Strategies for Stereocontrolled Synthesis

Chemistry 5.512
Synthetic Organic Chemistry II

Lecture 2

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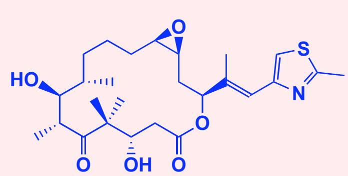
Massachusetts Institute of Technology

Strategies for Stereocontrolled Synthesis

★ Thermodynamic control strategies
- What determines the relative E of stereoisomers
- Tactics for establishing thermodynamic control



epothilone A

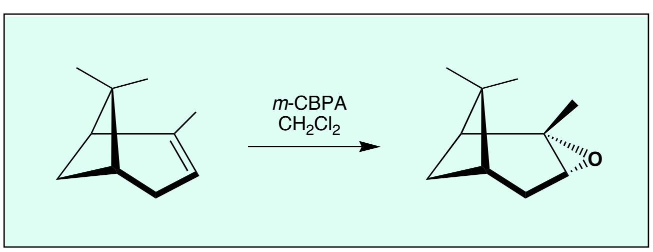
Strategies for Stereocontrolled Synthesis

- ★ Thermodynamic control strategies
  - ✻ What determines the relative E of stereoisomers
  - ✻ Tactics for establishing thermodynamic control
- ★ Kinetic control strategies
  - ✻ Substrate control strategies
  - ✻ Reagent control strategies
  - ✻ Dynamic kinetic resolution

Strategies for Stereocontrolled Synthesis

Substrate Kinetic Control Strategies

Steric Approach Control



Strategies for Stereocontrolled Synthesis

- ★ Thermodynamic control strategies
- ★ Kinetic control strategies
  - **Substrate control strategies**
    - Steric approach control
    - Stereoelectronic control
    - Internal stereodirection and chirality transfer
  - **Reagent control strategies**
    - Achiral substrate: enantiotopic face selectivity
    - Achiral substrate: enantiotopic group selectivity
    - Chiral substrate: double asymmetric synthesis
  - **Dynamic kinetic resolution**

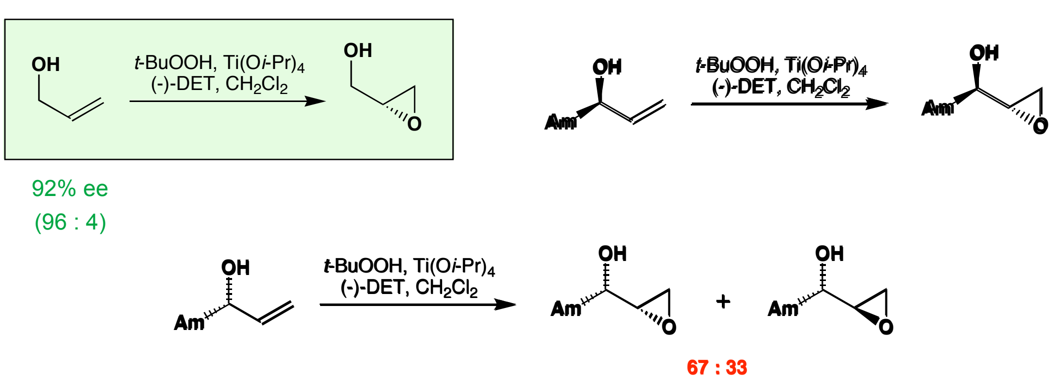
Strategies for Stereocontrolled Synthesis

Reagent Kinetic Control Strategies

Achiral Substrate: Enantiotopic Face Selectivity

Katsuki-Sharpless Asymmetric Epoxidation

Chiral Substrates



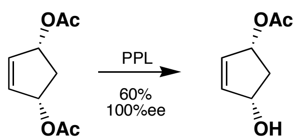
Strategies for Stereocontrolled Synthesis

Reagent Kinetic Control Strategies

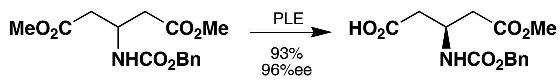
Achiral Substrate: Enantiotopic Group Selectivity

Lipase-Based Desymmetrization Reactions

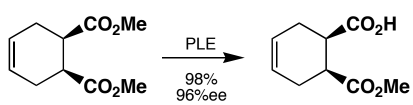
Review on enzymatic enantioselective group desymmetrization:
V. Gotor *Chem. Rev.* **2005**, *105*, 313



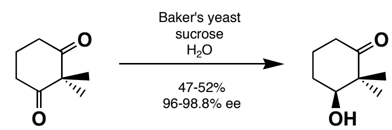
J. Nokami
Tetrahedron Lett. 32, 2409, **1991**



M. Ohno
J. Am. Chem. Soc. **1981**, *103*, 2405



M. Ohno
Tetrahedron Lett. **1984**, *25*, 2557



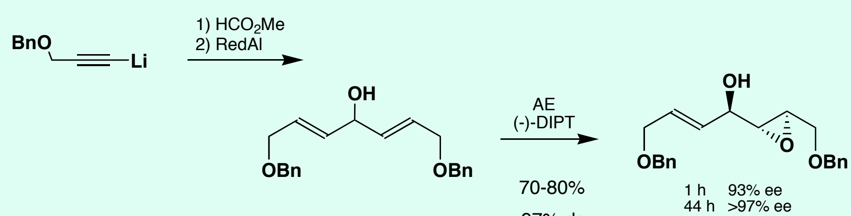
K. Mori and H. Mori
Org. Synth. Coll. Vol. 8, 312, **1993**

Another example of biotransformations in asymmetric synthesis

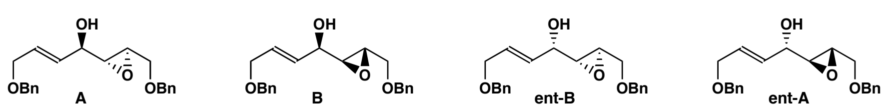
Strategies for Stereocontrolled Synthesis

Reagent Kinetic Control Strategies

Achiral Substrate: Enantiotopic Group Selectivity Coupled to Kinetic Resolution



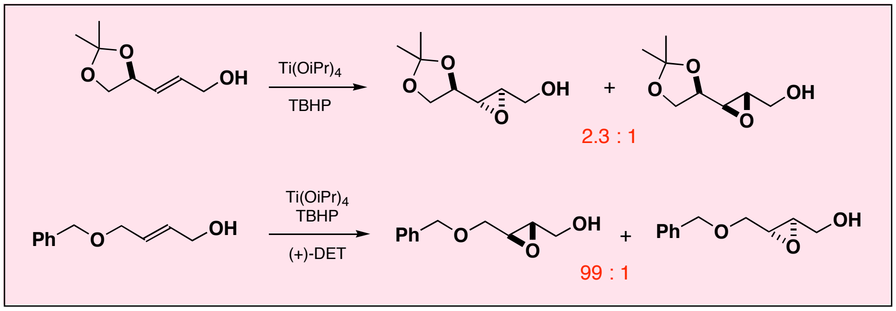
S. L. Schreiber
J. Am. Chem. Soc. **1987**, *109*, 1525



Strategies for Stereocontrolled Synthesis

Reagent Kinetic Control Strategies

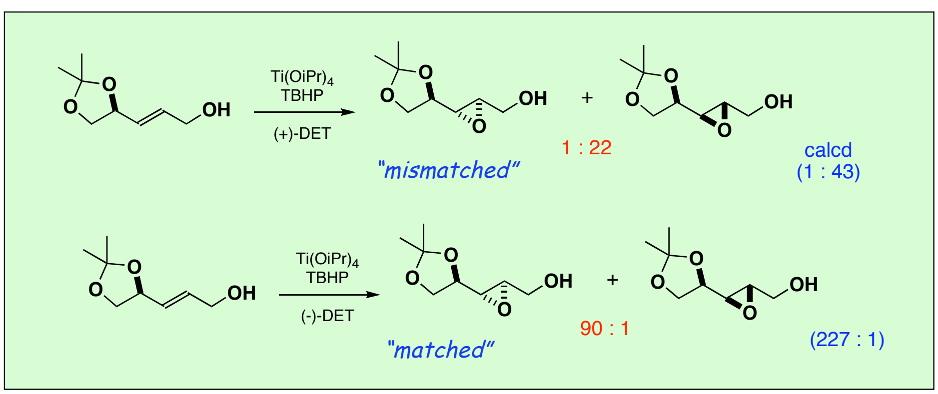
Chiral Substrate: Double Asymmetric Synthesis



Strategies for Stereocontrolled Synthesis

Reagent Kinetic Control Strategies

Chiral Substrate: Double Asymmetric Synthesis



Selectivity Benchmarks	Useful selectivity	91:9 (10:1)
	Double asymmetric synthesis	98:2 (50:1)

Strategies for Stereocontrolled Synthesis

Reagent Kinetic Control Strategies

Chiral Substrate: Double Asymmetric Synthesis

"What changes may organic synthesis undergo? . . . . With appropriate chiral reagents and catalysts at hand, the synthetic design of many natural (and unnatural) products will become straightforward, and as a result some of the aesthetic elements of traditional organic synthesis, as exemplified by the synthesis of erythronolide A in Section 7, may well be lost. . . . . However, the power of the new strategy has already made possible what appeared to be almost impossible even a few years ago. In this sense a new era which is characterized by the evolution from substrate-controlled to reagent-controlled organic synthesis is definitely emerging."

S. Masamune et al., "Double Asymmetric Synthesis and a New Strategy for Stereochemical Control in Organic Synthesis", *Angew. Chem. Int. Ed.* **1985**, *24*, 1.

Strategies for Stereocontrolled Synthesis

Reagent Kinetic Control Strategies

Chiral Substrate: Double Asymmetric Synthesis

Comparison of Substrate and Reagent Control Strategies

" . . . . Less commendable is the use of this insightful new chemistry as a platform for offering futuristic and murky pontifications about "reagent control" vs. "substrate control" as strategic frameworks in stereospecific synthesis. In the opinion of this reader, the substantive importance of this distinction has been vastly overstated. Clearly in many instances so-called substrate control works very well. In other cases, where the stereochemical connectivity between the "in place" stereogenicity, and the stereogenicity to be created is tenuous, recourse to so-called "reagent control" may be the only solution. To debate, as an abstract matter, the general superiority of one method over the other is not unlike debating whether steamship transportation or rail transportation is the more effective. Obviously, this is a type of circumstance-dependent question which does not permit a general resolution. It must be handled on a case-to-case basis by sensible people."

Samuel Danishefsky
C&EN August 26, 1985

Strategies for Stereocontrolled Synthesis

Reagent Kinetic Control Strategies

Chiral Substrate: Double Asymmetric Synthesis

Comparison of Substrate and Reagent Control Strategies

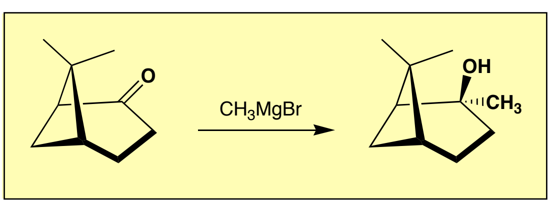
	Advantages	Disadvantages
Substrate Control	★ Exploits resident chirality	★ Requires strong bias in substrate ★ Different strategy needed for each epimer
Reagent Control	★ Same strategy sometimes applicable to synthesis of both epimers ★ Applicable to substrates with low bias	★ Not applicable if substrate has strong bias ★ Requires reagents with very strong bias

Strategies for Stereocontrolled Synthesis

Reagent Kinetic Control Strategies

Chiral Substrate: Double Asymmetric Synthesis

Comparison of Substrate and Reagent Control Strategies

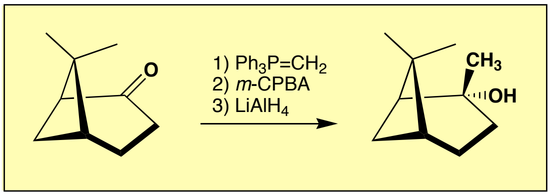


Strategies for Stereocontrolled Synthesis

Reagent Kinetic Control Strategies

Chiral Substrate: Double Asymmetric Synthesis

Comparison of Substrate and Reagent Control Strategies



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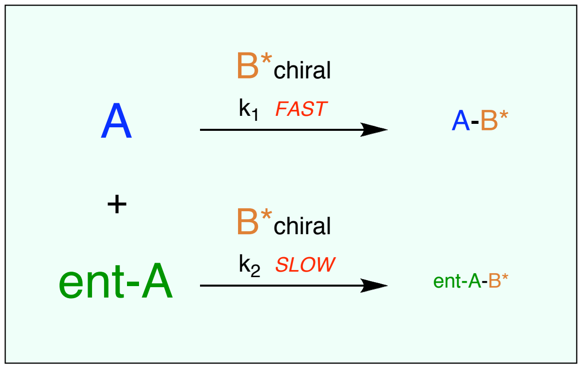
Strategies for Stereocontrolled Synthesis

Kinetic Control Strategies

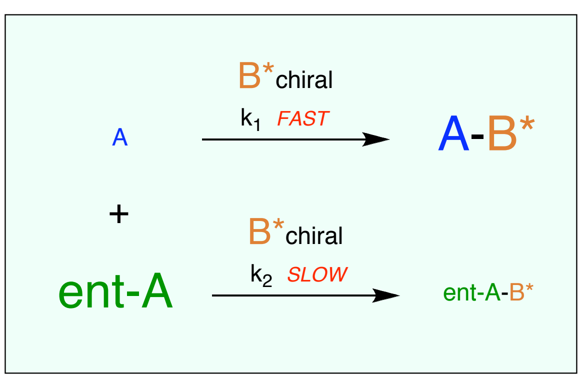
Classical Kinetic Resolution



Strategies for Stereocontrolled Synthesis

Kinetic Control Strategies

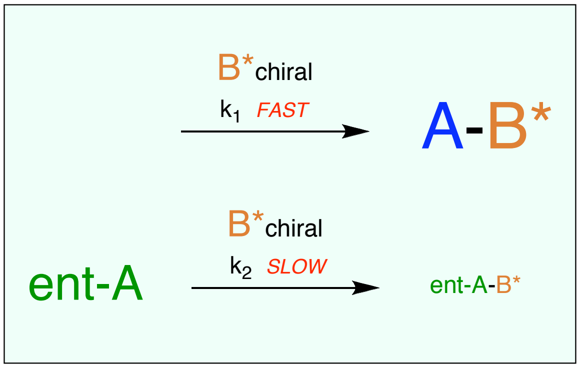
Classical Kinetic Resolution



Strategies for Stereocontrolled Synthesis

Kinetic Control Strategies

Classical Kinetic Resolution



Selectivity Factor

$s = k_1/k_2$

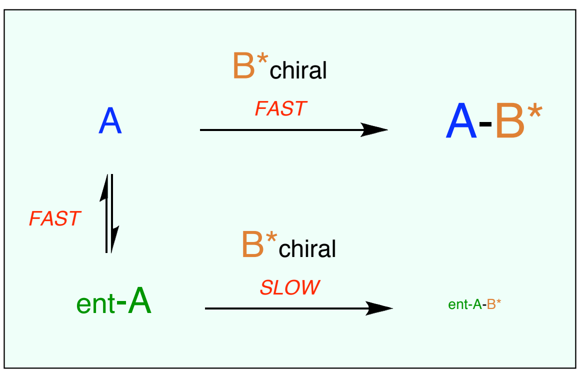
10

50

Strategies for Stereocontrolled Synthesis

Kinetic Control Strategies

Dynamic Kinetic Resolution



Review: H. Pellissier *Tetrahedron* **2003**, *59*, 8291

Strategies for Stereocontrolled Synthesis

General Strategies for the Stereocontrolled Synthesis of Acyclic Target Molecules

- Chiron Approach
- Ring Template Approach
- Chirality Transfer
- Acyclic Asymmetric Synthesis

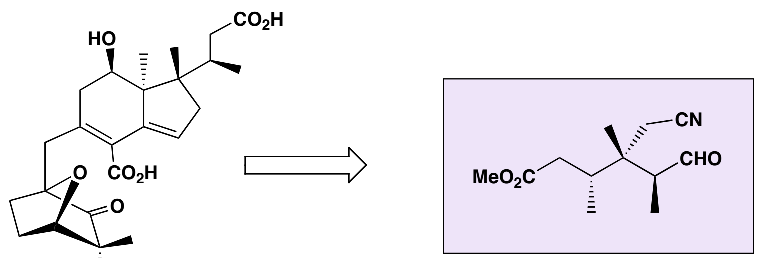
Strategies for Stereocontrolled Synthesis

- ★ Thermodynamic Control Strategies
- ★ Kinetic Control Strategies
- ★ Strategies for the Synthesis of Acyclic Target Molecules: Case Studies
  - **Glycinoeclepin A Intermediate** (Danheiser)
  - Prostaglandins from Sugars (Stork)

Strategies for Stereocontrolled Synthesis

Case Studies

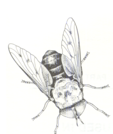
(1) Glycinoeclepin A Intermediate (Danheiser)



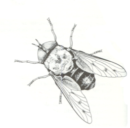
Glycinoeclepin A

Hunger and Its Contribution to Human Misery

- ★ *1.5 Billion human beings are malnourished*
- ★ *Almost 48% of the potential world food supply is lost to pests each year*



> *"And the locusts came . . . . and settled on the whole country of Egypt . . . and they ate all the plants in the land and all the fruit of the trees . . . not a green thing remained. Neither tree nor plant of the field through all the land."*
>
> Exodus 10:14-15

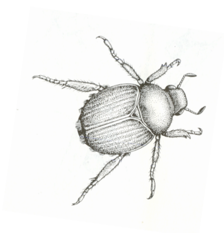


> *"Let's get our priorities in perspective. . . . We must feed ourselves and protect ourselves against the health hazards of the world. To do that, we must have agricultural chemicals. Without them, the world population will starve."*
>
> N. E. Borlaug
> (1970 Nobel Peace Prize)

> *"This means that we have to find in the next 25 years, food for as many people again as we have been able to develop in the whole history of man."*
>
> Jean Mayer

Classical Approaches to Pest Control

★ *Approximately 2.5 million tons of pesticides are deployed annually*
★ *One-third of world crops are currently treated with pesticides*



"A mosquito was heard to complain
That a chemist had poisoned his brain
The cause of his sorrow
Was para-dichloro-
diphenyltrichloroethane"
D. D. Perrin

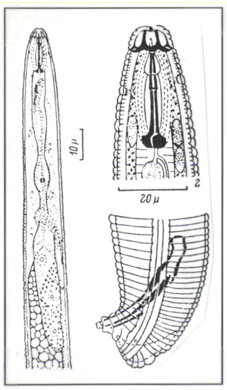
Alternative Approaches to Pest Control

Semiochemicals:
Behavior modifying substances, usually highly selective and highly active

★ **Pheromones**
Substances used by members of a species to communicate with each other

★ **Allelochemicals**
Substances produced by one species with an effect on a different species
- ☆ **Allomones:** result is favorable to emitter but not to receiving species
- ☆ **Kairomones:** result is favorable to receiving species but not to emitter

Heterodera Glycines
The Soybean Cyst Nematode



- ★ Nematodes destroy ca. $100 billion in crops worldwide per year
- ★ *H. glycines* parasitizes a number of economically important plants including soybeans, kidney beans, and adzuki beans
- ★ *H. glycines* causes *daizu iwo byo* ("yellow dwarf disease") in soybean plants; ca. $2.5 billion in crop loss annually
- ★ The hatching of dormant second-stage larvae from eggs and emergence of the hatched larvae from the cysts occurs in response to a substance (**glycinoeclepin A**) in the root diffusate secreted by the host plants

O Rose, thou are sick!
The invisible worm
That flied in the night,
In the howling storm,

Has found out thy bed
Of crimson joy,
And his dark secret love
Does thy life destroy.
William Blake

Illinois Soybean Cyst Nematode (SCN) Coalition http://scn.cropsci.uiuc.edu/

www.ilscncoalition.org

Take the test. Beat the pest.

- Economic Impact, Distribution
- Life History
- Symptoms Identification
- Management
- Events
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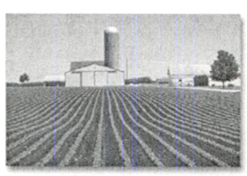
Illinois Soybean Cyst Nematode (SCN) Coalition



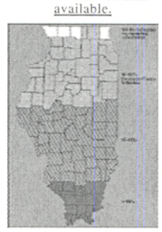
Welcome to the World Wide Web home for the Illinois SCN Coalition. This site was developed for soybean producers, agribusiness people and others interested in learning more about the soybean cyst nematode (SCN). By browsing through this site's pages, you can learn how to detect and to manage a pest that robs U.S. soybean producers of more than $1 billion in yield losses each year.

Bookmark this site, add it to your favorite places - information will be updated regularly.

This site is brought to you by the Illinois Soybean Association and the Illinois Soybean Checkoff Board. Let us know what you like about the Illinois SCN Coalition site and write to us with your SCN questions. We'll be sure to reply.

Latest Updates

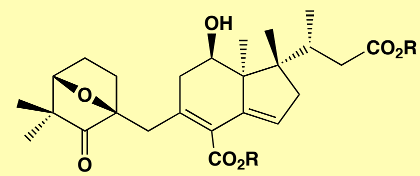
<> There are no current updates on the SCN site. Please visit later for more information.
Click here.
New SCN Education and Cyst counts by county available.



Isolation of Glycinoeclepin A

Dried and powdered kidney bean roots (1,058 Kg) → Extraction with water and evaporation under reduced pressure → 380 l → Extraction with chloroform at pH 2-3 → 1,011 g → Extraction with EtOAc-aq $NaHCO_3$ → 636 g → Five chromatographic separations → 951 mg → *p*-bromophenacylation → 2.057 g (as *p*-BPE) → Four chromatographic separations → **Glycinoeclepin A** (as *p*-BPE)

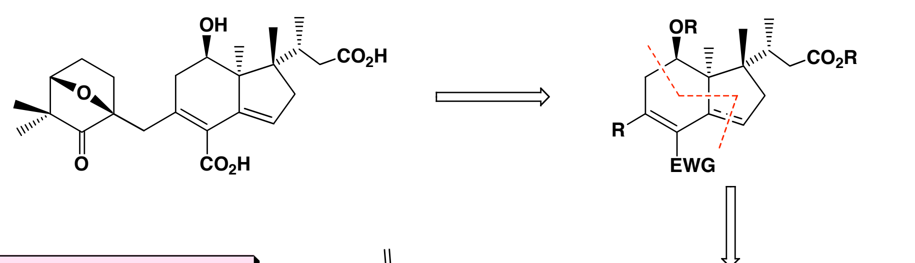
1.25 mg



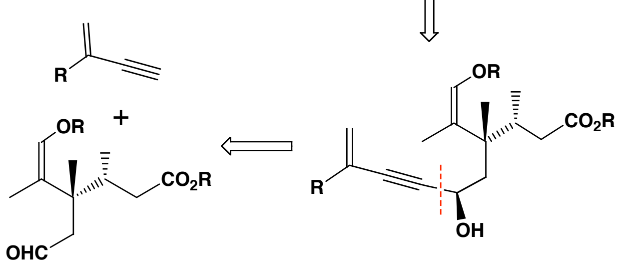
R=$CH_2COC_6H_4Br$-*p*

Fukuzawa, A.; Furusaki, A.; Ikura, M.; Masamune, T. *J. Chem. Soc., Chem. Commun.* **1985**, 222

An Efficient Strategy for the Synthesis of the Bicyclic C–D Core of Glycinoeclepin A



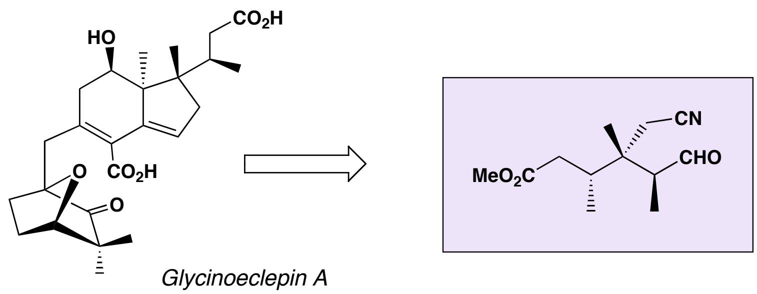
The first principle of retrosynthetic planning: **convergent strategies** are the most efficient strategies for the assembly of complex molecules



Strategies for Stereocontrolled Synthesis

Case Studies

(1) Glycinoeclepin A Intermediate (Danheiser)



Glycinoeclepin A

★ Asymmetric synthesis approach would be very challenging

★ Our strategy: **ring template approach**

Strategies for Stereocontrolled Synthesis

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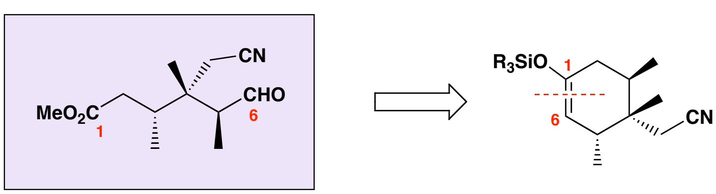

★ 1,6-Dicarbonyl compound:
retron for **oxidative cleavage** of a cyclohexene

Strategies for Stereocontrolled Synthesis

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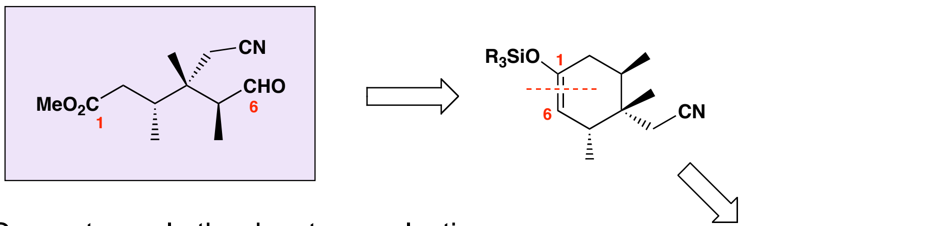
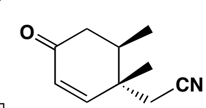
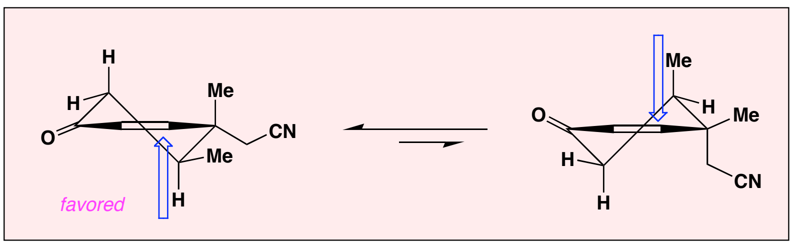




★ Generate enol ether by stereoselective conjugate addition with enolate trapping



Strategies for Stereocontrolled Synthesis

Case Studies

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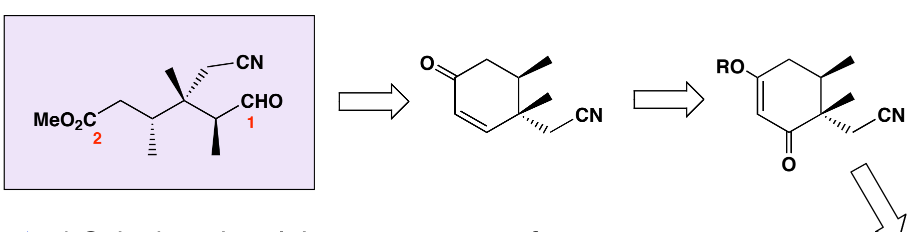
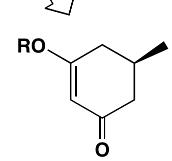
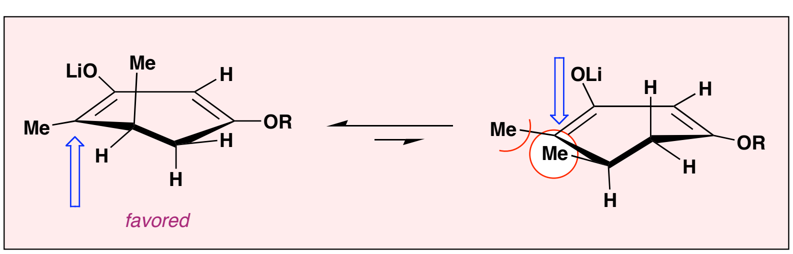




★ 4-Substituted cyclohexenone: retron for Stork-Danheiser Alkylation



Require enantioselective route to this intermediate

Strategies for Stereocontrolled Synthesis

Case Studies

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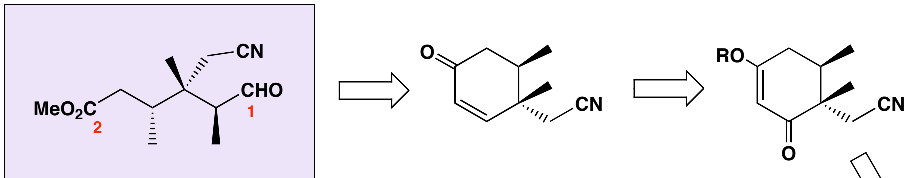
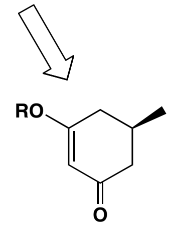


★ Employ resolution strategy for synthesis of alkoxy enone

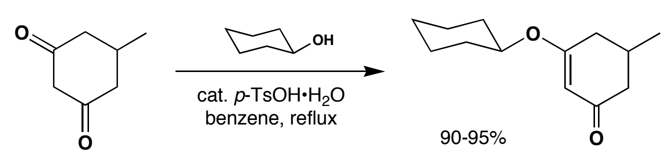


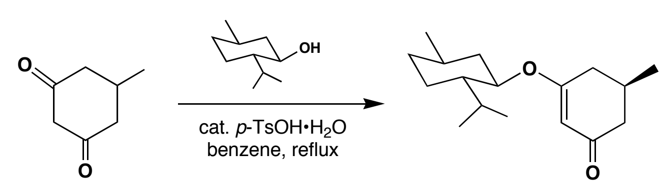
Require enantioselective route to this intermediate

Disadvantages of Classical Resolutions

- ★ Adds two additional steps to synthetic sequence
- ★ Half of material is discarded as wrong isomer
- ★ Wasteful when late-stage resolution is carried out

Synthesis of 3–Alkoxycyclohexenones





17-25%

>98:2 by gc analysis

separate diastereomers by recrystallization; undesired isomer converted to mixture of diastereomers by hydrolysis and exposure to above conditions

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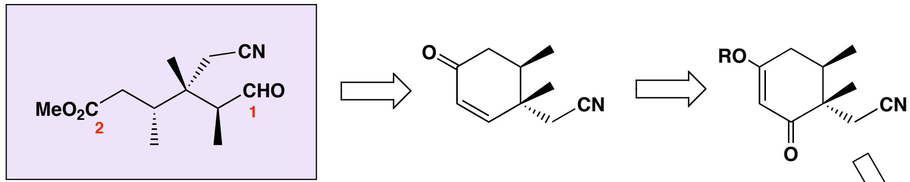
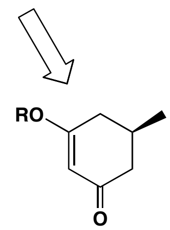




★ Employ resolution strategy for synthesis of alkoxy enone

Require enantioselective route to this intermediate

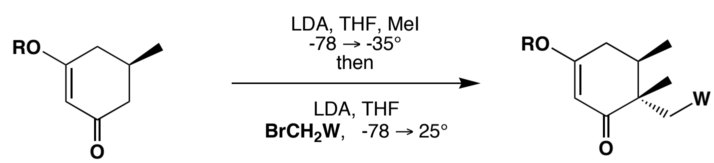
Advantages of Our Resolution Strategy

★ No additional steps added to synthetic sequence

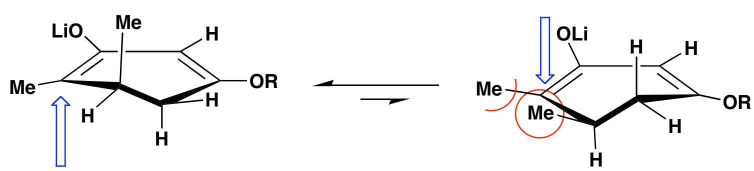
★ Wrong isomer can be recycled & converted to desired

★ Resolution is carried out in first step of the synthesis

Stereoselective Stork–Danheiser Alkylation



R = Cyh	$BrCH_2CO_2$*t*-Bu	61% (one isomer)
R = Cyh	$BrCH_2CONMe_2$	94% (80:20)
R = Menth	$BrCH_2CN$	80-83% (95:5)



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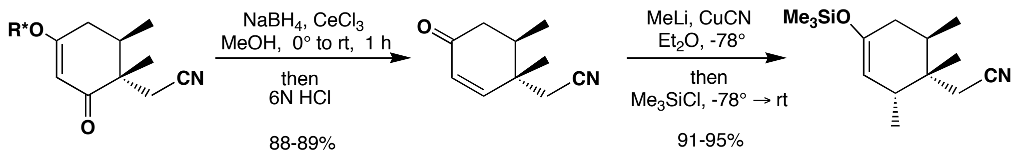
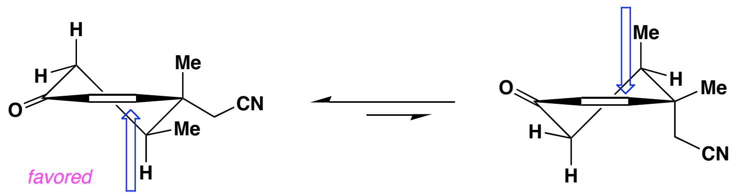
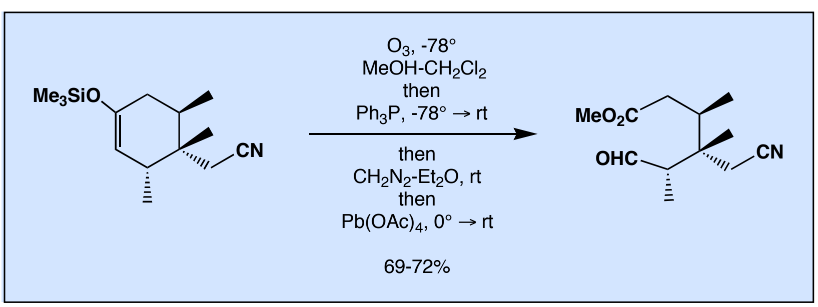
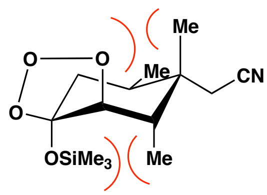
Reduction and Cuprate Addition

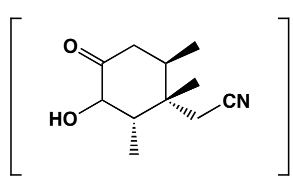




Ozonolysis of the Silyl Enol Ether



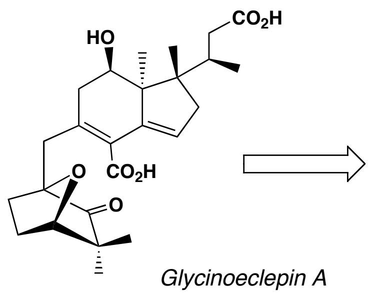




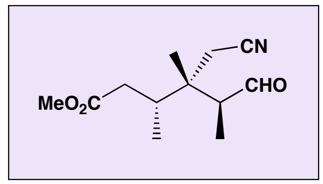
Strategies for Stereocontrolled Synthesis

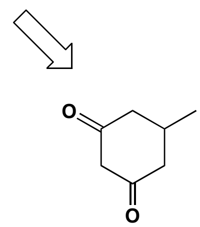
Case Studies

(1) Glycinoeclepin A Intermediate (Danheiser)



Glycinoeclepin A





★ 5 steps required for synthesis of key intermediate from 5-methylcyclohexane-1,3-dione