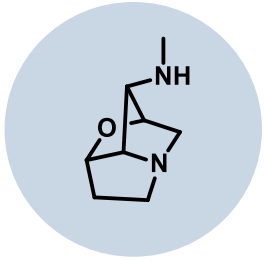
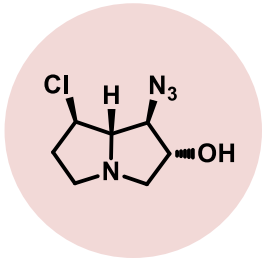
Total Synthesis of Loline Alkaloids





Cakmak, M.; Mayer, P.; Trauner, D. *Nature Chemistry,* **2011**, *3*, 543–545.

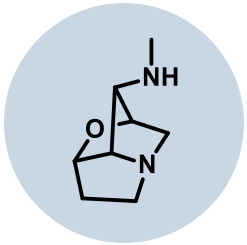
Yongzhao Yan

Current lit.

2012.5.8

History of Loline Alkaloids

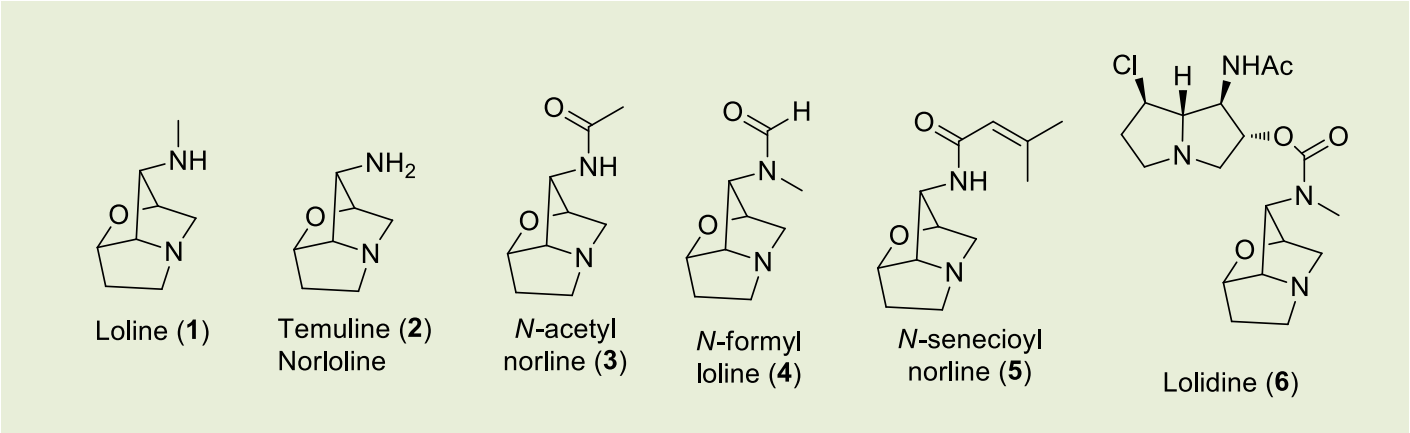
- First isolated from *Lolium temulentum* L. in 1892.[2]
- Hofmeister identified a compound with the elemental formula $C_7H_{12}N_2O$.[2]
- Yunusov and Akramov (1966) suggested an *endo*-*N*-methyl-1-aminopyrrolizidine structure with a C2–O–C7 bridge.[3]



- Aasen and Culvenor (1969) confirmed this assignment by IR and proton NMR spectroscopy studies.[4]
- The absolute configuration of loline was finally established by anomalous dispersion X-ray diffraction analysis (Bates and Morehead, 1972).[5]

1. Picture source: Prof. Otto Wilhelm Thomé *Flora von Deutschland, Österreich und der Schweiz* 1885, Gera, Germany.
2. Hofmeister, F. *Arch. Exp. Pathol. Pharmakol*. **1892**. *30*, 203–230.
3. Akramov, S.T.; Yunusov, S.Y. *Chem. Nat. Compd*. **1966**. *1*, 203–209.
4. Aasen, A.J.; Culvenor, C.C.J. *Aust. J. Chem*. **1969**. *22*, 2021–2024.
5. Bates, R.B.; Morehead, S.R. *Tetrahedron Lett*. **1972**. *13*, 1629–1630.

Members of Loline Alkaloids



- **2** was isolated *Lolium temulentum* L. and named norloline.[1,2]
- *N*-acetyl norline **3** was found in Festua arundinancea together with some other loline members.[3]
- **4** was the most abundant loline alkaloid.[4]
- **5** was found in urine of horses, which enjoy grazing on tall fescue grass.[4,5]
- **6** was proposed on MS data, but the compound could not be further evaluated due to scarcity of material.[6]

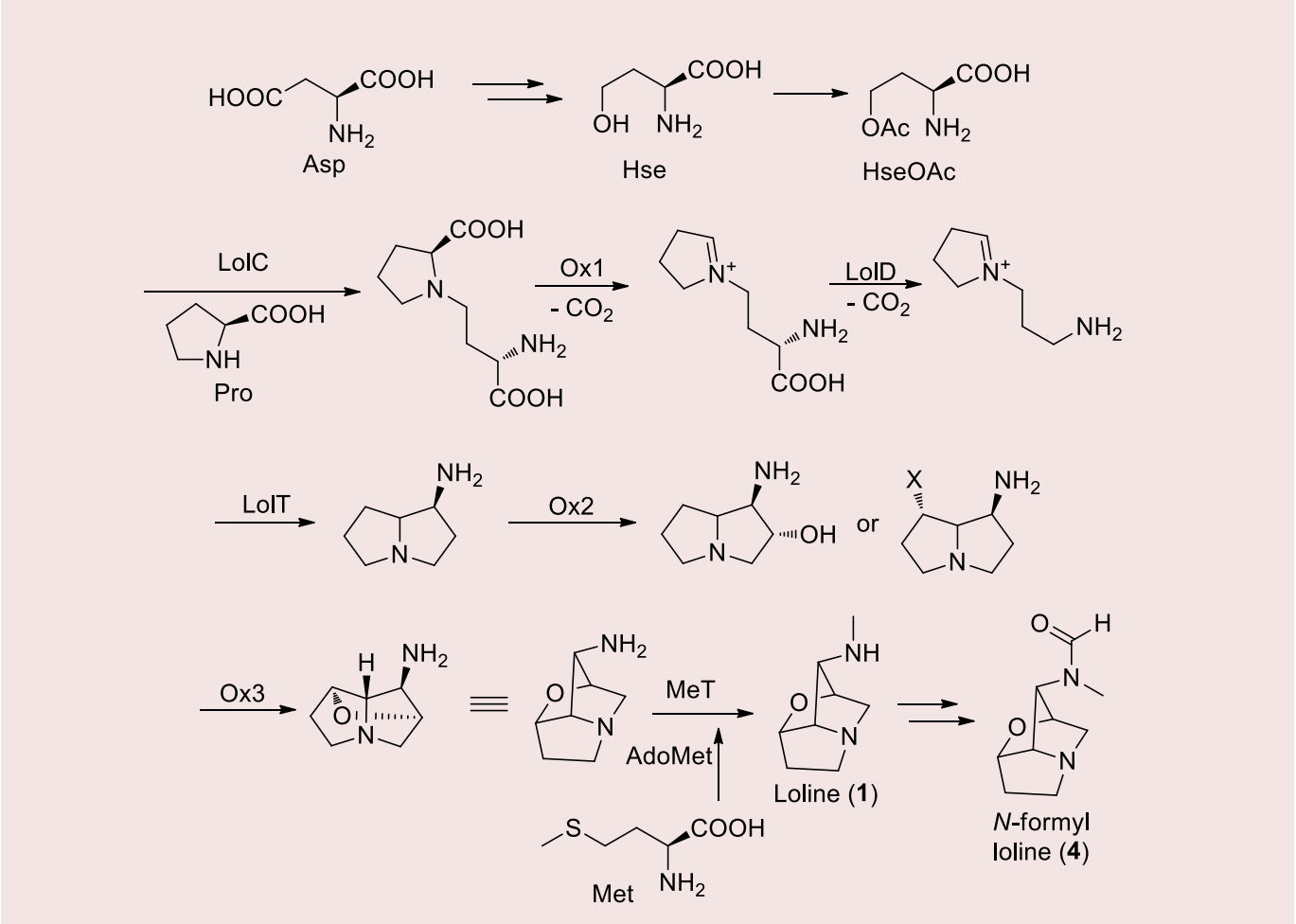
1. Hofmeister, F. *Arch. Exp. Pathol. Pharmakol*. **1892**. *30*, 203–230.
2. Dannhardt, G.; Steindl, *L. Planta Med.* **1985**. *51*, 212–214.
3. Robbins, J. D.; Sweeny, J. G.; Wilkinson, S. R.; Burdick, D. *J. Agric. Food Chem.* **1972**. *20*, 1040–1043.
4. Schardl, C. L.; Grossman, R. B.; Nagabhyru, P.; Faulkner, J. R.; Mallik, U. P. *Phytochemistry* **2007**. *8*, 980–996.
5. Takeda, A.; Suzuki, E.; Kamei, K.; Nakata, H. *Chem. Pharm. Bull.* **1991**. 39, 964–968.
6. Batirov, E. K.; Malikov, V. M.; Yunusov, S. Y. *Chem. Nat. Prod.* **1977**, *12*, 52–54.

Biological activities of Loline Alkaloids

- Loline alkaloids are produced by **endophytic fungi**.[1]
- These alkaloids provided **chemoprotection** to their host plant.[1]
- Toxic to **insects** and **aphids** but have few negative effects towards mammals.[1]
- Early studies of loline alkaloid effects on mammalian systems employed crude or partially purified tall fescue extracts that probably had significant amounts of **ergot alkaloids**.[1]
- Derivatives of lolines with acyl chain lengths of 8-12 were cytotoxic to tumors and in brine-shrimp assays.[2]
- Considering the abundance of lolines in some grass-endophyte symbiota, possible additional effects on plant stress and physiology are worth further investigation.[1]

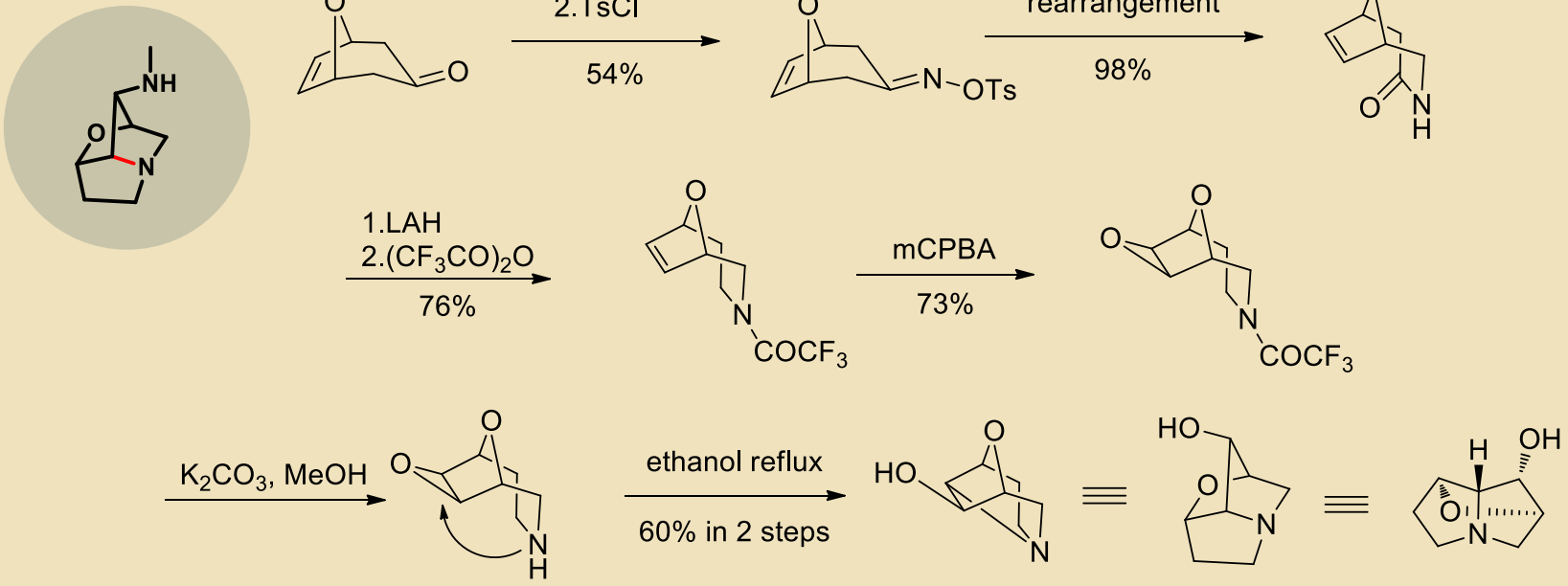
1. Schardl, C. L.; Grossman, R. B.; Nagabhyru, P.; Faulkner, J. R.; Mallik, U. P. *Phytochemistry* **2007**. *8*, 980–996.
2. Petroski, R.J.; Powell, R.G.; Sunil, R.; McLaughlin, J.L., *Int. J. Pharmacognosy* **1994**. 32, 409–412.

Biosynthesis of Loline Alkaloids



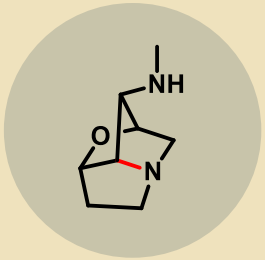
1. Schardl, C. L.; Grossman, R. B.; Nagabhyru, P.; Faulkner, J. R.; Mallik, U. P. *Phytochemistry* **2007**. *8*, 980–996.
2. Blankenship, J.D.; Houseknecht, J.B.; Pal, S.; Bush, L.P.; Grossman, R.B.; Schardl, C.L. *Chembiochem* **2005**. *6*, 1016–1022.
3. Faulkner, J.R.; Hussaini, S.R.; Blankenship, J.D.; Pal, S.; Branan, B.M.; Grossman, R.B.; Schardl, C.L. *Chembiochem* **2006**. *7*, 1078–1088.

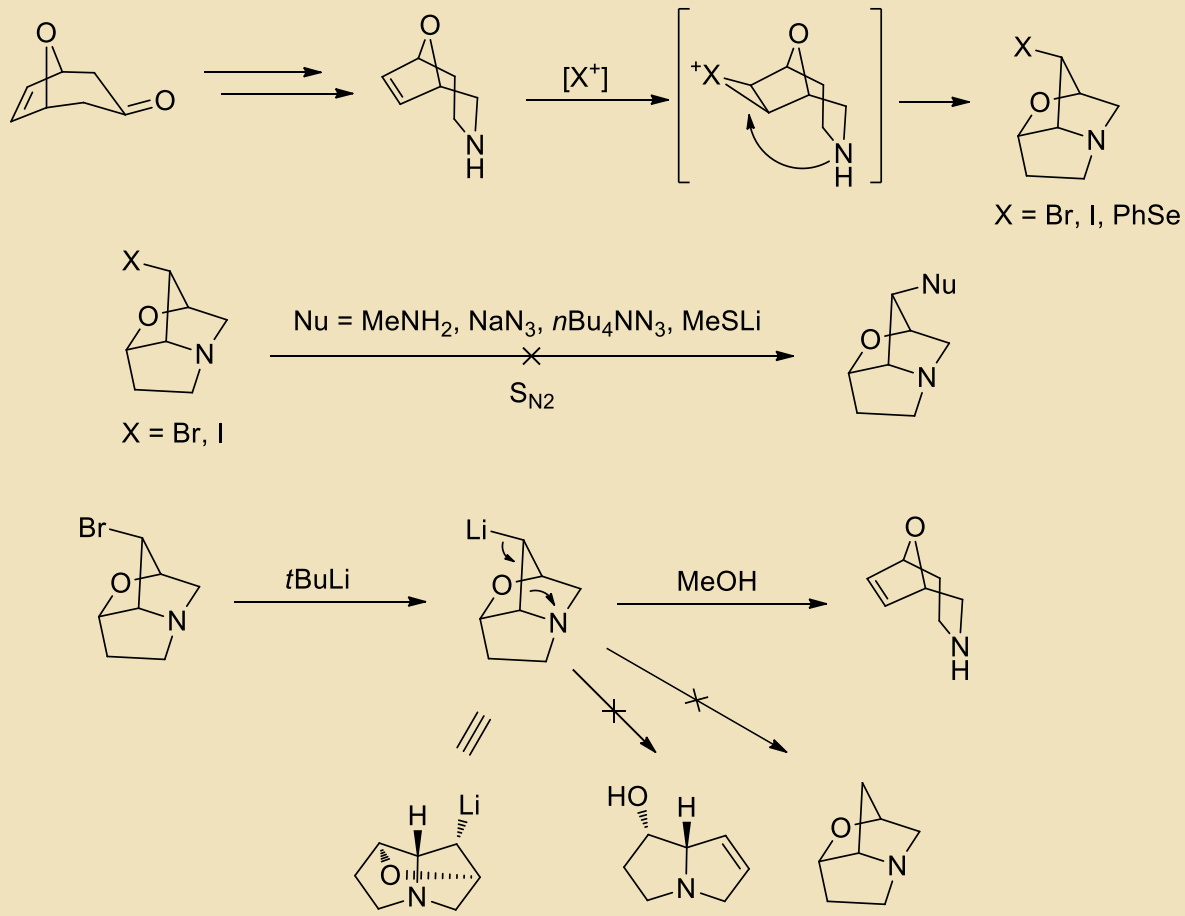
Previous Synthesis of Loline Alkaloids



1. Glass, R. S.; Deardorff, D. R.; Gains, L. H. *Tetrahedron Lett.* **1978**. *19*, 2965–2968.

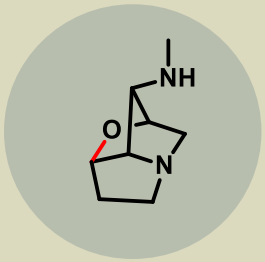
Previous Synthesis of Loline Alkaloids

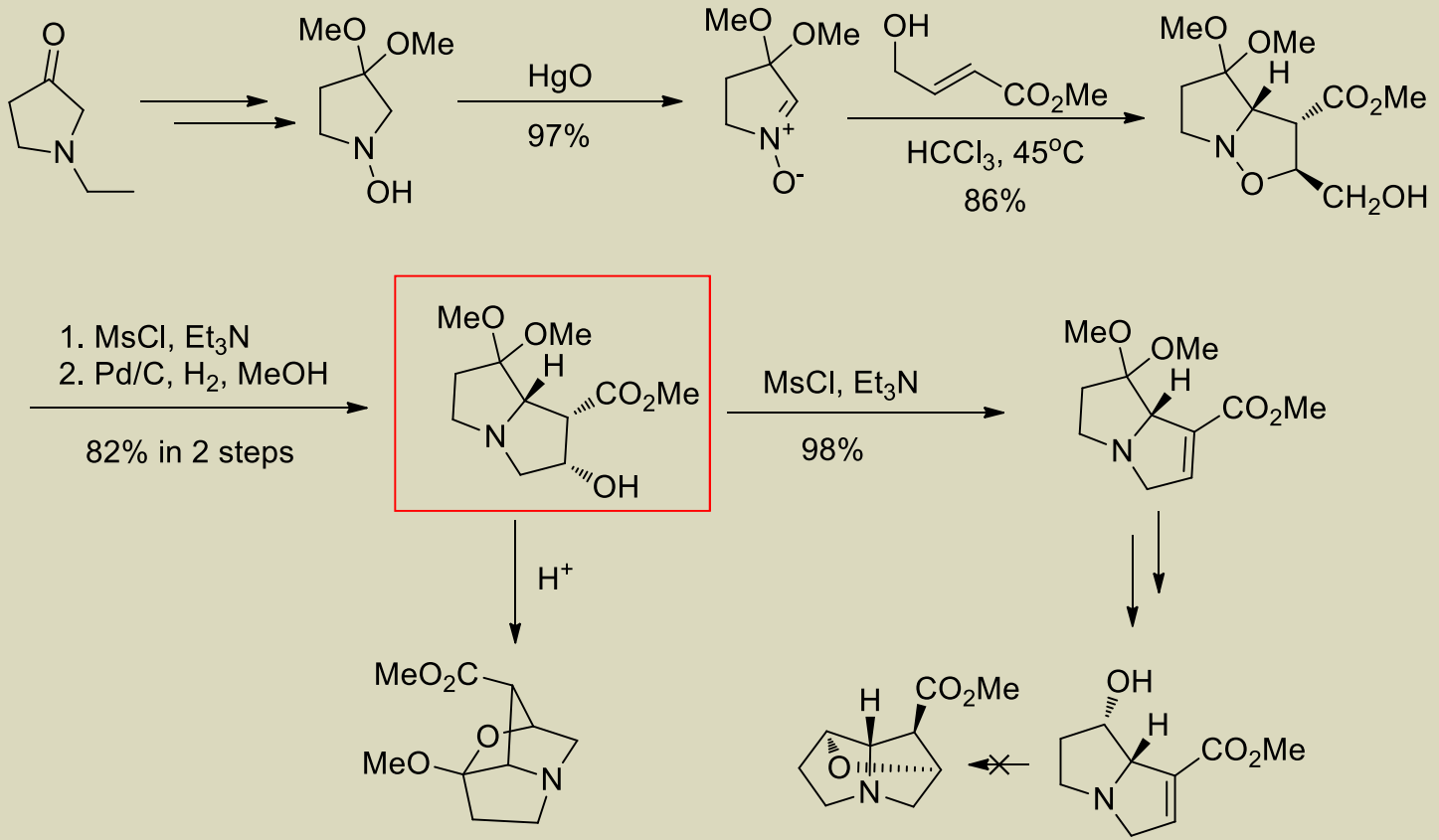




1. Wilson, S. R.; Sawicki, R. A.; Huffman, J. C. *J. Org. Chem*. **1981**. *46*, 3887–3891.

Previous Synthesis of Loline Alkaloids





1. Tufariello, J. J., Meckler, H., Winzenberg, K. *J. Org. Chem*. **1986**. *51*, 3556–3557.

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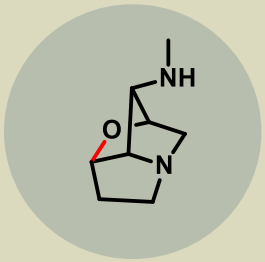

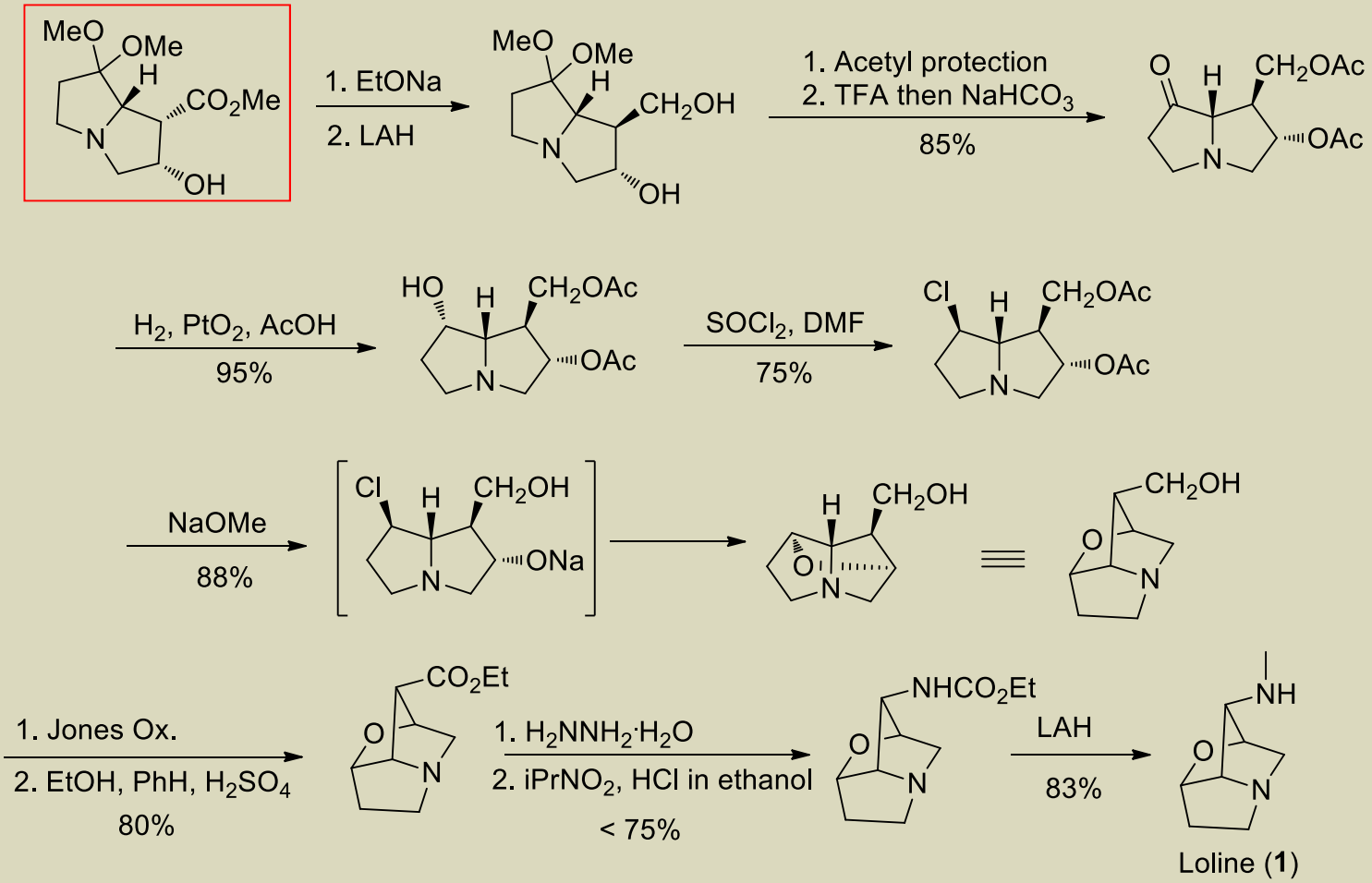

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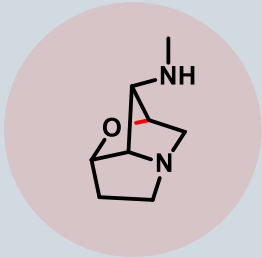
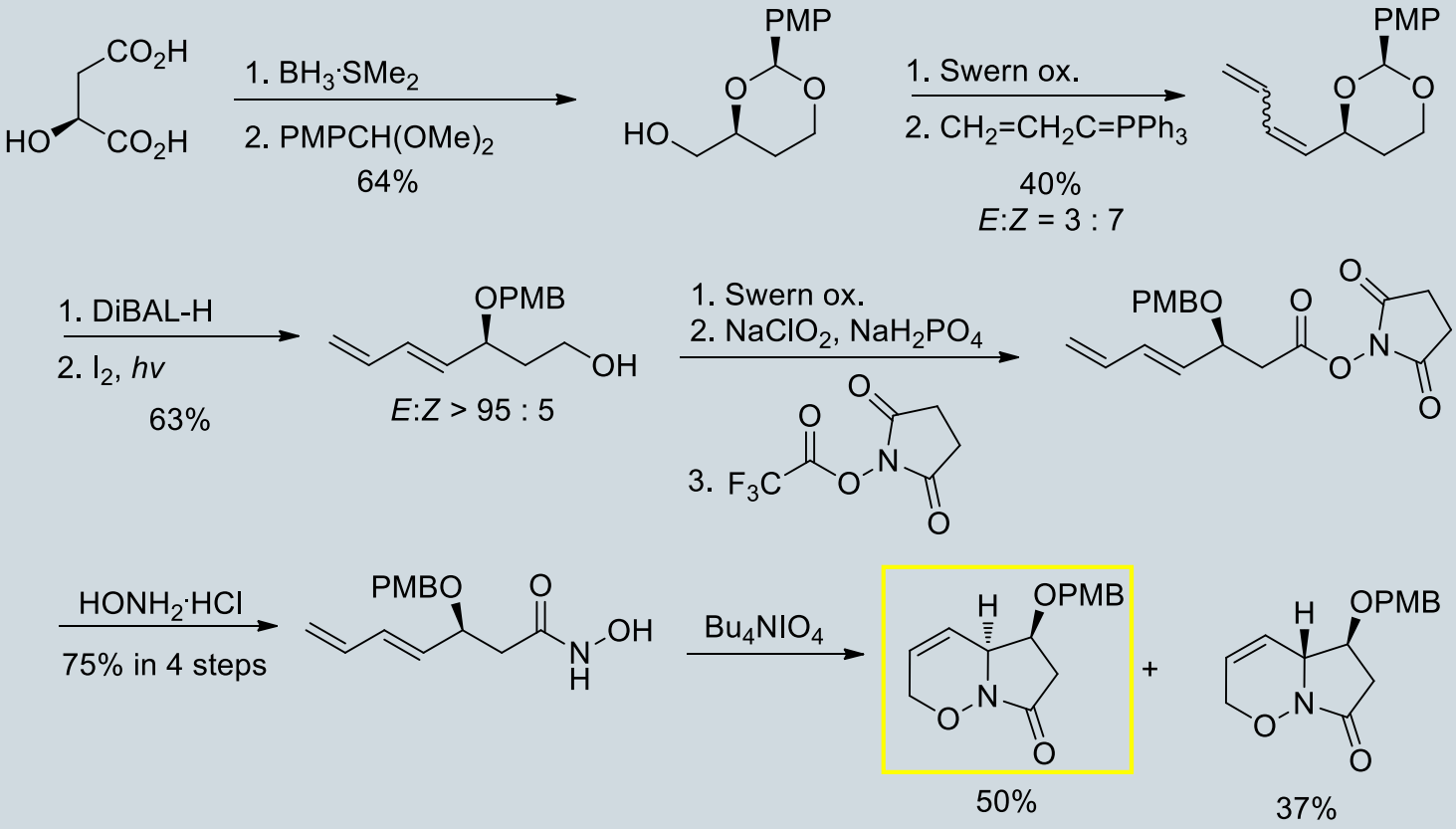
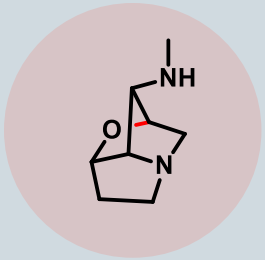
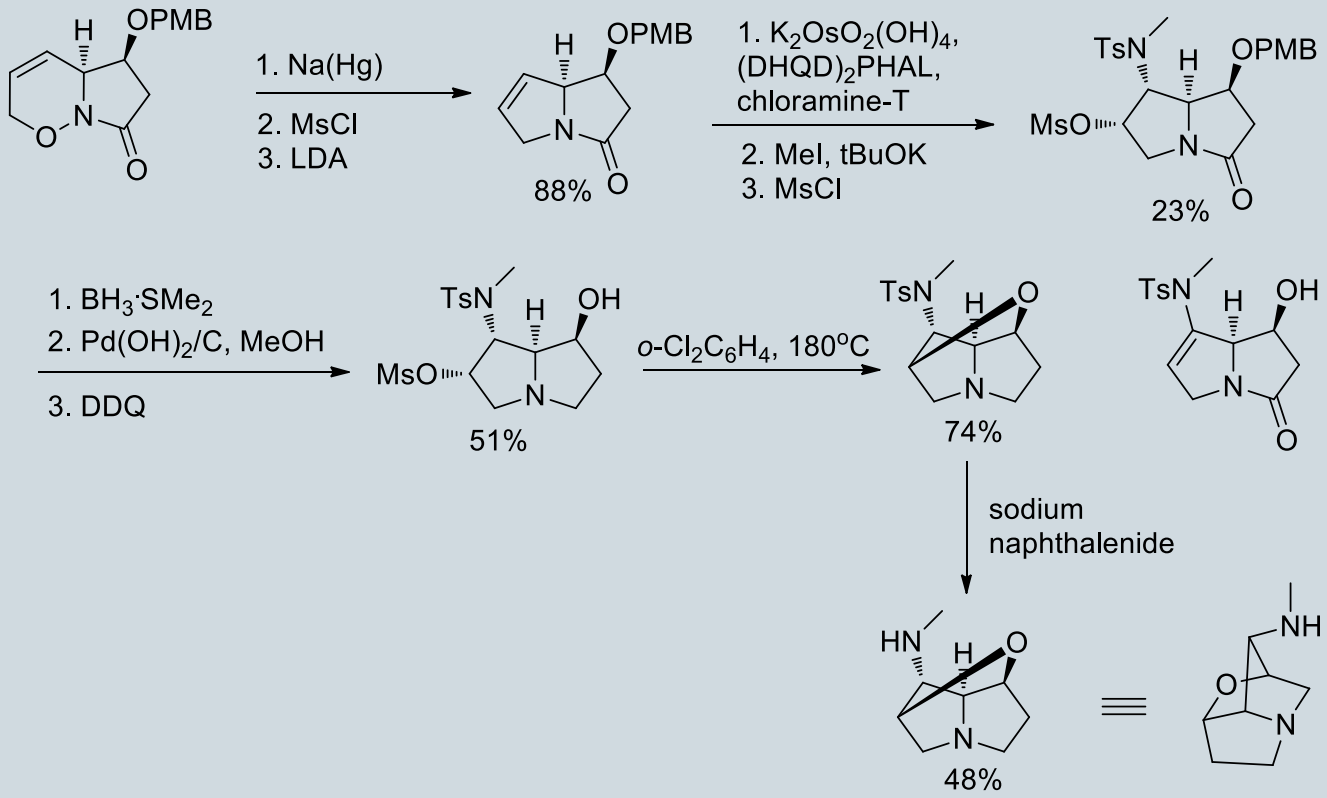




1. Blakemore, P. R.; Schulze, V. K.; White, J. D. *Chem. Commun.* **2000**. 1263–1264.

Previous Synthesis of Loline Alkaloids





1. Blakemore, P. R.; Schulze, V. K.; White, J. D. *Chem. Commun.* **2000**. 1263–1264.

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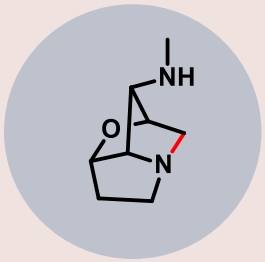

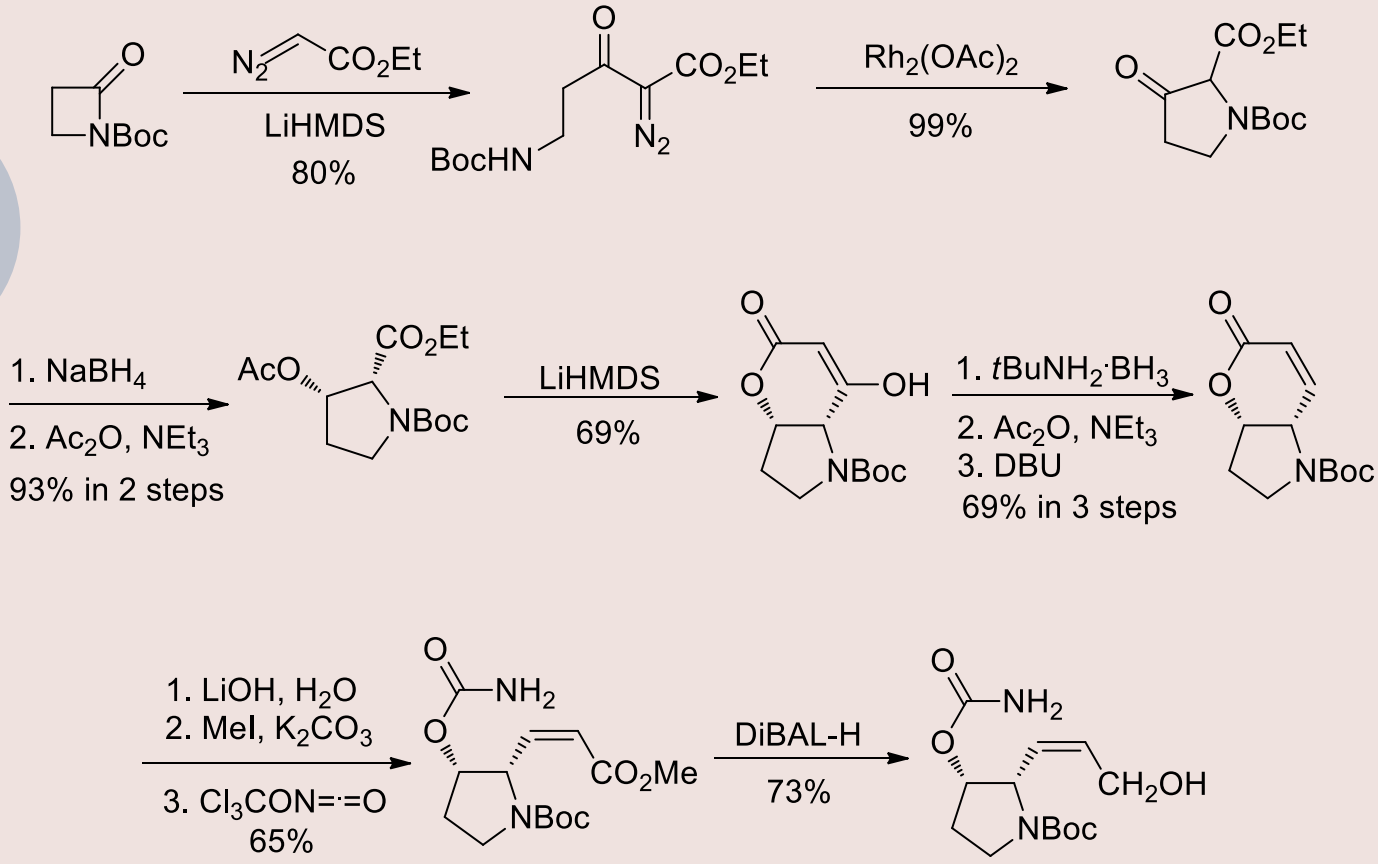

1. Hovey, M. T.; Eklund, E. J.; Pike, R. D.; Mainkar, A. A.; Scheerer, J. R. *Org. Lett.* **2011**. *13*, 1246–1249.

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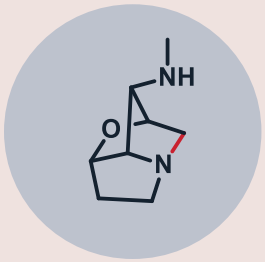
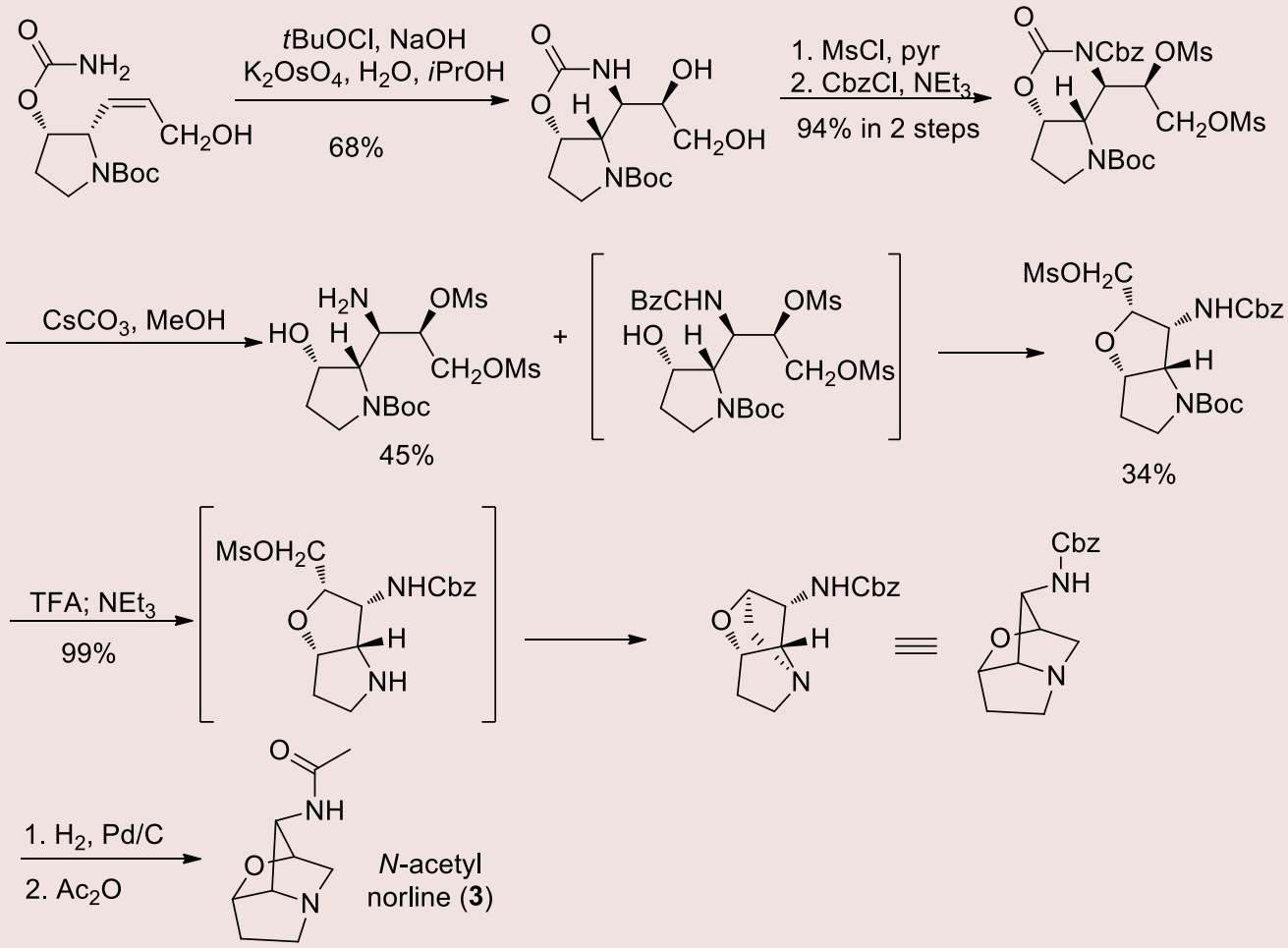
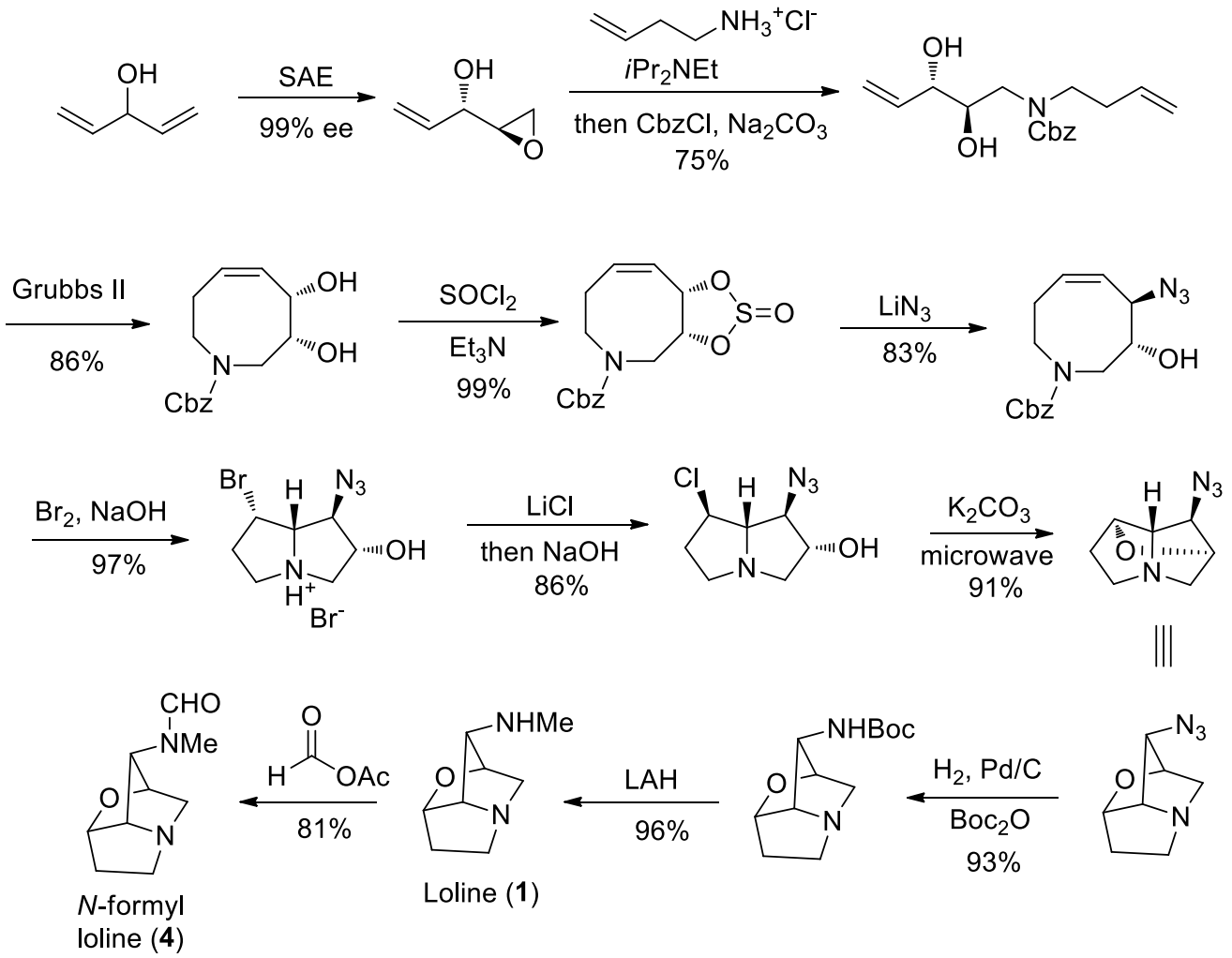




1. Hovey, M. T.; Eklund, E. J.; Pike, R. D.; Mainkar, A. A.; Scheerer, J. R. *Org. Lett.* **2011**. *13*, 1246–1249.

Efficient Synthesis of Loline Alkaloids



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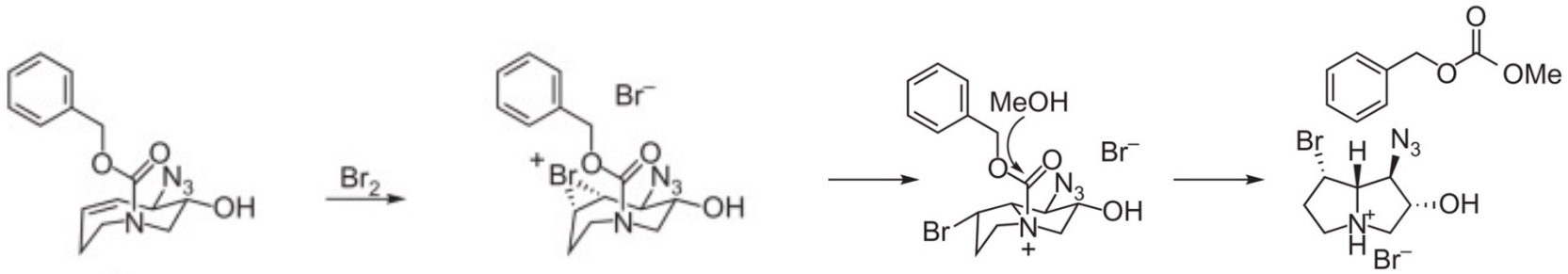

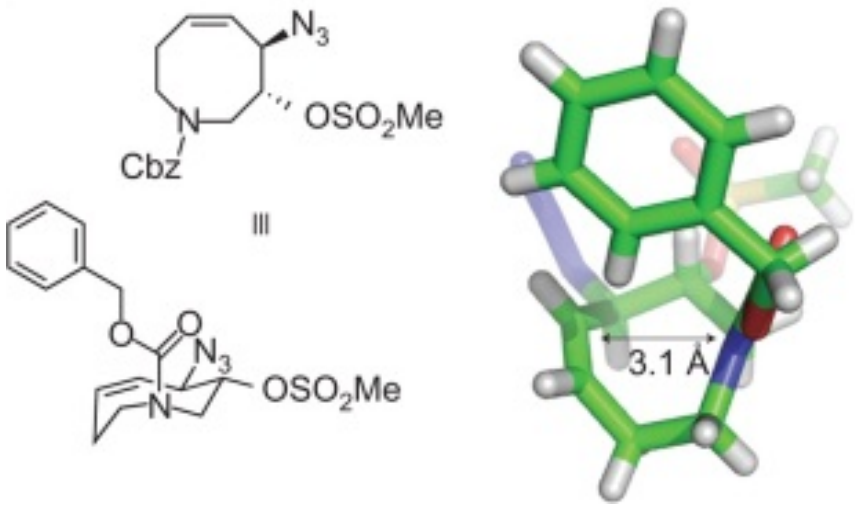

1. Cakmak, M.; Mayer, P.; Trauner, D. *Nature Chemistry,* **2011**, *3*, 543–545.

Summary

- 8 steps to build loline skeleton
- Key transformation is transannular attack of carbamate nitrogen to yield the pyrrolizidine skeleton.
- Only 1 protecting group is used and lost in course of a strategic bond formation.
- Scalable, diversifiable and should give access to other members of loline alkaloids.