Synthesis of (1*R*,4*S*,5*R*)-*endo*-*N*,*N*-Dimethyl-2-azabicyclo[2.2.1]methanamine

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Starting from *trans*-4-hydroxy-L-proline, (1*R*,4*S*,5*R*)-*endo*-*N*,*N*-dimethyl-2-azabicyclo[2.2.1]methanamine **1** has been synthesized. The target compound is precursor of antibacterial quinolone carboxylic acids.

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The interest in the synthesis of (1*R*,4*S*,5*R*)-*endo*-*N*,*N*-dimethyl-2-azabicyclo[2.2.1]methanamine **1**, a conformationally restricted analog of piperidine, arose from the fact, that quinolones substituted with chiral bases have been reported to possess interesting antibacterial activity [2-4]. We report herein the synthesis of **1** *via* a route that establishes the absolute configuration of this bicyclic system.

It has been reported that *trans*-4-hydroxy-L-proline **2** can be utilized in the synthesis of chiral azabicyclo[2.2.1]-heptane systems containing different heteroatoms [5,6]. A similar approach was employed for the synthesis of the title compound.

trans-4-Hydroxy-L-proline **2** was converted to *N*-tosyl-2-azabicyclo[2.2.1]heptane-5-carboxylic acid **3a** and **b** by the method of Portoghese [7]. This intermediate then was reduced with borane-tetrahydrofuran or borane-dimethylsulfide complex to the bicyclic alcohols **4a** and **b** in 88% yield (Scheme 1). Portoghese and coworkers [7] have established that **3** was obtained as a mixture of *endo* and *exo*-carboxylic acids in the ratio of 20:80 (*exo*:*endo*) and fractional crystallization of bicyclic acids **3a** and **b** from benzene did not afford a complete separation. However, fractional crystallization of **4a** and **b** from ether did afford a complete separation. The first crop of crystals afforded pure *endo*-alcohol **4a** as indicated by ^{1}H nmr. Concentration of the filtrate afforded another crystalline fraction which was found to be *exo*-alcohol **4b**.

The bicyclic amine derivative **1** was obtained by tosylation of **4a** with tosyl chloride and subsequent displacement of the *O*-tosyl group with dimethylamine, to afford intermediate **6**. Deprotection of **6** to the desired **1** was carried out by refluxing a solution of **6** in 48% hydrobromic acid, red phosphorus and water. Reaction of **1** with quinolones **7** and **8** [8] gave the desired chiral quinolone derivatives **9** and **10**.

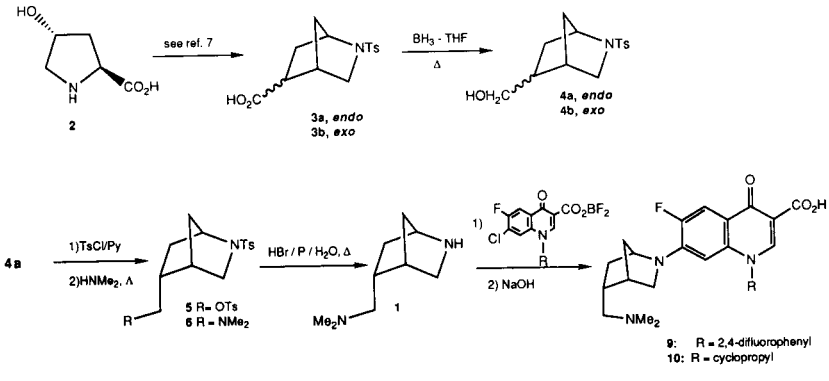
EXPERIMENTAL

The melting points were obtained on a Kofler melting point apparatus and are uncorrected. The ^{1}H nmr spectra were obtained on JEOL FX90Q (90 MHz) or Bruker WM 250 (250 MHz) spectrometer with TMS as an internal standard. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. Elemental analyses were determined by Dr. J. Zak at the Microanalytical Laboratory of the Institute of Physical Chemistry, University of Vienna, Austria. The tlc was performed on Merck TLC-alumina-plates Kiesel gel 60 F_{254} (Art. No. 5554). For the column chromatography Merck silica gel 60 (0.04-0.63 mm, Art. No. 9358) was used. Tosyl chloride was purified as described [9].

endo-2-Tosyl-2-azabicyclo[2.2.1]heptane-5-methanol **4a** and *exo*-2-Tosyl-2-azabicyclo[2.2.1]heptane-5-methanol **4b**.

To a solution of *N*-tosyl-2-azabicyclo[2.2.1]heptane-5-carboxylic acids **3a** and **b** (4 g, 13.56 mmoles) in dry tetrahydrofuran (30 ml) a solution of 1 *M* borane-tetrahydrofuran (50 ml, 35 mmoles) in dry tetrahydrofuran (30 ml) was added dropwise, and the mixture was refluxed for 18 hours. To the cold reaction mixture absolute

Scheme 1



methanol (10 ml) was added dropwise and volatiles were removed by rotary evaporation. The residual liquid was coevaporated several times with methanol. After trituration with petroleum ether a mixture of crude **4a** and **b** (3.4 g, 89%) was obtained as a colorless solid. This mixture of **4a** and **b** was refluxed with ether until a partial solution resulted and then stored in a refrigerator. The precipitated solid was collected by filtration to give the *endo*-isomer **4a** (3 g, 79%), mp 74-75°; $[\alpha]_D^{20}$ +14.8° (c = 1, methanol); ^{1}H nmr (90 MHz, deuteriochloroform): δ 1.03 (1H, d, J = 7.2 Hz, 7-H), 1.32 (2H, m, 7-H and 5-H), 1.80 (1H, m, 6-H_{exo}), 2.19 (2H, b s, 1H and 5-H), 2.44 (3H, s, CH_3-Ph), 2.57 (2H, b, H_2O of crystallization), 2.91 (1H, m, $J_{H4\text{-}H5exo}$ = 8.33 Hz, $J_{H4\text{-}H7syn}$ = 3.33 Hz, 4-H), 3.06-3.66 (4H, m, CH_2-N and CH_2-O), 4.13 (1H, s, OH), 7.26 (2H, d, aromatics), 7.63 (2H, d, aromatics).

Anal. Calcd. for $C_{14}H_{19}NO_3S\cdot 5/4H_2O$ (303.89) (Hygroscopic): C, 55.33; H, 7.13; N, 4.61. Found: C, 55.68; H, 6.79; N, 4.67.

Concentration of the filtrate gave the *exo*-isomer **4b** (400 mg, 10%), mp 70-72°; $[\alpha]_D^{20}$ + 12.8° (c = 1, methanol); ^{1}H nmr (90 MHz, deuteriochloroform): δ 0.9 (1H, d, J = 7.2 Hz, 7-H), 1.33 (2H, m, 7-H and 5-H), 1.82 (1H, m, 6-H_{endo}), 2.36 (2H, b s, 1H and 5-H), 2.36 (3H, s, CH_3-Ph), 2.49 (2H, b, H_2O of crystallization), 2.94 (1H, m, $J_{H4\text{-}H5exo}$ = 8.0 Hz, $J_{H4\text{-}H7syn}$ = 3.5 Hz, 4-H), 3.23-3.74 (4H, m, CH_2-N and CH_2-O), 4.15 (1H, s, OH), 7.25 (2H, d, aromatics), 7.61 (2H, d, aromatics).

endo-2-Tosyl-2-azabicyclo[2.2.1]heptane-5-methanol-*O*-*p*-toluenesulfonate **5**.

A solution of **4a** (3 g, 10.67 mmoles) in dry pyridine (30 ml) was cooled to -5° and then freshly recrystallized tosyl chloride (4 g, 21.05 mmoles) was added in one portion. After stirring the reaction mixture for 2 hours at -5°, it was stored in a refrigerator for 24 hours. To the cold reaction mixture water (150 ml) was added dropwise to precipitate the crude product, which was washed with toluene and petroleum ether and then recrystallized from methanol to give **5** (4 g, 86%), mp 95-98°; $[\alpha]_D^{20}$ +17.9° (c = 1, acetone); ^{1}H nmr (250 MHz, deuteriochloroform): δ 1.09 (1H, d, J = 5 Hz, 7-H), 1.27 (2H, m, 7-H and 1-H), 1.62-1.75 (2H, m, 5-H), 2.43 (3H, s, CH_3-Ph), 2.46 (3H, s, CH_3-Ph), 2.86 (1H, dd, J = 1.6 Hz and J = 6 Hz, 6-H), 3.05 (2H, d, J = 7 Hz, CH_2-N), 3.86 (1H, dd, J = 1.6 Hz and J = 8 Hz, 4-H), 4.13 (2H, m, CH_2-O), 7.14-7.65 (8H, m, aromatics).

Anal. Calcd. for $C_{21}H_{25}NO_5S_2$ (435.56): C, 57.91; H, 5.79; N, 3.22. Found: C, 57.62; H, 5.81; N, 3.05.

endo-*N*,*N*-Dimethyl-2-tosyl-2-azabicyclo[2.2.1]heptane-5-methaneamine **6**.

A saturated methanolic dimethylamine solution was prepared by bubbling anhydrous dimethylamine gas in cold, dry methanol (200 ml). To this methanolic dimethylamine solution **5** (11 g, 25.25 mmoles) was added and the resulting solution was heated at 120° in a sealed tube for 20 hours. After cooling to room temperature, solvent was removed by rotary evaporation and the residue was recrystallized from small amount of methanol to afford **6** (6.41 g, 83%), mp 225-228°; $[\alpha]_D^{20}$ +19.6° (c = 1, methanol); ^{1}H nmr (250 MHz, deuteriowater): δ 1.09 (1H, d, J = 5 Hz, 7-H), 1.27 (2H, m, 7-H and 1-H), 1.62 (1H, b, 6-H), 2.01 (2H, m, 5-H), 2.43 (3H, s, CH_3-Ph), 2.86 (2H, m, CH_2-N), 3.15 (1H, m, 4-H), 3.26 (6H, s, Me_2-N), 4.06-4.18 (2H, m, CH_2-O), 7.14-7.65 (4H, m, aromatics).

Due to the hygroscopic nature of this compound a correct elemental analysis could not be obtained.

(1*R*,4*S*,5*R*)-*endo*-*N*,*N*-Dimethyl-2-azabicyclo[2.2.1]heptane-5-methanamine **1**.

A solution of **6** (6 g, 19.48 mmoles), 48% aqueous hydrobromic acid (25 ml), red phosphorus (1 g) and water (20 ml) was heated to reflux for 24 hours. After cooling to room temperature, insolubles were removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in 4 *N* sodium hydroxide (75 ml) and then extracted continuously for 24 hours with ether. The organic phase was dried over magnesium sulfate and rotary evaporated to dryness to obtain a liquid. After distillation (kugelrohr) at 140°/10 mm, **1** (1.13 g, 40%) was obtained as an oil, $[\alpha]_D^{20}$ + 21.5° (c = 1, methanol); ^{1}H nmr (90 MHz, deuteriochloroform): δ 0.93 (2H, d, J = 11.5 Hz, 7-H), 1.34-2.46 (7H, m, 1-H, 4-H, 5-H, 6-H and CH_2-NMe_2), 2.17 (6H, s, NMe_2), 2.82 (2H, m, CH_2-N), 3.30 (1H, b s, NH).

For the purpose of elemental analysis, a small amount of **1** was converted to the dipicrate.

Anal. Calcd. for $C_9H_{18}N_2\cdot 2C_6H_3N_3O_7$ (612.47): C, 41.18; H, 3.95; N, 18.30. Found: C, 41.04; H, 3.87; N, 17.96.

6-Fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-7-{*endo*(1*R*,4*S*,5*R*)-5-dimethylaminomethyl-2-azabicyclo[2.2.1]hept-2-yl}-4-oxo-quinoline-3-carboxylic Acid **9**.

A mixture of 300 mg (0.75 mmole) of **7** and 170 mg (1.17 mmoles) of **1** in DMSO (5 ml) was heated at 60° for 3 hours. After cooling to room temperature 15 ml of water was added and the precipitate was collected by filtration. The precipitate was dissolved in 2*N* sodium hydroxide (15 ml) and refluxed for 1 hour. The cold reaction mixture was acidified with concentrated hydrochloric acid (*p*H 6.5-5.5) and extracted several times with chloroform. The organic layer was evaporated and the residual solid was suspended in methanol. Hydrogen chloride gas was bubbled to saturate the methanolic suspension. Removal of methanol gave 278 mg (69%) of **9** as the dihydrochloride, mp 228-232° dec.

Anal. Calcd. for $C_{25}H_{24}F_3N_3O_3\cdot 2HCl\cdot 0.5H_2O$ (553.41): C, 54.26; H, 4.92; N, 7.59. Found: C, 54.08; H, 4.94; N, 7.57.

1-Cyclopropyl-6-fluoro-1,4-dihydro-7-{*endo*(1*R*,4*S*,5*R*)-5-dimethylaminomethyl-2-azabicyclo[2.2.1]hept-2-yl}-4-oxo-quinoline-3-carboxylic Acid **10**.

Compound **10** prepared in 61% yield, according to the procedure described for **9**, mp 240-245° dec.

Anal. Calcd. for $C_{22}H_{26}FN_3O_3\cdot 2HCl$ (472.39): C, 55.94; H, 5.97; N, 8.90. Found: C, 55.96; H, 5.90; N, 8.96.

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