A Practical Synthesis of (S)- and (R)-4-Hydroxy-2-pyrrolidinone *via* 1-Phenylethylamine Mediated Resolution

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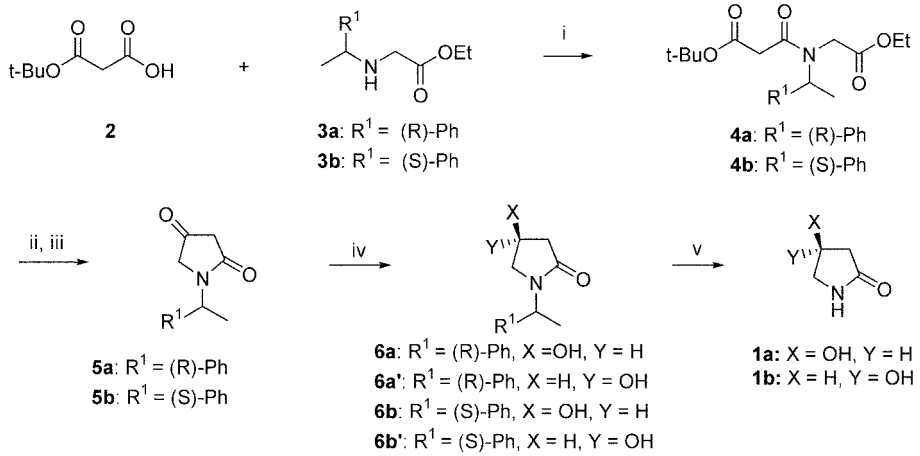
The synthesis of natural or unnatural pyrrolidine and pyrrolidinone derivatives has recently attracted considerable interest due to their wide range of biological properties.[1] A large number of pyrrolidine alkaloids and γ-amino acids have been prepared by using structurally unique 2-pyrrolidinones, which could be utilized as common synthetic subunits and/or chiral templates of biologically active compounds.[2] In the course of our investigations concerning the synthesis of γ-aminobutyric acid derivatives which are important in neurobiology,[3] we have been interested in the synthesis of both enantiomers of 4-hydroxy-2-pyrrolidinone (**1**), a useful synthetic precursor of a variety of γ-amino acids (GABA) and pyrrolidinone alkaloids.[4] A few reports of the synthesis of the enantiopure pyrrolidinone **1** have been found in literature.[4,5,6] The reported stereoselective syntheses of **1** were mostly involved in the synthetic methods of (S)-enantiomer of **1** starting from ethyl (S)-4-chloro-3-hydroxybutanoate[5] obtained enzymetically from ethyl 4-chloro-3-oxobutanoate, from (S)-4-amino-3-hydroxybutanoic acids,[6] and from (S)-malic acid.[4] We wish to report herein a practical synthesis of enantiomerically pure (R)- and (S)-isomers of **1** in multigram scale.

Our synthetic approach involved the preparation of the enantiomeric malonamide derivatives **4** bearing a chiral N-phenylethyl moiety for a facile cyclization and the easy separation of the corresponding sec-alcoholic diastereomers **6**, followed by deblocking of the chiral moiety as shown on Scheme 1. In order to examine the most appropriate precursor of **1**, two enantiomeric malonamides **4** were prepared from readily available starting materials.

Thus, condensation of half acid of t-butyl malonate **2** and glycine esters **3a**, **b** using 1,1'-carbonyldiimidazole (CDI) as an activating agent afforded the N-phenylethyl-protected amides **4a**, **b** in respective yields of 91 and 90%. Cyclization of malonamides **4a** and **4b** was readily effected with 1.1 equiv of potassium *tert*-butoxide in toluene (rt, 5-6 h), followed by acdification with 1 N HCl to afford white solids of the corresponding 4-oxoamides **5a** and **5b** in excellent yields (>92%). It is worth noting that the reaction of **4a**, **b** with potassium *tert*-butoxide in toluene at room temperature gave directly the decarboxylated 4-oxopyrrolidinones **5a**, **b** without further treatment of the cyclized pyrrolidinones having the *t*-butoxycarbonyl group at C-3. Subsequent reduction of the carbonyl group of **5a**, **b** with $NaBH_4$ produced nearly 1 : 1 diastereomeric mixtures of 4-hydroxy-pyrrolidinones **6a**, **a'** and **6b**, **b'** in respective yields of 79% and 78%. In the courses of several attempted isolations of the diastereomeric mixtures **6a**, **a'** and **6b**, **b'**, we found that one of the diastereomers had a relatively low solubility in acetonitrile and could be isolated by recrystallization from this solvent. Thus, the diastereomeric mixture **6a**, **a'** was readily separated by recrystallization in acetonitrile to give a



Scheme 1. *Reagents and conditions:* (i) CDI, CH_3CN, rt, 3 h (**4a** 91%, **4b** 90%); (ii) *t*-BuOK, toluene, rt, 5-6 h; (iii) 1 N HCl, rt (**5a** 92%, **5b** 90%); (iv) $NaHBH_4$, CH_3OH, 0 °C, 2 h (**6a** 38%, **6a'** 39%, **6b** 38%, **6b'** 35%); (v) CH_3SO_3H, toluene, reflux, 6-10 h (**1a** 92% from **6a**, **1b** 84% from **6a'**).

white solid (38%) of (1'R,4S)-4-hydroxy-1-(1'-phenylethyl)-2-pyrrolidinone (**6a**); (1'R,4R)-pyrrolidinone **6a'** was obtained in 39% yield after chromatographic separation on silica gel of the remaining residue.[9] Under nearly identical condition, (1'S,4S)-pyrrolidinone **6b** was also obtained in 38% yield; chromatographic separation on silica gel of the remaining residue yielded (1'S,4R)-pyrrolidinone **6b'** in 35% yield.[9] In the final step, deprotection of the N-phenylethyl blocking group of pyrrolidinones **6** was required. It has been generally known that N-(1-phenylethyl)amines and N-(1-phenylethyl)amides are less susceptible to catalytic hydrogenolysis than benzyl ether and benzyl esters, and hydrogenolysis of benzylamines and benzylamides can be facillitated by acid.[7] Moreover, Frahm and co-workers recently reported N-(1-phenylethyl)-protected α-aminonitriles were readily converted to the corresponding carboxamides with conc. H_2SO_4 at 25 ^oC resulting in a total loss of the 1-phenylethyl moiety.[8] Based on this information about the sensitivity of the N-phenylethyl moiety of amines and amides under acidic conditions, deprotection of the 1-phenylethyl moiety in **6a** and **6b** was surprisingly accomplished through use of methanesulfonic acid in toluene. Thus, treatment of **6a** and **6a'** in refluxing toluene in the presence of 5 equiv of methanesulfonic acid for 5-6 h afforded the final enantiopure **1a** and **1b** in respective yields of 92 and 84% after chromatographic separation on silica gel. To our knowledge, this is the first example of highly efficient removal of the N-phenylethyl group on amides using metanesulfonic acid.

In summary, we have described a practical route of the preparation of both (R)- and (S)-4-hydroxy-2-pyrrolidinone from a single precusor **4a** or **4b** through use of N-phenylethyl-mediated resolution of pyrrolidinones **6** in respective overall yields of 32 and 30% starting from **4a** via **6a**, **a'**.

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9. Data for **6**. **6a**: $[\alpha]^{18} = +118.8^o$ (c 1.0, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.25 (5H, m), 5.46 (1H, q, *J* = 7.1 Hz), 4.43 (1H, m), 3.52 (1H, dd, *J* = 10.8, 5.5 Hz), 2.95 (1H, dd, *J* = 10.8, 2.0 Hz), 2.68 (1H, dd, *J* = 17.3, 6.5 Hz), 2.39 (1H, dd, *J* = 17.3, 0.5 Hz), 1.48 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 139.9, 128.5, 127.4, 126.9, 64.3, 51.5, 48.7, 41.5, 16.5. **6a'**: $[\alpha]^{18} = +177.6^o$ (c 1.0, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.26 (5H, m), 5.50 (1H, q, *J* = 7.1 Hz), 4.40 (1H, brs), 3.34 (1H, s), 3.26 (1H, dd, *J* = 10.8, 2.4 Hz), 3.20 (1H, dd, *J* = 10.8, 5.6 Hz), 2.69 (1H, dd, *J* = 17.3, 6.6 Hz), 2.43 (1H, dd, *J* = 17.3, 2.7 Hz), 1.55 (3H, d, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 140.6, 129.3, 128.4, 127.8, 64.7, 51.7, 49.1, 41.8, 16.2. **6b**: $[\alpha]^{18} = -177.6^o$ (c 1.0, EtOH). **6b'**: $[\alpha]^{18} = -118.8^o$ (c 1.0, EtOH).