

Biotin

Molecule in Review

Dan Treitler (Snyder Group)
8-7-09

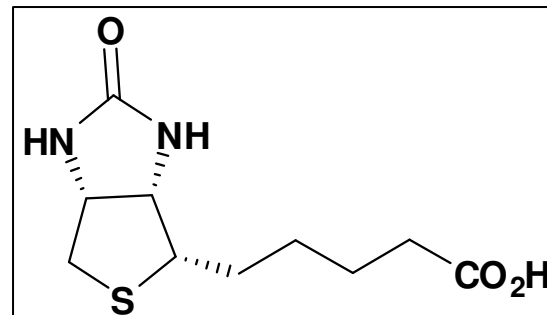
Synthesis Literacy Group
Columbia University Chemistry



Isolation and Background

- Isolation

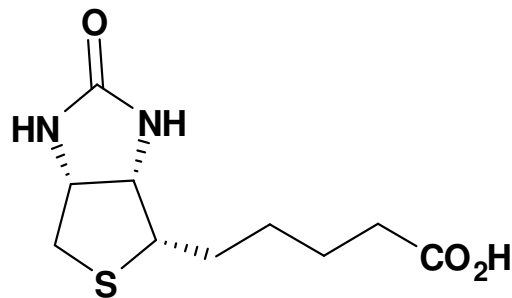
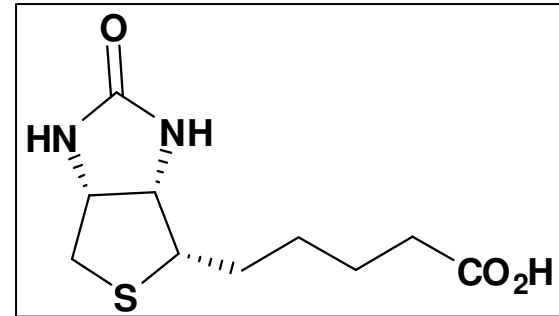
- Isolated from egg yolk in 1936.
- Structure postulated in 1942.
- Structure confirmed by first total synthesis in 1945.



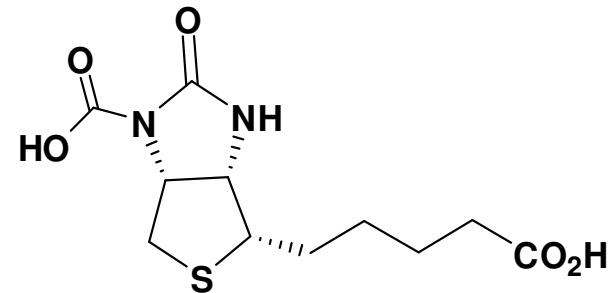
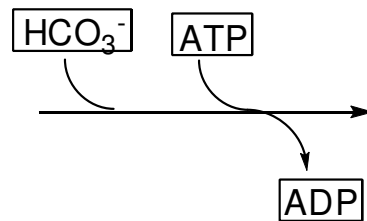
Isolation and Background

- Biochemistry

- Water soluble B vitamin (B7).
- Essential cofactor for metabolism.
- Most important function is in carboxyl transfer reactions:



biotin

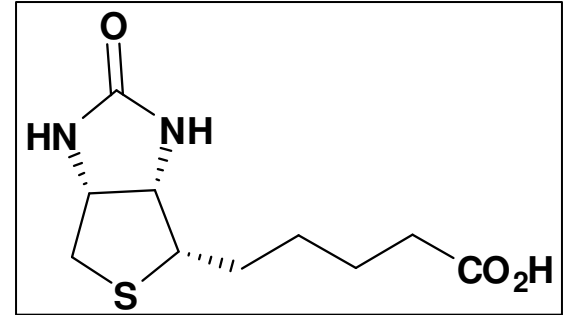


N-carboxy-biotin

Isolation and Background

- Importance

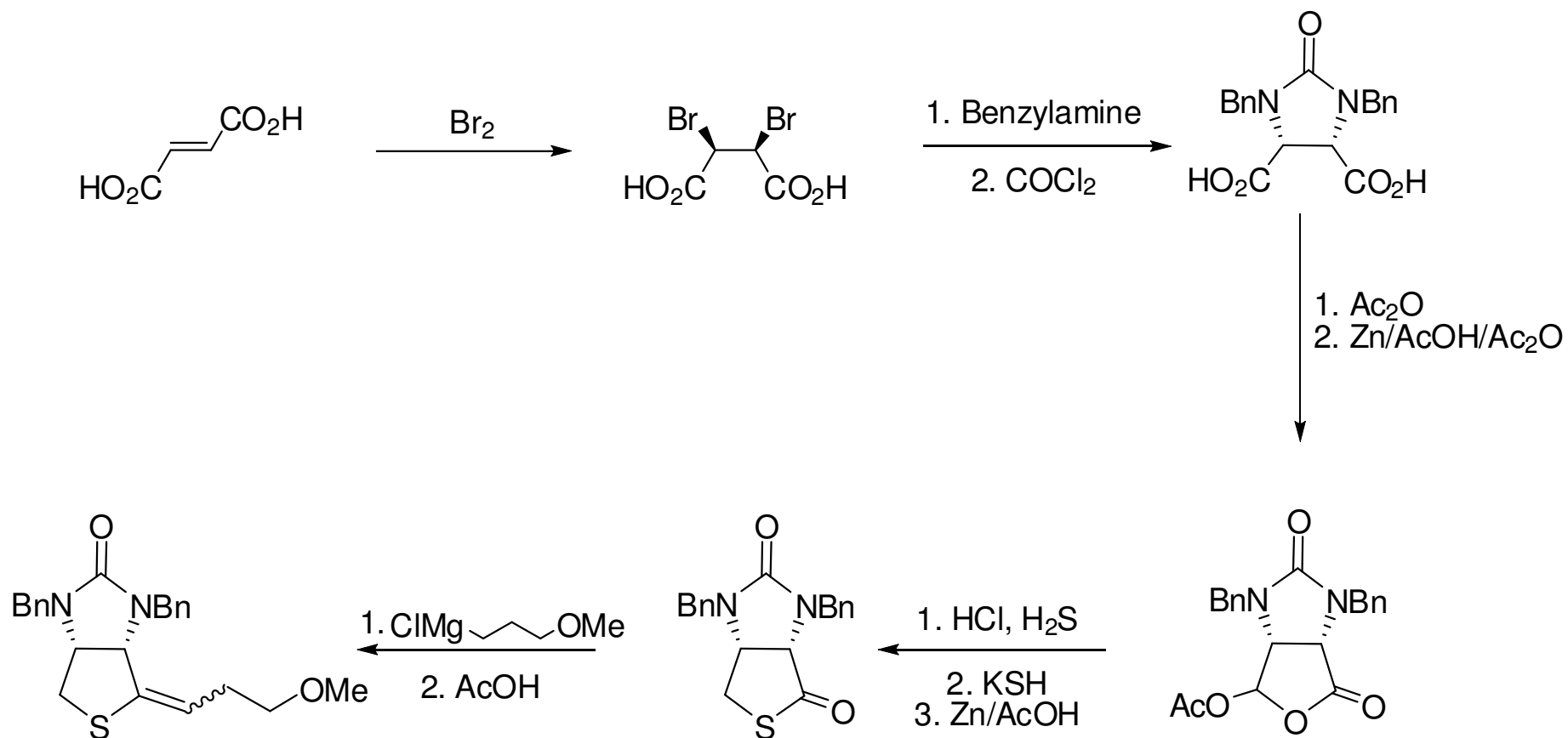
- Used by biochemists for tagging and isolating proteins and other macromolecules of interest.
- Necessary additive in pig/cattle feed.
 - 20 mg/animal/day =
 - $0.00002 \times 160,000,000 \times 365 =$
 - 1.2 million kg/year
- Fermentation processes are not efficient sources of biotin. Total synthesis is **ACTUALLY NECESSARY!**



Total Syntheses

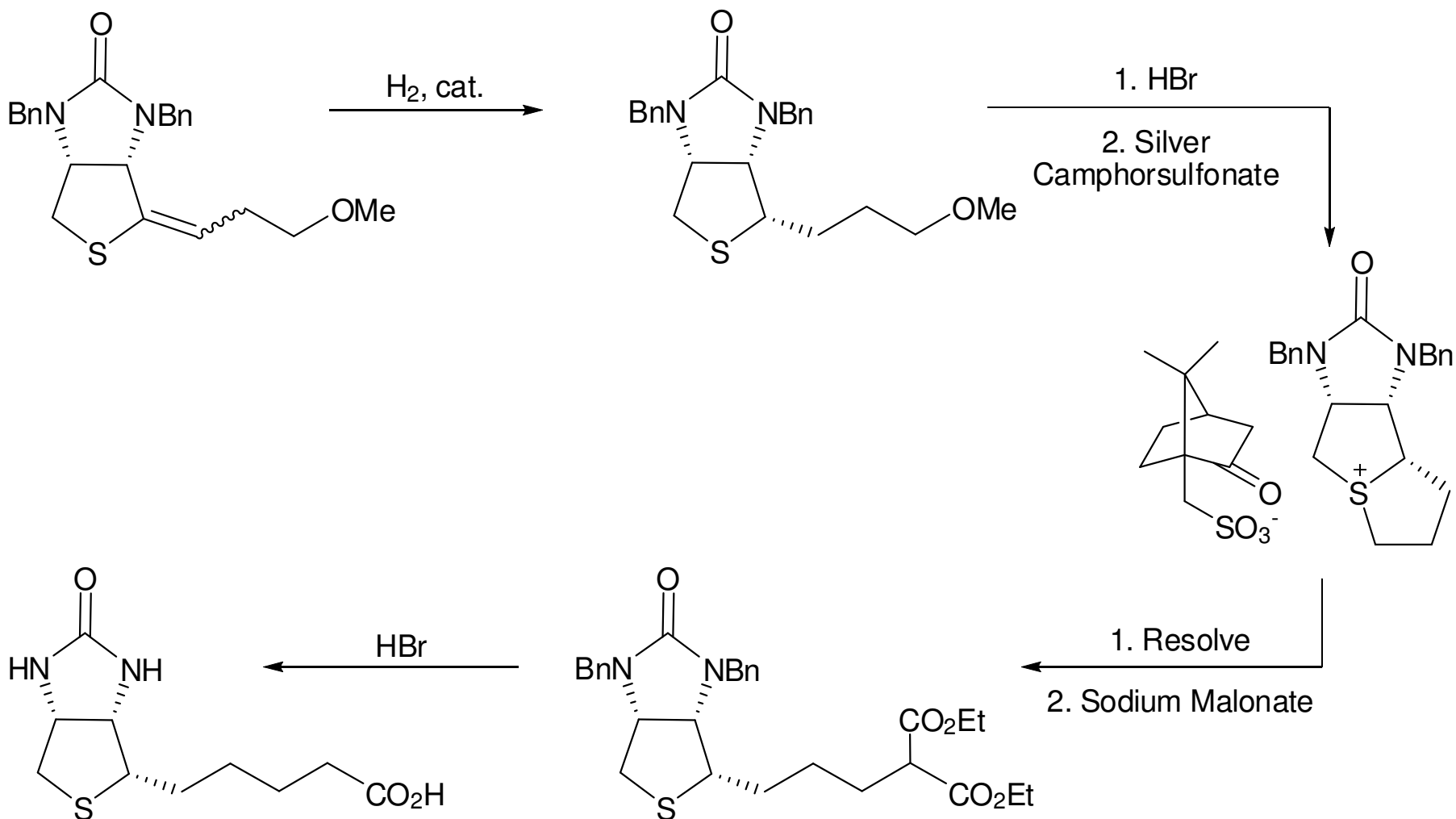
- ≥ 54 published total syntheses.
 - Approx. half published by industry groups.
- **Four Key Total Syntheses:**
 - First Non-racemic Synthesis:
 - 1949: Goldberg and Sternbach (HLR)
 - “Classic” Synthesis:
 - 1982: Baggiolini et al. (HLR)
 - Shortest Synthesis:
 - 1983: Volkmann et al. (Pfizer)
 - Recent Enantioselective Synthesis:
 - 2008: Chen et al. (Fudan University)

Goldberg and Sternbach (1949)



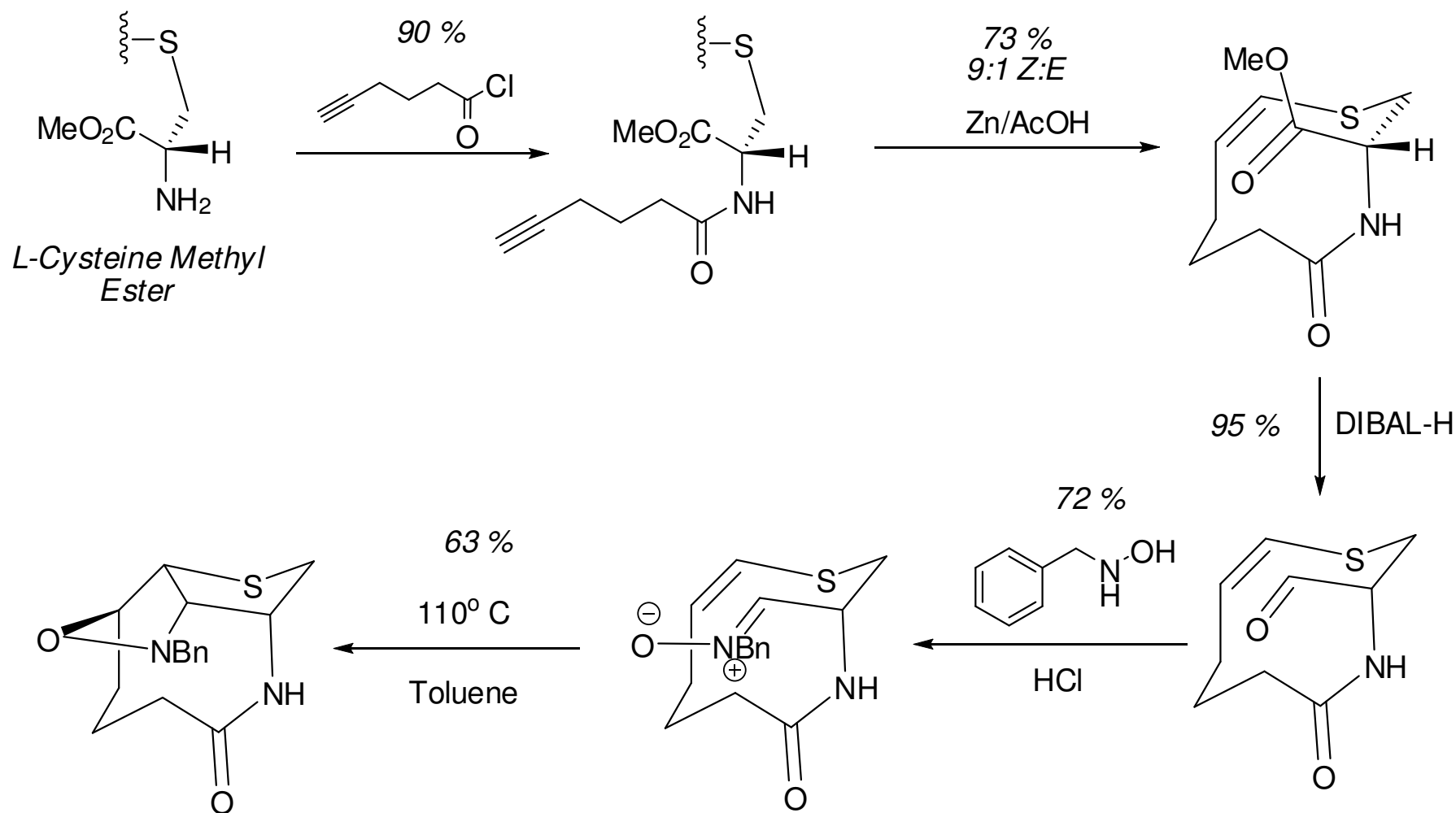
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Goldberg and Sternbach (1949)



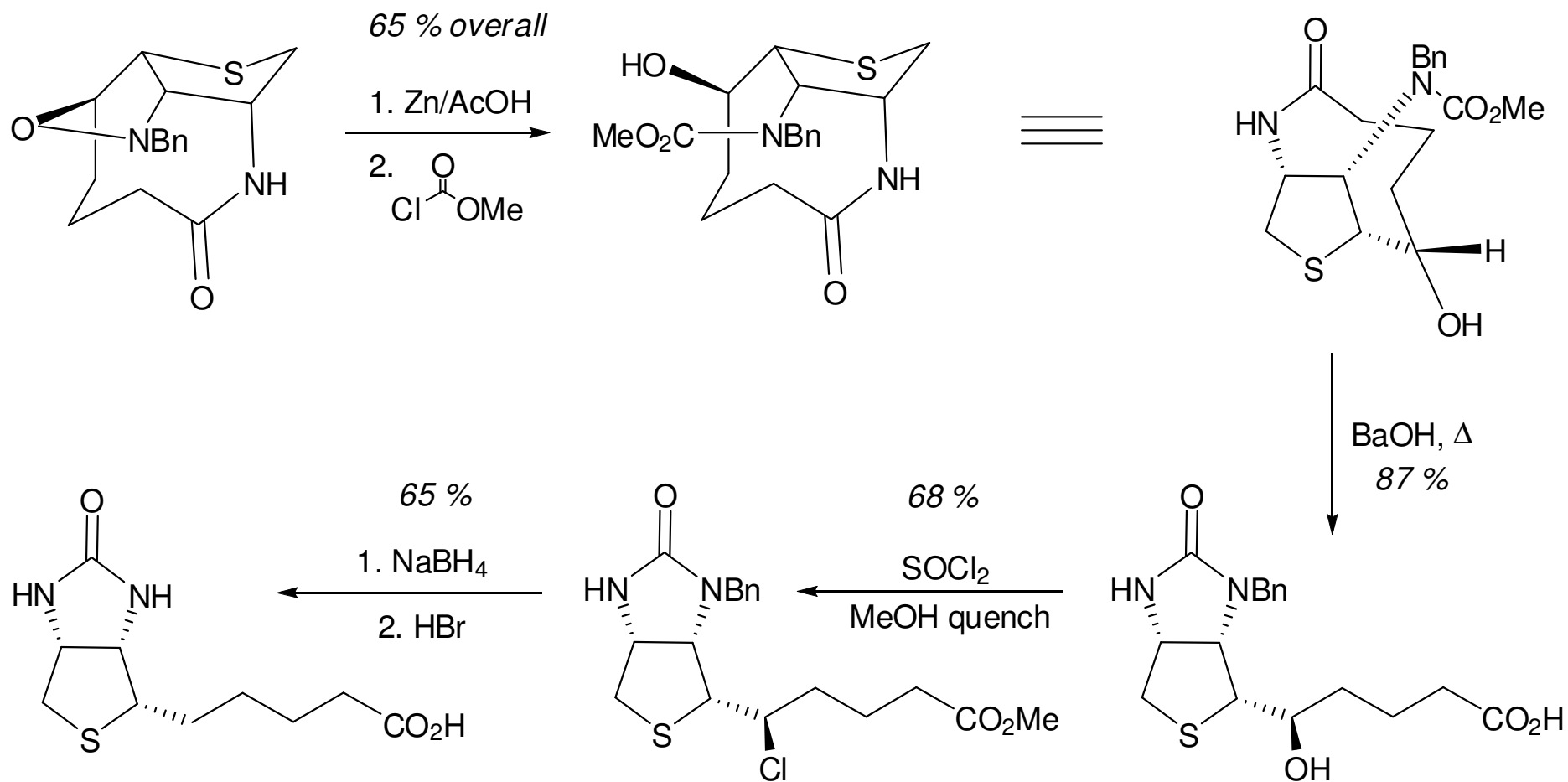
Treitler 7 - CU Synthesis Lit Group - Biotin

Baggiolini (1982)



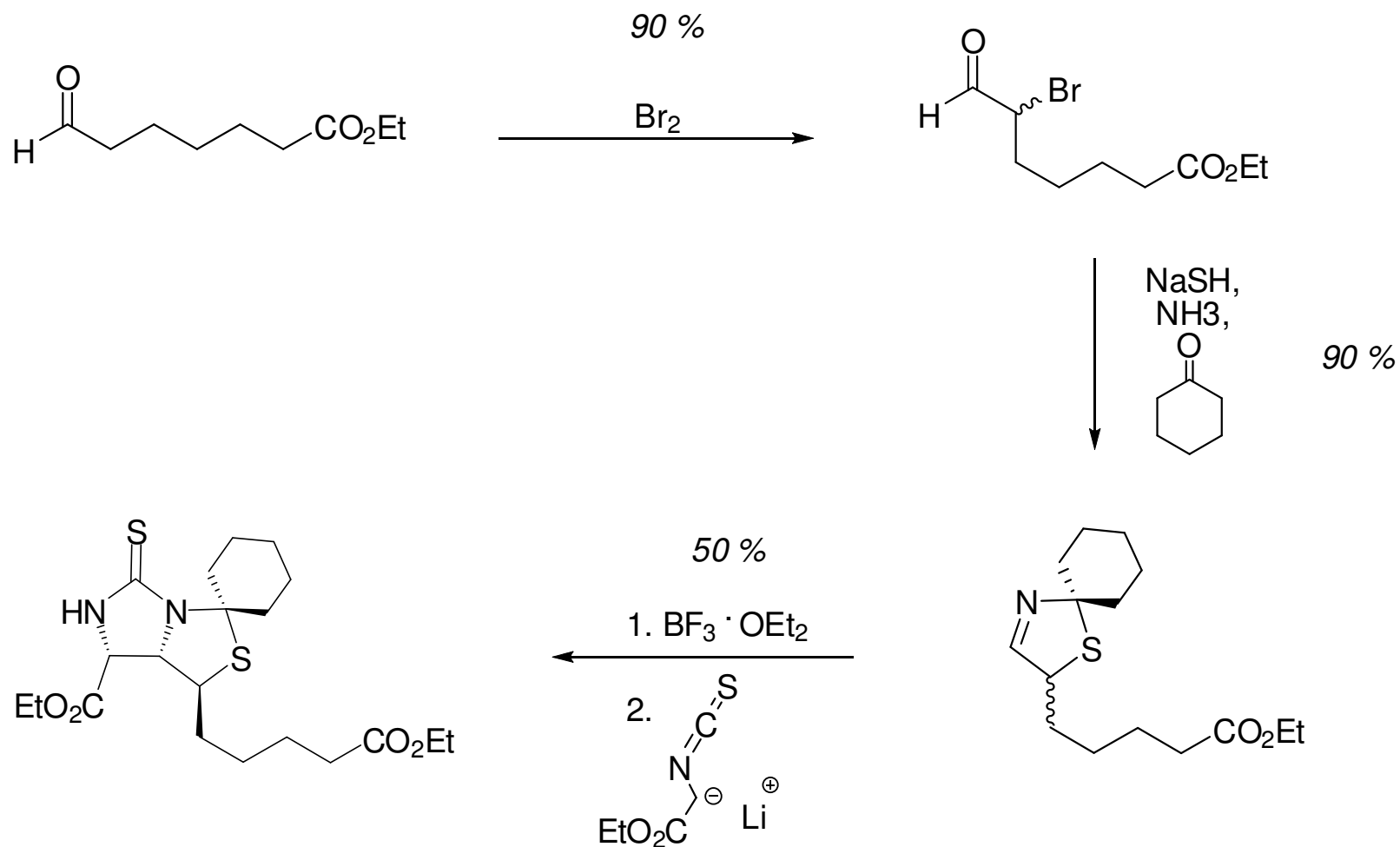
Treitler 8 - CU Synthesis Lit Group - Biotin

Baggiolini (1982)



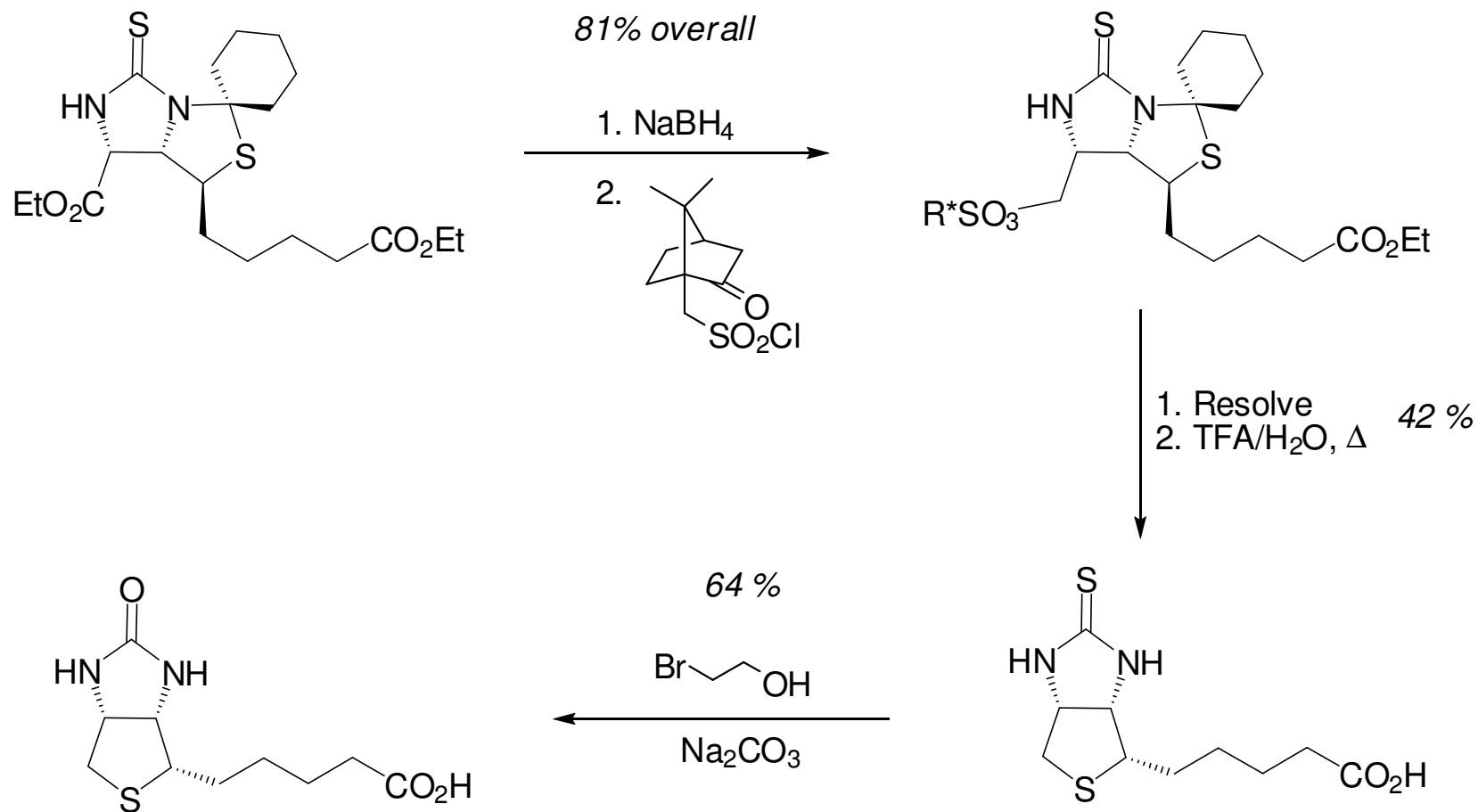
Treitler 9 - CU Synthesis Lit Group - Biotin

Volkmann (1983)



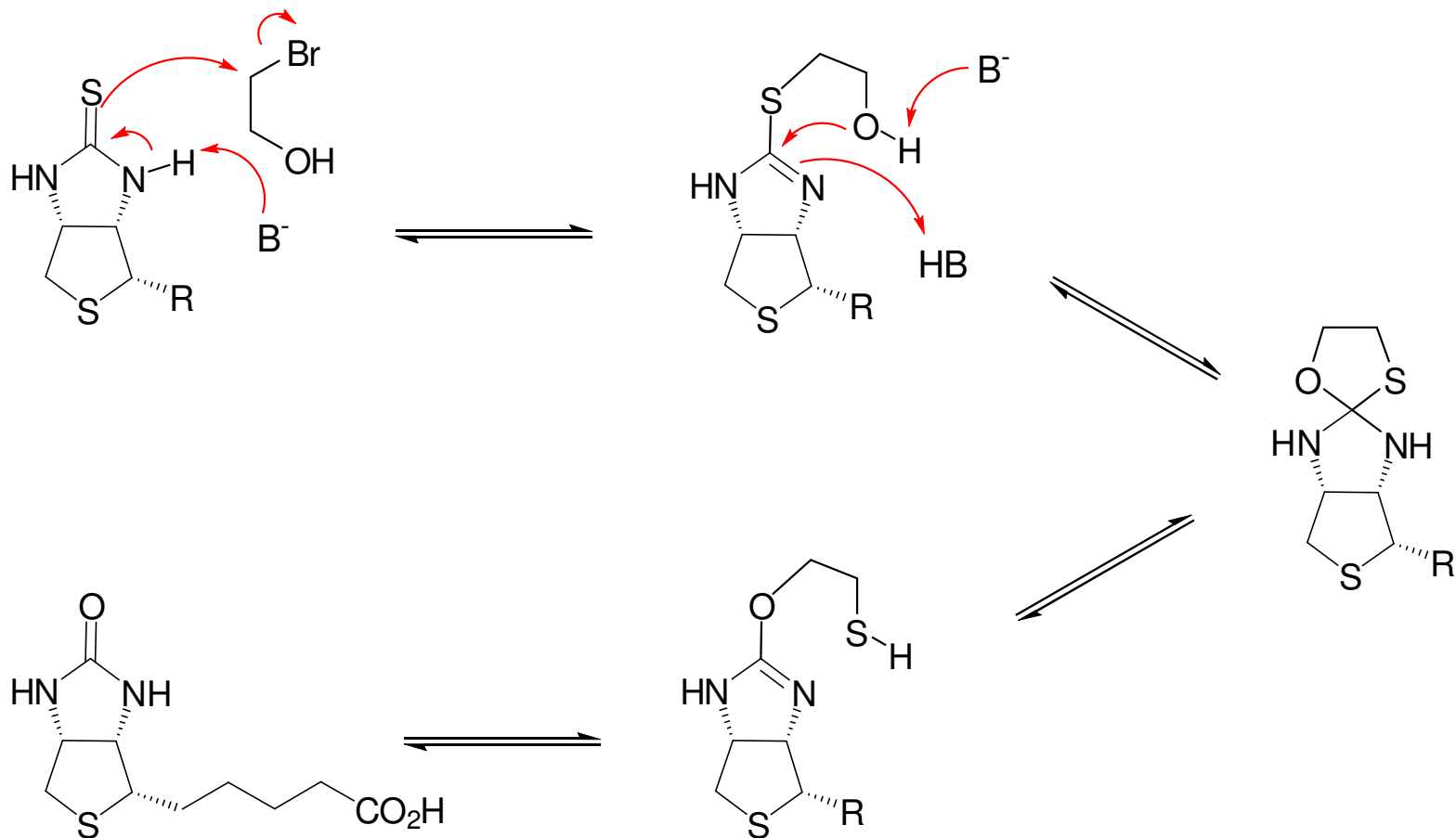
Treitler 10 - CU Synthesis Lit Group - Biotin

Volkmann (1983)



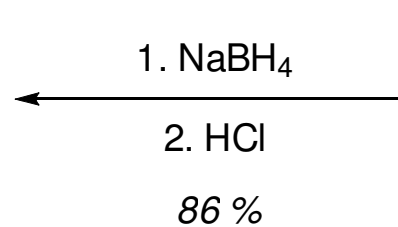
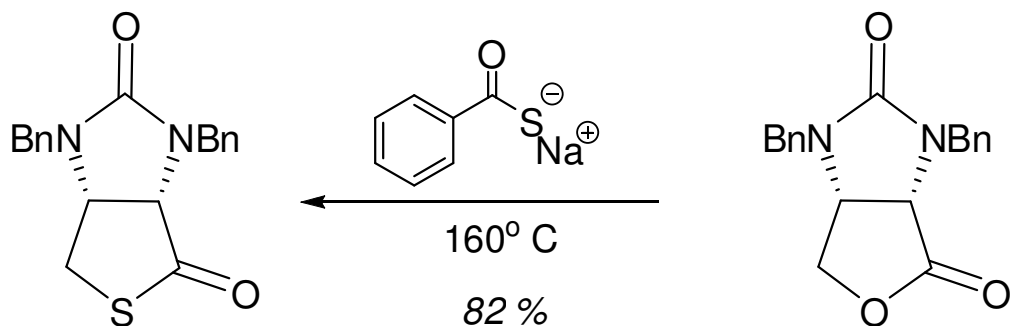
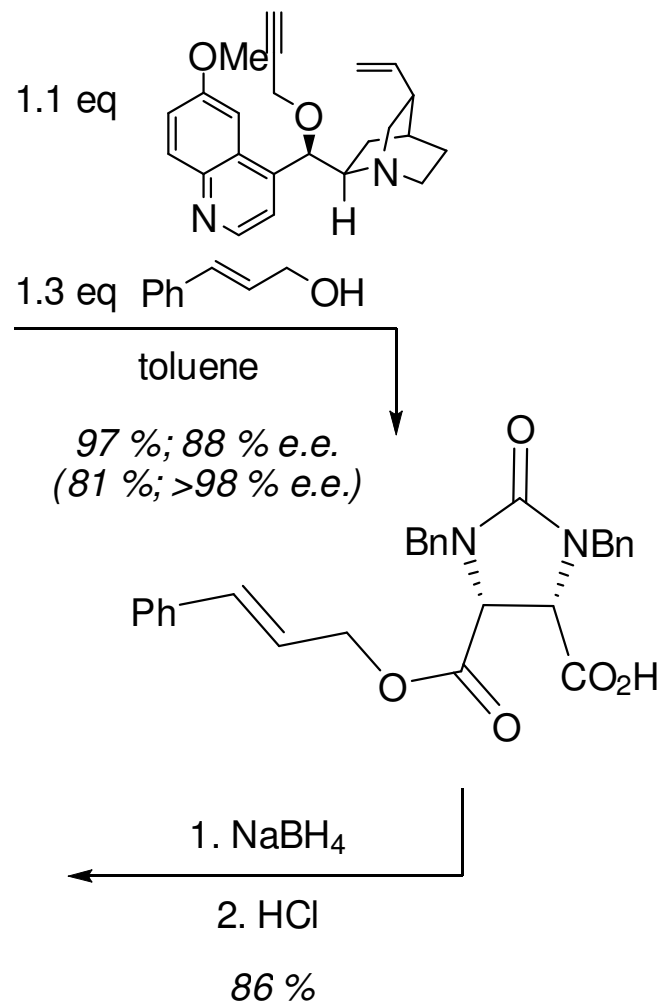
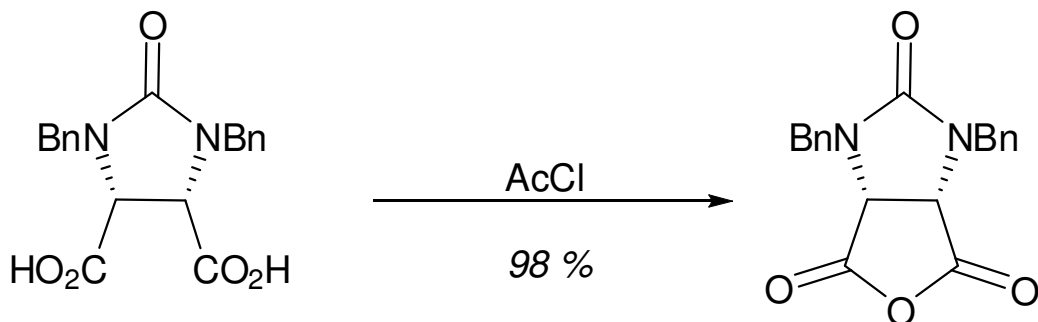
Treitler 11 - CU Synthesis Lit Group - Biotin

Volkman (1983)



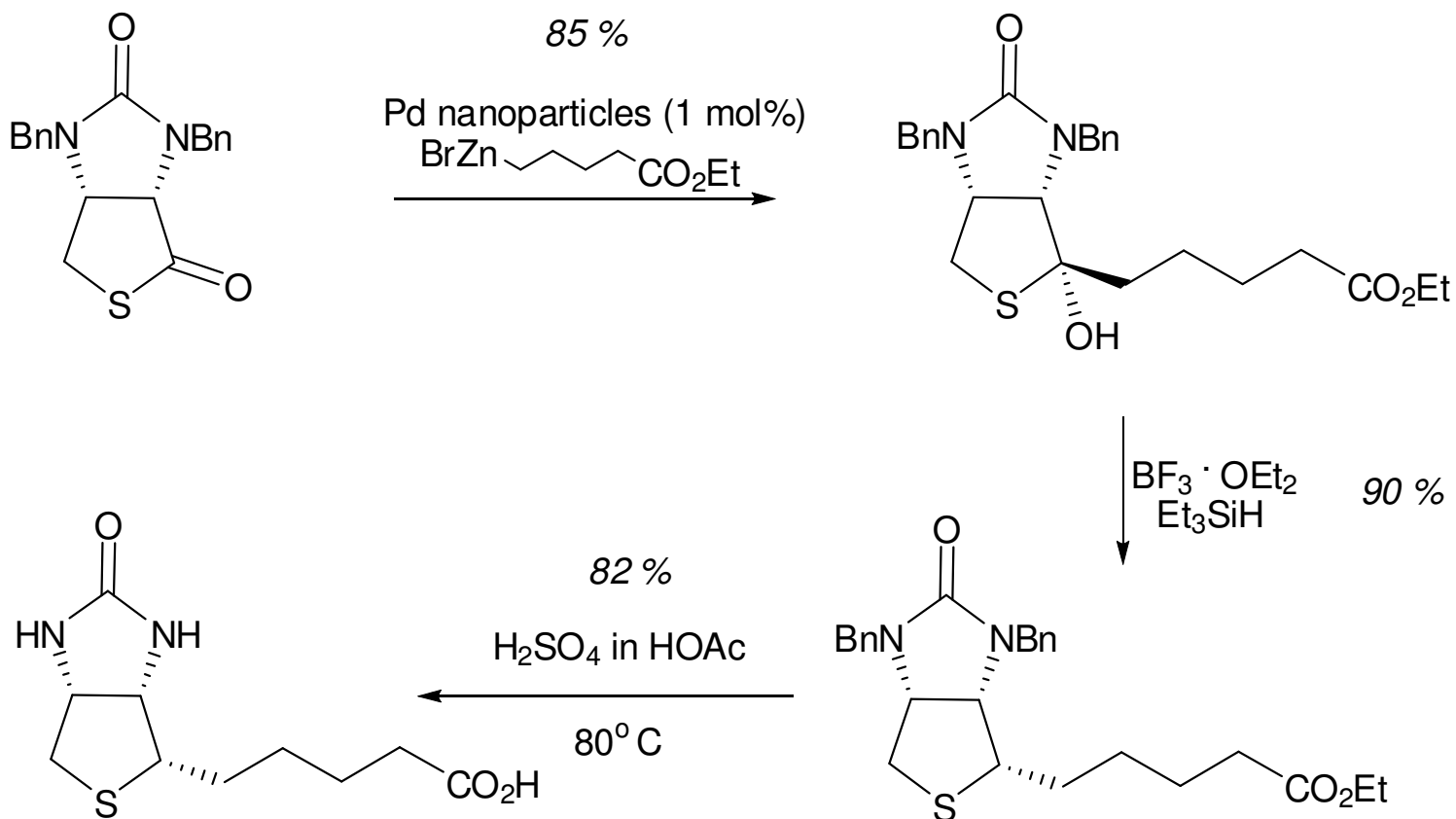
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Chen (2008)



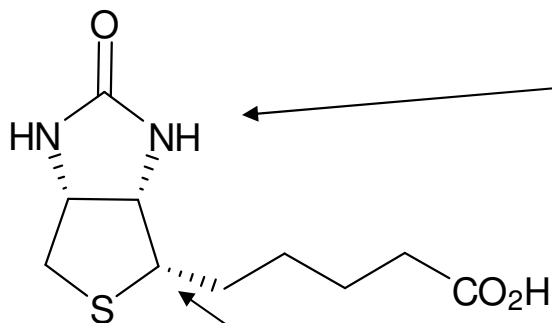
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Chen (2008)



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1949 vs. 2008



Construction of Imidazolinone Ring

1949: 3 steps from fumaric acid.

2008: Aldrich.

Installation of Side Chain

1949: Addition of Grignard reagent followed by malonate and decarboxylation (6 steps).

2008: Fukuyama coupling between thiolactone and organozinc reagent; reduction of 3° alcohol (2 steps).

Introduction of Chirality

1949: Fractional crystallization of diastereomeric salts.

2008: Enantioselective desymmetrization.

Summary

- 1949: Goldberg and Sternbach (HLR)
 - First enantioselective synthesis; simple but elegant (15 steps; ?% yield).
- 1982: Baggiolini et al. (HLR)
 - Unique trans-annular [3+2] reaction (11 steps; 7% yield).
- 1983: Volkmann et al. (Pfizer)
 - Shortest route. Highly original core formation (7 steps; 9% yield).
- 2008: Chen et al. (Fudan University)
 - Enantioselective desymmetrization and Fukuyama Pd coupling (8 steps; 35% yield).

References

- De Clercq, P.J. *Chem Rev.*, **1997**, *97*, 1755-1792.
- Baggiolini, E.G.; Lee, H.L.; Pizzolato, G; Uskokovic, M.R. *J. Am. Chem. Soc.*, **1982**, *104*, 6460-6462.
- Volkmann, R.A.; Davis, J.T.; Meltz, C.N. *J. Am. Chem. Soc.*, **1983**, *105*, 5946-5948.
- Dai, H-F.; Chen, W-X; Zhao, L.; Xiong, F.; Sheng, H.; Chen, F-E. *Adv. Synth. Catal.* **2008**, *350*, 1635-1641.
- K.C. Nicolau and E.J. Sorensen. *Classics in Total Synthesis*. VCH: New York, 2003.
- United States Census, 2000. <http://www.usda.gov/nass/>
- Hutjens, Michael F. *Feed Additives in Dairy Nutrition and Management*. Texas Animal Nutrition Council Proceedings, 2001.