

# Fluoronaphthyridines and -quinolones as Antibacterial Agents. 5. Synthesis and Antimicrobial Activity of Chiral 1-*tert*-Butyl-6-fluoro-7-substituted-naphthyridones

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A series of novel 7-substituted-1-*tert*-butyl-6-fluoronaphthyridone-3-carboxylic acids has been prepared. These derivatives are characterized by chiral aminopyrrolidine substituents at the 7 position. In this paper we report the full details of the asymmetric synthesis of this series of compounds. Structure-activity relationship studies indicate that the absolute stereochemistry at the asymmetric centers of the pyrrolidine ring is critical for maintaining good activity. Compounds 60 and 61 (3-amino-4-methylpyrrolidine enantiomers) were selected for preclinical evaluation.

The quinolone anti-infectives, represented generally by the formula A, constitute a class of extremely potent and orally active broad-spectrum antibacterial agents. Structure-activity relationship (SAR) studies resulted in the discovery of a variety of new chemotherapeutic agents by chemical modification at various positions. Among the possible substituents at C-6, it is generally accepted that a fluorine atom is optimal.<sup>1-3</sup> Various combinations of functionalities at C-1, C-7, and C-8 led to a number of now-marketed quinolones (Figure 1) such as norfloxacin (1),<sup>1</sup> ofloxacin (2),<sup>4</sup> ciprofloxacin (3).<sup>5</sup> More recently, attention has been paid to the role of the chirality in maintaining good activity in this series. The chirality has been introduced by attaching a chiral substituent by two different modes: (1) at N-1 as exemplified with ofloxacin (2),<sup>6-8</sup> S-25930 (4),<sup>9</sup> and the substituted ciprofloxacin derivative 5,<sup>10</sup> and (2) at C-7. In this case, substituted

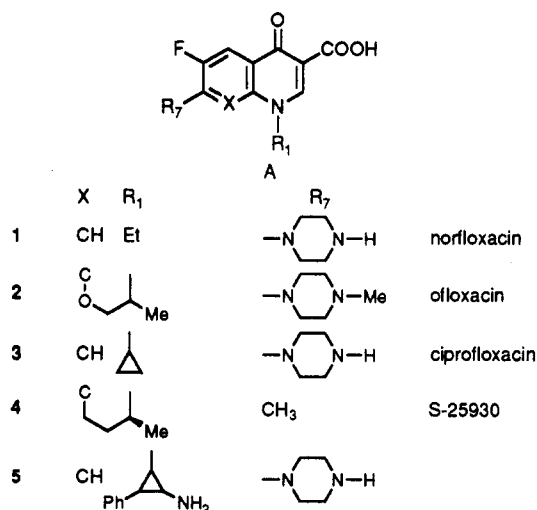


Figure 1.

piperazines,<sup>11,12</sup> 3-aminopyrrolidines,<sup>13,14</sup> 3-(amino-ethyl)pyrrolidines,<sup>15</sup> and 3-hydroxypyrrolidines<sup>16</sup> have been used.

In other respects, structure-activity studies<sup>17,18</sup> have demonstrated that amino-substituted pyrrolidines con-

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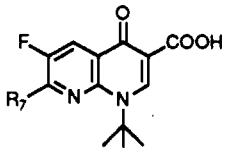
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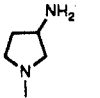
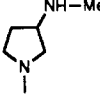
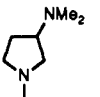
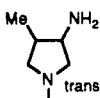
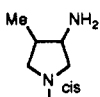
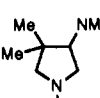
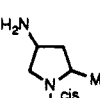
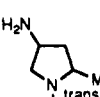
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Table I



| R <sub>7</sub>  | amine<br>R <sub>7</sub> H    | compd | formula <sup>b</sup>   | [α] <sub>D</sub> , deg                   | mp, °C  | %<br>yield <sup>a</sup> | recryst<br>solvent    | water solubility,<br>mg/mL, pH 7 |
|---|------------------------------|-------|--|--|---------|-------------------------|-----------------------|----------------------------------|
|    | 10 (3 <i>R</i> )             | 53    | C <sub>17</sub> H <sub>21</sub> FN <sub>4</sub> O <sub>3</sub> ·CH <sub>3</sub> SO <sub>3</sub> H·<br>H <sub>2</sub> O | -18.5 (c = 1, HCl 0.1 N)                 | 255     | 67.5                    | MeOH                  | 0.01                             |
|   | 17 (3 <i>S</i> )             | 54    | C <sub>17</sub> H <sub>21</sub> FN <sub>4</sub> O <sub>3</sub> ·CH <sub>3</sub> SO <sub>3</sub> H                      | +17.6 (c = 1, HCl 0.1 N)                 | 244     | 61                      | MeOH                  | 0.01                             |
|    | 13 (3 <i>R</i> )             | 55    | C <sub>18</sub> H <sub>23</sub> FN <sub>4</sub> O <sub>3</sub> ·HCl·H <sub>2</sub> O                                   | -19.4 (c = 0.4, HCl 0.1 N)               | 260     | 53                      | EtOH                  | 0.08                             |
|   | 18 (3 <i>S</i> )             | 56    | C <sub>18</sub> H <sub>23</sub> FN <sub>4</sub> O <sub>3</sub> ·HCl  | +20.0 (c = 2, HCl 0.1 N)                 | 260     | 48                      | EtOH                  | 0.08                             |
|    | racemic                      | 57    | C <sub>19</sub> H <sub>25</sub> FN <sub>4</sub> O <sub>3</sub>   | -  | 260     | 41                      | H <sub>2</sub> O      | 0.09                             |
|   | 19 (3 <i>S</i> )             | 58    | C <sub>19</sub> H <sub>25</sub> FN <sub>4</sub> O <sub>3</sub> ·HCl  | +9.1 (c = 1, H <sub>2</sub> O/MeOH, 1/1) | 292     | 56                      | EtOH/H <sub>2</sub> O | 0.09                             |
|    | 29 (3 <i>R</i> ,4 <i>S</i> ) | 59    | C <sub>18</sub> H <sub>23</sub> FN <sub>4</sub> O <sub>3</sub> ·CH <sub>3</sub> SO <sub>3</sub> H                      | -16.3 (c = 0.5, HCl 0.1 N)               | 270     | 32                      | EtOH                  | 0.25                             |
|   | 31 (3 <i>S</i> ,4 <i>R</i> ) | 60    | C <sub>18</sub> H <sub>23</sub> FN <sub>4</sub> O <sub>3</sub> ·CH <sub>3</sub> SO <sub>3</sub> H                      | +18.3 (c = 0.5, HCl 0.1 N)               | 236     | 85                      | EtOH/H <sub>2</sub> O | 0.25                             |
|    | 28 (3 <i>S</i> ,4 <i>S</i> ) | 61    | C <sub>18</sub> H <sub>23</sub> FN <sub>4</sub> O <sub>3</sub> ·CH <sub>3</sub> SO <sub>3</sub> H                      | -5.4 (c = 1, HCl 0.1 N)                  | 260     | 40                      | EtOH                  | 0.02                             |
|   | 30 (3 <i>R</i> ,4 <i>R</i> ) | 62    | C <sub>18</sub> H <sub>23</sub> FN <sub>4</sub> O <sub>3</sub> ·CH <sub>3</sub> SO <sub>3</sub> H                      | +6.5 (c = 0.5, HCl 0.1 N)                | 225 dec | 56                      | EtOH                  | 0.02                             |
|   | 36 (3 <i>S</i> )             | 63    | C <sub>19</sub> H <sub>25</sub> FN <sub>4</sub> O <sub>3</sub> ·CH <sub>3</sub> SO <sub>3</sub> H                      | -7.3 (c = 0.5, HCl 0.1 N)                | 270     | 12                      | EtOH                  | 0.3                              |
|   | 40 (3 <i>R</i> )             | 64    | C <sub>19</sub> H <sub>25</sub> FN <sub>4</sub> O <sub>3</sub> ·HCl  | +6.3 (c = 0.1, HCl 0.1 N)                | 260     | 24                      | EtOH                  | 0.3                              |
|  | 49 (2 <i>R</i> ,4 <i>S</i> ) | 65    | C <sub>18</sub> H <sub>23</sub> FN <sub>4</sub> O <sub>3</sub> ·CH <sub>3</sub> SO <sub>3</sub> H                      | +32.4 (c = 0.5, H <sub>2</sub> O)        | 200 dec | 14                      | MeOH                  | 1.7                              |
|   | 52 (2 <i>S</i> ,4 <i>R</i> ) | 66    | C <sub>18</sub> H <sub>23</sub> FN <sub>4</sub> O <sub>3</sub> ·HCl·H <sub>2</sub> O                                   | -39.0 (c = 0.5, HCl 0.1 N)               | 270     | 39.2                    | EtOH                  | 1.7                              |
|  | 50 (2 <i>R</i> ,4 <i>R</i> ) | 67    | C <sub>18</sub> H <sub>23</sub> FN <sub>4</sub> O <sub>3</sub> ·HCl·H <sub>2</sub> O                                   | -36.0 (c = 0.5, HCl 0.1 N)               | 260     | 35.5                    | EtOH                  | 0.17                             |
|   | 51 (2 <i>S</i> ,4 <i>S</i> ) | 68    | C <sub>18</sub> H <sub>23</sub> FN <sub>4</sub> O <sub>3</sub> ·HCl  | +37.6 (c = 0.5, HCl 0.1 N)               | 260     | 63                      | MeOH/ether            | 0.17                             |

<sup>a</sup> Yields are given for the halogen exchange reaction and saponification. <sup>b</sup> C, H, and N analysis were within ±0.4% of theoretical values, except as otherwise noted.

ferred remarkable improvements in the Gram-positive (*Staphylococci* and *Streptococci*) antibacterial potency in vitro. Moreover, studies in our laboratories<sup>19-21</sup> involving the 1-position of the quinolones and naphthyridones have established that a *tert*-butyl moiety for R<sub>1</sub> improves the in vitro and in vivo potencies particularly against Gram positive strains. These different observations have led us to focus on a series of chiral 7-(substituted aminopyrrolidinyl)-6-fluoro-1-*tert*-butyl-naphthyridone-

3-carboxylic acids to evaluate the importance of the chirality and the substituent effect on the pyrrolidinyl moiety in the series of the 1-*tert*-butyl-substituted naphthyridones. In this paper, we report new synthetic methods for the preparation of chiral pyrrolidines, the antibacterial activity, and the biological properties of the resulting chiral naphthyridones.

## Chemistry

The compounds 53-68 listed in Table I were synthesized by standard procedures from naphthyridine ester nucleus 6<sup>19</sup> and the corresponding aminopyrrolidine as outlined in the general Scheme I. The synthesis of the above cited compounds required the preparation of substituted aminopyrrolidines with the indicated relative and absolute stereochemistry. We chose the known (*S*)-1-benzyl-3-

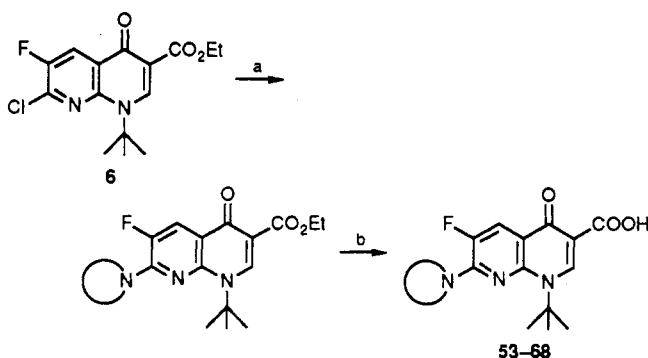
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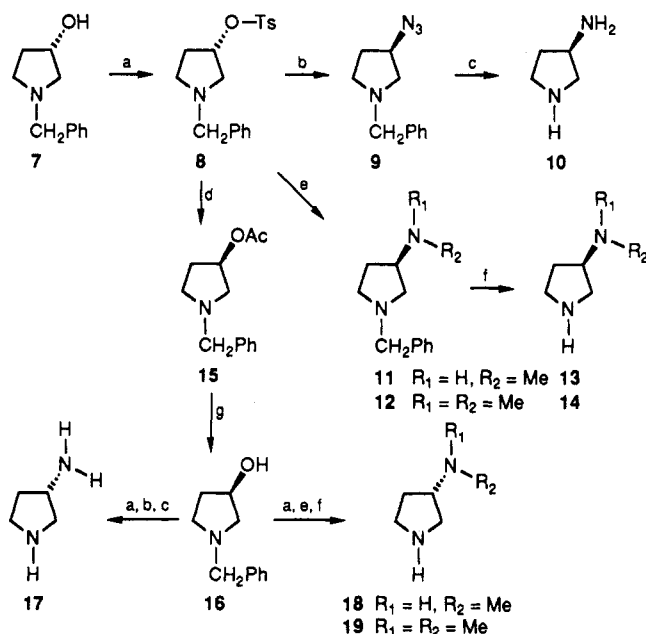
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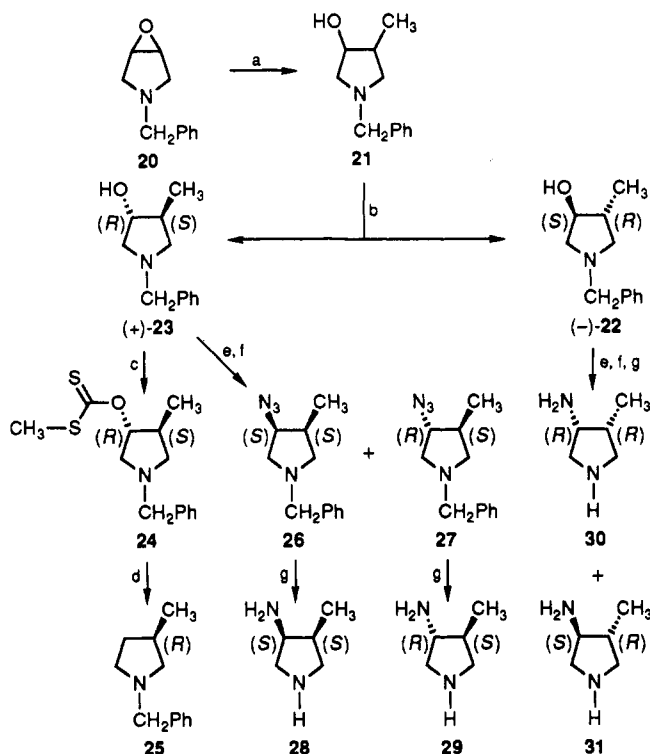
Scheme I<sup>a</sup>

<sup>a</sup> (a)  $\text{NH}$ , DBU,  $\text{CH}_3\text{CN}$ ; (b) aqueous 2 N NaOH, reflux.

Scheme II<sup>a</sup>

<sup>a</sup> (a) TsCl, pyridine; (b)  $\text{NaN}_3$ , DMF; (c)  $\text{H}_2$ , Pd/C; (d)  $\text{Et}_4\text{N}^+\text{AcO}^-$ ; (e)  $\text{R}_1\text{R}_2\text{NH}$ ; (f)  $\text{H}_2$ , Pd/C; (g)  $\text{Na}_2\text{CO}_3$ , MeOH.

pyrrolidinol (7)<sup>22-24</sup> as a chiron for the (*R*)- and (*S*)-3-aminopyrrolidines 10 and 17, (*R*)- and (*S*)-3-(*N*-methylamino)pyrrolidines 13 and 18, (*R*)- and (*S*)-3-(*N,N'*-dimethylamino)pyrrolidines 14 and 19 as described in Scheme II. In this sequence, the nitrogen was introduced at the 3-position of the pyrrolidine ring by sequential toluenesulfonate ester formation and  $\text{S}_{\text{N}}2$  displacement with azide ion or methylamine or dimethylamine. Tosylation of the alcohol 7 (TsCl, pyridine) afforded the key intermediate 8. Subsequent  $\text{S}_{\text{N}}2$  displacement with azide ion gave enantiomerically pure (*R*)-3-azido derivative 9. Reduction of the azide and debenzoylation were accom-

Scheme III<sup>a</sup>

<sup>a</sup> (a)  $\text{CH}_3\text{MgBr}$ , CuCN, THF; (b) (-)-DTTA; (c) NaH, DMF,  $\text{CS}_2$ , MeI; (d)  $\text{Bu}_3\text{SnH}$ , AIBN; (e) TsCl, pyridine; (f)  $\text{NaN}_3$ ,  $\text{CH}_3\text{CN}/\text{DMF}$ ; (g)  $\text{H}_2$ , Pd/C.

plished by hydrogenation over palladium on charcoal in one step to afford (*R*)-3-aminopyrrolidine (10). The displacement of the tosyloxy group with methylamine or dimethylamine followed by hydrogenolysis gave (*R*)-3-(*N*-methylamino)- and (*R*)-3-(*N,N'*-dimethylamino)pyrrolidines 13 and 14. The *R* enantiomer 16 of 7 was obtained from 8 by displacement of the tosylate with tetraethylammonium acetate and alkaline hydrolysis of the resulting acetate 15. Then, starting with 16, compounds with the 3*S* configuration (17, 18, and 19) were obtained as described for their *R* enantiomers. In the series of 7-(3-amino-4-methylpyrrolidinyl)quinolones, racemic derivatives have been described in some cases.<sup>25,26</sup> For the preparation of pure enantiomers of the corresponding pyrrolidines in our series we have chosen to operate an optical resolution.

The known epoxide 20<sup>27</sup> served as starting material for the four stereoisomers 3-amino-4-methylpyrrolidines as described in Scheme III. Treatment of 20 with methylmagnesium bromide and copper cyanide in THF gave the ( $\pm$ )-*trans*-3-methyl-4-hydroxypyrrolidine 21. The (+) and (-) isomers were separated by resolution ( $\pm$ )-21 using (-)-ditoluoyl-L-tartaric acid as resolving agent to afford the diastereoisomeric salts which were separated by crystallization. After three recrystallizations in water-ethanol, the obtained tartrate was decomposed with aqueous sodium hydroxide to afford pure (+)-isomer 23. Pure

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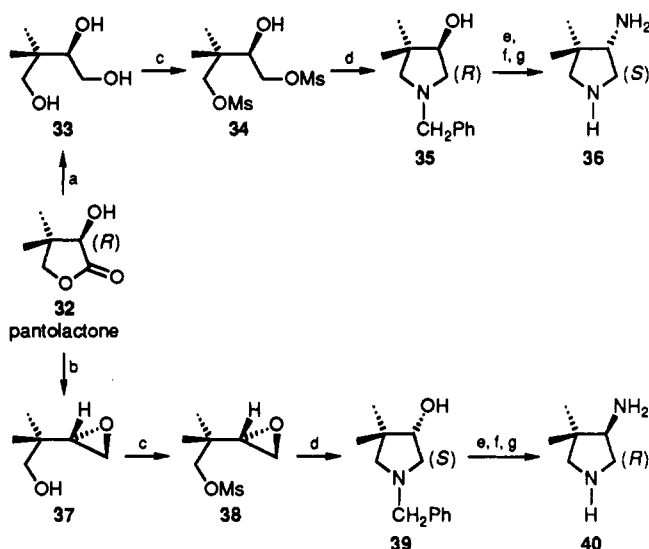
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Scheme IV<sup>a</sup>

<sup>a</sup> (a) Reference 30; (b) ref 31; (c) MsCl, pyridine; (d) PhCH<sub>2</sub>NH<sub>2</sub>; (e) TsCl, pyridine; (f) NaN<sub>3</sub>, DMF; (g) H<sub>2</sub>, Pd/C, EtOH, HCl.

(-)-22 was obtained from the mother liquor and (+)-ditoluoyl-D-tartaric acid. The absolute configuration (3*R*,4*R*) of (+)-23 was determined by chemical correlation with the known (*R*)-(-)-*N*-benzyl-3-methylpyrrolidine (25).<sup>28,29</sup> Treatment of the methyl xanthate 24 with Bu<sub>3</sub>SnH and AIBN gave the *R* derivative 25 [ $[\alpha]_D^{25} = -14.8^\circ$  ( $c = 2$ , EtOH), lit.:  $-10.1^\circ$  ( $c = 3.2$ , EtOH)]. After tosylation of the (3*R*,4*S*)-(+)-*N*-benzyl-3-hydroxy-4-methylpyrrolidine (23), displacement of the tosylate with sodium azide in acetonitrile containing 10% of DMF afforded a mixture of *cis* and *trans* azido derivatives 26 and 27 separated by chromatography on silica gel. When performed in pure DMF at 80 °C, displacement of the tosylate with azide occurred in an S<sub>N</sub>2 manner affording only the pure *cis* isomer 26 without detectable formation of the *trans* isomer 27 after 3 h.

Next, hydrogenolysis over palladium on charcoal gave *cis*-(3*S*,4*S*)-3*a*-amino-4-methylpyrrolidine (28) and (3*R*,4*S*)-3-amino-4-methylpyrrolidine (29). Analogous transformation of (-)-pyrrolidinol 22 afforded *cis*-(3*R*,4*R*) and *trans*-(3*S*,4*R*) pyrrolidines 30 and 31 enantiomers of 28 and 29. Starting with the commercially available (*R*)-(-)-pantolactone and using two different pathways, the synthesis of the two enantiomeric 3-amino-4,4-dimethylpyrrolidines was achieved as described in Scheme IV. In the first sequence, (*R*)-(-)-pantolactone (32) was reduced by a reported method<sup>30</sup> into the corresponding triol 33; mesylation of the two primary hydroxy groups followed by cyclization with benzylamine provided (3*R*)-*N*-benzyl-3-hydroxy-4,4-dimethylpyrrolidine (35). In the second sequence, the epoxide 37 prepared as reported by P. Lavalée<sup>31</sup> from (*R*)-(-)-pantolactone was mesylated and cyclized with benzylamine to obtain the (3*S*)-*N*-benzyl-

4,4-dimethyl-3-hydroxypyrrolidine (39). Then (3*S*)- and (3*R*)-aminopyrrolidines 36 and 40 bearing a quaternary *gem*-dimethyl carbon center were synthesized starting with 35 and 39 as described in the preceding series after tosylation, S<sub>N</sub>2 displacement with azide ion, and hydrogenation.

Natural 4-hydroxy-L-proline served as starting material for the synthesis of the four *N*-tosyl-4-(tosyloxy)-2-methylpyrrolidines, key intermediates of the preparation of the 4-amino-2-methylpyrrolidines 49–52 (Scheme V). The tritosyl derivative 41 prepared by a published procedure<sup>32</sup> was selectively reduced by LiAlH<sub>4</sub> in THF at 45 °C to (2*R*,4*R*)-*N*-tosyl-2-methyl-4-(tosyloxy)pyrrolidine (42). The strategy used to invert the stereochemistry at the 4-position of 42 was identical to that used in the 3-aminopyrrolidinyl series. Thus, the (2*R*,4*R*) epimer 43 was obtained. Tosylation of the free amine of the *cis*-4-hydroxy-D-proline ethyl ester<sup>24</sup> was followed by the reduction of the ester 44 with lithium borohydride in THF to produce the diol 45 which was tosylated to obtain the tritosylate 46. Then, pyrrolidines 47 and 48 were prepared from 46 by steps outlined for their enantiomers 43 and 42. Standard S<sub>N</sub>2 displacement with NaN<sub>3</sub> and hydrogenation followed by detosylation with HBr in acetic acid afforded the four expected diastereoisomers 49–52 from 42, 43, 47, and 48, respectively. The enantiomeric purity of the resulting substituted naphthyridones was checked by derivatization of the corresponding ethyl ester intermediate with (+)-10-camphorsulfonyl chloride in dichloromethane at 0 °C. The <sup>1</sup>H NMR spectrum of the resulting camphorsulfonamides of racemic, (+), and (-) isomers showed different chemical shifts for the C-6 proton of the naphthyridone nucleus. In all cases the enantiomeric excess was evaluated higher than 95%.

## Biological Evaluation

Compounds 53–68 were evaluated for their *in vitro* antibacterial activity against three Gram-positive bacteria (*Enterococcus faecalis* A 9809, *Enterococcus faecium* A 24885, and *Staphylococcus aureus* A 9537) and against six Gram-negative bacteria (*Escherichia coli* A 15119, *Klebsellia pneumoniae* A 9664, *Enterobacter cloacae* A 9656, *Morganella morganii* A 15153, *Serratia marcescens* A 20019, *Pseudomonas aeruginosa* A 9843) (Table II). The data for ciprofloxacin (3) are included for comparison. The *in vivo* potency expressed as the median protective dose (PD<sub>50</sub> mg/kg) was determined by using previously described methods.<sup>19–21</sup> The results of the *in vivo* tests are summarized in Table III. *In vivo* testing was generally performed on compounds that exhibit good *in vitro* (MIC) activity. By evaluating the MICs of the Gram-negative and Gram-positive organisms it was established that compound 54 which bears an unsubstituted (3*S*)-aminopyrrolidine substituent was the most potent member of this series but exhibited the lowest solubility.

The degree of substitution of the pyrrolidine was increased in two manners: by N-substitution of the 3-amino group or by C-substitution on the ring. Looking at the N-substitution, monomethylation and dimethylation resulted in a general decrease in *in vitro* potency most notably against Gram-positive strains. Here again, the difference in activity of the monomethylated derivatives was in favor of the *S* isomer versus the *R* isomer. These mono- and disubstitutions were accompanied by an

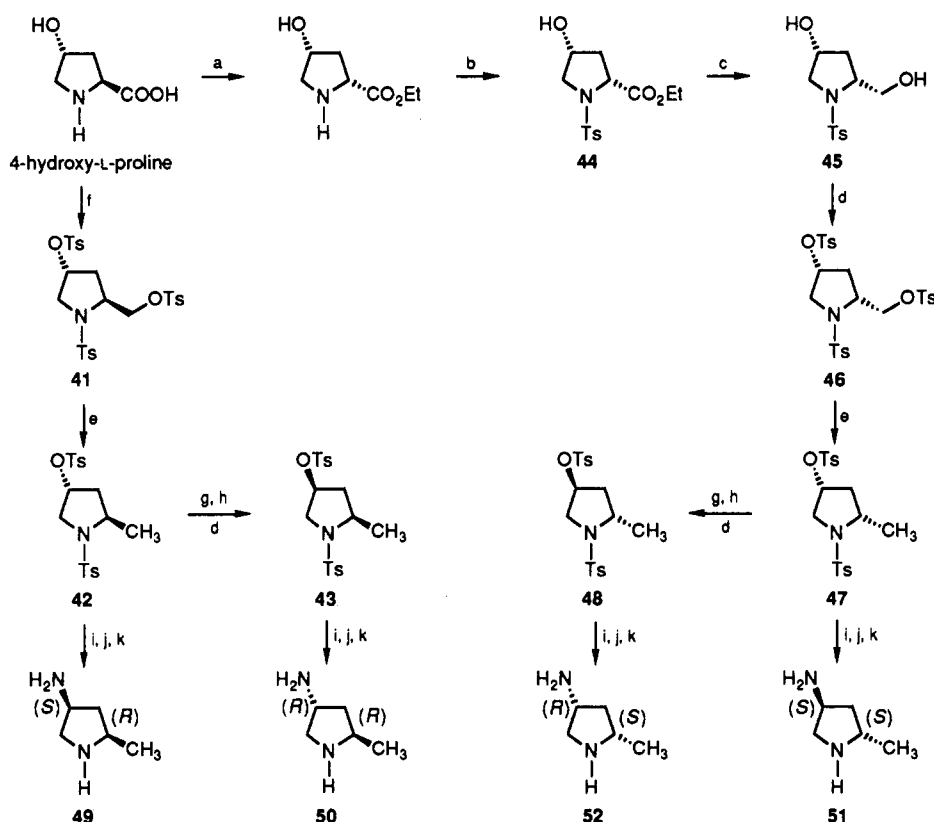
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Scheme V<sup>a</sup>

<sup>a</sup> (a) Reference 24; (b) TsCl, TEA; (c) LiBH<sub>4</sub>, THF; (d) TsCl, pyridine; (e) LiAlH<sub>4</sub>; (f) ref 32; (g) Et<sub>4</sub>N<sup>+</sup> AcO<sup>-</sup>; (h) K<sub>2</sub>CO<sub>3</sub>; (i) NaN<sub>3</sub>, DMF; (j) H<sub>2</sub>, Pd/C; (k) HBr, AcOH.

Table II. In Vitro Antibacterial Activity (MIC, mg/L)

| compd | <i>E. faeca.</i><br>A9809 | <i>E. faeci.</i><br>A24885 | <i>S. aur.</i><br>A9537 | <i>E. coli</i><br>A15119 | <i>K. pneu.</i><br>A9664 | <i>E. cloa.</i><br>A9656 | <i>M. morg.</i><br>A15153 | <i>S. mars.</i><br>A20019 | <i>P. aeru.</i><br>A9243 |
|-------|---------------------------|----------------------------|-------------------------|--------------------------|--------------------------|--------------------------|---------------------------|---------------------------|--------------------------|
| 3     | 0.5                       | 4.0                        | 0.06                    | 0.006                    | 0.06                     | 0.03                     | 0.06                      | 0.03                      | 0.25                     |
| 53    | 0.13                      | 1                          | 0.015                   | 0.06                     | 0.13                     | 0.06                     | 0.25                      | 0.25                      | 0.25                     |
| 54    | 0.03                      | 0.5                        | 0.0005                  | 0.015                    | 0.03                     | 0.13                     | 0.13                      | 0.13                      | 0.13                     |
| 55    | 1                         | 8                          | 0.03                    | 0.06                     | 0.13                     | 0.13                     | 0.5                       | 0.5                       | 1                        |
| 56    | 1                         | 2                          | 0.015                   | 0.03                     | 0.06                     | 0.06                     | 0.25                      | 0.25                      | 0.25                     |
| 57    | 1                         | 8                          | 0.03                    | 0.25                     | 0.13                     | 1                        | 0.5                       | 1                         | 1                        |
| 58    | 0.5                       | 4                          | 0.03                    | 0.015                    | 0.06                     | 0.03                     |                           | 1                         | 2                        |
| 59    | 0.25                      | 4                          | 0.015                   | 0.06                     | 0.25                     | 0.03                     | 0.25                      | 0.5                       | 2                        |
| 60    | 0.06                      | 0.5                        | 0.002                   | 0.016                    | 0.03                     | 0.016                    | 0.25                      | 0.25                      | 0.5                      |
| 61    | 0.25                      | 1                          | 0.008                   | 0.016                    | 0.5                      | 0.13                     | 0.13                      | 0.13                      | 1                        |
| 62    | 0.5                       | 4                          | 0.015                   | 0.13                     | 0.06                     | 0.03                     | 0.5                       | 0.5                       | 1                        |
| 63    | 0.25                      | 2                          | 0.015                   | 0.06                     | 0.13                     | 0.03                     | 0.5                       | 0.5                       | 2                        |
| 64    | 4                         | 4                          | 0.03                    | 0.06                     | 0.25                     | 0.25                     | 0.25                      | 0.25                      | 4                        |
| 65    | 0.5                       | 2                          | 0.13                    | 0.25                     | 0.25                     | 0.25                     | 2                         | 2                         | 8                        |
| 66    | 0.25                      | 2                          | 0.015                   | 0.03                     | 0.06                     | 0.03                     | 0.5                       | 0.5                       | 2                        |
| 67    | 1                         | 8                          | 0.13                    | 0.25                     | 0.5                      | 0.5                      | 4                         | 2                         | 16                       |
| 68    | 0.03                      | 0.5                        | 0.002                   | 0.016                    | 0.5                      | 0.13                     | 0.25                      | 0.5                       | 0.5                      |

improvement of the solubilities of each compound, without substantial difference between mono- and disubstituted derivatives.

By C-substitution, a second chiral center was introduced which generated *cis* and *trans* isomers. Looking at the 3-amino-4-methylpyrrolidine series, the best activity in this series was obtained here too for compounds having the *S* configuration at the N-substituted chiral center, i.e. 60 and 61, with comparable activities against Gram-negative, the *trans* isomer 60 being more active against Gram-positive strains than 61 in accordance with recent observations of Miyamoto et al.<sup>26</sup> With a higher degree of substitution at C-4 of the pyrrolidine ring, the activity of the *gem*-dimethyl *S* isomer 63 was comparable to that of the *cis*-(3*S*,4*S*) isomer 61 but lower than that of the *trans*-(3*S*,4*R*) isomer 60.

In the 4-amino-2-methylpyrrolidine series the absolute configuration at the carbon C-2 bearing the methyl group was more critical than in the precedent series. The best in vitro activity was obtained for the *trans* derivative 68 with the *S* configuration for the two asymmetric centers in accordance with recent reports from T. Rosen et al.<sup>13,14</sup> The water solubility of C-methylated compounds were more dissimilarly modified than for the N-methylated. If the solubility of the *cis*-3,4-substituted pyrrolidines 61 and 62 were not significantly enhanced by the presence of the methyl group, the increases for the corresponding *trans* derivatives were by a factor of 10 and the solubility was higher for the *cis*-2,4-disubstituted-pyrrolidinyl derivatives. Efficacy in systemic infections due to *S. aureus*, *P. aeruginosa*, *E. coli*, and *K. pneumoniae* in mice of several selected compounds and of ciprofloxacin is shown

**Table III.** Efficacy on Systemic Infections and Acute Toxicity with Oral Administration in Mice

| compd | in vivo PD <sub>50</sub> <sup>a</sup> (mg/kg) po |                               |                          |                               | LD <sub>50</sub> <sup>b</sup><br>po |
|-------|--|-------------------------------|--------------------------|-------------------------------|-------------------------------------|
|       | <i>S. aureus</i><br>A9537                        | <i>P. aeruginosa</i><br>A9843 | <i>E. coli</i><br>A15119 | <i>K. pneumoniae</i><br>A9664 |                                     |
| 3     | 4  | 5                             | 0.7                      | 1.5                           | 5000                                |
| 53    | 1.8  | 11                            | 4.9                      | 4.9                           | —                                   |
| 54    | 1.0  | 4.6                           | 1.2                      | 3.5                           | 350                                 |
| 56    | 0.31   | 6.1                           | 1.2                      | 2.6                           | >1000                               |
| 60    | 1.2  | 5.5                           | 2.1                      | 0.81                          | 4750                                |
| 61    | 1.0  | 4.7                           | 1.4                      | 3.9                           | 2500                                |
| 68    | 0.9  | 14.4                          | 2.6                      | 8.2                           | 1750                                |

<sup>a</sup> Dose to protect 50% of mice from lethal infection po. <sup>b</sup> See Experimental Section.

**Table IV.** Pharmacokinetic Properties of Selected Compounds after Oral Administration in Mice<sup>a</sup> (50 mg/kg)

| compd | C <sub>max</sub><br>μg/mL | t <sub>1/2</sub> , h | AUC <sup>b</sup> | UR <sup>c</sup> |
|-------|---------------------------|----------------------|------------------|-----------------|
| 3     | 5.9                       | 0.9                  | 7                | 29              |
| 53    | 5.9                       | 1.2                  | 9                | 18              |
| 54    | 4.4                       | 1.1                  | 6.2              | 10              |
| 56    | 9.8                       | 1.4                  | 2.6              | 3.2             |
| 60    | 8.2                       | 0.9                  | 15               | 7               |
| 61    | 9.1                       | 0.7                  | 9.9              | 4.6             |
| 68    | 7.7                       | 0.6                  | 7.8              | 5.4             |

<sup>a</sup> See Experimental Section. <sup>b</sup> Areas under the curve, concentration/time, μg/mL per h. <sup>c</sup> Urinary recovery after 24 h. Percent of administered dose.

in Table III. It is noticeable that the *N*-methyl derivative 56, less active in vitro, is as active or better than the parent compound 54. In comparison to ciprofloxacin (3), the in vivo efficacy of the tested naphthyridones on the experimental infections due to *S. aureus* was better upon oral administration. Compounds 54, 56, 60, and 61 were as potent as ciprofloxacin (3) against *P. aeruginosa* but in the case of *E. coli*, ciprofloxacin was 2–5-fold more active. Against *K. pneumoniae* only compound 60 exhibits a better activity. In every case the *S* configuration at the carbon bearing the amino group of the pyrrolidine remained important in order to maintain a good activity.

Pharmacokinetic properties of selected compounds are displayed in Table IV for mice (after oral administration (50 mg/kg)) and in Table V for dogs (25 mg/kg). In mice, unsubstituted aminopyrrolidine derivative 53 attains the same blood levels than ciprofloxacin. Interestingly *C*-methylated (*S*)-aminopyrrolidine derivatives 60, 61, and 68 achieved higher blood AUC than ciprofloxacin (3) with improved solubility (Table II) associated with the introduction of a methyl substituent. Urinary recoveries were low in all cases as previously observed with aminopyrrolidine derivatives.<sup>19,20</sup> In dogs, blood levels and AUC attain higher values in comparison with ciprofloxacin (3), the values for the *trans*-(3*S*,4*R*)-3-amino-4-methylpyrrolidinyl derivative 60 being twice that of ciprofloxacin (3) demonstrating a better bioavailability.

## Summary of Results

These investigations demonstrated the impact of chirality of the aminopyrrolidine ring on the activity of *N*1-*tert*-butyl-substituted naphthyridines. These results are in agreement with reported results from other studies.<sup>12–15</sup> We can state that *S* absolute configuration at the chiral center bearing the nitrogen is associated with better in vitro and in vivo activities. A difference ranking around a factor of 2 is generally observed between isomers of naphthyridones bearing a chiral amino substituent at C-7

**Table V.** Pharmacokinetic Properties of Selected Compounds after Oral Administration to Dogs (25 mg/kg)

| compd | C <sub>max</sub> | t <sub>1/2</sub> , h | AUC  | UR  |
|-------|------------------|----------------------|------|-----|
| 3     | 3                | 3.5                  | 20   | 17  |
| 54    | 4.5              | —                    | 23   | 9.5 |
| 60    | 6.0              | 4                    | 44   | 6   |
| 61    | 3.7              | 3.1                  | 28.5 | 9.7 |
| 68    | 4.8              | —                    | 32   | 3.5 |

while the difference is more important for quinolones bearing a chiral center closer to N-1 as reported for ofloxacin analogs.<sup>6–8</sup> On the other hand, lower toxicity and better pharmacokinetic properties can be associated with *C*-methyl substitution of the pyrrolidine ring. Association of these two criteria (*S* configuration and *C*-methyl substitution) led us to select compound 60 (BMV 41802) and compound 61 (BMV 41889) for preclinical development.<sup>33</sup>

## Experimental Section

**General Methods.** Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. All melting points were determined with a Büchi 510 capillary apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory, operated by the Bristol-Myers-Squibb Analytical Department. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 783 infrared spectrophotometer. All <sup>1</sup>H NMR spectra were determined on a Bruker AC200 apparatus. Chemical shifts are expressed in ppm (δ) relative to internal tetramethylsilane. Column chromatography was performed with Merck silica gel 60, 70–230 mesh ASTM. Thin-layer chromatography (TLC) was performed with Merck silica gel 60F254 TLC plates, and compound visualization was effected with iodine or a UV lamp. Optical rotations were measured in a 1-dm cell with a Perkin-Elmer Model 241 polarimeter.

**Microbiology. General Procedures. In Vitro Studies.** The in vitro antibacterial activity was studied by a side-by-side comparison with norfloxacin and ciprofloxacin and determined by the serial 2-fold dilution technique using nutrient broth. The inoculum size was adjusted to 10<sup>6</sup> cfu/mL, and the concentration of the compounds ranged from 0.0005 to 250 μg/mL. Minimum inhibitory concentration (MIC) was defined as the lowest concentration of the compound that prevents visible growth of bacteria after incubation at 37 °C for 18 h.

**Acute Toxicity on Oral Administration to Mice.** A solution of each test compound in sterile water was administered orally to OF1 strain female Swiss mice (18–25 g body weight, five per group). Seven days later, LD<sub>50</sub> values were determined by using the Karber and Behrens method.<sup>34</sup>

**Pharmacokinetics in Mice.** Levels of selected compounds in blood and urine samples from mice were determined as previously described.<sup>21</sup> Each compound was administered orally with a blunt needle and syringe set and intramuscularly to different groups of mice at a dose of 40 mg/kg. Blood samples were collected from the orbital sinus at 5, 15, 30, 60, 120, and 180 min after administration of drug. Urine samples were collected over 24 h. Concentrations of antibiotics in blood and urine were measured by the agar disk diffusion microbiology assay method with *Salmonella enteridis* A9531 as the assay organism.

**Pharmacokinetics in Dogs.** Plasma and urine levels in dogs were determined by microbiological assay. The selected compounds were administered in solution by oral gavage. Blood samples were obtained at 0.5, 1, 1.5, 2, 4, 6, 8, and 24 h after dosing. Plasma was separated by centrifugation and frozen until tested. Urine was collected 0–4, 4–8, and 8–24 h after dosing and frozen until analysis. Plasma levels and urinary excretion of test

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compounds were determined by using the agar plates system. The test organism was *Bacillus subtilis* ATCC 6633, and the standard used was the test substance itself.

**Solubility Studies. General Procedures.** A known weight of the compound was shaken overnight with a known volume of buffered water (pH 7) for injection. The contents were filtered, and the clear filtrate was analyzed after appropriate dilution by HPLC (UV absorbance detection).

**Preparation of Amines. (3*S*)-3-[(4-Tolylsulfonyl)oxy]-1-(phenylmethyl)pyrrolidine (8).** To a solution of 16.4 g (92.5 mmol) of (*S*)-3-hydroxy-1-(phenylmethyl)pyrrolidine (7)<sup>23</sup> in 164 mL of pyridine cooled to +5 °C was added 19.35 g (101.7 mmol) of 4-toluenesulfonyl chloride. The mixture was stirred 48 h at +10 °C. The solvent was removed in vacuo, and the residue was purified by chromatography using dichloromethane/acetone (95/5) to yield 18.8 g (63%) of the pyrrolidine 8: mp 68 °C;  $[\alpha]_D^{20}$  -30° (*c* = 5, MeOH); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 1.6–1.9 (m, 1 H), 2.1–2.35 (m, 1 H), 2.4 (s, 3 H, CH<sub>3</sub>Ar), 2.55–3.1 (m, 3 H), 3.8 (s, 2 H, CH<sub>2</sub>Ar), 5.04 (m, 1 H, H-3), 7.32 (broad s, 5 H, CH<sub>2</sub>Ar), 7.48 and 7.78 (m, 4 H, CH<sub>3</sub>ArSO<sub>2</sub>). Anal. (C<sub>18</sub>H<sub>21</sub>NO<sub>3</sub>S) C, H, N.

**(3*R*)-3-Azido-1-(phenylmethyl)pyrrolidine (9).** To a solution of 17.1 g (51.6 mmol) of 8 in 200 mL of anhydrous dimethylformamide preheated to 65 °C was added 33.5 g (516 mmol) of sodium azide. The mixture was stirred for 7 h at 60 °C. The insoluble material was filtered off, and the solvent was removed in vacuo. The residue was dissolved in ethyl acetate, washed twice with water, and dried over magnesium sulfate to yield 7.95 g (76.5%) of compound 9 as an oil:  $[\alpha]_D^{20}$  -7.2° (*c* = 5, MeOH); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 1.65–1.85 (m, 1 H), 2.05–2.35 (m, 2 H), 2.45–2.80 (m, 3 H), 3.58 (s, 2 H, CH<sub>2</sub>Ar), 4.0 (m, 1 H, H-3), 7.29 (broad s, 5 H, Ar). Anal. (C<sub>11</sub>H<sub>14</sub>N<sub>4</sub>) C, H, N.

**(3*R*)-3-Aminopyrrolidine Dihydrochloride (10).** To a solution of 7.05 g (34.8 mmol) of 9 and 34.8 mL of aqueous 1 N hydrochloric acid in 245 mL of ethanol was added 3.5 g of 10% palladium on carbon under nitrogen. The mixture was hydrogenated at atmospheric pressure for 30 min. A further 3.5 g of the catalyst was added and hydrogenation continued for 2 h. The catalyst was filtered off, and 34.8 mL of 1 N hydrochloric acid was added to the filtrate which was evaporated in vacuo. The residue was taken up with 70 mL of ethanol. The solution was filtered and concentrated in vacuo. This operation was repeated twice. The dihydrochloride crystallized in a minimum amount of ethanol to give 4.45 g (80.5%) of product 10:  $[\alpha]_D^{20}$  = -1.2° (*c* = 0.5, 0.1 N HCl); <sup>1</sup>H NMR δ (Me<sub>2</sub>SO-*d*<sub>6</sub>) 1.9–2.15 (m, 1 H), 2.15–2.35 (m, 1 H), 3.1–3.55 (m, 4 H), 3.8 (m, 1 H, H-3), 8.7 (broad s, exchangeable). Anal. (C<sub>4</sub>H<sub>10</sub>N<sub>2</sub>·2HCl) C, H, N.

**(3*R*)-1-Benzyl-3-(methylamino)pyrrolidine (11).** To 70 mL of a solution of methylamine in ethanol (14.6% w/w) was added 10 g (30.1 mmol) of 8 in a pressure bottle. The pressure bottle was heated in an oil bath at 140 °C for 20 h. After cooling, the mixture was evaporated in vacuo and the residue was dissolved in 50 mL of water. The aqueous solution was washed twice with 20 mL of dichloromethane, and then 12 g of potassium carbonate was added. The insoluble material was filtered off and the aqueous solution extracted three times with dichloromethane. The organic layers were combined, dried (MgSO<sub>4</sub>), and evaporated in vacuo to give 4.2 g (72%) of 11 as an oil which was used without further purification for the next step: <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 1.35–1.6 (m, 1 H), 1.8–2.1 (m, 1 H), 2.2 (s, 3 H, NCH<sub>3</sub>), 2.35–2.8 (m, 4 H), 3.05 (m, 1 H, H-3), 3.52 (s, 2 H, CH<sub>2</sub>Ar), 7.1–7.4 (m, 5 H, Ar).

**(3*R*)-3-(Methylamino)pyrrolidine Dihydrochloride (13).** Pyrrolidine 11 (4 g, 21 mmol) was dissolved in ethanol (140 mL), and 1 N HCl was added (21 mL). The mixture was hydrogenated for 90 min. The catalyst was filtered off and 1 N HCl was added (21 mL) to the filtrate. The solvent was removed in vacuo. The residue was taken up with ethanol to give a crystalline product:  $[\alpha]_D^{20}$  -3.7° (*c* = 1.0, 1 N HCl); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.05–2.4 (m, 2 H), 2.56 (s, 3 H, NCH<sub>3</sub>), 3.1–3.6 (m, 6 H), 3.83 (m, 1 H, H-3), 9.7 (broad s, 4 H, exchangeable). Anal. (C<sub>5</sub>H<sub>12</sub>N<sub>2</sub>·HCl) C, H, N.

**(3*R*)-3-Acetoxy-1-(phenylmethyl)pyrrolidine (15).** A suspension of 2.9 g (11 mmol) of tetraethylammonium acetate tetrahydrate in 100 mL of ethyl acetate was azeotropically dehydrated. Then 3.3 g (10 mmol) of compound 8 were added, and the mixture was refluxed for 2 h. After cooling, the organic layer was washed with water, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by chroma-

tography using dichloromethane/methanol (98/2) to yield 1.4 g of pure compound 15 as an oil:  $[\alpha]_D^{20}$  +22.0° (*c* = 5, MeOH); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 1.7 (m, 1 H), 2.06 (s, 3 H, CH<sub>3</sub>CO<sub>2</sub>), 2.11–2.71 (m, 5 H), 3.55 (s, 2 H, CH<sub>2</sub>Ar), 5.03 (m, 1 H, H-3), 7.26 (m, 5 H, Ar). Anal. (C<sub>13</sub>H<sub>17</sub>NO<sub>2</sub>) C, H, N.

**(3*R*)-1-Benzyl-3-pyrrolidinol (16).** To a solution of 31.4 g (mmol) of 15 in a mixture of 365 mL of methanol and 145 mL of water was added 7 g of sodium carbonate. The mixture was stirred for 4 h and evaporated in vacuo. The residue was taken up with water and dichloromethane. The aqueous layer was extracted twice with dichloromethane. The organic layers were combined, dried over magnesium sulfate, and evaporated to dryness in vacuo. The residue was dissolved in 97 mL of acetone, and 21.16 g of (*S*)-mandelic acid was added. The mixture was heated until dissolution and then kept at +5 °C until crystallization occurred. The solid was collected by filtration and recrystallized from 2-propanol to give 26.4 g of a pure salt. This salt was dissolved in chloroform and the resulting solution treated with saturated aqueous sodium carbonate. The organic layer was dried over magnesium sulfate and evaporated to dryness to yield 14.6 g of (*R*)-1-benzyl-3-pyrrolidinol (16):  $[\alpha]_D^{20}$  +3.5° (*c* = 5, MeOH); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.0 (m, 1 H), 2.2–2.75 (m, 4 H), 3.4–3.6 (m, 2 H, CH<sub>2</sub>Ar), 4.22 (m, 1 H, H-3), 4.71 (broad s, 1 H, exchangeable), 7.18–7.31 (m, 5 H, Ar). Anal. (C<sub>11</sub>H<sub>15</sub>NO) C, H, N.

**(3*S*)-3-Aminopyrrolidine Dihydrochloride (17).** The transformation of 16 into 17 was carried out as described for the transformation of 8 into 10 to obtain the dihydrochloride salt with an optical rotation of  $[\alpha]_D^{20}$  +1.3° (*c* = 0.5, 0.1 N HCl).

**(3*S*)-3-(Methylamino)pyrrolidine Dihydrochloride (18).** Starting from 16 the (*S*) isomer 18 was obtained as described for 13 with an optical rotation of  $[\alpha]_D^{20}$  +3.4° (*c* = 1, 0.1 N HCl).

**(3*S*)-3-(Dimethylamino)pyrrolidine Dihydrochloride (19).** By using a solution of aqueous dimethylamine in ethanol (1–2 v/v) instead of methylamine in ethanol, the compound 19 was obtained from 3(*R*)-pyrrolidinol 16 by a procedure analogous to that used to convert 16 into 18. A dihydrochloride salt was isolated:  $[\alpha]_D^{20}$  -2.8° (*c* = 0.5, H<sub>2</sub>O–MeOH 50/50); <sup>1</sup>H NMR (D<sub>2</sub>O) δ 2.15–2.4 (m, 1 H), 2.55–2.8 (m, 1 H), 3.00 (s, 6 H, N(CH<sub>3</sub>)<sub>2</sub>), 3.35–3.75 (m, 3 H), 3.80–4.0 (m, 1 H), 4.10–4.30 (m, 1 H). Anal. (C<sub>6</sub>H<sub>14</sub>N<sub>2</sub>·2HCl) C, H, N.

**trans-N-Benzyl-3-hydroxy-4-methylpyrrolidine (21).** To a solution of 25 g of *N*-benzyl-3,4-epoxypyrrolidine (140 mmol) in 370 mL of anhydrous THF were added 12.6 g of copper(II) cyanide (140 mmol) under nitrogen. The resulting suspension was cooled to -20 °C. Then 127 mL of a 2.25 M solution of methylmagnesium chloride in THF was added dropwise. The reaction mixture was stirred at this temperature for 1 h. At this time, 100 mL of a 10% solution of ammonium chloride were added slowly and the temperature kept below 20 °C. After 1 h at room temperature, a precipitate was filtered off and the solution evaporated to dryness. To the resulting syrup were added 250 mL of dichloromethane and 250 mL of water. The organic layer was separated, dried over magnesium sulfate, and evaporated to dryness to afford 22.4 g of a crude product used without further purification in the next step.

**Separation of (3*S*,4*R*)-*N*-Benzyl-3-hydroxy-4-methylpyrrolidine (22) and (3*R*,4*S*)-*N*-Benzyl-3-hydroxy-4-methylpyrrolidine (23).** To a solution of 77.3 g of the racemic pyrrolidine 21 (400 mmol) in 4 L of a mixture of ethanol/water (50/50 v/v) was added 156 g of (-)-ditoluoyltartaric acid (400 mmol) and the mixture heated in a water bath until dissolution. After filtration, the solution was kept at room temperature. A precipitate was formed after 3 days. This precipitate was collected, dried, and recrystallized three times from 30 volumes of a mixture of ethanol/water (50/50 v/v) to afford 6.5 g of a ditoluoyltartrate: mp 147–148 °C;  $[\alpha]_D^{20}$  -92.3° (*c* = 1, MeOH/0.1 N HCl 50/50). A portion of 6.4 g of this salt was treated with 230 mL of a 10 N aqueous sodium hydroxide solution. The resulting mixture was extracted three times with 250 mL of diethyl ether. The organic layer was dried over magnesium sulfate and evaporated to dryness to give 2.01 g of (3*R*,4*S*)-*N*-benzyl-3-hydroxy-4-methylpyrrolidine as an oil:  $[\alpha]_D^{20}$  +26.3° (*c* = 1.8, MeOH). From the mother liquor of this first crystallization, 31 g of ditoluoyltartrate were obtained after removal of the solvent in vacuo. This salt was dissolved in 1 L of 1 N sodium hydroxide and extracted with diethyl ether to afford 9.7 g of *trans*-*N*-benzyl-

3-hydroxy-4-methylpyrrolidine. This compound was dissolved in 290 mL of ethanol/water (50/50 v/v), and 19.6 g of (+)-ditoluoyltartaric acid was added and dissolved by heating on a water bath. The resulting solution was allowed to stand at room temperature for 1 day. A precipitated salt was collected and recrystallized twice from 30 volumes of ethanol/water (1/1 v/v). After treatment with aqueous sodium hydroxide as described before, 3 g of (3*S*,4*R*)-*N*-benzyl-3-hydroxy-4-methylpyrrolidine was recovered as an oil:  $[\alpha]_D -26.6^\circ$  ( $c = 1$ , MeOH);  $^1\text{H NMR}$  ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$  0.97 (d,  $J = 6.8$  Hz, 3 H,  $\text{CH}_3$ ), 1.98 (m, 2 H), 2.4 (m, 1 H), 2.55–2.85 (m, 3.52 (m, 2 H,  $\text{CH}_2\text{Ar}$ ), 3.65 (m, 1 H), 4.76 (m, 1 H, exchangeable), 7.27 (m, 5 H, Ar).

***N*-Benzyl-3-[[[(methylthio)thiocarbonyl]oxy]-4-methylpyrrolidine (24).** To a solution of 2.01 g of compound (+)-23 (10.5 mmol) in 15 mL of dimethylformamide was added 0.530 g of sodium hydride (50% in oil suspension) (11 mmol) under nitrogen. The mixture was stirred at room temperature for 30 min, and the solvent removed in vacuo. The residue was taken up with diethyl ether. The organic layer was filtered, washed with water, dried over magnesium sulfate, and evaporated to dryness to give 0.78 g of an oil which was chromatographed (ethyl acetate/hexane, 20:80) to give 2.90 g of a pure product as an oil:  $[\alpha]_D +45.5^\circ$  ( $c = 1.35$ , MeOH);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.15 (d,  $J = 7$  Hz, 3 H,  $\text{CH}_3$ ), 2.05 (m, 1 H), 2.5 (m, 1 H), 2.57 (s, 3 H,  $\text{SCH}_3$ ), 2.75–3.1 (m, 2 H,  $\text{CH}_2\text{Ar}$ ), 7.30 (m, 5 H, Ar). Anal. ( $\text{C}_{14}\text{H}_{19}\text{NOS}_2$ ) C, H, N.

***N*-Benzyl-3-methylpyrrolidine (25).** To a solution of 0.45 g of compound 24 (1.66 mmol) in 15 mL of anhydrous toluene under nitrogen was added 0.720 g of tributyltin hydride (2.47 mmol) and AIBN. The reaction mixture was refluxed for 30 min. The toluene was removed in vacuo to leave a thick residue. This residue was dissolved in aqueous 0.1 N HCl. The resulting solution was washed with ether and then made basic by adding solid potassium carbonate. After extraction with dichloromethane, the organic layer was washed with water and dried over magnesium sulfate, and the solvent was removed in vacuo to give 1.6 g of an oil which was purified by column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 95:5) to give 0.750 mg of pure product:  $[\alpha]_D -10.5^\circ$  ( $c = 3.25$ , EtOH; in accordance with the literature<sup>28,29</sup> for the *R* isomer);  $^1\text{H NMR}$  ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$  0.92 (d,  $J = 6.7$  Hz, 3 H,  $\text{CH}_3$ ), 1.23 (m, 1 H), 1.92 (m, 2 H), 2.1 (m, 1 H), 2.30–2.7 (m, 3 H), 3.48 (broad s, 2 H,  $\text{CH}_2\text{Ar}$ ), 7.20 (broad s, 5 H, Ar). Anal. ( $\text{C}_{12}\text{H}_{17}\text{N}$ ) C, H, N.

**(3*S*,4*S*)- and (3*R*,4*S*)-*N*-Benzyl-3-azido-4-methylpyrrolidines (26) and (27).** Tosylation of 1.9 g of pyrrolidinol (+)-23 by the procedure described for compound 8 gave 3.01 g of a tosylated derivative (8.7 mmol). This was dissolved in 35 mL of acetonitrile and 0.35 mL of dimethylformamide. To this solution was added 5.3 g of sodium azide (81.5 mmol) and the mixture refluxed for 48 h. After cooling, the mixture was filtered and the filtrate evaporated to dryness. The *cis* and *trans* derivatives were separated by column chromatography (ethyl acetate/hexane 30/70) to give 0.43 g of compound 26 and 0.45 g of compound 27. The more polar compound 26 was identical to the compound obtained by using pure dimethylformamide as solvent and identified as a *cis* derivative:  $[\alpha]_D -23.5^\circ$  ( $c = 1$ , MeOH);  $^1\text{H NMR}$  ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$  0.98 (d,  $J = 6.8$  Hz, 3 H,  $\text{CH}_3$ ), 2.16 (t,  $J = 6.8$  Hz, H-4), 2.25–2.60 (m, 2 H), 2.69 (m, 1 H), 2.95 (m, 1 H), 3.58 (m, 2 H,  $\text{CH}_2\text{Ar}$ ), 4.0 (m, 1 H, H-3), 7.29 (m, 5 H, Ar). Anal. ( $\text{C}_{12}\text{H}_{16}\text{N}_4$ ) C, H, N. Compound 27:  $[\alpha]_D +31.9^\circ$  ( $c = 1$ , MeOH);  $^1\text{H NMR}$  ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$  1.04 (d,  $J = 7$  Hz, 3 H,  $\text{CH}_3$ ), 1.91 (t,  $J = 7$  Hz, H-4), 2.15 (m, 1 H), 2.65 (m, 2 H), 2.93 (m, 1 H), 3.51 (m, 1 H, H-3), 3.55 (m, 2 H,  $\text{CH}_2\text{Ar}$ ), 7.26 (m, 5 H, Ar). Anal. ( $\text{C}_{12}\text{H}_{16}\text{N}_4$ ) C, H, N.

***cis*-(3*S*,4*S*)-3-Amino-4-methylpyrrolidine Dihydrochloride (28).** The hydrogenolysis of 0.42 g of compound 26 (1.85 mmol) as described for the preparation of compound 10 gave 0.286 g of a solid: mp 200 °C dec;  $^1\text{H NMR}$  ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$  1.04 (d, 3 H,  $J = 6.8$  Hz,  $\text{CH}_3$ ), 3.1 (m, 1 H), 3.3 (m, 2 H), 3.50 (m, 1 H), 3.6–3.9 (m, 2 H), 8.5–10 (broad s, 4 H, exchangeable).

***trans*-(3*R*,4*S*)-3-Amino-4-methylpyrrolidine dihydrochloride (29):** mp 250 °C dec;  $^1\text{H NMR}$  ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$  1.12 (d,  $J = 7$  Hz, 3 H,  $\text{CH}_3$ ), 2.40 (m, 1 H), 2.7 (m, 1 H), 3.15–3.6 (m, 4 H), 8.3–10 (broad s, 4 H, exchangeable).

**(3*R*)-1,4-Bis[(methylsulfonyl)oxy]-2,2-dimethyl-3-hydroxybutane (34).** A solution of 33 (9.25 g, 68.9 mmol) in 92 mL of dry pyridine was cooled in an ice bath, and methanesulfonyl

chloride (10.7 mL, 138.2 mmol) was added slowly (20 min). The reaction mixture was then allowed to stand at room temperature overnight. After filtration, the solvent was removed in vacuo. The residue was taken up with water. The aqueous layer was adjusted to pH 1 with 5 N HCl and extracted with dichloromethane (three times). The organic layers were combined, washed with water, dried over magnesium sulfate, and evaporated to dryness to afford 18.5 g of crude product. Purification of an aliquot by chromatography using hexane/ethyl acetate (40/60) gave pure product:  $[\alpha]_D -10.8^\circ$  ( $c = 5$ , MeOH);  $^1\text{H NMR}$  ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$  0.9 and 0.94 (2s,  $2 \times 3$  H,  $\text{C}(\text{CH}_3)_2$ ), 3.17–3.19 (2s,  $2 \times 3$  H,  $2 \text{SO}_2\text{CH}_3$ ), 3.5 (m, 1 H), 3.9–4.15 (m, 3 H), 4.31 (dd, 1 H, H-3,  $J_{3,2} = 10.6$  Hz,  $J_{3,\text{OH}} = 2.5$  Hz), 5.51 (broad s, 1 H, exchangeable). Anal. ( $\text{C}_8\text{H}_{18}\text{O}_5\text{S}_2$ ) C, H, N.

**(3*R*)-*N*-Benzyl-4,4-dimethyl-3-hydroxypyrrolidine (35).** A solution of compound 34 (4 g, 13.8 mmol) and benzylamine (4.5 mL, 42 mmol) in 60 mL of ethanol was heated in a 100-mL Teflon bomb using an oil bath at 130 °C overnight. After cooling, the solution was evaporated to dryness. The residue was taken up in diethyl ether. The ethereal layer was filtered, and water was added. The aqueous layer was adjusted to pH 4 with 1 N HCl and separated from the ethereal layer. The aqueous solution was made basic with 2 N NaOH (pH 10) and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and evaporated to dryness. The residue was taken up with diethyl ether, the insoluble material was removed by filtration, and the ethereal solution was evaporated to dryness to afford a crude product. Purification of 2.89 g of this material by column chromatography on silica gel (methanol/chloroform, 4/95) gave 2.03 g of pure 35:  $[\alpha]_D +34.1^\circ$  ( $c = 1$ , MeOH);  $^1\text{H NMR}$  ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$  0.9 and 0.96 (2s,  $2 \times 3$  H,  $\text{C}(\text{CH}_3)_2$ ), 2.25–2.40 (m, 3 H), 2.9–3.0 (m, 1 H), 3.5–3.65 (m, 2 H,  $\text{CH}_2\text{Ar}$ ), 3.65–3.70 (m, 1 H, H-3), 4.65 (d, 1 H,  $J = 5$  Hz, OH), 7.27 (m, 5 H, Ar). Anal. ( $\text{C}_{13}\text{H}_{19}\text{NO}$ ) C, H, N.

**(3*S*)-3-Amino-4,4-dimethylpyrrolidine Hydrochloride (36).** A cold solution (+4 °C) of 0.6 g (2.9 mmol) of compound 35 in 6 mL of pyridine was treated with 0.67 g (3.5 mmol) of 4-toluenesulfonyl chloride. The reaction mixture was kept 48 h at +4 °C. Pyridine was removed under reduced pressure. Water and dichloromethane were added. The organic layer was separated, washed with water and saturated  $\text{NaHCO}_3$  solution, dried over magnesium sulfate, and evaporated in vacuo. The crude product was purified by column chromatography on silica gel ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 98/2) to afford 0.49 g of (3*R*)-*N*-benzyl-4,4-dimethyl-3-(4-toluenesulfonyl)oxypyrrolidine:  $[\alpha]_D +43.5^\circ$  ( $c = 1$ , MeOH). To a solution of this compound (0.205 g, 0.57 mmol) in 2 mL of dimethylformamide was added sodium azide (0.225 g, 3.4 mmol). The mixture was heated at 85 °C for 24 h. After cooling, the solution was filtered and evaporated to dryness in vacuo. The residue was chromatographed on silica gel (dichloromethane/methanol, 90/10) to afford 57 mg of pure product with  $[\alpha]_D +12^\circ$  ( $c = 1$ , MeOH). A solution of 0.52 g (2.25 mmol) of (3*S*)-*N*-benzyl-3-azido-4,4-dimethylpyrrolidine, prepared as above in 18 mL of ethanol and 2.25 mL of 1 N hydrochloric acid, was hydrogenated over 0.26 g of 10% palladium on carbon for 100 min. The catalyst was filtered off over a Celite pad. The resulting solution was evaporated to dryness and the residue taken up twice with absolute ethanol to give 0.34 g of the compound 36 as an oil:  $[\alpha]_D +6^\circ$  ( $c = 1$ ,  $\text{H}_2\text{O}$ );  $^1\text{H NMR}$  ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$  0.94 and 1.01 (2s,  $2 \times 3$  H,  $\text{C}(\text{CH}_3)_2$ ), 2.75–2.9 (m, 2 H), 2.95–3.15 (m, 2 H), 3.20–3.5 (m, 1 H, H-3), 6.0 (broad s, 3 H, exchangeable). Anal. ( $\text{C}_8\text{H}_{14}\text{N}_2\text{HCl}$ ) C, H, N.

**(*S*)-[2-[(Methylsulfonyl)oxy]-1,1-dimethylethyl]oxirane (38).** To a cold solution (+5 °C) of 1.575 g (13.5 mmol) of the oxirane 37 in 15 mL of dichloromethane were added 2.5 mL of triethylamine (17.9 mmol) and 1.3 mL (16.8 mmol) of methanesulfonyl chloride. The mixture was then stirred at room temperature for 30 min. A precipitate was removed by filtration. The organic layer was washed with water until neutral, dried over magnesium sulfate, and evaporated to dryness to afford 2.58 g of a crude product as an oil which was used without further purification for the next step:  $[\alpha]_D +5.62^\circ$  ( $c = 2$ ,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$  0.87 (broad s, 6 H,  $\text{C}(\text{CH}_3)_2$ ), 2.62 (m, 2 H), 2.86 (m, 1 H), 3.18 (s, 3 H,  $\text{CH}_3\text{SO}_2$ ), 4.01 (m, 2 H,  $\text{CH}_2\text{OMs}$ ). Anal. ( $\text{C}_7\text{H}_{14}\text{O}_4\text{S}$ ) C, H.

**(3*S*)-*N*-Benzyl-4,4-dimethyl-3-hydroxypyrrolidine (39).** A solution of 2.516 g (13 mmol) of the oxirane 38 and

2.2 mL (20.1 mmol) of benzylamine in 20 mL of ethanol was heated in a 100-mL teflon bomb using an oil bath at 130 °C overnight. After cooling, the solution was evaporated to dryness. Water and dichloromethane were added, and the pH of the aqueous layer was adjusted to 1 with 1 N HCl. The aqueous layer was separated, made basic with 1 N NaOH, and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and evaporated to dryness to afford a crude product which was purified as described for the *R* isomer 35 giving 2.58 g of compound 39 as an oil:  $[\alpha]_D -34^\circ$  ( $c = 1$ , MeOH).

**(3*R*)-3-Amino-4,4-dimethylpyrrolidine Hydrochloride (40).** This compound was prepared from 39 as described for the preparation of the *S* isomer:  $[\alpha]_D -5.3^\circ$  ( $c = 0.5$ , H<sub>2</sub>O).

**1-(4-Tolylsulfonyl)-4-hydroxy-D-proline Ethyl Ester (44).** To a cold solution (+5 °C) of 10 g (50 mmol) of 4-hydroxy-D-proline ethyl ester 24 in 100 mL of anhydrous pyridine were added portionwise 10.66 g (56 mmol) of 4-toluenesulfonyl chloride. The resulting dark solution was stirred 24 h at +5 °C and then evaporated to dryness. The residue was taken up in 2 L of dichloromethane and was washed successively with 2 N hydrochloric acid solution and water. The organic layer was dried over magnesium sulfate and evaporated to dryness. The oily residue crystallized in diisopropyl ether to yield 13.7 g of compound 44: mp 78 °C;  $[\alpha]_D +79.4^\circ$  ( $c = 1.8$ , ethanol); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  1.17 (t,  $J = 7$  Hz, 3 H, OCH<sub>2</sub>CH<sub>3</sub>), 1.8–2.1 (m, 2 H, H-3,3'), 2.39 (s, 3 H, CH<sub>3</sub>Ar), 3.05–3.25 (m, 3 H), 3.96 (m, 1 H, H-4), 4.09 (q,  $J = 7$  Hz, 2 H, OCH<sub>2</sub>CH<sub>3</sub>), 5.07 (broad s, 1 H, exchangeable), 7.38–7.76 (m, 4 H, Ar). Anal. (C<sub>14</sub>H<sub>19</sub>NO<sub>5</sub>S) C, H, N.

**(2*R*,4*R*)-4-Hydroxy-2-(hydroxymethyl)-1-(4-tolylsulfonyl)pyrrolidine (45).** To a solution of 354 g (1.13 mmol) of the ester 44 in 3.5 L of tetrahydrofuran at –3 °C was added portionwise 24.7 g (1.134 mmol) of lithium borohydride. During the addition, the temperature rose to +16 °C. The reaction mixture was kept at room temperature overnight and then acidified to pH = 3 with 6 N HCl. The resulting mixture was concentrated in vacuo, and the resulting slurry was poured into 2 L of ice-cooled water. The precipitate was collected by filtration, washed with water, and dried in vacuo to give 237.6 g of compound 45: mp 106 °C;  $[\alpha]_D +54.6^\circ$  ( $c = 2$ , ethanol); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  1.55–1.85 (m, 2 H, H-3,3'), 2.40 (s, 3 H, CH<sub>3</sub>Ar), 3.13 (m, 2 H), 3.56 (m, 3 H), 3.65 (m, 1 H), 4.97 and 5.13 (2 m, 2 H, exchangeable), 7.40–7.72 (m, 4 H, Ar). Anal. (C<sub>12</sub>H<sub>17</sub>NO<sub>4</sub>S) C, H, N.

**(2*R*,4*R*)-1-(4-Tolylsulfonyl)-4-[(4-tolylsulfonyl)oxy]-2-[[4-(4-tolylsulfonyl)oxy]methyl]pyrrolidine (46).** A solution of 10 g (3 mmol) of the pyrrolidine 45 in 50 mL of pyridine was cooled in an ice bath. To this solution was added 17.1 g (90 mmol) of 4-toluenesulfonyl chloride. The reaction mixture was stirred at room temperature for 2 days and then poured into 100 mL of ice-cooled water. The resulting precipitate was collected by filtration, washed successively with water, a 2 N hydrochloric acid solution, and finally with water. The resulting product was recrystallized in ethanol to give 19.6 g of the tritosyl derivative 46: mp 152 °C;  $[\alpha]_D +53.7^\circ$  ( $c = 1.8$ , chloroform); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  1.7–1.9 (m, 2 H), 2.39, 2.43, 2.44 (3 s, 3  $\times$  3 H, 3 CH<sub>3</sub>Ar), 3.1–3.35 (m, 2 H), 3.71 (m, 1 H), 3.92 (m, 1 H), 4.16 (m, 1 H), 4.72 (m, 1 H), 7.35–7.85 (m, 12 H, Ar). Anal. (C<sub>26</sub>H<sub>29</sub>NO<sub>8</sub>S<sub>3</sub>) C, H, N.

**(2*S*,4*S*)-*N*-(4-Tolylsulfonyl)-2-methyl-4-[(4-tolylsulfonyl)oxy]pyrrolidine (47).** A suspension of 21.28 g (560 mmol) of lithium aluminum hydride in 300 mL of anhydrous tetrahydrofuran (THF) was heated to 70 °C. A solution of 162 g (279 mmol) of compound 46 in 1200 mL of THF was added dropwise over 2.5 h. The reflux was maintained for a further 2 h. Then 100 mL of water was added dropwise. Subsequently 1 L of ethyl acetate was added, and the mixture was heated at 65 °C for 30 min. After cooling, the reaction mixture was filtered and the solid residue washed with ethyl acetate (1.5 L). The organic layers were collected and evaporated to dryness. The resulting residue was taken up in 300 mL of 2-propanol. After cooling in an ice bath the solid was collected by filtration to give 34 g of compound 42 as a solid: mp 140 °C;  $[\alpha]_D -2.6^\circ$  ( $c = 2$ , acetone); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  1.26 (d,  $J = 6.4$  Hz, CH<sub>3</sub>), 1.62 (m, 1 H), 2.41 (m, 6 H, 2 CH<sub>3</sub>Ar), 3.18 (m, 1 H), 3.35 (m, 1 H), 4.76 (m, 1 H, H-4). Anal. (C<sub>19</sub>H<sub>23</sub>NO<sub>5</sub>S<sub>2</sub>) C, H, N.

**(2*S*,4*R*)-*N*-(4-Tolylsulfonyl)-2-methyl-4-[(4-tolylsulfonyl)oxy]pyrrolidine (48).** The epimerization of 42 was performed as described for 8 to give the compound 48 as a solid.

**(2*S*,4*R*)-4-Amino-2-methylpyrrolidine Dihydrobromide (52).** To a solution of 10.6 g (25.9 mmol) of the ditosylate derivative 48 in 100 mL of anhydrous DMF was added 16.9 g (260 mmol) of sodium azide. The mixture was stirred for 7 h at 60 °C. After cooling at room temperature, the insoluble material was filtered off and the solvent removed in vacuo. The residue was dissolved in ethyl acetate, washed twice with water, and dried over magnesium sulfate to yield 7.17 g of a crude intermediate (2*S*,4*R*)-4-azido-2-methyl-1-(4-tolylsulfonyl)pyrrolidine which was used without further purification in the next step: mp 85 °C;  $[\alpha]_D -9.8^\circ$  ( $c = 2$ , MeOH). To a solution of 6.8 g (24.4 mmol) of the above intermediate in 140 mL of ethanol was added 4 g of 10% palladium on carbon. The mixture was hydrogenated for 2 hours, the catalyst was filtered off, and the filtrate was evaporated to dryness in vacuo. The residue was taken up in diethyl ether to give 3.65 g of a crystalline product which was recovered by filtration. This 4-amino-2-methyl-1-(4-tolylsulfonyl)pyrrolidine intermediate was dissolved in 32 mL of acetic acid. To the resulting solution was added 8.6 mL of HBr in acetic acid (33%), and the mixture was heated for 3 h at 80 °C. After cooling at 50 °C, 2 g of Norit were added and the mixture was stirred for 20 min. After filtration over Celite, the solvent was removed under reduced pressure. The residue was triturated with acetonitrile giving a solid which was dried at 50 °C in vacuo for 2 h to provide 2.4 g of compound 52 as a dihydrobromide: mp 178 °C;  $[\alpha]_D = 0.4^\circ$  ( $c = 0.7$ , EtOH); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  1.35 (d,  $J = 6.4$  Hz, 3 H, CH<sub>3</sub>), 1.64 (m, 1 H), 2.6 (m, 1 H), 3.22 (m, 1 H), 3.75 (m, 2 H), 3.90 (m, 1 H), 8–9.5 (broad signal, exchangeable). Anal. (C<sub>9</sub>H<sub>12</sub>N<sub>2</sub>·2HBr) C, H, N.

Compounds 49–51 were prepared from 42, 43, and 47, respectively, as described for the preparation of 52. **(2*R*,4*R*)-4-Amino-2-methylpyrrolidine dihydrobromide (49):** mp 179 °C;  $[\alpha]_D +0.45^\circ$  ( $c = 2$ , EtOH); <sup>1</sup>H NMR identical to 52. **(2*R*,4*R*)-4-Amino-2-methylpyrrolidine dihydrobromide (50):** mp 176 °C;  $[\alpha]_D +0.7^\circ$  ( $c = 1$ , EtOH); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  1.28 (d,  $J = 6.5$  Hz, 3 H, CH<sub>3</sub>), 1.75–2.3 (m, 2 H), 3.12 (m, 2 H), 3.61 (m, 2 H), 8–9.5 (broad signal, exchangeable). **(2*S*,4*S*)-4-Amino-2-methylpyrrolidine dihydrobromide (51):** mp 175 °C;  $[\alpha]_D -0.75^\circ$  ( $c = 2$ , EtOH); <sup>1</sup>H NMR identical to 50.

**Preparation of Naphthyridones. General Procedure.** As an example, the preparation of the naphthyridone 59 is described. Analytical results are given in Table I.

**(3*R*,4*S*)-7-(3-Amino-4-methylpyrrolidinyl)-1-(1,1-dimethylethyl)-1,4-dihydro-6-fluoro-4-oxo-1,8-naphthyridine-3-carboxylic Acid, Methanesulfonate (59).** To a suspension of 490 mg (1.5 mmol) of 7-chloro-1-(1,1-dimethylethyl)-1,4-dihydro-6-fluoro-4-oxo-1,8-naphthyridine-3-carboxylic acid ethyl ester in 9.5 mL of acetonitrile were added successively 295 mg (1.7 mmol) of the amine 29 as a dihydrochloride and 0.8 mL (5.3 mmol) of DBU. The resulting mixture was heated at 70 °C to 40 min. After cooling, a precipitate was collected by filtration, and it was washed with cold acetonitrile and dried in vacuo to give 370 mg of a crystalline product (3*R*,4*S*)-7-(3-amino-4-methylpyrrolidinyl)-1-(1,1-dimethylethyl)-1,4-dihydro-6-fluoro-4-oxo-1,8-naphthyridine-3-carboxylic acid ethyl ester: mp 232 °C;  $[\alpha]_D -25.41^\circ$  ( $c = 0.5$ , 0.1 N HCl). This compound (345 mg) was suspended in 0.9 mL of 2 N NaOH. The mixture was heated under reflux until dissolution. After cooling to room temperature, the solution was made neutral with 2 N HCl. The resulting mixture was cooled in an ice bath, and the precipitate was collected by filtration, washed with water, and dried in vacuo. A suspension of the obtained solid in 2.4 mL of methanol was heated, and 0.05 mL of methanesulfonic acid was added. The hot solution was filtered and evaporated to dryness to give a residue which was recrystallized from ethanol to give 222 mg of compound 62 as a solid: mp > 270 °C dec;  $[\alpha]_D -16.3^\circ$  ( $c = 0.5$ , 0.1 N HCl); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  1.16 (d,  $J = 6.8$  Hz, 3 H, CH<sub>3</sub>-pyrrolidinyl), 1.89 (s, 9 H, *t*-Bu), 2.3 (s, 3 H, CH<sub>3</sub>SO<sub>3</sub>H), 3.25–3.75 (m, 5 H), 3.82 (m, 1 H), 4.15–4.3 (m, 2 H), 8.09 (d,  $J_{H-F} = 12.8$  Hz, H-5), 8.86 (s, 1 H, H-2). Anal. (C<sub>18</sub>H<sub>23</sub>FN<sub>4</sub>O<sub>3</sub>·CH<sub>3</sub>SO<sub>3</sub>H) C, H, N.