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RESEARCH ARTICLE

Efficient Synthesis of Novel 1-Substituted β-Carboline Derivatives via Pictet-Spengler Cyclization of 5-Hydroxy-L-Tryptophan

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Abstract A facile synthesis of novel 1-substituted β-carboline derivatives by using three efficient reaction steps was described. The synthetic route began with the construction of β-carboline frameworks involving the coupling of 5-hydroxy-L-tryptophan with different substituted phenylglyoxal *via* Pictet-Spengler condensation. Subsequent reduction of carbonyl functionality on carbon-7' by using Wolff-Kishner reaction followed by N-alkylation afforded a practical access to a series of 1-substituted β-carboline derivatives in moderate yields. These novel derivatives were successfully synthesized without the use of expensive metal catalyst, prolonged reaction hours or critical reaction conditions. The molecular structures of all synthesized derivatives were confirmed by infrared (IR), gas chromatography–mass spectrometry (GC-MS) and nuclear magnetic resonance (NMR) spectroscopy.

Keywords: Pictet-Spengler condensation, Wolff-Kishner reaction, β-carbolines, 5-hydroxy-L-tryptophan.

Introduction

β-Carboline or 9*H*-pyrido[3,4-b]indole, belongs to the group of indole alkaloids and comprises of pyridine ring fused to an indole skeleton. The structure of β-carboline is similar to that of tryptamine, with the ethylamine chain reconnected to the indole ring *via* an extra carbon atom, to produce a tricyclic ring structure (see figure 1). Commonly known as norharmane, this compound and its derivatives such as harmane, harmine, and harmaline (see figure 1) are reported to occur in a number of plants, including *Peganum harmala*, a medicinal plant with antimicrobial [1], antioxidant [2], anti-inflammatory, and analgesic properties [3]. Extensive studies on β-carboline have proven the remarkable diversity of biological efficacy displayed by this natural compound. Hence, β-carbolines obtained from different parts of *P. harmala* are used in the treatment of various diseases [4]. For instance, the extract of *P. harmala* contains harmine and harmaline that are known to possess hypothermic and hallucinogenic properties. It is therefore used as a medical remedy employed in the treatment of syphilis, fever, hysteria, malaria, parkinsonism, asthma and eye complaints [5,6,7].

It has also been reported that the medicinal activities of β-carbolines were improved by the introduction of appropriate substitution into carbon-1 [8]. Daibucarboline A (see figure 1) is an example of 1-substituted β-carboline that is recognized as a potential anti-inflammatory agent. This tetracyclic compound is originally isolated from the roots of *Neolitsea daibuensis* in 2011 by Wong and co-workers [9], followed by Jani and co-workers in 2018 from the stems of *Neolitsea kedahensis* in trace amount [10]. The daibucarboline A has been discovered to display anti-inflammatory property when examined

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using inducible nitric oxide synthase (iNOS) assay with the IC_{50} values of 18.41 μM. Intrigued by the biological significance of simple β-carbolines as well as a range of β-carboline derived compounds, there have been many reported strategies concerning their syntheses.

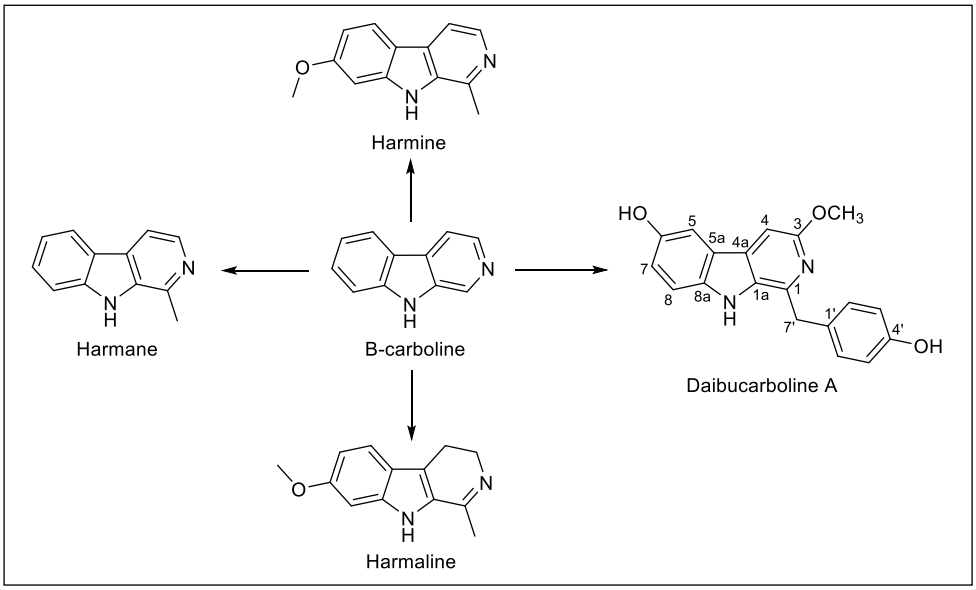


Figure 1. Chemical structure of β-carboline and its derivatives

The Pictet-Spengler reaction has long been an important reaction for the synthesis of β-carboline alkaloids [11]. To date, it has remained as one of the most powerful methods for the formation of this ring system *via* C-C bond formation using indole-based compound as the starting material [12]. This reaction is one of the most direct, efficient, and variable synthetic method for the construction of privileged and widely synthesized pharmacophores such as tetrahydro-isoquinolines (THIQs), tetrahydro-β-carbolines (THβCs), and polyheterocyclic frameworks [13]. Generally, Pictet-Spengler reaction can be characterized by the formation of iminium salt after an acid-catalyzed condensation of β-arylethylamine with an aldehyde or a ketone, followed by ring closure [14]. This method continues to be a prominent focus of research over the years as scientists continue to refine the methodology by applying novel reaction conditions. It is interesting to note that under modified Pictet-Spengler conditions, a convenient one-step conversion of tryptophan derivatives and aldehydes directly to β-carbolines without generation of tetrahydro intermediates has been described [15]. The simplicity of this one-pot oxidation procedure prompted us to investigate the scope and synthesis of a range of 1-substituted β-carboline derivatives. Thus, we report herein the successful application of this reaction to the synthesis of naturally occurring 1-substituted β-carboline derivatives using 5-hydroxy-L-tryptophan as the starting material.

Materials and methods

Comercially available reagents were used as supplied from Sigma-Aldrich and Biotek Abadi Sdn. Bhd, without further purification, unless stated otherwise. Air and sensitive compounds were stored in a desiccator over self-indicating silica pellets, under nitrogen atmosphere. Column chromatography was carried out using Merck 9385 Kieselgel 60 (230-400 mesh ASTM) and hand bellows were used to apply pressure to the column. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF254. Plates were visualized under UV light (at 254 nm), staining with potassium permanganate solution followed by heating, or exposing to iodine vapour.

Melting points for solid compounds were determined using electrothermal melting points apparatus or an automatic FP62 melting point apparatus from Mettler Toledo and the range values were recorded and uncorrected. Fourier Transformed Infrared absorption spectra were recorded on Varian 3100 excalibur series instruments Spectrum 2000 or Spectrum One, both in the spectral range of 4000 to 400 cm^{-1}.

Molecular weights of all synthesized compounds were recorded on GCMS Agilent Technologies 7890 A (GC System). The Agilent Technologies used was 5975C inert XLEI/CI MSD with Triple-Axis Detecter. Proton and Carbon-13 nuclear magnetic resonance spectra were recorded using JEOL NMR spectrometer instrument operating at 400 MHz and 100 MHz respectively.

General procedure for the synthesis of compounds 1a-d:
To a stirred suspension of 5-hydroxy-L-tryptophan (4.541 mol, 1.3 equiv.) in 1.0 equiv. of *p*-toluenesulfonic acid monohydrate, phenylglyoxal monohydrate (3.493 mol, 1.0 equiv.) was added. The resulting solution was stirred at 50 °C for 2 h, and the phenylglyoxal was monitored by TLC to be completely consumed. The reaction mixture was poured into water and the precipitate was filtered and purified by silica gel column chromatography eluted with a gradient of n-hexane and ethyl acetate (7:3) to afford **1a-d**.

(6-hydroxy-9H-pyrido[3,4-b]indol-1-yl)(phenyl)methanone **(1a)**. Yellow powder, 0.49 g, 38%, mp 135-138 °C; IR v_{max} cm^{-1}: 3492, 3432, 1642, 1621; ^{1}H NMR δ (CD_3OD, 400 MHz) ppm: 12.06 (1H, br s, NH), 9.22 (1H, br s, OH), 8.53 (1H, d, H-3), 8.46 (1H, d, H-4), 8.33 (1H, d, H-5), 8.18 (2H, d, H-2' and H-6'), 7.81 (1H, d, H-8), 7.69–7.55 (4H, m, H-7, H-3', H-4', and H-5'); ^{13}C NMR δ (CD_3OD, 100 MHz): 194.1, 141.9, 137.7, 137.3, 136.5, 136.1, 132.4, 131.2, 131.0, 129.4, 128.1, 121.9, 120.4, 120.3, 119.0, 113.2; MS: *m/z* 288.0.

(6-hydroxy-9H-pyrido[3,4-b]indol-1-yl)(4-methoxyphenyl)methanone **(1b)**. Brown solid, 0.46 g, 32%, mp 185-187 °C; IR v_{max} cm^{-1}: 3500, 3423, 1697; ^{1}H NMR δ (CD_3OD, 400 MHz) ppm: 11.98 (1H, br s, NH), 9.20 (1H, br s, OH), 8.52 (1H, d, H-3), 8.41 (1H, d, H-4), 8.31 (2H, d, H-2' and H-6'), 8.30 (1H, d, H-5), 7.79 (1H, d, H-8), 7.59 (1H, dd, H-7), 7.10 (2H, d, H-3' and H-5'), 3.87 (3H, s, OCH_3); ^{13}C NMR δ (CD_3OD, 100 MHz): 191.8, 163.0, 141.8, 137.2, 137.1, 135.9, 133.6, 131.0, 130.0, 129.0, 122.0, 120.3, 118.6, 113.6, 113.1, 55.7; MS: *m/z* 318.1.

(6-hydroxy-9H-pyrido[3,4-b]indol-1-yl)(4-hydroxyphenyl)methanone **(1c)**. Light brown solid, 0.28 g, 20%, mp 155-158 °C; IR v_{max} cm^{-1}: 3499, 3456, 1678; ^{1}H NMR δ (CD_3OD, 400 MHz) ppm: 12.18 (1H, br s, NH), 9.68 (1H, br s, OH), 9.23 (1H, br s, OH), 8.68 (1H, d, H-3), 8.51 (1H, d, H-4), 8.43 (2H, d, H-2' and H-6'), 8.32 (1H, d, H-5), 7.87 (1H, d, H-8), 7.52 (1H, dd, H-7), 7.12 (2H, d, H-3' and H-5'); ^{13}C NMR δ (CD_3OD, 100 MHz): 170.8, 165.0, 143.9, 138.2, 136.1, 135.2, 133.2, 131.8, 130.0, 129.0, 122.0, 120.8, 118.4, 113.6, 114.5; MS: *m/z* 304.0.

(6-hydroxy-9H-pyrido[3,4-b]indol-1-yl)(4-nitrophenyl)methanone **(1d)**. Brown solid, 0.69 g, 46%, mp 194-196 °C; IR v_{max} cm^{-1}: 3443, 3389, 1644; ^{1}H NMR δ (CD_3OD, 400 MHz) ppm: 12.09 (1H, br s, NH), 9.19 (1H, br s, OH), 8.51 (1H, d, H-3), 8.44 (1H, d, H-4), 8.31 (1H, d, H-5), 8.15 (2H, d, H-2' and H-6'), 7.82 (1H, d, H-8), 7.77 (2H, d, H-3' and H-5'), 7.60 (1H, t, H-7); ^{13}C NMR δ (CD_3OD, 100 MHz): 192.8, 141.9, 137.4, 136.6, 136.0, 133.0, 131.3, 131.2, 129.2, 126.5, 122.0, 120.4, 120.2, 119.3, 113.2; MS: *m/z* 333.0.

General procedure for the synthesis of compounds 2a-d:
A mixture of **1a-d** (1.0 equiv.), potassium hydroxide (4.0 equiv.), and hydrazine hydrate (6.0 equiv.) in ethylene glycol was heated at 120 °C for 1 h, then kept at 165 °C for 5 h. The reaction mixture was cooled to room temperature and acidified with 2M HCl to pH~4. The aqueous layer was washed and basified to pH~7 and extracted with ethyl acetate. The combined organic layers were dried magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography eluted with a gradient of n-hexane and ethyl acetate (7:3) to furnish **2a-d**.

1-benzyl-9H-pyrido[3,4-b]indol-6-ol **(2a)**. Yellow solid, 0.20 g, 41%, mp 143-145 °C; IR v_{max} cm^{-1}: 3500, 3442, 1465; ^{1}H NMR δ (CD_3OD, 400 MHz) ppm: 11.07 (1H, br s, NH), 9.02 (1H, br s, OH), 8.63 (1H, d, H-3), 7.96 (1H, d, H-4), 7.83 (1H, d, H-5), 7.78 (2H, d, H-2' and H-6'), 7.72 (1H, d, H-8), 7.69–7.55 (4H, m, H-7, H-3', H-4', and H-5'), 4.23 (2H, s, CH_2); ^{13}C NMR δ (CD_3OD, 100 MHz): 157.9, 141.9, 137.7, 137.3, 136.5, 136.1, 132.4, 131.2, 131.0, 129.4, 128.1, 121.9, 112.7, 112.6, 112.5, 106.2, 34.2; MS: *m/z* 274.1.

1-(4-methoxybenzyl)-9H-pyrido[3,4-b]indol-6-ol **(2b)**. Brown solid, 0.15 g, 35%, mp 165-166 °C; IR v_{max} cm^{-1}: 3490, 3453, 1462; ^{1}H NMR δ (CD_3OD, 400 MHz) ppm: 11.92 (1H, br s, NH), 9.39 (1H, br s, OH), 8.52 (1H, d, H-3), 8.31 (1H, d, H-4), 8.01 (2H, d, H-2' and H-6'), 7.83 (1H, d, H-5), 7.64 (1H, d, H-8), 7.26 (1H, dd, H-7), 6.95 (2H, d, H-3' and H-5'), 4.18 (2H, s, CH_2), 3.81 (3H, s, OCH_3); ^{13}C NMR δ (CD_3OD,

100 MHz): 163.4, 155.6, 141.3, 137.2, 137.1, 135.9, 133.6, 133.4, 130.1, 125.4, 122.9, 120.3, 115.6, 113.7, 113.1, 55.8, 36.5; MS: *m/z* 304.1.

1-(4-hydroxybenzyl)-9H-pyrido[3,4-b]indol-6-ol **(2c)**. Light brown solid, 0.10 g, 35%, mp 182-184 °C; IR v_{max} cm^{-1}: 3489, 3456, 1466; ^{1}H NMR δ (CD_3OD, 400 MHz) ppm: 11.07 (1H, br s, NH), 9.61 (1H, br s, OH), 9.15 (1H, br s, OH), 8.63 (1H, d, H-3), 8.51 (1H, d, H-4), 7.86 (2H, d, H-2' and H-6'), 7.73 (1H, d, H-5), 7.52 (1H, d, H-8), 7.32 (1H, dd, H-7), 7.05 (2H, d, H-3' and H-5'), 4.14 (2H, s, CH_2); ^{13}C NMR δ (CD_3OD, 100 MHz): 158.6, 143.0, 141.8, 137.2, 137.1, 135.9, 133.6, 131.0, 130.0, 129.0, 122.0, 120.3, 118.6, 113.6, 106.7, 35.7; MS: *m/z* 290.1.

1-(4-nitrobenzyl)-9H-pyrido[3,4-b]indol-6-ol **(2d)**. Yellow solid, 0.25 g, 38%, mp 192-195 °C; IR v_{max} cm^{-1}: 3499, 3479, 1465; ^{1}H NMR δ (CD_3OD, 400 MHz) ppm: 11.95 (1H, br s, NH), 9.16 (1H, br s, OH), 8.74 (1H, d, H-3), 8.42 (1H, d, H-4), 8.31 (1H, d, H-5), 7.99 (2H, d, H-2' and H-6'), 7.56 (1H, d, H-8), 7.43 (2H, d, H-3' and H-5'), 7.10 (1H, t, H-7), 4.28 (2H, s, CH_2); ^{13}C NMR δ (CD_3OD, 100 MHz): 166.2, 141.9, 137.4, 136.6, 136.0, 133.0, 131.3, 131.2, 130.2, 126.5, 122.8, 120.4, 116.2, 115.3, 111.2, 34.7; MS: *m/z* 319.1.

General procedure for the synthesis of compounds 3a-d:
To a solution of compounds **2a-d** (1.0 equiv.) in THF (20 mL) was added NaH (60% dispersion in mineral oil, 3.0 equiv.) portion wise and the resulting reaction mixture was stirred at room temperature for 1 h. Next, a solution of iodomethane (1.2 equiv.) in DMF (2 mL) was added drop wise to reaction mixture and stirred for 12 h at room temperature. Upon completion of reaction, the contents were poured over crushed ice and extracted with DCM (3 × 30 mL), dried and removed the excess solvent under *vaccuo*. The residue obtained was purified by column chromatography eluted with a gradient of n-hexane and ethyl acetate (7:3) to provide derivatives **3a-d**.

1-benzyl-9-methyl-9H-pyrido[3,4-b]indol-6-ol **(3a)**. Yellow solid, 0.11 g, 54%, mp 158-159 °C; IR v_{max} cm^{-1}: 3488, 2810,1465; ^{1}H NMR δ (CD_3OD, 400 MHz) ppm: 9.23 (1H, br s, OH), 8.77 (1H, d, H-3), 8.02 (1H, d, H-4), 7.86 (1H, d, H-5), 7.73 (2H, d, H-2' and H-6'), 7.70 (1H, d, H-8), 7.55–7.25 (4H, m, H-7, H-3', H-4', and H-5'), 4.60 (2H, s, CH_2), 4.45 (3H, s, CH_3); ^{13}C NMR δ (CD_3OD, 100 MHz): 158.9, 140.9, 136.7, 136.3, 135.5, 135.3, 131.4, 130.2, 129.0, 128.5, 126.1, 122.9, 114.6, 112.5, 106.2, 34.7, 33.6; MS: *m/z* 288.1.

1-(4-methoxybenzyl)-9-methyl-9H-pyrido[3,4-b]indol-6-ol **(3b)**. Yellow solid, 0.08 g, 51%, mp 160-162 °C; IR v_{max} cm^{-1}: 3492, 2817,1460; ^{1}H NMR δ (CD_3OD, 400 MHz) ppm: 9.46 (1H, br s, OH), 8.01 (1H, d, H-3), 8.38 (1H, d, H-4), 8.01 (2H, d, H-2' and H-6'), 7.77 (1H, d, H-5), 7.65 (1H, d, H-8), 7.25 (1H, dd, H-7), 6.23 (2H, d, H-3' and H-5'), 4.32 (2H, s, CH_2), 3.83 (3H, s, CH_3), 3.78 (3H, s, OCH_3); ^{13}C NMR δ (CD_3OD, 100 MHz): 159.4, 157.2, 141.8, 137.2, 137.1, 136.8, 133.6, 133.4, 128.6.1, 125.6, 122.9, 120.3, 115.6, 113.9, 113.1, 55.8, 37.4, 36.6; MS: *m/z* 318.1.

1-(4-hydroxybenzyl)-9-methyl-9H-pyrido[3,4-b]indol-6-ol **(3c)**. Brown solid, 0.04 g, 43%, mp 162-164 °C; IR v_{max} cm^{-1}: 3489, 2820,1466; ^{1}H NMR δ (CD_3OD, 400 MHz) ppm: 9.22 (1H, br s, OH), 9.02 (1H, br s, OH), 8.77 (1H, d, H-3), 8.51 (1H, d, H-4), 8.12 (2H, d, H-2' and H-6'), 7.93 (1H, d, H-5), 7.62 (1H, d, H-8), 7.52 (1H, dd, H-7), 7.48 (2H, d, H-3' and H-5'), 4.51 (2H, s, CH_2), 3.70 (3H, s, CH_3); ^{13}C NMR δ (CD_3OD, 100 MHz): 158.9, 143.0, 142.2, 137.3, 137.9, 135.4, 133.1, 132.5, 130.0, 126.7, 124.2, 120.7, 118.6, 113.6, 113.2, 111.2, 35.9, 35.7; MS: *m/z* 304.1.

9-methyl-1-(4-nitrobenzyl)-9H-pyrido[3,4-b]indol-6-ol **(3d)**. Yellow solid, 0.61 g, 58%, mp 176-177 °C; IR v_{max} cm^{-1}: 3499, 2816,1465; ^{1}H NMR δ (CD_3OD, 400 MHz) ppm: 9.23 (1H, br s, OH), 8.74 (1H, d, H-3), 8.51 (1H, d, H-4), 7.98 (1H, d, H-5), 7.75 (2H, d, H-2' and H-6'), 7.46 (1H, d, H-8), 7.06 (2H, d, H-3' and H-5'), 6.87 (1H, t, H-7), 4.28 (2H, s, CH_2), 3.82 (3H, s, CH_3); ^{13}C NMR δ (CD_3OD, 100 MHz): 157.1, 145.5, 137.4, 136.9, 136.0, 132.4, 131.3, 130.2, 129.5, 126.5, 122.0, 118.4, 117.2, 116.3, 113.7, 36.6, 34.8; MS: *m/z* 333.1.

Result and discussion

For almost one century, the Pictet-Spengler reaction has remained as one of the most powerful methods for the formation of β-carboline ring system *via* C-C bond formation using tryptophan as the starting material. Common synthesis of β-carbolines *via* Pictet-Spengler cyclization as the first step of the strategy would afford the tetrahydro-β-carboline (THβC) intermediates and a subsequent aromatization reaction of the respective intermediate would then construct the β-carboline ring moiety [16,17]. Over the years, several groups have studied the detail mechanistic aspects of this reaction, and it is interesting to note that the method continues to be a significant focus of reasearch as chemists continue to improve upon the methodology by applying new reaction conditions. In this study, we described a useful approach for the preparation of 1-substituted β-carboline derivatives *via* acid-mediated coupling of methyl ester of 5-hydroxy-L-tryptophan and substituted phenylglyoxals. As a result, we recognized the conversion of 5-hydroxy-L-tryptophan and phenylgloxal directly to 1-substituted β-carboline in the presence of acid *via* a single step Pictet-Spengler reaction. This strategy improved the scope of the Pictet-Spengler cyclization as the THβC intermediate directly oxidized to the targeted β-carboline in this one-pot oxidation reaction, which also allows for product diversification at C-1 position.

On the other hand, most of the reported method for the aromatization of the THβC intermediate generally involve troublesome drawbacks in driving the reaction. Eagon and Anderson employed the use of palladium-mediated reactions that requires high temperature, long reaction hours, along with the possibility of C-N bond cleavage [18]. Sulphur-mediated reactions by Cain et al. deliver aromatized product in two days with low yields [19] whereas selenium-mediated reactions by Hao et al. require large quantity of SeO_2 (10 equiv.) offering less yield [20]. Also, iodine-mediated reactions by Gaikwad et al. incorporate the use of DMSO as the solvent [21], which is difficult to be removed upon the completion of the reaction prior to the purification step. Hence, our synthetic strategy offers the advantage of a brief and concise synthetic route to β-carboline derivatives, with a more economical and convenient approach.

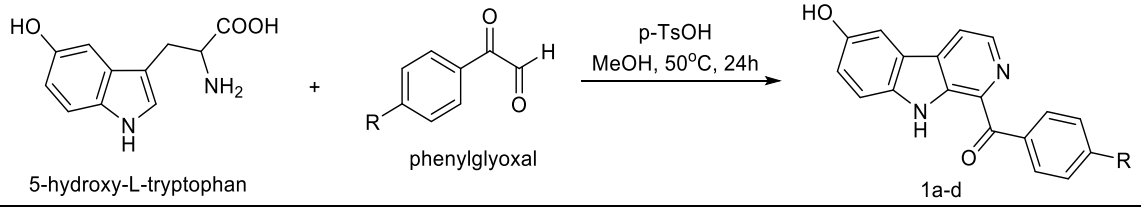
As mentioned earlier, the synthetic studies described herein were directed at modified single-step Pictet-Spengler reaction without the formation of tetrahydro derivatives according to literature [22]. Initial attention was focused on the use of 5-hydroxy-L-tryptophan as the nucleophile employing its cyclocondensation with phenylglyoxal in TFA as model reaction leading to derivative **1a**. The transformation was then explored using different acid catalyst (AcOH, *p*-TsOH, and HCl), solvent systems (MeOH, DCM and AcOH), reaction temperatures, reaction condition and time. A representative collection of results is summarized in Table 1. Among these conditions, addition of *p*- TsOH to the mixture of 5-hydroxy-L-tryptophan and phenylglyoxal in MeOH at 50 °C for 2 h (entry 3) yielded the best results. A decrease in the polarity of solvent resulted in lower yield of products (entries 1, 2 and 4 using DCM, AcOH and ACN), owing to reduced conversion of 5-hydroxy-L-tryptophan, probably due to its poor solubility. Also, temperature was discovered to have a profound effect on the reaction course; lowering the reaction temperature lengthened the reaction time (entries 1 and 4). Further optimization of entry 3 were conducted (entries 3a and 3b) to ensure a more reliable and comprehensive result. Using MeOH as the solvent with fixed reaction temperature (50 °C) and time (2 h), the reactions were tested with another two acid catalysts having pKa values in close proximity. As a result, it was found that entry 3 with p-TsOH as the acid catalyst still provide the best yield as it is common in acid catalytic reactions that mild conditions were preferred.

Having established a practical set of reaction conditions, these optimized conditions were applied to the coupling of 5-hydroxy-L-tryptophan with other substituted phenylglyoxal, furnishing product **1b-d** as shown in Scheme 1. Based on the result obtained, a general conclusion on the electronic effects of electron-withdrawing group (EWG) and electron-donating groups (EDG) could be deduced. Having EDG as substituent increased the electrophilicity of the carbonyl carbon, resulting in a weaker reactivity with the nucleophile and hence, the lower yield (**1b** and **1c**) than that of phenylglyoxal (**1a**). The effect is reversed in the case of EWG substituted product **(1d)**.

Table 1. Optimization of reaction involving preparation of 1-substituted β-carbolines using 5-hydroxy-L-tryptophan and phenylglyoxal under different Pictet–Spengler protocols

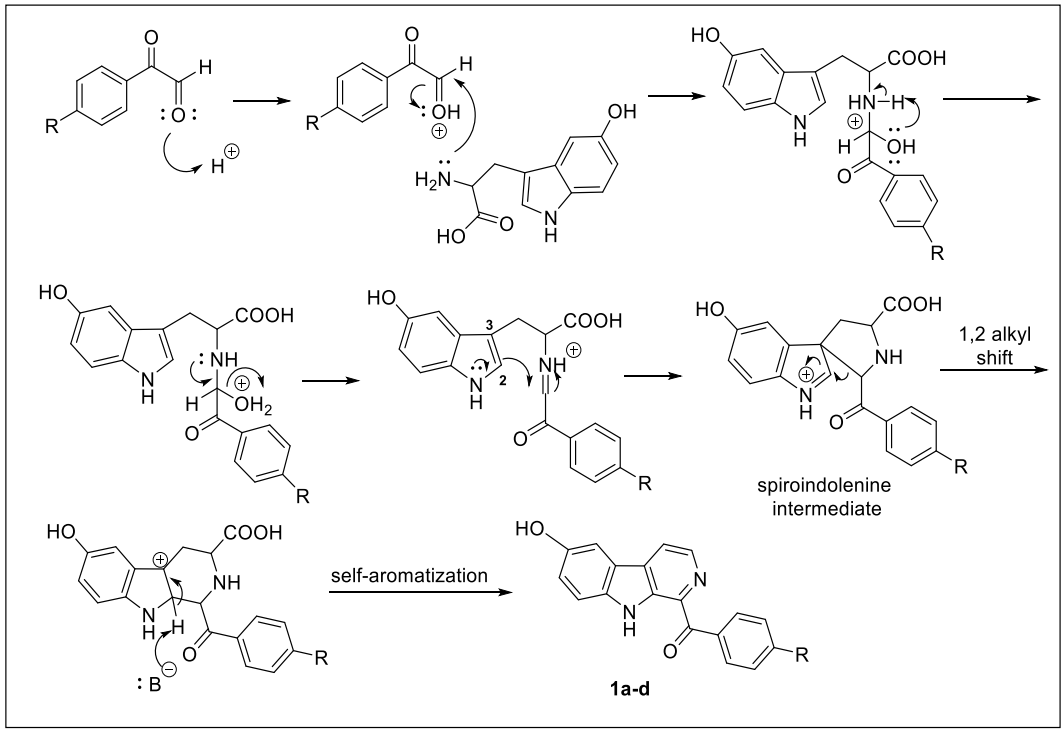
Entry	Acid Catalyst	pKa	Solvent	Conditions (*T* (°C), time (h))	Yield (%)
1	TFA	0.52	DCM	Stir (rt, 24)	22
2	AcOH	4.76	AcOH	Reflux (120 °C, 3)	18
3	*p*-TsOH	-2.1	MeOH	Stir (50 °C, 2)	38
3a	H_2SO_4	-2.8	MeOH	Stir (50 °C, 2)	13
3b	HCl	-6.3	MeOH	Stir (50 °C, 2)	28
4	HCl	-6.3	ACN	Stir (40 °C, 4)	25

Scheme 1. Scope of the reaction of 5-hydroxy-L-tryptophan with different substituted phenylglyoxal



Entry	R	Yield (%)
1a	H	38
1b	OCH_3	32
1c	OH	20
1d	NO_2	46

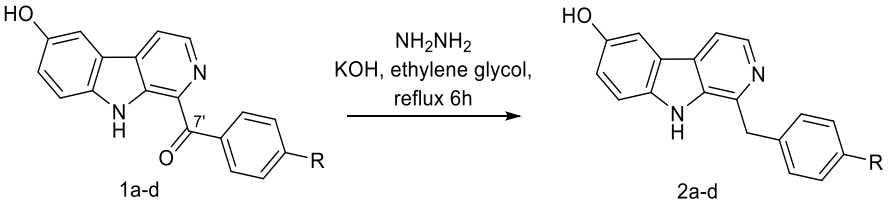
The reaction mechanism occurs by the initial formation of iminium ion followed by electrophilic addition at the C-2 position to directly yield the six-membered ring intermediate. However, both carbon-2 and -3 of tryptamine are nucleophilic. Therefore, the reaction can also proceed by the attack of carbon-3 to yield a spiroindolenine intermediate that would then undergo a 1,2-alkyl shift to form the product as depicted in Scheme 2. Both mechanisms have been proven to be true, yet the prevailing mechanism is still unknown [23].



Scheme 2. Mechanism of Pictet-Spengler reaction with electrophilic addition at carbon-3

The pathway proceeded with the reduction of carbonyl functionality on carbon-7' by procedure similar to those described in previous paper [24]. The Wolff Kishner reduction was achieved by refluxing **1a-d** with hydrazine hydrate with potassium hydroxide in ethylene glycol for 6 hours as depicted in Scheme 3. The reaction mechanism begins with the condensation of the carbonyl with hydrazine, forming the hydrazone, and treatment with base induces the reduction of the carbon coupled with oxidation of the hydrazine to gaseous nitrogen, yielding the corresponding methylene group. Complementary to this reaction, Clemmensen reduction can effect a similar conversion under strongly acidic conditions, and is useful if the starting material is base-labile.

Scheme 3. Reduction of carbonyl functionality on carbon-7'



Entry	*R*	Yield (%)
2a	H	41
2b	OCH_3	35
2c	OH	35
2d	NO_2	38

In the final step, derivatives **2a-d** were converted to N-alkyl derivatives by the reaction of alkylating reagents, CH_3I with indole moiety in the presence of sodium hydride as the base. The use of sodium has the benefit of allowing the reaction to take place in a non-hydrolytic solvent. It was assumed that using sodium hydride would also provide this benefit yet safer and easier to handle than the metal. With this in mind, the preparation of N-alkylated 1-substituted β-carbolines was undertaken by the general reaction shown in Scheme 4.

According to the literature [25], the N-methylation of the 1-substituted β-carboline derivatives were successfully obtained in 77-80% yield. However, by employing the same procedure, we only managed to get the alkylated derivatives in much lower yields (43-58%). This is due to the subtituent effect on C-1 that influences the reactivity of the nucleophilic substitution in both reactions. In the literature, 1-alkyl substituted β-carbolines were used as the starting material, whereas in our study, 1-aryl substituted β-carbolines were employed (see figure 2). As anticipated, the bulkiness of the aryl group at C-1 position contributes to steric hinderence at the reaction site, thus reducing the efficiency of the alkylation process and lowering the reaction yield.

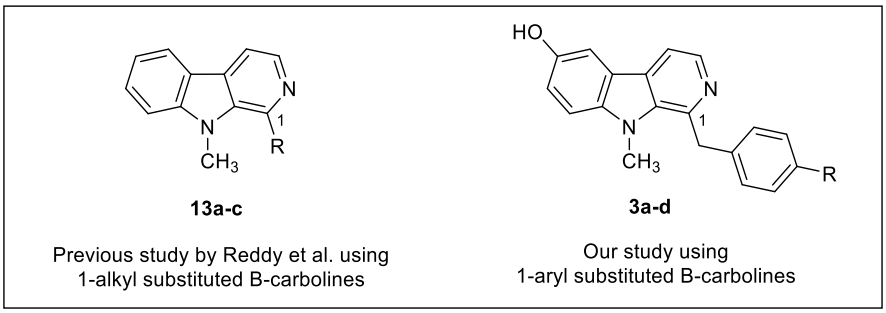
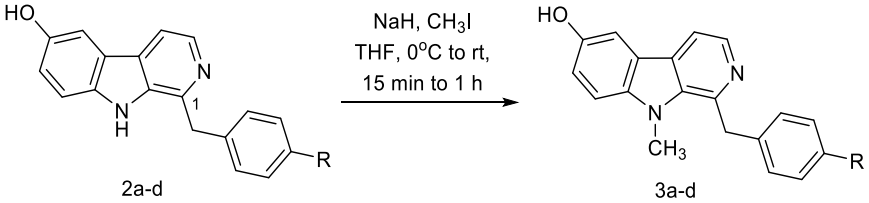


Figure 2. Comparison of the structure of 1-substituted β-carbolines used in both reactions

Scheme 4. N-alkylation of 1-substituted β-carboline derivatives



Entry	*R*	Yield (%)
3a	H	54
3b	OCH_3	51
3c	OH	43
3d	NO_2	58

Conclusions

In summary, we have successfully synthesized a series of 1-substituted β-carboline derivatives in moderate yields. The synthetic strategies involve cyclization and a subsequent reduction reaction, followed by N-alkylation. Further application of the scope and mechanism of reaction in the study towards total synthesis of daibucarboline A and other additional biologically active natural products is currently in progress.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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