Strategies for Stereocontrolled Synthesis

Chemistry 5.512
Synthetic Organic Chemistry II

Lecture 3

March 5, 2007

Rick L. Danheiser
Massachusetts Institute of Technology

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**
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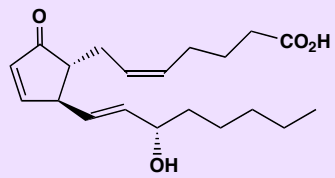
- **Chirality Transfer**
- Acyclic Asymmetric Synthesis

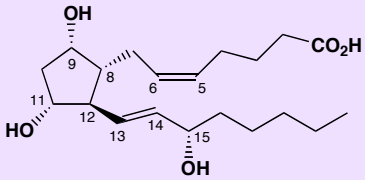
Strategies for Stereocontrolled Synthesis

Case Studies

(2) Prostaglandins from Sugars (Stork)



Prostaglandin A_2



Prostaglandin $F_{2\alpha}$

G. Stork and S. Raucher *J. Am. Chem. Soc.* **1976**, *98,* 1583
G. Stork, T. Takahashi, I. Kawamoto, and T. Suzuki *J. Am. Chem. Soc.* **1978**, *100*, 8272

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

(1) S. Hanessian "Total Synthesis of Natural Products: The 'Chiron Approach' ", Pergamon Press: Oxford, 1983.
(2) T.-L. Ho "Enantioselective Synthesis: Natural Products from Chiral Terpenes", Wiley Interscience: New York, 1992.

Strategies for Stereocontrolled Synthesis

Case Studies

(2) Prostaglandins from Sugars (Stork)

Chiral Synthesis of Prostaglandins from Carbohydrates. Synthesis of (+)-15-(*S*)-Prostaglandin A_2

Sir:

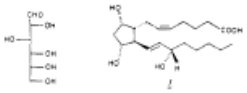
Traditional syntheses of natural prostaglandins[1] involve at least one resolution. We have been devoting some effort to total syntheses of these substances which would not require separation of enantiomers, and now record the first total synthesis of a natural prostaglandin, PGA_2 (**1**)[2] from a simple sugar. The specific route we chose features the use of two Claisen rearrangements: one to produce the necessary trans geometry of a double bond (**3** → **4**) and the other as the means of transferring the chirality of a carbon–oxygen bond to that of a nonadjacent carbon–carbon bond (**5** → **7**).

Gilbert Stork,* Stanley Raucher
Department of Chemistry, Columbia University
New York, New York 10027
Received December 8, 1975

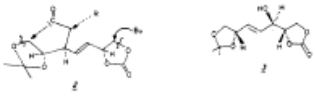
Total Synthesis of Prostaglandin $F_{2\alpha}$ by Chirality Transfer from D-Glucose[1,2]

Sir:

We describe herein the successful construction of prostaglandin $PGF_{2\alpha}$ (**1**) from D-glucose.



The synthetic plan involves the assumption that the transformations shown by arrows on **2** could be effected. A molecule of type **2** should in turn result from C–O → C–C chirality transfer from **3**. It is this molecule which thus became our initial synthetic target.



Gilbert Stork,* Takashi Takahashi
Isao Kawamoto, Toshio Suzuki
Department of Chemistry, Columbia University
New York, New York 10027
Received July 28, 1978

G. Stork and S. Raucher *J. Am. Chem. Soc.* **1976**, *98*, 1583
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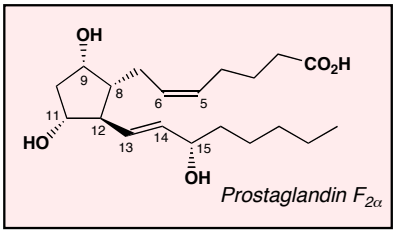
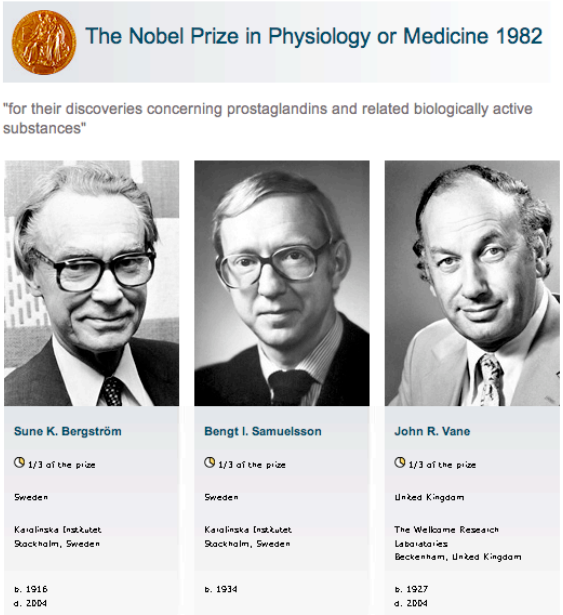
Strategies for Stereocontrolled Synthesis

Case Studies

(2) Prostaglandins from Sugars (Stork)

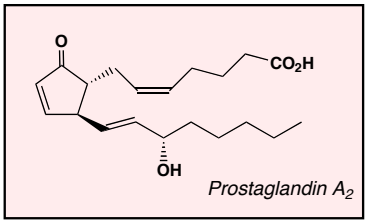




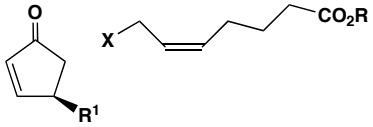
Strategies for Stereocontrolled Synthesis

Case Studies

(2) Prostaglandins from Sugars
(Gilbert Stork)



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



Strategies for Stereocontrolled Synthesis

Case Studies

(2) Prostaglandins from Sugars
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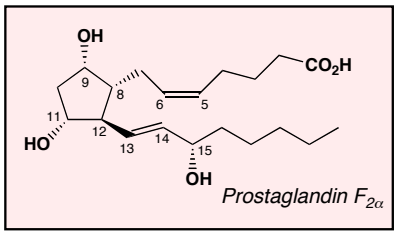
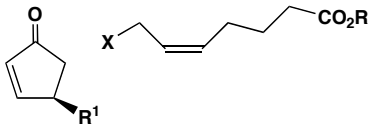
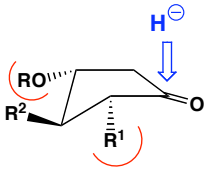


- ★ Install C-8 side chain by enolate alkylation
- ★ Thermodynamic control of stereochemistry at C-8
- ★ [For $PGF_{2\alpha}$] C-9 stereochemistry by steric approach substrate control





Strategies for Stereocontrolled Synthesis

Case Studies

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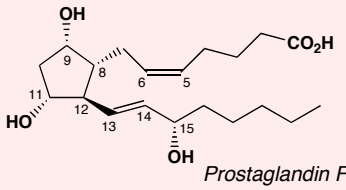
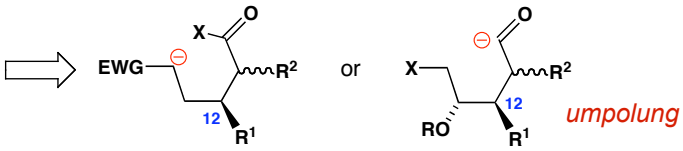
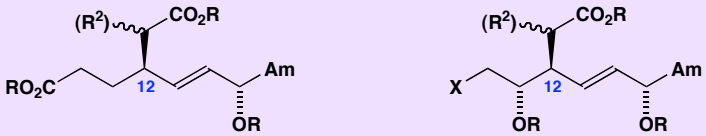


★ Form cyclopentanone from acyclic precursor by **nucleophilic cyclization**



New Subtargets



Strategies for Stereocontrolled Synthesis

Case Studies

(2) Prostaglandins from Sugars
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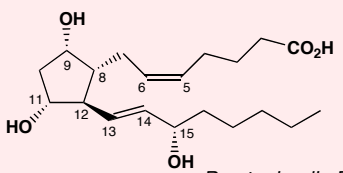
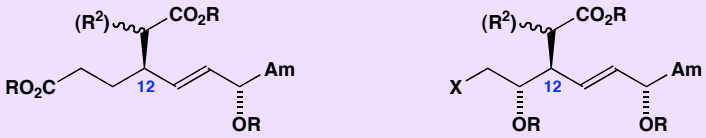
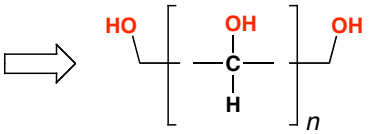


★ The **"sugar connection"**: requires translation of **C-OH** stereogenic centers into **C-C** centers

New Subtargets



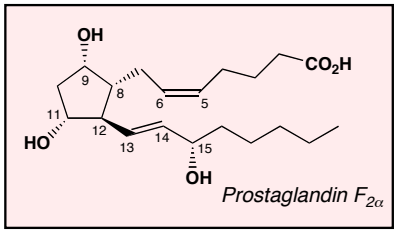


Sugars as starting materials

Strategies for Stereocontrolled Synthesis

Case Studies

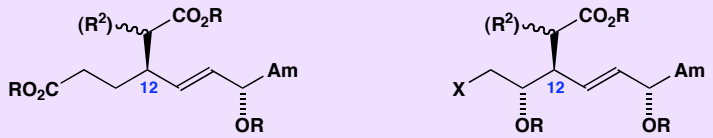
(2) Prostaglandins from Sugars
(Gilbert Stork)

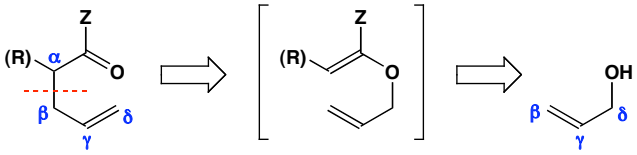


★ Set C-12 stereochemistry by

chirality transfer via [3,3] sigmatropic rearrangement

Subtargets





Retron for [3,3] sigmatropic shift: *γ,δ-unsaturated carbonyl compound*

Strategies for Stereocontrolled Synthesis

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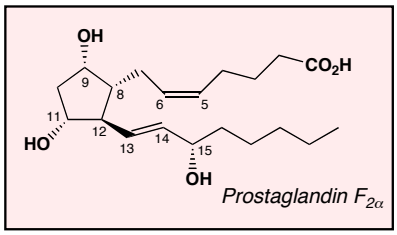

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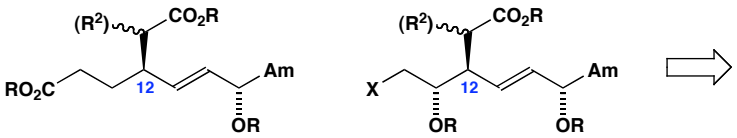

New Subtargets

Strategies for Stereocontrolled Synthesis

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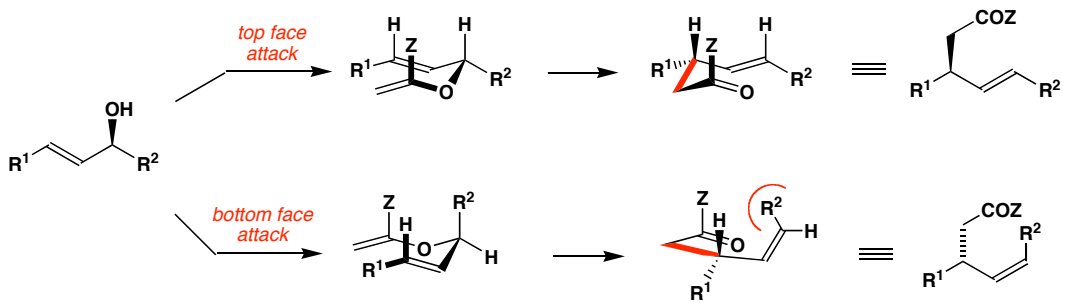

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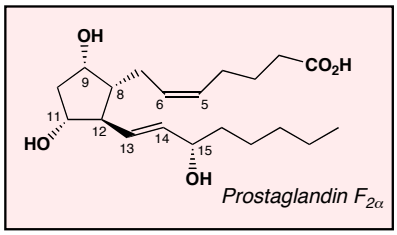

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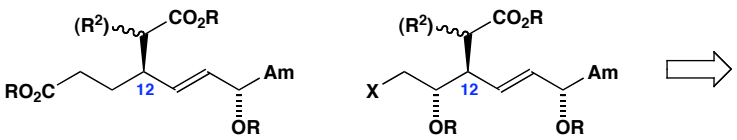

New Subtargets

Strategies for Stereocontrolled Synthesis

Case Studies

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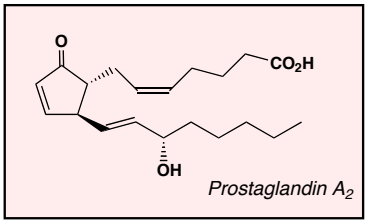
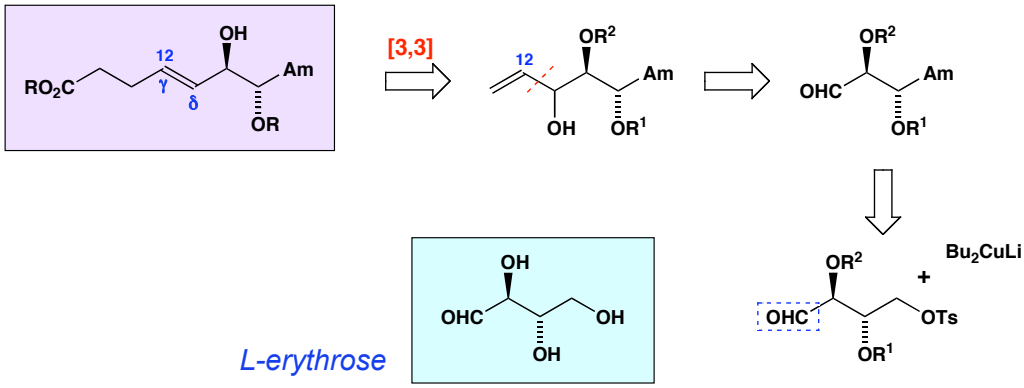


For PGA_2



Strategies for Stereocontrolled Synthesis

Case Studies

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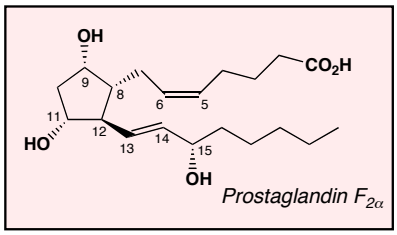
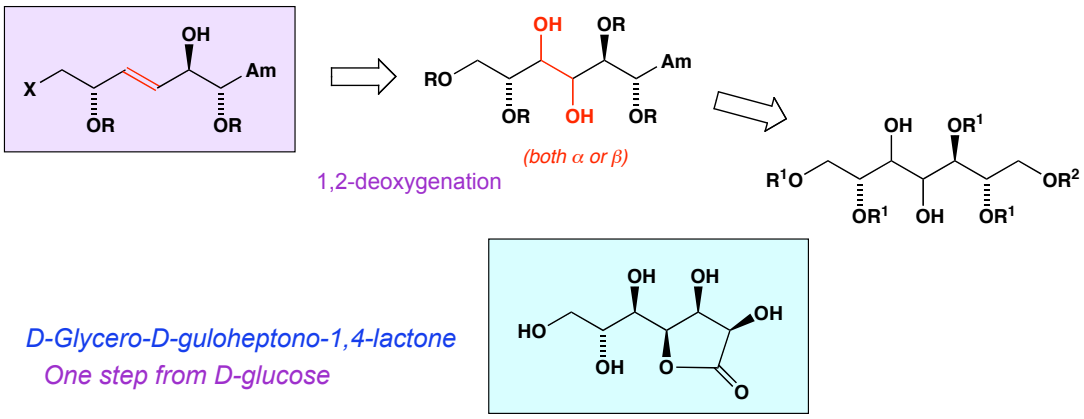


For $PGF_{2\alpha}$

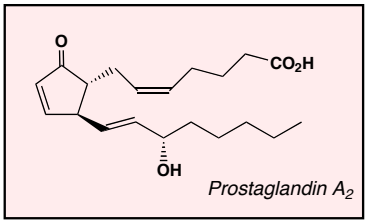


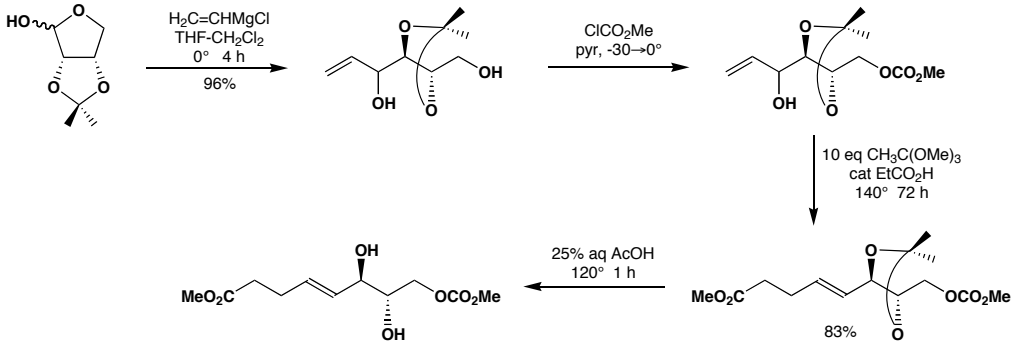
Strategies for Stereocontrolled Synthesis

Case Studies

(2) Prostaglandins from Sugars (Stork)

Total Synthesis of PGA_2





Strategies for Stereocontrolled Synthesis

Case Studies

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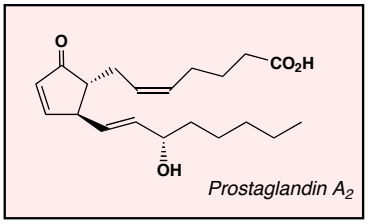

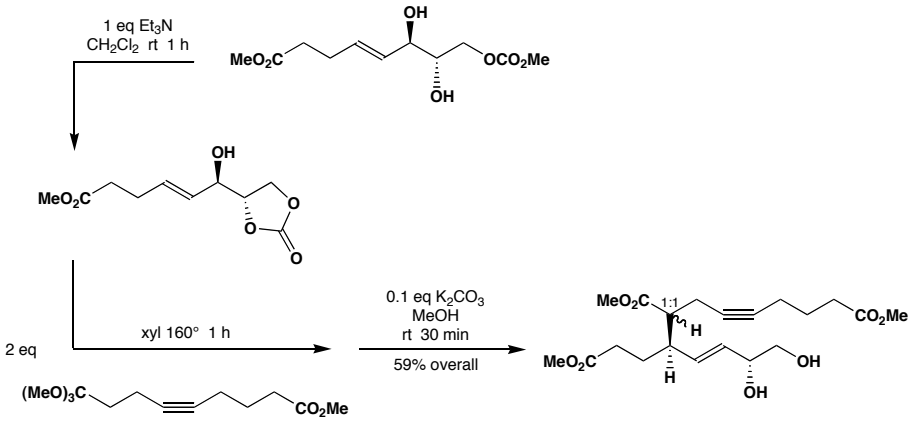

Strategies for Stereocontrolled Synthesis

Case Studies

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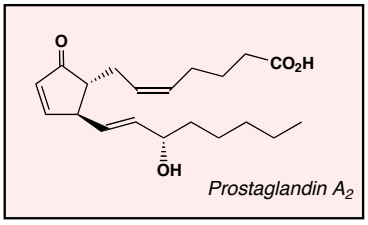

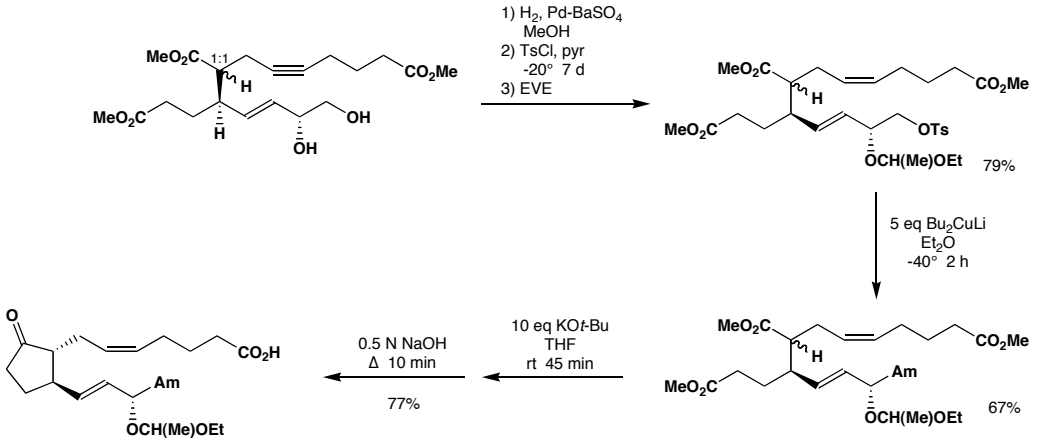

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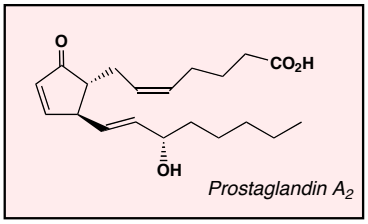

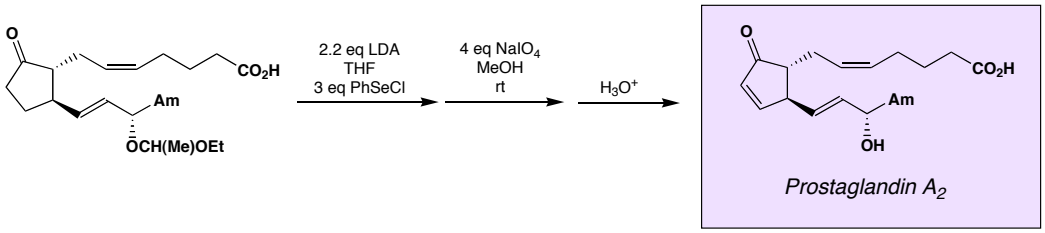

16 steps in the longest linear sequence

Strategies for Stereocontrolled Synthesis

Case Studies

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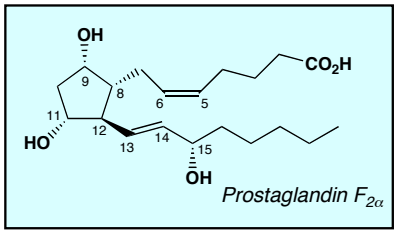
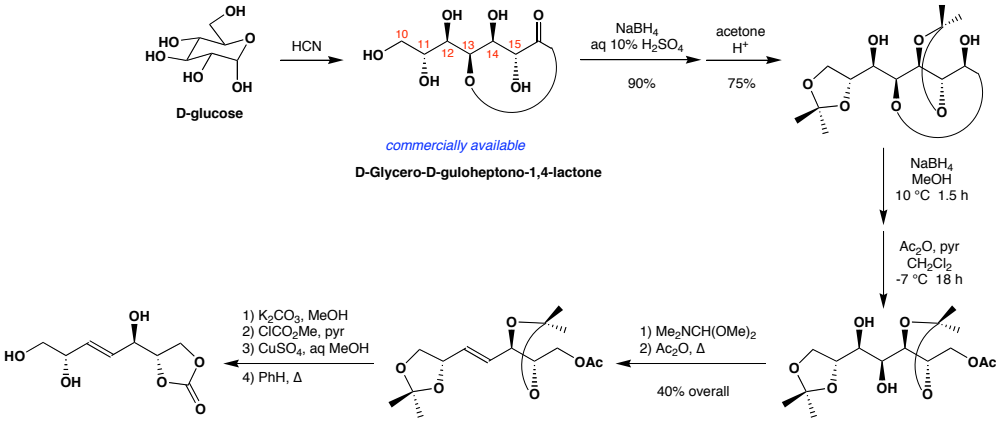


Total Synthesis of $PGF_{2\alpha}$



Strategies for Stereocontrolled Synthesis

Case Studies

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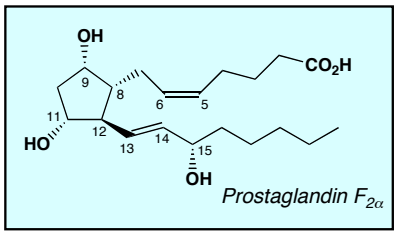
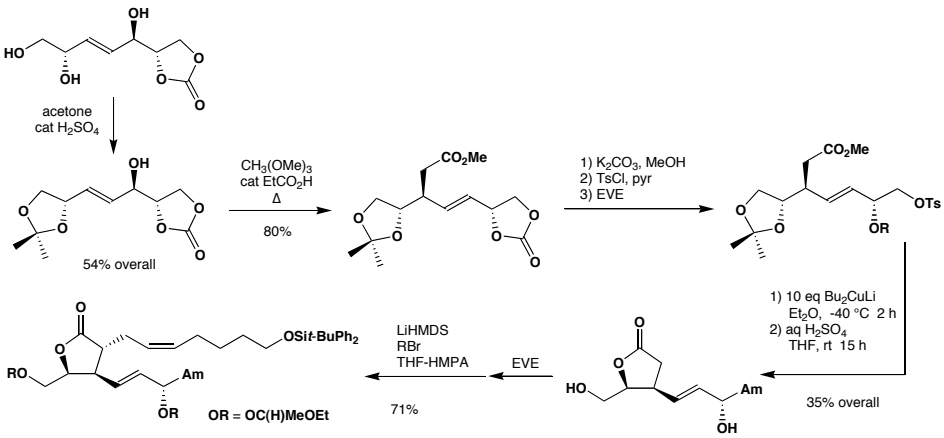


Total Synthesis of $PGF_{2\alpha}$



Strategies for Stereocontrolled Synthesis

Case Studies

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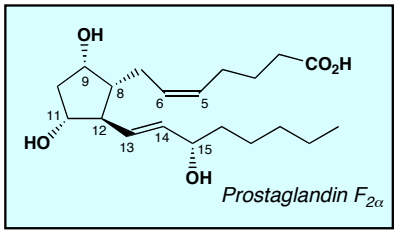
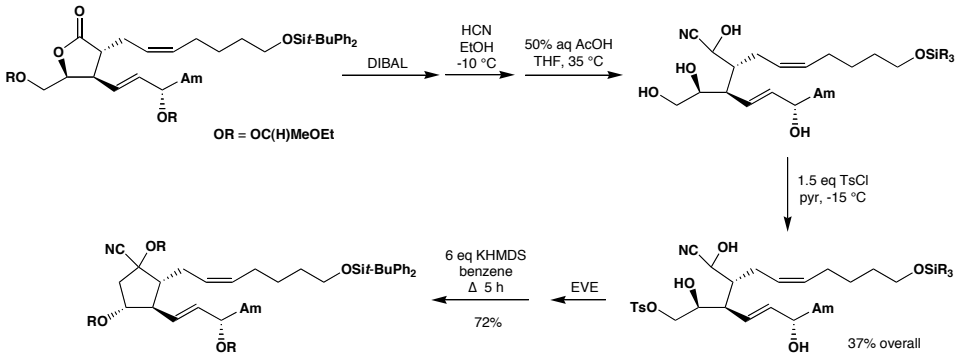
Total Synthesis of $PGF_{2\alpha}$





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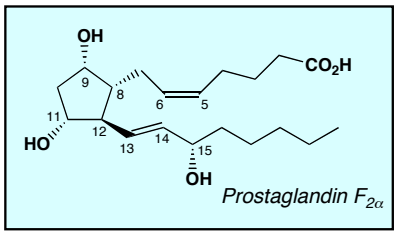
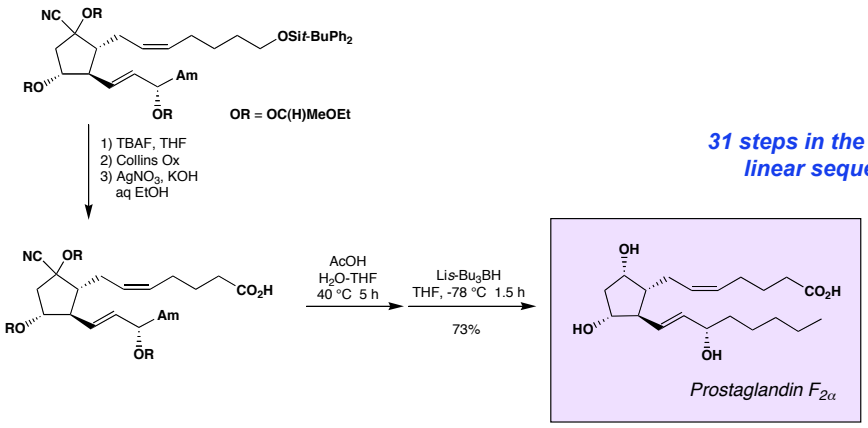
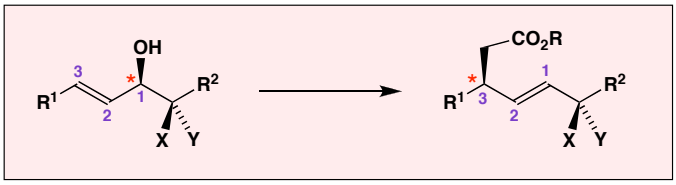




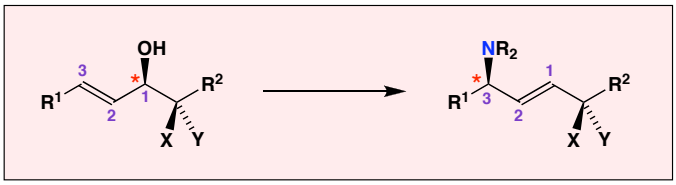
31 steps in the longest linear sequence

Strategies for Stereocontrolled Synthesis

[1,3] O→C Chirality Transfer



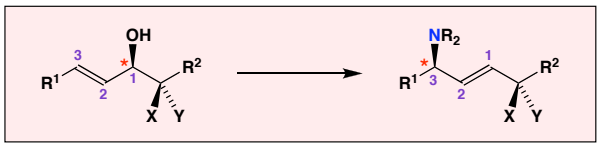
[1,3] O→N Chirality Transfer



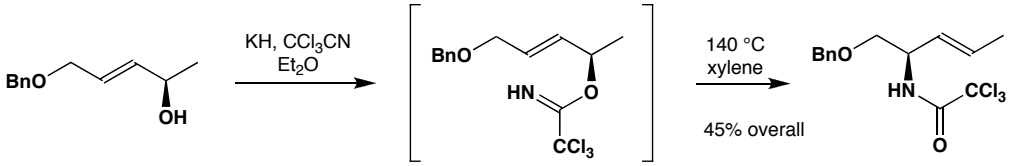
Review of chirality transfer via sigmatropic rearrangements
Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, pp 503-572

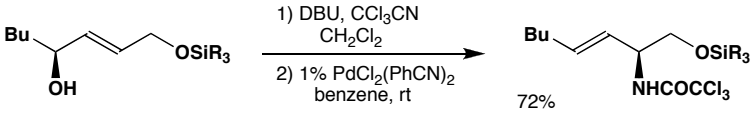
Strategies for Stereocontrolled Synthesis

[1,3] O→N Chirality Transfer



Overman Rearrangement
of Allylic Trihaloacetimidates





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