ADVANCED SYNTHESIS

Stereochemistry

Introduction

• One of the most important issues in modern organic synthesis
• Most natural compounds are enantiomerically pure
• Frequently different enantiomers have different biological properties

![Image of (S)-thalidomide]

• Only one stereocentre so two possible compounds

![Image of D-glucose]

• Glucose has four stereocentres so \(2^4 = 64\) possible diastereoisomers
• So need effective means of isolating the one compound we want

Resolution

• The separation of enantiomers
• Can be achieved by chiral chromatography
• Can be achieved by selective recrystallisation (although this requires luck)
• Can be achieved by derivatisation
• Convert enantiomers into diastereoisomers

![Image of two enantiomers]

• 2 enantiomers can not be separated by standard chromatography
• Equivalent by nmr and all physical data except optical rotation

• Diastereoisomers, physically different and seperable by chromatography

• Biggest disadvantage with such a route is the waste
• Maximum yield of 50 % as the wrong enantiomer is discarded
• So various methods have been developed for stereoselective synthesis
Stereoselective Organic Chemistry

- There are five broad strategies for the synthesis of optically pure compounds
- Over the next few lectures we will look at:

1. The Chiral Pool (chiral starting materials) (1/2 lecture)
2. Substrate Control (1/2 lecture)
3. Chiral Auxiliaries (1 lecture)
4. Chiral Reagents (1 lecture)
5. Chiral Catalysis (2 lectures)

The Chiral Pool
(Chiral Starting Materials)

- Use the stereochemistry available in readily available natural materials
- Most commonly used materials used are amino acids and carbohydrates
- Remember you can destroy stereocentres by oxidation, reduction and displacement
- Wasteful but sometimes useful

α-Amino Acids

- Synthesis of the pharmaceutically important benzodiazepines
- Incorporate stereocentre from alanine
- Amino acids used to prepare chiral auxiliaries and chiral ligands (the use of which should become apparent)
Lecture 1

**Carbohydrates**

- Carbohydrates are (frequently) cheap, readily available materials.
- Contain up to 5 stereocentres so offer plenty of opportunity.
- Ideally use all stereocentres.

**benzyl D-mannose**

- Acetal formation (2nd year).

**Due to the ready availability of carbohydrates and their low cost frequently destroy chirality to get desired compound.**
- Glyceraldehyde intermediate derived from D-mannitol (open chain form of mannose).
- Used in preparation of Tomolol, a potent $\beta$-adrenergic blocking agent.

**Swern oxidation**

1. TBS-Cl, base
2. acetone, $H^+$

**Swern & Wittig (2nd year)**

1. DMSO, $(COCl)_2$
2. NaBH$_4$
3. Ms-Cl, Et$_3$N
4. NaN$_3$

**Deprotection**

1. TBAF
2. DMSO, $(COCl)_2$ then Et$_3$N
3. Br$^-$Ph$_3$P$^+$CHCHO

**Acetal hydrolysis**

1. Pd / C, $H_2$
2. Pd / black, $H_2$, AcOH

**Swern & Wittig**

1. Pd / C, $H_2$

**Dehydration**

1. Pd / black, $H_2$, AcOH

**Only one of the 5 stereocentres remains yet a profitable synthesis.**

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Lecture 1

- Carbohydrate used in the synthesis of a fragment of indanomycin antibiotic
- Destroy 2 chiral centres
- But use one of the remaining centres to form **two** new ones
- **Transfer / induction of chirality**

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

- **Ireland-Claisen rearrangement**

\[
\begin{align*}
\text{Substrate Control} & \quad \text{do chemistry} \quad \text{New chirality} \\
\end{align*}
\]

- Use of chirality present within the substrate to control the introduction of new chirality
- This is a **diastereoselective reaction**
- If the starting material is enantiopure then the product will be enantiomerically pure
- Last year you would have briefly met:

**Felkin-Ahn Model**

- place largest substituent perpendicular to carbonyl
- nucleophile will attack along Bürgi-Dunitz angle passed smallest group
Lecture 1

- Stereochemistry of the substrate influences the face of the carbonyl the nucleophile adds to.
- If there is chelating heteroatom:

**Cram-Chelation Control**

- again attacks passed smallest group

- There are many other directing effects
- In Steve Caddick's course last year you would have seen conjugate (Michael) additions

**Epoxidation**

- Allylic alcohols undergo diastereoselective epoxidation
- If we use a free hydroxyl group then the peracid hydrogen bonds to the hydroxyl group
- Results in a pseudo-intramolecular reaction
- If alcohol is protected then epoxidation occurs from least hindered face

**What have we learnt?**

- It is very important to perform stereoselective synthesis
- It can be achieved in a number of ways
- Resolution is (normally) wasteful
- Utilising the chiral pool allows incorporation of stereochemistry
- Substrate control allows diastereoselective reactions

As you may have noticed there are some gaps in the notes. A fully annotated version will be placed on the Web at the end of course.

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