General Method of Diastereo- and Enantioselective Synthesis of \(\beta\)-Hydroxy-\(\alpha\)-amino Acids by Condensation of Aldehydes and Ketones with Glycine


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Abstract: The condensation of formaldehyde with a Ni(II) complex of glycine Schiff base with (S)-2-[N-(benzylprolyl)-amino]acetophenone (1) or (S)-2-[N-(benzylprolyl)amino]benzophenone (2) in CH\(_3\)OH at 25 °C in the presence of Et\(_3\)N yields (S)-Ser with an enantiomeric excess (ee) of 80-98%. The same reaction gives rise to (R)-Ser with an ee greater than 80% in the presence of more than 0.2 N CH\(_2\)ONa, \(\alpha\)-(hydroxymethyl)serine being formed in negligible quantities. The reaction of benzaldehyde, 3,4-(methylenedioxy)benzaldehyde, and acetaldehyde with these Gly complexes in 0.2 N CH\(_2\)ONa at 25 °C yields \(\beta\)-hydroxy-\(\alpha\)-amino acids: (R)-3-phenylserine, (R)-3,4-(methylenedioxy)-\(\beta\)-phenylserine, and (R)-threonine, respectively, with a three/allo ratio ranging from 10:1 up to over 50:1 and ee more than 80%. Condensation with acetone yields (R)-\(\beta\)-hydroxyvaline with an enantiomeric purity of 70%. The enantiomerically pure \(\beta\)-hydroxy-\(\alpha\)-amino acids can be obtained from pure diastereomers, isolated by chromatography on silica or Toyopearl HW-60. The initial reagents 1 and 2 were recovered with 60-98% yield. The stereochemical mechanism of the reaction is discussed.

\(\beta\)-Hydroxy-\(\alpha\)-amino acids (3) represent an important group of natural products. In spite of the recent progress in the field of asymmetric synthesis of amino acids in general\(^1\) and 3 in particular,\(^2\) convenient preparative methods for chemical enantiomeric synthesis of \(\alpha\)-3 are not still available.

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Scheme 1

Here we wish to describe our approach to the solution of this problem by means of aldol condensation of chiral Gly derivatives with aldehydes and ketones.
Condensation of free Gly seems to be the simplest way of 3 synthesis. However, this reaction can rarely be of synthetic value due to the low CH acidity of Gly, the undesirable reactivity of aldehydes or ketones, and the consequent predominance of side reactions. The only exception is the condensation of aromatic aldehydes with Gly as a preparative method for substituted β-phénylséringé synthesis. However, this method yields achiral products as a mixture of threo and allo isomers.

The use of Gly complexes with transition-metal ions rather than free Gly improves yields of reaction products and results in a significant increase in the diastereoselectivity of the process. For example, the condensation of acetaldehyde with a Gly metal complex yields racemic threonine with a threo/allo ratio of up to 3:1 (Scheme I).

Unfortunately, alkali-labile aldehydes (like sugar derivatives) cannot be used in this reaction due to the drastic experimental conditions involved, whereas condensation with formaldehyde yields mainly the product of bis addition, α-(hydroxymethyl)serine. Furthermore, attempts to induce the condensation asymmetrically were unsuccessful.

The use of transition-metal complexes of Gly Schiff bases with salicylaldehyde or pyruvic acid instead of free (Gly) complexes improves the yields and widens the scope of the reaction.

We demonstrated earlier that asymmetric synthesis of threo-alanine and threonine with an enantiomeric excess (ee) of 95% can be carried out by condensation of Cu(II) complexes of chiral Schiff bases of glycine and Gly with acetaldehyde. Optically pure α-methyl-α-amin acids could also be produced via alkylation of the nickel(II) Schiff base of (R)-alanine with (S)-2-N-(N'-benzyldiamino)benzaldehyde.

The present study is concerned with a general method of asymmetric synthesis of 3 including serine via condensation of Cu(II) and Ni(II) complexes of Gly Schiff bases with methanol at room temperature. Both 1 and 2 may be recovered and reused after the reaction.

An important advantage of this reaction is its high diastereoselectivity which permits us to obtain almost pure (R)-threo-3 with an ee greater than 80%. The unusual feature of this reaction is that it provides the opportunity to obtain either (S)-Ser or (R)-Ser with an ee of 80–95% and with the same chiral reagent by simply changing the pH of the solution. It was shown that the serine configuration is dependent on the pH due to substitution at a high pH of the carboxylate group by an ionized hydroxy group of the amino acid side chain (at the main plane of Cu(II) and Ni(II) square complexes). The proposed stereochemical mechanism accounts for all the data observed.

CD spectra of Ni(II) complexes of 1 and 3 Schiff bases allow us to make an unambiguous assignment of the absolute configuration of 3 formed.

Results

1. Synthesis of 1 and 2. The condensation of (S)-N-benzylproline hydrazine with 2-aminooctanenitrile or 2-aminobenzazepine in the presence of DCC improves the yields of 1 and 2 in comparison with the method previously described.

2. Synthesis and Structure of Ni(II) and Cu(II) Complexes of Schiff Bases of Amino Acids of (S)-Valinol with 1 and 2. The interaction between the excess of Gly, (R)-Ser, (S)-Ser or (S)-valinol, Ni(NO3)2·6H2O or CuSO4·5H2O, and 1 or 2 in the
minimization calculations, this conformation is the most stable earlier in Ni complexes with similar ligands. The benzyl group stereomeric Ni(I) complexes of Schiff bases of (S)-Ser and diastereomers in the region of metal d-d transition are almost rative TLC on SOz. IH NMR spectra of these compounds in in approximately a 1:1 ratio. The electronic spectra of both SOz and Sephadex LH-20, their elemental analyses (see Ex-

Scheme III

presence of CH3ONa at 45 °C in MeOH under Ar gives rise to red complexes according to Scheme II.

The complexes formed are neutral, soluble in CHCl3, and in the case of Ni(II) complexes diamagnetic. After purification on SiO2 and Sephadex LH-20, their elemental analyses (see Experimental Section) correspond to the calculated values. Diastereomeric Ni(II) complexes of Schiff bases of (S)-Ser and (R)-Ser with 1 (4 and 5, respectively) were separated by preparative TLC on SiO2. 1H NMR spectra of these compounds in CDC13 possess the same set of signals, differing only in chemical shifts (see Experimental Section). Decomposition of all the complexes with HCl resulted in initial 1 and (S)-Ser (or (R)-Ser) in approximately a 1:1 ratio. The electronic spectra of both diastereomers in the region of metal d-d transition are almost identical. CD spectra are different in this region and exhibit two maxima (Cotton effects at 550 and 450 nm) Figure 1) as is expected for diastereomers. The structure of 4 was confirmed by X-ray diffraction analysis (Figure 2). The Schiff base shown in Scheme II is coordinated as a tetradentate ligand by one oxygen atom of ionized carboxyl group and by nitrogen atoms of pyrroline ring, Ser moiety, and ionized amide group. The lengths

Figure 2. Structure of 4. Selected bond lengths: N(1)-Ni, 1.857 (3); N(2)-Ni, 1.837 (2); N(3)-Ni, 1.937 (3); O(1)-Ni, 1.874 (2); O(3)-Ni, 3.33 Å.

3. Dependence of Equilibrium between Diastereomers 4 and 5 on the Concentration of CH3ONa. Similar to analogous complexe16,14 the α-proton of the amino acid fragment in 4 and 5 is labile. The equilibrium between the diastereomers is established at 25 °C under the action of CH3ONa or Et3N in MeOH. The position of this equilibrium can be easily determined after separating the mixture of diastereomers by TLC on SiO2. The decomposition of the equilibrium mixture gives a ratio of Ser enantiomers (by GLC analysis15) that coincides with that of the initial mixture of diastereomers, which proves that during decomposition no equilibration takes place. The same state of equilibrium is reached starting from each diastereomer. The epimerization rate increases with the pH. The rate constant of the process in 10-3 M Et3N in the presence of formaldehyde is (3.2 ± 0.06) × 10-4 s-1. The unusual feature of the reaction is the dependence of its equilibrium on the pH of the solution. With an increase in the pH, the equilibrium is shifted toward 5. Figure 3 exhibits the dependence of the (S)-Ser (or 4) content in the equilibrium mixture of diastereomers on the CH3ONa concentration. The latter was calculated taking into account the acidity of diastereomers and the initial amount of CH3ONa (see below). The spectral characteristics of 5 (electronic and CD spectra) are also reversibly dependent on the pH. With an increase in the pH, the absorption of the complex at 400 nm decreases accordingly, as shown in Figure 3. The absorption maximum is shifted to 410 nm and the isosbestic point is observed at 420 nm.

It can be seen from Figure 3 that the spectral changes and variation in diastereomer ratio in the equilibrium mixture are described by similar typical titration curves.

Since spectral variations with an increase in the pH are not observed in the case of 8a, the changes in properties of Ser complexes may be ascribed to the base-induced ionization of the amino acid side chain OH group. Provided the pKb of methanol is equal to 16.7,16 the observed pKb value of Ser OH group in complexes can be estimated as 14.10 ± 0.03.

4. Condensation of Formaldehyde with 6a and 8a and Asymmetric Synthesis of Ser. Formaldehyde undergoes condensation with both 6a and 8a in methanol under the action of Et3N or CH3COOH according to Scheme IV.

When complete equilibrium was reached (i.e., when the diastereomer distribution ceased to change), the reaction mixture was neutralized by aqueous CH3COOH and the complexes were extracted by CHCl3 and decomposed by HCl. The initial 1 or 2 were recovered with 70-98% yield. The enantiomeric analysis of Ser was carried out by GLC technique15 and quantitative

(14) Belokon', Yu. N.; Malnyev, V. I.; Vitu, S. V.; Ryzhov, M. G.; Korda-


The ratio of threo and allo decreased (Table 11, run determined qualitatively by paper chromatography or by TLC on cellulose. This ratio was quantitatively estimated by GLC. The presence of threo and allo forms of Thr as well as its enantiomeric composition may be determined by GLC. The threo and allo forms of Thr as well as its enantiomeric composition may be determined by GLC.15 The presence of threo and allo forms of thr as well as its enantiomeric composition may be determined by GLC.15

Two asymmetric centers (α and β). The ratio of three and allo forms of Thr as well as its enantiomeric composition may be determined by GLC. The presence of three and allo forms of β-phenylserine and 3,4-(methylenedioxy)-β-phenylserine has been determined qualitatively by paper chromatography or by TLC on cellulose. This ratio was quantitatively estimated by 'H NMR (200 MHz). According to the data obtained, the threo form of Thr was isolated from diastereomerically pure complex purified by chromatography.

Table I. Condensation of 5a and 5a with Formaldehyde

<table>
<thead>
<tr>
<th>run</th>
<th>[CH3O]+</th>
<th>complex/CH3O</th>
<th>t, °C</th>
<th>yield of ser. %</th>
<th>unreacted gly. %</th>
<th>(hydroxymethyl)serine, %</th>
<th>ee (config)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.15</td>
<td>1:1</td>
<td>25</td>
<td>67</td>
<td>20</td>
<td>82 (R)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.20</td>
<td>1:1</td>
<td>25</td>
<td>66</td>
<td>18</td>
<td>88 (R)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.20</td>
<td>1:10</td>
<td>25</td>
<td>77</td>
<td>20</td>
<td>89 (R)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.20</td>
<td>1:10</td>
<td>50</td>
<td>67</td>
<td>1</td>
<td>87 (R)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.10</td>
<td>1:1</td>
<td>25</td>
<td>65</td>
<td>13</td>
<td>8 (R)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.01</td>
<td>1:10</td>
<td>25</td>
<td>55</td>
<td>11</td>
<td>87 (S)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.01</td>
<td>1:10</td>
<td>50</td>
<td>82</td>
<td>14</td>
<td>96 (S)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Et3N</td>
<td>1:10</td>
<td>75</td>
<td>17</td>
<td>7.3</td>
<td>96 (S)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>0.15</td>
<td>1:15</td>
<td>25</td>
<td>95</td>
<td>6</td>
<td>88 (R)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Et3N</td>
<td>1:10</td>
<td>50</td>
<td>67</td>
<td>3.2</td>
<td>33 (S)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Et3N/Et3N-HCl</td>
<td>1:10</td>
<td>50</td>
<td>75</td>
<td>6</td>
<td>83 (S)</td>
<td></td>
</tr>
</tbody>
</table>

*The initial concentration of the complexes in methanol was 0.05-0.2 M; the reaction was completed when the equilibrium was reached according to TLC data. Experiments 1-8 were performed with 8a; experiments 9-11 were performed with 8a. The initial concentration of CH3ONa (mol/L). The temperature was maintained with CH3ONa. According to HPLC.18

Table II. Condensation of Aldehydes or Acetone with 6 and 8

<table>
<thead>
<tr>
<th>run</th>
<th>complex</th>
<th>reactant</th>
<th>init concn of CH3ONa, M</th>
<th>complex reactant</th>
<th>yield of 3, %</th>
<th>three allo</th>
<th>ee (config)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8a</td>
<td>CH3CHO</td>
<td>1.50</td>
<td>1:10</td>
<td>72</td>
<td>20:1</td>
<td>84 (R), 98 (R)</td>
</tr>
<tr>
<td>2</td>
<td>8a</td>
<td>CH3CHO</td>
<td>Et3N/Et3N-HCl</td>
<td>1:10</td>
<td>52</td>
<td>2:1</td>
<td>78 (S), allo-Thr 76 (S)</td>
</tr>
<tr>
<td>3</td>
<td>8a</td>
<td>(CH3)2CO</td>
<td>1.45</td>
<td>1:20</td>
<td>54, 31%</td>
<td>2:1</td>
<td>72 (R), 97 (R)</td>
</tr>
<tr>
<td>4</td>
<td>8b</td>
<td>(CH3)2CO</td>
<td>1.70</td>
<td>1:10</td>
<td>55, 30%</td>
<td>2:1</td>
<td>70 (R), 98 (R)</td>
</tr>
<tr>
<td>5</td>
<td>8b</td>
<td>C6H5CHO</td>
<td>1.70</td>
<td>1:10</td>
<td>67</td>
<td>50:1</td>
<td>74 (R)</td>
</tr>
<tr>
<td>6</td>
<td>8a</td>
<td>C6H5CHO</td>
<td>1.45</td>
<td>1:4</td>
<td>67</td>
<td>34:1</td>
<td>82 (R)</td>
</tr>
<tr>
<td>7</td>
<td>8a</td>
<td>C6H5CHO</td>
<td>1.45</td>
<td>1:3</td>
<td>73</td>
<td>20:1</td>
<td>84 (R)</td>
</tr>
<tr>
<td>8</td>
<td>6a</td>
<td>C6H5CHO</td>
<td>1.50</td>
<td>1:3</td>
<td>68, 60%</td>
<td>50:1</td>
<td>88 (R), 95 (R)</td>
</tr>
<tr>
<td>9</td>
<td>6a</td>
<td>(CH3)2CO</td>
<td>1.30</td>
<td>1:10</td>
<td>56</td>
<td>50:1</td>
<td>98 (R)</td>
</tr>
<tr>
<td>10</td>
<td>6a</td>
<td>(CH3)2CO</td>
<td>1.30</td>
<td>1:3</td>
<td>59</td>
<td>50:1</td>
<td>80 (R)</td>
</tr>
</tbody>
</table>

*In methanol at 25 °C, the initial concentration of the complexes was 0.2 M. Determined by 'H NMR by addition of a standard solution of dioxan in D2O to 3 solution in D2O. According to 'H NMR (200 MHz). According to GLC. According to potentiometric analysis. After recrystallization from aqueous CH3OH. According to HPLC.18 3 was isolated from diastereomerically pure complex purified by chromatography. Et3N/Et3N-HCl = 1:1, concentration of Et3N, 0.14 M.

Scheme IV

To determine the absolute configuration of C(α) of the major 3 enantiomer, the CD spectra of the complexes formed upon condensation were recorded. Figure 4 demonstrates the calculated vicinal contribution of 3 to CD spectra of the mixture of diastereomeric complexes obtained at CH3ONa concentration greater than 0.5 N and then neutralized. The calculated contribution of the fragments of (S)-Ser and (R)-Ser is also presented for comparison. It may be deduced from these data that diastereomers
containing (R)-3 prevail at a high pH regardless of the aldehyde or ketone structure.

The ratio of enantiomers of the aromatic 3 was determined by polarimetry and ligand-exchange chromatography. The racemic samples of 3 were specially synthesized starting from racemic 8a for HPLC instrument calibration. The enantiomeric purity of β-hydroxyvaline was measured by polarimetry. The results are given in Table II. As well as in the case of Ser, the enantiomeric purity and absolute configuration of 3 depend on the pH. At a low pH (Et3N) the formation of (S)-3 is favorable (Table II, run 2); at a high pH (R)-3 is predominantly obtained (Table II, runs 1, 3–10).

The Ni(II) and Cu(II) complexes give (R)-3 with similar optical yields and threo:allo ratio (Table II, runs 5, 6, 9, 10). 1 and 2 recovered from the reaction mixture retain their enantiomeric purity according to 1H NMR with Eu(TFC). In order to obtain the enantiomerically pure 3, the mixture of diastereomeric complexes may be separated by chromatography on SiO2 or Toyopearl HW-60.

Discussion

The mechanism of aldol condensation of aldehydes or acetone with 6 or 8 seems to be similar to the generally accepted one for the condensation of other Gly metal complexes with aldehydes. Actually, the Gly fragment in 6 or 8 has a significant CH acidity, and its α-protons are easily exchanged for deuterium in CH3OD under the action of such a weak base as Dabco. At a low pH (Et3N) the observed enantioselectivity at the β-carbon (threo:allo ratio) of condensation of 6 or 8a with acetaldehyde is actually low (Table II, run 2). However, the enantioselectivity of the process at the α-atom is high and this should be discussed in detail, taking into account that the diastereoselcitivity of the reaction is thermodynamically controlled at all pHs of the solution (see Results).

It has been found earlier that in a series of analogous complexes, a diastereomer with (S)-amino acid is energetically favorable. The thermodynamic preference of the diastereomer with (S)-Ser (see Figure 3), as well as the formation of (S)-Ser upon condensation of 8a with formaldehyde in CH3OH at a low pH, is in accord with this trend. Thus, the observed preferential formation of (S)-Ser upon condensation of 8a with acetaldehyde at a low pH could be expected. Finally, the conformational calculations on Ni(II) complexes of the Schiff bases of (S)-Thr and (R)-Thr with 3 (10 and 11) show an energy difference equal to 1.7 kJ/mol in favor of the (S)-Thr diastereomer. The threo:allo ratio for this diastereomer was calculated as 1:2, which reasonably correlates with experimental results (Table II, run 2).

However, even in the case of energetically favorable diastereomers, strong intramolecular nonbonding interactions are already present. For example, the mutual repulsion of the substituent at the ketimine double bond and amino acid side chain results in the pseudoaxial orientation of this chain. Such a conformation was observed in similar complexes earlier and is clearly seen in 4 (see Figure 2). As a consequence, the α-hydrogen of amino acid fragment adopts a pseudoaxial orientation and is shielded by the substituent at the C=N bond (CH3 or Ph). The substitution of this hydrogen atom for a more bulky group like, for example, a hydroxymethyl group, would cause a strong repulsive interaction, which in a rigid polycyclic system of chelate rings could not be easily minimized. Therefore, upon condensation of 6 or 8 with formaldehyde, the product of addition of the second aldehyde molecule to the Ser fragment (α-(hydroxymethyl)serine) was either formed in small amounts or not formed at all (see Table I). This product did not form at a high pH either. But preferable formation of (R)-3 at a high pH cannot be understood on the basis of the usual structure of the complexes under study (see Figure 2). Clearly, ionization of the side chain hydroxy group plays an important part in making (R)-3-containing diastereomer thermodynamically more stable (see Results). The question to be answered then is what kind of complex structure was realized in these solutions.

By analogy with the mechanism of condensation of aldehydes and metal Gly complexes, we assumed that it could be a negatively charged oxazolidine particle according to Scheme V (route a).

The second possible reaction pathway involves ionization of the hydroxyl group in the condensation product, which is followed by a rearrangement leading to the substitution of an ionized carbonyl group for an ionized hydroxy group in the main coordination sphere of Ni(II) or Cu(II) (Scheme V, route b).

The latter type of transformation was already proposed to account for the changes in spectra of the (Thr)2CuII complex as the pH was increased.

Products a and b (see Scheme V) should have different spectral properties in the region of 380–400 nm.

It is known that a strong charge-transfer π-π* transition (ε 1000–10 000; λ 380–400 nm) is a typical feature of the metal complexes of the Schiff bases formed by salicylaldehyde and pyridoxal with amino acids or β-amino alcohols. All the
of (S)-valinol fragment to the CD spectra of vicinal contribution of the (R)-Ser fragment to the CD spectra from that in pure CH$_3$OH (see Figure 1). Figure 5 shows the intensity is close to that of medium as it is presented in Scheme somewhat less than in the initial nonionized complex and its intense transition at 410 nm, although its magnitude is complete ionization of this complex occurs (see Figure 5), imitating the product b.

We synthesized the product of reduction of the ketimine double bond in 8a (9) (see Scheme III), which should imitate the product a by its spectral parameters (see Scheme V), and 7 (see Scheme II), imitating the product b. As expected, the spectrum of 9 does not actually contain a 400-nm $\pi-\pi^{*}$ transition band (see Figure 5), but the electronic spectrum of 5 in 0.1 N CH$_3$ONa when the complete ionization of this complex occurs (see Figure 3) retains the intense transition at 410 nm, although its magnitude is somewhat less than in the initial nonionized complex and its intensity is close to that of 7 (see Figure 5). This seems to support the structure of the condensation product in a strongly basic medium as it is presented in Scheme V, route b.

Additional proof comes from the analysis of the CD spectrum of 5 in a strongly basic solution. As expected, this spectrum differs from that in pure CH$_3$OH (see Figure 1). Figure 5 shows the vicinal contribution of the (R)-Ser fragment to the CD spectra of 5 in a basic solution, and for comparison the vicinal contribution of (S)-valinol fragment to the CD spectra of 7 is also presented.

As revealed by these data, both contributions resemble each other.

These results may be explained by assuming that Cotton effects in the region of metal d-d transitions are mainly associated with chiral conformation of chelate rings.\textsuperscript{17,25}

The conformation of amino acid or $\beta$-amino alcohol chelates is dictated in our case by the preference for a pseudooxial disposition of the side chain (see Figure 2), which has already been discussed. Both the isopropyl group in the case of (S)-valinol and the carboxylate group in the case of (R)-Ser in the b-type compound (see Scheme V; $R = R' = H$) are positioned on the side of the coordination plane opposite to the phenyl ring of the benzyl group. The distortion of the $\beta$-amino alcohol fragment forces it to adopt in both cases a $\alpha$-conformation. The chiral distortions of other chelate rings incorporated into the common rigid polycyclic structure should follow a similar tendency for both complexes.

When the pH is decreased, the complex having b structure should become protonated and rearrange itself into the regular structure with coordinated carboxyl group (see Figure 2) and both the UV-vis and CD spectra become usual ones, as in fact was observed.

The stereochemistry of the condensation process could also be related to the formation of product b in the course of a high-pH condensation. In fact, the position of carboxylate and alkyl (phenyl) groups on opposite sides of the amino alcohol chelate cycle ($R^2 = H$; $R = alkyl$ or phenyl) out to be more sterically favorable than a one-sided disposition (see Scheme V) producing the three isomer as a major product. Moreover, the thermodynamically favorable orientation of the carboxylate group opposite to the phenyl ring of the N-benzyl substituent is possible for the isomer with $R$ configuration of the $\alpha$-carbon atom, whereas, in the case of the $S$ isomer, the unfavorable steric interaction of the carboxylate with the N-benzyl group would appear, which explains the preferable (R)-3 formation at a high pH of the solution.

**Experimental Section**

**General.** The amino acids were supplied by Reanal (Budapest) and Reakhim (Moscow). (S)-Valinol, $\alpha$-aminoacetoephone, and $\alpha$-amino benzophenone were purchased from Fluka and were used without further purification. (S)-N-Benzylproline was obtained earlier\textsuperscript{19} and used in this work. CH$_3$ONa was prepared by adding metallic Na to CH$_3$OH under argon with cooling. $^1$H NMR spectra were recorded on Bruker 200 and Tesla NMR-BS-467A instruments using Me$_3$SiOSiMe$_3$ as an internal reference. For the D$_2$O solutions Me$_3$SiOSiMe$_3$ sealed in a glass capillary was used as an external reference. Optical rotations were determined on a Perkin-Elmer 241 Polarimeter. CD spectra were recorded on a JASCO-20 spectropolarimeter. UV-vis spectra were obtained on a Specord UV-vis spectrophotometer. The molecular weights of the complexes were determined ebulliometrically on a EP-75 instrument. Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Thin-layer or preparative-layer

The enantiomeric purity of Thr and Ser was determined by GLC. The enantiomeric analysis of $\beta$-phenylserine and 3,4-(methylenedioxy)benzylamine was carried out by HPLC on chiral enantiomeric plates. The enantiomeric purity of 3,4-(methylenedioxy)-phenylalanine was determined similarly on the phase described earlier. The enantiomeric purity of $\beta$-hydroxyvaline was determined by polarimetry. In the latter case, the amino acid was dissolved in 1 N HCl and evaporated to dryness, then a certain volume of dioxane solution in D$_2$O was added, and the amount of amino acid in the solution was determined by $\text{H NMR}$. The measurement of optical rotation was performed after evaporation of the sample followed by dissolving it in a certain volume of 6 N HCl.

(S)-N-Benzylproline hydrochloride was obtained after the dissolving of (S)-N-benzylproline in 1 N HCl. The solution was evaporated in vacuo and the resulting solid dried under reduced pressure over P$_2$O$_5$, mp 179–180 °C. Analog (C$_4$H$_9$O$_2$Cl): C, H, N.

Synthesis of (S)-2-(N-benzylprolyl)aminocetophenone and (S)-2-(N-benzylprolyl)amino/benzophenone (1 and 2). Both 1 and 2 were obtained by the same procedure described below. Dicyclohexylcarbodiimide (DCC) (3.75 mmol) was dissolved in three portions of 0.6 g (2.5 mmol) of (S)-N-benzylproline hydrochloride and 0.36 g (2.5 mmol) of $\alpha$-aminocetophenone in 2 mL of dry CH$_2$Cl$_2$ with stirring and cooling at $-20$ °C. The reaction was monitored by TLC on silica gel in CHCl$_3$–benzene–ethanol–acetic acid (10:10:2.5:2.5). The mixture was stirred further for 2 h upon cooling, and after the addition of 1 mL of H$_2$O and 20 mL of benzene, the pH of the aqueous layer was adjusted to 9 with dry Na$_2$CO$_3$. The organic layer was removed and the aqueous layer was extracted (5 $\times$ 10 mL) with benzene. The organic layer and extracts were combined and the solvent was evaporated until dicyclohexylurea precipitated and then was filtered. The filtrate was washed with 1 mL of H$_2$O and the solvent removed in vacuo, the product was recrystallized from petroleum ether (bp 40–70 °C) to give 0.4 g (1.24 mmol) (50% of 1): mp 118–119 °C, [a]$_D^{119}$ = –112.5° (c 0.08, CH$_3$OH) (lit. 35, mp 115–116 °C, [a]$_D^{119}$ = –110.7° (c 0.08, CH$_3$OH)).

Anal. Calcd for C$_9$H$_9$NO$_2$: C, H, N.

Analog (C$_9$H$_9$NO$_2$Cl): C, H, N.


The procedure is illustrated by the synthesis of the enantiomerically pure mixture with aqueous CH₃COOH followed by extraction with CHCl₃. Until the disappearance of the complex, then the solution was evaporatedextracted with CHCl₃ (5 mL). When the reaction was completed, the reaction mixture was slowly added to the mixture of 100 mL of CHCl₃ and 200 mL of 5% aqueous CH₃COOH under vigorous stirring. The aqueous and the organic layers were separated and the former was extracted with chloroform (2 × 20 mL). The chloroform extracts were combined and evaporated in vacuo. The residue was separated, washed with 5% aqueous Na₂CO₃, and evaporated in vacuo. 2. 0.45 g (1.2 mmol), was isolated. The aqueous solution was desalted on Dowex-50 (H⁺ form) and (R)-β-hydroxyvaline was isolated: 0.15 g (1.13 mmol), 56%, mp 200–201 °C, [α]D = -11.1° (c 0.64, 6 N HCl) (lit.² [α]D = -11.2° (c 2, 5 N HCl)); H NMR (D₂O—DCI) δ 1.60, 1.75 (6 H, 2 × 2 × Me₃), 4.25 (1 H, s, +H). Anal. Calc. for C₁₇H₂₆N₃O₄: C, 54.10; H, 8.32; N, 10.51. Found: C, 45.12; H, 8.28; N, 10.36.

(R)-threo-β-phenylserine was obtained according to this procedure with a yield of 60%, [α]D = +47.9° (c 0.44, 6 N HCl), ee 95%.

(R)-threo-(3,4-Methylenedioxy)-β-phenylserine: yield 73%, mp 160 °C dec. [α]D = +29.0° (c 1.56, 6 N HCl); H NMR (D₂O—DCI) δ 4.50 (1 H, d, J = 5 Hz, -H), 5.47 (1 H, s, -H), 6.02 (2 H, s, CH₂), 7.00–7.27 (3 H, m, Ar H). Anal. Calc. for C₂₂H₂₅N₃O₃: C, 53.33; H, 4.92; N, 6.22. Found: C, 52.70; H, 5.15; N, 6.19.

Comments. The complexes of 3 are unstable in a polar medium and decompose forming the initial complex of Gly. The slow decrease of the pH upon neutralization of a reaction mixture (procedure B) or slow decomposition of the 3 complex (procedure A) may result also in the increase of the amount of other diastereomer.

Regeneration of 1 or 2 was performed after completion of the reaction and decomposition of the complexes as it was described above. The recovery yield was 70–98%. These reagents may be reused without an additional crystallization. They did not undergo any racemization, as proved by using Eu(TFC)³. In the 'H NMR spectra of racemic 1 recorded in CDCl₃ in the presence of 0.2 M Eu(TFC), the signals of aromatic protons in the 3-position were shifted to a weaker field (δ 12.2 ppm) and were well separated (δΔΔ = 0.40 ppm). In the 'H NMR spectrum of the regenerated chiral 1 recorded under the same conditions, the signals of the second enantiomer were absent.

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Registry No. (S)-1, 82704-15-2; (R)-1, 96346-91-7; (S)-2, 96293-17-3; 4, 96293-18-4; 5, 96293-19-5; 6, 96293-20-8; 7, 96293-21-9; 8a, 95824-15-0; 8b, 82704-29-8; 9, 96293-22-0; HNCH₂CO₂H, 54–60; dl-H₂NCH₂CH₂OHCO₂H, 302–84–1; (S)-H₂NCH₂CH₂OH, 2026–46–4; C₃H₅CHO, 100–52–7; (CH₃)₂CO, 67–64–1; CH₃CHO, 75–07–0; CH₃O₂CH₂CH₃, 120–57–0; CH₃O, 50–00–0; (S)-N-benzylproline, 31795–93–4; (S)-N-benzylproline hydrochloride, 92086–93–6; α-aminoacetophenone, 551–93–9; α-amino benzophenone, 2833–77–0; dl-N-benzylproline, 60169–72–4; paraformaldehyde, 30525–89–4; (S)-serine, 56–45–1; (S)-allothreonine, 2835–77–0; (R)-threo-(3,4-Methylenedioxy)-β-phenylserine, 88375–62–6; (R)-serine, 312–84–5; (R)-threonine, 632–20–2; (S)-threonine, 72–19–5.

Supplemental Material Available: Tables of atomic coordinates and their thermal parameters (3 pages). Ordering information is given on any current masthead page.
