Total Synthesis of (-)-Mersicarpine
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*Current Literature*
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Isolation and Background

• (-)-Mersicarpine was isolated from the bark of *K. fruiticosa* and *K. arborea* in 2004.

• *Kopsia* genus comprises over 23 shrubs and trees in tropical Asia with the highest concentration found in Malaysia

• Over 50 different alkaloids have been isolated from *K. arborea*.

• A select few of the isolated alkaloids, most notably, valparicine, have demonstrated cytotoxic properties against drug-resistant KB cells ($IC_{50} 2.72 \mu M$).

\[ \text{valparicine} \]


Proposed Biosynthesis

- Water adds from the less hindered face.

Postulated biosynthesis of other isolated alkaloids by the Kerr group

- Different theories on the location of (-)-mersicarpine along the biosynthetic route

The Kerr group’s synthesis of (±)-mersicarpine

- Very labile indole-amide functionality.

Magolan, J.; Carson, C. A.; Kerr, M. A. *Org Lett.* **2008**, *10*, 1437-1440
The Kerr group’s synthesis of (±)-mersicarpine

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The Zard group’s formal synthesis of (±)-mersicarpine

\[
\text{CO}_2\text{H} \quad \xrightarrow{1) (COCl)_2} \quad \text{CO}_2\text{tBu} \\
\text{H} \quad \xrightarrow{2) KO-t-Bu, t-BuOH} \quad \text{H}
\]

• The t-butyl ester serves to stabilize the radical intermediate and can be easily removed at a later stage.

55% over 2 steps

The Zard group’s formal synthesis of (±)-mersicarpine

The Zard group’s formal synthesis of (±)-mersicarpine

For preparation of 4-ethyl-4-pentenoic acid see: McCaffery, E. L.; Shalaby, S. w. J. Organomet. Chem. 1967, 8, 17-27
The Zard group’s formal synthesis of (±)-mersicarpine

1) A (3 equiv), DLP (1.4 equiv)  
1,2-DCE  
2) MnO₂  
78% over 2 steps

1) TFA, toluene  
2) NEt₃, Boc₂O  
84% over 2 steps

• 10 steps to Kerr’s advanced intermediate in 18% yield (1 fewer step).

Kerr's advanced intermediate


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Title Paper: Unexpected oxidation

\[
\begin{align*}
\text{Nakajima, R.; Ogino, T.; Yokoshima, S.; Fukuyama, T.} & \quad J. Am. Chem. Soc. \quad \text{ASAP}
\end{align*}
\]

• Unexpected formation of (-)-mersicarpine after prep-TLC purification. Yield were low and irreversible however.

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(-)-mersicarpine

96% yield over 3 steps
16 steps, 0.032 %

Autoxidation; 

Me₂S

Degassed reaction mixture
Title Paper: Proposed mechanism of final oxidation

The addition of $^{18}\text{O}_2$ gave full incorporation of $^{18}\text{O}$ in the product.


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Summary

- 2 distinct approaches to assemble the core

- The Kerr group constructed (±)-mersicarpine in 14 steps and 11% yield utilizing an oxidation/radical cyclization sequence to construct the 6 membered ring followed by an imine cyclization to install the 7-membered ring.

- The Zard group constructed an advanced intermediated of the Kerr group’s (±)-mersicarpine synthesis in 10 steps and 18% yield utilizing an a radical annulation sequence to construct the 6 membered ring.

- The Fukuyama group completed the total synthesis of (−)-mersicarpine in 10 steps and 3.2% yield from known cyclohexane. They utilized a Sonogashira coupling and gold catalyzed annulation to install the indole moiety followed by acylation sets the 6 membered ring.