

JACK E. BALDWIN-SHORT BIO

- ◆ Born in London in 1938.
- ◆ Undergraduate studies at Imperial College, London. Obtained his B.Sc. (1st class) in 1960.
- ◆ Graduate studies at Imperial under the supervision of Nobel laureate, Professor Sir Derek Barton. Structure elucidation of byssochalmic acid using chemical methods. Awarded his Ph.D. in 1964.
- ◆ Appointed assistant lecturer at Imperial College in 1965.
- ◆ 1967-Moved to the US to join Pennsylvania State University as Assistant Professor of Chemistry.
- ◆ 1969-Promoted to Associate Professor.
- ◆ 1970-Joined the chemistry department at MIT.
- ◆ 1971-Promoted to full Professor.
- ◆ March 1972-Returned to the UK as the Daniel Professor of Chemistry at King's College.
- ◆ November 1972-Back to MIT.
- ◆ 1978-Elected Fellow of the Royal Society and appointed Waynflete Professor of Chemistry at the University of Oxford, UK.
- ◆ Held the Waynflete chair at Dyson Perrins Laboratory and then at the Chemistry Research Laboratory for 27 years until his retirement in 2005.
- ◆ 1997. Awarded a knighthood for his contributions to organic chemistry.
- ◆ Still maintains an active group at Oxford University.
- ◆ Awarded many prestigious awards and prizes.
- ◆ Published more than 600 papers. Second most cited author in Chemical Communications. Author of their most cited publication ever, "Rules for Ring Closure".

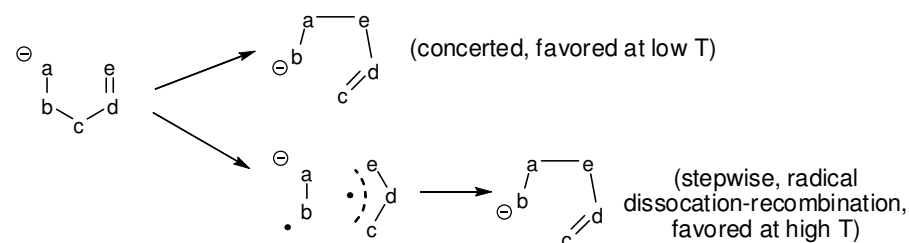


AREAS OF INVESTIGATION

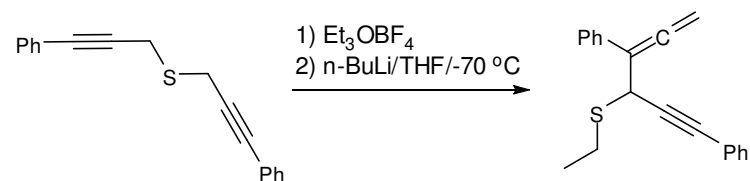
- ◆ Biomimetic synthesis of natural products, especially sponge alkaloids and fungal metabolites.
- ◆ Development of synthetic methodology.
- ◆ Chemical and biological studies on the biosynthesis of beta-lactam antibiotics.
- ◆ Parallel synthesis methodology.

REARRANGEMENTS

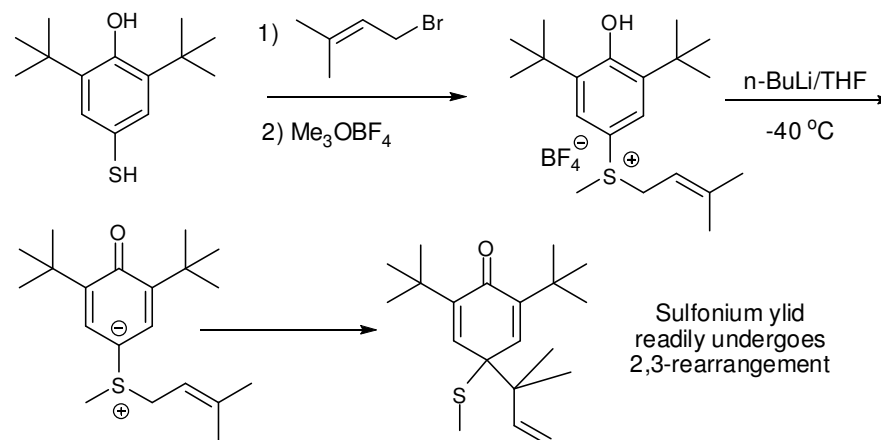
>>> 2,3-Sigmatropic rearrangements



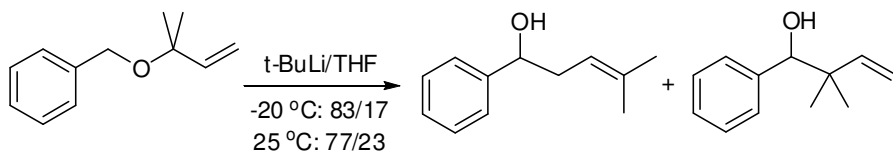
Sulfonium ylids, *Chem. Commun.* **1968**, 18, 1083-1084



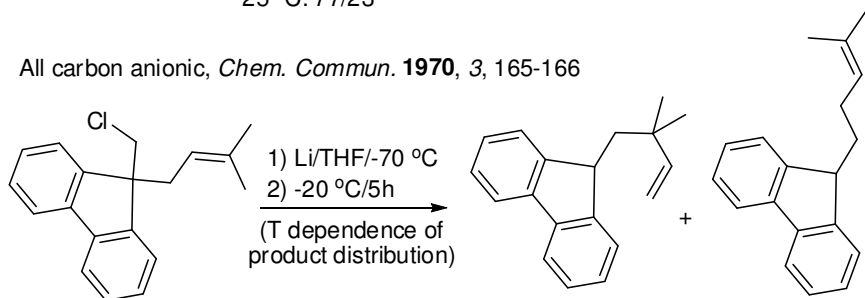
Sulfonium ylids, *Chem. Commun.* **1971**, 7, 359



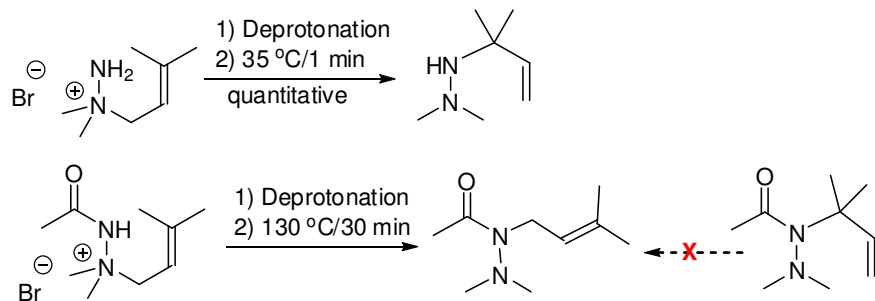
Allylic ether anions, *Tetrahedron Lett.* **1970**, 5, 353-356



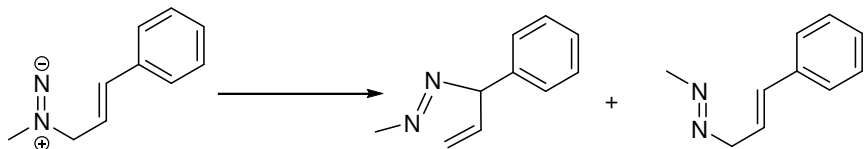
All carbon anionic, *Chem. Commun.* **1970**, 3, 165-166



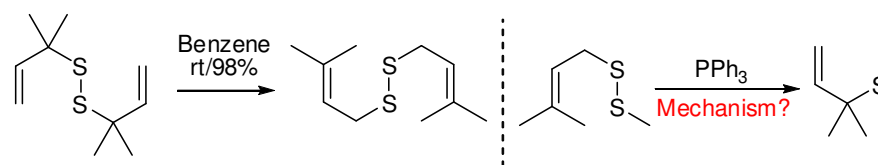
N-Ammonio-amidates, *Chem. Commun.* **1970**, 1, 31-32



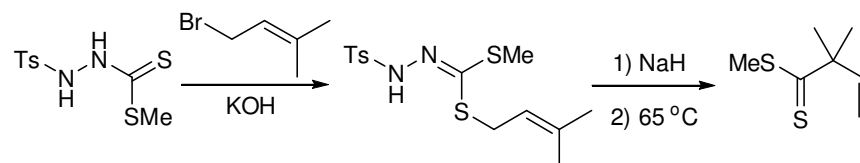
Diazenes, *J. Am. Chem. Soc.* **1971**, 93, 788-789



Allylic disulfides, *J. Am. Chem. Soc.* **1971**, 93, 6307-6308

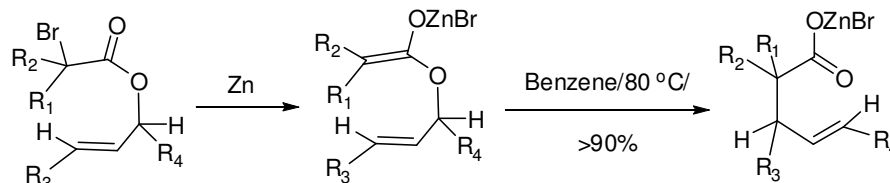


Nucleophilic carbenes, *Chem. Commun.* **1972**, 6, 354-355

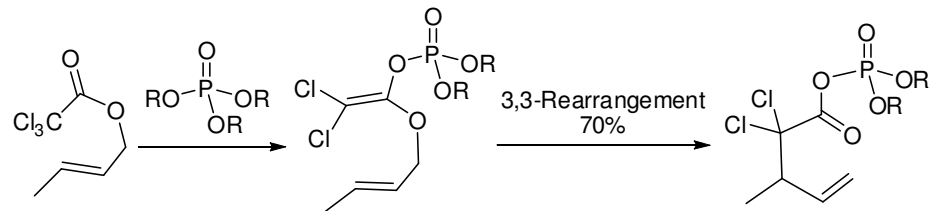


>>> 3,3-Sigmatropic rearrangements

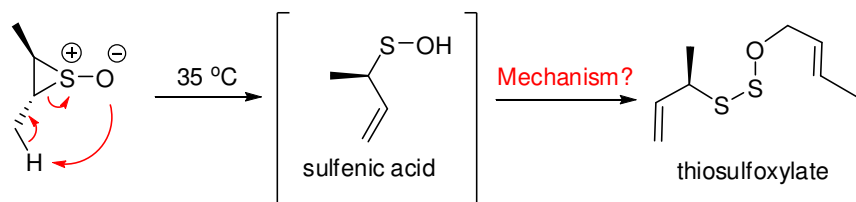
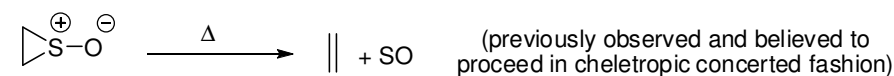
Reformatsky-Claisen, *Chem. Commun.* **1973**, 4, 117-118



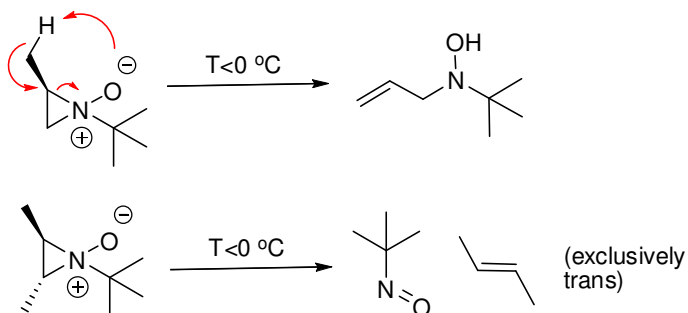
Enol phosphate variant, *Chem. Commun.* **1973**, 4, 117-118



>>> Rearrangements of strained dipolar species

Episulfoxides, *J. Am. Chem. Soc.* **1971**, 93, 2810-2812

At high T (>150 °C) olefin products are observed. Given that mixtures of cis and trans 2-butene are obtained, SO loss likely goes through radical pathway (T-dependent).

Aziridine-N-oxides, *J. Am. Chem. Soc.* **1971**, 93, 4082-4084

Multisubstituted aziridine oxide gives rise to alternative products. Concerted or radical?

BALDWIN'S RULES FOR RING CLOSURE

>>> Primary literature

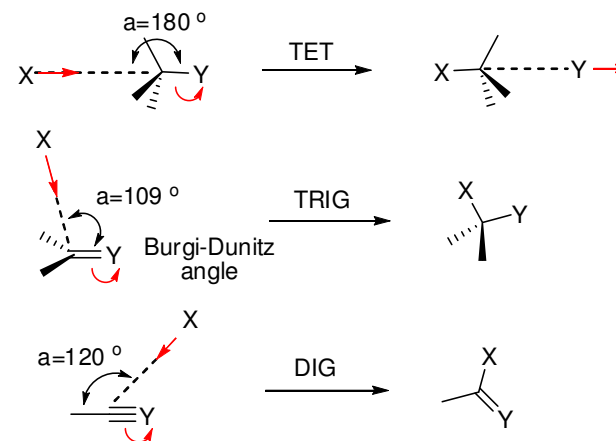
Chem. Commun. **1976**, 18, 734-736*Chem. Commun.* **1976**, 18, 736-738*Chem. Commun.* **1977**, 3, 77*Chem. Commun.* **1977**, 7, 233-235*J. Org. Chem.* **1977**, 42, 3846-3852*Tetrahedron* **1982**, 38, 2939-2947

◆ Rules apply to cyclic transition states leading to ring formation or intramolecular group transfer. Nucleophilic, radical and cationic processes follow the rules, but not electrocyclic reactions!

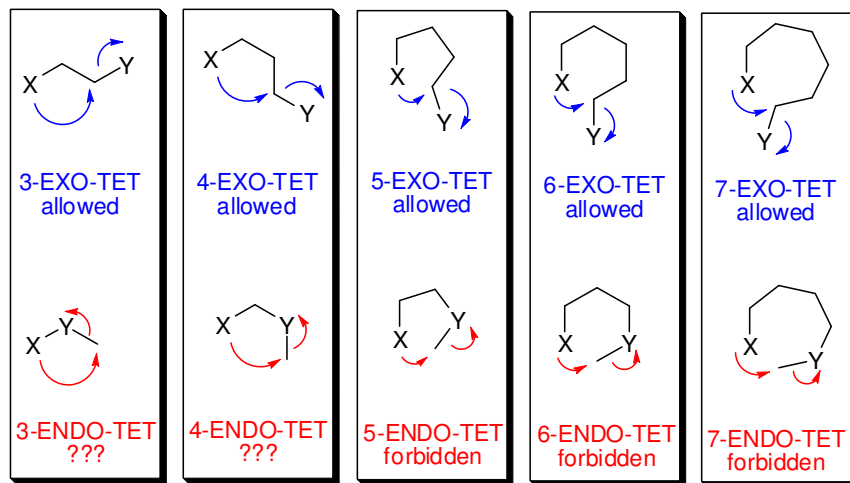
◆ Rules only apply to first row elements-"violations" reported for larger atoms (S, Si, etc) due to larger atomic radii/orbital size/bond lengths.

◆ EXO process-breaking bond positioned exocyclic to smallest formed ring.
 ENDO process-breaking bond positioned endocyclic to smallest formed ring.

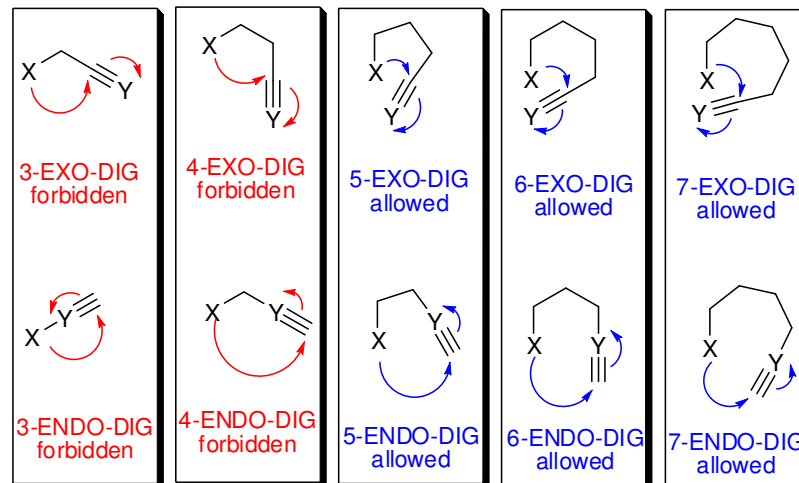
◆ The rationale lies in the stereochemical requirements of the transition state (distances/ angles) and ability of the system to achieve the required trajectory.



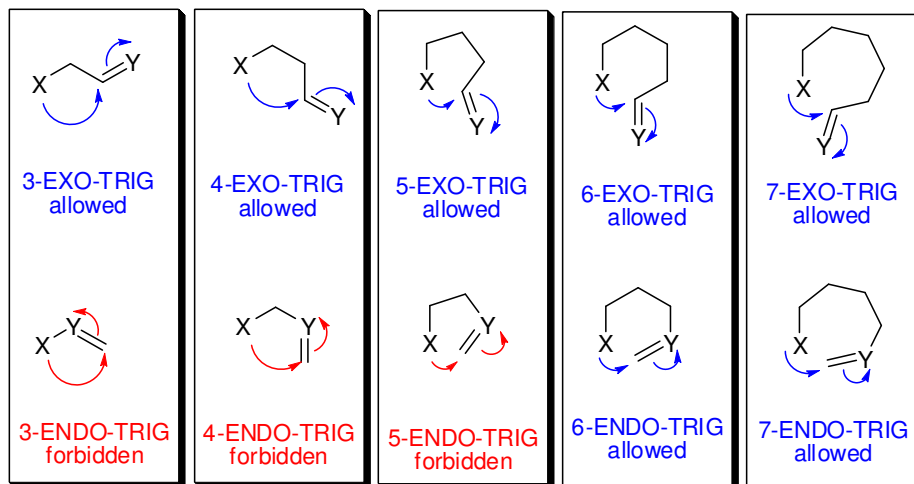
>>> Tetrahedral Systems (TET)



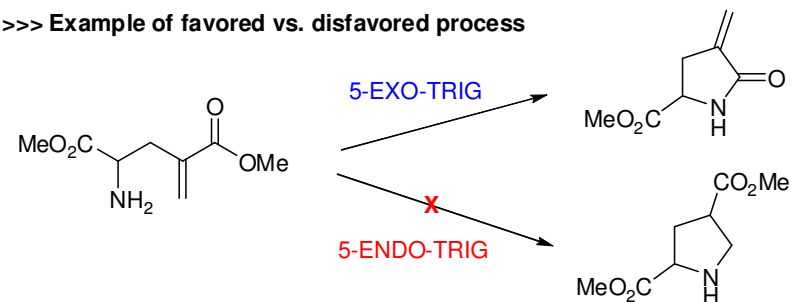
>>> Digonal Systems (DIG)



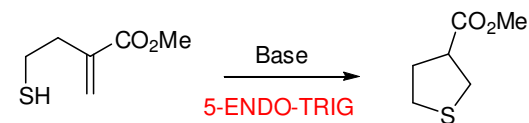
>>> Trigonal Systems (TRIG)



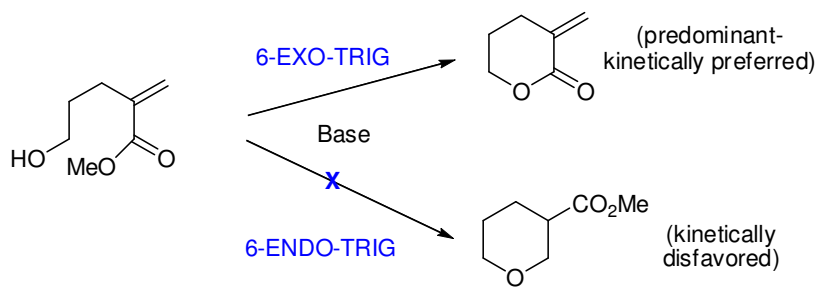
>>> Example of favored vs. disfavored process



>>> Example of exception for second row element:

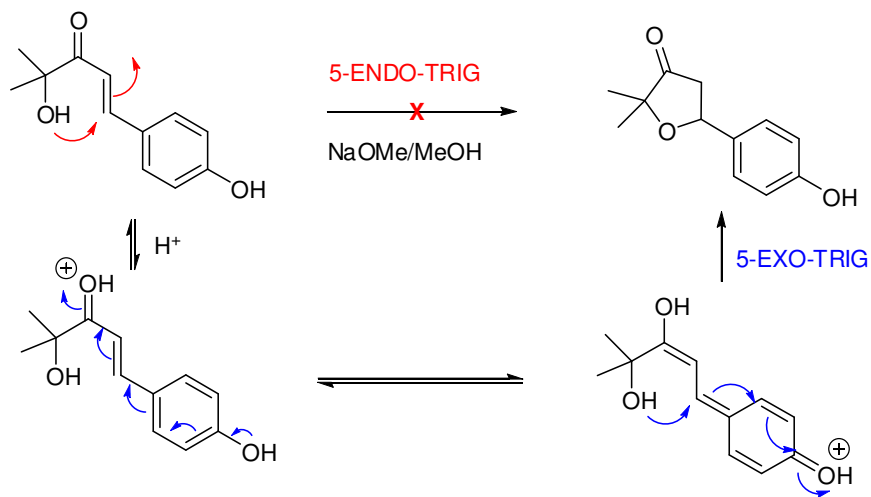


>>> Example of competing allowed processes

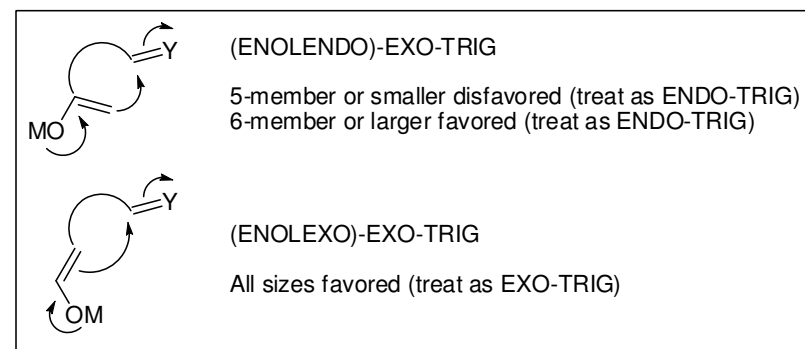
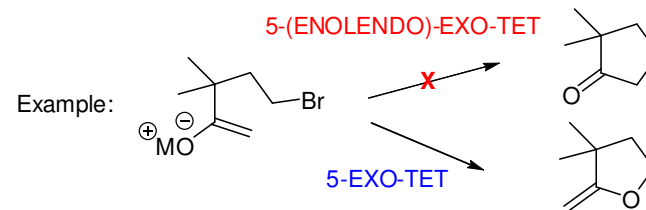
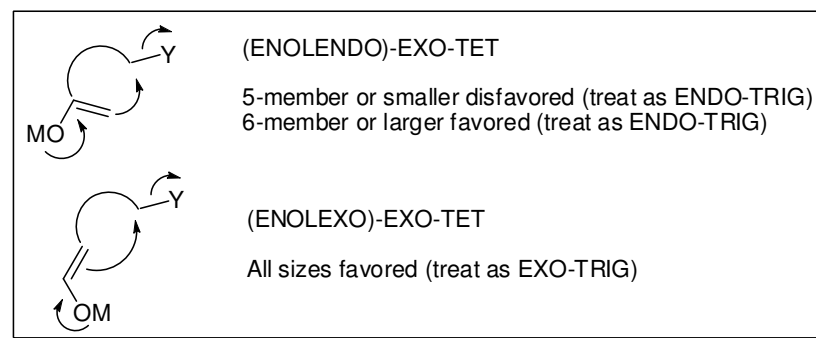


- ◆ In cases where an EXO and an ENDO process compete, EXO appears to be predominant for TRIG systems whereas ENDO is predominant for DIG systems.
- ◆ In many cases kinetics rather than thermodynamics dictate the outcome of the cyclization reaction.

>>> Turning a forbidden into an allowed cyclization process

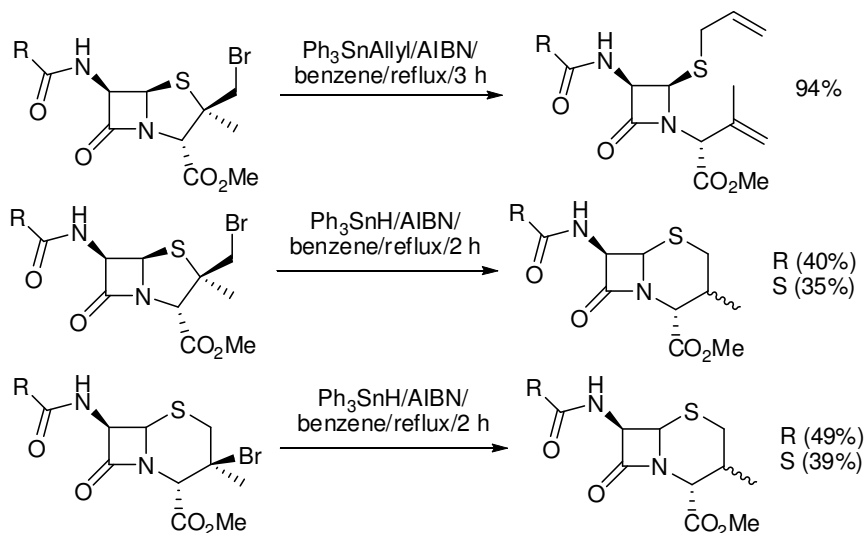


>>> Ring closures involving enolates

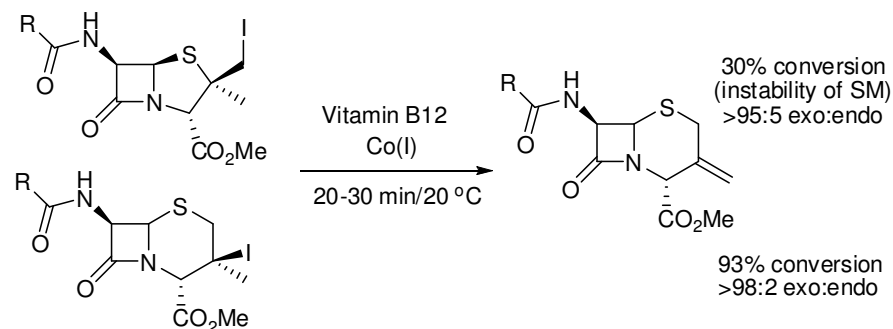


BETA-LACTAM TRANSFORMATIONS

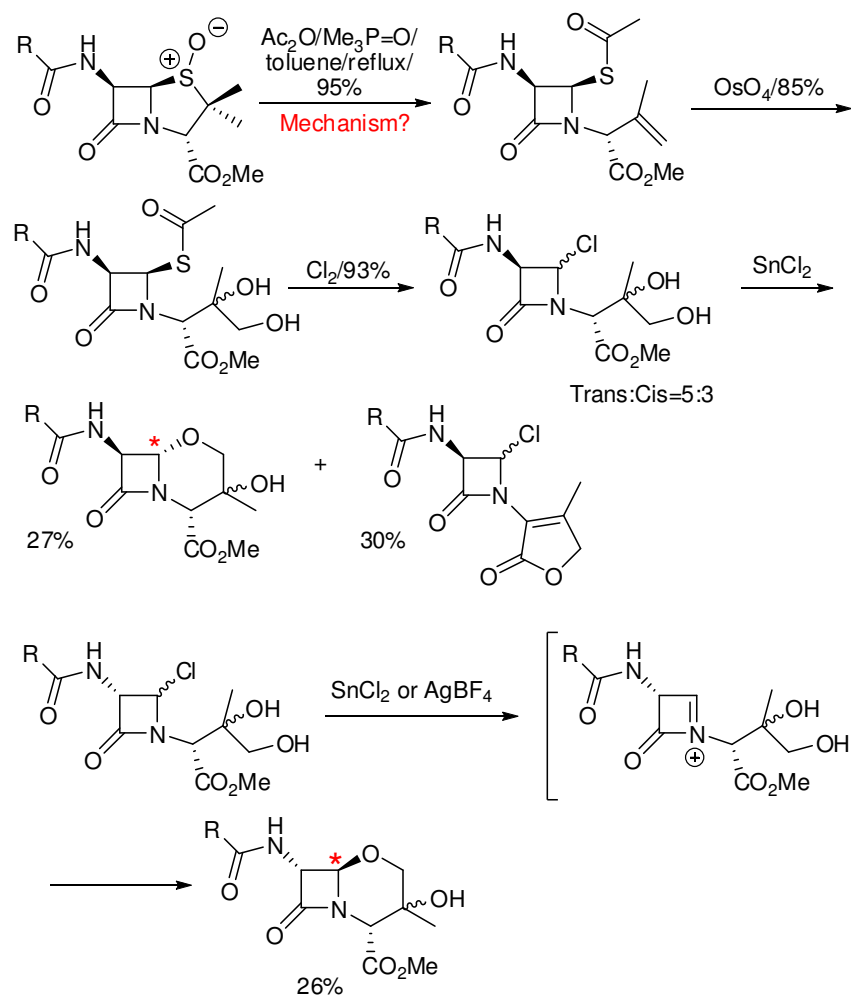
>>> Ring expansion of penicillins to cephalosporins

Chem. Commun. **1987**, 2, 104-106

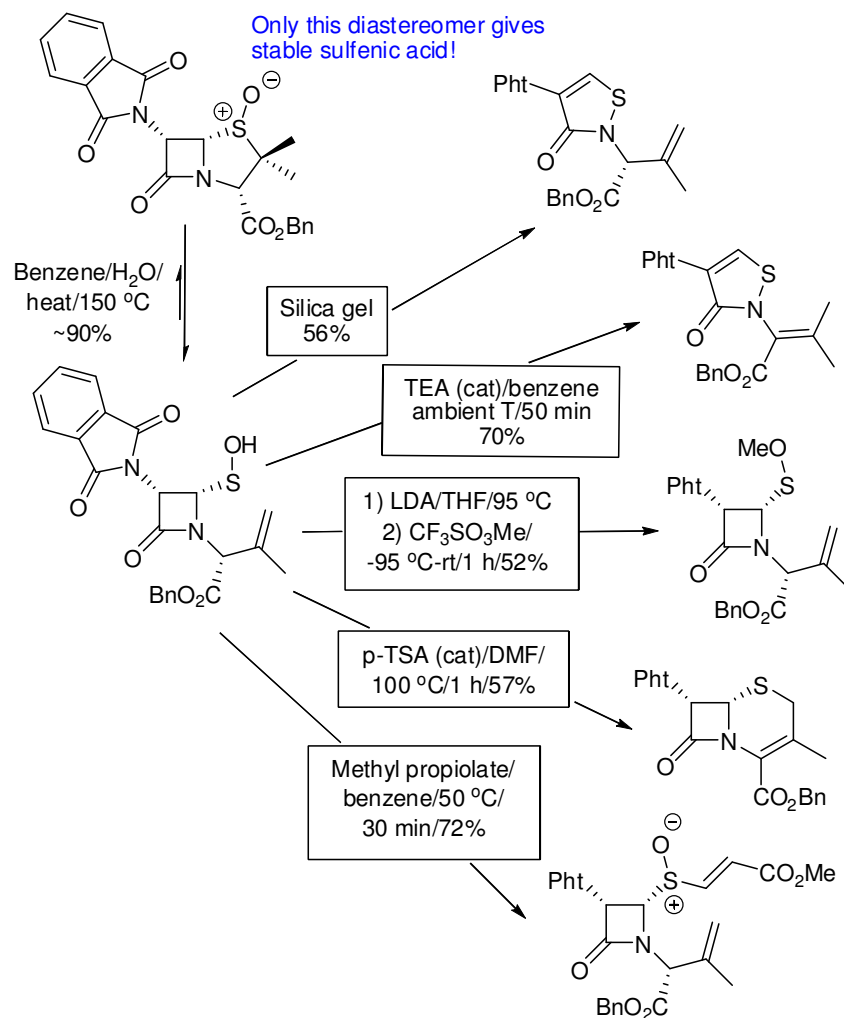
>>> Ring expansion of penicillins to 3-exomethylene cephalosporins

Tetrahedron Lett. **1991**, 32, 7093-7096

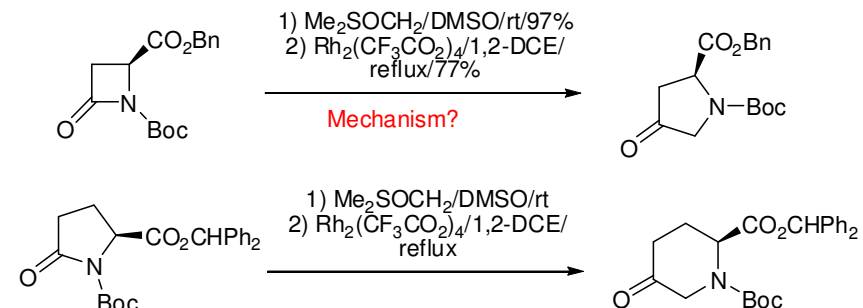
>>> Conversion of penicillin sulfoxides into 6,7-epi-1-oxocephams:

Tetrahedron **1980**, 36, 1628-1630

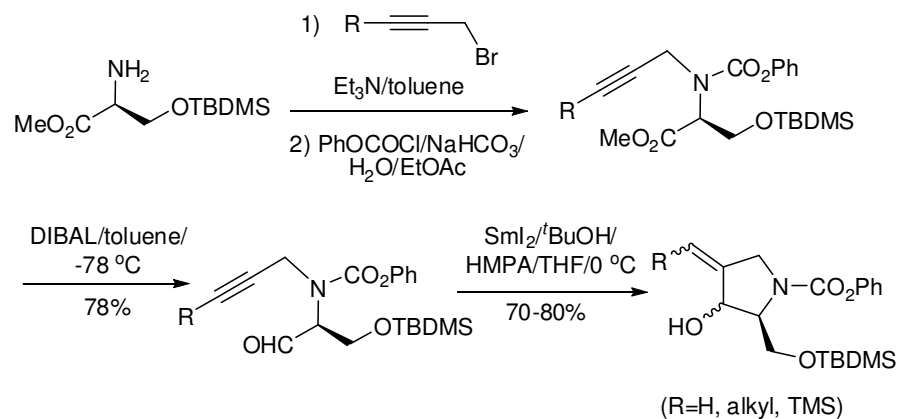
>>> Conversion of penam sulfoxides to stable azetidinone sulfenic acids

Tetrahedron Lett. **1998**, 39, 6983-6986

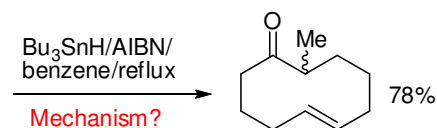
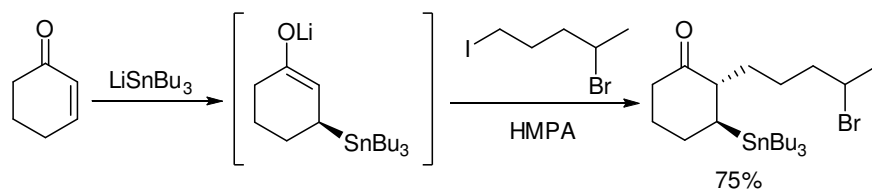
>>> Conversion of n-membered lactams to (n+1)-membered oxonitrogen heterocycles

Chem. Commun. **1993**, 18, 1434-1435

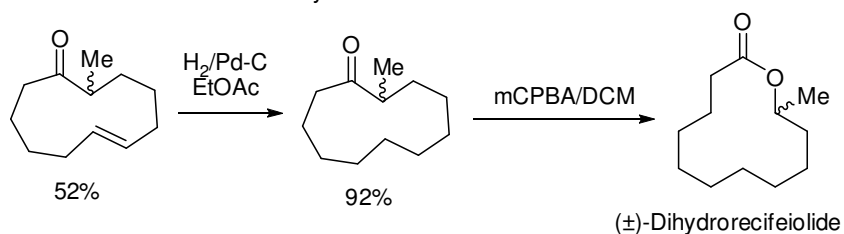
SYNTHETIC METHODOLOGY

>>> Synthesis of substituted pyrrolidines by Sml₂-mediated ring closure*Tetrahedron* **1994**, 50, 9425-9438*Tetrahedron* **1994**, 50, 9411-9424

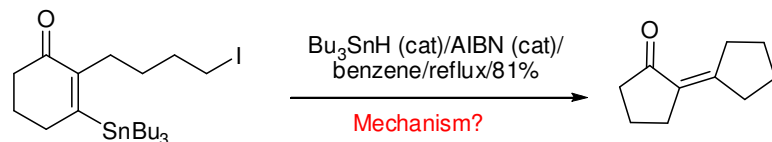
>>> Carbocyclic ring expansions via free radical pathways

Chem. Commun. **1988**, 21, 1404-1406*Tetrahedron* **1989**, 45, 909-922*Tetrahedron* **1991**, 47, 6795-6812*Tetrahedron* **1992**, 48, 3385-3412

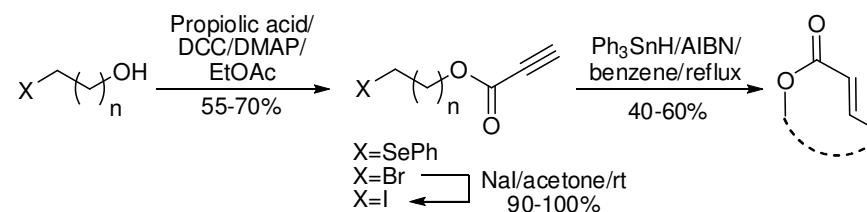
Further refinement to macrocyclic lactones



Another synthetically useful variant



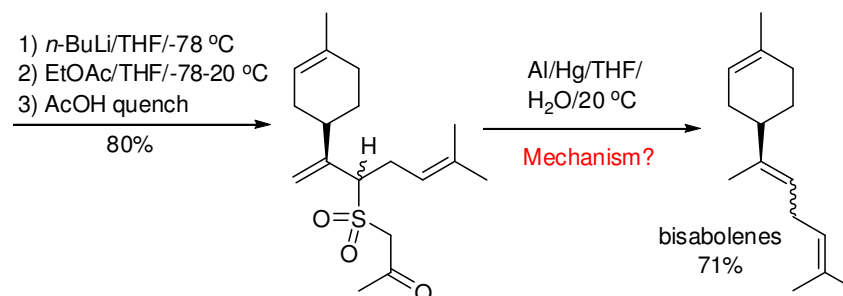
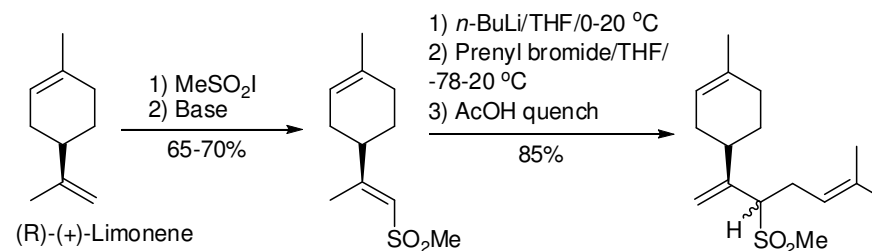
>>> Free radical macrocyclization via propiolate esters

Tetrahedron **1992**, 48, 3413-3428

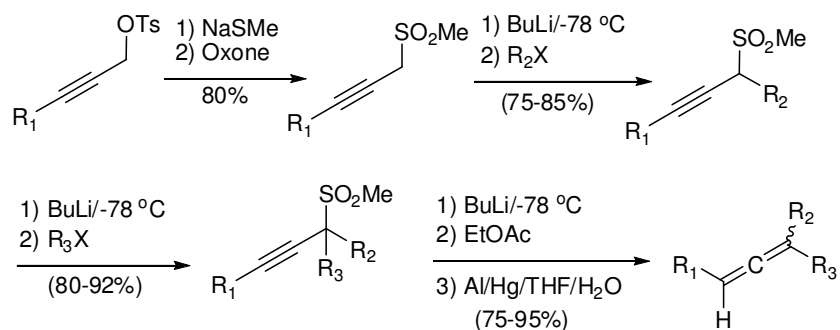
n=9-11: 14-16 membered trans a,b-unsaturated lactones

n<9: Reduction at radical center prevents cyclization

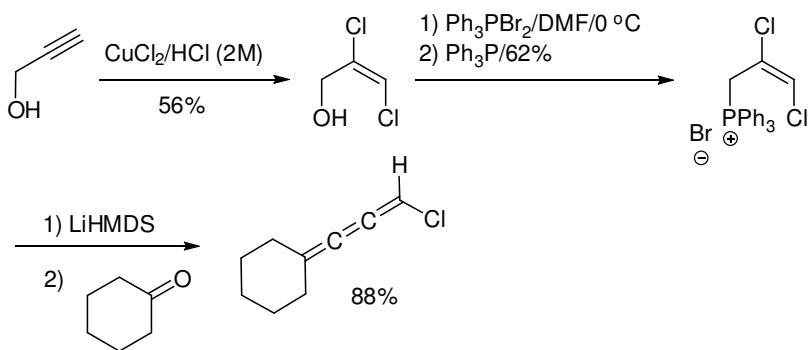
>>> C-C Coupling of terminal alkenes via sulfonylation-alkylation-desulfinylation sequence

Chem. Commun. **1988**, 11, 702-704

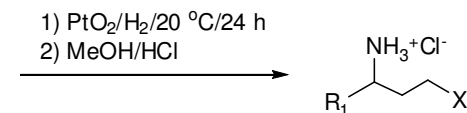
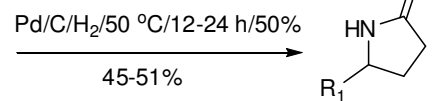
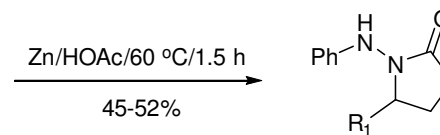
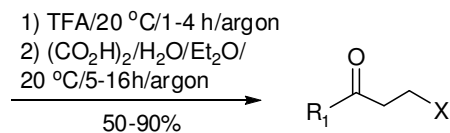
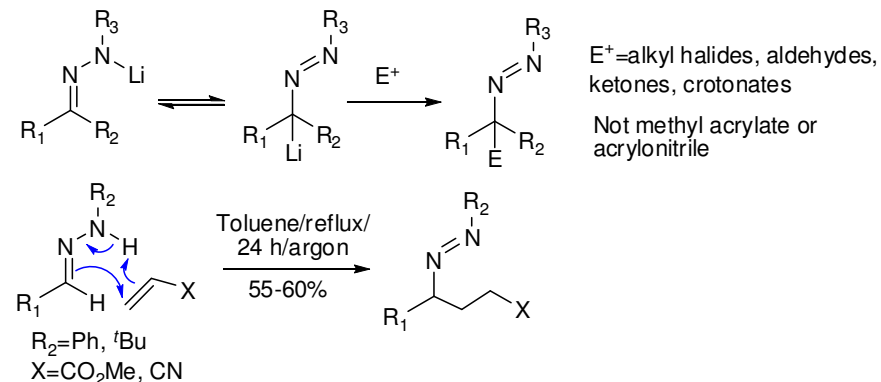
>>> Synthesis of trisubstituted allenes

Tetrahedron Lett. **1995**, *36*, 7925-7928(R₁, R₂, R₃=alkyl, alkenyl, benzyl, etc)

>>> Preparation of chloro-3-cumulenes

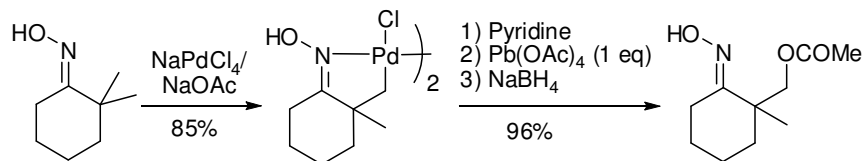
Chem. Commun. **1984**, *3*, 152-153

Mechanism?

>>> Thermal ene reaction of aldehydes and ^tbutyl- or phenylhydrazones*Chem. Commun.* **1984**, *16*, 1095-1096*Tetrahedron* **1986**, *42*, 4247-4252

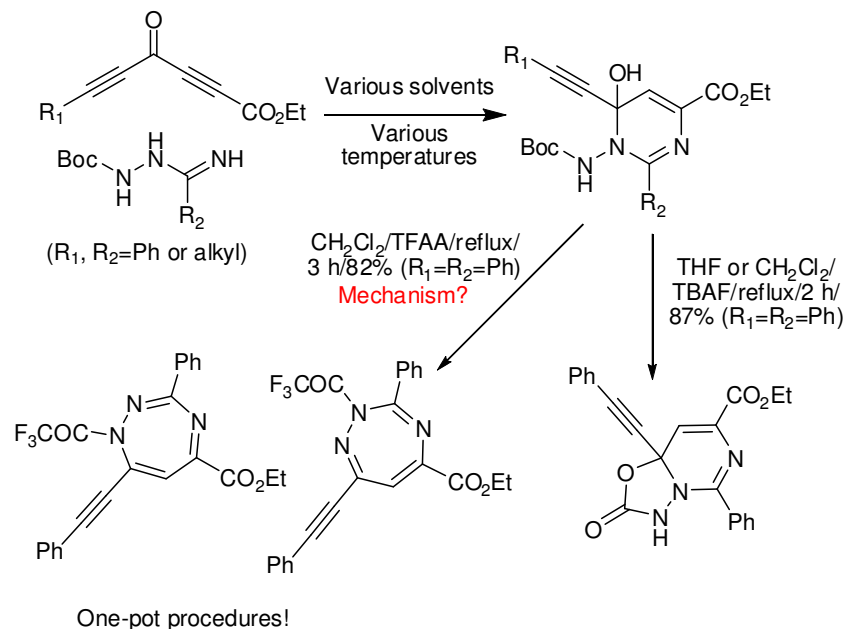
>>> Functionalization of unactivated methyl groups through organopalladation

Chem. Commun. **1985**, 3, 126-127
Tetrahedron **1985**, 41, 699-711



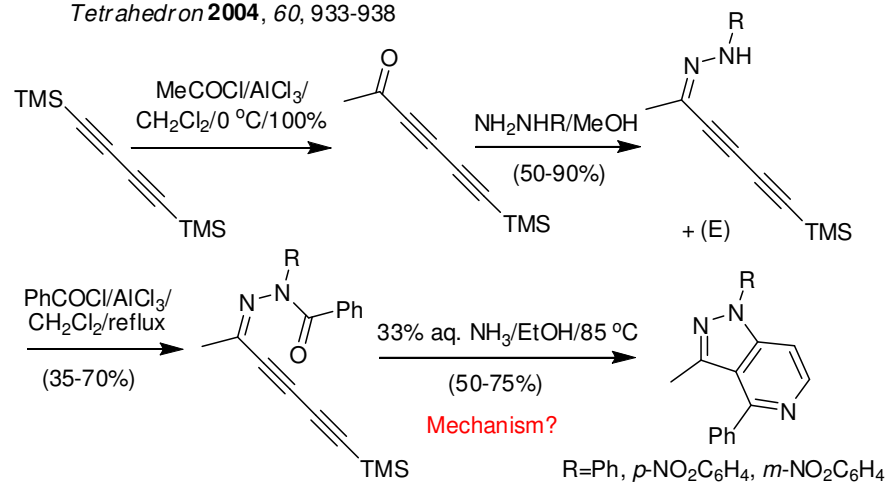
>>> Formation of 1,2,4-triazepines and oxatriazaindenones from bis-acetylenic ketones

J. Org. Chem. **2005**, 70, 3307-3308



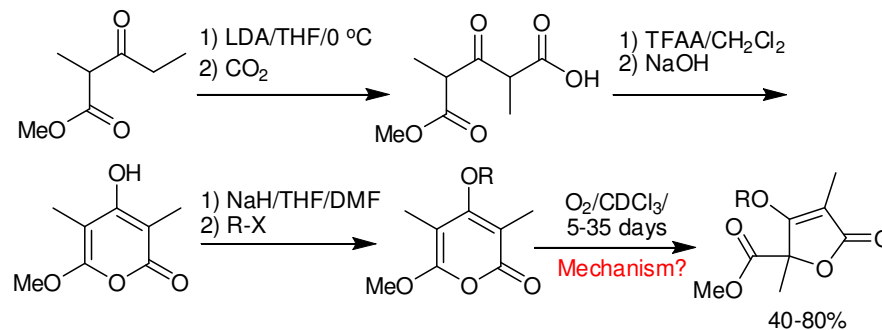
>>> Formation of 1H-pyrazolo[4,3-c]pyridines from bis-acetylenic-N-benzoyl-hydrazones

Tetrahedron **2004**, 60, 933-938



>>> Oxidative Rearrangement of 6-Methoxy-2-pyrone

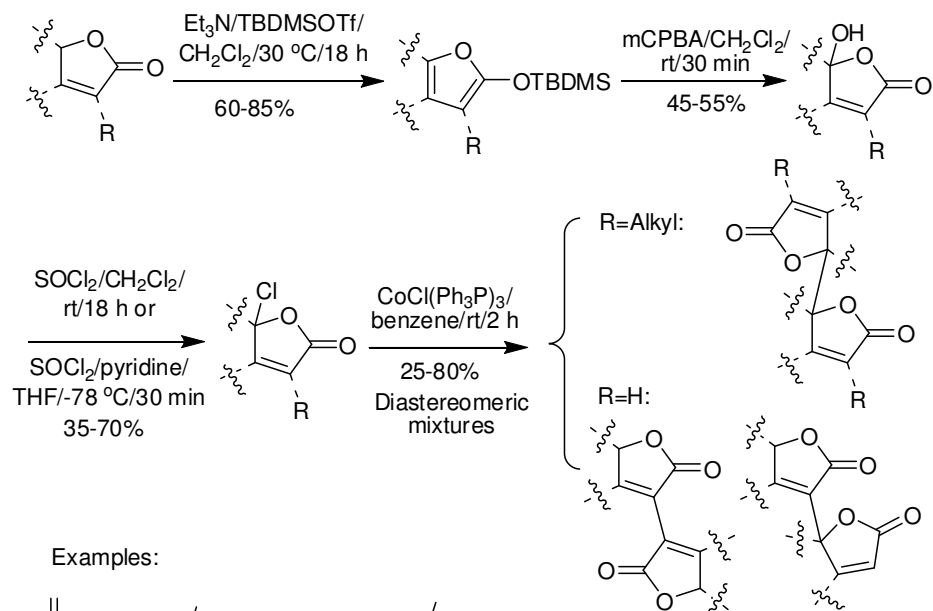
Org. Lett. **2005**, 7, 3705-3707



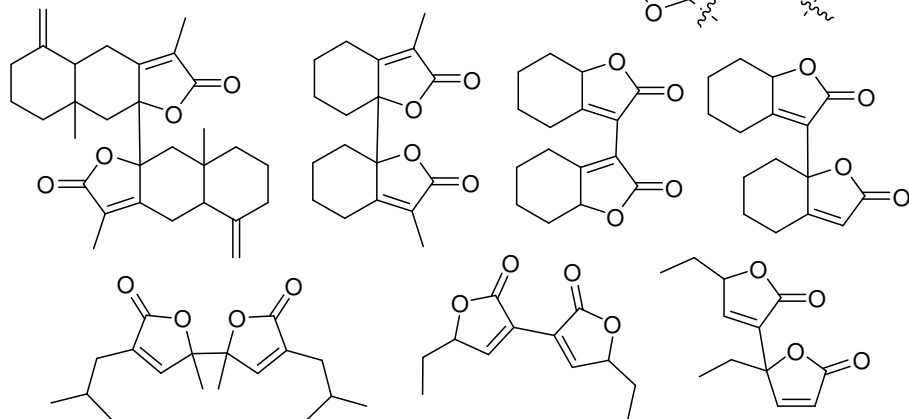
Baldwin invokes a second molecule to explain product formation!

>>> Dimerization of butenolides

Org. Lett. **2003**, *5*, 3049-3052
J. Org. Chem. **2004**, *69*, 9100-9108
Tetrahedron Lett. **2005**, *46*, 4633-4637

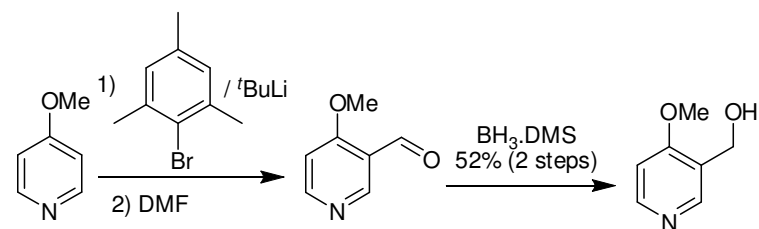
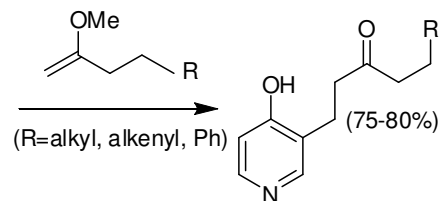
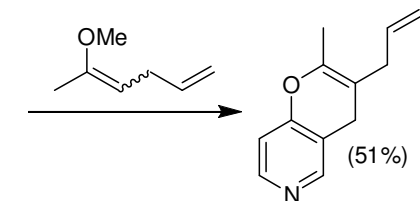
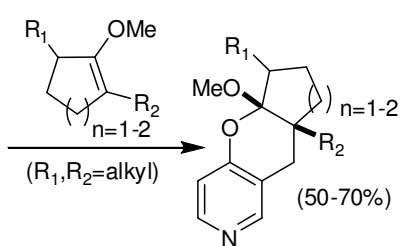
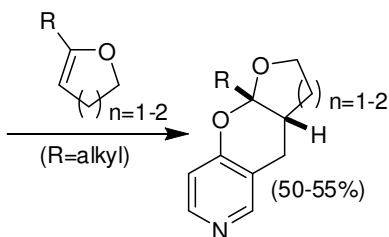
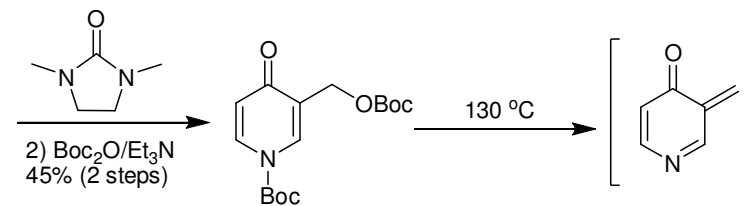


Examples:

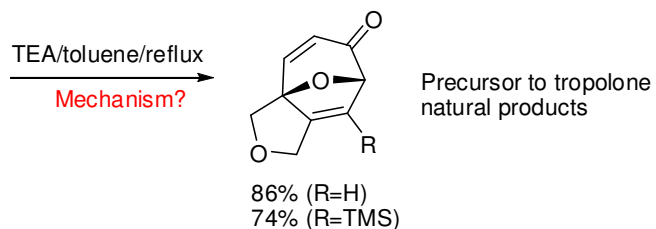
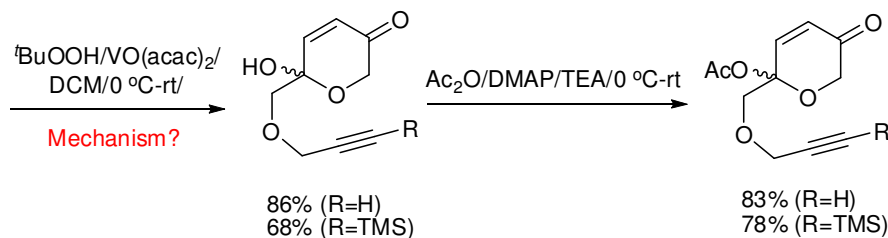
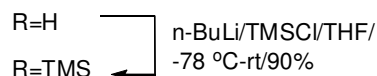
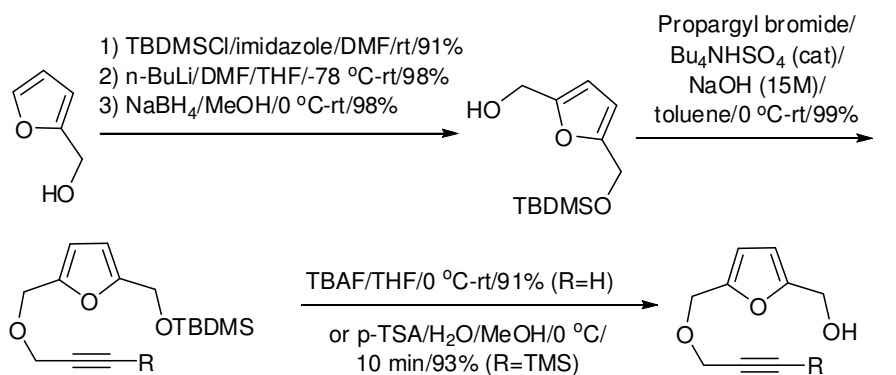


>>> Formation of substituted pyrano[3,2-c]pyridines via Diels-Alder rxn of 3-methylenepyridin-4-ones:

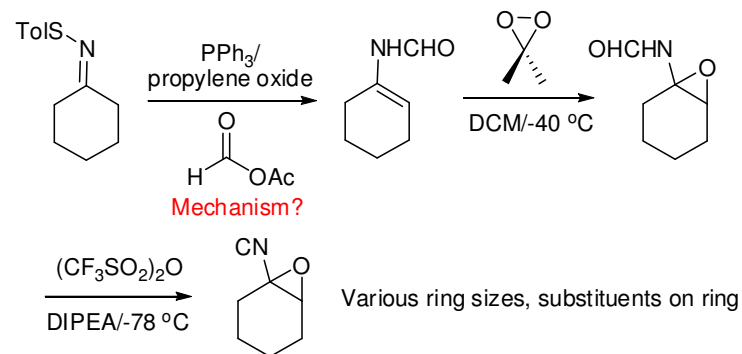
Tetrahedron Lett. **2006**, *47*, 39-41

1) (TMS)₂S/NaOMe/

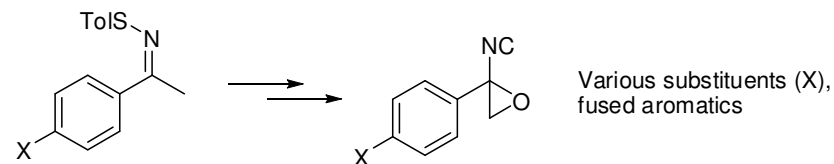
No rxn with simple alkenes

>>> Synthesis of oxa-tricyclo[5.3.1.0^{1,5}]undecanones*Tetrahedron* **2005**, *61*, 3025-3032

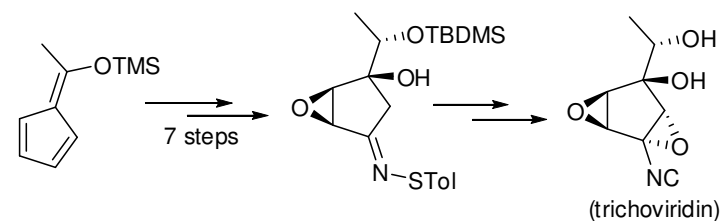
>>> Preparation of epoxyisocyanides from thiooximes

Tetrahedron Lett. **1990**, *31*, 2051-2054*Tetrahedron Lett.* **1990**, *31*, 2047-2050

Aromatic exo-epoxide variant

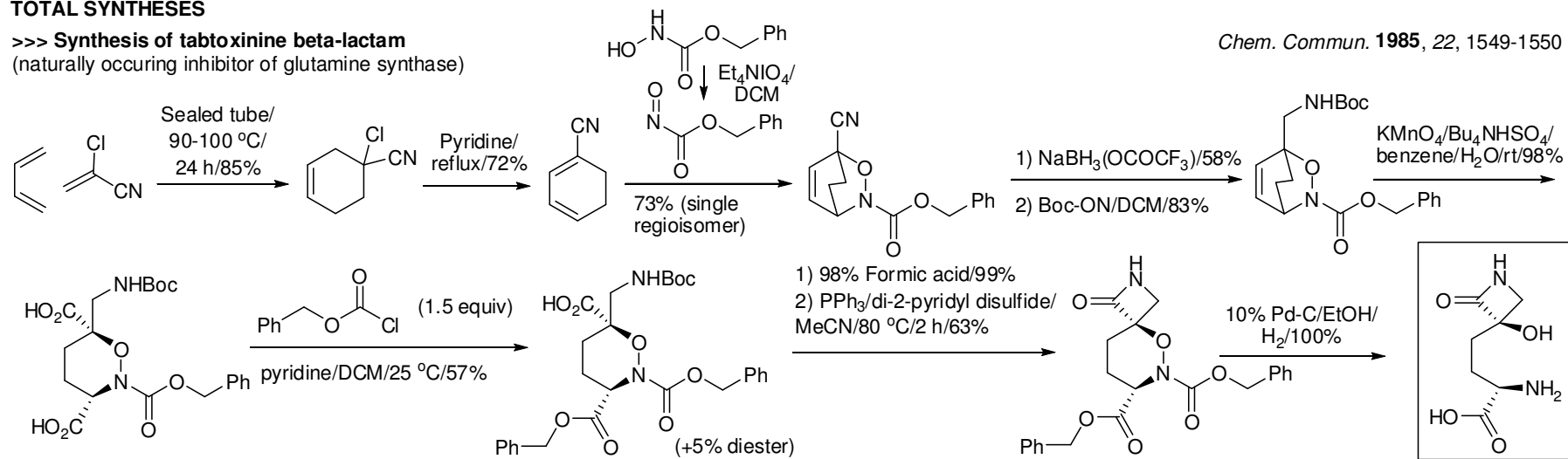


Application in the total synthesis of trichoviridin

Chem. Commun. **1996**, *1*, 41-42

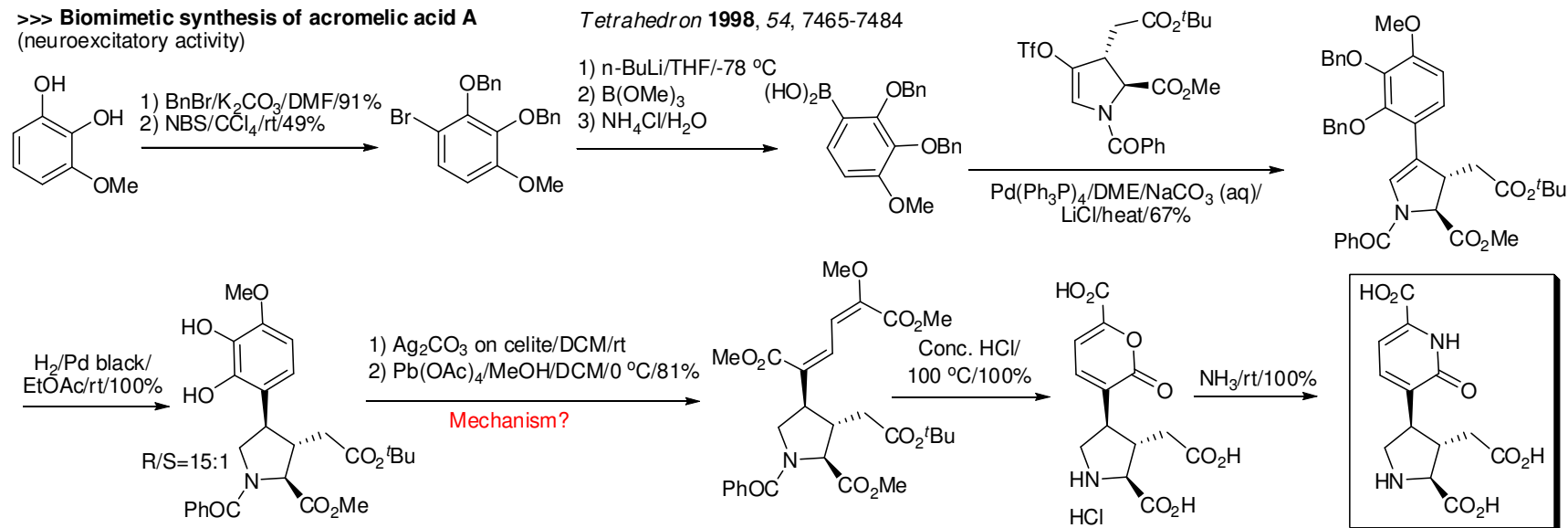
TOTAL SYNTHESSES

>>> **Synthesis of tabtoxinine beta-lactam**
(naturally occurring inhibitor of glutamine synthase)



>>> **Biomimetic synthesis of acromelic acid A**
(neuroexcitatory activity)

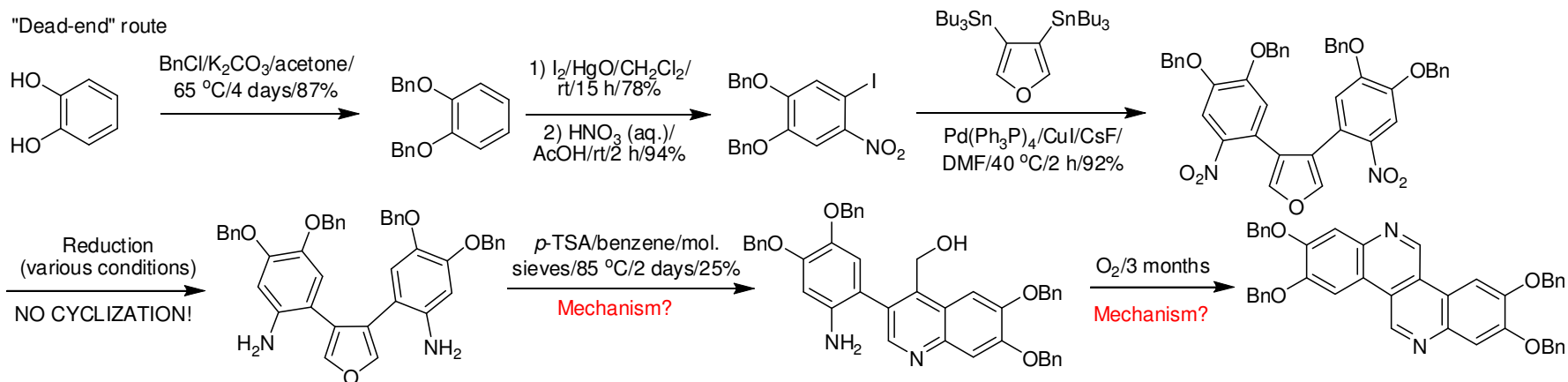
Tetrahedron 1998, 54, 7465-7484



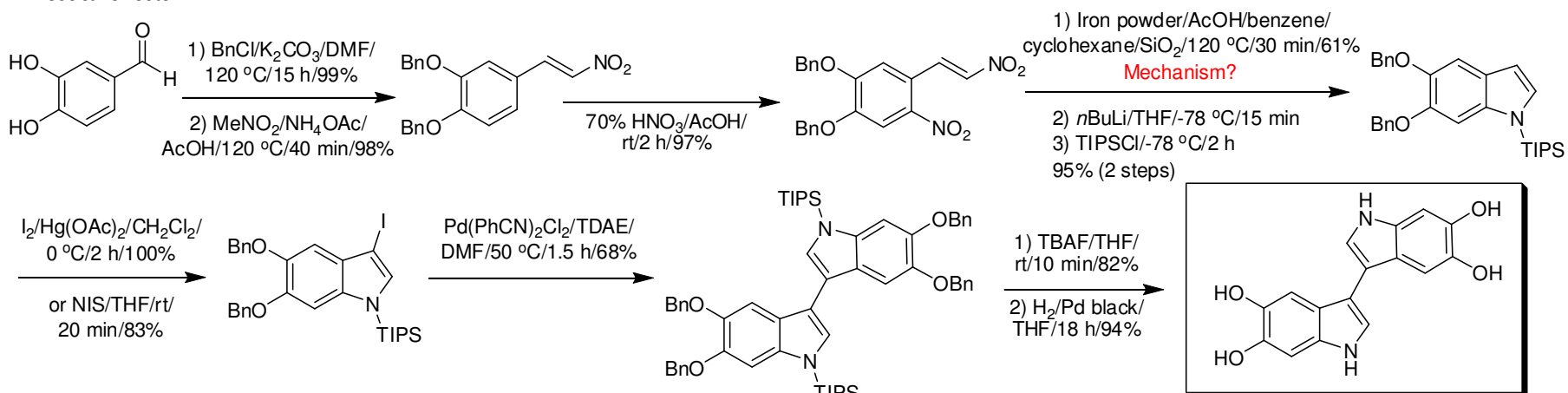
>>> **Synthesis of 5,5',6,6'-tetrahydroxy-3,3'-biindolyl**
(antioxidant from beetroot)

Tetrahedron **2004**, *60*, 3695-3712

"Dead-end" route

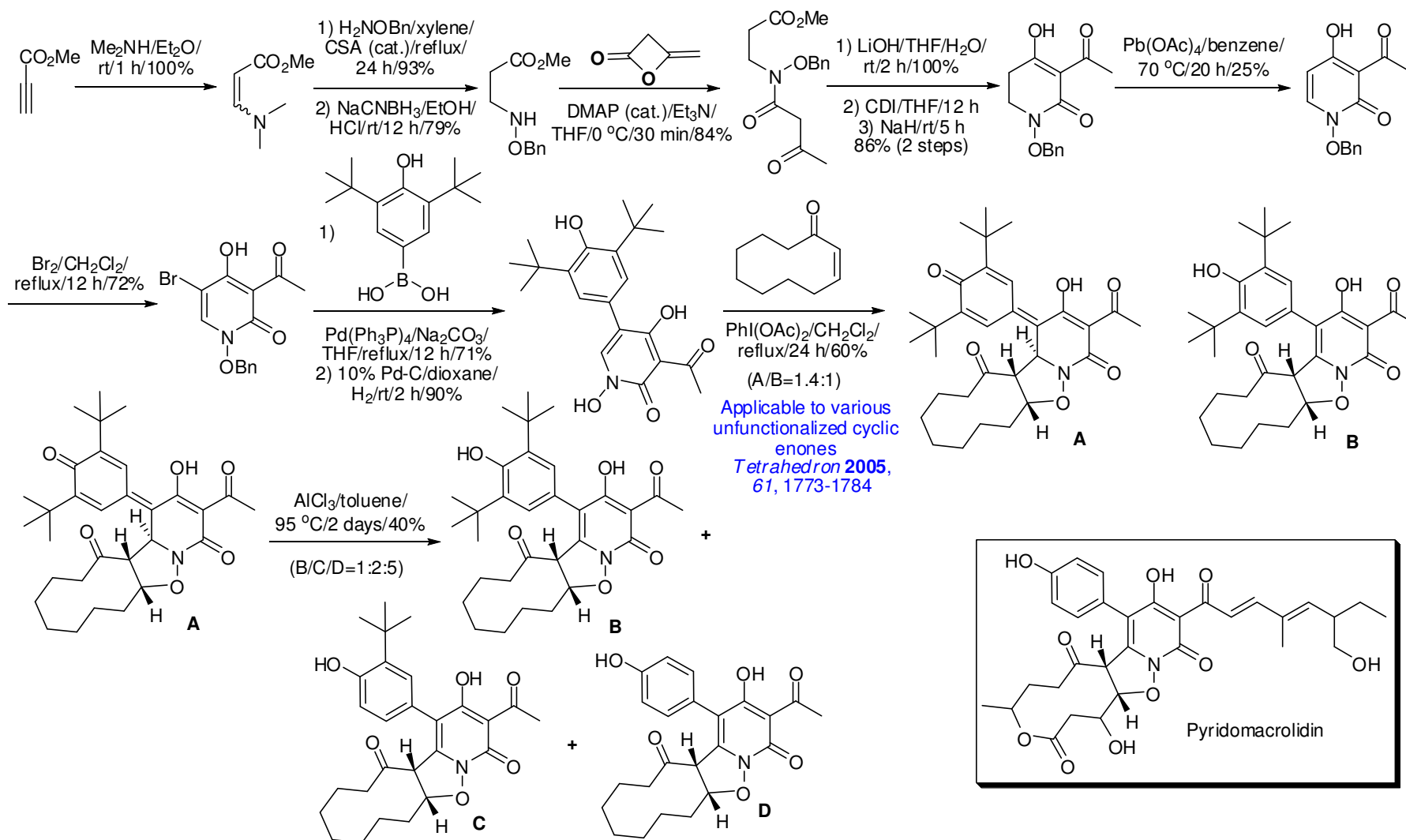


Productive route



>>> Studies towards a biomimetic synthesis of pyridomacrolidin (protein tyrosine kinase inhibitor)

Org. Lett. **2003**, *5*, 2351-2354
Tetrahedron **2006**, *62*, 4603-4614



>>> Biomimetic synthesis of (+)-Panepophenanthrin (novel inhibitor of the ubiquitin-activating enzyme)

Org. Lett. **2003**, *5*, 2987-2988
Tetrahedron **2006**, *62*, 9892-9901

