The Lupin Alkaloids

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10/11/2006

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Lupin

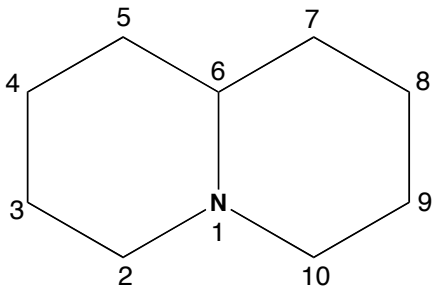
- Grain legume, high in protein, commonly used for livestock feed in Europe, Africa, Australia, and Asia
- Also used in cereals, baby formula, pasta, soups and salads in the United States (22 states, 42,000 pounds/year)
- Seeds used in traditional Chinese medicine
- Has been cultivated for over 2000 years
- Over 500 species of the genus *Lupinus* known
- In its raw form, the mildly toxic lupin alkaloids present in the plants causes a bitter taste, and are used as a defensive mechanism against herbivores
- Alkaloids are commonly removed (or reduced) by soaking the raw seeds in water prior to use
- In the 1920's, German plant breeders produced the first alkaloid-free, "sweet" lupin

Lupin Alkaloids - Biological Properties

- (-)-Cytisine has been identified as a selective partial nicotinic receptor agonist (nicotinic acetylcholine recepters are affected by Parkinson's and Alzheimer's diseases) (Nicotine is a full agonist at neuronal nAChR's, and has additional undesirable biological effects)
- Alkaloid extracts from *Lupinus* species have recently shown antimicrobial activity
- *L. albus* showed inhibitory effects on Gram negative bacteria
- *L. varius* and *L. densiflorus* strongly inhibited Gram positive bacteria
- Many known lupin alkaloids show significant antifungal activity
- matrine has shown antiulcerogenic and anticancer activities.



Quinolizidine Core Structure







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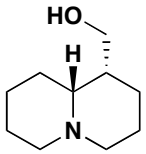
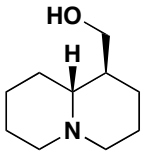
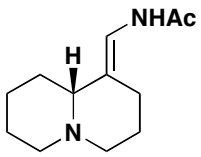


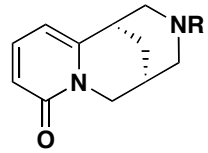
(-)-Lupinine



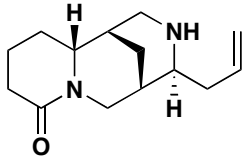
(+)-Epilupinine



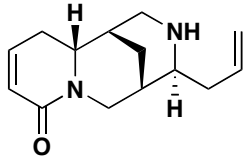
Lusitanine



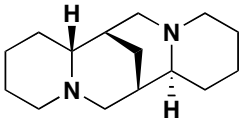
(-)-Cytisine (R = H)
(many alkylated derivatives)



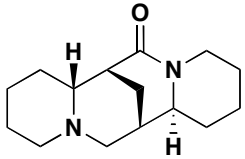
Angustifoline



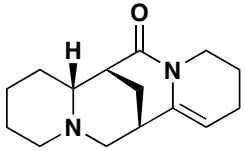
Albine



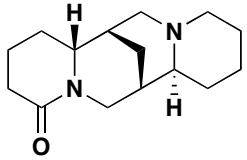
(-)-Sparteine



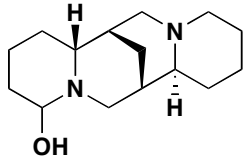
Aphylline



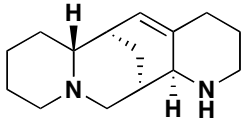
Aphyllidine



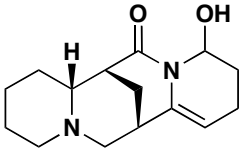
(+)-Lupanine



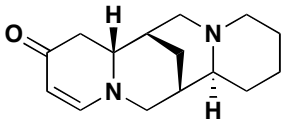
Retamine



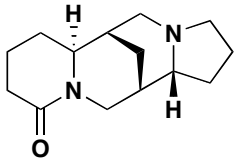
(+)-aloperine



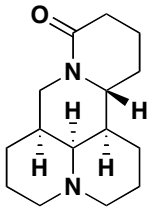
Baptifoline



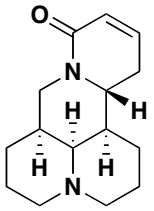
Multiflorine



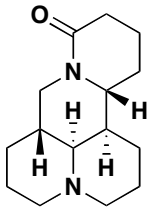
Camoensidine



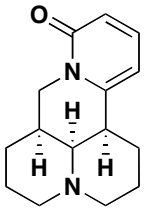
(+)-Matrine



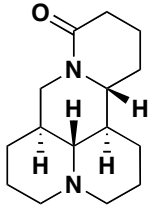
(-)-Sophocarpine



(-)-Sophoridine



(-)-Sophoramine



(+)-Allomatrine

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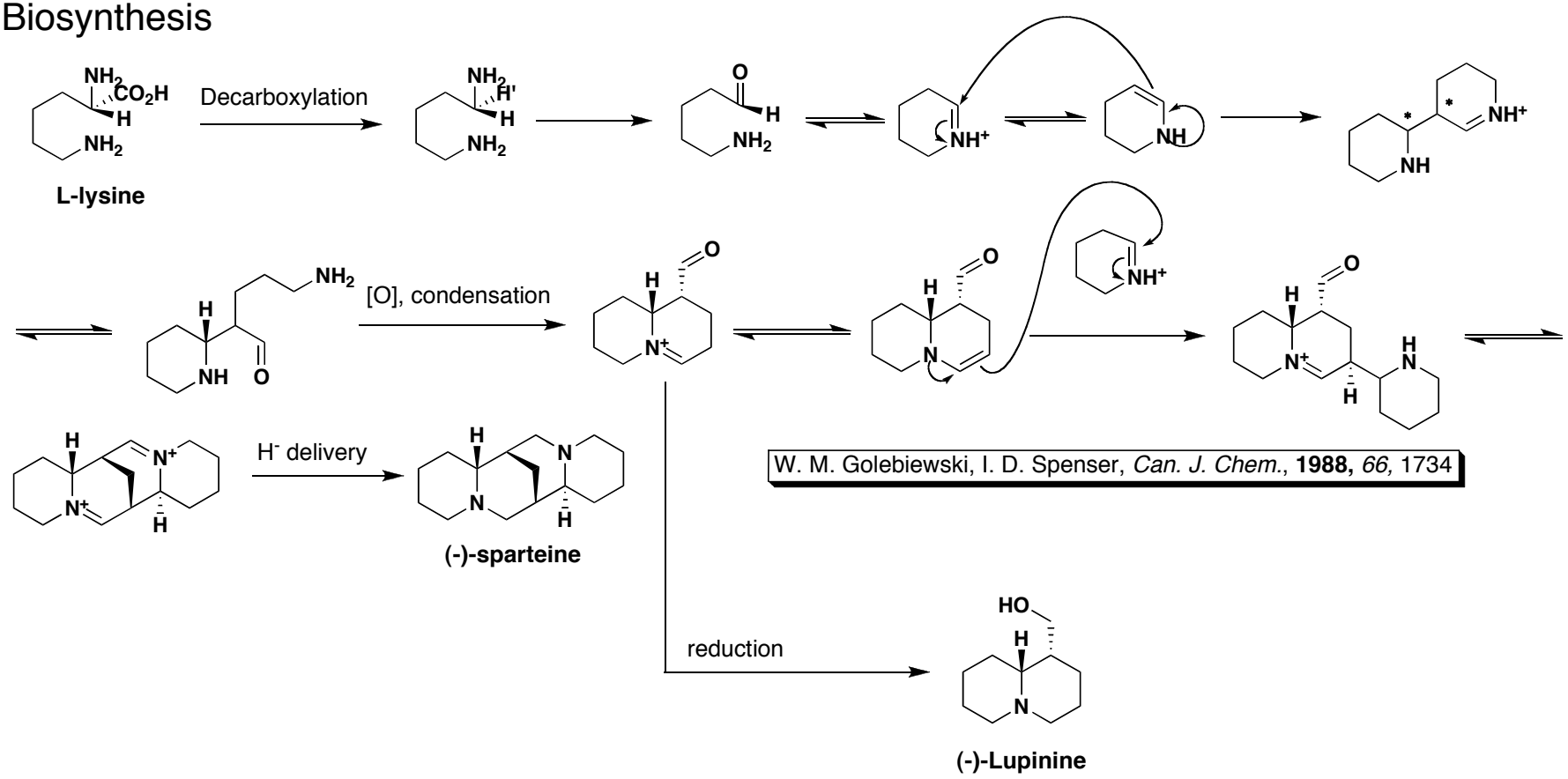
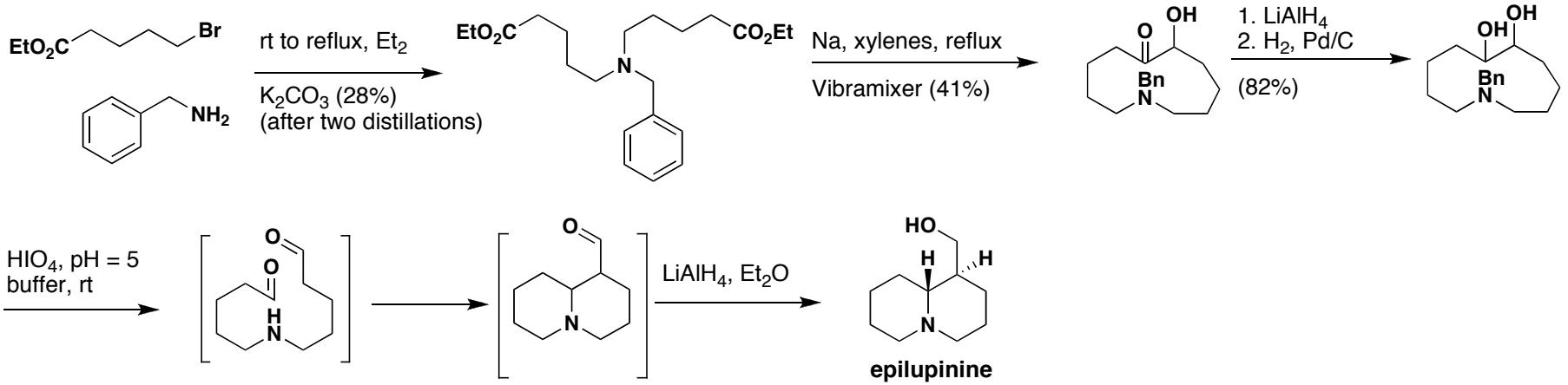
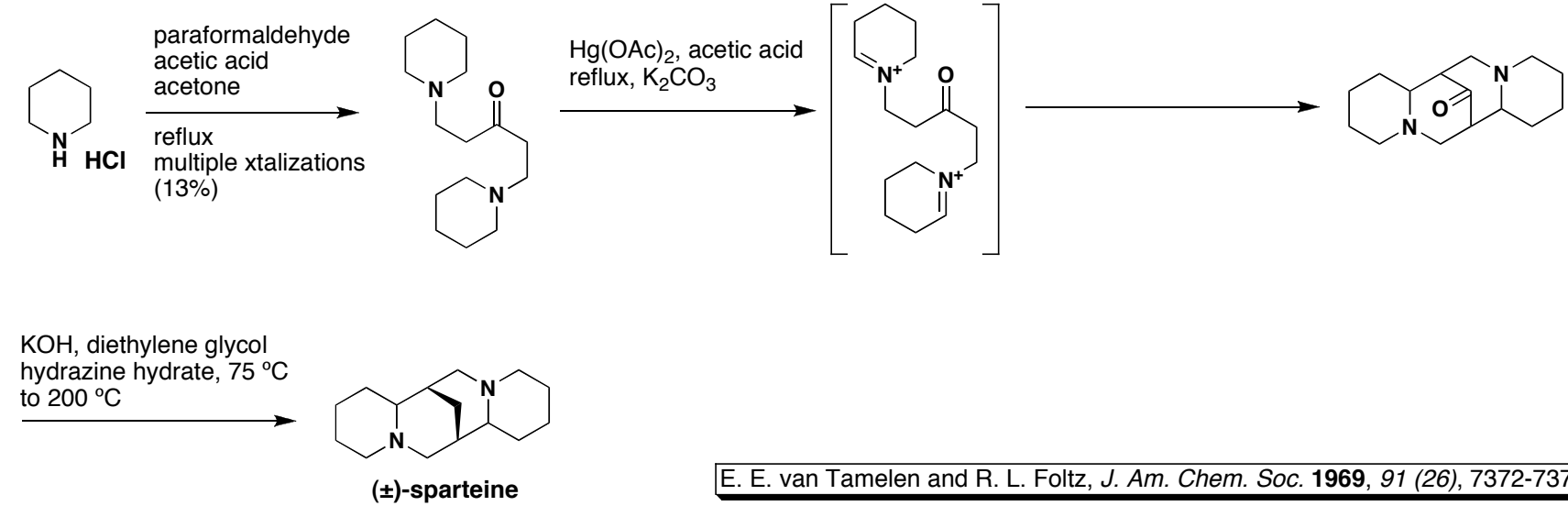
Biosynthesis



W. M. Golebiewski, I. D. Spenser, *Can. J. Chem.*, **1988,** *66,* 1734

The Lupin Alkaloids





E. E. van Tamelen and R. L. Foltz, *J. Am. Chem. Soc.* **1969**, *91 (26)*, 7372-7377

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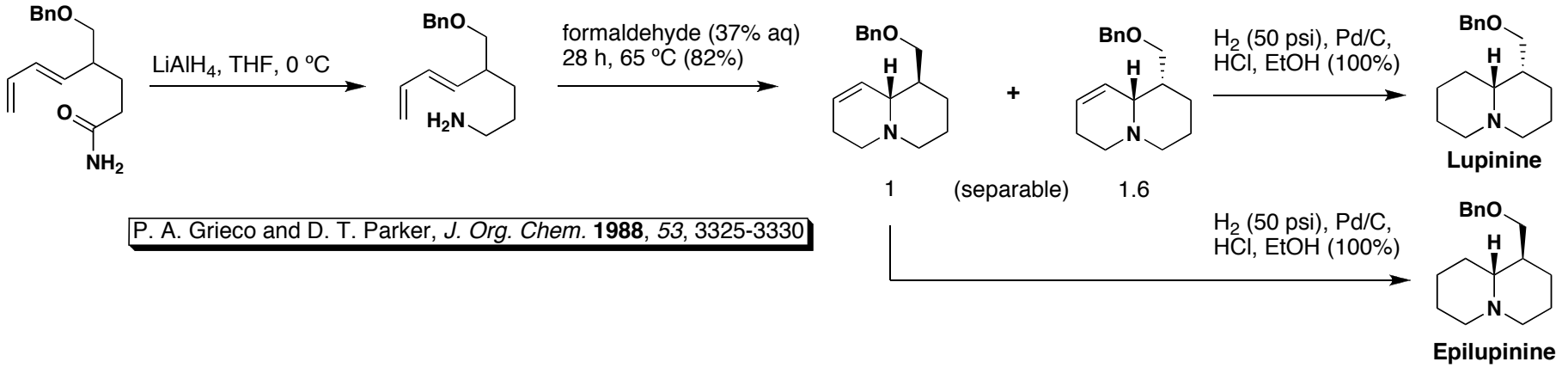
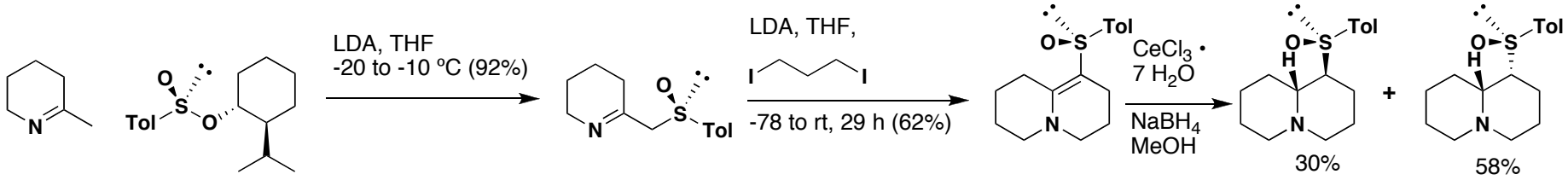
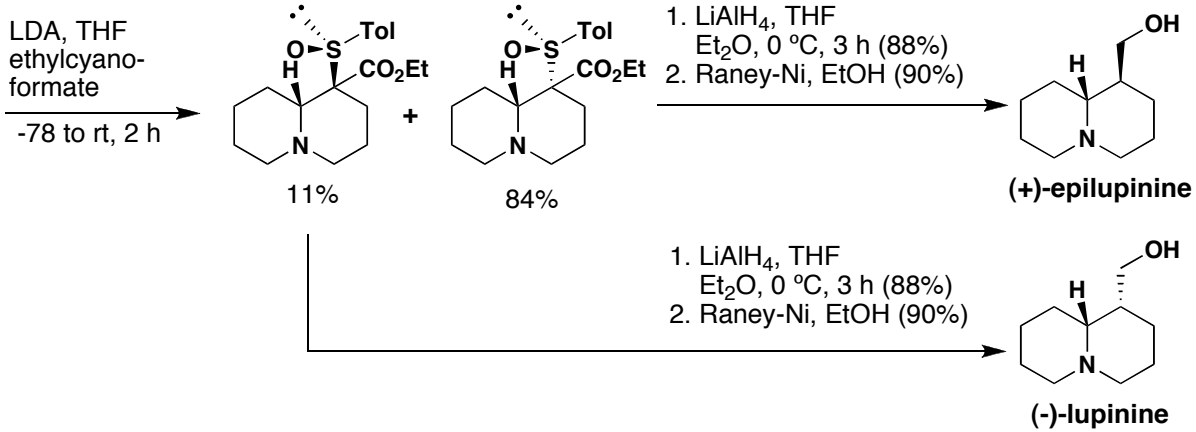


P. A. Grieco and D. T. Parker, *J. Org. Chem.* **1988**, *53*, 3325-3330





Also, Al-Hg removal of the sulfer was attempted before reduction, resulting in a 1:3.6 ratio, with a slightly reduced yield.

It is also important to note that starting with the enantiomer of the menthyl sulfinate yields (-)-lupinine as the major product in similar ratios.

D. H. Hua *et al*, *Synthesis*, **1991**, 970-974

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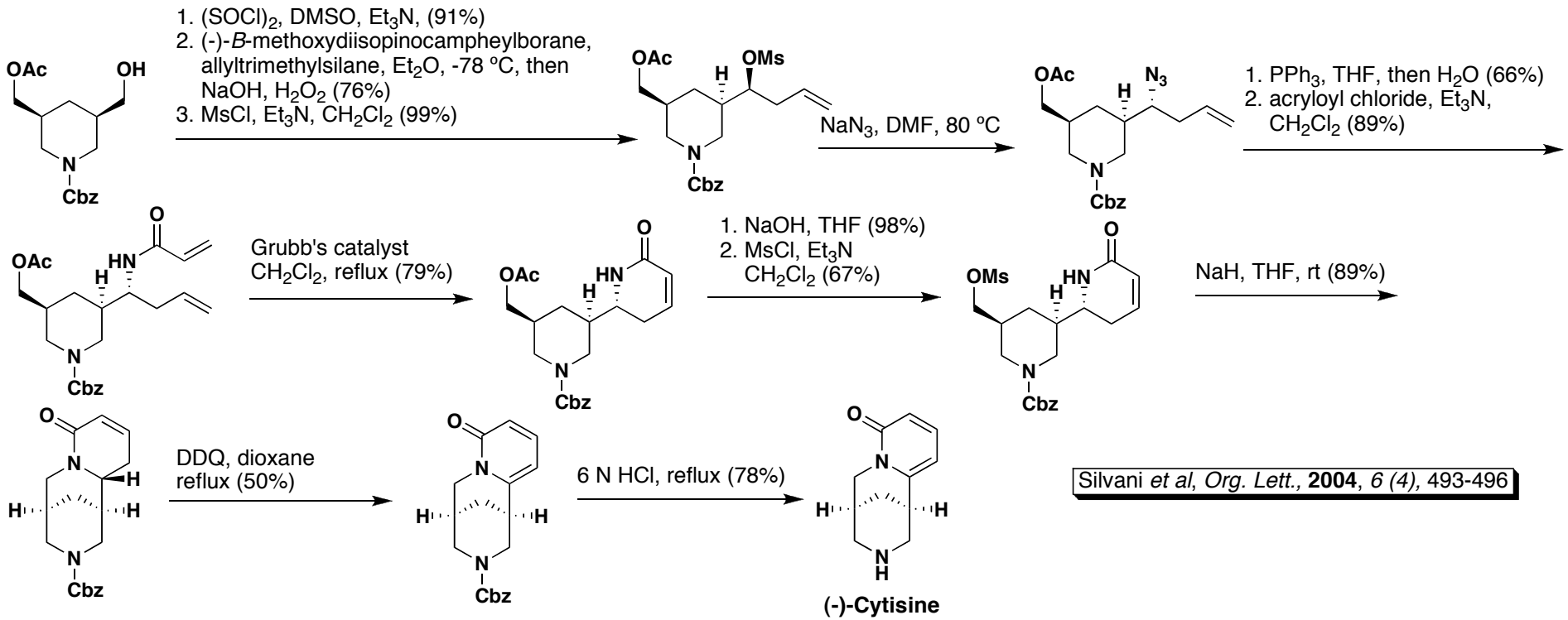
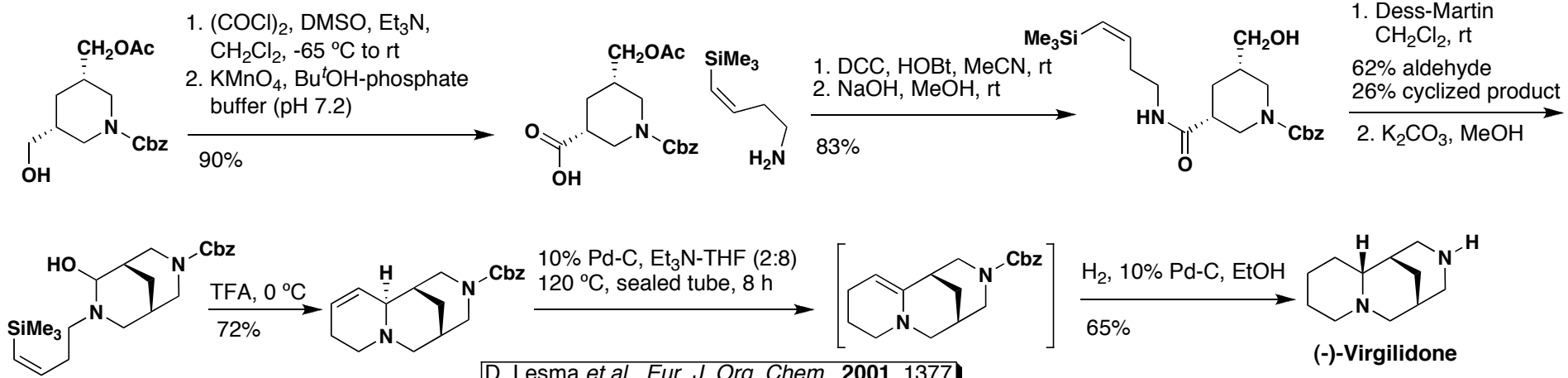


Silvani *et al*, *Org. Lett.*, **2004**, *6 (4)*, 493-496

(-)-Cytisine



D. Lesma *et al*., *Eur. J. Org. Chem.*, **2001**, 1377

(-)-Virgilidone

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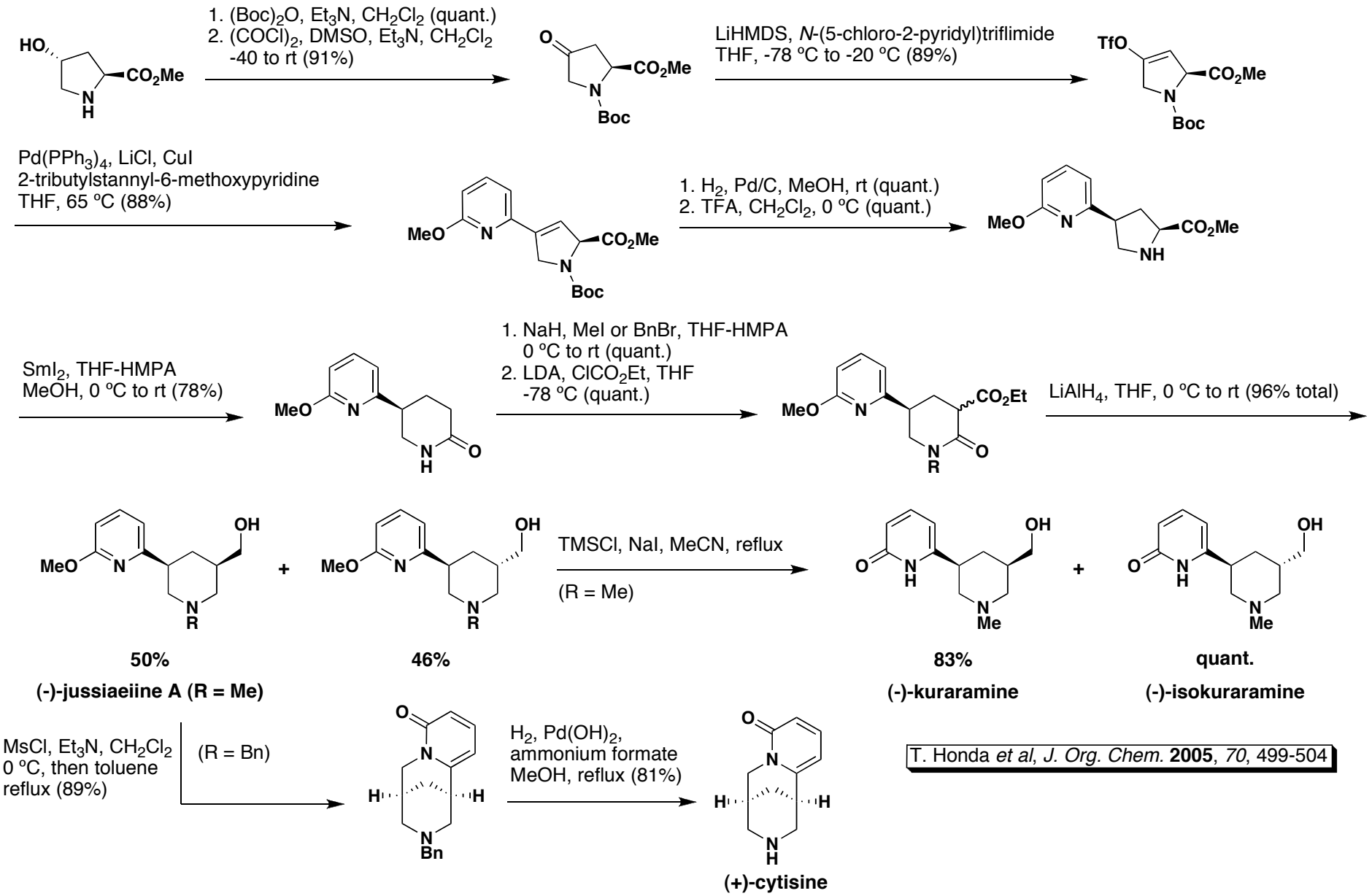

T. Honda *et al*, *J. Org. Chem.* **2005**, *70*, 499-504

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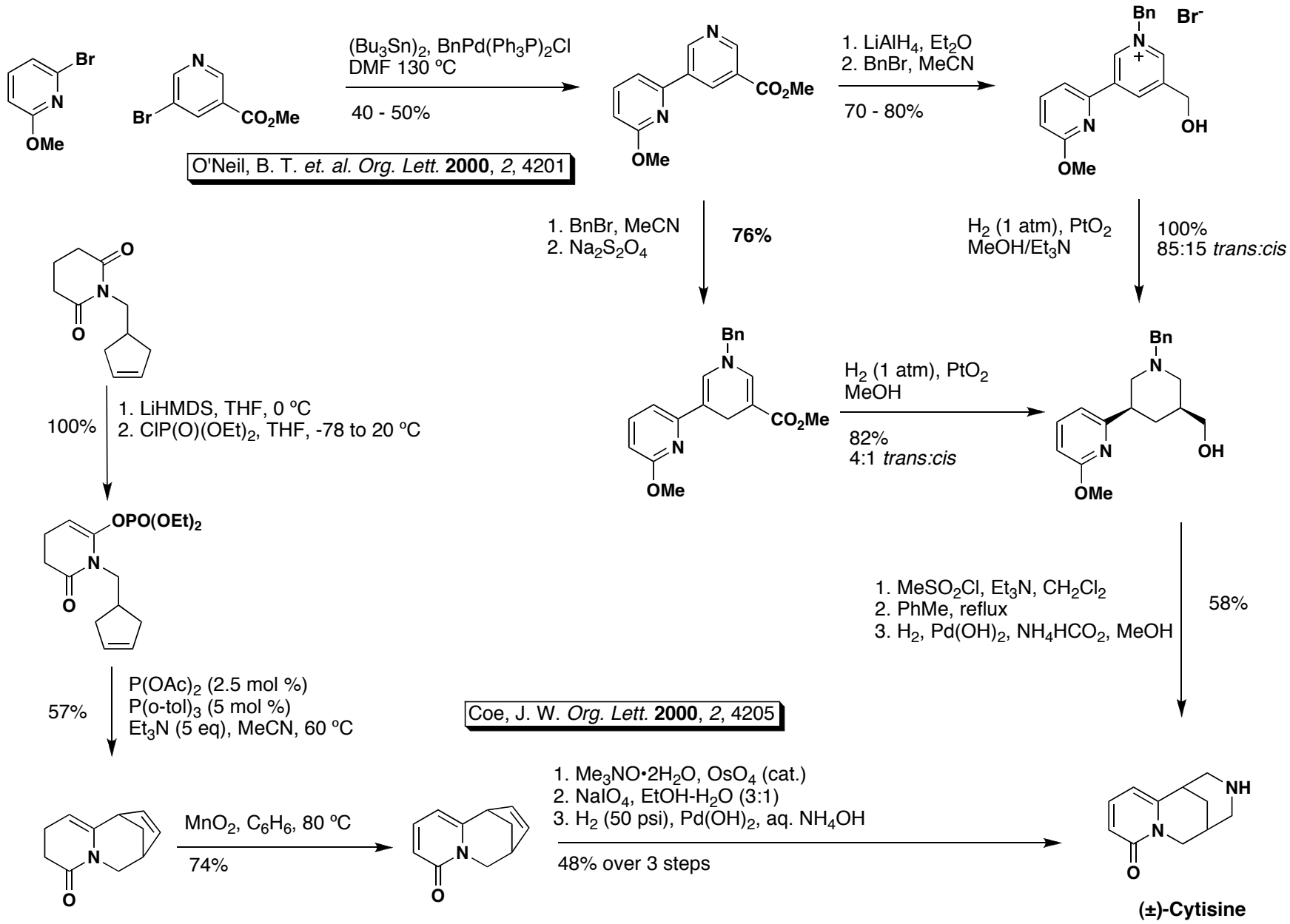

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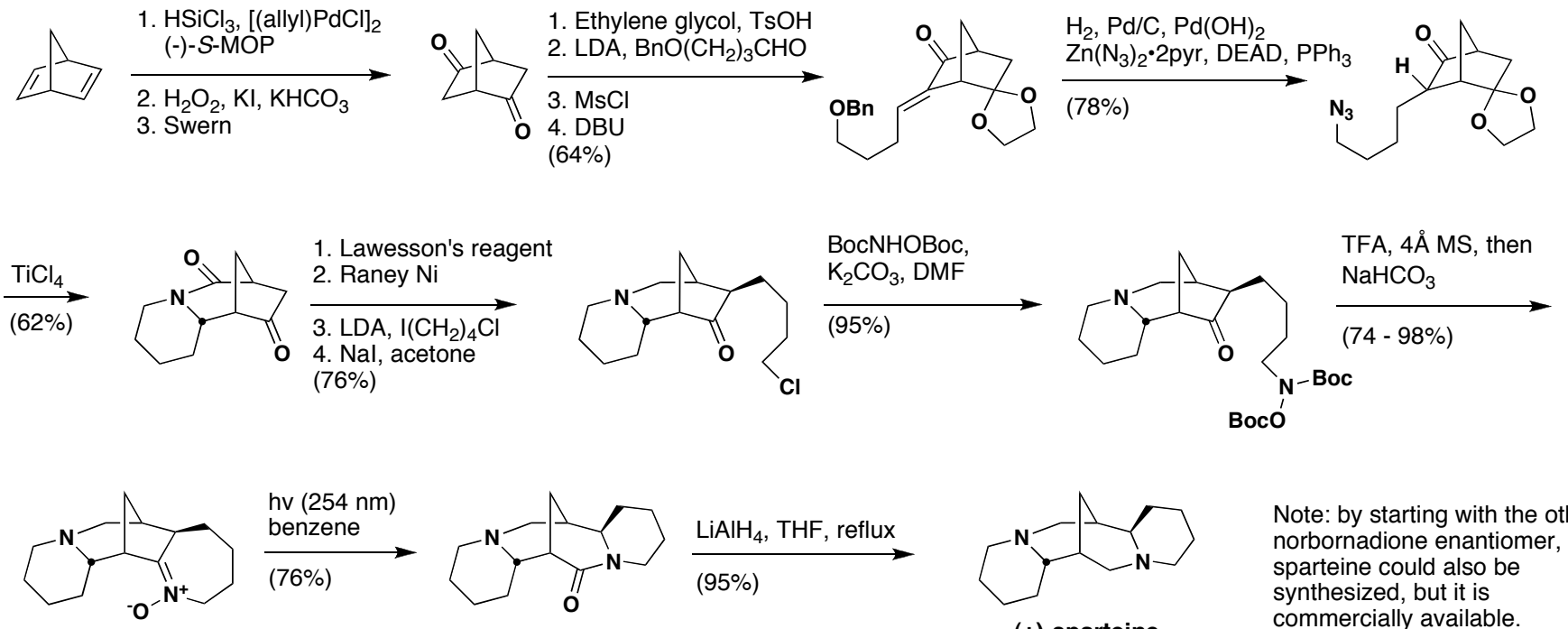

(+)-sparteine

15.7% overall

Note: by starting with the other norbornadione enantiomer, (-)-sparteine could also be synthesized, but it is commercially available.

J. Aube´ *et al.*, *Org. Lett.*, **2002**, *4* (15), 2577-2579

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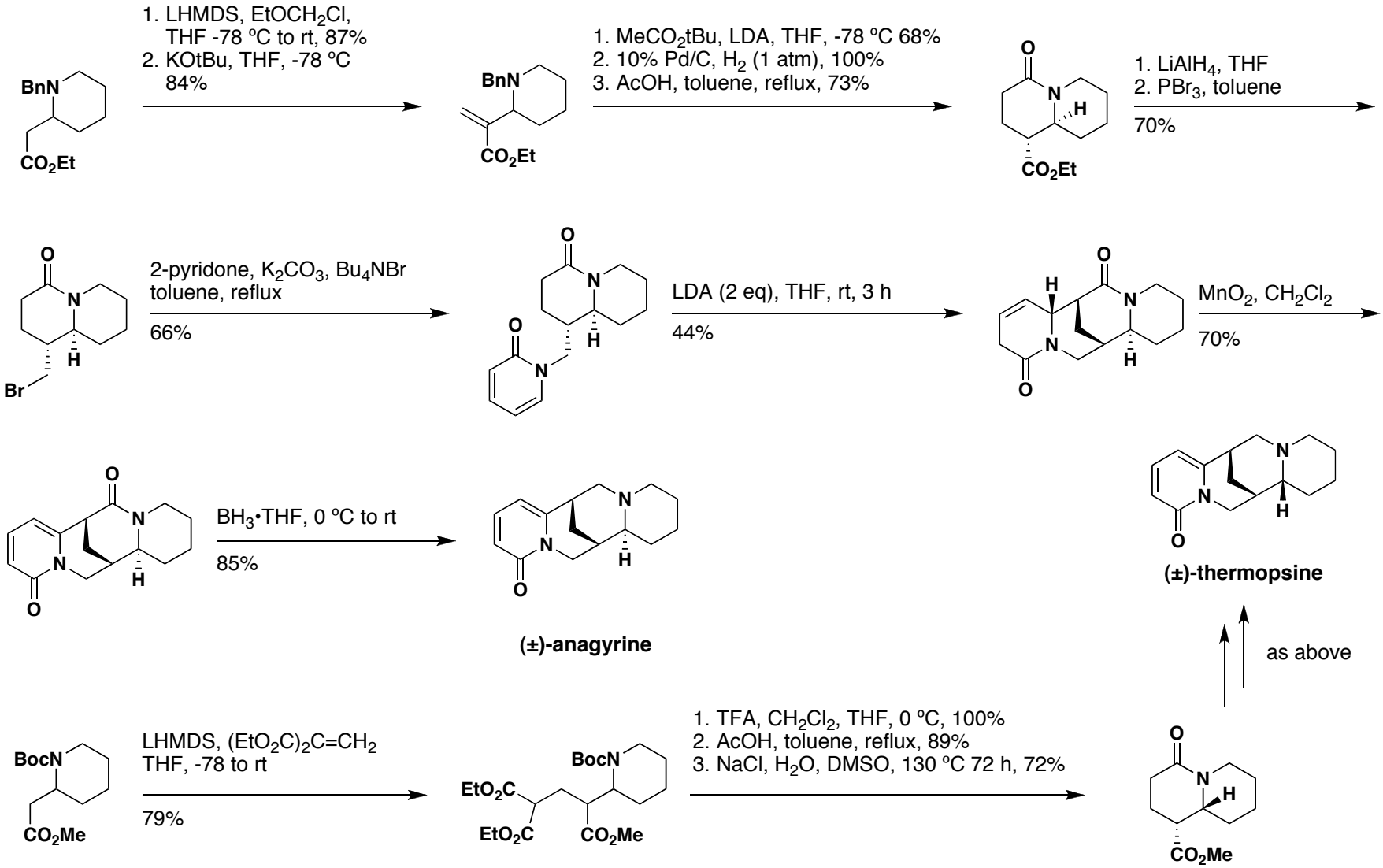

Gallagher, T.; Gray, D. *Angew. Chem. Int. Ed.* **2006**, *45*, 2419-2423

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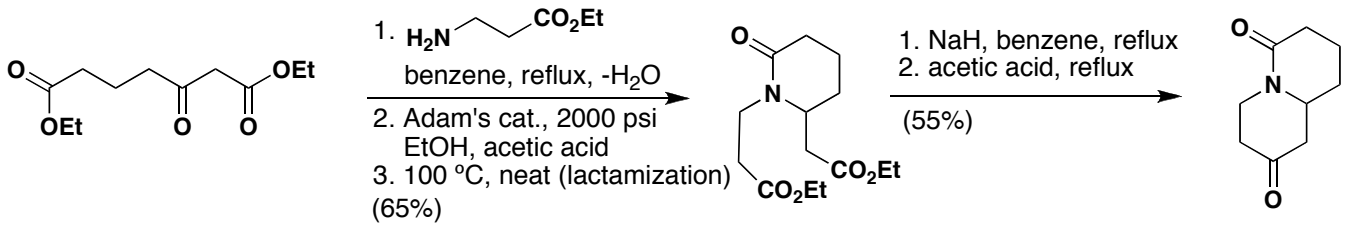
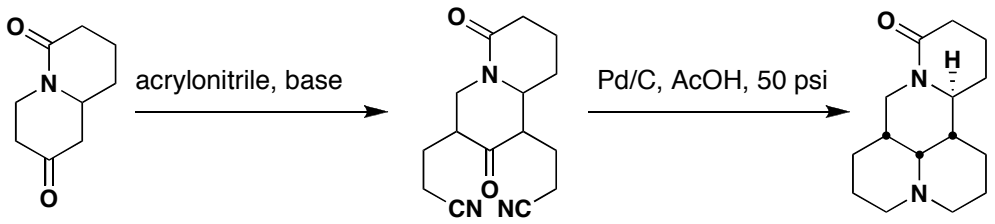
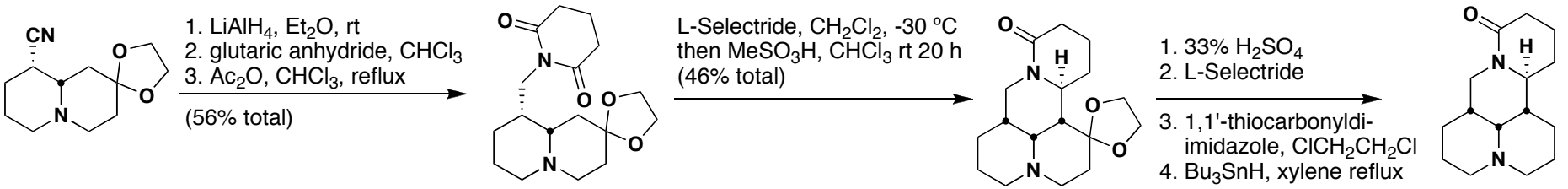




***d,l*-matrine**

L. Mandell *et al*, *J. Am. Chem. Soc.* **1963**, *85*, 2683-2684



***d,l*-matrine**
(23% overall)

Jen Chen, *J. Chem. Soc.,Chem. Comm.* **1986**, 905-907

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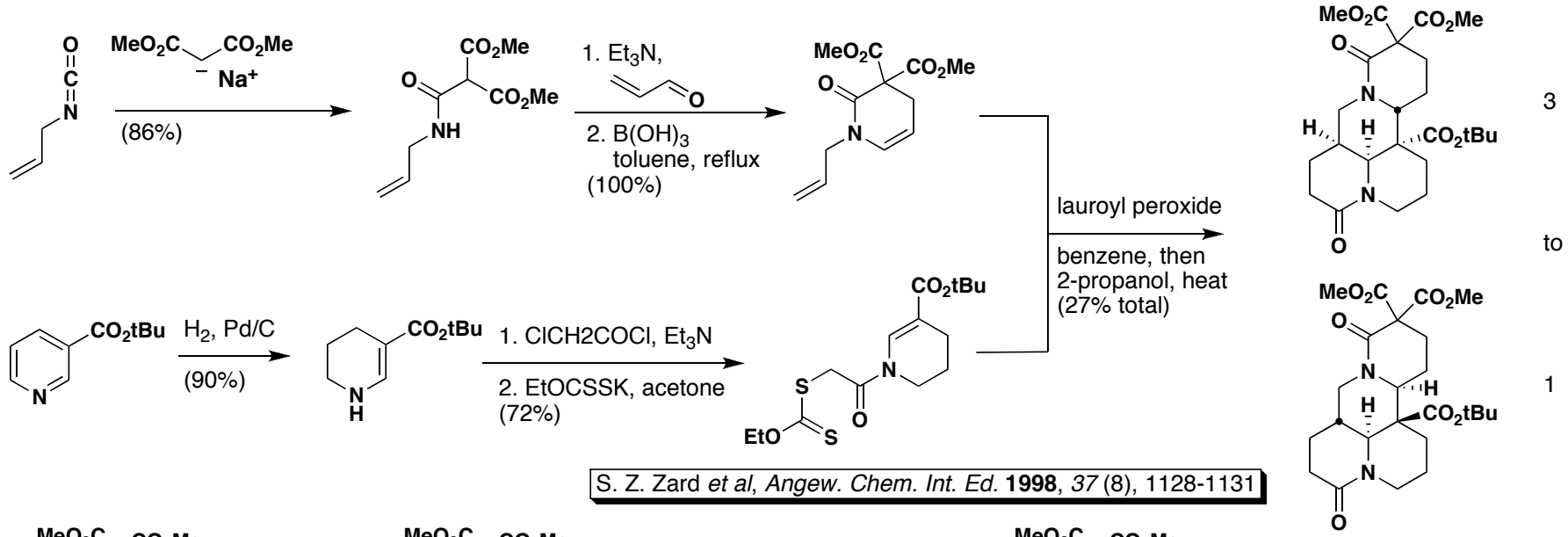

S. Z. Zard *et al*, *Angew. Chem. Int. Ed.* **1998**, *37* (8), 1128-1131

