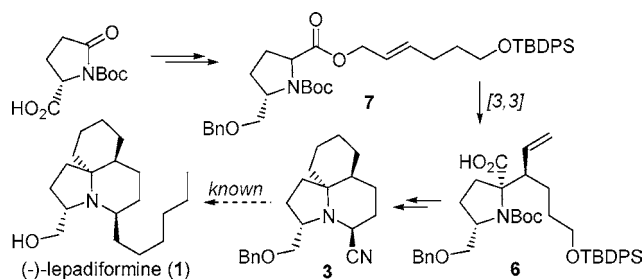# Formal Total Synthesis of (−)-Lepadiformine

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ABSTRACT

A stereocontrolled approach to the preparation of the Weinreb intermediate 3 has been developed. The important features of this approach are the creation of stereogenic centers through a cyclic amino acid ester–enolate Claisen rearrangement and the use of ring-closing metathesis for the construction of the azaspirocyclic skeleton.

Lepadiformine is a tricyclic perhydropyrrolo[2,1-*j*]quinolone that was initially isolated from the tunicate *Clavelina lepadiformis* by Biard in 1994.[1] This marine alkaloid exhibits moderate cytotoxic activity against various tumor cell lines in vitro,[1] as well as high in vitro and in vivo cardiovascular effects.[2] The originally proposed structure **2** (Figure 1) for
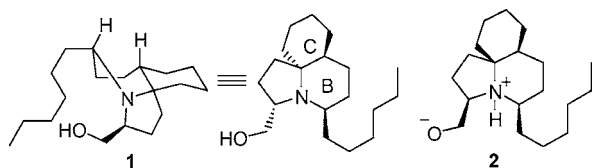

Figure 1. The revised structure **1** of lepadiformine and its originally proposed structure **2**.

this alkaloid was revised in 2000 by Kibayashi and co-workers[3] to the correct structure **1** through their first total

synthesis. X-ray crystallographic analysis of synthetic lepadiformine hydrochloride verified the relative stereochemistry unambiguously; it also indicated that the B ring of lepadiformine exists in an unusual twist-boat form.[3] In 2002, the Weinreb group determined the absolute configuration through the first enantioselective total synthesis[4] of the alkaloid and the Kibayashi group reconfirmed this assignment shortly thereafter.[5]

The significant amount of synthetic interest in lepadiformine stems from its intriguing structural features and interesting bioactivity. Before the correct structure of lepadiformine was established, many efforts were directed toward the synthesis of the incorrectly assigned structure and other possible isomers.[6] These efforts eventually resulted in the assignment

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(1) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691−2694.
(2) Juge, M.; Grimaud, N.; Biard, J. F.; Sauviat, M. P.; Nabil, M.; Verbist, J. F.; Petit, J. Y. *Toxicon* **2001**, *39*, 1231−1237.
(3) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583−4592.
(4) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, *67*, 4337−4345.
(5) Kibayashi, C.; Aoyagi, S.; Abe, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3017−3020.

of the correct structure, which signified the pivotal role of total synthesis in natural product structure determinations.[7] Since the report of the first total synthesis of lepadiformine in its correct form, several other elegant syntheses have been reported.[8]

In this paper, we report a novel formal stereoselective synthesis of (−)-lepadiformine (**1**). Our strategy was based on the use of an amino acid ester−enolate Claisen rearrangement and a ring-closing metathesis (RCM) reaction, as presented in the retrosynthetic Scheme 1.[9]

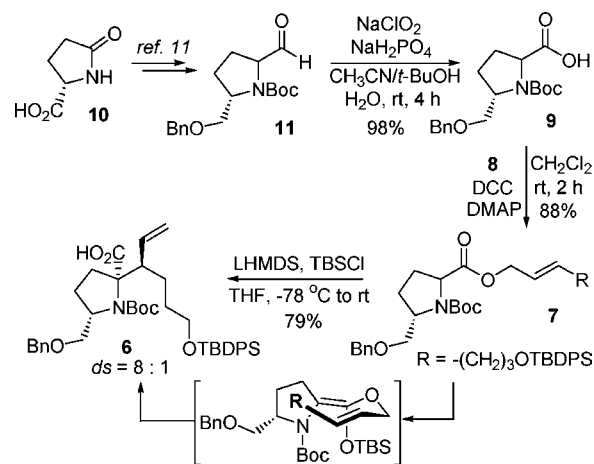**Scheme 1.** Retrosynthetic Analysis of (−)-Lepadiformine
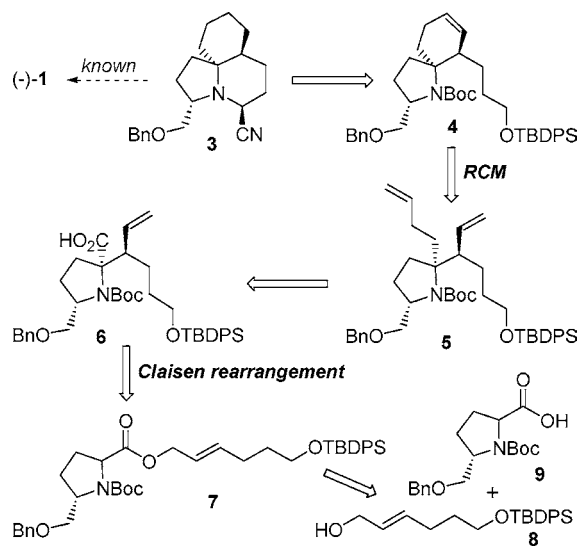
The tricyclic amino nitrile **3** (Scheme 1) was a key advanced intermediate in previous total syntheses of lepadiformine.[4,8a] We envisioned that this intermediate **3** could be synthesized from the cyclohexene **4**. We envisaged that the azaspirocyclic skeleton of **4** could be constructed through a RCM of diene **5**, which, in turn, would be accessible from the densely functionalized cyclic amino acid **6**. The presence of the γ,δ-unsaturated carbonyl unit in compound **6** suggested the use of a Claisen rearrangement of the cyclic amino acid allylic ester **7**. In this transformation, the relative stereochemistry of three stereocenters could be determined by the choice of the enolate geometry and the transition state geometry. Further analysis indicated the known allylic alcohol **8**[10] and the protected cyclic amino acid **9**, as the source of chirality, to be suitable synthetic precursors for the Claisen rearrangement substrate **7**.

Our synthesis began by preparing the known amino aldehyde **11** (Scheme 2) from commercially available (S)-pyro-

Scheme 2

glutamic acid **10**, through a conventional seven-step sequence, according to Terashima and co-workers' previously reported procedure.[11] Oxidation of the aldehyde group of **11** with NaClO$_2$ gave the corresponding carboxylic acid **9** in 98% yield. Esterification of **9** with the known allylic alcohol **8** under Steglich's DCC coupling conditions[12] provided the allylic ester **7** (88%).

With multigram quantities of the diastereoisomeric mixture **7** in hand, we explored the stereoselective Ireland−Claisen rearrangement of the cyclic amino acid ester. To obtain the desired stereoisomer, the selective formation of the (Z)-silyl ketene acetal was a prerequisite prior to the Claisen rearrangement occurring via its well-established chairlike transition state (as indicated within the brackets). To the best of our knowledge, however, there were no examples in the literature describing selective ester enolate formation in cyclic α-amino acid ester compounds possessing an exocyclic N-carbonyl group.[13] After several attempts, we found that treatment of **7** with LHMDS and TBSCl in THF at −78 °C,

(6) For syntheses of the originally proposed structure **2**, 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*, 4865−4673. (c) Abe, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2000**, *41*, 1205−1208. (d) See also ref 3. For syntheses 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.

(7) Weinreb, S. M. *Acc. Chem. Res.* **2003**, *36*, 59−65.

(8) For synthesis of racemic **1**, see: (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. For the asymmetric synthesis of (−)-**1**, see: (c) Liu, J.; Hsung, R. P.; Peters, S. D. *Org. Lett.* **2004**, *6*, 3989−3992. (d) See also refs 4 and 5.

(9) For the application of a similar strategy in the total synthesis of perhydrohistrionicotoxin, see: Kim, S.; Ko, H.; Lee, T.; Kim, D. *J. Org. Chem.* **2005**, *70*, 5756−5759.

(10) (a) Kim, D.; Jang, Y. M.; Kim, I. O.; Park, S. W. *J. Chem. Soc., Chem. Commun.* **1988**, 760−761. (b) Murphy, J. A.; Rasheed, F.; Roome, S. J.; Scott, K. A.; Lewis, N. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2331−2340.

(11) Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron* **1994**, *21*, 6221−6238.

(12) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522−524.

(13) Chelation-controlled stereoselective ester enolate formation of acyclic α-amino acid ester compounds having both N-carbonyl groups and NH protons have been reported. See: (a) Kazmaier, U.; Maier, S. *Tetrahedron* **1996**, *52*, 941−954. (b) Miller, J. F.; Termin, A.; Koch, K.; Piscopio, A. D. *J. Org. Chem.* **1998**, *63*, 3158−3159. (c) Kazmaier, U.; Maier, S. *Chem. Commun.* **1998**, 2535−2536. (d) Kazmaier, U.; Zumpe, F. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1468−1470. (e) Qiu, W.; Gu, X.; Soloshonok, V. A.; Carducci, M. D.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *42*, 145−148. (f) Morimoto, Y.; Takaishi, M.; Kinoshita, T.; Sakaguchi, K.; Shibata, K. *Chem. Commun.* **2002**, 42−43. (g) Ndungu, J. M.; Gu, X.; Gross, D. E.; Cain, J. P.; Carducci, M. D.; Hruby, V. J. *Tetrahedron Lett.* **2004**, *45*, 4139−4142.

followed by gradual warming to room temperature, afforded predominantly the desired rearrangement product **6**, along with a minor amount of its stereoisomer, in 79% combined yield and 8:1 diastereoselectivity. We established the relative stereochemistry of the two newly generated stereocenters of **6** ultimately through its conversion to **3**. This relative stereochemistry suggests that chelation control might have existed between the enolate oxygen atom and the heteroatom of the *N*-Boc group, which influenced the stereochemistry of enolate formation and, hence, the stereochemical course of the rearrangement.

Next we turned our attention to the conversion of the carboxylic acid group of **6** into a homoallyl group for the preparation of the metathesis precursor **5** (Scheme 3). Thus,

Scheme 3
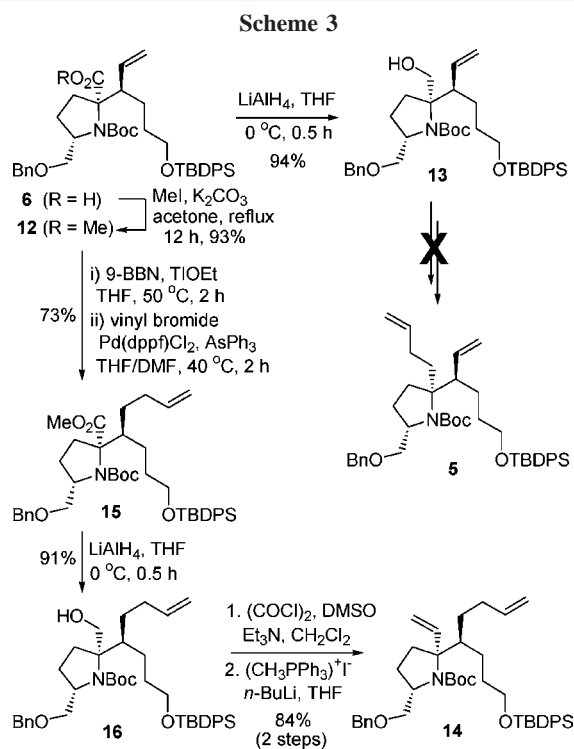
methylation of the carboxylic acid **6** with MeI/K_2CO_3 in acetone afforded the ester **12** (93%), which we then reduced with $LiAlH_4$ to the corresponding primary alcohol **13** (94%). Unfortunately, all of our attempts to convert the primary alcohol group in **13** to the homoallyl group in **5** were unsuccessful, presumably because of the high degree of steric hindrance. This failure led us to devise an alternative RCM substrate **14** for construction of the azaspirocyclic skeleton. Thus, as a first step we converted the terminal olefin of **12** to the two-carbon-atom-homologated terminal olefin. Hydroboration of the olefin **12** with 9-BBN gave the alkyl borane; a subsequent in situ B-alkyl Suzuki−Miyaura reaction with vinyl bromide provided **15** in 73% yield.[14] Treatment of **15** with $LiAlH_4$ effected the reduction of the hindered ester to afford the alcohol **16** in 91% yield. Swern oxidation of **16**, followed by a Wittig reaction of the resulting aldehyde with methylidene triphenylphosphorane, provided the desired RCM substrate **14** in 84% overall yield.

The crucial ring-closing metathesis of **14** was successfully performed with a second-generation Grubbs' catalyst **17**[15] in CH_2Cl_2 at 40 °C, to produce the desired azaspiro-cyclohexene derivative **18** in 98% yield (Scheme 4). Hydrogena-

Scheme 4
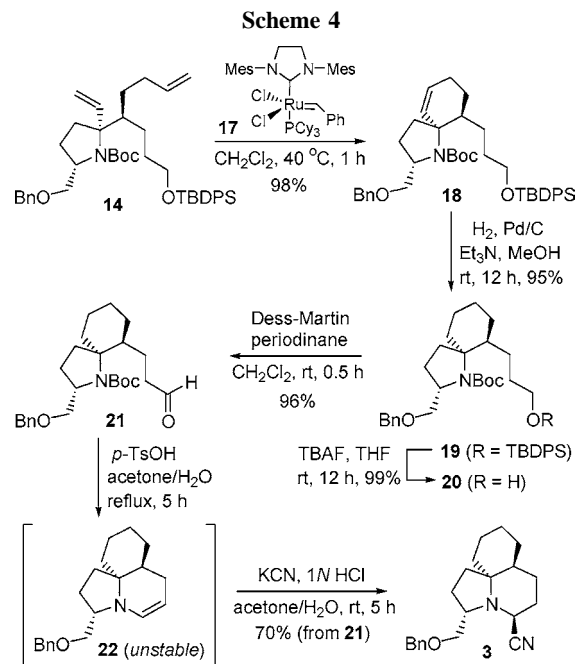
tion of the olefinic bond of **18** with H_2 and 10% Pd/C in the presence of Et_3N as a catalyst poison afforded **19** without effecting hydrogenolysis of the *O*-benzyl protecting group.[16]

Next, we directed our efforts toward the construction of the cyano group-functionalized lepadiformine B-ring to complete the formal synthesis. Toward that end, deprotection of the silyl ether **19** with TBAF and oxidation of the resulting alcohol **20** with the Dess−Martin periodinane[17] led to the isolation of the aldehyde **21** in 95% overall yield. Upon treatment with *p*-TsOH in aqueous acetone under reflux, the Boc-protected amino aldehyde **21** cyclized to the known tricyclic enamine **22**, which was unstable, as reported previously.[4,8a] Without purification, we employed reaction conditions analogous to those described by Weinreb et al.[4,8a] to convert **22** into the more-stable α-amino nitrile **3** in 70% overall yield. Our ^{1}H and ^{13}C NMR spectroscopic data for **3** were identical with those reported previously.

In summary, we have accomplished a formal stereoselective synthesis of (−)-lepadiformine from readily available starting materials. Our strategy differs from those of previous

(14) Chemler S. R.; Danishefsky S. J. *Org. Lett.* **2000**, *2*, 2695−2698 and references therein.

(15) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(16) For examples of the use of amines as catalyst poisons, see: (a) Czech, B. P.; Bartsch, R. A. *J. Org. Chem.* **1984**, *49*, 4076−4078. (b) Sajiki, H.; Hirota, K. *Tetrahedron* **1998**, *54*, 13981−13996. (c) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Masayuki, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 11893−11899.

(17) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

approaches in that we established the stereogenic centers of lepadiformine through an amino acid ester−enolate Claisen rearrangement and employed a ring-closing metathesis to construct its azaspirocyclic skeleton.

Supporting Information Available: Full experimental procedures and analytical data of compounds; copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **3**, **12**, **14**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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