Asian Journal of Chemistry Vol. 22, No. 3 (2010), 1835-1840

New Strategy for the Synthesis of (±) Cherylline Dimethyl Ether

S. Venugopal†, J. Ramanatham‡, N. Devanna¶, A. Sanjeev Kumar, Samir Ghosh, R. Soundararajan*, Bhima Kale and G.N. Mehta
Chemistry Section, Applied Sciences and Humanities Department, Sardar Vallabhbhai National Institute of Technology, Surat-395 007, India
E-mail: soundara1959@rediffmail.com

A concise route for the synthesis of (±) cherylline dimethyl ether is reported. The key steps involved are Grignard addition of 3,4-dimethoxy benzene magnesium bromide to the *p*-methoxy nitrostyrene, reduction of nitro intermediate followed by Pictet-Spangler cyclization.

Key Words: Grignard reaction, Reduction, Tetrahydroisoquinolines, Pictet-Spangler cyclization.

INTRODUCTION

Synthetic studies on aryl-l,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-phenyltetrahydro isoquinoline 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-aryltetrahydro isoquinoline 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[9-28] 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 efficient synthesis of (±) cherylline dimethyl ether. The key steps involved are Grignard addition of 3,4-dimethoxy benzene magnesium bromide to the *p*-methoxy nitrostyrene, reduction of nitro intermediate followed by Pictet-Spangler cyclization.

†Custom Pharmaceutical Services, Dr. Reddy's Laboratories Limited, Bollaram Road, Miyapur, Hyderabad, India.
‡Department of Chemistry, AstraZeneca Research Foundation India, Bangalore-560 024, India.
¶Department of Chemistry, Jawaharlal Nehru Technological University, Anantapur, India.

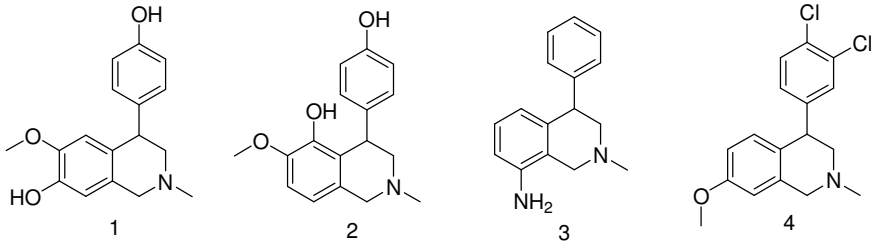


Fig. 1. Tetrahydroisoquinolines

EXPERIMENTAL

All the solvents and reagents were purchased from the 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 $60F_{254}$ plates. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ using 400 MHz, on a Varian Gemini 400 MHz FT NMR spectrometer. The chemical shifts were reported in δ ppm relative to TMS. IR spectra were recorded in the solid state as KBr dispersion using Perkin Elmer FT-IR spectrophotometer. 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.

1-(1-(3,4-Dimethoxyphenyl)-2-nitroethyl)-4-methoxybenzene (7): 3,4-Dimethoxy benzene magnesium bromide was prepared in the usual manner from magnesium (1.3 g, 0.055 mol) and 4-bromo veratrole (10.0 g, 0.046 mol) in tetrhydrofuran (100 mL). Copper iodide (10 mg) was added to this solution of the reagent under ice salt cooling. To this solution was added a solution of *p*-methoxy nitrostyrene **8** (7.0 g 0.039 mol) in tetrahydrofuran (35 mL) at 0-5 ºC, this solution was stirred at room temperature for 5 h. After addition of aqueous solution of ammonium chloride, the mixture was stirred was diluted with ethyl acetate (100 mL). The ethyl acetate layer was washed with water and dried over sodium sulphate and concentrated. The residue was purified by column chromatography on silica gel (7:3 hexane and ethyl acetate) to yield **7** as a residue (6.1 g, 50 %); IR (KBr, cm^{-1}): 1550 (NO_2); ^{1}H NMR (DMSO-d_6) (δ ppm): 3.62 (3H, s, -OCH_3), 3.64 (3H, s, -OCH_3), 3.66 (3H, s, -OCH_3), 4.63 (1H, t, J = 8.8 Hz, Ar-CH-Ar), 5.21 (2H, d , J = 8.8 Hz, CH_2-NO_2), 6.77-7.27 (7H, m, ArH); ^{13}C NMR (DMSO-d_6) (δ ppm); 47.8 (ArCHAr), 55.4 (OCH_3), 55.8 (OCH_3), 55.9 (OCH_3), 79.1 (CH_2-NO_2), 111.9 (CH_{ar}), 112.2 (CH_{ar}), 114.3 (2XCH_{ar}), 119.8 (C_{ar}), 129.0 (2XC_{ar}), 132.8 (C_{ar}), 133.3 (C_{ar}), 148.1 (OC_{ar}), 149.1 (OC_{ar}),158.5 (OC_{ar}); MS (m/z): 318 [M^+ + 1].

2-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)ethanamine (9): To a solution of 1-(1-(3,4-dimethoxyphenyl)-2-nitroethyl)-4-methoxybenzene **7** (6.0 g, 0.018 mol) in THF (60 mL) and acetic acid (60 mL) was added iron lot wise (10.5 g, 0.189

mol). The reaction mixture stirred at reflux for 3 h. After cooling to room temperature, the reaction mixture filtered through celite bed and basified with 50 % NaOH solution. This basified solution was extracted with ethyl acetate (3 × 25 mL), dried, filtered and concentrated to obtain 5.3 g of crude product. Purification of crude product by column chromatography using 10 % methanol in dichloromethane as an eluent gave **9** (4.0 g, 74 %), as a residue; IR (KBr, cm^{-1}): 3320 (NH_2); ^1H NMR (DMSO-d_6) (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), 6.68-7.11 (7H, m, ArH); ^{13}C NMR (DMSO-d_6) (δ ppm); 47.2 (ArCHAr), 53.7 (CH_2-NH_2), 55.3 (OCH_3), 55.8 (OCH_3), 55.9 (OCH_3), 112.2 (CH_{ar}), 112.3 (CH_{ar}), 114.1 (2XCH_{ar}), 119.9 (C_{ar}), 129.1 (2XC_{ar}), 136.3 (C_{ar}), 136.8 (C_{ar}), 147.5 (OC_{ar}), 149.0 (OC_{ar}),157.9 (OC_{ar}); MS (m/z): 288 [M^+ + 1].

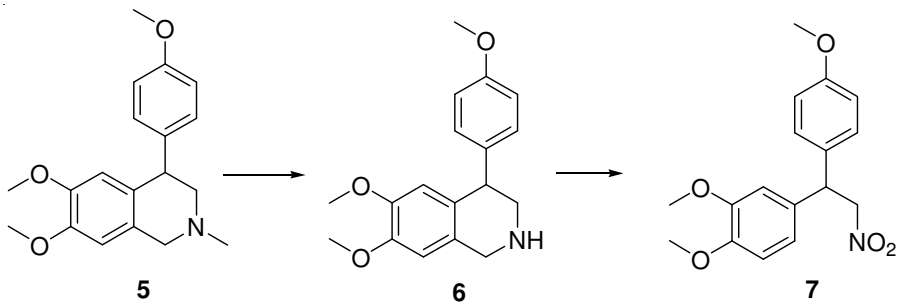
2-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-N-methylethanamine (6): To a solution of 2-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanamine **9** (3.5 g, 0.012 mol) in THF (35 mL) and triethyl amine (1.85g, 0.018 mol) was added di-*tert*-butyl dicarbonate (3.9 g, 0.018 mol) at 0-5 ºC. The reaction mixture stirred at 25-35 ºC for 1 h. Reaction progress monitored by TLC, which was pure and proceeded as such for reduction purpose. Intermediate, *tert*-butyl 2-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)ethylcarbamate (**10**) was slowly added to the suspension of lithium aluminium hydride (2.3 g, 0.06 mol) in THF (15 mL) under inert atmosphere. After refluxing for 4 h, the reaction mixture was cooled to 5 ºC and chilled water was slowly added to it. The aluminium hydroxide formed was filtered over celite and washed with chloroform. The filtrate was also extracted with chloroform (3 × 20 mL). All the organic extracts and washings were combined, dried over sodium sulphate, filtered and concentrated to obtain **6** as a brown residue 3.3 g (90.0 %); IR (KBr, cm^{-1}): 3120 (NH); HRMS m/z calculated for $C_{18}H_{23}NO_3$ 302.3801 [M + 1], found: 302.37; ^1H NMR ($CDCl_3$) (δ ppm): 2.44 (3H, s, NCH_3), 3.12 (2H, d , J = 8.0 Hz, HCH-N-CH_3), 3.78 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.08 (1H, t, J = 7.6 Hz, Ar-CH-Ar), 6.74-7.26 (7H, m, ArH); ^{13}C NMR ($CDCl_3$) (δ ppm); 43.9 (NCH_3), 49.4 (ArCHAr), 55.3 (OCH_3), 55.81 (OCH_3), 55.86 (OCH_3), 56.6 (NCH_2Ar), 112.1 (CH_{ar}), 112.2 (CH_{ar}), 114.1 (2 × CH_{ar}), 119.8 (C_{ar}), 129.0 (2 × C_{ar}), 136.2 (C_{ar}), 136.8 (C_{ar}), 147.5 (OC_{ar}), 148.9 (OC_{ar}),157.9 (OC_{ar}).

(±) Cherylline dimethyl ether (5): A mixture of **6** (2.0 g, 0.006 mol), formaldehyde (0.64 g, 0.007 mol) and acetic acid (5 mL) was stirred at 90 ºC under inert atmosphere for 2.0 h. After cooling to room temperature, the reaction mixture was basified with saturated $NaHCO_3$ solution. This basified solution was extracted ethyl acetate (3 × 25 mL), dried, filtered and concentrated to obtain 1.1 g of crude product. Purification of crude product by column chromatography using 1 % methanol in dichloromethane as an eluent gave **5** (0.93 g, 45 %), as a white solid, m.p. 90-92 ºC (Lit.[17] m.p. 90-92 ºC); IR (KBr, cm^{-1}): 1610, 1514; HRMS m/z calculated for $C_{19}H_{23}NO_3$ 314.1756 [M + 1], found - 314.175; ^1H NMR ($CDCl_3$) (δ ppm): 2.41 (3H, s, NCH_3), 2.44 (1H, m, CH-HCH-N), 2.98 (1H, m, CH-HCH-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, Ar-CH-Ar), 6.34 (1H, s, 5-CH), 6.56 (1H, s, 8-CH), 6.84 (2H, d, J = 8.8 Hz, 2'-CH), 7.11 (2H, d, J = 8.8 Hz, 3'-CH); ^{13}C NMR ($CDCl_3$) (δ ppm); 43.9 (NCH_3), 45.9 (ArCHAr), 55.3 (OCH_3), 55.81 (OCH_3), 55.86 (OCH_3), 57.7 (NCH_2-), 61.6 (NCH_2Ar), 109.7 (CH_{ar}), 112.5 (CH_{ar}), 113.9 ($2XCH_{ar}$), 127.7 (C_{ar}), 129.2 (C_{ar}), 130.0 ($2XC_{ar}$), 137.7 (C_{ar}), 147.5 (OC_{ar}), 147.6 (OC_{ar}), 158.0 (OC_{ar}).

RESULTS AND DISCUSSION

Our retrosynthetic analysis of (±) cherylline dimethyl ether **5** is depicted in **Scheme-I**. It is anticipated that **5** could be constructed from amine **6** *via* a Pictet-Spangler ring annulation which, in turn, could be obtained by reduction of the corresponding nitro intermediate **7**. The required nitro intermediate would arise from the by Grignard addition of 3,4-dimethoxy benzene magnesium bromide to *p*-methoxy nitrostyrene.



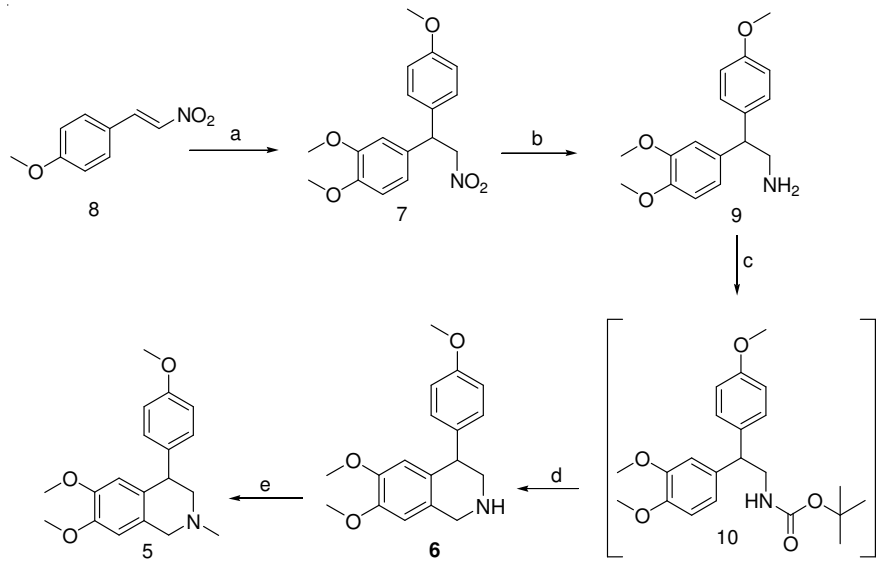
5 **6** **7**

Scheme-I

Grignard addition of 3,4-dimethoxy benzene magnesium bromide to the *p*-methoxy nitrostyrene (**8**) in presence of small amount of copper iodide to obtain 1-(1-(3,4-dimethoxyphenyl)-2-nitroethyl)-4-methoxybenzene (**7**) in 50 % yield. Reduction of nitro group with iron under acidic condition in THF at room temperature gave 2-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl) ethanamine (**9**) in 74 % yield. Reaction with di-*tert*-butyl dicarbonate using trimethylamine at room temperature gave *tert*-butyl 2-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)ethylcarbamate intermediate **10** and immediate reduction by lithium aluminium hydride gave N-methyl amine **6** in 90 % yield. The crude amine **6**, on Pictet-Spangler reaction gave (±) cherylline dimethyl ether 5 in 60 % yield (**Scheme-II**).

Conclusion

In short, we have devised a 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.



Scheme-II. (a) 4-Bromoveratrole, Mg, THF, 25-35 ºC, 5.0 h, 50 %; (b) Fe, acetic acid, THF, 70 ºC, 3.0 h, 74 %; (c) di-*tert*-butyl dicarbonate, TEA, THF, 0-5 ºC (d) LAH, THF, reflux, 4.0 h, 90 % (e) HCHO, acetic acid, 90 ºC, 2.0 h, 60 %

ACKNOWLEDGEMENTS

The authors are grateful to Jawaharlal Nehru Technological University, Hyderabad, Sardar Vallabhbhai National Institute of Technology, Surat and Indian Institute of Chemical Technology, Hyderabad for analytical support.

REFERENCES

1. A. Brossi, G. Grethe, S. Teitel, W.C. Wildman and D.T. Bailey, *J. Org. Chem*., **35**, 1100 (1970).
2. S. Kobayashi, T. Tokumoto and Z. Taira, *J. Chem. Soc., Chem. Commun*., 1043 (1984).
3. P.S. Charifson, *Drugs Fut*., **14**, 1179 (1989).
4. J. Guillon, P. Dallemagne, H. Leveque, R. Duval and S. Rault, *Pharm Sci.,* 325 (1997).
5. E. Zara-Kaczaim, L. Gyorgy, G. Deak, A. Seregi and M. Doda, *J. Med. Chem*., **29**, 1189 (1986).
6. J. Ulin, A.D. Gee, P. Malmborg, J. Tedroff and B. Laangstroem, *Appl. Radiat. Isot*., **40**, 171 (1989).
7. C. Cherpillod and L.M. Omer, *J. Int. Med. Res*., **9**, 324 (1981).
8. L.M. Omer, *Int J. Clin. Pharmacol. Ther. Toxicol*., **20**, 324 (1982).
9. A. Brossi and S. Teitel, *Tetrahedron Lett*., 417 (1970).
10. M.A. Schwartz and S.W. Scott, *J. Org. Chem*., **36**, 1827 (1971).
11. T. Kametani, K. Takahashi and C. Van Loc, *Tetrahedron*, **31**, 235 (1975).
12. D.J. Hart, P.A. Cain and D.A. Evans, *J. Am. Chem. Soc*., **100**, 1548 (1978).
13. H. Irie, A. Shiina, T. Fushimi, J. Katakawa, N. Fujii and H. Yajima, *Chem. Lett*., 875 (1980).
14. S.V. Kessar, P. Singh, R. Chawla and P. Kumar, *J. Chem. Soc. Chem. Commun*., 1074 (1981).
15. T. Kametani, K. Higashiyama, T. Honda and H. Otomasu, *J. Chem. Soc., Perkin Trans I*, 2935 (1982).
16. H. Hara, R. Shirai, O. Hoshino and B. Umezawa, *Heterocycles*, **20**, 1945 (1983).
17. H. Hara, R. Shirai, O. Hoshino and B. Umezawa, *Chem. Pharm. Bull*., **33**, 3107 (1985).

18. S. Takano, M. Akiyama and K. Ogasawara, *Chem. Lett*., 505 (1985).
19. S. Kobayashi, T. Tokumoto, S. Iguchi, M. Kihara, Y. Imakura and Z. Taira, *J. Chem. Res. (S)*, 280 (1986).
20. N.S. Narashimhan and P.A. Patil, *J. Chem. Soc. Chem. Commun*., 191 (1987).
21. V.G. Gore and N.S. Narashimhan, *J. Chem. Soc. Perkin Trans I*, 481 (1988).
22. J. Katakawa, H. Yoshimatsu, M. Yoshida, Y. Zhang, H. Irie and H. Yajima, *Chem. Pharm. Bull*., **36**, 3928 (1988).
23. A. Couture, E. Deniau, S. Lebrun and P. Grandclaudon, *J. Chem. Soc. Perkin Trans I*, 789 (1999).
24. J. Toda, A. Sonobe, T. Ichikawa, T. Saitoh, Y. Horiguchi and T. Sano, *Arkivoc*, 165 (2000).
25. T. Honda, H. Namiki and F. Satoh, *Org. Lett*., **3**, 631 (2001).
26. A. Couture, E. Deniau, S. Lebrun and P. Grandclaudon, *Tetrahedron: Asymm.*, **14**, 1309 (2003).
27. A. Couture, E. Deniau, S. Lebrun and P. Grandclaudon, *Org. Biomol. Chem*., **1**, 1701 (2003).
28. K. Reshma, K. Suvidaha, T. Santosh and K. Janardan, *Arkivoc*, 256 (2008).

(*Received*: 30 March 2009; *Accepted*: 21 November 2009) AJC-8063