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Synthesis of the Cytotoxic Sponge Metabolite Haliclamine A

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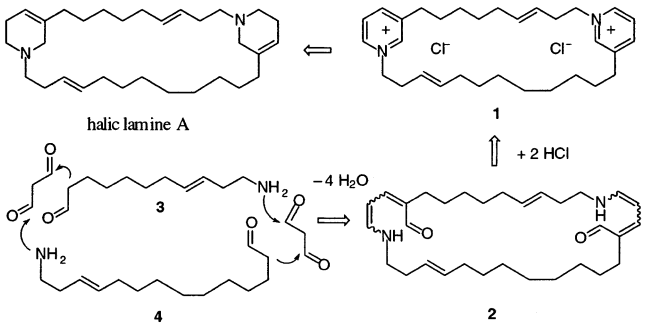
A new convergent and unified synthesis of the marine natural alkaloid haliclamine A is described. The synthesis of 3-alkylpyridine monomers **8** and **9** was first achieved from a common thiophene intermediate **5**. These syntheses make use of thiophene chemistry and the ability of cyclopropylcarbinols **20** and **21** to rearrange to the homoallylic bromides **22** and **23**, respectively. The Zincke procedure for the synthesis of pyridinium salts was then applied to the corresponding amino derivatives **8** and **9** to give efficiently unsymmetrical bis-pyridinium macrocycle **1**, whose reduction afforded haliclamine A.

Introduction

The bis-tetrahydropyridine macrocycle haliclamine A[1] (Scheme 1) was isolated from a sponge *Haliclona* sp. and reported to inhibit cell division of fertilized sea urchin eggs. It also possesses in vitro cytotoxicity against P388 leukemia cells with an IC_{50} value of 0.75 mg/mL. This alkaloid belongs to an original class of natural products produced by sponges in the order *Haplosclerida* ("manzamine family of alkaloids").[2] A likely precursor of haliclamine A is the bis-pyridinium macrocycle **1**, whose analogues, cyclostelletamines A−F, have also been isolated from sponges in the same order.[3] After the first biogenetic proposal published by Whitehead and Baldwin,[4a] it was recently proposed that the biosynthesis of these pyridinium salts can be the result of the cyclization, in acidic conditions, of aminopentadienal derivatives (e.g., intermediate **2** for haliclamine A).[5] Macrocycles such as **2** can result from condensation of two long-chain aminoaldehydes (**3** and **4**) with two three-carbon units possessing the oxidation degree of malondialdehyde. For experimental support favoring this biogenetic proposal, a synthetic approach to cyclostelletamines that partially mimics this process and makes use of the Zincke synthesis of pyridinium salts was reported.[4b]

SCHEME 1



Previous syntheses of haliclamine A involved access to bis-pyridinium macrocycle **1** via a stepwise condensation involving formation of pyridinium salts from mesylate derivatives, in the presence of KI, of appropriate 3-alkyl pyridines.[6] In this case, temporary protection of one pyridine ring as an *N*-oxide was necessary. Syntheses of bis-pyridinium macrocycles related to **1** have also been reported.[4f,7]

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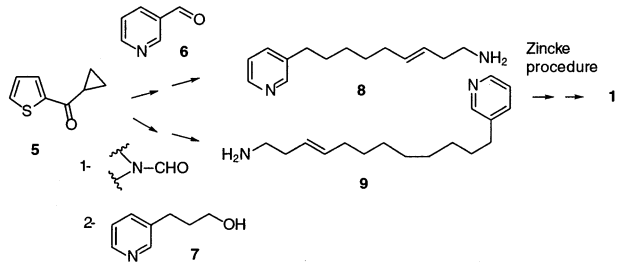
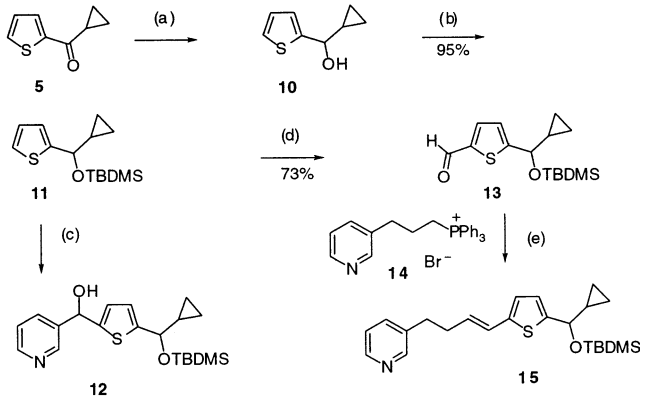
SCHEME 2



SCHEME 3[a]



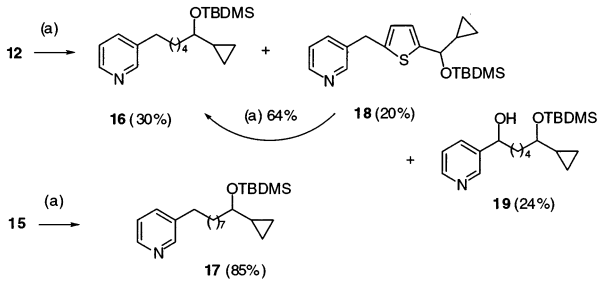
[a] Reagents and conditions: (a) $NaBH_4$, MeOH, rt (100% yield); (b) TBDMSCl, imidazole, DMF, rt (95% yield); (c) *n*-BuLi, THF, −78 °C, and then addition of nicotin aldehyde **6** (70% yield); (d) *n*-BuLi, THF, −78 °C, then formylpiperidine, 2.5 equiv (73% yield); (e) **14**, NaH, THF, 0 °C, then addition of **13** at −78 °C (55% yield).

In this paper, we describe a new synthesis of haliclamine A displaying two essential features (Scheme 2). The first is the synthesis, from a common and commercially available thiophene **5** and pyridines **6** or **7**, of 3-alkylpyridine derivatives **8** or **9**, respectively. The thiophene derivative **5** offered the advantages of being a four-carbon precursor of the alkyl side chain (reductive desulfurization of the thiophene ring),[8] as well as permitting access to the homoallylic primary amine moiety via opening of the cyclopropane ring according to a method originally described by Julia.[9] The second future is the easy construction from primary amines **8** and **9** of the bis-pyridinium macrocycle **1** by using our reported Zincke procedure.[4b]

Results and Discussion

Commercial cyclopropyl 2-thienyl ketone **5** (Scheme 3) was first reduced to alcohol **10** and then silylated to give protected derivative **11** in 95% overall yield. This thiophene derivative was deprotonated with *n*-BuLi in THF at −78 °C and allowed to react with nicotinaldehyde (**6**) to furnish the 3-alkylpyridine **12** (pyridine substituted by a nine-carbon side chain) in 70% yield. In principle, two diastereoisomeric derivatives were expected, but on the basis of the results of chromatography and NMR studies showing a single product, we could not firmly establish the stereoselectivity inferred for the reaction. Reaction of thiophene **11**, in the same conditions but using *N*-formylpiperidine instead of nicotinaldehyde, provided the aldehyde **13** in 95% yield. Wittig condensation of this last aldehyde with phosphonium salt **14**[10] led to the 3-alkylpyridine derivative **15** (12-carbon side chain) in 55% yield.

SCHEME 4[a]



[a] Reagents and conditions: (a) Na_2CO_3, Ni (Raney), EtOH, Δ.

With pyridines **12** and **15** in hand, we next explored their reduction to give cyclopropyl derivatives **16** and **17**, respectively (Scheme 4). This task proved to be nontrivial. Among the catalysts and reaction conditions used so far, reflux in ethanol with a large excess of Raney nickel and sodium bicarbonate was found to give the best results. Thus, treatment of pyridine **12** in the later conditions gave the desired reduced compound **16** but only in 30% yield due to the unavoidable formation of partially reduced species **18** and **19**. These compounds were easily separated by flash chromatography. While **18** was recycled into **16** by reduction under the same conditions, resulting in a 43% combined yield for **16**, alcohol **19** remained resistant to further reduction. This can be rationalized if one considers the bis-benzylic position of the alcohol position in **12** compared to the monobenzylic position of the corresponding alcohol in **19**. Removal of a similar hydroxyl group was achieved by Tanouchi et Al.[11] after acetylation or chlorination followed by reduction with $ZnCl_2$ in acetic acid, but the use of this procedure was also found to be unsuccessful for reduction of alcohol **19**. Reduction of this thiophen derivative **15** gave the desired product **17** in 85% yield.

Desilylation of pyridines **16** and **17**, using $BuNF_4$, gave alcohols **20** and **21** in 95 and 78% yields, respectively (Scheme 5). Homoallylic rearrangement of the obtained alcohols into the corresponding bromides is usually carried out by the Julia (HBr)[9] or Barton conditions ($MgBr_2$).[12] In our hands, the isomerization of cyclopropyl derivatives **20** and **21** was found to proceed better under the mild conditions described by Nefedov and co-workers.[13] Thus, treatment of **20** and **21** with Me_3SiBr in the presence of $ZnBr_2$ at −20 °C gave the rather unstable homoallylic bromides **22** and **23**, which reacted with sodium azide to produce the azido derivatives **24** and **25**,

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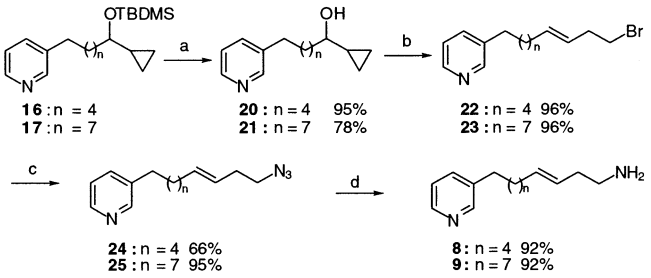
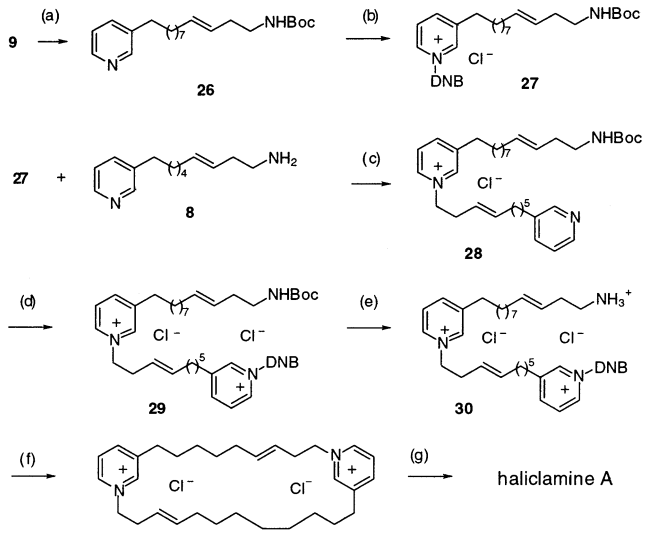
SCHEME 5[a]



[a] Reagents and conditions: (a) Bu_4NF, 6 equiv, THF, rt; (b) $ZnBr_2$, 0.5 equiv, TMSBr, 2.5 equiv, CH_2Cl_2, −20 °C; (c) NaN_3, 5 equiv, DMF, 60 °C; (d) PPh_3, 1.7 equiv, 0 °C, rt, overnight, then NH_2OH at 0 °C.

SCHEME 6[a]



[a] Reagent and conditions: (a) Boc_2O (93% yield); (b) 2,4-DNBCl, 3-equiv, MeOH, Δ, 48 h (80% yield); (c) *n*-BuOH, Δ, 15 min (88% yield); (d) 2,4-DNBCl, 3 equiv, MeOH, Δ, 48 h (74% yield); (e) CF_3CO_2H, 1 equiv, CH_2Cl_2, 1 h (100% yield); (f) Et_3N, *n*-BuOH, Δ (71% yield); (g) $NaBH_4$, $MeOH \cdot H_2O$ (68% yield).

respectively, in good yield. Finally, reduction of these derivatives, using triphenylphosphine at 0 °C, followed by treatment with ammonia, afforded primary amines **8** and **9**, respectively.

The next step was the synthesis, from these 3-alkylamino pyridine derivatives, of the bis-pyridinium macrocycle **1** (Scheme 6) using our reported methodology.[4b] The Boc-protected derivative **26** was first reacted with 1-chloro-2,4-dinitrobenzene to give the Zincke salt **27**. This salt, when treated with amine **8** in refluxing *n*-butanol, easily afforded the pyridinium salt **28** in 88% yield. After new activation of the pyridine ring of **28** as the Zincke salt **29**, deprotection of the primary amino group in acidic medium furnished the ammonium salt **30**. This salt was stable, but liberation of the amino group with triethylamine resulted in formation of a deep red color, indicating an attack of the Zincke salt by the primary amine function to give open chain intermediates. These intermediates were not isolated, but reflux of the crude mixture in *n*-butanol over 45 min gave, as expected, bis-pyridinium macrocycle **1** in 71% yield.

Finally, sodium borohydride reduction of salt **1**[5] gave haliclamine A in 68% yield. The spectroscopic data for the synthetic product were shown to be identical[14] in all respects to the data reported for haliclamine A.[1]

Conclusion

In conclusion, we have developed an efficient and convergent synthesis of haliclamine A **1**. Our new synthetic route employed a combination of thiophen and cyclopropyl chemistry. We have exploited simple and convenient synthetic methods for the convergent preparation of functionalized 3-alkylpyridines. This strategy offers some advantages over the existing methods, in particular easy purification and characterization of synthetic intermediates as well as the possibility of modulating the length of the side chains through the thiophen reactivity and the choice of the pyridine moiety. The Zincke procedure appears as a practical and selective approach to unsymmetrical *bis*-pyridinium macrocycles.

Experimental Section

{5-[(*tert*-Butyl-dimethyl-silanyloxy)-cyclopropyl-methyl]-thiophen-2-yl}-pyridine-3-yl Methanol (12). To a solution of silyl derivative **11** (20.14 g, 75.1 mmol) in THF (50 mL) was added dropwise, at −78 °C under N_2, *n*-BuLi (1.6 M in hexane, 50.1 mL, 75.1 mmol). The resulting mixture was stirred for 30 min at the same temperature, and 3-pyridinecarboxaldehyde (6.44 mL, 68.2 mmol) in THF (20 mL) was added dropwise. After the mixture was stirred for 1.5 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with AcOEt (4 × 100 mL). The organic layer was washed with H_2O (100 mL) and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was subjected to column chromatography (70/30 heptane/AcOEt) on silica gel to furnish the pyridine derivative **12** (17.81 g, 70% yield) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.05 (s, 3H), −0,03 (s, 3H), 0.07 (s, 3H), 0.32−0.57 (m, 4H), 0.89 (s, 9H), 1.15 (m, 1H), 3.86 (s, 1H), 4.47 (dd, J = 2, 7 Hz, 1H), 6.13 (s, 1H), 6.78 (dd, J = 1, 4 Hz, 1H), 6.86 (dd, J = 1, 4 Hz, 1H), 7.39 (m, 1H), 7.93 (m, 1H), 8.57 (m, 1H), 8.69 (d, J = 2 Hz); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ −4.8, −4.6, 2.7, 3.2, 18.2, 20.0, 25.8, 70.2, 73.5, 122.2, 123.3, 124.3, 134.1, 138.8, 145.4, 148.0, 148.8, 150.9; IR (neat) 3179, 2929, 2857, 1472, 1055, 939 cm^{-1}; MS (IC) *m*/*z* 376 (MH^+), 358 ($C_{20}H_{28}NOSSi^+$), 244 ($C_{14}H_{14}NOS^+$); HRMS (IC) calcd for $C_{20}H_{30}NO_2SSi$ (MH^+) 376.1767, found 376.1771.

5-[(*tert*-Butyl-dimethyl-silanyloxy)-cyclopropyl-methyl]-thiophen-2-carbaldehyde (13). To a solution of thiophene **11** (17.7 g, 66 mmol) in THF (100 mL) at 0 °C under N_2 was added dropwise *n*-BuLi (1.5 M in hexane, 46.2 mL, 69.3 mmol). The mixture was stirred for 30 min at the same temperature, and *N*-formylpiperidine (18.3 mL, 160 mmol) was added dropwise. After stirring at room temperature for 5 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl (250 mL) and extracted with AcOEt (3 × 250 mL). The organic layer was washed with water (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (98/2 heptane/AcOEt) on silica gel to afford aldehyde **13** (14.32 g, 73% yield) as a yellow paste: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.10 (s, 3H), 0.44−0.54 (m, 4H), 0.9 (s, 9H), 1.17 (m, 1H), 4.51 (d, J = 7 Hz, 1H), 7.08 (d, J = 4 Hz, 1H), 7.68, (d, J = 4 Hz, 1H), 9.9 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ −4.7, −4.4, 3.0, 3.5, 18.3, 20.3, 25.8, 73.7, 123.7, 136.5, 142.0, 162., 183.2; IR (neat) 2930, 2857, 1671, 1459 cm^{-1}; MS (IC) *m*/*z* 297 (MH^+), 183 ($C_9H_{11}SO_2^+$), 165 ($C_9H_9SO^+$), 137 ($C_8H_9S^+$).

(14) All complex structures were resolved by intensive NMR spectroscopy studies, including one- and two-dimensional NMR experiments (COSY 90, HMQC, HMBC).

3-[6-(*tert*-Butyl-dimethyl-silanyloxy)-6-cyclopropyl-hexyl]-pyridine (16). To a solution of pyridine derivative **12** (17.8 g, 47.4 mmol) in EtOH (500 mL) was added Na_2CO_3 (9 g) and a large excess of freshly prepared Raney nickel. After 2 h at reflux, another excess of Raney nickel was added and the mixture was refluxed for 2 days. The resulting mixture was decanted; the EtOH was collected and the catalyst washed with petroleum ether (2 × 100 mL), diisopropyl ether (3 × 100 mL), and CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification of the residue by column chromatography (85/15 heptane/AcOEt) on silica gel afforded pure derivative **16** (4.8 g, 30% yield) as a colorless oil, thiophene **18** (20% yield), and alcohol **19** (24% yield). Pyridine **16**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.09 (s, 3H), 0.15−0.46 (m, 4H), 0.92 (s, 9H), 1.27−1.72 (m, 4H), 2.59 (t, J = 8 Hz, 2H), 3.04 (m, 1H), 7.24 (dd, J = 5, 8 Hz, 1H), 7.52 (dt, J = 2, 8 Hz, 1H), 8.44 (m, 2H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ −4.4, −3.8, 2.3, 3.5, 17.5, 18.2, 25.3, 26.0, 29.4, 31.3, 33.1, 38.2, 76.2, 123.3, 135.8, 138.0, 147.3, 150.1; IR (neat) 2928, 2853, 1249, 1051, 834 cm^{-1}; MS (IC) m/z 334 (MH^+), 202 ($C_{14}H_{20}N^+$). Thiophene derivative **18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.05 (s, 3H), 0.06 (s, 3H), 0.32−0.59 (m, 4H), 0.88 (s, 9H), 1.05−1.32 (m, 1H), 4.13 (s, 2H), 4.43 (d, J = 7 Hz, 1H), 6.64 (dt, J = 1, 7 Hz, 1H), 6.84 (d, J = 5 Hz, 1H), 7.29 (dd, J = 1, 8 Hz, 1H), 7.64 (dt, J = 3, 14 Hz, 1H), 8.58 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ −4.7, −4.5, 2.8, 3.2, 18.3, 20.1, 25.8, 60.4, 73.5, 122.5, 123.5, 124.6, 136.0, 136.1, 140.8, 147.9, 149.3, 149.9; MS (IC) m/z 360 (MH^+), 228 ($C_{14}H_{14}NS^+$). Alcohol **19**: ^{1}H NMR (200 MHz, $CDCl_3$) δ −0.06 (s, 3H), 0.00 (s, 3H), 0.05−0.44 (m, 4H), 0.83 (s, 9H), 0.97−1.81 (m, 9H), 2.90 (q, J = 6 Hz, 1H), 4.57 (t, J = 7 Hz, 1H), 7.11 (dd, J = 5, 8 Hz, 1H), 7.57 (dt, J = 2, 8 Hz, 1H), 8.58 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ −4.5, −4.0, 2.2, 3.4, 17.2, 18.1, 25.3, 25.9, 39.2, 71.7, 76.1, 123.5, 134.0, 141.0, 147.4, 147.9; IR (neat) 3350, 2931, 1254, 1057, 836 cm^{-1}; MS (IC) m/z 350 (MH^+), 292 ($C_{17}H_{30}NOSi^+$), 218 ($C_{14}H_{20}NO^+$), 200 ($C_{14}H_{18}N^+$), 185 ($C_{11}H_{16}NO^+$). HRMS (MALDI) calcd for $C_{20}H_{35}NOSi$ (MH^+) 334.25662, found 334.25662.

1-Cyclopropyl-9-pyridin-3-yl-nonan-1-ol (21). Treatment of silyl derivative **17** under the conditions used for deprotection of **16** to **20** gave alcohol **21** (2.16 g, 78% yield) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.13−0.53 (m, 4H), 0.89 (m, 1H), 1.29−1.53 (m, 10H), 1.58 (m, 4H), 2.57 (t, J = 8 Hz, 2H), 2.86 (dt, J = 2, 8 Hz, 1H), 3.52 (s, 1H), 7.20 (dd, J = 5, 8 Hz, 1H), 7.51 (dt, J = 2,10 Hz, 1H), 8.42 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 2.1, 17.4, 25.4, 28.6, 28.9, 29.1, 29.3, 30.6, 32.5, 37.1, 75.3, 122.8, 135.4, 137.5, 146.3, 149.0; IR (neat) 3350, 2928, 2855, 1423, 1028, 713 cm^{-1}; MS (IC) m/z 262 (MH^+), 244 ($C_{17}H_{26}N^+$); HRMS (IC) calcd for $C_{17}H_{28}NO$ (MH^+) 262.2171, found 262,2200.

3-(9-Bromo-non-6-enyl)-pyridine (22). To a vigorously stirred suspension of alcohol **20** (2.66 g, 12 mmol) and $ZnBr_2$ (1.65 g, 6 mmol) in CH_2Cl_2 (10 mL) was added dropwise, at −20 °C under N_2, a solution of Me_3SiBr (4 mL, 30 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was kept at the same temperature for 15 min, treated at −10 °C with a saturated aqueous solution of $NaHCO_3$ (100 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo to yield the bromo-alkyl pyridine **22** (3.28 g, 96% yield) as a brown oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (m, 4H), 1.64 (q, J = 2 Hz, 2H), 2.07 (m, 2H), 2.62 (m, 4H), 3.41 (t, J = 5 Hz, 2H), 5,42 (dt, J = 4, 14 Hz, 1H), 5.56 (dt, J = 4, 14 Hz, 1H), 7.27 (dd, J = 3, 5 Hz, 1H), 7.56 (dt, J = 2, 8 Hz, 1H), 8.54 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 28.6, 29.0, 31.0, 32.4, 33.0, 36.0, 123.3, 126.8, 133.7, 135.8, 137.9, 147.3, 150.0; IR (neat) 2929, 2855, 1435, 1061, 970 cm^{-1}; MS (ESI) m/z 282 (MH^+).

3-(12-*tert*-Butoxycarbonylamino-dodec-9-enyl)-1-(2,4-dinitrophenyl)-pyridinium Chloride (27). A mixture of the protected amine **26** (425 mg, 1.2 mmol) and 1-chloro-2,4-dinitrobenzene (478 mg, 2.4 mmol) in MeOH (5 mL) was refluxed over 48 h. The solvent was evaporated, and the residue was purified by column chromatography (CH_2Cl_2 then 90/10 CH_2Cl_2/MeOH) on silica gel to afford the Zincke salt **27** (537 mg, 80% yield) as an orange powder: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.17−1.38 (m, 10H), 1.41 (s, 9H), 1.76 (m, 2H), 1.98 (m, 2H), 2.17 (m, 2H), 2.81 (t, J = 6 Hz, 2H), 3,12 (m, 2H), 4.62 (s, 1H), 5.38 (dt, J = 5, 18 Hz, 1H), 5.51 (dt, J = 5, 18 Hz, 1H), 8.29 (t, J = 5 Hz, 1H), 8.60 (m, 2H), 8.82 (d, J = 6 Hz, 1H), 9.10 (s, 1H), 9.67 (m, 1H), 9.83 (d, J = 4 Hz, 1H); ^{13}C NMR (69.82 MHz, $CDCl_3$) δ 28.4, 29.0, 29.3, 30.3, 32.5, 32.8, 33.1, 40.3, 121.9, 126.5, 128.0, 130.4, 132.6, 133.3, 138.5, 143.2, 144.0, 144.4, 145.0, 147.7, 149.2, 156.0; MS (ESI) m/z 527 (M − Cl)$^+$.

3-(12-*tert*-Butoxycarbonylamino-dodec-9-enyl)-1-(9-pyridin-3-yl-non-3-enyl)-pyridinium Chloride (28). To Zincke salt **27** (522 mg, 0.93 mmol) in *n*-BuOH was added dropwise, at 80 °C, the amine **8** (223 mg, 1.02 mmol). The resulting deep red solution was refluxed for 15 min. After removal of solvent, the residue was filtered over silica gel using a gradient of CH_2Cl_2/MeOH (from 100/0 to 85/15) to give salt **28** (488 mg, 88% yield) as a brown oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.12−1.37 (m, 14H), 1.44 (s, 9H), 1.52 (m, 2H), 1.67 (m, 2H), 1.86 (m, 2H), 1.96 (m, 2H), 2.15 (m, 2H), 2.56 (t, J = 6 Hz, 2H), 2.71 (m, 2H), 2.86 (t, J = 6 Hz, 2H), 3.12 (m, 2H), 4.61 (s, 1H), 5.06 (t, J = 5 Hz, 2H), 5.15−5.35 (m, 2H), 5.38−5.54 (m, 2H), 7.22 (dd, J = 3, 5 Hz, 1H), 7.45 (d, J = 5 Hz, 1H), 7.93 (t, J = 5 Hz, 1H), 8.13 (d, J = 5 Hz, 1H), 8.34 (m, 2H), 9.18 (s, 1H), 9.33 (d, J = 5 Hz, 1H); ^{13}C NMR (69.82 MHz, $CDCl_3$) δ 28.5, 29.1, 29.4, 30.6, 30.9, 32.3, 32.6, 32.9, 33.1, 35.0, 40.2, 61.0, 123.4, 126.6, 127.6, 133.2, 135.9, 136.3, 136.9, 143.1, 143.9, 144.0, 144.4, 147.3, 149.9, 156.0; IR (neat) 3369, 2928, 2855, 1698, 1365, 1174, 971 cm^{-1}; MS(ESI) m/z 562 [(M − Cl)$^+$], 253.5 [(M − C_4H_8 − ClH)$^{2+}$].

Zincke Salt 29. The salt **28** (445 mg, 0.74 mmol) and 1-chloro-2,4-dinitrobenzene (453 mg, 2.2 mmol) in MeOH (5 mL) were heated under reflux for 48 h. The solvent was evaporated. Filtration of the residue by column chromatography on silica gel using a gradient of CH_2Cl_2/MeOH (from 100/0 to 80/20) afforded the corresponding Zincke salt **29** (439 mg, 74% yield) as an orange powder: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12−1.37 (m, 14H), 1.42 (s, 9H), 1.59−1.79 (m, 4H), 1.89 (m, 2H), 1.95 (m, 2H), 2.15 (m, 2H), 2.66 (m, 2H), 2.84 (m, 2H), 2.96 (m, 2H), 3.08 (m, 2H), 4.63 (s, 1H), 4.89 (m, 2H), 5.23−5.37 (m, 2H), 5.40−5.52 (m, 2H), 8.06 (t, J = 4 Hz, 1H), 8.25 (d, J = 8 Hz, 1H), 8.34 (t, J = 4 Hz, 1H), 8.57 (d, J = 8 Hz, 1H), 8.64 (d, J = 8 Hz, 1H), 8.78 (d, J = 8 Hz, 1H), 9.08 (m, 1H), 9.23 (m, 1H), 9.35 (d, J = 4 Hz, 1H), 9.69 (m, 1H), 10.15 (m, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 27.6, 28.0, 28.5, 29.1, 29.4, 29.7, 30.6, 31.6, 32.6, 32.7, 33.1, 35.1, 40.3, 61.0, 122.0, 123.8, 126.5, 127.9, 128.0, 130.4, 132.6, 133.3, 135.6, 138.7, 143.1, 143.4, 143.9, 144.8, 145.6, 148.1, 149.2; IR (neat) 3382, 2928, 2855, 1694, 1345, 972, 733 cm^{-1}; MS(ESI) m/z 764 [(M − Cl)$^+$], 364.5 [(M − 2Cl)$^{2+}$].

Deprotected Zincke Salt 30. To Zincke salt **29** (245 mg, 0.31 mmol) dissolved in CH_2Cl_2 (5 mL) was added dropwise, at 0 °C, trifluoroacetic acid (24 mL, 0.31 mmol). After the mixture was stirred for 3 h at 0 °C, the solvent was evaporated to yield ammonium salt **30** (250 mg, quantitative yield) as a brown paste: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12−1.39 (m, 14H), 1.50−1.69 (m,4H), 1.74−1.95 (m, 4H), 2.23 (q, J = 6 Hz, 2H), 2.57 (m, 2H), 2.76 (t, J = 6 Hz, 2H), 2.83 (m, 4H), 4.57 (t, J = 6 Hz, 2H), 5.2−5.41 (m, 3H), 5.49−5.61 (m, 1H), 7.91 (t, J = 6 Hz, 1H), 8.18 (m, 2H), 8.34 (d, J = 6 Hz, 1H), 8.71 (m, 2H), 8.78 (m, 2H), 9.08 (d, J = 6 Hz, 1H), 9.17 (s, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 27.4, 27.9, 28.1, 28.2, 28.3, 28.4, 29.2, 29.6, 31.2, 31.6, 33.5, 38.5, 60.4, 121.1, 122.7, 123.1, 126.8, 127.1, 129.1, 130.6, 134.3, 135.1, 138.1, 141.3, 142.6, 143.1, 143.6, 143.8, 144.4, 144.6, 147.9, 149.0, 158.3, 158.8, 159.3, 159.8; IR (neat) 3071, 2933, 2860, 1782, 1349, 813, 705 cm^{-1}; MS (ESI) m/z 742 [(M − HCl − Cl)$^+$], 315 [(M − HCl − Cl − CF_3CO_2)$^{2+}$], 210 [(M − 2Cl − CF_3COO)$^{3+}$].

Bis-pyridinium Macrocycle 1. To refluxing *n*-BuOH (30 mL) were added, dropwise and simultaneously over a period of 0.5 h, a solution of salt **30** (250 mg, 0.31 mmol) in *n*-BuOH (3 mL) and a solution of Et_3N (0.2 mL, 1.5 mmol) in *n*-BuOH (3 mL). After the addition was complete, additional Et_3N (0.3 mL) was added and the mixture was further refluxed during 15 min. After removal of the solvent, the residue was purified by column chromatography over alumina (6 g) using a gradient of CH_2Cl_2/MeOH (from 100/0 to 90/10) to afford macrocycle **1** (112 mg, 71% yield) as a brown paste: ^{1}H NMR (300 MHz, CD_3OD) δ 0.92−1.38 (m, 14H), 1.52−1.72 (m, 4H), 1.77−1.94 (m, 4H), 2.65 (m, 4H), 2.72−2.87 (t, J = 8 Hz, 4H), 4.60 (m, 4H), 5.03−5.16 (m, 2H), 5.23−5.42 (m, 2H), 7.92 (t, J = 7 Hz, 2H), 8.35 (t, J = 7 Hz, 2H), 8.67 (m, 4H); ^{13}C NMR (75.47 MHz, CD_3OD) δ 29.8, 30.2, 30.4, 31.4, 31.7, 33.4, 35.1, 35.2, 62.1, 124.5, 124.7, 128.9, 137.3, 137.7, 143.2, 143.4, 144.9, 145.2, 145.3, 145.5, 146.4, 146.7; MS (ESI) m/z 481 [$(M - Cl)^+$], 223 [$(M - 2Cl)^{2+}$].

Haliclamine A. To a solution of bis-pyridinium salt **1** (56 mg, 0.11 mmol) in MeOH (35 mL) and H_2O (25 mL) was added, at 0 °C, an excess of $NaBH_4$. After stirring at 0 °C for 1 h and then at room temperature for 3 h, the mixture was concentrated in vaccuo. The residue was hydrolyzed with 1 M aqueous NaOH (50 mL) and extracted with CH_2Cl_2 (5 × 50 mL). After removal of the solvent, the crude product was purified by column chromatography over alumina using a gradient of heptane/AcOEt (from 100/0 to 80/20) to afford haliclamine A (33 mg, 68% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13−1.44 (m, 12H), 1.95 (m, 4H), 2.13 (m, 4H), 2.25 (m, 4H), 2.51 (m, 8H), 2.91 (m, 4H), 5.49 (m, 6H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 25.8, 25.8, 26.4, 27.5, 27.8, 28.1, 28.3, 28.9, 29.0, 29.2, 29.8, 30.7, 32.0, 32.2 (15C), 35.5 (2C), 50.2 (2C), 55.6, 55.8 (2C), 58.6 (2C), 119.0 (2C), 128.5, 128.6 (2C), 131.6, 131.7, 136.3, 136.4 (2C); HRMS (IC) calcd for $C_{31}H_{53}N_2$ (MH^+) 453.4208, found 453.4176.

Supporting Information Available: Experimental conditions for the preparation of compounds **8**−**11**, **15**, **17**, **20**, and **23**−**26** and copies of ^{1}H and ^{13}C NMR spectra of derivatives **1**, **8**−**13**, **15**−**30**, and haliclamine A with attribution of signals. This material is available free of charge via the Internet at http://pubs.acs.org.

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