Strategies Towards Medium-Sized Rings in Total Synthesis

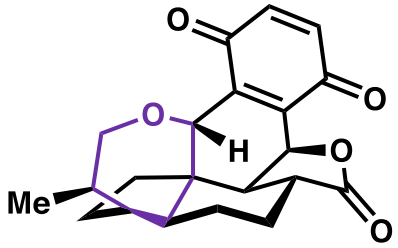
Sarah Korb

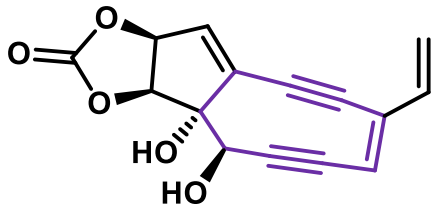
Literature Presentation

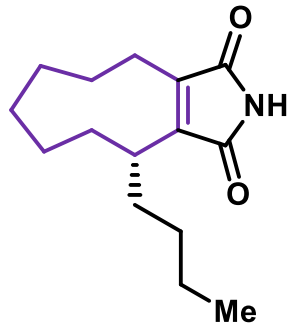
January 30, 2026

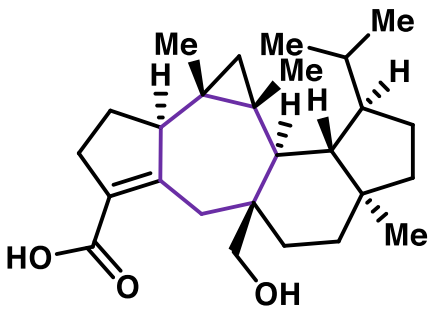
Introduction

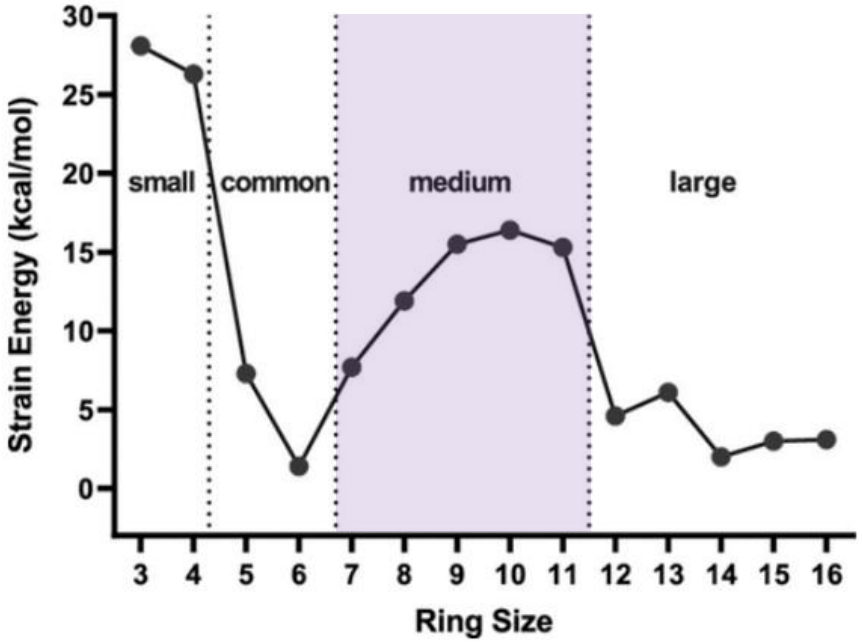
Definitions and Relevance

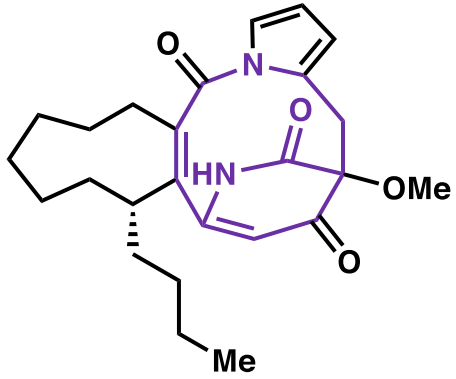








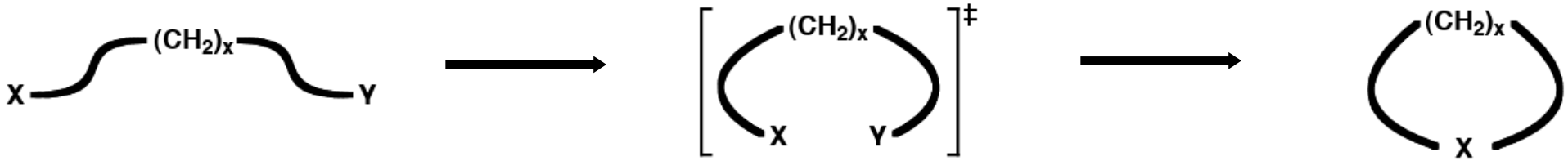




Chem. Rev. **2020**, *120* (13), 5910-5953.

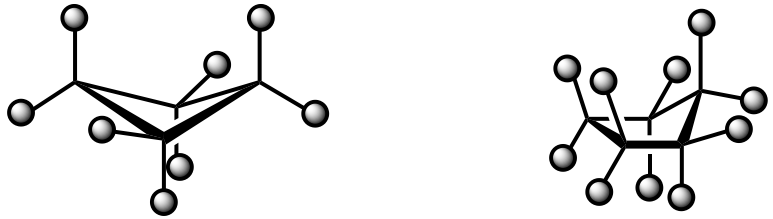
Introduction

Challenges



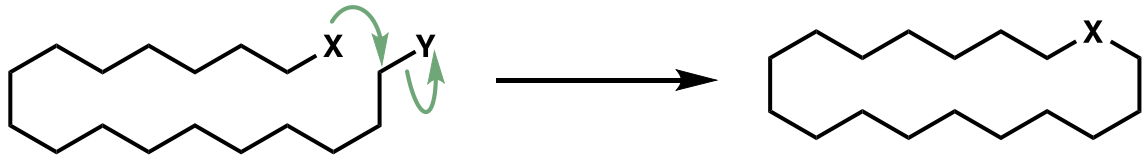
Small Rings- enthalpic penalty

- bond angle distortion (Baeyer)
- bond opposition (Pitzer)



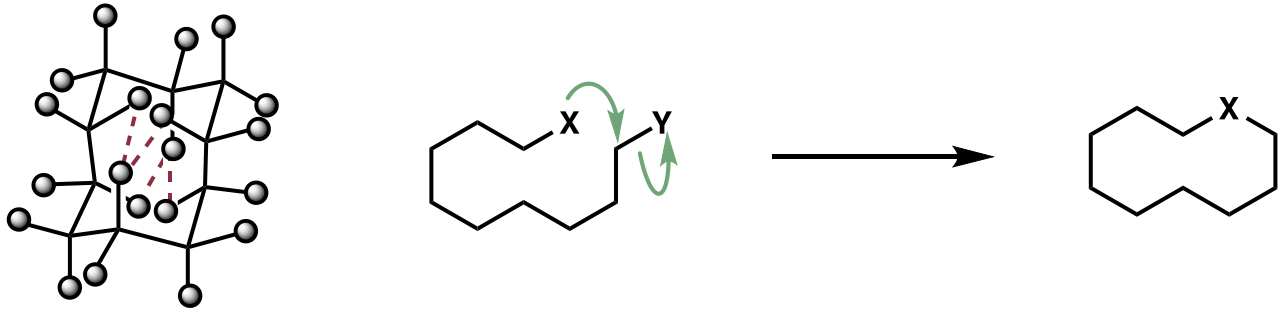
Large Rings- entropic penalty

- rotation allowed in transition state and product
- quantified by torsional degrees of freedom



Medium Rings

- Enthalpic and entropic penalties

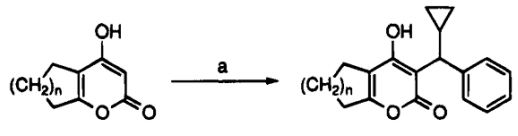


Eur. J. Org. Chem. **2000**, *18*, 3117-3125.

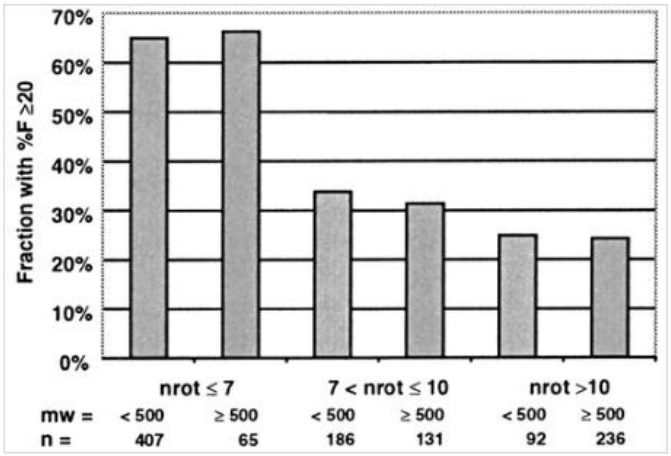
Introduction

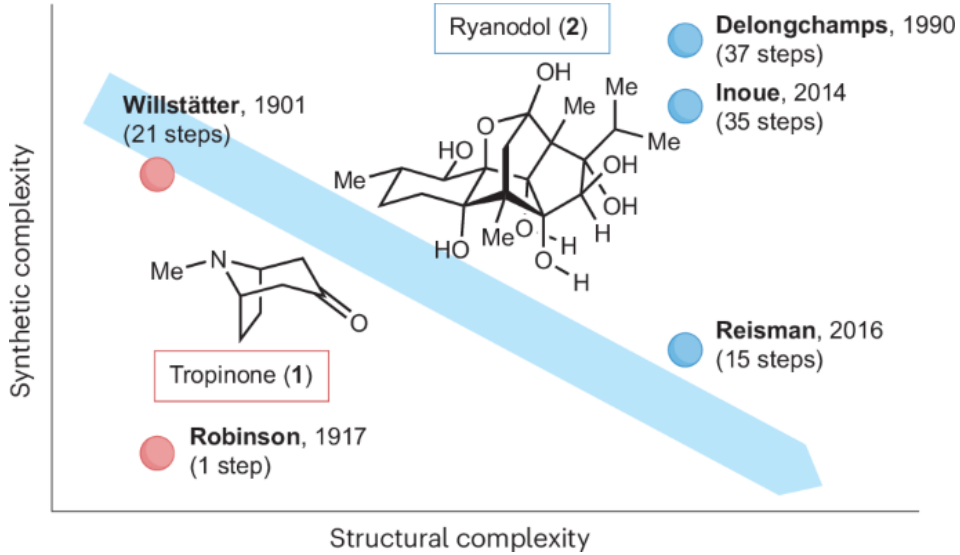
Considerations for Synthesis

Medium-Sized Alkyl Rings Enhance Secondary Binding



no.	n	no.	n	inhibition @ 1 μM	K_i (nM)[b]
3a	1	**5a**	1	40%	nd
3b	2	**5b**	2	62%	180
3c	3	**5c**	3	70%	96
3d	4	**5d**	4	95%	15 ± 5
3e	5	**5e**	5	94%	37
3f	6	**5f**	6	23%	560
3g	8	**5g**	8	<10%	nd





Biological Relevance

- binding affinity
- cellular permeability
- oral bioavailability

Synthetic Ease

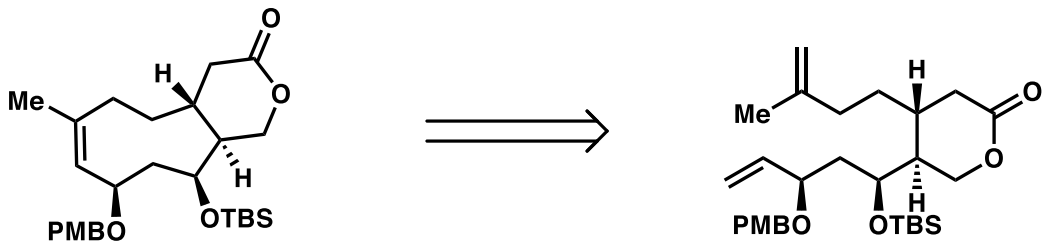
- structural complexity vs. step count
- amount of stereocenters, quaternary centers, rings and oxidation state

J. Med. Chem. **2002**, *45* (12), 2615-2623.; *J. Med. Chem.* **1995**, *38*, 1884-1891.; *Chem. Rev.* **2020**, *121* (14), 8926-8947.; *Nat. Rev. Chem.* **2024**, *8*, 776-792.

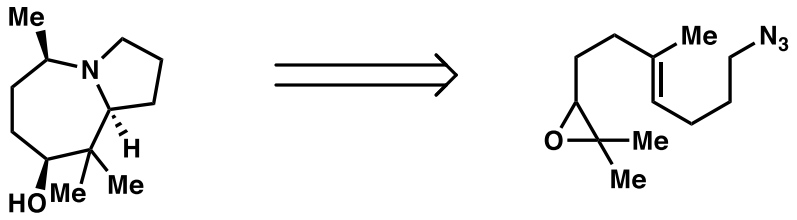
Outline

Strategies Towards Medium Rings in Total Synthesis

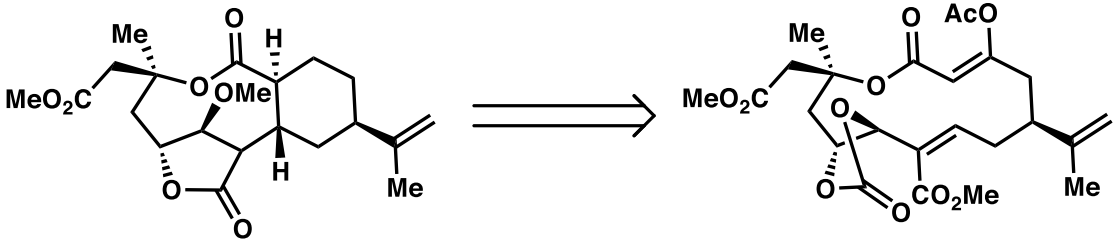
The Ol' Reliable



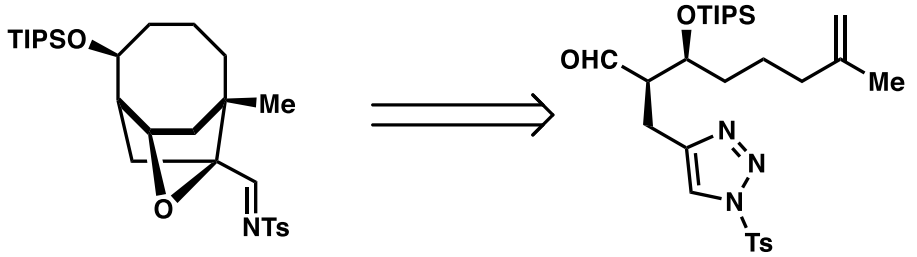
Rearrangements



Transannular



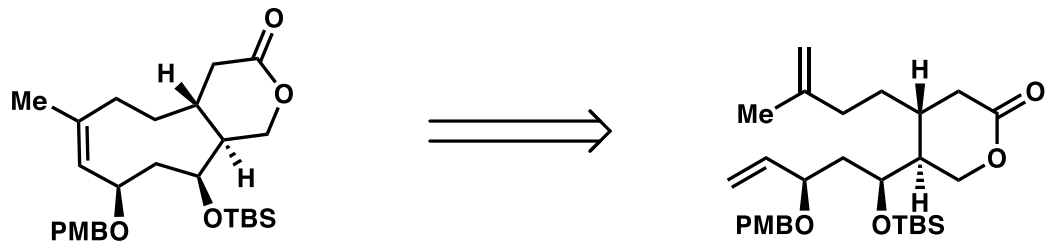
Pericyclic and Radical



Outline

Strategies Towards Medium Rings in Total Synthesis

The Ol' Reliable



Rearrangements



Transannular

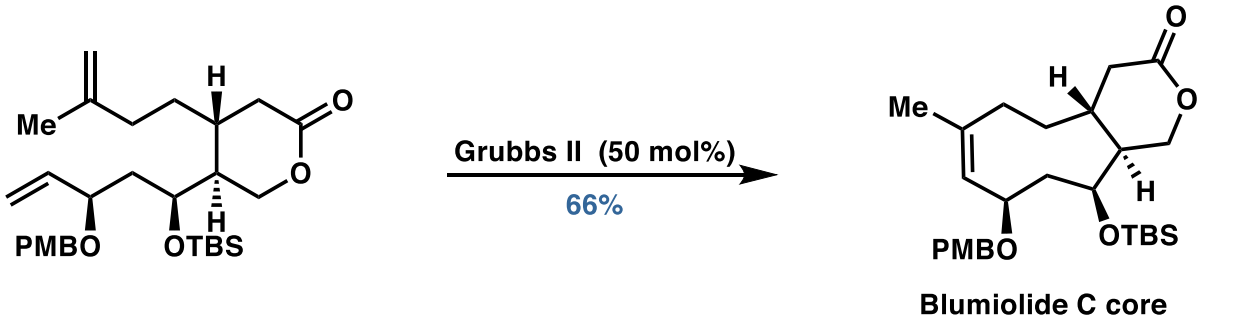


Pericyclic and Radical

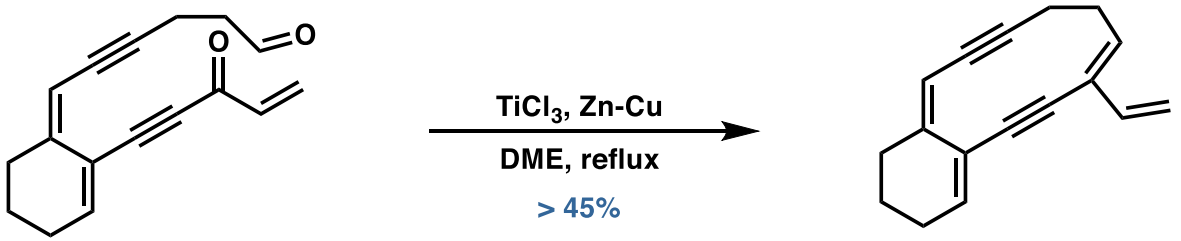


The Ol' Reliable

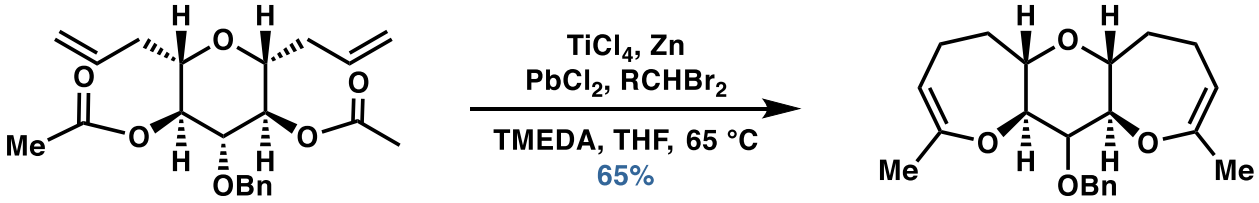
Metathesis



Blumiolide C core



Neocarzinostatin core

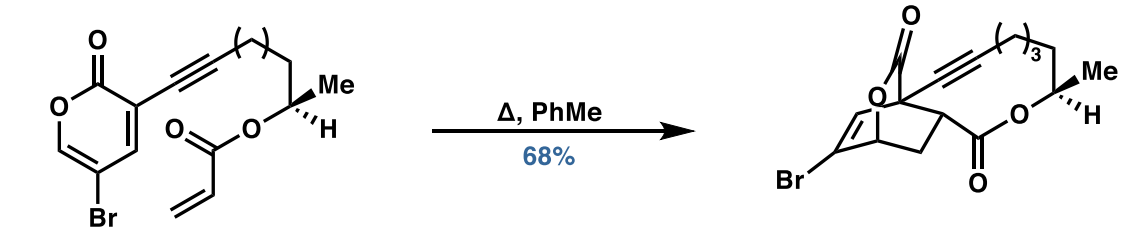


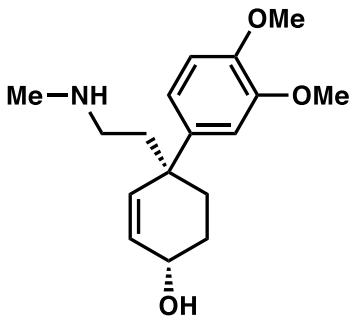
Gambierol subunit

Angew. Chem. Int. Ed. **2008**, *47* (52), 10081-10085.; *Liebigs Annalen* **1997**, *1997* (5), 947-959.

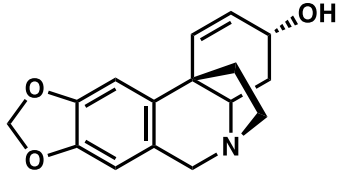
The Ol' Reliable

Diels-Alder

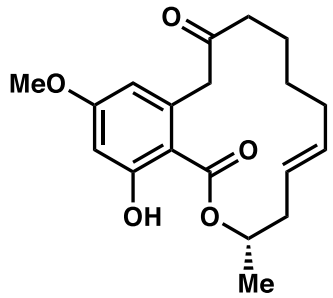




Joubertinamine



Crinine

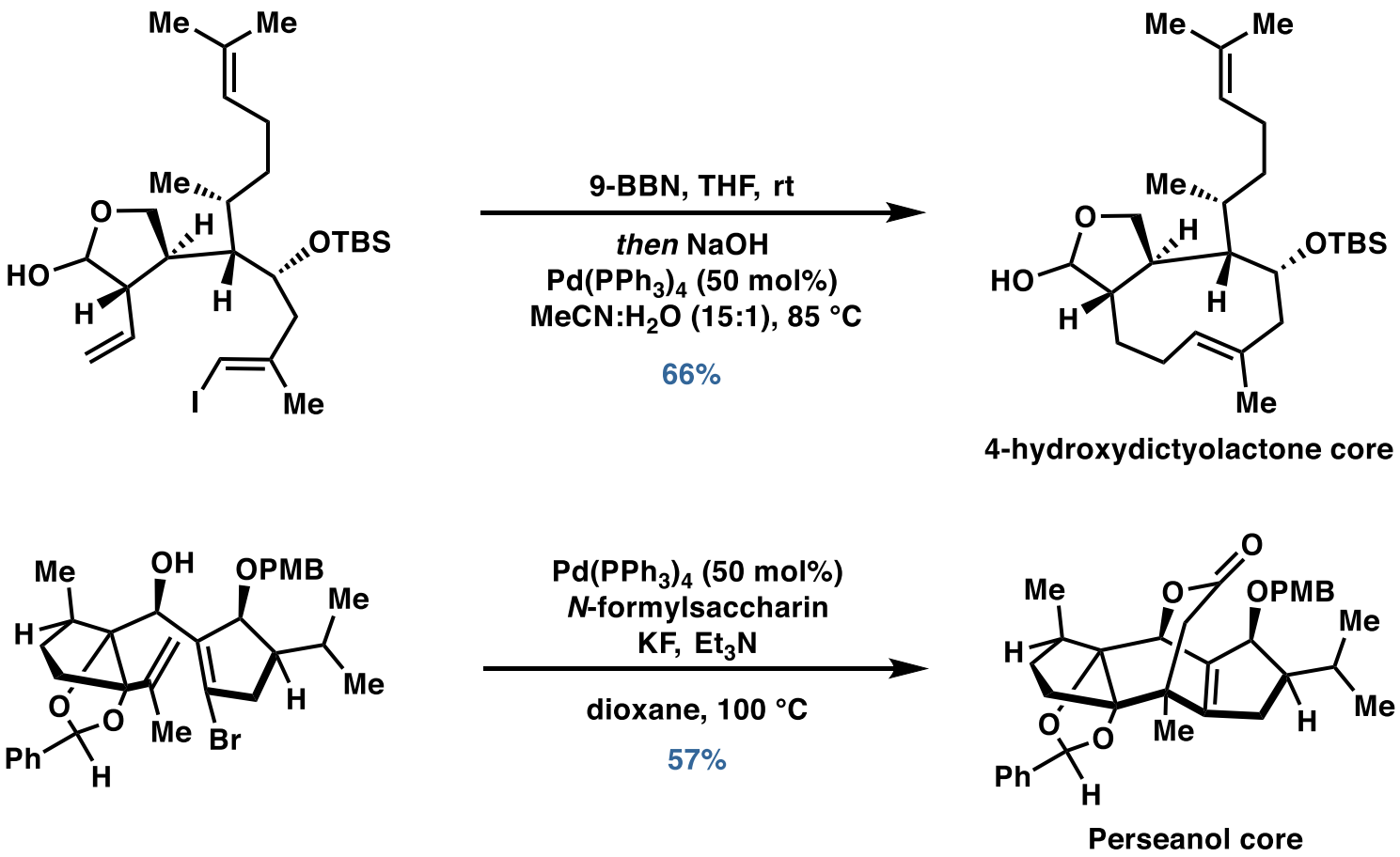


Neocosmosin A

Org. Lett. **2006**, *8* (15), 3339-3341.; *Org. Lett.* **2007**, *9* (17), 3391-3392.; *J. Org. Chem.* **2008**, *73* (16), 6258-6264.; *Org. Lett.* **2016**, *18* (19) , 5126-5129.

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Cross-Coupling

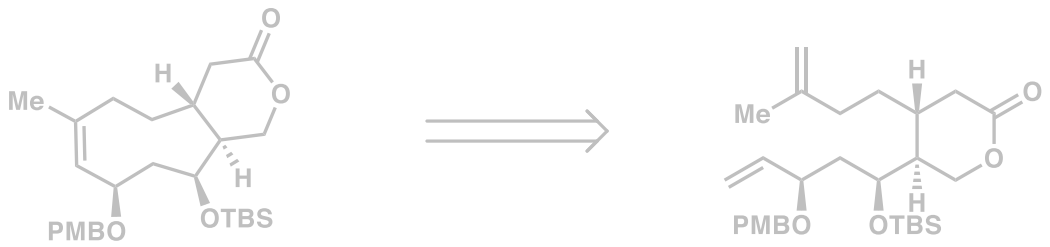


Nature **2019**, *573* (7775), 563-567.; *J. Am. Chem. Soc.* **2009**, *131* (25), 9038-9045.

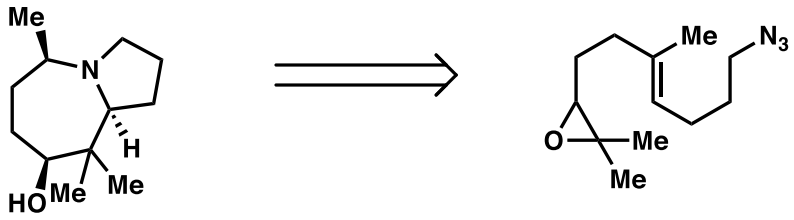
Outline

Strategies Towards Medium Rings in Total Synthesis

The Ol' Reliable



Rearrangements



Transannular

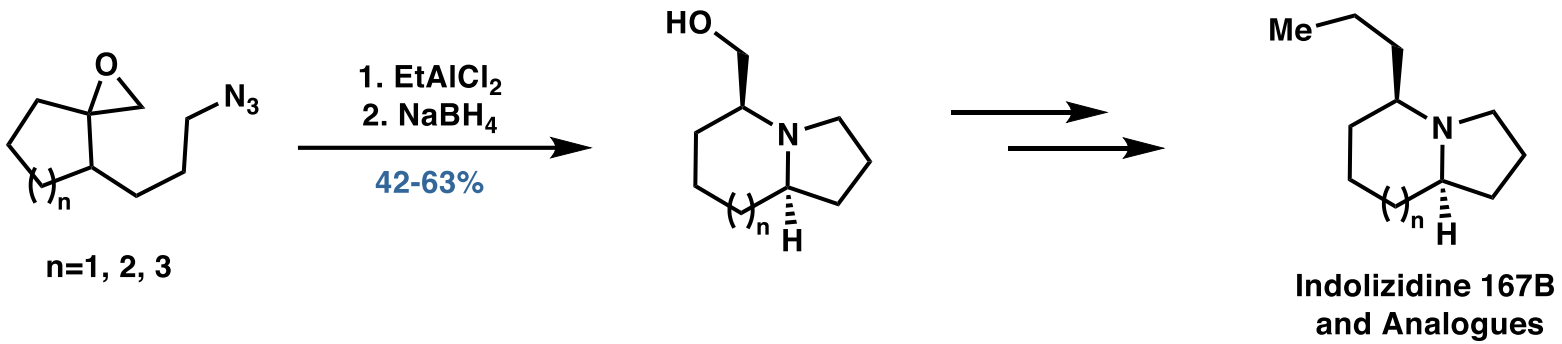


Pericyclic and Radical



Rearrangements

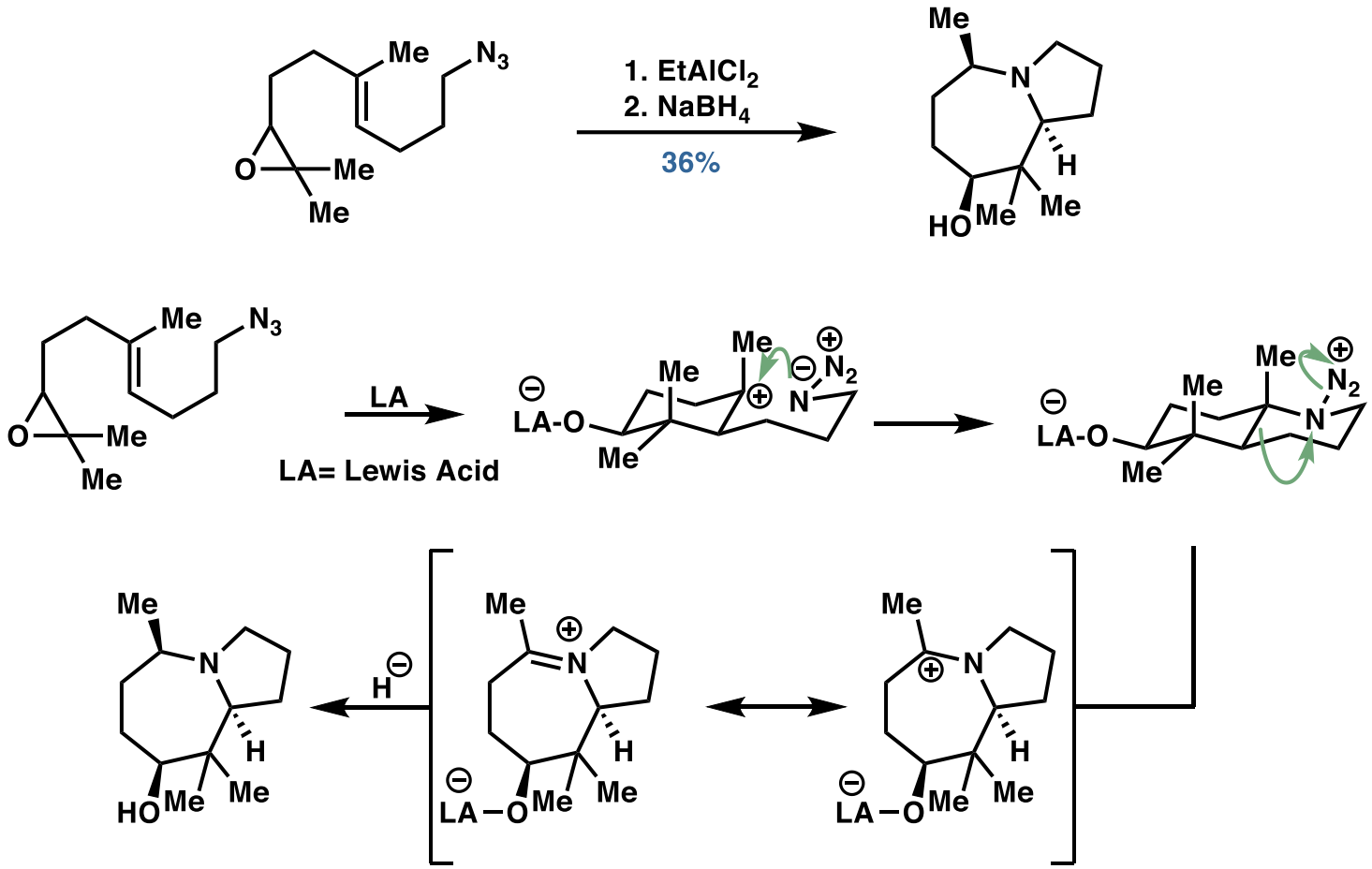
Schmidt Rearrangement Towards Indolizidine 167B and Analogues by Baskaran Group



Org. Lett. **2003**, *5* (4), 583-585.

Rearrangements

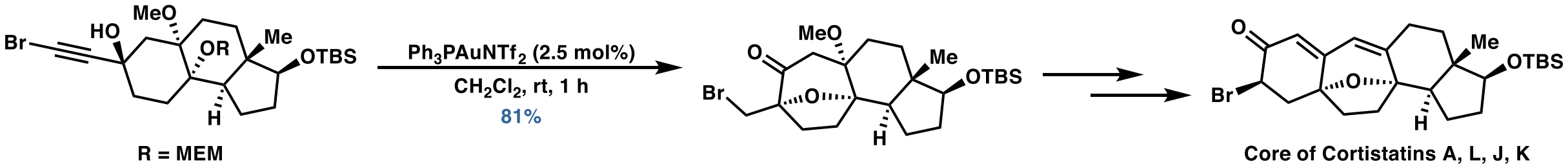
Schmidt Rearrangement Towards Indolizidine 167B and Analogues by Baskaran Group

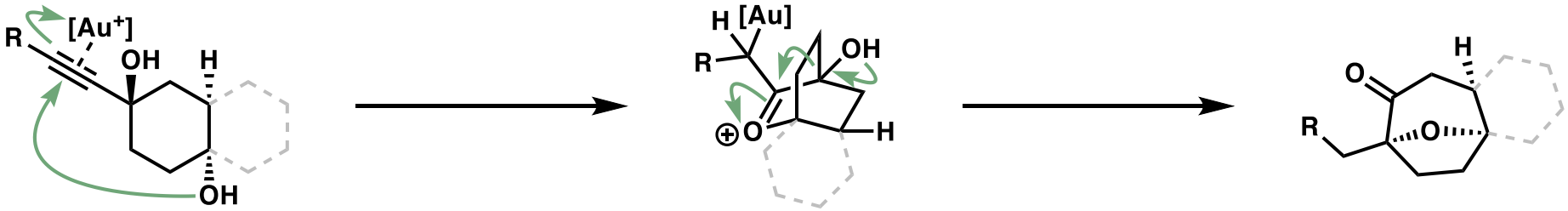


Org. Lett. **2003**, *5* (4), 583-585.

Rearrangements

Au-catalyzed Annulation Towards Cortistatin Core by Yang Group

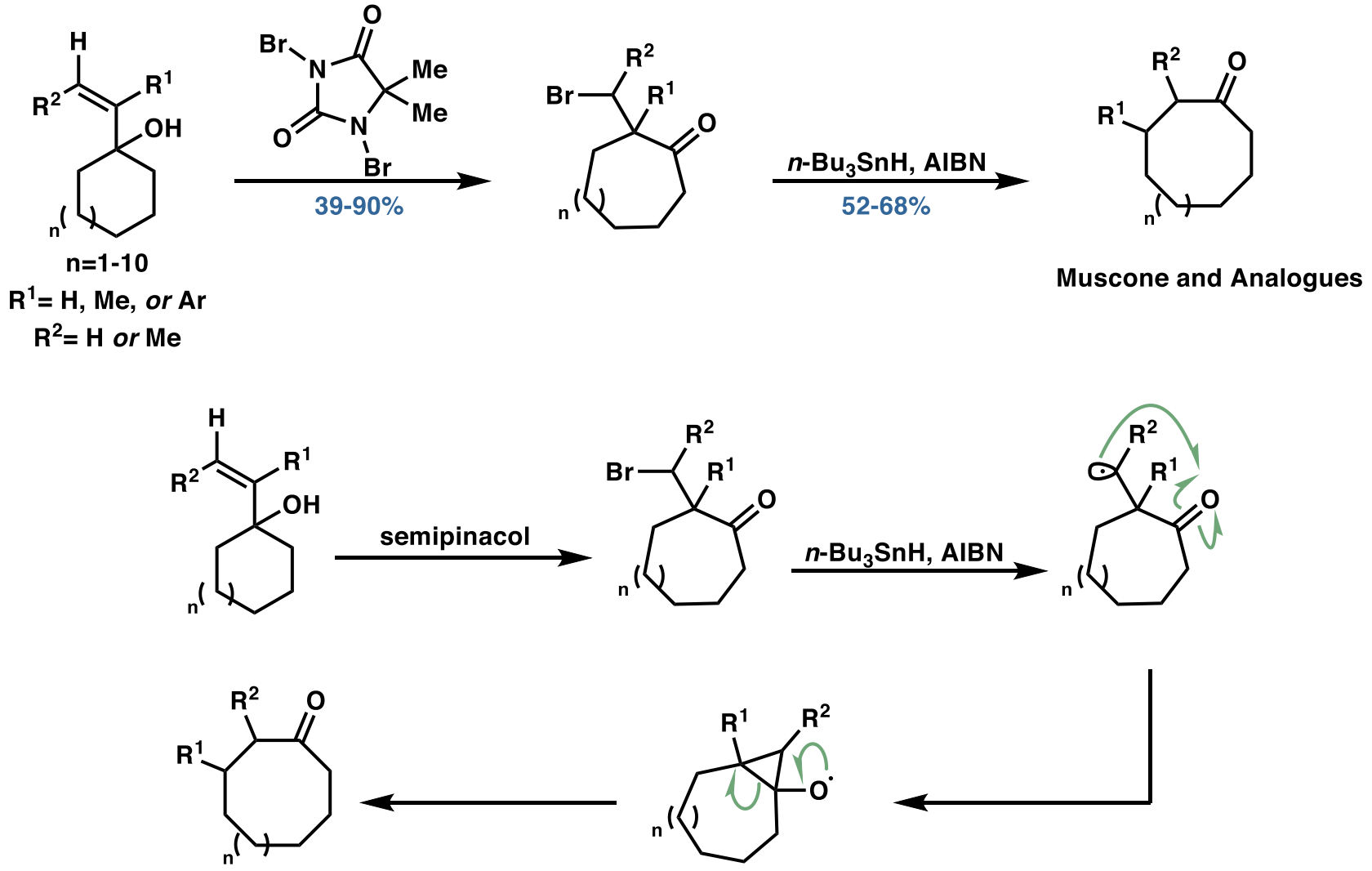




Nat. Commun. **2015** *6*, 8617.

Rearrangements

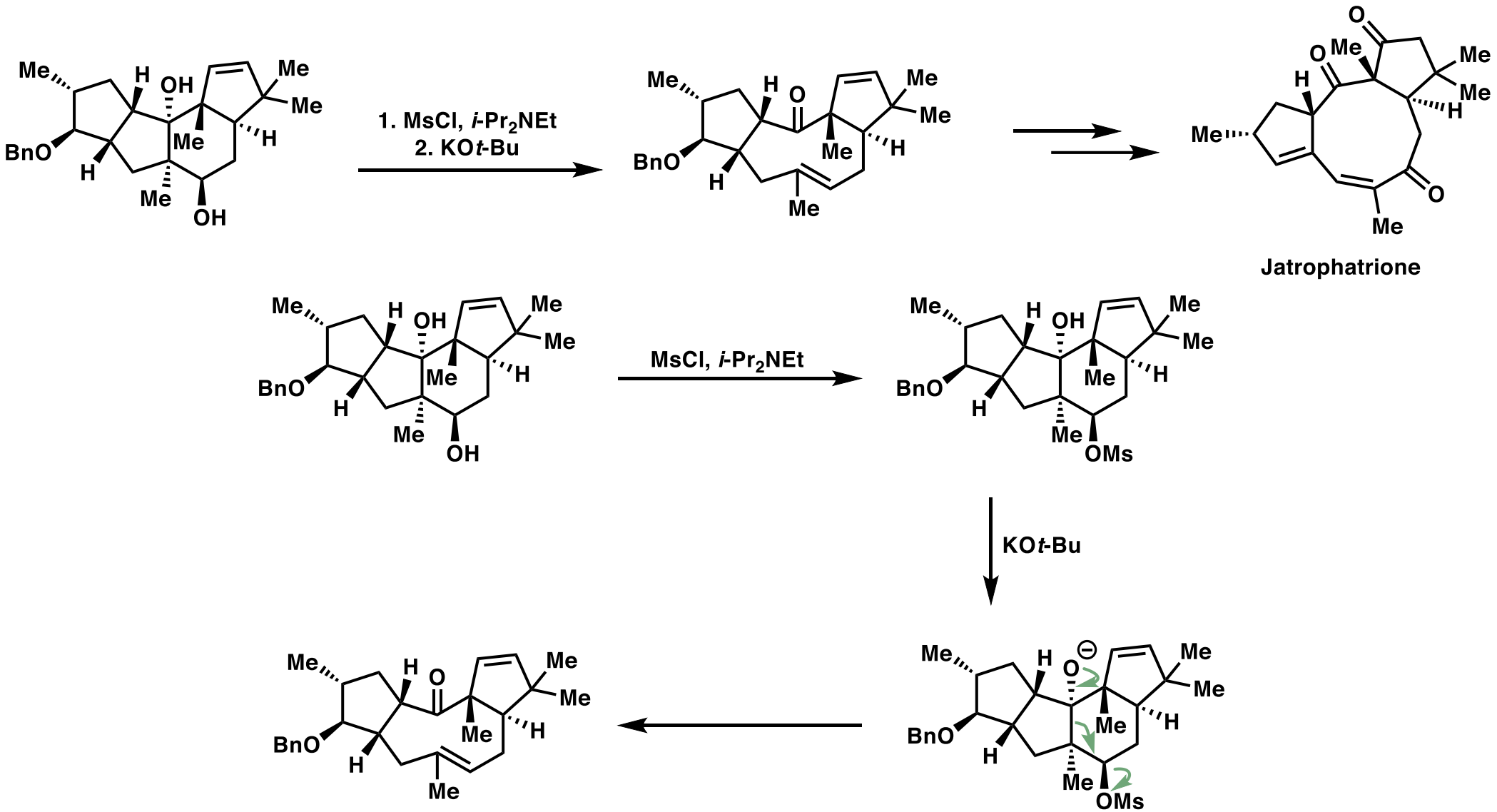
Semipinacol & Dowd-Beckwith Rearrangement Towards Muscone and Analogues by Yeung Group



Org. Lett. **2017**, *19* (6), 1422-1425.

Rearrangements

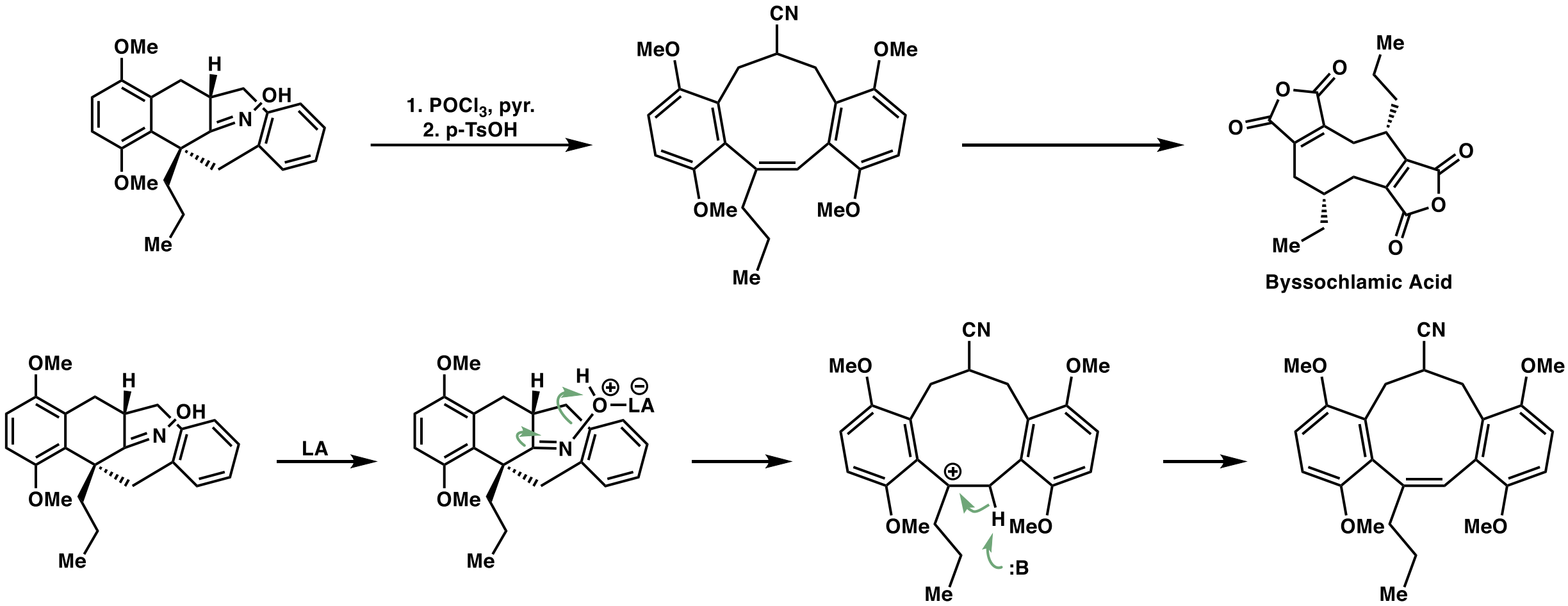
Grob Fragmentation Towards Jatrophatrione by Paquette Group



J. Am. Chem. Soc. **2002**, *124* (23) 6542-6543.

Rearrangements

Beckmann Fragmentation Towards Byssochlamic Acid by Stork Group

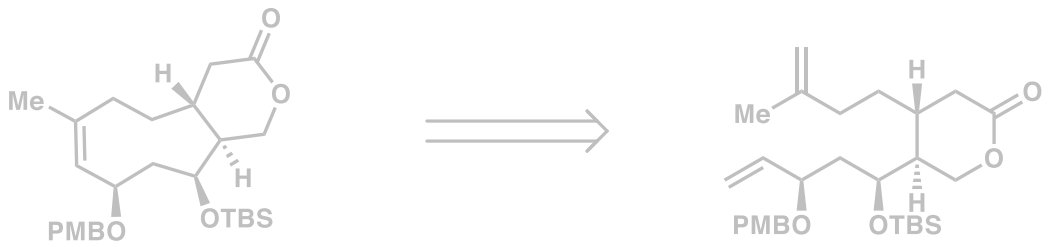


J. Am. Chem. Soc. **1972**, *94* (13), 4735-4737.; *Chem. Eur. J.* **2018**, *24*, 12107.

Outline

Strategies Towards Medium Rings in Total Synthesis

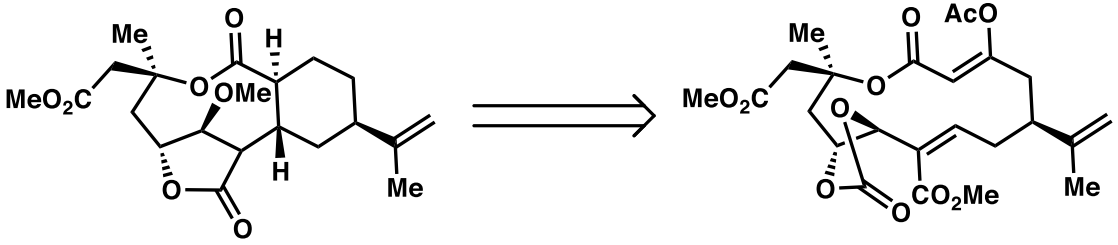
The Ol' Reliable



Rearrangements



Transannular

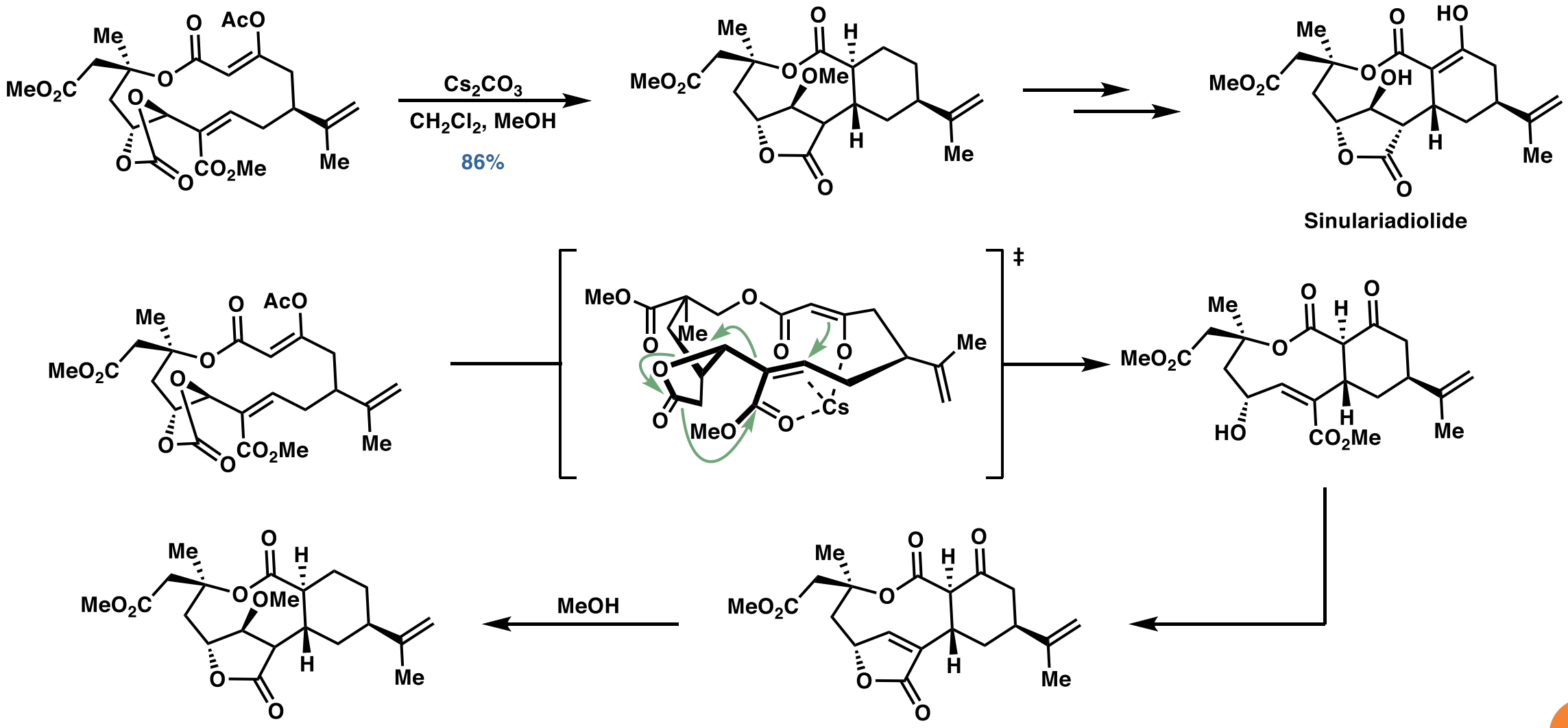


Pericyclic and Radical



Transannular

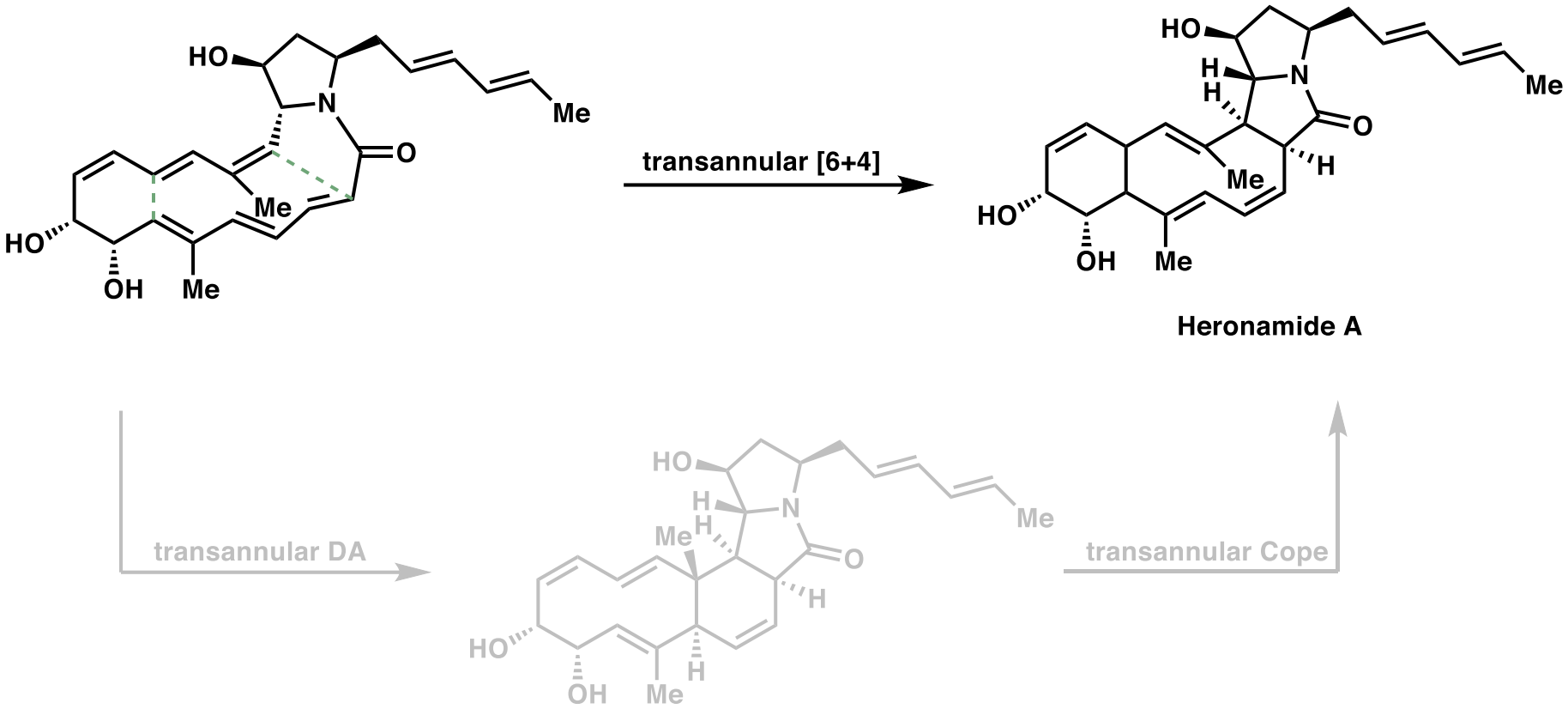
Cascade Towards Sinulariadiolide by Fürstner Group



J. Am. Chem. Soc. **2019**, *141* (2), 805-809.

Transannular

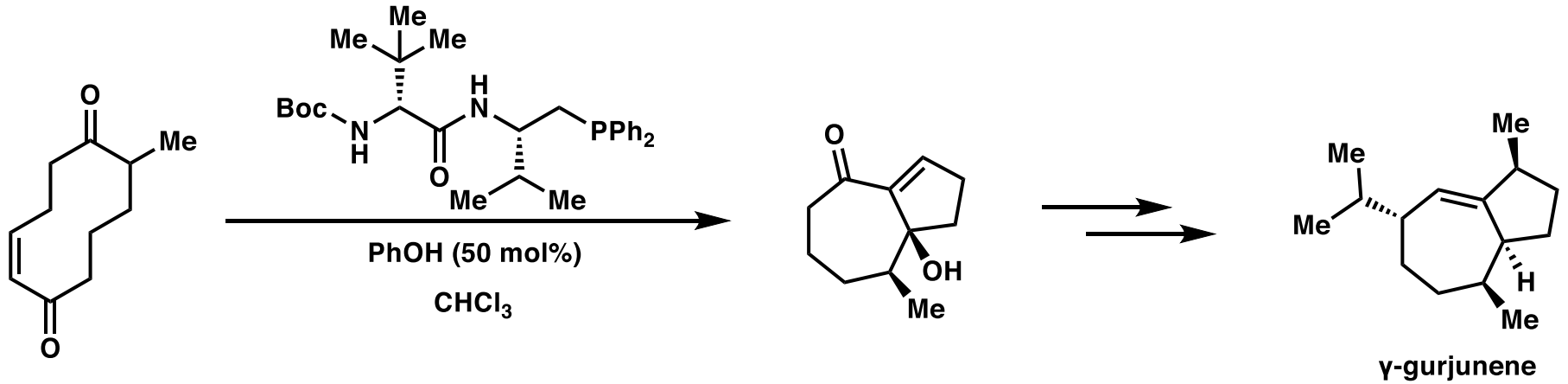
DA & Cope or [6+4] Towards Heronamide A by Houk Group

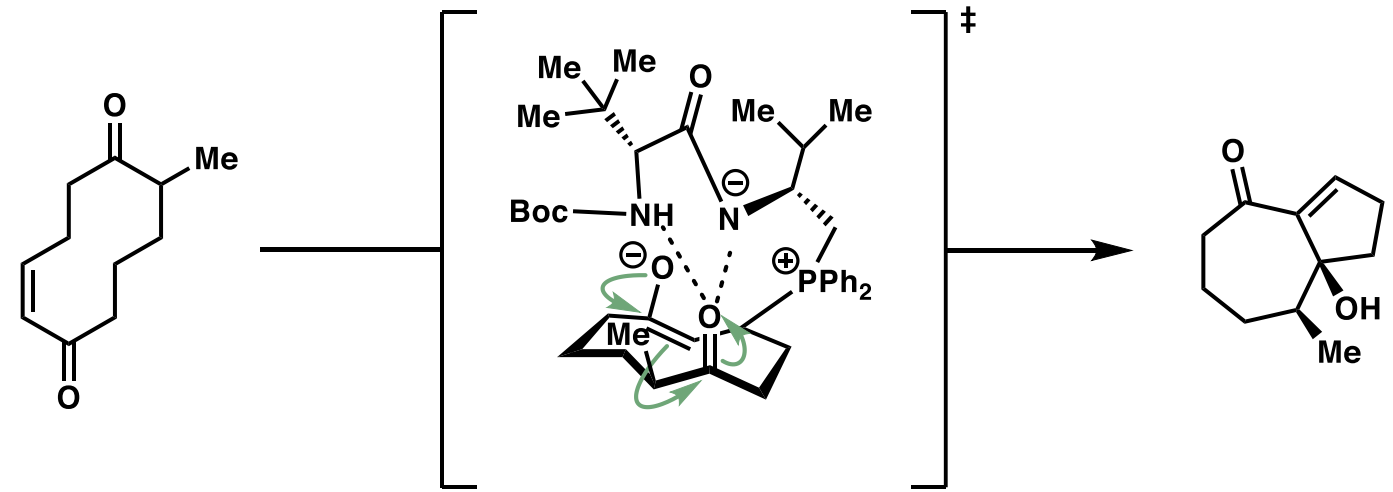


J. Am. Chem. Soc. **2015**, *137* (42), 13518-13523.

Transannular

Morita-Baylis-Hillman Towards γ-gurjunene by Vicario Group

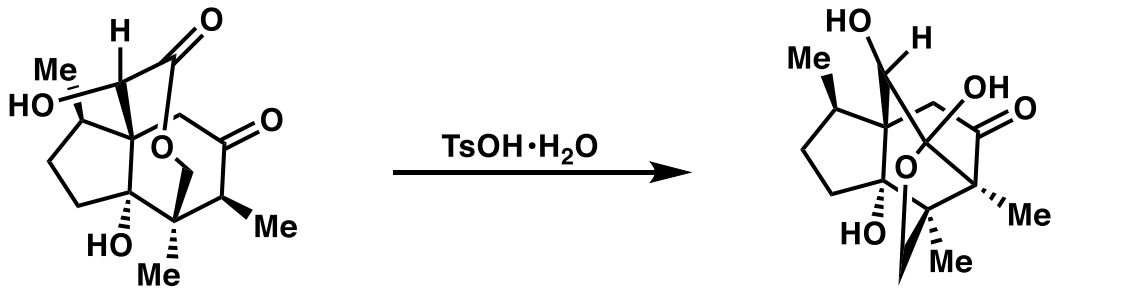




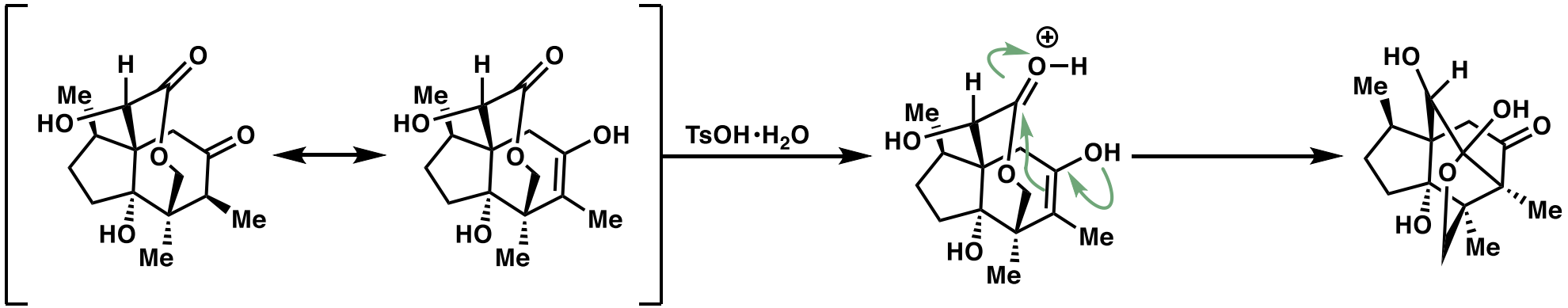
J. Am. Chem. Soc. **2019**, *141* (24), 9495-9499.

Transannular

Dieckmann-type Reaction Towards 11-O-debenzoyltashironin by Shenvi Group



11-*O*-debenzoyltashironin

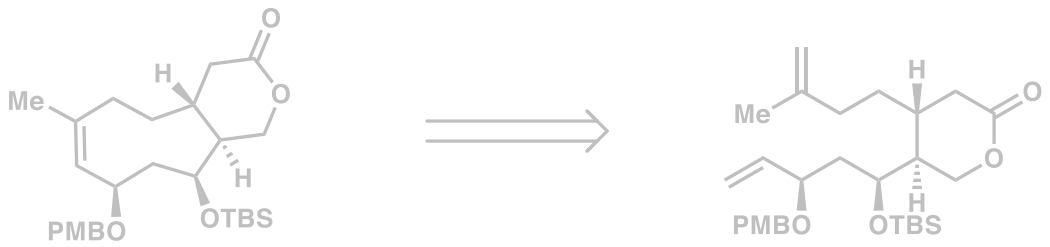


J. Am. Chem. Soc. **2017**, *139* (28), 9637-9644.

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Strategies Towards Medium Rings in Total Synthesis

The Ol' Reliable



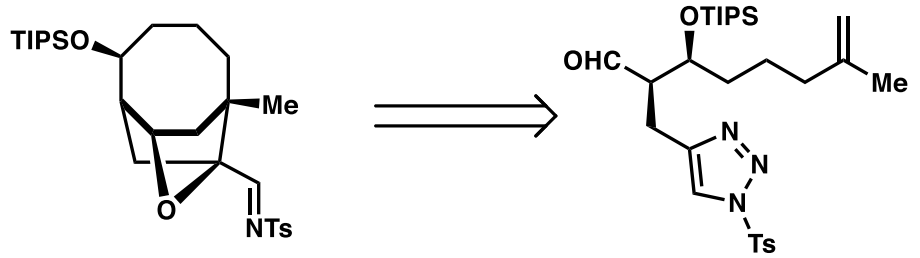
Rearrangements



Transannular

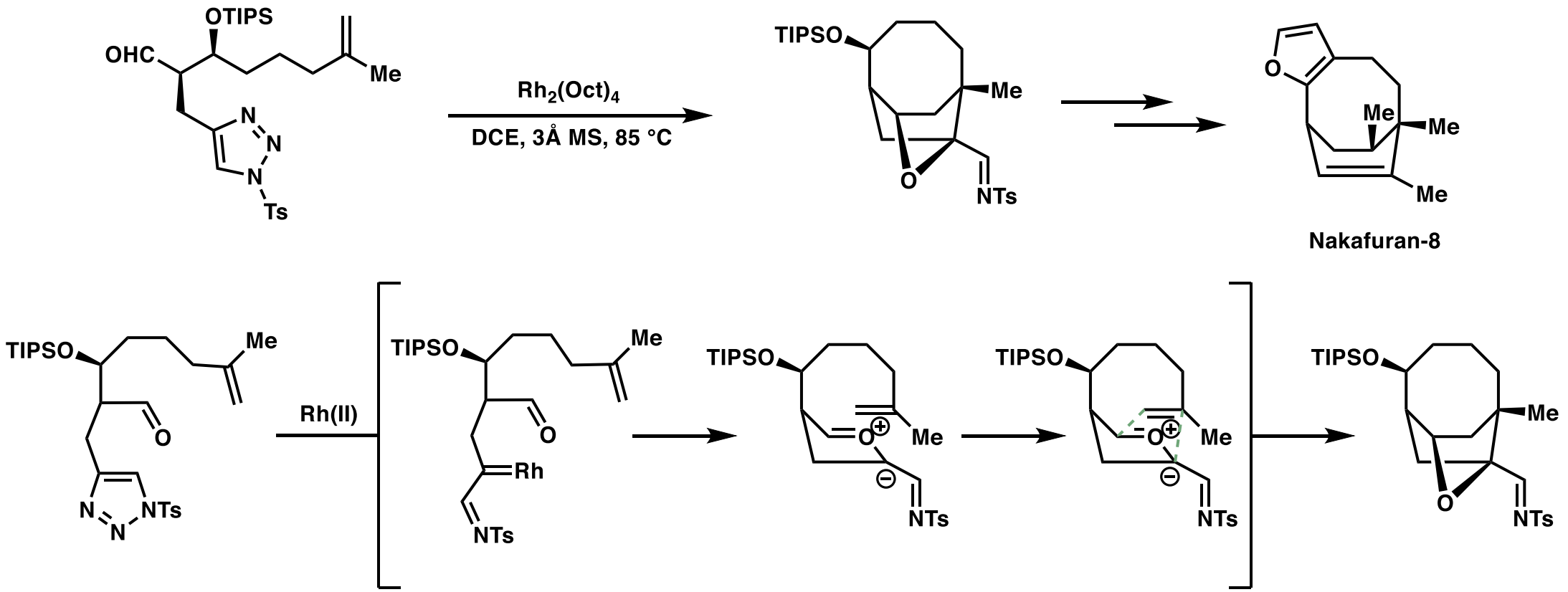


Pericyclic and Radical



Pericyclic and Radical

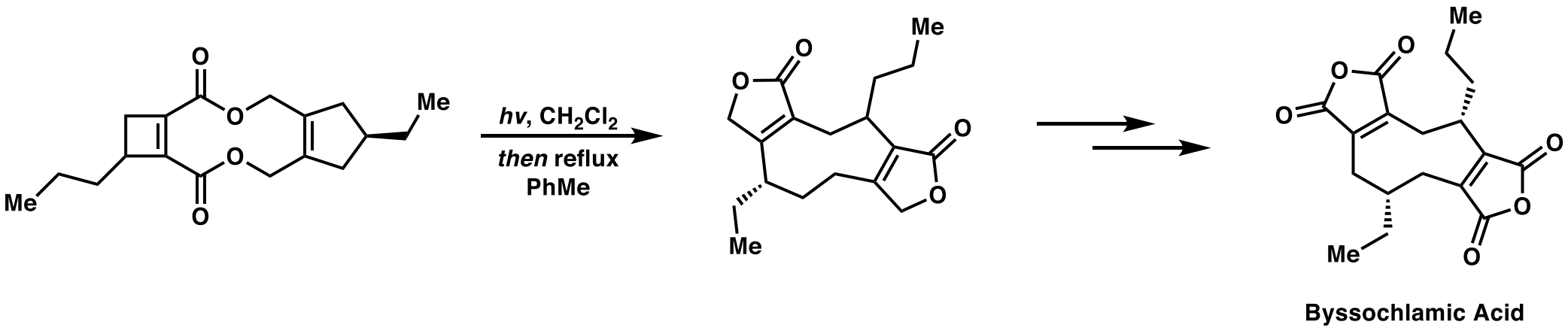
[3+2] Dipolar Cycloaddition Towards Nakafuran-8 by Houk & Li Groups



Nat. Commun. **2021**, *12* (1), 5239.

Pericyclic and Radical

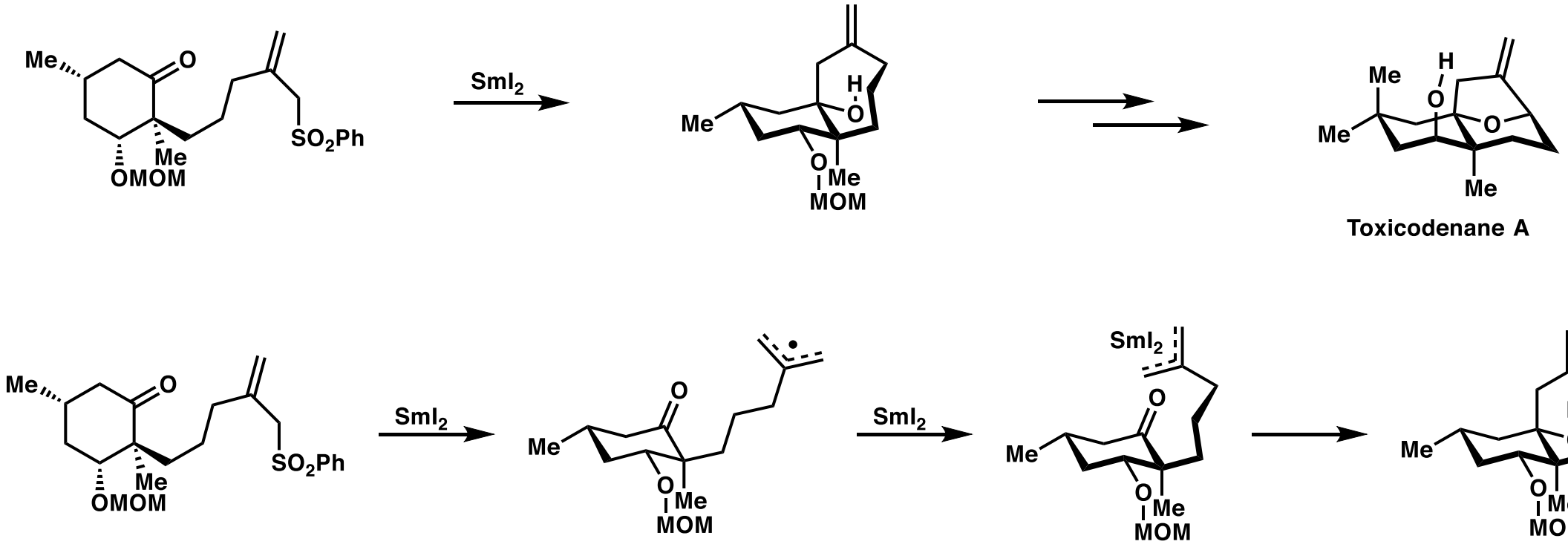
[2+2] Photoaddition & Cycloreversion Towards Byssochlamic Acid by White Group



J. Am. Chem. Soc. **1992**, *114* (24), 9673-9674.

Pericyclic and Radical

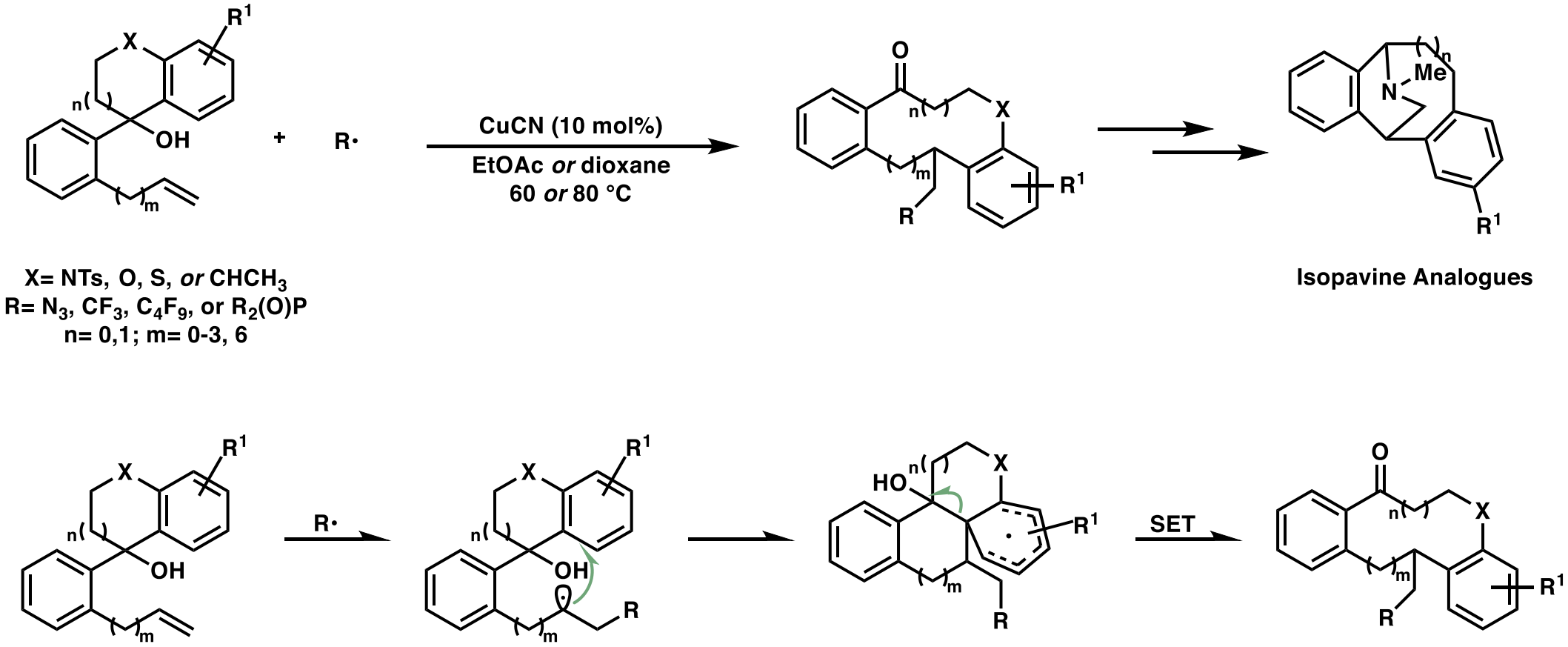
Barbier-Type Cyclization Towards Toxicodenane A by Morimoto Group



Org. Lett. **2022**, *24* (2), 531-535.; *Org. Lett.* **2004**, *6* (4), 545-547.

Pericyclic and Radical

Radical Aryl Migration Towards Isopavine Analogues by Liu Group

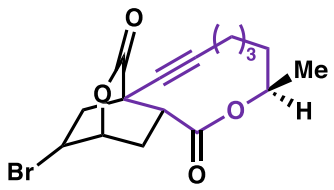


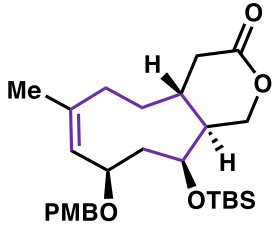
Nat. Commun. **2016**, *7* (1), 13852.

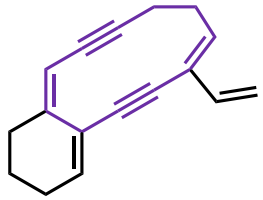
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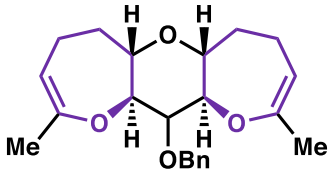
Strategies Towards Medium Rings in Total Synthesis

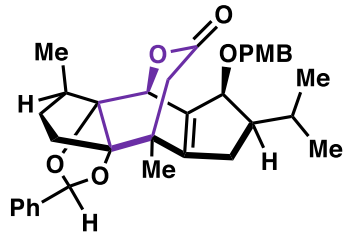
The Ol' Reliable

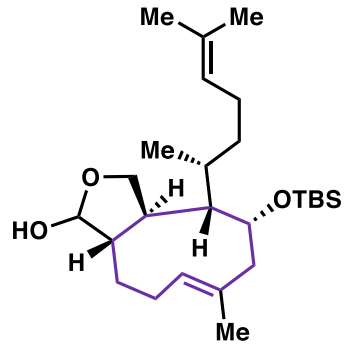




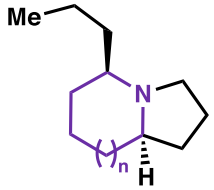


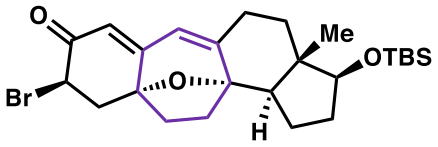


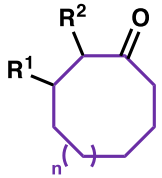


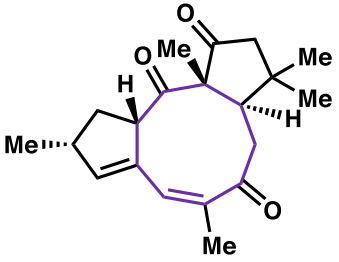


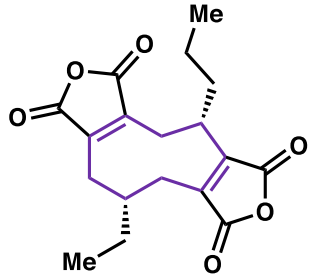
Rearrangements



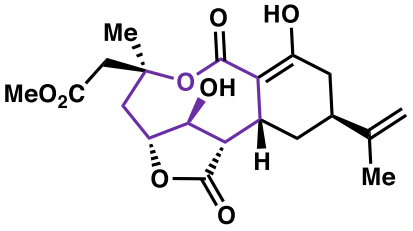








Transannular



Pericyclic and Radical

