# An efficient synthesis of (+/-) cherylline dimethyl ether

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A concise route for the synthesis of (+/-) cherylline dimethyl ether is reported. The key steps involved are Grignard reaction, conversion of alcohol to nitrile using (N-(*p*-toluene sulfonyl)imidazole and sodium cyanide), reduction of the nitrile intermediate followed by Pictet–Spengler cyclisation and reductive N-methylation in a single step to provide cherylline dimethyl ether as a racemate.

**Keywords:** Grignard reaction, reduction, tetrahydroisoquinolines, Pictet-Spengler cyclisation, reductive N-methylation

Synthetic studies on aryl-l,2,3,4-tetrahydroisoquinolines have attracted much attention from the 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, characterisation and synthesis. Cherylline **1** and latifine **2** are the two 4-aryltetrahydroisoquinoline alkaloids isolated from Amaryllidaceae plants.[1-2] Apart from the natural existence, 4-aryltetrahydroisoquinolines are of interest due to various pharmacological activities.[3,4] For example, nomifensine[5,6] **3** and dichlofensine[7,8] **4** exhibit central nervous system activity and inhibit serotonin and dopamine uptake mechanisms (Fig. 1).

There are several reports[9-29] on the syntheses of (+/-) cherylline and of (+/-) latifine which include some efficient chiral syntheses. Most of the reported methods for the synthesis of (+/-) cherylline are multistep. We report herein an alternative synthesis of (+/-) cherylline dimethyl ether.

## Results and discussion

Our retrosynthetic analysis of (+/-) cherylline dimethyl ether **5** is depicted in Scheme 1. We anticipated that **5** could be constructed from amine **6** via a Pictet–Spengler ring annulation which, in turn, could be obtained by reduction of the corresponding nitrile intermediate **7**. The required nitrile intermediate would arise from the Grignard reaction of *p*-methoxyphenyl magnesium bromide with 3, 4-dimethoxy-benzaldehyde **8,** followed by conversion of alcohol to nitrile by N-(*p*-toluene sulfonyl) imidazole and sodium cyanide.

Veratraldehyde was subjected to Grignard reaction with *p*-methoxyphenyl magnesium bromide to obtain (3,4-dimethoxyphenyl)(4-methoxyphenyl)methanol **9** in 90% yield. The obtained alcohol was converted to 2-(3,4-dimethoxyphenyl)-2-(4-methoxy phenyl) acetonitrile **7** using (N-(*p*-toluene sulfonyl)imidazole and sodium cyanide) in 60% yield. Reduction of the nitrile group with LAH in THF at reflux temperature gave 2-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanamine **6** in 90% yield. Reaction with formaldehyde and formic acid for 18 hours at reflux leads to Pictet–Spengler reaction with N-methylation reaction in a single step and provides (+/-) cherylline dimethyl ether **5** in 60% yield (Scheme 2).

In short, we have devised a short and efficient method for the synthesis of (+/-) cherylline dimethyl ether. The simple nature of tetrahydroisoquinoline synthesis should allow the construction of a wide variety of interesting and useful analogous molecules.

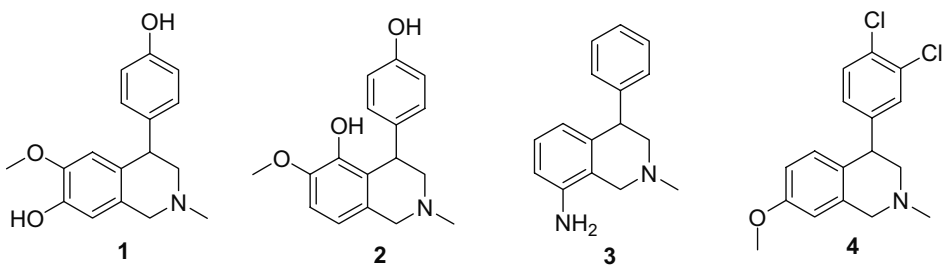
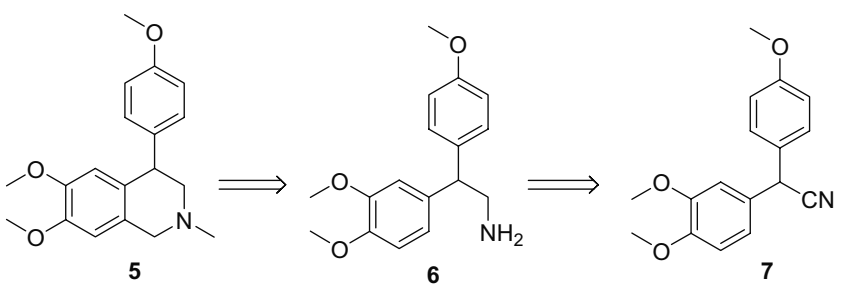



**Fig. 1**




**Scheme 1**

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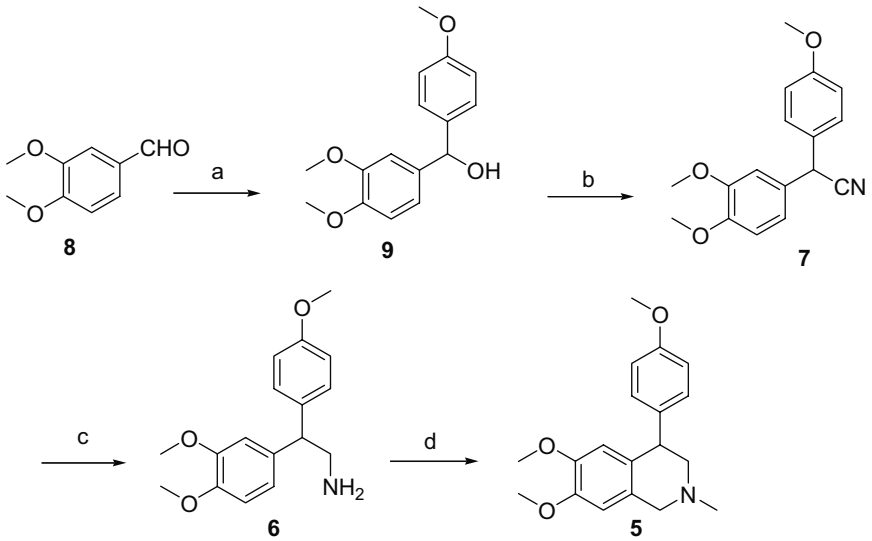


**Scheme 2** (a) 4-bromoanisole, Mg, THF, 0–5 °C, 5.0 h, 80%; (b) N-(*p*-toluene sulfonyl) imidazole, NaCN, TEA, DMF, reflux, 12.0 h, 60.0%; (c) LAH, THF, 70 °C, 24.0 h, 90%; (d) formaldehyde, formic acid, 90 °C, 18.0 h, 60%.

## Experimental

All solvents and reagents were purchased from Aldrich supplier 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 $60F_{254}$ plates. $^1H$ and $^{13}C$ NMR spectra were recorded in DMSO-$d_6$ using 400 MHz, on a Varian Gemini 400 MHz FT NMR spectrometer. The chemical shifts were reported in δ 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.

*(3,4-Dimethoxyphenyl)(4-methoxyphenyl)methanol* **(9):** *p*-Methoxyphenyl magnesium bromide was prepared in the usual manner from magnesium, (3.0 g, 0.128 mol) and 4-bromoanisole (20.0 g, 0.106 mol) in tetrahydrofuran (100 mL). To this solution was added a solution of 3, 4-dimethoxybenzaldehyde **8** (12.0 g, 0.072 mol) in tetrahydrofuran (35 mL) at 0–5 °C, this solution was stirred at room temperature for 5 hours. After completion of the reaction, the reaction mixture was cooled to 0–5 °C and to this was added (50 mL) of saturated ammonium chloride solution and ethyl acetate (100 mL). The separated organic layer was washed twice with water (50 mL). The separated organic layer was dried over sodium sulfate and evaporated under vacuum. The residue was chromatographed on silica gel eluting with hexane:ethyl acetate 80:20 to get the title compound **9** as an oil (17.9 g, 90%); HRMS *m/z* calculated for $C_{16}H_{18}O_4$ –275.1205 [M + 1], found –275.1212; $^1H$ NMR (400 MHz, $CDCl_3$) (δ ppm): 2.22 (1H, d, $J$ = 3.2 Hz, –OH), 3.79 (3H, s, $–OCH_3$), 3.84 (3H, s, $–OCH_3$), 3.85 (3H, s, $–OCH_3$), 5.75 (1H, d, $J$ = 3.2 Hz, Ar-CH-Ar), 6.82–6.91 (5H, m, ArH), 7.26 (2H, d, $J$ = 8.8 Hz, ArH); $^{13}C$ NMR (400 MHz, $CDCl_3$) (δ ppm); 55.2, 55.8, 55.9, 75.5, 109.6, 110.8, 113.8, 118.7, 127.7, 136.2, 136.7, 148.3, 148.9, 158.9.

*2-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)acetonitrile* **(7)**: A mixture of (3,4-dimethoxyphenyl)(4-methoxyphenyl)methanol **9** (3.0 g, 0.01 mol), N-(*p*-toluene sulfonyl)imidazole (3.6 g, 0.016 mol), triethylamine (2.2 g, 0.02 mol), NaCN (1.0 g, 0.02 mol) and a catalytic amount of tetrabutylammonium bromide (0.1 g) in DMF (30 mL). was refluxed for 12.0 h. Reflux was continued until TLC monitoring indicated no further improvement in the conversion. The solvent was evaporated under vacuum and the remaining foam was dissolved in dichloromethane (50 mL) and subsequently washed with water (2 × 50 mL). The separated organic layer was dried over sodium sulfate and evaporated under vacuum. The residue was chromatographed on silica gel eluting with hexane:ethyl acetate 80:20 to get the title compound **7** as an oil (1.85 g, 60%); HRMS *m/z* calculated for $C_{17}H_{17}NO_3$-284.1208 [M + 1], found –284.1231; $^1H$ NMR (400 MHz, $CDCl_3$) (δ ppm): 3.80 (3H, s, $–OCH_3$), 3.84 (3H, s, $–OCH_3$), 3.86 (3H, s, $–OCH_3$), 5.04 (1H, s, Ar-CH-Ar), 6.79–6.90 (5H, m, ArH), 7.26 (2H, d, $J$ = 8.8 Hz, ArH); $^{13}C$ NMR (400 MHz, $CDCl_3$) (δ ppm); 41.3, 55.4, 55.8, 55.9, 110.6, 111.3, 114.4, 120.0, 128.0, 128.7, 136.2, 136.5, 148.9, 149.4, 159.3.

*2-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)ethanamine* **(6)**. To a slurry of lithium aluminuim hydride (0.72 g, 0.019 mol) in THF (20 mL) at 0 °C, was added a solution of 2-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)acetonitrile **7** (1.8 g, 0.006 mol) in THF (20 mL). After refluxing for 24 h, the reaction 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 (3 × 20 mL). All the organic extracts and washings were combined, dried over sodium sulfate, filtered and concentrated to obtain **6** as a brown residue 1.6 g (90.0%); HRMS *m/z* calculated for $C_{17}H_{21}NO_3$-288.1521 [M + 1], found – 288.1509; $^1H$ NMR (400 MHz, $CDCl_3$) (δ ppm): 3.03 (2H, d, $J$ = 7.8 Hz, $–CH–CH_2–$), 3.62 (3H, s, $–OCH_3$), 3.63 (3H, s, $–OCH_3$), 3.65 (3H, s, $–OCH_3$), 3.73 (1H, t, $J$ = 7.8 Hz, $CH–CH_2$), 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); $^{13}C$ NMR (400 MHz, $CDCl_3$) (δ 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* **(5):** A mixture of **6** (1.5 g, 0.005 mol), formaldehyde 37% solution in water (1.56 g, 0.052 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 30% aqueous NaOH solution. This basified solution was extracted with ethyl acetate (3 × 25 mL); dried, filtered and concentrated to obtain crude product (1.1 g.). Purification of the crude product by column chromatography using 1% methanol in dichloromethane as an eluent gave **5** (0.97 g, 60%), as a white solid, m.p. 89–91 °C (lit[28] m.p. 90–92 °C); and the solid was dissolved in ethanol, acidified with ethanolic hydrogen chloride, and evaporated. The resulting solid was recrystallised twice from methanol-ether to give (0.8 g.) of **6**.HC1: m.p. 226–228 °C (lit[20] m.p. 227–229 °C); HRMS *m/z* calculated for $C_{19}H_{23}NO_3$ 314.1677 [M + 1], found – 314.1651; $^1H$ NMR (400 MHz, $CDCl_3$) (δ ppm): 2.41 (3H, s, $NCH_3$), 2.44 (1H, dd, $J$ = 11.8 Hz, CH–*H*CH–N), 2.98 (1H, dd, $J$ = 11.8 Hz, CH–HC*H*–N), 3.56 (2H, s (br), Ar-$CH_2$-N), 3.65 (3H, s, $OCH_3$), 3.80 (3H, s, $OCH_3$), 3.86 (3H, s, $OCH_3$), 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); $^{13}C$ NMR (400 MHz, $CDCl_3$) (δ 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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