STRATEGIES IN SYNTHESIS

Professor T. J. Donohoe

MT 2006

6 Lectures: Tuesday at 10 am; Thursday at 9 am (weeks 6-8)
DP: Lecture Theatre

Monensin


A copy of this handout is available at:
http://users.ox.ac.uk/%7Emagd1571/finalpage/teaching2.html
Strategies in Synthesis

Synopsis

1) **Introduction to synthesis**: why do we want to synthesise molecules- what sort of molecules do we need to make?

What aspects of selectivity do we need to exert to accomplish a good synthesis (chemo-, regio- and stereoselectivity)

2) **Protecting group chemistry** is central to any synthetic effort (examples)

3) **Retrosynthesis**- learning to think backwards (revision from first year).
   Importance of making C-C bonds and controlling oxidation state.
   Umpolung

4) **Examples of retrosynthesis/synthesis in action.**

5) **Handy hints** for retrosynthesis

**Recommended books:**
General: Organic Chemistry (Warren et al)
Organic Synthesis: The Disconnection Approach (S. Warren)
Classics in Total Synthesis Volumes I and II (K. C. Nicolaou)
The Logic of Chemical Synthesis (E. J. Corey)
1) Why do we want to synthesise complex molecules?

**Taxol**

![Taxol structure](image)

**Strychnine**

![Strychnine structure](image)

**Sildenafil**

![Sildenafil structure](image)
In order to undertake the synthesis of a complex organic molecule, we need to control the following:

1) Carbon

2) Functional

3) Stereochemistry

In order to control 1) and 2)

**Chemoselectivity**

![Chemoselectivity Diagram]

**Regioselectivity**

![Regioselectivity Diagram]

**Protecting group strategy**

![Protecting group strategy Diagram]
A) CHEMoselectivity

Using different tactics we can reduce each of the

a) H₂, Pd-C. This reagent is sensitive to steric

b) Na, NH₃, tBuOH (1 eq.)
Q. What would happen if we added >2 eq. of tBuOH?

\[ \text{Na, NH}_3 \rightarrow \text{?} \]

2 eq. tBuOH

\[ \text{NaBH}_4, \text{CeCl}_3 \] (Luche reduction)

\[ \text{NaBH}_4 \rightarrow \text{NaBH}_4 + \text{MeOH} \rightarrow \text{B} + \text{MeOH} \]

What does CeCl$_3$ do to sodiumborohydride?

This process is promoted by

\[ \text{Ce(III)} \]
B) REGIOSELECTIVITY

How to influence regioselectivity by
C) PROTECTING GROUPS (are essential to most syntheses)

There are tactics for protecting the least and the most hindered groups.
RETROSYNTHESIS

The theory (Corey- Nobel prize

1) Think about reactions in reverse

\[ \text{A} \rightarrow \text{B} \]
\[ \text{A} \rightarrow \text{B} \quad X \]
\[ \text{C} \rightarrow \text{D} \]

2) Use disconnections to break down molecules

[Chemical structures and reactions are depicted here.]

Make sure that your disconnections correspond to known and

3) Synthons: These are simply

There are two ways of analysing a single

A number shows the position of the charge relative to the
You have to decide which synthon is realistic and

Remember the concept of UMPOLUNG is helpful (especially) with carbonyl groups:
1) Normal reactivity of the carbonyl group
2) Use **UMPOLUNG** to reverse the reactivity of the carbonyl group

The hard part is choosing a particular disconnection (from several others) in a complex molecule.

4) Sometimes **functional group interconversion on the target helps**

**Simple**

\[
\begin{array}{c}
\text{Simple} \\
\text{FGI} \\
\rightarrow \\
\end{array}
\]

**More difficult**

\[
\begin{array}{c}
\text{COOEt} \\
\text{FGI} \\
\rightarrow \\
\end{array}
\]
Even stereochemistry can be altered in this way.

Some problems: How would you synthesise the following? (Hint: think about Diels Alder)
Synthesis 1) Eletriptan (Pfizer) Migraine

The synthesis:

[Chemical structures and reaction arrows]
Mechanism for this step is:

To finish the synthesis

1) Most substituents on each ring are

2) The only axially disposed groups are

3) The ANOMERIC
Further disconnections are possible

Now only

The synthesis in full:

1) Preparation of the starting materials

Putting these pieces together:
And finally,

Now the synthesis.

The other half:
The end-game

The end-game

The end-game

The end-game

The end-game

The end-game

The end-game

The end-game
And finally,

[Chemical structures and reactions]

Synthesis 4) Prostaglandin F$_{2\alpha}$ (*Journal of the American Chemical Society*, 1969, P5675) E. J. Corey

- Wittig Reaction and protection
- Reconnect Lactol and change oxidation state
- Wadsworth Emmons
Problem:

The synthesis:
mechanism of iodide reduction:
Reduction of the C=O bond

Why do

\[ \text{MeO-P-O-C_5H_11} \]

\[ \text{P-O} \rightarrow \]

\[ \text{P-O} \rightarrow \]

\[ \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O}
\end{array} \]

\[ \text{NaBH}_4 \]

\[ \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O}
\end{array} \]

\[ (i) \text{K}_2\text{CO}_3 \]

\[ (i) \text{TsOH} \]

\[ \begin{array}{c}
\text{O} \\
\text{O}
\end{array} \]
How do you make the ylid?

\[ \text{Ph}_3\text{P} - \text{Ph}_2\text{P} - \text{CO}_2 \]

Why do non-stabilised
Finally, to complete the synthesis:

Some handy hints for retrosynthesis

1) Make the synthesis

Use convergent rather than

2) Use only disconnections corresponding to

3) Disconnect C-X bonds wherever possible (this includes RCO
4) Disconnect C-C bonds by using nearby functional groups or by

Also, it makes more sense to disconnect in the middle

5) Disconnect back to readily recognisable
Some problems to think about:
Disconnect the following and then devise forward syntheses: