Chemo- and Regiospecific Modification of D,L-Tryptophan by Reaction with α,β-Acetylenic γ-Hydroxy Nitriles

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Abstract: D,L-Tryptophan reacts with α,β-acetylenic γ-hydroxy nitriles, chemo- and regiospecifically, under mild, green conditions via a hydroamination-type process involving the primary amine group. The hydroxycyanopropanyl substituent of the initial adducts undergoes cyclization to afford a 2,5-dihydro-5-iminofuranyl moiety. Several novel amino acids are obtained in almost quantitative yields (95-98%), which exist in an unusual zwitterionic form where the positive charge is located on the remote nitrogen atom of the imino group of the dihydrofuran ring.

Key words: D,L-tryptophan, α,β-acetylenic γ-hydroxy nitriles, nucleophilic addition, hydroamination, amino acids, 2,5-dihydroiminofurans

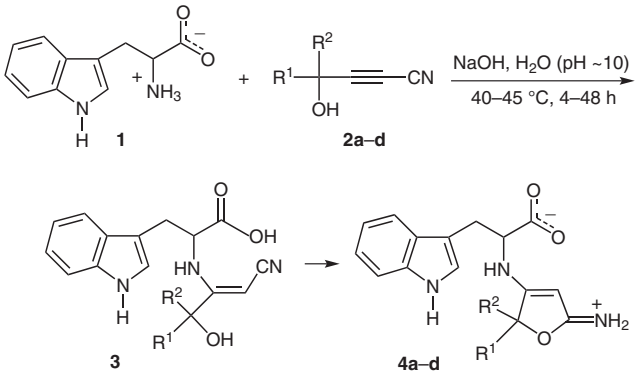
The indole ring system is a very common scaffold in Nature,[1] indeed the large number of known biologically active indoles has led to them being employed as key structural units in many pharmaceuticals.[2] Substituted indoles can bind selectively to many receptors with high affinity.[3] The significance of the essential amino acid tryptophan in human nutrition has been widely recognized.[1d,4] In plants, tryptophan is used to synthesize proteins and compounds responsible for control of their growth.[5]

Derivatives of tryptophan are able to activate osteoblasts and amongst these, therapeutic agents for the treatment of osteoporosis have been found.[6] They are also recommended for the specific treatment of serotonin-producing tumors.[7] Certain tryptophan congeners exhibit matrix metalloproteinase (MMP) inhibitory activity.[8] Therefore, the development of new synthetic strategies for the modification of tryptophan is important. Furthermore, as tryptophan exists as a polyfunctional molecule, containing amine, carboxylic acid and indole functional groups, its chemo- and regioselective modification is an obvious challenge.

For example, the reaction of tryptophan residues of enzymes with *N*-halosuccinimide has been reported.[9] The complex transformations of tryptophan in foods, and the significant diversity of its derivatives, have been reviewed. Carbolines have been obtained from tryptophan and carbonyl compounds.[5a] Peptides containing two tryptophan units underwent acid-promoted macrocyclization and oxidation to afford peptides demonstrating unique fluorescent properties.[10] In addition, Pictet–Spengler condensation of tryptophan with quinoline or quinoline-5,8-dione aldehydes has led to the synthesis of the antibiotic, lavendamycin.[11] Amino acids displaying antibacterial and antifungal properties were obtained by reaction of L-tryptophan with 2-hydroxy-1-naphthaldehydes.[12]

In this paper, we report on the modification of D,L-tryptophan (**1**) by reaction with α,β-acetylenic γ-hydroxy nitriles **2a–d**. The reaction takes place in water under mild conditions (sodium hydroxide, pH ~10, 40–45 °C, 4–48 hours), and proceeds via nucleophilic addition of the amino function across the triple bond, resulting in the formation of a novel family of unnatural amino acids **4a–d** containing a 2,5-dihydro-5-iminofuranyl substituent. The iminofuranyl moiety is assembled by ring-closure involving the cyano and hydroxy functionalities of the initial adducts **3**. The modified tryptophans **4a–d** were formed chemo- and regioselectively, in almost quantitative yields (95–98%) (Table 1).

Table 1 Synthesis of Amino Acids **4a–d**



Product	R^1	R^2	Yield (%)
4a	Me	Me	98
4b	Me	Et	96
4c	$-(CH_2)_5-$		95
4d	$-(CH_2)_6-$		95

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It is clear that the true catalyst here is the sodium salt of D,L-tryptophan. The role of the base is to increase the concentration of the non-zwitterionic form of the amino acid. The latter, possessing an uncharged amino group, is able to undergo nucleophilic addition at the triple bond of the hydroxy nitrile.

It should be noted that, in this case, the amino group of the indole ring remained completely inactive towards the highly electrophilic acetylenes **2a–d**. This is surprising as the latter typically undergo addition to a number of diverse NH-containing heterocycles, such as imidazole,[13] benzimidazole,[13c,e,14] pyrazole, triazole,[13c–e] and tetrazole,[15] to furnish the corresponding adducts without undergoing cyclization into iminodihydrofurans.

The amino acids **4a–d** exist, both in solid and solution states, in peculiar zwitterionic forms, protonated at the remote nitrogen atom of the iminodihydrofuran residue instead of at the expected tryptophan amino group. Similar long-range proton transfer has been observed in adducts of aliphatic amino acids[16] and 2-aminobenzoic acid[17] with α,β-acetylenic γ-hydroxy nitriles.

The reaction time depends on the structure of the starting acetylenes **2a–d**: aliphatic acetylenes **2a**,**b** underwent the reaction in four hours, while in the case of acetylenes **2c**,**d** possessing cycloalkyl substituents, the reaction was complete after two days. This was probably due to the steric effects of the cyclic substituents in **2c**,**d**, and also due to the lower solubility of these acetylenes in water. Amino acids **4a–d** were obtained as light-yellow powders which were highly soluble in water, methanol and ethanol, but were insoluble in most organic solvents.

The spectroscopic data of adducts **4a–d** [multinuclear ^{1}H, ^{13}C and 2D (HMBC) NMR, IR and UV] were in agreement with the proposed structures. The ^{1}H NMR spectra of compounds **4a–d** exhibited an alkene proton (H-4) signal at 4.63–4.76 ppm (Figure 1). The CH and CH_2 protons of the propanoyl chain appeared as three doublet of doublets (three-spin ABX system) in the regions 4.06–4.10, 3.48–3.49 and 3.11–3.16 ppm, respectively. The aromatic protons were present as two doublets (7.61–7.67 and 7.20–7.29 ppm) and two doublet of doublets (6.99–7.06 and 6.98–7.06 ppm), or as a multiplet at 7.06 ppm (in the case of **4c**), assigned to the benzene ring, and as a singlet (7.05–7.08 ppm) due to the pyrrole moiety. In the ^{1}H NMR spectrum of **4a** in DMSO-d_6, the NH (H-15) proton of the indole and those of the $=N^+H_2$ fragment appeared at 10.78 and 8.99 ppm, respectively. In the case of **4b**, doubling of the alkyl and alkene hydrogen signals, corresponding to a 1:1 [*R*,*R*(*S*,*S*):*R*,*S*(*S*,*R*)] diastereomeric mixture was observed. The ^{13}C NMR spectra further confirmed the structures of amino acids **4a–d**. The carbon signals of the *C*OO$^-$, HN-*C*=CH and *C*=N^+H_2 groups were assigned using ^{1}H–^{13}C HMBC spectroscopy. The HMBC spectrum of adduct **4a** showed cross peaks between the alkene proton (H-4) and the quaternary carbons at C-2 and C-5 of the iminodihydrofuran ring, and between the methyl group protons and carbon C-3 (Figure 2).

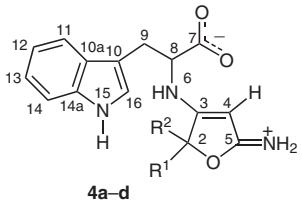


Figure 1 The atom numbering used for NMR assignments in compounds **4a–d**

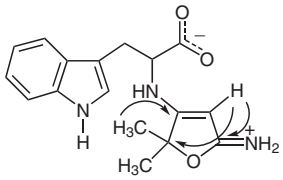


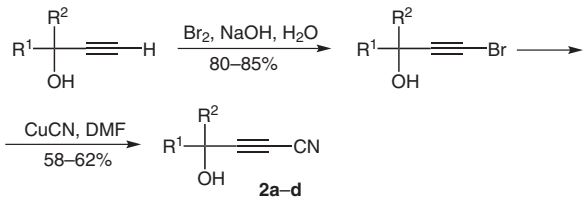
Figure 2 Diagnostic cross peaks in the HMBC (^{1}H–^{13}C) spectrum of amino acid **4a**

The zwitterionic form of amino acids **4a–d** was supported by their IR (KBr) spectra in which strong, broad absorptions were apparent in the region 3500–2600 cm^{-1} (with peaks at 3405–3219, 3115–3049, 2985–2930 and 2876–2865 cm^{-1}). These bands were attributed to the NH, $=N^+H_2$, C=CH and CH groups. The carboxylate anion was evident as a broad absorption in the region 1700–1500 cm^{-1}, overlapping with the stretching vibration of the C=C bond at 1611–1618 cm^{-1}, and the bending vibrations of the $=N^+H_2$ moiety at 1572–1535 cm^{-1}. Stretching vibrations due to the $=N^+H_2$ fragment were present as weak, broad absorption bands at 2205–2216 cm^{-1}.

The zwitterionic structures of amino acids **4a–d** follow by analogy to the previously reported addition of glycine[16] and 2-aminobenzoic acid[17] to α,β-acetylenic γ-hydroxy nitrile **2a**, where the transfer of positive charge to the iminodihydrofuran ring was confirmed, unambiguously, by single crystal X-ray structure analysis.

An advantage of these modified tryptophans is the combination of an indole amino acid and a 2,5-dihydro-5-iminofuranyl moiety in their structures. The dihydrofuran moiety is present in numerous biologically active compounds, for example, tetronic acids and their thiol analogs,[18] vitamin C,[19] penicillic acid, and in anti-AIDS drugs such as 1-(2′,3′-dideoxy-γ-D-glyceropent-2-enofuranosyl)thymine (d4T) and 1-[4-azido-5-(hydroxymethyl)tetrahydrofuran-2-yl]-5-methylpyrimidine-2,4-(1*H*,3*H*)-dione (AZT).[20] The dihydrofuran structural unit also occurs in cardenolides[21] (cardioactive steroid lactones), dysidiolide (the only known natural inhibitor of the protein phosphatase cdc25A[22]), as well as in many other natural molecules such as sesquiterpenes[23] and pulvinic acid derivatives.[24] In strigol and its analogs, the dihydrofuranone unit is primarily responsible for the germination of seeds.[25]

The starting α,β-acetylenic γ-hydroxy nitriles **2a–d** are readily available compounds which are prepared from acetylenic alcohols in two simple steps[13e,26] (Scheme 1).



R^1, R^2 = alkyl; R^1–R^2 = cycloalkyl

Scheme 1 Synthesis of α,β-acetylenic γ-hydroxy nitriles **2a–d**

These powerful building blocks have attracted significant attention in organic synthesis.[13c,e,26b,27]

In summary, a new synthetic strategy for the chemical modification of D,L-tryptophan into unnatural derivatives containing a 2,5-dihydro-5-iminofuranyl moiety, and displaying an unusual zwitterionic distribution (where the most distal NH basic center is protonated) has been developed. The strategy involves the chemo- and regiospecific addition of D,L-tryptophan to α,β-acetylenic γ-hydroxy nitriles in water under gentle heating. These unnatural amino acids represent potential pharmaceuticals, and promising building blocks and auxiliaries for drug design, proteomics and controlled peptide modification.

Melting points were obtained using a Kofler micro hot stage apparatus. IR spectra were recorded using a Bruker Vertex-70 instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer in CD_3OD or DMSO-d_6 at room temperature. The NMR signals were assigned using 2D NMR techniques (HMBC ^{1}H–^{13}C). ^{1}H and ^{13}C NMR assignments are made according to the numbering system shown in Figure 1. UV/Vis spectra were measured on a Perkin-Elmer Lambda 35 spectrometer at room temperature (EtOH, d = 0.1, 1.0 cm). Elemental analyses were performed on a FLASH EA 1112 Series instrument. The reaction was monitored by TLC on neutral Al_2O_3 (Merck) (eluent: $CHCl_3$–benzene–EtOH, 20:4:1). D,L-Tryptophan (**1**) was commercially available (Merck). α,β-Acetylenic γ-hydroxy nitriles **2a–d** were prepared according to the literature.[26]

Amino Acids 4a–d; General Procedure

A soln of NaOH (20 mg, 0.5 mmol) in H_2O (2 mL) was added to a suspension of D,L-tryptophan (**1**) (204 mg, 1.0 mmol) in H_2O (5 mL), and the mixture heated at 40–45 °C. The appropriate acetylene **2a–d** (1.0 mmol) was added and the resulting mixture stirred for 4 h (**2a**,**b**) or 48 h (**2c**,**d**). The H_2O was evaporated, the residue filtered through neutral Al_2O_3 [2–3 cm, eluent: 50–70 mL of hot EtOH (50–60 °C)] and the solvent evaporated under reduced pressure to afford amino acids **4a–d**.

2-[(5-Iminio-2,2-dimethyl-2,5-dihydrofuran-3-yl)amino]-3-(1*H*-indol-3-yl)propanoate (4a)

Light-yellow powder; yield: 307 mg (98%); mp 232–236 °C (dec.).

IR (KBr): 3500–2600 with peaks at 3272, 3226 (NH, $=N^+H_2$), 3115, 3058 (C=CH), 2985, 2932, 2871 (CH), 1700–1500 with peaks at 1698 (C=O), 1618 (C=C), 1535 ($=N^+H_2$) cm^{-1}.

^{1}H NMR (400.13 MHz, CD_3OD): δ = 7.64 (d, ^3J = 7.8 Hz, 1 H, H-14), 7.20 (d, ^3J = 8.1 Hz, 1 H, H-11), 7.08 (s, 1 H, H-16), 7.05 (dd, $^3J_{13-14} \sim {}^3J_{13-12}$ = 7.8 Hz, 1 H, H-13), 7.00 (dd, $^3J_{13-12} \sim {}^3J_{11-12}$ = 8.0 Hz, 1 H, H-12), 4.65 (s, 1 H, H-4), 4.08, 3.49, 3.15 (ABX, dd, $^2J_{AB}$ = 14.9 Hz, $^3J_{AX}$ = 4.2 Hz, $^3J_{BX}$ = 9.4 Hz, 3 H, CH_2CH), 1.52 and 1.29 (s, 6 H, 2 × CH_3).

^{1}H NMR (400.13 MHz, DMSO-d_6): δ (selected resonances) = 10.78 (s, 1 H, H-15), 8.99 (br s, 2 H, $=N^+H_2$).

^{13}C NMR (100.62 MHz, CD_3OD): δ = 178.2 (COO^-), 177.4 (HN-*C*=CH), 176.7 ($C=N^+H_2$), 138.0 (C-14a), 128.9 (C-10a), 124.6, 122.4, 119.8, 119.4 (C-11, C-12, C-13, C-14), 112.3 (C-16), 111.7 (C-10), 92.2 (C-2), 76.6 (C-4), 63.7 (CH_2CH), 29.5 (CH_2CH), 25.0, 24.7 (2 × CH_3).

UV/Vis (EtOH): λ_{max} (log ε) = 222 (4.65), 273 (4.61), 291 (shoulder, 4.24), 372 nm (3.26).

Anal. Calcd for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.40; H, 6.33; N, 13.38.

2-[(2-Ethyl-5-iminio-2-methyl-2,5-dihydrofuran-3-yl)amino]-3-(1*H*-indol-3-yl)propanoate (4b)

Light-yellow powder; yield: 314 mg (96%); mp 194–200 °C (dec.).

IR (KBr): 3500–2600 with peaks at 3397, 3249 (NH, $=N^+H_2$), 3056 (C=CH), 2973, 2931, 2876 (CH), 2205 (br w, $=N^+H_2$), 1700–1500 with peaks at 1680 (C=O), 1616 (C=C), 1570 ($=N^+H_2$) cm^{-1}.

^{1}H NMR (400.13 MHz, CD_3OD): δ (1:1 mixture of diastereomers) = 7.67 and 7.64 (d, ^3J = 8.0 Hz, 2 H, H-14), 7.29 (d, ^3J = 8.3 Hz, 2 H, H-11), 7.08 (s, 2 H, H-16), 7.06 (dd, $^3J_{13-12} \sim {}^3J_{11-12}$ = 8.3 Hz, 2 H, H-12), 6.99 (dd, $^3J_{13-14} \sim {}^3J_{13-12}$ = 8.0 Hz, 2 H, H-13), 4.76 and 4.68 (s, 2 H, H-4), 4.09, 3.49, 3.15 (ABX, dd, $^2J_{AB}$ = 14.7 Hz, $^3J_{AX}$ = 3.8 Hz, $^3J_{BX}$ = 10.4 Hz, 3 H, CH_2CH), 4.07, 3.49, 3.11 (ABX, dd, $^2J_{AB}$ = 14.7 Hz, $^3J_{AX}$ = 4.2 Hz, $^3J_{BX}$ = 9.4 Hz, 3 H, CH_2CH), 1.90 and 1.74 (dq, ^2J = 6.7 Hz, ^3J = 7.3 Hz, 4 H, CH_2CH$_3$), 1.53 and 1.28 (s, 6 H, CH_3), 0.77 and 0.32 (t, ^3J = 7.3 Hz, 6 H, CH_2CH_3).

^{13}C NMR (100.62 MHz, CD_3OD): δ (1:1 mixture of diastereomers) = 177.9[a] (COO^-), 177.0[a] (HN-*C*=CH), 176.8 and 176.7 ($C=N^+H_2$), 138.2 and 138.0 (C-14a), 128.9 and 128.7 (C-10a), 124.5, 124.4, 122.4,[a] 119.8,[a] 119.4, 119.3 (C-11, C-12, C-13, C-14), 112.3[a] (C-16), 111.8 and 111.7 (C-10), 94.8[a] (C-2), 78.0 and 77.9 (C-4), 63.9 and 63.7 (CH_2CH), 31.7 and 31.4 (CH_2CH), 29.6 and 29.5 (CH_3CH_2), 23.9 and 23.5 (CH_3), 7.3 and 6.8 (CH_3CH_2). [a] The carbon signals for the two diastereomers are equivalent.

UV/Vis (EtOH): λ_{max} (log ε) = 222 (4.50), 272 (4.42), 291 (shoulder, 4.06), 371 nm (3.44).

Anal. Calcd for $C_{18}H_{21}N_3O_3$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.95; H, 6.33; N, 13.03.

2-[(2-Iminio-1-oxaspiro[4.4]non-3-en-4-yl)amino]-3-(1*H*-indol-3-yl)propanoate (4c)

Light-yellow powder; yield: 321 mg (95%); mp 164–166 °C (dec.).

IR (KBr): 3500–2600 with peaks at 3405, 3258 (NH, $=N^+H_2$), 3054 (C=CH), 2964, 2936, 2874 (CH), 2216 (br w, $=N^+H_2$), 1700–1500 with peaks at 1680 (C=O), 1617 (C=C), 1572 ($=N^+H_2$) cm^{-1}.

^{1}H NMR (400.13 MHz, CD_3OD): δ = 7.61 (d, ^3J = 7.7 Hz, 1 H, H-14), 7.29 (d, ^3J = 8.2 Hz, 1 H, H-11), 7.06 (m, 1 H, H-13), 7.05 (s, 1 H, H-16), 6.98 (dd, $^3J_{13-12} \sim {}^3J_{11-12}$ = 8.0 Hz, 1 H, H-12), 4.72 (s, 1 H, H-4), 4.10, 3.49, 3.16 (ABX, dd, $^2J_{AB}$ = 15.0 Hz, $^3J_{AX}$ = 4.0 Hz, $^3J_{BX}$ = 9.2 Hz, 3 H, CH_2CH), 2.00–1.60 [m, 8 H, $(CH_2)_4$].

^{13}C NMR (100.62 MHz, CD_3OD): δ = 176.0 (COO^-), 175.4 (HN-*C*=CH), 174.3 ($C=N^+H_2$), 136.7 (C-14a), 127.6 (C-10a), 123.2, 121.1, 118.4, 118.0 (C-11, C-12, C-13, C-14), 110.9 (C-16), 110.4 (C-10), 100.7 (C-2), 76.6 (C-4), 62.3 (CH_2CH), 37.6 (CH_2CH), 37.1, 28.0, 24.2, 24.1 (4 × CH_2).

UV/Vis (EtOH): λ_{max} (log ε) = 223 (4.56), 274 (4.45), 291 (shoulder, 4.12), 375 nm (3.64).

Anal. Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 67.40; H, 6.50; N, 12.28.

2-[(2-Iminio-1-oxaspiro[4.5]dec-3-en-4-yl)amino]-3-(1*H*-indol-3-yl)propanoate (4d)

Light-yellow powder; yield: 355 mg (95%); mp 194–196 °C (dec.).

IR (KBr): 3500–2600 with peaks at 3371, 3219 (NH, $=N^+H_2$), 3114, 3049 (C=CH), 2930, 2865 (CH), 2212 (br w, $=N^+H_2$), 1700–1500 with peaks at 1687 (C=O), 1611 (C=C), 1562 ($=N^+H_2$) cm^{-1}.

^{1}H NMR (400.13 MHz, CD_3OD): δ = 7.62 (d, ^3J = 7.7 Hz, 1 H, H-14), 7.29 (d, ^3J = 8.1 Hz, 1 H, H-11), 7.06 (dd, $^3J_{13-12} \sim {}^3J_{11-12}$ = 8.0 Hz, 1 H, H-12), 7.05 (s, 1 H, H-16), 6.99 (dd, $^3J_{13-14} \sim {}^3J_{13-12}$ = 7.7 Hz, 1 H, H-13), 4.63 (s, 1 H, H-4), 4.06, 3.48, 3.13 (ABX, dd, $^2J_{AB}$ = 14.9 Hz, $^3J_{AX}$ = 4.0 Hz, $^3J_{BX}$ = 9.3 Hz, 3 H, $CHCH_2$), 1.80–1.20 [m, 10 H, $(CH_2)_5$].

^{13}C NMR (100.62 MHz, CD_3OD): δ = 176.9 (COO^-), 176.3 (HN-*C*=CH), 175.5 ($C=N^+H_2$), 136.8 (C-14a), 127.7 (C-10a), 123.3, 121.1, 118.5, 118.2 (C-11, C-12, C-13, C-14), 111.0 (C-16), 110.4 (C-10), 92.5 (C-2), 75.6 (C-4), 62.4 (CH_2CH), 33.3 (CH_2CH), 32.9, 28.2, 23.6, 21.6 (5 × CH_2).

UV/Vis (EtOH): λ_{max} (log ε) = 222 (4.64), 273 (4.54), 291 (shoulder, 4.19), 375 nm (3.70).

Anal. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 67.57; H, 6.50; N, 12.18.

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