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Synthesis of tetrazole analogs of γ- and δ-amino acids

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Abstract: *N*-benzyloxycarbonyl-protected α- or β-amino alcohols, easily prepared from α- and β-amino acids, were converted into aldehydes and directly reacted with (triphenyl phosphoranylidene) acetonitrile, leading to unsaturated nitriles. Treatment of nitriles with NaN_3 and $ZnBr_2$ produced unsaturated γ- and δ-amino tetrazoles, which were deprotected and converted to the corresponding saturated compounds by catalytic hydrogenation. For the case of δ-amino tetrazole, the methylation of the acidic moiety occurred after treatment with CH_2N_2, leading to the N^1- and N^2-methylated constitutional isomers, which were separated by column chromatography and hydrogenated. Copyright © 2006 European Peptide Society and John Wiley & Sons, Ltd.

Keywords: γ-amino acids; δ-amino acids; tetrazoles

INTRODUCTION

Nonnatural amino acids play an important role in the design and synthesis of pharmacologically relevant molecules, analogs of bioactive peptides and peptide mimetics [1–3]. As recently demonstrated [4], β- and γ-peptides are completely stable to common proteases, without inhibiting their normal activity, and their helix stability increases upon homologation of the residues [5]. Moreover, the recent development of new chemical and biochemical approaches has made it possible to add new amino acids to the genetic codes of both prokaryotic and eukaryotic organisms [6], so that the limitation imposed by the existing 20 amino acid code has been removed. Owing to the growing interest in nonnatural amino acids, the development of new synthetic approaches leading to these compounds is a blossoming area of research, and we have recently presented methods for the synthesis of β-, γ-, δ- and ω-amino acids [7–9].

The aim of this work was to develop a new efficient method for the synthesis of tetrazole analogs of γ- and δ-amino acids, starting from natural optically active α- or β-amino acids, either commercially available or easily prepared.

The tetrazole group is considered isosteric to the carboxyl group [10] and there are several examples in medicinal chemistry where the replacement of a carboxyl by tetrazole leads, in many cases, to products with improved biological properties [11]. As far as the field of peptides is concerned, it is known that 1,5-disubstituted tetrazoles are effective bioisosters for cis–amide bonds in peptidomimetics [12–15]. On the other hand, tetrazole analogs of α-amino acids and peptides often appear in the literature [16,17].

RESULTS AND DISCUSSION

As depicted in Figure 1, our method is based on the oxidation of 2-protected amino alcohols **2a–f**, prepared from α- and β-amino acids **1a–f** [18], to the aldehydes using NaOCl in the presence of a catalytic amount of 4-acetamido-2,2,6,6-tetramethylpiperidine-1-yloxy free radical (AcNH-TEMPO) [19]. These aldehydes were immediately treated with (triphenyl phosphoranylidene) acetonitrile, leading to the unsaturated nitriles **3a–f**. In this way, the expected elongation of the carbon chain occurred, leading to γ- and δ-unsaturated nitriles from the α- and β-amino acids respectively.

For the conversion of nitriles to the 5-substituted tetrazole moiety, several strategies have been reported, the most common being addition of N_3^- in the presence of ammonium chloride, a procedure that leads to the *in situ* generation of hydrazoic acid. Solvents like dimethylformamide, *N*-methylpyrrolidinone and others have also been used. For numerous other methods applied to the synthesis of 5-substituted tetrazoles, the review article of R. J. Herr [20] is proposed. Among them, the recently published method by Sharpless [21,22] gave the best results in our hands.

In this method, sodium azide and the Lewis acid zinc(II) bromide are used as reagents and water–propanol (2 : 1) as solvents at reflux. The yields for the desired tetrazoles **4a–f** were 40–67%. The unprotected and saturated γ- and δ-amino tetrazoles **5a–c,e–g** were finally obtained in quantitative yield by catalytic hydrogenation.

For our needs, the acidic moiety of the tetrazole of compound **4e** (Figure 2) was methylated by treatment with CH_2N_2 [23], leading to the two N^1- and

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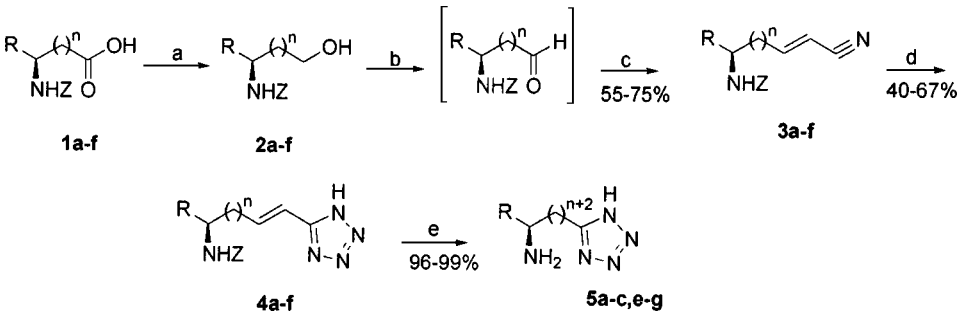

n=0	R	n=1	R
a	$CH_2CH(CH_3)_2$	e	H
b	CH_2OBn	f	$CH_2C_6H_5$
c	$CH_2C_6H_5$		
d	$(CH_2)_4NHZ$		
g	$(CH_2)_4NH_2$		

Figure 1 Reagents and conditions: (a) (i) $ClCO_2Et$, NMM, THF, −10 °C (ii) $NaBH_4$, MeOH, 0 °C, (b) NaOCl, AcNH-TEMPO, NaBr, $NaHCO_3$, EtOAc-toluene-H_2O (3 : 3 : 0.5), −5 °C, (c) $Ph_3P^+CHCN^-$, THF, reflux, 1 h, (d) NaN_3, $ZnBr_2$, iPrOH : H_2O 1 : 2, reflux, 16–48 h (e) H_2, 10%Pd/C, MeOH, 10 h.

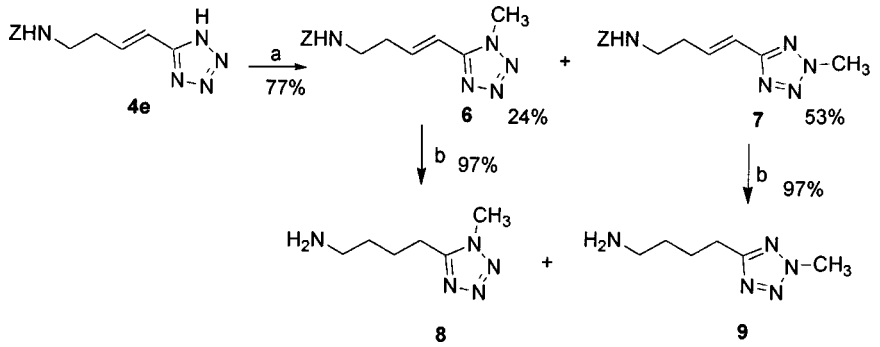

Figure 2 Reagents and conditions: (a) CH_2N_2, THF (b) H_2, 10% Pd/C, MeOH 10 h.

N^2-methylated isomers **6** and **7**, which were separated by column chromatography. ^{13}C-NMR revealed that the main difference between the two isomers was that the resonance of the C of the tetrazole moiety appeared almost 10 ppm higher in the case of the N^2-substituted tetrazoles than in that of the N^1-substituted tetrazoles, a result which is in accordance with literature [24]. The final unprotected products **8** and **9** were well defined, and ready for further reaction.

MATERIALS AND METHODS

Melting points are uncorrected. Specific rotations were measured at 25 °C on a polarimeter using a 10-cm cell. NMR spectra were recorded in $CDCl_3$ on a 200 MHz spectrometer, unless otherwise indicated. Starting amino acid derivatives **1a–e** were, when chiral, of L-configuration and were purchased from Fluka Chemical Co. They were converted to the corresponding alcohols **2a–e** by previously reported procedures [18]. TLC plates (silica gel 60 F_{254}) and silica gel 60 (70–230 or 230–400 mesh) for column chromatography were purchased from Merck. Visualization of spots was effected with UV light and/or phosphomolybdic acid and/or ninhydrin, both in EtOH stain and/or permanganate. THF, toluene and Et_2O were dried by standard procedures and stored over molecular sieves or Na. All other solvents and chemicals were of reagent grade and used without further purification. The phosphonium salt triphenyl phosphoranylidene acetonitrile, used in the Wittig reaction, was purchased from Aldrich.

Preparation of (3S)-3-{((benzyloxy)carbonyl)amino}-4-phenylbutanoic acid (β-phenylalanine) (1f) (25)

N-Benzyloxycarbonyl-L-phenylalanine (16.7 mmol) was dissolved in dry Et_2O (36 ml) and Et_3N (16.7 mmol). The solution was cooled and stirred at −5 °C, and ethyl chloroformate (16.7 mmol) was added. After 5–10 min, the triethylamine hydrochloride precipitate was filtered off, and a solution of CH_2N_2 in Et_2O was added to the filtrate until the intensive yellow color persisted over a longer period. The reaction mixture was stirred overnight at 5–20 °C. The solvent was evaporated

under reduced pressure and the yellow residue was dissolved in EtOAc (30 ml) and washed with 5% $NaHCO_3$ (20 ml) and H_2O (20 ml). The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude diazomethyl ketone (2.56 g) was dissolved in THF (25 ml) and H_2O (10 ml), with the exclusion of light, and 10 drops of a solution of silver benzoate (0.45 g) dissolved in Et_3N (4.20 ml) were added. The reaction mixture was stirred at room temperature for 20 h. The solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc (20 ml) and H_2O (20 ml). The organic layer was washed with 5% $NaHCO_3$ (10 ml). The aqueous layer was acidified with 5% H_2SO_4 and washed with EtOAc (3 × 30 ml). The combined organic layers were extracted with H_2O and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. Yield (40%); white solid; melting point 122.2–124.4 °C; $[\alpha]_D$ −25.65 (c 2 CH_3COOH). ^1H NMR ($CDCl_3$): δ 2.56 (s, 2H, CH_2COOH), 2.92 (t, J = 7.8 Hz, 2H, $C_6H_5CH_2$), 4.24 (d, J = 6.2 Hz, 1H, CH), 5.07 (s, 2H, $C_6H_5CH_2O$), 5.34 (d, J = 8.2 Hz, OCONH), 7.19–7.33 (m, 10H, 2 × C_6H_5). ^{13}C NMR: δ 37.3 (CH_2COOH), 40.3 ($C_6H_5CH_2$), 49.3 (CHNH), 67.0 ($C_6H_5CH_2O$), 127.0, 128.3, 128.1, 128.8, 128.9, 129.6, 137.5, 155.9 (OCONH), 177.2 (COOH).

Benzyl-N-((1S)-1-benzyl-3-hydroxypropyl) carbamate (2f). Prepared by the method [18]. Yield (82%); white solid; melting point 79–81 °C, $[\alpha]_D$ +16.5 (c 1 $CHCl_3$). ^1H NMR: ($CDCl_3$): δ 1.41–1.48 (m, 1H, $CHHCH_2OH$), 2.51 (bs, 1H, OH), 2.82 (d, J = 6.6 Hz, 2H, $C_6H_5CH_2$), 3.61–3.67 (m, 2H, CH_2OH), 4.15 (bs, 1H, CH), 4.79 (bs, OCONH), 5.07 (s, 2H, $C_6H_5CH_2O$), 7.15–7.32 (m, 10H, 2 × C_6H_5). ^{13}C NMR: δ 37.3, 41.2, 48.9, 58.8 (CH_2OH), 66.7 ($C_6H_5CH_2O$), 126.4, 127.8, 128.0, 128.4, 129.2, 136.3, 137.5, 156.91 (OCONH).

General Procedure for the Preparation of Unsaturated Nitriles (3a–f)

To a solution of *N*-benzyloxycarbonyl-protected 2-amino alcohol **2a–f** (4.00 mmol) in a mixture of toluene-EtOAc (1 : 1; 24 ml) a solution of NaBr (0.44 g, 4.2 mmol) in H_2O (2 ml) was added followed by AcNH-TEMPO (8 mg, 0.04 mmol). To the resulting biphasic system, which was cooled to −5 °C, an aqueous 0.35 M solution of NaOCl (12.6 ml, 4.4 mmol) containing $NaHCO_3$ (1.0 g, 12 mmol) was added drop wise under vigorous stirring, at −5 °C for over 1 h. After the mixture was stirred for an additional 15 min at 0 °C, EtOAc (24 ml) and H_2O (8 ml) were added. The aqueous layer was separated and washed with EtOAc (24 ml). The combined organic layers were washed with aqueous 5% citric acid (24 ml) containing KI (0.14 g), aqueous 10% $Na_2S_2O_3$ (24 ml), and brine and dried (Na_2SO_4). The solvents were evaporated under reduced pressure, and the obtained crude aldehyde was immediately used in the next step as given below.

To a solution of the *N*-benzyloxycarbonyl-protected α-aminoaldehyde (4.00 mmol) in dry THF (40 ml), $Ph_3P{=}CHCN$ (1.32 g, 4.4 mmol) was added and the solution was refluxed for 1 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (36 ml) and extracted with Et_2O (3 × 8 ml). The combined organic phases were washed with brine and dried (Na_2SO_4). The solvent was removed and the residue was purified by column chromatography using EtOAc as eluent.

Benzyl-N-((1S,2E)-3-cyano-1-isobutyl-2-propenyl) carbamate (3a). Yield (75%); yellow solid; melting point 58–60 °C; $[\alpha]_D$ −8.1 (c 1.1 $CHCl_3$). ^1H NMR: δ 0.93 [d, J = 6.2 Hz, 6H, $CH(CH_3)_2$], 1.38 (m, 2H, CH_2CH) 1.66 [m, 1H, $CH(CH_3)_2$], 4.36 (m, 1H, CH CH_2), 4.87 (m, 1H, OCONH), 5.11 (s, 2H, $CH_2C_6H_5$), 5.47 (d, J = 16.2 Hz, 1H, CHCH=CH), 6.59 (dd, J_1 = 16.2 Hz, J_2 = 5.6 Hz, 1H, CHCH=CH), 7.35 (m, 5H, C_6H_5). ^{13}C NMR: δ 21.8 (CH_3), 22.6 (CH_3), 24.5 [OCO$CH(CH_3)_2$], 42.9 (CH_2), 51.0 (CH), 67.1 ($CH_2C_6H_5$), 99.6 (CH=), 116.8 (CN), 128.1, 128.3, 128.4, 128.5, 135.9, 154.8, 155.5.

Benzyl-N-{(1R,2E)-1-((benzyloxy)methyl)-3-cyano-2-propenyl} carbamate (3b). Yield (65%); yellow oil; $[\alpha]_D$ +5.3 (c 0.8 CH_3OH). ^1H NMR: δ 3.58 (m, 2H, $CHCH_2O$), 4.44–4.58 (m, 3H, $OCH_2C_6H_5$, CH), 5.12 (s, 2H, $C_6H_5CH_2OCO$), 5.38 (d, J = 7.8 Hz, 1H, OCONH), 5.53 (d, J = 16.2 Hz, 1H, CH=CHCN), 6.70 (dd, J_1 = 16.2 Hz, J_2 = 4.8 Hz, 1H, CHCH=CH), 7.27–7.38 (m, 10H, 2 × C_6H_5). ^{13}C NMR: δ 52.3 (CH), 67.2 ($OCOCH_2C_6H_5$), 70.2 (CH_2), 73.4 (CH_2), 101.2 (CH=), 116.8 (CN), 127.7, 128.1, 128.2, 128.3, 128.5, 135.8, 136.9, 152.1 (CH=), 155.6 (OCONH).

Benzyl-N-((1S,2E)-1-benzyl-3-cyano-2-propenyl) carbamate (3c). Yield (56%); white solid; melting point 110–112 °C; $[\alpha]_D$ +10.65 (c 1.2 $CHCl_3$). ^1H NMR: δ 2.91 (d, J = 6.6 Hz, 2H, $CHCH_2C_6H_5$), 4.58–4.78 (m, 2H, CH, OCONH), 5.09 (s, 2H, $C_6H_5CH_2OCO$), 5.40 (d, J = 16.2 Hz, 1H, CH=CHCN), 6.68 (dd, J_1 = 16.2 Hz, J_2 = 5.0 Hz, 1H, CH=CHCN), 7.11–7.38 (m, 10H, $2C_6H_5$). ^{13}C NMR: δ 40.2 ($CHCH_2C_6H_5$), 53.4 (CH), 67.3 ($OCOCH_2C_6H_5$), 100.5 (CH=), 116.7 (CN), 127.4, 128.2, 128.4, 128.6, 128.9, 129.2, 135.1, 135.8, 153.5, 155.3. MS(FAB): m/z (%): 613 (40) $[2M+H]^+$, 307 (100) $[M+H]^+$, 263 (71), 215 (40), 173 (25).

Benzyl-N-((1S,2E)-1-(4-benzyloxycarbonyl aminobutyl)-3-cyano-2-propenyl) carbamate (3d). Yield (60%); yellow oil; $[\alpha]_D$ −1.8 (c 1.3 $CHCl_3$). ^1H NMR: δ 1.30–1.58 (m, 6H, 3 × CH_2), 3.08 (m, 2H, CH_2NH), 4.18 (m, 1H, CH), 4.93–5.05 (m, 4H, 2 × $CH_2C_6H_5$), 5.19 (m, 1H, OCONH), 5.40 (d, J = 16.2 Hz, 1H, CH=CHCN) 5.66 (d, J = 7.8 Hz, 1H, OCONH), 6.52 (dd, J_1 = 16.2 Hz, J_2 = 5.2 Hz, 1H, CHCH=CH), 7.18–7.38 (m, 10H, 2 × C_6H_5). ^{13}C NMR: δ 22.1, 29.2, 32.7, 39.8 (CH_2NH), 52.4 (CH), 66.4 ($CH_2C_6H_5$), 66.8 ($CH_2C_6H_5$), 99.4 (CH=), 116.8 (CN), 127.7, 127.8, 128.0, 128.2, 128.3, 129.2, 135.9, 136.3, 154.6, 155.7 (OCONH), 156.6.

Benzyl-N-((E) and (Z)-4-cyano-3-butenyl) carbamate (3e). Yield (55%); pale yellow oil. ^1H-NMR ($CDCl_3$): δ 2.42 (q, J = 6.4 Hz, 1.5H, CH_2, E isomer), 2.6 (q, J = 6.4 Hz, 0.5H, CH_2, Z isomer), 3.3 (q, J = 6.8 Hz, 2H, CH_2NH), 4.90 (1H, OCONH), 5.08 (s, 2H, $C_6H_5CH_2$), 5.35 (d, J = 12.4 Hz, 0.33H, CH=CHCN, Z isomer), 5.36 (d, J = 16 Hz, 0.66H, CH=CHCN, E isomer), 6.5 (dt, J_1 = 12.4 Hz, J_2 = 6.8 Hz, 0.33H, CH=CHCN, Z isomer), 6.63 (dt, J_1 = 16 Hz, J_2 = 6.8 Hz, 0.66H, CH=CHCN, E isomer), 7.34 (s, 5H, C_6H_5). ^{13}C-NMR: δ 32.6 (CH_2CH=CH, E isomer), 33.7 (CH_2CH=CH, Z isomer), 38.9 (CH_2NH, E isomer), 39.2 (CH_2NH, Z isomer), 66.7 ($C_6H_5CH_2$), 101.6 (CH=, Z isomer), 101.9 (CH=, E isomer), 116.9 (CN), 128.1, 128.5, 136.1, 151.1 (CH=, Z isomer), 152.0 (CH=, E isomer), 156.2 (OCONH).

Benzyl-N-((1R,3E and 1R,3Z)-1-benzyl-4-cyano-3-butenyl) carbamate (3f). Yield (65%); pale yellow solid; melting point

83–85 °C; $[\alpha]_D$ −27.2 (c 1 $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.30–2.62 (m, 2H, $CH_2CH{=}CH$), 2.79 (m, 2H, $C_6H_5CH_2$), 4.05 (m, 1H, CH), 4.65 (d, $J = 7.2$ Hz, 1H, OCONH), 5.06 (s, 2H, $C_6H_5CH_2O$), 5.31 (d, $J = 11.4$ Hz, 0.33H, $CH{=}CHCN$, Z isomer), 5.33 (d, $J = 16.2$ Hz, 0.66H, $CH{=}CHCN$, E isomer), 6.52 (dt, $J_1 = 11.4$ Hz, $J_2 = 7.8$ Hz, 0.33H, $CH{=}CHCN$, Z isomer), 6.65 (dt, $J_1 = 16.2$ Hz, $J_2 = 7.8$ Hz, 0.66H, $CH{=}CHCN$, E isomer), 7.11–7.31 (m, 10H, $2 \times C_6H_5$). ^{13}C NMR: 37.4 ($CH_2CH{=}CH$, E isomer), 38.0 ($CH_2CH{=}CH$, Z isomer), 40.9 ($C_6H_5CH_2$, E isomer), 41.5 ($C_6H_5CH_2$, Z isomer), 51.3 (CH, E isomer), 51.6 (CH, Z isomer), 67.0 ($C_6H_5CH_2O$), 102.4 (CH=, Z isomer), 102.7 (CH=, E isomer), 116.9 (CN), 127.2, 128.3, 128.5, 128.8, 128.9, 129.4, 136.9, 137.0, 151.3 (CH=, Z isomer), 151.6 (CH=, E isomer), 156.0 (OCONH).

General Procedure for the Preparation of Unsaturated Tetrazoles (4a–f)

To a solution of compound **3a–f** (2.00 mmol) in a mixture of isopropanol–water 1 : 2 (9 ml) sodium azide (0.26 g, 4 mmol) and zinc bromide (0.23 g, 1 mmol) were added. The reaction mixture was stirred at reflux for 16–48 h. To the reaction mixture, 1 ml of 3N HCl and 6 ml ethyl acetate were added. The organic layer was isolated and the aqueous layer extracted again with ethyl acetate twice (2×10 ml). The organic phase was washed with saturated aqueous solution of $NaHCO_3$ (2×20 ml). The aqueous extracts were combined, 5% H_2SO_4 was added until the pH reached 3, and the mixture was extracted with EtOAc (3×30 ml). The combined organic layers were washed with H_2O and dried with Na_2SO_4. The solvents were evaporated under reduced pressure. Purification was achieved with alkalization of the organic phase with 5% $NaHCO_3$ solution, thus converting the aminotetrazole compound to the corresponding salt, followed by the acidification of the aqueous phase and further extraction with EtOAc (3×30 ml). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were evaporated under reduced pressure.

Benzyl-N-((1S,2E)-1-isobutyl-3-(1H-1,2,3,4-tetrazol-5-yl)-2-propenyl) carbamate (4a). Yield (55%); yellow oil; $[\alpha]_D$ −4.8 (c 1.2 $CHCl_3$). ^{1}H NMR: δ 0.88 [d, $J = 6.2$ Hz, 6H, $CH(CH_3)_2$], 1.44 (m, 2H, CH_2CH) 1.67 [m, 1H, $CH(CH_3)_2$], 4.43 (m, 1H, NHCH), 5.08 (m, 2H, $C_6H_5CH_2$), 5.65 (d, J = 8.0 Hz, 1H, OCONH), 6.69 (d, $J = 16.2$ Hz, 1H, $CHCH{=}CH$), 6.92 (dd, $J_1 = 16.2$ Hz, $J_2 = 5.8$ Hz, 1H, $CHCH{=}CH$), 7.26 (m, 5H, C_6H_5). ^{13}C NMR: δ 22.0 (CH_3), 22.6 (CH_3), 24.6 [$CH(CH_3)_2$], 43.2 (CH_2), 51.3 (CH), 67.1 ($CH_2C_6H_5$), 111.5 (CH=), 127.8, 128.2, 128.5, 135.8, 143.0 (CH=), 153.5, 156.4. MS(APCI): $m/z = 316$ (100) $(M + H)^+$, 65 (34).

Benzyl-N-((1R,2E)-1-((benzyloxy)methyl)-3-(1H-1,2,3,4-tetrazol-5-yl)-2-propenyl) carbamate (4b). Yield (40%); yellow oil; $[\alpha]_D$ −2.0 (c 1.0 CH_3OH). ^{1}H NMR (CD_3OD): δ 3.61 (d, $J = 6.0$ Hz, 2H, $CHCH_2O$), 4.54–4.66 (m, 4H, OCONH, $OCH_2C_6H_5$, NHCH), 5.10 (s, 2H, $C_6H_5CH_2OCO$), 6.69 (d, $J = 16.4$ Hz, 1H, $CHCH{=}CH$), 6.89 (dd, $J_1 = 16.4$ Hz, $J_2 = 4.8$ Hz, 1H, $CHCH{=}CH$), 7.25–7.34 (m, 10H, $2 \times C_6H_5$). ^{13}C NMR: δ 53.8 (CH), 67.7 (CH_2), 72.3 (CH_2), 74.2 (OCH_2), 114.0 (CH=), 128.0, 128.8, 128.9, 129.0, 129.4, 138.2, 139.3, 140.8 (CH=), 155.1, 158.4.

Benzyl-N-((1S,2E)-1-benzyl-3-(1H-1,2,3,4-tetraazol-5-yl)-2-propenyl) carbamate (4c). Yield (60%); white solid; melting point 176–178 °C; $[\alpha]_D$ −9.7 (c 1.00 CH_3OH). ^{1}H NMR (DMSO): δ 2.89 (m, 2H, $CHCH_2C_6H_5$), 4.51 (m, 1H, CH), 4.98 (s, 2H, $C_6H_5CH_2OCO$), 6.56 (d, $J = 16.2$ Hz, 1H, $CHCH{=}CH$), 6.84 (dd, $J_1 = 16.2$ Hz, $J_2 = 5.8$ Hz, 1H, $CHCH{=}CH$), 7.27–7.32 (m, 10 H, $2 \times C_6H_5$), 7.74 (d, $J = 9.2$ Hz, 1H, OCONH)

^{13}C NMR: δ 41.6 ($CHCH_2C_6H_5$), 55.6 (CH), 67.4 ($OCOCH_2 - C_6H_5$), 112.9 (CH=), 127.7, 128.7, 128.9, 129.5, 130.4, 138.3, 138.8, 143.2 (CH=), 155.0, 158.2.

Benzyl-N-((1S,2E)-1-(4-benzyloxycarbonyl aminobutyl)-3-(1H-1,2,3,4-tetraazol-5-yl)-2-propenyl) carbamate (4d). Yield (65%); yellow oil; $[\alpha]_D$ −3.1 (c 0.9 $CHCl_3$). ^{1}H NMR: δ 1.30–1.58 (m, 6H, $3 \times CH_2$), 3.11 (m, 2H, CH_2NH), 4.31 (m, 1H, CH), 4.94–5.18 (m, 4H, $2 \times CH_2C_6H_5$), 5.21 (m, 1H, OCONH), 5.65 (d, $J = 6.6$ Hz, 1H, OCONH), 6.61 (d, $J = 16.2$ Hz, 1H, $CH{=}CH$) 6.82 (dd, $J_1 = 16.2$ Hz, $J_2 = 5.1$ Hz, 1H, $CHCH{=}CH$), 7.14–7.38 (m, 10H, $2 \times C_6H_5$). ^{13}C NMR: δ 22.4 (CH_2), 29.3 (CH_2), 33.6 (CH_2), 40.3 (CH_2NH), 52.6 (CH), 66.8 (CH_2), 67.1 (CH_2), 112.0 (CH=), 127.9, 128.1, 128.5, 136.0, 136.1, 142.2 (CH=), 153.6, 156.3, 157.1. MS(APCI): $m/z = 465$ (97) $(M + H)^+$, 421 (27), 91 (46).

Benzyl-N-((E)-4-(1H-1,2,3,4-tetrazol-5-yl)-3-butenyl) carbamate (4e). Yield (67%); white solid; melting point 119–121 °C. ^{1}H-NMR (CD_3COCD_3): δ 2.56 (m, 2H, CH_2), 3.36 (t, $J = 6.4$ Hz, 2H, CH_2NH), 5.08 (s, 2H, $C_6H_5CH_2$), 6.54 (m, 1H, OCONH), 6.60 (d, $J = 16.6$ Hz, 1H, $CH_2CH{=}CH$), 6.90 (dt, $J_1 = 16.6$ Hz, $J_2 = 6.4$ Hz, 1H, $CH_2CH{=}CH$), 7.32 (s, 5H, C_6H_5).

^{13}C-NMR: δ 33.6 (CH_2), 39.8(CH_2), 65.7 ($C_6H_5CH_2$), 114.4 (CH=), 127.9, 128.1, 128.5, 137.7, 139.5 (CH=), 153.9, 156.6.

Benzyl-N-((1R,3E)-1-benzyl-4-(1H-1,2,3,4-tetrazol-5-yl)-3-butenyl) carbamate (4f). Yield (60%); yellow solid; melting point 148–150 °C; $[\alpha]_D$ −32.6 (c 1 CH_3OH). ^{1}H NMR (CD_3OD): δ 2.37–2.63 (m, 2H, $CH_2CH{=}CH$), 2.81 (d, $J = 6.6$ Hz, 2H, $C_6H_5CH_2$), 3.99 (m, 1H, CHNH), 4.95 (m, 3H, $C_6H_5CH_2O$, OCONH), 6.52 (d, $J = 16.2$ Hz, 1H, $CH_2CH{=}CH$), 6.80 (dt, $J_1 = 16.2$ Hz, $J_2 = 7.2$ Hz, 1H, $CH_2CH{=}CH$), 7.19–7.24 (m, 10H, $2 \times C_6H_5$). ^{13}C NMR: δ 38.2 ($CH_2CH{=}CH$), 40.9 ($C_6H_5CH_2$), 52.3 (CHNH), 65.9 ($C_6H_5CH_2O$), 114.2 (CH=), 126.3, 127.2, 127.6, 128.1, 128.2, 129.2, 137.2, 138.5, 139.6 (CH=), 153.8, 157.2.

General Method for the Preparation of *N*-Methyl Tetrazoles (6, 7)

To a solution of compound **4e** (2.00 mmol) in 18-ml THF, an ethereal solution of diazomethane was added. After the vigorous evolution of nitrogen, the reaction mixture was evaporated under reduced pressure. The two constitutional isomers **6** and **7** were separated by column chromatography using AcOEt : PE 9 : 1 as eluent.

Benzyl-N-((E)-4-(1-methyl-1H-1,2,3,4-tetrazol-5-yl)-3-butenyl) carbamate (6). Yield (24%); pale yellow solid; melting point 100–102 °C. ^{1}H NMR ($CDCl_3$): δ 2.53 (m, 2H, $CH_2CH{=}$), 3.42 (m, 2H, CH_2NH), 3.92 (s, 3H, CH_3), 5.07 (s, 2H, $C_6H_5CH_2$), 6.34 (d, $J = 16$ Hz, 1H, $CH_2CH{=}CH$), 6.95 (dt, $J_1 = 16$ Hz, $J_2 = 7.4$ Hz, 1H, $CH_2CH{=}CH$), 7.29 (s, 5H, C_6H_5). ^{13}C-NMR: δ 33.6 (CH_3), 33.9, 39.7, 66.7 ($C_6H_5CH_2$), 112.3 (CH=), 128.1, 128.2, 128.6, 136.7, 141.4 ($CH{=}C_6H_5$), 152.1, 156.7. MS(APCI): $m/z = 288$ (61) $(M + H)^+$, 91 (100).

Benzyl-N-((E)-4-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-3-butenyl) carbamate (7). Yield (53%); white solid; melting point 93–95 °C. ^{1}H-NMR ($CDCl_3$): δ 2.48 (q, $J = 6.2$ Hz, 2H, CH_2CH=), 3.37 (m, 2H, CH_2NH), 4.28 (s, 3H, CH_3), 4.89 (b, 1H, OCONH), 5.08 (s, 2H, $C_6H_5CH_2$), 6.51 (d, $J = 16.2$ Hz, 1H, CH_2CH=C*H*), 6.76 (dt, $J_1 = 16.2$ Hz, $J_2 = 6.2$ Hz, 1H, CH_2CH=CHC), 7.32 (s, 5H, C_6H_5). ^{13}C-NMR: δ 33.5, 39.5, 40.2, 66.9 ($C_6H_5CH_2$), 118.3 (CH=), 126.7, 128.3, 135.9, 136.6, 156.4 (OCONH), 163.9 (NCNH).

Preparation of Saturated Tetrazoles (5a–c, e-g; 8, 9)

To a solution of compounds **4a–f**, **6**, **7** (1.00 mmol) in MeOH (10 ml), 10% Pd/C catalyst (10 mg) was added. The mixture was stirred for 10 h under H_2 at room temperature. The catalyst was removed by filtration through a pad of Celite and the solvent was evaporated under reduced pressure.

(3R)-5-Methyl-1-(1H-1,2,3,4-tetrazol-5-yl)-3-hexanamine (5a). Yield (99%); yellow oil; $[\alpha]_D$ +2.4 (c 1.5 CH_3OH). ^{1}H NMR (CD_3OD): δ 0.93 [d, $J = 6.2$ Hz, 6H, $CH(CH_3)_2$], 1.54 [m, 2H, $CH_2CH(CH_3)_2$] 1.73 [m, 1H, $CH(CH_3)_2$], 2.09 (m, 2H, $CHCH_2CH_2$), 3.07 (t, $J = 7.7$ Hz, 2H, $CHCH_2CH_2$), 3.35 (m, 1H, CH). ^{13}C NMR (CD_3OD): δ 21.0 (CH_2), 22.5 (CH_3), 22.8 (CH_3), 25.4 [$CH(CH_3)_2$], 32.1 (CH_2), 42.8 (CH_2), 50.6 (CH), 159.0 (NCNH).

(2R)-1-(Benzyloxy)-4-(1H-1,2,3,4-tetrazol-5-yl)-2-butanamine (5b). Yield (99%); yellow oil; $[\alpha]_D$ −2.2 (c 0.8 CH_3OH). ^{1}H NMR (CD_3OD): δ 2.01 (m, 2H, $CHCH_2CH_2$), 2.94 (m, 2H, $CHCH_2CH_2$), 3.42–3.80 (m, 3H, CH, OCH_2CH), 4.55 (s, 2H, $C_6H_5CH_2O$), 7.32 (m, 5H, C_6H_5). ^{13}C NMR: δ 21.8 (CH_2), 29.3 (CH_2), 52.2 (CH), 69.6 ($CHCH_2OCH_2$), 74.4 ($OCH_2C_6H_5$), 129.0, 129.2, 129.5, 138.8 (C_6H_5), 160.8 (NCNH). MS(APCI): $m/z = 248$ (100) $(M + H)^+$, 65 (34).

(2R)-1-Phenyl-4-(1H-1,2,3,4-tetrazol)-5-yl)-2-butanamine (5c). Yield (99%); yellow solid; melting point 223–224 °C; $[\alpha]_D$ +4.6 (c 0.8 EtOH). ^{1}H NMR (DMSO): δ 1.90 (m, 2H, $CHCH_2CH_2$), 2.67 (m, 2H, $C_6H_5CH_2$), 3.09 (m, 2H, $CHCH_2CH_2$), 3.61 (m, 1H, CH), 6.86 (m, 2H, NH_2), 7.36–7.45 (m, 5H, C_6H_5). ^{13}C NMR: δ 21.5 (CH_2), 30.1 (CH_2), 40.8 (CH_2), 52.3 (CH), 126.8, 128.7, 129.3, 136.7 (C_6H_5), 159.1 (NCNH). MS(APCI): $m/z = 218$ (100) $(M + H)^+$, 175 (27).

4-(1H-1,2,3,4-Tetrazol-5-yl)-1-butanamine (5e). Yield (99%); colorless oil. ^{1}H NMR (CD_3OD): δ 1.56–1.88 (m, 4H, $2 \times CH_2$), 2.84–2.96 (m, 4H, $2 \times CH_2$). ^{13}C NMR: δ 23.9, 25.3, 26.7, 39.1, 160.9 (NCNH). MS(APCI): $m/z = 142$ (100) $(M + H)^+$, 142 (51).

(2R)-1-Phenyl-5-(1H-1,2,3,4-tetrazol-5-yl)-2-pentanamine (5f). Yield (96%); colorless oil; $[\alpha]_D$ −2.6 (c 1 CH_3OH). ^{1}H NMR (CD_3OD): 1.55–1.96 (m, 4H, $2 \times CH_2$), 2.66–2.92 (m, 4H, CH_2, $C_6H_5CH_2$), 3.44 (m, 1H, C*H*NH), 7.19–7.36 (m, 10H, 2 C_6H_5). ^{13}C NMR: 23.9, 24.1, 31.5, 38.6, 52.7 (CH), 127.2, 128.8, 129.2, 135.8, 160.9 (NCNH). MS (APCI): $m/z = 232$ (100) $(M + H)^+$, 246 (19) $(M + Na)^+$, 189 (31).

(5S)-7-(1H-1,2,3,4-Tetrazol-5-yl)-1,5-heptanediamine (5g). Yield (99%); yellow oil; $[\alpha]_D$ +1.3 (c 1.0 DMSO). ^{1}H NMR (DMSO): δ 1.24–1.78 (m, 6H, $3 \times CH_2$), 1.99 (m, 2H, $CHCH_2CH_2$), 2.77 (t, $J = 7.2$ Hz, 2H, $CHCH_2CH_2$), 2.99 (t, $J = 7.6$ Hz, 2H, CH_2NH_2), 3.17 (m, 1H, CH). ^{13}C NMR: δ 19.7 (CH_2), 21.3, 26.5, 30.0, 31.1, 40.7, 50.0 (CH), 156.6 (NCNH).

4-(1-Methyl-1H-1,2,3,4-tetrazol-5-yl)-1-butanamine (8). Yield (97%); colorless oil. ^{1}H NMR (CD_3OD): δ 1.58–1.71 (m, 2H, CH_2), 1.78–1.93 (m, 2H, CH_2), 2.78 (t, $J = 5.8$ Hz, 2H, CH_2), 2.94 (t, $J = 7.2$ Hz, 2H, CH_2), 4.03 (s, 3H, CH_3). ^{13}C NMR: δ 22.1, 23.6, 30.3, 32.7, 40.2, 155.7 (NCNH).

4-(2-Methyl-2H-1,2,3,4-tetrazol-5-yl)-1-butanamine (9). Yield (97%); colorless oil. ^{1}H NMR (CD_3OD): δ 1.52–1.89 (m, 4H, 2 CH_2), 2.73–2.92 (m, 4H, $2 \times CH_2$), 4.32 (s, 3H, CH_3). ^{13}C NMR: δ 24.5, 25.0, 30.1, 38.6, 40.3, 166.4 (NCNH). MS(APCI): $m/z = 156$ (100) $(M + H)^+$.

CONCLUSION

Efficient protocols for the synthesis of tetrazole analogs, as well as their N^1- and N^2-methylated derivatives of γ- and δ-amino acids with proteinogenic side chains, are proposed in the present study. The proposed method is compatible with the commonly applied *N*-benzyloxycarbonyl group. Deprotection of this group and saturation of the intermediate double bond are achieved in one step by catalytic hydrogenation, leading to the γ- and δ-amino tetrazoles ready for further incorporation in the desired substrate.

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