Strategies for the Construction of Medium-Sized Rings

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Medium-Sized Ring Natural Products

- jasmine lactone
- octalactin
- xestodecalactone A
- punctaporonine
- zhijiangunsu
- CGS25155
- periplanone B
- dihydrocostunolide
- ferrulactone I
- asteriscanolide
- taxusin
- anadensin
- citreofuran
- eremantholide A
- cripowellin glycon
- magallanesine
- epoxydictyymene
- caryophyline
Classification of Medium-Sized Rings

Rings containing 12 or more atoms fall into the large ring category.
Rings containing 17 or more atoms are so large they are barely distinguishable from their acyclic analogs.

The Difficulty with Medium-Sized Rings

**ENTROPY**

**Kinetic Implications:**
The probability of an end to end reaction in a bifunctional linear chain molecule decreases as the length of the chain increases.

**Torsional degrees of freedom are limited by the ring-like transition state for cyclization.**

**Thermodynamic Implications:**
The product cycle limits the number of torsional degrees of freedom between covalently bonded groups compared to the linear chain molecule.

**ENTHALPY**

**Kinetic Implications:**
The activation energy for ring closure reflects the ring strain of the transition state for cyclization.

**Thermodynamic Implications:**
Strain present in the product cycle destabilizes medium-sized rings.
**Origins of Ring Strain in Medium-Sized Rings**

Bond Opposition Forces (also known as Pitzer strain)
The result of unfavorable eclipsing interactions in a given conformation
Dominant source of strain for common rings (5-, 6-, 7-membered rings)

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**Origins of Ring Strain in Medium-Sized Rings**

Bond Angle Distortion (also known as Baeyer strain)
Often broken down into two categories: small angle and large angle strain
Dominant source of strain for small rings (3- and 4-membered rings)
**Origins of Ring Strain in Medium-Sized Rings**

Transannular Orbital Interactions

Often confused with van der Waal radii compression
Results from unfavorable steric interactions between groups that lie across the ring from one another

Cannot be avoided in medium-sized rings without adding severe torsional and bond angle distortion!

Elimination of transannular interactions comes at the cost of minimized Baeyer and Pitzer strains

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**Entropy vs. Enthalpy**

For small ring formations:

- Large enthalpic cost (Pitzer and Baeyer strain) in the transition state and product cycle

- Relatively small entropic cost in the transition state with significant entropic cost in the product cycle due to loss of torsional degrees of freedom
Entropy vs. Enthalpy

For small ring formations:
- Large enthalpic cost (Pitzer and Baeyer strain) in the transition state and product cycle
- Relatively small entropic cost in the transition state with significant entropic cost in the product cycle due to loss of torsional degrees of freedom

For large ring formations:
- Small enthalpic cost
- Large entropic cost in the transition state but little to no entropic cost in the product cycle

For medium ring formations:
- Very large enthalpic cost due to transannular interactions in the transition state and product
- Substantial entropic cost in the transition state with smaller entropic costs in the product cycle
Quantitative Evaluation of Cyclization Reactions: Effective Molarity

Effective Molarity (EM): Quantitative measure of the ease of ring closure

For studies of reaction rates:

\[ EM = \frac{k_{\text{intra}}}{k_{\text{inter}}} \]  

(1)

For equilibrium studies:

\[ EM = K_{\text{intra}}/K_{\text{inter}} \]  

(2)

In case that's not enough math:

\[ EM = \exp \left(-\frac{\Delta H_{\text{inter}} - \Delta H_{\text{intra}}}{RT} \right) \cdot \exp \left(\frac{\Delta S_{\text{inter}} - \Delta S_{\text{intra}}}{R}\right) \]  

(3)

\( \Delta H \) and \( \Delta S \) should be read as \( \Delta H^\circ \) and \( \Delta S^\circ \) (equilibrium case) and \( \Delta H^f \) and \( \Delta S^f \) (rate case)

(derived from applying either TS theory or thermodynamics to Eq. 1 and 2)

But we can make Eq. 3 easier to handle:

\[ EM = EM_H \times EM_S \]  

(4)

Bottom line: Enthalpy and Entropy independently affect the ease of ring closure


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Quantitative Evaluation of Cyclization Reactions: Effective Molarity

The EM for a system represents an intramolecular reactivity that has been corrected for the inherent reactivity of the end groups

Just a few comments on Eq. 3:

\[ EM = \exp \left(-\frac{\Delta H_{\text{intra}} - \Delta H_{\text{inter}}}{RT} \right) \cdot \exp \left(\frac{\Delta S_{\text{intra}} - \Delta S_{\text{inter}}}{R}\right) \]  

(3)

\( (\Delta H_{\text{intra}} - \Delta H_{\text{inter}}) \) = strain energy of the ring

\( (\Delta H_{\text{intra}} - \Delta H_{\text{inter}}) \) = strain energy of the ring-shaped TS

\( (\Delta S_{\text{intra}} - \Delta S_{\text{inter}}) \) depends solely on the number of skeletal bonds in the bifunctional precursor undergoing cyclization

**Quantitative Evaluation of Cyclization Reactions: Effective Molarity**

$\Delta S_{\text{intra}} - \Delta S_{\text{inter}}$ depends solely on the number of skeletal bonds in the bifunctional precursor undergoing cyclization.

**Alleviating Strain: Heteroatom Effects**


**Overcoming Entropy: The Thorpe-Ingold and Gem-Dialkyl Effects**

Thorpe-Ingold Effect

Gem-Dialkyl Effect

\[ q_1 > q_2 > q_3 \]

Overcoming Entropy:
The Thorpe-Ingold and Gem-Dialkyl Effects

Thorpe-Ingold Effect

Gem-Dialkyl Effect

q1 > q2 > q3


Strategies for the Synthesis of Medium-Sized Rings

Macrocyclization Reactions

Fragmentation Reactions

including carbocyclizations, macrolactonizations, and macrolactamizations

including ionic and radical processes

Ring Expansion (and Contraction) Reactions

including pericyclic methods
Macrocyclization Methods

**Alkylation of Stabilized Anions**

\[
\text{KHMD}\rightarrow \text{Raney-Ni} \rightarrow \text{(-)-phoracantholide I}
\]


\[
\text{n-BuLi} \rightarrow \text{OH} \rightarrow \text{(-)-4-hydroxyallchedycaryl}
\]


\[
\text{Bu}_3\text{Sn} \rightarrow \text{Me}_2\text{AlCl} \rightarrow \text{(-)-humulene}
\]


**Macrocyclization Methods**

**Aldol Condensation**

\[
\text{KHMD}\rightarrow \text{(-)-eremantholide A}
\]


**Reformatsky Cyclizations**

\[
\text{Br} \rightarrow \text{(-)-diplodialide A}
\]


**Carbonyl Couplings**

\[
\text{(-)-helminthoagermacrene}
\]

**Macrocyclization Methods**

*Radical Cyclizations*

![Chemical reaction and yield illustration]


![Chemical reaction and yield illustration]


![Chemical reaction and yield illustration]


**Macrocyclization Methods: The Nozaki-Hiyama-Kishi Reaction**

![Chemical reaction and yield illustration]


![Chemical reaction and yield illustration]

Macrocyclization Methods: Ring-Closing Metathesis

**RCM: Heteroatom Effects**

Grubbs 1 (4 mol%) → Oligomers

Grubbs 1 (4 mol%)
(90% yield)


**RCM: Site of Ring Closure**

Grubbs 1 (5 mol%)

No Reaction

Grubbs 1 (5 mol%)
(84% yield)

**RCM: Substituent Effects**

**Allylic Substitution**

- R = H (52% yield)
- R = Me (10% yield)


**Gauche Effects**

- Grubbs 1 (4 mol%)
- High dilution


**RCM in the Total Synthesis of Medium-Sized Ring Natural Products**

- (+)-asteriscanolide
- jasmine lactone


Fürstner, A.; Müller, T. *Synlett* 1997, 1010.

Macrolactonization Methods

**Acid Activation**

[Chemical diagram showing the process of acid activation]

**Alcohol Activation**

[Chemical diagram showing the process of alcohol activation]


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Macrolactonization Methods

**Acid Activation**

*Corey-Nicolaou Reagent and Variants*

[Chemical diagrams showing various reagents and their reactions]

**Gerlach Modification**

[Chemical diagram showing the Gerlach modification process]

Corey-Brunelle: No Reaction

**Macrolactonization Methods**

*Acid Activation*

**Mukaiyama’s Salt**

\[
\text{prostaglandin } F_{2a} \xrightarrow{\text{BnEt}_2\text{NCl, CICH}_2\text{CH}_2\text{Cl}} \xrightarrow{\text{reflux}} \text{prostaglandin } F_{2a}1,9\text{-lactone}
\]


**Yamaguchi-Yonemitsu**

\[
\text{halicholactone}
\]

Yonemitsu Conditions: Acid chloride, base and DMAP in one pot


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**Macrolactonization Methods**

*Acid Activation*

**Yamamoto Lactonization**

\[
\text{Sc}(OTf)}_2 (10-20 \text{ mol}) \xrightarrow{\text{MeCN : THF reflux}} \text{ScLn} \xrightarrow{\text{n = 6 (71\% yield)}} \text{n = 7 (52\% yield)} \xrightarrow{\text{n = 8 (87\% yield)}}
\]

**Boeckman’s Method**

\[
\text{(+)-diptodialide A}
\]

\[
\text{salicylihalamide A}
\]

Macrolactonization Methods

Alcohol Activation

Mitsunobu Reactions

\[
\text{OH} \quad \overset{\text{DEAD, PPh}_3}{\underset{(70\% \text{ yield})}{\rightarrow}} \quad \text{OH}
\]

\[
\text{MeO} \quad \text{OMPM} \quad \overset{\text{hypothemycin}}{\rightarrow} \quad \text{MeO} \quad \text{OMPM}
\]

Sp² Displacements of Mesylates and Halides

\[
\text{Br} \quad \overset{\text{K}_2\text{CO}_3}{\underset{\text{DMSO}, 80 ^\circ C}{\rightarrow}} \quad \text{O}
\]

(55% yield, 10% dimer)

phoracantholide I


Macrolactamization Methods

\[
\text{NHBoc} \quad \overset{1. \text{EDC}}{\rightarrow} \quad \overset{2. \text{C}_6\text{F}_5\text{OH}}{\underset{(93\% \text{ yield})}{\rightarrow}} \quad \overset{\text{EDC}}{\underset{\text{Et}}{\rightarrow}} \quad \overset{\text{EDC}}{\underset{\text{Et}}{\rightarrow}}
\]

(93% yield)

For R = Me, Me₃Al in CH₂Cl₂, 72% yield

Strategies for the Synthesis of Medium-Sized Rings

Macrocyclization Reactions

Fragmentation Reactions

including carbocyclizations, macrolactonizations, and macro lactamizations

including ionic and radical processes

Ring Expansion (and Contraction) Reactions

including pericyclic methods

The Grob and Wharton Fragmentations

The Wharton Fragmentation

Y = OSO₂R, Cl, Br, I
X = OH, NR₂, CH₂MgBr

Grob-Type Fragmentations

E = anion-stabilizing or electron-withdrawing group
**The Grob and Wharton Fragmentations**

*Synthetic Examples*

![Chemical diagram showing the Grob and Wharton Fragmentations with specific reactions and yields.]


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**The Grob and Wharton Fragmentations**

*Synthetic Examples*

![Chemical diagram showing another set of reactions and yields.]


**Radical Fragmentation Methods**


**Radical Fragmentation Methods**


**Miscellaneous Fragmentation Methods**

\[
\begin{align*}
\text{Falbe, J.; Korte, F. Chem. Ber. 1963, 96, 919.} \\
\end{align*}
\]

**Strategies for the Synthesis of Medium-Sized Rings**

- **Macrocyclization Reactions**
- **Fragmentation Reactions**
  - including carbocyclizations, macro lactonizations, and macro lactamizations
  - including ionic and radical processes

**Ring Expansion (and Contraction) Reactions**
- \[
\begin{align*}
\text{including pericyclic methods}
\end{align*}
\]
**Pericyclic Ring Expansive Processes**

*Cope Rearrangements*

\[ (-\text{E})\text{-santonin} \rightarrow (\text{E})\text{-dehydroausurea lactone} \rightarrow (\text{E})\text{-costunolide} \]


\[ (-\text{E})\text{-epi-isolineralactone} \rightarrow (\text{E})\text{-neolineralactone} \]


*Pericyclic Ring Expansive Processes*

**Tandem Pericyclic Rearrangements**

\[ \text{shyobunone} \overset{\Delta}{\rightarrow} \text{(E)}\text{-acoragermacrone} \overset{\text{SI}O_2}{\rightarrow} \text{(E)}\text{-preisocalamendiol} \]


**Anionic Oxy-Cope Rearrangements**

\[ \text{KH} \overset{\text{Li}}{\rightarrow} \text{(E)}\text{-acoragermacrone} \]

**Pericyclic Ring Expansive Processes**

*Claisen Rearrangements*


**Pericyclic Ring Expansive Processes**

*Electrocyclic Ring Openings*


Strategies for the Synthesis of Medium-Sized Rings

**Macrocyclization Reactions**

![Diagram of macrocyclization reaction](image)

**Fragmentation Reactions**

![Diagram of fragmentation reaction](image)

including carbocyclizations, macrolactonizations, and macrolactamizations

including ionic and radical processes

**Ring Expansion (and Contraction) Reactions**

![Diagram of ring expansion reaction](image)

including pericyclic methods

Periplanone B

![Diagram of Periplanone B](image)

S<sub>2</sub>2 Displacement Carbocyclization

Ring Expansion

[3,3] Sigmatropic Rearrangement

Fragmentation

[3,3] Sigmatropic Rearrangement

Heterolytic Cleavage
**Periplanone B**

1. LiHMDS
2. H$_2$O$_2$
3. NaOH (60% yield)


**Periplanone B**

1. LiHMDS
2. H$_2$O$_2$
3. NaOH (60% yield)


**Periplanone B**

![Chemical structure diagram of Periplanone B]

- **Oxy-Cope Rearrangement**

1. TMSCI
2. mCPBA
(57% yield, 3 steps)

**Intermediate advanced to 4 different diastereomers of periplanone B**


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**Periplanone B**

![Chemical structure diagram of Periplanone B]

- **Wharton Fragmentation**

1. n-BuLi (2 equiv)
2. Ti(OiPr)4
(44% yield)

**Periplanone B**

![Chemical Reaction Diagram]


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**Conclusions**

![Chemical Reaction Diagram]

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**Macrocyclization Reactions**

**Fragmentation Reactions**

**Ring Expansion (and Contraction) Reactions**

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$S_N$2 Displacement Carboacyclization

Ring Expansion

Fragmentation