

Conformational Analysis of Medium Rings And Applications to Total Synthesis

A MacMillan Group Meeting

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6 June 2003

- I. Introduction
- II. Eight-membered rings
 - A. Conformational preferences
 - B. Applications to total synthesis
- III. Ten-membered rings
 - A. Conformational preferences
 - B. Applications to total synthesis
- IV. Conclusion

Lead references:

Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 1981

Vedejs, E.; Dent III, W. H.; Gapinski, D. M.; McClure, C. K. *J. Am. Chem. Soc.* **1987**, *109*, 5437

Introduction

- Medium rings are defined as rings of eight to (usually) fourteen atoms.
- Seven membered rings are not included. The upper limit on the size of these rings is still a matter of debate.
- Medium rings obey different sets of rules regarding conformational analysis, than cyclohexanes, usually emphasizing avoidance of transannular nonbonded interactions.
- Simple computations (i.e. MM2) can usually predict the conformations of these rings with reasonable accuracy.
- Clark Still was the first to recognize this and make use of computation to predict the reactivity of medium ring compounds. He used starting materials, products, or intermediates to approximate transition states (according to the Hammond Postulate).
- The reactivity of eight- and ten- membered rings can be predicted qualitatively with the most reliability. Nine-membered rings or larger often require computational analysis.

Conformational Preferences of Eight-Membered Rings

Diaxial interactions not necessarily paramount

■ Lowest energy conformers of cyclooctane



"Boat-Boat" (BB) Conformation

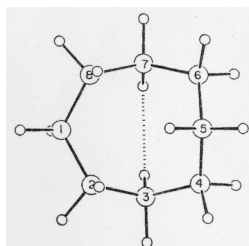
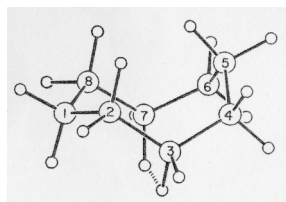


"Chair-Chair" (CC) Conformation



"Boat-Chair" (BC) Conformation
energetically preferred

■ Effect of (methyl) substitution

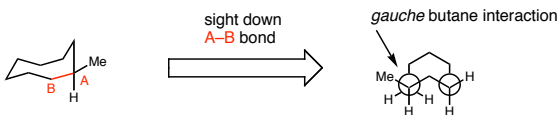


Position	Pseudo A value kcal mol ⁻¹
1	1.8
2	2.8
3	> 4.5
4	-0.3
5	6.1

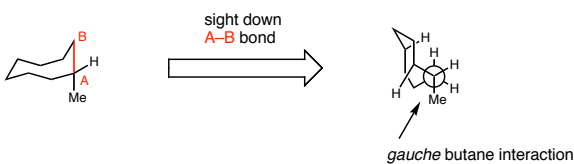
Take home lesson: avoidance of unfavorable transannular interactions dictates conformational preferences

Why is the corner position favored for substitution?

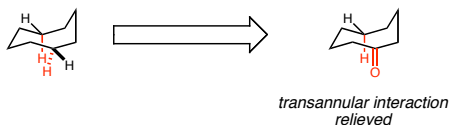
■ Pseudoequatorial substitution



■ Pseudoaxial substitution



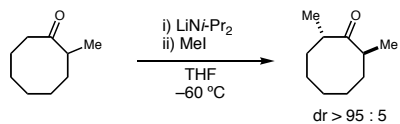
■ Also, sp^2 carbons will primarily go to the 3 or 7 positions



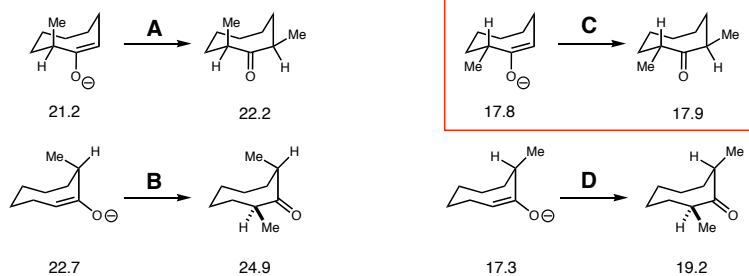
Enolate Alkylation of Methylcyclooctanone Derivatives

Boat-chair model proves useful in prediction of stereoselectivity

■ Alkylation of 2-Methylcyclooctanone



■ Analysis of enolate intermediates (MM2 minimization)

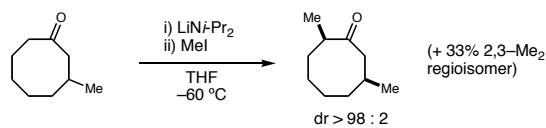


Conformers in **C** avoid transannular interaction in alkylation transition state

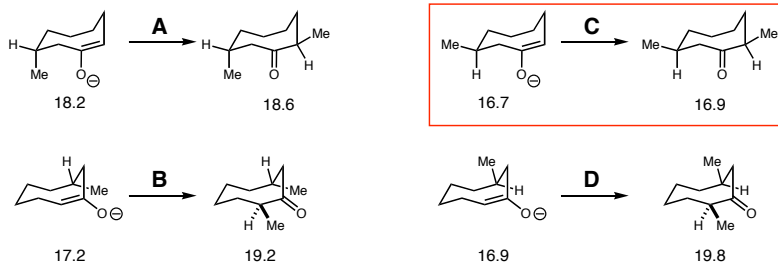
Enolate Alkylation of Methylcyclooctanone Derivatives

Different regioisomers lead to different diastereoselectivity

■ Alkylation of 3-methylcyclooctanone



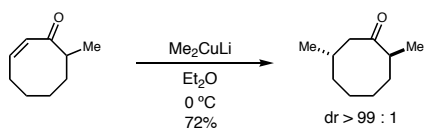
■ Analysis of enolate intermediates (MM2 minimization)



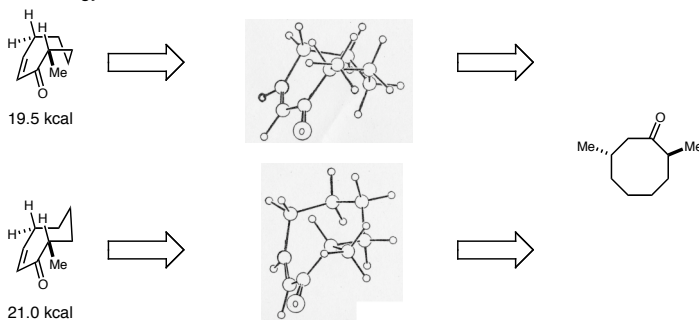
Conformers in **C** avoid transannular interaction in alkylation transition state

Conjugate Addition to Methylcyclooctenone

Planarity of π -system enforces different conformation



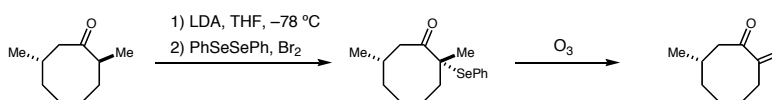
■ Two low energy conformers accessible



Conformers with pseudoaxial methyl groups are destabilized by > 4 kcal

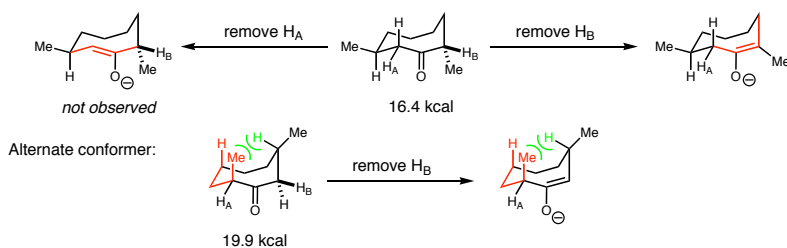
Hydrogenation of α -Methylenemethylcyclooctanone

Preparation of substrate yields unexpected regioisomer



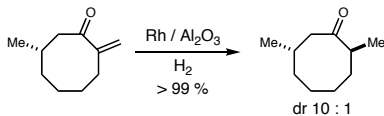
■ Stereoelectronic effect explains unusual regioselectivity

- Assume: 1) Only protons perpendicular to the carbonyl π -system can be removed
2) Enolates with *trans*-cyclooctene resonance forms strongly disfavored

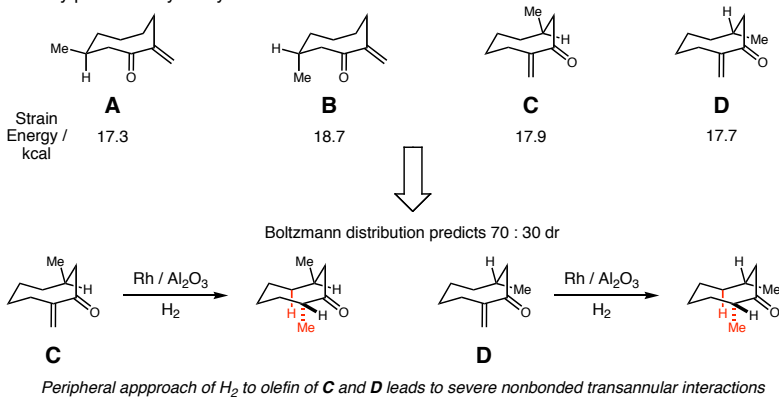


Hydrogenation of α -Methylenemethylcyclooctanone

Good selectivity for trans diastereomer observed

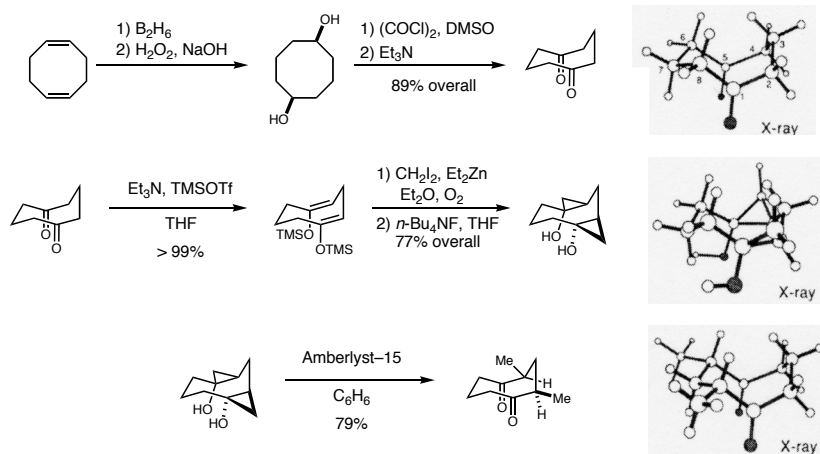


■ Selectivity predicted by analysis of reactant conformers



Schreiber: X-Ray Analysis of Cyclooctadiene Derivatives

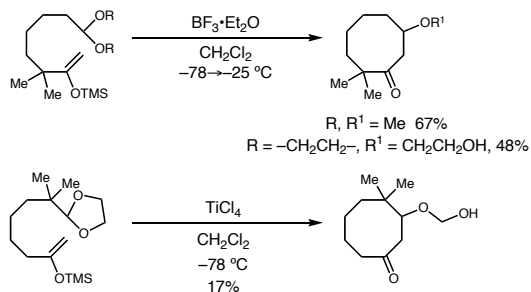
Tangible proof of conformational preferences



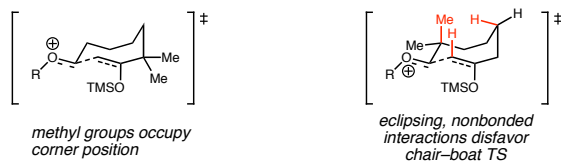
Schreiber, S. L.; Smith, D. B.; Schulte, G. *J. Org. Chem.* **1989**, *54*, 5994.

Kocienski: Intramolecular Mukaiyama Aldols

Conformational analysis applied to transition states



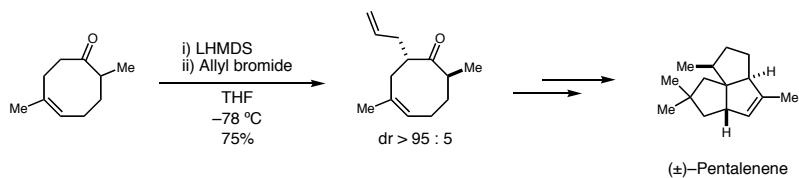
■ Explanation for diminution in yield:



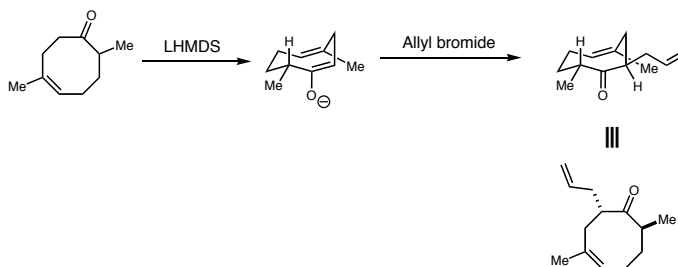
Cockerill, G. S.; Kocienski, P.; Treadgold, R. *J. Chem. Soc. Perkin Trans. 1* **1985**, 2101.

Application to Total Synthesis of (\pm)-Pentalenene

Enolate alkylation exploited to set relative stereochemistry



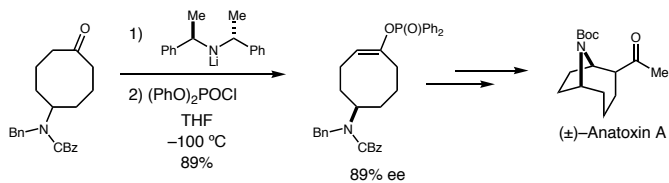
■ Stereochemical rationale:



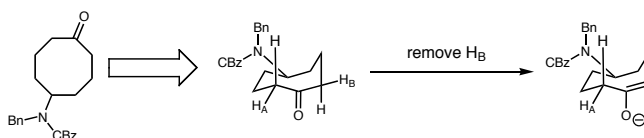
Mehta, G.; Rao, K. W. *J. Am. Chem. Soc.* **1986**, 108, 8015.

Application to Formal Total Synthesis of (+)-Anatoxin A

Asymmetric deprotonation used to desymmetrize intermediate



■ Rationale for selectivity in deprotonation:

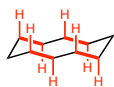


Aggarwal, V. K.; Humphries, P. S.; Fenwick A. *Angew. Chem. Int. Ed.* **1999**, *38*, 1985.

Conformational Preferences of Ten-Membered Rings

Preferred conformers minimize eclipsing interactions

■ Lowest energy conformers of cyclooctane

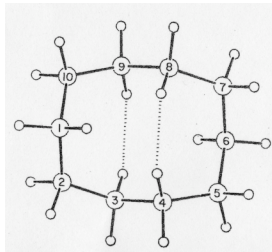
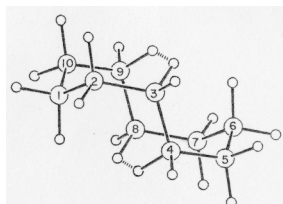


"Chair-Chair-Chair" (CCC) Conformation



"Boat-Chair-Boat" (BCB) Conformation
energetically preferred

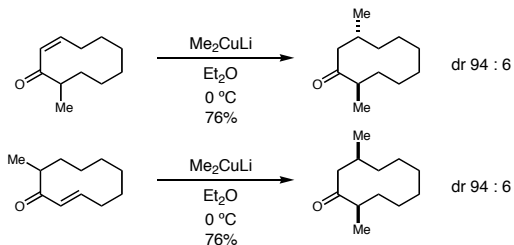
■ Effect of (methyl) substitution



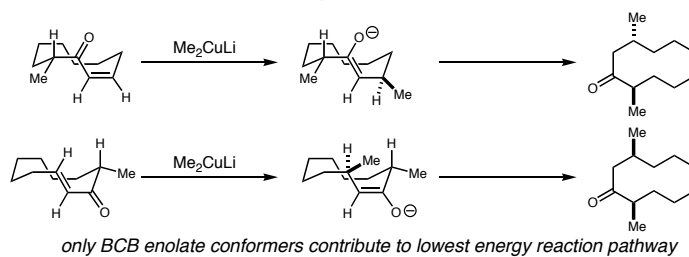
Position	Pseudo A value kcal mol^{-1}
1	6.6
2	0.0
3	9.2

Conjugate Addition to Methylcyclodecenones

BCB ground state successfully predicts products



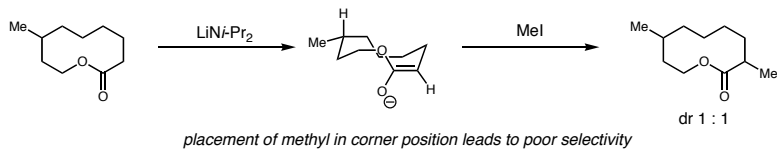
■ Peripheral attack of methyl nucleophile gives observed selectivity



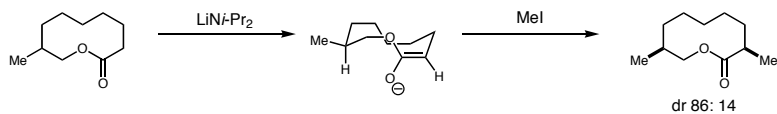
Enolate Alkylation of Methylcyclodecanones

Regioisomers drastically affect diastereoselectivity

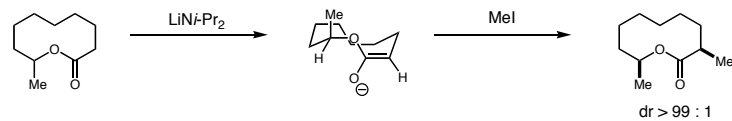
■ 7-Methyl derivative



■ 8-Methyl derivative



■ 9-Methyl derivative

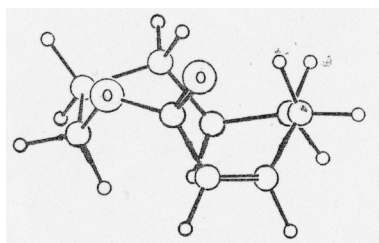


Proximity of methyl group to enolate directly proportional to diastereoselectivity

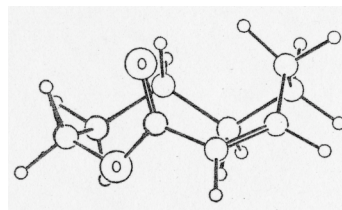
Conjugate Addition to Methylcyclodecenoates

Planarity of π -system requires consideration of alternate conformers

- Energetically accessible conformers:



BCB (25.6 kcal)



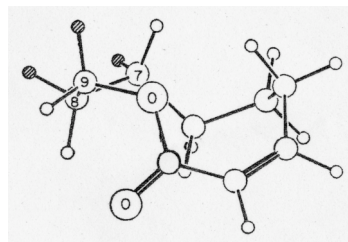
BCC (24.9 kcal)

These conformations inhibit planarity of enone; loss in ester resonance costs ~ 10 kcal

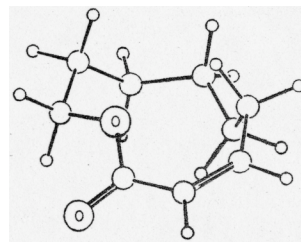
Conjugate Addition to Methylcyclodecenoates

Planarity of π -system requires consideration of alternate conformers

- Alternate conformers allowing planarity:

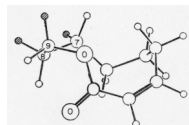


distorted BCB (25.9 kcal)

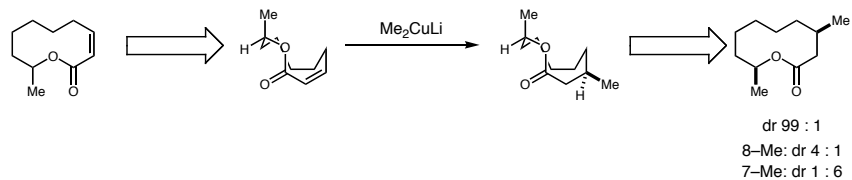


27.0 kcal

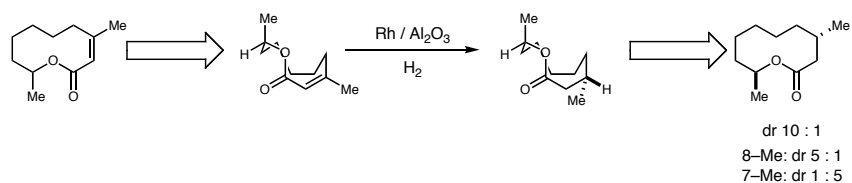
Conjugate Addition to Methylcyclodecenoates (cont'd)



distorted BCB (25.9 kcal)



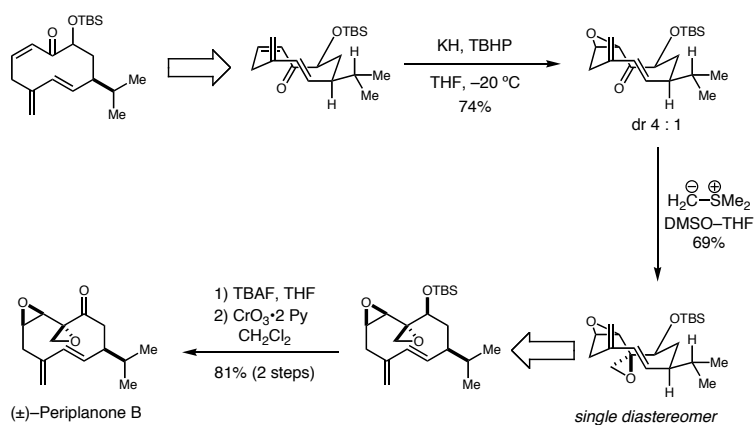
■ Same conformational bias predicts result of hydrogenation



Still: Total Synthesis of (±)-Periplanone B

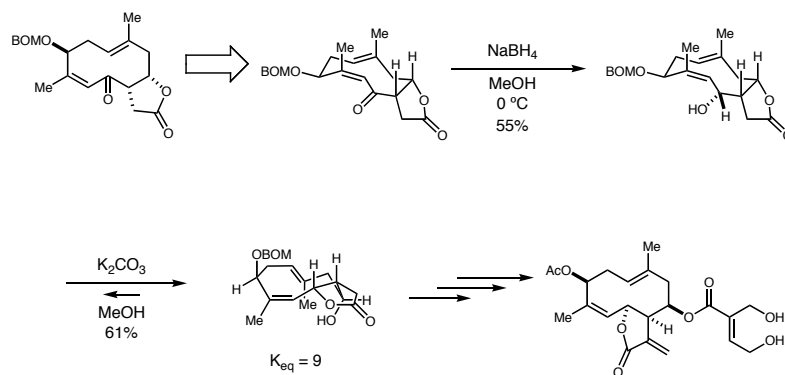
Peripheral attack of reagents on BCB conformer provides stereocontrol

- Periplanone B: sex pheromone of American female cockroach
- Attempts to isolate from cockroaches: 75,000 virgin female cockroaches → 200 µg periplanone B



Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493.

Still: Total Synthesis of Eucannabinolide

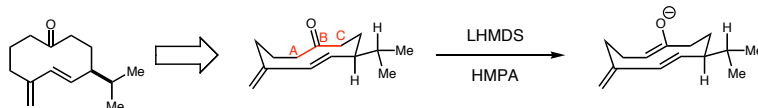


Still, W. C. *J. Am. Chem. Soc.* **1983**, *105*, 625.

Schreiber: Total Synthesis of Germacrene-D

Conformational preference dictates regio- and stereo- selectivity of enolization

- BCC conformation predicted by MM2 minimization



- Newman projection of A-B bond:



antiperiplanar alignment set up for enolization

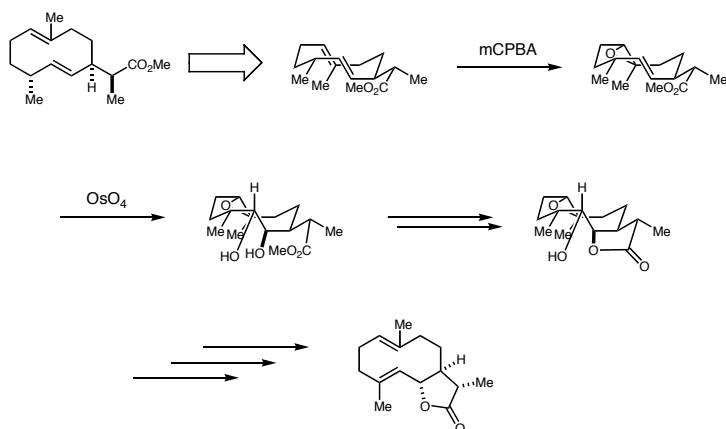
- Newman projection of C-B bond:



formation of enolate requires reorientation and additional strain due to gauche relationship

Schreiber, S. L.; Hawley, R. C. *Tetrahedron Lett.* **1985**, *26*, 5971.

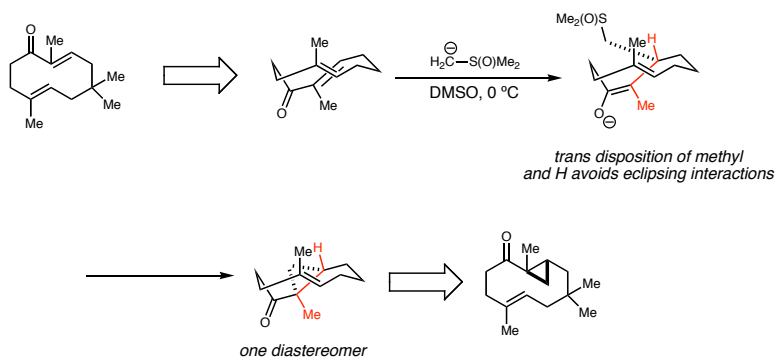
Total Synthesis of (+)-Dihydrocostunolide



Raucher, S.; Chi, K.-W.; Hwang, K.-J.; Burks, Jr., J. E. *J. Org. Chem.* **1986**, *51*, 5503.

Total Synthesis of Bicyclohumulenone

Cyclopropanation directed by preferred enolate conformation



Takahashi, T.; Yamashita, Y.; Doi, T.; Tsuji, J. *J. Org. Chem.* **1989**, *54*, 4273.

Conclusion

- The conformational analysis of medium rings relies on mainly on avoidance of transannular strain, and is usually more complicated than with cyclohexanes.
 - Eight- and ten-membered rings often have predictable ground state conformations ("boat-chair" and "boat-chair-boat", respectively).
 - When these ground state conformations do not accurately predict or explain reactivity, molecular modeling (on a simple level) can often predict reactivity in a semiquantitative fashion.
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