiments. s = C, d = CH, t = CH_2.

[b] NMR obtained in d_6-acetone.

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