Synthesis of the Cyclostellettamines A−F and Related Bis(3-alkylpyridinium) Macrocycles

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Received December 12, 1997

Keywords: Sponge alkaloids / Protecting groups / Macrocycles

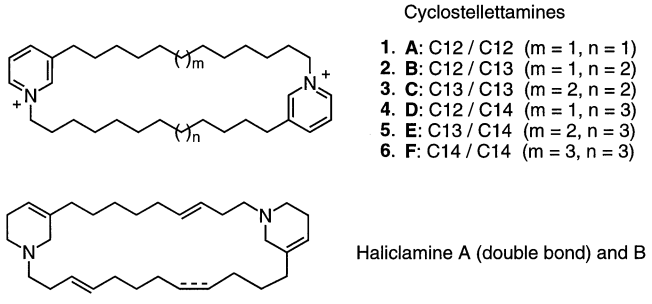
A general method was developed for the synthesis of a variety of symmetric and asymmetric macrocyclic bispyridines. 3-Hydroxyalkylpyridines **18**−**20** were prepared, converted to the corresponding iodides and protected on the pyridine nitrogen with a *p*-methoxybenzyl group to give the crystalline precursors **21**, **22** and **23**. Reaction with a second 3-hydroxyalkylpyridine gave the corresponding bis (3-alkylpyridinium) salts, which could easily be deprotected by refluxing in pyridine (**24**−**29**). Cyclization of the iodides in refluxing acetonitrile under high dilution conditions (1−2 mM) gave the desired macrocyles in overall yields between 65 and 74%. This efficient procedure resulted in the synthesis of the muscarinic receptor antagonists cyclostellettamines A−F (**1**−**6**) and some unnatural cyclophanes (**12** and **31**).

Marine sponges form a rich source of bioactive secondary metabolites, which provide leads for the development of new drugs. In a steadily growing family of complex, macrocyclic marine alkaloids, 3-alkyl substituted pyridine or piperidine units are present, which suggests a biosynthetic relationship. 3-Alkylpiperidine monomers, cyclic "dimers" and more complex alkaloids such as the ingenamines, saraines and manzamines all seem to be formed from the same biogenetic precursors.[1] Recently the occurence and biogenesis of these alkaloids, all obtained from sponges in the order Haplosclerida was reviewed by Andersen, van Soest and Kong, emphasizing their diversity and complexity.[2]

In 1994 a publication appeared describing the isolation and structure elucidation of six macrocyclic bioactive bispyridinium alkaloids from *Stelletta maxima*.[3][4] The cyclostellettamines A−F (Scheme 1) inhibit binding of methyl quinuclidinyl benzylate to muscarinic acetylcholine receptors at concentrations between 0.15−0.026 (IC_{50}, μg/ml),[3][5] thus stimulating interest in these compounds as potential drugs. Direct structural comparison can be made between the cyclostellettamines and e.g. the cytotoxic 3-alkylpiperidine dimer skeletons of haliclamine A and B, obtained from *Haliclona* species.[6] In order to get access to this large group of biologically interesting 3-alkylpyridine dimers we decided to develop a general strategy for their synthesis by way of a controlled dimerization reaction.

In the literature only one synthesis is known, describing a small scale preparation of the symmetric C_{13}/C_{13} cyclostellettamine C (**3**) via a rather lenghty sequence of reactions.[5] Direct cyclodimerization reactions were performed with 3-substituted pyridines by Faulkner et al.,[7] Marazano et al.[8] and Baldwin et al.,[9] providing moderate amounts of several symmetric dimers, together with tri, tetra and higher oligomers, depending on the conditions used. It is

Scheme 1



obvious that these methods have no application in the preparation of unsymmetrical dimeric pyridinium salts as they are present in the haliclamines[6] (Scheme 1), in the cyclostellettamines B, D and E and in precursors for e.g. the ingamine and ingenamine alkaloids.[10][11] The pyridine protection approach we describe herein contains no chromatographic separations of pyridinium salts and gives a controlled entry to a variety of bis pyridinium macrocycles in good yield.

Results and Discussion

To apply the synthesis of bis pyridinium macrocycles shown in Scheme 2 (**9b** → **10**), one of the pyridine nitrogen atoms has to be blocked. This protection procedure is not widely used although removal of alkyl substituents from pyridinium salts by nucleophiles is described in the literature.[12] Our first choice was the MOM group, which can be introduced easily and subsequently removed using acid hydrolysis or nucleophilic conditions. As a model compound 3-(3-pyridyl)-1-propanol (**7**) was chosen which was converted into the corresponding iodide **8** by the triphenylphosphane/iodine/imidazole method.[5][9][13] Advantage of iodides compared with e.g. triflates or tosylates is

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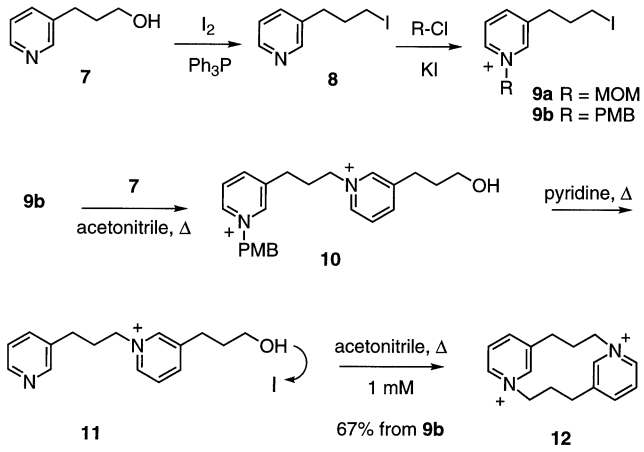
their relative stability towards premature pyridine *N*-alkylation at room temperature. Reaction of **8** with MOM-chloride gave the MOM-protected pyridine **9a** which appeared to be instable. The ^{1}H-NMR spectrum showed a mixture of the expected propyliodide **9a** containing increasing amounts of the corresponding propyl chloride, as a result of S_N2-substitution by the chloride counterion. This side reaction could be easily avoided by using a small excess of potassium iodide in the protection procedure with chlorides. However, during alkylation reactions of iodide **9a** with **7** in refluxing acetonitrile the MOM group migrated between the nitrogen atoms, yielding a mixture of randomly protected di- and monomers.

Scheme 2



Counterions (I^-) are not shown.

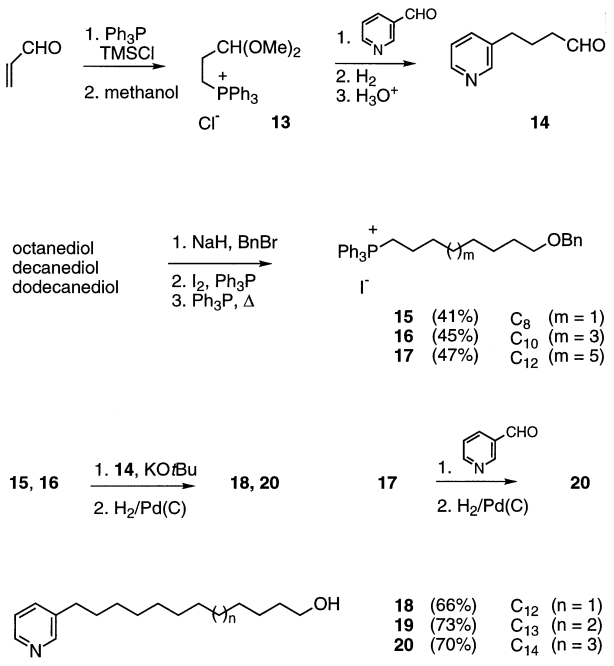
To overcome this migration problem we investigated the comparable, but more stable *p*-methoxybenzyl (PMB) protecting group. PMB-chloride in the presence of KI was coupled with iodide **8** and the resulting PMB-protected pyridine **9b** (82%, 2 steps) was coupled with **7**, yielding the required bis pyridinium salt **10** in almost quantitative yield. Deprotection was easily achieved with refluxing pyridine and the resulting mixture of **11** and PMB-pyridinium iodide was not separated but used directly in the macrocyclization reaction. Replacement of the hydroxyl group by iodide was performed as described before and the resulting crude iodide was cyclized in refluxing acetonitrile under high dilution (1mM). It should be noted that no special anhydrous conditions are required for this reaction. The highly crystalline symmetric macrocycle **12** was obtained from the reaction mixture as its di-iodide salt after concentration and filtration (57% overall from **7**).

This sequence of reactions could be applied to a number of 3-pyridinealkanols, varying from the C_3/C_3 system mentioned to the C_{14}/C_{14} macrocycle of cyclostellettamine F (**6**), thus showing the versatility of the method.

The hydroxyalkyl-pyridines **18**–**20** as precursors for the cyclostellettamines, were prepared as shown in Scheme 3.

Synthesis of **18** and **20** from nicotinaldehyde requires a Wittig reaction with C_{11} and C_{13} diols, which are not readily available. Aldehyde **14**, obtained by 3-carbon homologation of nicotinaldehyde, proved to be a useful precursor

Scheme 3



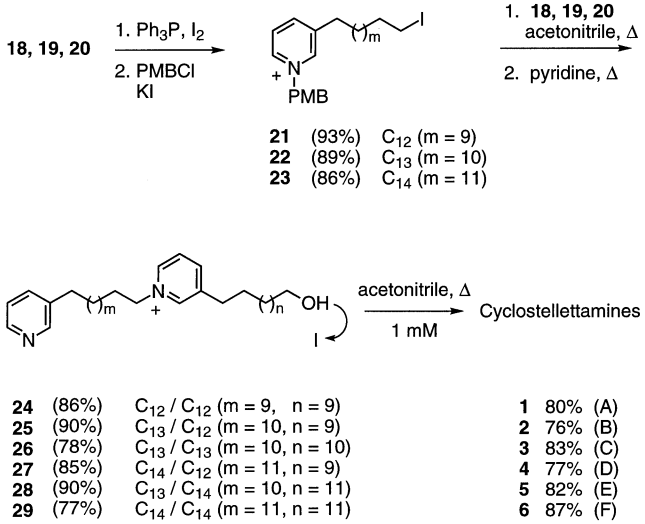
for chain-extension with C_8 and C_{10} diols to give the required dodecylalcohol **18** and tetradecylalcohol **20**. The 3-carbon phosphonium salt **13**, prepared in a one-pot procedure from acrolein,[14] was converted via a Wittig reaction to C_4-aldehyde **14** in 48% overall yield from acrolein.[15] Phosphonium salts **15** and **16** were prepared from commercially available octanediol and decanediol respectively. Conversion in two steps, Wittig reaction and hydrogenation gave the required alcohols **18** and **20**. Alcohol **19** can be prepared easily by a Wittig reaction of nicotinaldehyde with phosphonium salt **17**, obtained from 1,12-dodecanediol.[5]

Crystalline, PMB-protected iodides **21**, **22** and **23** were obtained from these alcohols (Scheme 4) and they were coupled to the pyridine-alkohols **18**, **19** and **20** to give, after deprotection in refluxing pyridine, cyclostellettamine precursors **24**–**29** in good yield. The macrocyclization was performed with the corresponding iodides at high dilution, to yield the cyclostellettamines A to F (**1**–**6**) as yellow crystalline iodide salts. The overall yields, starting from the alcohols **18**, **19** and **20** varied between 56 and 66%.

With several additional examples we have demonstrated the versatility of this approach. For instance the "Baldwin-precursor" **31** (Scheme 5) could be prepared in 61% overall yield from the corresponding alcohol.[9]

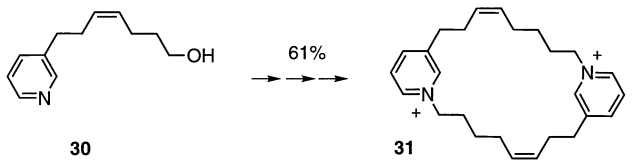
In conclusion, a general method was developed for the synthesis of symmetric and asymmetric macrocyclic bispyridines. 3-Hydroxyalkylpyridines can be converted to the desired macrocycles in high overall yields, and can be easily obtained in crystalline form. Extension of this protection approach to the synthesis of linear, oligomeric pyridinium salts is currently under investigation.

Scheme 4



Counterions (I^-) are not shown.

Scheme 5



Experimental Section

General: Melting points: Uncorrected values. − IR: Bruker IFS 28 FT. − NMR: Bruker WM 250 (1H: 250 MHz, 13C: 63 MHz) or Bruker ARX 400 (1H: 400 MHz, 13C: 100 MHz). − MS: VG Micromass ZAB-HFqQ or JEOL JMS-SX/SX102A Tandem Mass Spectrometer. − TLC: Silica gel-coated plastic sheets (Merck silica gel 60 F_{254}). − Flash chromatography: Janssen Chimica silica gel (0.030−0.075 mm). − Dry THF was distilled from sodium benzophenone ketyl; acetonitrile, benzene, toluene and pyridine were dried with MS 3Å. All other solvents and reagents were used as received, unless indicated otherwise.

PMB Protected Pyridine **9b** − *Method A:* Iodine (5.33 g, 21.0 mmol) was added to a vigorously stirred mixture of 3-(3-pyridyl)-1-propanol (**7**) (Aldrich, 1.37 g, 10.0 mmol), Ph_3P (6.03 g, 23 mmol) and imidazole (1.56 g, 23.0 mmol) in a mixture of toluene (40 ml) and acetonitrile (20 ml). After 20 min the reaction mixture was diluted with PE 60/80 (40 ml), water (30 ml) and acetonitrile (15 ml) and transferred to a separatory funnel, leading after mixing, to a 3-layer system. The upper layer, containing the excess Ph_3P and part of the Ph_3PO, was washed with a mixture of acetonitrile (5 ml) and water (5 ml) and the combined lower layers were washed twice with a mixture of PE 60/80 (10 ml) and toluene (10 ml). The product was liberated from its HI salt by adding solid Na_2CO_3 and after addition of EtOAc the layers were separated. The aqueous layer was extracted once more with a 1:1 mixture of EtOAc and acetonitrile and the combined organic layers were dried with Na_2SO_4. After evaporation of the solvents in vacuo (bath temperature below 30°C) the iodide was immediately dissolved in MeCN (30 ml). To this solution potassium iodide (2.49 g, 15 mmol) and *p*-methoxybenzyl chloride (PMBCl, 1.36 ml, 10 mmol) were added and the mixture was stirred vigorously for 20 h. Addition of water (30 ml), diethyl ether (25 ml) and PE 60/80 (25 ml) produced a three-layer system. The yellow middle layer contained product **9b**, which was obtained as a solid after drying (Na_2SO_4), evaporation of the solvents and trituration with 2-propanol (ca 40 ml) (3.86g, 78%). Mp: 95−97°C. − ^1H NMR ($CDCl_3$): δ = 2.99 (m, 2 H), 3.16 (t, *J* = 6.5 Hz, 2 H), 3.63 (m, 2 H), 3.75 (s, 3 H), 6.08 (s, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 7.64 (d, *J* = 8.6 Hz, 2 H) 7.92 (m, 1 H) 8.25 (d, *J* = 8.0 Hz, 1 H), 9.16 (d, *J* = 6.0 Hz, 1 H), 9.45 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 5.43, 32.93, 33.04, 55.39. 66.35, 114.8, 124.3, 127.9, 131.4, 141.9, 143.6, 144.0, 145.3, 160.7. MS (FAB^+); *m/z* (%): 368 (100) [M^+ − I], 121 (97). − HRMS: found [M^+ − I] 368.0535, calcd for $C_{16}H_{29}INO$ 368.0512. − $C_{16}H_{19}I_2NO$ (495.1): calcd. C 38.81, H 3.87, N 2.83; found C 38.92, H 3.94, N 2.82.

Method B: A mixture of 3-(3-pyridyl)-1-propanol (**7**) (0.82 g, 6.0 mmol), potassium iodide (0.83 g, 5.0 mmol) and *p*-methoxybenzyl chloride (PMBCl, 4.07 ml, 6.2 mmol) in acetonitrile (10 ml) was stirred vigorously for 20 h. Dichloromethane (20 ml) was added and the salts were removed by filtration. The solvents were evaporated and the residue was dissolved in acetonitrile (18 ml). Toluene (30 ml), Ph_3P (3.40 g, 13 mmol) and imidazole (0.88 g, 13 mmol) were added and the reaction was started by the addition of iodine (3.15 g, 12.4 mmol). After stirring at room temperature during 25 min the reaction mixture was diluted with water (50 ml), PE 60/80 (60 ml) and acetonitrile (20 ml) and transferred to a separatory funnel, leading after mixing, to a 3-layer system. The upper layer, containing the excess Ph_3P, was removed and washed twice with a mixture of acetonitrile (4 ml) and water (2 ml). The combined acetonitrile/water layers were mixed with dichloromethane (30 ml) and the organic layer was separated. The aqueous layer was extracted twice with dichloromethane. After drying the extracts with Na_2SO_4, the solvents were evaporated. Trituration with 2-propanol (ca 25 ml) gave **9b** (2.44 g, 82%) as a solid.

PMB-Protected **10**: Pyridinium iodide (**9b**) (6.58 g, 13.3 mmol) and 3-(3-pyridyl)-1-propanol (**7**) (1.822 g, 13.3 mmol) were refluxed in acetonitrile (50 ml) during 20 h. Evaporation of the solvent gave **10** as a glass. − ^1H NMR ($CDCl_3$ + 10% CD_3OD): δ = 1.83 (m, 2 H), 2.49 (m, 2 H), 2.85 (br. t, *J* = 7.6 Hz, 2 H), 3.02 (br. t, *J* = 7.6 Hz, 2 H), 3.46 (br. t, *J* = 5.8 Hz, 2 H), 3.62 (s, 3 H), 4.77 (br. t, *J* = 7.8 Hz, 2 H), 5.72 (s, 2 H), 6.75 (d, *J* = 8.6 Hz, 2 H), 7.45 (d, *J* = 8.6 Hz, 2 H), 7.87 (m, 2 H), 8.23 (d, *J* = 8.0 Hz, 1 H), 8.51 (m, 2 H), 8.70 (d, *J* = 6.0 Hz, 1 H), 9.07 (d, *J* = 6.0 Hz, 1 H), 9.20 (s, 1 H), 9.34 (s, 1 H). − ^{13}C NMR ($CDCl_3$ + 10% CD_3OD): δ = 28.60, 28.95, 32.01, 32.30, 55.25, 59.89, 60.05, 63.86, 114.8, 123.9, 127.7, 127.9, 131.1, 141.5, 141.7, 141.9, 144.0, 144.05, 144.1, 145.6, 146.1, 160.6.

Deprotection of **10** *to* **11**: Crude PMB-protected dimer **10** (obtained from 13.3 mmol **9b**) was refluxed in pyridine (150 ml) for about 16 h. Evaporation of the pyridine and coevaporation with a 1:1 mixture of acetonitrile and toluene gave a mixture of **11** and *N*-*p*-methoxybenzylpyridinium iodide which was not separated but used directly in the next step.

Macrocyclization to **12**: Iodine (7.62 g, 30.0 mmol) was added to a vigorously stirred mixture of **11** (crude, from 13.3 mmol **11**), Ph_3P (8.38 g, 32.0 mmol) and imidazole (2.18 g, 32.0 mmol) in a mixture of toluene (75 ml) and acetonitrile (40 ml) at room temperature. After 20 min the reaction mixture was diluted with water (100 ml) and acetonitrile (15 ml) and transferred to a separatory funnel, resulting after mixing, in a 3-layer system. The upper layer, containing the excess Ph_3P and part of the Ph_3PO, was washed with a mixture of acetonitrile (5 ml) and water (5 ml). The product was liberated from its HI-salt by adding aqueous Na_2CO_3 to the 2 lower

layers and after addition of dichloromethane the layers were separated. The aqueous layer was extracted three times with dichloromethane and the combined organic layers were quickly dried over Na_2SO_4. After evaporation of the solvents (bath $T < 30°C$) the residue was cyclized in two portions. One half was dissolved in acetonitrile (4 l) and refluxed during 30 h. The second half (kept at −20°C) was added and refluxing was continued during 44 h. Evaporation of the acetonitrile and trituration of the solid residue with hot acetonitrile (ca 50 ml) gave upon cooling crude **12** (3.45 g). Recrystallization from methanol (ca 100 ml) gave pure **12** (2.20 g, 8.91 mmol, 67% from **9**) as pale yellow crystals, m.p. 281−283°C. − ^{1}H NMR ($CDCl_3$ + 25% CD_3OD): δ = 2.55−2.70 (br, 4 H), 3.15−3.7 (br, 4 H), 4.75−5.0 (br, 4 H), 7.73 (dd, *J* = 7.8 Hz, *J* = 6.2 Hz, 2 H), 8.27 (d, *J* = 7.8 Hz, 2 H), 8.72 (br. d, 2 H), 10.06 (s, 2H). − ^{1}H NMR (D_2O): δ = 2.45 − 2.70 (br, 4 H), 3.15 − 3.35 (br, 4 H), 4.75 - 4.9 (br, 4 H), 7.73 (dd, *J* = 7.9 Hz, *J* = 6.2 Hz, 2 H), 8.24 (d, *J* = 7.9 Hz, 2 H), 8.59 (d, *J* = 6.2 Hz, 2 H), 9.03 (s, 2H). − ^{13}C NMR (D_2O): δ = 31.60 (br.), 3266, 65.46, 132.0. 144.3, 145.0, 145.1, 148.8. − IR (KBr): $\tilde{\nu}$ = 1631, 1502 cm^{-1}. − MS (FAB^+); *m/z* (%): 367 (96) [M^+ − I], 240 (97), 239 (100) [M^+ − I − HI]. − HRMS: found (M^+ − I) 367.0697, calcd for $C_{16}H_{20}IN_2$ 367.0672. − $C_{16}H_{20}I_2N_2$ (494.2): calcd. C 38.89, H 4.08, N 5.67; found C 39.16, H 4.09, N 5.69.

Phosphonium Chloride **13**: Freshly distilled acrolein (20.02 ml, 0.3 mol) was added in 20 min to a stirred solution of Ph_3P (78.6 g, 0.3 mol) and TMSCl (39.3 ml, 0.31 mol) in toluene (400 ml) at room temp. The phosphonium salt immediately separated as a glass. After 45 min the mixture was cooled in an ice/salt freezing mixture and the supernatant was decanted. Absolute methanol (500 ml) and TMSCl (2 ml) were added to the residue and the resulting solution was stirred at room temp. during 20 h. Triethyl amine (10 ml) was added and the solvents were evaporated in vacuo. The glassy residue was coevaporated twice with THF (50 ml) and the resulting **13**, which contains some TEA.HCl, was used directly in the Wittig reaction with nicotinaldehyde. − ^{1}H NMR ($CDCl_3$): δ = 1.88 (m, 2 H), 3.37 (m, 6 H), 4.8 (m, 2 H), 4.73 (t, *J* = 5.0 Hz, 1 H), 7.6 - 7.8 (m, 15 H).

4-(3-Pyridyl)-butanal (**14**): To a mechanically stirred mixture of crude phosphonium salt **13** (from 0.3 mol acrolein) in THF (400 ml) at 0°C was added potassisum *t*-butoxide (39.2 g, 0.35 mol) in 3 portions. The orange mixture was stirred at room temp. during 2 h. and cooled in ice. Nicotinaldehyde (29.2 ml, 0.31 mmol) was added in 2 min and the reaction mixture was for about 16 h at room temp. Extractive workup gave a syrup from which most of the Ph_3PO was removed by crystallization from diethyl ether. The filtrate was concentrated and distilled, giving the alkene as a mixture consisting predominantly of the (*E*) isomer according to NMR, b.p. 65−85°C at 0.04 mbar. − ^{1}H NMR ($CDCl_3$): δ = 2.54 (m, 2 H), 3.35 (s, 6H), 4.46 (t, *J* = 5.6 Hz, 1 H), 6.25 (m, 1H 6.42 (d, *J* = 16.1 Hz, 1 H), 7.19 (dd, *J* = 4.8 Hz, *J* = 7.9 Hz, 1 H), 7.64 (m, 1H), 8.40 (dd, *J* = 2.0 Hz, *J* = 4.8 Hz, 1 H), 8.53 (d, *J* = 2.0 Hz, 1 H).

The mixture of alkenes from the preceding reaction was dissolved in ethanol (200 ml) and hydrogenated over Pd/C (10%, 0.30 g) at 1 atm. of H_2 during 3 h. After filtration and evaporation of the solvent the acetal was dissolved in 5% HCl (250 ml) and stirred during 1 h. The solution was made alkaline with solid Na_2CO_3 and extracted 3 times with EtOAc. Drying (Na_2SO_4), evaporation of solvents and distillation gave aldehyde **14** (21.42 g, 0.144 mol, 48% overall from acrolein).[15], b.p. 70−75°C at 0.08 mbar. − ^{1}H NMR ($CDCl_3$): δ = 1.95 (m, 2 H), 2.50 (t, *J* = 7.2 Hz, 1 H), 2.67 (t, *J* = 7.3 Hz, 2 H), 7.22 (m, 1 H), 7.50 (m, 1 H), 8.44 (m, 2 H), 9.77 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 23.12, 31.94, 42.79, 123.3, 135.7, 136.4, 147.5, 149.7, 201.5. − IR ($CHCl_3$): $\tilde{\nu}$ = 1724, 1577 cm^{-1}.

Phosphonium Salt **15**: Sodium hydride (4.0 g, 100 mmol, 60% disp. in oil) was washed with pentane, suspended in THF (150 ml) and stirred with 1,8-octanediol (14.6 g, 100 mmol) at 60°C (bath *T*) during 1 h. Benzyl bromide (11.9 g, 100 mmol) was added and stirring was continued at 60−70°C for 5h. Extractive workup and chromatography (EtOAc/PE, 60:80, 2:3) gave 1,8-octanediolmonobenzyl ether (11.6 g, 49%) as an oil.[16] − ^{1}H NMR ($CDCl_3$): δ = 1.5−1.6 (m, 4 H), 1.2−1.4 (m, 8 H), 3.45 (t, *J* = 6.6, 2 H), 3.6 (m, 2 H), 4.49 (s, 2 H), 7.2−7.4 (m, 5 H).

Iodine (25.4 g, 100 mmol) was added to a vigorously stirred mixture of the alcohol obtained from the previous reaction (11.6 g, 49 mmol), Ph_3P (32.0 g, 122 mmol) and imidazole (8.3 g, 122 mmol) in benzene (150 ml). After 30 min stirring at room temp. water was added and the layers were separated, using diethyl ether as cosolvent. The organic layer was washed with water followed by a semi-saturated Na_2CO_3 solution untill the yellow colour disappeared. The combined water layers were extracted with ether. Drying of the organic layers (Na_2SO_4) and evaporation of the solvents (bath $T < 30°C$) gave a semi-solid residue. Immediately most of the Ph_3PO was removed by crystallization from ether. Evaporation of the solvent gave the iodide which was refluxed with Ph_3P (11.8 g, 45 mmol) in toluene for 4 h. During the reaction the product separated as an oil. The product layer was frozen by cooling the mixture in dry ice/ethanol. The supernatant was decanted and the resulting glass was stirred with toluene (50 ml) at room temp. for 30 min This cooling/decanting/washing process was repeated three times. Drying of the resulting phosphonium salt at 0.1 mbar and 50−60°C during several hours yielded **15** (24.6 g, 83%) as a glass. − ^{1}H NMR ($CDCl_3$): δ = 1.1−1.3 (m, 8 H), 1.5−1.7 (m, 4 H), 3.43 (t, *J* = 6.6 Hz, 2 H) 3.6 (br. d, 2 H), 4.49 (s, 2 H), 7.0−7.8 (m, 20 H).

Phosphonium Salt **16**: Decanediol (17.4 g, 100 mmol) was converted to the corresponding mono-benzyl ether (12.6 g, 48%) as described in the synthesis of **15**. − ^{1}H NMR ($CDCl_3$): δ = 1.2−1.4 (m, 12 H), 1.5−1.6 (m, 4H), 3.43 (t, *J* = 6.6, 2 H), 3.6 (m, 2 H), 4.48 (s, 2H), 7.2−7.4 (m, 5 H). This alcohol (12.6 g, 48 mmol) was converted to **16** by the procedure described for **15**, yielding **16** (27.7 g, 89%) as a glass. − ^{1}H NMR ($CDCl_3$): δ = 1.1−1.4 (m, 12 H), 1.5−1.7 (m, 4 H), 3.41 (t, *J* = 6.6 Hz, 2 H), 3.6 (br. d, 2 H), 4.49 (s, 2 H), 7.0−7.8 (m, 20 H).

Phosphonium Salt **17**:[5] Dodecanediol (40.46 g, 200 mmol) was converted to the corresponding monobenzyl ether (solid, 29.2 g, 50%) as described in the synthesis of **15**, m.p. 34−36°C. − ^{1}H NMR ($CDCl_3$): δ = 1.2−1.4 (m, 16 H), 1.5−1.6 (m, 4 H), 3.43 (t, *J* = 6.6, 2 H), 3.55 (m, 2 H), 4.49 (s, 2 H), 7.2−7.4 (m, 5 H). This alcohol (23.36 g, 80 mmol) was converted to **17** by the procedure described for **15**, yielding **17** (49.5 g, 93%) as a glass. − ^{1}H NMR ($CDCl_3$): δ = 1.1−1.4 (m, 16 H), 1.5−1.7 (m, 4 H), 3.44 (t, *J* = 6.6 Hz, 2 H), 3.6 (br. d, 2 H), 4.49 (s, 2 H), 7.0−7.8 (m, 20 H).

12-(3-Pyridyl)-1-dodecanol (**18**): Potassium *t*-butoxide (2.46 g, 28.0 mmol) was added to a solution of phosphonium salt **15** (17.0 g, 26.7 mmol) in THF (125 ml) at 0°C. After stirring at room temp. for 2 h., the mixture was cooled to 0°C and aldehyde **14** (3.87 g, 26.0 mmol) was added in one portion. The mixture was stirred at room temp. overnight and purified by extractive workup. Removal of most of the Ph_3PO by crystallization from ether and chromatography (EtOAc/PE 60/80 1:1) gave the (*Z*)-alkene (13.5 mmol, 67%) as an oil. − ^{1}H NMR ($CDCl_3$): δ = 1.2−1.5 (m, 8 H), 1.55−1.75 (m, 4 H), 1.98 (m, 2 H), 2.07 (m, 2 H), 2.60 (t, *J* = 7.8 Hz, 2 H), 3.46 (t, *J* = 6.6 Hz, 2 H), 4.49 (s, 2 H), 5.34−5.42 (m, 2 H), 7.16

(m, 1 H), 7.28 (m, 1 H), 7.46 (m, 5 H), 7.47 (br. d, J = 7.7 Hz, 2 H), 8.44 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 26.05−32.38 (9 × CH_2), 70.37, 72.73, 123.1, 127.3, 127.5, 128.2, 128.6, 130.7, 135.6, 137.5, 138.6, 147.2, 149.9. Hydrogenation of this product was performed with $Pd(OH)_2$ (20% on carbon, 0.5 g) in a mixture of ethanol (60 ml) and aqueous HCl (25%, 3 ml) at 1 atm. H_2. After 2 h. the catalyst was removed by filtration over Hyflow and the solvents were evaporated. The product was obtained (3.51 g, 99%) by extractive workup using aqueous Na_2CO_3 and ether. **18**: M.p. 48−50°C. − ^{1}H NMR ($CDCl_3$): δ = 1.2−1.4 (m, 16 H), 1.5−1.6 (m, 4 H), 2.54 (t, J = 7.7 Hz, 2 H), 3.06 (br. s, 1 H), 3.58 (t, J = 6.6 Hz, 2 H), 7.15 (dd, J = 7.8, 4.8 Hz, 1 H), 7.44 (br. d, J = 7.8 Hz, 1 H), 8.35 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 25.68−32.82 (11 × CH_2), 62.48, 123.1, 135.8, 137.9, 146.8, 149.6. − HRMS: found 264.2307, calcd for $C_{17}H_{30}NO$ (M + 1) 264.2328. − $C_{17}H_{29}NO$ (263.4): calcd. C 77.51, H 11.10, N 5.32; found C 77.64, H 10.81, N 5.30.

13-(3-Pyridyl)-1-tridecanol (**19**): Wittig reaction of phosphonium salt **17** (49.5 g, 74.5 mmol) with nicotinaldehyde (7.07 ml, 75.0 mmol) as described for **18** yielded the corresponding (*Z*)-alkene (20.87 g, 77%). − ^{1}H NMR ($CDCl_3$): δ = 1.2−1.5 (m, 16 H), 1.55 (m, 2 H), 2.23 (m, 2 H), 3.44 (t, J = 6.6 Hz, 2 H), 5.76 (dt, J = 11.6, 4.4 Hz, 1 H), 6.33 (br. d, J = 11.6 Hz, 1 H), 7.2−7.4 (m, 6 H), 7.56 (br. d, J = 7.8 Hz, 1 H),8.42 (d, J = 4.8, 1.3 Hz, 1 H), 8.51 (br. s, 1 H). Hydrogenation gave alcohol **19** (15.09 g, 95%) as a solidifying syrup.[5], m.p. 44−46.5°C. − Spectroscopic data: See alcohol **18**, except for two additional CH_2 protons (δ = 1.2−1.4) and one extra carbon atom. − HRMS: found 278.2509, calcd for $C_{18}H_{32}NO$ (M + 1) 278.2489. − $C_{18}H_{31}NO$ (277.5): calcd. C 77.92, H 11.26, N 5.05; found C 78.07.64, H 11.11, N 5.03.

14-(3-Pyridyl)-1-tetradecanol (**20**): The Wittig reaction was performed as described for **18**, by using phosphonium salt **16** (17.0 g, 26.7 mmol) and aldehyde **14** (3.87 g, 26.0 mmol), to give the (*Z*)-alkene (7.00 g, 71%) as an oil. − Except for four additional CH_2 protons (δ 1.2−1.4) and two extra carbon atoms, the NMR data were identical to those described for **18**. Hydrogenation gave alcohol **20** (5.22 g, 98%) as a solidifying syrup, m.p. 57−59°C. − Spectroscopic data: See alcohol **18**, except for four additional CH_2 protons (δ 1.2−1.4) and two extra carbon atoms. − HRMS: found 292.2646, calcd for $C_{19}H_{34}NO$ (M + 1) 292.2641. − $C_{19}H_{33}NO$ (291.5): calcd. C 78.29, H 11.41, N 4.81; found C 78.24, H 11.17, N 4.69.

PMB-Protected Pyridinium Iodide **21**: Iodine (1.52 g, 6.0 mmol) was added to a vigorously stirred mixture of the alcohol **18** (0.789 g, 3.0 mmol), Ph_3P (1.6 g, 6.1 mmol) and imidazole (0.45 g, 6.1 mmol) in benzene (25 ml). After 15 min dichloromethane (4 ml) and triethylamine (1.4 ml, 10 mmol) were added in order to deprotonate the pyridine nitrogen. PE 60/80 (25 ml) was added and stirring was continued for 5 min. Solids were removed by filtration over Hyflow and the filtrate was directly subjected to chromatography over a short silica gel column, eluting with EtOAc/PE 60/80 (4:1) to remove excess Ph_3P and eluting with EtOAc/PE 60/80 (1:1) to obtain the product. After evaporation of the solvents in vacuo (bath temperature <30°C) the resulting iodide was immediately dissolved in MeCN (15 ml). To this solution, potassium iodide (0.83 g, 5.0 mmol) and *p*-methoxybenzyl chloride (PMBCl, 0.407 ml, 3.0 mmol) were added. The mixture was stirred vigorously for 20 h, during which time the product crystallized. Dichloromethane was added to the reaction mixture to dissolve the product and next the potassium salts were removed by extraction with water. The organic layer was washed with aqueous potassium iodide to remove traces of chloride ions, dried (Na_2SO_4) and evaporated. Crystallization from dichloromethane and diethyl ether gave **21** (1.74 g, 93%) as a pale yellow solid, m.p. 92−93°C. − ^{1}H NMR ($CDCl_3$): δ = 1.2−1.4 (m, 16 H), 1.65 (m, 2 H), 1.79 (q, J = 7.0 Hz, 2 H), 2.82 (m, 2 H), 3.17 (t, J = 7.0 Hz, 2 H), 3.78 (s, 3 H), 6.10 (s, 2 H), 6.89 (d, J = 8.6 Hz, 2 H), 7.59 (d, J = 8.6 Hz, 2 H), 7.89 (m, 1 H), 8.13 (br. d, J = 8.0 Hz, 1 H), 9.13 (br. d, J = 6.1 Hz, 1 H), 9.18 (br. s, 1H). − ^{13}C NMR ($CDCl_3$): δ = 7.35, 28.35−33.39 (11 × CH_2), 55.31, 63.21, 114.8, 124.47, 127.7, 131.3, 141.7, 143.6, 144.0, 144.8, 160.6. − IR (KBr): $\tilde{\nu}$ = 1611, 1514, 1508, 1462 cm^{-1}. − HRMS: found 494.1880, calcd for $C_{25}H_{37}INO$ (M − I) 494.1920. − $C_{25}H_{37}I_2NO$ (621.4): calcd. C 48.32, H 6.00, N 2.25; found C 48.23, H 5.92, N 2.15.

PMB-Protected Pyridinium Iodide **22**: Prepared on a 20 mmol scale from **20** following the same procedure, yielding **22** (11.25 g, 89%) as a solid, m.p. 95−97°C. − HRMS: found 509.2180, calcd for $C_{26}H_{40}INO$ (M − I) 509.2155. − $C_{26}H_{39}I_2NO$ (635.4): calcd. C 49.15, H 6.19, N 2.20; found C 49.24, H 6.18, N 2.18.

PMB-Protected Pyridinium Iodide **23**: Prepared on a 10 mmol scale from **19** following the procedure described for **21**, yielding **23** (5.57 g, 86%) as a solid, m.p. 97−98°C. − HRMS: found 522.2227, calcd for $C_{27}H_{42}INO$ (M − I) 522.2233. − $C_{27}H_{41}I_2NO$ (649.4): calcd. C 49.94, H 6.36, N 2.16; found C 50.06, H 6.30, N 2.12.

Bispyridinium Salts **24**−**29**: Equimolar amounts of PMB-protected iodides **21**−**23** and alcohols **18**−**20** were refluxed in MeCN during 20 h. In general the reactions were performed on a 2 mmol scale, using 8 ml solvent. Evaporation of the solvent gave the coupled products, which were dissolved in pyridine (45 ml) and refluxed during 20 h. The solvent was removed in vacuo and the residue was dissolved in hot acetonitrile. The crystalline products were obtained by filtration after standing for 2 to 4 h. in the refrigerator. Longer periods of time caused co-crystallization of the side product PMB-pyridinium iodide.

24 *(From Reaction of* **21** *with* **18***):* Yield 86%, m.p. 102−105°C. − ^{1}H NMR ($CDCl_3$): δ = 1.1−1.4 (m, 32 H), 1.45−1.55 (m, 4 H), 1.65 (m, 2 H) 1.97 (m, 2 H), 2.53 (t, J = 7.7 Hz, 2 H), 2.85 (t, J = 7.7 Hz, 2 H), 3.55 (t, J = 6.6 Hz, 2 H), 4.85 (t, J = 7.5 Hz, 2 H), 7.15 (dd, J = 7.8, 4.9 Hz, 1 H), 7.44 (d, J = 7.8 Hz, 1 H), 8.04 (dd, J = 7.8 Hz, 6.2 Hz, 1 H), 8.23 (br. d, J = 8.0 Hz, 1 H), 8.33 (m, 2 H), 9.16 (d, J = 6.0 Hz, 1 H), 9.21 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 25.63−32.80 (22 × CH_2), 61.66, 62.47, 123.2, 128.0, 135.8, 137.9, 141.5, 143.8, 144.1, 144.9, 146.8, 149.6.

25 *(From Reaction of* **22** *with* **18***):* Yield 90%, m.p. 109−112°C. − ^{1}H NMR ($CDCl_3$): δ = 1.15−1.35 (m, 34 H), 1.4−1.6 (m, 4 H), 1.66 (m, 2 H) 1.96 (m, 2 H), 2.53 (t, J = 7.7 Hz, 2 H), 2.85 (t, J = 7.7 Hz, 2 H), 3.55 (t, J = 6.6 Hz, 2 H), 4.83 (t, J = 7.5 Hz, 2 H), 7.14 (dd, J = 7.8, 4.9 Hz, 1 H), 7.43 (d, J = 7.8 Hz, 1 H), 8.04 (dd, J = 7.8 Hz, 6.2 Hz, 1 H), 8.23 (br. d, J = 8.0 Hz, 1 H), 8.33 (m, 2 H), 9.15 (d, J = 6.0 Hz, 1 H), 9.22 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 25.63−32.80 (23 × CH_2), 61.64, 62.45, 123.2, 128.0, 135.8, 137.9, 142.1, 143.8, 144.1, 144.9, 146.8, 149.6.

26 *(From Reaction of* **22** *with* **20***):* Yield 78%, m.p. 102−105°C. − ^{1}H NMR ($CDCl_3$): δ = 1.1−1.35 (m, 36 H), 1.45−1.54 (m, 4 H), 1.66 (m, 2 H) 1.98 (m, 2 H), 2.53 (t, J = 7.7 Hz, 2 H), 2.85 (t, J = 7.7 Hz, 2 H), 3.55 (t, J = 6.6 Hz, 2 H), 4.85 (t, J = 7.5 Hz, 2 H), 7.15 (dd, J = 7.8, 4.9 Hz, 1 H), 7.44 (d, J = 7.8 Hz, 1 H), 8.05 (dd, J = 7.8 Hz, 6.2 Hz, 1 H), 8.23 (br. d, J = 8.0 Hz, 1 H), 8.33 (m, 2 H), 9.16 (d, J = 6.0 Hz, 1 H), 9.22 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 25.64−32.81 (24 × CH_2), 61.66, 62.50, 123.2, 128.0, 135.8, 137.9, 142.1, 143.8, 144.1, 144.8, 146.8, 149.6.

27 *(From Reaction of* **23** *with* **18***):* Yield 85%, m.p. 107−110°C. − ^{1}H NMR ($CDCl_3$): δ = 1.2−1.4 (m, 36 H), 1.52−1.57 (m, 4 H),

1.72 (m, 2 H), 2.04 (m, 2 H), 2.68 (t, J = 7.7 Hz, 2 H), 2.90 (t, J = 7.7 Hz, 2 H), 3.65 (t, J = 6.6 Hz, 2 H), 4.94 (t, J = 7.5 Hz, 2 H), 7.52 (dd, J = 7.8, 4.9 Hz, 1 H), 7.84 (d, J = 7.8 Hz, 1 H), 8.04 (dd, J = 7.8, 6.2 Hz, 1 H), 8.23 (br. d, J = 8.0 Hz, 1 H), 8.50 (m, 2 H), 9.16 (s, 1 H), 9.21 (d, J = 6.0 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 25.53−32.63 (24× CH_2), 61.76, 62.14, 123.2, 128.0, 135.8, 137.9, 142.0, 143.5, 144.2, 144.9, 146.8, 149.6.

28 *(From reaction of* **22** *with* **19***):* Yield 80%, m.p. 97−100°C. − ^{1}H NMR ($CDCl_3$): δ = 1.2−1.3 (m, 38 H), 1.45−1.55 (m, 4 H), 1.67 (m, 2 H) 1.98 (m, 2 H), 2.53 (t, J = 7.7 Hz, 2 H), 2.84 (t, J = 7.7 Hz, 2 H), 3.56 (t, J = 6.6 Hz, 2 H), 4.85 (t, J = 7.5 Hz, 2 H), 7.15 (dd, J = 7.8, 4.9 Hz, 1 H), 7.44 (d, J = 7.8 Hz, 1 H), 8.05 (dd, J = 7.8, 6.2 Hz, 1 H), 8.23 (br. d, J = 8.0 Hz, 1 H), 8.33 (m, 2 H), 9.17 (d, J = 6.0 Hz, 1 H), 9.21 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 25.65−32.82 (25 × CH_2), 61.68, 62.52, 123.2, 128.0, 135.8, 137.9, 142.1, 143.7, 144.1, 144.8, 146.8, 149.6.

29 *(From reaction of* **23** *with* **19***):* Yield 77%, m.p. 109−112°C. − ^{1}H NMR ($CDCl_3$): δ = 1.15−1.35 (m, 40 H), 1.45−1.55 (m, 4 H), 1.65 (m, 2 H) 1.98 (m, 2 H), 2.53 (t, J = 7.7 Hz, 2 H), 2.85 (t, J = 7.7 Hz, 2 H), 3.56 (t, J = 6.6 Hz, 2 H), 4.85 (t, J = 7.5 Hz, 2 H), 7.15 (dd, J = 7.8, 4.9 Hz, 1 H), 7.44 (d, J = 7.8 Hz, 1 H), 8.04 (dd, J = 7.8, 6.2 Hz, 1 H), 8.23 (br. d, J = 8.0 Hz, 1 H), 8.35 (m, 2 H), 9.16 (d, J = 6.0 Hz, 1 H), 9.20 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 25.64−32.82 (26 × CH_2), 61.69, 62.54, 123.2, 128.0, 135.8, 137.9, 142.1, 143.8, 144.1, 144.8, 146.8, 149.6.

Macrocylization Reactions: Cyclostellettamines A−F (**1**−**6**): The reactions were performed on a 1 to 2 mmol scale. Iodine (1.07 g, 4.2 mmol) was added to a vigorously stirred solution of one of the alcohols **24**−**29** (2.0 mmol), Ph_3P (1.13 g, 4.3 mmol) and imidazole (0.29 g, 4.3 mmol) in a mixture of toluene (12 ml) and acetonitrile (5 ml) at room temp. After 20 min the reaction mixture was diluted with PE 60/80 (30 ml), water (10 ml) and acetonitrile (15 ml) and transferred to a separatory funnel resulting, after mixing, in a 3-layer system. The upper layer, containing the excess Ph_3P and part of the Ph_3PO, was washed with a mixture of acetonitrile (4 ml) and water (2 ml). The combined lower layers were washed with a mixture of PE 60/80 (10 ml) and toluene (5 ml). The product was liberated from its HI salt by adding aqueous Na_2CO_3 to the two lower layers and after addition of EtOAc the layers were separated. The aqueous layer was extracted three times with EtOAc and the combined organic layers were washed with Na_2CO_3-solution and quickly dried with Na_2SO_4. After evaporation of the solvents (bath temperature < 30°C) the residue was immediately dissolved in acetonitrile (2 l) and refluxed during 44 h. Evaporation of the solvent and trituration of the solid residue with acetonitrile (ca 10 ml) gave the pure cyclostellettamines as their iodide salts. Additional amounts of product could be obtained by concentrating the filtrate. Recrystallization could be achieved from methanol or water/acetone.

Cyclostellettamine A (**1**): Yield 1.19 g (80%), m.p. 221−223°C. − ^{1}H NMR ($CDCl_3$ + 10% CD_3OD): δ = 1.1−1.3 (m, 32 H), 1.64 (m, 4 H), 1.94 (m, 4 H), 2.82 (t, J = 7.5 Hz, 4 H), 4.70 (t, J = 7.3 Hz, 4 H), 7.95 (m, 2 H), 8.19 (d, J = 8.0 Hz, 2 H), 8.86 (d, J = 6.0 Hz, 2 H), 9.18 (s, 2 H). − ^{13}C NMR ($CDCl_3$ + 10% CD_3OD): δ = 25.30, 28.07, 28.13, 28.27, 28.30, 28.41, 28.43, 28.47, 29.92, 31.42, 32.16, 61.57, 127.9, 141.8, 143.9, 144.3, 145.0. − IR (KBr): $\tilde{\nu}$ = 1626, 1501, 1468 cm^{-1}. − MS (FAB^+); *m/z* (%): 619 (100) [M^+ − I], 491 (38) [M^+ − I − HI]. − HRMS: found (M^+ − I) 619.3514, calcd for $C_{34}H_{56}IN_2$ 619.3488. − $C_{34}H_{56}I_2N$ (746.6): calcd. C 54.69, H 7.56, N 3.75; found C 54.81, H 7.49, N 3.86.

Cyclostellettamine B (**2**): Yield 76%, m.p. 221−223°C (from acetonitrile), 222−224°C (from methanol). − ^{1}H NMR ($CDCl_3$ + 10% CD_3OD): δ = 1.1−1.3 (m, 32 H), 1.57 (m, 4 H), 1.89 (m, 4 H), 2.77 (m, 4 H), 4.65 (m, 4 H), 7.91 (m, 2 H), 8.17 (m, 2 H), 8.86 (m, 2 H), 8.98 (br. s, 2 H). − ^{13}C NMR ($CDCl_3$ + 10% CD_3OD): δ = 25.35−32.24 (18 × CH_2), 61.55, 128.0, 141.8, 143.7, 144.1, 145.1, 145.15. − MS (FAB^+); *m/z* (%): 633 (100) [M^+ − I], 505 (78) [M^+ − I − HI]. − HRMS: (M^+ − I) found 633.3638, calcd for $C_{35}H_{58}IN_2$ 633.3645. − $C_{35}H_{58}I_2N_2$ (760.7): calcd. C 55.27, H 7.69, N 3.68; found C 55.15, H 7.62, N 3.68.

Cyclostellettamine C (**3**): Yield 83%, m.p. 233−236°C. − ^{1}H NMR ($CDCl_3$ + 10% CD_3OD): No chemical shift differences were observed compared with **1**. − ^{13}C NMR ($CDCl_3$ + 10% CD_3OD): δ = 25.54, 28.24, 28.51, 28.75, 28.82, 28.89, 28.95, 29.92, 31.28, 32.29, 61.72, 128.0, 141.9, 143.9, 144.1, 145.1. − MS (FAB^+); *m/z* (%): 773 (2) [M^+ − H], 647 (100) [M^+ − I], 519 (74) [M^+ − I − HI], 260 (23). − HRMS: found 647.3797, calcd for $C_{36}H_{60}IN_2$ 647.3801. − $C_{36}H_{60}I_2N_2$ (774.7): calcd. C 55.82, H 7.81, N 3.62; found C 55.76, H 7.79, N 3.52.

Cyclostellettamine D (**4**): Yield 77%, m.p. 188−192°C (from acetonitrile), 194−196°C (from methanol). − ^{1}H NMR ($CDCl_3$ + 10% CD_3OD): δ = 1.1−1.3 (m, 36 H), 1.67 (m, 4 H), 1.96 (m, 4 H), 2.85 (t, J = 7.6 Hz, 4 H), 4.70 (t, J = 7.4 Hz, 4 H), 7.94 (m, 2 H), 8.19 (m, 2 H), 8.78 (d, J = 6.0 Hz, 1 H), 8.82 (d, J = 6.0 Hz, 1 H), 9.03 (s, 1 H), 9.06 (s, 1 H). − ^{1}H NMR ([D_6]DMSO): δ = 1.0−1.35 (m, 36 H), 1.67 (m, 4 H), 1.92 (m, 4 H), 2.84 (m, 4 H), 4.70 (m, 4 H), 8.12 (dd, J = 7.9 Hz, 6.1 Hz, 2 H), 8.51 (d, J = 7.9 Hz, 2 H), 8.96 (d, J = 6.1 Hz, 2 H), 9.06 (s, 2 H). − ^{13}C NMR ([D_6]DMSO): δ = 24.84−31.35 (18 × CH_2, 60.54, 127.8, 142.80, 142.82, 143.8, 145.35, 145.4. − MS (FAB^+); *m/z* (%): 647 (97) [M^+ − I], 519 (100) [M^+ − I − HI], 260 (75). − MS (FAB^+, B/E 519); *m/z* (%): 246 (12), 274 (13). − HRMS: found (M^+ − I) 647.3820, calcd for $C_{36}H_{60}IN_2$ 647.3801. − $C_{36}H_{60}I_2N_2$ (774.7): calcd. C 55.82, H 7.81, N 3.62; found C 55.94, H 7.82, N 3.56.

Cyclostellettamine E (**5**): Yield 82%, m.p. 222−224°C. − ^{1}H NMR ($CDCl_3$ + 10% CD_3OD): δ = 1.1−1.4 (m, 38 H), 1.70 (m, 4 H), 2.00 (m, 4 H), 2.89 (m, 4 H), 4.77 (t, J = 7.3 Hz, 4 H), 7.99 (dd, J = 8.0 Hz, 6.1 Hz, 2 H), 8.21 (d, J = 8.0 Hz, 2 H), 8.92 (m, 2 H), 9.09 (m, 2 H). − ^{13}C NMR ($CDCl_3$ + 10% CD_3OD): δ = 25.38−32.27 (18 × CH_2, 61.63, 128.0, 141.9, 143.6, 144.0, 145.1, 145.2. − MS (FAB^+); *m/z* (%): 661 (100) [M^+ − I], 533 (43) [M^+ − I − HI]. − HRMS: found (M^+ − I) 661.3961, calcd for $C_{37}H_{62}IN_2$ 661.3958. − $C_{37}H_{62}I_2N_2$ (788.7): calcd. C 56.35, H 7.92, N 3.55; found C 55.38, H 7.77, N 3.54.

Cyclostellettamine F (**6**): Yield 87%, m.p. 227−231°C. − ^{1}H NMR ($CDCl_3$ + 10% CD_3OD): δ = 1.1−1.3 (m, 40 H), 1.65 (m, 4 H), 1.95 (m, 4 H), 2.81 (t, J = 7.4, 4 H), 4.71 (t, J = 7.1 Hz, 4 H), 7.96 (m, 2 H), 8.19 (m, 2 H), 8.86 (d, J = 5.9 Hz, 2 H), 8.95 (s, 2 H). − ^{13}C NMR ($CDCl_3$ + 10% CD_3OD): δ = 25.42−32.22 (12 × CH_2, 61.67, 128.0, 141.8, 143.6, 144.1, 145.1. − MS (FAB^+); *m/z* (%): 675 (100) [M^+ − I], 547 (43) [M^+ − I − HI], 274 (28). − HRMS: found (M^+ − I) 675.4088, calcd for $C_{38}H_{64}IN_2$ 675.4114. − $C_{38}H_{64}I_2N_2$ (802.7): calcd. C 56.86, H 8.04, N 3.49; found C 56.85, H 7.94, N 3.37.

Dimerization of 1-(3-Pyridyl)-3-octene-8-ol to **31**:[9] As described for the synthesis of **21**, iodine (2.08 g, 8.2 mmol) was added to a vigorously stirred solution of 1-(3-pyridyl)-3-octene-8-ol **30**[9] (0.82 g, 4.0 mmol), Ph_3P (2.23 g, 8.5 mmol) and imidazole (0.578 g, 8.5 mmol) in benzene (35 ml). After reaction with PMB-Cl (0.542 ml, 4.0 mmol) and potassium iodide (0.996 g, 6.0 mmol) the PMB-protected iodide (2.29 g, 100%) was obtained as an oil. − ^{1}H NMR ($CDCl_3$): δ = 1.17 (m, J = 7.5 Hz, 2 H), 1.58 (m, 2 H), 2.16 (m, 2 H), 2.86 (t, J = 7.3 Hz, 2 H), 3.02 (t, J = 6.9 Hz, 2 H), 3.69 (s, 3 H), 5.25 (m, 2 H), 6.01 (s, 2 H), 6.79 (d, J = 8.7 Hz, 2 H), 7.61 (d,

J = 8.7 Hz, 2 H), 7.89 (dd, J = 7.9, 6.2 Hz, 1 H), 8.16 (d, J = 7.9 Hz, 1 H), 9.17 (d, J = 8.7 Hz, 1 H), 9.35 (s, 1 H).

Reaction of this PMB-protected iodide (4.0 mmol) with alcohol **30** (0.82 g, 4.0 mmol) in refluxing acetonitrile (15 ml) during 22 h. gave the corresponding product, which after evaporation of the solvent, was deprotected by refluxing in pyridine (75 ml) during 20 h. The alcohol obtained after evaporation of the pyridine was converted to the iodide and macrocyclized as described for cyclostellettamine A using I_2 (2.29 g, 9.0 mmol), Ph_3P (2.4 g, 9.5 mmol) and imidazole (0.646 g, 9.5 mmol) in a mixture of toluene (20 ml) and acetonitrile (8 ml). Product **31** (1.55 g, 61% overall yield from **30**) was obtained as pale-white crystals from this macrocyclization reaction (2 mM in acetonitrile), m.p. 207−209°C. − ^{1}H NMR ($CDCl_3$ + 10% CD_3OD): δ = 1.35 (m, 4 H), 1.75 (m, 4 H), 2.06 (m, 4 H), 2.58 (q, J = 7.0 Hz, 4 H), 2.90 (t, J = 7.1 Hz, 4 H), 4.68 (m, 4 H), 5.34 (m, 4 H), 7.86 (dd, J = 7.9, 6.1 Hz, 2 H), 8.05 (d, J = 7.9 Hz, 2 H), 8.79 (d, J = 6.1 Hz, 2 H), 9.63 (s, 2 H). − ^{13}C NMR ([D_6]DMSO): δ = 25.04, 25.86, 27.91, 30.82, 31.30, 60.36, 127.3, 127.4, 130.9, 142.2, 144.2, 143.2, 145.8.

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