mL and DMF and saturated with methylamine gas at 0 °C. The vessel was sealed and agitated for 1 day. The polymer was washed successively in dioxane, ethanol, 2 N NaOH/*i*-PrOH (1:1), water (until eluate neutral), ethanol, and ether. After drying in vacuo, the polymer (3.7 g/3.8 mequiv of amino groups/1 g of dry weight) was suspended in a mixture of water (1.5 mL), ethanol (0.5 mL), triethylamine (7 mL), and 4-chloropyridine hydrochloride (4.7 g) in a glass pressure vessel, sealed and heated for 4 days at 140 °C. The polymer was washed as before, and unreacted amino groups were blocked by acetylation (acetic anhydride in CH_2Cl_2, then base wash). The washed DMAP polymer was dried at 150 °C in vacuo until constant weight. Incorporation of pyridine groups was determined by potentiometric chloride titration of the hydrochloride salt bound to the polymer: 2.53 mequiv/g compared to 3.15 mequiv/g prior to acetylation.

Polymeric 1-Acyl-4-(dialkylamino)pyridinium Chlorides. In a typical experiment, the anhydrous 4-(dialkylamino)pyridine polymer was swelled in methylene chloride (freshly distilled from P_2O_5 under argon) and treated with excess benzoyl chloride at 0 °C. The polymer was filtered and washed with methylene chloride under anhydrous conditions until the washings contained negligible amounts of benzoyl chloride—by the silver nitrate test in alcohol (less than 0.1% of total pyridine groups as indicated by GC). The polymer was dried under vacuum at room temperature and was stable at −10 °C for several months. After treatment with a primary (e.g., benzyl) amine in methylene chloride, a pure amide was recovered by filtration and acid/base wash. The amount of amide corresponded to 0.8 mequiv/g of acyl substitution on the polymer.

Anhydrous manipulation as above and those involving transfer between two polymers were most conveniently carried out by using a circulating system described in Figure 1, containing Teflon columns (1-4-mL volume) joined to the solvent distillation apparatus, waste, and vacuum pump via Teflon tubing.

In summary, we have shown for the first time the possibility to perform highly efficient condensation reactions, by transferring polymer-bound electrophiles (i.e., active esters) via a mediator (shadchan) to polymer-bound nucleophiles (i.e., amines). We have also shown the possibility of on-line monitoring which is relevant for automation.

The mediator methodology developed here is believed not to be limited to acylation and related processes but to be expandable to other chemical processes that involve the creation of activated intermediates. These possibilities are currently under investigation.

Acknowledgment. We thank the Etta P. Schiff Trust and the Bantrell Fund for financial support. This work is dedicated to Prof. Arieh Berger on the 10th anniversary of his death.

Registry No. Boc-Phe-OH, 13734-34-4; Boc-Gly-OH, 4530-20-5; Boc-Tyr(OBz)-OH, 2130-96-3; Boc-Tyr(OBz-2,6-Cl)-OH, 40298-71-3; Boc-Phe-Leu-OCH_3, 64152-76-7; H_2NPhe-Leu-OH, 3303-55-7; H_2NAla-Leu-OH, 3303-34-2; H_2NGly-Phe-Leu-OH, 15373-56-5; H_2NGly-Gly-Phe-Leu-OH, 60254-83-3; Boc-Tyr(OBz)-Gly-Gly-Che-Leu-OCH_3, 63631-33-4; H_2NTyr-Gly-Gly-Phe-Leu-OH, 58822-25-6; $HOCH_2Ph$, 100-51-6; HOC_6H_4-*p*-NO_2, 100-02-7; HSC_6H_4-*p*-NO_2, 1849-36-1; PhCOOH, 65-85-0; CH_3COOH, 64-19-7; H_2NCH_2Ph, 100-46-9; $CH_3CO_2CH_2Ph$, 140-11-4; $PhCO_2C_6H_4$-*p*-NO_2, 959-22-8; $PhCOSC_6H_4$-*p*-NO_2, 1219-32-5; CH_3CO_2COPh, 2819-08-1; PhCOF, 455-32-3; *i*-BuOCONHCH$_2$Ph, 69805-82-9; *p*-tosyl-NHCH$_2$Ph, 1576-37-0; methylamine, 74-89-5; 4-chloropyridine hydrochloride, 7379-35-3; benzoyl chloride, 98-88-4; menthol, 89-78-1; menthol benzoate, 612-33-9; benzoic anhydride, 93-97-0; 1-methylethyl 2-chlorophenyl dimethylphosphoramidate, 96227-79-1; 2-chlorophenyl methyl 1-methylethyl phosphorate, 96227-80-4.

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General Method of Diastereo- and Enantioselective Synthesis of β-Hydroxy-α-amino Acids by Condensation of Aldehydes and Ketones with Glycine

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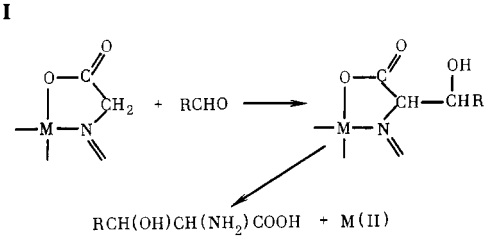
Abstract: The condensation of formaldehyde with a Ni(II) complex of glycine Schiff base with (*S*)-2-[*N*-(benzylprolyl)-amino]acetophenone (**1**) or (*S*)-2-[*N*-(benzylprolyl)amino]benzophenone (**2**) in CH_3OH at 25 °C in the presence of Et_3N yields (*S*)-Ser with an enantiomeric excess (ee) of 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_3ONa, α-(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_3ONa at 25 °C yields β-hydroxy-α-amino acids: (*R*)-β-phenylserine, (*R*)-3,4-(methylenedioxy)-β-phenylserine, and (*R*)-threonine, respectively, with a threo/allo ratio ranging from 10:1 up to over 50:1 and ee more than 80%. Condensation with acetone yields (*R*)-β-hydroxyvaline with an enantiomeric purity of 70%. The enantiomerically pure β-hydroxy-α-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.

β-Hydroxy-α-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 enantioselective synthesis of *threo*-**3** are still not available.

Scheme I



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.

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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-phenylserine synthesis.[3,4] However, this method yields achiral products as a mixture of threo and allo isomers.[4]

The use of Gly complexes with transition-metal ions rather then free Gly improves yields of reaction products and results in a significant increase in the diastereoselectivity of the process.[5,6] For example, the condensation of acetaldehyde with a Gly metal complex yields racemic threonine[5] 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.[7] Furthermore, attempts to induce the condensation asymmetrically were unsuccessful.[8,9]

The use of transition-metal complexes of Gly Schiff bases with salicylaldehyde[10] or pyruvic acid[11] instead of free $(Gly)_2$ complexes improves the yields and widens the scope of the reaction.

We demonstrated earlier that asymmetric synthesis of threonylglycine[12] and threonine[13] with an enantiomeric excess (ee) of 95% can be carried out by condensation of Cu(II) complexes of chiral Schiff bases of glycylglycine and Gly with acetaldehyde. Optically pure α-methyl-α-amino acids could also be produced via alkylation of the nickel(II) Schiff base of (*R*,*S*)-alanine with (*S*)-2-*N*-(*N'*-benzylprolyl)aminobenzaldehyde.[13c]

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 **1** or **2** in 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 diastereo- and enantioselectivity which permit 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.

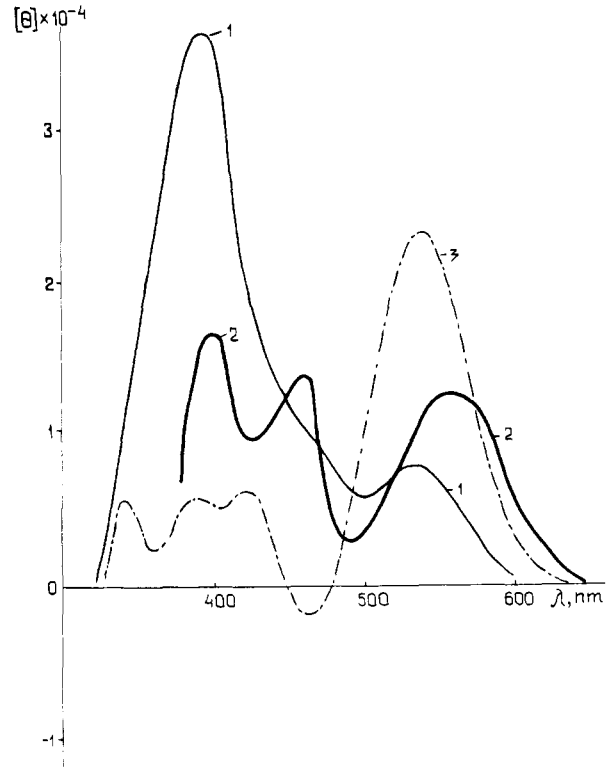
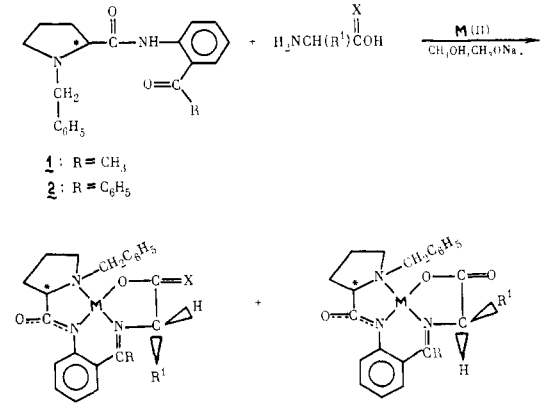


Figure 1. CD spectra at 23 °C: (1) **5** in CH_3OH, (2) **5** in 0.1 N methanol solution of CH_3ONa, (3) **4** in CH_3OH.

Scheme II



Results

1. Synthesis of 1 and 2. The condensation of (*S*)-*N*-benzylproline hydrochloride with 2-aminoacetophenone or 2-aminobenzophenone in the presence of DCC improves the yields of **1** and **2** in comparison with the method previously described.[13b]

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, $Ni(NO_3)_2 \cdot 6H_2O$ or $CuSO_4 \cdot 6H_2O$, and **1** or **2** in the

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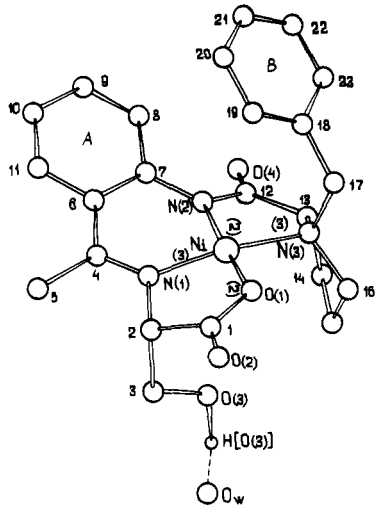
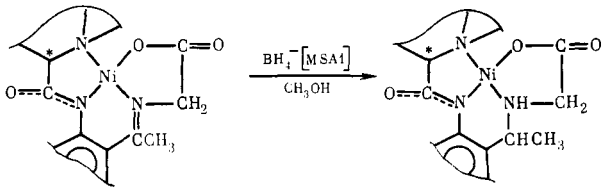


Figure 2. Structure of **4**. Selected bond lengths: N(1)–Ni, 1.857 (3); N(2)–Ni, 1.837 (2); N(3)–Ni, 1.937 (3); O(1)–Ni, 1.874 (2); O(3)–Ni, 3.33 Å.

Scheme III



8a **9**

presence of CH_3ONa at 45 °C in MeOH under Ar gives rise to red complexes according to Scheme II.

The complexes formed are neutral, soluble in $CHCl_3$, and in the case of Ni(II) complexes diamagnetic. After purification on SiO_2 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 SiO_2. ^1H NMR spectra of these compounds in $CDCl_3$ 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 pyrrolidine ring, Ser moiety, and ionized amide group. The lengths of Ni–O and Ni–N bonds (see Figure 2) are close to those found earlier in Ni complexes with similar ligands.[14] The benzyl group (B ring) is turned toward the metal atom (torsion angle Ni–N-(3)–C(17)–C(18) 60.6 (4)°). According to the strain energy minimization calculations, this conformation is the most stable one (see Experimental Section). The pyrrolidine nitrogen atom acquires an *R* configuration like in other complexes of Cu(II) or Ni(II) and amino acid Schiff bases with **1**.

The structures of Ni(II) and Cu(II) complexes of Gly Schiff base with **2** (**6a** and **6b**, respectively) and Ni(II) complex of (*S*)-valinol Schiff base with **1** (**7**) have been assigned by analogy with Ni(II) and Cu(II) complexes previously described[14] and also on the basis of chemical and physical data (see Experimental Section). The double ketimine bond in these complexes is readily reduced in MeOH by BH_4^- immobilized on Dowex MSA-I resin as illustrated in the case of Ni(II) complex of Gly Schiff base with **1** (**8a**) (Scheme III).

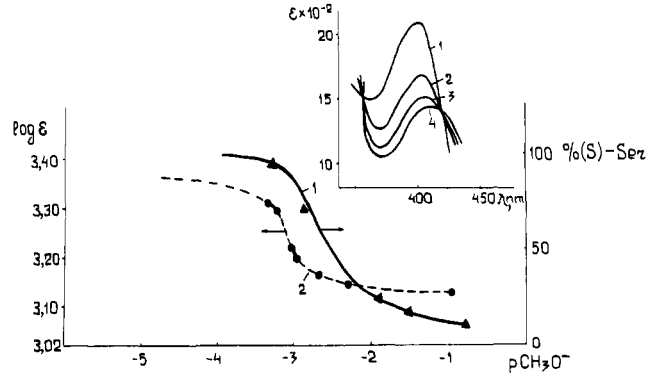


Figure 3. (1) Dependence of diastereomeric ratio of **4** and **5** on -log CH_3O^- ($p(CH_3O^-)$). (2) Dependence of absorption (log ε) of **5** at 400 nm on $p(CH_3O^-)$. The inset is the change of electronic spectrum of **5** as a function of CH_3O^- concentration: (1) 4.5×10^{-4}, (2) 7.2×10^{-4}, (3) 1.8×10^{-3}, (4) 0.1 M (the concentration of **5** is 2.8×10^{-4} M).

3. Dependence of Equilibrium between Diastereomers 4 and 5 on the Concentration of CH_3ONa. Similar to analogous complexes[13b,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 CH_3ONa or Et_3N in MeOH. The position of this equilibrium can be easily determined after separating the mixture of diastereomers by TLC on SiO_2. The decomposition of the equilibrium mixture gives a ratio of Ser enantiomers (by GLC analysis[15]) 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 Et_3N in the presence of formaldehyde is $(3.2 \pm 0.06) \times 10^{-4}$ 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 CH_3O^- concentration. The latter was calculated taking into account the acidity of diastereomers and the initial amount of CH_3ONa (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 pK_a of methanol is equal to 16.7,[16] the observed pK_a 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 Et_3N or CH_3O^- 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 CH_3COOH and the complexes were extracted by $CHCl_3$ 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 technique[15] and quantitative

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Table I. Condensation of **8a** and **6a** with Formaldehyde[a]

run[b]	$[CH_3O^-]$[c]	complex/CH_2O	t, °C[d]	yield of ser, %[f]	unreacted gly, %[f]	(hydroxymethyl)-serine, %[e]	ee (config)[f]
1	0.18	1:1	25	67	20		82 (*R*)
2	0.20	1:1	25	66	18		88 (*R*)[g]
3	0.20	1:10	25	77			89 (*R*)
4	0.20	1:10	50	67	1		87 (*R*)
5	0.10	1:1	25	65	13		8 (*R*)
6	0.01	1:10	25	55	11		87 (*S*)
7	0.01	1:10	50	82	14		96 (*S*)
8	Et_3N	1:10	50	75	17	7.3	96 (*S*)[h]
9	0.18	1:1.5	25	95			88 (*R*)
10	Et_3N	1:10	50	67	3.2		33 (*S*)[h]
11	$Et_3N/Et_3N{\cdot}HCl$	1:10	50	75		6	83 (*S*)[h,i]

[a] 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. [b] Experiments 1–8 were performed with **8a**; experiments 9–11 were performed with **6a**. [c] The initial concentration of CH_3ONa (mol/L). [d] The temperature was maintained with 0.5 °C accuracy. [e] Determined by HPLC.[18] [f] Determined by GLC.[15] [g] The initial complex was obtained with **1** recovered from previous experiments. [h] The initial concentration of Et_3N, 0.14 M. [i] Et_3N:$Et_3N{\cdot}HCl$ = 2:1.

Table II. Condensation of Aldehydes or Acetone with **6** and **8**[a]

run	complex	reactant	init concn of CH_3ONa, M	complex reactant	yield of **3**, %[b]	threo allo[c]	ee (config)
1	**8a**	CH_3CHO	1.50	1:10	72	20:1	84 (*R*),[d] 98 (*R*)[h]
2	**8a**	CH_3CHO	$Et_3N/Et_3N{\cdot}HCl$[e]	1:10	32	2:1	Thr 78 (*S*),[d] *allo*-Thr 76 (*S*)[d]
3	**8a**	$(CH_3)_2CO$	1.45	1:20	54, 31[f]		72 (*R*),[e] 97 (*R*)[e,f]
4	**8b**	$(CH_3)_2CO$	1.70	1:10	55, 30[f]		70 (*R*), 98 (*R*)[e,f]
5	**8b**	C_6H_5CHO	1.70	1:10	67	50:1	74 (*R*)[e,g]
6	**8a**	C_6H_5CHO	1.45	1:4	67	34:1	82 (*R*)[e,g]
7	**8a**	$CH_2O_2C_6H_3CHO$	1.45	1:3	73	20:1	84 (*R*)[g]
8	**6a**	C_6H_5CHO	1.50	1:3	68, 60[h]	50:1	88 (*R*),[e] 95 (*R*)[e,h]
9	**6a**	$(CH_3)_2CO$	1.30	1:100	56		98 (*R*)[e,h]
10	**6b**	C_6H_5CHO	1.30	1:3	59	50:1	80 (*R*)[e]

[a] In methanol at 25 °C, the initial concentration of the complexes was 0.2 M. [b] Determined by ^1H NMR by addition of a standard solution of dioxan in D_2O to **3** solution in D_2O. [c] According to ^1H NMR (200 MHz). [d] According to GLC.[15] [e] According to polarimetric analysis. [f] After recristallization from aqueous C_2H_5OH. [g] According to HPLC.[18] [h] **3** was isolated from diastereomerically pure complex purified by chromatography. [i] Et_3N:$Et_3N{\cdot}HCl$ = 2:1, concentration of Et_3N, 0.14 M.

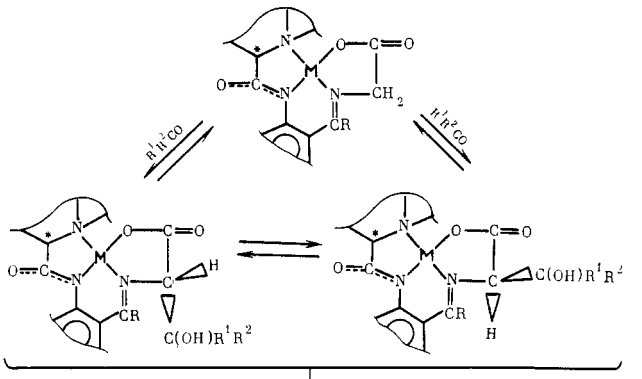
analysis by HPLC. The main experimental results are given in Table I. According to these data, Ser is the major reaction product. The bis-addition product, α-(hydroxymethyl)serine, was obtained only in small amounts at a low pH (see Table I, runs 8, 11). The data indicate that both the enantiomeric purity and the absolute configuration of the Ser formed depend on the pH in the same way as the ratio of enantiomers isolated from the equilibrium mixture of diastereomers **4** and **5** (see above). At a low pH (<0.01 N CH_3ONa) (*S*)-Ser predominates (Table I, runs 6, 7, 8, 10, 11); at a high pH (>0.1 N CH_3ONa) (*R*)-Ser is the major product (Table I, runs 1, 5, 9). The acidity range for **2** complexes where (*S*)-Ser is predominant is shifted to a low pH in comparison with **1** complexes (Table II, runs 8, 10, 11).

1 and **2** may be repeatedly used for asymmetric synthesis without a noticeable change in the asymmetric yield (see Table I, run 2) as shown in the case of **1**.

5. Condensation of Acetaldehyde, Benzaldehyde, 3,4-(methylenedioxy)benzaldehyde, and Acetone with 6 and 8. Condensation was carried out similarly to serine synthesis according to Scheme IV. The equilibrium of the reactions, however, is shifted to a greater extent toward the initial products; therefore, the greater excess of aldehydes or ketones is required (see Table II). TLC has been used to monitor the reaction. When the ratio of diastereomers ceased to change, the reaction mixture was treated as described in the Experimental Section.

Unlike formaldehyde, all the other aldehydes yield **3**, having two asymmetric centers (α and β). The ratio of 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 β-phenylserine and 3,4-(methylenedioxy)-β-phenylserine has been determined qualitatively by paper chromatography[4e] or by TLC on cellulose. This ratio was quantitatively estimated by ^1H NMR (200 MHz). According to the data obtained, the threo form of **3** was formed (>96%) at a high pH, whereas at a low pH (Et_3N) the threo:allo ratio decreased (Table II, run 2).

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[17] of **3** to CD spectra of the mixture of diastereoisomeric complexes obtained at CH_3ONa concentration greater then 0.5 N and then neutralized. The vicinal contribution of the fragments of (*S*)-Ser and (*R*)-Ser is also presented for comparison. It may be deduced from these data that diastereomers

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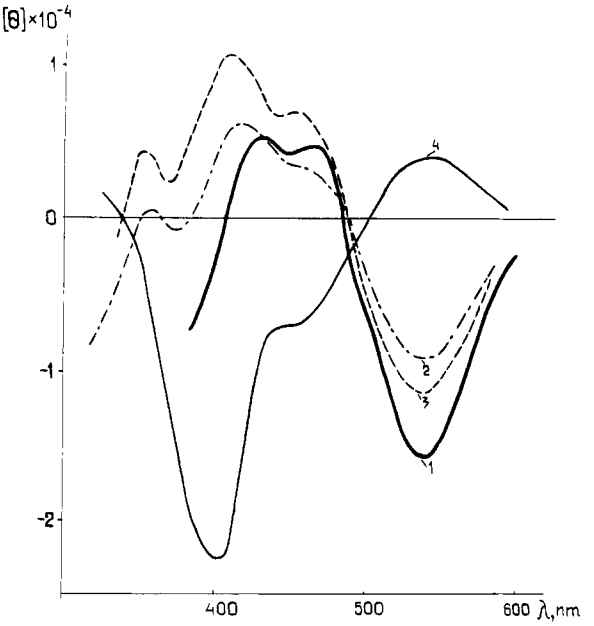

Figure 4. Vicinal contributions of amino acid fragments to the CD spectra of a neutralized reaction mixture upon condensation of **8a** with (1) 3,4-(methylenedioxy)benzaldehyde and (2) benzaldehyde; (3 and 4) vicinal contributions calculated for pure diastereomers containing (*R*)-Ser and (*S*)-Ser, respectively.

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.[18] 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 (Et_3N) 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 $Eu(TFC)_3$.

In order to obtain the enantiomerically pure **3**, the mixture of diastereomeric complexes may be separated by chromatography on SiO_2 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.[7,19] It is assumed to consist of several steps, the first of which is a base-catalyzed abstraction of an α-proton from the Gly fragment followed by the addition of the resulting carbanion to a carbonyl group.[7,19]

If the condensation step is not accompanied by the formation of oxazolidines, the threo:allo ratio is close to 1:1.[10,12,19b]

Actually, the Gly fragment in **6** or **8** has a significant CH acidity, and its α-protons are easily exchanged for deuterium in CH_3OD under the action of such a weak base as Dabco.[14] At a low pH (Et_3N) 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 diastereoselectivity 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.[14] 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 CH_3OH at a low pH, is in accord with this trend. Thus, the observed preferential formation of (*S*)-Thr 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 **1** (**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[14] and is clearly seen in **4** (see Figure 2). As a consequence, the α-hydrogen of amino acid fragment adopts a pseudoequatorial orientation and is shielded by the substituent at the C=N bond (CH_3 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 formaldehyde 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,[20,21] 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 carboxyl group for an ionized hydroxyl 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 $(Thr)_2Cu^{II}$ complex as the pH was increased.[22]

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 $\pi-\pi^*$ transition (ϵ 1000–10000; λ 380–400 nm) is a typical feature of the metal complexes of the Schiff bases formed by salicylic aldehyde and pyridoxal with amino acids[23] or β-amino alcohols.[24] All the

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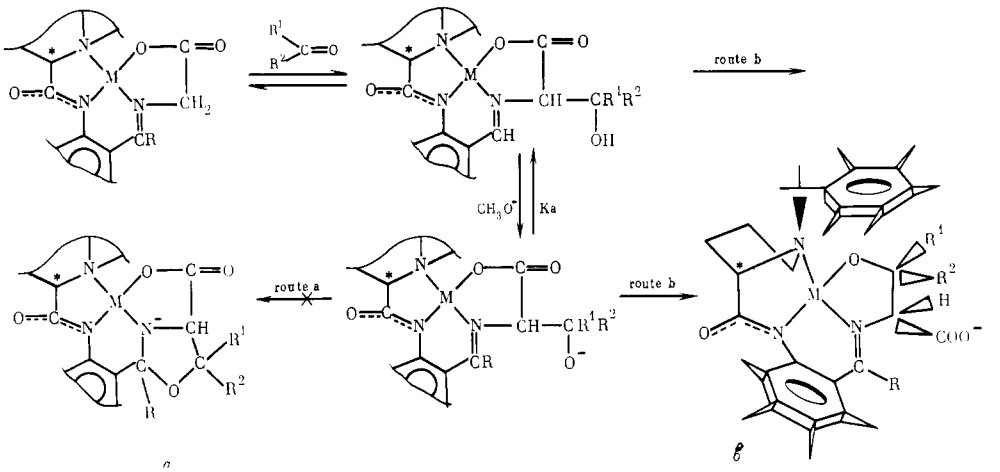
Scheme V



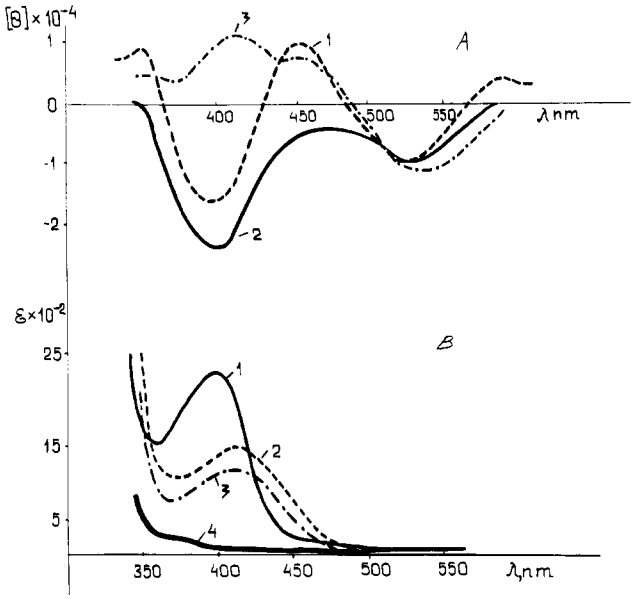


Figure 5. (A) Vicinal contributions of amino acid fragments to CD spectra: (1) **5** in 0.1 N CH_3ONa, (2) **7** in CH_3OH, (3) **5** in CH_3OH. (B) Electronic spectra of the complexes: (1) **5** in CH_3OH, (2) **5** in 0.1 N CH_3ONa, (3) **7** in CH_3OH, (4) **9** (the product of ketimine bond reduction in **8a**) in CH_3OH.

electronic spectra of the complexes under study also have a band in this region[13b,14] (see also Figure 5), which could be tentatively accounted for by the charge-transfer transition from the ionized amide group to the ketimine double bond. The formation of oxazoline (product a) would result in the disappearance of the ketimine double bond along with the disappearance of the 400-nm transition.

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_3ONa 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_3OH (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 be assuming that Cotton effects in the region of metal d–d transitions are mainly associated with chiral conformation of chelate rings.[17,25]

The conformation of amino acid or β-amino alcohol chelates is dictated in our case by the preference for a pseudoaxial 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^2 = H) are positioned on the side of the coordination plane opposite to the phenyl ring of the benzyl group. The distortion of the β-amino alcohol fragment forces it to adopt in both cases a λ-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 threo 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 α-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, *o*-aminoacetophenone, and *o*-aminobenzophenone were purchased from Fluka and were used without further purification. (*S*)-*N*-Benzylproline was obtained earlier[13b] and used in this work. CH_3ONa was prepared by adding metallic Na to CH_3OH under argon with cooling. ^1H NMR spectra were recorded on Brucker 200 and Tesla NMR-BS-467A instruments using $Me_3SiOSiMe_3$ as an internal reference. For the D_2O solutions $Me_3SiOSiMe_3$ 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

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plates were made of E. Merk A6 Darmstadt silica gel PF_{254}.

X-ray Experiments. Crystals of **4** were obtained from CH_3OH. The unit cell parameters and intensities of reflections were measured with a four-circle automatic Hilger and Watt diffractometer (Mo K irradiation, graphite monochromator) at room temperature. The rhomboid crystals had $a = 9.658$ (2) Å, $b = 11.782$ (3) Å, $c = 19.322$ (3) Å, $V = 2199$ (1) Å^3, $z = 4$, $d_{calcd} = 1.41$ g cm^{-1}, the spatial group p is $2_12_12_1$. The intensities of 2355 independent reflections with $I > 2e$ were measured by $\theta/2\theta$ scanning method ($\theta \leq 30°$). The structure was solved by the heavy atom method and refined in a full-matrix anisotropic approximation to $R = 0.029$, $R_w = 0.038$. The hydrogen atoms were located objectively.

Conformation energy calculations of some complexes were done according to a published procedure[26] using the MOLBD-3 program,[27] which was kindly supplied by Professor R. H. Boyd. The conformation energy (U_t) is represented by the summation $\sum U_t = \sum U_B = \sum U_{NB} + \sum U_\theta + \sum U_\phi$, where the terms are functions describing contributions from bond stretching, nonbond interactions, angle deformation, and bond torsion, respectively. The form and parametrization of these contributions were taken from ref 26. The strain energy minimization procedure was continued until the shift of the coordinates was not more than 0.001 Å. All the calculations were done on a Soviet-made ES-1060 computer. The first approximated atom coordinates were based on X-ray data for **4** and analogous complexes.[14]

For diastereomers **10** and **11**, the conformation energies were calculated for different benzyl group orientations with torsion angle, τ (Ni–N(3)–C(17)–C(18)), varied with 20° intervals. The torsion barrier was found to be 21 kJ/mol and three energy minima were found at $\tau = +60°$, 180°, and −60°, the latter being the deepest. The rotation of the Thr side chain around the C–C bond indicates the presence of three minima with similar energies. The calculated value of the rotation barrier is ca. 30 kJ/mol.

The enantiomeric purity of Thr and Ser was determined by GLC.[15] The enantiomeric analysis of β-phenylserine and 3,4-(methylenedioxy)-β-phenylserine was carried out by HPLC on chiral enantiomeric phases.[18] The ratio of Ser and α-(hydroxymethyl)serine was determined similarly on the phase described earlier.[18b] The enantiomeric purity of β-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 dioxan solution in D_2O was added, and the amount of amino acid in the solution was determined by ^1H 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.

α-(Hydroxymethyl)serine was prepared according to the method reported in ref 7. Anal. ($C_4H_9O_4N$): C, H, N.

(*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_2O_5, mp 179–180 °C. Anal. ($C_{12}H_{16}NO_2Cl$): C, H, N.

Synthesis of (*S*)-2-[(*N*-Benzylprolyl)amino]acetophenone and (*S*)-2-[(*N*-Benzylprolyl)amino]benzophenone (1 and 2). Both **1** and **2** were obtained by the same procedure described below. Dicyclohexylcarbodiimide (DCC), 0.36 g (3.75 mmol), was added in three portions to the mixture of 0.6 g (2.5 mmol) of (*S*)-*N*-benzylproline hydrochloride and 0.36 g (2.5 mmol) of *o*-aminoacetophenone in 2 mL of dry CH_2Cl_2 with stirring and cooling at −20 °C. The reaction was monitored by TLC on silica gel in $CHCl_3$–benzene–ether–ethanol–acetic acid (10:10:10:2.5:2.5). The mixture was stirred further for 2 h upon cooling, and after the addition of 10 mL of H_2O and 20 mL of benzene, the pH of the aqueous layer was adjusted to 9 with dry Na_2CO_3. The organic layer was removed and the aqueous layer was extracted (5 × 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 collected 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, $[\alpha]^{25}_{578}$ −112.5° (*c* 0.08, CH_3OH) (lit.[13b] mp 115–116 °C, $[\alpha]^{25}_{578}$ −110.71° (*c* 0.08, $CHCl_3$)). Anal. ($C_{20}H_{22}N_2O_2$): C, H, N.

2 was obtained similarly with a 60% yield: mp 101–102 °C, $[\alpha]^{25}_D$ −134.5° (*c* 0.5, CH_3OH); UV-vis (CH_3OH) λ (log ε) 240 (max) (4.35), 300 (min) (3.30), 333 nm (3.57); ^1H NMR ($CDCl_3$) δ 1.5–2.5 (*m*, 7 H, Pro), 3.40, 3.83 (AB, J = 12 Hz, 2 H, CH_2 Bzl), 6.75–8.50 (m, 15 H, Ar H). Anal. Calcd for $C_{25}H_{24}N_2O_2$: C, 78.10; H, 6.29; N, 7.28. Found: C, 78.21, H, 6.48; N, 7.53.

Racemic 1 was obtained similarly from racemic (*R,S*)-*N*-benzylproline, mp 92–93 °C.

Synthesis of 6a was conducted as described below. To 1 g (2.6 mmol) of **2** and 1.49 g (5.1 mmol) of $Ni(NO_3)_2 \cdot 6H_2O$ in 15 mL of MeOH was added 0.97 g (1.3×10^{-2} mol) of Gly in 15 mL of 1.2 N MeONa, the mixture was then stirred for 2 h at 50 °C under argon. The reaction was monitored by TLC (SiO_2, $CHCl_3$–acetone, 5:1). When the composition of the reaction mixture ceased to change, 50 mL of H_2O was added and the complex was extracted by $CHCl_3$ (4 × 25 mL), the solvent evaporated in vacuo, and the complex purified on silica gel (3 × 50 cm column) in $CHCl_3$–acetone (5:1) and on Sephadex LH-20 in C_6H_6–C_2H_5OH. The yield of **6a** was 1.25 g (2.5 mmol), 93%, mp 208–212 °C dec; UV-vis λ (log ε) 540 (sh) (2.27), 420 (3.45), 330 (3.67), 260 nm (sh) (4.35); [M] (CH_3OH) λ ([M]) 578 (10635), 546 (6906), 436 (4558), 365 nm (−9945); ^1H NMR ($CDCl_3$) δ 1.85–3.90 (m, 7 H, Pro), 3.5, 4.4 (AB, J = 12 Hz, 2 H, CH_2 Bzl), 3.68 (2 H, s, CH_2 Gly), 6.5–8.1 (14 H, m, Ar H). Anal. Calcd for $C_{27}H_{24}N_3O_3Ni \cdot H_2O$: C, 62.81; H, 5.27; N, 8.14. Found: C, 62.40; H, 4.91; N, 8.42.

6b was obtained according to a similar procedure: mp 131–139 °C; UV-vis λ (log ε) 575 (1.98), 365 (3.62), 255 nm (4.41); [M] (CH_3OH) λ ([M]) 578 (9467), 546 (2663), 436 (−4733), 365 (−5917). Anal. Calcd for $C_{27}H_{25}N_3O_3Cu$: C, 64.46; H, 5.01; N, 8.34. Found: C, 64.28; H, 4.79; N, 8.24.

Synthesis of 8a: A mixture of 3.22 g (10 mmol) of **1**, 5.82 g (20 mmol) of $Ni(NO_3)_2 \cdot 6H_2O$ in 60 mL of CH_3OH, and 3.75 g (50 mmol) of Gly in 45 mL of 1.33 N CH_3ONa was stirred at 40–50 °C under argon. The dense precipitate formed within an hour and was dissolved by the addition of 11 mL of H_2O. Then 4 mL of 1.33 N CH_3ONa was added. The reaction was monitored by TLC (SiO_2, $CHCl_3$–acetone (5:1)). When the composition of the reaction mixture ceased to change, 100 mL of 5% aqueous CH_3COOH was added and the complex was extracted by $CHCl_3$ (4 × 50 mL). The combined extracts were washed with 5% aqueous CH_3COOH and evaporated in vacuo. Then the residue was dissolved in 15 mL of acetone and 100 mL of hexane was added. The precipitated complex was filtered; 3.35 g (7.7 mmol) 77% of **8a** was isolated. Its spectral and other characteristics were identical with those previously obtained.[14]

8b was available from the previous work.[13b]

Diastereomeric complexes 4 and 5 were obtained from (*R,S*)-Ser similarly to complexes of Gly and separated by preparative chromatography on silica gel in a $CHCl_3$ (CH_2Cl_2)–acetone (5:1) system and purified on Sephadex LH-20 in a C_6H_6–C_2H_5OH (3:1) system.

5: mp 212–213 °C dec; UV-vis (CH_3OH) λ (log ε) 500 (1.89), 400 (3.38), 320 (3.73), 260 nm (4.19); [M] (CH_3OH) λ ([M]) 578 (7944), 546 (8143), 436 (11539), 365 nm (−30844); ^1H NMR ($CDCl_3$) δ 1.93 (1 H, m, δ-Pro), 2.13 (2 H, m, γ, δ-Pro), 2.23 (2 H, m, β-Pro), 2.45 (3 H, s, CH_3), 2.85 (1 H, m, γ-Pro), 3.60, 4.25 (2 H, AB, J = 12 Hz, CH_2 Bzl), 3.40 (1 H, m, α-H Pro), 3.75 (2 H, m, β-H Ser), 4.25 (1 H, m, α-H Ser), 6.75–8.12 (9 H, m, Ar H). Anal. Calcd for $C_{23}H_{25}N_3O_4Ni$: C, 59.20; H, 5.41; N, 9.01. Found: C, 59.50; H, 6.05; N, 8.74. Calcd 466; found 467.

4: mp 187 °C dec; UV-vis (CH_3OH) λ (log ε) 500 (1.89), 408 (3.35), 320 (3.35), 260 nm (3.94); [M] (CH_3OH) λ ([M]) 578 (8446), 546 (5446), 436 (−1092), 365 nm (−2912); ^1H NMR ($CDCl_3$) δ 1.75–3.62 (7 H, m, H Pro), 2.50 (3 H, s, CH_3), 3.75, 4.22 (2 H, AB, J = 10 Hz, CH_2 Bzl), 3.87 (2 H, m, β-Ser), 4.47 (1 H, m, α-H Ser), 7.00–8.30 (9 H, m, Ar H). Anal. Calcd for $C_{23}H_{25}N_3O_4Ni \cdot 2H_2O$: C, 55.0; H, 5.82; N, 8.36. Found: C, 55.53; H, 5.83; N, 8.16.

7 was obtained as above. The only difference was that the molar ratio (*S*)-valinol/**1** was 3:1; the yield was 90%: mp 98–100 °C dec; UV-vis (CH_3OH) λ (log ε) 410 (3.09), 540 nm (2.01); [M] (CH_3OH) λ ([M]) 578 (5948), 548 (−1342), 436 (−1342), 364 nm (−4025); ^1H NMR ($CDCl_3$) δ 1.9–3.2 (7 H, m, Pro), 1.05, 1.20 (6 H, dd, J = 6 Hz, 2 CH_3), 2.67 (1 H, m, α-H valinol), 2.85–3.27 (2 H, m, CH_2OH), 3.24 (1 H, m, β-H valinol), 3.42, 4.32 (2 H, AB, J = 15 Hz, CH_2 Bzl), 6.7–8.1 (9 H, m, Ar H). Anal. Calcd for $C_{25}H_{31}N_3O_2Ni \cdot H_2O$: C, 62.26; H, 6.89; N, 8.71. Found: C, 61.99; H, 6.40; N, 8.64. Calcd 482, found 485.

9: A solution of 0.15 g (0.34 mmol) of **8a** in 20 mL of CH_3OH was added to 10 g of MSA-I resin in BH_4^- form,[28] and the mixture was stirred for 12 h, after which the resin was filtered and the reaction products separated by preparative TLC on SiO_2 ($CHCl_3$–Me_2CO–C_2H_5OH, 11:1:1). Four fractions were isolated. The yield of the major fraction (second one) was 0.06 g (0.13 mmol) 37%: mp 138–140 °C dec; UV-vis (CH_3OH) λ (log ε) 460 (1.99), 400 (2.29), 285 nm (4.62); [M] (CH_3OH) λ ([M]) 578 (−3778), 436 (4568), 364 nm (1628); ^1H NMR

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($CDCl_3$) δ 1.99–3.10 (7 H, m, Pro), 1.65 (3 H, d, J = 6 Hz, CH_3), 2.91 (1 H, m, HCN), 3.42 (2 H, m, CH_2N), 3.24 (2 H, AB, J = 12 Hz, CH_2 Bzl), 6.8–8.0 (9 H, m, Ar H). Anal. Calcd for $C_{22}H_{25}N_3O_3Ni$: C, 60.30; H, 5.75; N, 9.58. Found: C, 60.10; H, 5.98; N, 9.16. Calcd 438, found 460.

Isolation of amino acids and recovery of 1 and 2 from the complexes were carried out according to the standard procedure described for **4**. The suspension of 1.9 g (4 mmol) of the complex in 50 mL of CH_3OH was slowly added to a vigorously stirred 0.5 N aqueous HCl solution (25 mL) at 50–60 °C. After the complex was decomposed (10–20 min), the pH of the solution was adjusted to 9.0 by adding a concentrated ammonia solution and **1** was extracted with $CHCl_3$, yield 96%. The amino acid was isolated from the aqueous layer on Dowex-50 (H^+ form) with a yield of 92%. The internal standard, (*S*)-Ala, was added sometime before the complex was decomposed to make a precise quantitative analysis possible. The complexes of aromatic **3** or β-hydroxyvaline were added to the HCl solution either directly as a reaction mixture (see below) or as a solution of the complex in THF (or in a THF–benzene mixture). The rate of decomposition of Cu(II) complexes was significantly greater than that of Ni(II) ones.

Equilibrium between 4 and 5. The initial concentration of the complexes was 0.43 M. The equilibrium concentration of CH_3O^- ions was calculated taking into account the initial concentration of CH_3O^- ion and acidity of **4** and **5**. The pH of Et_3N solutions in CH_3OH ws assessed spectrophotometrically by using **5** as an indicator.

Condensation of Aldehydes and Acetone with 6 and 8. (a) Synthesis of (*S*)-Ser and (*S*)-Thr was performed according to a typical procedure, described below for **8a**. To 1.8 g (4 mmol) of **8a** in 15 mL of CH_3OH were added 0.3 mL of H_2O, 2.2 mL of Et_3N, and 1.29 g (43 mmol) of paraformaldehyde. The reaction mixture was stirred for 5 h at 50 °C. The reaction was monitored by TLC of neutralized samples (SiO_2, $CHCl_3$–Me_2CO, 5:1). When the composition of the reaction mixture ceased to change, it was poured into the mixture of 100 mL of 5% aqueous CH_3COOH, 50 mL of $CHCl_3$, and 40 mL of C_2H_5OH. The aqueous layer was extracted with $CHCl_3$ (5 × 50 mL). The chloroform was evaporated in vacuo; the complex **4** was dissolved in CH_3OH and decomposed as described above.

The experiment for **6a** differed in addition to the reaction mixture of Et_3N·HCl in molar ratio to Et_3N of 1:2.

(b) Syntheses of (*R*)-Ser, (*R*)-β-hydroxyvaline, (*R*)-Thr, (*R*)-*threo*-β-(*o*-hydroxyphenyl)serine, and (*R*)-*threo*-3,4-(methylenedioxy)-β-phenylserine were performed according to procedures A or B.

Procedure A is illustrated by the synthesis of (*R*)-*threo*-β-phenylserine. To 1.5 g (3 mmol) of **6a** in 15 mL of 1.5 N CH_3ONa was added 1.0 g (94 mmol) of benzaldehyde in 2 mL of THF and the mixture was stirred for 20 min, then the reaction mixture was added dropwise to 100 mL of 5.5 N HCl during vigorous stirring at 50 °C, the stirring was continued until the disappearance of the complex, then the solution was evaporated in vacuo to 20–30 mL, and 5% aqueous NH_3 was added to pH 9. **2** was extracted with $CHCl_3$ (5 × 50 mL); the yield was 1.1 g (2.7 mmol), 90%. The amino acid was isolated from the aqueous layer with Dowex-50 (H^+ form). The yield of (*R*)-*threo*-β-phenylserine was 0.37 g (2 mmol), 68%: $[\alpha]^{25}_D$ +44.0° (*c* 0.6, 6 N HCl), ee 88% (lit.[29] for (*S*)-*threo*-β-phenylserine, $[\alpha]^{25}_D$ −50.0° (*c* 2, 6 N HCl)); ^1H NMR (D_2O–DCl) δ 4.50 (1 H, d, J = 4 Hz, β-H), 5.67 (1 H, d, J = 4 Hz, α-H), 7.70 (5 H, m, Ar H). Anal. ($C_9H_{11}NO_3$): C, H, N. The results for other (*R*)-**3** are summarized in Tables I and II.

Procedure B differs from procedure A in neutralization of the reaction mixture with aqueous CH_3COOH followed by extraction with $CHCl_3$. The chloroform layer was evaporated and the residue chromatographed. The procedure is illustrated by the synthesis of the enantiomerically pure (*R*)-β-hydroxyvaline. To 1 g (2 mmol) of **6a** in 3 mL of 1.33 N CH_3O-Na and 0.4 mL of H_2O after it was stirred for 15 min was added 15 mL (0.21 mol) of acetone. The reaction course was controlled by TLC (neutralized samples, SiO_2, THF–C_6H_6 (1:1)). When the reaction was completed, the reaction mixture was slowly added to the mixture of 100 mL of $CHCl_3$ and 200 mL of 5% aqueous CH_3COOH 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 on Toyopearl HW-60 resin (50 × 5 cm) in THF–C_6H_6 (2:7). The first fraction without evaporation was added dropwise to 100 mL of 0.5 N HCl during vigorous stirring at 40 °C. Then the organic layer was separated and the aqueous layer was evaporated in vacuo to a minimal volume; the pH of the aqueous layer was adjusted to 9 with a 5% solution of NH_3 and was extracted with chloroform (4 × 50 mL). The extracts were combined, washed with 5% aqueous Na_2CO_3, 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, $[\alpha]^{25}_D$ −11.1° (*c* 0.64, 6 N HCl) (lit.[30] $[\alpha]^{25}_D$ −11.2° (*c* 2, 5 N HCl)): ^1H NMR (D_2O–DCl) δ 1.60, 1.75 (6 H, 2 s, 2 Me) 4.25 (1 H, s, α-H). Anal. Calcd for $C_5H_{11}NO_3$: C, 45.10; 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%, $[\alpha]^{25}_D$ +47.9° (*c* 0.44, 6 N HCl), ee 95%.

(*R*)-*threo*-(3,4-Methylenedioxy)-β-phenylserine: yield 73%, mp 160 °C dec, $[\alpha]^{25}_D$ +29.0° (*c* 1.56, 6 N HCl); ^1H NMR (D_2O–DCl) δ 4.50 (1 H, d, J = 5 Hz, β-H), 5.47 (1 H, d, J = 5 Hz, α-H), 6.02 (2 H, s, CH_2), 7.00–7.27 (3 H, m, Ar H). Anal. Calcd for $C_{10}H_{11}NO_5$: 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 ^1H NMR spectra of racemic **1** recorded in $CDCl_3$ in the presence of 0.2 M $Eu(TFC)_3$, 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 ^1H 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; (±)-**1**, 96346-91-7; (S)-[2], 96293-17-3; **4**, 96293-18-4; **5**, 96346-93-9; **6α**, 96293-19-5; **6β**, 96293-20-8; **7**, 96293-21-9; **8α**, 95824-15-0; **8β**, 82704-29-8; **9**, 96293-22-0; $H_2NCH_2CO_2H$, 56-40-6; DL-$H_2NCH(CH_2OH)CO_2H$, 302-84-1; (*S*)-$H_2NCH(CHMe_2)CH_2OH$, 2026-48-4; C_6H_5CHO, 100-52-7; $(CH_3)_2CO$, 67-64-1; CH_3CHO, 75-07-0; $CH_2O_2C_6H_3CHO$, 120-57-0; CH_2O, 50-00-0; (*S*)-*N*-benzylproline, 31795-93-4; (*S*)-*N*-benzylproline hydrochloride, 92086-93-6; *o*-aminoacetophenone, 551-93-9; *o*-aminobenzophenone, 2835-77-0; DL-*N*-benzylproline, 60169-72-4; paraformaldehyde, 30525-89-4; (*S*)-serine, 56-45-1; (*S*)-allothreonine, 28954-12-3; (*R*)-*threo*-β-phenylserine, 6254-48-4; (*R*)-β-hydroxyvoline, 2280-48-0; (*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.

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

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