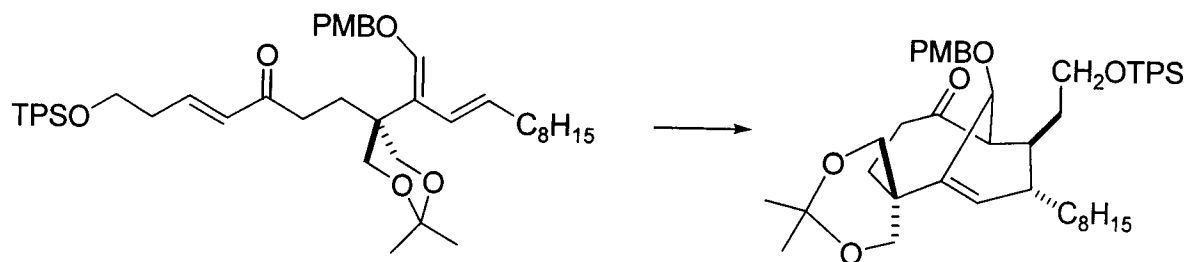
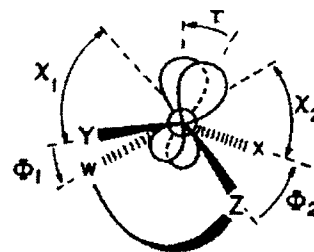
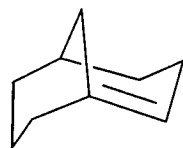


Bridgehead Alkenes and the Type 2 Intramolecular Diels-Alder Reaction

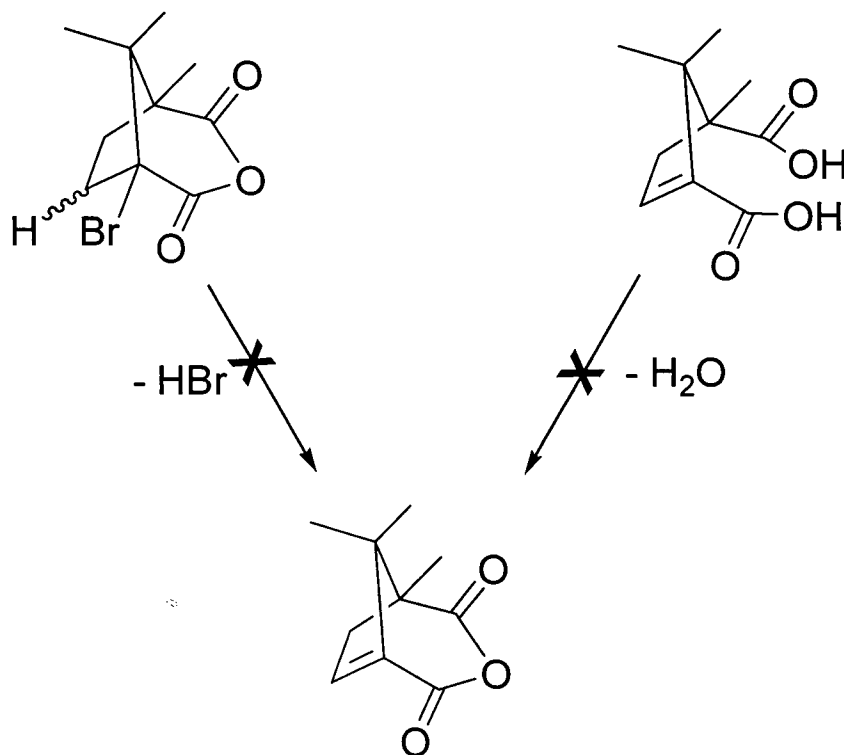
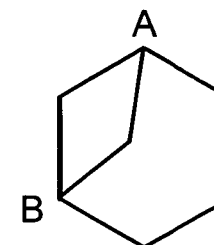
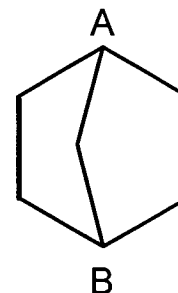


Justin Montgomery

August 14, 2001

Bredt's Rule

- “On the basis of our conceptions of the positions of atoms in space, in the systems of the camphane and pinane series, as well as in similarly constituted compounds, a carbon double bond cannot occur at the branching positions A and B of a carbon bridge (the bridgeheads).”

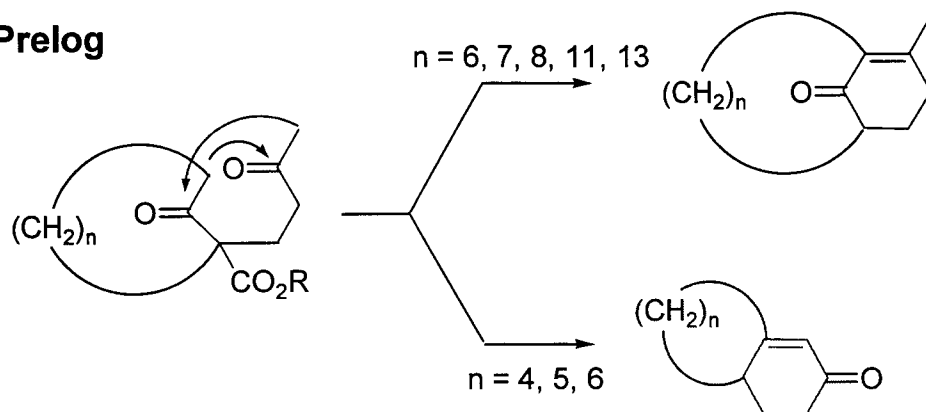


Result

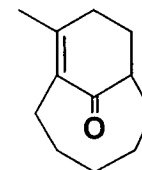
- Previously assigned structures that violated the rule were corrected

Establishing Boundaries

Prelog



Smallest Anti-Bredt Compound:



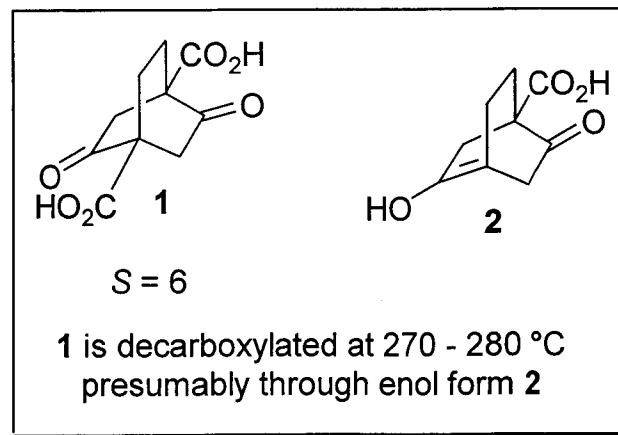
[5.3.1] System

Fawcett

- Strain number (S) in a bicyclo(x, y, z)alk-1-ene as

$$S = x + y + z$$

- Upper limit for isolation is $S = 8$
- Limit for “transient reaction intermediates” probably $S = 6$



V. Prelog, *JCS*, **1950**, 420.

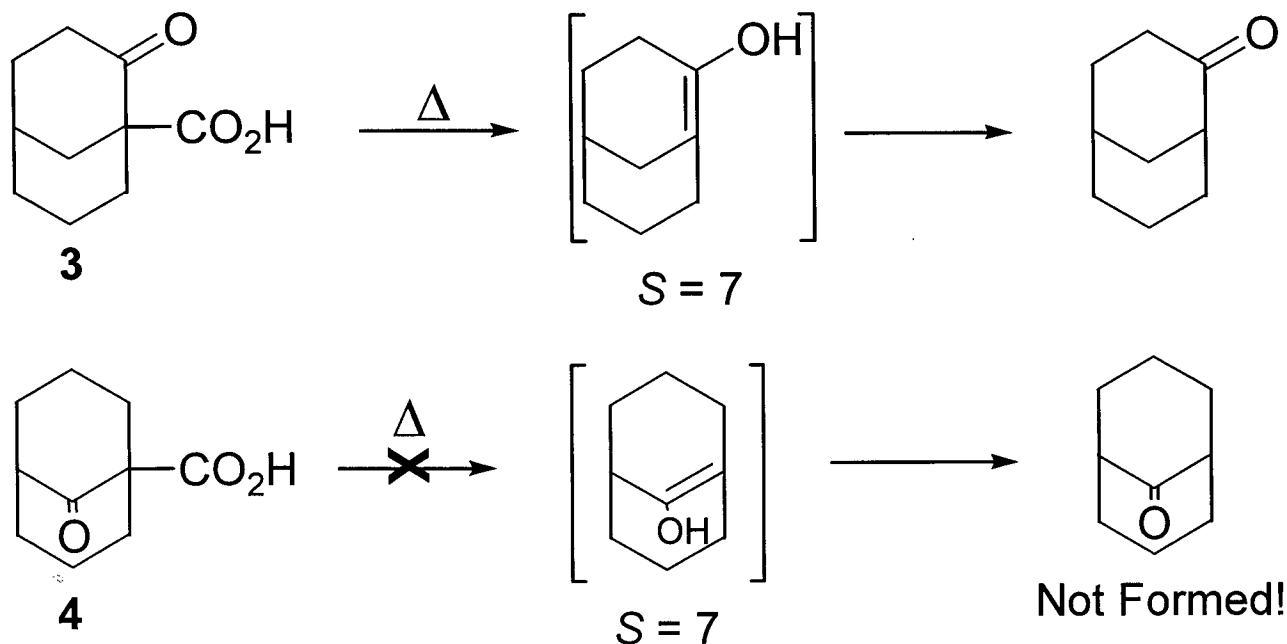
F. Fawcett, *Chem. Rev.*, **1950**, 219.

However...

- Prelog System

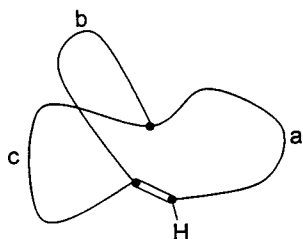
- Only bridged cyclohexenones with the carbonyl group in the smallest bridge – hardly representative of all
- All under thermodynamic control

- Fawcett System

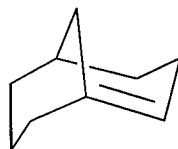


Weissman's Proposal

- “We believe the strain of bridgehead double bonds is closely related to the strain of *trans*-cycloalkenes.”



- *trans*-cyclooctene – unstable but isolable
- *trans*-cycloheptene – transient reactive species

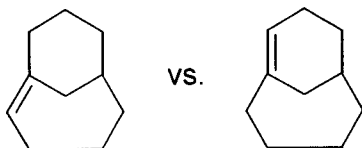


bicyclo[3.3.1]non-1-ene

$S = 7$

Contains *trans*-cyclooctene ring and is a stable compound

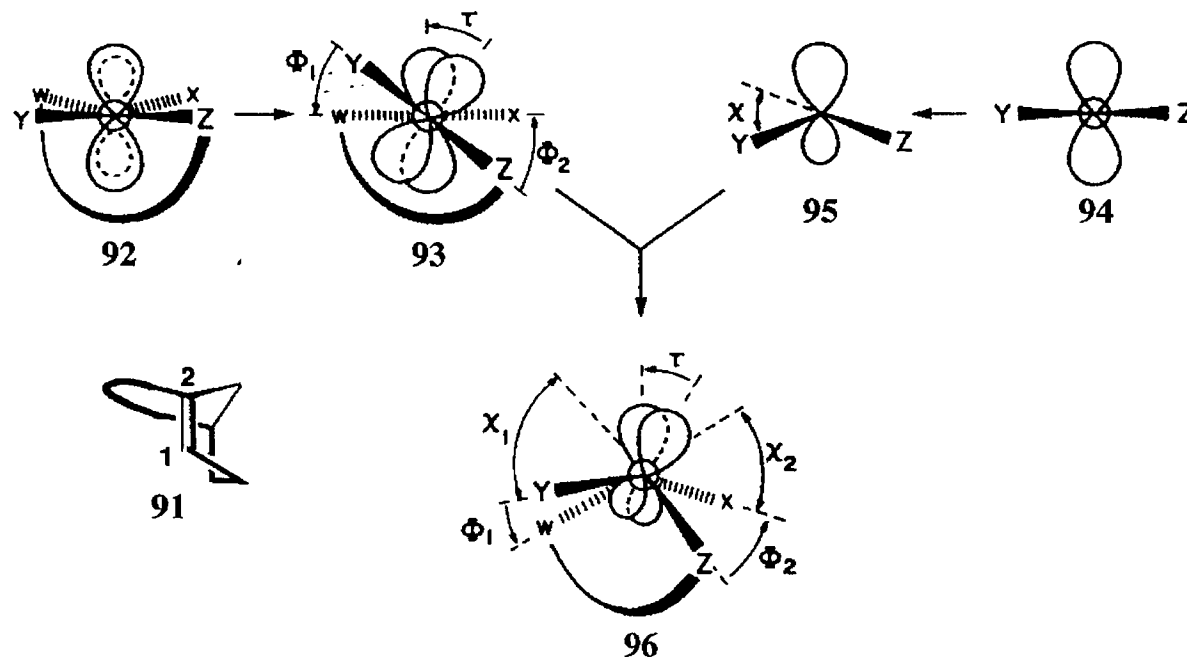
What about?



See: W.F. Maier, P.R. Schleyer; *JACS*, **1981**, 1891.

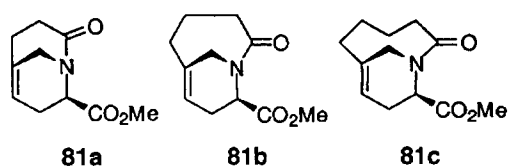
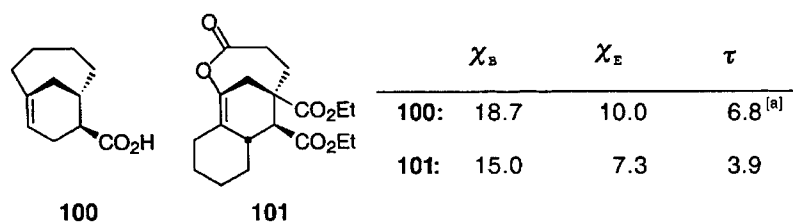
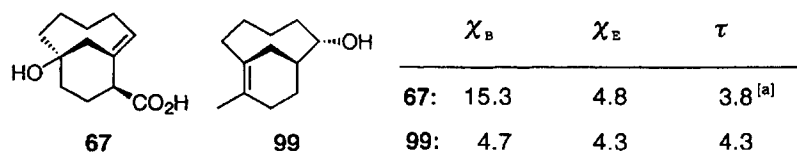
(nice computational study with many examples)

Structure of Bridgehead Alkenes



- Distortions can be quantified by:
 - Torsion angle (τ) between the p orbitals of the the double bond
 - Measured by average of Φ_1 and Φ_2 (not equivalent after pyramidalization)
 - Pyramidalization angle (χ) of the constituent atoms of the π system
 - $sp^{2.00}$ atoms have $\chi = 0.0^\circ$ while $sp^{3.00}$ atoms have $\chi = 60.0^\circ$

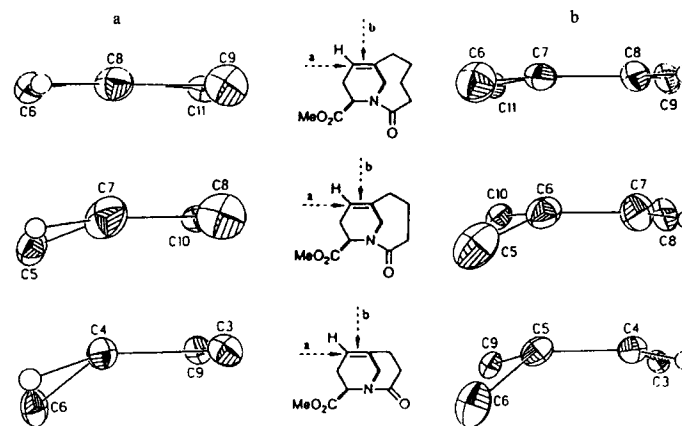
Crystallographic Data



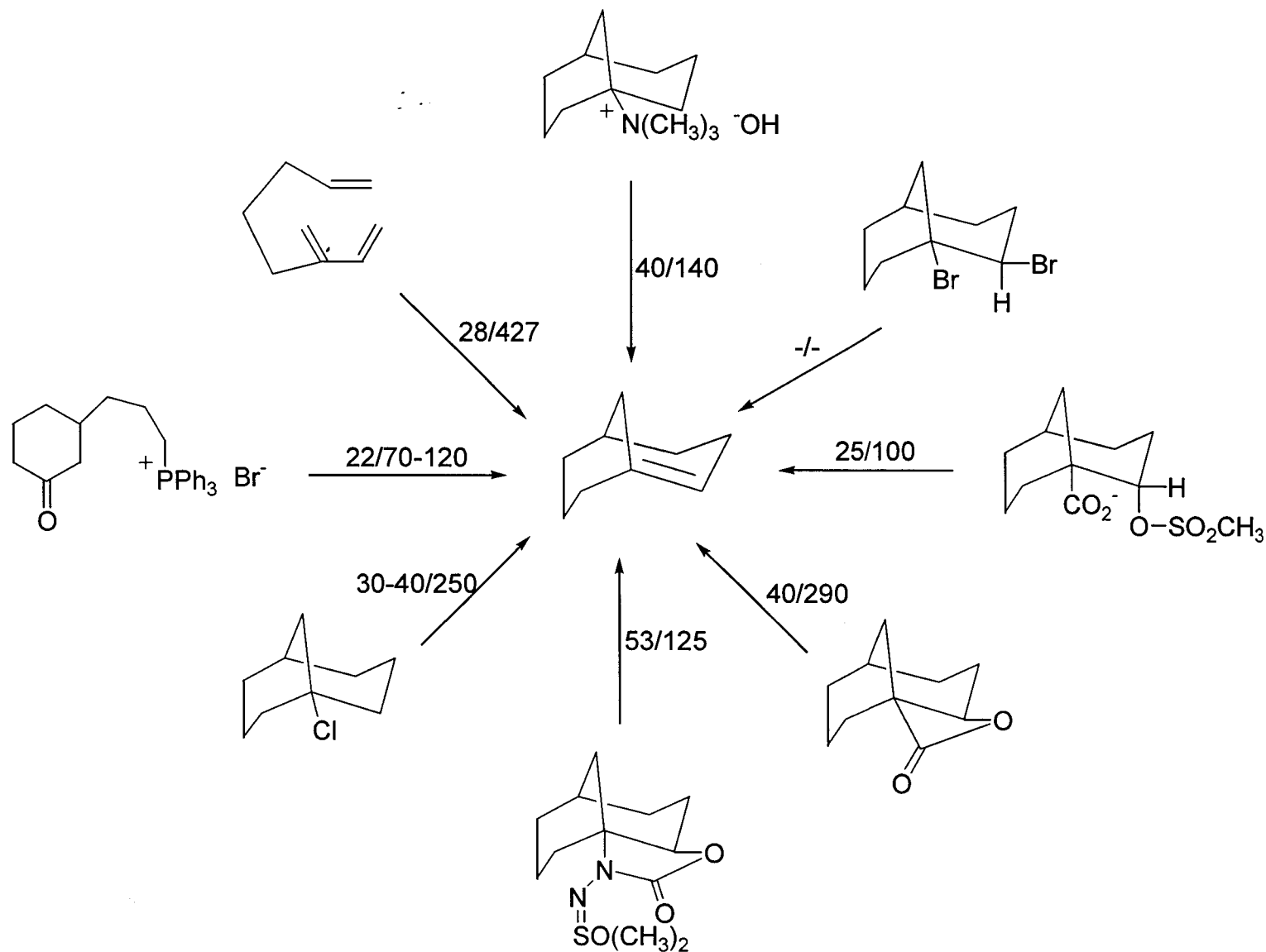
	χ_B	χ_E	τ
81a:	39.1	18.7	10.4
81b:	22.7	8.2	6.5
81c:	8.4	0.0	0.4

Scheme 9. Geometric distortions of bicyclo[5.3.1]undecenes **67** and **99**, bicyclo[4.3.1]decenes **100** and **101**, and the homologous alkenes **81a–c**. χ_B corresponds to the pyramidalization of the bridgehead carbon, χ_E corresponds to the pyramidalization of the exocyclic carbon. [a] Average derived from calculated hydrogen atom position in the X-ray crystal structure.

- Ten-membered *trans*-cycloalkene
 - No special reactivity
- Nine-membered *trans*-cycloalkene
 - More strained
- Progression to eight-membered *trans*-cycloalkene
 - Bicyclo[3.3.1]nonenes are $>10^6$ times more reactive in electrophilic additions

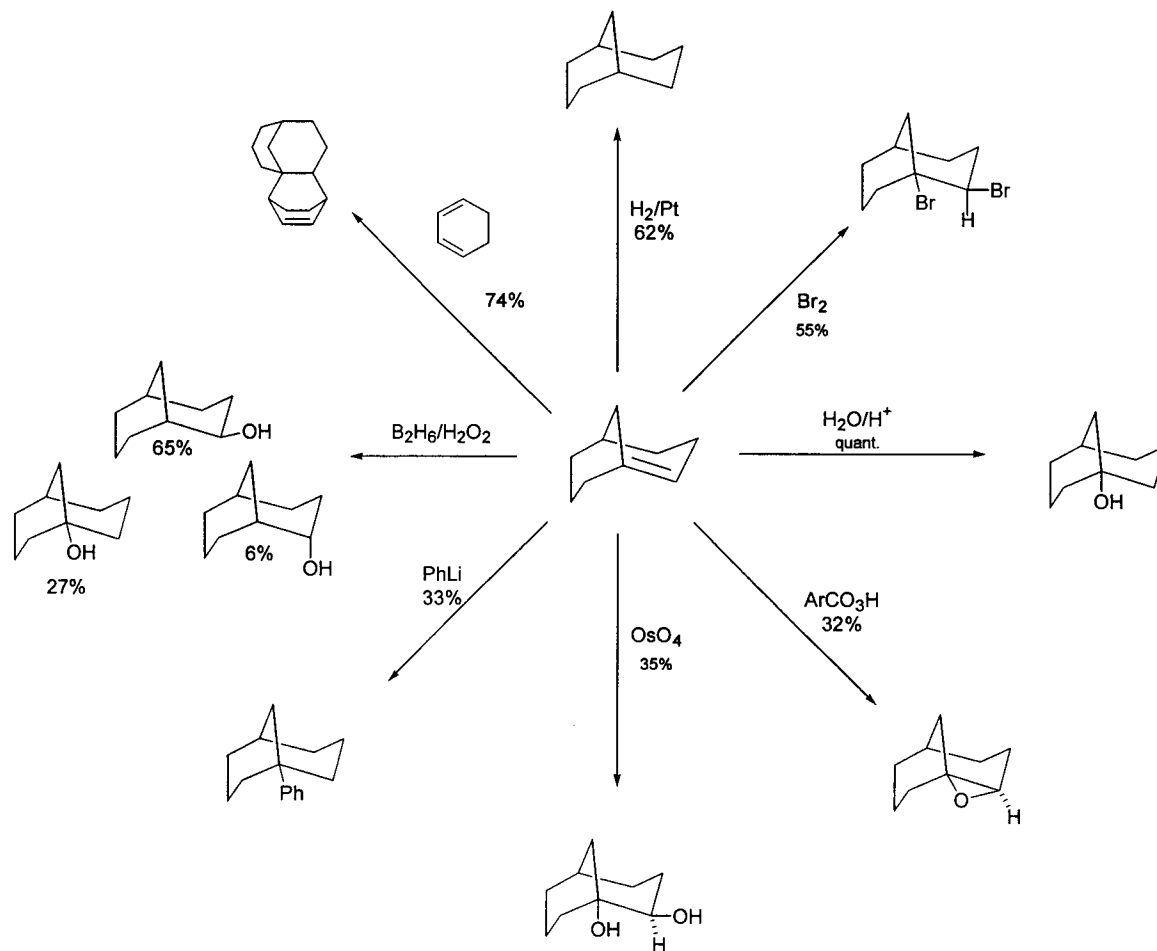


Synthesis of Bridgehead Alkenes

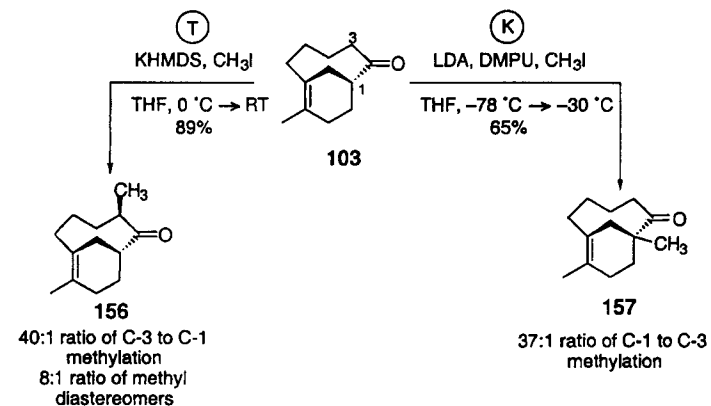


Numerical Values are % Yield / Temp (°C)

Reactions of Bridgehead Alkenes



Kinetic vs. Thermodynamic Deprotonation



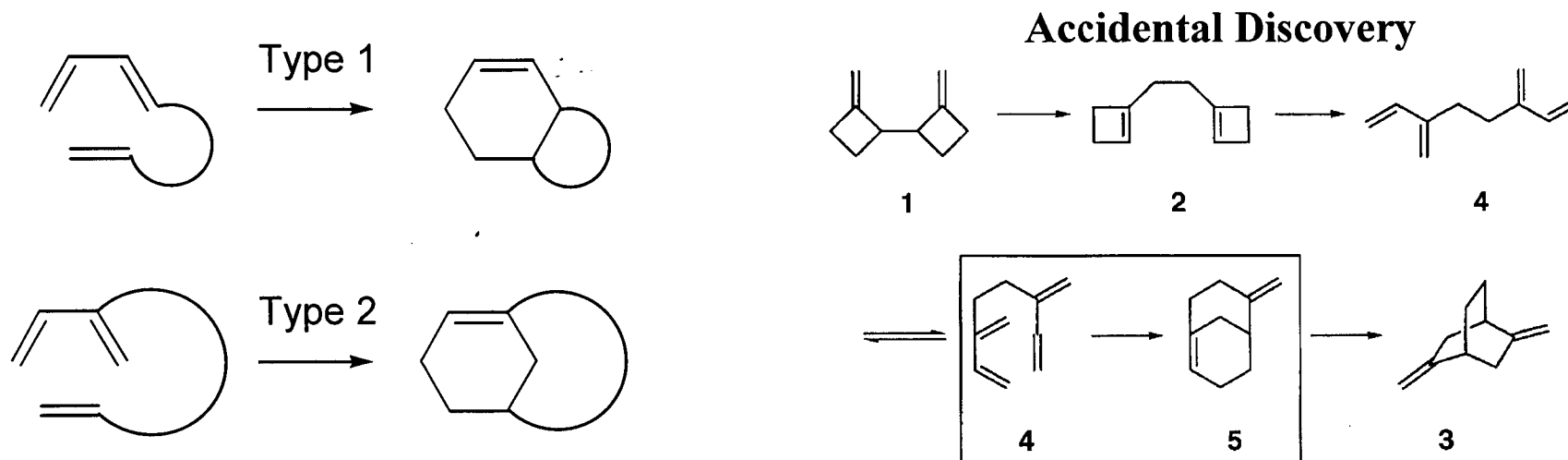
Scheme 21. Kinetic \textcircled{K} versus thermodynamic control \textcircled{T} in the alkylation of ketone 103. KHMDS = potassium salt of hexamethyldisilazane, DMPU = 1,3-dimethylhexahydro-2-pyrimidinone.

All references contained in:

G. Szeimies in *Reactive Intermediates*, Vol 3 (Ed.: R.A. Abranovitch), Plenum, New York, 1983, pp. 344 - 345.

S.L. Gwaltney II, S.T. Sakata, K.J. Shea, *J. Org. Chem.*, 1996, 7438.

Type 2 Intramolecular Diels-Alder Reaction



Initial Results

Starting material	Conditions	Product	Conversion [%]
 6	420°C, 23 s	 7	32
 8	455°C, 5 s	 9	55
 10	510°C, 8 s	 11	29

K.J. Shea, S. Wise, *JACS*, **1978**, 6519.

B.R. Bear, S.M. Sparks, K.J. Shea, *Angew. Chem. Int. Ed.*, **2000**, 821.

Activated Dienophiles and Lewis Acid Catalysis

Starting material	Conditions ^[a]	Product	Yield [%] ^[b]
	201 °C, 15 min		57
	206 °C, 2 h		80 ^[c] (91)
	232 °C, 4 h		65
	232 °C, 4 h		63

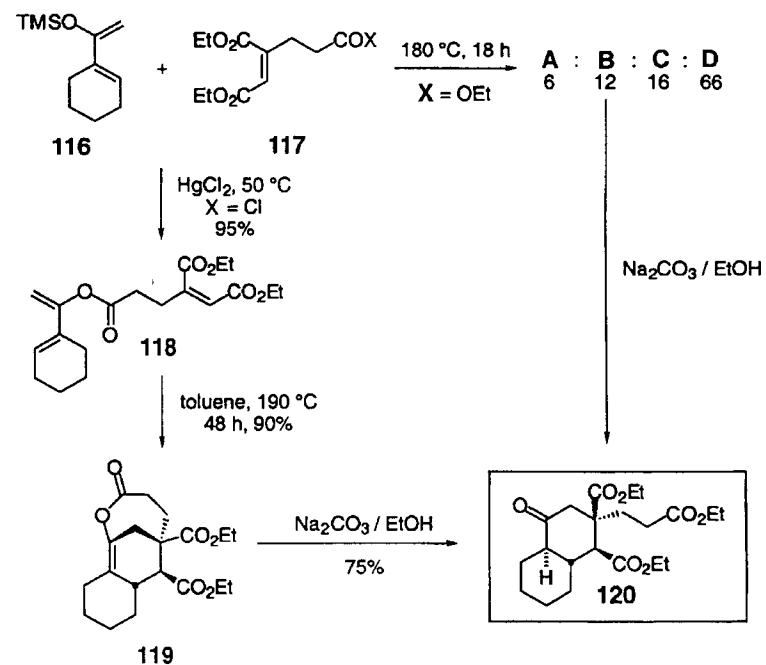
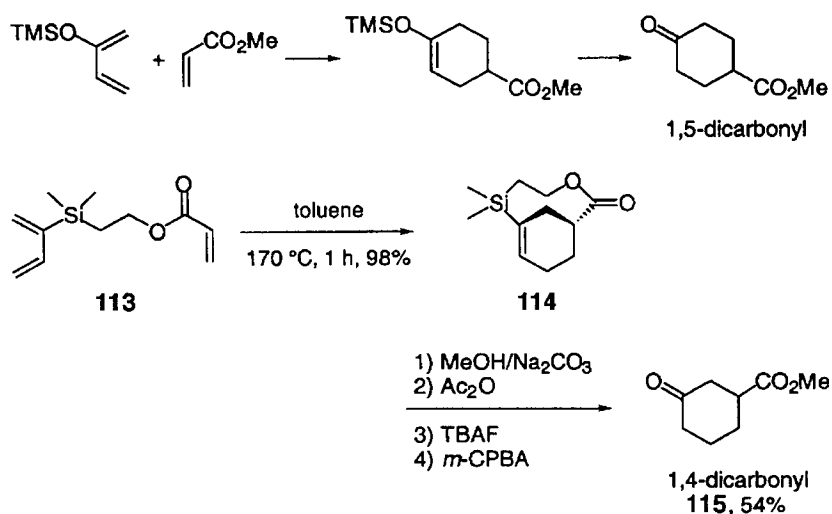
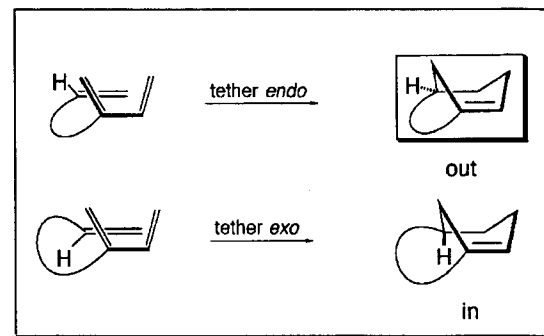
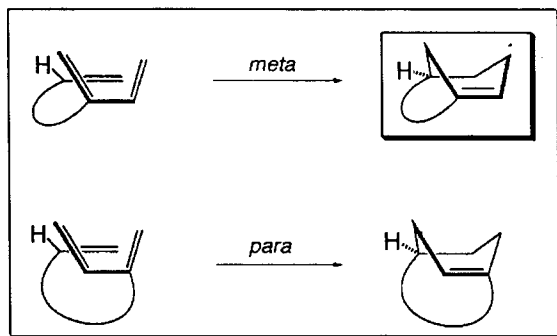
[a] Reactions were run in dilute (0.04–0.09 M) xylene solution. [b] Yields are calculated by GC referenced to an internal standard. [c] Yield of isolated product.

Starting triene	Conditions ^[a]	Product	Yield [%]
	4 h, 21 °C		50
	2 h, 21 °C		75
	1 h, 21 °C		71
	< 5 min, 21 °C		70
	12 h, 21 °C		85
	1 h, 21 °C	 	90 (36:37 = 4:1)

[a] In CH₂Cl₂ with Et₃AlCl as Lewis acid; thermolysis temperature and reaction time are given.

Lower Reaction Temperatures and Better Yields!

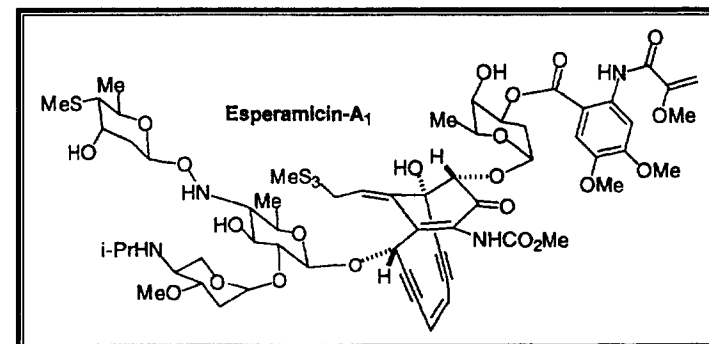
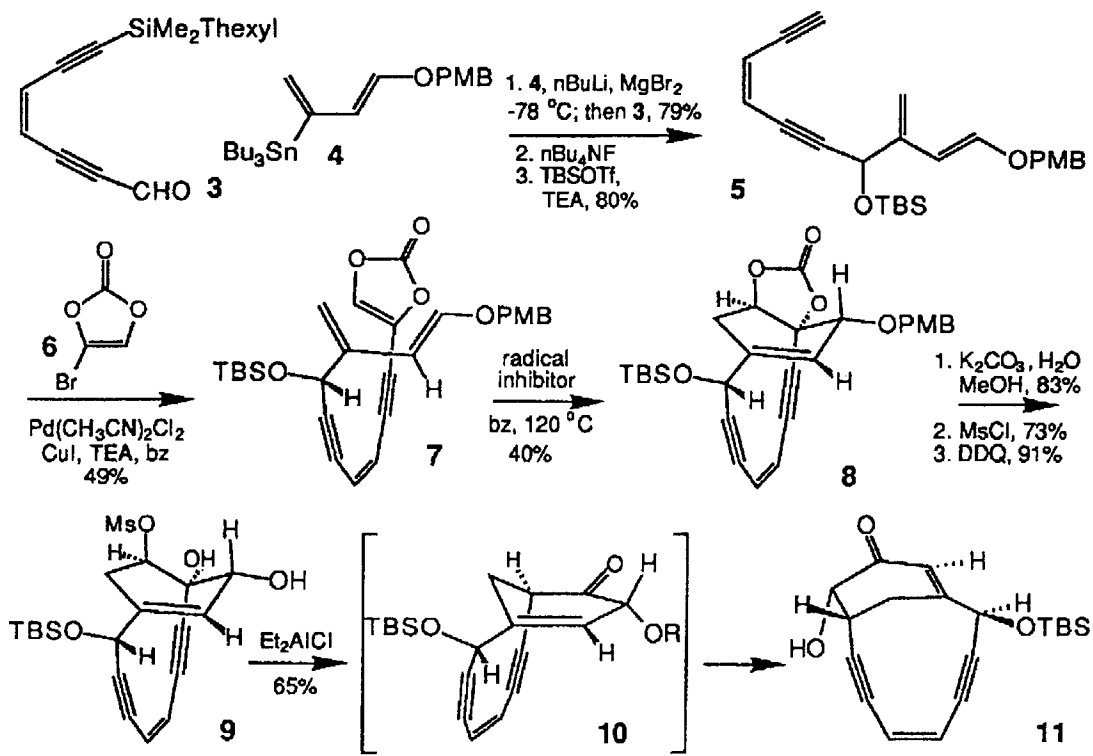
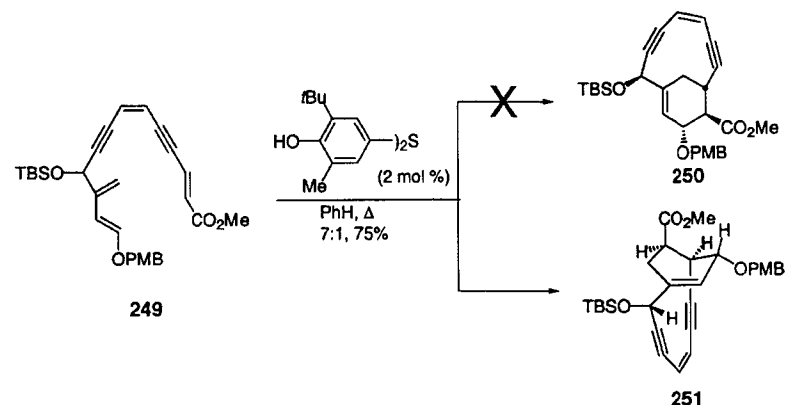
Regio- and Stereochemical Control



Synthesis of Esperamicin Core

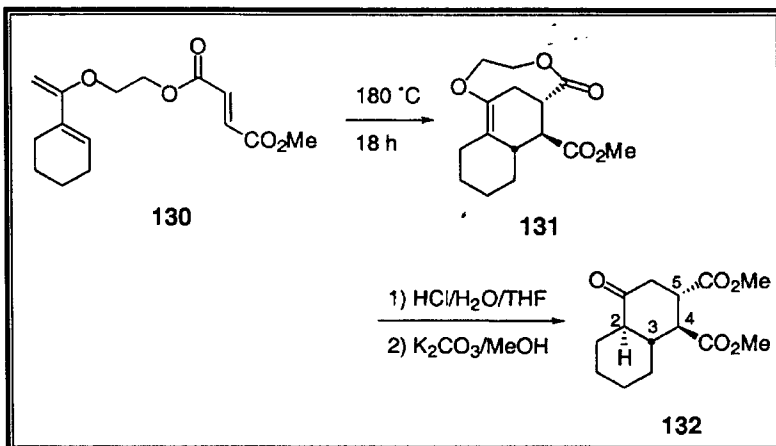
• Initial study gave wrong regiochemistry

• Isomerization to 1,3 regioisomer was necessary

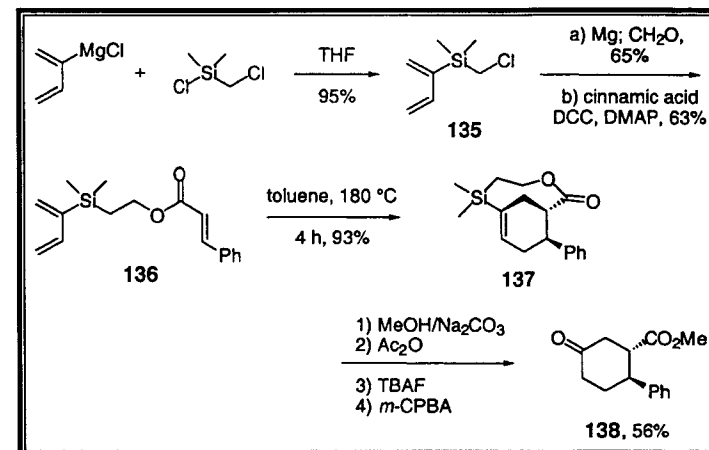


Disposable Tethers

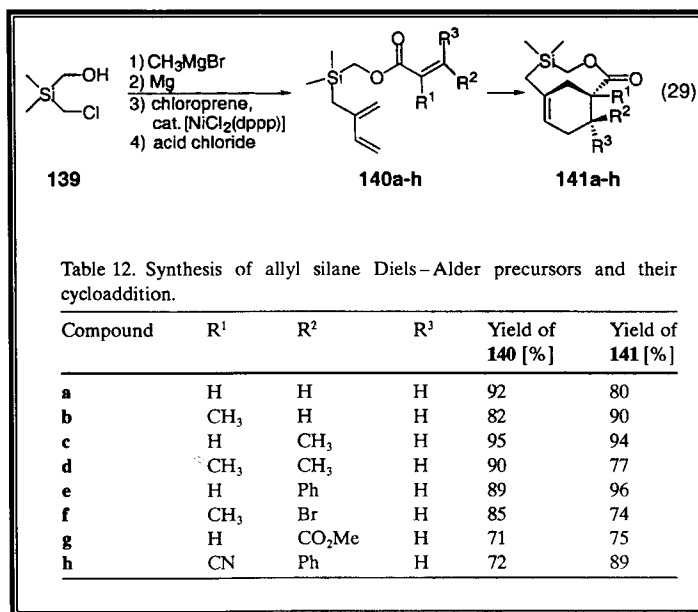
Vinyl Ethers



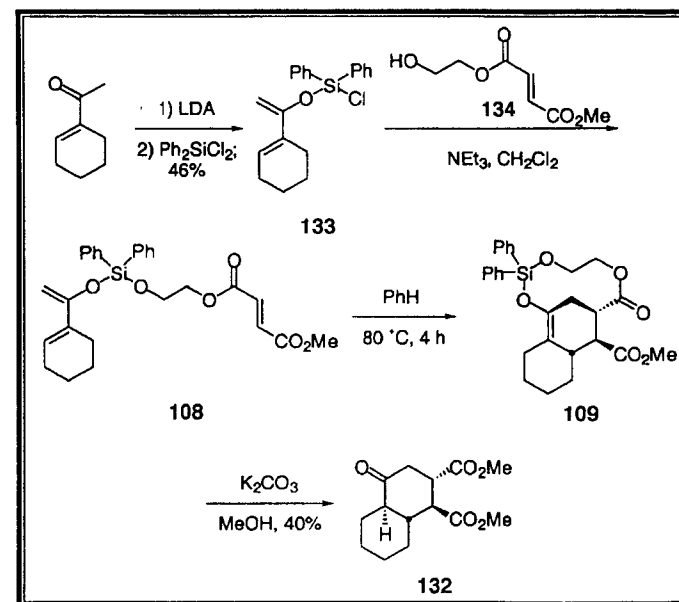
Vinyl Silanes



Allyl Silanes

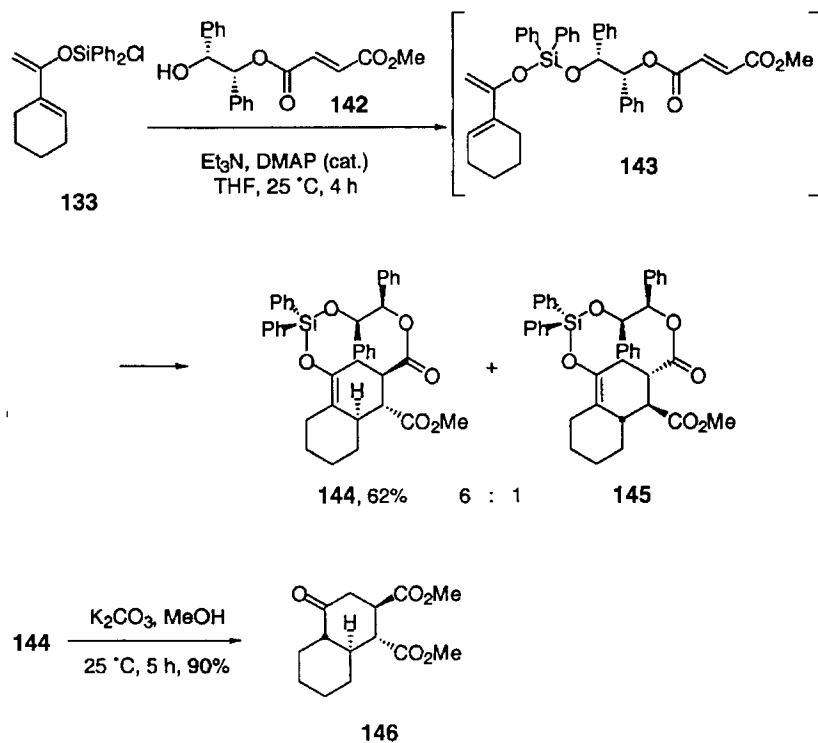


Silyl Acetals

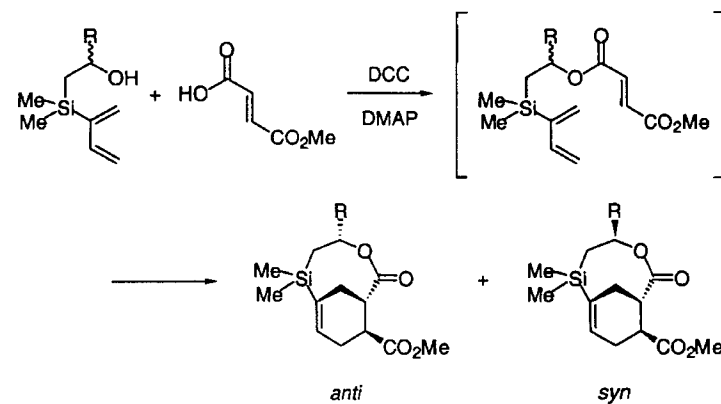


Facial Selectivity

Silyl Acetals

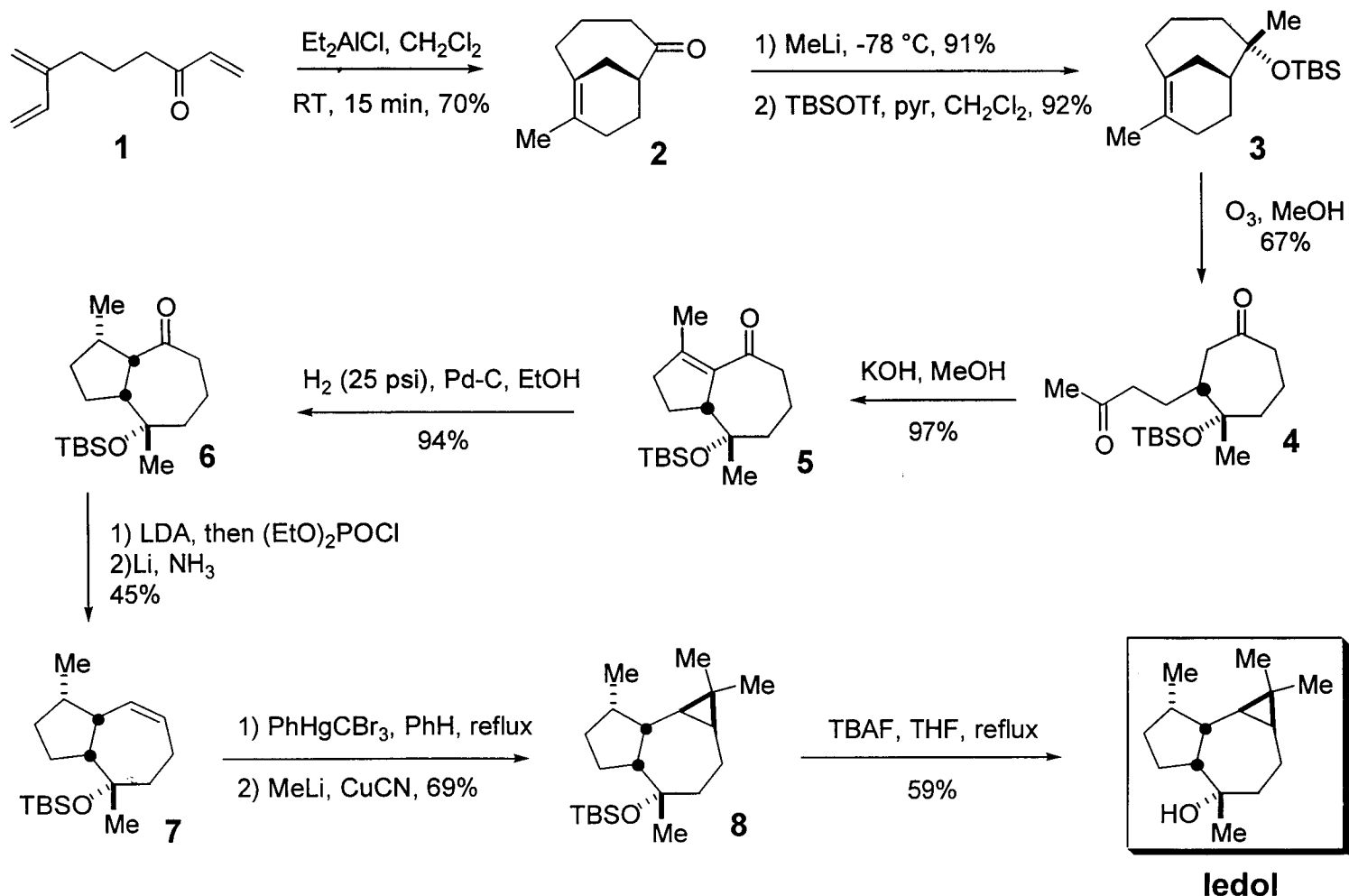
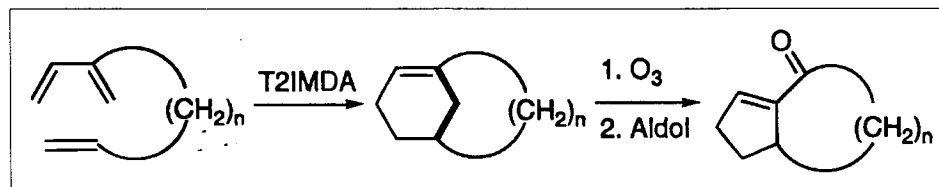


Vinyl Silanes

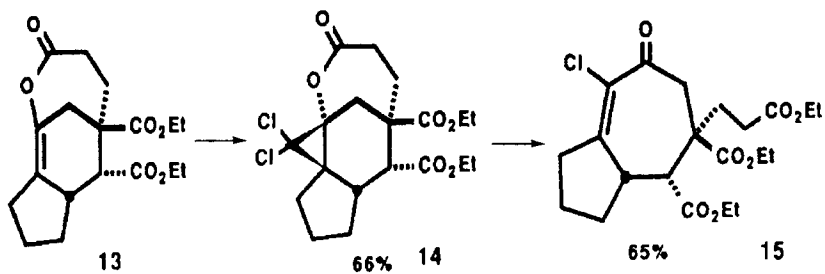
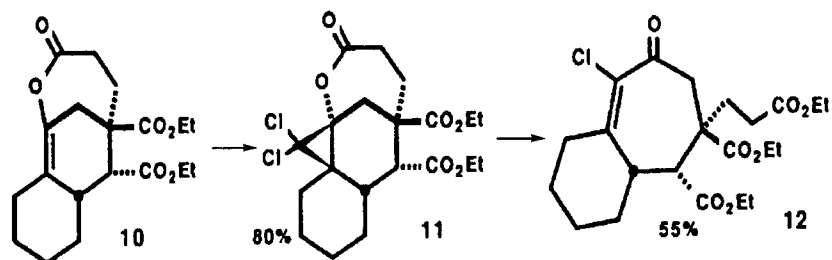
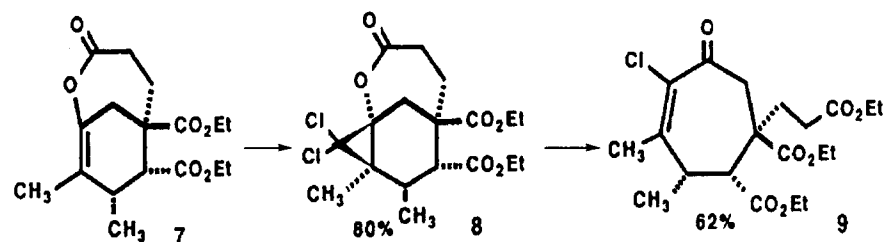
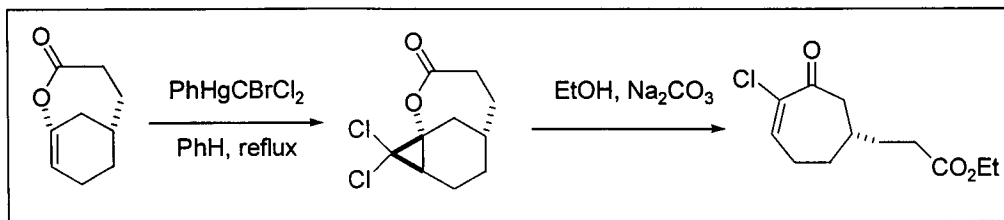


R	Conditions	Yields [%]	<i>anti/syn</i>
H	60 °C, 18 h	89	--
Me	65 °C, 13 h	77	3.1 : 1
Ph	65 °C, 16 h	54	4.2 : 1
<i>i</i> Pr	60 °C, 14 h	75	4.8 : 1
<i>i</i> Bu	25 °C, 18 h	75	9.4 : 1

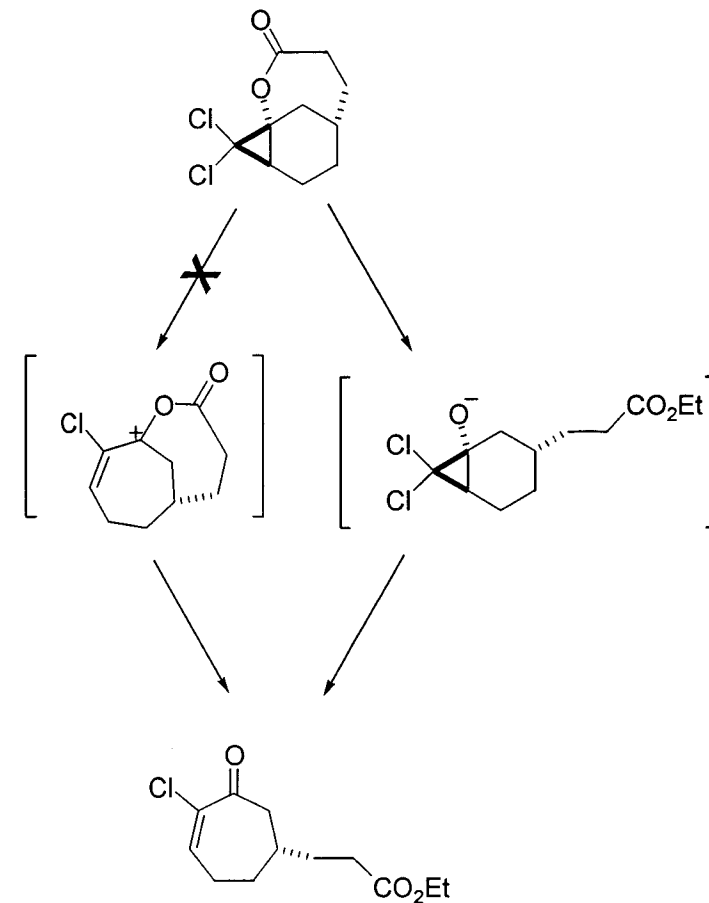
Bridged to Fused Interchange



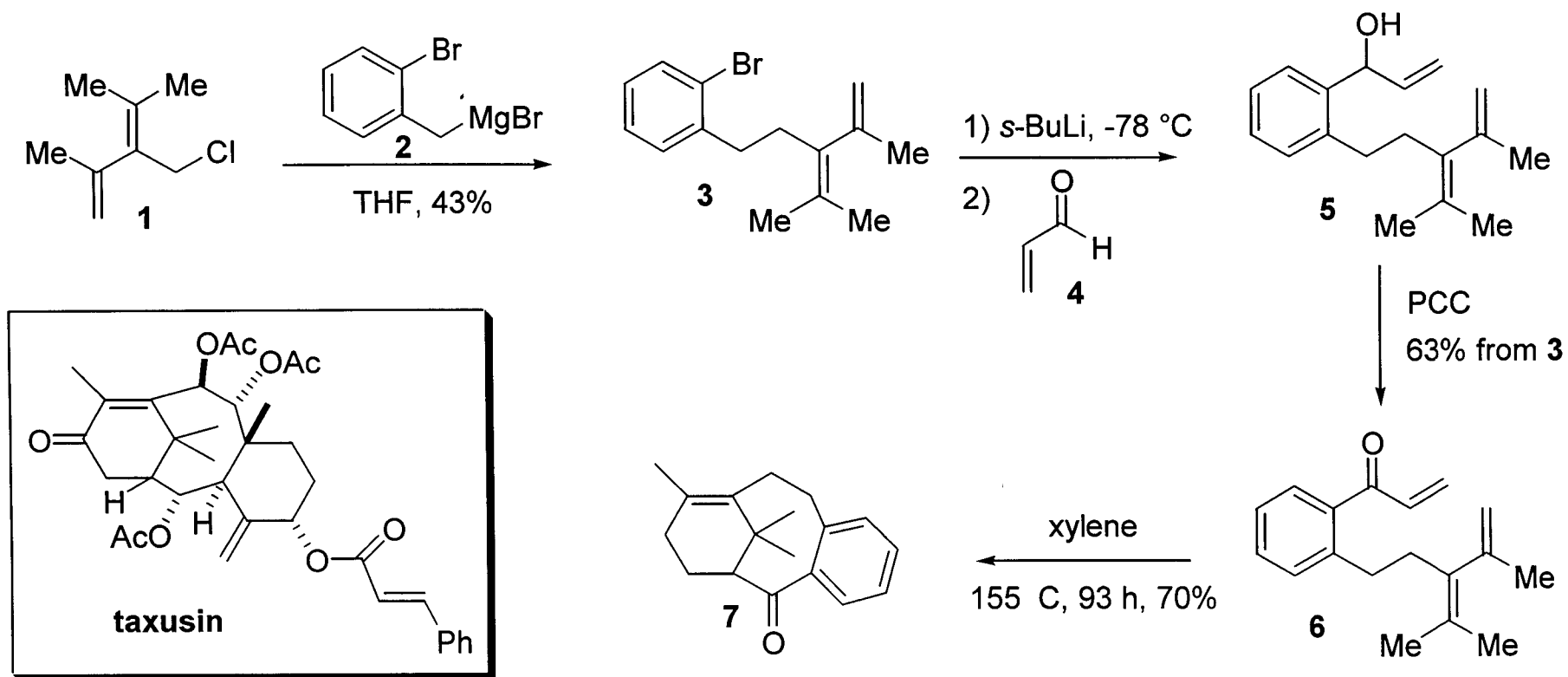
Ring Expansion



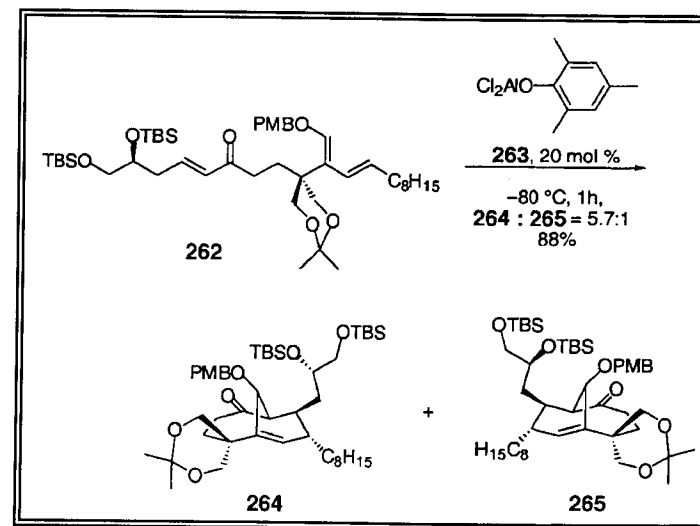
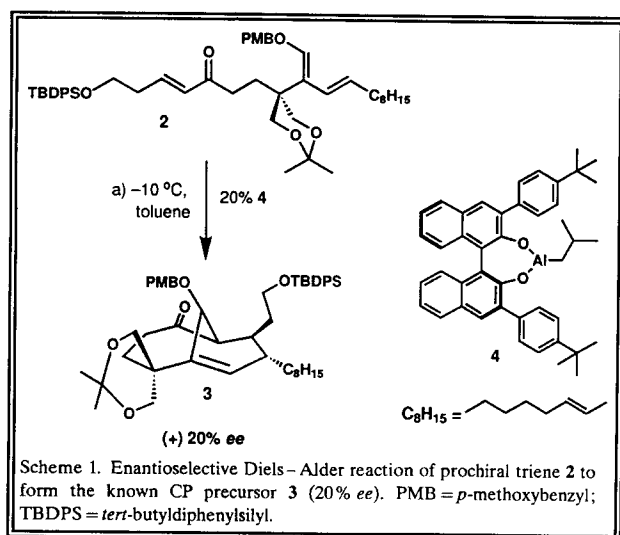
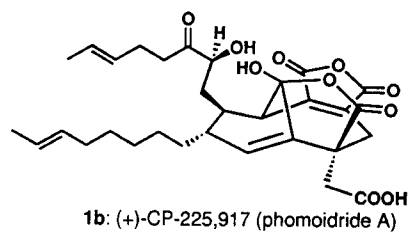
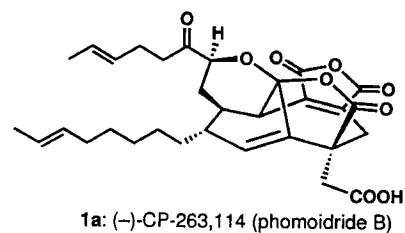
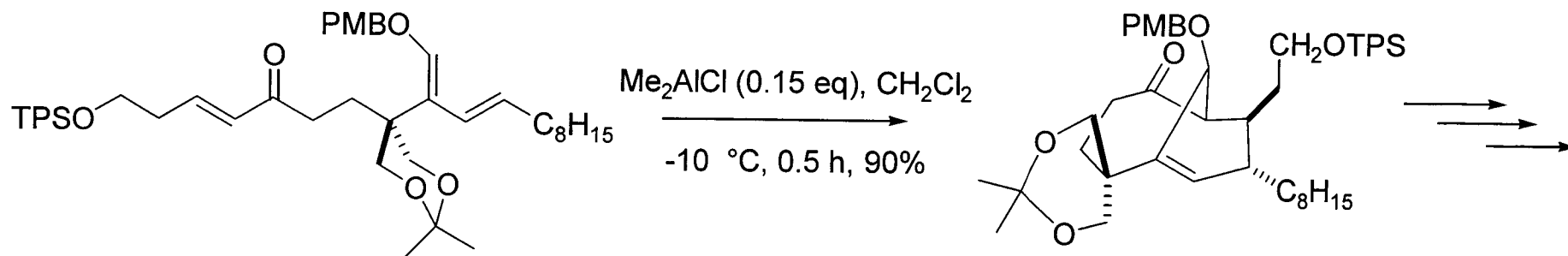
Mechanistic Insight



Synthesis of Taxane Skeleton



CP-263,114 and CP-225,917



K.C. Nicolaou, P.S. Baran, Y.L. Zhong, H.A. Choi, W.H. Yoon, Y. Hee, K.C. Fong, *Angew. Chem. Int. Ed.*, **1999**, 1669.

K.C. Nicolaou, J.K. Jung, W.H. Yoon, Y. Hee, Y.L. Zhong, P.S. Baran, *Angew. Chem. Int. Ed.*, **2000**, 1829.

B.R. Bear, S.M. Sparks, K.J. Shea, *Angew. Chem. Int. Ed.*, **2000**, 821.

Conclusions

- Bridgehead Alkenes
 - Relate to *trans*-cycloalkenes
 - Can contain highly distorted π -bonds
 - Undergo *exo* addition to the bridgehead double bond
 - Relative stabilities of systems with similar *trans*-cycloalkenes are best calculated on a case to case basis
- Type 2 Diels-Alder Reaction
 - Provides bridgehead alkenes directly from acyclic precursors
 - Broad scope and high selectivities
 - Most successful when forming seven and eight-membered rings embedded in the bicyclic structure (four or five atom tethers)
 - Access to other compounds through disposable tethers, bridged to fused interchange, and ring expansion
 - Used in natural product synthesis