# Structure Elucidation of Submilligram Quantities of Natural Products – Application to Haliclamines G and H from the Arctic Marine Sponge *Haliclona viscosa*

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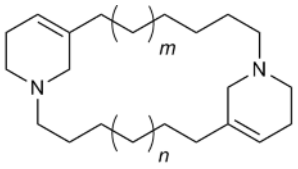
*Z. Naturforsch.* **2012**, *67b*, 944 – 950 / DOI: 10.5560/ZNB.2012-0039
Received February 7, 2012

Two new haliclamines were identified directly from the crude extract of the Arctic sponge *Haliclona viscosa* using improved chromatographic conditions and a detailed knowledge about the fragmentation pattern of haliclamines. These are haliclamine G (**1**) with two alkyl chains of equal length (10 methylene groups) and haliclamine H (**2**) with alkyl chains of 10 and 12 methylene groups. Due to the limited amount of sponge material available, the haliclamines were not isolated, and the structure elucidation relied on the chromatographic and mass spectrometric comparison with synthetic compounds.

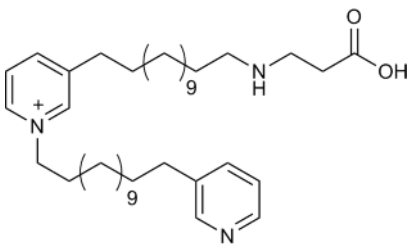
*Key words:* Marine Sponges, *Haliclona viscosa*, 3-Alkyl Pyridine Alkaloids, Mass Spectrometry, Fragmentation Pattern

## Introduction

The Arctic marine sponge *Haliclona viscosa* has been shown to be a valuable source for novel 3-alkyl pyridinium/pyridine alkaloids (3-APAs). Within the past years we have published three new structural classes of 3-APAs which were first described from this Spitsbergen specimen: a) the macrocyclic monomeric haliclocyclins [1, 2], b) the linear dimers viscosalines (3-alkyl pyridinium alkaloid/amino acid adducts) [3, 4], and c) the macrocyclic trimeric viscosamines [5, 6]. Another group of 3-APAs are the haliclamines, cyclic dimeric 3-alkyl tetrahydropyridine alkaloids in which two tetrahydropyridine moieties are connected in 1- and 3-position [7] by alkyl chains of variable length (Scheme 1, Table 1). While the originally described haliclamines A (**3**) and B (**4**) possess at least one double bond in each alkyl chain [8], haliclamines C to F (**5**–**8**) [9, 10] contain saturated alkyl chains. Mono-, di-, tri-, and polymeric 3-alkyl pyridinium compounds have been identified in six different sponge families of the order Haplosclerida from all over the world. In contrast to the 3-APAs in general, the dimeric haliclamines have been reported to date from only two locations: a) Hiburi-jima, Japan, source of haliclamines A and B (**3** and **4**) and b) the Svalbard archipelago, source of haliclamines C to F (**5**–**8**), and only from the sponge genus *Haliclona*. Therefore, they have an exceptional role within the 3-APAs.




Haliclamines A–H (**1**–**8**)




Viscosaline C (**9**)

Scheme 1. Haliclamines A–H (**1**–**8**) and viscosaline C (**9**). The assignment of the indices $(m,n)$ to the different haliclamines is given in Table 1.

Table 1. Chain lengths of haliclamines A–H (**1**–**8**).

| | *m* | *n* | ∑ double bonds[a] |
|---|---|---|---|
| Haliclamine G (**1**, 10/10) | 5 | 5 | |
| Haliclamine H (**2**, 10/12) | 5 | 7 | |
| Haliclamine A (**3**, 9/12) | 4 | 7 | 2 (1 + 1) |
| Haliclamine B (**4**, 9/12) | 4 | 7 | 3 (2 + 1) |
| Haliclamine C (**5**, 9/11) | 4 | 6 | |
| Haliclamine D (**6**, 10/11) | 5 | 6 | |
| Haliclamine E (**7**, 9/10) | 4 | 5 | |
| Haliclamine F (**8**, 11/11) | 6 | 6 | |

[a] Total number of double bonds in the alkyl chains.

Recently, the comparison of the crude extract of the Arctic sponge *Haliclona viscosa* with retention times and spectrometric data of two synthetic haliclamines led to the identification of haliclamines E and F (**7** and **8**) [10], with alkyl chains of 9 and 10 methylene groups and two equal alkyl chains of 11 methylene groups, respectively. The subsequent systematic investigation of the MS fragmentation of haliclamines served as a basis for further detailed HPLC-HRMS examinations of crude extracts of *H. viscosa* [11].

## Results and Discussion

The detailed knowledge about haliclamine fragmentation in mass spectrometry now enabled us to identify two additional haliclamines, haliclamine G (**1**, 10/10) and H (**2**, 10/12), from a crude extract of the *Haliclona viscosa* specimen collected in 2000 that had also yielded the haliclamines E (**7**, 9/10) and F (**8**, 11/11) (Fig. 1). Isolation of the compounds was not possible due to the limited amount of sponge material available. The two new compounds were not recognized in earlier HPLC-MS analyses since **1** co-eluted with haliclamine C (**5**, 9/11) and **2** with haliclamine F (**8**, 11/11) as well as viscosaline C (**9**), a linear 3-APA combining two 1,3-dialkyl pyridine/pyridinium with the amino acid $\beta$-alanine. Both new compounds had the same retention time as known haliclamines, which had the same total number of methylene groups in the alkyl chains, 20 and 22 respectively; the separation of these compounds presented a challenge of this investigation. Changing the HPLC condition to an acidified acetonitrile (0.1 % formic acid) improved the peak resolution, and the new compounds **1** and **2** became distinguishable from the known haliclamines. However, the separation of haliclamine F (**8**) and viscosaline C (**9**) was still not possible.

Table 2. Comparison of the mass spectrometric data of the natural and the synthetic haliclamine G (**1**).

| Ion[a] | Natural **1**[b] | Synthetic **1** |
|---|---|---|
| $[M+H]^+$ | $m/z = 443.4370$ | $m/z = 443.4369$ |
| | $\Delta m = 2.3$ ppm | $\Delta m = 2.0$ ppm |
| TFA salt $[M+H]^+$ | n. d. | $m/z = 557.4298$ |
| | | $\Delta m = 1.7$ ppm |
| $[M+2H]^{2+}$ | n. d. | $m/z = 222.2225$ |
| | | $\Delta m = 3.9$ ppm |
| Fragment $C_n = C_m$ | $m/z = 222.2225$ | $m/z = 222.2220$ |
| | $\Delta m = 3.9$ ppm | $\Delta m = 1.8$ ppm |

[a] The doubly charged pseudo-molecular ion and the TFA salt originated from an experiment with a low voltage difference between capillary exit and skimmer. The singly charged fragments $C_m = C_n$ were mass-equivalent with a tetrahydropyridinium moiety and a side chain of 10 methylene groups;
[b] n. d.: not detected.

Compound **1** with a retention time of 13.7–13.8 min showed a singly charged pseudo-molecular ion $[M+H]^+$ at $m/z = 443.4370$ and a doubly charged pseudo-molecular ion $[M+2H]^{2+}$ at $m/z = 222.2225$ corresponding to the molecular formula $C_{30}H_{55}N_2$ for $[M+H]^+$ ($\Delta m = 2.3$ ppm for $[M+H]^+$ and $\Delta m = 3.9$ ppm for $[M+2H]^{2+}$) (Table 2 and Fig. S3 of the Supporting Information available online only). The same molecular formula and $[M+H]^+$ and $[M+2H]^{2+}$

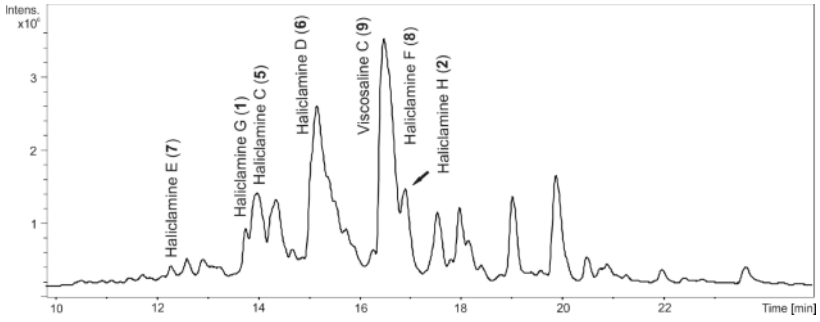



Fig. 1. HPLC-MS chromatogram of the crude extract of *Haliclona viscosa*. Known haliclamines and viscosaline C (**9**) are marked.

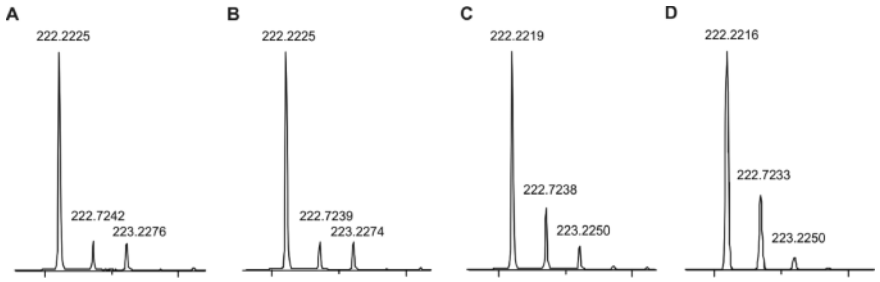
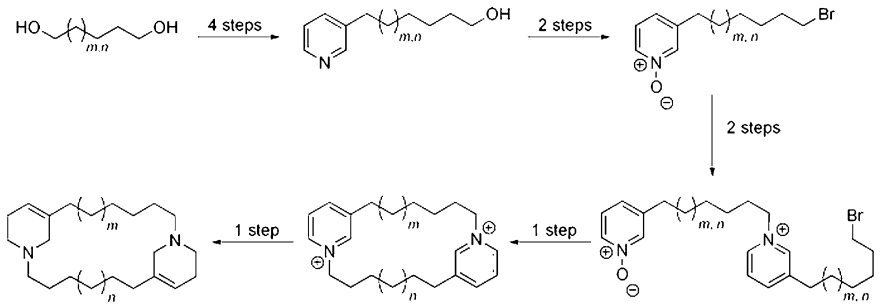



Fig. 2. Peak pattern of the $[M+2H]^{2+}$ of the natural haliclamine G (**1**, A), the synthetic haliclamine G (**1**, B), the natural haliclamine C (**5**, C), and the calculated peak pattern for the doubly charged ion of haliclamine C (**5**, D) $[C_{30}H_{56}N_2]^{2+}$ (capillary exit 150 V, skimmer 50 V). Peak intensity of A (100 : 13.3 : 12.5) and B (100 : 12.7 : 12.7) indicated the overlying singly charged fragments $C_m = C_n$.




Scheme 2. Schematic synthesis of haliclamines with saturated alkyl chains.

were assigned to haliclamine C (**5**, 9/11) but eluted at a retention time of 13.8 – 14.1 min. The high-resolution mass spectrum of haliclamine C (**5**) showed peaks of two fragments: $C_m$ at $m/z = 208.2090$ and $C_n$ at $m/z = 236.2331$, representing the mass-equivalent of a tetrahydropyridinium moiety connected to either alkyl chain (Fig. S7; Supporting Information). In contrast, the mass spectrum of compound **1** did not show obvious fragments. The different retention time to haliclamine C (**5**) and the absence of fragment masses $C_m$ and $C_n$ suggested the alkyl chains of **1** to be of equal length of 10 methylene groups. The fragmentation of haliclamine F (**8**, 11/11) with equal alkyl chains also showed only the singly charged pseudo-molecular ion $[M+H]^+$ and a doubly charged pseudo-molecular ion $[M+2H]^{2+}$ in the MS spectrum [10]. Another aspect emerges when comparing the expected isotopic peak intensity of the doubly charged pseudo-molecular ion and the observed isotopic pattern: it indicates a superimposed singly charged mass. While the calculated peak intensity for $[M+2H]^{2+}$ was 100 : 33.3 : 5.5, the observed peak intensity for **1** was 100 : 13.3 : 12.5 (Fig. 2). The increase in intensity of the X+2 isotopic peak of the doubly charged ion was caused by an overlying X+1 isotopic peak of the singly charged fragments $C_m = C_n$. The X+2 isotopic peak of the singly charged fragments appear at $m/z = 224.2244$. These results suggested that compound **1** should be a haliclamine with two saturated alkyl chains of ten methylene groups each.

To verify the structure of natural haliclamine G (**1**), it was synthesized *via* the cyclostellettamine pathway [12, 13] with a subsequent reduction step [14, 15] (Scheme 2). The aim was to compare the chromatographic and mass spectrometric data of the natural compound with that of the synthetic compound. Synthetic **1** eluted at a retention time of 13.7 min, equal to compound **1** in the crude extract of *Haliclona viscosa* and a solution of *H. viscosa* crude extract enriched with the synthetic **1** effected an enlargement of the relative peak area of **1** in relation to **5** (Fig. 3).

The ESI mass spectrum of the synthetic haliclamine G (**1**) displayed a pseudo-molecular ion peak $[M+H]^+$ at $m/z = 443.4369$ ($\Delta m = 2.0$ ppm for $[M+H]^+$), and a doubly charged pseudo-molecular ion $[M+2H]^{2+}$ at $m/z = 222.2225$ ($\Delta m = 3.9$ ppm for $[M+2H]^{2+}$)

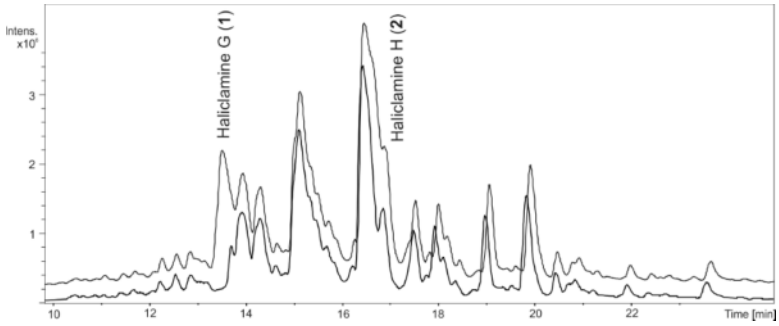



Fig. 3. HPLC-MS chromatogram of a mixture of synthetic haliclamines G (**1**) and H (**2**) with the crude extract of *Haliclona viscosa* (above) compared to the crude extract of *H. viscosa* without addition (below).

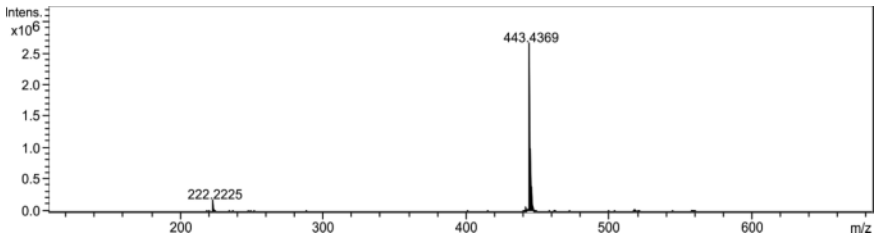



Fig. 4. Direct infusion ESI-TOF MS spectrum of synthetic haliclamine G (**1**).

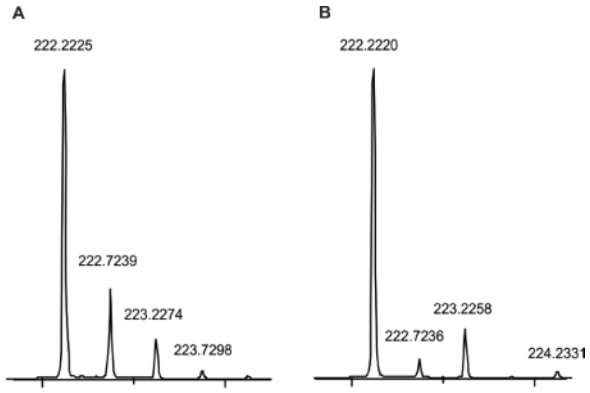



Fig. 5. Peak pattern of the doubly charged pseudomolecular ion $[M+2H]^{2+}$ (capillary exit 120 V, skimmer 50 V, A) and the fragments $C_m = C_n$ (capillary exit 180 V, skimmer 80 V, B) of synthetic haliclamine G (**1**).

(Fig. 4). The peak intensity for $[M+2H]^{2+}$ was similar to that of the natural compound **1**, 100 : 12.7 : 12.7 and indicated an overlapping of $[M+2H]^{2+}$ with the fragments $C_m = C_n$ which represent the mass-equivalent of a tetrahydropyridinium moiety with a side chain of ten methylene groups (Fig. 2). The X+2 isotopic peak of an overlapping singly charged fragment at $m/z = 224.2331$ was also present. The overlapping of the doubly charged pseudo-molecular ion $[M+2H]^{2+}$ with the fragments $C_m = C_n$ was verified by direct infusion mass spectrometry (Fig. 5). A low voltage difference between capillary exit and skimmer revealed the doubly charged pseudo-molecular ion $[M+2H]^{2+}$ at $m/z = 222.2225$ ($\Delta m = 3.9$ ppm for $[M+2H]^{2+}$). In contrast, a high voltage difference increased the fragmentation of the synthetic compounds **1**, with the spectrum showing fragments $C_m = C_n$ at $m/z = 222.2220$ ($\Delta m = 1.8$ ppm). These results proved the proposed structure of a haliclamine with two alkyl chains of 10 methylene groups for haliclamine G (**1**).

Compound **2** which eluted at 16.8 – 17.0 min showed a singly charged pseudo-molecular ion $[M+H]^+$ at $m/z = 471.4699$ and a doubly charged pseudo-molecular ion $[M+2H]^{2+}$ at $m/z = 236.2385$ (Fig. 6). This corresponds to a molecular formula of $C_{32}H_{59}N_2$ for $[M+H]^+$ ($\Delta m = 5.5$ ppm for $[M+H]^+$ and $\Delta m = 5.2$ ppm for $[M+2H]^{2+}$) (Table 3 and Fig. S6 of the Supporting Information), and indicated a haliclamine with a total number of 22 methylene groups. Therefore the most probable distributions of 22 methylene groups to the two alkyl chains are 9/13, 10/12, or 11/11 like haliclamine F (**8**) which eluted at a retention time of 16.6 – 16.8 min together with viscosaline C (**9**) [see Fig. S8, Supporting Information, for the ESI-TOF MS spectrum of haliclamine F (**8**)]. With the alkyl chains of **8** being of equal length of 11 methylene groups, the fragments $C_m = C_n$ that represent the mass-equivalent of a tetrahydropyridinium moiety connected to an alkyl chain concur with the doubly charged pseudo-molecular

Table 3. Comparison of the mass spectrometric data of the natural and the synthetic haliclamine H (**2**).

| Ion[a] | Natural **2**[b] | Synthetic **2** |
|---|---|---|
| $[M+H]^+$ | $m/z = 471.4699$ | $m/z = 471.4667$ |
| | $\Delta m = 5.5$ ppm | $\Delta m = 1.3$ ppm |
| TFA salt $[M+H]^+$ | n. d. | $m/z = 585.4617$ |
| | | $\Delta m = 2.6$ ppm |
| $[M+2H]^{2+}$ | $m/z = 236.2385$ | $m/z = 236.2371$ |
| | $\Delta m = 5.2$ ppm | $\Delta m = 0.7$ ppm |
| Fragment $C_n$ | $m/z = 222.2218$ | $m/z = 222.2214$ |
| | $\Delta m = 0.8$ ppm | $\Delta m = 1.2$ ppm |
| Fragment $C_m$ | $m/z = 250.2538$ | $m/z = 250.2530$ |
| | $\Delta m = 3.5$ ppm | $\Delta m = 0.4$ ppm |

[a] The singly charged fragments $C_m$ and $C_n$ were mass-equivalent with a tetrahydropyridinium moiety and a side chain of 10 or 12 methylene groups;
[b] n. d.: not detected.

ion. In the mass spectrum of compound **2** however, two fragment peaks were visible at $m/z = 222.2218$ and $m/z = 250.2538$, corresponding to the fragments $C_m$ ($C_{15}H_{28}N$, $\Delta m = 0.8$ ppm) and $C_n$ ($C_{17}H_{32}N$, $\Delta m = 3.5$ ppm), *i. e.* mass-equivalents of tetrahydropyridinium moieties with alkyl chains of 10 and 12 methylene groups, respectively.

To prove the proposed structure of haliclamine H (**2**), it was synthesized in a similar way as described for haliclamine G (**1**) (Scheme 2). In addition, a haliclamine with alkyl chains of 9 and 13 methylene groups and therefore the same total number of methylene groups as **2** and **8** was prepared. The synthetic haliclamine H (**2**) eluted at the same retention time (16.9 min) as the natural compound **2** in the crude extract of *Haliclona viscosa*. Crude extract enriched with synthetic **2** showed an increased peak area for the natural haliclamine H (**2**) (Fig. 3). The direct infusion ESI mass spectrum of synthetic **2** showed a pseudo-molecular ion $[M+H]^+$ at $m/z = 471.4667$ ($\Delta m = 1.3$ ppm for $[M+H]^+$), a doubly charged pseudo-molecular ion $[M+2H]^{2+}$ at $m/z = 236.2371$ ($\Delta m = 0.7$ ppm for $[M+2H]^{2+}$) and the fragments $C_m$ at $m/z = 222.2214$ ($\Delta m = 1.2$ ppm) and $C_n$ at $m/z = 250.2530$ ($\Delta m = 0.4$ ppm) (Fig. 7). The synthetic haliclamine with alkyl chains of 9 and 13 methylene groups eluted at a retention time of 17.4 min, and the ESI mass spectrum displayed a pseudo-molecular ion peak $[M+H]^+$ at $m/z = 471.4684$ ($\Delta m = 2.3$ ppm for $[M+H]^+$), a doubly charged pseudo-molecular ion $[M+2H]^{2+}$ at $m/z = 236.2384$ ($\Delta m = 4.7$ ppm for $[M+2H]^{2+}$), as well as the peaks of two fragments: $C_m$ at $m/z = 208.2074$ and $C_n$ at $m/z = 264.2696$. These results

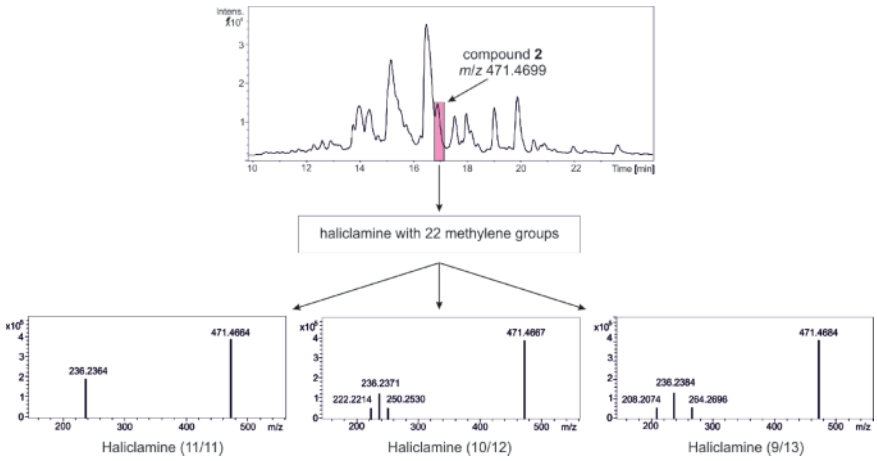



Fig. 6 (color online). Possible distributions of 22 methylene groups to the two alkyl chains: 9/13, 10/12, and 11/11 with the corresponding schematic mass spectra of the three haliclamines.

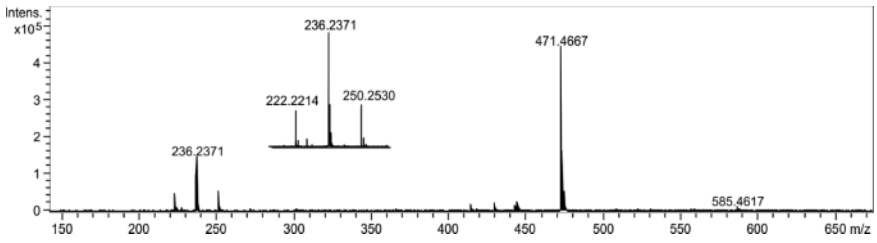



Fig. 7. Direct infusion ESI-TOF MS spectrum of the synthetic haliclamine H (**2**).

verified the hypothesis that the new haliclamine H (**2**) contained two tetrahydropyridine moieties connected with alkyl chains of 10 and 12 methylene groups.

## Conclusion

Our investigations proved that it is possible to elucidate the structure of natural products of submilligram quantities. This approach was demonstrated on two new haliclamines G (**1**) and H (**2**) from the Arctic sponge *Haliclona viscosa*. The two new members of the haliclamine family, the haliclamines G (**1**) and H (**2**), were directly identified from a sponge crude extract using a HPLC-HRMS method. In this context the identification was supported by the known biosynthetic origin of the 3-alkyl pyridinium alkaloids which are a common theme in sponges of the order Haplosclerida. Additionally, a detailed knowledge of fragmentation pathways of the haliclamines supported this approach. The final proof for the structure was obtained by the synthesis of the compounds with a subsequent comparison of their mass spectrometric and NMR spectroscopic data.

## Experimental Section

The specimen of *Haliclona viscosa* was collected by SCUBA diving (15 – 25 m depth, June 2000) near Hansneset, off the coast of Blomstrandhalvøya in Kongsfjorden, which is located on the West coast of Svalbard at 79° N, 12° E. A voucher specimen was deposited under registration no. ZMA POR. 17008 at the Zoological Museum, University of Amsterdam (The Netherlands). Sponge identification was kindly conducted by W. H. de Weerdt and Dr. R. W. M. van Soest, Institute for Biodiversity and Ecosystem Dynamics (Zoological Museum), University of Amsterdam (The Netherlands). Samples of *H. viscosa* were immediately frozen after collection, freeze-dried and kept at −20 °C. The sponge tissue was extracted at room temperature with a 1 : 1 mixture of methanol/dichloromethane (3 × 1000 mL). The resulting crude extract was partitioned between *n*-hexane (3 × 150 mL) and methanol (80 mL). The methanol extract was concentrated and further partitioned between ethyl acetate (3 × 150 mL) and $H_2O$ (80 mL), and finally the aqueous layer was extracted with *n*-butanol (3 × 150 mL). HPLC-MS analysis was performed with an Agilent 1100 HPLC system coupled to a Bruker Daltonics micrOTOF$_{LC}$ (Waters XTerra RP$_{18}$ column [3.0 mm × 150 mm, 3.5 μm] with a MeCN/$H_2O$ gradient with 0.1 % HCOOH in both solvents, at 35 °C [0 min: 20 % MeCN/80 % $H_2O$; 25 min: 55 % MeCN/45 % $H_2O$; 27 min: 100 % MeCN with a flow rate of 0.4 mL min$^{-1}$], capillary exit 150 V, skimmer 50 V).

### *Haliclamine G (**1**) and haliclamine H (**2**)*

The syntheses of the cyclostellettamines as precursors of the haliclamines followed the description of Baldwin *et al.* [13] and is based on methods published by Oediger and Joop [15]. In each case, the cyclostellettamines were obtained as TFA salts after purification. To reduce the cyclostellettamines, 1 g of the salt was dissolved in 100 mL methanol/dichloromethane (1 : 1). At −40 °C, an excess (50 equiv.) of sodium borohydride was added. The solution was stirred at the same temperature for 2 h. After warming to room temperature, the solution was quenched with concentrated sodium hydroxide solution and further diluted by adding 100 mL of $H_2O$. The extraction with dichloromethane was followed by drying over magnesium sulfate. After vaporization of the solvent, the haliclamines were obtained as light-yellow powders. Preparative chromatography was performed with a Jasco 1500 series HPLC equipped with a Prontosil Eurobond RP$_{18}$ column (20 mm × 250 mm, 5 μm), a tempered column compartment, an evaporative light scattering detector and a MeCN/$H_2O$ gradient with 0.1 % TFA in both solvents, at 40 °C (0 min: 30 % MeCN/70 % $H_2O$ isocratic for 5 min; to 60 % MeCN/40 % $H_2O$ in 30 min; isocratic for 5 min; to 100 % MeCN in 10 min with a flow rate of 8 mL min$^{-1}$). Direct infusion ESI-TOF MS spectra were acquired using a Bruker Daltonics micrOTOF$_{LC}$ (capillary exit 120 V, skimmer 50 V; increasing fragmentation: capillary exit 180 V, skimmer 80 V). $^1$H and $^{13}$C NMR spectra were conducted on a Bruker 400 MHz NMR spectrometer at 298 K with $CDCl_3$ as solvent. Figs. S1, S2, S4 and S5 show the $^1$H and $^{13}$C NMR spectra of **1** and **2** (Supporting Information available online).

### *Supporting information*

The $^1$H and $^{13}$C NMR spectra of **1** and **2** and the ESI-TOF MS spectra of **1**, **2**, **5**, and **8** are given as Supporting Information available online (DOI: 10.5560/ZNB.2012-0039).

### *Acknowledgement*

Financial support from the Deutsche Forschungsgemeinschaft (DFG) (Ko 1314/5-1 and 5-2, DFG-Forschergruppe FOR 934) is gratefully acknowledged. Sponge collection was carried out by the AWI diving team during the annual summer expedition 2000 at Koldewey Station, Ny-Ålesund, Svalbard. During this period the project was also sponsored by the DFG (Ko 1314/3-1 to 3-4). We would like to acknow-

ledge W. H. de Weerdt and Dr. R. W. M. van Soest for sponge identification and Dr. C. Timm for the synthesis of cyclostellettamine H. We further thank E. Lichte for performing preparative HPLC analyses.

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