DISCONNECTION APPROACH:
Retrosynthetic Principles and Synthetic Applications

XV Summer School in Pharmaceutical and Medicinal Chemistry
Rio de Janeiro, Brasil 09-13 February 2009

Pier Giovanni Baraldi
Department of Pharmaceutical Sciences
Ferrara University, Italy
Disconnection Approach

**Retrosynthetic Analysis**: the logical process of analysing the structure of a target molecule to discern a possible synthesis step by step

**Retrosynthetic arrow is**: \[ \text{A} \rightarrow \text{B} \] (B is a precursor of A) \\
(Means “can be made from”)

**Functional group interconversion (FGI)**

**Functional group addiction (FGA)**

**Functional group removal (FGR)**

**Disconnection**: the formal reverse of a bond forming reaction (conceptual cleavage of a bond to break the molecule into possible starting materials)

**dₙ synthon**: Functionalized nucleophile (d, donor) with the heteroatom of the functional group joined to the nᵗʰ carbon atom

**aₙ synthon**: Functionalized electrophile (a, acceptor) with the heteroatom of the functional group joined to the nᵗʰ carbon atom

**Reagent**: A chemical compound used in practice for a synthon
Disconnection Approach
Synthons and Reagents

d\text{n} \text{ synthon:} \text{ Functionalized nucleophile (d, donor) with the heteroatom of the functional group joined to the n}^{\text{th}} \text{ carbon atom.}

\begin{align*}
d_1 & \odot \text{ CN} \\
d_2 & \odot \text{ CH}_2\text{CHO}
\end{align*}

a\text{ synthon:} \text{ Functionalized electrophile (a, acceptor) with the heteroatom of the functional group joined to the n}^{\text{th}} \text{ carbon atom.}

\begin{align*}
a_1 & \oplus \text{ CH}_2\text{OH} \\
a_2 & \oplus \text{ CH}_2\text{CHO} \\
a_3 & \oplus \text{ CH}_2\text{CH}_2\text{CHO}
\end{align*}

Reagent: A chemical compound used in practice for a synthon.

\begin{center}
\begin{tabular}{c|c}
\text{Synthon} & \text{Reagent} \\
\hline
\odot \text{ CH}_3 & \text{ CH}_3\text{I or CH}_3\text{oTs} \\
\odot \text{ CH}_3 & \text{ CH}_3\text{MgBr} \\
\oplus \text{ CH}_2\text{CH}_2\text{CHO} & \end{tabular}
\end{center}
Retrosynthesis of Benzocaine

Retrosynthetic Pathway: Benzocain from toluene

Benzocaine

- Toluene is a readily available starting material
- Me is activating and ortho/para-directing
- We know reagents for the synthon NO₂⁺

Synthesis

H₂SO₄, HNO₃

O₂N

K₅MnO₄

Oxidation

H₂ Pd/C

Chemoselective reduction

EtOH/ H⁺
Eletrophilic Aromatic Substitution

How to identify the most suitable synthons and reagents?
Which disconnection and which sense of polarity?

Synthons

Reagents

Synthesis

o/p directing and activating
# Eletrophilic Aromatic Substitution

**How to identify the suitable synthons and reagents?**

Key reactions and Reagents for FGI in the contest of Aromatic Chemistry

![Eletrophilic Aromatic Substitution Diagram](image)

<table>
<thead>
<tr>
<th>Synthon</th>
<th>Reagent</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>R⁺</td>
<td>RBr with Lewis acid</td>
<td>Friedel Craft alkylation</td>
</tr>
<tr>
<td></td>
<td>ROH/H⁺</td>
<td></td>
</tr>
<tr>
<td>RCO⁺</td>
<td>RCOCl with Lewis Acid</td>
<td>Friedel Craft acylation</td>
</tr>
<tr>
<td>NO₂⁺</td>
<td>HNO₃/H₂SO₄</td>
<td>Nitration</td>
</tr>
<tr>
<td>Cl⁺</td>
<td>Cl₂/FeCl₃</td>
<td>Chlorination</td>
</tr>
<tr>
<td>Br⁺</td>
<td>Br₂ and Lewis Acid</td>
<td>Bromination</td>
</tr>
<tr>
<td>SO₃</td>
<td>H₂SO₄</td>
<td>Sulfonation</td>
</tr>
</tbody>
</table>
Eletrophilic Aromatic Substitution

How to identify the most suitable synthons and reagents?

Key reactions and Reagents for FGI in the contest of Aromatic Chemistry

<table>
<thead>
<tr>
<th>Y</th>
<th>X</th>
<th>Reagent</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>NH₂</td>
<td>( \text{H}_2 )</td>
</tr>
<tr>
<td>COR</td>
<td>CH(OH)R</td>
<td>( \text{NaBH}_4 )</td>
</tr>
<tr>
<td>COR</td>
<td>CH₂R</td>
<td>( \text{Zn/Hg} )</td>
</tr>
<tr>
<td>CH₃</td>
<td>COOH</td>
<td>( \text{KMnO}_4 )</td>
</tr>
<tr>
<td>COR</td>
<td>OCOR</td>
<td>( \text{RCO}_3\text{H} )</td>
</tr>
<tr>
<td>CN</td>
<td>COOH</td>
<td>Hydrolysis</td>
</tr>
</tbody>
</table>
Eletrophilic Aromatic Substitution

Retrosynthesis of BHT

BHT is an antioxidant and is used as a food preservative.

Synthons

Reagents

OR

Reagents
Eletrophilic Aromatic Substitution

Friedel-Craft alkylation or acylation

PROBLEMS:
1. Rearrangement of alkyl for more stable carbocation.
2. Problem of polyalkylation

Synthesis
Nucleophilic Aromatic Substitution

SN$_1$ for nucleophilic aromatic substitution: Diazonium Chemistry

\[
\text{C}_6\text{H}_4\text{X} \xrightarrow{\text{NaNO}_2/\text{HCl}} \text{C}_6\text{H}_4\text{N}_2^+ \xrightarrow{-\text{N}_2} \text{C}_6\text{H}_4\text{X}
\]

<table>
<thead>
<tr>
<th>X</th>
<th>Reagent</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td>H$_2$O</td>
</tr>
<tr>
<td>OR</td>
<td>ROH</td>
</tr>
<tr>
<td>CN</td>
<td>CuCN</td>
</tr>
<tr>
<td>Cl</td>
<td>CuCl</td>
</tr>
<tr>
<td>Br</td>
<td>CuBr</td>
</tr>
<tr>
<td>I</td>
<td>KI</td>
</tr>
<tr>
<td>ArH</td>
<td>ArH</td>
</tr>
<tr>
<td>H</td>
<td>H$_3$PO$_2$</td>
</tr>
</tbody>
</table>

Addition-Elimination

\[
\text{C}_6\text{H}_4\text{X} \xrightarrow{\text{Nu}^-} \text{C}_6\text{H}_4\text{Nu} + \text{X}^-
\]

More reactive

\[\text{O}_2\text{N} \quad > > \quad \text{O}_2\text{N} \quad > > \quad \text{O}_2\text{N}\]

Less reactive
Aromatic Substitution

Retrosynthesis of Trifluoralin B Herbicide

Retrosynthesis of biphenyl derivative
Aromatic Substitution

The use of removable group to control selectivity

Retrosynthesis of Propoxycaine
Local anaesthetic

Synthetic Route to Propoxycaine

Solution:
Introduction of a temporary group that will be removed at a later stage of the synthesis.

Problem of Regiocontrol

Salicylic acid or aspirin readily available

Ortho/para directing

Meta directing

Target
Aromatic Substitution

The importance of order of events - disconnection

Retrosynthesis of Dinocap (Fungicide)

Good disconnection - Correct order of events

Poor disconnection - Wrong order of events

Para position not blocked to force alkylation ortho
One Group and Two Groups Disconnection

One Group C-X Disconnection

For compounds consisting of two parts joined by a heteroatom (X), disconnect next to the heteroatom. This guideline works for esters, amides, ethers, sulfides etc.

Retrosynthesis of Propanil Weed killer

Retrosynthesis of Chlorbenside

Synthons

Reagents
Chemoselectivity arising from two groups of different reactivity. The preferential retrosynthetic route should avoid chemoselectivity problems. In practice, this means that one should disconnect reactive groups first. To solve chemoselectivity problems, it is very often critical to choose carefully reaction conditions for the forward synthetic step.

Retrosynthesis of Cyclomethycaine (anaesthetic)

Synthesis of Cyclomethycaine

Both groups ionised pH > 10

pKa phenol ~ 10
pKa benzoic acid ~
One Group and Two Groups Disconnection

Chemoselectivity

Retrosynthesis of Paracetamol (Analgesic)

Synthesis of Paracetamol

Under conditions that keep phenol unionised
Two Groups C- X Disconnection

1,1-Difunctionalised compounds

Example 1

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{HO}
\end{align*}
\]

\[
\text{acidic conditions}
\]

Example 2

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{H}_2\text{N} \\
\text{COOH} & \quad \text{CN}
\end{align*}
\]

1,1 diX

Example 3

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{NH}_2 & \quad \text{CN}
\end{align*}
\]

1,1 diX

\[
\begin{align*}
a_1 & \quad d_1
\end{align*}
\]

KCN/H^+
Two Groups C- X Disconnection

1,2-difunctionalised compounds

ALCOHOLS

\[
\begin{align*}
\text{HO} & \quad \text{NR}_2 \\
\text{HO} & \quad \Theta \\
\text{NR}_2 & \quad \Theta
\end{align*}
\]

Important synthon Reagent is epoxide

Example 1: Phenyramidol (muscle relaxant)

Example 2: Propranolol (beta-blocker reduces blood pressure)

Propranolol allows for two possible 1,2-diX but it is best to disconnect the more reactive amine group first.
Two Groups C-X Disconnection

1,2-difunctionalised compounds

CARBONYLS

\[ R\text{C}O\text{R} \rightarrow R\text{C}(\text{Nu})\text{Nu} \]

Important synthon

Reagent

Note: \( \alpha \)-chloro or bromo highly reactive electrophiles and Control of mono-versus polyhalogenation.

<table>
<thead>
<tr>
<th>Reagent</th>
<th>k rel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me-Cl</td>
<td>200</td>
</tr>
<tr>
<td>iPrCl</td>
<td>0.02</td>
</tr>
<tr>
<td>allylCl</td>
<td>80</td>
</tr>
<tr>
<td>MeOCH\textsubscript{2}Cl</td>
<td>920</td>
</tr>
<tr>
<td>PhCOCH\textsubscript{2}Cl</td>
<td>10000</td>
</tr>
</tbody>
</table>
Two Groups C- X Disconnection

1,3-difunctionalised compounds

CARBONYLS

Example 1: Atropine (Muscle relaxant)
Two Groups C- X Disconnection

1,3-difunctionalised compounds

NITRILES

\[
\text{O} \quad \text{FGI} \quad \text{O} \\
\text{NH}_2 \quad \text{CN} \quad \text{OH} + \text{CN}
\]
Protecting Group Chemistry

To avoid if you can... Each protection event adds two steps: protection-deprotection

Synthesis requiring protecting group chemistry

Revised Synthesis:
Amines and One Group C-C Disconnections

Synthesis of secondary amines

Retrosynthesis of Fenfluramine (Drug CNS)

Reagent for reductive amination:
Carbonyl derivative, amine and NaBH4 NaOAc/HOAc pH 6
Amines and One Group C-C Disconnections

Synthesis of primary amines

These targets are not conveniently prepared from unsubstituted imines [unstable] or primary amides.

Alternative and better solutions are available and include:
- the reduction of cyano group
- the reduction of azido group
- the reduction of oximes
- alkylation and reduction of nitro compounds
- the Ritter reaction followed by hydrolysis
- the Gabriel synthesis
Amines and One Group C-C Disconnections

The synthesis of amines is slightly more complicated in comparison with the synthesis of e.g. ethers or sulfides because the product of an N-alkylation is at least as reactive as the starting material, therefore leading to complex reaction mixtures.

\[
\begin{align*}
\text{R}_1 & \quad \text{NH}_2 \\
\text{R}_2 & \quad \xrightarrow{\text{C-N}} \\
\text{R}_1 & \quad \text{NH}_2 + \\
\end{align*}
\]

Bad disconnection

The problem of polyalkylation

Secondary amine
More reactive than primary amine

The solution: FGI prior to disconnection

Suitable FGI involved amides, imines or oximas.

\[
\begin{align*}
\text{RNH}_2 & \quad \xrightarrow{\text{R}_1\text{COCl}} \\
\text{RNH}_2 & \quad \xrightarrow{\text{LiAlH}_4} \\
\end{align*}
\]

\[
\begin{align*}
\text{RNH}_2 & \quad \xrightarrow{\text{R}_1\text{COR}_2} \\
\end{align*}
\]
Amines and One Group C-C Disconnections

Example 1

\[
\text{NH}_2 + \text{CN}^- \rightarrow \text{C}_4\text{H}_4\text{N}^+ \text{+ CN}^-
\]

AMINES

Reagent for reduction of cyano into amine is LiAlH\textsubscript{4}

Example 2

\[
\text{R}_1\text{CH}_2\text{NO}_2 \rightarrow \text{R}_1\text{R}_2\text{R}_3\text{CNO}_2 \rightarrow \text{R}_1\text{R}_2\text{R}_3\text{CNH}_2
\]

Reagent for reduction of azide into amine: PPh\textsubscript{3} + NaN\textsubscript{3}

Example 3

\[
\text{R}_1\text{CH}_2\text{NO}_2 \rightarrow 2\times \text{alkylation} \rightarrow \text{R}_1\text{R}_2\text{R}_3\text{CNO}_2 \rightarrow \text{H}_2 \text{cat} \rightarrow \text{R}_1\text{R}_2\text{R}_3\text{CNH}_2
\]
Amines and One Group C-C Disconnections

**AMINES**

**Example 4  Ritter Reaction**

\[
\begin{align*}
R_1R_2R_3\text{COH} & \xrightarrow{\text{MeCN/ H}^+} R_1R_2R_3\text{CNHCOCH}_3 \quad \xrightarrow{\text{Hydrolisis}} R_1R_2R_3\text{CNH}_2 \\
\end{align*}
\]

**Ritter Reaction: VIA CARBOCATION \( R_1R_2R_3\text{C}^+ \)**

**Example 5  Gabriel Reaction**

1. \( \text{NH}_3 \)
2. \( \text{KOH/ EtOH then RBr} \)
3. \( \text{NH}_2\text{NH}_2 \)

\[
\begin{align*}
\text{NH}_3 & \xrightarrow{} \text{NH}_3 \quad \text{KOH/ EtOH then RBr} \quad \text{NH}_2\text{NH}_2 \\
\end{align*}
\]
Amines and One Group C-C Disconnections

One Group C-C Disconnection

1,1 CC

1,2 CC

1,2 CC

1,3 CC

SYNTHONS

REAGENTS

RMgBr + R1COR2

RMgBr +

RBr + R1COMe

RMgBr/ CuX + CH2=CHCOR1
Amines and One Group C-C Disconnections

One Group C-C Disconnection - Alcohols

1,2CC Disconnections leading to alcohols

Reagents: PBr$_3$ or the Apple Reaction [PPh$_3$/CBr$_4$]
Amines and One Group C-C Disconnections

One Group C-C Disconnection- Alcohols

1,1CC Disconnection leading to alcohols

\[
\text{OH} \quad \text{1,1 CC} \quad \text{OEt} \quad + \quad 2\text{eq MeMgBr}
\]

Retrosynthesis of Pirindol- Muscle Relaxant

1,1CC Disconnection leading to carboxylic acid

\[
\text{Synthons} \quad \text{Reagents}
\]

\[
\text{COOH} \quad \text{CO}_2 \quad \text{NaCN}
\]
Amines and One Group C-C Disconnections

One Group C-C Disconnection - Carbonyl Compound as Target

1,1 CC

1) The use of ester and Grignard as double addition will generate the alcohol

2) The use of less reactive organocadmium like R1CdR2

Alternative routes are: ketones from nitriles, from acids and from Weinreb amides

1,2 CC

Example:
Amines and One Group C-C Disconnections
One Group C-C Disconnection - Carbonyl Compound as Target

1,3CC

Example:

Keys aspects for the synthesis:
• organocopper chemistry
• stereoselectivity of Michael addition and reduction
Synthesis of Alkenes via elimination

\[ \text{Ph} \xrightarrow{\text{FGI}} \text{Ph} - \text{R} \] or
\[ \text{Ph} \xrightarrow{\text{FGI}} \text{Ph} - \text{HO} \xrightarrow{2 \times 1,1 \text{CC}} \text{EtO} - \text{R} + \text{PhMgBr} \]

Synthesis of Alkenes via Wittig Olefination

Wittig Reagent
\[ \text{R}_1\text{CH}_2\text{Br} \xrightarrow{\text{PPh}_3} \text{R}_1\text{CH}_2\text{PPh}_3 \]

Phosphorus Ylide
\[ \text{R}_1\text{CHPPh}_3 \xrightarrow{\text{base}} \text{R}_1\text{CHPPh}_3^{+} \]

Wittig Reaction
\[ \text{R}_1\text{CHPPh}_3^{+} + \text{R}_2\text{CHO} \rightarrow \text{R}_1\text{CH} = \text{CHR}_2 + \text{OPPh}_3 \]

Decision making:
\[ \xrightarrow{\text{octane-PPH}_3 + \text{O=CH}_2} \]
\[ \xrightarrow{\text{octane-O} + \text{Ph}_3\text{P=CH}_2} \]
Synthesis and Use of alkenes and Alkynes

Elimination or Wittig Olefination?

Problem of elimination: product selectivity

Stereochemistry of the Wittig Reaction

E/Z geometry is a function of the structural features of the phosphorus ylid
Synthesis and Use of alkenes and Alkynes

Stereochemistry of the Wittig Reaction

E/Z geometry is a function of the structural features of the phosphorus ylid

**Z selective Wittig IRREVERSIBLE**

**E selective Wittig REVERSIBLE**

oxaphosphetane formation is reversible
Synthesis and Use of Alkenes and Alkynes

Synthesis of E,E or E,Z Diene

Solution needs to take into account E,Z or E,E geometry of the diene.

\[
\text{Wittig} \quad \begin{array}{c} \\
\text{E-stabilised ylid} \quad \rightarrow \\
\text{Z-unstabilised ylid} \quad \rightarrow \\
\end{array} \ \\
\text{PPh}_3 + \text{O} = \text{PPh}_3 + \text{O} = 
\]

Synthesis Alkenes upon reduction of Alkenes

For Z isomer Hydrogenation [Lindlar's catalyst]
For E isomer Na/NH\(_3\) reduction

Revision: Mechanism of Na-ammonia reduction SET - origin of E selectivity
Synthesis and Use of Alkenes and Alkynes

Problem for trisubstituted alkenes: Control over E/Z geometry

One solution to the problem: Synthesis involving a cyclic intermediate

Revise Birch reduction: the Mechanism and the issue of Product Selectivity
Synthesis and Use of Alkenes and Alkynes

pKa and key transformations

\[ R\equiv H \rightarrow R\equiv^- + Na^+ \]
\[ R\equiv H \rightarrow R\equiv MgBr + RH \]

alkylation

addition onto carbonyl derivatives

epoxide ring opening

Conversion of terminal Alkynes into Carbonyl Derivatives

\[ R\equiv H \xrightarrow{Hg^{2+} / H_2SO_4} R\equiv Me \]
\[ R\equiv H \xrightarrow{t-hexyl_2BH / H_2O_2 / NaOH} R\equiv H \]
Synthesis and Use of Alkenes and Alkynes

Example 1

\[
\text{Br} \quad \xrightarrow{\text{FGI}} \quad \text{OH} \quad \xrightarrow{\text{FGI}} \quad \text{OH} 
\]

\[
\text{Br} \quad \xrightarrow{\text{FGI}} \quad \text{OH} \quad \xrightarrow{\text{FGI}} \quad \text{OH} 
\]

acrolein readily available

\[
\text{FGI} + \text{FGI} \quad \xrightarrow{1,1 \text{ C-C}} \quad \text{OH} \quad \xrightarrow{\text{FGI}} \quad \text{OH} 
\]

Example 2

\[
\text{FGI} \quad \xrightarrow{\text{FGI}} \quad \text{HO} \quad \xrightarrow{\text{FGI}} \quad \text{HO} 
\]

\[
\text{HO} \quad \xrightarrow{1,1 \text{ C-C}} \quad \text{O} \quad + \quad \text{H} 
\]
Synthesis and Use of Alkenes and Alkynes

Multistriatatin Retrosynthesis

1,1-diX 1,2-CC + Br

FGI

MeMgBr

Reagents

FGI
Two Group Disconnections

1,3-, 1,5- and 1,2- Difunctionalised Compounds

• 1,3-Dicarbonyl Compounds and their derivatives

Note: Mechanism of Claisen condensation

• Example 1: Synthesis of Pival (Rat Poison)
Two Group Disconnections

1,3-Difunctionalised Compounds

• Example 2

O
\[ \overset{\text{COOEt}}{\text{OEt}} \]
\[ \overset{\text{COOEt}}{\text{OEt}} \]

\[ \overset{\text{B}}{\leftrightarrow} \]


• Example 3

\[ \overset{\text{Ph}}{\overset{\text{OCOR}}{\text{N}}} \]

\[ \overset{\text{C-C}}{\longrightarrow} \]

\[ \overset{\text{NH}}{\overset{\text{Me}}{\text{O}}} \]

\[ \overset{\text{unstable}}{\longrightarrow} \]

\[ \overset{\text{NH}}{\overset{\text{Me}}{\text{O}}} \]

\[ \overset{\text{COOEt}}{\text{EtOOC}} \]

\[ \overset{\text{Me}}{\overset{\text{N}}{\text{COOEt}}} \]

\[ \overset{\text{Me}}{\overset{\text{N}}{\text{COOEt}}} \]

\[ \overset{\text{FGA}}{\downarrow} \]

Add a group!


• Example 4 Route to symmetrical ketones

\[ \overset{\text{R}}{\overset{\text{R}}{\overset{\text{Add a group!}}{\longrightarrow}}} \]

\[ \overset{\text{R}}{\overset{\text{R}}{\overset{\text{FGA}}{\longrightarrow}}} \]

\[ \overset{\text{R}}{\overset{\text{R}}{\overset{\text{COOEt}}{\longrightarrow}}} \]

\[ \overset{\text{R}}{\overset{\text{R}}{\overset{\text{EtOEt}}{\longrightarrow}}} \]

• A and B are the two possible disconnections

• B corresponds to the Dickmann cyclisation

• Example 4 Route to symmetrical ketones
Two Group Disconnections

1,3-Difunctionalised: $\beta$–Hydroxycarbonyl and $\alpha,\beta$-Unsaturated carbonyls

• Example 1

• Example 2 Oxanamide (tranquilliser)

• Example 3 Doxpicomine (analgesic)
Two Group Disconnections

1,3-Difunctionalised Compounds – Amino alcohols

- Reduction of nitriles

\[ R-CN \xrightarrow{R'-CO-R'} \text{C-C formation} \xrightarrow{\text{reduction}} R'-CN \]

Example Venlafaxine (Antidepressant)

- Mannich Reaction

\[ \text{HO-NR}_2 \xrightarrow{\text{FGI}} \text{O-\text{NR}_2} \xrightarrow{\text{O-H}} \text{NHR}_2 \]

Example Clobutinol (Cough Medicine)
Two Group Disconnections

1,3-Difunctionalised Compounds – Summary

- **ALDOL and Variants**
  - Reaction: \( R=\text{FGI} \rightarrow R' \)
  - Products: \( R \rightarrow R' \)
- **CLAISEN and Variants**
  - Reaction: \( R=\text{FGI} \rightarrow R' \)
  - Products: \( R \rightarrow R' \)
- **MANNICH and Variants**
  - Reaction: \( R=\text{FGI} \rightarrow R' \)
  - Products: \( R \rightarrow R' \)
- **NITRILE and Variants**
  - Reaction: \( R=\text{FGI} \rightarrow R' \)
  - Products: \( R \rightarrow R' \)
Two Group Disconnections

1,5-Difunctionalised Compounds

• 1,5-Dicarbonyl Derivatives

Example

Example Rogletimide (Sedative)
Two Group Disconnections

1,5-Difunctionalised Compounds

- **Robinson Annulation**

- **Synthesis of Coccinelline**

- **Synthesis involving an intermediate featuring a 1,5-Difunctionality**

pKa = 10
Two Group Disconnections

1,2-Difunctionalised Compounds

• 1,2-Diols via alkenes

R OH

R OH

R' OH

R

R' OH

R

R' OH

R

FGI

FGI

\[
\begin{align*}
R & \quad \text{FGI} \quad R' \\
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{FGI} \\
\end{align*}
\]

• 1,2-Diols via cyanhydrins

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

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

• \(\alpha\)-Hydroxyketones via benzoin condensation

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

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{OH} & \quad \text{OH} \\
da1 & \quad da1 \\
\end{align*}
\]

Also Revise: acyloin condensation

• \(\alpha\)-Functionalisation of carbonyl compounds

Diphepanol

spasmolytic
Two Group Disconnection
1,4-Difunctionalised Compounds: Strategy 1

Example: Precursor of antibiotic methylenomycin

Synthesis:
Two Group Disconnection

1,4-Difunctionalised Compounds: Strategy 2

Example:

1,4-Difunctionalised Compounds: Strategy 3

Reagents

With nitrile or nitro derivative
Two Group Disconnection

1,4-Difunctionalised Compounds: Strategy 3 Nitrile

Synthesis:

\[ \text{PhCHO} + \text{NCCH}_2\text{COOEt} \xrightarrow{\text{NaOEt}} \text{Ph} - \text{NC} - \text{COOEt} \xrightarrow{\text{H}^+ / \text{H}_2\text{O}} \text{Ph} - \text{N} - \text{COOEt} \]

Then KCN

Then MeNH₂

1,4-Difunctionalised Compounds: Strategy 3 Nitro
Two Group Disconnection

1,4-Diols and derivatives: Strategy 4 Alkynes

Example:

1,4-Difunctionalised Compounds: Strategy 5 Allylation

1,4-Difunctionalised Compounds: Strategy 5 Allylation
“Reconnection” is a reliable strategy for synthesising 1,6-difunctionalised compounds since the cyclohexenes required for the oxidative cleavage are easily accessible.

Example:

1,6-Difunctionalised Compounds: Baeyer-Villiger

“Revision”: mechanism of Baeyer-Villiger reaction and migratory aptitude
Two Group Disconnection
1,6-Difunctionalised Compounds

Synthesis

Two Group Disconnection
Two Group Disconnection
1,6-Difunctionalised Compounds

Retrosynthesis - Solution 1

Retrosynthesis - Solution 2
Dithianes are d1 Reagents

Acyl anion equivalents

Which dithiane?

Example

Revision: pKa and mechanism/reagents to transform dithianes into aldehydes or ketones HgCl₂, oxidation or alkylation
Ring Synthesis

Three-membered rings

• Three-membered rings

Mechanisms
Epoxidation
Ring closure

Synthesis a:

H₂O₂, base

Synthesis b:

EtO⁻/acetone
Ring Synthesis

*Three-membered rings*

- *Three-membered rings*

\[ \text{C-C} \quad \text{FGI} \quad \text{EtOOC} \]

- *Three-membered rings*
Ring Synthesis

Four-membered rings

\[
\begin{align*}
\text{BuLi} & \quad \rightarrow \\
\text{R-S-R} & \quad \rightarrow \\
\text{R-C=O} & \quad \rightarrow \\
\end{align*}
\]
Ring Synthesis

Five-membered rings

• Five-membered rings: chemoselectivity ozonolysis, control over recyclisation step

\[
\begin{align*}
\text{Limonene} & \quad \text{Natural Product} \\
\text{Corylone} & \quad \text{Spicy coffee}
\end{align*}
\]

• Acyloin condensation as a key step for the synthesis of 5-membered rings

• Favorskii Ring Contraction
Ring Synthesis

Six-membered rings

• Six-membered rings via Diels-Alder Cycloaddition

• Six-membered rings via complete Reduction

• Six-membered rings via partial Reduction
Synthesis of Nuciferal

*Bisbolane type sesquiterpene isolated from wood oil of Torreya Nucifera*

1. Suggest a synthesis for the starting material A
2. Suggest reagents for stages 1, 2 and 3
3. Draw out the retrosynthetic analysis with suitable labelling for all retrosynthetic steps
4. Which synthon does the starting material A represent?
Synthesis of Coccinelline

*Ladybird compound*

\[
\begin{align*}
\text{NaOMe} \quad &\xrightarrow{\text{MeOH/H}^+} \quad \text{MeOOCCOOMe} \\
\text{NaCl, DMSO} \quad &\xrightarrow{\text{Krapcho dealkoxy-decarboxylation}} \\
\text{pH 5, H}_2\text{O} \quad &\xrightarrow{\text{MeO}_2\text{C}} \\
\end{align*}
\]
Retrosynthesis of Terfenadine

Antagonist H₁
Retrosynthesis of Minaprine - Antidepressant

\[
\begin{align*}
\text{FGI} & \quad \text{RNH}_2, \Delta \\
\text{FGI} & \quad \text{POCl}_3, \Delta \\
\text{FGI} & \quad \text{Br, AcOH, } \Delta \\
\text{FRIEDEL - CRAFT} & \quad \text{RETRO ACILAZ.}
\end{align*}
\]
Retrosynthesis of (+)-Norgestrel
19-Nor Steroid

[Chemical diagrams and reactions]

Retrosynthesis involving various reactions such as FGI, RETRO ETINILAZIONE, FGA, FGI, RETRO KNOEVENAGEL, FGI, and RETRO TORGOR, with key steps including the use of Li/NH2(l), Al(OR)3, H2/Pd/CaCO3, KOH, MeOH, etc.

*a, d*
Retrosynthesis of Avenaciolide
Retrosynthesis of Pentenomicina

(-)-Pentenomicina
Retrosynthesis of 11-Deoxy-8-aza-PGE₁

11-Deoxy-8-aza-PGE₁

![Chemical structure](image)

Retrosynthesis of $\pm 4$-oxocyclopentane-1,2-dicarboxylic acid
Retro-synthesis of cis-3-oxabicyclo[3.3.0]octan-7-one

Baraldi, P.G. et al., Tetrahedron, 1984, 40, 761
Retrosynthesis of Diidroiasmone

Synthetic scheme of PGE$_{2\alpha}$

Retrosynthetic Route to Geiparvarin

Baraldi, P.G. et al. Tet. Lett. 1985, 43, 531
Retro synthesis of Sarcomycin

Retrosynthesis of Carbaprostacycline
Retrosynthesis of a intermediate for Carbaprostacycline

Synthesis and Retrosynthesis $A_{2B}$ Agonists

$R = \text{Ph}$

$\text{hA}_1 K_i = 8.5\text{nM}$

$\text{hA}_{2A} K_i = >1000\text{nM}$

$hA_{2B} EC_{50} = 7.3\text{nM}$

$hA_3 K_i = 38.4\text{nM}$

Synthesis and Retrosynthesis $A_{2B}$ Antagonists

$hA_1 K_i > 1000 \text{nM}$
$hA_{2A} K_i > 1000 \text{nM}$
$hA_{2B} IC_{50} = 7 \text{nM}$
$hA_3 K_i > 1000 \text{nM}$
