thesis, Universität Stuttgart, **1989**; e) D. Andrae, U. Häussermann, M. Dolg, H. Stoll, H. Preuss, *Theor. Chim. Acta* **1990**, *77*, 123.
[16] P. D. Rege, O. L. Malkina, N. S. Goroff, *J. Am. Chem. Soc.* **2002**, *124*, 371.
[17] Our experience with Lewis acidic iodides has shown that 1,7-phenanthroline is an effective cocrystallizing agent, which forms robust, easily analyzed crystals. We have been unable to isolate crystals of **2** that are suitable for X-ray crystallography.
[18] a) S. Uji, C. Terakura, T. Terashima, H. Aoki, H. M. Yamamoto, J. Yamaura, R. Kato, *Synth. Met.* **1999**, *103*, 1978; b) H. M. Yamamoto, J. I. Yamaura, R. Kato, *Synth. Met.* **1999**, *102*, 1448; c) H. M. Yamamoto, J. Yamaura, R. Kato, *Synth. Met.* **1999**, *102*, 1515; d) H. M. Yamamoto, J. I. Yamaura, R. Kato, *J. Am. Chem. Soc.* **1998**, *120*, 5905; e) H. M. Yamamoto, J. I. Yamaura, R. Kato, *J. Mater. Chem.* **1998**, *8*, 15.
[19] Mass spectra measured on an Agilent 5973 spectrometer. The mass limit of the instrument ($m/z_{max} = 800$) does not allow the observation of the parent ion of **2** with $M_W = 810$.
[20] SHELX97—Programs for Crystal Structure Analysis (Release 97-2): G. M. Sheldrick, SHELXS-98, Program for the Solution of Crystal Structures, University of Göttingen, Göttingen (Germany), **1998**.

Atom-Transfer Tandem Radical Cyclization Reactions Promoted by Lewis Acids**

Dan Yang,* Shen Gu, Yi-Long Yan, Hong-Wu Zhao, and Nian-Yong Zhu

Tandem radical cyclization reactions are powerful methods for the synthesis of a wide range of highly functionalized polycyclic natural products as multiple stereocenters can be constructed in one step under mild conditions.[1,2] However, no enantioselective tandem radical cyclization reactions have been reported.[3] Herein we describe a Lewis acid catalyzed atom-transfer tandem radical cyclization method for the formation of various bicyclic and tricylic ring skeletons. Furthermore, the first enantioselective tandem radical cyclization was achieved by using chiral Lewis acids as catalysts.

We recently reported an enantioselective atom-transfer radical monocyclization catalyzed by a chiral Lewis acid to prepare cyclic 2,3-disubstituted ketones.[4] $Yb(OTf)_3$ (OTf = trifluoromethanesulfonate) and $Mg(ClO_4)_2$ were found to be the best Lewis acids in these monocyclization reactions. Therefore, the two Lewis acids were further used to promote tandem cyclization of α-bromo β-keto esters **1a–f** with Et_3B/O_2 as the radical initiator (Table 1). Substrates **1a** and **1b** with two C=C bonds in the same carbon chain exclusively underwent 6-*endo* and then 5-*exo* cyclization for **1a** and 6-*exo* cyclization for **1b** in the presence of a Lewis acid to give the fused ring products 6,5-*cis*-**2a** and 6,6-*trans*-**2b**, respectively (Table 1, entries 1–4). In each case, four stereocenters of the cyclization products **2a**/**2b** were set up in one step. Furthermore, as little as 0.3 equivalents of $Yb(OTf)_3$ was sufficient to catalyze the cyclization of **1a** to give **2a** in 69% yield (Table 1, entry 2), and a decrease in the amount of $Mg(ClO_4)_2$ (to 0.5 equiv) did not decrease the yield of **2b** in the cyclization of **1b** (Table 1, entry 4). For substrates **1c—e**,[5] which have an allyl substituent in the α-position, 6-*endo* (6-*exo* for substrate **1d**) followed by 5-*exo* cyclization gave the corresponding bicyclic products **2c–e** in moderate yields in the presence of a stoichiometric amount of $Mg(ClO_4)_2$ (Table 1, entries 5–7). Furthermore, triple cyclization of **1f** gave product **2f** as one of 16 possible stereoisomers in 26% yield (Table 1, entry 8). When $Yb(OTf)_3$ was used as the Lewis acid catalyst, no more than 16% yield can be obtained in the cyclization of substrates **1b–f**. For all the substrates investigated, no atom-transfer radical cyclization was observed in the absence of Lewis acids. These results demonstrate that the Lewis acids not only promote tandem radical cyclization reactions, but also control the stereoselectivities of the cyclization products.[6] The major side products of those tandem cyclization reactions were the corresponding reductive debromination products (< 12% yield), monocyclization products (< 30% yield), and even a bicyclization product (for **1f** only; 12% yield).[7] Especially for substrate **1b**, the 1,3-diaxial interaction of two methyl groups made the second ring cyclization unfavorable, and as a result the radical chain process was partially terminated in the monocyclization stage with the isolation of a monocyclization product in up to 30% yield.

Then we investigated the enantioselective tandem cyclization of **1a** and **1b** by using $Mg(ClO_4)_2$ and bisoxazoline ligand **L1** as a chiral catalyst (Table 2). Poor *ee* values were observed in the cyclization of **1a** (Table 2, entry 1). Although the addition of activated 4-Å molecular sieves[4,8] improved the *ee* value, it decreased the yield dramatically (Table 2, entry 2). High *ee* values (82–84%) were observed in the cyclization of **1b** at higher temperature, despite lower yields (Table 2, entries 3 and 4). With $Yb(OTf)_3$ as the catalyst,[9] the effects of chiral ligands,[10] additives,[11] and solvents on the enantioselective tandem cyclization of **1a** were evaluated. As shown in Table 3, the **L3**/Yb complex gave the best results (60% yield and 66% *ee*; Table 3, entry 4). Dichloromethane was found to be a better solvent than toluene in this tandem cyclization system (Table 3, entry 4 vs. 6). The addition of Et_2O or water had negative effects on these reactions (Table 3, entries 2 and 3). Surprisingly, the addition of molecular sieves led to reversed enantiofacial selectivity of the cyclization[11e] (Table 3, entry 5).

The stereochemistry of tandem radical cyclization reactions in the presence of the chiral complex [Yb(Ph-pybox)$(OTf)_3$] (pybox = 2,6-bis(2-oxazolin-2-yl)pyridine) can be explained using the transition-state model shown in Scheme 1. Similar to the chiral complex [Sc(Ph-pybox)(ethyl glyoxylate)$(OTf)]^{2+}$ proposed by Evans et al.,[12] the ytterbium center adopts a square-pyramidal geometry with the ester carbonyl group

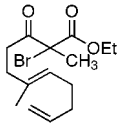
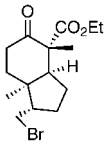
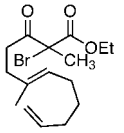
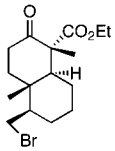
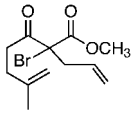
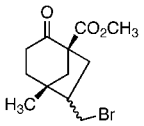
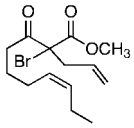
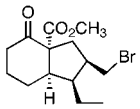
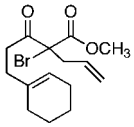
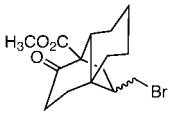
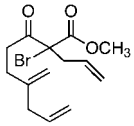
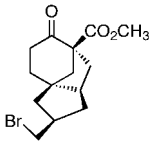
[*] Prof. D. Yang, S. Gu, Y.-L. Yan, H.-W. Zhao, N.-Y. Zhu
Department of Chemistry, The University of Hong Kong
Pokfulam Road, Hong Kong (P. R. China)
Fax: (+852) 2859-2159
E-mail: yangdan@hku.hk

[**] This work was supported by The University of Hong Kong and the Hong Kong Research Grants Council. D.Y. acknowledges the Bristol-Myers Squibb Foundation for an Unrestricted Grant in Synthetic Organic Chemistry and the Croucher Foundation for a Croucher Senior Research Fellowship.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

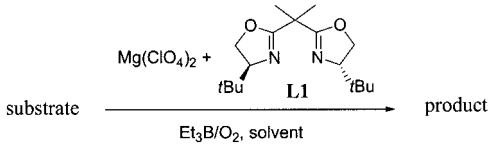
  0044-8249/02/4116-3014 $ 20.00+.50/0

Table 1. Lewis acid promoted free-radical tandem cyclization reactions.[a]

Entry	Substrate	Lewis acid	Solvent	*t* [h]	Product	Yield [%][b]
1	 **1a**	$Yb(OTf)_3$	Et_2O	2	 **2a**	85
2[c]		$Yb(OTf)_3$	Et_2O	2		69
3[d]	 **1b**	$Mg(ClO_4)_2$	toluene	2	 **2b**	20
4[d,e]		$Mg(ClO_4)_2$	toluene	4		20
5	 **1c**	$Mg(ClO_4)_2$	CH_2Cl_2	2	 **2c**	51 (α/β 1:1.8)[f]
6	 **1d**	$Mg(ClO_4)_2$	CH_2Cl_2	2.5	 **2d**	47
7	 **1e**	$Mg(ClO_4)_2$	CH_2Cl_2	2	 **2e**	40 (α/β 1.2:1)[f]
8	 **1f**	$Mg(ClO_4)_2$	CH_2Cl_2	2	 **2f**	26

[a] Unless otherwise indicated, all reactions were carried out at −78 °C with the indicated Lewis acid (1.0 equiv), Et_3B/O_2 (5.0 equiv) in the indicated solvent (0.025 M). [b] Yield of isolated product. [c] $Yb(OTf)_3$ (0.3 equiv). [d] The reaction was carried out at −40 °C. [e] $Mg(ClO_4)_2$ (0.5 equiv). [f] Ratio of epimers.

Table 2. Chiral Lewis acid promoted enantioselective atom-transfer radical tandem cyclization reactions.[a]



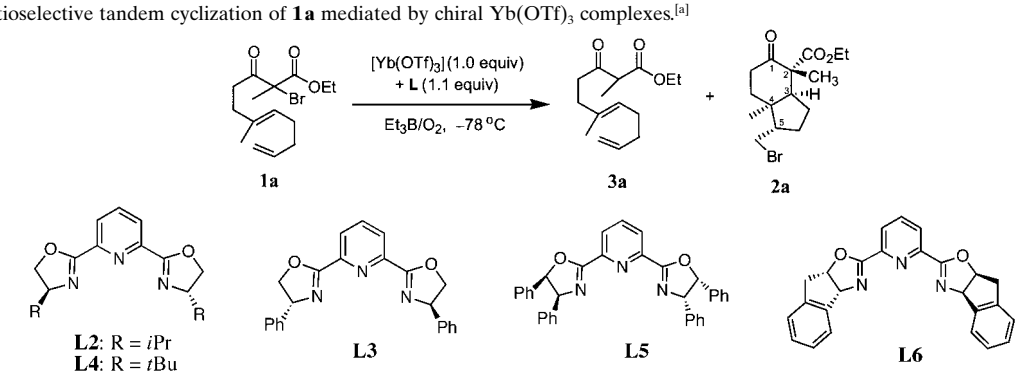
Entry	Substrate	*T* [°C]	Solvent	Product	Yield [%][b]	*ee* [%][c]
1	**1a**	−78	CH_2Cl_2	**2a**	41	13[d]
2[e]	**1a**	−78	CH_2Cl_2	**2a**	24	33[d]
3	**1b**	−40	toluene	**2b**	23	82[f]
4	**1b**	−20	toluene	**2b**	16	84[f]

[a] Unless otherwise indicated, all reactions were carried out with substrate (0.2 mmol) in the indicated solvent (0.025 M), $Mg(ClO_4)_2$ (1.0 equiv), and (*S*, *S*)-**L1** (1.1 equiv). [b] Yield of isolated product. [c] The enantiomeric excess was determined by HPLC analysis with a Chiralcel OD or AD column. [d] The absolute configuration of product **2a** was determined to be (2*R*,3*S*,4*S*,5*S*) by X-ray analysis. [e] Activated molecular sieves (4 Å, powder, 500 mg/mmol substrate) were added. [f] The absolute configuration of product **2b** was not determined.

bound in the equatorial position and the ketone carbonyl group in the apical position. To avoid steric interactions between the alkyl chain of the substrate and the phenyl groups of ligand **L3**, the *Re*-face cyclization is favored over the *Si*-face cyclization (not shown). In the 6-*endo* cyclization, a chairlike transition state is preferred, which gives a tertiary radical

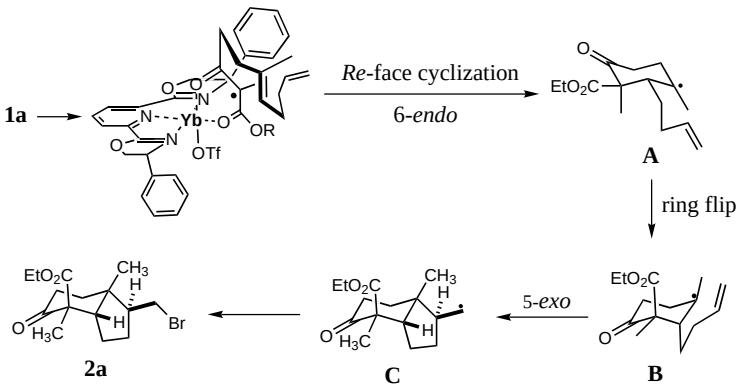
  0044-8249/02/4116-3015 $ 20.00+.50/0

Table 3. Enantioselective tandem cyclization of **1a** mediated by chiral $Yb(OTf)_3$ complexes.[a]



Entry	Ligand	Solvent	Additive	t [h]	Yield [%][b] (**3a**)	Yield [%][b] (**2a**)	*ee* [%][c] (**2a**)
1	**L2**	CH_2Cl_2	–	13	11	28	−37
2[d]	**L2**	CH_2Cl_2	H_2O	24	–[e]	–[e]	–[e]
3[f]	**L2**	CH_2Cl_2	Et_2O	24	14	26	−13
4	**L3**	CH_2Cl_2	–	15	23	60	66[g]
5[h]	**L3**	CH_2Cl_2	4-Å MS	13	68	11	−56
6	**L3**	toluene	–	12	30	37	50
7	**L4**	CH_2Cl_2	–	21	66	18	< 1
8	**L5**	CH_2Cl_2	–	12	51	13	< 1
9	**L6**	toluene	–	10	64	17	−43

[a] Unless otherwise indicated, all reactions were carried out at −78 °C in the indicated solvent at 0.025 M concentration with $Yb(OTf)_3$, the indicated ligand (1.1 equiv), and Et_3B/O_2 (5 equiv). [b] Yield of isolated product. [c] The enantiomeric excess was determined by HPLC analysis using a Chiralcel OD column. [d] H_2O (1.0 equiv) was added. [e] The major product was the corresponding debromination compound **3a** (TLC analysis), but no attempt was made to isolate the products. [f] Et_2O (1.0 equiv) was added. [g] The absolute configuration of the major enantiomer was determined to be 2*R*,3*S*,4*S*,5*S* by X-ray crystallographic analysis. [h] Activated molecular sieves (MS; 4 Å, powder, 500 mg/mmol substrate) were added.



Scheme 1. Proposed transition-state model for the {Yb(Ph-pybox)} complex promoted radical cyclization reaction of **1a**.

intermediate **A** with an equatorial homoallylic group. After a ring flip from **A** to **B**, 5-*exo* cyclization affords a 6,5-*cis* ring-fused primary radical **C**, which abstracts the bromine atom from **1a** to yield (2*R*,3*S*,4*S*,5*S*)-**2a**.

In summary, we have developed an efficient and stereoselective Lewis acid catalyzed atom-transfer radical tandem cyclization method for the construction of polycyclic ring skeletons under mild and neutral conditions. Furthermore, the first enantioselective version of those atom-transfer tandem cyclization reactions was developed with the *ee* values up to 84%. This method should have great potential for the enantioselective synthesis of complex natural products with significant biological activities.

Received: February 12, 2002
Revised: June 11, 2002 [Z18697]

[1] For recent reviews on tandem radical cyclization reactions, see: a) M. Malacria, *Chem. Rev.* **1996**, *96*, 289; b) A. J. McCarroll, J. C. Walton, *Angew. Chem.* **2001**, *113*, 2282; *Angew. Chem. Int. Ed.* **2001**, *40*, 2224; for recent examples, see: c) D. P. Curran, J. Sisko, A. Balog, N. Sonoda, K. Nagahara, I. Ryu, *J. Chem. Soc. Perkin Trans. 1* **1998**, *10*, 1591; d) S. Kim, J. H. Cheong, J. Yoo, *Synlett* **1998**, 981; e) D. Yang, X.-Y. Ye, S. Gu, M. Xu, *J. Am. Chem. Soc.* **1999**, *121*, 5579; f) M. Kizil, B. Patro, O. Callaghan, J. A. Murphy, M. B. Hursthouse, D. Hibbs, *J. Org. Chem.* **1999**, *64*, 7856; g) C.-K. Sha, F.-K. Lee, C.-J. Chang, *J. Am. Chem. Soc.* **1999**, *121*, 9875; h) B. Patro, J. A. Murphy, *Org. Lett.* **2000**, *2*, 3599; i) S. T. Hiton, K. Jones, C. T. Tim, G. Pljevaljcic, M. Schulte, *Chem. Commun.* **2001**, 209; j) C. Ollivier, P. Renaud, *J. Am. Chem. Soc.* **2001**, *123*, 4717; k) D. Yang, M. Xu, *Org. Lett.* **2001**, *3*, 1785; l) J. T. Njardarson, I. M. McDonald, D. A. Spiegel, M. Inoue, J. L. Wood, *Org. Lett.* **2001**, *3*, 2435; m) Y. Haruo, T. Hasegawa, H. Tanaka, T. Takahashi, *Synlett* **2001**, 1935; n) S. Zhou, S. Bommezijn, J. A. Murphy, *Org. Lett.* **2002**, *4*, 443.

[2] For recent reviews on free radical reactions in the synthesis of natural products, see: a) C. P. Jasperse, D. P. Curran, T. L. Fevig, *Chem. Rev.* **1991**, *91*, 1237; b) P. J. Parsons, C. S. Penkett, A. J. Shell, *Chem. Rev.* **1996**, *96*, 195.

[3] For a recent review on enantioselective radical reactions, see: a) M. P. Sibi, N. A. Porter, *Acc. Chem. Res.* **1999**, *32*, 163; for recent examples, see: b) U. Iserloh, D. P. Curran, S. Kanemasa, *Tetrahedron: Asymmetry* **1999**, *10*, 2417; c) M. P. Sibi, J. Chen, *J. Am. Chem. Soc.* **2001**, *123*, 9472; d) M. P. Sibi, Y. Asano, J. B. Sausker, *Angew. Chem.* **2001**, *113*, 1333; *Angew. Chem. Int. Ed.* **2001**, *40*, 1293; e) M. P. Sibi, J. B. Sausker, *J. Am. Chem. Soc.* **2002**, *124*, 984.

[4] D. Yang, S. Gu, Y.-L. Yan, N.-Y. Zhu, K.-K. Cheung, *J. Am. Chem. Soc.* **2001**, *123*, 8612.

[5] See: D. P. Curran, T. M. Morgan, C. E. Schwartz, B. B. Snider, M. A. Dombroski, *J. Am. Chem. Soc.* **1991**, *113*, 6607; the atom-transfer cyclization of substrates **1c** and **1d** by using $(Me_3Sn)_2/h\nu$ as the radical initiator in the absence of Lewis acid has been reported; cyclization of **1c** afforded the same products; both *trans* and *cis* products (9:1) were obtained in the cyclization of **1d**.

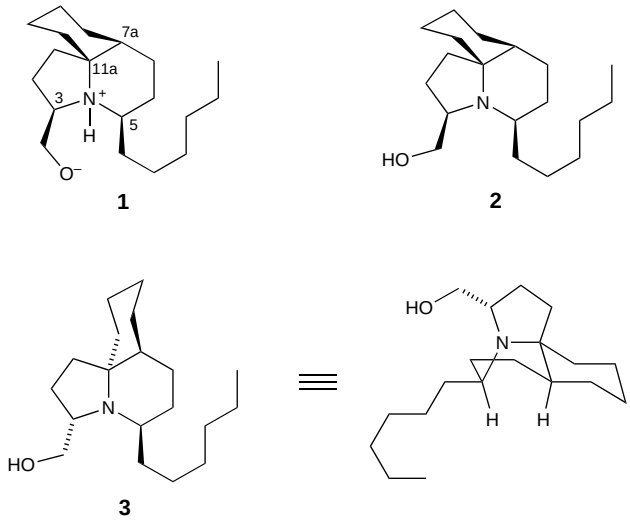
  0044-8249/02/4116-3016 $ 20.00+.50/0

[6] a) For an excellent review of Lewis acid mediated radical reactions, see: P. Renaud, M. Gerster, *Angew. Chem.* **1998**, *110*, 2704; *Angew. Chem. Int. Ed.* **1998**, *37*, 2562; for recent examples of Lewis acid promoted atom-transfer radical reactions, see: b) C. L. Mero, N. A. Porter, *J. Am. Chem. Soc.* **1999**, *121*, 5155; c) A. J. Clark, F. D. Campo, R. J. Deeth, R. P. Filik, S. Gatard, N. A. Hunt, D. Lastecoueres, G. H. Thomas, J.-B. Verlhac, H. Wongtap, *J. Chem. Soc. Perkin Trans. 1* **2000**, 671; d) O. Kitagawa, H. Fujiwara, T. Taguchi, *Tetrahedron Lett.* **2001**, *42*, 2165; e) O. Kitagawa, Y. Yamada, H. Fujiwara, T. Taguchi, *J. Org. Chem.* **2002**, *67*, 922.
[7] For details about side products, see Supporting Information.
[8] For examples on the use of 4-Å molecular sieves in asymmetric reactions, see: a) R. M. Hanson, K. B. Sharpless, *J. Org. Chem.* **1986**, *51*, 1922; b) K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima, J. Sugimoto, *J. Am. Chem. Soc.* **1989**, *111*, 5340; c) K. Mikami, M. Terada, T. Nakai, *J. Am. Chem. Soc.* **1990**, *112*, 3949; d) D. A. Evans, M. M. Faul, M. T. Bilodeau, B. A. Anderson, D. M. Barnes, *J. Am. Chem. Soc.* **1993**, *115*, 5328; e) T. Iida, N. Yamamoto, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 4783.
[9] For recent reviews on lanthanide Lewis acids catalysis, see: a) S. Kobayashi, *Synlett* **1994**, 689; b) M. Shibasaki, K.-I. Yamada, N. Yoshikawa in *Lewis Acids in Organic Synthesis, Vol. 2* (Ed: H. Yamamoto), Wiley, New York, **2000**, chap. 20, p. 911.
[10] For recent reviews on the use of C_2-symmetric chiral bisoxazoline ligands in asymmetric catalysis, see: a) A. Pfaltz, *Acta Chem. Scand.* **1996**, *50*, 189; b) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1; c) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325.
[11] a) For a recent review on the effect of additives on asymmetric reactions, see: E. M. Vogl, H. Gröger, M. Shibasaki, *Angew. Chem.* **1999**, *111*, 1672; *Angew. Chem. Int. Ed.* **1999**, *38*, 1570; for examples of the additive effect in chiral ytterbium triflate mediated asymmetric reactions, see: b) S. Kobayashi, H. Ishitani, *J. Am. Chem. Soc.* **1994**, *116*, 4083; c) S. Kobayashi, H. Ishitani, I. Hachiya, M. Araki, *Tetrahedron* **1994**, *50*, 11623; d) T. Saito, M. Kawamura, J.-I. Nishimura, *Tetrahedron Lett.* **1997**, *38*, 3231; e) M. Kawamura, S. Kobayashi, *Tetrahedron Lett.* **1999**, *40*, 3213.
[12] D. A. Evans, Z. K. Sweeney, T. Rovis, J. S. Tedrow, *J. Am. Chem. Soc.* **2001**, *123*, 12095.

Total Synthesis of the Natural Enantiomer of (−)-Lepadiformine and Determination of Its Absolute Stereochemistry**

Hideki Abe, Sakae Aoyagi, and Chihiro Kibayashi*

Lepadiformine was isolated by Biard et al. in 1994 from the marine tunicates *Clavelina lepadiformis* collected in Tunisia[1] and from *Clavelina moluccensis* found along the Djibouti coast.[2] It has been shown to exhibit moderate cytotoxic activity against various tumor cell lines in vitro.[1] Moreover, a recent study indicated that lepadiformine is very active in the cardiovascular system in vivo and in vitro and suggested that it has antiarrhythmic properties.[2] On the basis of extensive NMR spectroscopic experiments, its structure and relative stereochemistry were reported as the zwitterion **1** (Scheme 1) with a novel azatricyclic skeleton.[1] Although its specific rotation value in a chloroform solution was reported to be zero, it was believed that lepadiformine is not racemic. However, the absolute configuration has remained hitherto unknown. The unique structural features and biological significance of this novel marine alkaloid have made it an important target for synthesis. Weinreb and co-workers[3] reported the synthesis of the structure **1** proposed for lepadiformine and found that the synthetic material exists as a nonzwitterionic form **2** and that neither the free amine nor its hydrochloride salt corresponds to the natural product. Moreover, Pearson et al.[4] synthesized the other three C3/C5 diastereomers of **2** and found that they different from lepadiformine (Scheme 1). Following these synthetic efforts, we recently published the total synthesis of compound **3** in the racemic form, based on an intramolecular acylnitroso Diels–Alder-based approach and found by spectral comparison that the corresponding hydrochloride salt was identical to the reported natural product.[5] We thus concluded that the originally assigned structure of lepadiformine was actually that of the hydrochloride salt and that its relative stereochemistry should be revised to be that of **3** (Scheme 1).



Scheme 1. The originally proposed structure of lepadiformine was that of **1**. The revised structure is that of **3**.

After establishment of the relative stereochemistry, two syntheses of racemic lepadiformine were reported by the groups of Weinreb[6] and Funk[7] based on a spirocyclization of an allylsilane N-acyliminium ion and on a amidoacrolein-derived Diels–Alder reaction, respectively. However, because the natural product is not crystalline and its derivatives could not be prepared, efforts to obtain an X-ray structure of natural lepadiformine for the determination of the absolute configuration have so far been unsuccessful.[1,8] This prompted us to undertake the enantioselective synthesis of lepadiformine and to determine the absolute configuration of the natural product.

[*] Prof. Dr. C. Kibayashi, H. Abe, S. Aoyagi
School of Pharmacy, Tokyo University of Pharmacy & Life Science
1432-1 Horinouchi, Hachioji, Tokyo, 192-0392 (Japan)
Fax: (+81) 426-76-4475
E-mail: kibayasi@ps.toyaku.ac.jp

[**] This work was supported in part by a Grant for Private Universities provided by the Ministry of Education, Sports, and Culture of Japan and the Promotion and Mutual Aid Corporation for Private Schools of Japan. We are grateful to Professor J. F. Biard for a sample of natural lepadiformine.

  0044-8249/02/4116-3017 $ 20.00+.50/0