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Total Syntheses of Macrocyclic Marine Alkaloids, Haliclamines A and B: A Convenient and Expeditious Assembly of 3-Substituted Pyridine Derivatives with Different Alkyl Chains to the Bispyridinium Macrocycle

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Abstract: The total syntheses of haliclamines A (**1**) and B (**2**), macrocyclic marine alkaloids closely related to the key bisdihydropyridine intermediate **3** of the biogenetically unique manzamine family, have efficiently been achieved via stepwise controlled inter- and intramolecular *N*-alkylations of 3-alkylpyridine derivatives such as **40** and **41**. The general synthetic methodology toward the bispyridinium macrocycle **44**, a key biogenetic equivalent of the polycyclic marine alkaloids, has been proposed through the total syntheses.

INTRODUCTION

Recently, an increasing number of structurally and bioactively unique macrocyclic alkaloids have been isolated from various marine sponges over the past decade.[1,2] Manzamine A, a β-carboline alkaloid having a novel heterocyclic system, is the primary and most representative member of these alkaloids.[3] Since Baldwin and Whitehead have proposed the fascinating biogenesis of the manzamines in 1992,[4] it has been suggested that a variety of alkaloids such as ingamine A,[5] xestocyclamine A,[6] madangamine A,[7] haliclonacyclamine A,[8] and halicyclamine A[9] may also be produced through the similar biogenetic pathway. The key feature of the biogenesis is an intramolecular Diels-Alder reaction of the bisdihydropyridine intermediate possessing various 3-alkyl chains linking the two heterocycles such as **3** (Fig. 1). The appearance of the hypothetical biogenesis has prompted extensive work directed toward the biomimetic synthesis of these alkaloids.[10–16]

Two kinds of biogenetically stimulating alkaloids have been isolated from different marine sponges by Fusetani *et al.* and their structures are most closely related to the key bisdihydropyridine intermediate **3** of macrocyclic alkaloids ever isolated. One type is cytotoxic haliclamines A (**1**) and B (**2**), isolated from a marine sponge of the genus *Haliclona*, consisting of two tetrahydropyridines linked through C_9 and C_{12} alkyl chains (Fig. 1).[17] Another type is cyclostellettamines A–F, isolated as muscarinic receptor binding inhibitors from the marine sponge *Stelletta maxima*, which are bispyridinium macrocycles linked through two C_{12}–C_{14} alkyl chains.[18,19] Therefore, the establishment of the synthetic methodology toward these alkaloids must give general access to the key bisdihydropyridine intermediate **3** with 3-alkyl chains variously bridging the two heterocycles. In this paper, we report total syntheses of haliclamines A (**1**) and B (**2**) through a convenient and expeditious assembly of 3-substituted pyridine derivatives with different alkyl chains to the bispyridinium macrocycle as a general approach to the key bisdihydropyridine intermediate **3**.[20]

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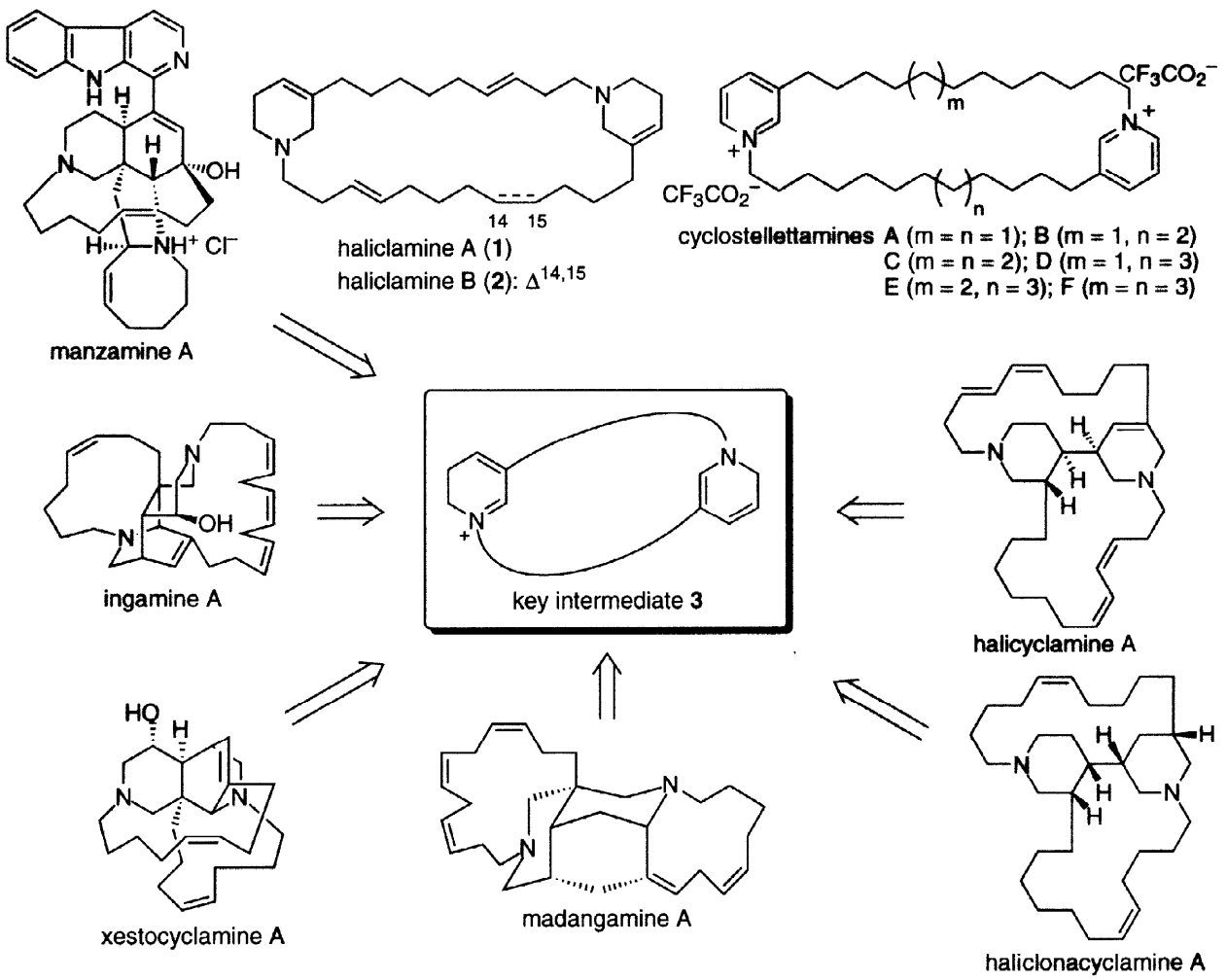
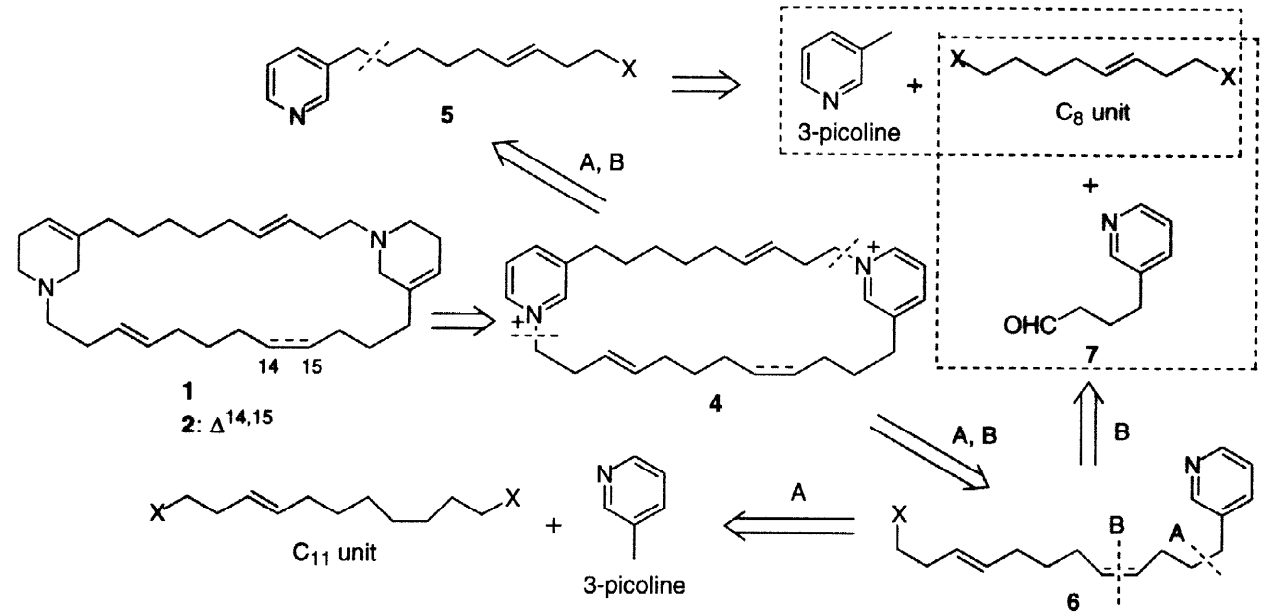


Fig. 1. Structurally unique macrocyclic alkaloids biogenetically originating from the bisdihydropyridine intermediate **3** with various 3-alkyl chains linking the two heterocycles.

RESULTS AND DISCUSSION

The retrosynthetic analyses of haliclamines A (**1**) and B (**2**) are outlined in Scheme 1. It is easily anticipated that **1** and **2** will be obtained by reduction of the bispyridinium macrocycle **4** as exemplified in many similar precedents.[10–15] The macrocycle **4** will be constructed by the convergent intermolecular *N*-alkylation of the two 3-alkylpyridine derivatives **5** and **6** followed by the intramolecular version. In the case of haliclamine A (**1**), the disconnections at the positions shown in **5** and **6** lead to simple 3-picoline and appropriate carbon chains (C_8 and C_{11} units, respectively). On the contrary, the 3-alkylpyridine derivatives **5** and **6** could be divided into 3-picoline, the known aldehyde **7**,[21] and the common C_8 unit to both **5** and **6** in the case of haliclamine B (**2**).

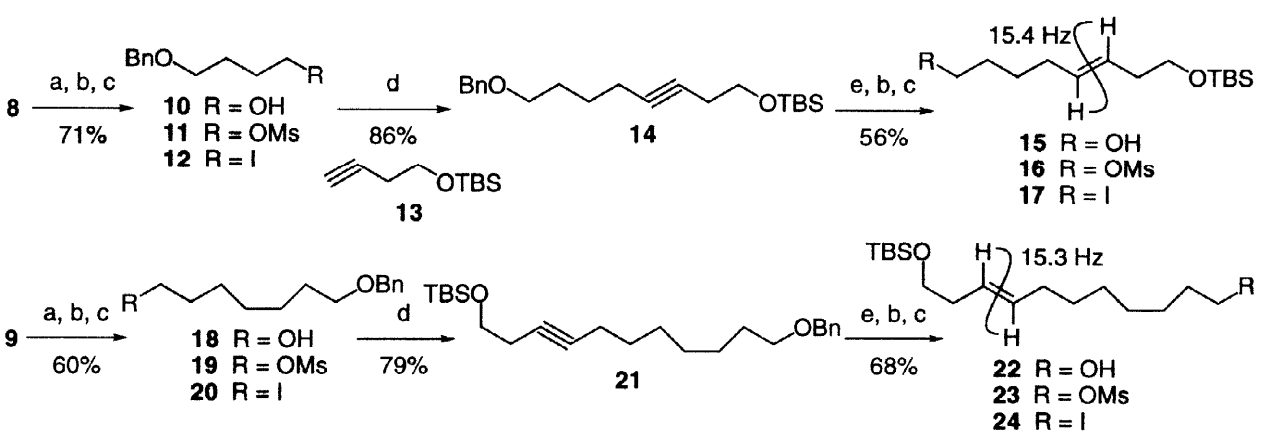
The preparation of alkyl chains **17** and **24** with *trans* disubstituted double bond corresponding to the C_8 and C_{11} units began with monoprotection of commercially available 1,4-butanediol (**8**) and 1,7-heptanediol (**9**), respectively (Scheme 2). The alkylation of iodide **12**, which was derived from the monobenzyl ether **10** via mesylation, with the lithium acetylide of **13**[22] in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU)–THF (1:1) as mixed solvent system[23] afforded acetylene **14** in 86% yield. The reduction of triple bond to *trans*



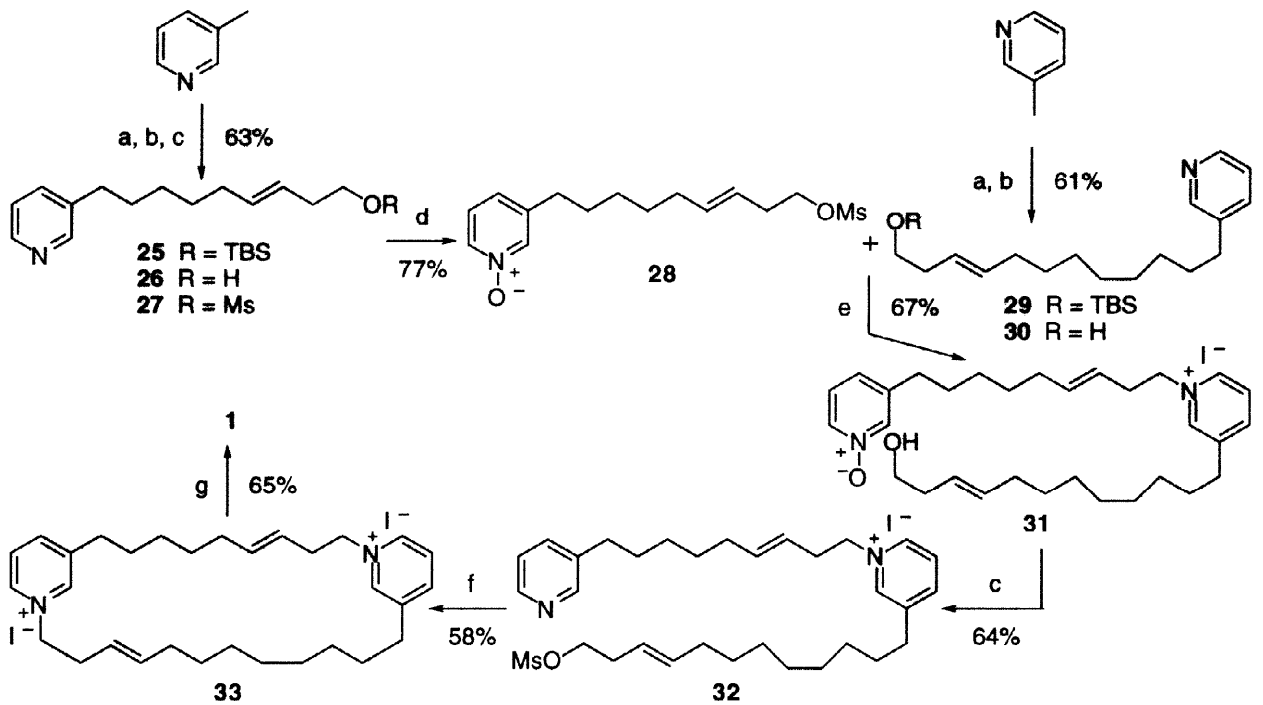
Scheme 1. Retrosynthetic analyses of halicalmines A (**1**) and B (**2**).

double bond and removal of the benzyl protective group in the acetylene **14** were simultaneously carried out by treatment with a large excess of metallic sodium in the presence of *t*-BuOH at –40 °C for a long time to stereoselectively yield *trans* olefin **15** as a single isomer. The stereochemistry of **15** could be secured by the coupling constant of 15.4 Hz between the olefinic protons in its ^{1}H NMR spectrum. The *trans* olefinic alcohol **15** was converted into the desired iodide **17** in the usual manner. The same sequence of reactions starting from 1,7-heptanediol (**9**) provided another favorable iodide **24** in comparable overall yields with the iodide **17**.

With the requisite alkyl chains **17** and **24** in hand, the next stage is preparation of 3-alkylpyridine derivatives **27** and **30** corresponding to **5** and **6**, respectively, and their convergent assembly (Scheme 3). Lithiation of 3-picoline was performed with lithium diisopropylamide in THF at –78 °C[24] and subsequent addition of the iodide **17** furnished the alkylated adduct **25** in good yield, which was converted to the mesylate **27** via



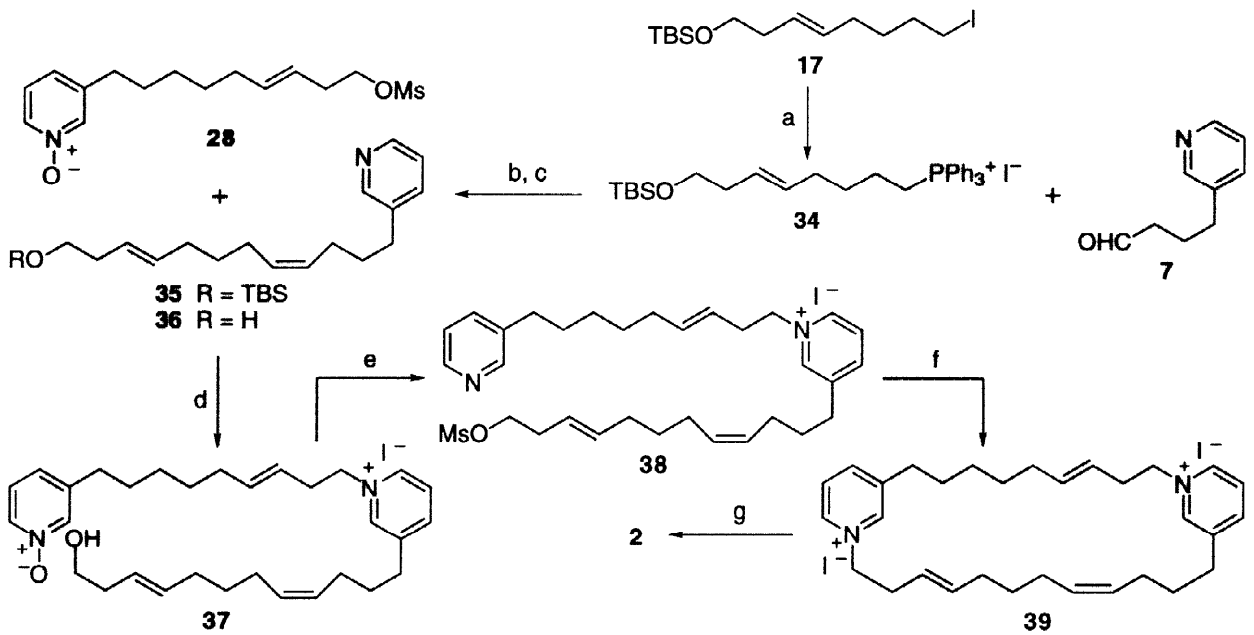
Scheme 2. Reagents and conditions: (a) NaH, BnBr, DMF, 0 °C → rt, 15 h; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (c) NaI, acetone, reflux, 3–4 h; (d) lithium acetylide of **13**, DMPU–THF (1:1), –15 °C, 30 min, then rt, overnight; (e) an excess of Na, *t*-BuOH, NH_3–Et_2O, –40 °C, 3–4 d.



Scheme 3. Reagents and conditions: (a) LDA, 3-picoline, THF, –78 °C, 20 min, then **17** or **24**, –78 °C → rt, 5–6 h; (b) AcOH–H_2O (3:2), rt, 2–3 h; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (d) *m*-CPBA, CH_2Cl_2, 0 °C, 2 h, then rt, 10 h; (e) KI, CH_3CN, reflux, 4 d; (f) KI, 1 mM of **32** in CH_3CN, reflux, 5 d; (g) $NaBH_4$, MeOH–H_2O (3:2), 0 °C → rt, 11 h.

deprotection of *t*-butyldimethylsilyl ether. To avoid self-polymerization or intramolecular *N*-alkylation of **27** in the face of coupling **27** with **30** prepared by the same way, the nucleophilic nitrogen functionality in **27** was protected as an *N*-oxide. The intermolecular *N*-alkylation of **30** with the *N*-oxide **28** in the presence of potassium iodide in refluxing acetonitrile[12] afforded the desired pyridinium alcohol **31** in 67% yield. The usual mesylation of hydroxyl group in **31** concurrently resulted in an expedient deoxygenation of the pyridine *N*-oxide for the next macrocyclization. The intramolecular *N*-alkylation of **32** in the presence of potassium iodide proceeded under high dilution conditions (1 mM solution of **32** in refluxing CH_3CN)[12,14,19b] to yield the ring closed bispyridinium macrocycle **33**. Finally, reduction of the bispyridinium **33** with sodium borohydride[25,26] gave the synthetic haliclamine A (**1**), the spectroscopic data of which was identical with the natural **1**[17] in all respects.

Since the total synthesis of haliclamine A (**1**) has been accomplished as shown in Scheme 3, the same methodology was applied to another target haliclamine B (**2**) (Scheme 4). The (*Z*)-selective Wittig olefination of the known aldehyde **7**[21] with the phosphonium salt **34** prepared from iodide **17**, followed by deprotection of the silyl ether **35**, yielded the 3-alkylpyridine derivative **36** necessary for the coupling with *N*-oxido mesylate **28**. The intermolecular *N*-alkylation of **36** with the mesylate **28** in the presence of potassium iodide in refluxing acetonitrile afforded the pyridinium alcohol **37** in 64% yield. Although in the route of the total synthesis of haliclamine A (**1**), the mesylation of **31** in dichloromethane was simultaneously accompanied with the favorable deoxygenation of pyridine *N*-oxide (Scheme 3), reproducibility of the reaction was somewhat problematic. It has, however, been found that the use of acetonitrile instead of dichloromethane as the solvent reproducibly optimizes the yield of the mesylation and deoxygenation. Treatment of the *N*-oxide **37** with a large excess of methanesulfonyl chloride and triethylamine in acetonitrile at 0 °C for 1 h could provide the desirable mesylate **38**

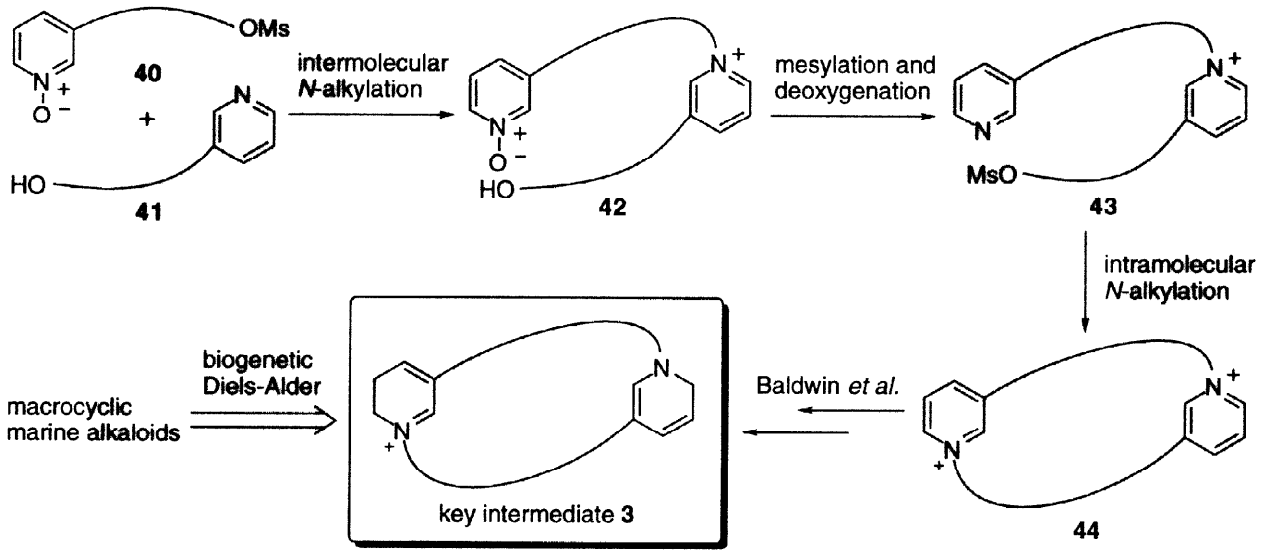


Scheme 4. Reagents and conditions: (a) PPh_3, $NaHCO_3$, CH_3CN, reflux, 24 h, 94%; (b) KHMDS, **7**, THF, −78 °C → rt, 24 h, 61%; (c) AcOH–H_2O (3:2), rt, 5 h, 84%; (d) KI, **28**, CH_3CN, reflux, 3 d, 64%; (e) MsCl, Et_3N, CH_3CN, 0 °C, 1 h, 77%; (f) KI, 1 mM of **38** in CH_3CN, reflux, 5 d, 60%; (g) $NaBH_4$, MeOH–H_2O (3:2), 0 °C → rt, 13 h, 63%.

in 77% yield in a single step. The intramolecular *N*-alkylation of **38** proceeded still under high dilution conditions to produce the ring closed bispyridinium macrocycle **39** in 60% yield, whose reduction with sodium borohydride gave the synthetic haliclamine B (**2**). The spectral characteristics of the synthetic **2** thus obtained were identical to those reported[17] in all respects.

In view of studies on the biomimetic synthesis of such macrocyclic marine alkaloids as shown in Fig. 1, the significance for total syntheses of haliclamines A (**1**) and B (**2**) may be summarized as follows. That is, the convergent assembly of 3-substituted pyridine derivatives **40** and **41** with different alkyl chains to the bispyridinium macrocycle **44**, a synthetic equivalent of the key bisdihydropyridine intermediate **3** implied in the biogenesis,[27] can be considered to be the general synthetic methodology toward the bisdihydropyridine intermediate **3** linked through a variety of 3-alkyl chains between the two heterocycles (Scheme 5). The methodology has the following characteristics. Protecting one of the two nucleophilic nitrogen functional groups as an *N*-oxide can avoid self-polymerization or intramolecular *N*-alkylation in the face of coupling **40** with **41** to control the construction of an arbitrary macrocycle. The mesylation of hydroxyl group (conversion into a leaving group) and deoxygenation of the pyridine *N*-oxide (deprotection of the nitrogen function) in the coupling product **42** required for the next macrocyclization can be carried out in a single step by treatment with inexpensive and popular reagents (MsCl and Et_3N in CH_3CN) under mild conditions. The utilization of mesylate possessing an appropriate leaving ability as the leaving group makes isolation and purification of **43** with both nucleophilic and electrophilic sites possible.

The sequence of reactions will allow the convenient and expeditious access to the bisdihydropyridine intermediate **3** having a variety of 3-alkyl chains linking the two heterocycles. The research on biomimetic synthesis of the macrocyclic marine alkaloids employing this methodology is in progress.



Scheme 5. General synthetic methodology to the bispyridinium macrocycle **44**.

EXPERIMENTAL SECTION

General Procedures

^{1}H NMR spectra were recorded on JEOL model JNM-LA 300 (300 MHz) and 400 (400 MHz) spectrometers. ^{13}C NMR spectra were measured on JEOL model JNM-LA 300 (75 MHz) and 400 (100 MHz) spectrometers. Infrared (IR) spectra were recorded on a JASCO A-102 spectrophotometer. Mass spectra were determined on a JEOL model AX-500 spectrometer. Analytical thin layer chromatography was carried out by precoated silica gel (Merck TLC plates Silica gel 60 F_{254}). Silica gel used for column chromatographies was Merck Silica gel 60 (70–230 mesh). All reactions were performed in oven-dried glassware. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), diisopropylamine, acetonitrile (CH_3CN), and 1,1,1,3,3,3-hexamethyldisilazane (HMDS) were distilled from calcium hydride. Acetone was distilled from potassium permanganate. *tert*-Butyl alcohol (*t*-BuOH) was distilled from magnesium activated with iodine. *N,N*-Dimethylformamide (DMF), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), and 3-picoline were distilled from calcium hydride at reduced pressure.

4-Benzyloxy-1-butanol (10). To a solution of NaH (60% in oil suspension, 4.43 g, 111 mmol) in 100 mL of DMF at room temperature was added dropwise 1,4-butanediol (**8**) (9.83 mL, 111 mmol) and the solution was stirred at the same temperature for 1 h under N_2. After the reaction vessel was cooled to 0 °C, 9.24 mL (77.7 mmol) of BnBr was added dropwise to the solution and the resulting mixtures were stirred at room temperature for 15 h. The reaction was quenched with saturated aqueous NH_4Cl and the reaction mixture was poured into water, followed by extraction with ether (× 3). The combined ethereal layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography (hexane:EtOAc = 80:20) on 300 g of silica gel to give benzyl ether **10** (10.9 g, 77.7% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.19 (5H, m), 4.52 (2H, s), 3.64 (2H, t, J = 6.0 Hz), 3.52 (2H, t, J = 5.9 Hz), 2.35–1.85 (1H, br s), 1.77–1.62 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 128.4, 127.7, 127.6,

73.0, 70.3, 62.7, 30.1, 26.6; IR (neat) 3345, 2895, 2810, 1080, 1048, 720, 680 cm^{-1}; EI-MS *m/z* (relative intensity) 180 (M^+, 6.0), 162 (3.0), 149 (13), 107 (76), 91 (100); EI-HRMS calcd for $C_{11}H_{16}O_2$ (M^+) 180.1150, found 180.1164.

1-Benzyloxy-4-methanesulfonyloxybutane (11). To a solution of alcohol **10** (5.00 g, 30.4 mmol) in 60 mL of CH_2Cl_2 at 0 °C under N_2 were sequentially added 6.42 mL (45.7 mmol) of Et_3N and 2.82 mL (36.5 mmol) of MsCl, and then the mixture was stirred for 1 h. The reaction mixture was poured into water and extracted with CH_2Cl_2 (× 2) and EtOAc (× 2). The extracted organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residual oil was subjected to column chromatography (hexane:EtOAc = 70:30) on 100 g of silica gel to provide mesylate **11** (7.63 g, 97.0% yield) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.26 (5H, m), 4.50 (2H, s), 4.26 (2H, t, J = 6.5 Hz), 3.52 (2H, t, J = 6.1 Hz), 2.97 (3H, s), 1.91–1.84 (2H, m), 1.76–1.70 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 128.5, 127.7, 73.1, 70.0, 69.4, 37.4, 26.3, 25.8; IR (neat) 2990, 2900, 2815, 1337, 1158, 1082, 920, 800, 721, 683 cm^{-1}; EI-MS *m/z* (relative intensity) 258 (M^+, 20), 186 (3.0), 162 (15), 161 (27), 107 (93), 91 (100); EI-HRMS calcd for $C_{12}H_{18}O_4S$ (M^+) 258.0926, found 258.0925.

1-Benzyloxy-4-iodobutane (12). A solution of mesylate **11** (6.85 g, 26.5 mmol) and NaI (7.95 g, 53.1 mmol) in 70 mL of acetone under N_2 was heated at reflux with stirring. After 3 h, an oil bath was removed and the reaction vessel was cooled to room temperature. The reaction mixture was poured into water and extracted with EtOAc (× 3). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography (hexane:EtOAc = 97:3) on 70 g of silica gel to furnish iodide **12** (7.24 g, 94.2% yield) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.23 (5H, m), 4.50 (2H, s), 3.49 (2H, t, J = 6.2 Hz), 3.21 (2H, t, J = 7.0 Hz), 1.98–1.90 (2H, m), 1.75–1.68 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 128.4, 127.58, 127.56, 72.9, 69.0, 30.6, 30.4, 6.78; IR (neat) 2985, 2880, 2805, 1432, 1342, 1205, 1085, 715, 678 cm^{-1}; EI-MS *m/z* (relative intensity) 163 [$(M - I)^+$, 3.0], 149 (8.0), 91 (100), 58 (84); FAB-MS *m/z* (relative intensity) 290 (M^+, 7.0); EI-HRMS calcd for $C_{11}H_{15}O$ [$(M - I)^+$] 163.1123, found 163.1112.

4-*tert*-Butyldimethylsilyloxy-1-butyne (13). To a solution of 3-butyn-1-ol (10.8 mL, 143 mmol) and 872 mg (7.14 mmol) of 4-dimethylaminopyridine in 150 mL of CH_2Cl_2 at 0 °C under N_2 was added 30.1 mL (214 mmol) of Et_3N. To the solution at the same temperature was added dropwise 23.7 g (157 mmol) of *t*-$BuMe_2SiCl$ dissolved in 100 mL of CH_2Cl_2 and the resulting mixture was stirred at room temperature for 5 h. The reaction mixture was poured into water and extracted with CH_2Cl_2 (× 2) and EtOAc (× 2). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc = 98:2) on 200 g of silica gel to give silyl ether **13** (24.8 g, 94.2% yield) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 3.74 (2H, t, J = 7.2 Hz), 2.40 (2H, dt, J = 2.6, 7.1 Hz), 1.96 (1H, t, J = 2.7 Hz), 0.90 (9H, s), 0.08 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.5, 69.3, 61.7, 25.9, 22.8, 18.3, –5.31; IR (neat) 3310, 2940, 2865, 2130, 1250, 1100, 825, 770 cm^{-1}; EI-MS *m/z* (relative intensity) 169 (67), 127 [$(M - t\text{-Bu})^+$, 100], 97 (84), 73 (43), 58 (59); EI-HRMS calcd for $C_6H_{11}OSi$ [$(M - t\text{-Bu})^+$] 127.0579, found 127.0590.

8-Benzyloxy-1-*tert*-butyldimethylsilyloxy-3-octyne (14). To a solution of alkyne **13** (4.19 g, 22.8 mmol) in 40 mL of THF at –15 °C under N_2 was added dropwise 18.0 mL (29.1 mmol) of *n*-BuLi (1.6 M in hexane) and the solution was stirred at the same temperature for 30 min. To the solution at –15 °C was added dropwise iodide **12** (7.24 g, 25.0 mmol) dissolved in 40 mL of DMPU and the mixture was stirred at the same temperature for additional 30 min. After stirred at room temperature for 10 h, the reaction was quenched with

saturated aqueous NH_4Cl. The reaction mixture was poured into water and extracted with ether (× 3). The ethereal layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography (hexane:EtOAc = 99:1) on 150 g of silica gel to give alkylated alkyne **14** (7.43 g, 85.9% yield) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (5H, m), 4.50 (2H, s), 3.68 (2H, t, J = 7.2 Hz), 3.49 (2H, t, J = 6.3 Hz), 2.36 (2H, tt, J = 7.3, 2.4 Hz), 2.17 (2H, tt, J = 7.0, 2.4 Hz), 1.77–1.65 (2H, m), 1.64–1.51 (2H, m), 0.89 (9H, s), 0.07 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 128.3, 127.6, 127.5, 81.0, 77.2, 72.9, 69.9, 62.4, 28.9, 25.9, 25.7, 23.2, 18.5, 18.3, –5.28; IR (neat) 2900, 2825, 1443, 1350, 1240, 1095, 900, 822, 761, 720, 682 cm^{-1}; CI-MS *m/z* (relative intensity) 347 [$(M + H)^+$, 33], 289 (17), 255 (9.0), 239 (17), 215 (100), 197 (62), 107 (18), 91 (94); CI-HRMS calcd for $C_{21}H_{35}O_2Si$ [$(M + H)^+$] 347.2406, found 347.2394.

(5*E*)-8-*tert*-Butyldimethylsilyloxy-5-octen-1-ol (15). To a solution of alkyne **14** (4.00 g, 11.5 mmol), 5.45 mL (57.8 mmol) of *t*-BuOH, and 12 mL of Et_2O in 600 mL of liquid ammonia at –40 °C under N_2 was added portionwise Na (4.35 g, 189 mmol) and the mixture was stirred at the same temperature for 3 d. The reaction was quenched with NH_4Cl at –40 °C and the resulting mixture was allowed to warm to room temperature. The mixture was stirred for some time until ammonia has been removed. The reaction mixture was poured into water and extracted with EtOAc (× 3). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc = 93:7) on 120 g of silica gel to yield alcohol **15** (1.80 g, 60.2% yield) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.47 (1H, dt, J = 15.4, 6.0 Hz), 5.40 (1H, dt, J = 15.3, 6.0 Hz), 3.64 (2H, t, J = 6.5 Hz), 3.61 (2H, t, J = 6.8 Hz), 2.21 (2H, q, J = 6.5 Hz), 2.03 (2H, q, J = 6.7 Hz), 1.80–1.60 (1H, br s), 1.61–1.54 (2H, m), 1.46–1.38 (2H, m), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.0, 126.9, 63.3, 62.9, 36.3, 32.3, 32.2, 25.9, 25.5, 18.3, –5.26; IR (neat) 3310, 2870, 2800, 1243, 1090, 957, 825, 762 cm^{-1}; EI-MS *m/z* (relative intensity) 257 [$(M - H)^+$, 0.26], 201 [$(M - t\text{-}Bu)^+$, 44], 183 (5.0), 131 (13), 109 (58), 105 (90), 75 (100), 67 (63); EI-HRMS calcd for $C_{10}H_{21}O_2Si$ [$(M - t\text{-}Bu)^+$] 201.1311, found 201.1296.

(3*E*)-1-*tert*-Butyldimethylsilyloxy-8-methanesulfonyloxy-3-octene (16). To a solution of alcohol **15** (512 mg, 1.98 mmol) in 20 mL of CH_2Cl_2 at 0 °C under N_2 were sequentially added 0.42 mL (2.97 mmol) of Et_3N and 0.18 mL (2.38 mmol) of MsCl, and then the mixture was stirred for 1 h. The reaction mixture was poured into water and extracted with CH_2Cl_2 (× 2) and EtOAc (× 2). The extracted organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residual oil was subjected to column chromatography (hexane:EtOAc = 90:10) on 10 g of silica gel to provide mesylate **16** (642 mg, 96.3% yield) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.46–5.41 (2H, m), 4.22 (2H, t, J = 6.5 Hz), 3.61 (2H, t, J = 6.9 Hz), 3.00 (3H, s), 2.25–2.17 (2H, m), 2.08–1.99 (2H, m), 1.80–1.70 (2H, m), 1.52–1.42 (2H, m), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.3, 127.6, 69.9, 63.2, 37.4, 36.2, 31.9, 28.5, 25.9, 18.4, –5.25; IR (neat) 2900, 2830, 1340, 1240, 1161, 1090, 955, 920, 822, 763 cm^{-1}; CI-MS *m/z* (relative intensity) 337 [$(M + H)^+$, 7.0], 279 (0.3), 241 (1.8), 109 (100); CI-HRMS calcd for $C_{15}H_{33}O_4SiS$ [$(M + H)^+$] 337.1869, found 337.1874.

(3*E*)-1-*tert*-Butyldimethylsilyloxy-8-iodo-3-octene (17). A solution of mesylate **16** (632 mg, 1.88 mmol) and NaI (563 mg, 3.76 mmol) in 10 mL of acetone under N_2 was heated at reflux with stirring. After 3 h, an oil bath was removed and the reaction vessel was cooled to room temperature. The reaction mixture was poured into water and extracted with EtOAc (× 3). The organic layer was washed with brine, dried over

anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography (hexane:EtOAc = 98:2) on 15 g of silica gel to furnish iodide **17** (668 mg, **96.6% yield**) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 (1H, dt, J = 15.1, 5.1 Hz), 5.40 (1H, dt, J = 15.2, 5.2 Hz), 3.61 (2H, t, J = 6.8 Hz), 3.18 (2H, t, J = 7.1 Hz), 2.24–2.18 (2H, m), 2.05–1.98 (2H, m), 1.82 (2H, quintet, J = 7.3 Hz), 1.46 (2H, quintet, J = 7.5 Hz), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.5, 127.3, 63.2, 36.2, 32.9, 31.5, 30.2, 26.0, 18.4, 6.94, –5.23; IR (neat) 2930, 2855, 1456, 1250, 1097, 965, 830, 770 cm^{-1}; EI-MS *m/z* (relative intensity) 311 [(M – *t*-Bu)$^+$, 4.0], 253 (31), 183 (68), 127 (43), 109 (100), 75 (93); FAB-MS *m/z* (relative intensity) 367 [(M – H)$^+$, 4.0]; EI-HRMS calcd for $C_{10}H_{20}OSiI$ [(M – *t*-Bu)$^+$] 311.0328, found 311.0323.

7-Benzyloxy-1-heptanol (18). To a solution of NaH (60% in oil suspension, 3.02 g, 75.6 mmol) in 100 mL of DMF at room temperature was added dropwise 1,7-heptanediol (**9**) (10.4 mL, 75.6 mmol) and the solution was stirred at the same temperature for 1 h under N_2. After the reaction vessel was cooled to 0 °C, 6.29 mL (52.9 mmol) of BnBr was added dropwise to the solution and the resulting mixtures were stirred at room temperature for 15 h. The reaction was quenched with saturated aqueous NH_4Cl and the reaction mixture was poured into water, followed by extraction with ether (× 3). The combined ethereal layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography (hexane:EtOAc = 80:20) on 250 g of silica gel to give benzyl ether **18** (7.53 g, 64.1% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.24 (5H, m), 4.50 (2H, s), 3.63 (2H, t, J = 6.6 Hz), 3.47 (2H, t, J = 6.6 Hz), 1.74 (1H, br s), 1.66–1.52 (4H, m), 1.48–1.24 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 128.3, 127.6, 127.4, 72.8, 70.4, 62.9, 32.7, 29.7, 29.2, 26.1, 25.7; IR (neat) 3380, 2920, 2850, 1448, 1355, 1095, 728, 690 cm^{-1}; EI-MS *m/z* (relative intensity) 222 (M$^+$, 35), 204 (4.0), 107 (100), 91 (100); EI-HRMS calcd for $C_{14}H_{22}O_2$ (M$^+$) 222.1620, found 222.1628.

1-Benzyloxy-7-methanesulfonyloxyheptane (19). To a solution of alcohol **18** (6.72 g, 30.2 mmol) in 50 mL of CH_2Cl_2 at 0 °C under N_2 were sequentially added 6.37 mL (45.3 mmol) of Et_3N and 2.81 mL (36.3 mmol) of MsCl, and then the mixture was stirred for 1 h. The reaction mixture was poured into water and extracted with CH_2Cl_2 (× 2) and EtOAc (× 2). The extracted organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residual oil was subjected to column chromatography (hexane:EtOAc = 70:30) on 130 g of silica gel to provide mesylate **19** (8.94 g, 98.5% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.24 (5H, m), 4.50 (2H, s), 4.21 (2H, t, J = 6.6 Hz), 3.47 (2H, t, J = 6.5 Hz), 2.99 (3H, s), 1.79–1.70 (2H, m), 1.66–1.57 (2H, m), 1.46–1.27 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 128.3, 127.6, 127.5, 72.9, 70.3, 70.1, 37.3, 29.6, 29.0, 28.8, 26.0, 25.3; IR (neat) 2895, 2820, 1440, 1340, 1160, 1085, 955, 920, 810, 720, 682 cm^{-1}; EI-MS *m/z* (relative intensity) 300 (M$^+$, 12), 204 (3.0), 186 (4.0), 107 (100), 91 (90); EI-HRMS calcd for $C_{15}H_{24}O_4S$ (M$^+$) 300.1395, found 300.1415.

1-Benzyloxy-7-iodoheptane (20). A solution of mesylate **19** (8.94 g, 29.8 mmol) and NaI (8.92 g, 59.5 mmol) in 70 mL of acetone under N_2 was heated at reflux with stirring. After 4 h, an oil bath was removed and the reaction vessel was cooled to room temperature. The reaction mixture was poured into water and extracted with EtOAc (× 3). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography (hexane:EtOAc = 97:3) on 180 g of silica gel to furnish iodide **20** (9.45 g, 95.6% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.25 (5H, m), 4.50 (2H, s), 3.46 (2H, t, J = 6.5 Hz), 3.18 (2H, t, J = 7.0 Hz), 1.82 (2H, quintet, J = 7.2 Hz), 1.66–1.56 (2H, m), 1.44–1.24 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 128.4, 127.7, 127.6, 73.0, 70.4, 33.6,

30.5, 29.7, 28.4, 26.1, 7.28; IR (neat) 2880, 2800, 1435, 1342, 1185, 1085, 715, 677 cm^{-1}; EI-MS *m/z* (relative intensity) 332 (M^+, 6.0), 241 (5.0), 205 (3.0), 91 (100); EI-HRMS calcd for $C_{14}H_{21}OI$ (M^+) 332.0637, found 332.0653.

11-Benzyloxy-1-*tert*-butyldimethylsilyloxy-3-undecyne (21). To a solution of alkyne **13** (4.77 g, 25.9 mmol) in 50 mL of THF at –15 °C under N_2 was added dropwise 20.7 mL (33.2 mmol) of *n*-BuLi (1.6 M in hexane) and the solution was stirred at the same temperature for 30 min. To the solution at –15 °C was added dropwise iodide **20** (9.44 g, 28.4 mmol) dissolved in 50 mL of DMPU and the mixture was stirred at the same temperature for additional 30 min. After stirred at room temperature for 10 h, the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was poured into water and extracted with ether (× 3). The ethereal layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography (hexane:EtOAc = 99:1) on 300 g of silica gel to give alkylated alkyne **21** (8.68 g, 78.6% yield) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.26 (5H, m), 4.50 (2H, s), 3.69 (2H, t, *J* = 7.2 Hz), 3.46 (2H, t, *J* = 6.6 Hz), 2.36 (2H, tt, *J* = 7.3, 2.4 Hz), 2.13 (2H, tt, *J* = 6.9, 2.3 Hz), 1.65–1.55 (2H, m), 1.50–1.25 (8H, m), 0.90 (9H, s), 0.07 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 128.3, 127.6, 127.5, 81.4, 76.9, 72.8, 70.4, 62.4, 29.7, 29.0, 28.9, 28.8, 26.1, 25.9, 23.2, 18.7, 18.3, –5.27; IR (neat) 2900, 2820, 1448, 1347, 1240, 1095, 822, 762, 719, 681 cm^{-1}; EI-MS *m/z* (relative intensity) 331 [(M – *t*-Bu)$^+$, 10], 183 (13), 107 (18), 91 (100), 75 (69); FAB-MS *m/z* (relative intensity) 389 [(M + H)$^+$, 9.0]; EI-HRMS calcd for $C_{20}H_{31}O_2Si$ [(M – *t*-Bu)$^+$] 331.2093, found 331.2104.

(8*E*)-11-*tert*-Butyldimethylsilyloxy-8-undecen-1-ol (22). To a solution of alkyne **21** (2.00 g, 5.18 mmol), 2.91 mL (30.9 mmol) of *t*-BuOH, and 6 mL of Et_2O in 400 mL of liquid ammonia at –40 °C under N_2 was added portionwise Na (2.84 g, 124 mmol) and the mixture was stirred at the same temperature for 3 d. The reaction was quenched with NH_4Cl at –40 °C and the resulting mixture was allowed to warm to room temperature. The mixture was stirred for some time until ammonia has been removed. The reaction mixture was poured into water and extracted with EtOAc (× 3). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc = 93:7) on 60 g of silica gel to yield alcohol **22** (1.15 g, 74.0% yield) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.51–5.34 (2H, m), 3.64 (2H, t, *J* = 6.6 Hz), 3.61 (2H, t, *J* = 6.8 Hz), 2.20 (2H, q, *J* = 6.6 Hz), 2.02–1.93 (2H, m), 1.59–1.52 (2H, m), 1.40–1.24 (9H, m), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.5, 126.4, 63.4, 63.1, 36.3, 32.8, 32.6, 29.4, 29.3, 29.1, 26.0, 25.7, 18.4, –5.25; IR (neat) 3310, 2880, 2810, 1445, 1238, 1085, 1035, 950, 819, 757 cm^{-1}; EI-MS *m/z* (relative intensity) 243 [(M – *t*-Bu)$^+$, 7.0], 225 (3.0), 167 (8.0), 151 (9.0), 105 (62), 95 (91), 75 (100); FAB-MS *m/z* (relative intensity) 301 [(M + H)$^+$, 6.0]; EI-HRMS calcd for $C_{13}H_{27}O_2Si$ [(M – *t*-Bu)$^+$] 243.1781, found 243.1760.

(3*E*)-1-*tert*-Butyldimethylsilyloxy-11-methanesulfonyloxy-3-undecene (23). To a solution of alcohol **22** (1.15 g, 3.83 mmol) in 50 mL of CH_2Cl_2 at 0 °C under N_2 were sequentially added 0.81 mL (5.75 mmol) of Et_3N and 0.36 mL (4.60 mmol) of MsCl, and then the mixture was stirred for 1 h. The reaction mixture was poured into water and extracted with CH_2Cl_2 (× 2) and EtOAc (× 2). The extracted organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residual oil was subjected to column chromatography (hexane:EtOAc = 90:10) on 30 g of silica gel to provide mesylate **23** (1.42 g, 98.0% yield) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.47 (1H, dt, *J* = 15.3, 5.9 Hz), 5.38 (1H, dt, *J* = 15.3, 6.1 Hz), 4.22 (2H, t, *J* = 6.6 Hz), 3.61 (2H, t, *J* = 7.0 Hz), 3.00 (3H, s), 2.20 (2H, q, *J* = 6.6 Hz), 2.02–1.94 (2H, m), 1.80–1.69 (2H, m), 1.45–1.24 (8H, m), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.4,

126.5, 70.1, 63.3, 37.4, 36.3, 32.6, 29.4, 29.3, 29.1, 28.9, 26.0, 25.4, 18.4, –5.24; IR (neat) 2890, 2805, 1448, 1340, 1239, 1159, 1082, 950, 817, 756 cm^{-1}; EI-MS *m/z* (relative intensity) 225 [(M – *t*-Bu – MsOH)$^+$, 19], 153 (97), 109 (63), 95 (100), 75 (88); FAB-MS *m/z* (relative intensity) 379 [(M + H)$^+$, 1.6]; EI-HRMS calcd for $C_{13}H_{25}OSi$ [(M – *t*-Bu – MsOH)$^+$] 225.1675, found 225.1684.

(3*E*)-1-*tert*-Butyldimethylsilyloxy-11-iodo-3-undecene (24). A solution of mesylate **23** (1.98 g, 5.23 mmol) and NaI (1.57 g, 10.5 mmol) in 30 mL of acetone under N_2 were heated at reflux with stirring. After 4 h, an oil bath was removed and the reaction vessel was cooled to room temperature. The reaction mixture was poured into water and extracted with EtOAc (× 3). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography (hexane:EtOAc = 98:2) on 60 g of silica gel to furnish iodide **24** (2.02 g, 93.7% yield) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47 (1H, dt, *J* = 15.4, 5.7 Hz), 5.38 (1H, dt, *J* = 15.5, 6.1 Hz), 3.61 (2H, t, *J* = 6.9 Hz), 3.19 (2H, t, *J* = 7.1 Hz), 2.20 (2H, q, *J* = 6.5 Hz), 2.03–1.93 (2H, m), 1.82 (2H, quintet, *J* = 7.1 Hz), 1.45–1.23 (8H, m), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.4, 126.5, 63.4, 36.3, 33.5, 32.6, 30.4, 29.3, 28.9, 28.4, 26.0, 18.4, 7.25, –5.23; IR (neat) 2910, 2845, 1455, 1246, 1095, 960, 828, 765 cm^{-1}; EI-MS *m/z* (relative intensity) 353 [(M – *t*-Bu)$^+$, 15], 225 (13), 215 (32), 151 (24), 95 (100), 75 (72); FAB-MS *m/z* (relative intensity) 409 [(M – H)$^+$, 20]; EI-HRMS calcd for $C_{13}H_{26}OSiI$ [(M – *t*-Bu)$^+$] 353.0798, found 353.0803.

3-[(6*E*)-9-*tert*-Butyldimethylsilyloxy-6-nonenyl]pyridine (25). To a solution of diisopropylamine (0.40 mL, 2.86 mmol) in 7.0 mL of THF at 0 °C under N_2 was added dropwise 1.79 mL (2.86 mmol) of *n*-BuLi (1.6 M in hexane) and the mixture was stirred for 30 min at the same temperature. After cooled to –78 °C, 3-picoline (0.27 mL, 2.73 mmol) was added dropwise to the solution and the mixture was stirred at –78 °C for additional 20 min. To the solution at –78 °C was added dropwise iodide **17** (402 mg, 1.09 mmol) dissolved in 3.0 mL of THF and the solution was allowed to warm to room temperature. After stirred for 5 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was poured into water and extracted with EtOAc (× 3). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane:EtOAc = 93:7) on 16 g of silica gel yielded alkylated pyridine **25** (235 mg, 64.7% yield) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47–8.38 (2H, m), 7.52–7.45 (1H, m), 7.19 (1H, ddd, *J* = 7.7, 4.8, 0.7 Hz), 5.52–5.30 (2H, m), 3.60 (2H, t, *J* = 6.9 Hz), 2.60 (2H, t, *J* = 7.7 Hz), 2.20 (2H, q, *J* = 6.4 Hz), 2.07–1.92 (2H, m), 1.67–1.56 (2H, m), 1.44–1.25 (4H, m), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 147.2, 137.8, 135.7, 132.3, 126.6, 123.2, 63.3, 36.3, 32.9, 32.5, 31.0, 29.2, 28.6, 25.9, 18.3, –5.25; IR (neat) 2900, 2825, 1565, 1460, 1450, 1410, 1242, 1090, 955, 825, 763, 700 cm^{-1}; EI-MS *m/z* (relative intensity) 332 [(M – H)$^+$, 0.6], 318 [(M – Me)$^+$, 3.0], 276 [(M – *t*-Bu)$^+$, 82], 202 (13), 149 (39); EI-HRMS calcd for $C_{19}H_{32}ONSi$ [(M – Me)$^+$] 318.2253, found 318.2280.

3-[(6*E*)-9-Hydroxy-6-nonenyl]pyridine (26). A solution of silyl ether **25** (235 mg, 0.705 mmol) in 12 mL of AcOH and 8.0 mL of H_2O was stirred at room temperature for 2 h. The reaction mixture was treated with 21 mL of 10 M aqueous NaOH and extracted with CH_2Cl_2 (× 3). The extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$:acetone = 95:5) on 12 g of silica gel to furnish alcohol **26** (152 mg, 98.5% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44–8.41 (2H, m), 7.50–7.46 (1H, m), 7.23–7.17 (1H, m), 5.59–5.46 (1H, m), 5.44–5.32 (1H, m), 3.62 (2H, t, *J* = 6.3 Hz), 2.61 (2H, t, *J* = 7.7 Hz), 2.30–2.20 (2H, m), 2.06–1.96 (2H, m), 1.73 (1H, br s), 1.68–1.55 (2H, m), 1.46–1.23 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 147.2, 137.8, 135.8, 133.8, 126.1,

123.2, 62.0, 36.0, 32.9, 32.4, 30.9, 29.1, 28.5; IR (neat) 3275, 2890, 2820, 1565, 1467, 1445, 1410, 1035, 1015, 955, 700 cm^{-1}; EI-MS *m/z* (relative intensity) 218 [$(M - H)^+$, 2.4], 202 [$(M - OH)^+$, 6.0], 189 (13), 134 (10), 120 (5.0), 106 (31); EI-HRMS calcd for $C_{14}H_{20}N$ [$(M - OH)^+$] 202.1596, found 202.1599.

3-[(6*E*)-9-Methanesulfonyloxy-6-nonenyl]pyridine (27). To a solution of alcohol **26** (864 mg, 3.94 mmol) in 35 mL of CH_2Cl_2 at 0 °C under N_2 were sequentially added 1.11 mL (7.88 mmol) of Et_3N and 0.46 mL (5.91 mmol) of MsCl, and then the mixture was stirred for 1 h. The reaction mixture was poured into water and extracted with CH_2Cl_2 (× 2) and EtOAc (× 2). The extracted organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residual oil was subjected to column chromatography ($CHCl_3$:acetone = 90:10) on 25 g of silica gel to provide mesylate **27** (1.15 g, 98.1% yield) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 8.48–8.39 (2H, m), 7.52–7.45 (1H, m), 7.25–7.16 (1H, m), 5.62–5.48 (1H, m), 5.43–5.29 (1H, m), 4.21 (2H, t, *J* = 6.8 Hz), 3.00 (3H, s), 2.60 (2H, t, *J* = 7.5 Hz), 2.49–2.38 (2H, m), 2.09–1.94 (2H, m), 1.73–1.53 (2H, m), 1.46–1.27 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 147.2, 137.8, 135.7, 134.6, 123.6, 123.2, 69.5, 37.4, 32.9, 32.3, 30.9, 28.9, 28.5; IR (neat) 2900, 2820, 1563, 1418, 1352, 1175, 972, 910, 798, 748, 710 cm^{-1}; EI-MS *m/z* (relative intensity) 218 [$(M - Ms)^+$, 4.0], 202 [$(M - MsO)^+$, 7.0], 201 (16), 106 (12), 58 (100); FAB-MS *m/z* (relative intensity) 298 [$(M + H)^+$, 63]; EI-HRMS calcd for $C_{14}H_{20}N$ [$(M - MsO)^+$] 202.1596, found 202.1566.

3-[(6*E*)-9-Methanesulfonyloxy-6-nonenyl]pyridine *N*-oxide (28). To a solution of pyridine derivative **27** (823 mg, 2.77 mmol) in 30 mL of CH_2Cl_2 at 0 °C under N_2 was added portionwise *m*-CPBA (72% purity, 664 mg, 2.77 mmol) and the solution was stirred at the same temperature for 2 h. After stirred at room temperature for additional 10 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (× 3). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$:acetone = 80:20) on 50 g of silica gel to afford *N*-oxide **28** (664 mg, 76.5% yield) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (2H, br s), 7.23 (1H, t, *J* = 7.3 Hz), 7.15 (1H, d, *J* = 7.7 Hz), 5.55 (1H, dt, *J* = 15.2, 6.6 Hz), 5.36 (1H, dt, *J* = 15.2, 6.7 Hz), 4.21 (2H, t, *J* = 6.8 Hz), 3.01 (3H, s), 2.59 (2H, t, *J* = 7.6 Hz), 2.44 (2H, q, *J* = 6.4 Hz), 2.06–1.94 (2H, m), 1.66–1.53 (2H, m), 1.44–1.24 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 139.0, 136.8, 134.3, 127.2, 125.5, 123.9, 69.5, 37.4, 32.6, 32.3, 32.2, 30.1, 28.8, 28.2; IR (neat) 2880, 2805, 1420, 1330, 1242, 1153, 945 cm^{-1}; CI-MS *m/z* (relative intensity) 314 [$(M + H)^+$, 22], 298 (48), 234 (48), 218 (82), 202 (43), 97 (100); CI-HRMS calcd for $C_{15}H_{24}O_4NS$ [$(M + H)^+$] 314.1426, found 314.1422.

3-[(9*E*)-12-*tert*-Butyldimethylsilyoxy-9-dodecenyl]pyridine (29). To a solution of diisopropylamine (1.80 mL, 12.9 mmol) in 40 mL of THF at 0 °C under N_2 was added dropwise 8.08 mL (12.9 mmol) of *n*-BuLi (1.6 M in hexane) and the mixture was stirred for 30 min at the same temperature. After cooled to –78 °C, 3-picoline (1.19 mL, 12.3 mmol) was added dropwise to the solution and the mixture was stirred at –78 °C for additional 20 min. To the solution at –78 °C was added dropwise iodide **24** (2.02 g, 4.91 mmol) dissolved in 10 mL of THF and the solution was allowed to warm to room temperature. After stirred for 6 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was poured into water and extracted with EtOAc (× 3). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane:EtOAc = 93:7) on 60 g of silica gel yielded alkylated pyridine **29** (1.28 g, 69.4% yield) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 8.44–8.40 (2H, m), 7.48 (1H, dt, *J* = 7.8, 1.9 Hz), 7.19 (1H, dd, *J* = 7.7, 4.6 Hz), 5.47 (1H, dt, *J* = 15.3, 5.9 Hz), 5.37 (1H, dt, *J* = 15.2, 6.2 Hz), 3.60 (2H, t, *J* = 7.0 Hz), 2.60 (2H, t, *J* = 7.8 Hz), 2.20 (2H, q, *J* = 6.6 Hz), 2.03–1.93 (2H, m), 1.70–1.55

(2H, m), 1.40–1.23 (10H, m), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 147.2, 138.0, 135.7, 132.6, 126.4, 123.2, 63.4, 36.3, 33.0, 32.6, 31.1, 29.5, 29.4, 29.3, 29.14, 29.12, 25.9, 18.4, –5.24; IR (neat) 2890, 2810, 1560, 1445, 1407, 1238, 1082, 950, 818, 756, 695 cm^{-1}; EI-MS *m/z* (relative intensity) 375 (M^+, 1.3), 360 (4.1), 318 [(M – *t*-Bu)$^+$, 100], 244 (8.0), 115 (3.0), 106 (6.0); EI-HRMS calcd for $C_{19}H_{32}ONSi$ [(M – *t*-Bu)$^+$] 318.2253, found 318.2260.

3-[(9*E*)-12-Hydroxy-9-dodecenyl]pyridine (30). A solution of silyl ether **29** (934 mg, 2.49 mmol) in 40 mL of AcOH and 27 mL of H_2O was stirred at room temperature for 3 h. The reaction mixture was treated with 70 mL of 10 M aqueous NaOH and extracted with CH_2Cl_2 (× 3). The extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$:acetone = 95:5) on 21 g of silica gel to furnish alcohol **30** (571 mg, 87.9% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45–8.41 (2H, m), 7.50 (1H, d, *J* = 7.9 Hz), 7.21 (1H, dd, *J* = 7.6, 4.9 Hz), 5.55 (1H, dt, *J* = 15.2, 6.6 Hz), 5.38 (1H, dt, *J* = 15.1, 6.9 Hz), 3.63 (2H, t, *J* = 6.3 Hz), 2.61 (2H, t, *J* = 7.6 Hz), 2.60–2.10 (1H, br s), 2.26 (2H, q, *J* = 6.2 Hz), 2.01 (2H, q, *J* = 6.6 Hz), 1.68–1.54 (2H, m), 1.41–1.20 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 146.9, 138.1, 136.0, 134.2, 125.8, 123.3, 62.0, 36.0, 33.0, 32.6, 31.0, 29.4, 29.30, 29.28, 29.0; IR (neat) 3260, 2875, 2805, 1561, 1406, 1032, 952, 895, 715 cm^{-1}; EI-MS *m/z* (relative intensity) 261 (M^+, 15), 243 (29), 230 (33), 176 (22), 162 (18), 148 (16), 134 (13), 120 (22), 106 (100), 93 (85); EI-HRMS calcd for $C_{17}H_{27}ON$ (M^+) 261.2092, found 261.2120.

***N*-Oxide 31.** A solution of mesylate **28** (255 mg, 0.814 mmol), alcohol **30** (213 mg, 0.814 mmol), and KI (270 mg, 1.63 mmol) in 30 mL of CH_3CN was vigorously stirred at reflux for 4 d under N_2. An oil bath was removed and the mixture was cooled to room temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2 (× 3). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography ($CHCl_3$:MeOH = 90:10) on 15 g of silica gel to provide *N*-oxide **31** (331 mg, 67.0% yield) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (1H, s), 9.13 (1H, d, *J* = 6.1 Hz), 8.29 (1H, d, *J* = 7.8 Hz), 8.10 (2H, br s), 8.06 (1H, dd, *J* = 7.8, 6.3 Hz), 7.30 (1H, t, *J* = 7.2 Hz), 7.24 (1H, d, *J* = 7.8 Hz), 5.57–5.30 (4H, m), 4.93 (2H, t, *J* = 6.6 Hz), 3.61 (2H, t, *J* = 6.5 Hz), 2.90 (2H, t, *J* = 7.8 Hz), 2.75 (2H, q, *J* = 6.5 Hz), 2.68–2.40 (5H, m), 2.25 (2H, q, *J* = 6.3 Hz), 1.98 (2H, q, *J* = 6.7 Hz), 1.96–1.87 (2H, m), 1.78–1.66 (2H, m), 1.68–1.52 (2H, m), 1.41–1.20 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 144.3, 144.0, 142.2, 141.6, 138.9, 136.8, 136.4, 134.0, 127.6, 127.1, 126.1, 125.8, 123.1, 62.0, 61.5, 36.0, 34.9, 32.8, 32.6, 32.4, 32.1, 30.5, 29.8, 29.3, 29.2, 29.1, 29.0, 28.9, 28.5, 27.8; IR (neat) 3390, 2930, 2855, 1620, 1435, 1260, 1160, 1025, 970, 798, 680 cm^{-1}; FAB-MS *m/z* (relative intensity) 479 [(M – I)$^+$, 81], 463 (42), 262 (8.0), 244 (3.0), 218 (12), 185 (100), 106 (14), 93 (100); FAB-HRMS calcd for $C_{31}H_{47}O_2N_2$ [(M – I)$^+$] 479.3637, found 479.3647.

Mesylate 32. To a solution of alcohol **31** (75.0 mg, 0.124 mmol) in 20 mL of CH_2Cl_2 at 0 ℃ under N_2 were sequentially added 6.52 mL (3.72 mmol) of Et_3N and 0.140 mL (1.86 mmol) of MsCl, and then the mixture was stirred for 1 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (× 3). The extracted organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to column chromatography ($CHCl_3$:MeOH = 94:6) on 8 g of silica gel to provide mesylate **32** (53.1 mg, 64.0% yield) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (1H, d, *J* = 5.4 Hz), 8.81 (1H, s), 8.48 (2H, br s), 8.16 (1H, d, *J* = 8.1 Hz), 7.97 (1H, t, *J* = 6.5 Hz), 7.62 (1H, d, *J* = 7.8 Hz), 7.34 (1H, br s), 5.61–5.47 (1H, m), 5.47–5.23 (3H, m), 4.86 (2H, t, *J* = 6.5 Hz), 4.21 (2H, t, *J* = 6.7 Hz), 3.01 (3H, s), 2.86 (2H, t, *J* = 7.8 Hz), 2.70 (2H, q, *J* = 6.4 Hz), 2.63 (2H, t, *J* = 7.4 Hz), 2.44 (2H, q, *J*

= 6.7 Hz), 2.00 (2H, q, J = 6.8 Hz), 1.91 (2H, q, J = 6.2 Hz), 1.73–1.53 (4H, m), 1.42–1.16 (14H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 147.2, 144.4, 143.8, 143.14, 143.07, 136.3, 135.9, 134.8, 127.8, 125.7, 123.6, 123.4, 69.7, 61.8, 37.5, 34.8, 32.9, 32.7, 32.5, 32.4, 32.3, 30.8, 30.5, 29.7, 29.25, 29.19, 29.1, 29.0, 28.9, 28.5; IR (neat) 2905, 2845, 1623, 1445, 1335, 1180, 1100, 1032, 960, 680 cm^{-1}; FAB-MS *m/z* (relative intensity) 541 [(M – I)$^+$, 83], 445 (7.0), 244 (10), 202 (14), 120 (17), 106 (27), 93 (100); FAB-HRMS calcd for $C_{32}H_{49}O_3N_2S$ [(M – I)$^+$] 541.3463, found 541.3450.

Bispyridinium macrocycle 33. A solution of mesylate **32** (88.2 mg, 0.132 mmol) and KI (87.6 mg, 0.528 mmol) in 132 mL of CH_3CN was stirred at reflux for 5 d under N_2. An oil bath was removed and the mixture was cooled to room temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2 (× 3). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$:MeOH = 93:7) on 5 g of silica gel to afford bispyridinium macrocycle **33** (53.6 mg, 58.0% yield) as a pale yellow oil: ^{1}H NMR (300 MHz, CD_3OD) δ 8.96–8.72 (4H, m), 8.49 (2H, d, J = 8.1 Hz), 8.10–7.97 (2H, m), 5.57–5.34 (2H, m), 5.30–5.16 (2H, m), 4.74–4.65 (4H, m), 2.95–2.81 (4H, m), 2.78–2.65 (4H, m), 1.95–1.81 (4H, m), 1.78–1.60 (4H, m), 1.42–1.01 (14H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 146.9, 146.6, 145.6, 145.4, 145.2, 145.0, 143.3, 143.2, 137.7, 137.3, 129.0, 124.7, 124.5, 62.2, 35.3, 35.1, 33.5, 33.4, 33.3, 33.2, 31.7, 31.5, 30.43, 30.35, 30.1, 30.0, 29.9, 29.8; IR (neat) 2920, 2850, 1620, 1225, 1065 cm^{-1}; FAB-MS *m/z* (relative intensity) 573 [(M – I)$^+$, 24], 244 (15), 202 (12), 93 (100); FAB-HRMS calcd for $C_{31}H_{46}N_2I$ [(M – I)$^+$] 573.2706, found 573.2714.

Haliclamine A (1). To a solution of bispyridinium **33** (24.3 mg, 34.7 μmol) in 12 mL of MeOH and 8 mL of H_2O at 0 °C was added a portion of $NaBH_4$ (26.2 mg, 0.694 mmol) and the solution was stirred at the same temperature for 1 h under N_2. After stirred at room temperature for additional 10 h, the reaction mixture was poured into 1 M aqueous NaOH and extracted with CH_2Cl_2 (× 3). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography ($CHCl_3$:MeOH = 99:1) on 5 g of silica gel to give synthetic haliclamine A (**1**) (10.2 mg, 64.8% yield) as a colorless oil: ^{1}H NMR (300 MHz, C_6D_6) δ 5.68–5.35 (6H, m), 2.95–2.82 (4H, m), 2.50–2.41 (8H, m), 2.32–2.21 (4H, m), 2.16–1.86 (12H, m), 1.50–1.15 (18H, m); ^{13}C NMR (75 MHz, C_6D_6) δ 136.6, 131.5, 131.4, 129.2, 119.4, 119.3, 58.6, 58.5, 55.8, 55.6, 50.3, 35.7, 35.6, 32.7, 32.6, 30.9, 29.7, 29.5, 29.4, 29.3, 28.8, 28.7, 28.3, 28.1, 26.3, 26.2; IR (neat) 2870, 2840, 1460, 1432, 965 cm^{-1}; EI-MS *m/z* (relative intensity) 452 (M$^+$, 100), 437 (30), 341 (13), 264 (35), 246 (59), 204 (96), 192 (17), 150 (19), 136 (22), 122 (13), 110 (66), 96 (34), 81 (17); EI-HRMS calcd for $C_{31}H_{52}N_2$ (M$^+$) 452.4130, found 452.4110.

(5*E*)-8-*tert*-Butyldimethylsilyloxy-5-octenyltriphenylphosphonium iodide (34). A solution of iodide **17** (1.07 g, 2.90 mmol), PPh_3 (913 mg, 3.48 mmol), and $NaHCO_3$ (292 mg, 3.48 mmol) in 60 mL of CH_3CN was stirred at reflux for 24 h under N_2. An oil bath was removed and the reaction vessel was cooled to room temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2 (× 3). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$:acetone = 90:10) on 70 g of silica gel to afford phosphonium iodide **34** (1.72 g, 94.1% yield) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89–7.65 (15H, m), 5.37–5.32 (2H, m), 3.80–3.66 (2H, m), 3.54 (2H, t, J = 7.0 Hz), 2.20–2.08 (2H, m), 2.08–1.98 (2H, m), 1.80–1.55 (4H, m), 0.87 (9H, s), 0.03 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.03, 134.99, 133.6, 133.4, 130.8, 130.5, 130.3, 127.4, 118.5, 117.3, 63.0, 53.7, 36.0, 31.7, 29.5, 29.1, 25.8, 18.2, –5.37; IR (neat) 2940, 2865, 1435, 1360, 1250, 1105,

833, 720 cm^{-1}; FAB-MS *m/z* (relative intensity) 503 [$(M - I)^+$, 100], 262 (18), 183 (8.0); FAB-HRMS calcd for $C_{32}H_{44}OSiP$ [$(M - I)^+$] 503.2899, found 503.2871.

3-[(4*Z*,9*E*)-12-*tert*-Butyldimethylsilyloxy-4,9-dodecadienyl]pyridine (35). To a solution of KH (35% dispersion in mineral oil, 441 mg, 3.85 mmol) in 25 mL of THF at 0 °C under N_2 was added dropwise 0.81 mL (3.85 mmol) of HMDS and the solution was stirred at the same temperature for 1 h. To the solution at 0 °C was added dropwise phosphonium iodide **34** (1.62 g, 2.57 mmol) dissolved in 30 mL of THF and then the solution was stirred at room temperature for 1 h. After the solution was cooled to –78 °C, to the solution was added dropwise aldehyde **7**[21] (383 mg, 2.57 mmol) dissolved in 50 mL of THF and the solution was stirred at the same temperature for 20 min. The solution was allowed to warm to room temperature and further stirred for additional 24 h. The reaction was quenched with saturated aqueous NH_4Cl and the mixture was poured into water, followed by extraction with CH_2Cl_2 (× 3). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography (hexane:EtOAc = 90:10) on 25 g of silica gel to yield silyl ether **35** (588 mg, 61.0% yield) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 8.48–8.40 (2H, m), 7.49 (1H, ddd, *J* = 7.8, 2.2, 1.7 Hz), 7.23–7.17 (1H, m), 5.52–5.32 (4H, m), 3.61 (2H, t, *J* = 7.0 Hz), 2.62 (2H, t, *J* = 7.8 Hz), 2.21 (2H, q, *J* = 6.5 Hz), 2.12–1.94 (6H, m), 1.68 (2H, quintet, *J* = 7.6 Hz), 1.40 (2H, quintet, *J* = 7.5 Hz), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 147.2, 137.6, 135.8, 132.2, 130.5, 129.0, 126.7, 123.2, 63.3, 36.3, 32.5, 32.2, 31.1, 29.5, 26.8, 26.6, 25.9, 18.4, –5.24; IR (neat) 2980, 2900, 1585, 1485, 1475, 1435, 1265, 1112, 980, 846, 785, 723 cm^{-1}; CI-MS *m/z* (relative intensity) 374 [$(M + H)^+$, 82], 358 (16), 316 (100), 242 (7.0), 92 (2.0); CI-HRMS calcd for $C_{23}H_{40}ONSi$ [$(M + H)^+$] 374.2879, found 374.2874.

3-[(4*Z*,9*E*)-12-Hydroxy-4,9-dodecadienyl]pyridine (36). A solution of silyl ether **35** (391 mg, 1.05 mmol) in 25 mL of AcOH and 17 mL of H_2O was stirred at room temperature for 5 h. The reaction mixture was treated with 43 mL of 10 M aqueous NaOH and extracted with CH_2Cl_2 (× 3). The extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$:acetone = 90:10) on 20 g of silica gel to furnish alcohol **36** (228 mg, 84.0% yield) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 8.44 (2H, s), 7.52 (1H, d, *J* = 7.9 Hz), 7.23 (1H, dd, *J* = 7.7, 5.0 Hz), 5.53 (1H, dt, *J* = 15.3, 6.5 Hz), 5.47–5.29 (3H, m), 3.63 (2H, t, *J* = 6.3 Hz), 3.12 (1H, br s), 2.63 (2H, t, *J* = 7.7 Hz), 2.26 (2H, q, *J* = 6.4 Hz), 2.11–1.94 (6H, m), 1.69 (2H, quintet, *J* = 7.5 Hz), 1.41 (2H, quintet, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 146.8, 137.8, 136.1, 133.5, 130.4, 129.0, 126.3, 123.4, 62.0, 36.0, 32.4, 32.2, 30.9, 29.3, 26.7, 26.5; IR (neat) 3380, 2925, 2850, 1580, 1480, 1422, 1360, 1263, 1190, 1045, 1028, 968, 790, 708 cm^{-1}; EI-MS *m/z* (relative intensity) 259 (M^+, 22), 258 (67), 241 (10), 229 (39), 174 (48), 106 (97), 93 (100); EI-HRMS calcd for $C_{17}H_{25}ON$ (M^+) 259.1936, found 259.1928.

***N*-Oxide 37.** A solution of mesylate **28** (275 mg, 0.877 mmol), alcohol **36** (228 mg, 0.877 mmol), and KI (291 mg, 1.76 mmol) in 20 mL of CH_3CN was vigorously stirred at reflux for 3 d under N_2. An oil bath was removed and the mixture was cooled to room temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2 (× 3). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography ($CHCl_3$:MeOH = 90:10) on 15 g of silica gel to provide *N*-oxide **37** (337 mg, 63.5% yield) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 9.15 (1H, s), 9.10 (1H, d, *J* = 6.1 Hz), 8.25 (1H, d, *J* = 7.7 Hz), 8.09 (2H, br s), 8.01 (1H, dd, *J* = 7.9, 6.2 Hz), 7.25 (1H, t, *J* = 7.1 Hz), 7.17 (1H, d, *J* = 7.9 Hz), 5.58–5.28 (6H, m), 4.96 (2H, t, *J* = 6.8 Hz), 3.90–3.38 (1H, br s), 3.63 (2H, t, *J* = 6.3 Hz), 2.91 (2H, t, *J* = 7.8 Hz), 2.74 (2H, q, *J* = 6.5 Hz), 2.58 (2H, t, *J* = 7.1 Hz), 2.27

(2H, q, J = 6.4 Hz), 2.13 (2H, q, J = 7.6 Hz), 2.07–1.95 (4H, m), 1.93–1.89 (2H, m), 1.85–1.73 (2H, m), 1.59 (2H, quintet, J = 7.1 Hz), 1.42 (2H, quintet, J = 7.3 Hz), 1.37–1.17 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 144.1, 143.9, 142.2, 141.6, 138.9, 136.7, 136.6, 133.0, 128.1, 127.6, 127.5, 127.2, 126.8, 125.7, 123.1, 61.9, 61.3, 36.0, 34.8, 32.4, 32.2, 32.00, 31.97, 31.7, 30.9, 30.4, 29.1, 27.9, 26.6, 26.5; IR (neat) 3395, 2915, 2900, 1628, 1501, 1432, 1358, 1259, 1158, 1040, 970, 795, 679 cm^{-1}; FAB-MS *m/z* (relative intensity) 477 [(M – I)$^+$, 35], 461 (50), 259 (9.0), 154 (100); FAB-HRMS calcd for $C_{31}H_{45}O_2N_2$ [(M – I)$^+$] 477.3481, found 477.3468.

Mesylate 38. To a solution of alcohol **37** (100 mg, 0.165 mmol) in 10 mL of CH_3CN at 0 °C under N_2 were sequentially added 0.70 mL (4.96 mmol) of Et_3N and 0.19 mL (2.48 mmol) of MsCl, and then the mixture was stirred for 1 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (× 3). The extracted organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to column chromatography ($CHCl_3$:MeOH = 92:8) on 8 g of silica gel to afford mesylate **38** (84.4 mg, 76.7% yield) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (1H, d, J = 6.2 Hz), 8.76 (1H, s), 8.43 (2H, br s), 8.18 (1H, d, J = 7.9 Hz), 7.95 (1H, dd, J = 7.7, 6.4 Hz), 7.50 (1H, d, J = 8.1 Hz), 7.29–7.20 (1H, m), 5.62–5.25 (6H, m), 4.80 (2H, br t, J = 6.4 Hz), 4.22 (2H, t, J = 6.7 Hz), 3.01 (3H, s), 2.86 (2H, t, J = 8.1 Hz), 2.69 (2H, q, J = 6.3 Hz), 2.58 (2H, t, J = 7.6 Hz), 2.45 (2H, q, J = 6.7 Hz), 2.13 (2H, q, J = 6.8 Hz), 2.10–1.81 (6H, m), 1.75 (2H, quintet, J = 7.7 Hz), 1.57 (2H, quintet, J = 7.2 Hz), 1.42 (2H, quintet, J = 7.2 Hz), 1.40–1.12 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 147.0, 144.5, 144.1, 143.6, 142.9, 136.1, 134.3, 131.0, 130.8, 128.7, 128.2, 127.7, 124.0, 123.3, 69.7, 61.4, 37.4, 34.8, 32.3, 32.2, 31.9, 30.7, 30.4, 29.6, 29.2, 29.0, 28.8, 28.4, 26.6, 26.5; IR (neat) 2930, 2855, 1630, 1502, 1455, 1345, 1220, 1170, 1040, 1010, 970, 800, 745, 685 cm^{-1}; FAB-MS *m/z* (relative intensity) 539 [(M – I)$^+$, 40], 443 (15), 242 (12), 202 (44), 188 (27), 120 (53), 106 (92), 92 (100); FAB-HRMS calcd for $C_{32}H_{47}O_3N_2S$ [(M – I)$^+$] 539.3307, found 539.3294.

Bispyridinium macrocycle 39. A solution of mesylate **38** (140 mg, 0.210 mmol) and KI (139 mg, 0.840 mmol) in 210 mL of CH_3CN was stirred at reflux for 5 d under N_2. An oil bath was removed and the mixture was cooled to room temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2 (× 3). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$:MeOH = 95:5) on 5 g of silica gel to afford bispyridinium macrocycle **39** (88.0 mg, 60.0% yield) as a pale yellow oil: ^{1}H NMR (300 MHz, CD_3OD) δ 9.00 (2H, br s), 8.86–8.77 (2H, m), 8.53 (1H, d, J = 8.1 Hz), 8.48 (1H, d, J = 8.1 Hz), 8.06 (1H, dd, J = 7.8, 6.1 Hz), 8.02 (1H, dd, J = 7.7, 6.2 Hz), 5.52 (2H, dt, J = 15.1, 7.2 Hz), 5.45–5.19 (4H, m), 4.74 (4H, t, J = 6.1 Hz), 2.93 (2H, t, J = 7.6 Hz), 2.84 (2H, t, J = 7.9 Hz), 2.78–2.67 (4H, m), 2.07 (2H, q, J = 7.0 Hz), 1.97–1.72 (6H, m), 1.72–1.55 (2H, m), 1.40–1.10 (8H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 146.9, 146.7, 145.6, 145.0, 144.9, 143.2, 143.1, 137.3, 137.2, 131.4, 129.9, 129.0, 128.9, 125.0, 124.8, 62.1, 62.0, 35.3, 33.4, 33.1, 33.0, 32.9, 31.7, 31.5, 30.5, 29.9, 29.6, 27.7, 27.5; IR (neat) 2950, 2875, 1630, 1503, 1460, 1242, 1025, 805, 685 cm^{-1}; FAB-MS *m/z* (relative intensity) 571 [(M – I)$^+$, 28], 443 (18), 202 (27), 106 (71), 93 (100); FAB-HRMS calcd for $C_{31}H_{44}N_2I$ [(M – I)$^+$] 571.2550, found 571.2567.

Haliclamine B (2). To a solution of bispyridinium **39** (50.0 mg, 71.6 μmol) in 12 mL of MeOH and 8 mL of H_2O at 0 °C was added a portion of $NaBH_4$ (81.3 mg, 2.15 mmol) and the solution was stirred at the same temperature for 3 h under N_2. After stirred at room temperature for additional 10 h, the reaction mixture was poured into 1 M aqueous NaOH and extracted with CH_2Cl_2 (× 3). The organic layer was dried over anhydrous

$MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography ($CHCl_3$:MeOH = 99:1) on 5 g of silica gel to give synthetic haliclamine B (**2**) (20.4 mg, 63.0% yield) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.47–5.39 (6H, m), 5.38–5.33 (2H, m), 2.92–2.82 (4H, br s), 2.58–2.38 (8H, m), 2.34–2.10 (8H, m), 2.10–1.88 (12H, m), 1.52–1.15 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 136.0, 131.5, 131.3, 130.0, 129.7, 128.5, 119.1, 118.8, 58.6, 58.5, 56.1, 55.5, 50.3, 50.0, 35.4, 34.8, 31.8, 31.7, 30.6, 29.3, 28.5, 27.7, 27.5, 27.2, 27.0, 26.1, 25.8; IR (neat) 2940, 1460, 1435, 965 cm^{-1}; FAB-MS *m/z* (relative intensity) 451 [$(M + H)^+$, 75], 244 (7.0), 204 (8.0), 190 (8.0), 150 (9.0), 136 (13), 122 (25), 110 (32), 109 (20), 96 (25), 93 (100), 81 (35), 79 (38), 67 (62); FAB-HRMS calcd for $C_{31}H_{51}N_2$ [$(M + H)^+$] 451.4052, found 451.4036.

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