Pergamon

Tetrahedron, Vol. 52, No. 33, pp. 10849-10860, 1996
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0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00628-X

Total Synthesis of Cyclostellettamine C, a Bispyridinium Macrocyclic Alkaloid Having Muscarinic Acetylcholine Receptor Antagonistic Activity

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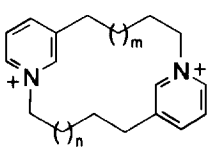
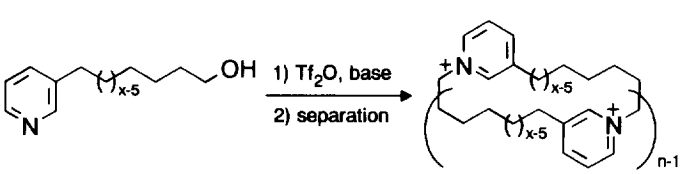
Abstract: Cyclostellettamine C (**1**), a bispyridinium macrocyclic compound having muscarinic acetylcholine receptor antagonistic activity, was synthesized by the stepwise ring closure method *via* 3-(13-hydroxytridecyl)-1-[13-(3-pyridyl)tridecyl]pyridinium trifluoromethanesulfonate (**21**). Through this study, the structure of naturally originating **1** was synthetically and biologically confirmed.Copyright © 1996 Published by Elsevier Science Ltd

Bioactive alkaloids of natural sources have been well investigated for drug serendipity; some pyridinium compounds have been discovered from marine sponges.[1] Previously, we reported that novel macrocyclic pyridinium alkaloids, cyclostellettamines A-F, were isolated as muscarinic acetylcholine receptor antagonists.[2] Cyclostellettamines consist of two 1,3-disubstituted pyridinium moieties linked to long aliphatic chains.



cyclostellettamines A-F
(m,n=9,10,11)
1: m=n=10

Faulkner and coworkers isolated polymeric pyridinium compounds from marine sponges as activators of epidermal growth factor (EGF).[3] In order to confirm their structures, they synthesized the cyclic pyridinium dimer, trimer, tetramer, and oligomer, in which hydroxyalkylpyridines were cyclized under high concentration conditions (330 mM), and each cyclic oligomer was chromatographically isolated (Scheme 1). In this case, however, the mass-to-charge ratios of the oligomers $(C_xH_yN^+)_n$ are the same overall values of n.

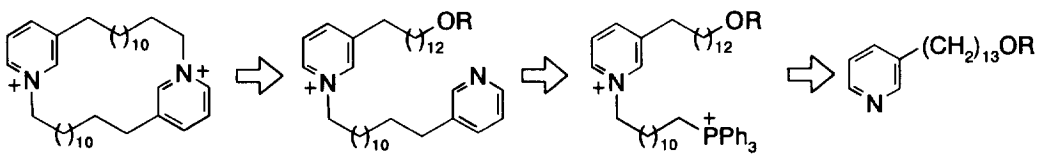


Scheme 1

We also attempted to confirm the proposed structures of cyclostellettamines by the synthesis of cyclostellettamine C (**1**), the major compound of the cyclostellettamines, by a stepwise ring construction strategy. The synthetic compound was identical with natural cyclostellettamine C in several respects.

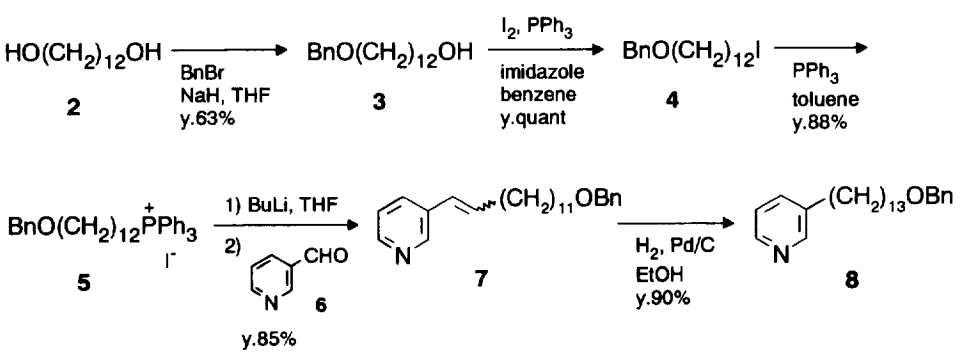
SYNTHESIS

Our strategy was as follows (Scheme 2); the ω-phosphonized alkyl group was connected to the nitrogen of the ω-O-protected alkylpyridine and condensed with the second pyridyl group by Wittig reaction. Cyclization was then performed under highly dilute conditions to avoid polymerization.



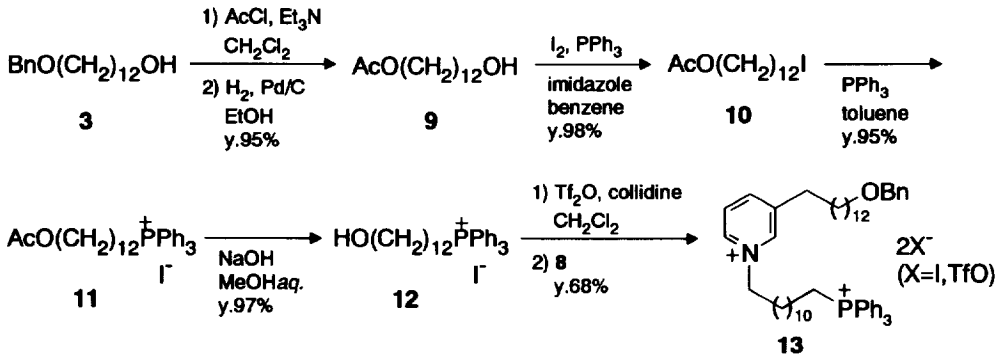
Scheme 2

12-Benzyloxydodecanol (**3**), which was obtained by monobenzylation of 1,12-dihydroxydodecane (**2**), was treated with I_2, PPh_3 and imidazole at rt to give iodide **4** in an excellent yield.[4] **4** was phosphonized by heating under reflux with PPh_3 in toluene. The phosphonium salt **5** thus obtained was treated with BuLi followed by nicotinaldehyde (**6**) in THF at -20 °C to give monoolefinic product **7**, which furnished 13-benzyloxytridecylpyridine (**8**) upon hydrogenation.



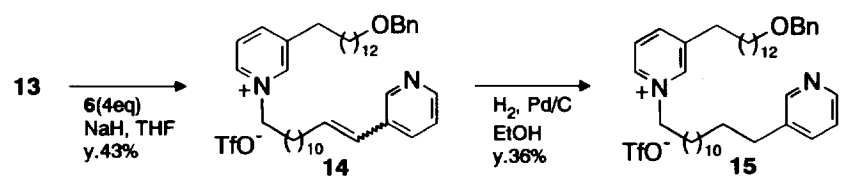
Scheme 3

For preparation of the other long chain, an acetyl group was chosen instead of the benzyl group in **3**. As shown in Scheme 4, the alcohol **9** was converted to 12-acetoxyphosphonium salt (**11**) in the same manner as described above. Saponification of **11** with NaOH in aqueous MeOH afforded alcohol **12**, which was condensed with benzyloxytridecylpyridine (**8**) by treating with Tf_2O and collidine in CH_2Cl_2 to give the pyridiniophosphonium salt **13**.[5]



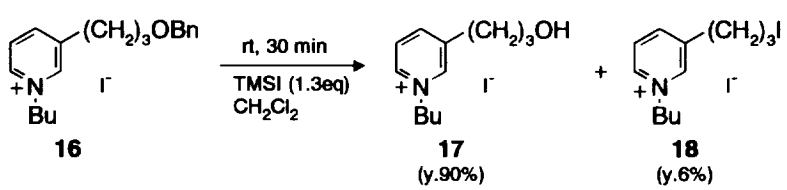
Scheme 4

Because the reactivity of the ylide generated from **13** was low, excess amounts of **6** were required (Scheme 5). An equivalent amount of **6** led to production of only diphenylphosphinoxide, which was produced by the hydration of the ylide. The use of 4 equivalents of **6** resulted in the desired vinylpyridine **14** in 43% yield.



Scheme 5

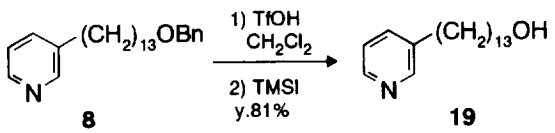
In spite of the fact that **14** had four reducible functional groups, namely a benzyl ether, an olefin, pyridine and pyridinium rings, catalytic hydrogenation of **14** on 10% Pd/C at rt over 85 min afforded **15** (36% yield).[6]



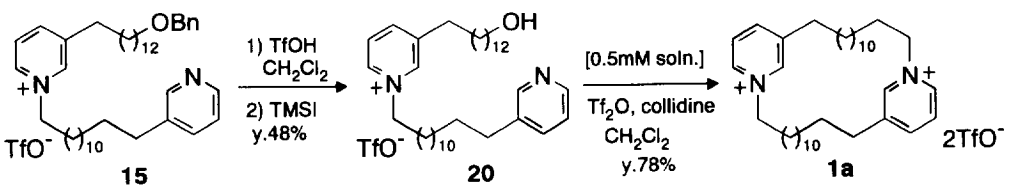
Scheme 6

The next problem was selective deprotection of a benzyl group of **15**. Reaction conditions were therefore examined with simple model compounds **8** and **16**. 1-Butyl-3-(3-benzyloxypropyl)pyridinium iodide (**16**) was easily deprotected with TMSI in CH_2Cl_2.[7] A large excess of TMSI and a longer reaction time converted the hydroxyl group to iodide. However, in the case of **8**, 13-hydroxytridecylpyridine (**19**) was produced in low yield

(<20%). Based on this result, it was thought that *N*-benzylation with benzyliodide might occur. This side reaction was, however, easily avoided by protonation of the basic pyridine nitrogen with TfOH; deprotection of **8** with TMSI at rt overnight furnished **19** in 81% yield (Scheme 7).[8] Similarly, intermediate **15** gave the desired alcohol **20** (Scheme 8).

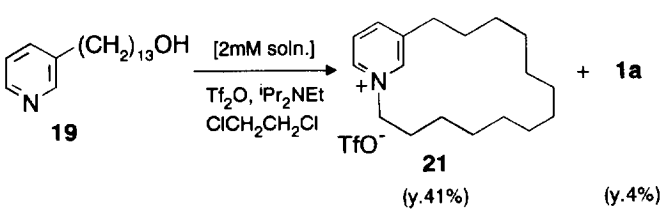


Scheme 7



Scheme 8

Ring closure in the final step was carried out under highly dilute conditions: the 0.5 mM solution of alcohol **20** in CH_2Cl_2 was treated with Tf_2O and collidine to yield **1·2(TfO) (1a)** in a good yield (78%). Also, **1·2(CF_3CO_2) (1b)** and **1·2Cl (1c)** was obtained using an anion exchange resin.



Scheme 9

In order to confirm the structure of **1a**, the mono-pyridinium cyclic compound **21** was synthesized; a 2 mM solution of 13-hydroxytridecylpyridine (**19**) in 1,2-dichloroethane was treated in the same manner to give **21** in 41% yield.

RESULTS AND DISCUSSION

As shown in Figure 1A, the dimeric compound **1a** revealed a base peak at *m/z* 669 which was assigned to

$[M+TfO]^+$ by high resolution FAB mass spectral analysis. Also, **1b** and **1c** revealed prominent peaks assigned to $[M+CF_3CO_2]^+$ (*m/z* 633) and $[M+Cl]^+$ (*m/z* 555), respectively. In the case of natural cyclostellettamine C (**1**), a base peak (*m/z* 519) and prominent peaks (*m/z* 633, 260) were observed, which were assigned to $[M-H]^+$, $[M+CF_3CO_2]^+$, and $[M/2]^+$, respectively.[9] Of course, synthetic **1a-c** revealed prominent peaks at *m/z* 260 and 519. Relative intensities of $[M-H]^+$ peaks vs $[M+X]^+$ peaks were 14%, 127%, and 97% for **1a**, **1b**, and **1c**, respectively. In this series, the $[M-H]^+$ ion was thought to be produced by a Hoffman-type elimination during the FAB ionization process.[2, 3] This result indicated that the $(M^{2+}+CF_3CO_2^-)$ ion pair caused a Hoffman-type elimination more easily than the $(M^{2+}+TfO^-)$ ion pair. Thus, natural cyclostellettamine C (**1**) might reveal a relatively weak prominent peak at *m/z* 633. In contrast, the monomeric compound **21** exhibited a prominent peak only at *m/z* 260 (Figure. 1D).

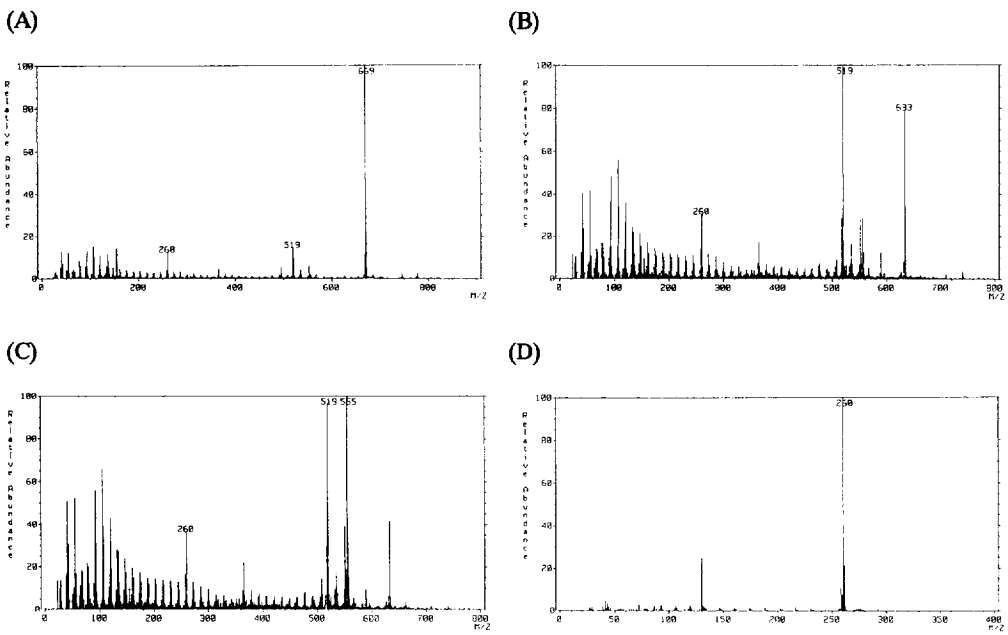


Fig. 1. Positive FAB-MS spectra of **1a** (A), **1b** (B), **1c** (C), and **21** (D).

Because natural cyclostellettamines[2] blocked the binding of [^{3}H]-methyl quinuclidinyl benzilate to muscarinic receptor subtypes M_1 (rat brain), M_2 (rat heart), and M_3 (rat salivary gland),[10] synthetic **1a** and related compounds **19**, **20** and **21** were examined in the same assay. As shown in Table 2, natural and synthetic **1** showed almost the same activity; whereas, synthetic derivatives **19**, **20** and **21** were less active. This demonstrated the structural identity of natural and synthetic **1**. **20** and **21** each have one positively charged pyridinium ion, which may be responsible for binding to the TM III (transmembrane helix III) Asp residue in the ligand-binding domain of muscarinic receptors as in the case of cyclostellettamines.[11]

Table. Antagonistic Activity of Synthetic and Natural Compounds for Muscarinic Receptors (IC_{50}: mean±SE, μg/mL).

	M_1	M_2	M_3
1a	0.090 ± 0.003	0.089 ± 0.015	0.195 ± 0.010
1 (natural)	0.121[a)]	0.054[a)]	0.144[a)]
19	4.007 ± 0.174	4.883 ± 0.169	3.307 ± 0.131
20	0.768 ± 0.014	1.090 ± 0.025	0.917 ± 0.036
21	1.707 ± 0.079	2.843 ± 0.042	2.947 ± 0.038

a) see reference 2.

In conclusion, the structure of **1** was synthetically and biologically confirmed. During this study, we found the relative compounds of **1**, which had positively charged pyridinium ions, showed muscarinic receptor binding affinity. However, their structure-activity relationships were not clear.

EXPERIMENTAL SECTION

All solvents except tetrahydrofuran were used without purification and dried on molecular sieves if necessary. Tetrahydrofuran was distilled over sodium benzophenone ketyl. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL GSX-400, GSX-500, or EX90 spectrometer using Me_4Si as an internal standard. GC mass spectra were recorded on a VG TRIO 1000 or HP 5890GC and 5970MSD in CI or EI mode, respectively. FAB and high-resolution mass spectra were recorded on JEOL DX-300 and VG ZAB-VSE mass spectrometers, respectively. UV spectra were measured with a Shimadzu UV-2200. Melting points were determined with a Yanaco MP-500D and were uncorrected. Elemental analysis was performed on a Yanaco MT-5. HPLC was carried out using a Hitachi L-6200 intelligent pump, L-4000 UV detector, D-2500 recorder and Shiseido CAPCELL PAK C_{18} SG120 (4.6 x 250 mm) or L-column ODS (4.6 x 250 mm). For thin-layer chromatography (TLC), Merck Silica gel 60 F_{254} precoated plates were used. For column chromatography, Wakogel C-200, Cosmosil 75C_{18}-opn, YMC-GEL ODS and Sephadex LH-20 were used. For anion exchange, Amberlite IRA-400 was used.

12-Benzyloxydodecanol (3). Sodium hydride (5.93 g, 247 mmol) was added to a solution of 1,12-dihydroxydodecane (**2**, 50 g, 247 mmol) in THF (800 mL) and the mixture was stirred at 40 °C for 80 min. Benzylbromide (14.7 mL, 124 mmol) was added to the mixture, and the mixture was heated at 60 °C for 19 h. After quenching with iced saturated NH_4Cl aqueous solution, the aqueous layer was extracted three times with

EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (EtOAc-hexane, 1:20 to 1:4) to give **3** (22.9 g, 63%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.1-1.7 (m, 21H), 3.46 (t, 2H, *J*=6.4 Hz), 3.66 (t, 2H, *J*=5.1 Hz), 4.50 (s, 2H), 7.33 (m, 5H); GC-MS (EI) 292 $(M)^+$; HRMS (EI) obsd. *m/z*=292.2396, $C_{19}H_{32}O_2$ requires *m/z* 292.2402.

Benzyl-12-iodododecylether (4). Imidazole (8.61 g, 126 mmol), triphenylphosphine (33.2 g, 127 mmol) and iodine (25.7 g, 101 mmol) were added to a solution of **3** (14.8 g, 50.6 mmol) in benzene (300 mL), and the mixture was stirred at ambient temperature for 30 min. To the reaction mixture was added saturated Na_2SO_3 aqueous solution until the yellow color disappeared. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (benzene-hexane, 1:10 then EtOAc-hexane, 1:3) to afford **4** (20.3 g, 100%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.1-1.9 (m, 20H), 3.18 (t, 2H, *J*=7.0 Hz), 3.46 (t, 2H, *J*=6.3 Hz), 4.50 (s, 2H), 7.3-7.4 (m, 5H); GC-MS (EI) 402 $(M)^+$; HRMS (EI) obsd. *m/z*=402.1424, $C_{19}H_{31}OI$ requires *m/z* 402.1420.

12-Benzyloxydodecyltriphenylphosphonium iodide (5). A solution of **4** (20.2 g, 50.1 mmol) and triphenylphosphine (12.5 g, 47.7 mmol) in toluene (200 mL) was heated to reflux for 18 h. After cooling to rt, hexane (50 mL) was added to the mixture. The lower layer was collected and concentrated to give **5** (27.7 g, 88%) as a colorless viscous syrup: ^{1}H NMR ($CDCl_3$) δ 1.1-1.7 (m, 20H), 3.46 (t, 2H, *J*=6.3 Hz), 3.5-3.8 (m, 2H), 4.49 (s, 2H), 7.3-7.3 (m, 5H), 7.7-8.0 (m, 15H); MS (FAB) 537 $(M)^+$; HRMS (FAB) obsd. *m/z*=537.3321, $C_{37}H_{46}OP$ requires *m/z* 537.3286.

3-(13-Benzyloxy-1-tridecenyl)-pyridine (7). 1.61 M BuLi in hexane (28.4 mL, 45.7 mmol) was added to a solution of **5** (27.6 g, 41.6 mmol) in THF (420 mL) at -20 °C and the mixture was stirred for 30 min at the same temperature. Nicotinaldehyde (4.11 mL, 43.7 mmol) and THF (50 mL) was then added to the mixture, which was stirred at the same temperature for 40 min and then warmed to 4 °C for 13 h. The reactant was quenched with ice and the organic layer was separated. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc-hexane, 1:5) to furnish **7** (*E,Z*-mixture, 13.0 g, 85%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.1-1.7 (m, 18H), 2.15-2.45 (m, 2H), 3.46 (t, 2H, *J*=6.3 Hz), 4.5 (s, 2H), 5.66-5.96 (m, 1H), 6.28-6.46 (m, 1H), 7.1-7.25 (m, 1H), 7.29-7.32 (m, 5H), 7.50-7.66 (m, 1H), 8.40-8.60 (m, 2H); GC-MS (EI) 365 $(M)^+$; HRMS (EI) obsd. *m/z*=365.2689, $C_{25}H_{35}NO$ requires *m/z* 365.2719.

3-(13-Benzyloxytridecyl)pyridine (8). A mixture of **7** (12.9 g, 35.3 mmol), 10% Pd/C (646 mg) and EtOH (650 mL) was stirred vigorously under a H_2 atmosphere. After absorption of a theoretical amount of H_2, the mixture was filtered and concentrated. The residue was purified by silica gel column chromatography (EtOAc-hexane, 1:5) to give **8** (11.7 g, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.05-1.7 (m, 22H), 2.60 (t, 2H, *J*=8.0 Hz), 3.46 (t, 2H, *J*=6.4 Hz), 4.50 (s, 2H), 7.15 (d, 1H, *J*=8.0 Hz), 7.29-7.35 (m, 5H), 7.48 (dt, 1H, *J*=2.0, 8.0), 8.38-8.50 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 26.14, 29.09, 29.34, 29.42, 29.47, 29.52, 29.71, 31.06, 32.94, 70.47, 72.78, 123.14, 127.37, 127.53, 128.24, 135.69, 137.90, 138.67, 147.06, 149.88; MS (FAB) 368 $(M+H)^+$; HRMS (EI)

obsd. *m/z*=367.2837, $C_{25}H_{37}NO$ requires *m/z* 367.2875.

12-Hydroxydodecylacetate (9). Acetylchloride (0.806 mL, 11.3 mmol) was added to a solution of **3** (3.0 g, 10.3 mmol) in CH_2Cl_2 (30 mL), and triethylamine (1.58 mL, 11.3 mmol) in CH_2Cl_2 (5 mL) was added to the mixture at 4°C. After stirring at rt for 90 min, the reaction was quenched by the addition of ice-water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (EtOAc-hexane, 1:20) to give 12-benzyloxydodecylacetate (3.31 g, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.1-1.75 (m, 20H), 2.04 (s, 3H), 3.47 (t, 2H, *J*=6.4 Hz), 4.05 (t, 2H, *J*=6.5 Hz), 4.5 (s, 2H), 7.33 (s, 5H); GC-MS (CI) 335 $(M+H)^+$; HRMS (EI) obsd. *m/z*=334.2472, $C_{21}H_{34}O_3$ requires *m/z* 334.2508.

A mixture of the above ester (3.24 g, 9.69 mmol), 10% Pd/C (160 mg), and EtOH (130 mL) was stirred vigorously under a H_2 atmosphere. After absorption of a theoretical amount of H_2, the mixture was filtered and concentrated to give **9** (2.34 g, 99%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.1-1.8 (m, 21H), 2.04 (s, 3H), 3.64 (q, 2H, *J*=5.5 Hz), 4.05 (t, 2H, *J*=6.5 Hz); GC-MS (CI) 245 $(M+H)^+$; HRMS (EI) obsd. *m/z*=245.2121, $C_{14}H_{29}O_3$ requires *m/z* 245.2117.

12-Iodododecylacetate (10). This was prepared in the same manner as described above for **4** in a 98% yield (a slightly yellowish oil): ^{1}H NMR ($CDCl_3$) δ 1.2-2.0 (m, 20H), 2.04 (s, 3H), 3.19 (t, 2H, *J*=7.0 Hz), 4.05 (t, 2H, *J*=6.5 Hz); GC-MS (CI) 355 $(M+H)^+$; HRMS (EI) obsd. *m/z*=355.1121, $C_{14}H_{28}O_2I$ requires *m/z* 355.1134.

12-Acetoxydodecyltriphenylphosphonium iodide (11). This was prepared in the same manner as described above for **5** in a 95% yield (a colorless oil): ^{1}H NMR ($CDCl_3$) δ 1.1-1.9 (m, 20H), 2.03 (s, 3H), 3.48-3.85 (m, 2H), 4.04 (t, 2H, *J*=6.4 Hz), 7.65-8.05 (m, 15H); MS (FAB) 489 $(M)^+$; HRMS (FAB) obsd. *m/z*=489.2894, $C_{32}H_{42}O_2P$ requires *m/z* 489.2922.

12-Hydroxydodecyltriphenylphosphonium iodide (12). A solution of **11** (5.92 g, 9.60 mmol) and 1 M NaOH (10.1 mL) in MeOH (59 mL) was stirred at rt for 140 min. 1 M HCl (0.48 mL) was then added to the solution and the solution was concentrated. The residue was purified by silica gel (inactivated with 6%w/w water) column chromatography ($CHCl_3$-MeOH, 20:1) to give **12** (5.35 g, 97%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.0-1.8 (m, 21H), 3.4-3.85 (m, 4H), 7.5-8.0 (m, 15H); MS (FAB) 447 $(M)^+$; HRMS (FAB) obsd. *m/z*=447.2859, $C_{30}H_{40}OP$ requires *m/z* 447.2817.

3-(13-Benzyloxytridecyl)-1-[(12-triphenylphosphonio)dodecyl]pyridinium (13). Tf_2O (2.56 mL, 15.3 mmol) and collidine (2.02 mL, 15.3 mmol) were added to a solution of **12** (6.8 g, 11.8 mmol) in CH_2Cl_2 (60 mL), and **8** (4.35 g, 11.8 mmol) in CH_2Cl_2 (10 mL) was added to the mixture. The solution was stirred at rt for 75 min and then at 30 °C for 90 min. MeOH (30 mL) was added to the solution at 4 °C, to which Na_2SO_3 was added, and the mixture was stirred at rt for 30 min. After filtration and concentration, the residual mixture was purified by silica gel (inactivated with 15%w/w water) column chromatography ($CHCl_3$-MeOH-NH_3aq, 100:10:1) to give **13** (7.39 g, 68%[5]) as a yellowish viscous syrup: ^{1}H NMR ($CDCl_3$) δ 1.16-1.40 (m, 32H), 1.52-1.72 (m, 8H), 2.00 (m, 2H), 2.85 (t, 2H, *J*=8.1 Hz), 3.23-3.32 (m, 2H), 3.46 (t, 2H, *J*=6.6 Hz), 4.49 (s, 2H), 4.67 (t, 2H, *J*=7.8 Hz), 7.25-7.35 (m, 5H), 7.63-7.84 (m, 15H), 7.96 (dd, 1H, *J*=6.1, 7.8 Hz), 8.18 (d, 1H, *J*=7.8 Hz), 8.94 (d, 1H, *J*=6.1 Hz),

8.98 (s, 1H); MS (FAB) 796 $(M-H)^+$, 946 $(M+TfO)^+$; HRMS (FAB) obsd. *m/z*=796.5591, $C_{55}H_{75}NOP$ requires *m/z* 796.5586; obsd. *m/z*=946.5180, $C_{56}H_{76}NO_4F_3PS$ requires *m/z* 946.5185.

3-(13-Benzyloxytridecyl)-1-[13-(3-pyridyl)tridec-12-enyl]pyridinium Trifluoromethanesulfonate (14). **13** (817 mg, 0.747 mmol) in THF (7.5 mL) was added to a mixture of sodium hydride (54 mg, 2.24 mmol) and THF (7.5 mL)at -20 °C, and **6** (0.281 mL, 2.99 mmol) was added to the mixture. The mixture was stirred at rt for 16 h and then at 30 °C for 3 h. The reaction was quenched by the addition of saturated NH_4Cl aqueous solution at 4 °C and extracted with EtOAc. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ twice. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by reversed phase column chromatography (MeOH-H_2O, 9:1) followed by LH-20 gel column chromatography (MeOH) to afford **14** (249 mg, 43%) as a slightly yellowish oil: ^{1}H NMR ($CDCl_3$) δ 1.00-1.52 (m, 30H), 1.55-1.73 (m, 6H), 1.95-2.02 (m, 2H), 2.10-2.30 (m, 4H), 2.84 (t, 2H, *J*=7.6 Hz), 3.46 (t, 2H, *J*=6.8 Hz), 4.50 (s, 2H), 4.97 (t, 2H, *J*=7.3 Hz), 5.77-5.82 (m, 1H), 6.30-6.36 (m, 1H), 7.10-7.38 (m, 6H), 7.55-7.66 (m, 1H), 7.84, 7.98 (dd, 1H, *J*=6.1, 7.6 Hz), 8.11, 8.15 (d, 1H, *J*=7.6 Hz), 8.43, 8.52 (br, 2H), 9.11, 9.17 (s, 1H), 9.37, 9.42 (d, 1H, *J*=6.1 Hz); MS (FAB) 625 $(M)^+$; HRMS (FAB) obsd. *m/z*=625.5087, $C_{43}H_{65}N_2O$ requires *m/z* 625.5097.

3-(13-Benzyloxytridecyl)-1-[13-(3-pyridyl)tridecyl]pyridinium Trifluoromethanesulfonate (15). A mixture of **14** (53.0 mg, 68.5 μmol), 10% Pd/C (5 mg) and EtOH (5 mL) was stirred vigorously under a H_2 atmosphere for 85 min. After filtration and concentration, the residue was purified by reversed phase column chromatography (MeOH-H_2O, 9:1) to give **15** (19.0 mg, 36%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.05-1.40 (m, 34H), 1.55-1.72 (m, 8H), 2.01 (quint., 2H, *J*=7.3 Hz), 2.62 (t, 2H, *J*=7.6 Hz), 2.86 (t, 2H, *J*=7.9 Hz), 3.46 (t, 2H, 6.7 Hz), 4.50 (s, 2H), 4.98 (t, 2H, *J*=7.3 Hz), 7.23-7.37 (m, 6H), 7.55 (d, 1H, *J*=7.3 Hz), 7.99 (dd, 1H, *J*=5.5, 7.9 Hz), 8.17 (d, 1H, *J*=7.9 Hz), 8.40-8.50 (br, 2H), 9.09 (s, 1H), 9.43 (d, 1H, *J*=5.5 Hz); ^{13}C NMR ($CDCl_3$) δ 26.14, 26.21, 29.06, 29.26, 29.32, 29.44, 29.49, 29.59, 29.78, 30.44, 31.02, 32.09, 32.82, 33.00, 62.09, 70.56, 72.87, 123.63, 127.47, 127.62, 127.92, 128.35, 136.64, 138.73, 143.05, 143.81, 144.18, 144.40, 144.40, 146.34, 149.06; MS (FAB) 627 $(M)^+$; HRMS (FAB) obsd. *m/z*=627.5241, $C_{43}H_{67}N_2O$ requires *m/z* 627.5253.

3-(13-Hydroxytridecyl)-1-[13-(3-pyridyl)tridecyl]pyridinium Trifluoromethanesulfonate (20). TfOH (11.8 μL, 134 μmol) was added to a solution of **15** (52.0 mg, 66.9 μmol) in CH_2Cl_2 (2 mL) at rt, followed by the addition of TMSI (19.0 μL, 134 μmol). After 1 h, TMSI (9.5 μL, 66.9 μmol) was again added to complete the reaction, and the mixture stirred for a further 1 h. MeOH (3 mL) and 40% $MeNH_2$ in MeOH (2 mL)[12] were added to the mixture, which was stirred at rt for 2 h. After concentration, the residue was purified by LH-20 gel column chromatography (MeOH) followed by reversed phase column chromatography (MeOH-H_2O, 9:1) to give **20** (22.0 mg, 48%) as a colorless amorphous solid: ^{1}H NMR ($CDCl_3$) δ 1.05-1.40 (m, 34H), 1.56 (quint., 4H, *J*=7.4 Hz), 1.62 (quint., 2H, *J*=7.3 Hz), 1.71 (quint., 2H, *J*=7.9 Hz), 2.02 (quint., 2H, *J*=7.3 Hz), 2.34 (br, 1H), 2.62 (t, 2H, *J*=7.6 Hz), 2.88 (t, 2H, *J*=7.7 Hz), 3.63 (t, 2H, 6.7 Hz), 4.98 (t, 2H, *J*=7.3 Hz), 7.27 (br, 1H), 7.57 (d, 1H, *J*=7.9 Hz), 8.03 (dd, 1H, *J*=5.5, 7.9 Hz), 8.20 (d, 1H, *J*=7.9 Hz), 8.46 (br, 2H), 9.13 (s, 1H), 9.41 (d, 1H, *J*=5.5 Hz); ^{13}C NMR ($CDCl_3$) δ 25.72, 26.09, 28.94, 29.02, 29.12, 29.28, 29.32, 29.40, 29.45, 30.37, 30.98, 32.05, 32.76,

32.96, 62.03, 62.81, 123.63, 127.93, 136.68, 138.53, 142.98, 143.87, 144.15, 144.41, 146.24, 148.94; MS (FAB) 537 $(M)^+$; HRMS (FAB) obsd. *m/z*=537.4797, $C_{36}H_{61}N_2O$ requires *m/z* 537.4784.

Cyclostellettamine C bis(trifluoromethanesulfonate) (1a). Collidine (16.7 μL, 127 μmol) and Tf_2O (21.3 μL, 127 μmol) were added to a solution of **20** (29 mg, 42.2 μmol) in CH_2Cl_2 (84 mL) at -20 °C. The solution was stirred at rt for 30 min and then at 30 °C for 30 min. MeOH was then added to the solution at 0 °C. The solution was concentrated and the residual oil was purified by LH-20 gel column chromatography (MeOH and then $CHCl_3$-MeOH, 1:1) to give **1a** (27 mg, 78%) as a colorless amorphous solid: mp 123-124 °C (crystallized from EtOAc-hexane); ^{1}H NMR ($CDCl_3$) δ 1.20-1.38 (m, 36H), 1.71 (m, 4H), 2.00 (m, 4H), 2.88 (t, 4H, *J*=7.3 Hz), 4.65 (t, 4H, *J*=7.1 Hz), 7.97 (dd, 2H, *J*=5.9, 7.8 Hz), 8.23 (d, 2H, *J*=7.8 Hz), 8.72 (d, 2H, *J*=5.9 Hz), 8.81 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 25.66, 28.22, 28.29, 28.38, 28.42, 28.51, 29.28, 29.50, 30.07, 31.71, 32.66, 62.25, 120.82 (*J*=313 Hz), 127.89, 141.81, 144.40, 144.71, 144.90; MS (FAB) 260 $(M/2)^+$, 519 $(M-H)^+$, 669 $(M+TfO)^+$; HRMS (FAB) obsd. *m/z*=519.4655, $C_{36}H_{59}N_2$ requires *m/z* 519.4678; obsd. *m/z*=669.4277, $C_{36}H_{60}N_2{\cdot}CF_3O_3S$ requires *m/z* 669.4277; UV (MeOH) λ_{max} 266 nm (ε 6230). *Anal.* Calcd. for $C_{38}H_{60}N_2O_6F_6S_2$: C, 55.73; H, 7.38; N, 3.42; F, 13.92; S, 7.83. Found: C, 55.18; H, 7.21; N, 3.47; F, 13.95; S, 8.08.

1·2(CF_3CO_2) (1b). HRMS (FAB) obsd. *m/z*=519.4699, $C_{36}H_{59}N_2$ requires *m/z* 519.4678; obsd. *m/z*=633.4620, $C_{36}H_{60}N_2{\cdot}CF_3CO_2$ requires *m/z* 633.4607.

1·2Cl (1c). HRMS (FAB) obsd. *m/z*=519.4708, $C_{36}H_{59}N_2$ requires *m/z* 519.4678; obsd. *m/z*=555.4448, $C_{36}H_{60}N_2{\cdot}Cl$ requires *m/z* 555.4445.

3-(13-Hydroxytridecyl)pyridine (19). TfOH (0.217 mL, 2.45 mmol) and TMSI (0.413 mL, 2.90 mmol) were added to a solution of **8** (820 mg, 2.23 mmol) in CH_2Cl_2 (30 mL) and stirred at rt for 13 h. The reactant was poured into MeOH (30 mL) to quench the reaction. Anhydrous Na_2SO_3 was added, and the mixture was stirred at rt for 30 min. After filtration, 40% $MeNH_2$ in MeOH (6 mL)[12] was added, and the mixture stirred at rt for 30 min. The reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (EtOAc-hexane, 1:5 to 1:1) to give **19** (500 mg, 81%) as colorless needles: mp 46-47 °C; ^{1}H NMR ($CDCl_3$) δ 1.20-1.40 (m, 18H), 1.53-1.66 (m, 4H), 1.82 (br, 1H), 2.60 (t, 2H, *J*=7.6 Hz), 3.64 (t, 2H, *J*=6.6 Hz), 7.20 (dd, 1H, *J*=4.9, 7.8 Hz), 7.49 (d, 1H, *J*=7.8 Hz), 8.44 (m, 2H); MS (FAB) 278 $(M+H)^+$; HRMS (EI) obsd. *m/z*=277.2417, $C_{18}H_{31}NO$ requires *m/z* 277.2406.

Cyclic monomer (21). Tf_2O (66 μL, 389 μmol) and $^iPr_2NEt$ (68 μL, 389 μmol) were added to a solution of **19** (83 mg, 299 μmol) in 1,2-dichloromethane (150 mL) at -20 °C. After stirring at the same temperature for 30 min then at rt for 3 h, Tf_2O (15 mL, 90 μmol) was added again. After 18 h, MeOH (2 mL) was added to the mixture, which was concentrated. The residue was purified by LH-20 gel column chromatography (MeOH) and reversed phase column chromatography (MeOH-H_2O, 9:1) to afford **21** (50 mg, 41%) and **1a** (9.8 mg, 4%). **21** (a colorless amorphous solid): ^{1}H NMR ($CDCl_3$) δ 1.08-1.32 (m, 18H), 1.80 (m, 2H), 2.06 (m, 2H), 2.96 (t, 2H, *J*=6.4 Hz), 4.94 (t, 2H, *J*=5.8 Hz), 8.05 (dd, 1H, *J*=6.1, 7.9 Hz), 8.26 (d, 1H, *J*=7.9 Hz), 8.98 (s, 1H), 9.29 (d, 1H, *J*=6.1

Hz); ^{13}C NMR ($CDCl_3$) d 24.08, 26.20, 26.26, 26.33, 26.76, 26.83, 26.88, 28.95, 30.58, 31.88, 61.79, 120.71 (*J*=320 Hz), 128.03, 142.96, 143.79, 144.12, 145.13; HRMS (FAB) obsd. *m/z*=260.2376, $C_{18}H_{30}N$ requires *m/z* 260.2378; UV (MeOH) λ_{max} 267 nm (ε 4100).

1-Butyl-3-(3-benzyloxypropyl)pyridinium iodide (16). A mixture of 3-(3-benzyloxypropyl)pyridine (3.3 g, 14.5 mmol), which was synthesized from 3-(3-hydroxypropyl)pyridine in a 67% yield in the same manner as **3**, and butyliodide (1.65 mL, 14.5 mmol) in THF (20 mL) was heated under reflux for 6 h. The reaction mixture was concentrated, and the residue was purified by silica gel column chromatography ($CHCl_3$-MeOH, 10:1) to give **16** (2.88 g, 48%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H, *J*=7.3 Hz), 1.16-1.55 (m, 2H), 1.80-2.25 (m, 4H), 3.06 (t, 2H, *J*=7.6 Hz), 3.56 (t, 2H, *J*=5.8 Hz), 4.47 (s, 2H), 4.84 (t, 2H, *J*=7.4 Hz), 7.20-7.40 (m, 5H), 7.95 (dd, 1H, *J*=6.3, 8.0 Hz), 8.25 (d, 1H, *J*=8.0 Hz), 9.14 (d, 1H, *J*=6.3 Hz), 9.18 (s, 1H); MS (FAB) 284 $(M)^+$; HRMS (FAB) obsd. *m/z*=284.2011, $C_{19}H_{26}NO$ requires *m/z* 284.2014.

1-Butyl-3-(3-hydroxypropyl)pyridinium iodide (17). The typical procedure is as follows: TMSI (0.22 mL, 1.58 mmol) was added to a solution of **16** (500 mg, 1.22 mmol) in CH_2Cl_2 (12 mL), and the mixture stirred at rt for 30 min. MeOH (12 mL) was added to the mixture, followed by the addition of Na_2SO_3. After stirring for 30 min, the reaction mixture was concentrated after filtration and purified by silica gel (deactivated with 6%w/w water) column chromatography ($CHCl_3$-MeOH, 10:1) to furnish **17** (351 mg, 90%) and **18** (31 mg, 6%). **17**: ^1H NMR (CD_3OD) δ 0.99 (t, 3H, *J*=6.8 Hz), 1.15-1.68 (m, 2H), 1.82-2.25 (m, 4H), 3.01 (t, 2H, *J*=7.9 Hz), 3.63 (t, 2H, *J*=6.2 Hz), 4.70 (t, 2H, *J*=7.6 Hz), 8.06 (dd, 1H, *J*=5.9, 8.0 Hz), 8.53 (d, 1H, *J*=8.0 Hz), 8.94 (d, 1H, *J*=5.9 Hz), 9.07 (s, 1H); MS (FAB) 194 $(M)^+$; HRMS (FAB) obsd. *m/z*=194.1561, $C_{12}H_{20}NO$ requires *m/z* 194.1545. **18**: ^1H NMR ($CDCl_3$) δ 0.99 (t, 3H, *J*=6.7 Hz), 1.21-1.70 (m, 2H), 1.78-1.50 (m, 4H), 3.11 (t, 2H, *J*=7.9 Hz), 3.25 (t, 2H, *J*=6.4 Hz), 4.93 (t, 2H, *J*=7.5 Hz), 8.05 (dd, 1H, *J*=5.8, 8.5 Hz), 8.36 (d, 1H, *J*=8.5 Hz), 9.13 (d, 1H, *J*=5.8 Hz), 9.43 (s, 1H); MS (FAB) 304 $(M)^+$; HRMS (FAB) obsd. *m/z*=304.0556, $C_{12}H_{19}NI$ requires *m/z* 304.0562.

ACKNOWLEDGMENT

We are grateful to Mr. Fukushi Hirayama and Mr. Jun-ichi Kazami for their kind advice and to the staff of the Division of Analytical Research Laboratory for the elemental analyses and spectral measurements.

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(*Received in Japan* 11 *April* 1996; *accepted* 1 *July* 1996)