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 antiinfectives, 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.[1-3] 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**),[1] ofloxacin (**2**),[4] ciprofloxacin (**3**).[5] 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 examplified with ofloxacin (**2**),[6-8] S-25930 (**4**),[9] and the substituted ciprofloxacin derivative **5**,[10] and (**2**) at C-7. In this case, substituted

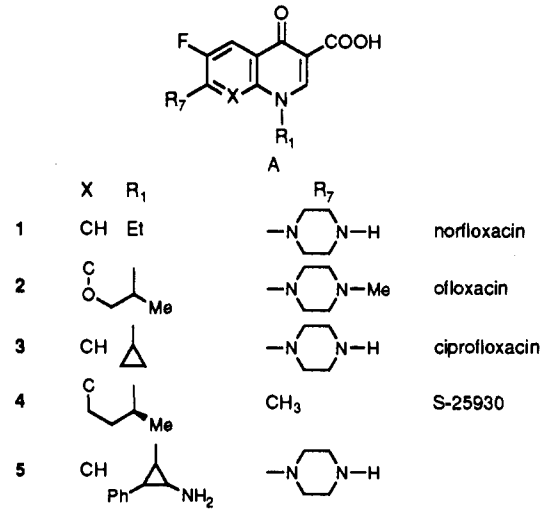

Figure 1.

piperazines,[11,12] 3-aminopyrrolidines,[13,14] 3-(aminoethyl)pyrrolidines,[15] and 3-hydroxypyrrolidines[16] have been used.

In other respects, structure–activity studies[17,18] have demonstrated that amino-substituted pyrrolidines con-

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(1) Koga, H.; Itoh, A.; Murayama, S.; Seigo, S.; Irikura, T.; Tsutomu, I. Structure-Activity Relationships of Antibacterial 6,7- and 7,8-Disubstituted 1-Alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids. *J. Med. Chem* **1980**, *23*, 1358–1363.

(2) Wentland, M. P.; Bailey, D. M.; Cornett, J. B.; Dobson, R. A.; Powles, R. G.; Wagner, R. B. Novel Amino-substituted 3-Quinolinecarboxylic Acid Antibacterial Agents: Synthesis and Structure–Activity Relationships. *J. Med. Chem* **1984**, *27*, 1103–1108.

(3) Domagala, J. M.; Hanna, L. D.; Heifetz, C. L.; Hutt, M. P.; Mich, T. F.;Sanchez, J. P.; Solomon, M. New Structure–Activity Relationships of the Quinolone Antibacterials Using the Target Enzyme. *J. Med. Chem* **1986**, *29*, 394–404.

(4) Hayakawa, I.; Hiramatsu, T.; Tanaka, Y. Synthesis and Antibacterial Activities Of Substituted 7-Oxo-2,3-dihydro-7H-pyrido[1,2,3,de]-benzoxazine-6-carboxylic Acids. *Chem. Pharm. Bull.* **1984**, *28*, 4907–4913.

(5) Wise, R.; Andrews, J. M.; Edwards, L. J. In Vitro Activity of Bay 09867, a New Quinoline Derivative, Compared with Those of Other Antimicrobial Agents. *Antimicrob. Agents Chemother.* **1983**, *23*, 559–564.

(6) Mitscher, L. A.; Sharma, P. D.; Chu, Daniel, T. W.; Shen, Linus, L.; Pernet, A. Chiral DNA Gyrase Inhibitors. 2. Asymmetric Synthesis and Biological Activity of the Enantiomers of 9-Fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic Acid. *J. Med. Chem* **1987**, *30*, 2283–2286.

(7) Hayakawa, I.; Atarashi, S.; Yokohama, S.; Imamura, M.; Sakano, K.; Furukawa, M. Synthesis and Antimicrobial Activities of Optically Active Ofloxacin. *Antimicrob. Agents Chemother.* **1986**, *29*, 163–164.

(8) Egawa, H.; Miyamoto, T.; Matsumoto, J. Pyridonecarboxylic Acids as Antibacterial Agents. *Part* 6. A New synthesis of 7*H*-Pyrido[1,2,3-*de*]benzoxazine Derivatives Including an Antibacterial Agent, Ofloxacin. *Chem. Pharm. Bull.* **1986**, *34*, 4098–4102.

(9) Gerster, J. F.; Rohlfing, S. R.; Pecore, S. E.; Winandy, R. M.; Stern, R. M.; Landmesser, J. E.; Olsen, R. A.; Gleason, W. B. Synthesis, Absolute Configuration and Antibacterial Activity of 6,7-Dihydro-5,8-dimethyl-9-fluoro-9-fluoro-1-Oxo-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylic Acid. *J. Med. Chem.* **1987**, *30*, 839–843.

(10) Mitscher, L. A.; Sharma, P. N.; Chu, Daniel, T. W.; Shen, L. L.; Pernet, A. G. Chiral DNA Gyrase Inhibitors. 1. Synthesis and Antimicrobial Activity of the Enantiomers of 6-Fluoro-7-(1-Piperazinyl)-1-(2-*trans*-phenylcyclopropyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid. *J. Med. Chem* **1986**, *29*, 2044–2047.

(11) Miyamoto, T.; Matsumoto, J.; Chiba, K.; Egawa, H.; Shibamori, K.; Minamida, A.; Nishimura, Y.; Okada, H.; Kataoka, M.; Eujita, M.; Hirose, T.; Nakano, J. Synthesis and Structure–Activity Relationships of 5-Substituted 6,8-Difluoroquinolones, Including Saprfloxacin, a New Quinolone Antibacterial Agent With Improved Potency. *J. Med. Chem.* **1990**, *33*, 1645–1656.

(12) 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.

(13) Rosen, T.; Chu, D. T. W.; Lico, I. M.; Fernandes, P. B.; Marsh, K.; Shen, L.; Gepa, V. G.; Pernet, A. G. Design, Synthesis, and Properties of (4*S*)-7-(4-Amino-2-substituted-pyrrolidin-1-yl)quinolone-3-carboxylic Acids. *J. Med. Chem.* **1988**, *31*, 1598–1611.

(14) Rosen, T.; Chu, D. T. W.; Lico, I. M.; Fernandes, P. B.; Shen, L.; Borodkin, S.; Pernet, A. G. Asymmetric Synthesis and Properties of the Enantiomers of the Antibacterial Agent 7-(3-Aminopyrrolidin-1-yl)-1-(2,4-difluorophenyl)-1,4-dihydro-6-fluoro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Hydrochloride. *J. Med. Chem.* **1988**, *31*, 1586–1590.

(15) Culbertson, T. P.; Domagala, J. M.; Nichols, J. B.; Priebe, S.; Skeean, R. N. Enantiomers of 1-Ethyl-7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid: Preparation and Biological Activity. *J. Med. Chem.* **1987**, *30*, 1711–1715.

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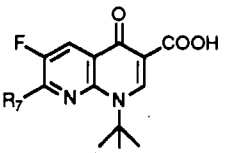
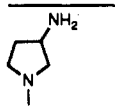
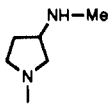
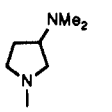
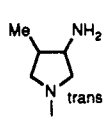
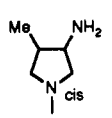
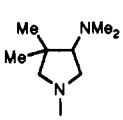
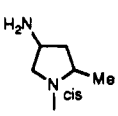
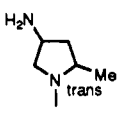
Table I



R_7	amine R_7H	compd	formula[b]	$[\alpha]_D$, deg	mp, °C	% yield[a]	recryst solvent	water solubility, mg/mL, pH 7
	**10** (3*R*)	**53**	$C_{17}H_{21}FN_4O_3 \cdot CH_3SO_3H \cdot H_2O$	−18.5 (*c* = 1, HCl 0.1 N)	255	67.5	MeOH	0.01
	17 (3*S*)	**54**	$C_{17}H_{21}FN_4O_3 \cdot CH_3SO_3H$	+17.6 (*c* = 1, HCl 0.1 N)	244	61	MeOH	0.01
	**13** (3*R*)	**55**	$C_{18}H_{23}FN_4O_3 \cdot HCl \cdot H_2O$	−19.4 (*c* = 0.4, HCl 0.1 N)	260	53	EtOH	0.08
	18 (3*S*)	**56**	$C_{18}H_{23}FN_4O_3 \cdot HCl$	+20.0 (*c* = 2, HCl 0.1 N)	260	48	EtOH	0.08
	racemic	**57**	$C_{19}H_{25}FN_4O_3$	-	260	41	H_2O	0.09
	19 (3*S*)	**58**	$C_{19}H_{25}FN_4O_3 \cdot HCl$	+9.1 (*c* = 1, H_2O/MeOH, 1/1)	292	56	EtOH/H_2O	0.09
	**29** (3*R*,4*S*)	**59**	$C_{18}H_{23}FN_4O_3 \cdot CH_3SO_3H$	−16.3 (*c* = 0.5, HCl 0.1 N)	270	32	EtOH	0.25
	31 (3*S*,4*R*)	**60**	$C_{18}H_{23}FN_4O_3 \cdot CH_3SO_3H$	+18.3 (*c* = 0.5, HCl 0.1 N)	236	85	EtOH/H_2O	0.25
	**28** (3*S*,4*S*)	**61**	$C_{18}H_{23}FN_4O_3 \cdot CH_3SO_3H$	−5.4 (*c* = 1, HCl 0.1 N)	260	40	EtOH	0.02
	30 (3*R*,4*R*)	**62**	$C_{18}H_{23}FN_4O_3 \cdot CH_3SO_3H$	+6.5 (*c* = 0.5, HCl 0.1 N)	225 dec	56	EtOH	0.02
	**36** (3*S*)	**63**	$C_{19}H_{25}FN_4O_3 \cdot CH_3SO_3H$	−7.3 (*c* = 0.5, HCl 0.1 N)	270	12	EtOH	0.3
	40 (3*R*)	**64**	$C_{19}H_{25}FN_4O_3 \cdot HCl$	+6.3 (*c* = 0.1, HCl 0.1 N)	260	24	EtOH	0.3
	**49** (2*R*,4*S*)	**65**	$C_{18}H_{23}FN_4O_3 \cdot CH_3SO_3H$	+32.4 (*c* = 0.5, H_2O)	200 dec	14	MeOH	1.7
	52 (2*S*,4*R*)	**66**	$C_{18}H_{23}FN_4O_3 \cdot HCl \cdot H_2O$	−39.0 (*c* = 0.5, HCl 0.1 N)	270	39.2	EtOH	1.7
	**50** (2*R*,4*R*)	**67**	$C_{18}H_{23}FN_4O_3 \cdot HCl \cdot H_2O$	−36.0 (*c* = 0.5, HCl 0.1 N)	260	35.5	EtOH	0.17
	51 (2*S*,4*S*)	**68**	$C_{18}H_{23}FN_4O_3 \cdot HCl$	+37.6 (*c* = 0.5, HCl 0.1 N)	260	63	MeOH/ether	0.17

[a] Yields are given for the halogen exchange reaction and saponification. [b] 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[19-21] involving the 1-position of the quinolones and naphthyridones have established that a *tert*-butyl moiety for R_1 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**[19] 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-

(16) Uno, T.; Iuch, K.; Kawahata, Y.; Tsukamoto, G. Synthesis of Antimicrobial Agents. II. Syntheses and Antibacterial Activities of Optically Active 7-(3-Hydroxypyrrolidin-1-yl)quinolones. *J. Heterocycl. Chem.* **1987**, *24*, 1025–1028.

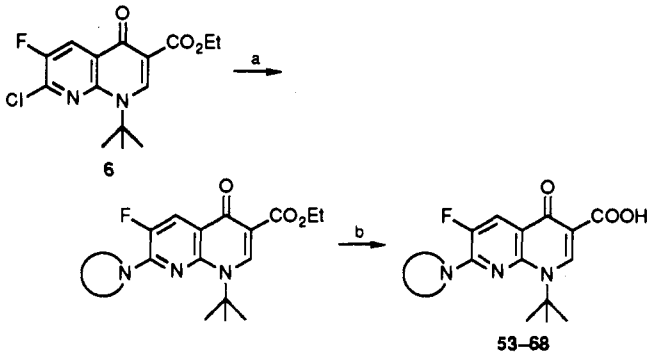
(17) Domagala, J. M.; Heifetz, C. L.; Mich, T. F.; Nichols, J. B. 1-Ethyl-7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid. New Quinolone Antibacterial with Potent Gram-Positive Activity. *J. Med. Chem.* **1986**, *29*, 445–448.

(18) Cohen, D.; Griffin, T. J.; Bien, P. A.; Heifetz, C. L.; Domagala, J. M. In vitro Activity of Cl-934, a Quinolone Carboxylic Acid Active against Gram-Positive and -Negative Bacteria. *Antimicrob. Agents Chemother.* **1985**, *28*, 766–772.

(19) Bouzard, D.; Di Cesare, P.; Essiz, M.; Jacquet, J. P.; Remuzon, P.; Weber, A.; Oki, T.; Masuyoshi, M. Fluoronaphthyridines and Quinolones as Antibacterial Agents. 1. Synthesis and Structure–Activity Relationships of New 1-Substituted Derivatives. *J. Med. Chem.* **1989**, *32*, 537–542.

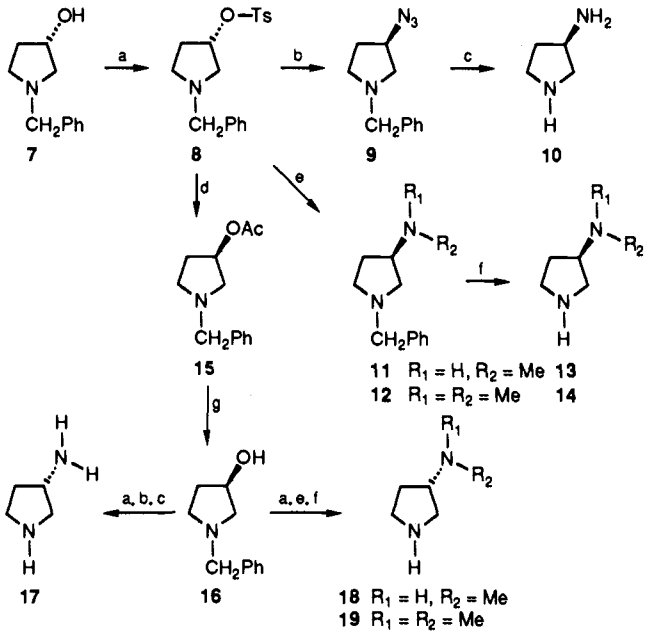
(20) Bouzard, D.; Di Cesare, P.; Essiz, M.; Jacquet, J. P.; Kiechel, J. R.; Remuzon, P.; Weber, A.; Oki, T.; Masuyoshi, M.; Kessler, R. E.; Fung-Tomc, J.; Desiderio, J. Fluoronaphthyridines and Quinolones as Antibacterial Agents. 2. Synthesis and Structure–Activity Relationships of New 1-*tert*-Butyl 7-Substituted Derivatives. *J. Med. Chem.* **1990**, *33*, 1344–1352.

Scheme I [a]



[a] (a) ◯NH, DBU, CH_3CN; (b) aqueous 2 N NaOH, reflux.

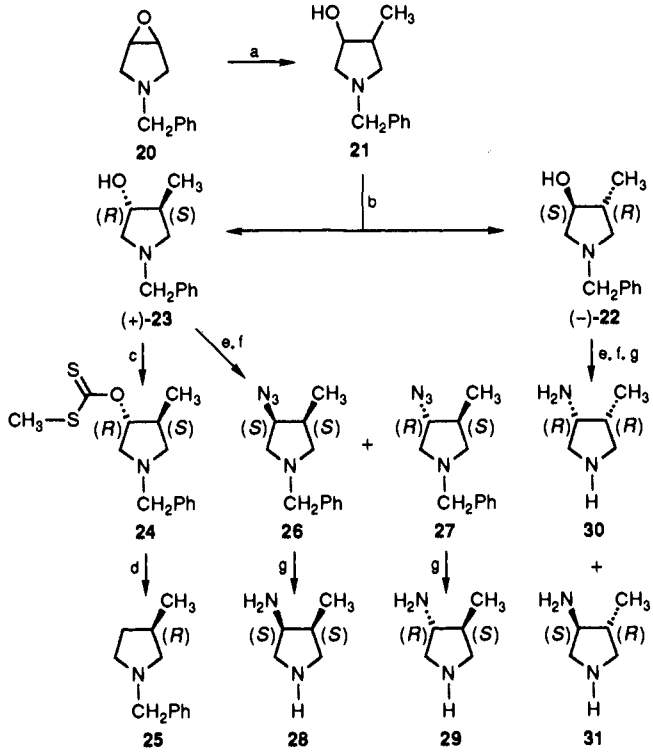
Scheme II [a]



[a] (a) TsCl, pyridine; (b) NaN_3, DMF; (c) H_2, Pd/C; (d) $Et_4N^+AcO^-$; (e) R_1R_2NH; (f) H_2, Pd/C; (g) Na_2CO_3, MeOH.

pyrrolidinol (**7**)[22-24] 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 s_N2 displacement with azide ion or methylamine or dimethylamine. Tosylation of the alcohol **7** (TsCl, pyridine) afforded the key intermediate **8**. Subsequent s_N2 displacement with azide ion gave enantiomerically pure (*R*)-3-azido derivative **9**. Reduction of the azide and debenzylation were accomplished 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.[25,26] For the preparation of pure enantiomers of the corresponding pyrrolidines in our series we have chosen to operate an optical resolution.

Scheme III [a]



[a] (a) CH_3MgBr, CuCN, THF; (b) (−)-DTTA; (c) NaH, DMF, CS_2, MeI; (d) Bu_3SnH, AIBN; (e) TsCl, pyridine; (f) NaN_3, CH_3CN/DMF; (g) H_2, Pd/C.

The known epoxide **20**[27] 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 (±)-*trans*-3-methyl-4-hydroxypyrrolidine **21**. The (+) and (−) isomers were separated by resolution (±)-**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 hydroxyde to afford pure (+)-isomer **23**. Pure

(21) Remuzon, P.; Bouzard, D.; Di Cesare, P.; Essiz, M.; Jacquet, J. P.; Kiechel, J. R.; Ledoussal, B.; Kessler, R. E.; Fung-Tomc, J. Fluoronaphthyridines and -quinolones as Antibacterial Agents. 3. Synthesis and Structure–Activity Relationships of New 1-(1,1-Dimethyl-2-fluoroethyl), 1-[1-Methyl-1-(fluoromethyl)-2-fluoroethyl, and 1-[1,1-(Difluoromethyl)-2-fluoroethyl] Substituted Derivatives. *J. Med. Chem.* **1991**, *34*, 29–37.

(22) Bowers Nemia, M. M.; Lee, J.; Joulli'e, M. M. Synthetic Routes to 3-Pyrrolidinol. *Synth. Commun.* **1983**, *13*, 1117–1123.

(23) Tamazawa, K.; Arima, H.; Kojima, T.; Isomura, Y.; Okado, M.; Fujita, S.; Furuya, T.; Takenaka, T.; Inagaki, O.; Terai, M. Stereoselectivity of a Potent Calcium Antagonist, 1-Benzyl-3-pyrrolidinyl Methyl 2,6-Dimethyl-4-(m-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate. *J. Med. Chem.* **1986**, *29*, 2504–2511.

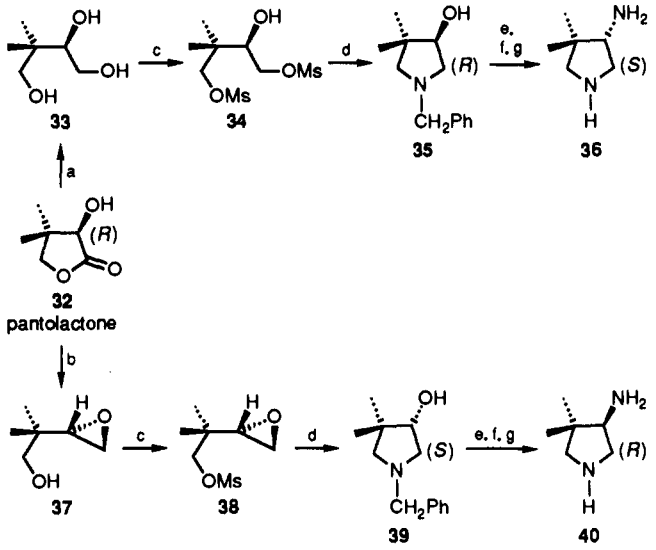
(24) Baker, G. L.; Fristchel, S. J.; Stille, J. R.; Stille, J. K. Transition-Metal-Catalyzed Asymmetric Organic Synthesis via Polymer-Attached Optically Active Phosphine Ligands. 5. Preparation of Amino Acids in Hgh Optical Yield via Catalytic Hydrogenation. *J. Org. Chem.* **1981**, *46*, 2954–2960.

(25) Hagen, S. E.; Domagala, J. M.; Heifetz, C. L.; Sanchez, J. P.; Solomon, M. New Quinolone Antibacterial Agents. Synthesis and Biological Activity of 7-(3,3- or 3,4-disubstituted-1-pyrrolidinyl)quinoline-3-carboxylic Acids. *J. Med. Chem.* **1990**, *33*, 849–854.

(26) Miyamoto, H.; Ueda, H.; Otsuka, T.; Aki, S.; Tamaoka, H.; Tominaga, H.; Nakagawa, K. Studies on Antibacterial Agents. 3. Synthesis and Antibacterial Activities of Substituted 1,4-Dihydro-8-methyl-4-oxoquinoline-3-carboxylic Acids. *Chem. Pharm. Bull.* **1990**, *38*, 2472–2475.

(27) Walsh, D. A.; Welstead, W. J., Jr. *Cis*- and *Trans*-Isomers of 3-Aryloxy-4-hydroxypyrrolidines and their derivatives. DE 3000625. *Chem. Abstr.* **1981**, *94*, 121306d.

Scheme IV [a]



[a] (a) Reference 30; (b) ref 31; (c) MsCl, pyridine; (d) $PhCH_2NH_2$; (e) TsCl, pyridine; (f) NaN_3, DMF; (g) H_2, 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 determinated by chemical correlation with the known (*R*)-(−)-*N*-benzyl-3-methylpyrrolidine (**25**).[28,29] Treatment of the methyl xanthate **24** with Bu_3SnH and AIBN gave the *R* derivative **25** {$[\alpha]_D = -14.8°$ ($c = 2$, EtOH), lit.: −10.1° ($c = 3.2$, 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_N2 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*)-3a-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[30] 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[31] 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_N2 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[32] was selectively reduced by $LiAlH_4$ 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[24] 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_N2 displacement with NaN_3 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 ^1H 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_{50} mg/kg) was determined by using previously described methods.[19–21] The results of the in vivo tests are summerized 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

(28) Ringdahl, B.; Dahlbom, R. Acetylene Compounds of Potential Pharmalogical Value. 27. Stereoselectivity of Oxotremorine Antagonists Containing a Chiral Pyrrolidine Group. *Acta Pharm. Sued.* **1978**, *15*, 255–263.

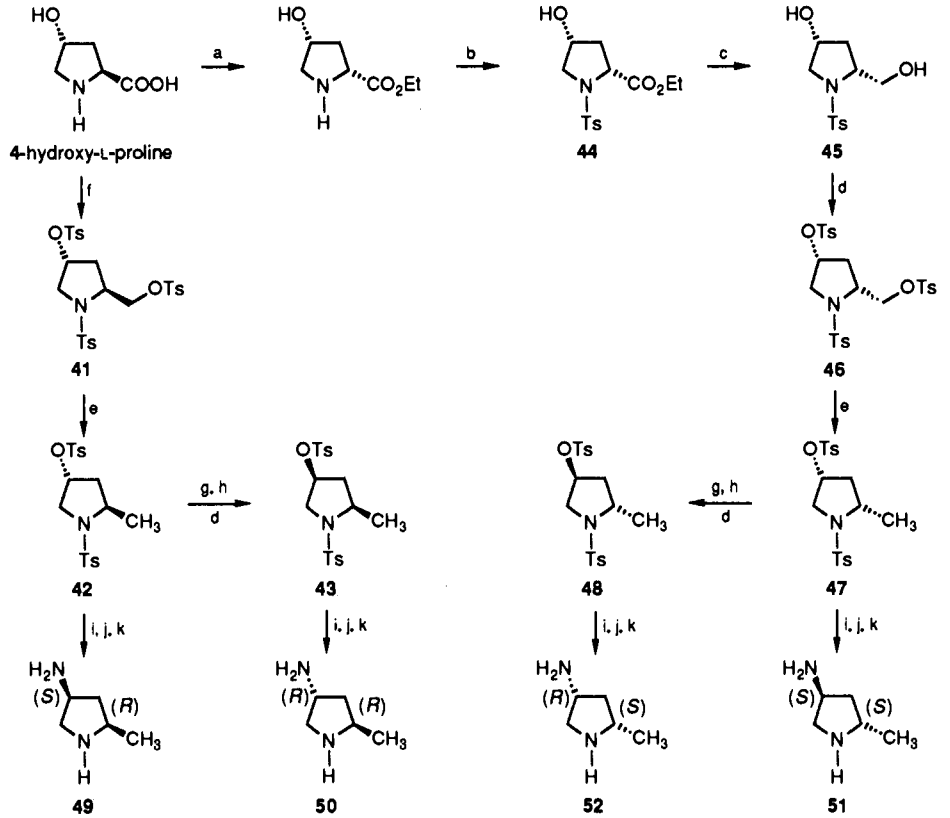
(29) Ringdahl, B.; Dahlbom, R. Absolute Configuration and Circular Dichroism of 3-Methyl-2-pyrrolidone. *Tetrahedron Lett.* **1978**, *37*, 3475–3478.

(30) Brocquet, C.; Bedin, J. Etude de Composés Obtenus par Réduction et Oxydation de l'Hydroxy-2 Diméthyl-3,3-Butanolide-1,4. *Bull. Soc. Chim. Fr.* **1967**, 1909–1913.

(31) Lavallée, P.; Ruel, R.; Grenier, L.; Bissonnette, M. Convenient Access to Two Enantiomeric Oxirane Synthons Bearing a Quaternary Gem-dimethyl Carbon Center. Synthesis of 3S-(+)- and 3R-(−)-Pantolactone. *Tetrahedron Lett.* **1986**, *27*, 679–682.

(32) Portoghese, P. S.; Adel, A. M. Bicyclic Bases. Synthesis of 2,5-Diazabicyclo[2.2.1]heptanes. *J. Org. Chem.* **1966**, *31*, 1059–1062.

Scheme V [a]



[a] (a) Reference 24; (b) TsCl, TEA; (c) $LiBH_4$, THF; (d) TsCl, pyridine; (e) $LiAlH_4$; (f) ref 32; (g) Et_4N^+ AcO^-; (h) K_2CO_3; (i) NaN_3, DMF; (j) H_2, Pd/C; (k) HBr, AcOH.

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

compd	*E. faeca.* A9809	*E. faeci.* A24885	*S. aur.* A9537	*E. coli* A15119	*K. pneu.* A9664	*E. cloa.* A9656	*M. morg.* A15153	*S. mars.* A20019	*P. aeru.* 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.[26] 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.[13,14] 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

	in vivo PD_{50}[a] (mg/kg) po				
compd	*S. aureus* A9537	*P. aeruginosa* A9843	*E. coli* A15119	*K. pneumoniae* A9664	LD_{50}[b] po
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

[a] Dose to protect 50% of mice from lethal infection po. [b] See Experimental Section.

Table IV. Pharmacokinetic Properties of Selected Compounds after Oral Administration in Mice[a] (50 mg/kg)

compd	C_{max}, μg/mL	$t_{1/2}$, h	AUC[b]	UR[c]
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

[a] See Experimental Section. [b] Areas under the curve, concentration/time, μg/mL per h. [c] 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.[19,20] 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-methylpyrroldinyl 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.[12–15] 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 while the difference is more important for quinolones bearing a chiral center closer to N-1 as reported for ofloxacin analogs.[6–8] 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** (BMY 41802) and compound **61** (BMY 41889) for preclinical development.[33]

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

compd	C_{max}	$t_{1/2}$, 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

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 ^1H 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 Merk 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 106 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 administred orally to OF1 strain female Swiss mice (18–25 g body weight, five per group). Seven days later, LD_{50} values were determined by using the Karber and Behrens method.[34]

Pharmacokinetics in Mice. Levels of selected compounds in blood and urine samples from mice were determined as previously described.[21] Each compound was administered orally with a blunt needle and syringe set and intramusculary 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 microbioassay 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 administred 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

(33) Bouzard, D.; Kessler, R. E.; Di Cesare, P.; Desiderio, J.; Essiz, M.; Fung-Tomc, J.; Jacquet, J. P.; Ledoussal, B.; Kiechel, J. R.; Remuzon, P.; Tsai, Y. Antibacterial Activities and Pharmacokinetics of BMY 41802 and BMY 41889. *30th ICAAC*, Atlanta, *Oct 21–24*, 1990; Abstract no. 392.

(34) Behrens, B.; Karber, G. *Arch. Exp. Pathol. Pharm.* **1935**, *177*, 379–388.

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)[23] 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; $[\alpha]_D$ −30° (*c* = 5, MeOH); ^{1}H NMR (Me_2SO-d_6) δ 1.6–1.9 (m, 1 H), 2.1–2.35 (m, 1 H), 2.4 (s, 3 H, CH_3Ar), 2.55–3.1 (m, 3 H), 3.8 (s, 2 H, CH_2Ar), 5.04 (m, 1 H, H-3), 7.32 (broad s, 5 H, CH_2Ar), 7.48 and 7.78 (m, 4 H, CH_3ArSO$_2$). Anal. ($C_{18}H_{21}NO_3S$) 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: $[\alpha]_D$ −7.2° (*c* = 5, MeOH); ^{1}H NMR (Me_2SO-d_6) 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_2Ar), 4.0 (m, 1 H, H-3), 7.29 (broad s, 5 H, Ar). Anal. ($C_{11}H_{14}N_4$) 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: $[\alpha]_D$ = −1.2° (*c* = 0.5, 0.1 N HCl); ^{1}H NMR δ (Me_2SO-d_6) 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. ($C_4H_{10}N_2$·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 ($MgSO_4$), 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: ^{1}H NMR (Me_2SO-d_6) δ 1.35–1.6 (m, 1 H), 1.8–2.1 (m, 1 H), 2.2 (s, 3 H, NCH_3), 2.35–2.8 (m, 4 H), 3.05 (m, 1 H, H-3), 3.52 (s, 2 H, CH_2Ar), 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: $[\alpha]_D$ −3.7° (*c* = 1.0, 1 N HCl); ^{1}H NMR (Me_2SO-d_6) δ 2.05–2.4 (m, 2 H), 2.56 (s, 3 H, NCH_3), 3.1–3.6 (m, 6 H), 3.83 (m, 1 H, H-3), 9.7 (broad s, 4 H, exchangeable). Anal. ($C_5H_{12}N_2$·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 chromatography using dichloromethane/methanol (98/2) to yield 1.4 g of pure compound 15 as an oil: $[\alpha]_D$ +22.0° (*c* = 5, MeOH); ^{1}H NMR (Me_2SO-d_6) δ 1.7 (m, 1 H), 2.06 (s, 3 H, CH_3CO_2−) 2.11–2.71 (m, 5 H), 3.55 (s, 2 H, CH_2Ar), 5.03 (m, 1 H, H-3), 7.26 (m, 5 H, Ar). Anal. ($C_{13}H_{17}NO_2$) 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 occured. 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): $[\alpha]_D$ +3.5° (*c* = 5, MeOH); ^{1}H NMR (Me_2SO-d_6) δ 2.0 (m, 1 H), 2.2–2.75 (m, 4 H), 3.4–3.6 (m, 2 H, CH_2Ar), 4.22 (m, 1 H, H-3), 4.71 (broad s, 1 H, exchangeable), 7.18–7.31 (m, 5 H, Ar). Anal. ($C_{11}H_{15}NO$) 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 $[\alpha]_D$ +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 $[\alpha]_D$ +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: $[\alpha]_D$ −2.8° (*c* = 0.5, H_2O–MeOH 50/50); ^{1}H NMR (D_2O) δ 2.15–2.4 (m, 1 H), 2.55–2.8 (m, 1 H), 3.00 (s, 6 H, N(CH_3)$_2$), 3.35–3.75 (m, 3 H), 3.80–4.0 (m, 1 H), 4.10–4.30 (m, 1 H). Anal. ($C_6H_{14}N_2$·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; $[\alpha]_D$ −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: $[\alpha]_D$ +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 hydroxyde 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° (*c* = 1, MeOH); ^{1}H NMR (Me_2SO-d_6) δ 0.97 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.98 (m, 2 H), 2.4 (m, 1 H), 2.55–2.85 (m, 3.52 (m, 2 H, CH_2Ar), 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 chromatographied (ethyl acetate/hexane, 20:80) to give 2.90 g of a pure product as an oil: $[\alpha]_D$ +45.5° (*c* = 1.35, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.15 (d, *J* = 7 Hz, 3 H, CH_3), 2.05 (m, 1 H), 2.5 (m, 1 H), 2.57 (s, 3 H, SCH_3), 2.75–3.1 (m, 2 H, CH_2Ar), 7.30 (m, 5 H, Ar). Anal. ($C_{14}H_{19}NOS_2$) 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 (CH_2Cl_2/MeOH, 95:5) to give 0.750 mg of pure product: $[\alpha]_D$ -10.5° (*c* = 3.25, EtOH; in accordance with the literature[28,29] for the *R* isomer); ^{1}H NMR (Me_2SO-d_6) δ 0.92 (d, *J* = 6.7 Hz, 3 H, 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, CH_2Ar), 7.20 (broad s, 5 H, Ar). Anal. ($C_{12}H_{17}N$) 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° (*c* = 1, MeOH), ^{1}H NMR (Me_2SO-d_6) δ 0.98 (d, *J* = 6.8 Hz, 3 H, 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, CH_2Ar), 4.0 (m, 1 H, H-3), 7.29 (m, 5 H, Ar). Anal. ($C_{12}H_{16}N_4$) C, H, N. Compound **27**: $[\alpha]_D$ +31.9° (*c* = 1, MeOH); ^{1}H NMR (Me_2SO-d_6) δ 1.04 (d, *J* = 7 Hz, 3 H, 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, CH_2Ar), 7.26 (m, 5 H, Ar). Anal. ($C_{12}H_{16}N_4$) 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}H NMR (Me_2SO-d_6) δ 1.04 (d, 3 H, *J* = 6.8 Hz, 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}H NMR (Me_2SO-d_6) δ 1.12 (d, *J* = 7 Hz, 3 H, 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° (*c* = 5, MeOH); ^{1}H NMR (Me_2SO-d_6) δ 0.9 and 0.94 (2s, 2 × 3 H, $C(CH_3)_2$), 3.17–3.19 (2s, 2 × 3 H, 2 SO_2CH_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, $J_{3,OH}$ = 2.5 Hz), 5.51 (broad s, 1 H, exchangeable). Anal. ($C_8H_{18}O_7S_2$) 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 etheral 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° (*c* = 1, MeOH); ^{1}H NMR (Me_2SO-d_6) δ 0.9 and 0.96 (2 s, 2 × 3 H, $C(CH_3)_2$), 2.25–2.40 (m, 3 H), 2.9–3.0 (m, 1 H), 3.5–3.65 (m, 2 H, CH_2Ar), 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. ($C_{13}H_{19}NO$) 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 $NaHCO_3$ solution, dried over magnesium sulfate, and evaporated in vacuo. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 98/2) to afford 0.49 g of (3*R*)-*N*-benzyl-4,4-dimethyl-3-(4-toluenesulfonyl)oxy]pyrrolidine: $[\alpha]_D$ +43.5° (*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° (*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° (*c* = 1, H_2O); ^{1}H NMR (Me_2SO-d_6) δ 0.94 and 1.01 (2 s, 2 × 3 H, $C(CH_3)_2$), 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. ($C_6H_{14}N_2$·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° (*c* = 2, $CHCl_3$); ^{1}H NMR (Me_2SO-d_6) δ 0.87 (broad s, 6 H, $C(CH_3)_2$), 2.62 (m, 2 H), 2.86 (m, 1 H), 3.18 (s, 3 H, CH_3SO_2), 4.01 (m, 2 H, CH_2OMs). Anal. ($C_7H_{14}O_4S$) 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° (*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° (*c* = 0.5, H_2O).

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° (*c* = 1.8, ethanol); ^{1}H NMR (Me_2SO-d_6) δ 1.17 (t, *J* = 7 Hz, 3 H, OCH_2CH_3), 1.8–2.1 (m, 2 H, H-3,3′), 2.39 (s, 3 H, CH_3Ar), 3.05–3.25 (m, 3 H), 3.96 (m, 1 H, H-4), 4.09 (q, *J* = 7 Hz, 2 H, OCH_2CH_3), 5.07 (broad s, 1 H, exchangeable), 7.38–7.76 (m, 4 H, Ar). Anal. ($C_{14}H_{19}NO_5S$) 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 rosed 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° (*c* = 2, ethanol); ^{1}H NMR (Me_2SO-d_6) δ 1.55–1.85 (m, 2 H, H-3,3′), 2.40 (s, 3 H, CH_3Ar), 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. ($C_{12}H_{17}NO_4S$) C, H, N.

(2*R*,4*R*)-1-(4-Tolylsulfonyl)-4-[(4-tolylsulfonyl)oxy]-2-[[(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° (*c* = 1.8, chloroform); ^{1}H NMR (Me_2SO-d_6) δ 1.7–1.9 (m, 2 H), 2.39, 2.43, 2.44 (3 s, 3 × 3 H, 3 CH_3Ar), 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. ($C_{26}H_{29}NO_8S_3$) 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° (*c* = 2, acetone); ^{1}H NMR (Me_2SO-d_6) δ 1.26 (d, *J* = 6.4 Hz, CH_3), 1.62 (m, 1 H), 2.41 (m, 6 H, 2 CH_3Ar), 3.18 (m, 1 H), 3.35 (m, 1 H), 4.76 (m, 1 H, H-4). Anal. ($C_{19}H_{23}NO_5S_2$) 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° (*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° (*c* = 0.7, EtOH); ^{1}H NMR (Me_2SO-d_6) δ 1.35 (d, *J* = 6.4 Hz, 3 H, CH_3), 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. ($C_5H_{12}N_2 \cdot 2HBr$) C, H, N.

Compounds **49–51** were prepared from **42**, **43**, and **47**, respectively, as described for the preparation of **52**. **(2*R*,4*S*)-4-Amino-2-methylpyrrolidine dihydrobromide (49)**: mp 179 °C; $[\alpha]_D$ +0.45° (*c* = 2, EtOH); ^{1}H NMR identical to **52**. **(2*R*,4*R*)-4-Amino-2-methylpyrrolidine dihydrobromide (50)**: mp 176 °C; $[\alpha]_D$ +0.7° (*c* = 1, EtOH); ^{1}H NMR (Me_2SO-d_6) δ 1.28 (d, *J* = 6.5 Hz, 3 H, CH_3), 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° (*c* = 2, EtOH); ^{1}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° (*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° (*c* = 0.5, 0.1 N HCl); ^{1}H NMR (Me_2SO-d_6) δ 1.16 (d, *J* = 6.8 Hz, 3 H, CH_3-pyrrolidinyl), 1.89 (s, 9 H, *t*-Bu), 2.3 (s, 3 H), CH_3SO_3H), 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. ($C_{18}H_{23}FN_4O_3 \cdot CH_3SO_3H$) C, H, N.