Concise Total Synthesis of Glucosepane

Advanced Glycation End-Products (AGEs)

AGEs are formed by reactions between sugars and proteins.

AGEs often give rise to cross-links in long-lived proteins (collagen, crystallins).

AGEs have been implicated in diabetes and aging

Glucosepane Nonenzymatic Biosynthesis

\[
\begin{align*}
\text{Glucose} & \xrightarrow{\text{Lys}} \text{Amadori Product} \xrightarrow{\text{Carbonyl Mobility}} \text{dideoxyosone} \\
\text{dideoxyosone} & \xrightarrow{\text{Arg}^+\text{N}==\text{NH}_2} \text{glucosepane}
\end{align*}
\]

Glucosapene heterogeneity

\[
\begin{align*}
\begin{array}{c}
\text{Glucosepane} \\
\text{Heterogeneity}
\end{array}
\end{align*}
\]

Targeting the Correct Tautomer for Total Synthesis

Previous NMR data was consistent with the nonaromatic \textit{4H-imidazole}

\begin{align*}
\text{H-Imidazole} & \xrightarrow{\Delta G} \text{4H-Imidazole} \\
\end{align*}

Computational modeling showed the EDGs at the 2- and 5- positions favored the nonaromatic tautomer.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Y</th>
<th>$\Delta G$ (kcal/mol)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>26.7</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>NHMe</td>
<td>10.5</td>
</tr>
<tr>
<td>3</td>
<td>NMe$_2$</td>
<td>H</td>
<td>-1.5</td>
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<tr>
<td>4</td>
<td>NMe$_2$</td>
<td>NHMe</td>
<td>-14.8</td>
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</tbody>
</table>

*All calculations were performed using the Gaussian 09 program suite using the CBS-QB3 method. All calculations implemented a continuum model to account for the effects of water solvent.

Model Compound Supports 4H-Imidazole Tautomer
Glucosepane Retrosynthesis

Synthesis of Chiral Epoxide

1. NaH, CS₂, Mel, THF, 99%
2. Bu₃SH, AIBN, Toluene, 90 °C, 76%

90% aq. AcOH, 60 °C, 45 min. 93%
TsCl, pyr, O °C, 8 h 84%
NaOH, MeOH, O °C to RT 83%
From Chiral Epoxide to Amadori Product

Azepane Formation

Analysis of crude reaction always showed 15-20% of hemiaminal

Amadori Rearrangement

Amadori Product
60% yield
Attempted Oxidation / Arginine Condensation

Aldehyde Formation

Aldehyde Not Suitable for Arginine Condensation

Difference in preferred conformations?
New Approach to Retrosynthesis

In the Forward Direction

1. H₂N₆NH₂, 1.1 eq.
2. MeOH, RT, 3 h, 78%
3. H₂N₂NH₂, 1 eq.
4. CHCl₃, 95 °C, 24 h, aq. quench
5. TMS-Cl (3 eq.)

35% overall
4:1 mixture of epimers
A More Concise Route to Glucosepane

Overall: 8 synthetic steps, 12% overall yield
Glucosepane Conformational Exchange

\[ k = \frac{1}{t_m} \ln \frac{r+1}{r-1} \]

\[ r = \left( \frac{4X_a X_b (I_{aa} + I_{bb})}{I_{ab} + I_{ba}} \right) - (X_a - X_b)^2 \]

\[ k = 2.89 \text{ s}^{-1} \]

**Figure S1:** 2D NOESY with \( t_m = 1000 \text{ ms} \)
Conclusion and Significance

• Site-specific incorporation of glucosepane into synthetic oligopeptides
• Preparation of affinity reagents to identify molecular targets of glucosepane
• Development of immunogens for raising antibodies against glucosepane
• Identification of novel therapeutic strategies for breaking glucosepane cross-links.
Mechanism of Carbonyl Mobility

Carbohydrate Research 2004, 339, 1609-1618
### ΔG Calculations Accounting for Different Protonation States

![Diagram showing imidazole and iso-imidazole structures with ΔG calculations.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>ΔG (kcal/mol)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ΔG (kcal/mol)&lt;sup&gt;b&lt;/sup&gt;</th>
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All calculations were performed using the Gaussian 09 program suite. <sup>a</sup> Calculations employed the CBS-QB3 method. <sup>b</sup> Geometry optimizations were performed using the 6-31+G(d) basis set, and single-point energies determined at the 6-311++G(2df,2p) levels. <sup>c</sup> l.p. = lone pair. All calculations implemented a continuum model to account for the effects of water solvent.