ORGANIC LETTERS

2001
Vol. 3, No. 22
3507−3510

# A New Total Synthesis of the Marine Tunicate Alkaloid Lepadiformine

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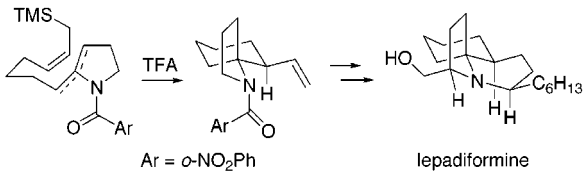
**Received August 16, 2001**

## ABSTRACT




**A total synthesis of racemic lepadiformine has been achieved via a route that utilizes as key steps a novel stereocontrolled intramolecular spirocyclization of an allylsilane/*N*-acyliminium ion and the application of our radical-based methodology for production of *N*-acylimines from *o*-aminobenzamides.**

During the past decade a number of structurally related tricyclic alkaloids have been isolated from various marine ascidians. The most common and numerous alkaloids of this type are the cylindricines, isolated from *Clavelina cylindrica* collected off the coast of Tasmania, whose structures were established by the Blackman group.[1] The cylindricines are comprised of two subclasses: the pyrrolo-quinolines represented by **1**−**4**, and the pyrido-quinolines typified by **6**. Interestingly, cylindricines A (**1**) and B (**6**) form a 3:2 equilibrium mixture presumably via interconversion through aziridinium intermediate **5**. In addition, several cylindricines exist within both classes that have a butyl group and/or differing stereochemistry at C2. In 1997 another alkaloid, fasicularin (**7**), was isolated from the ascidian *Neptheis fasicularis*.[2] Compound **7** is related structurally to the cylindricine B pyrido-quinoline alkaloids, but it is epimeric at the C10 quaternary center and in addition lacks the C4 oxygenation found in the cylindricines. Fasicularin is active against a DNA repair deficient strain of yeast and is also cytotoxic.

In 1994, Biard and co-workers reported the isolation of the alkaloid lepadiformine from the tunicate *Clavelina lepadiformis* Muller collected in the Mediterranean near Tunisia.[3] The compound has also been found in *Clavelina moluccensis* collected near Djibouti. Primarily on the basis of NMR spectroscopic data, lepadiformine was formulated as having the pyrrolo-quinoline constitution **8** related to the cylindricine A series of alkaloids. The compound was also suggested to have the very unusual zwitterionic structure shown. Lepadiformine was found to have moderate in vitro cytotoxic activity against several tumor lines.[3] In addition, various cardiovascular effects of lepadiformine in vivo and in vitro have been described.[4]

We recently reported the synthesis of the structure **8** proposed for lepadiformine and demonstrated that the compound does not exist as a zwitterion and that neither the free amine nor its hydrochloride salt correspond to the natural product.[5] Simultaneously, Pearson et al. prepared the other three diastereomers of this structure at C2 and C13 and found

(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) 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.

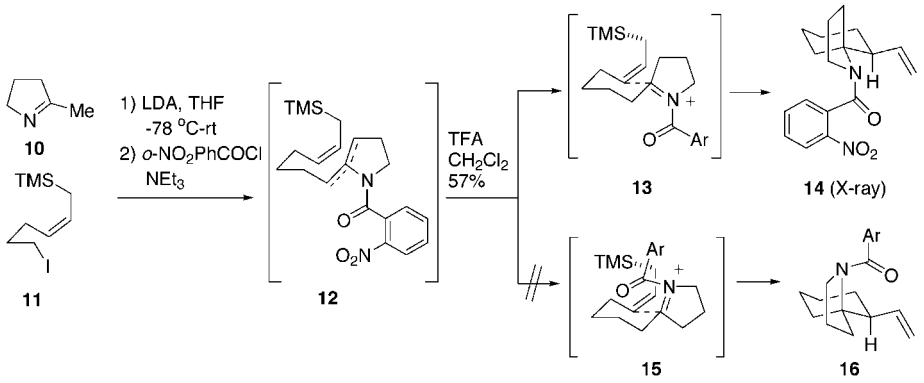
(3) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691. The absolute configuration of lepadiformine is presently unknown.

(4) Juge, M.; Grimaud, N.; Biard, J. F.; Sauviat, M. P.; Nabil, M.; Verbist, J. F.; Petit, J. Y. *Toxicon* **2001**, *39*, 1231.

(5) Werner, K. M.; De los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 686. Werner, K. M.; De los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 4865.

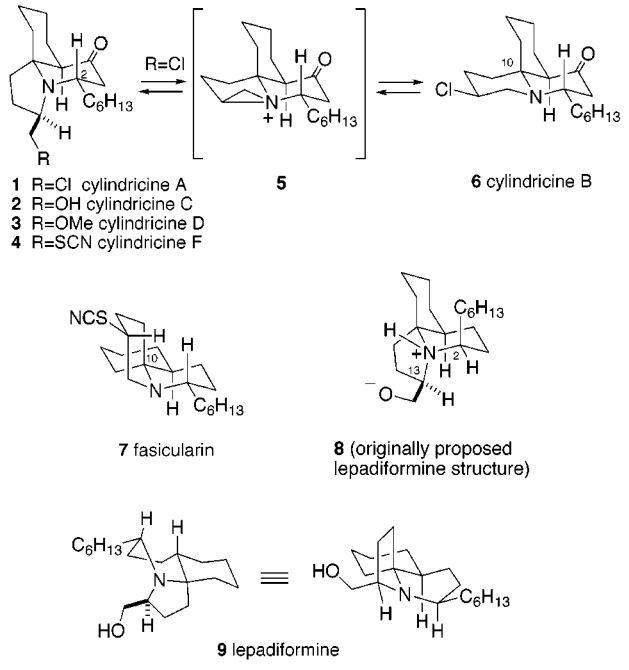
10.1021/ol010179y CCC: $20.00 
**Published on Web 10/02/2001**

**Scheme 1**




that none of these isomers were lepadiformine.[6] This structural problem was finally settled by Kibayashi and coworkers, who prepared compound **9** by total synthesis using an intramolecular nitroso Diels−Alder based approach and found that its hydrochloride salt is identical to natural lepadiformine.[7] Moreover, it was determined by X-ray crystallography that the alkaloid exists with the ring bearing the hexyl group in the boat conformation indicated. Thus, lepadiformine is in the fasicularin (**7**) stereochemical series but with a pyrrolo-quinoline ring system.

Our synthetic approach to the original lepadiformine structure **8** was based upon a pivotal intramolecular nitrone-diene dipolar cycloaddition.[5,8] However, this strategy cannot be modified to establish the requisite stereochemistry at the C10 quaternary center in **9**. Thus we have investigated a new approach to lepadiformine (**9**) based on a novel stereoselective intramolecular allylsilane/*N*-acyliminium ion spirocyclization[9] followed by an application of our radical-based methodology for generation of *N*-acylimines as key steps.[10] In this communication we report the results of this study.




The synthesis commenced with commercially available 2-methyl-1-pyrroline (**10**), which was first lithiated[11] and then alkylated with known iodide *Z*-allylsilane **11** (Scheme 1).[12] Without purification, the product of this reaction was *N*-acylated with *o*-nitrobenzoyl chloride to afford a mixture of regioisomeric enamides **12**, which was directly treated with trifluoroacetic acid to produce spirocycle **14** as a single stereoisomer (57% overall yield based upon **10**).[13] The structure and conformation of this cyclization product were established by X-ray crystallography.[14] We believe **14** forms via *N*-acyliminium ion conformation **13**. Conformer **15**, which would lead to the isomeric spirocycle **16**, is probably destabilized relative to **13** as a result of a steric interaction between the *N*-*o*-nitrobenzoyl group and the newly forming cyclohexane ring.

With spirocycle **14** in hand, we next turned to activation of the compound at C13 in order to introduce the requisite hydroxymethyl group of the natural product. Thus, the nitro functionality of **14** was cleanly reduced with $NaBH_4$/Cu(acac)$_2$[15] to provide *o*-aminobenzamide **17**, which was

(6) Pearson, W. H.; Barta, N. S.; Kampf, J. W. *Tetrahedron Lett.* **1997**, *38*, 3369. Pearson, W. H.; Ren, Y. *J. Org. Chem.* **1999**, *64*, 688.

(7) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583.

(8) For synthetic work on the cylindricines, see: Snider, B. B.; Liu, T. *J. Org. Chem.* **1997**, *62*, 5630. Molander, G. A.; Ronn, M. *J. Org. Chem.* **1999**, *64*, 5183. Liu, J. F.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8263.

(9) Reviews of the chemistry of *N*-acylimines: (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (b) Hiemstra, H.; Speckamp, W. N. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1988; Vol. 32, p 271. (c) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1047. (d) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

(10) (a) Han, G.; McIntosh, M. C.; Weinreb, S. M. *Tetrahedron Lett.* **1994**, *35*, 5813. (b) Han, G.; LaPorte, M. G.; McIntosh, M. C.; Weinreb, S. M.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 9483. (c) Chao, W.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 9199.

(11) For C-alkylations of metalated endocyclic imines, see: (a) Gramain, J.-C.; Husson, H.-P.; Troin, Y. *J. Org. Chem.* **1985**, *50*, 5517. (b) Evans, D. A. *J. Am. Chem. Soc.* **1970**, *92*, 7593.

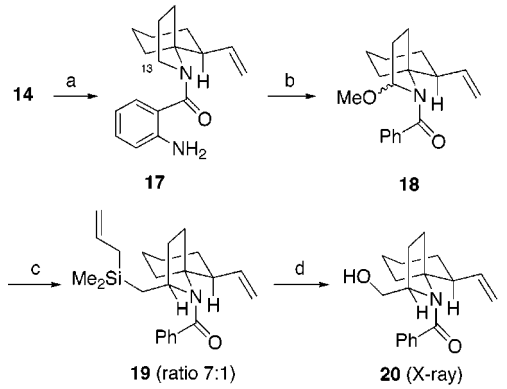
(12) Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014.

(13) For some related spirocyclizations leading to histrionicotoxins see, *inter alia*: Tanner, D.; Hagberg, L. *Tetrahedron* **1998**, *54*, 7907. Evans, D. A.; Thomas, E. W.; Cherpeck, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 3695. David, M.; Dhimane, H.; Vanucci-Bacque, C.; Lhommet, G. *Heterocycles* **2001**, *55*, 941.

(14) We are grateful to Dr. Louis Todaro (Hunter College, CUNY) for the X-ray analyses of compounds **14** and **20**.

subjected to the conditions we developed for conversion of such functionality to an α-methoxybenzamide ($NaNO_2$, HCl, MeOH, cat. CuCl), thereby producing **18** in good yield (Scheme 2).[10] It was then possible to alkylate α-methoxybenzamide **18** with the cuprate derived from (allyldimethylsilyl)methylmagnesium bromide[16] to afford an 87% yield of a 7:1 mixture of diastereomeric products, with the desired silane **19** being the major isomer. This transformation presumably occurs via the preferred attack of the cuprate from the least hindered face of an intermediate *N*-acyliminium ion. A Tamao oxidation[16] then served to convert silane **19** to the hydroxymethyl compound **20,** whose structure was confirmed by X-ray crystallography.[14]

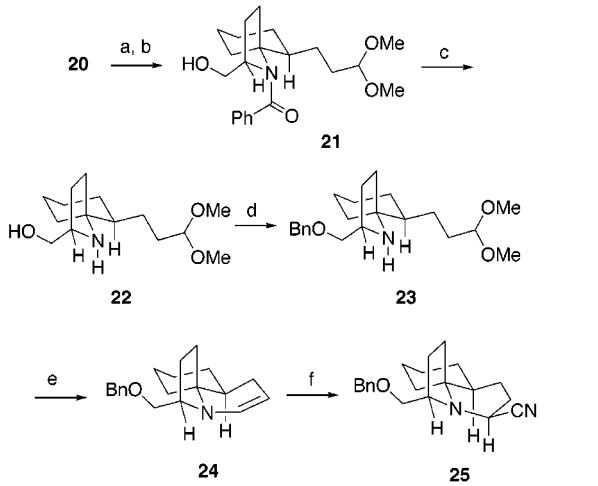
**Scheme 2**[a]




[a] Reagents: (a) $NaBH_4$, $Cu(acac)_2$, EtOH, rt, 95%; (b) $NaNO_2$, HCl, CuCl, MeOH, 0 °C−rt, 81%; (c) $CH_2$═$CHCH_2Si(Me_2)CH_2$-MgBr, $BF_3$-$Et_2O$, $CuBr_2$-$Me_2S$, $Et_2O$, −78 °C−rt, 87%; (d) (i) $BF_3$−HOAc, $CH_2Cl_2$, rt; (ii) 35% $H_2O_2$, $NaHCO_3$, MeOH, THF, Δ, 95%.

Continuing the synthesis, terminal alkene **20** was hydroformylated[17] to produce an aldehyde that was immediately converted to the corresponding dimethyl acetal **21** (Scheme 3). Hydrolytic cleavage of the benzoyl group of **21** with LiOH in aqueous ethanol then provided amino alcohol **22**. After some experimentation, it was eventually concluded that for introduction of the C2 hexyl chain (vide infra) it was necessary to protect the hydroxyl group of **22**.[18] Therefore, amino alcohol **22** was converted to the benzyl ether **23**, and exposure of this compound to acid led to the unstable tricyclic enamine **24**. Without purification, this material was transformed to the somewhat more stable amino nitrile **25** using HCl/KCN. Compound **25** appears to be a single stereoisomer, which we have tentatively assigned as having the boat structure shown on the basis of $^1$H NMR coupling constant data and by analogy with lepadiformine (**9**).[19]

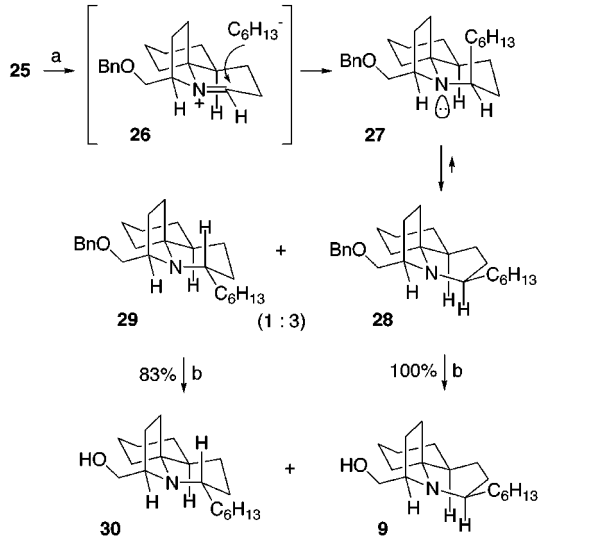
**Scheme 3**[a]




[a] Reagents: (a) $Rh(CO)_2$acac, $CO/H_2$ (1:1), THF, $P(OPh)_3$, 60 °C; (b) MeOH, HCl, $(MeO)_3CH$, rt, 81% from **20**; (c) 15% LiOH, Δ, EtOH, $H_2O$, 99%; (d) BnBr, NaH, THF, −8 °C−rt, 75%; (e) *p*-TsOH, $Me_2CO$, $H_2O$, Δ; (f) HCl, MeOH, KCN, $Me_2CO$, $H_2O$, rt.

It was then possible to introduce the hexyl chain by treating crude amino nitrile **25** with commercially available hexylmagnesium bromide in the presence of boron trifluoride etherate to produce a 3:1 mixture of the desired alkylation product **28** along with its C2 epimer **29** (56% overall yield from amino acetal **23**) (Scheme 4).[20] The results of this reaction can be rationalized on the basis of the stereoelectronic principles delineated by Stevens.[21] Thus, anti-periplanar addition of the Grignard reagent to intermediate iminium

**Scheme 4**[a]




[a] Reagents: (a) $C_6H_{13}MgBr$, $BF_3$-$Et_2O$, THF, −20 °C−rt, 67% from **23**; (b) Na, $NH_3$, THF, −78 °C.

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(16) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4249.
(17) Ojima, I.; Tsai, C.-Y.; Tzamarioudaki, M.; Bonafoux, D. *Org. React.* **2000**, *56*, 1.
(18) The unprotected hydroxymethyl analogue of amino nitrile **24** could be prepared, but this compound could not be alkylated successfully with hexyl Grignard reagents or cuprates.
(19) However, we cannot distinguish between the structure shown in **24** and the epimeric one in which the cyano group is equatorial in a chair conformation.

salt **26** from a preferred "axial" direction would lead to an initial chair **27**, which ring flips to the more stable lepadiformine boat conformation **28**. Attack on iminium species **26** from the opposite ("equatorial") direction initially produces an unfavorable boat, which converts to the more stable chair/equatorial hexyl conformer **29**.

Cleavage of the benzyl ether group from the C2 epimers **28** and **29** using sodium/ammonia afforded racemic lepadiformine (**9**) and the epimeric alcohol **30**, respectively, in high yields. Synthetic alkaloid **9** and its HCl salt have spectral data identical to those of authentic material.[22] Thus, we have prepared lepadiformine in approximately 15 steps and 11% overall yield starting from readily available 2-methyl-1-pyrroline (**10**).

**Acknowledgment.** We are grateful to the National Institutes of Health (CA-34303) for financial support of this research.

**Supporting Information Available:** Experimental procedures for the preparation of new compounds, including spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL010179Y

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