The Manzamine Synthetic Problem

Lecture Notes

Key Literature

J. E. Baldwin, R. C. Whitehead, Tetrahedron Lett. 1992, 33, 2059.
J. E. Baldwin and co-workers, Angew. Chem. Int. Ed. 1998, 110, 2806.

J. D. Winkler, J. M. Axten, J. Am. Chem. Soc. 1998, 120, 6425.
J. D. Winkler and co-workers, Tetrahedron 1998, 54, 7045.

S. F. Martin and co-workers, J. Am. Chem. Soc. 1999, 121, 866.
S. F. Martin and co-workers, J. Am. Chem. Soc. 2002, 124, 8584.

Key Reviews

K. C. Nicolaou, S. A. Snyder, Classics in Total Synthesis II, 2003, Chapter 8.

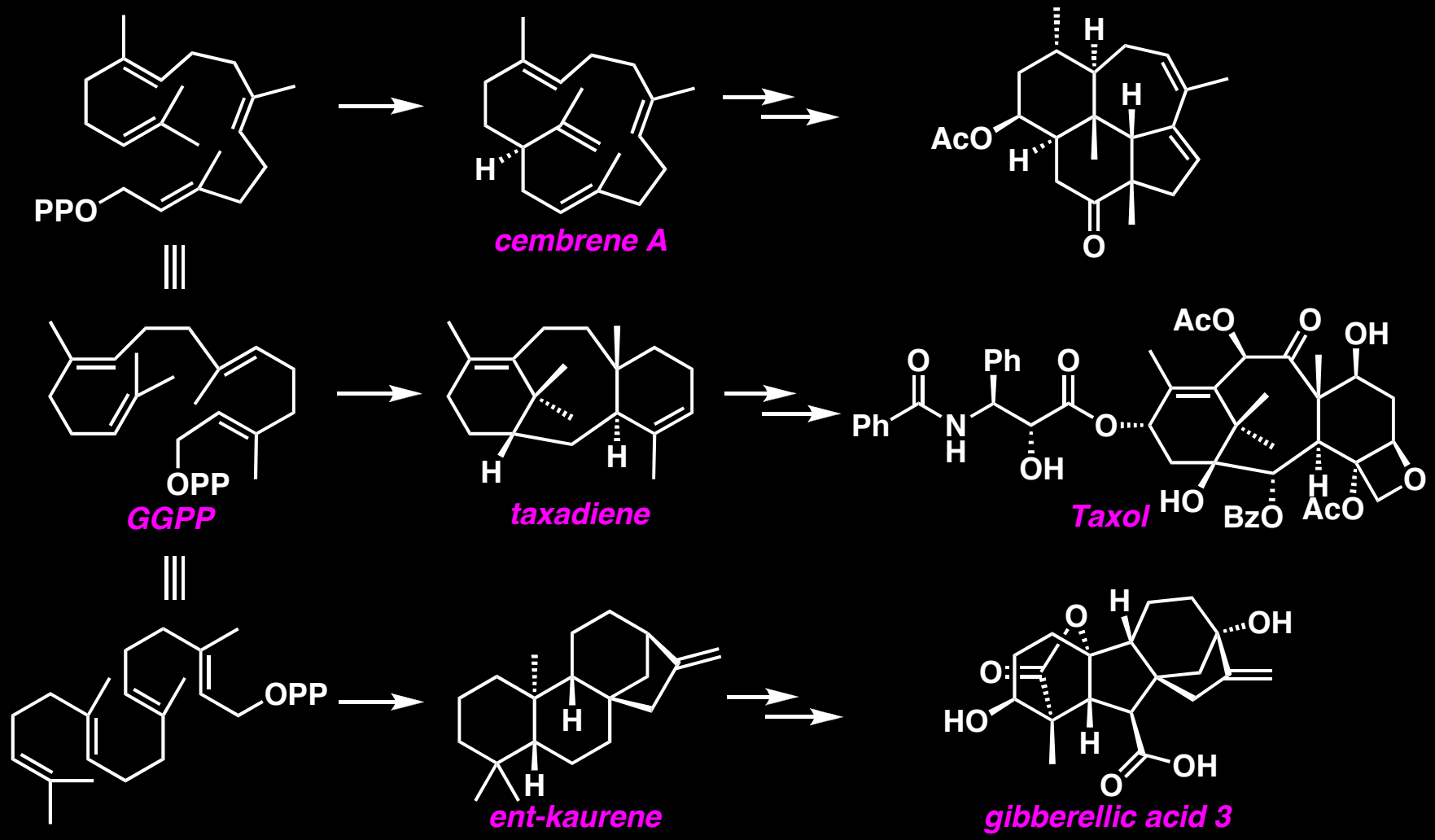
Words of Wisdom from Our Synthetic Elders

R. B. Woodward

Although the specific objective in synthetic work is defined with unique precision, the manner of reaching it most emphatically is not. It would be possible to synthesize a molecule in countless different ways, no one of which would resemble any other except in its outcome. Much of the charm and fascination of this kind of work lies in the free reign which the imagination may be permitted in planning the adventure, as well as in executing it.

R. B. Woodward, Harvey Lecture Ser. 1963 - 1964, 59, 31.

Privileged Starting Points For Molecular Diversity



For a review, see: M. A. Fischbach, J. Clardy, Nature: Chem. Biol. 2007, 3, 353.

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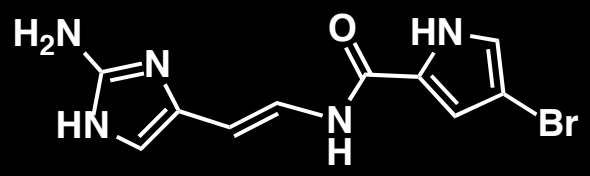
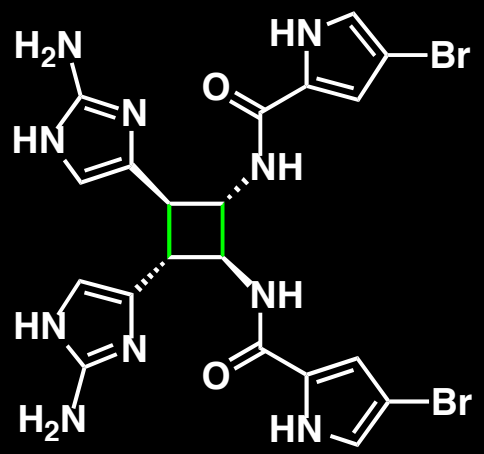
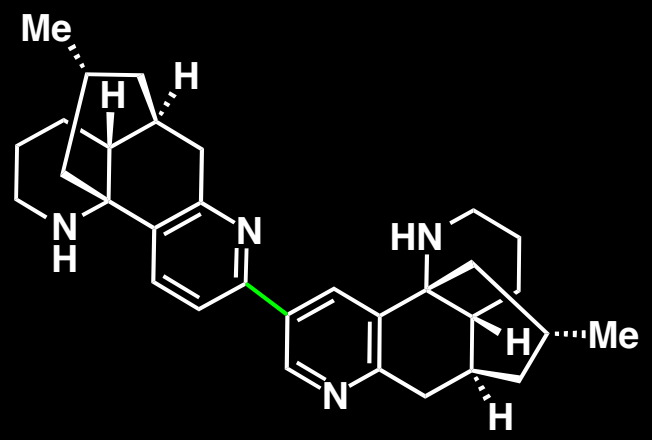


hymenidin

lycodine



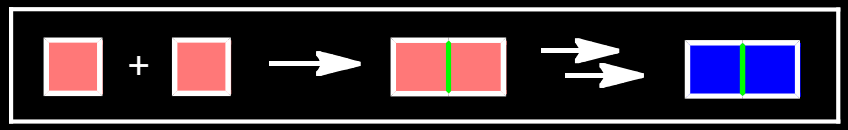
sceptrin



(+)-complanadine A

For a perspective, see: S. A. Snyder, Nature 2010, 465, 560.

Early-Stage Dimerization and Elaboration to Final Target



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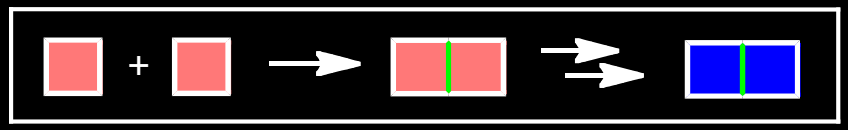

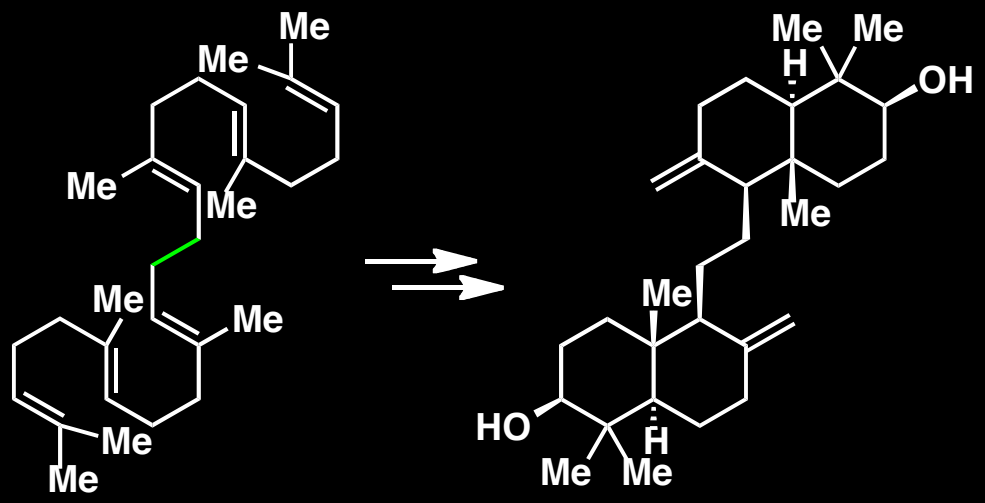

squalene *onocerin*

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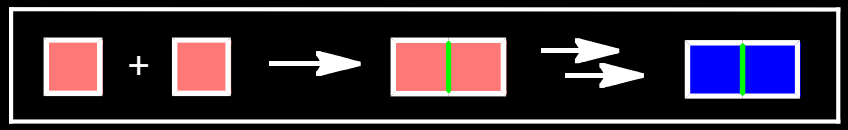

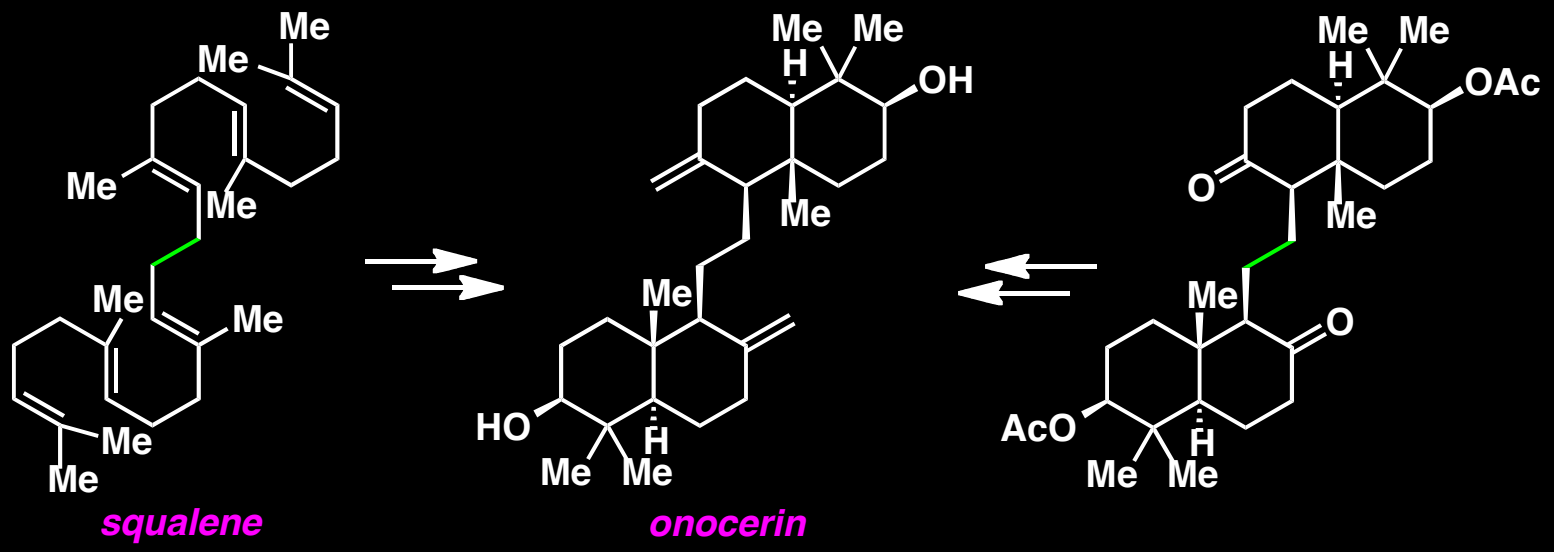

G. Stork, A. Meisels, J. E. Davies, J. Am. Chem. Soc. 1963, 85, 3419.

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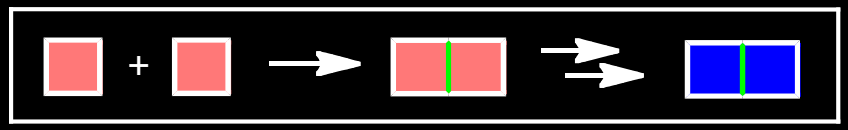
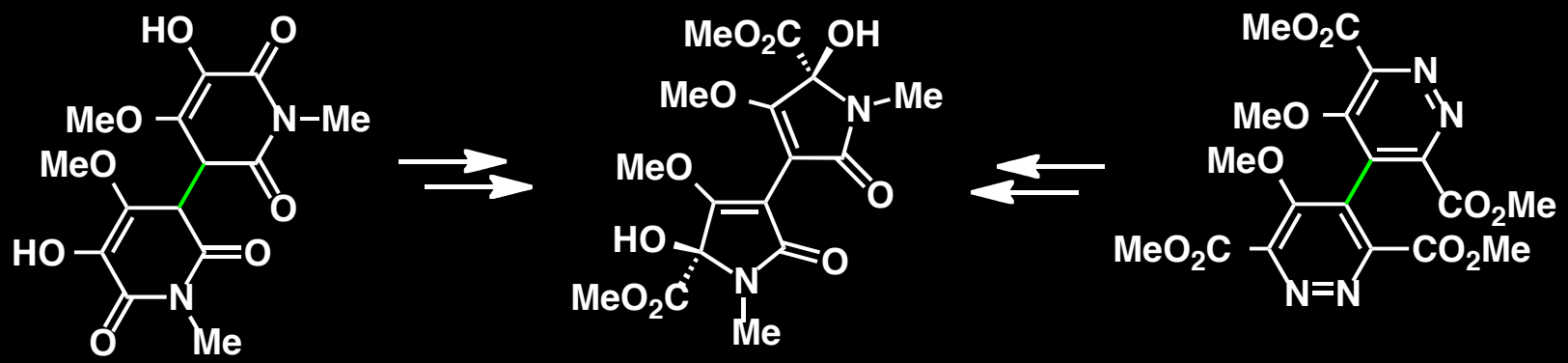
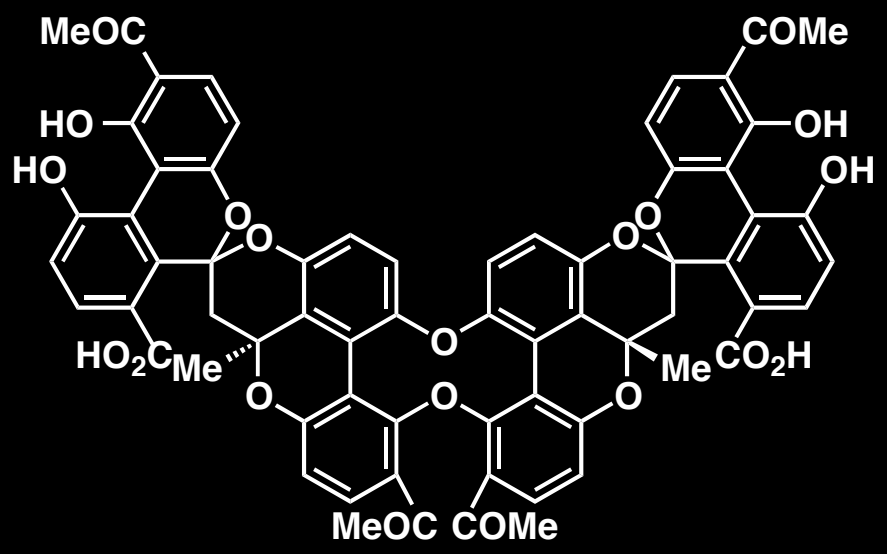




meso-isochrysohermidin

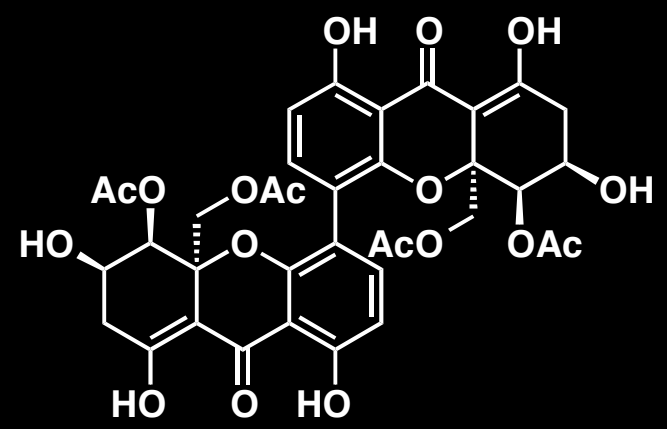
D. L Boger, C. M. Baldino, J. Am. Chem. Soc. 1993, 115, 11418.

Dimeric Natural Products: A Common Occurrance



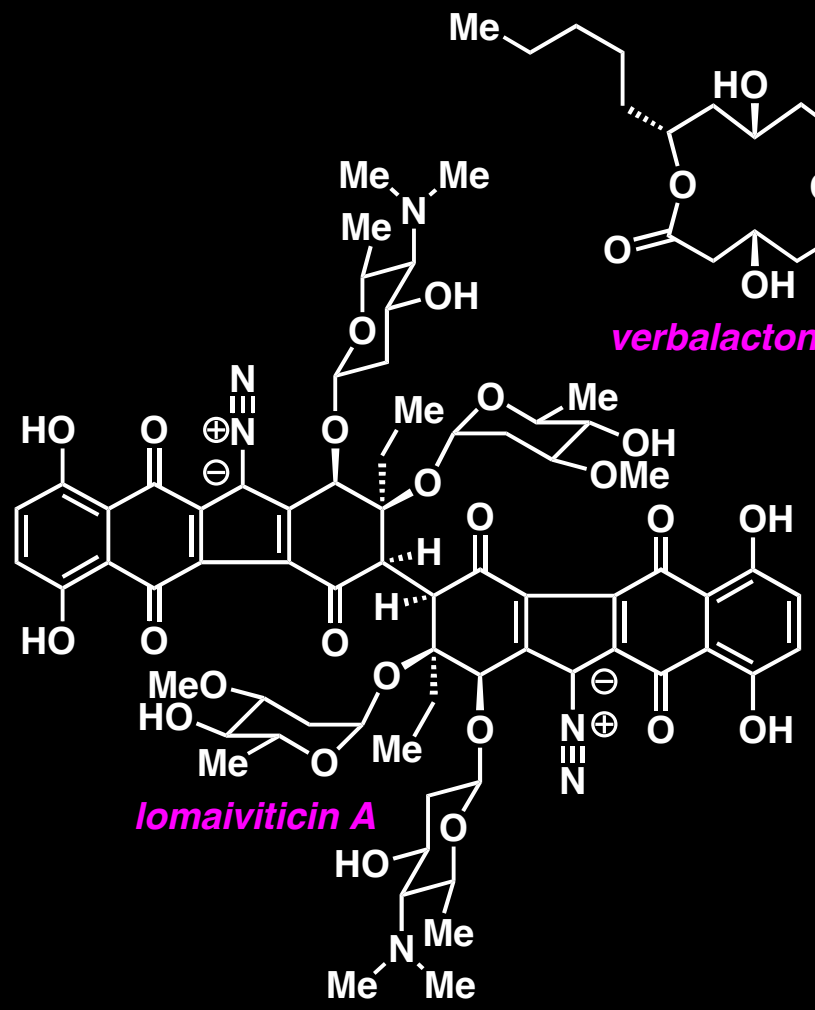
cynantetrone

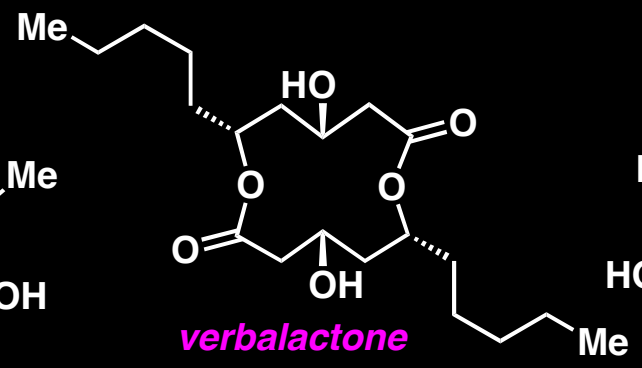
psycholeine

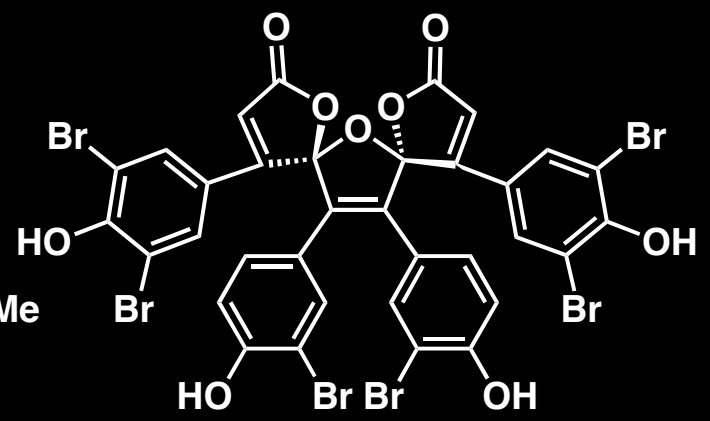


phomoxanthone A

Dimeric Natural Products: A Common Occurrance







For a review on strategies to access such targets, see:
M. Vrettou, A.A. Gray, A.R.E. Brewer, A.G.M. Barrett, Tetrahedron 2007, 63, 1487.

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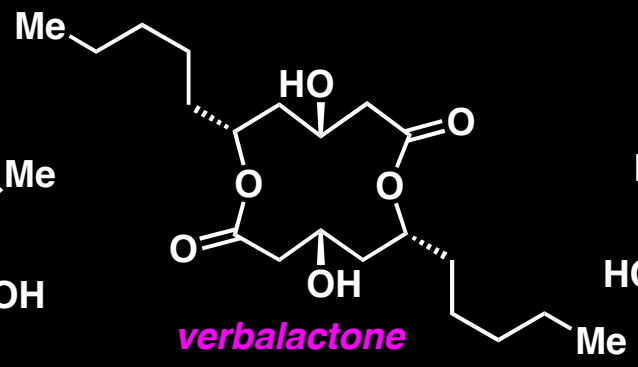
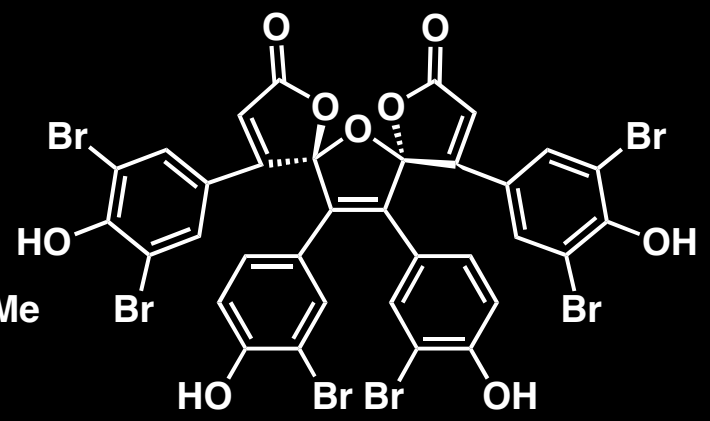
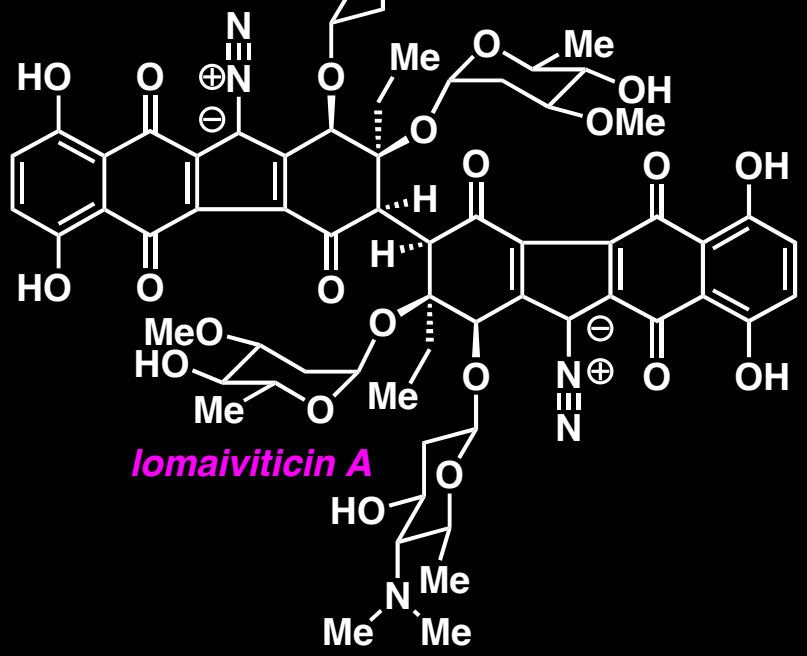


verbalactone



prunolide B



lomaiviticin A

CP-225,917 (phomoidride A)

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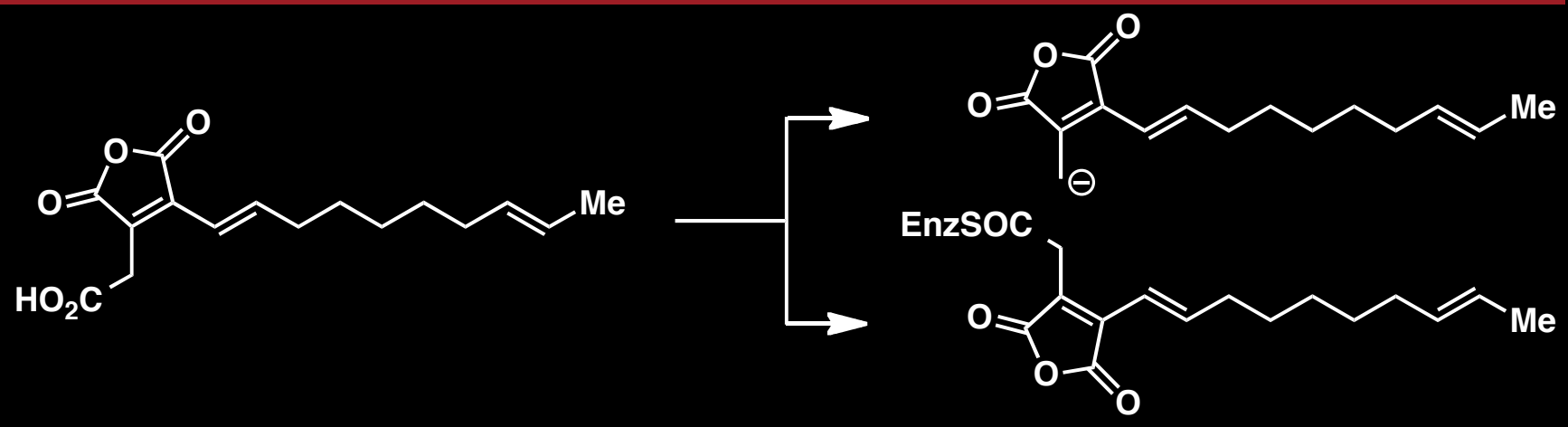
Hidden Symmetry within the CP-Molecules



G. A. Sulikowski and co-workers, Org. Lett. 2002, 4, 1451 and references therein.

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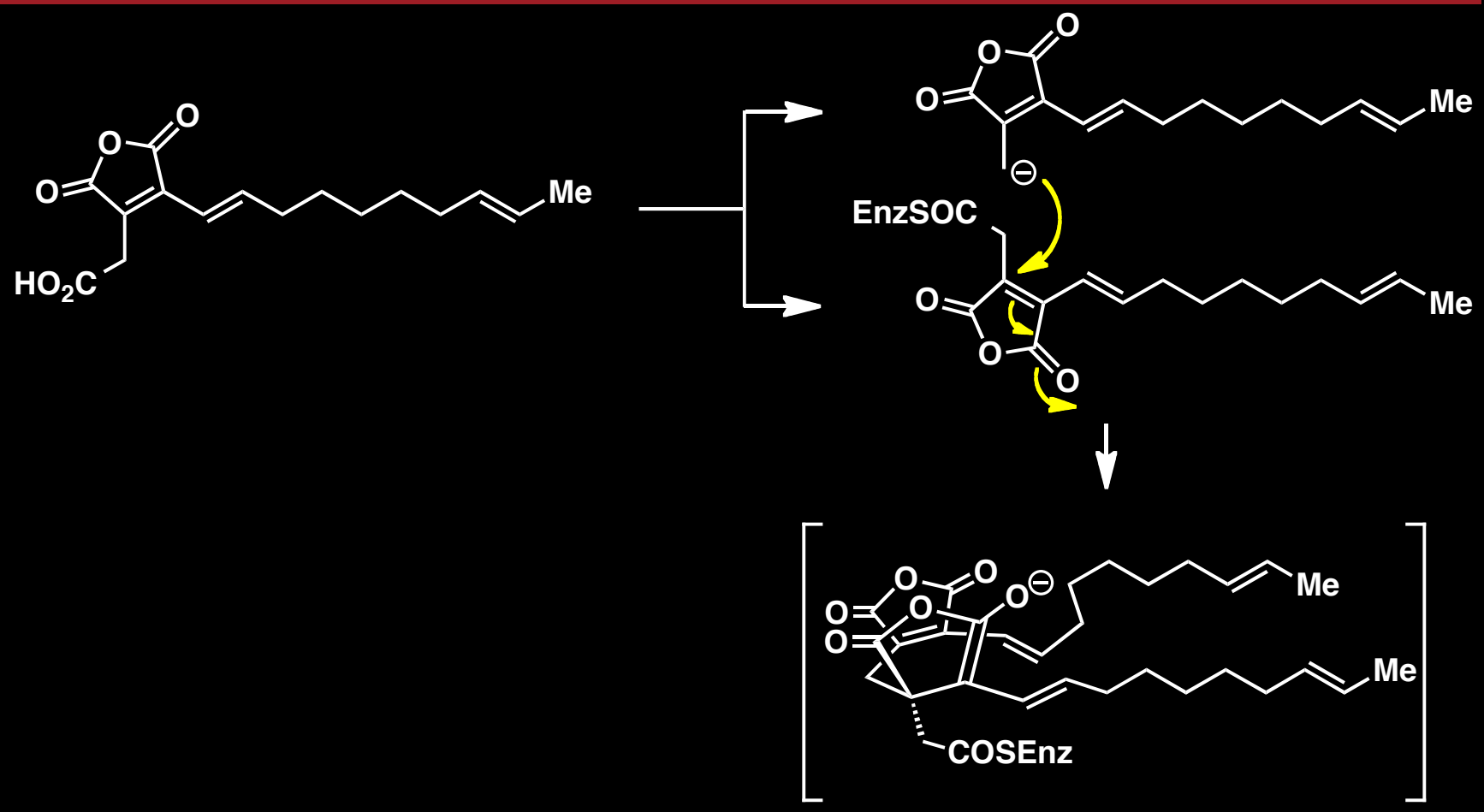

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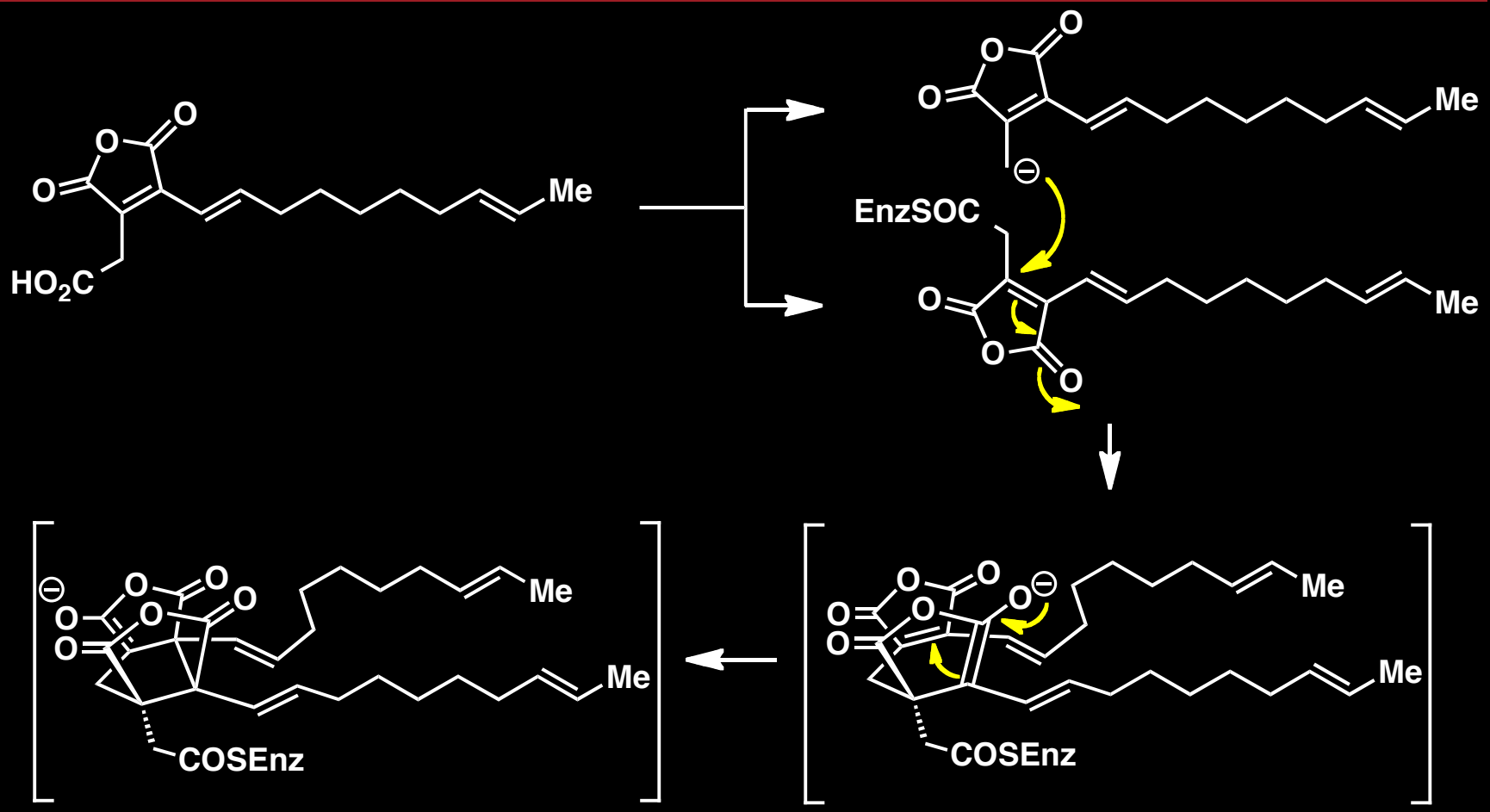

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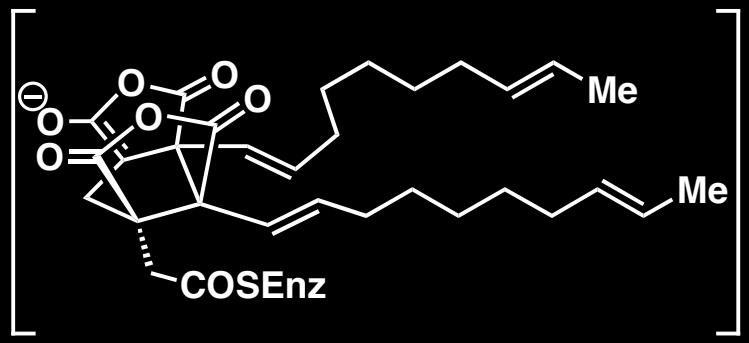

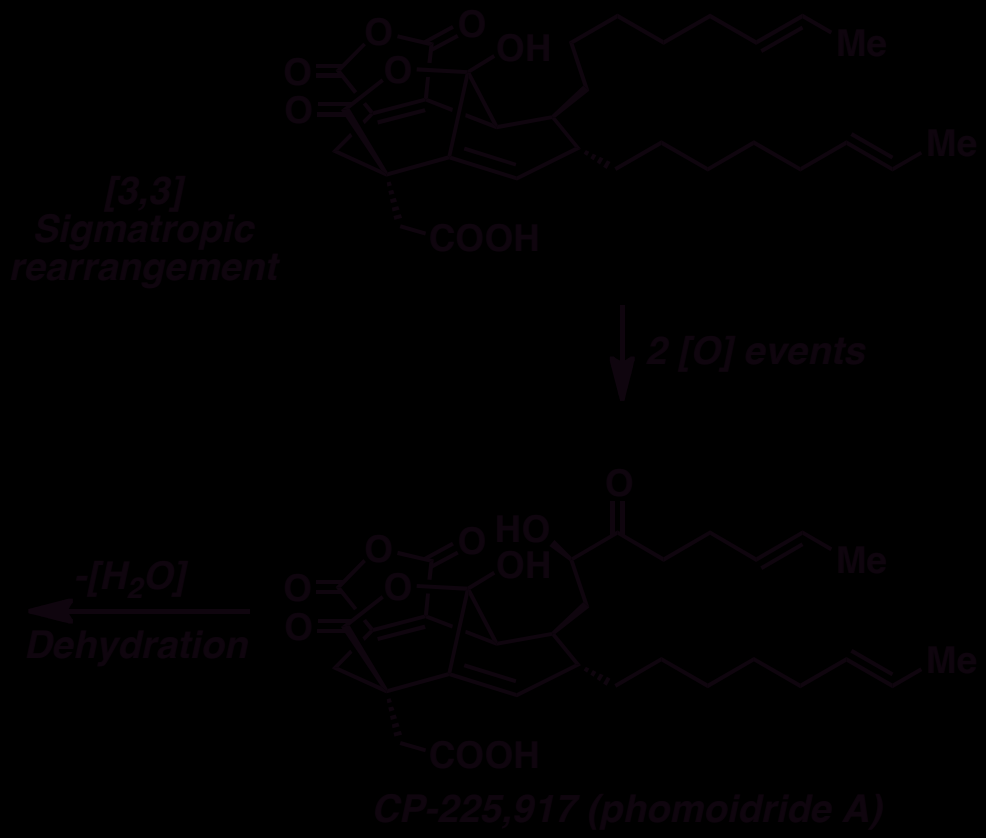

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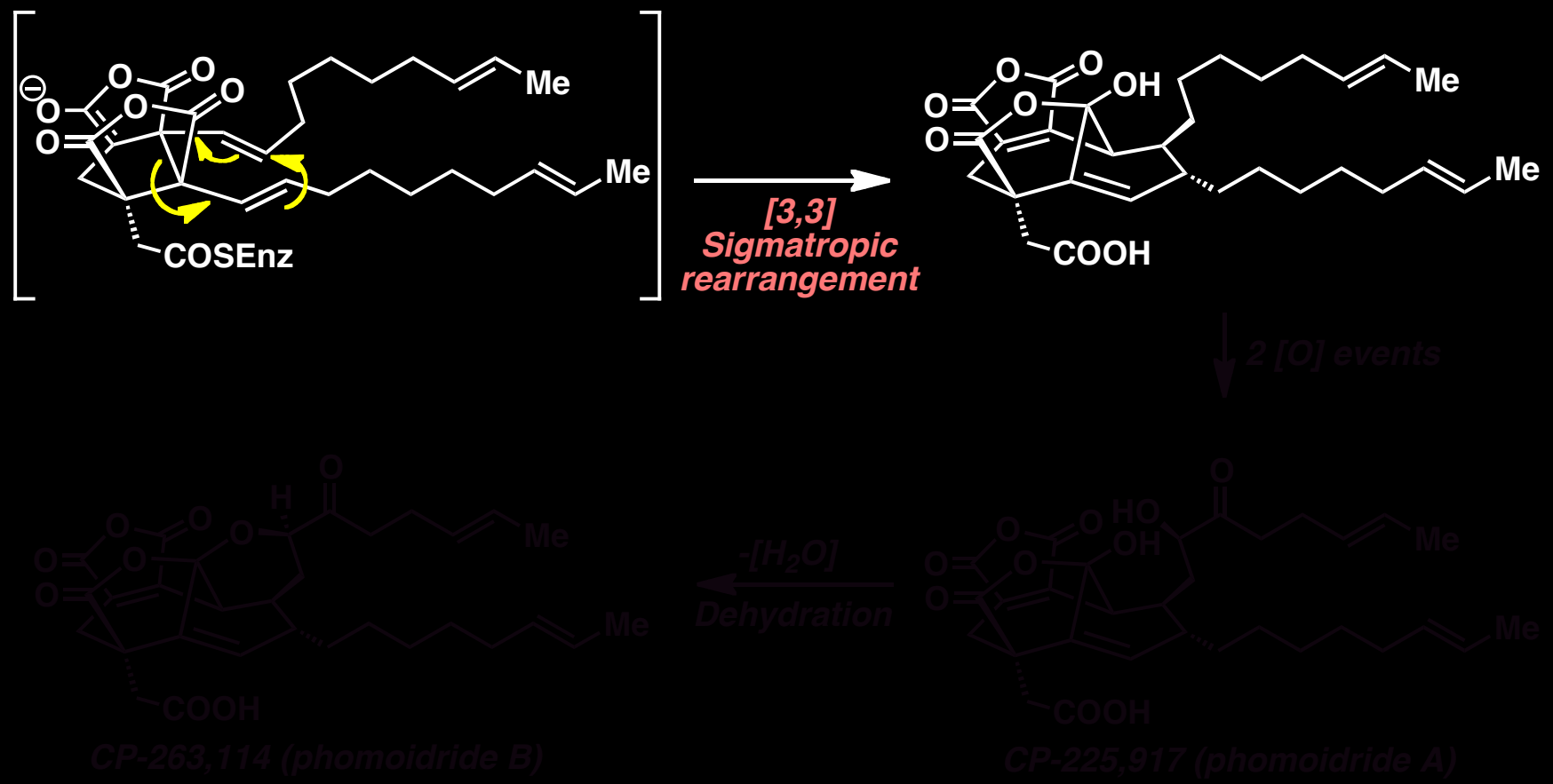

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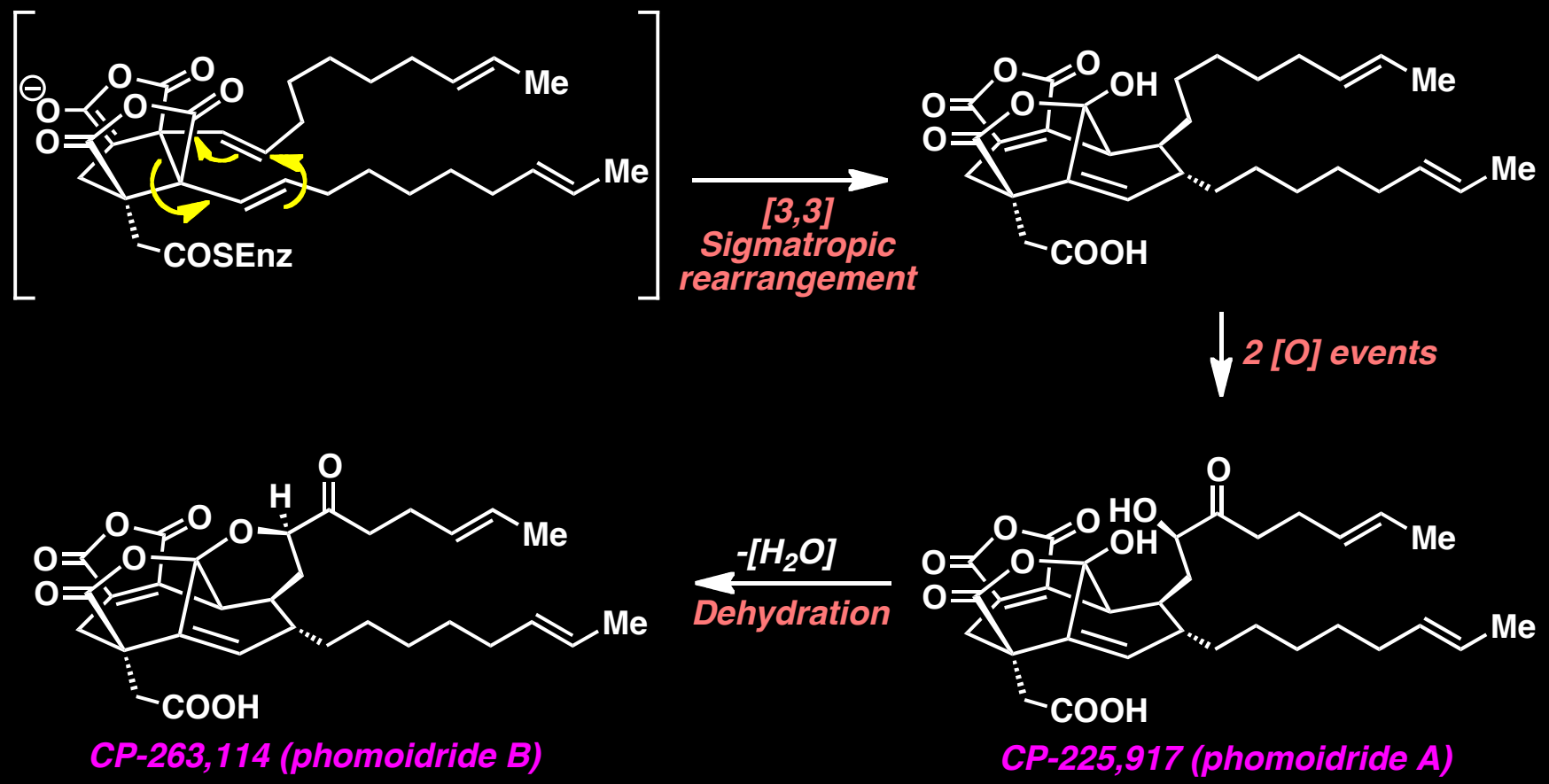

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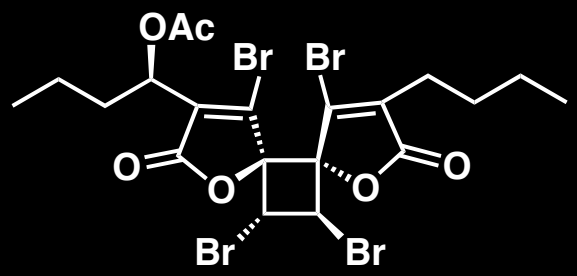
Similar Late-Stage Oxidative Desymmetrization?



pulchralide C

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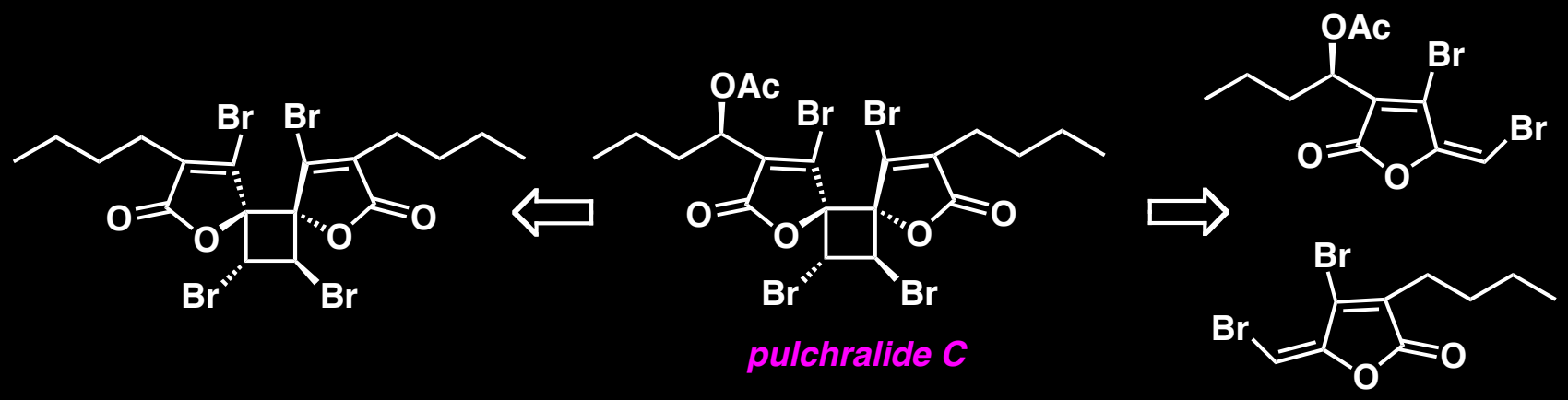
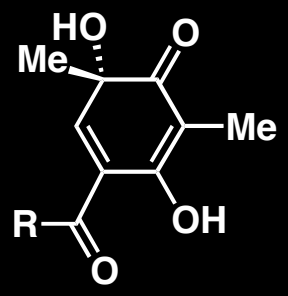
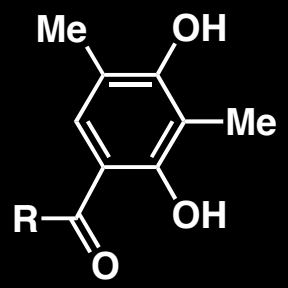


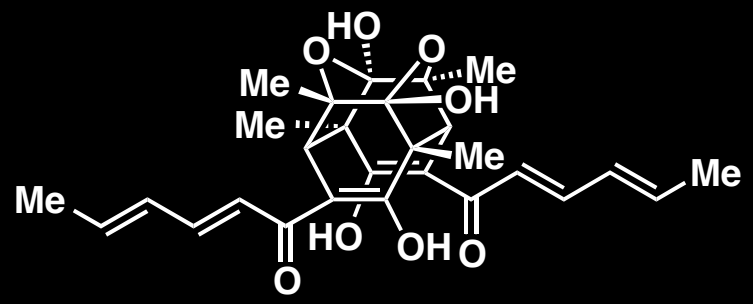
The Bisorbicillinoids



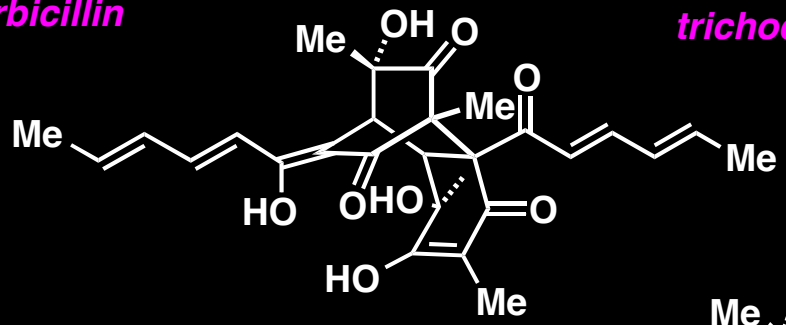
sorbicillinol



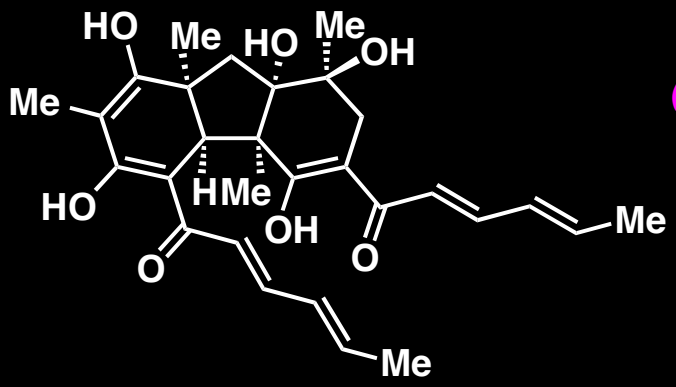
sorbicillin



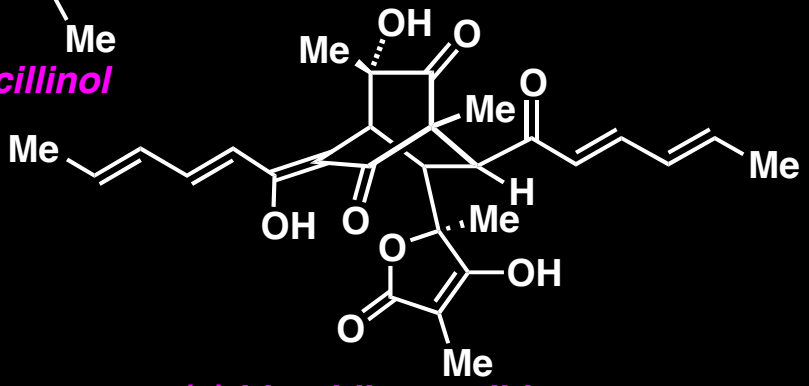
trichodimerol



(+)-bisorbicillinol



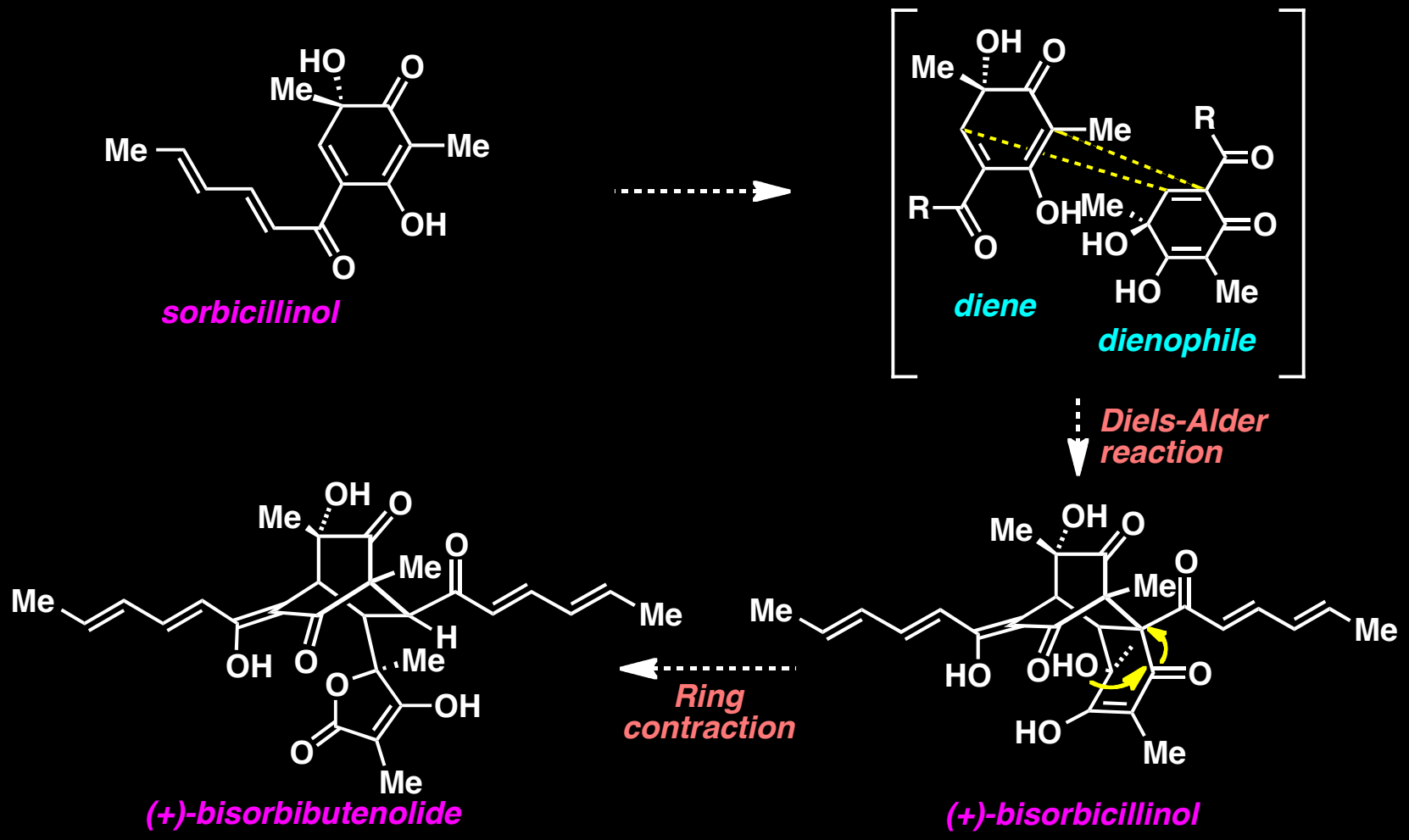
bisvertinol



(+)-bisorbibutenolide

K. C. Nicolaou, K. B. Simonsen, G. Vassilikogiannakis, et al. Angew Chem Int. Ed. 1999, 38, 3555.

The Bisorbicillinoids



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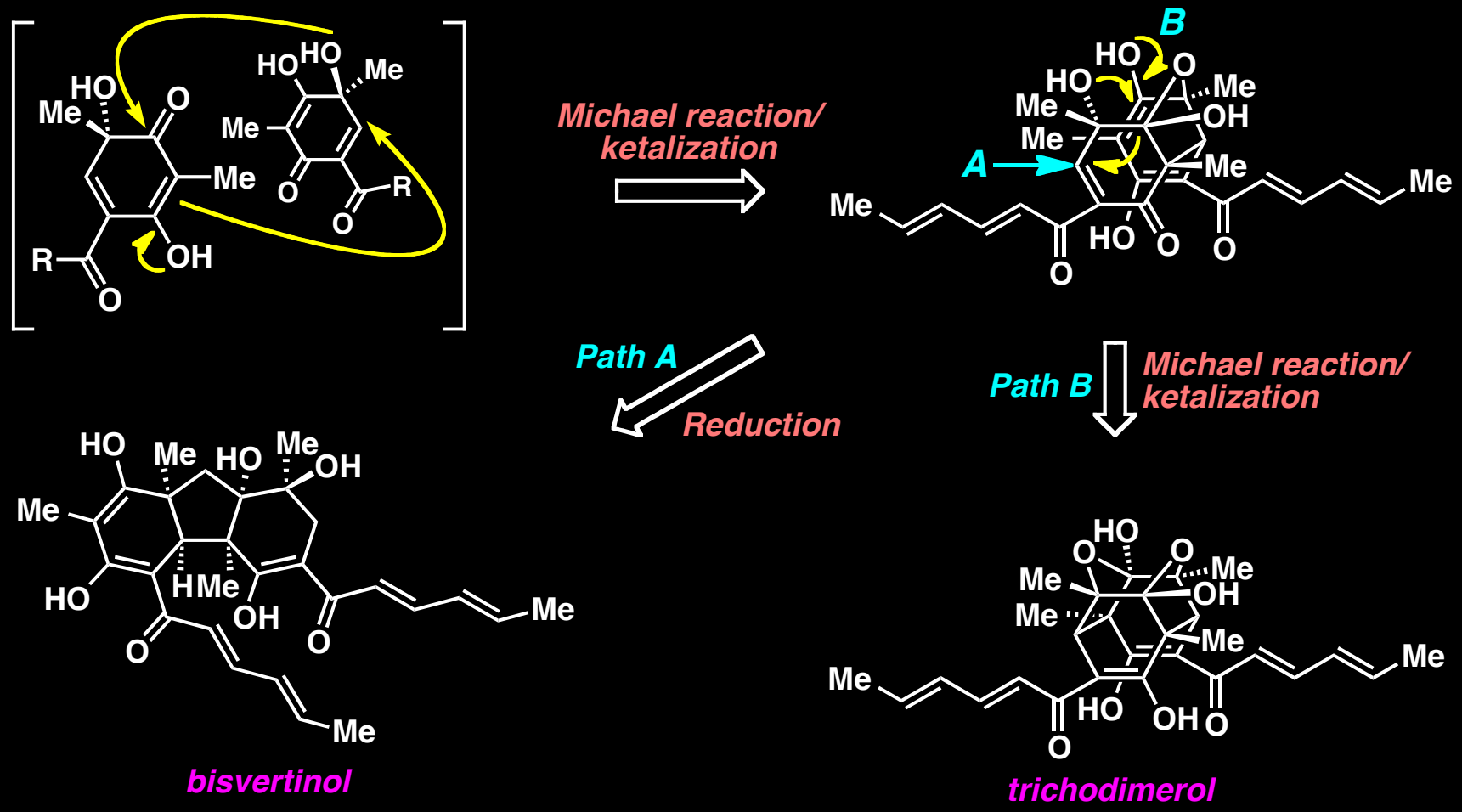

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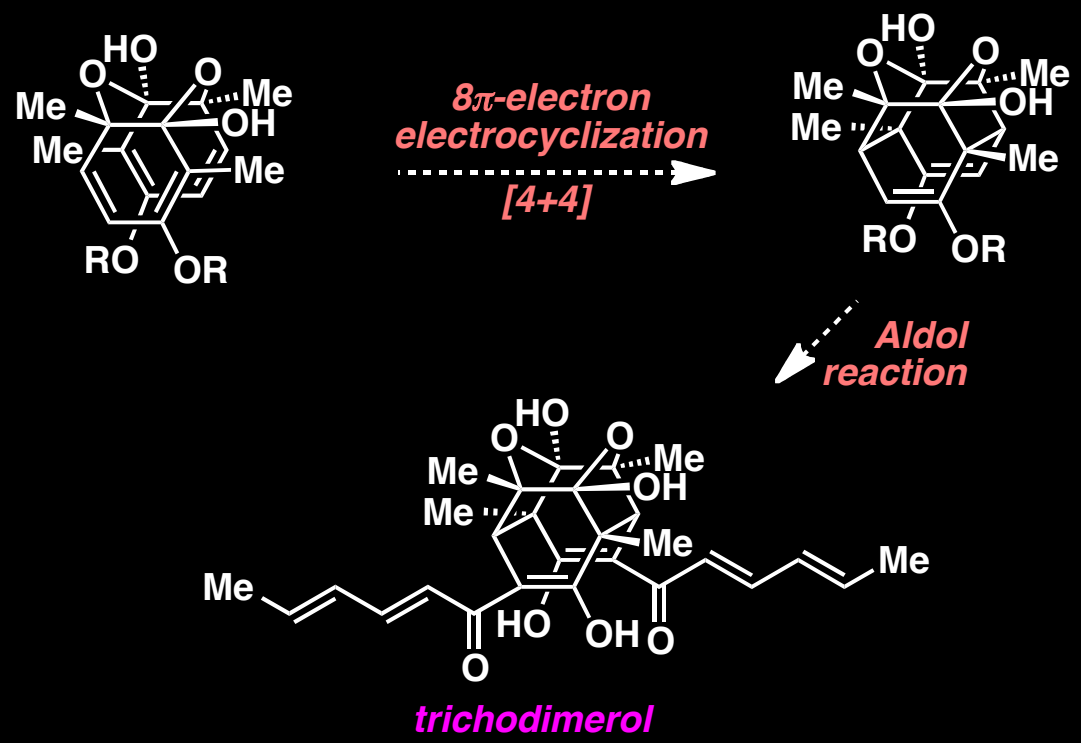
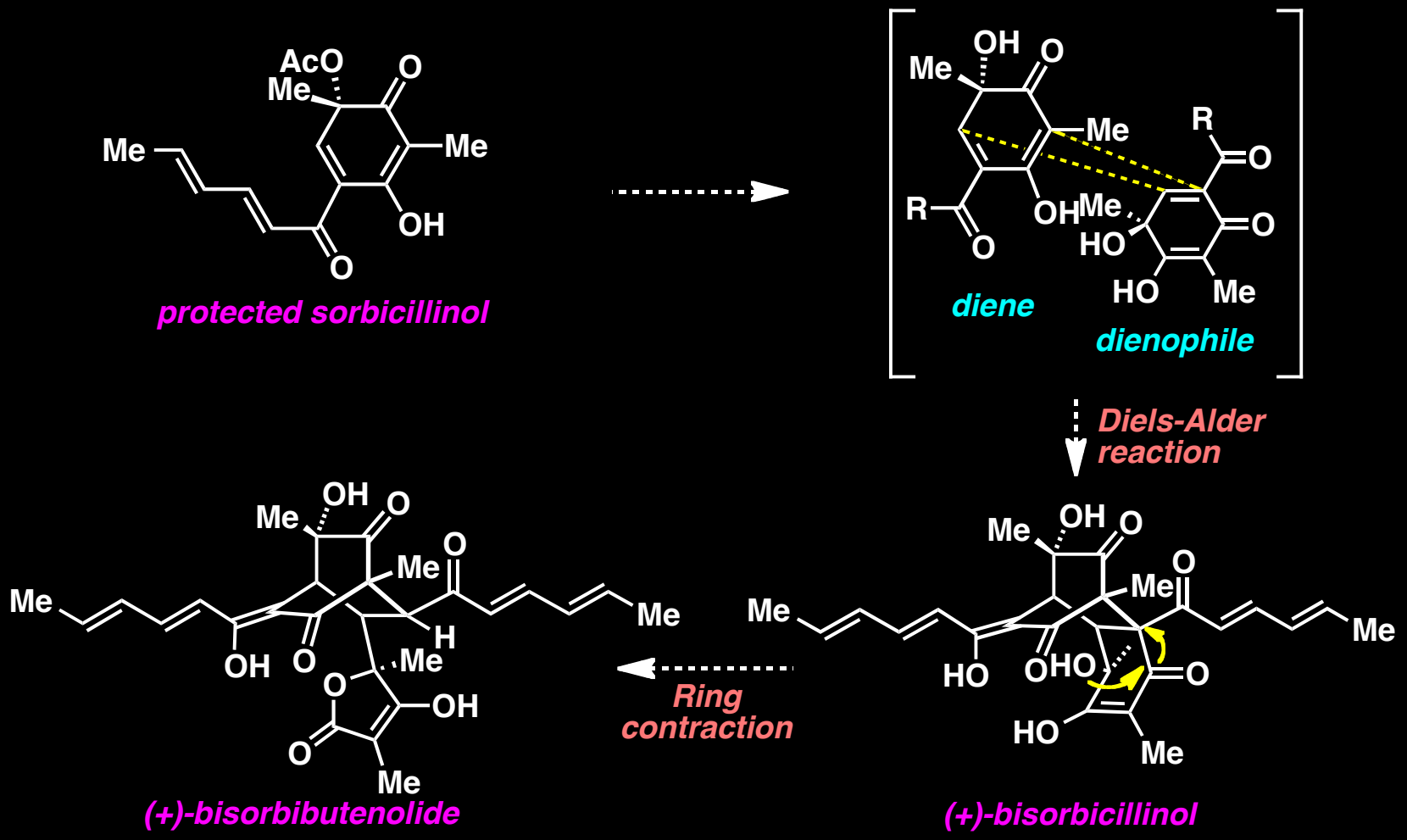


trichodimerol

K. C. Nicolaou, K. B. Simonsen, G. Vassilikogiannakis, et al. Angew Chem Int. Ed. 1999, 38, 3555.

Dimerization in Action: Total Synthesis of the Bisorbicillinoids



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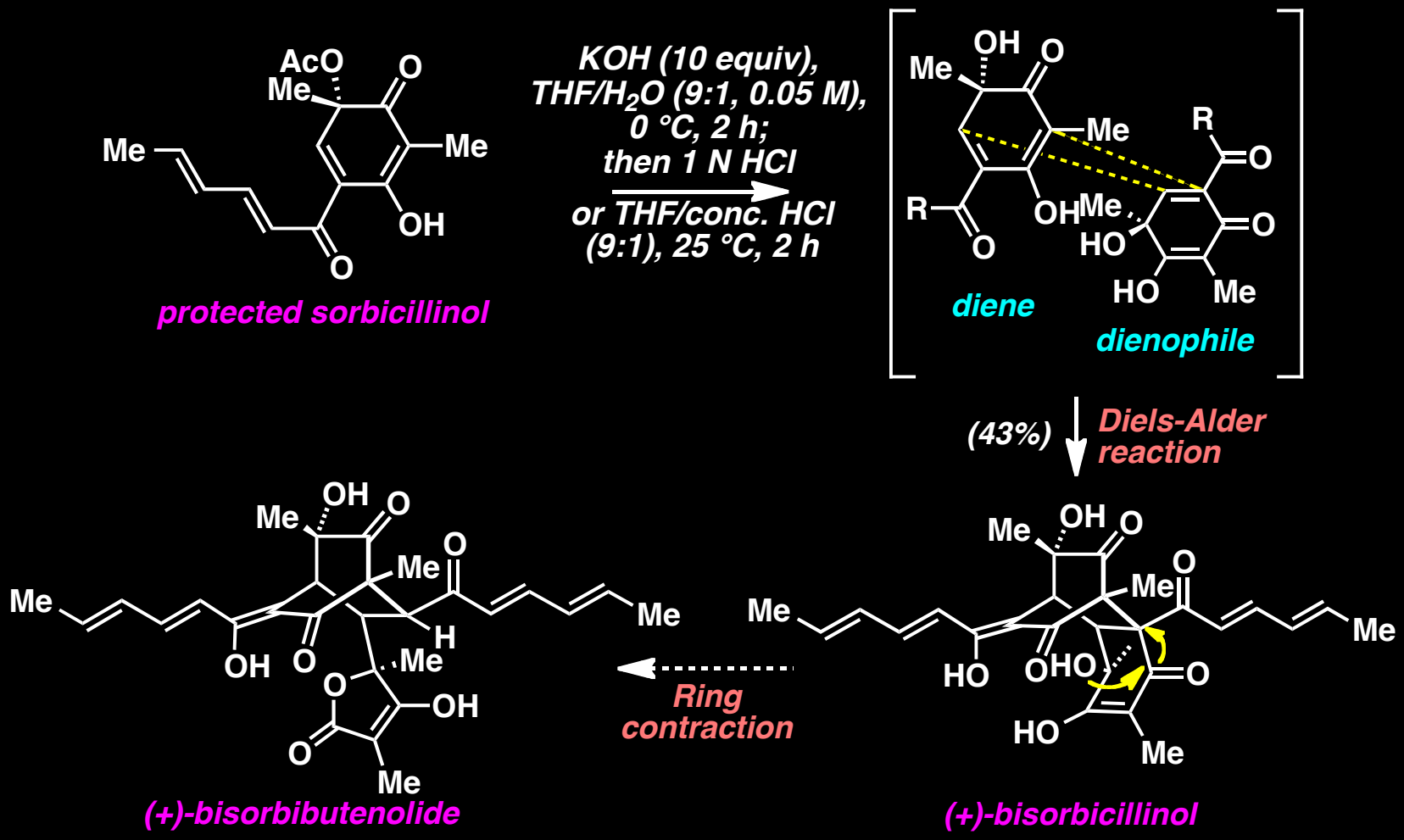

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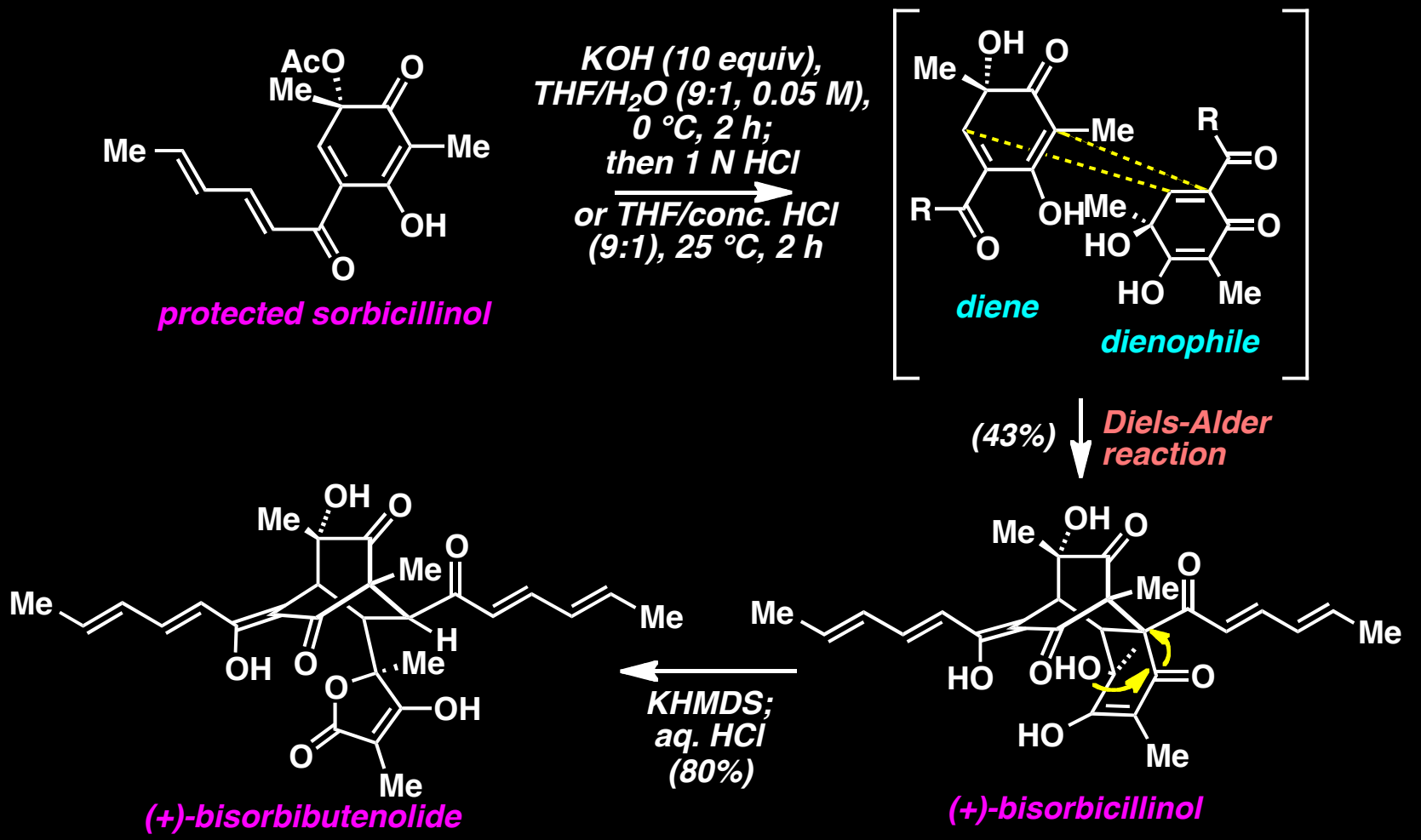

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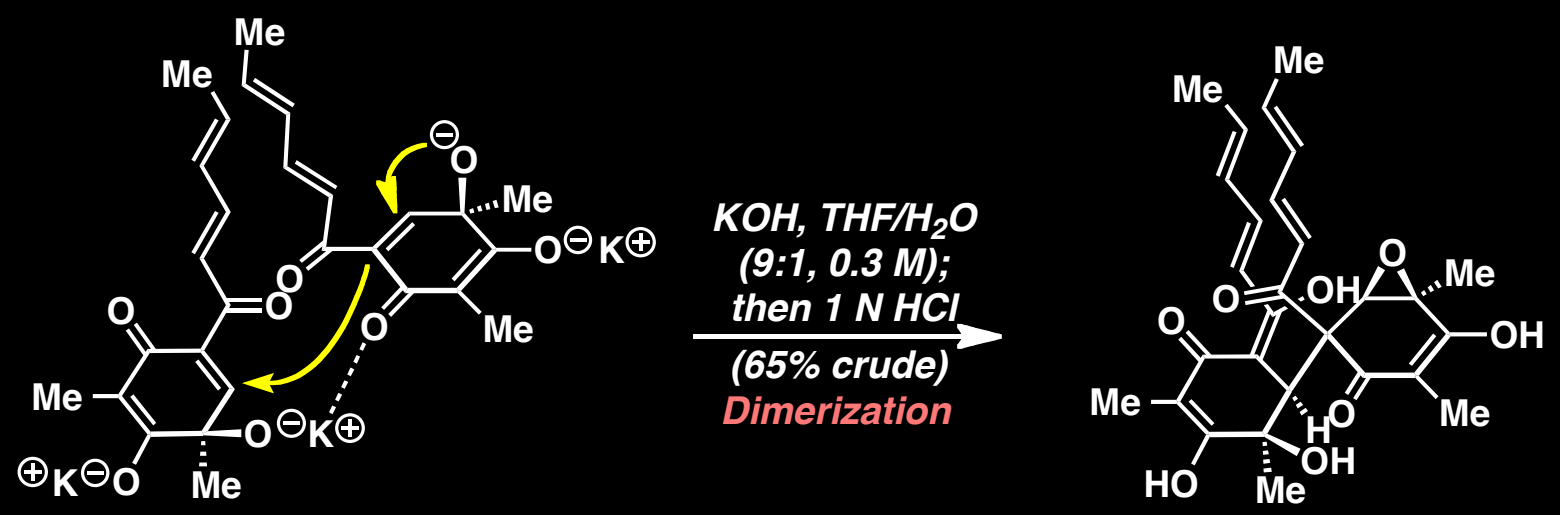

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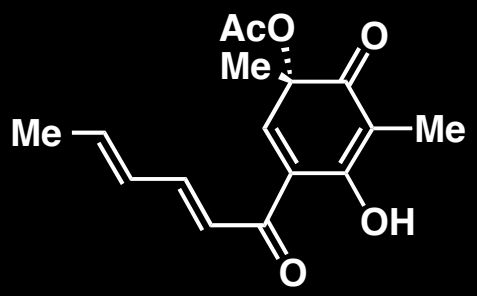
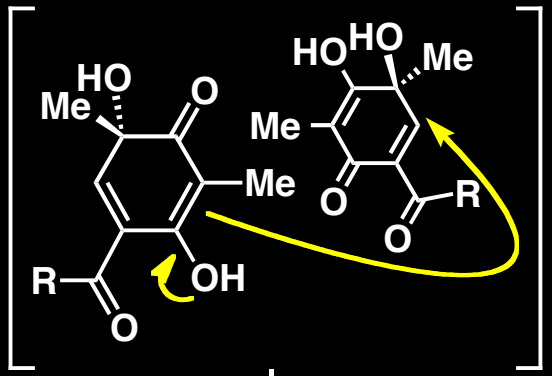
Direct Dimerization of Monomers



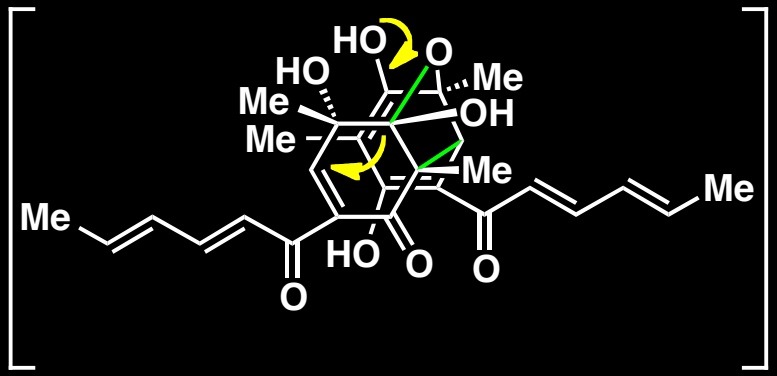
protected sorbicillin

NaOMe, MeOH;
NaH_2PO_4, HCl

or $CsOH{\cdot}H_2O$,
MeOH;
NaH_2PO_4

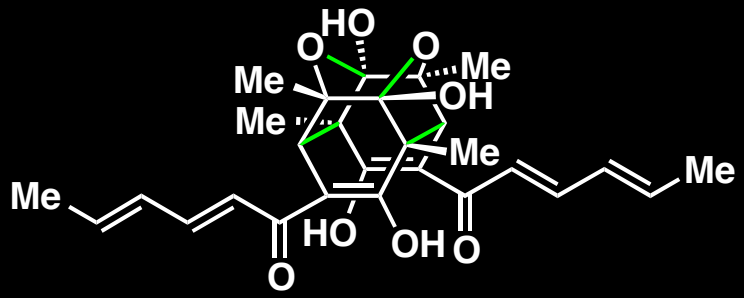


[Michael reaction-
ketalization]



[Michael
reaction-
ketalization]

(10-16%)



trichodimerol

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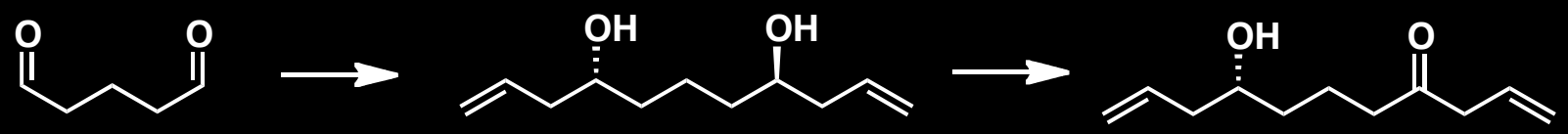
D. Barnes-Seeman, E. J. Corey, Org. Lett. 1999, 1, 1503

Bidirectional Synthesis and Desymmetrizing Advanced Materials



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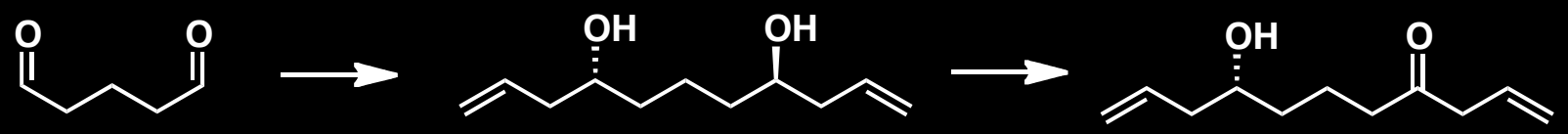

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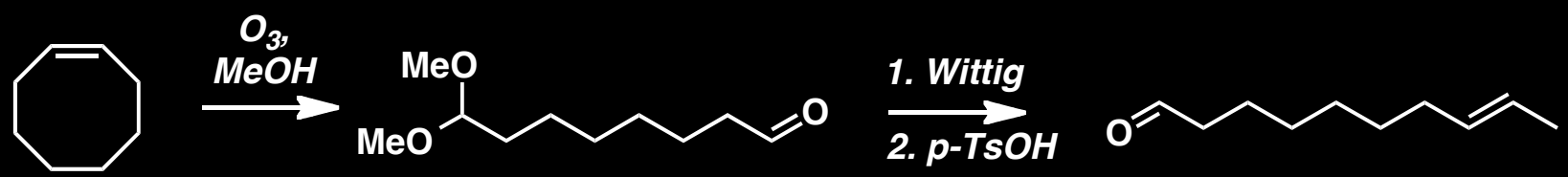
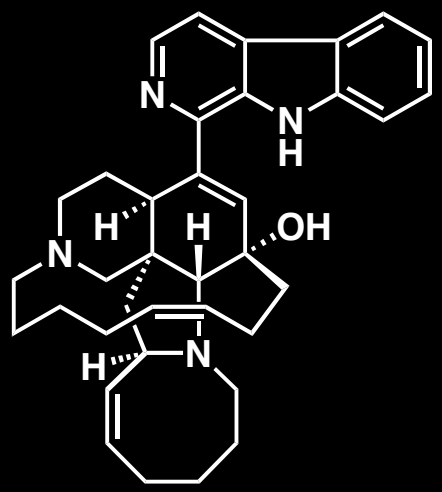
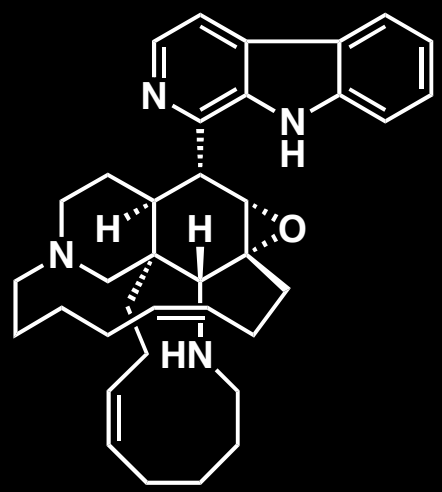


K. C. Nicolaou and co-workers, J. Am. Chem. Soc. 2002, 124, 2183.

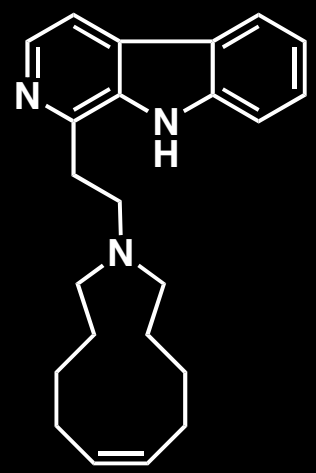
The Manzamine Alkaloids: An Impressive Array of Natural Products



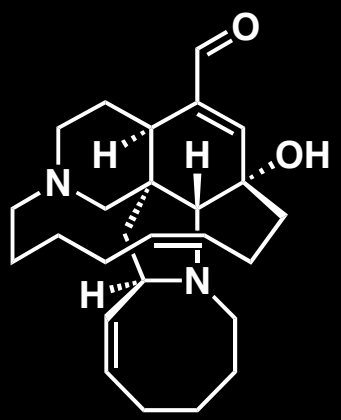
manzamine A



manzamine B



manzamine C



ircinal A

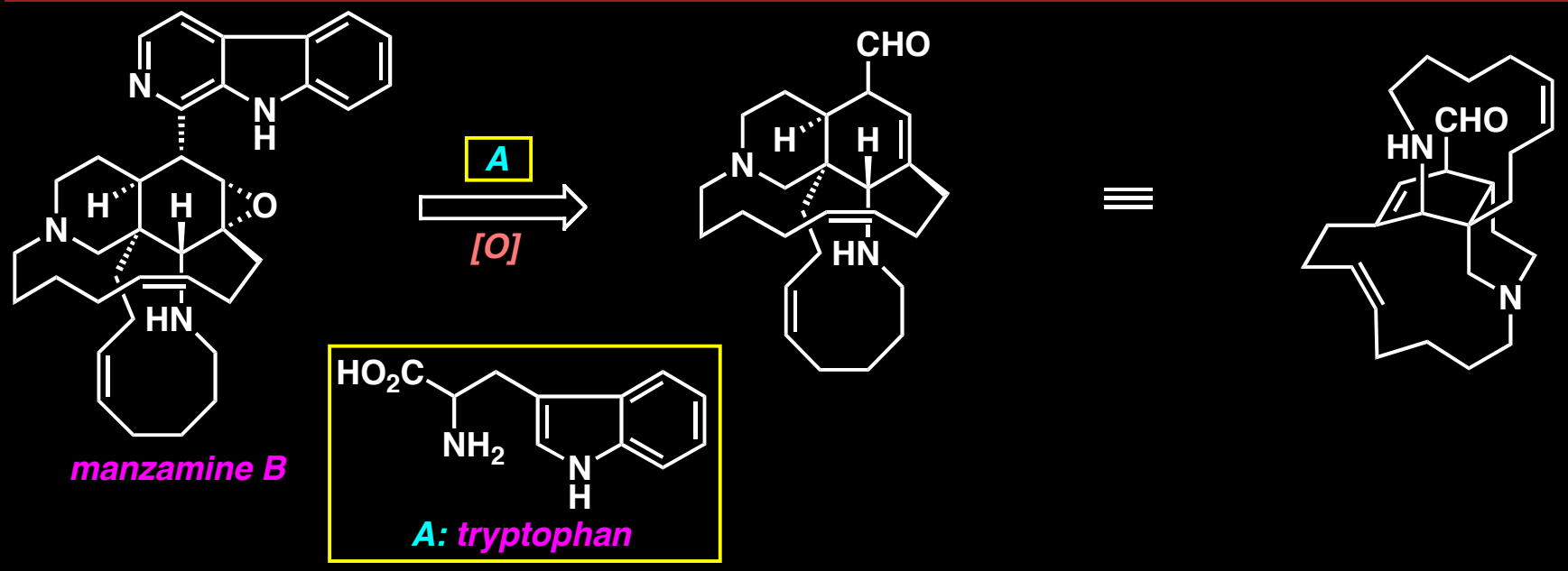
All are isolated from okinawan sea sponges of the Haliclona variety

Most are extremely cytotoxic

Comment from isolation chemists: "Its (i.e. manzamine A) provenance is problematical as there appears to be no obvious biogenetic path."

R. Saki, T. Higa, C. W. Jefford, G. Bernardinelli, J. Am. Chem. Soc. 1986, 108, 6404.

Baldwin's Biosynthetic Hypothesis for Manzamine B: A Potential Route to Keramaphidin B



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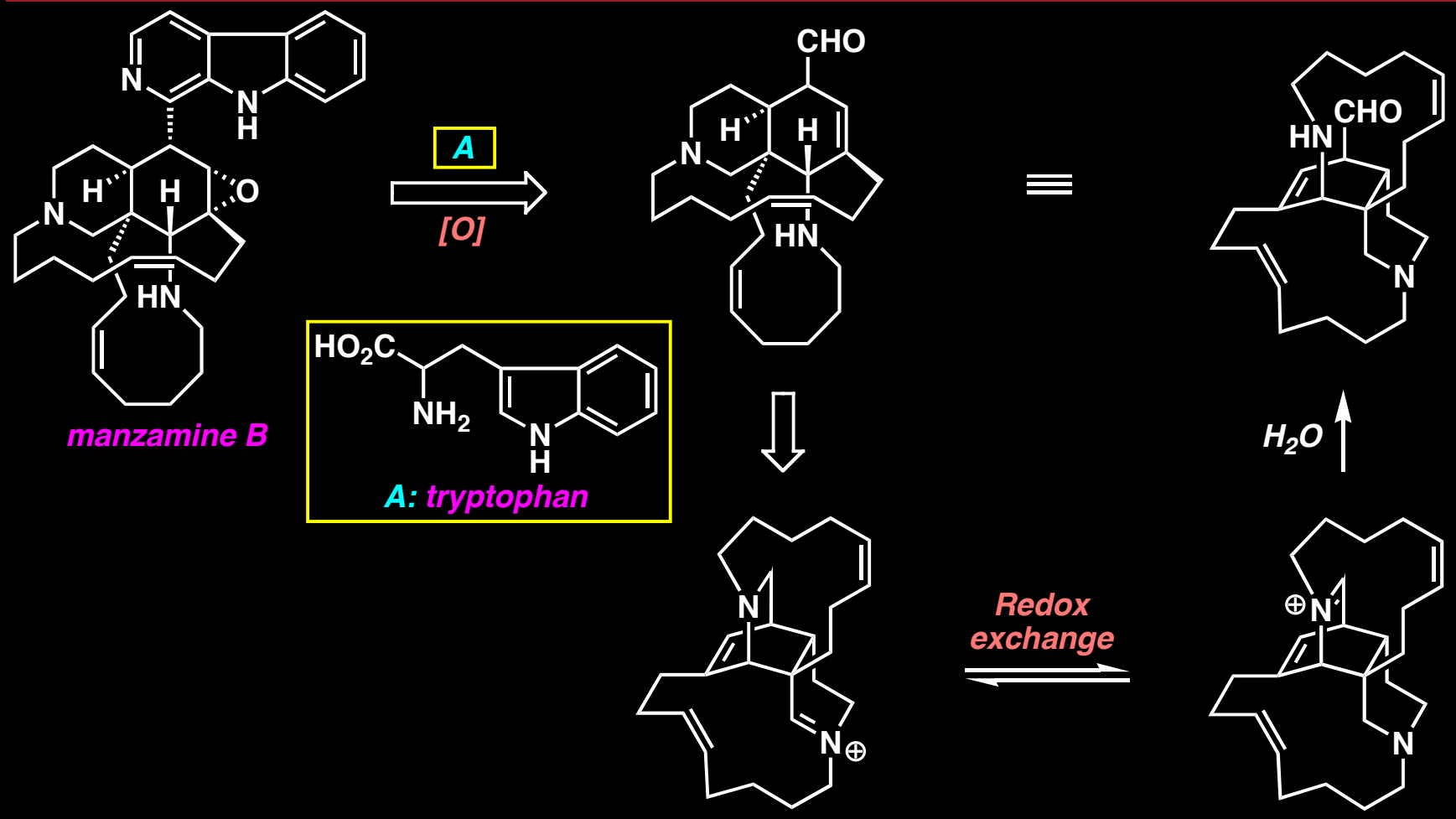

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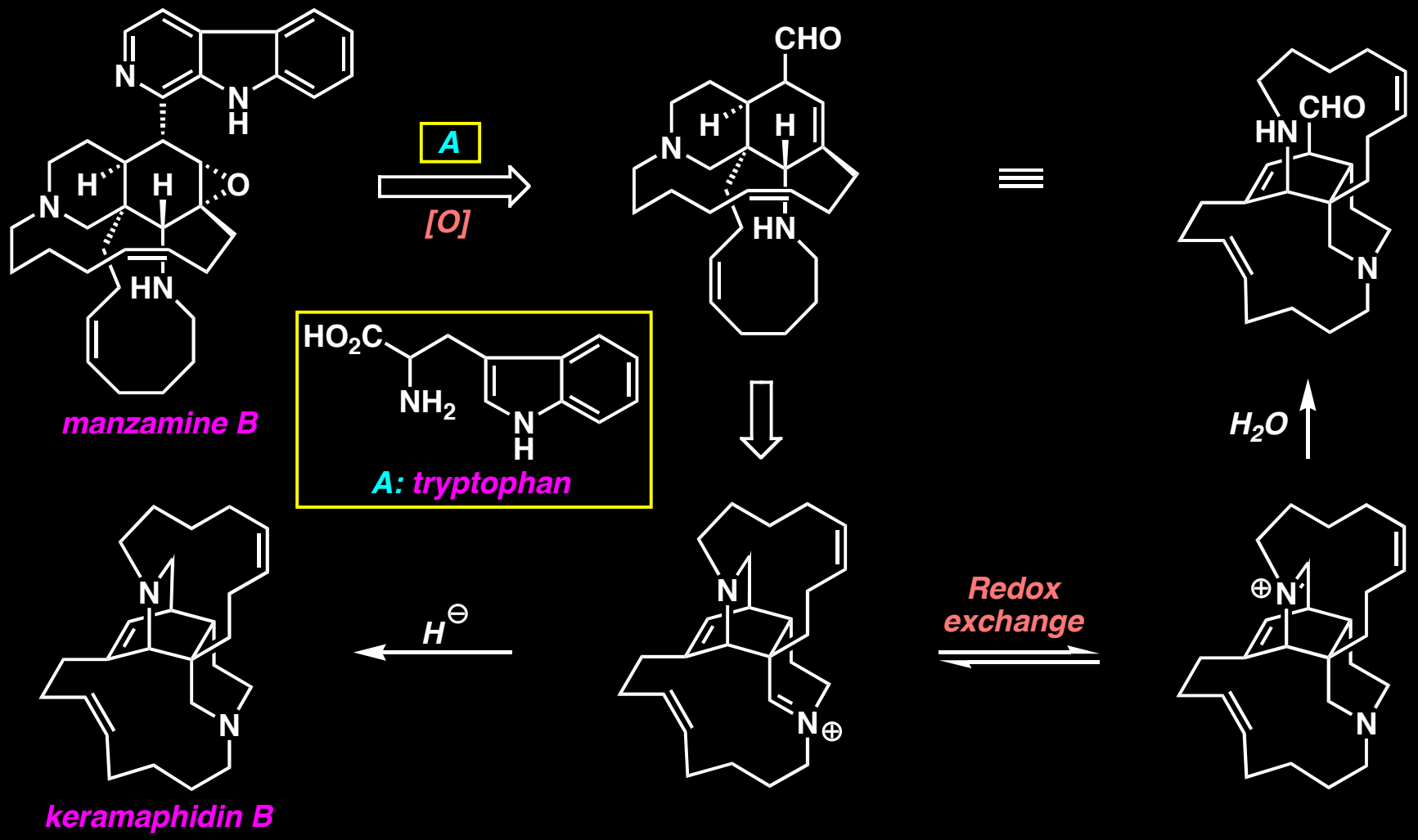

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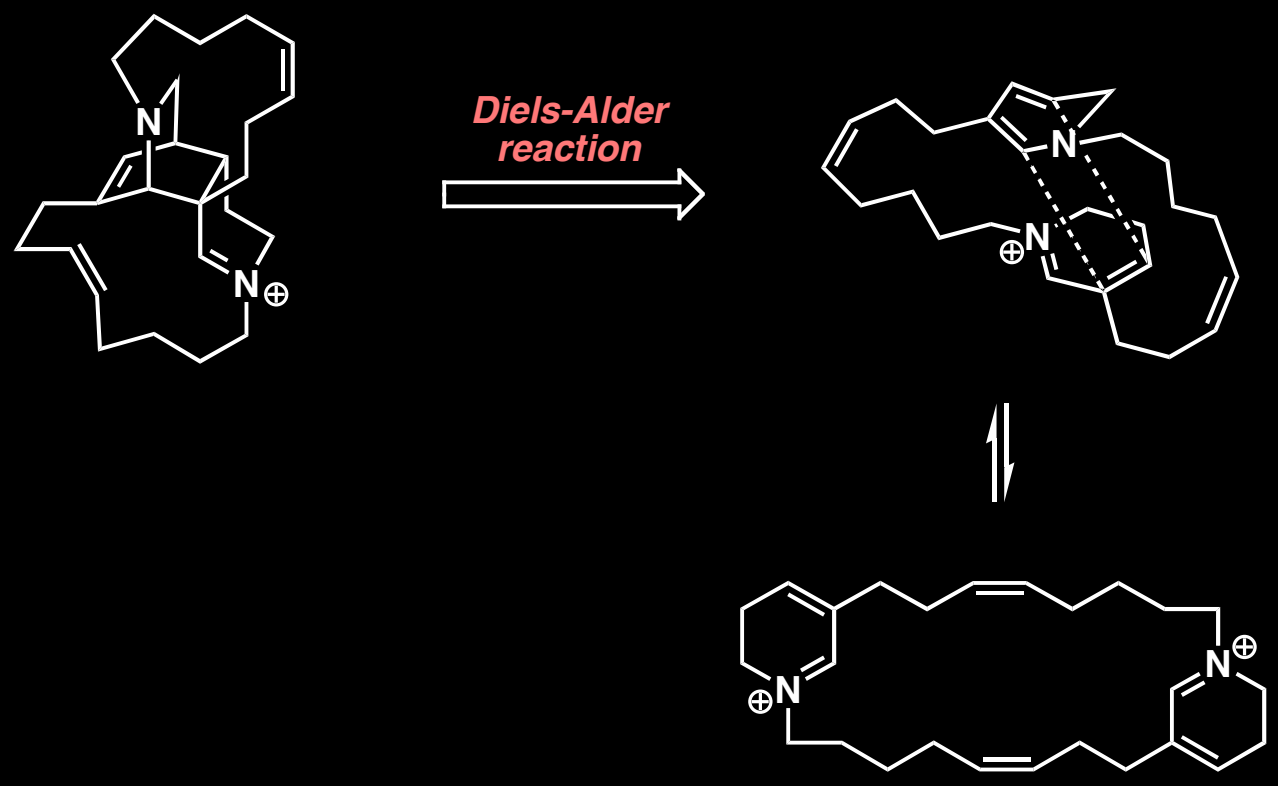

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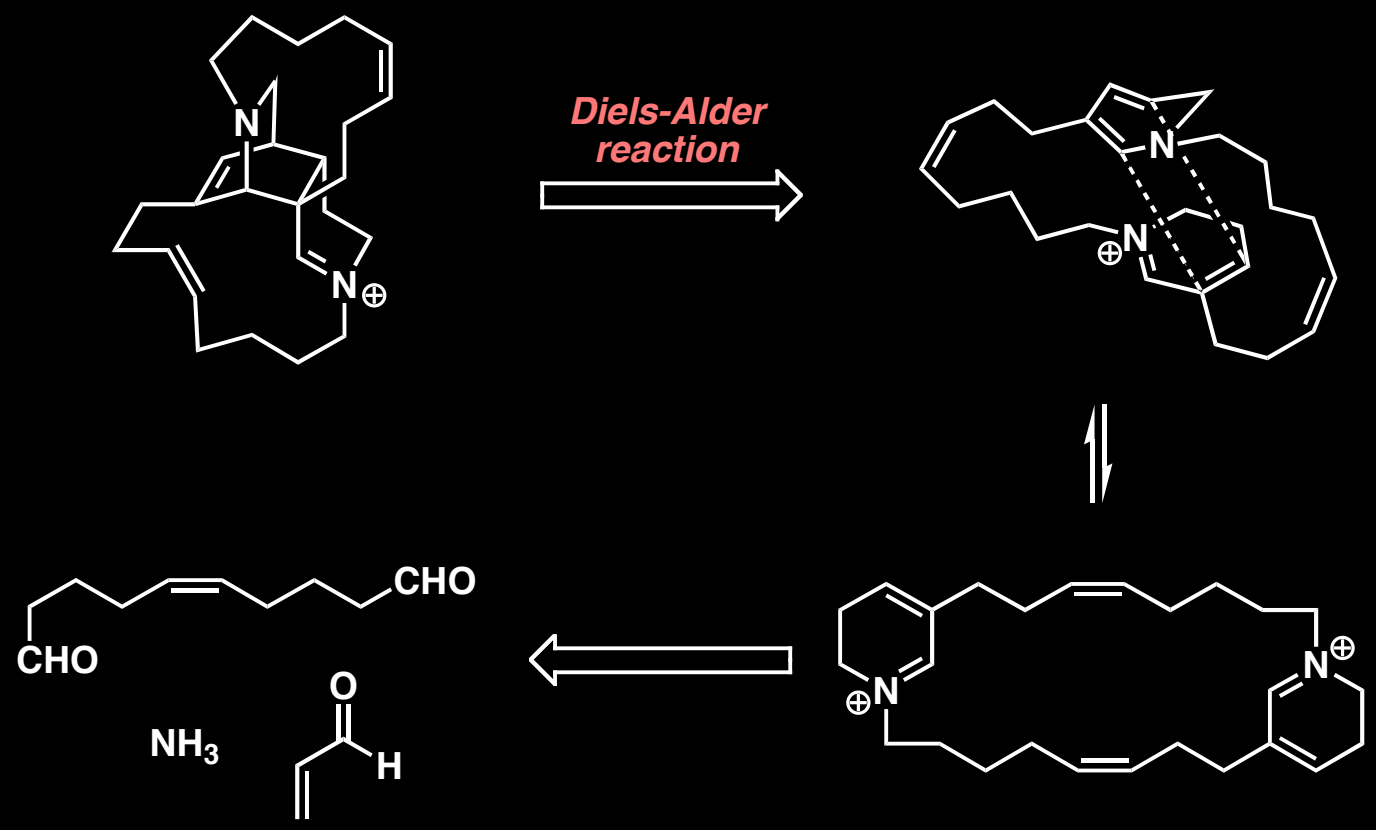

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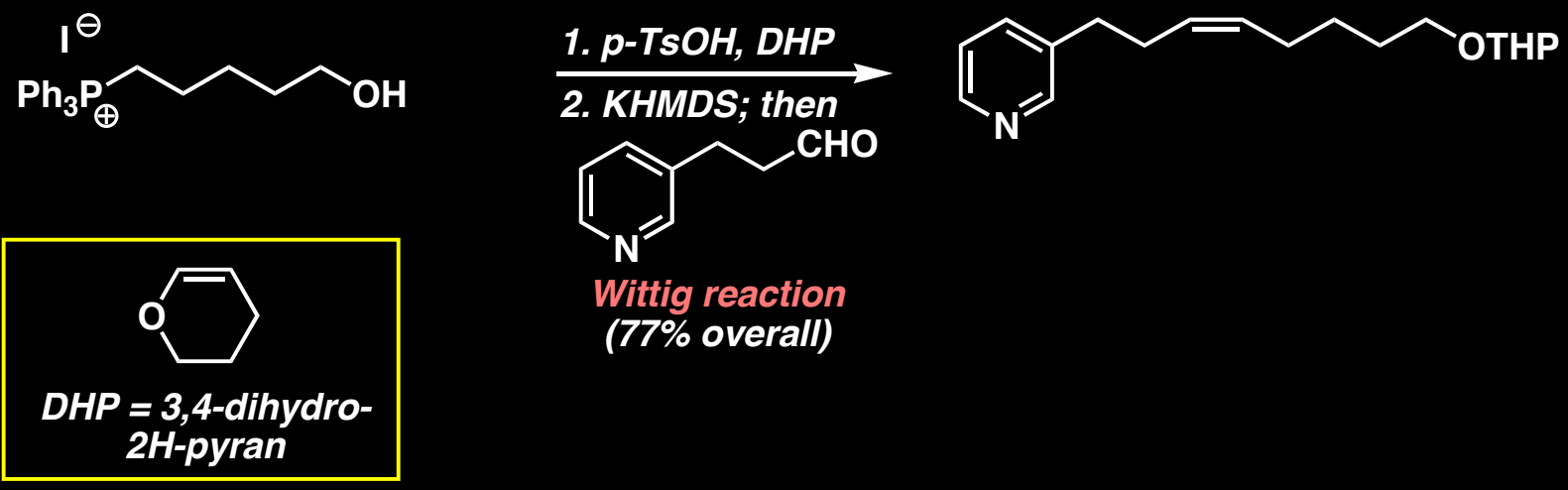

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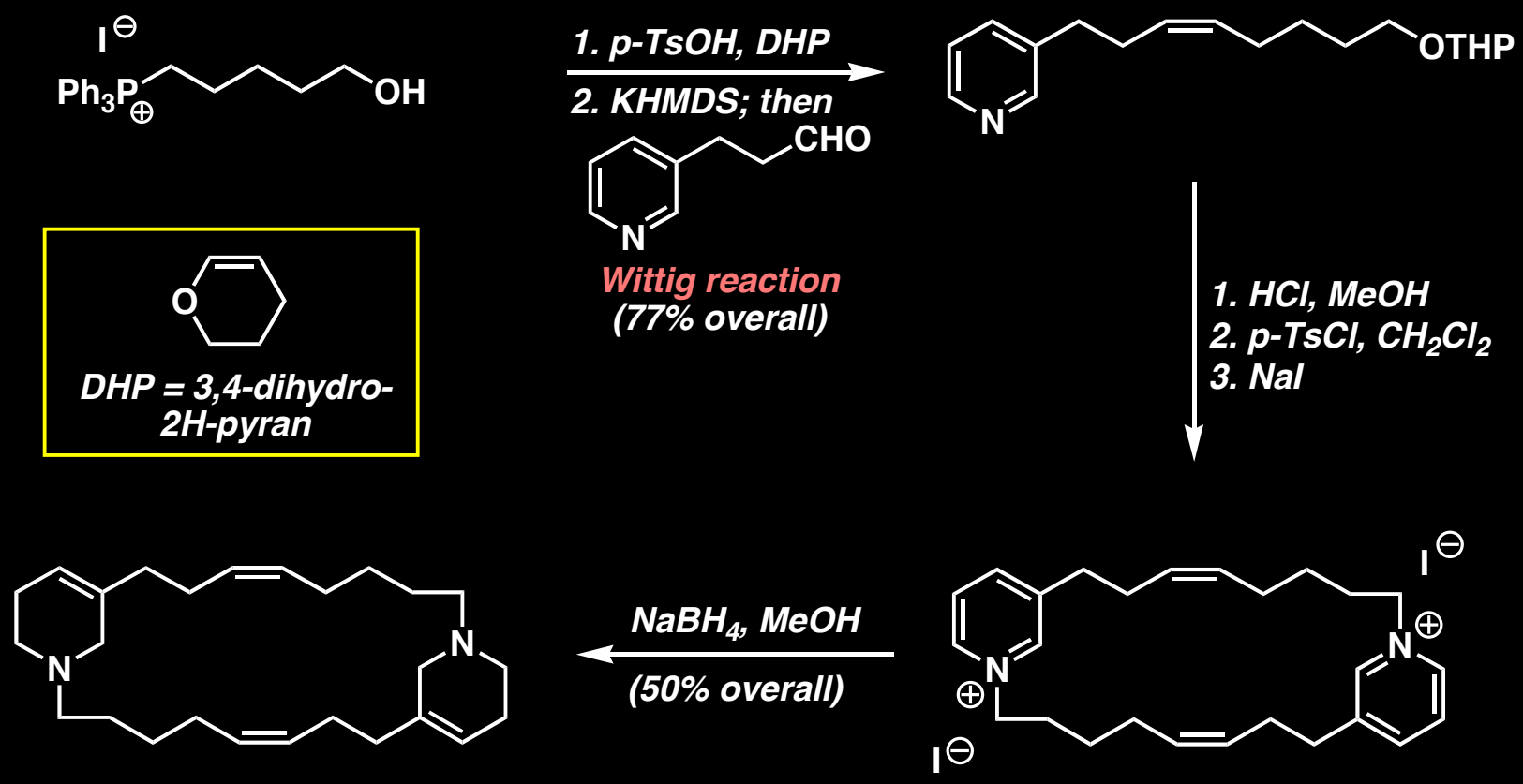

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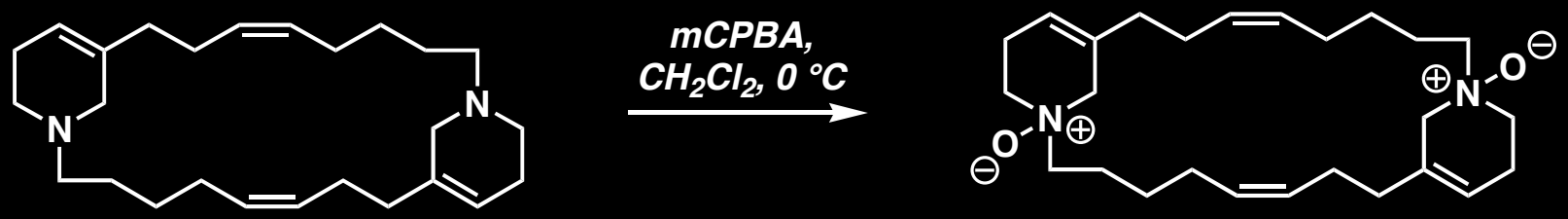

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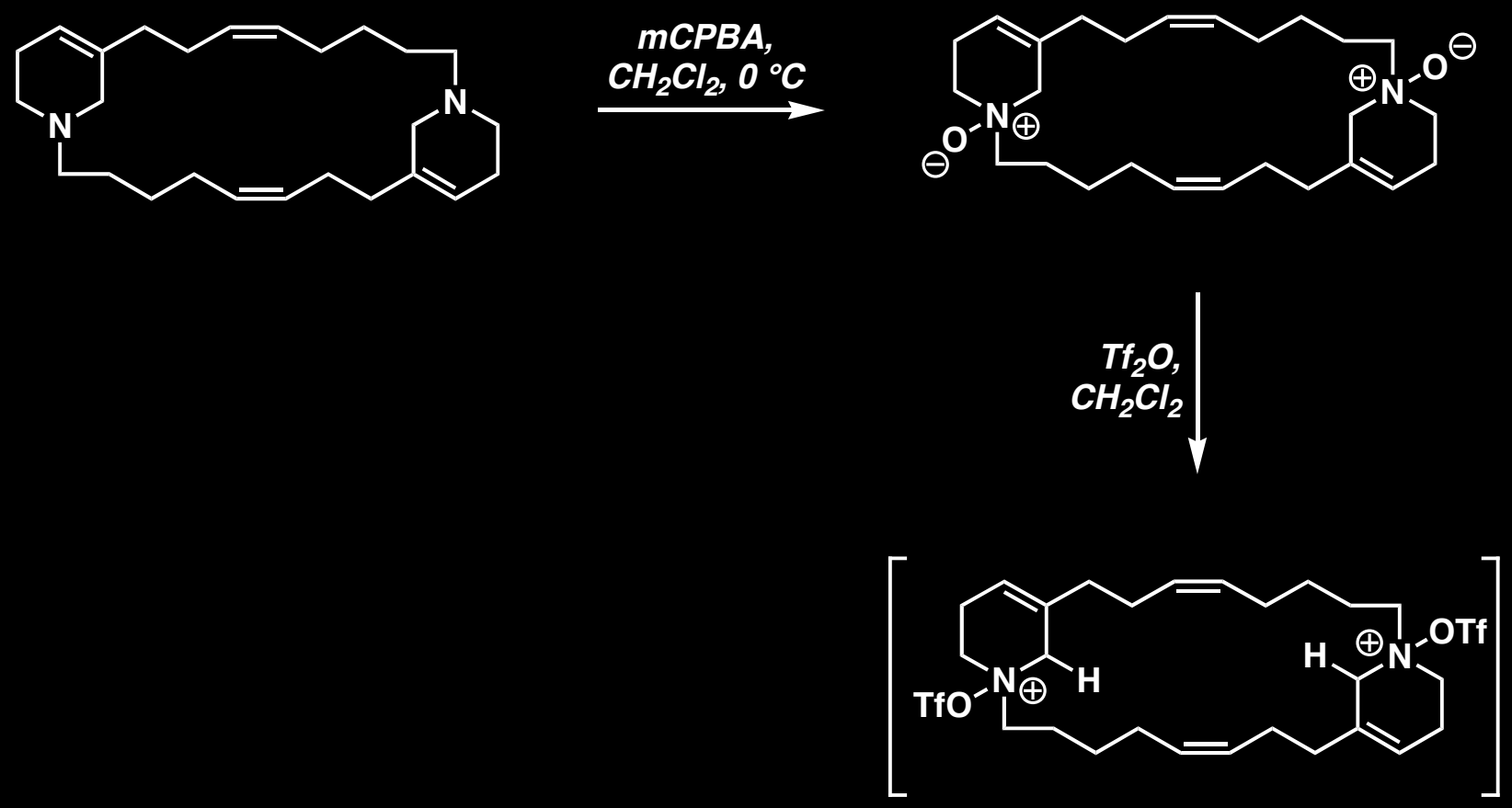

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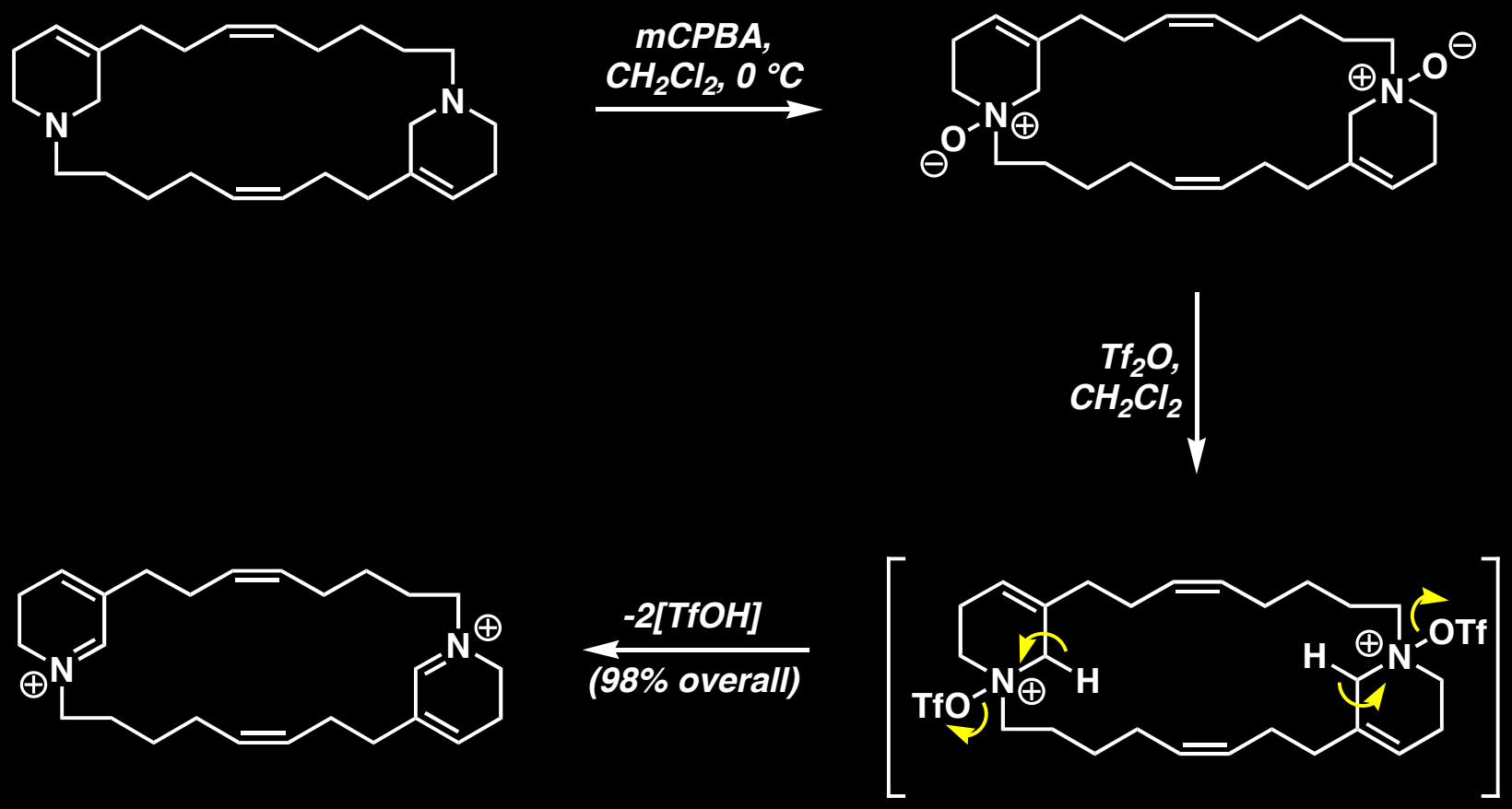

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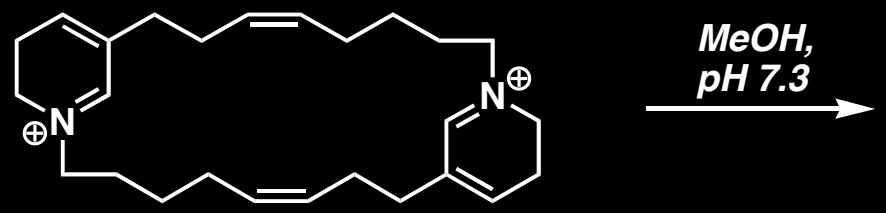

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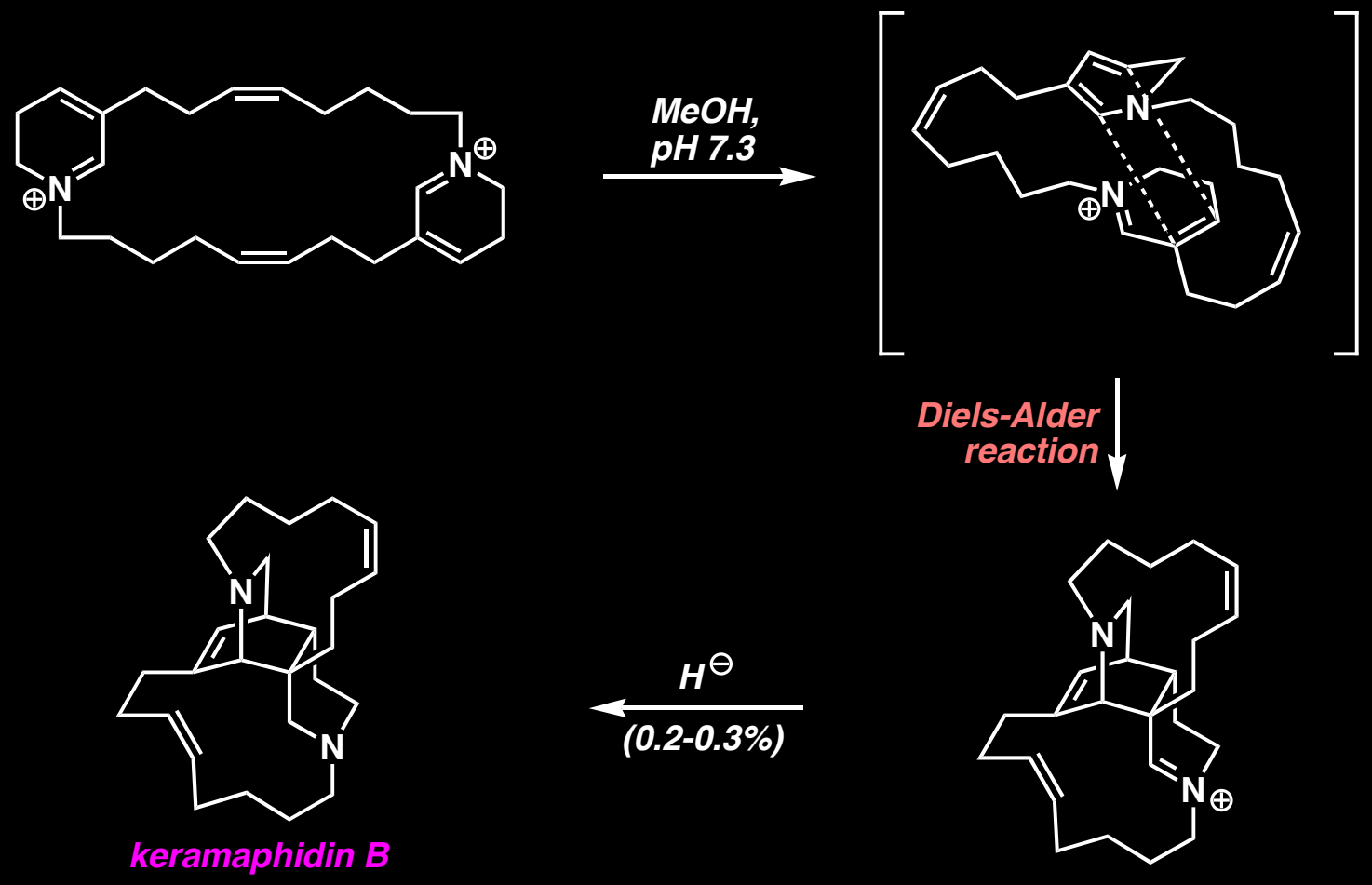

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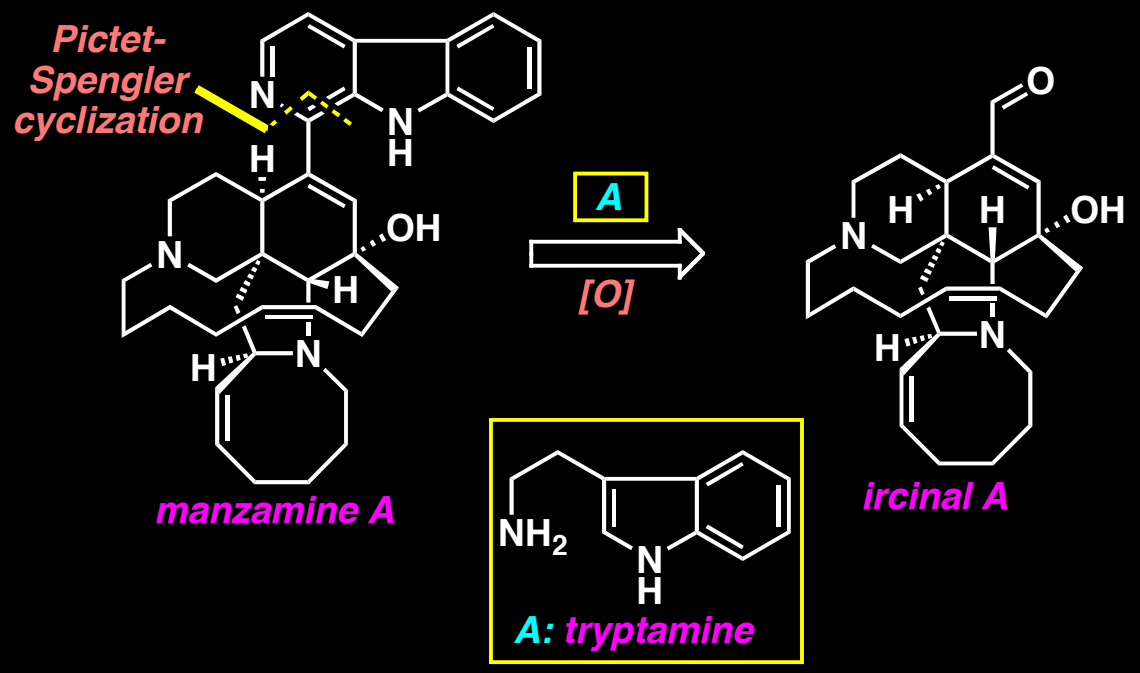

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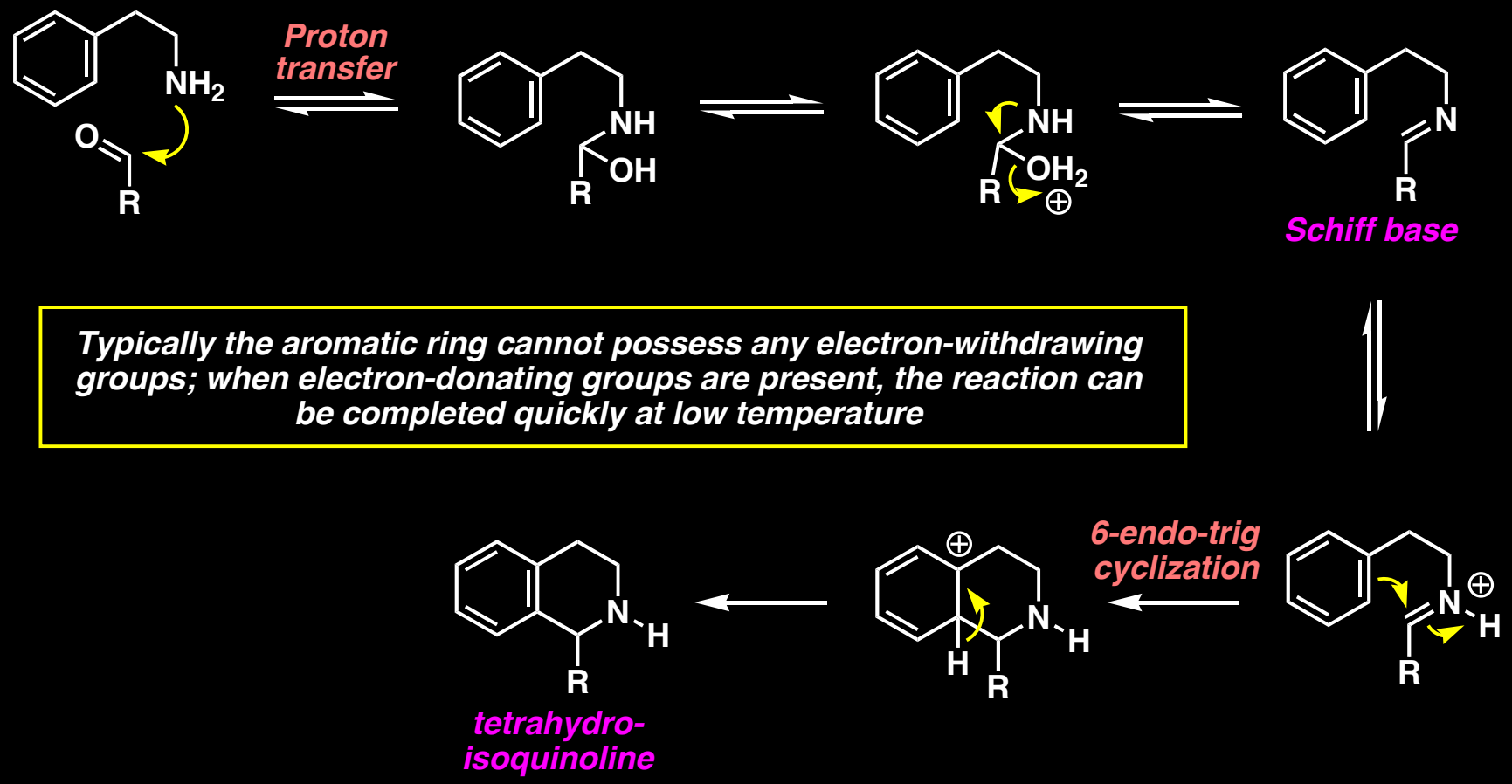
The Pictet-Spengler Reaction: Mechanism and General Considerations



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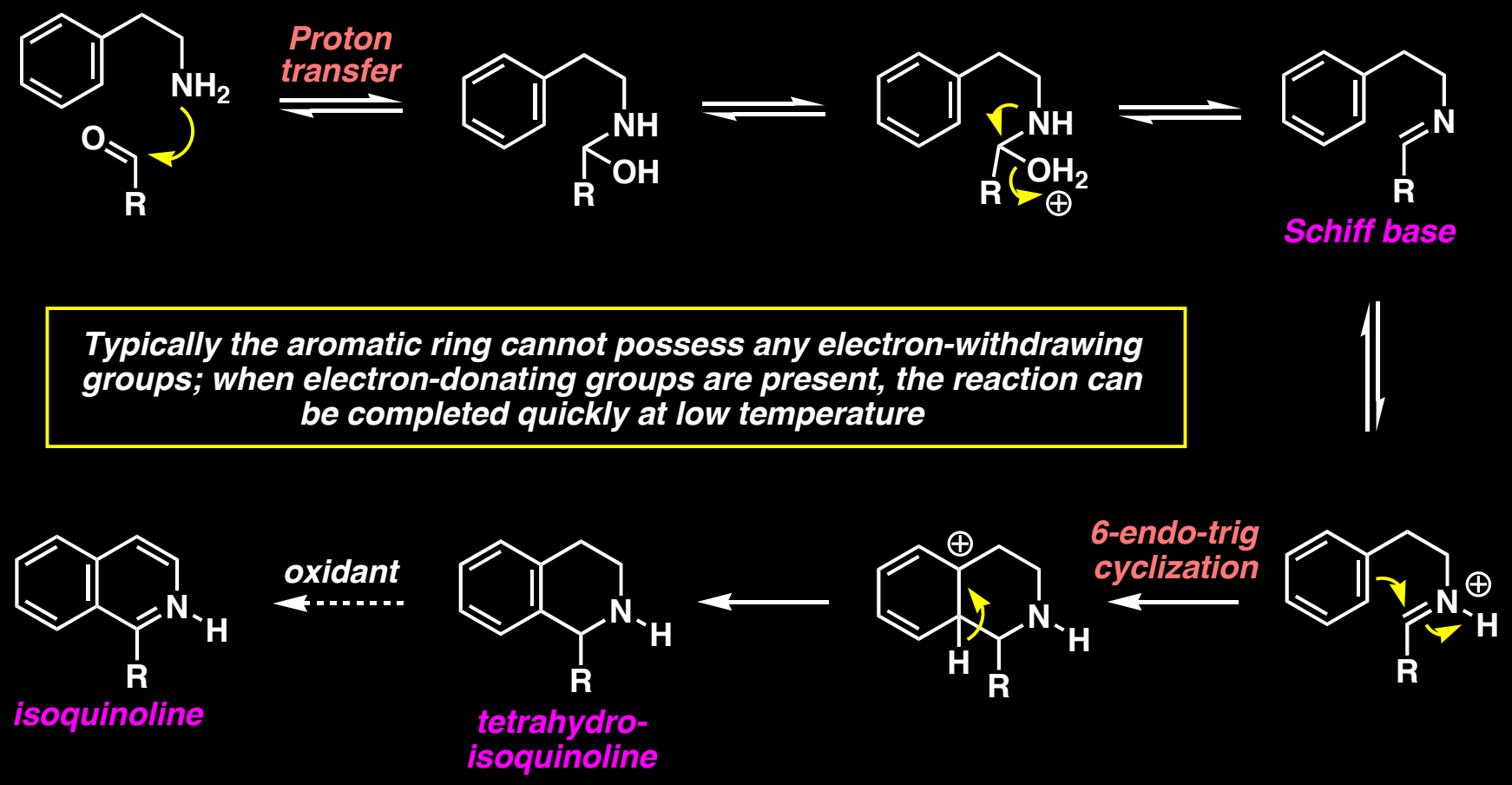

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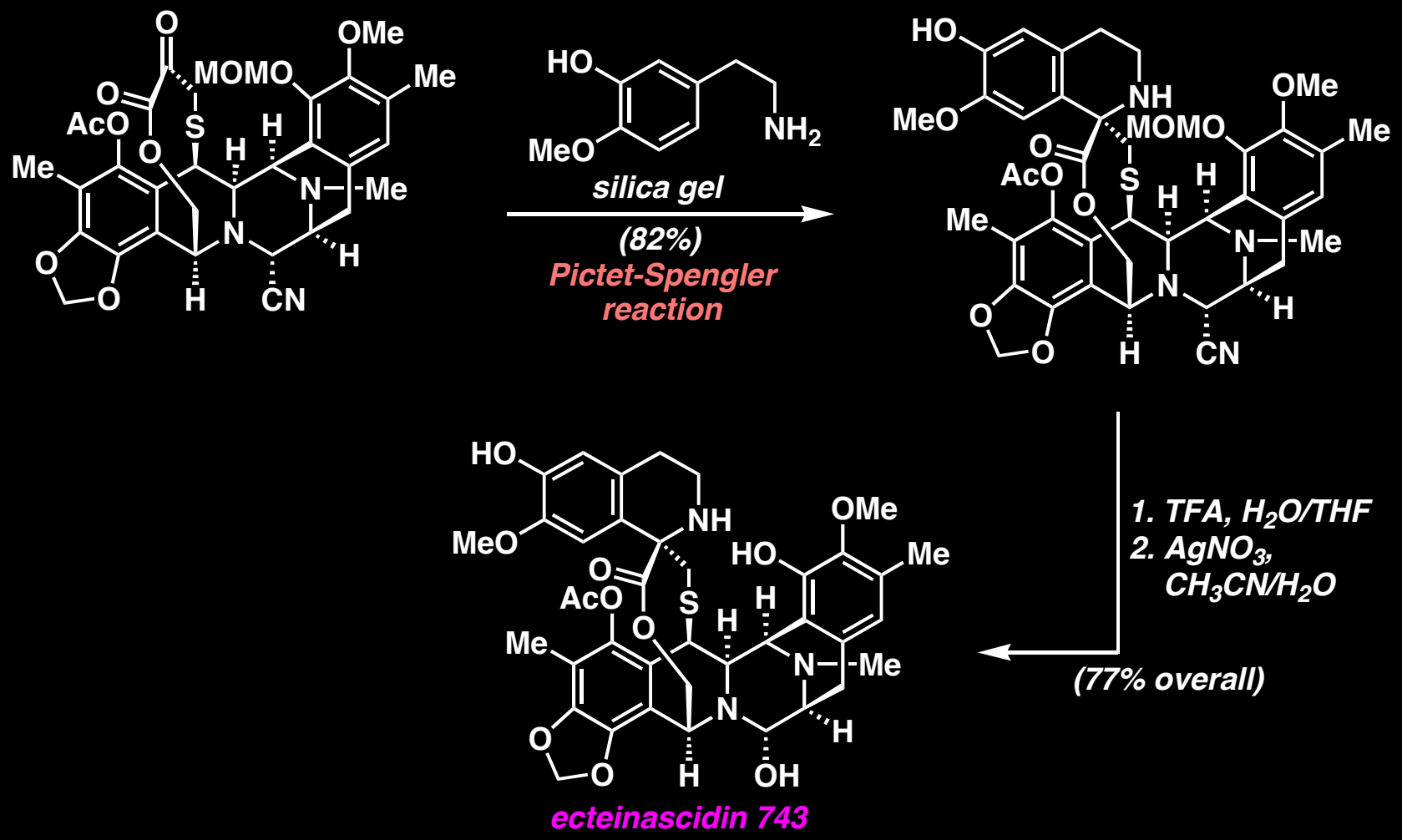

E. J. Corey, D. Y. Gin, R. Kania, J. Am. Chem. Soc. 1996, 118, 9202.

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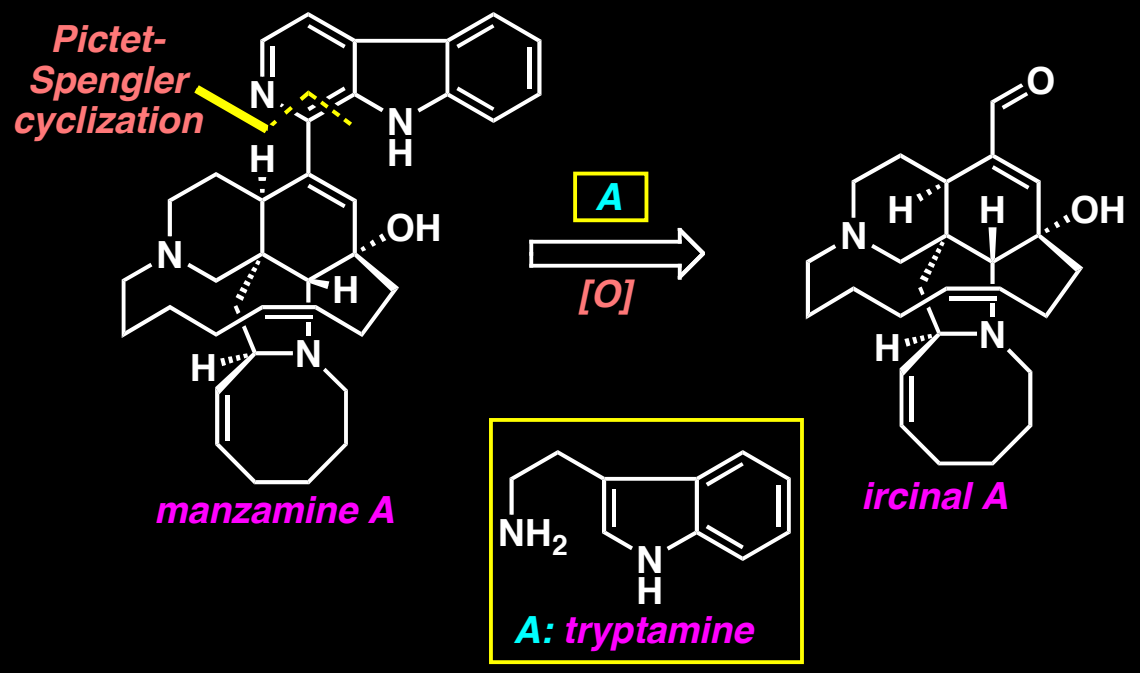

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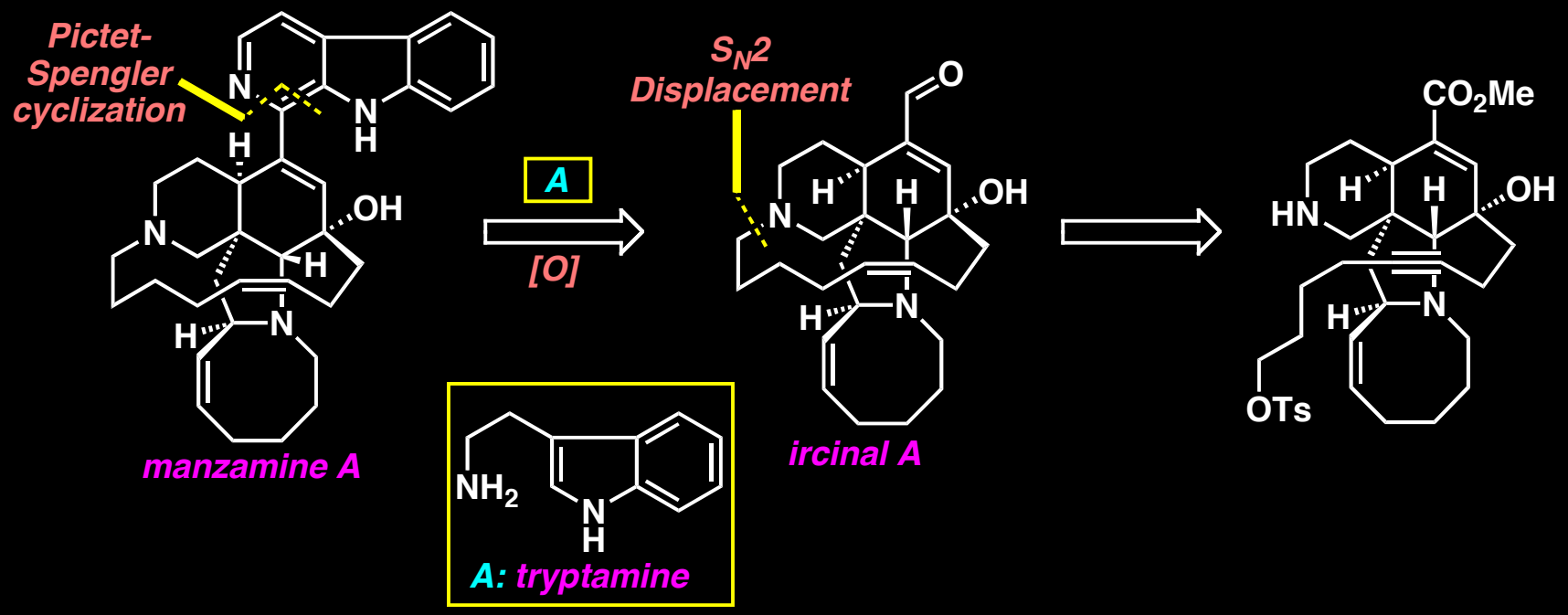

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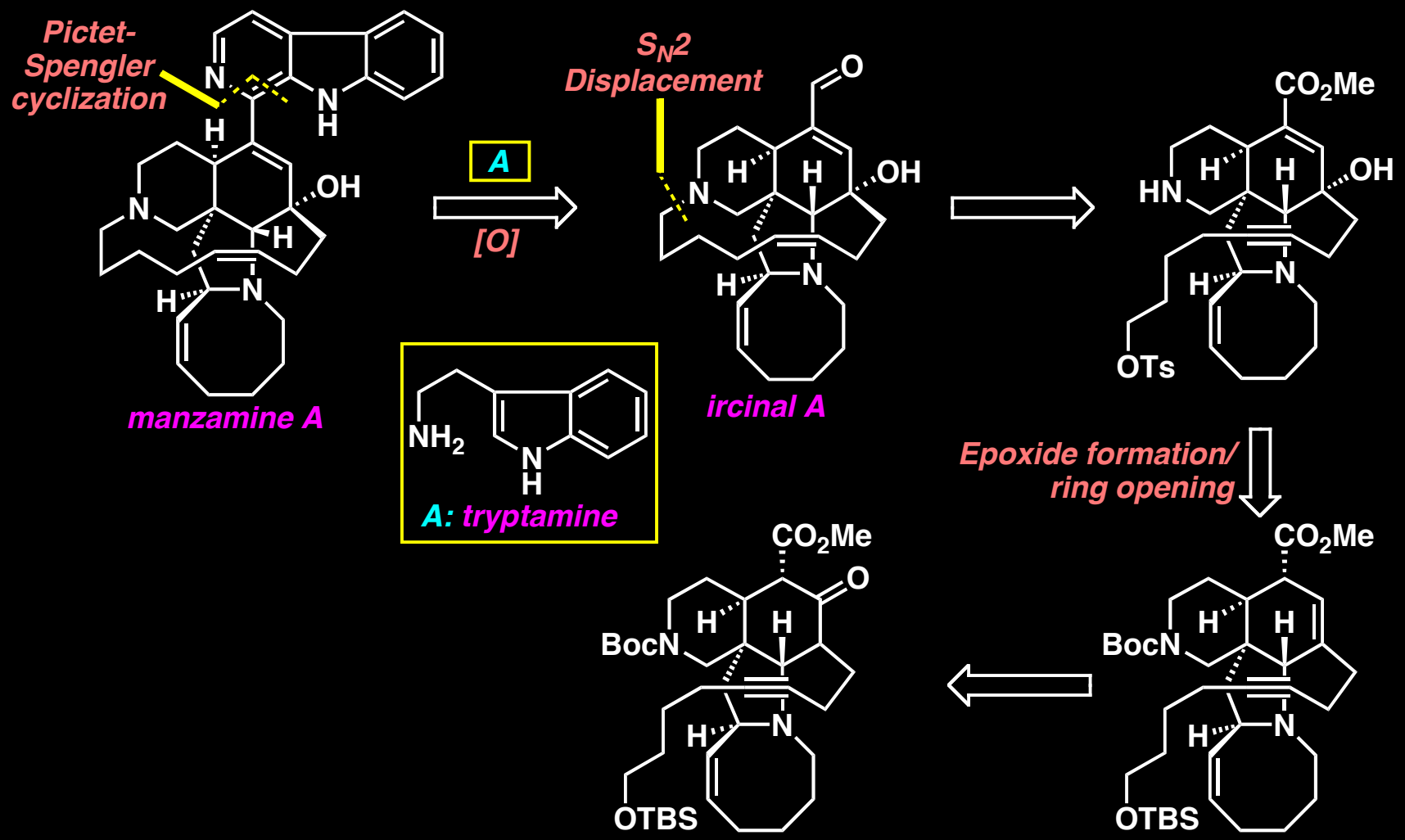

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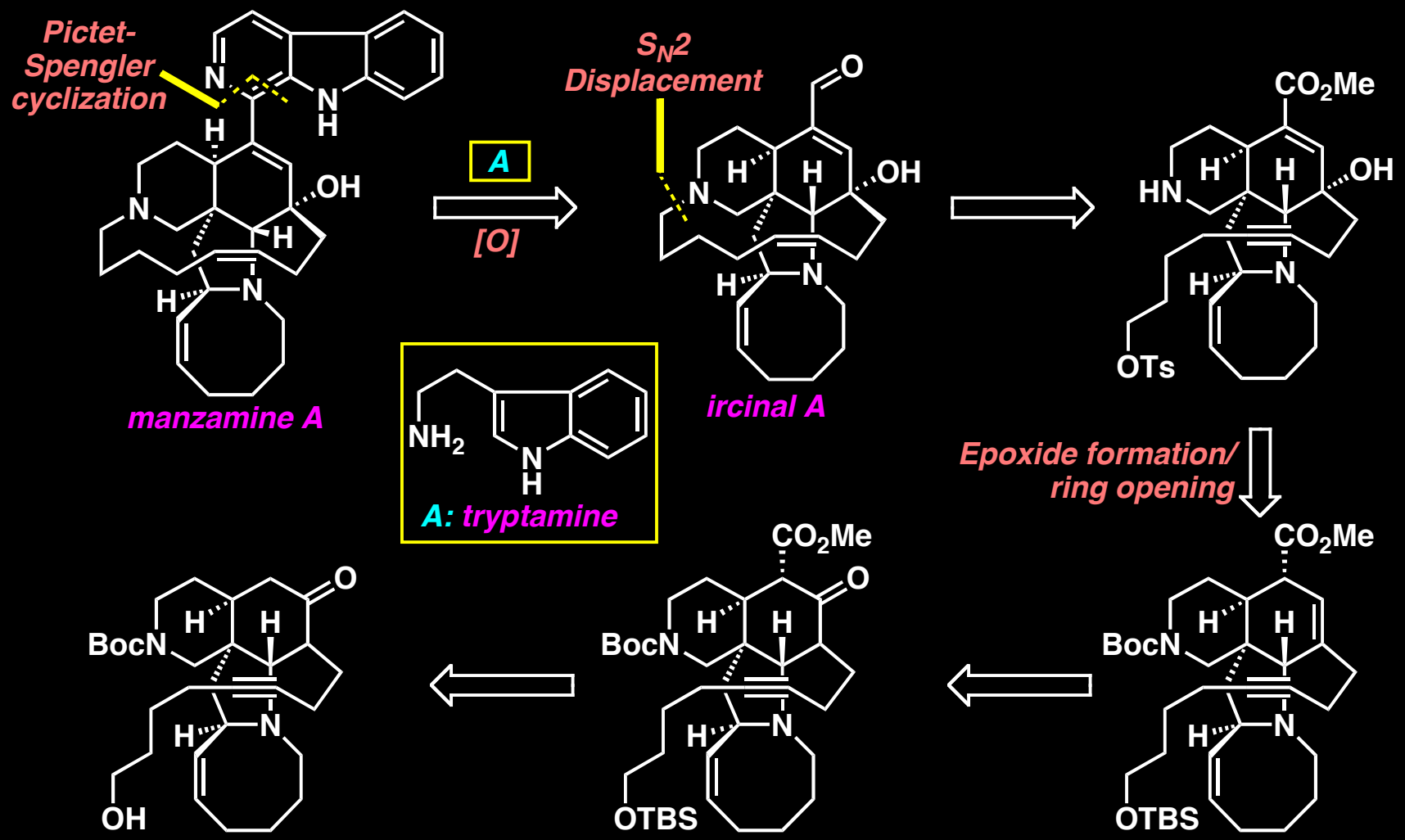

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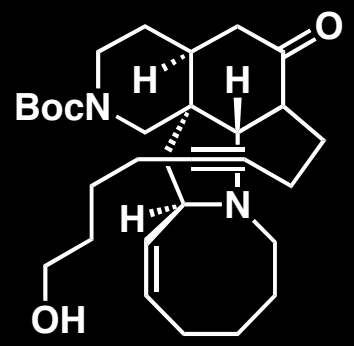

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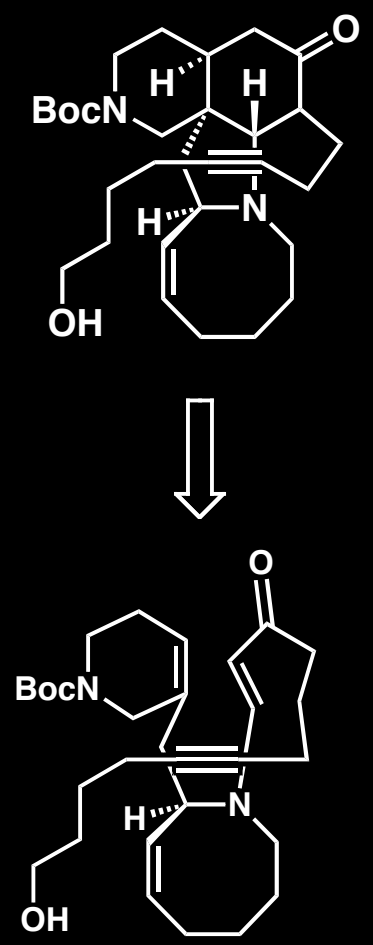

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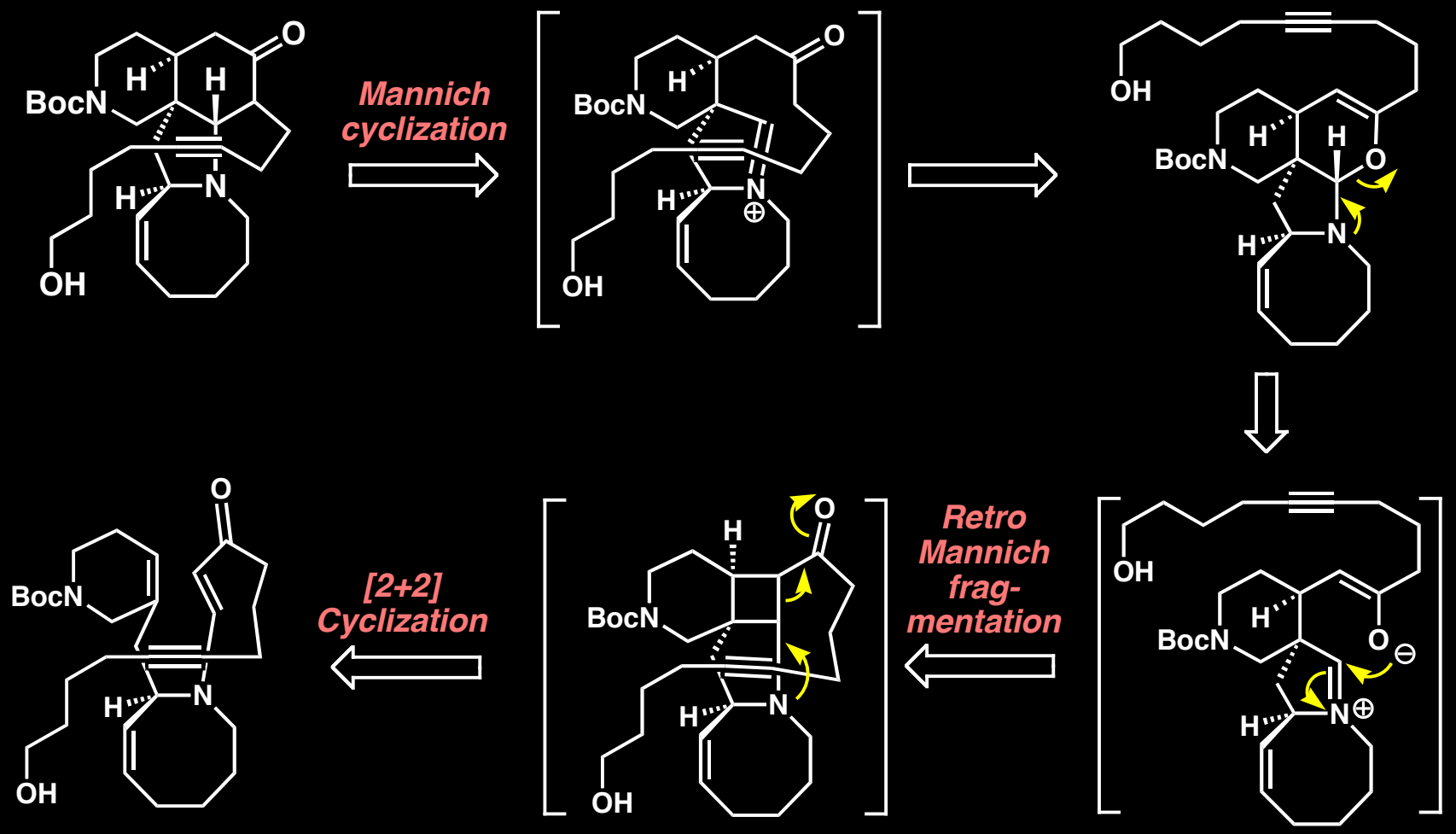

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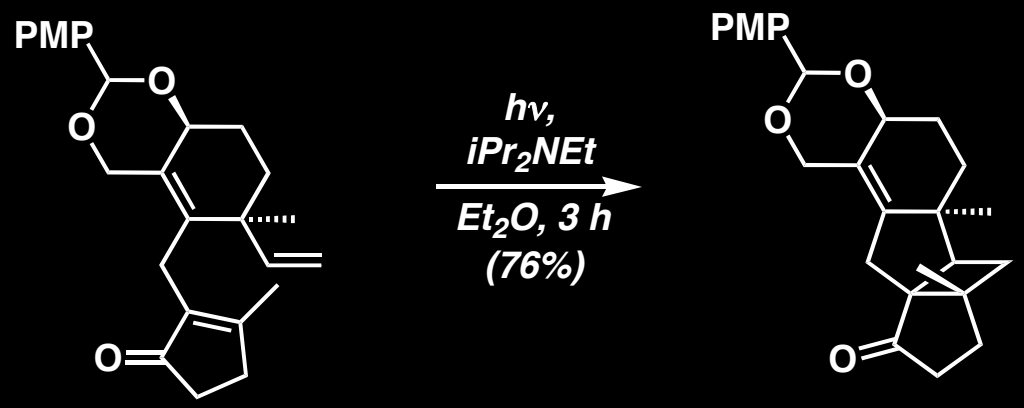
The De Mayo Reaction: Enone-Alkene [2+2] Cycloaddition



The reaction is most often utilized in an intramolecular fashion as regio- and stereoselectivity are easy to control. Typically used to forge 5-4 bicyclic systems. Arguably, 80-85% of all De Mayo reactions in complex contexts are intramolecular.

In intermolecular additions, the stereochemistry of the starting alkene is often scrambled, indicating a non-concerted process. Regio- and stereoselectivity can be high, but is often impossible to predict a priori.

For a review, see: M. T. Crimmins, Chem. Rev. 1988, 88, 1453.
W. D. Shipe, E. J. Sorensen, Org. Lett. 2002, 4, 2063.

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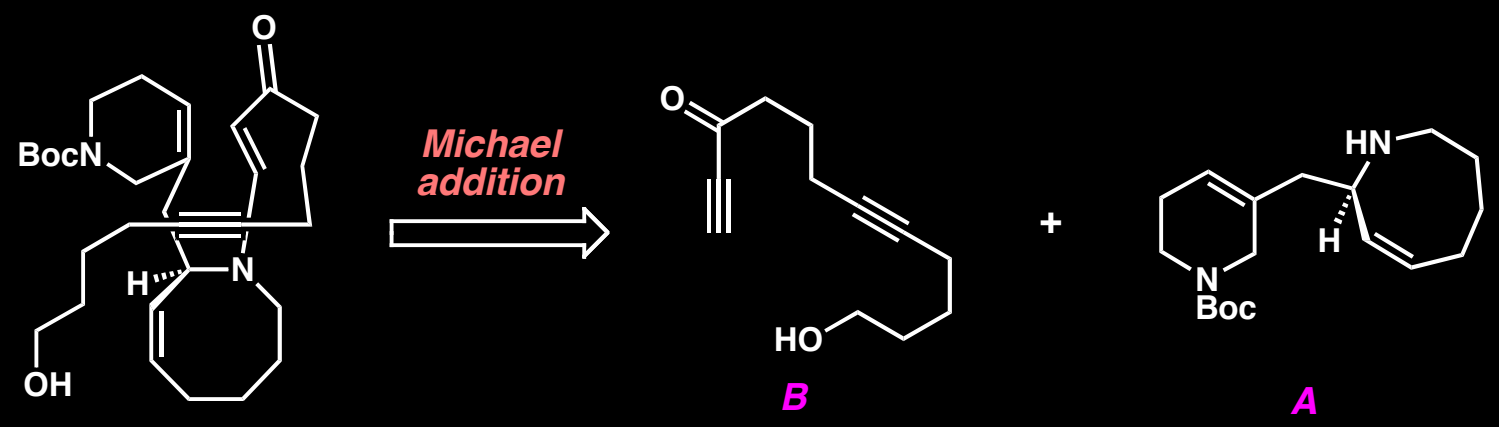

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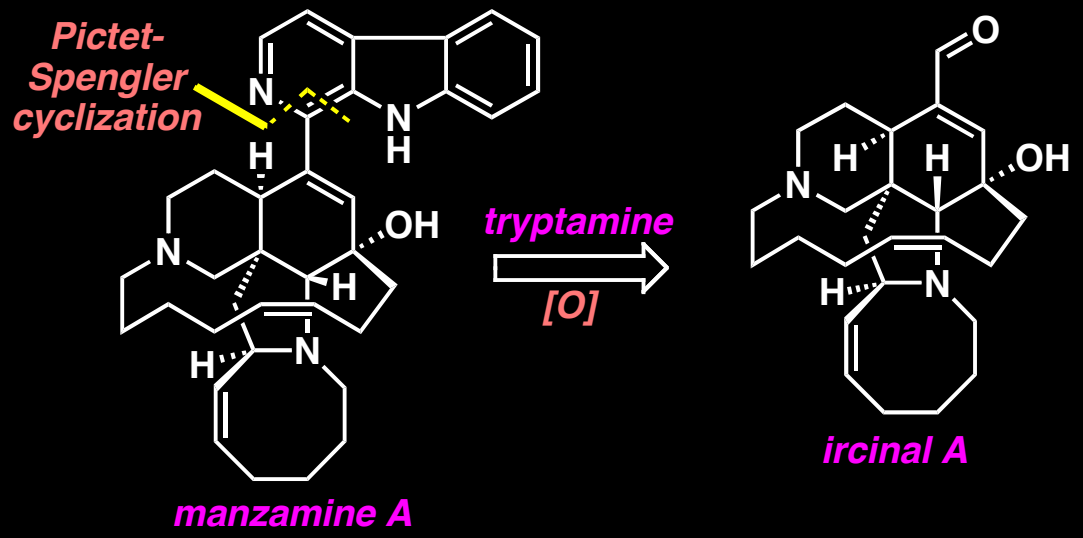

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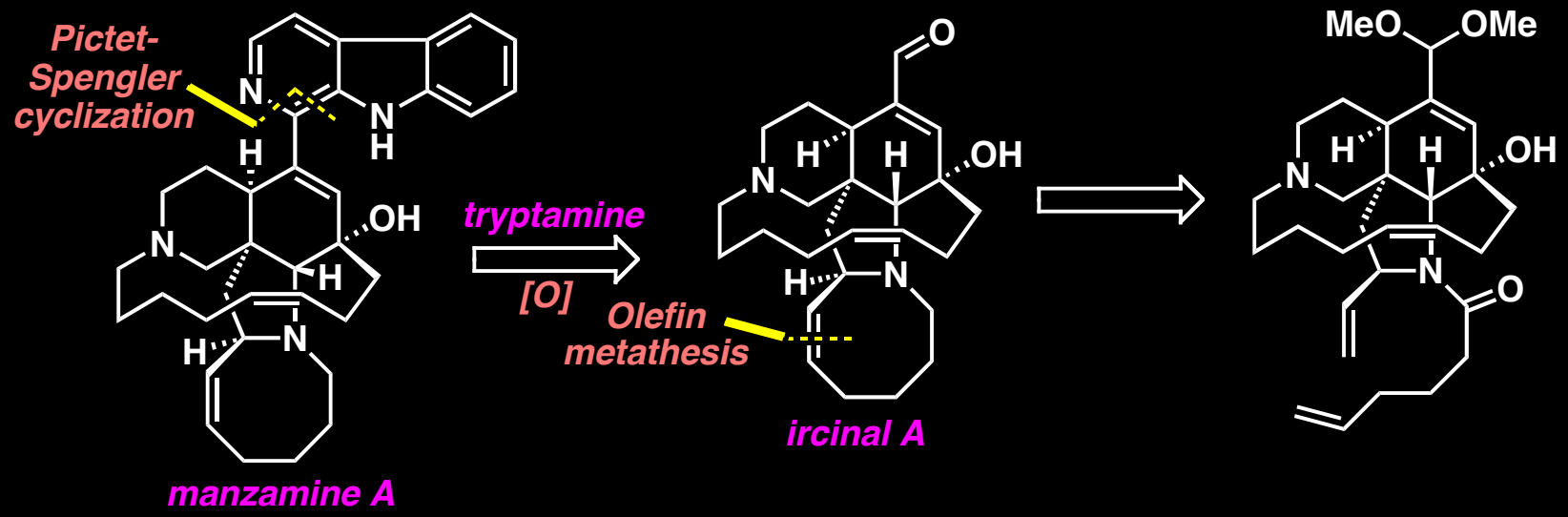

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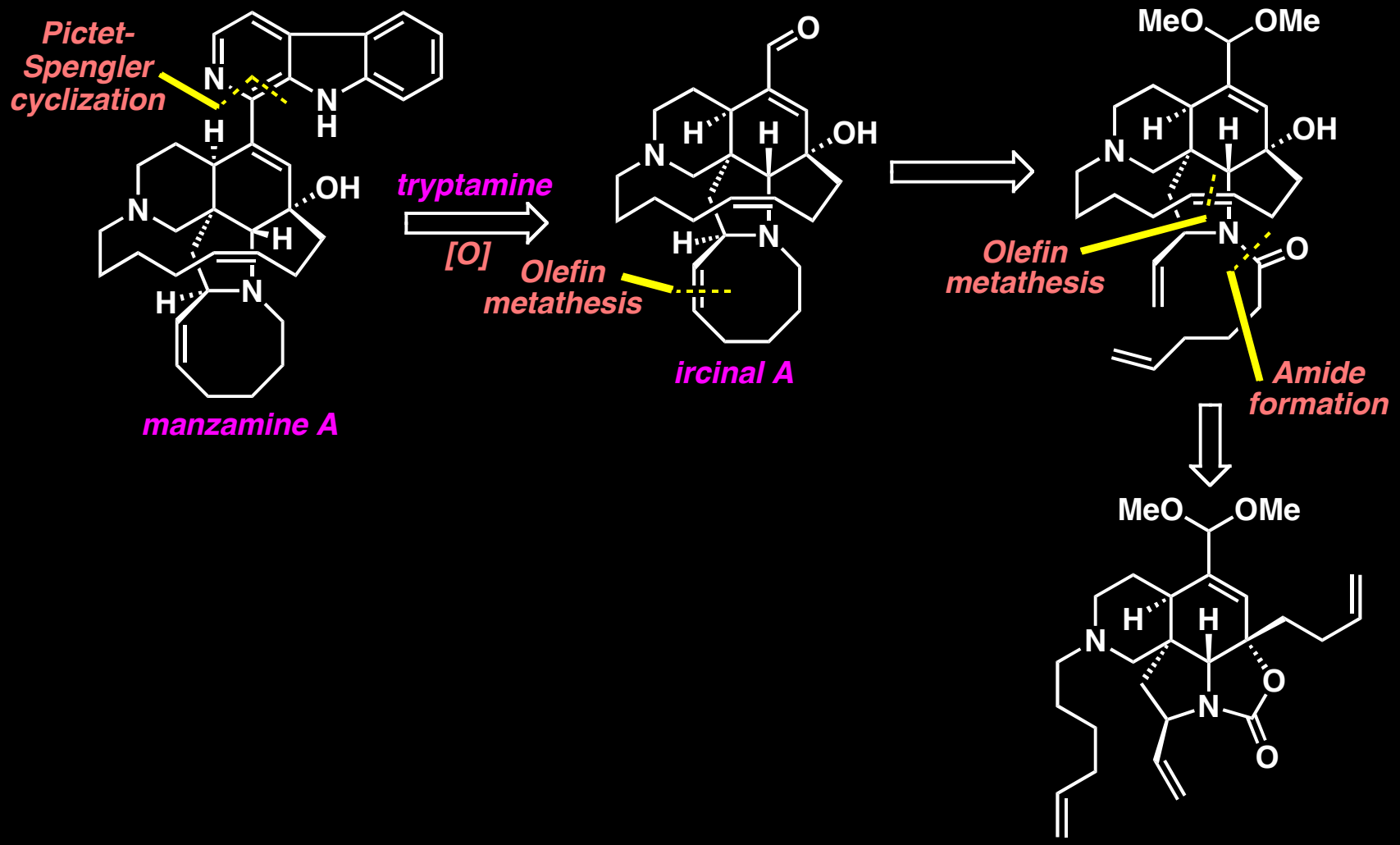

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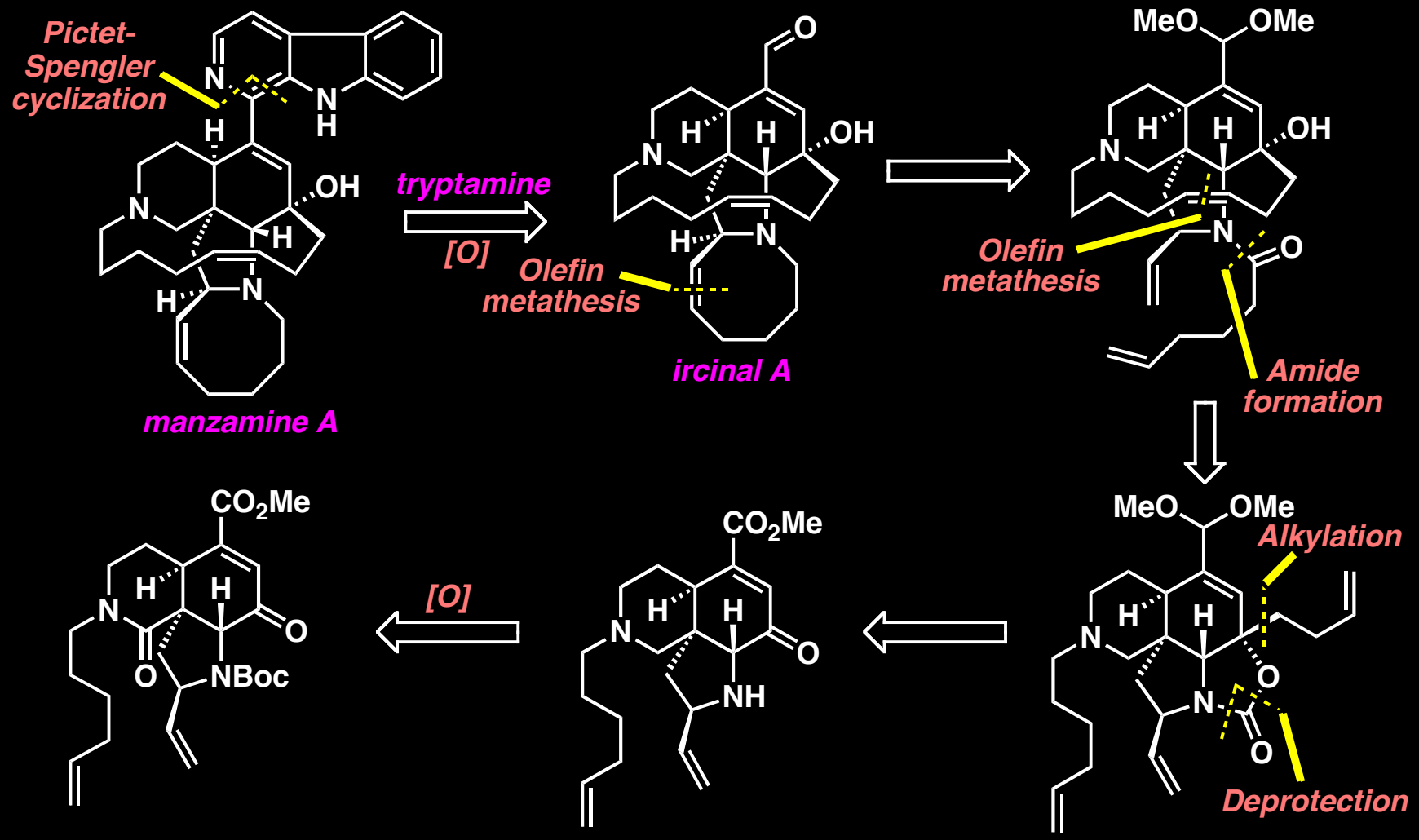

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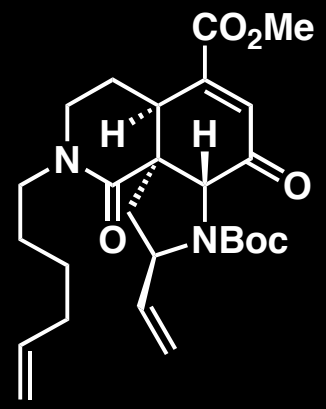

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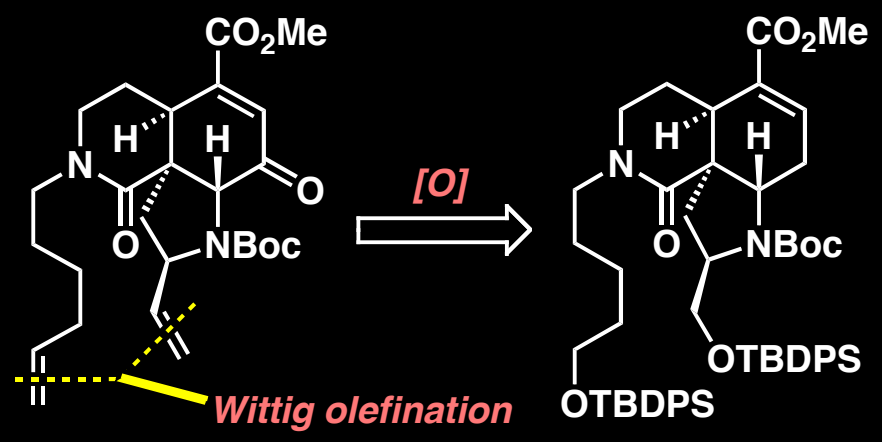

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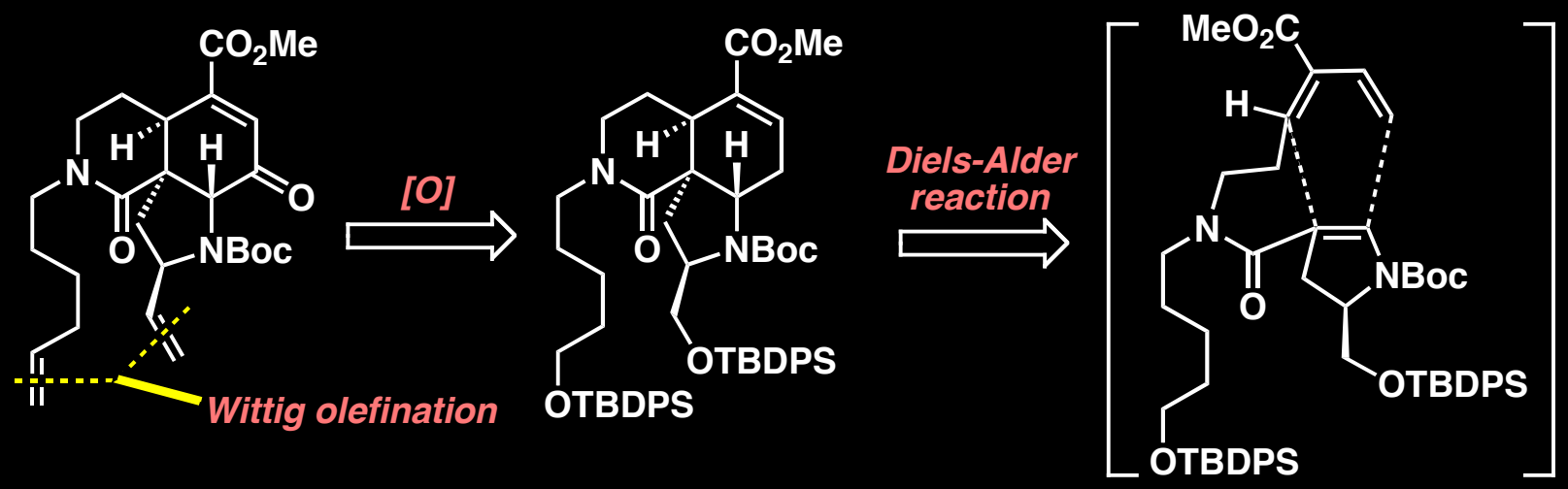

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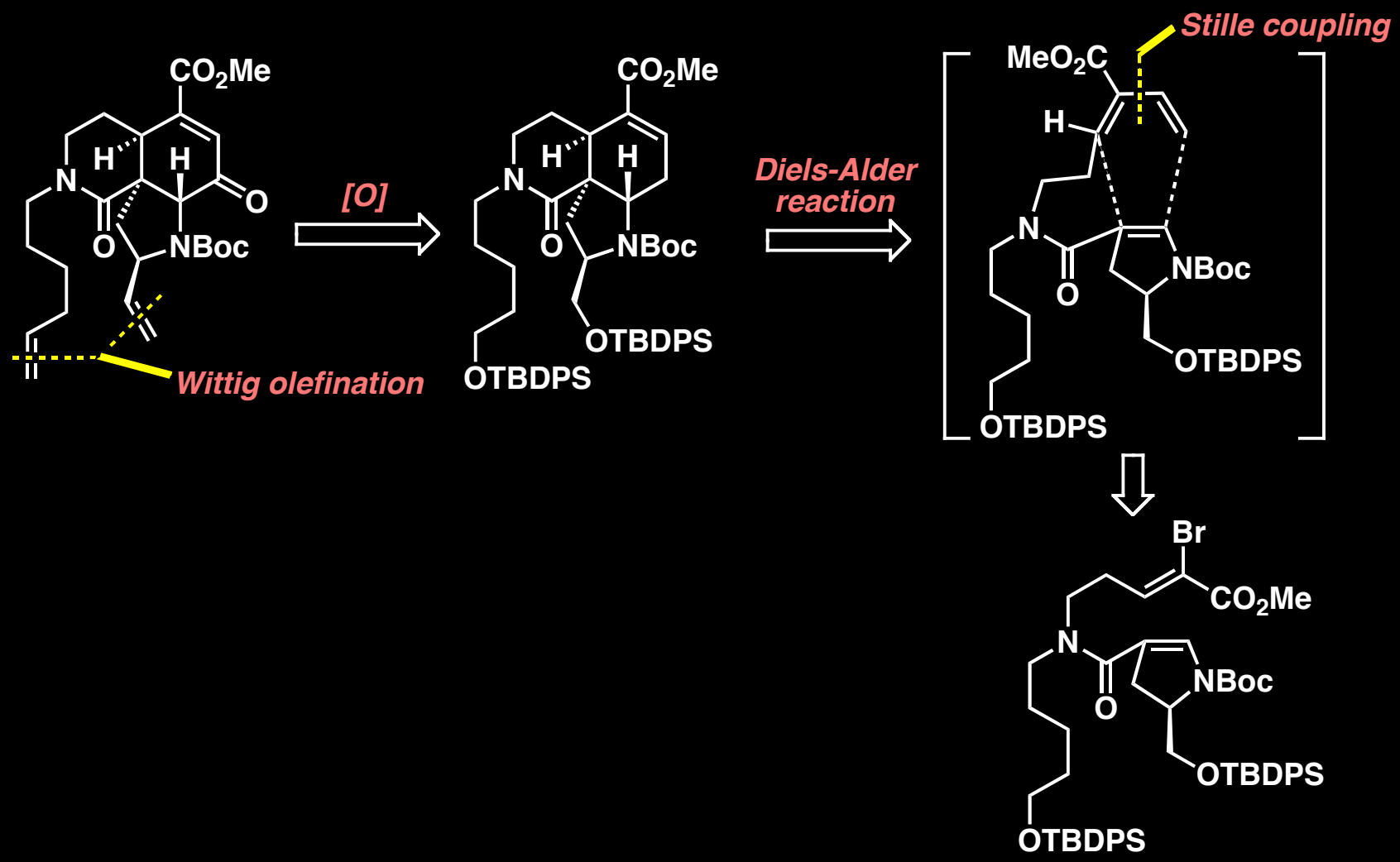

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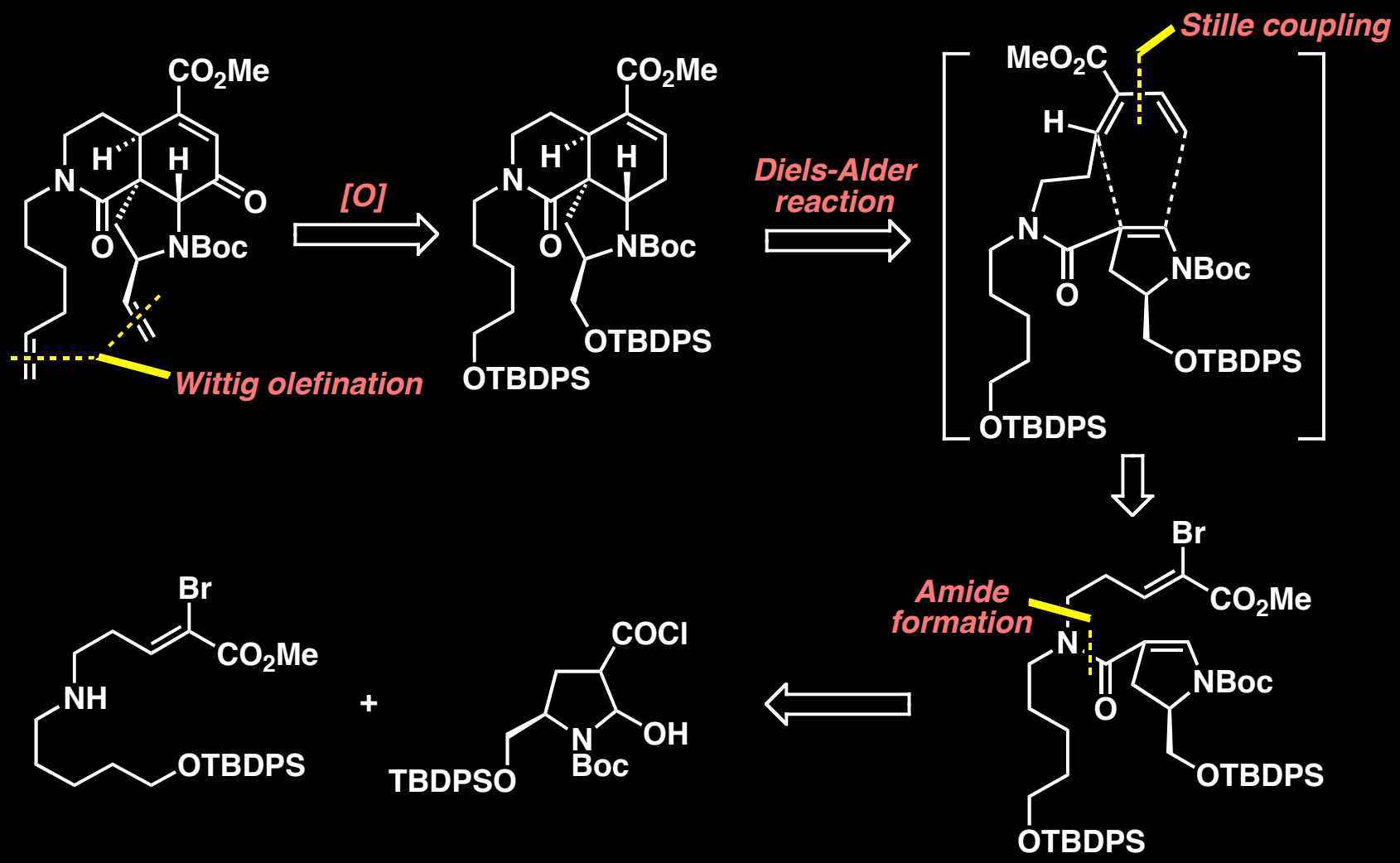

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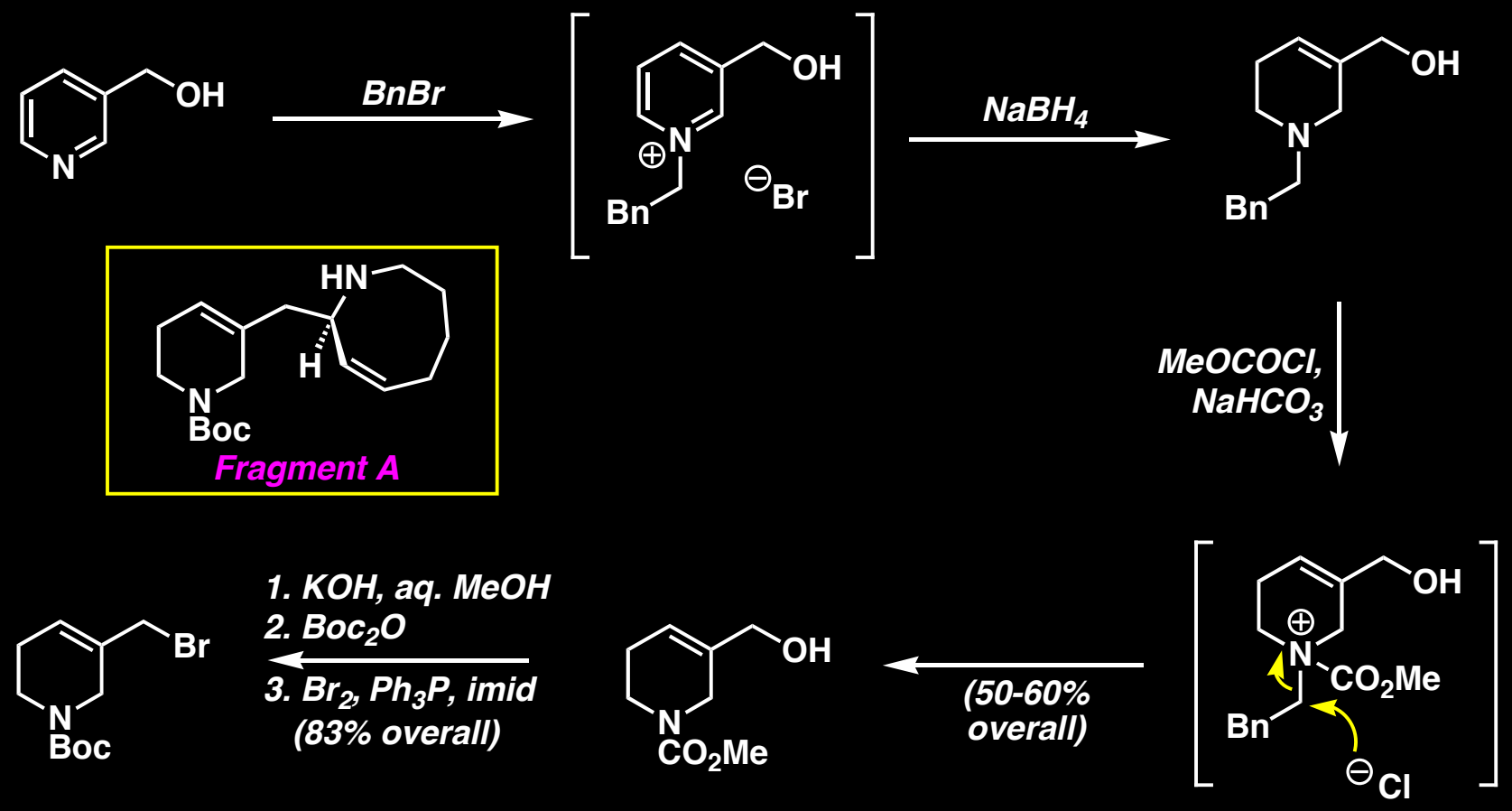
Winkler's Total Synthesis of Manzamine A: Synthesis of Fragment A



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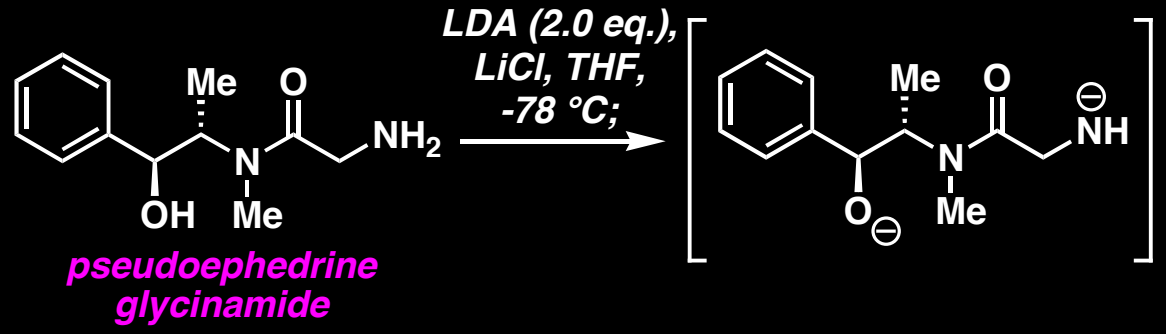

For the initial step, see: A. G. Myers and co-workers, J. Am. Chem. Soc. 1995, 117, 8488.

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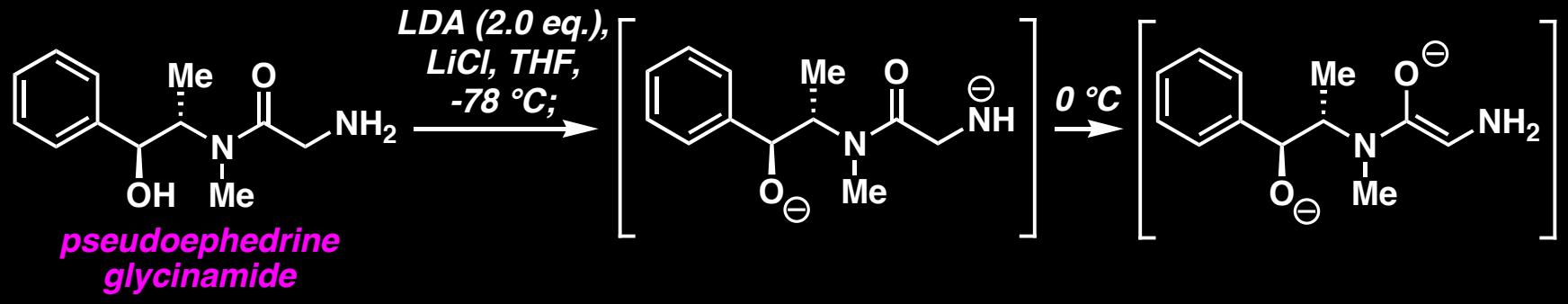

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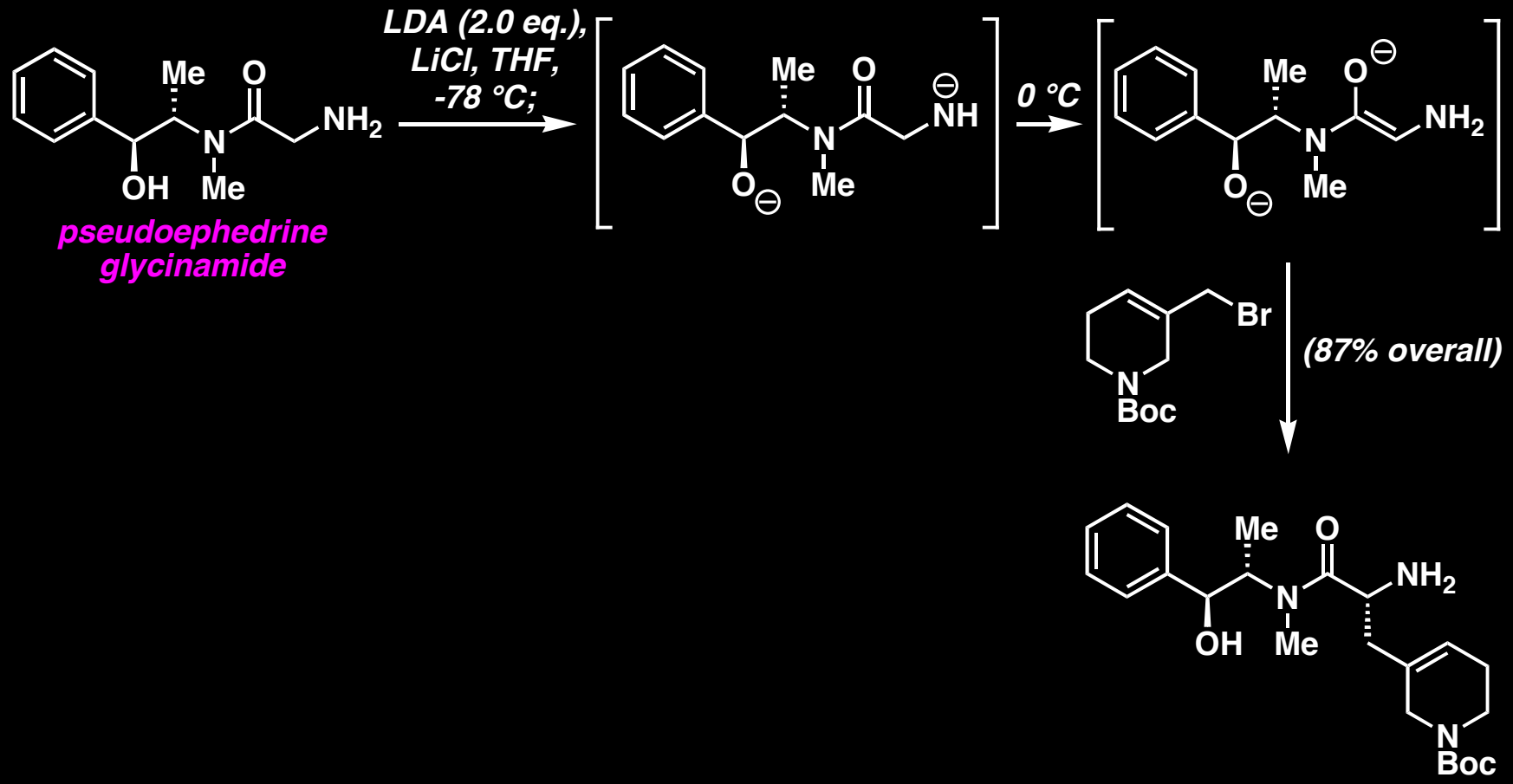

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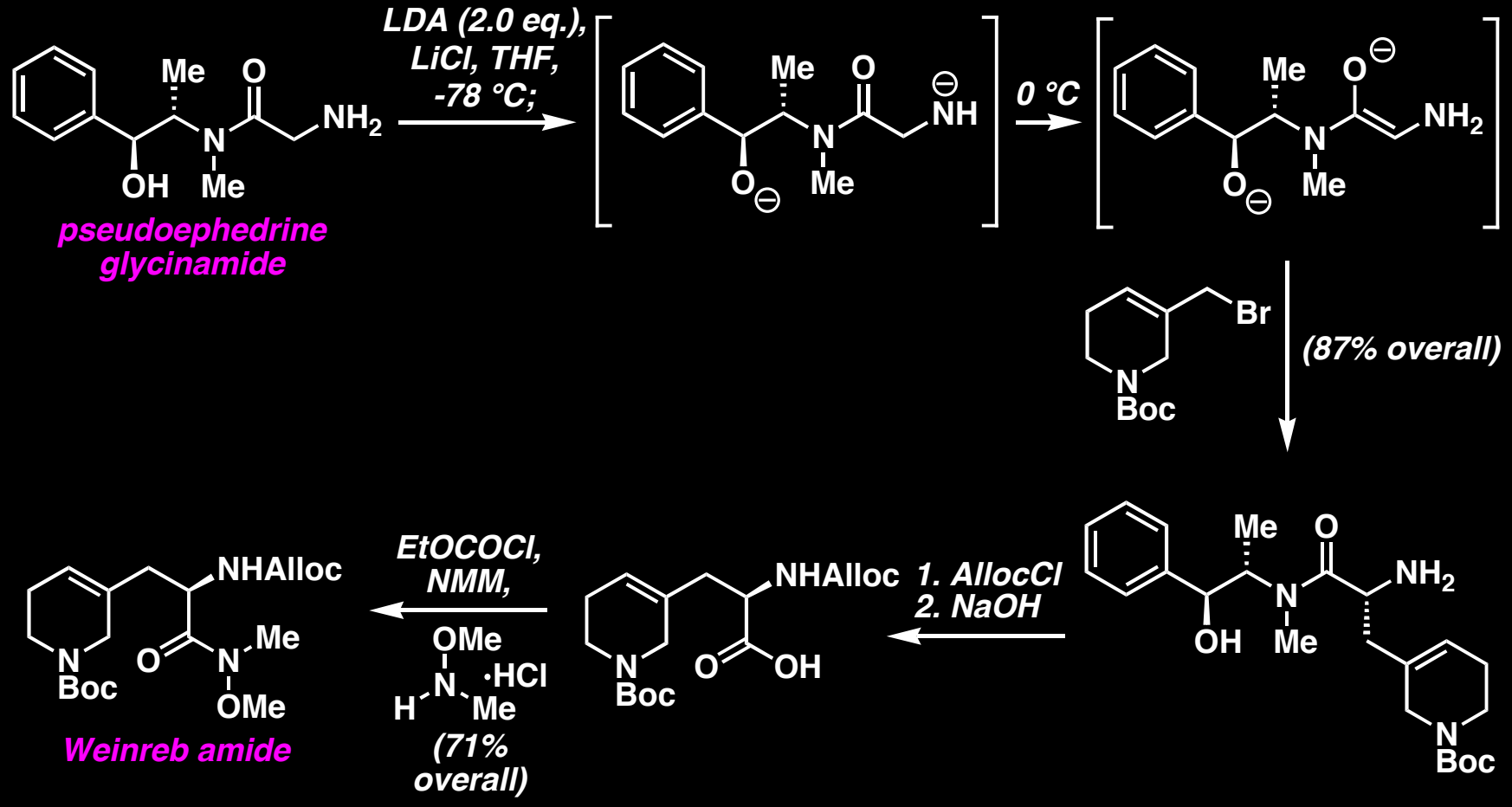

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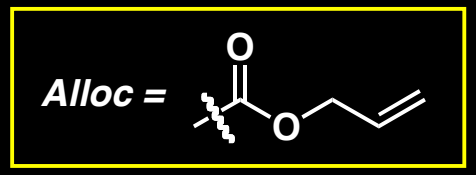

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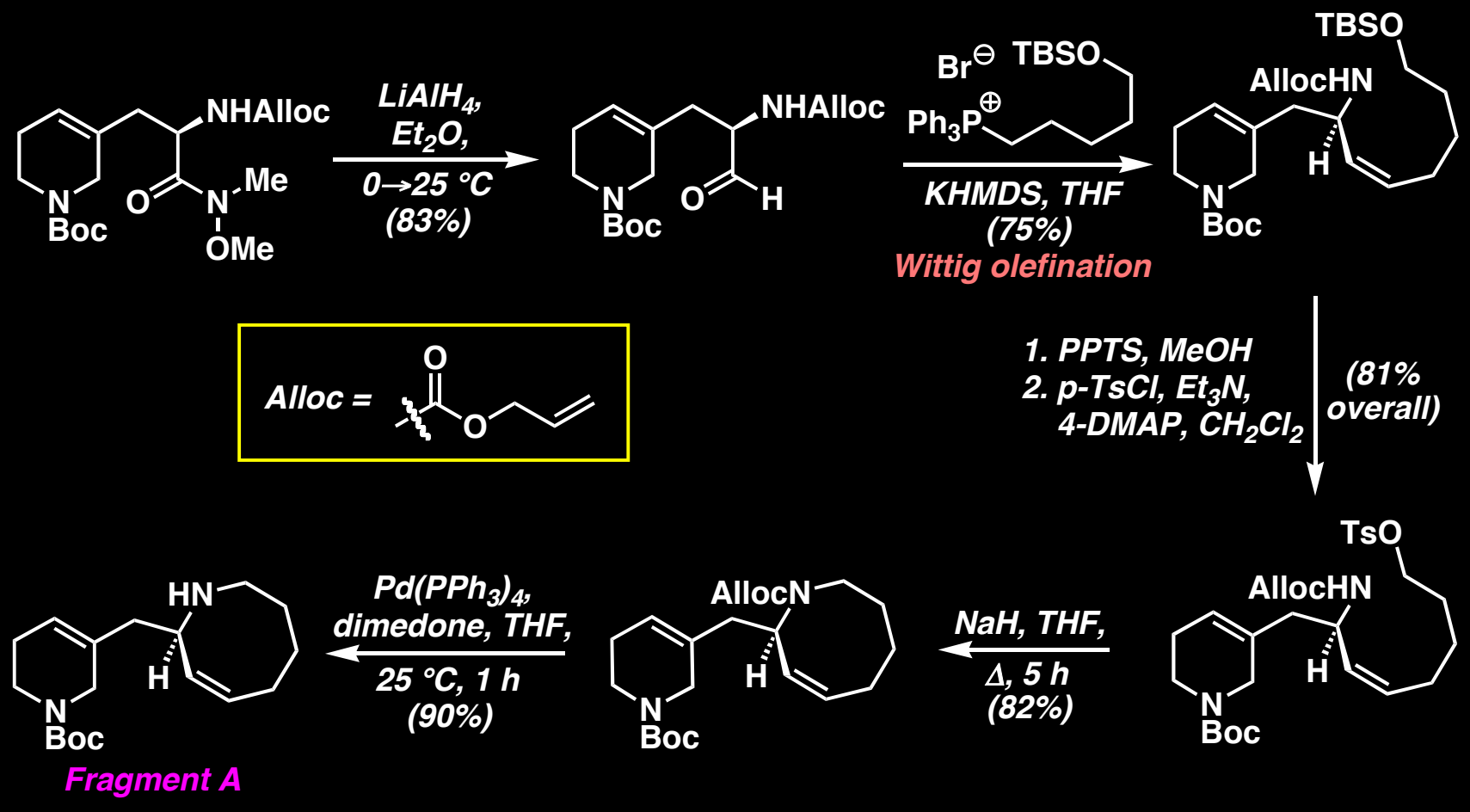

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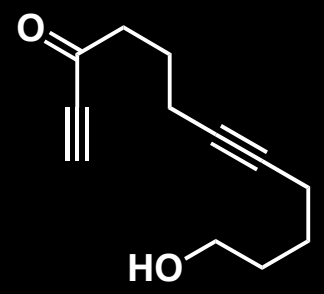
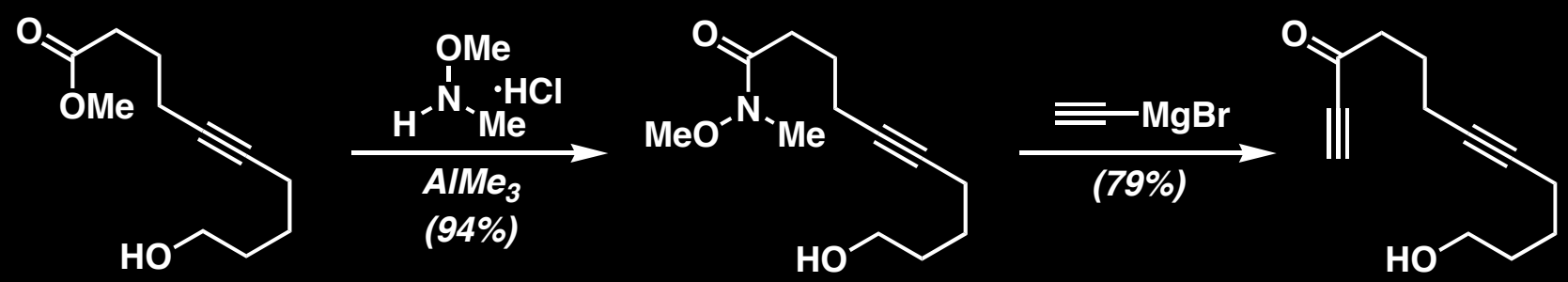
Winkler's Total Synthesis of Manzamine A: Synthesis of Fragment B



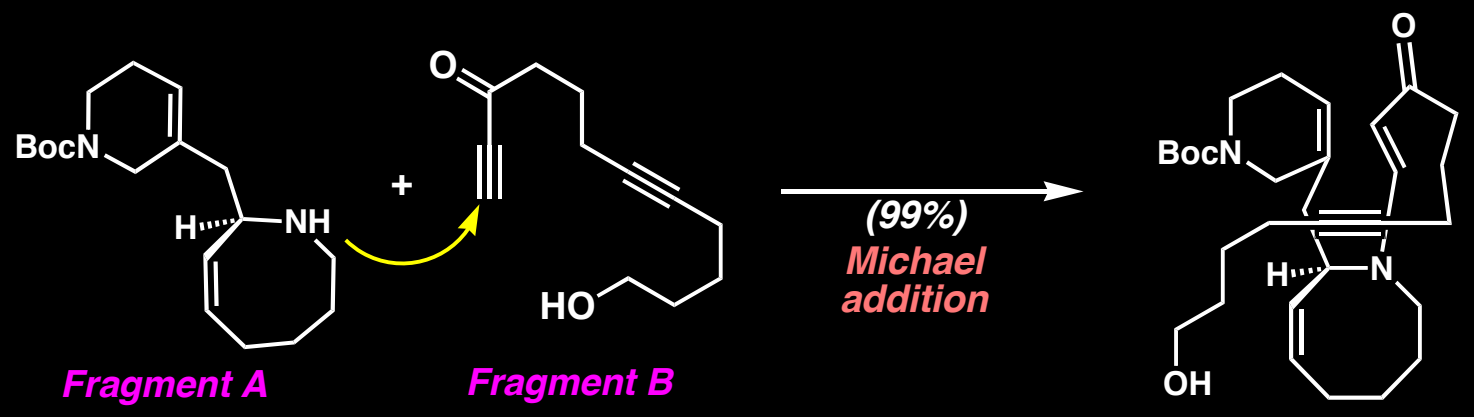
Fragment B



Fragment B

For starting fragment, see: W. Nowak, H. Gerlach, Liebigs Ann. Chem. 1993, 153.

Winkler's Total Synthesis of Manzamine A: Fragment Coupling and Key Synthetic Operations



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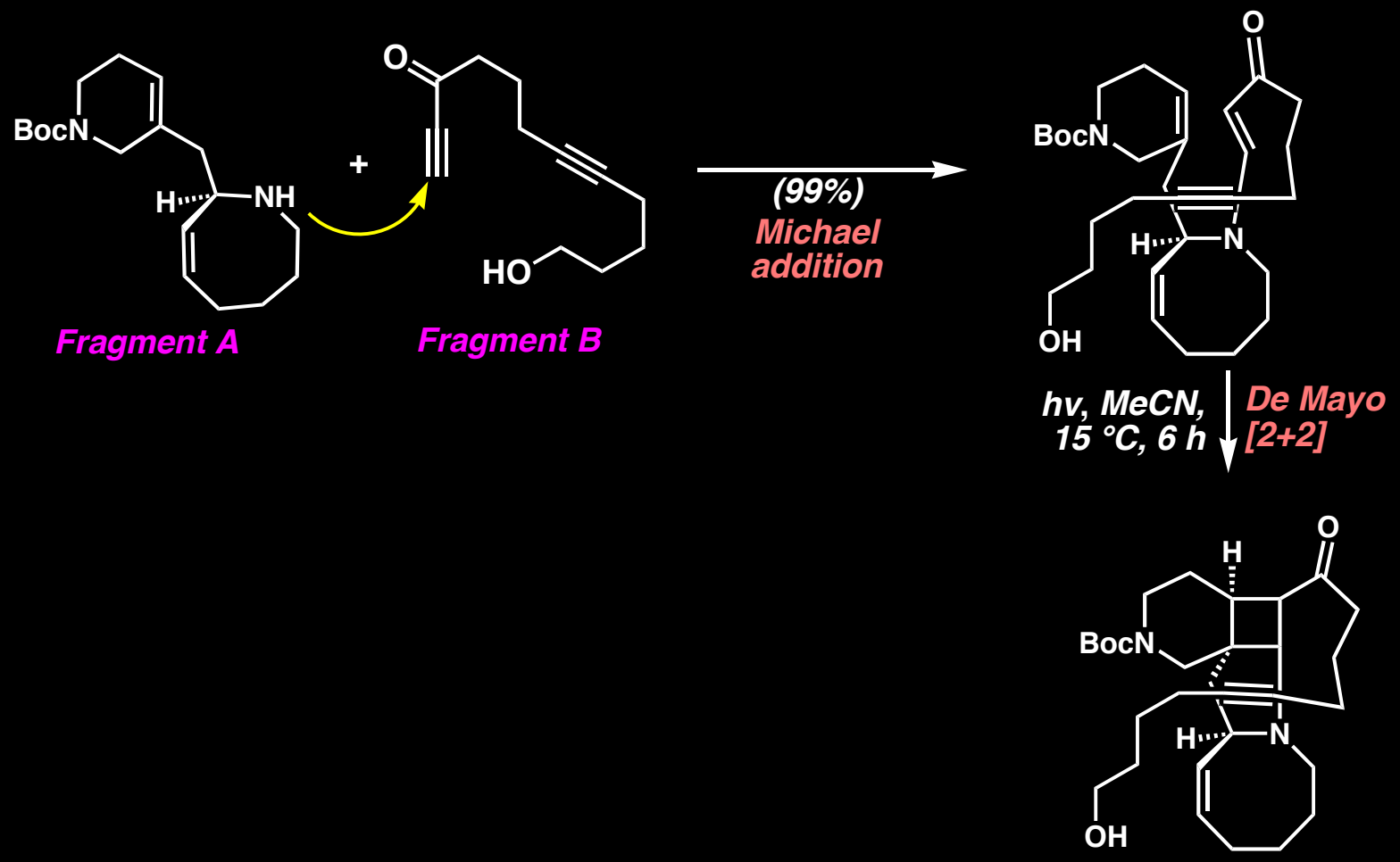

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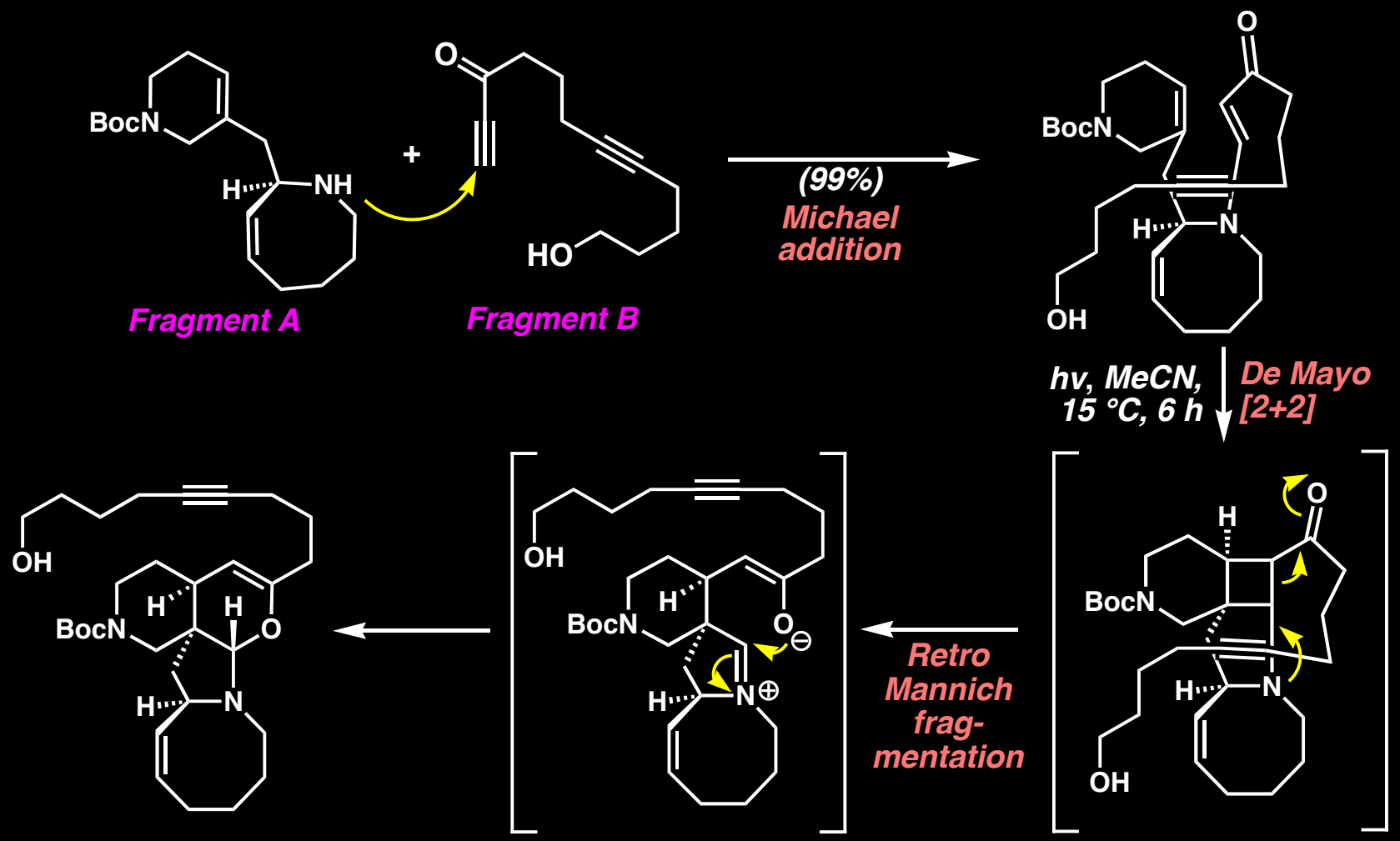

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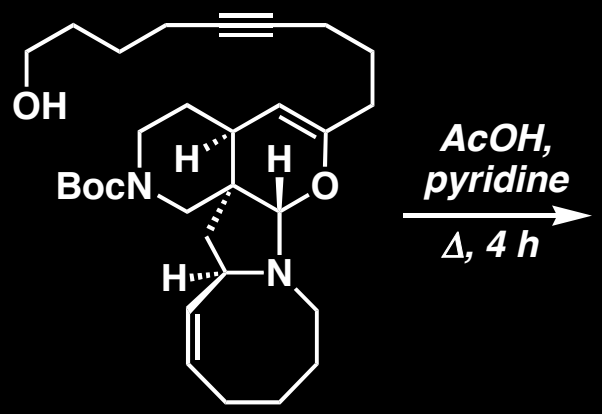
Winkler's Total Synthesis of Manzamine A: Completion of the Synthesis



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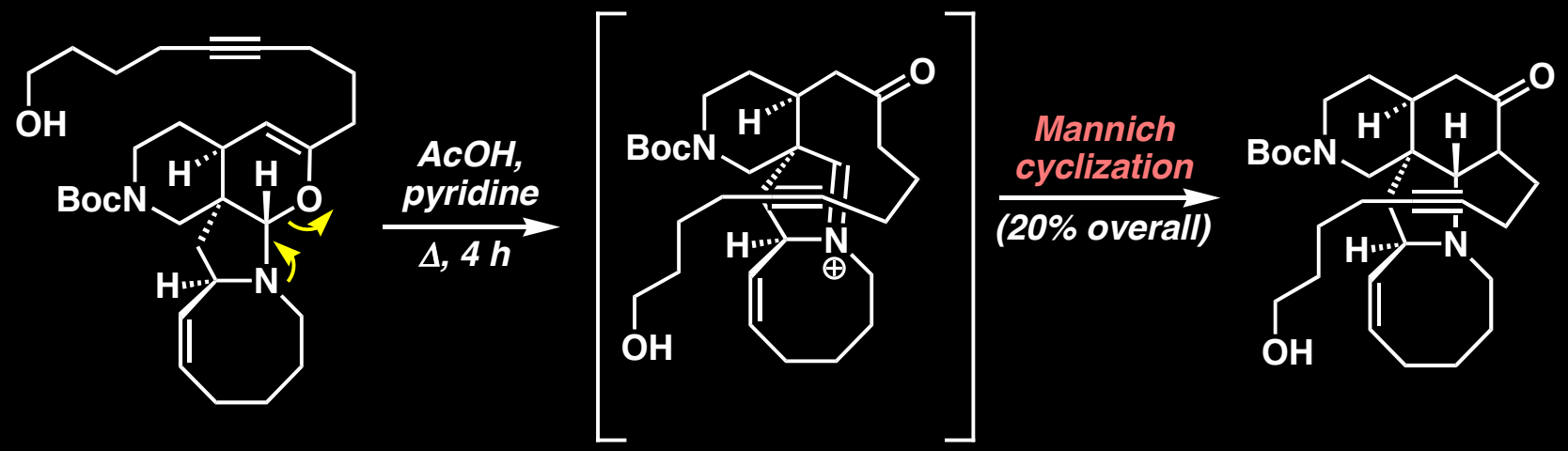

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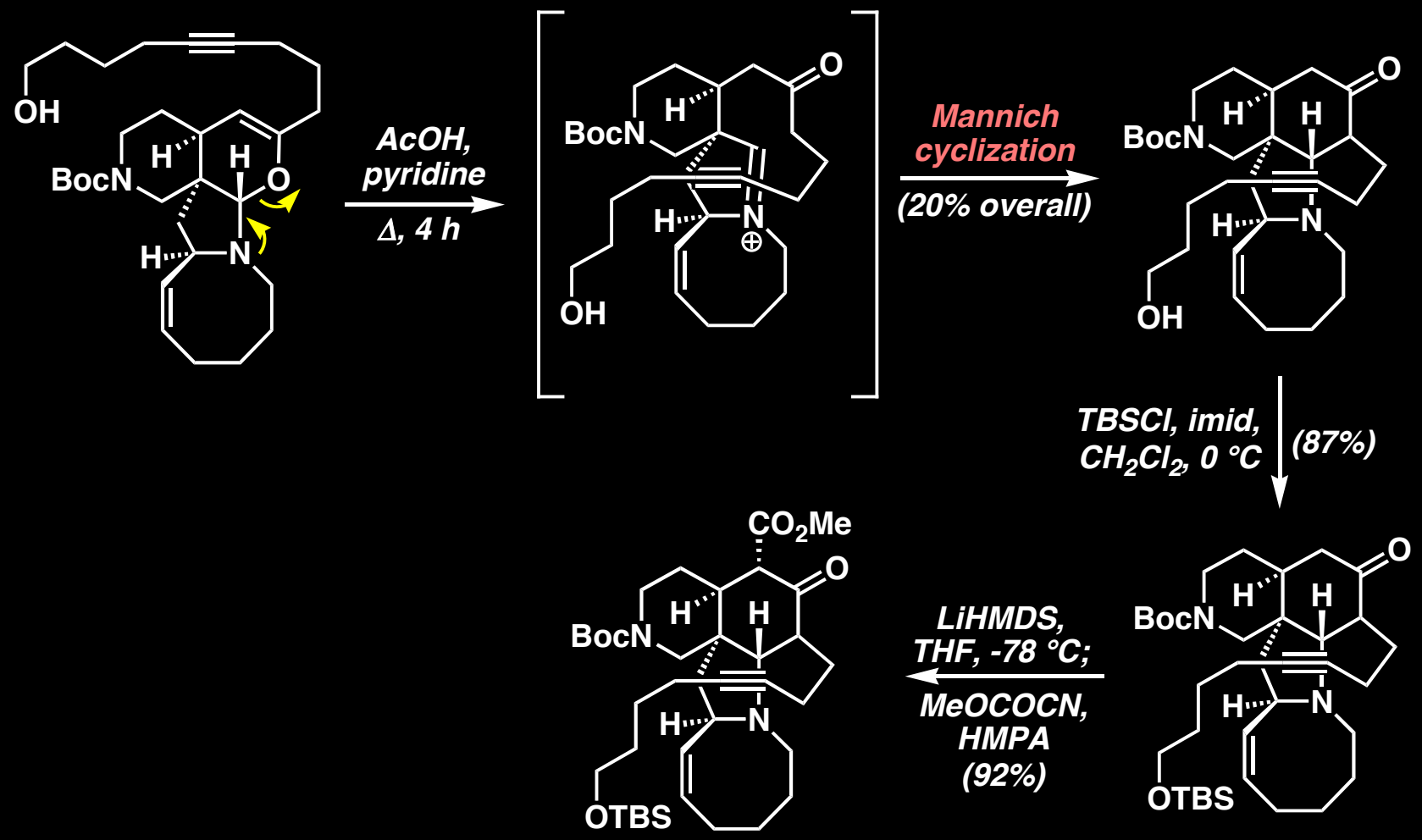

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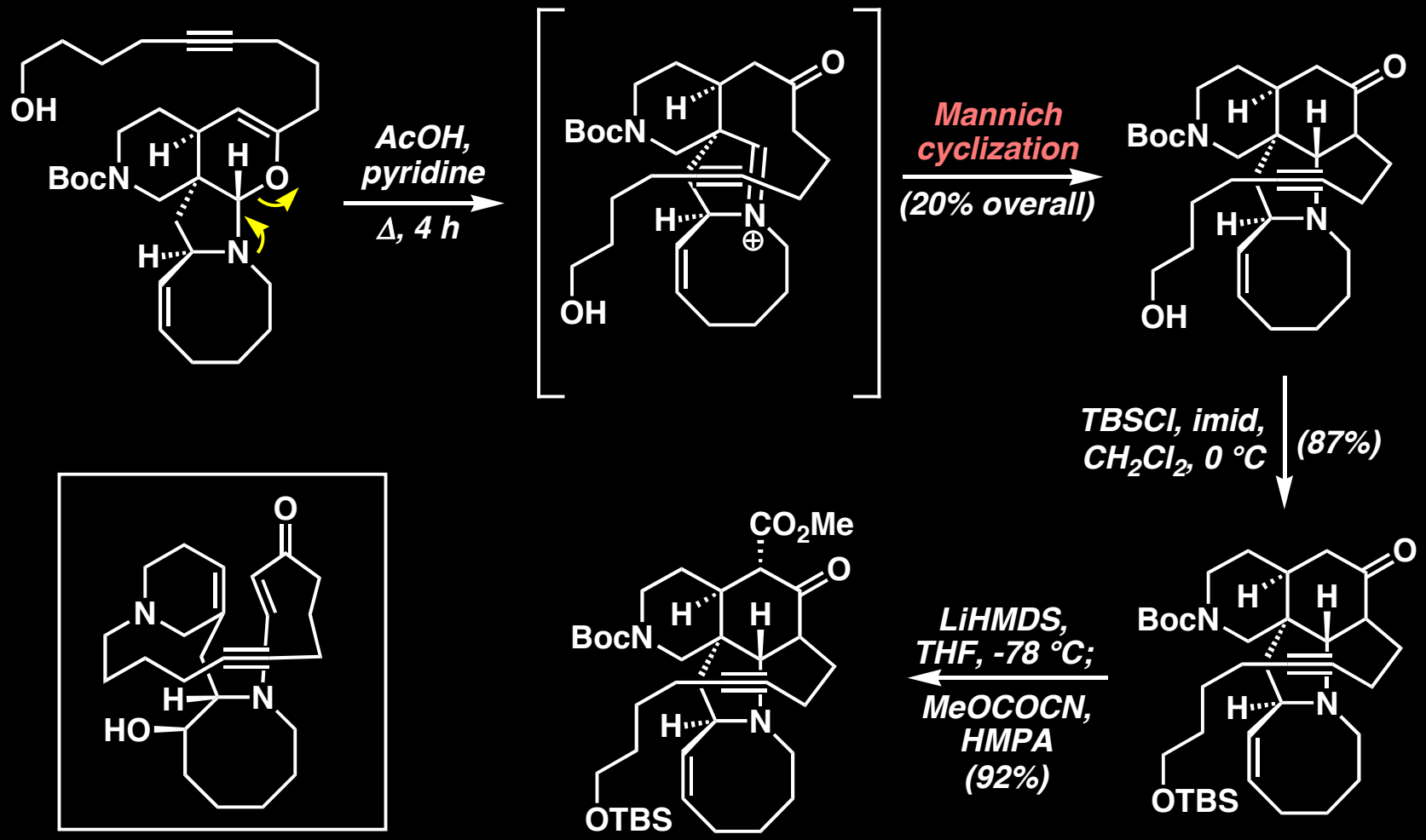

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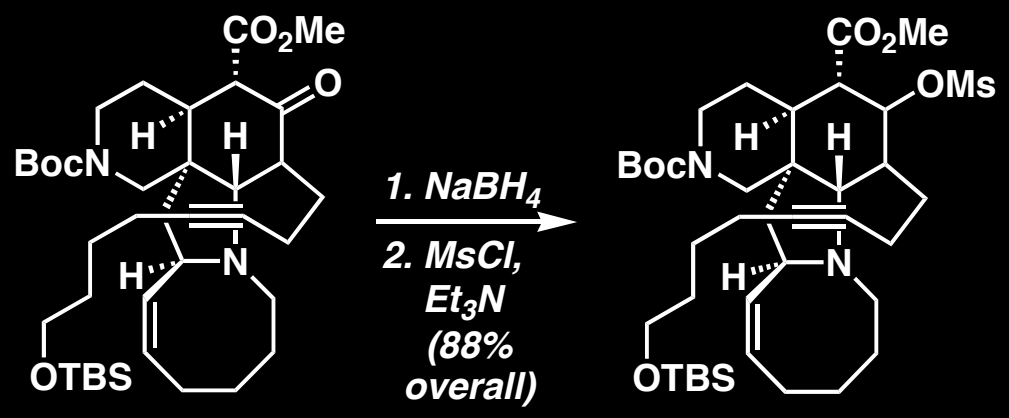

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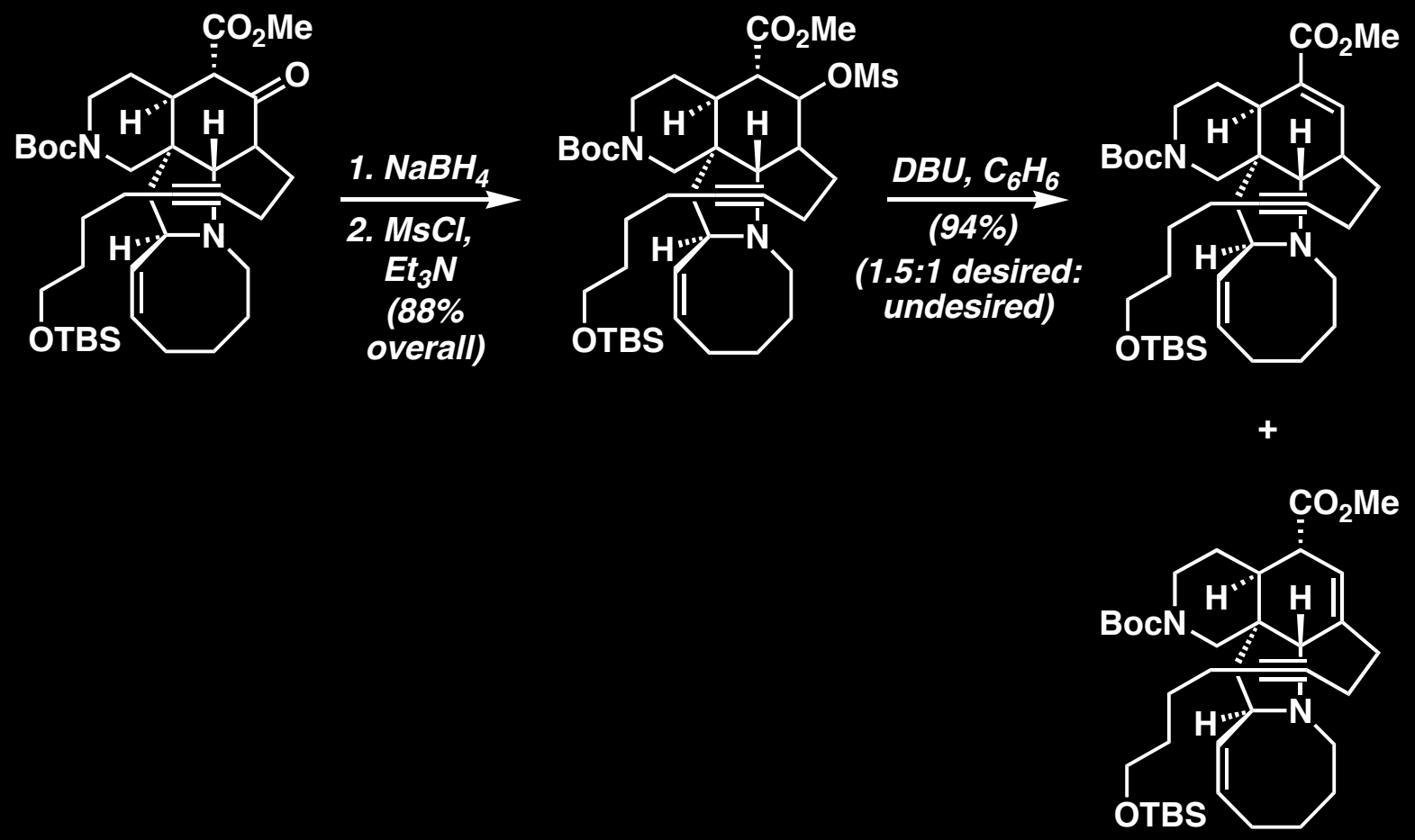

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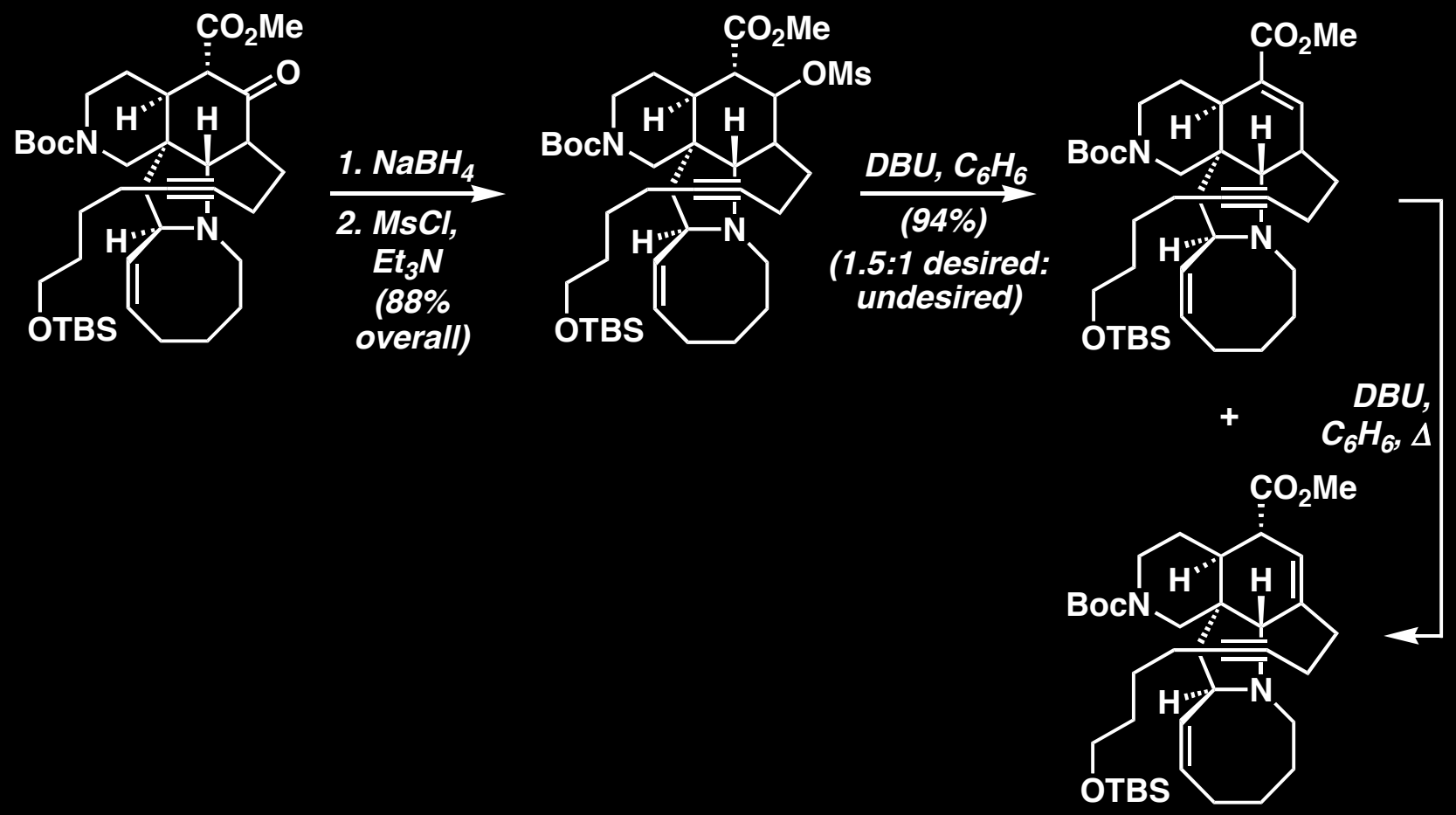

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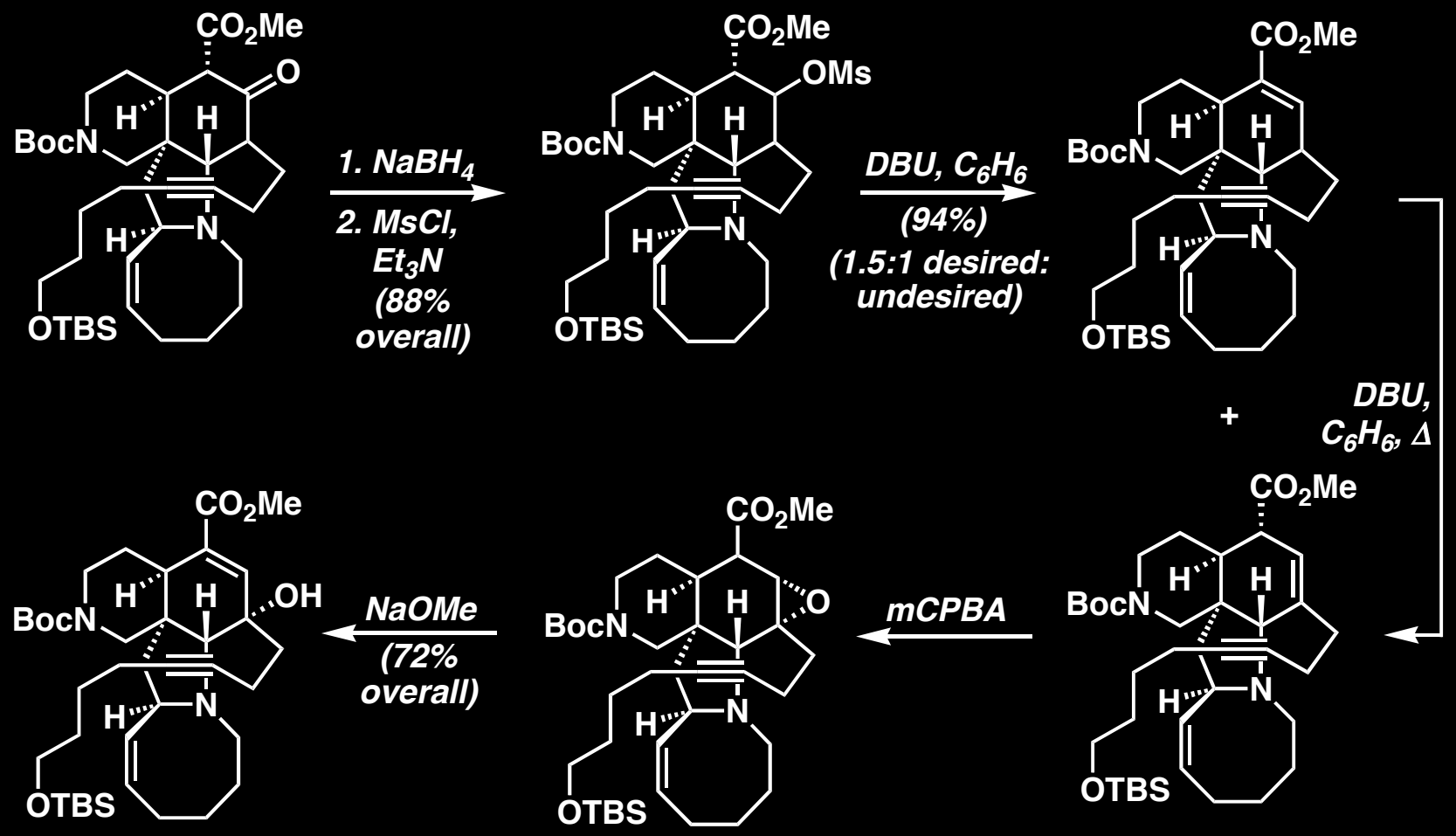

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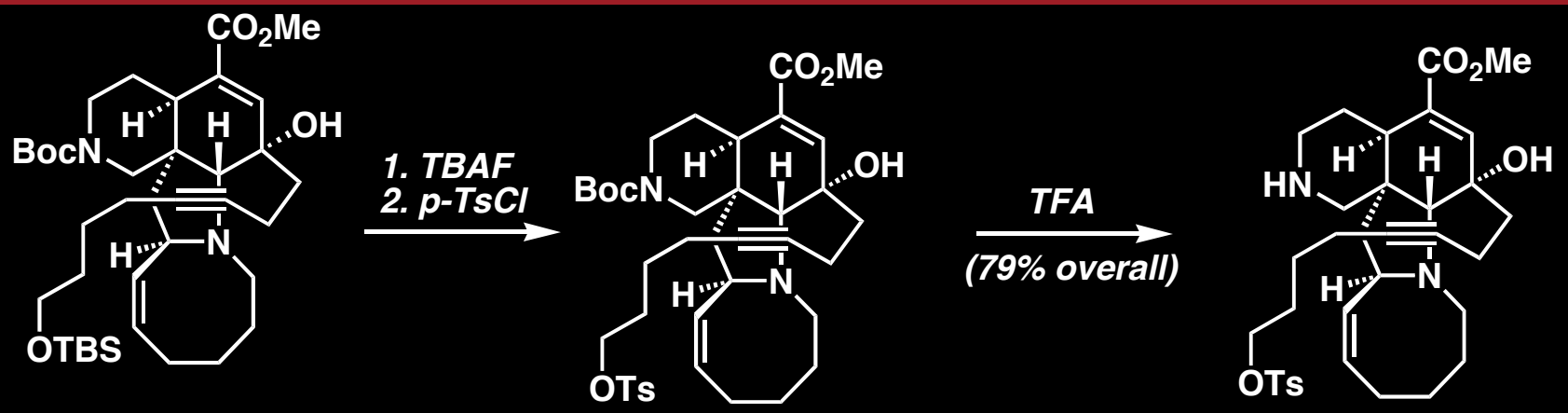

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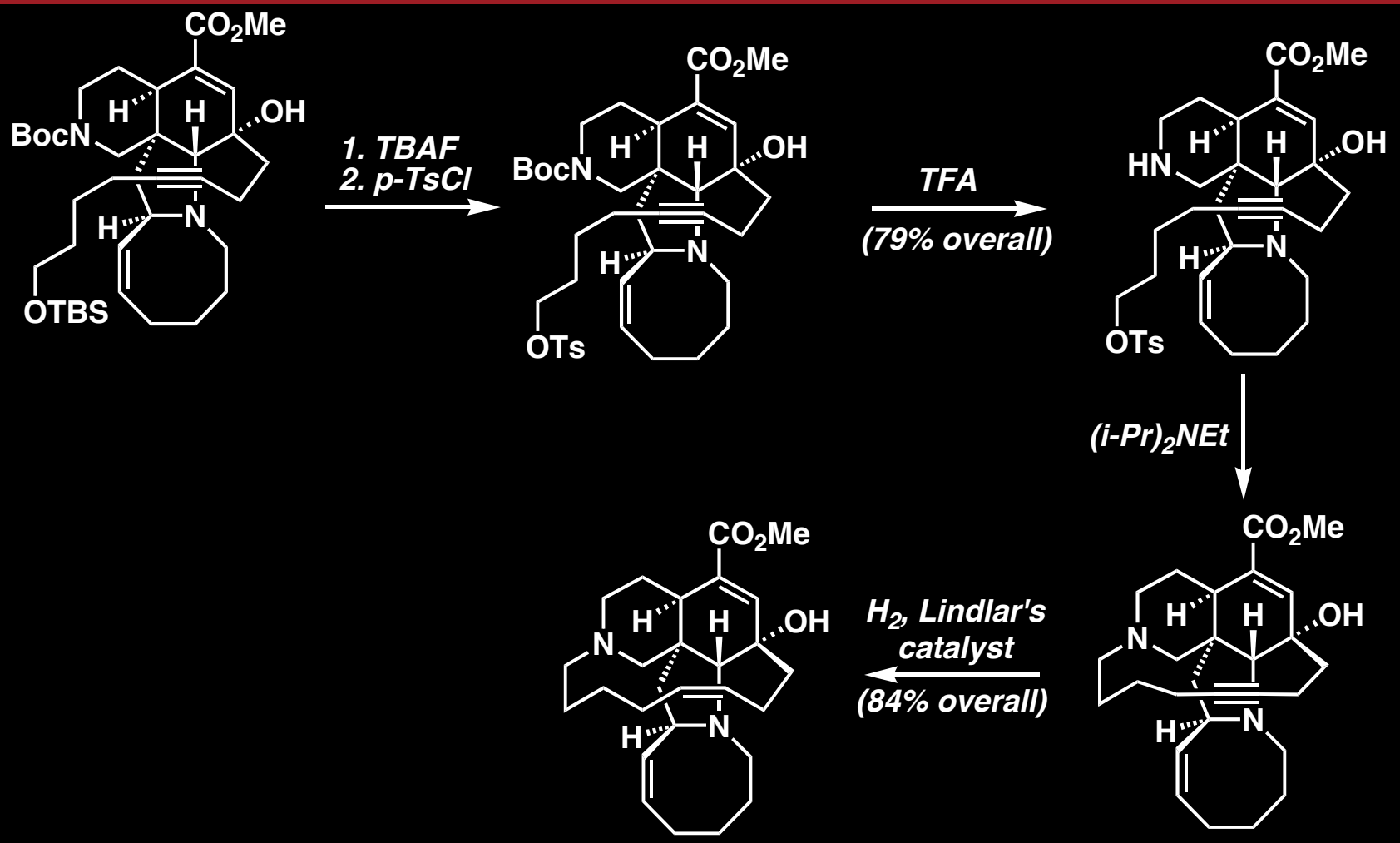

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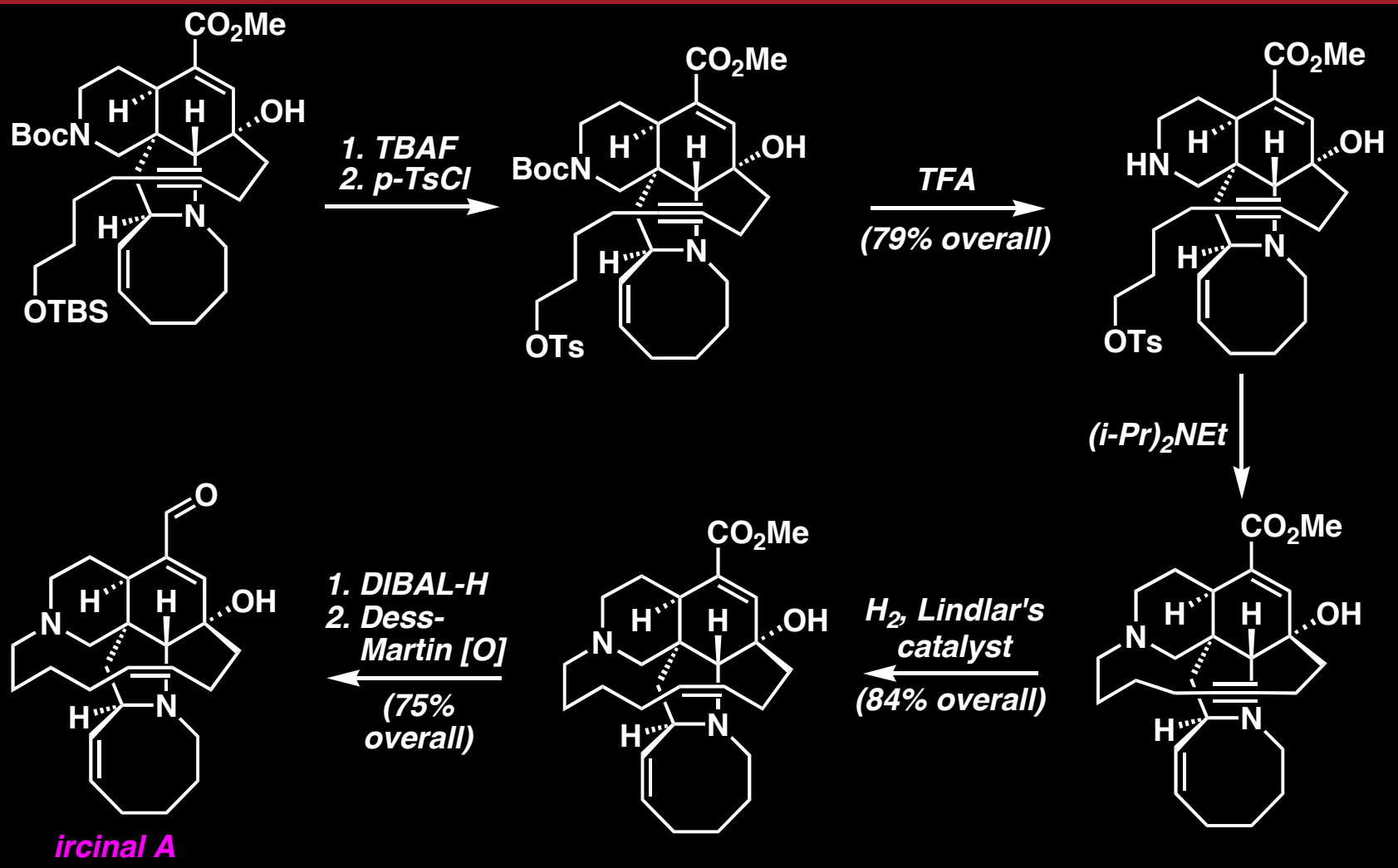

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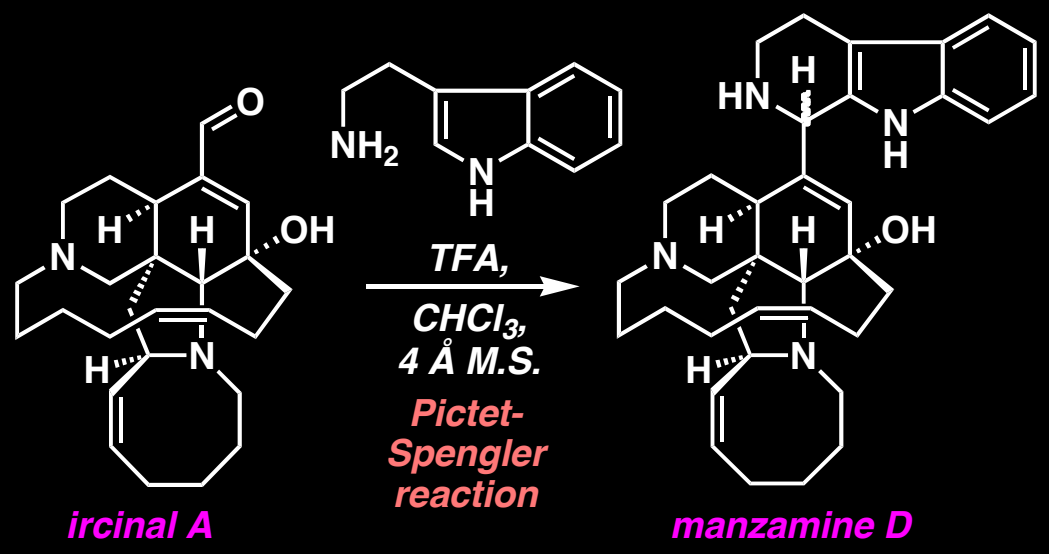

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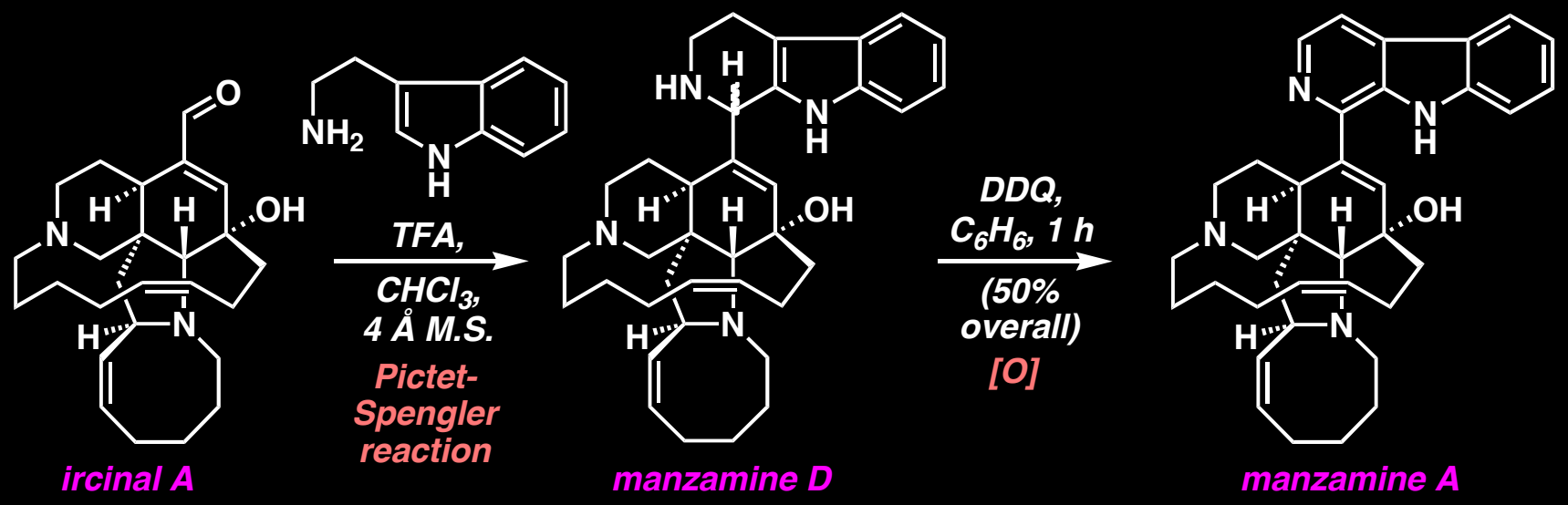

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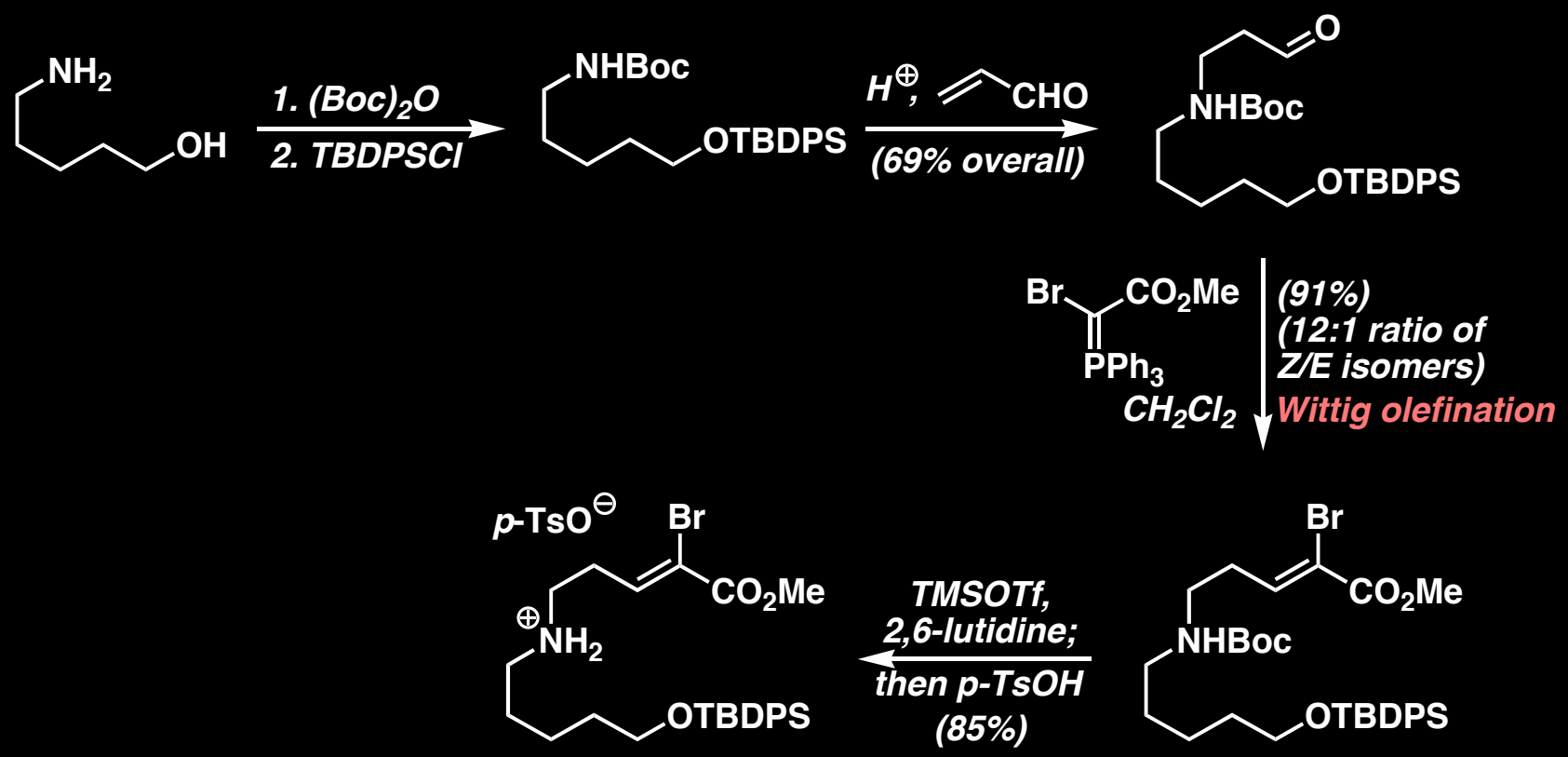
Martin's Total Synthesis of Manzamine A: Synthesis of Fragment A



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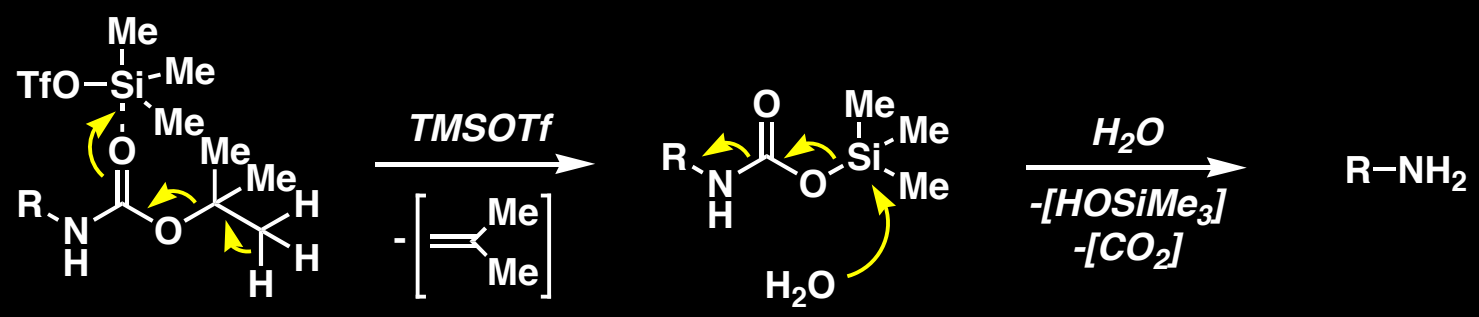
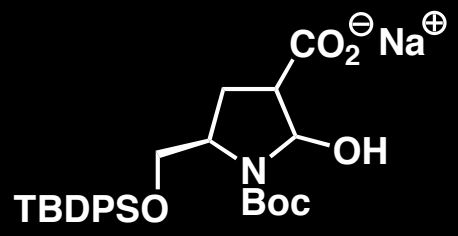
Martin's Total Synthesis of Manzamine A: Mechanism for TMSOTf-Promoted Boc Deprotection



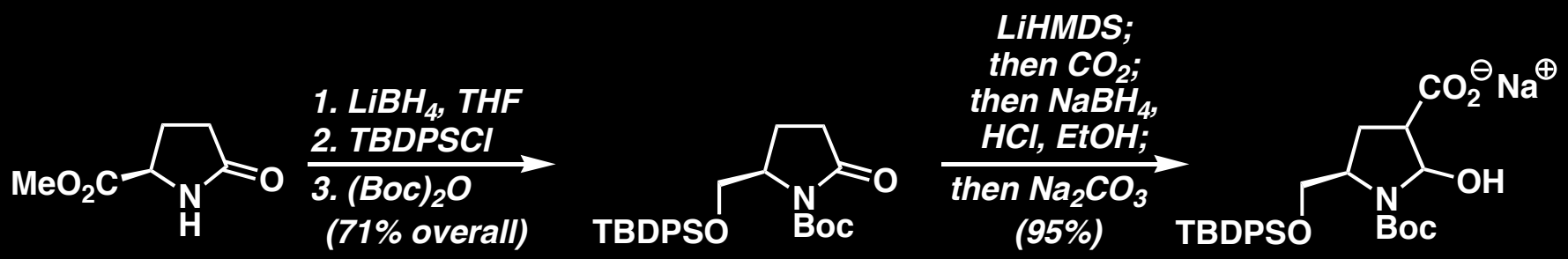
- *Generally a mild technique*
- *Usually highly chemoselective*
- *One of only two methods that succeeds with proton sensitive molecules; the other is heat (150-180 °C) which not all molecules can obviously tolerate*

M. Sakaitani, Y. Ohfune, J. Org. Chem. 1990, 55, 870.

Martin's Total Synthesis of Manzamine A: Preparation of Building Block B



Fragment B



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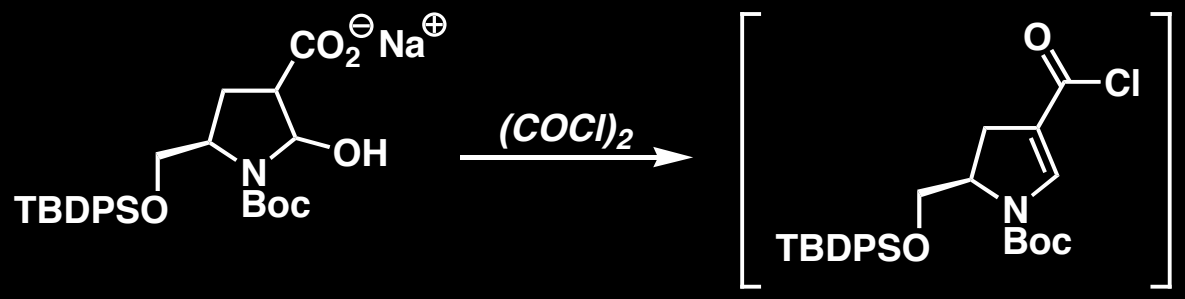
Martin's Total Synthesis of Manzamine A: Coupling of Building Blocks



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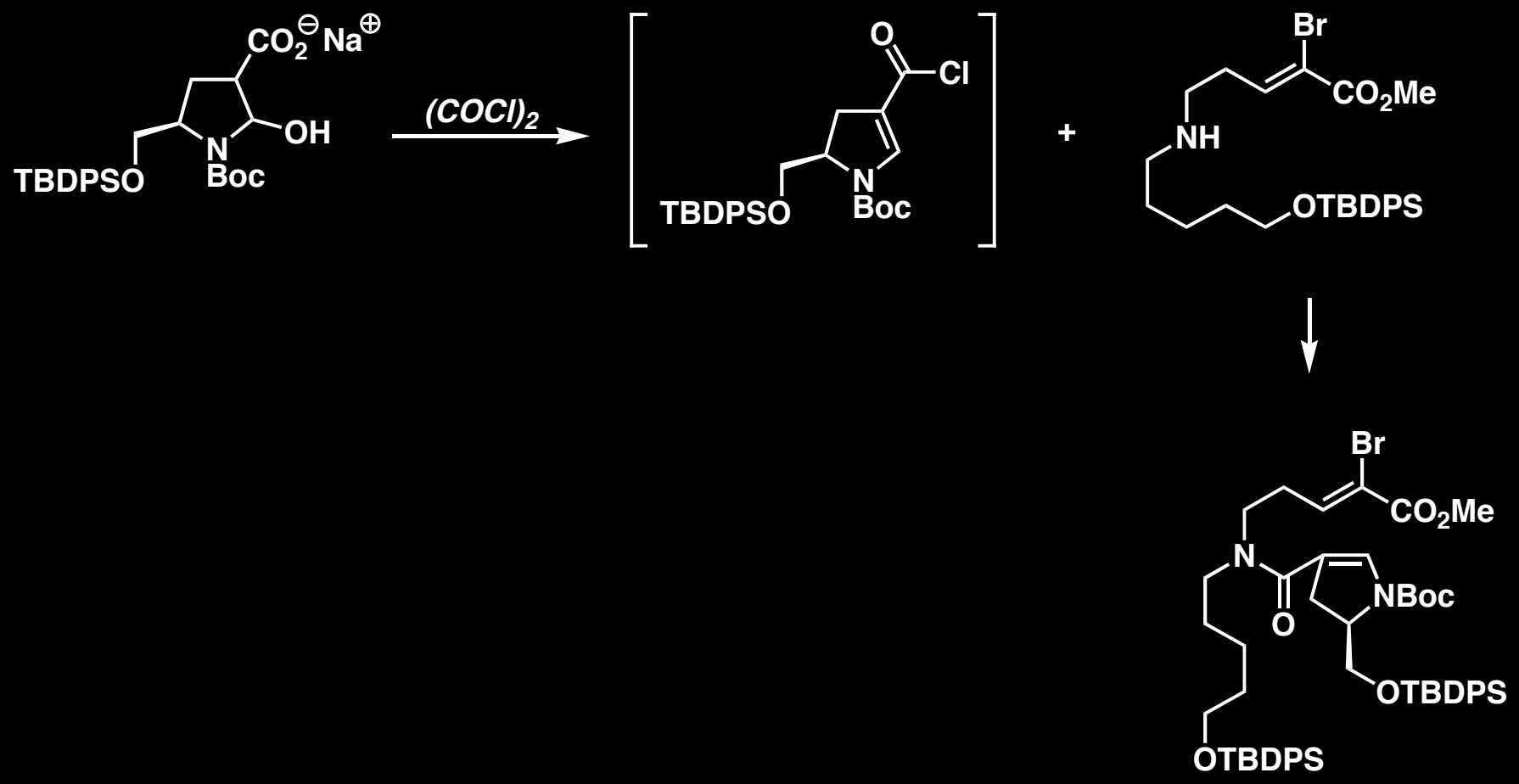

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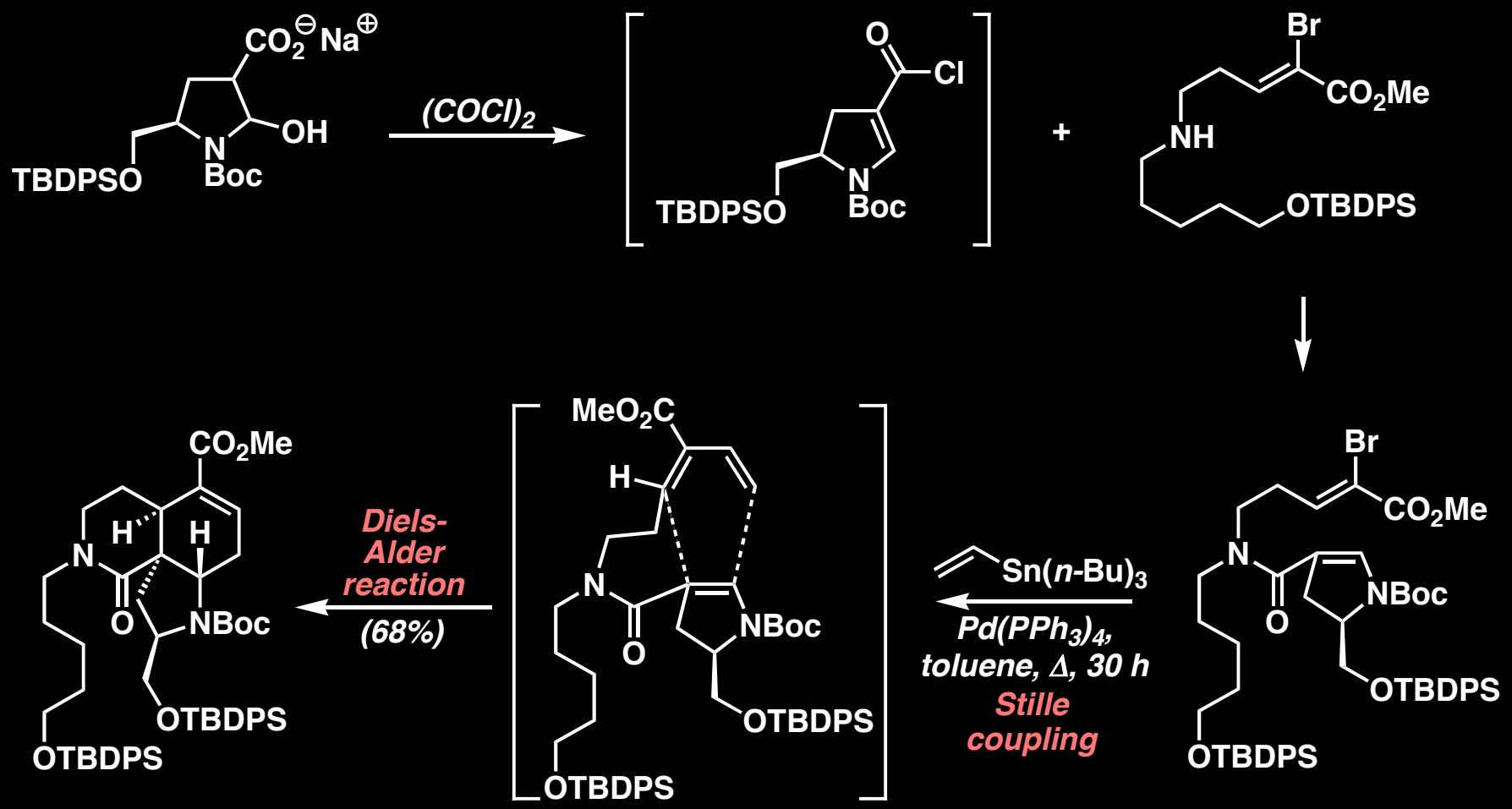

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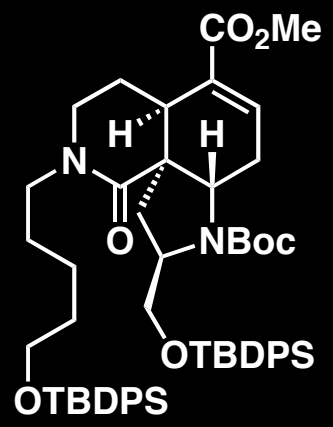
Martin's Total Synthesis of Manzamine A: Completion of the Total Synthesis



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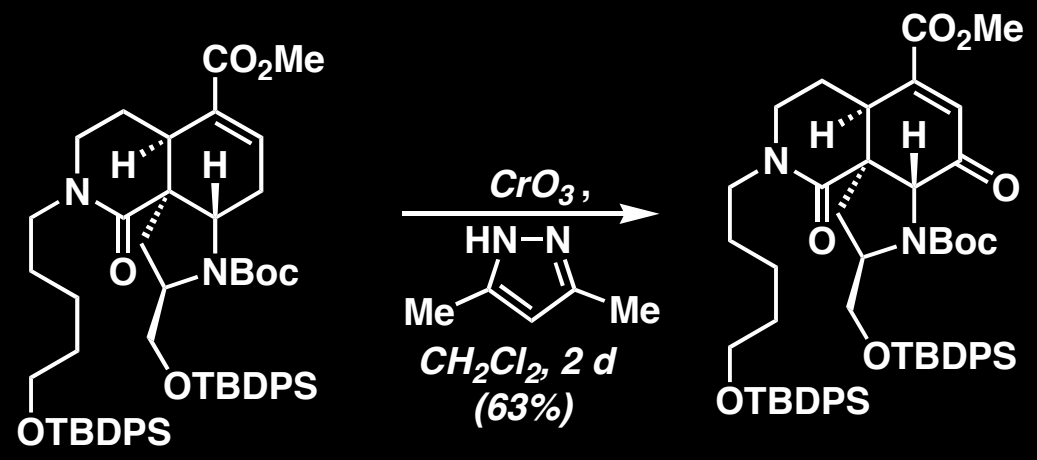

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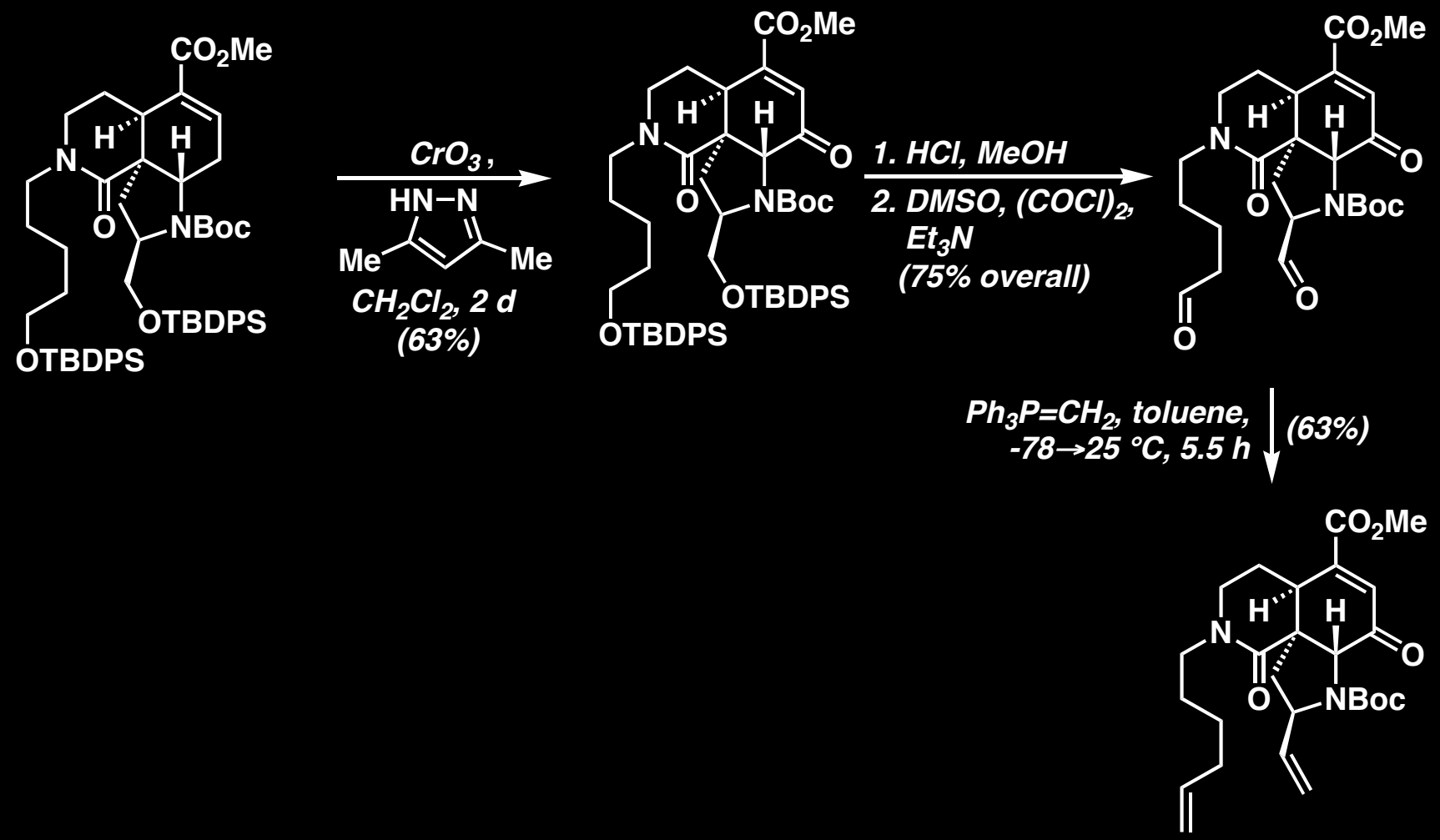

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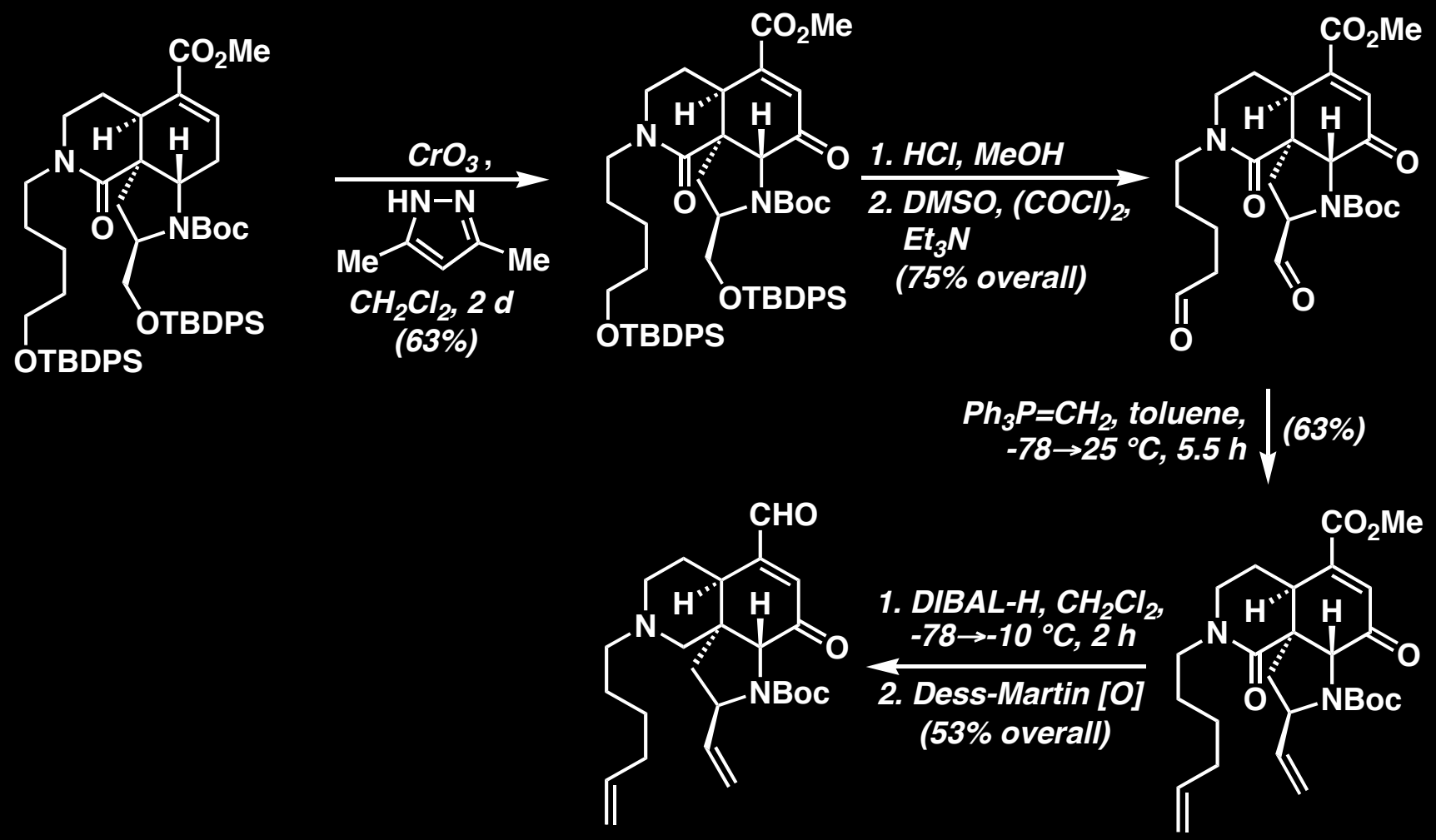

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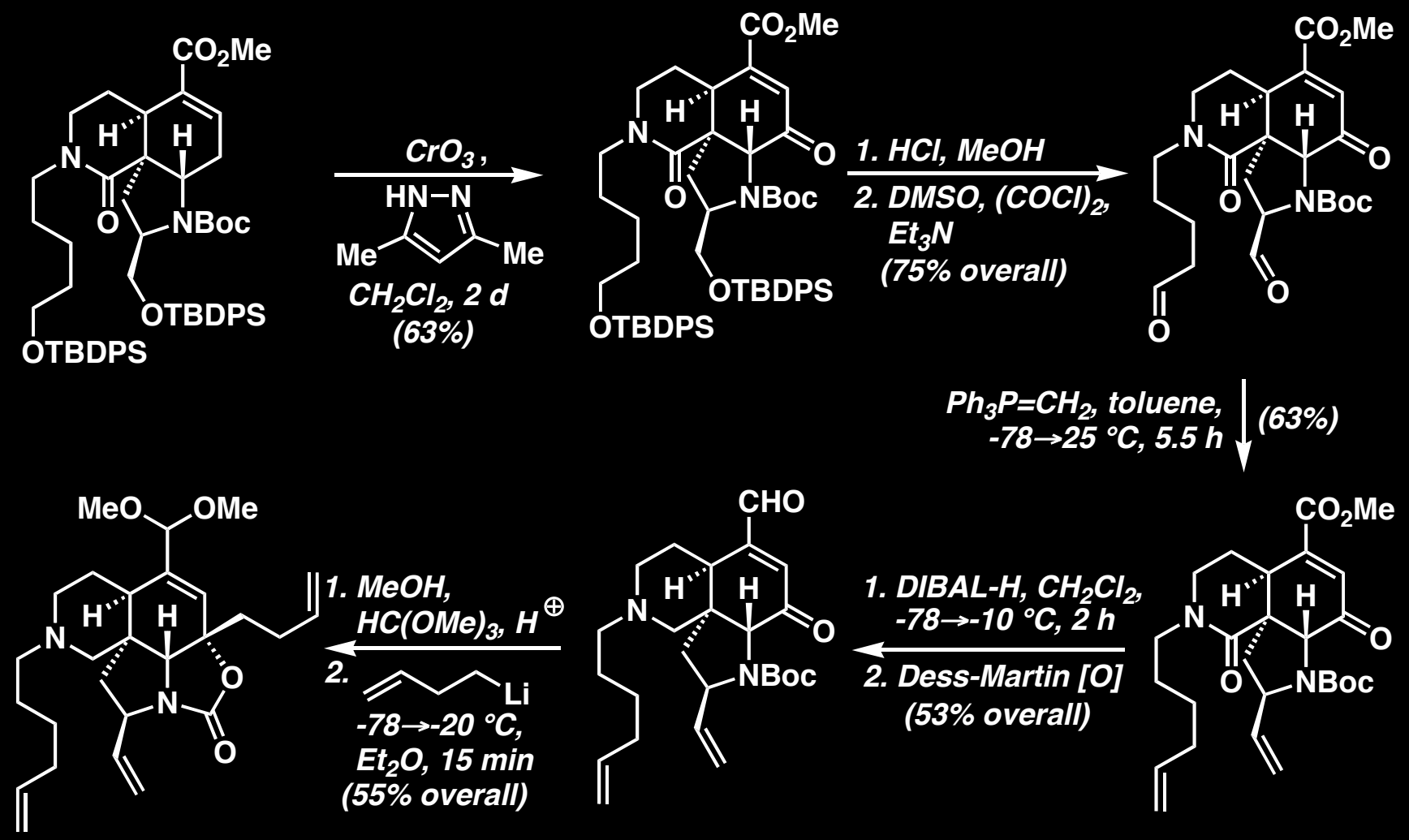
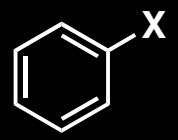
Martin's Total Synthesis of Manzamine A: Completion of the Total Synthesis



For the chromium oxidation, see: E. J. Corey, G. W. J. Fleet, Tetrahedron Lett. 1973, 14, 4499.
W. G. Salmond, M. A. Barta, J. L. Havens, J. Org. Chem. 1978, 43, 2057.

Formation of Alkyllithium Reagents: Mechanism and General Considerations



Clean lithiation with n-Buli or t-BuLi in ethereal solvents at low temperature; done in minutes

Prior to 1990 required Li metal, days of reaction time at room temperature, many side products

E. Negishi, D. R. Swanson, C. J. Rousset, J. Am. Chem. Soc. 1990, 55, 5406.

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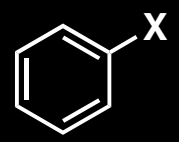

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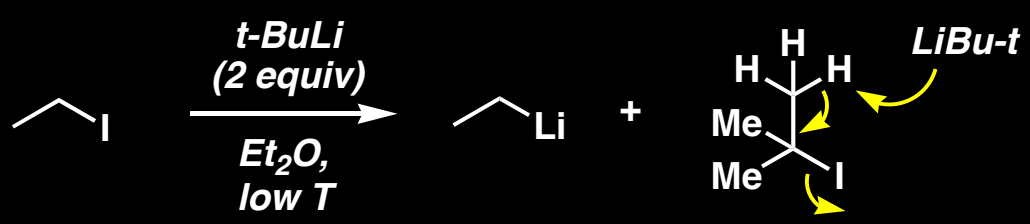

Second equivalent of t-BuLi required to effect β-elimination of the iodide from initial reaction. If not present, the newly formed alkyllithium will do the same task and quench itself!

Note: Alkyl bromides sometimes work, but are lithiated via radical-type mechanisms. Alkyl chlorides do not work at all. In addition, ether is essential as solvent due to how it affects the aggregation state of the product.

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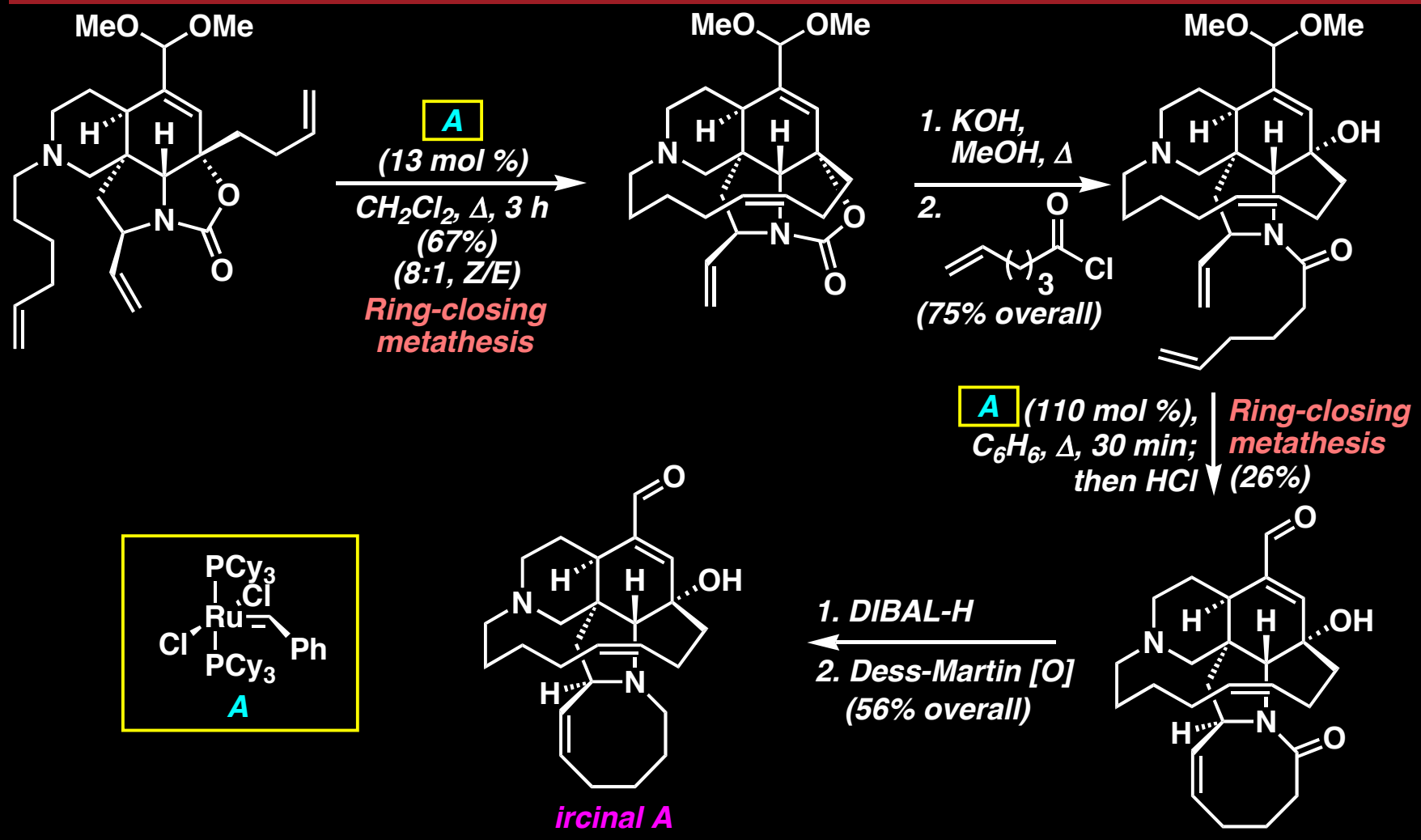
Martin's Total Synthesis of Manzamine A: Completion of the Total Synthesis



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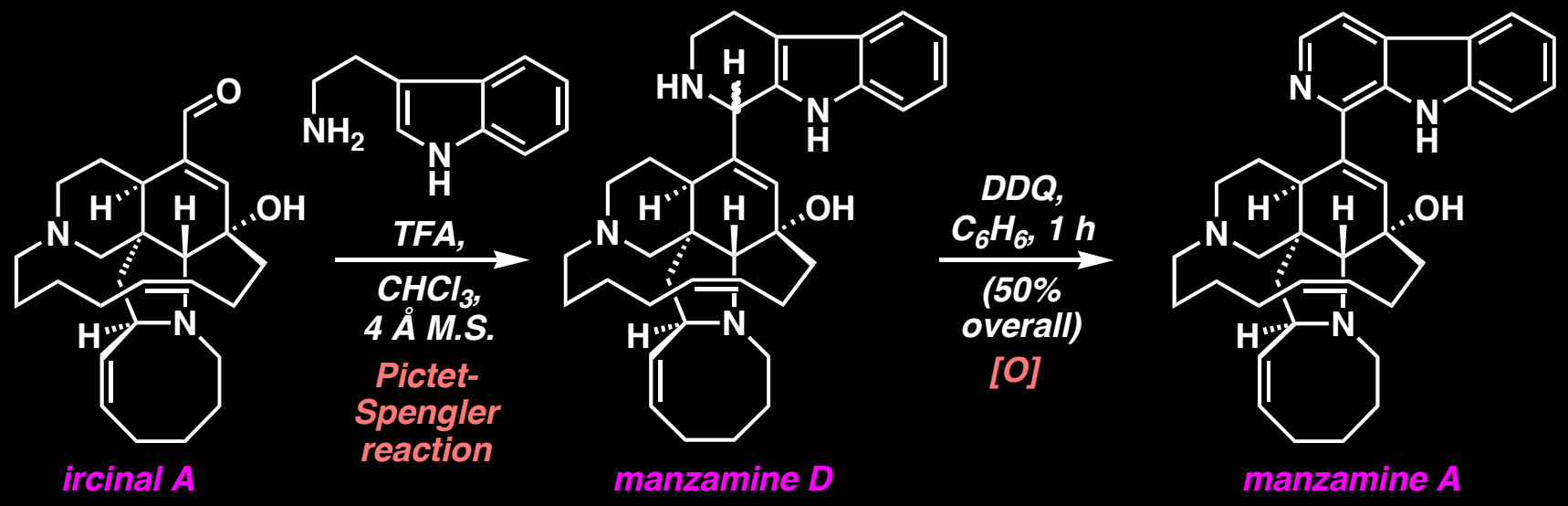

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The Two Total Syntheses of Manzamine A: Overall Comparison

Both syntheses featured:

- ***The establishment of one chiral center through an asymmetric reaction, a center which would serve as the guiding element for the installation of all subsequent stereocenters***
- ***A cascade sequence of reactions to establish several of the ring systems within the core molecular framework***
- ***True tests of several transformations in an extremely complex setting***
- ***Creative solutions to a complex problem***

Winkler route

33 steps overall
31 steps in longest linear sequence
(17 after building block union)

Martin route

24 steps overall
21 steps in longest linear sequence
(17 after building block union)