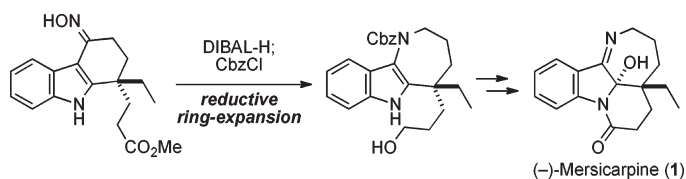


Concise Total Synthesis of
(–)-MersicarpineYusuke Iwama, Kentaro Okano, Kenji Sugimoto,[†] and Hidetoshi Tokuyama*Graduate School of Pharmaceutical Sciences, Tohoku University, Aramaki, Aoba-ku,
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Received March 22, 2012

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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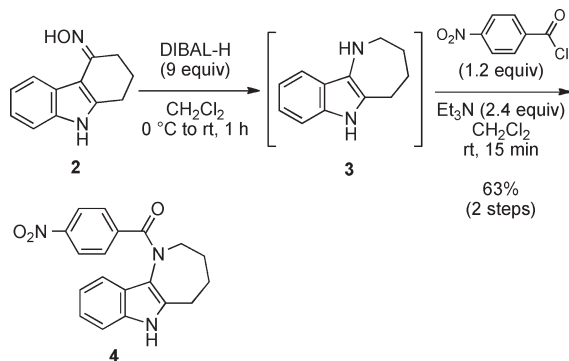
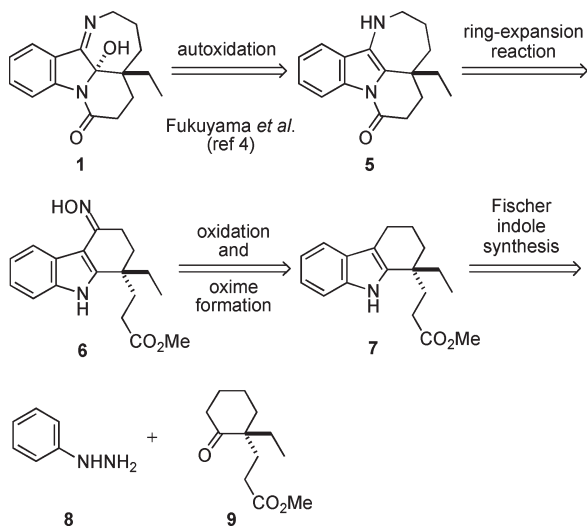
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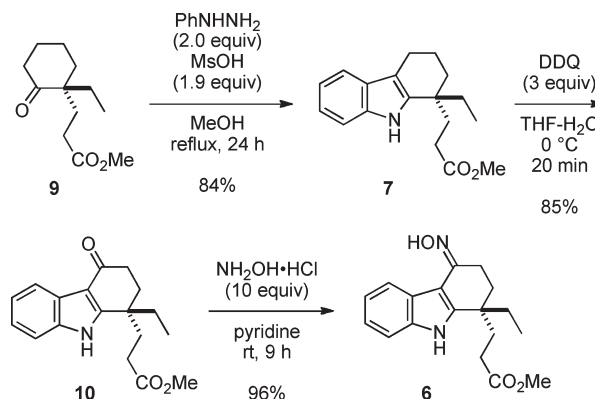
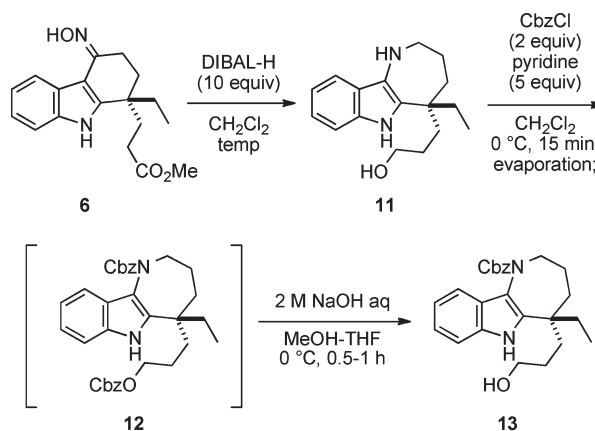
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(8) Formation of **3** was monitored by TLC. However, purification of **3** by silica gel column chromatography resulted in decomposition due to instability.

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 protocol⁹ (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%

acid¹¹ 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

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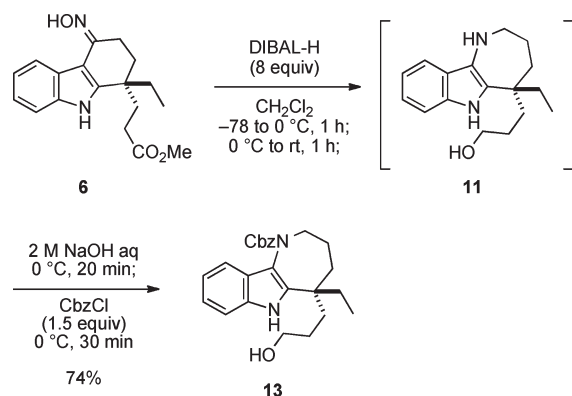
(10) The enantiomeric excess of keto-ester **9** was determined to be >99% by chiral HPLC after conversion of **9** to the corresponding benzyl ester. For the detailed experimental procedure, see Supporting Information.

(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. H₂SO₄, HCl, MsOH, TFA, ClH₂CCO₂H, AcOH, and PPTS, MsOH was the most effective.

(12) Lactam was isolated in 7% yield.

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



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 $-78\text{ }^{\circ}\text{C}$, followed by gradual warming of the reaction mixture to $0\text{ }^{\circ}\text{C}$ 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.

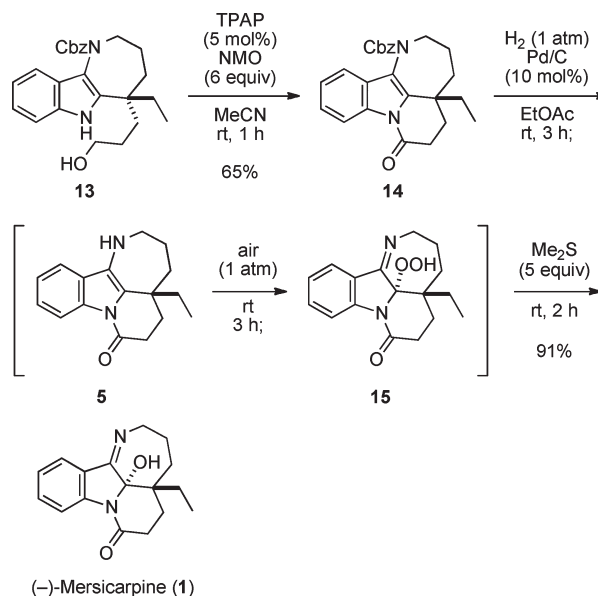
Furthermore, we established a one-pot protocol for the reductive ring-expansion-protection sequence (Scheme 5). After extensive optimization, the reductive ring-expansion reaction was best effected with 8 equiv of DIBAL-H. The reaction mixture was then directly subjected to Schotten–Baumann conditions¹⁴ 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 azepi-

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



noindole 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 ¹H and ¹³C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.