A Short and Efficient Synthesis of (*S*)-(+)-2-(Hydroxymethyl)-6-piperidin-2-one

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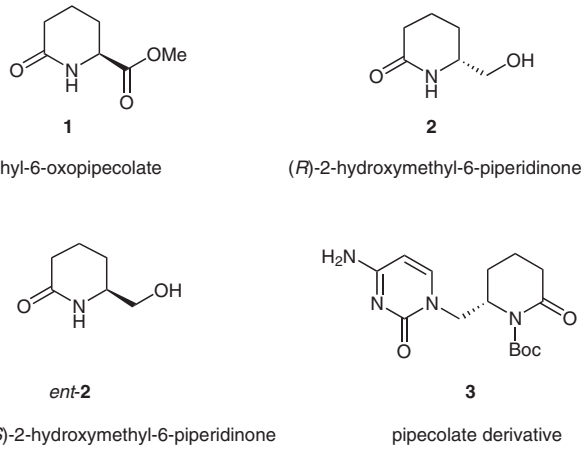
Abstract: A concise synthesis of (*S*)-(+)-2-(hydroxymethyl)-6-piperidin-2-one is described that employs L-aspartic acid as chiral pool starting material and Wittig reaction as the key step.

Key words: Wittig reaction, amino acid, piperidone, L-aspartic acid, hydrogenation, pipecolate

There has been considerable interest in the development of synthetic routes to substituted piperidines, piperidinones and indolizidines due to their widespread occurrence in nature and important biological activity.[1] In particular, the development of a general methodology for the preparation of substituted piperidines in a diastereoselective and enantioselective manner has attracted a great deal of interest amongst synthetic organic chemists.[2,3] Moloney et al.[1] reported the synthesis of both racemic and enantiopure 6-oxopipecolic acid derivatives **1** and **2** from L-lysine and racemic pipecolic acid, which can readily be converted into substrates that are amenable to further ring functionalisation (Figure 1).



1 methyl-6-oxopipecolate

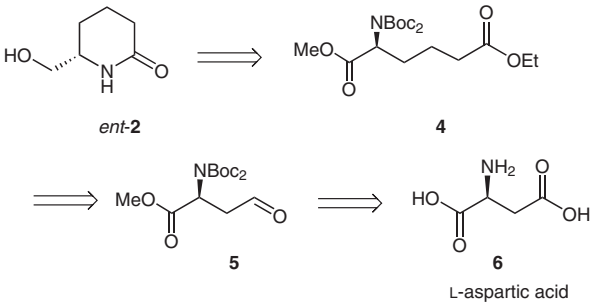
2 (*R*)-2-hydroxymethyl-6-piperidinone

ent-**2** (*S*)-2-hydroxymethyl-6-piperidinone

3 pipecolate derivative

Figure 1 Structure of various piperidone derivatives

The title compound is part of an important class of antitumor agents and is useful for the synthesis of pipecolic acid derivatives.[4] As part of our research programme on the asymmetric synthesis of hydroxylated piperidines,[5] we became interested in developing a route to 2-piperidone derivatives. Herein, we wish to report a facile synthesis of (*S*)-2-hydroxymethyl-6-piperidin-2-one using L-aspartic acid as starting material and Wittig olefination as the key step.



Scheme 1 Retrosynthetic route to *ent*-**2**

The retrosynthetic analysis of target molecule *ent*-**2** is outlined in Scheme 1. We envisioned that the target molecule could be obtained from its precursor **4** which, in turn, could be derived from aldehyde **5** through a 2C-Wittig olefination reaction. Aldehyde **5** would be obtained by diisobutylaluminum hydride (DIBAL-H) mediated reduction of an ester, which could be easily accessed from commercially available starting material, L-aspartic acid (**6**).

The synthesis of *ent*-**2** began from commercially available L-aspartic acid (**6**). Thus, the amino moiety of L-aspartic acid was protected with di-*tert*-butyl dicarbonate (Boc_2O) in the presence of sodium hydroxide and, subsequently, both carboxylic groups were esterified with iodomethane in the presence of potassium carbonate in *N*,*N*-dimethylformamide (DMF) at 0 °C to give the diester **7** in 87% yield (Scheme 2). The amino group of **7** was again protected with Boc_2O in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) to afford the *N*-diBoc-derivative of L-aspartic acid **8** in 93% yield.[6a,b] Regioselective reduction of the β-methyl ester with DIBAL-H at –78 °C afforded the L-aspartic acid semi-aldehyde **5** which, on subsequent treatment with 2C-Wittig reagent, gave the unsaturated ester **9** in 86% yield. Compound **9** was reduced with Pd/C under hydrogenation conditions to furnish the saturated ester **4** in 87% yield. Finally, deprotection of the Boc group with 50% trifluoroacetic acid (TFA) followed by neutralization with saturated sodium hydrogen carbonate gave pipecolate **1** in 81% yield. The spectroscopic data of compound **1** was in accordance

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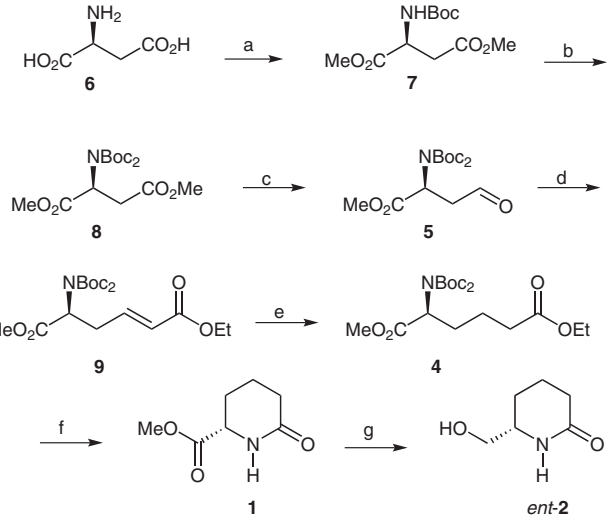
with data reported in the literature.[1a,b] Finally, the ester group was reduced to furnish the target molecule *ent*-**2**[1a,b] using known conditions.



Scheme 2 Synthesis of *ent*-**2**. *Reagents and conditions*: (a) (i) Boc_2O, 1 N NaOH, dioxane/H_2O, 5 °C→r.t., 3.5 h; (ii) K_2CO_3, MeI, DMF, 0 °C→r.t., 1 h, 87%; (b) Boc_2O, DMAP, MeCN, r.t., overnight, 93%; (c) DIBAL-H, anhyd Et_2O, –78 °C, 5 min; (d) $Ph_3P{=}CHCO_2Et$, anhyd THF, 60 °C, 86%; (e) H_2, Pd/C, EtOAc, r.t., 2 h, 87%; (f) TFA, CH_2Cl_2, 0 °C→r.t., 2 h, $NaHCO_3$, 81%; (g) ref. 2.

In summary, we have accomplished a short synthesis of (*S*)-2-(hydroxymethyl)-6-piperidin-2-one starting from L-aspartic acid as a chiral pool starting material and using Wittig olefination as a key step.

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-tight syringes, cannula and septa. Solvents and reagents were purified and dried by standard methods prior to use. Progress of all the reactions were monitored by TLC using glass plates precoated with silica gel 60 F254 to a thickness of 0.25 mm (Merck). Column chromatography was performed on silica gel (60–120 mesh) using petroleum ether (PE)–EtOAc mixture as the eluent. PE refers to the fraction boiling in the 60–80 °C range. Optical rotations were measured with a JASCO DIP-360 digital polarimeter at 25 °C. IR spectra were recorded with a Perkin–Elmer FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-200 spectrometer at 200 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard. ESI-MS were obtained with an API-Q-Star Applied Biosystems spectrometer. Elemental analyses were carried out with a Carlo Erba CHNSO analyzer.

(*S*)-Dimethyl 2-(*tert*-Butoxycarbonylamino)succinate (7)

A solution of Boc_2O (9.03 g, 41.2 mmol) in dioxane (45 mL) was added to an ice-cold magnetically stirred solution of L-aspartic acid (**6**; 5.0 g, 37.6 mmol) in 1 N NaOH (3.0 g in 75.2 mL H_2O) by means of an addition funnel. The two-phase mixture was stirred at 5 °C for 30 min then allowed to warm to 25 °C over 3.5 h, at which time TLC analysis showed the reaction to be complete. The reaction mixture was concentrated to half of the original volume at 45 °C, cooled in ice bath, acidified to pH 2–3 by the slow addition of 1 N $KHSO_4$ (13.6 g in 100 mL) and then extracted with EtOAc (3 × 150 mL). The combined extract was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated to give *N*-Boc-L-aspartic acid as colorless sticky compound which was used in the next reaction without further purification.

To an ice-cold solution of *N*-Boc-L-aspartic acid (8.2 g, 31.42 mmol) in DMF (50 mL), was added solid K_2CO_3 (9.54 g, 69.12 mmol). After stirring for 10 min in an ice bath, MeI (7.8 mL, 125.7 mmol) was added to the white suspension and stirring was continued at 0 °C for 30 min, whereupon the mixture solidified. The reaction mixture was warmed to r.t. and stirred for an additional 1 h, at which point TLC analysis indicated complete formation of the methyl ester. The reaction mixture was filtered by suction and the filtrate was partitioned between EtOAc (3 × 100 mL) and H_2O (50 mL). The organic phase was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography of the crude product (PE–EtOAc, 8.5:1.5) gave (*S*)-dimethyl 2-(*tert*-butoxycarbonylamino)succinate (**7**).

Yield: 8.5 g (87% over two steps); white solid; mp 61 °C (Lit.[6b] 60 °C); $[\alpha]_D^{25}$ +30.4 (*c* 2.1, $CHCl_3$) [Lit.[6b] +30.8 (*c* 2.1, $CHCl_3$)].

IR (neat): 3445, 3032, 1731, 1720 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 2.76–3.06 (m, 2 H), 3.69 (s, 3 H), 3.76 (s, 3 H), 4.53–4.62 (m, 1 H), 5.5 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.5, 35.3, 51.5, 52.1, 54.5, 83.1, 151.2, 169.8, 170.6.

ESI-MS: *m*/*z* = 284.32 $[M + Na]^+$.

(*S*)-Dimethyl 2-[Bis(*tert*-butoxycarbonyl)amino]succinate (8)

To a mixture of *N*-Boc amino ester **7** (1.0 g, 3.83 mmol) and DMAP (0.094 g, 0.8 mmole) in anhyd MeCN (10 mL) was added Boc_2O (1.3 g, 5.75 mmol) at r.t. The reaction mixture became slightly red and gas evolution was observed. After stirring for 2 h, TLC showed some starting material remained. Excess Boc_2O (0.42 g, 1.92 mmol) was added and the mixture was stirred overnight. After completion of reaction, solvent was evaporated in vacuo and the crude residue was purified by silica gel column chromatography (EtOAc–PE, 1:9) to give bis-carbamate **8**.

Yield: 1.3 g (93%); oily compound; $[\alpha]_D^{25}$ –60.5 (*c* 2.0, $CHCl_3$) [Lit.[6b] –61.0 (*c* 2.0, $CHCl_3$)].

IR (neat): 3032, 1731, 1720 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.43 (s, 18 H), 2.66–2.77 (m, 1 H), 3.18–3.30 (m, 1 H), 3.69 (s, 3 H), 3.72 (s, 3 H), 5.41–5.47 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.5, 35.2, 51.4, 52.0, 54.4, 83.0, 151.1, 169.7, 170.5.

ESI-MS: *m*/*z* = 384.55 $[M + Na]^+$, 400.54 $[M + K]^+$.

(*S*,*E*)-1-Ethyl 6-Methyl 5-[Bis(*tert*-butoxycarbonyl)amino]hex-2-enedioate (9)

To a solution of the dimethyl ester **8** (1.0 g, 2.77 mmol) in anhyd Et_2O (27.7 mL), was added dropwise DIBAL-H (1.32 mL, 2.3 M in toluene, 2.77 mmol) at –78 °C. The reaction mixture was stirred for 5 min and quenched with H_2O (0.35 mL, 19.4 mmol). After stirring for 30 min, the reaction mixture was dried over Na_2SO_4 and filtered through a pad of Celite. The solvent was evaporated to give aldehyde **5** as a colorless oil.

To a solution of aldehyde **5** (0.92 g, 2.78 mmol) in anhyd THF (15 mL), was added ethyl (triphenylphosphoranylidene)acetate (1.5 g, 4.2 mmol) at r.t., and the reaction mixture was stirred overnight. After completion of the reaction, solvent was evaporated and the crude residue was purified by silica gel column chromatography (EtOAc–PE, 5:95) to furnish **9**.

Yield: 0.96 g (86% over two steps); colorless oil; $[\alpha]_D^{25}$ –50.3 (*c* 1.0, $CHCl_3$).

IR (neat): 1743, 1654 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.0 Hz, 3 H), 1.48 (s, 18 H), 2.73–3.06 (m, 2 H), 3.73 (s, 3 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 5.00–5.07 (m, 1 H), 5.86 (d, *J* = 14.3 Hz, 1 H), 6.81–6.96 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 27.9, 33.0, 52.4, 56.9, 60.2, 83.5, 124.3, 144.0, 151.7, 166.0, 170.3.

ESI-MS: *m*/*z* = 424.66 $[M + Na]^+$, 440.66 $[M + K]^+$.

(*S*)-6-Ethyl 1-Methyl 2-[Bis(*tert*-butoxycarbonyl)amino]hexanedioate (4)

To a solution of olefin **9** (0.4 g) in anhyd EtOAc (10 mL), was added 10% Pd/C (25 mg) and the mixture was stirred in a hydrogen atmosphere. After 2 h stirring, the reaction mixture was filtered on Celite and the filtrate was evaporated in vacuo. The crude compound was purified by silica gel column chromatography (EtOAc–PE, 1:9) to afford **4**.

Yield: 0.35 g (87%); oil; $[\alpha]_D^{25}$ –43.8 (*c* 1.0, $CHCl_3$).

IR (neat): 1740 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.0 Hz, 3 H), 1.49 (s, 18 H), 1.63–1.73 (m, 2 H), 1.98–2.11 (m, 2 H), 2.29–2.37 (m, 2 H), 3.70 (s, 3 H), 4.09 (q, *J* = 7.2 Hz, 2 H), 4.83–4.91 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 21.5, 27.7, 29.1, 33.6, 51.9, 57.5, 60.0, 82.9, 151.8, 170.9, 172.8.

ESI-MS: *m*/*z* = 204.48 $[M^+ + 1 - 2\ Boc]$.

(*S*)-(–)-Methyl 6-Oxo-2-piperidinecarboxylate (1)

To a solution of compound **4** (0.2 g, 0.5 mmol) in anhyd CH_2Cl_2 (1.0 mL), TFA (0.1 mL, 1.0 mmol) was added at 0 °C and reaction mixture was stirred at r.t. for 2 h. Solvent was evaporated and neutralized with sat. $NaHCO_3$ (2 mL), then extracted with CH_2Cl_2 (3 × 10 mL). The extract was evaporated in vacuo and the crude residue was purified by silica gel column chromatography (EtOAc–PE, 2:8) to give pipecolate derivative **1**.

Yield: 65 mg (81%); pale-yellow liquid; $[\alpha]_D^{25}$ –9.4 (*c* 1.06, $CHCl_3$) [Lit.[1b] –9.6 (*c* 1.06, $CHCl_3$)].

IR (neat): 3019, 1743, 1666 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.78–1.93 (m, 3 H), 2.10–2.22 (m, 1 H), 2.31–2.38 (m, 2 H), 3.76 (s, 3 H), 4.06–4.12 (m, 1 H), 6.68 (br s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.3, 25.3, 30.9, 52.6, 54.6, 171.6.

ESI-MS: *m*/*z* = 180.21 $[M + Na]^+$.

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