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Total Synthesis of the Marine Alkaloid (±)-Lepadiformine via a Radical Carboazidation

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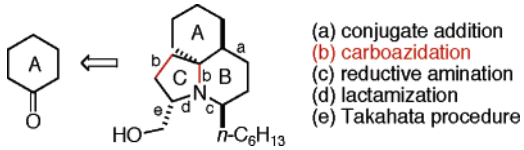
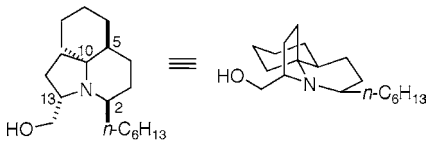
ABSTRACT



The total synthesis of lepadiformine has been achieved in 10 steps and 15% overall yield from cyclohexanone. The amino-substituted quaternary carbon center is created through a radical carboazidation reaction. The tricyclic core of lepadiformine is built via an efficient hydrogenation process, involving reduction of the azide and intramolecular reductive amination of a ketone, followed by lactamization of the intermediate γ-aminoester. The hydroxymethyl side chain is introduced according to a modified Takahata procedure after conversion of the lactam into a thiolactam.

Lepadiformine is a marine alkaloid which was isolated in 1994 from the tunicate *Clavelina lepadiformis* and later from *Clavelina moluccensis*.[1] It showed moderate cytotoxic activity against several tumor cell lines as well as various cardiovascular effects in vitro and in vivo. Its discovery triggered a series of synthetic efforts. In several attempts toward the total synthesis, it soon became obvious that the structure originally proposed based on NMR experiments had to be corrected. It was not until 6 years after its discovery that the structure of lepadiformine was finally revised to **1** after the first total synthesis by Kibayashi.[2a] This process has recently been reviewed by Weinreb, who emphasizes the value of total synthesis for natural product structure elucidation in this context.[3] A number of syntheses for racemic[2] as well as for optically pure lepadiformine have been reported.[4]



lepadiformine **1**

A key structural feature of lepadiformine is a *trans*-azadecalin framework including an amino-substituted quaternary carbon center (C10). We report here a very concise synthesis of lepadiformine starting from cyclohexanone and using a radical carboazidation step to create the quaternary carbon center at C10.

Recently, we developed a radical carboazidation reaction and applied it to the preparation of mono- and polycyclic lactams such as indolizidinones and spirocyclic lactams.[5] In the latter case, the reaction proceeds via a tertiary alkyl radical, which is particularly well suited to react with the sulfonyl azide radical trap because of its nucleophilic character. Therefore, this procedure is particularly efficient

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

(2) (a) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583. (b) Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **2001**, *3*, 3507. (c) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3511.

(3) (a) Weinreb, S. M. *Acc. Chem. Res.* **2003**, *36*, 59. (b) Kibayashi, C.; Aoyagi, S.; Abe, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2059. (c) Schär, P.; Cren, S.; Renaud, P. *Chimia* **2006**, *60*, 131.

(4) (a) Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3017. (b) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, *67*, 4337. (c) Liu, J.; Hsung, R. P.; Peters, S. D. *Org. Lett.* **2004**, *6*, 3989. (d) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2005**, *127*, 1473.

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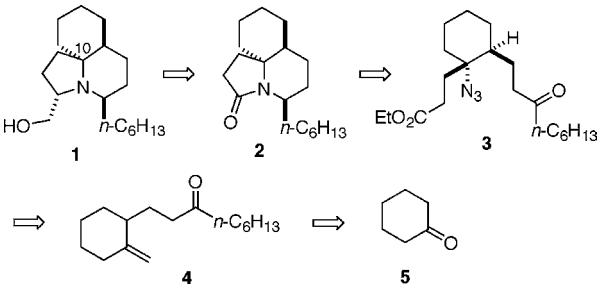
to prepare amino-substituted quaternary carbon centers, such as C10 of lepadiformine. Our synthetic strategy to prepare lepadiformine is depicted in Scheme 1. Tricyclic lactam **2**

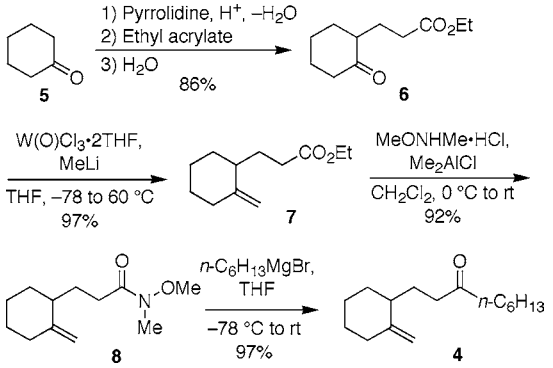
Scheme 1. Retrosynthetic Approach



will be obtained by two consecutive ring closures from azidoketoester **3**. The azidoester **3** will be prepared by carboazidation of the methylenecyclohexane **4**, easily prepared from cyclohexanone **5**.

Interestingly, **4** had already been reported as an intermediate in the total synthesis of 5,13-diepilepadiformine by Pearson.[6] The ketoester **6** was prepared according to a literature procedure in 86% yield (Scheme 2).[7] Methylenation

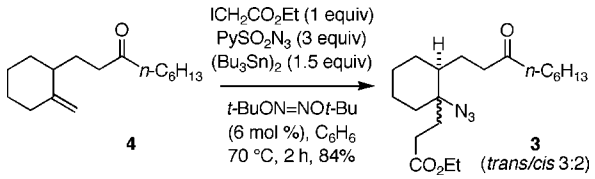
Scheme 2. Preparation of Methylenecyclohexane **4**



of the ketone **6** was examined under several reaction conditions. Wittig olefination gave the desired product in moderate yield (60%). A better result was obtained with Kauffmann's tungsten carbene that gave the desired methylenecyclohexane **7** in nearly quantitative yield.[8] The *n*-hexyl side chain was then introduced by conversion of the ester **7** to the Weinreb amide **8** followed by reaction with *n*-hexylmagnesium bromide as previously reported by Pearson.[6]

The tin-mediated carboazidation was carried out at 70 °C with a 1:1 ratio of alkene **4** and ethyl iodoacetate and using pyridine sulfonyl azide as the radical trap to facilitate chromatographic separation of the product.[9] This gave the azidoester **3** in good yield as a 3:2 mixture of *trans*/*cis* diastereomers (Scheme 3).

Scheme 3. Radical Carboazidation

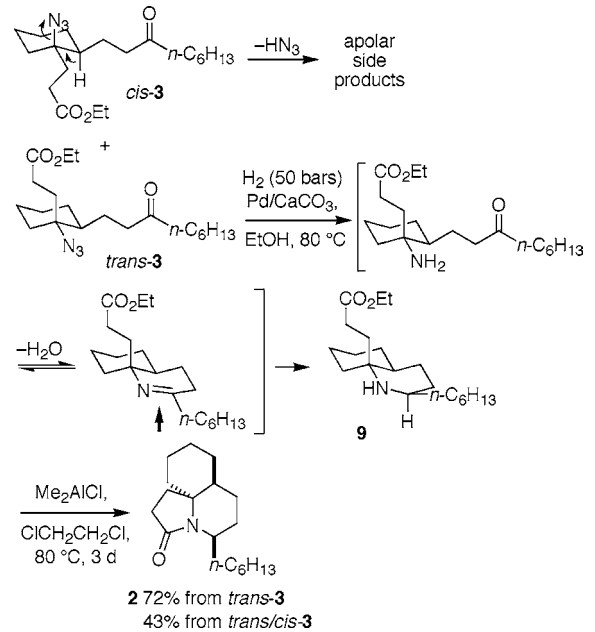


Attempts to run the reaction at lower temperature did not enhance the diastereoselectivity.

Separation of the *trans* and cis diastereomers of **3** was possible. However, the synthesis was carried on with the mixture of diastereomers since an easier separation was possible at a later stage.

To prepare cycle B, the azide moiety was reduced to an amine by hydrogenation in the presence of palladium on calcium carbonate. This catalyst was found to be superior to Pd/C which led mainly to elimination of hydrazoic acid. We later discovered that the minor azide *cis*-**3** is much more prone to elimination due to the *anti* arrangement of the proton and the azide (Scheme 4). Thus, when the diastereomeric

Scheme 4. Formation of Tricyclic Lactam **2**



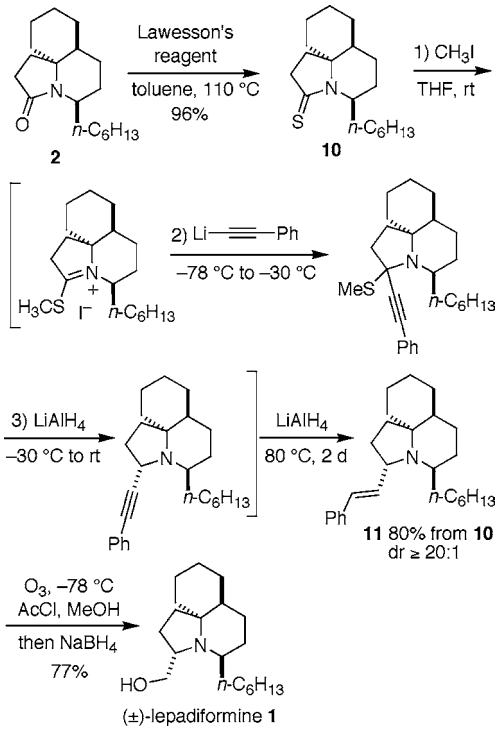
mixture of **3** was hydrogenated, the minor *cis*-**3** was completely converted to apolar products and *trans*-**3** underwent the desired reduction followed by a stereoselective

(5) (a) Panchaud, P.; Ollivier, C.; Renaud, P.; Zigmantas, S. *J. Org. Chem.* **2004**, *69*, 2755. (b) Chabaud, L.; Landais, Y.; Renaud, P. *Org. Lett.* **2005**, *7*, 2587. (c) Panchaud, P.; Chabaud, L.; Landais, Y.; Ollivier, C.; Renaud, P.; Zigmantas, S. *Chem. Eur. J.* **2004**, *10*, 3606. (d) Panchaud, P.; Renaud, P. *Chimia* **2004**, *57*, 232. (e) Renaud, P.; Ollivier, C.; Panchaud, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3460.

(6) Pearson, W. H.; Barta, N. S.; Kampf, J. W. *Tetrahedron Lett.* **1997**, *38*, 3369.

(7) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

Scheme 5. Conversion of Lactam **2** to (±)-Lepadiformine **1**



intramolecular reductive amination leading to the bicyclic azadecaline **9**. In analogy to lepadiformine, we assume that the *trans*-azadecalin prefers an unusual boat conformation as depicted in Scheme 4 and is reduced from the less hindered face *anti* to the axial $CH_2CH_2CO_2Et$. After filtration of the catalyst, the crude amine was treated with Me_2AlCl to promote lactamization, and the tricyclic lactam **2** was obtained in a respectable 43% yield for the mixture of *trans*- and *cis*-**3** (72% yield based on pure *trans*-**3**).

The last part of the synthesis concerned the conversion of the γ-lactam into a hydroxymethyl-substituted pyrrolidine. This simple transformation proved to be much more complicated to run than expected since all methods involving reduction of the lactam to a hemiaminal followed by reaction with a nucleophile failed. Takahata reported that thioamidinium salts, formed by treatment of thiolactams with methyl iodide, react with lithium acetylides to give propargylamines after reduction of the intermediate *N*,*S*-acetal with lithium aluminum hydride.[10] By enforcing the reducing conditions, a direct access to allylamines was envisaged. Conversion of **2** to the thiolactam **10** with Lawesson's reagent[11] was straightforward. Treatment of thiolactam **10** with methyl iodide and then with lithium 2-phenylacetylide followed by heating with an excess of $LiAlH_4$ afforded the allylic amine **11** as a single diastereoisomer. Conversion of **11** to (±)-lepadiformine was achieved by ozonolysis under acidic conditions (AcCl in MeOH) followed by reductive treatment with $NaBH_4$ (Scheme 5).

In conclusion, the total synthesis of (±)-lepadiformine was achieved in 10 linear steps from cyclohexanone with an overall yield of 15%. This synthesis is expected to be easily amenable to the preparation of the enantiomerically pure natural product by preparing the methylenecyclohexane **4** in optically pure form. Work in this direction will be reported in due course. The stereochemical outcome of the carboazidation step is also under investigation and strategies to achieve a high level of stereocontrol are being developed.

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Supporting Information Available: Experimental procedures and product characterization for all compounds mentioned in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Kauffmann, T.; Abeln, R.; Welke, S.; Wingbergmühle, D. *Angew. Chem.* **1986**, *98*, 927.
(9) Panchaud, P.; Renaud, P. *Adv. Synth. Catal.* **2004**, *346*, 925.
(10) Takahata, H.; Takahashi, K.; Wang, E.-C.; Yamazaki, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1211.
(11) Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S.-O. *Org. Synth.* **1984**, *62*, 158.