ORGANIC LETTERS

2012
Vol. 14, No. 9
2320–2322

Concise Total Synthesis of (−)-Mersicarpine

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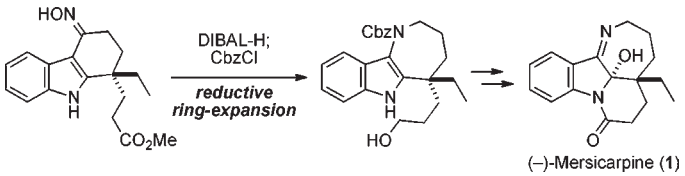
Received March 22, 2012

ABSTRACT



A concise total synthesis of (−)-mersicarpine from a known cyclohexanone was accomplished. The azepinoindole core was constructed by a DIBAL-H-mediated reductive ring-expansion reaction of oxime.

Mersicarpine (**1**), isolated from the *Kopsia* species of plants by Kam and co-workers in 2004,[1] has an unusual tetracyclic structure, in which indoline, seven-membered cyclic imine, and δ-lactam are fused with each other around a tertiary hydroxyl group adjacent to the quaternary carbon center. The bioactivity of **1** has not been reported so far; however, these unique structural features have attracted considerable attention in the synthetic community. In 2008, Kerr and co-workers reported the first total synthesis of (±)-**1** using $Mn(OAc)_3$-mediated radical cyclization of keto-ester.[2] The synthesis was carried out from indoline in 14 steps in 11% overall yield. In 2009, Zard and a co-worker reported the formal synthesis of (±)-**1** by an intermolecular radical addition−cyclization cascade using lauroyl peroxide, which describes an improved synthesis of Kerr's intermediate.[3] In 2010, Fukuyama and co-workers reported the first enantioselective synthesis of (−)-**1** including mechanistic studies on the autoxidation of azepinoindole using oxygen isotope labeling.[4] The synthesis features a gold-catalyzed indole formation and a stepwise introduction of the nitrogen atom at the 3-position of indole that required ten steps (14% overall yield) from the known keto-ester **9**. Herein, we describe a nine-step, six-pot synthesis of (−)-mersicarpine (**1**) from keto-ester **9** utilizing the DIBAL-H-mediated reductive ring-expansion reaction established in our group.

Recently, we extensively investigated a reductive ring-expansion reaction of oximes with DIBAL-H for its reaction scope and mechanistic details.[5] In contrast to a Beckmann rearrangement,[6] aromatic ring fused cyclic ketoximes gave the corresponding reductive ring-expansion products with an aromatic ring-nitrogen bond that was independent of the geometry of the oxime. For example, treatment of oxime **2** with excess DIBAL-H gave azepinoindole **3** as an exclusive product, which was isolated as benzamide **4** due to instability under air (Scheme 1).[7,8]

We considered that this methodology should be highly useful for synthesis of 3-amino indoles from easily accessible precursors, which cannot be executed in a straightforward manner.[4] To demonstrate the utility of this reaction, we selected (−)-mersicarpine (**1**) as a synthetic target and planned a synthetic strategy as shown in Scheme 2. Mersicarpine (**1**) would be derived from tetracyclic azepinoindole **5** according to Fukuyama's autoxidation

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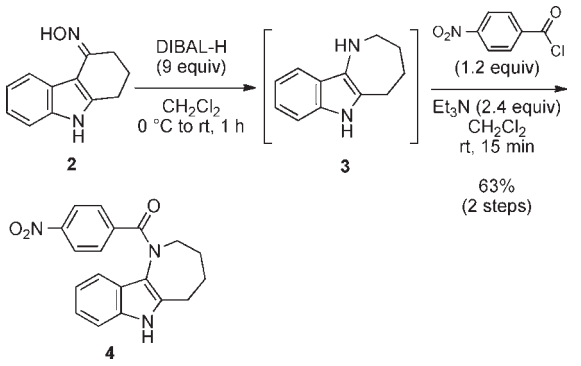
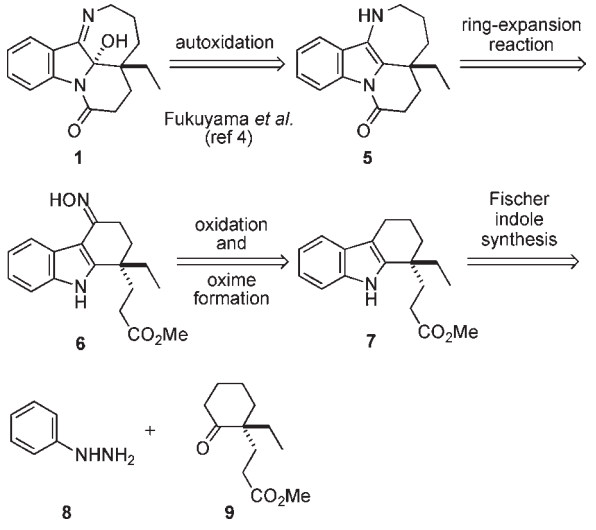
(1) Kam, T.-S.; Subramaniam, G.; Lim, K.-H.; Choo, Y.-M. *Tetrahedron Lett.* **2004**, *45*, 5995.
(2) Magolan, J.; Carson, C. A.; Kerr, M. A. *Org. Lett.* **2008**, *10*, 1437.
(3) Biechy, A.; Zard, S. Z. *Org. Lett.* **2009**, *11*, 2800.
(4) Nakajima, R.; Ogino, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 1236.
(5) (a) Cho, H.; Iwama, Y.; Sugimoto, K.; Kwon, E.; Tokuyama, H. *Heterocycles* **2009**, *78*, 1183. (b) Cho, H.; Iwama, Y.; Sugimoto, K.; Mori, S.; Tokuyama, H. *J. Org. Chem.* **2010**, *75*, 627. (c) Cho, H.; Sugimoto, K.; Iwama, Y.; Mitsuhashi, N.; Okano, K.; Tokuyama, H. *Heterocycles* **2011**, *82*, 1633.
(6) Donaruma, L. G.; Heldt, W. Z. *Org. React.* **1960**, *11*, 1.
(7) Hester, J. B., Jr. *J. Org. Chem.* **1967**, *32*, 3804.
(8) Formation of **3** was monitored by TLC. However, purification of **3** by silica gel column chromatography resulted in decomposition due to instability.

10.1021/ol300735g
Published on Web 04/18/2012

Scheme 1. DIBAL-H-Mediated Construction of Azepinoindole



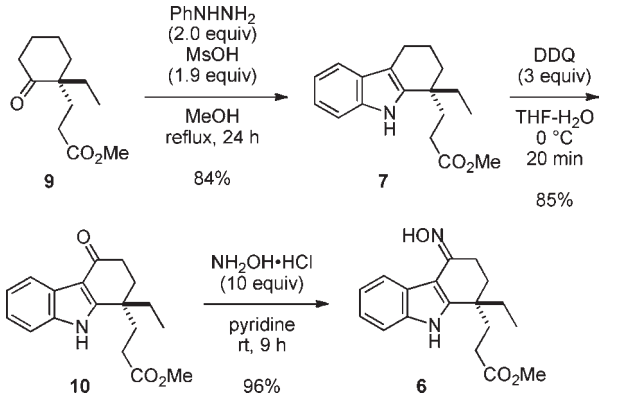
Scheme 2. Retrosynthetic Analysis of (−)-Mersicarpine (**1**)



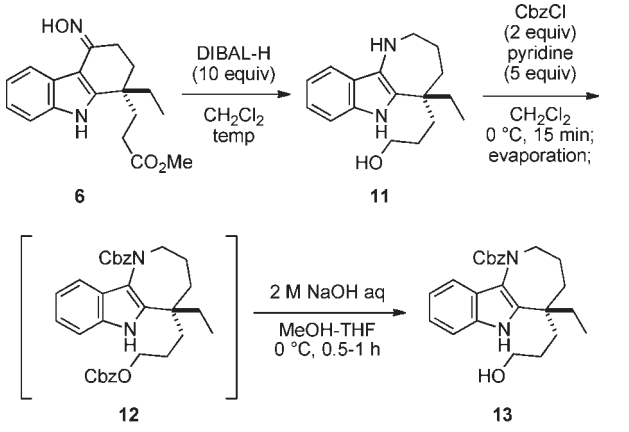
protocol. The azepine ring would be constructed by our reductive ring-expansion reaction of six-membered oxime **6**, which should be accessible from carbazole derivative **7** via oxidation at the C-4 position. Carbazole derivative **7** would be easily synthesized by Fischer indole synthesis using phenylhydrazine (**8**) and optically active cyclohexanone **9**.

Synthesis of (−)-mersicarpine (**1**) was initiated by preparation of tricyclic oxime **6** from optically active cyclohexanone **9**,[9,10] which was readily prepared by asymmetric Michael addition according to the d'Angelo protocol[9] (Scheme 3). Next, we examined Fischer indole synthesis of **9** and phenylhydrazine (**8**). Treatment of ketone **9** with 2.0 equiv of phenylhydrazine and 1.9 equiv of methanesulfonic

Scheme 3. Preparation of Tricyclic Oxime **6**



Scheme 4. Reductive Ring-Expansion Reaction Followed by Protection of Azepine **11** with Cbz Group



entry	temp	time	**13**
1	0 °C to rt	1 h	25-33%
2	−78 to 0 °C; 0 °C to rt	3 h	55%

acid[11] in refluxing methanol afforded the desired tricyclic indole **7** in 84% yield.[12] Regioselective oxidation of **7** with DDQ gave the corresponding ketone **10** in high yield,[13] which was converted to oxime **6** in 96% yield.

With oxime **6** in hand, we then examined the crucial reductive ring-expansion reaction (Scheme 4). Upon treatment of oxime **6** with 10 equiv of DIBAL-H at 0 °C, the expected reductive ring-expansion reaction proceeded to give the desired azepinoindole **11**. Due to the instability, the yield of the reaction was estimated after conversion of the crude **11** to Cbz carbamate **13**, in which partially generated mixed carbonate **12** was converted to **13** by treatment with 2 M NaOH. Disappointingly, the initial

(9) Desmaële, D.; d'Angelo, J. *J. Org. Chem.* **1994**, *59*, 2292.

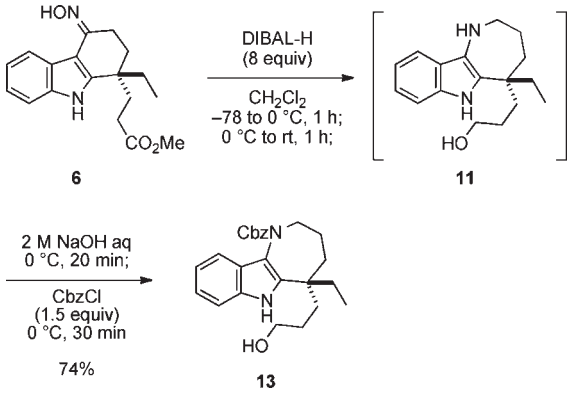
(10) The enantiomeric excess of keto-ester **9** was determined to be >99% by chiral HPLC after conversion of **9** to the corresponding benzyl ester. For the detailed experimental procedure, see Supporting Information.

(11) Under the conventional Fischer conditions, the resultant indole **7** was readily cyclized to give lactam. The use of an additional acid was effective to suppress the lactam formation. Among a variety of acids such as TfOH, conc. H_2SO_4, HCl, MsOH, TFA, ClH_2CCO_2H, AcOH, and PPTS, MsOH was the most effective.

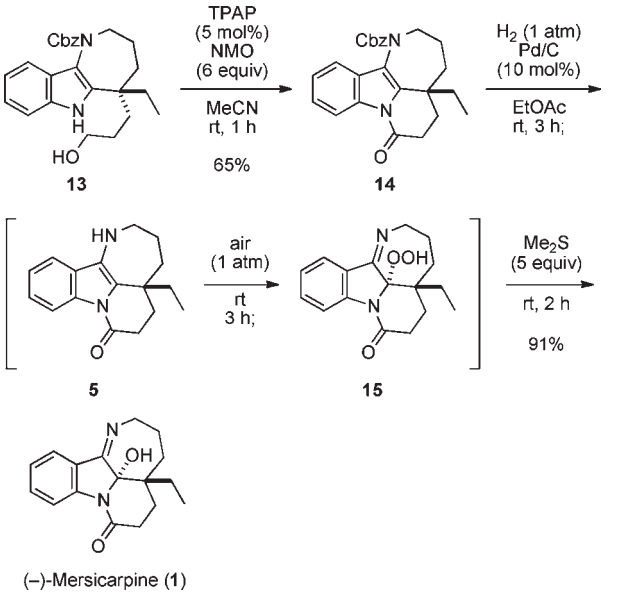
(12) Lactam was isolated in 7% yield.

(13) (a) Oikawa, Y.; Yoshioka, T.; Mohri, K.; Yonemitsu, O. *Heterocycles* **1979**, *12*, 1457. (b) Sissouma, D.; Collet, S. C.; Guingant, A. Y. *Synlett* **2004**, 2612.

Scheme 5. One-Pot Procedure of Reductive Ring-Expansion Reaction and Protection with a Cbz Group



Scheme 6. Total Synthesis of (−)-Mersicarpine (**1**)



trial resulted in only a low yield of the desired azepinoindole **13** (entry 1). We found that careful control of the reaction temperature was important for the high-yielding process. Thus, treatment of **6** with DIBAL-H at −78 °C, followed by gradual warming of the reaction mixture to 0 °C over 2 h and then to room temperature over 1 h, dramatically improved the yield and reproducibility (entry 2), and **13** was obtained in 55% yield.

Furthermore, we established a one-pot protocol for the reductive ring-expansion-protection sequence (Scheme 5). After extensive optimization, the reductive ring-expansion reaction was best effected with 8 equiv of DIBAL-H. The reaction mixture was then directly subjected to Schotten−Baumann conditions[14] to give the desired product **13** in 74% yield.

Finally, the total synthesis of (−)-mersicarpine (**1**) was completed by two-pot operations including lactam formation and autoxidation (Scheme 6). A one-pot direct conversion of primary alcohol **13** to lactam **14** proceeded quite smoothly with a combination of TPAP and NMO. After removal of the Cbz group under hydrogenolysis, air was purged to the reaction mixture to initiate autoxidation of tetracyclic azepinoindole **5**. Finally, dimethyl sulfide was added to the reaction mixture to promote reduction of the resultant peroxide **15** to furnish (−)-**1** in 91% yield from **14**.[4]

In summary, we have achieved a concise total synthesis of (−)-mersicarpine (**1**) from known keto-ester **9** in a nine step, six-pot process in 30% overall yield. Our synthesis features a regiospecific and DIBAL-H-mediated reductive ring-expansion reaction for the construction of the azepinoindole core of mersicarpine from the six-membered cyclic ketoxime **6**, which was readily available by Fischer indole synthesis.

Acknowledgment. This work was financially supported by the Cabinet Office, Government of Japan through its "Funding Program for Next Generation World-Leading Researchers (LS008), the Ministry of Education, Culture, Sports, Science, and Technology, Japan, the KAKENHI, a Grant-in-Aid for Scientific Research (B) (20390003), Tohoku University Global COE program 'International Center of Research and Education for Molecular Complex Chemistry', Nagase Science and Technology Foundation, and a JSPS predoctoral fellowship for Y.I. Professor Hidetsura Cho (Tohoku University) is also acknowledged for the valuable discussions on the DIBAL-H-mediated reductive ring expansion.

Note Added after ASAP Publication. The authors affiliation was incorrect in the version published ASAP on April 18, 2012; this reposted on April 26, 2012.

Supporting Information Available. Experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) (a) Sonntag, N. O. V. *Chem. Rev.* **1953**, *52*, 237. (b) Challis, B. C.; Butler, A. R. *Chem. Amino Group* **1968**, 277.

The authors declare no competing financial interest.