Stereoselective Synthesis

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Reference Texts:


“Stoichiometric Asymmetric Synthesis” by Mark Rizzacasa and Michael Perkins, Sheffield Academic Press 2000
Total Synthesis of the Macrolide Antibiotic Cytovaricin

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Abstract: A convergent asymmetric synthesis of the antineoplastic macrolide antibiotic cytovaricin has been achieved through the synthesis and coupling of the illustrated spiroketal and polyl glycoside subunits. All absolute stereochemical relationships within the target structure were ultimately controlled by the use of asymmetric aldol, alkylation, or epoxidation methodology. Union of the two subunits was accomplished by Julia–Lythgoe trans olefination, providing direct access to a suitable macrolactonization substrate. A high-yielding ring closure (92%) and subsequent three-step refucionalization of the macrocyclic product afforded cytovaricin. In supporting studies, the solution conformation and chemical reactivity of the natural product were also examined. Three-dimensional overlay of cytovaricin with rutamycin A indicates an unexpected homology between the two structures, in turn suggesting a potential mode of action for cytovaricin.
Scheme 25. a) Strategic bond disconnections and retrosynthetic analysis of cytoracin, b) key asymmetric alkylation and aldol reactions, and c) outline of the total synthesis (Evans et al., 1990).[137]
A Highly Stereoselective Anti Aldol. The C8–C9 syn aldol bond construction between aldehyde 52 and the boron enolate derived from carboximide 53 was anticipated to be unexceptional in stereochemical outcome since we had recorded numerous examples of such double stereodifferentiating reactions in prior work (Scheme XVI). In all such documented cases, reaction stereodifferentiation was completely controlled by the enolate chirality, irrespective of the chirality of the aldehyde. We were therefore surprised to discover that this reaction proceeded with complete stereocontrol to yield the anti aldol adduct 54 in 78% yield as a single diastereomer. In fact, it was only through conversion of this aldol adduct to 8-epi-cytovarinic that this errant stereocenter was ultimately discovered. That this aldol adduct was actually the unanticipated anti aldol product was subsequently determined by X-ray crystallographic analysis of triol 56, a derivative of a more advanced synthetic intermediate containing all of the stereocenters in the polyol glycoside subunit (Figure 3). Because of the history of reliability of these aldol reactions, we committed the cardinal error of not immediately confirming the stereochemical outcome of the reaction between 52 and 53.

(a) Ca, NH3, THF, -63 to -45 °C; (b) (COCl)2, DMSO, CH2Cl2, -78 °C; Et3N, -78 to -22 °C; (c) imide 53, n-Bu2BOTf, Et3N, toluene, -50 °C; aldehyde 52; H2O2; (d) AlMe3, MeONHMe–HCl, THF, 0 °C.
**Terminology**

- **Chiral Centre**: older term, that for carbon corresponds to the asymmetric carbon of van't Hoff (1874)

  ![Chiral Centre Diagram]

- **Diastereomers** often contain two or more centres with 4 different groups, but this is not necessarily the case. eg. the two diastereoisomers below are neither chiral nor contain “chiral” centres

  ![Diastereoisomers Diagram]
A Better term to use is

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  **Stereogenic centre**: (stereocentre) any centre where interchange of two ligands (groups atoms etc) leads to a stereoisomer
Introduction of Stereogenic Centres

• Introduction of new stereocentre into target molecule is normally achieved by one of two fundamentally distinct processes:
  – either through addition to one or other stereoheterotopic (enantiotopic or diastereotopic) faces of a double bond
Introduction of Stereogenic Centres

– less commonly by selective modification or replacement of stereoheterotopic (enantiotopic or diastereotopic) ligands
– another important group of processes is based on the substitution of groups or ligands in **meso** substrates
Terminology

- **Enantioselectivity**: one of two enantiomers is formed preferentially. There may be an enantioselective step or an overall enantioselective conversion over several steps. The degree of selectivity is indicated as enantiomeric excess (% ee)

  \[
  \text{Enantiomeric excess (\% ee)} = \frac{\# \text{ moles major enantiomer} - \# \text{ moles minor enantiomer}}{\# \text{ moles of both isomers}} \times 100
  \]

- **Diastereoselectivity**: one of two or more diastereomers is formed preferentially. The degree of diastereoselectivity is given as \% ds, the percentage of a certain diastereomer in a mixture of two or more diastereomers

- **Should not use the term de as often more than two isomers can be produced in a reaction**
• **Terminology**

  - **stereospecific**
    - used when the configuration of the product is related to that of the reactant and the reaction is mechanistically constrained to proceed in a sterochemically defined manner
    - also different isomer of starting material gives different product
      - eg.

\[ 	ext{trans - 2-butene} \xrightarrow{\text{Br}_2} \text{meso only} \]
• stereospecific
  • eg.
  \[ \text{cis - 2-butene} \]
  \[ \text{Br}_2 \] 
  \[ (\pm) \text{racemate} \]

• via
Terminology

• **stereoselective**
  
  – used to describe the stereochemical outcome of a reaction when it is possible for more than one isomer to be formed, but one is formed in excess

That the Boron and H are added from the same side is stereospecific!
Stereoselective Synthesis

– stereochemical outcome is determined by differences in free energy associated with diastereomeric transition states ($\Delta \Delta G^{\pm}$)

– eg. for SM $\Rightarrow$ Prod A or Prod B
Stereoselective Synthesis

• Three classes of diastereoselective reactions
  – stereochemically controlled synthesis of achiral diastereomeric compounds
  – introduction of new stereogenic centres into chiral substrates
  – coupling of two compounds at prostereogenic centres with formation of two new stereocenters
Diastereoselective Synthesis

• Synthesis of Achiral Diastereomers
  – for example reduction of t-Butyl cyclohexanone
  – presence or lack of plane of symmetry has no bearing (provided the other reactant is achiral)
Diastereoselective Synthesis

• Introduction of new stereogenic centres into chiral molecules
  – diverse class of diastereoselective reaction
  – configuration of new stereocenters are established in a relative relationship to preexisting stereocenters
  – racemic substrates react with achiral reagents to give the same relative relationship
Diastereoselective Synthesis

- Introduction of new chiral centres into chiral molecules (cont)

\[
\begin{align*}
\text{Racemate} & \quad \sim 90 : 10 \\
\end{align*}
\]
Diastereoselective Synthesis

- formation of two stereogenic centres
- eg the aldol and Michael reaction
Enantioselective Synthesis

- generally the substrates are achiral and stereoselectivity in the formation of new stereogenic centres will require reagents that are chiral
- potential for catalysed reactions!

\[
\begin{align*}
\text{Et}_2\text{Zn} & \quad \text{OH} \\
\text{N(CH}_3\text{)}_2 & \quad \text{HO} \\
\text{8 Mole\%} & \quad \text{HO} \\
\text{(95 \% ee)} & \quad \text{8 Mole\%}
\end{align*}
\]

- potential useful alternative is where a racemate is resolved into its individual enantiomers, which are then utilised in the synthesis, either by recycling or use of a complimentary sequence
- enantioselective synthesis depend on the availability of enantiomerically pure compounds from biological sources