Problem Set
1.22.2010
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Workshop on Retrosynthesis

Most of the material was commandeered from Corey’s “The Logic of Chemical Synthesis”
Information regarding order of events is contained in the target molecule, (TGT) that is not as obvious in the components.
Recognizing patterns is key to disconnecting the TGT molecule.
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Diels-Alder retrons.
Provide the transform products.
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Diels-Alder retrons.
Provide the transform products.
Provide the products of this transform.

\[ \text{MeO}_2C-N-\text{MeO}_2C-NH-\text{OH} \implies ??? \]

\[ \text{??} \]

\[ \text{??} \]

\[ \text{MeO}_2C-\text{H}_2\text{C}=\text{ONPh} \implies ??? \]

\[ \text{??} \]
Provide the products of this transform.
Provide the products of this transform.
Provide the products of this transform.
Other patterns to identify

- E-enolate Aldol
- Michael addition
- Organometallic addition to carbonyl
- Robinson Aldol + Michael
Transforms and connection patterns to identify

- Mannich
- Claisen Rearrangement
- Fisher Indole
- Oxy-lactonization of Olefin
- Pinacol Rearrangement
Transforms and connection patterns to identify
3,3-rearrangements-synthon

1,2-stereochemistry transferred to 1,4
Problem
Problem

\[ \text{Oxy-Cope Rearrangement} \]

\[ \overset{\text{OH}}{\text{CH}} = \text{CH} \]
Problem

\[
\begin{align*}
\text{Oxy-Cope Rearrangement} & \\
\text{Br}
\end{align*}
\]
Another Problem

Hint: Don't Panic! Just Rearrange It.
Another Problem

Hint: Don't Panic! Just Rearrange It.

\[
\begin{align*}
\text{Ph} & \quad \text{nPr} \\
\text{Ph} & \quad \text{nPr}
\end{align*}
\]
Another Problem

Hint: Don’t Panic! Just Rearrange It.
Another Problem

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Hint: Don’t Panic!  Just Rearrange It.

Mannich/Aza-Cope Rearrangement
Another Problem

Hint: Don’t Panic! Just Rearrange It.
Another Problem

Hint: Don’t Panic! Just Rearrange It.

\[
\text{Ph-} \text{N}^+ \text{Ph} \rightleftharpoons \text{Ph-} \text{C}=\text{N} \rightleftharpoons \text{Ph-} \text{C}=\text{N} \rightleftharpoons \text{Ph-} \text{C}=\text{N}
\]
Another Problem

Hint: Don’t Panic! Just Rearrange It.
Another Problem

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Another Problem

Hint: Don’t Panic! Just Rearrange It.

Mannich/Aza-Cope Rearrangement
Disconnections: Try to remove appendages to rings.

Functional Group Equivalents

Not easily Accessible
Disconnections
Disconnections

Functional Group Equivalents

Not easily Accessible

Poor Selectivity

A

B
Disconnections

Functional Group Equivalents

Not easily Accessible

A

B

Poor Selectivity

O

Et

O

Et

TMS

SePh

O

Et

TMS

SePh

O

Et

N

O

Br

Li

Et

HO

N

Et

Et

HO

N

Et
Problem. Hint: when disconnecting, consider the acylic form.
Problem. Hint: when disconnecting, consider the acyclic form.
Problem. Hint: when disconnecting, consider the acyclic form.

Use Acyclic Form
Problem. Hint: when disconnecting, consider the acyclic form.

Use Acyclic Form
Problem. Hint: when disconnecting, consider the acyclic form.
Suggest a retrosynthesis

Perhydrohistrionicotoxin
Suggest a retrosynthesis

\[
\text{Perhydrohistrionicotoxin} \quad \text{=} \quad \begin{array}{c}
\text{nBu} \\
\text{OH}
\end{array} \quad \begin{array}{c}
\text{nAm} \\
\text{OH}
\end{array}
\]
Suggest a retrosynthesis

Perhydrohistrionicotoxin

\[
\begin{align*}
\text{nBu} & \quad \text{OH} \\
\text{nAm} & \quad \text{NH} \\
\text{nBu} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{nBu} & \quad \text{NH} \\
\text{nAm} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\Rightarrow & \quad \text{nBu} \\
\Rightarrow & \quad \text{NH} \\
\Rightarrow & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{nBu} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{nBu} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{O}
\end{align*}
\]
Suggest a retrosynthesis

Perhydrohistrionicotoxin

\[ \text{nBu} \quad \text{OH} \quad \text{nAm} \quad \text{NH} \quad \text{nBu} \quad \text{OH} \]

\[ \text{OH} \quad \text{NH} \quad \text{nBu} \quad \text{O} \quad \text{nBu} \quad \text{OH} \]

\[ \text{N} \quad \text{nBu} \quad \text{OH} \quad \text{nBu} \quad \text{OH} \]

\[ \Rightarrow \]

\[ \text{N} \quad \text{OH} \quad \text{OH} \]

\[ \Rightarrow \]

\[ \text{OH} \quad \text{OH} \]

\[ \Rightarrow \]

\[ \text{OH} \quad \text{OH} \]
Suggest a retrosynthesis

Perhydrohistrionicotoxin

\[
\begin{align*}
\text{nBu} & \text{OH} \\
\text{NH} & \text{nAm} \\
\text{nBu} & \text{OH} \\
\text{nAm} & \text{nAm} \\
\end{align*}
\]

\[
\begin{align*}
\text{nBu} & \text{OH} \\
\text{NH} & \text{nAm} \\
\text{nBu} & \text{OH} \\
\text{nBu} & \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
\text{nBu} & \text{OH} \\
\text{NH} & \text{nAm} \\
\text{nBu} & \text{OH} \\
\text{nBu} & \text{OH} \\
\end{align*}
\]
Suggest a retrosynthesis

Perhydrohistrionicotoxin

\[ \text{nBu} \text{NH} \text{nAm} \text{OH} = \text{nBu} \text{NH} \text{nAm} \text{OH} \]

\[ \Rightarrow \text{nBu} \text{OH} \Rightarrow \text{N} \text{K} \text{OH} \Rightarrow \text{N} \text{OH} \]

\[ \text{nBu} \text{OH} \quad \text{nBu} \text{OH} \]

\[ \text{nBu} \text{OH} \quad \text{nBu} \text{OH} \]

\[ \text{nBu} \text{OH} \quad \text{nBu} \text{OH} \]
Suggest a retrosynthesis
Suggest a retrosynthesis