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# ASYMMETRIC SYNTHESIS OF β-SUBSTITUTED α-AMINO ACIDS VIA A CHIRAL $Ni^{II}$ COMPLEX OF DEHYDROALANINE

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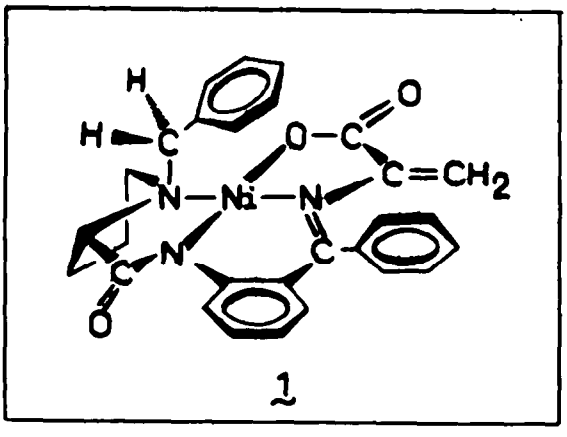
An efficient approach to the asymmetric synthesis of β-substituted (S)-alanines is described. The chiral $Ni^{II}$ complex of a Schiff base derived from (S)-o-*N*-(*N*-benzylprolyl)aminobenzophenone (BBP) and glycine was treated with formaldehyde and sodium methoxide to give a corresponding (R)-serine complex which, in turn, was converted to the chiral $Ni^{II}$ dehydroalanine complex. Michael type base catalyzed addition of nucleophiles (including MeOH, $Me_2NH$, $PhCH_2NH_2$, imidazole, PhSH, $PhCH_2SH$, malonic ester and benzylmagnesium chloride) produced a mixture of diastereoisomeric complexes with a 70-90% excess of S,S (or L,L) isomers over the S,R (or L,D) ones. The cleavage of pure diastereoisomers with aqueous HCl gave, in good yields, β-substituted (S) (or L)-alanines and regenerated the chiral auxiliary (BBP).

Non-proteinogenic amino acids constitute an important group of either biologically active compounds or their components. In particular, optically active non-proteinogenic β-substituted α-amino acids are constituents of some antibiotics and physiologically active peptides.[1]

The synthesis of proteinogenic (and some non-proteinogenic) β-substituted α-amino acids in nature is catalyzed by pyridoxal dependent enzymes.[2] The chain of events includes the intermediate formation of a Schiff base derived from dehydroalanine and pyridoxal on the active site of the enzyme.[2] The double bond of the dehydroalanine fragment is activated toward nucleophilic attack. Depending on the type of the nucleophile and the enzyme employed, different β-substituted α-amino acids could be obtained. Only a few reports have appeared concerning the biomimetic synthesis of this type of α-amino acids via achiral Schiff bases.[3]

In the present paper we report the asymmetric synthesis of β-substituted α-amino acids via a chiral $Ni^{II}$ complex 1 derived from a Schiff base of (S)-o-*N*-(N-benzylprolyl)aminobenzophenone (BBP) and dehydroalanine.

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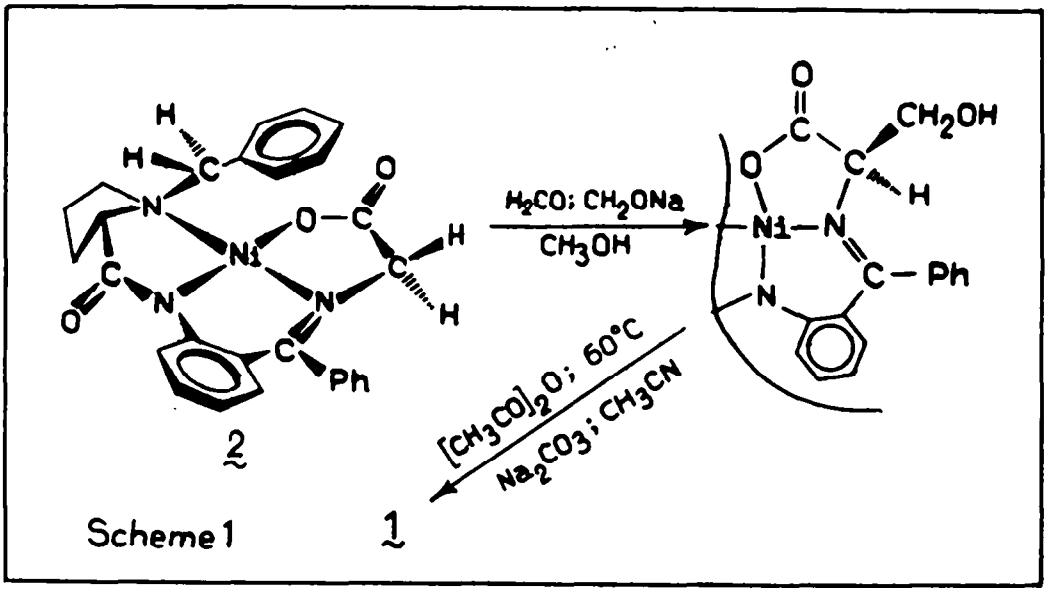
Earlier we developed a simple general method of α-amino acid asymmetric synthesis starting from the achiral Schiff base $Ni^{II}$ complex 2 of BBP and glycine.[4-6] Alkylation with alkyl halides,[5] Michael addition[6] and aldehyde condensation[4] results, respectively, in β-alkyl substituted (S)-α-amino acids,[5] β- and γ-substituted (S)-glutamic acids,[6a] (S)-prolines,[6b] and (R)-β-hydroxy-α-amino acids[4] in good chemical and optical yields. The method has several attractive features, including simplicity, a relatively low cost of reagents, a possibility of BBP recycling, and, thus, can be regarded as a viable supplement to the already existing methods of α-amino acid asymmetric synthesis.[7]

The scope of our method has now been broadened by including a new sequence of reactions, leading to optically active β-substituted α-amino acids, as an alternative to the recently published procedures for their synthesis.[8]

## Results and Discussion

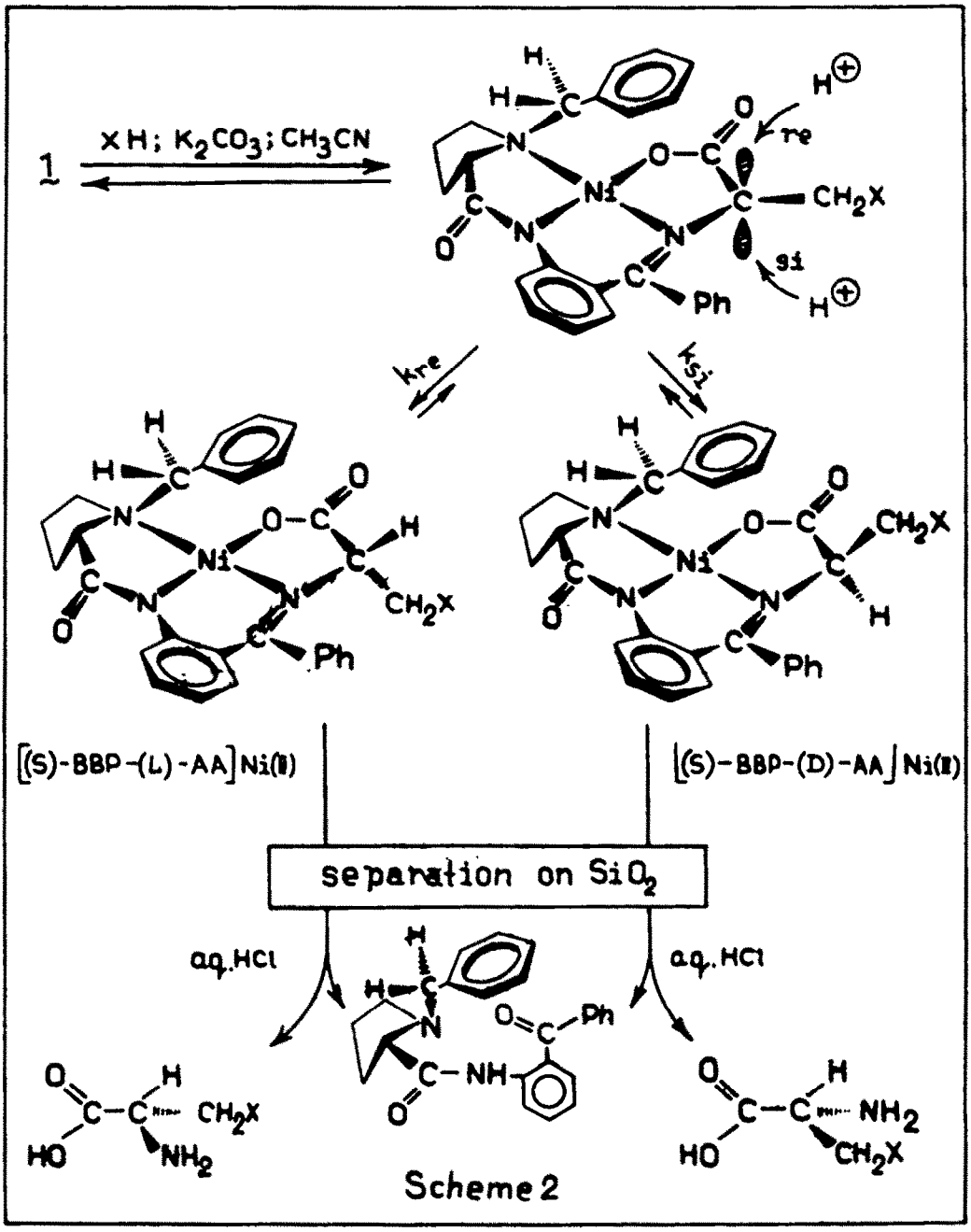
Synthesis of 1 was conducted according to Scheme 1




Chiral complex 2 was converted to the corresponding (R)-serine complex via MeONa catalyzed condensation with formaldehyde. The (R)-serine fragment of the resulting complex could be dehydrated by the action of $Ac_2O$ in MeCN using solid $Na_2CO_3$ as a catalyst. Following chromatographic purification on $SiO_2$, 1 is a stable red-colored compound that can be stored without deterioration for a significant period of time (Scheme 2).

Methanol, benzyl amine, dimethyl amine, thiophenol, α-mercapto toluene, malonic ester, benzylmagnesium chloride and imidazole, added to complex 1, yielded a mixture of the corresponding diastereoisomeric complexes, as shown in Scheme 2, whereas phenol and halide anions were inert in the reaction. The course of the reaction was monitored by TLC on $SiO_2$. If the epimerization of the obtained diastereoisomers was slow under the experimental conditions, their initial ratio reflected the relative preference of re or si-attack by a proton on the intermediate carbanion formed after the nucleophilic addition to 1 (see Scheme 2). As was shown earlier,[5c] the transition state of the deuteration (or protonation) reaction of similar carbanions is a mixture of "steric approach" and "product development" control types. If the side chain of the α-amino acid is bulky, the deuteration gives an excess of the (S,S)-diastereoisomer containing 2-[$^2$H]-amino acid because the isomer is thermodynamically favorable and a greater share of product development control is realized in the transition state.[4-6] On the other hand, if the side chain is small and the thermodynamic effects of the final state are no longer important, the product of the si-side deuteration, (S,R)-diastereoisomer, is predominant in the solution because the re-side of the carbanion is shielded by the phenyl group of the n-benzyl substituent (see Scheme 2). These mutually compensating effects are probably responsible for the relatively low diastereoselectivity in the case of kinetically controlled addition of benzyl amine to 1 (Table 1).

As expected,[4-6] the equilibration of the resulting complexes produced a large excess of (S,S) or (L,L) isomers over the (R,S) or (L,D) ones in the solution (Table 1). Diastereoisomeric complexes were separated by flash chromatography on $SiO_2$. The absolute configuration of the α-amino acid fragment was established by comparing the ORD curves of the diastereoisomers with those of known isomers[8] (Fig. 1). The sign of the Cotton effect in the 500-700 nm region was always positive for (S) (or L) α-amino acids and negative for their enantiomers. This general trend was not influenced by the structure of the α-amino acid side chain (Fig. 1).




Scheme 2

Table 1. Asymmetric synthesis of β-substituted L-alanines

| Nucleophile | Solvent | Yield of Diastereoisomers[a],% S,R [L,D] | S,S [L,L] | (S)- (or L) Amino acid | Chemical yield,%[b] | Enantiomeric purity,% |
|---|---|---|---|---|---|---|
| $PhCH_2SH$ | MeCN | 3 | 90 | 2-Amino-3-(benzylthio)propanoic acid | 90 | 98[c] |
| PhSH | MeCN | 4.8 | 93 | 2-Amino-3-(phenylthio)propanoic acid | 92 | 98[d] |
| $CH_2(COOEt)_2$ | MeCN | 8.1 | 90 | Glutamic acid | 80 | 80[d] |
| $PhCH_2NH_2$ | MeCN | 5(33[e]) | 90(66[e]) | 2-Amino-3-benzylaminopropanoic acid | 75 | >90[c] |
| Imidazole | MeCN | 5 | 90 | 2-Amino-3-(imidazol-1-yl)propanoic acid | 85 | >90[c] |
| $Me_2NH$ | MeCN | 5 | 85 | 2-Amino-3-dimethylaminopropanoic acid | 93[a] | 70.4[c] |
| $PhCH_2MgCl$ | THF | 55[g] | | 2-Amino-4-phenylbutanoic acid | 82 | 50[d] |
| MeOH | MeOH | 2 | 90 | 2-Amino-3-methoxypropanoic acid | 90 | 90[d] |

[a] Based on complex 1. [b] Based on pure diastereoisomer. [c] Determined by $^1H$ n.m.r., using a chiral shift reagent.[12] [d] G.l.c. analysis data.[11] [e] Kinetically controlled ratio of isomers. [f] Recovered from the reaction mixture. [g] Yield of the mixture of diastereoisomers based on 1.

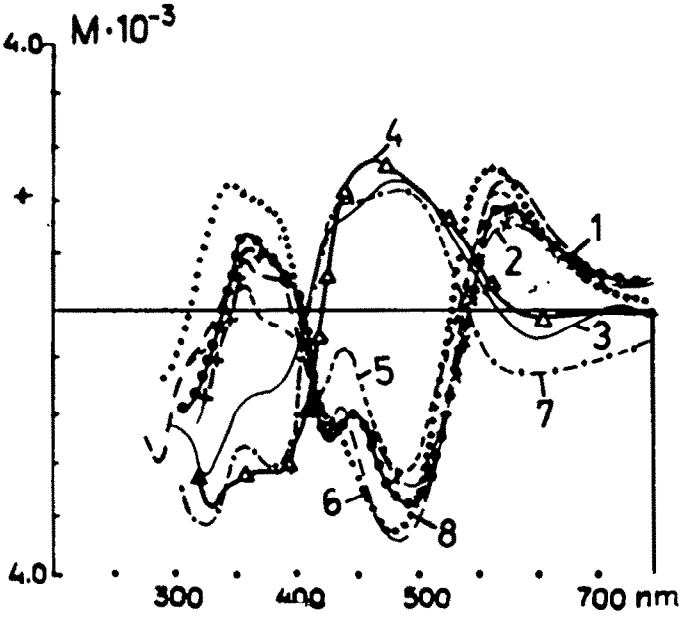



Figure 1. ORD curves of $Ni^{II}$ complexes derived from (S)-O-*N*-(*N*-benzylpropyl)-aminobenzophenone and β-substituted α-amino acids in $CH_3OH$ at 25°C

1 L-2-amino-3-(benzylthio)propanoic acid
2 L-2-amino-3-(phenylthio)propanoic acid
3 D-2-amino-3-(phenylthio)propanoic acid
4 (R)-Serine
5 (S)-2-amino-3-methoxypropanoic acid
6 (S)-2-amino-3-(N-acetyl, benzylamino)propanoic acid
7 (R)-2-amino-3-(N-acetyl, benzylamino)propanoic acid
8 (S)-2-amino-3-(imidazol-1-yl)propanoic acid

Decomposition of diastereomerically pure complexes with aqueous HCl furnished β-substituted (S) or (L) alanines and regenerated the original BBP.

Unfortunately, the mixture of diastereoisomeric complexes, obtained from amines and complex 1, is highly unstable and decomposes during the chromatographic procedure into compound 1 and the initial amine. In order to achieve the chromatographic separation, the β-amino group in the complex should be protected or protonated. Crystallization of isomers could also be used, as illustrated by the procedure for separating the isomeric complexes derived from 2-amino-3-(imidazol-1-yl)propanoic acid. If the final optical purity of amino acids, equal to 70-98%, is considered satisfactory for a particular purpose, the reaction mixture can be decomposed without the preliminary isomer separation.

Thus, complex 1 constitutes a potentially useful initial compound that can be successfully employed for the synthesis of a variety of the β-substituted (S)- (or L)- α-amino acids in high optical and chemical yields. It is noteworthy that this procedure furnishes selectively β-group protected, β-substituted α-amino acids in a single step, as illustrated by the benzylamine, thiol and methanol addition reactions.

## Experimental

General. Reagents were purchased from Reakhim (USSR), with the exception of o-aminobenzophenone and Silica Gel 60 $F_{254}$ purchased from Merck, Sephadex LH-20 purchased from Pharmacia and Silicagel L 40-/100 obtained from Chemapol. Reagents and solvents were purified in the usual way. Sodium methoxide was prepared by dissolving metallic sodium in methanol under an argon atmosphere.

Spectra were recorded with the following instruments: UV-visible Specord M-40. $^1$H NMR: Bruker WP-200 (200 MHz) and Tesla 467 A. HMDS was used as an internal reference in organic solvents, and HMDS sealed in a glass capillary was employed for water solutions. ORD: Jasco ORD/UV-5, specific rotations were measured on a Perkin-Elmer 241 polarimeter.

(S)-o-*N*-(*N*-Benzylprolyl)aminobenzophenone (BBP) and the $Ni^{II}$ complex of the Schiff base derived from BBP and glycine were obtained as described earlier.[4]

$Ni^{II}$ complex (1) of the Schiff base derived from BBP and dehydroalanine. To a 10 mL MeCN solution of a mixture of [(S)-BBP-(*R*)-Ser] $Ni^{II}$ and [(S)-BBP-(S)-Ser] $Ni^{II}$ [5.07 g, 9.6 mmol., (S,R) to (S,S) ratio 95:5], obtained according to ref. 4, was added $Na_2CO_3$ (4.9 g, 46 mmol) and acetic anhydride (7.5 g, 74.4 mmol) under stirring and Ar atmosphere. The stirring was continued at 60°C until conversion of the initial complex to compound 1 was complete (5-8 h), as monitored by TLC ($SiO_2$, $CHCl_3$: EtOAc, 3:1). The mixture was cooled, filtered, the precipitate was washed with $CHCl_3$, the filtrate and washings were combined and evaporated under reduced pressure, the residue was subjected to flash chromatography ($SiO_2$, 150x5 cm, $CHCl_3$: EtOAc, 3:1). Fractions containing complex 1 were combined and evaporated to give 4.6 g (92%) of complex 1.

1: UV-vis ($CH_3OH$) λ (log ε) 546 (2.85), 440 (3.55), 278 (4.29), 235 (4.48 sh); [M] ($CH_3OH$, 25°C) λ ([M]) 578 (15000), 546 (-15400), 436 (7600), 365 (-1300); $^1$H NMR ($CDCl_3$) δ 1.9-3.45 (6H, m, β, γ and δ-H Pro), 3.38, 4.3 (2H, AB, $J$ = 12.5 Hz, $CH_2Ph$), 3.52 (1H, m, α-H Pro), 4.1 (1H, s) and 5.8 (1H, s, $H_2C$=), 6.6-8.15 (14H, m, ArH). Anal. Calcd for $C_{28}H_{25}O_3N_3Ni$: C, 65.92; H, 4.90; N, 8.24. Found: C, 65.61; H, 4.76; N, 7.95.

L-2-Amino-3-(benzylthio)propanoic acid. To a solution of 2 g (3.9 mmol) of complex 1 in 6 mL of MeCN (or DMF) was added 7.8 mmol of $K_2CO_3$ (or $Na_2CO_3$) and 4.12 mmol of α-mercapto toluene with stirring under Ar at 50-55°C. After the reaction had stopped (no change in the ratio of diastereoisomers was detected by TLC) the mixture was filtered, the filtrate and $CHCl_3$ washings were combined and evaporated. The residue was subjected to chromatography on $SiO_2$ (3.5 x 30 cm, $CHCl_3$:acetone, 5:1). Two major fractions were obtained. The first fraction (2.23 g, 90%) containing [(S)-BBP-L-Cys((S-Bzl)] $Ni^{II}$ was further purified on Sephadex LH-20 (PhH:$C_2H_5OH$, 3:1). UV-vis ($CH_3OH$) λ (log ε) 536 (2.34), 422 (3.49), 340 (3.65), 264 (4.23); [M] ($CH_3OH$, 25°C) λ ([M]) 578 (14500), 546 (460), 436 (-17200), 365 (11000); $^1$H NMR ($CDCl_3$) δ 1.8-3.68 (6H, m, β, γ, δ-H Pro), 3.4 (1H, m, α-H Pro), 2.3, 2.6 (1H, ABX, β-H Cys), 3.52, 4.35 (2H,

AB, $J$ = 12.5 Hz, N-$CH_2$Ph), 3.7, 3.9 (2H, AB, $J$ = 13 Hz, S-$CH_2$Ph), 4.1 (1H, m, α-H Cys), 6.42-8.3 (19H, m, Ar-H). Anal. Calcd for $C_{35}H_{33}O_3N_3Ni$: C, 66.26; H, 5.24; N, 6.62. Found: C, 66.8; H, 5.20; N, 6.62.

The second fraction (0.07 g, 2.8%) contained [(S)-BBP-D-Cys (S-Bzl)] $Ni^{II}$. UV-vis ($CH_3OH$) λ (log ε) 533 (2.22), 422 (3.48), 340 (3.63), 264 (4.2); [M] ($CH_3OH$, 25°C) λ ([M]) 546 (6700), 436 (11100), 365 (-23000); $^1H$ NMR ($CDCl_3$) δ 1.5-2.6 (6H, m, γ, β, δ-H Pro), 2.5, 2.72 (2H, ABX, $J_{AB}$ = 13 Hz, $J_{AX}$ = 3 Hz, $J_{BX}$ = 6 Hz,β-H Cys), 3.5 (1H, m, α-H Pro), 3.7, 3.82 (2H, AB, $J$ = 13 Hz, -$SCH_2$Ph), 4.0, 4.95 (2H, AB, $J$ = 13 Hz, -$CH_2$Ph), 4.07 (1H, m, α-H Cys), 6.5-8.7 (19H, m, Ar-H). Anal. Calcd for $C_{35}H_{33}O_3N_3Ni$: C, 66.26; H, 5.24; N, 6.62. Found: C, 65.89; H, 5.06; N, 6.28.

The fractions were decomposed with aqueous HCl, and the amino acid obtained and BBP recovered using EDTA, as earlier described for the water insoluble α-amino acids.[5b]

L-2-Amino-3-(benzylthio)propanoic acid was obtained from the first fraction (0.67 g, 90%). $[\alpha]^{25}_D$ -18.6° (*c* 1.0, 6 N HCl) (lit.[9] $[\alpha]^{25}_D$ -19.5° (*c* 10, 5 N HCl)).

D-2-Amino-3-(benzylthio)-propanoic acid was obtained from the second fraction. $[\alpha]^{25}_D$ +19.2° (*c* 1.4, 5 N HCl) (lit.[9] $[\alpha]^{25}_D$ +19.3° (*c* 10, 5 N HCl)).

L-2-Amino-3-(phenylthio)propanoic acid. Condensation of complex 1 (2 g) and thiophenol, as well as separation of diastereoisomers, were conducted similarly to the synthesis described above. Decomposition of the first major fraction (2.25 g, 93%) gave L-2-amino-3-(phenylthio)propanoic acid in a yield of 92% (0.71 g). $[\alpha]^{25}_D$ +47.6° (*c* 10, 5 N HCl) (lit.[10] $[\alpha]^{25}_D$ +70.2° (*c* 10, 1 N, HCl)).

According to the GLC analysis data[11], the α-amino acid was enantiomerically pure. D-2-Amino-3-(phenylthio)propanoic acid was obtained from the second major fraction (4.75%) in a yield of 90%. $[\alpha]^{25}_D$ -47.8° (*c* 9.2, 6 N HCl) (lit.[10] $[\alpha]^{25}_D$ -70.5° (*c* 10, 1 N HCl)).

(S)-Glutamic acid. Condensation of complex 1 (2 g) with malonic ester (1.1 g) was conducted as described above. Separation of the diastereoisomers on $SiO_2$ (5 x 30 cm, $CHCl_3$:acetone, 3:1) furnished two major fractions: 0.16 g (0.23 mmol) and 1.78 g (2.6 mmol) (in the order of their emergence from the column). The fractions were decomposed as described earlier.[4-6] After the BBP had been recovered the water solution was evaporated, 6N HCl (10 mL) was added to the residue, and the resulting mixture was boiled for 1 h. The solvent was removed under reduced pressure. The residue was subjected to cation exchange chromatography on Dowex 50 x 8 resin. (R)-Glu was obtained from the first fraction in an enantiomeric excess (ee) of more than 80%, according to GLC[11] (S)-Glu (ee > 80%) was recovered from the second major fraction in a yield of 80% (0.41 g).

(S)-2-Amino-3-(benzylamino)propanoic acid. Condensation of complex 1 (2 g) with benzylamine (0.9 mL, 8.2 mmol) was conducted as described above. After the ratio of the diastereoisomers had ceased changing (the epimerization reaction could be accelerated if solid KOH was added to the reaction mixture), acetic anhydride (2 mL) was added to the reaction mixture under stirring at 50-55°C, and the course of the acylation reaction was monitored by TLC. After the completion of the reaction $CHCl_3$ (5 mL) was added to the mixture, which was then filtered. The filtrate and $CHCl_3$ washings were combined and evaporated *in vacuo*. The residue was flash chromatographed on $SiO_2$ ($CHCl_3$:acetone, 3:1). Four orange colored bands separated. According to their $^1H$ NMR spectra, C, H, N analysis and ORD curves, the second fraction (in the order of emergence from the column) was found to be (S)-serine containing complex (0.7 g), the third (0.38 g, 0.6 mmol) and the fourth (1.90 g, 2.9 mmol) were the complexes derived from (R)-2-amino-3-(N-acetyl)benzylaminopropanoic acid and (S)-2-amino-3-(N-acetyl)benzylaminopropanoic acid, respectively. The first fraction (0.2 g) was not identified. The third and the fourth fractions were decomposed in the usual way,[4-6] the α-amino acids were further hydrolyzed with boiling 6N HCl (2 h) and desalted with Dowex 50 x 8, using 15% $NH_3$ in a 10% aqueous EtOH solution. (S)-2-amino-3-(benzylamino)propanoic acid (0.4 g, 75%) was recrystallized from EtOH. $[\alpha]^{25}_D$ +26.8° (*c* 10, 6 N HCl); $^1H$ NMR ($D_2O$) δ 3.61, 3.9 (2H, ABX, $J_{AB}$ = 12 Hz, $J_{AX}$ = 7.5 Hz, $J_{BX}$ = 6.25 Hz, β-$CH_2$), 4.62 (1H, m, ABX, $J_{AX}$ = 7.5 Hz, $J_{BX}$ = 6.25 Hz, α-H), 7.41-7.58 (5H, m, ArH).

(R)-2-amino-3-(benzylamino)propanoic acid: $[\alpha]^{25}_D$ -23° (*c* 10, 6 N HCl). Same NMR spectrum and as (S)-2-amino-3-(benzylamino)propanoic acid.

(S)-2-Amino-3-(imidazol-1-yl)propanoic acid. Condensation of complex 1 (2 g) with imidazole (0.638 g, 9.2 mmol) was conducted as described above. After 5 h the reaction mixture was filtered, the filtrate and washings were evaporated under reduced pressure, and the residue recrystallized from PhH:acetone (6:1).

Diastereomerically pure complex of (S)-2-amino-3-(imidazol-1-yl)propanoic acid (2.02 g, 3.5 mmol, 90%) was filtered off and dried *in vacuo*. Its structure was established by the usual chemical and physical methods. The complex was decomposed with aqueous HCl, and the α-amino acid obtained via the routine exchange technique.[4-6] (S)-2-Amino-3-(imidazol-1-yl)propanoic acid was obtained in a yield of 85% (0.46 g). $[\alpha]^{25}_D$ -2.2° (*c* 10, 6 N HCl); $^1$H NMR (DCl) δ 5.71 (1H, t, *J* = 5.2 Hz, α-H), 6.08 (2H, d, *J* = 5.2 Hz, β-H), 8.22 (1H, s, Im-H), 8.4 (1H, s, Im-H), 8.97 (1H, s, Im-H). Anal. Calcd for $C_6H_9N_3O_2 \cdot 1.5\ H_2O$: C, 39.56; H, 6.64; N, 23.06. Found: C, 39.41; H, 6.42; N, 21.86.

(S)-2-Amino-3-(dimethylamino)propanoic acid. Condensation of complex 1 (2 g) with dimethylamine hydrochloride (0.64 g, 7.8 mmol) was conducted as described above. A solution of pure dimethylamine in MeCN could also be used. The reaction mixture was treated in the usual way, and, after solvent removal *in vacuo*, the residue was dissolved in a minimum amount of a mixture of $CHCl_3$: PhH: $Et_2O$: THF: HOAc (20:19:16:10:5). The solution was placed at the top of a short column filled with $SiO_2$ (3 x 6 cm) and eluted with the same solvent mixture until the side reaction products and unreacted complex 1 were removed. The mixture of diastereoisomeric complexes was finally washed from the column with EtOH. The washing were combined and evaporated under reduced pressure to a 10 mL volume. Decomposition of the mixture of diastereoisomers, recovery of BBP and the α-amino acid were conducted in the usual way.[4-6] Enriched in the (S)-enantiomer (e.e. 70%, according to $^1$H NMR spectroscopy using water soluble Na[Eu(R)-pdta] shift reagent[12]), 2-amino-3-(dimethylamino)propanoic acid was obtained in a chemical yield of 93% (0.48 g, 3.6 mmol). $[\alpha]^{25}_D$ +22.0° (*c* 5, 6 N HCl) {after crystallization from aqueous $C_2H_5OH$ $[\alpha]^{25}_D$+34° (*c* 8, 6 N HCl)}; $^1$H NMR ($D_2O$) δ 2.53 (6H, s, $Me_2N$), 2.78-2.98 (2H, m, β-H), 3.5 (1H, ABX, $J_{AX} = J_{BX}$ = 5.8 Hz, α-H).

(S)-2-Amino-4-phenylbutanoic acid. To complex 1 (1 g, 1.9 mmol) in an-hydrous THF (10 mL) at -30°C under Ar was added a solution of phenylmagnesium chloride (3.9 g, 26 mmol). The reaction mixture was stirred at -30°C for 4-5 minutes, then the reaction was quenched with 20 mL of aqueous HOAc (20 mL, 0.92 mL HOAc, 7.8 mmol). The stirring was continued for 2 minutes, then $CHCl_3$ (20 mL) was added, the organic layer was separated, washed with $H_2O$ (2 x 10 mL) and evaporated *in vacuo*. The residue was chromatographed on $SiO_2$ (5 x 24 cm, $CHCl_3$ acetone, 3:1) The first major orange band consisted of a mixture of the diastereoisomeric complexes of 2-amino-4-(phenyl)butanoic acid (0.6 g, 0.9 mmol, 50%). According to NMR spectroscopy and ORD curves, the mixture contained an excess of the S-enantiomer. BBP was recovered and the α-amino acid (0.13 g, 0.74 mmol, 82%) was obtained as described earlier for the water insoluble α-amino acids.[5b] (S)-2-amino-4-(phenyl)-butanoic acid (50% enantiomeric purity according to GLC[11]) was recrystallized from EtOH:$H_2O$, 1:1. $[\alpha]^{25}_D$ +23° (*c* 11, 6 N HCl) (lit.[13] $[\alpha]^{25}_D$ +43° (*c* 20, 1 N HCl)); $^1$H NMR (DCl) δ 2.4 (2H, $A_2XY_2$, $J_{AX}$ = 6 Hz, $J_{AY}$ = 7 Hz, β-H), 3.09 (2H, $ABY_2$, $J_{AY}$ = 7 Hz, $J_{AB}$ = 12 Hz, γ-H), 4.1 (1H, t, *J* = 6 Hz, α-H). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.3; N, 7.8. Found: C, 66.93; H, 7.10; N, 8.04.

(S)-2-Amino-3-methoxypropanoic acid. To complex 1 (2 g) under Ar was added 0.2 N solution of NaOMe in MeOH (20 mL) at 50°C. After the reaction had been completed (TLC) the reaction mixture was neutralized with a calculated amount of aqueous HOAc, the solution was then evaporated *in vacuo*, the residue was washed with cold water and chromatographed on $SiO_2$ (2.5 x 38 cm, PhH:acetone, 1:1). The major fraction (1.9 g, 3.5 mmol, 90%) contained (S)-2-amino-3-(methoxy)-propanoic acid, according to $^1$H NMR and the ORD curve. Decomposition of the complex, recovery of BBP and α-amino acid were conducted in the usual way.[4-6] 2-Amino-3-(methoxy)propanoic acid (0.37 g, 3.15 mmol, 90%, e.e. > 90%) was recrystallized from aqueous EtOH. $[\alpha]^{25}_D$ +13° (*c* 10, 6 N HCl); $^1$H NMR ($D_2O$) δ 3.5 (3H, s, MeO), 4.0 (2H, m, β-H), 4.42 (1H, t, α-H). Anal. Calcd for $C_4H_9NO_3$: C, 40.3; H, 7.61; N, 11.75. Found: C, 39.98; H, 7.53; N, 11.96.

## References

(a) H. Yoshioka, T. Aoki, H. Goko, K. Nakatsu, T. Noda, H. Sakakibara, T. Take, A. Nagata, J. Abe, T. Wakamiya, T. Shiba and T. Kaneko, *Tetrahedron Lett.*, 1971, 2043; (b) T. Takita, Y. Muraoka, T. Yoshioka, A. Fuji, K. Naeda and H. Umezawa, *J. Antibiot.*, 1972, **25**, 755; (c) H-D Jakubke and H. Jeschkeit, "Aminosäuren, Peptide, Proteine", Akademie-Verlag, Berlin, 1982.

2 L. Davis and D.E. Metzler, "The Enzymes", ed. P.D. Boyer, New York, Acad. Press, 3rd Ed., 1972, vol. 7, p. 33.

3 (a) W.J. Greenlee, D. Taub, and A.A. Patchett, *Tetrahedron Lett.*, 1978, 3999; (b) G. Wulff and H. Böhnke, *Angew. Chem. Int. Ed. Engl.*, 1984, **23**, 380; (c) G. Wulff and H. Bohnke, *Angew. Chem. Int. Ed. Engl.*, 1986, **25**, 90.

4 Yu. N. Belokon', A.G. Bulychev, S.V. Vitt, Yu. T. Struchkov, A.S. Batsanov, T.V. Timofeeva, V.A. Tsyryapkin, M.G. Ryzhov, L.A. Lysova, V.I. Bakhmutov and V.M. Belikov, *J. Am. Chem. Soc.*, 1985, **107**, 4252.

5 (a) Yu.N. Belokon', N.I. Chernoglazova, N.S. Garbalinskaya, M.B. Saporovskaya, K.A. Kochetkov and V.M. Belikov, Izv. Akad. *Nauk SSSR, Ser. Khim.*, 1986, 2340; (b) Yu.N. Belokon', V.I. Bakhmutov, N.I. Chernoglazova, K.A. Kochetkov, S.V. Vitt, N.S. Garbalinskaya and V.M. Belikov, *J. Chem. Soc., Perkin Trans. I*, 1988, 305; (c) N.I. Chernoglazova, Thesis Institute of Organoelement Compounds, Moscow, (1987).

6 (a) Yu.N. Belokon', A.G. Bulychev, M.G. Ryzhov, S.V. Vitt, A.S. Batsanov, Yu.T. Struchkov, V.I. Bakhmutov and V.M. Belikov, *J. Chem. Soc., Perkin Trans. I*, 1986, 1865; (b) Yu.N. Belokon', A.G. Bulychev, V.A. Pavlov, E.B. Fedotova, V.A. Tsyryapkin, V.I. Bakhmutov and V.M. Belikov, *J. Chem. Soc., Perkin Trans. I*, submitted for publication.

7 (a) U. Schöllkopf, *Top. Curr. Chem.*, 1983, **109**, 65; (b) U. Schöllkopf, *Pure Appl. Chem.*, 1983, **55**, 1799; (c) U. Schöllkopf, *Chimica Scripta*, 1985, **25**, 105; (d) D. Seebach, Jurasti, D. Miller, C. Schickli and T. Weber, *Helv. Chim. Acta*, 1987, **70**, 237; (e) P.J. Sinclair, D. Zhai, J. Reibenspies and R.M. Williams, *J. Am. Chem. Soc.*, 1986, **108**, 1103; (f) D.A. Evans and A.E. Weber, *J. Am. Chem. Soc.*, 1986, **108**, 6757; (g) D.A. Evans, J.A. Ellman and R.L. Dorow, *Tetrahedron Lett.*, 1987, **28**, 1123; (h) W. Oppolzer, R. Pedrosa and R. Moretti, *Tetrahedron Lett.*, 1986, **27**, 831; (i) W. Oppolzer and R. Moretti, *Helv. Chim. Acta*, 1986, **69**, 8.

8 (a) J.E. Baldwin, R.M. Adlington, D.J. Birch, *J. Chem. Soc., Chem. Commun.*, 1985, 256; (b) L.D. Arnold, Th.H. Kalantar and J.C. Vederas, *J. Am. Chem. Soc.*, 1985, **107**, 7105; (c) J.E. Baldwin, R.M. Adlington, D.J. Birch, J.A. Crawford, J.B. Sweeney, *J. Chem. Soc., Chem. Commun.*, 1986, 1339; (d) J.E. Baldwin, R.M. Adlington, N.G. Robinson, *J. Chem. Soc., Chem. Commun.*, 1987, 153; (e) L.D. Arnold, J.C.G. Drover, J.C. Vederas, *J. Am. Chem. Soc.*, 1987, **109**, 4649.

9 J.P. Greenstein, S.M. Birnbaum, M.C. Otey, *J. Biol. Chem.*, 1953, **204**, 307.

10 H.T. Clarke, J.M. Inonye, *J. Biol. Chem.*, 1931, **94**, 541.

11 S. Nakaparskin, P. Birrell, E. Gil-Av and I. Ogo, *J. Chromatogr. Sci.*, 1972, **8**, 117.

12 K. Kabuto and Y. Sasaki, *J. Chem. Soc., Chem. Commun.*, 1984, 316.

13 H.N. Weller, E.M. Gordon, *J. Org. Chem.*, 1982, **470**, 4160.