STEREOSELECTIVE SYNTHESIS OF AMINO ACID DERIVATIVES USING CARBOHYDRATES AS TEMPLATES

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Introduction

Carbohydrates carry numerous functional and chiral informations on one molecular unit. Inspired by mechanistic considerations of the easy base-catalyzed β-elimination of the carbohydrate part from O-glycosyl serine and threonine derivatives, a difficult problem in the synthesis of glycopeptides,¹ we have developed the concept of utilizing the functionality and chirality of carbohydrates together with their marked complexing abilities towards Lewis acids for the specified steering of stereoselective reactions.² As a part of this concept, the glycosylamines have been applied in the asymmetric synthesis of amino acid derivatives.

Results

Glycosylamines contain the easily cleavable semi-aminal-type N-glycosidic bond. O-Protected glycosylamines, therefore, can advantageously be used as a form of "asymmetric ammonia", for instance, in Strecker syntheses and in Ugi reactions to give amino acid amides as well as in modifications of the Mannich reaction.

Strecker Synthesis

The O-pivaloyl protected galactopyranosylamine 1 reacts with aldehydes to furnish the corresponding Schiff bases 2. Upon treatment of these N-galactosyl imines 2 with trimethylsilyl cyanide in the presence of zinc chloride in isopropanol or tin tetrachloride in tetrahydrofuran at -78°C to 0°C, the N-galactosyl α-amino nitriles are formed almost quantitatively and with a preponderance of the D-amino nitrile diastereomer 3 in a ratio of 7-
15:1. It is a particular advantage of this synthesis, that pure D-amino nitrile derivatives are obtained by simple recrystallization from n-heptane in yields of 70-90\%\textsuperscript{3,4}.

\[ \text{R} \quad \text{method} \quad \text{yield (\%)} \quad \text{ratio of diastereomers} \quad \text{pure (R)} \]

\begin{align*}
\text{Cl} & \quad \text{A} \quad 95 \quad 7 : 1 \quad 78\% \\
\text{NO}_2 & \quad \text{A} \quad 90 \quad >50 : 1 \quad 91\% \\
\text{Cl} & \quad \text{B} \quad 95 \quad 11 : 1 \quad 84\% \\
\text{H}_3C & \quad \text{B} \quad 95 \quad 12 : 1 \quad 87\% \\
\text{(CH}_3\text{)}_3\text{C} & \quad \text{B} \quad 93 \quad 13 : 1 \quad 86\% \\
\end{align*}

The Strecker reaction can alternatively be carried out in an one-pot procedure starting from the galactosylamine 1, an aldehyde and sodium cyanide/acetic acid in isopropanol.\textsuperscript{4} However, this modified process requires prolonged reaction times and shows a reduced diastereoselectivity.

A further interesting feature of the Strecker synthesis using the N-galactosylamines, e.g. 1, or their imines 2, respectively, consists in the possibility to reverse the sense of asymmetric induction by simply changing the solvent. If the reaction of the galactosyl imines 2 with trimethylsilyl cyanide in the presence of zinc chloride is carried out in chloroform, then the N-galactosyl L-amino nitrile diastereomers L-3 are formed preferably in a ratio of 3:9:1.\textsuperscript{5}

The N-galactosyl amino nitriles 3 can be transformed to the corresponding amino acids by acidolytic cleavage of the N-glycosidic bond and subsequent hydrolysis of the nitrile group using hydrogen bromide/acetic acid or hydrogen chloride/formic acid.\textsuperscript{3-5}
Stereoselective Syntheses of Amino Acids via Ugi Reactions

The N-galactosylamines 1 revealed to be an efficient stereoselecting tool in the Ugi four-component-condensation to give N-galactosyl amino acid amide derivatives 4. The process is conveniently carried out in an one-pot procedure and delivers almost quantitative yields within 6 to 8 hours. The diastereoselectivity of this reaction at -78°C to -25°C is even higher than that of the Strecker synthesis. If the reaction is performed in tetrahydrofuran in the presence of zinc chloride, the (D)-amino acid amides 4 are formed in high excess (15-30:1). Recrystallization or flash-chromatography delivers pure diastereomers of D-amino acid derivatives in yields of 75-95%. The enantiomerically pure D-amino acids are smoothly released from the carbohydrate matrix by simple acidolysis of the N-galactosyl amino acid amides 4, carried out in methanol and, subsequently, in conc. hydrochloric acid.
The concept outlined above can be extended to the synthesis of enantiomerically pure L-amino acid derivatives by using the D-arabinopyranosylamine as a chiral matrix which is formally enantiomeric to the galactosylamine.

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>T (°C)</th>
<th>(D) : (L)</th>
<th>pure (D), yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CH₃)₂C−</td>
<td>(CH₃)₂C−</td>
<td>−78</td>
<td>&gt;100 : 1</td>
<td>80</td>
</tr>
<tr>
<td>C₆H₅−CH₂−</td>
<td>(CH₃)₂C−</td>
<td>−78</td>
<td>19 : 1</td>
<td>80</td>
</tr>
<tr>
<td>Cl−</td>
<td>(CH₃)₂C−</td>
<td>−25</td>
<td>30 : 1</td>
<td>92</td>
</tr>
<tr>
<td>S−</td>
<td>(CH₃)₂C−</td>
<td>−25</td>
<td>22 : 1</td>
<td>93</td>
</tr>
<tr>
<td>O₂N−</td>
<td>(CH₃)₂C−</td>
<td>0</td>
<td>16 : 1</td>
<td>91</td>
</tr>
</tbody>
</table>

The application of the O-pivaloyl protected D-arabinopyranosylamine 5 as the chiral template in the Ugi reactions results in the stereoselective formation of the N-arabinosyl-L-amino acid amide derivatives 6. The ratios of diastereomers amount to 25-30:1. Pure L-amino acid diastereomers 6 are isolated in high yield (85-95%) after recrystallization or flash-chromatography.\(^8\)
The diastereofacial differentiation on aldmines exhibited by the glycan portion is not only useful for the nucleophilic attack of C1 synthons, e.g. the cyanide in the Strecker synthesis and the isocyanide in the Ugi reaction, but can also be adopted to reactions with C2 fragments, e.g. in Mannich reactions. For reactions of the N-galactosyl imines 2 with 1-methoxy-3-trimethylsilyloxy-buta-1,3-diene\textsuperscript{7} in the presence of zinc chloride in THF, it was shown, that intermediary Mannich bases 8, and from these dihydropiperidinone derivatives 9, are formed in high yield and with an excellent diastereoselectivity.\textsuperscript{10}

The absolute configuration of the major diastereomer of the 2-n-propyl derivative of 9 was assigned by means of its transformation to the natural alkaloid (S)-coniin.\textsuperscript{10}
As the efficient stereoselection in these processes occurs in the initial Mannich reactions, the same prevailing stereofacial differentiation can be adopted for the asymmetric synthesis of \( \beta \)-amino acid derivatives. To this end, silyl ketene acetal, e.g., 10, are reacted with the N-galactosyl imines 2. As a rule, the reactions proceed in the presence of zinc chloride in THF at \(-78^\circ\text{C}\) to \(-40^\circ\text{C}\) and deliver the chiral \( \beta \)-amino acid derivatives 11 in high yields.\[11\]

\[
\begin{align*}
\text{PivO} & \quad \text{Piv} \\
\text{PivO} & \quad \text{Piv} \\
\text{PivO} & \quad \text{Piv} \\
\text{NsC} & \quad \text{R} \\
\text{H} & \quad \text{H} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Phenyl} & \\
\text{4-Cl-Ph} & \\
\text{3-Cl-Ph} & \\
\text{4-F-Ph} & \\
\text{4-Me-Ph} & \\
\text{2-Naphthyl} &
\end{align*}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>Ratio of Diastereomers (S) : (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenyl</td>
<td>89</td>
<td>147 : 1</td>
</tr>
<tr>
<td>(+30°C)</td>
<td>95</td>
<td>105 : 1</td>
</tr>
<tr>
<td>4-Cl-Ph</td>
<td>92</td>
<td>68 : 1</td>
</tr>
<tr>
<td>3-Cl-Ph</td>
<td>89</td>
<td>210 : 1</td>
</tr>
<tr>
<td>4-F-Ph</td>
<td>88</td>
<td>146 : 1</td>
</tr>
<tr>
<td>4-Me-Ph</td>
<td>90</td>
<td>75 : 1</td>
</tr>
<tr>
<td>2-Naphthyl (+20°C)</td>
<td>89</td>
<td>12 : 1</td>
</tr>
</tbody>
</table>

The ratios of diastereomers 11 formed in this Mannich-type reactions of the imines 2 with the silyl ketene acetal as the cabanion or enol equivalents indicate an extraordinarily efficient stereodifferentation exhibited by the carbohydrate template, which is, furthermore, amplified by the complexation of the Lewis acid. Even at room temperature, the reactions proceed with high diastereoselectivity.
Since the β-amino acid esters can easily be released from the N-galactosyl β-amino acid esters and subsequently hydrolyzed, the described synthesis offers an effective and highly stereoselective access to enantiomerically pure β-amino acids. During work up of the hydrolyzed reaction mixture, the carbohydrate template 2,3,4,6-tetra-O-pivaloyl-D-galactopyranose can be re-isolated in yields of >95% by simple extraction procedures.

In conclusion, the carbohydrates can be used advantageously as the stereodifferentiating auxiliaries in asymmetric syntheses of α- and β-amino acids with both, proteinogenic and non-proteinogenic structure. The compounds, thus accessible, are interesting components for the construction of peptide analogs, peptidomimetics or other interesting products, e. g. β-lactam antibiotics.

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References


