ASPECTS OF ORGANIC SYNTHESIS
STRATEGY / RETROSYNTHESIS

Course outline:
- **Organic Synthesis** – what is it all about?
- **Retrosynthesis** – terminology
- **Guidelines** – reactions
- strategic disconnections
- strategic bonds
- functional groups
- transformations
- selectivity
- routes
- **Total synthesis** – here's one somebody else prepared earlier


Gareth Rowlands (g.rowlands@sussex.ac.uk) Ar402, http://www.sussex.ac.uk/Users/kafj6, Retrosynthesis 2001
ORGANIC SYNTHESIS

TOTAL SYNTHESIS

METHODOLOGY

NATURAL PRODUCTS
STRUCTURE DETERMINATION
PHARMACEUTICALS
INDUSTRIAL
BIOLOGICALLY RELEVANT

NUMBER OF STEPS
YIELDS
CONTROL / SELECTIVITY
PURIFICATION
COST

STRATEGY
(Overall plan)
• Retrosynthesis
• Key transformations
• Methodology

COMPREHENSION
(Knowledge)
• Reading / remembering
• Mechanism
• Stereoelectronics
• Conformation

TACTICS
(nuts and bolts)
• Reagents / conditions
• Protecting groups
• Selectivity

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**RETROSYNTHESIS – INTRODUCTION**

**TERMINOLOGY**

- **Retrosynthesis** - the sequential simplification of a compound to a recognisable starting material
  - all about simplification
  - draw compound in simplest form
  - represents reverse of a chemical reaction
  - always indicate transformation
  - a necessary evil (briefly discussed sect 7b)

- **protecting groups**
  - hydrolysis

- **functional group interconversion**
  - self explanatory
  - protection of carbonyl
  - also addition of extra functionality to aid simplification (sect 4aii)

- **disconnection** - breaking a bond to simplify structure
  - indicate bond being broken and transformation to achieve this

- **synthon** - an idealised unit to aid visualisation / identification of transformation
  - it is NOT an intermediate

- **strategic transformation** - reliable method to introduce stereochemistry

- **strategic bond** - certain bonds readily lend themselves to simplification (sect 3b)

**Repeat process**

- iterative transformations can be good

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TOTAL SYNTHESIS

- Of course, retrosynthetic analysis is useless unless it can be achieved in the laboratory

- sets up 2 out of 4 stereocentres

- Payne rearrangement gives epoxide

- thiol opens epoxide and drives equilibrium

- Pummerer reaction (via thionium species) gives protected aldehyde

- stereodivergent-synthesis allows the preparation of a number of isomers from a common intermediate—very useful

- used by Sharpless and Masumune to synthesize 8 natural hexoses (90T245)

**What have we learnt?**
- the need for synthesis
- the concept of retrosynthesis
- the terminology of retrosynthesis
- how to make sugar

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**RETROSYNTHESIS: GUIDELINES**

- How do we plan such a synthesis?
- The following set of guidelines give a simple starting point
- Ultimately practise is the only way to learn
- Work through total syntheses in the literature

**Guideline 1: Knowledge of reactions**

- Each possible reaction produces a different intermediate, which in turn results in a different retrosynthetic analysis. Could use:
  - Julia olefination (sulfone & carbonyl)
  - Wittig (phosphorane & carbonyl)
  - Ring closing metathesis (two alkenes)
  - McMurry reaction (two carbonys)
  - Peterson (silane & carbonyl)

- Knowledge of mechanism / stereoelectronics etc allows you to devise new solutions to problems and that's where the real fun lies.
- **Be imaginative and creative** (SVL)

**Guideline 2: Simplicity**

- Ideally each step should reduce the molecular complexity

- cleaving fused / spiro rings simplifies structure

- **PLEASE NOTE: IN ALL THE RETROSYNTHESSES IN THIS COURSE I HAVE IGNORED PROTECTING GROUPS AND JUST SHOW THE KEY STEPS**

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**Guideline 3: Strategic Bonds**

**3a. C-X Bonds**

- The simplest disconnection to spot
- Very reliable

- recognition pattern—the necessary structural motif required to be able to apply a disconnection

- so which bonds do we consider first

- proceeds via π-allyl species
- interconversion of Pd between enantiotopic faces rapid compared to nucleophilic attack
- ligand differentiates both faces so Pd resides on one preferentially
- amine approaches from opposite face

**Swainsonine 87T3083**

- both rings made by C–N reductive hydrogenation
- hemi-acetal is protected aldehyde

- guideline 3b

**D-mannose**

- sugar provides all the stereocentres

**PMB**

91% ee

L = \[
\begin{align*}
\text{NH} & \text{N} \\
\text{HN} & \text{Pd(0) 1%} \\
\text{Ph} & \text{Ph} \\
\text{PPh}_2 & \text{PPh}_2 \\
\end{align*}
\]

- guideline 3b

- so which bonds do we consider first
**Swinholide A**

- C–X disconnections frequently offer a good starting point

- two halves are identical except protecting groups
- convergent synthesis
- guidelines 2 & 5f

1. ArCHO
2. TBAF
3. CH$_2$N$_2$

- use of common precursors greatly simplifies synthesis (cf. hexoses)

*What have we learnt?*

- Hopefully that we all need to keep reading / learning
- C–X bond disconnection is readily achieved
- C–X bond disconnection easily spotted
- Most helpful in cyclic structures
- Also reliable means of combining molecules

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3b. C=C Bonds

- Alkenes are wonderful
- They are readily functionalised in a myriad of ways
- There are a large number of reliable ways of generating them

\[
R^1\underbrace{\begin{array}{c}+\quad R^2 \quad or \quad R^3 \quad or \quad R^4 \quad + \quad PhSO_2R' \quad etc
\end{array}}_{\text{divide molecule in half}}
\]

\textbf{Julia Reaction}

- Diels-Alder and IMDA very useful (guideline 6)
- 2 C-C bonds, 2 rings, and 4 stereocentres predictably set up

\textit{indanomycin 84JOC3503}

\begin{itemize}
  \item 1. SEM-pyrrole / BuLi
  \item 2. PhS-succinimide, PBU₃
  \item 3. mCPBA
\end{itemize}

- In Ley’s original synthesis tetrahydropyran ring formed from sugar
- A later synthesis by Nicolaou (85JOC1440) formed THP via Wittig chemistry

\textit{Wadsworth-Emmons}

\textit{Guideline 3a}

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• bromide more successful than Julie reaction in their hands
• often add alkene to aid simplification (see below & guideline 4aii)

• two fragments made from same precursor
• elegant use of material

• Sometimes hard concept to grasp BUT simplification can be aided by the addition of functionality (see guideline 4aii)

**Fluvirucin B** 97JACS10302

1. \( \text{H}_2 \text{Pd} / \text{C} \)
2. \( \text{N}_2\text{H}_4 \)

• adding functionality allows the use of RCM (guideline 3b)

• good use of guideline 3a

• molecule divided into three fragments for convergency (guideline 2 & 5f)
• Many other methods for the formation of alkenes
• Asymmetric RCM 98JACS9720
• McMurry reaction 98CEJ567

![Chemical structure](image)

• Peterson olefination 00Ang377

![Chemical structure](image)

• Tebbe reagent
• Takeda thioacetals

**What have we learnt?**

• C=C a versatile bond to make
• Easy to introduce stereoselectively
• Often useful to add a double bond to allow further disconnection
• Large molecules can be readily formed with only a few basic reactions
3c. Adjacent to Functional Groups

- Bonds adjacent to functional groups are readily disconnected via a huge variety of transformations.
- Examples include carbonyl additions (& the aldol), sulfoxones, Stille couplings, dithianes etc.

**i) alcohols**

- Alcohol functionality invaluable as there are many ways to control stereochemistry.
- Reductions (BINAP, CBS), allylation (Brown, Roush), aldol (Evan’s, boron) etc.

**ii) aldol reaction**

- The aldol reaction has proved to be invaluable in the synthesis of natural products.
A-B spirocycle of altohyrtin A

96TL8581 & 97TL8241

Grignard addition

- alcohol oxidised

ketalisation

1. ppts
2. [O]
3. CH$_3$MgBr

aldol

all aldols proceeded with excellent selectivity

asymmetric boron enolate

C–C

(−)-IpcBCl

C–C

(−)-IpcBCl

C=C

Cp$_2$TiMe$_2$

ozonolysis

Brown allylation

Brown allylation

C–C

iii) sp$^2$ couplings

Examples include the Heck (93CR2037;94Ang2379), Stille (92Syn803), Suzuki (82ACR187) or sp-sp$^2$ couplings Sonogashi (75TL4467)