A Facile Synthesis of (*S*)-4-Hydroxypyrrolidin-2-one from (*S*)-Malic Acid

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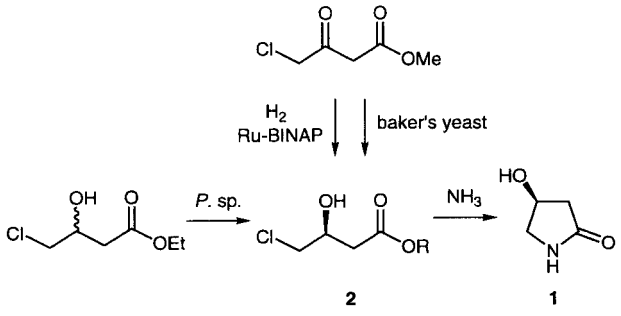
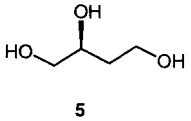
Abstract: The chiral diol methyl 3,4-dihydroxybutanoate **4b** obtained from (*S*)-malic acid dimethyl ester **(3b)** was subjected to regioselective tosylation to give the tosylate **6** in good yield. Subsequent treatment of **6** with aqueous ammonia afforded (*S*)-4-hydroxypyrrolidin-2-one **(1)** through three steps in 32% overall yield from **3b**.

Key words: tosylation, amination, reduction, regioselective reaction

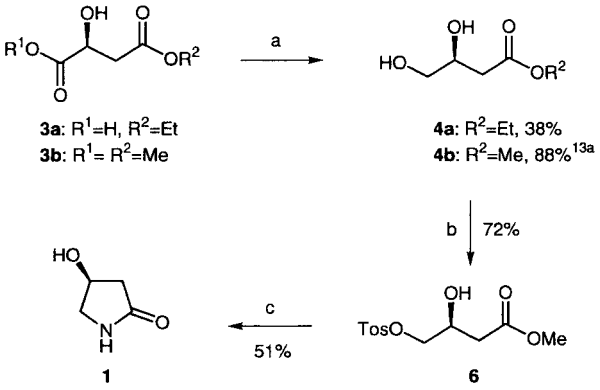
(*S*)-4-Hydroxypyrrolidin-2-one (**1**), a component of *Amantia muscaria*,[1] has recently aroused considerable attention as a cyclic γ-aminobutyric acid (GABA) analog[2] and as a key precursor for useful compounds such as (*S*)-γ-amino-β-hydroxybutyric acid (GABOB)[3] and the C2 side chains of 1-β-methylcarbapenems.[4] There are various methods available for the synthesis of optically active 4-hydroxypyrrolidin-2-one which utilize: (2*S*,4*R*)-4-hydroxyproline as a chiral pool;[5] the enzymatic hydroxylation of pyrrolidine-2-one;[6] and asymmetric syntheses.[7] Of more importance is the synthesis involving amination and cyclization of (*S*)-4-chloro-3-hydroxybutanoate **2**[8] obtained by enzymatic[8,9] or asymmetric reduction[10] of the keto derivative or by microbial dechlorinative resolution of the racemates[11] (Scheme 1). We envisaged the possible use of the corresponding tosyloxy derivative **6** instead of the chloride **2** for the reaction (Scheme 2). This would provide a more simple and practical access to **1** since the tosylate **6** might be easily obtained from (*S*)-malic acid via the regioselective tosylation of the chiral diol **4**.



Scheme 1



Reduction of the carboxy group of (*S*)-malic acid β-ethyl ester **(3a)** was first attempted to obtain the required chiral diol **4a**. Treatment of **3a** with two equivalents of a borane–methyl sulfide complex,[12] however, resulted in a poor yield of the diol **4a** with concomitant over-reduction to the triol derivative **5**. As an alternative approach, the use of (*S*)-malic acid dimethyl ester **(3b)** was then undertaken as the starting material. According to the procedure reported by Saito et al.,[13] the desired diol **4b** was obtained in excellent yield (88%) by the treatment of **3b** with borane–methyl sulfide complex in the presence of a catalytic amount of sodium borohydride. The primary hydroxy group of **4b** was selectively tosylated by the standard procedure to give the 4-tosyloxy derivative **6** in good yield in crystals. The subsequent epoxide formation, ring-opening with ammonia and lactamization were simultaneously achieved by a simple treatment of **6** with aqueous ammonia to afford the target compound **1** in 51% yield. The compound **1** synthesized by this method had an optical rotation of $[\alpha]_D^{25}$ –57.8 (*c* = 1.0, H_2O) in good accordance with the reported value ($[\alpha]_D^{25}$ –55.5 (*c* = 1.04, H_2O)).[14]



a: $Me_2S{\cdot}BH_3$, THF (for **3a**); $Me_2S{\cdot}BH_3$, $NaBH_4$ (cat.), THF (for **3b**); b: TosCl, pyridine; c: aq NH_3

Scheme 2

In conclusion, a facile synthesis of (*S*)-4-hydroxypyrrolidin-2-one **(1)** was worked out. It required just three steps from (*S*)-malic acid dimethyl ester (or four steps from (*S*)-malic acid) by the use of a simple procedure and inexpensive reagents. Although the yield of the final step was moderate,[15] the short steps required and the economical operation make the present synthesis much more advantageous over previously documented methods. The process

has already been applied to multi-kilogram scale preparation and similar yields were reproduced.

IR spectra were recorded on a Perkin–Elmer 1640 IR spectrophotometer and are reported as λ_{max} (cm^{-1}). ^1H NMR spectra were recorded on a Bruker AC-200 (200 MHz) spectrometer and were reported in δ values. MS were taken on a Hitachi M-2000A spectrometer at an ionizing potential of 70 eV. Microanalysis were performed by Perkin–Elmer 2400 Series II CHNS/O Analyzer. Flash chromatography was accomplished by using Kieselgel 60 (230–400 mesh, E. Merck).

Ethyl (*S*)-3,4-Dihydroxybutanoate (4a)

To a solution of **3a**[12] (1 g, 6.17 mmol) in THF (10 mL) was added 10 M $Me_2S{\cdot}BH_3$ in THF (1.23 mL, 12.3 mmol) at 5 °C and the mixture was stirred at 25 °C for 3 h. MeOH (5 mL) was carefully added to the mixture and evaporated. The residue was purified by column chromatography (silica gel, hexane/EtOAc 1:1 to 1:3 and then EtOAc/MeOH 85:15) to give **4a** (348 mg, 38%) and triol **5** (222 mg, 34%) both as colorless oil.

4a:

$[\alpha]_D^{25}$ +6.3 (*c* = 1.0, $CDCl_3$) (lit.[13b] $[\alpha]_D^{25}$ +6.22 (*c* = 1.22, $CDCl_3$))
IR (KBr): ν_{max} = 3365, 1734 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.32 (t, *J* = 7 Hz, 3 H), 2.48 (dd, *J* = 4.6, 16 Hz, 1 H), 2.58 (dd, *J* = 7.8, 16 Hz, 1 H), 2.73 (s, 2 H), 3.54 (dd, *J* = 6.2, 10 Hz, 1 H), 3.66–3.74 (m, 1 H), 4.19 (q, *J* = 7 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 14.12 (q), 37.90 (t), 60.95 (t), 65.70 (t), 68.75 (d), 172.53 (s).

SIMS: *m/z* = 149 (M^+ + 1).

5:

$[\alpha]_D^{25}$ –25.6 (*c* = 0.66, MeOH)
IR (Nujol): ν_{max} = 3348, 2940 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.29–1.67 (m, 2 H), 3.16–3.34 (m, 2 H), 3.39–3.60 (m, 3 H), 4.33–4.40 (m, 2 H), 4.46–4.51 (m, 1 H).

^{13}C NMR (DMSO-d_6): δ = 36.27 (t), 57.57 (t), 65.65 (t), 68.29 (d).

SIMS: *m/z* = 107 (M^+ + 1).

$C_4H_{10}O_3$	calcd	C	45.27	H	9.50
(106.124)	found		44.99		9.56

Methyl (*S*)-3,4-Dihydroxybutanoate (4b)[13a]

To a solution of **3b** (1 kg, 6.17 mol) in THF (13.3 L) was added portionwise 10 M $Me_2S{\cdot}BH_3$ (617 mL) at 20 °C for 30 min and the mixture was stirred at 20 °C for 30 min. $NaBH_4$ (11.7 g, 0.31 mol) was added at 10 °C and stirred at 10 °C for 30 min and then at 25 °C for 1 h. To the mixture was added EtOH (2.1 L) and $TosCl{\cdot}H_2O$ (58.5 g, 0.31 mol) and the mixture was stirred at 25 °C for 30 min. The mixture was evaporated. Into the residue was added a mixture of toluene/EtOH (1:1, 13.3 L) and the mixture was evaporated. Into the residue was added toluene (10 L) and the solution was evaporated. The residue was chromatographed (silica gel, 4.2 kg, EtOAc) to afford **4b**[13a] (728 g, 88%) as a colorless oil.

IR (Nujol): ν_{max} = 3380, 1734 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.49 (dd, *J* = 5, 17 Hz, 1 H), 2.63 (dd, *J* = 6, 17 Hz, 1 H), 3.08 (s, 2 H), 3.53 (dd, *J* = 6, 12 Hz, 1 H), 3.70 (dd, *J* = 3.4, 12 Hz, 1 H), 3.72 (s, 3 H), 4.08–4.20 (m, 1 H).

SIMS: *m/z* = 135 (M^+ + 1).

Methyl (*S*)-3-Hydroxy-4-(tosyloxy)butanoate (6)

To a solution of **4b**[13a] (1.1 kg, 8 mol) in pyridine (5 L) was added TosCl (1.72 kg, 9 mol) in one portion at 10 °C and the mixture was allowed to warm to 25 °C and stirred for 17 h. The mixture was diluted with EtOAc (10 L) and washed with 2 N HCl (2 × 10 L) and water (10 L), dried (anhyd $MgSO_4$), and then evaporated. The crystals formed were collected by adding hexane to afford **6** (1.69 kg, 72%) as colorless crystals; mp 79–80 °C; $[\alpha]_D^{25}$ –7.1 (*c* = 1.0, $CHCl_3$).

IR (KBr): ν_{max} = 3583, 1743, 1725 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.45 (s, 3 H), 2.53 (d, *J* = 2 Hz, 1 H), 2.56 (s, 1 H), 3.69 (s, 3 H), 4.03 (s, 1 H), 4.05 (s, 1 H), 4.20–4.31 (m, 1 H), 7.36 (d, *J* = 8 Hz, 2 H), 7.80 (d, *J* = 8 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 21.7 (q), 37.2 (t), 52.0 (q), 66.0 (d), 72.0 (t), 128.0 (d), 130.0 (d), 132.5 (s), 145.2 (s), 171.9 (s).

SIMS: *m/z* = 289 (M^+ + 1).

$C_{12}H_{16}O_6S$	calcd	C	49.98	H	5.59
(288.326)	found		49.91		5.48

(*S*)-4-Hydroxypyrrolidin-2-one (1)

A mixture of **6** (3 kg, 10.4 mol), concd aq NH_3 (24%, 6 kg) and water (7.5 L) was warmed up to 70 °C for 30 min and refluxed for 3 h. The mixture was evaporated, and EtOH (15 L) was added to dissolve the residue. The mixture was gradually cooled down to 30 °C for 1 h and stirred at 5 °C for 1 h. The crystals formed were filtered off and the solid collected was washed with EtOH (2.88 L). The filtrate and washings were combined and evaporated. The residue was dissolved in water (62 ml) and charged on ion exchange column (IRA-400, OH– form, 9 L) for 1 h. Developing was carried out for 2.5 h by using water (24 L), and fractions collected were evaporated. EtOH (2.88 L) was added to the residue and evaporated. The resulting residue was dissolved in EtOH (5.96 L) and cooled down to 30 °C for 1 h and stirred at 5 °C for 1 h. The crystals formed were collected and washed with cold EtOH (865 mL) to afford **1** (538 g, 51%) as colorless crystals; mp 154–155 °C (lit.[14] mp 155–157 °C); $[\alpha]_D^{20}$ –57.8 (*c* = 1.0, H_2O) (lit.[14] $[\alpha]_D^{20}$ –55.5 (*c* = 1.04, H_2O) for (*S*)-isomer and +57.5 (*c* = 1.40, H_2O) for (*R*)-isomer).

IR (KBr): ν_{max} = 3247, 1674 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.93 (dd, *J* = 2.8, 16 Hz, 1 H), 2.40 (dd, *J* = 6.8, 16 Hz, 1 H), 3.02 (dd, *J* = 0.9, 10 Hz, 1 H), 3.38–3.48 (m, 1 H), 4.27–4.38 (m, 1 H), 5.14 (d, *J* = 4 Hz, 1 H), 7.54 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 40.13 (t), 50.72 (t), 65.86 (d), 175.48 (s).

SIMS: *m/z* = 102 (M^+ + 1).

$C_4H_7NO_2$	calcd	C	47.52	H	6.98	N	13.85
(101.108)	found		47.67		7.16		13.83

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