The practical, efficient, diastereoselective synthesis of
\((3R, 1'S)-3-[(1'-N\text{-methylamino})\text{ethyl}]\text{pyrrolidine}: \text{A chiral side}
chain unit for quinolone type anti-fungal agents

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\((3R, 1'S)-3-[(1'-N\text{-methylamino})\text{ethyl}]\text{pyrrolidine} \ 1\), which is an important chiral building block, has been synthesized
from 3-acetyl-1-benzyl-2-pyrrolidione \(5\) by diastereoselective hydrogenation using the Ru-BINAP complex as the key step,
followed by hydride reduction, methanesulfonylation, inverse amination and debenzylation.

Keywords: \(N\text{-Methylaminoethylpyrrolidine, quinolone type anti-fungal agents, chiral building block, diastereoselective}
hydrogenation, Ru-BINAP complex catalyst

\((3R, 1'S)-3-[(1'-N\text{-methylamino})\text{ethyl}]\text{pyrrolidine} \ 1\) is
known as an important chiral building block, for
example, it is a structural constituent of the
quinolone-type anti-fungal agents\(^1\) such as
premafloxacin \(2\) (Ref 2) (Figure 1).

Several preparations of \(1\) are known:
(i) The synthesis from optically-active phenyl-
ethylamine in many steps\(^2\).
(ii) The synthesis from L-alanine as the starting
material\(^3\).
(iii) The preparation of racemates of \(1\) from
4-carboxy-\(N\text{-benzyl-2-pyrrolidone}^4\).

On the other hand, the enantioselective
hydrogenation with the Ru-BINAP complex catalyst
is one of the most powerful tools for the synthesis
of optically-active compounds\(^5\). Moreover, new
chiral phosphorous ligands for enantioselective
hydrogenation are used and their review has been
reported by Zhang\(^6\). In particular, the enantioselective
hydrogenations of a diketone, \(\beta\text{-ketoesters and}

\(\beta\text{-ketoesters and enamide esters are well known, however, that of a}

cyclic diketamide such as 3-acetyl-1-benzyl-2-
pyrrolidione \(5\), is little known. Furthermore, the
chiral 1-benzyl-3-[(1'\text{-hydroxy})\text{ethyl}]2-pyrrolidinone \(6\)

obtained by diastereoselective hydrogenation using the
Ru-BINAP complex could be converted to pyrrolidine
\(7\) by hydride reduction followed by mesylation,
inversion amination and de-benzylation, which
are known methods, to afford the pyrrolidine \(1\).
The author has studied the diastereoselective
hydrogenation of \(5\) in order to develop the synthesis
of \(1\) and now reports the efficient synthesis of \(1\) from
\(5\) via the diastereoselective hydrogenation of \(5\) using
the Ru-BINAP complex catalyst\(^7\).

Results and Discussion

The preparation of 3-acetyl-1-benzyl-2-pyrrolidinone \(2\)
as a substrate for the diastereoselective hydrogenation

![Figure 1 — The structures of \((3R, 1'S)-3-[(1'-N\text{-methylamino})\text{ethyl}]\text{pyrrolidine} \ 1\) and premafloxacin \(2\)](image-url)
is illustrated in Scheme I. Pyrrolidinone 5 was prepared by the benzylation of 2-pyrrolidinone 3 (Ref 8) with NaH at 50°C for 4 h that afforded 1-benzyl-pyrrolidone 4 in 75% yield, then the 3-acetylation of 1-benzylpyrrolidone in dimethylacetamide with LDA at −60°C in 72% yield (Scheme I).

The author examined the hydrogenation of 3-acetyl-1-benzylpyrrolidinone 5 in the presence of the Ru-(R)-p-tolyl-BINAP complex 7 as a catalyst under several different conditions. Therefore, the hydrogenation of 5 in the case of using [NH2Et2][{RuCl((R)-p-tolyl-BINAP)}2(μ-Cl)]9 as a catalyst obtained the best result and the solvent effect was evaluated. The results are summarized in Table I and the best solvent was CH2Cl2.

The absolute configuration of 6 was determined by comparison with the optical rotations in the literature2 after conversion to 1. The enantiomeric excess of (3S, 1ʹR)-1-benzyl-3-{(1ʹ-hydroxy)ethyl}-2-pyrrolidinone 6 was determined by HPLC (Experimental Section). Compound 6 was then reduced to the pyrrolidine 7 by LiAlH4 in THF and followed by reacting with methanesulfonyl chloride in the presence of Et3N to give 8. The resulting product 8 was used in the subsequent step without purification. Thus, 8 was treated with methylamine in a THF solution at 80°C for 15 h to give the aminopyrrolidine 9 in 77% isolated yield. The effect of the optical concentration of methylamine is shown in Table II. The 30 % methylamine in THF produced the best result between 10 – 50% concentrations (Table II, Entry 3).

The final step was accomplished by the de-benzylation of 9 by hydrogenation in the presence of 5% Pd-carbon at 65°C for 18 h to afford 1 in 85% yield (Scheme II).

**Experimental Section**
Methylamine was purchased from Koei Chemical (Japan). All reagents and solvents were obtained from commercial sources and used without further purification. The melting points were determined using a Yanagimoto micromelting apparatus and are uncorrected. The IR spectra were obtained using a JASCO IR-810. The NMR spectra were recorded in CDC13 with TMS as the internal standard using a Bruker AM-400 (400MHz) spectrometer. The MS spectra were obtained using a Hitachi M-80A spectrometer at 70 eV. The optical rotations were recorded using a JASCO DIP-4 digital polarimeter. The HPLC was done using a Hitachi L-6000 [column, with an L-4000 UV as the detector, Optical purity: CHIRALPAK AD, 4.6 mm ID × 250 mm; eluent: ethanol/2-propanol/n-hexane = 5:5:90, flow rate, 0.5 mL/min; detector, UV (220 nm)]; chemical purity: [column: Inertsil ODS-2 (4.6 mm ID× 250 mm); eluent: MeCN/H2O, 7:3 (pH 2.3; adjusted by using H3PO4); flow rate: 0.5 mL/min; detection: UV (254 nm)].

### Table I — Solvent effect of asymmetric hydrogenation of 5

<table>
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<th>Entry</th>
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<th>Time (h)</th>
<th>D.e. (%)</th>
<th>E.e. (%)</th>
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<td>1</td>
<td>IPA</td>
<td>16</td>
<td>95</td>
<td>48</td>
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<tr>
<td>2</td>
<td>Acetone</td>
<td>16</td>
<td>97</td>
<td>74</td>
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<td>82</td>
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<td>81</td>
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<td>84</td>
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<tr>
<td>6</td>
<td>c-Hexanone</td>
<td>14</td>
<td>94</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>CH2Cl2</td>
<td>14</td>
<td>97</td>
<td>84</td>
</tr>
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</table>

The reaction times are for approximately 100% conversion.

### Table II — Effect of MeNH2 concentration on amination of 8

<table>
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<th>Entry</th>
<th>Conc. MeNH2 (%)A</th>
<th>Yield (%)B</th>
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<tr>
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<td>20</td>
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<td>3</td>
<td>30</td>
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<td>4</td>
<td>40</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>65</td>
</tr>
</tbody>
</table>

AReaction conditions: THF, 80°C, 18 h
BIsolated yield.
1-Benzylpyrrolidone, 4
To 60% NaH suspended in toluene (1L), 2-pyrrolidinone (212.5 g, 2.5 mol) was added for 40 min. The mixture was heated at 50°C for 30 min. and benzyl chloride (316.3 g, 2.5 mol) was then drop-wise added and stirred for 3.5 h. After cooling, the mixture was poured into ice water (1.5L) and the organic layer was washed with 5% NaCl (1L). The solvent was removed in vacuo and to the residue was added n-heptane (400 mL) and separated. The bottom layer was distilled under reduced pressure to give 1-benzylpyrrolidone (317 g, 78%). bp 130-140°C/1 torr. 1H NMR (CDCl3) δ 1.95-2.01 (m, 2H), 2.43 (t, J 8.2, 2H), 3.25 (t, J 7.2, 2H), 4.46 (s, 2H), 2.66-2.69 (m, 1H), 7.23-7.25 (m, 2H), 7.27-7.34 (m, 3H); 13C NMR (CDCl3) δ 17.58 (CH2), 30.79 (CH2), 46.44 (CH2), 127.38 (CH), 127.97 (CH ×2), 128.51 (CH × 2), 136.45 (C), 174.78 (CO); IR νmax (neat): 3062, 3029, 2917, 1685, 1495, 1425 cm⁻¹; MS: m/z 176 (14%, M⁺+1), 175 (90, M⁺), 174 (18), 146 (52), 104 (42), 91 (100), 41 (22).

3-Acetyl-1-benzyl-2-pyrrolidinone, 5
Diisopropylamine (176 g, 1.74 mol) in THF (900 mL) was cooled at -60°C, then 15% n-butyl lithium in hexane (1L) was added for 2h and stirred for 30 min. 1-Benzyl-2-pyrrolidinone (152 g, 869 mmol) was added over 40 min. After stirring over 30 min, dimethylacetamide (142 g, 1.64 mol) was added over 30 min and warmed to RT. The mixture was poured into 10%HCl (1.5L) and extracted with EtOAc (1.5 L), then washed with 10%NaHCO3 (1L), 5%NaCl (1L) and dried using anhydrous MgSO4. The solvent was concentrated and the residue was distilled under reduced pressure to give 2 (124.9 g, 73%). bp 160-170°C/1 torr. 1H NMR (CDCl3) δ 1.98-2.04 (m, 1H), 2.45 (s, 3H), 2.46-2.53 (m, 2H), 2.67-3.22 (m, 1H), 3.28-3.31 (m, 1H), 3.62-3.66 (m, 1H), 4.43 (dd, J 14.7, 35.3, 2H), 7.19-7.21 (m, 2H), 7.26-7.34 (m, 3H); 13C NMR (CDCl3) δ 19.39 (CH2), 29.89 (CH3), 44.83 (CH2), 46.83 (CH2), 55.55 (CH), 127.59 (CH), 129.90 (CH×2), 128.63 (CH×2), 135.84 (C), 169.69 (CO), 203.60 (CO); IR νmax (neat): 3063, 3030, 2921, 1685, 1605, 1495, 1430 cm⁻¹; MS: m/z 218 (8%, M⁺+1), 217 (43, M⁺), 202 (2), 189 (9), 174 (90), 161 (2), 146 (5), 118 (11), 106 (8), 91 (100), 84 (6), 65 (19), 43 (15).

(3S, 1'R)-1-Benzyl-3-[(1'-hydroxy)ethyl]-2-pyrrolidinone, 6
Into a 1L autoclave were charged 3-acetyl-1-benzyl-2-pyrrolidinone, 5 (113 g, 521 mmol) in CH2Cl2 (340 mL) and [NH2Et][{RuCl((R)-p-tolyl-BINAP)}2(μ-Cl)] (590mg, 0.65 mmol) under an
atmosphere of N₂. The atmosphere was then replaced with H₂ of 5 MPa at 50-55°C for 20 h. The optical yield and diastereomeric selectively as determined by HPLC column were 83%ee and 98%de, respectively. The reaction solution was concentrated and the solid residue was recrystallized from toluene at 0°C to give 6 (95.6 g, 84%) as a solid. The optical yield and diastereomeric selectively were 99%ee and 99%de, respectively. mp 82-82.5°C.

\[ \alpha \] D²O = 10.4 (c 1.15, CHCl₃). ¹H NMR (CDCl₃) δ 1.18 (d, J = 6.6, 3H), 1.91-2.04 (m, 2H), 2.52-2.62 (m, 1H), 3.36 (d, J = 5.6, 1H), 3.12-3.20 (m, 2H), 4.21-4.38 (m, 1H), 4.47 (dd, J = 14.7, 19.5, 2H), 7.16-7.29 (m, 5H); ¹³C NMR (CDCl₃) δ 18.63 (CH₂), 19.88 (CH), 45.09 (CH₂), 46.59 (CH₂), 48.37 (CH), 66.24 (CH), 127.52 (CH), 127.98 (CH × 2), 128.65 (CH × 2), 136.25 (C), 175.23 (CO); IR v max (CHCl₃): 3431, 3019, 2929, 1670, 1495, 1440 cm⁻¹; MS: m/z 220 (99%, M⁺+1), 219 (68, M⁺), 201 (9), 186 (25), 174 (53), 158 (9), 146 (3), 118 (25), 106 (9), 91 (100), 84 (6), 65 (15), 45 (9). Anal. Calcd for C₁₃H₁₉NO₂: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.23; H, 7.90; N, 6.37.

(3R, 1'R)-1-Benzyl-3-[(1'-methanesulfonyloxy)ethyl]-2-pyrrolidine, 7

6 (30 g, 0.137 mol) was dissolved in THF (60 mL), cooled at 10°C, then added drop-wise added to a suspension of lithium aluminum hydride in THF (150 mL) over 30 min. The mixture was refluxed while heating at 70°C for 2 h. The reaction mixture was cooled and the THF was removed under reduced pressure to give 6 (26.7 g, 95%) as an oil. bp 107-110°C/0.3 torr. [α] D²O = 9.0 (c 1.1, CHCl₃). ¹H NMR (CDCl₃) δ 1.89-2.01 (m, 2H), 2.59-2.62 (m, 1H), 2.62-2.69 (m, 1H), 3.58 (s, 3H), 3.83-3.89 (m, 1H), 7.24-7.32 (m, 5H); ¹³C NMR (CDCl₃) δ 20.99 (CH₃), 23.04 (CH₃), 43.24 (CH), 53.49 (CH₂), 59.19 (CH₂), 59.86 (CH₂), 71.27 (CH), 127.01 (CH), 128.28 (CH × 2), 128.54 (CH × 2), 138.58 (C); IR v max (neat): 3395, 3028, 2965, 2795, 1604, 1494, 1453 cm⁻¹; MS: m/z 206 (12%, M⁺+1), 205 (72, M⁺), 204 (72), 188 (10), 172 (5), 160 (12), 128 (45), 114 (41), 91 (100), 65 (29), 42 (30). HRMS calcd for C₁₃H₁₉NO: 205.2961, Found: 205.2963.

(3R, 1'R)-1-Benzyl-3-[(1'-methanesulfonyloxy)ethyl]-2-pyrrolidine, 8

Compound 7 (25.0 g, 122 mmol) and Et₃N (14.8 g, 146 mmol) were dissolved in toluene (120 mL) and cooled at 10°C. To the mixture, methanesulfonyl chloride (16.7 g, 146 mmol) in toluene (15 mL) was added over 40 min and stirred for 1 h. The water (140 mL) was added and the organic layer was extracted and washed with brine. The organic layer was dried with anhydrous MgSO₄ and the solvent was removed under reduced pressure to give 8 (32.8 g, 95%) as a viscous oil. ¹H NMR (CDCl₃) δ 1.39 (d, J = 6.3, 3H), 1.70-1.77 (m, 1H), 2.00-2.03 (m, 1H), 2.27-2.31 (m, 1H), 2.45-2.47 (m, 1H), 2.51-2.57 (m, 1H), 2.98 (s, 3H), 3.65 (dd, J = 21.0, 12.9, 2H), 7.24-7.34 (m, 5H); ¹³C NMR (CDCl₃) δ 19.85 (CH₃), 26.80 (CH₃), 38.82 (CH₂), 43.22 (CH), 53.67 (CH₂), 55.77 (CH₂), 60.22 (CH₂), 81.80 (CH), 127.26 (CH), 128.34 (CH × 2), 128.37 (CH × 2), 138.19 (C); IR v max (neat): 3027, 2925, 2786, 1604, 1493, 1452 cm⁻¹; MS: m/z 283 (7%, M⁺), 282 (4, M⁺-1), 206 (5), 188 (19), 172 (12), 158 (8), 143 (3), 132 (6), 120 (9), 110 (8), 91 (100), 81 (46), 69 (9), 57 (15), 43 (28). HRMS calcd for C₁₃H₂₁NO₃S: 283.1242, Found: 283.1242.

(3R, 1'S)-1-Benzyl-3-[(1'-N-methylamino)ethyl]-2-pyrrolidine, 9

Into a previously cooled 500-mL pressure-resistant vessel were charged methylamine (16.8 g, 0.32 mmol) and Et₃N (25.5 g, 90 mmol) in THF (45 mL). The mixture was stirred at 80°C for 1.5 h. After cooling, the solvent was removed under reduced pressure, then toluene (120 mL) and water (120 mL) were added. The toluene layer was separated and concentrated to give an oil. The oil was distilled under reduced pressure to give 9 (15.9 g, 58.5%). bp 115-118°C/1.5 torr. [α] D²O = 6.0 (c 1.0, EtOH). ¹H NMR (CDCl₃) δ 1.02 (d, J = 6.2, 3H), 1.46-1.54 (m, 1H), 1.87-1.95 (m, 1H), 2.09-2.19 (m, 1H), 2.25-2.27 (m, 1H), 2.37 (s, 3H), 2.37-2.46 (m, 2H), 2.62-2.66 (m, 1H), 2.74-2.79 (m, 1H), 3.57 (d, J = 12.9, 1H), 3.61 (d, J = 12.9, 1H), 7.21-7.33 (m, 5H); ¹³C NMR (CDCl₃) δ 17.57 (CH₃), 27.65 (CH₃), 33.85 (CH₂), 43.79 (CH), 54.13 (CH₂), 57.76 (CH₂), 58.99 (CH), 60.71 (CH₂), 126.75 (CH), 128.12 (CH × 2), 128.71 (CH × 2), 139.24 (C); IR v max (neat): 3061, 3027, 2960, 2915, 2786, 1604,
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1493, 1476, 1452 cm$^{-1}$; MS: $m/z$ 218 (2, M$^+$), 203 (4), 187 (95), 172 (86), 160 (10), 127 (6), 120 (18), 110 (8), 91 (100), 84 (13), 65 (13), 58 (45), 42 (10). HRMS calcd for C$_{14}$H$_{22}$N$_2$: 218.3380, Found: 218.3385.

(3R, 1'S)-3-[(1'-N-Methylamino)ethyl]-2-pyrrolidine, 1

Into a 1-L autoclave were charged 5% Pd-C (4.5 g) and 9 (45.0 g, 206 mmol) in MeOH (225 mL) under an atmosphere of N$_2$. The atmosphere was then replaced with H$_2$ of 3 MPa. for 18 h at 65°C. The catalyst was removed by filtration and the solvent was evaporated, then the residue was distilled under reduced pressure to give 1 (37.9 g, 85%) as an oil. bp 80-82°C/11 torr. $[\alpha]_{D}^{23}$ +37.3 (c 1.1, EtOH). $^1$H NMR (CDCl$_3$) $\delta$ 1.06 (d, $J$ = 6.2, 3H), 1.36-1.45 (m, 1H), 1.72 (br s, 1H), 1.81-1.89 (m, 1H), 1.95-2.06 (m, 1H), 2.40 (s, 3H), 2.38-2.45 (m, 2H), 2.59-2.64 (m, 1H), 2.86-2.97 (m, 2H), 3.08-3.13 (m, 1H); 13C NMR (CDCl$_3$) $\delta$ 17.89 (CH$_3$), 29.51 (CH$_2$), 33.82 (CH$_3$), 46.06 (CH), 47.08 (CH$_2$), 50.12 (CH$_2$), 58.66 (CH); IR $\nu_{max}$ (neat): 3275, 2961, 2869, 2788, 1445 cm$^{-1}$; MS: $m/z$ 129 (2, M$^+$+1), 128 (1, M$^+$), 111 (2), 97 (55), 82 (62), 68 (18), 58 (100), 42 (18).

Conclusion

The author has described the efficient synthesis of the important structural constituent of the quinolone type anti-fungal agents. (3R, 1'S)-3-[(1'-N-Methylamino)ethyl]pyrrolidine 1 was synthesized from (3S, 1'R)-1-benzyl-3-[(1'-hydroxy)ethyl]-2-pyrrolidine 3 via the diastereoselective hydrogenation of 3-acetyl-1-benzyl-2-pyrrolidione 2 using an optically-active $p$-tolyl-BINAP complex catalyst.

References


