Organic Chemistry

Asymmetric synthesis of (*S*)- and (*R*)-α-methylserine based on the chiral recyclable reagent (*S*)-*N*-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide

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Both enantiomers of α-methylserine were synthesized with the use of Ni^{II} complexes based on the chiral recyclable reagent (*S*)-*N*-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide. Intermediate diastereomeric complexes were separated by crystallization of their *O*-acetyl derivatives.

Key words: asymmetric synthesis, chiral reagent, (*S*)-2-methylserine, (*R*)-2-methylserine, Ni^{II} complexes.

Protein amino acids, which are of paramount importance and in great demand, are generally prepared by microbiological methods.[1] Presently, there is also a need for non-protein amino acids because enantiomerically pure α,α-disubstituted amino acids are constituents of peptide antibiotics[2] and are of great importance in contemporary pharmacology as potential amino acid decarboxylase inhibitors,[3] neuroendogenic regulators of hormonal systems,[4] and medicines for the treatment of epilepsy, Altzheimer's and Parkinson's diseases, schizophrenia, ischemia, and Huntington's fever.[5]

We have developed (and successfully used over 15 years) a method for the synthesis of protein, non-protein, and isotopically labeled amino acids with the use of a chiral recyclable reagent based on proline, *viz.*, (*S*)-*N*-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide (BPB). In Ni^{II} complexes of Schiff's bases of glycine and alanine with BPB (Ni-BPB-Gly and Ni-BPB-Ala, respectively), the C_α atom of the amino acid residue possesses rather high C—H-acidity[6] due to which these complexes readily react with different alkyl halides and add substrates containing the C=O and activated C=C bonds. The starting compounds, *viz.*, BPB, Ni-BPB-Gly, and Ni-BPB-Ala, are available in amounts of up to 1 kg.[7]

A concrete application of this procedure is the synthesis of α-methylserine (α-MeSer),[8] which is an important non-protein amino acid (peptide χ-spacer).[9] It should be noted that the possibility of the synthesis of both enantiomers of the amino acid in one experiment or with the use of a single chiral inducing agent was taken into account when developing the method proposed.

Results and Discussion

We used the Ni-BPB-(*S*,*R*)-Ala complex (**1**) as the starting compound and performed its condensation with formaldehyde (Scheme 1). The stereoselectivity of the

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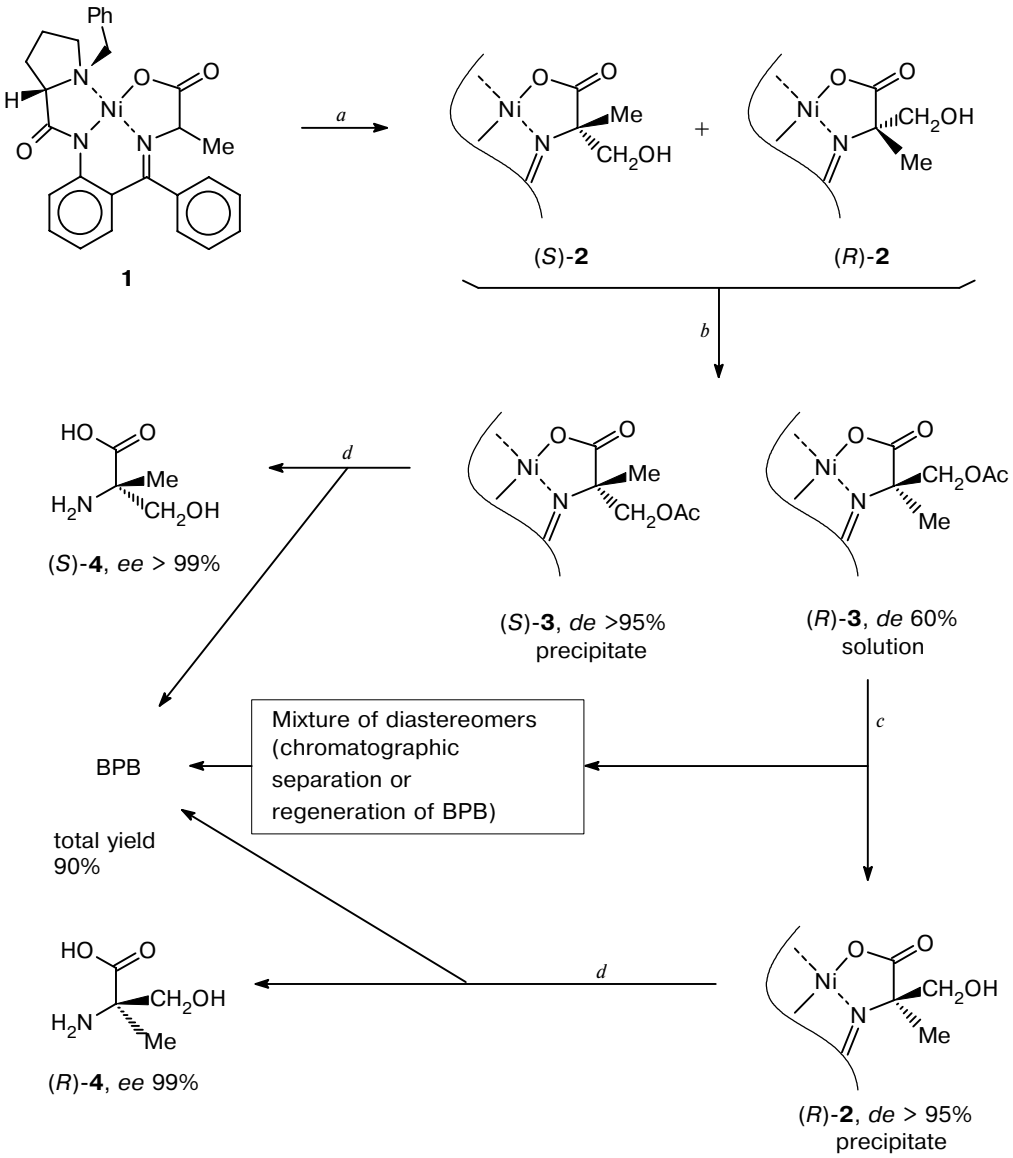
Scheme 1



Reagents and conditions: *a*, CH_2O/KOH, MeOH; *b*, 1) Ac_2O, MeCN, 75 °C, 2) Crystallization from MeOH; *c*, 1) MeONa, 2) Crystallization from an MeOH + H_2O mixture; *d*, HCl—MeOH

reaction carried out under conditions of both kinetic and thermodynamic control was at most 35%.[8] We failed to improve the stereoselectivity by changing the structure of the chiral reagent due apparently to a small difference in the size of the Me and CH_2OH groups. Previously, both enantiomers of α-MeSer have been obtained using chromatographic separation of the diastereomeric complexes Ni-BPB-(*S*)-α-MeSer ((*S*)-**2**) and Ni-BPB-(*R*)-α-MeSer ((*R*)-**2**).[8] Attempts to crystallize the reaction mixture made it possible to isolate (in poorly reproducible experiments) only the prevailing diastereomeric complex (*S*)-**2** in the pure form. Thereafter attempts to isolate any diastereomerically pure complex from the mixture (containing the diastereomeric complexes in a ratio of ~1 : 1) failed.

In the course of these attempts, we found the following empirical regularity: the diastereomeric complexes are inseparable by crystallization if the (*S*)-**2**/(*R*)-**2** ratio is in the range of 1.25—0.8.

In the present study, we separated the diastereomeric complexes by crystallization of the *O*-acetyl derivatives (*S*)-**3** and (*R*)-**3** prepared by acylation of the initial mixture of (*S*)-**2** and (*R*)-**2** in the ratio of 2 : 1. In this case, the major isomer (*S*)-**3** was isolated much more completely. The ratio between the diastereomers (*S*)-**3** and (*R*)-**3** that remained in the mother liquor was 1 : 4,

unlike 1 : 1 obtained in the case of the nonacylated complexes. The mixture of the diastereomers from the mother liquors was deacetylated and recrystallized. This made it possible to isolate the second diastereomeric complex (*R*)-**2** in the pure form. An insignificant amount of a mixture of the diastereomeric complexes remained in the mother liquor can be separated by column chromatography to obtain an additional amount of each diastereomer as described previously.[8] After decomposition of the diastereomerically pure complexes, the target amino acids, *viz.*, (*S*)- and (*R*)-α-MeSer, (*S*)-**4** and (*R*)-**4**, were obtained with the optical purity higher than 99%. The chiral reagent BPB was regenerated in 90% yield. The optical activity of BPB is retained[7] and the reagent was re-usable.

To summarize, we developed a procedure for the preparation of both enantiomers of important non-protein amino acid α-MeSer using the single chiral recyclable reagent BPB, the diastereomeric nickel complexes (*S*)-**3** and (*R*)-**3** being separated by crystallization.

Experimental

The amino acids used were purchased from Reanal (Hungary). All solvents were distilled before use. The NMR spectra were recorded on a Bruker WP-200 instrument with Me_4Si (δ 0.00; in organic solvents) and formic acid (δ 8.20; in aqueous solutions) as the internal standards. The optical rotation was measured on a Perkin—Elmer 241 polarimeter in a thermostatically controlled cell at 25 °C. Enantiomeric analysis of the amino acids as *N*-trifluoroacetyl derivatives of their *n*-propyl esters was carried out by GLC on 40 m × 0.23-mm capillary quartz columns with the Chirasil-L-Val chiral phase (thickness 0.12 μm) at 125 °C using helium as the carrier gas. The starting complex Ni—BPB-(*S*,*R*)-Ala was prepared according to a known procedure.[7]

Condensation of complex 1 with formaldehyde. The Ni—BPB-(*S*,*R*)-Ala complex (**1**) (10 g, 0.0195 mol) and $(CH_2O)_n$ (11.7 g, 0.39 mol) were added to a solution of KOH (8.2 g, 0.146 mol) in MeOH (50 mL) under argon at 25 °C. The reaction mixture was stirred under argon at 25 °C for 6 h and neutralized with AcOH (10 mL). Then H_2O (21 mL) was added to precipitate a mixture of diastereomers (*S*)-**2** and (*R*)-**2**. Precipitation was completed in 10—12 h. The precipitate was filtered off, washed with water, and dried in air. The mixture of complexes (*S*)-**2** and (*R*)-**2** (2 : 1) with an admixture (less than 2.5%) of the starting alanine complex (according to the ^{1}H NMR spectral data) was obtained in a yield of 8 g. Storage of the mother liquor for additional 24 h gave an oil, which slowly crystallized on seeding with complex (*S*)-**2** to give the precipitate (1.87 g) consisting of (*S*)-**2** and the initial complex **1** in a ratio of ~7 : 1 (^{1}H NMR spectral data). The total yield of the crude mixture of complexes (*S*)-**2** and (*R*)-**2** was 9.87 g (89%), their ratio was ~3 : 1.

Synthesis of complexes 3. Ac_2O (30 mL, 0.318 mol) was added to a solution of the resulting mixture of diastereomers **2** (9.87 g) in dry MeCN (65 mL) and the reaction mixture was refluxed for 3—4 h. The course of the reaction was monitored by TLC on silica gel in a 7 : 1 $CHCl_3$—Me_2CO solvent system. After completion of the reaction, the solvent was distilled off *in vacuo*. The residue was twice concentrated with PhMe to remove traces of Ac_2O and recrystallized from MeOH (20 mL). The mixture was kept at 0 °C for 1 h and the precipitate that formed was filtered off, washed with cold MeOH, and dried in air. Pure complex (*S*)-**3** was obtained as bright-red crystals in a yield of 4.88 g (8.4 mmol, 46%), m.p. 240—242 °C. Found (%): C, 64.06; H, 5.36; N, 7.21. Calculated for $C_{31}H_{31}N_3NiO_5$: C, 63.72; H, 5.35; N, 7.19. ^{1}H NMR ($CDCl_3$), δ: 1.25 (s, 3 H, Me); 1.9—2.2 (m, 2 H, CH_2, β,γ-Pro); 2.31 (s, 3 H, OAc); 2.4—2.6 (m, 1 H, CH_2, β-Pro); 2.6—2.8 (m, 1 H, CH_2, γ-Pro); 3.4—3.6 (m, 2 H, CH_2, δ-Pro); 3.6—3.8 (m, 1 H, CH, α-Pro); 3.97 and 4.03 (AB, 2 H, CH_2OAc, J_{AB} = 11.5 Hz); 3.70 and 4.43 (AB, 2 H, $ArCH_2N$, J_{AB} = 12.8 Hz); 6.5—8.1 (m, 14 H, Ar). The mother liquor was concentrated to dryness and the residue was recrystallized from CCl_4 (20 mL) and dried in air. A product containig diastereomeric complexes (*S*)-**3** and (*R*)-**3** in a ratio of 1 : 4 (NMR spectral data) was obtained in a yield of 3.85 g (6.6 mmol).

Synthesis of diastereomeric complexes (*S*)-2 and (*R*)-2. A 4.6 *M* MeONa solution (0.21 mL, 6.6 mmol) was added to a solution of the mixture of diastereomeric complexes (*S*)-**3** and (*R*)-**3** (3.85 g, 6.6 mol) in MeOH (50 mL). The reaction mixture was kept at 25 °C for 2 h, neutralized with AcOH (0.2 mL), and concentrated to dryness. The dry residue was crystallized from a 2 : 1 MeOH—H_2O mixture (25 mL). The precipitate that formed was filtered off and washed successively with 2 : 1 and 1 : 1 MeOH—H_2O mixtures to obtain pure (*R*)-**2** in a yield of 2.13 g (3.94 mmol). Mother liquors were concentrated to dryness. The dry residue (1.43 g, (S)-**2** : (R)-**2** = 0.85) can be decomposed to regenerate BPB, chromatographed to isolate the diastereomers, or repeatedly acetylated (a solution of Ac_2O (4 mL) in MeCN (12 mL)) and then crystallized as described above. Crystallization from MeOH afforded pure (*R*)-**3** as bright-red crystals in a yield of 0.43 g (0.74 mmol), m.p. 221—223 °C. Found (%): C, 64.12; H, 5.56; N, 7.12. $C_{31}H_{31}N_3NiO_5$. Calculated (%): C, 63.72; H, 5.35; N, 7.19. ^{1}H NMR ($CDCl_3$), δ: 1.68 (s, 3 H, Me); 1.95—2.25 (m, 2 H, CH_2, β,γ-Pro); 2.16 (s, 3 H, OAc); 2.4—2.55 (m, 1 H, CH_2, β-Pro); 2.55—2.7 (m, 1 H, CH_2, γ-Pro); 3.3—3.5 (m, 2 H, CH_2, δ-Pro, CH, α-Pro); 3.55—3.7 (m, 1 H, CH_2, δ-Pro); 3.17 and 4.09 (AB, 2 H, CH_2OAc, J_{AB} = 12 Hz); 3.62 and 4.50 (AB, 2 H, $ArCH_2N$, J_{AB} = 12.6 Hz); 6.5—8.1 (m, 14 H, Ar).

Isolation of (*S*)-α-methylserine ((*S*)-4). 6 *M* HCl (24 mL) was added to a solution of complex (*S*)-**3** (4.88 g, 8.4 mmol) in MeOH (12 mL). The reaction mixture was refluxed for 20 min and MeOH was evaporated. The precipitate of BPB hydrochloride that formed was filtered off, washed several times with water, and dried in air. The yield was 3.2 g (90%). The aqueous layer was neutralized with a 25% NH_3 solution and BPB that remained was extracted with $CHCl_3$. (*S*)-**4** was isolated from the aqueous solution by ion-exchange chromatography on a KU-2 (H^+) cation-exchange resin; the amino acid was eluted from the column with aqueous NH_3. The eluate was concentrated and the residue (0.74 g) was crystallized from 80% aqueous EtOH (9 mL). The yield was 0.6 g (63%), colorless crystals, m.p. 293 °C. Found (%): C, 40.08; H, 7.41; N, 11.70. $C_4H_9NO_3$. Calculated (%): C, 40.33; H, 7.62; N, 11.75. $[\alpha]_D^{25}$ −3.31 (*c* 5, 6 *M* HCl) (*cf.* Ref. 10: $[\alpha]_D^{25}$ −3.4 (*c* 1.2, 6 *M* HCl)). ^{1}H NMR (D_2O), δ: 1.33 (s, 3 H, Me); 3.56 and 3.81 (AB, 2 H, CH_2, J_{AB} = 12 Hz). According to the data from enantiomeric analysis, the optical purity of amino acid (*S*)-**4** was 98.8%.

Decomposition of a mixture of (*R*)-2 and (*R*)-3 and isolation of (*R*)-α-methylserine ((*R*)-4) were carried out as described above for the complexes with the (*S*)-amino acid. The yield of BPB hydrochloride was 1.75 g (88%). (*R*)-**4** was

isolated from the mixture of (*R*)-**2** and (*R*)-**3** (2.56 g) as colorless crystals in a yield of 0.35 g (67%), m.p. 294 °C. Found (%): C, 40.24; H, 7.58; N, 11.75. $C_4H_9NO_3$. Calculated (%): C, 40.33; H, 7.62; N, 11.75. $[\alpha]_D^{25}$ +3.48 (*c* 5, 6 *M* HCl) (*cf.* Ref. 11: $[\alpha]_D^{25}$ +3.6 (*c* 2.5, 5 *M* HCl)). ^{1}H NMR (D_2O), δ: 1.32 (s, 3 H, Me); 3.57 and 3.82 (AB, 2 H, CH_2O, J_{AB} = 12 Hz). According to the data from enantiomeric analysis, the optical purity of amino acid (*R*)-**4** was 99%.

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