Synthesis of β-carboline derivatives

César Bernardo, Ana Cristina Dias Olival, António Ribeiro, Lígia M. Rodrigues, , Ana Paula A. Esteves, Ana Maria F. Oliveira-Campos*

Chemistry Centre, School of Sciences, University of Minho

e-mail: amcampos@quimica.uminho.pt

Abstract: The preparation of β-carbolines and of three alkynyl esters, two of them derived from carbolines, is described. Two new glycoconjugates were obtained, one by a click approach from an alkynyl derivative with tetracetyl-β-D-glucosylazide and the other one by linking a carboline carboxylic acid with tetracetyl-β-D-glucosylamine. .

Keywords: tetra-acetylglucose, click chemistry, β-carbolines, alkynyl esters

Introduction

β-Carboline alkaloids represent a number of natural and synthetic compounds, containing a pyridoindole structure, and they are associated with a vast spectrum of biochemical effects and pharmacological properties.[1,2]

The Pictet-Spengler condensation is commonly used to synthesize β-carbolines, due to its analogy to the biosynthesis of these systems. This reaction needs an arylethylamine, an aldehyde and an acid catalyst.

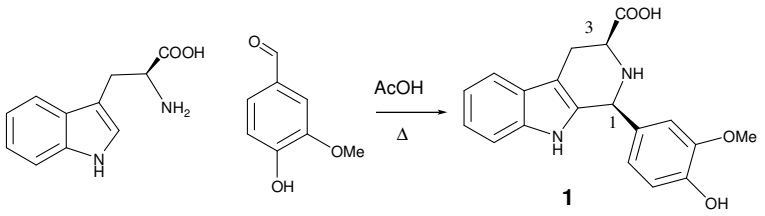
Some groups[2] describe a sequence of Pictet-Spengler condensation followed by oxidation, without the isolation of the intermediate tetrahydrocarbolines (THC), to prepare the carbolines.

In this work it was decided to prepare two conjugates derived from carbolines, and it was used the above sequence to obtain the carbolines. The synthesis of conjugates between carbolines and glucose derivatives followed two methods: make an alkynyl ester then use click chemistry, by a Cu(I) catalysed cycloaddition, [3] to obtain a triazole ring or react a carboline containing an acid group with a glucosylamine.

Results and Discussion

The work started with the synthesis of compound 1, by Pictet-Spengler reaction between tryptophan and vanillin, in glacial acetic acid (Scheme 1). In the mass spectrum (ESI^-) of the product obtained the base peak coincided with the molecular ion

(M^+-1) at 337. It may be deduced from the NMR spectrum that the *cis*-isomer was obtained.

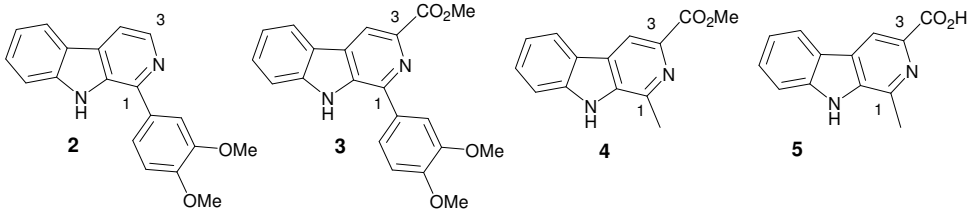


Scheme 1. Formation of compound **1**

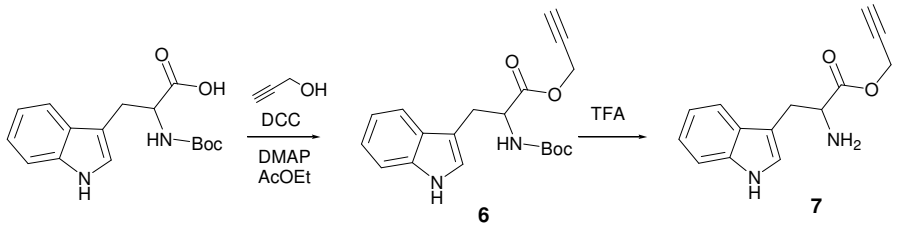
The Pictet-Spengler reaction between tryptophan and dimethoxybenzaldehyde, followed by oxidation of the crude product, gave the carboline **2** as a yellowish solid, in 8% yield. The doublets at 8.06 and 8.41 ppm (*J* 5.1 Hz) were identified as protons H-4 and H-3, thus confirming that decarboxylation had occurred. Taking into account the result obtained with vanillin, where the carboxylated THC **1** was isolated, one may conclude that decarboxylation possibly happened during the oxidation step.

In order to keep the carboxylic group intact, it was decided to use the methyl ester of tryptophan, as starting material, for the next reactions. Compound **3** was obtained in high yield (88%) using the sequence Pictet-Spengler and $KMnO_4$ oxidation,[2] without isolation of the intermediates. The proton NMR spectrum, namely the signals at 3.91, for OMe, and at 8.89 ppm (s) for H-4, proved that the product had the expected structure.

The carboline 4 was prepared in 34 % yield by the same method and its melting point and NMR data agreed with the literature.[4] Basic hydrolysis of the ester **4** gave the acid **5** in 73% yield.



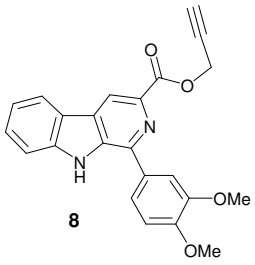
It was also an objective of this work to introduce an alkyne on the carboline structure and for this purpose, the ester derivative of tryptophan **6** was prepared in 77% yield from Boc-Trp and propargyl alcohol and the protecting group was removed in TFA, to give the corresponding amine **7** (Scheme 2). This amine was obtained as an oil and it was used without purification for further preparations. One pure sample was obtained by PLC for characterization.



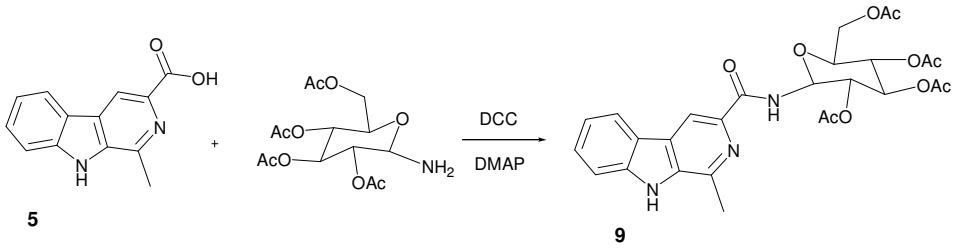
Scheme 2

The ^{1}H NMR spectrum of **7** showed the disappearance of the signal due to the *tert*-butoxycarbonyl group and a new signal due to NH_2 at 2.05 ppm.

The carboline **8** was prepared from the crude compound **7** and 3,4-dimethoxy benzaldehyde by Pictet-Spengler condensation and oxidation in 19 % yield, and it was obtained as an oil. The typical pattern for the propargyl group, at 5.03 (d, *J* 2.4 Hz, CH_2) and 3.62 (t, *J* 2.4 Hz, ≡CH) ppm, is observed.



The heteroglycoconjugate **9** was prepared, in low yield (6%), from acid **5** and tetracetylglucosylamine (Scheme 3) by peptide methodology. The tetracetylglucosylamine [5] was prepared from acetobromoglucose by reaction with NaN_3 followed by hydrogenation. It was possible to confirm the structure of the product by proton NMR, due to the presence of the glucosyl moiety signals.

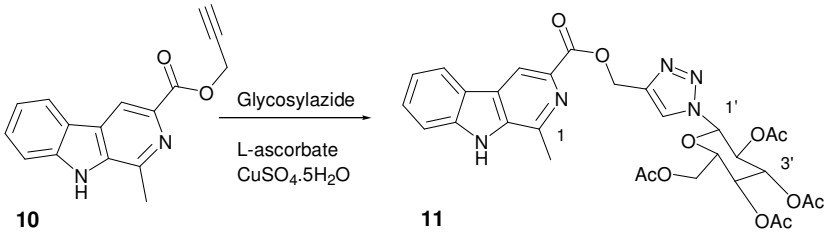


Scheme 3

Compound **10** was obtained from the acid **5** and propargyl bromide, in 53% yield as an oil. Another method of preparation, the Pictet-Spengler reaction from compound **7** and ethanal, followed by oxidation, gave the same product in 16% yield.

The basic hydrolysis of the ester **3** to the corresponding acid was attempted without success and thus it was not possible to obtain derivative **8** by esterification as in the case of **10**.

Compound **10** was used for the click reaction (scheme 4) with the glycosylazide produced *in situ* from treatment of α-acetobromoglucose with sodium azide. Compound **11** was obtained, as an oil, in good yield, and it was characterized by proton NMR. For example the signal (s) at 5.46 ppm for O-CH_2 and two singlets at 8.59 and 8.80 ppm accounted for both, the protons H-triazole and H-4.



Scheme 4

Conclusions

β-Carbolines were obtained by Pictet-Spengler reaction followed by oxidation, with fair global yields. Two new glycoconjugates were prepared, one by a click approach from an alkynyl derivative and the other one by joining a carboline carboxylic acid to tetracetyl-glucosylamine.

Experimental

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were recorded on a Varian Unity Plus Spectrometer at 298 K or on a Bruker Avance III 400 spectrometer (400 MHz for ^{1}H and 100.6 MHz for ^{13}C). Chemical shifts are reported in ppm relative to solvent peak or TMS; coupling constants (*J*) are given in Hz. Double resonance, HMQC (heteronuclear multiple quantum coherence) and HMBC (heteronuclear multiple bond correlation) experiments were carried out for complete assignment of ^{1}H and ^{13}C signals in the NMR spectra. High-resolution mass spectra (ESI-TOF) were obtained on a Bruker FTMS APEXIII spectrometer. Elemental analyses were obtained on a Leco CHNS-932 instrument. TLC was carried out on plates coated with silica gel 60 F_{254}. Column chromatography was performed on silica gel (70-230 or 230-400 mesh). Light petroleum refers to the fraction boiling in the range 40-60ºC.

General method for the preparation of β-carbolines (compounds 2, 3, 4, 8, 10)

To a solution of tryptophan or tryptophan methyl ester or 2-amino-3-(1*H*-indol-3-yl)-propionic acid prop-2-ynyl ester (**7**) (5.3 mmol), in glacial acetic acid (35 mL), 3,4-dimethoxybenzaldehyde or ethanal (5.83 mmol) was added and the solution was refluxed for 2 hours (except when stated otherwise). After cooling, ammonia was added until pH =7, a yellow solid precipitated and this was filtered and washed with water and dried. The crude product was dissolved in DMF (10 mL), cooled in ice and then $KMnO_4$ (7.95 mmol) was added in portions during a 30 minutes period. The reaction mixture was left stirring, at 0ºC, for 1 h and at room temperature for 3 hours. The precipitate was filtered, the solid was washed with ethyl acetate and the filtrate was diluted with ethyl acetate (100 mL). This solution was washed with water (4x 30 mL) and saturated NaCl solution. The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness.

Synthesis of *cis*-1-(4-hydroxy-3-methoxy-phenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylic acid (1)

To a tryptophan (1.000 g, 4.9 mmol) solution in AcOH (50 mL), vanillin ((1.174 g, 7.7 mmol) was added and the mixture was refluxed for 2 hours. After cooling, ammonia was added until pH =5 was reached, a beige solid precipitated and this was filtered and washed with water and dried, which proved to be the tetrahydrocarboline **1** (0.556 g, 33.3%, m.p.=243.4-253.0 ºC).

^{1}H (300 MHz, DMSO-d_6) δ: 2.94 (1H, dd, *J* 15.3 and 8.3 Hz, H-4a); 3.13 (1H, dd *J* 15.6 and 5.4 Hz, H-4); 3.64 (1H,dd, *J* 8.3 and 5.4 Hz, H-3); 3.73 (3H, s, OMe); 5.48 (1H, s, H-1); 6.48 (1H, dd *J* 7.8 and 2.4 Hz, H-6`); 6.71 (1H, d, *J* 8.1 Hz, H-5`); 6.97 (1H, dt, *J* 7.8 and 1.2 Hz, H-7); 7.02 (1H, d, *J* 2.4 Hz, H-2´); 7.04 (1H, dt, *J* 7.8 and 1.2 Hz, H-6); 7.24 (1H, d, *J* 7.8 Hz, H-8); 7.46 (1H, d, *J* 7.8 Hz, H-5); 8.9- 9.4 (1H, brs, OH); 10.69 (1H, s, NH) ppm. It was not possible to locate the signals due to one of the NH and the CO_2H. m/z (ESI$^-$) 337 ([M-1]$^+$, 100%). This compound is referred in the literature.[6]

Synthesis of 1-(3,4-dimethoxy-phenyl)-9*H*-β-carboline (2)

This compound was prepared by the general method described above, starting from tryptophan and 3,4-dimethoxybenzaldehyde. It was obtained as a yellowish solid, in 8% yield, m.p.181.5-183.0 ºC.

^{1}H (300 MHz, DMSO-d_6) δ: 3.86 (3H, s, OMe); 3.88 (3H, s, OMe); 7.17 (1H, d, *J* 8.7 Hz, H-8); 7.24 (1H, t, *J* 7.2 Hz, H-6); 7.48-7.68 (4H, m, Ar-H); 8.06 (1H, d, *J* 5.1 Hz, H-4); 8.24 (1H, d, *J* 7.5 Hz, H-5); 8.41 (1H, d, *J* 5.1 Hz, H-3); 11.47 (1H, s, NH) ppm.

^{13}C (75.4 MHz, DMSO-d_6) δ: 55.42 (OMe); 55.69 (OMe); 111.74 (C-5´); 112.45 (C-8); 113.40 (C-4); 119.46 (C-6); 120.76 (C-4b); 120.90 (C-2´); 121.58 (C-5); 128.05 (C-7); 128.97 (C-1); 131.08 (C-1´); 132.82 (C-9a); 138.20 (C-3); 141.04 (C-8a); 142.29 (C-4a); 148.89 (C-4´); 149.28 (C-3´) ppm.

Synthesis of 1-(3,4-dimethoxy-phenyl)-9*H*-β-carboline-3-carboxylic acid methyl ester (3)

To a solution of tryptophan (2.032 g, 9.96 mmol), in sulphuric acid (0.2 M, 50 mL), 3,4-dimethoxybenzaldehyde (1.883 g, 11,3 mmol) was added and the solution was refluxed for 10.5 hours. After cooling, ammonia was added until pH =5, a beige solid precipitated and this was filtered and washed with water and dried. The crude product (2.0 g) was dissolved in DMF (20 mL), cooled in ice and then $KMnO_4$ (13 mmol) was added in portions during a 60 minutes period. The reaction mixture was left stirring, at 0ºC, for 1 h and at room temperature for 3 hours. The precipitate was filtered through kieselgur, the solid was washed with ethyl acetate and the filtrate was diluted with ethyl acetate (200 mL). This solution was washed with water (4x 40 mL) and saturated NaCl solution. The organic layer was dried (MgSO4), filtered and evaporated to dryness, to give the crude product **3**, as a brown oily solid, (1.680g) whose ^1H NMR showed to be a mixture which was purified by column chromatography. The compound was obtained as a yellowish solid (0.599, 17%), m.p. 237-239ºC and later recrystallised from methanol to give a beige solid (0.333g, 9.2%), m.p. 238.9-239.4 ºC (Lit. [7], m.p. 238.9-239.4 ºC).

^1H (400 MHz, DMSO-d_6) δ: 3.92; 3.89 and 3.91 (9H, 3s, 3xOMe); 7.20 (1H, d, *J* 8.8 Hz, H-5'); 7.31 (1H, t, *J* 7.4 Hz, H−6); 7.51-7.57 (2H, m, H-2' e H-6'); 7.60 (1H, d, *J* 8.0 Hz, H-7); 7.69 (1H, d, *J* 8.4 Hz, H-8); 8.40 (1H, d, *J* 8.0 Hz, H-5); 8.86 (1H, s, H-4); 11.88 (1H, s, NH) ppm.

^{13}C (100.62 MHz, DMSO-d_6) δ: 52.03 (CO_2Me); 55.53 (Me-C-3'); 55.71 (Me-C-4'); 111.59 (C-7); 111.88 (C-5'); 112.07 (C-2'); 112.78 (C-8); 116.25 (C-4); 120.35 (C-6); 121.20 (C-4b); 121.26 (C-6'); 121.49 (C-5); 128.54 (C-7); 128.88 (C-1); 130.16 (C-1'); 134.50 (C-3); 136.55 (C-4a); 141.40 (C-8a); 142.34 (C-1); 148.82 (C-3'); 149.64 (C-4'); 166.10 (C=O) ppm. Anal. Calcd para $C_{21}H_{18}N_2O_4$1/2 H_2O: C, 67.91; H, 5.16; N, 7.54. Found: C, 67.91; H, 5.30; N,7.42.

The compound **3** was also prepared by the general procedure, starting from tryptophan methyl ester and 3,4-dimethoxybenzaldehyde with reflux in acetic acid for 4h, followed of oxidation of the crude dry tetrahydrocarboline mixture. Compound **3** was obtained

as a brown solid (88%), m.p.=235-237 ºC. The ^{1}H NMR was similar to the described above.

Synthesis of 1-methyl-9*H*-β-carboline-3-carboxylic acid methyl ester (4)

The general procedure, starting from tryptophan methyl ester and ethanal gave the ester **4** as an off-white solid (34%), m.p.= 242-244ºC (Lit. [4], m.p.= 243-244ºC).

^{1}H (400 MHz, DMSO-d_6) δ: 2.81 (3H, s, CH_3); 3.88 (3H, s, OMe); 7.29 (1H, td, *J* 7.6 and 1.2 Hz, H-6 ou H-7); 7.58 (1H, td, *J* 8.0 and 0.8 Hz, H-6 ou H-7); 7.65 (1H, d, *J* 8.4 Hz, H-8); 8.34 (1H, d, *J* 8 Hz, H-5); 8.76 (1H, s, H-4); 12.10 (1H, s, NH) ppm. m/z (ESI$^+$) 263.08 ([M+Na]$^+$,100%).

1-Methyl-9*H*-β-carboline-3-carboxylic acid (5)

A solution of the ester **4** (1.37 g, 5.70mmol) in aqueous sodium hydroxide (2M, 10.0 mL) was stirred at room temperature for 3 hours. After cooling HCl was added until pH 7, when a solid precipitated out. It was filtered and dried and the acid **5** was obtained as a yellow solid (73% yield), m.p. 291-293 ºC (Lit. [4], 292-293ºC).

^{1}H (300 MHz, DMSO-d_6) δ: 2.82 (3H, s, CH_3); 7.29 (1H, t, *J* 7.5 Hz, H-6 or H-7); 7.58 (1H, t, *J* 7.5 Hz, H-6 or H-7); 7.65 (1H, d, *J* 7.8 Hz, H-8); 8.34 (1H, d, *J* 7.8 Hz, H-5); 8.74 (1H, s, H-4); 12.00 (1H, s, NH) ppm. The CO_2H signal was not observed.

Preparation of 2-tert-butoxycarbonylamino-3-(1*H*-indol-3-yl)-propionic acid prop-2-ynyl ester (6)

To a solution of 2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl) propanoic acid (0.456 g, 1.5 mmol), in ethyl acetate (10 mL) at 0ºC DCC (0.330 g, 1.6 mmol) and DMAP (0.10 g – catalytic amount) were added. Later another portion of propargyl alchool (0.084 g, 1.5 mmol, 0.087 ml) was added and the mixture was left stirring at 0ºC for 30 minutes and at room temperature for 24 hours. The precipitated urea was filtered off and the filtrate was extracted with saturated $NaHCO_3$ and water, and dried ($MgSO_4$). After evaporation the ester **6** was obtained as a light brown solid (0.393 g, 1.15 mmol, 77%), m.p. 96.0-97.0ºC.

^{1}H (300 MHz, DMSO-d_6) δ: 1.32 (9H, s, Boc); 3.0 (1H, dd, *J* 9.0 and 15.3 Hz, H-3a); 3.1 (1H, dd, *J* 7.1 *J* 14.7 Hz, H-3b); 3.56 (1H, t, *J* 2.1 Hz, CH_2); 4.16-4.26 (1H, m, H-2); 4.71 (2H, d, *J* 2.1Hz, CH_2); 6.98 (1H, t, *J* 6.9 Hz, H-5´); 7.07 (1H, t, *J* 7.1Hz, H-6´); 7.15 (1H, d, *J* 1.5 Hz, H-2´); 7.27 (1H, d, *J* 7.8 Hz, NH-Boc exchanges with D_2O); 7.33 (1H, d, *J* 7.1 Hz, H-7´); 7.49 (1H, d, *J* 7.8 Hz, H-4´); 10.86 (1H, s, NH) ppm.

^{13}C (75.4 MHz, DMSO-d_6) δ: 26.56 (C-3); 28.12 (3-CH_3); 52.16 (CH_2); 54.63 (C-2); 77.89 (CH_2); 78.21-78.32 (CqBoc and C≡); 109.56 (C-3´); 111.45 (C-7´); 117.94 (C-4´); 118.43 (C-5´) ; 120.96 (C-6´); 123.84 (C-2´); 127.00 (C-3´a); 136.08 (C-7´a); 155.37 (C=ONH); 171.72 (C=O ester) ppm. Anal. calcd for $C_{19}H_{22}N_2O_4$: C, 66.67; H, 6.43; N, 8.19. Found: C, 67.00; H, 6.61; N, 8.42. m/z (ESI$^+$) 365.33 ([M+Na]$^+$,100%).

2-Amino-3-(1*H*-indol-3-yl)-propionic acid prop-2-ynyl ester (7)

The ester **6** (0.346 g, 1.01 mmol) was treated with TFA (3 mL) at room temperature. The mixture was stirred occasionally. One hour and a half later excess reagent was removed by evaporation, and a brown oil was obtained. Purification of part of the crude material by PLC gave compound **7** as an oil (13 mg, 0.054 mmol, 5.4%). The crude product, from another preparation, was used without purification for the following transformation.

^{1}H (300 MHz, $CDCl_3$) δ: 2.05 (2H, s, NH_2, exchanges with D_2O) 2.52 (1H, t, *J* 2.4 Hz, ≡CH); 3.10 (1H, dd, *J* 14.1 and 7.5 Hz, H-3´b); 3.31 (1H, dd, *J* 14.1 and 3.8 Hz, H-3´a); 3.85 (1H, dd, *J* 7.5 and 4.8 Hz, H-2´); 4.71 (2H, d, *J* 2.4 Hz, O-CH_2); 7.05 (1H, brs, H-2); 7.13 (1H, td, *J* 6.9 and 0.9 Hz, H-5 or H-6); 7.20 (1H, td, *J* 6.9 and 0.9 Hz, H-5 or H-6); 7.34 (1H, d, *J* 7.8 Hz, H-7); 7.63 (1H, d, *J* 7.5 Hz, H-4); 8.52 (1H, br s, NH) ppm.

1-(3,4-Dimethoxy-phenyl)-9*H*-β-carboline-3-carboxylic acid prop-2-ynyl ester (8)

This compound was prepared by general method, using compound **7** and 3,4-dimethoxybenzaldehyde, and it was obtained as an oil (19%).

^{1}H (300 MHz, DMSO-d_6) δ: 3.62 (1H, t, *J* 2.4 Hz, ≡CH); 3.83 (3H, s, OMe); 3.89 (3H, s, OMe); 5.03 (2H, d, *J* 2.4 Hz, CH_2); 7.22 (1H, d, *J* 9.0 Hz, H-5´); 7.32 (1H, td, *J* 1.2 and 7.5 Hz, H-6); 7.54-7.59 (2H, m, H-6´ e H-2´); 7.60 (1H, td, *J* 1.2 and 7.5 Hz; H-7); 7.69 (1H, d, *J* 8.4 Hz, H-8); 8.43 (1H, d, *J* 7.5 Hz, H-5); 8.90 (1H, s, H-4); 11.93 (1H, brs, NH) ppm.

^{13}C (75.4 MHz, DMSO-d_6) δ: 52.31 (CH_2); 55.50 (OMe); 55.71 (OMe); 77.77 (≡CH); 78.80 (C≡); 111.89 (C-5´); 112.04 (C-2´); 112.80 (C-8); 116.63 (C-4); 120.43 (C-6); 121.17 (C-4b); 121.25 (C-6´); 122.03 (C-5); 128.60 (C-7); 128.85 (C-4a); 130.03 (C-1´); 134.62 (C-9a); 135.87 (C-3); 141.30 (C-8a); 142.49 (C-1); 148.80 (C-3´or C-4´); 149.67 (C-4´ or C-3´); 164.68 (C=O) ppm.

Acetic acid 4,5-diacetoxy-2-acetoxymethyl-6-[(1-methyl-9*H*-β-carboline-3-carbonyl)-amino]-tetrahydro-pyran-3-yl ester (9)

To a solution of tetracetyl-β-D-glucosylamine (100 mg, 0.29 mmol) in dichloromethane (30 mL), DCC (0.317 mmol), compound **5** (65.6mg, 0.29 mmol) and DMAP (0.171 mmol) were added and the mixture stirred at room temperature for 5 hours. The *N,N'*-dicyclohexylurea was filtered off and the solution washed successively with water (2x30 mL), 5% aqueous solution of acetic acid and water (3x20 mL) and dried over Na_2SO_4. Evaporation of the solvents, and purification by column chromatography, followed by PLC yielded product **9** as an oil, 10 mg, 6%.

^{1}H (300 MHz, $CDCl_3$) δ: 2.03, 2.07, 2.08, 2.11 (4 s, 12H, 4 x OAc); 3.63 (3H, s, CH_3); 3.80-4.30 (3H, m, H-5', H-6'a and H-6'b); 5.20-5.50 (3H, m, H-2', H-3' and H-4'); 6.07 (1H, ap s, H-1'); 8.12 (1H, d, *J* 9.0 Hz, H-8 or H-5); 8.23 (1H, d, *J* 9.0 H-5 or H-8); 8.77 (1H, s, H-4); 14.42 (1H, br s, NH) ppm. The other NH signal was hidden within the aromatic region.

Synthesis of 1-methyl-9*H*-β-carboline-3-carboxylic acid prop-2-ynyl ester (10)

To a solution of compound **5** (200 mg, 0.88 mmol) in DMSO (3 mL) were added anhydrous K_2CO_3 (123 mg, 0.89 mmol) and propargyl bromide (0.097 ml, 0.88 mmol), and the reaction mixture was stirred at room temperature for 24 hours. Water was added, it was extracted with ethyl acetate and the organic extracts were combined, dried ($MgSO_4$) and evaporated to dryness. The alkyne **10** was obtained as an oil (121 mg, 0.46 mmol, 53 %).

^{1}H (300 MHz, DMSO-d_6) δ: 2.82 (3H, s, CH_3); 3.60 (1H, t, *J* 2.4 Hz, ≡CH); 4.99 (2H, d, *J* 2.4 Hz, CH_2); 7.30 (1H, td, *J* 8.1 and 0.9 Hz, H-6); 7.59 (1H, td, *J* 8.1 and 0.9 Hz, H-7); 7.65 (1H, d, *J* 8.1 Hz, H-8); 8.37 (1H, d, *J* 7.8 Hz, H-5); 8.79 (1H, s, H-4); 12.07 (1H, s, NH) ppm.

^{13}C (75.4 MHz, DMSO-d_6) δ: 20.36 (CH_3); 52.13 (CH_2); 77.70 (CH_2); 78.83 (CH_2); 112.34 (C-8); 116.38 (C-4); 120.24 (C-6); 121.31 (C-4b); 122.18 (C5); 126.74 (C-4a); 128.43 (C7); 135.28 (C-3); 136.31 (C-9a); 140.83 (C-8a); 142.39 (C-1); 164.88 (C=O) ppm.

The same compound **10** was prepared by the general method, described before, from compound **7** and ethanal, in 16% yield.

1-Methyl-9*H*-β-carboline-3-carboxylic acid 1-(3,4,5-triacetoxy-6-acetoxymethyl-tetrahydro-pyran-2-yl)-1*H*-[1,2,3]triazol-4-ylmethyl ester (11)

To a solution of α-acetobromoglucose (150 mg, 0.36 mmol) in dry DMSO (4 mL), dry NaN_3 (28.5 mg, 0.44 mmol) was added and the resulting mixture stirred at room temperature for 20 min. To the glycosylazide formed *in situ*, compound **10 (**101 mg, 0.38 mmol), sodium L-ascorbate (1M, 0.9 mL) and $CuSO_4.5H_20$ (1M, 0.9 mL) were added. The reaction mixture was left stirring for 3 hours. The product **11** precipitates, after addition of water to the reaction mixture, as a greenish oily solid (206 mg, 0.323 mmol, 90%).

^{1}H (300 MHz, DMSO-d_6) δ: 1.79,1.94,1.98 and 2.03 (12H, 4s, 4xOAc); 2.70 (3H, CH_3); 4.00–4.20 (2H, m, 2xH-6´); 4.43-4.44 (1H, m, H-5´); 5.55 (1H, t, *J* 9.6 Hz, H-4´); 5.46 (2H, s, O-CH_2); 5.55 (1H, t, *J* 9.6 Hz, H-2´ or 3´); 5.70 (1H, t, *J* 9.3 Hz, H-2´or 3´); 6.38 (1H, d, *J* 9.0 Hz, H-1´); 7.29 (1H, t, *J* 7.8 Hz, H-6 or H-7); 7.58 (1H, t, *J* 7.4 Hz, H-6 ou H-7); 7.64 (1H, d, *J* 7.8 Hz, H-8); 8.35 (1H, d, *J* 7.8 Hz, H-5); 8.59 (1H, s, H-triazole or H-4); 8.80 (1H, brs, H-triazole or H-4); 12.05 (1H, s, NH) ppm.

Acknowledgements

To the Foundation for the Science and Technology (FCT, Portugal) for financial support to the NMR portuguese network (PTNMR, Bruker Avance III 400-Univ. Minho) and to FCT and FEDER (European Fund for Regional Development)-COMPETE-QREN-EU for financial support to the Research Centre, CQ/UM [PEst-C/QUI/UI0686/2011 (FCOMP-01-0124-FEDER-022716)]

References

1. Cao, R.; Peng, W.; Wang Z.; Xu A., *Curr Med Chem*. 2007, 14, 479-500.

2. Wu, Q.; Cao, R. ; Feng, M.; Guan, X.; Ma, C.; Liu, J.; Song, H.; Peng, W., *Eur. J. Med. Chem*. 2009, 44, 533-540.

3. Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. Eur. *J. Org. Chem*. 2006, 51-68.

4. Zhao, M.; Wang, L. Bi, W.; Wang, C.; Baudy-Floc'h M.; Ju, J.; Peng, S., *Bioorg. & Med. Chem.* 2006, 14, 6998–7010.

5. Silva, M.E.T.F, "Glicopéptidos fluorescentes: Síntese e caracterização", PhD Thesis, Universidade do Minho, 2009.

6. Bi, W.; Bi, Y.; Xue, P.; Zhang , Y.; Gao, X.; Wang, Z.; Meng L.; Baudy-Floc'h, M.; Ngerebara, N.; Gibson, K.M.; Bi, L., *Eur. J. Med. Chem*. 2011, 46, 1453-1462.

7. Ribeiro, A.M.P.; Oliveira-Campos, A.M.F.; Rodrigues, L.M.; Gonçalves, L.F.F.F.; Silva, C.J.R., 2PYCheM, poster comm. nº 43, 2nd Portuguese Young Chemists Meeting, Universidade de Aveiro, 21-23 Abril, 2010.