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Stereoselective Synthesis of Functionalized Tetrahydro-β-Carbolines via Pictet–Spengler Reaction

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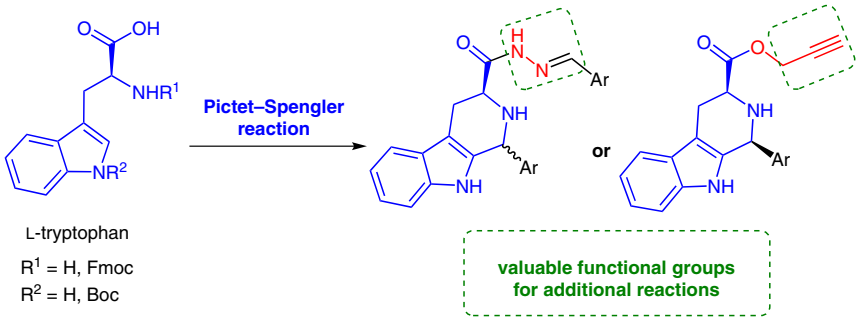
Dedicated to Prof. Habib Bagheri on the occasion of his birthday



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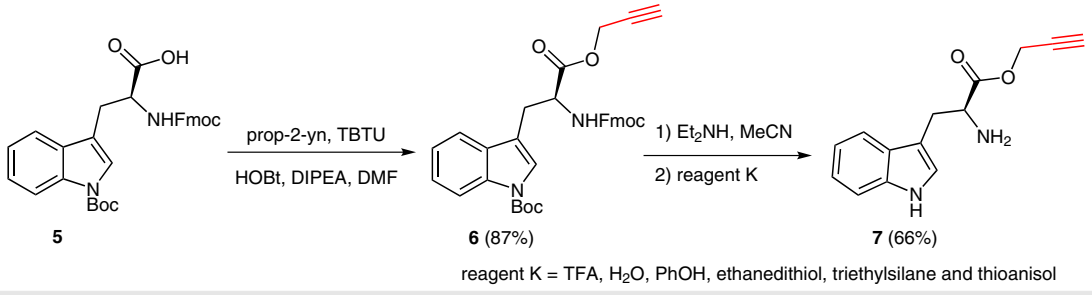
Abstract A TFA-catalyzed Pictet–Spengler reaction of synthesized tryptophan propargyl ester with aromatic and heteroaromatic aldehydes resulted in *cis*-tetrahydro-β-carbolines with remarkably high stereocontrol under kinetically controlled conditions. In another approach, a diastereomeric mixture of tetrahydro-β-carboline hydrazides was synthesized. The tetrahydro-β-carboline hydrazides were prepared through the reaction of tryptophan hydrazide with carbonyl compounds via Pictet–Spengler reaction.

Key words tetrahydro-β-carboline, Pictet–Spengler reaction, L-tryptophan, asymmetric synthesis

Tetrahydro-β-carboline is an important structural framework found in a variety of natural products, such as compounds **1**[1] and **2**[2] (Figure 1), exhibiting significant biological activities including antimalaria,[3] anti-HIV,[4] anticancer,[5] and antiallergic effects[6] and also inhibition of brain benzodiazepine receptors.[7] In this regard, various synthetic methods were developed for the construction of such structures[8] in which the most direct method is the Pictet–Spengler reaction (PSR).[9]

Asymmetric synthesis centers on the use of chiral substrates, catalysts, chiral auxiliaries, and/or solvents to result in stereoselective reactions.[10] Natural α-amino acids, such as L-tryptophan, are suitable precursors for the asymmetric synthesis.[11] Recently, derivatives of L-tryptophan have been used for the synthesis of indole alkaloids and were used for the construction of *cis*-1,3-disubstituted tetrahydro-β-carboline via PSR.[12]

In this paper, we wish to delineate the efficient asymmetric synthesis of tetrahydro-β-carboline derivatives **3** and **4** (Figure 2) starting from L-tryptophan via PSR. The stereoisomers of propargyl esters **3a**–**g** and hydrazide tetrahydro-β-carbolines **4a**–**e** have valuable functional groups which can undergo further transformations. For example, hydrazide functional groups can be converted into tetrazoles,[13] α-hydrazino tetrazoles,[14] hydrazino amides,[15] spiroquinazolinones,[16] pseudopeptides,[17] and oxadiazole[18]



Scheme 1 Synthesis of Trp-*O*-propargyl using Fmoc-Trp(Boc)-OH

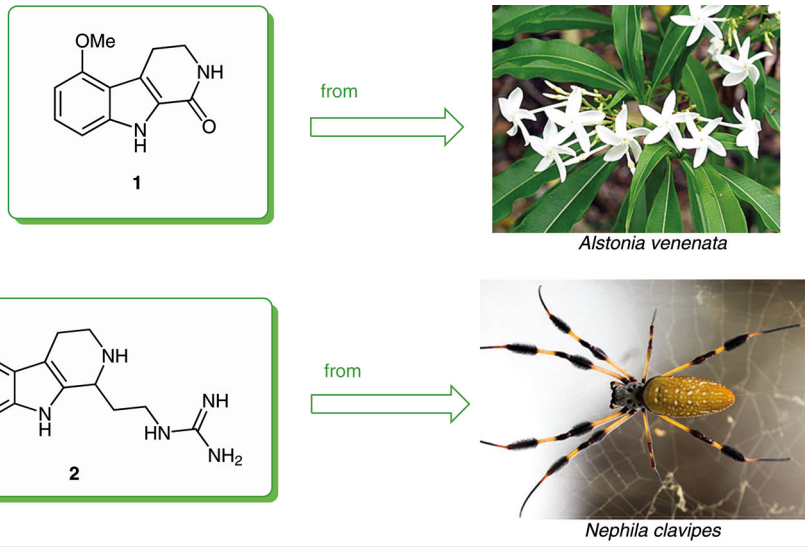


Figure 1 Tetrahydro-β-carboline-based structures found in nature

whereas the propargyl group is a good precursor for click[19] and Diels–Alder[20] reactions.

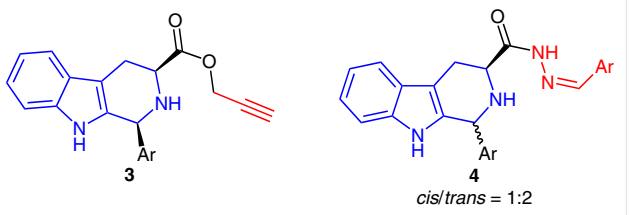
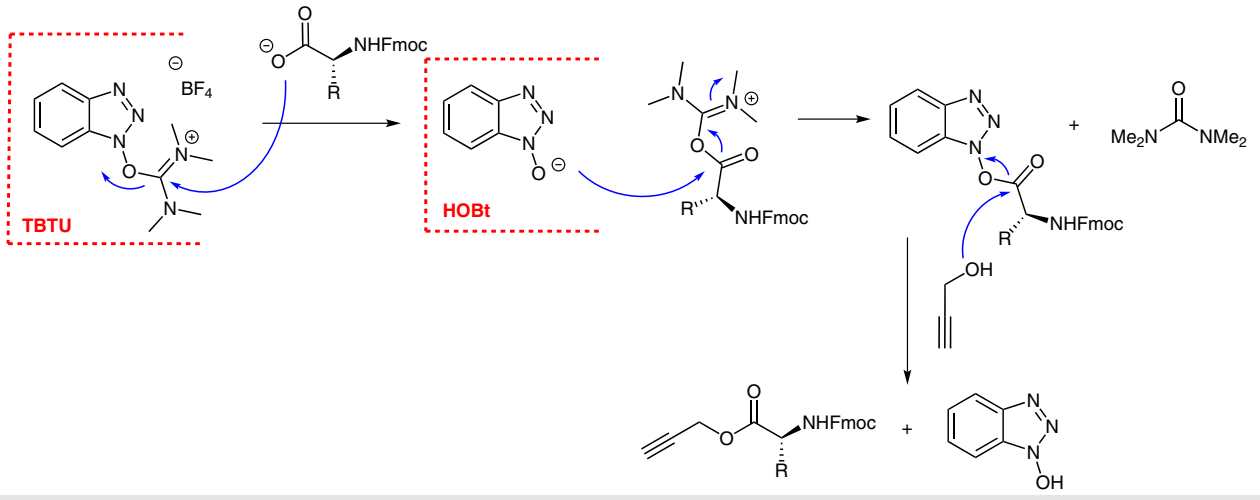


Figure 2 The structure of functionalized tetrahydro-β-carbolines

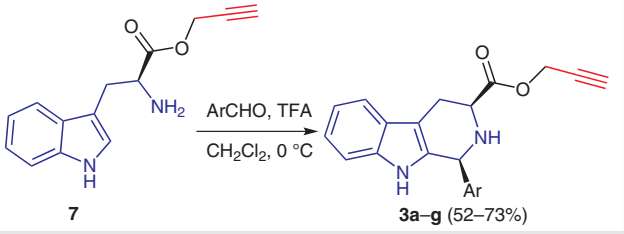
In the synthesis of tetrahydro-β-carboline derivatives **3a–g** via the PSR of L-tryptophan, a Boc/Fmoc protecting-group strategy was adopted. According to the synthetic route shown in Scheme 1, Boc/Fmoc-protected L-tryptophan **5** was treated with propargyl alcohol in the presence of TBTU and HOBt as coupling agents to obtain propargyl ester **6** in 87% yield (Scheme 1). Although, HOBt is formed during the deprotection reaction, HOBt is used at the beginning of the reaction to prevent the racemization of the reaction (Scheme 4). Then, the Fmoc amine segment of compound **6** was deprotected using diethylamine and acetonitrile. The ready removal of diethylamine from the reaction mixture makes it a better base than piperidine for this reac-



Scheme 2 Proposed mechanism for the synthesis of Fmoc-Trp(*O*-propargyl)-OH

tion. Care was necessary during the deprotection of the Boc amine group to avoid Friedel–Crafts reaction of the released *tert*-butyl carbocation with the reactive indole ring. For this purpose, the reagent K was chosen since it has a nucleophilic component to trap the carbocation. Thus, Boc amine deprotection was conducted by adding cooled reagent K to the mixture. Finally, the pure tryptophan propargyl ester (**7**)[22] was achieved in overall yield of 66% in three reaction steps. The proposed mechanism for the synthesis of Fmoc-Trp(*O*-propargyl)-OH is illustrated in Scheme 2.

The PSR of tryptophan propargyl ester (**7**) with aromatic and heteroaromatic aldehydes produced *cis*-tetrahydro-β-carboline propargyl esters **3a**–**g**[23] with remarkably high stereocontrol (Scheme 3), the exothermic reaction leading to *trans* thermodynamic products. Therefore, the reaction was performed at 0 °C to prevent the formation of *trans* isomer. This reaction was accomplished using different aldehyde derivatives, and the results are summarized in Table 1. In all cases, the reactions carried out at 0 °C gave the kinetic products.



Scheme 3 Synthesis of tetrahydro-β-carbolines contained propargyl ester **3a**–**g**

Table 1 Synthesis of *cis*-Tetrahydro-β-carboline Propargyl Ester **3a**–**g** Using TFA as Catalyst

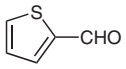
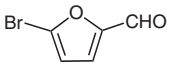
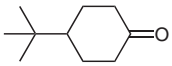
Entry	Aldehyde	Product	Time (h)	Yield (%)
1	PhCHO	**3a**	6	73
2	4-ClC_6H_4CHO	**3b**	5	52
3	4-$MeOC_6H_4CHO$	**3c**	4.5	66
4	4-(*i*-Pr)C_6H_4CHO	**3d**	5.5	62
5	3-$O_2NC_6H_4CHO$	**3e**	5	67
6	4-$O_2NC_6H_4CHO$	**3f**	6	64
7		**3g**	6.5	57

Table 2 Synthesis of Tetrahydro-β-carboline Hydrazides **4a**–**e** Using TFA as Catalyst[a]

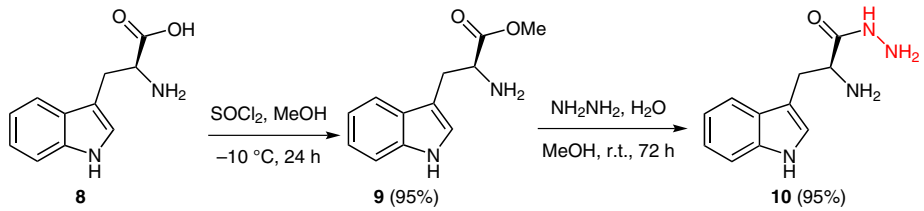
Entry	Aldehyde	Product	Yield (%)
1	4-ClC_6H_4CHO	**4a**	80
2	4-$MeOC_6H_4CHO$	**4b**	78
3	4-FC_6H_4CHO	**4c**	83
4		**4d**	85
5		**4e**	65

[a] In all cases, the reaction time was 24 h.

The second aim of our approach was the synthesis of *cis*- and *trans*-tetrahydro-β-carboline hydrazides **4a**–**e**. Firstly, tryptophan methyl ester (**9**) was produced in high yield through the treatment of L-tryptophan (**8**) with thionyl chloride and methanol (Scheme 4). Then, the tryptophan hydrazide (**10**) [24] was obtained by hydrazination of tryptophan methyl ester (**9**) in methanol at room temperature. It is noteworthy that preservation of the enantiomeric purity was observed during these steps.

Tryptophan hydrazide (**10**) was then reacted with cyclohexanone derivative **11**, and aromatic and/or heteroaromatic aldehydes in the presence of a catalytic amount of TFA at room temperature to obtain tetrahydro-β-carboline hydrazides **4a**–**e** (Scheme 5).[25] The results are summarized in Table 2. 4-Bromobenzaldehyde, 4-hydroxybenzaldehyde, 2-propargyloxybenzaldehyde, and isobutyraldehyde failed to react efficiently as mixtures of products were observed and purification was not efficient.

Ungemach and co-workers[21] used ^{13}C NMR spectroscopy to assign the stereochemistry of tetrahydro-β-carbolines. Based on these results, the chemical shifts related to C-1 and C-3 in the *trans* isomers would be expected to appear downfield compared to the *cis* isomers. On the other hand, the ^{13}C NMR chemical shifts of C-1 and C-3 in compound **3a** are similar to data reported for *cis* isomers of **12a** and **13** in the Ungemach publication (Figure 3). Hence, it was concluded that **3a** was a *cis*-tetrahydro-β-carboline and it is reasonable that this result can be generalized to the other derivatives **3b**–**g**.



Scheme 4 Synthesis of tryptophan hydrazide (**10**)

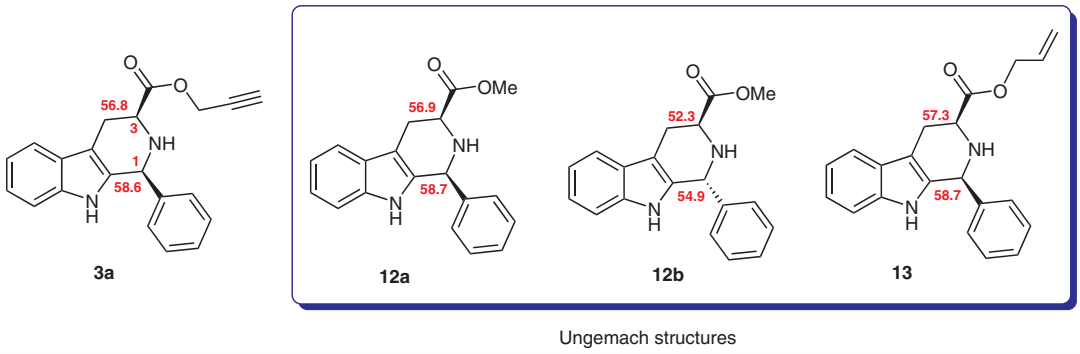


Figure 3 ^{13}C NMR chemical shifts of C-1 and C-3 in the structures of tetrahydro-β-carbolines

Moreover, investigation of the ^{1}H NMR spectrum of compound **4a** showed that it has two stereogenic centers, but one of them is fixed by tryptophan. Observation of two resonances at δ = 4.89 and 4.08 ppm indicates that both *cis* and *trans* isomers of compound **4a** were formed. Comparison of *cis*-**4a** and *trans*-**4a** ^{13}C NMR chemical shifts is shown in Figure 4. The diastereomeric ratios were measured by ^{1}H NMR spectral data, it showed that the cyclization reaction provided a *cis*/*trans* isomer ratio of 2:1.

In this paper we prepared two new derivatives of L-tryptophan including tryptophan propargyl ester (**7**) and tryptophan hydrazide (**10**). Then, these derivatives were used in a Pictet–Spengler reaction in the presence of TFA. The *cis*-tetrahydro-β-carboline propargyl esters obtained were pure stereoisomers; whereas the tetrahydro-β-carboline hydrazides were obtained as a mixture of *cis* and *trans* isomers with a ratio of 2:1.

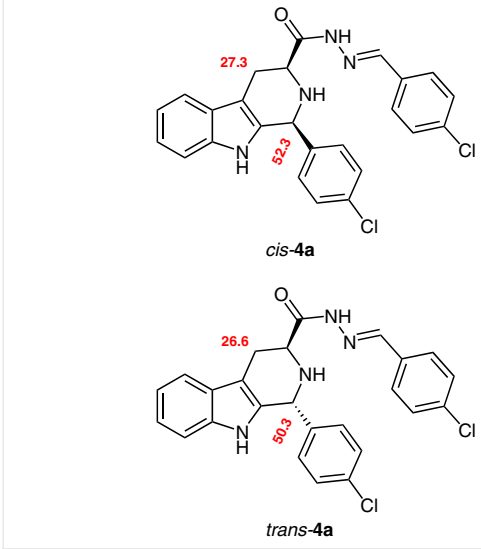
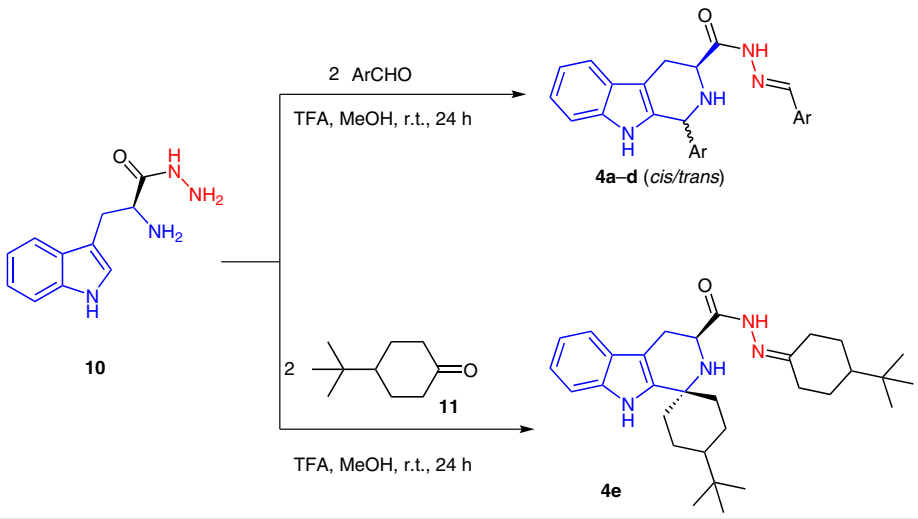


Figure 4 ^{13}C NMR chemical shifts of C-1 and C-3 in *cis*-**4a** and *trans*-**4a**



Scheme 5 Reaction of tryptophan hydrazide (**10**) with aldehydes and 4-*tert*-butylcyclohexane to access **4a**–**e**

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378727.

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(22) **Synthesis of Tryptophan Propargyl Ester (7)**
Fmoc-Trp(Boc)-OH (**5**, 5.27 g, 10 mmol) was added to *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (3.52 g, 11 mmol), *N*,*N*-diisopropylethylamine (3.9 mL, 22 mmmol), and hydroxybenzotriazole hydrate (1.48 g, 11 mmol) in DMF, (5mL). The mixture was left at r.t. for 10 min, then propargyl alcohol (1.2 mL, 20 mmol) was added and the reaction mixture stirred for 3 h until completion (monitored by TLC). It was diluted with EtOAc (50 mL) and then washed with Na_2CO_3 solution (3%), H_2O, and finally brine three times in each case. The organic phase was collected and dried over $MgSO_4$ followed by filtering and evaporation of the solvent to obtain pure **6** (2.98 g. 78%) as a pale yellow oil. In the Fmoc deprotection compound **6** was dissolved in MeCN (6 mL) and stirred at r.t. in the presence of Et_2NH (10 mL). After completion of the reaction (1 h), the solvent was evaporated under reduced pressure, the residue was diluted twice with MeCN (10 mL), and the solvent was removed under reduced pressure to remove the residual Et_2NH. The viscous oil obtained was purified by column chromatography (gradient eluting from 100% PE to 50:50 PE–EtOAc) affording the pure intermediate as a viscous oil (90%). Finally, Boc deprotection was accomplished by reagent K (a mixture of TFA, PhOH, ethanedithiol, triethylsilane, and thioanisol in H_2O). Purified intermediate was added to cooled reagent K (ice-water bath, 20 mL). After 2 h, the TFA was removed, H_2O was added (20 mL), and the mixture was extracted with Et_2O (40 mL), followed by washing the organic extract with H_2O, drying over $MgSO_4$, filtering, and removing the solvent under reduced pressure to obtain pure tryptophan propargyl ester (**7**) as a yellow oil (85%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.50 (t, *J* = 2.4 Hz, C≡CH), 3.11 (dd, *J* = 14.4, 7.4 Hz, 1 H, ArC*H*H), 3.31 (dd, *J* = 14.4, 4.8 Hz, 1 H, ArCH*H*), 3.80 (dd, *J* = 7.4, 4.9 Hz, 1 H, ArCH_2C*H*), 4.71 (*d*, *J* = 2.4 Hz, 2 H, OCH_2C≡CH), 7.08–7.66 (*m*, 5 H, ArH), 8.17 (s, 1 H, indole NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.9, 38.6, 53.8, 76.0, 76.4, 105.7, 111.7, 118.0, 119.7, 122.3, 125.6, 126.4, 136.3, 168.5 ppm.
(23) **General Procedure of the Synthesis of *cis*-Tetrahydro-β-carboline Propargyl Esters 3a–g**
The general procedure for PSR was followed by addition of tryptophan propargyl ester (**7**, 2.42 g, 1 mmol) to a solution of the appropriate aldehyde (1.2 mmol) in CH_2Cl_2 (10 mL) cooled in an ice-bath (0 °C). Then, TFA (0.23 g, 2 mmol) was slowly added to

the reaction mixture. After the reaction was complete (monitored by TLC), it was quenched by the addition of CH_2Cl_2 (20 mL) and a solution of $NaHCO_3$ (10 mL, 10%). The organic phase was separated, washed with brine, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The pure product was obtained after thick-layer chromatography.

(1*S*,3*S*)-Prop-2-ynyl-1-phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4*b*]indole-3-carboxylate (3a)

Pale oil, 73% yield. IR (KBr): ν = 3388, 3281, 2135, 1750 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.06 (br s, 1 H, NH), 2.54 (t, *J* = 2.5 Hz, C≡CH), 3.05 (ddd, *J* = 15.0, 11.2, 2.2 Hz, 1 H, H_{4a}), 3.15 (ddd, *J* = 15.0, 4.2, 2.2 Hz, 1 H, H_{4b}), 4.07 (dd, *J* = 11.2, 4.2 Hz, 1 H, H_3), 4.81 (dABq, *J* = 15.6, 2.5 Hz, 2 H, $OCH_2C{\equiv}CH$), 5.23 (s, 1 H, H_1), 7.12–7.27 (m, 3 H, ArH), 7.39 (s, 5 H, ArH),7.52 (s, 1 H, indole NH), 7.57 (m, 1 H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.7, 52.6, 56.8, 58.6, 75.4, 77.3, 108.7, 110.9, 118.2, 119.6, 121.9, 127.1, 128.6, 129, 134.6, 136.2, 140.7, 172.0 ppm. EI-MS: *m/z* (%) = 331 23) [M^+ + 1], 330 (87) [M^+], 291 (26), 247 (56), 218 (100), 204 (11), 169 (24), 144 (30), 57 (13), 43 (26). Anal. Calcd for $C_{21}H_{18}N_2O_2$ (330.38): C, 76.34; H, 5.49; N, 8.47. Found: C, 76.14; H, 5.36; N, 8.38; O, 9.53.

(24) **Synthesis of Tryptophan Hydrazide (10)**

Hydrazine monohydrate (80%, 0.16 mL, 3.4 mmol) was added to a mixture of tryptophan methyl ester (**9**, 218 mg, 1 mmol) in MeOH (2.5 mL), and the mixture was stirred for 72 h, monitoring by TLC. After evaporation of the solvent, a yellow oil was obtained. IR (KBr): ν = 3420, 1681 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 2.77 (dd, 1 H *J* = 7.5, 15 Hz, H_a), 3.05 (dd, 1 H *J* = 6.0, 15 Hz, $H_{a'}$), 3.48 (t, 1 H *J* = 7.2 Hz, CHN), 4.46 (br s, 4 H, $NHNH_2$, $CHNH_2$), 7.15 (s, 1 H, CH_{indol}), 6.96 (t, 1 H, *J* = 6.8 Hz, HAr), 7.04 (d, 1 H *J* = 7.0 Hz, HAr), 7.34 (d, 1 H *J* = 8.0 Hz, HAr), 7.55 (d, 1 H, *J* = 8.0 Hz, HAr), 11.00 (s, 1 H, $NHNH_2$), 11.04 (s, 1 H, NH_{Indole}) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 31.3, 54.3, 110.5, 111.6, 118.4, 118.6, 121.0, 124.0, 128.0, 136.3, 174.0 ppm.

(25) **General Procedure for the Synthesis of *cis*- and *trans*-Tetrahydro-β-carboline Hydrazide 4a–e**

The general procedure of PSR was followed by addition of tryptophan hydrazide (**10**, 218 mg, 1 mmol) to a solution of the appropriate aldehyde (2 mmol) in MeOH (5 mL) containing a catalytic amount of TFA (100 µL), and the mixture was stirred at r.t. for 24 h monitoring by TLC. Then CH_2Cl_2 (10 mL) was added, and the resultant precipitate of the product was collected by filtration. Column chromatography was also used for further purification of **4b**–**e**.

(*S*,*E*)-*N*′-(4-Chlorobenzylidene)-1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carbohydrazide (4a)

White solid. IR (KBr): ν = 3349, 1694 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ (*cis*/*trans* = 1:2) =3.10–3.40 [m, 4 H, $H_{4a,a'}$ (for two diastereomers)], 3.25–3.45 [m, 2 H, H_3 (for two diastereomers)], 4.08 [t, 1 H, *J* = 6.7 Hz, H_1 (*cis*)], 4.89 [t, 1 H, *J* = 6.3Hz, H_1 (*trans*)], 6.98 [t, 1 H, HAr (for two diastereomers)], 7.07 [t, 1 H, HAr (for two diastereomers)], 7.21 [br s, 1 H, NH (*trans*)], 7.30 [d, 1 H, *J* = 7.8 Hz, HAr (*trans*)], 7.36 [d, 1 H, *J* = 8.1 Hz, HAr (*cis*)], 7.44 [d, 2 H, *J* = 8.1 Hz, HAr (for two diastereomers)], 7.51 [d, 2 H, *J* = 8.1 Hz, HAr (for two diastereomers)], 7.53 [d, 2 H, *J* = 8.1 Hz, HAr (for two diastereomers)], 7.56 [d, 2 H, *J* = 8.1 Hz, HAr (for two diastereomers)], 7.66 [d, 1 H, *J* = 7.5 Hz, HAr (*cis*)], 7.74 [d, 1 H, *J* = 8.4 Hz, HAr (*trans*)], 8.02 [br s, 1 H, NH (*cis*)], 8.22 [br s, 1 H, =CH (*cis*)], 8.32 [br s, 1 H, =CH (*trans*)], 10.99 [s, 1 H, NH amide (*trans*)], 11.06 [s, 1 H, NH amide (*cis*)], 11.95 [br s, 1 H, NH indole (*trans*)], 12.18 [br s, 1 H, NH indole (*cis*)] ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 26.6 [$C_{4a,a'}$ (*trans*)], 27.3 [$C_{4a,a'}$ (*cis*)], 50.3, 52.3 [$C_{1'}$, C_3 (for two diastereomers)], 106.7, 108.9, 111.7, 115.3, 117.9, 118.5, 119.3, 121.2, 124.8, 127.0, 128.6, 128.8, 128.9, 129.0, 132.5, 132.7, 134.6, 134.9, 136.3, 144.1, 147.3 (for two diastereomers), 158.0 [C=N (*cis*)], 158.4 [C=N (*trans*)], 158.4 [C=O (*cis*)], 158.4 [C=O (*trans*)] ppm. ESI-HRMS: *m/z* calcd for $C_{18}H_{17}ClN_4O$ [(M – C_7H_3Cl) + H]$^+$: 341.11627; found: 341.11629.