ORGANIC LETTERS

2007
Vol. 9, No. 7
1367−1369

Highly Convergent Route to Cyclopeptide Alkaloids. Total Synthesis of Ziziphine N

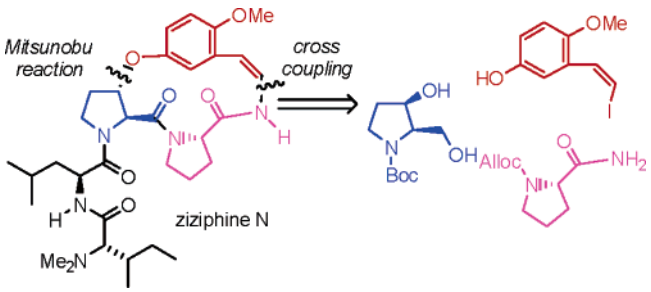
Gang He, Jing Wang, and Dawei Ma*

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

madw@mail.sioc.ac.cn

Received February 2, 2007

ABSTRACT



A highly convergent protocol to cyclopeptide alkaloids, as demonstrated by the first total synthesis of antiplasmodial agent ziziphine N, is developed. The key elements include construction of its aryl ether unit via Mitsunobu reaction, installation of its enamide part via CuI/*N*,*N*-dimethylglycine-catalyzed coupling reaction, and ring closure with coupling agents such as FDDP and DPPA.

Cyclopeptide alkaloids are a growing family that contains over 200 members discovered from a wide range of plant species.[1] Since historically many of these species have been used for medicinal purposes in the treatment of a variety of ailments, it is not surprising that cyclopeptide alkaloids are found to possess significant biological properties (such as sedative, antibacterial, antiplasmodial, and antifungal activities)[1a] and thus may serve as leads for drug discovery. However, restricted natural availability of these compounds and lack of practical synthetic methods do not allow systematic studies on the biological properties.[1a] This fact, together with their intriguing structures, has caused a steady stream of studies directed toward synthesis of these natural products during the past decades.[2−7]

Structurally, cyclopeptide alkaloids contain a 13-, 14-, or 15-membered macrocycle bearing a peptide unit, which is connected to a benzene ring with either a 1,4- or a

(1) For a recent review, see: (a) Gournelis, D. C.; Laskaris, G. G.; Verpoorte, R. *Nat. Prod. Rep.* **1997**, 75−82. For recent reports on isolation, see: (b) Lin, H.; Chen, C.-H.; You, B.-J.; Liu, K. C. S. C.; Lee, S.-S. *J. Nat. Prod.* **2000**, *63*, 1338−1343. (c) Morel, A. F.; Araujo, C. A.; Silva, U. F.; Hoelzel, S. C. S. M.; Záchia, R.; Bastos, N. R. *Phytochemistry* **2002**, *61*, 561−566. (d) Lin, H.; Chen, C.-H.; Liu, K. C. S. C.; Lee, S.-S. *Helv. Chim. Acta* **2003**, *86*, 127−138. (e) Suksamrarn, S.; Suwannapoch, N.; Aunchai, N.; Kuno, M.; Ratananukul, P.; Haritakun, R.; Jansakul, C.; Ruchirawat, S. *Tetrahedron* **2005**, *61*, 1175−1180. (f) Morel, A. F.; Maldaner, G.; Ilha, V.; Missau, F.; Silva, U. F.; Dalcol, I. I. *Phytochemistry* **2005**, *66*, 2571−2576.

(2) For a comprehensive review, see: Joullié, M. M.; Richard, D. J. *Chem. Commun.* **2004**, 2011−2015.

(3) For macrocyclization studies, see: (a) Lagarias, J. C.; Houghten, R. A.; Rapoport, H. *J. Am. Chem. Soc.* **1978**, *100*, 8202−8212 and references cited therein. (b) Schmidt, U.; Griesser, H.; Lieberknecht, A.; Talbiersky, J. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 280−281. (c) Nutt, R. F.; Chen, K.-M.; Joullié, M. M. *J. Org. Chem.* **1984**, *49*, 1013−1021.

(4) (a) Schmidt, U.; Lieberknecht, A.; Griesser, H.; Häusler, J. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 281−282. (b) Schmidt, U.; Lieberknecht, A.; Griesser, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1026−1027. (c) Schmidt, U.; Schanbacher, U. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 152−153. (d) Schmidt, U.; Zäh, M.; Lieberknecht, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1002−1004. (e) Heffner, R. J.; Jiang, J.; Joullié, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 10181−10189. (f) East, S. P.; Joullié, M. M. *Tetrahedron Lett.* **1998**, *39*, 7211−7214. (g) East, S. P.; Shao, F.; Williams, L.; Joullié, M. M. *Tetrahedron* **1998**, *54*, 13371−13390.

(5) Kim, Y.-A.; Shin, H.-N.; Park, M.-S.; Cho, S.-H.; Han, S.-Y. *Tetrahedron Lett.* **2003**, *44*, 2557−2560.

10.1021/ol070271f CCC: $37.00
Published on Web 03/09/2007

1,3-orientation. The previous studies have revealed that the synthetic challenges for these targets include formation of the strained macrocycles and introduction of their enamide unit.[2−6] For macrocyclization, Schmidt and co-workers developed an activated ester method,[3b] which greatly facilitated the total synthesis of the macrolactams,[4] while Zhu's S_NAr cyclization[6] and Lipshutz's oxazolophane approach[7] also showed ideal capability for assembling a number of cyclopeptide alkaloids. However, all these protocols chose elaboration of the enamide moiety via different elimination methods after macrocyclization.[2−6] Such tedious and low-yielding manipulations remarkably decreased the synthetic efficiency. Herein, we wish to report a new strategy for assembling cyclopeptide alkaloids in a highly convergent manner, as demonstrated by the first total synthesis of antiplasmodial agent ziziphine N (**1**, Figure 1).[1e] In this

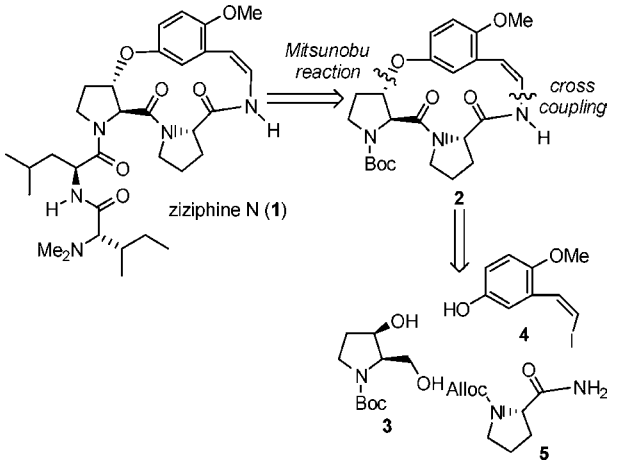
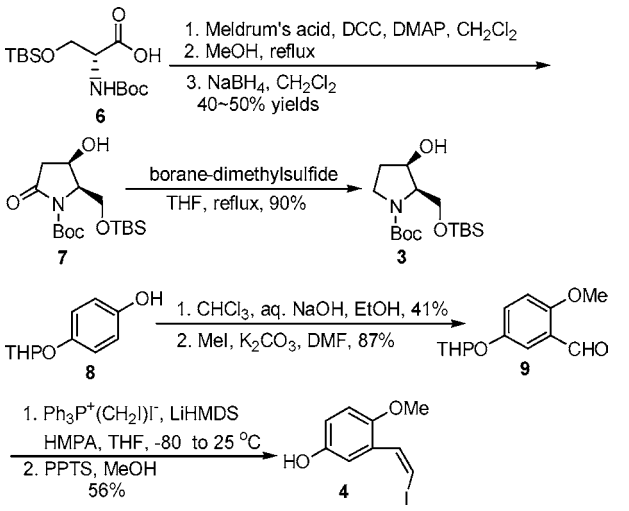


Figure 1. Structure and retrosynthetic analysis of ziziphine N.

protocol, the formation of the enamide unit in the key intermediate **2** was set up at an early stage via a CuI/*N*,*N*-dimethylglycine-catalyzed coupling reaction of the amide **5** with a Mitsunobu reaction product of vinyl iodide **4** and alcohol **3**.[8a]

Ziziphine N is a new member of the ziziphine family that displayed potent antiplasmodial activity with an IC_{50} value of 3.92 μg/mL. Its structure was tentatively inferred to **1** by comparing the spectroscopic data with those of ziziphine A.

Scheme 1



As outlined in Scheme 1, our synthesis of ziziphine N started from the preparation of pyrrolidine **3**[9a] and vinyl iodide **4**. By using our modified procedure (replacement of isopropenyl chloroformate with inexpensive DCC),[9b] we converted protected D-serine **6** into pyrrolidinone **7** in 40∼50% yields. Reduction of **7** with borane-dimethyl sulfide provided the desired alcohol **3**. In a parallel procedure, Reimer−Tiemann reaction of monoprotected hydroquinone **8** and subsequent methylation of phenol afforded aldehyde **9**.[10] Subjecting the aldehyde **9** to a Wittig olefination reaction with $Ph_3P^+(CH_2I)I^-$ gave rise to a vinyl iodide as a mixture of the *Z*- and *E*-isomers.[11] The stereoselectivity was not satisfactory in this case, as a ratio of about 3:1 was determined by ^1H NMR. Fortunately, pure isomer **4** (56% yield from **9**) could be isolated via chromatography after treatment of the above mixture with PPTS in methanol.

Connection of **3** and **4** via a Mitsunobu reaction[12] was our next planned step. This reaction was found to be rather sluggish at room temperature mainly because **4** was an electron-rich phenol. However, a reasonable yield for the desired product **10** was obtained by raising the reaction temperature to 80 °C (Scheme 2). Coupling of **10** and *N*-alloxycarbonyl-L-proline amide **5** under our standard conditions (CuI/*N*,*N*-dimethylglycine, Cs_2CO_3, dioxane, 80 °C) produced enamide **11**.[8a] Cleavage of the silyl ether in **11** followed by stepwise oxidation of the liberated alcohol gave an acid, which was exposed to $Pd(PPh_3)_4/Et_2NH$[13] to provide the desired amino acid **12** in 56% overall yield.

The stage was now set for the crucial macrocyclization. We assumed that Schmidt's protocol[3b,4] would not be suitable because the enamide moiety may not survive the Pd/C-

(6) (a) Zhu, J.; Laïb, T.; Chastanet, J.; Beugelmans, R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2517−2519. (b) Laïb, T.; Bois-Choussy, M.; Zhu, J. *Tetrahedron Lett.* **2000**, *41*, 7645−7649. (c) Temal-Laíb, T.; Chastanet, J.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 583−590. (d) Cristau, P.; Temal-Laíb, T.; Bois-Choussy, M.; Martin, M.-T.; Vors, J.-P.; Zhu, J. *Chem.−Eur. J.* **2005**, *11*, 2668−2679.

(7) Lipshutz, B. H.; Huff, B. E.; McCarthy, K. E.; Miller, T. A.; Mukarram, S. M. J.; Siahaan, T. J.; Vaccaro, W. D.; Webb, H.; Falick, A. M. *J. Am. Chem. Soc.* **1990**, *112*, 7032−7041.

(8) (a) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809−1812. For related studies, see: (b) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 7889−7901. (c) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667−3669. (d) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr. *Org. Lett.* **2004**, *6*, 27−30. (e) Coleman, R. S.; Liu, P.-H. *Org. Lett.* **2004**, *6*, 577−580. (f) Hu, T.; Li, C. *Org. Lett.* **2005**, *7*, 2035−2038.

(9) (a) Jiang, J. J.; Li, W.-R.; Przeslawski, R. M.; Joullié, M. M. *Tetrahedron Lett.* **1993**, *34*, 6705. (b) Ma, D.; Ma, J.; Ding, W.; Dai, L. *Tetrahedron:Asymmetry* **1996**, *7*, 2365−2370.

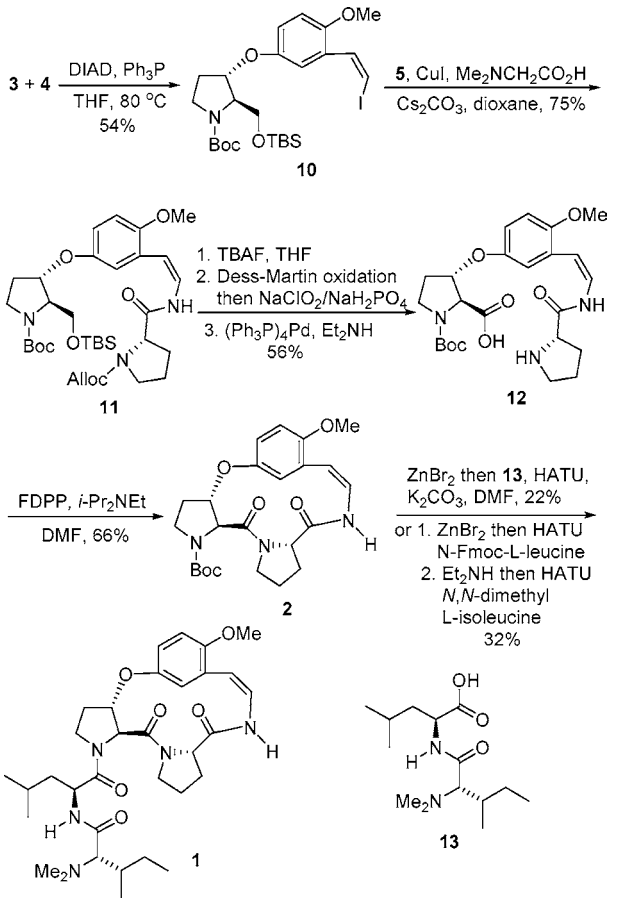
(10) Satoh, Y.; Stanton, J. L.; Hutchison, A. J.; Libby, A. H.; Kowalski, T. J.; Lee, W. H.; White, D. H.; Kimble, E. F. *J. Med. Chem.* **1993**, *36*, 3850−3594.

(11) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173−2174.

(12) Mitsunobu, O. *Synthesis* **1981**, 1−28.

(13) Ciommer, M.; Kunz, H. *Synlett* **1991**, 593−596.

Scheme 2



catalyzed hydrogenolysis. As a consequence, the use of coupling reagents was considered, although only one successful example had been reported recently.[5] To our delight, the pentafluorophenyl diphenylphosphinate (FDPP) mediated macrocyclization[14] of the amino acid **12** worked well and furnished the lactam **2** in 66% yield. It is noteworthy that the conversion of the commonly used intermediate **3** to the lactam **2** only took six steps with an overall yield of about 15%. Obviously, the present approach is much more efficient than all previous routes from related amino alcohols to the similar lactams.[2−6]

(14) Chen, S.; Xu, J. *Tetrahedron Lett.* **1991**, *32*, 6711−6714.

With lactam **2** in hand, we completed the synthesis of **1** via cleavage of the Boc group with $ZnBr_2$ and subsequent coupling of the liberated secondary amine with *N*,*N*-dimethyl-L-isoleucyl-L-leucine **13** under no-racemization conditions reported by Zhu and co-workers[6b] (or stepwise couplings with *N*-Fmoc-L-leucine and *N*,*N*-dimethyl L-isoleucine). The spectroscopic data of synthetic **1**[15] ($[\alpha]_D^{22}$ −324.8 (*c* 0.24 in $CHCl_3$), lit.[1e] $[\alpha]_D^{22}$ −326.6 (*c* 0.18 in $CHCl_3$)) are identical in all respects to those reported in the literature, and our results hereby confirm the proposed structure for ziziphine N.

In conclusion, we have developed a very convergent strategy to elaborate cyclopeptide alkaloids illustrated through the first total synthesis of ziziphine N.[16] The key elements include installation of the enamide part via our CuI/*N*,*N*-dimethylglycine-catalyzed coupling reaction and ring closure with coupling agents such as FDDP. This new strategy makes the elaboration of this class of natural products much easier than previous protocols and would therefore benefit their further pharmacological evaluation and SAR studies.

Acknowledgment. The authors are grateful to the Chinese Academy of Sciences, the National Natural Science Foundation of China (grant 20321202 & 20572119), and the Science and Technology Commission of Shanghai Municipality (grant 02JC14032 & 03XD14001) for their financial support.

Supporting Information Available: Experimental procedures and characterizations for compounds **1**, **2**, **4**, and **10**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070271F

(15) Selected data for **1**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.9 Hz, 6H), 0.95 (t, J = 6.8 Hz, 3H), 1.14 (m, 1H), 1.48 (m, 2H), 1.56 (m, 1H), 1.64 (m, 1H), 1.75 (m, 2H), 1.94 (m, 2H), 2.24 (s, 6H), 2.36 (m, 1H), 2.46 (m, 1H), 2.55 (d, J = 5.6 Hz, 1H), 3.26 (m, 1H), 3.57 (m, 1H), 3.80 (s, 3H), 4.21 (m, 2H), 4.38 (d, J = 5.8 Hz, 1H), 4.52 (dd, J = 9.0, 4.2 Hz, 1H), 4.75 (dd, J = 7.9, 7.6 Hz, 1H), 5.94 (d, J = 8.8 Hz, 1H), 6.80 (br s, 1H), 6.82 (d, J = 7.3 Hz, 1H), 6.86 (d, J = 11.6 Hz, 1H), 6.92 (dd, J = 11.5, 8.8 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 8.34 (d, J = 11.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 14.3, 21.4, 22.9, 24.4, 24.6, 26.7, 28.8, 32.4, 34.0, 40.6, 42.8, 45.1, 47.6 (2C), 55.7, 61.8, 62.5, 74.1, 78.4, 106.4, 110.5, 113.6, 116.7, 121.4, 123.9, 150.7, 151.0, 167.5, 171.0, 171.3, 171.6; MS *m*/*z* 634.2 $[M + Na]^+$; HRMS calcd for $C_{33}H_{49}N_5O_6Na$ $[M + Na]^+$ 634.3575, found 634.3578.

(16) During the preparation of this manuscript, Evano and co-workers reported the synthesis of paliurine F, a structurally related alkaloid of ziziphine N, by using two Cu-catalyzed couplings. See: Toumi, M.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 572−575.