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An Efficient Method for the Synthesis of (*R*)-3-(1-Amino-1-methylethyl)pyrrolidines for the Antiinfective Agent, PD 138312

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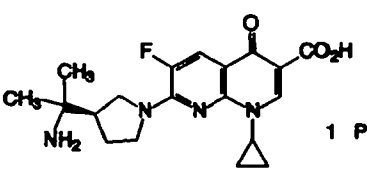
Abstract: Methylcerium dichloride has been found to undergo bis addition to nitriles to produce tertiary carbinamines with retention of optical purity at the *α* position. This result is used in the development of a short, economical synthesis of the 1,8-naphthyridine antiinfective agent, PD 138312.

Recently Domagala and coworkers[1] have discovered a new, potent, broad spectrum antiinfective agent with an excellent safety profile. One of the more challenging aspects of the development of PD 138312 (**1**) has been the search for an efficient method to prepare a suitably protected (*R*)-3-(1-amino-1-methylethyl)pyrrolidine side chain for use in the coupling reaction with 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid to prepare PD 138312. The pyrrolidine ring in **1** contains an unusual asymmetric center situated adjacent to a tertiary carbon that is attached to a primary amine (tertiary carbinamine).

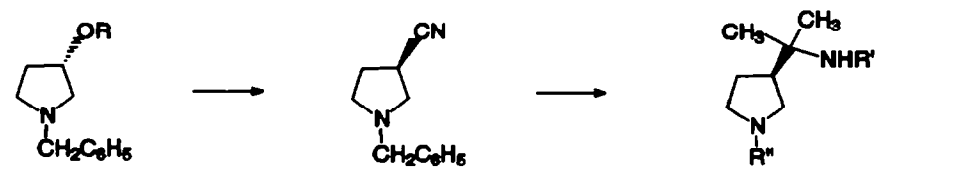


1 PD 138312

The initial process to prepare the side chain was costly. It included many steps with several chromatographic separations and proceeded in low overall yield.[2] We were interested in finding a safe, economical approach to a prepare this pyrrolidine derivative which would be workable for scale-up and manufacturing. An attractive raw material appeared to be (*S*)-1-benzyl-3-pyrrolidinol (**2**) due to its wide availability via several synthetic methods.[3] In particular, a two step, high yield approach to **2** is available[4] from inexpensive (*S*)-malic acid. Activation of the alcohol function in **2** followed by

displacement with cyanide would give the corresponding (*R*)-3-cyanopyrrolidine and treatment of the latter with two equivalents of methyl carbanion would generate the desired (*R*)-3-(1-amino-1-methylethyl)-1-substituted pyrrolidine system.

In most cases the reaction of nitriles with carbanions gives the corresponding imine.[5] Double addition of carbanions to nitriles to give tertiary carbinamines has been reported in only a few, special cases.[6] Furthermore, there is no example of addition of carbanions to nitriles to give tertiary carbinamines in which the chiral integrity of an asymmetric center alpha to the nitrile group is preserved. Recently Ciganek[7] reported the double addition of alkylcerium dichlorides to nitriles to give good yields of tertiary carbinamines. This result suggested to us the possibility that alkylcerium dichlorides may also be useful for preparation of tertiary carbinamines from nitriles without causing significant racemization at the *α* carbon. Success here would provide an efficient method to prepare the pyrrolidine unit in PD 138312.



2 R = H
3 R = SO_2CH_3

4

5 R' = H, R" = $CH_2C_6H_5$
6 R' = CO_2tBu, R" = $CH_2C_6H_5$
7 R' = CO_2tBu, R" = H

Preparation of mesylate derivative **3** of commercially available (*S*)-1-benzyl-3-pyrrolidinol (**2**)[8] proceeded in high yield by using methanesulfonyl chloride and triethylamine in toluene.[9] We were concerned that the cyanide displacement reaction conditions, if not chosen carefully, could lead to racemization resulting from a double inversion process catalyzed by mesylate anion or alternatively base induced *α*-proton removal in the nitrile product. We found that high yields (91%) of the desired nitrile **4** could be obtained using 1.85 equivalents of tetra-n-butylammonium cyanide,[10,11] in acetonitrile at 65°C for 6 h. Addition of **4** to four equivalents of $MeCeCl_2$ (prepared according to the method of Ciganek[7]) in THF at -70°C followed by a 3 h stir period before quenching with 28% NH_4OH and workup gave a 86% yield of (*R*)-3-(1-amino-1-methylethyl)-1-benzylpyrrolidine (**5**). The optical purity of **5** was assessed by using ^{1}H-NMR with chiral shift reagent, (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol,[10] and found to be 97% *R* with 3% *S* isomer. For comparison purposes in this NMR study of **5**, the corresponding *S* isomer[12] of 3-(1-amino-1-methylethyl)-1-benzylpyrrolidine was synthesized from (*R*)-1-benzyl-3-pyrrolidinol[10] by using the same methods. Alteration of pyrrolidine **5** for the purpose of carrying out the coupling reaction with 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid required two steps. Initially **5** was treated with di-*tert*-butyl dicarbonate and triethylamine in methylene chloride to give the Boc derivative **6** (85% yield) and the latter was then reduced in methanol over 20% palladium on carbon according to the method of Hagen[1b] to give the

desired pyrrolidine, **7**[13] (92% yield).

EXPERIMENTAL

^{1}H-NMR spectra were recorded at 200 MHz on a Varian XL 200 NMR spectrometer. Infra-red spectra were recorded with a Analect DS-20 FT spectrophotometer. Mass spectra were obtained on a Finnigan MAT 900Q instrument. Optical rotations were recorded on a Jasco DIP-370 polarimeter with a path length of 1dm. Concentrations are given in g/100 ml. Melting points were obtained with a Thomas-Hoover capillary melting point apparatus. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Tetra-n-butylammonium cyanide: Tetra-n-butylammonium hydrogen sulfate (687.6 g) was added to 24% NaOH (330 ml) with ice bath cooling. Toluene (2 L) and sodium cyanide (98.0 g) were added and the resulting mixture stirred at room temperature for 1 h. The mixture was concentrated at atmospheric pressure to remove water and toluene and the residue diluted with acetonitrile (1.5 L) and filtered to remove solids. The filtrate was concentrated under reduced pressure to give tetra-n-butylammonium cyanide (546 g) which was used in the next step without further purification.

(*R*)-1-Benzyl-3-cyanopyrrolidine (4): (*S*)-1-Benzyl-3-methanesulfonyloxypyrrolidine (**3**)[9] (206.2 g) was dissolved in acetonitrile (288 mL) and tetra-n-butylammonium cyanide (399.5 g) was added. The resulting mixture was heated at 65°C for 6 h and then cooled to room temperature. Saturated $NaHCO_3$ (1.0 L) was added and the mixture extracted with toluene (1 L and 0.5 L). The combined organic layers were washed with water (3x250 mL), and concentrated under reduced pressure to give (*R*)-1-benzyl-3-cyanopyrrolidine (**4**) as a brown oil (141.6 g; 91%) which was used in the next step without further purification. A portion was distilled (108-110°C, 1.1 torr) to give **4** as a colorless oil: IR: 2239 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.0-2.4 (m, 2H), 2.6-2.8 (m, 3H), 2.85-3.1 (m, 2H), 3.65 (s, 2H), 7.2-7.4 (m, 5H). Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.18; H, 7.59; N, 14.67.

(*R*)-3-(1-Amino-1-methylethyl)-1-benzylpyrrolidine (5): $CeCl_3 \cdot 7H_2O$ (316 g), was dried under vacuum at 150-170°C for 7 h. The dry salt was treated with anhydrous THF (2.5 L) and stirred and sonicated for 3.5 h. The resulting mixture was cooled to -70°C and CH_3Li (1.0 M in diethyl ether stabilized by LiBr, 800 mL) was added. A solution of **4** (49.4 g) in THF (100 mL) was added. After 3 h at -60 to -70°C the reaction was quenched with 28% NH_4OH (125 mL) and then warmed to room temperature. CH_2Cl_2 (1 L) was added to the resulting slurry and the solids removed by filtration. The filtrate was concentrated under reduced pressure and the residue dissolved in a solution of glacial acetic acid (30 g) and water (1.6 L). The solution was washed with CH_2Cl_2 (2x500 mL), neutralized with 28% NH_4OH (100 mL) and the product extracted with CH_2Cl_2 (2x500 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give **5** as a yellow oil (40.3 g; 86%): $[\alpha]_D^{25}$ - 9.5(c 1.1, MeOH); ^{1}H-NMR ($CDCl_3$): δ 1.05 (s, 6H), 1.73 (bs) superimposed on 1.5-1.95 (m) (4H), 2.1-2.55 (m, 3H), 2.6-2.75 (m, 2H), 3.54, 3.63 (AB, 2H, J = 13 Hz), 7.2-7.4 (m, 5H); FAB HRMS M + H calcd for $C_{14}H_{23}N_2$ 219.1861, found 219.1857.

(*R*)-3-[1-(*tert*-Butoxycarbonylamino)-1-methylethyl]-1-benzylpyrrolidine (6): (*R*)-3-(1-Amino-1-methylethyl)-1-benzylpyrrolidine (**5**) (36.3 g) was dissolved in CH_2Cl_2 (500 mL) and triethylamine (25.8 g) followed by di-*tert*-

butyl dicarbonate (36.5 g) were added. The solution was stirred overnight at room temperature. Water (100 mL) was added and the organic layer separated, washed with water (100 mL) and dried over $MgSO_4$ and concentrated under reduced pressure to give **6** as a yellow oil (44.2 g, 85%) which was used in the next step without further purification. The oil crystallized on standing, mp 106-107°C (hexanes); ^{1}H-NMR ($CDCl_3$): δ 1.30 (s, 6H), 1.47 (s, 9H), 1.75-1.95 (m, 2H), 2.1-2.3 (m, 3H), 2.75-2.95 (m, 2H), 3.59 (s, 2H), 6.10 (bs, 1H), 7.2-7.4 (m, 5H). Anal. Calcd for $C_{19}H_{30}N_2O_2$: C, 71.66; H, 9.50; N, 8.80. Found: C, 71.26; H, 9.52; N, 8.78.

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12) For (*S*)-3-(1-amino-1-methylethyl)-1-benzylpyrrolidine, (*S*)-**5**: $[\alpha]_D^{24}$ +11.7(c 1.3, MeOH); ^{1}H-NMR ($CDCl_3$): δ 1.05 (s, 6H), 1.50 (bs, 2H), 1.5-1.95 (m, 2H), 2.1-2.55 (m, 3H), 2.6-2.75 (m, 2H), 3.56, 3.65. (AB, J = 13Hz, 2H), 7.2-7.4 (m, 5H).

13) For (*R*)-3-[1-(*tert*-butoxycarbonylamino)-1-methylethyl]pyrrolidine, **7**: $[\alpha]_D^{25}$ +21.0(c 1.1, MeOH). Reported for **7** prepared according to the method of Hagen[1b], $[\alpha]_D^{24}$ +22.0(c 1.0, MeOH).

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