Asymmetric Synthesis of \(\alpha,\alpha\)-Disubstituted \(\alpha\)-Amino Acids via an Intramolecular Strecker Synthesis

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Abstract: A series of optically active \(\alpha,\alpha\)-disubstituted \(\alpha\)-amino acids have been synthesized starting with an achiral or a racemic 2-hydroxy ketone. The key transformation to the present synthesis is an intramolecular version of Strecker synthesis. An \(\alpha\)-keto ester having a chiral amino acid as the ester group afforded cyclic amino nitrile, in a highly stereoselective manner, in which the amino group and the chirality were diastereoselectively transplanted into the internal ketone group via an imine-enamine equilibrium of the cyclic ketimine intermediate. Oxidation of the amino group followed by removal of the resulting imino group and hydrolysis of the nitrile group afforded \(\alpha\)-hydroxymethyl \(\alpha\)-amino acid. The use of L-amino acid as the chirality transferring group gave R enantiomer, and its S enantiomer was obtained when D-amino acid was employed. The syntheses of optically active \(\alpha\)-substituted serines, \(\alpha\)-methylthreonines, and 1-amino-2-hydroxycycloalkanecarboxylic acids are described.

1. Introduction

There is an ever-growing interest in the synthesis, pharmacology, and conformational properties of non-proteinogenic amino acids. In particular, \(\alpha,\alpha\)-disubstituted \(\alpha\)-amino acids of type A or B have been the subject of numerous investigations over the decades (eq 1). They are often found in nature, either in free form or as constituents of biologically active compounds, and are known as enzyme inhibitors and as conformational modifiers in physiologically important peptides (ref. 1). For an example, it is well accepted that \(\alpha,\alpha\)-disubstituted \(\alpha\)-amino acids with a methyl group at the \(\alpha\)-position tend to induce \(\alpha\)-helical conformation when incorporated into peptides (ref. 2). Therefore, numerous attempts for the synthesis of the amino acids of type A and B have been performed (ref. 3), which involved an optical resolution of the racemic form (ref. 4). Recent efforts to these amino acids are...
mainly asymmetric transformations based on the alkylation of enolates from bislactims, oxazinones, imidazolidinones, and other procedures (refs. 3, 5). Among these amino acids, we focused on their β-hydroxy congeners which can be viewed as the analogous amino acids of serine or threonine and would have marked effects on peptide conformation as well as biological activity (ref. 6). Furthermore, a number of natural products possess β-hydroxy α,α-disubstituted α-aminocarboxylic acid as their partial structures (ref. 7). These facts prompted us to study a new method for the synthesis of this class of amino acids.

\[
\begin{array}{c}
\text{X} \quad \text{Y} \\
\text{H}_2\text{N} \quad \text{CO}_2\text{H} \\
\text{R} \\
\text{X} \quad \text{Y} \\
\text{H}_2\text{N} \quad \text{CO}_2\text{H} \\
\text{R} \\
\text{X} \quad \text{Y} \\
\text{H}_2\text{N} \quad \text{CO}_2\text{H} \\
\text{R} \\
\end{array}
\]
\[= \text{eq 2}\]

It has been proposed that the biosynthetic pathway of α,α-disubstituted α-amino acid involves an asymmetric transformation of an amino group of α-amino acid to a ketone (ref. 8). As a result, the chirality of the starting amino acid was transferred to the prochiral ketone group and that of the amino acid was oxidatively removed as the corresponding pyruvate derivative (eq 2). Under the consideration of the hypothetical biosynthetic route in eq 2, our synthetic plan to these amino acids was an intramolecular version of an asymmetric Strecker synthesis. The initially formed internal Schiff base (ketimine intermediate) from an amino ester would undergo stereoselective amino nitrile formation to give 1,4-oxazine, and subsequent hydrolysis of the nitrile group and oxidative removal of the chirality transferring group would yield optically active β-hydroxy α-substituted α-amino acid (eq 3). We wish to describe here an efficient route for the synthesis of each optically active enantiomer and diastereomer of α-methylserine, α-benzylserine, α-carboxymethylserine, α-methylthreonine, 1-amino-2-hydroxy-cyclopentanecarboxylic acid, and 1-amino-2-hydroxycyclohexanecarboxylic acid (ref. 9) (Figure 1).

\[
\begin{array}{c}
\text{X} = \text{alkyl or aryl}, \\
\text{Y} = \text{H, alkyl or aryl} \\
\end{array}
\]
\[= \text{eq 3}\]
2. Synthesis of $\alpha$-Methylserine

Condensation of acetal with $N$-tert-butoxycarbonyl (Boc)-L-valine with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSCD) HCl salt gave N-Boc-valine acetal ester in 96% yield. After removal of the Boc group with trifluoroacetic acid (TFA), treatment of the resulting TFA salt with 2 equiv of NaCN in 2-propanol for 2 h gave in 72% isolated yield a mixture of cyclic amino nitriles (Scheme 1). The mixture was composed of $5S$ isomer as the major product and a small amount of its $5R$ isomer ($5S : 5R = 25 : 1$) which was removed by recrystallization or column chromatography on silica gel. The structure of the major product possessing a $5S$ configuration was determined by converting it to the known ($R$)-$\alpha$-methylserine (refs. 5, 9). Next, the effect of the amino acid side chain on the $5S/5R$ selectivity was examined by the use of other amino acids with a sterically less bulky side chain. Reaction of L-alanine acetal ester gave a mixture of $5S$ and $5R$ cyclic amino nitriles in 3 : 1 ratio, and L-phenylalanine acetal ester afforded the mixture in 10 : 1 ratio, respectively. Thus, valine was found to be an excellent chirality transferring group in the stereoselective formation of the cyclic amino nitrile. It is noted that a prolonged reaction time (entry 4, Table 1) significantly affected the $5S/5R$ ratio from 3 : 1 to 10 : 1. These results suggested that the reaction involved an equilibrium between $5S$ and $5R$ adducts.

Table 1. Effect of the amino acid side chain on the stereoselective formation of the cyclic amino nitriles.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>(3S,5S) : (3S,5R)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>iPr (Val)</td>
<td>25 : 1</td>
<td>2</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>Benzyl (Phe)</td>
<td>11 : 1</td>
<td>2</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>Me (Ala)</td>
<td>3 : 1</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>Me (Ala)</td>
<td>10 : 1</td>
<td>10</td>
<td>60</td>
</tr>
</tbody>
</table>

In order to understand the present reaction mechanisms and to estimate the extent of racemization at C3 under the reaction conditions, we examined the following experiments using 2-propanol D and $^{13}$C NaCN: (i) the use of 2-propanol D as the solvent afforded the Strecker product where the deuterium atom was partially incorporated into the methyl group (15%) and the C6 methylene group (25%), and (ii) treatment of the $5S$ adduct using $^{13}$C NaCN in 2-propanol in the presence of TFA (1 equiv) gave,
after 2 h, a mixture of $^{12}$CN and $^{13}$CN products (9 : 1). After 8 h, the ratio changed to 55 : 45. Without TFA, the exchange reaction with $^{13}$CN did not occur, suggesting that a trace amount of acid accelerates the above equilibrium. Based on these experimental results, the reaction is clearly understood to involve a ketimine intermediate Ia, coexisting at equilibrium via an enamine-type intermediate Ib, and that both the 5S and 5R products are equilibrated via the ketimine intermediate. The highly diastereoselective formation of 5S-isomer would be due to an attack of the cyanide ion to the sterically less hindered si-face of the ketimine intermediate Ia where a boatlike conformation with the isopropyl group oriented to a pseudoaxial position seemed to be plausible (Scheme 2). Therefore, the 5S isomer is a kinetically as well as thermodynamically more favored product than the 5R isomer. The fact that no deuterium atom was incorporated into the C3 methine group clearly indicates that no racemization occurred under the reaction conditions to give an enantiomerically pure adduct.

Scheme 2

Removal of the valine moiety from the 5S isomer and its conversion into (R)-$\alpha$-methylserine were carried out by the following sequence of reactions: (i) oxidation of the amino nitrile with tert-butyl hypochlorite and triethylamine, and (ii) hydrolytic removal of the resulting imino lactone moiety and hydrolysis of the nitrile group with concentrated HCl. These treatments gave in 84% yield the desired (R)-$\alpha$-methylserine (Scheme 3). The use of D-valine afforded (S)-$\alpha$-methylserine. Note that the configuration of the new amino acid is opposite to that of valine. Thus, both enantiomers of $\alpha$-methylserine were prepared in 5 steps, and their overall yields were ~55% (refs. 9a, 9b).

Scheme 3
3. Synthesis of α-Benzylserine and α-Carboxymethylserine

The present method is characterized by the use of optically active amino acid as an amino and a chirality transferring group to the ketone (eq 3). It was considered that the use of α-hydroxymethyl ketones with various substituents instead of a methyl group would undergo stereoselective amino nitrile formation under the Strecker synthesis to give the corresponding α-substituted serines. As an extension of its application, we examined the synthesis of both enantiomers of α-benzylserine and α-carboxymethylserine which have not yet been synthesized in an optically active form (ref. 10).

The synthesis was started with the known phenyl acetol (ref. 11), which was newly prepared from cinnamyl alcohol in two steps (Scheme 4). Esterification of the starting hydroxy ketone with Boc-L-valine and subsequent removal of the Boc group with TFA afforded an amino ester. Treatment under the standard Strecker conditions gave in 77% yield a mixture of amino nitriles which consisted of the 5S isomer as the major product (5S : 5R = 16 : 1). The reaction process involving an imine-enamine equilibrium and the extent of racemization of the product were clearly elucidated by an incorporation experiment of a deuterium atom using 2-propanol D. Significant amounts of the deuterium atom were incorporated into both the C6 methylene group (38% at 61-H and 50% at 6α-H) and the benzyl methylene group (20%), respectively. It was also ascertained that no racemization took place because no deuterium atom was incorporated into the C3 position. Conversion of the amino nitrile into the target amino acid was performed in the same manner as that of α-methylserine. Thus, α-benzylserine was obtained in 78% yield from the amino nitrile.

Scheme 4

Since the phenyl group of α-benzylserine is a masked form of a carboxyl group, we next examined its conversion to (R)-α-carboxymethylserine, in other words, α-hydroxymethyl aspartate which has attracted interest in view of its neuroexcitatory actions at excitatory amino acid receptors (ref. 12). Since oxidation of unprotected α-carboxymethylserine was found to be sluggish and gave a complex mixture of products, the amino group was protected with a Boc group. Ozonolysis of the protected amino acid in acetic acid at room temperature followed by treatment with conc. HCl afforded...
(R)-α-carboxymethylserine in 25% yield (Scheme 5). The S enantiomers of both α-benzyl- and α-carboxymethylserines were synthesized by the use of D-valine, respectively (ref. 9c).

**Scheme 5**

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{NHR} \\
\text{OH} & \\
\text{R} = \text{H}, \ (R)-\alpha\text{-benzylserine} & \quad \text{1. Ozone, AcOH/H}_2\text{O, rt} \\
\text{R} = \text{Boc} & \quad \text{2. conc HCl, 100 °C, 6 h} \\
& \quad \text{3. 1 N NaOH, 50 °C, 5 min} \\
& \quad \text{(25%)}
\end{align*}
\]

**4. Syntheses of Four Enantiomers and Diastereomers of α-Methylthreonine**

During the course of the synthesis of α-substituted serine analogs, we found that the reaction process under the internal Strecker synthesis involved a significant imine-enamine equilibrium, which was ascertained by the incorporation experiments of the deuterium atom using 2-propanol D. These observations were quite important when a 2-hydroxy ketone with a substituent at C2 such as acetoin was employed as the starting material (eq 3). The resulting Strecker product possesses an additional chiral center at C6. Therefore, we were interested in examining whether the C3 stereogenic center of the ketimine intermediate would affect the stereochemistry of the C6 position. Thus, our next approach was the syntheses of four enantiomers and diastereomers of α-methylthreonine according to the procedure as shown in eq 2 (Figure 2).

**Figure 2**

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2\text{H} & \quad \text{Me} & \quad \text{CO}_2\text{H} & \quad \text{Me} & \quad \text{CO}_2\text{H} & \quad \text{Me} & \quad \text{CO}_2\text{H} \\
\text{Me} & \quad \text{NH}_2 & \quad \text{Me} & \quad \text{NH}_2 & \quad \text{Me} & \quad \text{NH}_2 & \quad \text{Me} & \quad \text{NH}_2 \\
\text{OH} & \\
\text{H} & \\
\text{H} & \\
\text{OH} & \\
\end{align*}
\]

(2S,3R) L-allo-form (2S,3S) (2R,3S) (2R,3R) D-allo-form

*dl*-Acetoin was chosen as the starting material. Esterification with N-Boc-L-phenylalanine 2-pyridyl thiol ester gave a diastereomeric mixture of N-Boc-L-phenylalanine D- and L-acetoin esters. The key to the synthesis was whether a diastereomeric transformation of the mixture would be achieved under the Strecker conditions where the formation of the 4 diastereomers was feasible. Thus, treatment with TFA followed by 2 equiv of NaCN in 2-propanol for 2 h gave a 4 : 1 mixture of the cyclic amino nitriles, 5S,6S isomer and its 5S,6R isomer. None of the 5R isomers was detected by the ^1H NMR and HPLC analyses. In the presence of an additional 1 equiv TFA in 2-propanol, the mixture was further equilibrated to afford a 1 : 9 mixture of 5S,6S isomer and its 5S,6R isomer.

The reaction produced only the two diastereomers, both possessing the 5S configuration, and the major product was the 6S-isomer which was equilibrated to the 6R isomer under the acidic conditions. These results suggest that the reaction involves an enamine type intermediate IIb and that both the ketimine-type intermediates, IIa and IIc, coexist at equilibrium via IIb. This was proven by the fact that the reaction using 2-propanol-D as the solvent gave a 4 : 1 mixture of the mono-deuterated products in which the C6-H was completely exchanged with a deuterium atom. Therefore, the rate-determining step of the reaction would be an attack of the cyanide ion to the ketimine intermediates,
where a boatlike conformation with a pseudoaxial benzyl group might sterically hinder the re-face. An attack of the cyanide ion to the si-face on C5 of the ketimines would yield, exclusively, the 5S products (Scheme 6). No deuterium atom was incorporated at C3 of the products, indicating that no racemization at C3 accompanied the reaction process. Thus, the amino nitriles with the 6S and 6R configuration were obtained from dl-acetoin using phenylalanine in an enantiomerically convergent manner, respectively. When L-valine instead of L-phenylalanine was used, the ratio of the cyclic amino nitriles was 1:2 (82% yield). After equilibration of the mixture with TFA, the ratio changed to 1:8. Therefore, phenylalanine was found to be a superior amino transferring group to valine in view of the fact that each 5S,6S and 5S,6R isomer was obtained.

Scheme 6

Removal of the phenylalanyl moiety and their conversions into (2R,3S)- and (2R,3R)-α-methylthreonine were carried out in a manner similar to the preparation of α-methylserine. The use of D-phenylalanine afforded (2S,3R)- and (2S,3S)-α-methylthreonine, respectively, in the same manner as for the 2R-isomers. Thus, α-methylated threonine and its allo isomers were prepared in a short number of steps and their overall yields were 44-50% (Scheme 7) (ref. 9a).
5. Syntheses of Optically Active 1-Amino-2-hydroxycyclopentancarboxylic Acid and 1-Amino-2-hydroxycyclohexanecarboxylic Acid

The synthesis of α-methylthreonine has demonstrated that the newly introduced two consecutive chiral centers could be stereochemically controlled by the amino and chirality transferring amino acid. Of particular interest prompted by these results was its application to cyclic systems. Optically active 1-amino-2-hydroxycyclopentancarboxylic acid (ref. 14) is a target amino acid starting from 2-hydroxycyclopentanone, and 1-amino-2-hydroxycyclohexanecarboxylic acid from 2-hydroxycyclohexanone. Both the 5- and 6-membered ring amino acids can be viewed as conformational variants of L-serine, which in peptides and proteins plays a crucial role not only as a hydrophilic residue but also as either an active site or a catalytic site of a variety of enzymatic transformations and biochemical signal transductions in the cell (eq 4) (refs. 8, 13).

\[ \text{D-Phe} \rightarrow (2S,3S) \text{ and (2S,3R) diastereomers} \]

(2S,3S) and (2S,3R) diastereomers
The synthesis of the cyclic serine analogs with a 5-membered ring was started with \( dl-1,1\)-dimethoxy-2-cyclopentanol, readily available from cyclopentanone (ref. 15) (Scheme 8). This was condensed with Boc-L-phenylalanine to give an amino ester, which, upon treatment with a catalytic amount of \( p\)-toluenesulfonic acid in acetone, gave a mixture of diastereomeric keto esters. After removal of the Boc group with TFA, the resulting amine was subjected to the standard reaction conditions (NaCN, 2-propanol) to give the desired 5S,6S isomer (cis isomer) as the major product. However, both the stereoselectivity (cis/trans = 80 : 20) and the yields (less than 50%) were not satisfactory, probably due to instability of the product under the reaction conditions or the isolation processes. In addition, a small amount of the ketimine IIIa was detected by the \(^1\)H NMR spectra of the crude reaction mixture. Both the yield and 5S,6S selectivity was much improved by the initial isolation of IIIa and the use of another cyano transferring reagent. Thus, treatment of the amino ester with MgSO\(_4\)-NaOAc in acetonitrile gave the ketimine IIIa. Subsequent reaction with trimethylsilyl cyanide (TMSCN) and ZnCl\(_2\) gave the crude amino nitrile in quantitative yield. \(^1\)H NMR analysis of the crude product revealed that the product was composed of a mixture of diastereomers (cis/trans = 98 : 2) and none of the imine IIIa was detected. Finally, the mixture, which appeared to be unstable to column chromatography on silica gel, was purified by a single recrystallization from ethyl acetate-hexane to give diastereomerically pure 5S,6S isomer (3 steps, 87% yield) (Scheme 8).

**Scheme 8**

![Scheme 8](image)
The present reaction process was also examined using 2-propanol D as the solvent. No deuterium atom was incorporated into the C3 and C9 positions of the product. On the other hand, 70% of the C6-H was exchanged with a deuterium atom. These results indicated that the enamine was formed only at the endo side of the ring to give IIIb, which was isomerized to IIIc (Scheme 8). The 5S,6S isomer derived from IIIc would be a kinetically as well as thermodynamically more favored product than the trans isomer. According to the routine transformation, (1R,2S)-1-amino-2-hydroxycyclopentane-carboxylic acid was synthesized from the 5S,6S isomer in excellent yield. The use of D-phenylalanine afforded (1S,2R)-1-amino-2-hydroxycyclopentane-carboxylic acid. Thus, both enantiomers of the 5-membered carbocyclic serine analogs were prepared, and the overall yields were ca. 50% (ref. 9d). The structure of (1R,2S)-1-amino-2-hydroxycyclopentane-carboxylic acid corresponds to the partial structure of the antibiotic, altermicidine (ref. 7b). The work toward its total synthesis is in progress in our laboratories.

Scheme 9
The syntheses of the 6-membered ring analogs were started with dl-trans-1,2-cyclohexanediol. Condensation with Boc-L-phenylalanine followed by Jones oxidation gave a diastereomeric mixture of amino esters. After removal of the Boc group with TFA, the resulting amine was subjected to the reaction with NaCN in 2-propanol. Contrary to the cyclopentane system, the reaction proceeded smoothly to give in 85% yield a mixture of the Strecker adducts which were composed of 5S,6S isomer (cis) and trans isomer (cis/trans = 80 : 20). None of the 5R isomer was detected. The reaction using 2-propanol-D gave partially deuterated products in which 79% of the C6-H of the cis isomer and 42% of the C6-H of the trans isomer were exchanged with a deuterium atom. This experiment clearly indicates that (i) no racemization occurred at C3, and (ii) the reaction involved significant imine-enamine equilibrium between IVa and IVc via IVb (Scheme 9). On the other hand, treatment of each isomer with Na¹³CN in 2-propanol afforded none of the corresponding ¹³C incorporated product, indicating that the reaction did not accompany an equilibrium between the amino nitriles and the ketimine intermediates, IVa and IVc, due probably to the conformational rigidity of the cyclohexane ring. Therefore, the reaction would proceed via an attack of the cyano group to the imines prior to completing the imine-enamine equilibrium, although further studies are needed to elucidate the present stereoselectivity employing a diastereomerically pure amino ester.

Oxidation of the cis isomer followed by hydrolysis gave (1R,2S)-1-amino-2-hydroxycyclohexancarboxylic acid. The minor 5S,6R isomer was also converted into (1R,2R)-1-amino-2-hydroxycyclohexancarboxylic acid. The use of D-phenylalanine gave the 1S,2R isomer and 1S,2S isomer, respectively (ref. 9d). Thus, four enantiomers and diastereomers of 1-amino-2-hydroxycyclohexancarboxylic acid were synthesized. Studies regarding the incorporation of these cyclic serine analogs into biologically active peptide will be described, separately.

6. Conclusion

Several types of optically pure α-substituted serine and threonine including their cyclic analogs were synthesized from achiral or racemic starting material. The chiral transfer process from the amino acid moiety which involved diastereoselective construction of one or two consecutive chiral centers was found to be highly efficient. Its reaction process was clearly understood by an incorporation experiment of a deuterium atom or ¹³CN. Noteworthy is that, in all cases we examined in the present studies, the nitrile group attacked the ketimine intermediates I-IV from the opposite side of the C3 substituent. These events would be explained as a result of not only steric reasons but also unclarified stereoelectronic factors. The present efficiency of the chirality transfer from valine or phenylalanine and the overall yields were excellent. These amino acids attract much interest in view of their biological activities and their ability to constrain peptide conformation. Extensive studies related to the synthesis of a peptide having these amino acids as conformational variants of serine or threonine are currently in progress in our laboratories.

Acknowledgement: We wish to acknowledge the contribution of our colleagues and their names are reported in the references. The financial support of a grant-in-aid from Yamada Science Foundation, the Ministry of Education, Science, and Culture, Japan, and New Energy and Industrial Technology Development Organization (NEDO), Ministry of International Trade and Industry, Japan, is appreciated.

References and Notes


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(Received June 26, 1997)