Pergamon

Tetrahedron Letters, Vol. 38, No. 52, pp. 8981-8984, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10368-9

Total Synthesis of Haliclamine A, a Macrocyclic Marine Alkaloid Related to the Key Biogenetic Intermediate of Manzamines

Yoshiki Morimoto* and Chiho Yokoe

Department of Chemistry, Faculty of Science, Osaka City University, Sumiyoshiku, Osaka 558, Japan

Abstract: The first total synthesis of haliclamine A (**1**), a macrocyclic marine alkaloid closely related to the key bisdihydropyridine intermediate **3** of the biogenetically unique manzamine family, has been efficiently achieved via stepwise inter- and intramolecular *N*-alkylations of 3-alkylpyridine derivatives **26** and **28**. © 1997 Elsevier Science Ltd.

Recently, an increasing number of structurally and bioactively unique macrocyclic alkaloids have been isolated from different marine sponges. Among them, the sponge of the genus *Haliclona* produces a variety of alkaloids such as halitoxin,[1] papuamine,[2] haliclonadiamine,[3] haliclamines,[4] halicyclamine A,[5] and haliclonacyclamines[6] as well as manzamines[7] which are representative of these alkaloids. In 1992, Baldwin and Whitehead have proposed the fascinating biogenesis of these unique alkaloids, wherein the key feature is an intramolecular Diels-Alder reaction of bisdihydropyridine intermediate possessing various 3-alkyl chains linking the two heterocycles such as **3** (Fig. 1).[8] The appearance of the hypothetical biogenesis has prompted extensive work directed toward the biomimetic synthesis of these alkaloids.[9]

Two novel cytotoxic alkaloids haliclamines A (**1**) and B (**2**), isolated from a marine sponge of the genus *Haliclona* by Fusetani *et al.*, consist of two tetrahydropyridines linked through C_9 and C_{12} alkyl chains,[4] and their structures are most closely related to the key bisdihydropyridine intermediate **3** of macrocyclic alkaloids isolated ever.[10] In this communication we report the first convergent total synthesis of biogenetically stimulating haliclamine A (**1**) via inter- and intramolecular *N*-alkylations as a part in the course of our biomimetic synthetic studies on these marine alkaloids.

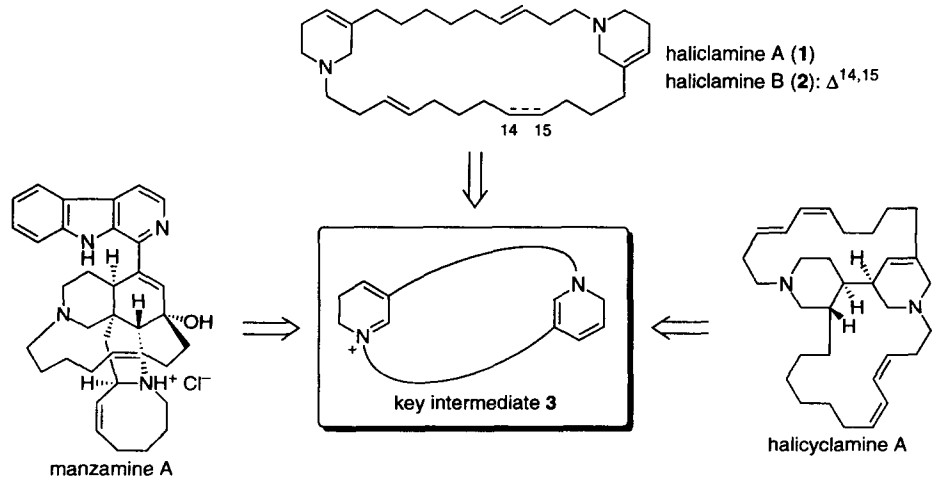
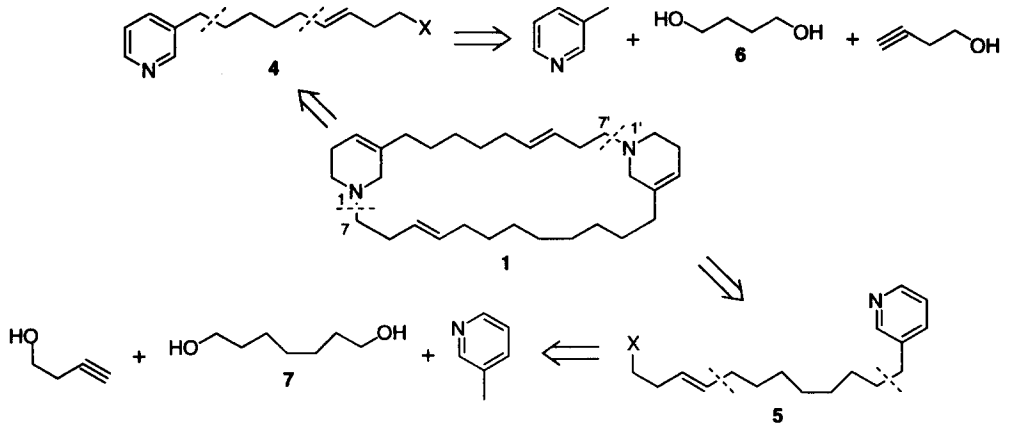


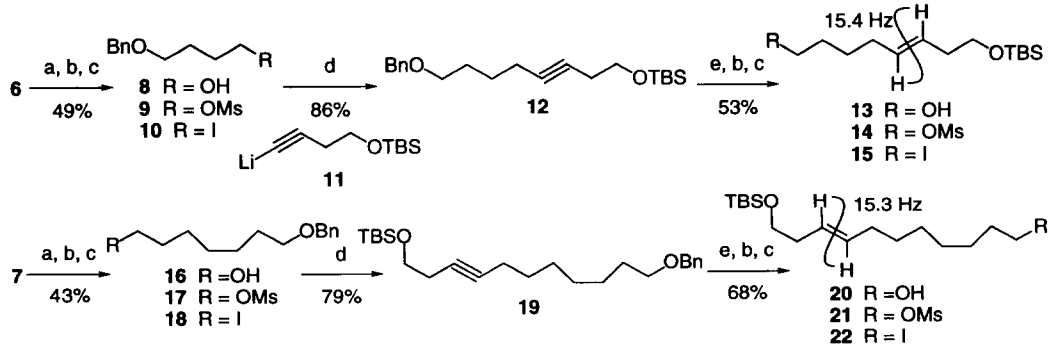
Fig. 1. Some representative alkaloids from sponges of the genus *Haliclona* which are considered to be biosynthesized by way of the bisdihydropyridine intermediate **3**.



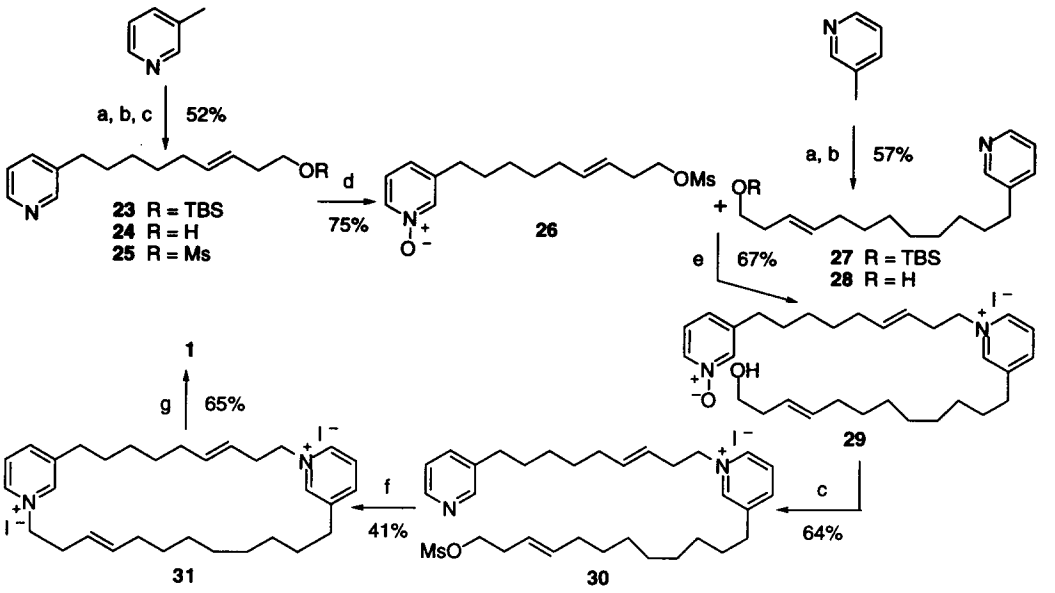
Scheme 1. Retrosynthetic analysis of haliclamine A (**1**).

The retrosynthetic analysis of haliclamine A (**1**) is outlined in Scheme 1. The disconnections of the N1-C7 and N1'-C7' bonds in **1** can envisage two 3-alkylpyridine derivatives **4** and **5** as valid precursors. It was anticipated that the macrocycle of **1** would be constructed by the convergent intermolecular *N*-alkylation of the two 3-alkylpyridine derivatives **4** and **5** followed by the intramolecular version. The further disconnections at the positions shown in **4** and **5** straightforwardly lead to the commercially available units, i.e. 3-picoline, 3-butyn-1-ol, and the appropriate diols **6** and **7**, respectively.

The preparation of alkyl chains **15** and **22** required for a coupling with 3-picoline began with monoprotection of the commercially available diols **6** and **7**, respectively (Scheme 2). The alkylation of iodide **10**, which was converted from the monobenzyl ether **8** via mesylation, with lithium acetylide **11**[11] in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU)-THF (1:1) as mixed solvent system[12] afforded acetylene **12** in 86% yield. The reduction of triple bond to *trans* double bond and removal of the benzyl protective group in the acetylene **12** were simultaneously carried out by treatment with a large excess of sodium in the presence of *t*-BuOH at –40 ~ –30 ℃ for a long time to yield stereoselectively *trans* olefin **13** as a single isomer, the stereochemistry of which 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 **13** was led to the desired iodide **15** in the usual manner. The same sequence of reactions starting from 1,7-heptanediol (**7**) gave the another desirable iodide **22** in comparable overall yields with the iodide **15**.



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) **11**, DMPU-THF (1:1), –15 °C, 30 min → rt, overnight; (e) an excess of Na, *t*-BuOH, NH_3-Et_2O, –40 ~ –30 °C, 3 ~ 4 d.



Scheme 3. Reagents and conditions: (a) LDA, 3-picoline, THF, –78 °C, 30 min, then **15** or **22**, –78 °C → rt, 4.5 h; (b) AcOH-H_2O (3:2), rt, 2 h; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (d) *m*-CPBA, CH_2Cl_2, 0 °C, 5 h → rt, overnight; (e) KI, CH_3CN, reflux, 4 d; (f) KI, 2 mM of **30** in CH_3CN, reflux, 2 d; (g) $NaBH_4$, MeOH-H_2O (3:2), 0 °C → rt, overnight.

With the appropriate alkyl chains **15** and **22** in hand, the next stage is preparation of 3-alkylpyridine derivatives **25** and **28** corresponding to **4** and **5**, respectively, and their convergent assembly (Scheme 3). Lithiation of 3-picoline was performed with lithium diisopropylamide in THF at –78 °C[10a] and subsequent addition of the iodide **15** provided alkylated adduct **23** in good yield, which was converted to the mesylate **25** via deprotection of *t*-butyldimethylsilyl ether. To avoid self-polymerization or intramolecular *N*-alkylation of **25** in the face of coupling **25** with **28** prepared by the same way, the nucleophilic nitrogen functionality in **25** was protected as *N*-oxide. The intermolecular *N*-alkylation of **28**[13] with the *N*-oxide **26**[13] in the presence of potassium iodide in refluxing acetonitrile[9c] affoded the desired pyridinium alcohol **29** in 67% yield. The usual mesylation of hydroxyl group in **29** concurrently resulted in an expedient deoxygenation of pyridine *N*-oxide for the next macrocyclization. The intramolecular *N*-alkylation of **30** in the presence of potassium iodide proceeded under high dilution condition (2 mM solution of **30** in refluxing CH_3CN)[9c,e] to yield ring closed bispyridinium macrocycle **31**.[14] Finally, reduction of the bispyridinium **31** with sodium borohydride[15] gave the synthetic haliclamine A (**1**),[13] the spectroscopic data of which was identical with the natural **1**[4] in all respects.

In summary the first total synthesis of haliclamine A (**1**), a macrocyclic marine alkaloid closely related to the key biogenetic intermediate of manzamines, has been efficiently accomplished through a convergent coupling of the 3-alkylpyridine derivatives **26** and **28**. Application of this strategy to haliclamine B (**2**) and an effort directed toward the biomimetic synthesis via bisdihydropyridine macrocycle **3** will be reported in due course.

Acknowledgment. This work was partly supported by the Saneyoshi Scholarship Foundation.

REFERENCES AND NOTES

1. Schmitz, F. J.; Hollenbeak, K. H.; Campbell, D. C. *J. Org. Chem.* **1978**, *43*, 3916-3922.
2. Baker, B. J.; Scheuer, P. J.; Shoolery, J. N. *J. Am. Chem. Soc.* **1988**, *110*, 965-966.

3. Fahy, E.; Molinski, T. F.; Harper, M. K.; Sullivan, B. W.; Faulkner, D. J.; Parkanyi, L.; Clardy, J. *Tetrahedron Lett.* **1988**, *29*, 3427-3428.
4. Fusetani, N.; Yasumuro, K.; Matsunaga, S.; Hirota, H. *Tetrahedron Lett.* **1989**, *30*, 6891-6894.
5. Jaspars, M.; Pasupathy, V.; Crews, P. *J. Org. Chem.* **1994**, *59*, 3253-3255.
6. Charan, R. D.; Garson, M. J.; Brereton, I. M.; Willis, A. C.; Hooper, J. N. A. *Tetrahedron* **1996**, *52*, 9111-9120.
7. (a) Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 6404-6405. (b) Sakai, R.; Kohmoto, S.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *Tetrahedron Lett.* **1987**, *28*, 5493-5496. (c) Kobayashi, M.; Chen, Y.-J.; Aoki, S.; In, Y.; Ishida, T.; Kitagawa, I. *Tetrahedron* **1995**, *51*, 3727-3736.
8. Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, *33*, 2059-2062.
9. (a) Baldwin, J. E.; Claridge, T. D. W.; Heupel, F. A.; Whitehead, R. C. *Tetrahedron Lett.* **1994**, *35*, 7829-7832. (b) Gil, L.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. *Tetrahedron Lett.* **1995**, *36*, 707-710. (c) Gil, L.; Gateau-Olesker, A.; Wong, Y.-S.; Chernatova, L.; Marazano, C.; Das, B. C. *Tetrahedron Lett.* **1995**, *36*, 2059-2062. (d) Gil, L.; Baucherel, X.; Martin, M.-T.; Marazano, C.; Das, B. C. *Tetrahedron Lett.* **1995**, *36*, 6231-6234. (e) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Smrcková, S.; Whitehead, R. C. *Tetrahedron Lett.* **1996**, *37*, 6919-6922. (f) Baldwin, J. E.; Bischoff, L.; Claridge, T. D. W.; Heupel, F. A.; Spring, D. R.; Whitehead, R. C. *Tetrahedron* **1997**, *53*, 2271-2290.
10. For biologically active polymeric or cyclic pyridinium alkaloids relevant to the bisdihydropyridine intermediate **3**, see: reference 1 and (a) Davies-Coleman, M. T.; Faulkner, D. J.; Dubowchik, G. M.; Roth, G. P.; Polson, C.; Fairchild, C. *J. Org. Chem.* **1993**, *58*, 5925-5930. (b) Fusetani, N.; Asai, N.; Matsunaga, S.; Honda, K.; Yasumuro, K. *Tetrahedron Lett.* **1994**, *35*, 3967-3970.
11. This lithium acetylide **11** was prepared from 3-butyn-1-ol in two steps: 1) TBSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C → rt, 5 h, 94%; 2) *n*-BuLi, THF, −15 °C, 30 min.
12. Torisawa, Y.; Hashimoto, A.; Nakagawa, M.; Seki, H.; Hara, R.; Hino, T. *Tetrahedron* **1991**, *47*, 8067-8078.
13. These compounds were characterized as follows: **28**, ^{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, 29.3, 29.0; IR (neat) 3260, 1561 cm^{-1}; EI-MS *m/z* 261 (M^+); EI-HRMS calcd for $C_{17}H_{27}ON$ (M^+) 261.2092, found 261.2120. **26**, ^{1}H 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, 1588, 1550 cm^{-1}; CI-MS *m/z* 314 [$(M + H)^+$]; CI-HRMS calcd for $C_{15}H_{24}O_4NS$ [$(M + H)^+$] 314.1426, found 314.1422. **1**, ^{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* 452 (M^+), 437, 264, 246, 204, 110, 96; EI-HRMS calcd for $C_{31}H_{52}N_2$ (M^+) 452.4130, found 452.4110.
14. For total synthesis of cyclostellettamine C related to this bispyridinium macrocycle **31**, see: Anan, H.; Seki, N.; Noshiro, O.; Honda, K.; Yasumuro, K.; Ozasa, T.; Fusetani, N. *Tetrahedron* **1996**, *52*, 10849-10860.
15. (a) Lyle, R. E.; Anderson, P. S. *Adv. Heterocycl. Chem.* **1966**, *6*, 45-93. (b) Wenkert, E.; Massy-Westropp, R. A.; Lewis, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 3732-3736.

(*Received in Japan* 19 *September* 1997; *revised* 8 *October* 1997; *accepted* 9 *October* 1997)