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Stereoselective synthesis of (3*R*,4*S*)-3-amino-4-methyl pyrrolidine

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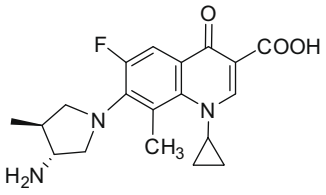
ABSTRACT

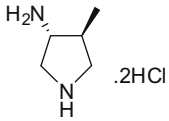
A stereoselective approach for the synthesis of (3*R*,4*S*)-3-amino-4-methyl pyrrolidine, a part of the structure of a quinoline antibacterial compound and the naphthyridine antitumor agent, is described. The key reaction is the one-pot reduction and regioselective cyclization of azidoditosyl derivative **9** to pyrrolidine **10**.

1. Introduction

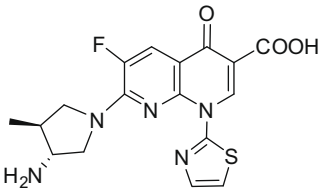
Chiral, non-racemic pyrrolidines are common building blocks for many natural and unnatural compounds[1] that possess important biological activity. Amino substituted chiral pyrrolidines provided a noticeable improvement in the biological activity of quinoline and naphthyridine compounds[2] by attachment at the C-7 position. Miyamoto et al.[3] showed that a new series of quinoline compounds, for example **1a**, bearing (3*R*,4*S*)-3-amino-4-methyl pyrrolidine **2** at the C-7 position exhibited highly potent activity equal or superior to those of ciprofloxacin[4] and ofloxacin[5] against both gram positive and gram negative bacteria including *Pseudomonas aeruginosa*. Tomita et al.[6] reported that amino methylpyrrolidine **2** attached to the naphthyridine ring at C-7 of **1b** possessed potency that was comparable to that of cisplatin with an IC_{50} value of 0.011 μg/mL against Murine P388 Leukemia cells.



1a



2



1b

Therefore, the pyrrolidine moiety **2** is an essential structural feature for the activity of compounds **1a** and **1b**; and this important activity of **2** prompted us to undertake its synthesis. Although synthetic approaches for compound **2** are known in the literature,[7] they have the disadvantage of requiring the separation of the isomers to obtain the enantiomerically pure form of **2**, which is essential for biological activity. In continuation of our work on the synthesis of polysubstituted pyrrolidines,[8a–e] piperidines,[9] we reported the synthesis of chiral 3-methoxy-4-methyl amino pyrrolidine.[8a,b] Herein, we report the stereoselective synthesis of (3*R*,4*S*)-3-amino-4-methyl pyrrolidine **2** starting from D-glucose.

2. Results and discussion

Our approach to the synthesis of (3*R*,4*S*)-3-amino-4-methyl pyrrolidine is outlined in Scheme 1. D-Glucose was converted into compound **3** by the sequence of reactions reported earlier.[10] The primary alcohol was converted into azide **5** via the mesylate using MsCl–Et_3N and NaN_3 in DMF. Compound **5**, upon hydrolysis with cat. HCl and 60% aq AcOH, furnished 1,2-diol **6**. Oxidative cleavage of diol **6** with $NaIO_4$ in MeOH–H_2O and subsequent reduction with $NaBH_4$ gave diol **8**, which was converted into ditosyl derivative **9** using TsCl/Et_3N. Reaction of compound **9** in TPP/MeOH at reflux resulted in azide reduction and regioselective cyclization to give the pyrrolidine derivative, which was subsequently treated with Boc_2O to give **10**. Next, the tosyl group in compound **10** underwent S_N2 displacement with NaN_3 in DMF to furnish azide **11**, which on further reduction with Pd/C, H_2, and protection with Boc_2O afforded compound **12**; finally, deprotection of the Boc group by using HCl–MeOH gave compound **2** as its HCl salt.

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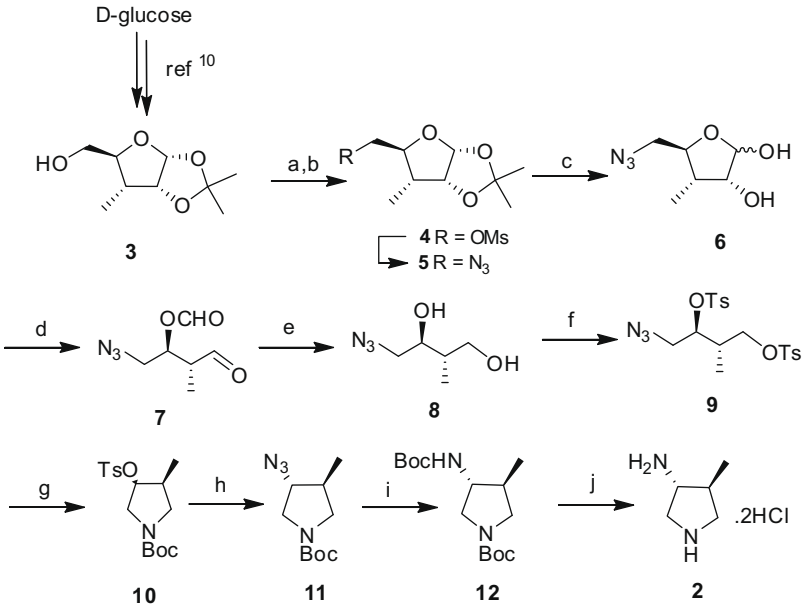

Scheme 1. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C–rt, 30 min, 86%; (b) NaN_3, DMF, 90 °C, 12 h, 82%; (c) 60% aq AcOH, concd HCl, 12 h, 72%; (d) $NaIO_4$, MeOH–H_2O, 30 min; (e) $NaBH_4$, MeOH, 0 °C–rt, 30 min, 82%; (f) TsCl, Et_3N, DMAP, CH_2Cl_2, 4 h, 81%; (g) (i) PPh_3, MeOH, reflux, 12 h; (ii) Boc_2O, Et_3N, THF, 51%; (h) NaN_3, DMF, 90 °C, 12 h, 78%; (i) (i) H_2, Pd/C, MeOH, 2 h, (ii) Boc_2O, Et_3N, CH_2Cl_2, 14 h, 91% (j) MeOH, HCl, 0 °C–rt, 30 min, 91%.

3. Conclusion

In conclusion, a stereoselective synthesis of enantiomerically pure pyrrolidine **2** was achieved via a simple reaction sequence starting from D-glucose, involving the regioselective cyclization of the azidoditosyl compound **9**. This approach is helpful in obtaining analogues of **2**.

4. Experimental

TLC was performed on Merck Kiesel Gel 60, F254 plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate and hexane mixture as eluents. Melting points were determined on a Fisher John's melting point apparatus, and are uncorrected. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^{1}H NMR and ^{13}C NMR spectra were recorded using Varian Gemini-200 MHz or Bruker Avance-300 MHz spectrometers. Chemical shifts are expressed in ppm (δ) with tetramethylsilane as an internal standard, followed by multiplicity (s-singlet; d-doublet; t-triplet; q-quartet; m-multiplet), number of proton(s), and coupling constant(s) J (Hz). ^{13}C NMR chemical shifts are expressed in ppm. Optical rotations were measured with Horiba-SEPA-300 digital polarimeter. Accurate mass measurement was performed on a Q STAR mass spectrometer.

4.1. (3a*R*,5*S*,6*R*,6a*R*)-2,2,6-Trimethylperhydrofuro[2,3-*d*]-[1,3]dioxol-5-yl]methylmethanesulfonate 4

A solution of methanesulfonyl chloride (1.36 mL, 17.55 mmol) in CH_2Cl_2 (5 mL) was added to a mixture of compound **3** (3 g, 15.95 mmol) and triethylamine (6.66 mL, 47.85 mmol) in CH_2Cl_2 (25 mL) under 0 °C. The reaction mixture was brought to rt in 30 min under stirring, then extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with hexane–EtOAc (6:1) to give compound **4** as a white solid (3.65 g, 86%): $[\alpha]_D^{30} = +29.7$ (c 1.32, $CHCl_3$); mp 57–59 °C; IR ν_{max} 2924, 2856, 1456, 1217, 1168, 948 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, 3H, J = 6.8 Hz), 1.32 (s, 3H), 1.49 (s, 3H), 2.02 (m, 1H), 3.03 (s, 3H), 3.92 (m, 1H), 4.21 (dd, 1H J = 4.5, 11.3 Hz), 4.39 (dd, 1H J = 2.2, 11.3 Hz), 4.53 (t, 1H, J = 3.8 Hz), 5.74 (d, 1H, J = 3.0 Hz); MS (LC) m/z 289 [M+Na]$^+$.

4.2. (3a*R*,5*S*,6*R*,6a*R*)-5-(Azidomethyl)-dihydro-2,2,6-trimethyl-5*H*-furo[2,3-*d*][1,3]dioxole 5

A mixture of compound **4** (3 g, 11.27 mmol) and sodium azide (2.93 g, 45.11 mmol) in DMF (15 mL) was heated at 90 °C for 12 h. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography with hexane–EtOAc (24:1) to give compound **5** as a colorless oil (1.96 g, 82%): $[\alpha]_D^{30} = +62.0$ (c 0.34, $CHCl_3$); IR ν_{max} 2984, 2933, 2101, 1457, 1378, 1113, 1014 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.05 (d, 3H, J = 7.5 Hz), 1.31 (s, 3H), 1.48 (s, 3H), 2.02 (m, 1H), 3.15 (dd, 1H, J = 4.1, 13.3 Hz), 3.58 (dd, 1H, J = 2.49, 13.3 Hz), 3.80–3.93 (m, 1H), 4.52 (t, 1H, J = 4.15 Hz), 5.77 (d, 1H, J = 3.3 Hz); MS (EI) m/z 213 [M]$^+$.

4.3. (3*R*,4*S*,5*S*)-5-(Azidomethyl)-4-methyltetrahydrofuran-2,3-diol 6

To compound **5** (1.8 g, 8.45 mmol) was added 60% aq AcOH (20 mL) and catalytic amount of concd HCl after which the mixture was stirred for 12 h at rt. The reaction mixture was then neutralized with solid $NaHCO_3$ until pH 7, and the reaction mixture was filtered by washing with EtOAc. The organic layer was dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography using hexane–EtOAc (2:1) to give compound **6** as a colorless oil as a mixture of anomers (~1:1) (1.05 g, 72%). $[\alpha]_D^{30} = +88.0$ (c 1.86, $CHCl_3$); IR ν_{max} 3304, 2929, 2857, 2104, 1690, 1643, 1531, 1072 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (d, 3H, J = 4.7 Hz), 1.09 (d, 3H, J = 4.7 Hz), 2.15 (m, 1H), 2.36 (m, 1H), 3.18 (dd, 1H J = 4.7, 13.2 Hz), 3.32 (dd, 1H J = 5.4, 13.0 Hz), 3.56 (dd, 2H, J = 3.0, 13.0 Hz), 3.94–4.23 (m, 4H), 5.29 (s, 1H), 5.47 (br s, 1H); MS (EI) m/z 155 [M$^+$−18].

4.4. (2*S*,3*S*)-4-Azido-2-methylbutane-1,3-diol 8

To a solution of compound **6** (1 g, 5.78 mmol) in 80% aq MeOH (10 mL) was added $NaIO_4$ (2.47 g, 11.56 mmol). The reaction mixture was stirred for 30 min. The solvent was then removed under reduced pressure and the residue was extracted with EtOAc, dried over Na_2SO_4, and concentrated to afford the crude product **7**. A solution of compound **7** in dry MeOH was added to $NaBH_4$ (0.55 g, 14.45 mmol) at 0 °C. The reaction mixture was stirred at 0 °C to rt for 30 min. The methanol was then removed under vacuo and the residue was quenched with NH_4Cl, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was column chromatographed with hexane–EtOAc (2:1) to give compound **8** as a colorless oil (0.68 g, 82%): $[\alpha]_D^{30} = +35.6$ (*c* 1.73, $CHCl_3$); IR ν_{max} 3353, 2967, 2928, 2887, 2094, 1439, 1273, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.9 (d, 1H, *J* = 6.8 Hz), 1.9 (m, 1H), 3.31 (dd, 1H, *J* = 6.8, 12.0 Hz), 3.48 (dd, 1H, *J* = 3.0, 12.8 Hz), 3.60–3.72 (m, 2H), 3.77 (dd, 1H, *J* = 3.8, 10.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 37.5, 55.3, 67.0, 75.8; MS (ESI) *m*/*z* 168 $[M+Na]^+$.

4.5. (2*S*,3*S*)-4-Azido-2-methyl-3(4-methylphenylsulfonyloxy)-butyl-4-methyl-1-benzene sulfonate 9

A solution of tosyl chloride (2.3 g, 12.06 mmol) in CH_2Cl_2 (15 mL) was added to a mixture of compound **8** (0.5 g, 3.44 mmol), triethylamine (3.35 mL, 24.13 mmol) in CH_2Cl_2 (10 mL) and a catalytic amount of DMAP under 0 °C. The reaction mixture was stirred at rt for 4 h, after which it was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was column chromatographed with hexane–EtOAc (17:3) to give compound **9** as a white solid (1.26 g, 81%): $[\alpha]_D^{30} = -22.0$ (*c* 1.44, $CHCl_3$); mp 87–90 °C; IR ν_{max} 2923, 2853, 2104, 1360, 1174 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (d, 3H, *J* = 6.7 Hz), 2.26 (m, 1H), 2.47 (s, 3H), 2.49 (s, 3H), 3.26 (dd, 1H, *J* = 4.17, 13.3 Hz), 3.67 (dd, 1H, *J* = 4.17, 13.3 Hz), 3.76–3.95 (m, 2H), 4.46–4.57 (m, 1H), 7.31 (d, 2H, *J* = 3.3 Hz), 7.35 (d, 2H, *J* = 3.3 Hz), 7.72 (d, 2H, *J* = 5.8 Hz); 7.76 (d, 2H, *J* = 5.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7, 21.6, 34.9, 51.5, 70.3, 80.3, 127.8, 127.9, 129.9, 130.0, 132.5, 133.2, 145.0, 145.4; MS (LC) *m*/*z* 476 $[M+Na]^+$.

4.6. (3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-(4-methylphenylsulfonyloxy)-4-methyl pyrrolidine 10

A solution of compound **9** (1 g, 2.20 mmol) in methanol (20 mL) was added to triphenylphosphene (0.39 g, 1.47 mmol) and refluxed for 12 h. Methanol was then removed from the reaction mixture under vacuo. The residue was dissolved in THF (15 mL) after which were added triethylamine (0.92 mL, 6.62 mmol), and then Boc_2O (0.50 mL, 2.20 mmol) under ice cooling and stirred for 14 h at rt. The reaction mixture was then taken in water and extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography with hexane–EtOAc (9:1) to give compound **10** as a white solid (0.4 g, 51%): $[\alpha]_D^{30} = -7.4$ (*c* 0.40, $CHCl_3$); mp 103–106 °C; IR ν_{max} 2975, 2928, 1696, 1408, 1175, 900, 766 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ *1.02 (2d, 3H, *J* = 6.6–18.4 Hz), 1.42 (s, 9H), 2.20–2.39 (m, 1H), 2.47 (s, 3H), 3.0 (t, 1H, *J* = 10.3 Hz) 3.32–3.64 (m, 3H), 4.87 (m, 1H), 7.33 (d, 2H, *J* = 8.0 Hz), 7.77 (d, 2H, *J* = 8.0 Hz), (*rotamers); MS (LC) *m*/*z* 378 $[M+Na]^+$.

4.7. (3*R*,4*S*)-3-Azido-1-*tert*-butoxycarbonyl-4-methyl pyrrolidine 11

A mixture of compound **10** (0.2 g, 0.56 mmol) and sodium azide (0.15 g, 2.25 mmol) in DMF (5 mL) was heated at 90 °C for 12 h. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was column chromatographed with hexane–EtOAc (24:1) to give compound **11** as a colorless oil (0.1 g, 78%): $[\alpha]_D^{30} = +34.2$ (*c* 1.31, $CHCl_3$); IR ν_{max} 2924, 2854, 2105, 1701, 1402, 1173 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.13 (br d, 3H, *J* = 5.2 Hz), 1.46 (s, 9H), 2.10–2.37 (m, 1H), 2.90–3.10 (m, 1H), 3.15–3.39 (m, 1H), 3.47–3.84 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 28.4, 38.1 and 38.8*, 49.3 and 49.7*, 50.7 and 51.1*, 65.2 and 65.9*, 79.6, 154.2; *rotamers; MS (ESI) *m*/*z* 227 $[M+1]^+$.

4.8. (3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-*tert*-butoxycabonylamino-4-methylpyrrolidine 12

A solution of compound **11** (50 mg, 0.22 mmol) in MeOH (5 mL) was hydrogenated over 10% Pd–C for 2 h at rt. The mixture was filtered and $(Boc)_2O$ (50 mg, 0.23 mmol) was added under ice cooling. The reaction mixture was stirred at rt for 14 h, and then concentrated in vacuo. The residue was column chromatographed with hexane–EtOAc (4:1) to give compound **12** as a colorless oil (60 mg, 91%): $[\alpha]_D^{30} = +36.7$ (*c* 1.86, $CHCl_3$); IR ν_{max} 3351, 2926, 2857, 1686, 1411, 1169 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.07 (d, 3H, *J* = 6.6 Hz), 1.45 (s, 18H), 1.91–2.11 (m, 1H), 2.88–3.14 (m, 2H), 3.47–3.86 (m, 3H), 4.43–4.60 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8, 28.3, 28.4, 38.5 and 39.6*, 50.3 and 50.8*, 51.1 and 51.4*, 55.6 and 56.2*, 79.4, 79.7, 154.4, 155.4; *rotamers; MS (ES) *m*/*z* 301 $[M+1]^+$.

4.9. (3*R*,4*S*)-3-Amino-4-methylpyrrolidine dihydrochloride 2

To a solution of compound **12** (30 mg, 0.1 mmol) in MeOH (5 mL) was added 4 M HCl–MeOH (1 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Then MeOH was removed under reduced pressure, washed with dry ether, and dried to give compound **2** as a white solid (15.7 mg, 91%): $[\alpha]_D^{30} = +15.3$ (*c* 0.19, MeOH); mp 250 °C dec; IR ν_{max} 3376, 2971, 1613, 1515, 1459, 1045 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.11 (d, 3H, *J* = 6.8 Hz), 2.42 (m, 1H), 2.9 (dd, 1H, *J* = 9.8, 12.0 Hz), 3.32 (dd, 1H, *J* = 7.5, 12.8 Hz), 3.54–3.65 (m, 2H), 3.75 (dd, 1H, *J* = 8.3, 12.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 37.5, 47.8, 51.0, 54.9; HRMS (ESI) Calcd for $C_5H_{13}N_2$ $[M+1]^+$ 101.1078, found 101.1083.

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