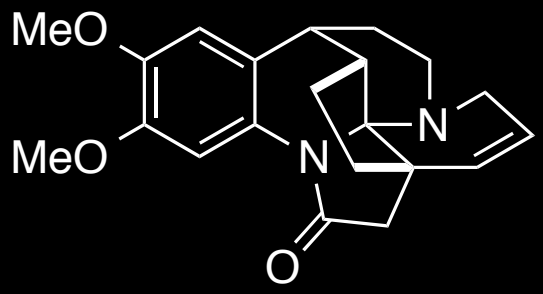
Total Synthesis of (-)-Isoschizogamine

Miura, Y.; Hayashi, N.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2012**, ASAP

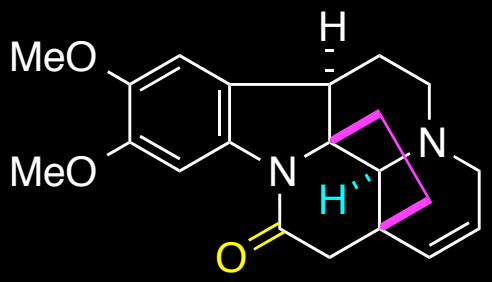


isoschizogamine

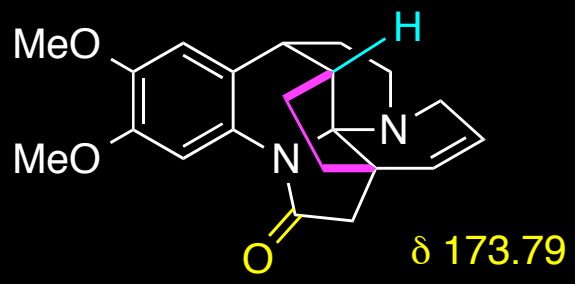
Eric E. Buck
Current Literature
August 25, 2012

Isolation and Background

- Isoschizogamine was isolated in 1963 from *Schizozygia caffaeoides*.[1]
- In Kenya this plant is used to treat several ailments:[2]
  - Leaf extracts are used to treat ringworm
  - The steam from boiling the leaves is used to soothe inflamed eyes.
  - Sores on the skin were treated with root extracts and coconut oil.
- In 1998 the structure was revised based on NMR-spectroscopy.[3]



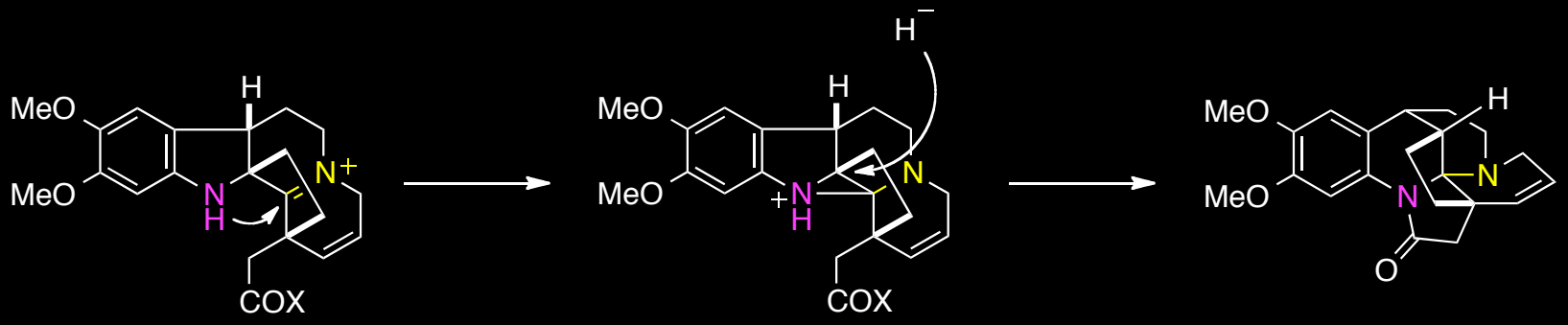
original structure



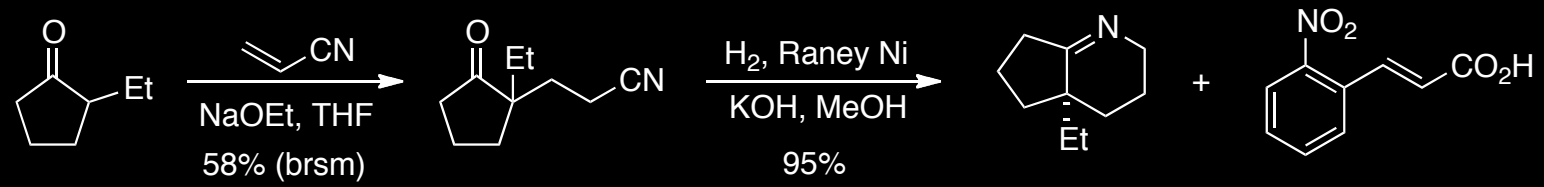
isoschizogamine

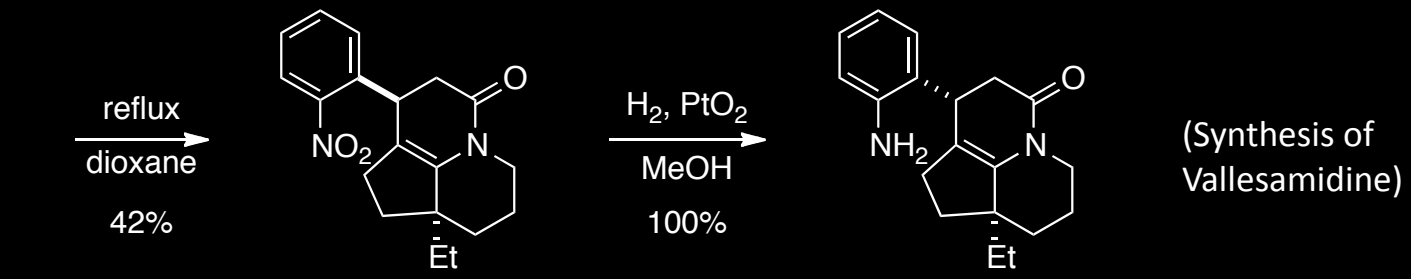
[1] Renner, U.; Kernweis, P. *Experientia*. **1963**, 19, 244. [2] Kariba, R. M.; Siboe, G. M.; Dossaji, S. F. *J Ethnopharmacol*. **2001**, 74, 41-44. [3] Hájíček, J.; Buděšínský, M. *Tetrahedron Lett.* **1998**, 39, 505.

Heathcock: First synthesis (racemic)



isoschizogamine





(Synthesis of Vallesamidine)

[1] Hubbs, J. L.; Heathcock, C. H. *Org Lett*. **1999**, 1, 1315-1317. [2] Dickman, D. A.; Heathcock, C. H. *J. Am. Chem. Soc*. **1989**, 111, 1528-1530.

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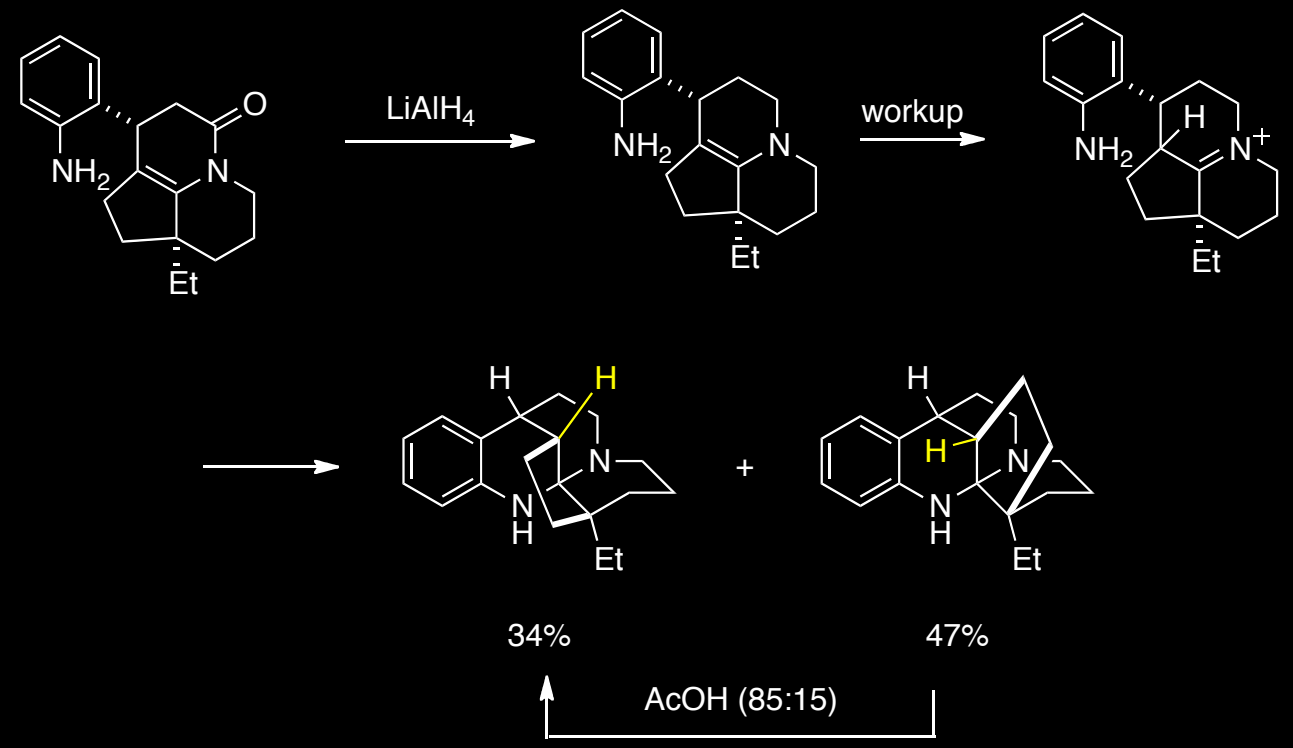

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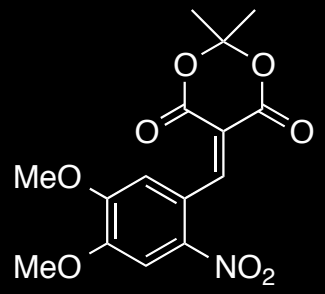
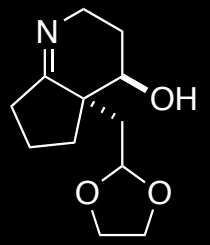


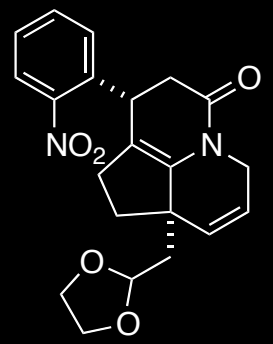
Note: acid, acid chloride, azide, anhydride, ester all failed

+



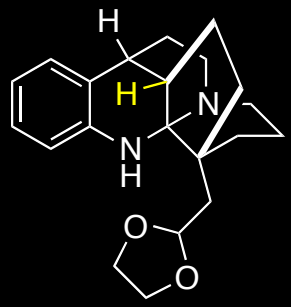
4-steps
Note: i. KHMDS, 2. Bu_2BOTf
3. 3-azidopropanal

1. -40 °C
2. PhMe, reflux, 74%
3. Martin's sulfurane, 74%



88:12 dr

1. $NaBH_4$, $Cu(acac)_2$
2. $LiAlH_4$; workup



Note: AcOH (rt) gives 3:7 dr

1. AcOH, H_2O,reflux
2. PDC, CH_2Cl_2
27% 4 steps

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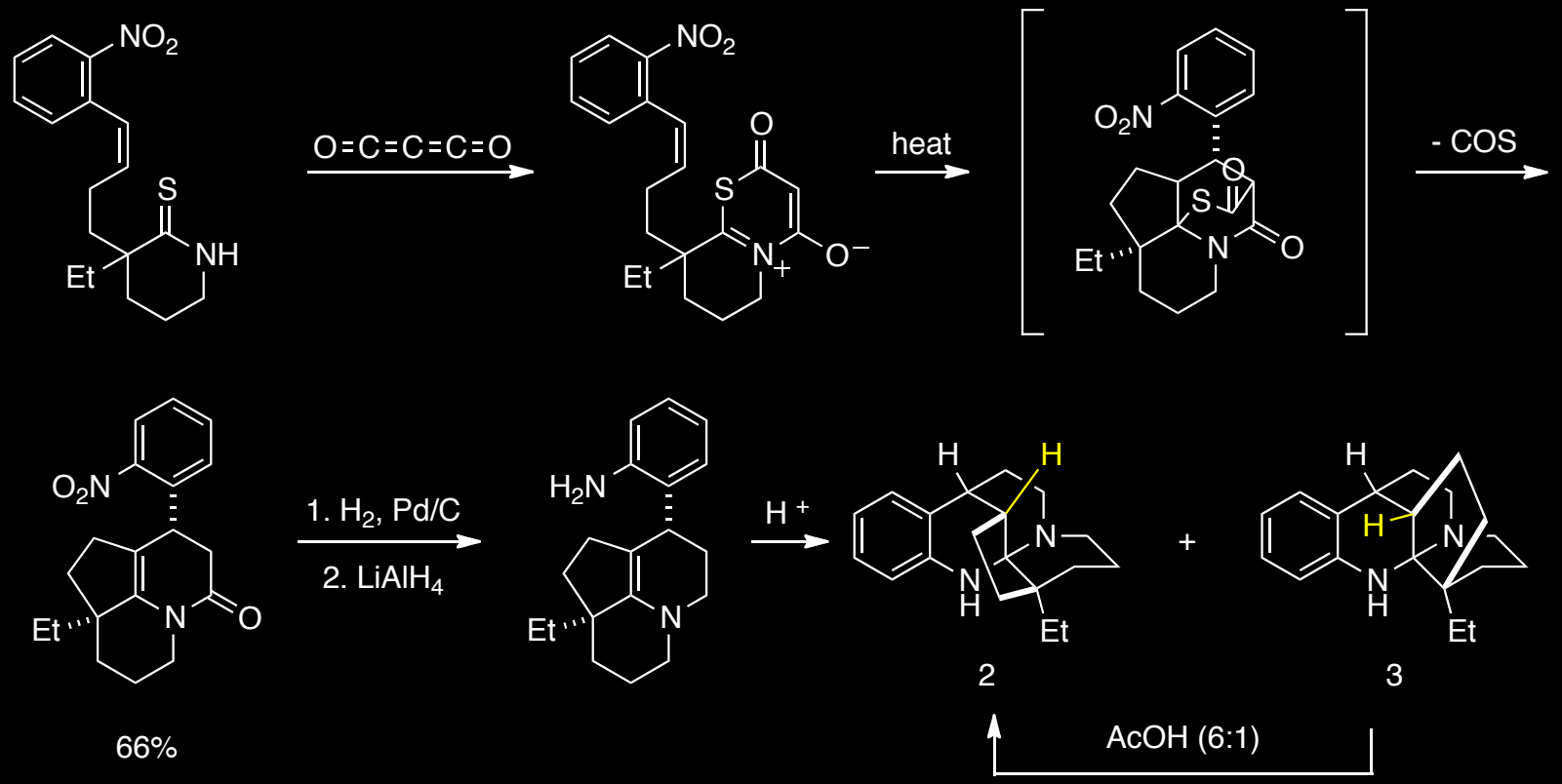
8 steps, 7% overall yield from ketone

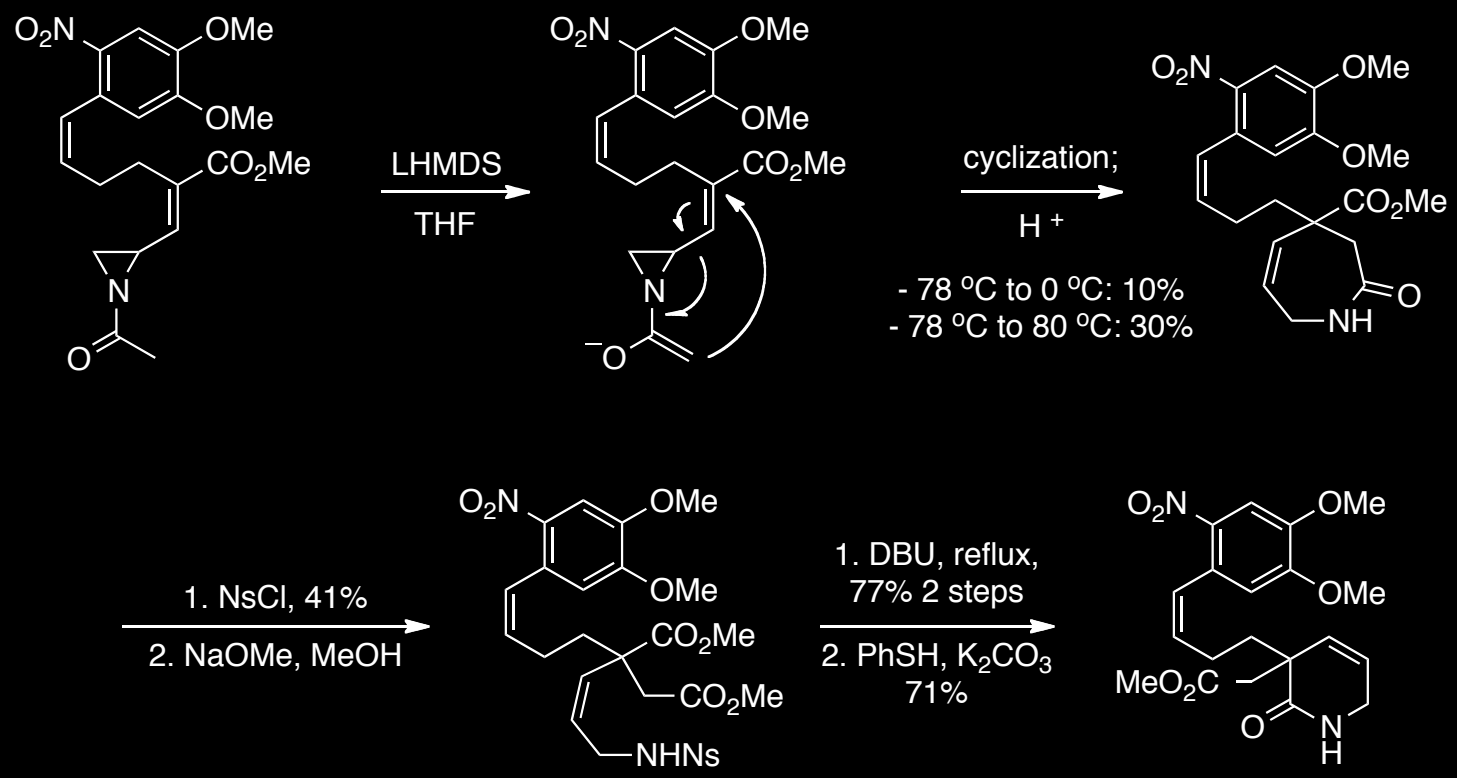
[1] Hubbs, J. L.; Heathcock, C. H. *Org Lett*. **1999**, 1, 1315-1317. [2] Dickman, D. A.; Heathcock, C. H. *J. Am. Chem. Soc*. **1989**, 111, 1528-1530.

Padwa's Synthetic Studies



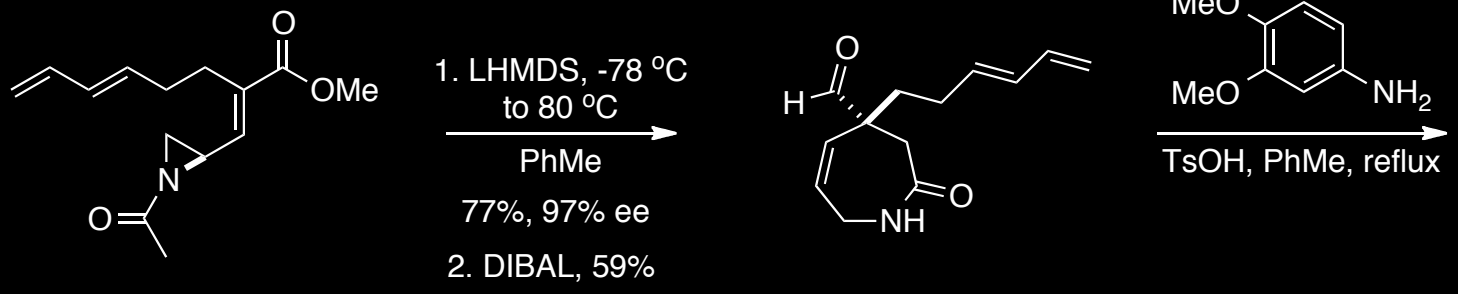
Padwa, A.; Flick, A.; Lee, H. *Org Lett*. **2005**, 7, 2925-2928.

Padwa's Synthetic Studies



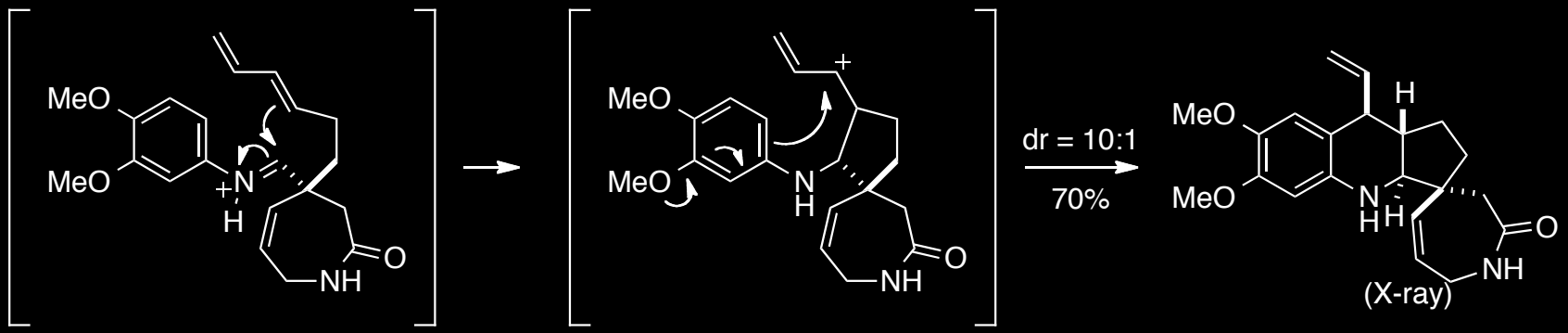
[1] Padwa, A.; Bobek, D. R.; Mmutlane, E. M. *ARKIVOC*. **2010**, 7-21. [2] Linström, U. M.; Somfai, P.; *Chem. Eur. J.* **2001**, 7, 94-98

Magomedov: Explorations Towards Asymmetric Synthesis



(Note: Precursor Aldehyde Synthesized from serine)

Note: DIBAL reduction was better than $LiBHEt_3$ (diene reduction), and $LiAlH_4$/Swern (Low yield)



[1] Zhou, J.; Magomedov, N. A. *J. Org. Chem.* **2007**, 72, 3808-3815. [2] Kato, S.; Harada, H.; Morie, T. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 3219-3225. [3] Linström, U. M.; Somfai, P.; *Chem. Eur. J.* **2001**, 7, 94-98

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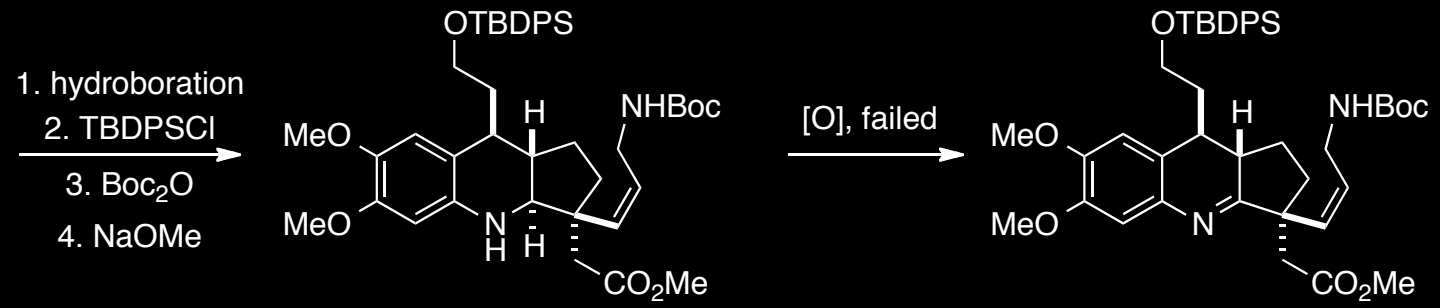
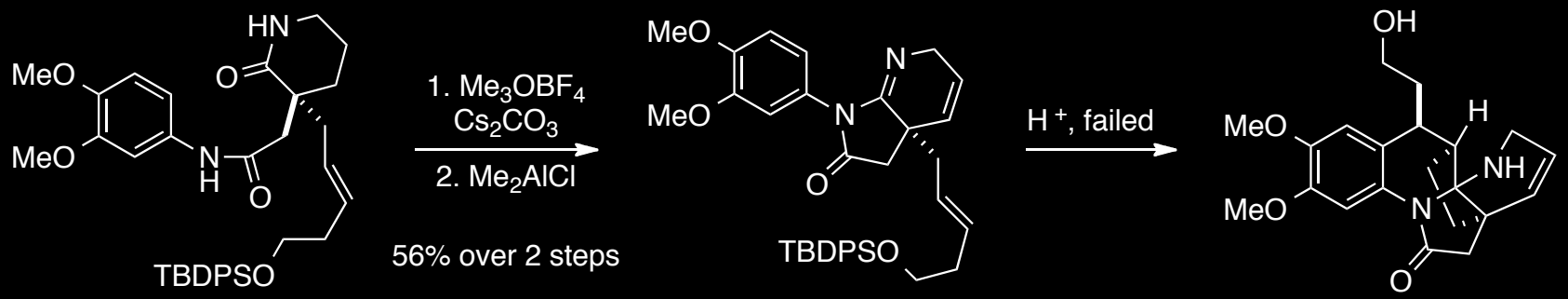
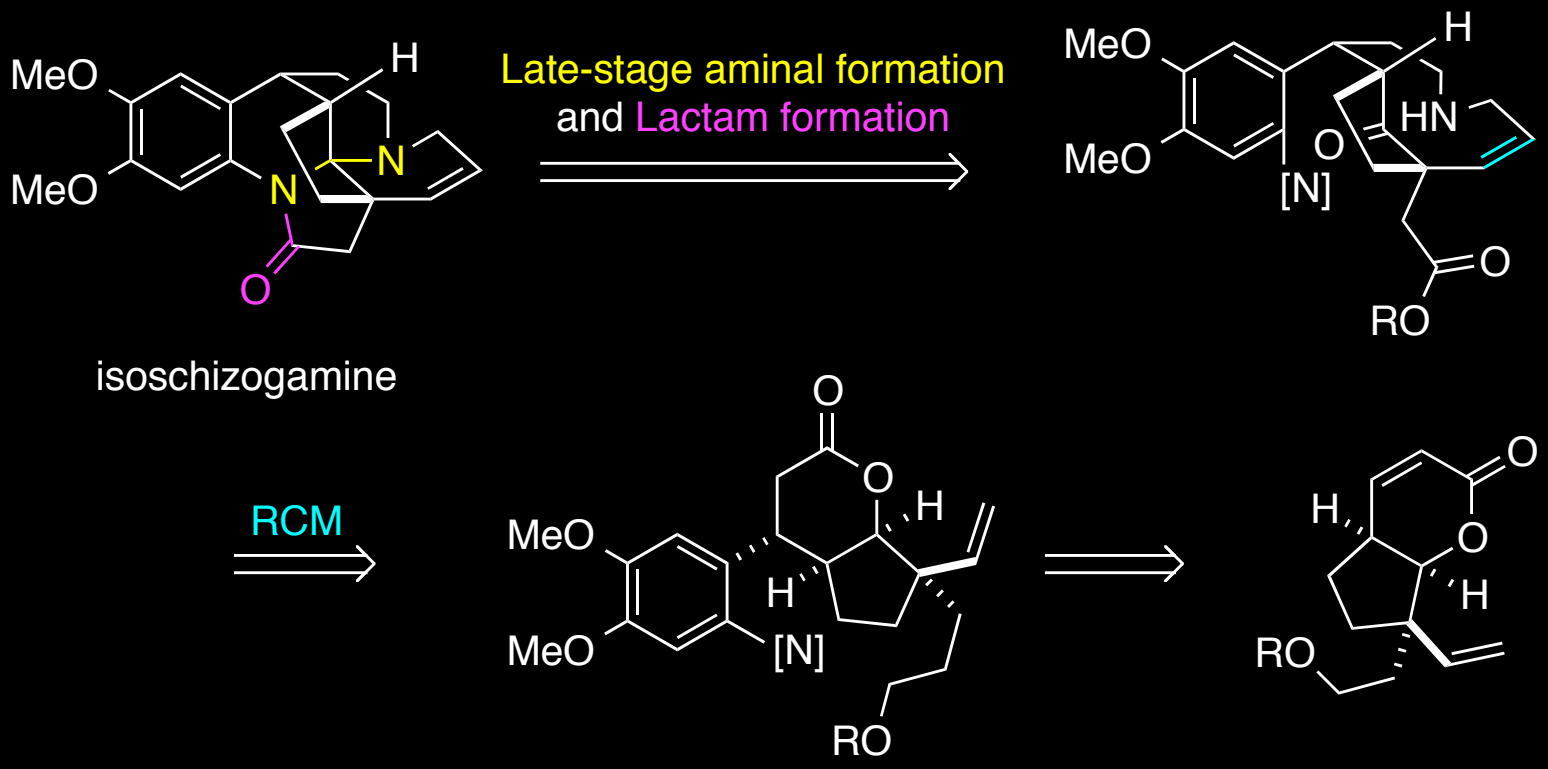




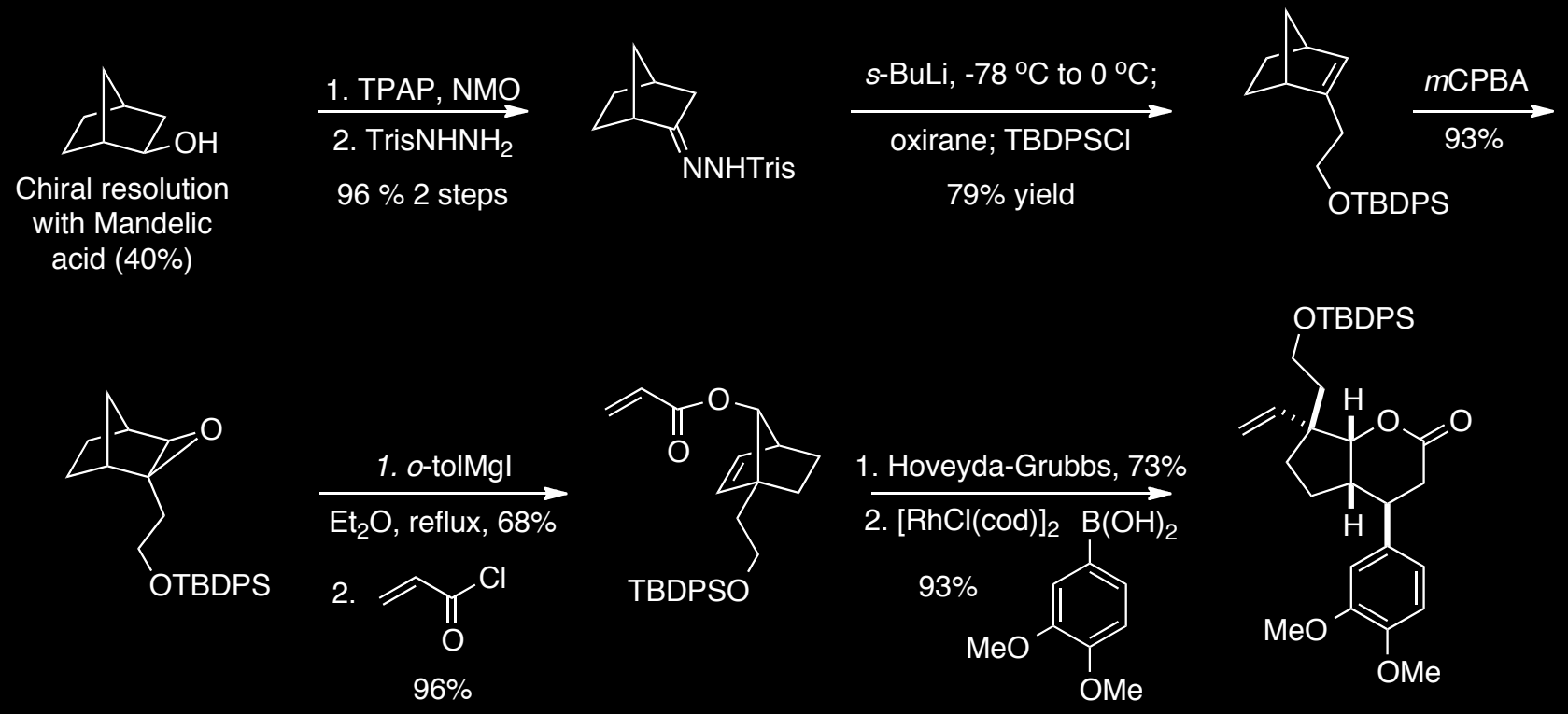
[1] Zhou, J.; Magomedov, N. A. *J. Org. Chem.* **2007**, 72, 3808-3815. [2] Kato, S.; Harada, H.; Morie, T. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 3219-3225. [3] Linström, U. M.; Somfai, P.; *Chem. Eur. J.* **2001**, 7, 94-98

Title Paper: Retrosynthesis



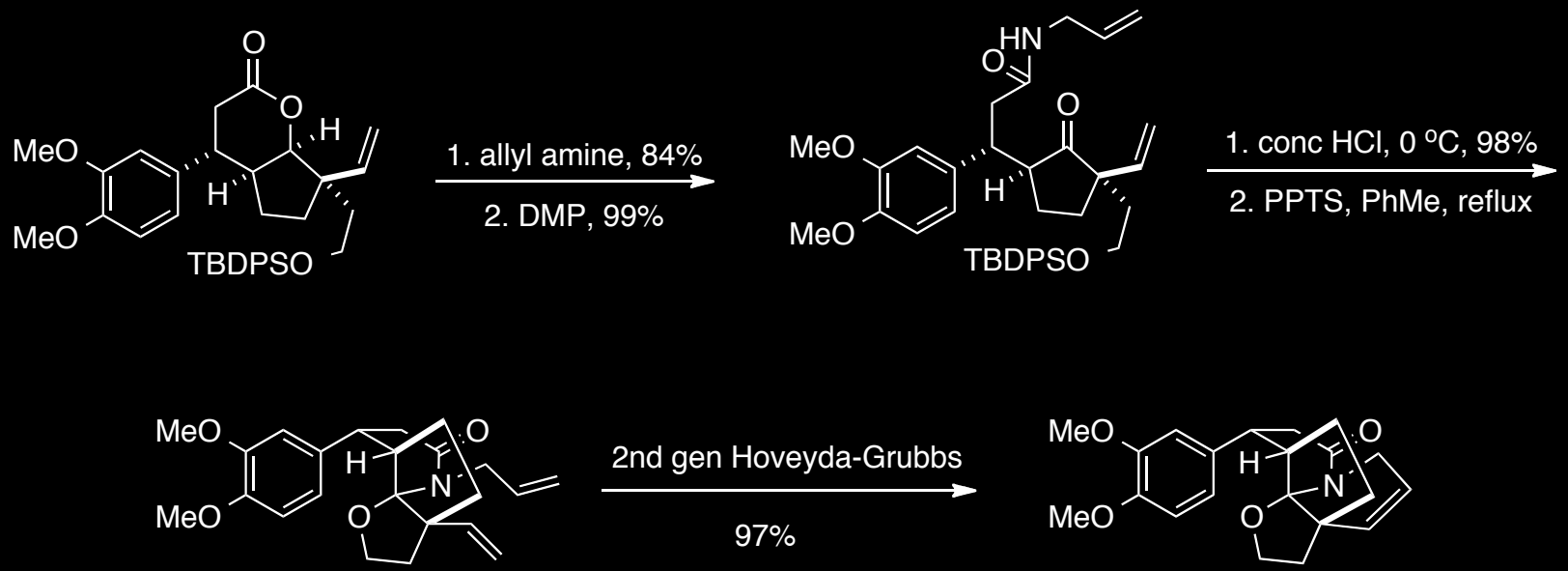
[1] Miura, Y.; Hayashi, N.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc*. **2012**, ASAP

Title Paper: Installation of Quaternary Center



[1] Miura, Y.; Hayashi, N.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc*. **2012**, ASAP

Title Paper: Ring Construction



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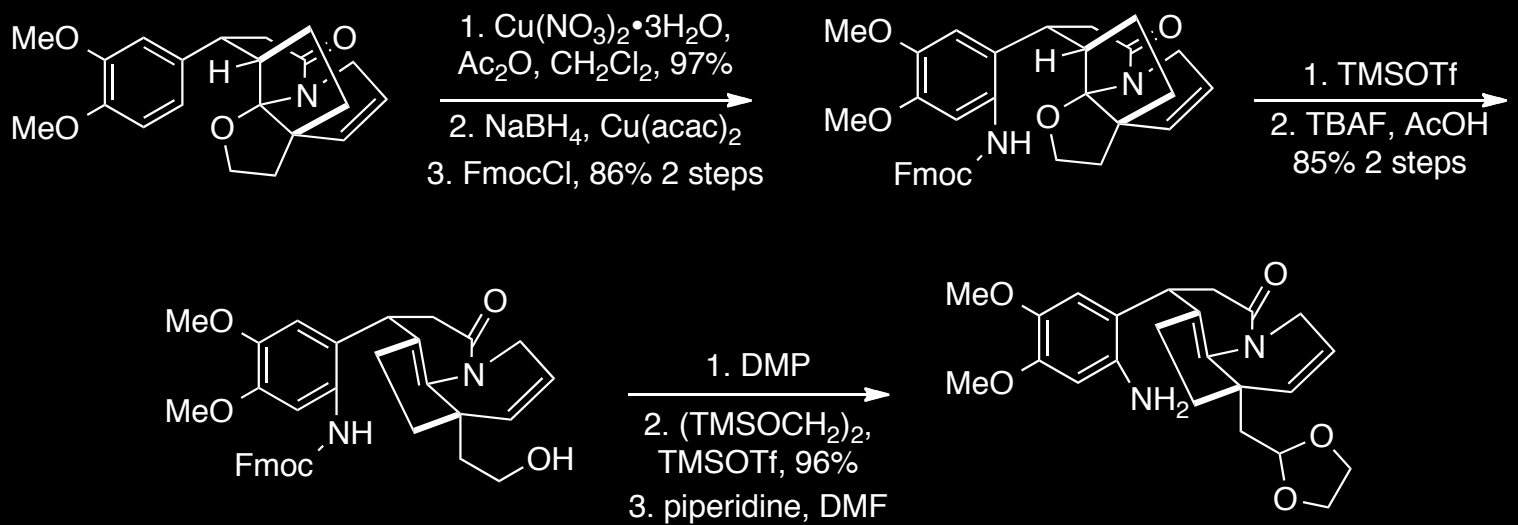
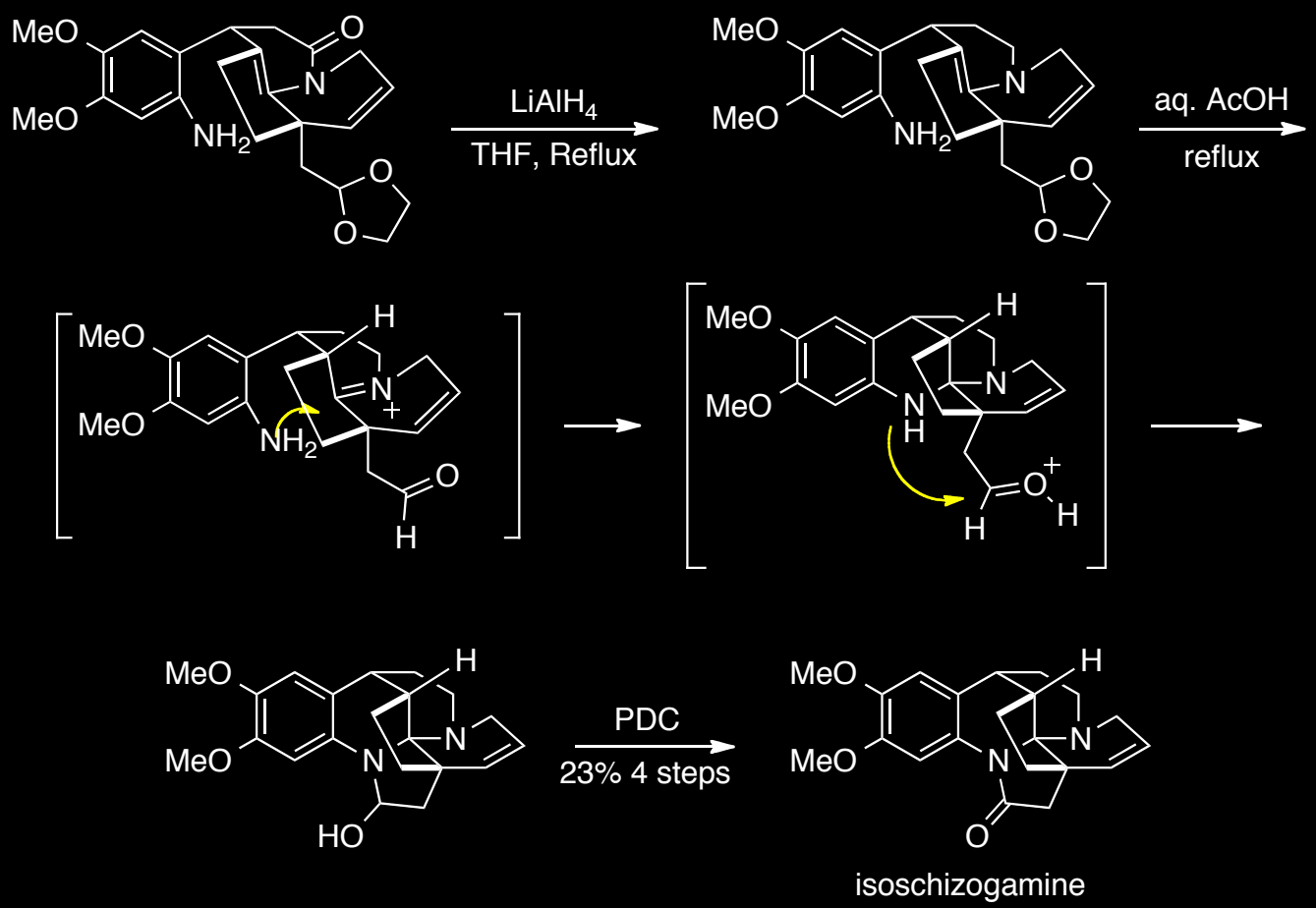


[1] Miura, Y.; Hayashi, N.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc*. **2012**, ASAP

Title Paper: End Game



[1] Miura, Y.; Hayashi, N.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc*. **2012**, ASAP

Final thoughts

• The synthesis of 3.7 mg of (-)-Isoschizogamine was achieved in 25 steps in 1.5 % yield.

• Norbornene rearrangement to install quaternary center, substrate controlled 1,4-addition, and cleaver use of pendent oxygen.

• Heathock: First synthesis (racemic). Laid the grown work for aminal formation .

• Padwa: 1,4-dipolar cycloaddition and aza-claisen rearrangement.

• Magomedov: Asymmetric aza-claisen rearrangement and imine formation to cation cascade.

[1] Miura, Y.; Hayashi, N.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc*. **2012**, ASAP