Natural Products

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Structural Assignment of Tetrabromostyloguanidine: Does the Relative Configuration of the Palau'amines Need Revision?**

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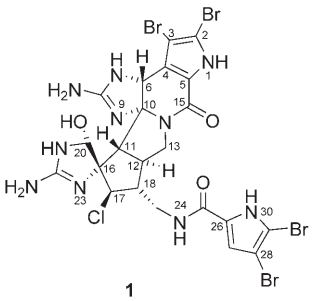
The total synthesis of palau'amine and its congeners is currently a major topic in synthetic organic chemistry.[1] So far, none of the research groups involved in the syntheses have managed to reach the complete structure of palau'amine. Herein, we present a new congener of palau'amine, tetrabromostyloguanidine (**1**; Scheme 1) which was isolated from the marine sponge *Stylissa caribica*. In contrast to the relative configuration of the palau'amine congeners that have been published, our studies on **1** have revealed a different relative configuration. Dibromopalau'amine (**2c**) was also isolated from the same sponge.



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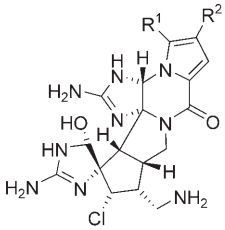
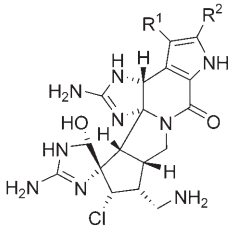


2a: R^1, R^2 = H
2b: R^1 = H, R^2 = Br
2c: R^1, R^2 = Br



3a: R^1, R^2 = H
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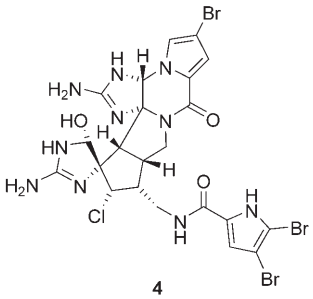

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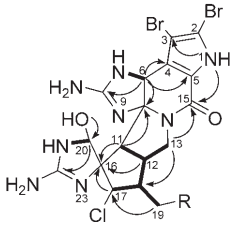
Scheme 1. Structural formulas of tetrabromostyloguanidine (**1**), palau'amine (**2a**), dibromostyloguanidine (**3c**), and konbu'acidin A (**4**).

Sponges of the families Axinellidae and Dictyonellidae are among the most investigated marine invertebrates,[2] with many secondary metabolites having been isolated and reported from these sponges, especially pyrrole-imidazole alkaloids. Approximately 100 members of this alkaloid family are biosynthetically related to oroidin.[3,4] The marine sponge *Stylissa caribica*[5] was studied by using MS-guided fractionation to afford several new pyrrole-imidazole alkaloids: 4-bromopyrrole-2-carboxy-*N*(ε)-lysine,[6] 4-bromopyrrole-2-carboxyarginine,[6] oxocyclostylidol,[7] and the stylissadines A and B.[8] In the course of this study, a compound with a previously unobserved mass and with a Br_4Cl isotopic pattern was detected. We report the isolation and structure elucidation of this new compound **1**, with a particular focus on the relative configuration of the azabicyclo[3.3.0]octane core (Scheme 1).

The molecular mass of tetrabromostyloguanidine (**1**, *m*/*z* 824.8242) and the isotopic pattern were consistent with the molecular formula $C_{22}H_{22}N_{10}O_4Br_4Cl$ ($[M+H]^+$). Application of ESIMS/MS techniques (APICIDMS/MS, CIDMS/MS; ESI = electrospray ionization, API = atmospheric pressure ionization, CID = collision-induced dissociation) gave a typical fragmentation pattern for the noncyclized pyrrole-imidazole alkaloids. The loss of 18 amu indicated loss of one hydroxy group, whereas a fragment at *m*/*z* 577.5 (corresponding to the loss of 251 amu) suggests a 4,5-dibromopyrrole-2-carbamide moiety.[9] The carbon/nitrogen skeleton of **1** was identified on the basis of data from $^1H,^1H$ COSY, $^1H,^{13}C$ and $^1H,^{15}N$ HMBC NMR spectroscopy; the most important correlations are shown in Scheme 2. Tetrabromostyloguanidine (**1**) possesses a hexacyclic core structure with a molecular constitution identical to that of dibromostyloguanidine (**3c**)[10] and related to konbu'acidin A (**4**).[11]



Scheme 2. Part of the structure of tetrabromostyloguanidine (**1**). Bonds in bold mark $^1H,^1H$ COSY correlations and the arrows indicate the $^1H,^{13}C$ HMBC correlations.

The similar chemical shifts in the ^{13}C NMR spectrum for the eight stereogenic centers of **1** compared to dibromostyloguanidine (**3c**)[10] and konbu'acidin A (**4**)[11] suggested an identical relative configuration for all three compounds (Figure 1). Dibromopalau'amine (**2c**)[12] was also isolated from the same sponge specimen as tetrabromostyloguanidine (**1**), thus providing the opportunity to compare the relative configuration of **1** directly to a palau'amine derivative.[13] The chemical shifts in the ^{13}C NMR spectrum recorded in D_2O of

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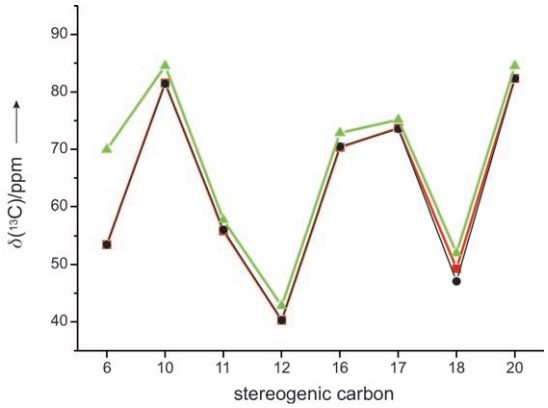

Figure 1. $\delta(^{13}C)$ values of the eight stereogenic centers of **1** (black circles), **3c** (red squares), and **4**(green triangles) in [D_6]DMSO. Alkaloid **4** differs from **1** and **3c** in the orientation of the pyrrole moiety.[14]

2c isolated from *Stylissa caribica* match with those published,[12] which indicates an identical relative configuration. Next, the ^{13}C chemical shifts of **2c** in [D_6]DMSO were compared to those of **1** (Figure 2). The shifts at C10, C11, C12,

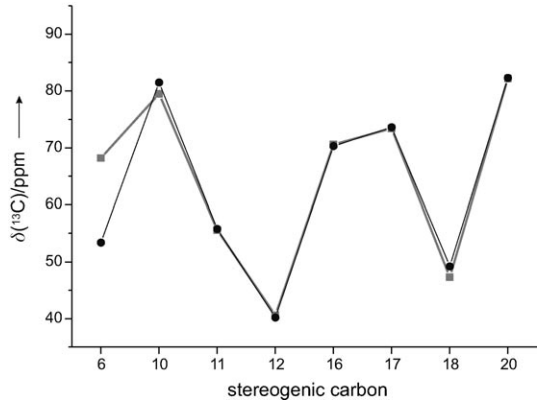

Figure 2. $\delta(^{13}C)$ values of the eight stereogenic centers of **1** (black circles) with those in **2c** (gray squares) in [D_6]DMSO. Alkaloids 2c and 1 differ in their orientation of the pyridine moiety.[14]

C16, C17, C18, and C20 were of nearly identical values in both spectra, whereas the difference for C6 can be explained by the change of a phakellin to an isophakellin moiety. The high degree of similarity between the chemical shifts of the stereogenic centers in the ^{13}C NMR spectra strongly hinted that tetrabromostyloguanidine (**1**) and dibromopalau'amine (**2c**) possess the same relative configuration.

The qualitative interpretation of the ROESY spectra of **1** revealed a weak signal for H11/H17 and a strong signal for H12/H17. This result along with the large $^1H,^1H$ coupling constant for the *cis*-fused five-membered rings (Table 1) was the first clue to tetrabromostyloguanidine (**1**) having a different relative configuration than the currently accepted structure of dibromostyloguanidine (**3c**).[10] To examine this difference a quantitative ROESY analysis was performed and the distances between the protons obtained from the ROESY

Table 1: $^1H,^1H$ coupling constants [Hz] for **1** and **2c**.[a]

Proton		1	2c
H11	H12	14.4	14.5
H12	H13	7.6	7.6
H12	H13′	10.6	10.3
H12	H18	10.1[b]	–
H17	H18	9.9	8.4
H18	H19	4.1[b]	–
H18	H19′	6.5[b]	–

[a] 1D ^1H spectrum measured in [D_6]DMSO (400 MHz). [b] From homodecoupling (HD) spectra (see the Supporting Information); the value obtained for H12/H13′ from the HD spectrum is 10.1 Hz.

spectra with different mixing times (100, 150, and 200 ms) of **1** were used for the configurational assignment.[15]

A computational approach was chosen since eight stereogenic centers needed to be determined. A combination of distance geometry (DG)[16] and distance-bounds-driven dynamics (DDD)[17] calculations using NOE-derived distance restraints (r) has previously been successfully applied in assigning the relative configuration of organic molecules.[18] For these calculations, the floating-chirality (fc) approach can be adopted, in which the change in the configuration of the stereogenic centers during the simulation is allowed.[19,20] In principle, the DG/DDD approach can calculate all the 256 possible stereoisomers for **1**. Since NMR cannot distinguish between the enantiomers, the stereogenic center at C6 was set as a reference and thus leaves the possibility to calculate 128 diastereomers.[21,22]

An fc-rDG/DDD calculation with 27 interproton distances (without H11/H12) used as distance restraints[23] delivered three structural families (I, II, and III) according to their total errors (Figure 3).[24] Family I (structures 1–67) exhibited the lowest total errors with values between 5.50 and 6.62. All 67 structures in this family have the same relative configuration as shown for **1** (Figure 4). Family II (structures 68–87)

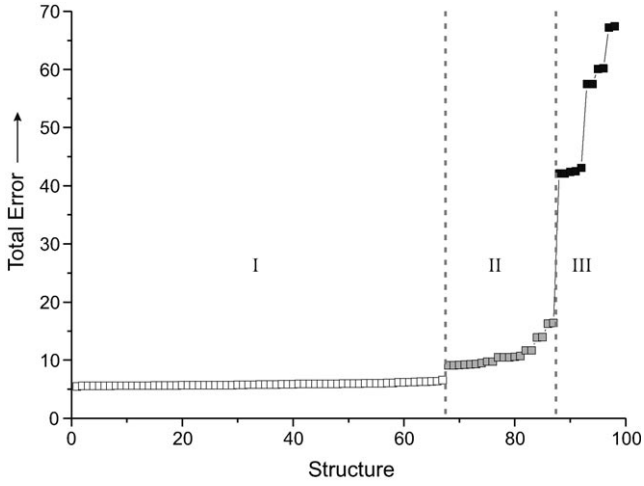

Figure 3. Result of the fc-rDG/DDD calculations for **1**. The 98 generated structures are ordered according to their total error and are clustered in three families: I (hollow squares), II (gray squares), and III (black squares).

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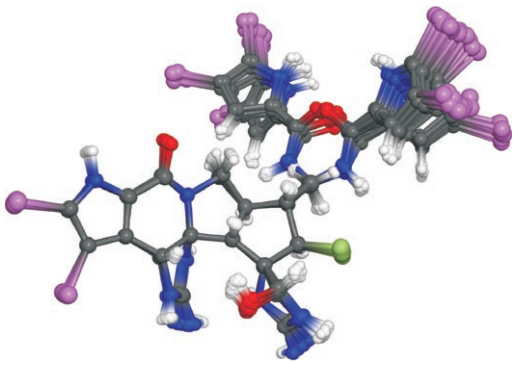


Figure 4. Representation of the 67 superimposed structures of family I from the fc-rDG/DDD calculation of **1**. The structures only differ in the orientation of the bromopyrrole side chain. Atom labels: C black, H white, O red, N blue, Br pink, Cl green.[26]

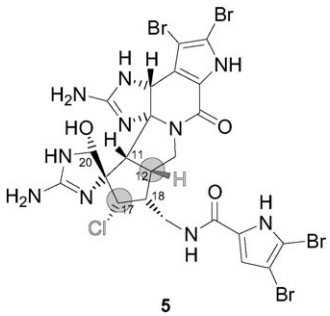
exhibited total errors with values from 9.09 to 16.4. All these structures have the same relative configuration as **1** but differ in the assignment of the two diastereotopic protons of both of the methylene groups (C13 and C19).[25] The last 11 structures (88–98, family III) exhibited high total errors with values from 42.1 to 67.4. The reason for this result is that 2 or 3 stereogenic centers are inverted in comparison with **1**. Altogether, only 5 out of the 128 possible diastereomers are generated by the fc-DG/DDD calculation using the experimental restraints. The 87 structures with lowest total errors all have the same relative configuration as given for **1**.

To achieve greater certainty about the results from the fc-rDG/DDD analysis, the calculations were also carried out with fixed chiral centers (rDG/DDD) for several selected relative configurations (Table 2). The hypothetical structure **5** represents tetrabromostyloguanidine (**1**) in the relative configuration that has been published for palau'amine (**2a**), in

Table 2: Results of the rDG/DDD calculations for **1** and **5**.[a]

Configuration	Total error	Configuration	Total error
H11,H12 *trans*		H11,H12 *cis*	
1	2.3	**5**	55.8
11-*epi*-**1** + 12-*epi*-**1**	113.0	11-*epi*-**5** + 12-*epi*-**5**	64.2
17-*epi*-**1**	15.2	17-*epi*-**5**	50.7
20-*epi*-**1**	14.9	18-*epi*-**5**	55.8
17-*epi*-**1** + 20-*epi*-**1**	21.6	17-*epi*-**5** + 18-*epi*-**5**	50.7

[a] The calculations were carried out using 27 experimental ROEs obtained for tetrabromostyloguanidine (**1**).



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which the configuration at C12 and C17 is inverted (indicated by gray circles). This approach represents a parametrized fit of minimized errors. As soon as the *trans*-fused five-membered rings are changed to *cis* in the starting structure, the total error increases dramatically. The results become even more pronounced when the total errors of the four diastereomers (C11 and C12) are compared: for the relative configuration of **1**, a value of 2.3 is obtained, whereas for the *cis* diastereomers (in which the configuration of C11 or C12 is inverted) values of approximately 60 are obtained. For the second *trans* diastereomer (inversion at C11 and C12), the total error reaches a value of 113. These results also clearly indicate that the configuration of **1** best matches the available spectroscopic data.

Since this relative configuration of tetrabromostyloguanidine (**1**) is in contradiction with the configurations published for compounds **2a**, **3c**, and **4** (different at positions C12 and C17 in the cyclopentane ring), a detailed discussion of the results from the ROESY spectroscopy combined with the coupling constants must be carried out. The published configurations for **2a**, **3c**, and **4** show the protons H11, H12, H17, and H18 of the cyclopentane ring to be aligned to one side of the molecular plane,[10–12] which result in short distances between these four protons. However, Kinnel et al. reported a weak ROESY correlation from H11 to H17.[12]

In compound **1**, the interproton distance H11/H17 is large (330 pm), whereas H12/H17 is short (240 pm). This observation is not in accordance with the published configurations at centers C11, C12, C17, and C18 of **2a**, **3c**, and **4**. The interproton distances H11/H18 (235 pm) and H17/H18 (280 pm) further support a different relative configuration. Kinnel et al. proposed that the aza-bicyclo[3.3.0]octane ring system is *cis* fused,[12] which was concluded from the coupling constant of 14.1 Hz between H11 and H12. Although, a coupling constant of this magnitude does not preclude a *cis* ring fusion, it is more consistent with a *trans* junction.[27] For **1**, we have observed a similar coupling constant (14.4 Hz), but all coupling constants measured for **1** (Table 1) in combination with the results from the ROESY experiments favor a *trans*-fused azabicyclo[3.3.0]octane (inversion at C12) along with an inverted configuration at C17. This proposal differs from the previously reported structures of compounds **2**, **3**, and **4**. There are only a few examples of *trans*-fused bicyclo-[3.3.0]octane compounds that have been reported, which suggests that although these structures are not common, they exist and are stable under standard conditions.[27a,28]

It should be noted that calculation of the distances between the H11 and H12 atoms would offer a more direct method for assigning a *cis* or *trans* configuration to the azabicyclo[3.3.0]octane moiety. The cross-peak in the ROESY spectrum would exist regardless of the relative configuration of the bicycle (as observed for **4**),[9] but a quantitative analysis should yield an interproton distance in the range of 220–240 pm for a *cis*-fused system or 280–300 pm for a *trans*-fused system. Unfortunately, the cross-peak between H11 and H12 could not be quantified in our investigation of **1** because of an overlap of a TOCSY artifact with the actual peak. In spite of the apparent disadvantage of

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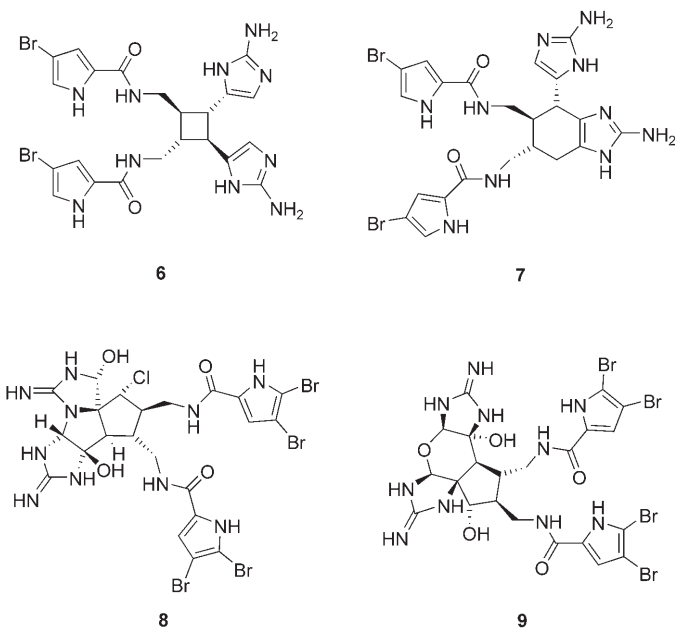
this missing key peak, enough information could be derived from the other interproton distances of H11, H12, H17, and H18 to assign the relative configuration of the azabicyclo-[3.3.0]octane moiety without needing direct information for the fusion of the two five-membered rings.

Biosynthetically, the core structures of tetrabromostyloguanidine (**1**), axinellamine A (**8**), and massadine (**9**, Scheme 3)[29] could be derived from the same pathway,[30]



Scheme 3. Structural formulas of the dimeric pyrrole-imidazole alkaloids sceptrin (**6**), ageliferin (**7**), axinellamine A (**8**), and massadine (**9**).

and therefore an identical configuration at C17 is probable. The research group of Baran recently proposed that sceptrin (**6**) is the biosynthetic precursor to axinellamine A (**8**) as well as to the palau'amines (**2**).[31] This proposal supports the five-membered rings being *trans*-fused since both bromopyrrole side chains are in an *anti* arrangement that is common in all other dimeric pyrrole-imidazole alkaloids such as sceptrin (**6**), ageliferin (**7**), axinellamine A (**8**), and massadine (**9**). A *trans*-fused system would also be consistent with the two-step cyclization proposed by Al Mourabit and Potier for the biosynthesis of compounds **1** to **4** and **6** to **9**.[3]

In summary, the new palau'amine congener tetrabromostyloguanidine (**1**) has been assigned by using spectroscopic and computational methods. The relative configuration at the stereogenic centers C12 and C17 has been proven to be different than the currently accepted structures of the palau'amines (**2**), styloguanidines (**3**), and konbu'acidin A (**4**). A DG/DDD approach using ROE-derived interproton distances and the comparison of data from ^{13}C NMR spectroscopy for all the mentioned compounds indicates that the palau'amines (**2a–c**), styloguanidines (**3a–c**), and konbu'acidin A (**4**) have a different relative configuration to those currently accepted. Although, final confirmation requires the successful synthesis or crystallization of these compounds, the available data strongly suggest a revised relative configuration of the known molecules belonging to the palau'amine family.

Experimental Section

Sponge collection, extraction, and isolation were performed as previously described.[6,7] The crude extract and each fraction obtained from Sephadex LH20 chromatography were analyzed by HPLC-MS. Final purification of the isolated compounds was achieved by preparative C_{18} HPLC (MeCN/H_2O/TFA gradient) to afford **1** (47.6 mg, 0.05% of dry weight) and **2c** (68.4 mg, 0.07% of dry weight).

^1H NMR and ^{13}C NMR spectra were recorded at 25°C (Bruker AV 400). The $^1H,^1H$ DQF COSY, $^1H,^{13}C$ HSQC, $^1H,^{13}C$ HMBC, $^1H,^{15}N$ HSQC, $^1H,^{15}N$ HMBC, and $^1H,^1H$ ROESY experiments were carried out using standard parameters. HPLC-MS: Agilent 1100 HPLC system and Bruker Daltonics microTOF$_{LC}$. Chromatography: Waters XTerra RP$_{18}$ column (3.0 × 150 mm, 3.5 μm) with a MeCN/H_2O/HCOOH gradient (0 min: 10% MeCN/90% HCOOH (0.01%); 30 min: 60% MeCN/40% HCOOH (0.01%)) with a flow rate of 0.4 mL min^{-1}. UV spectra were recorded during HPLC analysis with a DAD (Agilent). APICIDMS/MS and CIDMS/MS: Bruker Daltonics microTOF$_{LC}$ and Esquire 3000plus.

1: light yellow powder; $[\alpha]_D^{23}$ −42 (c = 1.26, MeOH); ^1H NMR (400.14 MHz, [D$_6$]DMSO, 25°C): δ = 13.36 (s, 1H, H1), 12.73 (d, J = 2.6 Hz, 1H, H30), 9.41 (s, 1H, H21), 9.25 (s, 1H, H9), 9.00 (s, 1H, H7), 8.79 (s, 1H, H23), 8.38 (t, J = 6.0 Hz, 1H, H24), 8.17 (s, 2H, 8-NH$_2$), 7.66 (s, 2H, 22-NH$_2$), 7.65 (d, J = 5.3 Hz, 1H, 20-OH), 6.95 (d, J = 2.7 Hz, 1H, H27), 5.72 (d, J = 5.3 Hz, 1H, H20), 5.52 (s, 1H, H6), 4.30 (d, J = 9.9 Hz, 1H, H17), 3.77 (m, 1H, H13), 3.55 (m, 1H, H19), 3.35 (m, 1H, H19), 3.00 (m, 1H, H13), 2.85 (d, J = 14.6 Hz, 1H, H11), 2.43 (m, 1H, H12), 2.11 ppm (m, 1H, H18); ^{13}C NMR (100.61 MHz, [D$_6$]DMSO, 25°C): δ = 159.1 (C25), 157.3 (C8), 157.3 (C22), 154.9 (C15), 127.9 (C26), 123.0 (C4), 122.0 (C5), 112.8 (C27), 108.7 (C2), 104.8 (C29), 97.9 (C28), 96.1 (C3), 82.3 (C20), 81.5 (C10), 73.6 (C17), 70.3 (C16), 55.8 (C11), 53.4 (C6), 49.2 (C18), 44.8 (C13), 40.2 (C12), 38.5 ppm (C19); ^{15}N NMR (40.56 MHz, [D$_6$]DMSO, 25°C): δ = 166 (N30), 161 (N1), 130 (N14), 104 (N21), 103 (N24), 102 (N9), 93 (N23), 89 (N7), 74 (N8-H$_2$), 73 ppm (N22-H$_2$); further NMR data may be found in the Supporting Information, Table S1; UV (DAD) λ_{max} 280 nm; HPLC/HR(+)ESI-MS: R_t = 25.2 min, m/z 824.8242 $[M+H]^+$, calcd for $C_{22}H_{22}{}^{79}Br_4{}^{35}ClN_{10}O_4$, m/z 824.8293, Δm = 6.1 ppm.

2c: light yellow powder; $[\alpha]_D^{23} = -60$ (c = 0.49, MeOH); NMR data may be found in the Supporting Information, Table S5; UV (DAD) λ_{max} 280 nm; HPLC/HR(+)ESI-MS: R_t = 2.5 min, m/z 575.9852 $[M+H]^+$, calcd for $C_{17}H_{22}{}^{79}Br_2{}^{35}ClN_9O_2$, m/z 575.9868, Δm = 2.7 ppm.

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[5] The sponge were collected by Dr. Michael Assmann during a expedition to the Bahamas in 2000. During this time the project was sponsored by the DFG (Ko1314/3-1 to 3-4). We would like to

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[13] Since the elucidation of the relative stereochemistry of **2c** by integrated ROESY spectra was not possible because of an overlap of the ^{1}H chemical shifts of H11 and H19, a comparison of the shifts in the ^{13}C NMR spectrum of **2c** and **1** was performed.
[14] The coherent lines do not represent a mathematical function, but give the best overview for the comparison of the different compounds.
[15] After volume integration of all cross-peaks in the ROESY spectra, the intensity data were calibrated using the geminal protons at C13 (178 pm). Each ROESY spectrum was analyzed separately (linear approximation). Since the distances for the different mixing times were identical, the assumption is valid.
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[22] The visualization and manipulation of the structures were carried out with the program MolArch^{+} (S. Immel, MolArch^{+} - Molecular Architecture Modeling Program V9.02, TU Darmstadt, 2006).
[23] The interproton distances obtained from the ROESY spectra were used as distance restraints in the DDD calculations. To account for experimental errors, the distances with $\pm 10\,\%$ were used.
[24] The total error (also called pseudoenergy E_{pseudo}) is not a real energy but a quality factor that describes the degree of compliance of the distances and the chiral volumes. The distance term consists of experimental and holonomic restraints. The latter restraints are given by the geometry of the molecule. $E_{pseudo} = 0.5\,k_{dr}\Sigma_i\,(r_i - r_i^{exp})^2 + 0.5\,k_{chir}\Sigma(V_{chir} - V_{chir}^{exp})^2$
[25] In family II, the diastereotopic protons of the methylene groups at C13 (10:10) and C19 (8:12) are almost equally distributed between *pro-S* and *pro-R*.
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