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Total Synthesis of (±)-Lepadiformine via an Amidoacrolein Cycloaddition

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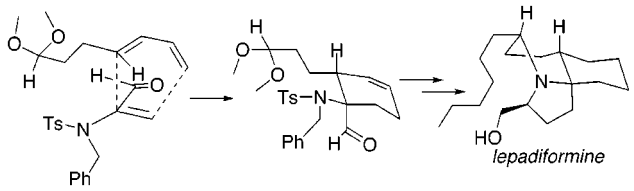
ABSTRACT



The total synthesis of the cytotoxin lepadiformine is described. The intermolecular cycloaddition of a 2-amidoacrolein with the dimethyl acetal of 4,6-heptadienal gave a cycloadduct that was strategically functionalized for elaboration of the tricyclic ring system. These steps include a diastereoselective addition of an organoytterbium reagent to an aldehyde, cyclization to the *trans*-perhydroquinoline substructure via a Mitsunobu reaction, and an iodine-promoted amine cyclization with an alkene to introduce the pyrrolidine ring.

Several structurally intriguing and biologically active tricyclic alkaloids were discovered in the mid-1990s and include the cytotoxins lepadiformine,[1] fasicularin,[2] cylindricines A/B,[3] and the immunosuppressent FR901483.[4] Not surprisingly, numerous groups have undertaken total syntheses of these novel structures.[5] Our interest in these natural products emanated from methodology we had developed for the preparation of the simplest common substructure among these natural products, namely, a 1-alkyl-1-aminocyclohexane. Specifically, we have prepared this central subunit via Diels−Alder cycloaddition reactions of 2-amidoacroleins with dienes, work which culminated in the total synthesis of FR901483.[5h] We now wish to report on the further application of this basic strategy in the total synthesis of (±)-lepadiformine.

Several groups contributed to the structural elucidation of lepadiformine. Thus, lepadiformine was isolated by Biard and co-workers from the tunicate *Clavelina lepadiformis* and assigned the rather unusual zwitterionic structure (Figure 1) primarily on the basis of extensive NMR experiments,[1] although the absolute configuration of lepadiformine was not determined. However, Weinreb and co-workers synthesized the structure assigned to lepadiformine and found that the synthetic material was not identical with the natural product, nor did it exist in a zwitterionic form.[6] Moreover, Pearson and co-workers synthesized three of the four diastereomers of lepadiformine at C(2) and C(13) and found them to be different from lepadiformine.[7] They speculated that lepadiformine was epimeric at C(10) and possessed a *trans*-perhydroquinoline substructure like fasicularin.[7b] This con-

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

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

(3) (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.

(4) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37.

(5) For completed total syntheses of lepadiformine and fasicularin, see: (a) Abe, H.; Aoyagi, S.; Kibayashi, D. *J. Am. Chem. Soc.* **2000**, *122*, 4583. For cylindricines, see: (b) Snider, B. B.; Liu, T. *J. Org. Chem.* **1997**, *62*, 5630. (c) Molander, G. A.; Rönn, M. *J. Org. Chem.* **1999**, *64*, 5183. (d) Liu, J. F.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8263. For FR901483, see: (e) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778. (f) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593. (g) Ousmer, M.; Braun, N. A.; Ciufolini, M. A. *Org. Lett.* **2001**, *3*, 765. (h) Funk, R. L.; Maeng, J. H. *Org. Lett.* **2001**, *3*, 1125.

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

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

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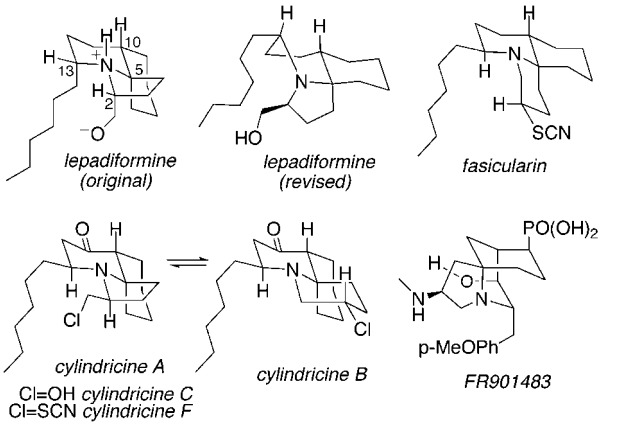
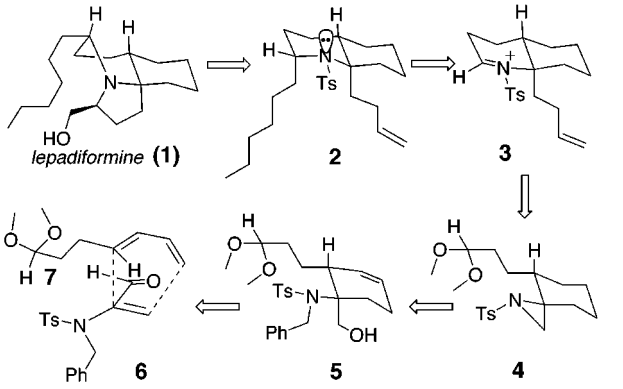


Figure 1.

jecture was confirmed by Kibayashi and co-workers, who reported the total synthesis of the revised structure shown in Figure 1 and discovered that the corresponding hydrochloride salt was identical to the natural product.[5a] This structure was unambiguously determined on the basis of X-ray crystallographic analysis, which also showed that the *trans*-perhydroisoquinoline substructure prefers to adopt a chair-boat conformation.[8] Parenthetically we note that these combined efforts signify the continuing value of contemporary organic synthesis in natural product structure determinations.

We were intrigued to learn that lepadiformine embodies a *trans*- rather than *cis*-perhydroisoquinoline subunit as found in the cylindricines, since the former stereochemistry is more accessible using our amidoacrolein-cycloaddition-based methodology. In our retrosynthetic analysis (Scheme 1), we

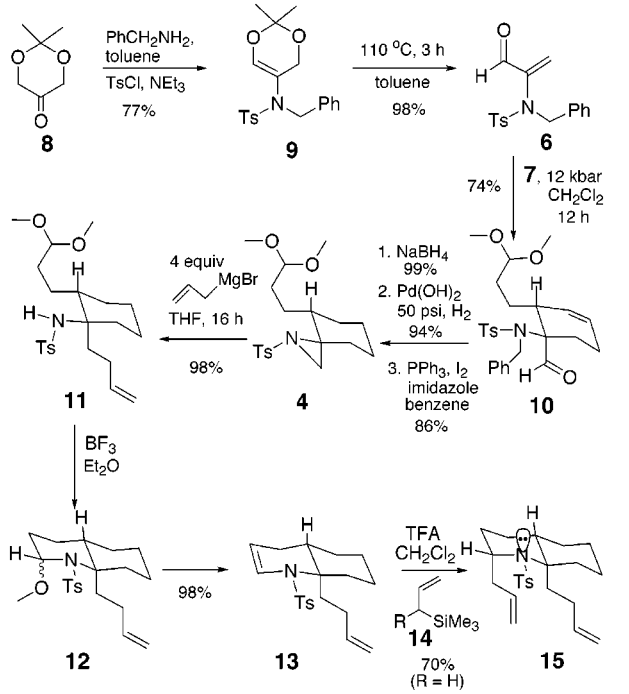
Scheme 1



envisaged the pyrrolidine ring of lepadiformine (**1**) to arise from a stereoselective electrophile-promoted cyclization of the amine derived from tosylamide **2** with the angular

(8) This is likely the solution structure as well. Molecular mechanics calculations (MMX, PCMODEL) place the chair-chair conformer 4.7 kcal/mol higher in energy than the chair-boat conformer shown in Figure 1.

Scheme 2



3-butenyl substituent.[9] The hexyl substituent of sulfonamide **2** could be introduced by stereoelectronically controlled[10] addition (α via chair vs. *β* via boat) of an organometallic reagent to the *N*-tosyl- (or *N*-acyl-) iminium ion **3**. The butenyl substituent of **3** could be elaborated by addition of an allylic organometallic reagent to the activated aziridine **4**, in turn, available by Mitsunobu ring closure of the debenzylated derivative of the tosylamide **5**. Finally, tosylamide **5** could be prepared by straightforward application of our methodology, namely, a regio- and *endo*-selective cycloaddition of the amidoacrolein **6** with the diene **7**, thereby establishing the eventual *trans*-perhydroquinoline stereochemistry.

To that end, the amidoacrolein **6** was prepared using our standard protocol. Thus, 2,2-dimethyl-1,3-dioxin-5-one[11] (**8**) was condensed with benzylamine to afford the corresponding imine, which was sulfonylated with tosyl chloride to furnish the desired 5-amido-1,3-dioxin **9**. Retrocycloaddition of dioxin **9** in refluxing toluene gave the amidoacrolein **6** in nearly quantitative yield, which when subjected to diene **7**[12] under the influence of high pressure (12 kbar) gave only the

(9) For reviews, see: (a) Bartlett, P. A. in *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3, p 411. (b) Frederickson, M.; Grigg, R. *Org. Prep. Proced. Int.* **1997**, *29*, 33. (c) Frederickson, M.; Grigg, R. *Org. Prep. Proced. Int.* **1997**, *29*, 63.

(10) For reviews, see: (a) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289. (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983; p 209.

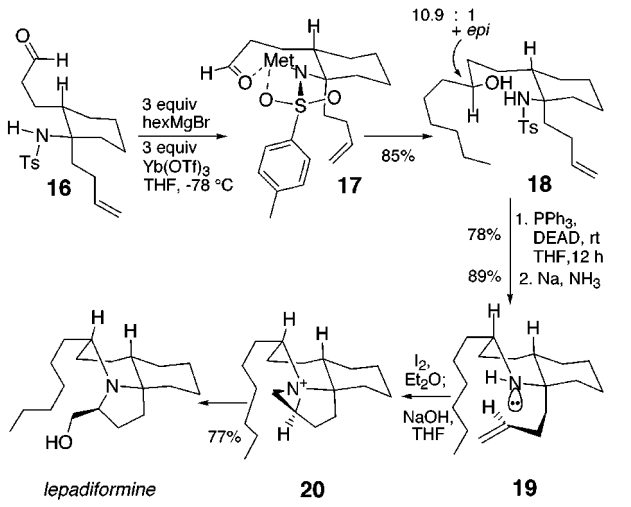
(11) Prepared in two steps from tris(hydroxymethyl)aminomethane hydrochloride. Hoppe, D.; Schmincke, H.; Kleemann, H.-W. *Tetrahedron* **1989**, 45, 687.

(12) Prepared from 4,6-heptadienenitrile (Grieco, P. A.; Larsen, S. D. *J. Org. Chem.* **1985**, *50*, 1768) by DIBALH reduction (CH_2Cl_2, −60 °C, 88%) and acetalization of the resulting aldehyde (trimethyl orthoformate, amberlyst 15 ion-exchange resin, 12 h, rt, 98%).

endo cycloadduct **10** (74%).[13] The aldehyde functionality of **10** was reduced ($NaBH_4$) followed by simultaneous debenzylation and reduction of the alkene moiety (Pearlman's catalyst, H_2) to furnish an alcohol that underwent a Mitsunobu-type ring closure to *N*-tosylaziridine **4** upon treatment with triphenylphosphine, iodine, and imidazole. Finally, the butenyl group of tosylamide **11** was installed by nucleophilic ring opening of *N*-tosylaziridine **4** with excess allylmagnesium bromide.

We had intended to introduce the hexyl substituent of lepadiformine by subjecting α-methoxytosylamide **12** to BF_3 in the presence of a hexyl Grignard or cuprate reagent.[14] However, all attempts to cyclize acetal **11** to α-methoxytosylamide **12** using a variety of acid catalysts were unsuccessful and in many cases afforded the enamide **13** (BF_3, 0.5 h, 0 °C, 98%). Moreover, aldehyde **16** (Scheme 3), which could

Scheme 3



be prepared by hydrolysis of acetal **11** (1 M HCl, H_2O, THF, 2 h, 98%), showed no tendency to exist in the cyclic α-hydroxytosylamide form in a variety of solvents (^1H NMR) and could not be converted to α-methoxytosylamide **12**.[15]

Accordingly, we turned to generating tosyliminium ion **3** by protonation of enamide **13** and its interception by an allylsilane.[14−16] Indeed, we were pleased to find that treatment of enamide **13** with 4 equiv of trifluoroacetic acid and 6 equiv of allyltrimethylsilane (**14**, R = H) in methylene chloride at −20 °C gave a single product to which we assigned structure **15** on the basis of the aforementioned stereoelectronic considerations[10] and spectral similarities with tosylamide **2** (vide infra). Unfortunately, all attempts to employ (3-hexenyl)trimethylsilane (**14**, R = Pr)[17] in this transformation gave only recovered enamide **13**.[18]

We also examined an alternative approach to the fully substituted *trans*-perhydroquinoline ring system concurrent with the previously discussed tosyliminium ion strategy, specifically, stereoselective introduction of the hexyl group *prior* to ring closure (Scheme 3). Initial experiments were not encouraging. For example, treatment of aldehyde **16** with hexylmagnesium bromide (5 equiv, −78 °C) in THF gave **18** and its inseparable C(13) epimer in a ratio of 1.1:1, respectively, and an even less desirable ratio (1:2.7) was obtained using hex_2CuLi in ether. The stereoselectivity was improved somewhat (2.5:1) by using hexylmagnesium bromide (5 equiv) in ether and, interestingly, even further if THF (10 equiv) was added (4.1:1). However, the most dramatic improvement (10.9:1) was observed when an organoytterbium reagent was employed following the Molander protocol[19] (3 equiv of hexMgBr, 3 equiv of $Yb(OTf)_3$, THF, −78 °C; an inferior ratio of 3.4:1 was obtained if hexyllithium was used to prepare the organoytterbium reagent). We tentatively rationalize this stereoselectivity on the basis of the chelation control depicted in structure **17**.[20] The superiority of the organoytterbium reagent may be a consequence of its greater steric bulk as well as attenuated reactivity with a magnesium-chelated aldehyde (slow disappearance of aldehyde **16** with the organoytterbium reagent versus instantaneous disappearance with the Grignard reagent).

The stereochemical assignment for alcohol **18** was confirmed upon its three-step transformation to lepadiformine (**1**). Thus, subjection of alcohol **18** to Mitsunobu conditions smoothly effected cyclization to the *trans*-perhydroquinoline **2** (and its separable C(13) epimer in 78% and 5% yields, respectively), whose tosyl group could be removed using standard conditions to provide amine **19**. Treatment of amine **19** with iodine in ether (−40 °C to room temperature, 1 h) gave rise to an (iodomethyl)pyrrolidinium salt that was concentrated and directly taken up in THF and aqueous NaOH containing 10% tetrabutylammonium iodide to deliver racemic lepadiformine (77%). This transformation presumably proceeds through regioselective attack of hydroxide on the aziridinium ion intermediate **20**.[21] We could not detect any product derived from ring opening at the more substituted site (cf. cylindricines A and B). The spectral properties of

(13) In contrast to other examples of 2-amidoacrolein Diels−Alder cycloaddition reactions performed in our laboratories,[5h] the cycloaddition of 2-tosylamidoacrolein **6** could not be accomplished under thermal conditions as a result of competing polymerization of dienophile **6** (150 °C). In addition, the acid sensitivity of the acetal functionality of diene **7** precluded the use of Lewis acid catalysts.

(14) Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131.

(15) For the preparation of the parent system by DIBAL-H reduction of *N*-tosylcaprolactam to afford the corresponding α-hydroxytosylamide and further transformation to the α-methoxytosylamide by treatment with methanol, trimethyl orthoformate, and PPTS, see: Åhman, J.; Somfai, P. *Tetrahedron* **1992**, *48*, 9537.

(16) Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* **1989**, *37*, 57.

(17) Smith, J. G.; Drozda, S. E.; Petraglia, S. P.; Quinn, N. R.; Rice, E. M.; Taylor, B. S.; Viswanathan, M. *J. Org. Chem.* **1984**, *49*, 4112.

(18) In a competition experiment, (3-hexenyl)trimethylsilane was preferentially consumed over allyltrimethylsilane by trifluoroacetic acid (^1H NMR).

(19) (a) Molander, G. A.; Burkhardt, E. R.; Weinig, P. *J. Org. Chem.* **1990**, *55*, 4990. (b) Molander, G. A.; Estévez-Braun, A. M. *Bull. Soc. Chim. Fr.* **1997**, *134*, 275. (c) For a very recent example of the utility of these reagents, see: Johnston, D.; Francon, N.; Edmonds, J. J.; Procter, D. J. *Org. Lett.* **2001**, *3*, 2001.

(20) Kibayashi also invokes chelation control in the stereoselective addition of hexylmagnesium bromide (2.0:1) to a spirocyclic aldehyde similar to **16** that possesses a Cbz-protected alkoxypyrrolidine ring; see ref 5a.

(21) For a related example, see: Guo-qiang, L.; Chun-min, A.; Zhi-cai, S. *Heterocycles* **1995**, *41*, 277.

compound **1** were identical to those reported by Kibayashi and the spectra of the hydrochloride salt of **1** were indistinguishable from those of authentic material.[22]

In conclusion, we have completed a stereoselective total synthesis of the cytotoxin (±)-lepadiformine in 16 steps in 13% overall yield from ethyl sorbate. Moreover, we have once again demonstrated that amidoacrolein-derived Diels−Alder cycloadducts can be easily elaborated to the ring systems of tricyclic alkaloids. The further development and application of this methodology in natural product synthesis is underway.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) We thank Professor Weinreb for sharing Professor J. F. Biard's authentic ^{1}H and ^{13}C NMR spectra of lepadiformine with us. For their approach to lepadiformine, see the accompanying communication in this issue: Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **3**, 3507−3510.