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Synthesis of Enantiomerically Enriched 1,2,3-Triazole-derivatized Homoalanines

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Abstract. **In recent decades, the synthesis of amino acid – triazole conjugates has become an emerging area. L- and D-azidohomoalanine derivatives readily undergo copper(I)-catalyzed azide-alkyne dipolar cycloaddition reaction. The expected 4-substituted-1*H*-1,2,3-triazol-1-yl-homoalanines are obtained in the reactions of either *N*- and *O*-protected or protecting-group-free azidohomoalanines with various alkynes. 1,2,3-Triazole conjugate formation tolerates various functional groups. The synthetic approach that uses *N*- and *O*-protected starting materials relays on the standard chromatographic purification of intermediates that are further deprotected by hydrogenolysis. In this way, the purification of final products is not required. The synthetic approach that uses protecting-group-free azidohomoalanine is faster from a synthetic point of view as it includes only one step. However, the purification of protecting-group-free amino acid derivatives is laborious. Additionally, we have shown that the chiral stationary phase CROWNPAK® CR(+), which is based on chiral crown ether as a selector, is applicable for direct chromatographic determination of enantiomeric ratio of the title products.**

Keywords: **azidohomoalanine, 1,2,3-triazolyl homoalanines, alkynes, azide-alkyne cycloaddition, *click* chemistry, CROWNPAK® CR(+) stationary phase, enantiomeric purity**

I. Introduction

Triazoles belong to the class of privileged molecular motifs that are often used to obtain certain biological activities. Triazole containing compounds are known to possess antibacterial, antihelmintic, antifungal and anticancer properties [1]. When attached to a carbohydrate core, triazole derivatives have found applications as antiviral drugs [2,3] and inhibitors of glycosidases [4,5].

Since 2002, 1,2,3-triazoles are regioselectively assembled in copper-catalyzed azide-alkyne cycloaddition reaction, which was independently discovered by the research groups of Meldal [6] and Sharpless [7].

Also in amino acid chemistry their conjugates with triazoles have found notable applications. Thus, triazolyl amino acid based multidentate chelating systems have been investigated as potential diagnostic and therapeutic tools [8]. Triazoles were used to prepare bis-amino acids that are useful as protein crosslinkers [9]. Variable conjugates of amino acids were made via triazole linkers. Those include triazole tethered ferrocenyl-amino acids [10] and both *C*- and *N*-glycosyl α-amino acids [11,12]. On the other hand, both azide- and alkyne-modified amino acids were incorporated into *pseudo*-natural peptides to gain site-specific recombinant infrared probes [13,14]. These modified amino acid residues were also used as bioorthogonal chemical reporters [15]. More recently, metal-free strain-promoted azide-alkyne cycloaddition, developed by Bertozzi [16], has evolved as an important biological tool [17]. Also this approach requires the use of azide-modified entities, including amino acids. The aforementioned facts have aroused the interest in the synthesis and transformations of azide-derivatized amino acids [18].

Despite the various applications, including a potential biological activity, only a few series of simple amino acid - triazole conjugates have been prepared. These are triazolyl alanines **1** (Fig. 1) that have been studied as selective AMPA receptor ligands [19] and substrates for neutral amino acid transport protein SN1 [20]. Hence, we were intrigued to develop the synthesis of -CH_2- homologs of the reported structures **1**: namely 1,2,3-triazolyl homoalanines **2** (Fig. 1).

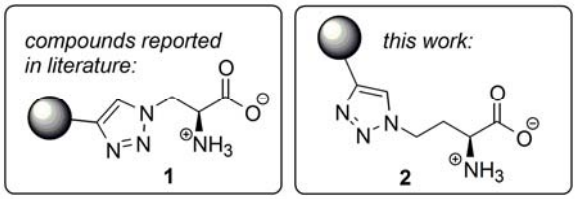


Fig. 1. 1,2,3-Triazolyl alanines **1** versus 1,2,3-triazolyl homoalanines **2**

II. Results and Discussion

Here we report the synthesis and enantiomeric purity analysis of 1,2,3-triazolyl-L-homoalanines **2** [21,22]. Both (*S*)-((*S*)-**3a**) and (*R*)-4-azido-2-amino-butyric acid ((*R*)-**3a**) or L- and D-azidohomoalanine (often abbreviated as *Aha*) are commercially available in unprotected and variously protected forms, but can be easily prepared from aspartic acid [23] (Fig. 2.).

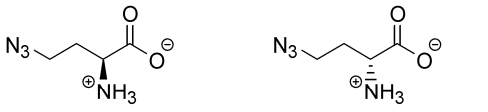
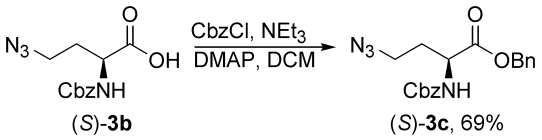


Fig. 2. L- and D-Azidohomoalanines

Our synthetic plan included two distinct approaches: 1) the use of fully protected amino acid followed by deprotection as the last step; 2) the use of unprotected amino acid. As unprotected amino acids are usually difficult to purify, we have started our research with fully protected amino acid (*S*)-**3c.** The latter was synthesized from *N*-benzyloxycarbonyl-L-

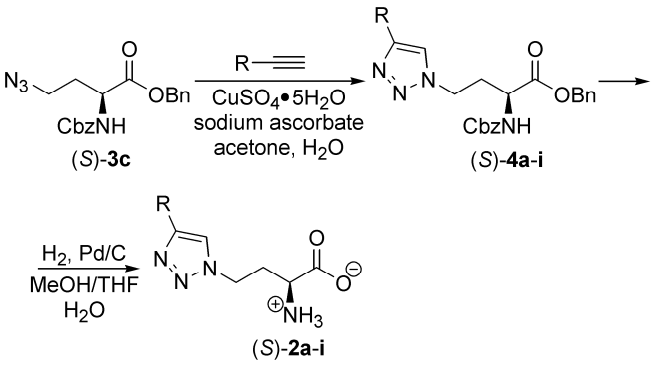
azidohomoalanine ((*S*)-**3b**) and CbzCl *via* decarboxylative benzylation procedure in 69% yield (Scheme 1) [24].



Scheme 1. Synthesis of *N*-benzyloxycarbonyl-L-azidohomoalanine benzyl ester ((*S*)-**3c**)

With starting material (*S*)-**3c** in hand, we proceeded to triazole formation. Various reaction conditions for copper-catalyzed azide-alkyne cycloaddition reaction were screened, including the well-established $CuSO_4$•$5H_2O$/sodium ascorbate system, Cu^0/$CuSO_4$ and CuI. Various solvent systems (acetone/water, CH_2Cl_2/water, *tert*-butanol/water, THF) and temperature regimes (20–80 °C) were also explored. A compromise between slow reaction rates and possible racemization at the α-carbon of the amino acid had to be found. Thus, $CuSO_4$•$5H_2O$/sodium ascorbate catalytic system in acetone/water as a reaction medium was chosen due its mildness regardless of relatively long reaction times (up to 48 hours) (Scheme 2).

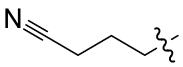
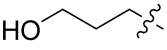
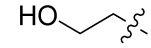
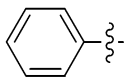
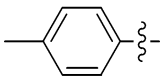
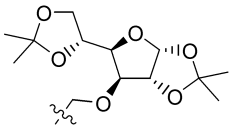
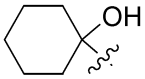
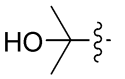
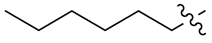
A typical experimental procedure for triazole (*S*)-**4a-i** formation includes mixing of 1 equivalent of azide component (*S*)-**3c** with 1.5 equivalents of alkyne component (R–≡) in acetone/water mixture followed by sequential addition of aqueous solutions containing 10 mol% of copper(II) sulfate and 20 mol% of sodium ascorbate. After stirring of the reaction mixture at ambient temperature for 48 h, the products (*S*)-**4a-i** were isolated by an extractive work-up with CH_2Cl_2. The yields of the products (*S*)-**4a-i** ranged from satisfactory (44% for **4f**) to excellent (84% for **4b**) (Scheme 2, Table 1). It should be mentioned that the lipophilic character of the intermediate products (*S*)-**4a-i** allows their purifications by classic silica gel column chromatography. On the contrary, the purification of the target products (*S*)-**2a-h** is feasible only by precipitation/crystallization techniques, ion exchange and reverse phase chromatography. This fact prompted us to choose *N*-Cbz and *O*-Bn protecting groups as the latter are cleanly cleaved under catalytic hydrogenolysis and produce only volatile side products (CO_2 and toluene). This allows avoiding the extensive purification of the final products, if the intermediates are properly purified. The aforementioned approach is frequently used when the target products are hydrophilic [25]. Thus, hydrogenolysis of (*S*)-**4a-i** in the presence of catalytic amounts of palladium on activated charcoal (10% palladium content) produced cleanly the expected 4-substituted-1*H*-1,2,3-triazol-1-yl-L-homoalanines (*S*)-**2a-h** (Scheme 2, Table 1). Somewhat lower yields of products are explained by partial adsorption on activated charcoal.



Scheme 2. Synthesis of 1,2,3-triazolyl-L-homoalanines (*S*)-**2a-h** *via* *N*-Cbz-*O*-Bn-protected intermediates (*S*)-**4a-i**

TABLE 1

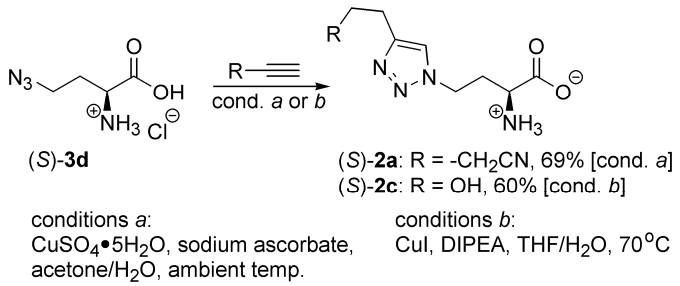
SYNTHESIS OF PRODUCTS (*S*)-**2a-h** and (*S*)-**4a-i** ACCORDING TO SCHEME 2

Entry	R	Product (*S*)-**4a-i**, Yield	Product (*S*)-**2a-e** and (*S*)-**2g,h**, Yield
1.		**4a**, 84%	**2a**, 63%
2.		**4b**, 56%	**2b**, 15%
3.		**4c**, 58%	**2c**, 36%
4.		**4d**, 74%	**2d**, 55%
5.		**4e**, 65%	**2e**, 70%
6.		**4f**, 44%	-*
7.		**4g**, 74%	**2g**, 45%
8.		**4h**, 70%	**2h**, 49%
9.		**4i**, 80%	-*

* – *experiment not performed*

The latter fact prompted us to explore shortly the possibility of target product synthesis without the use of protecting groups (Scheme 3). Thus, hydrochloride (*S*)-**3d** was mixed either with 5-hexynnitrile or with 3-butyn-1-ol in the presence of catalytic systems containing Cu(I). Expected products (*S*)-**2a,c** were isolated in 69% and 60% yield, respectively. The isolated yields are attributed to highly pure compounds (>98%) that were obtained after semi-preparative HPLC

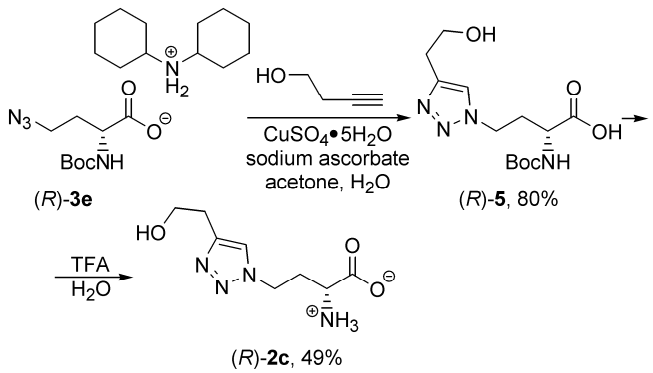
purification (C18 column *Nihon Waters Ltd*. 3.9 × 300 mm; eluent system water → 10% MeOH in water in 8 min). Other methods, such as filtration through activated charcoal, manual column chromatography on reverse phase C18 silica gel and ion exchange chromatography, did not provide sufficiently pure material.



Scheme 3. Direct synthesis of 4-substituted-1*H*-1,2,3-triazol-1-yl-L-homoalanines from L-azidohomoalanine

At this point, one can conclude that the direct synthesis of triazolyl homoalanines (Scheme 3: **3d→2**) is possible and gives comparable or even better yields than a two-step procedure (Scheme 2: **3d→4→2**), but is not very effective due to the laborious purification.

Finally, we turned to the analysis of the enantiomer composition (enantiomeric purity) of the final compounds (*S*)-**2a-h**. It is well accepted that the best methods for quantitation of the presence of each of the enantiomers is chromatography on chiral stationary phase [26]. For this reason, the reference sample of (*R*)-**2** was required to find the chromatographic conditions. As a representative example, the analysis of (*S*)-**2c** and (*R*)-**2c** is described here. A sample of (*R*)-**2c** was synthesized from (*R*)-**3e** (Scheme 4). In this case, dicyclohexylammonium salt of *N*-Boc-D-homoalanine ((*R*)-**3e**) was used. Copper(I) catalyzed azide-alkyne cycloaddition provided intermediate (*R*)-**5** in 80% yield. The cleavage of *N*-Boc protection in water/trifluoroacetic acid followed by semi-preparative HPLC (C18 column *Nihon Waters Ltd*. 3.9 × 300 mm; eluent system water → 10% MeOH in water in 8 min) provided the target product (*R*)-**2c** in 49% yield.



Scheme 4. Synthesis of 1,2,3-triazolyl-D-homoalanine (*R*)-**2c**

Mixing of equal amounts of (*R*)-**2c** and (*S*)-**2c** gave an "*artificial racemate*" that was used to develop the chromatographic analysis on chiral stationary phase. The best results were achieved by CROWNPAK® CR(+) column, which bears a chiral crown ether as a chiral selector coated onto a 5μm silica support (Fig. 3). It shows that the direct synthesis of (*S*)-**2c** with CuI as the catalyst at +70 °C results in partial racemization at α-carbon: isolated product possesses enantiomeric purity of 95%. However, compound (*R*)-**2c** obtained at ambient temperature possesses enantiomeric purity greater than 99.5%. Similarly, compounds (*S*)-**2a-h** (Table 1) revealed excellent enantiomeric purity. In the case of carbohydrate derivative **4f**, the diastereomeric purity was additionally proved by ^{1}H- and ^{13}C-NMR as the spectra revealed only one set of the signals.

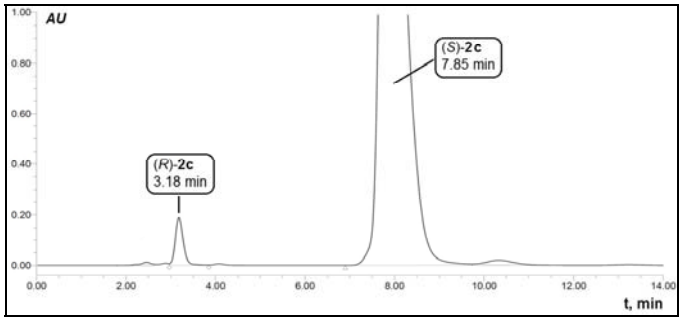


Fig. 3. A chromatogram of (*S*)-**2c** obtained in the process (*S*)-**3d** → (*S*)-**2c** representing e.r. 97.5 : 2.5 (95% ee). Conditions: CROWNPAK® CR(+) column 4.6 × 150 mm; eluent: aqueous $HClO_4$, pH 1 in isocratic mode; flow: 0.5 ml/min; DAD detector at 220 nm; sample conc.: 4 mg/mL; injection vol.: 10 μL.

III. CONCLUSIONS

A straightforward way to 4-substituted-1*H*-1,2,3-triazol-1-yl-L-homoalanines is designed starting from L-azidohomoalanine. The synthesis can be accomplished either with or without protecting groups. The synthetic route that includes the use of protecting groups uses well-established laboratory scale purification techniques, such as silica gel column chromatography, and is obviously longer. On the contrary, the direct synthesis of triazolyl homoalanines is possible and at first glance looks simpler. Nevertheless, it requires laborious purification techniques, preferably preparative HPLC. We have shown that chiral homoalanine derivatives are rather resistant towards racemization under given experimental conditions. However, care should be taken when the reactions are performed at elevated temperatures and prolonged reaction times. The developed method is useful for a small scale synthesis of the aforementioned potentially biologically active amino acid derivatives.

IV. EXPERIMENTAL SECTION

Starting materials (*S*)-**3b,d** and (*R*)-**3e** were obtained from Bapeks Ltd (Riga, Latvia). Other reagents were obtained from *Acros* and used without further purification. Yields refer to chromatographically homogeneous compounds. HPLC analysis was performed on *Agilent Technologies 1200 series* system with DAD detector and *Agilent Zorbax SB* C18, 4.6 ×

150 mm column. Chromatographic conditions (1 mL/ min) for compounds (*S*)-**3c** and (*S*)-**4a-i**: eluent A: aqueous 0.01 M KH_2PO_4 + 6% MeOH, pH 4.6; eluent B: MeOH; gradient: B 0%→B 50% in 10 min. Chromatographic conditions for compound series (*S*)-**2a-h**: gradient: water 100 %→50% MeOH in water in 10 min. For conditions of chromatography on chiral stationary phase see Fig. 3 in the text of publication. Preparative column chromatography was performed on *Rocc* silica gel (40-63 μm). *Merck Silica gel* 60 F_{254} plates were used for TLC analysis of reaction mixtures; visualization was done by UV light or by 1% ninhydrin in EtOH followed by heating. Infrared spectra were performed on *Perkin-Elmer FT-IR* system, ^{1}H- and ^{13}C-NMR analysis were performed on Bruker Ultra Shield apparatus at 300 MHz and 75.5 MHz, respectively. The proton signals for residual non-deuterated solvents (δ 7.26 for $CDCl_3$, 4.79 for D_2O and δ 2.50 for $DMSO_{d6}$) and carbon signals (δ 77.1 for $CDCl_3$ and δ 39.5 for $DMSO_{d6}$) were used as internal references for ^{1}H-NMR and ^{13}C-NMR spectra, respectively. Coupling constants are reported in Hz.

General procedure for the synthesis of 1,2,3-triazolyl-L-homoalanines (*S*)-2a-h according to Scheme 2 and Table 1: **(*S*)-2-Amino-4(4-(3-cyanopropyl)-1*H*-1,2,3-triazol-1-yl)butyric acid ((*S*)-2a).** Hydrogen atmosphere at ambient pressure was applied to a solution of **(*S*)-4a** (0.31 g, 0.67 mmol) in a mixture of MeOH (5 mL), THF (2 mL) and water (0.5 mL) containing 10% Pd/C (30 mg) for 5 hours. The resulting reaction mixture was filtered through a celite pad and washed with MeOH (10 mL). The filtrate was evaporated to dryness. The residue was dissolved in water and lyophilized. Product (*S*)-**2a** (101 mg, 63%) was obtained as amorphous white powder. IR (KBr): 3420, 3125, 3070, 2946, 2602, 1586, 1412, 1349, 1328, 1253, 1216, 1166, 1116, 1075, 1057, 1028. ^{1}H-NMR (D_2O, 300 MHz): 7.87 (s, 1H, H-C(5')), 4.58 (t, 2H, ^3J = 7.4 Hz, H-C(4)), 3.69 (t, 1H, ^3J = 6.6 Hz, H-C(2)), 2.85 (t, 2H, ^3J = 7.2 Hz H-C(1'')), 2.46 (m, 4H, H-C(3); H-C(3'')), 2.00 (quint, 2H, ^3J = 7.2 Hz H-C(2'')). ^{13}C-NMR (D_2O, 75.5 MHz): 171.1, 144.2, 121.7, 119.1, 49.9, 44.3, 28.8, 22.0, 21.3, 13.4. Elem. Anal.: Calcd for $C_{10}H_{16}N_5O_2$ (237.26) C 50.62, H 6.37, N 29.52; Found C 50.31, H 6.55, N 29.27.

(*S*)-2-Amino-4(4-(3-hydroxypropyl)-1*H*-1,2,3-triazol-1-yl)butyric acid ((*S*)-2b). IR (KBr): 3337, 3138, 2945, 2874, 2604, 1586, 1433, 1412, 1390, 1350, 1329, 1254, 1219, 1165, 1148, 1116, 1065, 1052, 1031, 1010. ^{1}H-NMR ($DMSO_{d6}$, 300 MHz): 7.85 (s, 1H, H-C(5')), 4.59 (t, 2H, ^3J = 7.4 Hz, H-C(4)), 3.72 (t, 1H, ^3J = 6.6 Hz, H-C(2)), 3.63 (t, 2H, ^3J = 6.3 Hz H-C(3'')), 2.78 (t, 2H, ^3J = 7.4 Hz H-C(1'')), 2.73 (s, 1H, OH), 2.47 (m, 2H, H- C(3)), 1.91 (quint, 2H, ^3J = 7.0 Hz, H-C(2'')). ^{13}C-NMR ($DMSO_{d6}$, 75.5 MHz): 173.0, 147.6, 123.3, 60.9, 52.0, 46.4, 31.0, 30.9, 20.9.

(*S*)-2-Amino-4(4-(2-hydroxyethyl)-1*H*-1,2,3-triazol-1-yl)butyric acid ((*S*)-2c). IR (KBr): 3133, 2932, 2600, 2091, 1598, 1462, 1411, 1391, 1350, 1329, 1254, 1219, 1073, 1052, 1025. ^{1}H-NMR (D_2O, 300 MHz): 7.89 (s, 1H, H-C(5')), 4.61 (t, 2H, ^3J = 7.4 Hz, H-C(4)), 3.87 (t, 2H, ^3J = 6.3 Hz, H-C(2'')), 3.73 (t, 1H, ^3J = 6.6 Hz H-C(2)), 2.96 (t, 2H, ^3J = 6.3 Hz, H-C(1'')), 2.47 (m, 2H, H-C(3)). ^{13}C-NMR (D_2O, 75.5 MHz): 173.2, 145.2, 124.0, 60.5, 52.0, 46.5, 34.0, 27.7. HRMS (ESI-TOF): Calcd $[C_8H_{14}N_4O_3+H]^+$ 215.1144; Found 215.1168.

(*S*)-2-Amino-4(4-phenyl-1*H*-1,2,3-triazol-1-yl)butyric acid ((*S*)-2d). IR (KBr): 3424, 3087, 2926, 1587, 1412, 1385, 1348, 1335, 1145, 1114, 1082. ^{1}H-NMR ($DMSO_{d6}$, 300 MHz): 8.40 (s, 1H, H-C(5')), 7.86 (dd, 2H, ^3J = 7.0 Hz, ^4J = 1.2 Hz, H-C(Ph)), 7.57 (dd, 2H, ^3J = 7.0 Hz, ^4J = 1.2 Hz, H-C(Ph)), 4.49 (m, 1H, H-C(Ph)), 4.69 (t, 2H, ^3J = 7.8 Hz, H-C(4)), 3.73 (t, 1H, ^3J = 6.6 Hz, H-C(2)), 2.51 (m, 2H, H-C(3)).

(*S*)-2-Amino-4(4-(4-methylphenyl)-1*H*-1,2,3-triazol-1-yl)butyric acid ((*S*)-2e). IR (KBr): 3409, 2924, 1581, 1456, 1385, 1150. ^{1}H-NMR ($DMSO_{d6}$, 300 MHz): 8.35 (s, 1H, H-C(5')), 7.75 (d, 2H, ^3J = 7.8 Hz, H-C(Ph)), 7.39 (d, 2H, ^3J = 7.4 Hz, H- C(Ph)), 4.69 (m, 2H, H-C(4)), 3.61 (t, 1H, ^3J = 6.3 Hz, H-C(2)), 2.51 (m, 2H, H-C(3)), 2.40 (s, 3H, Ph-$\underline{CH_3}$).

(*S*)-2-Amino-4(4-(1-hydroxycyclohexyl)-1*H*-1,2,3-triazol-1-yl)butyric acid ((*S*)-2g). IR (KBr): 3257, 3135, 2931, 2858, 1631, 1557, 1454, 1440, 1404, 1352, 1333, 1184, 1168, 1130, 1078, 1058. ^{1}H-NMR ($DMSO_{d6}$, 300 MHz): 8.00 (s, 1H, H-C(5')), 4.62 (t, 2H, ^3J = 7.4 Hz, H-C(4)), 3.73 (t, 1H, ^3J = 6.6 Hz, H-C(2)), 2.48 (m, 2H, H-C(3)), 2.10 (m, 2H, H-C(Cy)), 1.84 (m, 2H, H-C(Cy)), 1.69 (m, 2H, H- C(Cy)), 1.52 (m, 2H, H- C(Cy)), 1.44 (m, 2H, H-C(Cy)). ^{13}C-NMR ($DMSO_{d6}$, 75.5 MHz): 173.0, 145.2, 122.8, 69.7, 52.0, 46.6, 36.9, 36.8, 31.0 (2C), 24.7, 21.8. HRMS (ESI-TOF): Calcd $[C_{12}H_{20}N_4O_3+H]^+$ 269.1614; Found 269.1640.

(*S*)-2-Amino-4(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)butyric acid ((*S*)-2h). IR (KBr): 3272, 3123, 3076, 2985, 2761, 2599, 1609, 1557, 1539, 1472, 1442, 1417, 1385, 1369, 1353, 1323, 1303, 1221, 1161, 1144, 1050, 956. ^{1}H-NMR ($DMSO_{d6}$, 300 MHz): 7.98 (s, 1H, H-C(5')), 4.62 (t, 2H, ^3J = 7.0 Hz, H-C(4)), 3.79 (s, 1H, OH), 3.73 (t, 1H, ^3J = 6.6 Hz, H-C(2)), 2.47 (m, 2H, H-C(3)), 1.62 (s, 6H, CH_3). ^{13}C-NMR ($DMSO_{d6}$, 75.5 MHz): 173.2, 154.8, 121.9, 68.1, 52.0, 46.5, 30.9, 28.8. HRMS (ESI-TOF): Calcd $[C_9H_{16}N_4O_3+H]^+$ 229.1301; Found 229.1311.

Synthesis of (*S*)-2-Amino-4(4-(3-cyanopropyl)-1*H*-1,2,3-triazol-1-yl)butyric acid ((*S*)-2a) according to Scheme 3: 5-Hexynnitrile (87 μL, 0.83 mmol) was added to a solution of (*S*)-**3d** (100 mg, 0.55 mmol) in acetone (2 mL) at ambient temperature followed by addition of a solution of $CuSO_4$•$5H_2O$ (14 mg, 0.06 mmol) in water (1 mL) and a solution of sodium ascorbate (22 mg, 0.11 mmol) in water (1 mL). The resulting reaction mixture was stirred at ambient temperature for 48 hours. Then it was evaporated to dryness and redissolved in 10% aqueous trifluoroacetic acid (2 mL). The latter solution was passed through a pad of C18 reversed phase silica gel and further eluted with water (25 mL) and methanol (30 mL). The product-containing fractions were evaporated and additionally purified by semi-preparative HPLC purification (C18 column *Nihon Waters Ltd*. 3.9 × 300 mm; eluent system water → 10% MeOH in water in 8 min). After lyophilisation **(*S*)-2a** (91 mg, 69%) was obtained as white amorphous powder.

Synthesis of (*S*)-2-Amino-4(4-(2-hydroxyethyl)-1*H*-1,2,3-triazol-1-yl)butyric acid ((*S*)-2c) according to Scheme 3:

CuI (20 mg, 0.11 mol) and DIPEA (38 μL, 0.22 mmol) were added to a stirred solution of (*S*)-**3d** (190 mg, 1.05 mmol) and 3-butyn-1-ol (123 μL, 1.62 mmol) in a mixture of water (3 mL) and THF (1 mL). The resulting reaction mixture was heated at 70 °C for 5 hours. The reaction mixture was evaporated to dryness, redissolved in water (3 mL) and the resulting solution was passed through a pad of activated charcoal. The charcoal pad was further eluted with water (50 mL) and methanol (50 mL). The product-containing fractions were evaporated and additionally purified by semi-preparative HPLC purification (C18 column *Nihon Waters Ltd*. 3.9 × 300 mm; eluent system water → 10% MeOH in water in 8 min). After lyophilisation **(*S*)-2c** (136 mg, 60%) was obtained as white amorphous powder.

Synthesis of (*R*)-2-Amino-4(4-(2-hydroxyethyl)-1*H*-1,2,3-triazol-1-yl)butyric acid ((*R*)-2c) according to Scheme 4: 3-butyn-1-ol (31 μL, 0.43 mmol) was added to a solution of (*R*)-**3e** (102 mg, 0.24 mmol) in acetone (2 mL) at ambient temperature followed by addition of a solution of $CuSO_4$•$5H_2O$ (8 mg, 0.03 mmol) in water (1 mL) and a solution of sodium ascorbate (12 mg, 0.06 mmol) in water (1 mL). The resulting reaction mixture was stirred at ambient temperature for 20 hours. Then it was evaporated to dryness and redissolved in 1M aqueous Na_2SO_4 solution (10 mL) acidified with $NaHSO_4$ to pH 2.5. The aqueous phase was extracted with DCM (6 × 7 mL). The combined organic layer was dried (Na_2SO_4), filtered and evaporated. Silica gel column chromatography provided (*R*)-**5** (60 mg, 80%) as yellowish oil. The latter was emulsified in a mixture consisting of water (1 mL) and trifluoroacetic acid (100 μL) and stirred for 2 hours at ambient temperature. Then the reaction mixture was evaporated to dryness. Water (2 mL) was added and the evaporation was repeated until no trifluoroacetic acid could be detected. The product was purified by semi-preparative HPLC purification (C18 column *Nihon Waters Ltd*. 3.9 × 300 mm; eluent system water → 10% MeOH in water in 8 min). After lyophilisation **(*R*)-2c** (20 mg, 49% [40% after 2 steps]) was obtained as white amorphous powder.

(S)-Benzyl 4-azido-2-(benzyloxycarbonyl-amino)butanoate ((*S*)-3c). CbzCl (1.28 mL, 8.98 mmol) was slowly added to an ice-cold solution of (*S*)-3**b** (2.50 g, 8.98 mmol) and NEt_3 (1.38 mL, 9.88 mmol) in DCM (50 mL). After 5 minutes DMAP (0.11 g, 0.90 mmol) was added at 0 °C and the resulting mixture was stirred at ambient temperature for 17 hours. Then it was transferred into a separatory funnel and washed with saturated aqueous solution of $NaHCO_3$ (3×15 mL). Organic phase was additionally washed with 2% aqueous HCl (3×15 mL) and brine (20 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (10% hexanes in toluene). Product (*S*)-**3c** (2.30 g, 69%) was obtained as colourless oil; HPLC purity 98% (t_R = 3.23 min).

General procedure for the synthesis of 1,2,3-triazolyl-l-homoalanines (*S*)-4a-i according to Scheme 2 and Table 1: **(*S*)-Benzyl 2-(benzyloxycarbonylamino)-4-(4-(3-cyanopropyl)-1*H*-1,2,3-triazol-1-yl)butanoate ((*S*)-4a).** 5-Hexynnitrile (214 μL, 2.04 mmol) was added to a solution of (*S*)-**3c** (501 mg, 1.36 mmol) in acetone (6 mL) at ambient temperature followed by addition of a solution of $CuSO_4$•$5H_2O$ (35 mg, 0.14 mmol) in water (1 mL) and a solution of sodium ascorbate (55 mg, 0.28 mmol) in water (1 mL). The resulting reaction mixture was stirred at ambient temperature for 48 hours and the acetone was evaporated under reduced pressure. The residue was diluted with DCM (15 mL) and the resulting biphasic mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with DCM (5 mL). The combined organic layer was washed with brine (2 × 10 mL), dried (Na_2SO_4), filtered and evaporated. Silica gel column chromatography provided (*S*)-**4a** (527 mg, 84%) as yellowish oil. IR (KBr): 3335, 3141, 3035, 2954, 1722, 1530, 1499, 1455, 1381, 1382, 1268, 1216, 1054. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.35 (m, 11H, H-C(Ph), H-C(5')), 5.65 (d, 1H, ^3J = 8.1 Hz, NH), 5.12, 5.11 (2s, 4H, O-$\underline{CH_2}$-Ph), 4.38 (m, 3H, H-C(4, 2)), 2.82 (t, 2H, ^3J = 7.2 Hz, H-C(1'')), 2.50-2.27 (m, 2H, H-C(3)), 2.38 (t, 2H, ^3J = 7.4 Hz, H-C(3'')), 2.03 (quin, 2H, ^3J = 7.2 Hz H-C(2'')). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 170.4, 155.6, 144.9, 135.4, 134.3 128.1, 128.0, 127.9, 127.7, 127.7, 127.5, 121.5, 118.9, 67.0, 66.6, 51.0, 45.8, 32.2, 24.2, 23.5, 15.7.

(*S*)-Benzyl 2-(benzyloxycarbonylamino)-4-(4-(3-hydroxypropyl)-1*H*-1,2,3-triazol-1-yl)butanoate ((*S*)-4b). IR (KBr): 3339, 3143, 3065, 3035, 2948, 1722, 1534, 1499, 1455, 1382, 1337, 1268, 1216, 1056. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.30 (m, 11H, H-C(Ph), H-C(5')), 6.06 (d, 1H, ^3J = 8.1 Hz, HN), 5.09; 5.08 (2s, 4H, O-$\underline{CH_2}$-Ph), 4.34 (m, 3H, H-C(2), H-C(4)), 3.63 (t, 2H, ^3J = 6.2 Hz, H-C(3'')), 3.31 (bs, 1H, OH), 2.75 (t, 2H, ^3J = 7.4 Hz, H-C(1'')), 2.45-2.26 (m, 2H, H-C(3)), 1.86 (quin, 2H, ^3J = 6.9 Hz, H-C(2'')). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 171.0, 156.1, 147.3, 135.8, 134.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 121.6, 67.3, 67.0, 61.2, 51.5, 46.1, 32.5, 31.7, 21.7.

(*S*)-Benzyl 2-(benzyloxycarbonylamino)-4-(4-(2-hydroxyethyl)-1*H*-1,2,3-triazol-1-yl)butanoate ((*S*)-4c). IR (KBr): 3308, 3145, 3065, 3035, 2953, 1721, 1535, 1499, 1455, 1381, 1336, 1268, 1216, 1054. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.41 (bs, 1H, H-C(5')), 7.33 (m, 10H, H-C(Ph)), 5.74 (d, 1H, ^3J = 7.9 Hz, NH), 5.10, 5.09 (2s, 4H, O-$\underline{CH_2}$-Ph), 4.36 (m, 3H, H-C(2), H-C(4)), 3.89 (bs, 1H, OH), 2.89 (m, 2H, H-C(1'')), 2.73 (m, 2H, H-C(2'')), 2.49-2.28 (2m, 2H, H-C(3)). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 171.4, 156.5, 148.5, 136.2, 135.1, 134.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 67.8, 67.4, 61.7, 51.8, 46.7, 31.0, 29.0.

(*S*)-Benzyl 2-(benzyloxycarbonylamino)-4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)butanoate ((*S*)-4d). IR (KBr): 3394, 3135, 3092, 3063, 3031, 2945, 1725, 1713, 1500, 1463, 1455, 1430, 1289, 1274, 1215, 1049. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.81 (d, 2H, ^3J = 7.2 Hz, H-C(Ph)), 7.80 (s, 1H, H-C(5')), 7.44 (d, 2H, ^3J = 7.2 Hz, H-C(Ph)), 7.42 (m, 1H, H-C(Ph)) 7.34 (m, 10H, H-C(Ph)), 5.53 (d, 1H, ^3J = 8.1 Hz, NH), 5.12, 5.11 (2s, 4H, O-$\underline{CH_2}$-Ph), 4.46 (m, 3H, H-C(2;4)), 2.52-2.35 (2m, 2H, H-C(3)). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 170.9, 156.1, 147.6, 135.9, 134.7, 130.4, 128.7, 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 125.6, 120.3, 67.6, 67.2, 51.6, 46.5, 32.9.

(*S*)-Benzyl 2-(benzyloxycarbonylamino)-4-(4-(4-methylphenyl)-1*H*-1,2,3-triazol-1-yl)butanoate ((*S*)-4e). IR (KBr): 3393, 2924, 1711, 1458, 1376, 1303, 1155, 1051. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.74 (s, 1H, H-C(5')), 7.69 (d, 2H, ^{3}J = 8.1 Hz H-C(Ph)), 7.35 (m, 10H, H-C(Ph)), 7.21 (m, 2H, H-C(Ph)), 5.51 (d, 1H, ^{3}J = 7.4 Hz, NH), 5.12, 5.11 (2s, 4H, O-$\underline{CH_2}$-Ph), 4.45 (m, 3H, H-C(2,4)), 2.57-2.33 (2m, 2H, H-C(3)), 2.38 (s, 3H, Ph-$\underline{CH_3}$)). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 170.5, 155.6, 147.4, 137.6 (2C), 134.3 (2C), 129.0, 128.3, 128.1, 128.0, 127.9, 127.7, 127.2, 125.2, 119.5, 67.3, 66.9, 51.3, 46.0, 32.8, 20.8.

L-homoalanine – 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose conjugate ((*S*)-4f). IR (KBr): 3386, 3339, 3143, 3111, 3091, 3066, 3035, 2938, 2988, 2102, 1960, 1881, 1725, 1609, 1587, 1525, 1455, 1383, 1327, 1265, 1215, 1164, 1122, 1082. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.63 (s, 1H, H-C(5')), 7.34 (m, 10H, H-C(Ph)), 5.84 (d, 1H, ^{3}J = 3.6 Hz, H-C(1'')), 5.59 (d, 1H, ^{3}J = 7.9 Hz, NH), 5.12, 5.11 (2s, 4H, O-$\underline{CH_2}$-Ph), 4.77 (2d, 2H, AB syst, ^{2}J = 12.6 Hz, H-C(1''')), 4.59 (d, 1H, ^{3}J = 3.8 Hz, H-C(2'')), 4.40 (m, 3H, H-C(2); H-C(4)), 4.31 (m, 1H, H-C(4''), 4.13 – 3.97 (m, 3H, H-C(3''), H-C(5''), H-C(6'')), 2.52, 2.30 (2m, 2H, H-C(3)), 1.48 (s, 3H, CH3), 1.41 (s, 3H, CH3), 1.34 (s, 3H, CH3), 1.29 (s, 3H, CH3). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 170.8, 155.8, 134.7, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 128.1, 111.8, 109.0, 105.1, 82.6, 81.7, 81.0, 73.3, 68.4, 67.7, 67.3, 63.9, 51.6, 46.5, 33.1, 30.9, 26.8, 26.7, 26.6, 26.1, 25.4.

(*S*)-Benzyl 2-(benzyloxycarbonylamino)-4-(4-(1-hydroxycyclohexyl)-1*H*-1,2,3-triazol-1-yl)butanoate ((*S*)-4g). IR (KBr): 3344, 3150, 3089, 3063, 3036, 2927, 2855, 1737, 1691, 1534, 1497, 1455, 1385, 1338, 1286, 1263, 1217, 1185, 1140, 1084, 1054, 1037, 1001. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.35 (m, 11H, H-C(Ph), H-C(5')), 5.51 (d, 1H, ^{3}J = 6.8 Hz, NH), 5.13, 5.11 (2s, 4H, O-$\underline{CH_2}$-Ph), 4.39 (m, 3H, H-C(2); H-C(4)), 2.52 (bs, 1H, OH), 2.40-1.16 (m, 12H, H-C(3); Cy). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 170.5, 155.6, 146.2, 135.5, 134.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 121.1, 67.2, 66.8 (2C), 51.3, 46.2, 37.7, 36.8, 32.5 (2C), 24.9, 21.5.

(*S*)-Benzyl 2-(benzyloxycarbonylamino)-4-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)butanoate ((*S*)-4h). IR (KBr): 3332, 3160, 3090, 3068, 3035, 2971, 2931, 1690, 1537, 1497, 1456, 1382, 1284, 1262, 1206, 1175, 1148, 1087, 1052. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.48 (bs, 1H, H-C(5')), 7.35 (m, 10H, H-C(Ph)), 5.55 (d, 1H, ^{3}J = 7.7 Hz, NH), 5.13, 5.11 (2s, 4H, O-$\underline{CH_2}$-Ph), 4.38 (m, 3H, H-C(4); H-C(2)), 2.52, 2.31 (2m, 2H, H-C(3)), 1.62(s, 6H, H-C(1''); H-C(3'')). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 170.9, 156.1, 147.9, 135.9, 134.8, 128.7 (2C), 128.5, 128.4, 128.3, 128.1 (2C), 67.7, 67.3 (2C), 51.7, 46.5, 33.0, 30.4.

(*S*)-Benzyl 2-(benzyloxycarbonylamino)-4-(4-hexyl-1*H*-1,2,3-triazol-1-yl)butanoate ((*S*)-4i). IR (KBr): 3366, 3125, 3069, 3031, 2957, 2927, 1744, 1698, 1514, 1454, 1378, 1351, 1294, 1259, 1239, 1062, 1025. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.35 (m, 11H, H-C(Ph), H-C(5')), 5.50 (d, 1H, ^{3}J = 7.5 Hz, NH), 5.12, 5.11 (2s, 4H, O-$\underline{CH_2}$-Ph), 4.40 (m, 2H, H-C(2)), 2.68 (m, 2H, H-C(1'')), 2.50 (m, 1H, H-C(4)), 2.30 (m, 2H, H-C(3)), 1.65 (m, 2H, H-C(2'')), 1.31 (m, 6H, H-C(3''); H-C(4''); H-C(5'')), 0.88 (t, 3H, ^{3}J = 6.4 Hz H-C(6'')). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 170.7, 156.1, 148.1, 135.9, 134.8, 128.7, 128.7, 128.6, 128.4, 128.3, 128.1 (2C), 67.7, 67.2, 51.7, 33.2, 31.6, 29.7, 29.3, 28.9, 25.6, 22.5, 14.0.

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Māris Turks, Nataļja Streļņikova, Viktors Kumpiņš, Udo Kalējs. Enantiomēri bagātinātu homoalanīnu 1,2,3-triazolilatvasinājumu sintēze

Dabasvielu, to skaitā aminoskābju, konjugāti ar triazoliem ieguvuši īpašu uzmanību pēdējā desmitgadē, kopš *klik* ķīmijas koncepta attīstības. Komerciāli pieejamie L- un D-azidohomoalanīna (4-azido-2-amino-butānskābes) atvasinājumi viegli stājas vara(I) katalizētās azīdu alkīnu dipolārajās cikopievienošanās reakcijās ar dažādiem terminālajiem alkīniem. Pie C(4)-aizvietoti 1*H*-1,2,3-triazol-1-il-homoalanīni iegūstami gan no neaizsargātiem enantiomēri tīriem homoalanīniem, piemēram, no attiecīgā hidrohlorīda, gan no *N*- un *O*-aizsargātām izejvielām. Šajā kontekstā darbā lietoti *N*-Cbz-*O*-Bn-L-homoalanīns un *N*-Boc-D-homoalanīna dicikloheksilamonija sāls. 1,2,3-Triazolu konjugātu sintēze tolerē dažādas funkcionālās grupas: iegūti cikloadukti no 5-heksīnnitrila, 3-butīn-1-ola, 4-pentīn-1-ola, fenilacetilēna, tolilacetilēna, 3-*O*-propagil-1,2:5,6-di-*O*-izopropilidēn-α-D-glikofuranozes, 1-etinil-1-cikloheksanola, 2-metil-3-butīn-2-ola un 1-oktīna. *N*- un *O*-aizsarggrupu lietošana atvieglo starpproduktu attīrīšanu, kurai var lietot silikagēla kolonnu hromatogrāfiju. Šādi attīrītus triazola ciklu saturošus starpproduktus iespējams katalītiski hidrogenēt, tādējādi iegūstot praktiski tīrus galaproduktus, jo aizsarggrupu nošķelšanas blakusprodukti ir toluols un CO_2. *N*-Cbz-*O*-Bn-L-homoalanīna gadījumā triazolu sintēzē sasniegti iznākumi līdz 84% un aizsargrupu nošķelšanā līdz 70%. Arī 1*H*-1,2,3-triazol-1-il-homoalanīni, kas iegūti no *N*-Boc-D-homoalanīna dicikloheksilamīnija sāls, ir attīrāmi ar tiešās fāzes hromatogrāfijas palīdzību. Pēc citas pieejas iespējams lietot neaizsargātu aminoskābi tās hidrohlorīda veidā. Šī metode, būdama īsāka no sintētiskā viedokļa, raksturojama ar darbietilpīgu attīrīšanu – puspreparatīvo AEŠH. Citas aminoskābju ķīmijā raksturīgās attīrīšanas metodes – jonapmaiņas hromatogrāfija un manuālā kolonnu hromatogrāfija uz C18 apgrieztās fāzes – nedeva vēlamos rezultātus. Parādīts, ka pie C(4)-aizvietotu 1*H*-1,2,3-triazol-1-il-homoalanīnu enantiomēru attiecības tiešai AEŠH analīzei pielietojama CROWNPAK® CR(+) stacionārā fāze, kas veidota no hirāla krauna ētera selektora. Iegūtajiem hirālajiem L- un D-homoalanīna triazolu konjugātiem noteikts to enantiomērais pārākums, kas svārstījās no 95% līdz >99.5%. Produkti ar augstu enantiomēro tīrību iegūti sintēzēs, kas veiktas 20-25 °C temperatūrā katalītiskās sistēmas $CuSO_4$/nātrija askorbāts klātienē. Reakcijas maisījuma sildīšana līdz 70 °C vara(I) katalizatora un trešējo amīnu klātienē inducē daļēju produktu racemizāciju līdz 95% ee.

Марис Туркс, Наталья Стрельникова, Викторс Кумпиньш, Удо Калейс. Синтез энантиомерно обогащенных производных 1,2,3-триазолилгомоаланина

Конъюгаты природных веществ, в том числе аминокислот, и триазолов получили особое внимание в прошедшее десятилетие после открытия концепции клик-химии. Коммерчески доступные производные D- и L-азидогомоаланина (4-азидо-2-аминобутановая кислота) реагируют с различными терминальными алкинами в катализируемых медью(I) реакциях 1,3-диполярного циклоприсоединения. Замещенные 1*H*-1,2,3-триазол-1-ил-гомоаланины получают как из энантиомерно чистых гомоаланинов, к примеру, из соответствующего гидрохлорида, так и из *N*- и *O*-защищенных исходных веществ. В данной работе использованы *N*-Cbz-*O*-Bn-L-гомоаланин и дициклогексиламмониевая соль *N*-Boc-D-гомоаланина. Синтез 1,2,3-триазолов позволяет использовать различные функциональные группы, благодаря чему получены аддукты 5-гексиннитрила, 3-бутин-1-ола, 4-пентин-1-ола, фенилацетилена, п-толилацетилена, 3-*O*-пропаргил-1,2:5,6-ди-*O*-изопропилиден-α-D-глюкофуранозы, 1-этинил-1-циклогексанола, и 1-октина. Использование *N*- и *O*-защитных групп облегчает процесс очистки промежуточных продуктов, для которого можно использовать колонную хроматографию на силикагеле. Очищенные таким образом триазолы можно каталитически гидрогенировать с целью получения практически чистых продуктов, ведь в результате снятия защитных групп выделяются толуол и углекислый газ. В синтезах продуктов циклоприсоединения *N*-Cbz-*O*-Bn-L-гомоаланина выходы достигали 84%, а в реакциях снятия защитных групп – 70%. Продукты, полученные из дициклогексиламмониевой соли *N*-Boc-D-гомоаланина, также могут быть очищены при помощи колонной хроматографии на прямой фазе. Другой подход необходим при использовании гидрохлорида гомоаланина. В таком случае, при меньшей синтетической работе, для очистки используется работоемкая полупрепаративная высокоэффективная жидкостная хроматография. Другие методы очистки аминокислот – ионобменная хроматография и колонная хроматография на обратной фазе – не дали желаемого результата. Показано, что для анализа энантиомерного состава при C(4)-замещенных 1*H*-1,2,3-триазол-1-ил-гомоаланинов может быть использована хиральная стационарная фаза CROWNPAK® CR(+), состоящая из хирального краун-эфира. Для полученных хиральных конъюгатов D- и L-гомоаланинов определен избыток энантиомера, который колебался от 95% до 99,5%. Продукты с высокой энантиомерной чистотой получены в реакциях при 20-25 °C с использованием каталитической системы $CuSO_4$/аскорбат натрия. Нагревание реакционной смеси до 70 °C в присутствии меди(I) и третичных аминов приводит к частичной рацемизации продукта до 95% э.и.