ORGANIC LETTERS

2003
Vol. 5, No. 17
3017−3020

New Stereoselective Entry to Azaspirocyclic Nucleus of Halichlorine and Pinnaic Acids by Radical Translocation/Cyclization Reaction

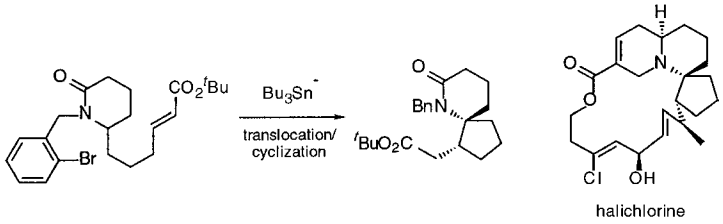
Kiyosei Takasu,* Hiroshi Ohsato, and Masataka Ihara*

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Sendai 980-8578, Japan

mihara@mail.pharm.tohoku.ac.jp

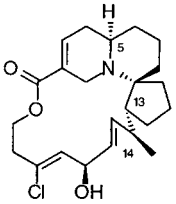
Received May 29, 2003

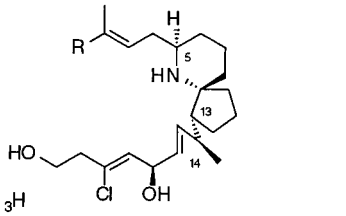
ABSTRACT



A stereoselective approach to the spirocyclic nucleus of halichlorine and pinnaic acids has been developed starting from a piperidine derivative. A key transformation in this sequence involves a cascade radical translocation/cyclization process.

Halichlorine (**1**)[1] and pinnaic acids (**2**)[2] are structurally related new marine alkaloids isolated from the Japanese sponge *Halichondria okadai* and the Okinawan bivalve *Pinna muricata*, respectively. It has been found that halichlorine significantly inhibits the induction of VCAM-1 (vascular cell adhesion molecule-1), and alkaloids **2a** and **2b** show the specific inhibition of cPLA$_2$ (cytosolic phospholipase A$_2$) activity. Structurally, **1** and **2** possess unique tetra- and bicyclic skeletons, respectively, involving the azaspiro[4.5]-decane system. There have been several reports on synthetic studies of these alkaloids,[3,4] concentrating on stereoselective construction of the azaspirocyclic core. Danishefsky and co-workers have accomplished the total synthesis of optically active **1** and **2a**,[3a] and Arimoto's group has recently reported the total synthesis of racemic **2a**.[3d] In both studies, the construction of azaspirocycle was achieved by intramolecular nucleophilic N−C bond formation reaction of cyclopentylamines, which have already possessed the essential stereochemical centers about the cyclopentane ring.





We envisioned that the azaspirocyclic framework would be constructed from a simple piperidine derivative by utilizing a cascade radical reaction, which involves radical translocation and continuous radical cyclization reactions.[5] In our plan, an aryl radical would homolytically dissociate a C−H bond, which is generally inactive or less active, by [1,5]-radical translocation, and then the resulting α-aminyl radical

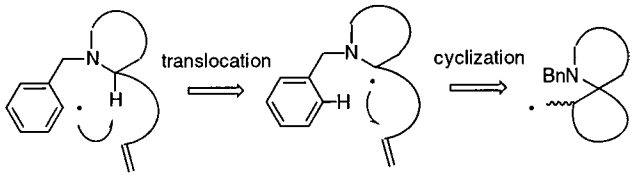
(1) Kuramoato, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867−3870.

(2) Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871−3874. The proposed structure in their report has been revised by Danishefsky's goup. See ref 3c.

(3) (a) Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542−3544. (b) Carson, M. W.; Kim, G.; Hentemann, M. F.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4450−4452. (c) Carson, M. W.; Kim, G.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4453−4456. (d) Hayakawa, I.; Arimoto, H.; Uemura, D. *Heterocycles* **2003**, *59*, 441−444.

10.1021/ol034942v CCC: $25.00
Published on Web 08/01/2003

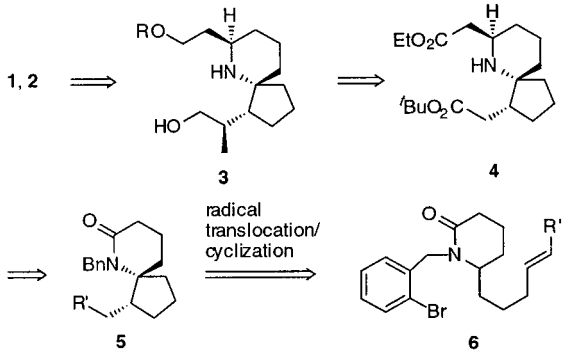
Scheme 1. Radical Translocation/Cyclization Strategy



would successively react with an intramolecular olefinic bond (Scheme 1).[6] Thus, this sequence would provide azaspirocyclic structures having consecutive quaternary and tertiary stereogenic centers from amine-containing monocyclic compounds.

We here describe a novel approach toward the azaspiro[4.5]decane framework of halichlorine and pinnaic acids by utilizing the cascade radical translocation and addition reaction. Furthermore, we demonstrate the stereoselective installation of substituents at C(5) and C(14) positions. Retrosynthetically, the target alkaloids **1** and **2** could be bisected into a spirocyclic subunit such as alcohol **3** and a C(15)−C(21) chlorodienyl moiety[7] (Scheme 2). A methyl

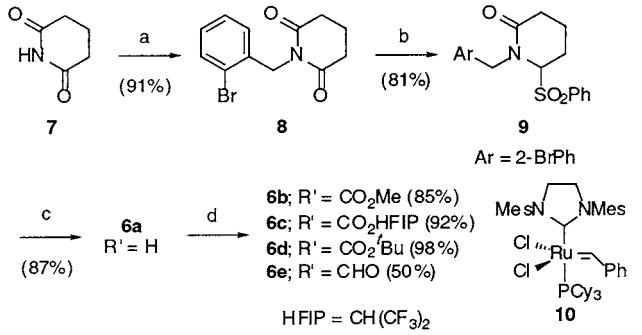
Scheme 2. Retrosynthetic Analysis of Halichlorine (**1**) and Pinnaic Acids (**2**)



substituent at C(14) position of **3** would be formed by stereoselective methylation of *tert*-butyl ester **4**. Diester **4** would arise from benzylamide **5**, which could be constructed from **6** by the above cascade strategy. We have anticipated that the rate and stereoselectivity in the radical reaction would be controlled by the olefinic substituent (R′).

Preparation of the radical precursors of **6a**−**e** started with the alkylation of glutalimide (**7**) with 2-bromobenzyl bromide to provide benzylimide **8** (Scheme 3). Reduction of **8** with

Scheme 3[a]



[a] Reagents and conditions: (a) 2-bromobenzyl bromide, KOH, DMF, rt. (b) (i) $NaBH_4$, 2 N HCl, EtOH, rt; (ii) $PhSO_2H$, $CaCl_2$, CH_2Cl_2, rt. (c) CH_2═$CH(CH_2)_3MgBr$, $ZnCl_2$·Et_2O, Et_2O−CH_2Cl_2, rt. (d) R′CH═CH_2 (2 equiv), **10** (5 mol %), CH_2Cl_2, rt (reflux for the preparation of **6d**).

$NaBH_4$ in the presence of a catalytic amount of HCl followed by treatment with benzenesulfinic acid afforded sulfone **9** in good overall yield.[8] The sulfone **9** was converted into 6-substituted piperidin-2-one **6a** (R′ = H) by Grignard reaction in the presence of Lewis acidic $ZnCl_2$. The transformation of **6a** into electron-deficient alkenes **6b**−**e** was accomplished by cross-metathesis reaction.[9] Namely, **6a** was treated with 2 equiv of acrylate or acrolein and 5.0 mol % Grubbs' second-generation catalyst (**10**) to furnish the corresponding activated alkenes **6b**−**e** in medium to good yield. In all the reactions, *trans*-alkenes were selectively produced.

Next, the cascade radical translocation/cyclization reaction of **6a**−**e** was examined under the radical conditions. To a refluxing solution of **6** in benzene was added a benzene solution of Bu_3SnH (2.0 equiv) and AIBN (0.5 equiv) by using a syringe pump over a period of 18 h, and the mixture was refluxed for additional 1 h. Conventional workup and chromatographic purification furnished the desired spirolactam **5** and its diastereomer *epi*-**5**. The results are summarized in Table 1. Reaction of **6a** possessing unactivated olefin furnished a mixture of **5a** and *epi*-**5a** (diastereomeric ratio = 3:1) in 54% yield along with noncyclized debrominated compound **11a** (entry 1). Introduction of an ester function into the olefinic substituent resulted in higher production of spirocyclic compounds (entries 2−4), while the reaction of

(4) (a) Arimoto, H.; Asano, S.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 3583−3586. (b) Trauner, D. Danishefsky, S. J. *Tetrahedron Lett.* **1999**, *40*, 6513−6516. (c) Lee, S.; Zhao, Z. *Tetrahedron Lett.* **1999**, *40*, 7921−7924. (d) Clive, D. L.; Yeh, V. S. C. *Tetrahedron Lett.* **1999**, *40*, 8503−8507. (e) Koviach, J. L.; Forsyth, C. J. *Tetrahedron Lett.* **1999**, *40*, 8529−8532. (f) Shindo, M.; Fukuda, Y.; Shishido, K. *Tetrahedron Lett.* **2000**, *41*, 929−932. (g) Wright, D. L.; Schulte, J. P., II; Page, M. A. *Org. Lett.* **2000**, *2*, 1847−1850. (h) White, J. D.; Blakemore, P. R.; Korf, E. A.; Yokochi, A. F. T. *Org. Lett.* **2001**, *3*, 413−415.

(5) For a review of radical translocation reactions, see: (a) Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, *30*, 94−103. For examples of radical translocation/cyclization reaction in synthesis, see: (b) Snieckus, V.; Cuevas, J.-C.; Sloan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 896−898. (c) Curran, D. P.; Abraham, A. C.; Liu, H. *J. Org. Chem.* **1991**, *56*, 4337−4339. (d) Sha, C.-K.; Hsu, C.-W.; Chen, Y.-T.; Cheng, S.-Y. *Tetrahedron Lett.* **2000**, *41*, 9865−9869. (e) Sato, T.; Yamazaki, T.; Nakanishi, Y.; Uenishi, J.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1438−1443. (f) Curran, D. P.; Liu, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377−1394.

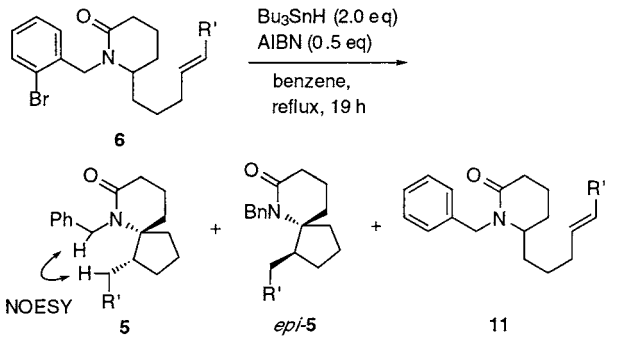
(6) Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8209−8217.

(7) Keen, S. P.; Weinreb, S. M. *J. Org. Chem.* **1998**, *63*, 6739−6741.

(8) Ley, S. V.; Lygo, B.; Sternfield, F.; Wonnacott, A. *Tetrahedron* **1986**, *42*, 4333−4342.

(9) Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783−3784.

Table 1. Cascade Radical Reaction of **6** Leading to Azaspirocycle **5**[a]



entry	R′	% yield of (**5** + *epi*-**5**)	ratio of **5**:*epi*-**5**	% yield of **11**
1	H	54	75:25[c]	7
2	CO_2Me	88	78:22[c]	0
3	CO_2HFIP[b]	71	56:44[d]	nd[e]
4	$CO_2{}^t$Bu	78	91:9[d]	0
5	CHO	trace		nd[e]

[a] Reactions were performed using 2.0 equiv of Bu_3SnH and 0.5 equiv of AIBN in refluxing benzene for 19 h. [b] HFIP means 1,1,1,3,3,3-hexafluoroisopropyl. [c] Ratios were determined by ^{1}H NMR. [d] Ratios were determined on the basis of isolated yields. [e] Not determined.

α,β-unsaturated aldehyde **6e** was unsuccessful (entry 5). The best result was obtained in the case of *tert*-butyl ester **6d** to afford **5d** in 71% yield with a high diastereoselectivity (entry 4; *epi*-**5d** was obtained in 7% yield). Spirolactam **5d**, which has the same relative configuration as the natural products, could be easily separated from *epi*-**5d** by recrystallization, and its stereochemistry was confirmed by NOESY experiment. It is noteworthy that preparation of **5d** could be performed as a multigram-scale reaction. Although the detailed reaction mechanism remains to be clarified, possible conformations of the transition state can be drawn for an explanation of the substrate-controlled selectivity observed (Figure 1). In the cyclization step, there would be sterically

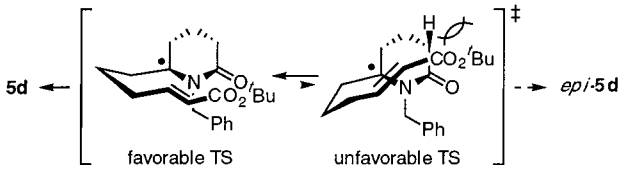
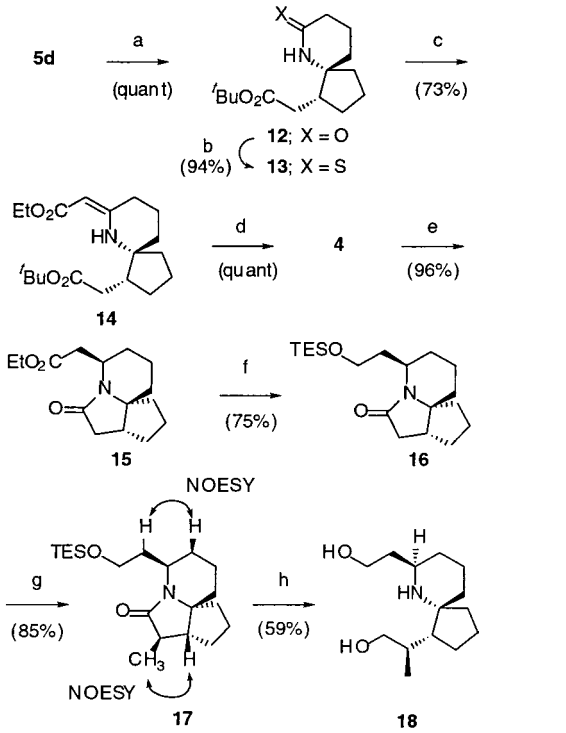


Figure 1. Plausible transition states in the radical translocation/cyclization reaction.

repulsive interaction between the R′ substituent and an axially oriented proton on the piperidine ring.

The stereoselective transformation of **5d** into the fully functionalized spiro-system **3** is shown in Scheme 4. Debenzylation of **5d** with $Pd(OH)_2-H_2$ in acidic media quantitatively furnished amide **12**. Introduction of a two-

Scheme 4[a]



[a] Reagents and conditions: (a) cat. $Pd(OH)_2$, H_2, cat. HCl (concd), ^{t}BuOH, reflux. (b) Lawesson's reagent, toluene, reflux. (c) (i) ethyl 2-bromoacetylacetate, $NaHCO_3$, CH_2Cl_2, rt; (ii) NaOEt, EtOH, 40 °C. (d) PtO_2, H_2, EtOH, rt. (e) (i) TFA, CH_2Cl_2, rt; (ii) EDCl, CH_2Cl_2, rt. (f) (i) $LiEt_3BH$, THF, 0 °C; (ii) TESCl, NEt_3, cat. DMAP, CH_2Cl_2, rt. (g) LDA, THF, −78 °C; then MeI, −78 °C. (h) $Li(NH_2)BH_3$, THF, 40 °C.

carbon atom chain at the C(5) position was accomplished by Eschenmoser reaction.[10] Namely, lactam **12** was converted into thiolactam **13** (94% yield), and then coupling of **13** with ethyl 2-bromoacetoacetate, followed by deacetylation, served to generate vinylogous carbamate (*E*)-**14** in 73% overall yield. According to a method for stereoselective reduction of a structurally analogous compound reported by Shishido's group,[4f] catalytic hydrogenation of **14** was successful in exclusively giving piperidine **4**, whose stereochemistry was deduced by two-dimensional NMR results.

The next critical issue in the path towards halichlorine and pinnaic acids is the stereoselective installation of methyl group at the C(14) position. Initial experiments showed that the C(14)-methylation of spirocyclic compounds such as **5d** was unsuccessful under a variety of conditions. We next planned to utilize the stereochemical character (e.g., concave vs convex selection) of a fused ring system, which would be easily derived from **4**. Tricyclic lactam **15** was prepared by selective hydrolysis of **4** under acidic conditions and the subsequent lactamization. The ester **15** was submitted to reduction using Super-hydride at 0 °C followed by protection by TESCl to give **16**. Simple computer modeling by

(10) (a) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710−734. (b) Tanino, H.; Nakata, T.; Kaneko, T.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 2818−2819.

molecular mechanics has encouraged us that the β-face at the C(14) position of azatricyclo[7.3.0.0^{1,5}]dodecane **16** corresponds to the less bulky convex face. Exposure of lithium enolate of **16** to methyl iodide at −78 °C gave rise to **17** as a sole diastereomer in 85% yield. NOESY experiment supported the introduction of the methyl group from the desired direction, as expected.

With all the required configuration of stereogenic centers except for the C(17) position in hand, we attempted cleavage of the amide bond. It was found that treatment of lactam **17** with $Li(NH_2)BH_3$, prepared from $BH_3{\cdot}NH_3$ and BuLi,[11] lead to reductive cleavage of C−N bond to give **18** in 59% yield.

In summary, we have developed a novel concise route for the synthesis of the azaspirocyclic core structure of halichlorine and pinnaic acids possessing four of five stereogenic centers in a highly stereoselective manner. The key cascade radical translocation/cyclization reaction allows the creation of the azaspiro[4.5]decane skeleton with creation of two adjacent stereogenic centers from a readily available piperidine derivative. The application of the cascade radical reaction should provide stereocontrolled access to a wide variety of spirocyclic compounds.[12] Further studies toward the total syntheses of the natural products will be reported in due course.

Acknowledgment. This work was supported in part by Fujisawa Pharmaceutical Company Award in Synthetic Organic Chemistry, Japan, and Grants-in-Aid for Encouragement of Young Scientists and for Scientific Research on Priority Areas (A) "Exploitation of Multi Element Cyclic Molecules" from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034942V

(11) (a) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623−3626. (b) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583−4592.

(12) We have proven that a variety of heteroatom-containing spirocycles can be synthesized by our strategy. The efforts will be published elsewhere.