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A new method of synthesising (±)-thalictroidine and (±)-hygrine

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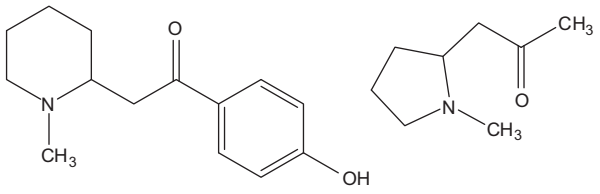
ABSTRACT

A new route to synthesise (±)-thalictroidine and (±)-hygrine by tandem S_N2-Micheal reaction is described.

Nitrogen containing heterocycles are well known for their biological activity.[1] This has led to a great number of studies concerning the development of new methodology towards these molecules over the years.[2] Thalictroidine (**1**), a piperidine alkaloid, was originally isolated in 1999 by Kennelly et al.[3] from a North American 'Blue Cohosh' (*Caulophyllum thalictroides*). This alkaloid is used in certain dietary preparations. Hygrine (**2**) is a pyrrolidine alkaloid found in a variety of plants including coca leaves. Hygrine has been the subject of several biological and pharmacological studies,[4] as it is the precursor of tropane skeleton.[5] The synthesis of thalictroidine (**1**) has been reported[6] and a number of routes available towards the synthesis of hygrine (**2**).[7] These methods have some disadvantages—either they involve multiple steps or result in low yield. In this Letter, we wish to report a method of synthesising (±)-thalictroidine (**1**) and (±)-hygrine (**2**) (Fig. 1) by a simple route in high yield.

Bunce et al.[8] developed a methodology for the preparation of five-membered and six-membered nitrogen and sulphur heterocycles through tandem S_N2-Micheal reaction. Recently, Duenren Hou et al. have applied the tandem S_N2 substitution and intramolecular aza-Micheal addition sequence to prepare ethyl 2-piperidineacetate as an intermediate towards the syntheses of (−)-allosedridine and (−)-2-*epi*-ethylnorlobelol.[9] Asymmetric synthesis of natural (−)-sparteine has also been achieved by a similar route[10] and this tandem procedure is extensively used.[11] This strategy is now extended for the synthesis of natural products (±)-thalictroidine (**1**) and (±)-hygrine (**2**) and the results are presented here.



(+)-Thalictroidine (**1**) (+)-Hygrine (**2**)

Figure 1.

A retrosynthetic analysis of the alkaloids **1** and **2** (Scheme 1) identifies the respective precursors for the synthesis of **1** and **2**. Accordingly, Wittig reaction between 5-bromo-1-pentanal (**3**)[12] and 4-methoxyphenacylphosphonium bromide (**4**)[13] in the presence of aqueous sodium hydroxide yielded 84% of **5** (Scheme 2).[14] Tandem S_N2 substitution and aza-Michael addition of **5** and methylamine hydrochloride in the presence of potassium carbonate gave quantitative yield of **6** even at room temperature.[15]

Initially, the demethylation of **6** was effected with 3 equiv of BBr_3 and the yield of **1** was only 50%. When four equivalents of BBr_3 were employed, it resulted in 60% of **1**. Further increase in the quantity of BBr_3 failed to improve the yield. It must be mentioned that when the demethylation was conducted under neutral condition, using lithium chloride (5 equiv) in refluxing DMF, only 5% of **1** was obtained. As acidic and neutral conditions did not

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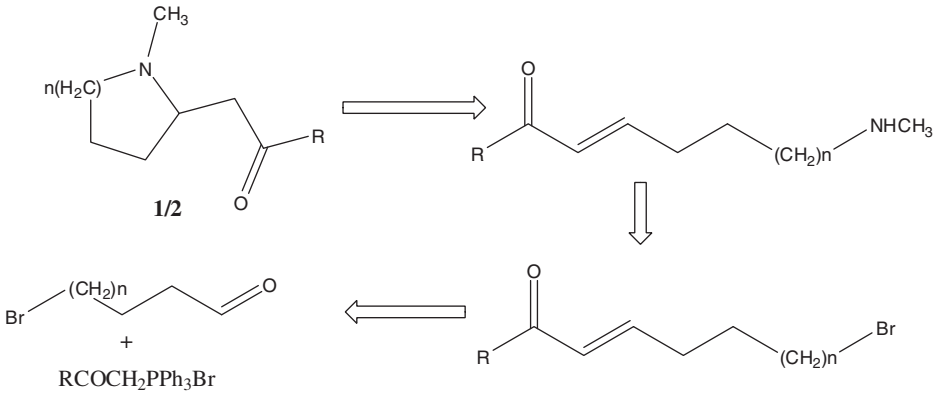
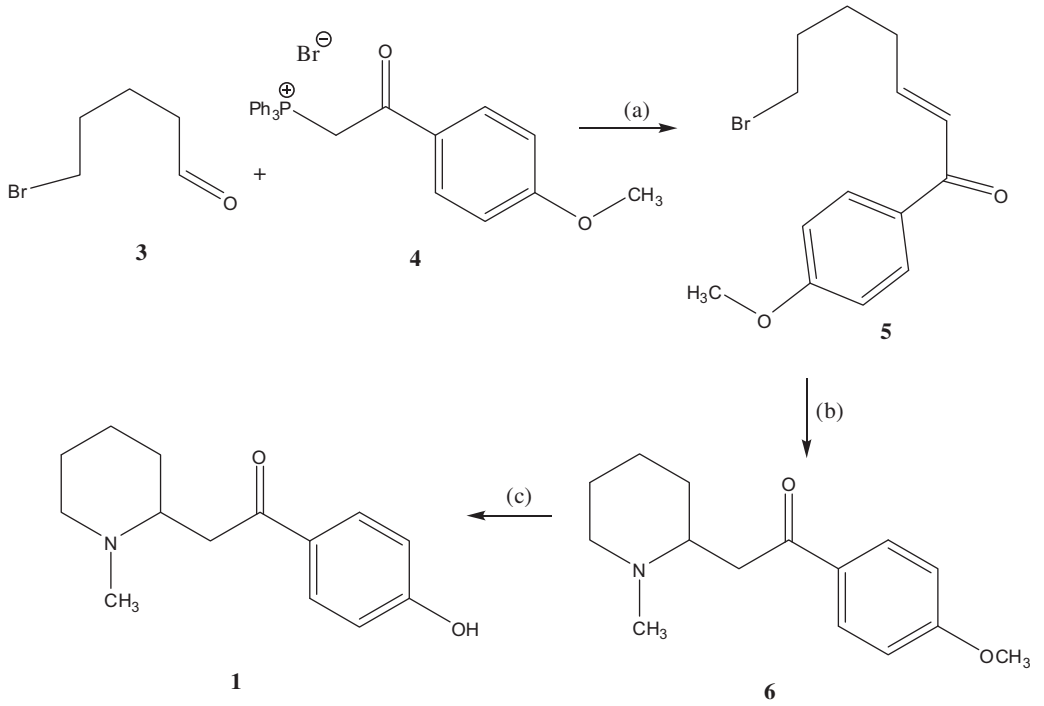


1: R = 4-Hydroxyphenyl, n = 2

2: R = Methyl, n = 1

Scheme 1.



Scheme 2. Reagents and conditions: (a) aq NaOH, dichloromethane, 84%; (b) CH_3NH_2·HCl, K_2CO_3, acetonitrile, rt, 7 h, 99%; (c) EtSNa, DMF, 90 °C, 3 h, 92%.

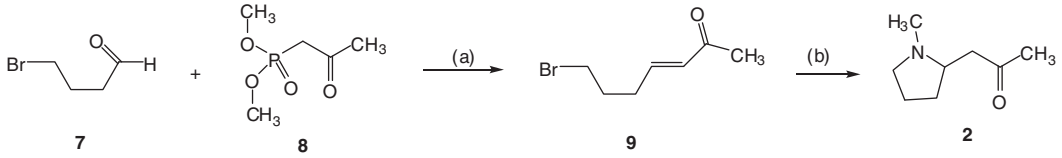
Table 1
Demethylation of **6** under different conditions

No.	Reagent	Temperature (°C)	Reaction time (h)	Yield (%) of **1**
1	3 equiv BBr_3, MDC	rt[a]	36	50
2	4 equiv BBr_3, MDC	rt[a]	36	60
3	5 equiv BBr_3, MDC	rt[a]	36	60
4	5 equiv LiCl, DMF	130	24	5
5	5 equiv EtSNa, DMF	90	3	92

[a] Addition of the reagent at −78 °C.

result in satisfactory yield of **1**, the demethylation was tried under basic condition employing sodium ethanethiolate (5 equiv) in DMF at 90 °C. Excellent yield (92%) was obtained under this condition[16] and the product obtained did not require further tedious purification (Scheme 2, Table 1).

A similar approach has led to the formation of (±)-hygrine (**2**) from 4-bromo-1-butanal (**7**)[17] and dimethyl (2-oxopropyl)phosphonate (**8**). The enone formed (**9**)[18] undergoes tandem S_N2 substitution and intramoleculer aza-Micheal addition with methylamine hydrochloride to give **2** (Scheme 3). The tandem process requires



Scheme 3. Reagents and conditions: (a) NaH, −10 °C, 1 h, 83%; (b) CH_3NH_2·HCl, K_2CO_3, acetonitrile, 70 °C, 24 h, 85%.

three days for completion, when the reaction was carried out at room temperature. However, the reaction gets completed within 24 h at 70 °C,[19] though the yields were almost same in both the conditions.

Thus (±)-thalictroidine and (±)-hygrine have been synthesised through a common strategy involving the tandem S_N2 substitution—aza-Micheal addition as a key step with relatively good yield and minimum number of steps compared to the reported methods.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.132.

References and notes

1. O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435.
2. (a) Yang, Q.; Alper, H.; Xiao, W. *Org. Lett.* **2007**, *9*, 769; (b) Coldham, I.; Price, K. N.; Rathmell, R. E. *Org. Biomol. Chem.* **2003**, *1*, 2111; (c) Enders, D.; Thiebes, C. *Pure Appl. Chem.* **2001**, *73*, 573.
3. Kennelly, E. J.; Flynn, T. J.; Mazzola, E. P.; Roach, J. A.; McCloud, T. G.; Danford, D. E.; Betz, J. M. *J. Nat. Prod.* **1999**, *62*, 1385.
4. For example: (a) Berkov, S.; Zayed, R.; Doncheva, T. *Fitoterapia* **2006**, *77*, 179; (b) Doncheva, T.; Berkov, S.; Philipov, S. *Biochem. Syst. Ecol.* **2006**, *34*, 478; (c) Humam, M.; Munoz, O.; Christen, P.; Hostettmann, K. *Nat. Prod. Commun.* **2007**, *2*, 743.
5. Leete, E.; Kim, S. H. *Chem. Commun.* **1989**, 1899.
6. Riley, D. L. Synthesis of Amphibian Indolizidine Alkaloids and Related Compounds from Enaminone Precursors, Ph.D. Thesis, University of the Witwatersrand, Johannesburg, October 2007. http://wiredspace.wits.ac.za/handle/10539/4967?show=full.
7. For example: (a) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172; (b) Langenskiold, T.; Lounasmaa, M. *Heterocycles* **1983**, *20*, 671; (c) Nagasaka, T.; Yamamoto, H.; Hayashi, H. *Heterocycles* **1989**, *29*, 155; (d) Sud, A.; Sureshkumar, D.; Klussmann, M. *Chem. Commun.* **2009**, 3169; (e) Majik, M. S.; Tilve, S. G. *Tetrahedron Lett.* **2010**, *51*, 2900; (f) Arévalo-Garcia, E. B.; Colmenares, J. C. Q. *Tetrahedron Lett.* **2008**, *49*, 3995; (g) Lee, J. H.; Jeong, B. S.; Ku, J. M.; Jew, S. S.; Park, H. G. *J. Org. Chem.* **2006**, *71*, 6690; (h) Galinovsky, F.; Zuber, H. *Monatsh. Chem.* **1953**, *84*, 798.
8. Bunce, R. A.; Peeples, C. J.; Jones, P. B. *J. Org. Chem.* **1992**, *57*, 1727.
9. Hou, D. R.; Chen, L. J. *Tetrahedron: Asymmetry* **2008**, *19*, 715.
10. Hermet, J. R.; McGrath, M. J.; O'Brien, P.; Porter, D. W.; Gilday, J. *Chem. Commun.* **2004**, 1830.
11. Bunce, R. A.; Allison, J. C. *Synth. Commun.* **1999**, *29*, 2175.
12. Dolbier, W. R.; Rong, X. X.; Bartberger, M. D.; Koroniak, H.; Smart, B. E.; Yang, Z. Y. *J. Chem. Soc., Perkin Trans. 2* **1998**, 219.
13. Triphenylphosphine (3.4 g, 13.1 mmol) was added to a solution of 4-methoxyphenacyl bromide (3 g, 13.1 mmol) in acetonitrile (20 mL) under nitrogen atmosphere at 20 °C. The reaction mixture was heated in an oil bath (85 °C) for 2 h, cooled and then poured slowly into diethyl ether (200 mL). The white solid obtained was filtered and dried to give **4** (92%). mp 228–229 °C; ^1H δ_H (400 MHz, $CDCl_3$) δ 3.87 (3H, s), 6.22 (2H, d), 6.98 (2H, d), 7.62–7.67 (m, 6H), 7.73–7.75 (m, 3H), 7.91–7.96 (m, 6H), 8.43 (2H, d).
14. To a solution of **4** (5.5 g, 11.2 mmol) in dichloromethane (25 mL) was added 2 M aqueous sodium hydroxide (12 mL). The mixture was stirred at room temperature for 14 h. The aqueous layer was extracted with dichloromethane (8 mL). 5-Bromo-1-pentanal **3**[12] (1.85 g, 11.2 mmol) was added to the dichloromethane extract over a period of 45 min at room temperature. The reaction mixture was stirred for 1 h. The solvent was removed under vacuum, and the product was purified by column chromatography (SiO_2, ethyl acetate/hexane, 1:10; R_f 0.25) to yield **5** (84%) as a light-yellow oil. δ_H (300 MHz, $CDCl_3$) 1.69 (2H, quintet), 1.92 (2H, quintet), 2.35 (2H, quartet), 3.44 (2H, t), 3.87 (3H, s), 6.89–7.07 (4H, m), 7.95 (2H, d); δ_C (75 MHz, $CDCl_3$) 26.6, 31.7, 32.1, 33.2, 55.4, 113.7, 125.9, 130.6, 130.7, 147.5, 163.3, 188.8; *m/z* 297.0.
15. A suspension of **5** (1 g, 3.4 mmol), methylamine hydrochloride (0.30 g, 4.4 mmol) and potassium carbonate (1.4 g, 10.1 mmol) in acetonitrile (25 mL) was stirred at room temperature for 7 h. The suspension was filtered and concentrated to give **6** (99%) as a light-yellow oil. δ_H (300 MHz, $CDCl_3$) 1.34–1.36 (2H, m), 1.63–1.69, (4H, m), 2.27 (3H, s), 2.58 (1H, br s), 2.80–2.88 (3H, m), 3.32 (1H, dd), 3.87 (3H, s), 6.94 (2H, d), 7.95 (2H, d); δ_C (75 MHz, $CDCl_3$) 23.6, 25.7, 32.2, 41.8, 43.5, 55.4, 56.3, 59.6, 113.7, 130.3, 130.4, 163.5, 197.8; *m/z* 248.1.
16. To a slurry of sodium hydride [58 mg, (2.4 mmol) of a 57% mineral oil dispersion washed twice with *n*-hexane (8 mL)] in dry DMF (1 mL) cooled to 5 °C was added ethanethiol (126 mg, 2 mmol) in dry DMF (1 mL) dropwise slowly preventing foaming under nitrogen atmosphere. The mixture was stirred for 15 min after the addition and then **6** (100 mg, 0.4 mmol) in dry DMF (1 mL) was added. The resultant mixture was heated at 90 °C for 3 h, cooled to room temperature, poured into water (20 mL) and extracted with dichloromethane. The aqueous layer was neutralized with dilute acetic acid, saturated with sodium chloride and extracted with dichloromethane. The combined organic solution was dried over anhydrous sodium sulfate, filtered, and concentrated to give **1** (92%) as a colourless gum. δ_H (300 MHz, $CDCl_3$) 1.41–1.78 (6H, m), 2.38 (3H, s), 2.40–2.44 (1H, m), 2.85–3.06 (3H, m), 3.40 (1H, dd), 6.84 (2H, d), 7.82 (2H, d); δ_C (75 MHz, $CDCl_3$) 196.5, 163.8, 131.0, 128.0, 116.4, 60.0, 56.4, 42.7, 41.2, 31.2, 24.5, 23.3; ν_{max} cm^{-1} (Neat) 3435, 2928, 1660, 1601, 1582, 1166, 847 cm^{-1}; *m/z* 234.1.
17. Vedejs, E.; Arnost, M. J.; Hagen, J. *J. Org. Chem.* **1979**, *18*, 3230.
18. To a solution of 4-bromo-1-butanal (**7**)[17] (1 g, 6.6 mmol) and dimethyl (2-oxopropyl)phosphonate **8** (1.1 g, 6.6 mmol) in THF (15 mL) was added sodium hydride (6 × 0.03 g, 7.9 mmol, 57% dispersion in mineral oil, in intervals of 10 min) at −10 °C. The reaction mixture was stirred for 1 h at −10 °C. It was then quenched with water (15 mL) and extracted with ethyl acetate. The combined organic solution was dried over anhydrous sodium sulfate, filtered and concentrated. Purification by column chromatography (SiO_2, ethyl acetate/hexane, 1:10; R_f 0.2) gave **9** (83%) as a light yellow oil. δ_H (300 MHz, $CDCl_3$) 2.00–2.09 (2H, m), 2.26 (3H, s), 2.33–2.45 (2H, m), 3.43 (2H, t), 6.14 (1H, dd), 6.77 (1H, dt); δ_C (75 MHz, $CDCl_3$) 27.0, 30.6, 30.8, 32.4, 132.0, 145.6, 198.2.
19. A suspension of **9** (100 mg, 0.52 mmol), methylamine hydrochloride (42 mg, 0.63 mmol) and potassium carbonate (220 mg, 1.6 mmol) in acetonitrile (5 mL) was heated at 70 °C for 24 h. The suspension was filtered and concentrated to give **2** (63 mg, 0.46 mmol, 85%) as light yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.69–1.80 (m, 4H), 2.05–2.13 (m, 1H), 2.16 (s, 3H), 2.31 (s, 3H), 2.40–2.46 (dd, 1H), 2.53–2.56 (m, 1H), 2.78–2.83 (dd, 1H), 3.03–3.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 31.1, 31.4, 40.6, 48.5, 56.9, 61.9, 208.2; IR ν_{max} cm^{-1} (Neat) 1713; *m/z* 142.1.