**Conformational Analysis of Medium Rings**

**And Applications to Total Synthesis**

A MacMillan Group Meeting  
Presented by Brian Kwan  
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:  

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**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

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

<table>
<thead>
<tr>
<th>Position</th>
<th>Pseudo A value kcal mol$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td>2</td>
<td>2.8</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 4.5</td>
</tr>
<tr>
<td>4</td>
<td>−0.3</td>
</tr>
<tr>
<td>5</td>
<td>6.1</td>
</tr>
</tbody>
</table>

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 Methyloctanone Derivatives**

_Boat–chair model proves useful in prediction of stereoselectivity_

- **Alkylation of 2-Methylcyclooctanone**

  ![Chemical structure](image)

  i) LiN[Pr₂]
  ii) Mel
  THF
  -60 °C
  dr > 95 : 5

- **Analysis of enolate intermediates (MM2 minimization)**

  ![Chemical structures](image)

  Conformers in C avoid transannular interaction in alkylation transition state

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**Enolate Alkylation of Methyloctanone Derivatives**

_Different regioisomers lead to different diastereoselectivity_

- **Alkylation of 3-methyloctane**

  ![Chemical structure](image)

  i) LiN[Pr₂]
  ii) Mel
  THF
  -60 °C
  (+ 33% 2,3-Me₂ regioisomer)
  dr > 98 : 2

- **Analysis of enolate intermediates (MM2 minimization)**

  ![Chemical structures](image)

  Conformers in C avoid transannular interaction in alkylation transition state
Conjugate Addition to Methylclooctenone

Planarity of \( \pi \)-system enforces different conformation

\[
\begin{align*}
\text{Me,CuLi} & \quad \text{Et}_{2}O \\
\text{0 °C} & \quad \text{dr} > 99 : 1
\end{align*}
\]

- Two low energy conformers accessible

Conformers with pseudoaxial methyl groups are destabilized by > 4 kcal

Hydrogenation of \( \alpha \)-Methylenemethylcyclooctanone

Preparation of substrate yields unexpected regioisomer

- Stereoelectronic effect explains unusual regioselectivity

Assume:
1. Only protons perpendicular to the carbonyl \( \pi \)-system can be removed
2. Enolates with trans-cycloctene resonance forms strongly disfavored

Alternate conformer:

Typical kinetic bias for formation of less substituted enolate: 1.5–3 kcal mol\(^{-1}\)
**Hydrogenation of α-Methylenemethylcyclooctanone**

Good selectivity for trans diastereomer observed

![Chemical structure and reaction]

Selectivity predicted by analysis of reactant conformers

<table>
<thead>
<tr>
<th>Conformer</th>
<th>Strain Energy / kcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>17.3</td>
</tr>
<tr>
<td>B</td>
<td>18.7</td>
</tr>
<tr>
<td>C</td>
<td>17.9</td>
</tr>
<tr>
<td>D</td>
<td>17.7</td>
</tr>
</tbody>
</table>

Boltzmann distribution predicts 70:30 dr

Peripheral approach of H₂ to olefin of C and D leads to severe nonbonded transannular interactions

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**Schreiber: X–Ray Analysis of Cyclooctadiene Derivatives**

Tangible proof of conformational preferences

![Chemical structure and reaction]

**Kocienski: Intramolecular Mukaiyama Aldols**

Conformational analysis applied to transition states


- Explanation for diminution in yield:

  methyl groups occupy corner position

  eclipsing, nonbonded interactions disfavor chair–boat TS

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**Application to Total Synthesis of (±)-Pentalenene**

Enolate alkylation exploited to set relative stereochemistry

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

Asymmetric deprotonation used to desymmetrize intermediate

Rationale for selectivity in deprotonation:


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

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<thead>
<tr>
<th>Position</th>
<th>Pseudo A value kcal mol⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.6</td>
</tr>
<tr>
<td>2</td>
<td>0.0</td>
</tr>
<tr>
<td>3</td>
<td>9.2</td>
</tr>
</tbody>
</table>
**Conjugate Addition to Methylcyclodecenones**

*BCB* ground state successfully predicts products

\[
\begin{align*}
\text{MeCPLi} & \quad \text{EtO} \quad 0 \degree \text{C} \quad 76\% \\
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\end{align*}
\]

- Peripheral attack of methyl nucleophile gives observed selectivity

\[
\begin{align*}
\text{MeCPLi} & \quad \text{EtO} \quad 0 \degree \text{C} \quad 76\%
\end{align*}
\]

only *BCB* enolate conformers contribute to lowest energy reaction pathway

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**Enolate Alkylation of Methylcyclodecanones**

*Regioisomers drastically affect diastereoselectivity*

- 7–Methyl derivative

\[
\begin{align*}
\text{MeCPLi} & \quad \text{EtO} \quad 0 \degree \text{C} \quad 76\%
\end{align*}
\]

placement of methyl in corner position leads to poor selectivity

- 8–Methyl derivative

\[
\begin{align*}
\text{MeCPLi} & \quad \text{EtO} \quad 0 \degree \text{C} \quad 76\%
\end{align*}
\]

- 9–Methyl derivative

\[
\begin{align*}
\text{MeCPLi} & \quad \text{EtO} \quad 0 \degree \text{C} \quad 76\%
\end{align*}
\]

Proximity of methyl group to enolate directly proportional to diastereoselectivity
Conjugate Addition to Methylcyclodecenoates

Planarity of \( \pi \)-system requires consideration of alternate conformers

- Energetically accessible conformers:

  ![Conformers](image1.png)

  BCB (25.6 kcal)  
  BCC (24.9 kcal)

  These conformations inhibit planarity of enone; loss in ester resonance costs \( \sim 10 \text{ kcal} \)

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Conjugate Addition to Methylcyclodecenoates

Planarity of \( \pi \)-system requires consideration of alternate conformers

- Alternate conformers allowing planarity:

  ![Conformers](image2.png)

  distorted BCB (25.9 kcal)  
  27.0 kcal
Conjugate Addition to Methylcyclodecenoates (cont'd)

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: Total Synthesis of Eucannabinolide**

Schreiber, S. L.; Hawley, R. C. Tetrahedron Lett. 1985, 26, ... of C–B bond:

**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

Total Synthesis of (+)-Dihydrocostunolide


Total Synthesis of Bicyclohumulenone

Cyclopropanation directed by preferred enolate conformation

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.