JOC Note

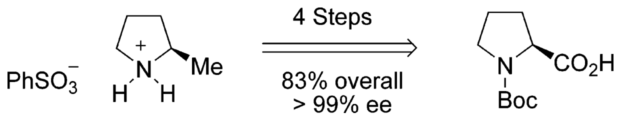
Efficient and Practical Synthesis of (*R*)-2-Methylpyrrolidine

Dalian Zhao,* Jeffrey T. Kuethe, Michel Journet,
Zhihui Peng, and Guy R. Humphrey

*Department of Process Research, Merck & Company, Inc.,
P.O. Box 2000, Rahway, New Jersey 07065*

dalian_zhao@merck.com

Received February 15, 2006



An efficient, practical, and high yielding synthesis of (*R*)-2-methylpyrrolidine is described. The sequence allows for the scalable preparation of the target compound in just four synthetic steps and proceeds in 83% overall yield and >99% optical purity from readily available starting materials.

Substituted pyrrolidines can be found in numerous natural products and pharmaceutically active compounds possessing a wide range of biological activity.[1] Often the type and degree of substitution about the pyrrolidine ring can have a profound effect on the biological activity of a given substrate. In connection with an ongoing program, we required an efficient and practical method for the preparation of kilogram quantities of (*R*)-2-methylpyrrolidine **1**. Classical resolution of racemic 2-methylpyrrolidine with L-tartaric acid has been known since 1951.[2] Recently, an optimized large-scale resolution of **1** as its tartrate salt was reported.[3] However, this procedure required large reaction volumes and multiple recrystallizations (4×) to achieve >97% ee and only proceeded in 28% overall yield. Although there have been a number of methods reported for the synthesis of enantiomerically pure **1**, most suffer from inefficient enzymatic resolution protocols of synthetic intermediates or involve multiple steps employing toxic reagents or costly chiral auxiliaries.[4,5] While investigating an enantioselective synthesis of **1**, a report by Ku and co-workers at Abbott[6] appeared describing the synthesis and preparation of **1** which was closely related to our own route and that described by Kostyanovsky and co-workers (Scheme 1).[7] The Abbott preparation involved a five-step synthesis beginning with expensive L-prolinol **2**, required the use of a large excess (10 equiv) of costly LiI, and resulted in the isolation of **1** as an extremely hygroscopic HCl salt in 63% overall yield from **2**. The Kostyanovsky route utilized an *N*-tosyl-protecting group, required LAH in refluxing THF to reduce the *O*-tosyl functionality, and isolated compound **1** by distillation of the free base in an overall yield of 38% from **2**. It is against this background that we now report our improved four-step synthesis of (*R*)-2-methylpyrrolidine **1** that is both practical and amenable to the large-scale preparation of enantiopure **1**.

Our synthesis began with inexpensive and readily available *N*-Boc-L-proline **7** (Scheme 2). Reduction of **7** with borane, generated in situ from sodium borohydride and boron trifluoride etherate, provided prolinol **8** in 97% HPLC assay yield.[8,9] Prolinol **8** was obtained in pure form and in 94% isolated yield by crystallization of the crude reaction mixture from heptane. Treatment of **8** with methanesulfonyl chloride in the presence of Et_3N and 5 mol % of DMAP furnished mesylate **3** in 96% yield. The use of DMAP served to both increase the reaction rate and improve the overall yield of **3**. Interestingly, mesylate **3** was found to be unstable at room temperature as a neat oil and was found to slowly decompose to mesylate salt **9**. Presumably, the decomposition of **3** to **9** was triggered by trace amounts of MsOH in the concentrated product. This problem was completely eliminated by storing **3** as a solution in MTBE which was stable upon prolonged storage. The reduction of mesylate **3** to the corresponding *N*-Boc-2-methylpyrrolidine **4** was routinely achieved by treating **3** with Super-Hydride[10] in THF at room temperature for 3−5 h and provided **4** in 95−96% HPLC assay yield.[9] Alternatively, reduction of **3** with $LiBH_4$ (2.0 equiv) in MTBE at 35 °C for 16 h provided **4** in 80−82% HPLC assay yield. The reduction of **3** with $NaBH_4$ was also extensively examined. Aprotic solvents such as DMSO or DMF were required, and the reactions only gave HPLC assay yields of 50−70%. When other solvents and conditions were employed, either no reaction was observed or decomposition to unidentified byproducts resulted.

Removal of the Boc-protecting group of **4** and isolation of **1** as a stable, crystalline, nonhygroscopic solid were examined

---

(1) (a) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435−446. (b) Lewis, J. R. *Nat. Prod. Rep.* **2001**, *18*, 95−128. (c) Daly, J. W.; Spende, T. F. In *Alkaloids: Chemical and Biological Perspectives;* Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, Chapter 1.

(2) (a) Karrer, P.; Ehrhart, K. *Helv. Chim. Acta* **1951**, *34*, 2202. (b) Kuil, L. A.; Veldhuizen, Y. S. J.; Grove, D. M.; Zwikker, L. J. W.; Jenneskens, L. W.; Drenth, W.; Smeets, W. J. J.; Spek, A. L.; Koten, G. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 267.

(3) (a) Pu, Y.-M.; Grieme, T.; Gupta, A.; Plata, D.; Bhatia, A. V.; Cowart, M.; Ku, Y.-Y. *Org. Process Res. Dev.* **2005**, *9*, 45.

(4) For enantioselective syntheses of **1**, see: (a) Nguyen, T.; Sherman, D.; Ball, D.; Solow, M.; Singaram, B. *Tetrahedron: Asymmetry* **1993**, *4*, 189. (b) Kim, M.-J.; Lim, I. T.; Choi, G.-B.; Whang, S.-Y.; Ku, B.-C.; Choi, J.-Y. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 71. (c) Donner, B. G. *Tetrahedron Lett.* **1995**, *36*, 1223. (d) Gagne, M. R.; Brard, L.; Conticello, V. P.; Giadello, M. A.; Stern, C. L.; Marks, T. J. *Organometallics* **1992**, *11*, 2003. (e) Toshimitsu, A.; Fuji, H. *Chem. Lett.* **1992**, *10*, 2017.

(5) For racemic syntheses of **1**, see: (a) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471. (b) Douglass, M. R.; Ogasawara, M.; Hong, S.; Metz, M. V.; Marks, T. *Organometallics* **2002**, *21*, 283−292. (c) Gagne, M. R.; Nolan, S. P.; Marks, T. J. *Organometallics* **1990**, *9*, 1716. (d) Gagñe, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 4108. (e) Dow Chemical Co. U.S. Patent US1983/4418201. (f) Pugin, B.; Venanzi, L. M. *J. Organomet. Chem.* **1981**, *214*, 125. (g) Minisci, F.; Galli, R.; Perchinunno, M. *Org. Prep. Proced.* **1969**, *1*, 77. (h) Minisci, F.; Galli, R. *Tetrahedron Lett.* **1966**, 2532.

(6) Ku, Y.-Y.; Cowart, M. D.; Sharma, P. N. U.S. Patent US 2004/0171845 A1.

(7) Kostyanovsky, R. G.; Gella, I. M.; Markov, V. I.; Smojlova, Z. E. *Tetrahedron* **1974**, *30*, 39.

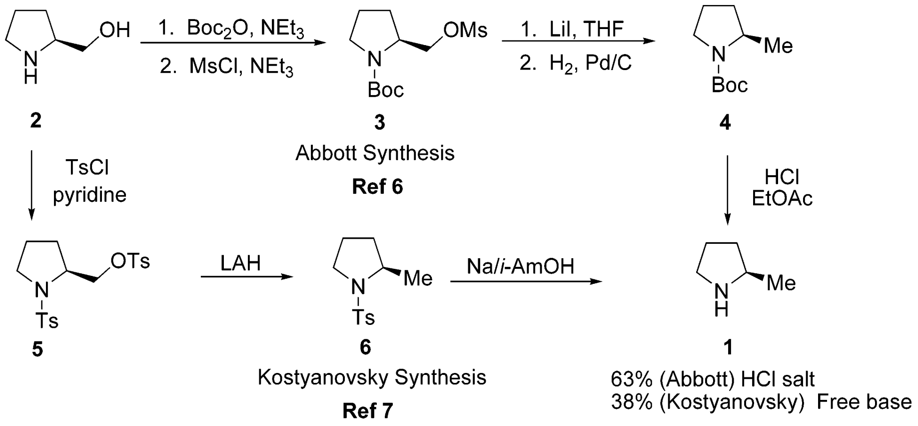
(8) (a) Brown, H. C. *Organic Syntheses via Boranes*; J. Wiley: New York, 1975. (b) Zweifel, G.; Brown, H. C. *Org. React*. **1963**, *13*, 1. (c) Miller, R. A.; Humphrey, G. R.; Lieberman, D. R.; Ceglia, S. S.; Kennedy, D. J.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **2000**, *65*, 1399.

(9) HPLC assay yield refers to quantitative HPLC analysis of reaction mixtures using an analytically pure standard.

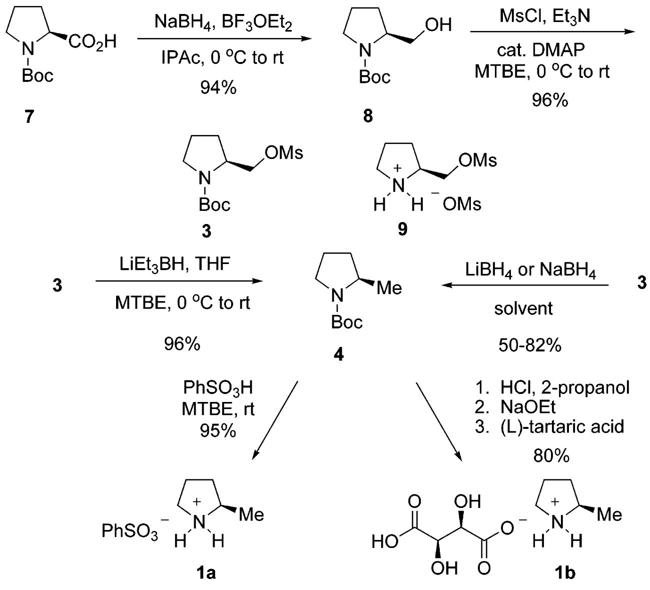
(10) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064.

10.1021/jo060319n CCC: $33.50

SCHEME 1



SCHEME 2



next. Although deprotection could be accomplished with anhydrous HCl or HBr, the resulting workup of these reactions absolutely required decanting the liquors several times to obtain a crystalline solid.[6] Furthermore, both the HCl and HBr salts of **1** are extremely hygroscopic and become amorphous syrups or thick oils when exposed to air for even short periods of time. Although the L-tartrate salt of **1** is highly crystalline and nonhygroscopic, its direct preparation from **4** was not straightforward. Not surprisingly, reaction of **4** with L-tartaric acid resulted in no detectable reaction even at refluxing temperatures. Therefore, an alternative procedure was developed whereby the Boc group of **4** was removed by treatment with 5 N HCl in 2-propanol (2.5 equiv). Neutralization with NaOEt and filtration of the resulting sodium salts gave a solution of the freebase of **1** in 2-propanol. Addition of L-tartaric acid and azeotropic distillation to remove water afforded the crystalline tartrate salt **1b** in 83% yield which was contaminated with a number of sodium salts (i.e., NaCl and sodium tartrate). Although the tartrate salt **1b** could be used uneventfully in subsequent transformations, a more practical procedure for the preparation of **1** in highly pure form was desired. After considerable experimentation, it was discovered that reaction of crude **4** in MTBE with benzenesulfonic acid (1.4 equiv) at room temperature resulted in smooth deprotection and concomitant crystallization of the stable, nonhygroscopic, and highly crystalline benzenesulfonic acid salt **1a** which was isolated from the reaction mixture in 95% yield and in greater than 99.5% optical purity.[11]

In summary, an effective four-step synthesis of (*R*)-2-methylpyrrolidine **1** as its benzenesulfonate salt has been demonstrated. This synthetic sequence utilized readily available, inexpensive starting materials and reagents, required no chromatographic purifications, and proceeded in an excellent 83% overall yield providing **1b** in >99% optical purity. The efficiency and practicality of the protocol should also be applicable to the synthesis of the corresponding (*S*)-enantiomer of **1** and now represents the most practical synthesis of **1** to date.

Experimental Section

General Methods. Melting points are uncorrected. All solvents and reagents were used as received from commercial sources. Analytical samples were obtained by silica gel chromatography using an ethyl acetate−hexane mixture as the eluent unless specified otherwise. Water content (KF) was determined by Karl Fisher titration on a Metrohm 737 KF Coulometer.

Preparation of 2-(*S*)-Hydroxymethylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (8). To a heterogeneous mixture of sodium borohydride powder (37.94 g, 1.00 mol) in isopropyl acetate (540 mL) was added *N*-Boc-L-proline **7** (135 g, 0.627 mol), at −5 to 0 °C in one portion. A gentle evolution of hydrogen gas was observed after the addition. After the reaction mixture was stirred at −5 to 0 °C for 1 h, boron trifluoride etherate (178 g, 1.254 mol) was added via an addition funnel over 1.5 h maintaining the internal temperature between −5 and 5 °C. The resulting reaction slurry was stirred for an additional 1−2 h at the same temperature and was quenched by the addition of 0.5 N NaOH (800 mL) over 30 min at 0−10 °C. The resulting mixture was heated to 45 °C with vigorous stirring for 10 min to give two clear separated layers which were separated. The lower aqueous layer was back extracted with isopropyl acetate (150 mL). The combined organic extracts were washed with 5% NaCl (200 mL) and saturated NaCl (200 mL). The organic solution was azeotropically concentrated, and the solvent was switched to heptane. The final volume was adjusted to approximately 230−250 mL. The solution was seeded with analytically pure **8** while stirring at 35−40 °C, and the product gradually crystallized. The resulting white slurry of the product was stirred at room temperature for 2 h and then at −5 to 0 °C for

---

(11) The optical purity of **1a** and **1b** was determined by chiral HPLC by derivitization with Cbz-valine; see ref 3.

(12) The compound is also available from Aldrich Chemical Company.

2 h and was filtered. The wet cake was dried at room temperature under vacuum/N_2 sweep to afford **8** (120 g, 99.2 wt %, 94% yield) as a white solid.[12]

Preparation of 2-(*S*)-Methanesulfonyloxymethylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (3). To a solution of prolinol **8** (120 g, 99.2 wt %, 0.591 mol) in MTBE (600 mL) was added DMAP (3.6 g, 29.5 mmol) and triethylamine (119.6 g, 1.182 mol) at room temperature. The mixture was stirred at the same temperature for 10 min until all the solids were dissolved. The reaction solution was cooled to −5 to 0 °C, and a solution of methanesulfonyl chloride (88 g, 0.768 mol) in MTBE (300 mL) was added via an addition funnel over 1.5 h maintaining the internal reaction temperature between −5 and 0 °C. An off-white slurry was formed during the addition. The reaction mixture was stirred for an additional 1−2 h at the same temperature and was quenched by the addition of 1 M H_3PO_4 (500 mL) over 20 min at 5−15 °C with vigorous stirring. The organic layer was sequentially washed with saturated $NaHCO_3$ (200 mL), 5% NaCl (200 mL), and saturated NaCl (200 mL). The organic solution was azeotropically concentrated and filtered through a pad of Solka Floc (filter agent) to obtain **5** (160 g, 96% HPLC assay) as an MTBE (∼800 mL) solution (KF = 125 μg/mL). The solution was used directly in the next step reaction without further purification.

Preparation of 2-(*S*)-Methanesulfonyloxymethylpyrrolidine Methanesulfonic Acid Salt (9). Mesylate salt **9** was formed from the concentrated oil of mesylate **4** after standing at room temperature for several days and was isolated as a crystalline white solid (hygroscopic): mp 53−54 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.37 (br, 1H), 8.94 (br, 1H), 4.56 (dd, 1H, J = 11.1, 4.1 Hz), 4.50 (dd, 1H, J = 11.1, 6.5 Hz), 4.08−3.95 (m, 1H), 3.52−3.37 (m, 2H), 3.22 (s, 3H), 2.78 (s, 3H), 2.28−2.00 (m, 2H), 1.98−1.82 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.6, 58.4, 46.3, 39.4, 37.5, 26.6, 23.7. Anal. Calcd for $C_7H_{17}NO_6S_2$: C, 30.53; H, 6.22; N, 5.09. Found: C, 30.49; H, 6.21; N, 5.11.

Preparation of 2-(*R*)-Methylpyrrolidine-1-carboxylic *tert*-Butyl Ester (4). Method A. To a solution of mesylate **3** (160 g, 0.573 mol) in MTBE (∼800 mL) was added $LiEt_3BH$ (Super-Hydride, 1.146 L, 1.146 mol, 1 M in THF) over 1 h at −5 to 0 °C. The reaction mixture turned hazy during the addition. The reaction mixture was allowed to warm to room temperature and was stirred for an additional 3−5 h. The reaction was inversely quenched into a biphasic mixture of MTBE (360 mL) and water (360 mL) at 0−10 °C with vigorous stirring over 20 min. The organic layer was sequentially washed with 1 M H_3PO_4 (800 mL), saturated $NaHCO_3$ (250 mL), 5% NaCl (250 mL), and saturated NaCl (250 mL). The organic solution was azeotropically concentrated and filtered through a pad of Solka Floc (filter agent) to obtain product **4** (102 g, 96% HPLC assay) as an MTBE (140 mL) solution. The solution was used directly in the next step without further purification. A small amount of product was distilled under reduced pressure to give **4** as a colorless oil: bp 75 °C (7.7 mmHg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.99−3.77 (br, 1H), 3.42−3.26 (br, 2H), 2.05−1.72 (m, 3H), 1.61−1.47 (br, 1H), 1.46 (s, 9H), 1.16 (d, 3H, J = 5.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 78.8, 52.8, 46.3, 33.0, 28.6, 23.3, 20.5.

Method B. To a solution of mesylate **3** (2.54 g, 9.1 mmol) in MTBE (25 mL) was added $LiBH_4$ (297 mg, 13.65 mmol) at room temperature. The reaction mixture was heated to 35 °C for 3 h. Additional $LiBH_4$ (99 mg, 4.55 mmol) was added, and the mixture was stirred at 35 °C for 15 h. The reaction was quenched by transferring the mixture into a mixture of 1 M H_3PO_4 (10 mL), water (5 mL), and MTBE (10 mL) at 0 °C with vigorous stirring. The organic layer was washed with saturated $NaHCO_3$ (10 mL) and saturated NaCl (10 mL). The organic solution was azeotropically concentrated and filtered through a pad of Solka Floc (filter agent) to provide **4** (1.37 g, 81% HPLC assay) as a solution in MTBE.

Preparation of (*R*)-2-Methylpyrrolidine Benzenesulfonic Acid Salt (1a). To a solution of benzenesulfonic acid (121.8 g, 0.77 mol) in MTBE (400 mL) was added *N*-Boc-(*R*)-2-methylpyrrolidine **4** (102 g, 0.55 mol) in MTBE (140 mL) at room temperature over 1 h. Gas was evolved during the addition. The reaction mixture was seeded with **1a** (150−200 mg) after about 75% of **4** was added, and the product **1a** crystallized during the course of the rest of the addition of **4**. The reaction mixture was stirred at room temperature for 12−16 h. The solid product was isolated by filtration, and the wet cake was washed with MTBE (300 mL). The solid was dried under vacuum at 35 °C under a nitrogen sweep to afford **1a** (130 g, 95%, 99.6% ee[12]) as a white solid: mp 119−120 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.82 (br s, 1H), 8.35 (br s, 1H), 7.67 (m, 2H), 7.35 (m, 3H), 3.49 (m, 1H), 3.16 (m, 2H), 2.04−1.79 (m, 3H), 1.45 (m, 1H), 1.24 (d, 1H, J = 6.63 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 147.9, 129.4, 128.3, 125.9, 55.8, 44.7, 31.5, 23.3, 17.3. Anal. Calcd for $C_{11}H_{17}NO_3S$: C, 54.30; H, 7.04; N, 5.76. Found: C, 54.29; H, 6.96; N, 5.75.

Preparation of (*R*)-2-Methylpyrrolidine Tartrate Salt (1b). A 50 L flask was charged with *N*-Boc-(*R*)-2-methylpyrrolidine **4** (2.54 kg HPLC assay, 13.7 mol) in EtOH (13 L) and 5 N HCl (6.86 L, 34.3 mol). The resulting solution was heated to 50 °C, aged for 1 h, and cooled to 5 °C. To the cooled solution was added slowly phenolphthalein (2.54 g) and NaOEt (21 wt % in EtOH) (temp <25 °C) until the solution turned pale pink (ca. 10.2 L, 27.3 mol). The slurry was filtered with the receiving pot cooled in a dry ice/acetone bath. The wet cake (NaCl) was washed with EtOH (2 L). The filtrate was transferred to a 50 L flask, and L-tartaric acid (2.26 Kg, 15.1 mol) was added. The mixture was stirred at 50 °C for 3 h and cooled to room temperature. The slurry was azeotropically concentrated under reduced pressure with addition of IPA (at a constant total volume of ∼30 L and a temperature of ∼30 °C; a total of ∼38 L of IPA was needed). The slurry was cooled to room temperature, stirred for 2 h, and filtered. The wet cake was washed with IPA (4 L) and dried at 40 °C under vacuum for 48 h to give **1b** (2.87 kg, 83 wt %, 2.38 Kg assay, >99.6% ee[12]) as an off-white solid: mp 129−130 °C. ^{1}H NMR (400 MHz, CD_3OD): δ 4.38 (s, 2H), 3.63 (m, 1H), 3.27 (m, 2H), 2.17 (m, 1H), 2.02 (m, 2H), 1.62 (m, 1H), 1.37 (d, 3H, J = 6.6 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 175.8, 72.9, 55.9, 44.7, 31.4, 23.1, 16.2.

Acknowledgment. We thank Robert Reamer and Lisa DiMichele for valuable NMR assistance. We also thank Mirlinda Biba, Magareta Figus, and Scott Thomas for the optical and chemical purity analysis.

JO060319N