Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 47 (2006) 7237–7239
Tetrahedron Letters

Itampolins A and B, new brominated tyrosine derivatives from the sponge *Iotrochota purpurea*

Hagit Sorek,[a] Amira Rudi,[a] Maurice Aknin,[b] Emile Gaydou[c] and Yoel Kashman[a,*]

[a]*School of Chemistry, Tel-Aviv University, Ramat Aviv 69978, Israel*
[b]*Laboratoire de Chimie des Substances Naturelles et des Aliments, Faculté des Sciences et Techniques, Université de la Réunion, 15 Avenue Rene cassin, BP 7151, 97715 Saint Denis, Cedex 9, France*
[c]*Université de Droit, d'Economie et des Sciences d'Aix Marseille III, France*

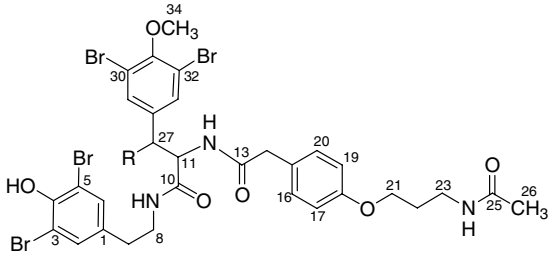
Received 9 June 2006; revised 16 July 2006; accepted 25 July 2006
Available online 17 August 2006

Abstract—Two new compounds, designated as itampolins A (**1**) and B (**2**) were isolated from the sponge *Iotrochota purpurea* collected at Itampolo, southwest of Tuléar, Madagascar. The structures of the compounds were elucidated mainly on the basis of 1D and 2D NMR and mass spectroscopic data and, in the case of **1**, also by chemical degradation.

In the search for bioactive substances from marine invertebrates,[1,2] two novel brominated tyrosine-derived metabolites, designated as itampolins A (**1**) and B (**2**), were isolated from the Madagascan sponge, *Iotrochota purpurea* (Bowerbank, 1873, order *Poecilosclerida*). Brominated tyrosine-derivatives are commonly found in marine metabolites, mainly in marine sponges of the *Verongida* order.[3–5]

Homogenized *I. purpurea* (193 g, wet weight), collected in Itampolo, 150 km southwest of Tuléar, Madagascar at a depth of 15 m,[6] was extracted with a 2:1 mixture of chloroform–methanol to give, after evaporation, a brown gum (3.3 g). This gum was subjected to partition by the method of Kupchan et al.[7] to afford five fractions (hexane, CCl_4, $CHCl_3$, *n*BuOH, and water). The chloroform fraction (400 mg) was repeatedly chromatographed on a Sephadex LH-20 column, eluting with a mixture of heptane–CH_2Cl_2–MeOH (2:1:1) to afford itampolin A (**1**, 10 mg, 0.005% dry weight)[8] and itampolin B (**2**, 3 mg, 0.0015% dry weight).[9]

The mass spectrum of itampolin A (**1**) exhibited a molecular ion $[M+Na]^+$ as a cluster of peaks at *m*/*z* 882/884/886/888/890 in the ratio of 1:4:6:4:1, an isotope pattern characteristic of a tetrabrominated compound. Accordingly, based on HRMS,[8] the molecular formula $C_{31}H_{33}Br_4N_3O_6$, with 15 degrees of unsaturation, was determined. The ^1H NMR, ^{13}C NMR, and 2D spectra (Table 1) revealed the presence of the following moieties: (a) an *o*,*o*′-dibromoanisole unit [δ_C 153.2 s and 60.6 q; δ_H 7.39 s (2H) and 3.84 s (3H)]; (b) an *o*,*o*′-dibromophenol unit [δ_C 150.7 s and δ_H 7.15 s (2H)]; (c) a *para*-substituted phenyl ether [δ_C 155.3 s and 6.48 d ($J = 8.3$, 2H) and 7.00 d ($J = 8.3$, 2H)]; (d) an acetamide group [δ_C 171.7 s and 23.2 q; δ_H 6.59 br t (1H) and 2.05 s (3H)]; (e) two amide groups (δ_C 170.8 s and 171.1 s and δ_H 6.79 br d and 7.12 br t). The above three benzene rings, together with the three amide carbonyl groups, account for the 15 degrees of unsaturation of **1**.



itampolin A (**1**), R=H
itampolin B (**2**), R=OH

Keywords: Marine sponge; Dibromo tyrosine; Alkaloids; NMR.
* Corresponding author. Tel.: +972 3 6408419; fax: +972 3 6409293; e-mail: kashman@post.tau.ac.il

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.07.128

Table 1. NMR data of itampolin A (**1**)[a]

Position	δ_C	δ_H (J in Hz)[b]	COSY[c]	HMBC (H to C)	NOESY
1	137.8 s				
2 (6)	132.7 d	7.15 s		2 (6), 3 (5), 7	7a, 7b
3 (5)	118.2 s				
4-OH	150.7 s				
7	34.4 t	2.70 m	8	1, 2 (6, 8)	2, 6, 8a, 8b
		2.60 m			
8	40.5 t	3.60 m	7, 9	1, 7, 10	7a, 7b, 9
		3.35 m			
9-NH		7.12 br t (5.1)	8	10	8a, 8b, 11
10	170.8 s				
11	54.4 t	4.52 br q (7.9)	12, 27	13, 27, 28	9, 27a, 27b, 29 (33)
12-NH		6.79 br d (8.4)	11	13	27a
13	171.1 s				
14	43.0 t	3.50 br s		13, 15, 16 (20)	16 (20)
15	125.4 s				
16 (20)	131.0 d	7.00 d (8.3)	17, 19	16 (20), 17 (19), 18	14, 17, 19
17 (19)	115.7 s	6.48 d (8.3)	16, 20	15, 16 (20), 17 (19)	16, 20
18	155.3 s				
21	73.4 t	3.93 t (5.2)	22	18, 22, 23	22
22	28.8 t	1.90 m	21, 22	21, 23	21, 23, 24
23	38.9 t	3.60 m	22, 24	21, 22, 25	22, 24
24-NH		6.59 br t (4.9)	23	25	22, 23
25	171.7 s				
26	23.2 q	2.05 s		25	
27	36.7 t	3.01 dd (13.6, 7.6)	11	10, 11, 28, 29 (33)	11, 12
		2.82 dd (13.6, 7.1)			
28	135.0 s				
29 (33)	133.3 d	7.39 s		27, 29 (33), 30 (32), 31	11, 27a, 27b
30 (32)	118.2 d				
31	153.2 s				
34-OMe	60.6 q	3.84 s		31	

[a] Data recorded in $CDCl_3$ on a Bruker Avance-400 instrument.
[b] The CH correlations were assigned from the HSQC spectrum.
[c] a and b denote the downfield and upfield resonances, respectively, of a geminal pair.

Determination of the structure of compound **1** was quite straightforward by interpretation of the COSY and HMBC data (Fig. 1 and Table 1). The COSY spectrum revealed the presence of four spin systems, namely H-7–NH-9; H-16(20)–H-17(19); H-21–NH-24 and H-27–NH-10. Most informative was the HMBC experiment. The various two- and three-bond CH-correlations, depicted in Figure 1, connected the segments suggested by the COSY experiment, establishing the complete structure of itampolin A (**1**). Further confirmation of the structure came from both ESMS fragments shown in Figure 2 as well as the ^{15}NH-HMBC and ^{15}NH-HSQC-TOCSY experiments.

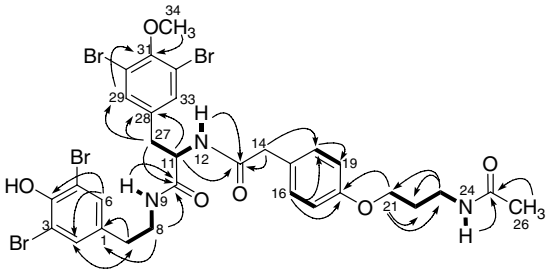


Figure 1. COSY (▬) and selected HMBC (→) correlations of itampolin A (**1**).

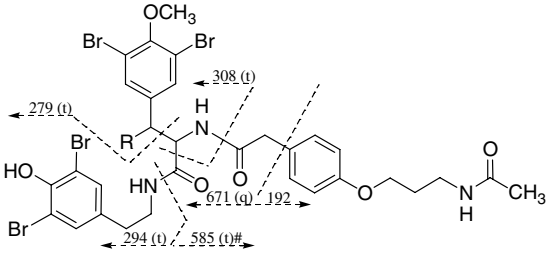


Figure 2. ESMS fragmentation of itampolin A (**1**). (t) and (q = quin) represent the cluster of peaks in the MS spectra # seen for **2** (R = OH).

The ^{15}NH-HMBC and ^{15}NH-HSQC-TOCSY correlations (Table 2) determined the resonances of the three nitrogen atoms as well as their $^1J_{NH}$-values, namely,

Table 2. ^{15}N data of itampolin A (**1**)[a,b]

Position	δ_N (ppm)	$^1J_{NH}$ (Hz)	^{15}NH-HSQC-TOCSY
9	116.5	88	7, 8, NH-9
12	123.8	90	11, NH-12, 27
24	122.3	93	21, 22, 23, NH-24

[a] The experimental data were taken from both ^{15}NH-HMBC and ^{15}NH-HSQC-TOCSY experiments.
[b] Data recorded in $CDCl_3$ on a Bruker Avance-400 instrument.

δ_N 116.5 ($J = 88$), 122.3 ($J = 93$) and 123.8 ($J = 90$ Hz). The coupling constants were measured from the residual one bond-couplings. ^{15}NH-HMBC $^{3}J_{NH}$ correlations were observed between CH_3-26 and the nitrogen atom resonating at 122.3 ppm and between CH_2-27 and the nitrogen atom resonating at 123.8 ppm. Further support for the structure came from the ^{15}NH-HSQC-TOCSY experiment (Table 2).

The structure of itampolin A (**1**), composed of four subunits—a dibromotyrosine methyl ether, a dibromotyramine moiety, a phenoxyacetyl group and a propyloxy-3-acetamide moiety—possesses a single chiral center, C-11. The chirality of the latter center was determined to be 11*R* upon hydrolysis of **1** with 6 N HCl at 110 °C overnight, affording D-dibromotyrosine as the only chiral compound which has previously been reported from the marine Verongid sponges *Ianthella* sp.[10] and an unidentified sponge.[11]

The spectral data of the second isolated compound, itampolin B (**2**), pointed to a very similar structure to that of **1**. The isotope pattern of 1:4:6:4:1 in the HRESMS for the $[M+Na]^+$ peak at 898/900/902/904/906 indicated the presence of four bromine atoms in the molecule and an additional oxygen atom. The major difference in the NMR data of **2** was the disappearance of the CH_2(27) group of **1**, and the appearance of a methinoxy group resonating at δ_C 70.6 d and δ_H 5.00 d ($J = 3.5$ Hz). The 2D NMR experiments confirmed the suggested C-27-hydroxyl group. The small available amount of **2** prevented derivatization for determination of the chirality of the second chiral center. Unfortunately, neither the vicinal proton–proton coupling constants nor the α_D-values[12] for the *erythro* and the *threo* configurations could be expected to distinguish the two possible diastereomers. The itampolins are unique in their combination of the various structural units.

Previous studies on the genus *Iotrochota* resulted in highly oxygenated sterols,[13] ceramides,[14,15] brominated 3-indolinone,[16] the polycyclic pyrrole derivative purpurone,[17] and also, from *I. birotulata*, brominated and iodinated tyrosine derivatives.[18] The latter brominated tyrosine-derived compounds were the first from the sponge-order *Poecilosclerida*. Bromotyrosine derivatives are well known derivatives produced from algae and *Verongida* sponges.[5] Of these compounds, only a few still possess the carboxylic group of the dibromotyrosine precursor (e.g., ianthesine A–D)[10] while the brominated building block of more than 80 others is the decarboxylated dibromotyramine. The latter contain compounds incorporating one to three dibromotyramine moieties (e.g., nakirodin A,[11] aplyzanzine A,[19] and fistularin[20]). The itampolins contain both di-bromotyrosine and tyramine building blocks.

Acknowledgment

We thank Dr. Ayelet Sacher (of the Maiman Institute for Proteome Research, Tel Aviv University) for performing the electrospray mass spectra measurements.

References and notes

1. Rudi, A.; Erez, Y.; Benayahu, Y.; Kashman, Y. *Tetrahedron Lett.* **2005**, *46*, 8613–8616.
2. Chill, L.; Rudi, A.; Aknin, M.; Loya, S.; Hizi, A.; Kashman, Y. *Tetrahedron* **2004**, *60*, 10619–10626.
3. Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2005**, *22*, 15–61, and earlier reports in the series.
4. Faulkner, D. J. *Nat. Prod. Rep.* **2003**, *20*, 1–48, and earlier reports in the series.
5. Munro, M. H. G.; Blunt, J. W. Marine Literature Database, Department of Chemistry, University of Canterbury, New Zealand, 2006.
6. The sponge was collected at Itampolo in January 2005, at a depth of 15 m. It is a purple-green sponge of the order *Poecilosclerida*, family Iotrochotidae.
7. Kupchan, S. M.; Komoda, Y.; Branfman, A. R.; Sneden, A. T.; Court, W. A.; Thomas, G. J.; Hintz, H. P. J.; Smith, R. M.; Karim, A.; Howie, G. A.; Verma, A. K.; Nagao, Y., ; Dailey, R. G., Jr.; Zimmerly, V. A.; Sumner, W. C., Jr. *J. Org. Chem.* **1977**, *42*, 2349–2357.
8. Itampolin A (**1**): pale green oil, $[\alpha]_D^{21}$ +6.0 (*c* 0.66, MeOH), ^{1}H and ^{13}C NMR data, see Table 1; IR (KBr) ν_{max} 2925, 2852, 1649, 1539, 1512, 1454, 1380, 1260 cm^{-1}, ESMS *m/z* 886 $[M+Na]^+$, HRESMS *m/z* 885.8956 (calcd for $C_{31}H_{33}N_3O_6NaBr_4$, 885.8959).
9. Itampolin B (**2**): pale green oil, $[\alpha]_D^{21}$ −2.5 (*c* 0.25 MeOH), ^{1}H NMR (KBr) ν_{max} 3392, 2926, 1645, 1539, 1515, 1455, 1384, 1259 cm^{-1}, ESMS *m/z* 902 $[M+Na]^+$, HRESMS *m/z* 901.8907 (calcd for $C_{31}H_{33}N_3O_7NaBr_4$, 901.8909).
10. Okamoto, Y.; Ojika, M.; Kato, S.; Sakagami, Y. *Tetrahedron* **2000**, *56*, 5813–5818.
11. Tsuda, M.; Endo, T.; Watanabe, K.; Fromont, J.; Kobayashi, J. *J. Nat. Prod.* **2002**, *65*, 1670–1671.
12. Davis, F. A.; Srirajan, V.; Fanelli, D. L.; Portonovo, P. *J. Org. Chem.* **2000**, *65*, 7663–7666.
13. Costantino, V.; Dell'Averno, C.; Fattorusso, E.; Mangoni, A. *Steroids* **2000**, *65*, 138–142.
14. Deng, S.; Tian, C.; Xiao, D.; Wu, H. *Chin. J. Chem.* **2001**, *19*, 362–364.
15. Muralidhar, P.; Krishna, N.; Kumar, M. M.; Rao, C. B.; Rao, D. V. *Chem Pharm. Bull.* **2003**, *51*, 1193–1195.
16. Carletti, I.; Banaigs, B.; Amade, P. *J. Nat. Prod.* **2000**, *63*, 981–983.
17. Chan, G. W.; Francis, T.; Thureen, D. R.; Offen, P. H.; Pierce, N. J.; Westley, J. W.; Johnson, R. K.; Faulkner, D. J. *J. Org. Chem.* **1993**, *58*, 2544–2546.
18. Constantino, V.; Fattorusso, E.; Mangoni, A.; Pansini, M. *J. Nat. Prod.* **1994**, *57*, 1552–1556.
19. Evan, T.; Rudi, A.; Ilan, M.; Kashman, Y. *J. Nat. Prod.* **2001**, *64*, 226–227.
20. Gopichand, Y.; Schmitz, F. J. *Tetrahedron Lett.* **1979**, *20*, 3921–3924.