Strategies for Stereocontrolled Synthesis

Chemistry 5.512
Synthetic Organic Chemistry II

Lecture 20
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Strategies for Stereocontrolled Synthesis

Case Studies
Synthesis of the L-Hexoses (Sharpless, Masamune)

S. Y. Ko. A. W. M. Lee, S. Masamune, L. A. Reed, K. B. Sharpless, and F. J. Walker
*Science* 1983, 220, 949
Strategies for Stereocontrolled Synthesis

Case Studies

Synthesis of the L-Hexoses (Sharpless, Masamune)

Total Synthesis of the L-Hexoses

Abstract. Enantiomerically pure polyhydroxylated natural products are synthesized by using a reiterative two-carbon extension cycle consisting of four steps. The generality and efficiency of this methodology are demonstrated in the total synthesis of all eight L-hexoses.

We describe here the systematic, stereoselective synthesis of all eight L-hexoses by a synthetic methodology developed in our laboratories for the preparation of polyhydroxylated natural products (1). Most monosaccharide syntheses have involved modification of sugars that occur naturally (2), and recorded total syntheses have usually been carried out in a racemic form and with poor stereoselection (3). The stereochemical challenge involved in a general synthesis of monosaccharides, though purely academic, has now been met, and a high degree of stereoselection is attainable (4-6).

Our strategy is based on the reiterative two-carbon extension cycle, which consists of four steps (Fig. 1): I, conversion of an aldehyde into its corresponding allylic alcohol; II, asymmetric epoxidation (AE) with titanium tetraisopropoxide, r-butyldihydroperoxide, and diethyl (+) or (-) tartrate; III, treatment of the epoxy alcohol with benzenethiolate anion in a basic medium; and IV, oxidation and Pummerer reaction of the sulfide followed by the net hydrolysis of the resulting gem-aceetoxy sulfide with or without inversion of the C(2) center (7). Because of the presence of four hydroxymethylene centers in the hexoses, the synthesis of these compounds requires a double application of the basic cycle.

The synthesis described here begins with a single fundamental building block, 4-benzyloxy-2-butyrolactone (1), a compound which is readily prepared from (Z)-2-buten-1,4-diol (8). Step I of the extension cycle is therefore eliminated in this initial case. The selection of the benzyldiyl protecting group rather than a more common group such as benzyl has proved to be critical (see below), and the benzhydril serves its purpose through the entire synthesis, which is shown in Fig. 2 with the yield and selectivity for each step. Conversion of 1 into used with R = benzyl, the AE reaction was accompanied by a subsequent titanium-catalyzed epoxide opening. This process involved participation of the oxygen atom of the C(6) benzyloxy group, which led to formation of the undesired corresponding tetrahydrofuran. Use of 6b, however, prevents this etheral oxygen participation and AE proceeds smoothly. The selectivity of this reaction appears perfect, as no trace of the diastereomer 9 is detected by the usual techniques of analysis. (8 - 16).

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Science 1983, 220, 949
“Looking Glass Sugars”

Hannah Sharpless
Chemistry in Britain
1986, 22, 38
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Case Studies

Synthesis of the L-Hexoses (Sharpless, Masamune)

Satoru Masamune
1928 - 2003
Strategies for Stereocontrolled Synthesis

Case Studies

Synthesis of the L-Hexoses (Sharpless, Masamune)

K. Barry Sharpless
1941-
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Case Studies

Synthesis of the L-Hexoses (Sharpless, Masamune)

TOTAL SYNTHESIS OF THE L-HEXOSES
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(Received in Canada 5 April 1989)

Abstract - Enantiomerically pure polyhydroxylated natural products are synthesized by using a reiterative two-carbon extension cycle consisting of four key transformations. The generality and efficiency of this methodology are demonstrated in the total synthesis of all eight L-hexoses.

GENERAL APPROACH AND KEY REACTIONS

Organic chemistry of this decade has witnessed the advent of a conceptually new synthetic strategy. Thanks to the discovery of powerful asymmetric reagents and catalysts which enhance or override the inherent diastereofacial preferences of substrate molecules, it is now possible to construct at will any stereochemical combinations, including those that otherwise appear impossible to make. This approach has been called "reagent-control" strategy,2 contrasted to the traditional "substrate-control" strategy where stereochemistries of newly formed chiral centers are dependent upon the inherent diastereofacial preference of the substrate molecule. Such powerful reagents and catalysts have been prepared for major organic reaction classes such as the aldol reaction,3,4 epoxidation of allylic alcohols,5 the hydroboration reaction,6 and ketone reduction.7

Monosaccharides such as the hexoses are excellent targets to demonstrate the power of the "reagent-control" strategy, since all the possible stereoisomers are known. Construction of the hexose stereoisomers by the "substrate-control" strategy would require a totally different synthetic sequence for each isomer, and the stereoselectivities are normally expected to be low.8

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Tetrahedron 1990, 46, 245
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Case Studies

Synthesis of the L-Hexoses (Sharpless, Masamune)

Liberation from the tyranny of substrate control?

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Tetrahedron 1990, 46, 245
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Case Studies
Synthesis of the L-Hexoses (Sharpless, Masamune)

1. Stereocontrolled Olefination
   Substrate Control

2. Stereocontrolled Epoxidation
   Reagent Control

3. Stereocontrolled Epoxide Opening
   Substrate Control
   Regiocontrolled opening with inversion at C-2
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Case Studies
Synthesis of the L-Hexoses (Sharpless, Masamune)

1. Stereocontrolled Olefination
   - Substrate Control
   - RCHO

2. Stereocontrolled Epoxidation
   - E Alkene
   - Z Alkene
   - Substrate Control

3. Stereocontrolled Epoxide Opening
   - Regiocontrolled opening with inversion at C-2
   - Substrate Control

(-)-DET  (+)-DET
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Case Studies
Synthesis of the L-Hexoses (Sharpless, Masamune)

1. Stereocontrolled Olefination
   Substrate Control

2. Stereocontrolled Epoxidation
   Reagent Control

3. Stereocontrolled Epoxide Opening
   Substrate Control
   Regiocontrolled opening with inversion

4. Regioselective Oxidation

RCHO

\[
\begin{align*}
\text{RCHO} & \rightarrow \text{Substrate} \\
\text{or} & \\
\text{or} & \\
\text{or} & \\
\text{or} & \\
\text{or} & \\
\end{align*}
\]
Strategies for Stereocontrolled Synthesis

Case Studies

Synthesis of the L-Hexoses (Sharpless, Masamune)

Methods for both $E$ and $Z$ olefination are available e.g. via $\text{Ph}_3\text{P}=\text{CHCHO}$ for $E$ alkene
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Case Studies
Synthesis of the L-Hexoses (Sharpless, Masamune)

L-Glucose

Epoxidation highly selective for E allylic alcohols

Stereocontrolled Olefination
Substrate Control

RCHO

Stereocontrolled Epoxidation
Reagent Control

R
OH
or

R

OH

R

OH

R

OH

R

OH

★
Strategies for Stereocontrolled Synthesis

Case Studies
Synthesis of the L-Hexoses (Sharpless, Masamune)

Epoxidation works poorly with Z allylic alcohols with minimal loss of selectivity. The monobenzyl ether of (Z)-2-buten-1,4-diol (entry 9) was not successfully epoxidized using the procedure described here, since after 43 h, the reaction was still far from complete.
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Case Studies

Synthesis of the L-Hexoses (Sharpless, Masamune)

\[
\begin{align*}
RCHO & \rightarrow \text{Stereoc controlled Olefination} \\
& \rightarrow \text{Substrate Control}
\end{align*}
\]

\[
\begin{align*}
RCH(OH) & \text{or} \\
& \text{Stereoc controlled Epoxidation} \\
RCH(OH) & \text{or} \\
\end{align*}
\]

\[
\begin{align*}
(\text{--})-\text{DET} & \text{Alkene} \\
(\text{++})-\text{DET} & \text{Not available}
\end{align*}
\]

\[
\begin{align*}
RCH(OH) & \text{or} \\
& \text{Reagent Control} \\
\end{align*}
\]

\[
\begin{align*}
RCH(OH) & \text{or} \\
& \text{Stereoc controlled Epoxide Opening} \\
\end{align*}
\]

\[
\begin{align*}
RCH(OH) & \text{or} \\
& \text{Substrate Control} \\
& \text{Regiocontrolled opening with inversion at C-2}
\end{align*}
\]
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Case Studies

Synthesis of the L-Hexoses (Sharpless, Masamune)

(-)-DET
(+)-DET

E Alkene
Not available

Base
Strategies for Stereocontrolled Synthesis

Case Studies

Synthesis of the L-Hexoses (Sharpless, Masamune)

Epoxide opening with hydroxide not always selective and would require awkward protection-deprotection steps
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Case Studies

Synthesis of the L-Hexoses (Sharpless, Masamune)

L-Glucose

Solution: use Payne Rearrangement of thiolate
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Case Studies
-
Synthesis of the L-Hexoses (Sharpless, Masamune)

- Stereocontrolled Epoxide Opening
- Substrate Control
- Regioselective Oxidation

- Conversion of Payne product to aldehyde
- 1) Protect
- 2) m-CPBA

- Pummerer Rearrangement
- NaOAc, Ac₂O, Δ

- Hydrolyze (Base or hydride)
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Case Studies

Synthesis of the L-Hexoses (Sharpless, Masamune)

Each cycle requires 8 steps

1. Stereocontrolled Olefination

2. Stereocontrolled Epoxidation

3. Stereocontrolled Epoxide Opening

4. Regioselective Oxidation

Regiocontrolled opening with inversion
Strategies for Stereocontrolled Synthesis

Case Studies

Synthesis of the L-Hexoses (Sharpless, Masamunue)

L-Glucose

\[
\text{HO} \quad \text{OH} \quad \text{OH} \\
\text{OH} \quad \text{OH} \quad \text{CHO}
\]

\[
\text{HO} \quad \text{OH} \quad \text{CH}_2\text{Cl}_2 \\
\text{Ph}_{\text{2}} \quad \text{CHO} \quad \text{MeOH}
\]

\[
\text{Ph}_{\text{2}} \quad \text{CHO} \quad \text{CH}_2\text{Cl}_2 \\
\text{Ph} \quad \text{OH} \quad \text{NaBH}_4
\]

\[
\text{Ph} \quad \text{OH} \quad \text{CH}_2\text{Cl}_2 \\
\text{Ph} \quad \text{OH} \quad \text{TIBuOOH}
\]

\[
\text{Ph} \quad \text{OH} \quad \text{TIBuOOH} \\
\text{Ph} \quad \text{OH} \quad \text{TIBuOOH}
\]

\[
\text{Ph} \quad \text{OH} \quad \text{TIBuOOH} \\
\text{Ph} \quad \text{OH} \quad \text{TIBuOOH}
\]

93% overall
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Case Studies

Synthesis of the L-Hexoses (Sharpless, Masamune)

\[
\text{L-Glucose}
\]

1. 2.15 eq DIBAL
   \[\text{CHOOPh} \text{Ph} \text{OPh} \text{Ph} \text{SPh} \text{OAc} \rightarrow \text{Ph} \text{O} \text{O} \text{SPh} \text{OAc} \rightarrow 91\% \]
   \[\text{2.5 eq } \text{K}_2\text{CO}_3 \text{ MeOH rt } 16 \text{ h} \rightarrow 100\% \]

2. 1.2 eq \( \text{Ph}_3\text{P}=\text{CHCHO} \)
   \[\text{PhH, rt } 16 \text{ h} \rightarrow 88\% \]

3. \( \text{NaBH}_4 \)
   \[\text{MeOH } -40 ^\circ \text{C } 3 \text{ h} \rightarrow 91\% \]

4. \( \text{t-BuOOH} \)
   \[\text{Ti(Oi-Pr)}_4, (\text{-})\text{-DIT} \text{CH}_2\text{Cl}_2, -20 ^\circ \text{C } 16 \text{ h} \rightarrow 84\% >95\% \text{ ee} \]

5. PhSH, NaOH
   \[\text{H}_2\text{O}-\text{t-BuOH} \rightarrow 63\% \]

[70:30 regio in crude]
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Case Studies
Synthesis of the L-Hexoses (Sharpless, Masamunne)

19 steps in each route
Strategies for Stereocontrolled Synthesis

Case Studies

Synthesis of the L-Hexoses (Sharpless, Masamune)

\[(\text{Intermediate A}) \rightarrow \text{t-BuOOH, Ti(Oi-Pr)₄, (+)-DIT} \rightarrow 76\% >95\% \text{ ee} \rightarrow \text{PhSH, NaOH, H₂O-t-BuOH} \rightarrow [94:6 \text{ regio in crude}]\]

L-Glucose
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Case Studies

Synthesis of the L-Hexoses (Sharpless, Masamune)

L-Glucose

L-Allose

L-Altrose

19 steps in each route