Selective Entry to the Dimeric or Oligomeric Pyridinium Sponge Macrocycles via Aminopentadienal Derivatives. Possible Biogenetic Relevance with Manzamine Alkaloids

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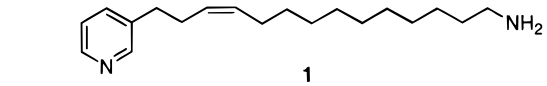
Abstract: A general entry to dimeric or oligomeric pyridinium macrocycles related to natural products **2** and **3**, recently extracted from sponges, is reported. A series of 3-(ω-aminoalkyl)pyridines **6a**−**c** has been synthesized first. The Zincke synthesis of pyridinium salts starting from such derivatives opened a new and efficient route to cyclic dimer **11** and natural cyclostellettamine B. It allowed, in addition, the highly selective syntheses of oligomers **18** and **21** and of the corresponding macrocycles, tetramer **23** and octamer **25**. These results suggest a plausible pathway for the biosynthesis by sponges of 3-alkylpyridine and pyridinium alkaloids (**1**−**3**). The newly contrived biogenetic hypothesis focuses on the chemistry of aminopentadienal derivatives, very likely to be obtained from the condensation of malondialdehyde and long chain aminodialdehydes, all these natural intermediates being derived from the metabolism of fatty acids. The possible involvement of such reactive species in the biogenesis of manzamine A and related alkaloids is also discussed. Some features of the biological activity of the natural and synthetic products are briefly presented.

Introduction

A new family of alkaloids isolated from marine sponges (order *Haplosclerida*) has progressively emerged from a number of reports in the literature.[1] These natural products were recently classified as "3-alkylpiperidine alkaloids".[1a,2] The simplests ones, such as theonelladin A (**1**), feature a 3-alkylpyridine unit, and about 30 different pyridine analogues have been discovered to date.[1a] On the other hand, a series of polypyridinium alkaloids **2** have also been isolated from sponges. These polycations can be considered as oligomers, arranged in a head-to-tail fashion, of the corresponding 3-alkylpyridine monomers. Typical among them are halitoxin **2a**,[3a] a toxic complex occurring in several marine sponges of the genus *Haliclona*, the EGF-active polypyridinium alkaloid **2b**[3b] from *Callyspongia fibrosa* and related polymers[3c] from *Reniera sarai*, and an unsaturated analogue amphitoxin from *Amphimedon compressa*.[3d]



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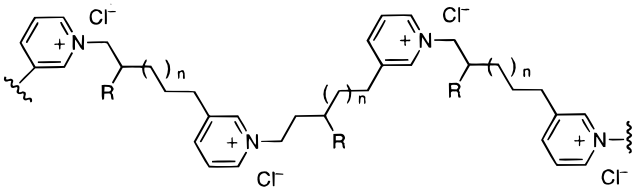
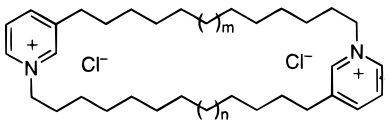
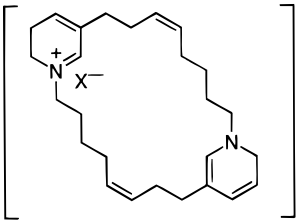


2 a R = Me, n =2-5
b R = H, n = 4



3 (m = 1-3, n = 1-3)



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The ^{1}H NMR spectra of these compounds suggested a large macrocyclic structure rather than linear polymers. These natural toxins were in fact isolated as mixtures constituted of polymers

(1) For recent comprehensive reviews, see: (a) Andersen, R. J.; Van Soest, R. W. M.; Kong, F. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press, Elsevier Science: Oxford, U.K., 1996; pp 301−355. See also: (b) Tsuda, M.; Kobayashi, J. *Heterocycles* **1997**, *46*, 765−794.

(2) We prefer to use the name "manzamine alkaloids" for designating this new family of natural products since the term "3-alkylpiperidine alkaloids" used in ref 1a seems to us somewhat imprecise. In addition, it does not refer to all these alkaloids since some of them feature only pyridine (pyridinium) or tetrahydropyridine rings or even do not possess any six-membered nitrogen heterocycle at all (manzamine C). Albeit arbitrary, this reference to manzamines considers the privileged position now occupied in this group by manzamine A, due to its original structure, biological activity, and biogenetic proposals.[5−8]

(3) (a) Schmitz, F. J.; Hollenbeak, K. H.; Campbell, D. C. *J. Org. Chem.* **1978**, *43*, 3916−3922. (b) Davies-Coleman, M. T.; Faulkner, D. J.; Dubowchik, G. M.; Roth, G. P.; Polson, C.; Fairchild, C. *J. Org. Chem.* **1993**, *58*, 5925−5930. (c) Sepcic, K.; Guella, G.; Mancini, I.; Pietra, F.; Dalla Serra, M.; Menestrina, G.; Tubbs, K.; Macek, P.; Turk, T. *J. Nat. Prod.* **1997**, *60*, 991−996.(d) Albrizio, S.; Ciminiello, P.; Fatorusso, E.; Magno, S. *J. Nat. Prod.* **1995**, *58*, 647−652.

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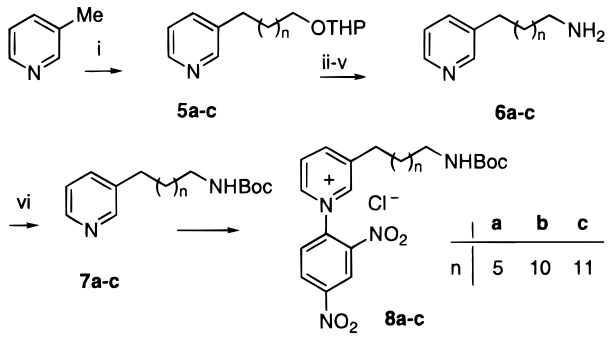
containing a variable number of units. In addition, bispyridinium macrocycles (cyclostellettamines A−F (**3**)) have also been recently isolated from marine sponge *Stelletta maxima*.[4] Importantly, Baldwin and Whitehead proposed[5] that a reduced form of a related dimer, an hypothetical bis(dihydropyridine) macrocycle **4**, could react to give the basic skeleton of manzamine A in a few steps (vide infra). Analogous unstable bis(dihydropyridine) species were later postulated as intermediates in the biogenesis of a number of related alkaloids of the manzamine family.[6] Initial experiments carried out by Baldwin's group[7] and also by us[8] suggested that the generation of intermediates such as **4** may be envisaged from the corresponding bispyridinium macrocycles analogous to **3**. From the above considerations it became clear that efficient and general methods for the selective syntheses of macrocycles such as **2** and **3** should be highly desirable. The first attempts toward this goal, reported until now, used the traditional approach to pyridinium salts, i.e. intramolecular displacement of a leaving group (alkyl halides or triflates) by pyridines. While this approach led to symmetric bispyridinium macrocycles in appreciable yield,[3b,7,8b] it is not convenient for the selective syntheses of unsymmetrical macrocyclic dimers (two different chains linking the two pyridine units as in **3** when $m \neq n$)[9] and for the syntheses of oligomeric macrocycles containing a definite number of 3-alkylpyridinium units.[8b] We now report the use of the Zincke reaction, recently developed in our laboratory,[10] as a method of choice to overcome these problems since it allows us, by an iterative process, to control the number of units in a 3-alkylpyridinium polymer, to obtain selectively such polymers with different aliphatic chains linking the pyridinium rings and, in addition, offers a practical access to natural dimeric or oligomeric polycationic macrocycles **2** and **3** by an efficient macrocyclization process.

Results and Discussion

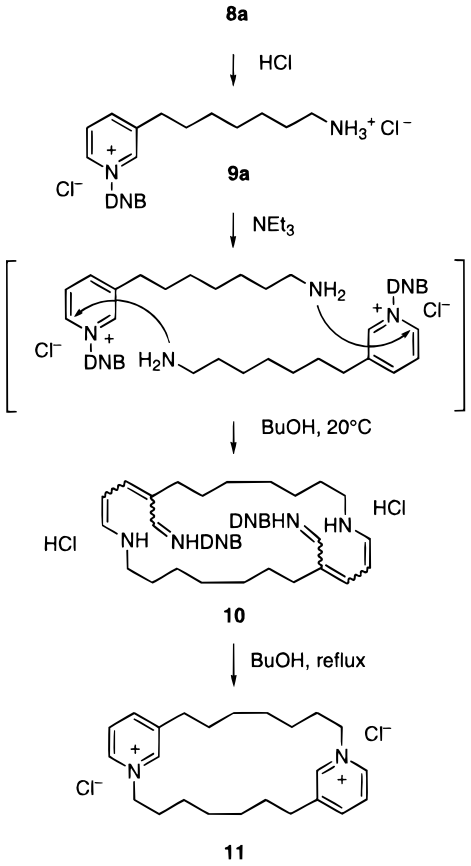
Synthesis. We first prepared a series of 3-(ω-aminoalkyl)-pyridines **6a**−**c** from 3-picoline using standard methods as depicted in Scheme 1. This procedure allowed, for example, an access to natural theonelladin C (**6c**)[11] in 45−50% overall yield from 3-picoline. Treatment of protected (aminoalkyl)-pyridines **7a**−**c** with 1-chloro-2,4-dinitrobenzene gave the Zincke salts **8a**−**c** in practically quantitative yield.

Scheme 1[a]



[a] Reagents and conditions: (i) LDA, $BrCH_2(CH_2)_nCH_2OTHP$, THF, 75%; (ii) H^+, 90%; (iii) HBr, 110 °C, 90%; (iv) NaN_3, DMF, 95%; (v) PPh_3, 95%; (vi) Boc_2O; (vii) 1-chloro-2,4-dinitrobenzene, acetone, reflux, 90%.

Scheme 2



Removal of the amine protecting group of **8a** in acidic medium gave the stable salt **9a** (Scheme 2, DNB = 2,4-dinitrobenzene residue). Addition of an excess of triethylamine to this salt, dissolved in an alcoholic solvent, resulted in an instantaneous reaction attested by the formation of a deep red color. This color was characteristic of the usual ring opening reactions of Zincke salts by amines, probably giving dimeric species such as **10** (or their regioisomers) which were not characterized. Refluxing in *n*-butanol resulted in the disappearance of this red color and in the formation of the symmetric bispyridinium dimer **11**, which was isolated in 43% by a simple extraction procedure. The macrocycle **11** was easily characterized by NMR and mass spectroscopy (vide infra). The

(4) Fusetani, N.; Asai, N., Matsunaga, S.; Honda, K.; Yasumoro, K. *Tetrahedron Lett.* **1994**, *35*, 3967−3970. Reduced analogues of dimeric salts **2** such as haliclamines have also been reported: Fusetani, N.; Yasumuro, K.; Matsunaga, S.; Hirota, H. *Tetrahedron Lett.* **1989**, 6891−6894.

(5) Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, 2059−2062.

(6) For a presentation of all of these contributions to date, see ref 1.

(7) Baldwin, J. E.; Bischoff, L.; Claridge, T. D. W.; Heupel, F. A.; Spring, D. R.; Whitehead, R. *Tetrahedron* **1997,** *53*, 2271−2290 and references therein.

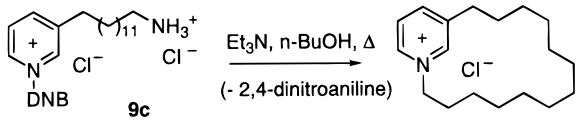
(8) (a) Gil, L.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. *Tetrahedron Lett.* **1995**, *36*, 707−710. (b) Gil, L.; Gateau-Olesker, A.; Wong, Y.-S.; Chernatova, L.; Marazano, C.; Das, B. C. *Tetrahedron Lett.* **1995**, *36*, 2059−2062. (c) Gil, L.; Baucherel, X.; Martin, M.-T.; Marazano, C.; Das, B. C. *Tetrahedron Lett.* **1995**, *36*, 6231−6234.

(9) For recent approaches to such macrocycles, see: (a) Anan, H.; Seki, N.; Noshiro, O.; Honda, K.; Yasumuro, K.; Ozasa, T.; Fusetani, N. *Tetrahedron* **1996**, *52*, 10849−10860 (synthesis of cyclostellettamine C). (b) Morimoto, Y.; Chiho Yokoe *Tetrahedron Lett.* **1997**, *38*, 8981−8984 (synthesis of haliclamine A).

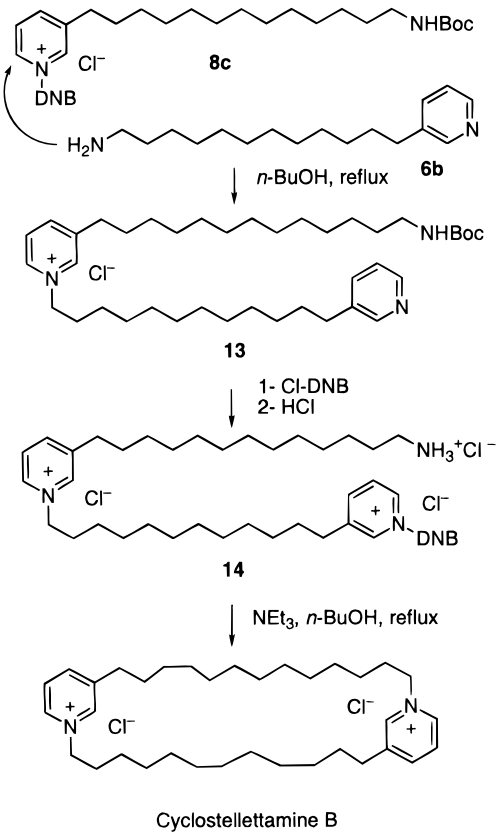
(10) (a) Genisson, Y.; Marazano, C.; Mehmandoust, M.; Gnecco, D.; Das, B. C.*Synlett* **1992**, 431. (b) Génisson, Y.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1993**, *58*, 2052. (c) Génisson, Y.; Mehmandoust, M.; Marazano, C.; Das, B. C. *Heterocycles* **1994**, *39* (2), 811. (d) Barbier, D.; Marazano, C.; Das, B. C.; Potier, P. *J. Org. Chem.* **1996**, *61*, 9596−9598. (e) Wong, Y.-S.; Marazano, C.; Dino Gnecco, D.; Génisson, Y.; Chiaroni, A.; Das, B. C. *J. Org. Chem.* **1997**, *62*, 729−733.

(11) Kobayashi, J.; Murayama, T.; Ohizumi, Y.; Sasaki, T.; Ohta, T.; Nozoe, S. *Tetrahedron Lett.* **1989**, *30*, 4833−4836. Rama Rao, A. V.; Ravindra Reddy, G.; Venkateswara Rao, B. *J. Org. Chem.* **1991**, *56*, 4545−4547.

Scheme 3



Scheme 4

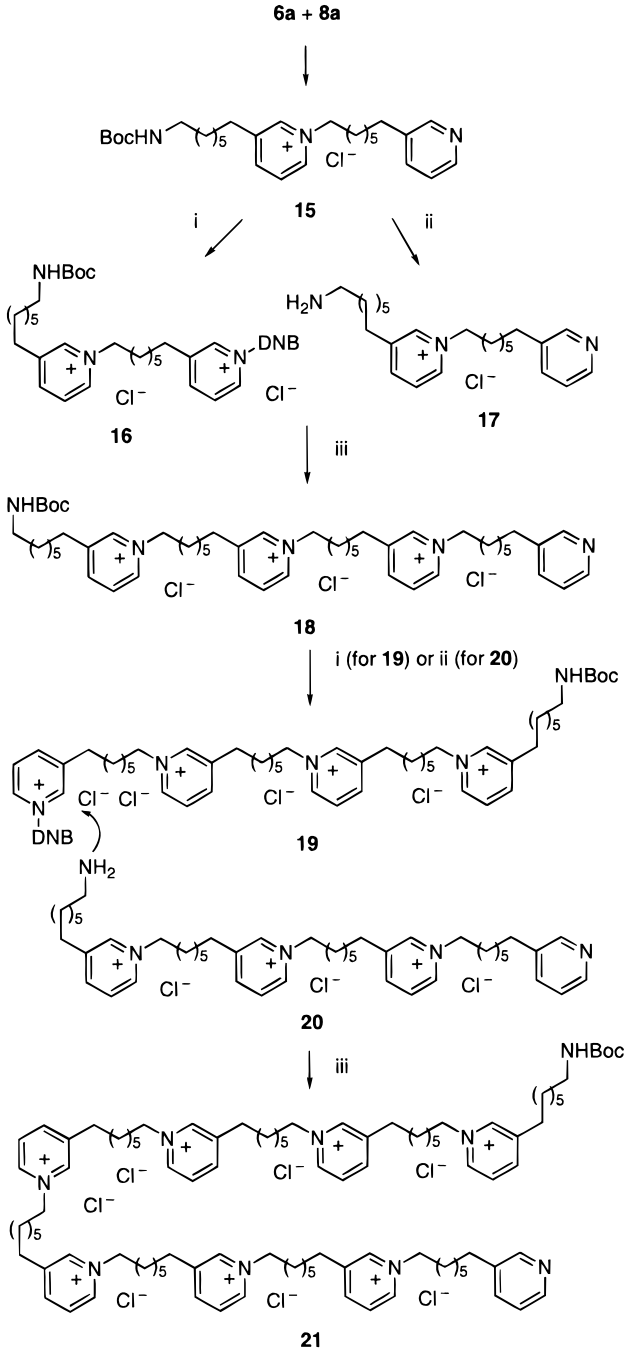


macrocyclization process was very selective, no oligomeric products being found in the reaction mixture.

By contrast, under the same conditions, salt **9c** possessing a larger side chain gave preferentially monomeric salt **12** in 70% yield (Scheme 3).

To obtain analogues of dimer **11** with longer aliphatic chains linking the two pyridinium rings, we developed a two-step sequence, an example of which is depicted in Scheme 4. This sequence, obviating formation of monomeric macrocycles such as **12**, offers in addition an entry to pyridinium dimers possessing two different chains linking the pyridinium rings as illustrated by an efficient synthesis of cyclostellettamine B (**3**, $m = 1$, $n = 2$), a natural bispyridinium macrocycle possessing two different aliphatic chains (12 and 13 methylene groups, respectively).[4] Thus, thanks to the differentiation of all nitrogen fonctionalities in the reactants (amine **6b** and salt **8c**, Scheme 1), the reaction led to a single product, salt **13**, in practically quantitative yield. Activation of the pyridine ring, followed by deprotection with HCl, gave the new salt **14**. This salt was treated with triethylamine, resulting in the immediate formation of deep red ring-opened intermediates, followed by reflux in *n*-butanol under the conditions found appropriate for the synthesis of dimer **11**. The resultant macrocyclization process turned out to be particularly easy, giving natural cyclostellettamine B, which was isolated, after crystallization, in 71% overall yield from the intermediate **13** (20−25% overall yield from 3-picoline).

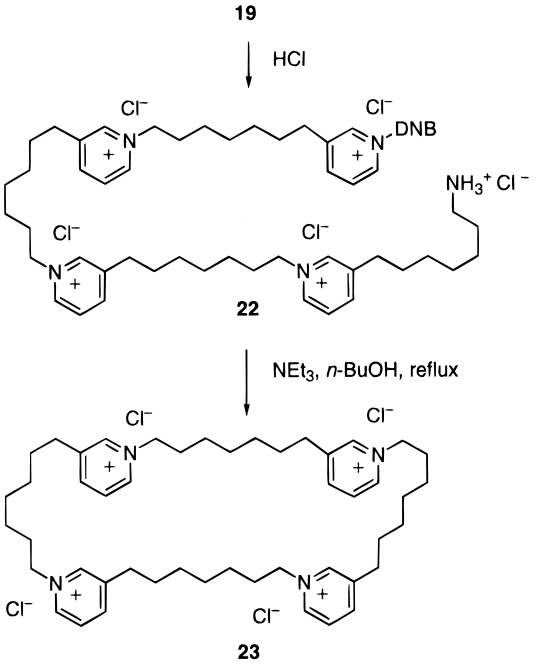
Scheme 5[a]



[a] Reagents amd conditions: (i) 1-chloro-2,4-dinitrobenzene; (ii) H^+; (iii) *n*-BuOH, reflux.

Another unique advantage offered by this approach is the now possible syntheses of larger oligomers with full control of the number of 3-alkylpyridinium units. The experimental feasibility of this process is demonstrated by the synthetic sequence depicted in Scheme 5. Condensation of amine **6a** with salt **8a** gave dimer **15**, which was treated in two batches, one being activated with 2,4-chlorodinitrobenzene to give salt **16**, the other deprotected to amine **17**. New condensation was then performed to give tetramer **18**. By the same process, condensation of the two tetramers **19** and **20** gave octameric salt **21**. It should be emphasized that the reaction scheme allowed, in principle, the condensation of units differing in length and also possessing different chains linking the pyridinium rings. In each case, the yield of both pyridine activation and Zincke reaction

Scheme 6



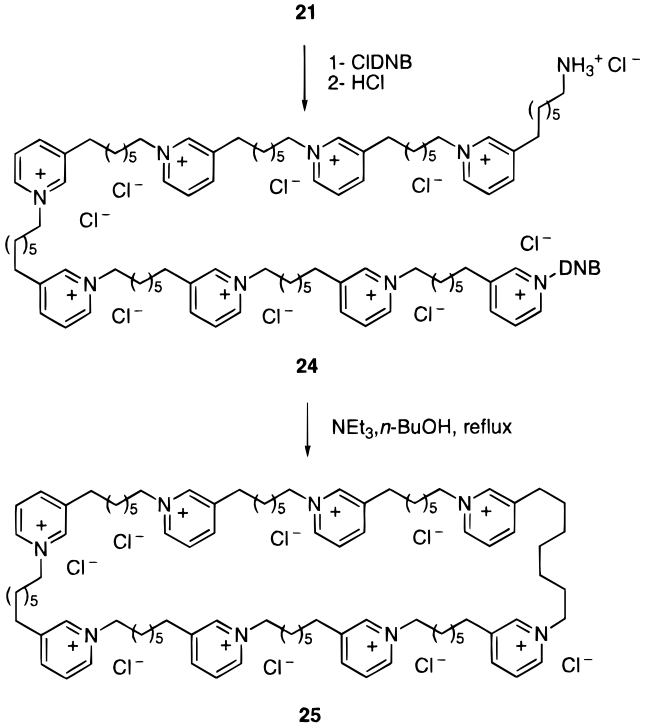
were very likely to be practically quantitative, the only difficulty which can lower the yields being purification of large polymers possessing a number of positively charged pyridinium rings. We believe that the future use of solid support will simplify the synthetic process, allowing even larger polymers to be obtained.

Finally, since the natural toxins **2** are very likely to exist as large macrocycles, we investigated the macrocyclization reaction of the new pyridinium oligomers **18** and **21**. For this purpose, we first deprotected salt **19** to amino derivative **22** (Scheme 6), which was stable as a salt of the primary amine function. As in the case of amine **8a**, treatment with triethylamine resulted in an immediate attack of the dinitrobenzene activated pyridinium ring. Working in high dilution conditions, i.e. adding dropwise and simultaneously *n*-butanol solutions of salt **22** and triethylamine in reluxing *n*-butanol, resulted in the formation of the macrocycle **23**, which was isolated in 39% yield.

Use of the same protocol gave cyclic octamer **25** (Scheme 7) in 29% yield from salt **21**. Macrocyclic pyridinium oligomers **23** and **25** can be considered as analogues of natural toxins **2** which consist of mixtures of products of different size (from 2 to 3 units to up to about 100 units).[3]

Structural Assignments. Structural assignments and determination of purity of the newly synthesized linear and macrocyclic oligomers deserve some comments. The NMR experiments are of little value for establishing the number of units present in a particular oligomer since, for example, the ^{1}H and ^{13}C NMR spectra of dimeric, tetrameric, and octameric macrocycles **11**, **23**, and **25** are very similar. In addition, while in linear oligomers such as **18** or **21** integration of the corresponding proton signals allowed a measure of the number of pyridinium rings versus pyridine ring, this must not be considered as an absolute criterion of purity since it can represent an average value of a mixture of oligomers of different lengths as well. Mass spectrometry is more accurate for establishing these structures. The FAB mass spectra of cyclic bispyridinium macrocycle **11** and cyclostellettamine B were of pre-eminent value for establishing the structure of these compounds.[3b,4] By contrast, and as previously reported,[3b] the larger oligomers do not give good FAB or electrospray mass spectral data. Nevertheless, we obtained a satisfactory electrospray mass spectrum of tetramer **23** after exchange of the chloride anions with BF_4 anions (precipitation with $AgBF_4$). For securing this result, we also reduced cyclic tetramer **23** with $NaBH_4$ in methanol. Albeit reduction was not fully selective, giving a mixture of tetrahydro- and hexahydropyridines (also contaminated by borane adducts), the FAB mass spectrum of the crude mixture displayed an expected series of intense MH^+ peaks between *m*/*z* 721 and 729. The cyclic octamer gave, after exchange with BF_4 anions, an electrospray mass spectra showing characteristic molecular peaks (with two, three, and four positive charges, corresponding to the presence of six, five, and four BF_4 anions), but these signals are of low intensity. In contrast, reduction with $NaBH_4$ of linear octamer **21** gave, as for **23**, the expected mixture of tetra- and hexahydropyridines as demonstrated by electrospray mass spectroscopy. Finally, gel exclusion HPLC experiments on a Ultrahydrogel 120 column were of great value for further assessing the purity of these compounds as shown in Figure 1.[12]

Scheme 7



Biogenic Considerations. We believe that the above results can contribute to a better understanding of the biosynthetic origin in sponges of natural products such as pyridine and pyridinium derivatives **1**−**3**. The key feature of the above syntheses is the formation of imine equivalents of 5-diamino-2,4-pentadienal intermediates (amino derivatives of glutacondialdehyde), resulting from the ring opening of Zincke salts (see for example derivative **10**), and their subsequent cyclization. It is likely that related species, i.e. substituted 5-amino-2,4-pentadienal derivatives **26** (Scheme 8), could be generated in sponges as precursors of pyridine and pyridinium salts. The formation of such intermediates is conceivable from condensation of malondialdehyde[13] with an aldehyde in the presence of an amino group.

(12) The high retention time of cyclostellettamine B compared to dimer **11** suggests that the reverse phase phenomena are also operating.

(13) Malondialdehyde is a natural product resulting, in particular, from the degradation of fatty acids. For references and details of the chemistry of this very reactive intermediate, see: Gomez-Sanchez, A.; Hermosin, I.; Lassaleta, J.-M.; Maya I. *Tetrahedron* **1993**, *49*, 1237−1250.

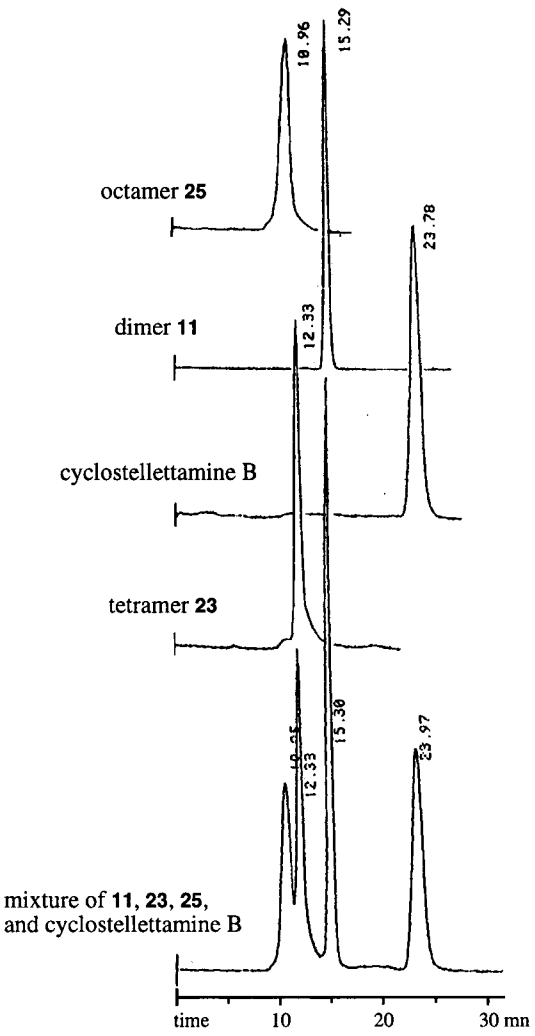
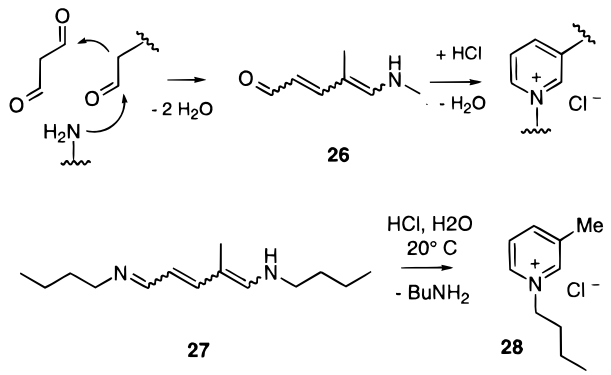


Figure 1. HPLC chromatogram of synthetic marcocycles **11**, **23**, and **25** and cyclostellettmamine B on Waters Ultrahydrogel-120 (cross-linked hydroxylated polymethacrylate gel with residual carboxyl groups). Solvent: $H_2O-5\%$ Na_2PO_4:MeCN (7:3) (0.6 mL/min).

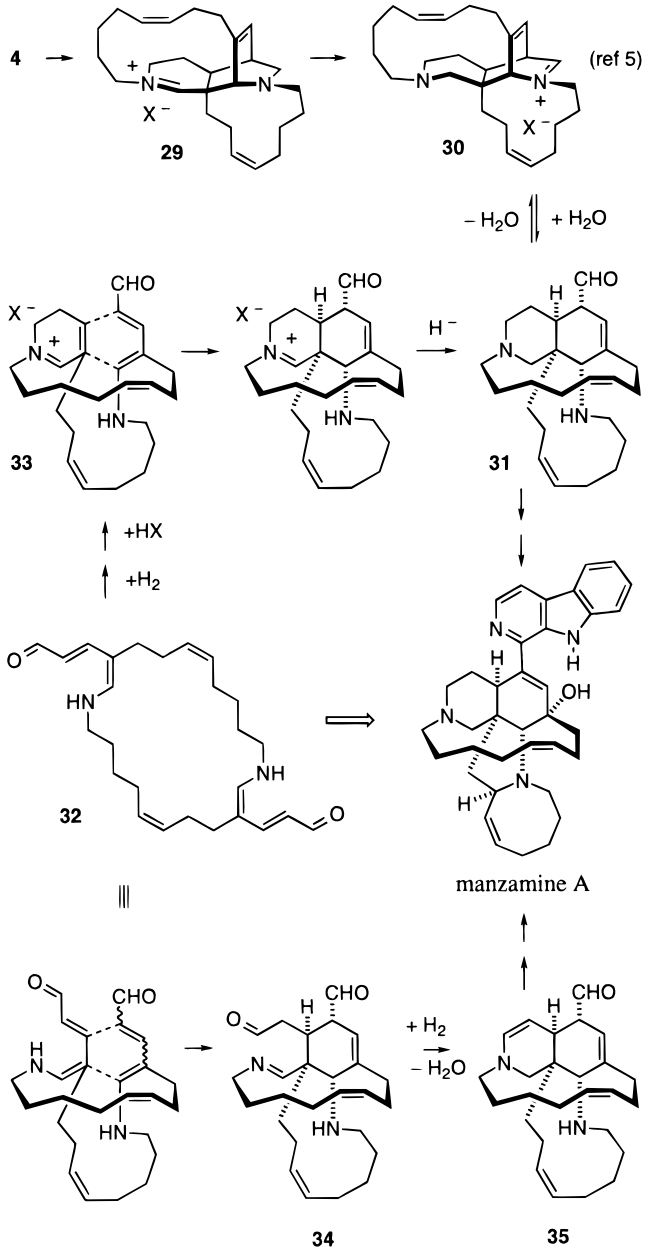
Scheme 8



Compounds **26** are also well-known[14] to be prone to cyclization to give pyridinium heterocycles. The reaction is clean and can be carried out in mild conditions as we have recently observed[15] for the diamino derivative **27**, which spontaneously cyclized, within 1 day at ambient temperature in acidic aqueous solution, to give the corresponding pyridinium salt **28** in quantitative yield.

(14) Becher, I. *Synthesis* **1980**, 589−612.
(15) Jakubowicz, K. Ph.D. Thesis in preparation.

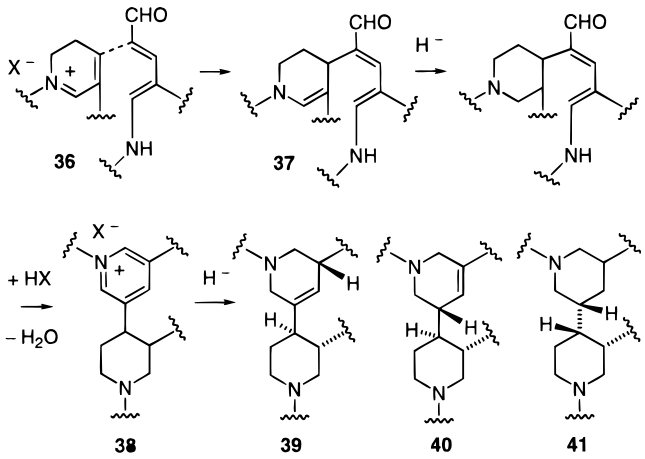
Scheme 9



The pathway depicted in Scheme 8 seems to us more likely rather than the generally accepted one in which natural sponge pyridines and pyridinium salts are derived from the condensation of an aldehyde, ammonia, and acrolein, this process producing dihydropyridine species (such as **4**) which could then undergo further oxidation to pyridines or pyridinium salts.[1a]

This latter hypothesis was based on Baldwin and Whitehead's model for the biosynthesis of manzamine alkaloids.[5] In this model condensation of ammonia, acrolein, and a long chain unsaturated dialdehyde would produce a bis(dihydropyridine) intermediate **4**, which after cyclization should give the polycyclic iminium salt **29** (Scheme 9). Isomerization of **29** to iminium salt **30**, followed by hydrolysis, would then afford aldehyde **31** possessing the basic skeleton of manzamine A. This last model has been tested independently by the Baldwin's group and our laboratory. Whereas intermolecular reactions were at first encouraging,[7,8] as illustrated in particular by the successful synthesis of the core skeleton of natural keramaphidin B (product resulting from the reduction of iminium intermediate **29**), the main limitation of this approach was the formation, as major

Scheme 10



products, of derivatives resulting from oxido-reduction reactions of the intermediate dihydropyridine species. In addition, the intramolecular version of the cycloaddition of macrocycles such as **4** remains to be achieved. Model reactions, effected in our laboratory on an oxygenated model[8b] related to **4**, were totally unsuccessful in producing species corresponding to salt **29**, the only products obtained being those resulting from oxido-reduction reactions. In view of these negative results we believe that more flexible intermediates, not prone to oxido-reduction processes, should be considered. Substituted 5-amino-2,4-pentadienals, possessing such features, seem to be deserving candidates. These species not only can produce pyridinium salts (Scheme 8) but also can lead to the complex skeleton of manzamines as depicted in Scheme 9. In a first step, condensation of malondialdehyde (instead of acrolein in the preceding model), ammonia, and an appropriate unsaturated dialdehyde could produce the key macrocycle **32**. Two possible routes to manzamine A starting from this macrocycle are then to be envisaged. In the first route, adapted from the Baldwin and Whitehead's model, reductive cyclization of **32** produces a dihydropyridinium species **33** (which can also be obtained from acrolein). This heterocycle can react to give directly the aldehyde **31**. An alternative pathway would be the direct cyclization of **32** to give **34**, followed by reduction of the resulting imine function and cyclization to the enamine **35**.[16]

The biosyntheses of the other related alkaloids can be explained in a similar way. For example, formation of only one bond in dihydropyridinium **36** (two bonds are formed in **33**) would result in a substituted new 5-amino-2,4-pentadienal intermediate **37** which, after reduction of the enamine bond, can cyclize to a pyridinium salt **38**. Reduction of such salts can give access to halicyclamine type alkaloids **39**,[17a] **40**,[17b] and **41**[17c] (Scheme 10).

Biological Activity. A number of biological activities have been reported for natural products **1**−**3** to date.[1] While the 3-alkylpyridine monomers (see **1**) already display significant cytotoxicity in vitro,[1] the oligomers possess stronger activity. Thus the ED_{50} against KB cells of the crude extract of halitoxins **2a** was reported to be 5−7 μg/mL.[3a] A related synthetic polymer from our laboratory was even more active (0.5 μg/mL).[8b] Halitoxins **2a** are antibacterial and toxic to mice and fish; they also caused haemolysis at a threshold concentration of 1 μg/mL.[3a] Halitoxin analogues **2b** inhibit epidermal growth factor[2b] and are anticholinesterase active.[3c] Strong antifeeding activity to fish has also been reported for amphitoxin.[3d] In addition, the cyclostellettamines **3** bind to muscarinic receptors.

Some of our synthetic products were tested in vitro against murine leukemia L1210, giving additional results. Thus the cyclic dimer **11** was found to be inactive at concentration levels up to 100 μM, while in sharp contrast the ED_{50} concentration of synthetic cyclostellettamine B, possessing longer hydrophobic chains, was 1.6 μM in the same conditions. The number of positive charges is also important since the ED_{50} of the octamer **25** is 1.8 μM. The most active compound tested is linear oligomer **21** (ED_{50} 0.15 μM) which is more lipophilic than macrocycle **25** due to the presence of a Boc group. The difference of activities between cyclic dimer **11** and cyclostellettamine B was further observed on the growth inhibition of KB cells (ED_{50} > 50 μg/mL and ED_{50} = 0.4 μg/mL, respectively). In addition, the last compounds were found to interfere with the cell cycle, causing 50% inhibition at 25 μM (G_2M phase) for **25**, 70% at 1 μM (G_1 phase) for **21**, and 90−100% at 5 μM (G_1 phase) for cyclostellettamine B. These activities can be compared with those of doxorubicin in the same conditions which have an ED_{50} level concentration of 0.025 μM against murine leukemia L1210 and a cell cycle inhibition of 90−100% at 0.1 μM (G_2M phase).

These activities can thus be rationalized if one considers that these natural and synthetic classes of products share in common two important features: the presence of one or more relatively delocalized positive charge (protonated pyridine for monomers or pyridinium rings for dimers and oligomers) and hydrophobic alkyl chains. These features are known to be sufficient for significant toxicity against mammalian, bacterial, and fungal cells, as in particular examplified by pyridinium salts possessing long alkyl chains at nitrogen.[18] Such properties are likely to be attributed to disruption of membranes which cause lysis of the cell. But it is clear that these compounds have also the ability, for the same reasons, to cross membranes and further interact with other targets in the cell, thus reinforcing their activity. The different activities found for cyclostellettamine B suggest effectively interactions with the cell at different levels. Possible targets are likely to be (poly)anions such as (poly)-phosphates, in particular DNA.[19]

Conclusion

We have designed a new, selective, and practical entry to natural 3-alkylpyridinium macrocycles **2** and **3** or their analogues using the Zincke synthesis of pyridinium salts. This method offers a general and selective access to a wide range of new large polycationic macrocycles which could be eventually of some interest for anion recognition. Selective reduction of these polypyridinium salts to tetrahydropyridines should in principle lead to aza-crown macrocycles and cryptands which are of current interest.[20] The results obtained can give a new insight

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(17) (a) Jaspars, M.; Pasupathy, V.; Crews, P. *J. Org. Chem.* **1994**, *59*, 3253−3255. (b) Harrisson, B.; Talapatra, S.; Lobkovsky, E.; Clardy, J.; Crews, P. *Tetrahedron Lett.* **1996**, *51*, 9151−9154. (c) Charan, R. D.; Garson, M. J.; Brereton, I. M.; Willis, A. C.; Hooper, J. N. A. *Tetrahedron* **1996**, *52*, 9111−9120.

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(20) Krakowiak, K. E.; Bradshaw, J. S.; Izatt R. M. *Synlett* **1993**, 611−620.

on the biogenetic origin of the natural alkaloids belonging to the manzamine family. These new proposals which focus on the chemistry of malondialdehyde and aminopentadienal derivatives are now under investigation in our laboratory.

Experimental Section

3-(7-Ammonioheptyl)-1-(2,4-dinitrophenyl)pyridinium Dichloride (9a). A stream of HCl gas was bubbled in a solution of protected derivative **8a** (7.0 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C for 10 min and then at room temperature for 30 min. Evaporation of the solvent provided the crude deprotected salt **9a**. For further purification, the material was taken up in minimum amount of MeOH (5−10 mL), ether (200 mL) was added in portions, and the mixture was allowed to stand for 1.5 h. The supernatant liquid was decanted and the residue treated with ether (2 × 70 mL). Traces of solvents were removed under reduced pressure to give pure salt **9a** in quantitative yield: ^{1}H NMR (300 MHz, CD_3OD) δ 1.36−1.60 (m, 6 H), 1.69 (m, 2 H), 1.83 (m, 2 H), 2.92, (br s, 2 H), 3.02 (t, J = 7.3 Hz, 2 H), 8.31 (dd, J = 8.0, 6.0 Hz, 1 H), 8.36 (d, J = 8.6 Hz, 1 H), 8.83 (d, J = 8.0 Hz, 1 H), 8.88 (dd, J = 8.6, 2.3 Hz, 1 H), 9.19 (d, J = 6.0 Hz, 1 H), 9.24 (d, J = 2.3 Hz, 1 H), 9.36 (s, 1 H); ^{13}C NMR (75.47 MHz, CD_3OD) δ 27.03, 28.18, 29.40, 29.49, 31.02, 33.38, 40.66, 123.00, 128.92, 131.03, 132.60, 139.90, 144.42, 145.59, 146.26, 149.67, 150.80; IR (film) 3365, 3200−2400, 1541, 1345 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 359 (100) $[M]^+$.

Cyclic Dimer (11). To Zincke salt **9a** (0.43 g, 1.0 mmol) in *n*-BuOH (100 mL) was added dropwise, at 20 °C, triethylamine (0.65 mL, 4.66 mmol). The resulting deep red solution was refluxed for 2 h. After removal of solvent, the residue was chromatographed over alumina (9 g) using a gradient of CH_2Cl_2/MeOH (100/0 to 92/8) as an eluent to give salt **11** (0.092 g, 43% yield) as a yellow solid when triturated with acetone. Recrystallization from *i*PrOH−acetone gave pure dimer **11** as light yellow crystals (0.072 g): mp 277 °C; MS (FAB) *m*/*z* (rel intensity) 389 (33) $[MCl_{37}]^+$, 387 (100) $[MCl_{35}]^+$, 351 (40) $[M]^+$. Anal. Calcd for $C_{24}H_{36}Cl_2N_2 \cdot 0.5H_2O$: C, 66.65; H, 8.62; N, 6.48. Found: C, 66.30; H, 8.63; N, 6.46. NMR data were in agreement with those reported in the literature.[3b]

Cyclic Monomer (12). Deprotection of derivative **8c** under the conditions used for deprotection of **8a** gave stable salt **9c** in quantitative yield: ^{1}H NMR (250 MHz, CD_3OD) δ 1.22−1.55 (m, 18 H), 1.68 (m, 2H), 1.81 (m, 2 H), 2.92 (t, J = 7.7 Hz, 2 H), 3.00 (t, J = 7.7 Hz, 2 H), 8.31 (dd, J = 8.0, 6.0 Hz, 1 H), 8.35 (d, J = 8.6 Hz, 1 H), 8.82 (d, J = 8.0 Hz, 1 H), 8.90 (dd, J = 8.6, 2.4 Hz, 1 H,), 9.20 (d, J = 6.0 Hz, 1 H), 9.25 (d, J = 2.4 Hz, 1 H), 9.33 (s, 1 H); ^{13}C NMR (62.89 MHz, CD_3OD) δ 27.33, 28.34, 29.83, 30.02, 30.22, 30.31, 30.46, 31.31, 33.51, 40.63, 122.96, 128.87, 131.00, 132.58, 139.88, 144.39, 145.66, 146.18, 149.69, 150.66; IR (film) 3411, 3200−2500, 1546, 1345 cm^{-1}; MS (FAB) *m*/*z* (relative intensity) 443 (100) $[M - H]^+$. Treatment of this salt (0.515 mg, 1 mmol) using the procedure described above for the preparation of dimer **11** gave a residue which was chromatographed over alumina (12.0 g) using a gradient of CH_2Cl_2/MeOH (100/0 to 94/6) as an eluent. Salt **12** (0.207 g, 0.7 mmol, 70% yield) was isolated as a yellow solid. Recrystallization from acetone afforded an analytical sample of **12** (0.139 g, 47% yield) as slightly yellow crystals (the corresponding triflate has recently been described):[9] mp 190 °C; ^{1}H NMR (250 MHz, CD_3OD) δ 1.13−1.40 (m, 18 H), 1.85 (m, 2 H), 2.09 (m, 2 H), 2.98 (t, J = 6.2 Hz, 2 H), 4.74 (t, J = 6.0 Hz), 8.10 (dd, J = 8.0, 6.0 Hz, 1 H, pyr H-5), 8.51 (d, J = 8.0 Hz, 1 H, pyr H-4), 8.95 (d, J = 6.0 Hz, 1 H, pyr H-6), 9.04 (s, 1 H); ^{13}C NMR (250 MHz, CD_3OD) δ 25.02, 27.10, 27.19, 27.77, 27.92, 29.88, 31.19, 32.45, 62.50, 129.04, 143.41, 145.14, 146.95; MS (FAB) *m*/*z* (relative intensity) 260 (100) $[M]^+$. Anal. Calcd for $[C_{18}H_{30}N]Cl \cdot 0.5H_2O$: C, 70.91; H, 10.25; N, 4.59. Found: C, 71.10; H, 10.62; N, 4.65.

Synthesis of Cyclostellettamine B: **3-[13-(*tert*-Butoxycarboxamido)tridecyl]-1-[12-(3-pyridinyl)dodecyl]pyridinium Chloride (13).** To the Zincke salt **8c** (14 mmol), dissolved in *n*-BuOH (60 mL), was added a solution of crude amine **6b** (17.8 mmol) in *n*-BuOH (30 mL) under stirring. The flask was placed in an oil bath at 100 °C, temperature was raised to reflux, and stirring continued under reflux for 0.2 h. After cooling, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (gradient from CH_2Cl_2/MeOH, 100/0 to 84/16) to afford a yellow oil (8.75 g), which crystallized upon standing. Recrystallization from EtOAc gave pure **13** (7.35 g, 80% yield): mp 55 °C; ^{1}H NMR (250 MHz, CD_3OD) δ 1.17−1.80 (m, 49 H), 2.16 (m, 2 H), 2.64 (t, J = 7.5 Hz, 2 H), 2.89 (t, J = 7.6 Hz, 2 H), 3.01 (t, J = 7.0 Hz, 2 H), 4.63 (t, J = 7.5 Hz, 2 H), 7.34 (dd, J = 7.8, 4.8 Hz, 1 H), 7.67 (d, J = 7.8 Hz, 1 H), 8.03 (dd, J = 7.9, 6.0 Hz, 1 H), 8.30−8.40 (m, 2 H), 8.45 (d, J = 7.9 Hz, 1 H), 8.87 (d, J = 6.0 Hz, 1 H), 8.95 (s, 1 H); ^{13}C NMR (75.47 MHz, CD_3OD) δ 26.92, 27.67, 28.86, 28.83, 29.87, 30.22, 30.38, 30.45, 30.77, 31.33, 32.00, 32.39, 33.35, 33.64, 41.23, 62.70, 79.52, 124.83, 128.88, 137.84, 139.76, 143.10, 144.91, 145.44, 146.34, 147.20, 149.76, 158.07; IR (KBr) 3369, 1696 cm^{-1}; MS (FAB) *m*/*z* (relative intensity) 622 (100) $[M]^+$. Anal. Calcd for $[C_{40}H_{68}N_3O_2]Cl$, H_2O: C, 71.02; H, 10.43; N, 6.21. Found: C, 70.97; H, 10.41; N, 6.14.

3-{12-[3-(13-Ammoniotridecyl)pyridinio]dodecyl}-1-(2,4-dinitrophenyl)pyridinium Trichloride (14). The salt **13** (9.0 mmol) and 1-chloro-2,4-dinitrobenzene (5.47 g, 27 mmol) in MeOH (55 mL) were heated under reflux for 48 h. The solvent was evaporated, and the residue was purified by column chromatography on silica gel using a gradient of CH_2Cl_2/MeOH to afford the corresponding Zincke salt [1-(2,4-dinitrophenyl)-3-{12-{3-[13-(*tert*-butoxycarboxamido) tridecyl]-pyridinio}dodecyl}pyridinium dichloride, 7.2 g, 93% yield] as a yellow oil: ^{1}H NMR (250 MHz, CD_3OD) δ 1.25−1.55 (m, 45 H), 1.78 (m, 4 H), 2.03 (m, 2 H), 2.91 (t, J = 7.7 Hz, 2 H), 2.97−3.06 (m, 4 H), 4.67 (t, J = 7.4 Hz, 2 H), 8.07 (dd, J = 8.0, 6.0 Hz, 1 H), 8.32 (dd, J = 8.0, 6.0 Hz, 1 H), 8.36 (d, J = 8.7 Hz, 1 H), 8.47 (d, J = 8.0 Hz, 1 H), 8.83 (d, J = 8.0 Hz, 1 H), 8.87−8.94 (m, 2 H,), 9.00 (s, 1 H), 9.22 (d, J = 6.0 Hz, 1 H), 9.23 (d, J = 2.4 Hz, 1 H), 9.34 (s, 1 H); ^{13}C NMR (62.89 MHz, CD_3OD) δ 26.93, 27.66, 28.83, 29.77, 29.86, 30.19, 30.34, 30.45, 30.77, 31.23, 31.34, 32.42, 33.37, 33.46, 41.23, 62.73, 79.55, 122.90, 128.90 (2C), 131.00, 132.57, 139.81, 143.10, 144.33, 144.89, 145.49, 145.58 (3C), 146.08, 146.37, 149.62, 150.67, 158.12 (C═O); IR (film) 3394, 1544, 1345 cm^{-1}. Deprotection of the Boc amino group was done by using HCl gas in CH_2Cl_2 under the conditions used for the preparation of salt **9a** and gave salt **14** in quantitative yield: ^{1}H NMR (300 MHz, CD_3OD) δ 1.14−1.44 (m, 36 H, 18 CH_2), 1.60−1.86 (m, 6 H), 2.03 (m, 2 H), 2.83−2.95 (m, 4H), 2.99 (t, J = 7.5 Hz), 4.63 (t, J = 7.4 Hz, 2 H,), 8.03 (dd, J = 8.0, 6.1 Hz, 1 H), 8.30 (dd, J = 8.0, 6.1 Hz, 1 H), 8.33 (d, J = 8.7 Hz, 1 H), 8.45 (d, J = 8.0 Hz, 1 H), 8.80 (d, J = 8.0 Hz, 1 H), 8.87 (d, J = 6.1, 1 H), 8.95 (m, 1 H), 9.16 (d, J = 6.0 Hz, 1 H), 9.26 (d, J = 2.4 Hz, 1 H), 9.28 (s, 1 H); ^{13}C NMR (75.47 MHz, CD_3OD) δ 26.95, 27.31, 28.29, 29.78, 29.86, 29.98, 30.19, 30.39, 30.45, 31.25, 31.38, 32.44, 33.37, 33.46, 40.59, 62.71, 122.91, 128.87, 130.97, 132.58, 139.83, 143.11, 144.36, 144.91, 145.49 (3C), 146.13, 146.39, 149.63, 150.70; IR (film) 3415, 1541, 1345 cm^{-1}; MS (FAB) *m*/*z* (relative intensity) 690 (40) $[M - H]^+$.

Cyclostellettamine B. To refluxing *n*-BuOH (80 mL) were added dropwise and simultaneously, over a period of 1.5 h, a solution of salt **14** (1 mmol) in *n*-BuOH (10 mL) and a solution of Et_3N (0.65 mL, 4.66 mmol) in *n*-BuOH (10 mL). After addition was complete, additional Et_3N (0.9 mL, 6.46 mmol) was added and the mixture was heated under reflux for 10 min. The solvent was evaporated and the residue purified by column chromatography over alumina (12 g) using a gradient of CH_2Cl_2/MeOH (100/0 to 98/2) as an eluent. Trituration with acetone and recrystallization from *i*-PrOH/acetone gave cyclostellettamine B (0.410 g, 71% yield) as a slightly yellow solid: mp 261 °C; MS (FAB) *m*/*z* (relative intensity) 543 (33) $[MCl_{37}]^+$, 541 (100) $[MCl_{35}]^+$, 506 (98) $[M]^+$, 253 (98) $[M]^{2+}$. Anal. Calcd for $[C_{35}H_{58}N_2]Cl_2 \cdot H_2O$: C, 70.56; H, 10.15; N, 4.70. Found: C, 70.78; H, 10.15; N, 4.78. NMR data were in agreement with those reported in the literature.[3b]

Syntheses of Linear Oligomers: 3-[7-(*tert*-Butoxycarboxamido)-heptyl]-1-[7-(3-pyridinyl)heptyl]pyridinium Chloride (15). Condensation of **6a** and **8a** under the conditions used for the preparation of **13** gave salt **15**. The residue was taken with H_2O (190 mL) and extracted with EtOAc (3 × 140 mL). Evaporation of the aqueous phase under reduced pressure afforded **15** (5.24 g, 74% yield) as a yellow oil. The product was used in subsequent experiments without further purification: ^{1}H NMR (300 MHz, CD_3OD) δ 1.29−1.53 (m, 23 H), 1.61 (m, 2 H), 1.79 (m, 2 H), 2.03 (m, 2 H), 2.66 (t, J = 7.6 Hz, 2 H), 2.89 (t, J = 7.8 Hz, 2 H), 3.03 (t, J = 7.0 Hz, 2 H), 4.64 (t, J = 7.5

Hz, 2 H), 7.35 (dd, J = 7.8, 4.8 Hz, 1 H), 7.68 (d, J = 7.8 Hz, 1 H), 8.04 (dd, J = 8.0, 6.0 Hz, 1 H), 8.33−8.38 (m, 2 H), 8.46 (d, J = 8.0 Hz, 1 H), 8.88 (d, J = 6.0 Hz, 1 H), 8.97 (s, 1 H); ^{13}C NMR (75.47 MHz, CD_3OD) δ 26.77, 27.37, 28.86, 29.54, 29.61, 29.67, 30.58, 31.16, 31.74, 32.35, 33.26, 33.50, 41.05, 62.50, 79.43, 124.79, 128.86, 137.81, 139.54, 143.06, 144.84, 145.38, 146.29, 147.20, 149.71, 158.00; IR (film) 3365, 1700 cm^{-1}; MS (FAB) *m*/*z* (relative intensity) 468 (100) $[M]^+$.

1-(2,4-Dinitrophenyl)-3-{7-{3-[7-(*tert*-butoxycarboxamido)heptyl]-pyridinio}heptyl}pyridinium Dichloride (16). The salt **15** (9.0 mmol) and 1-chloro-2,4-dinitrobenzene (5.47 g, 27 mmol) in MeOH (55 mL) were heated under reflux for 48 h. The solvent was evaporated to afford the corresponding Zincke salt **16** (5.34 g, 84% yield) as a yellow foamy gum which was used in later experiments without further purification: ^{1}H NMR (250 MHz, CD_3OD) δ 1.28−1.60 (m, 23 H), 1.67−1.93 (m, 4 H), 2.05 (m, 2 H), 2.91 (t, J = 7.8 Hz, 2 H), 3.02 (t, J = 7.4 Hz, 4 H), 4.68 (t, J = 7.5 Hz, 2 H), 8.06 (dd, J = 8.0, 6.0 Hz, 1 H), 8.32 (dd, J = 8.0, 6.0 Hz, 1 H), 8.38 (d, J = 8.7 Hz, 1 H), 8.48 (d, J = 8.0 Hz, 1 H), 8.81−8.92 (m, 3 H), 9.03 (s, 1 H), 9.10 (d, J = 6.0 Hz, 1 H), 9.27 (d, J = 2.4 Hz, 1 H), 9.40 (s, 1 H); ^{13}C NMR (62.89 MHz, CD_3OD) δ 26.64, 27.45, 28.83, 29.22, 29.27, 29.77, 30.65, 30.87, 31.25, 32.27, 41.11, 62.61, 79.50, 122.95, 128.87 (2C), 131.02, 132.63, 139.84, 143.16, 144.36, 144.96, 145.46 (3C), 146.20, 146.36, 149.73, 150.67, 158.11; IR (film) 3380, 1694, 1542, 1347 cm^{-1}; MS (FAB) *m*/*z* (relative intensity) 670 (22) $[M + Cl]^+$, 635 (20) $[M]^+$.

α-[7-(3-Pyridinyl)heptyl]-ω-(*tert*-butoxycarboxamido)tris(pyridinium-1,3-diyl-1,7-heptanediyl chloride) (18). To Zincke salt **16** (4.31 g, 6.10 mmol), dissolved in *n*-BuOH (40 mL), was added a solution of amine hydrochloride **17**-HCl (7.0 mmol) in *n*-BuOH (40 mL) and triethylamine (1.7 mL) at 60 °C. The reaction mixture was refluxed for 45 min, cooled, and evaporated under reduced pressure. The residue was mixed with H_2O (60 mL) and extracted with EtOAc (3 × 80 mL). Evaporation of the aqueous phase gave Boc-protected tetramer **18** (3.44 g, 64% yield): ^{1}H NMR (200 MHz, CD_3OD) δ 1.44 (m, 33 H), 1.74 (m, 10 H), 2.04 (m, 6 H), 2.66 (t, J = 7.9 Hz, 2 H), 2.89 (t, J = 7.5 Hz, 6H), 3.02 (t, J = 7.0 Hz, 2 H), 4.63 (m, 6 H), 7.36 (dd, J = 5.2, 7.7 Hz, 1 H), 7.69 (d, J = 7.7 Hz, 1 H), 8.01 (m, 3 H), 8.35 (m, 2 H), 8.45 (d, J = 7.3 Hz, 3 H), 8.84 (m, 3 H), 8.98 (s, 3 H); ^{13}C NMR (62.89 MHz, CD_3OD) δ 26.83, 27.50, 28.77, 29.48, 29.67, 29.83, 30.71, 31.20, 31.28, 31.88, 32.37, 33.30, 33.55, 41.15, 62.71, 79.57, 125.03, 128.93, 135.79, 138.09, 143.21, 144.76, 145.16, 146.51, 147.38, 149.51, 159.88.

α-(2,4-Dinitrophenyl)-ω-(*tert*-butoxycarboxamido)tetrakis(pyridinium-1,3-diyl-1,7-heptanediyl chloride) (19). Boc-protected tetramer **18** (3.89 g, 4.2 mmol) and 1-chloro-2,4-dinitrobenzene (2.59 g, 12.8 mmol), dissolved in MeOH (25 mL), were heated under reflux for 48 h. After evaporation of the solvent, H_2O (60 mL) was added and the mixture extracted with EtOAc (6 × 60 mL). Evaporation of the aqueous phase gave Zincke salt **19** (4.43 g, 93% yield) as a brownish gum: ^{1}H NMR (300 MHz, CD_3OD) δ 1.43 (m, 33 H), 1.74 (m, 10 H), 2.04 (m, 6 H), 2.88 (t, J = 7.8 Hz), 3.01 (t, J = 6.6 Hz, 4 H), 4.63 (m, 6 H), 8.02 (t, J = 6.7 Hz, 3 H), 8.30 (t, J = 7.4 Hz, 1 H), 8.33 (d, J = 8.4 Hz, 1 H), 8.47 (d, J = 7.9 Hz, 3 H), 8.81−8.97 (m, 5 H), 9.02 (s, 3 H), 9.15 (d, J = 5.8 Hz, 1 H), 9.26 (d, J = 2.5 Hz, 1 H), 9.33 (s, 1 H).

α-[7-(3-Pyridinyl)heptyl]-ω-aminotris(pyridinium-1,3-diyl-1,7-heptanediyl chloride) (20-HCl). HCl was bubbled through a solution of **18** (2.20 g, 2.36 mmol) in CH_2Cl_2 (50 mL) at 0 °C for 15 min and at room temperature for 0.3 h. After evaporation of the solvent, the residue was taken up in MeOH, $CaCO_3$ was added, and the mixture was stirred for 20 min to remove residual HCl. Filtration and evaporation gave salt **20**-HCl in quantitative yield: ^{1}H NMR (300 MHz, CD_3OD) δ 1.42 (m, 24 H), 1.75 (m, 10 H), 2.03 (m, 6 H), 2.89 (m, 10 H), 4.65 (m, 6 H), 8.03 (m, 4 H), 8.47 (d, J = 7.3 Hz, 3 H), 8.57 (m, 1 H), 8.73 (m, 1 H), 8.80 (s, 1 H), 8.89 (m, 3 H), 9.02 (s, 3 H); ^{13}C NMR (75.47 MHz, CD_3OD) δ 26.92, 27.16, 28.38, 29.55, 29.73, 31.29, 32.47, 33.37, 41.15, 62.76, 128.34, 128.91, 140.09, 141.91 (2 C), 143.25, 145.20, 145.57, 146.52 (2C), 148.17.

α-[7-(3-Pyridinyl)heptyl]-ω-(*tert*-butoxycarboxamido)heptakis-(pyridinium-1,3-diyl-1,7-heptanediyl chloride) (21). Salt **20**-HCl (1.90 g, 2.1 mmol), dissolved in *n*-BuOH (20 mL), and Et_3N (2.0 mL, 14.4 mmol) were added successively to a solution of Zincke salt **19** (1.90 g, 1.76 mmol) in *n*-BuOH (25 mL) at 60 °C. The mixture was refluxed for 45 min, solvent was evaporated,and the residue was taken with H_2O (100 mL) and then extracted with EtOAc (6 × 100 mL). Evaporation of the aqueous phase afforded salt **21** (2.71 g, 86% yield): ^{1}H NMR (300 MHz, CD_3OD) δ 1.45 (m, 57 H), 1.66 (m, 4 H), 1.76 (m, 14 H), 2.06 (m, 14 H), 2.67 (t, J = 7.7 Hz, 2 H), 2.91 (t, J = 7.5 Hz, 14 H), 3.03 (t, J = 7.0 Hz, 2 H), 4.68 (m, 14 H), 7.36 (dd, J = 4.9, 7.5 Hz, 1 H), 7.70 (d, J = 7.5 Hz, 1 H), 8.05 (t, J = 7.0 Hz, 7 H), 8.35 (m, 2 H), 8.49 (d, J = 7.8 Hz, 7 H), 8.92 (m, 7 H), 9.06 (s, 7 H); ^{13}C NMR (75.47 MHz, CD_3OD) δ 26.47, 27.16, 28.49, 29.10, 29.30, 29.49, 30.85, 31.54, 32.07, 32.96, 33.23, 41.95, 62.34, 79.60, 124.62, 128.54, 137.66, 142.85, 144.76, 145.16, 146.11, 146.98, 149.51, 159.88.

Macrocyclization of Linear Oligomers via the Zincke Reaction. Preparation of Tetramer 23. Salt **19** (1.025 g, 0.656 mmol) was dissolved in MeOH (5 mL), and CH_2Cl_2 (20 mL) was added. This solution was treated with HCl gas at 0 °C for 5 min and at 20 °C for 0.5 h. Removal of the solvent afforded salt **22** in quantitative yield as a yellow foam. The solutions of **22** (0.70 g, 0.656 mmol) in *n*-BuOH (50 mL) and of Et_3N (0.65 mL, 4.7 mmol) in *n*-BuOH (50 mL) were added dropwise simultaneously to *n*-BuOH (450 mL) at 90 °C over a period of 1.3 h. After addition was complete, additional Et_3N (1.3 mL, 9.4 mmol) was added and the mixture was heated under reflux for 0.20 h. The solvent was evaporated and the residue purified by chromatography over alumina (20 g) using a gradient of CH_2Cl_2/MeOH (100/0 to 95/5) to give tetramer **23** (0.272 g, 0.321 mmol, 49% yield) as a yellow gum. NMR data from ref 4: ^{1}H NMR (CD_3OD) δ 1.30 (bs s, 24 H), 1.62 (m, 8 H), 1.92 (m, 8 H), 2.79 (t, 8 H), 4.53 (t, 2 H), 7.91(dd, 4 H), 8.83 (d, 4 H), 8.74 (d, 4 H), 8.91 (s, 4 H). See the Supporting Information for mass spectral data.

Preparation of Octamer 25. Salt **21** (0.71 g, 0.4 mmol) and DNCB (0.41 g, 2.02 mmol), dissolved in MeOH (5 mL), were heated under reflux for 48 h. The solvent was evaporated, and the residue was mixed with H_2O (10 mL) and extracted with EtOAc (5 × 10 mL). Evaporation of the aqueous phase gave α-(2,4-dinitrophenyl)-ω-(*tert*-butoxycarboxamido)octakis(pyridinium-1,3-diyl-1,7-heptanediyl chloride) (**24**) (0.70 g, 88% yield) as a brownish foamy gum: ^{1}H NMR (250 MHz, CD_3OD) δ 1.28−1.61 (m, 57 H), 1.76 (m, 18 H), 2.05 (m, 14 H), 2.91 (t, J = 7.8, 14 H), 3.02 (t, J = 6.8 Hz, 4 H), 4.67 (t, J = 7.6 Hz, 14 H), 8.04 (dd, J = 8.0, 6.2 Hz, 7 H), 8.31 (dd, J = 8.0, 6.2 Hz, 1 H), 8.37 (d, J = 8.8 Hz, 1 H), 8.48 (d, J = 8.0 Hz, 7H), 8.85 (d, J = 8.0 Hz, 1 H), 8.88−8.93 (m, 1 H), 8.92 (d, J = 6.2 Hz, 7 H), 9.05 (s, 7 H), 9.20 (d, J = 6.2 Hz, 1 H), 9.24 (d, J = 2.5 Hz, 1 H), 9.38 (s, 1 H); ^{13}C NMR (62.89 MHz, CD_3OD) δ 26.77, 27.49, 28.80, 29.26, 29.43, 29.59, 29.82, 30.72, 31.18, 32.38, 33.26, 41.16, 62.65, 123.04, 128.89, 131.16, 132.73, 139.95, 143.22, 144.45, 145.12, 145.48, 146.28, 146.48, 149.85, 150.76. Salt **24** (0.546 g, 0.285 mmol) was taken up in MeOH (1.5 mL). CH_2Cl_2 (20 mL) was added and the resulting solution treated with gaseous HCl at 0 °C for 5 min and at room temperature for 1 h. After the mixture was stirred for an 1 h at room temperature, the solvent was evaporated to give α-(2,4-dinitrophenyl)-ω-aminooctakis(pyridinium-1,3-diyl-1,7-heptanediyl chloride) (**24**) as a yellow foamy gum in quantitative yield: ^{1}H NMR (250 MHz, CD_3OD) δ 1.36−1.60 (m, 64 H), 1.66−1.90 (m, 18 H), 2.05 (m, 14 H), 2.90 (t, J = 7.8, 16 H), 3.00 (t, J = 7.1 Hz, 2H), 4.65 (t, J = 7.6 Hz, 14 H), 8.03 (dd, J = 8.1, 6.1 Hz, 7 H), 8.30 (dd, J = 8.0, 6.2 Hz, 1 H), 8.34 (d, J = 8.6 Hz, 1 H), 8.47 (d, J = 8.1 Hz, 7H), 8.83 (d, J = 8.0 Hz, 1 H), 8.86−8.92 (m, 1 H), 8.90 (d, J = 6.1 Hz, 7 H), 9.04 (s, 7 H), 9.16 (d, J = 6.2 Hz, 1 H), 9.25 (d, J = 2.5 Hz, 1 H), 9.36 (s, 1 H); ^{13}C NMR (62.89 MHz, CD_3OD) δ 26.82, 27.14, 28.23, 29.49, 29.62, 31.02, 31.22, 32.40, 33.28, 40.65, 62.67, 123.44, 128.91 (2C), 131.19, 132.86, 140.07, 143.33, 144.55, 145.26, 145.49 (4C), 146.40, 146.59, 149.96, 150.83. The solutions of **24** (0.514 g, 0.268 mmol) in *n*-BuOH (20 mL) and of Et_3N (0.25 mL, 1.8 mmol) in *n*-BuOH (20 mL) were added simultaneously to *n*-BuOH (170 mL) at 90 °C over a period of 90 min. After addition was complete, additional Et_3N (0.5 mL, 3.6 mmol) was added and the mixture was heated under reflux for 10 min. The solvent was evaporated and the residue purified by column chromatography over Al_2O_3 (4.5 g) (gradient from CH_2Cl_2/MeOH 100/0 to 90/10) to give **26** (0.133 g, 29% yield) as a yellow gum: ^{1}H NMR (300 MHz, CD_3-

OD) δ 1.33−1.53 (m, 48 H, 24 CH_2), 1.77 (m, 16 H), 2.06 (m, 16 H), 2.92 (t, J = 7.7 Hz, 16 H), 4.70 (t, J = 7.5 Hz, 16 H), 8.06 (dd, J = 8.0, 6.0 Hz, 8 H), 8.51 (d, J = 8.0 Hz, 8 H), 8.96 (d, J = 6.0 Hz, 8 H), 9.10 (s, 1 H); ^{13}C NMR (75.47 MHz, CD_3OD) δ 26.79, 29.45, 29.59, 31.19, 32.40, 33.28, 62.28, 128.91, 143.26, 145.18, 145.50, 146.52.

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Supporting Information Available: Experimental procedures for preparation of pyridine derivatives **5a**−**c, 6a**−**c, 7a**−**c,** and **8a**−**c**, copies of ^{1}H and ^{13}C NMR spectra of compounds **11**−**14**, cyclostellettamine B, oligomers **18**, **21**, and **24**, and macrocyle **25**, FAB mass spectra of salts **11**−**13** and crude $NaBH_4$ reduction product of **23**, and electrospray mass spectra of **23** (BF_4 anions) and crude $NaBH_4$ reduction product of **21** (32 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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