

A New Chiral Synthesis of Naturally Occurring (-)-(S)-4-Hydroxy-2-pyrrolidinone

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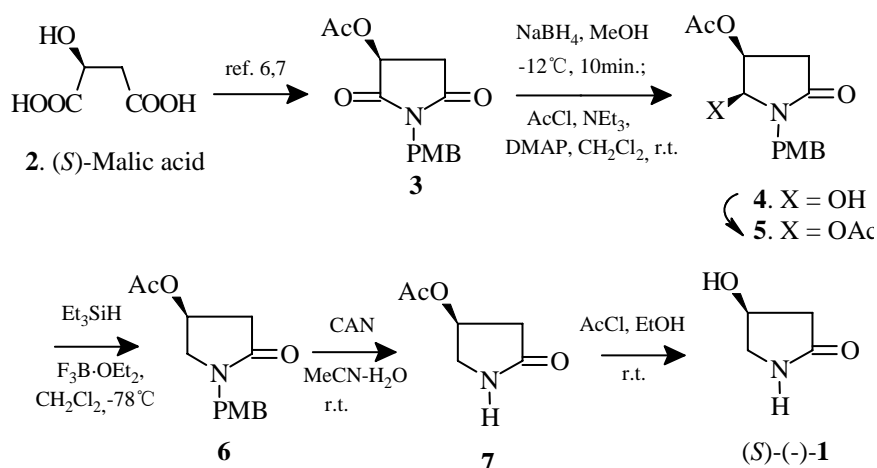
Abstract: A new and convenient chiral synthesis of naturally occurring (-)-(S)-4-hydroxy-2-pyrrolidinone from (S)-malic acid was reported.

Keywords: (S)-Malic Acid, (-)-(S)-4-hydroxy-2-pyrrolidinone, ionic hydrogenation.

4-Hydroxy-2-pyrrolidinone **1** is an attractive simple molecule. First, it has served as a key intermediate in the synthesis¹ of oxiracetam, a drug useful for improving learning and memory. Second, **1** can be easily transformed into antiepileptic and hypotensive drug GABOB², and hypolipidemic agent carnitine². Third, (-)-4-hydroxy-2-pyrrolidinone **1** has been isolated³ from the toadstool *Amanita muscaria*. Its absolute configuration has been erroneously assigned³ as (R). The first chiral synthesis of this compound has been reported by Pifferi⁴. However, not until 1984 did its absolute configuration been corrected to be (S) *via* another chiral synthesis⁵. In our program directed towards the asymmetric synthesis of bioactive compounds using easily available (S)-malic acid as chiron,⁶ we wish to report herein a new chiral synthesis of (-)-**1**.

As shown in **Scheme 1**, malimide⁷ **3** was prepared in one-pot reaction from (S)-malic acid following a procedure used for its *N*-benzyl analog^{6,7}. Regio- and stereoselective reduction of **3** followed by acetylation gave diacetate **5**⁷ in good overall yield. Borontrifluoride etherate mediated ionic hydrogenation of **5** with excess of triethylsilane⁶ gave desired lactam **6** as colorless oil [yield, 80%, $[\alpha]_{\text{D}} -32.6$ (*c* 1.2, CHCl₃)]. *N*-Deprotection of **6** under oxidative conditions provided white crystalline **7** (in 84% yield) [mp 56°C, $[\alpha]_{\text{D}} -46.7$ (*c* 0.9, CHCl₃)]. Finally, deacetylation of **7** afforded desired (-)-(S)-4-hydroxy-2-pyrrolidinone **1** [mp 152-154 °C, $[\alpha]_{\text{D}} -54.8$ (*c* 0.48, H₂O)]⁸ and in a yield of 77.2%. The ee of the (-)-**1** is estimated to be at least 95% by comparing the $[\alpha]_{\text{D}}$ value with those reported in the literature^{3-5, 8}.

In summary, we have developed a new chiral synthesis of naturally occurring (-)-(S)-4-hydroxy-2-pyrrolidinone from (S)-malic acid in high enantiomeric purity.

Scheme 1 (PMB = *p*-MeOC₆H₄CH₂-)**Acknowledgments**

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References and notes

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8. The reported optical rotation values for (S)-**1**: [α]_D -45.8 (H₂O)³; [α]_D -55.5 (c 1.04, H₂O)⁴; [α]_D -34.5 (c 1.4, H₂O), 60% ee⁵; (R)-**1**: [α]_D +58.6 (c 0.36, H₂O)²; [α]_D +57 (c 1.4, H₂O)⁴.

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