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A practical synthesis of *S*-quinuclidine-2-carboxylic acid and its enantiomer

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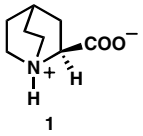
Abstract—A short and convenient synthesis of (*S*)- and (*R*)-quinuclidine-2-carboxylic acids has been developed. The resolution of enantiomers has been accomplished by both chemical and enzymic means.

One of the least studied types of α-amino acids are the bridgehead nitrogen bicyclic structures exemplified by quinuclidine-2-carboxylic acid (**1**, *S*-enantiomer). Although racemic **1** was first synthesized decades ago,[1] it remains an obscure, little studied compound despite its close structural relationship to the important α-amino acids proline and pipecolinic acid. Very little has been published on chiral **1**.[2] A simple and practical synthesis of **1** could facilitate its study as an *N*-terminal amino acid unit for synthetic peptides and other potential therapeutic agents,[3] and as a building block for enantioselective catalysts. Reported herein is a short and effective synthesis of **1** and its enantiomer.



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The synthetic pathway to **1**, which is summarized in Scheme 1, started with commercial 4-(2-hydroxyethyl)piperidine (**2**, Reilly Industries, Indianapolis, IN). N-Acylation of **2** with 1 equiv of di-*tert*-butylpyrocarbonate (in 4:3 H_2O–*t*-BuOH in the presence of 1.1 equiv of NaOH) at 23 °C for 30 h provided the *N*-*tert*-butoxycarbonyl (Boc) derivative of **2** in >99% yield (100 g scale). Swern oxidation of Boc-protected **2** (reaction with dimethyl sulfoxide-oxalyl chloride reagent at −60 °C for 30 min, addition of Et_3N and warming to ambient temperature) afforded the amide-aldehyde **3** after extractive isolation (96%). Treatment of **3** in ether solution with 2.5 equiv of aqueous NaCN at 0 °C followed by dropwise addition of concentrated hydrochloric acid (*DANGER*, hydrogen cyanide generated, must be carried out in a well ventilated hood) at 0 °C afforded cyanohydrin **4** (99.4%) as a colorless oil after extractive isolation.[4] Reaction of **4** with 1.2 equiv of methanesulfonyl chloride and 1.3 equiv of triethylamine in CH_2Cl_2 solution at −30 °C over 2 h gave cyanomesylate **5** as an oil (>99%) after extractive isolation. The mesylate **5** was transformed into cyanoquinuclidine **6** by the sequence: (1) N-deprotection with 5 equiv of CF_3CO_2H in CH_2Cl_2 at 0 °C for 5 min and 23 °C for 1 h, (2) concentration under reduced pressure and reaction with 4 equiv of Et_3N in CH_3CN at reflux for 24 h, and (3) extractive isolation, which provided **6** as a solid in 41% overall yield. The resolution of **6** was readily accomplished using (+)-tartaric acid (1 equiv) in absolute ethanol, which gave a crystalline salt as needles, and 2–3 further recrystallizations from methanol. Pure **6**, mp 70–71 °C, $[\alpha]_D^{23}$ −88.6 (*c* 3.3, $CHCl_3$) was obtained from the salt by treatment with wet $Ba(OH)_2$ or wet $NaHCO_3$ in CH_2Cl_2 and removal of solvent. The absolute configuration of (−)-**6** follows from the conversion to (−)-**1**, the absolute configuration of which had previously been established.[2] HPLC analysis using Chiral Technologies AD column with 10% *i*-PrOH in hexane for elution indicated an enantiomeric ratio of 98:2 (minor peak at 17.1 min, major peak at 19.3 min at 23 °C and a flow rate of 0.5 ml/min). From the mother liquors (+)-**6** was obtained via recrystallization of the salt with (−)-tartaric acid as a colorless solid $[\alpha]_D^{23}$ +84.2 (*c* 2.7, $CHCl_3$) with an enantiomeric ratio of 98.5:1.5 as determined by HPLC analysis.

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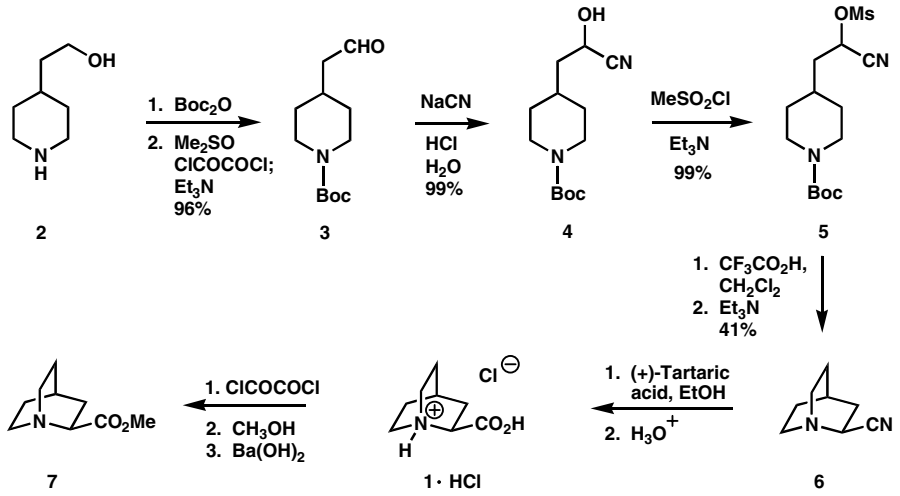
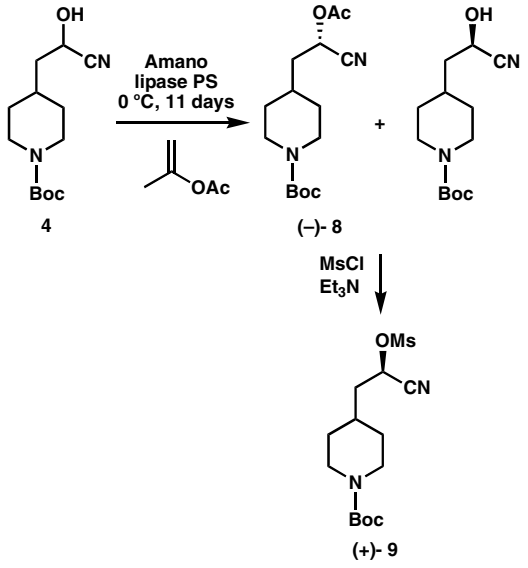


Scheme 1.



Scheme 2.

Hydrolysis of (−)-**6** was effected by heating at reflux with concentrated hydrochloric acid for 24 h to give after evaporation to dryness under reduced pressure the hydrochloride of **1** (*S*-enantiomer) as a crystalline solid in 99% yield, $[\alpha]_D^{23}$ −39.7 (*c* 1.6, H_2O).[1] Treatment of **1**·HCl with oxalyl chloride in CH_2Cl_2 containing a catalytic amount of dimethylformamide for 14 h generated the corresponding acid chloride, which by reaction with methanol afforded the hydrochloride of **7**. The hydrochloride was dissolved in CH_2Cl_2 and stirred with wet $Ba(OH)_2$ at 23 °C for 2 min to give after filtration and removal of solvent the methyl ester **7** (67%, $[\alpha]_D^{23}$ −3.6 (*c* 0.5, $CHCl_3$)).

Another efficient process for resolution has been developed using enantioselective enzyme-catalyzed acetylation of the racemic cyanohydrin **4**. Treatment of **4** in *i*-Pr_2O solution with Amano lipase PS and excess isopropenyl acetate at 0 °C for 11 days effected enantioselective O-acetylation to form **8**. The crude product was treated with CH_3SO_2Cl–Et_3N in CH_2Cl_2 at −30 °C for 1 h to form a mixture of **8** and mesylate **9** as shown in Scheme 2. Chromatography of this mixture on silica gel (EtOAc–hexane) provided the chiral acetate (−)-**8** (46%, 92% of theory, 94% ee by HPLC analysis, $[\alpha]_D^{23}$ −31.6 (*c* 2.0, $CHCl_3$)) and the chiral mesylate (+)-**9** (42%, 84% of theoretical yield).

The chiral quinuclidine derivatives **6** and **7** can be used to make not only a variety of useful amino alcohols but also chiral diamines, compounds that are of interest as chiral reagents. This is not conveniently accomplished by the previously described routes (most of which lead to racemic amino acid **1**[1]). The synthesis outlined in Scheme 1 is short, simple, and easy to scale up. Two simple and efficient methods of resolution allow convenient access to chiral material on a multigram scale. The best literature method for obtaining chiral[2] **1** involves resolution of 2-hydroxymethylquinuclidine and a low yield oxidation (aqueous $KMnO_4$) to **1**.[2b]

References and notes

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3. See, for example, Bencherif, M.; Schmitt, J. D.; Bhatti, B. S.; Crooks, P.; Caldwell, W. S.; Lovette, M. E.; Fowler, K.; Reeves, L.; Lippiello, P. M. *J. Pharm. Exp. Therapeut.* **1998**, *284*, 886–894.
4. Excess cyanide in the aqueous layer after extraction can be destroyed by the addition of aqueous NaOCl (commercial bleach).