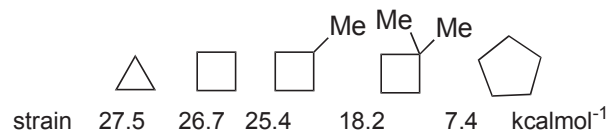
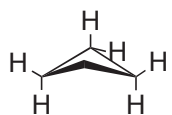
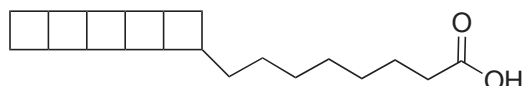


**Cyclobutanes:**  
-exist in puckered conformation where eclipsing interactions of C-H bonds are minimized.



-its inherent ring strain makes formation of cyclobutanes difficult, yet it is this strain that makes cyclobutanes extremely useful in organic synthesis.



**pentacycloanammoxic acid**

-ladderane with 5 fused cyclobutanes  
-3 times the strain of a single cyclobutane  
-found in bacteria-anammox process  
-protects organisms from NH<sub>2</sub>OH/NH<sub>2</sub>NH<sub>2</sub>,  
formed in production of N<sub>2</sub> and H<sub>2</sub>O from nitrites and nitrates

*Nature* **2002**, 419, 708

-cyclobutanes are the basic structural unit in bacteria, fungi, plants and marine invertebrates;  
-many biological activities: cpds like amino acids, peptides and nucleosides with cyclobutane often exhibit protective properties against UV. *J Nat. Med.* **2008**, 62, 1.

### Useful reviews on this topic:

"Cyclobutanes in Catalysis" Cramer, *ACIE* **2011**, 50, 7740.

"Photochemical Reactions as Key Steps in NP Synthesis" Bach, *ACIE* **2011**, 50,1000

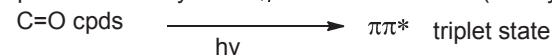
"Photocycloaddition in NP Synthesis" Greaney, *EJOC* **2007** 4801

"Cyclobutane Derivatives in Organic Synthesis" Kaufmann, *Chem. Rev.* **2003**, 103, 1485.

### Some methods to form cyclobutanes:

#### [2+2] cycloaddition of olefins:

- photochemically with  $\alpha,\beta$ -unsat. substrates (mostly cyclic)

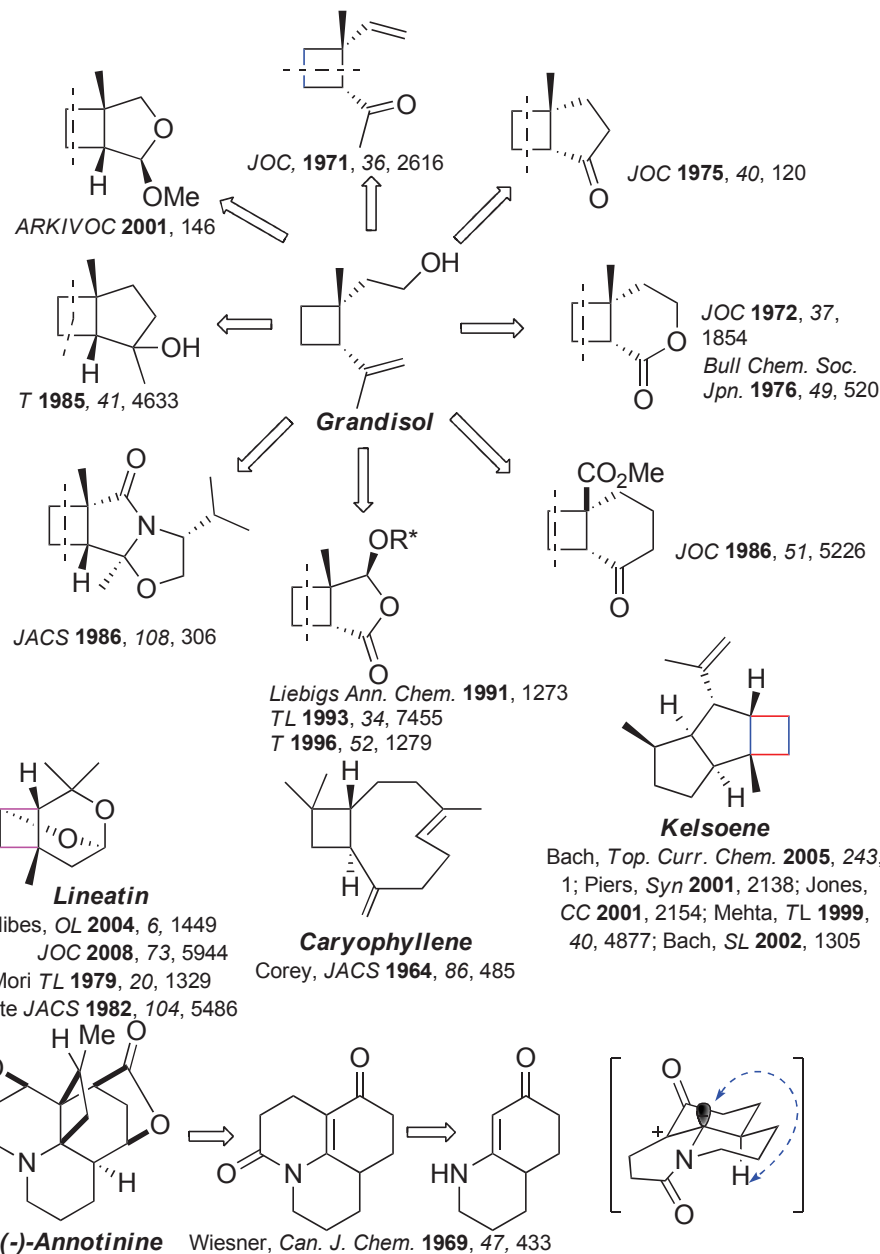


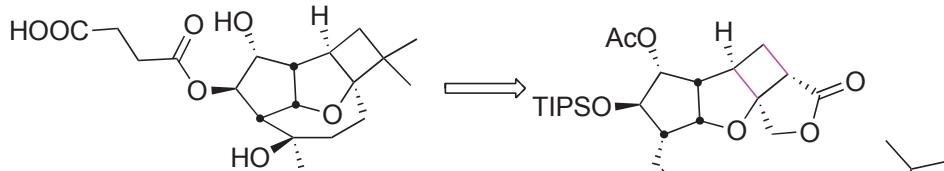
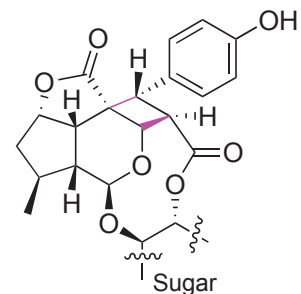
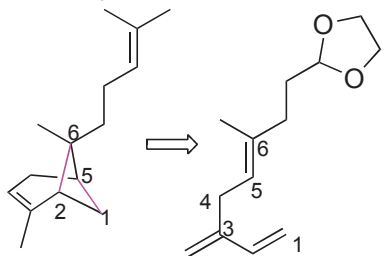
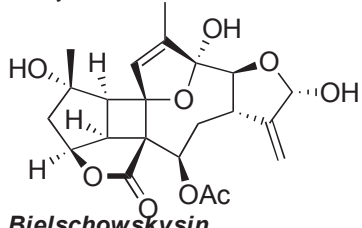
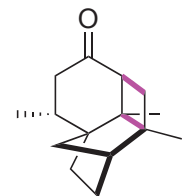
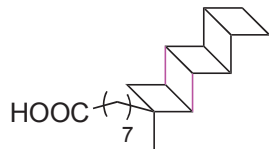
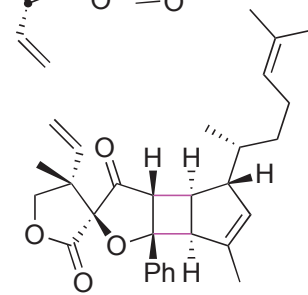
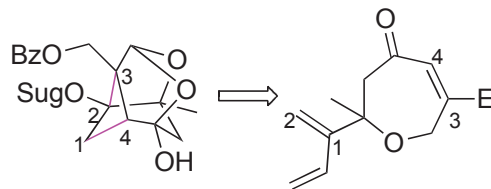
ring closure via 1,4-diradical

-common sensitizers (for population of triplet state) are acetone/benzophenone

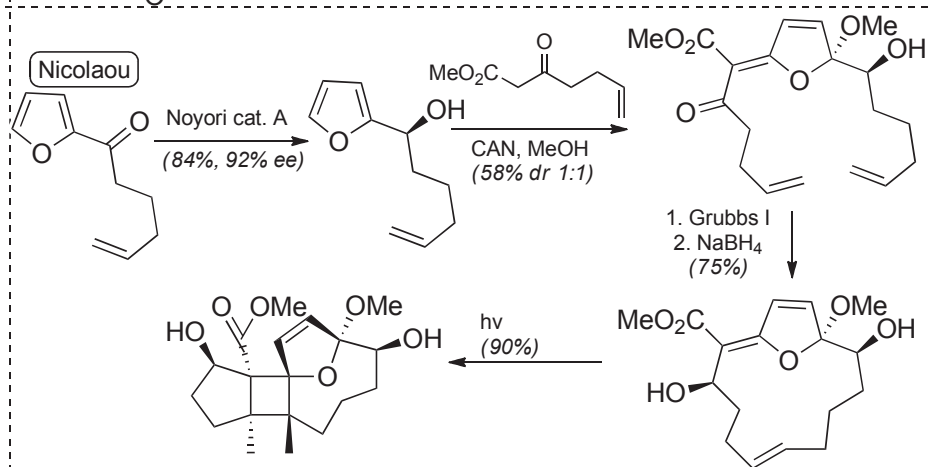
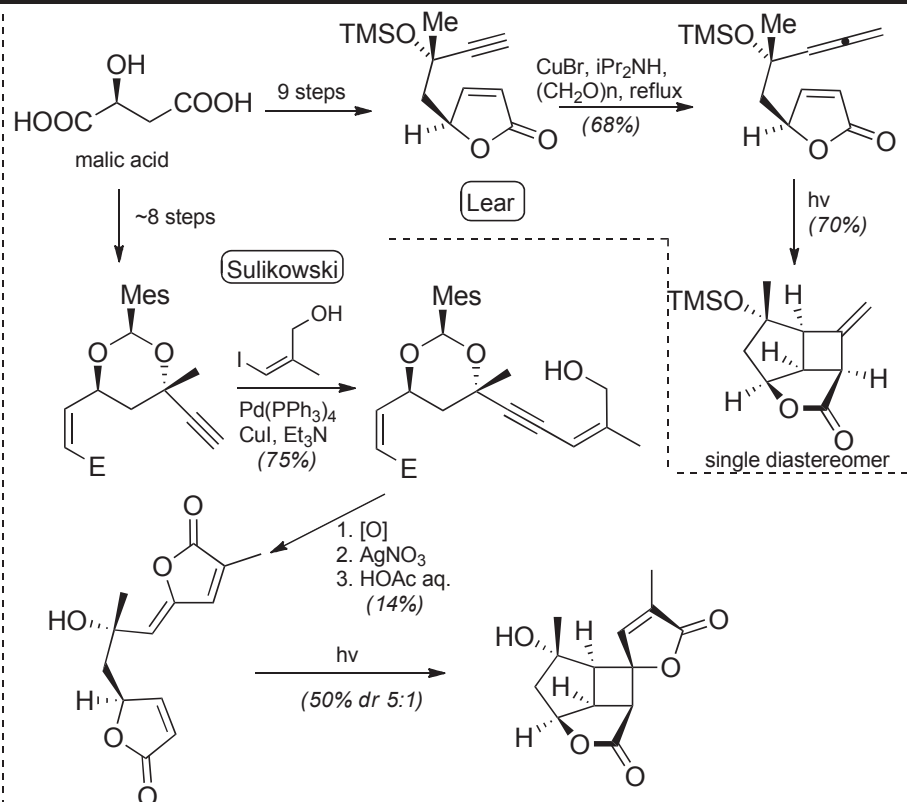
- OR TM-catalyzed [2+2]

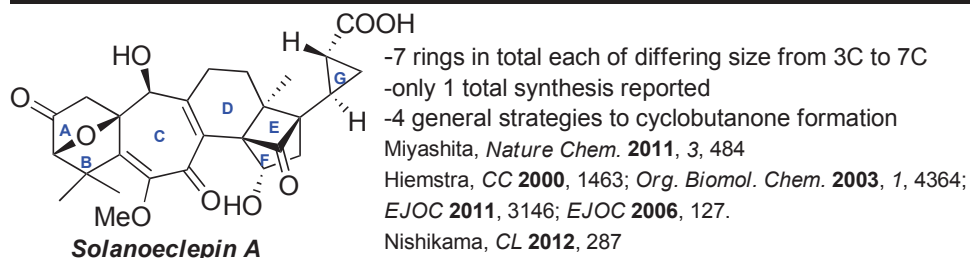
Most naturally occurring NP containing cyclobutanes were synthesized using [2+2] cycloadd. of olefins.



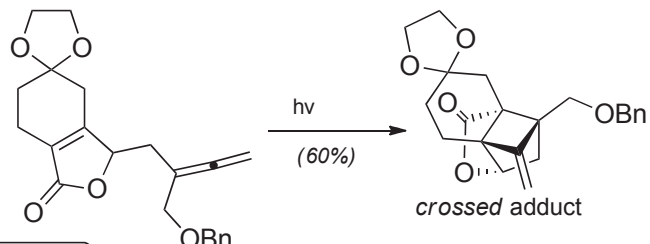
**Punctaporonin C**Bach, *ACIE* 2008, 47, 6189**(-)-Littoralisone**MacMillan, *JACS* 2005, 127, 3696- use of 1,5-dienes in intramolecular [2+2] photocycloaddition leads to *crossed* regioselectivity **$\alpha$ -trans-Bergamotene**Corey, *JACS* 1971, 93, 7016**Bielschowskysin****(+)-Solanascone**Ramaswamy, *TL* 2005, 46, 7373**(+)-pentacycloanammoxic acid**Corey, *JACS* 2004, 126, 15664*JACS* 2006, 128, 3118**(-)-Biyouyanagin A**Nicolaou, *ACIE* 2007, 46, 4708*JACS* 2008, 130, 11114**(-)-Paeoniflorin**Takano, *JACS* 2002, 124, 4081

-4 studies towards the skeleton core  
 -3 of which involves a [2+2] photocycloaddition  
 -11 stereocenters  
 Lear, *TL* 2009, 50, 1731  
 Sulikowski, *OL* 2006, 8, 903  
 Nicolaou, *ACIE* 2011, 50, 5149

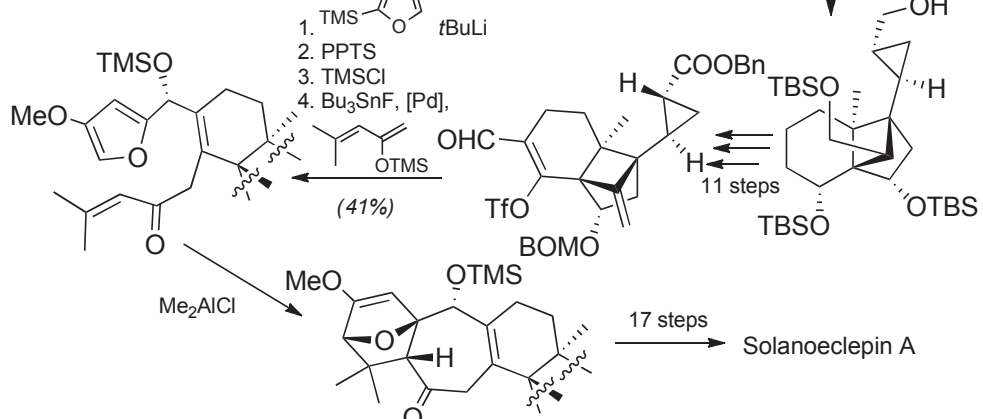
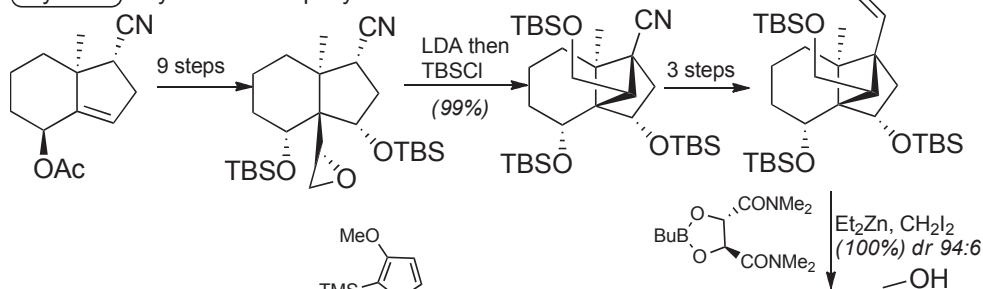




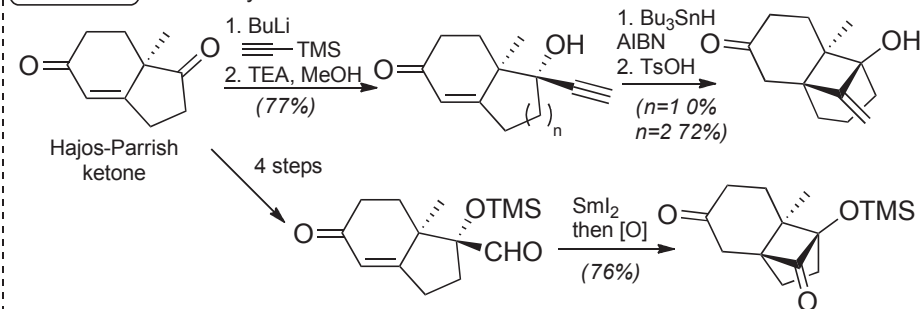
Hiemstra - via [2+2] photocycloaddition



Miyashita - cyclization of epoxynitrile

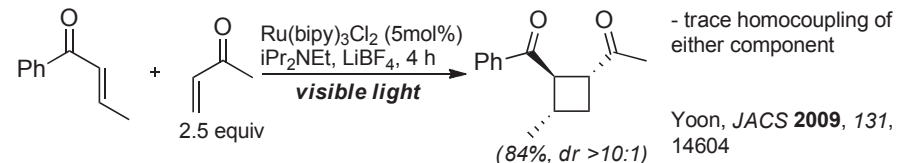


Nishikama - radical cyclization

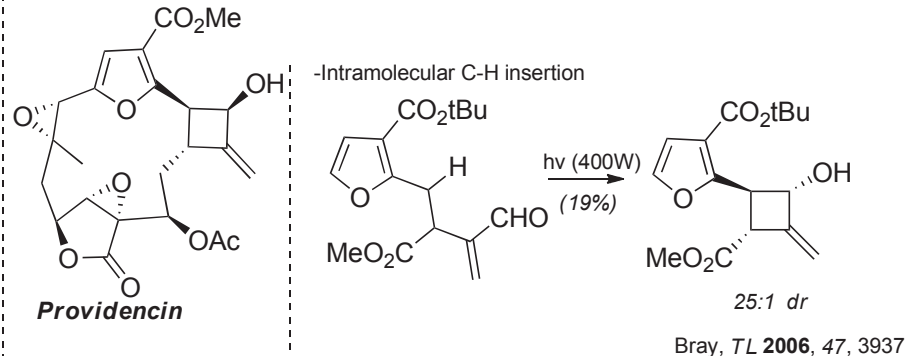
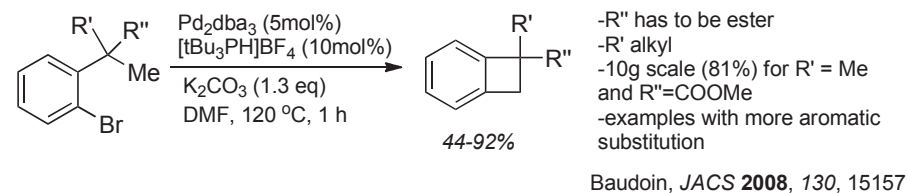


Other development of [2+2]-cycloaddition:

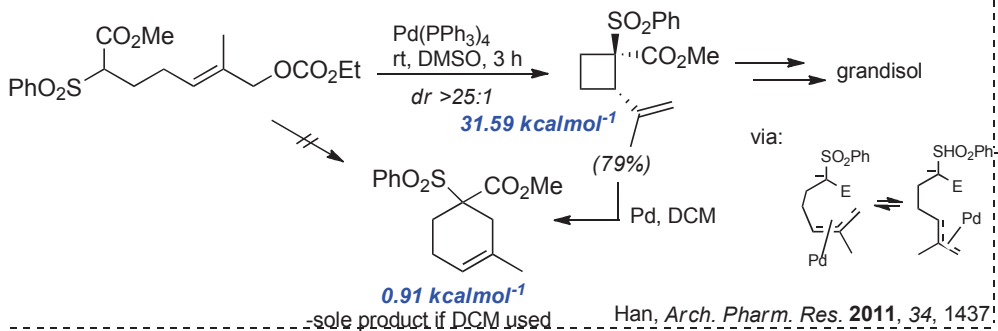
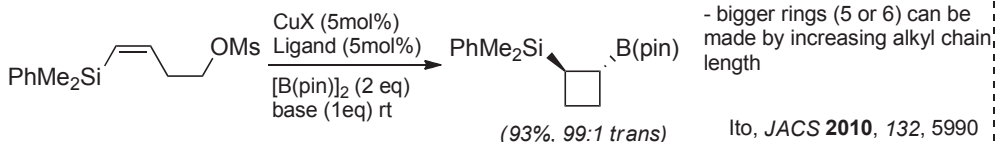
-[2+2] cycloaddition between 2 acyclic enones



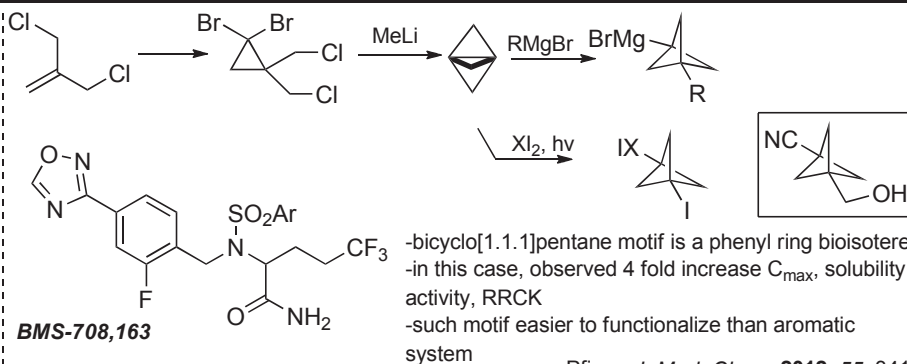
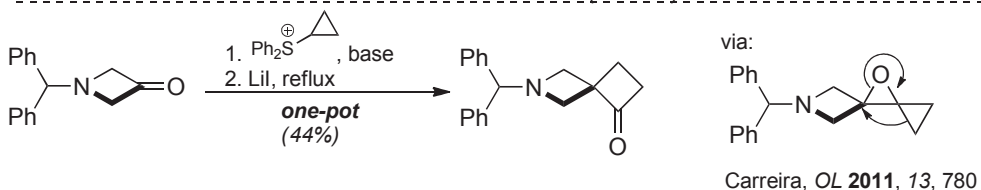
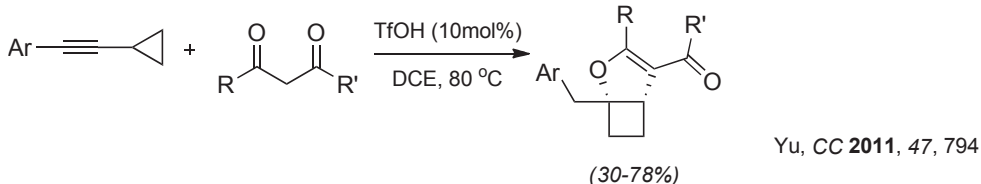
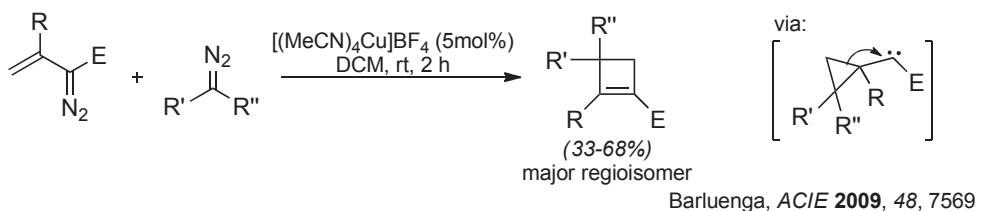
C-H activation to form cyclobutanes



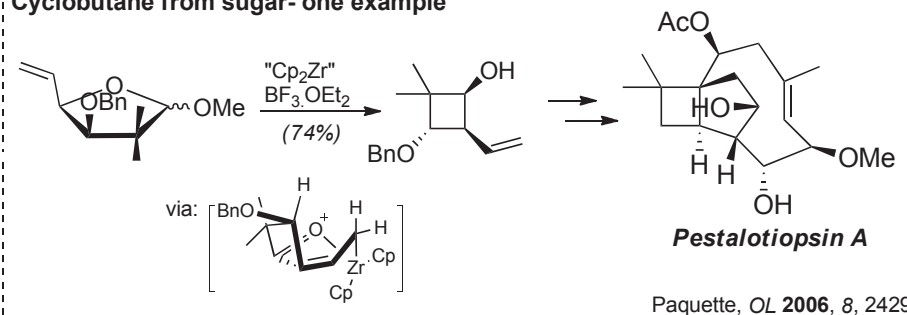
## Direct ring closure to cyclobutanes - some recent examples



## Cyclobutanes from cyclopropanes - some recent examples



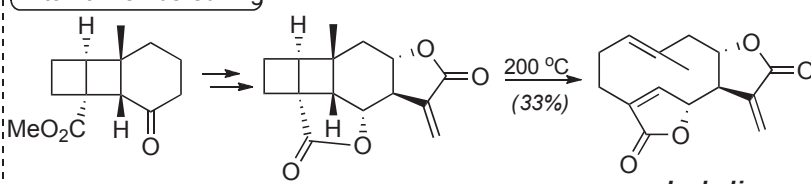
## Cyclobutane from sugar - one example



## Applications of cyclobutanes

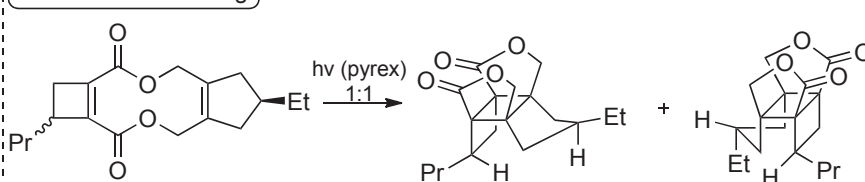
-many examples covered in previous group meetings

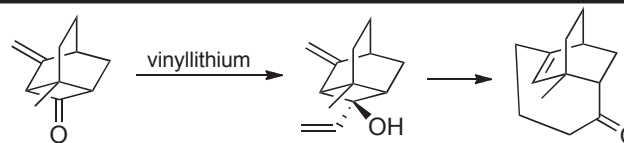
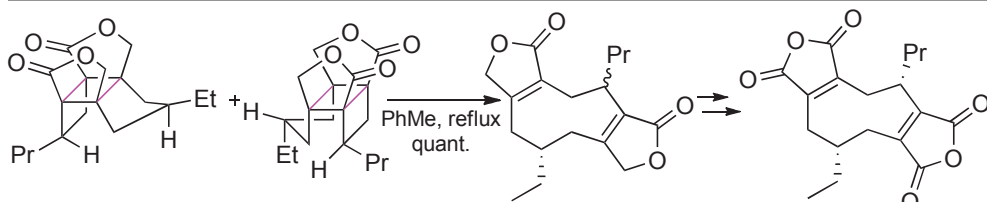
## 4 to 10 membered ring



(covered in Usui GM)

## 4 to 9 membered ring



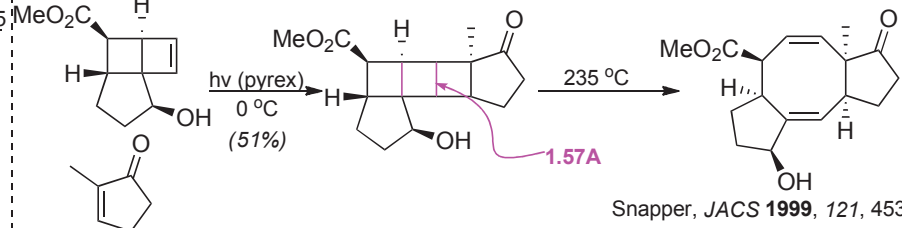
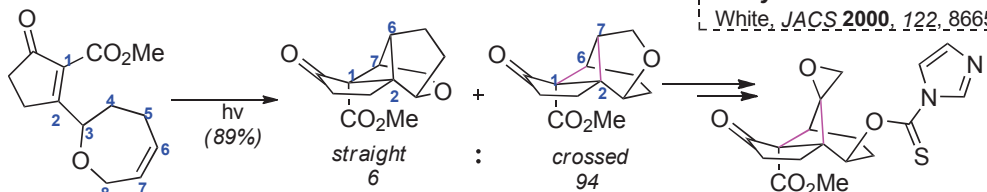


-attempted synthesis of seychellene  
-eg. of divinyl cyclobutane rearrangement

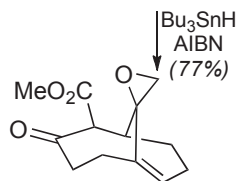
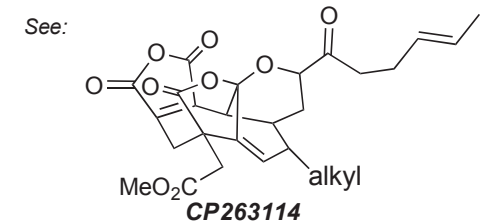
Snider, *JOC* **1988**, 53, 4508

### Byssochlamic acid

White, *JACS* **2000**, 122, 8665



Snapper, *JACS* **1999**, 121, 4534



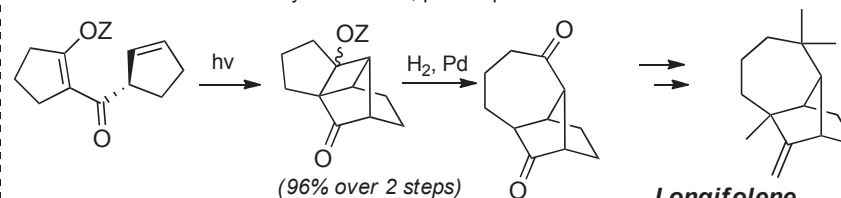
Crimmins, *OL* **2000**, 2, 281

4 to 7 membered ring

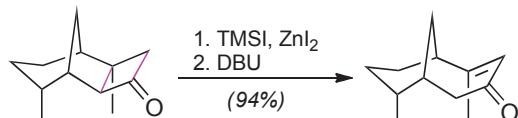
-Winkler's synthesis of ingenol: see *JACS* **2002**, 124, 9726

-Winkler's synthesis of saudin: see *JACS* **1999**, 121, 7425

- see Cherney GM "Guianes and Xanthes" for alismol, dehydrokessane, pelocarpenene.



Oppolzer, *JACS* **1978**, 100, 2583



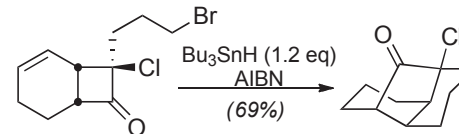
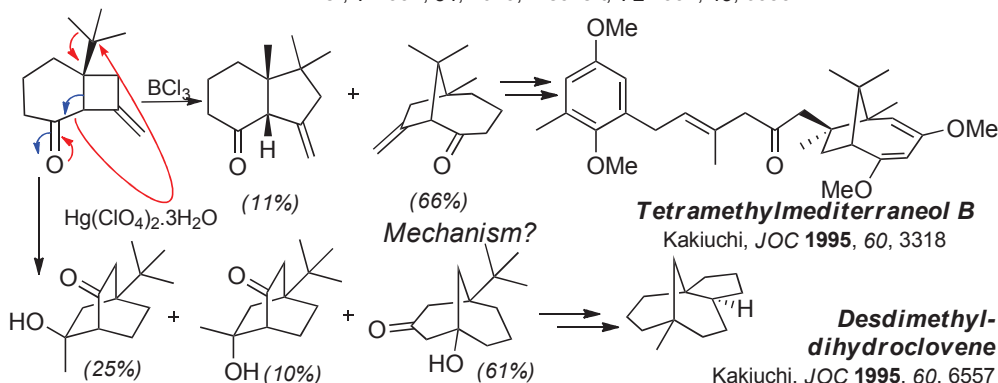
-a common strategy to open  
annulated cyclobutanone

T **1995**, 51, 3435

*JACS* **1992**, 115, 10084

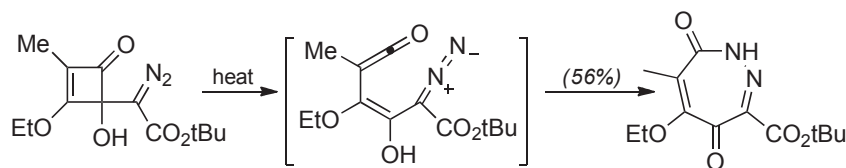
4 to 8 membered ring

- studies towards Taxol skeleton using cyclobutanes: see Wilde GM  
Winkler, *T* **1992**, 34, 7049; Blechert, *TL* **1992**, 48, 6953



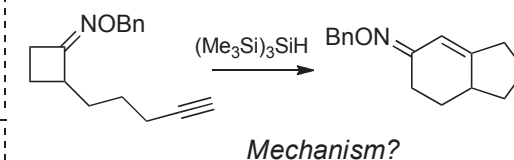
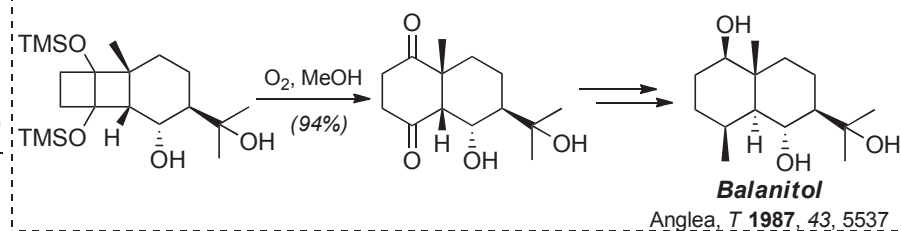
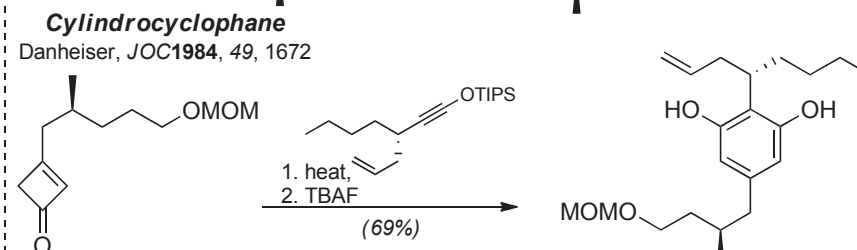
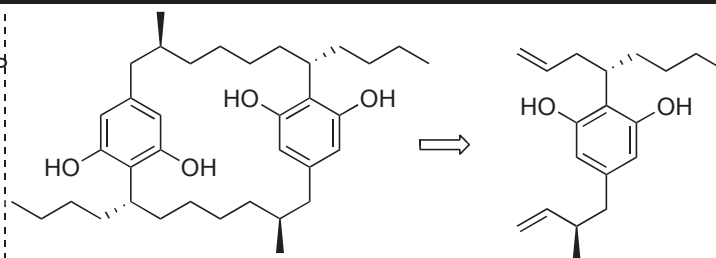
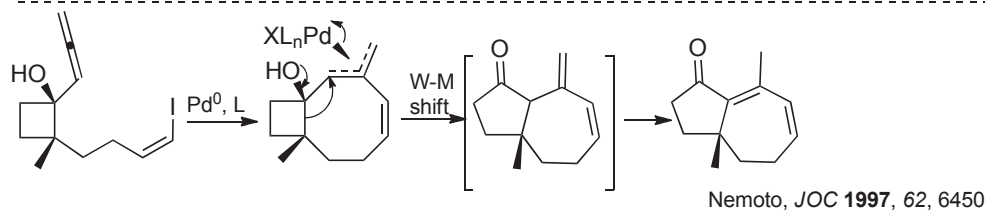
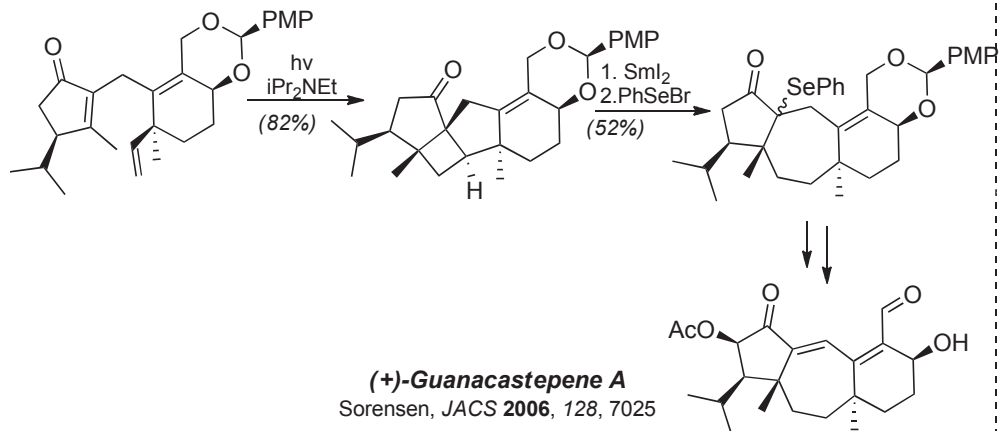
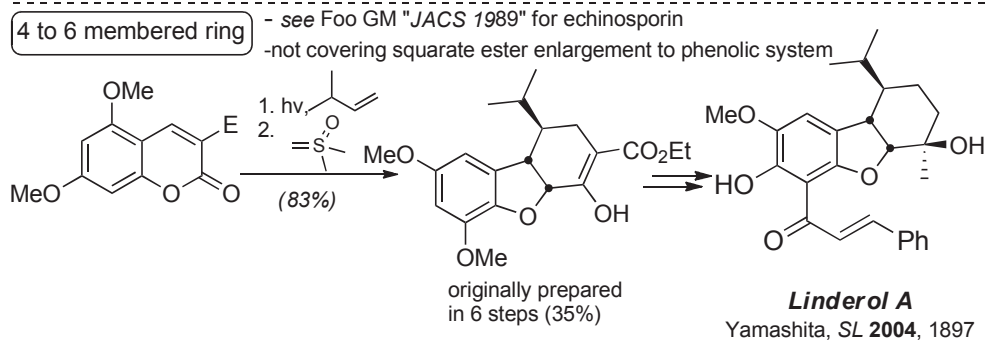
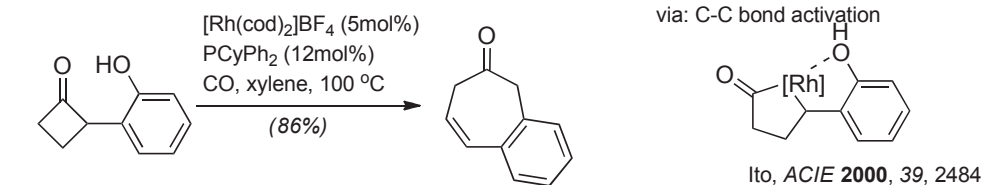
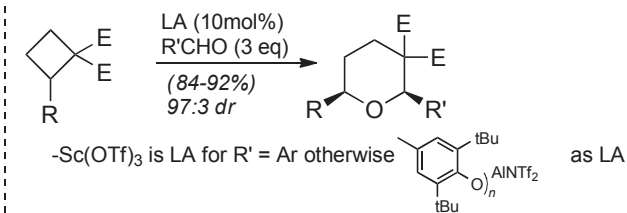
Mechanism?

Dowd, *T* **1995**, 51, 39

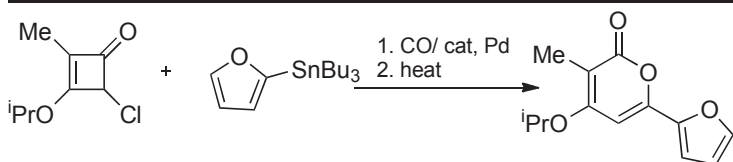


-4π + 8π exclusively 7-membered ring  
-5 membered ring product obtained if acid or Rh catalyzed.

Eguchi, *JOC* **1999**, 64, 707

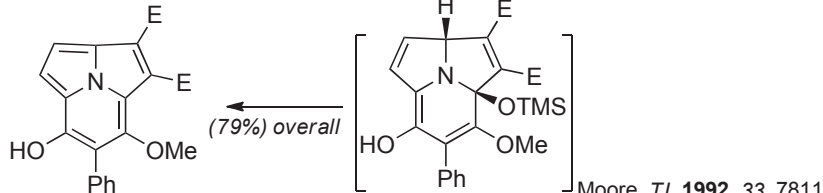
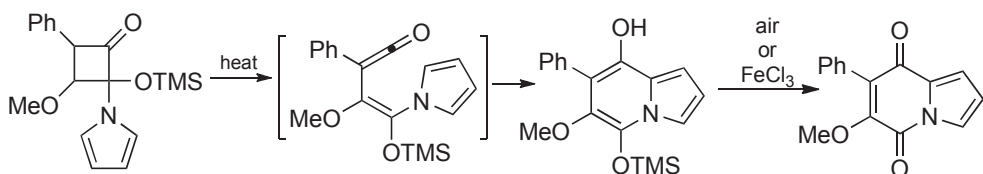
Pattenden, *TL* **1993**, 34, 6787**Mechanism?**-they also attempted a one-pot  $[[2+2]+2]$  - form cyclobutane then THP using same LA  
Johnson, *JACS* **2009**, 131, 14202





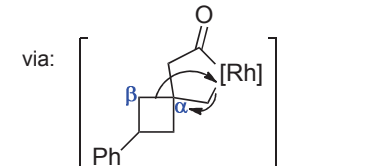
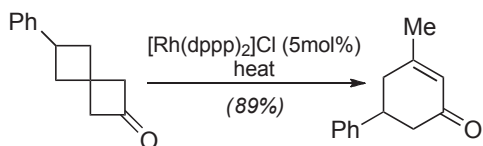
- good way to make 3,4,6-trisubstituted pyrones

Liebeskind, JACS 1992, 114, 1412

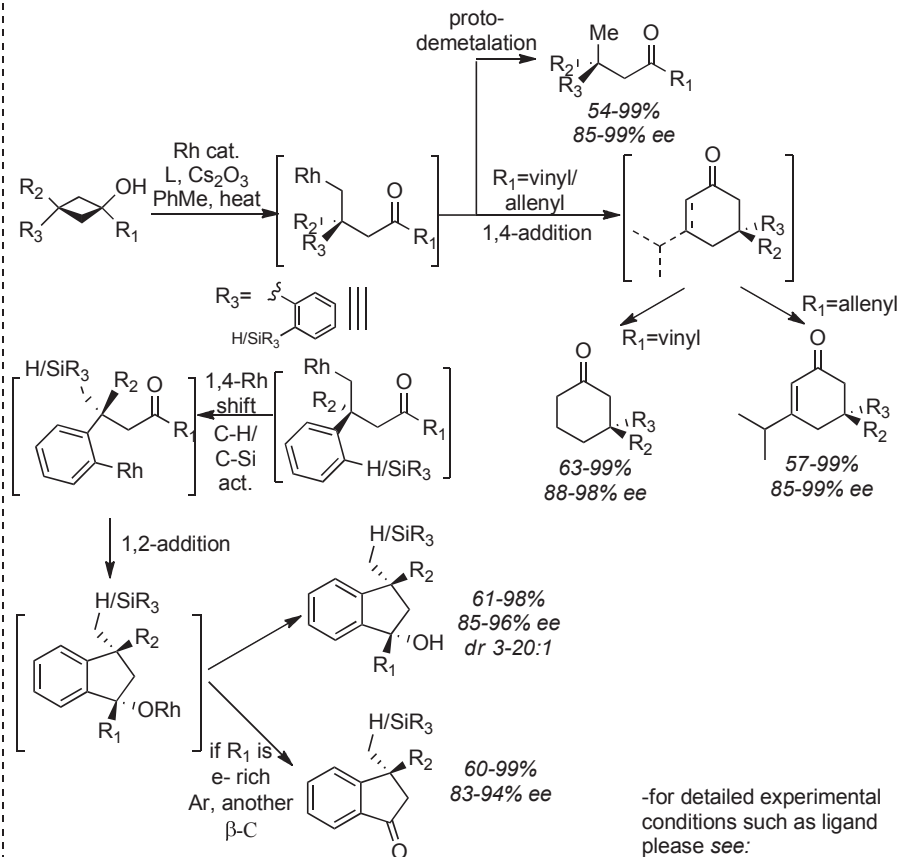
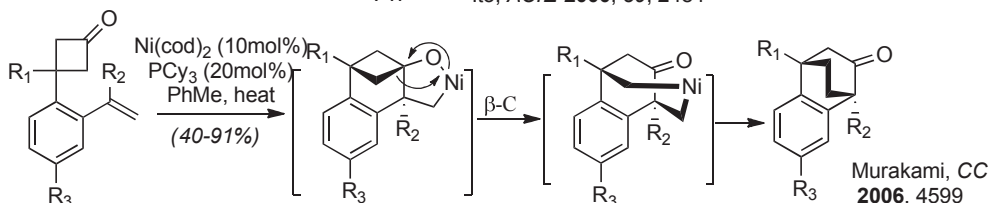
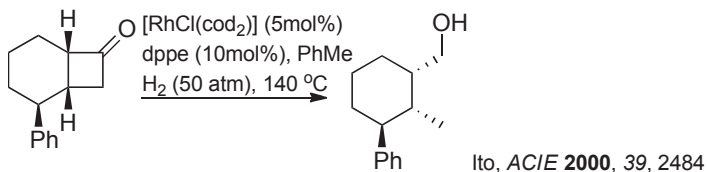


Moore, TL 1992, 33, 7811

more C-C bond activation



Ito, JACS 1997, 119, 9307



-for detailed experimental conditions such as ligand please see:

Cramer, ACIE 2008, 47, 9294; JACS 2010, 132, 5340; Chem. Eur. J. 2010, 16, 3383; ACIE 2009, 48, 6320; Chem. Eur. J. 2009, 15, 12929; SL 2010, 1699; ACIE 2010, 49, 10163.

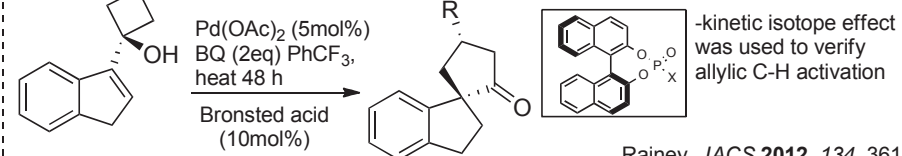
4 to 5 membered ring -for triquinanes see Wiedner GM; for meloscine see Goetz GM

-Baeyer-Villiger of cyclobutanones not included

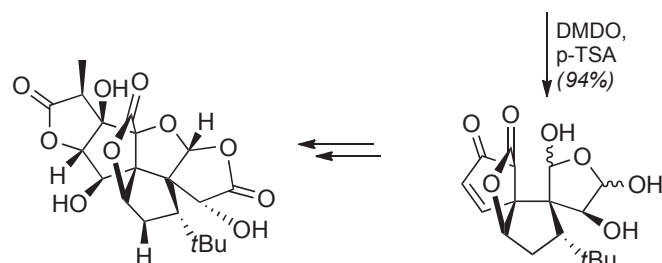
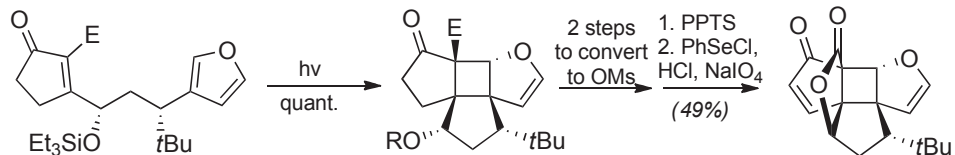
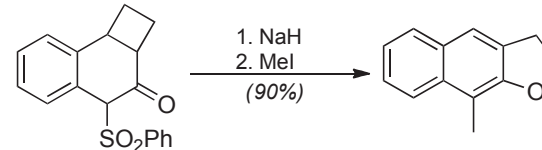
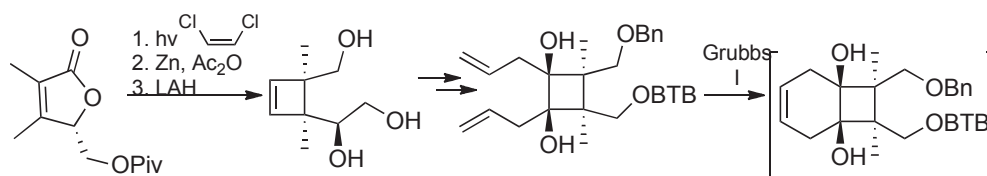
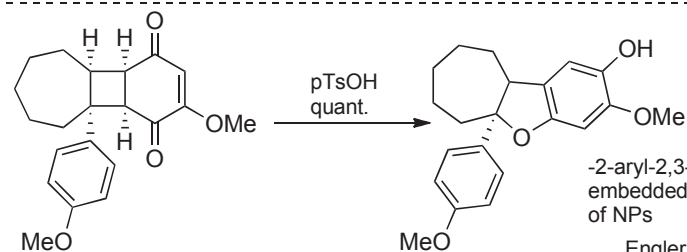
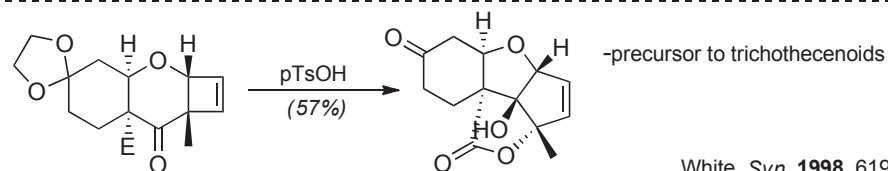
-Ring expansion with CH<sub>2</sub>N<sub>2</sub> of cyclobutanones not included

-for gloiosphone A see Rodriguez "Leo Paquette" GM

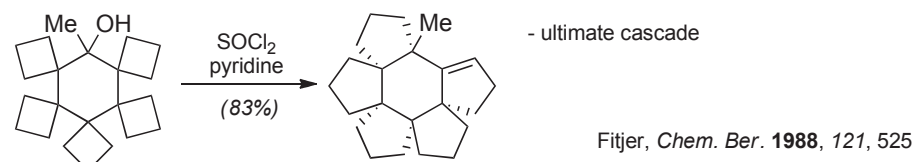
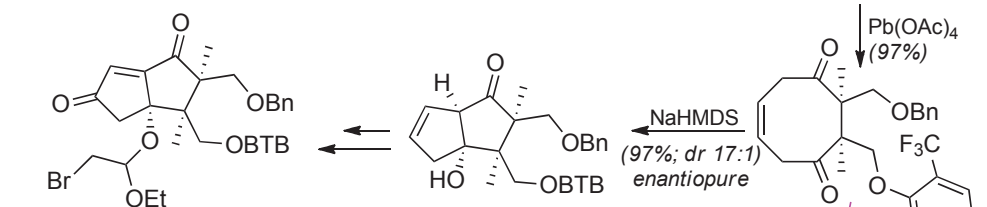
-see "Cyclopentane synthesis" O'Malley GM



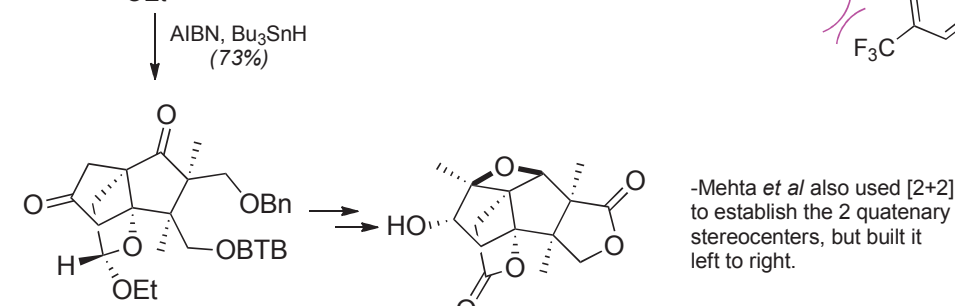
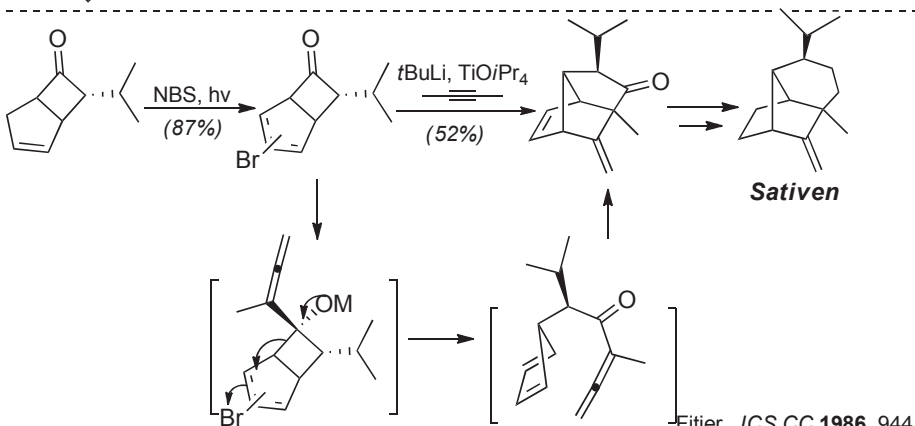
Rainey, JACS 2012, 134, 3615

**Gingkolide B**Crimmins, *JACS* **1999**, 121, 10249Ghera, *TL* **1987**, 28, 709-2-aryl-2,3-dihydrobenzofurans  
embedded in pterocarpan family  
of NPsEngler, *JOC* **1999**, 64,2391

-precursor to trichothecenoids

White, *Syn.* **1998**, 619

- ultimate cascade

Fitjer, *Chem. Ber.* **1988**, 121, 525**(-)-Merrilactone A**Inoue, *ACIE* **2006**, 45, 4843;*JACS* **2003**, 125, 10772-Mehta *et al* also used [2+2]  
to establish the 2 quaternary  
stereocenters, but built it  
left to right.**Sativen**Fitjer, *JCS CC* **1986**, 944



