

## New strategy for the syntheses of (+/-)-latifine and (+/-)-cherylline dimethyl ethers

A.Sanjeev Kumar,<sup>a</sup> Samir Ghosh,<sup>a</sup> R.Soundararajan,<sup>a\*</sup> and G. N. Mehta<sup>b</sup>

<sup>a</sup>Chemical Research and Development Department, Pfizer Ltd, Mumbai-400705, India

<sup>b</sup>Applied Chemistry Department, S. V. National Institute of Technology, Surat-395 007, India

Email: [soundara1959@rediffmail.com](mailto:soundara1959@rediffmail.com)

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### Abstract

A concise route for the synthesis of (+/-)-latifine and (+/-)-cherylline dimethyl ethers is reported. The key steps involved are the Michael type addition of *p*-methoxybenzene magnesium bromide to the (*E*)-1,2-dimethoxy-3-(2-nitrovinyl)benzene, reduction of the nitro intermediate obtained followed by the Pictet-Spengler cyclization and reductive *N*-methylation.

**Keywords:** Michael addition, Grignard reagent, reduction, tetrahydroisoquinolines, Pictet-Spengler cyclization, reductive N-methylation

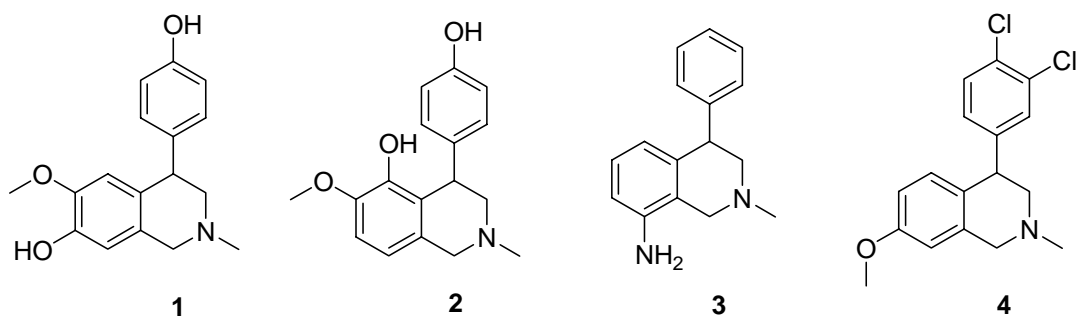
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### Introduction

Synthetic studies on aryl-1,2,3,4-tetrahydroisoquinolines have attracted much attention from synthetic community owing to the potential biological activities of this class of compounds and their increasing medicinal interest. Among these heterobicyclic compounds cherylline **1**, a rare phenolic 4-phenyltetrahydroisoquinoline alkaloid and its dimethylether **5** whose structures are unique for *Amaryllidaceae* alkaloids have long been fascinating targets for organic chemists as witnessed by a number of articles dealing with biogenesis isolation, characterization and synthesis. Cherylline **1** and latifine **2** are the two 4-aryltetrahydroisoquinoline alkaloids isolated from *Amaryllidaceae* plants.<sup>1-2</sup> Apart from the natural occurrence, 4-aryltetrahydroisoquinolines are of interest due to various pharmacological activities.<sup>3-4</sup> For example, nomifensine<sup>5-6</sup> **3** and dichlofensine<sup>7-8</sup> **4** exhibit central nervous system activity and inhibit serotonin and dopamine uptake mechanisms (Figure 1).

There are several reports<sup>9-28</sup> on the syntheses of latifine and cherylline which include some efficient chiral syntheses. Most of the reported methods for the synthesis of these molecules are multistep. We report herein an alternative synthesis of (+/-)-latifine and (+/-)-cherylline dimethyl ethers. The key steps for latifine was the Michael type addition of *p*-methoxybenzene magnesium bromide to the (*E*)-1,2-dimethoxy-3-(2-nitrovinyl)-benzene, for cherylline Michael type addition

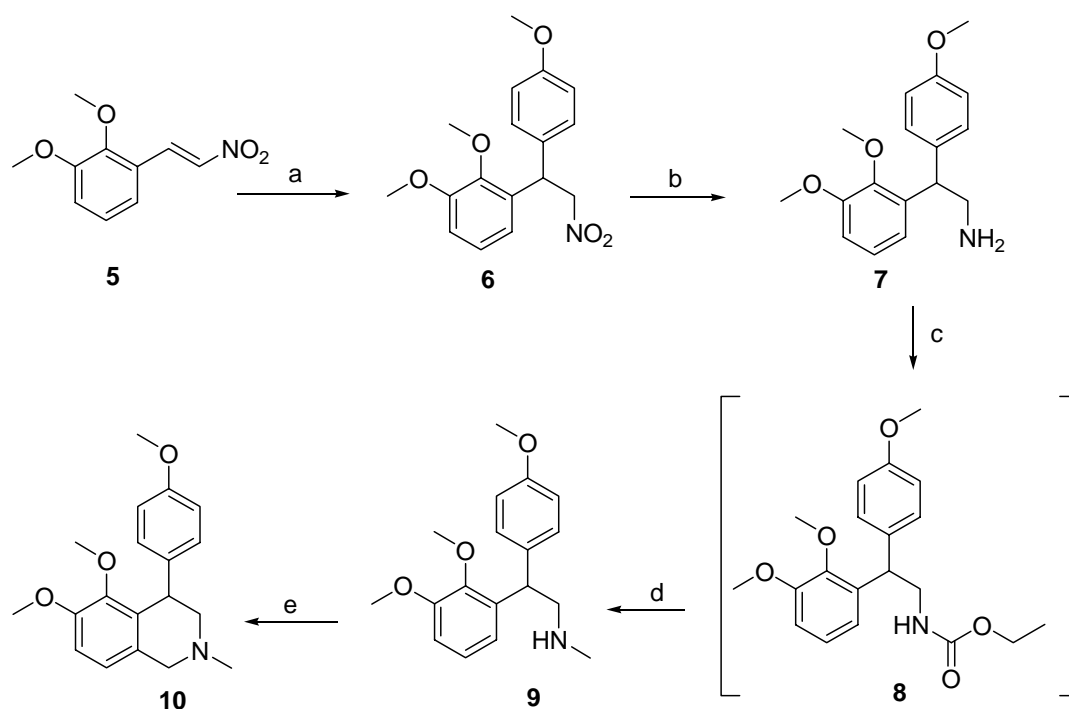
of anisole with (*E*)-1,2-dimethoxy-4-(2-nitrovinyl)benzene, reduction of nitro intermediate followed by the Pictet-Spengler cyclization and reductive *N*-methylation.



**Figure 1**

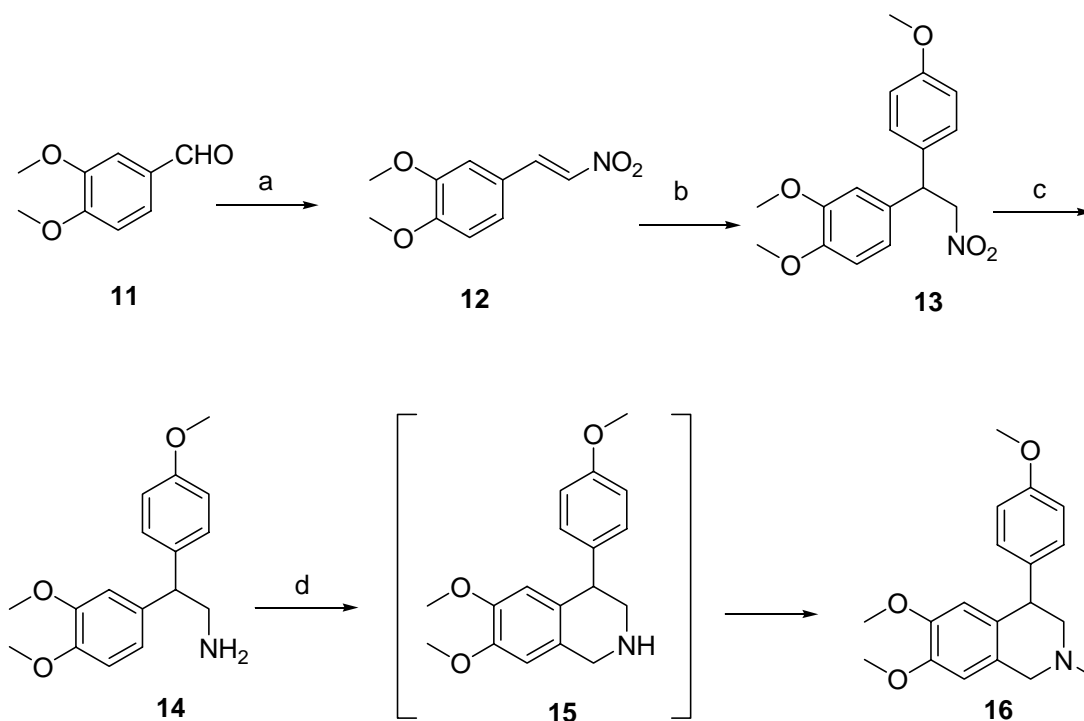
## Results and Discussion

The Michael type addition of *p*-methoxybenzenemagnesium bromide to (*E*)-1,2-dimethoxy-3-(2-nitrovinyl)benzene **5** in presence of small amount of copper iodide led to the formation of 1,2-dimethoxy-3-(1-(4-methoxyphenyl)-2-nitroethyl)benzene **6** in 50% yield. Reduction of the nitro group with iron under acidic conditions in THF gave 2-(2,3-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanamine **7** in 80% yield. Reaction with ethyl chloroformate using triethylamine as a base at room temperature gave the ethyl 2-(2,3-dimethoxyphenyl)-2-(4-methoxyphenyl)ethylcarbamate intermediate **8**. Immediate reduction of the latter by lithium aluminium hydride gave 2-(2,3-dimethoxyphenyl)-2-(4-methoxyphenyl)-*N*-methylethanamine **9** in 80% yield. The crude amine **6**, upon the Pictet-Spengler reaction gave (+/-)-latifine dimethyl ether **10** in 40% yield (Scheme 1).



**Scheme 1.** (a) *P*-Methoxyphenylmagnesium bromide, THF, 25-35 °C, 5.0 h, 50%. (b) Fe, Acetic acid, THF, 70 °C, 3.0 h, 80%. (c) Ethyl chloroformate, TEA, THF, 0-5 °C. (d) LAH, THF, reflux, 4.0 h, 80%. (e) HCHO, Acetic acid, 90 °C, 2.0 h, 40%.

Anisole on reaction with (*E*)-1,2-dimethoxy-4-(2-nitrovinyl)benzene **12** in presence of trifluoroacetic acid to obtain 1,2-dimethoxy-4-(1-(4-methoxyphenyl)-2-nitroethyl) benzene **13** in 90% yield. Reduction of the nitro group with iron under acidic conditions in THF at reflux gave 2-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanamine **14** in 74% yield. The amine **14**, upon the Pictet-Spengler reaction and reductive *N*-methylation gave (+/-)-cherylline dimethyl ether **16** in 43% yield (Scheme 2).



**Scheme 2.** (a) Nitromethane,  $\text{CH}_3\text{COONH}_4$ , Acetic acid, 100 °C, 4.0 h, 80%. (b) Anisole, TFA, reflux, 3.0 h, 90.0%. (c) Fe, Acetic acid, THF, 70 °C, 3.0 h, 74%. (d) Formaldehyde, Formic acid, 95 °C, 18.0 h, 43%.

In conclusion, we have devised a very short and efficient method for the synthesis of (+/-)-latifine and (+/-)-cherylline dimethyl ethers.

## Experimental Section

**General.** All solvents and reagents were purchased from Aldrich and Alfa aesar suppliers and used without further purification. All non-aqueous reactions were performed in dry glassware under an atmosphere of dry nitrogen. Organic solutions were concentrated under reduced pressure. Thin layer chromatography was performed on Merck precoated Silica-gel 60F<sub>254</sub> plates. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in DMSO-d<sub>6</sub> using 400 MHz, on a Varian Gemini 400 MHz FT NMR spectrometer. The chemical shifts were reported in  $\delta$  ppm relative to TMS. The mass spectra were recorded on Shimadzu LCMS-QP 800 LC-MS and AB-4000 Q-trap LC-MS/MS. Elemental analyses were performed on a Flash EA-1112 instrument. Melting points were obtained by using the open capillary method and are uncorrected.

**1,2-Dimethoxy-3-(1-(4-methoxyphenyl)-2-nitroethyl)benzene (6).** *P*-Methoxyphenyl magnesium bromide (1.0 M in THF, 14.8 g, 0.07 mol) was added to the mixture of **5** (7.0 g, 0.033 mol),

copper iodide (10 mg) and dry THF (50 mL) under inert atmosphere at 0 °C over 30 min. After stirring for 5 h at 25-35 °C, the reaction mixture was poured into a saturated ammonium chloride solution (50 mL). The product was extracted in ethyl acetate (2 x 50 mL) and combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to obtain 10.6 g of crude **6**. Purification of crude product by column chromatography on silica gel using ethyl acetate: hexane (20: 80) as an eluent gave **6** as an oil (5.3 g, 50%); IR (KBr, cm<sup>-1</sup>): 1550 (NO<sub>2</sub>); HRMS m/z calculated for C<sub>17</sub>H<sub>19</sub>NO<sub>5</sub> -318.1263 [M+1], found -318.1260; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) (δ ppm): 3.72 (3H, s, -OCH<sub>3</sub>), 3.74 (3H, s, -OCH<sub>3</sub>), 3.86 (3H, s, -OCH<sub>3</sub>), 4.65 (1H, t, *J* = 8.8 Hz, Ar-CH-Ar), 5.19 (2H, d, *J* = 8.8 Hz, CH<sub>2</sub>-NO<sub>2</sub>), 6.78-6.98 (5H, m, ArH), 7.21 (2H, d, *J* = 8.0 Hz, ArH); <sup>13</sup>C NMR (400 MHz, DMSO-d<sub>6</sub>) (δ ppm); 46.8, 55.4, 55.8, 60.5, 79.2, 111.6, 114.4, 120.3, 121.9, 129.1, 131.9, 132.7, 147.8, 152.4, 157.2.

**2-(2,3-Dimethoxyphenyl)-2-(4-methoxyphenyl)ethanamine (7)**. A mixture of **6** (6.0 g, 0.018 mol), iron (10.5 g, 0.189 mol), acetic acid (60 mL) and THF (60 mL) was stirred at 65 °C under inert atmosphere for 3.0 h. After cooling to 25 °C, the reaction mixture was filtered over celite and washed with THF (50 mL). The filtrate was basified with 50 % sodium hydroxide solution. This basified solution was extracted in ethyl acetate (3 x 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to obtain 9.6 g of crude **7**. Purification of crude product by column chromatography on silica gel using methanol: chloroform (10: 90) as an eluent gave **7** as an oil (4.3 g, 80%); IR (KBr, cm<sup>-1</sup>): 3320 (NH<sub>2</sub>); HRMS m/z calculated for C<sub>17</sub>H<sub>21</sub>NO<sub>3</sub>-288.1521 [M+1], found -288.1522; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) (δ ppm): 3.03 (2H, d, *J* = 7.8 Hz, -CH<sub>2</sub>-NH<sub>2</sub>), 3.54 (3H, s, -OCH<sub>3</sub>), 3.66 (3H, s, -OCH<sub>3</sub>), 3.72 (3H, s, -OCH<sub>3</sub>), 4.21 (1H, t, *J* = 7.8 Hz, CH-CH<sub>2</sub>), 6.78-6.98 (5H, m, ArH), 7.13 (2H, d, *J* = 8.0 Hz, ArH); <sup>13</sup>C NMR (400 MHz, DMSO-d<sub>6</sub>) (δ ppm); 47.2, 46.8, 55.3, 55.9, 60.4, 111.0, 114.0, 119.6, 124.2, 129.4, 135.9, 137.5, 147.0, 152.9, 157.9.

**2-(2,3-Dimethoxyphenyl)-2-(4-methoxyphenyl)-N-methylethanamine (9)**. Ethyl chloroformate (0.83 g, 0.007 mol) in dry THF (10 mL) was added to the mixture of amine **7** (2.0 g, 0.007 mol), triethyl amine (1.4 g, 0.013 mol) and THF (35 mL) under inert atmosphere at 0 °C over 30 min. the mixture was then stirred for 1.0 h at 0-5 °C. Concentration of reaction mixture under vacuum gave amide **8**, which was pure (by TLC). The amide **8** in dry THF (15 mL) was slowly added to the suspension of lithium aluminium hydride (0.52 g, 0.013 mol) in THF (15 mL) under inert atmosphere. After refluxing (65 °C) for 4.0 h, the reaction mixture was cooled to 0-5 °C and chilled water was slowly added to it. The aluminium hydroxide formed was filtered over celite and washed with chloroform. The filtrate also was extracted with chloroform (60 mL). All the organic extracts and washings were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to obtain **9** as a brown residue 1.6 g (80.0 %); IR (KBr, cm<sup>-1</sup>): 3120 (NH); HRMS m/z calculated for C<sub>18</sub>H<sub>23</sub>NO<sub>3</sub> 302.3801 [M+1], found -302.3811; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (δ ppm): 2.23 (3H, s, NCH<sub>3</sub>), 2.96 (2H, d, *J* = 7.6 Hz, CH<sub>2</sub>-NCH<sub>3</sub>), 3.55 (3H, s, OCH<sub>3</sub>), 3.65 (3H, s, OCH<sub>3</sub>), 3.72 (3H, s, OCH<sub>3</sub>), 4.40 (1H, t, *J* = 7.6 Hz, Ar-CH-Ar), 6.77-6.97 (5H, m, ArH), 7.13 (2H, d, *J* = 8.8 Hz, ArH); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) (δ ppm); 40.5, 42.5, 55.3, 55.9, 56.5, 60.4, 111.0, 114.0, 119.7, 124.2, 129.3, 135.9, 137.6, 146.8, 152.8, 157.9.

**(+/-)-Latifine dimethyl ether (10).** A mixture of **9** (2.0 g, 0.006 mol), formaldehyde (0.64 g, 0.007 mol) and acetic acid (5 mL) was stirred at 90 °C under inert atmosphere for 3.0 h. After cooling to room temperature, the reaction mixture was basified with 50% aqueous NaOH solution. This basified solution was extracted in ethyl acetate (75 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to obtain 1.1 g of crude product. The crude was chromatographed on silica gel eluting with 1% methanol in dichloromethane as an eluent gave **10** (0.82 g, 40 %), as a white solid, mp 86-88 °C (lit<sup>21</sup> mp 86-88 °C); IR (KBr, cm<sup>-1</sup>): 1620, 1520; HRMS m/z calculated for C<sub>19</sub>H<sub>23</sub>NO<sub>3</sub> 314.1756 [M+1], found - 314.1758; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (δ ppm): 2.32 (3H, s, NCH<sub>3</sub>), 2.70 (2H, d, *J* = 4.4 Hz, CH-CH<sub>2</sub>-N), 3.20 (3H, s, OCH<sub>3</sub>), 3.75 (3H, s, OCH<sub>3</sub>), 3.79 (3H, s, OCH<sub>3</sub>), 3.34 and 3.80 (each 1H, d, *J* = 14.4 Hz, Ar-*HCH*-N), 4.26 (1H, t, *J* = 4.4 Hz, Ar-CH-Ar), 6.76-6.80 (4H, m, ArH), 7.11 (2H, d, *J* = 8.8 Hz, ArH); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) (δ ppm); 40.5, 46.1, 55.1, 55.7, 57.9, 59.4, 61.5, 111.1, 113.1, 121.1, 128.7, 129.3, 130.2, 139.9, 147.8, 151.1, 157.6.

**(E)-1,2-Dimethoxy-4-(2-nitrovinyl)benzene (12).** A mixture of **11** (10.0 g, 0.06 mol), nitromethane (7.3 g, 0.12 mol), ammonium acetate (9.2 g, 0.12 mol) and glacial acetic acid (50 mL) was stirred at 100 °C under inert atmosphere for 4.0 h. After cooling to room temperature, the precipitated solid was filtered and washed with glacial acetic acid followed by hexane wash (50 mL) and dried to gave **12** (10.1 g, 80%), as a yellow solid, mp 142-143 °C (lit<sup>29</sup> mp 142-143 °C); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) (δ ppm): 3.77 (3H, s, -OCH<sub>3</sub>), 3.80 (3H, s, -OCH<sub>3</sub>), 7.01 (1H, d, *J* = 8.8 Hz, ArH), 7.39 (1H, d, ArH, *J* = 8.4 Hz, ArH), 7.45 (1H, s, ArH), 8.01 (1H, d, *J* = 14 Hz, -CH), 8.16 (1H, d, *J* = 14 Hz, -CH); <sup>13</sup>C NMR (400 MHz, DMSO-d<sub>6</sub>) (δ ppm); 55.8, 55.9, 111.9, 114.2, 121.4, 126, 138.4, 138.6, 149.7, 151.5; MS (m/z): 210 [M<sup>+</sup> + 1].

**1,2-Dimethoxy-4-(1-(4-methoxyphenyl)-2-nitroethyl) benzene (13).** A solution of **12** (6.0 g, 0.028 mol) and anisole (12.4 g, 0.114 mol) in trifluoroacetic acid (TFA) (30 mL) was refluxed for 3.0 h. TFA was distilled under vacuum and saturated NaHCO<sub>3</sub> (50 mL) was added. This aqueous phase was extracted in ethyl acetate (90 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to obtain 12.0 g of crude **13**. Purification of crude product by column chromatography on silica gel using ethyl acetate: hexane (20: 80) as an eluent gave **13** as an oil (9.6 g, 90 %); IR (KBr, cm<sup>-1</sup>): 1550 (NO<sub>2</sub>); HRMS m/z calculated for C<sub>17</sub>H<sub>19</sub>NO<sub>5</sub>-318.1263 [M+1], found -318.1259; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) (δ ppm): 3.62 (3H, s, -OCH<sub>3</sub>), 3.64(3H, s, -OCH<sub>3</sub>), 3.66 (3H, s, -OCH<sub>3</sub>), 4.63 (1H, t, *J* = 8.8 Hz, Ar-CH-Ar), 5.21 (2H, d, *J* = 8.8 Hz, CH<sub>2</sub>-NO<sub>2</sub>), 6.77 (2H, d, *J* = 8.8 Hz, ArH), 6.79-6.81 (2H, m, ArH), 6.94 (1H, s, ArH), 7.26 (2H, d, *J* = 8.8 Hz, ArH); <sup>13</sup>C NMR (400 MHz, DMSO-d<sub>6</sub>) (δ ppm); 47.8, 55.4, 55.8, 55.9, 79.1, 111.9, 112.2, 114.3, 119.8, 129.0, 132.8, 133.3, 148.1, 149.1, 158.5.

**2-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)ethanamine (14).** A mixture of **13** (6.0 g, 0.018 mol), iron (10.5 g, 0.189 mol), acetic acid (60 mL) and THF (60 mL) was stirred at 65 °C under inert atmosphere for 3.0 h. After cooling to 25 °C, the reaction mixture was filtered over celite and washed with THF (50 mL). The filtrate was basified with 50 % sodium hydroxide solution. This basified solution was extracted in ethyl acetate (3 x 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to obtain 9.6 g of crude **14**. Purification of crude product by column

chromatography on silica gel using methanol: chloroform (10: 90) as an eluent gave **14** as an oil (4.0 g, 74 %); IR (KBr,  $\text{cm}^{-1}$ ): 3320 ( $\text{NH}_2$ ); HRMS  $m/z$  calculated for  $\text{C}_{17}\text{H}_{21}\text{NO}_3$ -288.1521 [ $\text{M}+1$ ], found - 288.1529;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ ) ( $\delta$  ppm): 3.03 (2H, d,  $J = 7.8$  Hz, -CH- $\text{CH}_2$ -), 3.62 (3H, s, - $\text{OCH}_3$ ), 3.63 (3H, s, - $\text{OCH}_3$ ), 3.65 (3H, s, - $\text{OCH}_3$ ), 3.73 (1H, t,  $J = 7.8$  Hz, CH- $\text{CH}_2$ ), 6.69 (2H, d,  $J = 8.8$  Hz, ArH), 6.76-6.78 (2H, m, ArH), 6.80 (1H, s, ArH), 7.11 (2H, d,  $J = 8.8$  Hz, ArH);  $^{13}\text{C}$  NMR (400 MHz,  $\text{DMSO-d}_6$ ) ( $\delta$  ppm); 47.2, 53.7, 55.3, 55.8, 55.9, 112.2, 112.3, 114.1, 119.9, 129.1, 136.3, 136.8, 147.5, 149.0, 157.9.

(+/-)-**Cherylline dimethyl ether (16)**. A mixture of **14** (2.0 g, 0.007 mol), formaldehyde (2.81 g, 0.034 mol) and formic acid (6 mL) was stirred at 95 °C under inert atmosphere for 18.0 h. After cooling to room temperature, the reaction mixture was basified with 50% aqueous NaOH solution. This basified solution was extracted in ethyl acetate (60 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to obtain 1.3 g of crude product. Purification of this crude product by column chromatography using 1% methanol in dichloromethane as an eluent gave **16** (0.93 g, 43 %), as a white solid, mp 89-91 °C (lit<sup>28</sup> mp 90-92 °C); IR (KBr,  $\text{cm}^{-1}$ ): 1612; HRMS  $m/z$  calculated for  $\text{C}_{19}\text{H}_{23}\text{NO}_3$  314.1756 [ $\text{M}+1$ ], found - 314.1719;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) ( $\delta$  ppm): 2.41 (3H, s,  $\text{NCH}_3$ ), 2.44 (1H, dd,  $J = 11.8$  Hz, CH- $\text{HCH-N}$ ), 2.98 (1H, dd,  $J = 11.8$  Hz, CH- $\text{HCH-N}$ ), 3.56 (2H, s (br), Ar- $\text{CH}_2\text{-N}$ ), 3.65 (3H, s,  $\text{OCH}_3$ ), 3.80 (3H, s,  $\text{OCH}_3$ ), 3.86 (3H, s,  $\text{OCH}_3$ ), 4.12 (1H, t,  $J = 5.4$  Hz, Ar-CH-Ar), 6.34 (1H, s, ArH), 6.56 (1H, s, ArH), 6.84 (2H, d,  $J = 8.8$  Hz, ArH), 7.11 (2H, d,  $J = 8.8$  Hz, ArH);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ) ( $\delta$  ppm); 43.9, 45.9, 55.3, 55.81, 55.86, 57.7, 61.6, 109.7, 112.5, 113.9, 127.7, 129.2, 130.0, 137.7, 147.5, 147.6, 158.0.

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