Convenient synthesis of amaryllidaceae alkaloid, (+/–) latifine dimethyl ether

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

Key words: Grignard reaction, reduction, tetrahydroisoquinolines, Pictet–Spengler cyclisation, reductive N-methylation

Latifine **1** and cherylline **2** are the two 4-aryltetrahydroisoquinoline alkaloids isolated from *Amaryllidaceae plants*.[1,2] Latifine **2**, an isoquinoline alkaloid, has been isolated from *Crinum latifolium L.* and is reported to be a possible anabolic or catabolic metabolite of *O, N-dimethylnorbelladine*. Latifine has two novel features (i) it has a 4-aryl group in an isoquinoline system and (ii) it is oxygenated at the less usual 5,6-positions. Because of these features, synthesis by the usual methods is difficult.

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[9-34] on the syntheses of (+/–) latifine and (+/–) cherylline which include some efficient chiral syntheses. We report here an alternative synthesis of (+/–) latifine dimethyl ether.

Results and discussion

The retrosynthetic analysis of (+/–) latifine dimethyl ether **5** is depicted in Scheme 1.

2,3-Dimethoxy benzaldehyde was subjected to Grignard reaction with *p*-methoxyphenyl magnesium bromide to obtain (2,3-dimethoxyphenyl)(4-methoxyphenyl) methanol **8** in 85% yield. The obtained alcohol was converted to 2-(2,3-dimethoxyphenyl)-2-(4-methoxyphenyl)acetonitrile **7** using thionyl chloride and trimethylsilyl cyanide (TMSCN) in 60% yield. Reduction of the nitrile group with LAH in THF at reflux temperature gave 2-(2,3-dimethoxyphenyl)-2-(4-methoxyphenyl) ethanamine **6** in 27% yield. Reaction with formaldehyde and formic acid for 18 hours at reflux leads to Pictet-Spengler reaction then reductive N-methylation reaction in a single step provides (+/–) latifine dimethyl ether **5** in 58% yield (Scheme 2).

To obtain the optimised reaction conditions for cyanation, we chose the reaction of dibenzylic alcohol with various readily available cyanides. The effect of various cyanides on reaction times and yields were examined. The results are summarised in Table 1. As the data in Table 1 demonstrate, a higher yield of the nitrile and short time were obtained with trimethylsilyl cyanide (TMSCN) in comparison with other cyanides.

We have devised a short and efficient method for the synthesis of (+/–) latifine dimethyl ether. The simple nature of tetrahydroisoquinoline synthesis should allow the construction of a wide variety of interesting and useful analogous molecules.

Experimental

All solvents and reagents were purchased from Aldrich 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.

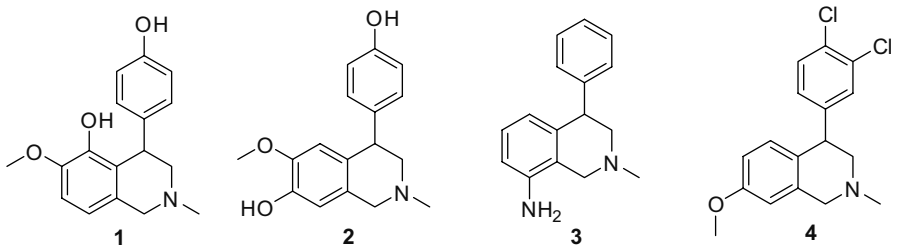
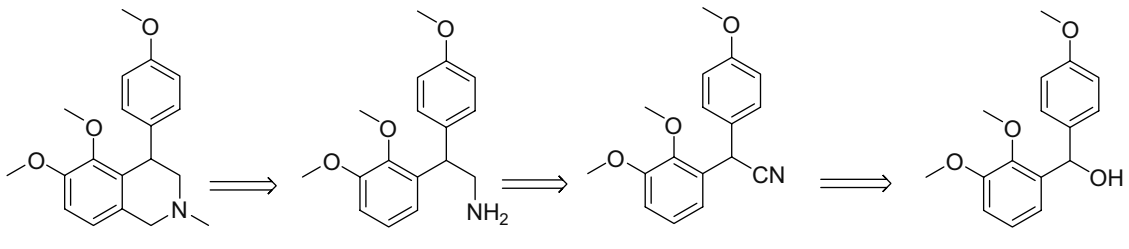


Fig. 1



Scheme 1

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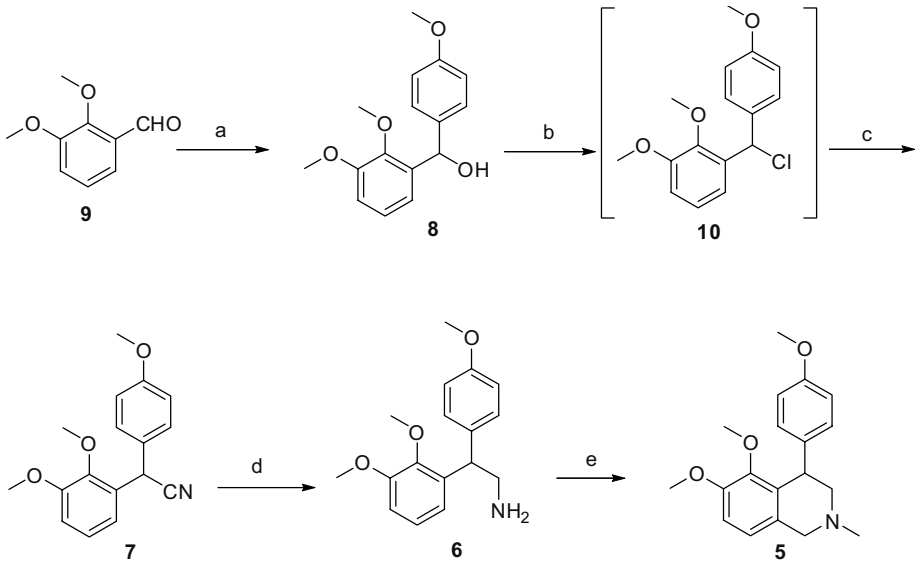

Scheme 2 (a) 4-Bromoanisole, Mg, THF, 0-5 °C, 5 h, 85%; (b) $SOCl_2$, CH_2Cl_2, 25 °C, 10 h, 100%; (c) trimethylsilycyanide, $TiCl_4$, CH_2Cl_2, 25–30 °C, 24 h, 60%; (d) LAH, THF, 70 °C, 24 h, 27%; (e) formaldehyde, formic acid, 90 °C, 18 h, 58%.

Table 1 Effect of various cyanides on conversion of dibenzylic alcohols into dibenzylic nitriles

Entry	Reagent	Catalyst	Solvent	Time/h	Yield/%
1	AgCN	–	MeCN	24	–
2	AgCN	18-crown-6	DMF	6	12
3	CuCN	–	$EtOH/H_2O$	16	10
4	KCN	–	$EtOH/H_2O$	15	12
5	KCN	18-crown-6	$EtOH/H_2O$	6	16
6	KCN	18-crown-6	MeCN	10	–
7	KCN	18-crown-6	DMF	10	16
8	NaCN	–	$EtOH/H_2O$	24	10
9	NaCN	18-crown-6	$EtOH/H_2O$	10	16
10	TMSCN	$SnCl_4$	CH_2Cl_2	24	55
11	TMSCN	$TiCl_4$	CH_2Cl_2	24	60

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. Melting points were obtained by using the open capillary method and are uncorrected.

(2,3-Dimethoxyphenyl)(4-methoxyphenyl)methanol **(8):** *p*-Methoxyphenyl magnesium bromide was prepared in the usual manner from magnesium, (3.0 g, 0.13 mol) and 4-bromoanisole (20.0 g, 0.11 mol) in tetrahydrafuran (100 mL). To this solution was added a solution of 2,3-dimethoxybenzaldehyde **9** (12.0 g, 0.07 mol) in THF (35 mL) at 0–5 °C, this solution was stirred at 25 °C for 5 hours. After completion of the reaction, the reaction mixture was cooled to 0–5 °C and to this was added saturated ammonium chloride solution (50 mL) and ethyl acetate (100 mL). The separated organic layer was washed twice with water (50.0 mL). The separated organic layer was dried over sodium sulfate, filtered and evaporated under vacuum. The residue was chromatographed on silica gel eluting with hexane/ethyl acetate 80:20 to get the title compound **8** as an oil (16.9 g, 85%); HRMS *m/z* calculated for $C_{16}H_{18}O_4$ –275.1205 [M + 1], found –275.1212; ^1H NMR (400 MHz, DMSO-d_6) (δ ppm): 3.52 (3H, s, $–OCH_3$), 3.65 (3H, s, $–OCH_3$), 3.72 (3H, s, $–OCH_3$), 5.85 (1H, d, J = 4.4 Hz, Ar-CH-Ar), 6.78–7.01 (5H, m, ArH), 7.26 (2H, d, J = 8.8 Hz, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) (δ ppm); 55.3, 55.8, 60.2, 68.6, 111.6, 113.6, 119.0, 124.1, 128.1, 138.1, 139.7, 145.6, 152.5, 158.5.

2-(2,3-Dimethoxyphenyl)-2-(4-methoxyphenyl)acetonitrile **(7)**. To a mixture of (2,3-dimethoxyphenyl)(4-methoxyphenyl)methanol **8** (3.0 g, 0.01 mol) in CH_2Cl_2 (30 mL) at 25 °C, was added a solution of thionyl chloride (2.6 g, 0.02 mol) in CH_2Cl_2 (20 mL). The mixture was stirred for 10 h. The solvent was evaporated under vacuum. To the obtained dibenzylic chloride **10** in CH_2Cl_2 (30 mL) was added trimethylsilyl cyanide (2.73 mL, 0.021 mol) and titanium tetrachloride (2.73 mL). After stirring under argon at 25 °C for 24 h, the reaction mixture was quenched with methanol (20 mL) and water (30 mL) and diluted with CH_2Cl_2 (30 mL). The separated organic layer was washed with saturated aqueous sodium bicarbonate (30 mL) and water (30 mL), dried over magnesium sulfate, filtered and evaporated under vacuum to get the crude product. 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): 3.76 (3H, s, $–OCH_3$), 3.77 (3H, s, $–OCH_3$), 3.78 (3H, s, $–OCH_3$), 5.47 (1H, s, Ar-CH-Ar), 6.83–7.03 (5H, m, ArH), 7.25 (2H, d, J = 8.8 Hz, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) (δ ppm); 35.9, 55.2, 55.7, 60.6, 112.6, 114.2, 120.2, 120.3, 124.3, 127.8, 1278.7, 130.1, 146.1, 152.7, 159.2.

2-(2,3-Dimethoxyphenyl)-2-(4-methoxyphenyl) ethanamine **(6):** To a slurry of lithium aluminuim hydride (0.72 g, 0.02 mol) in THF (20 mL) at 0 °C, was added a solution of 2-(2,3-dimethoxyphenyl)-2-(4-methoxyphenyl)acetonitrile **7** (1.8 g, 0.01 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 0.49 g (27%); HRMS *m/z* calculated for $C_{17}H_{21}NO_3$–288.1521 [M + 1], found –288.1522; ^1H NMR (400 MHz, DMSO-d_6) (δ ppm): 3.03 (2H, d, J = 7.8 Hz, $–CH_2–NH_2$), 3.54 (3H, s, $–OCH_3$), 3.66 (3H, s, $–OCH_3$), 3.72 (3H, s, $–OCH_3$), 4.21 (1H, t, J = 7.8 Hz, $CH–CH_2$), 6.78–6.98 (5H, m, ArH), 7.13 (2H, d, J = 8.0 Hz ArH); ^{13}C NMR (400 MHz, DMSO-d_6) (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.

(+/–) Latifine 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 ethyl acetate (3 × 25 mL), dried, filtered and concentrated to

obtain the crude product. Purification of the crude product by column chromatography using 1% methanol in dichloromethane as an eluent gave **5** (0.94 g, 58%), as a solid, m.p. 86–88 °C (lit[30] m.p. 86–88 °C); HRMS *m/z* calculated for $C_{19}H_{23}NO_3$ 314.1756 [M + 1], found – 314.1758; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 2.32 (3H, s, NCH_3), 2.70 (2H, d, J = 4.4 Hz, CH–CH_2–N), 3.20 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 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); ^{13}C NMR (400 MHz, $CDCl_3$) (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.

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