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Published on Web 01/11/2005

Total Synthesis of the Tricyclic Marine Alkaloids (−)-Lepadiformine, (+)-Cylindricine C, and (−)-Fasicularin via a Common Intermediate Formed by Formic Acid-Induced Intramolecular Conjugate Azaspirocyclization

Hideki Abe, Sakae Aoyagi, and Chihiro Kibayashi*

Contribution from the School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

Received September 13, 2004; Revised Manuscript Received November 3, 2004; E-mail: kibayasi@ps.toyaku.ac.jp

Abstract: A very short and efficient enantioselective total synthesis of the tricyclic marine alkaloids (−)-lepadiformine (**3**), (+)-cylindricine C (**1c**), and (−)-fasicularin (**4**) has been developed utilizing the formyloxy 1-azaspiro[4.5]decane **5** as a common intermediate. The key strategic element for the synthesis was the formic acid-induced intramolecular conjugate azaspirocyclization, which proved to be a highly efficient and stereoselective way to rapid construction of the 1-azaspirocyclic substructure of these natural products in a single operation. Thus, the common intermediate **5**, synthesized in two steps with 70% overall yield starting from the known (*S*)-*N*-Boc-2-pyrrolidinone **7** via the conjugate spirocyclization using an acyclic ketoamide **6**, was utilized for the concise and stereoselective total synthesis of (−)-lepadiformine (**3**), which was accomplished in seven steps with 45% overall yield from **5** (31% yield from **7**). The developed strategy based on the conjugate spirocyclization was also applied to the stereoselective total synthesis of (+)-cylindricine C (**1c**), which was achieved in 10 steps from **5** in 18% overall yield (12% yield from **7**). Further application of this approach using **5** led to the synthesis of (−)-fasicularin (**4**), wherein an extremely efficient method for the introduction of the thiocyanato group via an aziridinium intermediate at the last step was developed. Thus, the highly efficient first enantioselective total synthesis of (−)-fasicularin was accomplished in nine steps with an overall yield of 41% from **5** (28% yield from **7**).

Introduction

Tunicates (ascidians) have been proven to be a particularly rich source of a variety of structurally fascinating and bioactive nitrogen compounds.[1] Since the first members were reported in 1993 by Blackman et al., 11 cylindricines A−K (**1a**−**k**) have been identified from the Tasmanian ascidians *Clavelina cylindrica* as new marine alkaloids[2] with an azatricyclic ring system unprecedented among natural products, consisting of the perhydropyrrolo[2,1-*j*]quinoline or the perhydropyrido[2,1-*j*]quinoline. Shortly after the first isolation of cylindricines A (**1a**) and B (**1b**),[2a] Biard and co-workers reported the isolation and structure elucidation of a closely related marine alkaloid, named lepadiformine, from the marine tunicate *Clavelina lepadiformis* collected in the Mediterranean near Tunisia[3a] in 1994 and later from *Clavelina moluccensis* found along the Djibouti coast.[3b] It was found to be moderately cytotoxic toward various tumor cell lines in vitro. 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.[3b] On the basis of extensive spectral analysis, this alkaloid was assigned the unusual zwitterionic structure **2** including a *cis*-1-azadecalin BC ring system as seen in cylindricines **1a**−**k**. In addition to these tricyclic natural products, fasicularin (**4**) was discovered in 1997 by Patil and co-workers[4] from the Micronesian ascidian *Nephteis fasicularis*, which has selective activity against a DNA repair-deficient organism and is cytotoxic to Vero cells. The structure and relative stereochemistry of **4** were deduced on the basis of NMR studies, though the absolute configuration is still unknown.

The novel structural features and biological significance of these tricyclic alkaloids represent a promising new class of nitrogen heterocycles biosynthesized by ascidians (such as indolizidines, quinolizidines, and decahydroquinolines) and have been receiving increasing attention as challenging targets for total synthesis.[5] In 2000, we achieved the first total syntheses

(1) For recent reviews on marine natural products, see: (a) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771−1791. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1994**, *11*, 355−394. (c) Faulkner, D. J. *Nat. Prod. Rep.* **1995**, *12*, 223−269. (d) Faulkner, D. J. *Nat. Prod. Rep.* **1996**, *13*, 75−125. (e) Faulkner, D. J. *Nat. Prod. Rep.* **1998**, *15*, 113−158. (f) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155−198.

(2) (a) Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. W.; White, A. H. *Tetrahedron* **1993**, *49*, 8645−8656. (b) Li, C.; Blackman, A. J. *Aust. J. Chem.* **1994**, *47*, 1355−1361. (c) Li, C.; Blackman, A. J. *Aust. J. Chem.* **1995**, *48*, 955−965.

(3) (a) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691−2694. (b) Jugé, M.; Grimaud, N.; Biard, J. F.; Sauviat, M. P.; Nabil, M.; Verbist, J. F.; Petit, J.-Y. *Toxicon* **2001**, *39*, 1231−1237.

(4) Patil, A. D.; Freyer, A. J.; Reichwein, R.; Cartre, B.; Killmer, L. B.; Faucette, L.; Johnson, R. K.; Faulkner, D. J. *Tetrahedron Lett.* **1997**, *38*, 363−364.

(5) For brief reviews on the synthesis of lepadiformine and related tricyclic marine alkaloids, see: (a) Weinreb, S. M. *Acc. Chem. Res.* **2003**, *36*, 59−65. (b) Kibayashi, C.; Aoyagi, S.; Abe, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2059−2074.

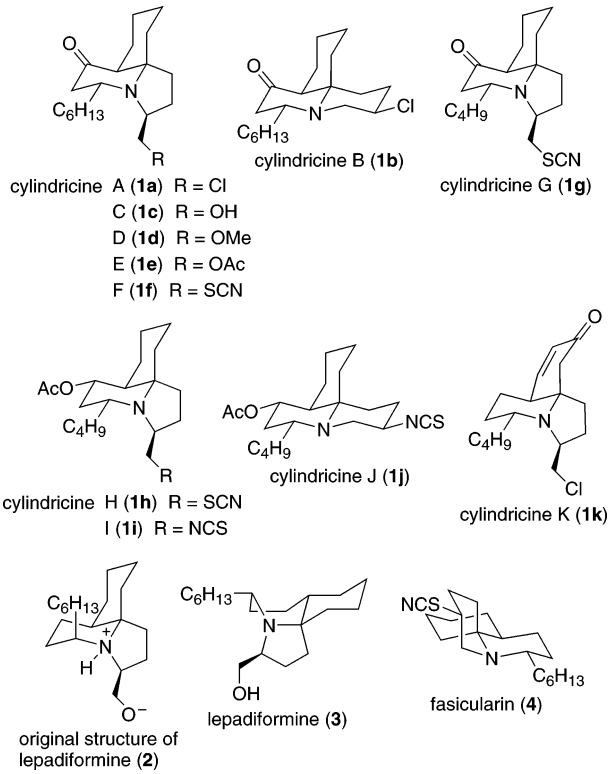
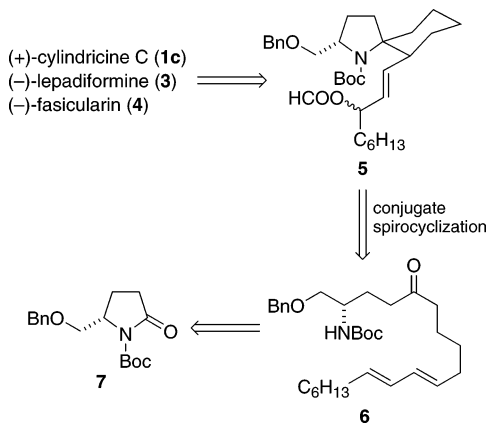


Figure 1. Tricyclic marine alkaloids isolated from the ascidians.

of racemic lepadiformine and fasicularin using an intramolecular acylnitroso Diels−Alder strategy.[6] This lepadiformine synthesis and X-ray crystallographic analysis of the lepadiformine hydrochlolide led to the revision of the proposed structure **2**[7] of lepadiformine to **3**, which has the trans-fused 1-azadecalin BC ring with the B ring in an unusual twist boat form, thereby having the hexyl group in an equatorial position. In addition, it was shown that the natural material isolated by Biard is actually the hydrochloride salt of **3** rather than a zwitterion as originally postulated. After the relative stereochemistry of lepadiformine was thus established,[8] its absolute configuration was first assigned as depicted in Figure 1 by the Weinreb group[8c] via the total synthesis of the natural enantiomer of lepadiformine using an intramolecular spirocyclization of a cyclic *N*-acyliminium ion with an allylsilane as a pivotal step. Shortly after this report, we independently came to the same conclusion for the absolute stereochemistry by the enantioselective synthesis of **3** and chiral HPLC analysis of the synthetic material and the natural product.[9] The strategy utilized in this approach to **3** was based on formic acid-induced intramolecular conjugate spirocyclization, which proved to be a very efficient way to rapid

Scheme 1



construction of the 1-azaspirocyclic core. In this article, we wish to describe in detail the development of this azaspirocyclization methodology and the general utility of this methodology for a highly efficient enantioselective total synthesis of the tricyclic marine alkaloids cylindricine C (**1c**), lepadiformine (**3**), and fasicularin (**4**).[10]

Results and Discussion

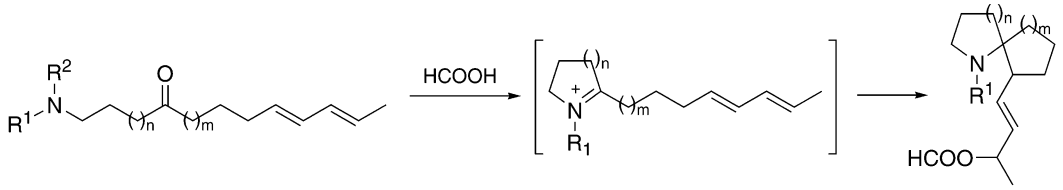
Formic Acid-Induced Intramolecular Spirocyclization of Conjugated Diene-Ketoamides. Intramolecular reaction of the *N*-acyliminium species with simple alkenes or alkenylsilanes has been of great importance for the synthesis of nitrogen heterocycles and has found widespread use in total synthesis of natural products,[11] but relatively few examples exist on the use of this reaction for the construction of azaspirocycles. Such *N*-acyliminium ion-based spirocyclization leading to spirolactams has been initially investigated by Speckamp[12] and Evans[13] and utilized for the synthesis of perhydrohistrionicotoxin, and recently this methodology was successfully applied by Weinreb[8c] in the total synthesis of lepadiformine.

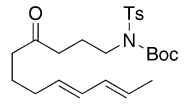
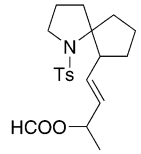
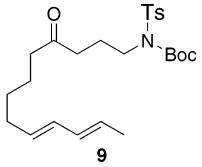
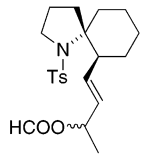
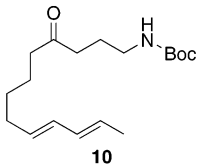
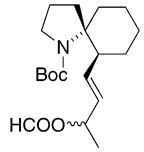
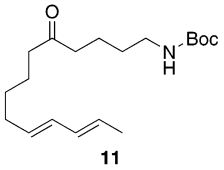
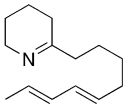
At the outset of our studies toward the total synthesis of the tricyclic alkaloids **1c**, **3**, and **4** as shown retrosynthetically in Scheme 1, we envisioned a new variant of *N*-acyliminium ion-based spirocyclization using an acyclic ketoamide **6** bearing a conjugated diene, which was anticipated to lead to the formation of the spirocyclic AC ring system, which is a common substructure present in this class of alkaloids, and simultaneous introduction of an oxygen functionality into the olefinic tether. The resulting spirocyclic formate **5** could serve as a common intermediate for the synthesis of each of the three target alkaloids **1c**, **3**, and **4** by way of the subsequent construction of the B ring.

As a test of the feasibility of this spirocyclization methodology, we first subjected various conjugated diene-ketoamides to formic acid-initiated azacyclization which may occur via an in

(6) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583−4592.
(7) For synthesis of the putative structure **2** of lepadiformine (as a non-zwitterionic form), see: (a) Werner, K. M.; de los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 686−687. (b) Werner, K. M.; de los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 4865−4873. (c) Abe, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2000**, *41*, 1205−1208. (d) See also ref 6. For synthesis of the other three diastereomers of **2**, see: (e) Pearson, W. H.; Barta, N. S.; Kampf, J. W. *Tetrahedron Lett.* **1997**, *38*, 3369−3372. (f) Pearson, W. H.; Ren, Y. *J. Org. Chem.* **1999**, *64*, 688−689.
(8) For syntheses of lepadiformine (**3**), which appeared after establishment (ref 6) of the relative stereochemistry of lepadiformine, see: Racemic **3**: (a) Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **2001**, *3*, 3507−3510. (b) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3511−3514. (−)-**3**: (c) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, *67*, 4337−4345.
(9) Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3017−3020.
(10) For a preliminary report of a part of this work on the synthesis of lepadiformine, see ref 9.
(11) For reviews of the chemistry of *N*-acyliminium ions, see: (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367−4416. (b) Hiemstra, H.; Speckamp, W. N. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, CA, 1988; Vol. 32, pp 271−339. (c) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1047−1109. (d) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856.
(12) (a) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1978**, 1515−1518. (b) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1978**, 4841−4844. (c) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1980**, *36*, 951−958.
(13) Evans, D. A.; Thomas, E. W. *Tetrahedron Lett.* **1979**, 411−414.

Table 1. Conjugated Diene-Iminium Ion Spirocyclization of Ketoamides by Treatment with Formic Acid[a]



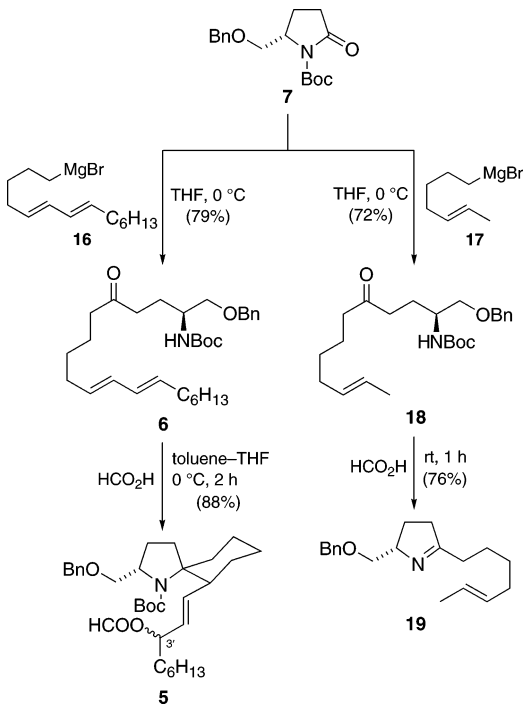
entry	compound	solvent	temp.	time (h)	product	yield (%) [b]
1	 **8**	CH_2Cl_2	rt	40	 **12**	43[c]
2	 **9**	CH_2Cl_2	rt	40	 **13**	55
3	 **10**	CH_3CN	0 °C	2	 **14**	54
4	**10**	toluene–THF	0 °C	1	**14**	66
5	 **11**	toluene–THF	0 °C	1	no reaction	
6	**11**	CH_3CN	rt	16	 **15**	79

[a] All reactions were performed at a substrate concentration of 0.05 M in the appropriate solvent containing formic acid in a 1:1 ratio. [b] Isolated yield. [c] The reaction was nonstereoselective.

situ generated cyclic *N*-tosyliminium and *N*-acyliminium species in 5- and 6-*exo-trig* modes[14] leading to spirocyclic formate esters (Table 1). When the Boc carbamate **8**, which bears a tosyl group on the nitrogen, was treated with formic acid in dichloromethane at room temperature, the intramolecular spirocyclization occurred via *N*-tosyliminium ion formation leading to the 1-azaspiro-[4.4]nonane ring system with introduction of the formyloxy group at the C3′ position as expected, producing **12** in 43% yield, although the reaction required long reaction time (40 h) for completion (entry 1). Under the same conditions, the *N*-tosyl Boc-carbamate **9** also underwent similar spirocyclization, thereby providing the 1-azaspiro[4.5]decane **13** in 55% yield (entry 2). When the Boc carbamate **10** lacking the tosyl substituent at the nitrogen was used, the spirocyclization in acetonitrile proceeded smoothly via cyclic *N*-acyliminium ion formation and was completed in 2 h at 0 °C to afford the 1-azaspiro[4.5]decane **14** in 54% yield (entry 3). The spirocyclization of **10** proceeded more smoothly by employing toluene−THF (19:1) as the solvent, which was completed in 1 h at 0 °C to yield **14** in 66% yield (entry 4). This is in marked contrast to the case with the reported cyclic acyliminium ion-olefin cyclization that requires long reaction time (e.g., 40 h at 36−40 °C[12c] and 32 h at 25 °C[13] for lactams with terminal olefins, and 8 days at 44 °C for a lactam with an inner olefin[12b]). On the other hand, when the same conditions used for **10** indicated in entry 4 were applied to the Boc carbamate **11**, no reaction was observed (entry 5). Even under the forcing conditions (CH_3CN, room temperature, 16 h), treatment of **10** with formic acid did not lead to spirocyclization to the expected 1-azaspiro-[5.5]undecane but instead removal of the Boc group to form the tetrahydropyridine **15** (entry 6).

(14) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736.

Scheme 2



These results suggested that the spirocyclization preferentially occurred via the intermediacy of five-membered ring *N*-tosyliminium and *N*-acyliminium ions generated from the ketoamides **8**−**10** rather than via the six-membered ring analogue formed from **11**. These observations are consistent with a recent report from Eberlin and co-workers[15] on electrophilic reactivity of a series of the cyclic *N*-acyliminium ions, which shows that the LUMO energy of five-membered ring *N*-acyliminium ions with exocyclic amide carbonyl groups is lower than that of six-membered ring analogues, and, indeed, the five-membered ring iminium ions were found to be more reactive toward electrophilic addition reactions than the six-membered ring analogues.

The conjugate spirocyclization protocol leading to spirocyclic formates in a single operation developed here seems to be particularly attractive for an efficient and rapid entry into the azatricyclic marine alkaloids, where the AC ring system is assembled, and which also allows the oxygenated functionality to be placed in the appropriate position in the olefinic side chain for potential future elaboration of the B ring. Thus, our initial efforts have focused on the preparation of the spirocyclic formate ester **5** using this methodology as indicated in Scheme 1. The synthesis commenced with the known (*S*)-*N*-Boc-2-pyrrolidinone **7**,[16] which upon treatment with the (5*E*,7*E*)-tetradeca-5,7-dienyl Grignard reagent **16** yielded the *N*-Boc-amino ketone **6**[17] (Scheme 2). Treatment of a solution of **6** in toluene−THF (95:5) with formic acid at 0 °C for 2 h initiated a sequence of conjugate spirocyclization culminating in the formation of the azaspirocyclic formate ester **5** in 88% yield.[18] In this reaction, the 1-azaspiro[4.5]decane ring formation proceeded with complete stereoselection in the desired sense, although the concomitant formate substitution at C3′ occurred with low diastereoselectivity in a ratio of 1.6:1 favoring the 3′β-formate as determined by HPLC analysis. It is noteworthy that the ketoamide bearing a conjugated diene system such as **6** smoothly underwent the conjugate spirocyclization because, contrary to this result, similar treatment of the ketoamide bearing the nonconjugated olefin, **18**, with formic acid in CH_2Cl_2 or without a solvent at room temperature resulted in no spirocyclization, but only removal of the Boc group took place to form the cyclized imine **19**.

The success of this conjugate spirocyclization using **6** can be accounted for by a π-complex theory (Scheme 3).[19] Thus, the cyclic *N*-acyliminium ion **20** generated in situ from **6** forms, in an equilibrium process, a π-complex **21** with a nitrogen-stabilized carbocation. Subsequently, formate anion attacks this π-complex **21** in such a manner that only a six-membered ring is formed with generation of a stable allyl cation moiety in the unsaturated alkyl side chain as in **22**, which is then attacked by formate ion leading to the spirocyclic product **5**. The stereochemical outcome observed for this cyclization is understandable in terms of nonbonded interactions in the π-complexes **21A**−**D** with chairlike six-membered transition structures, where nucleophilic attack of the olefin moiety would occur from the sterically less hindered β face (opposite to the 5-benzyloxymethyl group) of the cationic pyrrolidine ring (Figure 2). In the

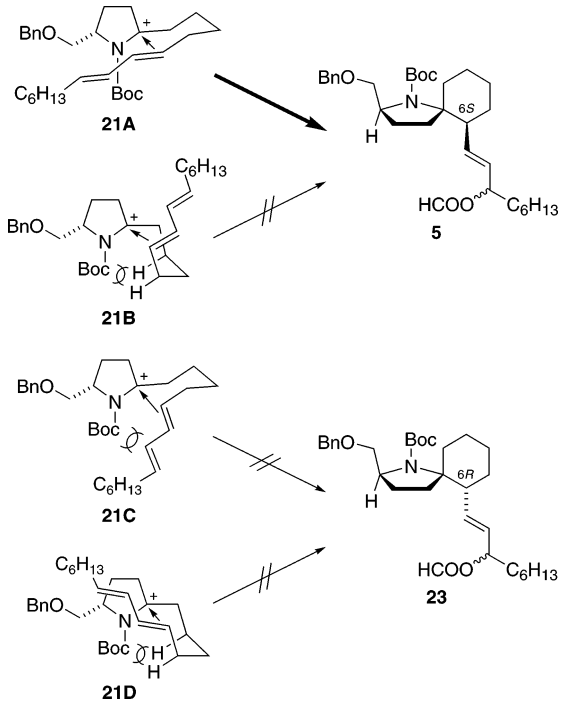
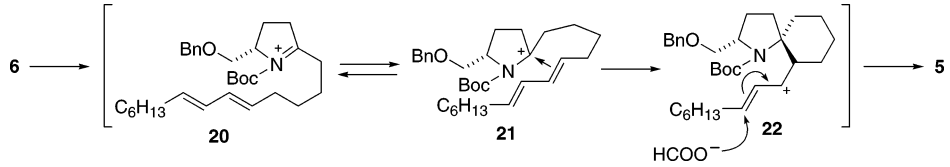


Figure 2. Stereoselective formation of the (6*S*)-formate **5** in the conjugated diene−*N*-acyliminium ion spirocyclization.

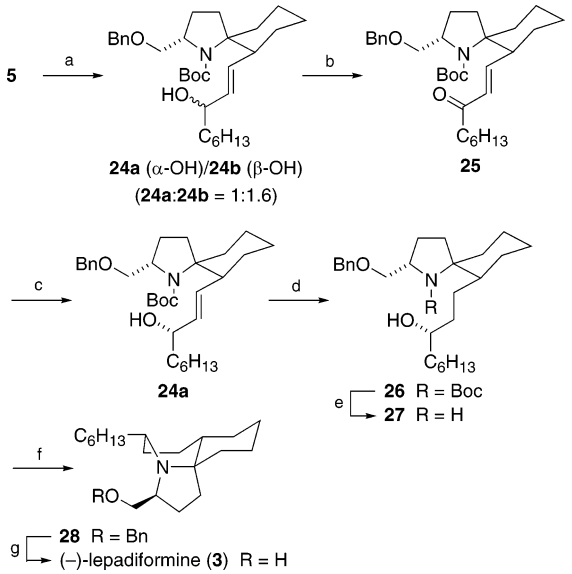
transition structures **21C** and **21D**, which lead to the (6*R*)-isomer **23**, the *N*-Boc group displays unfavorable nonbonded interactions with the axially oriented diene moiety and the 1,3-diaxial

(15) D'Oca, M. G. M.; Moraes, L. A. B.; Pilli, R. A.; Eberlin, M. N. *J. Org. Chem.* **2001**, *66*, 3854−3864.
(16) (a) Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron Lett.* **1993**, *34*, 5743−5746. (b) Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron* **1994**, *50*, 6221−6238.
(17) For the organometallic ring-opening reaction of *N*-alkoxycarbonyl lactams, see: Giovannini, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 228−234.
(18) When the reaction was carried out in formic acid without solvent at room temperature for 1 h, the spirocyclization was accompanied by cleavage of the *N*-Boc protecting group.
(19) Dewar, M. J. S.; Reynolds, C. H. *J. Am. Chem. Soc.* **1984**, *106*, 1744−1750.

Scheme 3



Scheme 4 [a]



[a] Reagents and conditions: (a) K_2CO_3, MeOH−H_2O, room temperature, 98%; (b) MnO_2, CH_2Cl_2, room temperature, 91%; (c) method A: (*R*)-oxazaborolidine, BH_3·THF, 0 °C, 77% (60% de); method B: (*S*)-BINAL-H, THF, −78 °C, 92% (97% de); (d) H_2, PtO_2, AcOEt, 86%; (e) CF_3CO_2H, CH_2Cl_2, room temperature, 91%; (f) Ph_3P, CBr_4, Et_3N, CH_2Cl_2, room temperature, 82%; (g) H_2, $Pd(OH)_2$−C, MeOH, 87%.

hydrogens of the newly formed cyclohexane ring, respectively. The latter steric interaction between the *N*-Boc group and the 1,3-diaxial hydrogens is also present in the transition structure **21B**, which leads to the (6*S*)-isomer **5**. Neither of these interactions is present in the transition structure **21A**, and therefore, of the four possible chairlike transition structures **21A**−**D**, **21A** is the least disfavored and leads to the observed (6*S*)-product **5**.

The Total Synthesis of (−)-Lepadiformine. The formate ester **5** (1.6:1 epimeric mixture) thus obtained underwent basic hydrolysis followed by MnO_2 oxidation to form the α,*β*-conjugated ketone **25** (Scheme 4). Since reduction of **25** to the corresponding alcohol with BH_3·THF (THF, 0 °C) was almost nonstereoselective (**24a**/**24b** = 1.15:1 based on HPLC analysis), Corey's (*R*)-oxazaborolidine-catalyzed asymmetric borane reduction[20] was performed to obtain enantioselectively the desired 3′α-alcohol **24a** (as a major isomer), but with somewhat disappointing diastereoselectivity (**24a**/**24b** = 80:20 in 77% total yield). However, when (*S*)-BINAL-H[21] was used, **24a** was obtained with much improved diastereoselectivity and in a higher yield (98.5:1.5 in 92% total yield). Catalytic hydrogenation of **24a** over 10% palladium on carbon in methanol was carried out in the presence of diethylamine (1 equiv) to prevent benzyl ether hydrogenolysis,[22] affording **26** in 64% yield. The use of PtO_2 catalyst and ethyl acetate as solvent without diethylamine for the same reaction remarkably improved the yield of **26** to 86%. After removal of the Boc protecting group with trifluoroacetic acid, the resultant amino alcohol **27** was subjected to cyclodehydration[23] using CBr_4 and PPh_3 with complete inversion of the configuration at C3′ to form the tricyclic amine **28** in 82% yield. Hydrogenolytic removal of the benzyl protecting group was done using $Pd(OH)_2$ on carbon in methanol furnished (−)-lepadiformine (**3**) whose spectral properties were identical in all respects with those of an authentic sample of racemic lepadiformine (±)-**3** previously prepared by us.[6] The optical rotation of synthetic alkaloid **3** was measured: $[\alpha]^{28}_D$ −15.0 (*c* 0.37, MeOH) for the free base (oil) and $[\alpha]^{26}_D$ +2.6 (*c* 0.54, $CHCl_3$) for the hydrochloride salt (colorless gum). Although comparison of the optical rotation of our synthetic sample with that of the natural product was impossible since the rotation of the natural product (actually the hydrochloride salt[6]) had been reported[3a] to be zero, synthetic **3** proved to be identical with natural lepadiformine, kindly provided by Professor Biard, on the basis of their chromatographic behavior on HPLC chiral phase.[9]

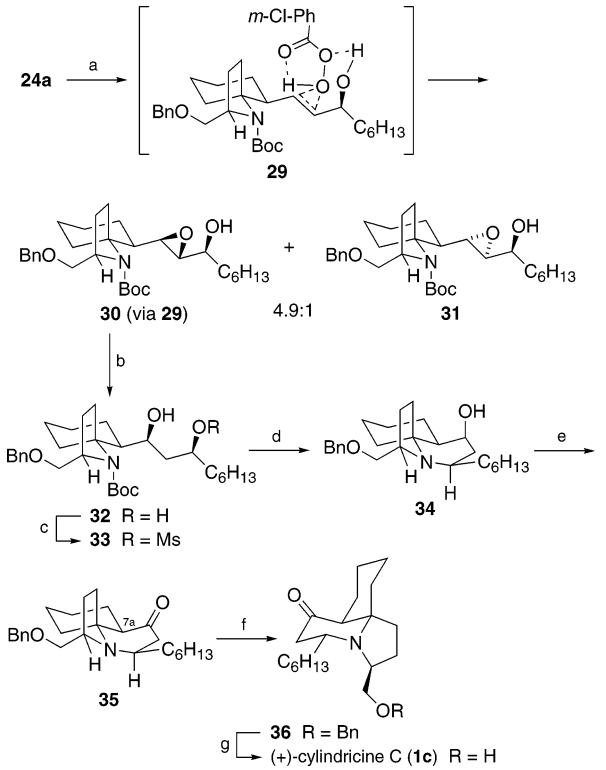
The enantioselective total synthesis of (−)-lepadiformine (**3**) has thus been accomplished by employing a conjugate azaspirocyclization methodology in seven steps with an overall yield of 45% from the common intermediate **5** (31% yield from the pyrrolidinone **7**), making this the most efficient and the shortest synthesis of **3** reported to date.[6,8]

The Total Synthesis of (+)-Cylindricine C. Having developed the extremely efficient approach to lepadiformine (**3**) utilizing the spirocyclic alcohol **24a** stereoselectively derived from the enone **25**, we next attempted to exploit this intermediate **24a** for the synthesis of the related marine alkaloid cylindricine C (**1c**).[24,25]

Cylindricine C (**1c**), possessing the perhydropyrrolo[2,1-*j*]-quinoline framework, is intimately related to lepadiformine (**3**), differing structurally only in the cis/trans stereorelationship of the BC ring system and the functionality at C7. While the synthesis of both enantiomers of cylindricine C has been achieved,[24] the absolute configuration of natural cylindricine C remains unassigned since the optical rotation of the natural product has not been determined and no sample remains of the isolated cylindricine C. Biogenetically, it can be envisaged that both tunicate alkaloids **1c** and **3** presumably arise from an amino acid-derived azaspirocyclic compound, corresponding to the AC

(20) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925−7926.
(21) Noyori, R.; Tanino, I.; Tanimoto, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3129−3131.
(22) For inhibition of hydrogenolysis of benzyl ether groups with Pd−C in the presence of ammonia and amines, see: Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465−3468.
(23) Shishido, Y.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876−2883.
(24) For synthesis of (−)-cylindricine C, see: (a) Molander, G. A.; Rönn, M. *J. Org. Chem.* **1999**, *64*, 5183−5187. For syntheses of (+)-cylindricine C, see: (b) Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 4599−4602. (c) Arai, T.; Abe, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2004**, *45*, 5921−5924.
(25) For syntheses of other cylindricine alkaloids, see: (a) (±)-cylindricine A, D, and E: Snider, B. B.; Liu, T. *J. Org. Chem.* **1997**, *62*, 5630−5633. (b) (±)-Cylindricine A and B: Liu, J. F.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8263−8266. (c) (+)-Cylidricine D and E: ref 24b.

Scheme 5 [a]



[a] Reagents and conditions: (a) *m*CPBA, Na_2HPO_4, CH_2Cl_2, 0 °C, 68% for **30**; (b) $LiAlH_4$, Et_2O, room temperature, 84%; (c) MsCl (1 equiv), Et_3N, DMAP, CH_2Cl_2, room temperature, 73%; (d) CF_3CO_2H, CH_2Cl_2, room temperature, then $NaHCO_3$ aq, room temperature, 30 min, 84%; (e) Swern ox; (f) K_2CO_3 aq, MeOH, room temperature, 2 h, 86% over two steps; (g) H_2, $Pd(OH)_2$−C, MeOH, 73%.

ring of these alkaloids, by closure of the B ring (bond formed C7−C7a). Consequently, we assumed that the correct absolute stereochemistry for natural cylindricine C is defined by **1c**, which is epimeric with the natural lepadiformine (**3**) at C7a.

Oxidation of the olefin in the unsaturated alcohol **24a** with *m*CPBA stereoselectively afforded the *syn*-hydroxy epoxide **30** (68% yield), presumably via a chelate transition state **29**,[26] along with the *anti*-hydroxy epoxide **31** (14% yield) (Scheme 5). Reductive ring opening of the epoxide **30** with $LiAlH_4$ proceeded regioselectively to give the 1,3-diol **32** in 84% yield along with a small amount of the 1,2-diol (ca. 4% yield). The observed regioselective formation of **32** may be due to hydride attack at the less sterically hindered C2′ position and/or neighboring-group participation by the 3′-secondary hydroxyl substituent. Mesylation of **32** took place at the less hindered 3′-hydroxyl group exclusively to give the mesylate **33**. Removal of the Boc group in **33** with trifluoroacetic acid followed by treatment with aqueous $NaHCO_3$ resulted in smooth ring closure (room temperature, 30 min), affording the tricyclic amino alcohol **34**, which was oxidized under Swern conditions to form the tricyclic ketone **35**. To define the conformation of **35** including the *trans*-1-azadecalin BC ring system, molecular mechanics (MM2) calculations using CAChe mechanics program (version 4.0) were carried out, showing that the piperidone ring (B ring) of **35** is in the boat conformation at lowest energy (Figure 3). On the other hand, MM2 calculations on its C7a epimer **36**, which possesses the cis-fused BC ring system with a chair−chair conformation, indicated that **36** is more stable by 5.5 kcal/mol than **35** in their optimized structures. These calculations suggested that **35** would easily epimerize to provide the more thermodynamically stable **36** having the stereochemistry required for the structure of cylindricine C. Thus, upon exposing **35** to aqueous K_2CO_3 in methanol at room temperature for 2 h, complete epimerization at C7a occurred to form **36** as a single isomer in 86% yield. Finally, the benzyl group of **36** was removed by hydrogenolysis using $Pd(OH)_2$ in MeOH to give (+)-cylindricine C (**1c**). The synthetic material of **1c** has an optical rotation of $[\alpha]^{21}_D$ +63.1 (*c* 0.44, CH_2Cl_2) (ref 24b $[\alpha]^{25}_D$ +61 (*c* 0.4, CH_2Cl_2); for (−)-cylindricine C[24a] $[\alpha]^{25}_D$ −64 (*c* 0.2, CH_2Cl_2)) and displayed spectroscopic data (^1H and ^{13}C NMR) identical to those reported[2b] for the natural product.

The Total Synthesis of (−)-Fasicularin. Encouraged by the results described above, we next explored the possibility of extending the conjugate spirocyclization methodology to the enantioselective synthesis of fasicularin (**4**). As described above, the total synthesis of (±)-fasicularin was first reported by us in 2000. After this report, the second synthesis of (±)-**4** using a 2-amidoacrolein Diels−Alder cycloaddition was published by Funk and Maeng,[27] and more recently the formal construction of **4** starting from (*S*)-5-hydroxy-2-piperidone has been reported by the Dake group.[28] However, these syntheses suffered from very poor overall yields (0.9 and 2.4%), mainly due to difficulty in incorporation of the thiocyanato group in the final step, which was performed by a Mitsunobu procedure (HSCN, Ph_3P, DEAD)[6] or an S_N2 displacement of the mesylate by Bu_4NSCN[27] resulting in very low yield (20%) of fasicularin in each case. Thus, there is a great need to develop a new thiocyanation method that can overcome this problem.

In the studies on the structure determination of cylindricines A (**1a**) and B (**1b**), these alkaloids are found to form a 3:2 equilibrium mixture, presumably via interconversion through an aziridinium ion intermediate.[2a] On the basis of this observation, we envisioned for the synthesis of fasicularin (**4**) using an aziridinium ion intermediate which may undergo nucleophilic attack of thiocyanate ion with a ring-opening process to form the thiocyanato-bearing A ring of fasicularin. With this strategy in mind, we investigated the following approach to **4** starting from the spirocyclic enone **25**. Thus, **25** was subjected to reduction with (*R*)-BINAL-H to give the (3′*R*)-alcohol **24b** with a 9:1 diastereoselectivity (Scheme 6). Hydrogenation of olefin, followed by deprotection of the amino group, afforded amino alcohol **38**, which was subjected to cyclocondensation (Ph_3P, CBr_4, Et_3N)[23] to yield the tricyclic amine **39**. After hydrogenolytic removal of the benzyl group, upon exposing the resulting tricyclic amino alcohol **40** to NH_4SCN under the Mitsunobu conditions, a 1:1 mixture of (−)-fasicularin (**4**) and **41** was obtained in 94% combined yield. When a solution of the latter product **41** in acetonitrile was allowed to stand at room temperature for 72 h, (−)-fasicularin was further obtained in 91% yield. Formation of fasicularin was thus attained in remarkably high combined yield of 90% from the tricyclic amino alcohol **40**. Fasicularin so obtained, having spectral properties in agreement with those previously reported,[4,6] proved to be enantiomerically pure by chiral HPLC analysis using a Daicel Chiralpak AD column in comparison with (±)-**4** previously

(26) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63−74.

(27) Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2002**, *4*, 331−333.
(28) Fenster, M. D. B.; Dake, G. R. *Org. Lett.* **2003**, *5*, 4313−4316.

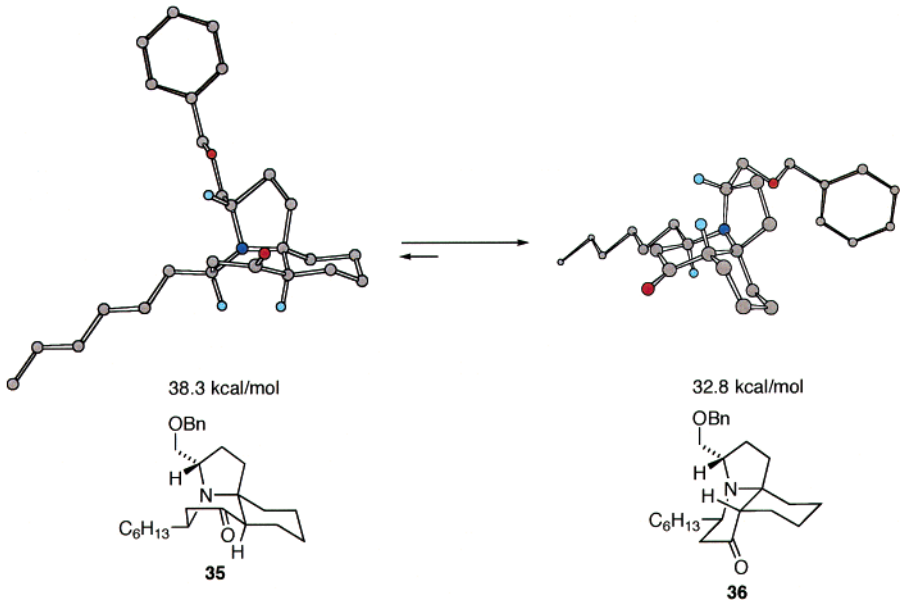
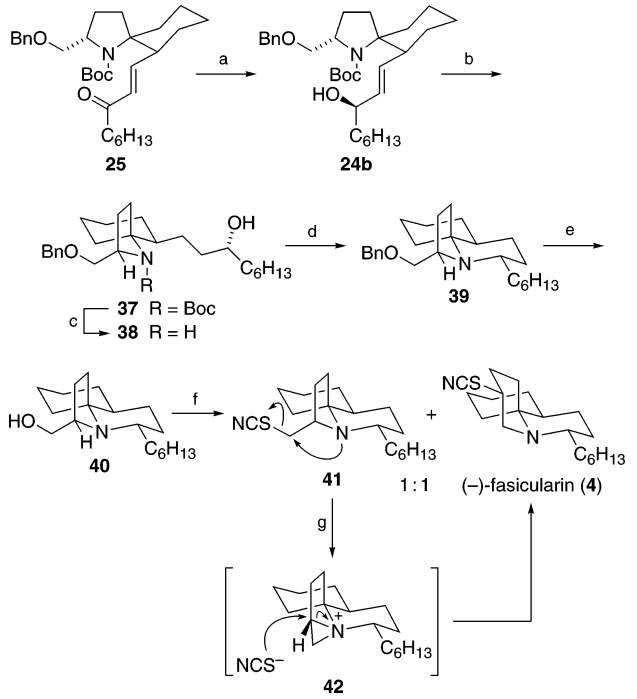


Figure 3. Energy-minimized structures of **35** and **36** (CAChe 4.0 MM2 calculation).

Scheme 6 [a]



[a] Reagents and conditions: (a) (*R*)-BINAL-H, THF, −78 °C, 84%, (80% de); (b) H_2, PtO_2, AcOEt, room temperature, 81%; (c) CF_3CO_2H, CH_2Cl_2, room temperature, 99%; (d) Ph_3P, CBr_4, Et_3N, CH_2Cl_2, room temperature, 88%; (e) H_2, $Pd(OH)_2$−C, MeOH, 95%; (f) method A: HSCN, Ph_3P, DEAD, toluene, room temperature, 24 h, 20%; method B: NH_4SCN, Ph_3P, DEAD, CH_2Cl_2, room temperature, 15 min, 94%; (g) CH_3CN, room temperature, 72 h, 91%.

obtained by us,[6] and was found to have $[\alpha]^{21}_D$ −4.4 (*c* 0.47, MeOH). The present fasicularin formation can be rationalized by considering the initial formation of the aziridinium ion **42** that undergoes nucleophilic attack of thiocyanate ion with subsequent expansion reaction of the aziridine.

The first enantioselective total synthesis of (−)-fasicularin was thus accomplished in nine steps with an overall yield of 41% from the common intermediate **5** (28% yield from the pyrrolidinone **7**). Although the absolute configuration and the optical rotation of fasicularin have not yet been determined (no literature data are available) and no original natural sample remains,[29] since the optical rotation value for **4** was first obtained by the present synthesis, determination of the absolute configuration of fasicularin will become possible by reisolation of the natural product and optical rotation measurement.

Conclusion

The very short and efficient enantioselective total synthesis of the tricyclic marine alkaloids (−)-lepadiformine (**3**), (+)-cylindricine C (**1c**), and (−)-fasicularin (**4**) has thus been developed utilizing the formyloxy 1-azaspiro[4.5]decane **5** as a common intermediate. The key common strategic element for the synthesis was the formic acid-induced intramolecular conjugate azaspirocyclization, which proved to be an efficient and stereoselective way to rapid construction of the 1-azaspirocyclic core of these natural products. Thus, the common intermediate **5** incorporating a 3′-oxygenated functionality, which is important for further ring construction, was synthesized in two steps with 70% overall yield starting from the known (*S*)-*N*-Boc-2-pyrrolidinone **7** via the conjugate spirocyclization using an acyclic ketoamide **6**. Using **5**, we achieved the concise and stereoselective total synthesis of (−)-lepadiformine (**3**) in seven steps with 45% overall yield (31% yield from **7**). The developed strategy based on the conjugate spirocyclization was also applied to the stereoselective total synthesis of (+)-cylindricine C (**1c**), which was achieved in 10 steps from **5** in 18% overall yield (12% yield from **7**). Further application of this approach using **5** led to the synthesis of (−)-fasicularin (**4**), wherein an extremely efficient method for the introduction of the thiocyanato group via an aziridinium intermediate at the last step was developed. Thus, the highly efficient first enantioselective total synthesis of (−)-fasicularin was accomplished in nine steps with an overall yield of 41% from **5** (28% yield from **7**). These studies demonstrated that the strategy developed in this project, conjugate azaspirocyclization and use of the oxygenated spirocyclic compound **5** as a common intermediate,

(29) Freyer, A. J. Personal communication.

represents a highly efficient method for the total synthesis of the tricyclic marine alkaloids and should be of general utility in the synthesis of these natural products.

Acknowledgment. We are grateful to Professor J. F. Biard (Université de Nantes) for a sample of natural lepadiformine. This work was supported in part by a grant for private universities provided by the Ministry of Education, Sports and Culture and The Promotion and Mutual Aid Corporation for Private School of Japan and also a Grant-in-Aid for Science Research from the Ministry of Education, Sports and Culture of Japan (No. 15790018) to which we are grateful.

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

JA040213E