Transition-Metal-Free Stereoselective and Regioselective Hydroamination of 2-Benzoylethynyl-4,5,6,7-tetrahydroindoles with Amino Acids

Lyubov N. Sobenina, Denis N. Tomilin, Igor A. Ushakov, Albina I. Mikhaleva, Boris A. Trofimov*

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, 1 Favorsky Str., 664033, Irkutsk, Russian Federation
Fax +7(3952)419346; E-mail: boris_trofimov@irioch.irk.ru

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Abstract: A new family of unnatural amino acids possessing a tetrahydroindole moiety is obtained by nucleophilic addition of various amino acids to the triple bond of 2-benzoylethynyl-4,5,6,7-tetrahydroindoles. The reaction proceeds chemo-, regio- and stereospecifically in the presence of sodium hydroxide to give the *Z*-isomeric products in 35–72% yields.

Key words: amino acids, 2-benzoylethynyl-4,5,6,7-tetrahydroindoles, nucleophilic addition, *Z*-isomers

The synthesis of unnatural amino acids has attracted significant attention in recent years.[1] They represent a growing group of compounds required for a number of biotechnological applications in pharmaceutical, cosmetics and agrochemical fields. When modified with different pharmacophore substituents, unnatural amino acids can also be used as building blocks for the synthesis of molecules with specific desired biological activity.[2] Hence, research on various derivatives of amino acids and the development of new synthetic strategies for amino acid modification is very important. The chemo- and regioselective transformations of amino acids are considered to be a major challenge and remain the subject of further investigations. It is envisaged that the synthesis of new amino acid derivatives containing highly reactive pyrrole or indole moieties would represent a promising approach in this field.

Examples of unnatural optically active amino acids containing a pyrrole moiety have been synthesized by condensation of 1-vinylpyrrole- and 1-vinylindole-2-carbaldehydes with L-lysine.[3]

Following the development of transition metal and solvent-free ethynylations of the pyrrole nucleus with electrophilic haloacetylenes on alumina,[4] or other active surfaces,[5] 2-ethynylpyrroles and 3-ethynylindoles possessing electron-withdrawing substituents, including an example with an acyl group on the triple bond, became readily available. This methodology has made 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynones **1**–**3** particularly accessible using large-scale manufactured 4,5,6,7-tetrahydroindole[6] as the starting material. Consequently, reactions of these compounds with amino acids can be considered as a short-cut route to amino acids containing a tetrahydroindole moiety.

These compounds, due to their easy aromatization, might be suitable intermediates for the synthesis of amino acids containing an indole function, for example, α-analogues of tryptophan. Herein, we disclose an expedient method for the synthesis of amino acid derivatives possessing a tetrahydroindole moiety

The method involves the nucleophilic addition of the natural amino acids glycine (**4**), β-alanine (**5**), γ-aminobutyric acid (**6**), phenylalanine (**7**) and tryptophan (**8**) to the C≡C bond of 2-benzoylethynyl-4,5,6,7-tetrahydroindoles **1**–**3**. The reaction was carried out in the presence of sodium hydroxide (reflux, 40 h, EtOH–H_2O), followed by subsequent treatment of the mixture with aqueous hydrochloric acid to afford amino acid derivatives **10a**–**k** and **11a**–**c** in 35–72% yields (Table 1 and Table 2).

In the absence of sodium hydroxide, addition of amino acids **4**–**8** to the acetylenic moiety of indoles **1**–**3** did not take place. The role of the base would seem to involve transformation of the zwitterionic form of the amino acid into the corresponding sodium salt and thus releasing the free amino group. The free amino group of the salt serves as a nucleophile undergoing addition to the triple bond of indoles **1**–**3** to deliver the sodium salt adducts **9a**–**k**. The latter, after treatment of the reaction mixture with aqueous hydrochloric acid, furnishes free amino acids **10a**–**k** (Table 1). In the case of L-tryptophan (Table 2), the corresponding products **11a**–**c** were isolated without the need for acidification of the reaction mixture.

The reaction proved to be regio- and stereoselective with only *Z*-isomers of the adducts being formed in all cases. Evidence for the *Z*-configuration of adducts **10a**–**k** was obtained from the 2D NOESY spectrum of compound **10f**. Cross-peaks were apparent between the alkene proton (5.65 ppm) and those at the *ortho*-positions of the phenyl (7.45 ppm) and the CH_2 of the benzyl fragment (5.19 ppm), and also between the pyrrolic proton (6.23 ppm) and those of the NCH_2 group (3.71 ppm) in conformer **A**. In the 2D NOESY spectrum of conformer **B**, cross-peaks were observed between the pyrrole and alkene protons, and also between the CH_2 protons of the benzyl and alanine fragments (Figure 1). It is noteworthy that the *N*-vinyl-substituted tetrahydroindole **3** tolerated the reaction conditions retaining the vinyl double bond intact (Table 1 and Table 2).

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As exemplified by the reaction with tryptophan (**8**), the elaborated method can be employed for the synthesis of amino acids containing both tetrahydroindolyl and indolyl substituents.

The reactions of 2-benzoylethynyl-4,5,6,7-tetrahydroindoles **1**–**3** with amino acids were accompanied by the formation of minor amounts of 2-acetyl-4,5,6,7-tetrahydroindoles. This might be the result of nucleophilic addition of water to adducts **10a**–**k** and subsequent decomposition of the intermediates **12** to give diketones **13**. Addition of a second molecule of water gives intermedi-

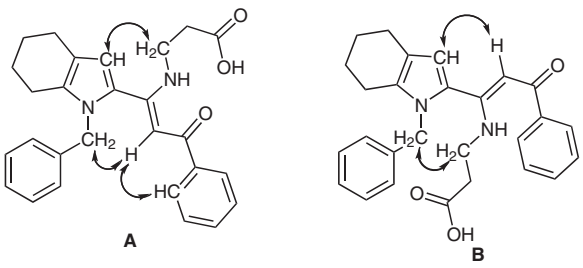
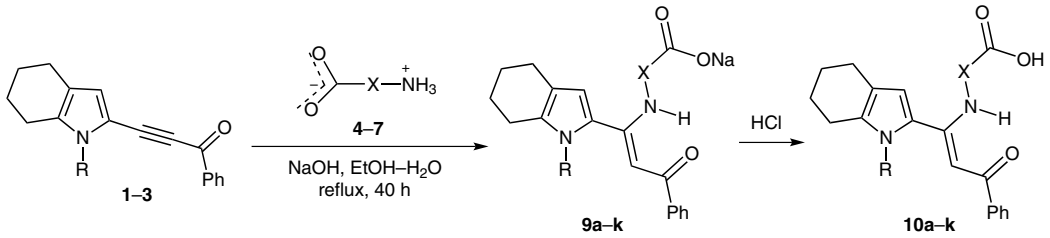


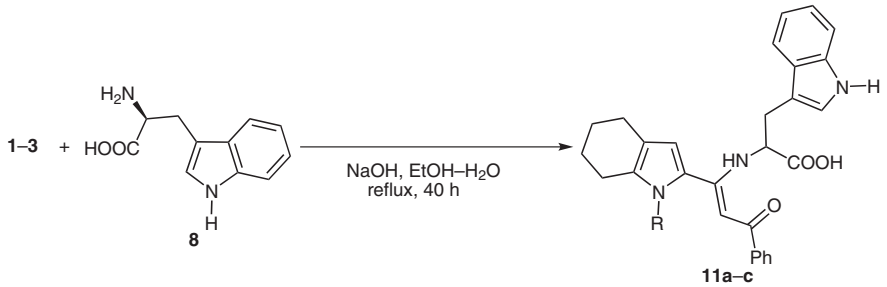
Figure 1 Relevant cross-peaks in the 2D (^{1}H–^{1}H) NOESY spectrum of amino acid **10f**

Table 1 Synthesis of Amino Acid Derivatives **10a**–**k**

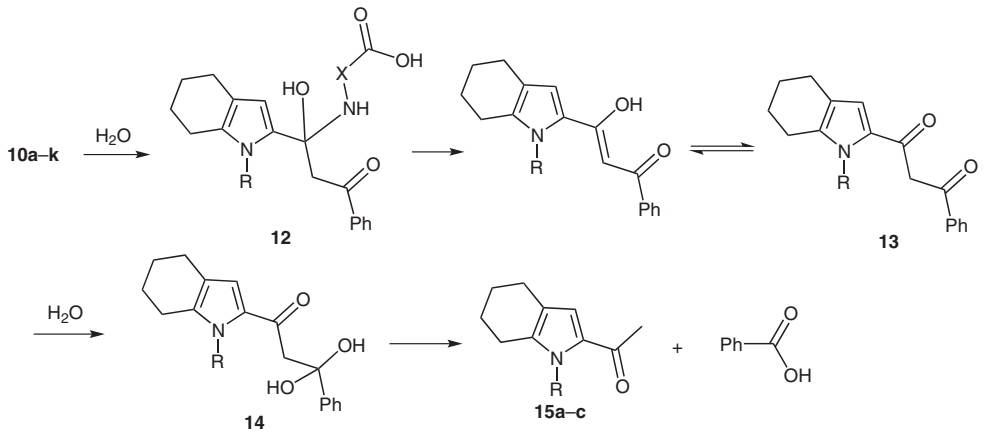


Entry	Substrate	R	Amino acid	X	Product	Yield (%)
1	**1**	Me	**4**	CH_2	**10a**	55
2	**1**	Me	**5**	$(CH_2)_2$	**10b**	48
3	**1**	Me	**6**	$(CH_2)_3$	**10c**	57
4	**1**	Me	**7**	$CH(CH_2Ph)$	**10d**	35
5	**2**	Bn	**4**	CH_2	**10e**	42
6	**2**	Bn	**5**	$(CH_2)_2$	**10f**	71
7	**2**	Bn	**6**	$(CH_2)_3$	**10g**	51
8	**3**	$CH=CH_2$	**4**	CH_2	**10h**	72
9	**3**	$CH=CH_2$	**5**	$(CH_2)_2$	**10i**	64
10	**3**	$CH=CH_2$	**6**	$(CH_2)_3$	**10j**	63
11	**3**	$CH=CH_2$	**7**	$CH(CH_2Ph)$	**10k**	49

Table 2 Synthesis of Amino Acid Derivatives **11a**–**c**



Entry	Substrate	R	Product	Yield (%)
1	**1**	Me	**11a**	71
2	**2**	Bn	**11b**	70
3	**3**	$CH=CH_2$	**11c**	67

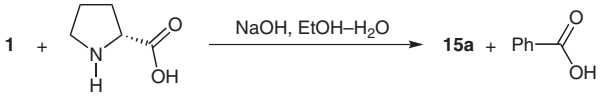


Scheme 1 Reaction of adducts **10a**–**k** with water

ates **14**, which decompose to 2-acetyl-4,5,6,7-tetrahydroindoles **15a**–**c** and benzoic acid (Scheme 1). Both these compounds were present in the reaction mixtures in approximately 1:1 molar ratio. Also, the direct nucleophilic addition of water to the triple bond of indoles **1**–**3** to generate diketones **13** cannot be ruled out.

Among the common proteinogenic amino acids, only proline exists as a secondary amine, and accordingly plays a distinct role in protein chemistry and biology. In addition, proline is of significant importance in organic chemistry as a chiral starting material for the synthesis of peptide mimetics,[7] alkaloids,[8] certain peptoid natural products,[9] and chiral molecules, which are used in asymmetric synthesis and catalysis.

The combination of a pharmacophoric indole ring and proline in the same molecule might result in synergism of the properties of these important chemical structures, and could expand substantially the fields of application of such a new class of amino acids. Unfortunately, the reaction of indole **1** with L-proline using the above-described conditions gave, almost quantitatively, 2-acetyl-4,5,6,7-tetrahydroindole (**15a**) and benzoic acid (Scheme 2).



Scheme 2 Reaction of 2-benzoylethynyl-4,5,6,7-tetrahydroindole **1** with L-proline

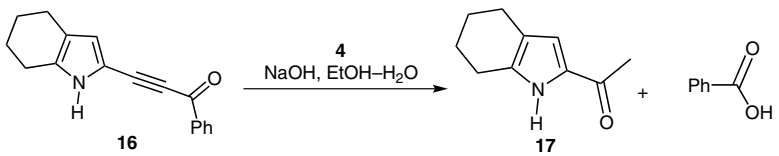
This may be rationalized as follows: the addition of L-proline to the triple bond of the indole substrate is sterically hindered, hence the competitive addition of water, catalyzed by proline acting as an active organic catalyst,[10] is the only possible outcome for the reaction.

Surprisingly, the reaction of N-unsubstituted 2-benzoylethynyl-4,5,6,7-tetrahydroindole (**16**) with glycine (**4**) under the same conditions did not form the expected adduct. Instead, almost quantitative cleavage into 2-acetyl-4,5,6,7-tetrahydroindole (**17**) and benzoic acid took place (Scheme 3).

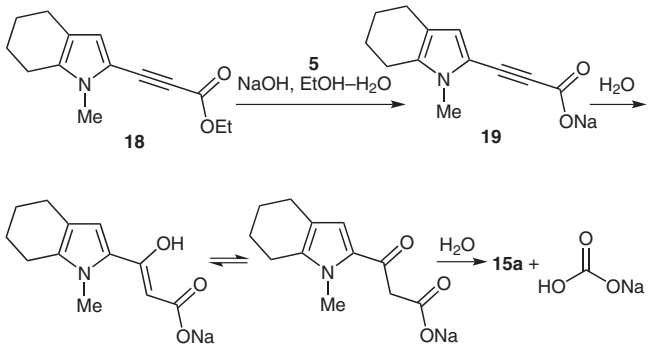
Of particular interest is the fact that, unlike 2-benzoylethynyl-4,5,6,7-tetrahydroindoles **1**–**3**, ethyl 3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)propynoate (**18**) did not form the expected adduct on reaction with amino acid **5** (reflux, 40 h, EtOH–H_2O). Surprisingly, a rather peculiar cleavage of the triple bond occurred to produce, almost quantitatively, 2-acetyl-4,5,6,7-tetrahydroindole (**15a**). Apparently, in this case, alkaline hydrolysis of the ester function occurred first, thereby consuming the sodium hydroxide. Consequently, the amino acid remained in zwitterionic form and was unable to take part in nucleophilic addition at the triple bond. Therefore, indole **18** underwent nucleophilic attack by hydroxide to give intermediate **19**, which decomposed to acetylindole **15a** and sodium carbonate (Scheme 4).

It should be emphasized that the formal one-pot cleavage of the triple bond under mild conditions, as described herein, is important since there are only a few examples of such reactions reported in the literature.[11]

In conclusion, a general method for the synthesis of a new family of unnatural amino acids, containing a tetrahydroindole moiety, has been developed. The procedure involves the regio- and stereoselective addition of amino acids to the triple bond of 2-benzoylethynyl-4,5,6,7-tetrahydroindoles. The synthesized products represent a com-



Scheme 3 Reaction of 2-benzoylethynyl-4,5,6,7-tetrahydroindole (**16**) with glycine (**4**)



Scheme 4 Reaction of ethyl 3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)propynoate (**18**) with alanine (**5**)

bination of pharmacophoric indole and amino acid moieties, and may serve as novel building blocks for drug design. The method was also shown to be applicable for the synthesis of amino acids containing *N*-vinyl-4,5,6,7-tetrahydroindole moieties. These compounds represent promising monomers which might take part in various addition reactions across the double bond.

Commercially available amino acids and sodium hydroxide were used. 2-Ethynyl-4,5,6,7-tetrahydroindoles **1**–**3**, **16** and **18** were obtained from 4,5,6,7-tetrahydroindoles and haloacetylenes using the reported method.[5] Column chromatography was performed using Sigma-Aldrich neutral Al_2O_3 (150 mesh). TLC was carried out using silica gel 60 F254 plates. Melting points were recorded on a Stuart melting point apparatus and are uncorrected. IR spectra were obtained using a Bruker IFS 25 spectrometer. ^{1}H (400.13 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on Bruker DPX 400 or AV-400 spectrometers with HMDS as the internal standard. The ^{1}H and ^{13}C NMR resonances were assigned with the aid of 2D homonuclear COSY and NOESY, and 2D heteronuclear HSQC and HMBC experiments. Elemental analyses were recorded using an EA FLASH 1112 Series (CHN Analyzer) instrument.

1-Phenyl-3-(1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-yn-1-one (3)

An equimolar mixture of 1-vinyl-4,5,6,7-tetrahydroindole (0.5 g, 3.4 mmol) and 1-benzoyl-2-bromoacetylene (0.711 g, 3.4 mmol) containing K_2CO_3 (12 g, 10 equiv by wt) was ground in a china mortar using a pestle at r.t. for 1–2 min. After 60 min, the products were extracted with Et_2O (5 × 20 mL). Evaporation of the solvent and purification of the residue by column chromatography on alumina (*n*-hexane) gave tetrahydroindole **3**.

Yield: 0.702 g (75%); yellow needles; mp 73–74 °C.

IR (KBr): 1645 (NCH=CH_2), 1596 (CO) cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.39–7.37 (m, 3 H, *m*,*p*-H_{Ph}), 7.14–7.12 (m, 2 H, *o*-H_{Ph}), 7.00 (dd, *J* = 16.0, 9.2 Hz, 1 H, $H_{N=CH}$), 6.71 (s, 1 H, H-3), 5.46 (d, *J* = 16.0 Hz, 1 H, H_{trans}), 5.05 (d, *J* = 9.2 Hz, 1 H, H_{cis}), 2.63–2.61 (m, 2 H, CH_2-7), 2.49–2.47 (m, 2 H, CH_2-4), 1.84–1.82 (m, 2 H, CH_2-5), 1.75–1.73 (m, 2 H, CH_2-6).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 177.3, 137.4, 135.2, 133.5, 130.0, 129.3, 128.5, 122.1, 121.3, 110.4, 105.1, 96.0, 89.1, 24.1, 23.0, 22.9, 22.8.

Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.64; H, 6.01; N, 4.74.

Amino Acids 10a–k; General Procedure

A soln of 2-benzoylethynyl-4,5,6,7-tetrahydroindole **1**–**3** (2.5 mmol), amino acid **4**–**7** (2.5 mmol) and NaOH (2.5 mmol) in EtOH–H_2O (1:1, 16 mL) was heated at reflux temperature for 40 h. After cooling to r.t., the mixture was diluted with H_2O (50 mL) and extracted with Et_2O (3 × 20 mL) to isolate the by-products. The aqueous layer was neutralized with 10% HCl and extracted with Et_2O (5 × 20 mL). The combined organic layer was washed with H_2O (5 × 20 mL), dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography on alumina (Et_2O) to give the pure product as a yellow solid. The structures of the products were confirmed by NMR and IR techniques.

(*Z*)-2-{[1-(1-Methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-3-oxo-3-phenylprop-1-en-1-yl]amino}acetic Acid (10a)

Yield: 0.465 g (55%); yellow solid; mp 186–188 °C.

IR (KBr): 3092–2500 (NH, OH), 1727 [C(=O)OH], 1592 (C=O) cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 11.45 (br s, 1 H, NH), 9.32 (br s, 1 H, OH), 7.87–7.85 (m, 2 H, *o*-H_{Ph}), 7.38–7.36 (m, 3 H, *m*,*p*-H_{Ph}), 6.13 (s, 1 H, H-3), 5.83 (s, 1 H, CH=), 4.19 (s, 2 H, NCH_2), 3.48 (s, 3 H, NMe), 2.55–2.53 (m, 2 H, CH_2-7), 2.50–2.48 (m, 2 H, CH_2-4), 1.85–1.83 (m, 2 H, CH_2-5), 1.74–1.72 (m, 2 H, CH_2-6).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 187.5, 171.9, 158.2, 139.5, 133.0, 130.5, 127.8, 126.7, 124.1, 117.9, 110.8, 94.7, 46.2, 31.0, 22.9, 22.5, 22.4, 21.8.

Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.64; H, 6.31; N, 8.42.

(*Z*)-3-{[1-(1-Methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-3-oxo-3-phenylprop-1-en-1-yl]amino}propanoic Acid (10b)

Yield: 0.422 g (48%); yellow solid; mp 152–153 °C.

IR (KBr): 3092–2500 (NH, OH), 1726 [C(=O)OH], 1592 (C=O) cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 11.49 (br s, 1 H, NH), 11.07 (br s, 1 H, OH), 7.80–7.78 (m, 2 H, *o*-H_{Ph}), 7.37–7.35 (m, 3 H, *m*,*p*-H_{Ph}), 6.10 (s, 1 H, H-3), 5.71 (s, 1 H, CH=), 3.62 (br s, 2 H, NCH_2), 3.45 (s, 3 H, NMe), 2.65 (br s, 2 H, CH_2COO), 2.55–2.53 (m, 2 H, CH_2-7), 2.50–2.48 (m, 2 H, CH_2-4), 1.85–1.83 (m, 2 H, CH_2-5), 1.74–1.72 (m, 2 H, CH_2-6).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 187.5, 173.9, 159.4, 140.1, 132.8, 130.7, 128.2, 127.1, 125.0, 118.1, 110.7, 94.8, 40.8, 35.1, 31.4, 23.4, 23.0, 22.9, 22.2.

Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.42; H, 6.99; N, 7.61.

(*Z*)-4-{[1-(1-Methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-3-oxo-3-phenylprop-1-en-1-yl]amino}butanoic Acid (10c)

Yield: 0.522 g (57%); yellow solid; mp 153–154 °C.

IR (KBr): 3058–2500 (NH, OH), 1711 [C(=O)OH], 1596 (C=O) cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 11.31 (br s, 1 H, NH), 9.05 (br s, 1 H, OH), 7.85–7.83 (m, 2 H, *o*-H_{Ph}), 7.38–7.36 (m, 3 H, *m*,*p*-H_{Ph}), 6.10 (s, 1 H, H-3), 5.75 (s, 1 H, CH=), 3.46 (s, 3 H, NMe), 3.38 (br s, 2 H, NCH_2), 2.55–2.53 (m, 2 H, CH_2-7), 2.50–2.48 (m, 2 H, CH_2-4), 2.43–2.41 (m, 2 H, CH_2COO), 1.93–1.91 (m, 2 H, CH_2), 1.85–1.83 (m, 2 H, CH_2-5), 1.74–1.72 (m, 2 H, CH_2-6).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 187.6, 177.2, 159.2, 140.3, 132.6, 130.7, 128.3, 127.1, 125.3, 118.1, 110.6, 94.4, 44.2, 31.4, 31.2, 25.8, 23.4, 23.1, 22.9, 22.2.

Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 71.87; H, 6.98; N, 7.71.

(*Z*)-2-{[1-(1-Methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-3-oxo-3-phenylprop-1-en-1-yl]amino}-3-phenylpropanoic Acid (10d)

Yield: 0.375 g (35%); yellow solid; mp 90–92 °C.

IR (KBr): 3060–2500 (NH, OH), 1736 [C(=O)OH], 1590 (C=O) cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 11.52 (br s, 1 H, NH), 7.78–7.76 (m, 2 H, *o*-H_{Ph}), 7.31–7.28 (m, 1 H, *p*-H_{Ph}), 7.20–7.16 (m, 2 H, *m*-H_{Ph}), 7.01–6.98 (m, 5 H, Ph), 6.46 (br s, 1 H, OH), 5.85 (s, 1 H, H-3), 5.68 (s, 1 H, CH=), 4.41–4.39 (m, 1 H, NCH), 3.27–3.23 (m, 1 H, CH_2-Ph), 3.15 (s, 3 H, NMe), 3.09–3.05 (m, 1 H, CH_2-Ph), 2.45–2.43 (m, 4 H, CH_2-4,7), 1.82–1.80 (m, 2 H, CH_2-5), 1.71–1.69 (m, 2 H, CH_2-6).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 188.1, 174.7, 158.5, 140.2, 136.8, 132.6, 130.9, 129.7, 128.4, 128.3, 127.3, 126.8, 124.5, 118.0, 110.6, 95.5, 59.9, 40.2, 30.9, 23.5, 23.1, 22.9, 22.2.

Anal. Calcd for $C_{27}H_{28}N_2O_3$: C, 75.68; H, 6.59; N, 6.54. Found: C, 75.30; H, 6.84; N, 6.15.

(*Z*)-2-{[1-(1-Benzyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-3-oxo-3-phenylprop-1-en-1-yl]amino}acetic Acid (10e)
Yield: 0.435 g (42%); yellow solid; mp 192–194 °C.

IR (KBr): 3060–2500 (NH, OH), 1726 [C(=O)OH], 1593 (C=O) cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 11.39 (br s, 1 H, NH), 9.66 (br s, 1 H, OH), 7.48–7.46 (m, 2 H, *o*-H_{Ph}), 7.30–7.25 (m, 6 H, Ph), 6.93–6.91 (m, 2 H, *o*-H_{Bn}), 6.21 (s, 1 H, H-3), 5.74 (s, 1 H, CH=), 5.16 (s, 2 H, CH_2-Ph), 4.15 (s, 2 H, NCH_2), 2.54–2.52 (m, 2 H, CH_2-7), 2.45–2.43 (m, 2 H, CH_2-4), 1.79–1.77 (m, 2 H, CH_2-5), 1.76–1.74 (m, 2 H, CH_2-6).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 187.6, 172.5, 158.5, 141.1, 140.2, 134.2, 132.2, 130.2, 129.7, 128.5, 128.0, 127.1, 126.1, 119.2, 112.7, 94.6, 48.8, 47.6, 24.6, 24.1, 24.0, 23.0.

Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76. Found: C, 74.97; H, 6.05; N, 6.95.

(*Z*)-3-{[1-(1-Benzyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-3-oxo-3-phenylprop-1-en-1-yl]amino}propanoic Acid (10f)
Yield: 0.760 g (71%); yellow solid; mp 158–160 °C.

IR (KBr): 3061–2500 (NH, OH), 1738, 1719 [C(=O)OH], 1588 (C=O) cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 11.44 (br s, 1 H, NH), 9.90 (br s, 1 H, OH), 7.48–7.45 (m, 2 H, *o*-H_{Ph}), 7.36–7.34 (m, 3 H, *m*,*p*-H_{Ph}), 7.30–7.25 (m, 3 H, *m*,*p*-H_{Ph}), 6.95–6.93 (m, 2 H, *o*-H_{Bn}), 6.23 (s, 1 H, H-3), 5.65 (s, 1 H, CH=), 5.19 (s, 2 H, CH_2-Ph), 3.71 (s, 2 H, NCH_2), 2.66 (m, 2 H, CH_2COO), 2.54–2.52 (m, 2 H, CH_2-7), 2.45–2.43 (m, 2 H, CH_2-4), 1.79–1.77 (m, 2 H, CH_2-5), 1.77–1.75 (m, 2 H, CH_2-6).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 187.2, 173.9, 159.2, 139.9, 138.5, 133.1, 130.6, 128.9, 128.2, 127.3, 127.1, 125.9, 125.0, 118.7, 111.8, 94.4, 47.9, 40.9, 35.1, 23.5, 23.2, 23.1, 22.4.

Anal. Calcd for $C_{27}H_{28}N_2O_3$: C, 75.68; H, 6.59; N, 6.54. Found: C, 75.38; H, 6.62; N, 6.53.

(*Z*)-4-{[1-(1-Benzyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-3-oxo-3-phenylprop-1-en-1-yl]amino}butanoic Acid (10g)
Yield: 0.564 g (51%); yellow solid; mp 168 °C.

IR (KBr): 3060–2500 (NH, OH), 1710 [C(=O)OH], 1586 (C=O) cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 11.28 (br s, 1 H, NH), 10.54 (br s, 1 H, OH), 7.53–7.51 (m, 2 H, *o*-H_{Ph}), 7.28–7.25 (m, 6 H, Ph), 6.91–6.89 (m, 2 H, *o*-H_{Bn}), 6.17 (s, 1 H, H-3), 5.68 (s, 1 H, CH=), 5.15 (s, 2 H, CH_2-Ph), 3.35–3.33 (m, 2 H, NCH_2), 2.54–2.52 (m, 2 H, CH_2-7), 2.46–2.44 (m, 2 H, CH_2-4), 2.36–2.33 (m, 2 H, CH_2COO), 1.81–1.79 (m, 2 H, CH_2-5), 1.77–1.75 (m, 2 H, CH_2-6), 1.75–1.73 (m, 2 H, CH_2).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 187.1, 177.2, 158.8, 140.1, 138.5, 132.8, 130.5, 128.8, 128.1, 127.2, 127.0, 125.9, 125.2, 118.6, 111.7, 93.8, 47.9, 44.4, 29.7, 25.7, 23.5, 23.1, 23.0, 22.4.

Anal. Calcd for $C_{28}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33. Found: C, 75.81; H, 6.60; N, 5.97.

(*Z*)-2-{[3-Oxo-3-phenyl-1-(1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-1-en-1-yl]amino}acetic Acid (10h)
Yield: 0.630 g (72%); yellow solid; mp 114–115 °C.

IR (KBr): 3087–2500 (NH, OH), 1727 [C(=O)OH], 1643 (N-CH=CH_2), 1592 (C=O) cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 11.38 (br s, 1 H, NH), 7.87–7.85 (m, 2 H, *o*-H_{Ph}), 7.38–7.36 (m, 3 H, *m*,*p*-H_{Ph}), 7.23 (br s, 1 H, OH), 6.77 (dd, *J* = 15.9, 8.9 Hz, 1 H, $H_{N=CH}$), 6.21 (s, 1 H, H-3), 5.93 (s, 1 H, CH=), 5.06 (d, *J* = 15.9 Hz, 1 H, H_{trans}), 4.85 (d, *J* = 8.9 Hz, 1 H, H_{cis}), 4.07 (s, 2 H, NCH_2), 2.64–2.62 (m, 2 H, CH_2-7), 2.49–2.47 (m, 2 H, CH_2-4), 1.82–1.80 (m, 2 H, CH_2-5), 1.74–1.72 (m, 2 H, CH_2-6).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 188.1, 172.0, 158.1, 139.5, 132.1, 130.8, 129.8, 127.9, 127.0, 124.3, 119.6, 113.5, 104.4, 95.1, 29.4, 23.5, 22.9, 22.7, 22.6.

Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 72.31; H, 6.67; N, 7.63.

(*Z*)-3-{[3-Oxo-3-phenyl-1-(1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-1-en-1-yl]amino}propanoic Acid (10i)
Yield: 0.582 g (64%); yellow solid; mp 69–70 °C.

IR (KBr): 3056–2500 (NH, OH), 1729 [C(=O)OH], 1643 (N-CH=CH_2), 1591 (C=O) cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 11.41 (br s, 1 H, NH), 8.31 (br s, 1 H, OH), 7.79–7.77 (m, 2 H, *o*-H_{Ph}), 7.37–7.35 (m, 3 H, *m*,*p*-H_{Ph}), 6.77 (dd, *J* = 15.9, 8.9 Hz, 1 H, $H_{N=CH}$), 6.19 (1 H, s, H-3), 5.81 (s, 1 H, CH=), 5.06 (d, *J* = 15.9 Hz, 1 H, H_{trans}), 4.86 (d, *J* = 8.9 Hz, 1 H, H_{cis}), 3.55 (br s, 2 H, NCH_2), 2.71–2.69 (m, 2 H, CH_2-7), 2.66–2.64 (m, 2 H, CH_2-4), 2.51–2.49 (m, 2 H, CH_2COO), 1.83–1.81 (m, 2 H, CH_2-5), 1.75–1.73 (m, 2 H, CH_2-6).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 187.7, 173.5, 159.0, 139.7, 131.6, 130.5, 129.9, 127.9, 126.9, 124.5, 119.5, 112.9, 104.1, 94.8, 40.4, 34.5, 23.5, 22.9, 22.7, 22.6.

Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.24; H, 6.43; N, 7.39.

(*Z*)-4-{[3-Oxo-3-phenyl-1-(1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-1-en-1-yl]amino}butanoic Acid (10j)
Yield: 0.595 g (63%); yellow solid; mp 60 °C.

IR (KBr): 3057–2500 (NH, OH), 1728 [C(=O)OH], 1643 (N-CH=CH_2), 1592 (C=O) cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 11.22 (br s, 1 H, NH), 8.84 (br s, 1 H, OH), 7.86–7.84 (m, 2 H, *o*-H_{Ph}), 7.38–7.36 (m, 3 H, *m*,*p*-H_{Ph}), 6.74 (dd, *J* = 15.9, 9.0 Hz, 1 H, $H_{N=CH}$), 6.17 (s, 1 H, H-3), 5.85 (s, 1 H, CH=), 5.04 (d, *J* = 15.9 Hz, 1 H, H_{trans}), 4.82 (d, *J* = 9.0 Hz, 1 H, H_{cis}), 3.26 (br s, 2 H, NCH_2), 2.65–2.63 (m, 2 H, CH_2-7), 2.50–2.48 (m, 2 H, CH_2-4), 2.40–2.38 (m, 2 H, CH_2COO), 1.89–1.87 (m, 2 H, $CH_2CH_2CH_2$), 1.82–1.80 (m, 2 H, CH_2-5), 1.74–1.72 (m, 2 H, CH_2-6).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 188.6, 177.7, 159.6, 140.8, 132.2, 131.4, 130.8, 128.9, 127.7, 125.7, 120.3, 113.6, 104.6, 95.2, 44.7, 31.8, 26.1, 24.4, 23.9, 23.6, 23.5.

Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.64; H, 6.57; N, 7.44.

(*Z*)-2-{[3-Oxo-3-phenyl-1-(1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-1-en-1-yl]amino}-3-phenylpropanoic Acid (10k)
Yield: 0.539 g (49%); yellow solid; mp 104–106 °C.

IR (KBr): 3060–2500 (NH, OH), 1735 [C(=O)OH], 1643 (N-CH=CH_2), 1593 (C=O) cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 11.37 (br s, 1 H, NH), 7.86–7.84 (m, 2 H, *o*-H_{Ph}), 7.38–7.36 (m, 3 H, *m*,*p*-H_{Ph}), 7.19–7.17 (m, 3 H, *m*,*p*-H_{Ph}), 7.15–7.13 (m, 2 H, *o*-H_{Ph}), 6.39 (dd, *J* = 16.0, 8.6 Hz, 1 H, $H_{N=CH}$), 5.75 (s, 1 H, H-3), 5.73 (s, 1 H, CH=), 4.85 (d, *J* = 16.0 Hz, 1 H, H_{trans}), 4.64 (d, *J* = 8.6 Hz, 1 H, H_{cis}), 4.58 (br s, 1 H, OH),

4.43–4.41 (m, 1 H, CHCOO), 3.21–3.18 (m, 1 H, CH_2Ph), 3.03–2.97 (m, 1 H, CH_2Ph), 2.59–2.57 (m, 2 H, CH_2-7), 2.42–2.40 (m, 2 H, CH_2-4), 1.77–1.75 (m, 2 H, CH_2-5), 1.71–1.69 (m, 2 H, CH_2-6).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 188.3, 174.7, 157.7, 140.2, 136.7, 131.8, 130.9, 130.1, 129.8, 128.4, 128.3, 127.3, 126.8, 124.4, 119.7, 113.4, 104.3, 95.8, 59.8, 40.3, 23.9, 23.3, 23.0, 22.9.

Anal. Calcd for $C_{28}H_{28}N_2O_3$: C, 76.34; H, 6.41; N, 6.36. Found: C, 76.66; H, 6.52; N, 5.99.

Amino Acids 11a–c; General Procedure

A soln of 2-benzoylethynyl-4,5,6,7-tetrahydroindole **1**–**3** (2.5 mmol), tryptophan (**8**) (2.5 mmol) and NaOH (2.5 mmol) in EtOH–H_2O (1:1, 16 mL) was heated at reflux temperature for 40 h. After cooling to r.t., the mixture was diluted with H_2O (50 mL) and extracted with Et_2O (5 × 30 mL). The combined organic layer was washed with H_2O (5 × 30 mL), dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography on alumina (Et_2O–*n*-hexane, 1:5, then Et_2O) to give the pure product as a yellow solid.

(*Z*)-3-(1*H*-Indol-3-yl)-2-{[1-(1-methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-3-oxo-3-phenylprop-1-en-1-yl]amino}propanoic Acid (11a)

Yield: 0.829 g (71%); yellow solid; mp 128–130 °C.

IR (KBr): 3412 (NH of indole), 3084–2500 (NH, OH), 1732 [C(=O)OH], 1589 cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 11.53 (br s, 1 H, NH), 8.45 (br s, 1 H, NH of indole), 7.87–7.85 (m, 2 H, *o*-H_{Ph}), 7.40–7.37 (m, 2 H, *m*-H_{Ph}), 7.36–7.34 (m, 1 H, *p*-H_{Ph}), 7.33–7.30 (m, 1 H, CH-4 of indole), 7.22–7.20 (m, 1 H, CH-7 of indole), 7.08–7.06 (m, 1 H, CH-6 of indole), 7.07–7.05 (m, 1 H, CH-2 of indole), 6.95–6.93 (m, 1 H, CH-5 of indole), 6.36 (br s, 1 H, OH), 5.92 (s, 1 H, H-3 of pyrrole), 5.71 (s, 1 H, CH=), 4.82 (m, 1 H, CH), 3.34–3.32 (m, 1 H, CH_2), 3.22–3.20 (m, 1 H, CH_2), 3.02 (s, 3 H, NMe), 2.56–2.54 (m, 2 H, CH_2-7), 1.83–1.81 (m, 2 H, CH_2-4), 1.79–1.77 (m, 2 H, CH_2-5), 1.70–1.68 (m, 2 H, CH_2-6).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 186.9, 173.4, 157.6, 140.4, 136.7, 132.3, 131.3, 128.8, 127.5, 127.4, 124.8, 124.6, 121.4, 118.8, 118.6, 117.2, 111.8, 110.1, 109.3, 94.5, 58.4, 31.0, 30.4, 23.6, 23.2, 23.1, 22.0.

Anal. Calcd for $C_{29}H_{29}N_3O_3$: C, 74.50; H, 6.25; N, 8.99. Found: C, 74.16; H, 6.18; N, 8.70.

(*Z*)-2-{[1-(1-Benzyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-3-oxo-3-phenylprop-1-en-1-yl]amino}-3-(1*H*-indol-3-yl)propanoic Acid (11b)

Yield: 0.950 g (70%); yellow solid; mp 76–78 °C.

IR (KBr): 3421 (NH of indole), 3057–2500 (NH, OH), 1731 [C(=O)OH], 1591 cm^{-1}.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 11.38 (br s, 1 H, NH), 10.92 (br s, 1 H, NH of indole), 7.39–7.34 (m, 3 H, *o*-H_{Ph}, CH-4 of indole), 7.31–7.23 (m, 8 H, *m*,*p*-H_{Ph}, CH-7 of indole, OH), 7.13–7.11 (m, 1 H, CH-6 of indole), 7.09–7.06 (m, 1 H, CH-2 of indole), 6.92–6.88 (m, 1 H, CH-5 of indole), 6.82–6.80 (m, 2 H, *o*-H_{Bn}), 5.92 (s, 1 H, H-3 of pyrrole), 5.49 (s, 1 H, CH=), 4.63 (m, 1 H, CH), 4.52 (s, 2 H, CH_2-Ph), 3.21–3.17 (m, 1 H, CH_2), 3.07–3.01 (m, 1 H, CH_2), 2.45–2.43 (m, 2 H, CH_2-7), 2.23–2.22 (m, 2 H, CH_2-4), 1.65 (m, 4 H, CH_2-5,6).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 186.3, 173.8, 157.1, 140.2, 139.3, 136.8, 132.3, 131.1, 129.2, 128.6, 127.6, 127.3, 127.0, 125.9, 125.1, 124.6, 121.4, 118.8, 117.8, 111.9, 110.8, 109.7, 93.7, 65.4, 58.9, 47.0, 23.6, 23.1, 23.0, 22.1.

Anal. Calcd for $C_{35}H_{33}N_3O_3$: C, 77.32; H, 6.12; N, 7.73. Found: C, 76.94; H, 6.01; N, 7.38.

(*Z*)-3-(1*H*-Indol-3-yl)-2-{[3-oxo-3-phenyl-1-(1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-1-en-1-yl]amino]propanoic Acid (11c)

Yield: 0.802 g (67%); yellow solid; mp 96–98 °C.

IR (KBr): 3425 (NH of indole), 3057–2500 (NH, OH), 1733 [C(=O)OH], 1643 (N-CH=CH_2), 1592 cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 11.44 (br s, 1 H, NH), 8.29 (br s, 1 H, NH of indole), 7.85–7.83 (m, 2 H, *o*-H_{Ph}), 7.40–7.36 (m, 5 H, *m*,*p*-H_{Ph}, CH-4 of indole, OH), 7.23–7.21 (m, 1 H, CH-7 of indole), 7.07–7.04 (m, 2 H, CH-2,6 of indole), 6.97–6.94 (m, 1 H, CH-5 of indole), 6.38 (dd, *J* = 15.6, 9.0 Hz, 1 H, $H_{N=CH}$), 5.81 (s, 1 H, H-3 of pyrrole), 5.78 (s, 1 H, CH=), 4.86 (d, *J* = 15.6 Hz, 1 H, H_{trans}), 4.60 (d, *J* = 9.0 Hz, 1 H, H_{cis}), 4.57 (m, 1 H, CH), 3.29–3.20 (m, 2 H, CH_2Ph), 2.54–2.52 (m, 4 H, CH_2-7,4), 1.80–1.71 (m, 4 H, CH_2-5,6).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 187.2, 173.2, 157.1, 140.3, 136.7, 131.5, 131.4, 130.6, 128.8, 127.6, 127.3, 124.6, 121.4, 119.2, 118.8, 118.6, 113.1, 111.8, 111.1, 109.2, 104.9, 95.0, 58.5, 41.6, 23.5, 23.0, 22.9, 21.8.

Anal. Calcd for $C_{30}H_{29}N_3O_3$: C, 75.13; H, 6.10; N, 8.76. Found: C, 75.40; H, 6.39; N, 8.66.

2-Acetyl-4,5,6,7-tetrahydroindole (17)

A soln of 2-benzoylethynyl-4,5,6,7-tetrahydroindole (**16**) (620 mg, 2.5 mmol), glycine (**4**) (189 mg, 2.5 mmol) and NaOH (100 mg, 2.5 mmol) in EtOH–H_2O (1:1, 16 mL) was heated at reflux temperature for 40 h. After cooling to r.t., the mixture was diluted with H_2O (50 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layer was dried over $MgSO_4$ and evaporated to afford the title product **17**. The aqueous layer was neutralized with 10% HCl, extracted with Et_2O (5 × 20 mL) and the combined organic layer dried over $MgSO_4$. The solvent was evaporated to give benzoic acid (244 mg, 80%).

Yield: 375 mg (91%); yellow oil.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 8.94 (br s, 1 H, NH), 6.62 (s, 1 H, H-3), 2.58 (m, 2 H, CH_2-7), 2.49 (m, 2 H, CH_2-4), 2.33 (s, 3 H, COMe), 1.79 (m, 2 H, CH_2-5), 1.73 (m, 2 H, CH_2-6).

2-Acetyl-1-methyl-4,5,6,7-tetrahydroindole (15a)

A soln of ethyl 3-(1-methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)propynoate (**18**) (542 mg, 2.5 mmol), alanine (**5**) (228 mg, 2.5 mmol) and NaOH (100 mg, 2.5 mmol) in EtOH–H_2O (1:1, 16 mL) was heated at reflux temperature for 10 h (TLC at this point did not show any traces of the starting acetylene). After cooling to r.t., the mixture was diluted with H_2O (50 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layer was dried over $MgSO_4$ and evaporated to afford tetrahydroindole **15a**.

Yield: 398 mg (89%); yellow oil.

IR (KBr): 1704 (CO) cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 6.71 (s, 1 H, H-3), 3.76 (s, 3 H, NMe), 2.52–2.48 (m, 4 H, CH_2-7,4), 2.35 (s, 3 H, COMe), 1.83–1.81 (m, 2 H, CH_2-5), 1.72–1.70 (m, 2 H, CH_2-6).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 187.6, 138.2, 129.4, 118.4, 118.0, 32.5, 26.9, 23.3, 22.8, 22.7, 22.1.

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