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Total Synthesis of (+)-Lepadin F

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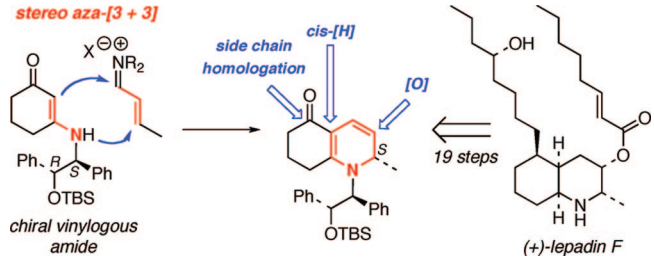
ABSTRACT



An enantioselective total synthesis of (+)-lepadin F is described. The synthetic sequence features an intermolecular aza-[3 + 3] annulation, homologation of a vinylogous amide via Eschenmoser's episulfide contraction, and a highly stereoselective hydrogenation essential for achieving the 1,3-anti relative stereochemistry at C2 and C8a.

The lepadin family (Figure 1), comprising eight *cis*-decahydroquinoline members, was identified from 1991 to 2002 from different sources such as tunicate *Clavelina lepadinformis*,[1] flatworm *Prostheceraeus villatus*,[2] tropical marine tunicate *Didemnum* sp.,[3] and Australian great barrier reef ascidian *Aplidium tabascum*.[4] They possess biological activities ranging from cytotoxicity, inhibitions of tyrosine kinase, antiplasmodial and antitrypanosomal properties, as well as antimalarial properties[1−4] and have attracted attention from several synthetic groups.[5−11]

While all contain a *cis*-1-azadecalinic motif, members of the lepadin family display a diversified array of relative stereochemical relationships at C2, C3, C4a, C5, and C8a (Scheme 1). For the 1,2-stereochemical relationship, the C2,3 relative configuration consists of two types: cis in A−C, F, and G and trans in D, E, and H for which the absolute configuration was recently confirmed by Ma.[9] The C4a,5 relative configuration also consists of two types: trans in A−C and cis in D−H. For the 1,3-stereochemical relationship, the C2,8a relative configuration consists of syn in A−E and H with a more challenging anti relative configuration in F and G. Consequently, the lepadin family can be divided into three major subfamilies based on their relative stereochemical relationships at C2, C3, C4a, C5, and C8a (Scheme 1).

(1) For isolation of (−)-lepadin A, see: Steffan, B. *Tetrahedron* **1991**, *47*, 8729.
(2) For isolation of (−)-B and (−)-C, see: Kubanek, J.; Williams, D. E.; de Silva, E. D.; Allen, T.; ersen, R. J. *Tetrahedron Lett.* **1995**, *36*, 6189.
(3) For isolation of (+)-D, (−)-E, and (−)-F, see: Wright, A. D.; Goclik, E.; König, G. M.; Kaminsky, R. *J. Med. Chem.* **2002**, *45*, 3067.
(4) For isolation of (+)-F, (+)-G, and (+)-H, see: Davis, R. A.; Carroll, A. R.; Quinn, R. J. *J. Nat. Prod.* **2002**, *65*, 454.
(5) For the first total synthesis of a lepadin family member, (−)-lepadin B, see: (a) Toyooka, N.; Okumura, M.; Takahata, H.; Nemoto, H. *Tetrahedron* **1999**, *55*, 10673. (b) Toyooka, N.; Okumura, M.; Takahata, H. *J. Org. Chem.* **1999**, *64*, 2182. Also see: (c) Toyooka, N.; Nemoto, H. *Trends Heterocycl. Chem.* **2002**, *8*, 145. (d) Toyooka, N. *Yakugaku Zasshi* **2001**, *121*, 467.
(6) For total synthesis of (−)-lepadin B, see: Ozawa, T.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2000**, *2*, 2955.
(7) For total syntheses of (−)-lepadin A and (−)-lepadin C, see: Ozawa, T.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **2001**, *66*, 3338.
(8) For a formal synthesiss of (±)-lepadin B, see: Kalaï, C.; Tate, E.; Zard, S. Z. *Chem. Commun.* **2002**, 1430.
(9) For total synthesis of lepadins A−E and H, see: (a) Pu, X.; Ma, D. *J. Org. Chem.* **2006**, *71*, 6562. (b) Pu, X.; Ma, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4222.
(10) For total syntheses of (+)-lepadin F and (−)-lepadin G, see: Niethe, A.; Fischer, D.; Blechert, S. *J. Org. Chem.* **2008**, *73*, 3088.
(11) For other studies, see: (a) Mena, M.; Valls, N.; Borreg, M.; Bonjoch, J. *Tetrahedron* **2006**, *62*, 9166. (b) Mena, M.; Bonjoch, J.; Pardo, D. G.; Cossy, J. *J. Org. Chem.* **2006**, *71*, 5930. (c) Mena, M.; Bonjoch, J. *Tetrahedron* **2005**, *61*, 8264. (d) Barbe, G.; Charette, A. B. *Abstracts of Papers*, 232nd National Meeting of the American Chemical Society, San Francisco, CA, Fall 2006; American Chemical Society: Washington, DC, 2006; ORGN-747.

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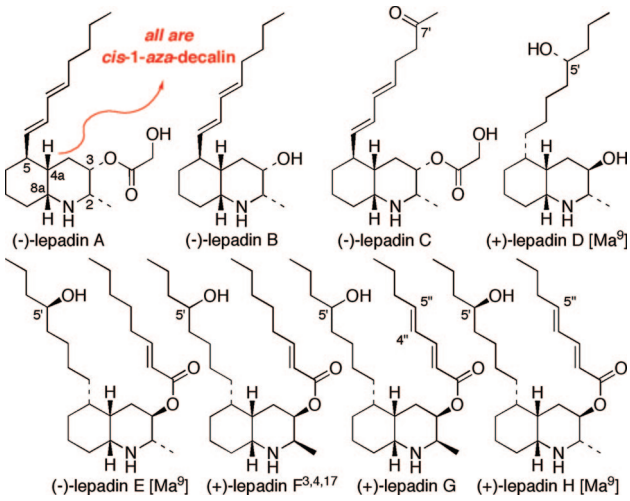
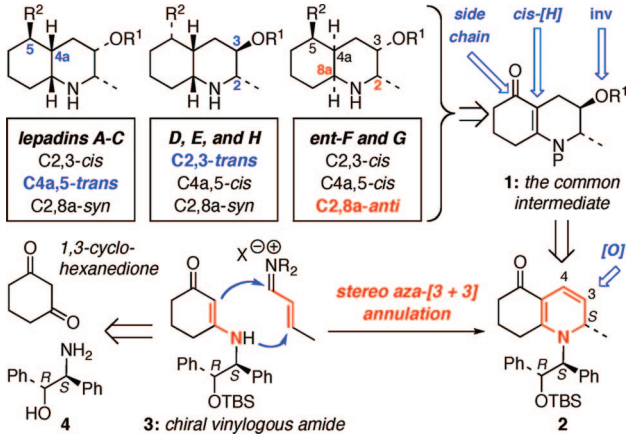


Figure 1. Lepadin family.

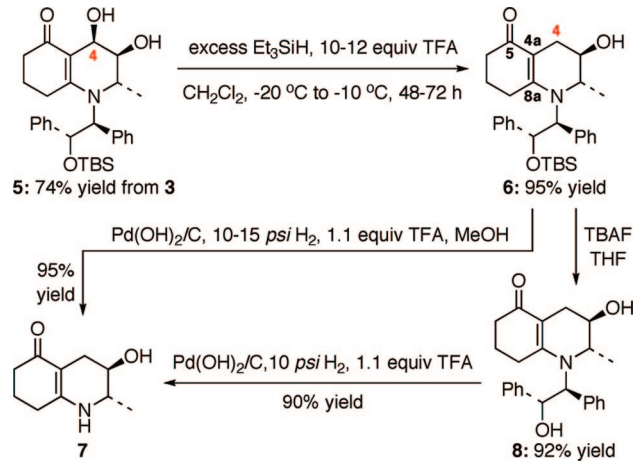
Scheme 1. General Approach to Lepadins



We[12] had envisioned that all three subfamilies could be accessed from the orthogonal protected common intermediate **1**, which could be prepared from a stereoselective intermolecular aza-[3 + 3] annulation[13−15] using chiral vinylogous amide **3**. Given our recent success in the alkaloid synthesis employing this annulation,[16] we elected to first pursue the most challenging member of the family, lepadin F,[17] containing the 1,3-anti relative configuration for C2,8a. Despite numerous efforts in the synthesis of lepadins, an elegant total synthesis of lepadin F was only accomplished very recently by Blechert.[10] We report here our total synthesis of (+)-lepadin F.

Our total synthesis efforts commenced with the known diol **5**[18] (Scheme 2), which was prepared from **3** in two steps

Scheme 2. Reductive Removal of the C4-OH Group



consisting of aza-[3 + 3] annulation and OsO_4 dihydroxylation[19,20] of C3,4 olefin of the initial annulation product **2**.[21] We focused on identifying a useful reductive protocol to

(12) Slafer, B.; Hsung, R. P.; Sklenicka, H. M. *Abstracts of Papers*, 227th National Meeting of the American Chemical Society, Anaheim, CA, Spring 2004; American Chemical Society: Washington, DC, 2006; ORGN-396.

(13) For reviews, see: (a) Harrity, J. P. A.; Provoost, O. *Org. Biomol. Chem.* **2005**, *3*, 1349. (b) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, 23. (c) Coverdale, H. A.; Hsung, R. P. *ChemTracts* **2003**, *16*, 238.

(14) For recent studies in this area, see: (a) Hayashi, Y.; Gotoh, H.; Masui, R.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4012. (b) Trost, B. M.; Dong, G. *Org. Lett.* **2007**, *9*, 2357. (c) Schmidt, A.; Gütlein, J.-P.; Mkrrchyan, S.; Görls, H.; Langer, P. *Synlett* **2007**, 1305. (d) Pattenden, L. C.; Wybrow, R. A. J.; Smith, S. A.; Harrity, J. P. A. *Org. Lett.* **2006**, *8*, 3089. (e) Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 6330. (f) Halliday, J. I.; Chebib, M.; Turner, P.; McLeod, M. D. *Org. Lett.* **2006**, *8*, 3399. (g) Katsuyama, I.; Funabiki, K.; Matsui, M.; Muramatsu, H.; Shibata, K. *Heterocycles* **2006**, *68*, 2087. (h) Bose, D. S.; Kumar, R. K. *Heterocycles* **2006**, *68*, 549. (i) Goodenough, K. M.; Raubo, P.; Harrity, J. P. A. *Org. Lett.* **2005**, *7*, 2993. (j) Goodenough, K. M.; Moran, W. J.; Raubo, P.; Harrity, J. P. A. *J. Org. Chem.* **2005**, *70*, 207. (k) Agami, C.; Dechoux, L.; Hebbe, S.; Ménard, C. *Tetrahedron* **2004**, *60*, 5433. (l) Ji, S.-J.; Jiang, Z.-Q.; Lu, J.; Loh, T.-P. *Synlett* **2004**, 831. (m) Hedley, S. J.; Moran, W. J.; Price, D. A.; Harrity, J. P. A. *J. Org. Chem.* **2003**, *68*, 4286.

(15) For our work on developing the *aza*-[3 + 3] annulation method, see: (a) Ghosh, S. K.; Buchanan, G. S.; Long, Q. A.; Wei, Y.; Al-Rashid, Z. F.; Sklenicka, H. M.; Hsung, R. P. *Tetrahedron* **2008**, *63*, 883. (b) Sydorenko, N.; Hsung, R. P.; Vera, E. L. *Org. Lett.* **2006**, *8*, 2611. (c) Gerasyuto, A. I.; Hsung, R. P.; Sydorenko, N.; Slafer, B. W. *J. Org. Chem.* **2005**, *70*, 4248. (d) Sydorenko, N.; Hsung, R. P.; Darwish, O. S.; Hahn, J. M.; Liu, J. *J. Org. Chem.* **2004**, *69*, 6732. (e) Sklenicka, H. M.; Hsung, R. P.; Wei, L.-L.; McLaughlin, M. J.; Gerasyuto, A. I.; Degen, S. J.; Mulder, J. A. *Org. Lett.* **2000**, *2*, 1161. (f) Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Douglas, C. J.; McLaughlin, M. J.; Mulder, J. A.; Yao, L. J. *Org. Lett.* **1999**, *1*, 509.

(16) (a) Wei, L.-L.; Sklenicka, H. M.; Gerasyuto, A. I.; Hsung, R. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1516. (b) Sklenicka, H. M.; Hsung, R. P.; McLaughlin, M. J.; Wei, L.-L.; Gerasyuto, A. I.; Brennessel, W. W. *J. Am. Chem. Soc.* **2002**, *124*, 10435. (c) McLaughlin, M. J.; Hsung, R. P.; Cole, K. C.; Hahn, J. M.; Wang, J. *Org. Lett.* **2002**, *4*, 2017. (d) Luo, S.; Zificsak, C. Z.; Hsung, R. P. *Org. Lett.* **2003**, *5*, 4709. (e) Sydorenko, N.; Zificsak, C. A.; Gerasyuto, A. I.; Hsung, R. P. *Org. Biomol. Chem.* **2005**, *3*, 2140. (f) Swidorski, J. J.; Wang, J.; Hsung, R. P. *Org. Lett.* **2006**, *8*, 777. (g) Wang, J.; Swidorski, J. J.; Sydorenko, N.; Hsung, R. P.; Coverdale, H. A.; Kuyava, J. M.; Liu, J. *Heterocycles* **2006**, *70*, 423. (h) Gerasyuto, A. I.; Hsung, R. P. *Org. Lett.* **2006**, *8*, 4899. (i) Gerasyuto, A. I.; Hsung, R. P. *J. Org. Chem.* **2007**, *72*, 2476.

(17) Both antipodes of lepadin F have been reported independently with Wright et al. [reference [3]] documenting (−)-F while Carroll et al. [reference 4] reporting (+)-F. Although no commitment was made regarding its absolute configuration, in Wright's paper, (−)-leapdin F was drawn as the enantiomer of the one shown in Figure 1, and we elected to show Carroll's drawing of (+)-F.

remove the C4-OH group. While the use of "Super Hydride" [$LiBEt_3H$] and Red-Al was not successful, an excess amount of Et_3SiH in the presence of 10−12 equiv of TFA[19] led to alcohol **6** in 95% yield. Removal of the chiral auxiliary in **6** was not eventful and could be achieved either directly by using 1.1 equiv of TFA and 10−15 psi of H_2 in the presence of Pearlman's catalyst $Pd(OH)_2/C$ or sequentially by first removing the TBS group. It is noteworthy that lowering the amount of TFA led to incomplete hydrogenation and a low yield of vinylogous amide **7**. When using >25 psi of H_2, over-reduction of **6** at C5 as well as C4a,8a was observed. Stereochemical assignment of alcohol **6** was achieved unambiguously using its single-crystal X-ray structure (Figure 2).

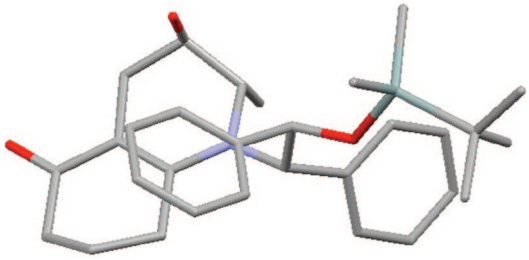
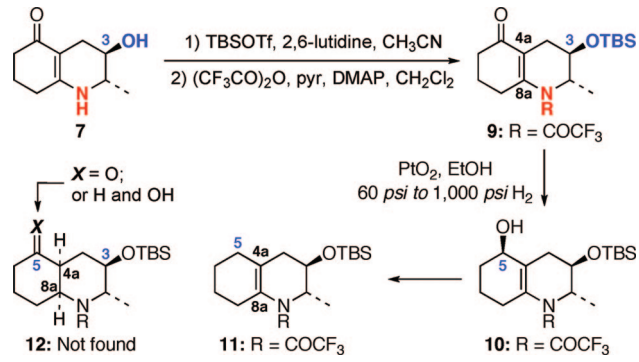


Figure 2. X-ray structure of alcohol **6**.

With vinylogous amide **7** in hand, we encountered difficulties in distinguishing nucleophilicities of the C3-OH group and the vinylogous amide. Silylation proved to be the only way to selectively protect the C3-OH group, and a subsequent trifluoroacetylation afforded the orthogonally protected vinylogous amide **9** (Scheme 3). However, hydrogenations of C4a,8a olefin in **9** employing standard conditions such as Pt/C and Pd/C were not successful with the reduction of C5 carbonyl being the major identifiable pathway when using Adam's catalyst PtO_2.

This failure detours our original plan for setting up the C2,8a-anti relative stereochemistry based on our earlier work.[16b] We had anticipated that by analogy to that of **13** (Figure 3), the pseudoaxially oriented *N*-trifluoroacetyl group would dictate the stereochemical outcome during the hydrogenation of the C4a,8a olefin in **9**. On one hand, the addition of C3-OTBS group in **9** should augment the desired stereochemical outcome by further shielding the top face of C4a,8a olefin. However, a close examination of its model reveals that to be mutually axial while minimizing the gauche

Scheme 3. Difficulties in Hydrogenating the C4a,8a-Olefin



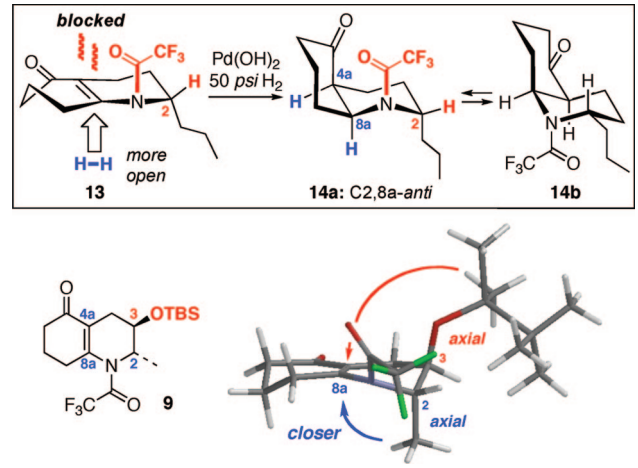


Figure 3. Additional steric impact of the C3-OTBS group.

interaction, the C3-OTBS group also pushes C2-Me group closer to C8a, thereby shielding the bottom face of the olefin.

Collective observations of over-reduction of the C5-carbonyl group[22] provoked us to explore an alternative route. As shown in Scheme 4, a high-yielding standard protection of alcohol **6** with Ac_2O gave acetate ester **15**. After failing with Wittig-type olefination,[23] a three-step sequence that features Eschenmoser's episulfide contraction[24,25] led to α,β-unsaturated ester **16** exclusively as an *E*-isomer (assigned via NOE experiments)[21] in 64% overall yield from **15**. A double hydrogenation of C4a,8a and C5,1′ olefins in **16** was achieved with surprising ease, leading to ester **17** in 91%

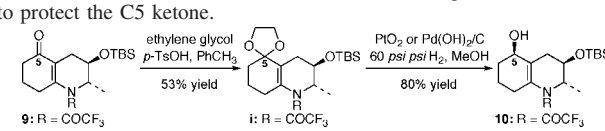
(18) Zehnder, L. R.; Wei, L.-L.; Hsung, R. P.; Cole, K. P.; McLaughlin, M. J.; Shen, H. C.; Sklenicka, H. M.; Wang, J.; Zificsak, C. A. *Org. Lett.* **2001**, *3*, 2141.

(19) For related reductions, see: (a) Cole, K. P.; Hsung, R. P.; Yang, X.-F. *Tetrahedron Lett.* **2002**, *43*, 3341. (b) Cole, K. P.; Hsung, R. P. *Tetrahedron Lett.* **2002**, *43*, 8791. (c) Hsung, R. P.; Cole, K. P.; Zehnder, L. R.; Wang, J.; Wei, L.-L.; Yang, X.-F.; Coverdale, H. A. *Tetrahedron* **2003**, *59*, 311.

(20) This dihydroxylation required a stoichiometric amount of OsO_4. The best conditions are: 1.0 equiv of OsO_4, 5.0 equiv of pyridine, CH_2Cl_2, rt and then workup with mannitol/10% aq KOH at rt for 48 h.

(21) See the Supporting Information.

(22) Another C5-over-reduction was observed using acetal **i** in an attempt to protect the C5 ketone.

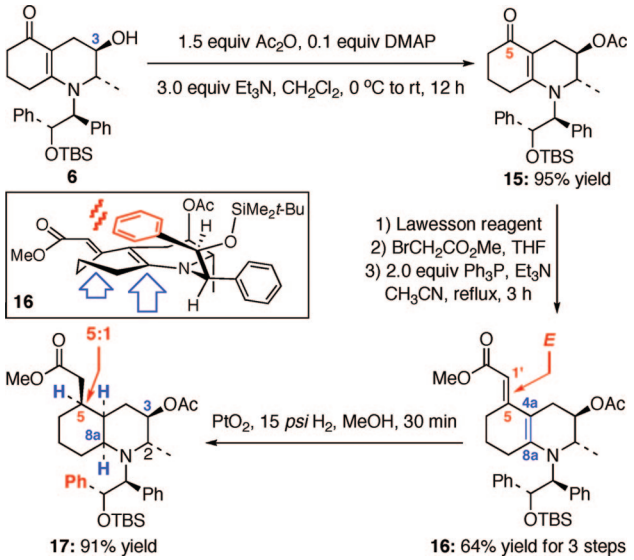


(23) The use of $Ph_3P{=}CHCHO$ in toluene afforded no desired product.

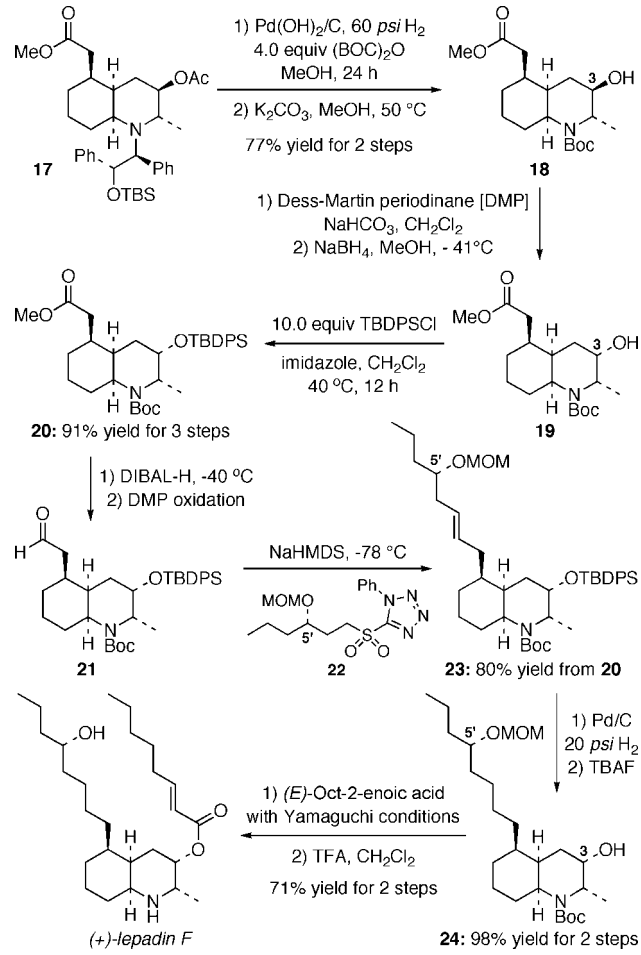
(24) (a) Shiosaki, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 865. (b) Roth, M.; Dubs, P.; Götchi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710.

(25) Toyooka, N.; Yoshida, Y.; Momose, T. *Tetrahedron Lett.* **1995**, *36*, 3715.

Scheme 4. Homologation of a Vinylogous Amide Motif



Scheme 5. Total Synthesis of (+)-Lepadin F



yield as a separable 5:1 mixture of diastereomers with respect to the C5 stereochemistry.

The anti relative stereochemistry at C2,8a as well as the all-cis relationship at C8a,4a,5 in **17** was confirmed using NOE experiments,[21] and these stereochemical outcomes are very reasonable judging from the model of **16** (inside the box in Scheme 4), which was drawn based on the conformation shown for the X-ray structure of alcohol **6**.

Success in executing this alternative plan allowed us to complete a total synthesis of (+)-lepadin F from ester **17** as summarized in Scheme 5. Key features are: (1) the reductive removal of the chiral auxiliary in **17** concomitant with Boc-protection; (2) inversion of C3-OH group in **18** through a sequence of Dess−Martin periodinane oxidation and $NaBH_4$-reduction; (3) capping of the inverted C3-OH in **19** with TBDPSCl under more forcing conditions to give silyl ether **20**; (4) C5-side chain elongation in aldehyde **21** with sulfone **22**[26] via adopting Julia−Kocienski olefination conditions to afford alkene **23**; and (5) esterification of alcohol **24** employing Yamaguchi conditions. This culminates a total synthesis of (+)-lepadin F in 20 steps with a 15.2% overall yield from chiral vinylogous amide **3**,

It is noteworthy that Ma's work with lepadin D, E, and H[9] as well as Blechert's recent synthesis of F[10] prompted us to choose sulfone **22** with (*S*)-configuration at C5′. Spectroscopically, our synthetic sample matched those reported by Carroll[4] using C_6D_6 as the NMR solvent.[27,28]

We have described here an enantioselective total synthesis of (+)-lepadin F that confirms its absolute configuration. The synthetic sequence features an intermolecular aza-[3 + 3] annulation, homologation of a vinylogous amide through Eschenmoser's episulfide contraction, and a highly stereoselective hydrogenation essential for achieving the 1,3-anti relative stereochemistry at C2 and C8a. Efforts are underway to construct other lepadin family members.

Acknowledgment. We thank the NIH (NS38049) for financial support.

Supporting Information Available: Experimental procedures as well as NMR spectra, characterizations, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) For the synthesis of **22**, see: (a) D'Souza, L. J.; Sinha, S. C.; Lu, S.; Keinan, E.; Sinha, S. C. *Tetrahedron* **2001**, *57*, 5255. (b) Blackemore, P. A.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26. (c) Also see ref 9a.

(27) When we used K_2CO_3-pretreated $CDCl_3$ to avoid protonation of the decahydroquinoline motif, our ^{13}C NMR matched Wright's data (ref 3) and the ^1H NMR comparison contains some minor variations. See the Supporting Information.

(28) Our optical rotations matched more closely with Blechert's numbers than with those reported by Carroll and Wright. See the Supporting Information.