Tetrahedron Letters, Vol. 34, No. 46, pp. 7441-7444, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Monodontamides A, B, and C, Three New Putrescine Alkaloids from the Marine Gastropod Mollusc *Monodonta labio* (Linné)

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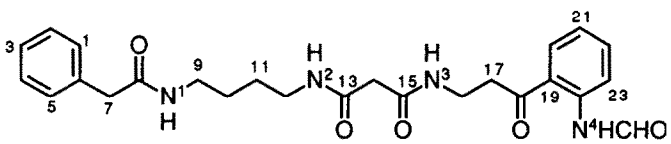
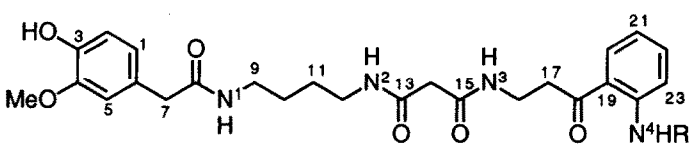
Abstract: Described are the structure determination and synthesis of three new alkaloids, monodontamides A (**1**), B (**2**), and C (**3**) isolated from the marine gastropod mollusc *Monodonta labio* (Linné).

Marine organisms have yielded a variety of architecturally novel and pharmacologically interesting compounds.[1] In connection with our research on the isolation of biologically active marine natural products, we have examined the constituents of the gastropod mollusc *Monodonta labio* (Linné) collected off the coast of Koka, Mie Prefecture, Japan and isolated three new alkaloids monodontamides A (**1**), B (**2**), and C (**3**) containing malonylated putrescine as the common structural part. We report herein the structural elucidation of these alkaloids on the basis of spectral data and unambiguous synthesis of **1**, **2**, and **3**.



1 monodontamide A



2 monodontamide B (R = CHO)
3 monodontamide C (R = H)

The EtOAc-soluble material obtained from the MeOH extract of the mollusc *M. labio* (Linné) was partitioned between hexane and MeOH–H_2O (9:1 v/v). The MeOH–H_2O soluble material was then subjected to repeated chromatography on silica gel followed by reversed-phase HPLC [Develosil ODS HG-5, MeOH–H_2O (40:60)]

Table I. ^{13}C and ^{1}H NMR Spectral Data of Monodontamides A (**1**), B (**2**), and C (**3**)[a]

	monodontamide A (**1**)		monodontamide B (**2**)		monodontamide C (**3**)	
No.	δ_C (m)	δ_H (m, J in Hz)	δ_C (m)	δ_H (m, J in Hz)	δ_C (m)	δ_H (m, J in Hz)
1	129.4 (d)	7.23–7.37 (5 H, m)	122.2 (d)	6.72 (1 H, dd, 7.9, 2.0)	122.2 (d)	6.73 (1 H, dd, 7.9, 2.0)
2	129.1 (d)		114.9 (d)	6.88 (1 H, d, 7.9)	114.9 (d)	6.89 (1 H, d, 7.9)
3	127.4 (d)		145.0 (s)		145.0 (s)	
4	129.1 (d)		147.0 (s)		147.0 (s)	
5	129.4 (d)		111.9 (d)	6.76 (1 H, d, 2.0)	111.9 (d)	6.77 (1 H, d, 2.0)
6	136.4 (s)		126.6 (s)		126.6 (s)	
7	43.8 (t)	3.55 (2 H, s)	43.4 (t)	3.47 (2 H, s)	43.4 (t)	3.48 (2 H, s)
8	171.3 (s)		171.7 (s)		171.6 (s)	
9	39.1 (t)[b]	3.21 (2 H, m)[j]	39.1 (t)	3.21 (2 H, m)[j]	39.0 (t)[g]	3.20 (2 H, m)[j]
10	26.3 (t)[c]	1.45 (4 H, m)	26.3 (t)[e]	1.45 (4 H, m)	26.5 (t)[h]	1.46 (4 H, m)
11	27.1 (t)[c]		27.0 (t)[e]		26.8 (t)[h]	
12	39.2 (t)[b]	3.21 (2 H, m)[j]	39.1 (t)	3.21 (2 H, m)[j]	39.1 (t)[g]	3.20 (2 H, m)[j]
13	167.2 (s)[d]		167.3 (s)[f]		167.0 (s)[i]	
14	42.9 (t)	3.13 (2 H, s)	42.7 (t)	3.13 (2 H, s)	42.9 (t)	3.11 (2 H, s)
15	167.3 (s)[d]		167.5 (s)[f]		167.6 (s)[i]	
16	34.5 (t)	3.66 (2 H, dt, 5.9, 5.9)	34.5 (t)	3.66 (2 H, dt, 5.9, 5.9)	34.7 (t)	3.66 (2 H, dt, 5.9, 5.9)
17	39.4 (t)	3.28 (2 H, t, 5.9)	39.3 (t)	3.30 (2 H, t, 5.9)	38.2 (t)	3.20 (2 H, m)[j]
18	203.1 (s)		203.0 (s)		200.7 (s)	
19	121.6 (s)		121.6 (s)		117.4 (s)	
20	121.8 (d)	8.73 (1 H, d, 8.3)	121.7 (d)	8.74 (1 H, d, 7.9)	130.9 (d)	7.67 (1 H, dd, 7.9, 1.3)
21	135.4 (d)	7.56 (1 H, ddd, 8.3, 8.3, 1.3)	135.4 (d)	7.57 (1 H, ddd, 7.9, 7.9, 1.3)	115.9 (d)	6.64 (1 H, ddd, 7.9, 7.9, 1.3)
22	123.2 (d)	7.15 (1 H, dd, 8.3, 8.3)	123.2 (d)	7.16 (1 H, dd, 7.9, 7.9)	134.7 (d)	7.27 (1 H, ddd, 7.9, 7.9, 1.3)
23	130.8 (d)	7.89 (1 H, dd, 8.3, 1.3)	130.8 (d)	7.89 (1 H, dd, 7.9, 1.3)	117.5 (d)	6.66 (1 H, dd, 7.9, 1.3)
24	139.9 (s)		139.9 (s)		139.8 (s)	
CHO	159.8 (d)	8.43 (1 H, s)	160.0 (d)	8.49 (1 H, s)		
N^1H		5.67 (1 H, br)		5.63 (1 H, br t, 5.9)		5.61 (1 H, br)
N^2H		7.17 (1 H, br)		7.04 (1 H, br t, 5.9)		7.16 (1 H, br)
N^3H		7.54 (1 H, br)		7.43 (1 H, br t, 5.9)		7.03 (1 H, br t, 5.9)
N^4H		11.50 (1 H, br s)		11.50 (1 H, br s)		6.28 (2 H, br s)
OH				5.78 (1 H, br s)		5.70 (1 H, br s)
OMe			56.0 (q)	3.88 (3 H, s)	56.0 (q)	3.88 (3 H, s)

a) ^{13}C NMR spectra were taken in $CDCl_3$ at 67.5 MHz. ^{1}H NMR spectra were taken in $CDCl_3$ at 270 MHz.
b-i) Signals with identical superscripts may be interchanged. j) Overlapped signals.

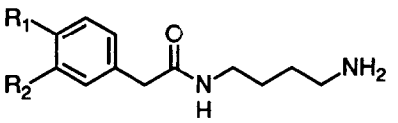
to give monodontamide A (**1**)[2] (colorless amorphous powder; 5.3 x 10^{-6}% wet weight), monodontamide B (**2**)[3] (colorless amorphous powder; 1.1 x 10^{-6}% wet weight), and monodontamide C (**3**)[4] (colorless amorphous powder; 2.5 x 10^{-6}% wet weight). The molecular formulas $C_{25}H_{30}O_5N_4$, $C_{26}H_{32}O_7N_4$, and $C_{25}H_{32}O_6N_4$ for **1**, **2**, and **3**, respectively, were determined by the high-resolution FAB mass spectra[2-4] coupled with the ^{13}C NMR spectra (Table I). IR[2-4] and ^1H NMR (Table I) spectra of **1** [ν_{max} (KBr) 1650 and 1525 cm^{-1}; δ 3.21 (4 H, m), 1.45 (4 H, m), and 3.13 (2 H, s)], **2** [ν_{max} ($CHCl_3$) 1670 and 1510 cm^{-1}; δ 3.21 (4 H, m), 1.45 (4 H, m), and 3.13 (2 H, s)], and **3** [ν_{max} ($CHCl_3$) 1670 and 1510 cm^{-1}; δ 3.20 (4 H, m), 1.46 (4 H, m), and 3.11 (2 H, s)] strongly suggested that all of these compounds possess an *N,N'*-diacylated putrescine (1,4-diaminobutane) moiety and a malonamide moiety as the common structural parts. This inference was confirmed by the comparison of ^1H NMR spectra of **1**, **2**, and **3** with those of *N,N'*-diacetylputrescine and malonamide. The ^1H and ^{13}C NMR spectra of **1**, **2**, and **3** clearly indicated the presence of two benzene rings in each compound: **1** has a phenyl group and a 1,2-disubstituted benzene ring, and each of **2** and **3** has a 1,2,4-trisubstituted benzene ring and a 1,2-disubstituted benzene ring. The presence of an *N*-formyl group in both **1** and **2** was also implied from their ^1H and ^{13}C NMR spectra [**1**, δ_H 8.43 (s) and δ_C 159.8 (d): **2**, δ_H 8.43 (s) and δ_C 160.0 (d)]. The detailed analysis of their ^1H and ^{13}C NMR, ^1H-^1H and ^{13}C-^1H COSY spectra together with NOE experiments revealed the structures of monodontamides A, B, and C to be as depicted in the formulas **1**, **2**, and **3**, respectively.

In order to establish the structures of monodontamides A, B, and C, unambiguously, we have performed the synthesis of the compounds having structures as shown in the formulas **1**, **2**, and **3**. Thus, a mixture of ethyl phenylacetate and five equivalents of putrescine was heated at 100 °C to afford putrescine monoamide **4**[5] in 70% yield from ethyl phenylacetate. Reaction of malonyl tryptamine **6**[6] with two equivalents of **4** in dioxane at reflux temperature provided triamide **7**[5] [mp 151–154 °C (MeOH)] in 79% yield from **6**. Ozonolysis[7] of the indole ring in **7** was conducted in MeOH at –78 °C followed by reductive work-up with dimethyl sulfide to yield **1**[5] (63%), whose spectral and chromatographic properties were completely identical with those of natural monodontamide A in all respects.

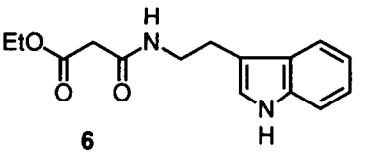
Similarly, putrescine monoamide **5**[5] (98%) was obtained by the reaction of methyl homovanillate with a large excess of putrescine at 100 °C. Reaction of **5** with two equivalents of **6** in dioxane at reflux temperature provided triamide **8**[5] in 80% yield. Prior to ozonolysis, **8** was converted (Ac_2O, pyridine) into acetate **9**[5] (96%). Ozonolysis of **9** in MeOH followed by reductive work-up with dimethyl sulfide yielded **10**[5] (52%), which upon methanolysis with NaOMe in MeOH at room temperature furnished **2**[5] in 66% yield. Finally, acidic hydrolysis of **2** with 1.5 M HCl in EtOH at reflux temperature provided **3**[5] in 66% yield. The spectral and chromatographic properties of synthetic **2** and **3** were completely identical with those of natural monodontamides B and C, in all respects, respectively.

Although putrescine is one of the biologically important aliphatic polyamines such as cadaverine, spermidine, and spermine,[8] the isolation of putrescine-containing secondary metabolites from marine sources is quite rare.[1] To our knowledge this is the first report on the isolation of natural products containing malonylated putrescine from marine organisms.

Monodontamides A, B, and C exhibit weak inhibitory activity against a serine protease, rat eosinophil chymase. Their activities are as follows: monodontamide A (**1**), 23% inhibition at 1.5 x 10^{-5} M; monodontamide B (**2**), 30% inhibition at 4.1 x 10^{-5} M; monodontamide C (**3**), 58% inhibition at 4.3 x 10^{-5} M.



4 $R_1 = R_2 = H$
5 $R_1 = OH$, $R_2 = OMe$



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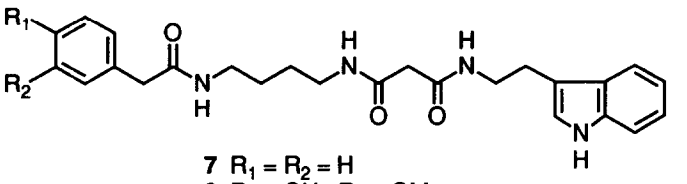
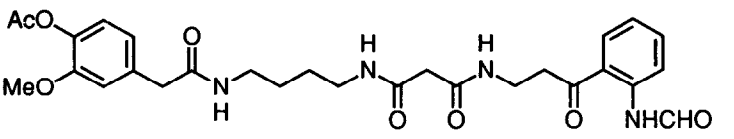


7 $R_1 = R_2 = H$
8 $R_1 = OH$, $R_2 = OMe$
9 $R_1 = OAc$, $R_2 = OMe$



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References and Notes

1. Faulkner, D. J. *Nat. Prod. Rep.*; **1984**, *1*, 251–280; **1984**, *1*, 551–598; **1986**, *3*, 1–33; **1987**, *4*, 539–576; **1988**, *5*, 613–663; **1990**, *7*, 269–309; **1991**, *8*, 97–147; **1992**, *9*, 323–364.
2. Monodontamide A (**1**): $C_{25}H_{30}O_5N_4$; HRFABMS *m/z* 467.2301 $(M+H)^+$, Δ 0.7 mmu; IR (KBr) 3300 (broad), 3080, 1675, 1650, 1605, 1590, 1525 cm^{-1}.
3. Monodontamide B (**2**): $C_{26}H_{32}O_7N_4$; HRFABMS *m/z* 513.2326 $(M+H)^+$, Δ –2.3 mmu; IR ($CHCl_3$) 3550, 3450, 3300 (broad), 3010, 1670, 1605, 1585, 1510 cm^{-1}.
4. Monodontamide C (**3**): $C_{25}H_{32}O_6N_4$; HRFABMS *m/z* 485.2419 $(M+H)^+$, Δ 1.9 mmu; IR ($CHCl_3$) 3550, 3450, 3350 (broad), 3010, 1670, 1605, 1585, 1510 cm^{-1}.
5. Satisfactory spectral and analytical data were obtained for all new compounds. All yields refer to materials purified by column chromatography on silica gel.
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(Received in Japan 20 July 1993)