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Total Synthesis of (−)-Mersicarpine

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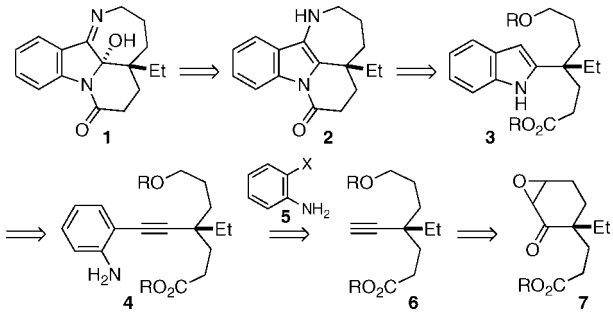
It is widely known that the indole alkaloids compose a major class of natural products. Among them, mersicarpine (**1**), isolated from the Kopsia species of plants by Kam and co-workers,[1] has an atypical tetracyclic structure, in which a nitrogen atom is substituted at the indoline 3-position and forms a seven-membered cyclic imine. A hemiaminal and a quaternary carbon are contiguously arranged adjacent to the imine. The overall structure includes three heterocycles, specifically indoline, cyclic imine, and δ-lactam, fused with each other around a tertiary hydroxy group. These intriguing structural features have attracted much attention in synthetic organic chemistry. The first total synthesis of mersicarpine in a racemic form was reported by Kerr and co-workers.[2] Mersicarpine was elegantly constructed via a malonic radical cyclization and an indole oxidation. Zard and a co-worker reported an alternative synthesis of Kerr's synthetic intermediate.[3] An enantioselective synthesis of mersicarpine, however, has not been reported to date. Herein we disclose the first total synthesis of (−)-mersicarpine.

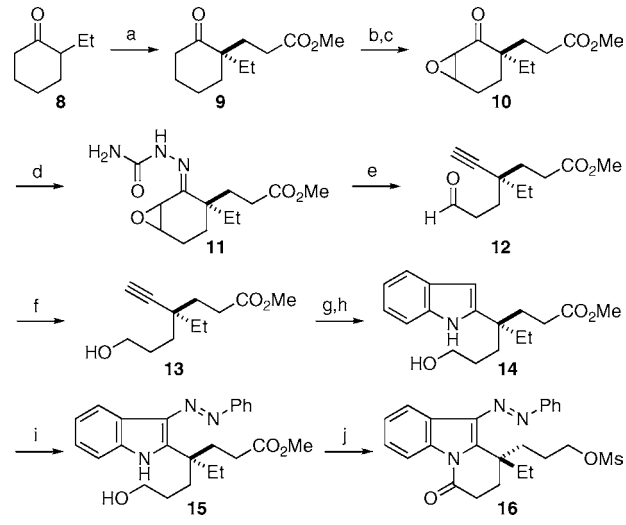
Our retrosynthetic analysis is illustrated in Scheme 1. We envisioned that the seven-membered cyclic imine and the hemiaminal moiety could be constructed via oxidation of electron-rich 3-aminoindole **2**, which could be derived from 2-substituted indole **3**. The indole core in **3** could be readily prepared by a Sonogashira coupling between haloaniline **5** and alkyne **6**, followed by cyclization of the resulting 2-alkynylaniline **4**. Sonogashira coupling partner **6** was to be synthesized using an Eschenmoser−Tanabe fragmentation of epoxyketone **7** containing a quaternary carbon center.

Scheme 1. Retrosynthetic Analysis of (−)-Mersicarpine



Our synthesis commenced with the preparation of known ketoester **9** using the asymmetric Michael addition developed by d'Angelo and co-workers (Scheme 2).[4] Oxidation of **9** with IBX[5] followed by epoxidation of the resulting enone afforded epoxyketone **10**. Attempted Eschenmoser−Tanabe fragmentation under standard conditions using tosyl or nosyl hydrazide,[6] however, resulted in recovery of the starting material. Harsher conditions led to extensive decomposition of the substrate. An alternative procedure using aminoaziridines[7] did not provide any desired product either. The poor reactivity of the ketone is presumably due to the presence of the quaternary carbon adjacent to the carbonyl group. After exhaustive investigation we found that **10** could react with semicarbazide to form semicarbazone **11**. According to Warkentin's procedure,[8] **11** was oxidized with lead tetraacetate to form the 1,3,4-oxadiazoline intermediate, which underwent an Eschenmoser−Tanabe-type fragmentation to furnish **12** in 60% yield.[9] Aldehyde **12** was then reduced with $NaBH_4$ to afford alcohol **13**. Sonogashira coupling of **13** with 2-iodoaniline proceeded uneventfully to give alkynylaniline, which was cyclized with a gold(III) catalyst to afford indole **14** in good yield.[10] It is known that a diazo coupling reaction is effective in installing a nitrogen atom at the 3-position of indoles.[11] Thus, reaction of **14** with benzenediazonium chloride proceeded cleanly to furnish **15**. Subsequent lactam formation by treatment with sodium hydride followed by mesylation of the primary alcohol afforded **16**.

Scheme 2. Synthesis of Intermediate **16**[a]



[a] Reagents and condition: (a) Supporting Information and ref 4; (b) IBX, DMSO, 85 °C, 72%; (c) H_2O_2, NaOH, H_2O-MeOH, 0 °C, 88%; (d) $H_2NCONHNH_2$·HCl, NaOAc, H_2O-EtOH, rt, 89%; (e) $Pb(OAc)_4$, CH_2Cl_2, −10 °C, 60%; (f) $NaBH_4$, MeOH, 0 °C, 87%; (g) *o*-iodoaniline, $Pd(PPh_3)_4$, CuI, DMF-Et_3N, 80 °C, 78%; (h) $NaAuCl_4$·$2H_2O$, EtOH, rt, 78%; (i) PhN_2Cl, NaOAc, *i*-PrOH-H_2O-1,4-dioxane, 0 °C, 97%; (j) NaH, MS4A, toluene, rt; MsCl, Et_3N, 0 °C, 77%.

Surprisingly, hydrogenolysis of **16** followed by purification with preparative TLC led to the unexpected formation of mersicarpine (**1**). The conversion to the natural product is likely to involve cyclization and oxidation. Since there were serious problems with reproducibility and yield, we examined these steps more closely (Scheme 3). Hydrogenolysis of **16** in the presence of Pd/C afforded 3-aminoindole **17**, which was prone to autoxidation during workup or purification. The structure of the oxidized product was tentatively assigned as **18** by ^{1}H NMR and HRMS analyses. Treatment of the labile 3-aminoindole **17** with sodium bicarbonate in refluxing

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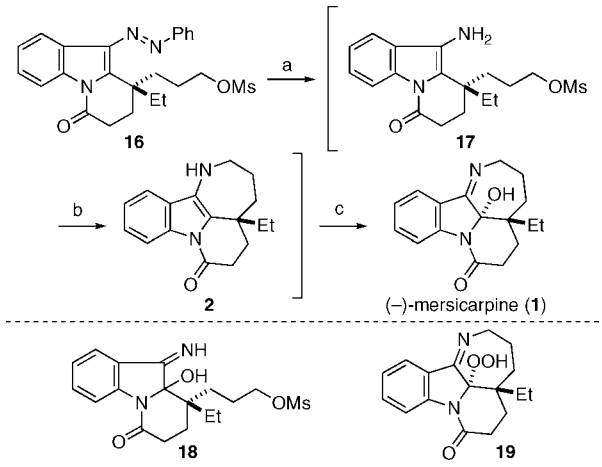
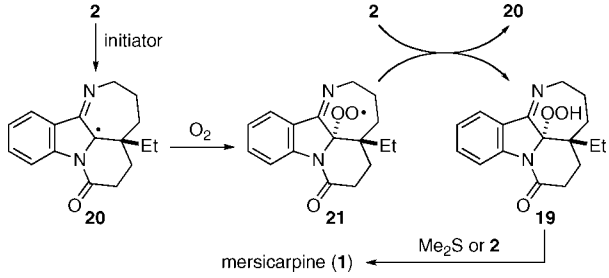
Scheme 3. Synthesis of (−)-Mersicarpine[a]



[a] Reagents and conditions: (a) H_2, Pd/C, *i*-PrOH-CH_2Cl_2, rt; (b) $NaHCO_3$, *i*-PrOH-CH_2Cl_2 (degassed), reflux; (c) autoxidation; Me_2S.

Scheme 4. Proposed Reaction Mechanism of Autoxidation of **2**



i-PrOH resulted in the formation of the mixture of **18** and **1**. Oxygen present in the reaction mixture proved to oxidize both the substrate and the cyclized product during the reaction. The poor yield of **1** was caused by the fact that attempted cyclization of **18** did not provide **1**. Degassing of the reaction mixture by freeze−thaw cycles prior to heating effectively prevented the unwanted oxidations, resulting in the clean formation of cyclic enamine **2**. Upon exposure to air, autoxidation of **2** proceeded to furnish an inseparable mixture of **1** and a byproduct. Since this mixture was smoothly converted into **1** by treatment with dimethyl sulfide, the structure of the byproduct was assumed to be hydroperoxide **19**. To further clarify the process, a labeling experiment was performed. While oxidation of **2** with $^{18}O_2$ produced the ^{18}O-labeled product, ^{18}O was not incorporated into the product when the oxidation was performed in air in the presence of $H_2{}^{18}O$.[12] These labeling experiments strongly suggest that **1** is derived from hydroperoxide **19**.

A proposed reaction mechanism of the autoxidation of **2** is summarized in Scheme 4. Autoxidation proceeds by free-radical chain processes that involve peroxyl radicals.[13] Abstraction of the hydrogen of NH in **2** forms tertiary radical **20**, which is stabilized by the nitrogen atom and the imine. Oxygen reacts with **20** from the less-hindered side opposite to the ethyl group to give peroxyl radical **21**, which in turn abstracts a hydrogen atom from **2** to furnish hydroperoxide **19** and tertiary radical **20**. Curiously, partial reduction of hydroperoxide **19** was observed in the absence of a reducing agent. This result might be attributed to nucleophilic attack of enamine **2** to hydroperoxide **19** to form two molecules of **1**.

After extensive optimization, the final step was conducted as a one-pot process to avoid unnecessary oxidations of the intermediates, giving **1** in 96% yield from **16** with high reproducibility. Comparison of our synthetic product with an authentic sample, graciously provided by Prof. Takayama at Chiba University, revealed that the ^1H NMR spectra of the synthetic and natural products were identical.[14,15] Other spectral and physical data, including ^{13}C NMR, COSY, HMQC, HMBC, NOESY, and $[\alpha]_D$, were consistent with the reported data.[1,2] In addition, the absolute configuration of (−)-mersicarpine, which was deduced on the basis of the biogenetic relationships, has been confirmed in our studies.

In summary the total synthesis of (−)-mersicarpine was achieved in 10 steps from known ketoester **9**. Our synthesis features an Eschenmoser−Tanabe-type fragmentation to synthesize alkyne unit **12**, a facile construction of the indole skeleton via a combination of a Sonogashira coupling and a gold(III) catalyzed cyclization, as well as a one-pot process to arrange the cyclic imine and the hemiaminal moieties.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Kam, T.-S.; Subramaniam, G.; Lim, K.-H.; Choo, Y.-M. *Tetrahedron Lett.* **2004**, *45*, 5995.
(2) Magolan, J.; Carson, B. A.; Kerr, M. A. *Org. Lett.* **2008**, *10*, 1437.
(3) Biechy, A.; Zard, S. Z. *Org. Lett.* **2009**, *11*, 2800.
(4) Desmaële, D.; d'Angelo, J. *J. Org. Chem.* **1994**, *59*, 2292 The ee of the initial product in the asymmetric Michael addition (87% ee) was upgraded to 99% ee by a recrystallization of the corresponding semicarbazone.
(5) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245.
(6) For reviews, see: (a) Felix, D.; Schreiber, J.; Ohloff, G.; Eschenmoser, A. *Helv. Chem. Acta* **1971**, *54*, 2896. (b) Weyerstahl, P.; Marschall, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, p 1041.
(7) Felix, D.; Müller, R. K.; Horn, U.; Joos, R.; Schreiber, J.; Eschenmoser, A. *Helv. Chem. Acta* **1972**, *55*, 1276.
(8) MacAlpine, G. A.; Warkentin, J. *Can. J. Chem.* **1978**, *56*, 308.
(9) While 2-oxo- or 2-imino-1,3,4-oxadiazoline intermediates in ref 8 were isolated before thermolysis to induce fragmentation, these intermediates could not be observed in the case of **11**. This might be attributed to the steric repulsion between the oxadiazoline ring and the adjacent quaternary carbon, which destabilized the intermediate.
(10) (a) Iritani, K.; Matsubara, S.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1799. (b) Arcadi, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, 610.
(11) Samsonia, S. A.; Chikvaidze, I. S.; Narindoshvili, T. G.; Suvorov, N. N. *Chem. Heterocycl. Compd.* **2001**, *37*, 827.
(12) Treatment of **1** with $H_2{}^{18}O$ under acidic or basic conditions did not result in incorporation of ^{18}O into the molecule.
(13) Ingold, K. U. *Acc. Chem. Res.* **1969**, *2*, 1.
(14) Wu. Y.; Takayama, H. Unpublished results. They also isolated **1** from *Kopsia arborea* and independently elucidated its structure.
(15) As Kerr and co-workers reported in ref 2, the ^1H-NMR chemical shifts of **1** proved to be acidity-dependent.

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