EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201403418

# First Practical and Efficient Synthesis of 3-Phosphorylated β-Carboline Derivatives Using the Pictet–Spengler Reaction

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**Keywords:** Synthetic methods / Drug design / Phosphorylation / Nitrogen heterocycles

We report here the first practical and efficient synthesis of the diethyl 1,2,3,4-tetrahydro-β-carboline-3-phosphonates **3** and **4** as well as diethyl 9*H*-β-carboline-3-phosphonates **5** and **6**. The target compounds were prepared in good yields by application of the Pictet–Spengler reaction of easily obtainable phosphotryptophan diethyl ester **7**. The procedure is based on simple preparation of racemic **7** followed by a Pictet–Spengler reaction with several aldehydes and subsequent oxidation chemistry.

## Introduction

Tetrahydro-β-carbolines (THβCs) and β-carbolines (βCs) are a class of pharmacophores present in a large number of natural indole alkaloids found in numerous plants, foods, beverages and animals; expression of potent biological activity is a common feature.[1] Specifically, the 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid **1** and 9*H*-β-carboline-3-carboxylic acid **2** have been used as key templates in the preparation of many naturally occurring and more complex synthetic compounds, that demonstrate a variety of important and potent pharmacological activities. It has been reported that compounds incorporating the 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid **1** and 9*H*-β-carboline-3-carboxylic acid **2** scaffolds display a wide spectrum of pharmacological capabilities including the expression of anticancer,[2] antithrombotic,[3] and antimalarial activities[4] as well as an affinity for binding the benzodiazepine receptor (Figure 1) and modulating its downstream pathways.[5] Additionally, in the area of organic synthesis, **1** has been used for the preparation of catalysts.[6] Due to the relevant properties displayed by **1** and **2** and their related derivatives, much effort have been dedicated to the preparation of these compounds; predominant approaches involve the use of tryptophan in Pictet–Spengler reactions.[7,8] However, generation of **1** and **2** analogues such as diethyl 1,2,3,4-tetrahydro-β-carboline-3-phosphonates **3**, and **4** and diethyl 9*H*-β-carboline-3-phosphonates **5** and **6** from phosphotryptophan diethyl ester **7**, using the Pictet–Spengler reaction, to the best of our knowledge, has not yet been described in the literature, despite their great potential in medicinal chemistry and organic synthesis, as reflected by the α-aminophosphonic acids and their derivatives.[9,10] Given the potential of these agents, it is of great importance that new methods be developed for their preparation.[11]

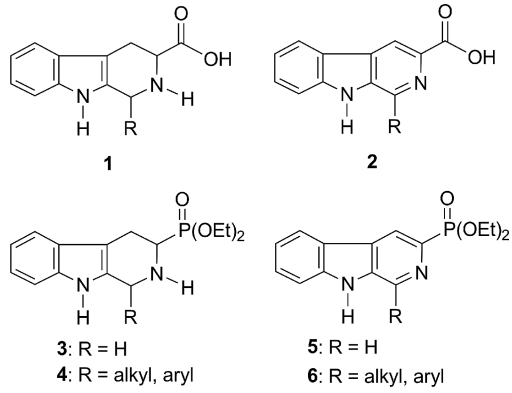


Figure 1. Structure of 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid **1**, 9*H*-β-carboline-3-carboxylic acid **2**, and their 3-phosphorylated analogues **3**–**6**.

Considering the high value of these non-coded compounds in connection with our current research interest in the synthesis of novel conformationally restricted α-aminophosphonic acids,[12] we now report herein the first convenient synthesis of diethyl 1,2,3,4-tetrahydro-β-carboline-3-phosphonates **3** and **4** as well as diethyl 9*H*-β-carboline-3-phosphonates **5** and **6** from phosphotryptophan diethyl ester **7** using the Pictet–Spengler reaction.

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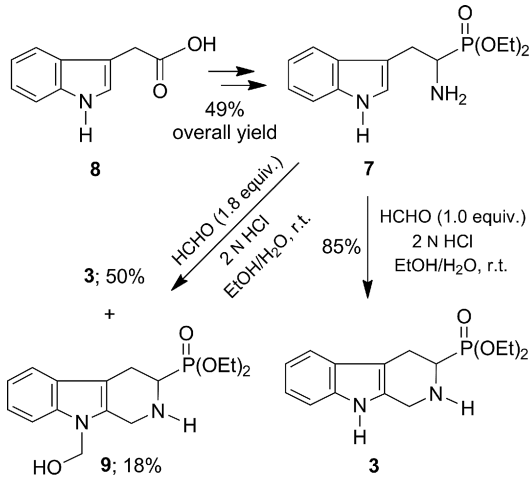
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201403418.

## Results and Discussion

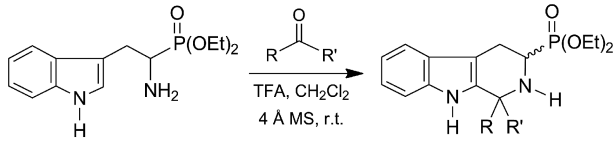
For the synthesis of target compound **3** (R = H) we envisaged that this could be obtained from **7** using an identical Pictet–Spengler protocol previously applied to the synthesis of compound **1** and its derivatives. The synthetic route is outlined in Scheme 1. The key phosphotryptophan diethyl ester intermediate **7** was obtained essentially according to the literature method,[13] starting from indole-3-acetic acid **8** with 49% overall yield. With compound **7** in hand, we initially carried out the Pictet–Spengler reaction with aqueous formaldehyde solution (1.8 equiv.) and 2 N HCl in an EtOH/$H_2O$ mixture as solvent at room temperature, affording target compound **3** in 50% yield along with hydroxymethyl derivative **8** in 18% yield. After several attempts, we found that reaction of **7** with aqueous formaldehyde (1.0 equiv.) and 2 N HCl in EtOH/$H_2O$ at room temperature, afforded compound **3** in 85% yield (Scheme 1).




Scheme 1. Synthetic route employed for the preparation of target compound **3**.

With these results, the next step was to explore the scope of the Pictet–Spengler reaction of phosphotryptophan diethyl ester **7** with several aromatic and aliphatic aldehydes. The goal was to identify conditions enabling Pictet–Spengler synthesis of diethyl 1,2,3,4-tetrahydro-β-carboline-3-phosphonates **4**. We first carried out the reaction of compound **7** with benzaldehyde, and, after several attempts, we were pleased to see that the Pictet–Spengler reaction in the presence of catalytic trifluoroacetic acid (TFA) in $CH_2Cl_2$ with molecular sieves (4 Å) at room temperature, proceeded smoothly to afford the *cis*- and *trans*-isomers **4a** (75:25) mixture in 86% yield (Table 1, Entry 1). After successfully optimizing the reaction conditions, we conducted a broader investigation of this reaction using various aldehydes and ketones, the results of which are summarized in Table 1. Thus, the reaction of **7** with 4-bromobenzaldehyde, gave desired product **4b** as a mixture of *cis*- and *trans*-isomers (62:38) in 81% yield (Table 1, Entry 2). Alternatively, the reaction of **7** with 4-methoxybenzaldehyde gave *cis*- and *trans*-isomers **4c** in 72% yield and with a 94:6 diastereoisomeric ratio (Table 1, Entry 3). Compound **7** was also found to react with acetaldehyde, and the diethyl *cis*- and *trans*-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-phosphonate **4d** (78:22) mixture was obtained in 68% yield (Table 1, Entry 4). The reaction with isobutyraldehyde gave the mixture of *cis*- and *trans*-isomers **4e** (68:32) in 83% yield (Table 1, Entry 5). However, in the reaction of **7** with ethyl glyoxalate it was not possible to isolate corresponding 1,2,3,4-tetrahydro-β-carboline **4f**; during reaction workup it appears that **4f** was oxidized to give directly β-carboline-3-phosphonate **6f**. Finally, the Pictet–Spengler reaction of phosphotryptophan diethyl ester **7** with acetone and cyclohexanone, provided cyclized products **4g** and **4h** in 75 and 69% yield, respectively (Table 1, Entries 7 and 8). The *cis*- and *trans*-1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines **4a**–**e** were separated by flash column chromatography and characterized using IR, NMR and MS.

Table 1. Synthesis of the 1,2,3,4-tetrahydro-β-carbolines **4a**–**h** by Pictet–Spengler reaction.




| Entry | Compound; R | R′ | *cis*/*trans* | Yield [%] |
|---|---|---|---|---|
| 1 | **4a**. $C_6H_5$ | H | 75:25 | 86 |
| 2 | **4b**; 4-Br$C_6H_4$ | H | 62:38 | 81 |
| 3 | **4c**; 4-MeO$C_6H_4$ | H | 94:06 | 72 |
| 4 | **4d**; Me | H | 78:22 | 68 |
| 5 | **4e**; *i*Pr | H | 68:32 | 83 |
| 6 | **4f**; $CO_2Et$ | H | –[a] | – |
| 7 | **4g**; Me | Me | – | 75 |
| 8 | **4h**; $-(CH_2)_5-$ | | – | 69 |

[a] The isolated product was the β-carboline **6f**.

The *cis*- and *trans*-stereochemistry for each 1,2,3,4-tetrahydro-β-carboline **4** listed in Table 1, was determined unequivocally by analyzing the correlation spots in its $^1H$-$^1H$ NOESY spectra as depicted in Figure 2. For *cis*-**4a**–**e**, there is a clear correlation signal (NOE) between H-3 and H-1, indicating that H-3 and H-1 are located on the same side of the piperidine ring; for *trans*-**4a**–**e** this correlation is absent. However, for the *trans* products one additional correlation signal (NOE) between H-1 and the $CH_3$ group at C-1 was observed for **4d**. A similar correlation between H-1 and the **H**C$(CH_3)_2$ at C-1 for **4e** was also observed. These data indicate that the methyl (for **4d**) or isopropyl group (for **4e**) and H-3 are, in both cases, located on the same side of the piperidine ring.

Having generated 1,2,3,4-tetrahydro-β-carboline **3** and the *cis*- and *trans*-1,3-disubstituted derivatives **4a**–**f** now in hand, we next attempted to produce diethyl 9*H*-β-carboline-3-phosphonates **5** and **6a**–**f**. Our studies showed that **3** and **4a**–**f** can be readily converted into compounds **5** and **6a**–**f**, respectively, by employing trichloroisocyanuric acid (TCCA) as an effective oxidizing agent[14] in the presence of triethylamine (TEA) and with dimethylformamide

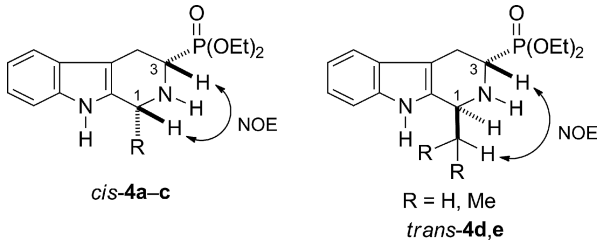
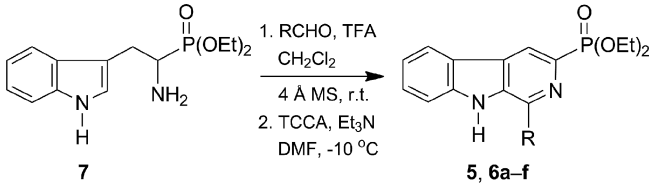



Figure 2. Determination of *cis*- and *trans*-stereochemistry of **4a**–**e** by NOESY.

(DMF) as solvent, according to the synthetic route outlined in Table 2. Thus, 1,2,3,4-tetrahydro-β-carbolines **3** and **4a**–**f**, obtained as described above, were subjected without further purification to TCCA and TEA in DMF at –10 °C, to afford 9*H*-β-carboline-3-phosphonates **5** and **6a**–**f** in moderate to good yields. The results are summarized in the Table 2.

Table 2. Synthesis of 9*H*-β-carboline-3-phosphonates **5** and **6a**–**f**.




| Entry | Compound; R | Yield [%] |
|---|---|---|
| 1 | **5**; H | 83[a] |
| 2 | **6a**. $C_6H_5$ | 63 |
| 3 | **6b**; 4-Br$C_6H_4$ | 76 |
| 4 | **6c**; 4-MeO$C_6H_4$ | 57 |
| 5 | **6d**; Me | 19 |
| 6 | **6e**; *i*Pr | 39 |
| 7 | **6f**; $CO_2$Et | 84 |

[a] 1. HCHO (1.0 equiv.), 2 N HCl, EtOH/$H_2O$, room temp.

## Conclusions

In summary, we have established the conditions and procedure for the first practical and efficient synthesis of diethyl 1,2,3,4-tetrahydro-β-carboline-3-phosphonates **3** and **4** as well as diethyl 9*H*-β-carboline-3-phosphonates **5** and **6**. Target compounds were prepared in good yields by application of Pictet–Spengler reactions with readily obtainable phosphotryptophan diethyl ester **7** and several aldehydes and ketones. This contribution represents the first Pictet–Spengler reaction using α-aminophosphonates as key intermediates in the preparation of novel cyclic α-aminophosphonates.

## Experimental Section

**General:** All reagents were used as received from commercial suppliers without further purification. Thin-layer chromatography (TLC) was performed with Macherey–Nagel Polygram® SIL G/$UV_{254}$ precoated silica gel polyester plates. The products were visualized by exposure to UV light (254 nm), iodine vapours or submersion in solutions of phosphomolybdic acid in ethanol or ninhydrin (ninhydrin/ethanol/acetic acid/ethylene glycol/dimethyl ether). Column chromatography was performed using 60 Å (0.04–0.063 mm) silica gel from Macherey–Nagel. Melting points were determined with a Gallenkamp apparatus. IR spectra were recorded with a Nicolet Avatar 360 FTIR spectrophotometer; $\nu_{max}$ is given for the main absorption bands. $^1$H, $^{13}$C and $^{31}$P NMR spectra were recorded with a Bruker AV-400 instrument at room temperature except when another temperature is specified; the residual solvent signal was used as the internal standard; chemical shifts ($\delta$) are expressed in parts per million and coupling constants ($J$) in Hertz. High-resolution mass spectra were obtained with a Bruker Microtof-Q spectrometer.

**Diethyl 1-Amino-2-(indol-3-yl)ethylphosphonate (7):** Oxalyl chloride (3.98 g, 2.7 mL, 31.4 mmol) was added dropwise over 5 min to a stirred solution of indole-3-acetic acid (5.0 g, 28.54 mmol) in dry dichloromethane (106 mL) at 0 °C under an argon atmosphere. The mixture was stirred at 0 °C for 5 min and then DMF (104 mg, 0.11 mL, 1.42 mmol) was added in one portion. The solution was warmed at room temperature and then stirred until the mixture no longer effervesced. The mixture was concentrated under reduced pressure to leave the corresponding acid chloride as a yellow oil, which was used straight away. The acyl chloride was dissolved in THF (18 mL) and cooled to 0 °C, and triethyl phosphite (4.72 g, 4.95 mL, 28.4 mmol) was added dropwise under anhydrous conditions. When the addition was complete, the reaction was warmed at 70 °C and stirred for 15 min. The solvent was evaporated under reduced pressure yielding the α-ketophosphonate, which was used without additional purification in the following step. The crude α-ketophosphonate was added to a solution of hydroxylamine hydrochloride (2.37 g, 34.1 mmol) in dry pyridine (5.1 mL) and EtOH (8.5 mL), and the mixture was stirred at room temperature for 12 h. After evaporation of solvent under reduced pressure, the crude residue was dissolved in dichloromethane (40 mL), washed with 3 N HCl (2 × 10 mL) and water (10 mL). The organic layer was dried with anhydrous sodium sulfate and evaporated under reduced pressure to obtain the crude oxime, which was added under argon to a suspension of zinc (7.42 g, 113.50 mmol) in formic acid (29 mL). The reaction was stirred overnight, and the suspension was filtered. The filtrate was evaporated and the crude product was purified by column chromatographic using an AcOEt/MeOH (95:5) mixture as eluent, affording **7** (4.13 g, 49% yield) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3246, 1221, 1052, 1026 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.36 (t, $J$ = 7.1 Hz, 3 H, $CH_3CH_2O$), 1.36 (t, $J$ = 7.1 Hz, 3 H, $CH_3CH_2O$), 1.42 (br. s, 2 H, $NH_2$), 2.86 (ddd, $J$ = 15.0, 11.6, 8.3 Hz, 1 H, $CH_2$CH), 3.35–3.44 (m, 2 H, $CH_2$CH, CH-P), 4.15–4.26 (m, 4 H, $OCH_2CH_3$), 7.07–7.13 (m, 2 H, $H_{arom}$), 7.19 (ddd, $J$ = 8.2, 7.1, 1.1 Hz, 1 H, $H_{arom}$), 7.37 (ddd, $J$ = 8.2, 0.8, 0.8 Hz, 1 H, $H_{arom}$), 7.60 (dd, $J$ = 7.9, 1.1 Hz, 1 H, $H_{arom}$), 8.62 (br. s, 1 H, indole-NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 16.7 (d, $J$ = 5.6 Hz, $CH_3CH_2O$), 27.9 ($CH_2$CH), 49.3 (d, $J$ = 154.9 Hz, CH-P), 62.4 (d, $J$ = 7.1 Hz, $OCH_2CH_3$), 62.5 (d, $J$ = 7.2 Hz, $OCH_2CH_3$), 111.4 (Ar), 111.5 (d, $J$ = 17.3 Hz, Ar), 118.7 (Ar), 119.5 (Ar), 122.2 (Ar), 123.3 (Ar), 127.3 (Ar), 136.6 (Ar) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 28.63 ppm. HRMS (ESI): calculated for $C_{14}H_{22}N_2O_3P$ [M + H]$^+$, $m/z$ 297.1368; found for [M + H]$^+$, $m/z$ 297.1356.

**Diethyl 1,2,3,4-Tetrahydro-β-carboline-3-phosphonate (3):** Formaldehyde (55 mg, 51 μL, 0.68 mmol, 37% aqueous solution) was added dropwise to a solution of the α-aminophosphonate **7** (200 mg, 0.67 mmol) and 2 N HCl (0.34 mL, 0.68 mmol) in EtOH/$H_2O$ (1.0:0.1 mL). The reaction mixture was stirred for 3 h at room temperature, was concentrated under reduced pressure, diluted with

$CH_2Cl_2$ (20 mL) and neutralized with satd. $NaHCO_3$ solution (20 mL). The layers were separated, and the aqueous phase was further extracted with $CH_2Cl_2$ (2× 10 mL). The organic extracts were combined and dried with anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography with $CH_2Cl_2$:*i*PrOH (85:15) as eluent to give **3** (170 mg, 85%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3232, 1259, 1054, 1028 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.37 (t, $J$ = 7.1 Hz, 3 H, C$H_3$CH$_2$O), 1.39 (t, $J$ = 7.1 Hz, 3 H, C$H_3$CH$_2$O), 1.92 (br. s, 1 H, NH), 2.88–3.05 (m, 2 H, 4-H), 3.31 (ddd, $J$ = 17.1, 10.5, 5.3 Hz, 1 H, 3-H), 4.03 (d, $J$ = 16.0 Hz, 1 H, 1-H), 4.08 (d, $J$ = 16.0 Hz, 1 H, 1-H), 4.19–4.29 (m, 4 H, OC$H_2$CH$_3$), 7.09 (ddd, $J$ = 7.7, 7.7, 1.1 Hz, 1 H, $H_{arom}$), 7.14 (ddd, $J$ = 7.7, 7.7, 1.3 Hz, 1 H, $H_{arom}$), 7.30 (dd, $J$ = 7.7, 1.1 Hz, 1 H, $H_{arom}$), 7.47 (dd, $J$ = 7.7, 1.3 Hz, 1 H, $H_{arom}$), 8.14 (br. s, 1 H, indole-NH) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 16.7 (d, $J$ = 5.6 Hz, C$H_3$CH$_2$O), 22.9 (C-4), 43.5 (d, $J$ = 18.4 Hz, C-1), 51.3 (d, $J$ = 161.6 Hz, C-3), 62.6 (d, $J$ = 6.8 Hz, OC$H_2$CH$_3$), 62.7 (d, $J$ = 6.8 Hz, OC$H_2$CH$_3$), 107.4 (d, $J$ = 16.1 Hz, Ar), 110.9 (Ar), 117.9 (Ar), 119.6 (Ar), 121.8 (Ar), 127.3 (d, $J$ = 2.6 Hz, Ar), 132.4 (d, $J$ = 2.5 Hz, Ar), 135.9 (Ar) ppm. $^{31}P$ NMR (162 MHz, $CDCl_3$): $\delta$ = 26.70 ppm. HRMS (ESI): calculated for $C_{15}H_{22}N_2O_3P$ [M + H]$^+$, $m/z$ 309.1368; found for [M + H]$^+$, $m/z$ 309.1356.

**Diethyl 9-Hydroxymethyl-1,2,3,4-tetrahydro-β-carboline-3-phosphonate (9):** Under the reaction conditions described for the preparation of **3**, when the formaldehyde (1.8 equiv.) was used, hydroxymethyl derivative **9** (39 mg, 18%) was obtained as a yellow oil. IR (neat): $\tilde{\nu}$ = 3232, 1267, 1027 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.27 (t, $J$ = 7.0 Hz, 3 H, C$H_3$CH$_2$O), 1.29 (t, $J$ = 7.1 Hz, 3 H, C$H_3$CH$_2$O), 2.48–2.59 (m, 1 H, 4-H), 2.67–2.76 (m, 1 H, 4-H), 2.89 (ddd, $J$ = 17.0, 11.4, 4.2 Hz, 1 H, 3-H), 3.92 (d, $J$ = 16.3 Hz, 1 H, 1-H), 4.00–4.09 (m, 4 H, OC$H_2$CH$_3$), 4.12 (d, $J$ = 16.3 Hz, 1 H, 1-H), 5.40 (d, $J$ = 11.5 Hz, 1 H, NC$H_2$O), 5.44 (d, $J$ = 11.5 Hz, 1 H, NC$H_2$O), 7.09 (ddd, $J$ = 8.1, 7.1, 0.5 Hz, 1 H, $H_{arom}$), 7.17 (ddd, $J$ = 7.7, 7.1, 0.8 Hz, 1 H, $H_{arom}$), 7.35 (dd, $J$ = 7.7, 0.5 Hz, 1 H, $H_{arom}$), 7.43 (dd, $J$ = 8.1, 0.8 Hz, 1 H, $H_{arom}$) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 16.5 (d, $J$ = 5.6 Hz, C$H_3$CH$_2$O), 16.6 (d, $J$ = 5.7 Hz, C$H_3$CH$_2$O), 22.4 (C-4), 42.4 (d, $J$ = 18.7 Hz, C-1), 50.8 (d, $J$ = 161.9 Hz, C-3), 62.6 (d, $J$ = 6.9 Hz, OC$H_2$CH$_3$), 63.1 (d, $J$ = 6.9 Hz, OC$H_2$CH$_3$), 66.5 (NC$H_2$O), 107.7 (d, $J$ = 16.4 Hz, Ar), 109.4 (Ar), 118.1 (Ar), 119.9 (Ar), 121.8 (Ar), 127.4 (d, $J$ = 2.7 Hz, Ar), 133.2 (d, $J$ = 2.6 Hz, Ar), 136.1 (Ar) ppm. $^{31}P$ NMR (162 MHz, $CDCl_3$): $\delta$ = 27.01 ppm. HRMS (ESI): calculated for $C_{16}H_{24}N_2O_4P$ [M + H]$^+$, $m/z$ 339.1474; found for [M + H]$^+$, $m/z$ 339.1472.

**General Procedure for the Preparation of Diethyl 1,2,3,4-Tetrahydro-β-carboline-3-phosphonates 4a–h:** To a stirred solution of phosphotryptophan ethyl ester (**7**; 200 mg, 0.67 mmol), a carbonyl compound (aldehyde or ketone, 0.67 mmol) and activated molecular sieves (4 Å, about 100 mg/mmol) in dry $CH_2Cl_2$ (7 mL), TFA (0.07 mL, 0.91 mmol) were added. The reaction mixture was stirred at room temperature and the progress was monitored by TLC ($CH_2Cl_2$:*i*PrOH, 8:2). Upon completion of the reaction (3–4 h), the volatiles were removed under reduced pressure and the crude material was diluted with $CH_2Cl_2$ (20 mL), washed with satd. $NaHCO_3$ solution, and the aqueous phase was further extracted with $CH_2Cl_2$ (2× 10 mL). The organic extracts were combined and dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by column chromatography with $CH_2Cl_2$:*i*PrOH (95:5) as eluent to provide pure *cis*- and *trans*-isomers **4a**–**e** as well as cyclization products **4g** and **4h**.

**Diethyl *cis*- and *trans*-(1-Phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-3-yl)phosphonate (4a):** According to the general procedure, a mixture of phosphotryptophan ethyl ester (**7**; 200 mg, 0.67 mmol), benzaldehyde (72 mg, 0.07 mL, 0.67 mmol), dry $CH_2Cl_2$ (7 mL) and TFA (0.07 mL, 0.91 mmol) was reacted in the presence of activated molecular sieves (4 Å, 70 mg) to give *cis*- and *trans*-isomers **4a** in a 75:25 ratio (calculated from the crude reaction mixture).

***cis*-4a:** White solid (160 mg, 62%); m.p. 188–190 °C. IR (nujol): $\tilde{\nu}$ = 3223, 1228, 1025, 963 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.39 (t, $J$ = 7.1 Hz, 3 H, C$H_3$CH$_2$O), 1.39 (t, $J$ = 7.1 Hz, 3 H, C$H_3$CH$_2$O), 2.08 (br. s, 1 H, NH), 3.03–3.18 (m, 2 H, 4-H), 3.53 (ddd, $J$ = 15.3, 10.8, 4.7 Hz, 1 H, 3-H), 4.16–4.31 (m, 4 H, OC$H_2$CH$_3$), 5.15 (s, 1 H, 1-H), 7.09–7.15 (m, 2 H, $H_{arom}$), 7.16–7.20 (m, 1 H, $H_{arom}$), 7.30–7.38 (m, 5 H, $H_{arom}$), 7.52–7.57 (m, 1 H, $H_{arom}$), 7.73 (br. s, 1 H, indole-NH) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 16.6 (d, $J$ = 5.6 Hz, C$H_3$CH$_2$O), 23.1 (C-4), 51.9 (d, $J$ = 159.7 Hz, C-3), 59.2 (d, $J$ = 18.5 Hz, C-1), 62.6 (d, $J$ = 6.6 Hz, OC$H_2$CH$_3$), 62.7 (d, $J$ = 6.4 Hz, OC$H_2$CH$_3$), 108.5 (d, $J$ = 17.1 Hz, Ar), 111.0 (Ar), 118.2 (Ar), 119.6 (Ar), 121.9 (Ar), 127.1 (d, $J$ = 2.6 Hz, Ar), 128.5 (Ar), 128.6 (Ar), 128.9 (Ar), 134.6 (d, $J$ = 2.5 Hz, Ar), 136.0 (Ar), 141.0 (Ar) ppm. $^{31}P$ NMR (162 MHz, $CDCl_3$): $\delta$ = 26.34 ppm. HRMS (ESI): calculated for $C_{21}H_{26}N_2O_3P$ [M + H]$^+$, $m/z$ 385.1681; found for [M + H]$^+$, $m/z$ 385.1675.

***trans*-4a:** Pale yellow solid (62 mg, 24%); m.p. 168–170 °C. IR (nujol): $\tilde{\nu}$ = 3187, 1226, 1030, 964 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.12 (t, $J$ = 7.0 Hz, 3 H, C$H_3$CH$_2$O), 1.15 (t, $J$ = 7.0 Hz, 3 H, C$H_3$CH$_2$O), 2.06 (br. s, 1 H, NH), 2.87–3.00 (m, 2 H, 4-H), 3.25 (ddd, $J$ = 16.5, 9.5, 5.9 Hz, 1 H, 3-H), 3.85–4.06 (m, 4 H, OC$H_2$CH$_3$), 5.14 (s, 1 H, 1-H), 7.01–7.11 (m, 4 H, $H_{arom}$), 7.14–7.21 (m, 4 H, $H_{arom}$), 7.46 (dd, $J$ = 7.4, 1.1 Hz, 1 H, $H_{arom}$), 8.12 (br. s, 1 H, indole-NH) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 16.4 (d, $J$ = 5.8 Hz, C$H_3$CH$_2$O), 16.5 (d, $J$ = 5.9 Hz, C$H_3$CH$_2$O), 22.7 (C-4), 45.7 (d, $J$ = 159.5 Hz, C-3), 55.3 (d, $J$ = 16.2 Hz, C-1), 62.3 (d, $J$ = 6.6 Hz, OC$H_2$CH$_3$), 62.7 (d, $J$ = 6.8 Hz, OC$H_2$CH$_3$), 109.0 (d, $J$ = 14.8 Hz, Ar), 111.1 (Ar), 118.3 (Ar), 119.6 (Ar), 122.1 (Ar), 127.0 (d, $J$ = 2.3 Hz, Ar), 127.9 (Ar), 128.5 (Ar), 128.6 (Ar), 133.1 (d, $J$ = 2.5 Hz, Ar), 136.1 (Ar), 141.7 (Ar) ppm. $^{31}P$ NMR (162 MHz, $CDCl_3$): $\delta$ = 27.08 ppm. HRMS (ESI): calculated for $C_{21}H_{26}N_2O_3P$ [M + H]$^+$, $m/z$ 385.1681; found for [M + H]$^+$, $m/z$ 385.1664.

**Diethyl *cis*- and *trans*-[1-(4-Bromophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-3-yl]phosphonate 4b:** According to the general procedure, a mixture of phosphotryptophan ethyl ester (**7**; 200 mg, 0.67 mmol), 4-bromobenzaldehyde (125 mg, 0.67 mmol), dry $CH_2Cl_2$ (7 mL) and TFA (0.07 mL, 0.91 mmol) was reacted in the presence of activated molecular sieves (4 Å, 70 mg) to give *cis*- and *trans*-isomers **4b** in a 62:38 ratio (calculated from the crude reaction mixture).

***cis*-4b:** White solid (154 mg, 49%); m.p. 221–223 °C. IR (nujol): $\tilde{\nu}$ = 3193, 1226, 1024, 965 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.38 (t, $J$ = 7.1 Hz, 6 H, C$H_3$CH$_2$O), 2.10 (br. s, 1 H, NH), 2.97–3.18 (m, 2 H, 4-H), 3.52 (ddd, $J$ = 15.1, 10.6, 4.9 Hz, 1 H, 3-H), 4.15–4.29 (m, 4 H, OC$H_2$CH$_3$), 5.14 (s, 1 H, 1-H), 7.08–7.17 (m, 2 H, $H_{arom}$), 7.18–7.25 (m, 3 H, $H_{arom}$), 7.47 (d, $J$ = 8.4 Hz, 2 H, $H_{arom}$), 7.53 (dd, $J$ = 5.8, 3.1 Hz, 1 H, $H_{arom}$), 7.58 (br. s, 1 H, indole-NH) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 16.7 (d, $J$ = 5.7 Hz, C$H_3$CH$_2$O), 23.1 (C-4), 51.9 (d, $J$ = 159.7 Hz, C-3), 58.7 (d, $J$ = 18.6 Hz, C-1), 62.8 (d, $J$ = 6.8 Hz, OC$H_2$CH$_3$), 62.9 (d, $J$ = 6.6 Hz, OC$H_2$CH$_3$), 108.9 (d, $J$ = 17.1 Hz, Ar), 111.1 (Ar), 118.4 (Ar), 119.8 (Ar), 122.2 (Ar), 122.6 (Ar), 127.1 (d, $J$ = 2.5 Hz, Ar), 130.4 (Ar), 132.1 (Ar), 134.0 (d, $J$ = 2.4 Hz, Ar), 136.1 (Ar), 140.0 (Ar) ppm. $^{31}P$ NMR (121 MHz, $CDCl_3$): $\delta$ = 26.04 ppm. HRMS

(ESI): calculated for $C_{21}H_{25}BrN_2O_3P$ [M + H]$^+$, *m/z* 463.0786; found for [M + H]$^+$, *m/z* 463.0784.

***trans*-4b:** White solid (101 mg, 32%); m.p. 206–208 °C. IR (nujol): ṽ = 3165, 1242, 1021, 954 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.24 (t, *J* = 7.0 Hz, 3 H, C$H_3$CH$_2$O), 1.25 (t, *J* = 7.1 Hz, 3 H, C$H_3$CH$_2$O), 2.16 (br. s, 1 H, NH), 2.94–3.06 (m, 2 H, 4-H), 3.25 (ddd, *J* = 17.1, 9.2, 6.3 Hz, 1 H, 3-H), 3.96–4.16 (m, 4 H, OC$H_2$CH$_3$), 5.16 (s, 1 H, 1-H), 7.04 (d, *J* = 8.4 Hz, 2 H, H$_{arom}$), 7.13 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1 H, H$_{arom}$), 7.18 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1 H, H$_{arom}$), 7.28 (dd, *J* = 7.7, 1.3 Hz, 1 H, H$_{arom}$), 7.37 (d, *J* = 8.4 Hz, 2 H, H$_{arom}$), 7.54 (dd, *J* = 7.7, 1.3 Hz, 1 H, H$_{arom}$), 8.34 (br. s, 1 H, indole-NH) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 16.4 (d, *J* = 5.8 Hz, C$H_3$CH$_2$O), 16.5 (d, *J* = 5.9 Hz, C$H_3$CH$_2$O), 22.7 (C-4), 45.7 (d, *J* = 160.3 Hz, C-3), 54.6 (d, *J* = 16.4 Hz, C-1), 62.3 (d, *J* = 6.8 Hz, OC$H_2$CH$_3$), 62.8 (d, *J* = 6.8 Hz, OC$H_2$CH$_3$), 109.0 (d, *J* = 14.7 Hz, Ar), 111.1 (Ar), 118.4 (Ar), 119.7 (Ar), 121.9 (Ar), 122.3 (Ar), 126.9 (d, *J* = 2.3 Hz, Ar), 130.3 (Ar), 131.5 (Ar), 132.5 (d, *J* = 2.5 Hz, Ar), 136.1 (Ar), 140.7 (Ar) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 26.78 ppm. HRMS (ESI): calculated for $C_{21}H_{25}BrN_2O_3P$ [M + H]$^+$, *m/z* 463.0786; found for [M + H]$^+$, *m/z* 463.0776.

**Diethyl *cis*- and *trans*-[1-(4-Methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-3-yl]phosphonate (4c):** According to the general procedure, a mixture of phosphotryptophan ethyl ester (**7**; 200 mg, 0.67 mmol), *p*-anisaldehyde (92 mg, 0.08 mL, 0.67 mmol), dry $CH_2Cl_2$ (7 mL) and TFA (0.07 mL, 0.91 mmol) was reacted in the presence of activated molecular sieves (4 Å, 70 mg) to give *cis*- and *trans*-isomers **4c** in a 94:06 ratio (calculated from the crude reaction mixture).

***cis*-4c:** White solid (180 mg, 64%); m.p. 184–186 °C. IR (nujol): ṽ = 3227, 1248, 1028, 966 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.40 (t, *J* = 7.1 Hz, 3 H, C$H_3$CH$_2$O), 1.40 (t, *J* = 7.1 Hz, 3 H, C$H_3$CH$_2$O), 2.05 (br. s, 1 H, NH), 3.02–3.18 (m, 2 H, 4-H), 3.55 (ddd, *J* = 15.5, 10.7, 5.0 Hz, 1 H, 3-H), 3.81 (s, 3 H, CH$_3$O), 4.19–4.31 (m, 4 H, OC$H_2$CH$_3$), 5.13 (s, 1 H, 1-H), 6.89 (d, *J* = 8.6 Hz, 2 H, H$_{arom}$), 7.10–7.17 (m, 2 H, H$_{arom}$), 7.19–7.24 (m, 1 H, H$_{arom}$), 7.27 (d, *J* = 8.6 Hz, 2 H, H$_{arom}$), 7.55 (dd, *J* = 5.9, 3.1 Hz, 1 H, H$_{arom}$), 7.63 (br. s, 1 H, indole-NH) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 16.6 (d, *J* = 5.6 Hz, C$H_3$CH$_2$O), 23.1 (C-4), 51.9 (d, *J* = 159.6 Hz, C-3), 55.3 (CH$_3$O), 58.5 (d, *J* = 18.5 Hz, C-1), 62.6 (d, *J* = 6.7 Hz, OC$H_2$CH$_3$), 62.7 (d, *J* = 6.6 Hz, OC$H_2$CH$_3$), 108.5 (d, *J* = 17.2 Hz, Ar), 111.0 (Ar), 114.2 (Ar), 118.1 (Ar), 119.5 (Ar), 121.8 (Ar), 127.1 (d, *J* = 2.6 Hz, Ar), 129.8 (Ar), 133.0 (Ar), 135.0 (d, *J* = 2.5 Hz, Ar), 136.0 (Ar), 159.7 (Ar) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 26.42 ppm. HRMS (ESI): calculated for $C_{22}H_{28}N_2O_4P$ [M + H]$^+$, *m/z* 415.1787; found for [M + H]$^+$, *m/z* 415.1782.

***trans*-4c:** Yellow solid (22 mg, 8%); m.p. 179–181 °C. IR (neat): ṽ = 3227, 1245, 1029, 967 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.23 (t, *J* = 7.1 Hz, 3 H, C$H_3$CH$_2$O), 1.26 (t, *J* = 7.1 Hz, 3 H, C$H_3$CH$_2$O), 1.84 (br. s, 1 H, NH), 2.98–3.12 (m, 2 H, 4-H), 3.38 (ddd, *J* = 16.3, 9.5, 5.7 Hz, 1 H, 3-H), 3.77 (s, 3 H, CH$_3$O), 4.01–4.16 (m, 4 H, OC$H_2$CH$_3$), 5.24 (s, 1 H, 1-H), 6.81 (d, *J* = 8.7 Hz, 2 H, H$_{arom}$), 7.11 (d, *J* = 8.7 Hz, 2 H, H$_{arom}$), 7.13 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1 H, H$_{arom}$), 7.18 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1 H, H$_{arom}$), 7.28 (dd, *J* = 7.7, 1.1 Hz, 1 H, H$_{arom}$), 7.55 (dd, *J* = 7.7, 1.1 Hz, 1 H, H$_{arom}$), 7.82 (br. s, 1 H, indole-NH) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 16.5 (d, *J* = 6.7 Hz, C$H_3$CH$_2$O), 16.6 (d, *J* = 6.2 Hz, C$H_3$CH$_2$O), 22.7 (C-4), 45.7 (d, *J* = 159.2 Hz, C-3), 54.8 (d, *J* = 16.0 Hz, C-1), 55.4 (CH$_3$O), 62.3 (d, *J* = 6.6 Hz, OC$H_2$CH$_3$), 62.7 (d, *J* = 6.8 Hz, OC$H_2$CH$_3$), 109.1 (d, *J* = 14.8 Hz, Ar), 111.0 (Ar), 113.9 (Ar), 118.4 (Ar), 119.7 (Ar), 122.2 (Ar), 127.1 (d, *J* = 2.3 Hz, Ar), 129.8 (Ar), 133.4 (d, *J* = 2.4 Hz, Ar), 133.8 (Ar), 136.0 (Ar), 159.4 (Ar) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 27.26 ppm. HRMS (ESI): calculated for $C_{22}H_{28}N_2O_4P$ [M + H]$^+$, *m/z* 415.1787; found for [M + H]$^+$, *m/z* 415.1776.

**Diethyl *cis*- and *trans*-(1-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-3-yl)phosphonate (4d):** According to the general procedure, a mixture of phosphotryptophan ethyl ester (**7**; 200 mg, 0.67 mmol), acetaldehyde (31 mg, 0.04 mL, 0.70 mmol), dry $CH_2Cl_2$ (7 mL) and TFA (0.07 mL, 0.91 mmol) was reacted in the presence of activated molecular sieves (4 Å, 70 mg) to give *cis*- and *trans*-isomers **4d** in a 78:22 ratio (calculated from the crude reaction mixture).

***cis*-4d:** Brown oil (98 mg, 45%). IR (neat): ṽ = 3254, 1228, 1027, 966 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.39 (t, *J* = 7.1 Hz, 3 H, C$H_3$CH$_2$O), 1.39 (t, *J* = 7.1 Hz, 3 H, C$H_3$CH$_2$O), 1.48 (d, *J* = 6.7 Hz, 3 H, C$H_3$CH), 1.76 (br. s, 1 H, NH), 2.89–3.01 (m, 2 H, 4-H), 3.39 (ddd, *J* = 17.1, 9.7, 6.3 Hz, 1 H, 3-H), 4.17–4.31 (m, 5 H, 1-H, OC$H_2$CH$_3$), 7.10 (ddd, *J* = 7.8, 7.8, 1.0 Hz, 1 H, H$_{arom}$), 7.15 (ddd, *J* = 7.8, 7.8, 1.0 Hz, 1 H, H$_{arom}$), 7.33 (dd, *J* = 7.8, 1.0 Hz, 1 H, H$_{arom}$), 7.48 (dd, *J* = 7.8, 1.0 Hz, 1 H, H$_{arom}$), 8.24 (br. s, 1 H, indole-NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 16.5 (d, *J* = 5.6 Hz, C$H_3$CH$_2$O), 16.6 (d, *J* = 5.5 Hz, C$H_3$CH$_2$O), 20.3 (C$H_3$CH), 23.2 (C-4), 49.3 (d, *J* = 18.3 Hz, C-1), 51.6 (d, *J* = 161.6 Hz, C-3), 62.5 (d, *J* = 6.8 Hz, OC$H_2$CH$_3$), 62.7 (d, *J* = 6.8 Hz, OC$H_2$CH$_3$), 107.2 (d, *J* = 16.9 Hz, Ar), 110.9 (Ar), 118.0 (Ar), 119.5 (Ar), 121.7 (Ar), 127.2 (d, *J* = 2.9 Hz, Ar), 135.7 (Ar), 136.7 (d, *J* = 2.6 Hz, Ar) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 26.66 ppm. HRMS (ESI): calculated for $C_{16}H_{24}N_2O_3P$ [M + H]$^+$, *m/z* 323.1525; found for [M + H]$^+$, *m/z* 323.1512.

***trans*-4d:** Brown oil (49 mg, 23%). IR (neat): ṽ = 3252, 1230, 1028, 966 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.36 (t, *J* = 7.1 Hz, 3 H, C$H_3$CH$_2$O), 1.37 (t, *J* = 7.1 Hz, 3 H, C$H_3$CH$_2$O), 1.46 (d, *J* = 6.9 Hz, 3 H, C$H_3$CH), 2.02 (br. s, 1 H, NH), 2.86–3.04 (m, 2 H, 4-H), 3.50 (ddd, *J* = 17.6, 10.4, 4.8 Hz, 1 H, 3-H), 4.16–4.26 (m, 4 H, OC$H_2$CH$_3$), 4.29 (q, *J* = 6.9 Hz, 1 H, 1-H), 7.10 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1 H, H$_{arom}$), 7.15 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1 H, H$_{arom}$), 7.31 (dd, *J* = 7.7, 1.1 Hz, 1 H, H$_{arom}$), 7.48 (dd, *J* = 7.7, 1.1 Hz, 1 H, H$_{arom}$), 7.90 (br. s, 1 H, indole-NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 16.7 (d, *J* = 5.2 Hz, C$H_3$CH$_2$O), 21.5 (C$H_3$CH), 23.0 (C-4), 46.3 (d, *J* = 160.4 Hz, C-3), 46.9 (d, *J* = 16.1 Hz, C-1), 62.4 (d, *J* = 6.8 Hz, OC$H_2$CH$_3$), 62.8 (d, *J* = 6.8 Hz, OC$H_2$CH$_3$), 107.0 (d, *J* = 15.0 Hz, Ar), 110.9 (Ar), 118.2 (Ar), 119.7 (Ar), 121.9 (Ar), 127.2 (d, *J* = 2.4 Hz, Ar), 135.8 (Ar), 136.8 (Ar) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 27.28 ppm. HRMS (ESI): calculated for $C_{16}H_{24}N_2O_3P$ [M + H]$^+$, *m/z* 323.1525; found for [M + H]$^+$, *m/z* 323.1515.

**Diethyl *cis*- and *trans*-(1-Isopropyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-3-yl)phosphonate (4e):** According to the general procedure, a mixture of phosphotryptophan ethyl ester (**7**; 200 mg, 0.67 mmol), isobutyraldehyde (49 mg, 62 µL, 0.68 mmol), dry $CH_2Cl_2$ (7 mL) and TFA (0.07 mL, 0.91 mmol) was reacted in the presence of activated molecular sieves (4 Å, 70 mg) to give *cis*- and *trans*-isomers **4e** in a 68:32 ratio (calculated from the crude reaction mixture).

***cis*-4e:** Pale yellow oil (131 mg, 55%). IR (nujol): ṽ = 3219, 1247, 1034, 968 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.84 [d, *J* = 6.9 Hz, 3 H, (C$H_3$)$_2$CH], 1.13 [d, *J* = 6.8 Hz, 3 H, (C$H_3$)$_2$CH], 1.39 (t, *J* = 7.1 Hz, 6 H, C$H_3$CH$_2$O), 1.65 (br. s, 1 H, NH), 2.20–2.30 [m, 1 H, C$H$(CH$_3$)$_2$], 2.85–3.00 (m, 2 H, 4-H), 3.33 (ddd, *J* = 15.3, 10.2, 5.4 Hz, 1 H, 3-H), 4.10 (d, *J* = 1.8 Hz, 1 H, 1-H), 4.18–4.35 (m, 4 H, OC$H_2$CH$_3$), 7.10 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1 H, H$_{arom}$), 7.15 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1 H, H$_{arom}$), 7.34 (dd, *J* = 7.6, 1.1 Hz, 1 H, H$_{arom}$), 7.49 (dd, *J* = 7.6, 1.1 Hz, 1 H, H$_{arom}$), 8.18

(br. s, 1 H, indole-NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 16.4 [$(CH_3)_2CH$], 16.6 (d, $J$ = 5.7 Hz, $CH_3CH_2O$), 16.7 (d, $J$ = 5.6 Hz, $CH_3CH_2O$), 19.2 [$(CH_3)_2CH$], 23.3 (C-4), 31.7 [$CH(CH_3)_2$], 51.5 (d, $J$ = 160.5 Hz, C-3), 58.6 (d, $J$ = 17.4 Hz, C-1), 62.7 (d, $J$ = 6.7 Hz, $OCH_2CH_3$), 62.9 (d, $J$ = 6.7 Hz, $OCH_2CH_3$), 109.0 (d, $J$ = 17.1 Hz, Ar), 110.9 (Ar), 118.0 (Ar), 119.5 (Ar), 121.7 (Ar), 127.3 (d, $J$ = 2.8 Hz, Ar), 135.2 (d, $J$ = 2.4 Hz, Ar), 136.0 (Ar) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 26.82 ppm. HRMS (ESI): calculated for $C_{18}H_{28}N_2O_3P$ [M + H]$^+$, $m/z$ 351.1838; found for [M + H]$^+$, $m/z$ 351.1830.

***trans*-4e:** Brown solid (66 mg, 28%); m.p. 148–150 °C. IR (nujol): $\tilde{\nu}$ = 3219, 1227, 1027, 965 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.03 [d, $J$ = 6.7 Hz, 3 H, $(CH_3)_2CH$], 1.13 [d, $J$ = 6.7 Hz, 3 H, $(CH_3)_2CH$], 1.35 (t, $J$ = 7.1 Hz, 3 H, $CH_3CH_2O$), 1.37 (t, $J$ = 7.1 Hz, 3 H, $CH_3CH_2O$), 1.93 (br. s, 1 H, NH), 2.04 [dhept, $J$ = 6.8, 6.7 Hz, 1 H, $CH(CH_3)_2$], 2.86–3.04 (m, 2 H, 4-H), 3.52 (ddd, $J$ = 17.9, 10.1, 5.2 Hz, 1 H, 3-H), 3.73 (d, $J$ = 6.8 Hz, 1 H, 1-H), 4.15–4.29 (m, 4 H, $OCH_2CH_3$), 7.09 (ddd, $J$ = 7.8, 7.8, 1.2 Hz, 1 H, $H_{arom}$), 7.15 (ddd, $J$ = 7.8, 7.8, 1.2 Hz, 1 H, $H_{arom}$), 7.32 (dd, $J$ = 7.8, 1.2 Hz, 1 H, $H_{arom}$), 7.49 (dd, $J$ = 7.8, 1.2 Hz, 1 H, $H_{arom}$), 8.05 (br. s, 1 H, indole-NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 16.6 (d, $J$ = 6.0 Hz, $CH_3CH_2O$), 16.7 (d, $J$ = 5.8 Hz, $CH_3CH_2O$), 19.5 [$(CH_3)_2CH$], 20.5 [$(CH_3)_2CH$], 22.9 (C-4), 33.1 [$CH(CH_3)_2$], 47.6 (d, $J$ = 159.3 Hz, C-3), 57.2 (d, $J$ = 15.1 Hz, C-1), 62.2 (d, $J$ = 6.9 Hz, $OCH_2CH_3$), 62.9 (d, $J$ = 6.7 Hz, $OCH_2CH_3$), 107.9 (d, $J$ = 14.8 Hz, Ar), 110.8 (Ar), 118.1 (Ar), 119.5 (Ar), 121.8 (Ar), 127.1 (d, $J$ = 2.4 Hz, Ar), 135.3 (d, $J$ = 2.5 Hz, Ar), 135.7 (Ar) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 27.70 ppm. HRMS (ESI): calculated for $C_{18}H_{28}N_2O_3P$ [M + H]$^+$, $m/z$ 351.1838; found for [M + H]$^+$, $m/z$ 351.1830.

**Diethyl (1,1-Dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-3-yl)phosphonate (4g):** According to the general procedure, a mixture of phosphotryptophan ethyl ester (**7**; 200 mg, 0.67 mmol), acetone (40 mg, 0.05 mL, 0.68 mmol), dry $CH_2Cl_2$ (7 mL) and TFA (0.07 mL, 0.91 mmol) was reacted in the presence of activated molecular sieves (4 Å, 70 mg), affording **4g** as a white solid (171 mg, 75%); m.p. 156–158 °C. IR (nujol): $\tilde{\nu}$ = 3251, 1220, 1027, 955 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.40 (t, $J$ = 7.0 Hz, 3 H, $CH_3CH_2O$), 1.40 (t, $J$ = 7.0 Hz, 3 H, $CH_3CH_2O$), 1.45 (s, 3 H, $CH_3$), 1.51 (s, 3 H, $CH_3$), 1.62 (br. s, 1 H, NH), 2.84–3.01 (m, 2 H, 4-H), 3.49 (ddd, $J$ = 18.9, 11.4, 4.5 Hz, 1 H, 3-H), 4.18–4.38 (m, 4 H, $OCH_2CH_3$), 7.09 (ddd, $J$ = 7.6, 7.6, 1.0 Hz, 1 H, $H_{arom}$), 7.15 (ddd, $J$ = 7.6, 7.6, 1.0 Hz, 1 H, $H_{arom}$), 7.33 (dd, $J$ = 7.6, 1.0 Hz, 1 H, $H_{arom}$), 7.47 (dd, $J$ = 7.6, 1.0 Hz, 1 H, $H_{arom}$), 8.26 (br. s, 1 H, indole-NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 16.7 (d, $J$ = 5.8 Hz, $CH_3CH_2O$), 23.6 (C-4), 28.3 ($CH_3$), 29.6 ($CH_3$), 47.6 (d, $J$ = 162.1 Hz, C-3), 51.4 (d, $J$ = 17.3 Hz, C-1), 62.4 (d, $J$ = 6.8 Hz, $OCH_2CH_3$), 63.0 (d, $J$ = 6.7 Hz, $OCH_2CH_3$), 106.2 (d, $J$ = 16.8 Hz, Ar), 110.9 (Ar), 118.3 (Ar), 119.5 (Ar), 121.8 (Ar), 127.2 (d, $J$ = 3.0 Hz, Ar), 135.7 (Ar), 140.3 (d, $J$ = 2.8 Hz, Ar) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 27.08 ppm. HRMS (ESI): calculated for $C_{17}H_{26}N_2O_3P$ [M + H]$^+$, $m/z$ 337.1681; found for [M + H]$^+$, $m/z$ 337.1680.

**Diethyl (2′,3′,4′,9′-Tetrahydrospiro[cyclohexane-1,1′-pyrido[3,4-*b*]-indol]-3′-yl)phosphonate (4h):** According to the general procedure, a mixture of phosphotryptophan ethyl ester (**7**; 200 mg, 0.67 mmol), cyclohexanone (66 mg, 0.07 mL, 0.67 mmol), dry $CH_2Cl_2$ (7 mL) and TFA (0.07 mL, 0.91 mmol) was reacted in the presence of activated molecular sieves (4 Å, 70 mg), affording **4h** as a white solid (176 mg, 69%); m.p. 175–177 °C. IR (nujol): $\tilde{\nu}$ = 3248, 1220, 1028, 966 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.24–1.36 (m, 1 H, $CH_2$), 1.40 (t, $J$ = 7.1 Hz, 3 H, $CH_3CH_2O$), 1.41 (t, $J$ = 7.1 Hz, 3 H, $CH_3CH_2O$), 1.49–2.01 (m, 10 H, NH, $CH_2$), 2.85–2.99 (m, 2 H, 4-H), 3.40 (ddd, $J$ = 19.3, 10.7, 5.3 Hz, 1 H, 3-H), 4.20–4.30 (m, 2 H, $OCH_2CH_3$), 4.30–4.40 (m, 2 H, $OCH_2CH_3$), 7.09 (ddd, $J$ = 7.5, 7.5, 1.1 Hz, 1 H, $H_{arom}$), 7.15 (ddd, $J$ = 7.5, 7.5, 1.1 Hz, 1 H, $H_{arom}$), 7.33 (dd, $J$ = 7.5, 1.1 Hz, 1 H, $H_{arom}$), 7.48 (dd, $J$ = 7.5, 1.1 Hz, 1 H, $H_{arom}$), 8.20 (br. s, 1 H, indole-NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 16.7 (d, $J$ = 5.9 Hz, $CH_3CH_2O$), 16.8 (d, $J$ = 5.8 Hz, $CH_3CH_2O$), 21.2 ($CH_2$), 21.5 ($CH_2$), 23.5 (d, $J$ = 1.7 Hz, C-4), 26.0 ($CH_2$), 34.9 ($CH_2$), 38.6 ($CH_2$), 47.0 (d, $J$ = 163.0 Hz, C-3), 53.1 (d, $J$ = 16.7 Hz, C-1), 62.1 (d, $J$ = 7.0 Hz, $OCH_2CH_3$), 63.4 (d, $J$ = 6.7 Hz, $OCH_2CH_3$), 106.7 (d, $J$ = 16.8 Hz, Ar), 110.9 (Ar), 118.2 (Ar), 119.5 (Ar), 121.7 (Ar), 127.3 (d, $J$ = 3.1 Hz, Ar), 135.5 (Ar), 141.0 (d, $J$ = 2.9 Hz, Ar) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 27.52 ppm. HRMS (ESI): calculated for $C_{20}H_{30}N_2O_3P$ [M + H]$^+$, $m/z$ 377.1994; found for [M + H]$^+$, $m/z$ 377.1979.

**General Procedure for the Preparation of Diethyl β-Carboline-3-phosphonates 5 and 6a–f:** To a stirred solution of crude 1,2,3,4-tetrahydro-β-carboline-3-phosphonate **3** and **4a–f**, obtained as described above, and TEA (136 mg, 0.19 mL, 1.34 mmol) in dry DMF (4 mL) at –10 °C under an argon atmosphere, a solution of trichloroisocyanuric acid (TCCA, 157 mg, 0.67 mmol) in dry DMF (1 mL) was slowly added. The mixture was stirred at 0 °C for 2 h and the progress was monitored by TLC ($CH_2Cl_2$:*i*PrOH, 95:5). Upon completion of the reaction (2–3 h), the reaction mixture was diluted with AcOEt and washed with satd. solution of NaCl. The organic layer was dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by column chromatography with $CH_2Cl_2$:*i*PrOH (97:3) as eluent to provide oxidation products **5** and **6a–f**, respectively.

**Diethyl 9*H*-Pyrido[3,4-*b*]indol-3-ylphosphonate (5):** According to the general procedure, a mixture of the crude **3**, TEA (136 mg, 0.19 mL, 1.34 mmol), dry DMF (4 mL) and a solution of trichloroisocyanuric acid (TCCA, 157 mg, 0.67 mmol) was reacted to afford **5** (171 mg, 83%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 1249, 1025, 968 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.31 (t, $J$ = 7.1 Hz, 6 H, $CH_3CH_2O$), 4.15–4.31 (m, 4 H, $OCH_2CH_3$), 7.29 (ddd, $J$ = 8.0, 7.1, 0.9 Hz, 1 H, $H_{arom}$), 7.53 (ddd, $J$ = 8.3, 7.1, 1.2 Hz, 1 H, $H_{arom}$), 7.64 (dd, $J$ = 8.3, 0.9 Hz, 1 H, $H_{arom}$), 8.08 (dd, $J$ = 8.0, 1.2 Hz, 1 H, $H_{arom}$), 8.71 (d, $J$ = 7.5 Hz, 1 H, $H_{arom}$), 9.11 (s, 1 H, $H_{arom}$), 10.78 (br. s, 1 H, indole-NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 16.5 (d, $J$ = 6.2 Hz, $CH_3CH_2O$), 62.9 (d, $J$ = 5.7 Hz, $OCH_2CH_3$), 112.5 (Ar), 120.7 (Ar), 121.1 (d, $J$ = 27.6 Hz, Ar), 121.2 (d, $J$ = 2.4 Hz, Ar), 121.9 (Ar), 127.8 (d, $J$ = 15.1 Hz, Ar), 128.9 (Ar), 135.5 (d, $J$ = 25.4 Hz, Ar), 137.3 (d, $J$ = 3.5 Hz, Ar), 138.1 (d, $J$ = 234.0 Hz, Ar), 141.1 (Ar) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 14.90 ppm. HRMS (ESI): calculated for $C_{15}H_{18}N_2O_3P$ [M + H]$^+$, $m/z$ 305.1055; found for [M + H]$^+$, $m/z$ 305.1056.

**Diethyl (1-Phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)phosphonate (6a):** According to the general procedure, a mixture of the crude **4a**, TEA (136 mg, 0.19 mL, 1.34 mmol), dry DMF (4 mL) and a solution of trichloroisocyanuric acid (TCCA, 157 mg, 0.67 mmol) was reacted to afford **6a** as a colourless oil (163 mg, 63%). IR (KBr): $\tilde{\nu}$ = 1242, 1026, 966 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.34 (t, $J$ = 7.1 Hz, 6 H, $CH_3CH_2O$), 4.17–4.33 (m, 4 H, $OCH_2CH_3$), 7.32 (ddd, $J$ = 7.9, 7.2, 1.0 Hz, 1 H, $H_{arom}$), 7.37 (tt, $J$ = 7.4, 1.3 Hz, 1 H, $H_{arom}$), 7.46 (dd, $J$ = 7.4, 7.1 Hz, 2 H, $H_{arom}$), 7.53 (ddd, $J$ = 8.2, 7.2, 1.1 Hz, 1 H, $H_{arom}$), 7.64 (dd, $J$ = 8.2, 1.0 Hz, 1 H, $H_{arom}$), 7.94 (dd, $J$ = 7.1, 1.3 Hz, 2 H, $H_{arom}$), 8.11 (dd, $J$ = 7.9, 1.1 Hz, 1 H, $H_{arom}$), 8.63 (d, $J$ = 7.2 Hz, 1 H, $H_{arom}$), 9.63 (br. s, 1 H, indole-NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 16.6 (d, $J$ = 6.3 Hz, $CH_3CH_2O$), 63.0 (d, $J$ = 5.9 Hz, $OCH_2CH_3$), 112.3 (Ar), 120.2 (d,

$J$ = 27.8 Hz, Ar), 121.0 (Ar), 121.8 (d, $J$ = 2.5 Hz, Ar), 121.9 (Ar), 128.5 (Ar), 128.8 (Ar), 128.9 (Ar), 129.0 (Ar), 129.1 (Ar), 134.5 (d, $J$ = 3.6 Hz, Ar), 137.9 (Ar), 139.4 (d, $J$ = 232.7 Hz, Ar), 140.7 (Ar), 144.0 (d, $J$ = 25.2 Hz, Ar) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 14.04 ppm. HRMS (ESI): calculated for $C_{21}H_{22}N_2O_3P$ [M + H]$^+$, $m/z$ 381.1368; found for [M + H]$^+$, $m/z$ 381.1372.

**Diethyl [1-(4-Bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl]phosphonate (6b):** According to the general procedure, a mixture of the crude **4b**, TEA (136 mg, 0.19 mL, 1.34 mmol), dry DMF (4 mL) and a solution of trichloroisocyanuric acid (TCCA, 157 mg, 0.67 mmol) was reacted to afford **6b** as a white solid (236 mg, 76%); m.p. 206–208 °C. IR (nujol): $\tilde{\nu}$ = 1213, 1024, 945 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.36 (t, $J$ = 7.1 Hz, 6 H, C$H_3$CH$_2$O), 4.18–4.34 (m, 4 H, OC$H_2$CH$_3$), 7.33 (ddd, $J$ = 8.0, 7.2, 0.9 Hz, 1 H, H$_{arom}$), 7.46 (d, $J$ = 8.6 Hz, 2 H, H$_{arom}$), 7.54 (ddd, $J$ = 8.2, 7.2, 1.1 Hz, 1 H, H$_{arom}$), 7.66 (dd, $J$ = 8.2, 0.9 Hz, 1 H, H$_{arom}$), 7.72 (d, $J$ = 8.6 Hz, 2 H, H$_{arom}$), 8.09 (dd, $J$ = 8.0, 1.1 Hz, 1 H, H$_{arom}$), 8.54 (d, $J$ = 7.1 Hz, 1 H, H$_{arom}$), 9.79 (br. s, 1 H, indole-NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 16.6 (d, $J$ = 6.3 Hz, C$H_3$CH$_2$O), 63.1 (d, $J$ = 6.0 Hz, OC$H_2$CH$_3$), 112.4 (Ar), 120.0 (d, $J$ = 27.6 Hz, Ar), 121.1 (Ar), 121.8 (d, $J$ = 2.4 Hz, Ar), 121.9 (Ar), 123.3 (Ar), 129.0 (Ar), 129.2 (d, $J$ = 14.9 Hz, Ar), 129.9 (Ar), 132.0 (Ar), 134.3 (d, $J$ = 3.6 Hz, Ar), 136.6 (Ar), 139.4 (d, $J$ = 233.9 Hz, Ar), 140.9 (Ar), 142.6 (d, $J$ = 25.4 Hz, Ar) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 13.71 ppm. HRMS (ESI): calculated for $C_{21}H_{21}BrN_2O_3P$ [M + H]$^+$, $m/z$ 459.0473; found for [M + H]$^+$, $m/z$ 459.0467.

**Diethyl [1-(4-Methoxyphenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl]phosphonate (6c):** According to the general procedure, a mixture of the crude **4c**, TEA (136 mg, 0.19 mL, 1.34 mmol), dry DMF (4 mL) and a solution of trichloroisocyanuric acid (TCCA, 157 mg, 0.67 mmol) was reacted to afford **6c** as a pale yellow solid (157 mg, 57%); m.p. 148–150 °C. IR (nujol): $\tilde{\nu}$ = 1245, 1021, 946 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.33 (t, $J$ = 7.1 Hz, 6 H, C$H_3$CH$_2$O), 3.67 (s, 3 H, CH$_3$O), 4.16–4.33 (m, 4 H, OC$H_2$CH$_3$), 6.84 (d, $J$ = 8.8 Hz, 2 H, H$_{arom}$), 7.30 (ddd, $J$ = 7.9, 7.2, 0.9 Hz, 1 H, H$_{arom}$), 7.52 (ddd, $J$ = 8.3, 7.2, 1.1 Hz, 1 H, H$_{arom}$), 7.69 (dd, $J$ = 8.3, 0.9 Hz, 1 H, H$_{arom}$), 7.83 (d, $J$ = 8.8 Hz, 2 H, H$_{arom}$), 8.07 (dd, $J$ = 7.9, 1.1 Hz, 1 H, H$_{arom}$), 8.55 (d, $J$ = 7.3 Hz, 1 H, H$_{arom}$), 9.89 (br. s, 1 H, indole-NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 16.5 (d, $J$ = 6.3 Hz, C$H_3$CH$_2$O), 55.3 (CH$_3$O), 62.9 (d, $J$ = 5.9 Hz, OC$H_2$CH$_3$), 112.4 (Ar), 114.1 (Ar), 119.6 (d, $J$ = 27.9 Hz, Ar), 120.8 (Ar), 121.7 (Ar), 121.8 (d, $J$ = 2.5 Hz, Ar), 128.6 (Ar), 128.7 (d, $J$ = 15.2 Hz, Ar), 129.7 (Ar), 130.3 (Ar), 134.3 (d, $J$ = 3.6 Hz, Ar), 138.9 (d, $J$ = 232.9 Hz, Ar), 140.8 (Ar), 143.9 (d, $J$ = 25.2 Hz, Ar), 160.2 (Ar) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 14.27 ppm. HRMS (ESI): calculated for $C_{22}H_{24}N_2O_4P$ [M + H]$^+$, $m/z$ 411.1474; found for [M + H]$^+$, $m/z$ 411.1484.

**Diethyl (1-Methyl-9*H*-pyrido[3,4-*b*]indol-3-yl)phosphonate (6d):** According to the general procedure, a mixture of the crude **4d**, TEA (136 mg, 0.19 mL, 1.34 mmol), dry DMF (4 mL) and a solution of trichloroisocyanuric acid (TCCA, 157 mg, 0.67 mmol) was reacted to afford **6d** as a yellow oil (41 mg, 19%). IR (nujol): $\tilde{\nu}$ = 1236, 1042, 969 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.34 (t, $J$ = 7.1 Hz, 6 H, C$H_3$CH$_2$O), 2.81 (s, 3 H, CH$_3$), 4.16–4.32 (m, 4 H, OC$H_2$CH$_3$), 7.27 (ddd, $J$ = 8.0, 7.2, 0.9 Hz, 1 H, H$_{arom}$), 7.50 (ddd, $J$ = 8.3, 7.2, 1.1 Hz, 1 H, H$_{arom}$), 7.62 (dd, $J$ = 8.3, 0.9 Hz, 1 H, H$_{arom}$), 8.02 (dd, $J$ = 8.0, 1.1 Hz, 1 H, H$_{arom}$), 8.54 (d, $J$ = 7.7 Hz, 1 H, H$_{arom}$), 10.44 (br. s, 1 H, indole-NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 16.5 (d, $J$ = 6.3 Hz, C$H_3$CH$_2$O), 20.6 (CH$_3$), 62.8 (d, $J$ = 5.8 Hz, OC$H_2$CH$_3$), 112.4 (Ar), 119.6 (d, $J$ = 27.6 Hz, Ar), 120.6 (Ar), 121.8 (Ar), 121.9 (Ar), 126.8 (d, $J$ = 15.7 Hz, Ar), 128.5 (Ar), 136.1 (d, $J$ = 3.6 Hz, Ar), 137.6 (d, $J$ = 234.0 Hz, Ar), 140.7 (Ar), 144.2 (d, $J$ = 25.3 Hz, Ar) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 15.22 ppm. HRMS (ESI): calculated for $C_{16}H_{20}N_2O_3P$ [M + H]$^+$, $m/z$ 319.1212; found for [M + H]$^+$, $m/z$ 319.1204.

**Diethyl (1-Isopropyl-9*H*-pyrido[3,4-*b*]indol-3-yl)phosphonate (6e):** According to the general procedure, a mixture of the crude **4e**, TEA (136 mg, 0.19 mL, 1.34 mmol), dry DMF (4 mL) and a solution of trichloroisocyanuric acid (TCCA, 157 mg, 0.67 mmol) was reacted to afford **6e** as a white solid (91 mg, 39%); m.p. 179–181 °C. IR (nujol): $\tilde{\nu}$ = 1230, 1037, 965 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.37 (t, $J$ = 7.1 Hz, 6 H, C$H_3$CH$_2$O), 1.41 [d, $J$ = 6.8 Hz, 6 H, (C$H_3$)$_2$CH], 3.72 [hept, $J$ = 6.8 Hz, 1 H, C$H$(CH$_3$)$_2$], 4.23–4.40 (m, 4 H, OC$H_2$CH$_3$), 7.28 (ddd, $J$ = 7.9, 7.2, 0.9 Hz, 1 H, H$_{arom}$), 7.52 (ddd, $J$ = 8.2, 7.2, 0.9 Hz, 1 H, H$_{arom}$), 7.69 (dd, $J$ = 8.2, 0.9 Hz, 1 H, H$_{arom}$), 8.04 (dd, $J$ = 7.9, 0.9 Hz, 1 H, H$_{arom}$), 8.61 (d, $J$ = 7.3 Hz, 1 H, H$_{arom}$), 10.53 (br. s, 1 H, indole-NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 16.5 (d, $J$ = 6.3 Hz, C$H_3$CH$_2$O), 21.5 [(C$H_3$)$_2$CH], 31.9 [C$H$(CH$_3$)$_2$], 63.2 (d, $J$ = 6.0 Hz, OC$H_2$CH$_3$), 112.4 (Ar), 119.5 (d, $J$ = 28.1 Hz, Ar), 120.4 (Ar), 121.5 (Ar), 121.9 (d, $J$ = 2.6 Hz, Ar), 127.3 (d, $J$ = 15.4 Hz, Ar), 128.3 (Ar), 134.7 (d, $J$ = 3.6 Hz, Ar), 137.7 (d, $J$ = 231.8 Hz, Ar), 140.6 (Ar), 152.1 (d, $J$ = 24.2 Hz, Ar) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 14.36 ppm. HRMS (ESI): calculated for $C_{18}H_{24}N_2O_3P$ [M + H]$^+$, $m/z$ 347.1525; found for [M + H]$^+$, $m/z$ 347.1539.

**Ethyl 3-(Diethoxyphosphoryl)-9*H*-pyrido[3,4-*b*]indole-1-carboxylate (6f):** To a stirred solution of phosphotryptophan ethyl ester (**7**; 200 mg, 0.67 mmol) was added ethyl glyoxylate (70 mg, 0.14 mL, 0.68 mmol, 50% solution in toluene), activated molecular sieves (4 Å, 70 mg) in dry $CH_2Cl_2$ (7 mL), and TFA (0.07 mL, 0.91 mmol). The reaction mixture was stirred at room temperature and the progress was monitored by TLC ($CH_2Cl_2$:*i*PrOH, 8:2). Upon completion of the reaction (4 h), volatiles were removed under reduced pressure and the crude material was diluted with $CH_2Cl_2$ (20 mL), washed with satd. $NaHCO_3$, and the aqueous phase further extracted with $CH_2Cl_2$ (2 × 10 mL). The organic extracts were combined and dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated to obtain **4f**, which due to its propensity to oxidize, was used without isolation in the following step. According to the general procedure, a mixture of the crude **4f**, TEA (136 mg, 0.19 mL, 1.34 mmol), dry DMF (4 mL) and a solution of trichloroisocyanuric acid (TCCA, 157 mg, 0.67 mmol) was reacted to afford **6f** as a yellow solid (213 mg, 84%); m.p. 157–159 °C. IR (nujol): $\tilde{\nu}$ = 1703, 1228, 1031, 974 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.39 [t, $J$ = 7.1 Hz, 6 H, (C$H_3$CH$_2$O)$_2$P(O)], 1.46 [t, $J$ = 7.1 Hz, 3 H, C$H_3$CH$_2$OC(O)], 4.24–4.40 [m, 4 H, P(O)(OC$H_2$CH$_3$)$_2$], 4.53 [q, $J$ = 7.1 Hz, 2 H, C(O)OC$H_2$CH$_3$], 7.36 (ddd, $J$ = 7.9, 6.4, 1.8 Hz, 1 H, H$_{arom}$), 7.58–7.64 (m, 2 H, H$_{arom}$), 8.14 (dd, $J$ = 7.9, 0.8 Hz, 1 H, H$_{arom}$), 8.82 (d, $J$ = 6.5 Hz, 1 H, H$_{arom}$), 10.20 (br. s, 1 H, indole-NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 14.4 [C$H_3$CH$_2$OC(O)], 16.5 [d, $J$ = 6.2 Hz, (C$H_3$CH$_2$O)$_2$P(O)], 62.0 [C(O)OC$H_2$CH$_3$], 63.3 [d, $J$ = 6.1 Hz, P(O)(OC$H_2$CH$_3$)$_2$], 112.3 (Ar), 121.0 (d, $J$ = 2.4 Hz, Ar), 121.5 (Ar), 122.2 (Ar), 123.6 (d, $J$ = 28.1 Hz, Ar), 129.9 (Ar), 130.8 (d, $J$ = 14.0 Hz, Ar), 131.0 (d, $J$ = 25.2 Hz, Ar), 137.5 (d, $J$ = 3.3 Hz, Ar), 139.8 (d, $J$ = 234.1 Hz, Ar), 140.8 (Ar), 166.6 (C=O) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 12.53 ppm. HRMS (ESI): calculated for $C_{18}H_{22}N_2O_5P$ [M + H]$^+$, $m/z$ 377.1266; found for [M + H]$^+$, $m/z$ 377.1253.

## Acknowledgments

The authors are thankful for financial support by the Mexican Consejo Nacional de Ciencia y Tecnología (CONACYT) for finan-

cial support via project 181816, by the Spanish Ministerio de Ciencia e Innovación (MICINN), FEDER (grant number CTQ2010-17436) and by the Gobierno de Aragón-FSE (research group E40). J. L. V.-C. also thank CONACYT for graduate scholarships.

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Received: November 1, 2014
Published Online: ■

  

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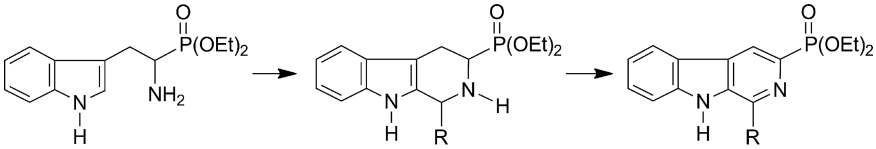


We report the first practical and efficient synthesis of diethyl 1,2,3,4-tetrahydro-β-carboline-3-phosphonates and diethyl 9*H*-β-carboline-3-phosphonate derivatives. The target compounds were prepared in good yields using Pictet–Spengler reactions of phosphotryptophan diethyl ester with several aldehydes followed by oxidation chemistry.



**Keywords:** Synthetic methods / Drug design / Phosphorylation / Nitrogen heterocycles

  