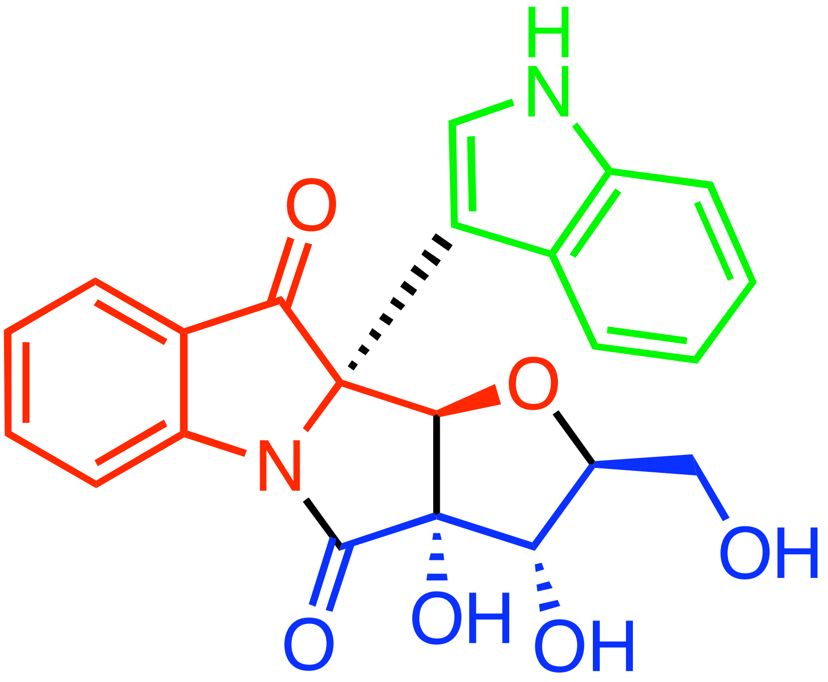
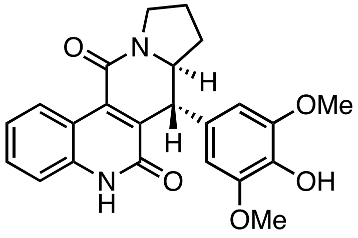
# Total Synthesis of (+)-Isatisine A

Karadeolian, A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2010**, *Early View* DOI:
10.1002/anie.200906632



Christopher J. Rosenker
Wipf Group - Current Literature
January 23, 2010

# *Isatis indigotica* Fort.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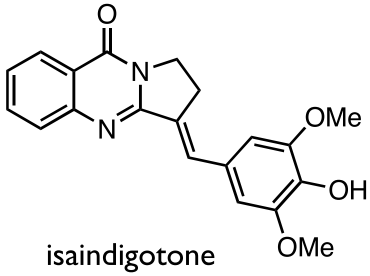
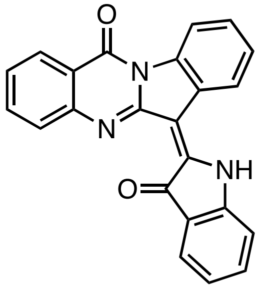

isaindigotone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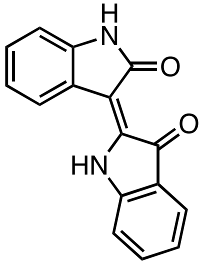
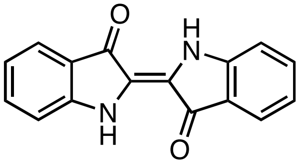
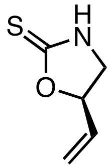

indirubin

- leaves of *Isatis indigotica* Fort. (Cruciferae); also known as Indigo-colored Woad Leaf
  - Used in traditional Chinese medicine for treating viral diseases (ie. influenza, viral pneumonia, and hepatitis)
  - Isolated several different compounds from the leaves and roots

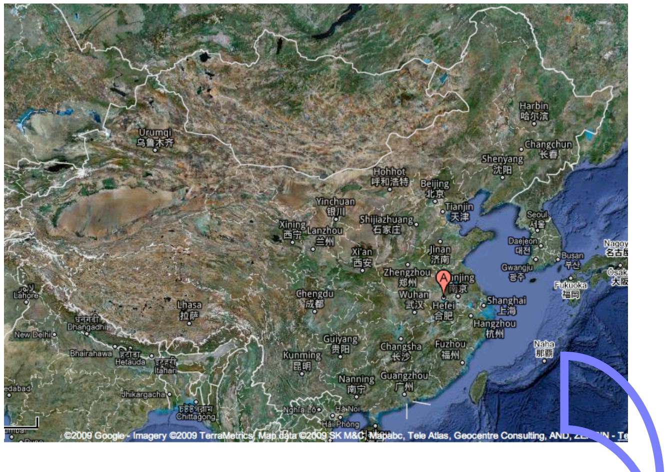

Indigo (indigotin)

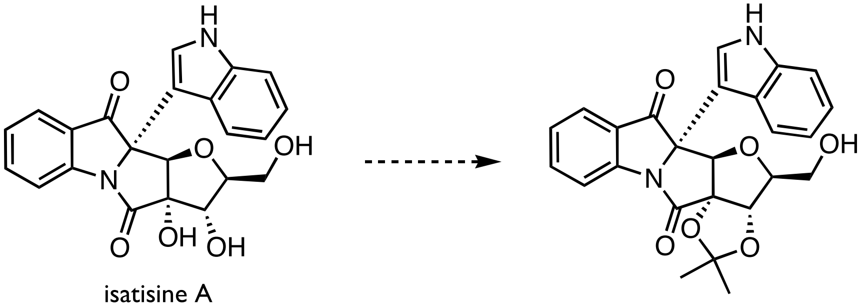

epigotrin

Liu, J.-F.; Jiang, Z.-Y.; Wang, R.-R.; Zheng, Y.-T.; Chen, J.-J.; Zhang, X.-M.; Ma, Y.-B. *Org. Lett.* **2007**, *9*, 4127.
Wu, X.; Qin, G.; Cheung, K.; Cheng, K. *Tetrahedron* **1997**, *53*, 13323.
Huang, Q. S.; Yoshihira, K.; Natori, S. *Planta Med.* **1981**, *42*, 308.
Wu, X. Y.; Liu, Y. H.; Sheng, W. Y.; Sun, J.; Qin, G. W. *Planta Med.* **1997**, *63*, 55.
Images copied from http://www.futianherbs.com/pages/herb_extracts.html and http://www.chinamedicinemall.com/cold_fever_flu.htm

# Isolation of isatisine A

- Isolated from the leaves of *Isatis indigotica* Fort. (Cruciferae)
  - Collected from Anhui province, China
  - Group sought an active anti-HIV agent
  - 50 kg provided 64 mg of acetonide
    - Characterized by 1D and 2D NMR, HRMS, $[\alpha]_D$, and X-ray crystallography
    - Absolute stereochemistry was not determined
    - 37.8 μM $EC_{50}$ anti-HIV-1 for acetonide
    - Acetonide artifact of isolation??



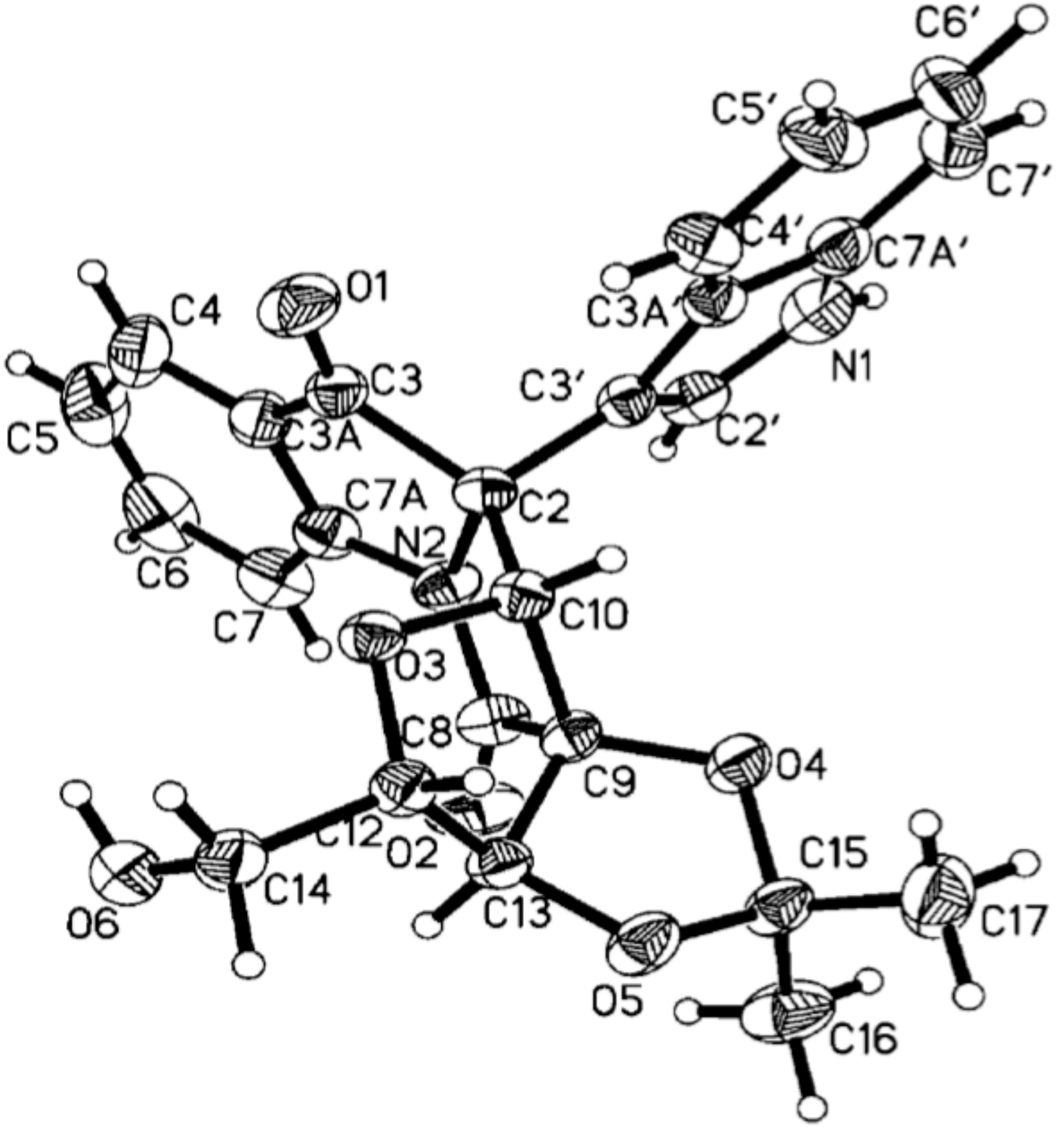


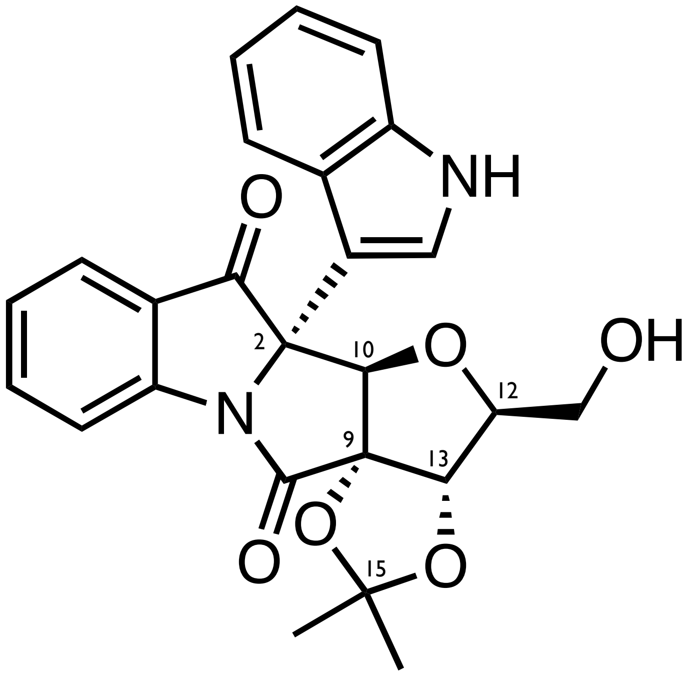
isatisine A

isatisine A acetonide

Liu, J.-F.; Jiang, Z.-Y.; Wang, R.-R.; Zheng, Y.-T.; Chen, J.-J.; Zhang, X.-M.; Ma, Y.-B. *Org. Lett.* **2007**, 9, 4127.
Images copied from Google Maps and http://4.bp.blogspot.com/_ZgtV2LusUZ8/SJspyUMZUAI/AAAAAAAAARI/En5ImwHXHaQ/s1600-h/leaves.jpg

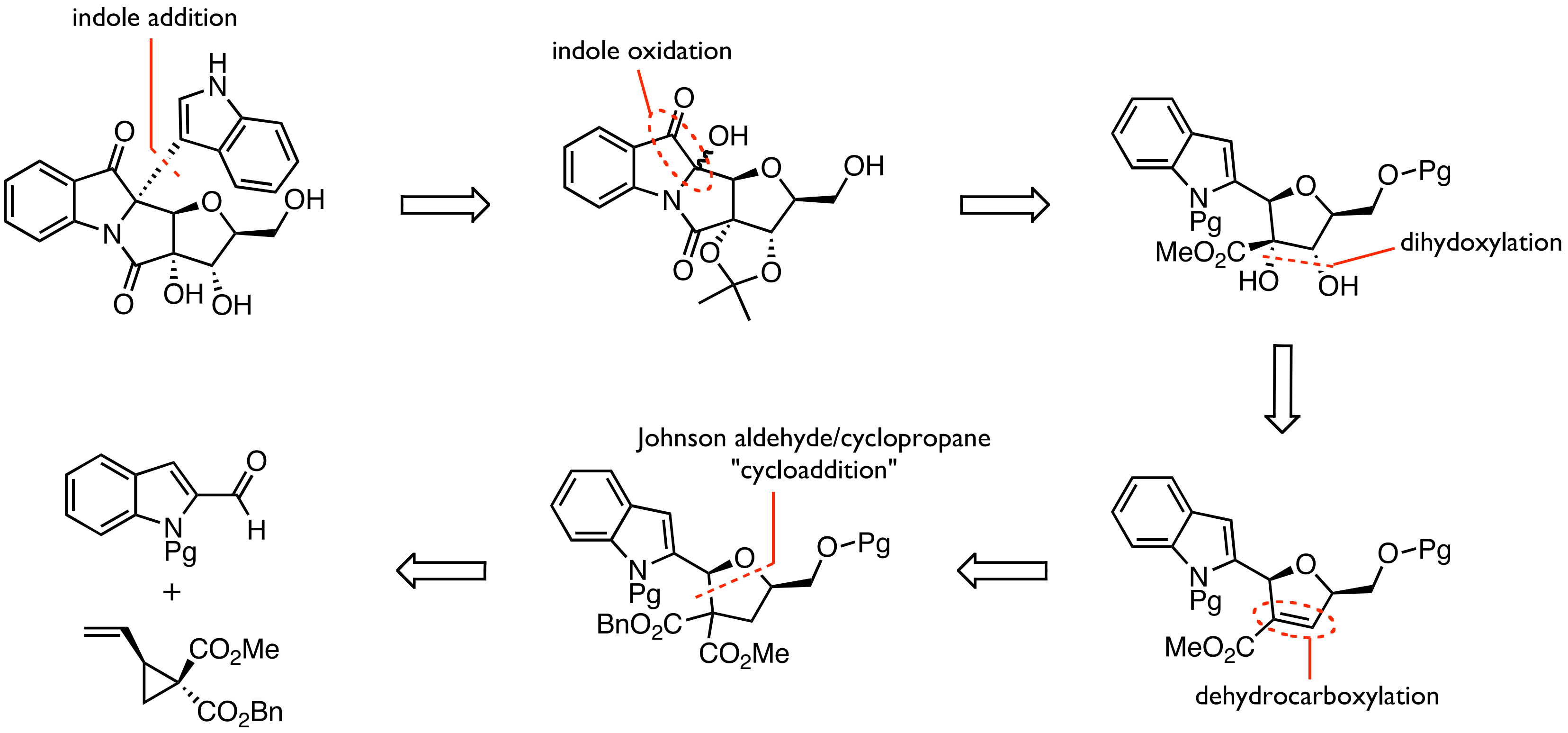
# Structure of isatisine A





Liu, J.-F.; Jiang, Z.-Y.; Wang, R.-R.; Zheng, Y.-T.; Chen, J.-J.; Zhang, X.-M.; Ma, Y.-B. *Org. Lett.* **2007**, *9*, 4127.

# Retrosynthetic analysis



- Passes through acetonide isolation artifact
- Elegant stereospecific cycloaddition approach to tetrahydrofuran
  - Starting with chiral cyclopropane allows for synthesis of single enantiomer

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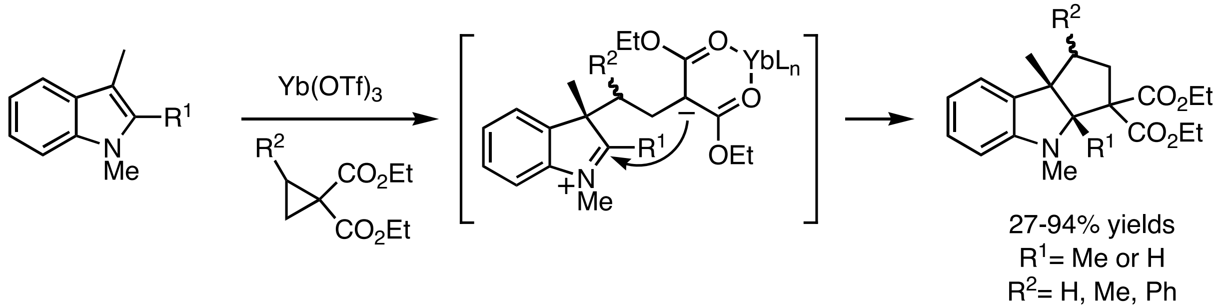
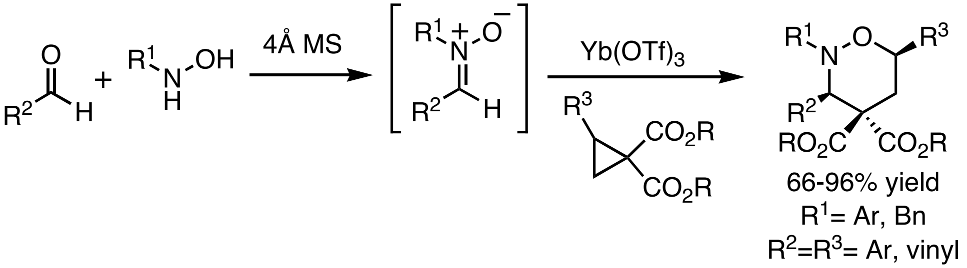
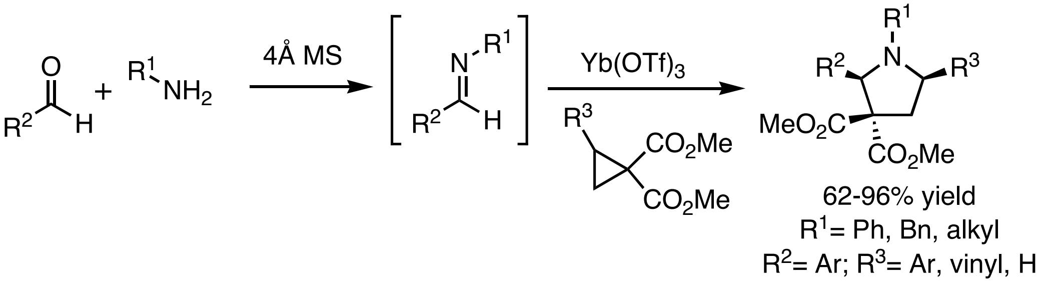
# Homo 3+2 cycloadditions using cyclopropanes



27-94% yields
$R^1$= Me or H
$R^2$= H, Me, Ph



66-96% yield
$R^1$= Ar, Bn
$R^2$=$R^3$= Ar, vinyl

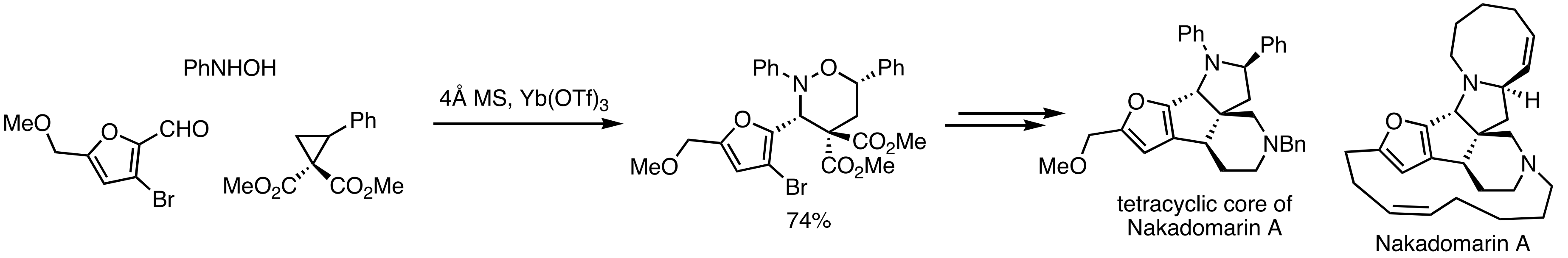


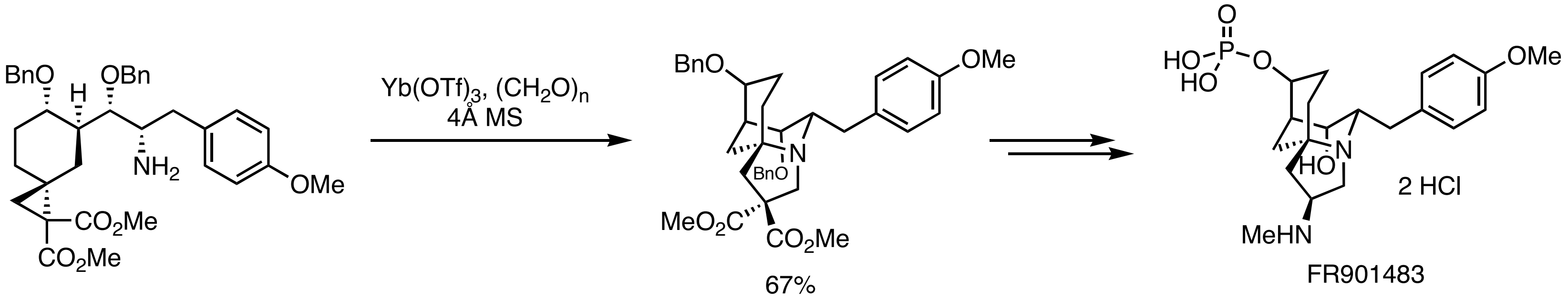
62-96% yield
$R^1$= Ph, Bn, alkyl
$R^2$= Ar; $R^3$= Ar, vinyl, H

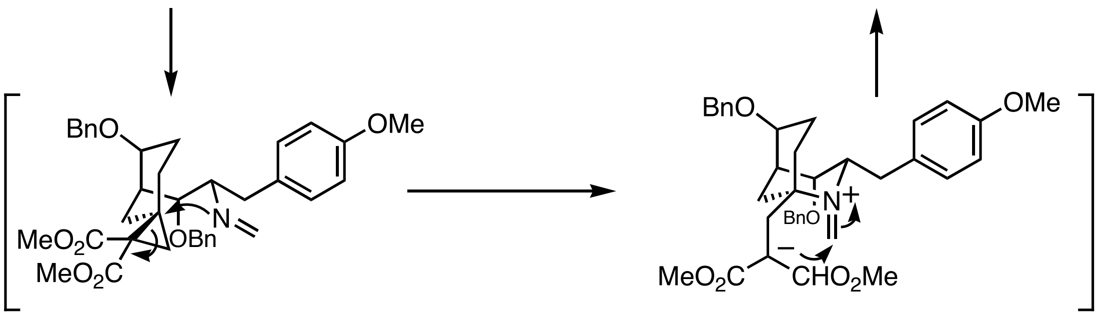
- Overall reactions provided compounds in high diastereoselectivity
- Other groups have performed reaction asymmetrically using chiral ligands

Harrington, P.; Kerr, M. *Tetrahedron Lett.* **1997**, *38*, 5949.
Kerr, M.; Keddy, R. *Tetrahedron Lett.* **1999**, *40*, 5671.
Young, I.; Kerr, M. *Org. Lett.* **2004**, *6*, 139.
Carson, C.; Kerr, M. *J. Org. Chem.* **2005**, *70*, 8242.

# Application of methodology



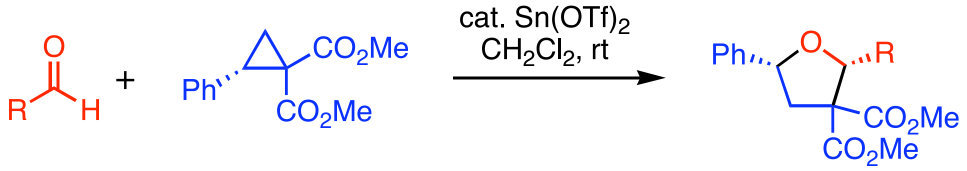




Interestingly, opening of the cyclopropane by the amine was not observed

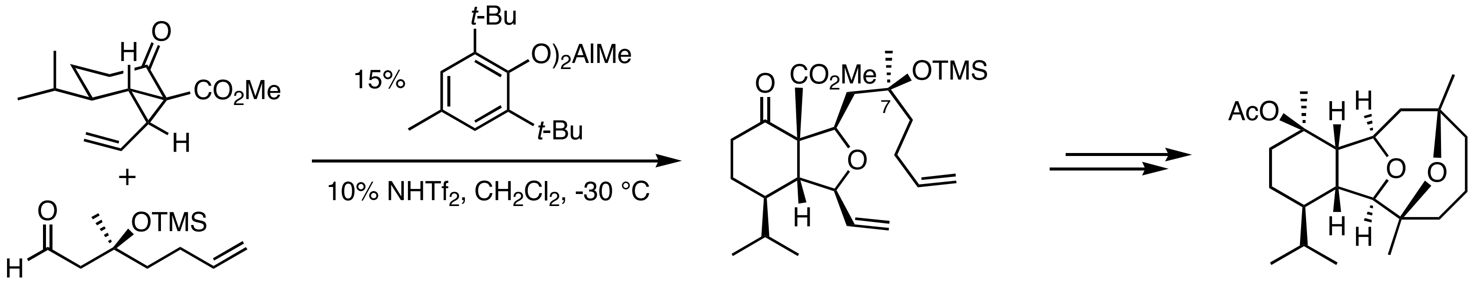
Young, I.; Williams, J.; Kerr, M. *Org. Lett.* **2005**, *7*, 953.
Carson, C.; Kerr, M. *Org. Lett.* **2009**, *11*, 777.

# Johnson's work



R= Ph, 2-furyl, 4-ClPh, alkyl
83-100% yield, 1.6:1 to >100:1 *dr*
88-99% *ee*

- Inspired by seminal work by Kerr, Johnson applied methodology to aldehydes
- Reaction occurs with inversion of stereochemistry at cyclopropane



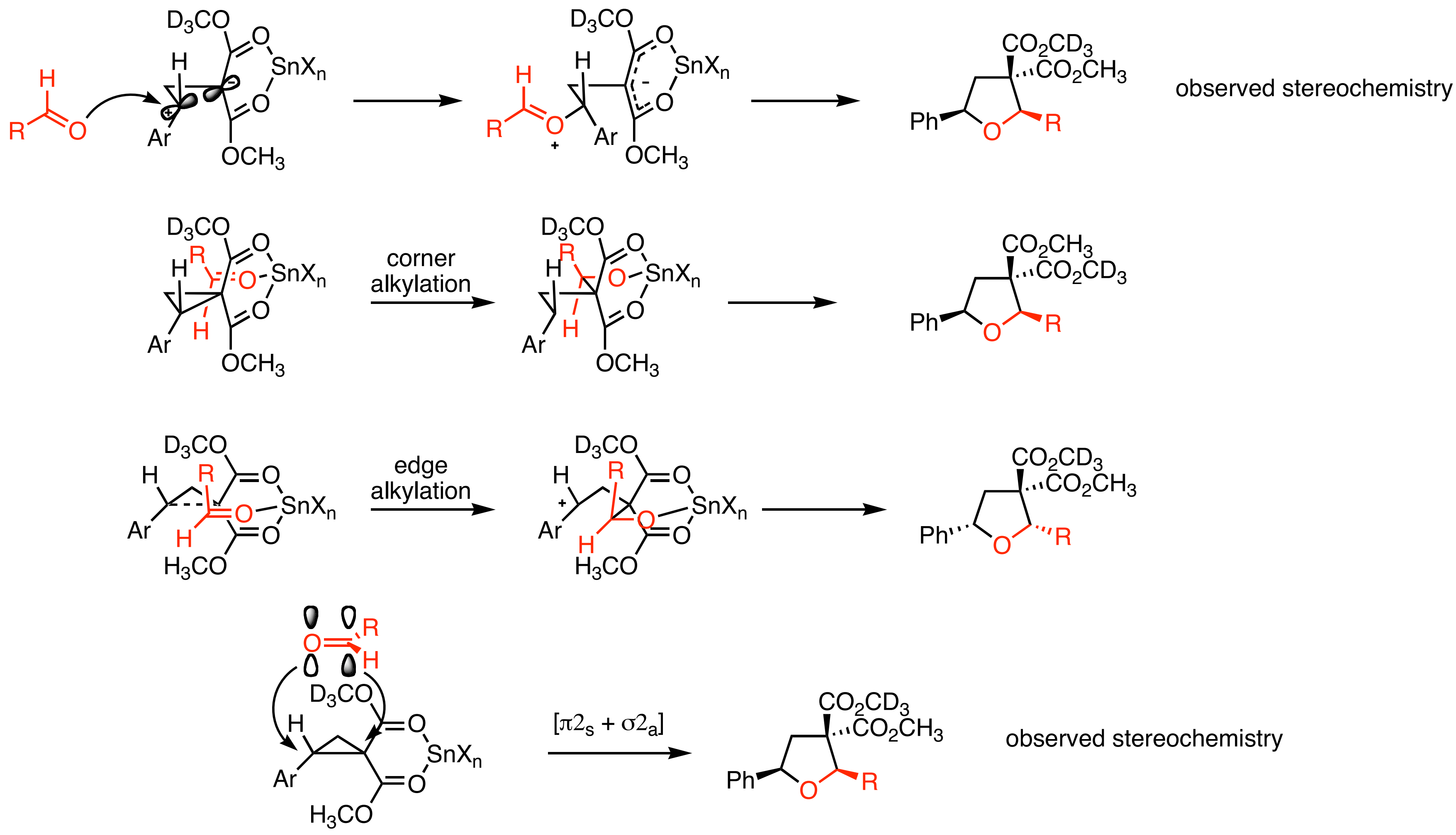
3 equiv.

76%
11:1:0.6 *dr*
(desired: epi C-7: trans furan)

(+)-polyanthellin A

Pohlhaus, P.; Sanders, S.; Parsons, A.; Li, W.; Johnson, J. *J. Am. Chem. Soc.* **2008**, *130*, 8642.
Campbell, M.; Johnson, J. *J. Am. Chem. Soc.* **2009**, *131*, 10370.

# Johnson’s work



observed stereochemistry

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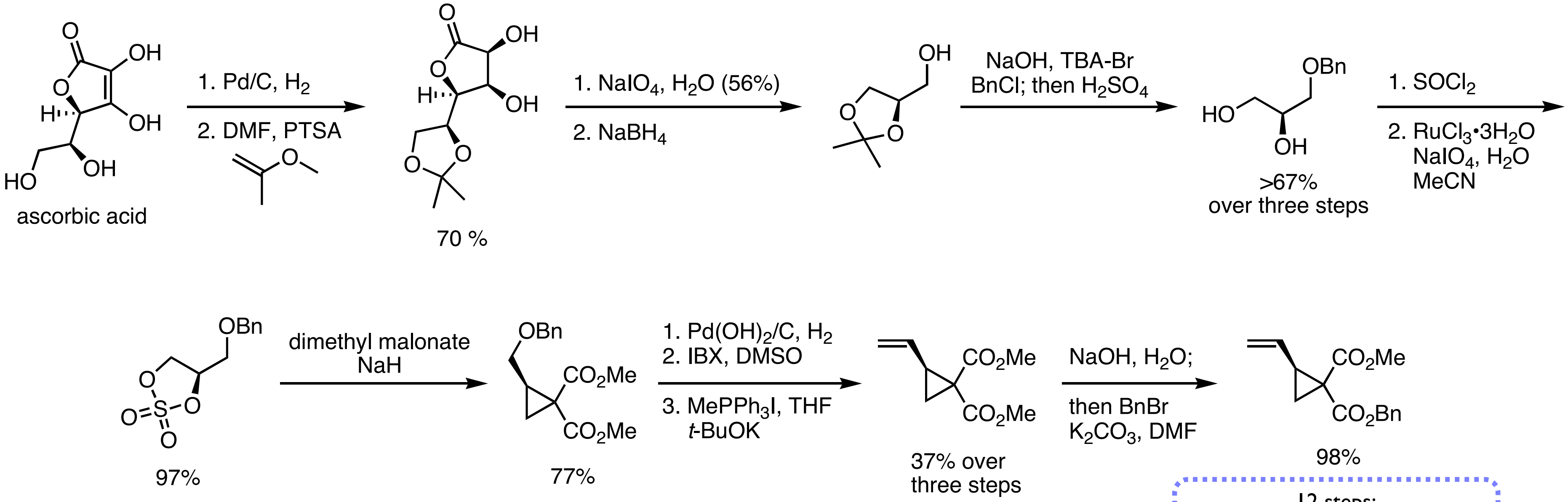
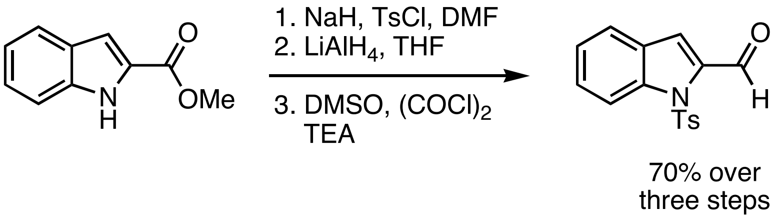
Pohlhaus, P.; Sanders, S.; Parsons, A.; Li, W.; Johnson, J. *J. Am. Chem. Soc.* **2008**, *130*, 8642.

# Preparation of Starting Materials



12 steps;
overall 13% from ascorbic acid



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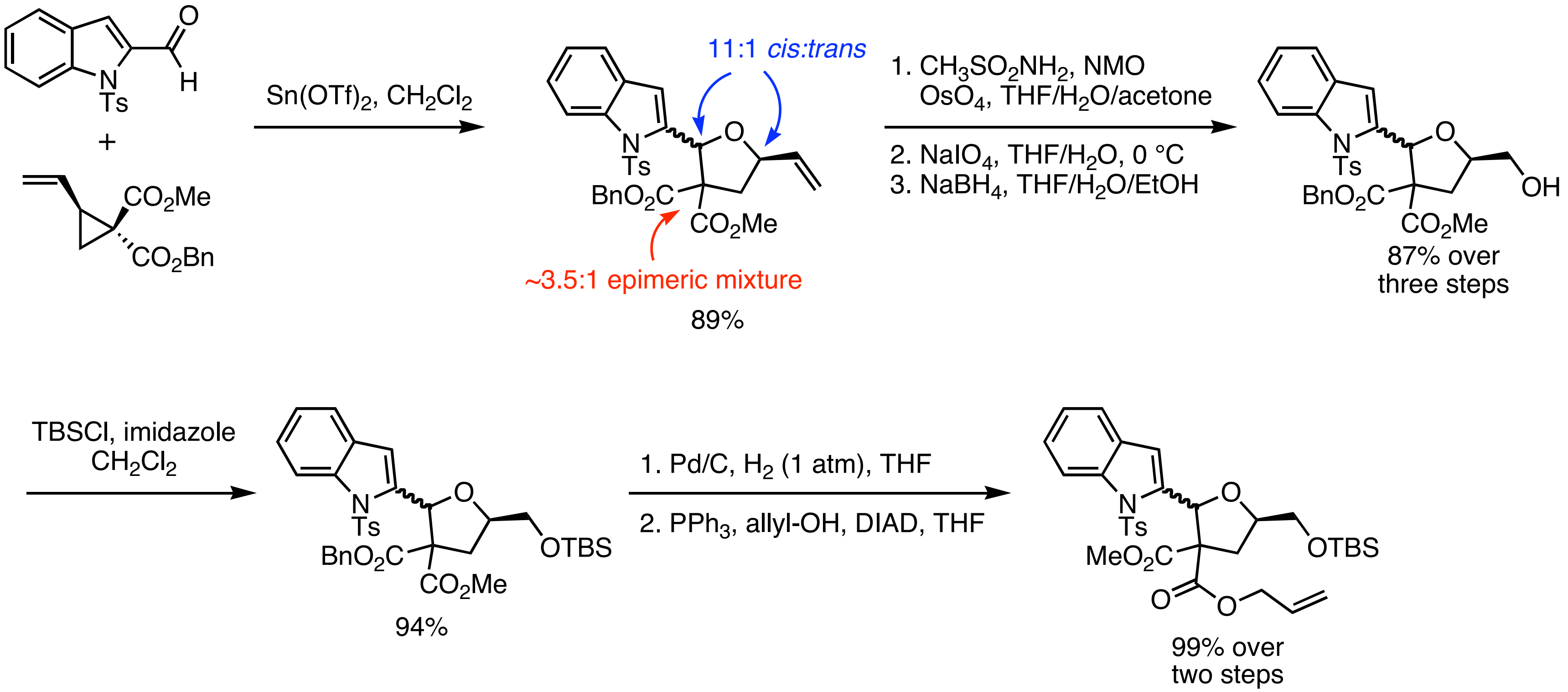
Burgess, K.; Ke, C.-Y. *Synthesis* **1996**, *1996*, 1463.
Carson, C. A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6560.

# Total synthesis of Isatisine A



- Cycloaddition is unsuccessful when cyclopropane has pendant hydroxyl group
  - Authors speculate necessity of π-donor for cycloaddition

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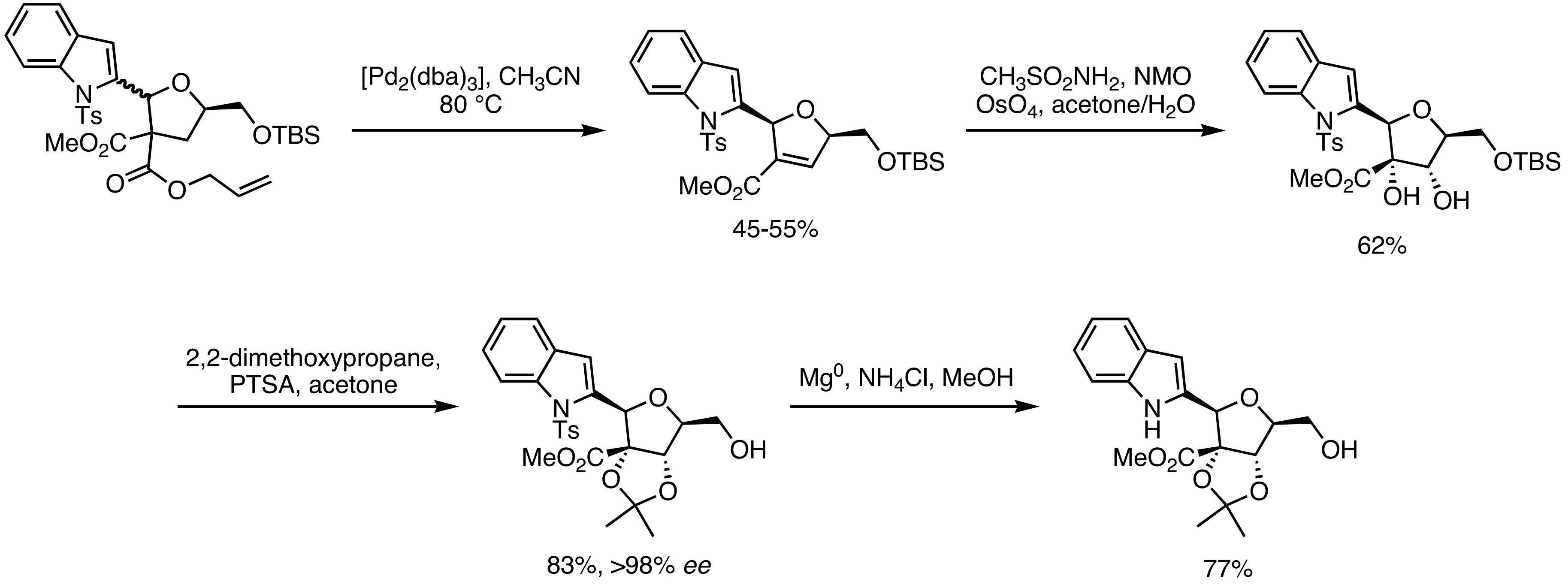

- Dehydrocarboxylation reaction additionally affords single diastereomer

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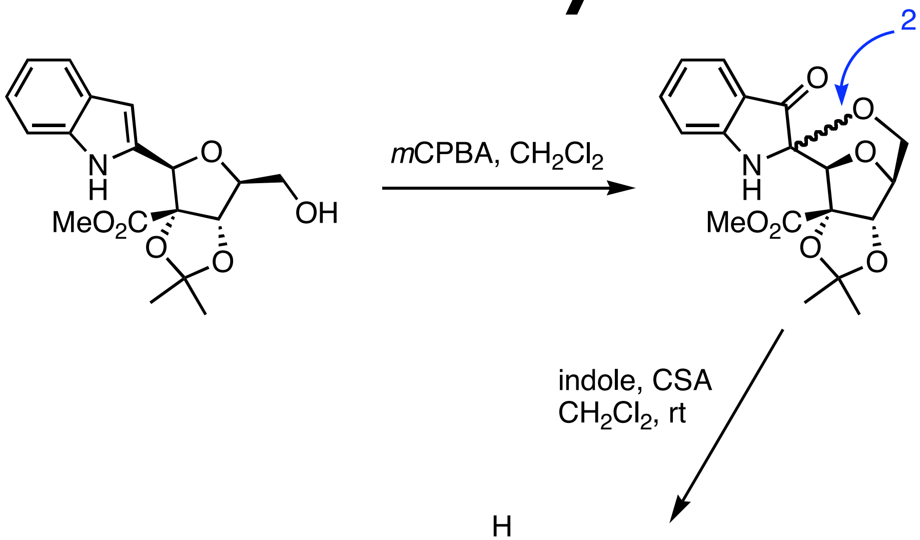
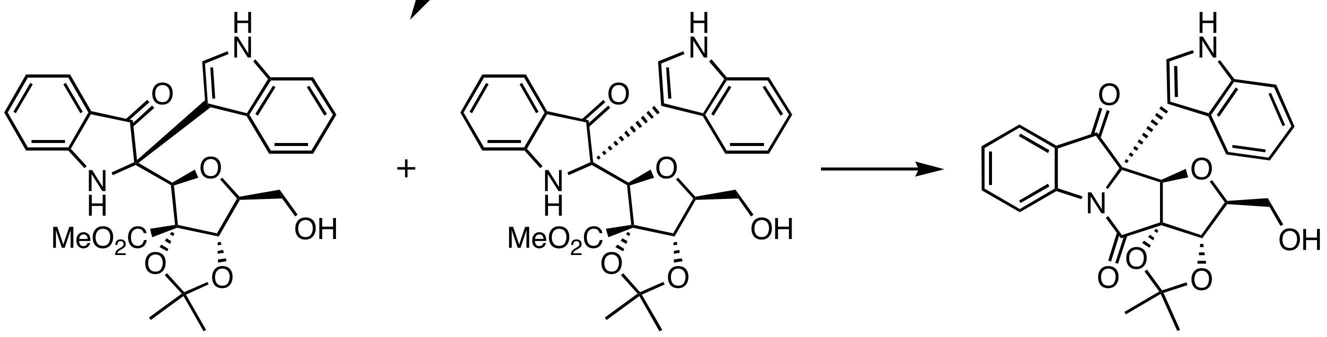


- Inconsequential epimeric mixture
- Indole alkylation occurs through acyl iminium
- Reversible alkylation provides 3:1 mixture of diastereomers
- Eventually cyclization occurs in competition with acid mediated decomposition



| **time** | | **relative product ratios** | |
|---|---|---|---|
| 4.5 h | 2.3 | 1 | 0 |
| 14 h | 0.33 | 1 | 0 |
| 24 h | 0.38 | 1 | 0.5 |
| 42 h | 0.44 | 1 | 6.3 (50% isolated yield, 98% *ee*) |

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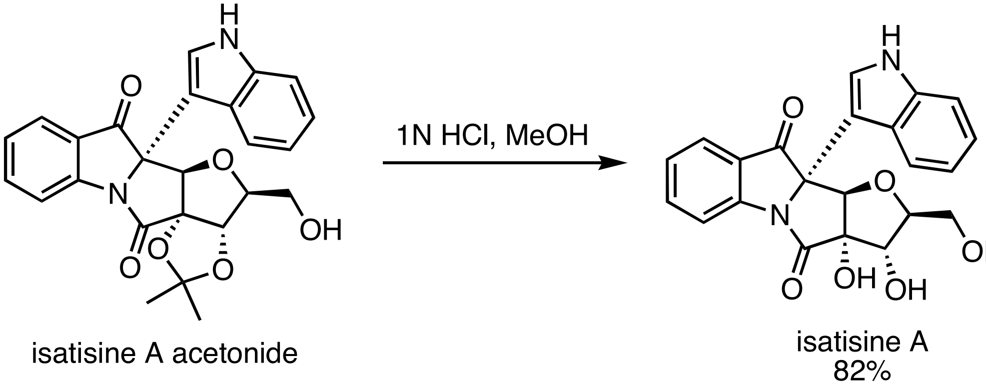
# Total synthesis of Isatisine A



Isolated acetonide product $[\alpha]^{14}_{D}$ = -283 (c= 0.46, MeOH)

synthetic acetonide product $[\alpha]^{25}_{D}$ = +271 (c= 1.6, MeOH)

- Isolated natural product is antipodal to synthesized product
- Starting from opposite cyclopropane enantiomer would provide natural enantiomer
- Total synthesis completed in 14 steps and 5.8% overall yield from cyclopropane

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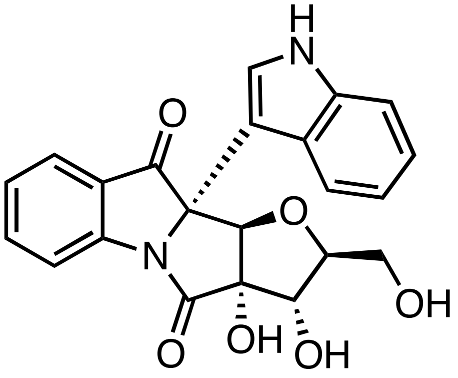
# Conclusions

- Completed the total synthesis of Isatisine A in 14 steps and 5.8% overall yield from cyclopropane
- Established the absolute stereochemistry
- Successful application of synthetic methodology
  - Methodology provides access to substituted tetrahydrofurans and pyrrolidines asymmetrically
- Work including synthesis and biological evaluation of natural product derivatives is ongoing



(+)-isatisine A