A Convergent Stereoselective Synthesis of the Putative Structure of the Marine Alkaloid Lepadiformine via an Intramolecular Nitrone/1,3-Diene Dipolar Cycloaddition

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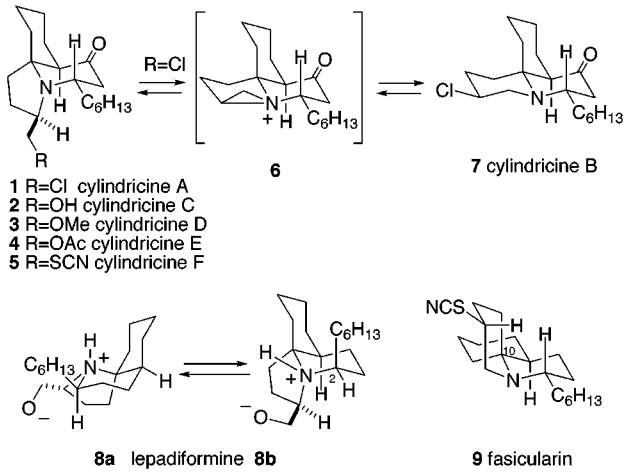
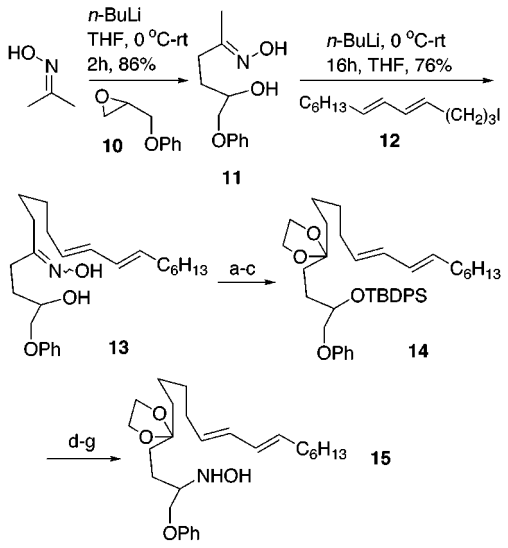
The marine ascidian *Clavelina cylindrica* produces a series of interesting tricyclic quinolizidine and indolizidine alkaloids that show toxicity in a brine shrimp assay.[1] Cylindricines A (**1**), C (**2**), D (**3**), E (**4**), and F (**5**) differ only in the functionality of the methylene substituent in the five-membered ring. Interestingly, cylindricines A and B (**7**) interconvert simply upon standing in solution, presumably via the aziridinium intermediate **6**. A structurally related



alkaloid lepadiformine (**8**), which has been isolated from *Clavelina lepadiformis*, shows in vitro cytotoxic activity toward several tumor strains.[2] Lepadiformine was postulated to be epimeric to cylindricine C (**2**) at C2 and also to lack the C4 ketone carbonyl functionality. It appears from published NMR NOE data that the molecule prefers to exist in conformation **8a** rather than **8b**.[2] On the other hand, molecular mechanics calculations (PCModel) indicate that conformer **8b** (axial hexyl group) is about 2.6 kcal/mol lower in energy than the flip form **8a** (equatorial hexyl). Interestingly, on the basis of ^{1}H NMR studies, it was proposed that lepadiformine (**8**) has the unusual zwitterionic structure shown. More recently, fasicularin (**9**) was found in a different ascidian genus.[3] This latter alkaloid, which is analogous to the cylindricine B quinolizidine subclass but is epimeric at C10, is cytotoxic and is also active against a DNA repair-deficient strain of yeast.

Scheme 1[a]



[a] Reagents: (a) $TiCl_3$, NH_4OAc, H_2O/HOAc (1/1), dioxane, 20 min, rt, 86%; (b) TBDPSCl, imidazole, CH_2Cl_2, 16 h, rt, 92%; (c) $(HOCH_2)_2$, *p*-TsOH, PhH (reflux), 16 h, 97%; (d) TBAF, THF, 16 h, rt, 99%; (e) Swern oxidation, 93%; (f) NH_2OH−HCl, pyr, EtOH, 30 min, rt, 100%; (g) $NaBH_3CN$, 2 N HCl, MeOH, 0 °C−rt, 2 h, 95%.

In 1997, Snider and Liu described the first total syntheses of cylindricines A, D, and E.[4a] Moreover, Pearson has described some interesting synthetic studies in this area involving azaallyl anion cycloadditions.[4b] In this paper, we disclose a convergent, stereoselective route to the tricyclic structure **8** proposed for lepadiformine via a strategy involving an intramolecular nitrone/diene dipolar cycloaddition as the key step.[5,6] We also report that structure **8** does *not* correspond to natural lepadiformine.

Our synthetic route commenced with acetone oxime, which can be dilithiated[7] and alkylated with commercially available epoxide **10** to give (*E*)-oxime alcohol **11** in good yield (Scheme 1).[8] Subsequent regiospecific C-alkylation of the trianion of oxime **11** with (*E*/*E*)-dienyl halide **12**[9] then provided diene **13** (as a mixture of (*E*/*Z*)-oxime geometric isomers after purification by chromatography).[10] The linear, acyclic compound **13**, which contains all of the carbons necessary for constructing the tricyclic skeleton of lepadiformine, was elaborated to the requisite cyclic nitrone

† Contact this author regarding the X-ray crystal structure determination.

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

(2) Baird, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691.

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

(4) (a) Snider, B. B.; Liu, T. *J. Org. Chem.* **1997**, *62*, 5630. (b) Pearson, W. H.; Barta, N. S.; Kampf, J. W. *Tetrahedron Lett.* **1997**, *38*, 3369.

(5) For other intramolecular nitrone/olefin spirocyclizations, see: (a) Grigg, R.; Hadjisoteriou, M.; Kennewell, P.; Markandu, J.; Thornton-Pett, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1388. (b) Grigg, R.; Hadjisoteriou, M.; Kennewell, P.; Markandu, J. *J. Chem. Soc., Chem. Commun.* **1992**, 1537. (c) Tufariello, J. J.; Trybulski, E. J. *J. Org. Chem.* **1974**, *39*, 3378.

(6) For an example of an intramolecular nitrone/conjugated diene cycloaddition, see: Holmes, A. B.; Hughes, A. B.; Smith, A. L.; Williams, S. F. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1089. Intermolecular [3 + 2]-cycloaddition reactions of nitrones with conjugated dienes leading to indolizidines and quinolizidines have been described: (a) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. (b) Tufariello, J. J.; Dyszlewski, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1138, and references cited.

(7) (a) Jung, M. E.; Blair, P. A.; Lowe, J. A. *Tetrahedron Lett.* **1976**, 1439. (b) Kofron, W. G.; Yeh, M.-K. *J. Org. Chem.* **1976**, *41*, 439.

(8) Oxime **11**, which is presumably initially *Z*,[7] was found to be a mixture of *E*/*Z* isomers after an aqueous workup and upon further chromatographic purification equilibrated totally to the *E* isomer. For NMR determination of oxime geometry, see: Bunnell, C. A.; Fuchs, P. L. *J. Org. Chem.* **1977**, *42*, 2614.

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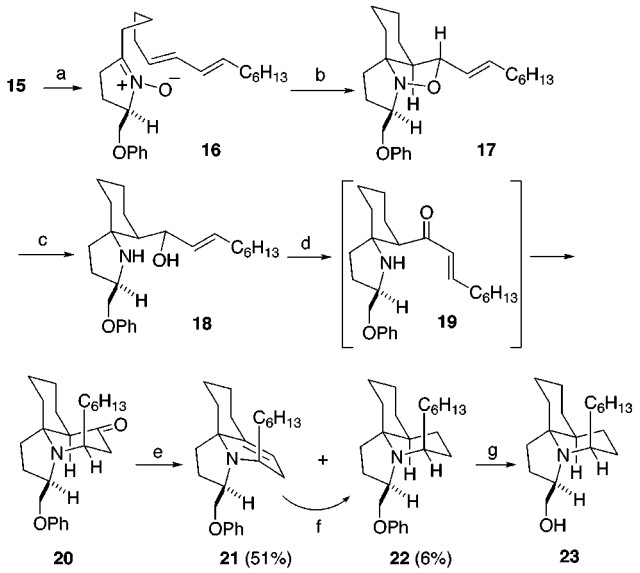
Scheme 2[a]



[a] Reagents: (a) 3 N HCl, THF, 4 h, rt, 92%; (b) DMSO, 190 °C, 16 h, 63%; (c) Zn dust, HOAc, H_2O, 45 °C, 3 h, 91%; (d) Dess−Martin, *t*-BuOH, CH_2Cl_2, 40 min, rt, 71%; (e) Zn(Hg), concd HCl, PhMe, 90 °C, 23 h; (f) H_2 (1 atm), 10% Pd/C, EtOH, 6 h, rt, 70%; (g) Li/NH_3, EtOH, THF, −50 °C, 4 h; 2 N HCl/MeOH, THF, 6 h, 71%.

precursor by a straightforward sequence as shown in Scheme 1. Thus, the oxime **13** was cleaved to the ketone,[11] the alcohol functionality of the product was protected, and the resulting silyl ether ketone was then converted to silyl ether ketal **14**. Removal of the silyl group of **14**, oxidation of the resulting alcohol to the corresponding ketone, and formation of hydroxylamine **15** via hydride reduction[12] of the oxime could be effected in good overall yield.

To continue the synthesis, oxime ketal **15** was transformed to the stable cyclic nitrone **16** using dilute acid (Scheme 2). Thermolysis of this diene/nitrone **16** in DMSO at 190 °C led to a single isoxazolidine cycloadduct **17** (63%).[13] The structure and stereochemistry of this product were ultimately established by X-ray analysis of a subsequent intermediate (vide infra). It should be added that it appears for stereoelectronic reasons that the linking chain in this nitrone probably assumes a boatlike conformation for the [3 + 2] cycloaddition as depicted in structure **16**. Also, for steric reasons the cycloaddition occurs exclusively on the cyclic nitrone face opposite to the large phenoxymethyl group.[5a,b]

The N−O bond of this cycloadduct **17** was cleaved with Zn dust to give amino alcohol **18**, which was oxidized with Dess−Martin reagent to afford a single stereoisomeric tricycle **20**, presumably via amino enone **19**. From inspection of models, it is clear that cyclization of enone **19** can only occur to give the lepadiformine stereochemistry at C2 for stereoelectronic reasons. It might also be noted that this cyclization must occur initally to generate the piperidone ring of **20** as a boat. The structure and conformation indicated in structure **20** were supported by 2D NMR experiments (NOESY, HMQC, and ^{13}C Inadequate).[14]

To correlate tricycle **20** with lepadiformine, it was necessary to remove the ketone carbonyl group. Rather surprisingly, exposure of **20** to Clemmensen conditions[15] led to a mixture of olefin **21** and the desired reduction product **22**, with the former compound predominating (ratio ~8.5:1). It was possible, however, to hydrogenate **21** from the more exposed olefin face to give **22**.[16] The structure and stereochemistry of tricycle **22** were confirmed by X-ray analysis of its picrate salt (see Supporting Information). Interestingly, compound **22** has a conformation in the crystal form corresponding to that of **8b**, as predicted by computer modeling (vide supra).

Finally, the *O*-phenyl protecting group was removed by Birch reduction, followed by acid hydrolysis, to yield amino alcohol **23** in good yield.[17] We were surprised to find, however, that comparison of the proton and carbon NMR spectra of our synthetic **23** with those of the natural material[18] indicated that the compounds were clearly different. In view of these results and those described by Pearson and Ren in the accompanying paper,[19] it appears that the originally proposed structure of lepadiformine requires revision.

Acknowledgment. We are grateful to the National Science Foundation (CHE-94-23670 and CHE-97-32038) for financial support of this research, to Dr. Kiyohiro Samizu for helpful suggestions during the initial design stages of the project, and to Dr. Alan Benesi for assistance with 2D NMR experiments. We also thank Professor Raymond L. Funk for helpful discussions and assistance with molecular mechanics calculations. J.M.D. acknowledges the Consejeria de Educacion del Gobierno Vasco (Spain) for a postdoctoral fellowship.

Supporting Information Available: Experimental details for preparation of new compounds and X-ray data, including an ORTEP diagram, for the picrate salt of intermediate **22**.

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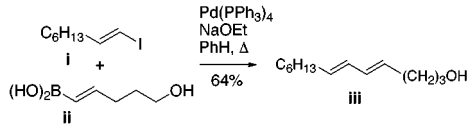
(9) This *E*/*E*-dienyl halide is accessible by the Suzuki coupling of known vinyl iodide **i** and hydroxy boronic acid **ii** to diene alcohol **iii** (cf. Miyaura, N.; Suginome, H.; Suzuki, A. *Tetrahedron* **1983**, *39*, 3271), followed by conversion of the alcohol to the iodide with PPh_3/I_2/imidazole (95%). We are grateful to Ann Bullion for performing these experiments. Experimental details will be provided in a full paper.

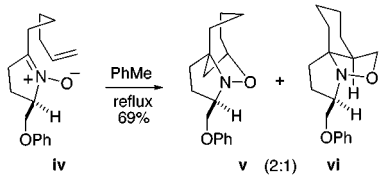


(10) Our original strategy was to intramolecularly *N*-alkylate the oxime functionality of an activated derivative of oxime alcohol **13** using methodology of Grigg[5a,b] to directly produce a cyclic nitrone like **16**. However, all attempts to effect such a transformation led only to a 1,2-oxazine resulting from oxime *O*-alkylation (cf. Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L.; Marini, F. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1989).

(11) Timms, G. H.; Wildsmith, E. *Tetrahedron Lett.* **1971**, 195.

(12) Borch, R. F.; Bernstein, M. D.; Durst, D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

(13) Interestingly, the simpler olefinic nitrone **iv** cyclizes thermally to afford the bridged regioisomeric isoxazolidine **v** as the major product along with the desired spirocyclic adduct **vi**.



(14) As further proof of the structure, ketone **20** was converted to the corresponding ethylene ketal, followed by Birch reduction and acidic hydrolysis, to give C2 *epi*-cylindricine C. Comparison of the spectra of this material with those of cyclindricine C showed that the compounds were in fact different.[18]

(15) Martin, E. L. *Org. React.* **1942**, *1*, 155. Olefins have previously been observed as minor byproducts in Clemmensen reductions.

(16) Since our synthetic compound does not correspond to natural lepadiformine, we have not attempted to optimize the direct removal of the carbonyl group from intermediate **20**.

(17) Aryl protection of alcohols has not been widely used. cf. Marshall, J. A.; Partridge, J. J. *J. Am. Chem. Soc.* **1968**, *90*, 1090. In this case, a *p*-chlorophenyl ether protecting group was used for oxygen.

(18) We are grateful to Professors Barry Snider and A. J. Blackman for copies of the proton and carbon NMR spectra of several of the cylindricines. We also thank Dr. J. F. Biard for the proton and carbon NMR spectra, as well as a sample of lepadiformine, and Professor William H. Pearson (University of Michigan) for helpful discussions and exchange of information.

(19) Pearson, W. H.; Ren, Y. *J. Org. Chem.* **1999**, *64*, 688.