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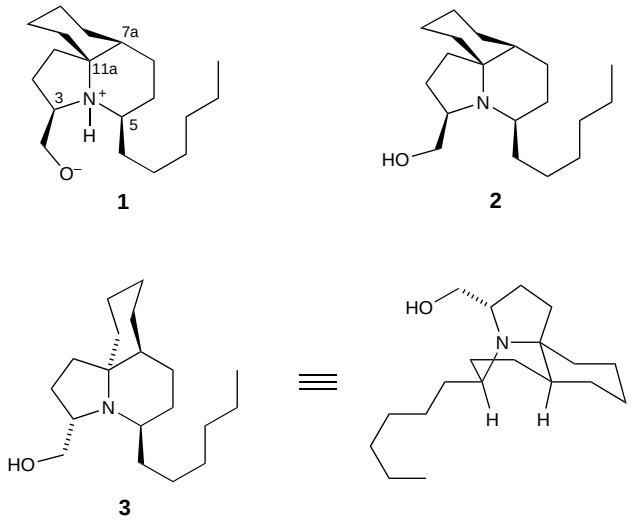
Total Synthesis of the Natural Enantiomer of (−)-Lepadiformine and Determination of Its Absolute Stereochemistry**

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.

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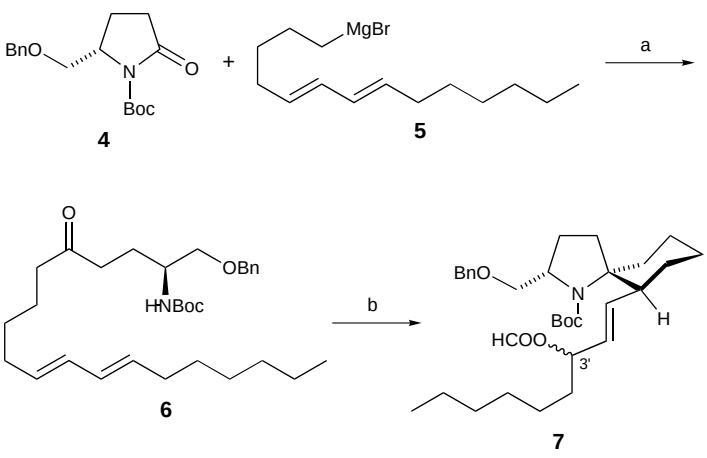
A crucial element in our approach to the target compound was the *N*-acyliminium-ion-initiated olefin azacyclization[9] to elaborate the azaspirocyclic core of lepadiformine (**3**). Such cyclizations, which lead to spirocyclic compounds, were initially developed by Speckamp and co-workers[10] and Evans et al.[11] Recently, this reaction was applied successfully by Weinreb and co-workers[6] in the total synthesis of (±)-**3**. Herein we describe the first total synthesis of (−)-lepadiformine (**3**) by using a new variant of the *N*-acyliminium-ion-initiated intramolecular spirocyclization in which a conjugated diene was exploited as a π nucleophile and has been proven to be quite effective for the highly stereoselective and extremely short approach to **3**. Furthermore, the synthesis of **3** allowed the absolute configuration of natural lepadiformine to be established as 3*S*,5*R*,7a*S*,11a*S* (Scheme 1).



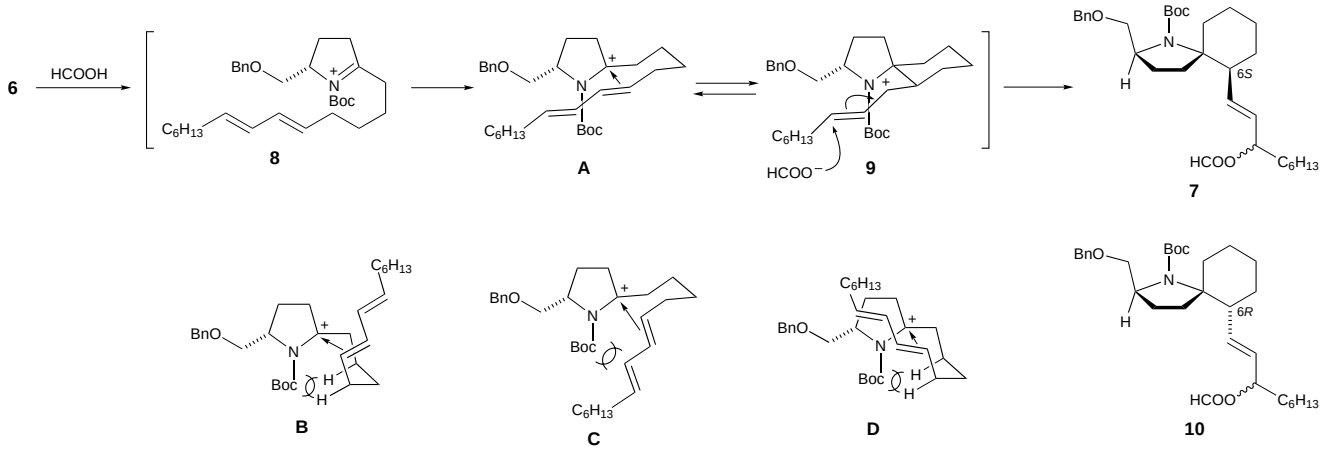
Scheme 2. Reagents and conditions: a) THF, 0 °C, 79 %; b) HCOOH, toluene/THF (95:5), 0 °C, 2 h, 88 %.

Our synthesis commenced with the known (*S*)-*N*-Boc-2-pyrrolidinone **4**,[12] which upon treatment with the (5*E*,7*E*)-tetradeca-5,7-dienyl Grignard reagent **5** underwent selective attack at the endocyclic (ring) carbonyl group[13] to yield ketone **6** (Scheme 2). When a solution of **6** in toluene/THF (95:5) was treated with formic acid at 0 °C for 2 h and neutralized with NH_4OH, in situ generation of the N-acyliminium ion followed by spirocyclization proceeded with synchronous formation of the new C–O bond at C3′ to furnish the 1-azaspirocyclic formate ester **7** in 88 % yield. Notably, the spirocyclization of the *N*-acyliminium ion generated from **6**, which bears a conjugated diene, proceeded quite smoothly and was completed in a short time, in marked contrast to the case with the reported spirocyclization of *N*-acyliminium ions that bear nonconjugated olefins which require long reaction times.[10,11]

The 6-*exo-trig* ring closure[14] gave **7** with complete regiocontrol, as predicted by considering the initially formed carbocation, which is stabilized through resonance with the olefin π bond in the alkene side chain. In this manner, the nucleophilic attack of the olefin moiety occurred exclusively at the sterically less hindered β face (opposite to the 5-benzyloxymethyl group) of the 1-pyrroline ring, with exclusive introduction of the desired 6*S* chirality. The concomitant formate substitution at C3′ occurred with low diastereoselectivity (1.6:1 favoring the 3′β-formate) as determined by HPLC analysis (see below).

Exclusive preferential formation of (6*S*)-**7** can be understood by comparison of the stabilities of the configurations of the six-membered chairlike π complexes **A**–**D**, which arise from the in situ generation of the *N*-acyliminium ion **8** as shown in Scheme 3. In the transition states **C** and **D**, which lead to (6*R*)-**10**, the N-Boc group displays unfavorable nonbonding interactions with the axially oriented diene moiety and the 1,3-diaxial hydrogen atoms of the newly formed cyclohexane ring, respectively. The latter steric interaction between the N-Boc group and the 1,3-diaxial hydrogen atoms is also present in the transition state **B**, which leads to (6*S*)-**7**. Neither of these interactions are present in the transition state **A** and therefore, of the four possible chairlike transition states **A**–**D**, **A** is the least disfavored and leads to the observed (6*S*)-**7**.

The formate ester **7**, which is epimeric at C3′, underwent basic hydrolysis to give the allylic alcohols **11a**/**11b**, whose diastereomeric ratio was determined to be 1:1.6 by HPLC.[15] This diastereomeric mixture was oxidized with MnO_2 to give



Scheme 3. The selective formation of **7** from **6** occurs via transition state **A**. Transition states **B**–**D** are disfavored.

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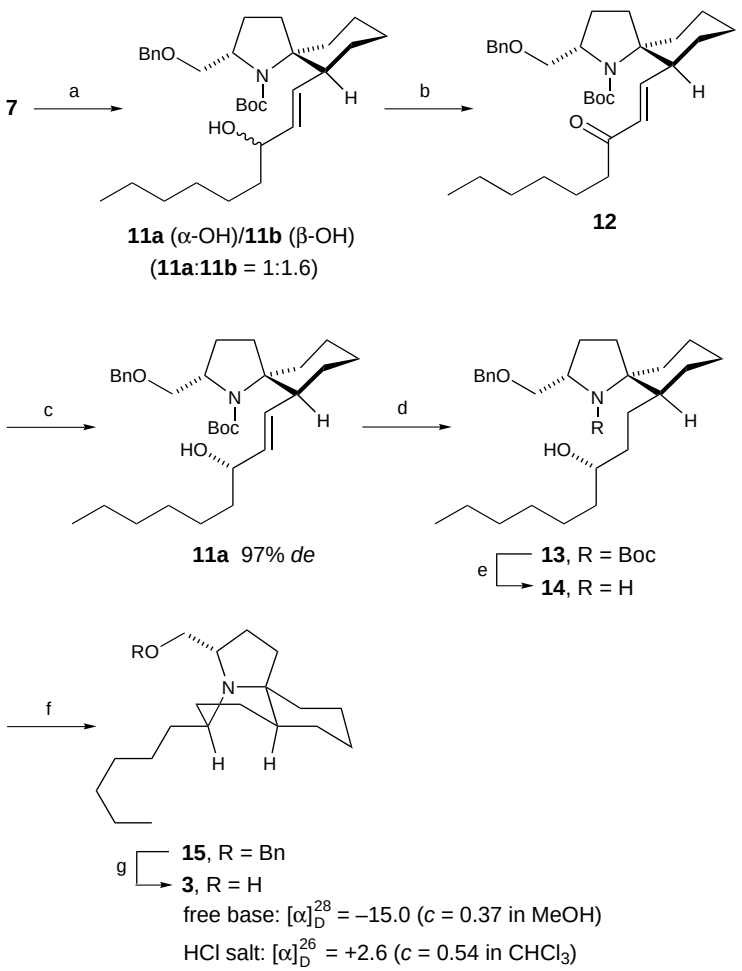

Scheme 4. Reagents and conditions: a) K_2CO_3, $MeOH/H_2O$, 98%; b) MnO_2, CH_2Cl_2, 91%; c) (*S*)-BINAL-H, THF, −78°C, 92%; d) H_2, PtO_2, EtOAc, 86%; e) TFA, CH_2Cl_2, 91%; f) CBr_4, PPh_3, Et_3N, CH_2Cl_2, 82%; g) H_2, $Pd(OH)_2$, MeOH, 87%; **3** (free base): $[\alpha]_D^{28} = -15.0$ ($c = 0.37$ in MeOH), **3**·HCl: $[\alpha]_D^{26} = +2.6$ ($c = 0.54$ in $CHCl_3$). (*S*)-BINAL-H = 2,2′-binaphthoxyaluminum hydride, TFA = trifluoroacetic acid.

the α,β-conjugated ketone **12** (Scheme 4). Reduction of **12** to the corresponding alcohol with BH_3·THF (THF, 0°C) was almost nonstereoselective (**11a**/**11b** 1.15:1). (*S*)-BINAL-H diastereoselective reduction[16] provided the alcohol (3′*S*)-**11a** in 92% yield with 97% *de*. Catalytic hydrogenation of **11a** over palladium on carbon (10%) in methanol was carried out in the presence of diethylamine (1 equiv) to prevent hydrogenolysis of the benzyl ether[17] and afforded **13** in 64% yield. Alternatively, the use of PtO_2 catalyst and ethyl acetate as solvent without diethylamine remarkably improved the yield of **13** to 86%. After removal of the Boc protecting group with trifluoroacetic acid, the resulting amino alcohol **14** was treated with CBr_4 and PPh_3 to form the tricyclic amine **15** in 82% yield, with complete inversion of the configuration at C3′. Hydrogenolytic removal of the benzyl protecting group afforded lepadiformine (**3**) whose spectral properties were identical in all respects with those of an authentic sample of racemic lepadiformine (±)-**3** previously prepared by us.[5b] The optical rotation of synthetic alkaloid **3** was measured: $[\alpha]_D^{28} = -15.0$ ($c = 0.37$ in MeOH) for the free base (oil) and $[\alpha]_D^{26} = +2.6$ ($c = 0.54$ in $CHCl_3$) for the hydrochloride salt (colorless gum). However, it was not possible to determine the absolute stereochemistry of natural lepadiformine by comparison of the optical rotations, since, as described above, the natural product (actually the hydrochloride salt) had been reported to have no optical rotation in chloroform.

The absolute stereochemistry was assigned successfully by comparison of synthetic and natural lepadiformine on a chiral HPLC column. In the chiral HPLC analysis, the authentic sample of racemic lepadiformine (±)-**3**[5b] gave peaks at different retention times [(+)-**3**, 45 min; (−)-**3**, 48 min] (Figure 1). Comparison of retention times and co-injection revealed that the synthetic (−)-enantiomer corresponds to the natural product, thus allowing the absolute stereochemistry of natural lepadiformine to be assigned as 3*S*,5*R*,7a*S*,11a*S*.

In summary, we have reported the first total synthesis of the natural enantiomer of lepadiformine (**3**) by employing an intramolecular conjugated diene cyclization of an *N*-acyliminium ion. The 1-azaspiro formate ester **7** is obtained in a single step from the simple keto amide **6**, which bears the conjugated diene. The total synthesis is highly stereoselective and is completed in nine steps with an overall yield of 31.4% starting from the (*S*)-*N*-Boc-2-pyrrolidinone **4** and provides a highly efficient and extremely short route to **3**. Furthermore, the present synthesis allowed us to establish the 3*S*,5*R*,7a*S*,11a*S* absolute configuration of natural lepadiformine.

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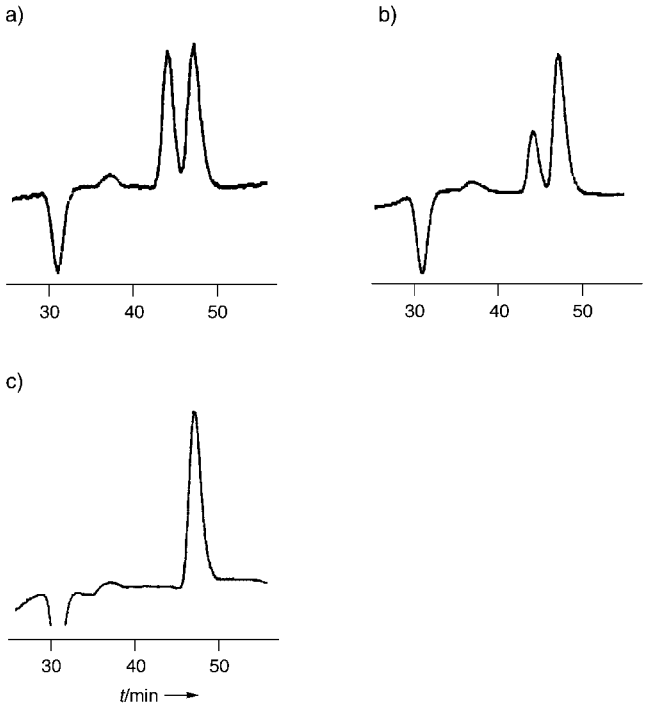

Figure 1. HPLC chromatogram of lepadiformine on a Daicel Chiralpak OD: a) racemate; b) mixture of racemate and natural; c) mixture of synthetic (−)-enantiomer and natural. Conditions: mobile phase, hexane/2-propanol/Et_2NH (500:10:1); flow rate: 0.1 mL min^{-1}; detection: RI (refractive index).

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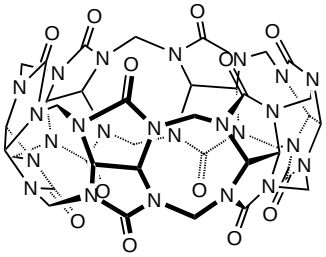
"Molecular" Molecular Sieves: Lid-Free Decamethylcucurbit[5]uril Absorbs and Desorbs Gases Selectively**

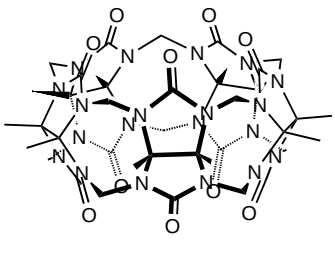
Yuji Miyahara,* Kazuaki Abe, and Takahiko Inazu

Several types of inorganic crystalline materials and organic polymers function as molecular sieves, the most common of which are numerous types of zeolites.[1] While some organic host molecules encapsulate small molecules in solution,[2] practical applications have never been attempted because of their inaccessibility. Here we report that the title compound, which can be readily synthesized from simple starting materials, shows potential for use as molecular sieves in the solid state by utilizing its molecular cavity.

In 1981 Mock and co-workers reported[3] that the compound which Behrend prepared from glycoluril and formalin in 1905[4] has a beautiful barrel-like macrocyclic structure composed of six glycoluril units; they named it cucurbituril (Cuc6). Since then extensive studies have been conducted on this unique host compound.[5]



Cuc6



MeCuc5

In 1982, in his PhD thesis on cucurbituril, Shih also described a compound, assumed to have a pentameric structure, which was obtained by heating dimethylglycoluril under reflux with formalin in dilute HCl;[6] Shih and Mock did not study the compound further because of its inactivity as a host molecule.[3b] In 1992, Stoddart and co-workers confirmed its basic structure by X-ray structure analysis of a crystal grown in dilute HNO_3 and named it decamethylcucurbit[5]uril (MeCuc5).[7] At the time when the paper by Stoddart and co-workers appeared we had already found that the product obtained under the reaction conditions contained two NH_4Cl

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

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