Fluoronaphthyridines as Antibacterial Agents. 6. Synthesis and Structure-Activity Relationships of New Chiral 7-(1-, 3-, 4-, and 6-Methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)naphthyridine Analogues of 7-[(1*R*,4*R*)-2,5-Diazabicyclo[2.2.1]heptan-2-yl]-1-(1,1-dimethylethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid. Influence of the Configuration on Blood Pressure in Dogs. A Quinolone-Class Effect

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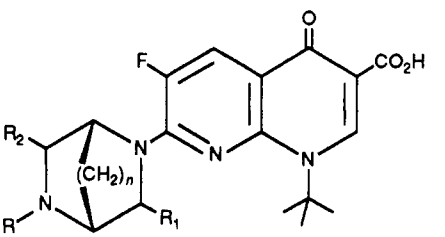
A series of novel chiral 7-(1-, 3-, 4-, and 6-methyl-[(1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-substituted naphthyridines has been prepared with the aim of obtaining good in vitro and in vivo antibacterial agents with a decrease of the pseudoallergic type reaction when compared to that observed with 7-[(1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(1,1-dimethylethyl)-1,4-dihydro-6-fluoro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**1a**) (BMY 40062). The derivatives 7-[(1*R*,4*R*,6*S*)-6-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(1,1-dimethylethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**41**) and 7-[(1*R*,4*R*,6*S*)-6-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**49**) showed potent in vitro and in vivo antibacterial activity against Gram-positive and Gram-negative bacteria. The derivative **49** displayed a less marked decrease in blood pressure (MAP), compared to that of **1a**, after intravenous infusion in dogs and was selected as a potential candidate for preclinical trials.

Introduction

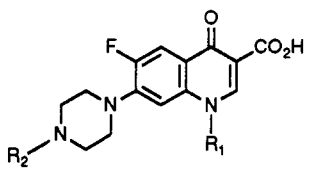
The synthesis of fluoroquinolones and subsequent demonstration of their broad and potent antibacterial activity has engendered great interest. On the other hand, through clinical trials, much attention has been paid to the side effects of these drugs.[1] In general the quinolones appear to be safe and well tolerated.[2] The most common reactions include headache, dizziness, and restlessness.[3] Seizures, hallucinations, and anaphylactic reactions with hypotension, which are rare in patients who receive these drugs, have also been observed.[4] Recently, 7-[(1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(1,1-dimethylethyl)-1,4-dihydro-6-fluoro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**1a**) (BMY 40062), a naphthyridine with a (1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptane appendage at C-7 and a *tert*-butyl group at N-1 was discovered in our laboratories[5,6] (Chart I). This large-spectrum naphthyridone showed improved pharmacokinetics in mouse, dog, and man as well as broader in vitro and in vivo activities than ciprofloxacin (CIP) especially after oral administration.[5] However, in clinical trials, **1a** was found to induce pseudoallergic type reactions such as skin flushing, pruritus, and erythema after oral administration.[7] In clinical studies, pefloxacin (PEF, Chart II), a quinolone already on the market, showed ichty erythematous reaction in few cases.[8] Similar adverse reactions were observed with

Chart I

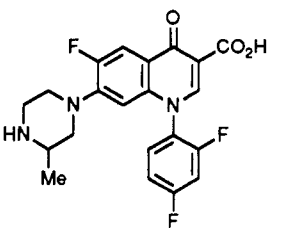


1a: R = R_1 = R_2 = H, *n* = 1 (1*R*,4*R*)
1b: R_1 = R_2 = H, R = Me, *n* = 1 (1*R*,4*R*)
2a: R = R_1 = H, R_2 = Me, *n* = 0
2b: R = R_2 = H, R_1 = Me, *n* = 0

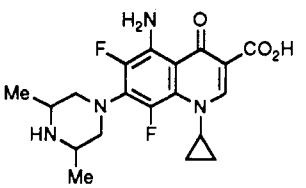
Chart II



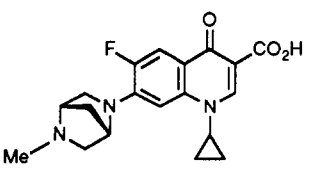
CIP (ciprofloxacin) R_1 = C_3H_5, R_2 = H
PEF (pefloxacin) R_1 = C_2H_5, R_2 = Me



3 (temafloxacin)



4 (sparfloxacin)

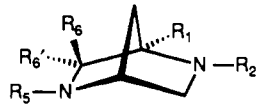


5 (danofloxacin)

(1) Stahlmann, R.; Lode, H. In *The Quinolones*; Andriole, V. T., Ed.; Academic Press: London, 1988; pp 201-233.
(2) Christ, W.; Lehnert, T.; Ulbrich, B. Specific Toxicologic Aspects of the Quinolones. *Rev. Infect. Dis.* **1989**, *11* (Suppl. 1), S141-146.
(3) Bergan, T. In *Antimicrobial Agents 2: Quinolones*; Peterson, P. K., Verhoef, J., Eds.; Elsevier Science Publishers: New York, 1987; pp 169-183.
(4) Bowie, W. R.; Willets, V.; Jewesson, P. J. Adverse Reactions in a Dose-Ranging Study with a New Long-Acting Fluoroquinolone, Fleroxacin. *Antimicrob. Agents Chemother.* **1989**, *33*, 1778-1782.
(5) Bouzard, D.; Di Cesare, P.; Essiz, M.; Jacquet, J. P.; Kiechel, J. R.; Remuzon, P.; Weber, A.; Oki, T.; Masuyoshi, M.; Kessler, R. E.; Fung-Tomc, J. and Desiderio, J. V. Fluoronaphthyridines and Quinolones as Antibacterial Agents. 2. Synthesis and Structure-Activity Relationships of New 1-*tert*-Butyl 7-Substituted Derivatives. *J. Med. Chem.* **1990**, *33*, 1344-1352.
(6) Fung-Tomc, J.; Desiderio, J. V.; Tsai, Y. H.; Warr, G.; Kessler, R. E. In Vitro and In Vivo Antibacterial Activities of BMY 40062, a New Fluoronaphthyridone. *Antimicrob. Agents Chemother.* **1989**, *33*, 906-914.
(7) Unpublished results.

0022-2623/92/1835-2898$03.00/0

Chart III

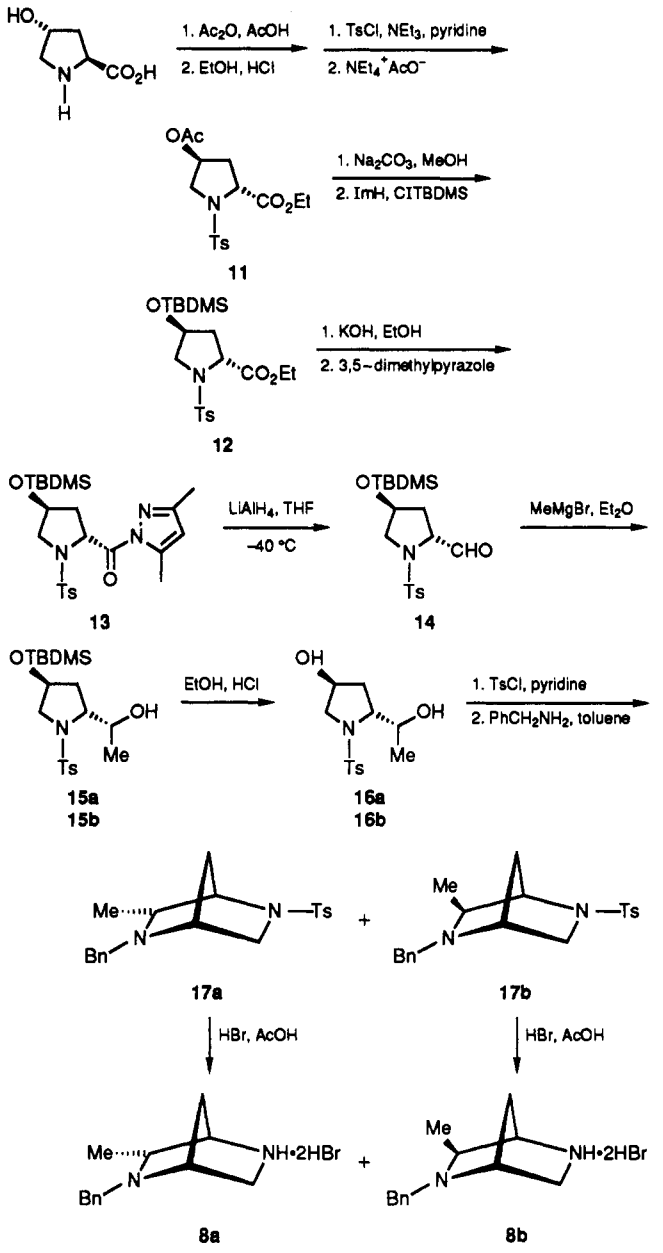


6: R_1 = Me, R_5 = Bn, R_2 = R_6 = $R_{6'}$ = H
7: R_1 = Me, R_2 = $COCF_3$, R_5 = R_6 = $R_{6'}$ = H
8a: R_5 = Bn, $R_{6'}$ = Me, R_1 = R_2 = R_6 = H
8b: R_5 = Bn, R_6 = Me, R_1 = R_2 = $R_{6'}$ = H
9a: R_2 = $COCF_3$, $R_{6'}$ = Me, R_1 = R_5 = R_6 = H
9b: R_2 = $COCF_3$, R_6 = Me, R_1 = R_5 = $R_{6'}$ = H

vancomycin after intravenous administration.[9] These pseudoallergic effects ("the Red Man Syndrome") are mediated in part by histamine release as demonstrated for vancomycin. In an animal model (the anesthetized dog), administration of **1a** was shown to also release histamine, causing a severe hypotension even at low dose.[7] This phenomena seems to be a quinolone-class effect as pefloxacin presented the same blood pressure depression after administration at 5 mg/kg iv, accompanied by bronchoconstriction and skin flushing.[8]

During the screening of analogues of **1a**, we observed that, when the nitrogen N-5 of the bridged bicyclic piperazine was substituted with a methyl group to give **1b**, hypotension in the dog was dramatically reduced, although the in vitro antimicrobial activity was reduced to a large extent. Recently we reported[10] that *N*-1-*tert*-butylnaphthyridines **2** substituted at C-7 with a 2-methylpiperazine (**2b**) gave better in vitro antibacterial activity than when substituted with a 3-methylpiperazine (**2a**) (Chart I). Furthermore the (2*S*)-2-methylpiperazine **2b** was found to be almost 4 times better than the 2*R* isomer analogue. It is also noticeable that 3-methyl- and 3,5-dimethylpiperazinyl 7-substituted quinolones **3** (temafloxacin)[11] and **4** (sparfloxacin)[12] (Chart II) with enhanced in vivo properties were brought to the market. Finally danofloxacin **5**, a quinolone substituted at C-7 with a (1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]heptane moiety, was shown to be useful for veterinary use (Chart II).[13]

Scheme I



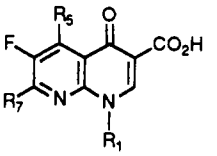
Given all these data on C-alkylated piperazine derivatives, we wondered if addition of a methyl group on the bridged piperazines would minimize pseudoallergic reactions and keep very good in vivo and in vitro activities. The six protected (1*R*)-1-methyl-, (3*R*)- and (3*S*)-3-methyl-, (4*R*)-4-methyl-, (6*R*)- and (6*S*)-6-methyl-(1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptanes **6**, **7**, **8a**, **8b**, **9a**, and **9b** (Chart III) were synthesized and condensed with the 7-chloronaphthyridines **20** to obtain the derivatives **38–50** (Table I).

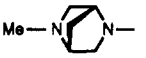
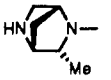
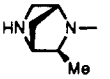
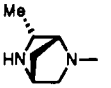
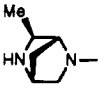
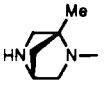
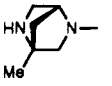
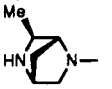
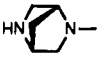
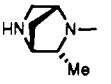
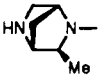
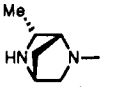
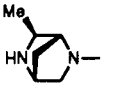
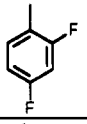
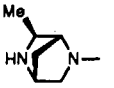
Chemistry

The main issue for the synthesis of the target naphthyridines **38–50** was to obtain mono-C-methylated 2,5-diazabicyclo[2.2.1]heptanes with the 1*R*,4*R* configuration. This was achieved by using, as starting material, the commercially available *trans*-4-hydroxy-L-proline already used for the synthesis of the bridged piperazine of **1a**.[5] The (1*R*,4*R*,6*R*)- and (1*R*,4*R*,6*S*)-6-methyl-5-benzyl-2-(4-tolylsulfonyl)-2,5-diazabicyclo[2.2.1]heptanes **17a** and **17b** (Scheme I) were prepared according to literature procedures.[14] From *trans*-4-hydroxy-L-proline the pyrrolidine

(8) Peflacine (pefloxacin); Investigative brochure, 1985, Laboratoire Roger Bellon, 159 avenue A. Peretti, 92200 Neuilly-sur-Seine, France.
(9) Healy, D. P.; Sahai, J. V.; Fuller, S. H.; Folk, R. E. Vancomycin-Induced Histamine Release and "Red Man Syndrome": Comparison of 1- and 2-Hour Infusions. *Antimicrob. Agents Chemother.* **1990**, *34*, 550–554.
(10) Bouzard, D.; Remuzon, P.; Di Cesare, P.; Essiz, M.; Jacquet, J. P.; Kiechel, J. R.; Kessler, R. E.; Fung-Tomc, J. Synthesis and Antibacterial Activity of New 1-t-Butyl Substituted Quinolones and Naphthyridines with Racemic or Chiral Methyl Piperazines. *Abstracts of Papers*, 29th Interscience Conference on Antimicrobial Agents and Chemotherapy, Houston, TX, Sept 17–20, 1989; Abstract 1247.
(11) Chu, D. T. W.; Nordeen, C. W.; Hardy, D. J.; Swanson, R. N.; Giardina, W. J.; Pernet, A. G.; Plattner, J. J. Synthesis, Antibacterial Activities and Pharmacological Properties of Enantiomers of Temafloxacin Hydrochloride. *J. Med. Chem.* **1991**, *34*, 168–174.
(12) Nakamura, S.; Minami, A.; Nakata, K.; Kurobe, N.; Kouno, K.; Sakaguchi, Y.; Kashimoto, S.; Yoshida, H.; Kojima, T.; Ohue, T.; Fujimoto, K.; Nakamura, M.; Hashimoto, M. and Shimizu, M. In Vitro and In Vivo Antibacterial Activities of AT-4140, a New Broad-Spectrum Quinolone. *Antimicrob. Agents Chemother.* **1989**, *33*, 1167–1173.
(13) McGuirk, P. R.; Jefson, M. R.; Mann, D. D.; Chang, E. P.; Cisek, E. P.; Cornell, C. P.; Gootz, T. D.; Haskell, S. L.; Hindahl, L. J.; LaFleur, L. J.; Rosenfeld, M. J.; Shryock, T. R.; Silvia, A. M. and Weber, F. H. Synthesis and Structure–Activity Relationships of 7-Diazabicycloalkylquinolones, Including Danofloxacin, a New Quinolone Antibacterial Agent for Veterinary Medicine. *J. Med. Chem.* **1992**, *35*, 611–620.

Table I. 7-Substituted Naphthyridines



no.	R_1	R_5	R_7	yield, %[a]	mp, °C	formula[b]	ref
CIP[c]							
1a		H					5
1b		H		90	200–1	$C_{19}H_{23}FN_4O_3$	
38		H		55	>260	$C_{19}H_{23}FN_4O_3$·HCl	
39		H		79	240 dec	$C_{19}H_{23}FN_4O_3$·HCl	
40		H		59	>260	$C_{19}H_{23}FN_4O_3$·HCl	
41		H		84	>260	$C_{19}H_{23}FN_4O_3$·HCl	
42		H		56	>260	$C_{19}H_{23}FN_4O_3$·HCl	
43		H		53	>260	$C_{19}H_{23}FN_4O_3$·HCl	
44		Me		53	>260	$C_{20}H_{25}FN_4O_3$·HCl	
45		Me					19
46		Me		76	>260	$C_{19}H_{21}FN_4O_3$·HCl	
47		Me		42	>260	$C_{19}H_{21}FN_4O_3$·HCl	
48		Me		34	>260	$C_{19}H_{21}FN_4O_3$·HCl	
49		Me		28	>260	$C_{19}H_{21}FN_4O_3$·HCl	
50		H		55	>260	$C_{21}H_{17}F_3N_4O_3$·HCl	

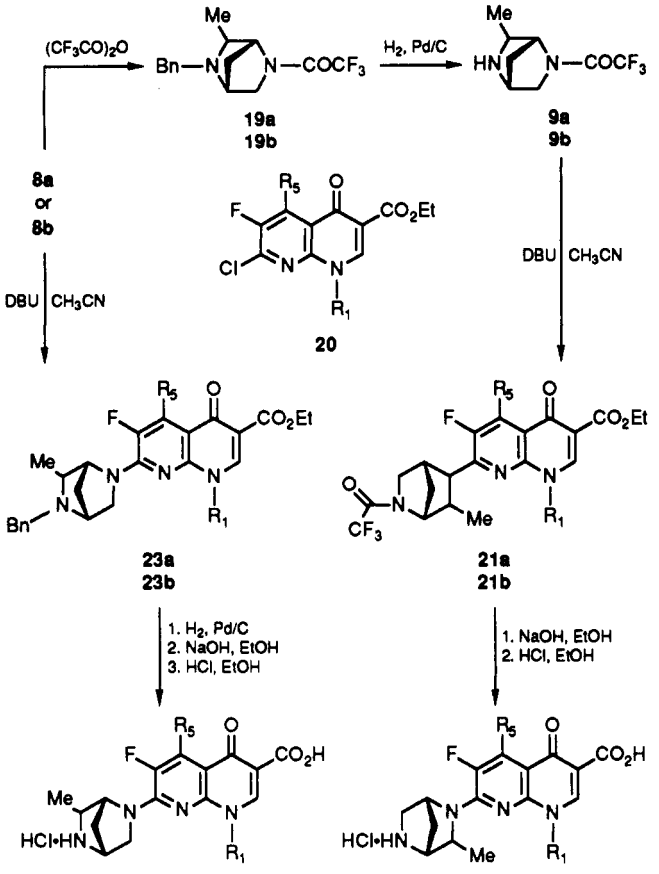
[a] Yields are those obtained from the final step (hydrolysis), including the salt formation. [b] The analyses are within ±0.4% of theoretical values. [c] Ciprofloxacin.

11 was obtained after inversion at C-2 and C-4.[5] Methanolysis of the 4-acetoxy group followed by silylation with chloro-*tert*-butyldimethylsilane (ClTBDMS) afforded **12**, which after alkaline hydrolysis of the ester function and acylation with the 3,5-dimethylpyrazole yielded the amide **13**. Reduction of **13** with lithium aluminum hydride, at low temperature,[15] gave the aldehyde **14**, which after Grignard reaction with methylmagnesium bromide led to the diastereoisomeric mixture of alcohols **15a** and **15b** (the two diastereoisomers could be separated by chromatography at this step).

(14) Remuzon, P.; Bouzard, D.; Dussy, C.; Jacquet, J. P.; Massoudi, M. Preparation of (6*R*) and (6*S*)-6-Methyl-2-(*p*-toluenesulfonyl)-5-phenylmethyl-2,5-diazabicyclo[2.2.1]Heptanes, Intermediates in the Synthesis of New Quinolones. *Heterocycles* **1992**, *34*, 241.

(15) German Patent DE 29 14 793, 1979; Natarajan, S. I.; Ondetti, M. A.; Squibb Company. *Chem. Abstr.* **1980**, *92*, 110842h.

Scheme II

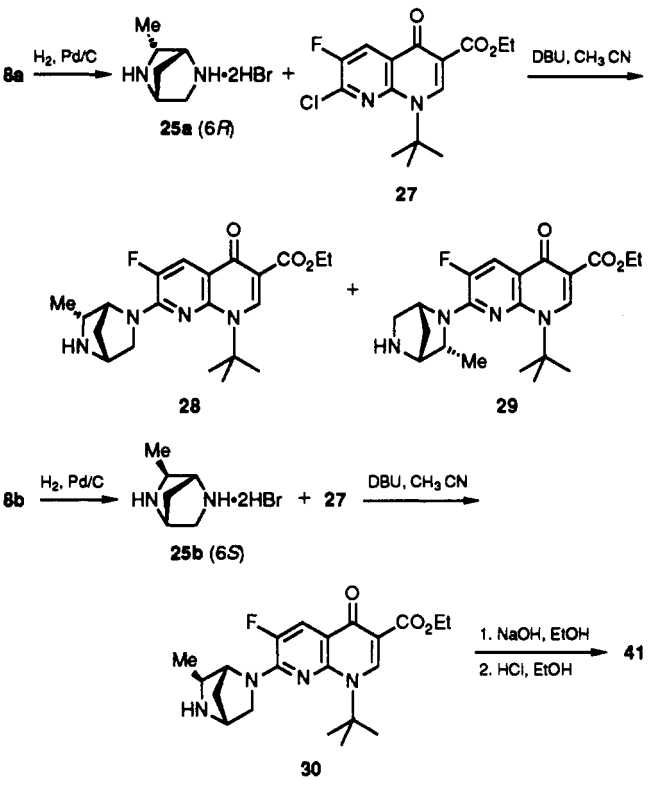


40: R_1 = t-Bu, R_5 = H (1*R*,4*R*,6*R*) **38:** R_1 = t-Bu, R_5 = H (1*R*,3*R*,4*R*)
41: R_1 = t-Bu, R_5 = H (1*R*,4*R*,6*S*) **39:** R_1 = t-Bu, R_5 = H (1*R*,3*S*,4*R*)
44: R_1 = t-Bu, R_5 = Me (1*R*,4*R*,6*S*) **46:** R_1 = C_3H_5, R_5 = Me (1*R*,3*R*,4*R*)
48: R_1 = C_3H_5, R_5 = Me (1*R*,4*R*,6*R*) **47:** R_1 = C_3H_5, R_5 = Me (1*R*,3*S*,4*S*)
49: R_1 = C_3H_5, R_5 = Me (1*R*,4*R*,6*S*)
50: R_1 = 2,4–DiFPh, R_5 = H (1*R*,4*R*,6*S*)

Desilylation of **15** with HCl in ethanol gave a mixture of diols **16a** and **16b**. The next step was tosylation of **16a** and **16b** in pyridine, which led to the corresponding tritosylated pyrrolidines. Cyclization with benzylamine in refluxing toluene yielded a ca. 50:50 mixture of the bridged piperazines **17a** and **17b**. Both diastereoisomers were obtained pure after separation on silica gel. NMR Noesy experiments showed a correlation between H-7 and the methyl group at C-6 position for **17b**, thus giving the 1*R*,4*R*,6*S* configuration for that diastereoisomer. No correlation was found between H-7 and the methyl group at C-6 for **17b** (1*R*,4*R*,6*R* configuration). After detosylation of **17a** or **17b** with 33% HBr in acetic acid, piperazine **8a** or **8b** were obtained, respectively. Direct condensation of **8a** and **8b** with 7-chloronaphthyridines **20** in the presence of a base led to the N-benzylated derivatives **23a** and **23b**, which were further submitted to hydrogenolysis and alkaline or acid hydrolysis to provide **24** or more precisely **40, 41, 44, 48, 49,** and **50** (Scheme II). Trifluoroacetylation of **8a** and **8b** produced the bicyclic bridged piperazines **19a** and **19b**, which after hydrogenolysis gave **9a** and **9b**. Further addition of **9a** and **9b** on **20** provided the regioisomers **21a** and **21b**, which were converted by alkaline hydrolysis to the target molecules **22** (**38, 39, 46,** and **47**, Scheme II).

Interesting was the different behavior of both unsubstituted diastereoisomers **25a** and **25b** obtained by hydrogenolysis of **8a** and **8b** when they were reacted with the naphthyridine ethyl ester **27** (Scheme III). With the first diastereoisomer **25a**, both 6-methyl and 3-methyl regioisomers **28** and **29** were formed in a 40:60 ratio. On the contrary, the piperazine **25b**, after condensation with **27**, afforded only one methyl regioisomer, the 6-methyl derivative **30**. Alkaline hydrolysis of **30** provided **41** (R_1 = *tert*-butyl, R_5 = Me, **24**).

Scheme III



For the bridged piperazines **6** and **7**,[16] after inversion at C-2 of the *trans*-4-hydroxy-L-proline, N-protection with a benzyloxycarbonyl group, followed by benzylation of the acid group, derivative **31** was obtained, using a similar methodology described by Barrett[17] for the 2*S*,4*R* isomer analogue (Scheme IV). The preparation of **32** was achieved after inversion at C-4 and cleavage by hydrogenolysis of the protective groups. The 4-acetoxyproline **32** was further transformed into the oxazolidinone **33** with pivaldehyde, according to the procedure described for its enantiomer by Seebach.[18] After deprotonation at C-2 using lithium diisopropylamide (LDA), the bicyclo compound **33** was alkylated with methyl iodide, with complete retention of configuration, to yield **34**. Acid hydrolysis of **34** in 6 N HCl gave **35a** (the specific rotation +68.1° found for **35a**, as a base was in good accordance with −71° described for its enantiomer).[18] Esterification of this C-2 methylated proline **35a** with HCl in EtOH gave **35b**. After N,O-ditosylation and reduction of the ester function with lithium borohydride, the alcohol **36** was obtained. Further tosylation of **36** and cyclization with benzylamine in refluxing xylene, as previously shown for **17a** and **17b**, pro-

(16) Remuzon, P.; Massoudi, M.; Bouzard, D.; Jacquet, J. P. Preparation of (1*R*)- and (4*R*)-1- and 4-Methyl-2-(*p*-toluenesulfonyl)-5-phenylmethyl-2,5-diazabicyclo[2.2.1]Heptanes, Intermediates in the Synthesis of New Quinolones. *Heterocycles*, in press.
(17) Barrett, A. G. M.; Pilipauskas, D. Electrochemical Oxidation of Proline Derivatives: Total Syntheses of Bulgecinine and Bulgecin C. *J. Org. Chem.* **1991**, *56*, 2787–2800.
(18) Seebach, D.; Weber, T. Alkylierung in der 2-Stellung von (2*S*,4*R*)-4-Hydroxyprolin unter Retention. *Helv. Chim. Acta* **1985**, *68*, 155–161.

Table II. In Vitro Antibacterial Activity of 7-Substituted Naphthyridines[a] (MIC, μg/mL)

no.	S.pn.	E.fa.	S.au.	E.co.	K.pn.	E.cl.	P.mi.	M.mo.	S.ma.	P.ae.	B.fr.
CIP	0.25	0.5	0.06	0.008	0.06	0.03	0.008	0.008	0.03	0.25	1
1a	0.13	0.13	0.03	0.008	0.016	0.016	0.06	0.03	0.06	0.25	0.5
1b	ND[b]	ND	0.13	0.25	0.13	0.13	1	0.5	0.25	2	ND
38	0.13	0.5	0.03	0.016	0.25	0.06	0.5	0.5	0.25	1	1
39	1	1	0.06	0.03	0.5	0.13	1	1	0.25	2	8
40	0.5	1	0.06	0.03	0.5	0.06	0.5	1	0.25	2	4
41	0.25	0.25	0.03	0.008	0.03	0.03	0.13	0.13	0.13	0.5	2
42	2	16	1	0.25	0.5	0.25	2	2	1	4	64
43	0.5	1	0.03	0.03	0.03	0.016	0.25	0.25	0.13	1	16
44	0.5	0.5	0.016	0.03	0.13	0.03	0.5	0.5	0.5	2	16
45	0.06	0.06	0.016	0.002	0.008	0.002	0.03	0.03	0.06	0.06	1
46	0.25	0.25	0.03	0.016	0.06	0.06	0.5	0.25	0.5	2	8
47	0.13	0.25	0.016	0.016	0.016	0.016	0.13	0.13	0.13	0.25	4
48	0.13	0.25	0.016	0.016	0.06	0.06	0.25	0.25	0.5	1	8
49	0.06	0.13	0.016	0.004	0.016	0.016	0.06	0.06	0.13	0.13	2
50	1	1	0.06	0.03	0.13	0.13	0.5	0.5	0.25	1	4

[a] Organisms selected for the table are as follows: S.pn., *Streptococcus pneumoniae A9585*; E.fa., *Enterococcus faecalis A9809*; S.au., *Staphylococcus aureus A9537*; E.co., *Escherichia coli A15119*; K.pn., *Klebsellia pneumoniae A9664*; E.cl., *Enterobacter cloacae A9656*; P.mi., *Proteus mirabilis A9900*; M.mo., *Morganella morganii A15153*; S.ma., *Serratia marcescens A20019*; P.ae., *Pseudomonas aeruginosa A9843*; B.fr., *Bacteroides fragilis A22862*. [b] ND: not determined.

vided the bridged piperazine **37**. Detosylation of **37** with HBr in acetic acid gave **6**. Addition of the resulting dihydrobromide salt to the naphthyridine **27** led to a N-benzylated derivative. This latter was hydrogenated over 10% Pd/C and hydrolyzed with aqueous NaOH in EtOH to obtain **43**. Trifluoroacetylation of **6**, followed by hydrogenolysis, led to **7**, which, after condensation with **27** and hydrolysis of the resulting ester, finally led to **42**.

Biological Results and Discussion

Table II summarizes the in vitro antibacterial data of naphthyridines **1a**, **1b**, and **38–50** against three Gram-positive bacteria (*Streptococcus pneumoniae A 9585*, *Enterococcus faecalis A 9809*, and *Staphylococcus A 9537*) and seven Gram-negative bacteria (*Escherichia coli A 15119*, *Klebsellia pneumoniae A 9664*, *Enterobacter cloacae A 9656*, *Proteus mirabilis A 9900*, *Morganella morganii A 15153*, *Serratia marcescens A 20019*, and *Pseudomonas aeruginosa A 9843*) and against *Bacteroides fragilis A 22862*. The data for ciprofloxacin (CIP) are included for comparison. With a N-1-*tert*-butyl appendage, the best in vitro antibacterial activity was demonstrated by the nonmethylated bridged piperazine **1a**. Methylation of the free nitrogen of the bridged piperazine seriously reduced the in vitro activity (**1b** vs **1a**).

The (3*R*)-3-methyl-bridged piperazine derivative **38** was found to be twice as active as its diastereoisomer 3*S* analogue **39**, while the (6*S*)-6-methylpiperazine naphthyridine **41** turned out to be 2–8 times better than its 6*R* analogue against either Gram-positive or Gram-negative strains. Among the last four compounds, the best one, **41**, was either equal to or twice less active than **1a** (**1a** ≥ **41** ≥ **38** > **40** = **39**). With the 1-cyclopropyl-5-methylnaphthyridine nucleus (**20**, R_1 = cyclopropyl, R_5 = Me), the four (3*R*)-, (3*S*)-, (6*R*)-, and (6*S*)-3- and 6-methyl-bridged piperazines were added at C-7 (**46–49**) and their antimicrobial activity compared to that of **45**. The nonmethylated bridged piperazine **45** was still found twice better than **49**, the best (6*S*)-6-methyl analogue. The order of in vitro potency was **45** > **49** ≥ **47** > **46** = **48**. The best (6*S*)-6-methyl-bridged piperazine was also condensed with the 1-*tert*-butyl-5-methylnaphthyridine **20** (R_1 = *tert*-butyl, R_5 = Me, **44**), and with the 1-(2,4-difluorophenyl)-substituted naphthyridine **20** (R_1 = 2,4-difluorophenyl, R_5 = H, **50**). The order of antimicrobial potency was **49** > **44** = **50**. As previously shown,[19] methylation at C-5 of the *N*-1-*tert*-butyl-

Scheme IV

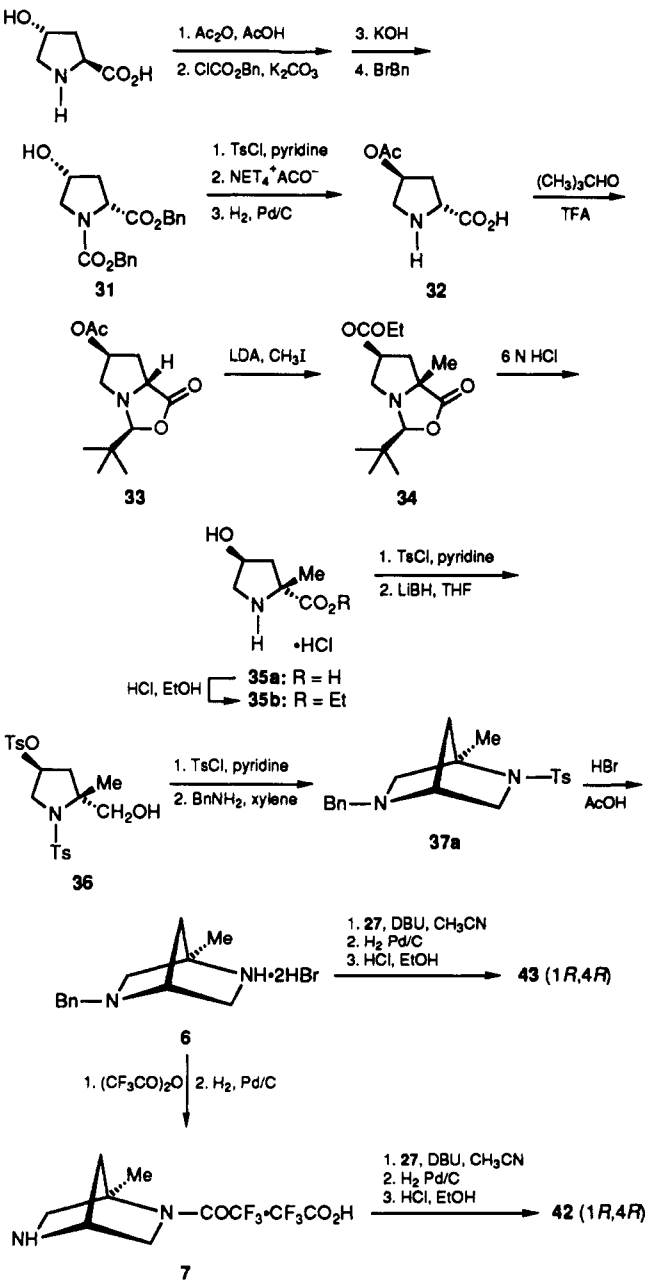


Table III. Efficacy on Systemic Infections and Acute Toxicity of Selected Compounds after Administration to Mice

		PD_{50}[a], mg/kg				LD_{50},[b] mg/kg	
no.		*S. aureus* A 15090	*P. aeruginosa* A 9843	*E. coli* A 15119	*S. pneumoniae* A 9585	iv	po
CIP	im	3.9 (2.3–5.9)	1.3 (0.8–2.2)	0.05 (0.02–0.1)	28.7 (13.5–51)	273	5000
	po	12.5 (8.4–19.2)	2.6 (1.6–3.1)	1.4 (0.8–2.7)	>50		
1a	im	0.9 (0.5–1.2)	1.4 (0.8–2.0)	0.5 (0.21–0.82)	18.9 (13–28.2)	303	5000
	po	1.6 (1.1–2.3)	4.7 (2.5–9.9)	1.8 (0.9–3.1)	28.0 (12.5–43.5)		
1b	im		4.7 (2.8–9.2)	1.0 (0.6–1.6)		188	1000
	po		10.2 (6.4–17)	2.4 (1.6–3.8)			
38	im	7.5 (3.6–11.1)	12.5 (8–17.5)	2.4 (1.6–3.5)			
	po	13.1 (8.7–18)	22.0 (11.5–30.6)	12.5 (8.2–17)			
39	im		12.5 (8.3–18.5)				
	po	5.4 (3.5–7.6)	22.0 (14.1–30.7)				
40	im		12.5 (7.8–18.3)				
	po	16.5 (12.2–21.2)	9.5 (5.2–14.5)				
41	im	0.9 (0.6–1.4)	1.6 (1.2–2.4)		14.4 (10.6–21.5)	263	>2500
	po	1.6 (1.4–2.3)	2.7 (1.8–3.5)		25.0 (18.8–35.8)		
45	im	2.4 (1.8–3.8)		0.2 (0.06–0.32)	>25	125	1750
	po	5.4 (3.8–8.5)	2.7 (2.1–3.8)	0.9 (0.7–1.3)	43.5 (38.9–55.4)		
49	im	0.34 (0.28–0.53)	0.78 (0.5–1.0)	0.1 (0.03–0.12)	18.9 (12.8–30.2)		
	po	1.8 (1.1–2.8)	0.34 (0.22–0.49)		18.9 (11.4–29.8)		
50	im	1.0 (0.6–1.5)	2.4 (1.4–4.1)		>50		
	po	1.4 (0.8–2.7)	3.1 (1.5–6.0)		>50		

[a] Dose to protect 50% of mice from lethal infection orally (po) and intramuscularly (im) (95% confidence limits). [b] See the Experimental Section.

naphthyridine led to a decrease in the in vitro activity (**41** > **44**).

An increase in in vitro activity can be seen in going from the (1*R*)-1-methyl derivative **42** to the (4*R*)-4-methyl analogue **43**. Nevertheless methylation at C-4 of the bridged piperazine was not found to be better than methylation at C-6 (**41** ≥ **43**).

The in vivo potency of **1a**, **1b**, **38**, **39**, **40**, **41**, **45**, and **49** as well as ciprofloxacin (CIP) is shown in Table III. Against *Staphylococcus aureus* infections, the best in vivo efficacy was shown with **41**, **49**, and **50** (all with the (6*S*)-6-methyl-bridged piperazine at C-7), which were comparable to **1a** (either im or po). With the other Gram-positive strain (*Streptococcus pneumoniae*), compound **41** or **49** was as active as **1a**. The in vivo efficacy against *Escherichia coli* of **49** and **45** was comparable to that of ciprofloxacin either im or po. Derivatives **1a**, **41**, **45**, and **50** showed excellent in vivo activity against *Pseudomonas aeruginosa*, similar to that of ciprofloxacin. The *N*-methyl analogue **1b** of **1a** did not show improved in vivo activity when compared to **1a**. Derivative **49**, which bears a (6*S*)-6-methyl-bridged piperazine at C-7, displayed the best in vivo efficacy of all compounds studied against either Gram-negative or Gram-positive infections. The derivative **41**, the (6*S*)-6-methyl analogue of **1a**, was as active as **1a** in vivo.

Acute toxicity studies in mice (Table III) showed that **41** was not more toxic than **1a**. The derivatives **1b** and **45**, with lower LD_{50}, appeared to be more toxic (iv and po).

Physicochemical Properties. In Table IV the water solubility (pH 7.2 buffer) and log *D* of selected compounds are summarized. While the (6*S*)-6-methyl-bridged piperazine at C-7 remained constant, addition of a methyl group at C-5 of the naphthyridine resulted in an increase of log *D* by 1.2 log unit and the solubility showed a 10-fold increase (**44** vs **41**). Addition of a methyl group at C-3 or C-6 of the bridged piperazine led to a large increase in solubility for **38** (3*R*), **39** (3*S*), and **40** (6*R*), but to a decrease for **41** (6*S*). It also increased the lipophilicity as reflected by the increase of log *D*. Addition of a methyl group in position 1 or 4 of the bridged piperazine resulted in a decrease of the solubility especially for **42**. Derivative **43** was found more lipophilic than **42**, itself as lipophilic as **1a**.

Table IV. Solubility and log *D* of Selected Compounds

no.	H_2O[a] solubility, mg/mL	log *D*[b]	no.	H_2O[a] solubility, mg/mL	log *D*[b]
CIP	0.07	−0.7	**43**	0.067	0.02
1a	0.08	−0.41	**44**	0.25	1.3
1b	0.31	0.21	**45**	0.02	0.48
38	11.8	0.17	**46**	0.22	1
39	1.33	−0.02	**47**	0.07	0.73
40	6.34	−0.12	**48**	0.15	0.71
41	0.025	0.1	**49**	0.006	0.71
42	0.006	−0.37	**50**	0.015	−0.14

[a] Solubility determined at 22 °C in a pH 7.2 buffer. See the Experimental Section. [b] Distribution coefficient. See the Experimental Section.

In the *N*-1-cyclopropyl, 5-methyl naphthyridine series, the lipophilicity seemed not to be affected by the place of methylation of the bridged piperazine except for **46**, with a 0.3 log *D* unit increase when compared to **47**, **48**, or **49**. The *N*-*tert*-butyl appendage of naphthyridine **44** produced an increase in lipophilicity, compared to the *N*-1-cyclopropyl analogue **49**. The difference of solubilities is less marked than in the *N*-1-*tert*-butylnaphthyridine series. However, the (6*S*)-6-methyl-bridged piperazine always showed the lowest water solubility (**49** vs **48**, **47**, and **46**).

The best PD_{50}s for *Escherichia coli* infection in mice was found with **49**, the least water-soluble derivative, and the lowest efficacy was found with **38**, the most water-soluble compound. The order of solubility was **38** > **1b** > **1a** > **45** > **49**, while the order of in vivo efficacy against *E. coli* was **49** > **45** > **1a** > **1b** > **38**. Optimal in vitro anti-streptococcal activity was observed with values of log *D* ranging from 0.2 to 0.8. For MIC ≤ 0.13 μg/mL, obtained with **38**, **45**, **47**, **48**, and **49**, log *D* was 0.17 for **38** and 0.73 for **47**. Above 0.8 and particularly below 0.2 log *D* values, a decrease of in vitro anti-streptococcal activity was observed.

(19) Bouzard, D.; Di Cesare, P.; Essiz, M.; Jacquet, J. P.; Ledoussal, B.; Remuzon, P.; Kessler, R. E.; Fung-Tomc, J. Fluoronaphthyridines as Antibacterial Agents. 4. Synthesis and Structure-Activity Relationships of 5-Substituted-6-Fluoro-7-cycloalkylamino-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids. *J. Med. Chem.* **1992**, *35*, 518–525.

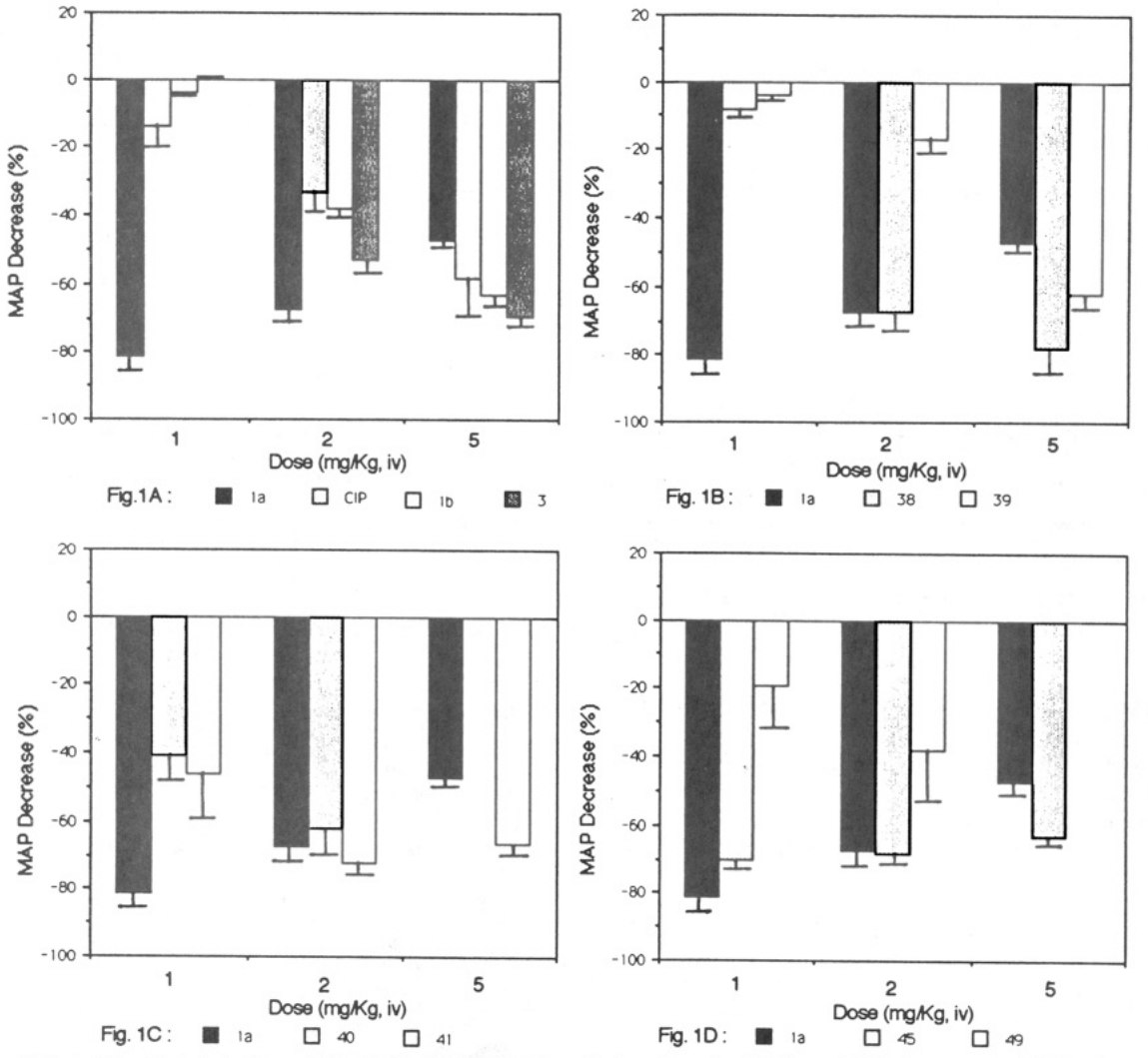


Figure 1. Effect of iv administration of **1a**, **1b**, **3**, **38** **39**, **40**, **41**, and ciprofloxacin (CIP) on MAP (mean arterial blood pressure) in dogs with cumulative doses of 1, 2, and 5 mg/kg. Vertical bars represent SEM (N = 3).

Pharmacokinetics in Mice. After intravenous or oral administration of derivatives **1b**, **38**, **39**, **40**, **41**, **45**, and **49**, the C_{max}, AUC, and UR were measured (Table V; ciprofloxacin and **1a** were included for comparison). The (6*S*)-6-methyl analogue (**41**) of **1a**, showed a similar peak concentration (po or iv) in blood to that of **1a** and **45**, but its blood half-life was longer than that of **1a** and **45** (**49** displayed the longest $t_{1/2}$ of all compounds tested). The area under the curve (blood) of **41** was 50% larger orally and 30% larger intravenously than that of **1a**. The best urinary recovery was reached with **45**, followed by **1a** and ciprofloxacin. The 6-methyl-bridged piperazines **39**, **40**, **41**, and **49** showed similar average urinary recoveries.

Cardiovascular Studies in Anesthetized Dogs. Figure 1 illustrates the blood pressure responses to iv cumulative doses of the tested quinolones **1a**, **1b**, **38**, **39**, **40**, **41**, **45**, and **49** in dogs. Ciprofloxacin (CIP) and temafloxacin (**3**) were included for comparison. Figure 1A shows that ciprofloxacin and temafloxacin (**3**) induced a dose-dependent decrease in blood pressure (MAP) with a marked effect at the highest dose (−51% and −69% for CIP and **3**, respectively, at 5 mg/kg). The nonmethylated bridged piperazine **1a** induced an immediate, severe, and sustained hypotension whatever the doses tested. However, the hypotensive responses to the highest doses fell in intensity and duration, suggesting a tachyphylaxia phenomena. Compound **1b**, the *N*-methyl-bridged piperazine derivative analogue of **1a**, exhibited a similar cardiovascular behavior to that of ciprofloxacin. Temafloxacin (**3**), which induced no hypotension at 1 mg/kg,

Table V. Pharmacokinetic Properties of Selected Compounds after Oral and Intravenous Administration to Mice

no.	route of administration[a]	C_{max},[b] μg/mL	$t_{1/2}$,[b] min	AUC,[b] μg/h·mL	% UR[b]
CIP	po	6	56	8	30
	iv	22	72	19	25
1a	po	10	96	25	34
	iv	20	73	34	30
1b	po	13	80	18	3
	iv	14	96	14	15
38	po	5	48	5	1
	iv	13	44	10	2
39	po	9	65	17	16
	iv	22	73	22	16
40	po	11	44	8	17
	iv	23	45	18	18
41	po	9	158	41	18
	iv	19	117	45	21
45	po	9	77	26	34
	iv	19	90	40	41
49	po	6	252	41	18
	iv	12	288	59	16

[a] Compounds were administered at 40 mg/kg orally (po) or at 20 mg/kg intravenously (iv). [b] C_{max}, peak concentration in blood; $t_{1/2}$, blood half-life; AUC, area under the curve (blood) 0 h to ∞; UR, urinary recovery in 24 h (percent dose), all C_{max}, AUC, and UR values are accurate to ±50% and have been obtained from duplicate or triplicate experiments.

showed nevertheless strong hypotension at 2 and 5 mg/kg. In Figure 1B, the (3*R*)-3-methyl-bridged piperazine derivative **38** induced no significant effect at the lower dose (1 mg/kg); in contrast, at doses of 2 and 5 mg/kg, this compound caused a significant and sustained fall in blood pressure. The (3*S*)-3-methyl analogue **39** was more or less like ciprofloxacin with a dose-dependent decrease in blood pressure. Figure 1C shows that the (6*R*)- and (6*S*)-6-methyl-bridged piperazine derivatives **40** and **41** induced similar cardiovascular responses, however less marked than that observed with **1a** at 1 mg/kg. Figure 1D shows that the hypotension induced by **1a** or **45** after intravenous administration are almost the same, indicating that the 2,5-diazabicyclo[2.2.1]heptane appendage needed C- or N-methylation to obtain a decrease of the cardiovascular side effect. Compound **49**, the (6*S*)-6-methyl analogue of **45**, produced a dramatically less marked cardiovascular effect than that of **1a** or **45** at least at lower doses.

Conclusion. As a summary of results, we demonstrated that by adding a methyl group on the (1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptane appendage at C-7 of naphthyridones, it was possible to maintain good in vitro and in vivo antibacterial activity especially for derivatives **41** and **49** when compared to the lead **1a**. The derivative **49** was found to reduce the pseudoallergic type reaction, associated with the decrease of blood pressure (MAP) in dogs observed with nonmethylated analogues. The naphthyridine **49**, substituted at C-7 by a (1*R*,4*R*,6*S*)-6-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl moiety, was chosen as a promising candidate for future preclinical development. Other *C*-methyl-bridged piperazines are currently under evaluation.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were taken with a Büchi 510 capillary apparatus and are uncorrected. Elemental analysis 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. ^{1}H NMR spectra were determined on a Bruker AC 200 apparatus. Chemical shifts are expressed in ppm (δ) relative to internal tetramethylsilane. Flash column chromatography was performed with Merck silica gel 60, 70–230 mesh ASTM. Specific rotations at 25 °C and wavelength of sodium D line were measured in a 1-dm cell Perkin-Elmer 241 polarimeter at a concentration of 0.5% in methanol unless otherwise noted.

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

In Vivo Studies (Mouse Protection Test). A solution of each test compound in sterile water was administered orally or intravenously to OF1-strain female Swiss mice (18–25 g body weight, five per group). Seven days later, LD_{50} values were determined using the Karber and Behrens[20] method.

Solubility Studies. A known excess of weight of the compound was shaken overnight with a known volume of pH 7.2 buffer at 22 °C for injection. The contents were filtered, and the clear filtrate was analyzed, after appropriate dilution by HPLC (UV absorbance detection at the maximum of absorption of each compound).

Distribution Coefficient Studies (log *D*). A 10-mL solution of 10 μg/mL of the tested compound in pH 7.2 buffer presaturated with 1-octanol was injected in 10 mL of 1-octanol presaturated with pH 7.2 buffer in a shaking cell at 25 °C. The mixture was stirred 12 h at 25 °C. The mixture was centrifuged, and the two phases were separated. The concentration of each phase was determined by HPLC (UV absorbance detection at the maximum of absorption of each compound). The concentration was calibrated with a standard curve of known concentration of the tested compound. The logarithm of the coefficient of distribution (log *D*) is defined as the ratio of the concentration of the tested compound in the 1-octanol phase to the concentration of all species in the aqueous phase (buffer pH 7.2 at 25 °C).

Pharmacokinetics in Mice. Levels of selected compounds in blood and urine samples from mice were determined as previously described.[6] Each compound was administered orally at a dose of 40 mg/kg by gavage and intravenously at a dose of 20 mg/kg to different groups of five mice. 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 microbioassay method with *Salmonella enteritidis A 9531* as the assay organism.

Cardiovascular Experiments. For each test compound, three fasting beagle dogs of either sex, weighing 9–13 kg, were anesthetized with pentobarbital sodium salt (30 mg/kg iv), intubated with an endotracheal cannula, and ventilated with a respiratory pump. A saphenous vein was cannulated to maintain continuous anesthesia by infusion of pentobarbital sodium salt (6 mg kg^{-1} h^{-1}) and to administer the test compounds. Systemic arterial blood pressure was monitored from the abdominal aorta using an angiographic catheter introduced via a femoral artery and a pressure transducer (Stratham P 23 I.D.) was recorded on an electrostatic Gould recorder and processed on line by a computer-based system (Hemos software). After each rapid iv administration of cumulative doses (1, 2, or 5 mg/kg) of the test compound, dissolved in sterile water for injection, maximal effect on mean arterial pressure (MAP) was measured.

Chemistry. (4*S*)-1-(4-Tolylsulfonyl)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-D-proline Ethyl Ester (12). To a solution of 230 g (0.734 mol) of (4*R*)-4-hydroxy-1-(4-tolylsulfonyl)-D-proline ethyl ester[5] and 116 g (1.7 mol) of imidazole in 440 mL of dry dimethylformamide (DMF) was added 123 g (0.876 mol) of dimethyl-*tert*-butylchlorosilane (CltBDMS). The solution was kept at 40 °C for 5 h. The solvent was evaporated under vacuo. The residue was partitioned between AcOEt and H_2O. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated to give 306.5 g of **12**: yield 98%; mp 90 °C; $[\alpha]_D$ +84.2°; ^{1}H NMR (DMSO-d_6) δ 0.01–0.02 (2 s, 6 H, 2 Me, tBDMS), 0.64 (s, 9 H, *t*-Bu, tBDMS), 1.21 (t, J = 7.0 Hz, 3 H, Me ester), 1.97 (m, 2 H, H-3 and H-3′), 2.37 (s, 3 H, Me tosyl), 3.07 (d, J = 11 Hz, 1 H, H-5), 3.57 (dd, J = 11 Hz, J = 4.0 Hz, H-5′), 4.05 (q, J = 4.0 Hz, 1 H, H-2), 4.14 (q, J = 7.0 Hz, 2 H, CH_2 ester), 4.36 (br s, 1 H, H-4), 7.40 and 7.66 (2 d, J = 8.2 Hz, 4 H, Ar tosyl).

(2*R*,4*S*)-1-(4-Tolylsulfonyl)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-[(3,5-dimethyl-1*H*-pyrazol-1-yl)carbonyl]pyrrolidine (13). To an ice-cooled solution of 305 g (0.713 mol) of **12** in 3 L of EtOH was carefully added 360 mL of 2 N aqueous KOH. The solution was stirred for 2 h at room temperature, cooled in an ice bath, and acidified with 375 mL of 2 N aqueous HCl. The solvent was evaporated and the residue was partitioned between $CHCl_3$ and H_2O. The organic layer was washed (H_2O), dried ($MgSO_4$), and evaporated to provide 274.7 g of the corresponding acid (yield 96%, mp 172 °C), which was used without further purification. To a solution of 273.8 g (0.685 mol) of the above acid and 65.9 g (0.685 mol) of 3,5-dimethylpyrazole in 3.5 L of $CHCl_3$, cooled at 10 °C, was added 157.1 g (0.664 mol) of dicyclohexylcarbodiimide (DCCI). The mixture was allowed to reach room temperature overnight. The precipitated urea was filtered and washed with $CHCl_3$. The filtrate was evaporated to dryness under vacuo. The residue was taken up with AcOEt (insoluble material was filtered off) and washed successively with 10% aqueous $NaHCO_3$, 0.5 N aqueous HCl, and brine. The organic layer was chromatographed over silica gel (CH_2Cl_2 as eluent) to give 322.3 g of **13**: yield 98%; mp 103 °C; $[\alpha]_D$ +154°. Anal. ($C_{23}H_{25}N_3O_4SSi$) C, H, N. IR 2959, 2925, 2651,

(20) Behrens, B.; Karber, G. Wie sind Reihenversuche für biologische Auswertungen am zweckmässigsten anzuordnen? *Arch. Exp. Pathol. Pharmakol.* **1935**, *177*, 379–388.

1738 cm^{-1}. ^1H NMR (DMSO-d_6) δ 0.01 and 0.02 (2 d, 6 H, 2 Me, tBDMS), 0.67 (s, 9 H, *tert*-butyl, tBDMS), 2.07 (m, 2 H, H-3, pyrrolidine), 2.23 (s, 6 H, 2 Me, pyrazole ring), 2.39 (s, 3 H, Me tosyl), 3.17 (d, J = 11 Hz, H-5, pyrrolidine), 3.63 (dd, J = 11 Hz, J = 4 Hz, H-5', pyrrolidine), 4.42 (br s, 1 H, H-4), 5.57 (m, 1 H, H-2, pyrrolidine), 6.26 (s, 1 H, H-4 pyrazole ring), 7.40 and 7.69 (2 d, J = 8 Hz, 4 H, Ar, tosyl).

(2*R*,4*S*)-1-(4-Tolylsulfonyl)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-formylpyrrolidine (14). A solution of 260 mL (0.26 mol) of 1 M lithium aluminum hydride ($LiAlH_4$) in tetrahydrofuran (THF) was added to 2.2 L of dry THF cooled to −40 °C.[15] To this solution was added dropwise over 1 h a solution of 85 g (0.178 mol) of **13** in 2.2 L of dry THF. The reaction was kept 0.5 h at −40 °C. Then 130 mL of 2 N aqueous HCl was added between −40 and −30 °C. After 15 min, the insoluble material was filtered off. The filtrate was evaporated under reduced pressure. The residue was taken up with $CHCl_3$, washed with H_2O, dried ($MgSO_4$), and concentrated under vacuo to give the product which was purified over silica gel (CH_2Cl_2) to afford 48.5 g of **14**: yield 71%; $[\alpha]_D$ +41°; IR 2953, 2928, 2855, 1735 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.01 and 0.02 (2 d, 6 H, 2 Me, tBDMS), 0.60 (s, 9 H, *tert*-butyl, *t*BDMS), 1.75 (m, 2 H, H-3, pyrrolidine), 2.09 (1 s, 1 H, H-3', pyrrol), 2.38 (s, 3 H, Me tosyl), 3.06 (d, J = 11 Hz, H-5 pyrrol), 3.64 (dd, J = 11 Hz, J = 4 Hz, H-5', pyrrol), 3.79 (m, 1 H, H-2, pyrrol), 4.36 (br s, 1 H, H-4, pyrrol), 7.42 and 7.66 (2 d, J = 8 Hz, 4 H, Ar, tosyl), 9.52 (d, J = 4 Hz, 1 H, CHO).

(2*R*,4*S*)-1-(4-Tolylsulfonyl)-2-(1-hydroxyethyl)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]pyrrolidine (15a and 15b). A solution of 44 mL (0.132 mol) of 3 M MeMgBr in Et_2O was added to 44 mL of dry Et_2O. To this solution, cooled at −10 °C, was added dropwise a solution of 48.5 g (0.126 mol) of **14** in 400 mL of dry Et_2O. The reaction mixture was stirred 15 min at 0 °C, and then 40 mL of 3 M aqueous H_2SO_4 was carefully added, followed by 50 mL of H_2O. The organic layer was decanted, washed with H_2O and brine, and dried ($MgSO_4$) to give 46.2 g of **15**; yield 91%; mp 98 °C.

Alternatively, both diastereoisomeric alcohols could be separated at this step by chromatography (CH_2Cl_2/AcOEt 95:5). From 10 g of the mixture of **15**, it was possible to obtain 5.6 g of the less polar diastereoisomer **15a** (2*R*,4*S*,1'*R*) (mp 102 °C; $[\alpha]_D$ +30°) and 4.25 g of the most polar diastereoisomer **15b** (2*R*,4*S*,1'*S*) (mp 62 °C; $[\alpha]_D$ +39°).

15a: ^1H NMR ($CDCl_3$) δ 0.01–0.05 (2 s, 6 H, 2 Me, tBDMS), 0.74 (s, 9 H, *t*-Bu, tBDMS), 1.16 (d, J = 6.4 Hz, 3 H, β-Me), 1.73 (m, 2 H, H-3 and H-3'), 2.43 (s, 3 H, Me, tosyl), 3.32 (dd, J = 2.0 Hz, 1 H, H-5), 3.60 (m, 2 H, H-2 and H-5'), 3.92 (m, J = 6.4 Hz, 1 H, Hα-1), 4.26 (m, 1 H, H-4), 7.30 and 7.76 (2 d, J = 8.2 Hz, 4 H, Ar, tosyl). **15b**: ^1H NMR ($CDCl_3$) δ 0.01–0.04 (2 s, 6 H, 2 Me, tBDMS), 0.72 (s, 9 H, *t*-Bu, tBDMS), 1.14 (d, J = 6.4 Hz, 3 H, β-Me), 1.67 and 2.0 (2 m, 2 H, H-3 and H-3'), 2.42 (s, 3 H, Me, tosyl), 3.29 (dd, J = 2.0 Hz, 1 H, H-5), 3.59 (m, 2 H, H-2 and H-5'), 4.27 (m, 1 H, H-4), 4.36 (m, 1 H, Hα-1), 7.30 and 7.73 (2 d, J = 8.2 Hz, 4 H, Ar, tosyl).

(2*R*,4*S*)-1-(4-Tolylsulfonyl)-2-(1-hydroxyethyl)-4-hydroxypyrrolidine (16a and 16b). To a solution of 10 g (25 mmol) of **15** in 200 mL of EtOH was added dropwise 7 mL (84.5 mmol) of concentrated HCl. The mixture was stirred for 5 h at room temperature, evaporated under reduced pressure, and crystallized from H_2O to give 6.2 g of a mixture of the corresponding diols **16a** and **16b**: yield 87%; mp 135 °C. Alternatively, desilylation of **15a** in the same conditions provided the pure diol **16a** (yield 90.5%; mp 142 °C; $[\alpha]_D$ +56.7°) and **15b** gave the diol **16b** (yield 83%; mp 175 °C; $[\alpha]_D$ +68°). **16a**: ^1H NMR ($CDCl_3$) δ 1.16 (d, J = 6.0 Hz, 3 H, β-Me), 1.80 (m, 2 H, H-3 and H-3'), 2.43 (s, 3 H, Me, tosyl), 3.49 (dd, J = 2.4 Hz, 2 H, H-5 and H-5'), 3.76 (m, 2 H, H-2 and Hα-1), 4.29 (m, 1 H, H-4), 7.33 and 7.79 (2 d, J = 8.2 Hz, 4 H, Ar, tosyl).

16b: ^1H NMR ($CDCl_3$) δ 1.13 (d, J = 6.6 Hz, 3 H, β-Me), 1.75 and 2.08 (2 m, 2 H, H-3 and H-3'), 2.43 (s, 3 H, Me, tosyl), 3.48 (m, 2 H, H-5 and H-5'), 3.71 (m, 1 H, H-2), 4.34 (m, 2 H, Hα-1 and H-4), 7.33 and 7.76 (2 d, J = 8.2 Hz, 4 H, Ar, tosyl).

(1*R*,4*R*,6*R*)- and (1*R*,4*R*,6*S*)-6-Methyl-5-(phenylmethyl)-2-(4-tolylsulfonyl)-2,5-diazabicyclo[2.2.1]heptanes (17a and 17b). To a solution of 80.1 g (0.281 mol) of the above diols **16a** and **16b** in 400 mL of dry pyridine at 0 °C was added 161 g (0.843 mol) of 4-toluenesulfonyl chloride. The reaction mixture was stirred 1 h at 5 °C and then overnight at room temperature and poured into 3 L of ice-cooled H_2O. The reaction mixture was extracted with AcOEt, washed successively with 1 N aqueous HCl and brine, and dried ($MgSO_4$) to yield 161 g of crude material, which was used without further purification (yield 96.4%).

A mixture of 160 g (0.27 mol) of the above resulting tritosylated derivatives and 95.5 g (0.89 mol) of benzylamine in 750 mL of toluene was heated under reflux for 88 h. After cooling of the reaction mixture, insoluble material was filtered and the filtrate was evaporated under reduced pressure to give 118 g of crude material. This was chromatographed over silica gel (CH_2Cl_2/AcOEt 97:3) to obtain 29.2 g (yield 30%) of diastereoisomer **17a** (1*R*,4*R*,6*R*) and 29.7 g (yield 31%) of **17b** (1*R*,4*R*,6*S*). Isomer **17a**: mp 127 °C; $[\alpha]_D$ −58.5°; IR 2954, 2880, 1594, 1452, 1340, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (d, J = 10 Hz, 1 H, H-7), 1.12 (d, J = 6 Hz, 3 H, Me-6), 1.68 (d, J = 10 Hz, 1 H, H-7'), 2.42 (s, 3 H, Me, tosyl), 2.75 (q, J = 6 Hz, 1 H, H-6), 3.02 (dd, J = 8 Hz, 1 H, H-3), 3.18 (br s, 1 H, H-4), 3.20 (dd, J = 8 Hz, 1 H, H-3'), 3.58 (q, J = 4 Hz, 2 H, CH_2Ph), 4.07 (br s, 1 H, H-1), 7.26 (m, 5 H, CH_2Ph), 7.29 (d, J = 8 Hz, 2 H, Ar, tosyl), 7.70 (d, J = 8 Hz, 2 H, Ar, tosyl). Anal. ($C_{20}H_{24}N_2O_2S$) C, H, N. Isomer **17b**: mp 133 °C; $[\alpha]_D$ −18°. IR 3436, 2974, 2925, 1596, 1452, 1343, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (d, J = 6 Hz, 3 H, Me-6), 0.93 (d, J = 10 Hz, 1 H, H-7), 1.66 (d, J = 10 Hz, H-7'), 2.44 (s, 3 H, Me, tosyl), 2.73 (q, J = 6 Hz, 1 H, H-6), 2.88 (d, J = 9.5 Hz, 1 H, H-3), 3.34 (br s, 1 H, H-4), 3.66 (s, 2 H, CH_2Ph), 3.71 (d, J = 9.5 Hz, 1 H, H-3'), 3.93 (br s, 1 H, H-1), 7.26 (s, 5 H, CH_2Ph), 7.28 (d, J = 8 Hz, 2 H, Ar, tosyl), 7.73 (d, J = 8 Hz, 2 H, Ar tosyl). Anal. ($C_{20}H_{24}N_2O_2S$) C, H, N. NOESY experiments (proton selective probe, amx 400, Brucker) showed a correlation between H-7 at 0.93 ppm and the methyl group at C-6 position for **17b**, thus giving the 1*R*,4*R*,6*S* configuration for that isomer.

(1*R*,4*R*,6*R*)- and (1*R*,4*R*,6*S*)-6-Methyl-5-(phenylmethyl)-2,5-diazabicyclo[2.2.1]heptanes, Dihydrobromides (8a and 8b). A mixture of 0.94 g (2.63 mmol) of **17b** was added to 2.4 mL of 33% HBr in AcOH. The reaction mixture was stirred at 80 °C overnight. The solvent was evaporated under reduced pressure and the residue was triturated in acetone, decanted, and finally crystallized (hygroscopic material) from ether to give 0.85 g (yield 88.5%) of **8b**.

Using the same methodology, the isomer **8a** was obtained in a 72% yield. The crude products **8a** and **8b** were used directly in the next step without further purification.

(1*R*,4*R*,6*R*)- and (1*R*,4*R*,6*S*)-6-Methyl-2,5-diazabicyclo[2.2.1]heptanes, Dihydrobromides (25a and 25b). A suspension of 0.81 g (2.22 mmol) of **8a** and 0.76 g of 10% Pd/C in 20 mL of methanol was hydrogenated for 2 h. After the catalyst was filtered off over a Celite pad, the filtrate was evaporated under vacuo to provide 0.54 g of crude material which was crystallized from hot 2-propanol to yield 0.36 g (yield 60%) of **25a**: mp >260 °C; $[\alpha]_D$ −23.2°. IR 3425, 2954, 1624, 1580, 1397, 1120 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.49 (d, J = 7.2 Hz, 3 H, Me-6), 2.11 and 2.24 (2 d, J = 12 Hz, 2 H, H-7 and H-7'), 3.40 and 3.46 (2 d, J = 12 Hz, 2 H, H-3 and H-3'), 3.91 (q, J = 7.2 Hz, 1 H, H-6), 4.46 (s, 2 H, H-1 and H-4). Anal. ($C_{16}H_{12}N_2$·2HBr) C, H, N.

In the same manner isomer **25b** was obtained from **8b**: yield 73%; mp >260 °C; $[\alpha]_D$ −29.4°. ^1H NMR (DMSO-d_6) δ 1.27 (d, J = 6.8 Hz, 3 H, Me-6), 2.01 and 2.10 (2 d, J = 12.6 Hz, 2 H, H-7 and H-7'), 3.33 and 3.45 (2 d, J = 12 Hz, 2 H, H-3 and H-3'), 3.93 (q, J = 6.8 Hz, 1 H, H-6), 4.30 (s, 1 H, H-1), 4.41 (s, 1 H, H-4). Anal. ($C_{16}H_{12}N_2$·2HBr) C, H, N.

(1*R*,4*R*,6*R*)- and (1*R*,4*R*,6*S*)-2-(Trifluoroacetyl)-5-(phenylmethyl)-6-methyl-2,5-diazabicyclo[2.2.1]heptanes (19a and 19b). A suspension of 10 g (27 mmol) of **8b** in the minimum amount of water was treated with an excess of 10 N aqueous NaOH, extracted with Et_2O (three times), dried (K_2CO_3), and evaporated. To the residual oil dissolved in 40 mL of CH_2Cl_2 at 10 °C was added dropwise 15 mL (21 mmol) of trifluoroacetic anhydride. After 2 h at room temperature, the reaction mixture was evaporated under reduced pressure and chromatographed over silica gel (CH_2Cl_2/MeOH 98:2) to provide 4.1 g (yield 67%) of **19b** as an oil. Isomer **19b**: ^1H NMR (DMSO-d_6) δ 0.88 (d, J = 6.4 Hz, 3 H, Me-6), 1.60 (m, 1 H, H-7), 2.06 (2 d, J = 9.4 Hz, 1 H, H-7'), 2.58 (m, 1 H, H-6), 3.25 (m, 1 H, H-3), 3.51 (m, 1 H, H-4), 3.69 (q, J = 8.6 Hz, 2 H, CH_2 benzyl), 3.84 (m, 1 H, H-3'),

4.15 and 4.40 (2 s, 1 H, H-1, two conformers), 7.25 (m, 5 H, Ar).

In the same manner **19a** was obtained from **8a** (yield 38%): ^{1}H NMR ($CDCl_3$) δ 0.79 (d, J = 6.4 Hz, 3 H, Me-6), 1.69 (m, 1 H, H-7), 2.05 (m, 1 H, H-7′), 2.89 (m, 1 H, H-6), 3.05 (m, 1 H, H-4), 3.37 (m, 2 H, H-3 and H-3′), 3.64 (q, J = 8 Hz, 2 H, CH_2 benzyl), 4.40 and 4.56 (2 s, 1 H, H-1, 2 conformers), 7.32 (m, 5 H, Ar).

(1*R*,4*R*,6*R*)- and (1*R*,4*R*,6*S*)-2-(Trifluoroacetyl)-6-methyl-2,5-diazabicyclo[2.2.1]heptanes (9a and 9b). A suspension of 3.9 g (13 mmol) of **19b** and 0.6 g 10% Pd/C in 35 mL of MeOH was hydrogenated for 1.5 h. After filtration of the catalyst, the filtrate was concentrated under vacuo to give 2.53 g of **9b** (yield 94%) as an oil. Isomer **9b**: ^{1}H NMR ($CDCl_3$) δ 0.9 (d, J = 6.5 Hz, 3 H, Me-6), 1.61 (m, 1 H, H-7), 2.07 (m, 1 H, H-7′), 2.56 (m, 1 H, H-6), 3.19–3.96 (m, 3 H, H-3, H-3′, and H-4), 4.15 and 4.42 (2 s, 1 H, H-1, 2 conformers).

According to the same procedure the isomer **9a** was obtained from **19a** (yield 92%). Isomer **9a**: ^{1}H NMR ($CDCl_3$) δ 1.18 (d, J = 6.4 Hz, 3 H, Me-6), 1.89 (2 d, J = 9 Hz, 1 H, H-7), 2.06 (m, 1 H, H-7′), 3.30–3.83 (m, 4 H, H-3, H-3′, H-4, and H-6), 4.50 and 4.78 (2 s, 1 H, H-1, 2 conformers).

7-[(1*R*,3*R*,4*R*)- and (1*R*,3*S*,4*R*)-3-Methyl-5-(trifluoroacetyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(1,1-dimethylethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (21a and 21b, R_1 = *t*-Bu, R_5 = H). A mixture of 2.5 g (12 mmol) of **9b**, 2.6 g (8 mmol) of **27** (R_1 = *tert*-butyl, R_5 = H, **20**), and 1.2 g (8 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 15 mL of DMF was stirred at 100 °C for 5.5 h. The solvent was evaporated under vacuo and the residue was purified by chromatography over silica gel (AcOEt, then AcOEt/MeOH 94:6) to provide 2.25 g of **21b** (yield 56.5%). In the same manner the isomer **21a** was obtained from **9a** and **27** (yield 98%). Isomer **21a** (R_1 = *t*-Bu, R_5 = H, (1*R*,3*R*,4*R*)): ^{1}H NMR (DMSO-d_6) δ 1.16 (d, J = 6.0 Hz, 3 H, Me-3, bridged piperazine), 1.27 (t, J = 6.8 Hz, 3 H, Me ester), 1.81 (s, 9 H, *t*-Bu), 2.05 (m, 1 H, H-7, pip.), 2.45 (m, 1 H, H-7′, pip.), 3.48–4.02 (m, 2 H, H-6 and H-6′, pip.), 4.21 (q, J = 6.8 Hz, 2 H, CH_2 ester), 4.44 (s, 1 H, H-4, pip.), 4.93 (br s, 2 H, H-1 + H-3, pip.), 8.00 (d, J = 12 Hz, 1 H, H-5), 8.70 (s, 1 H, H-2).

Isomer **21b** (R_1 = *t*-Bu, R_5 = H, (1*R*,3*S*,4*R*)): ^{1}H NMR (DMSO-d_6, at 80 °C because of conformers) δ 1.26 (t, J = 7.0 Hz, 3 H, Me ester), 1.33 (m, 3 H, Me-3, bridged piperazine), 1.81 (s, 9 H, *t*-Bu), 2.12 (m, 1 H, H-7, pip.), 2.37 (m, 1 H, H-7′, pip.), 3.40–3.78 (m, 2 H, H-6 and H-6′, pip.), 4.24 (q, J = 7.0 Hz, 2 H, CH_2 ester), 4.44 (s, 1 H, H-4, pip.), 4.65 (br s, 1 H, H-3, pip.), 5.11 (br s, 1 H, H-1, pip.), 8.00 (d, J = 12 Hz, 1 H, H-5), 8.69 (s, 1 H, H-2).

7-[(1*R*,3*R*,4*R*)- and (1*R*,3*S*,4*R*)-3-Methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(1,1-dimethylethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Hydrochloride (38 and 39). A mixture of 2.1 g (4.4 mmol) of **21b** (R_1 = *t*-Bu, R_5 = H) and 6 mL (12 mmol) of 2 N aqueous NaOH in 20 mL of EtOH was heated under reflux for 5 h. After evaporation under reduced pressure of the solvent, the residue was taken up in H_2O (insoluble material was discarded), and the pH of the filtrate was brought to 7 with concentrated HCl. The resulting amino acid (1.4 g) was transformed into 1.42 g of its hydrochloride salt **39** with 2 N aqueous HCl in EtOH (yield 79%): mp 240 °C dec; $[\alpha]_D$ +145° (c = 0.25, 0.1 N HCl); ^{1}H NMR (DMSO-d_6) δ 1.34 (d, J = 6.4 Hz, 3 H, Me-3, bridged piperazine), 1.86 (s, 9 H, *t*-Bu), 1.97 (m, 1 H, H-7, pip.), 2.45 (m, 1 H, H-7′, pip.), 3.27 (m, 2 H, H-6 and H-6′, pip.), 4.30 (s, 1 H, H-4, pip.), 4.64 (br s, 1 H, H-3, pip.), 5.11 (s, 1 H, H-1, pip.), 8.18 (d, J = 12 Hz, 1 H, H-5), 9.42 (s, 1 H, H-2). Anal. ($C_{19}H_{23}FN_4O_3$·HCl) C, H, N.

The compound **38** was obtained according to the same procedure (yield 55%): mp >260 °C; $[\alpha]_D$ +103° (c = 0.25, 0.1 N HCl); ^{1}H NMR (DMSO-d_6) δ 1.47 (d, J = 6.2 Hz, 3 H, Me-3, bridged piperazine), 1.90 (s, 9 H, *t*-Bu), 2.08 (d, J = 12 Hz, 1 H, H-7, pip.), 2.24 (d, J = 12 Hz, 1 H, H-7′, pip.), 3.48 (dd, J = 10 Hz, 2 H, H-6 and H-6′, pip.), 4.49 (br s, 2 H, H-3 and H-4, pip.), 5.03 (s, 1 H, H-1, pip.), 8.21 (d, J = 12 Hz, 1 H, H-5), 8.93 (s, 1 H, H-2). Anal. ($C_{19}H_{23}FN_4O_3$·HCl) C, H, N.

7-[(1*R*,4*R*,6*S*)-6-Methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(1,1-dimethylethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (30). A mixture of 0.426 g (1.55 mmol) of **25b**, 0.37 g (1.12 mmol) of **27**, and 0.65 g (4.3 mmol) of DBU in 35 mL of CH_3CN was heated under reflux for 2 h. The solvent was evaporated under vacuo and the residue was crystallized from H_2O to give 0.38 g of **30** (yield 85%): mp 184 °C dec; $[\alpha]_D$ +141.4°; ^{1}H NMR (DMSO-d_6) δ 0.96 (d, J = 6.4 Hz, 3 H, Me-6, bridged piperazine); 1.26 (t, J = 6.8 Hz, 3 H, Me ester), 1.68 (d, J = 9.4 Hz, 1 H, H-7, pip.), 1.82 (m, 10 H, *tert*-butyl and H-7′), 3.24 (m, 1 H, H-3, pip.), 3.53 (m, 1 H, H-6, pip.), 3.66 (s, 1 H, H-4, pip.), 3.72 (m, 1 H, H-3′, pip.), 4.20 (q, J = 6.8 Hz, 2 H, CH_2 ester), 4.49 (s, 1 H, H-1, pip.), 7.87 (d, J = 12 Hz, 1 H, H-5), 8.65 (s, 1 H, H-2). Anal. ($C_{21}H_{27}FN_4O_3$) C, H, N.

Alternatively the derivative **30** could be obtained (see Scheme II) following the sequence **8b** + **27** → **23b** (R_1 = *t*-Bu, R_5 = H, yield 54.8%; mp 203 °C) → **30** (yield 94.1%).

7-[(1*R*,4*R*,6*S*)-6-Methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(1,1-dimethylethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Hydrochloride (41). A suspension of 0.34 g (0.84 mmol) of **30** and 0.46 mL (0.92 mmol) of 2 N aqueous NaOH in 6 mL of EtOH was refluxed for 1.5 h. After the solution was cooled, 0.45 mL (0.9 mmol) of 2 N aqueous HCl was added. The precipitate was filtered to give 0.29 g of the corresponding amino acid which was transformed into the chlorhydrate salt **41** (0.29 g, yield 84%): mp >260 °C; $[\alpha]_D$ +146° (c = 0.25, 0.1 N HCl); IR 2936, 2404, 1669, 1631, 1537, 1438, 1212 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.36 (d, J = 7.0 Hz, 3 H, Me-6, bridged piperazine), 1.90 (s, 9 H, *tert*-butyl), 2.25 (m, 2 H, H-7 and H-7′, pip.), 3.95 (m, 2 H, H-3 and H-3′, pip.), 4.23 (m, 1 H, H-6), 4.50 (s, 1 H, H-4, pip.), 4.84 (s, 1 H, H-1, pip.), 8.15 (d, J = 12 Hz, 1 H, H-5), 8.90 (s, 1 H, H-2). Anal. ($C_{19}H_{23}FN_4O_3$·HCl) C, H, N.

7-[(1*R*,4*R*,6*R*)-5-(Phenylmethyl)-6-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(1,1-dimethylethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (23a, R_1 = *t*-Bu, R_5 = H). A mixture of 4.2 g (11.5 mmol) of **8a**, 3.6 g (11 mmol) of **27**, and 7.3 g (48 mmol) of DBU in 40 mL of CH_3CN was stirred overnight. The residue was evaporated under vacuo and the residue was partitioned between CH_2Cl_2 and H_2O, dried ($MgSO_4$), and chromatographed over silica gel (CH_2Cl_2/MeOH 94:6) to give 4 g of **23a** (R_1 = *t*-Bu, R_5 = H; yield 73.5%): ^{1}H NMR (DMSO-d_6) δ 0.71 (d, J = 7.0 Hz, 3 H, Me-6, bridged piperazine), 1.26 (t, J = 7.0 Hz, 3 H, Me ester), 1.80 (s, 9 H, *t*-Bu), 1.80–2.11 (m, 3 H, H-6, H-7, and H-7′, pip.), 3.61–3.86 (m, 5 H, H-3, H-3′, and H-4, pip. and CH_2Ph), 4.20 (q, J = 7.0 Hz, 2 H, CH_2 ester), 4.83 (br s, 1 H, H-1, pip.), 7.85–7.93 (m, 5 H, Ar), 8.10 (d, J = 13.2 Hz, 1 H, H-5), 8.65 (s, 1 H, H-2).

7-[(1*R*,4*R*,6*R*)-6-Methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(1,1-dimethylethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester Hydrochloride (28). A mixture of 3.4 g (6.9 mmol) of **23a** (R_1 = *t*-Bu, R_5 = H), 2.4 g of 10% Pd/C, and 6.5 mL (6.5 mmol) of 1 N aqueous HCl in 60 mL of MeOH was hydrogenated for 2 h. The catalyst was filtered off and the filtrate was evaporated to yield 3 g of **28** (yield 99.3%): mp 164 °C; $[\alpha]_D$ +67.7°.

7-[(1*R*,4*R*,6*R*)-6-Methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(1,1-dimethylethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Hydrochloride (40). A solution of 2.7 g (6.15 mmol) of **28** and 9 mL (9 mmol) of 1 N aqueous HCl in 45 mL of EtOH was heated under reflux for 3.5 h. After evaporation of the reaction mixture under reduced pressure, the residue was recrystallized from EtOH/H_2O 90:10 to provide 1.4 g of **40** (yield 59%): mp >260 °C; $[\alpha]_D$ +71.5° (c = 0.25, 0.1 N HCl). IR 3443, 3139, 2881, 2698, 2620, 2494, 1706, 1515, 1188 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.23 (d, J = 6.8 Hz, 3 H, Me-6, pip.), 1.88 (s, 9 H, *t*-Bu), 2.13 (d, J = 9.4 Hz, 1 H, H-7, pip.), 2.25 (d, J = 9.4 Hz, 1 H, H-7′, pip.), 3.95 (m, 3 H, H-3, H-3′, and H-6, pip.), 4.48 (s, 1 H, H-4, pip.), 5.11 (s, 1 H, H-1, pip.), 8.14 (d, J = 12 Hz, 1 H, H-5), 8.86 (s, 1 H, H-2). Anal. ($C_{19}H_{23}FN_4O_3$·HCl) C, H, N.

7-[(1*R*,4*R*,6*S*)-6-Methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(1,1-dimethylethyl)-5-methyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Hydrochloride (44). The derivative **44** was prepared according to the procedure described for **40** (see Scheme II) by condensation of **8b** with **20** (R_1 = *t*-Bu, R_5 = Me; oil (yield 62.5%)), followed by hydrogenolysis of the corresponding N-benzylated compound **23b** (R_1 = *t*-Bu, R_5 = Me) (yield 93.5%) and finally alkaline hydrolysis and salt formation of **44** (yield 53%): mp >260 °C; $[\alpha]_D$ +134° (c = 0.125, 0.1 N HCl/MeOH 50:50); IR 3471, 3421, 2975, 2932, 1693, 1629,

1542, 1465, 1182 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.34 (d, J = 6.4 Hz, 3 H, Me-6, pip.), 1.89 (s, 9 H, t-Bu), 2.23 (m, 2 H, H-7 and H-7′, pip.), 2.76 (s, 3 H, 5-Me), 3.8–4.2 (m, 3 H, H-3, H-3′, and H-6, pip.), 4.51 (s, 1 H, H-4, pip.), 4.84 (s, 1 H, H-1, pip.), 8.90 (s, 1 H, H-2). Anal. ($C_{20}H_{25}FN_4O_3$·HCl) C, H, N.

7-[(1*R*,3*R*,4*S*)-6-Methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-cyclopropyl-5-methyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Hydrochloride (46). According to Scheme II, **9a** (3*R*) was condensed with **20** (R_1 = C_3H_5, R_5 = Me) (yield 44%) and the resulting naphthyridine **21a** (R_1 = C_3H_5, R_5 = Me) was hydrolyzed in alkaline medium and transformed into the chlorhydrate **46** (yield 76%); mp >260 °C; $[\alpha]_D$ +56.2° (c = 0.125, 0.1 N HCl/MeOH 50:50). IR 3410, 2922, 2629, 1721, 1626, 1449, 1336, 1149 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.11–1.30 (2 m, 4 H, 2 CH_2, cyclopropyl), 1.54 (d, J = 6 Hz, 3 H, Me-6, pip.), 2.07 (d, J = 11 Hz, 1 H, H-7, pip.), 2.19 (d, J = 11 Hz, 1 H, H-7′, pip.), 2.73 (br s, 3 H, Me-5), 3.47 (m, 2 H, H-6 and H-6′, pip.), 3.71 (m, 1 H, CH, cyclopropyl), 4.48 (br s, 2 H, H-3 and H-4, pip.), 5.12 (s, 1 H, H-1, pip.), 8.60 (s, 1 H, H-2). Anal. ($C_{19}H_{21}FN_4O_3$·HCl) C, H, N.

7-[(1*R*,3*S*,4*S*)-6-Methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-cyclopropyl-5-methyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Hydrochloride (47). For **47** the same procedure described for the preparation of **46** was used (yield 42%): mp >260 °C; $[\alpha]_D$ +174.1° (c = 0.125, 0.1 N HCl/MeOH 50:50); IR 3414, 2977, 2726, 1694, 1629, 1465, 1181 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.94 and 1.18 (2 m, 4 H, 2 CH_2, cyclopropyl), 1.36 (d, J = 6.2 Hz, 3 H, Me-6, pip.), 1.92 (d, J = 11 Hz, 1 H, H-7, pip.), 2.17 (d, J = 11 Hz, 1 H, H-7′, pip.), 2.69 (d, J = 2.8 Hz, 3 H, Me-5), 3.22 (d, J = 11.4 Hz, 1 H, H-6, pip.), 3.32 (d, J = 11.4 Hz, 1 H, H-6′, pip.), 3.65 (m, 1 H, CH, cyclopropyl), 4.26 (s, 1 H, H-4, pip.), 4.60 (m, 1 H, H-3, pip.), 5.15 (s, 1 H, H-1, pip.), 8.55 (s, 1 H, H-2). Anal. ($C_{19}H_{21}FN_4O_3$·HCl) C, H, N.

7-[(1*R*,4*R*,6*R*)-6-Methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-cyclopropyl-5-methyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Hydrochloride (48). For **48** the same procedure described for the preparation of **46** was used (yield 34%): mp >260 °C; $[\alpha]_D$ +102° (c = 0.125, 0.1 N HCl/MeOH 50:50); IR 3410, 2870, 2721, 1719, 1627, 1450, 1036 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.11 and 1.28 (2 m, 7 H, 2 CH_2, cyclopropyl and Me-6, pip.), 2.10 (dd, J = 10 Hz, 2 H, H-7 and H-7′, pip.), 2.77 (d, J = 2.8 Hz, 3 H, Me-5), 3.71 (m, 1 H, H-6, pip.), 4.05 (m, 3 H, CH, cyclopropyl, H-3 and H-3′ pip.), 4.53 (s, 1 H, H-4, pip.), 5.31 (s, 1 H, H-1, pip.), 8.62 (s, 1 H, H-2). Anal. ($C_{19}H_{21}FN_4O_3$·HCl) C, H, N.

7-[(1*R*,4*R*,6*S*)-6-Methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-cyclopropyl-5-methyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Hydrochloride (49). The procedure described for the preparation of **40** was followed to achieve the synthesis of **49** (yield 28%): mp >260 °C; $[\alpha]_D$ +110° (c = 0.25, 0.1 N HCl); IR 3417, 2878, 2668, 2497, 1720, 1628, 1454 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.13 (m, 4 H, 2 CH_2, cyclopropyl), 1.34 (d, J = 6.4 Hz, 3 H, Me-6, pip.), 2.08 (m, 2 H, H-7 and H-7′, pip.), 2.71 (d, J = 2.8 Hz, 3 H, Me-5), 3.7–4.15 (m, 4 H, H-3, H-3′, and H-6, pip., and CH, cyclopropyl), 4.45 (s, 1 H, H-4, pip.), 4.88 (s, 1 H, H-1, pip.), 8.59 (s, 1 H, H-2). Anal. ($C_{19}H_{21}FN_4O_3$·HCl) C, H, N.

7-[(1*R*,4*R*,6*S*)-6-Methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Hydrochloride (50). Using the methodology described for **40**, the preparation of **50** was performed by condensation of **8b** and **20** (R_1 = 2,4-difluorophenyl, R_5 = H),[21] hydrogenolysis, and acidic hydrolysis (yield 50%): mp >260 °C; $[\alpha]_D$ +195° (c = 0.125, 0.1 N HCl/MeOH 50:50). IR 3064, 2858, 2658, 2497, 1731, 1634, 1482, 1217, 1150 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.07 (d, J = 6.4 Hz, 3 H, Me-6, pip.), 2.05 (m, 2 H, H-7 and H-7′, pip.), 3.38–4.20 (m, 4 H, H-3, H-3′, H-6, and H-4, pip.) 4.37 (s, 1 H, H-1, pip.), 7.64 and 7.82 (3 m, 3 H, 2,4-diF-phenyl), 8.21 (d, J = 12 Hz, 1 H, H-5), 8.86 (s, 1 H, H-2). Anal. ($C_{21}H_{17}F_3N_4O_3$·HCl) C, H, N.

(2*R*,4*R*)-4-Hydroxy-1,2-pyrrolidinedicarboxylic Acid 1,2-Bis(phenylmethyl) Ester (31). After inversion at C-2 of the *trans*-4-hydroxy-L-proline, according to a similar procedure described in the literature,[17] **31** was obtained (yield 38% from *trans*-4-hydroxy-L-proline): thick oil; $[\alpha]_D$ +34.2°; ^1H NMR (DMSO-d_6) δ 1.96 (m, 1 H, H-3), 2.35 (m, 1 H, H-3′), 3.25 (m, 1 H, H-5), 3.60 (m, 1 H, H-5′), 4.29 (br s, 1 H, H-4), 4.43 (dd, 1 H, 2 conformers, H-2), 5.01–5.08 (m, 5 H, 2 conformers, 2 CH_2Ph, OH), 7.31 and 7.35 (2 s, 10 H, Ar).

(2*R*,4*S*)-4-Acetoxy-D-proline (32). Tosylation of **31** in pyridine, followed by inversion at C-4 with tetraethylammonium acetate in AcOEt gave (2*R*,4*S*)-4-acetoxy-1,2-pyrrolidinedicarboxylic acid 1,2-bis(phenylmethyl) ester in 63.5% yield (from **31**), following the procedure described for the *N*-tosyl analogue:[5] $[\alpha]_D$ +53.2°. This latter 1,2-bis(phenylmethyl)ester was hydrogenated with 10% Pd/C in methanol to provide **32** (yield 78.5%): mp 176–8 °C dec; $[\alpha]_D$ +28° (c = 0.865, 0.5 N HCl) (lit.[18] $[\alpha]_D$ −26.6° (c = 0.865, 0.5 N HCl) for the 2*S*,4*R* isomer).

(2*S*,5*R*,7*S*)-2-*tert*-Butyl-4-oxo-3-oxa-1-azabicyclo[3.3.0]-oct-7-yl Acetate (33). To a suspension of 21 g (0.12 mmol) of **32** in 300 mL of CH_2Cl_2 were added 53 mL (0.48 mol) of trimethylacetaldehyde and 0.3 mL of trifluoroacetic acid. The mixture was refluxed overnight with continuous drying of the CH_2Cl_2 vapors on 4A molecular sieves. The solution was cooled, the little insoluble was filtered, and the filtrate was evaporated under vacuo. The oily residue was crystallized from pentane to yield 25 g of **33** (yield 86%; mp 100 °C); this instable compound was contaminated with 10% pivaldehyde and was used without further purification.

(2*S*,5*R*,7*S*)-2-*tert*-Butyl-5-methyl-4-oxo-3-oxa-1-azabicyclo[3.3.0]oct-7-yl Propionate (34). To a solution of 26.5 g (0.11 mol) of the adduct **33** in 850 mL of THF cooled at −75 °C was added dropwise a solution of 0.23 mol of LDA in 650 mL of THF at $\theta \leq -68$ °C. After 1.5 h at −75 °C, a solution of 45 mL (0.7 mol) of methyl iodide in 100 mL of THF was carefully added and the mixture was kept 1 h at −70 °C. The reaction mixture was allowed to reach −20 °C and was diluted with 500 mL of Et_2O and 200 mL of a saturated aqueous solution of NH_4Cl. The organic layer was decanted, washed with brine, and dried ($MgSO_4$). There was obtained 29 g of raw material which was rapidly chromatographed over a small silica gel pad (CH_2Cl_2/pentane/Et_2O 3.5:4.5:2) to provide 16.4 g of **34** (yield 55%) as a very instable oil which was rapidly hydrolyzed to **35a**.

(2*S*,4*R*)-4-Hydroxy-2-methylproline (35a). A suspension of 16.3 g (60 mmol) of **34** in 50 mL of 6 N aqueous HCl was refluxed for 1.5 h. The aqueous solution was washed with CH_2Cl_2 and evaporated to dryness under vacuo. The residue was dried and crystallized from acetone to give 8.9 g of the corresponding hydrochloride salt of the proline **35a** (yield 81%): mp 190 °C dec; $[\alpha]_D$ +48.1° (c = 1, H_2O). Anal. ($C_6H_{11}NO_3$·HCl) C, H, N.

The hydrochloride salt **35a** was passed through an Amberlite IR-48 anion exchange to give the free base which was crystallized from acetone after evaporation of water under reduced pressure: mp >260 °C; $[\alpha]_D$ +68.07° (c = 1, H_2O) (lit.[18] $[\alpha]_D$ −71° (c = 1, H_2O) for the 2*R*,4*S* enantiomer); ^1H NMR (DMSO-d_6) δ 1.47 (s, 3 H, Me-2), 1.65–1.70 (m, 1 H, H-3), 2.33–2.46 (m, 1 H, H-3′), 2.93 and 3.23 (m, 2 H, H-5 and H-5′), 4.25 (m, 1 H, H-4).

(2*S*,4*R*)-4-Hydroxy-2-methylproline Ethyl Ester (35b). To a solution of 10 g (55.1 mmol) of the above acid **35a** in 250 mL of absolute EtOH at reflux was bubbled dry HCl gas for 5 h. The solvent was evaporated to dryness. The residue was dissolved in a mixture of 100 mL of MeOH and 100 mL of TEA. The mixture was evaporated to dryness under vacuo and the residue was taken up in Et_2O, the insoluble material was filtered, and the filtrate was evaporated to give 7.5 g of **35b** (yield 79%): mp 50 °C; ^1H NMR ($CDCl_3$) δ 1.27 (t, J = 7.0 Hz, 3 H, CH_3, ester), 1.50 (s, 3 H, Me-2), 1.70–1.79 (m, 1 H, H-3), 2.53 and 2.60 (2 dd, J = 6.2 Hz, 1 H, H-3′), 3.01–3.03 (m, 2 H, H-5 and H-5′), 4.17 (q, J = 7.0 Hz, 2 H, CH_2, ester), 4.34 (m, 1 H, H-4). Anal. ($C_8H_{15}NO_3$) C, H, N.

(2*S*,4*S*)-1-(4-Tolylsulfonyl)-4-[(4-tolylsulfonyl)oxy]-2-methylprolinol (36). After tosylation of **35b** with 4-toluenesulfonyl chloride in pyridine, the N,O-ditosylated derivative of **35b** was obtained in 94% yield: ^1H NMR ($CDCl_3$) δ 1.24 (t, J = 7.0 Hz, 3 H, CH_3 ester), 1.63 (s, 3 H, Me-2), 2.06 and 2.13 (m, 1 H, H-3), 2.41 and 2.43 (2 s, 6 H, 2 Me, tosyl), 2.45–2.52 (m, 1 H, H-3′), 3.44–3.51 (m, 1 H, H-5), 3.76–3.84 (m, 1 H, H-5′), 4.16 (q, J = 7.0 Hz, 2 H, CH_2, ester), 5.02 (m, 1 H, H-4), 7.23–7.32 (2 d, J = 7.6 Hz, 4 H, Ar, tosyl), 7.64–7.69 (2 d, J = 7.6 Hz, 4 H, Ar, tosyl). To a solution of 2.4 g (5 mmol) of the above ester in 40 mL of THF cooled at 0 °C was added portionwise 0.24 g (11

mmol) of $LiBH_4$. After 2 h at 5 °C, the reaction mixture was allowed to reach room temperature overnight, cooled at 10 °C, and hydrolyzed with 6 N aqueous HCl. After dilution with H_2O, and extraction with AcOEt, and drying ($MgSO_4$), 1.7 g of raw material was obtained which was chromatographed over silica gel (CH_2Cl_2/MeOH 97:3) to yield 1.35 g of **36** as an oil (yield 61.6%): ^1H NMR ($CDCl_3$) δ 1.26 (s, 3 H, Me-2), 1.80–1.90 (m, 1 H, H-3), 2.42–2.46 (m, 7 H, Me, tosyl and H-3′), 3.30–3.71 (m, 3 H, C*H*$_2$OH and H-5), 3.93 (d, J = 12 Hz, 1 H, H-5′), 4.97 (m, 1 H, H-4), 7.27–7.34 (m, 4 H, Ar, tosyl), 7.66–7.77 (m, 4 H, Ar, tosyl).

(1*R*,4*R*)-1-Methyl-2-(4-tolylsulfonyl)-5-(phenylmethyl)-2,5-diazabicyclo[2.2.1]heptane (37). Tosylation of **36** afforded, after chromatography (CH_2Cl_2/MeOH 99:1), the corresponding tritosylated derivative (yield 29%): mp 106 °C; $[\alpha]_D$ −2.5° (c = 0.25, $CDCl_3$); ^1H NMR ($CDCl_3$) δ 1.39 (s, 3 H, Me-2), 1.92 and 1.99 (2 m, 1 H, H-3), 2.39–2.47 (m, 10 H, 3 Me-Ar, tosyl, and H-3′), 3.49–3.66 (m, 2 H, CH_2OTs), 4.02 (d, J = 9.6 Hz, 1 H, H-5), 4.26 (d, J = 9.6 Hz, 1 H, H-5′), 4.89 (m, 1 H, H-4), 7.24–7.39 (m, 6 H, Ar, tosyl), 7.62–7.80 (m, 6 H, Ar, tosyl). A suspension of the above tritosylated derivative and 7.7 mL (70 mmol) of benzylamine in xylene was heated at 160 °C for 12 h. The reaction mixture was cooled and the insoluble material was filtered and washed with toluene. The filtrate was evaporated under vacuo to afford 14.5 g of raw material which was chromatographed (CH_2Cl_2/AcOEt 90:10) to give 2.5 g of **37** (yield 30%): mp 77 °C; $[\alpha]_D$ +7.8°; ^1H NMR ($CDCl_3$) δ 1.62 (s, 3 H, Me-1), 1.76 (d, J = 9.6 Hz, 1 H, H-7), 1.86 (d, J = 9.6 Hz, 1 H, H-7′), 2.40–2.43 (m, 1 H, H-6), 2.46 (s, 3 H, Me-Ar, tosyl), 2.54 (br s, 1 H, H-6′), 3.35–3.41 (m, 2 H, H-3 and H-4), 3.55 (q, J = 13.4 Hz, 2 H, C*H*$_2$Ph), 3.75–3.87 (m, 1 H, H-3′), 7.12–7.35 (m, 7 H, Ar, tosyl and C*H*$_2$*Ph*), 7.80 (d, J = 8.2 Hz, 2 H, Ar, tosyl). Anal. ($C_{20}H_{24}N_2O_2S$).

(1*R*,4*R*)-4-Methyl-2-(phenylmethyl)-2,5-diazabicyclo-[2.2.1]heptane, Dihydrobromide (6). A suspension of 0.82 g (2.3 mmol) of **37** in 9 mL of 33% HBr in AcOH was heated at 70–80 °C for 4 h. Excess of HBr and AcOH was evaporated under vacuo. The residue was crystallized from Et_2O to provide 0.9 g of **6**, which was used without further purification.

(1*R*,4*R*)-1-Methyl-2-(trifluoroacetyl)-2,5-diazabicyclo-[2.2.1]heptane, Trifluoroacetate (7). To a solution of 2 g (5.5 mmol) of **6** in 50 mL of MeOH was added 15 g (10.8 mmol) of K_2CO_3. After 30 min, the insoluble material was filtered and the filtrate was evaporated. To 1.5 g of the resulting crude amine in 20 mL of CH_2Cl_2 was added 10 mL of trifluoroacetic anhydride. The reaction mixture was stirred overnight and evaporated under reduced pressure. The residue was partitioned between CH_2Cl_2 and H_2O. The organic layer was washed successively with 10% aqueous $NaHCO_3$ and brine and dried ($MgSO_4$) to give 1.6 g of raw material. Chromatography (CH_2Cl_2/MeOH 97.5:2.5) afforded 0.84 g of N-trifluoroacetylated **6**, trifluoroacetate salt (yield 37.2%). After hydrogenation over 10% Pd/C in MeOH of 0.83 g of the above *N*-benzyl-bridged piperazine for 3 h, 0.64 g of **7** was obtained (yield 99%): ^1H NMR ($CDCl_3$) δ 1.85 (s, 3 H, Me-1), 2.12 (m, 2 H, H-7 and H-7′), 3.23 (m, 1 H, H-3), 3.76 (m, 2 H, H-6 and H-6′), 4.20 (m, 1 H, H-3′), 4.41 (br s, 1 H, H-4).

7-[(1*R*,4*R*)-4-Methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(1,1-dimethylethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Hydrochloride (42). A mixture of 0.65 g (2 mmol) of **27**, 0.64 g (2 mmol) of **7**, and 0.7 g (4.6 mmol) of DBU in 13 mL of CH_3CN was stirred overnight, evaporated under vacuo, extracted with CH_2Cl_2, washed with H_2O, and dried ($MgSO_4$). The residue was chromatographed (CH_2Cl_2/MeOH 97:3) to provide 0.5 g of the N-trifluoroacetylated ethyl ester of **42** (yield 50%): mp 155 °C dec; ^1H NMR ($CDCl_3$) δ 1.40 (t, J = 7 Hz, 3 H, CH_3, ester), 1.84 (s, 9 H, t-Bu), 1.91 (s, 3 H, Me-4, pip.), 2.08 (m, 2 H, H-7 and H-7′, pip.), 3.75–3.77 (2 m, 1 H, H-3, pip.), 3.88 (m, 2 H, H-6 and H-6′, pip.), 3.97–3.98 (2 m, 1 H, H-3′, pip.), 4.38 (q, J = 7 Hz, 2 H, CH_2, ester), 5.04 (m, 1 H, H-1), 8.19 (d, J = 12 Hz, 1 H, H-5), 8.80 (s, 1 H, H-2). A suspension of 0.48 g (1 mmol) of the above ester and 3 mL (3 mmol) of 1 N NaOH in 3 mL of MeOH was refluxed for 2 h. The solvent was evaporated under vacuo. The residue was dissolved in H_2O and the pH was brought to 7 with 6 N aqueous HCl. The precipitate was collected and dried (0.32 g, mp >260 °C). The chlorhydrate of the amino acid was prepared with 2 N HCl in ethanol and recrystallized from EtOH/H_2O to give **42** (yield 53%): mp >260 °C; $[\alpha]_D$ +17.4°; IR 3506, 2872, 2660, 2457, 1742, 1626, 1459, 1181 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.73 (s, 3 H, Me-4, pip.), 1.90 (s, 9 H, t-Bu), 2.07 (d, J = 10.8 Hz, 1 H, H-7, pip.), 2.26 (d, J = 10.8 Hz, 1 H, H-7′, pip.), 3.48 (m, 2 H, H-6 and H-6′, pip.), 3.87 (d, J = 10.8 Hz, 1 H, H-3, pip.), 4.25 (d, J = 10.8 Hz, 1 H, H-3′, pip.), 5.12 (m, 1 H, H-1, pip.), 8.16 (d, J = 12.6 Hz, 1 H, H-5), 8.90 (s, 1 H, H-2). Anal. ($C_{19}H_{23}FN_4O_3$·HCl) C, H, N.

7-[(1*R*,4*R*)-1-Methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(1,1-dimethylethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Hydrochloride (43). A mixture of 0.86 g (2 mmol) of **6**, 0.42 g (1.28 mmol) of **27**, and 0.92 g (6 mmol) of DBU in 18 mL of CH_3CN was stirred at reflux overnight. After evaporation of the solvent, the residue was partitioned between CH_2Cl_2 and H_2O, dried ($MgSO_4$), and chromatographed (CH_2Cl_2/MeOH 98:2 to 94:6) to yield 0.16 g of the N-benzylated ethyl ester of **43** (yield 25.4%): ^1H NMR ($CDCl_3$) δ 1.40 (t, J = 7 Hz, 3 H, CH_3 ester), 1.75 (m, 1 H, H-7, pip.), 1.83 (m, 12 H, t-Bu and Me-1, pip.), 2.01 (m, 1 H, H-7′, pip.), 2.9 (d, J = 10 Hz, H-6, pip.), 3.35–3.50 (m, 2 H, H-6′ and H-4, pip.), 3.6–3.8 (m, 3 H, C*H*$_2$Ph and H-3, pip.), 4.06 (m, 1 H, H-3′, pip.), 4.38 (q, J = 7 Hz, 2 H, CH_2 ester), 7.24–7.33 (m, 5 H, CH_2*Ph*), 8.18 (d, J = 12.4 Hz, H-5), 8.82 (s, 1 H, H-2). A suspension of 0.16 g of the above ester was hydrogenated with 0.33 mL (0.33 mmol) of HCl in MeOH over 10% Pd/C to yield 0.075 g of the chlorhydrate of the ethyl ester of **43** (yield 53.6%). A mixture of 0.175 g (0.39 mmol) of the above ester and 0.83 mL (0.83 mmol) of 1 N NaOH in 4 mL of H_2O was heated at 70 °C for 2 h. The solution was cooled, and the pH was brought to 7 with 2 N HCl. The precipitate was collected and dried to give 0.14 g of the corresponding amino acid, which was transformed into 0.09 g of the chlorhydrate **43** after recrystallization from EtOH/H_2O (yield 56%): mp >260 °C; $[\alpha]_D$ +20.2°; IR 3432, 2842, 2722, 2678, 2571, 2457, 1734, 1632, 1437, 1189; ^1H NMR (DMSO-d_6) δ 1.89 (s, 3 H, Me-1, pip.), 1.93 (s, 9 H, t-Bu), 2.12 (d, J = 11 Hz, H-7, pip.), 2.38 (d, J = 11 Hz, H-7′, pip.), 3.29 (d, J = 10.6 Hz, 1 H, H-6, pip.), 3.76–3.81 (m, 2 H, H-6′ and H-3, pip.), 4.15 (m, 1 H, H-3′, pip.), 8.29 (d, J = 12.2 Hz, 1 H, H-5), 8.97 (s, 1 H, H-2). Anal. ($C_{19}H_{23}FN_4O_3$·HCl) C, H, N.

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