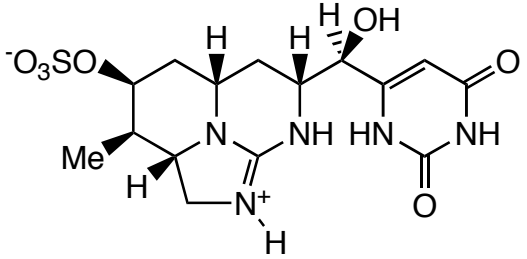
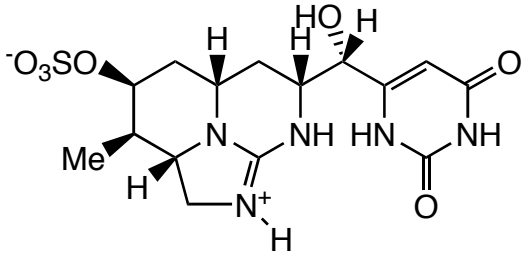
A Concise Asymmetric Synthesis of the Marine Hepatotoxin 7-Epicylindrospermopsin

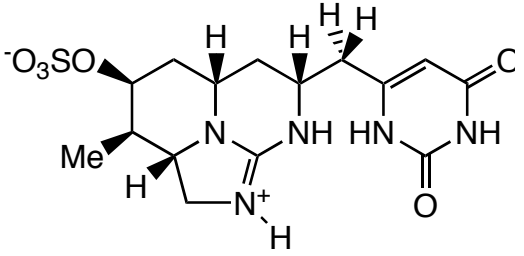
Looper, R. E.; Williams, R. M.
Angew. Chem. Int. Ed. **2004**, *43*, 2930-2933.



Cylindrospermopsin

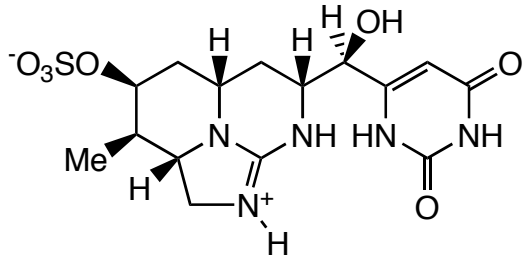


7-Epicylindrospermopsin

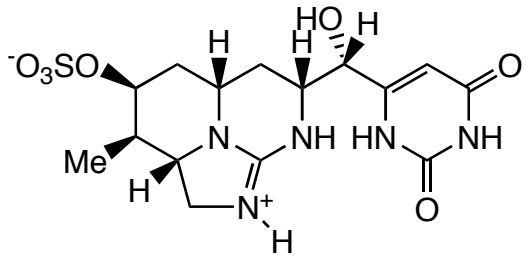


7-Deoxycylindrospermopsin

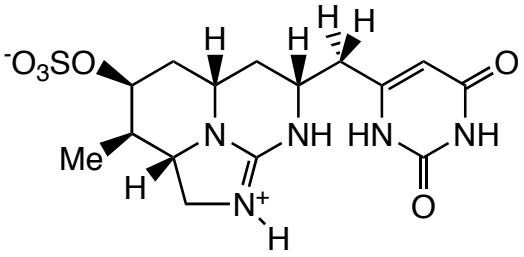
The Cylindrospermopsins



Cylindrospermopsin



7-Epicylindrospermopsin



7-Deoxycylindrospermopsin

- Produced by water-borne cyanobacteria found worldwide in temperate, sub-tropical and tropical areas
- Cylindrospermopsin and 7-Epicylindrospermopsin cause severe hepatoenteritis in mice and humans.
- Linked to higher rates of liver cancer in third world nations.
- 7-Deoxycylindrospermopsin is nontoxic in mice.
- Four synthetic routes of cylindrospermopsins have been reported.

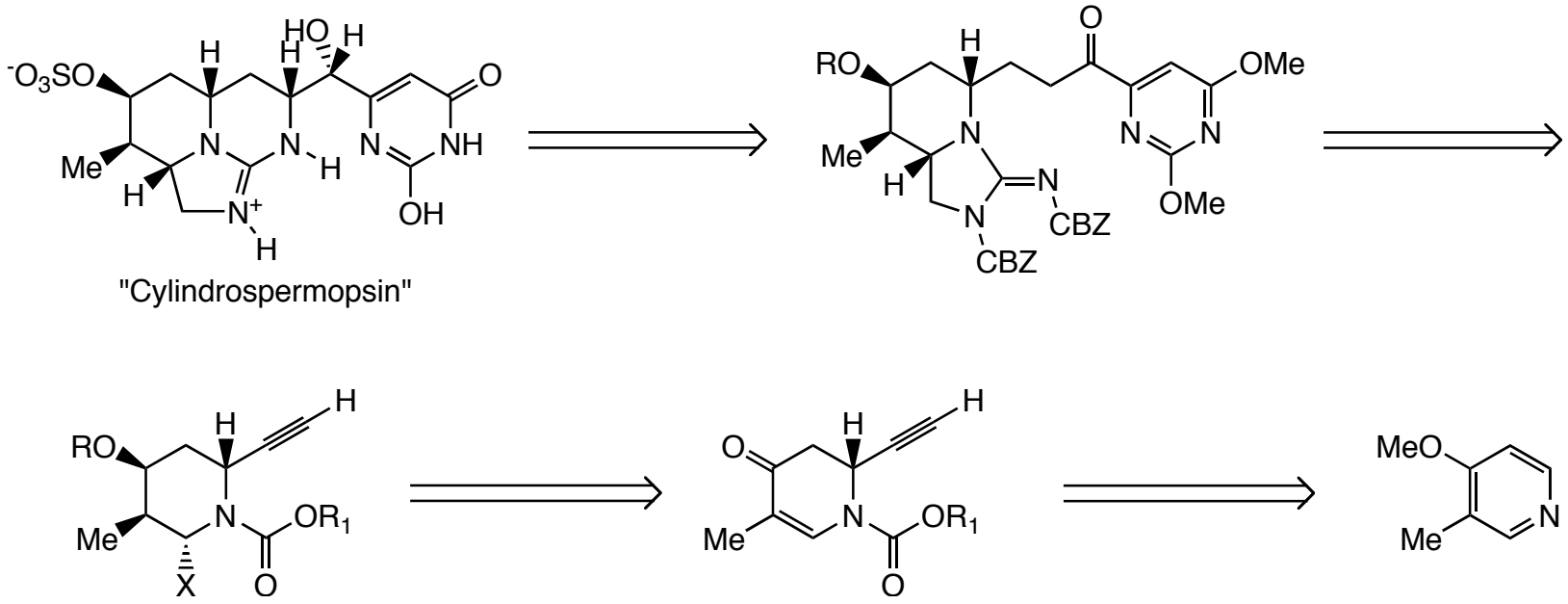
Ohtani, I.; Moore, R. E. *J. Am. Chem. Soc.* **1992**, *114*, 7941-7942.

Banker, R.; Teltsch, B.; Sukenik, A. Carmeli, S. *J. Nat. Prod.* **2000**, *63*, 387.

Norris, R. L.; Eaglesham, G. K.; Pierens, G; Shaw, G. R.; Smith, M. J.; Chiswell, R. K.; Seawright, A. A.; Moore, M. R. *Environ. Toxicol*. **1999**, *14*, 163.

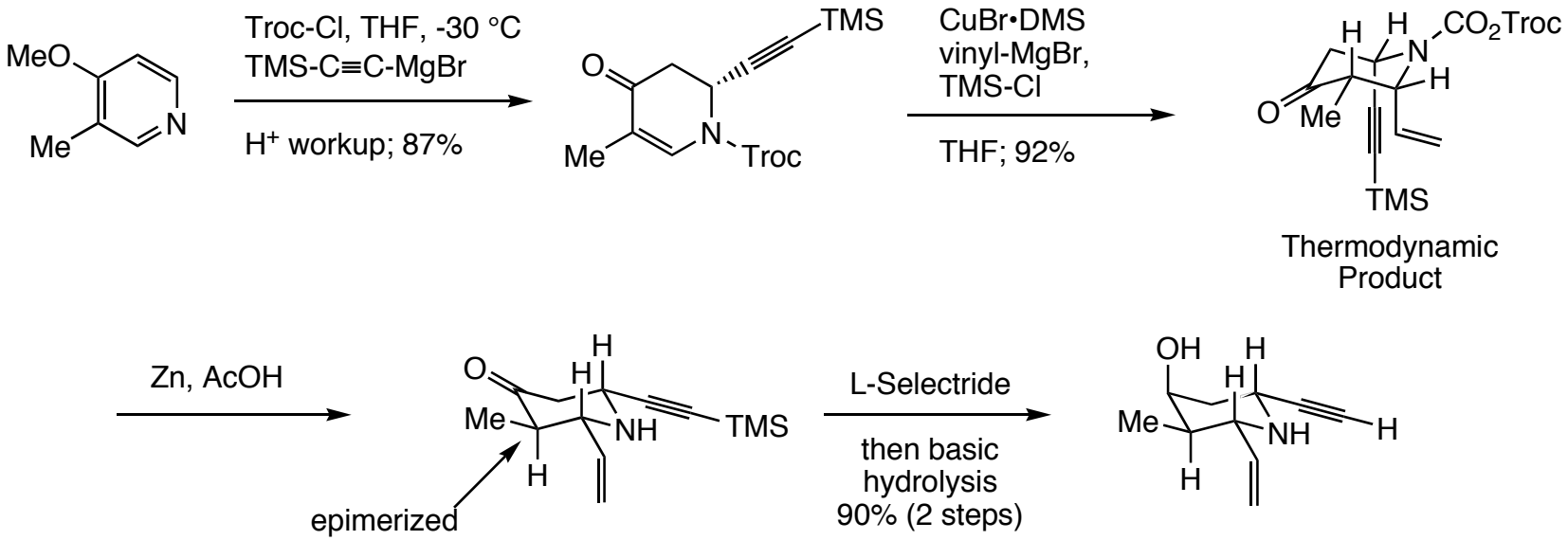
For a recent review, refer to: Murphy, P. J.; Thomas, C. W. *Chem. Soc. Rev.* **2001**, *30*, 303.

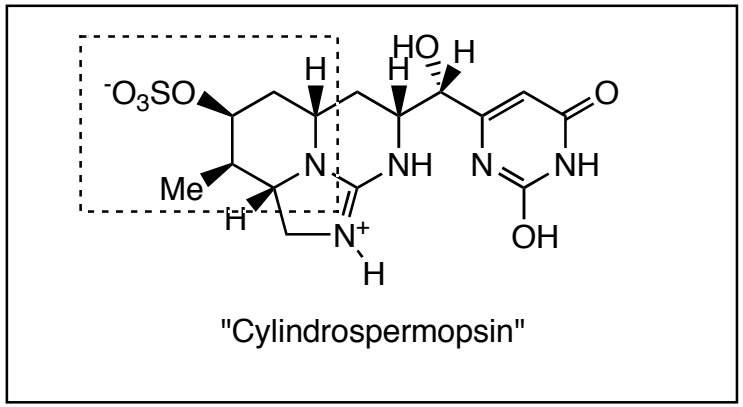
Snider's Retrosynthesis of (±)-Cylindrospermopsin



Xie, C; Runnegar, M. T. C.; Snider, B. B. *J. Am. Chem. Soc.* **2000**, *122*, 5017-5024.

Snider's Synthesis of (±)-Cylindrospermopsin





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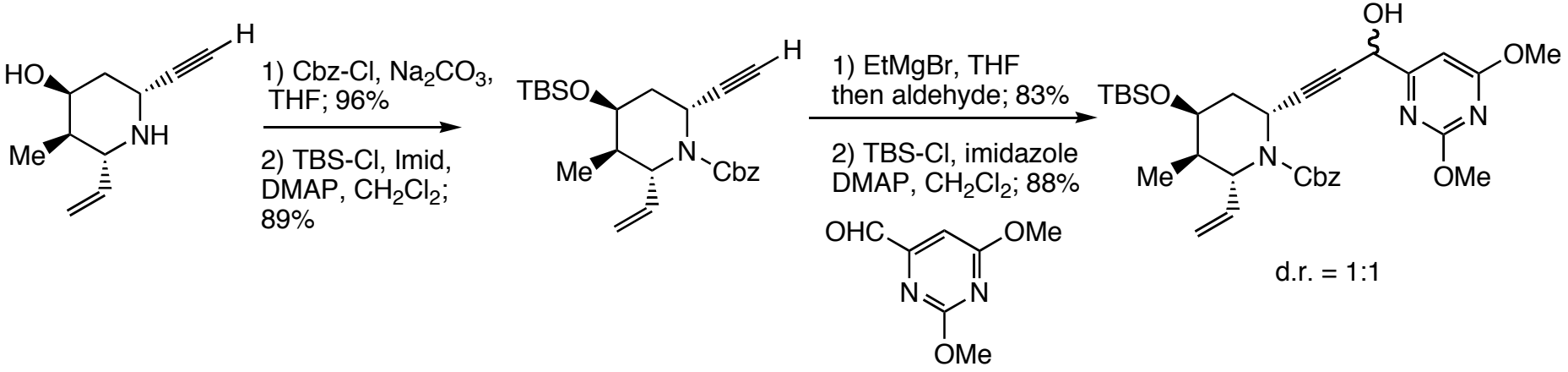
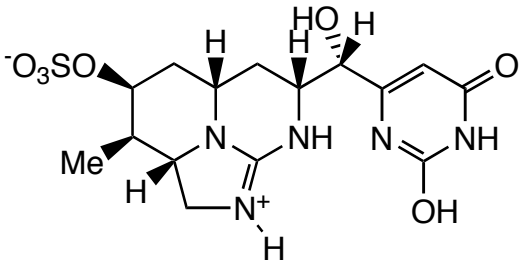
Snider's Synthesis of (±)-Cylindrospermopsin





"Cylindrospermopsin"

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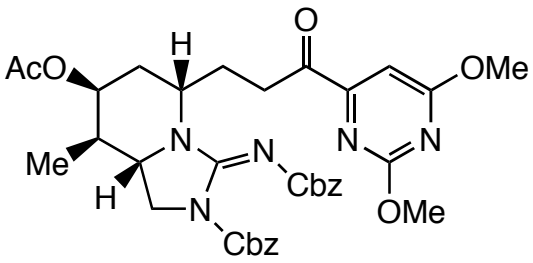
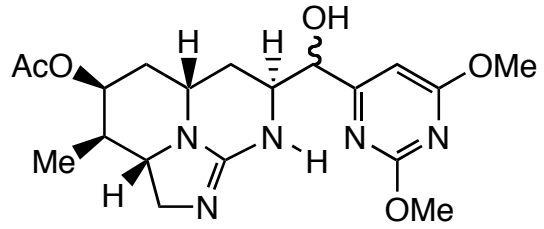
Snider's Synthesis of (±)-Cylindrospermopsin

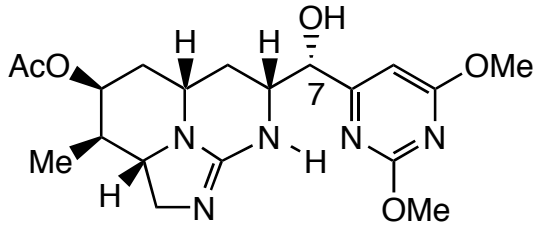


1) $CuBr_2$, EtOAc, rt
2) H_2, $Pd(OH)_2/C$, MeOH



28%

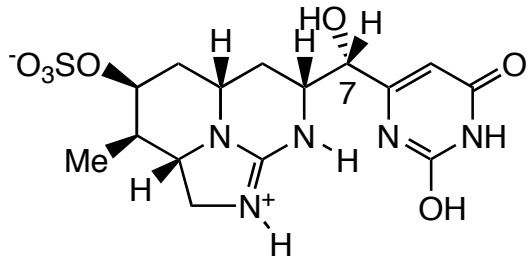
+



42%

- Stereochemistry at C_7 assigned by ^1H NMR coupling constants, assuming an intramolecular hydrogen-bonded structure.

1) conc HCl, reflux; 95%
2) SO_3•pyr, pyr, DMF; 60-80%



"(±)-Cylindrospermopsin"
^1H and ^{13}C match Natural Product
20 steps, 3.5 % overall yield

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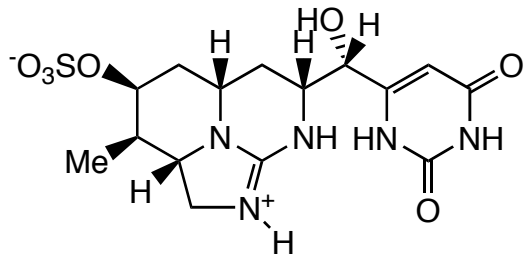
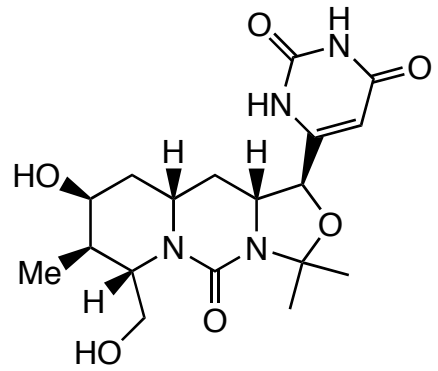
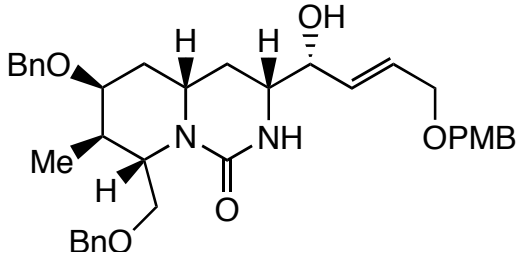
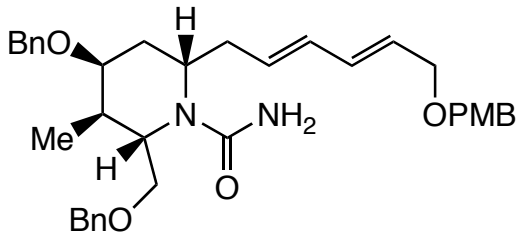
Weinreb's Retrosynthesis of Cylindrospermopsin

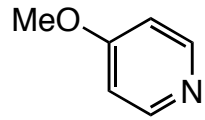


7-Epicylindrospermopsin



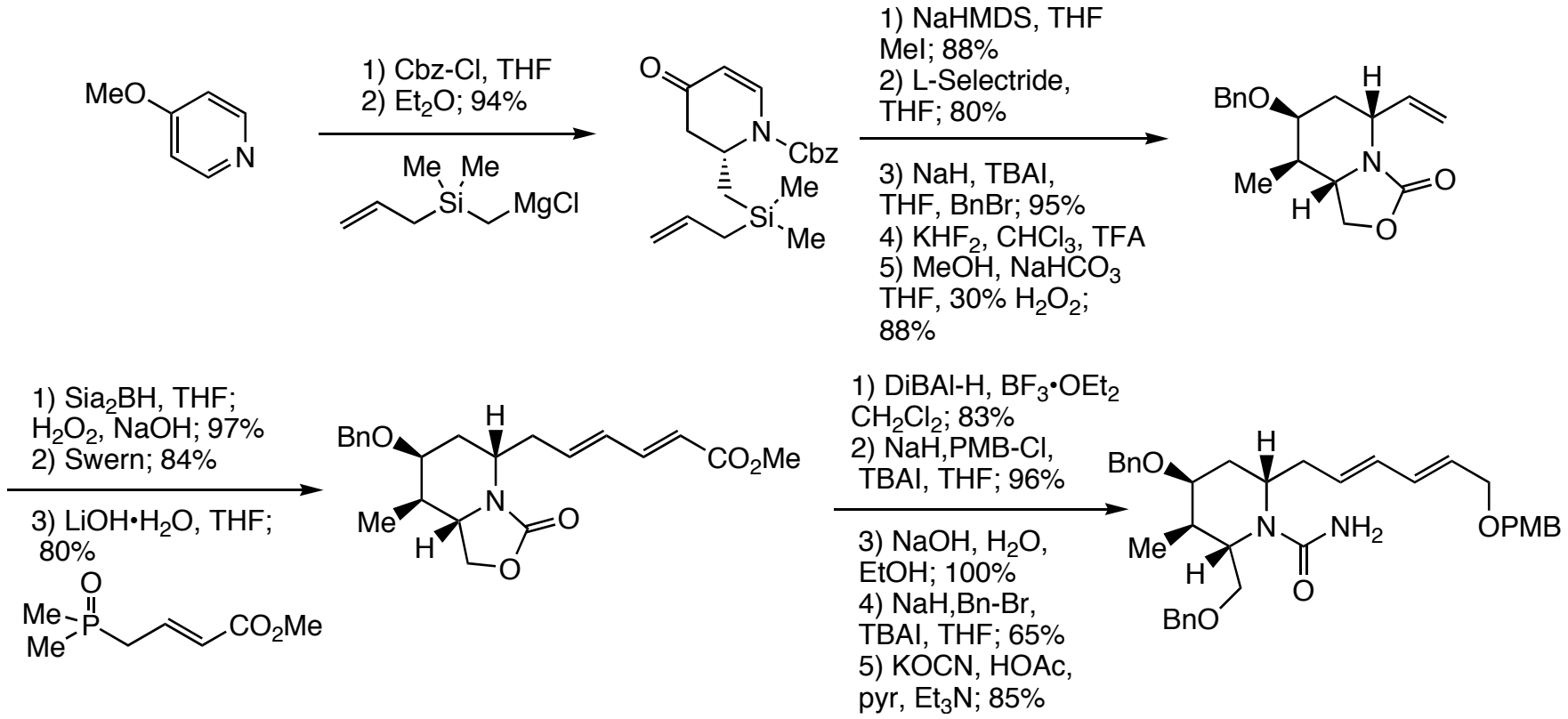






Heintzelman, G. R.; Fang, W-K.; Keen, S. P.; Wallace, G. A.; Weinreb, S. M.
J. Am. Chem. Soc. **2002**, *124*, 3939-3945.

Weinreb's Synthesis of Cylindrospermopsin



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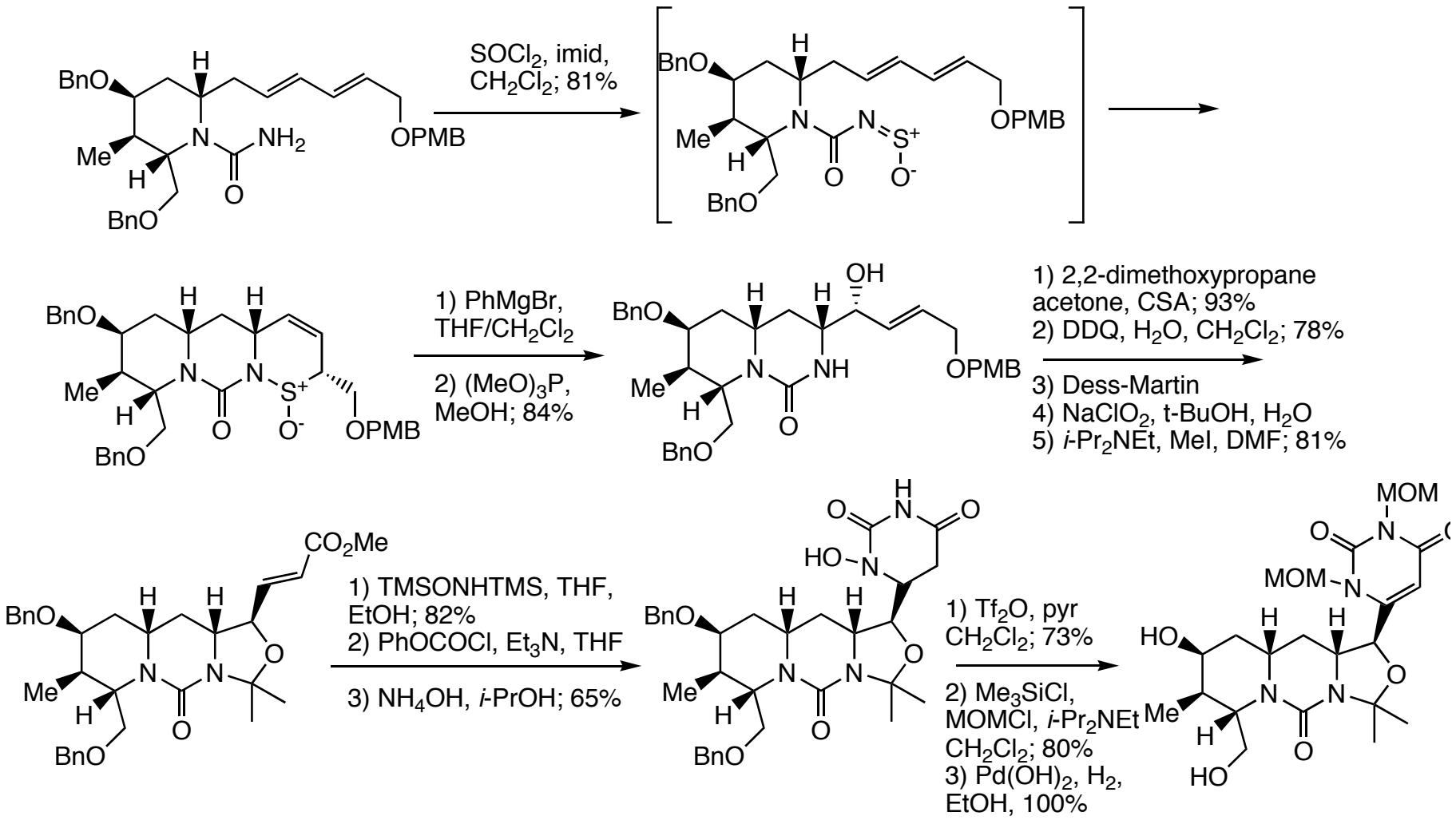

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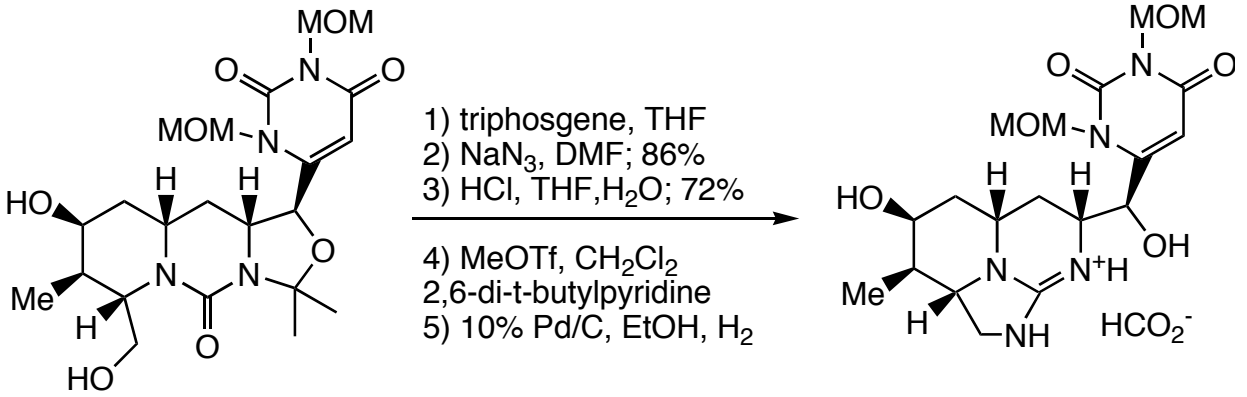

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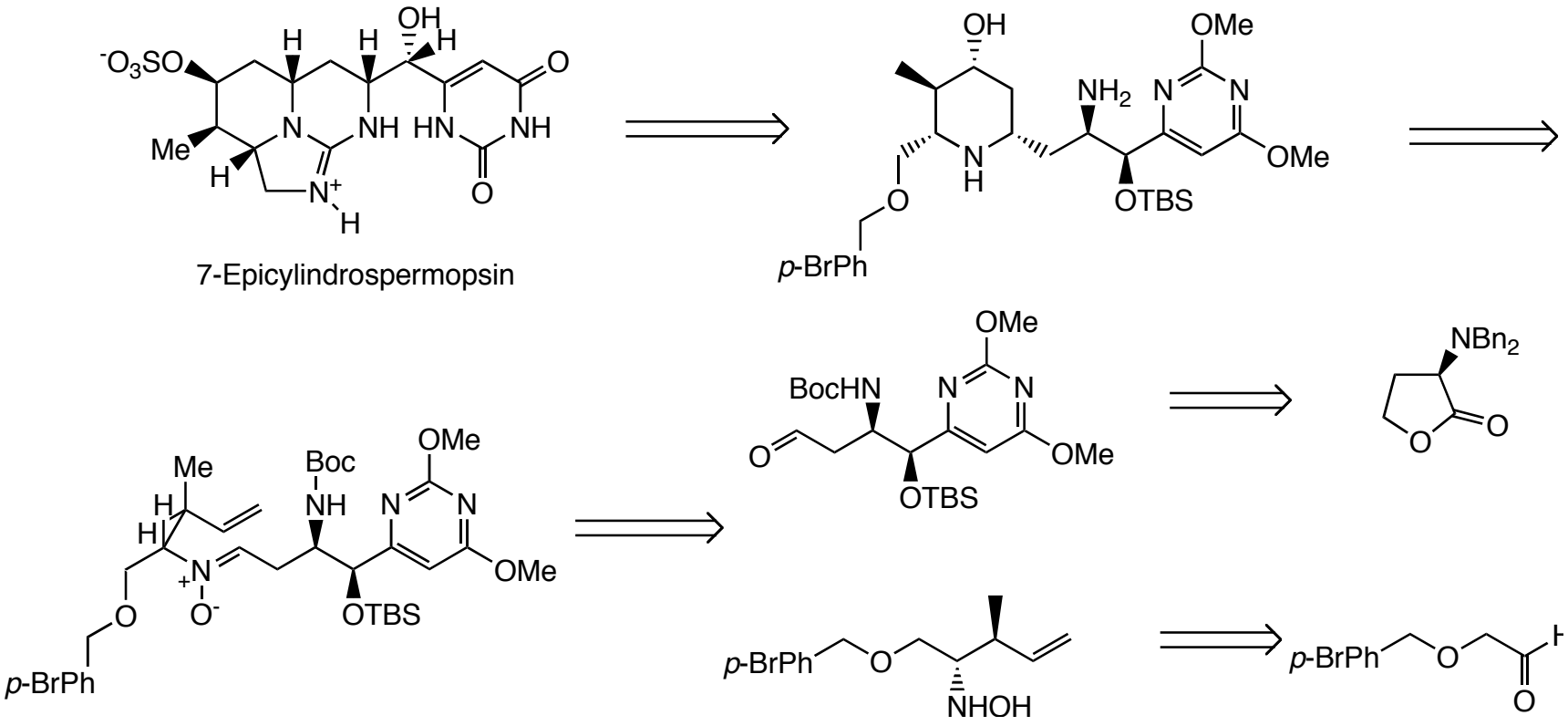
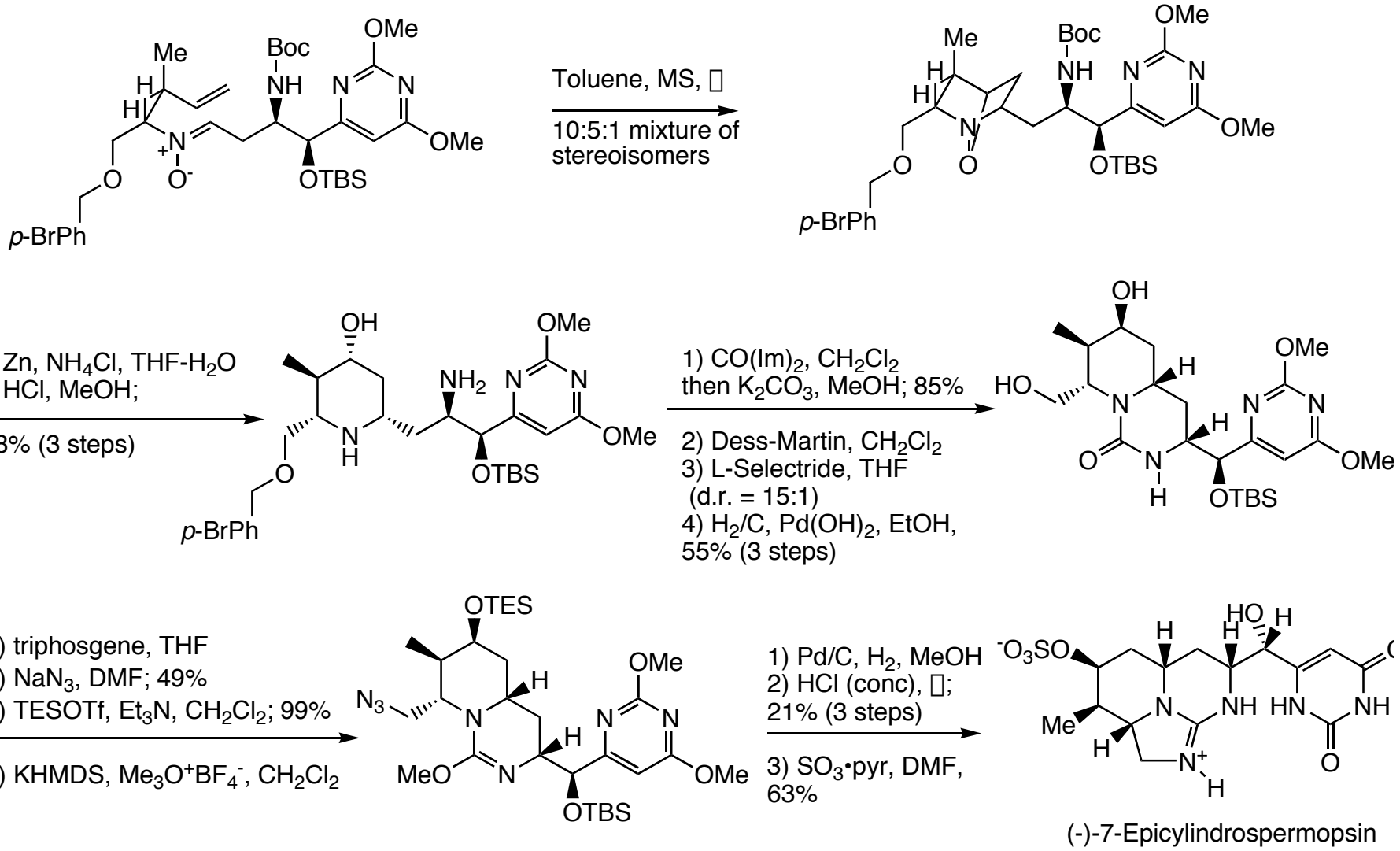
White's Retrosynthesis of (-)-7-Epicylindrospermopsin



White, J. D.; Hansen, J. D. *J. Am Chem. Soc*. **2002**, *124*, 4950-4951.

White's Synthesis of (-)-7-Epicylindrospermopsin



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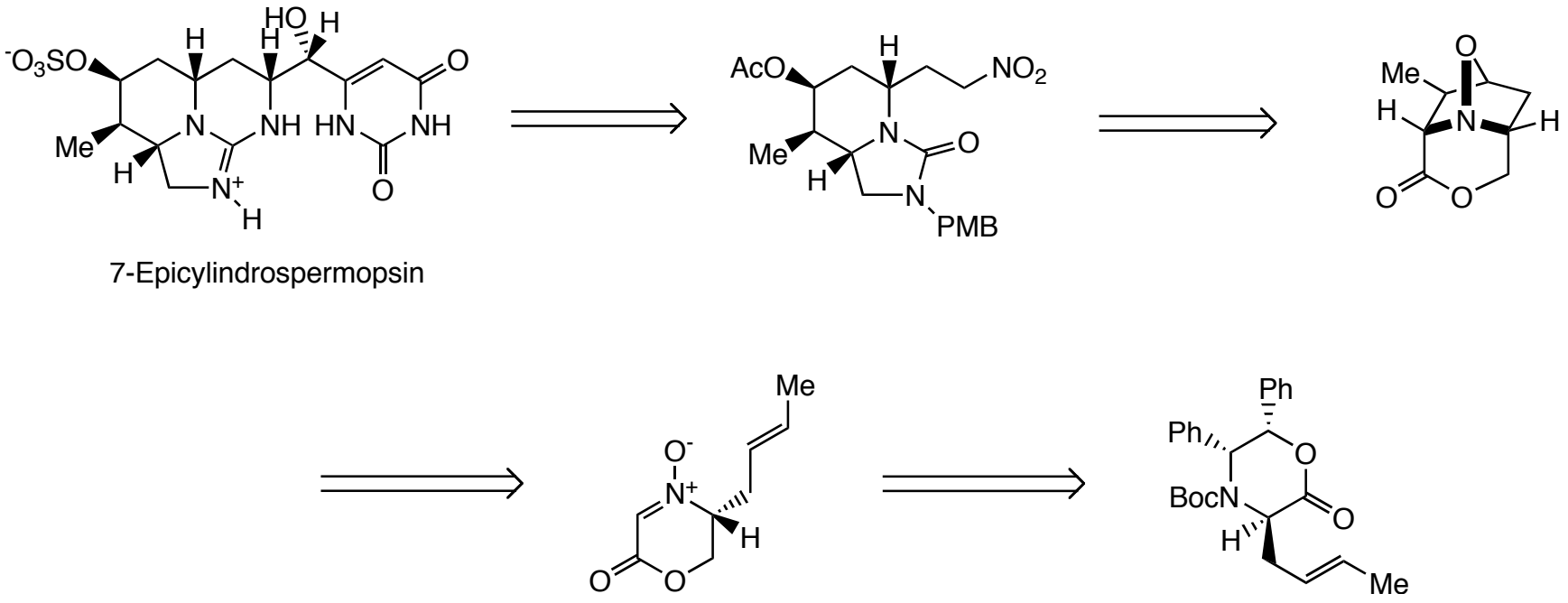
William's Retrosynthesis of 7-Epicylindrospermopsin



7-Epicylindrospermopsin

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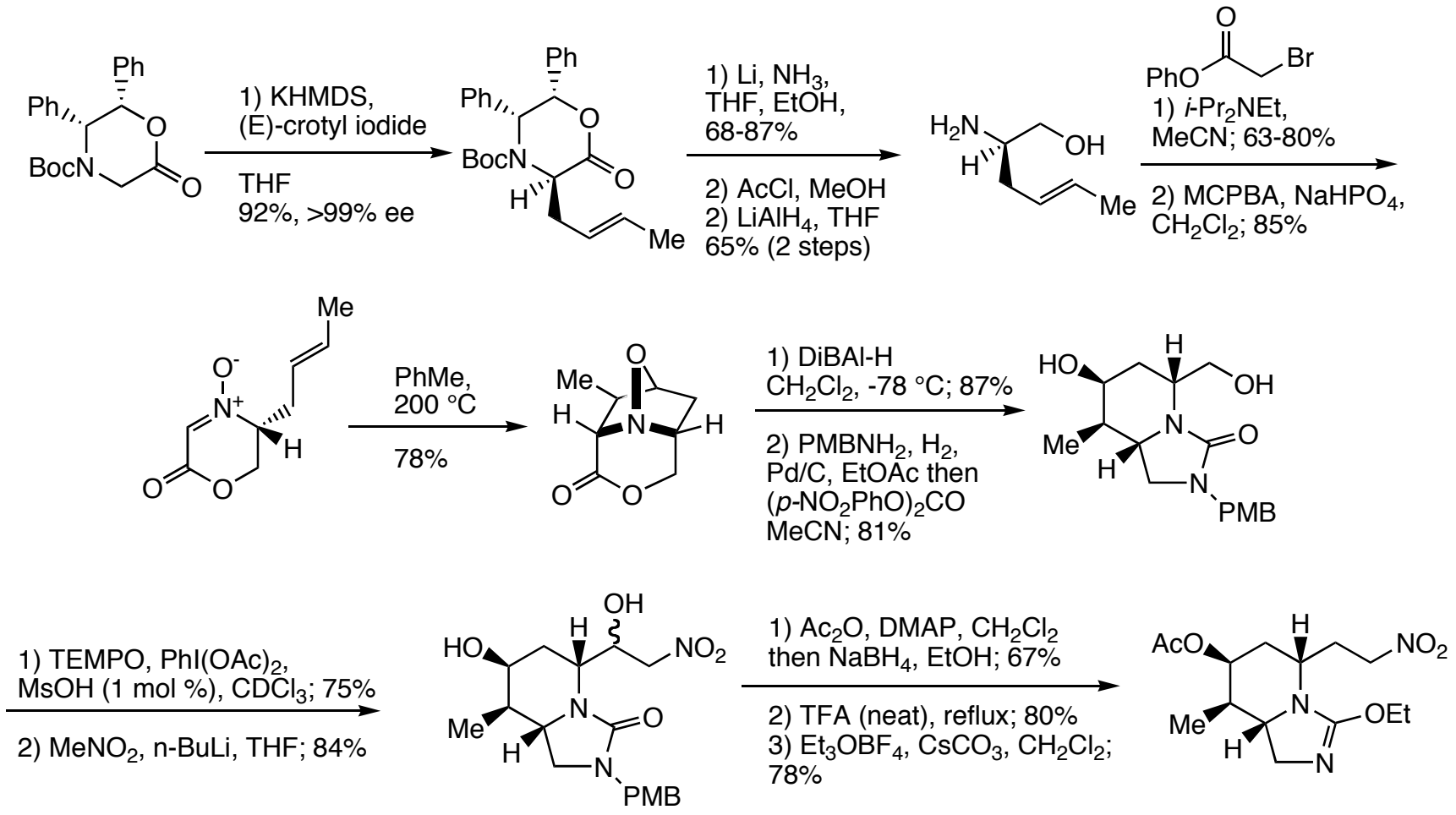

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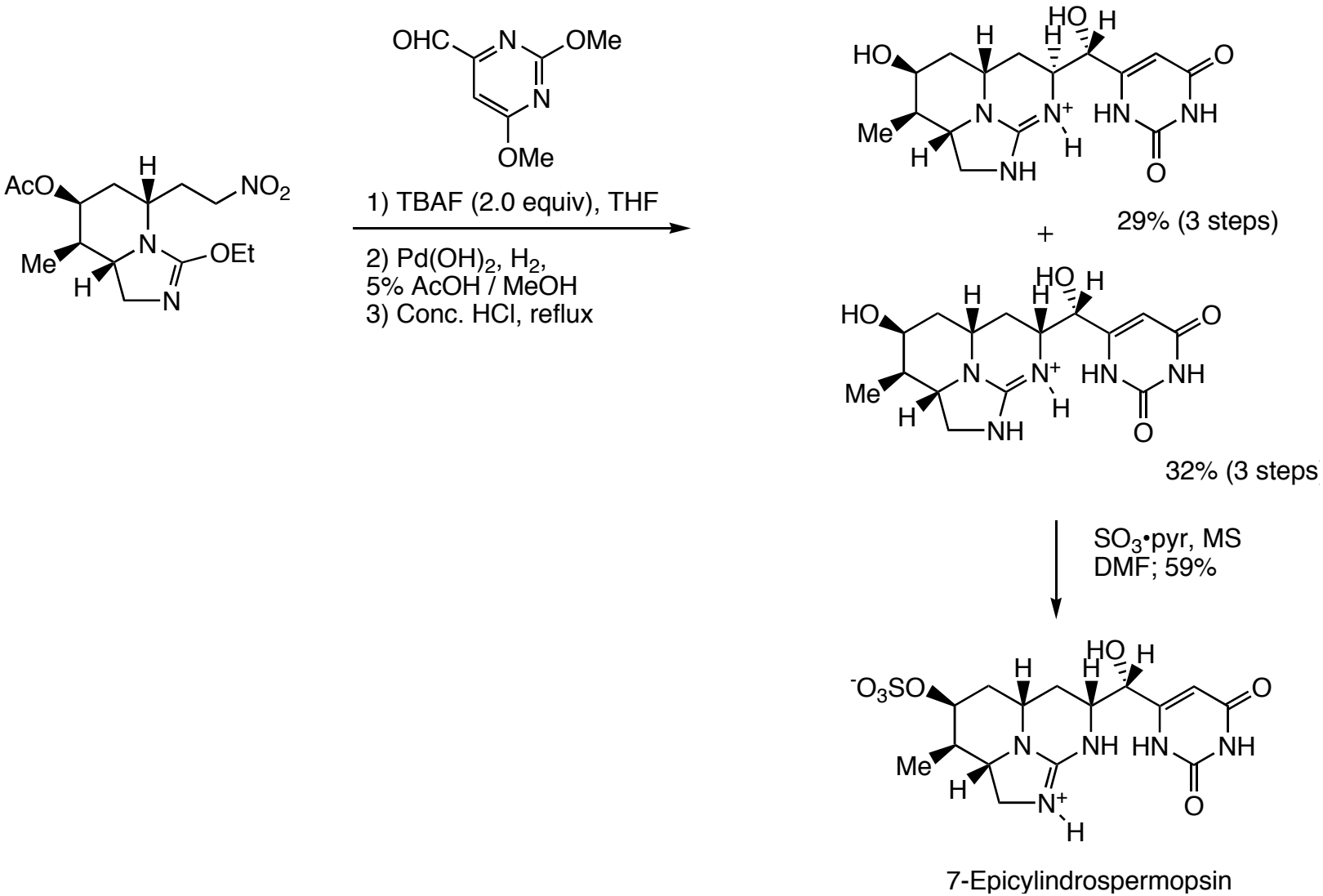

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Summary:

Four routes to the cylindrospermopsins have been published:

1) Snider and coworkers:
   - The first synthesis.
   - 20 steps, 3.5% overall yield, racemic.
   - The C_7-stereocenter could not be definitively assigned.
   - Key reaction: □-bromination/ hydrogenation/ intramolecular S_N2.

2) Weinreb and coworkers:
   - 30 steps, 0.2% overall yield, racemic.
   - The C_7-stereocenter was definitively assigned and led to a reassignment of the original structure.
   - Key reaction: N-Sulfinyl Diels-Alder.

3) White and Hansen:
   - 28 steps (19 longest linear), 0.9% overall yield, enantioselective.
   - absolute stereochemistry of 7-epicylindrospermopsin assigned as 7S, 8R, 10S, 12S, 13R, 14S.
   - Key reaction: intramolecular nitrone 1,3-dipolar cycloaddition.

4) Williams and Looper:
   - 18 steps, 1.0 % overall yield, enantioselective.
   - Shortest route with minimal protecting groups.
   - Key reaction: intramolecular nitrone 1,3-dipolar cycloaddition and Henry reaction.