Asymmetric synthesis of *S*-alkyl-substituted (*R*)-cysteines *via* a chiral Ni^{II} complex of the Schiff's base of dehydroalanine with (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone

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An efficient procedure was developed for the asymmetric synthesis of *S*-alkyl derivatives of (*R*)-cysteine by nucleophilic addition of alkanethiols (Bu^nSH, Bu^tSH, or *tert*-$C_5H_{11}SH$) to the C=C bond of the dehydroalanine fragment in the Ni^{II} complex of the Schiff's base of Δ-Ala with (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone [(*S*)-BPB-Δ-Ala]Ni^{II}. Under conditions of thermodynamic control of the reaction, the diastereomeric excess of the complexes with the (*S*,*R*)-configuration was 88—96%. After decomposition of the complexes, (*R*)-*S*-butylcysteine, (*R*)-*S*-*tert*-butylcysteine, and (*R*)-*S*-*tert*-pentylcysteine were isolated with an enantiomeric purity of >97%.

Key words: dehydroalanine, thiols, addition, diastereoselectivity, *S*-alkylcysteines, asymmetric synthesis.

Enantiomerically pure *S*-substituted derivatives of cysteine are important components of many physiologically active peptides, antibiotics, and other medicines[1—3] and are also successfully used in microbiology for the selection of highly active producer strains of protein amino acids.[4,5] By analogy with another sulfur-containing amino acid, *viz.*, (*S*)-methionine,[6] *S*-alkyl-substituted cysteines can be used as starting compounds for the synthesis of chiral ligands of the salen type for Ti^{IV}-containing catalysts employed in the asymmetric synthesis of cyanohydrins.

Previously,[7] we have developed a procedure for the asymmetric synthesis of *S*-phenyl and *S*-benzyl derivatives of (*R*)-cysteine by the addition of the corresponding thiols to Ni complexes of Schiff's bases of dehydroalanine with chiral reagents, (*S*)-2-*N*-(*N*-benzylprolyl)aminoacetophenone and (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone [(*S*)-BPB].

In the present work, we report the asymmetric synthesis of *S*-butyl-, *S*-*tert*-butyl-, and *S*-*tert*-pentyl-(*R*)-cysteine.

Results and Discussion

The chiral planar-square complex of the Ni^{II} ion with the Schiff's base of dehydroalanine and (*S*)-BPB, *viz.*, 2-{*N*-[2-(*N*-benzyl-L-prolyl)aminophenyl](phenyl)methylene}aminoacrylato-N,N′,N″,O}-nickel(II) (**1**), containing an active electrophilic C=C double bond, was prepared according to a procedure reported previously.[8]

The addition of thiols to complex **1** was carried out in MeCN or DMF in the presence of K_2CO_3 or NaOH, respectively (Scheme 1). The course of the reaction can be monitored by TLC or ^1H NMR spectroscopy by following the disappearance of signals for the vinyl protons of the Δ-Ala fragment of the initial complex **1** at δ 4.1 and 5.8.

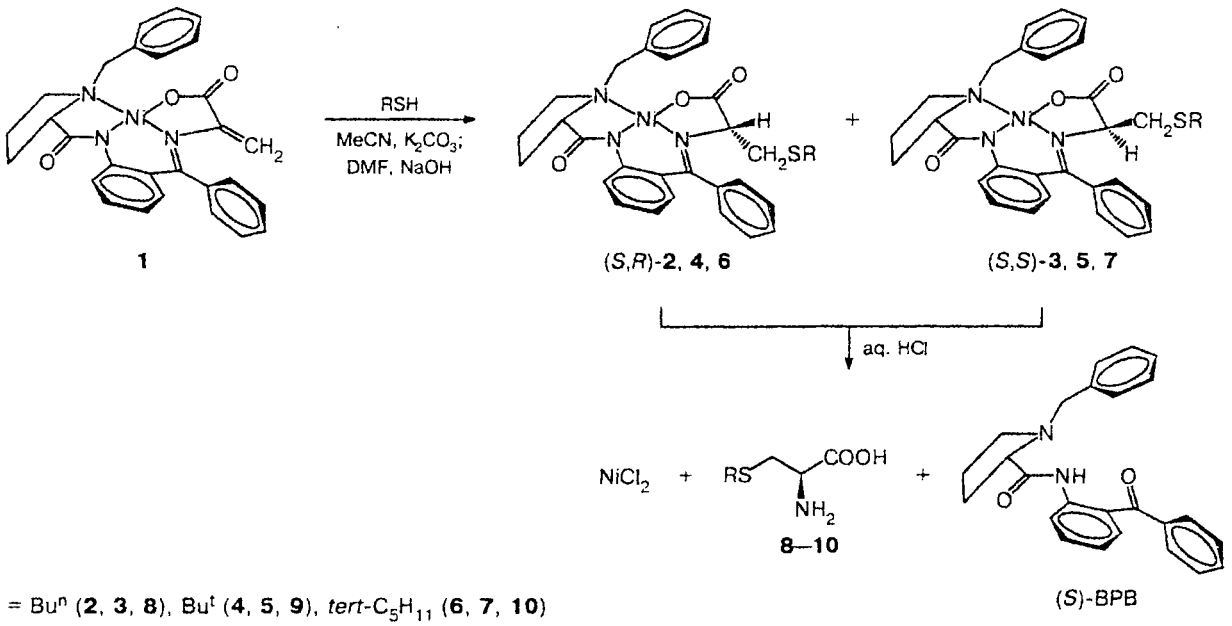
The addition afforded pairs of diastereomeric complexes with (*R*)- and (*S*)-configurations of the new stereogenic center, *viz.*, {*S*-alkyl-*N*-[2-(*N*-benzylprolyl)aminophenyl](phenyl)methylenecysteinato-N,N′,N″,O}nickel(II) (alkyl is Bu^n (**2** and **3**), Bu^t (**4** and **5**), or *tert*-C_5H_{11} (**6** and **7**)).

The absolute configurations of the diastereomeric complexes were determined by comparing the optical rotatory dispersion (ORD) curves (Fig. 1) of individual diastereomers (isolated by chromatography on SiO_2 in a $CHCl_3$—Me_2CO solvent system) with the ORD curves of the structurally similar complexes of (*R*)-*S*-benzylcysteine prepared previously.[7] The comparison demonstrated that the amino acid fragments in complexes **2**, **4**, and **6** characterized by higher R_f values on SiO_2 possess

Published in *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 8, pp. 1467—1470, August, 2000.

1066-5285/00/4908-1460 $25.00

Scheme 1



R = Bu^n (**2**, **3**, **8**), Bu^t (**4**, **5**, **9**), *tert*-C_5H_{11} (**6**, **7**, **10**)

the (*R*)-configuration, whereas these fragments in less mobile complexes **3**, **5**, and **7** have the (*S*)-configuration.

The diastereomeric composition of the products depends on the reaction time. At the beginning of the reaction (within 10 min after addition of RSH), the excess of the (*S*,*R*)-diastereomer characterized by the higher R_f value on silica gel was 70% as a result of a rather low kinetic enantioselectivity. Then the amount of this diastereomer gradually increased due to the attainment of thermodynamic equilibrium. The equilibrium ratios of the diastereomers and their chemical yields are given in Table 1.

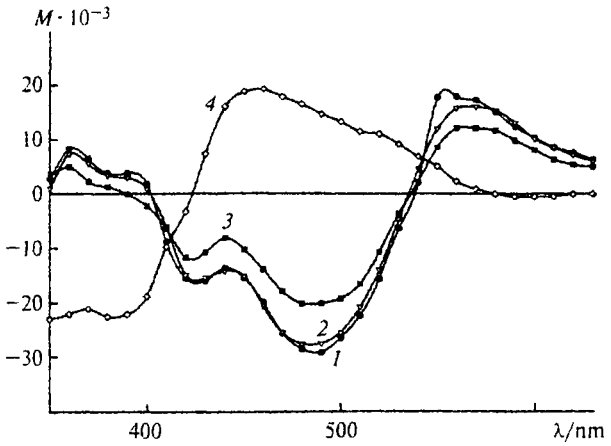


Fig. 1. Optical rotatory dispersion curves for the complexes in MeOH (25 °C): *1*, [(*S*)-BPB-(*R*)-(*S*-Bu^{t}Cys)]Ni^{II} (**4**); *2*, [(*S*)-BPB-(*R*)-(*S*-*tert*-C_5H_{11}Cys)]Ni^{II} (**6**); *3*, [(*S*)-BPB-(*R*)-(*S*-Bu^n-Cys)]Ni^{II} (**2**); and *4*, [(S)-BPB-(*S*)-(*S*-*tert*-C_5H_{11}Cys)]Ni^{II} (**7**).

The addition of the nucleophiles and the attainment of the thermodynamic equilibrium between the diastereomers occurred rather rapidly (0.5—1 h) in DMF under the action of NaOH at 45—50 °C. However, this process was accompanied by the formation of by-products in yields of up to 15%. By-products were not formed upon addition of alkanethiols to complex **1** in MeCN under the action of K_2CO_3 at 45—50 °C. Under these conditions, thermodynamic equilibrium between the diastereomeric complexes was established in 6—8 h.

After the attainment of thermodynamic equilibrium, decomposition of the mixture of diastereomers under the action of HCl in an aqueous-methanolic solution gave rise to *S*-alkyl-(*R*)-cysteines **8—10** with an optical purity of >97% and chemical yields of >80%. The initial chiral reagent (*S*)-BPB was recovered in a yield of >96% with retention of optical purity.

Table 1. Chemical yields and the ratios of the diastereomers prepared by addition of RSH to the C=C bond in complex **1**

RSH	Solvent	Base	(*S*,*R*)/(*S*,*S*)*	Yield (%)**
Bu^{n}SH	MeCN	K_2CO_3	94 : 6	86
Bu^{t}SH	MeCN	K_2CO_3	97 : 3	94
tert-C_5H_{11}SH	MeCN	K_2CO_3	98 : 2	92
Bu^{t}SH	DMF	NaOH	97 : 3	76
tert-C_5H_{11}SH	DMF	NaOH	96 : 4	70

* The ratio of the isomers was determined by enantiomeric analysis of the amino acids isolated from a mixture of the diastereomeric complexes without subsequent crystallization.
** The chemical yield of the mixture of the diastereoisomers.

Experimental

The amino acids were purchased from Reanal (Hungary); Bu^nSH, Bu^tSH, *tert*-$C_5H_{11}SH$, K_2CO_3, NaOH, Me_2CO, $CHCl_3$, MeCN, and DMF were purchased from Reakhim; and MeCN and DMF were purified according to known procedures[9,10] before use. The ^1H NMR spectra were recorded on a Mercury 300-BB instrument (300 MHz). The ORD curves were measured on a JASCO ORD/UV-5 instrument, and the $[\alpha]_D$ values were determined on a Perkin—Elmer M-241 polarimeter. The chemical shifts of the protons (δ) were measured relative to Me_4Si.

The enantiomeric GLC analysis of *S*-alkylcysteines was carried out using their *N*-trifluoroacetyl-*O*-*n*-propyl derivatives on a column with Chirasil-Val-type stationary phase.[11]

The chiral reagent (*S*)-BPB[12] and the starting complex [(*S*)-BPB-Δ-Ala]Ni (**1**)[8] were synthesized according to known procedures.

Addition of alkanethiols to complex 1 (general procedure). K_2CO_3 (7.87 g, 5.72 mmol) or NaOH (2.28 g, 5.72 mmol) and RSH (3.4 mmol) were added to a solution of complex **1** (14.6 g, 2.86 mmol) in MeCN or DMF (50 mL) under Ar. The reaction mixture was stirred at 40—45 °C. The course of the reaction can be monitored by ^1H NMR spectroscopy by following the disappearance of signals for the protons at the C=C bond (at δ 5.85 (s) and 4.1 (s)), by spectrophotometry (400—430 nm), and by TLC on silica gel using the 3 : 1 $CHCl_3$—Me_2CO solvent system. After the attainment of thermodynamic equilibrium (the ratio of the diastereomeric complexes ceased to change; TLC control), the reaction mixture was filtered, the precipitate was washed with $CHCl_3$, and the solution was concentrated to dryness. The chemical yields of the products and the ratios of the diastereomers are given in Table 1.

Individual diastereomers of the complexes were isolated from the reaction mixtures in which thermodynamic equilibrium was not established. For this purpose, a portion of the reaction mixture (~5 mL) was withdrawn, diluted with $CHCl_3$ (20 mL), and washed successively with 0.2 *N* HCl (3×10 mL), 1 *M* Na_2CO_3 (3×10 mL), and water. The solution was concentrated to dryness and the residue was chromatographed on a column with SiO_2 (3.5×30 cm) using the 2 : 1 $CHCl_3$—Me_2CO system as the eluent. The ORD curves for complexes **2**, **4**, **6**, and **7** are shown in Fig. 1. We failed to isolate complexes **3** and **5** in amounts sufficient to perform spectral analysis.

[(*S*)-BPB-(*R*)-(*S*-Bu^nCys)]Ni^{II} (2). ^1H NMR ($CDCl_3$), δ: 0.88 (t, 3 H, $\underline{Me}CH_2$, J = 7.24 Hz); 1.3—1.46 (m, 2 H, $MeC\underline{H}_2CH_2$, J = 7.24 Hz); 1.46—1.64 (m, 2 H, $MeCH_2C\underline{H}_2$, J = 7.24 Hz); 2.0—2.2 (m, 2 H, Pro); 2.42—2.70 (m, 4 H, Pro+CH$\underline{CH}_a$S+S$\underline{CH}_2CH_2$); 2.74—2.96 (m, 2 H, Pro+CH$\underline{CH}_b$S); 3.46 (dd, 1 H, $\underline{H}C—CH_2S$, J = 6.34 and 10.87 Hz); 3.60 (AB system, Δδ 0.84, 2 H, CH_2Ph, J_{AB} = 12.5 Hz); 3.58—3.82 (m, 2 H, Pro); 4.22 (dd, 1 H, $\underline{H}C—CH_2S$, J = 2.72 and 4.98 Hz); 6.5—8.3 (m, 14 H, ArH). UV (MeOH), λ_{max}/nm (lg ε): 334 (3.4), 418 (2.1). $[\alpha]_D^{25}$ +1880.0° (*c* 0.4, MeOH). Found (%): C, 64.22; H, 6.04; N, 6.72. $C_{32}H_{35}N_3NiO_3S$. Calculated (%): C, 64.01; H, 5.87; N, 6.99.

[(*S*)-BPB-(*R*)-(*S*-Bu^tCys)]Ni^{II} (4). ^1H NMR ($CDCl_3$), δ: 1.32 (s, 9 H, CMe_3); 1.96—2.16 (m, 2 H, Pro); 2.42—2.60 (m, 1 H, Pro); 2.55 (dd, 1 H, CH_2S, J_{AB} = 11.82 Hz, J_{AX} = 5.77 Hz); 2.77 (dd, 1 H, CH_2S, J_{AB} = 11.82 Hz, J_{BX} = 2.60 Hz); 4.29 (dd, 1 H, $\underline{H}C—CH_2S$, J_{XA} = 5.77 Hz, J_{XB} = 2.60 Hz); 2.90—3.05 (m, 1 H, Pro); 3.44 (dd, 1 H, $\underline{H}C—CH_2S$, J = 6.05 and 9.66 Hz); 3.62 (AB system, Δδ 0.82, 2 H, CH_2Ph, J_{AB} = 11.54 Hz); 3.6—3.9 (m, 2 H, Pro); 6.5—8.3 (m, 14 H, ArH). UV (MeOH), λ_{max}/nm (lg ε): 336 (3.6), 418 (2.2). $[\alpha]_D^{25}$ −2615.0° (*c* 0.038, MeOH). Found (%): C, 64.14; H, 5.98; N, 6.82. $C_{32}H_{35}N_3NiO_3S$. Calculated (%): C, 64.01; H, 5.87; N, 6.99.

[(*S*)-BPB-(*R*)-*S*-(*tert*-C_5H_{11}Cys)]Ni^{II} (6). ^1H NMR ($CDCl_3$), δ: 0.96 (t, 3 H, $\underline{Me}CH_2$, J = 7.16 Hz); 1.26 (s, 6 H, CMe_2); 1.50 (dq, 1 H, $\underline{CH}_aMe$, J = 7.16 and 14.7 Hz); 1.56 (dq, 1 H, $\underline{CH}_bMe$, J = 7.16 and 14.7 Hz); 1.95—2.15 (m, 2 H, Pro); 2.46 (dd, 1 H, CH_2S, J_{AB} = 11.71 Hz, J_{AX} = 5.71 Hz); 2.69 (dd, 1 H, CH_2S, J_{AB} = 11.71 Hz, J_{BX} = 2.57 Hz); 4.27 (dd, 1 H, $\underline{H}C—CH_2S$, J_{XA} = 5.71 Hz, J_{XB} = 2.57 Hz); 2.4—2.57 (m, 1 H, Pro); 2.88—3.04 (m, 1 H, Pro); 3.43 (dd, 1 H, $\underline{H}C—CH_2S$, J = 6.57 and 10.28 Hz); 3.61 (AB system, Δδ 0.83, 2 H, CH_2Ph, J_{AB} = 12.0 Hz); 3.6—3.9 (m, 2 H, Pro); 6.5—8.3 (m, 14 H, ArH). UV (MeOH), λ_{max}/nm (lg ε): 264 (10.9), 334 (3.4), 417 (2.02). $[\alpha]_D^{25}$ +2238.12° (*c* 0.042, MeOH). Found (%): C, 64.67; H, 6.18; N, 6.62. $C_{33}H_{37}N_3NiO_3S$. Calculated (%): C, 64.51; H, 6.07; N, 6.84.

[(*S*)-BPB-(*S*)-(*S*-*tert*-C_5H_{11}Cys)]Ni^{II} (7). ^1H NMR ($CDCl_3$), δ: 0.93 (t, 3 H, $\underline{Me}CH_2$, J = 7.44 Hz); 1.23 (s, 6 H, CMe_2); 1.50 (q, 2 H, $\underline{CH}_2Me$, J = 7.44 Hz); 1.70—2.27 (m, 3 H, Pro); 2.50—2.70 (m, 2 H, Pro); 2.67 (d, 2 H, CH_2S, J = 4.80 Hz); 3.60 (dd, 1 H, $\underline{H}C—CH_2S$, J = 4.80 and 10.80 Hz); 3.92 (AB system, Δδ 1.07, 2 H, CH_2Ph, J_{AB} = 13.2 Hz); 3.98—4.12 (m, 2 H, Pro); 4.22 (t, 1 H, $\underline{H}C—CH_2S$, J = 4.80 Hz); 6.6—8.8 (m, 14 H, ArH). UV (MeOH), λ_{max}/nm (lg ε): 265 (9.8), 335 (3.1), 420 (1.90). $[\alpha]_D^{25}$ −450.0° (*c* 0.04, MeOH). Found (%): C, 64.72; H, 6.21; N, 6.56. $C_{33}H_{37}N_3NiO_3S$. Calculated (%): C, 64.51; H, 6.07; N, 6.84.

Isolation of amino acids 8—10. An equilibrium mixture of the diastereomeric complexes was dissolved in MeOH (50 mL) and the solution was added with stirring to 2 *M* HCl heated to 45—50 °C. After the color typical of the complexes disappeared, the mixture was concentrated to dryness, water (50 mL) was added, and the initial chiral reagent (*S*)-BPB · HCl was filtered off. The target amino acids were isolated from the aqueous filtrates by ion-exchange techniques.[8] Amino acids **8**, **9**, and **10** were isolated in 64, 78, and 70% yields, respectively. Then these compounds were recrystallized from aqueous EtOH.

(*R*)-*S*-Butylcysteine (8). The yield was 64%, m.p. 218—220 °C. ^1H NMR (D_2O), δ: 0.81 (t, 3 H, Me, J = 7.50 Hz); 1.31 (m, 2 H, $MeCH_2$, J = 7.50 Hz); 1.50 (m, 2 H, $CH_2\underline{CH}_2CH_2$, J = 7.50 Hz); 2.55 (t, 2 H, CH_2S, J = 7.50 Hz); 3.04 (dd, 1 H, CH_2S, J_{AB} = 14.0 Hz, J_{AX} = 6.36 Hz); 3.35 (dd, 1 H, CH_2S, J_{AB} = 14.0 Hz, J_{BX} = 3.81 Hz); 4.24 (dd, 1 H, $\underline{H}C—CH_2S$, J_{XA} = 6.36 Hz, J_{XB} = 3.81 Hz). $[\alpha]_D^{25}$ +9.54° (*c* 1, 0.1 *N* NaOH) (*cf.* lit. data[13]: $[\alpha]_D^{20}$ +9.7° (*c* 1, aqueous NaOH)). According to the data from enantiomeric GLC analysis, the optical purity was 97%. Found (%): C, 47.94; H, 8.62; N, 7.75. $C_7H_{15}NO_2S$. Calculated (%): C, 47.43; H, 8.53; N, 7.90.

(*R*)-*S*-*tert*-Butylcysteine (9). The yield was 78%, m.p. 214—215 °C. ^1H NMR (D_2O), δ: 1.2 (s, 9 H, 3 Me); 3.10 (dd, 1 H, CH_2S, J_{AB} = 13.6 Hz, J_{AX} = 6.4 Hz); 3.24 (dd, 1 H, CH_2S, J_{AB} = 13.6 Hz, J_{BX} = 3.8 Hz); 4.0 (dd, 1 H, $\underline{H}C—CH_2S$, J_{XA} = 6.4 Hz, J_{XB} = 3.8 Hz). $[\alpha]_D^{25}$ +8.13° (*c* 1, 6 *N* HCl) (*cf.* lit. data[14]: $[\alpha]_D^{20}$ +6.35° (*c* 2, aqueous HCl)). According to the data from enantiomeric GLC analysis, the optical purity was 97.7%. Found (%): C, 47.78; H, 8.52; N, 7.87. $C_7H_{15}NO_2S$. Calculated (%): C, 47.43; H, 8.53; N, 7.90.

(*R*)-*S*-*tert*-Pentylcysteine (10). The yield was 70%, m.p. 206—207 °C. ^1H NMR (D_2O), δ: 0.98 (t, 3 H, $\underline{Me}CH_2$); 1.36 (s, 6 H, CMe_2); 1.62 (q, 2 H, $MeC\underline{H}_2$); 3.02 (dd, 1 H, CH_2S, J_{AB} = 14.0 Hz, J_{AX} = 6.4 Hz); 3.18 (dd, 1 H, CH_2S, J_{AB} = 14.0 Hz, J_{BX} = 3.82 Hz); 3.88 (dd, 1 H, $\underline{H}C—CH_2S$, J_{XA} = 6.4 Hz, J_{XB} = 3.82 Hz). $[\alpha]_D^{25}$ +11.31° (*c* 1, 6 *N* HCl) (was not described in the literature). According to the data from enantio-

meric GLC analysis, the optical purity was 99.5%. Found (%): C, 50.44; H, 9.02; N, 7.28. $C_8H_{17}NO_2S$. Calculated (%): C, 50.23; H, 8.96; N, 7.32

This work was financially supported by the INCO-COPERNICUS European Foundation (Grant ICIS-CT96-0722).

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Received November 12, 1999;
in revised form March 27, 2000