Ruben Martinez

Cheletropic Reactions

Baran Group Meeting
06/01/13

Background

"We define as cheletropic reactions those processes in which two σ bonds which terminate at a single atom are made, or broken, in concert."
Woodward, R.B.; Hoffman, R. *Angew. Chem. Int. Ed. Engl*. **1969**, *8*, 781–853.

Cheletropic reactions are a separate class of pericyclic reactions that are subject to orbital symmetry analysis. They must obey the Woodward-Hoffman rules the same way that cycloadditions and sigmatropic rearrangements do.

Linear approach vs. Non-linear approach

Cheletropic reaction analysis is typically done in the addition direction.

Consider fragment "**x**" to be a single atom that contributes two electrons to the pericyclic transition state. The approach of "**x**" can be either linear or non-linear. The rotation of the π system will be either disrotatory or conrotatory based on the approach of fragment "**x**"

Linear

The HOMO of **x** points directly at the π system.

Non-linear

The HOMO of **x** approaches the π system at a skew angle.

Disrotatory

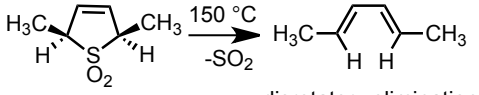
Conrotatory

Selection rules for cheletropic reactions

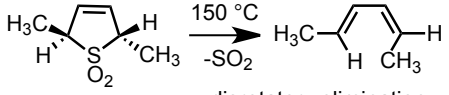
π electrons	Allowed Ground State Reactions	
	Linear	Nonlinear
4*n*	disrotatory	conrotatory
4*n*+2	conrotatory	disrotatory
	Allowed Excited State Reaction	
4*n*	conrotatory	disrotatory
4*n*+2	disrotatory	conrotatory

Angew. Chem. Int. Ed. Engl. **1969**, *8*, 781.
Sankararaman, S. *Pericyclic Reactions*; Wiley-VCH: Weinheim, 2005.

Stereochemical outcome



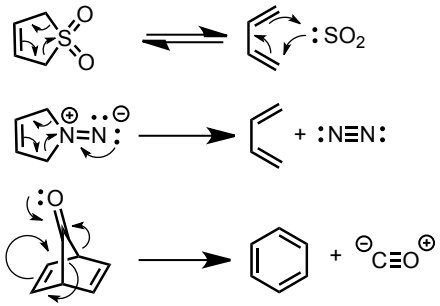
disrotatory elimination



disrotatory elimination

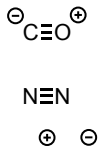
J. Am. Chem. Soc. **1966**, *88*, 2857.
J. Am. Chem. Soc. **1966**, *88*, 2858.

Most frequently encountered examples

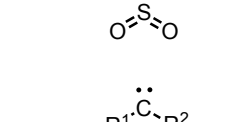


Reactivity general guidline

Cycloreversion Only



Cycloreversion & Cycloaddition



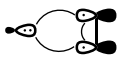
singlet carbenes

Singlet carbene addition to olefins

Singlet carbenes have an unoccupied *p* orbital and two non-bonding electrons in the σ orbital. Only singlet carbenes can participate in cheletropic reactions.

"The most importatnt cheletropic reaction is the addition of singlet carbenes to make cyclopropanes."
Anslyn and Dougherty

Linear approach



4-electron
Hückel forbidden

2-electron
Möbius forbidden

Non-linear approach

4-electron
Möbius allowed

2-electron
Hückel allowed

Only select carbene examples will be discussed here.
See K. Chen's GM on carbenes

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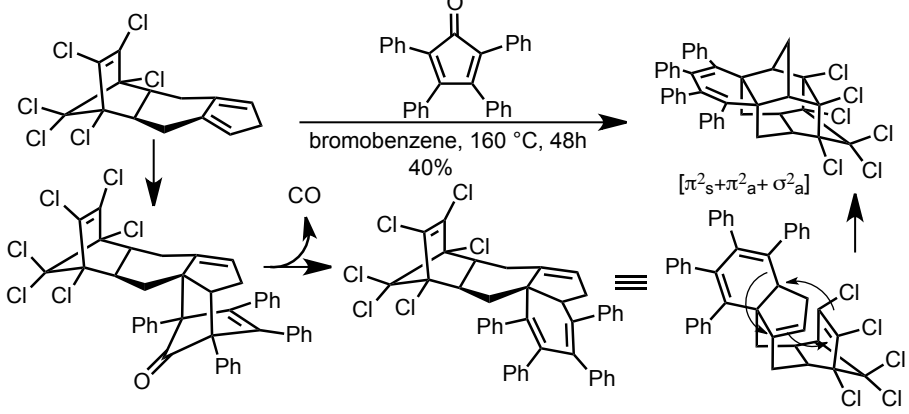
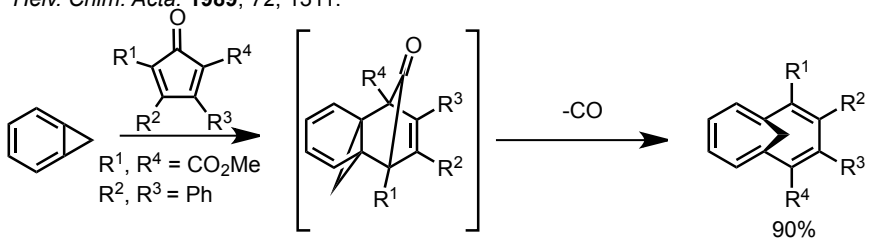
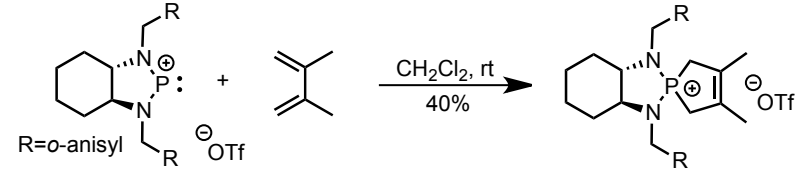
Sequential cycloaddition-cycloreversion and a strange caged structure
Howard, J. A. K. *Tetrahedron*, **1993**, *49*, 4699.



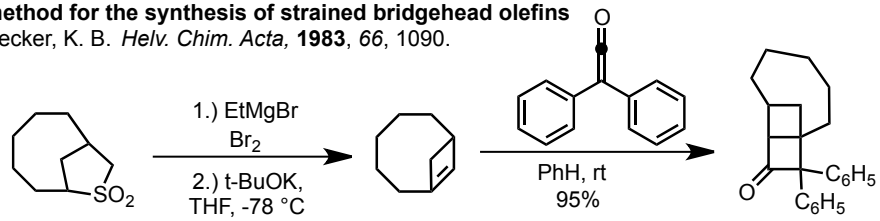
Cheletropic elimination of CO and formation of annulenes
Helv. Chim. Acta, **1989**, *72*, 1311.



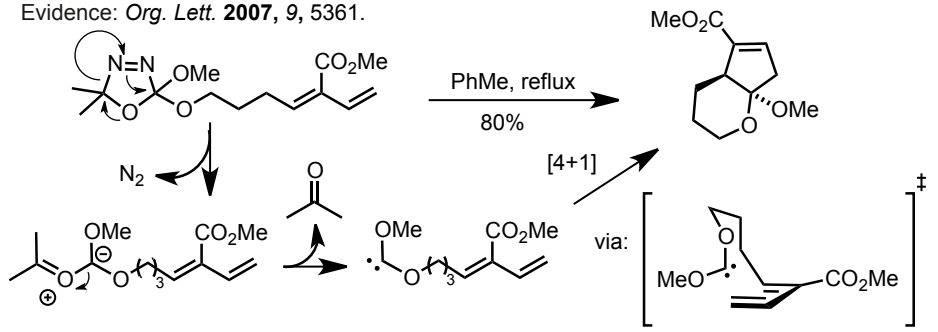
Synthesis of new chiral $\sigma^2\lambda^2$ -phosphenium cations
Buono, G. *Tetrahedron Lett.* **1999**, *40*, 4669.



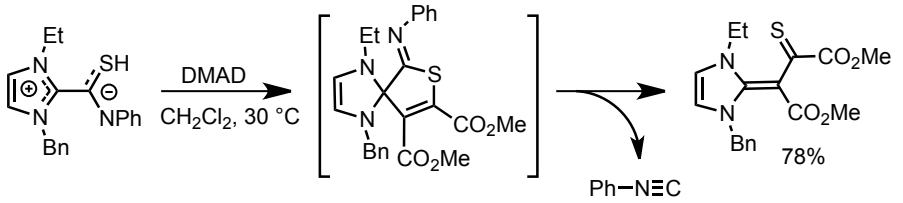
The intramolecular Ramberg-Bäcklund reaction: a convenient method for the synthesis of strained bridgehead olefins
Becker, K. B. *Helv. Chim. Acta,* **1983**, *66*, 1090.



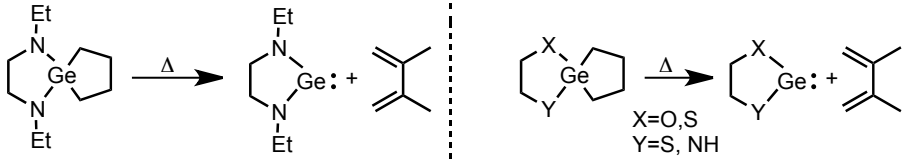
Intramolecular [4+1] Cycloaddition
Spino, C. *J. Am. Chem. Soc.* **2004**, *126*, 9926.
Evidence: *Org. Lett.* **2007, *9,*** 5361.



An unprecedented tandem 1,3-dipolar cycloaddition-cheletropic elimination: a facile approach to novel push-pull olefins
Cheng, Y. *Org. Biomol. Chem.* **2007**, *5,* 1282.

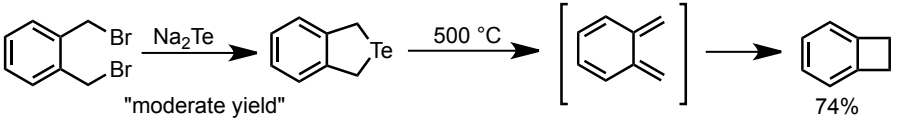


Germanium Analogues of Carbenes
Chrostowska. A. *J. Organomet. Chem.* **2009**, *694*, 43.



The Chemistry of Organic Germanium, Tin and Lead Compounds, John Wiley and Sons, Chichester, 2002 (Chapter 1)

Tellurium Extrusion: Synthesis of Benzocyclobutene
MacNicol, D.D. *Tetrahedron Lett.* **1975**, *24*, 1893.



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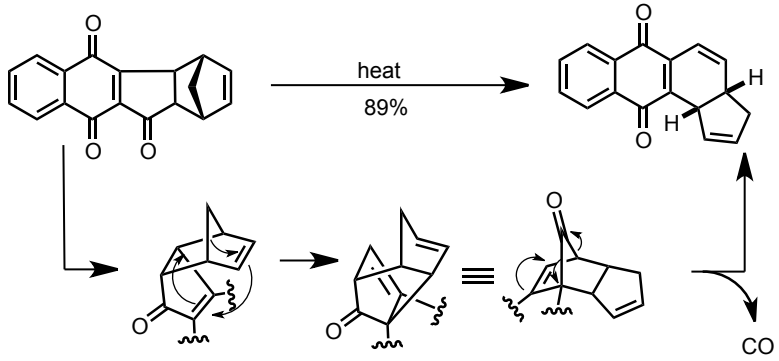
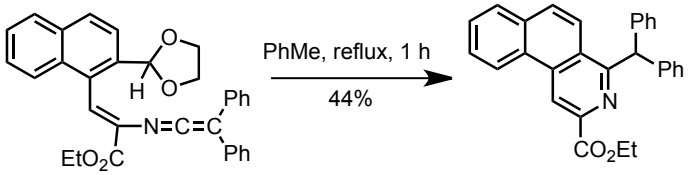
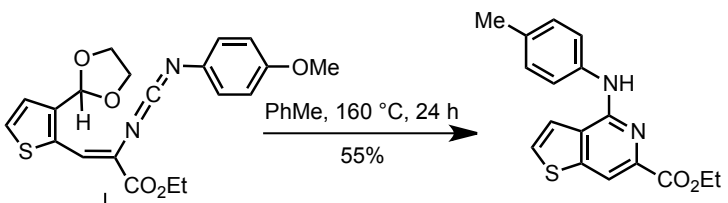
Tandem Cope-cheletropic reaction: a new molecular rearrangment
Mai, D. *Chem. Comm.* **1996**, 1181.

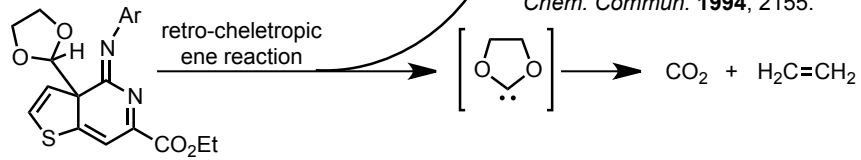


***retro*-Cheletropic ene Reactions with 2-carbena-1,3-dioxolane as the chelefuge**
Vidal, A.; Sanchez-Andrada, P. *Tetrahedron* **2011**, *67,* 5590.



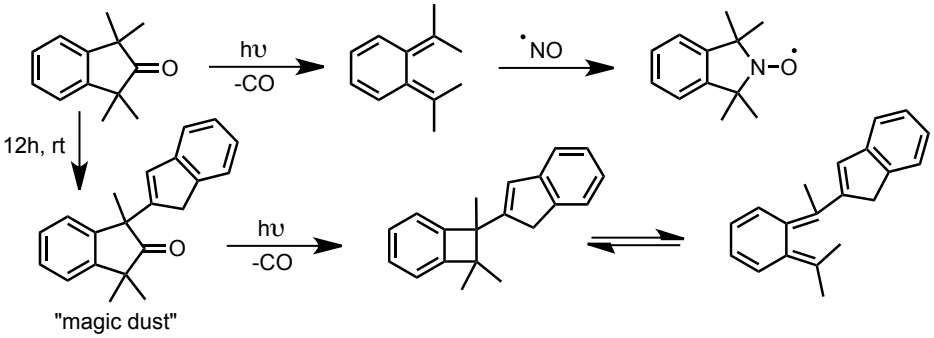


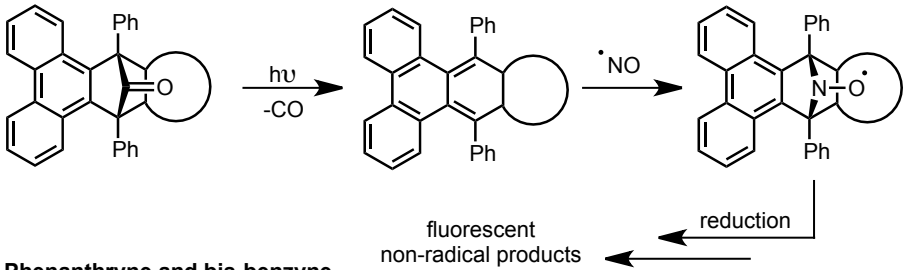
6π electrocyclic ring closure



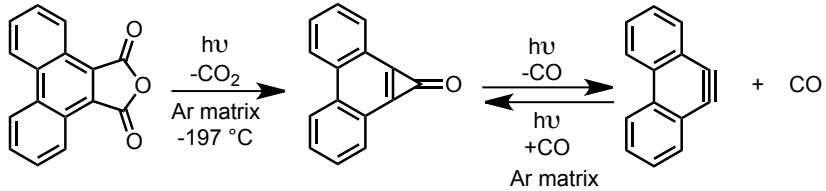
J. Am. Chem. Soc. **1966**, *88*, 582.
Chem. Commun. **1994**, 2155.

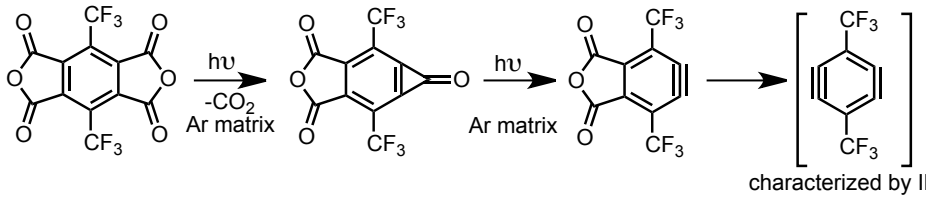
Nitric oxide cheletropic traps (NOCTs)
Ingold, K.U. *J. Am. Chem. Soc.* **1994**, *116*, 2767.
Korth, H.G. *Angew. Chem. Int. Ed. Engl.* ***1997***, *36*, *1501*.





Phenanthryne and bis-benzyne
Murata, S. *J. Org. Chem.* **1995**, *60,* 2344.
Yabe, A. *J. Am. Chem. Soc.* **2002**, *124,* 4512.





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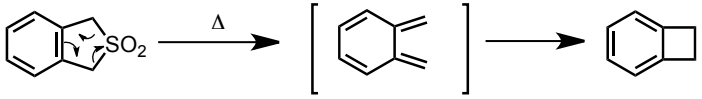
Applications in Total Synthesis

-The examples presented here will consist of the three main cheletropic reactions seen in total synthesis. Cheletropic reactions involving Fischer carbenes will not be discussed here beyond examples of the Simmons-Smith cyclopropanation. For an in depth presentation and discussion of Fischer carbenes see K. Chen's group meeting on Fischer carbenes.

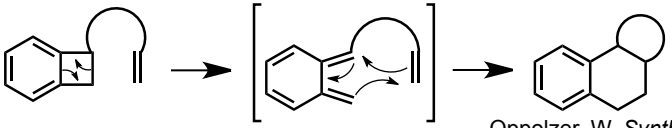
Early studies on the formation of cyclobutarene
Cava, M.P. *J. Am. Chem. Soc.* **1959**, *81,* 4266.



-The first report of this type of reactivity dates back to 1913. This topic remained unexplored until it was returned to in 1935.
Staudinger, H. German Patent 506,839; [*Chem. Abstr.* **1913**, *25*, 522]
Staudinger, H. *Chem. Ber.* **1935**, *68B,* 455.

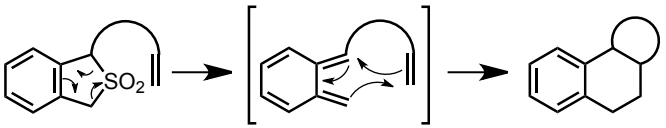
Cheletropic extrusion of SO_2: The search for a diene equivalent

Inspiration from W. Oppolzer

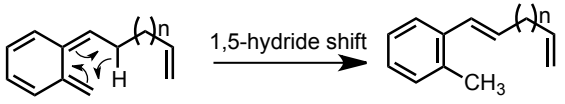


Oppolzer, W. *Synthesis* **1978**, *11*, 793.

K.C.N.'s idea: intramolecular trapping of o-quinodimethanes



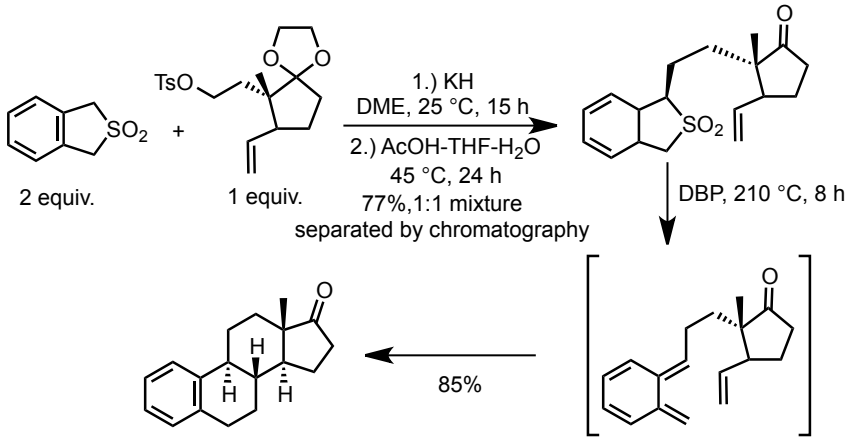
Potential problem



n= 2,3 n= 2,3

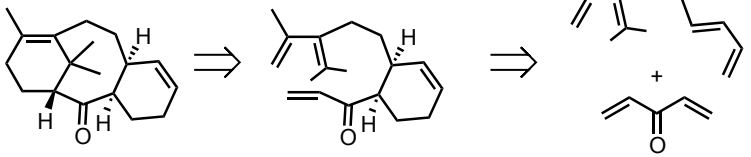
The methylstyrene side product was observed in only a small (unspecified) amount.

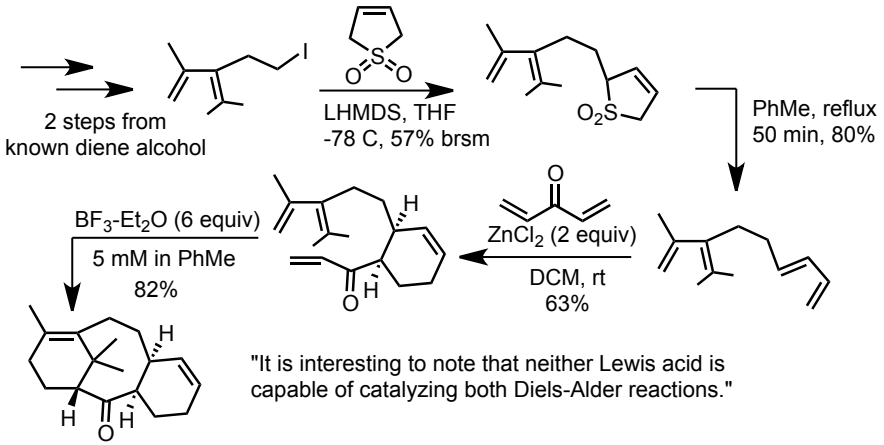
Synthesis of estra-1,3,5,(10)-trien-17-one
Nicolaou, K.C. *J. Org. Chem.* **1980**, *45*, 1463.



Stereoselective Synthesis of the Taxane Ring System.
Winkler. J.; Houk, K. *J. Org. Chem.* **1997**, *62*, 2957.

Winkler's retrosynthetic analysis:





"It is interesting to note that neither Lewis acid is capable of catalyzing both Diels-Alder reactions."

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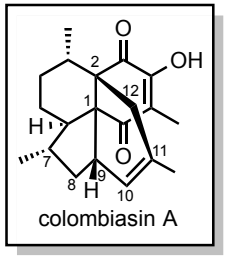
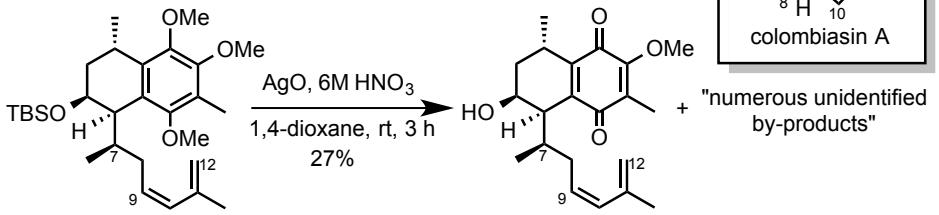
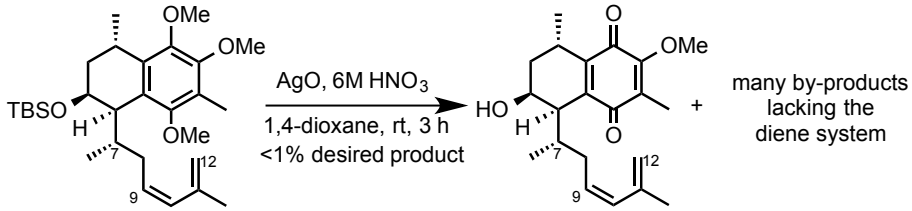
Total Synthesis of Colombiasin A
Nicolaou, K.C. *Angew. Chem. Int. Ed.* **2001**, *40*, 2482.
Full paper: *Chem. Eur. J.* **2001**, *7*, 5359.



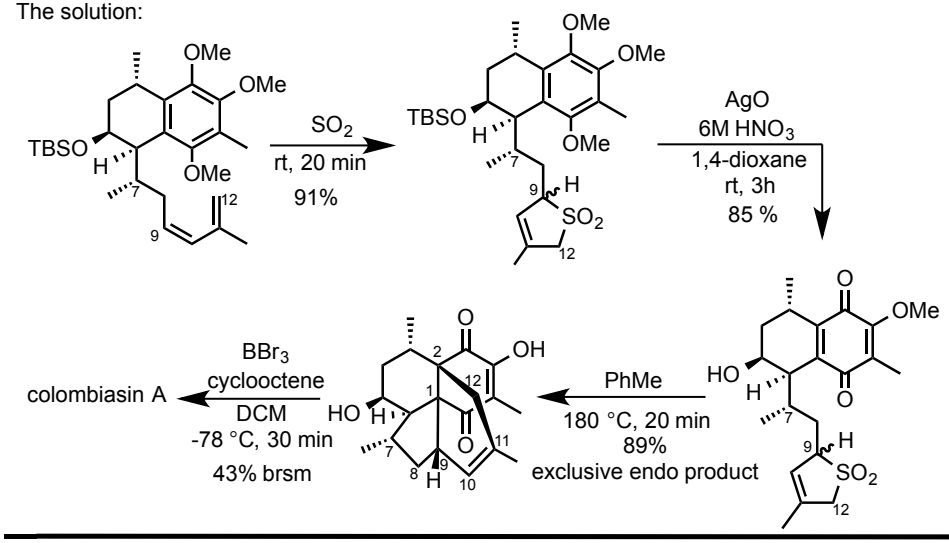
First generation:



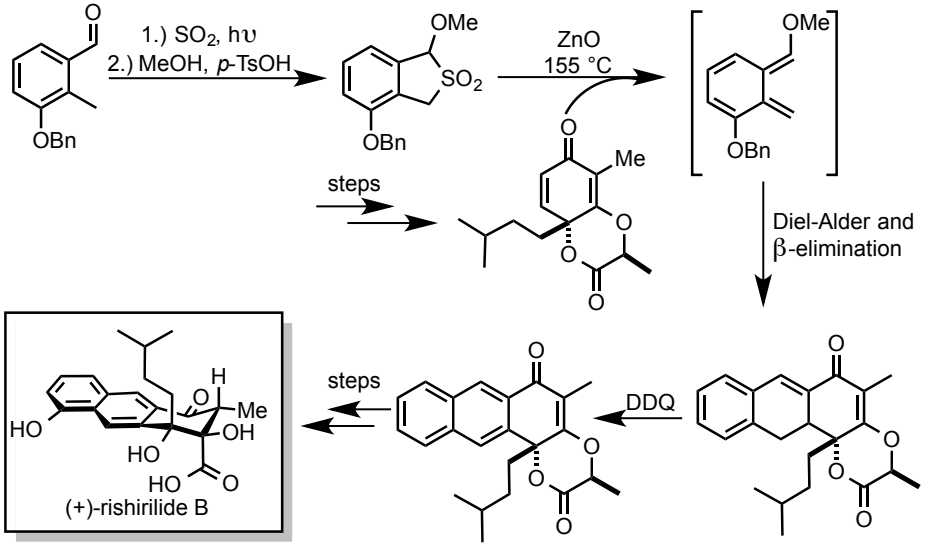
Second generation:



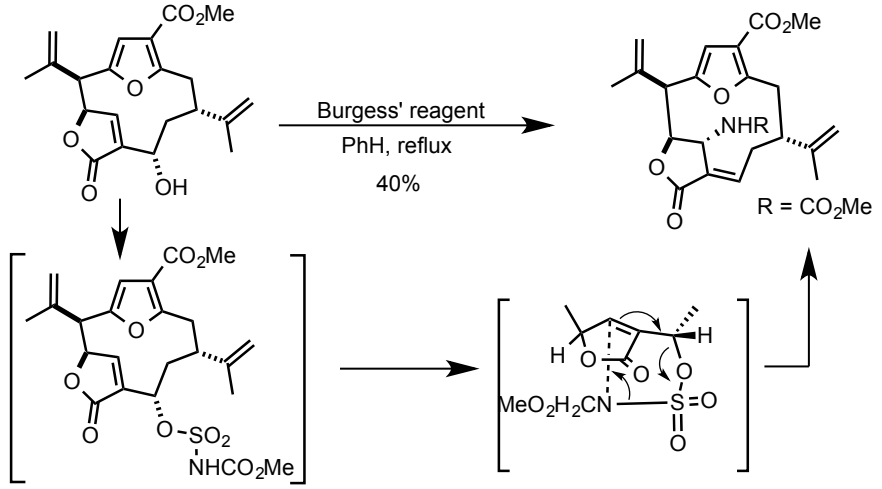
The solution:



Total Synthesis of (+)-Rishirilide B
Pettus, T. R. R. *J. Am. Chem. Soc.* **2006**, *128*, 15625.



An "almost" cheletropic elimination of SO_3 from 11-gorgiacerol
Gaich, T.; Mulzer, J. *Org. Lett.* **2012**, 14, 2834.



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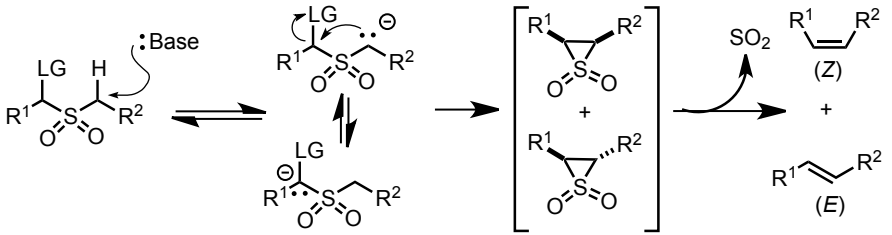
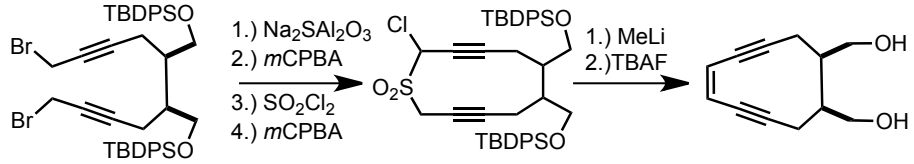
Ramberg–Bäcklund Reaction

The reaction was first discovered in 1940 but no further work was published until 1950.



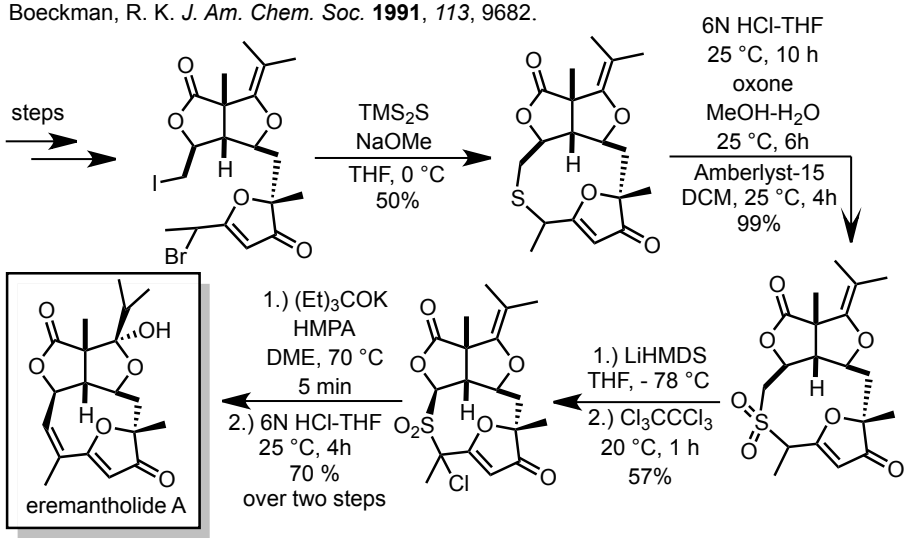
Early studies toward the synthesis of the enediyne moeity of calicheamicin

Nicolaou, K. C. *J. Am. Chem. Soc.* **1992**, *114*, 7360.



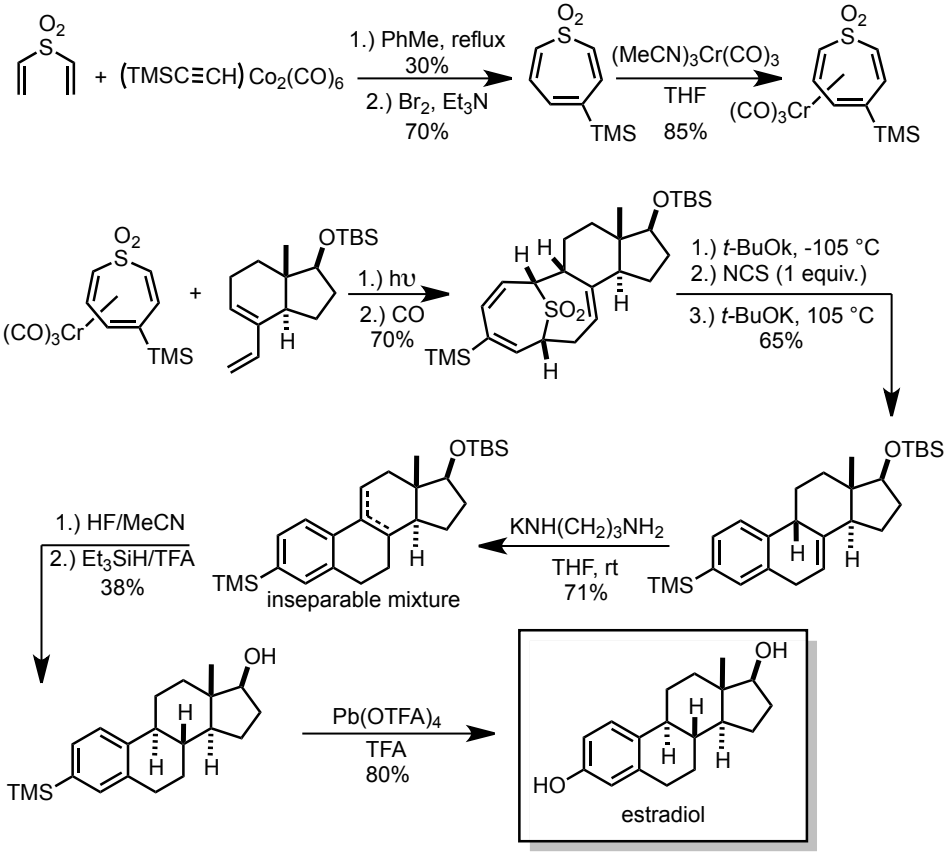
A Novel application of the Ramberg-Bäcklund Rearrangement to a Highly StereoselectiveSynthesis of (+)-Eremantholide A

Boeckman, R. K. *J. Am. Chem. Soc.* **1991**, *113*, 9682.



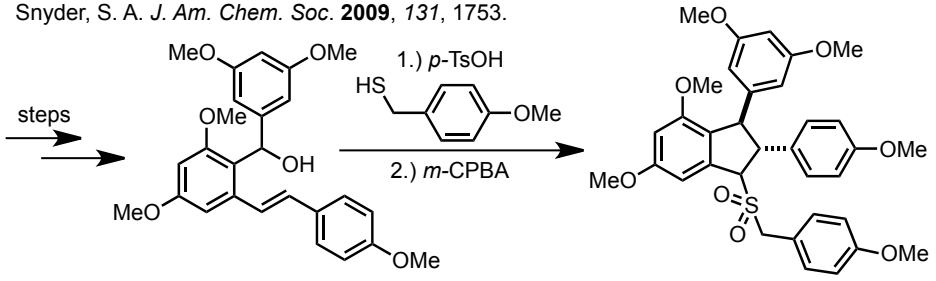
Total Synthesis of (+)-Estradiol

Rigby, J. H. *J. Am. Chem. Soc.* **1999**, *121*, 8237.



Total Synthesis of Ampelopsin D

Snyder, S. A. *J. Am. Chem. Soc.* **2009**, *131*, 1753.



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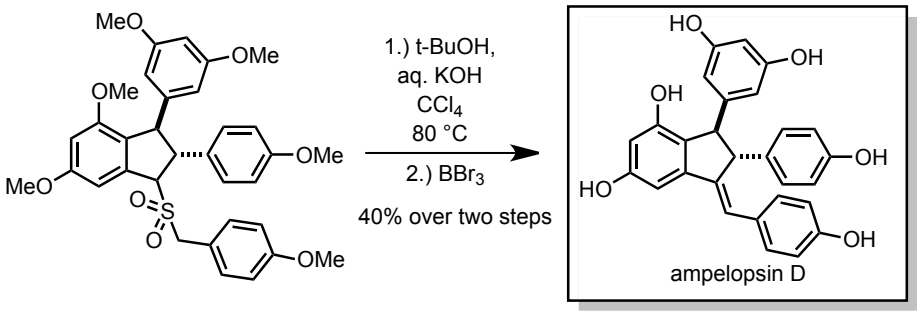
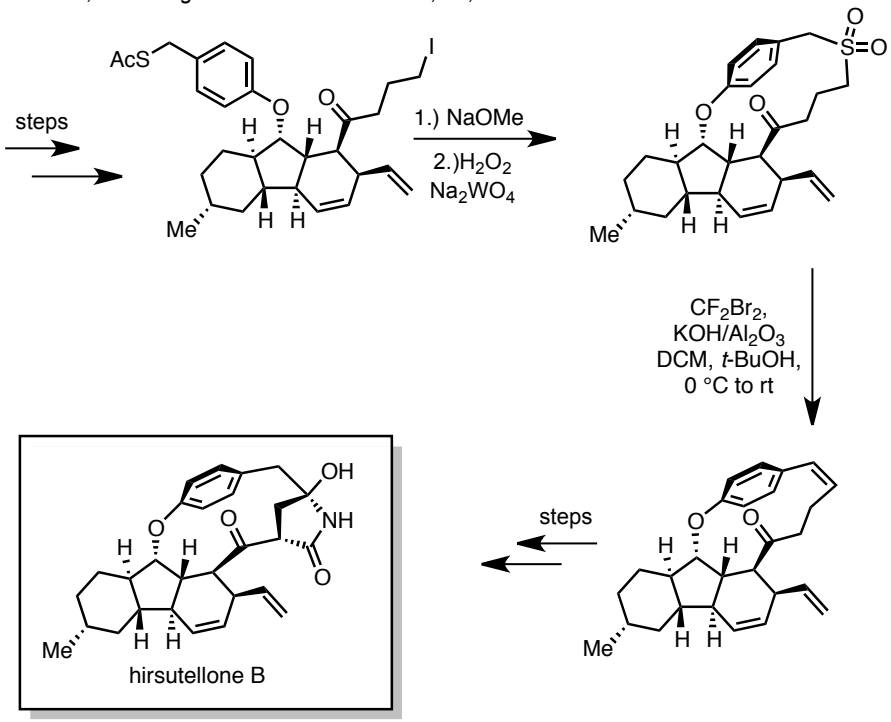
Total Synthesis of Ampelopsin D continued



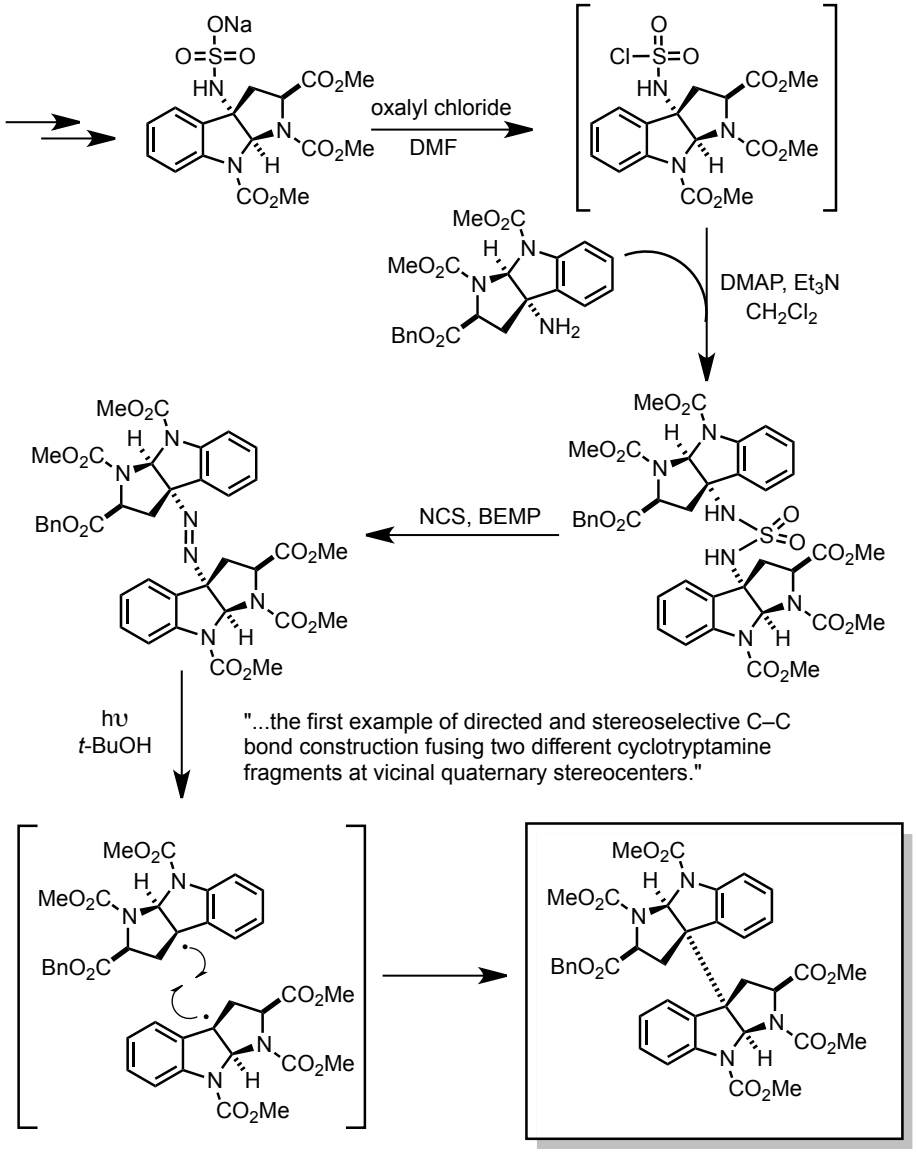
Total Synthesis of Hirsutellone B

Nicolaou, K. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 6870.



Directed Heterodimerization: Stereocontrolled Assembly via Solvent-Caged Unsymmetrical Diazene Fragmentation

Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 13002.



"...the first example of directed and stereoselective C–C bond construction fusing two different cyclotryptamine fragments at vicinal quaternary stereocenters."

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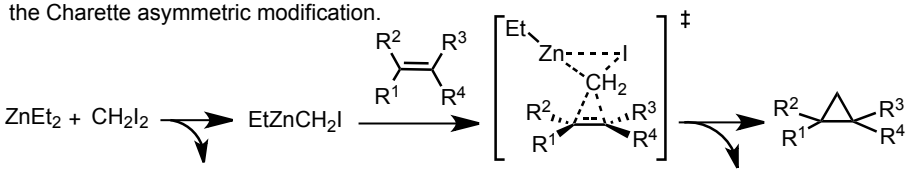
Simmons-Smith cyclopropanation

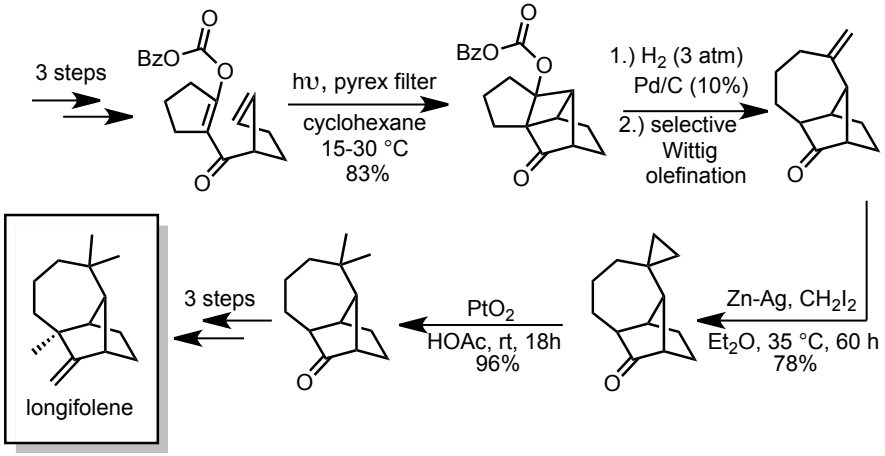
First discovered in 1944. Many asymmetric modifications have been throughout the years. The most notable being the Charette asymmetric modification.



For an excellent review on stereoselective cyclopropanation reactions see: *Chem. Rev.* **2003**, *103,* 977.

Total synthesis of (±)longifolene

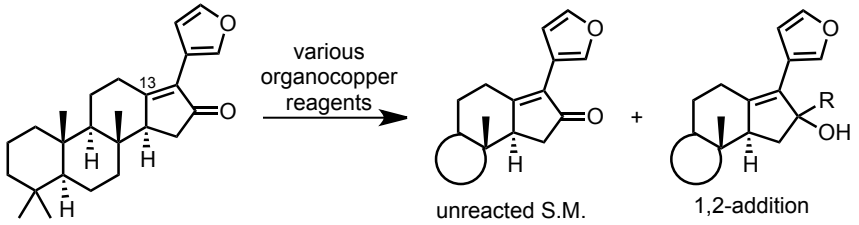
Oppolzer, W. *J. Am. Chem. Soc.* **1978**, *100*, 2583.



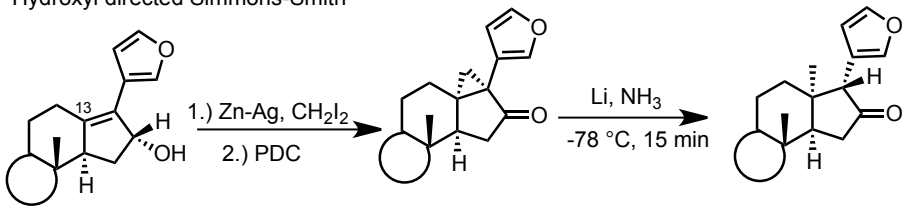
Simple synthetic route to the limonoid system

Corey, E.J. *J. Am. Chem. Soc.* **1987**, *109*, 918.

"The most obvious approach" gave poor results

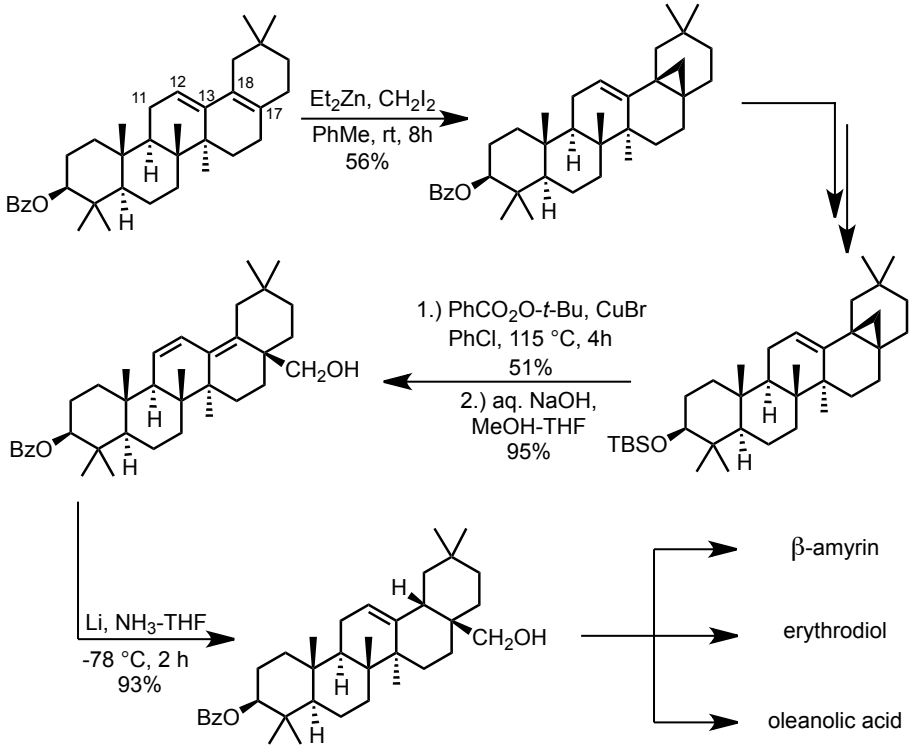


Hydroxyl directed Simmons-Smith



Enantioselective total synthesis of oleanolic acid, erythrodiol, β-amyrin, and other pentacyclic triterpenes from a common intermediate

Corey, E.J. *J. Am. Chem. Soc.* **1993**, *115*, 8873.

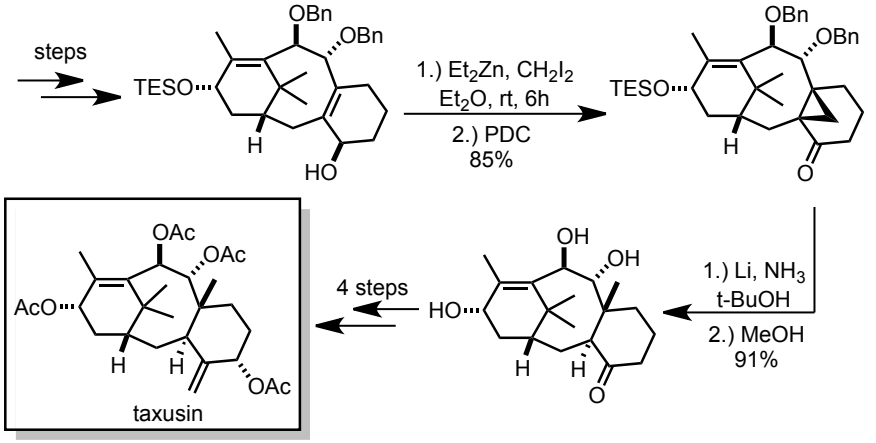


Ruben Martinez

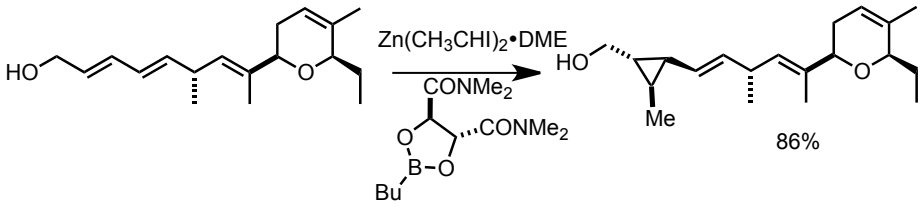
Cheletropic Reactions

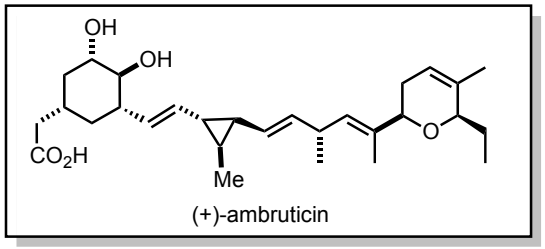
Baran Group Meeting
06/01/13

Total Synthesis of (±)-Taxusin
Kuwajima, I. *J. Am. Chem. Soc.* **1996**, *118*, 9186.

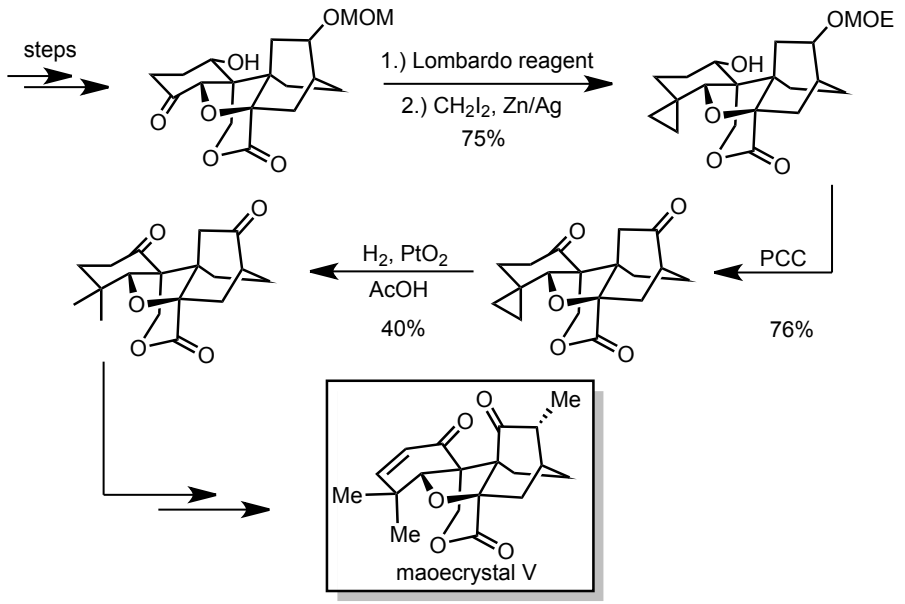


Total Synthesis of (+)-Ambruticin
Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772.
Regioselective, asymmetric cyclopropanation





Total Synthesis of (±)-Maoecrystal V
Danishefsky, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 18860.



Highly Enantioselective Simmons-Smith Fluorocyclopropanation of Allylic Alcohols
Charette A. B. *J. Am. Chem. Soc.* **2013**, *135*, 7819.

State of the art in cyclopropanation