

## FULL PAPER

# A facile and efficient method for the synthesis of tetrahydro- $\beta$ -carbolines via the Pictet-Spengler reaction in water/citric acid

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A effortless and efficient preparation of 1,2,3,4-tetrahydro- $\beta$ -carbolines in a single step the reaction of aldehydes and tryptamine from the environmentally friendly citric acid reagent in water was evaluated. This simple and smooth synthesis of numerous tryptolines was accelerated by natural citric acid with a good yield. The use of green reaction condition was simple for purification and a cost-effective protocol suggestion for production 1,2,3,4-tetrahydro- $\beta$ -carbolines derivatives.

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**KEYWORDS**Tetrahydro- $\beta$ -carbolines; tryptamine; aldehyde; water, citric acid.**Introduction**

Naturally, tricyclic alkaloids is a  $\beta$ -carboline with a pyridoindoles heterocyclic scaffolds available in the large number of natural products and medicinal important moiety [1]. The classification of  $\beta$ -carboline is on the basis of the position of the nitrogen at  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ - site of THBC. The scaffold tricyclic pyrido [3,4-*b*] indole ring [2] available in a broad range alkaloids products isolated from natural sources like marine sponge [3], territorial plants [4], fast food [5], and mammals [6]. Based on the percentage of pyridine ring, we call the  $\beta$ -carbolines like if the ring is full saturation in nature we called tetrahydro- $\beta$ -carbolines (TH $\beta$ -Cs), if the ring is half saturation dihydro- $\beta$ -carbolines (DH  $\beta$ -Cs) and fully aromatic is a  $\beta$ -carbolines ( $\beta$ -Cs) [7]. The product of Pictet-Spengler reaction TH  $\beta$ -Cs (tryptoline) ring develop in the numerous biologically important active scaffolds [8-12]. The TH $\beta$ C has a broad range

of medicinal activity such as anticonvulsant activities, anticancer, antiviral, antifungal, and anticancer. These give important activities and are of high interest in the synthesis of large number of active molecules [13,14].

The tryptolines act as the best chiral building blocks for the synthesis of TH $\beta$ C alkaloids [15]. In general, the *Pictet-Spengler* reaction tryptamine or tryptophan with carbonyl compound was performed with trifluoroacetic acid (TFA) and hydrochloric acid reagent [16]. In the literature, there are various methods reported for the TH $\beta$ C synthesis from the use of reagent such as TFA/H<sub>2</sub>O [17,18,19], microwave irradiation (MWI) [20], iodine in DMSO [21-24], NH<sub>4</sub>Cl in MeOH [25], tartaric acid in water [26], *Acacia concinnapods* (10% W/V) [27], CuCl<sub>2</sub>.2H<sub>2</sub>O [28], DTP/SiO<sub>2</sub> [29], *p*-toulenesulphonic acid [30], 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) [31], trichloro-1,3,5-triazine, and TCT [32]. The synthesis of environmental friendly reaction is more suitable for the human

health and environment, such a reaction has great important chemist trying to perform such a reaction avoiding that use organic solvents and toxic reagents. The reaction is safer for the environment and inexpensive green solvent [33].

Herein, we reported water/citric acid as a simple, efficient, and greener reagent for the preparation of TH $\beta$ C from the *Pictet-Spengler* experiment.

## Experimental

### General synthesis information

The M.P. was done by using the open capillary tube. All the used intermediates and starting material were purified and standard chemicals were used. The end point of the experiment was seen on the thin layer chromatography TLC, The Merck made silica sheets plates was used and seen with UV and stained by using iodine vapours. The FTIR was performed with spectrophotometer made by Perkin Elmer/Schimadzu/Bruker instruments. The Nuclear Magnetic Resonance of the novel compounds was recorded over the Bruker, Germany instrument Advanced spectrometer NMR for  $^1\text{H}$  and  $^{13}\text{C}$  spectra, while the internal standard as TMS, and splitting patter was recorded as s, d, t, and m (multiplet). The mass of novel compounds was measure with an EI-Shimadzu instrument made from Japan.

### Synthesis of TH $\beta$ C

Citric acid (1.0 equiv.) was taken in the seal tube/test tube alone with d aldehydes (1.0 equiv.) tryptamine hydrochloride (1.0 equiv.). The water was added to the reaction mixture, the reaction tube was closed and the reaction was kept at 60 °C for 24 hours, the completion of reaction was checked with thin layer chromatography techniques. The mixture of reaction was quenched with liquid ammonia, the formed solid was filtered and crude mass was purified by crystallization.

### 1-Phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3A)

Yield: 65% white solid, Mp. 240 ~ 243 °C.  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.61 (d, 1H,  $J=8.1\text{Hz}$ ), 7.57-7.54 (m, 3H), 7.50-7.47 (m, 2H), 7.34 (d, 1H,  $J =8.2\text{Hz}$ ), 7.21(t, 1H,  $J =8.2\text{Hz}$ ), 7.14 (t, 1H,  $J =8.2\text{Hz}$ ), 5.90 (s, 1H), 3.71- 3.62 (m, 1H), 3.64-3.54 (m, 1H), 3.30-3.22 (m, 1H), 3.25-3.21 (m, 1H).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 136.1, 134.2, 131.7, 131.3, 129.4, 129.2, 125.9, 122.8, 120.1, 119.1, 111.6, 107.2, 56.0, 18.5. HRMS [M+H]<sup>+</sup> m/z calcd. for  $\text{C}_{17}\text{H}_{17}\text{N}_2$ , 249.1392; found; 249.1315.

### 1-(p-tolyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3B)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79 (s, 1H), 7.58(d,  $J = 8.7$  Hz, 1H), 7.19 (d,  $J = 3.9$  Hz, 2H), 7.18-7.15 (m, 4H), 7.15 (s, 1H), 5.16 (s, 1H), 3.37 (dt,  $J = 12.0, 4.3$  Hz, 1H), 3.18- 3.10 (m, 1H), 2.98 (ddd,  $J = 17.5, 11.4, 4.4$  Hz, 2H).  $^{13}\text{C}$  (101MHz,  $\text{CDCl}_3$ ) 138.48, 138.05, 135.93, 134.44, 129.50, 128.51, 127.38, 121.72, 119.38, 118.23, 110.89, 110.05, 57.63, 42.62, 22.38, 21.18.

### 2-methoxy-5-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenol (3C)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  9.83 (s, 1H), 7.53 (d,  $J = 6.7$  Hz, 2H), 7.42 (d,  $J = 1.9$  Hz, 1H), 7.22 (d,  $J = 7.0$  Hz, 1H), 7.12 (tt,  $J = 12.7, 3.6$  Hz, 2H), 6.97 (d,  $J = 8.8$  Hz, 1H), 6.86 (s, 1H), 5.08 (s, 1H), 3.87 (s, 3H), 3.41-3.35 (m, 1H), 3.16-3.10 (m, 1H), 2.92-2.87 (m, 1H), 2.81 (dd,  $J = 9.4, 5.9$  Hz, 1H).

### 1-(pyridin-3-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3G)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  9.22 (s, 4H), 8.53 – 8.50 (m, 4H), 8.47 (dd,  $J = 4.8, 1.5$  Hz, 4H), 7.67 (dd,  $J = 10.8, 3.7$  Hz, 9H), 7.34 (d,  $J = 6.6$  Hz, 4H), 7.27 (dd,  $J = 7.8, 5.0$  Hz, 6H), 7.25 – 7.20 (m, 8H), 5.26 (s, 4H), 3.47-3.35 (m, 4H),

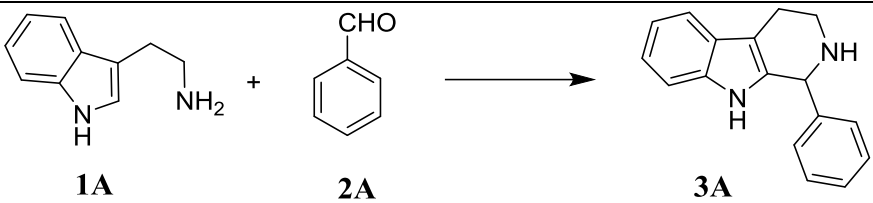
3.32-3.17 (m, 6H),  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  137.93, 136.51, 136.33, 133.39, 127.16, 123.83, 121.83, 119.34, 118.26, 111.07, 110.25, 55.49, 42.62, 22.41.

## Results and discussion

As reported per literature, Hong-Ju Byeon *et al.* used L-tartaric acid in water for the TH $\beta$ C preparation, but it has got very less yield compared with the other literature report. We started our study over the *Pictet-Spengler* reaction by selecting starting substrate for the test reaction, herein we selected tryptamine 1A and benzaldehyde 2A as the starting

moieties. The initial reaction was performed with 0.10 equiv. of citric acid (Table 1 and Entry 1); the experiment was performed about 24 hours, the product was appeared with 24%. When we tested the reaction with increasing with equiv. of citric acid from 0.25 equiv. to 0.50 equiv., it produced 35 to 40% yield (Table 1, Entries 2 and 3). Furthermore, we subsequently have increased the molar equiv. of citric acid to 1.0 equiv. and the reaction was carried out at 60 °C, the generation of TH $\beta$ C was noticed with 60% yield (Table 1 and Entry 4).

**TABLE 1** Development of the reaction protocol

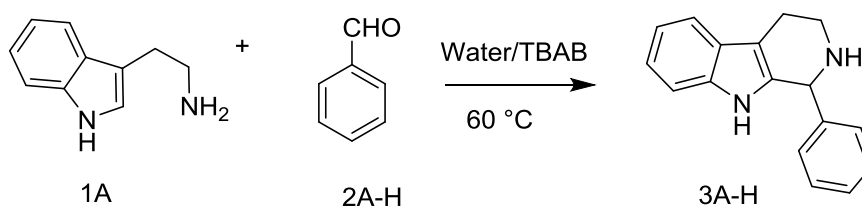


Entry	Reagent	Equiv.	Solvent	Temperature	Yield %
1	Citric acid	0.10	Water	60 °C	34%
2	Citric acid	0.25	Water	60 °C	35%
3	Citric acid	0.50	Water	60 °C	40%
4	Citric acid	1.0	Water	60 °C	60%
5	Citric acid	1.0	Water/TBAB	60 °C	75%
6	Citric acid	1.5	Water/TBAB	60 °C	76%
7	Tartaric acid	1.0	Water/TBAB	60 °C	64%

TBAB= As a phase transfer catalyst

For our further reaction investigation, the reaction was performed with 1 equiv. of citric acid with the addition of phase transfer catalyst one equiv. The formation of tetrahydro- $\beta$ -carboline was observed with 75% yield (Table 1, Entry 5), while by further increase in the equiv., there was no change in the yield of the product.

Whereas, once we developed the novel method for the TH $\beta$ C preparation, we checked the substrate scope of the developed protocol. Therefore, we checked our methodology on the substrate with EWG groups and ED functional groups on one position of substituted group, as displayed in Scheme 1.

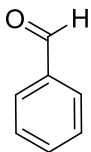
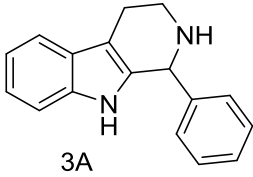
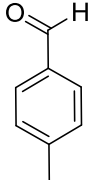
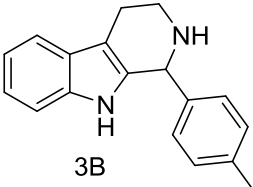
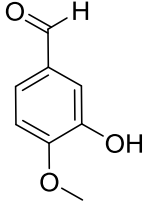
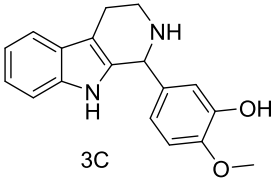
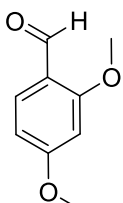
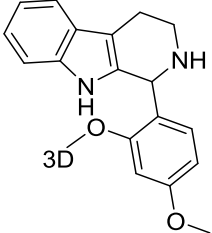
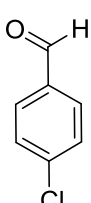
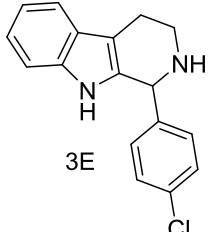
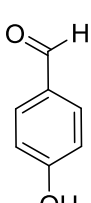
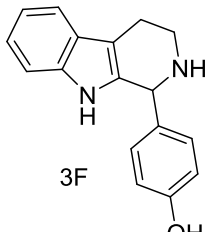


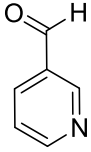
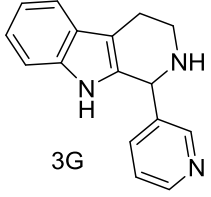
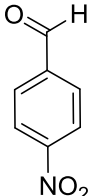
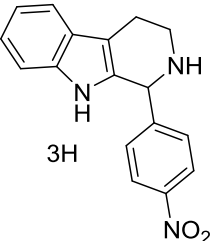
**SCHEME 1** TH $\beta$ C synthesis

The preparation of numerous TH $\beta$ C possessing EWG electron and EDG groups was done on one position of phenyl group. The TH $\beta$ C series was synthesized from the developed protocol with varying substrate (Scheme 1). When the aldehyde having EWG like Cl, F (Table 2), the formation of good

product good was observed, while aryl aldehyde with the EDG groups likes methoxy (OMe), hydroxy (OH), and methyl (Me) gave an excellent yield (Table 2), and in case of hetroaldehy, very less yield was observed as compared with the other substrate.

**TABLE 2** Preparation of tetrahydro- $\beta$ -Carboline derivatives

Sr no.	Starting substrate	Products	Yield (%)	M.P. observed	M.P. literature
11		 3A	65	162-164	162-164[34]
2		 3B	60	132-134 °C	135-137 [25]
3		 3C	62	185-186	185-186[25]
4		 3D	61	208-214	211-213[25]
5		 3E	64	162-163	165-166[27]
6		 3F	55	210-215	211-213[35]

7			5	Light yellow oil	-
8			64	168-172	170-171[36]

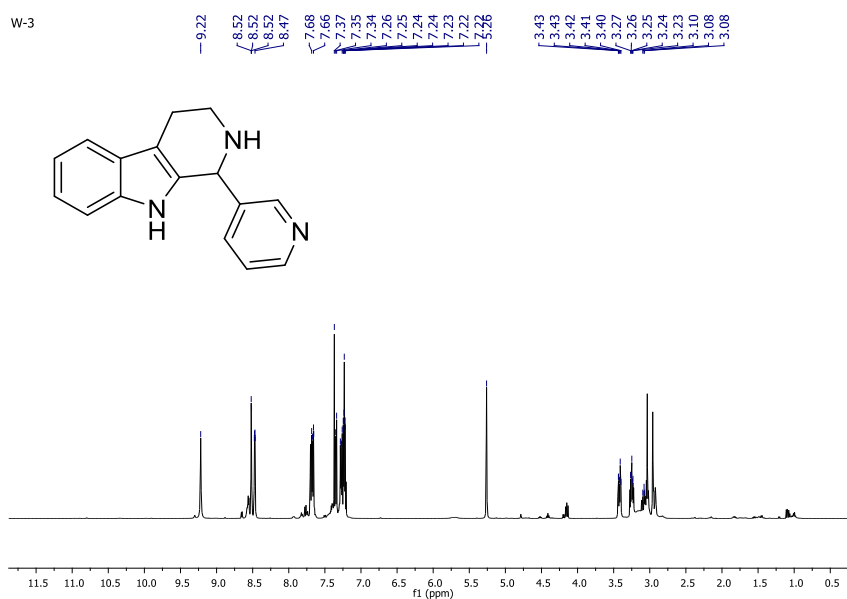


FIGURE 2  $^1\text{H}$  NMR for 1-(pyridin-3-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole [3G]

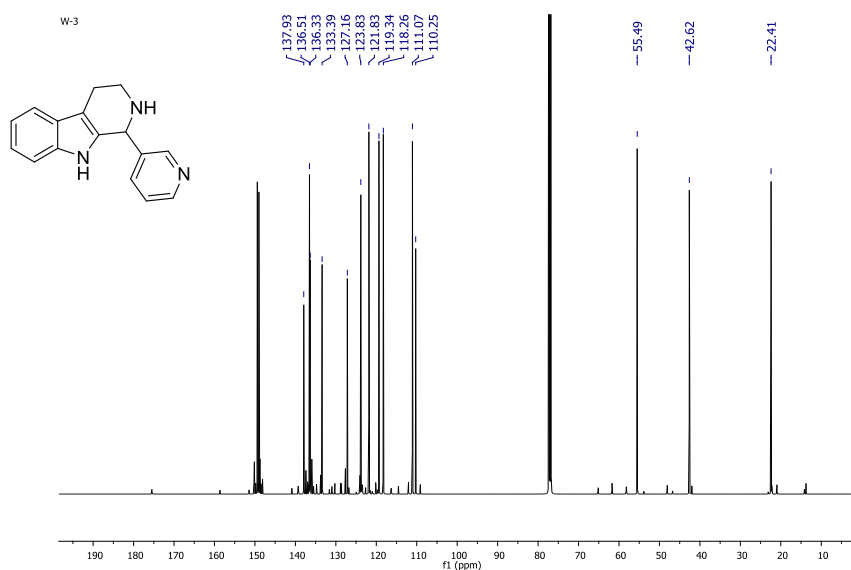
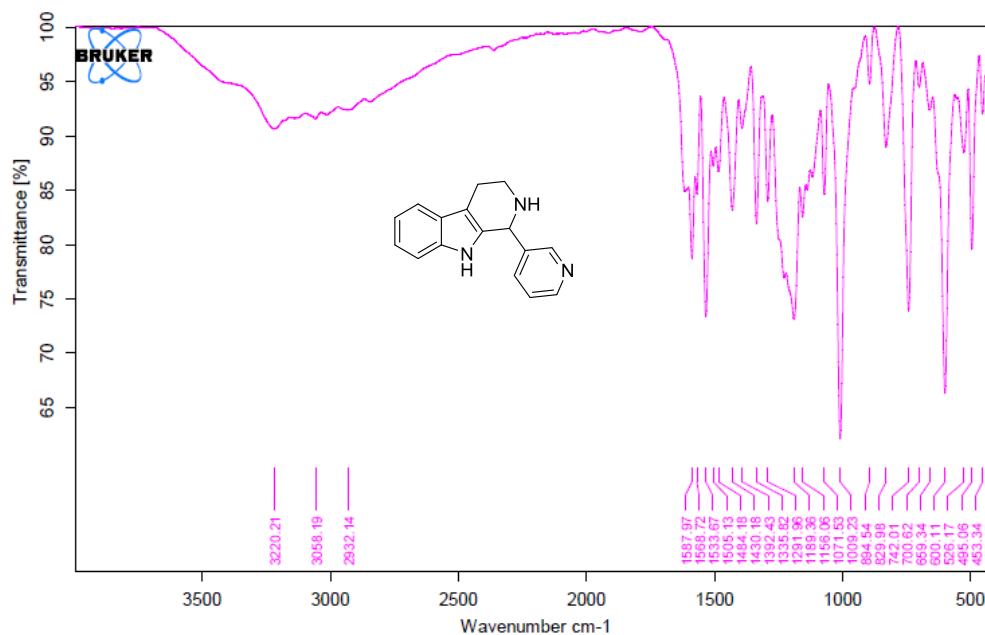


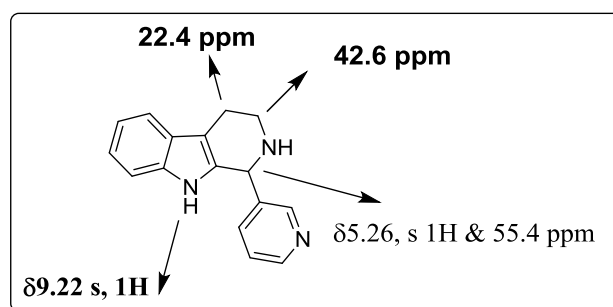
FIGURE 3  $^{13}\text{C}$  NMR for 1-(pyridin-3-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole



**FIGURE 4** FT-IR for 1-(pyridin-3-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole [3G]

The TH $\beta$ C with hero-aldehyde was characterised by the spectral study, the  $^1\text{H}$ NMR spectra for the compound (Figure 4) showed the singlet at 5.26 singlet for the  $^1\text{H}$ . This peak was belonged to the C-1 tertiary carbon proton, while the peak at  $\delta$  9.22 was belonged to N-H proton, this indicates that product are formed, as depicted in Figures 2 and 4. The  $^{13}\text{C}$  NMR spectra showed a

particular peak for the three carbons at aliphatic region and three carbons were observed at 55.4, 42.6, and 22.4 ppm (Figure 4). The FTIR spectra for the compound 3G indicates its peak at 3220  $\text{cm}^{-1}$  for NH stretching and the peak was belonged to 3058  $\text{cm}^{-1}$ , 2932  $\text{cm}^{-1}$  form C-H alkyl group stretching, while the band at 1587  $\text{cm}^{-1}$  was observed for the aromatic group.

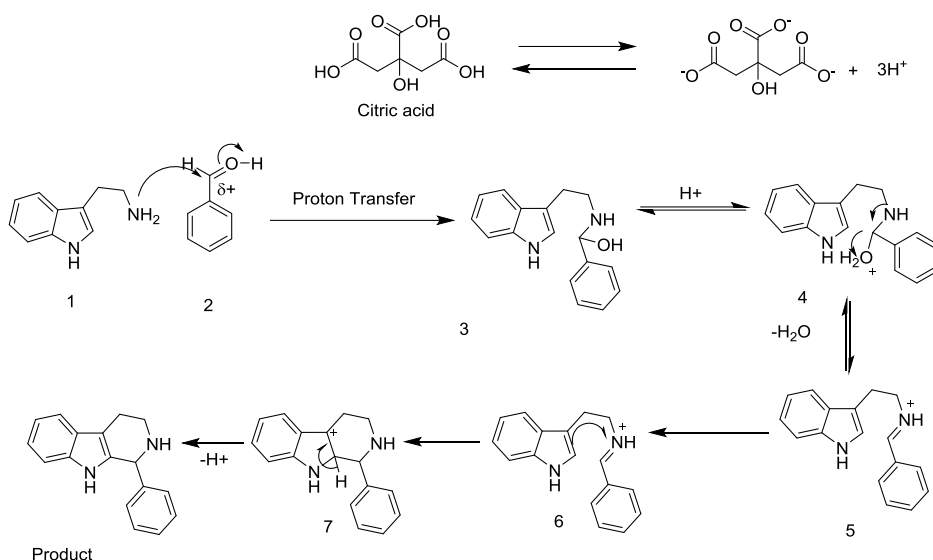


**FIGURE 4** Spectra study of TH $\beta$ C

### Mechanism

As reported per literature, the citric acid has an ionisable proton [37]. We predicted a mechanism of the reaction as citric acid generate proton which enhance the reaction of (1 and 2). Citric acid is a milder acid which can enhance the ketone group with bonding

by hydrogen accelerating the attack of amines 1 to the nucleophilic centre of aldehyde 2 (Scheme 2) [38-44]. The formation of the intermediate imines 5 is the initial step (Schiff base). The intermediate which was undergone 6-endo-trig cyclization gave 7, followed by dehydrogenation that produced the desired TH $\beta$ C products (Scheme 2).



**SCHEME 2** The proposed mechanism for *SP* reaction by using citric acid

## Conclusion

To sum up, we developed a novel greener protocol for the TH $\beta$ C preparation from the *Pictet-Spengler* reactions of tryptamine with aldehyde with an excellent yield compared with the literature. The reaction was performed by using the greener reagent citric acid and water as a solvent. The method is milder with a simple operation and the reagent was further dissolved in the H<sub>2</sub>O and it was easily detached, the product was purified by the laboratory techniques.

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## Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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