

Alternative synthesis of (+/-) Cherylline dimethyl ether

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Dedicated to Professor S. K. Paknikar on his 73rd birthday

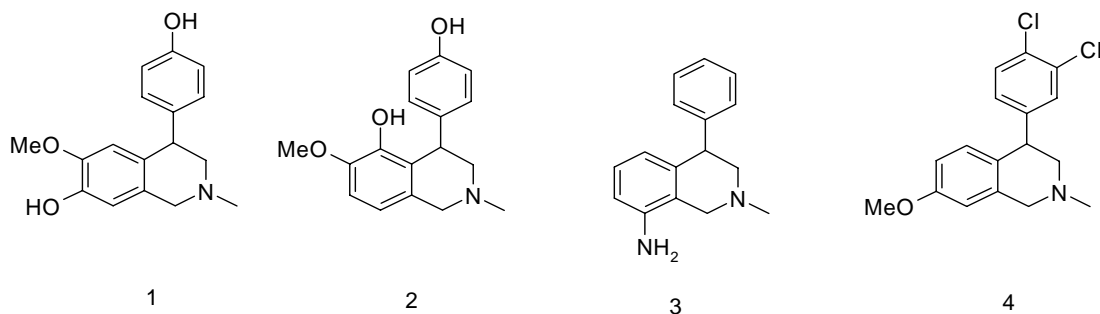
Abstract

An alternative synthesis of isoquinoline alkaloid (+/-) cherylline dimethyl ether is reported. The steps involved are acid-catalyzed Michael addition of veratrole to *p*-methoxycinnamic acid, Curtius rearrangement, reduction of isocyanate intermediate followed by Pictet-Spangler cyclization.

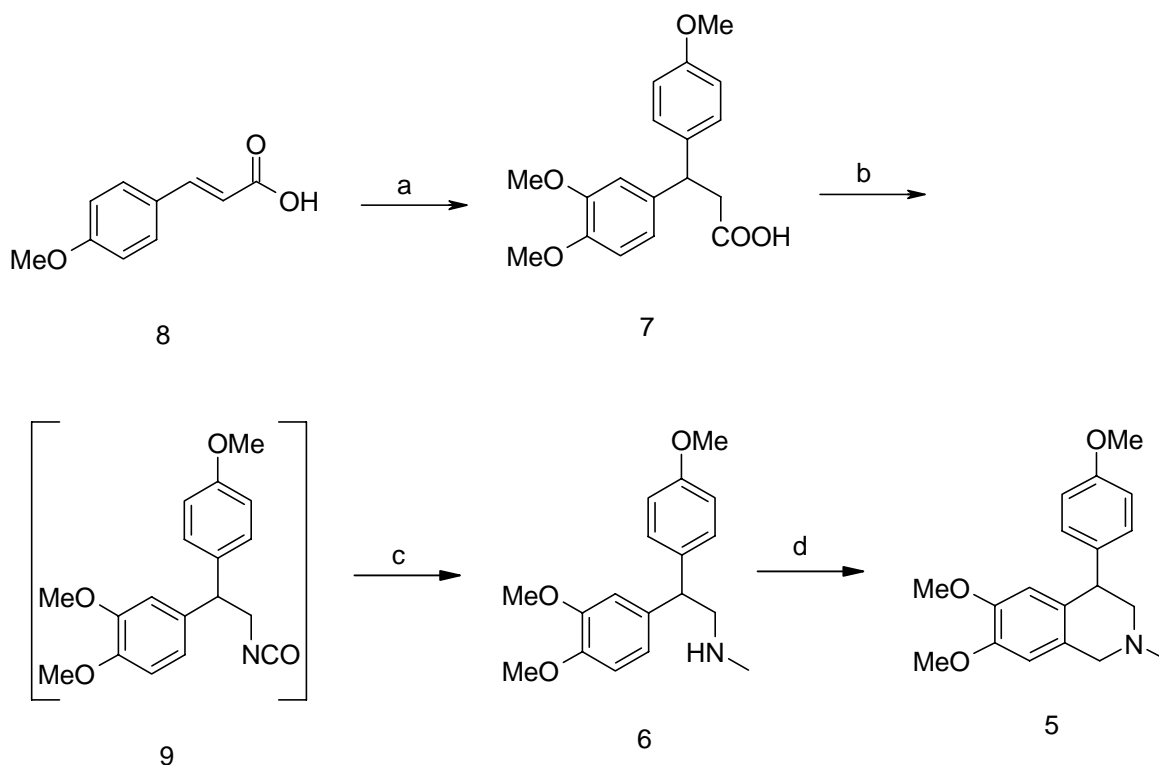
Keywords: Michael reaction, Curtius reaction, Pictet-Spangler cyclization, tetrahydroisoquinoline

Introduction

Cherylline **1** and latifine **2** are the two 4-aryltetrahydroisoquinoline alkaloids isolated from *Amaryllidaceae* plants.¹ Apart from the natural existence, 4-aryltetrahydroisoquinolines are of interest due to various pharmacological activities.² For example, nomifensine³ **3** and dichlofensine⁴ **4** exhibit central nervous system activity and inhibit serotonin and dopamine uptake mechanisms (Scheme 1).



Scheme 1



Scheme 3. (a) Veratrole, TFA, reflux, 2.0 h, 92.0% (b)(i) ClCO_2Et , N-methylmorpholine, acetone, $\text{NaN}_3/\text{H}_2\text{O}$, 0 °C (ii) Toluene, 110 °C, 1.0 h, 93.7% (c) LAH, THF, reflux, 18.0 h, 82.5% (d) HCHO, acetic acid, 80 °C, 3.0 h, 67%.

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

Experimental Section

General Procedures. Melting points were determined by Thiele's tube apparatus and are uncorrected. IR spectra were recorded on Shimadzu FT-IR, IR Prestige-21 (KBr pellet or neat sample). ^1H NMR and ^{13}C NMR spectra were recorded on 300 MHz Bruker instruments. The multiplicities of carbon signals were obtained from a distortionless enhancement by polarization transfer (DEPT). Coupling constants (J) are given in Hz and rounded to the nearest 0.1 Hz. The TLC plates were developed with ethyl acetate (EA)-hexanes. The silica gel used for column chromatography was Loba Chemie 60-120 mesh size. Nitrogen was used as the inert atmosphere. The glassware was equipped with a rubber septum and reagent transfer was effected by syringe techniques. Tetrahydrofuran (THF) was distilled over lithium aluminium hydride and stored over

sodium wire. Acetone was distilled from potassium permanganate before storage over anhydrous potassium carbonate.

Preparation of 3-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)propanoic acid (7). A solution of *p*-methoxycinnamic acid (0.75 g, 4.21 mmol) and veratrole (0.9 g, 6.52 mmol) in trifluoroacetic acid (TFA) (5 mL) was refluxed for 2 h. TFA was distilled at atmospheric pressure and saturated NaHCO₃ (15 mL) was added. This aqueous phase was washed with ether (3 X 10 mL) and acidified with conc HCl to give 1.47 g of crude 3-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)propanoic acid **7**. The crude **7** was purified by column chromatography on silica gel (ethyl acetate-hexanes 1:3) to yield **7** as white solid (1.22 g, 92 %); mp 83 °C. IR (KBr, cm⁻¹) 3100-3300 br (OH) and 1712 (C=O). ¹H NMR (300 MHz, CDCl₃) δ 3.04 (2H, d, J=7.8 Hz, -CH-CH₂-), 3.79 (3H, s, -OCH₃), 3.83 (3H, s, -OCH₃), 3.85 (3H, s, -OCH₃), 4.44 (1H, t, J = 7.8 Hz, CH-CH₂), 6.73-7.27 (7H, m, ArH). ¹³C NMR (75 MHz, CDCl₃) δ 40.89 (CH₂), 45.41 (Ar-CH-Ar), 55.15 (OCH₃), 55.76 (OCH₃), 55.79 (OCH₃), 111.20 (2 X CH_{ar}) 113.94 (2 X CH_{ar}), 119.17 (CH_{ar}) 128.24 (2 X CH_{ar}), 135.6 (C_{ar}), 136.23 (C_{ar}), 147.61 (OC_{ar}), 148.87 (OC_{ar}), 158.14 (OC_{ar}), 177.78 (COOH).

Preparation of (+/-) cherylline dimethyl ether (5). Ethyl chloroformate (0.65 mL, 6.65 mmol) in dry acetone (2 mL) was added to the mixture of acid **7** (2.00 g, 6.33 mmol), N-methylmorpholine (0.80 g, 7.85 mmol) and acetone (5 mL) under inert atmosphere at 0 °C over 35 min. The mixture was then stirred for 1.0 h at 0 °C. A chilled solution of sodium azide (0.82 g, 12.66 mmol) in 6 mL H₂O was added over a period of 20 min. After stirring for 1.0 h at 0 °C, the reaction mixture was poured into chilled water. The product was extracted in toluene (6 X 10 mL) and combined organic extracts were dried over Na₂SO₄. The toluene layer was stirred at 110 °C for 1.0 h. Concentration of reaction mixture under vacuum gave isocyanate **9** (1.86 g, 93.75 %), which was pure (TLC). IR (KBr, cm⁻¹) 2260 (N=C=O).

Isocyanate **9** (1.86 g, 5.94 mmol) in dry THF (5 mL) was slowly added to the suspension of lithium aluminium hydride (LAH) (1.2 g, 29.5 mmol) in THF (10 mL) under inert atmosphere. After refluxing for 18.0 h, the reaction mixture was cooled to 5 °C and chilled water was slowly added to it. The aluminium hydroxide formed was filtered over celite and washed with boiling chloroform. The filtrate also was extracted with boiling chloroform (6 X 15 mL). All the organic extracts and washings were combined, dried over Na₂SO₄, filtered and concentrated to obtain 1.56 g (82.1 %) of crude **6** which was pure enough (TLC). IR (film, cm⁻¹) 3124 (NH).

A mixture of **6** (1.26 g, 4.18 mmol), formaldehyde (0.44 g, 4.39 mmol) and acetic acid (0.26 g, 4.39 mmol) was stirred at 90 °C under inert atmosphere for 4.0 h. After cooling to room temperature, the reaction mixture was basified with saturated NaHCO₃ solution. This basified solution was extracted in hot chloroform (8 X 15 mL), dried, filtered and concentrated to obtain 1.1 g of crude product. Purification of crude product by column chromatography on basic alumina using Ethyl acetate: Hexanes (15:85) as an eluent gave **5** (0.87 g, 67 %), as a white solid, mp 90-92 °C (lit^{3a} mp 87-89 °C) UV (MeOH, nm, ε): 283 (5665), 277.5 (5683), 234 (11008), 226 (10876). IR (KBr, cm⁻¹): 1610, 1514. HRMS *m/z* calculated for C₁₉H₂₃NO₃ -

314.1756 [M+1], found - 314.1751. ¹H NMR (300 MHz, CDCl₃): δ 2.72 (3H, s, NCH₃), 2.85 (1H, s (br), Ar-HCH-N), 3.35 (1H, s (br), Ar-HCH-N), 3.65 (3H, s, OCH₃), 3.82 (3H, s, OCH₃), 3.87 (3H, s, OCH₃), 3.96 (2H, s (br), CH-CH₂-N), 4.49 (1H, s (br), Ar-CH-Ar), 6.35 (1H, s, 5-CH), 6.58 (1H, s, 8-CH), 6.87 (2H, d, J = 8.5 Hz, 2'-CH), 7.12 (2H, d, J = 8.5 Hz, 3'-CH). ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 42.38 (NCH₃), 43.97 (ArCHAR), 55.27 (OCH₃), 55.89 (OCH₃), 55.98 (OCH₃), 56.08 (NCH₂-), 59.83 (NCH₂Ar), 108.65 (CH_{ar}), 111.79 (CH_{ar}), 114.21 (2 X CH_{ar}), 127.87 (C_{ar}), 129.29 (C_{ar}), 129.94 (2 X C_{ar}), 133.84 (C_{ar}), 148.24 (OC_{ar}), 148.59 (OC_{ar}), 158.12 (OC_{ar}).

Acknowledgements

We thank University Grants Commission, New Delhi (India), and Council of Scientific and Industrial Research (CSIR), New Delhi (India), for financial support. We also thank National Institute of Oceanography, Dona-Paula, Goa, and Indian Institute of Science, Bangalore, for spectral analysis.

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