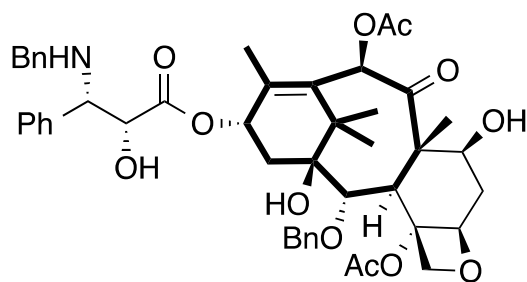
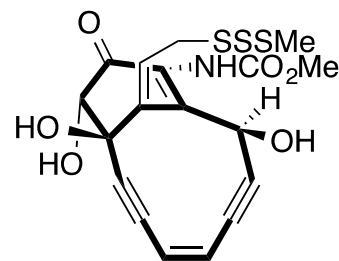


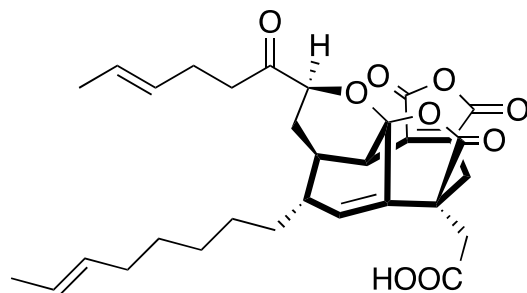
The Type II Intramolecular Diels-Alder Reaction: Synthesis and Chemistry of Bridgehead Alkenes



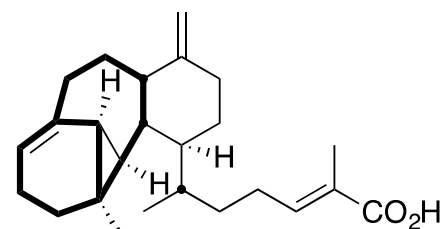
Taxol



Esperamicin A₁ aglycone



CP-264,114



Cerorubenic acid

2013. 10. 24
Haye Min Ko



Kenneth J. Shea

Kenneth J. Shea was born in Queens, New York. He received his B.S. and M.S. degrees in Chemistry from the University of Toledo. He did his graduate studies in physical organic chemistry at Pennsylvania State University. Following postdoctoral studies at the California Institute of Technology, he joined the faculty of the University of California at Irvine in 1974. His research interests are in synthetic and mechanistic organic chemistry and polymer and materials chemistry.

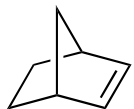
Bredt's Rule vs Bridged alkene

Bredt's Rule

Bredt's rule is an empirical observation in organic chemistry that states that a double bond can not be placed at the bridgehead of a bridged ring system, unless the rings are large enough.



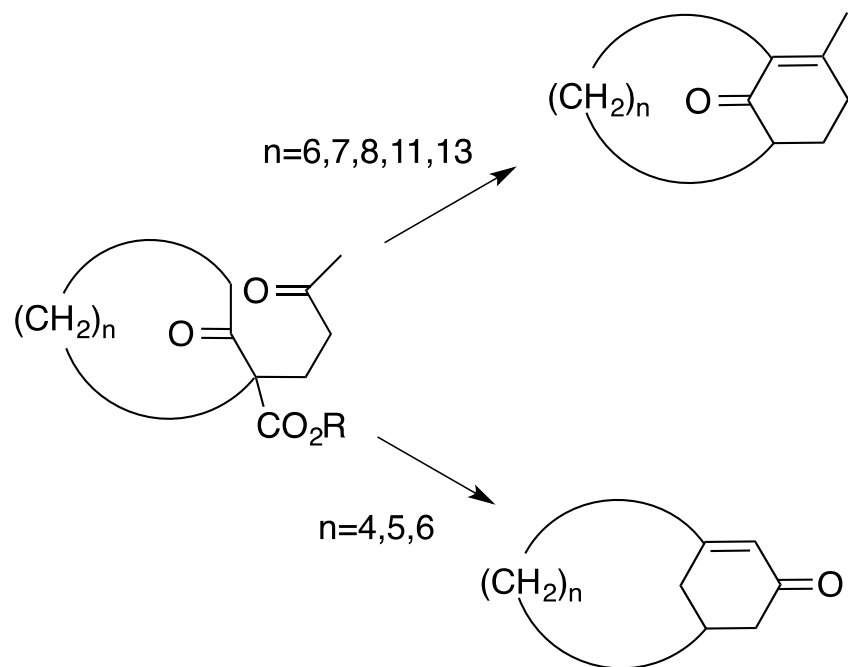
ex. norbornene



Forbidden norbornene isomers

Bredt, J., *Liebigs Ann. Chem.*, **1924**, 437, 1

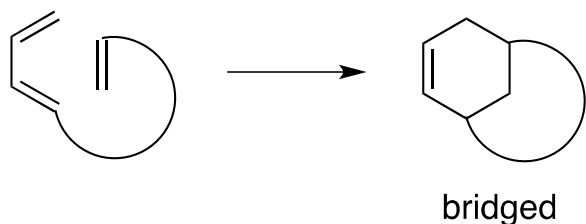
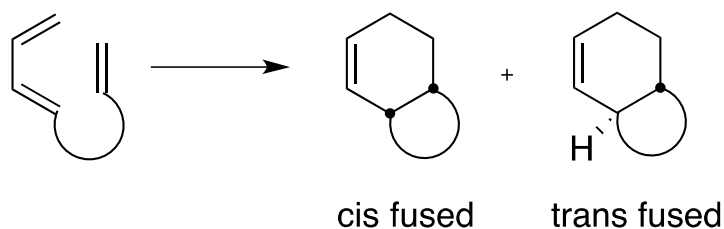
Prelog, Fawcett...: Establishing Boundaries (Anti-bredt alkene)



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

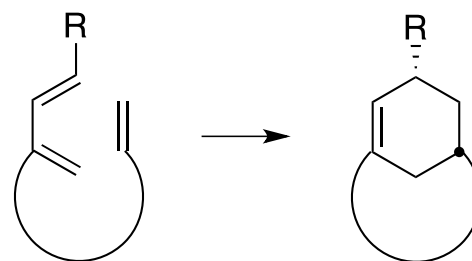
Introduction: Intramolecular Diels-Alder

Type I: Tether is attached at 4-position of diene.



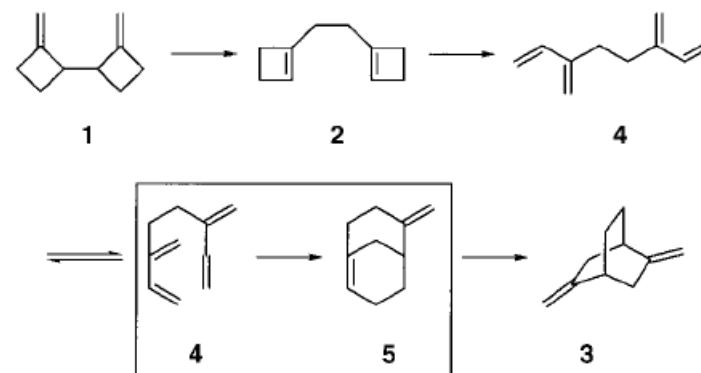
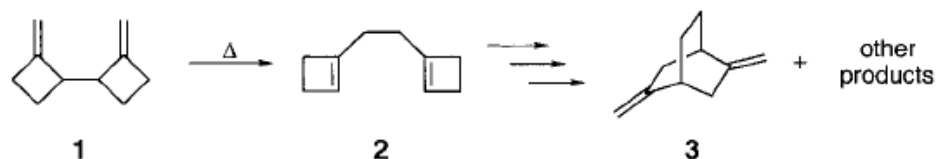
- i) Bridged products rarely observed.
(tether must be > 9 atoms)
- ii) Fused products usually have 3 or 4 atom tether.

Type II: Tether is attached at 3-position of diene.



Shea, K. J., *J. Am. Chem. Soc.*, **1978**, *100*, 6519
Shea, K. J., *J. Am. Chem. Soc.*, **1988**, *110*, 860
Shea, K. J., *Tetrahedron Lett.*, **1994**, *35*, 7311

Type II Intramolecular Diels-Alder



Scheme 1. Proposed reaction cascade leading to **3**.

Table 1. Type 2 IMDA cycloadditions of acyclic trienes.

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

> 300 °C

Accidental discovery during a mechanistic study of the Cope rearrangement.

Shea, K. J., *J. Am. Chem. Soc.*, **1978**, *100*, 6519
 Shea, K. J., *Angew. Chem. Int. Ed.*, **2001**, *40*, 820

Development of the Scope of the Reaction

Activated Dienophiles

Table 2. Gas-phase thermolysis of three-atom-bridged triene esters and ketones.

Starting material	Conditions ^[a]	Product	Yield [%] ^[b]
	420 °C, 23 s		32
	395 °C, 18 s		72
	318 °C, 18 s		76
	365 °C, 12 s		
	390 °C, 12 s		30

[a] Atmospheric pressure, N₂ carrier gas; thermolysis temperature and contact time are given. [b] Determined by GC, percentages based upon starting material remaining after thermolysis. [c] The *Z* isomer underwent isomerization to the *E* isomer under the thermolysis conditions. The cycloaddition product was identical with that obtained from (*E*)-14.

	455 °C, 8 s		55
	398 °C, 8 s		85
	420 °C, 8 s		80

[a, b] See Table 2.

Lewis Acid Catalyst

Table 5. Lewis acid catalyzed type 2 IMDA reactions.

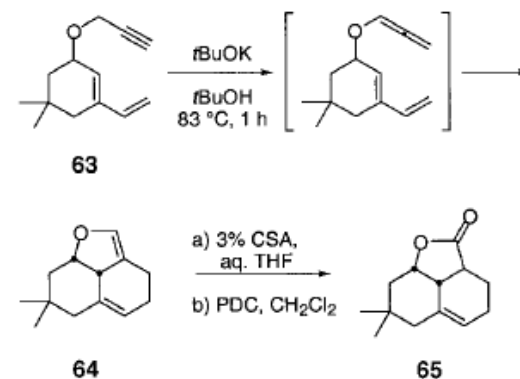
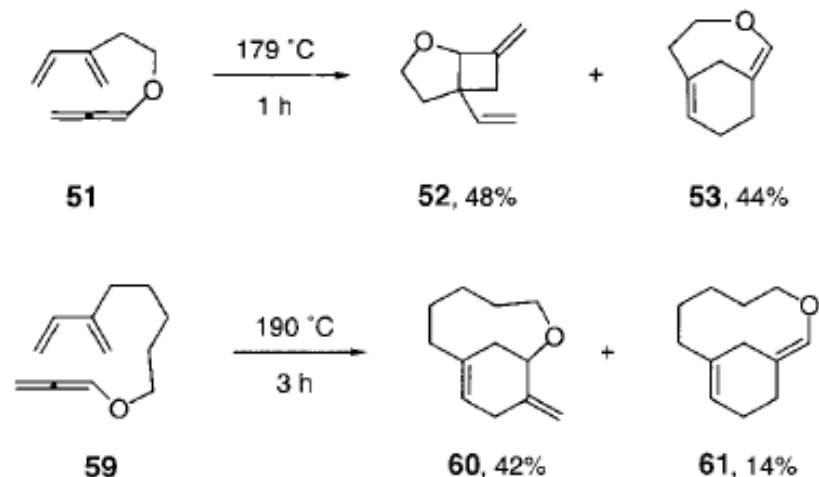
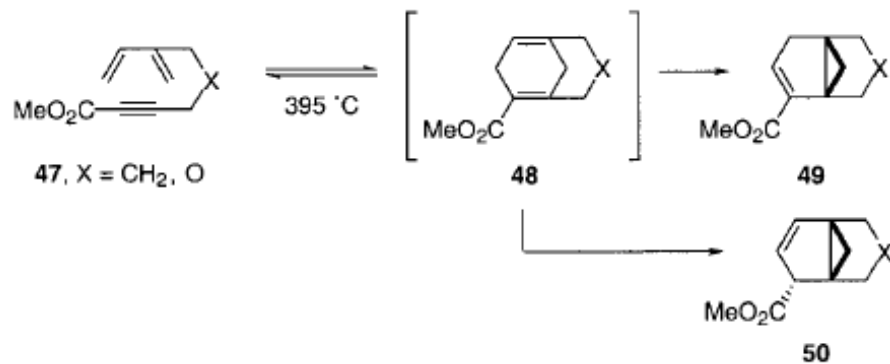
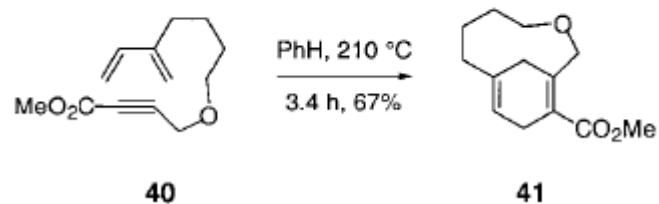
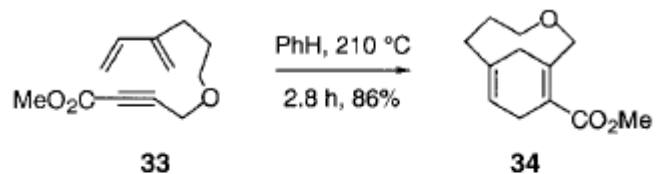
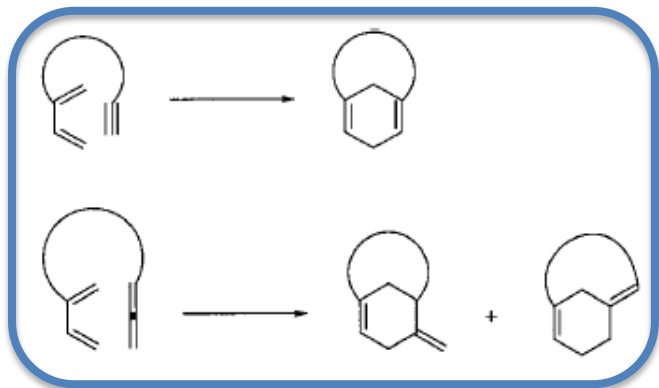
Starting triene	Conditions ^[a]	Product	Yield [%]
	4 h, 21 °C		50
	2 h, 21 °C		75
	1 h, 21 °C		71
	< 5 min, 21 °C		70
	12 h, 21 °C		85

[a] In CH₂Cl₂ with Et₂AlCl as Lewis acid; thermolysis temperature and reaction time are given.

Shea, K. J., *J. Am. Chem. Soc.*, **1982**, *104*, 5708

Shea, K. J., *J. Am. Chem. Soc.*, **1985**, *107*, 4791

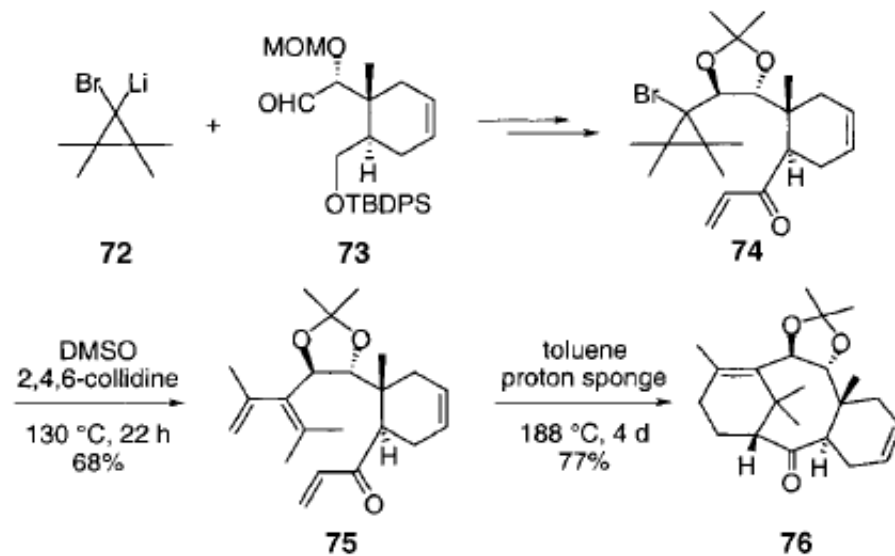
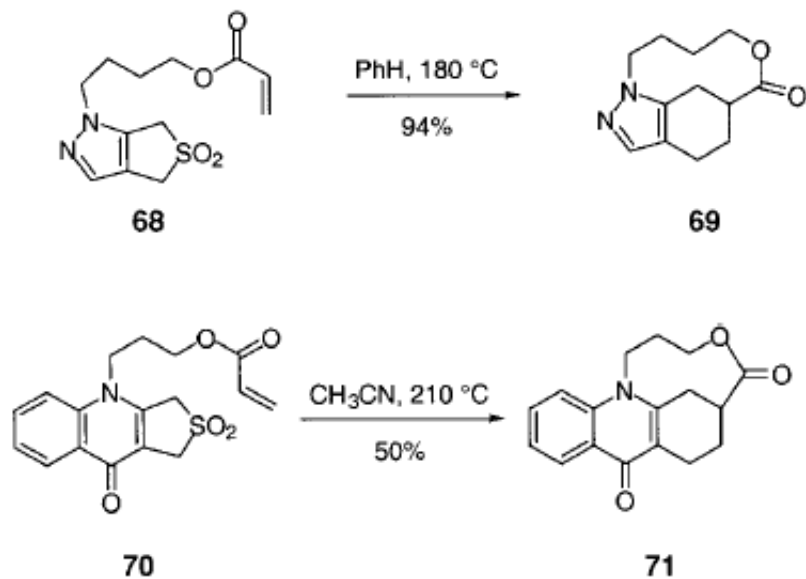
Acetylenic and Allenic Dienophiles



Scheme 5. Kanematsu's approach to tricyclic compounds using an allene dienophile. CSA = camphorsulfonic acid, PDC = pyridinium dichromate.

Shea, K. J., *Tetrahedron Lett.*, **1990**, *31*, 6843
 Kanematsu, K., *Tetrahedron Lett.*, **1986**, *27*, 4205

Masked Dienes and Dienophiles



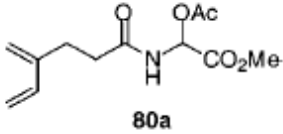
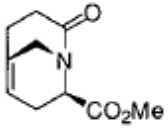
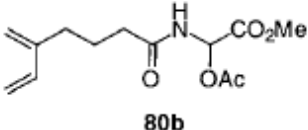
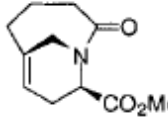
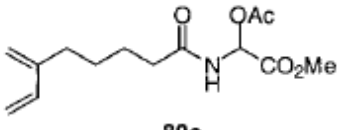
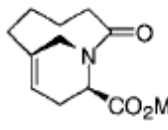
Scheme 7. Synthesis of advanced taxusin intermediate **76**.^[32]

Chou, T. S., Chen, H. C., *Tetrahedron Lett.*, **1996**, *37*, 7823

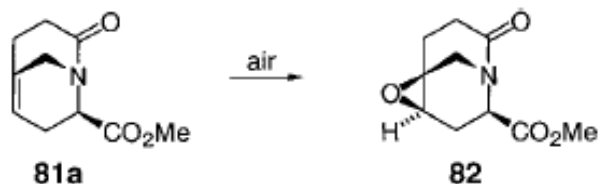
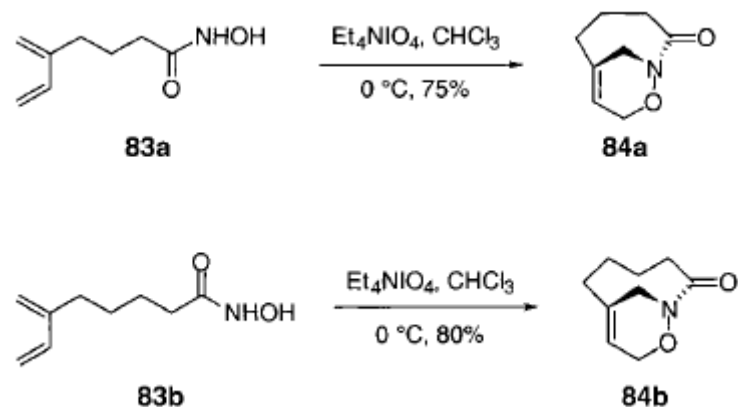
Chou, T. S., Chen, H. C., *Tetrahedron Lett.*, **1999**, *40*, 961

Hetero Diels-Alder Reactions

Table 7. Intramolecular acyl iminium Diels-Alder cycloadditions.

Starting material	Conditions ^[a]	Products	Yields [%] ^[b]
 <p>80a</p>	250 °C, 2 min	 <p>81a</p>	29
 <p>80b</p>	200 °C, 2 h	 <p>81b</p>	82
 <p>80c</p>	215 °C, 2 h	 <p>81c</p>	76

[a] Reactions were performed in xylenes at 0.01M. [b] Yields refer to isolated products after chromatography.

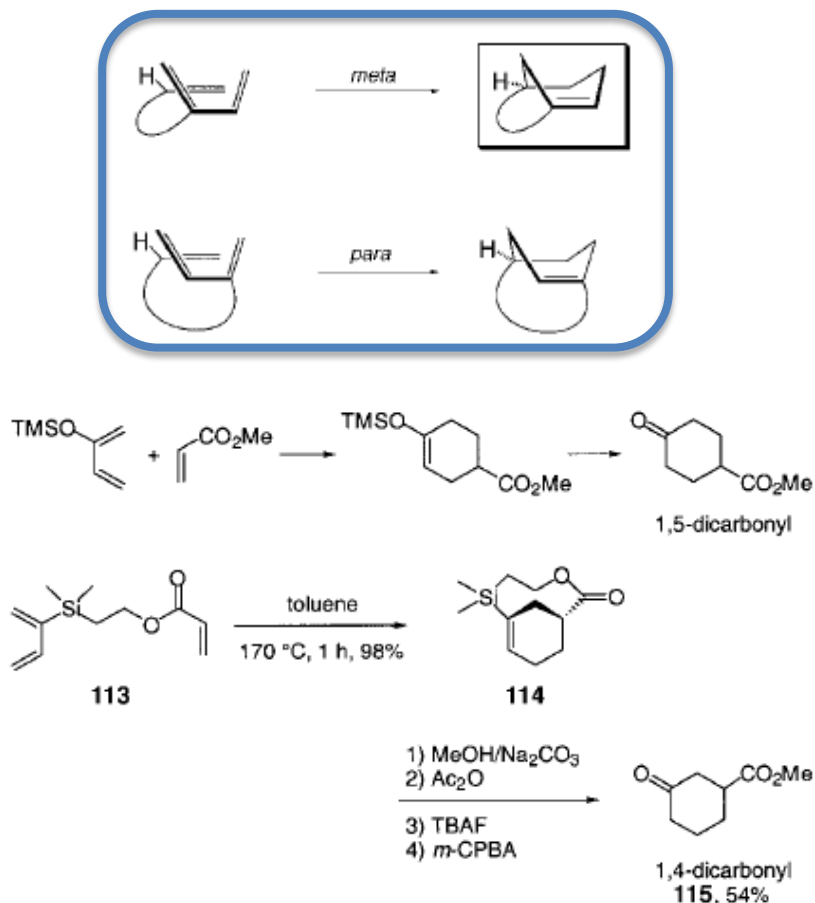


Shea, K. J., *J. Am. Chem. Soc.*, **1990**, *112*, 8627

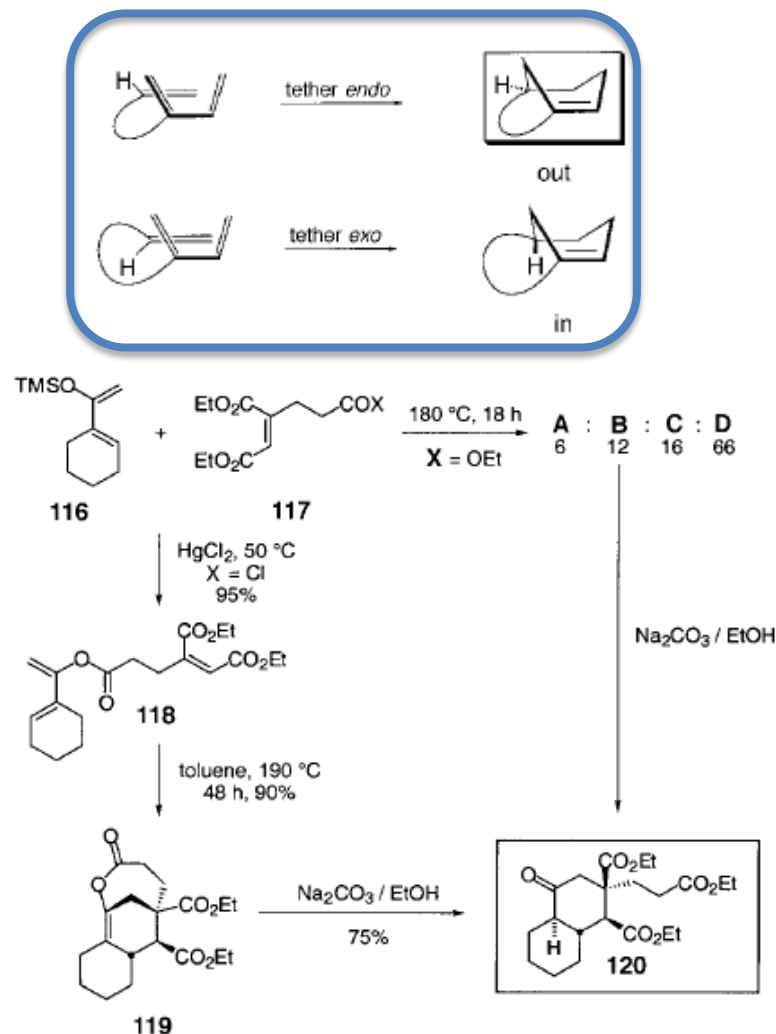
Shea, K. J., *J. Am. Chem. Soc.*, **1993**, *115*, 2248

Shea, K. J., *Org. Lett.*, **2000**, *2*, 1473

Regio- and Stereochemical Control



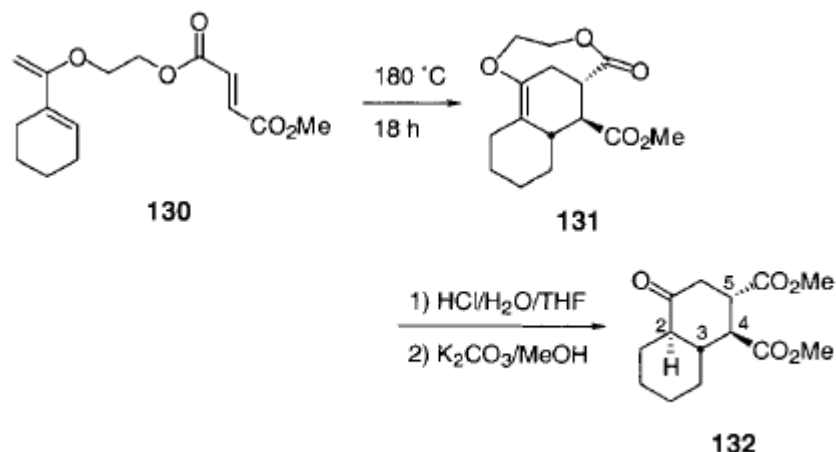
Scheme 11. Pericyclic umpolung applied to the synthesis of methyl 3-oxocyclohexanecarboxylate (**115**). The course of the normal Diels-Alder reaction is shown above. TBAF = tetrabutylammonium fluoride, *m*-CPBA = *meta*-chloroperoxybenzoic acid.



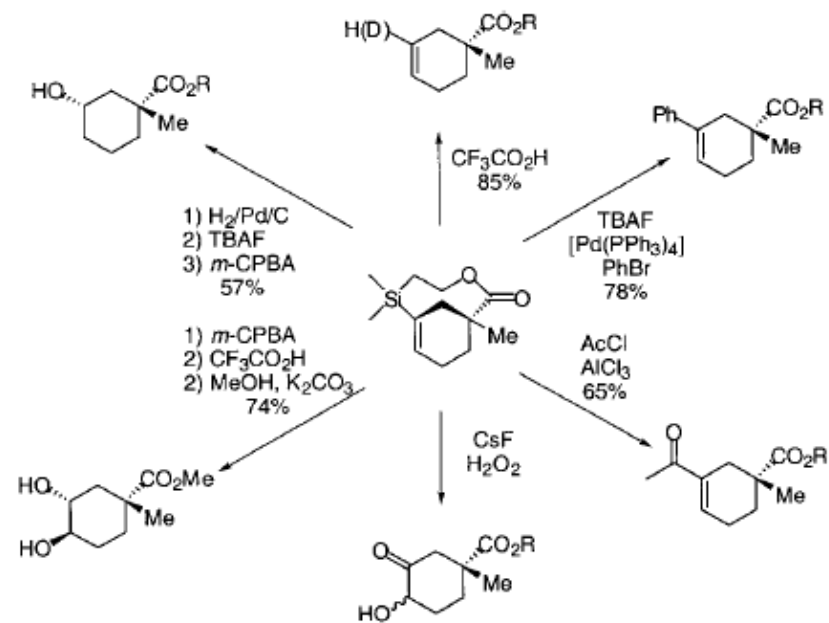
Scheme 12. Stereoselectivity of the type 2 IMDA reaction.

Jung, M. E., *Tetrahedron Lett.*, **1976**, 2935
 Shea, K. J., *J. Am. Chem. Soc.*, **1987**, 109, 447

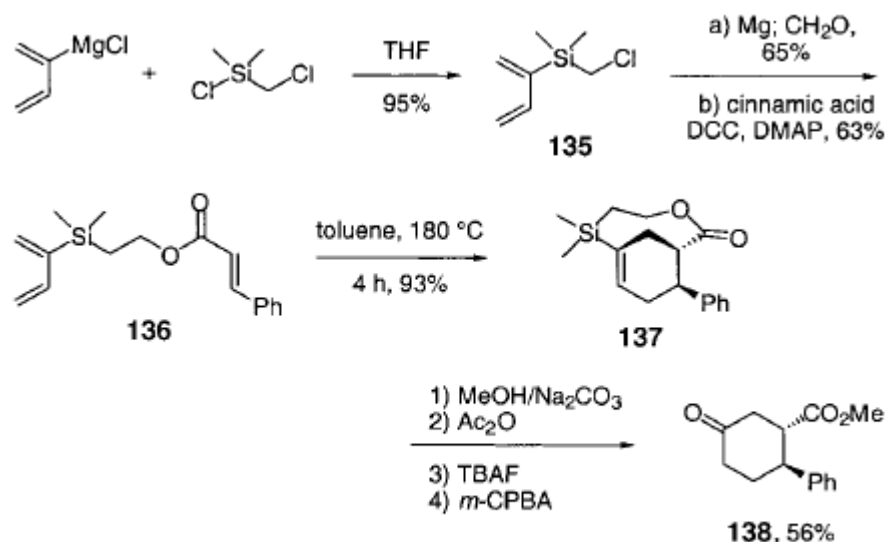
Disposable Tethers between Diene and Dienophile



Scheme 14. A disposable vinyl ether linker in the type 2 IMDA reaction.



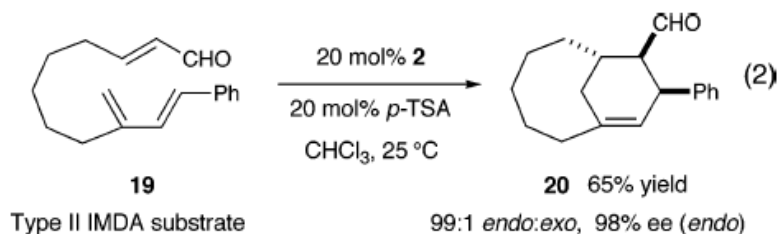
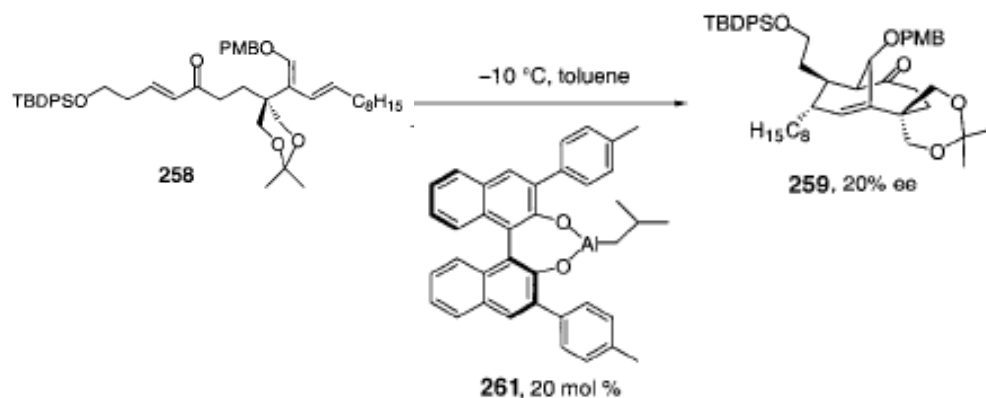
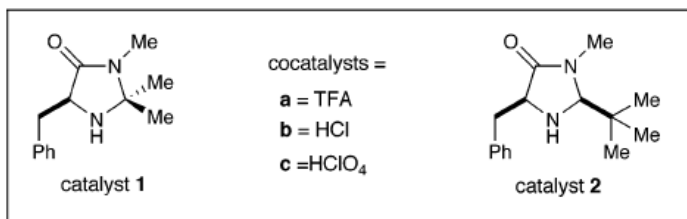
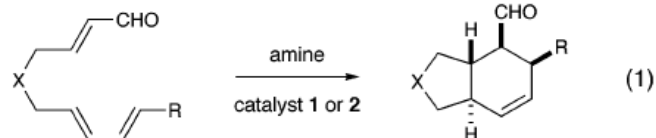
Scheme 17. Elaboration of bridgehead vinyl silanes.



Scheme 16. Synthesis of a cyclohexanone by using a vinyl silane tether.
DCC = dicyclohexylcarbodiimide, DMAP = dimethylaminopyridine.

Enantioselective Intramolecular Diels-Alder

Organocatalytic Intramolecular Diels-Alder (IMDA)



Macmillan, David W. C., *J. Am. Chem. Soc.*, **2005**, *127*, 11616
Nicolaou, K. C., *Angew. Chem. Int. Ed.*, **2000**, *39*, 1829

Stereoselective Elaboration

Addition to the Bridged Double Bond

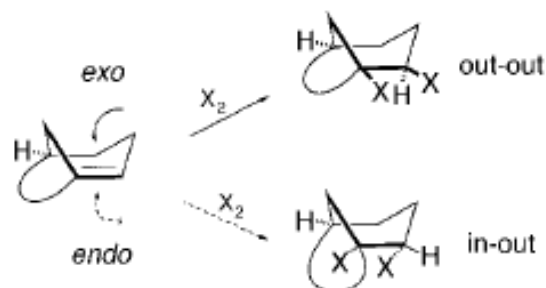
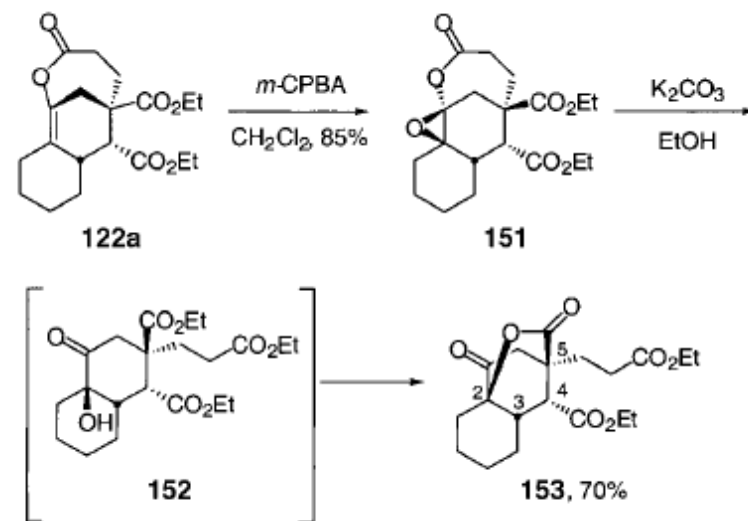
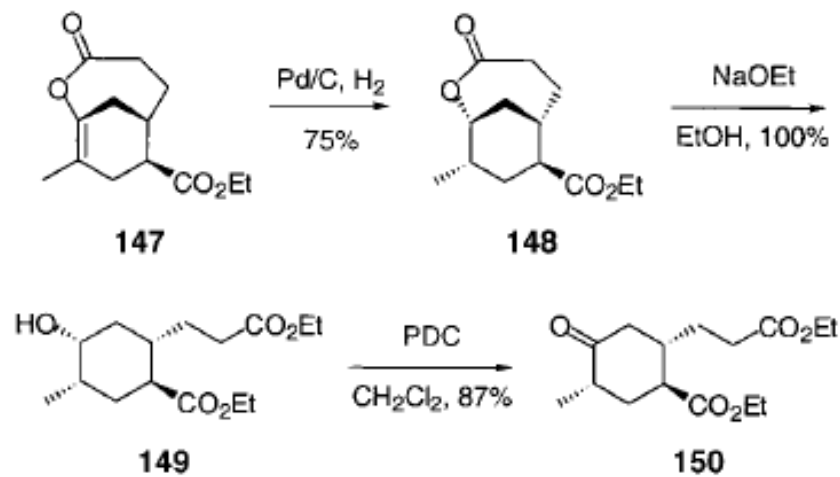
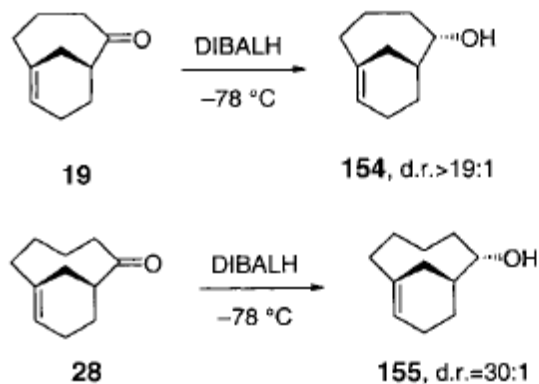


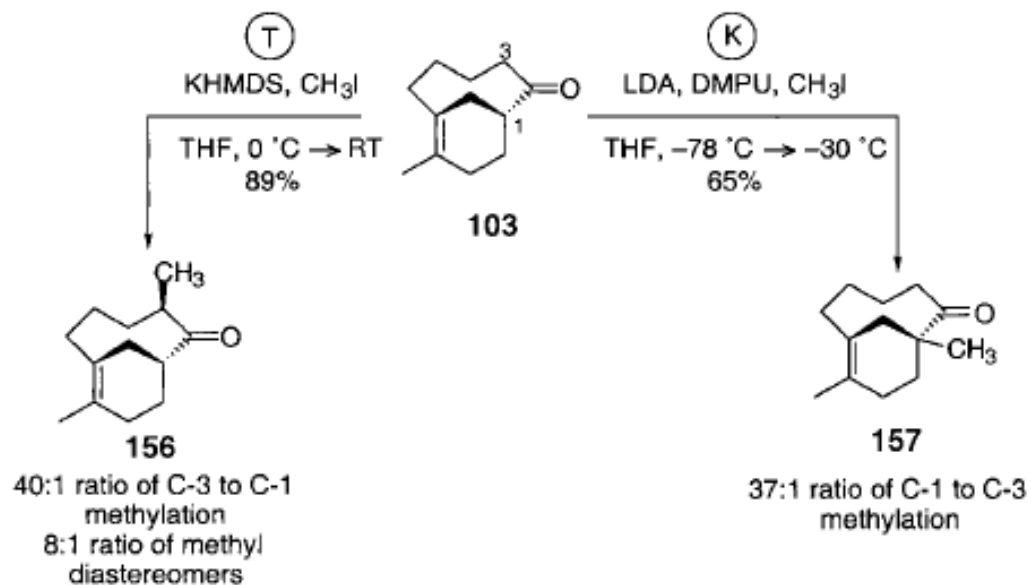
Figure 7. Stereochemistry of the addition to bridgehead double bonds.



Functionalization of the Bridged Ring System



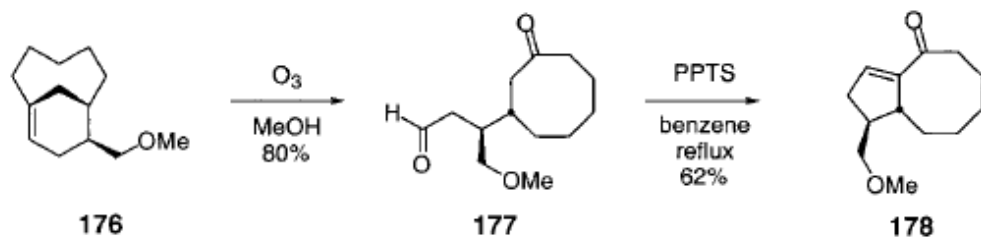
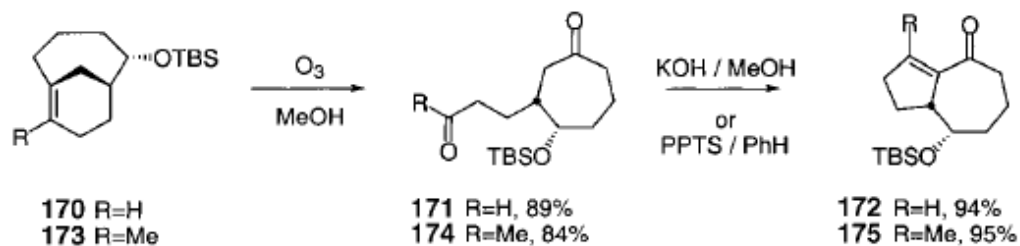
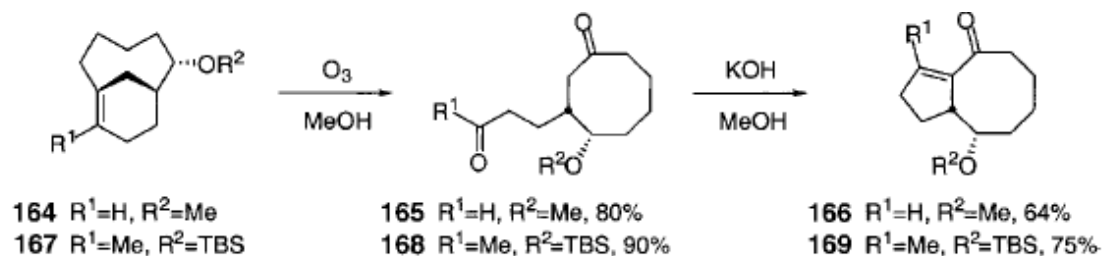
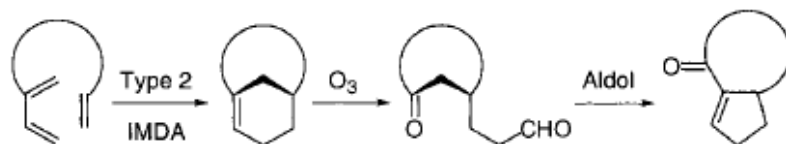
Scheme 20. Stereoselective reduction of bicyclo[*n*.3.1] ketones to give alcohols. DIBALH = diisobutylaluminum hydride.



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

Shea, K. J., *J. Org. Chem.*, **1996**, *61*, 7438
 Shea, K. J., *Tetrahedron Lett.*, **1992**, *33*, 4261

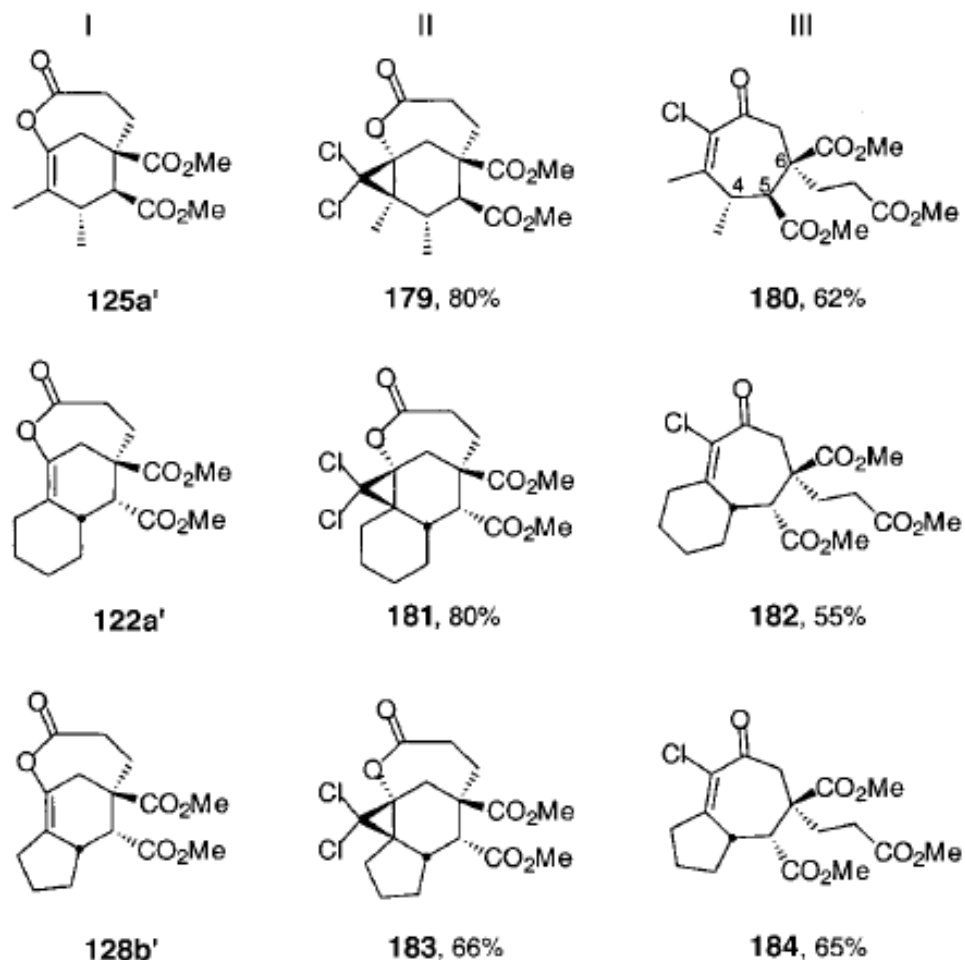
Bridged to Fused Ring Interchange



Scheme 24. Examples for bridged to fused ring interchange. PPTS = pyridinium *para*-toluenesulfonate.

Shea, K. J.,
Tetrahedron Lett., **1995**, *36*, 7177
Tetrahedron Lett., **1996**, *37*, 949

Ring Expansion of Bridged Alkenes

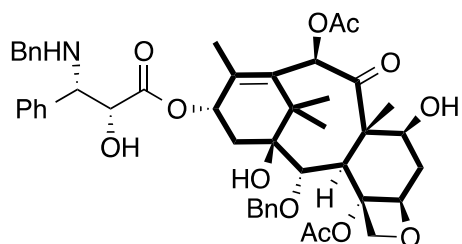


exo addition of dichlorocarbene

Scheme 25. Ring expansion in bridgehead enol lactones (I) to cycloheptenones (III) via cyclopropane intermediates (II).

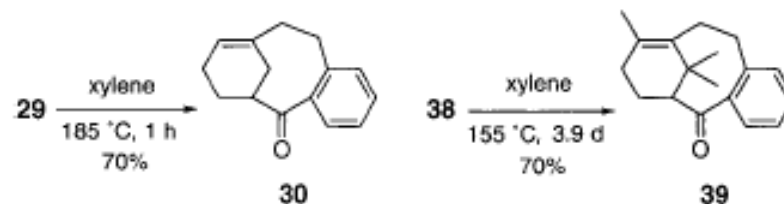
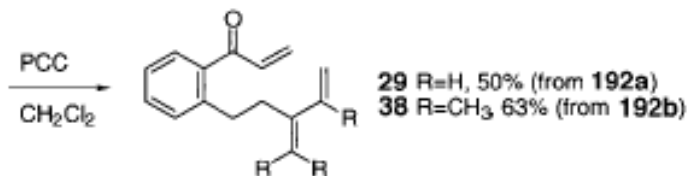
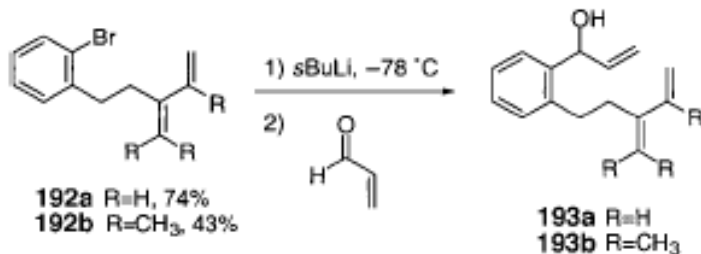
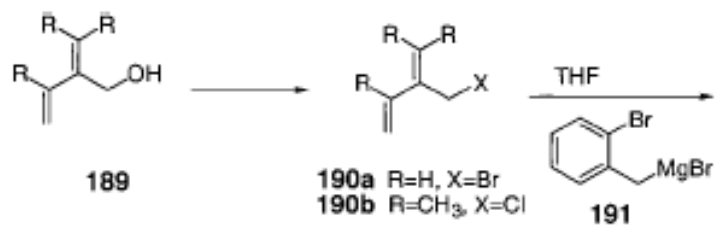
Applications in Natural Product Synthesis

Taxanes



Taxol

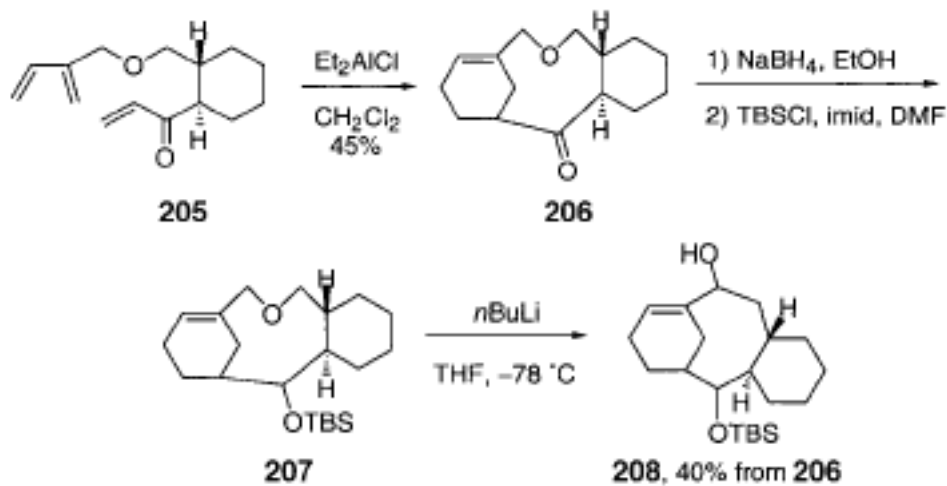
the most celebrated member of the taxane family of natural products
treatment of ovarian cancer
enormous synthetic effort toward the total synthesis of Taxol
bridged tricyclopentadecene ring system with 11 stereocenters and protected oxygen substituents



Scheme 27. Our synthesis of the C-aromatic taxane cores **30** and **39**.

Shea, K. J.,
Angew. Chem. Int. Ed., **1983**, 22, 419

Taxanes (Yadav)

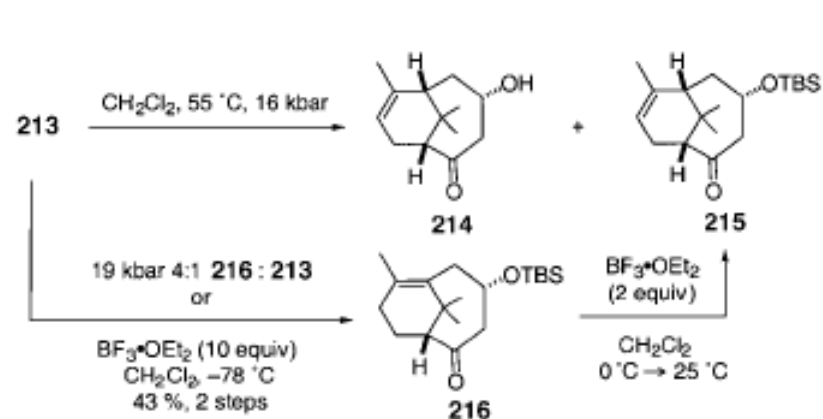
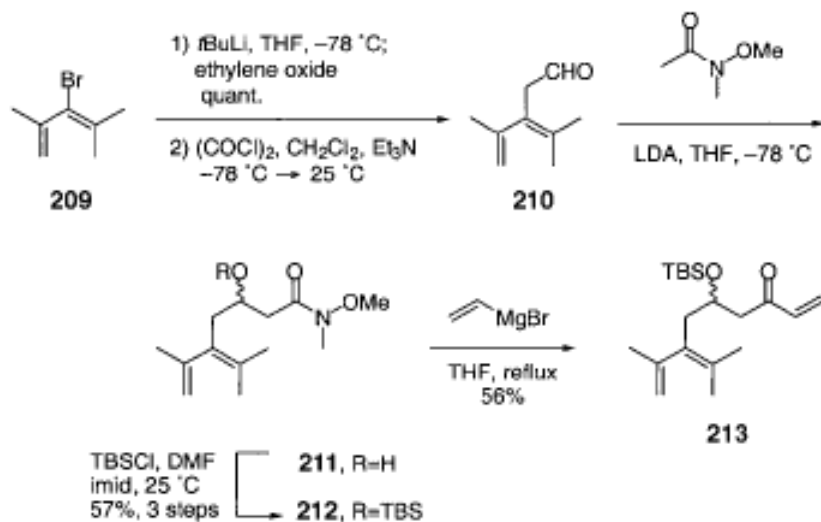


Scheme 30. Synthesis of taxane core **208** according to Yadav and Ravishankar. imid. = imidazole.

Type II IMDA & Wittig rearrangement

Yadav, J. S.,
Tetrahedron Lett., **1991**, 32, 2629

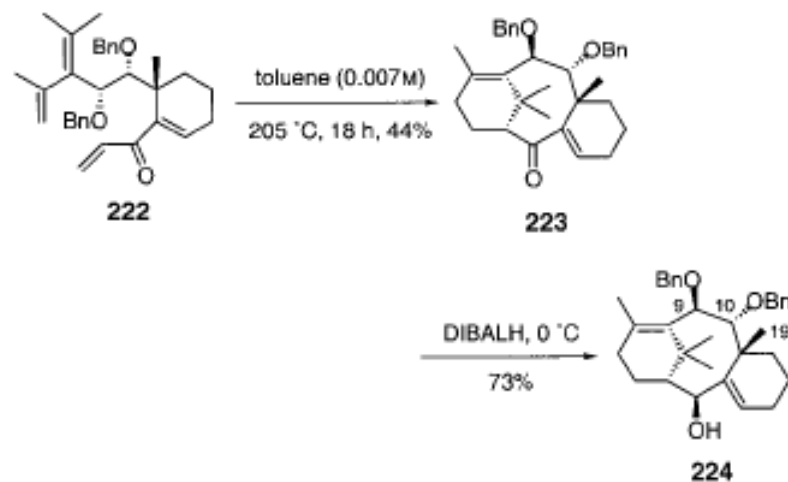
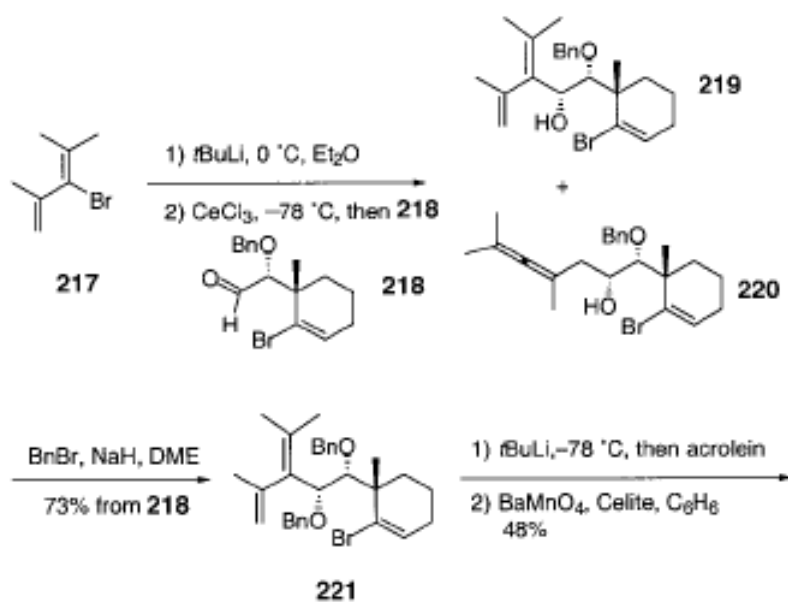
Taxanes (Phillips and Abell)



Scheme 31. Phillips and Abell's high-pressure type 2 IMDA reactions.

Phillips, A. J., Morris, J. C., Abell, A. D., *Tetrahedron Lett.*, **2000**, *41*, 2723

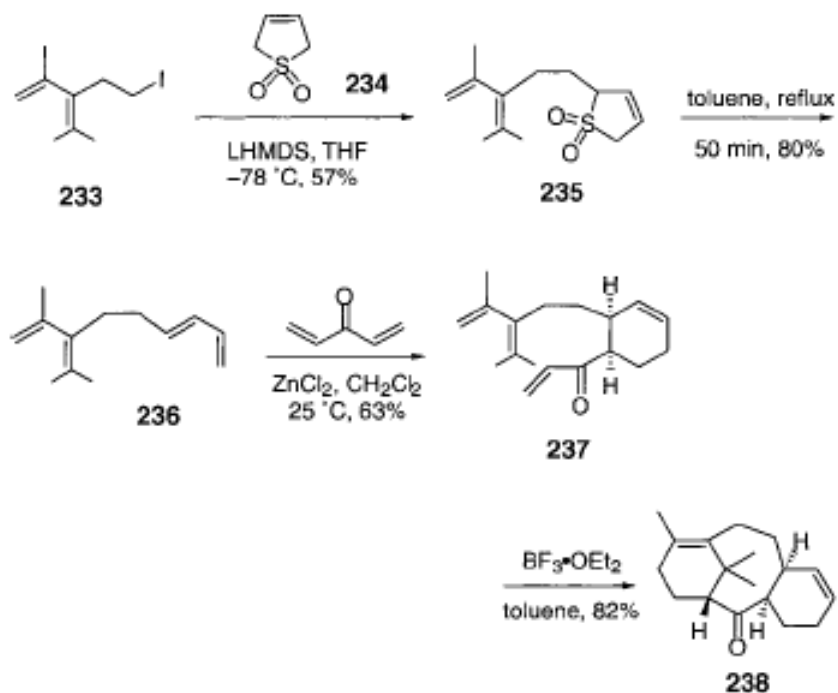
Taxanes



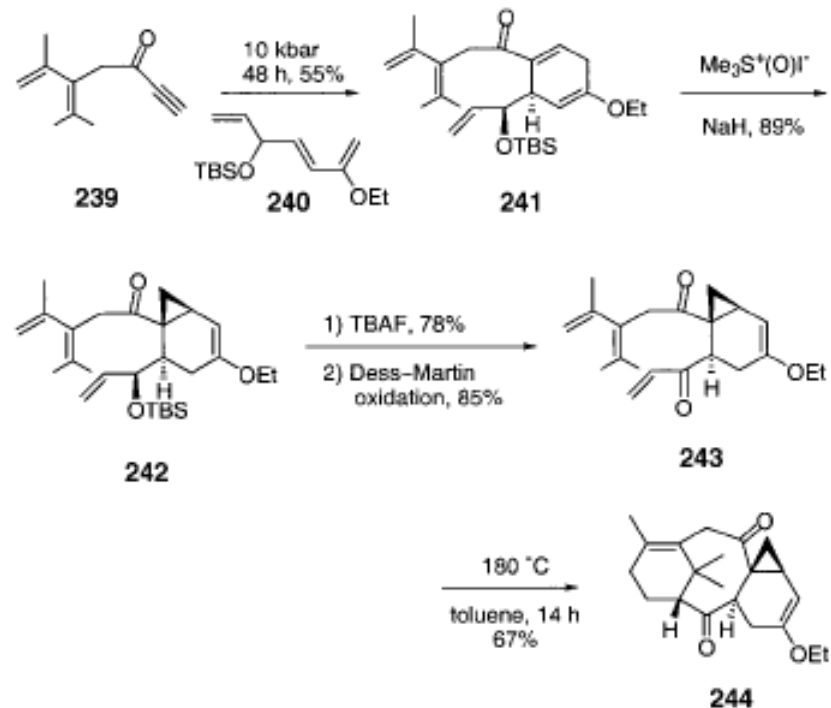
Scheme 32. Our synthesis of the functionalized taxane core **224**. DME = dimethoxyethane, Bn = benzyl.

Shea, K. J.,
Tetrahedron Lett., **1994**, 35, 1317

Taxanes



Scheme 34. Synthesis of taxane core **238** according to Winkler et al.

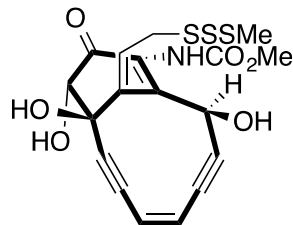


Scheme 35. Synthesis of cyclopropyl taxane derivative **244** according to Winkler et al.

Winkler, J. D.,
Tetrahedron Lett., **1995**, *36*, 687
J. Org. Chem., **1997**, *62*, 2957

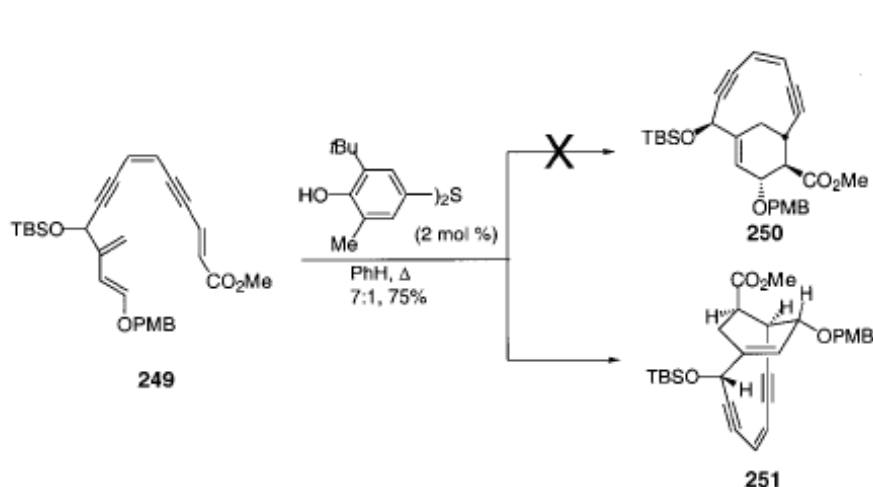
Applications in Natural Product Synthesis

Esperamicin

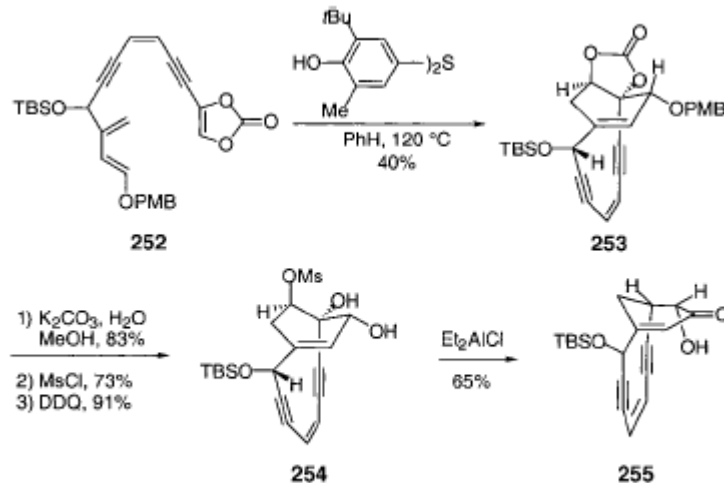


bicyclo[7,3,1]tridecanone bridged core
enediyne structural unit
antitumor agent

Esperamicin A₁ aglycone



Scheme 37. Type 2 IMDA cyclization of polyenyne **249**. PMB = *para*-methylbenzoyl.

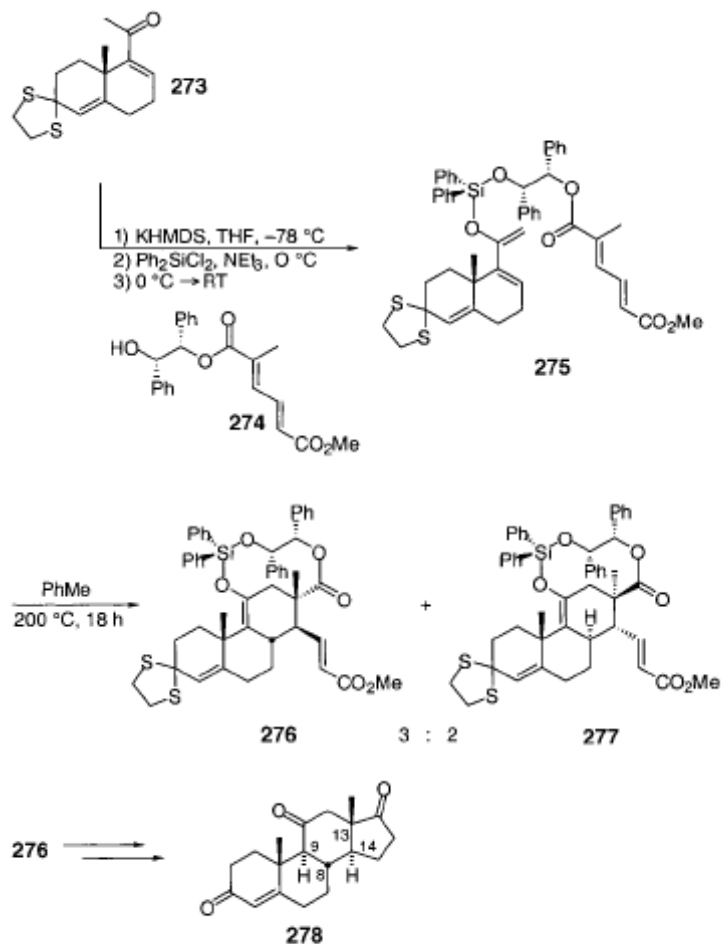


Scheme 38. Synthesis of esperamicin core **255** according to Schreiber et al.
Ms = methanesulfonyl, DDQ = dichlorodicyanobenzoquinone.

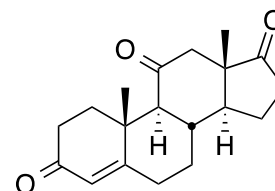
Shea, K. J.,
Angew. Chem. Int. Ed., **1983**, 22, 419

Applications in Natural Product Synthesis

Total Synthesis of (+)-Adrenosterone



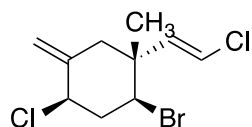
Scheme 43. Our enantioselective synthesis of (+)-adrenosterone (278).



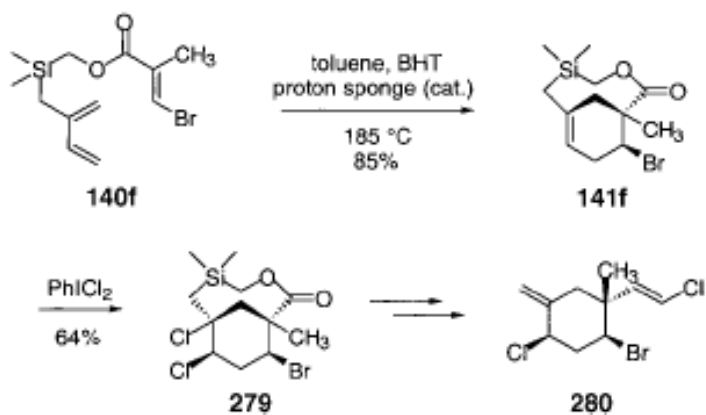
pharmaceutically useful steroids

Shea, K. J.,
J. Am. Chem. Soc., **1996**, *118*, 4711

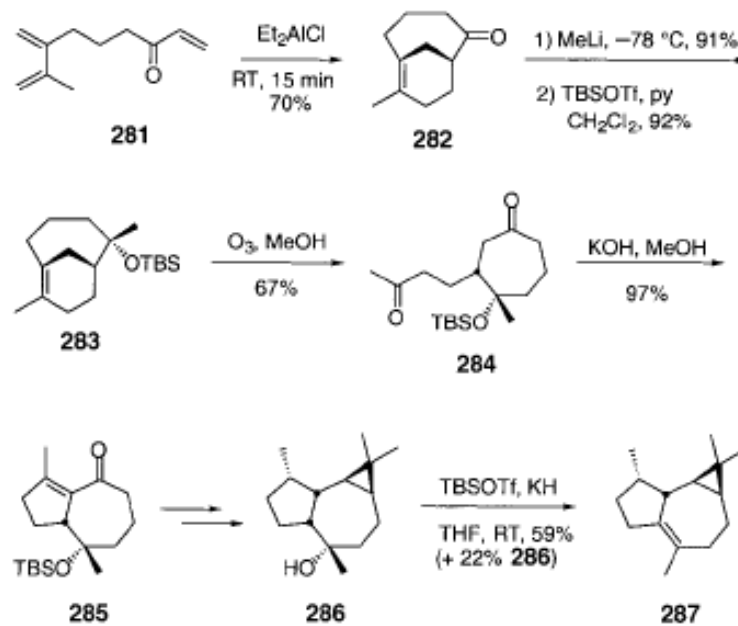
Total Syntheses of Plocamium monoterpene, ledol and ledene



insect antifeedant property
cyclohexane with 3 stereocenters and halogens



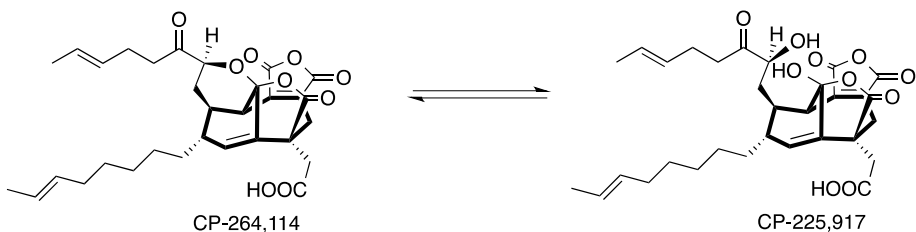
Scheme 44. Our synthesis of *Plocamium* monoterpene **280**.



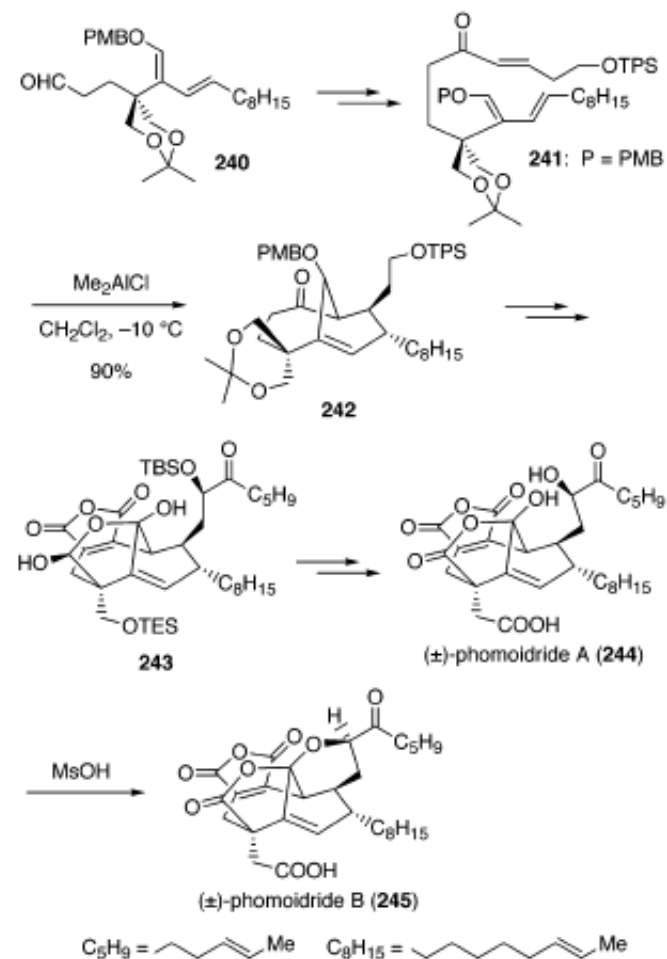
Scheme 45. Our synthesis of ledol (**286**) and ledene (**287**).

Shea, K. J.,
J. Org. Chem., **1996**, *61*, 7438
J. Org. Chem., **1997**, *62*, 8962

Total Synthesis of CP-264,114 (racemic)



cholesterol-lowering and anticancer agents
bicyclo[4,3,1]decene ring system

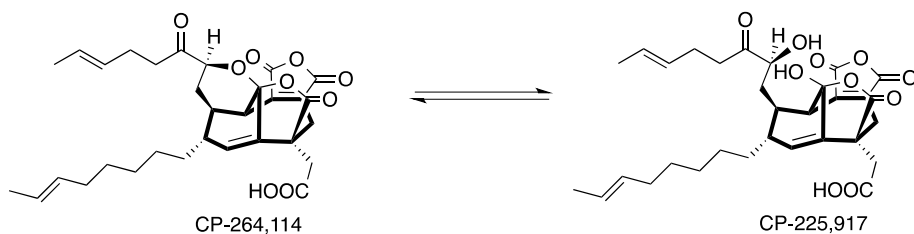


Nicolaou, K. C.,

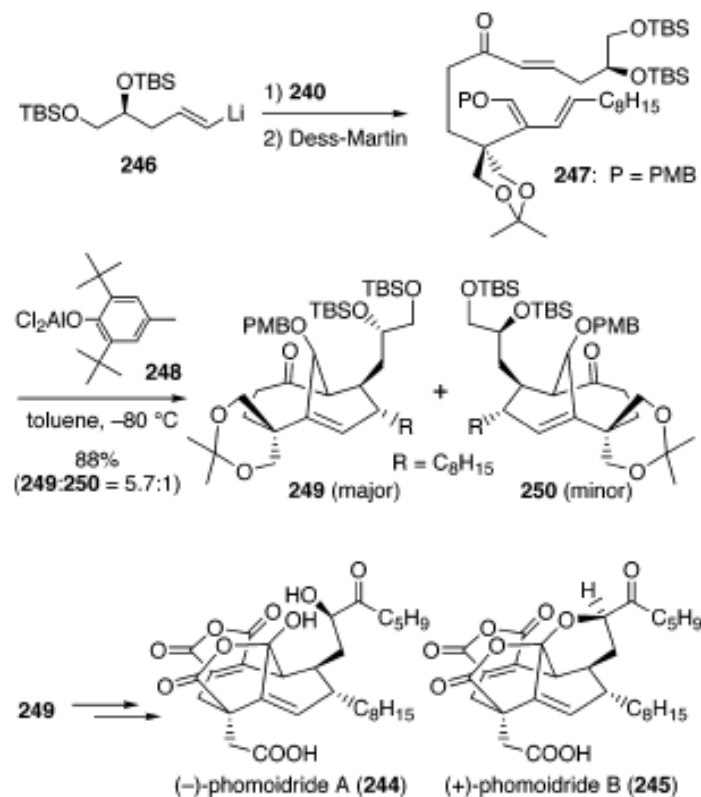
Angew. Chem. Int. Ed., **1999**, 38, 1676

Angew. Chem. Int. Ed., **2000**, 39, 1829

Total Synthesis of CP-264,114 (asymmetric)



cholesterol-lowering and anticancer agents
bicyclo[4,3,1]decene ring system



Nicolaou, K. C.,

Angew. Chem. Int. Ed., **1999**, 38, 1676

Angew. Chem. Int. Ed., **2000**, 39, 1829

Conclusion

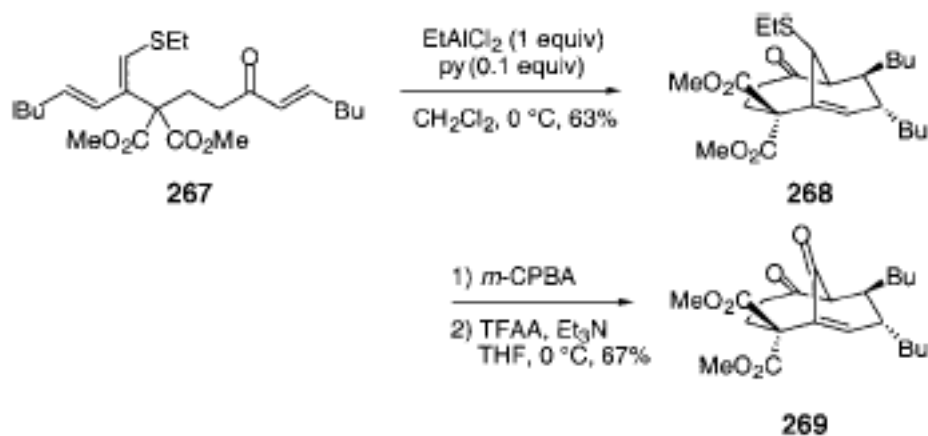
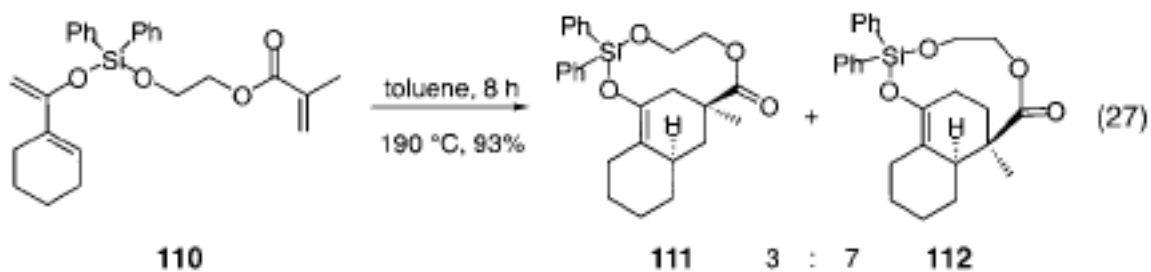
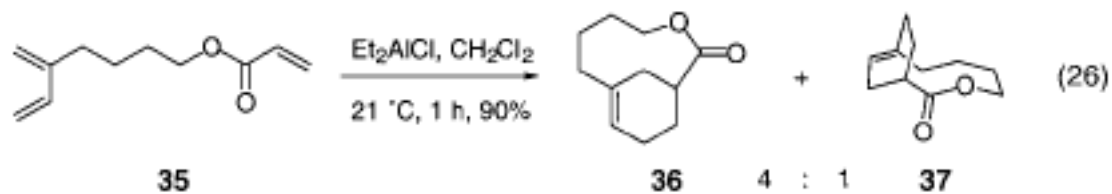
- Type II intramolecular Diels-Alder reaction
 - provides bridgedhead alkenes
 - access to other compounds through disposable tethers, bridged to fused interchange, and ring expansion
 - the most useful synthetic method for forming 7, 8-membered rings embedded in the bicyclic structure
 - used in natural product synthesis



Thank you



Quiz !



Quiz !

