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An efficient synthesis of varenicline ☆

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ABSTRACT

Synthesis of varenicline the antismoking drug has been achieved in six steps with 10% overall yield. A Diels–Alder reaction, oxidative cleavage of an olefin and reductive amination remain as key steps in the synthesis

Neuronal nicotinic acetylcholine receptors (nAChRs) belong to a heterogeneous family of pentameric ligand-gated ion channels which are differently expressed in many regions of the central nervous system (CNS) and peripheral nervous system.[1,2] Agonists and partial agonists of various subtypes of nicotinic acetylcholine receptors (nAChRs) are being pursued as potential treatments for a variety of central nervous system disorders, such as addiction, pain, depression, schizophrenia, Parkinson's disease, Alzheimer's disease, Attention-deficit hyperactivity disorder (ADHD), and alcoholism.[3–7] Moreover, as the addictive properties of tobacco products are due to the nicotine contained therein, nAChRs also became important targets for the discovery of medicines for use in smoking cessation.[8] Varenicline **1** an α4β2 nAChR partial agonist was approved by US FDA as an aid to smoking cessation treatment in May 2006.[9] Varenicline was discovered through the synthesis of a series of compounds inspired by the natural product (−)-cytisine **2**,[10] which was previously known to have partial agonist activity at the α4β2 nAChR (see Fig. 1).[11]

We herein, wish to report our efforts[12] on the synthesis of varenicline in an efficient manner by using a Diels–Alder reaction, oxidative cleavage of an olefin and reductive amination as shown retrosynthetically in Scheme 1.

As per the synthetic plan, our synthesis began with the conversion of 2,3-dimethylpyrazine **10** to its known analogue 2,3-bis-(dibromomethyl)pyrazine[13] **8**. Followed by NaI-mediated Diels–Alder[13,14] reaction between 2,3-bis (dibromomethyl)pyrazine **8** and commercially available norbornadiene **9** to furnish the adduct **7**.[15] Olefin **7** was converted[16] to its corresponding diol **6**[17] with OsO_4 in the presence of NMO. Oxidative cleavage[18] of the diol with $NaIO_4$ provided an intermediate dialdehyde. Subsequent reductive amination with 4-methoxy benzyl amine gave compound PMB-protected varenicline **5**.[19] Finally PMB group was removed by Pd/C in the presence of ammonium formate in methanol to yield varenicline **1**[20] (Scheme 2).

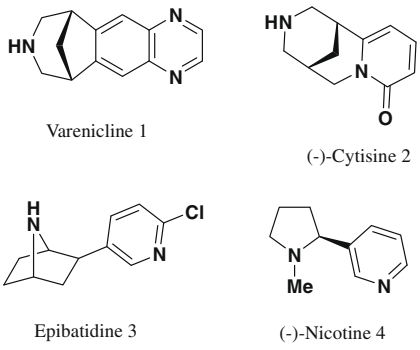
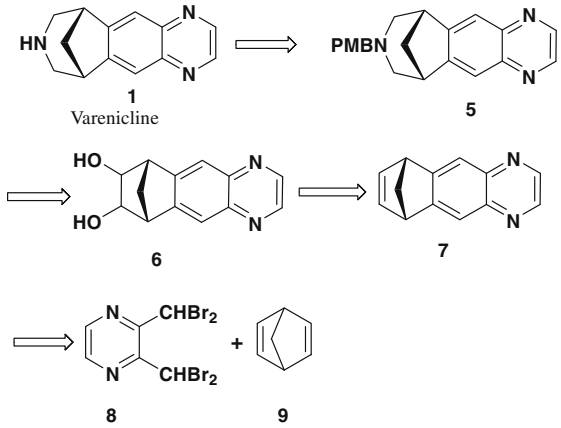


Figure 1. Natural products (**2**–**4**) and varenicline (**1**), ligands that can act as neuronal nicotinic acetylcholine receptors.



Scheme 1. Retrosynthesis of varenicline, **1**.

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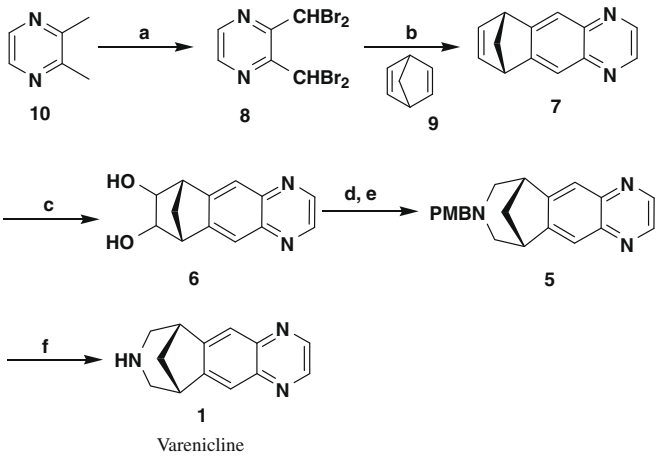

Scheme 2. Reagents and conditions: (a) NBS, CCl_4, hν, 16 h, 65%; (b) NaI, DMF, 60 °C, 30 min, 46%; (c) NMO, OsO_4, acetone/water/*t*-BuOH, rt, 16 h, 85%; (d) $NaIO_4$, DCM, silica gel, rt, 30 min; (e) $PMBNH_2$, $Na(CN)BH_3$, methanol, acetic acid, 0 °C to rt, 2 h, 62% for two steps; (f) Pd/C, HCO_2NH_4, methanol, reflux for 30 min, rt, 24 h, 64%.

In summary, total synthesis of varenicline has been achieved in a total of six steps with 10% overall yield. This procedure can be scaled up for commercial use.

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15. *Experimental procedure and spectral data for* **7**: Sodium iodide was added in small portions over a period of 2 min to a solution of the 2,3-bis (dibromomethyl)pyrazine **8** (2.0 g, 4.71 mmol) and norbornadiene **9** (2.16 g, 23.58 mmol) in dry DMF (23 mL) at 60 °C. The mixture was stirred for further 30 min. The reaction mixture was cooled to rt, diluted with EtOAc (46 mL), and passed through a small pad of Celite. The filtrate was washed with 10% sodium thiosulfate (3 × 20 mL), water (2 × 20 mL), and brine (1 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo and the residue was purified by flash column chromatography (silica gel, EtOAc–hexane, 10:90) to give 420 mg (46%) of **7** as a white solid. Mp: 120–123 °C; IR (KBr, cm^{-1}): 2519, 1708, 1649, 1215, 1182; ^1H NMR (400 MHz; DMSO-d_6): δ = 8.70 (s, 2H), 7.78 (s, 2H), 6.78 (t, *J* = 1.7 Hz, 2H), 4.08 (t, *J* = 1.7 Hz, 2H), 2.45–2.43 (m, 1H), 2.32–2.30 (m, 1H); ^{13}C NMR (50 MHz; $CDCl_3$): δ = 153.5, 143.2, 142.5, 142.1, 120.3, 66.3, 49.6; Mass (ESI): 195 $[M+H]^+$; HRMS(ESI): calcd for $C_{13}H_{11}N_2$ $[M+H]^+$ 195.0922, found 195.0931.
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17. *Spectral data of* **6**: Mp: 143–145 °C; IR (KBr, cm^{-1}): 3491, 3124, 2980, 1483, 1359, 1074, 956; ^1H NMR (400 MHz; DMSO-d_6): δ = 8.28 (s, 2H), 7.85 (s, 2H), 5.11 (s, 2H), 3.7 (s, 2H), 3.36 (s, 2H), 2.33 (d, *J* = 9.4 Hz, 1H), 1.85 (d, *J* = 9.4 Hz, 1H); ^{13}C NMR (50 MHz; DMSO-d_6): δ = 148.5, 144.1, 142.3, 120.9, 70.5, 50.3, 41.8; Mass (ESI): 229 $[M+H]^+$; HRMS(ESI): calcd for $C_{13}H_{13}N_2O_2$ $[M+H]^+$ 229.0977, found 229.0986.
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19. *Experimental procedure and spectral data for* **5**: A 0.65 M aq soln of $NaIO_4$ (3.5 mL, 2.14 mmol) was added drop-wise to a vigorously stirred suspension of chromatography-grade silica gel (3.5 g) in DCM (59 mL). After addition of **6** (350 mg, 1.53 mmol) in DCM (78 mL) to the resulting flaky soln, stirring was continued for another 30 min and then the mixture was passed through a filter pad onto a small amount of Na_2SO_4. The retained silica gel was washed with DCM (20 mL) and the washings were pooled with filtrate. Removal of the solvent left the dialdehyde as a solid reddish residue, which was dissolved in methanol (8 mL). PMB amine (210 mg, 1.53 mmol) in methanol (3 mL) followed by AcOH (9 μL, 0.15 mmol) was added to the above-mentioned soln at 0 °C and after stirring at rt for 10 min, $Na(CN)BH_3$ (145 mg, 2.3 mmol) was added at 0 °C and stirred at rt for 2 h. Methanol was evaporated and the residue was dissolved in water (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with water (2 × 15 mL) and brine (1 × 15 mL), dried (anhyd $MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography (Silica gel, EtOAc–hexane, 15:85) to give 315 mg (62%) of **5** as a brown-colored thick liquid. IR (Neat, cm^{-1}): 2947, 2789, 1512, 1244, 1031; ^1H NMR (400 MHz; $CDCl_3$): δ = 8.76 (s, 2H), 7.77 (s, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 2H), 3.72 (s, 3H), 3.41 (s, 2H), 3.35 (br s, 2H), 2.80 (d, *J* = 10.7 Hz, 2H), 2.54 (d, *J* = 10.3 Hz, 2H), 2.34–2.30 (m, 1H), 1.85 (d, *J* = 10.7 Hz, 1H); ^{13}C NMR (50 MHz; $CDCl_3$): δ = 158.4, 150.9, 143.4, 143.3, 130.0, 129.4, 120.4, 113.4, 60.9, 57.2, 55.1, 43.1, 41.2; Mass (ESI): 332 $[M+H]^+$; HRMS(ESI): calcd for $C_{21}H_{22}N_3O$ $[M+H]^+$ 332.1763, found 332.1775.
20. *Experimental procedure and spectral data for* **1**: To a solution of **5** (50 mg, 0.15 mmol) in methanol (2 mL) was added 10% Pd/C (125 mg, 2.5 equiv, wt/wt), followed by HCO_2NH_4 (100 mg, 2 equiv, wt/wt), and heated to reflux for 30 min. The reaction mixture was cooled to rt, and allowed to stand for 24 h. It was filtered through a small pad of Celite and was washed with methanol (10 mL). The filtrate was evaporated under reduced pressure and purified by flash chromatography (Silica gel, MeOH–$CHCl_3$, 2:98) to give 20 mg (64%) of **1** as a cream-colored solid. Mp: 137–139 °C; IR (KBr, cm^{-1}): 3342, 2949, 2924, 2852, 1473, 1354; ^1H NMR (400 MHz; $CDCl_3$): δ = 8.75 (s, 2H), 7.83 (s, 2H), 3.25 (br s, 2H), 3.15 (d, *J* = 13.0 Hz, 2H), 2.92 (d, *J* = 13.0 Hz, 2H), 2.48 (m, 1H), 2.09 (d, *J* = 8.8 Hz, 1H), 1.82 (br s, 1H); ^{13}C NMR (50 MHz; $CDCl_3$): δ = 149.6, 143.5, 143.6, 121.7, 50.5, 43.1, 42.2; Mass (ESI): 212 $[M+H]^+$; HRMS(ESI): calcd for $C_{13}H_{14}N_3$ $[M+H]^+$ 212.1188, found 212.1196.