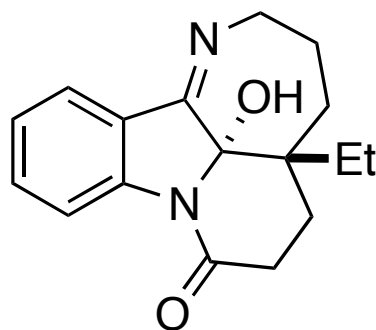


Total Synthesis of (-)-Mersicarpine

Rie Nakajima, Tsuyoshi Ogino, Satoshi Yokoshima, and Tohru Fukuyama. *J. Am. Chem.*

Soc. ASAP

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Isolation and Background

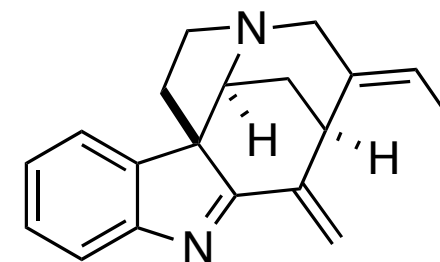


- (-)-Mersicarpine was isolated from the bark of *K. fruticosa* and *K. arborea* in 2004.

- *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 μ M).

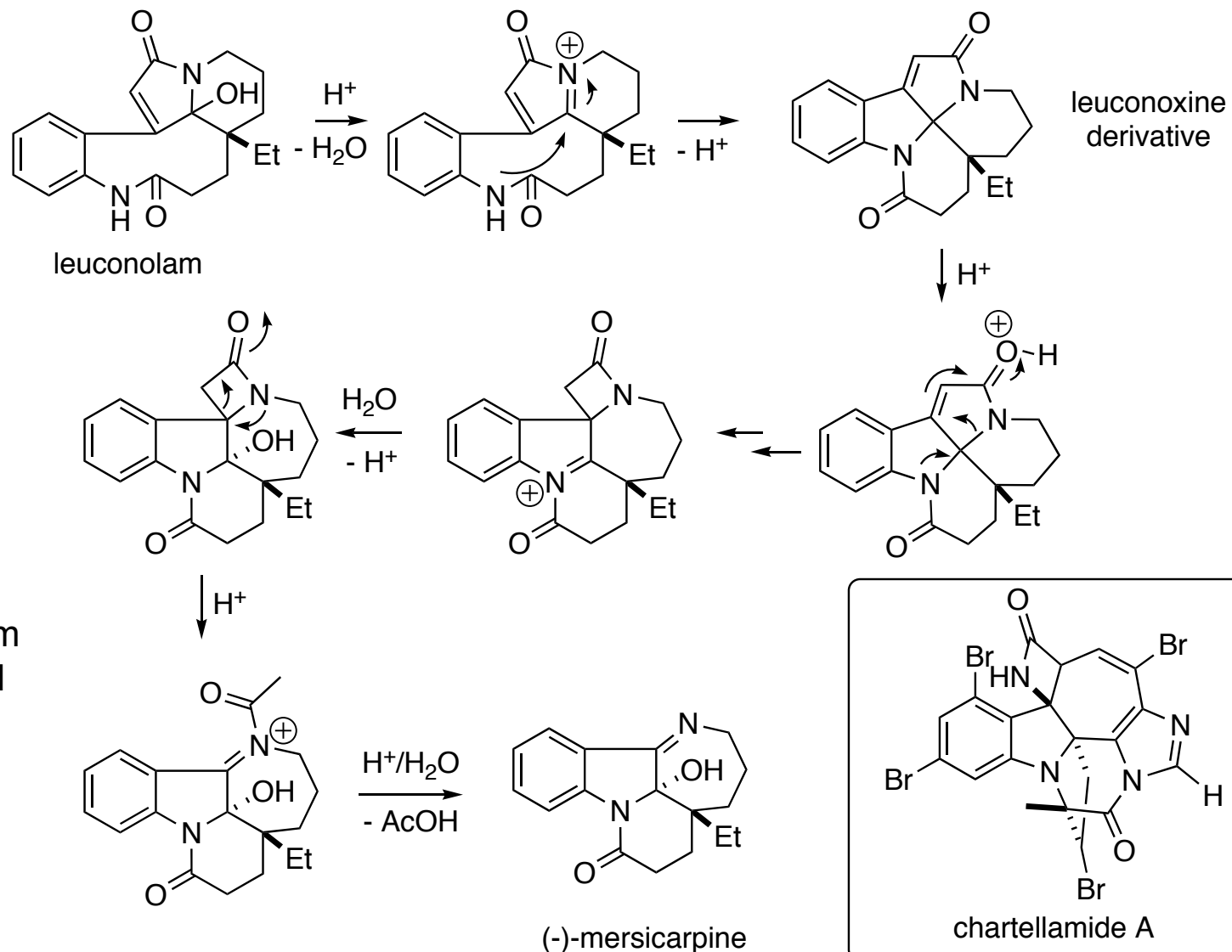


valparicine

Lim, K.; Hiraku, O.; Kanki, K.; Koyano, T.; Hayashi, M.; Kam, T. *J. Nat. Prod.* **2007**, 70, 1302-1307

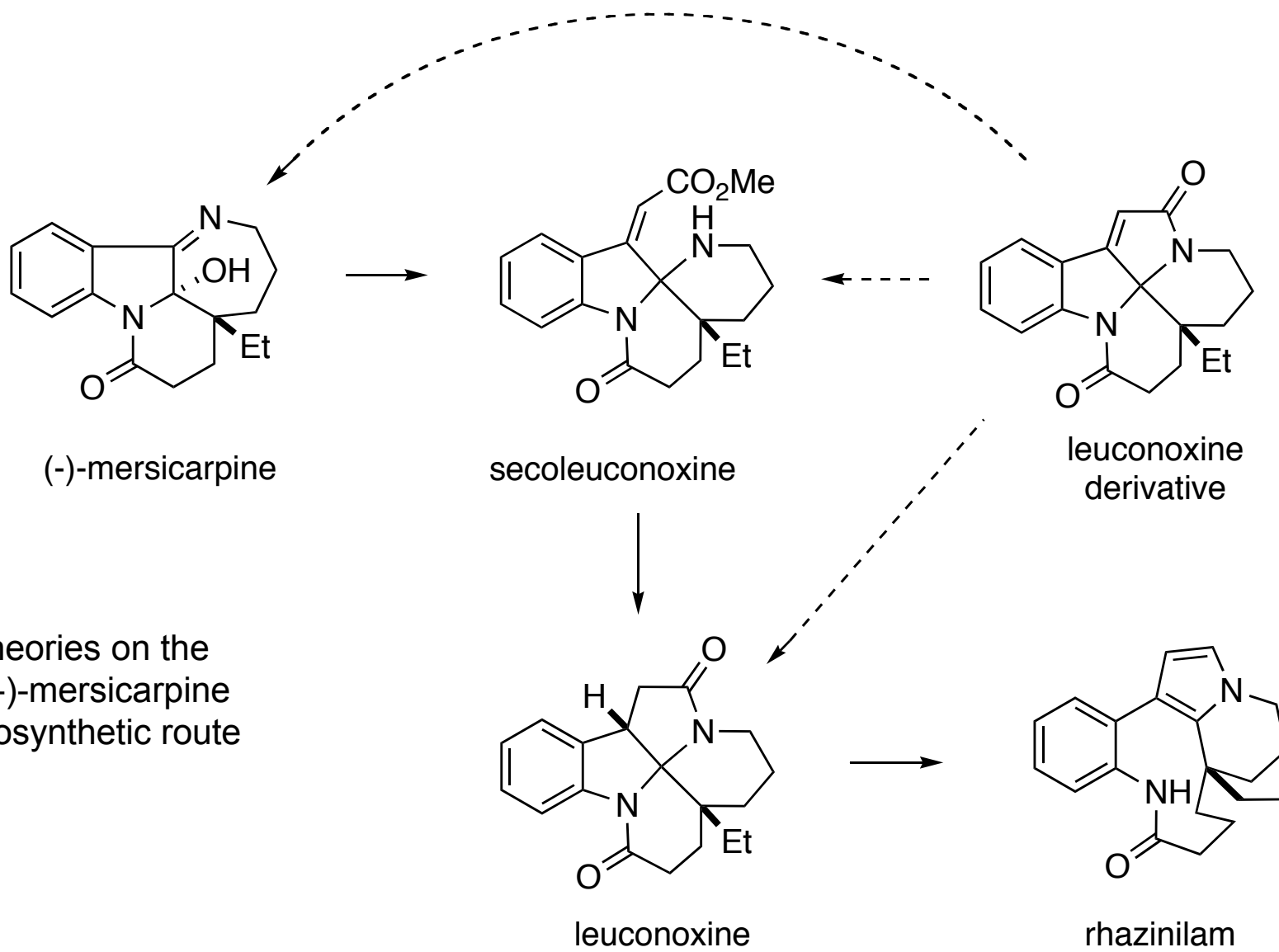
Kam, T.; Subramaniam, G.; Lim, K.; Choo, Y. *Tetrahedron Lett.* **2004**, 45, 5995-5998

Proposed Biosynthesis



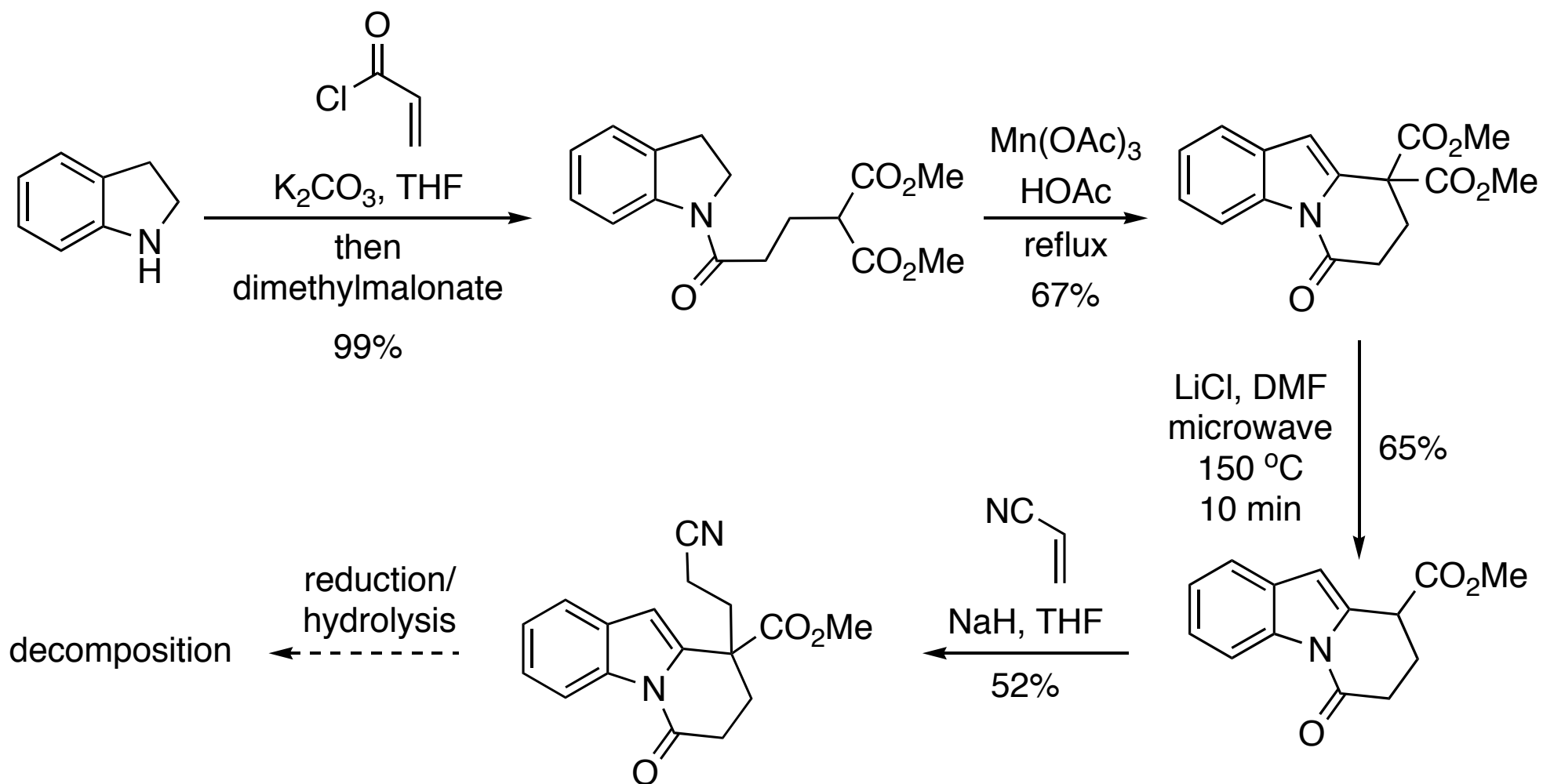
Kam, T.; Subramaniam, G.; Lim, K.; Choo, Y. *Tetrahedron Lett.* **2004**, 45, 5995-5998

Postulated biosynthesis of other isolated alkaloids by the Kerr group



Magolan, J.; Carson, C. A.; Kerr, M. A. *Org Lett.* **2008**, 10, 1437-1440

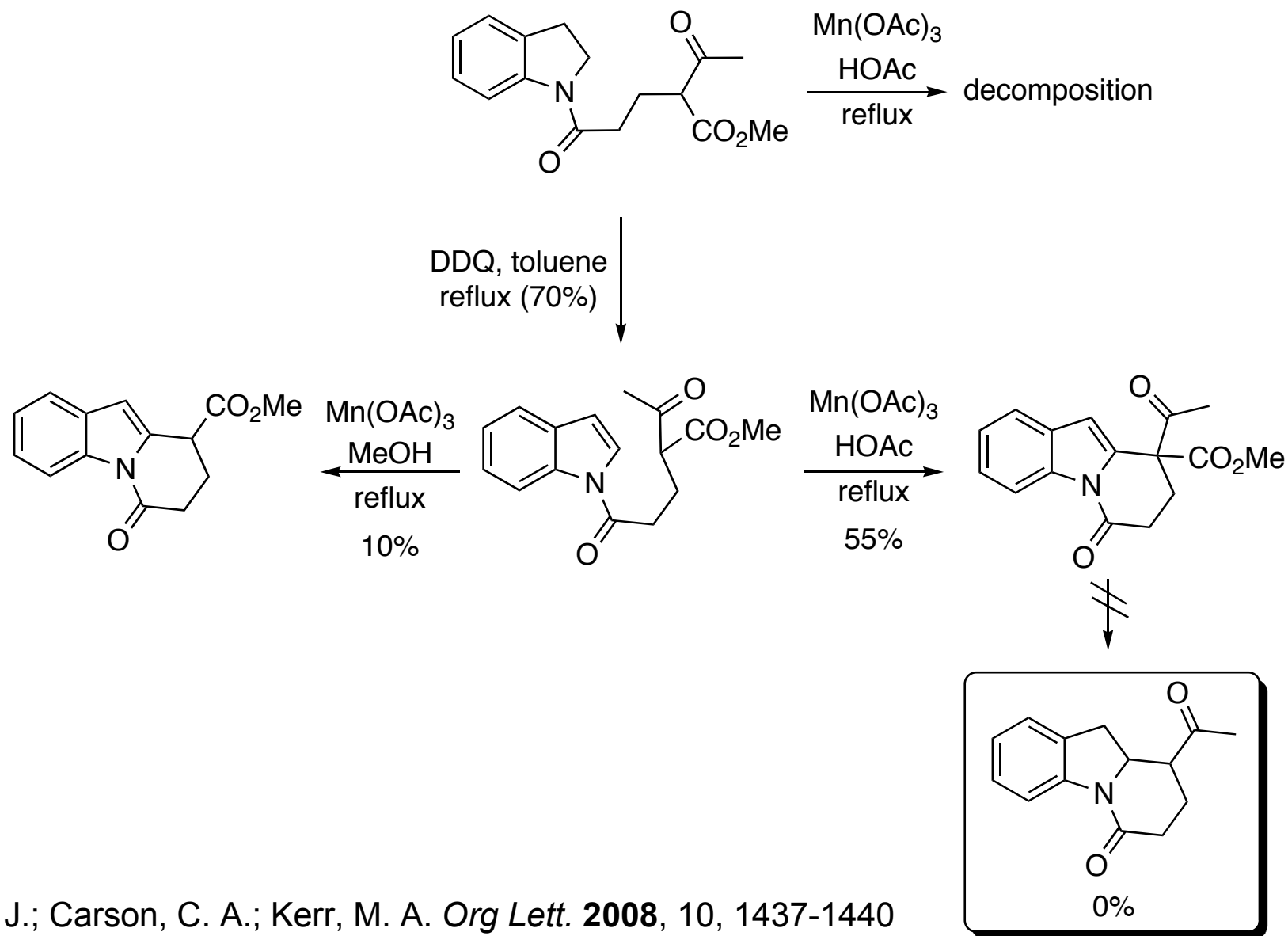
The Kerr group's synthesis of (±)-mersicarpine



- Very labile indole-amide functionality.

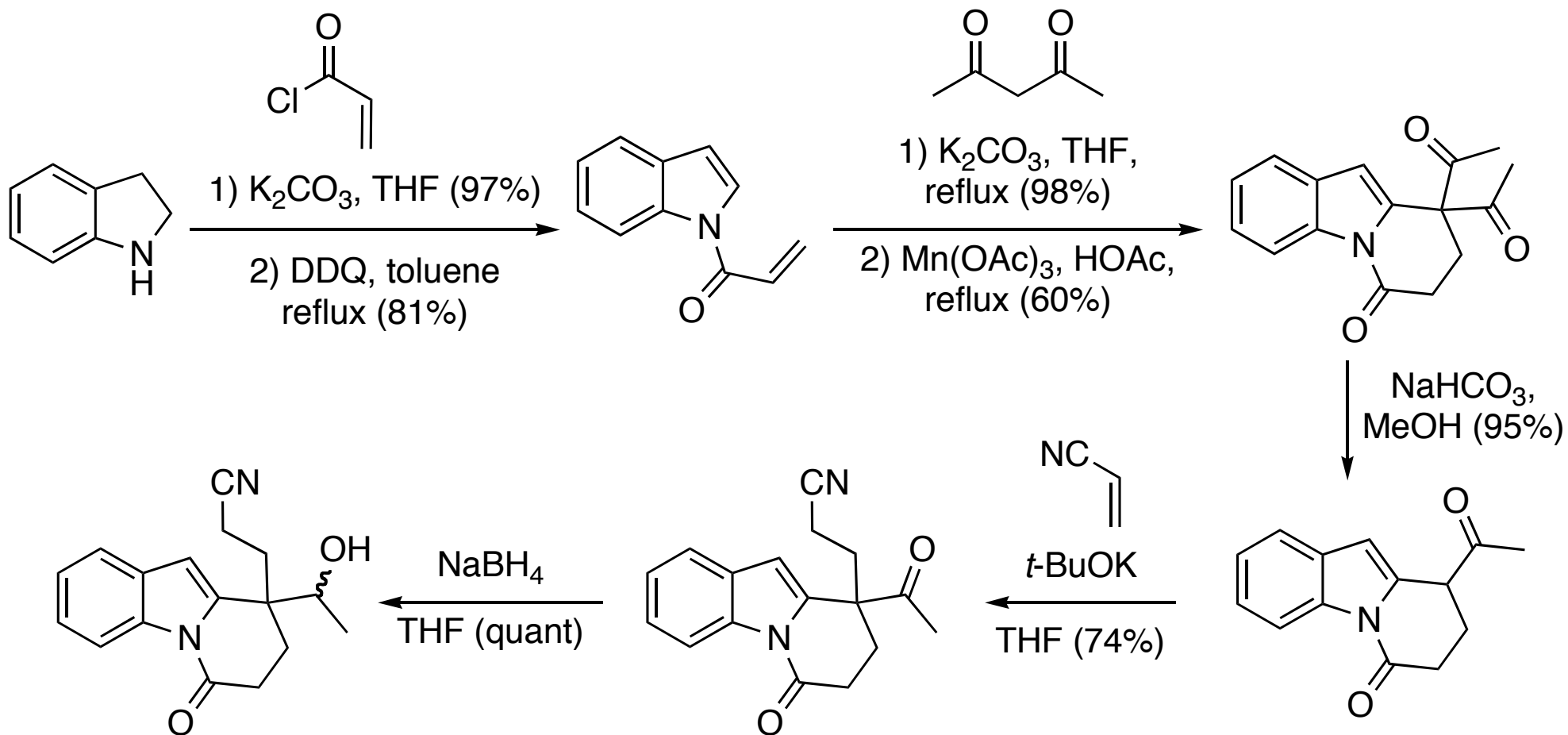
Magolan, J.; Carson, C. A.; Kerr, M. A. *Org Lett.* **2008**, 10, 1437-1440

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



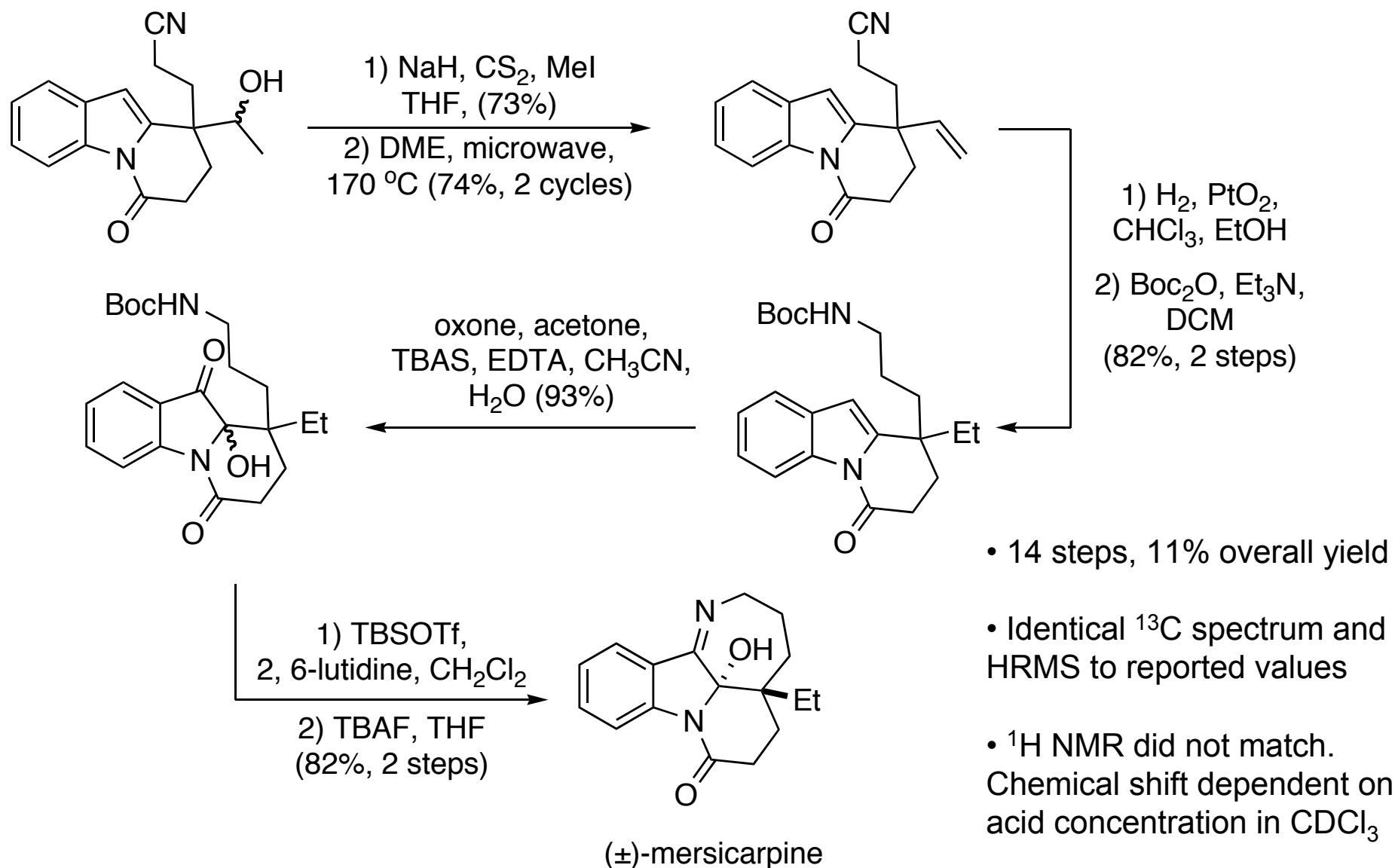
Magolan, J.; Carson, C. A.; Kerr, M. A. *Org Lett.* **2008**, 10, 1437-1440

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



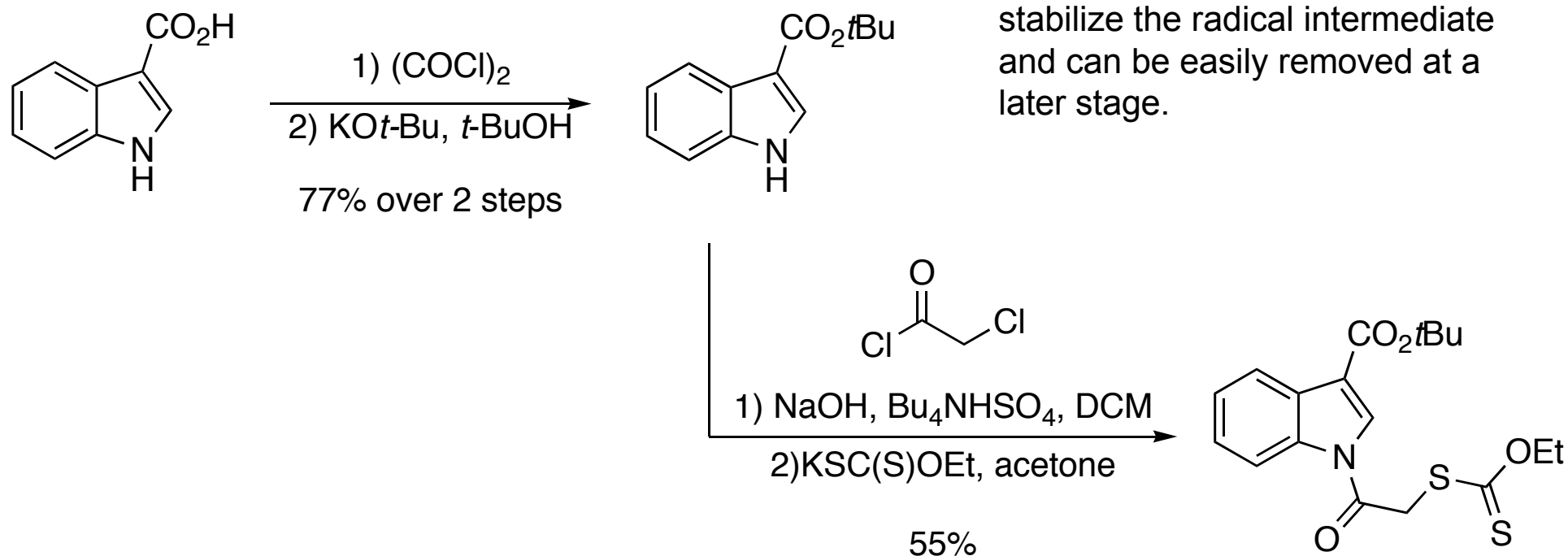
Magolan, J.; Carson, C. A.; Kerr, M. A. *Org Lett.* **2008**, 10, 1437-1440

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



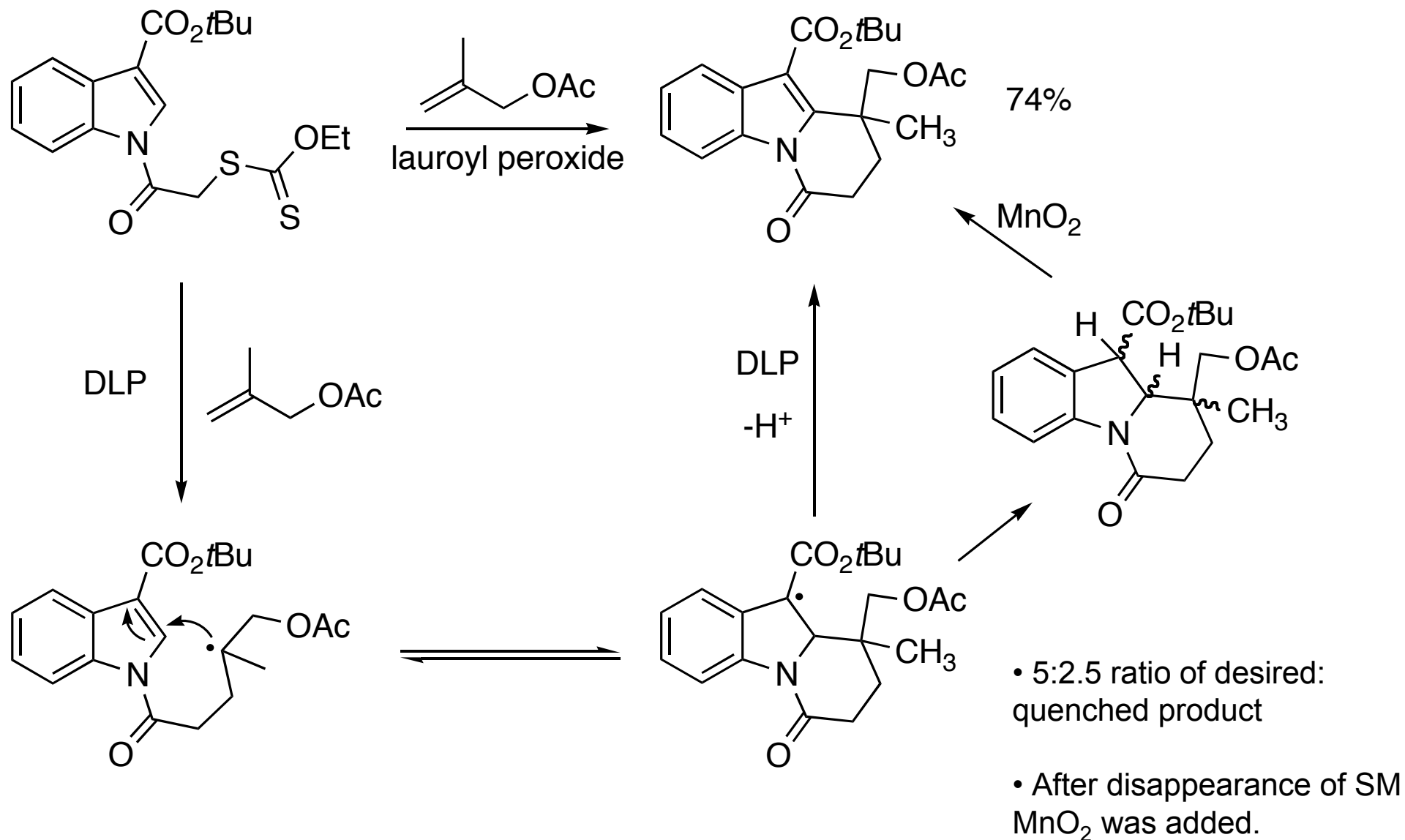
Magolan, J.; Carson, C. A.; Kerr, M. A. *Org Lett.* **2008**, 10, 1437-1440

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



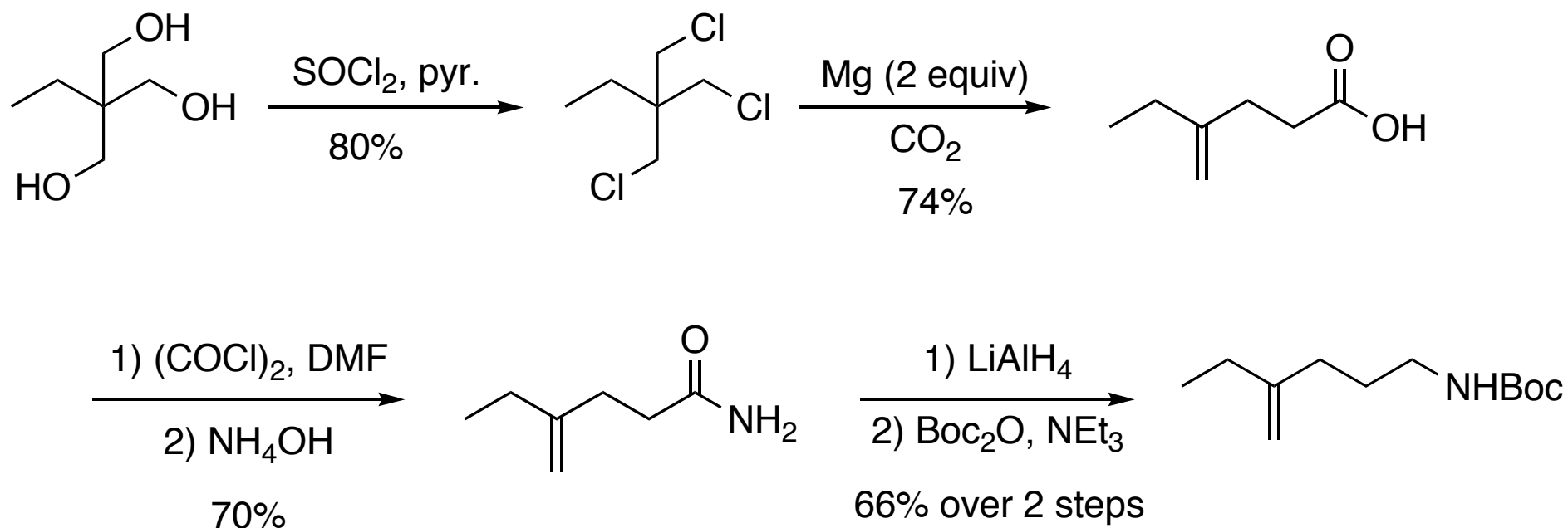
Biechy, A.; Zard, S. Z. *Org Lett.* **2009**, 11, 2800-2803

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



Biechy, A.; Zard, S. Z. *Org Lett.* **2009**, 11, 2800-2803

The Zard group's formal synthesis of (\pm)-mersicarpine

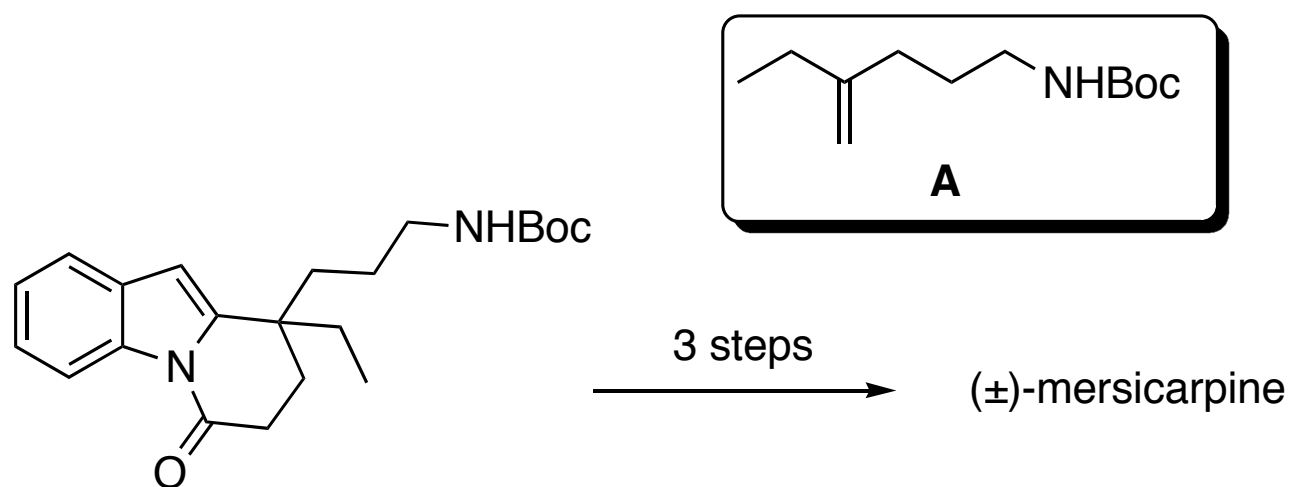
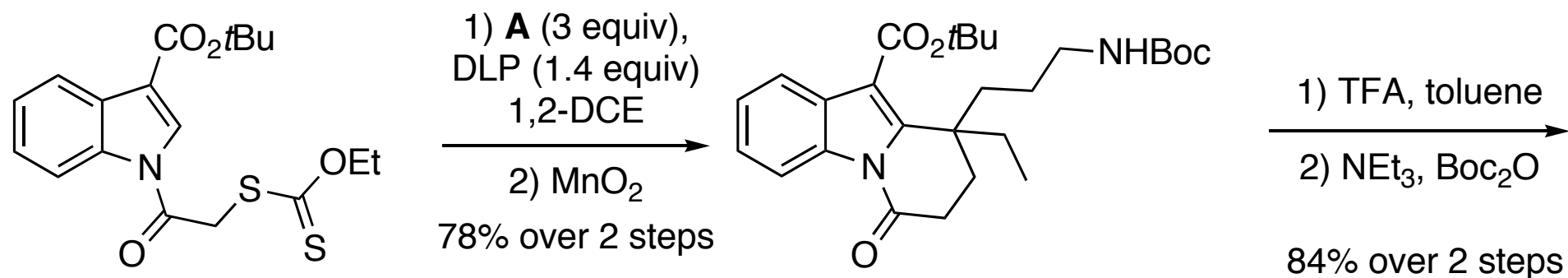


For preparation of 4-ethyl-4-pentenoic acid see: McCaffery, E. L.; Shalaby, S. w. *J. Organomet. Chem.* **1967**, 8, 17-27

For preparation of 4-ethyl-4-pentenamide see: Biechy, A.; Zard, S. Z. *Org Lett.* **2009**, 11, 2800-2803

Biechy, A.; Zard, S. Z. *Org Lett.* **2009**, 11, 2800-2803

The Zard group's formal synthesis of (\pm)-mersicarpine

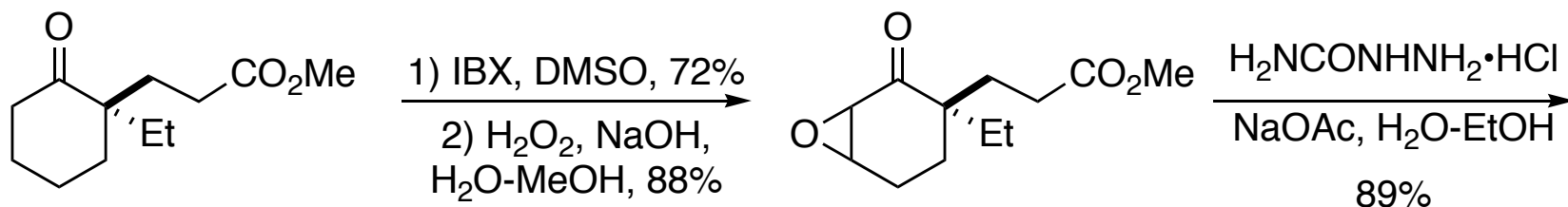


Kerr's advanced intermediate

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

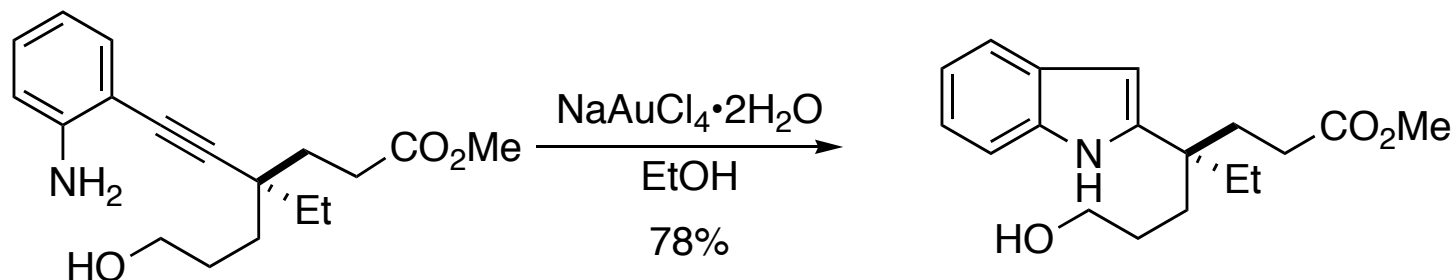
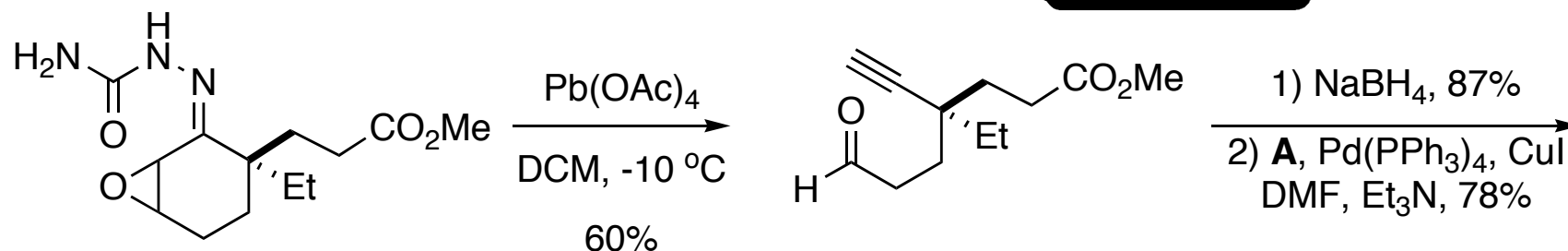
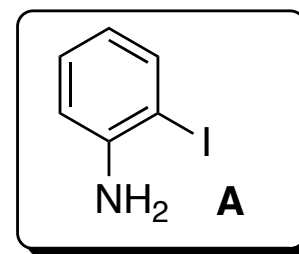
Biechy, A.; Zard, S. Z. *Org Lett.* **2009**, 11, 2800-2803

Title Paper: Eschenmoser-Tanabe fragmentation and indole formation



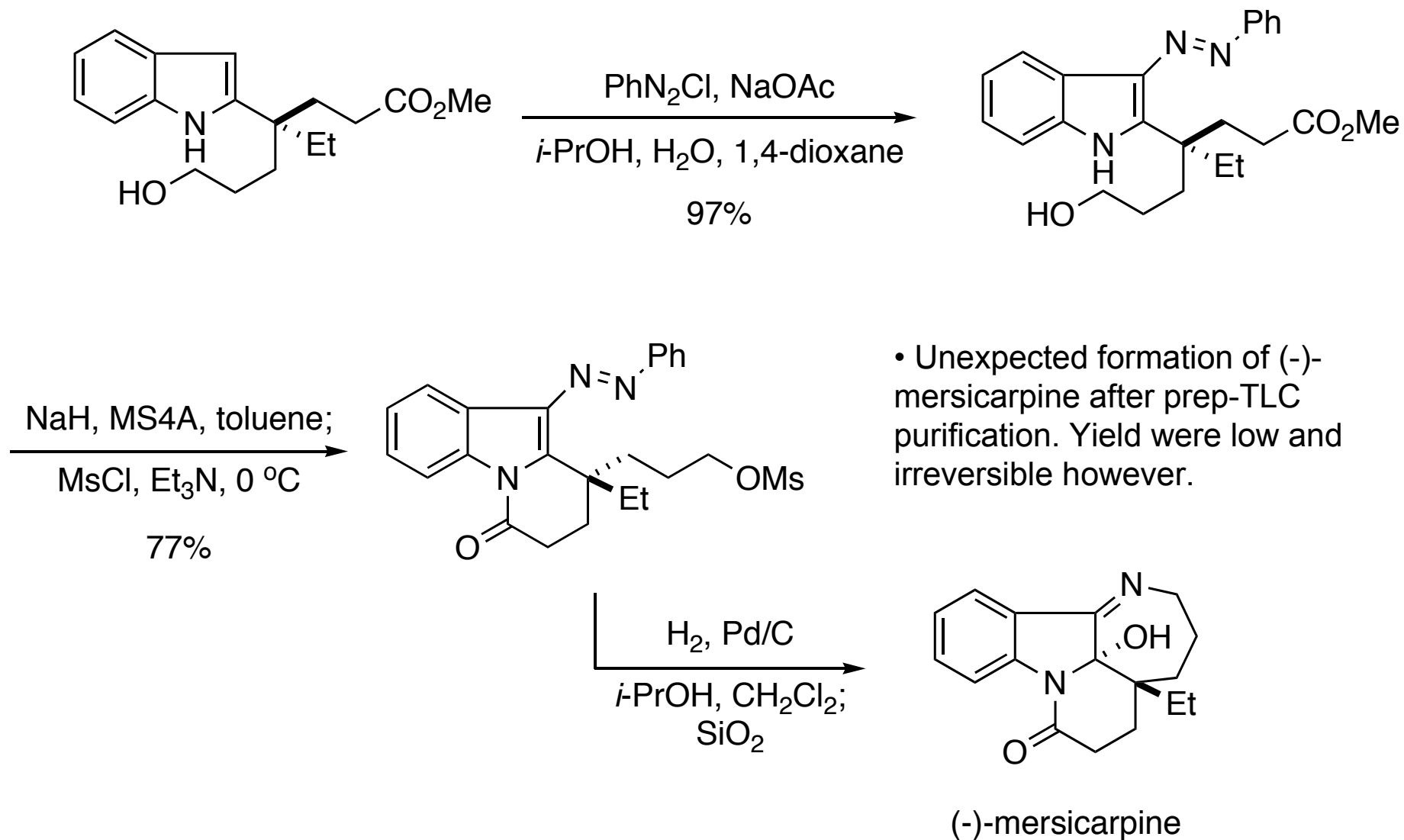
25% over 4 steps from
cyclohexanone

87% ee to 99% ee



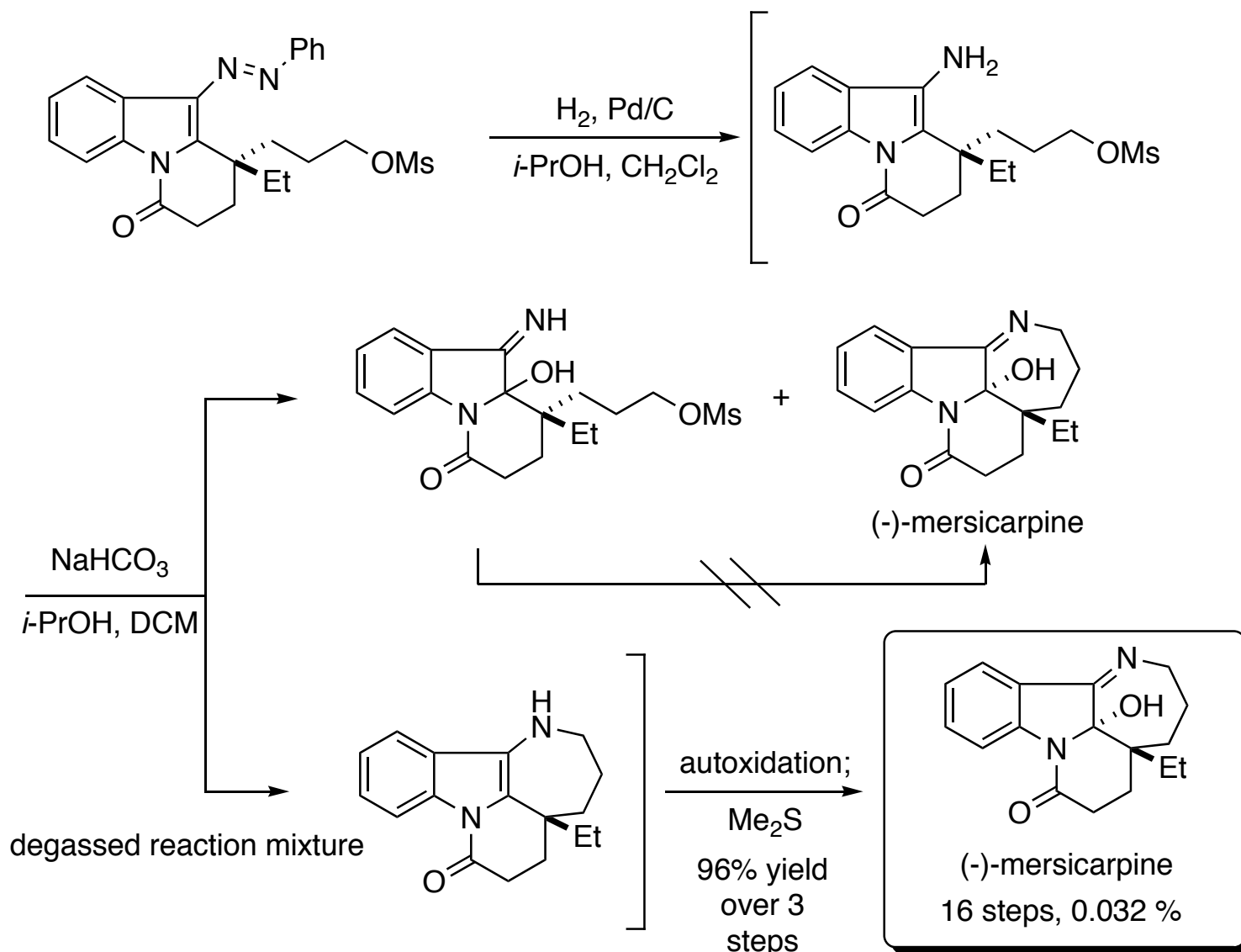
Nakajima, R.; Ogino, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* ASAP

Title Paper: Unexpected oxidation



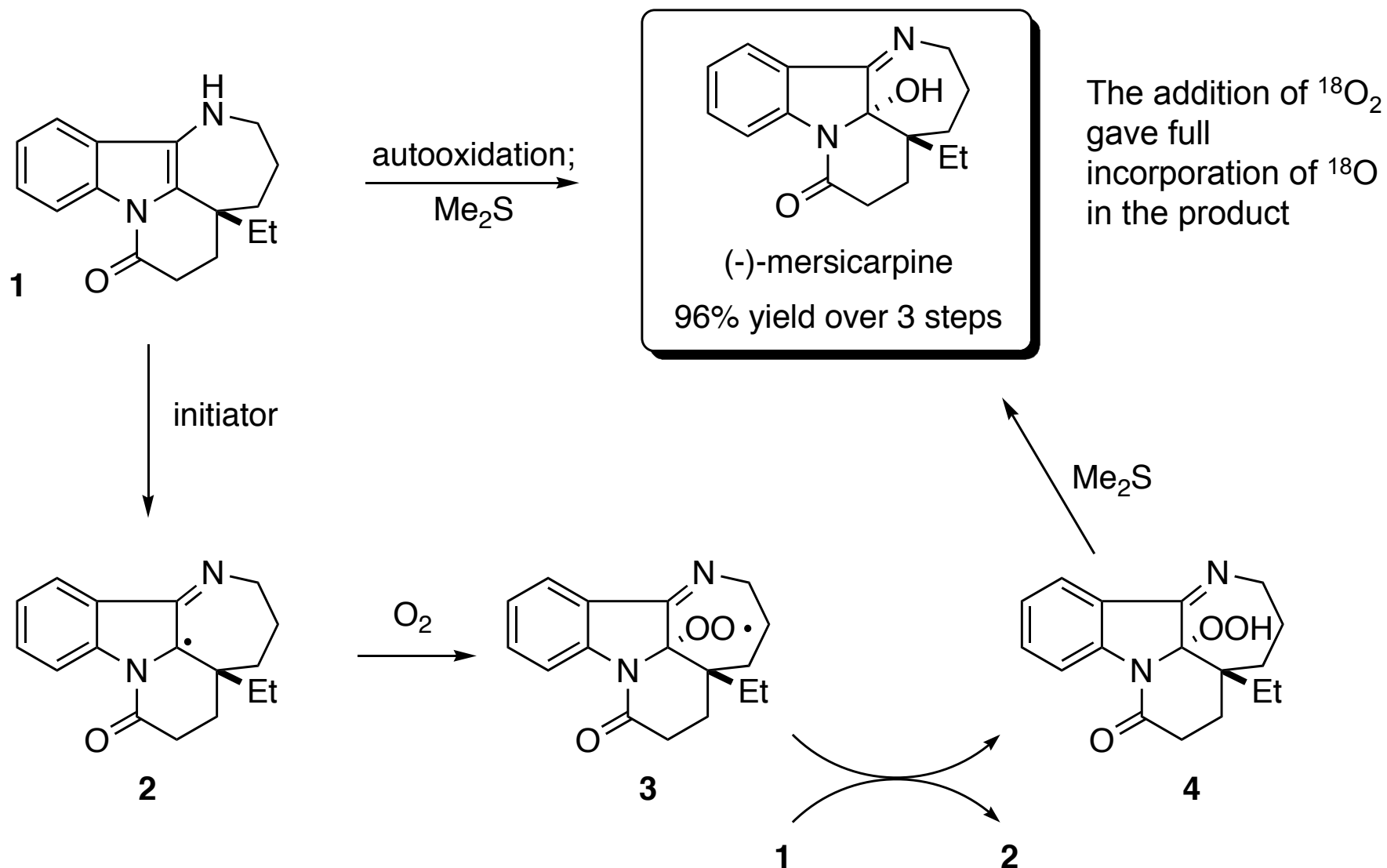
Nakajima, R.; Ogino, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* ASAP

Title Paper: Control of autoxidation



Nakajima, R.; Ogino, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* ASAP

Title Paper: Proposed mechanism of final oxidation



Nakajima, R.; Ogino, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* ASAP

Summary

- 2 distinct approaches to assemble the core
- The Kerr group constructed (\pm)-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 intermediate of the Kerr group's (\pm)-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.