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Total Synthesis of (±)-Mersicarpine

Jakob Magolan, Cheryl A. Carson, and Michael A. Kerr*

Department of Chemistry, The University of Western Ontario, London, Ontario, Canada N6A 5B7

makerr@uwo.ca

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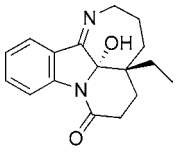
ABSTRACT



mersicarpine

The first total synthesis of the indole alkaloid mersicarpine is reported. Key steps include a *β*-dicarbonyl radical cyclization, as well as an oxidation of the benzopyrrole moiety to establish the masked 1,2-dicarbonyl functionality. An X-ray crystal structure and discussion of the ^{1}H NMR behavior of the natural product are also presented.

The *Kopsia* species of flowering plants have provided the natural product isolation chemist with a cornucopia of indole alkaloids.[1] A subgroup of these alkaloids has piqued our interest as synthetic chemists with its synthetically daunting structural architectures and proposed biosynthetic nexus (Figure 1). To illustrate their structural relation, one might

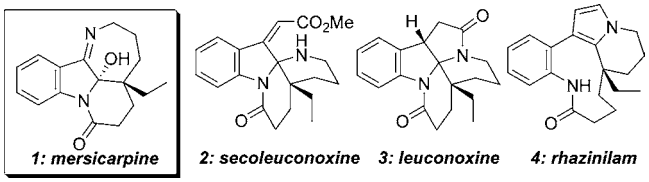


Figure 1. Indole alkaloids isolated from *Kopsia* species.

envision hydrolysis of the imine in mersicarpine (**1**)[2] and recyclization onto the hemiaminal to yield the skeleton found in secoleuconoxine (**2**).[3] Addition of an acetate unit would yield secoleuconoxine itself, which could upon olefin reduction lactamize to leuconoxine (**3**).[4] Aminal hydrolysis and adjustment of the oxidation state of leuconoxine could yield the pyrrole-containing rhazinilam (**4**).[5]

Mersicarpine is a particularly unusual natural product, bearing a seven-membered cyclic imine and an intricately oxidized indole moiety which is essentially a masked 1,2-dicarbonyl. Herein we present the first total synthesis of mersicarpine, the X-ray crystallographic analysis of its structure, and clarification of its sensitive NMR behavior with respect to solvent acidity.

Retrosynthetically, we envisioned that mersicarpine would be the product of imine formation from **5** (Scheme 1). This keto hemiaminal would in turn be formed by the oxidation of *N*-acylindole **6**.[6] It was our belief that the aminopropyl and ethyl moieties of **6** could be installed via elaboration of a suitable dicarbonyl species. We have recently disclosed a malonic radical cyclization route which would be effective in producing the substructure in **6** from a pendant malonic ester in **7**.[7]

(1) See (a) Lim, K.-H.; Hiraku, O.; Komiyama, K.; Koyano, T.; Hayashi, M.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1302−1307. (b) Lim, S.-H.; Sim, K.-M.; Abdulla, Z.; Hiraku, O.; Masahiko, H.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1380−1383. (c) Zhou, H.; He, H.-P.; Kong, N.-C.; Wang, Y.-H.; Liu, X.-D.; Hao, X.-J. *Helv. Chim. Acta.* **2006**, *89*, 515−519 and references therein.

(2) Kam, T.-S.; Subramaniam, G.; Lim, K.-H.; Choo, Y. M. *Tetrahedron Lett.* **2004**, *45*, 5995−5998.

(3) Lim, K.-H.; Kam, T.-S. *Helv. Chim. Acta* **2007**, *90*, 31−35.

(4) Abe, F.; Yamauchi, T. *Phytochemistry* **1994**, *35*, 169−171.

(5) Banerji, A.; Majumder, P. L.; Chatterjee, A. *Phytochemistry* **1970**, *9*, 1491−1493.

(6) (a) Altinis Kiraz, C. I.; Emge, T. J.; Jimenez, L. S. *J. Org. Chem.* **2004**, *69*, 2200−2202 and references therein. (b) Wang, Z.; Jimenez, L. S. *Tetrahedron Lett.* **1996**, *37*, 6049−6052. (c) Colandrea, V. J.; Rajaraman, S.; Jimenez, L. S. *Org. Lett.* **2003**, *5*, 785−788.

(7) Magolan, J.; Kerr, M. A. *Org. Lett.* **2006**, *8*, 4561−4564.

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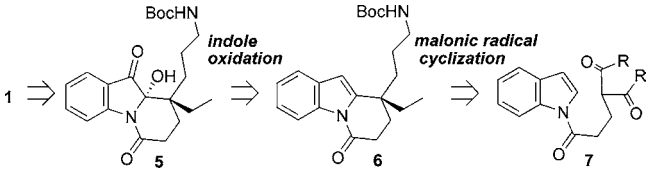
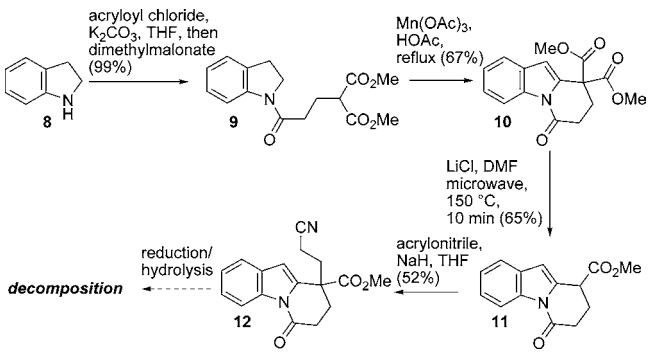
Scheme 1. Retrosynthesis of Mersicarpine



The inauguration of our synthetic efforts toward mersicarpine is presented in Scheme 2. *N*-Acylindoline **9** was

Scheme 2. Radical Cyclization to Form a Dihydropyridoindolone

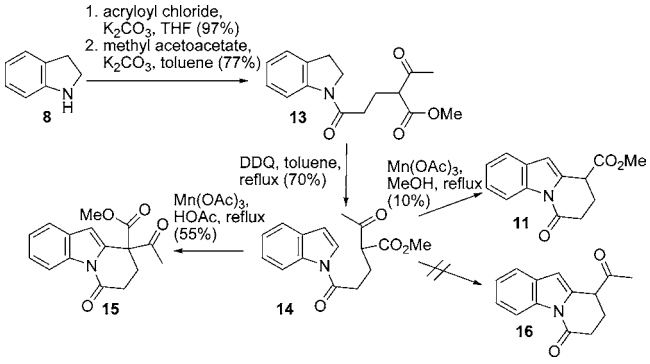


efficiently prepared via the acylation of indoline **8** with acryloyl chloride followed by the Michael addition of dimethylmalonate in a high yielding, operationally simple one-pot procedure. Subjection of **9** to $Mn(OAc)_3$ in refluxing acetic acid promoted a tandem indoline oxidation/malonic radical cyclization producing indole **10** in 67% yield.[8] In our experience, the direct *N*-acryloylation of indole is low yielding and suffers from multiple side reactions. As a result, the synthesis of substrates such as **10** by the aromatization of indolines, either using DDQ or the one-pot procedure depicted in Scheme 2, is advantageous.

All attempts to sequentially reduce or otherwise functionalize the geminal diesters of **10** were unsuccessful, in part due to the reductive and hydrolytic lability of the indole-amide. Fortunately, Krapcho decarboxylation under microwave conditions provided the monoester **11** in 65% yield. We were pleased to find that conjugate addition of the ester enolate of **11** into acrylonitrile could be effected to produce **12** bearing a latent aminopropyl group in the form of a cyanoethyl moiety. Unfortunately, once again the labile nature of the indole-amide functionality made elaboration of the remaining methyl ester unfeasible.

We reasoned that the use of an analogous keto-ester might be a more effective strategy with the methyl ketone offering facile options for conversion to an ethyl substituent (Scheme

Scheme 3. $Mn(OAc)_3$ Mediated Cyclization of a Keto-Ester



3). Indoline **13** was prepared in a similar fashion to malonic derivative **9**. As treatment of **13** with $Mn(OAc)_3$ led to decomposition of the starting material, the oxidation of **13** with DDQ to produce indole **14** was employed as an alternative. The malonic radical cyclization of **14** proceeded as expected when performed in acetic acid to yield **15** in 55% yield. We were disappointed to observe that all attempts at decarboxylation of **15** yielded only decomposition products. Fortuitously, while attempting the malonic radical cyclization of **14** in methanol, ester **11** was isolated, albeit in low yield (Scheme 3). The apparent propensity of **15** to undergo a retro-Claisen condensation was a useful observation given our inability to effect the desired decarboxylation reaction.

It now became apparent that the best route to mono-ketone **16** would be via a retro-Claisen condensation of diketone **18** (Scheme 4). Indole **18** was easily prepared in four steps from indoline **8**. Gratifyingly, fragmentation of **18** through a retro-Claisen condensation was indeed effective producing methyl ketone **16** in 95% yield upon treatment with sodium bicarbonate in methanol. Conjugate addition of **16** to acrylonitrile yielded **19** (74%), which was quantitatively reduced to secondary alcohol **20**. Dehydration of **20** to **21** was exceptionally difficult and failed to succumb to a large number of both standard and more elaborate measures. Preparation of the methyl xanthate followed by Chugaev elimination provided the most satisfactory results. Hydrogenation of **21** over Adam's catalyst saturated both the alkene and the nitrile producing, after Boc protection, carbamate **22**.[9] The eagerly anticipated oxidation of the *N*-acylindole **22** was extremely facile, proceeding in 93% yield upon treatment with dimethyl dioxirane, prepared in situ from acetone and OXONE.[10] Although **23** was obtained as a 1:1 mixture of diastereomers, we gambled that this would prove inconsequential given the epimerizable nature of the hemiaminal. The final step, amine deprotection and presumed imine formation, gave a single compound in 82% yield.[11]

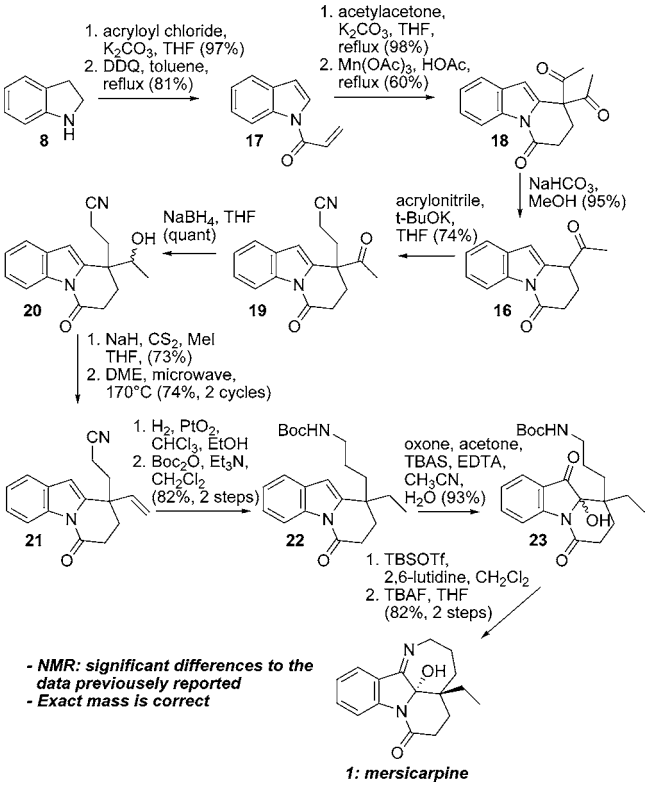
(8) For comprehensive reviews of $Mn(OAc)_3$ chemistry see (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339−363. (b) Snider, B. B. Manganese(III)-based oxidative free-radical cyclizations in *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004; Vol. 1, pp 483−490.

(9) Ackermann, J.; Aebi, J.; Dehmlow, H.; Hirth, G.; Maerki, H.-P.; Morand, O.; Panday, N. *U.S. Pat. Appl. Publ.* **2005**, 2005065210.

(10) (a) Curci, R.; Fiorentino, M.; Troisi, L. *J. Org. Chem.* **1980**, *45*, 4758−4760. (b) Waldemar, A.; Chantu, S.-M. R.; Zhao, C.-G. *Org. React.* **2002**, *61*, 219.

(11) (a) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1985**, *26*, 5543−5546. (b) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870−876.

Scheme 4. Total Synthesis of Mersicarpine



We were initially greatly disheartened to observe that several ^{1}H NMR resonances of the supposed natural product were quite different from those reported by Kam. Although we fully expected imine formation to be a trivial step, we were cognizant of several potential alternative reaction pathways. Diastereomer **24** (Figure 2) was one possible

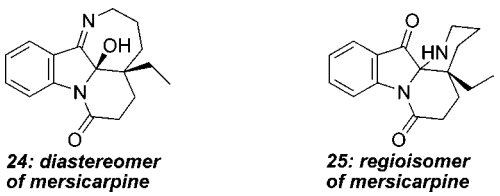


Figure 2. Alternative cyclization products.

reaction outcome as was regioisomer **25**, in which cyclization onto the hemiaminal would yield a six-membered ring. Formation of **24** was intuitively unlikely given that this unnatural diastereomer would have to be the thermodynamic sink to be produced in 82% yield from a 1:1 mixture of hemiaminal epimers. Cyclization to **25** appeared to be plausible as it would form a structural subunit of the leuconoxine series of natural products, however the ^{13}C and 2-D NMR data did not support this structure.

Some clarification was obtained when ^{1}H NMR analysis was performed in $CDCl_3$ passed through basic alumina, followed by treatment of the sample with incremental amounts of trifluoroacetic acid (Figure 3). The changes in

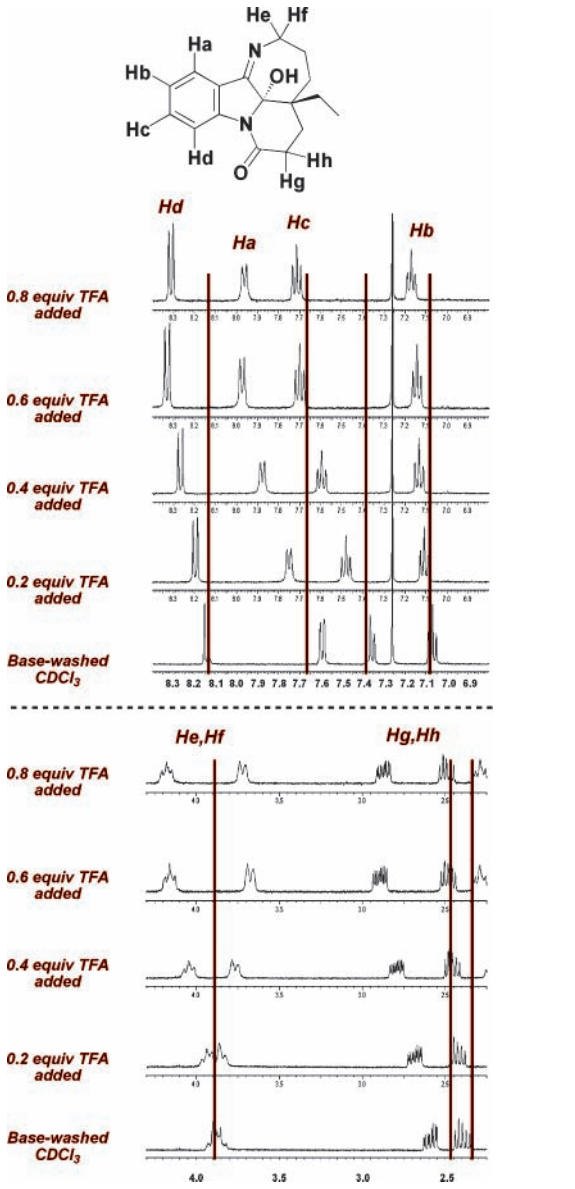


Figure 3. Variation of ^{1}H NMR resonances with added trifluoroacetic acid. Red lines indicate literature values for mersicarpine (ref 2).

chemical shift with the addition of acid were dramatic. Not only did protons adjacent to the basic imine nitrogen show significant variance (He and Hf), the four aromatic resonances as well as aliphatic protons He and Hg all varied in chemical shift with degree of protonation. Clearly, extended resonance stabilization of the iminium cation of this natural product has substantial effects on multiple proton environments. Being unaware of the degree $CDCl_3$ decomposition (i.e., DCl content) associated with the initial characterization of mersicarpine we were unable to precisely duplicate the literature data. Furthermore, it follows that the identity of the counteranion is also likely to have an effect on proton

resonances. The ^{13}C NMR data for our sample matches the reported data very well.

Finally, after the preparation of a sufficient amount of the natural product, we were able to induce the formation of X-ray quality crystals which offered definitive support of the success of our synthetic effort.[12] The structure obtained via X-ray diffraction is shown in Figure 4. Note that the disposition of the aminal hydroxyl group and the quaternary ethyl moiety are in fact trans, as required for correlation to the reported structure.

Figure 4. X-ray structure of synthetic mersicarpine.

(12) Note: there is disorder at the C6 position.

It is possible, however (in our opinion) highly unlikely, that the reported structure for mersicarpine is in fact incorrect. We were unable to secure an authentic sample for direct comparison. The fact that Kam and co-workers provide sound evidence for the reported connectivity and stereochemistry, as well as the fact that our NMR data is very close (almost identical for ^{13}C) lead us to be fully confident of that the reported structure is correct. The only resonance in the ^{1}H NMR spectrum that we were not able to rectify with acid titration (variable by 0.07 ppm) corresponds to the protons He and Hf, which are adjacent to the imine nitrogen and therefore expected to be sensitive to acid concentration.

In summary, we have reported the first total synthesis of mersicarpine and confirmed the reported structure by crystallographic analysis of our synthetic product. In addition, we note the dramatic chemical shift variance in the ^{1}H NMR spectra with respect to solvent acidity.

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Supporting Information Available: Full experimental procedures and spectroscopic data for all new compounds and crystal data for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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