Strategies for Stereocontrolled Synthesis

Chemistry 5.512
Synthetic Organic Chemistry II

Lecture 3
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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

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

General Strategies for the Stereocontrolled Synthesis of Acyclic Target Molecules

- Chiron Approach
- Ring Template Approach
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- Acyclic Asymmetric Synthesis

Strategies for Stereocontrolled Synthesis

Case Studies

(2) Prostaglandins from Sugars (Stork)


For discussions of the use of chiral natural products as starting materials for the synthesis of complex molecules, see
Strategies for Stereocontrolled Synthesis

Case Studies

(2) Prostaglandins from Sugars (Stork)

G. Stork and S. Raucher
Department of Chemistry, Columbia University
New York, New York 10027
received December 8, 1975


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Case Studies

(2) Prostaglandins from Sugars (Stork)
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Case Studies
(2) Prostaglandins from Sugars
(Gilbert Stork)

★ Install C-8 side chain by enolate alkylation
★ Thermodynamic control of stereochemistry at C-8

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Case Studies
(2) Prostaglandins from Sugars
(Gilbert Stork)

★ Install C-8 side chain by enolate alkylation
★ Thermodynamic control of stereochemistry at C-8
★ [For PGF_{2\alpha}] C-9 stereochemistry by steric approach substrate control
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Case Studies
(2) Prostaglandins from Sugars (Gilbert Stork)

★ Form cyclopentanone from acyclic precursor by nucleophilic cyclization

\[
\text{EWG}^+ \quad \text{or} \quad \text{RO}^+\n\]

New Subtargets

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Case Studies
(2) Prostaglandins from Sugars (Gilbert Stork)

★ The “sugar connection”: requires translation of C-OH stereogenic centers into C-C centers

\[
\text{Sugars as starting materials}\]
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Case Studies
(2) Prostaglandins from Sugars (Gilbert Stork)

★ Set C-12 stereochemistry by
chirality transfer via [3,3] sigmatropic rearrangement

Subtargets

Previous subtargets

New Subtargets

Retron for [3,3] sigmatropic shift: γ,δ-unsaturated carbonyl compound
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Case Studies
(2) Prostaglandins from Sugars (Gilbert Stork)

★ Set C-12 stereochemistry by

chirality transfer via [3,3] sigmatropic rearrangement

![Diagram showing the stereochemical transformation of C-12 atoms.](image)

New Subtargets

![New subtargets diagram.](image)

Previous subtargets
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Case Studies

(2) Prostaglandins from Sugars (Stork)

For \( \text{PGA}_2 \)

For \( \text{PGF}_{2\alpha} \)

D-Glycero-D-guloheptono-1,4-lactone
One step from D-glucose
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Case Studies

(2) Prostaglandins from Sugars (Stork)

Total Synthesis of PGA₂

1 eq Et₃N
CH₂Cl₂ rt 1 h

1 eq K₂CO₃
MeOH rt 30 min
59% overall

2 eq
(MeO)₂C

95% 4 h

10 eq CH₂C(O.Me)₃
cat EtCO₂H
140° 72 h

83%

25% eq AcOH
120° 1 h

83%

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Case Studies

(2) Prostaglandins from Sugars (Stork)

Total Synthesis of PGA₂

1) H₂, Pd-BaSO₄, MeOH
2) TsCl, pyr, -20°, 7 d
3) EVE

5 eq Bu₂CuLi
Et₂O, -40°, 2 h

5 eq K₂CO₃
MeOH
rt, 45 min

10 eq KOt-Bu
THF
16 steps in the longest linear sequence
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Case Studies
(2) Prostaglandins from Sugars (Stork)

Total Synthesis of PGF$_{2\alpha}$

![Chemical Structure and Synthesis Diagram]
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Case Studies

(2) Prostaglandins from Sugars (Stork)

Total Synthesis of PGF$_{2\alpha}$

Strategies for Stereocontrolled Synthesis

Case Studies

(2) Prostaglandins from Sugars (Stork)

Total Synthesis of PGF$_{2\alpha}$
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[1,3] \( \text{O} \rightarrow \text{C} \) Chirality Transfer

\[
\begin{array}{c}
\text{R}^1 \text{R}^2 \text{Y}^1 \text{OH} \\
\text{X} \\
\text{Y}
\end{array}
\xrightarrow{\text{KH, CCl}_3, \text{CN}, \text{Et}_2\text{O}}
\begin{array}{c}
\text{R}^1 \text{R}^2 \text{CO}_2 \text{R} \\
\text{X} \\
\text{Y}
\end{array}
\]

[1,3] \( \text{O} \rightarrow \text{N} \) Chirality Transfer

\[
\begin{array}{c}
\text{R}^1 \text{R}^2 \text{Y}^1 \text{OH} \\
\text{X} \\
\text{Y}
\end{array}
\xrightarrow{140 \ ^\circ \text{C, xylene}}
\begin{array}{c}
\text{R}^1 \text{R}^2 \text{NR}_2 \\
\text{X} \\
\text{Y}
\end{array}
\]

Review of chirality transfer via sigmatropic rearrangements

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Overman Rearrangement of Allylic Trihaloacetimidates

\[
\begin{array}{c}
\text{BnO} \text{CH}_2\text{OH} \\
\text{KH, CCl}_3, \text{CN, Et}_2\text{O}
\end{array}
\xrightarrow{140 \ ^\circ \text{C, xylene}}
\begin{array}{c}
\text{BnO} \text{CH}_2\text{HNCCl}_3 \\
\text{CCl}_3
\end{array}
\]

\[
\begin{array}{c}
\text{Bu} \text{CH}_2\text{OSiR}_3 \\
\text{1)} \text{DBU, CCl}_3, \text{CN, CH}_2\text{Cl}_2 \\
\text{2)} \% \text{PdCl}_2(\text{PhCN})_2, \text{benzene, rt}
\end{array}
\xrightarrow{72\%}
\begin{array}{c}
\text{Bu} \text{CH}_2\text{OSiR}_3 \\
\text{NHCCl}_3
\end{array}
\]