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# Asymmetric synthesis of (*R*)-*S*-(1,2,4-triazol-3-yl)cysteines by nucleophilic addition of triazolethiols to a Ni$^{II}$ complex with a chiral dehydroalanine Schiff base

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An efficient method was developed for the asymmetric synthesis of (*R*)-*S*-(1,2,4-triazol-3-yl)cysteines by the addition of 3,4-disubstituted 1,2,4-triazole-5-thiols at the electrophilic C=C bond in a Ni$^{II}$ complex of a Schiff base of dehydroalanine with (*S*)-*N*-(*N*-benzylprolyl)aminobenzophenone. The stereoselectivity of the formation of diastereomeric complexes with the (*S*,*R*) configuration under conditions of thermodynamic control of the nucleophilic addition exceeds 94%. Acid treatment of the reaction mixtures afforded enantiomerically pure (*R*)-*S*-hetarylcysteines (*ee* >98%).

**Key words:** dehydroalanine, triazolethiols, asymmetric synthesis, diastereoselectivity, enantiomeric purity, enantiomeric analysis.

Optically active β-substituted α-amino acids serve as important components of many physiologically active peptides, antibiotics, and other pharmaceuticals.[1,2] These compounds include *S*-substituted cysteines,[3,4] which are successfully used in microbiology for selection of highly active producer strains of proteinogenic amino acids.[5—7] (*R*)-Cysteine derivatives containing various heterocyclic substituents can also be of interest in this respect.

Earlier,[8—10] a method has been developed for the asymmetric synthesis of a series of (*R*)-*S*-alkyl- and (*R*)-*S*-arylcysteines by the addition of the corresponding aliphatic and aromatic thiols to a Ni$^{II}$ complex with a Schiff base of dehydroalanine and the chiral carbonyl reagent, *viz.*, (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone ((*S*)-BPB). Subsequent acid treatment of the resulting complexes yielded the target *S*-substituted (*R*)-cysteines.

In the present study, we report the asymmetric synthesis of *S*-substituted (*R*)-cysteines containing 3,4-disubstituted 1,2,4-triazole fragments in the side chain.

The chiral square-planar Ni$^{II}$ complex with the Schiff base formed by dehydroalanine and (*S*)-BPB, *viz.*, [(*S*)-BPB-Δ-Ala]Ni$^{II}$ (**1**), was prepared according to a known procedure.[10]

Thiols **2a—i**, which were synthesized as described earlier,[11,12] were added to complex **1** in MeCN or DMF in the presence of $K_2CO_3$ or NaOH at 25—50 °C. The reactions afforded pairs of diastereomeric complexes with (*R*) and (*S*) configurations of a new chiral center, *viz.*, (*S*,*R*)- and (*S*,*S*)-**3a—i** (Scheme 1).

The absolute configurations of the diastereomeric complexes of the addition products were determined by comparing the optical rotatory dispersion (ORD) curves of individual diastereomers, which were isolated by chromatography on $SiO_2$, with the ORD curves of the structurally similar (*R*)-*S*-benzylcysteine and (*S*)-*S*-benzylcysteine complexes prepared earlier.[8] The ORD curves of diastereomeric complexes (*S*,*R*)- and (*S*,*S*)-**3a,b** and the corresponding complexes with (*R*)- and (*S*)-*S*-benzylcysteines are shown in Fig. 1. The diastereomeric complexes with lower $R_f$ (TLC) have an (*R*) configuration ((*S*,*R*)-**3**), whereas the more mobile diastereomeric complexes have an (*S*) configuration of the amino acid residue ((*S*,*S*)-**3**).

The diastereomeric ratio of the addition products depends on the reaction time. At the beginning of the reaction (within ~10 min after the addition of thiol), the excess of the (*S*,*R*) diastereomer, which has a slower TLC mobility, was 85—90%, which is a consequence of relatively low kinetic enantioselectivity. Then the amount of this diastereomer gradually increases due to the establishment of thermodynamic equilibrium. The thermodynamic

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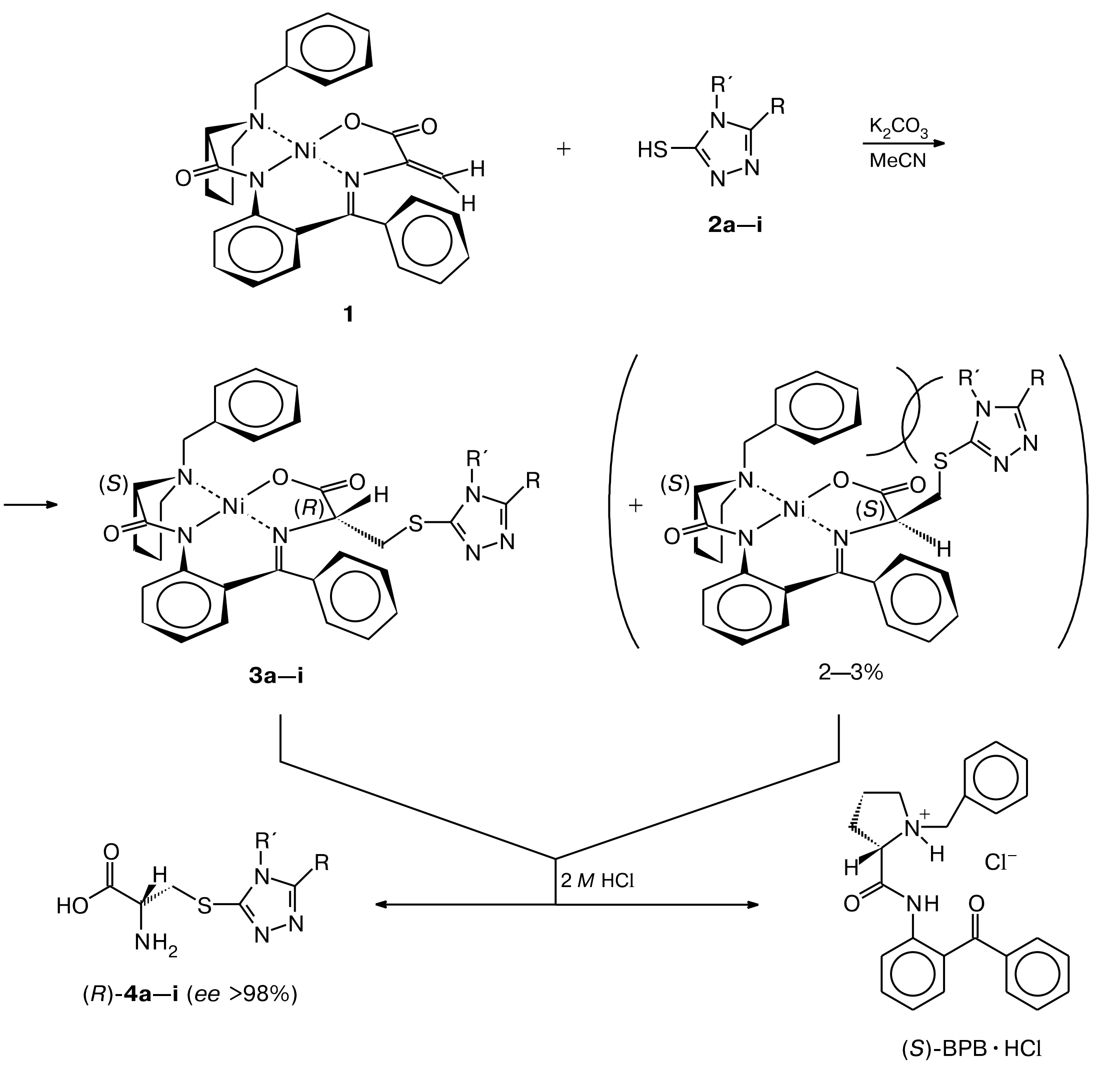
**Scheme 1**



| | R | R′ |
|---|---|---|
| **a** | $CH_2CH_2CH_2OH$ | Ph |
| **b** | $CH_2CH_2CH_2OH$ | $CH_2$—$CH=CH_2$ |
| **c** | Pr | Ph |
| **d** | Pr | $CH_2$—$CH=CH_2$ |
| **e** | $CH_2CH_2CH(OH)CH_2OCH_2CH_2CHMe_2$ | Ph |
| **f** | $CH_2CH_2CH(OH)CH_2OCH_2CH_2CHMe_2$ | $CH_2$—$CH=CH_2$ |
| **g** | *o*-$MeOC_6H_4$ | $CH_2$—$CH=CH_2$ |
| **h** | *o*-$ClC_6H_4$ | $CH_2$—$CH=CH_2$ |
| **i** | $CH_2CH_2CH(OH)C_5H_{11}$ | $CH_2$—$CH=CH_2$ |

diastereomeric ratio was determined from the $^1H$ NMR spectra of the reaction mixture by comparing the intensities of the signals for the protons of the benzyl group of the complex (AB system) at δ 4.2—4.4 for the (*S*) isomer and at δ 4.5—4.6 for the (*R*) isomer and spectrophotometrically based on the absorbance of solutions after chromatographic separation of the diastereomers. The equilibrium ratios of the diastereomers and their chemical yields are given in Table 1.

The addition of nucleophiles and establishment of thermodynamic equilibrium between diastereomers occurred rather rapidly (~1 h) in DMF in the presence of NaOH at 45—50 °C. However, this process was accompanied by the formation of up to 10% of by-products. In MeCN, the addition of heterocyclic thiols to complex **1** ($K_2CO_3$, 45—50 °C) did not afford by-products; however, the establishment of thermodynamic equilibrium between the diastereomeric complexes was more slow (>3 h).

Treatment of a mixture of the diastereomers with HCl after the establishment of thermodynamic equilibrium gave rise to (*R*)-*S*-triazolylcysteines **4a—i** in chemical yields of

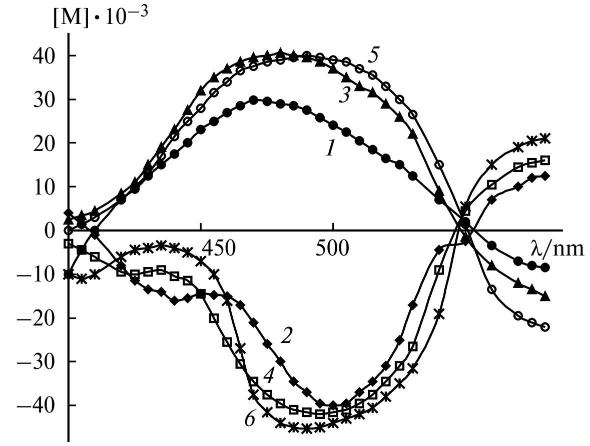


**Fig. 1.** ORD curves of the complexes in MeOH (25 °C): [(*S*)-BPB-*S*-benzyl-(*S*)-cysteine]Ni$^{II}$ (Ref. 8) (*1*), [(*S*)-BPB-*S*-benzyl-(*R*)-cysteine]Ni$^{II}$ (Ref. 8) (*2*), (*S*,*S*)-**3a** (*3*), (*S*,*R*)-**3a** (*4*), (*S*,*S*)-**3b** (*5*), and (*S*,*R*)-**3b** (*6*).

**Table 1.** Results of the asymmetric addition of 3,4-disubstituted 1,2,4-triazole-5-thiols **2a—i** to chiral complex **1** in MeCN at 50 °C for 3 h ($K_2CO_3$ as a base)

| Nucleophile | Yield of a mixture of complexes **3** | *de* of complexes **3*** | Yield of (*R*)-**4** | *ee* (*R*)-**4** |
|---|---|---|---|---|
| | % | | | |
| **2a** | 96 (87)** | 94 (96)** | 86 | 99.5 |
| **2b** | 96 (88)** | 94 (95)** | 87 | 99 |
| **2c** | 94 | 94 | 88 | 99.5 |
| **2d** | 96 | 94 | 84 | 99.5 |
| **2e** | 92 (84)** | 96 (96)** | 82 | 99 |
| **2f** | 90 | 96 | 89 | 99.5 |
| **2g** | 96 | 96 | 85 | 98.5 |
| **2h** | 95 (88)** | 94 (96)** | 80 | 99 |
| **2i** | 90 | 94 | 80 | 99 |

* The diastereomeric excess was determined from the $^1$H NMR spectra of a mixture of diastereomers and spectrophotometrically at 320—340 nm after separation of the mixture on $SiO_2$.

** The reaction conditions: DMF as the solvent, NaOH as the base, 1 h.

>80% with enantiomeric purity of >98%. The starting chiral reagent was recovered (yield >96%) without loss in its optical purity.

The optical purity of the amino acids synthesized was determined by chiral HPLC.

## Experimental

Silica gel L 40/100 μm (Chemapol Praha, Prague), a KU-2x8 cation-exchange resin, $K_2CO_3$, $CHCl_3$, $Ac_2O$, acetone, and MeCN (Reakhim) were used; MeCN was purified according to a known procedure[13] before use. The $^1$H NMR spectra were recorded on a Mercury-300 Varian instrument (300 MHz). The ORD curves were measured on a Jasco ORD/UV-5 spectropolarimeter. The optical rotation was measured on a Perkin—Elmer 341 polarimeter. The diastereomeric ratio was determined on a Specord M-40 spectrophotometer from the relative absorption at the wavelength of 320—340 nm after their chromatographic separation.

The optical purity of amino acids **4a—i** was determined by chiral HPLC on Chiralthech Crownpak CR(+) as a chiral phase ($HClO_4$ (pH 2) as the eluent, the elution rate 0.4 mL min$^{-1}$, 5 °C, the elution order: (*S*) and (*R*) isomers) at the Institute of Organic Catalysis of the University of Rostock (Germany).

**Synthesis of (*R*)-*S*-triazolylcysteines 4a—i (general procedure).** Potassium carbonate (2.5 g, 18 mmol) (or NaOH (0.79 g, 2 mmol)) and thiols **2a—i** (15 mmol) in MeCN (10 mL) were added with stirring to a solution of complex **1** (5.1 g, 10 mmol) in MeCN (or DMF) (20 mL). The reaction mixture was stirred at 50 °C. The course of the reaction was monitored by TLC on $SiO_2$ in a 2 : 1 $CHCl_3$—$Me_2CO$ solvent system by following the disappearance of the starting complex **1**, by $^1$H NMR spectroscopy by following the disappearance of the signals for the vinyl protons (δ 5.85 and 4.10), and spectrophotometrically (400—430 nm). After the establishment of thermodynamic equilibrium (no change in the ratio between the diastereomeric complexes), the reaction mixture was filtered, the precipitate was washed with $CHCl_3$, and the solution in $CHCl_3$ was concentrated *in vacuo* to dryness.

**Individual diastereomers of the complexes** were isolated from the reaction mixtures in the initial phase of the reaction (before the thermodynamic equilibrium was established). For this purpose, a portion of the reaction mixture (5 mL) was diluted with $CHCl_3$ (20 mL) and washed successively with 0.2 *M* 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 $SiO_2$ (30×3 cm) using a 2 : 1 $CHCl_3$—$Me_2CO$ mixture as the eluent. The ORD curves of complexes (*S*,*R*)- and (*S*,*S*)-**3a,b** are shown in Fig. 1.

**Isolation of amino acids 4a—i.** The equilibrium mixture of diastereomeric complexes was dissolved in MeOH (50 mL) and then 2 *M* HCl (40 mL) was slowly added with stirring at 50 °C. After the disappearance of the red color characteristic of the complex, the solution was concentrated to dryness, water (50 mL) was added to the residue, and the starting chiral reagent (*S*)-BPB • HCl was filtered off. To completely separate (*S*)-BPB, the aqueous layer was neutralized and extracted with $CHCl_3$ (2×20 mL). The target amino acids were isolated from aqueous filtrates by ion-exchange technique.[8—10] (*R*)-*S*-Hetarylcysteines were recrystallized from aqueous EtOH.

**(*R*)-*S*-[5-(3-Hydroxypropyl)-4-phenyl-1,2,4-triazol-3-yl]cysteine (4a),** m.p. 220—221 °C, $[\alpha]_D^{25}$ −22.3 (*c* 1, 6 *M* HCl). Found (%): C, 52.02; H, 5.48; N, 17.47. $C_{14}H_{18}N_4O_3S$. Calculated (%): C, 52.17; H, 5.59; N, 17.39. $^1$H NMR ($D_2O$), δ: 1.85 (m, 2 H, —C—$CH_2$—C—); 2.70 (t, 2 H, C—$CH_2$—Het, $J$ = 7.5 Hz); 3.60 (t, 2 H, $OCH_2$, $J$ = 6.5 Hz); 4.78 (X portion of an ABX system, 1 H, α-CH); 4.89 and 5.00 (AB portion of an ABX system, 2 H, —S—$CH_2$—, $J_{AB}$ = 15.0 Hz, $J_{AX}$ = 6.3 Hz, $J_{BX}$ = 4.5 Hz); 7.44—7.50 (m, 2 H, Ph); 7.74 (m, 3 H, Ph).

**(*R*)-*S*-[4-Allyl-5-(3-hydroxypropyl)-1,2,4-triazol-3-yl]cysteine (4b),** m.p. 195—196 °C, $[\alpha]_D^{25}$ −5.5 (*c* 1, 6 *M* HCl). Found (%): C, 46.32; H, 6.33; N, 19.44. $C_{11}H_{18}N_4O_3S$. Calculated (%): C, 46.15; H, 6.29; N, 19.58. $^1$H NMR ($D_2O$), δ:

1.61—1.73 (m, 2 H, —C—CH$_2$—C—); 2.48—2.54 (m, 2 H, —C—CH$_2$—Het); 3.35—3.41 (m, 2 H, HOC$\underline{H}_2$—); 3.94—4.00 (m, 1 H, α-CH); 4.39—4.43 (m, 4 H, —CH$_2$—S + —CH$_2$—C=); 4.98 (d, 1 H, =CH, $J$ = 10.6 Hz); 4.74 (d, 1 H, =CH, $J$ = 17.4 Hz); 5.58 (m, 1 H, —CH=).

**(*R*)-*S*-[4-Phenyl-5-propyl-1,2,4-triazol-3-yl]cysteine (4c),** m.p. 213—216 °C, $[\alpha]_D^{20}$ –24.0 (*c* 0.1, 6 *M* HCl). Found (%): C, 54.81; H, 5.97; N, 18.12. $C_{14}H_{18}N_4O_2S$. Calculated (%): C, 54.90; H, 5.88; N, 18.30. $^1$H NMR (DMSO-d$_6$), δ: 0.91 (t, 3 H, Me—C—C—, $J$ = 7.5 Hz); 1.57 (m, 2 H, —C—CH$_2$—C—); 2.43 (m, 2 H, C—C—CH$_2$—); 4.10 (X portion of an ABX system, 1 H, α-CH); 4.43 and 4.65 (AB portion of an ABX system, 2 H, —S—C$\underline{H}_2$—CH, $J_{AB}$ = 14.4 Hz, $J_{AX}$ = 9.6 Hz, $J_{BX}$ = 4.5 Hz); 7.39 and 7.55 (2 m, 5 H, Ph).

**(*R*)-*S*-[4-Allyl-5-propyl-1,2,4-triazol-3-yl]cysteine (4d),** m.p. 190—192 °C, $[\alpha]_D^{20}$ –5.0 (*c* 0.1, 6 *M* HCl). Found (%): C, 48.76; H, 6.79; N, 20.65. $C_{11}H_{18}N_4O_2S$. Calculated (%): C, 48.89; H, 6.67; N, 20.74. $^1$H NMR (D$_2$O), δ: 1.02 (t, 3 H, Me, $J$ = 7.4 Hz); 1.77 (m, 2 H, C—CH$_2$—C); 2.76 (t, 2 H, —CH$_2$—Het, $J$ = 7.4 Hz); 4.71—4.78 (m, 3 H, CH$_2$—C= + + α-CH); 4.81—5.00 (m, 2 H, CH$_2$—S); 5.06 (d, 1 H, C$\underline{H}_2$=CH, $J_{trans}$ = 17.2 Hz); 5.33 (d, 1 H, C$\underline{H}_2$=CH, $J_{cis}$ = 10.5 Hz); 5.92—6.04 (m, 1 H, —C$\underline{H}$=CH$_2$).

**(*R*)-*S*-[5-(3-Hydroxy-4-isopentyloxybutyl)-4-phenyl-1,2,4-triazol-3-yl]cysteine (4e),** m.p. 163—165 °C, $[\alpha]_D^{20}$ –17.0 (*c* 0.1, 6 *M* HCl). Found (%): C, 57.01; H, 7.16; N, 13.15. $C_{20}H_{30}N_4O_4S$. Calculated (%): C, 56.87; H, 7.11; N, 13.27. $^1$H NMR (D$_2$O), δ: 0.88 (d, 6 H, 2 Me, $J$ = 6.4 Hz); 1.70 (m, 2 H, —CH$_2$—C—O—); 1.55 (m, 1 H, Het—CH$_2$C$\underline{H}_2$CH(OH)CH$_2$—); 1.62 (m, 1 H, Me$_2$—C$\underline{H}$); 1.72 (m, 1 H, Het—CH$_2$C$\underline{H}_2$CH(OH)CH$_2$—); 2.53 (m, 2 H, —CH$_2$—Het); 3.12 and 3.21 (2 m, 2 H, O—CH$_2$—); 3.35 (m, 2 H, —CH$_2$—O); 3.55 (m, 1 H, O—C—CH—); 4.20 (m, 1 H, S—CH$_2$); 4.43 (m, 1 H, α-CH); 4.68 (m, 1 H, S—CH$_2$); 7.20—7.62 (m, 5 H, Ph).

**(*R*)-*S*-[4-Allyl-5-(3-hydroxy-4-isopentyloxybutyl)-1,2,4-triazol-3-yl]cysteine (4f),** m.p. 183—184 °C, $[\alpha]_D^{20}$ –4.5 (*c* 0.1, 6 *M* HCl). Found (%): C, 52.98; H, 7.77; N, 14.39. $C_{17}H_{30}N_4O_4S$. Calculated (%): C, 52.85; H, 7.77; N, 14.51. $^1$H NMR (D$_2$O), δ: 0.93 (d, 6 H, Me$_2$, $J$ = 6.3 Hz); 1.52 (m, 2 H, —C$\underline{H}_2$CH$_2$CH—); 1.70 (m, 1 H, Me$_2$C$\underline{H}$—); 1.80—2.20 (m, 2 H, CH$_2$—Het); 3.45—3.70 (m, 4 H, —C$\underline{H}_2$OC$\underline{H}_2$—); 3.90—3.98 (m, 1 H, —C$\underline{H}$(OH)—); 4.71—4.79 (m, 3 H, α-CH + + —CH$_2$—C=); 4.81—5.00 (m, 2 H, —CH$_2$S—); 5.08 and 5.35 (AB portion of an ABX system, 2 H, C$\underline{H}_2$=CH—, $J_{trans}$ = 17.2 Hz, $J_{cis}$ = 10.5 Hz); 5.93—6.10 (m, 1 H, —C—C$\underline{H}$=CH$_2$).

**(*R*)-*S*-[4-Allyl-5-(2-methoxyphenyl)-1,2,4-triazol-3-yl]cysteine (4g),** m.p. 210—212 °C, $[\alpha]_D^{20}$ –5.0 (*c* 0.1, 6 *M* HCl). Found (%): C, 54.17; H, 5.41; N, 16.47. $C_{15}H_{18}N_4O_3S$. Calculated (%): C, 53.89; H, 5.39; N, 16.77. $^1$H NMR (DMSO-d$_6$), δ: 3.85 (s, 3 H, Me); 3.96 (X portion of an ABX system, 1 H, α-CH); 4.43 and 4.65 (AB portion of an ABX system, 2 H, —S—CH$_2$, $J_{AB}$ = 14.4 Hz, $J_{AX}$ = 10.2 Hz, $J_{BX}$ = 3.9 Hz); 4.89 and 5.00 (AB portion of an ABX system, 2 H, —CH=C$\underline{H}_2$, $J_{trans}$ = 17.1 Hz, $J_{cis}$ = 10.5 Hz, $J_{gem}$ = 1.0 Hz); 5.68 (X portion of an ABX system, —C$\underline{H}$=CH$_2$); 7.06—7.54 (m, 4 H, C$_6$H$_4$).

**(*R*)-*S*-[4-Allyl-5-(2-chlorophenyl)-1,2,4-triazol-3-yl]cysteine (4h),** m.p. 215—217 °C, $[a]_D^{20}$ –2.0 (*c* 0.5, 1 *M* HCl). Found (%): C, 49.86; H, 4.45; N, 16.3. $C_{14}H_{15}ClN_4O_2S$. Calculated (%): C, 49.63; H, 4.43; N, 16.54. $^1$H NMR (DMSO-d$_6$), δ: 4.00 (X portion of an ABX system, 1 H, α-CH); 4.39 and 4.74 (AB portion of an ABX system, —SC$\underline{H}_2$CH, $J_{AB}$ = 14.1 Hz, $J_{AX}$ = 9.9 Hz, $J_{BX}$ = 3.3 Hz); 4.52 (d, 2 H, —C$\underline{H}_2$CH=, $J$ = 5.4 Hz); 4.90 and 5.03 (AB portion of an ABX system, —CH=C$\underline{H}_2$, $J_{trans}$ = 17.1 Hz, $J_{cis}$ = 10.5 Hz, $J_{gem}$ = 5.4 Hz); 5.70 (X portion of an ABX system, —C$\underline{H}$=CH$_2$); 7.40—7.70 (m, 4 H, C$_6$H$_4$).

**(*R*)-*S*-[4-Allyl-5-(3-hydroxyoctyl)-1,2,4-triazol-3-yl]cysteine (4i),** m.p. 180—181 °C, $[\alpha]_D^{20}$ –4.0 (*c* 0.1, 6 *M* HCl). Found (%): C, 53.81; H, 7.99; N, 15.65. $C_{16}H_{28}N_4O_3S$. Calculated (%): C, 53.93; H, 7.87; N, 15.73. $^1$H NMR (D$_2$O), δ: 0.88 (t, 3 H, Me); 1.18—1.40 (m, 8 H, —(CH$_2$)$_4$—); 1.64 and 1.78 (both m, 2 H, —C$\underline{H}_2$CH(OH)—); 2.64 and 2.76 (both m, 2 H, —CH$_2$Het—); 3.44 (m, 1 H, —C$\underline{H}$(OH)—); 3.80 (m, 1 H, α-CH); 4.22 and 4.60 (both m, 2 H, S—CH$_2$); 4.62 (m, 2 H, —C$\underline{H}_2$CH=); 5.14 (m, 2 H, —CH=C$\underline{H}_2$); 5.84 (m, 1 H, —C$\underline{H}$=CH$_2$).

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