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# Asymmetric synthesis of β-heterocycle substituted L-α-amino acids

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**Abstract**—A new efficient method of asymmetric synthesis of β-heterocycle substituted L-α-amino acids through the addition of 3-amino-1,2,4-thiodiazole and 5-mercapto-1,2,4-triazoles, containing various substituents at the 3 and 4 positions, to the C=C bond of dehydroalanine in the Ni(II) complex of its Schiff base with (*S*)-2-*N*-(*N*′-benzylprolyl)aminobenzophenone has been elaborated upon. Under thermodynamic control, the stereoselectivity of the nucleophilic addition exceeded 94%. After acidic decomposition of the reaction mixtures, the corresponding β-heterocycle substituted α-amino acids with high enantiomeric purity (ee >98.5%) were isolated.


## 1. Introduction

Optically active β-substituted α-amino acids are encountered in many physiologically active peptides, antibiotics, and other drugs.[1–4] Non-proteinogenic α-amino acids are successfully adapted in microbiology for the selection of strains producing proteinogenic amino acids.[5–7] The α-amino acids, β-substituted on the side chain with 1,2,4-triazole and thiodiazole were particularly active in the selection of strains producing histidine, alanine, valine, arginine, and isoleucine.[8,9] It should be noted that the synthetic procedures for producing β-heterocycle substituted non-proteinogenic α-amino acids, even as racemic mixtures, are quite rare. Undoubtedly general procedures for the synthesis of enantiomerically enriched amino acid derivatives, including those containing 1,2,4-triazole and thiodiazole substituents in the side chain could be of special interest.

Recently an asymmetric synthesis of β-substituted (*S*)-α-amino acids through various nucleophilic (thiols, amines, and alcohols) additions to the C=C bonds of dehydroamino acid moieties (dehydroalanine and dehydroaminobutanoic acid) in the Ni(II) complexes of their Schiff bases with (*S*)-2-*N*-(*N*′-benzylprolyl)aminobenzophenone [(*S*)-BPB] has been reported.[10–14]

Herein we report the asymmetric synthesis of (*S*) or L-β-(3′-amino-1,2,4-thiodiazolyl)-α-alanine and S-substituted (*R*)- or L-cysteines containing 1,2,4-triazole moieties with various aliphatic and aromatic substituents at the 3 and 4 positions of the heterocycle moieties.

## 2. Results and discussion

A chiral Ni(II) complex of a Schiff base of dehydroalanine and (*S*)-BPB [(*S*)-BPB-Δ-Ala]Ni(II) **1** was synthesized according to the method elaborated by us previously and modified herein.[15]

The following heterocyclic nucleophiles were used: 2-amino-1,3,4-thiodiazole, 3-(3′-hydroxypropyl)-4-phenyl-5-mercapto-1,2,4-triazole, 3-(3′-hydroxypropyl)-4-allyl-5-mercapto-1,2,4-triazole, 3-propyl-4-phenyl-5-mercapto-1,2,4-triazole, 3-propyl-4-allyl-5-mercapto-1,2,4-triazole, 3-(3′-hydroxy-4′-isoamyloxybutyl)-4-phenyl-5-mercapto-1,2,4-triazole, 3-(3′-hydroxy-4′-isoamyloxybutyl)-4-allyl-5-mercapto-1,2,4-triazole, 3-(2′-methoxyphenyl)-4-allyl-5-mercapto-1,2,4-triazole, 3-(2′-chlorophenyl)-4-allyl-5-mercapto-1,2,4-triazole, and 3-(3′-hydroxyoctyl)-4-allyl-5-mercapto-1,2,4-triazole.[16,17]

The asymmetric addition of heterocyclic nucleophiles to the C=C bond of **1** proceeded in either MeCN or DMF

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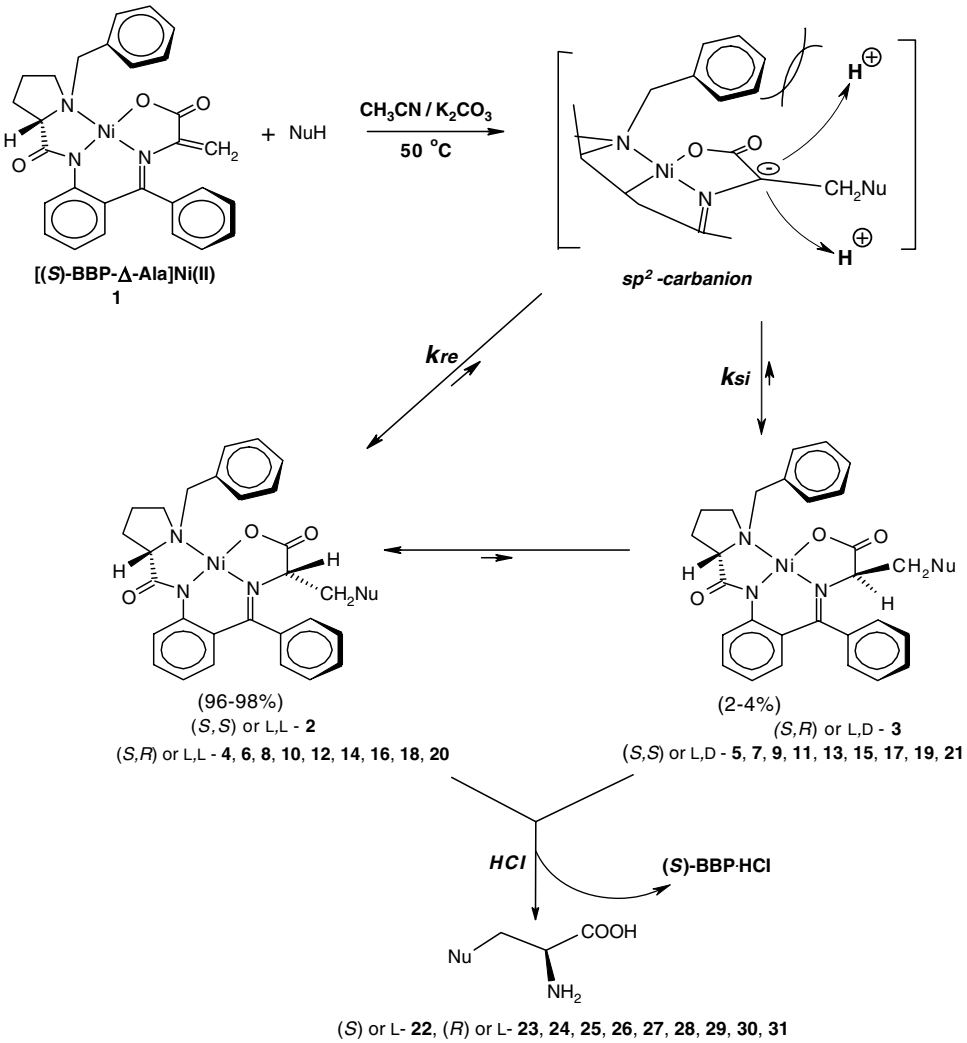
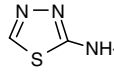
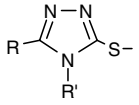



Nu =  **2**, **3**, **22**



R = -$CH_2CH_2CH_2OH$, R'= -$C_6H_5$, **4**, **5**, **23**;
R = -$CH_2CH_2CH_2OH$, R'= -$CH_2$-CH=$CH_2$, **6**, **7**, **24**;
R = -$C_3H_7$, R'= -$C_6H_5$, **8**, **9**, **25**;
R = -$C_3H_7$, R'= -$CH_2$-CH=$CH_2$, **10**, **11**, **26**;
R = -$CH_2CH_2CH(OH)CH_2OCH_2CH_2CH(CH_3)_2$, R'= -$C_6H_5$ , **12, 13, 27**;
R = -$CH_2CH_2CH(OH)CH_2OCH_2CH_2CH(CH_3)_2$ , R'= -$CH_2$-CH=$CH_2$ , **14, 15, 28**;
R = *o*-$CH_3O$-$C_6H_4$- , R'= -$CH_2$-CH=$CH_2$ , **16**, **17**, **29**;
R = *o*-Cl-$C_6H_4$- , R'= -$CH_2$-CH=$CH_2$ , **18**, **19**, **30**;
R = -$CH_2CH_2CH(OH)C_5H_{11}$ , R'= -$CH_2$-CH=$CH_2$, **20**, **21**, **31**;

**Scheme 1.**

in the presence of $K_2CO_3$ or NaOH at 25–50 °C (Scheme 1). The reaction was monitored either by TCL ($SiO_2$, $CHCl_3$–$CH_3COCH_3$, 2:1) thus monitoring the disappearance of **1** and establishing the equilibrium between the formed diastereoisomers, or by $^1H$ NMR following the disappearance of the vinyl protons of the dehydroalanine moiety of **1** at 4.1 and 5.8 ppm.

This addition resulted in the formation of diastereomeric complexes with both (*S*)- and (*R*)-configurations at the newly formed stereogenic centers (*S*,*S*) or L,L-**2**, (*S*,*R*)- or L,L-**4**, **6**, **8**, **10**, **12**, **14**, **16**, **18**, **20** and (*S*,*R*)- or L,D-**3**, (*S*,*S*)- or L,D-**5**, **7**, **9**, **11**, **13**, **15**, **17**, **19**, **21**. One of the diastereoisomers (L,L) was always formed in a greater excess over another. The complexes were separated by the preparative chromatography ($SiO_2$, $CHCl_3$–$CH_3COCH_3$, 3:1).

The absolute configurations of the diastereomeric complexes were assigned by comparing their ORD disper-

sion curves with those of the diastereoisomeric complexes of S-benzylcysteine and β-(*N*-benzylamino)alanine.[12] The ORD curves of the **2**, **3**, **4**, and **5** complexes and those of the corresponding diastereomers of S-benzylcysteines and β-(*N*-benzylamino)alanine are shown in Figure 1.

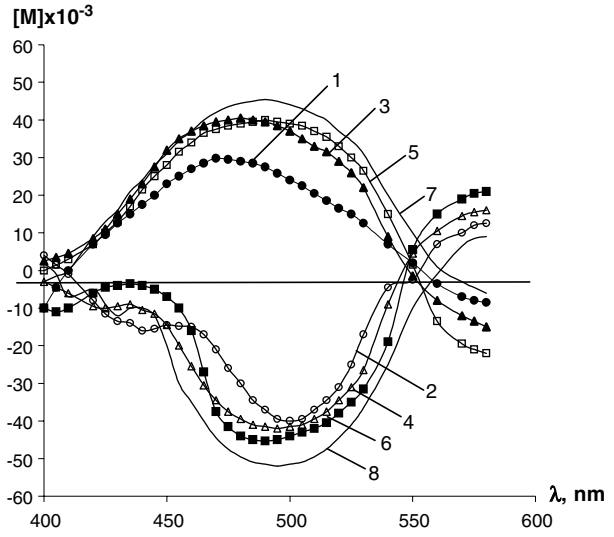



**Figure 1.** ORD curves of the complexes in $CH_3OH$ (25 °C): (1) [(*S*)-BBP-S-Bn-(*S*) or D-Cys]Ni(II);[10,12] (2) [(*S*)-BBP-S-Bn-(*R*) or L-Cys]Ni(II);[10,12] (3) [(*S*)-BBP-β-N-Bn-(*R*) or D-Ala]Ni(II);[12] (4) [(*S*)-BBP-β-N-Bn-(*S*) or L-Ala]Ni(II);[12] (5) (*S*,*R*) or L,D-**3**; (6) (*S*,*S*) or L,L-**2**; (7) (*S*,*S*) or L,D-**5**; (8) (*S*,*R*) or L,L-**4**.

The results showed that the amino acid moieties of the diastereomeric complexes with lower $R_f$ value on $SiO_2$ had either an (*S*)- or L-configuration as in case of **2** or an (*R*)- or L-configuration in the cases of **4**, **6**, **8**, **10**, **12**, **14**, **16**, **18**, and **20**. The configurations of the major isomers were the same L,L- with the α-protons of the amino acid moiety oriented toward *N*-benzyl substituents (see Scheme 1). The changeover from (*S*,*S*)-designation for L,L-isomers to (*S*,*R*)-designation in the cases of **4**, **6**, **8**, **10**, **12**, **14**, **16**, **18**, and **20** was formal, originating from the changing priorities of N and S-atoms in the side chain of the amino acid.

The ratio of diastereomers was evaluated by $^1$H NMR analysis of the reaction mixture in the region of 3.5–4.5 ppm for the proton resonances of $CH_2$Ph moiety of *N*-benzylproline fragment or spectrophotometrically after separation of the diastereoisomers on $SiO_2$.

The addition of the nucleophiles to **1** and their thermodynamic equilibration were complete within 1 h in DMF in the presence of NaOH at 45–50 °C. However this process was accompanied by the formation of about 10% of side products. On the other hand the addition of heterocyclic thiols to **1** in MeCN in the presence of $K_2CO_3$ at 45–50 °C proceeded without any side product accumulation. Under those terms, the equilibrium between the diastereoisomeric complexes was established within a 3–6 h period. The average data on de at the diastereoisomer equilibria and their chemical yields in the reaction are summarized in Table 1.

Decomposition of the diastereomeric complexes mixture with aqueous HCl resulted in the formation of (*S*)-β-(3′-amino-1,2,4-thiodiazolyl)-α-alanine **22** and S-heterocyclic substituted (*R*)-cysteines **23**–**31** with chemical yields >80% and enantiomeric purities >98.5% after recrystallization from a water/EtOH mixture. The initial auxiliary (*S*)-BPB was recovered in a yield >96% without any loss of its enantiomeric purity.

Enantiomeric purities of the synthesized amino acids **22**, **23**, **24**, **25**, and **29** were measured by HPLC analysis and found to exceed 98.5%. Although, the attempts at enantiomeric analysis of the other synthesized heterocyclic amino acids **26**, **27**, **28**, **30**, and **31** failed, the de of the initial complexes was high enough to expect high ee of the recovered amino acids.

## 3. Conclusion

A general method of asymmetric synthesis of β-heterocyclic substituted L-α-amino acids containing 1,2,4-thiodiazole and 3,4-disubstituted 1,2,4-triazole substituents on the side chain has been elaborated. The enantiomeric purities of the synthesized heterocyclic amino acids exceeded 98.5%.

## 4. Experimental

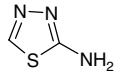
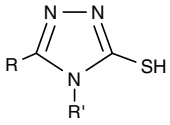
Amino acid 'Reanal' (Budapest), silica gel L-40/100μ 'Chemapol Praha' (Prague), ion-exchange resin Ku-2×8, $K_2CO_3$, $CHCl_3$, $(CH_3CO)_2O$, $(CH_3)_2CO$, $CH_3CN$ 'Reachim' were used in the present research. $CH_3CN$ was purified according to a literature.[17] $^1$H NMR spectra were run on 'Mercury-300 Varian' (300 MHz), ORD data curves on a Spectropolarimeter 'Jasco ORD/UV-5' and optical rotation measurements on a 'Perkin-Elmer-341' polarimeter. Diastereomer ratios in their solutions after separation on $SiO_2$ were evaluated on a 'Specord M-40' Spectrophotometer in the wavelength region of 360–400 nm.

The enantiomeric purities of the synthesized heterocyclic amino acids were assessed by HPLC: chiral phase—Crownpak CR(+), eluent—$HClO_4$ (pH = 2), elution rate 0.4 ml/min, $T = 5$ °C.

### 4.1. Modified synthesis of the complex 1

To a solution of 150 g (0.3 mol) of [(*S*)-BBP-Gly]Ni(II) and 320 mL of $CH_3OH$ were added 31 g (0.96 mol) of paraformaldehyde and 147 mL of 4.7 M $CH_3ONa$ under constant stirring and Ar atmosphere. The stirring was continued for another 3-h period at the ambient temperature. The reaction was monitored by TLC [$SiO_2$, $CHCl_3$–$CH_3COCH_3$; (3:1)]. Afterwards the reaction mixture was neutralized with 48.5 mL (0.8 mol) of acetic acid and left for an hour. The precipitated red colored

**Table 1.** Asymmetric addition of heterocyclic nucleophiles to 1 (at 50 °C in $CH_3CN/K_2CO_3$; 3–6 h)

| Run | Heterocyclic nucleophiles | | Main diastereomer, de (%)[a,b] | C.Y.[c] (%) |
|---|---|---|---|---|
| 1 |  | | (*S*,*S*) or L,L-**2**<br>92 | 88 |
| |  | | | |
| | R | R′ | | |
| 2 | $HOCH_2CH_2CH_2$ | $C_6H_5$ | (*S*,*R*) or L,L-**4**<br>94 | 96 |
| 3 | $HOCH_2CH_2CH_2$ | $CH_2{-}CH{=}CH_2$ | (*S*,*R*) or L,L-**6**<br>94 | 96 |
| 4 | $C_3H_7$ | $C_6H_5$ | (*S*,*R*) or L,L-**8**<br>94 | 94 |
| 5 | $C_3H_7$ | $CH_2{-}CH{=}CH_2$ | (*S*,*R*) or L,L-**10**<br>94 | 96 |
| 6 | $(CH_3)_2CHCH_2CH_2OCH_2(OH)CHCH_2CH_2$ | $C_6H_5$ | (*S*,*R*) or L,L-**12**<br>96 | 92 |
| 7 | $(CH_3)_2CHCH_2CH_2OCH_2(OH)CHCH_2CH_2$ | $CH_2{-}CH{=}CH_2$ | (*S*,*R*) or L,L-**14**<br>96 | 90 |
| 8 | *o*-$CH_3O$–$C_6H_4$ | $CH_2{-}CH{=}CH_2$ | (*S*,*R*) or L,L-**16**<br>96 | 96 |
| 9 | *o*-CI–$C_6H_4$ | $CH_2{-}CH{=}CH_2$ | (*S*,*R*) or L,L-**18**<br>94 | 95 |
| 10 | $C_5H_{11}(OH)CHCH_2CH_2$ | $CH_2{-}CH{=}CH_2$ | (*S*,*R*) or L,L-**20**<br>94 | 90 |

[a] De (%) was recorded by $^1H$ NMR analysis of the diastereomers mixture and/or spectrophotometrically at $\lambda = 310$–340 nm after separation of the diastereoisomers on $SiO_2$.
[b] De (%) was determined after the establishment of the equilibrium between the diastereoisomeric complexes.
[c] Chemical yield of a mixture of both diastereisomeric complexes.

crystals were filtrated, washed with 30 mL of distilled water and dried under vacuum at 50 °C to give 148 g (0.28 mol) of diastereomerically pure [(*S*)-BBP-(*R*)-Ser]Ni(II). The compound was dissolved in 850 mL of acetonitrile and to the solution were added 63.6 g (0.6 mol) of dry $Na_2CO_3$ and 178 mL (1.76 mol) of $(CH_3CO)_2O$ at room temperature while stirring. The stirring was continued for another ~2 h at room temperature, the temperature then raised to 70 °C and the mixture stirred for a further hour. The reaction course was monitored by TLC [$SiO_2$, $CHCl_3$–$CH_3COCH_3$; (2:1)]. The reaction mixture was filtered and the precipitant of $Na_2CO_3$ and $CH_3COONa$ washed with 50 mL $CHCI_3$. Afterwards the chloroform filtrate was washed with 150 mL of 0.1 M $Na_2CO_3$ solution (3 × 50 mL), vacuum-evaporated to dryness at 50 °C. 139.7 g (0.27 mol) of the [(*S*)-BPB-Δ-Ala]Ni(II) **1** complex was obtained, 90% yield. Data of the synthesized complex **1** corresponded to the literature data.[12]

### 4.2. Standard procedure for the asymmetric synthesis of 22–31

To a solution of 5.1 g (10 mmol) of **1** in 20 mL of MeCN were added 2.5 g (18 mmol) of $K_2CO_3$ and 1.53 g (15 mmol) of 2-amino-1,3,4-thiodiazole in 10 mL of $CH_3CN$ while stirring at 50 °C. The reaction was monitored by TLC ($SiO_2$, $CHCl_3$–$CH_3COCH_3$; 2:1) and by $^1H$ NMR following the disappearance of the vinyl protons of dehydroalanine moiety of **1** at 5.85(s) and 4.1(s). The thermodynamic equilibrium was established (no changes in diastereomeric complexes ratio), usually within 3–6 h, the reaction mixture filtered, the precipitate washed with $CHCl_3$ and afterwards the chloroform solution vacuum-evaporated to dryness. The asymmetric addition of other nucleophiles was performed by analogy.

*Individual diastereomers of the complexes* were isolated from the reaction mixtures that did not reach their thermodynamic equilibrium. A small portion of the reaction mixture (~5 mL) was dissolved in 20 mL of $CHCl_3$, the solution washed with aq 0.2 M HCl (3 × 10 mL), aq 1 M $Na_2CO_3$ (3 × 10 mL) and water, consecutively; evaporated to dryness and the residue chromatographed [$SiO_2$, $CHCl_3$–$CH_3COCH_3$; (2:1)].

### 4.3. Complex (*S*,*R*)- or L,L-2

Calcd for $C_{30}H_{28}N_6O_3SNi$: C, 65.22; H, 5.07; N, 15.2. Found: C, 65.34; H, 5.13; N, 15.9%. Mp = 205–207 °C. $[\alpha]_D^{20} = +44.0$ (*c* 0.05, MeOH); $^1H$ NMR ($CDCl_3$): 1.95–2.15 (2H, m, Pro-H), 2.38–2.52 (2H, m, Pro-H), 2.58

(1H, dd, β-CH, $J_1 = 11.8$ Hz, $J_2 = 6$ Hz), 2.75 (1H, dd, β-CH, $J_1 = 12.0$ Hz, $J_2 = 2.8$ Hz), 3.36–3.48 (1H, m, Pro-H), 3.68, 3.82 (1H, dd, α-CH, $J_1 = 6.04$ Hz, $J_2 = 9.8$ Hz), 3.72–4.1 (2H, m, Pro-H), 3.58, 4.32 (2H, AB, $CH_2Ph$, $J_{AB} = 12.0$ Hz), 7.18–8.2 (14H, m, ArH), 8.28 (1H, s, N–CH–S).

### 4.4. Complex (*S*,*R*)- or L,L-4

Calcd for $C_{39}H_{38}N_6O_4SNi$: C, 63.85; H, 4.92; N, 7.98. Found: %. C, 63.32; H, 4.72; N, 8.68%. Mp = 138–140 °C. $[\alpha]_D^{25} = +2108.3$ (*c* 0.05, $CHCl_3$); $^1H$ NMR ($CDCl_3$): 1.84 (2H, m, C–$CH_2$–C), 2.1–2.4 (2H, m, Pro-H), 2.62–2.84 (4H, m, Pro-H and $CH_2$–C–C), 3.0 (1H, m, Pro-H), 3.74–3.82 (4H, m, C–C–$CH_2$ and Pro-H), 3.95, 4.85 (2H, AB, $CH_2Ph$, $J_{AB} = 11.92$ Hz), 4.62 (1H, m, α-CH), 4.74–5.0 (2H, m, β-$CH_2$), 6.7–8.4 (19H, m, ArH).

### 4.5. Complex (*S*,*R*)- or L,L-6

Calcd for $C_{36}H_{38}N_6O_4SNi$: C, 60.96; H, 5.36; N, 11.85. Found: C, 60.85; H, 5.28; N, 11.96%. Mp = 144–146 °C. $[\alpha]_D^{25} = +1610.0$ (*c* 0.04, MeOH); $^1H$ NMR ($CDCl_3$): 1.76 (2H, m, C–$CH_2$–C), 2.05–2.32 (4H, m, $CH_2$–C–C and Pro-H), 2.58–2.8 (2H, m, Pro-H), 3.44–3.6 (5H, m, C–C–$CH_2$ and Pro-H), 3.54, 4.38 (2H, AB, $CH_2Ph$, $J_{AB} = 12$ Hz), 4.22 (1H, m, α-CH), 4.44–4.82 (4H, m, $CH_2$—C= and —C=$CH_2$), 5.08–5.16 (2H, m, β-$CH_2$), 5.8–5.92 (1H, m, —CH=), 6.6–8.2 (14H, m, ArH).

### 4.6. Complex (*S*,*R*)- or L,L-8

Calcd for $C_{39}H_{38}N_6O_3SNi$: C, 64.22; H, 5.21; N, 11.53. Found: C, 64.31; H, 5.42; N, 11.48%. Mp = 102–103 °C. $[\alpha]_D^{25} = +1896.3$ (*c* 0.05, $CHCl_3$); $^1H$ NMR ($CDCl_3$): 1.22 (3H, m, $CH_3$), 1.56–1.62 (2H, m, C–$CH_2$–C), 2.06–2.2 (2H, m, Pro-H), 2.32 (2H, m, Pro-H), 2.43 (2H, m, C–C–$CH_2$), 3.48 (1H, m, α-H Pro) 3.60–3.84 (2H, m, Pro-H), 3.56, 4.42 (2H, AB, $CH_2Ph$, $J_{AB} = 12$ Hz), 4.52 (1H, t, α-CH), 4.64, 5.18 (2H, dd, β-$CH_2$), 6.7–8.2 (19H, m, ArH).

### 4.7. Complex (*S*,*R*)- or L,L-10

Calcd for $C_{36}H_{38}N_6O_3SNi$: C, 60.76; H, 5.27; N, 10.74. Found: C, 60.88; H, 5.46; N, 10.03%. Mp = 95–97 °C. $[\alpha]_D^{25} = +1961.9$ (*c* 0.05, $CHCl_3$). $^1H$ NMR ($CDCl_3$): 1.2 (3H, m, $CH_3$), 1.50 (2H, m, C–$CH_2$–C), 1.92 (2H, m, Pro-H), 2.40 (2H, m, C–C–$CH_2$), 2.7–3.0 (3H, m, Pro-H) 3.60–4.0 (2H, m, Pro-H), 3.78, 4.6 (2H, AB, $CH_2Ph$, $J_{AB} = 11.86$ Hz), 4.66 (1H, m, α-CH), 4.88, 5.18 (2H, mm, β-$CH_2$), 4.75–5.5 (4H, m, $CH_2$—C= and —C=$CH_2$), 6.04 (1H, m, —CH=), 6.8–8.4 (14H, m, ArH).

### 4.8. Complex (*S*,*R*)- or L,L-12

Calcd for $C_{45}H_{50}N_6O_5SNi$: C, 63.93; H, 5.92; N, 9.94. Found: C, 64.04; H, 5.98; N, 9.62%. Mp = 69–71 °C. $[\alpha]_D^{25} = +1463.6$ (*c* 0.05, $CHCl_3$); $^1H$ NMR ($CDCl_3$): 0.82 (6H, m, 2·$CH_3$), 1.35–1.74 (3H, m, O–C–$CH_2$ and O–C–C–CH), 1.94–3.8 (m, 16H, O–$CH_2$, $CH_2$–$CH_2$–CH(OH)–$CH_2$–O and Pro-H), 3.52, 4.32 (2H, AB, $CH_2Ph$, $J_{AB} = 12$ Hz), 4.24, 5.0 (2H, mm, β-$CH_2$), 4.62 (1H, m, α-CH), 6.7–8.2 (19H, m, ArH).

### 4.9. Complex (*S*,*R*)- or L,L-14

Calcd for $C_{42}H_{50}N_6O_5SNi$: C, 62.32; H, 6.18; N, 10.39. Found: C, 62.29; H, 6.20; N, 10.42. Mp = 86–88 °C. $[\alpha]_D^{25} = +1821.7$ (*c* 0.05; $CHCl_3$); $^1H$ NMR ($CDCl_3$): 0.8 (6H, m, 2·$CH_3$), 1.2–1.8 (3H, m, O–C–$CH_2$– and O–C–C–CH–), 2.0–3.7 (16H, m, O–$CH_2$–, –$CH_2CH_2$-CH(OH)$CH_2$O and Pro-H), 3.58, 4.4 (2H, AB, $CH_2Ph$, $J_{AB} = 12$ Hz), 4.42, 5.08 (2H, mm, β-$CH_2$), 4.56 (1H, m, α-CH), 4.6–5.2 (4H, m, $CH_2$—C=C—, C—C=$CH_2$), 5.8 (1H, m, —CH=), 6.56–8.2 (14H, m, ArH).

### 4.10. Complex (*S*,*R*)- or L,L-16

Calcd for $C_{40}H_{38}N_6O_4SNi$: C, 63.43; H, 5.02; N, 11.10. Found: C, 63.49; H, 4.59; N, 11.08%. Mp = 91–93 °C. $[\alpha]_D^{25} = +1649.35$ (*c* 0.05, $CHCl_3$); $^1H$ NMR ($CDCl_3$): 2.1–2.18 (2H, m, Pro-H), 2.4–3.08 (3H, m, Pro-H), 3.4–3.6 (2H, m, Pro-H), 3.82, 4.8 (2H, AB, $CH_2Ph$, $J_{AB} = 11.86$ Hz), 3.86 (3H, s, $OCH_3$), 4.56 (1H, m, α-CH), 4.2–4.9 (4H, m, $CH_2$—C=C and C—C=$CH_2$), 4.76, 5.0 (2H, mm, β-$CH_2$), 5.66 (1H, m, —CH=), 6.8–8.4 (18H, m, ArH).

### 4.11. Complex (*S*,*R*)- or L,L-18

Calcd for $C_{39}H_{35}N_6O_3ClSNi$: C, 61.48; H, 4.60; N, 11.04. Found: C, 61.43; H, 4.57; N, 11.08%. Mp = 84–86 °C. $[\alpha]_D^{25} = +1713.7$ (*c* 0.05, $CHCl_3$); $^1H$ NMR ($CDCl_3$): 2.08–2.14 (2H, m, Pro-H), 2.42–3.12 (3H, m, Pro-H), 3.48–3.6 (2H, m, Pro-H), 3.82, 4.78 (2H, AB, $CH_2Ph$, $J_{AB} = 12$ Hz), 4.43 (1H, m, α-CH), 4.48–4.95 (4H, m, $CH_2$—C=C and C—C=$CH_2$), 4.8–5.0 (2H, mm, β-$CH_2$), 5.64 (1H, m, —C—CH=), 6.6–8.4 (18H, m, ArH).

### 4.12. Complex (*S*,*R*)- or L,L-20

Calcd for $C_{41}H_{48}N_6O_4SNi$: C, 63.18; H, 6.16; N, 10.79. Found: C, 63.22; H, 6.12; N, 10.83. Mp = 70–71 °C. $[\alpha]_D^{25} = +1854.55$ (*c* 0.05, $CHCl_3$); $^1H$ NMR ($CDCl_3$): 1.1 (3H, m, $CH_3$), 1.30–1.72 (8H, m, $(CH_2)_4$), 1.9–3.8 (12H, m, $CH_2CH_2CH$ and Pro-H), 3.65, 4.56 (2H, AB, $CH_2Ph$, $J_{AB} = 12$ Hz), 4.51 (1H, m, α-CH), 4.64, 5.46 (2H, mm, β-$CH_2$), 4.95, 5.56 (4H, m, $CH_2$—C=C and C—C=$CH_2$), 6.1 (1H, m, —C—CH=), 6.9–8.4 (14H, m, ArH).

### 4.13. Isolation of amino acids 22–31 from the reaction mixtures

The mixture of the diastereomeric complexes after the establishment of their equilibria was dissolved in 50 mL of $CH_3OH$ and the solution was added slowly to 40 mL

of aq 2 M HCl while being stirred. After disappearance of the red color of the solution, it was evaporated to dryness and 50 mL of water added to it with the initial chiral reagent (*S*)-BPB·HCl filtered. The water solution was extracted with $CHCl_3$ (2×20 mL) in order to secure complete recovery of the reagent. The final amino acids were isolated from the filtrates by ion-exchange techniques.[10–14] The amino acids were recrystallized from a water/EtOH mixture.

### 4.14. (*S*)- or L-β-(2′-amino-1,3,4-thiodiazolyl)-α-alanine 22

Yield: 1.45 g (7.7 mmol), 77%. Calcd for $C_5H_8N_4O_2S$: C, 31.6; H, 4.21; N, 30.52. Found: C, 32.11; H, 4.69; N, 30.89%. Mp = 207–208 °C. $[\alpha]_D^{25} = +31.5$ (*c* 1, 5.7 M HCl); enantiomeric purity by HPLC analysis >98.5%; $^1$H NMR ($D_2O$): 3.88, 3.96 (1H, dd, β-$CH_A$), 4.04, 4.09 (1H, dd, β-$CH_B$), 4.14, 4.16 (1H, dd, α-CH), 8.74 (1H, s, N–CH–S).

### 4.15. (*R*)- or L-(*S*)-5-(3′-hydroxypropyl)-4-phenyl-1,2,4-triazol-3-yl-cysteine 23

Yield: 2.77 g (8.6 mmol), 86%. Calcd for $C_{14}H_{18}N_4O_3S$: C, 48.54; H, 7.19; N, 12.25. Found: C, 49.34; H, 7.11; N, 12.92%. Mp = 220–221 °C. $[\alpha]_D^{25} = -22.3$ (*c* 1, 6 M HCl); Enantiomeric purity by HPLC analysis >99%; $^1$H NMR ($D_2O$): 1.85 (2H, m, C–$CH_2$–C, $J_1 = 6.5$ Hz, $J_2 = 7.5$ Hz), 2.7 (2H, t, C–C–$CH_2$, $J = 7.5$ Hz), 3.6 (2H, t, O–$CH_2$, $J = 6.5$ Hz), 4.78 (1H, dd, α-CH, $J = 4.5$ Hz and 6.3 Hz), 4.89 (1H, dd, S–$CH_A$, $J = 6.3$ Hz and 15 Hz), 5.0 (1H, 2d, S–$CH_B$, $J = 4.5$ Hz and 15 Hz), 7.44–7.5 (2H, m, PhH), 7.74 (3H, m, PhH).

### 4.16. (*R*)- or L-(*S*)-5-(3′-hydroxypropyl)-4-allyl-1,2,4-triazol-3-yl-cysteine 24

Yield: 2.49 g (8.7 mmol), 87%. Calcd for $C_{11}H_{18}N_4O_3S$: C, 46.15; H, 6.29; N, 19.58. Found: C, 46.32; H, 6.33; N, 19.44%. Mp = 195–196 °C. $[\alpha]_D^{25} = -5.5$ (*c* 1, 6 M HCl); Enantiomeric purity by HPLC analysis >98.5%. $^1$H NMR ($D_2O$): 1.61–1.73 (2H, m, C–$CH_2$–C), 2.48–2.54 (2H, t, C–C–$CH_2$), 3.35–3.41 (2H, t, O–$CH_2$), 3.94–4.00 (1H, m, α-CH), 4.39–4.43 (4H, m, β-$CH_2$ and $CH_2$—C=C), 4.98 (1H, d, C=CH, $J = 10.58$ Hz), 4.74 (1H, d, C=CH), 5.58 (1H, m, —CH=).

### 4.17. (*R*)- or L-(*S*)-5-propyl-4-phenyl-1,2,4-triazol-3-yl-cysteine 25

Yield: 2.69 g (8.8 mmol), 88%. Calcd for $C_{14}H_{18}N_4O_2S$: C, 54.90; H, 5.88; N, 18.30. Found: C, 54.81; H, 5.97; N, 18.12%. Mp = 213–216 °C. $[\alpha]_D^{20} = = -24.0$ (*c* 0.1, 6 M HCl); Enantiomeric purity by HPLC analysis >99%; $^1$H NMR (DMSO): 0.91 (3H, m, $CH_3$), 1.57 (m, 2H, C–$CH_2$–C, $J = 7.50$ Hz), 2.43 (2H, m, C–C–$CH_2$, $J = 7.50$ Hz), 4.10 (1H, dd, α-CH, $J_1 = 9.60$ Hz, $J_2 = 4.50$ Hz), 4.43 (1H, dd, AB, S–$CH_A$, $J_1 = 14.40$ Hz, $J_2 = 9.60$ Hz), 4.65 (1H, dd, AB, S–$CH_B$, $J_1 = 14.40$ Hz, $J_2 = 4.50$ Hz), 7.39, 7.55 (5H, mm, $C_6H_5$).

### 4.18. (*R*)- or L-(*S*)-5-propyl-4-allyl-1,2,4-triazol-3-yl-cysteine 26

Yield: 2.27 g (8.4 mmol), 84%. Mp = 190–192 °C. $[\alpha]_D^{20} = -5.0$ (*c* 0.1, 6 M HCl); Calcd for $C_{11}H_{18}N_4O_2S$: C, 42.73; H, 7.2; N, 11.03. Found: C, 42.54; H, 7.8; N, 12.76%. $^1$H NMR ($D_2O$): 1.02 (3H, t, $CH_3$), 1.77 (2H, m, C–$CH_2$–C, $J = 7.4$ Hz), 2.76 (2H, t, C–C–$CH_2$, $J = 7.4$ Hz), 4.71–4.78 (3H, m, $CH_2$—C=C and α-CH), 4.81–5.00 (2H, m, β-$CH_2$), 5.06 (1H, d, CH=C (cys), $J = 17.2$ Hz), 5.33 (1H, d, CH=C (trans), $J = 10.5$ Hz), 5.92–6.04 (1H, m, C—CH=C).

### 4.19. (*R*)- or L-(*S*)-5-(3′-hydroxy-4′-isoamyloxybutyl)-4-phenyl-1,2,4-triazol-3-yl-cysteine 27

Yield: 3.46 g (8.2 mmol), 82%. Calcd for $C_{20}H_{30}N_4O_4S$: C, 56.87; H, 7.11; N, 13.27. Found: C, 57.01; H, 7.16; N, 13.15%; Mp = 163–165 °C. $[\alpha]_D^{20} = -17.0$ (*c* 0.1, 6 M HCl); $^1$H NMR ($D_2O$): 0.88 (6H, dd, $2CH_3$), 1.7 (2H, m, –$CH_2$–C–O–), 1.55 (1H, m, O–C–C–C–$CH_A$), 1.62 (1H, m, $Me_2CH$), 1.72 (1H, m, O–C–C–$CH_B$), 2.53 (2H, m, $CH_2$-Het), 3.12, 3.21 (2H, 2m, O–$CH_2$), 3.35 (2H, t, $CH_2$-O), 3.55 (1H, m, O–C–CH), 4.2 (1H, m, S–$CH_A$), 4.43 (1H, m, α-CH), 4.68 (1H, m, S–$CH_B$), 7.2–7.62 (5H, m, $C_6H_5$).

### 4.20. (*R*)- or L-(*S*)-5-(3′-hydroxy-4′-isoamyloxybutyl)-4-allyl-1,2,4-triazol-3-yl-cysteine 28

Yield: 3.44 g (8.91 mmol), 89%. Calcd for $C_{17}H_{30}N_4O_4S$: C, 56.67; H, 7.14; N, 13.33. Found: C, 56.64; H, 7.16; N, 13.36%; Mp = 183–184 °C. $[\alpha]_D^{20} = -4.5$ (*c* 0.1, 6 M HCl); $^1$H NMR ($D_2O$): 0.93 (6H, t, $(CH_3)_2$), 1.52 (2H, m, O–C–$CH_2$–C), 1.7 (1H, m, $Me_2CH$–), 1.8–1.2 (2H, m, $CH_2$-Het), 3.45–3.70 (4H, m, –$CH_2OCH_2$–), 3.9–3.98 (1H, m, CH(OH)), 4.71–4.79 (3H, m, α-CH and $CH_2$—C=), 4.81–5.0 (2H, m, β-$CH_2$), 5.08 (1H, d, $CH_{cys}$=C, $J = 17.2$ Hz), 5.35 (1H, d, $CH_{trans}$=C, $J = 10.5$ Hz), 5.93–6.1 (1H, m, C—CH=C).

### 4.21. (*R*)- or L-(*S*)-5-(2′-methoxyphenyl)-4-allyl-1,2,4-triazol-3-yl-cysteine 29

Yield: 2.84 g (8.5 mmol), 85%. Calcd for $C_{15}H_{18}N_4O_3S$: C, 53.89; H, 5.39; N, 16.77. Found: C, 54.17; H, 5.41; N, 16.47%; Mp = 210–212 °C. $[\alpha]_D^{20} = -5.0$ (*c* 0.1, 6 M HCl); Enantiomeric purity by HPLC analysis >99%; $^1$H NMR (DMSO): 3.85 (3H, s, $CH_3$), 3.96 (1H, dd, α-CH, $J_1 = 10.2$ Hz, $J_2 = 3.9$ Hz), 4.36 (1H, dd, S–$CH_A$, $J_1 = 14.4$ Hz, $J_2 = 10.2$ Hz), 4.50 (2H, m, $CH_2$—C=C, $J = 5.4$ Hz), 4.72 (1H, dd, S–$CH_B$, $J_1 = 14.4$ Hz, $J_2 = 3.9$ Hz), 4.89 (1H, dd, C—C=$CH_A$, $J_1 = 17.1$ Hz, $J_2 = 1.0$ Hz), 5.0 (1H, dd, C—C=$CH_B$, $J_1 = 10.5$ Hz, $J_2 = 1.0$ Hz), 5.68 (1H, dd, m, C—CH=C,

$J_1 = 17.1$ Hz, $J_2 = 10.5$ Hz, $J_3 = 5.4$ Hz), 7.06–7.54 (4H, m, $C_6H_4$).

### 4.22. (*R*)- or L-(*S*)-5-(2′-chlorophenyl)-4-allyl-1,2,4-triazol-3-yl-cysteine 30

Yield: 2.7 g (8 mmol), 80%; Mp = 215–217 °C. $[\alpha]_D^{20} = -2.0$ (*c* 0.5, 1 M HCl); Enantiomeric purity by HPLC analysis >99%; Calcd for $C_{14}H_{15}N_4O_2SCl$: C, 49.63; H, 4.43; N, 16.54. Found: C, 49.86; H, 4.45; N, 16.3%; $^1$H NMR (DMSO): 4.00 (1H, dd, α-CH, $J_1 = 9.9$ Hz, $J_2 = 3.3$ Hz), 4.39 (1H, dd, S–$CH_A$, $J_1 = 14.1$ Hz, $J_2 = 9.9$ Hz), 4.52 (2H, d, $CH_2$—C═C, $J = 5.4$ Hz), 4.74 (1H, dd, S–$CH_B$, $J_1 = 14.1$ Hz, $J_2 = 3.3$ Hz), 4.90 (1H, dd, C—C═$CH_A$, $J = 17.1$ Hz), 5.03 (1H, dd, C—C═$CH_B$, $J = 10.5$ Hz), 5.7 (1H, dd, m, C—CH═C, $J_1 = 17.1$ Hz, $J_2 = 10.5$ Hz, $J_3 = 5.4$ Hz), 7.4–7.7 (4H, m, $C_6H_4$).

### 4.23. (*R*)- or L-(*S*)-5-(3′-hydroxyoctyl)-4-allyl-1,2,4-triazol-3-yl-cysteine 31

Yield: 2.85 g (8 mmol), 80%; Calcd for $C_{16}H_{28}N_4O_3S$: C, 53.93; H, 7.87; N, 15.73. Found: C, 53.81; H, 7.99; N, 15.65%; Mp = 180–181 °C. $[\alpha]_D^{20} = -4.0$ (*c* 0.1, 6 M HCl); $^1$H NMR ($D_2O$): 0.88 (3H, t, $CH_3$), 1.18–1.4 (8H, m, $(CH_2)_4$; 1.64, 1.78 (2H, mm, C–$CH_2$–C(OH)), 2.64, 2.76 (2H, 2m, $CH_2$–C–C(OH)), 3.44 (1H, m, CH(OH)), 3.8 (1H, m, α-H), 4.22, 4.6 (2H, mm, S–$CH_2$), 4.62 (2H, m, —$CH_2$—C═), 5.14 (2H, m, —C═$CH_2$), 5.84 (1H, m, —CH═C).

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